Controlling the geometry of double bonds

31

Connections

Building on:

- Carbonyl chemistry ch6, ch12, & ch14
- Kinetic and thermodynamic control |ch13|
- Wittig reaction ch14
- Conjugate addition ch10
- Stereochemistry ch16
- Elimination reactions ch19
- Reduction ch24
- Chemistry of enol(ate)s ch26–ch29

Arriving at:

- What makes *E*- and *Z*-alkenes different?
- Why *E*/*Z* control matters
- Eliminations are not stereoselective
- Cyclic alkenes are *cis*
- Equilibration of alkenes gives *trans*
- Effects of light and how we see
- Julia olefination and the Wittig reaction at work
- Reliable reduction of alkynes

Looking forward to:

- Diastereoselectivity ch33–ch34
- Pericyclic reactions ch35–ch36
- Fragmentations ch38
- Radicals and carbenes ch39–ch40
- Main group chemistry ch46–ch47
- Asymmetric synthesis ch45
- Polymerization ch52
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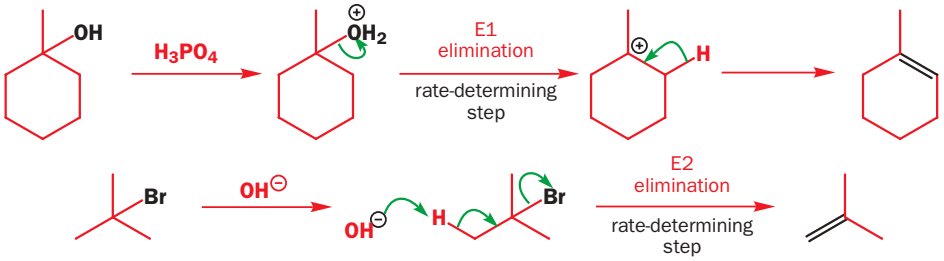
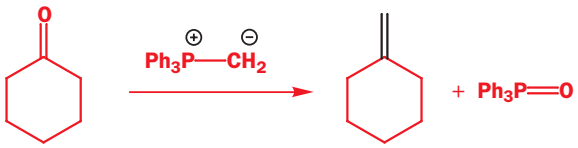
The properties of alkenes depend on their geometry

You have met alkenes participating in reactions in a number of chapters, but our discussion of how to *make* alkenes has so far been quite limited. Chapter 19 was about elimination reactions, and there you met E1 and E2 reactions.

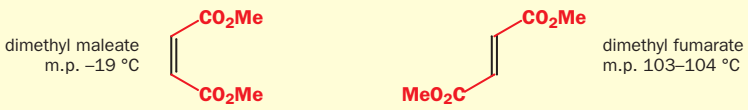


In Chapter 14, you met an important reaction known as the **Wittig reaction**, which also forms alkenes.



Different physical properties: maleate and fumarate

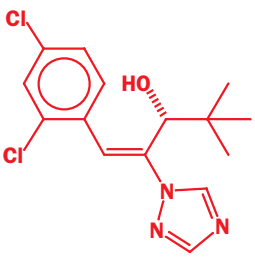
These two compounds, (*Z*)- and (*E*)-dimethyl but-2-enedioate, are commonly known as dimethyl maleate and dimethyl fumarate. They provide a telling example of how different the physical properties of geometrical isomers can be. Dimethyl maleate is a liquid with a boiling point of 202 °C (it melts at –19 °C), while dimethyl fumarate is a crystalline compound with a melting point of 103–104 °C.



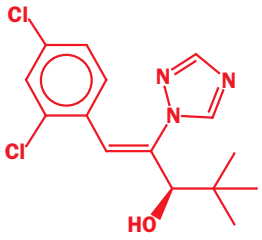
In this chapter we shall talk about reactions similar to the ones on the previous page and we shall be interested in *how to control the geometry of double bonds*. Geometrical isomers of alkenes are different compounds with different physical, chemical, and biological properties. They are often hard to separate by chromatography or distillation, so it is important that chemists have methods for making them as single isomers.

Why is double bond control important?

The activity of the fungicide diniconazole is dependent on the geometry of its double bond: the *E*-isomer disrupts fungal metabolism, while the *Z*-isomer is biologically inactive.

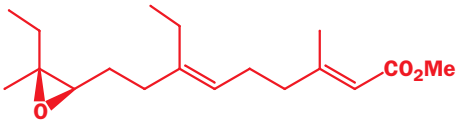


diniconazole: *E*-isomer has fungicidal activity

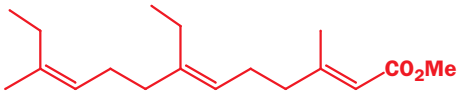


Z-isomer is inactive

If insect pests can be prevented from maturing they fail to reproduce and can thus be brought under control. Juvenile insects control their development by means of a 'juvenile hormone', one of which is the monoepoxide of a triene.



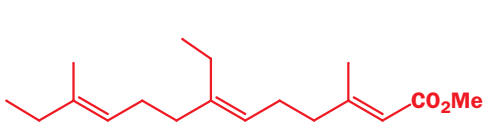
cecropia juvenile hormone: activity = 1000



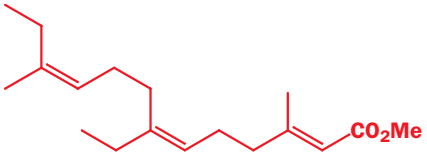
the *Z, E, E*-triene; activity = 100

Synthetic analogues of this compound, such as the trienes, are also effective at arresting insect development, *providing that the double bond geometry is controlled*. The *Z,E,E* geometrical isomer of the triene is over twice as active as the *E,E,E*-isomer, and over 50 times as active as the *E,Z,Z*- or *Z,E,Z*-isomers.

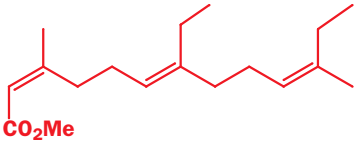
activity of juvenile hormone analogues (natural hormone = 1000)



E,E,E-triene: 40



Z,Z,E-triene: <2

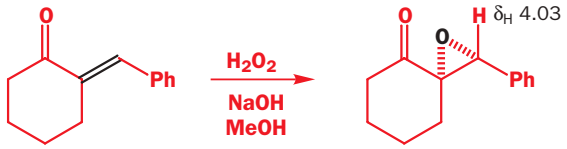


Z,E,Z-triene: <2

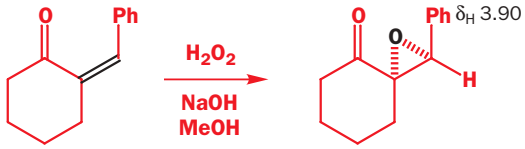
These are, of course, just two out of very many examples of compounds where the *E*- and *Z*-isomers have sufficiently different properties that it's no good having one when you need the other.

▶ We shall see later how to make these isomers.

Chemical reactions on *E*- and *Z*-isomers usually give the same type of product, though often with different stereochemistry. The two geometrical isomers may also react at very different rates. For example, the reaction of these conjugated *E*- and *Z*-enones with alkaline hydrogen peroxide gives in each case an epoxide, but with different stereochemistry and at very different rates.



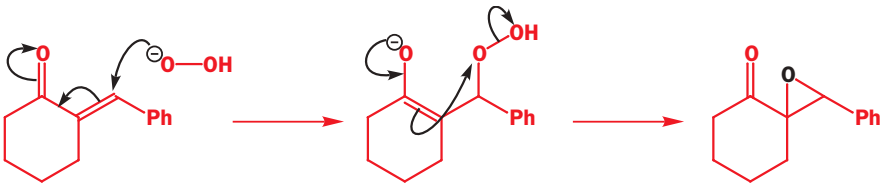
E-enone



Z-enone

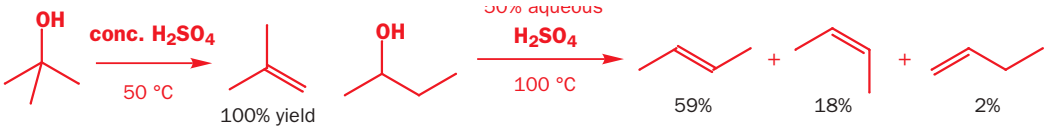
Epoxidation of the *E*-enone is complete in 2 hours and the epoxide can be isolated in 78% yield. The reaction on the *Z*-enone is very slow—only 50% is converted to the epoxide under the same

conditions in 1 week. The mechanism involves conjugate addition and ring closure with cleavage of the weak O–O bond (Chapter 23). The closure of the three-membered ring is fast enough to preserve the stereochemistry of the intermediate enolate.



Elimination reactions are often unselective

You saw in Chapter 19 that elimination reactions can be used to make alkenes from alcohols using acid or from alkyl halides using base. The acid-catalysed dehydration of tertiary butanol works well because the double bond has no choice about where to form. But the same reaction on *s*-butanol is quite unselective—as you would expect, the more substituted alkene is formed (almost solely, as it happens) but even then it's a mixture of geometrical isomers.



■ In Chapter 19 we explained why more substituted double bonds are formed preferentially (p. 000) and why *E*-alkenes are more stable than *Z*-alkenes (p. 000).

How, then, can we use elimination reactions to give single geometrical isomers? You have, in fact, already met one such reaction, on p. 000, and in this chapter we shall cover other reactions that do just this. These reactions fall into four main classes, and we shall look at each in turn before summarizing the most important methods at the end of the chapter.

▶ Some people call geometrical isomers diastereoisomers, which they are in a sense: they are stereoisomers that are not mirror images. However, we shall avoid this usage in the chapter since for most chemists the word *diastereoisomer* carries implications of three-dimensional stereochemistry.

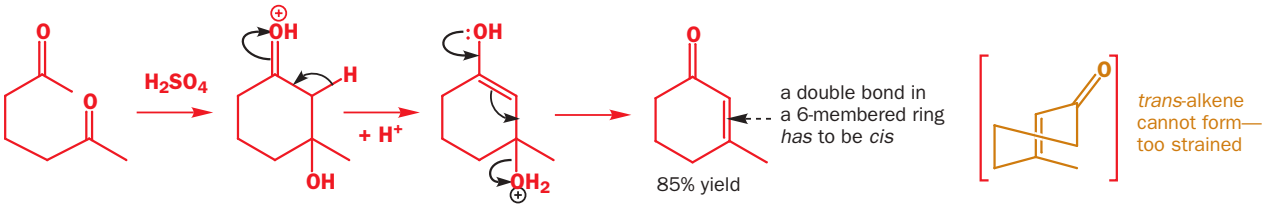
● Ways of making single geometrical isomers of double bonds

1. **Only one geometrical isomer is possible (for example, a *cis* double bond in a six-membered ring)**
2. **The geometrical isomers are in equilibrium and the more stable (usually *E*) is formed**
3. **The reaction is stereoselective and the *E*-alkene is formed as the main product by kinetic control**
4. **The reaction is stereospecific and the alkene geometry depends on the stereochemistry of the starting materials and the mechanism of the reaction**

In three- to seven-membered rings, only *cis*-alkenes are possible

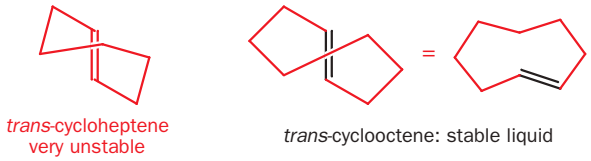
■ These reactions fall into class (1) of the list above.

In Chapter 28 you met the Robinson annelation as a method of making cyclohexenones. The product of the elimination step contains a double bond, but there is no question about its geometry because in a six-membered ring only a *cis* double bond can exist—a *trans* one would be far too strained.

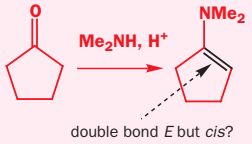


The same is true for three-, four-, five-, and seven-membered rings, though *trans*-cycloheptene has been observed fleetingly. An eight-membered ring, on the other hand, is just about large enough

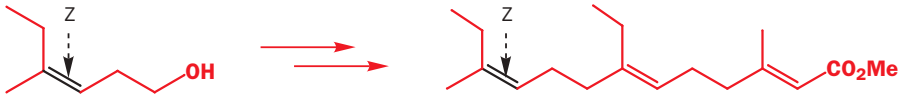
to accommodate a *trans* double bond, and *trans*-cyclooctene is a stable compound, though still less stable than *cis*-cyclooctene.



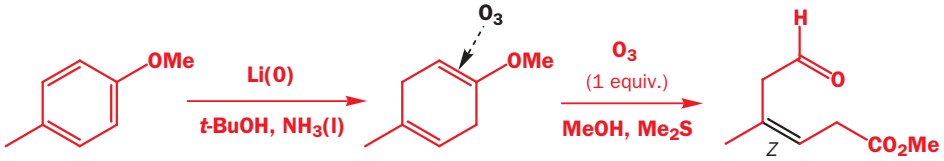
▶ Beware! The terms *cis* and *trans* do not always translate directly into *Z* and *E*.: Consider the preparation of an enamine from cyclohexanone, which forms a double bond that you'd probably call *cis* (it's in a ring). But applying the rigorous rules laid down for *E*/*Z* nomenclature (p. 000), it is *E*. As for the useful terms *syn* and *anti* (Chapter 16), there are no rigid rules for deciding whether a double bond is *cis* or *trans*.



You may think that this method is rather too trivial to be called a method for controlling the geometry of double bonds, as it's only of any use for making cyclic alkenes. Well, chemists are more ingenious than that! Corey needed this *cis*-alkene as an intermediate in his synthesis of the juvenile hormone we talked about above (it forms the left-hand end of the structure as shown there).



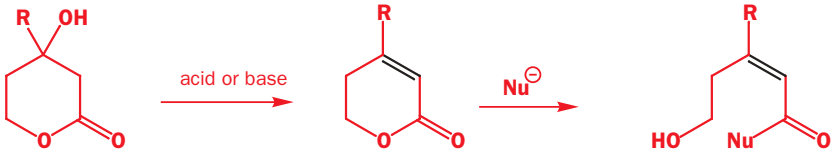
He realized that the *Z* double bond would be easy to make if he were to start with a cyclic molecule (in which only *cis* double bonds are possible) which could be ring-opened to the compound he needed. This is how he did it.



■ Ozone is a reagent for the oxidative cleavage of C=C double bonds. The products have carbonyl groups at the ends of the old alkene. The mechanism is described in Chapter 35.

Birch reduction (Chapter 24) of a simple aromatic ether generated two *cis* double bonds (notice that one of these is actually *E*!). The more reactive (because it is more electron-rich) of these reacts first with ozone to give an aldehyde-ester in which the *Z* geometry is preserved. $NaBH_4$ reduces the aldehyde group to a hydroxyl group, which needs to be got rid of: a good way to do this is to tosylate and reduce with $LiAlH_4$, which substitutes H for OTs. The $LiAlH_4$ also does the job of reducing the ester to an alcohol, giving the compound that Corey needed.

It is not necessary to have an all-carbon ring to preserve the *cis* geometry of a double bond. Lactones (cyclic esters) and cyclic anhydrides are useful too. A double bond in a five- or six-membered compound must have a *cis* configuration and compounds like these are readily made. Dehydration of this hydroxylactone can give only a *cis* double bond and ring-opening with a nucleophile (alcohol, hydroxide, amine) gives an open-chain compound also with a *cis* double bond. The next section starts with an anhydride example.

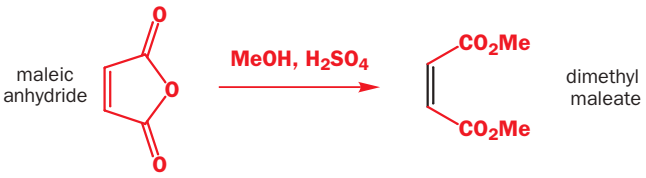


■ These reactions fall into class (2) of the list on p. 000.

Equilibration of alkenes to the thermodynamically more stable isomer

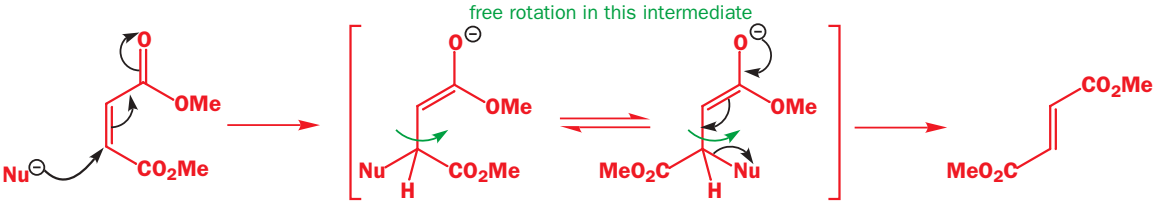
Acyclic *E*-alkenes are usually more stable than acyclic *Z*-alkenes because they are less sterically hindered. Yet *Z*-alkenes do not spontaneously convert to *E*-alkenes because the π bond prevents free rotation: the energy required to break the π bond is about 260 kJ mol^{-1} (rotation about a σ bond

requires about 10 kJ mol^{-1}). You may therefore find the following result surprising. Dimethyl maleate is easily made by refluxing maleic anhydride in methanol with an acid catalyst.

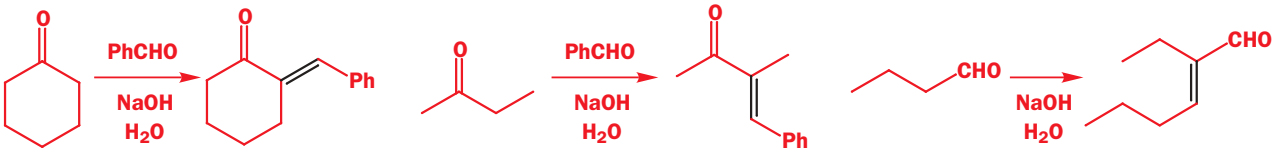


If the product is isolated straight away, a liquid boiling at 199–202 °C is obtained. This is dimethyl maleate. However, if the product is left to stand, crystals of *dimethyl fumarate* (the *E*-isomer of dimethyl maleate) form. How has the geometry been inverted so easily?

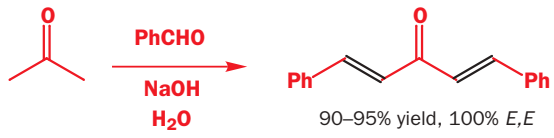
A clue is that the process is accelerated enormously by a trace of amine. Michael addition of this amine, or of methanol, or any other nucleophile, provides a chemical mechanism by which the π bond can be broken. There is free rotation in the intermediate, and re-elimination of the nucleophile can give either *E*- or *Z*-alkene. The greater stability and crystallinity of the *E*-alkene means that it dominates the equilibrium. Michael addition therefore provides a mechanism for the equilibration of *Z*-alkenes to *E*-alkenes.



Similar mechanisms account for the double bond geometry obtained in aldol reactions followed by dehydration to give α,β-unsaturated carbonyl compounds. Any *Z*-alkene that is formed is equilibrated to *E* by reversible Michael addition during the reaction.



The double aldol product from acetone and benzaldehyde, known as dibenzylidene acetone (dba), is a constituent of some sun-protection materials and is used in organometallic chemistry as a metal ligand. It is easily made geometrically pure by a simple aldol reaction—again, reversible Michael addition equilibrates any *Z* product to *E*.



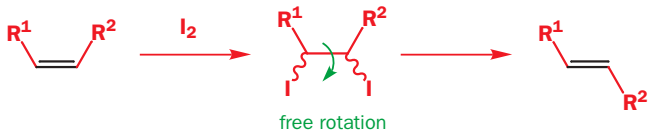
Equilibration of alkenes not conjugated with carbonyl groups requires different reagents

Iodine will add reversibly not only to Michael acceptors but also to most other alkenes. It can therefore be a useful reagent for equilibrating double bond geometrical isomers.

▶ This reaction is, of course, another simple example of the type we have just been discussing: the *Z*-alkene arises from the cyclic starting material.

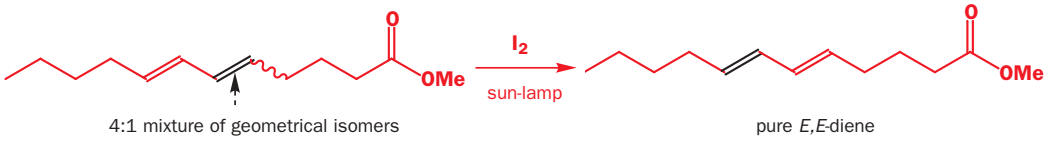
▶ For this reason, it can be very difficult to make *Z*-alkenes conjugated to reactive electrophilic groups such as aldehydes.

▶ The wiggly bonds usually mean that the stereochemistry is unknown or that the compound is a mixture. Here they also mean that it doesn't matter!



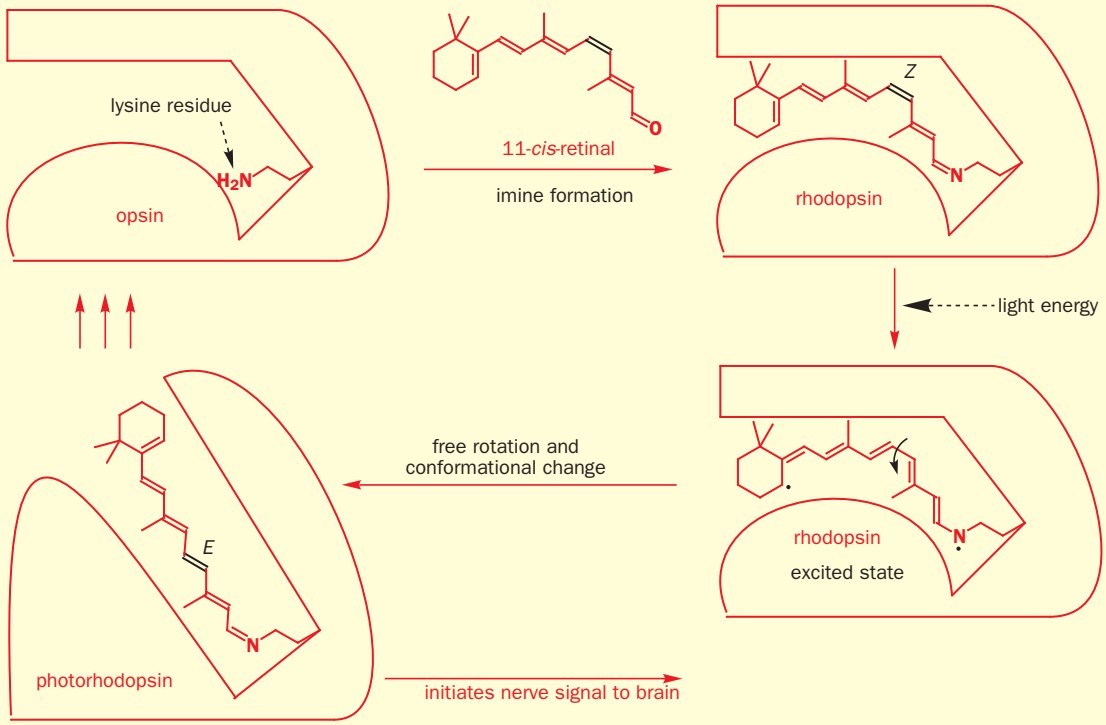
Some Japanese chemists needed the *E,E*-diene below for a synthesis of a neurotoxic compound that they had isolated from poison dart frogs. Unfortunately, their synthesis (which used a Wittig reaction—Chapter 14 and later in this chapter) gave only 4:1 *E* selectivity at one of the double bonds. To produce pure *E,E*-diene, they equilibrated the *E,Z*-diene to *E,E* by treating with iodine and irradiating with a sun-lamp.

▶ The addition–elimination of iodine can follow either an ionic or a radical pathway. The radical pathway is encouraged by irradiation with light—you will see why in Chapter 39. In this case, light is absorbed by the iodine not by the alkene.



The chemistry of vision

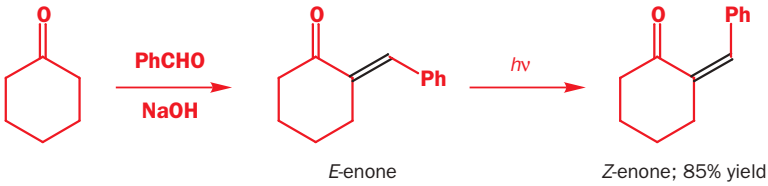
The human eye uses a *cis*-alkene, 11-*cis*-retinal, to detect light, and a *cis–trans* isomerism reaction is at the heart of the chemical mechanism by which we see. The light-sensitive pigment in the cells of the retina is an imine, formed by reaction of 11-*cis*-retinal with a lysine residue of a protein, opsin. Absorption of light by the opsin–retinal compound, known as rhodopsin, promotes one of the electrons in the conjugated polyene system to an antibonding orbital. Free rotation in this excited state allows the *cis* double bond to isomerize to *trans*, and the conformational changes in the protein molecule that result trigger a cascade of reactions that ultimately leads to a nerve signal being sent to the brain.



Using light to make *Z*-alkenes from *E*-alkenes

Light allows the equilibration of the two isomers of an alkene, by promoting a π electron into the π* orbital, but does not necessarily favour either isomer. One difference between *cis*- and *trans*-alkenes is that the *trans*-alkenes often absorb light better than the *cis*-alkenes do. They absorb light of a higher wavelength and they absorb more of it. This is particularly true of alkenes conjugated with carbonyl groups. Steric hindrance often forces the *cis*-alkene to twist about the σ bond joining the

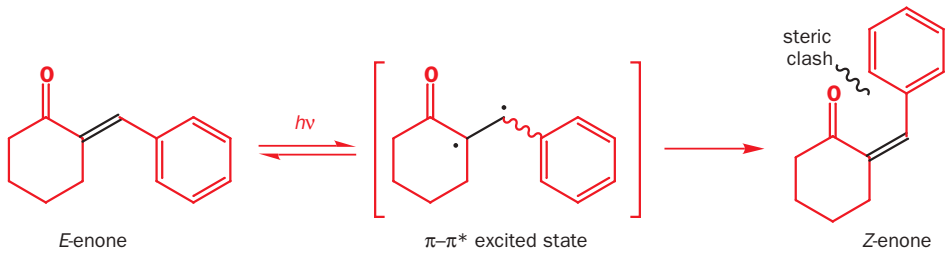
alkene to the carbonyl group and conjugation is then less efficient. A good example is the enone we saw a few pages back. Aldol condensation of cyclohexanone and benzaldehyde gives pure *E*-alkene. Irradiation with longer-wavelength UV light equilibrates this to the *Z*-alkene in excellent yield.



E-enone *Z*-enone; 85% yield

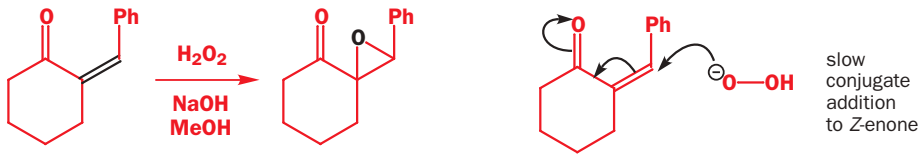
■ Light from a sun-lamp was used in a recent example to equilibrate an alkene with iodine. Iodine is brown and absorbs visible light well. In the present example there is no iodine and UV light is used, which is absorbed by the alkene itself. See Chapter 7 for orbital diagrams.

It is not possible for the benzene ring and the enone system to be planar in the *Z*-enone and so they twist and conjugation is not as good as in the *E*-enone. Longer-wavelength light is absorbed only by the *E*-enone, which is continually equilibrated back to the excited state. Eventually, all the *E*-enone is converted to the *Z*-enone, which is not as efficiently excited by the light.



E-enone π–π* excited state *Z*-enone

This twisting and loss of conjugation is also the cause of the very slow epoxidation of the *Z*-enone discussed above. Conjugate addition is obviously best when there is good conjugation between the alkene and the carbonyl group. The rate-determining step in the epoxidation is conjugate addition.



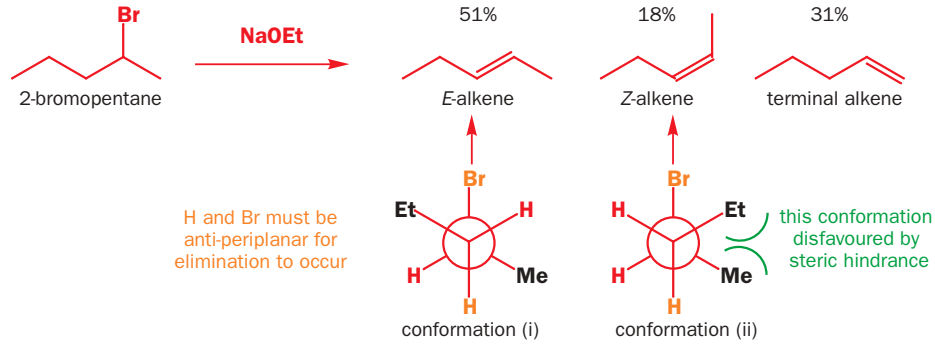
Z-enone

Predominantly *E*-alkenes can be formed by stereoselective elimination reactions

■ These reactions fall into class (3) of the list on p. 000.

In Chapter 19 you saw that E1 elimination reactions usually give mainly *E*-alkenes (there's an example earlier in this chapter) because the transition state leading to an *E* double bond is lower in energy than that leading to a *Z* double bond. In other words, E1 reactions are **stereoselective**, and their stereoselectivity is **kinetically controlled**. E2 reactions are similar if there is a choice of protons that can be removed. Treatment of 2-pentyl bromide with base gives about three times as much *E*-alkene as *Z*-alkene because the transition state leading to the *E*-alkene, which resembles conformation (i) below, is lower in energy than the transition state leading to the *Z*-alkene, resembling conformation (ii). Again, this is kinetic control.

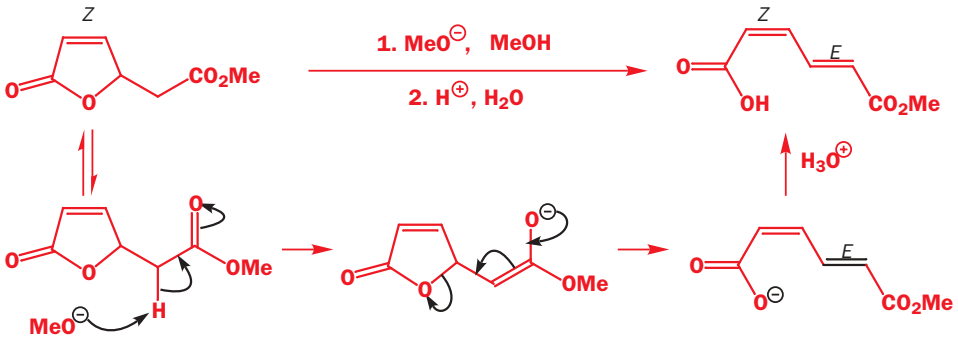
■ If you have forgotten the difference between *stereoselective* and *stereospecific* reactions, or between *kinetic* and *thermodynamic* control, go back and re-read Chapters 13 and 19—these concepts are very important for this chapter.



conformation (i) conformation (ii)

However, in neither this E2 reaction nor the E1 reaction on p. 000 is the stereoselectivity very good, and in this reaction the regioselectivity is bad too. The root of the problem is that one of the groups lost is always H (either as HBr or H_2O in these cases), and in most organic molecules there are lots of Hs to choose from!

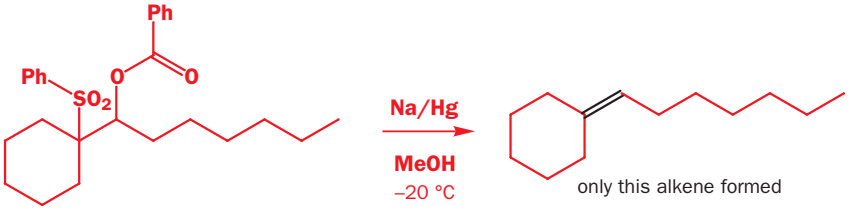
Both stereo- and regioselectivity are better in E1cB reactions, such as the opening of this unsaturated lactone in base. The double bond inside the ring remains *Z* but the new one, formed as the ring opens, prefers the *E* geometry. The transition state for the elimination step already has a product-like shape and prefers this for simple steric reasons.



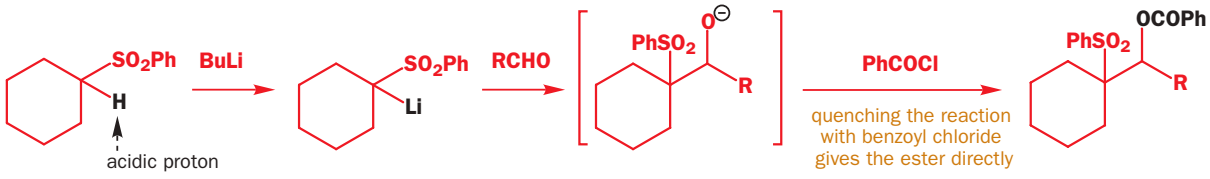
The Julia olefination is regiospecific and connective

This reaction is an elimination—the phenylsulfonyl ($PhSO_2$) and benzoate ($PhCO_2$) groups in the starting material are lost to form the double bond—but it is completely regioselective. Only the alkene shown is formed, with the double bond joining the two carbons that carried the $PhSO_2$ and $PhCO_2$ groups. This elimination is promoted by a reducing agent, usually sodium amalgam (a solution of sodium metal in mercury) and works for a variety of compounds providing they have a phenylsulfonyl group adjacent to a leaving group. It is called the **Julia olefination** after Marc Julia (1922–) who did his PhD at Imperial College, London, with Sir Derek Barton and now works at the École Normale in Paris and is best known for his work on sulfones.

▶ **Olefin** is an alternative name for alkene and **olefination** simply means alkene synthesis, usually by the formation of both σ and π bonds.



The most common leaving groups are carboxylates such as acetate or benzoate, and the starting materials are very easily made. As you will see in Chapter 46, sulfones are easily deprotonated next to the sulfur atom by strong bases like butyllithium or Grignard reagents, and the sulfur-stabilized anion will add to aldehydes. A simple esterification step, which can be done in the same reaction vessel as the addition, introduces the acetate or benzoate group. This is how the starting material for the elimination above was made.

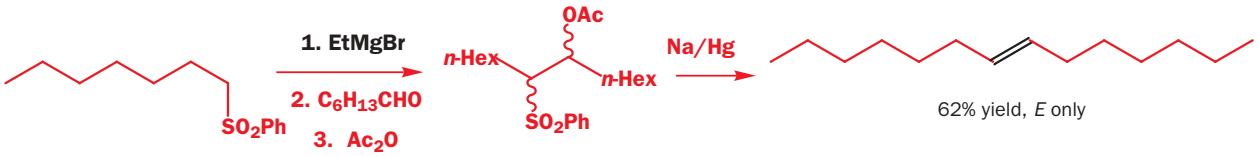


The short sequence of steps (starting with sulfone plus aldehyde and leading through to alkene) is known as the Julia olefination. It is our first example of a **connective double bond synthesis**—in other words, the double bond is formed by joining two separate molecules together (the aldehyde

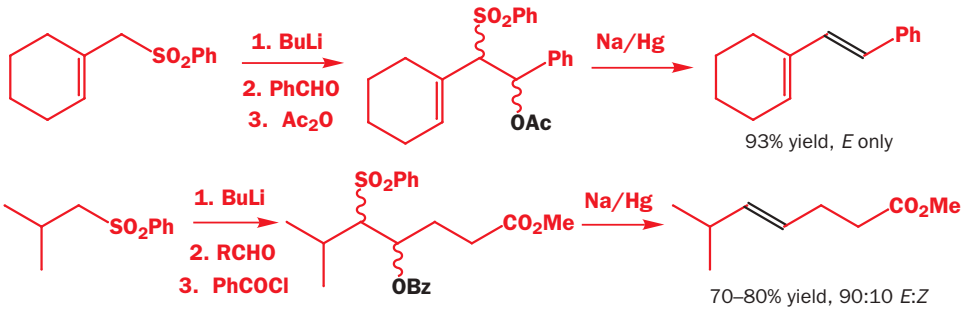
and sulfone). You will be reminded of the most important connective double-bond forming reaction, the Wittig reaction, later in the chapter.

The Julia olefination is stereoselective

Here are the results of a few simple Julia olefinations.

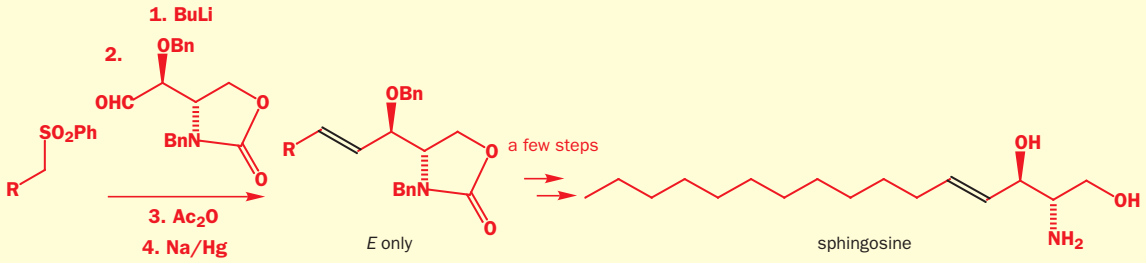


Notice that deprotonations can be with BuLi or EtMgBr and that the acylation step works with acetic anhydride or with benzoyl chloride. As you can see, they are all highly stereoselective for the *E*-isomer, and the Julia olefination is one of the most important ways of making *E* double bonds connectively.



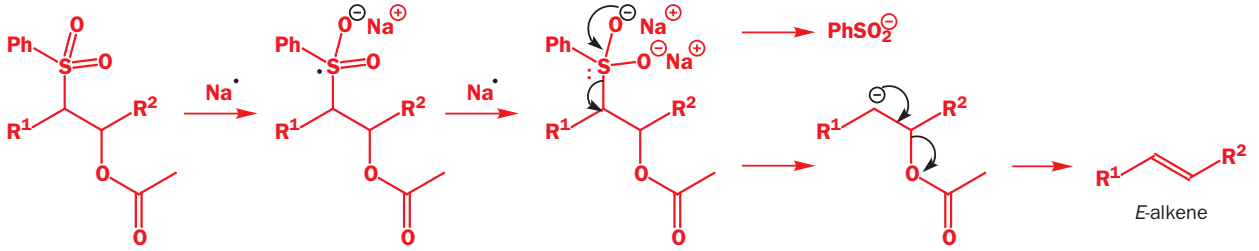
Further example—preparation of sphingosine

In 1987, American chemists were studying the synthesis of some biological molecules using enzymes. One of the compounds they were interested in was sphingosine, an amino-alcohol that forms the backbone of sphingolipids (fat-like molecules found in cell membranes). They wanted to compare the enzyme-produced material with an authentic sample, which they made by using a Julia olefination to introduce the *E* double bond.



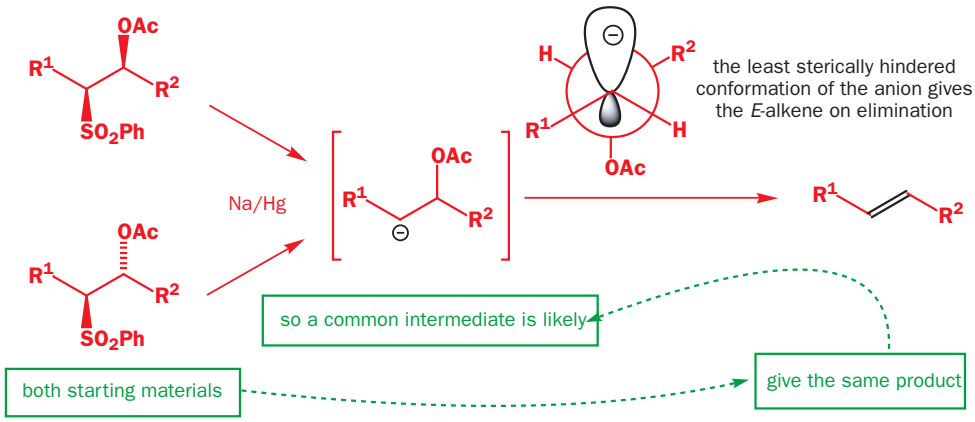
The Julia olefination is stereoselective and not stereospecific

The reason for the *E* selectivity lies in the mechanism of the elimination. The first step is believed to be two successive electron transfers from the reducing agent (sodium metal) to the sulfone. Firstly, a radical anion is formed, with one extra unpaired electron, and then a dianion, with two extra electrons and therefore a double negative charge. The dianion fragments to a transient carbanion that expels acetate or benzoate to give the double bond.



▶ A single-step E2 elimination would have to go via an anti-periplanar transition state and would be stereospecific. You will be able compare this *stereoselective* Julia olefination with the stereospecific Peterson elimination shortly.

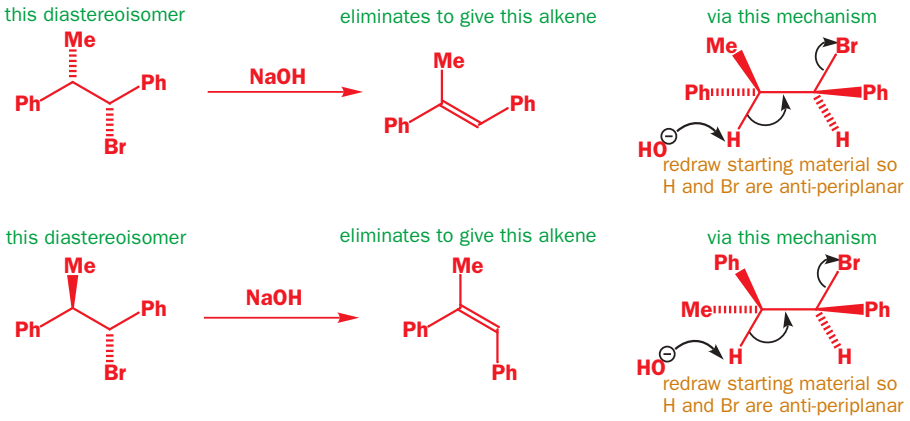
We know that there must be an anion intermediate because the elimination is *not stereospecific*—in other words, it doesn't matter which diastereoisomer of the starting material you use (all of the examples in this section have been mixtures of diastereoisomers) you always get the *E*-alkene product. The intermediate anion must have a long enough lifetime to choose its conformation for elimination.



Stereospecific eliminations can give pure single isomers of alkenes

■ These reactions fall into class (4) of the list on p. 000.

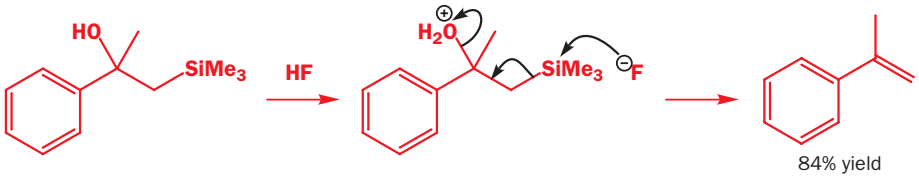
You met a stereospecific elimination in Chapter 19. The requirement for the H and the Br to be anti-periplanar in the E2 transition state meant that the two diastereoisomers of this alkyl bromide eliminated to alkenes with different double bond geometries (p. 000).



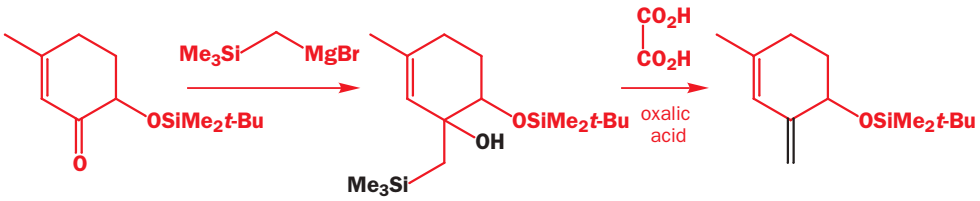
However, reactions like this are of limited use—their success relies on the base's lack of choice of protons to attack: provide an alternative H and we are back with the situation in the reaction on p. 000. Logic dictates, therefore, that only trisubstituted double bonds can be made stereospecifically in this way, because the reaction must not have a choice of hydrogen atoms to participate in the elimination. The answer is, of course, to move away from eliminations involving H, as we did with the Julia olefination. We shall look at this type of reaction for much of the rest of this chapter.

The Peterson reaction is a stereospecific elimination

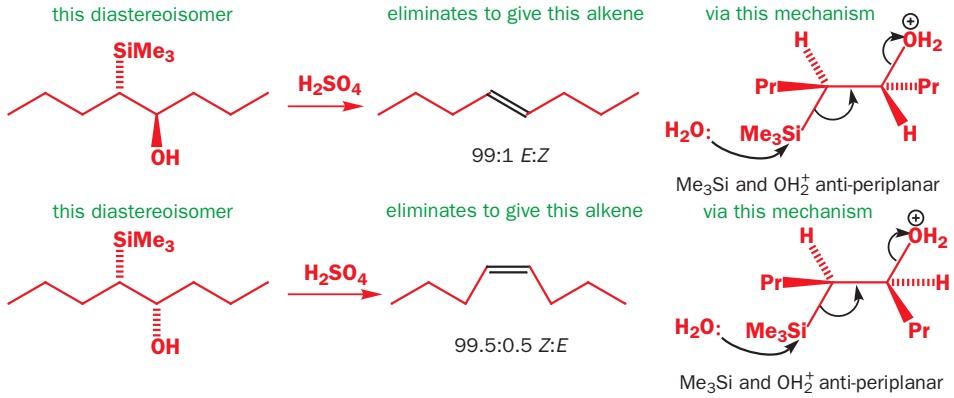
There are many reactions in organic chemistry in which an Me_3Si group acts like a proton—Chapter 47 will detail some more reactions of silicon-containing compounds. Just as acidic protons are removed by bases, silicon is readily removed by hard nucleophiles, particularly F^- or RO^-, and this can promote an elimination. An example is shown here.



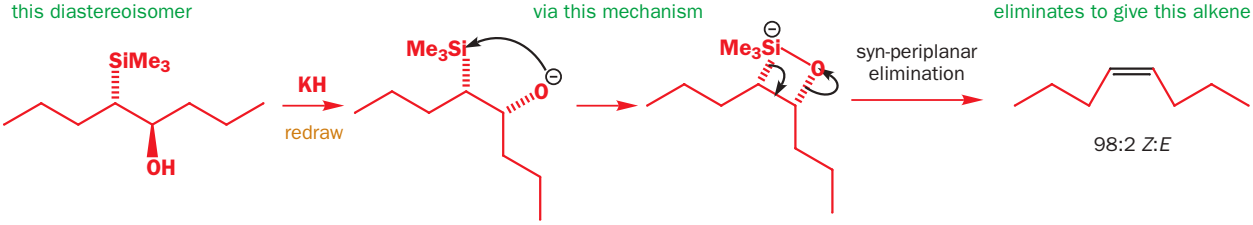
The reaction is known as the **Peterson reaction**. It is rather like those we discussed right at the beginning of this chapter—eliminations of alcohols under acidic conditions to give alkenes. But, unlike those reactions, it is fully regioselective (like the Julia olefination), and so is particularly useful for making double bonds where other elimination methods might give the wrong regioisomer or mixtures of regioisomers. In this next example only one product is formed, in high yield, and it has an exocyclic double bond. Just think what would have happened without the silicon atom (ignore the one attached to the oxygen—that's just a protecting group). This compound is, in fact, an intermediate in a synthetic route to the important anticancer compound Taxol.



You've probably spotted that this is another connective alkene synthesis. The Peterson reaction is particularly useful for making terminal or exocyclic double bonds connectively because the starting material (the magnesium derivative shown above) is easily made from available Me_3SiCH_2Br. The reaction is also stereospecific, because it is an E2 elimination proceeding via an anti-periplanar transition state. In principle, it can therefore be used to make single geometrical isomers of alkenes, the geometry depending on the relative stereochemistry of the starting material. However, this use of the Peterson reaction is limited by difficulties in making diastereoisomerically pure starting materials.



There is another, complementary version of the Peterson reaction that uses base to promote the elimination. The starting materials are the same as for the acid-promoted Peterson reaction. When base (such as sodium hydride or potassium hydride) is added, the hydroxyl group is deprotonated, and the oxyanion attacks the silicon atom *intramolecularly*. Elimination takes place this time via a *syn-periplanar* transition state—it has to because the oxygen and the silicon are now bonded together, and it is the strength of this bond that drives the elimination forward.

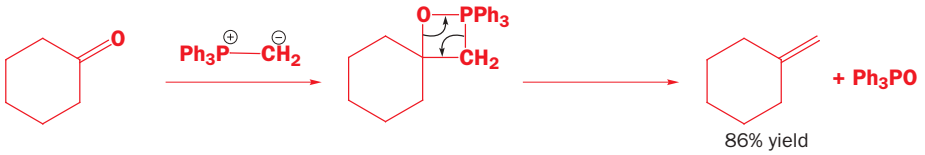


In Chapter 19 you saw that anti-periplanar transition states are usually preferred for elimination reactions because this alignment provides the best opportunity for good overlap between the orbitals involved. *Syn*-periplanar transition states can, however, also lead to elimination—and this particular case should remind you of the Wittig reaction (Chapter 14) with a four-membered cyclic intermediate.

The two versions of the Peterson reaction give opposite geometrical isomers from the same diastereoisomer of the starting material, so from any single diastereomer of hydroxy silane we can make either geometrical isomer of alkene product by choosing whether to use acid or base. The problem is still making those single diastereoisomers!

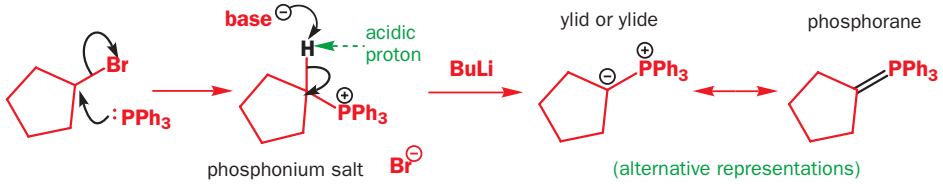
Perhaps the most important way of making alkenes—the Wittig reaction

The Wittig reaction is another member of the class we have been talking about—it's an elimination that does not involve loss of H. You met it in Chapter 14, where we gave a brief outline of its mechanism.

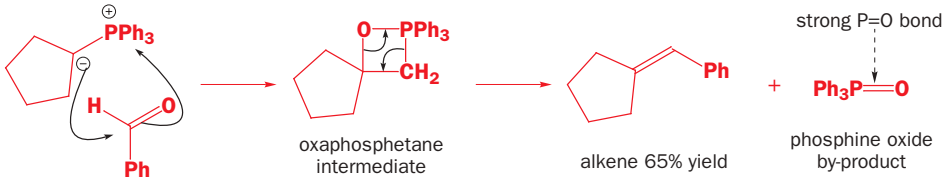


Conceptually, the Wittig reaction is like the base-promoted Peterson reaction: it is a *syn* elimination, driven by the strength of an oxygen–heteroatom bond, but in this case the heteroatom is phosphorus. But, unlike the other eliminations described above, the elimination step of the Wittig reaction occurs only from an intermediate and not from isolated starting materials. This intermediate is made *in situ* in the reaction and decomposes spontaneously: the Wittig reaction is therefore another connective alkene-forming reaction but, unlike either the Julia or Peterson reactions, it goes in one step, and for this reason is much more widely used.

We must start at the beginning. Phosphorus atoms, especially those that are positively charged or that carry electronegative substituents, can increase the acidity of protons adjacent to them on the carbon skeleton. Phosphonium salts (made in a manner analogous to the formation of ammonium salts from amines, in other words, by reaction of an alkyl halide with a phosphine) can therefore be deprotonated by a moderately strong base to give a species known as an **ylid**, carrying (formally) a positive and a negative charge on adjacent atoms. Ylids can alternatively be represented as doubly bonded species, called **phosphoranes**.



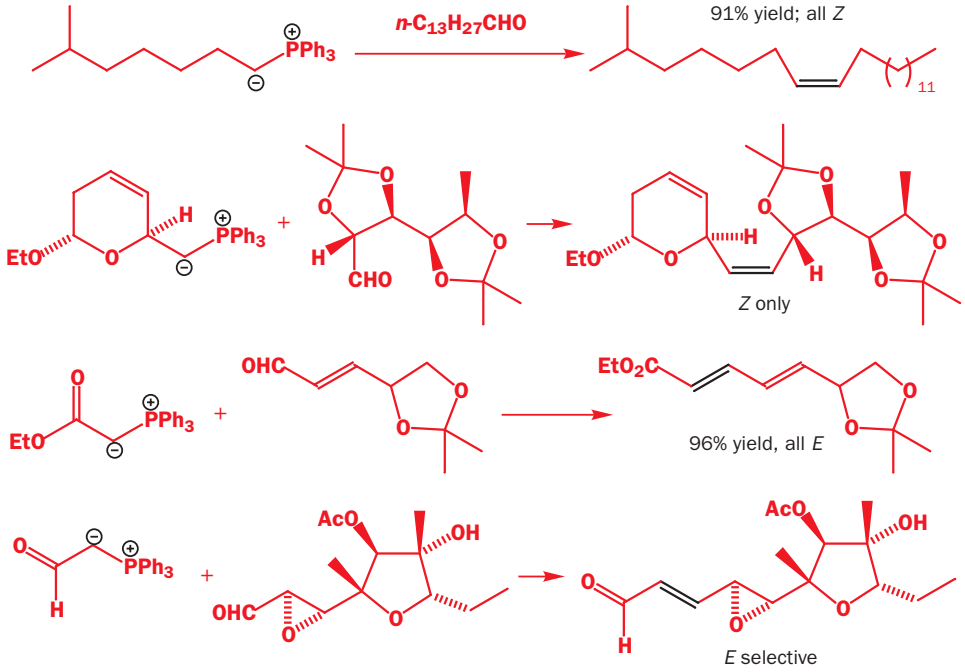
Ylids can be isolated, but are usually used in reactions immediately they are formed. They are nucleophilic species that will attack the carbonyl groups of aldehydes or ketones, generating the four-membered ring oxaphosphetane intermediates. Oxaphosphetanes are unstable: they undergo elimination to give an alkene (65% yield for this particular example) with a phosphine oxide as a by-product. The phosphorus–oxygen double bond is extremely strong and it is this that drives the whole reaction forward.



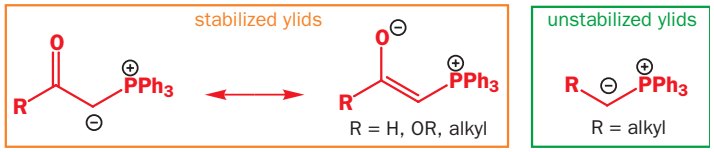
▶ Chemists are still unsure about the exact mechanism of this reaction, and what we have described here is certainly a very simplified picture of what actually happens.

Stereoselectivity in the Wittig reaction depends on the ylid

The Wittig reactions below were all used in the synthesis of natural products. You will notice that some reactions are *Z* selective and some are *E* selective. Look closer, and you see that the stereoselectivity is dependent on the *nature of the substituent* on the carbon atom of the ylid.



We can divide ylids into two types: those with conjugating or anion-stabilizing substituents adjacent to the negative charge (such as carbonyl groups) and those without. We call the first sort **stabilized ylids**, because the negative charge is stabilized not only by the phosphorus atom but by the adjacent functional group—we can draw an alternative enolate-type structure to represent this extra stabilization. The rest we call **unstabilized ylids**.



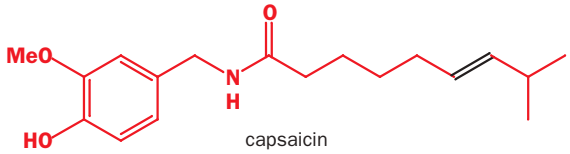
The stereochemistry of the Wittig reaction

The general rule is:

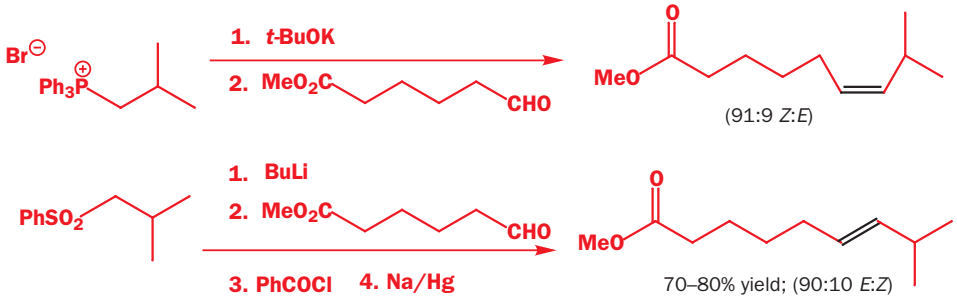
- with *stabilized* ylids the Wittig reaction is *E* selective
- with *unstabilized* ylids the Wittig reaction is *Z* selective

The *Z* selective Wittig reaction

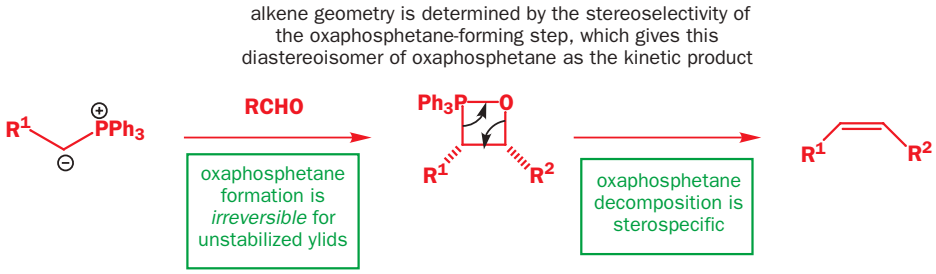
The *Z* selectivity observed with simple alkyl R groups is nicely complementary to the *E* selectivity observed in the Julia olefination. This complementarity was exploited by some chemists who wanted to make isomers of capsaicin (the compound that gives chilli peppers their 'hotness') after suggestions that capsaicin might be carcinogenic.



The key intermediates in the synthesis of the *E*- and the *Z*-isomers of capsaicin were the *E* and *Z* unsaturated esters shown below. By using a Wittig reaction with an unstabilized ylid it was possible to make the *Z*-isomer selectively, whilst the Julia olefination gave the *E*-isomer.

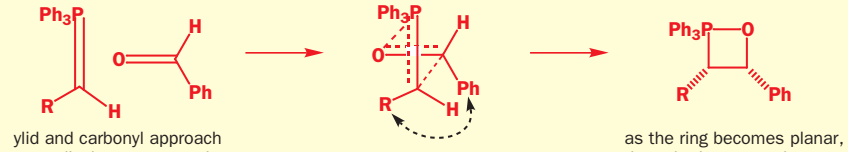


How can the *Z* selectivity in Wittig reactions of unstabilized ylids be explained? We have a more complex situation in this reaction than we had for the other eliminations we considered, because we have two separate processes to consider: formation of the oxaphosphetane and decomposition of the oxaphosphetane to the alkene. The elimination step is the easier one to explain—it is stereospecific, with the oxygen and phosphorus departing in a syn-periplanar transition state (as in the base-catalysed Peterson reaction). Addition of the ylid to the aldehyde can, in principle, produce two diastereomers of the intermediate oxaphosphetane. Provided that this step is irreversible, then the stereospecificity of the elimination step means that the ratio of the final alkene geometrical isomers will reflect the stereoselectivity of this addition step. This is almost certainly the case when R is not conjugating or anion-stabilizing; the *syn* diastereoisomer of the oxaphosphetane is formed preferentially, and the predominantly *Z*-alkene that results reflects this. The *Z* selective Wittig reaction therefore consists of a kinetically controlled stereoselective first step followed by a stereospecific elimination from this intermediate.



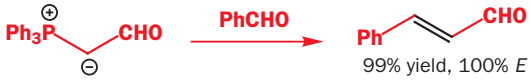
Why is formation of the *syn* oxaphosphetane favoured?

This question is the subject of much debate, because the mechanism by which the oxaphosphetane is formed is not entirely understood. One possible explanation relies on rules of orbital symmetry, which you will meet in Chapters 35 and 36—we need not explain them in detail here but suffice it to say that there is good reason to believe that, if the ylid and carbonyl compound react together to give the oxaphosphetane in one step, they will do so by approaching one another at right angles. Keeping the large substituents apart produces a transition state like that shown below, which (correctly) predicts that the oxaphosphetane will have *syn*



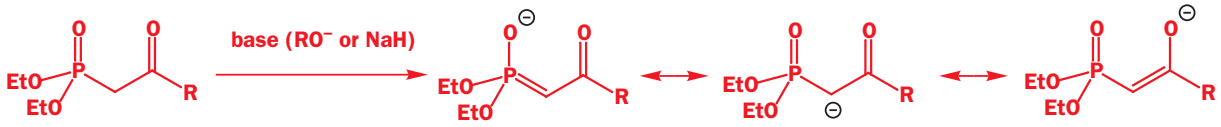
The *E* selective Wittig reaction

Stabilized ylids, that is ylids whose anion is stabilized by further conjugation, usually within a carbonyl group, give *E*-alkenes on reaction with aldehydes. These ylids are also enolates and were discussed in Chapter 27.



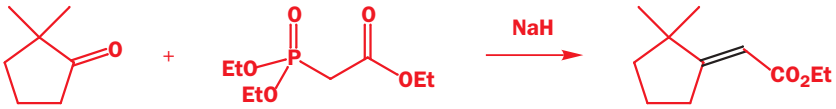
99% yield, 100% *E*

These stabilized ylids really are stable—this one, for example, can be recrystallized from water. This stability means though that they are not very reactive, and often it is better not to use the phosphonium salt but a phosphonate instead.

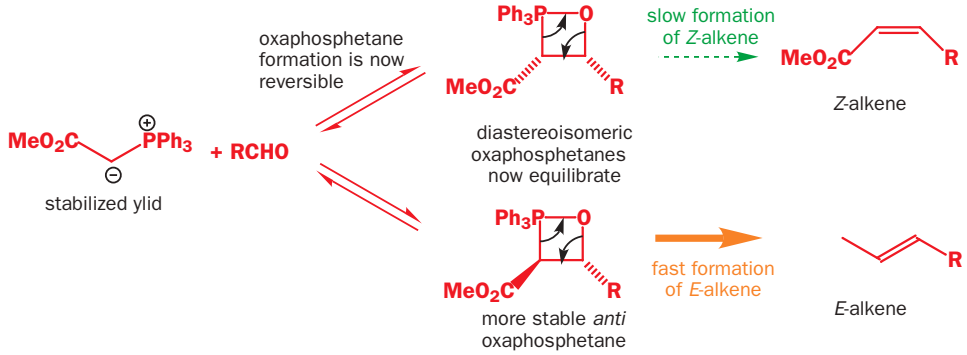


phosphonate ester

Phosphonate esters can be deprotonated with sodium hydride or alkoxide anions to give enolate-type anions that react well with aldehydes or ketones to give *E*-alkenes. Alkene-forming reactions with phosphonates are called **Horner–Wadsworth–Emmons** (or Horner–Emmons, Wadsworth–Emmons, or even Horner–Wittig) **reactions**. This example is a reaction that was used by some Japanese chemists in the synthesis of polyzonimine, a natural insect repellent produced by millipedes.



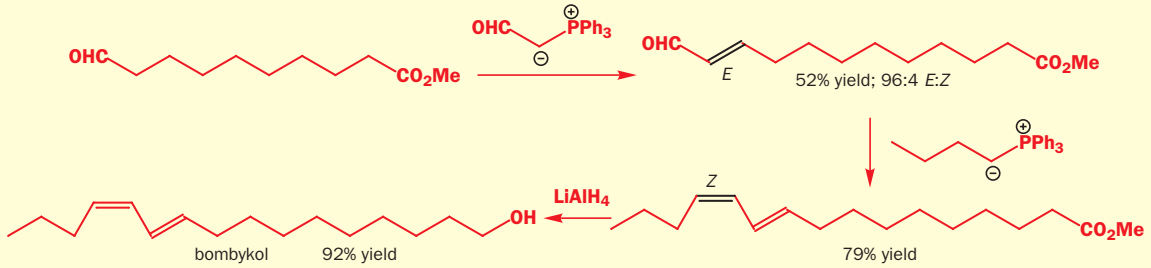
So why the change to *E* stereoselectivity when the ylid is stabilized? Again, chemists disagree about the details but a likely explanation is that the extra stability given to the ylid starting materials makes the reaction leading to the oxaphosphetane reversible. Stereoselectivity in this step is therefore no longer kinetically controlled but is **thermodynamically controlled**: reversal to starting materials provides a mechanism by which the oxaphosphetane diastereoisomers can interconvert. Providing the rate of interconversion is faster than the rate of elimination to alkene, the stereospecific step will no longer reflect the initial kinetic ratio of oxaphosphetane diastereoisomers. It is not unreasonable to suppose that the thermodynamically more stable of the oxaphosphetanes is the *trans*-diastereoisomer, with the two bulky groups on opposite sides of the ring, and that elimination of this gives *E*-alkene. What is more, the rate of elimination to give an *E*-alkene ought to be significantly faster than the rate of elimination to give a *Z*-alkene, simply by virtue of steric crowding in their respective transition states. The *anti* diastereoisomer is therefore 'siphoned off' to give *E*-alkene more rapidly than the *syn* diastereoisomer gives *Z*-alkene. Meanwhile equilibration of the two oxaphosphetane diastereomers via starting material replenishes the supply of *anti* diastereoisomer, and virtually only *E*-alkene is produced.



stabilized ylid

An *E,Z*-diene by two successive Wittig reactions

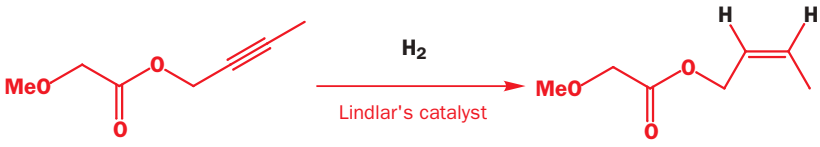
The female silkworm moth attracts mates by producing a pheromone known as bombykol. Bombykol is an *E,Z*-diene, and in this synthesis (dating from 1977) two successive Wittig reactions exploit the stereoselectivity obtained with stabilized and unstabilized ylids, respectively, to control the stereochemistry of the product.



E- and *Z*-alkenes can be made by stereoselective addition to alkynes

In this last section of the chapter we shall leave elimination reactions to look at addition reactions. Alkynes react with some reducing agents stereoselectively to give either the *Z* double bond or the *E* double bond. Some of these reactions were described briefly in Chapter 24.

Z selective reduction of alkynes uses Lindlar's catalyst

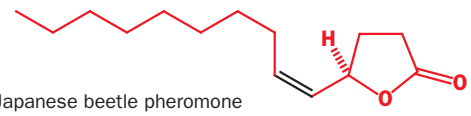


79% yield, all *Z*

This pure *Z*-alkene was needed for studies on the mechanism of a rearrangement reaction. In Chapter 24 you met catalytic hydrogenation as a means of reducing alkenes to alkanes, and we introduced Lindlar's catalyst (palladium and lead acetate on a support of calcium carbonate) as a means of controlling chemoselectivity so that *alkynes* could be reduced to *alkenes*. What we did not emphasize then was that the two hydrogen atoms add to the alkyne in a *syn* fashion and the alkene produced is a *Z*-alkene. The stereoselectivity arises because two hydrogen atoms, bound to the catalyst, are delivered simultaneously to the alkyne.

■ The reason that catalytic hydrogenation often results in *syn addition* of hydrogen to *alkenes* was discussed in Chapter 24.

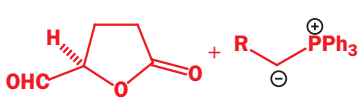
You can compare this method of forming *Z*-alkenes directly with the Wittig reaction in these two syntheses of another insect pheromone, that of the Japanese beetle.



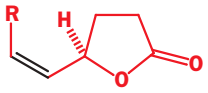
Japanese beetle pheromone

In this case, the Wittig reaction is not entirely *Z*-selective, and it generates some *E*-isomer. Lindlar-catalysed reduction, on the other hand, generates pure *Z*-alkene.

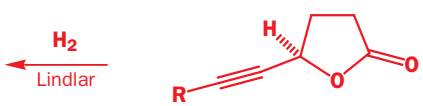
Z double bond by Wittig reaction



+ 10–15% *E* isomer



Z double bond by reduction of alkyne



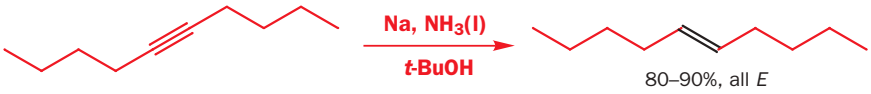
80–90% yield, *Z* isomer only

For a biologically active sample of this pheromone, it is better that the stereochemistry is the same as that of the natural compound—the *E* double bond isomer is more or less inactive. Even more

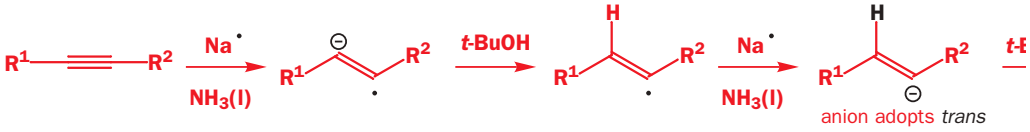
important is the configuration at the chiral centre in the pheromone—the wrong enantiomer is not only inactive, but it also inhibits the male beetles' response to the natural stereoisomer. In Chapter 45 we shall talk about ways of making single enantiomers selectively.

E selective reduction of alkynes uses sodium in liquid ammonia

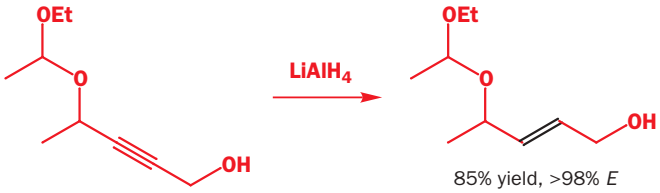
The best way of ensuring *anti* addition of hydrogen across any triple bond is to treat the alkyne with sodium in liquid ammonia.



The sodium donates an electron to the LUMO of the triple bond (one of the two orthogonal π^* orbitals). The resulting radical anion can pick up a proton from the ammonia solution to give a vinyl radical. A second electron, supplied again by the sodium, gives an anion that adopts the more stable *trans* geometry. A final proton quench by a second molecule of ammonia or by an added proton source (*t*-butanol is often used, as in the Birch reduction) forms the *E*-alkene.

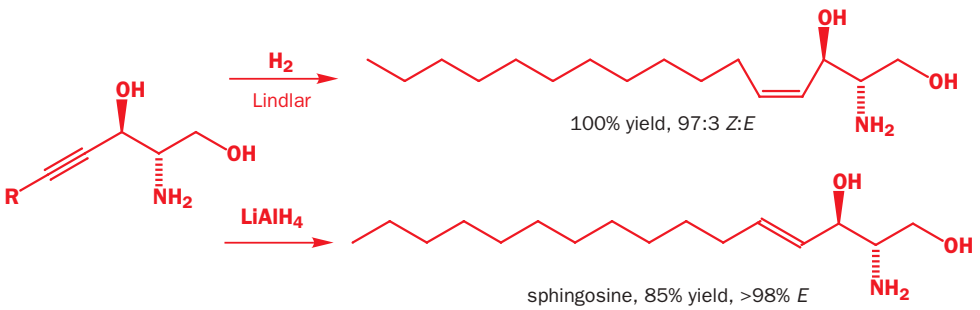


An alternative, and more widely used, method is to reduce alkynes with $LiAlH_4$. This reaction works only if there is a hydroxy or an ether functional group near to the alkyne, because it relies on delivery of the reducing agent to the triple bond through complexation to this oxygen atom.



Making alkenes by addition to alkynes offers two distinct advantages. Firstly, although the reaction is not connective in the sense that the Wittig and Julia reactions are, the starting materials can often be made straightforwardly by alkylation of alkynyl anions. Secondly, the same alkyne can be used to make either *E*- or *Z*-alkene—an advantage shared with the Peterson reaction but here the starting material is much easier to make. In some early work on sphingosine (a constituent of cell membranes), some Swiss chemists needed to make both *E*- and *Z*-isomers of the naturally occurring compound. This was an easy task once they had made the alkyne.

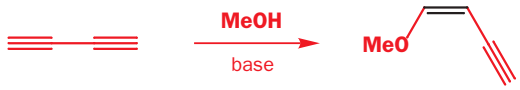
You saw a Julia reaction used to make sphingosine on p. 000.



Addition of nucleophiles to alkynes

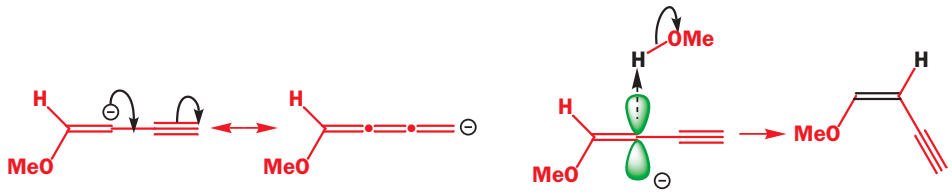
This rarer, and rather surprising, approach to *Z*-alkenes sometimes gives excellent results particularly in the addition of nucleophiles to butadiyne. The base-catalysed addition of methanol gives an

excellent yield of *Z*-1-methoxybut-1-en-3-yne. This reaction is so easy to do that the product is available commercially.



Notice that methanol adds once only: you would not expect nucleophiles to add to a simple alkyne and it is the conjugation that makes addition possible. Methoxide ion adds to one of the alkynes to give a conjugated anion.

The anion is linear with the negative charge delocalized along the conjugated system and the charge is therefore in a p orbital in the plane of the molecule. The other p orbital is involved in π bonding as well but at right angles to the plane of the molecule. When the anion reacts with a molecule of methanol, protonation occurs on the lobe of the p orbital away from the MeO group and the *Z*-alkene is formed. This product is mentioned in other chapters of the book: now you know why it is available.



Summary of methods for making alkenes stereospecifically

Here is a summary of the most important methods for making double bonds stereoselectively.

To make *cis* (*Z*)-alkenes

- **Wittig reaction of *unstabilized* ylid**
- **Constrain the alkene in a ring**
- ***syn* addition of hydrogen across an alkyne**
- **Peterson elimination**

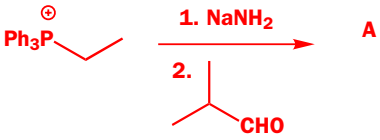
To make *trans* (*E*)-alkenes

- **Wittig reaction of *stabilized* ylid**
- **Equilibration to the more stable isomer**
- **Julia olefination**
- **Simple unselective elimination reactions**
- ***trans* selective reduction of alkyne**
- **Peterson elimination**

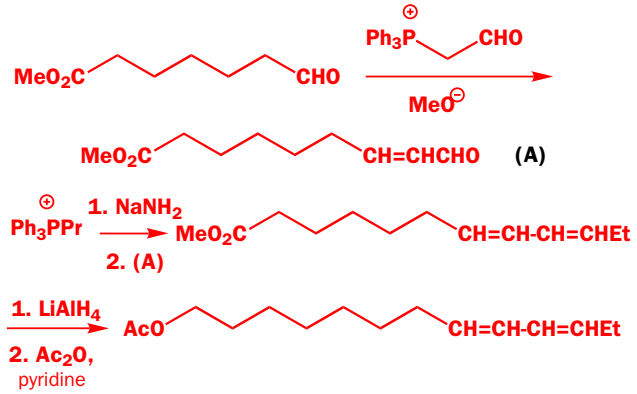
In this chapter we have dealt for the first time with the problem of producing compounds as single stereoisomers—the stereoisomers concerned were geometrical isomers of alkenes. The next two chapters will look in more detail at making stereoisomers, but we shall move out of two dimensions into three and consider reactions that have diastereoselectivity. The two subjects are closely related, since often single diastereoisomers are made by addition reactions of single geometrical isomers of double bonds and, as you saw with the Peterson and Wittig reactions, single diastereoisomers can lead stereospecifically to single geometrical isomers.

Problems

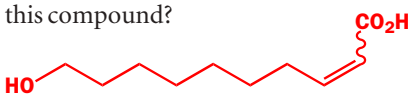
1 Deduce the structure of the product of this reaction from the spectra and explain the stereochemistry. Compound A has δ_H 0.95 p.p.m. (6H, d, *J* 7 Hz), 1.60 p.p.m. (3H, d, *J* 5 Hz), 2.65 p.p.m. (1H, double septuplet, *J* 4 and 7 Hz), 5.10 p.p.m. (1H, dd, *J* 10 and 4 Hz), and 5.35 p.p.m. (1H, dq, *J* 10 and 5 Hz).



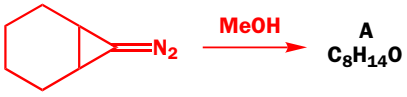
2 A single diastereoisomer of an insect pheromone was prepared in the following way. Which isomer is formed and why? Outline a synthesis of one other isomer.



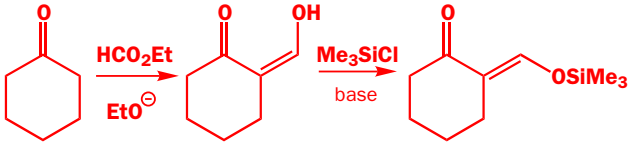
3 How would you prepare samples of both geometrical isomers of this compound?



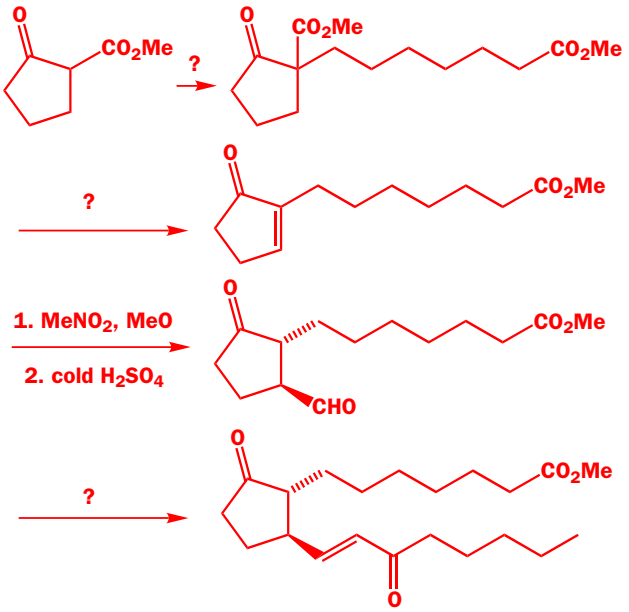
4 Decomposition of this diazocompound in methanol gives an unstable alkene A ($C_8H_{14}O$) whose NMR spectrum contains these signals: δ_H 3.50 p.p.m. (3H, s), 5.50 p.p.m. (1H, dd, *J* 17.9 and 7.9 Hz), 5.80 p.p.m. (1H, ddd, *J* 17.9, 9.2, and 4.3 Hz), 4.20 p.p.m. (1H, m), and 1.3–2.7 p.p.m. (8H, m). What is its structure and geometry? You are not expected to work out a mechanism for the reaction.



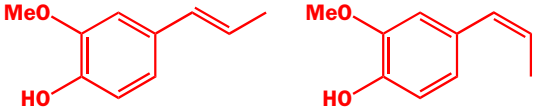
5 Why do these reactions give different alkene geometries?



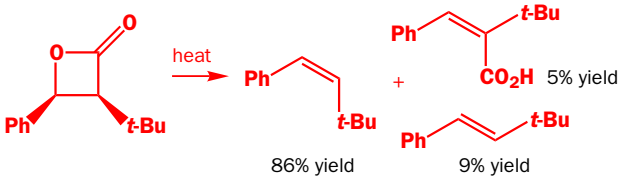
6 Here is a synthesis of a prostaglandin analogue. Suggest reagents for the steps marked '?', give mechanisms for those not so marked, and explain any control of alkene geometry.



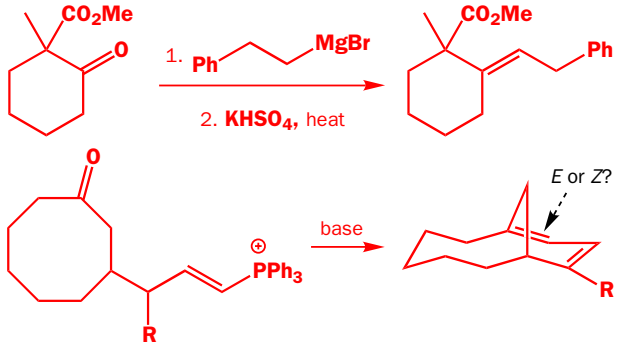
7 Isoeugenol, the flavouring principle of cloves, occurs in the plant in both the *E* (solid) and *Z* (liquid) forms. How would you prepare a pure sample of each and how would you purify each from any of the other isomer?



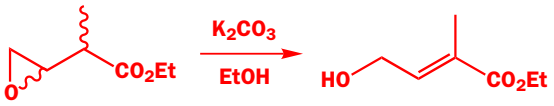
8 Thermal decomposition of this lactone gives mainly the *Z*-alkene shown with minor amounts of the *E*-alkene and an unsaturated acid. Suggest a mechanism for the reaction that explains these results.



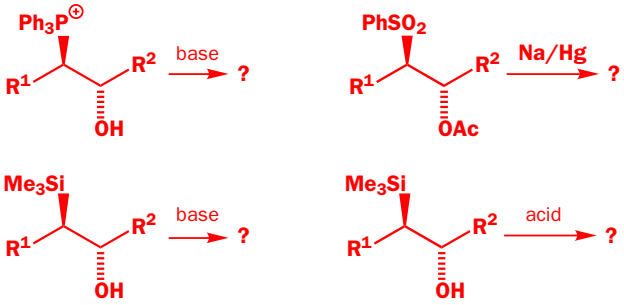
9 What controls the double bond geometry in these examples? In the second example, one alkene is not defined by the drawing.



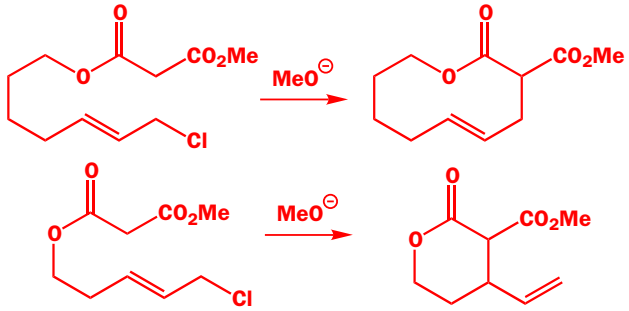
10 Treatment of this epoxide with base gives the same *E*-alkene regardless of the stereochemistry of the epoxide. Comment.



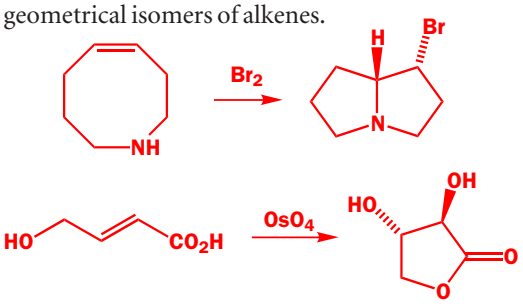
11 Which alkene would be formed in each of the following reactions? Explain your answer mechanistically.



12 Comment on the difference between these two reactions.



13 Give mechanisms for these stereospecific reactions on single geometrical isomers of alkenes.



Determination of stereochemistry by spectroscopic methods

32

Connections

Building on:

- Determining organic structures ch3
- Proton NMR spectroscopy ch11
- Review of spectroscopic methods ch15
- Stereochemistry ch16
- Conformation ch18
- Controlling double bond geometry ch31

Arriving at:

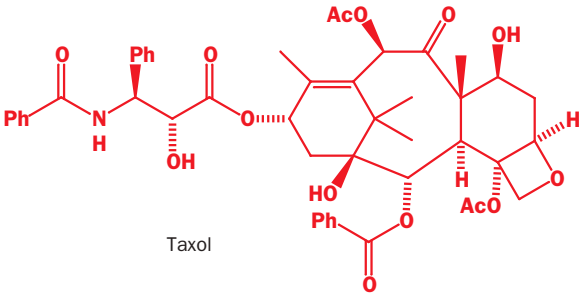
- How coupling varies with the angle between bonds
- How ring size affects coupling
- How electronegative atoms reduce coupling
- How π systems increase geminal coupling
- How protons attached to the same carbon can be different, and can couple to one another
- What homotopic, enantiotopic, and diastereotopic mean
- The nuclear Overhauser effect: what it is and how to exploit it

Looking forward to:

- Controlling stereochemistry with rings ch33
- Diastereoselectivity ch34
- Saturated heterocycles ch42
- Asymmetric synthesis ch45
- Organic synthesis ch 53

Introduction

From time to time throughout the book we have spread before your eyes some wonderful structures. Some have been very large and complicated (such as palytoxin, p. 000) and some small but difficult to believe (such as tetra-*t*-butyl tetrahedrane, p. 000). They all have one thing in common. Their structures were determined by spectroscopic methods and everyone believes them to be true. Among the most important organic molecules today is Taxol, an anticancer compound from yew trees. Though it is a 'modern' compound, in that chemists became interested in it only in the 1990s, its structure was actually determined in 1971.

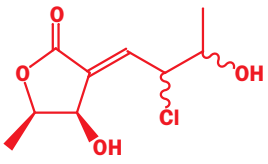


Taxol

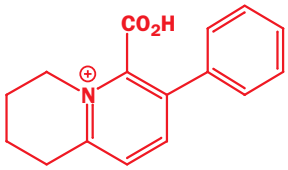
No one argued with this structure because it was determined by reliable spectroscopic methods—NMR plus an X-ray crystal structure of a derivative. This was not always the case. Go back another 25 years to 1946 and chemists argued about structures all the time. An undergraduate and an NMR spectrometer can solve in a few minutes structural problems that challenged teams of chemists for years half a century ago. In this chapter we will combine the knowledge presented systematically in Chapters 3, 11, and 15, add your more recently acquired knowledge of stereochemistry (Chapters 16, 18, and 31), and show you how structures are actually determined in all their stereochemical detail using all the evidence available.

In general, we will not look at structures as complex as Taxol. But it is worth a glance at this stage to see what was needed. The basic carbon skeleton contains one eight- and two six-membered rings. These can be deduced from proton and carbon NMR. There is a four-membered heterocyclic ring—a feature that caused a lot of argument over the structure of penicillin. The four-membered cyclic ether in Taxol is easily deduced from proton NMR as we will see soon. There are ten functional groups (at least—it depends on how you count) including six carbonyl groups. These are easily seen in the carbon NMR and IR spectra. Finally, there is the stereochemistry. There are eleven stereogenic centres, which were deduced mostly from the proton NMR and the X-ray crystal structure of a closely related compound (Taxol itself is not crystalline).

two recently discovered simple natural products



chlorocarolide A



clathryimine A

New structures are being determined all the time. A recent issue of one important journal (*Tetrahedron Letters* No. 14 of 1996) has a paper on Taxol but also reports the discovery and structure determination of the two new natural products in the margin. Both compounds were discovered in ocean sponges, one from Indonesia and one from a fungus living in a sponge common in the Pacific and Indian oceans. Both structures were determined largely by NMR and in neither case was an X-ray structure necessary. You should feel a bit more in tune with the chemists who deduced these structures as they look much simpler than Taxol or even than penicillin. We hope you will feel by the end of this chapter that you can tackle structural problems of this order of complexity with some confidence. You will need practice, and in this area above all it is vital that you try plenty of problems. Use the examples in the text as worked problems: try to solve as much as you can before reading the answer—you can do this only the first time you read because next time you will have your memory as a prompt.

■

It would be wise to review Chapter 18 now if what we said there is not fresh in your mind.

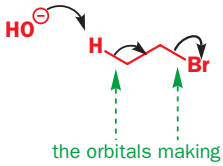
The stereochemistry at two of the stereogenic centres of chlorocarolide was unknown when this structure was published—stereochemistry is one of the hardest aspects of structure to determine. Nonetheless, NMR is second only to X-ray in what it tells us of stereochemistry, and we shall look at what coupling constants (J values) reveal about configuration, conformation, and reactivity. The first aspect we consider is the determination of conformation in six-membered rings.

^3J values vary with H–C–C–H dihedral angle

Remember

Parallel orbitals interact best.

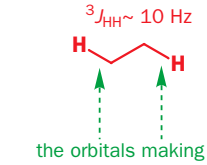
best arrangement for E2 elimination



the orbitals making up these bonds are parallel

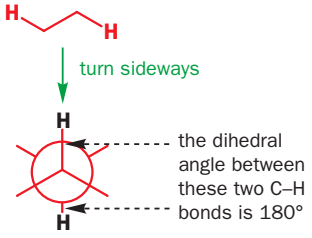
In the last chapter, we looked at some stereospecific eliminations to give double bonds, and you know that E2 elimination reactions occur best when there is an anti-periplanar arrangement between the proton and the leaving group.

largest ^3J from parallel orbitals



the orbitals making up these bonds are parallel

In the NMR spectrum, coupling between protons arises from through-bond and not through-space interactions: *trans* coupling in alkenes is *bigger* than *cis* coupling (see Chapter 11, p. 000). So the same arrangement that leads to the best reaction ought also to lead to the largest coupling constant. In other words, if we replace 'Br' in the diagram with a second hydrogen atom but keep the orbital alignment the same, we ought to get the biggest possible coupling constant for a saturated system.



The usual description of this situation is in terms of the dihedral angle between the H–C–C–H bonds. The dihedral angle is obvious in the Newman projection as it is the angle between the two C–H bonds projected on a plane orthogonal to the C–C bond. In a Newman projection this plane is the plane of the paper, and here the angle is 180°.

When the dihedral angle is zero, the two C–H bonds are again in the same plane but not perfectly parallel. The coupling constant is again large, but not so large as in the previous case. In fact, the two arrangements are very like *cis* and *trans* double bonds, but the C atoms are tetrahedral not trigonal.

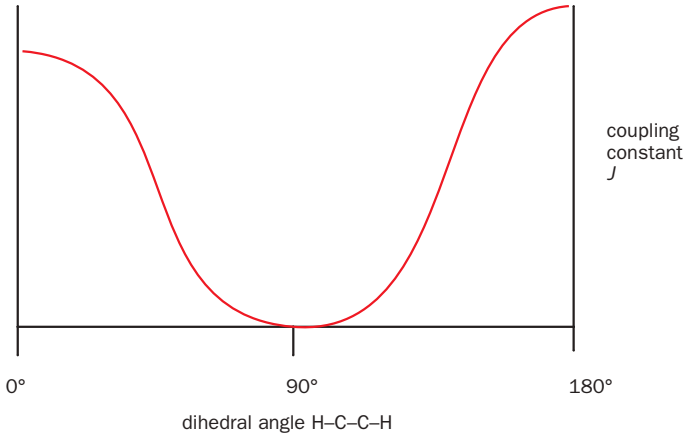
two C-H bonds are eclipsed in the plane of the paper – dihedral angle = 0°

You may guess that, when the dihedral angle is 90°, the coupling constant is zero. What happens in between these extremes was deduced by Karplus in the 1960s and the relationship is usually known as the **Karplus equation**. It is easiest to understand from a graph of J against dihedral angle.

Examine this graph carefully and note the basic features as you will need them as we go through the chapter. These features are:

- Coupling is largest at 180° when the orbitals of the two C–H bonds are perfectly parallel
- Coupling is nearly as large at 0° when the orbitals are in the same plane but not parallel
- Coupling is zero when the dihedral angle is 90°—orthogonal orbitals do not interact
- The curve is flattened around 0°, 90°, and 180°—J varies little in these regions from compound to compound

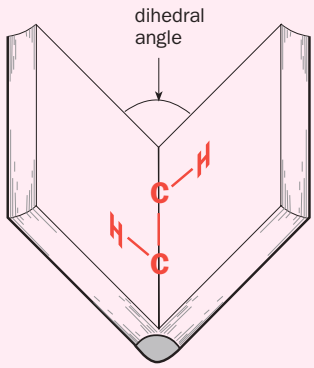
the Karplus relationship: J vs. dihedral angle



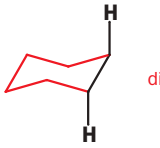
- The curve slopes steeply at about 60° and 120°—J varies a lot in this region with small changes of angle and from compound to compound
- Numerical values of J vary with substitution, ring size, etc., but the Karplus relationship still works—it gives good *relative* values

▶

As a reminder, the dihedral angle is most easily visualized by imagining the C–C bond lying along the spine of a partially-opened book. If the C–H bonds are written one on one page and the other on the other, then the dihedral angle is the angle between the pages of the book.



These ideas come to life in the determination of conformation in six-membered rings. *Trans* diaxial hydrogen atoms are aligned with a dihedral angle of 180° and give the largest J values.



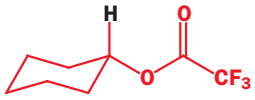
diaxial Hs
dihedral angle 180°
^3J ~ 10–12 Hz

The other two situations, where one or both hydrogen atoms are equatorial, both have angles of about 60°, though axial/equatorial couplings are usually slightly larger than equatorial/equatorial ones.

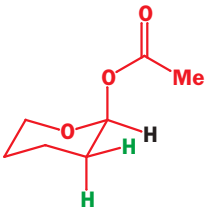
axial/equatorial Hs
dihedral angle 60°
^3J ~ 3–5 Hz

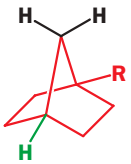
diequatorial Hs
dihedral angle 60°
^3J ~ 2–3 Hz

Now for some illustrations. The simple cyclohexyl ester has just one substituent, which we expect to be equatorial (Chapter 18). The black hydrogen therefore has four neighbours—two axial Hs and two equatorial Hs. We expect to see a triplet from each and that the axial/axial coupling constant will be large. In fact, there is a 1H signal at δ 4.91, it is a tt (triplet of triplets) with J = 8.8 and 3.8 Hz. Only an axial H can have couplings as big as 8.8 Hz, so now we *know* that the ester is equatorial.



By contrast, the next ester, which also has only one substituent, has a 1H signal at δ 6.0 p.p.m. which is a simple triplet with J = 3.2 Hz. With no large couplings this cannot be an axial proton and the *substituent* must now be axial. It so happens that the small equatorial/axial and equatorial/equatorial couplings to the green hydrogens are the same. This is not so surprising as the dihedral angles are both 60°.





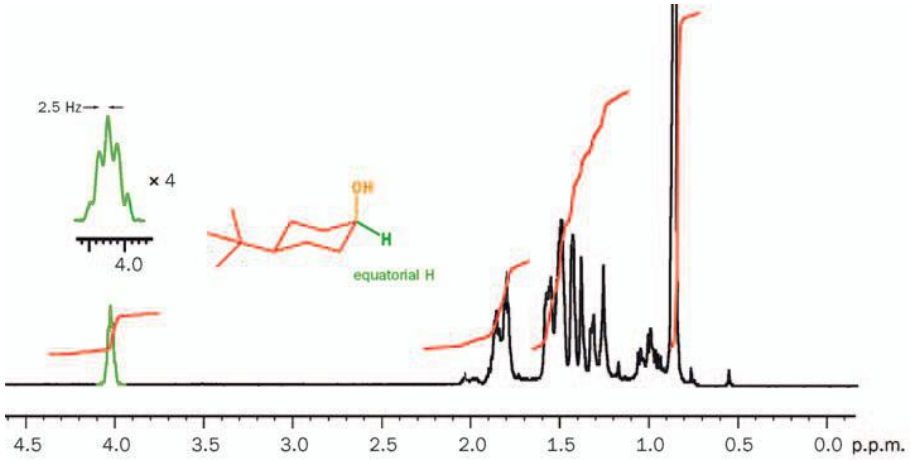
None of the dihedral angles in a six-membered ring are 90°, but in some bicyclic systems they are. Norbornane-type structures (bicyclo[2.2.0]heptanes), for example, typically have couplings of 0 Hz between the protons shown in black and green because the H–C–C–H dihedral angle is 90°.

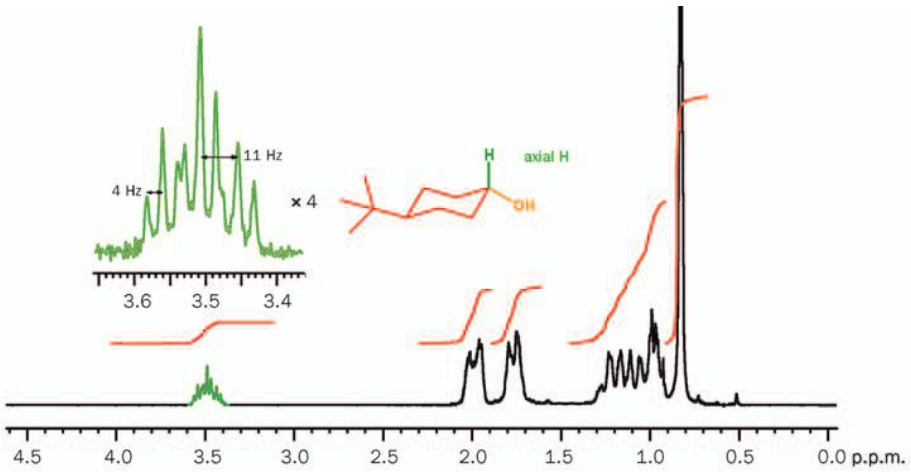
■

We discuss in Chapter 42 why this substituent prefers to be axial.

The determination of *conformation* by NMR may more importantly allow us to

determine *configuration* at the same time. This often occurs when there are two or more substituents on the ring. Here is a simple example: you saw in Chapter 18 that the reduction of 4-*t*-butylcyclohexanone can be controlled by choice of reagent to give either a *cis* or a *trans* alcohol. It is easy to tell them apart as the *t*-butyl group will always be equatorial.

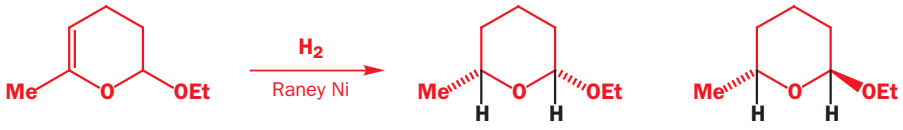




▶ You can draw a general conclusion from this observation: an NMR signal is roughly as wide as the sum of all its couplings. In any given compound, an axial proton will have a much *wider* signal than an equatorial proton.

The NMR spectrum of the green H is quite different in the two cases. Each has two identical axial neighbours and two identical equatorial neighbours (two are shown in black—there are two more at the front). Each green H appears as a triplet of triplets. In the *cis* alcohol both couplings are small (2.72 and 3.00 Hz) but in the *trans* alcohol the axial/axial coupling is much larger (11.1 Hz) than the axial/equatorial (4.3 Hz) coupling.

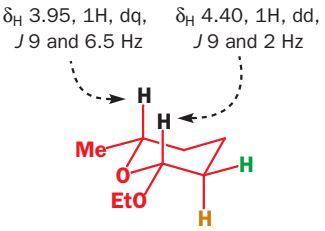
Hydrogenation of the double bond in this unsaturated acetal gives the saturated compound as a single isomer. But which one? Are the two substituents, Me and OEt, *cis* or *trans*?



unsaturated acetal | *cis* saturated acetal | *trans* saturated acetal

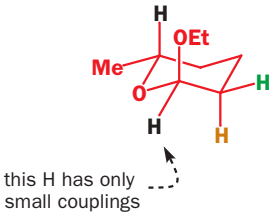
The appearance of the two black hydrogens in the NMR spectrum reveals the answer and also shows what conformation the molecule adopts. There is a 1H signal at 3.95 p.p.m. (which is therefore next to oxygen) and it is a double quartet. It must be the hydrogen next to the methyl group because of the quartet coupling. The quartet coupling constant has the 'normal' J value of 6.5 Hz. The doublet coupling is 9 Hz and this is too large to be anything other than an axial/axial coupling. This hydrogen is axial.

There is another 1H signal at 4.40 p.p.m. (next to *two* oxygens) which is a double doublet with J = 9 and 2 Hz). This must also be an axial proton as it shows an axial/axial (9 Hz) and an axial/equatorial coupling. We now know the conformation of the molecule.

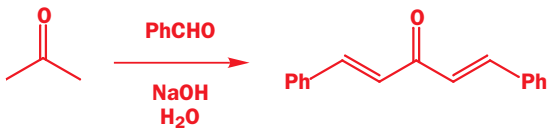


Both black hydrogens are axial so both substituents are equatorial. That also means in this case that they are *cis*. But note that this is because they are both on the same, upper side of the ring, not because they are both equatorial! The hydrogen at the front has two neighbours—an axial (brown) H, J = 9, and an equatorial (green) H, J = 2 Hz. All this fits the Karplus relationship as expected. You may have spotted that the H at the back appears to be missing a small coupling to its equatorial neighbour. No doubt it does couple, but that small coupling is not noticed in the eight lines of the double quartet. Small couplings can easily be overlooked.

When this compound is allowed to stand in slightly acidic ethanol it turns into an isomer. This is the *trans* compound and its NMR spectrum is again very helpful. The proton next to the methyl group is more or less the same but the proton in between the two oxygen atoms is quite different. It is at 5.29 p.p.m. and is an unresolved signal of width about 5 Hz. In other words it has no large couplings and must be an equatorial proton. The conformation of the *trans* compound is shown in the margin.

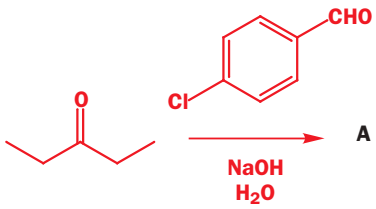


Now for a surprising product, whose structure and stereochemistry can be determined by NMR. Normally, reaction of a symmetrical ketone such as acetone with an aromatic aldehyde and base gives a double aldol condensation product in good yield.



■
You met this reaction in Chapter 28.

But in one particular case, the reaction between pentan-2-one and 4-chlorobenzaldehyde, a different product is formed. The mass spectrum shows that two aldehydes have reacted with one ketone as usual, but that only one molecule of water has been lost. Some of what we know about this compound is shown in the scheme.



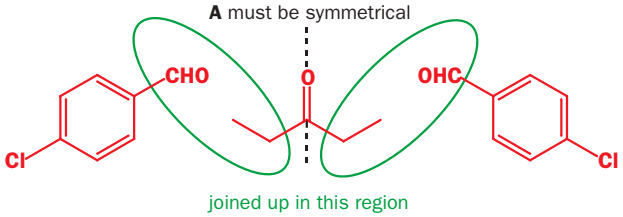
A = $C_{19}H_{18}Cl_2O_2$

m.p. 189–190 °C

IR: 1705, 1600 cm^{-1}

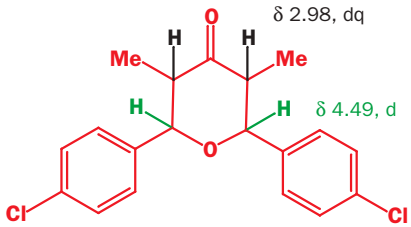
δ_H 7.73 (8H, s)
4.49 (2H, d, J 10.4)
2.98 (2H, dq, J 10.4, 6.6)
1.08 (6H, d, J 6.6)

The ^{13}C NMR spectrum shows that there is one ketone carbonyl group, as expected, but no alkene carbons. There is only one set of ^{13}C signals for the 4-Cl-phenyl ring and only two other carbons. This must mean that the molecule is symmetrical.



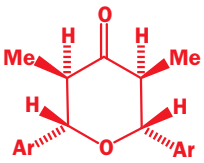
The three molecules must be joined up somewhere in the region marked. But how can we lose only one molecule of water and keep the symmetry?

The proton NMR spectrum gives the answer. Both methyl groups are still there, and they are identical, so we have two identical MeCH fragments. These CH protons (black) are *double* quartets so they have another neigh-

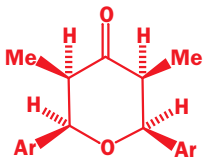


bour, the only remaining aliphatic proton (actually again two identical protons, in green) at δ_H 4.49 p.p.m. These protons must be next to both oxygen and the aromatic ring to have such a large shift. But there is only one spare oxygen atom so the protons at 4.49 p.p.m. must be next to the same oxygen atom—the structure is shown on the previous page.

All that remains is the stereochemistry. There are four stereogenic centres but because of the symmetry only two structures are possible. Both methyl groups must be on the same side and both aryl rings must be on the same side.

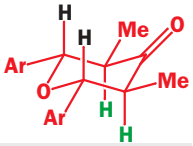


Me and Ar *trans*



Me and Ar *cis*

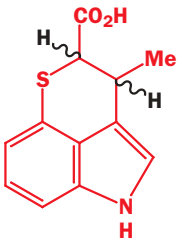
The coupling constant between the hydrogen atoms is 10.4 Hz and so they must both be axial. This means that the molecule has this structure and it is the *trans* compound: all the substituents are equatorial so it is the most stable structure possible.



■

We looked at the conformations of cyclohexenes and cyclohexene oxides in Chapter 18, and we will look again at the stereochemistry of reactions of six-membered rings containing double bonds in Chapter 33.

Only fully saturated six-membered rings are really chairs or boats. Even with one double bond in the ring, the ring is partly flattened: here we will look at an even flatter example. A unique antibiotic has been discovered in China and called 'chuangxinmycin' (meaning 'a new kind of mycin' where mycin = antibiotic). It is unique because it is a sulfur-containing indole: few natural products and no other antibiotics have this sort of structure.

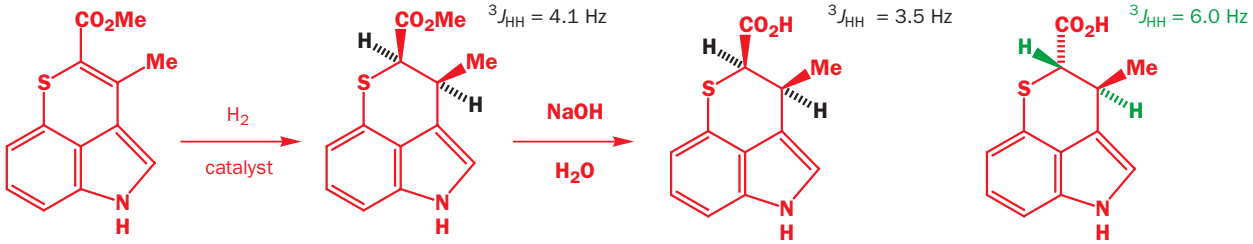


chuangxinmycin

The structure itself was easy to elucidate, but the stereochemistry of the two black hydrogens was not so obvious. The coupling constant (^3J) was 3.5 Hz. During attempts to synthesize the compound, Kozikowski hydrogenated the alkene ester below to give an undoubted *cis* product.

▶

Hydrogenation is *cis*-selective: see Chapter 24.



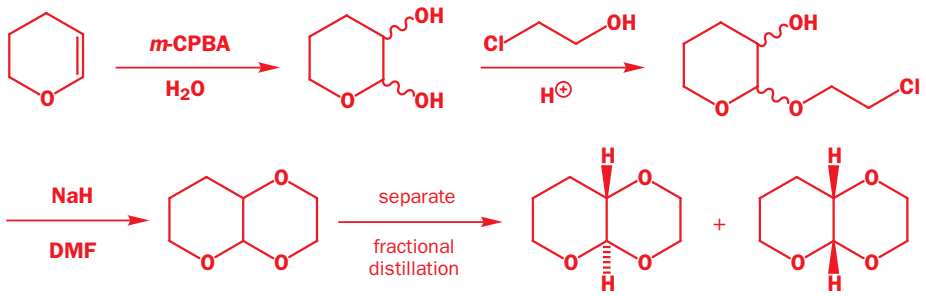
chuangxinmycin

minor by-product: *trans* stereoisomer

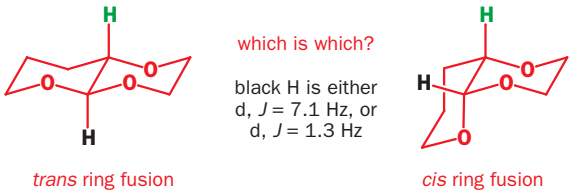
The ^3J coupling between the black hydrogens in this compound was 4.1 Hz, much the same as in the antibiotic and, when the ester group was hydrolysed in aqueous base, the main product was identical to natural chuangxinmycin. However, there was a minor product, which was the *trans* isomer. It had ^3J = 6.0 Hz. Note how much smaller this value is than the axial/axial couplings of 10 Hz or more in saturated six-membered rings. The flattening of the ring reduces the dihedral angle, reducing the size of *J*.

Stereochemistry of fused rings

Where rings are fused together (that is, have a common bond) determination of conformation may allow the determination of ring junction stereochemistry as well. Both isomers of this bicyclic ether were formed as a mixture and then separated.

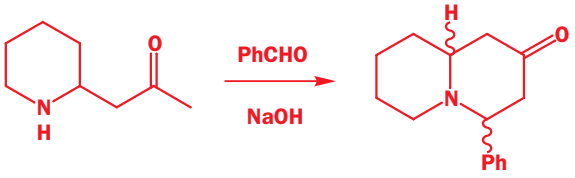


One proton at the ring junctions appears clearly in the NMR spectrum as it is next to two oxygen atoms (shown in black on the conformational diagrams alongside). In one compound it is a doublet, J = 7.1 Hz, and in the other a doublet J = 1.3 Hz. Which is which?



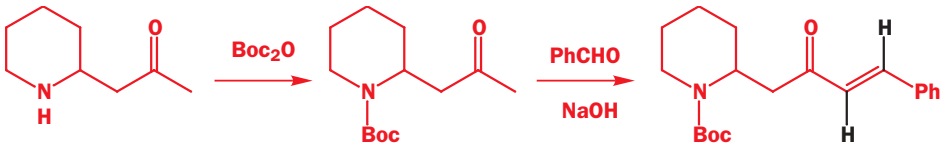
The coupling is to the green proton in each case and the dihedral angles are 180° for the *trans* compound but only 60° for the *cis* one, so the smaller coupling belongs to the *cis* compound. We shall discuss below why the *absolute* values are so low: this example illustrates how much easier stereochemical determination is if you have both stereoisomers to compare.

In the next example, unlike the last one, it eventually proved possible to make both compounds in high yield. But first the story: reaction of an amino-ketone with benzaldehyde in base gave a mixture of diastereoisomers of the product.

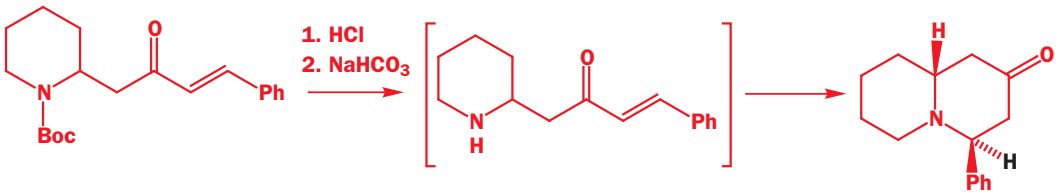


In unravelling the mechanism of the reaction, chemists protected the nitrogen atom with Boc (Chapter 25) before the reaction with benzaldehyde and found that a new product was formed that was clearly an *E*-alkene as its NMR spectrum contained δ_H 6.73 (1H, d, J 16). This is too large a coupling constant even for axial/axial protons and can be only *trans* coupling across a double bond. They quickly deduced that a simple aldol reaction had happened.

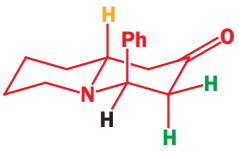
■ Couplings around double bonds were discussed in Chapter 11, p. 000.



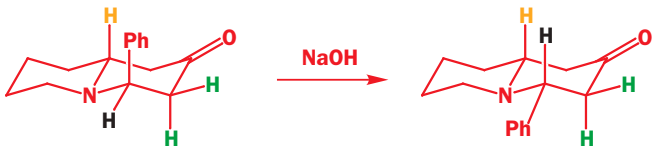
When the Boc protecting group was removed, the cyclization reaction occurred under very mild conditions but now a *single* diastereoisomer of the product was formed.



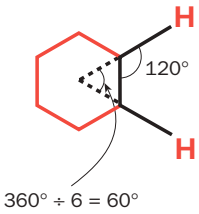
This isomer had one proton that could be clearly seen at δ_H 4.27 p.p.m.—well away from all the rest. This is the proton marked in black between nitrogen and the phenyl group. It was a double doublet with J = 6 and 4 Hz. Neither of these is large enough to be an axial/axial coupling but 6 Hz is within the range for axial/equatorial and 4 Hz for equatorial/equatorial coupling. The compound must have the conformation shown in the margin.



Treatment of this product with stronger base (NaOH) isomerized it to a compound in which the same proton, now at δ_H 3.27 p.p.m., was again a double doublet but with J = 10 and 5 Hz. It is now an axial proton so the new conformation is this.

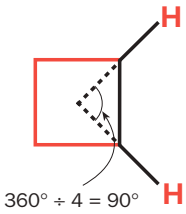


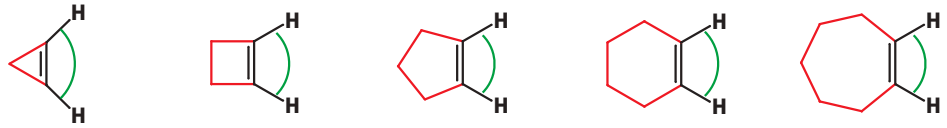
Notice that we have confidently assigned the configuration of these compounds without ever being able to 'see' the yellow proton at the ring junction. Since nitrogen can invert rapidly, we know that this decalin-like structure will adopt the more stable *trans* arrangement at the ring junction.



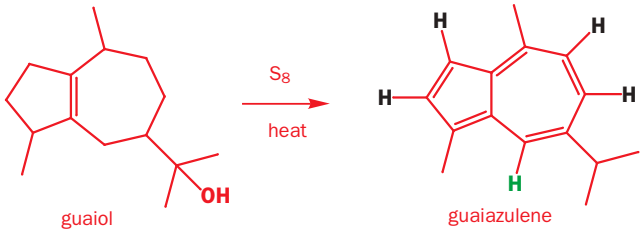
The dihedral angle is not the only angle worth measuring

We should also consider how the two C–H bonds are spread out in space. The dihedral angle is what we see when we look down the spine of the book in our earlier analogy (p. 000)—now we want to look at the pages in the normal way, at right angles to the spine, as if we were going to read the book. We can show what we mean by fixing the dihedral angle at 0° (the C–H bonds are in the same place) and looking at the variation of *J* with the ring size of cyclic alkenes.

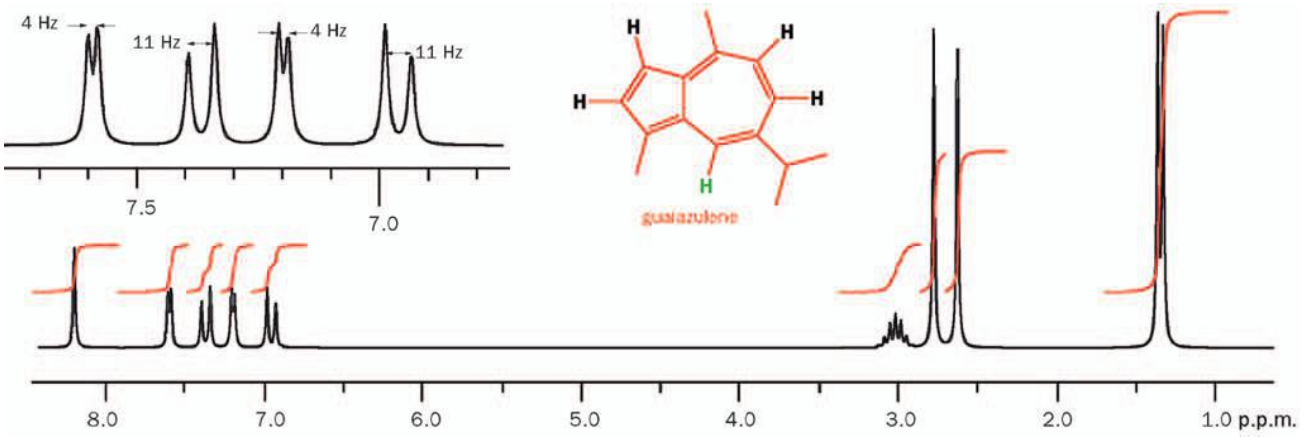




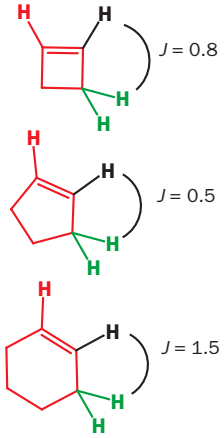
The wider apart the hydrogens are spread, the smaller the coupling constant. Remember, the dihedral angle stays the same (0°)—we are just varying the angle in the plane. A dramatic illustration of this comes with the product of dehydrogenation of the natural product guaiol with elemental sulfur. From the brown, smelly reaction mixture, guaiazulene, a deep blue oil, can be distilled.



δH 8.2 (1H, s),
7.6 (1H, d, *J* 4.0),
7.37 (1H, d, *J* 11.0),
7.2 (1H, d, *J* 4.0),
6.96 (1H, d, *J* 11.0),
3.02 (1H, septuplet, *J* 6.9),
2.78 (3H, s), 2.63 (3H, s),
and 1.35 (6H, d, *J* 6.9).



■ These would be the angles if the structures were regular, planar polyhedrals



Some assignments are clear. The 6H doublet and the 1H septuplet are the isopropyl group and the two 3H singlets belong to the two methyl groups—we can't really say which belongs to which. The 1H singlet must be the green hydrogen as it has no neighbours and that leaves us with two coupled pairs of protons. One pair has $J = 4$ Hz and the other $J = 11$ Hz. We expect to find larger coupling where the H–C–C–H angle is smaller, so we can say that the 4 Hz coupling is between the pair on the five-membered ring and the 11 Hz coupling is between the pair on the seven-membered ring.

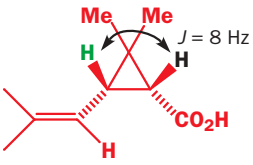
When protons on a double bond in a ring have neighbours on saturated carbon, the coupling constants are all small and for the same reason—the angles in the plane of the ring are approaching 90° even though the dihedral angles are 45–60° in these examples. A bizarre result of this is that the ^3J coupling between the red and black hydrogens is often about the same as the allylic (^4J) coupling between the red and the green hydrogens. An example follows in a moment.

Vicinal (^3J) coupling constants in other ring sizes

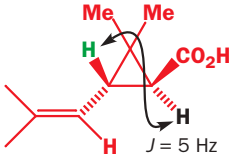
The 'spreading out' effect also affects vicinal (^3J) couplings in simple saturated rings. No other ring size has so well defined a conformation as that of the six-membered ring. We can still note useful trends as we move from 6 to 5 to 4 to 3. Briefly, in five-membered rings, *cis* and *trans* couplings are about the same. In four- and three-membered rings, *cis* couplings are larger than *trans*. But in all cases the absolute values of *J* go down as the ring gets smaller and the C–H bonds are 'spread out' more. Indeed, you can say that *all* coupling constants are smaller in small rings, as we shall see. We need to examine these cases a bit more.

Three-membered rings

Three-membered rings are flat with all bonds eclipsed so the dihedral angle is 0° for *cis* Hs and 109° for *trans* Hs. Looking at the Karplus curve, we expect the *cis* coupling to be larger, and it is. A good example is chrysanthemic acid, which is part of the pyrethrin group of insecticides found in the pyrethrum plant. Both *cis* and *trans* chrysanthemic acids are important.



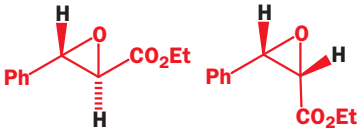
cis chrysanthemic acid



trans chrysanthemic acid

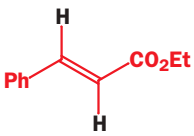
In both isomers the coupling between the green proton on the ring and its red neighbour on the double bond is 8 Hz. In the *cis* compound, the green proton is a triplet so the *cis* coupling in the ring is also 8 Hz. In the *trans* compound it is a double doublet with the second coupling, *trans* across the ring to the black H, of 5 Hz.

The most important three-membered rings are the epoxides. You saw in Chapter 11 (p. 000) that electronegative atoms reduce coupling constants by withdrawing electron density from the bonds that transmit the coupling 'information'. This means that epoxide couplings are very small—much smaller than those of their closely related alkenes, for example. Compare the four coupling constants in the diagram: for the epoxide, all couplings are small, but *cis* coupling is larger than *trans* coupling. In alkenes, *trans* coupling is larger (Chapter 11, p. 000). The table summarizes the coupling constants for alkenes, epoxides, and cyclopropanes.

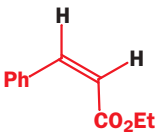


J 2.0 Hz

J 5.0 Hz



J 16 Hz



J 11 Hz

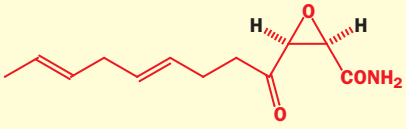
Coupling constants *J*, Hz

Stereochemistry	Alkene	Cyclopropane	Epoxide
cis	10–12	8	5
trans	14–18	5	2

▶ The epoxides have much smaller coupling constants because: (1) the C–C bond is longer; (2) there is an electronegative element; and (3) the 'spreading out' effect of the small ring comes into play.

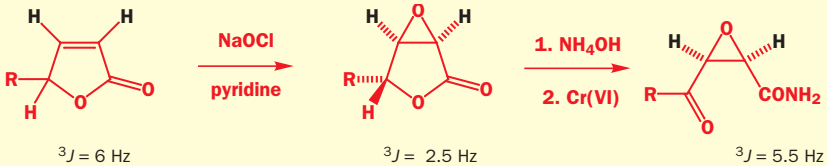
Cerulenin

The natural product cerulenin is an antibiotic containing a *cis* epoxide. The coupling constant between the black hydrogens is 5.5 Hz.



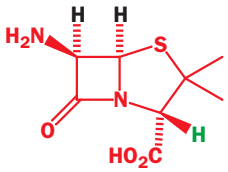
cerulenin

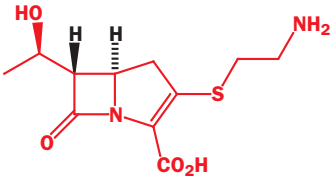
The compound has been made from an unsaturated lactone by epoxidation and ring opening. Follow what happens to the coupling constant between the black hydrogens as this sequence develops.



^3J = 6 Hz ^3J = 2.5 Hz ^3J = 5.5 Hz

The *cis* coupling in the alkene is small because it is in a five-membered ring. It gets smaller in the bicyclic epoxide because the black Hs are now in both five- and three-membered rings and both are next to oxygen, but it gets larger in cerulenin itself because the five-membered ring has been opened.





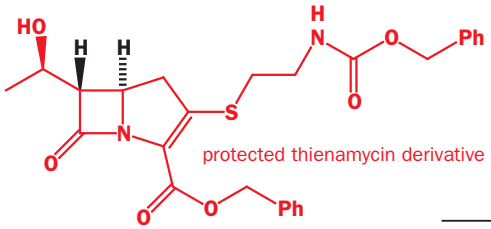
thienamycin

Four-membered rings

A similar situation exists with four-membered rings—the *cis* coupling is larger than the *trans* but they are generally both smaller than those in larger rings. A good example is the amino acid in the margin, the skeleton of the penicillins. The NMR spectrum contains three 1H signals in the middle regions. There is a singlet at δ_H 4.15 p.p.m. that clearly belongs to the isolated green proton and two doublets at δ_H 4.55 and 5.40 p.p.m. that must belong to the black protons. The coupling constant between them is 5 Hz and they are *cis*-related.

There are now large numbers of β-lactam antibiotics known and one family has the opposite (*trans*) stereochemistry around the four-membered ring. The typical member is thienamycin. We will analyse the spectrum in a moment, but first look at the differences—apart from stereochemistry—between this structure and the last. The sulfur atom is now outside the five-membered ring, the acid group is on a double bond in the same ring, and the amino group has gone from the β-lactam to be replaced by a hydroxyalkyl side chain.

Turning to the spectrum and the key question of stereochemistry, this is what the Merck discoverers said in their original article: '^{1}H NMR spectra of thienamycin (and derivatives) . . . show small vicinal coupling constants $J \leq 3$ Hz for the two β-lactam hydrogens. Past experience with penicillins . . . shows the *cis* relationship of the β-lactam hydrogens to be always associated with the larger coupling.' As we have just seen penicillins have $J \sim 5$ Hz for these hydrogens.



protected thienamycin derivative

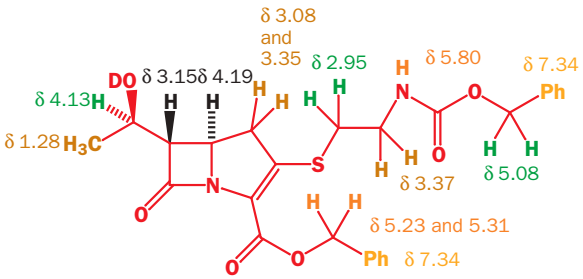
The NMR spectrum of a thienamycin derivative with protecting groups on the amine and carboxylic acids is shown below. Try your hand at interpreting it before you read the explanation below. Your aim is to find the coupling constant across the four-membered ring.

NMR spectrum of thienamycin derivative in CD_3OD

Shift (δ_H), p.p.m.	Integration	Multiplicity	Coupling constants (J), Hz
1.28	3H	d	6.5
2.95	2H	m	not resolved
3.08	1H	dd	9, 18
3.15	1H	dd	2.5, 7
3.35	1H	dd	9, 18
3.37	2H	m	not resolved
4.13	1H	dq	7, 6.5
4.19	1H	dt	2.5, 9
5.08	2H	s	—
5.23 and 5.31	2H	AB system[a]	12.5
5.80	1H	broad	—
7.34	10 H	m	not resolved

[a] See p. 000 for discussion of AB systems.

The simple answer is 2.5 Hz. The signals at 3.15 and 4.19 p.p.m. are the protons on the β-lactam ring and the 9 Hz extra coupling is to the CH_2 in the five-membered ring. If you went into this spectrum in detail you may have been worried about the 12.5 and especially the 18 Hz couplings. These are ^2J (geminal) couplings and we will discuss them in the next section.



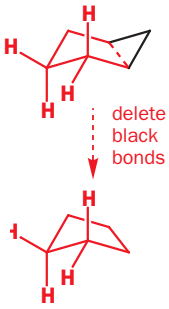
assignment of protons

The full assignment is shown above.

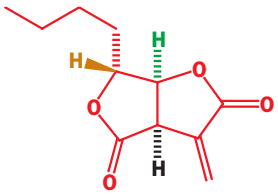
We should emphasize that a coupling constant of 5 or 2.5 Hz in isolation would not allow us to assign stereochemistry across the four-membered ring but, when we have both, we can say with confidence that the larger coupling is between *cis* Hs and the smaller coupling between *trans* Hs.

Five-membered rings

You can visualize this conformation of a five-membered ring simply as a chair cyclohexane with one of the atoms deleted. But this picture is simplistic because the five-membered ring flexes (rather than flips) and any of the carbon atoms can be the one out of the plane. All the hydrogen atoms are changing positions rapidly and the NMR spectrum 'sees' a time-averaged result. Commonly, both *cis* and *trans* couplings are about 8–9 Hz in this ring size.



The best illustration of the similarity of *cis* and *trans* couplings in five-membered rings is a structure that was incorrectly deduced for that very reason. Canadensolide is an antifungal compound found in a *Penicillium* mould. The gross structure was quite easy to deduce from the mass spectrum, which gave the formula $C_{11}H_{14}O_4$ by exact mass determination; the infrared, which showed (at 1780 and 1667 cm^{-1}) a conjugated 5-ring lactone; and some aspects of the proton NMR. The proposed structure is shown alongside.

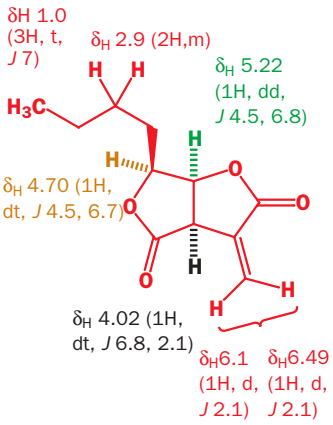


proposed structure for canadensolide

The stereochemistry of the ring junction Hs (shown in black and green) is not in question. They are certain to be *cis* as it is virtually impossible for two five-membered rings to be fused *trans*. The stereochemistry in question involves the third stereogenic centre on the left-hand ring. The coupling constant between the black and green Hs is 6.8 Hz, while that between the green and brown Hs is 4.5. Is this different enough for them to be *trans*? The original investigators decided that it was.

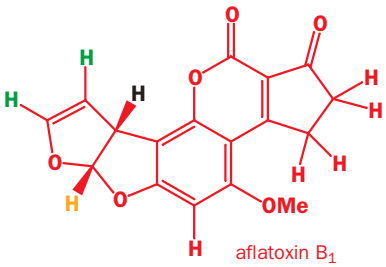
■ You can convince yourself of this by making a model.

The mistake emerged when some Japanese chemists made this compound by an unambiguous route. The NMR spectrum was quite like that of canadensolide, but not the same. In particular, the coupling between the green and brown Hs was 1.5 Hz—quite different! So they also made the other possible diastereoisomer and found that it was identical to natural canadensolide. The details are in the margin.



An example of vicinal coupling in structural analysis: aflatoxins

We can bring together a lot of these points in the structure of one compound, the dreaded aflatoxin. Aflatoxin B_1 is an example.



aflatoxin B_1

The four red protons on saturated carbons in the five-membered ring in the margin appear as two triplets: δ_H 2.61 (2H, t, J 5 Hz) and δ_H 3.42 (2H, t, J 5 Hz). The *cis* and *trans* couplings are the same. The yellow proton on the left, on the junction between the two five-membered cyclic ethers, is a doublet δ_H 6.89 (1H, d, J 7 Hz). This is, of course, the *cis* coupling to the black hydrogen. The black hydrogen has this coupling too, but it appears as a doublet of triplets with a triplet coupling of 2.5 Hz: δ_H 4.81 (1H, dt, J 7, 2.5, 2.5 Hz). These small couplings can only be to the two green hydrogens: the ^3J and ^4J couplings are indeed the same.

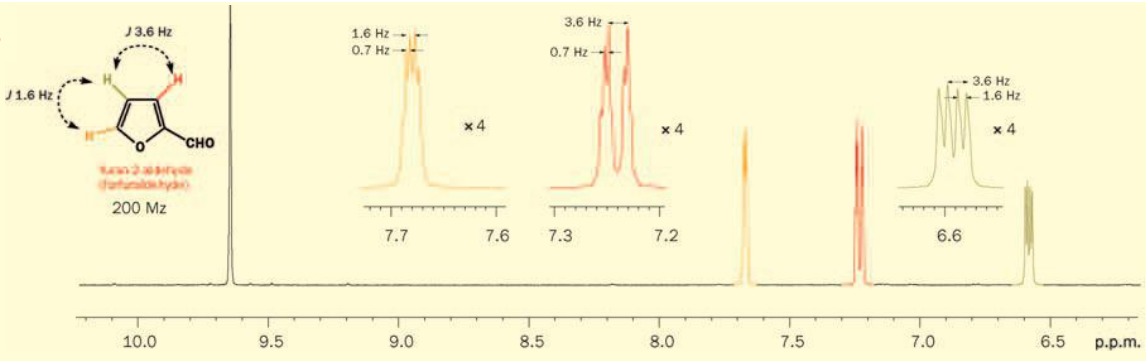
Finally there is another strange coincidence—each green hydrogen appears as a triplet with 2.5 Hz couplings. Evidently, the *cis* coupling across the double bond is also 2.5 Hz. We expect *cis* coupling in a cyclopentene to be small (it was 4 Hz in the azulene on p. 000), but not that small—it must be the electronegative oxygen atom that is reducing the value still further.

▶Aflatoxins

Aflatoxins were mentioned in Chapter 20: they occur in moulds, including those that grow on some foods, and cause liver cancer. These slow-acting poisons are among the most toxic compounds known.

Coupling in furans

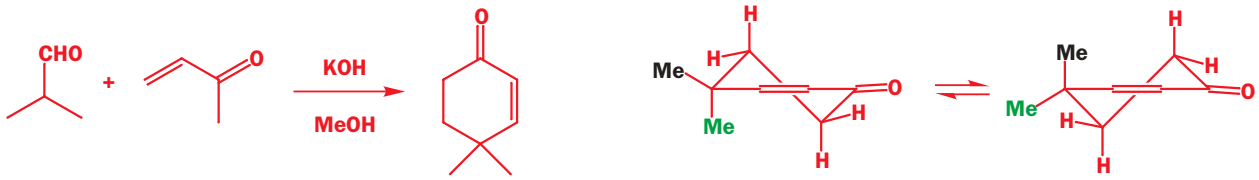
The size of coupling constants in five-membered rings containing oxygen is illustrated clearly in furfuraldehyde (furan-2-aldehyde): note how small the couplings are.



Geminal (^2J) coupling

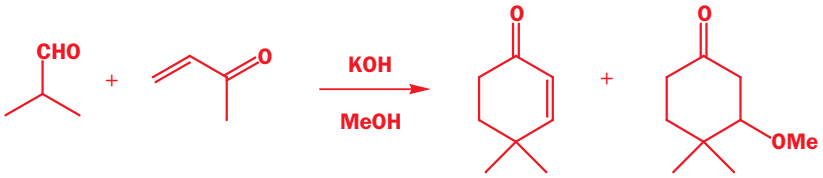
For coupling to be seen, the two hydrogen atoms in question must have different chemical shifts. For ^2J couplings the two hydrogen atoms are on the same carbon atom, so in order to discuss geminal coupling we must first consider what leads the two hydrogens of a CH_2 group to have different shifts.

To introduce the topic, an example. It may seem to you that any six-membered ring might show different chemical shifts for axial and equatorial groups. But this doesn't happen. Consider the result of this Robinson annelation reaction.

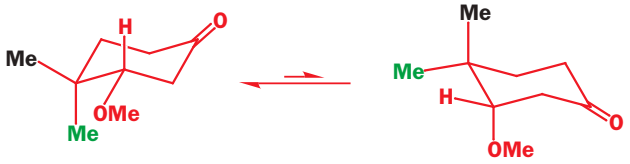


The two methyl groups at C4 give rise to a single signal in the ^{13}C NMR at 27.46 p.p.m. Even though one of them is (pseudo)axial and one (pseudo)equatorial, the molecule exists in solution as a rapidly equilibrating mixture of two conformations. The axial green methyl in the left-hand conformer becomes equatorial in the right-hand conformer, and vice versa for the black methyl group. This exchange is rapid on the NMR time-scale and the equilibrium position is 50:50. Time averaging equalizes the chemical shifts of the two methyl groups, and the same is true for the CH_2 groups around the back of the ring.

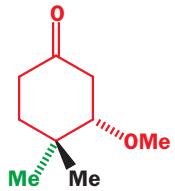
However, the enone is not the only product of this reaction. A methanol adduct is also formed by Michael addition of methanol to the conjugated enone.



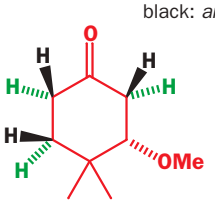
This product has two methyl signals at 26.1 and 34.7 p.p.m. If we examine the molecule by conformational analysis as we did for the first product we see a similar situation.



Similar but not the same. This time, the two conformations are not identical. One has the OMe group equatorial and the other has it axial. Even the two methyl groups do not entirely change places in the two conformations. True, the green methyl is axial on the left and equatorial on the right, but it has a gauche (dihedral angle 60°) relationship with the OMe group in *both* conformations. The black Me group is gauche to OMe on the left but anti-periplanar to the OMe group on the right. When two different conformations, in each of which the black and green methyl groups are different (that is, they don't just change places), are averaged, the two methyl groups are not equalized.



green: *syn* to OMe
black: *anti* to OMe



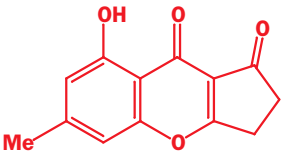
Perhaps a simpler way to discover this is to use a configurational, rather than a conformational, diagram. The green methyl group is on the same face of the molecule as the MeO group, while the black methyl group is on the other face. No amount of ring flipping can make them the same. They are *diastereotopic*, a term we shall define shortly. And so are all three CH_2 groups in the ring. The green Hs are on the same face of the molecule as the MeO group while the black Hs are on the other face.

A proton NMR example confirms this, and here is one from an odd source. There are fungi that live on animal dung, called coprophilous fungi. They produce antifungal compounds, presumably to

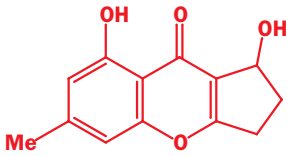
fight off competition! Anyway, in 1995 two new antifungal compounds were discovered in a fungus living on lemming dung. They were named coniochaetones A and B and their structures were deduced with the usual array of mass and NMR spectra. The proton spectra, run on a 600 MHz machine, are shown below, and they reveal considerable detail.

Coniochaetone A		Coniochaetone B	
δ_H, p.p.m.	Coupling	δ_H, p.p.m.	Coupling
2.41 (3H)	s	2.38 (3H)	s
		5.43 (1H)	ddd, *J* 1.4, 3.3, 7.6 Hz
2.70 (2H)	m	2.49 (1H)	m
		2.03 (1H)	m
3.07 (2H)	m	3.10 (1H)	dddd, *J* 1.4, 5.1, 9.4, 18 Hz
		2.81 (1H)	ddd, *J* 5.1, 9.3, 18 Hz
6.77 (1H)	broad s	6.70 (1H)	broad s
6.69 (1H)	broad s	6.62 (1H)	broad s
12.21 (1H)[a]	s	12.25 (1H)[a]	s

[a] Exchanges with D_2O.



coniochaetone A

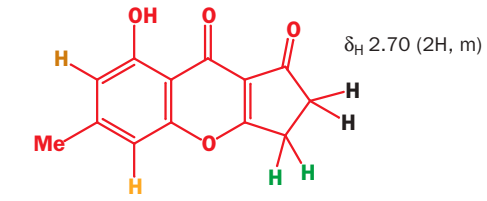


coniochaetone B

Some of the spectrum is essentially the same for the two compounds, but other parts are quite different. Coniochaetone A has a very simple spectrum, very easily assigned.

Coniochaetone B is rather more interesting. The spectrum is much more complicated, even though it has only one more C–H than coniochaetone A. The reason is that addition of that H atom creates a stereogenic centre and makes the top and bottom faces of the molecule different. Both CH_2 groups become diastereotopic.

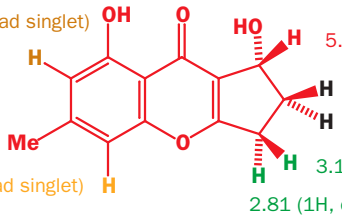
The green Hs are coupled to each other ($J = 18$ Hz) and to each of the black Hs with a different coupling constant. One of the green hydrogens also shows a long-range ($^4J = 1.4$ Hz) W-coupling to the red H. The black Hs are too complex to analyse, even at 600 MHz, but the different couplings to the red hydrogen are shown by the signal at 5.43 p.p.m.



δ_H 2.70 (2H, m)

δ_H 677 (1H, broad singlet) δ_H 3.07 (2H, m)

coniochaetone A



δ_H 6.69 (1H, broad singlet)

5.43 (1H, ddd, *J* 1.4, 3.3, 7.6 Hz)

δ_H 2.49 (1H, m)

δ_H 2.03 (1H, m)

δ_H 677 (1H, broad singlet)

3.10 (1H, dddd, *J* 1.4, 5.1, 9.4, 18 Hz)

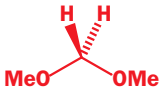
2.81 (1H, ddd, *J* 5.1, 9.3, 18 Hz)

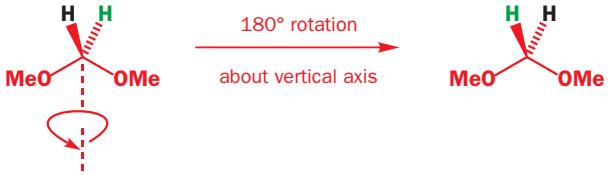
coniochaetone B

Diastereotopic CH_2 groups

The green protons in the last example couple to one another, so they must be different. Until this chapter, you may have thought it self-evident that two protons attached to the same carbon would be identical, but you have now seen several examples where they are not. It is now time to explain more rigorously the appearance of CH_2 groups in NMR spectra, and you will see that there are *three* possibilities. To do this, we shall have to discuss some aspects of symmetry that build on what you learned in Chapter 16.

First, an example in which the two hydrogens are indeed the same. We may draw one hydrogen coming towards us and one going away, but the two Hs are the same. This is easy to demonstrate. If we colour one H black and one green, and then rotate the molecule through 180°, the black H appears in the place of the green H and vice versa. The rotated molecule hasn't changed because the *other* two substituents (OMe here) are also the same.



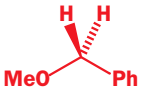


If we had given out uncoloured models of this molecule with this book, and asked each reader to paint one H green and one H black, we would have no way at all of giving instructions about which to paint what colour. But it wouldn't matter because, even without these instructions, every reader would produce an identical model, whichever way they painted their Hs.

The correct description for this pair of hydrogen atoms is **homotopic**. They are the same (*homo*) topologically and cannot be distinguished by chemical reagents, enzymes, NMR machines, or human beings. The molecule is achiral—it has no asymmetry at all.

Homotopic groups

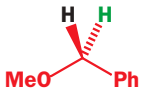
Homotopic groups cannot be distinguished by any means whatsoever: they are chemically entirely identical.



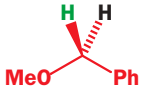
What happens when the other two substituents are different? At first sight the situation does not seem to have changed. Surely the two hydrogens are still the same as one another?

In fact, they aren't—not quite. If we had given out uncoloured models of this molecule and just said 'paint one H green and one H black', we would not have got just one type of model.

We would have got about 50% looking like this:



and 50% looking like this:



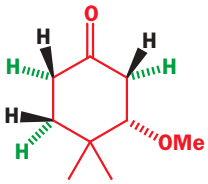
▶ To understand this discussion, it is very important that you appreciate points such as this which we covered in Chapter 16. You may need to refresh your memory of the stereochemical points there before you read further.

But this time, we *could* give instructions about which H we wanted which colour. To get the first of these two, we just need to say 'Take the MeO group in your *left* hand and the Ph group in your *right*, kink the carbon chain upwards. The hydrogen coming towards you is to be painted black.' All the models produced by readers would then be identical—*as long as the readers knew their left from their right*. This is a very important point: the green and black hydrogens in this molecule (unlike the first one) can be described only in phrases incorporating the words 'left' or 'right', and are distinguishable only by a system that knows its left from its right.

Human beings are such a system: so are enzymes, and the asymmetric reagents you will meet in Chapter 45. But NMR machines are not. NMR machines cannot distinguish right and left—the NMR spectra of two enantiomers are identical, for example. It is not a matter of enantiomers in the molecule in question—it has a plane of symmetry and is achiral. Nonetheless, the relationship between these two hydrogens is rather like the relationship between enantiomers (the two possible ways of colouring the Hs are enantiomers—mirror images) and so they are called **enantiotopic**. Enantiotopic protons appear identical in the NMR spectrum.

Enantiotopic groups

Enantiotopic groups can be distinguished by systems that can tell right from left, but are still magnetically equivalent and appear identical in the NMR spectrum.



The third situation usually arises when the molecule has a stereogenic centre. As an example we can take the Michael product from the beginning of this section.

It is now very easy to distinguish the two hydrogens on each ring carbon atom and, if we want to give instructions on how to paint a model of this molecule, we can just say 'Make all the Hs on the same side of the ring as OMe green, and the ones on the opposite side to OMe black.' We do not need to use the words 'right' or 'left' in the instructions, and it is not necessary to

know your right from your left to tell the two types of Hs apart. Ordinary chemical reagents and NMR machines can do it. These Hs are different in the way that diastereoisomers are different and they are **diastereotopic**. We expect them to have different chemical shifts in the proton NMR spectrum.

The same is true of the methyl groups: they too are diastereotopic and we expect them to have different shifts.

▶ NMR machines *can* tell the difference, but it does not follow that they *will*. There are many examples of protons that are different but have the same chemical shift (toluene, PhMe, shows a singlet in the NMR for all its aromatic protons even though they are of three different kinds). Sometimes diastereotopic protons have the same chemical shift, sometimes slightly different chemical shifts, and sometimes very different chemical shifts.

● Diastereotopic groups

Diastereotopic groups are chemically different: they can be distinguished even by systems that cannot tell right from left, and they appear at different chemical shifts in the NMR spectrum.

How to tell if protons are homotopic, enantiotopic, or diastereotopic

What we have said so far explains to you why homotopic and enantiotopic groups appear identical in the NMR spectrum, but diastereotopic protons may not. Now we will give a quick guide to determining what sort of pair you are dealing with in a given molecule.

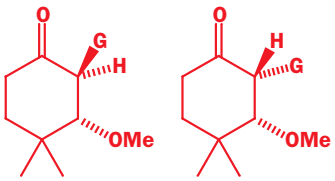
The key is to turn your molecules into two molecules. Replace one of the Hs (we'll assume we're looking at Hs, but the argument works for other groups too—Me groups, for example, as in the last example above) with an imaginary group 'G'. Write down the structure you get, with stereochemistry shown. Next, write down the structure you get by replacing the other H with the group G. Now the more difficult bit: identify the stereochemical relationship between the two molecules you have drawn.

- If they are identical molecules, the Hs are homotopic
- If they are enantiomers, the Hs are enantiotopic
- If they are diasatereoisomers, the Hs are diastereotopic

This is really just a simpler way of doing what we did with black and green above, but it is easy to do for any molecule. Take the first of our examples, and replace each H in turn by G.

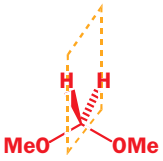
These two molecules are identical, because just turning one over gives the other: the protons are homotopic. Now for the next example.

The two molecules are not identical: to make one into the other you need to reflect in the plane of the paper, so they are enantiomers, and the Hs are *enantiotopic*. There is another term we must introduce you to in relation to this molecule, which will become useful in the next chapter, and that is 'prochiral'. The molecule we started with here was not chiral—it had a plane of symmetry. But by changing just one of the Hs to a different group we have made it chiral. Molecules that are achiral but can become chiral through one simple change are called **prochiral**.

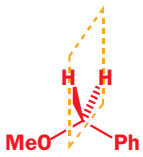


Now we will choose one of the three pairs of Hs in the cyclohexanone example. The starting molecule is, of course, now chiral, and the two molecules we get when we replace each H by G are now diastereoisomers: one has G and OMe *anti*, the other *syn*, and the pairs of hydrogens are *diastereotopic*.

Finally, one last look at symmetry in the three molecules. We will consider two planes as potential planes of symmetry—the plane that bisects the H–C–H angle of the two Hs we are interested in (this is the plane of the paper as we have drawn all three molecules), and a plane at right angles to that plane, passing through the carbon atom and both hydrogen atoms. This second plane is marked on the diagrams in yellow.



This molecule, the most symmetrical of the three, is achiral. The central carbon atom is completely nonstereogenic. Both planes are planes of symmetry and the hydrogens are homotopic. They are chemically and magnetically equivalent.



This slightly less symmetrical molecule is not chiral but *prochiral*. The carbon atom is a prochiral (or prostereogenic) centre. The plane of the paper is still a plane of symmetry, but the yellow plane containing the two H atoms is not and the hydrogen atoms are enantiotopic. They are magnetically equivalent and can be distinguished only by humans, enzymes, and other asymmetric reagents.

This least symmetrical molecule is chiral as it has a chiral (stereogenic) centre. The carbon atom we are discussing is not a stereogenic centre but is again a prochiral centre. Neither plane is a plane of symmetry and the hydrogen atoms are diastereotopic. They are chemically and magnetically different and can be distinguished by NMR or by chemical reagents.

Look back at the structures we have just been discussing and you should see that both the enone used to produce this molecule and coniochaetone A have a plane of symmetry bisecting their CH_2 groups while coniochaetone B does not. This gives another easy way of telling if a pair of groups will appear different in the NMR spectrum. If the plane passing through the carbon atom and bisecting the H–C–H bond angle (the plane of the paper in these diagrams) is a plane of symmetry, then the two Hs (which are reflected in that plane) are magnetically equivalent. (If they also lie in a plane of symmetry, they are homotopic; if they don't, they are enantiotopic.)

The shape of the NMR signal

A prochiral CH_2 group with diastereotopic Hs isolated from any other Hs will give rise to two signals, one for each H, and they will couple to each other so that the complete signal is a pair of doublets. You would expect geminal coupling constants to be larger than vicinal ones simply because the Hs are closer—we are talking about ^2J instead of ^3J couplings. A typical vicinal (^3J) coupling constant for a freely rotating open-chain system without nearby electronegative atoms would be 7 Hz. A typical geminal (^2J) coupling constant is just twice this, 14 Hz.

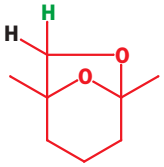
The chemical shift differences ($\Delta\delta$) between Hs on the same carbon atom tend to be small—usually less than 1 p.p.m.—and the coupling constants J tend to be large so the signals usually have $\Delta\delta \sim J$ and are distorted into an AB pattern. The signal may have any of the forms indicated here, depending on the relative sizes of $\Delta\delta$ (the chemical shift difference between the peaks) and J.

■ The shape of NMR signals where J and the chemical shift difference are of the same order of magnitude were discussed in Chapter 11. The arguments apply to any coupled protons of similar chemical shift—there we used disubstituted aromatic rings as the example—but are particularly relevant here.

some different shapes of an AB system in the proton NMR spectrum from a diastereotopic CH_2 group

The coupling constant is always the difference in Hz between the two lines of the same colour in these diagrams, but the chemical shifts are not so easily measured. The chemical shift of each proton is at the weighted mean of the two lines—the more distorted the signal, the nearer the chemical shift to that of the larger inner line.

▶ It is not usually easy to decide which proton gives rise to which signal. This is not important in assigning the structure, but may be important in assigning stereochemistry. We shall discuss how to assign the protons shortly in relation to the conformation of six-membered rings, and then again later using the nuclear Overhauser effect.



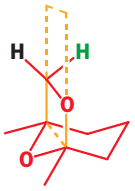
frontalin

Examples of AB systems from diastereotopic CH_2 groups

It is time to look at some examples. The insect pheromone frontalin can be drawn like this.

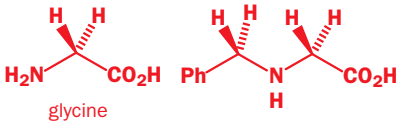
There is nothing wrong with this drawing except that it fails to explain why the black and green hydrogens are different and give a pair of doublets at δ_H 3.42 and 2.93 p.p.m., each 1H, J 7 Hz (an AB

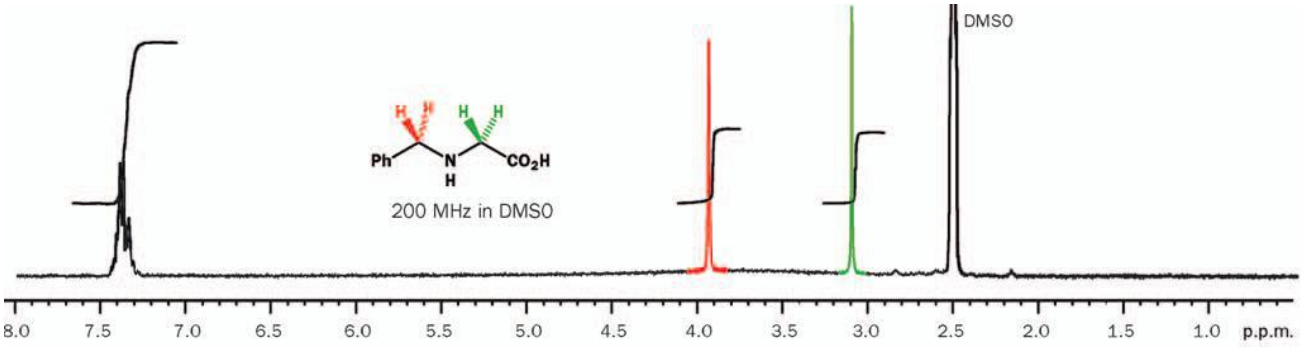
system) in the proton NMR. These protons must be diastereotopic. A conformational diagram should help.



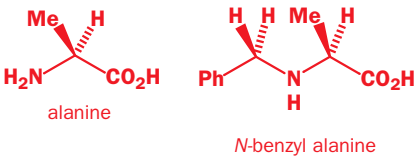
The vital H atoms are on a diaxial bridge across the six-membered ring. Under the black H is an oxygen atom, while under the green H is a three-carbon link. If there were a plane of symmetry between these two Hs, it would have to be the plane marked by the dashed yellow lines in the second diagram. This is *not* a plane of symmetry and the two Hs *are* diastereotopic. They have no neighbours, so they give a simple AB system. The coupling constant here is small for ^2J—only 7 Hz—but that should not surprise you since we have a five-membered ring and a nearby oxygen atom.

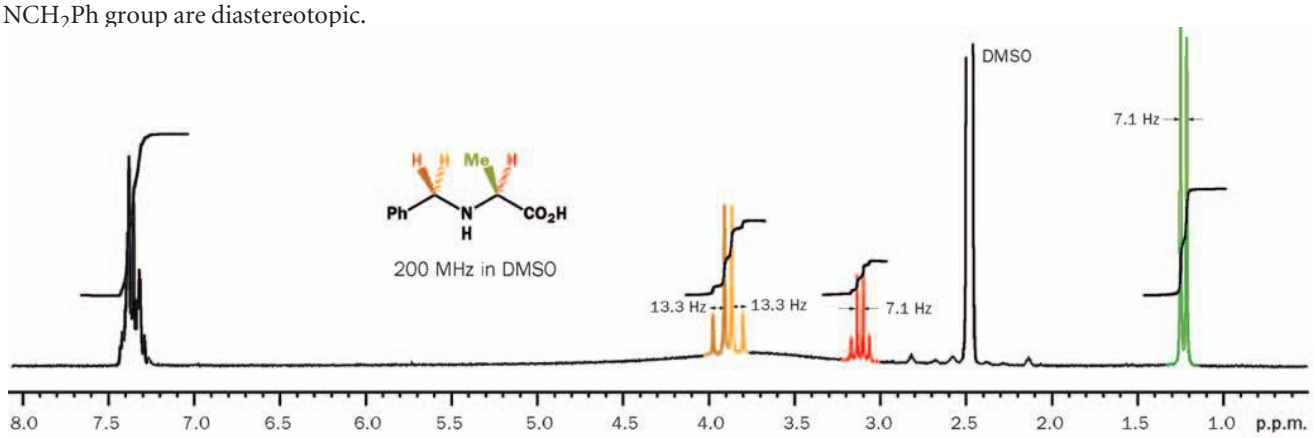
The same principles apply to open-chain compounds, such as amino acids. All of the amino acids in proteins except glycine are chiral. Glycine has a prochiral CH_2 group that gives a singlet in the NMR spectrum as the Hs are enantiotopic. Similarly, the *N*-benzyl derivative of glycine has a second prochiral CH_2 group (NCH_2Ph) that gives another singlet in the NMR spectrum as these Hs too are enantiotopic.





The plane of the paper is a plane of symmetry for both these CH_2 groups in the way they are drawn here. The *N*-benzyl derivatives of the other amino acids are quite different. Each shows an AB signal for the NCH_2Ph group because these molecules have stereogenic centres and there are no planes of symmetry. The Hs of the NCH_2Ph group are diastereotopic.



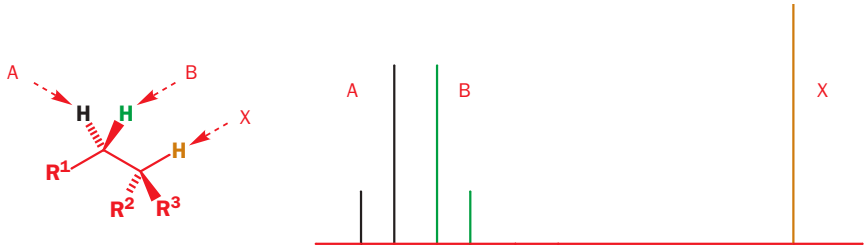


In the way in which the molecule is drawn, the brown H is on the same side as the Me group and the yellow H on the other. It does not matter that there is free rotation in this molecule—there is no conformation you can draw in which the important plane, passing between the diastereotopic Hs through their carbon atom, is a plane of symmetry.

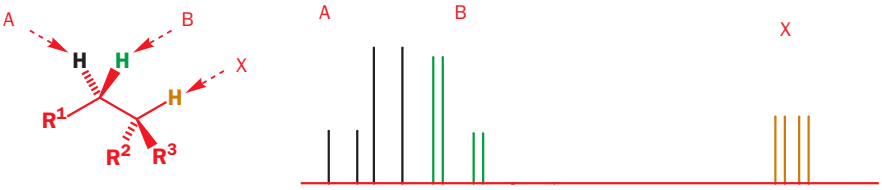
See p. 000 for the use of A, B, X, etc. to describe protons.

The ABX system

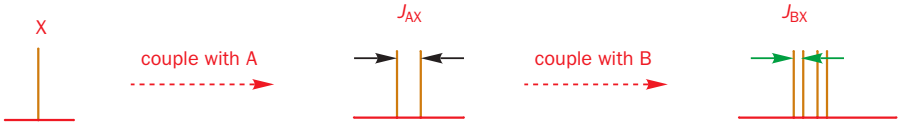
It is more common to find diastereotopic CH_2 groups with neighbours, and the most common situation is that in which there is one neighbour, giving an **ABX system**. We will outline diagrammatically what we expect . Let's start with the AB system for the diastereotopic CH_2 group and the singlet for the neighbour, which we call 'X' because it's at a quite different chemical shift.



Now we must add the coupling between A and X and between B and X. Since A and B are different, there is no reason why J_{AX} and J_{BX} should be the same. One is normally larger than the other, and both are normally smaller than J_{AB}, since J_{AX} and J_{BX} are vicinal ^3J couplings while J_{AB} is a geminal ^2J coupling. We shall arbitrarily put $J_{AX} > J_{BX}$ in this example.

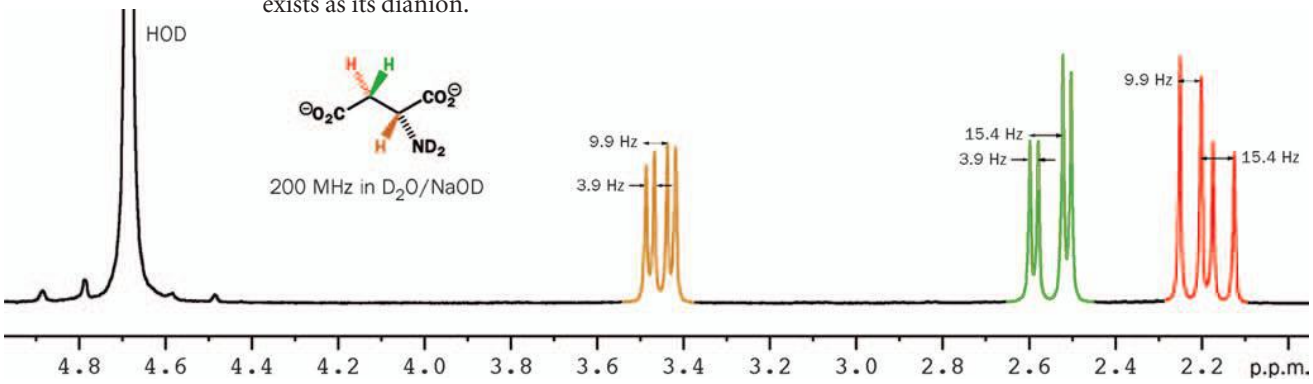


You can read J_{AX} and J_{BX} from the AB part of the signal quite easily by measuring the distance between each pair of lines, in Hz. If you want to read them from the X part, remember that it is made up like this.



In the signal for X, the larger coupling, J_{AX}, is the spacing between lines 1 and 3 or between lines 2 and 4 while the smaller coupling, J_{BX}, is the spacing between lines 1 and 2 or 3 and 4. Naturally, J_{AX} and J_{BX} are the same whether you measure them in the AB signal or in the X signal.

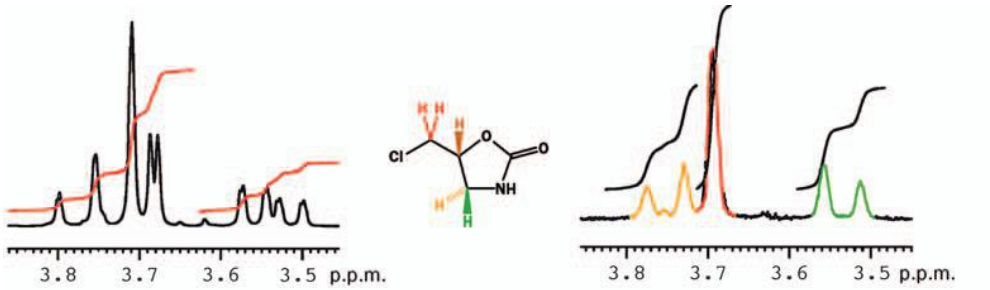
When aspartic acid is dissolved in D_2O with NaOD present, all OH and NH_2 protons are exchanged for deuterium atoms and do not show up in the spectrum—the molecule exists as its dianion.



The spectrum consists of a beautiful ABX system with the brown proton as a double doublet at δ_H 3.45 p.p.m. and the black and green protons as an AB pair between 2 and 3 p.p.m. The coupling between red and green is typical: 15 Hz.

More complex examples

We have stressed all along that diastereotopic CH_2 groups may be separated in the proton NMR but need not be. It may just happen that the chemical shift difference is zero giving an A_2 system. It is not possible to predict which diastereotopic CH_2 groups will be revealed in the NMR spectrum as AB systems and which as A_2. Both may even appear in the same molecule. As an example, consider the compound shown below. The brown hydrogen has a very complicated signal, coupling to four other hydrogens. The spectrum for these four hydrogens is also complicated but may be simplified by irradiating the brown hydrogen to remove any coupling to it. Then we can clearly see that one CH_2 group shows itself as diastereotopic while the other does not. From the chemical shifts we may guess that the CH_2Cl group is the A_2X system at 3.7 p.p.m. and that it is the one in the ring that gives the ABX system.

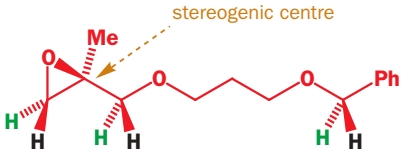


expanded region of 200 MHz NMR spectrum

same region with the coupling to the brown proton removed

As a general guide, CH_2 groups close to a stereogenic centre are more likely to be revealed as diastereotopic than those further away. Those in part of a structure with a fixed conformation are more likely to be revealed as diastereotopic than those in a flexible, freely rotating part of the molecule.

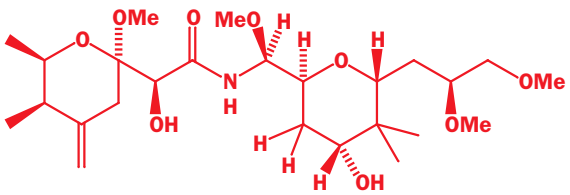
In this molecule, all three marked CH_2 groups are diastereotopic, but it is more likely that the ones next to the stereogenic centre, whether in the ring or in the open chain, will show up as AB systems in the NMR. The remote CH_2 group at the end of the chain is more likely to be A_2 in the NMR, but one cannot be sure. You must be able to recognize diastereotopic CH_2 groups and to interpret AB and ABX systems in the NMR. You must also not be surprised when a diastereotopic CH_2 group appears in the NMR spectrum as an A_2 or A_2X system.



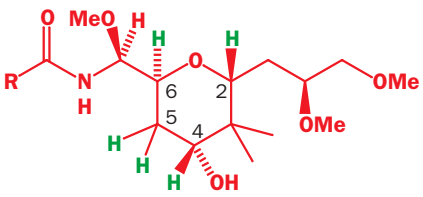
■ For another example, look back at thienamycin on p. 000. Compare the two OCH_2Ph groups: both have a diastereotopic CH_2 pair, but one appears as a singlet and one as an AB system.

Geminal coupling in six-membered rings

While we were discussing coupling in rings earlier in the chapter we avoided the question of geminal coupling by never considering the CH_2 groups in the ring. In practice there will often be diastereotopic CH_2 groups in six-membered rings. As an example, we will look at a problem in structure determination of a rather complex molecule. It is pederin, the toxic principle of the blister beetle *Paederus fuscipes*. After some incorrect early suggestions, the actual structure of the compound was eventually deduced.

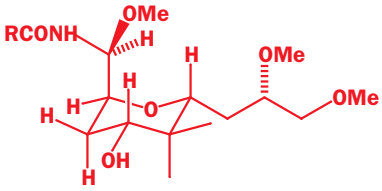


We are not going to discuss the full structure elucidation, but will concentrate on the stereochemistry of the right-hand ring. You can see that there is a CH_2 group in this ring and it has, of course, diastereotopic Hs. At first the OH group was placed at the wrong position on the ring, but a careful analysis of the NMR spectrum put this right and also gave the stereochemistry. The five (green) protons on the ring gave these signals (left-hand part of the molecule omitted for clarity).



δ_H 1.85 (1H, ddd, *J* 5, 10, 12)
2.10 (1H, ddd, *J* 3, 4, 12)
3.75 (1H, dd, *J* 4, 10)
3.85 (1H, ddd, *J* 3, 5, 8)
4.00 (1H dd, *J* 3, 7)

Three of the protons have shifts δ_H 3–4 p.p.m. and are obviously on carbons attached to oxygen atoms. The other two, δ_H about 2 p.p.m., must be the diastereotopic pair at C5. The coupling of 12 Hz, which appears in both signals, must be the geminal coupling and the other couplings are found in the signals at δ_H 3.75 and 3.85 p.p.m. The signal at δ_H 3.75 p.p.m. has no other couplings and must be from C4 so that leaves δ_H 3.85 p.p.m. for the hydrogen atom at C6 which is also coupled to the hydrogen in the side chain. The 10 Hz coupling is axial/axial but the others are all much smaller so we can draw the conformation immediately.



There is just the one axial/axial coupling and so the left-hand side chain must occupy an axial position. This is perhaps a bit surprising—it's large and branched—but the molecule has no choice but to place one of the two side chains axial.

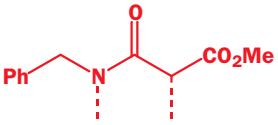
A surprising reaction product

Chapter 26 revealed that sodium chloride can be a surprisingly powerful reagent. It removes ester groups from malonate derivatives, like this.

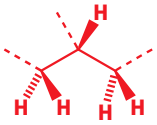
However, using this reaction to decarboxylate the malonate shown here did not merely remove the CO_2Me group. Instead, a compound was formed with a much more complicated NMR spectrum than that of the expected product (which was known as it could be made another way). The NMR data for both compounds are detailed below.

product X		product X		
$C_{14}H_{15}NO_3$		$C_{14}H_{15}NO_3$		$C_{13}H_{17}NO_2$
δ_H	7.35–7.25 (3H, m)	δ_C	169.1	δ_H 7.2–7.4 (5H, m, Ph)
	7.2 (2H, d, *J* 7)		169.0	3.65 (3H, s, OMe)
	4.45 (1H, d, *J* 14)		136.2	3.45 (2H, t, *J* 7)
	4.3 (1H, d, *J* 14)		128.6	2.95–2.85 (2H, m)
	3.8 (3H, s, OMe)		128.1	2.85–2.75 (1H, m)
	3.45 (1H, dd, *J* 7, 10)		127.6	2.6 (2H, t, *J* 7)
	3.1 (1H, d, *J* 10)		52.4	
	2.35–2.25 (1H, m)		46.45	
	1.9 (1H, dd, *J* 5, 10)		46.4	
	1.1 (1H, t, *J* 5		31.5	
			22.8	
			20.7	

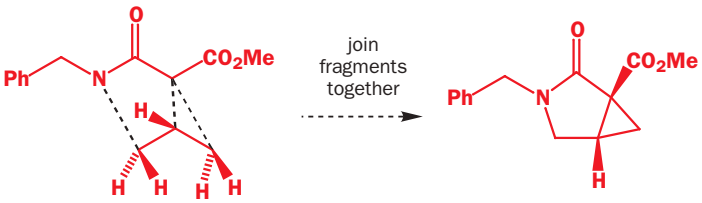
The unknown product has lost MeOH but retained both carbonyl groups (δ_C 169.1, 169.0 p.p.m. typical for acid derivatives). In the ^{1}H NMR, the phenyl ring and one OMe group are still there. The other striking thing about the ^{1}H NMR is the presence of so many couplings. It looks as if all the hydrogens are magnetically distinct. Indeed we can see one diastereotopic CH_2 at 4.45 and 4.3 p.p.m. with ^2J = 14 Hz. This is the 'normal' value and would fit well for the NCH_2Ph group. But note the chemical shift! For δ_H to be so large the nitrogen atom must be part of an amide, which would also explain the two acid derivative C=O groups. So we have the partial structure on the right.



All that is left is C_3H_5 and this must be fitted in where the dotted lines go. One reasonable interpretation from the NMR would be two diastereotopic CH_2 groups, one with ^2J = 10 and one with ^2J = 5 Hz, linked by a CH group.



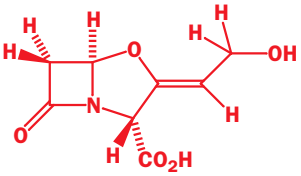
If this is the case, what has brought the values of ^2J down from 14 to 10 and even 5 Hz? Electronegative elements can't be the culprits as the only one is nitrogen, but small rings could. If, in fact, we simply join these two fragments together in rather a surprising way (the dotted lines show how), we get the correct structure.



In this case, the geminal couplings do not help to assign the stereochemistry—the three- and five-membered rings can only be fused *cis* (just try making a model of the *trans* compound!)—but they do help in assigning the structure.

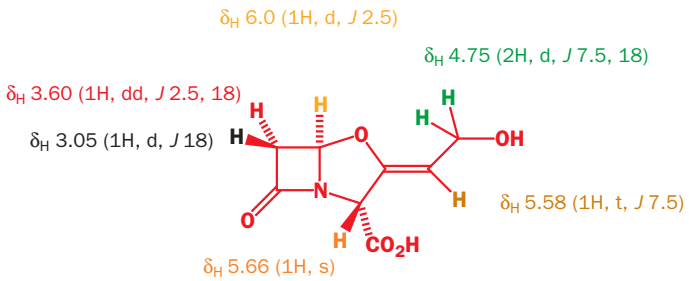
We should at this point just recap what we have done here—we made no attempt to work out the structure by thinking about what the mechanism of the reaction might be. We used, purely and simply, NMR to work out fragments of the structure which we then put together in a logical way. Considering reasonable mechanisms can be a help in structure determination—but it can also be a hindrance. If the product is unexpected, it follows that the mechanism is unexpected too.

For an example with a four-membered ring, we go back to β-lactams. A serious problem with β-lactam antibiotics is that bacteria develop resistance by evolving enzymes called β-lactamases, which break open the four-membered ring. In 1984, a team from Beechams reported the exciting discovery of some very simple inhibitors of these enzymes all based on the core structure named clavulanic acid. This too was a β-lactam but a much simpler one than the penicillins we saw earlier.



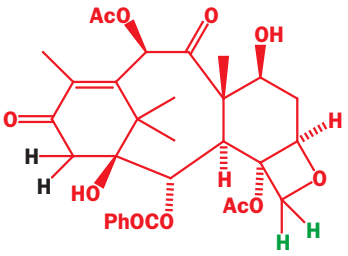
clavulanic acid

The structure elucidation used all the usual spectroscopic techniques as well as X-ray crystallography, but it is the ^{1}H NMR that is particularly interesting to us here. Here it is, with the assignments shown.



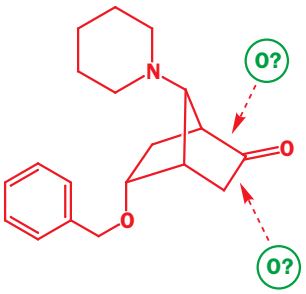
Notice the very large geminal coupling between the red and the black hydrogens (more of this later) and the fact that the green hydrogens, though actually diastereotopic, resonate at the same chemical shift. The *cis* coupling across the four-membered ring is larger (2.5 Hz) than the *trans* coupling (0 Hz) as expected.

The π contribution to geminal coupling



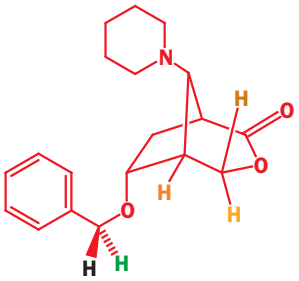
We began this chapter with a diagram of Taxol. This molecule is rather too complex for us to analyse in detail, but the geminal couplings of an important closely related compound are worth noting. Here are the details.

The coupling between the black Hs is 20 Hz while that between the green Hs is 6 Hz. This is a rather extreme example as the green Hs are in a four-membered ring and next to an oxygen atom, so they are expected to show a small J value, while the black Hs are in a six-membered ring and not next to an electronegative element. Nevertheless, 20 Hz is a very large coupling constant. The reason is the adjacent π bond. If a CH_2 group is next to an alkene, aromatic ring, C=O group, CN group, or any other π-bonded functional group, it will have a larger geminal coupling constant. This effect is quite clear in both Taxol and clavulanic acid.

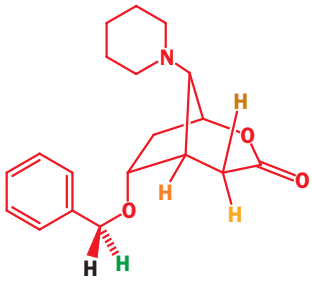


The oxidation of the bicyclic amino-ketone shown in the margin demonstrates how useful this effect can be. This is the Baeyer–Villiger rearrangement, which you will meet in Chapter 37. The mechanism is not important here: all you need to know is that it inserts an oxygen atom on one side or the other of the ketone C=O group. The question is—which side?

In fact, both lactones were isolated and the problem then became—which was which? In both NMR spectra there were AB systems at 4.6–4.7 for diastereotopic CH_2 groups isolated from the rest of the molecule, with $^2J = 11.8$ Hz. These are clearly the black and green hydrogens on the benzyl groups. The coupling constant is reduced by the oxygen atom and increased by the phenyl's π contribution, so it ends up about average.



product A



product B

Both lactones also had clear ABX systems in the NMR corresponding to the yellow, brown, and orange protons. In one compound $^2J = 10.8$ Hz and in the other $^2J = 18.7$ Hz. The smaller value has been reduced by neighbouring oxygen and this must be compound A. The larger value has been increased by the π contribution from the carbonyl group and this must be compound B.

The size of ^2J and ^3J coupling constants

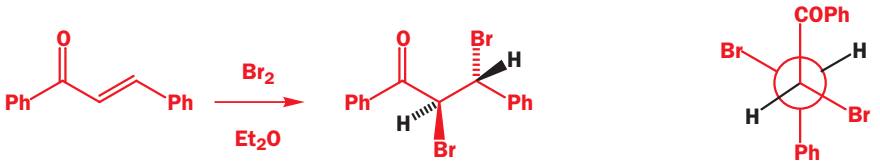
We have now covered all of the important influences on the size of coupling constants. They are:

- **dihedral angle: ^3J greatest at 180° and 0°; about 0 Hz at 90°**
- **ring size, which leads to 'spreading out' of bonds and lower ^2J *and* lower ^3J in small rings**
- **electronegative atoms, which decrease ^2J and ^3J coupling constants between protons**
- **π systems, which increase ^2J coupling constants between protons**

The nuclear Overhauser effect

Many occasions arise when even coupling constants do not help us in our quest for stereochemical information. Consider this simple sequence. Bromination of the alkene gives as expected *trans* addition and a single diastereoisomer of the dibromide.

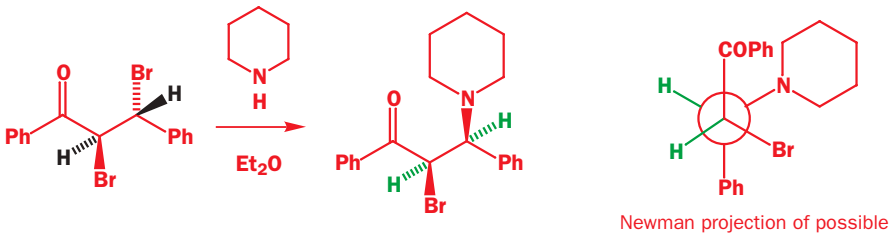
■ We looked at the stereoselectivity of electrophilic additions to double bonds in Chapter 20.



Newman projection of product

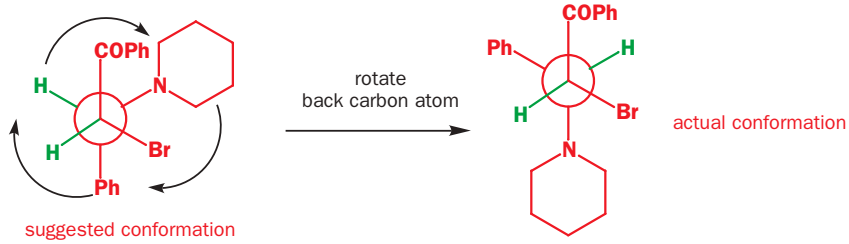
The vicinal (^3J) coupling constant between the two black Hs is 11 Hz. This is rather large and can be explained by a predominant conformation shown in the Newman projection, with the two large groups (PhCO and Ph) as far from each other as possible, the two medium groups (Br) as distant as possible, and the two black Hs in the places which are left. The dihedral angle between the black Hs is then 180° (they are anti-periplanar) and a large J is reasonable.

But now see what happens when we react the dibromide with piperidine. A single diastereoisomer of an amine is formed, and there is good evidence that it has the opposite configuration from the dibromide; in other words, replacement of Br by N has occurred with inversion.



Newman projection of possible conformation of product

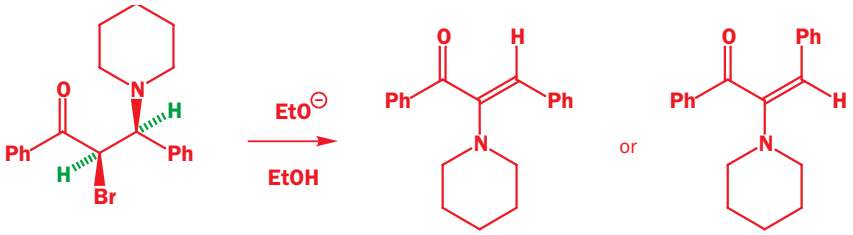
We might expect that the conformation would now be different and that, since inversion has occurred, the two green Hs would now be gauche instead of anti-periplanar. With a dihedral angle of 60° the coupling constant would be much less. But it isn't. The coupling constant between the green Hs is exactly the same (11 Hz) as the coupling constant between the black Hs in the starting material. Why? The new substituent (piperidine) is very big, much bigger than Br and probably bigger in three dimensions than a flat Ph group. The conformation must change (all we are doing is rotating the back carbon atom by 120°) so that the two green Hs also have a dihedral angle of 180°.



suggested conformation

actual conformation

A more serious situation arises when we treat this product with base. An unusual elimination product is formed, in which the amine group has moved next to the ketone. The reaction is interesting for this point alone, and one of the problems at the end of the chapter asks you to suggest a mechanism. But there is added interest, because the product is also formed as a single geometrical isomer, *E* or *Z*. But which one? There is a hydrogen atom at one end of the alkene but not at the other so we can't use ^3J coupling constants to find out as there aren't any.



What we need is a method that allows us to tell which groups are close to one another in space (though not necessarily through bonds) even when there are no coupling constants to help out. Very fortunately, an effect in NMR known as the **nuclear Overhauser effect** allows us to do this.

The details of the origin of the nuclear Overhauser effect are beyond the scope of this book, but we can give you a general idea of what the effect is. As you learned from Chapter 11, when a proton NMR spectrum is acquired, a pulse of radiofrequency electromagnetic radiation jolts the spins of the protons in the molecule into a higher energy state. The signal we observe is generated by those spins dropping back to their original states. In Chapter 11 it sufficed to assume that the drop back down was spontaneous, just like a rock falling off a cliff. In fact it isn't—something needs to 'help' the protons to drop back again—a process called **relaxation**. And that 'something' is other nearby magnetically active nuclei—usually more protons. Notice *nearby*—nearby in space not through bonds. With protons, relaxation is fast, and the number of nearby protons does not affect the appearance of the NMR spectrum.

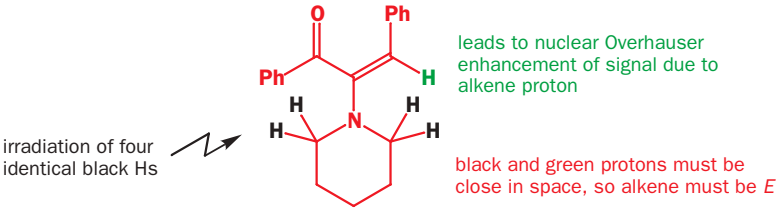
▶Why you can't integrate ^{13}C NMR spectra

Relaxation is the real reason why you can't integrate ^{13}C signals. Relaxation of ^{13}C is slow, but is fastest with lots of nearby protons. This is the reason that you will often find that $-CH_3$ groups show strong signals in the ^{13}C NMR, while quaternary carbons, with no attached protons, show weak ones: quaternary carbons relax only slowly, so we don't detect such an intense peak. Allowing plenty of time for all ^{13}C atoms to relax between pulses gives more proportionally sized peaks, but at the expense of a very long NMR acquisition time.

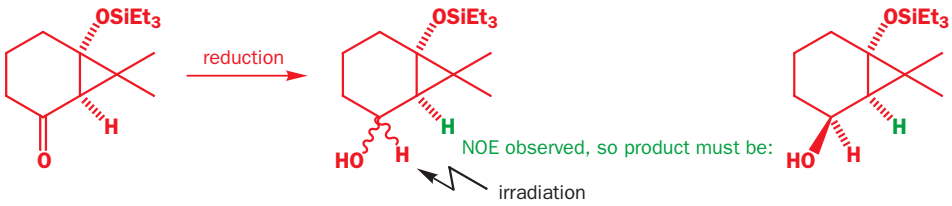
We find that, although peak intensity is independent of the number of nearby protons, by using methods whose description is beyond the scope of this book, it is possible to make the intensity respond, to a small extent, to those protons that are nearby. The idea is that as certain protons (or groups of identical protons) are irradiated selectively (in other words, they are jolted into their high-energy state and held there by a pulse of radiation at exactly the right frequency—not the broad pulse needed in a normal NMR experiment). Under the conditions of the experiment, this causes protons that *were* relying on the irradiated protons to relax them to appear as a slightly more intense (up to a few per cent) peak in the NMR spectrum. This effect is known as the nuclear Overhauser effect, and the increase in intensity of the peak the nuclear Overhauser enhancement. Both are shortened to 'NOE'.

All you need to be aware of at this stage is that irradiating protons in an NOE experiment gives rise to enhancements at other protons that are nearby in space—no coupling is required, and NOE is *not* a through-bond phenomenon. The effect also drops off very rapidly: the degree of enhancement is proportional to $1/r^6$ (where r is the distance between the protons) so moving two protons twice as far apart decreases the enhancement one can give to the other by a factor of 64. NOE spectra are usually presented as differences: the enhanced spectrum minus the unenhanced, so that those protons that change in intensity can be spotted immediately.

Applying NOE to the problem in hand solves the structure. If the protons next to the nitrogen atom in the piperidine ring are irradiated, the signal for the alkene proton increases in intensity, so these two groups of protons must be near in space. The compound is the *E*-alkene.

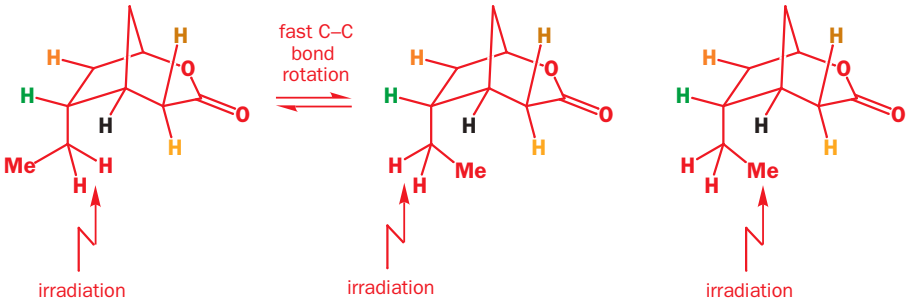


Data from NOE experiments nicely supplement information from coupling constants in the determination of three-dimensional stereochemistry too. Reduction of this bicyclic ketone with a bulky hydride reducing agent gives one diastereoisomer of the alcohol, but which? Irradiation of the proton next to the OH group leads to an NOE to the green proton.



This suggests that the two protons are on the same side of the molecule and that reduction has occurred by hydride delivery to the face of the ketone opposite the two methyl groups on the three-membered ring.

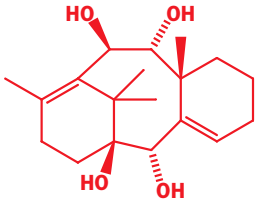
For a more complex example we can return to a lactone (shown in the margin) obtained by oxidation of a bicyclic ketone similar to the one we mentioned earlier (p. 000). When this compound was made, two questions arose. What was the stereochemistry of the ethyl group, and which signal in the NMR spectrum belonged to which hydrogen atom? In particular, was it possible to distinguish the signals of the diastereotopic brown and yellow Hs? Three experiments were carried out, summarized in the diagrams below. First the CH_2 and then the CH_3 protons of the ethyl group were irradiated and the other protons were observed. Finally, the green proton was irradiated.



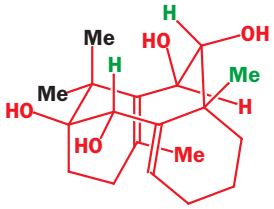
In the first experiment, enhancement of the signals of the black, yellow, and green Hs was observed. The ethyl group can rotate rapidly on the NMR time-scale so all the enhancements can be explained by the first two conformations. An NOE effect to the yellow but not to the brown H is particularly significant. Irradiation of the methyl group led to enhancement of the yellow proton but not the brown. Clearly, the ethyl group is in the position shown.

Irradiation of the green proton, whose stereochemistry is now clear, enhanced the orange proton and allowed its chemical shift to be determined. Previously, it had been lost in the many CHs in the rings.

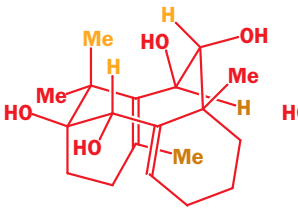
We shall finish this chapter by returning to Taxol once more. The tricyclic compound drawn here was made in 1996 as an intermediate for Taxol synthesis. The stereochemistry and the conformation of the molecule were deduced by a series of NOE experiments.

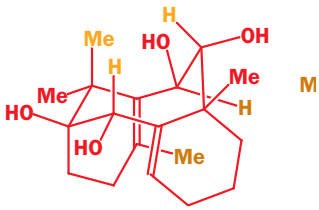


Four NOE experiments were carried out, summarized two at a time in the diagrams on the right. Irradiation of the methyl groups established that the black pair were on the same carbon atom and hence allowed assignment of the spectrum. Then irradiation of the remaining methyl group on saturated carbon established the proximity of the green hydrogens and gave the stereochemistry at three centres.

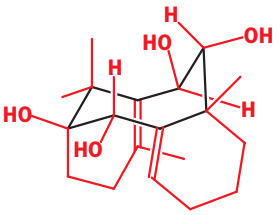


Next irradiation of the brown methyl group on a double bond showed it was close to the brown hydrogen and gave the stereochemistry at that centre. Finally, irradiation at one of the two methyl groups of the CMe_2 group (yellow) showed that it was close to the two green hydrogens and hence all these three groups were clustered in the centre of the molecule. It's important here to draw a conformational diagram as they do not look very close in the flat diagram shown.





These experiments fixed not only the stereochemistry at all the stereogenic centres but also allowed the conformation of the central eight-membered ring to be deduced. This ring is outlined in black on the diagram in the margin and has two chair-like sections. It is no trivial matter to work out such conformations without X-ray data and the NOE result tells us about the more important conformation *in solution*, rather than in the crystal. The alliance between coupling constants and NOE gives us a powerful method for structural determination.



To conclude . . .

As you leave this chapter, you should carry the message that, while X-ray crystallography is the 'final appeal' with regard to determining configuration, NMR can be a very powerful tool too. Analysis of coupling constants and nuclear Overhauser effects allows:

- determination of configuration, even in noncrystalline compounds
- determination of conformation in solution

As you embark on the next two chapters, which describe how to make molecules stereoselectively, bear in mind that many of the stereochemical outcomes were deduced using the techniques we have described in this chapter.

Problems

Note. All NMR shifts are in p.p.m. and coupling constants are quoted in hertz. The usual abbreviations are used: d = doublet; t = triplet; and q = quartet.

1 A revision problem to start you off easily. A Pacific sponge contains 2.8% dry weight of a sweet-smelling oil with the following spectroscopic details. What is its structure and stereochemistry?

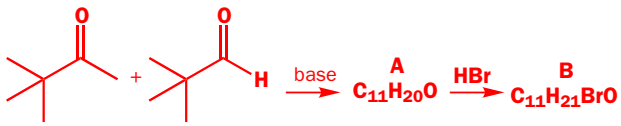
Mass spectrum gives formula: $C_9H_{15}O$

IR 1680, 1635 cm^{-1}

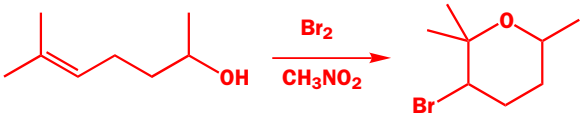
δ_H 0.90 (6H, d, *J* 7), 1.00 (3H, t, *J* 7), 1.77 (1H, m), 2.09 (2H, t, *J* 7), 2.49 (2H, q, *J* 7), 5.99 (1H, d, *J* 16), and 6.71 (1H, dt, *J* 16, 7)

δ_C 8.15 (q), 22.5 (two qs), 28.3 (d), 33.1 (t), 42.0 (t), 131.8 (d), 144.9 (d), and 191.6 (s)

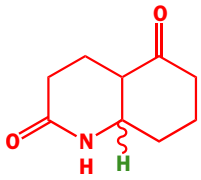
2 Reaction between this aldehyde and ketone in base gives a compound A with the ^1H NMR spectrum: δ 1.10 (9H, s), 1.17 (9H, s), 6.4 (1H, d, *J* 15) and 7.0 (1H, d, *J* 15). What is its structure? (Don't forget stereochemistry!) When this compound reacts with HBr it gives compound B with this NMR spectrum: δ 1.08 (9H, s), 1.13 (9H, s), 2.71 (1H, dd, *J* 1.9, 17.7), 3.25 (dd, *J* 10.0, 17.7), and 4.38 (1H, dd, *J* 1.9, 10.0). Suggest a structure, assign the spectrum, and give a mechanism for the formation of B.



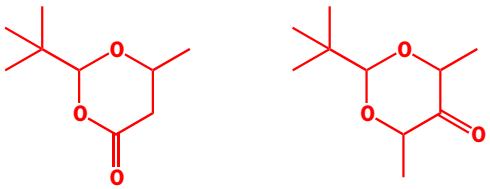
3 In Chapter 20 we set a problem asking you what the stereochemistry of a product was. Now we can give you the NMR spectrum of the product and ask: how do we *know* the stereochemistry of the product? You need only the partial NMR spectrum: δ_H 3.9 (1H, ddq, *J* 12, 4, 7) and 4.3 (1H, dd, *J* 11, 3).



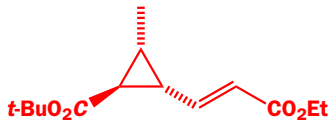
4 Two diastereoisomers of this cyclic keto-lactam have been prepared. The NMR spectra have many overlapping signals but the proton marked in green can clearly be seen. In isomer A it is δ_H 4.12 (1H, q, *J* 3.5), and isomer B has δ_H 3.30 (1H, dt, *J* 4, 11, 11). Which isomer has which stereochemistry?



5 How would you determine the stereochemistry of these two compounds?

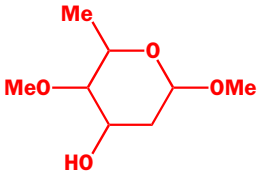


6 The structure and stereochemistry of the antifungal antibiotic ambruticin was in part deduced from the NMR spectrum of this simple cyclopropane. Interpret the NMR spectrum and show how it gives definite evidence on the stereochemistry.



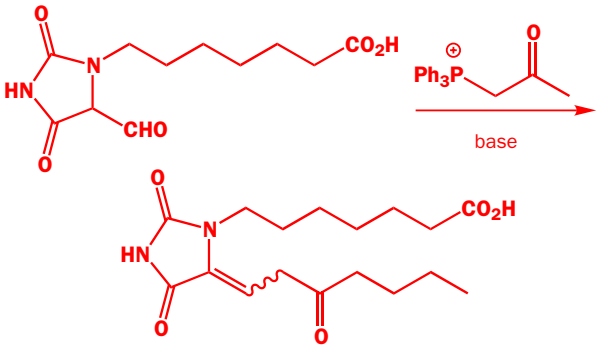
δ_H 1.13 (3H, d, *J* 8), 1.32 (3H, t, *J* 7), 1.47 (9H, s), 1.71 (1H, t, *J* 5), 2.2 (1H, ddq, *J* 5, 12, 7), 4.3 (2H, q, *J* 8), 6.05 (1H, d, *J* 17), and 6.75 (1H, dd, *J* 17, 12)

7 One of the sugar components in the antibiotic kijanimycin has the gross structure and NMR spectrum shown below. What is its stereochemistry? All couplings in Hz; signals marked * exchange with D_2O.

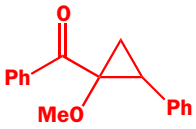


δ_H 1.33 (3H, d, *J* 6), 1.61* (1H, broad s), 1.87 (1H, ddd, *J* 14, 3, 3.5), 2.21 (1H, ddd, *J* 14, 3, 1.5), 2.87 (1H, dd, *J* 10, 3), 3.40 (3H, s), 3.47 (3H, s), 3.99 (1H, dq, *J* 10, 6), 1.33 (3H, d, *J* 6), 4.24 (1H, ddd, *J* 3, 3, 3.5), and 4.79 (1H, dd, *J* 3.5, 1.5)

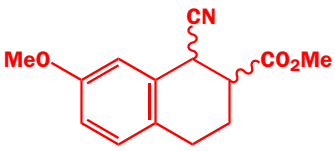
8 The structure of a Wittig product intended as a prostaglandin model was established by the usual methods—except for the geometry of the double bond. Irradiation of a signal at 3.54 (2H, t, *J* 7.5) led to an enhancement of another signal at δ_H 5.72 (1H, t, *J* 7.1) but not to a signal at δ_H 3.93 (2H, d, *J* 7.1). What is the stereochemistry of the alkene? How is the product formed?



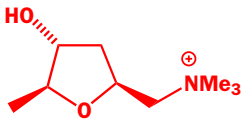
9 How would you determine the stereochemistry of this cyclopropane? The NMR spectra of the three protons on the ring are given: δ_H 1.64 (1H, dd, *J* 6, 8), 2.07 (1H, dd, *J* 6, 10), and 2.89 (1H, dd, *J* 10, 8).



10 A chemical reaction produces two diastereoisomers of the product. Isomer A has δ_H 3.08 (1H, dt, *J* 4, 9, 9) and 4.32 (1H, d, *J* 9, 4) while isomer B has δ_H 4.27 (1H, d, *J* 4). The other protons overlap. Isomer B is converted into isomer A on treatment with base. What is the stereochemistry of A and B?

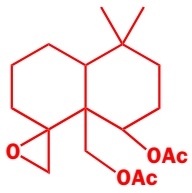


11 Muscarine, the poisonous principle of the death cap mushroom, has the following structure and proton NMR spectrum. Assign the spectrum. Can you see definite evidence for the stereochemistry? All couplings in Hz; signals marked * exchange with D_2O.



δ_H 1.16 (3H, d, *J* 6.5), 1.86 (1H, ddd, *J* 12.5, 9.5, 5.5), 2.02 (1H, ddd, *J* 12.5, 2.0, 6.0), 3.36 (9H, s), 3.54 (1H, dd, *J* 13, 9.0), 3.74 (1H, dd, *J* 13, 1.0), 3.92 (1H, dq, *J* 2.5, 6.5), 4.03 (1H, m), 4.30* (1H, d, *J* 3.5), and 4.68 (1H, m).

12 An antifeedant compound that deters insects from eating food crops has the gross structure shown below. Some of the NMR signals that can clearly be made out are also given. Since NMR coupling constants are clearly useless in assigning the stereochemistry, how would you set about it?



δ_H 2.22 (1H, d, *J* 4), 2.99 (1H, dd, *J* 4, 2.4), 4.36 (1H, d, *J* 12.3), 4.70 (1H, dd, *J* 4.7, 11.7), 4.88 (1H, d, *J* 12.3)

13 The seeds of the Costa Rican plant *Ateleia herbert smithii* are avoided by all seed eaters (except a weevil that adapts them for its defence) because they contain two toxic amino acids (IR spectra like other amino acids). Neither compound is chiral. What is the structure of these compounds? They can easily be separated because one (A) is soluble in aqueous base but the other (B) is not.

A is $C_6H_9NO_4$ (mass spectrum) and has δ_C 34.0 (d), 40.0 (t), 56.2 (s), 184.8 (s), and 186.0 (s). Its proton NMR has three exchanging protons on nitrogen and one on oxygen and two complex signals at δ_H 2.68 (4H, A_2B_2 part of A_2B_2X system) and 3.37 (X part of A_2B_2X system) with J_{AB} 9.5, J_{AX} 9.1, and J_{BX} small.

B is $C_6H_9NO_2$ (mass spectrum) and has δ_C 38.0 (d), 41.3 (t), 50.4 (t), 75.2 (s), and 173.0 (s). Its proton NMR spectrum contains two exchanging protons on nitrogen and δ_H 1.17 (2H, ddd, *J* 2.3, 6.2, 9.5), 2.31 (2H, broad m), 2.90 (1H, broad t, *J* 3.2), and 3.40 (2H, broad s).

Because the coupling pattern did not show up clearly as many of the coupling constants are small, decoupling experiments were used. Irradiation at δ_H 3.4 simplifies the δ_H 2.3 signal to (2H, ddd, *J* 5.8, 3.2, 2.3), sharpens each line of the ddd at 1.17, and sharpens the triplet at 2.9.

Irradiation at 2.9 sharpens the signals at 1.17 and 2.9 and makes the signal at 2.31 into a broad doublet, *J* about 6. Irradiation at 2.31 sharpens the signal at 3.4 slightly and reduces the signals at 2.9 and 1.17 to broad singlets. Irradiation at 1.17 sharpens the signal at 3.4 slightly so that it is a broad doublet, *J* about 1.0, sharpens the signal at 2.9 to a triplet, and sharpens up the signal at 2.31 but irradiation here had the least effect.

This is quite a difficult problem but the compounds are so small (C_6 only), have no methyl groups, and have some symmetry so you should try drawing structures at an early stage.

Stereoselective reactions of cyclic compounds

33

Connections

Building on:

- Stereochemistry ch16
- Conformational analysis ch18
- Determination of stereochemistry by spectroscopy ch32

Arriving at:

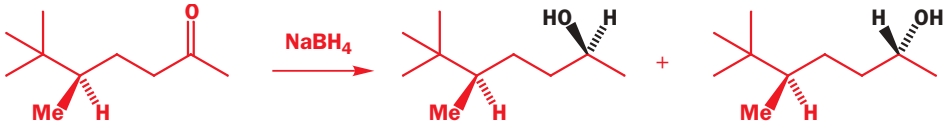
- Stereoselectivity in cyclic systems is easy to understand
- Flattened four- and five-membered rings are attacked *anti* to large substituents
- Flattened six-membered rings are attacked from an axial direction
- Bicyclic structures are attacked on the outside face
- Tethering together nucleophile and electrophile forces one stereochemical outcome
- Hydrogen-bonding can reverse the normal stereochemical outcome of a reaction

Looking forward to:

- Diastereoselectivity ch34
- Asymmetric synthesis ch45
- Organic synthesis ch53
- Pericyclic reactions ch35–ch36

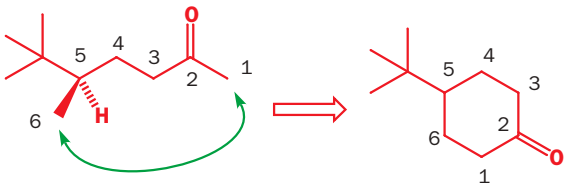
Introduction

This chapter is about rings and stereochemistry. Stereochemistry is easier to understand in cyclic compounds and that alone might make a separate chapter worthwhile. But there is something much more fundamental behind this chapter. Stereochemistry is better behaved in cyclic compounds. Suppose you were to reduce this ketone to one of the corresponding alcohols.



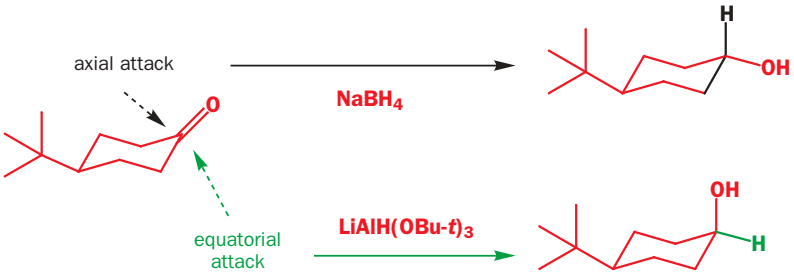
stereochemistry?

There would be very little chance of any control of stereochemistry at the new stereogenic centre (shown in black). A more or less 50:50 mixture of the two diastereoisomers would be expected. However, if we join up the molecule into a ring, things are suddenly quite different. (This is not, of course, a chemical reaction—just a thought process!)



The cyclic ketone has a fixed conformation controlled by the determination of the *t*-butyl group to be equatorial. Reduction can be controlled to give almost exclusively either the axial or the equatorial alcohol as we explained in Chapter 18. Large reagents prefer to approach equatorially while small reagents like to put the new OH group into an equatorial position. These are stereo-*selective* reactions, and, because the two different outcomes are diastereoisomers, we can call them **diastereoselective**.

■ If your memory of Chapter 18's discussion of axial and equatorial attack on cyclohexanones is dim, you should refresh it now. We shall use several examples that build on what we said there (p. 000).



The key to the difference is in the conformations. The cyclic ketone has one conformation and the two approaches to the faces of the ketone are very different. The open-chain compound has an indefinite number of conformations as rotation about all the C–C bonds is possible. In any one conformation, attack on one face of the ketone or the other may happen to be preferred, but on average there will be very little difference. There is all the difference in the world between cyclic and open-chain compounds when it comes to stereoselective reactions. This is why we have made this topic into two chapters: this one (33) dealing with rings, the next (34) with what happens without rings.

In this chapter we shall look at reactions happening to cyclic compounds, reactions that close rings (cyclizations), and reactions with cyclic intermediates and with cyclic transition states. We shall investigate what happens to stereochemistry when two (or even more) rings are joined together at a bond or at an atom. We shall see how stereochemical effects change as the ring size increases from three atoms to eight or more. You will find that you have met some of the reactions before in this book. This chapter collects them together and explains the principles of stereochemical control in cyclic systems as well as introducing some new reactions.

■ We introduced to you the usual conformations of small rings in Chapter 18. We will briefly revisit that material in this section, and show you how it affects the stereoselectivity of the reactions of rings.

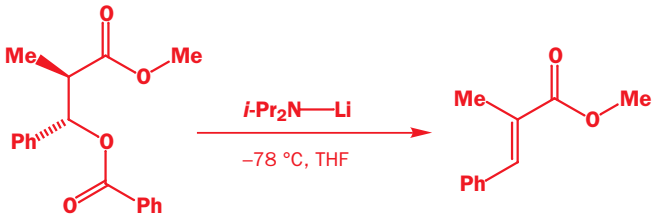
Reactions on small rings

Four-membered rings can be flat

The smallest ring that we can conveniently work on is four-membered. Saturated four-membered rings have a slightly bent conformation but four-membered lactones are flat. The enolates of these lactones can be made in the usual way with LDA at –78 °C and are stable at that temperature.

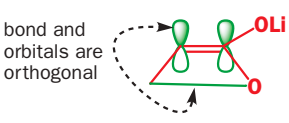
β-lactone lithium enolate

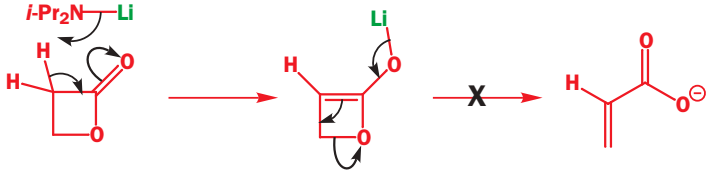
The formation of the lithium enolate is straightforward but it might be expected to be unstable because of a simple elimination reaction. It is not possible to make open-chain lithium enolates with β oxygen substituents like this because they do undergo elimination.



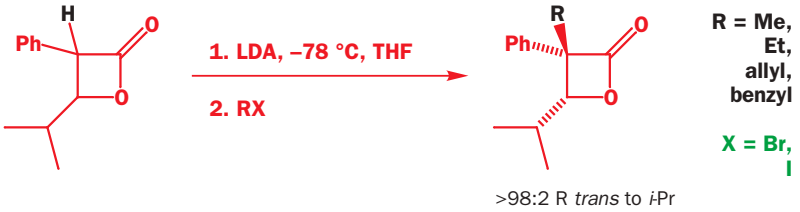
▶ This is a **stereoelectronic effect**, due to the spatial arrangement of orbitals, and we will discuss more of these in Chapters 38 and 42.

But, in the four-membered ring, the p orbitals of the enolate and the C–O single bond are orthogonal (see drawing in margin) so that no interaction between them, and no elimination, can occur. The enolate can be combined with electrophiles in the usual way (Chapters 26 and 27).



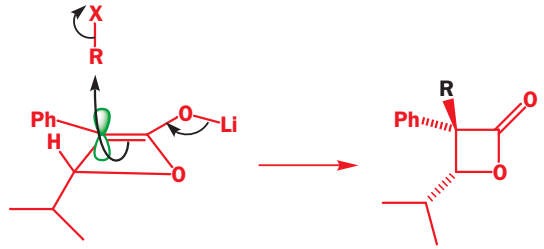


If the β-lactone has a substituent already then there may be a choice as to which face of the enolate is attacked by an electrophile. Simple alkylation with a variety of alkyl halides gives essentially only one diastereoisomer of the product.

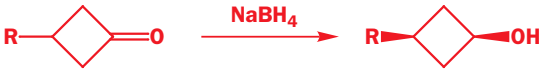


>98:2 R *trans* to *i*-Pr

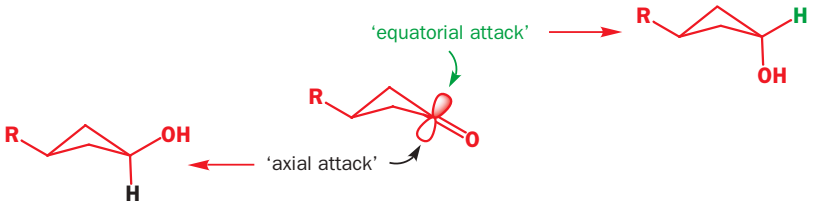
The enolate, as we have seen, is planar, the phenyl group is in the plane (so it doesn't matter which of the two possible diastereoisomers of the starting material is used), and the isopropyl group is the only thing out of the plane. The electrophile simply adds to the face of the enolate not blocked by the isopropyl group. This is a very simple case of a diastereoselective reaction.



Reduction of substituted four-membered ring ketones is usually reasonably stereoselective. If the substituent is in the 3-position and small reagents like $NaBH_4$ are used, the *cis* isomer is favoured.



This result sounds very like the results already noted for six-membered rings and the explanation is similar. Saturated four-membered rings—even the ketones—are slightly puckered to reduce eclipsing interactions between hydrogen atoms on adjacent carbon atoms, and 'axial' attack by the small nucleophile gives the more stable *cis* product having both substituents 'equatorial'.



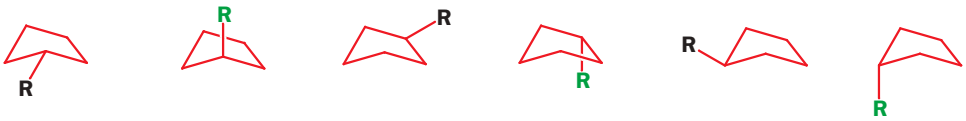
Five-membered rings are flexible

We discussed the conformation of some five-membered rings in Chapter 32: a saturated five-membered ring has a conformation variously called a 'half-chair' or an 'envelope'. It does look a bit like an opened envelope with one atom at the point of the flap, or it looks like most of (five-sixths rather than half?) a chair cyclohexane.

cyclohexane

cyclopentane

At any one moment, one of the carbon atoms is at the point of the envelope but rapid ring flipping equilibrates all these conformers so that all five atoms are, on average, the same. Substituted cyclopentanes can have substituents in pseudoaxial or pseudoequatoral positions or on the point position, like this.

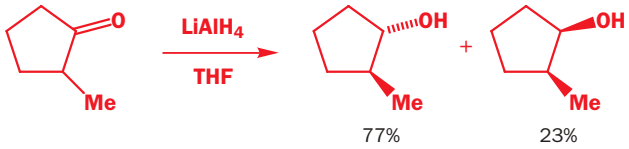


pseudoequatorial and pseudoaxial substituents on cyclopentanes

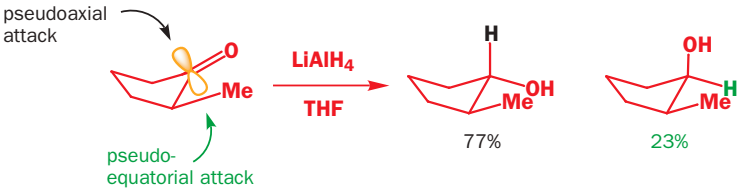
▶ The stereoselectivity we are discussing in this chapter is diastereoselectivity: we are not concerned with enantiomers, and all of our discussions are equally valid whether the starting materials are racemic or enantiomerically pure. The product here, as in many other examples in the chapter, is racemic, so we could write (±) underneath the structure.

▶ You may recall (Chapter 32) that *cis* and *trans* couplings in proton NMR spectra of five-membered rings are often the same.

The result is a very flexible system that often behaves in stereoselective reactions as if the two positions on any carbon atom are the same.

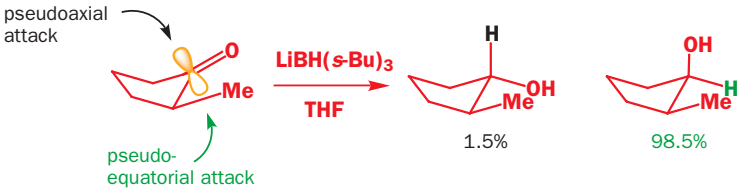


As you can see, reduction of 2-substituted cyclopentanones may not be very stereoselective. The substituent probably occupies a pseudoequatorial position and the two faces of the ketone are very similar.

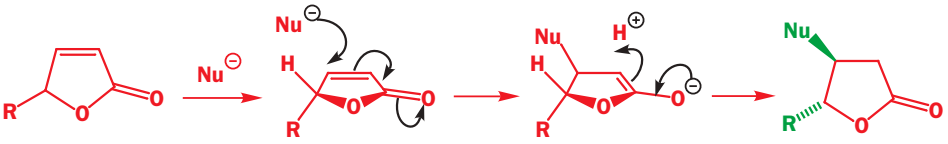


What selectivity there is (about 3:1) favours pseudoaxial attack in the conformation drawn as is reasonable for a small nucleophile. The use of a much more bulky reducing agent such as $LiBH(s\text{-}Bu)_3$ dramatically reverses and increases the stereoselectivity. Essentially only the *cis* compound is formed because the bulky reagent attacks the side of the carbonyl opposite to the methyl group.

■ If the conformation of the five-membered ring is fixed in a bridged (caged) structure, the stereoselectivity dramatically increases, even with $LiAlH_4$, as you will see later in the chapter (p. 000)



When there are two or three trigonal carbons in the ring, the ring is flatter, and reactions such as enolate alkylation and conjugate addition give excellent stereoselectivity even with a simple cyclopentane ring. Unsaturated five-membered lactones ('butenolides') give a very clear illustration of stereochemically controlled conjugate addition. There is only one possible stereogenic centre and the ring is almost planar so we expect nucleophilic attack to occur from the less hindered face. Cuprates are good nucleophiles for this reaction and here Me_2CuLi adds to the unsaturated lactone.



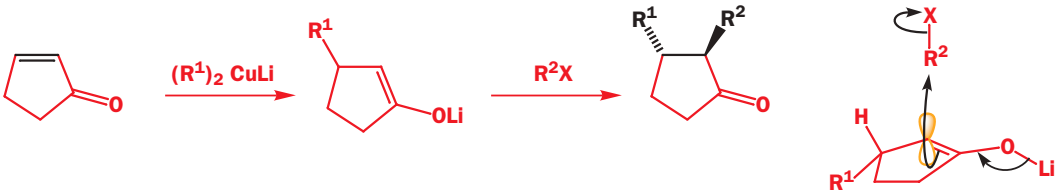
▶ This would be a good point at which to remind you of what we stressed in Chapter 16. If all the starting materials are achiral or racemic, the products must be too. That has been the case in many of the reactions so far in this chapter: we haven't put in (±) under every compound but we could have done. But here we do have a single enantiomer of starting material, so we get a single enantiomer of product. Diastereoselectivity is the same whether the starting material is enantiomerically pure or racemic.

The starting material was a single enantiomer and hence so is the product—an insect pheromone.

single enantiomer of starting material

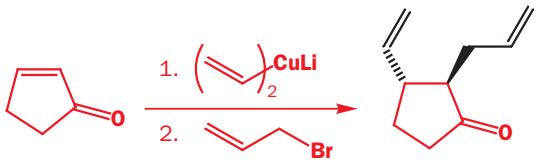
66% yield
(3*S*,4*R*)-(+)-eldanolide

It is not even necessary to have a stereogenic centre in an unsaturated ring if we want to create stereochemistry. A tandem conjugate addition and alkylation creates two new stereogenic centres in one operation. The conjugate addition of a lithium cuprate makes a lithium enolate, which will react in turn with an alkyl halide. The product is usually *trans*.

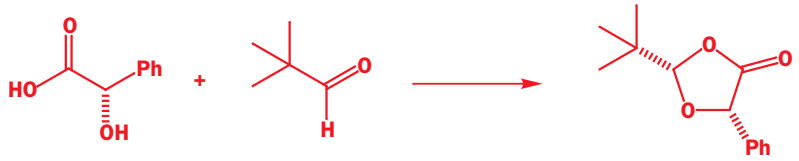


■ The conjugate addition forms a lithium enolate regiospecifically, and that was why you met this sequence in Chapter 26. We showed you a dramatic use of the stereoselectivity there as well, in a synthesis of a prostaglandin (p. 000).

The key step is the alkylation of the enolate intermediate. Enolates in five-membered rings are almost flat and the incoming alkyl halide prefers the less hindered face away from the recently added group R. The example below shows that, if both new groups have double bonds in their chains, it is easier to add a vinyl group as the nucleophile and an allyl group as an electrophile.

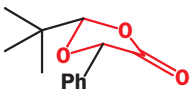


Our main example of enolate reactions in five-membered rings is one of some general importance. It illustrates how stereochemical information can be transmitted across a ring even though the original source of that information may be lost during the reaction. That may sound mysterious, but all will become clear. The first reaction is to make a five-membered cyclic acetal from an optically active hydroxy-acid. Our example shows (*S*)-(+)-mandelic acid reacting with *t*-BuCHO.



(*S*)-(+)-mandelic acid — 24:1 *cis*:*trans*

▶ Check that you can write the mechanisms for acetal formation (Chapter 14). Acetal formation is under thermodynamic control (Chapter 13), so the product produced is the more stable.

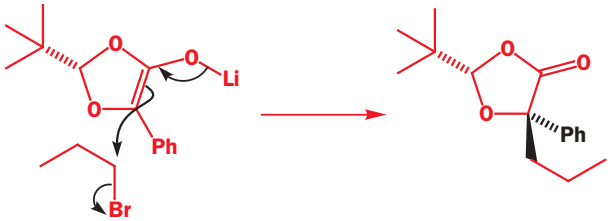


both substituents pseudoequatorial

Acetal formation involves nucleophilic attack of the OH group on the aldehyde so there is no change at the stereogenic centre. The stereochemistry of the new (acetal) centre may surprise you—why should the *cis*-isomer be so favoured? This is a conformational effect as both substituents can occupy pseudoequatorial positions.

Now, if we make the lithium enolate with LDA, the original stereogenic centre is destroyed as that carbon becomes trigonal. The only stereogenic centre left is the newly introduced one at the acetal position.

The ring is now flattened by the alkene and reaction of the enolate with an electrophile is again a simple matter of addition to the face of the enolate opposite to the *t*-butyl group.



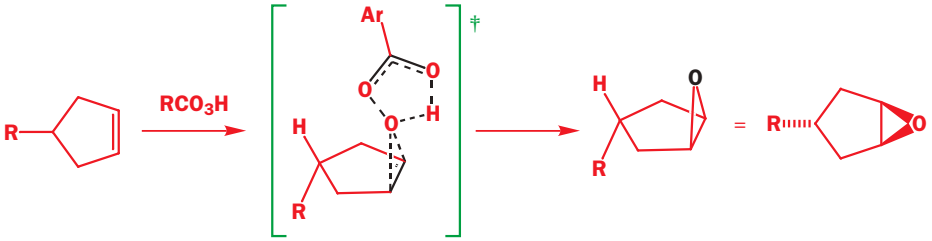
84% yield
>97:3 diastereoselectivity

If the acetal is now hydrolysed, the new stereogenic centre is revealed as an alkylated version of the starting material. It may appear that the alkylation has happened stereospecifically with retention, but what has really happened is that the new stereogenic centre in the acetal intermediate has relayed the stereochemical information through the reaction.

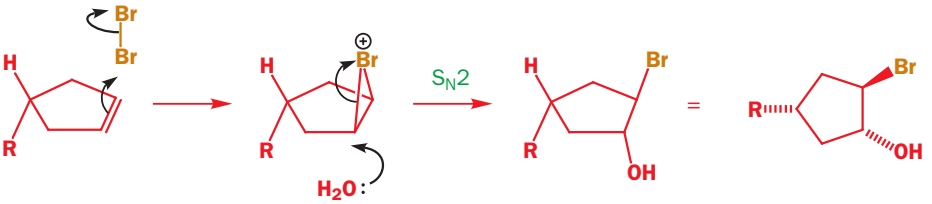
Five-membered rings also allow us to explore electrophilic attack on alkenes. A simple 4-substituted cyclopentene has two different faces—one on the same side as the substituent and one on the opposite side. Epoxidation with a peroxy-acid occurs preferentially on the less hindered face.

▶ Note that this reaction is diastereoselective—but neither starting material nor products are chiral. Diastereoselectivity need have nothing to do with chirality!

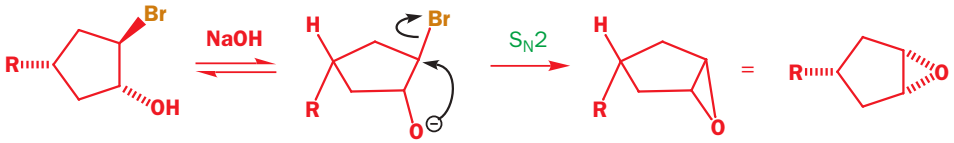
■ The mechanism of RCO_3H epoxidation was discussed on p. 000.



In the transition state (marked ‡) the peroxyacid prefers to be well away from R, even if R is only a methyl group. The selectivity is 76:24 with methyl. The opposite stereoselectivity can be achieved by bromination in water. The bromonium ion intermediate is formed stereoselectively on the less hindered side and the water is forced to attack stereospecifically in an S_N2 reaction from the more hindered side.

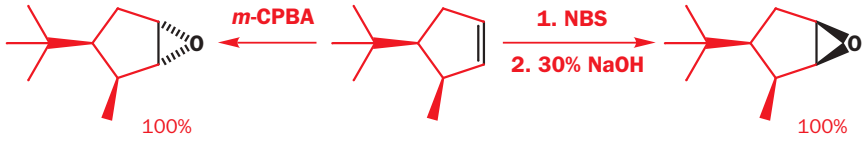


Treatment of the product with base (NaOH) gives an epoxide by another S_N2 reaction in which oxygen displaces bromide. This is again stereospecific and gives the epoxide on the same side as the group R.



Two substituents on the *same side* of a five-membered ring combine to dictate approach from the other side by any reagent, and the two epoxides can be formed each with essentially 100% selectivity.

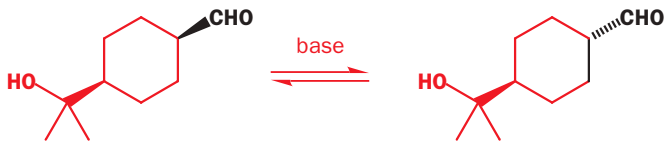
■ Remember—NBS acts as a source of electrophilic bromine: see p. 000 of Chapter 20.



Stereochemical control in six-membered rings

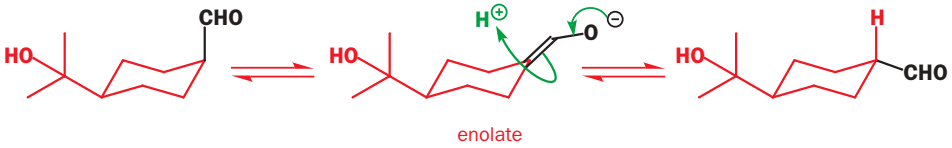
From five-membered rings we move on naturally to six-membered rings. As well as the opportunity for more stereogenic centres around the larger ring, we have the additional prospect of conformational control—something special to six-membered rings because of their well-defined conformational properties. We shall start with simple reactions occurring on the opposite face to existing substituents and move on to conformational control, particularly to one theme—axial addition.

First, something about thermodynamic control. Because of the strong preference for substituents to adopt the equatorial position, diastereoisomers may equilibrate by processes such an enolization. For example, this fine perfumery material is made worthless by enolization.



intense flowery perfume odourless

The situation is bad because the worthless compound is preferred in the equilibrium mixture (92:8). This is because the two substituents are both equatorial in the *trans*-isomer.



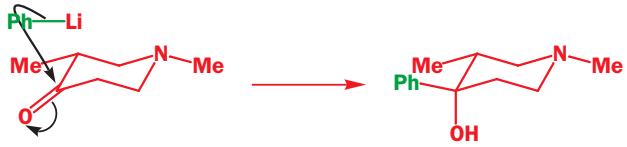
enolate

Although a disadvantage here, in other cases equilibration to the more stable all-equatorial conformation can be a useful source of stereochemical control. You will very shortly see an example of this.

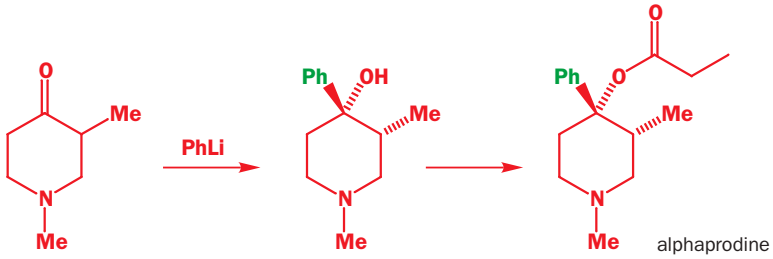
Stereoselectivity in reactions of six-membered rings

We discussed the reduction of cyclohexanones in Chapter 18 and established that reducing agents prefer the equatorial approach while small reagents may prefer to put the OH group in the more stable equatorial position. If the nucleophile is not H but something larger than OH then we can expect equatorial attack to dominate both because of ease of approach and because of product stability.

A simple example is the addition of PhLi to the heterocyclic ketone below which has one methyl group next to the carbonyl group. This methyl group occupies an equatorial position and the incoming phenyl group also prefers the equatorial approach so that good stereoselectivity is observed.



This product was used in the preparation of the analgesic drug alphaprodine. We shall represent the reaction now in configurational terms. It is important for you to recognize and be able to draw both configurational (as below) and conformational (as above) diagrams.

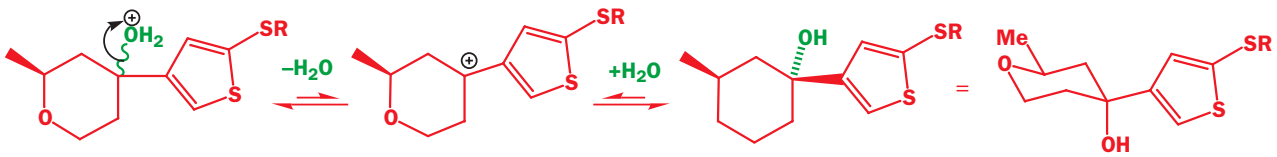


alphaprodine

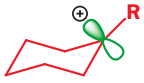
When the stereogenic centre is further away from the site of attack, the stereoselectivity may not be so good. Zeneca have announced the manufacture of a drug by the addition of a lithiated thiophene to another heterocyclic ketone, which initially gave a mixture of diastereoisomers.

mixture of diastereoisomers

Such a mixture is no good for manufacture of a pure drug, but the compound can be equilibrated in dilute acid by repeated S_N1 formation of a tertiary benzylic cation and recapture by water so that the required product (which is more stable as it has both Me and the thiophene equatorial) dominates by 92:8 and can be purified by crystallization. The unwanted isomer can be recycled in the next batch.



chair conformation of cyclohexyl cation



chair conformation of cyclohexanone

only one trigonal (sp^2) atom in the ring: chair conformation

■

We introduced this idea in Chapter 18, and we shall now develop it further.

In these reactions the molecule has a free choice whether to place a substituent in an axial or equatorial position and this is the only consideration because the starting materials in the reactions—ketones or carbocations—have six-membered rings that are already in the chair conformation even though they have one trigonal (sp^2) atom in the ring.

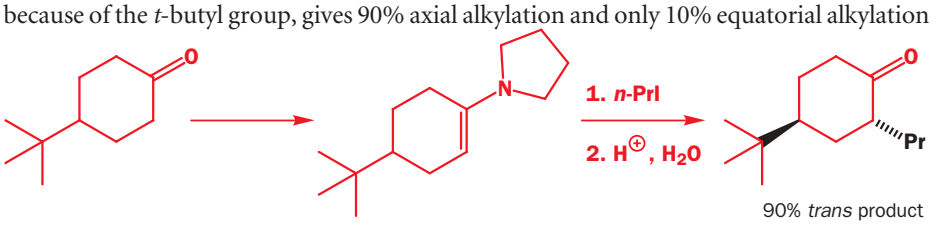
Axial attack is preferred with unsaturated six-membered rings

When the starting material for a reaction has two or more trigonal (sp^2) atoms in the ring, it is no longer in the chair conformation. In these cases, the stereochemistry of the reaction is likely to be driven by the need for the transition state and product to have a chair rather than a boat conformation. This can override the preference for substituents to go into equatorial positions. This is the basis for axial attack on enolates, cyclohexenes, and enones.

● The number of trigonal carbon atoms in the ring is important

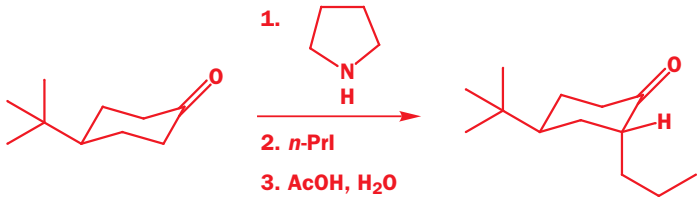
- **Six-membered rings with one trigonal (sp^2) carbon atom can undergo axial or equatorial attack**
- **Six-membered rings with two or more trigonal carbon atoms undergo *axial attack* in order to form chairs rather than boats. The final product may end up with axial or equatorial substitution, but this is not a consideration in the reaction itself**

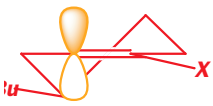
Alkylations of enolates, enamines, and silyl enol ethers of cyclohexanone usually show substantial preference for axial attack. The enamine of 4-*t*-butylcyclohexanone, which has a fixed conformation because of the *t*-butyl group, gives 90% axial alkylation and only 10% equatorial alkylation with *n*-PrI.



90% *trans* product

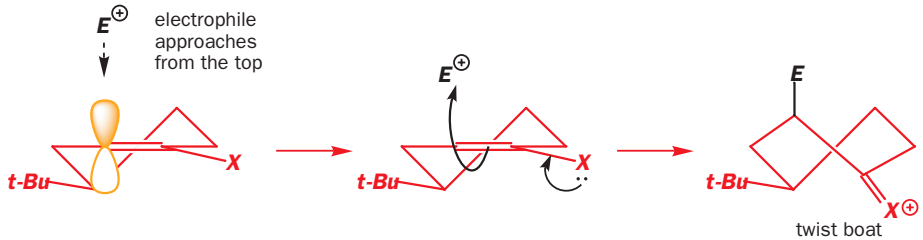
It is a simple matter to show that the preferred product has the new propyl group in the axial position because both the starting ketone and the product have chair conformations with the *t*-butyl equatorial.





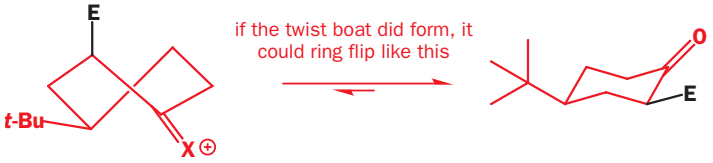
To get at the explanation we need to look at the conformation of the enamine intermediate. At this point we shall generalize a bit more and write a structure that represents any enol derivative where X may be OH, O^-, $OSiMe_3$, NR_2, and so on. The conformation has a double bond in the ring, and is a partially flattened chair, as described in Chapter 18.

The *t*-butyl group is in an equatorial position at the back of the ring. The electrophile must approach the enol derivative from more or less directly above or below because only then can it attack one of the lobes of the p orbital at the enol position shown in yellow. The top of the molecule looks to be more open to attack so we shall try that approach first.

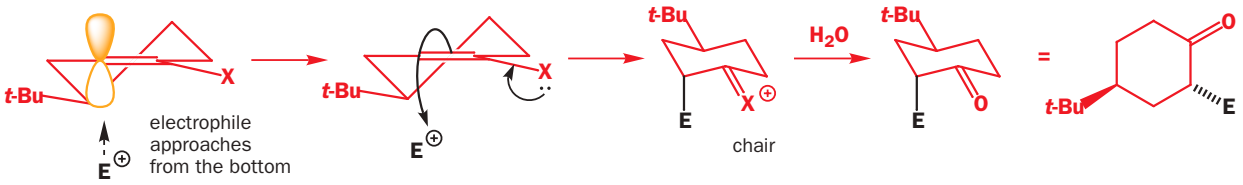


twist boat

As the electrophile bonds to the trigonal carbon atom, that atom must become tetrahedral and it does so by forming a vertical bond upwards. The result is shown in the diagram—the ring turns into a twist-boat conformation. Now, of course, after the reaction is over, the ring can flip into a chair conformation and the new substituent will then be equatorial, but that information is not present in the transition state for the reaction. We could say that, at the time of reaction, the molecule doesn't 'know' it can later be better off and get the substituent equatorial: all it sees is the formation of an unstable twist boat with a high-energy transition state leading to it.



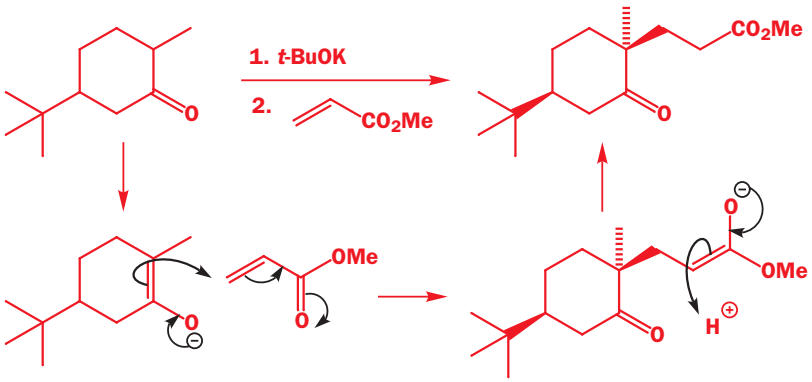
Attack from the apparently more hindered bottom face makes the trigonal carbon atom turn tetrahedral in the opposite sense by forming a vertical bond to the electrophile downwards. The ring goes directly to a chair form with the electrophile in the axial position.



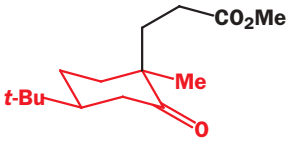
When the carbonyl group is restored by hydrolysis (if necessary—X may be O already) the ring need not flip: it's already a chair with the *t*-butyl equatorial, and the new substituent is axial on the chair. This is the observed product of the reaction.

It's important that you understand what is going on here. The reagent *has* to attack from an axial direction to interact with the p orbital. If it attacks from above, the new substituent is axial on an unstable twist boat. If it attacks from below, the new substituent is axial on a chair—granted, this is not as good as equatorial on a chair, but that's not an option—it has to be axial on something, and a chair is better than a twist boat. So this is the product that forms. It's just hard luck for the substituent that it can't know that *if it did* weather it out on the twist boat it could later get equatorial—it plumps for life on the easy chair and so has to be content with ending up axial.

Here is an example with an unsaturated carbonyl compound as an electrophile: the reaction is Michael addition. The ketone here is slightly different—it has the *t*-butyl group in the 3- rather than the 4-position and the reacting centre becomes quaternary during the Michael reaction. But the result is still axial attack.



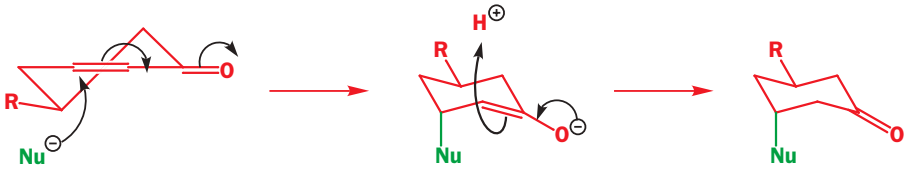
This result is more impressive because the large electrophile ends up on the *same* side of the ring as the *t*-butyl group, so the stereoselectivity cannot be based on any simple idea of reaction on the less hindered side of the ring. It is genuine axial attack, as the conformational diagram of the product confirms.



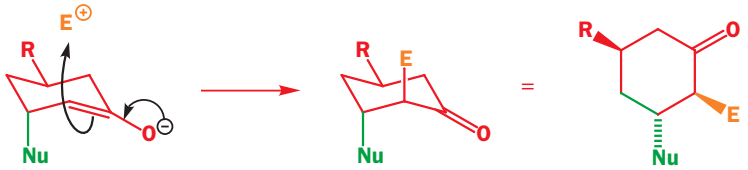
Cyclohexenones are even flatter than cyclohexenes, but it is convenient to draw them in a similar conformation. Conjugate addition to this substituted cyclohexenone gives the *trans* product.

▶ Beware: you also get the right answer for the wrong reason by saying that the nucleophile approaches from the less hindered side.

This is also axial addition to form a chair directly (rather than a twist boat) with the nucleophile approaching from the bottom. We must draw the ring as a flattened chair.

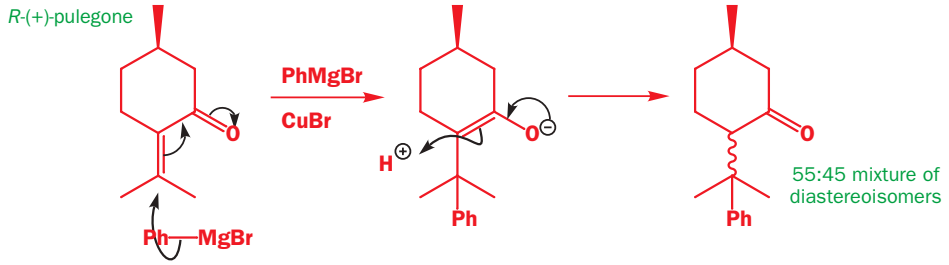


The 5-alkyl cyclohexenone that we have chosen as our example gives the best results. The mechanism suggests that the enolate intermediate is protonated on the top face (axial addition again) though we cannot tell this. But, if we carry out a tandem reaction with the enolate trapped by a different electrophile, the product is again that of axial attack.

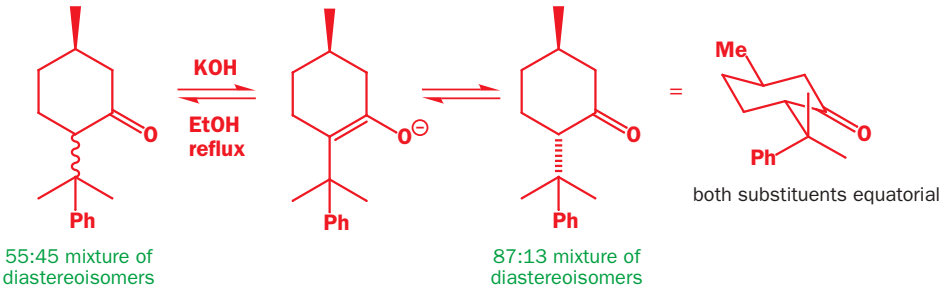


■ You will see 8-phenylmenthol used as a 'chiral auxiliary' in Chapter 45.

We shall end this section on conformational control in six-membered rings with the preparation of a useful chiral molecule 8-phenylmenthol from the natural product (*R*)-(+)-pulegone. The first step is a conjugate addition to an exocyclic alkene. A new stereogenic centre is formed by protonation of the enolate intermediate but with virtually no stereoselectivity.

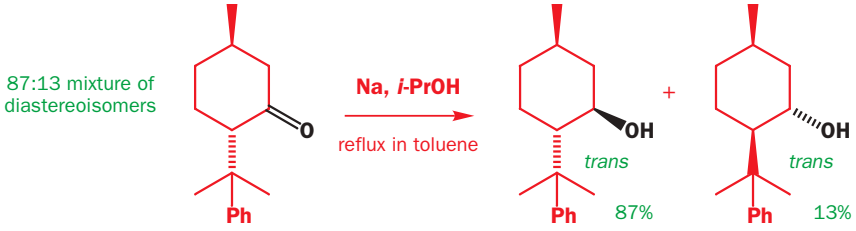


Now thermodynamic control can be brought into play. The position next to the ketone can be epimerized via the enolate to give the more stable isomer with both substituents equatorial. This improves the ratio of diastereoisomers from 55:45 to 87:13.



Now the ketone can be reduced with a small reagent—Na in *i*-PrOH works well—to put the hydroxyl group equatorial. This means that all the product has OH *trans* to the large group next to

the ketone, though it is still an 87:13 mixture of diastereoisomers with respect to the relative configuration at the centre bearing Me.

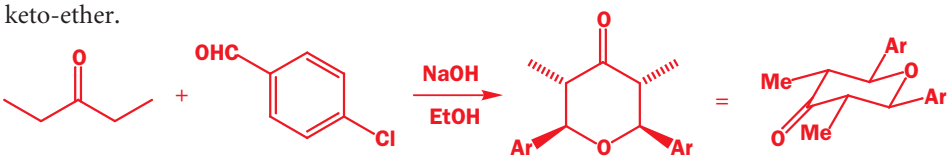


These alcohols can be separated (they are, of course, diastereoisomers and not enantiomers) and the major, all-equatorial one is useful one (see Chapter 45). This is an impressive example of conformational control by thermodynamic and by kinetic means using only a distant methyl group in a six-membered ring.

▶ Na in *i*-PrOH is a single-electron Birch-type reduction (Chapter 25). You can't get much smaller than an electron!

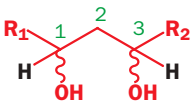
Conformational control in the formation of six-membered rings

In Chapter 32 we solved a structural problem from the aldol reaction of pentan-3-one and 4-chlorobenzaldehyde in basic solution. The product turned out to be a six-membered cyclic keto-ether.

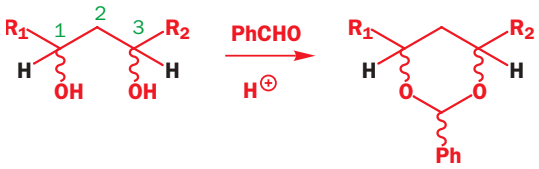


Once you know the gross structure of the product, the stereochemistry should be no surprise. This is a typical thermodynamically controlled formation of a six-membered ring with all the substituents equatorial.

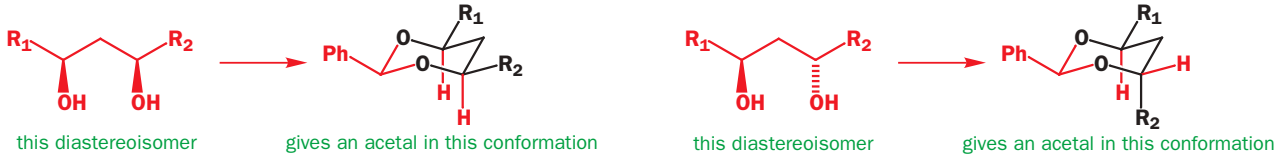
Any reaction that is reversible and that forms a six-membered ring can be expected to put as many substituents as possible in the thermodynamically favourable equatorial position. This principle can be used in structure determination too. Suppose you have one diastereoisomer of a 1,3-diol and you want to find out which stereoisomer it is.



Having read Chapter 32 you might think of using the NMR coupling constants of the two black protons. But that will do no good because the molecule has no fixed conformation. Free rotation about all the σ bonds means that the Karplus equation cannot be used as a time-averaged *J* value of about 6–7 Hz will probably be observed for both protons regardless of stereochemistry. But suppose we make an acetal from the 1,3-diol with benzaldehyde.



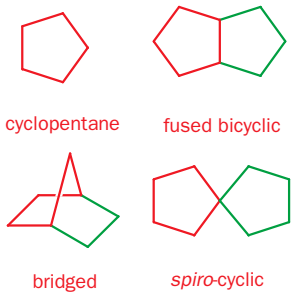
This may not seem to help much. But acetal formation is under thermodynamic control, so the most stable possible conformation will result with the large phenyl group equatorial and the two R groups either both equatorial or one equatorial and one axial, depending on which diastereoisomer you started with.



Now the molecule has a fixed conformation and the coupling constants of the black Hs to the neighbouring CH_2 group can be determined—an axial H will show one large *J* value, an equatorial H only small *J* values.

This section has been strong on thermodynamic control but weak on the more common kinetic control. This will be remedied in Chapter 35 where you will meet the most important cyclization reaction of all—the Diels–Alder reaction. It is under kinetic control and there is a great deal of stereochemistry associated with it.

Stereochemistry of bicyclic compounds

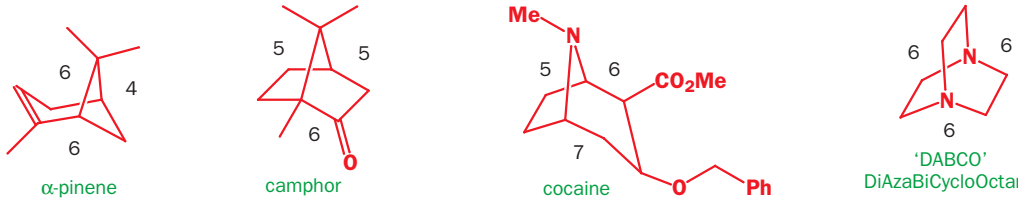


There are broadly three kinds of bicyclic compounds, some of which you have met before (Chapter 18, for example). If we imagine adding a new five-membered ring to one already there, we could do this in a bridged, fused, or *spiro* fashion. Bridged bicyclic compounds are just what the name implies—a bridge of atom(s) is thrown across from one side of the ring to the other. Fused bicyclic compounds have one *bond* common to both rings, while *spiro* compounds have one *atom* common to both rings.

You will notice that these three types of bicyclic compounds with five-membered rings have different numbers of atoms added to a 'parent' five-membered ring. The bridged compound has two extra atoms, the fused compound three, and the *spiro* compound four. These are marked in green with the original five-membered ring in red. We shall consider stereoselectivity in each of these types of bicyclic ring systems, starting with bridged structures.

▶ The bicyclic compound also has a six-membered ring across the bottom while the fused compound has an eight-membered ring round the perimeter.

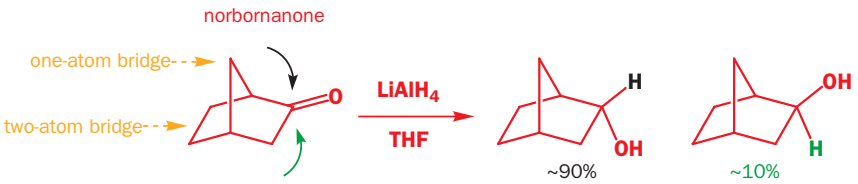
A selection of important bridged bicyclic compounds is shown below, with the various ring sizes indicated in black.



Bridged structures (sometimes called cage structures) are generally very rigid—the only exception among these examples is the bottom right-hand portion of cocaine. This rigidity is reflected in the stereochemistry of their reactions.

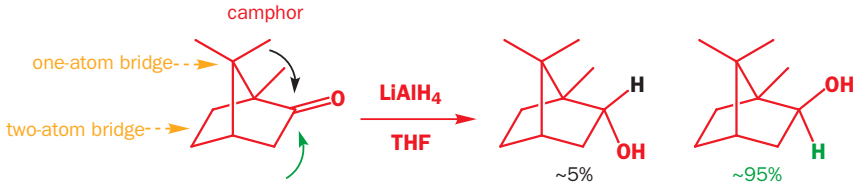
Attack on this unsubstituted bridged ketone—norbornanone—occurs predominantly from the side of the one-atom bridge rather than the two-atom bridge.

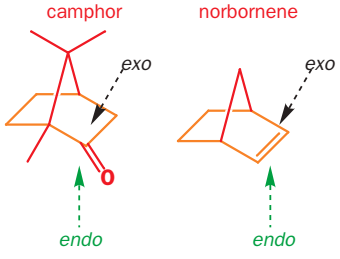
■ This result is in marked contrast to the outcome of $LiAlH_4$ attack on the flexible five-membered rings which we showed on p. 000.



■ We told you about the Bürgi–Dunitz angle—the line of approach of a nucleophile to a C=O group—in Chapter 6. Now you see one reason why it is important.

This selectivity is completely reversed in camphor because the one-atom bridge then carries two methyl groups. One of these must project over the line of approach of the hydride reducing agent.





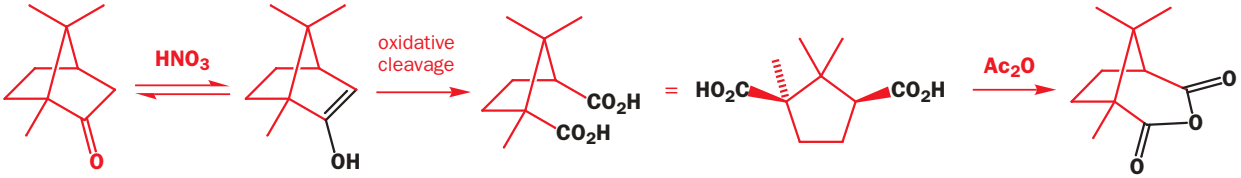
The two methyl groups on the bridge of the camphor molecule are key features in stereoselective reactions—take them away and the result often changes dramatically. This bicyclic system, with and without methyl groups, has been so widely used to establish stereochemical principles that the two faces of, say, the ketone group in camphor, or the alkene in norbornene, have been given the names *endo* and *exo*. These refer to inside (*endo*) and outside (*exo*) the boat-shaped six-membered ring highlighted in orange.

Like $LiAlH_4$ reduction, addition of a Grignard reagent to camphor occurs almost entirely from the *endo* face, but almost entirely from the *exo* face with norbornanone.

In a similar style, epoxidation of the two alkenes is totally stereoselective, occurring *exo* in norbornene and *endo* when methyl groups are present on the bridge. These stereoselectivities would be remarkable in a simple monocyclic compound, but in a rigid bridged bicyclic structure they are almost to be expected.

Reactions that break open bridged molecules preserve stereochemistry

Some powerful oxidizing agents are able to cleave C–C bonds, as you will see in Chapter 35. Oxidation of camphor in this way produces a diacid known as camphoric acid. The usual reagent is nitric acid (HNO_3) and oxidation goes via camphor's enol.



▶ Note that only one enol can form: enolization the other way would lead to an impossible planar carbon at the bridgehead position. See p. 000.

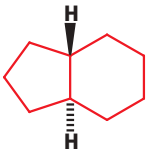
Because the bridge holds the molecule in a fixed conformation, the cleaved diacid has to have a specific stereochemistry. There is no change at the stereogenic centres, so the reaction must give retention of configuration. We can confidently write the structure of camphoric acid with *cis*-CO_2H groups, but any doubt is dispelled by the ability of camphoric acid to form a bridged bicyclic anhydride.

▶ Anhydride formation with acetic anhydride goes via attack of one acid group on Ac_2O to form a mixed anhydride, followed by displacement of AcOH by the other acid group.

Fused bicyclic compounds

trans-Fused rings

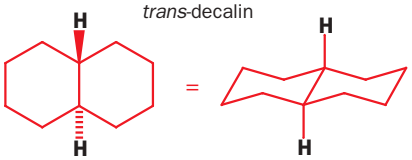
The ring junction of a fused 5/6-membered ring system can have *cis* or *trans* stereochemistry, and so can any pair of larger rings. For smaller rings, *trans* 5/5- and 4/6-ring junctions can be made, with difficulty, but with smaller rings *trans* ring junctions are essentially impossible.



5,6 can be *trans* or *cis*

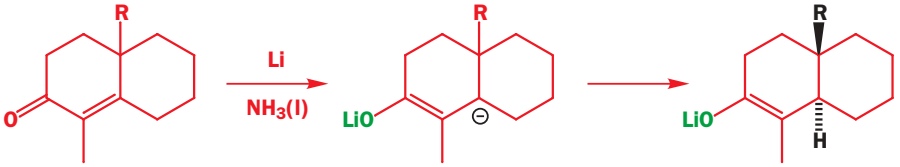
The *trans*-fused 6/6 systems—***trans*-decalins**—have been very widely studied because they appear in steroids (Chapter 51). Their conformation is discussed in Chapter 18 and conformational control simply extends what we saw with simple six-membered rings.

A 6/6 fused system will prefer a *trans* ring junction as *trans*-decalins (Chapter 18) have all-chair structures with every bond staggered from every other bond, as you can see from the diagram alongside. We can show



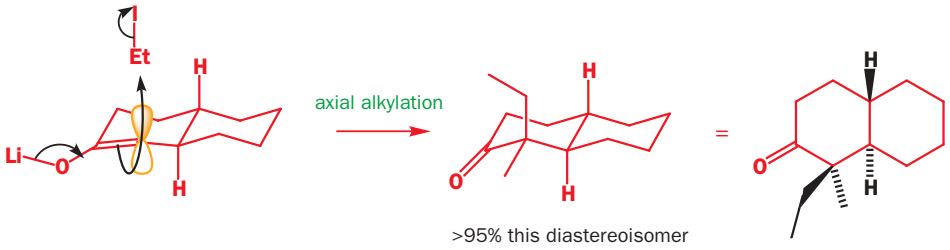
6,6 can be *trans* or *cis*, but prefers *trans*

this by giving a 6/6 system the choice: reducing this enone with lithium metal gives a lithium enolate (Chapter 26). Protonation of this anion with the solvent (liquid ammonia) gives a *trans* ring junction.

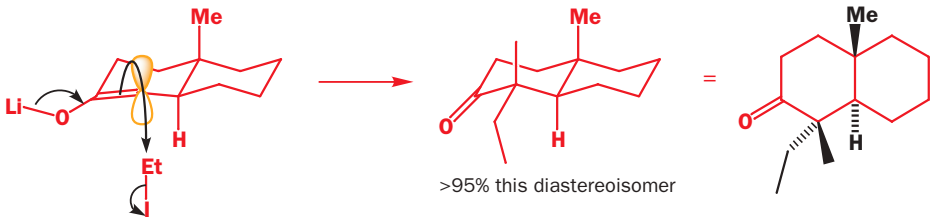


The lithium enolate remains and can be alkylated with an alkyl halide in the usual way. When there are hydrogen atoms at both ring junction positions, axial alkylation occurs just as you should now expect, and a new ketone with three stereogenic centres is formed with >95% stereoselectivity.

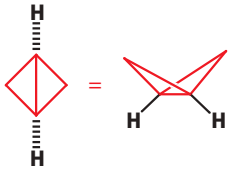
■ In this scheme, and the next, the methyl group attached at the yellow p orbital has been omitted for clarity.



However, if there is anything else—even a methyl group—at the ring junction, so that axial approach would give a bad 1,3-diaxial interaction in the transition state, the stereoselectivity switches to >95% equatorial alkylation. This unexpected reversal of normal stereoselectivity is a result of the extra rigidity of the *trans*-decalin system.

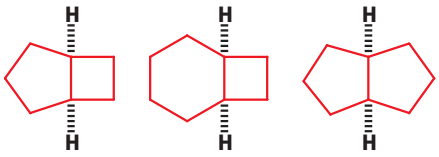


In most reactions of *trans*-decalins, the conformational principles of simple six-membered rings can be used, but you may expect tighter control from the greater rigidity. If you wish to design a molecule where you are quite certain of the conformation, a *trans*-decalin is a better bet than even a *t*-butyl cyclohexane as *trans*-decalins cannot flip.



bicyclo[1.1.0]butane

cis-Fused rings



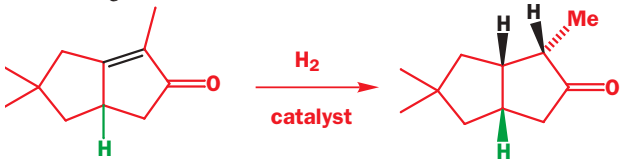
Almost any *cis*-fused junction from 3/3 upwards can be made. Bicyclo[1.1.0]butane exists, though it is not very stable. *cis*-Fused 4/5, 4/6, and 5/5 systems are common and are much more stable than their *trans*-isomers.

■ You met catalytic hydrogenation in Chapter 24.

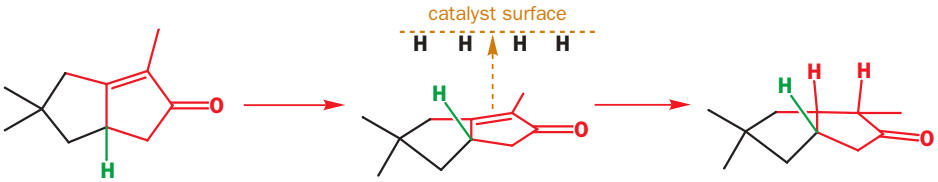
■ For a reminder of what **stereoselective** and **stereospecific** mean, see p. 000.

Any method of making such bicyclic compounds will automatically form this stereochemistry. An important method of stereochemical control that we have not used so far in this chapter is catalytic hydrogenation of alkenes, which adds a molecule of hydrogen stereospecifically *cis*. If the reaction also makes a fused ring system, it may show stereoselectivity too. Here is an example with 5/5 fused rings.

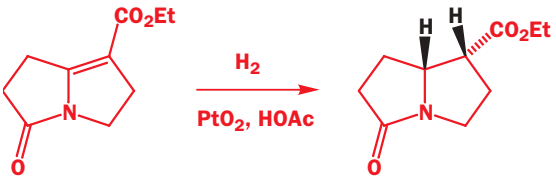
The two new hydrogen atoms (shown in black) must, of course, add *cis* to one another: this is a consequence of the stereospecificity of the reaction. What is interesting is that



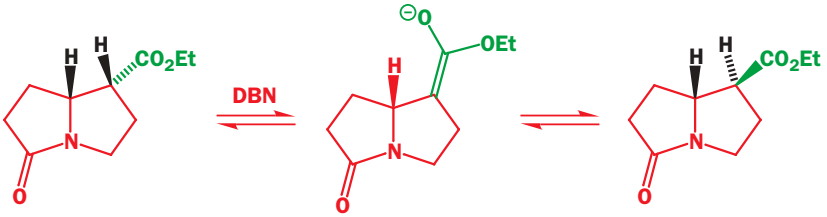
they have also added *cis* to the green hydrogen atom that was already there. This approach does give the more stable *cis* ring junction but the stereochemistry really arises because the other ring hinders approach to the other face of the alkene. Think of it this way: the alkene has two different faces. On one side there is the green hydrogen atom, and on the other the black parts of the second ring. To get hydrogenated, the alkene must lie more or less flat on the catalyst surface and that is easier on the top face as drawn.



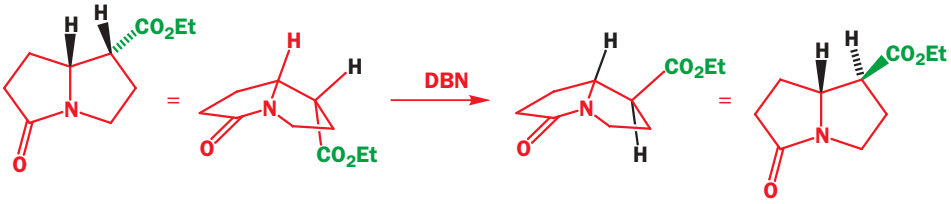
If one of the ring junctions is a nitrogen atom, we might think that there is no question of stereochemistry because pyramidal nitrogen inverts rapidly. So it does, but if it is constrained in a small ring, it usually chooses one pyramidal conformation and sticks to it. The next case is rather like the last.



Here again the two black hydrogens have added stereospecifically *cis*, but there is no stereogenic centre in the starting material to control stereoselectivity. So what is there to discuss? If the product is treated with a tertiary amine base (actually DBN is used), it equilibrates to the other diastereoisomer via the ester enolate.

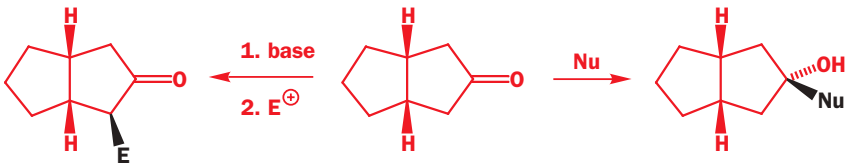


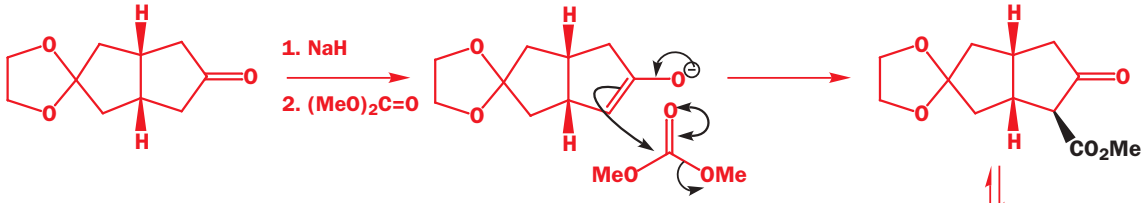
It is easy to see *how* the equilibration happens as the enolate can be protonated at the front or the back, but *why* should it prefer the second structure? This is thermodynamic control and results from the 'disguised' *cis* ring junction. Because it is more stable to have two five-membered rings *cis*-fused, the nitrogen atom is slightly (only slightly, because it is part of an amide) pyramidalized in that direction.



The molecule folds along the C–N bond common to both rings so that it looks rather like that half-opened book that you put face downwards on the table while you answered the phone. The ester group much prefers to be in free space outside the folded rings and not cramped inside them.

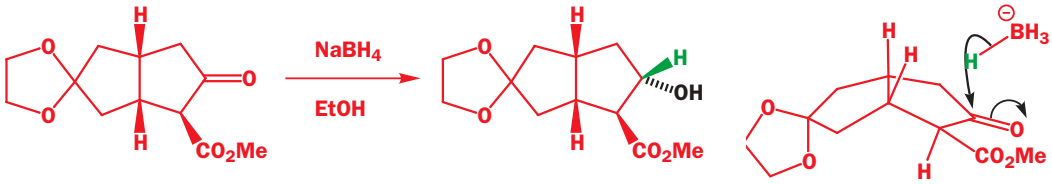
This is the key to *cis*-fused bicyclic rings—everything happens on the outside (on the cover of the book). Nucleophiles add to carbonyl groups from the outside, enolates react with alkyl halides or Michael acceptors on the outside, and alkenes react with peroxyacids on the outside. Notice that this means the same side as the substituents at the ring junction. The rings are folded away from these substituents that are on the outside.



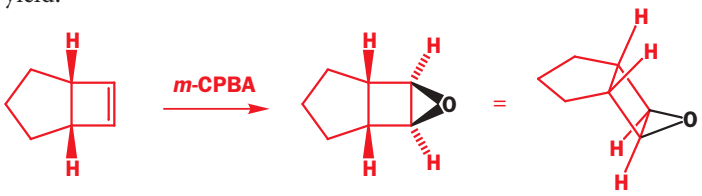


A real example comes in the acylation (Chapter 28) of the enolate from the keto-acetal above and alongside. The molecule is folded downwards and the enolate is essentially planar. Addition presumably occurs entirely from the outside, though the final stereochemistry of the product is controlled thermodynamically because of reversible enolization of the product: whatever the explanation, the black ester group prefers the outside.

Reduction of the ketone product also occurs exclusively from the outside and this has the ironic effect of pushing the new OH group into the inside position. Attack from the inside is very hindered in this molecule because one of the acetal oxygen atoms is right on the flight path. You will see more in a moment on how to force groups into the inside.

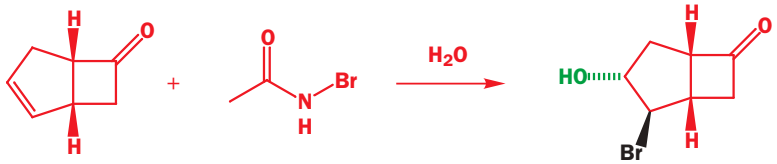


A simple example of epoxidation occurs on a cyclobutane fused to a five-membered ring. This is a very rigid system and attack occurs exclusively from the outside to give a single epoxide in good yield.



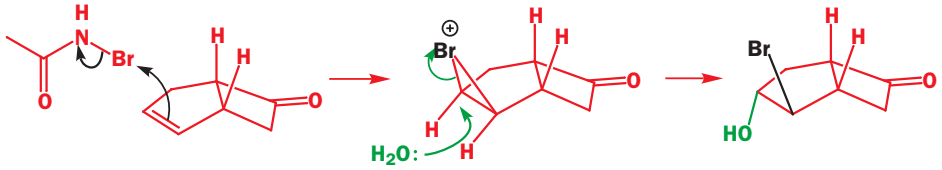
Epoxidation is stereospecific and *cis*—both new C–O bonds have to be on the same face of the old alkene. But Chapter 20 introduced you to several electrophilic additions to alkenes that were stereospecific and *trans*, many of them proceeding through a bromonium ion. If stereospecific *trans* addition occurs on a *cis*-fused bicyclic alkene, the electrophile will first add to the outside of the fold, and the nucleophile will then be forced to add from the inside. A telling example occurs when the 4/5 fused unsaturated ketone below is treated with *N*-bromoacetamide in water.

■ *N*-bromoacetamide is another source of electrophilic Br.

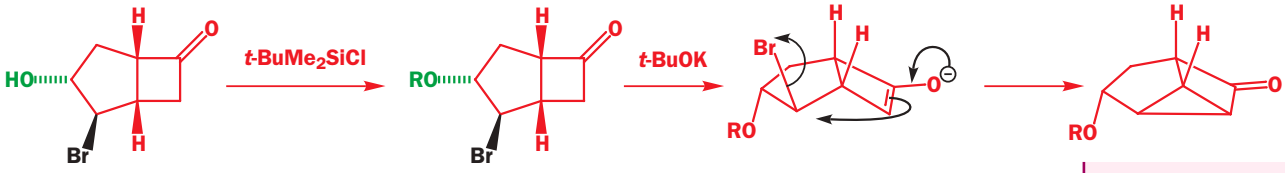


The bromonium ion is formed on the outside of the rigid structure and the water is then forced to add from the inside to get *trans* addition. As well as exhibiting stereospecificity (*trans* addition) and stereoselectivity (bromonium forms on outside), this reaction also exhibits regioselectivity in the

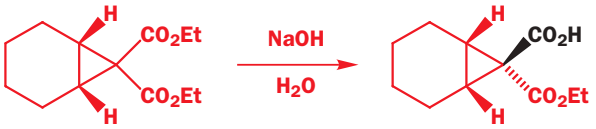
attack of water on the bromonium ion. Water must come from inside, but it attacks the less hindered end of the bromonium ion, keeping as far from the 'spine of the half-open book' as possible.



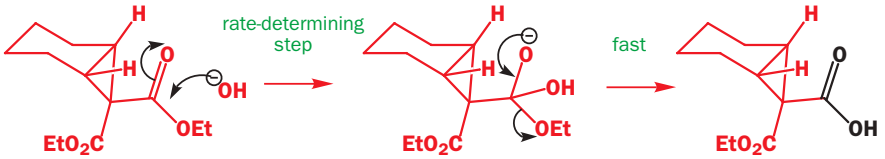
After protection of the OH group, treatment with base closes a three-membered ring to give a remarkably strained molecule. The ketone forms an enolate and the enolate attacks the alkyl bromide intramolecularly to close the third ring. This enolate is in just the right position to attack the C–Br bond from the back, precisely because of the folding of the molecule.



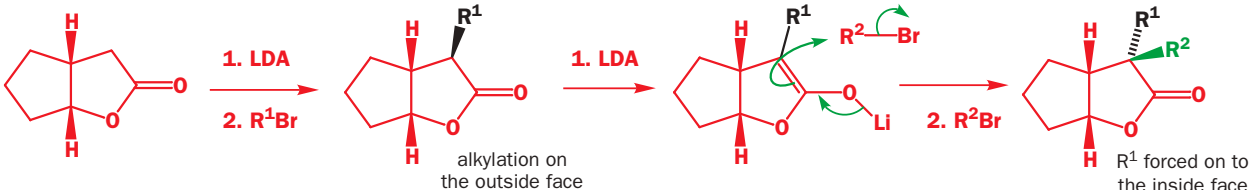
Inside/outside selectivity may allow the distinction between two otherwise similar functional groups. The *cis*-fused bicyclic diester below may look at first rather symmetrical but ester hydrolysis leaves one of the two esters alone while the other is converted to an acid.



Only the outside ester—on the same side as the ring junction Hs—is hydrolysed. In the mechanism for ester hydrolysis, the rate-determining step is the attack by the hydroxide ion so the functional group *increases* in size in the vital step. This will be much easier for the free outside CO_2Et group than for the one inside the half-open book.



The end result is that the larger of the two groups is on the inside! There are other ways to do this too. If we alkylate the enolate of a bicyclic lactone, the alkyl group (black) goes on the outside as expected. But what will happen if we repeat the alkylation with a different alkyl group? The new enolate will be flat and the stereochemistry at the enolate carbon will be lost. When the new alkyl halide comes in, it will approach from the outside (green) and push the alkyl group already there into the inside.

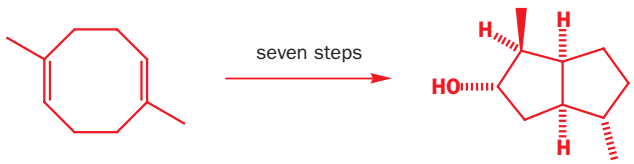


Should you wish to reverse the positions of the two groups, you simply add them in the reverse order. Whichever group is added first finishes on the inside; the other finishes on the outside.

Before we move on to *cis*-decalins, here is a sequence of reactions that starts with a symmetrical eight-membered ring with no stereogenic centres and ends with two fused five-membered rings with five stereogenic centres, all controlled by stereospecific reactions, some with stereoselective aspects controlled by *cis*-fused rings.

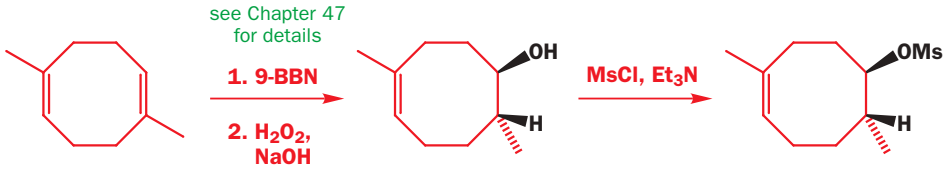
▶ This molecule now has three-, four-, and five-membered rings fused together in a tricyclic cage structure. This is nowhere near the limit for cage molecules. You saw tetra-*t*-butyl tetrahedrane in Chapter 15, and you will see in Chapter 37 how even molecules such as cubane can be made.

cubane



The first step is a reaction you haven't yet met—it comes in Chapter 47. All you need to know now is that the reagent, a boron-containing compound called 9-borabicyclononane (9-BBN), hydrates one of the double bonds in the reverse fashion to what you would expect with acid or Hg^{2+} (Chapter 20) and stereospecifically (H and OH go in *cis*). The resulting alcohol is mesylated (p. 000) in the usual way. This puts in H and OMs stereospecifically *cis* to each other.

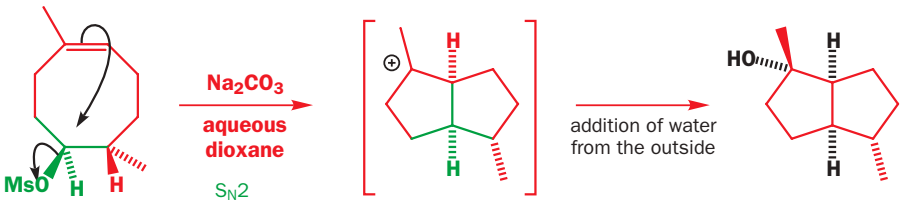
■ This is a hydroboration reaction, and the oxygen comes from the peroxide used to work up the reaction. You can read more about 9-BBN, and see its structure, on p. 000 of Chapter 47.



hydroboration: OH and H add *cis*

Now comes the first really interesting step. The other alkene does an intramolecular S_N2 reaction to displace the mesylate with inversion and form two fused five-membered rings. The ring junction is *cis*, of course.

▶ If you find it hard to see that the reaction has gone with inversion, look at the kink in the ring highlighted in green. The old OMs comes downwards from that kink and towards you, out of the page. The new bond forms upward from the kink, more or less 180° from where the old CO bond was, and the remaining three bonds accommodate this by 'inverting' like an inside-out umbrella.

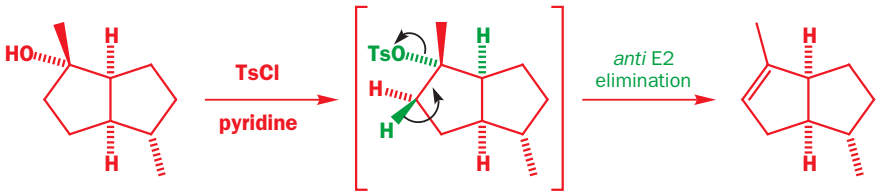


5,5-ring junction forms *cis*

The resulting tertiary cation is not isolated but quenched in the reaction mixture with water. One new stereogenic centre is set up in the cyclization and another in the reaction with water. In the cyclization the molecule prefers to fold in such a way that the new ring junction is *cis*.

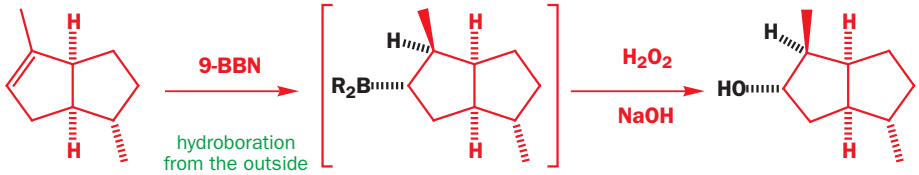
Addition of water to the cation occurs from the outside—but, in fact, this is unimportant as that stereogenic centre is about to be lost anyway. Treatment with TsCl causes an E2 *anti* elimination. The only proton *anti* to the OTs group is away from the ring junction, so this is where the new double bond goes.

■ The reaction is regioselective because of its stereospecificity. You saw a similar example on p. 000 of Chapter 20.



Finally, a second hydroboration with 9-BBN occurs regiospecifically and on the outside of the folded molecule. This reaction adds the last two centres making five in all.

■ Another feature of hydroboration that is relevant here and discussed in Chapter 47 is the fact that replacement of B by O in the second step goes with retention. The mechanism will come on p. 000.

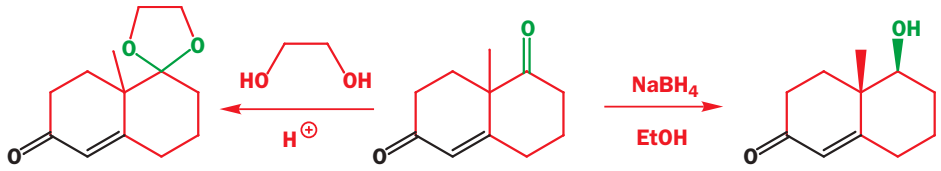


cis-Decalins: *cis*-fused six-membered rings

First a brief reminder of the conformation of *cis*-decalins (see Chapter 18). Unlike *trans*-decalins, which are rigid, they can flip rapidly between two all-chair conformations. During the flip, all

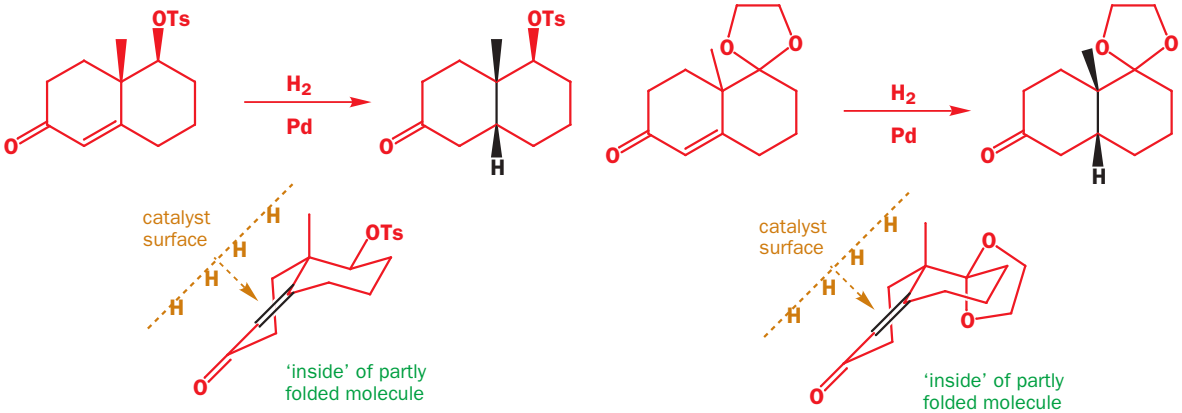
substitutents change their conformation. The substituent R is axial on ring B in the first conformation but equatorial in the second. The ring junction Hs are always axial on one ring and equatorial on the other. The green hydrogen is equatorial on ring A and axial on ring B in the first conformation and vice versa in the second. Of course, they are *cis* in both. Because R gets equatorial, the second conformation is preferred in this case.

A standard reaction that gives substituted decalins is the Robinson annelation (Chapter 29). A Robinson annelation product available in quantity is the keto-enone known sometimes as the **Wieland–Miescher ketone** and used widely in steroid synthesis. The nonconjugated keto group can be protected or reduced without touching the more stable conjugated enone.

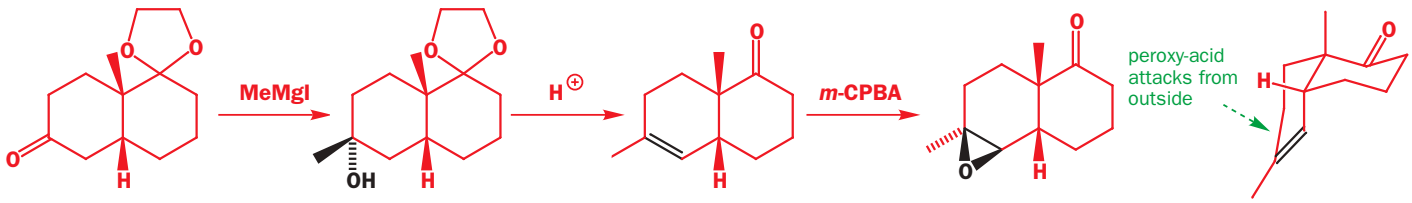


■ The synthesis of this ketone can be found in Chapter 29, p. 000.

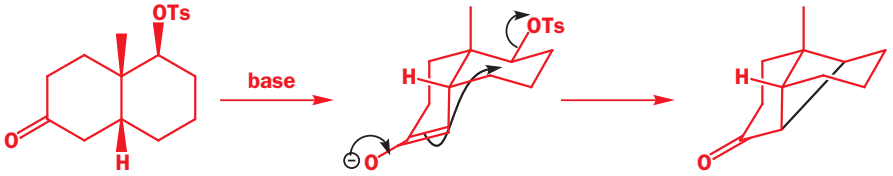
If either of these products is reduced with hydrogen and a Pd catalyst (the alcohol is first made into a tosylate), the *cis*-decalin is formed. We saw a few pages back that the same kind of enones can be reduced with lithium metal in liquid ammonia and that then the more stable *trans*-decalin results.



The *cis*-decalin is formed because the enone, though flattened, is already folded to some extent. A conformational drawing of either molecule shows that the top surface is better able to bind to the flat surface of the catalyst. Each of these products shows interesting stereoselective reactions. The ketal can be converted into an alkene by Grignard addition and E1 elimination and then epoxidized. Everything happens from the outside as expected with the result that the methyl group is forced inside at the epoxidation stage.

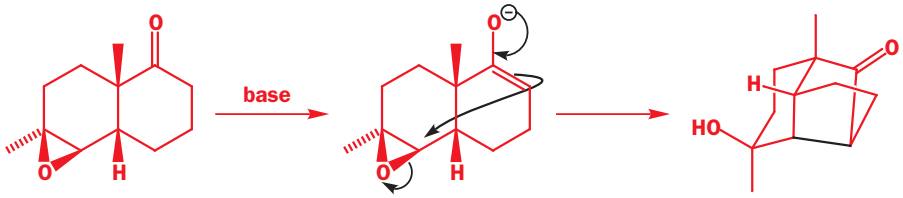


Treatment of the other product, the keto-tosylate, with base leads to an intramolecular enolate alkylation—a cyclization on the inside of the folded molecule that actually closes a four-membered ring. The reaction is easily seen in conformational terms and the product cannot readily be drawn in conventional diagrams.



A similar reaction happens on the epoxide to produce a beautiful cage structure. This time it is a five-membered ring that is formed, but the principle is the same—the molecule closes across the fold rather easily. The new stereogenic centres can only be formed the way they are.

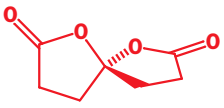
▶ Notice how the right-hand ring in the starting material has to go into a boat conformation for cyclization to be possible. This is unfavourable but still better than any intermolecular reaction.



● A summary of stereoselective reactions that occur on the *cis*-fused rings

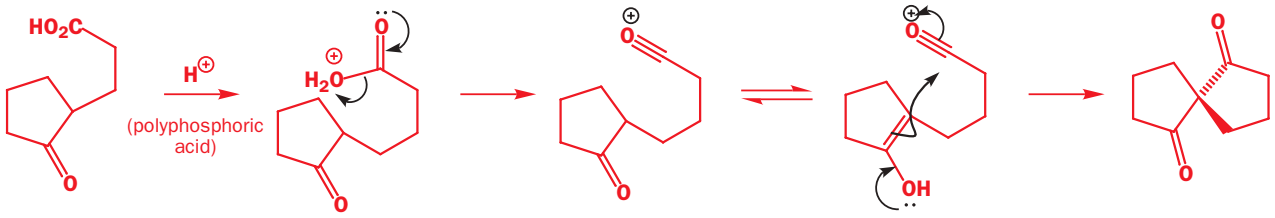
1. Reactions on the outside
   - Nucleophilic additions to carbonyl groups in the ring
   - Reactions of enolates of the same ketones with electrophiles: alkyl halides, aldols, Michael additions
   - *cis*-Additions to cyclic alkenes: hydrogenation, hydroboration, epoxidation
2. Reactions on the outside and the inside
   - *trans*-Additions to cyclic alkenes: bromination, epoxide openings
3. Reactions on the inside
   - Bond formation across the ring(s)

Spirocyclic compounds

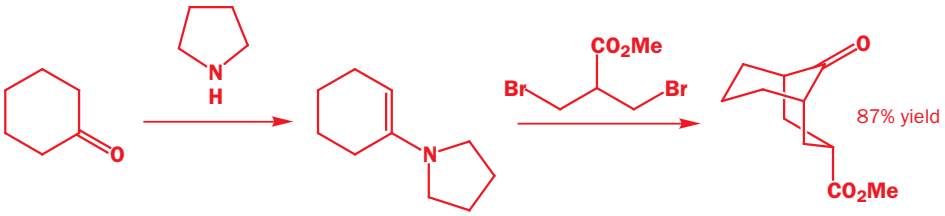


These rings meet at an atom alone. This means that the two rings are orthogonal about the tetrahedral atom that is common to both. Even symmetrical-looking versions are unexpectedly chiral. The compound in the margin, for example, is not superimposable on its mirror image, and its chirality is rather similar to that of an allene.

These sorts of compounds may look rather difficult to come by, but some simple ones are simply made. Cyclization of this keto-acid with polyphosphoric acid leads to a spirocyclic diketone.

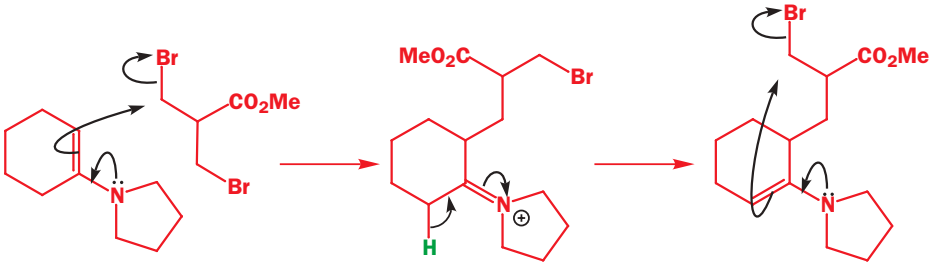


The *spiro* compound is formed because the more substituted enol is preferred in acid solution. In a different case, with an enamine, a bridged product is preferred.

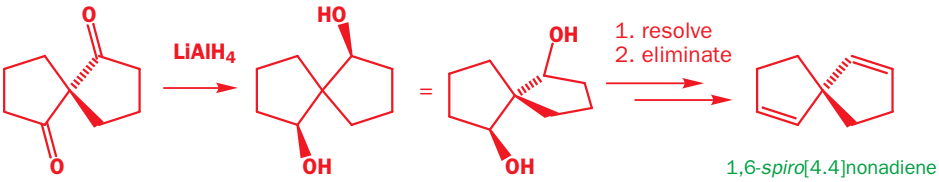


After the first alkylation, the enamine prefers to re-form on the less substituted side so that the second alkylation occurs on the other side of the ketone from the first. The spirocyclic compound is further disfavoured as it would have a four-membered ring in this case.

A less substituted enamine is usually preferred to a more substituted one: see p. 000.



It is much more difficult to pass stereochemical information from one ring to the other in spirocyclic compounds because each ring is orthogonal to the other. Nonetheless, some reactions are surprisingly stereoselective—one such is the reduction of the spirocyclic diketone that we made a moment ago. Treatment with $LiAlH_4$ gives one diastereoisomer of the spirocyclic diol.



The diol was resolved and used to make the very simple *spiro*-diene as a single enantiomer. It is chiral even though it has no chiral centre because it does not have a plane of symmetry.

In Chapter 16 we explained that planes of symmetry, not chiral centres, are the things to look for when deciding whether or a not a compound is chiral.

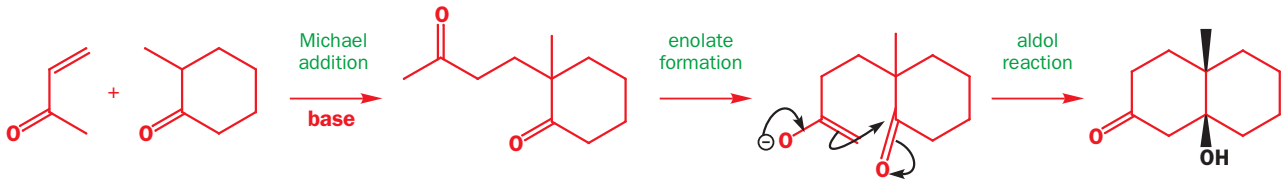
Reactions with cyclic intermediates or cyclic transition states

Rings are so good at controlling stereochemistry (as you have seen) that it's well worth introducing them where they are not really necessary in the final product, simply in order to enjoy those high levels of stereochemical control. In the rest of this chapter we shall consider the use of temporary rings in stereochemical control: these might be cyclic intermediates in a synthetic pathway, or cyclic reaction intermediates, or even merely cyclic transition states. All aid good stereocontrol. We shall concentrate on examples where the ring reverses the normal stereoselectivity so that some different result is possible.

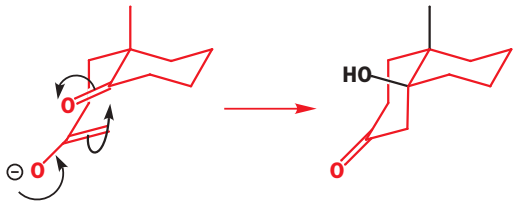
Tethered functional groups can reach only one side of the molecule

The proverbial donkey starved to death in the field with two heaps of hay because it could not decide which one to go for first. If the donkey had been tethered to a stake near one heap it would have been able to reach that heap alone and it could have feasted happily.

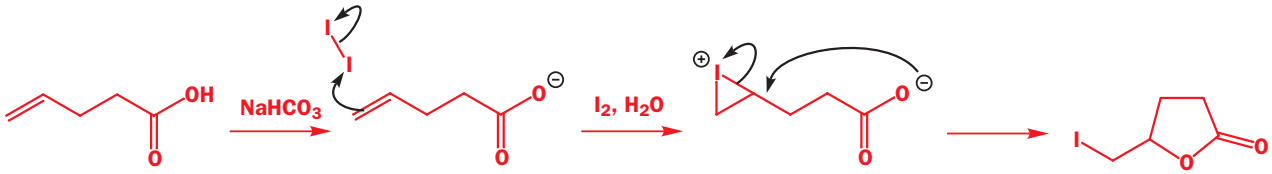
This principle is often applied to molecules. If a nucleophile is joined to the carbonyl group it is to attack by a short chain of covalent bonds, it may be able to reach only one side of the carbonyl group. An example from a familiar reaction concerns the Robinson annelation. The first step, Michael addition, creates a stereogenic centre but no relative stereochemistry. It is in the second step—the aldol cyclization—that the stereochemistry of the ring junction is decided.



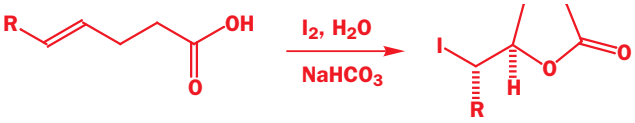
The enolate is tethered to the atom next to the ketone in the other ring. It can attack easily from the side to which it is attached through a stable chair-like transition state. Attacking the other face of the ketone (to give a *trans*-decalin) is much more difficult, even though it would give the thermodynamically more stable product.



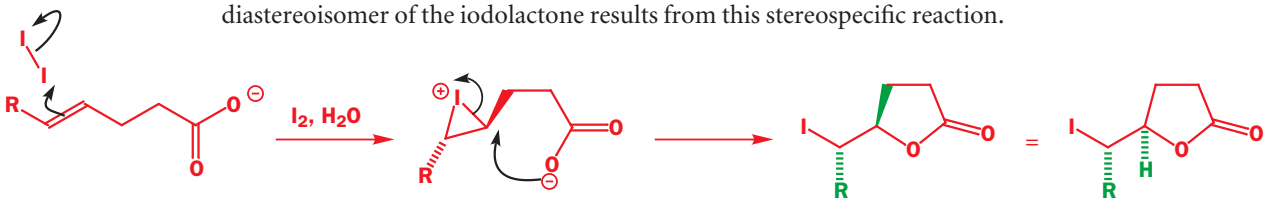
In fact, this is not such a good example because the aldol product is normally dehydrated and the second stereogenic centre is lost. More important examples are those in which a ring is formed but can later be cleaved, and among the best of this type of reaction are iodolactonizations, which you first met in Chapter 20. To remind you, iodolactonization involves treating a nonconjugated unsaturated acid with iodine in aqueous $NaHCO_3$. The product is an iodolactone.



The cyclization reaction is a typical two-stage electrophilic addition to an alkene (Chapter 20) with attack by the nucleophile at the more substituted end of the intermediate halonium ion. The iodonium ring opening is a stereospecific S_N2 and, in the simplest cases where stereochemistry can be observed, the stereochemistry of the alkene will be reproduced in the product.

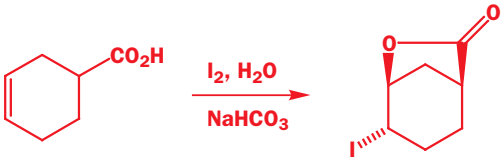


The starting acid contains an *E*-alkene that gives a *trans* iodonium ion. Inversion occurs in the attack of the carboxylate anion on the iodonium ion and we have shown this by bringing the nucleophile in at 180° to the leaving group with both bonds in the plane of the paper. A single diastereoisomer of the iodolactone results from this stereospecific reaction.



■ Chapter 35 describes how to make the unsaturated six-membered starting material.

The following cyclic example illustrates the stereoselective aspect of iodolactonization.

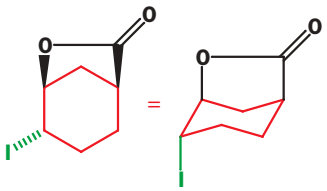


▶ Try making a model of, or even drawing, a two-atom bridge axial–equatorial or equatorial–equatorial between these two carbons and you will find that it's impossible.

The relationship between the two stereogenic centres on the old alkene is not an issue—that aspect of the reaction is stereospecific. A more interesting question is the relationship with the third centre. One way to look at this question would be to say that the structure shown is the only possible

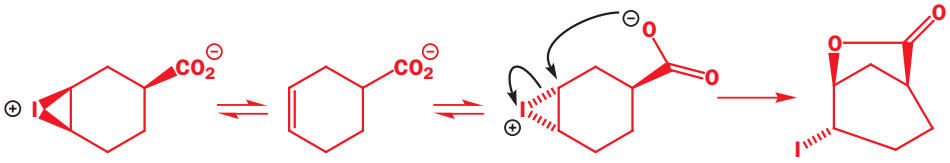
one. The lactone bridge has to be diaxial (and hence *cis*) if it is to exist and the O and I atoms have to be *trans*. End of story.

bridge must be diaxial

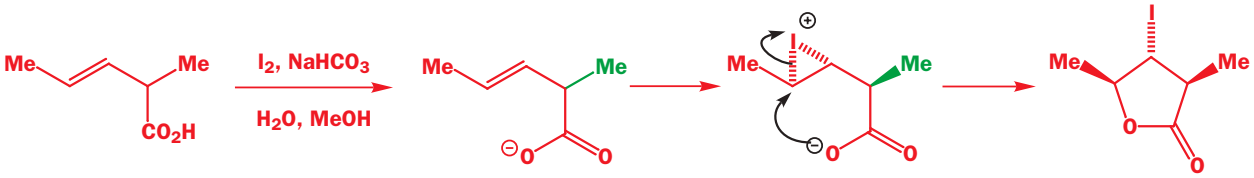


I must be *trans* to O

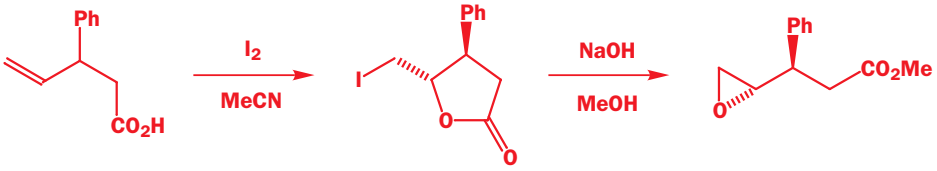
But it is still interesting to see how the product arises as it gives us insight into other less clear-cut reactions. The $-CO_2H$ group is too far away for us to argue seriously that the two faces of the alkene are sufficiently different for the iodine to attack one only. A more reasonable explanation is that iodine attacks both faces reversibly but that only the iodonium ion with the I and CO_2H groups *trans* to each other can cyclize. This turns out to be a general rule—iodolactonizations are reversible and under thermodynamic control.



One of the simplest open-chain examples is 2-methylbut-3-enoic acid, which cyclizes in >95% yield to a single iodolactone with three stereogenic centres. Two come from stereospecific *trans* addition to the *E*-alkene but the third reveals that iodine attacked the face of the alkene opposite the green methyl group in the conformation that can cyclize.

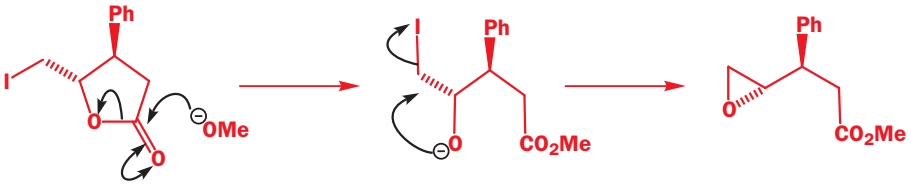


We have said little in this chapter about the stereospecific transformation of one ring into another but we now have an opportunity to remedy that defect. Iodolactonization of a terminal alkene with a stereogenic centre next to it is as stereoselective as (if not more than) the example we have just seen. The two side chains on the ring end up *trans* to one another as we should expect. This is a purely stereoselective process as the alkene has no geometry.

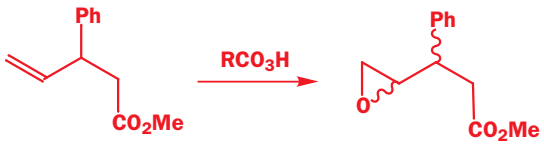


97% yield, 10:1 *trans*:*cis*

Reaction of the iodolactone product with alkaline methanol transforms it stereospecifically into the methyl ester of an epoxy acid. There is no change in stereochemistry here: methoxide opens the lactone and the oxyanion released carries out an internal S_N2 reaction on the primary alkyl iodide.

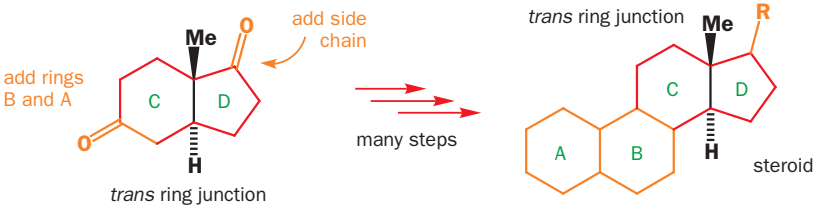


The more obvious way to make this epoxide would be by epoxidation of the ester of the original unsaturated acid. However, the stereoselectivity in that reaction is nowhere near as good as in the iodolactonization. We shall return to this subject when we discuss reactions in acyclic systems in the next chapter.

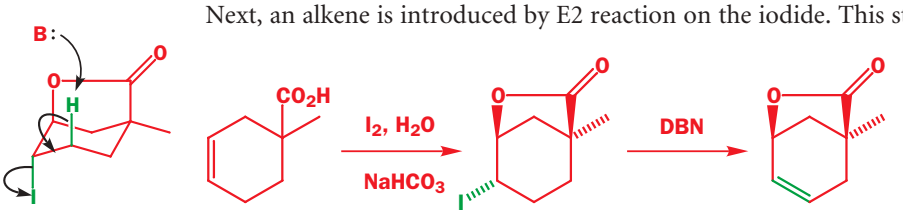


There is a brief introduction to steroids in Chapter 18, p. 000. Chapter 49 contains much more detail.

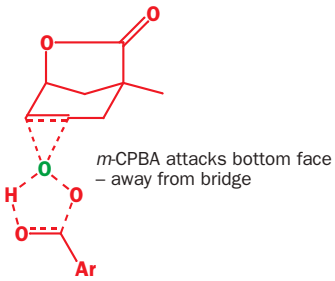
A general problem in the synthesis of steroid compounds is the construction of a diketone with 5/6 *trans*-fused rings and a quaternary carbon atom at the ring junction. **Tethering** can solve this problem, and we will present two strategies—one using a lactone derived from an iodolactonization reaction, and one using a sulfur atom.



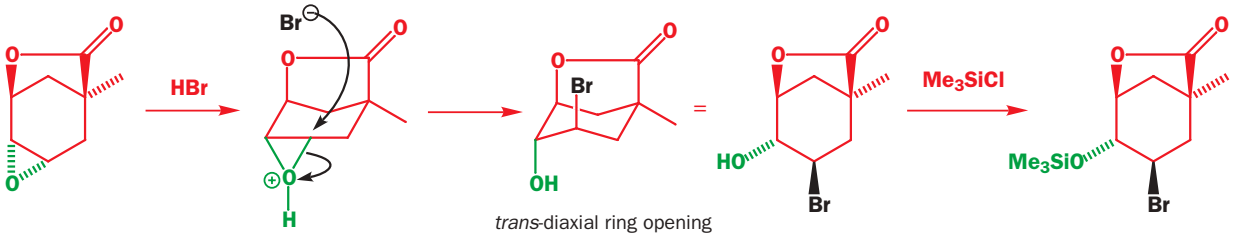
A lactone makes a good temporary tether because it can be hydrolysed or reduced to break the ring at the C–O bond and reveal new stereogenic centres on the old structure. In this sequence a lactone, formed by iodolactonization, controls all the subsequent stereochemistry of the molecule in two ways: it fixes the conformation rigidly in one chair form—hence forcing the iodide to be axial—and it blocks one face of the ring. The iodolactonization is very similar to one you saw on p. 000. Next, an alkene is introduced by E2 reaction on the iodide. This stereospecific reaction requires an anti-periplanar H atom so it has to take the only available neighbouring axial hydrogen atom—furthermore, reaction the other way would produce a bridgehead alkene.



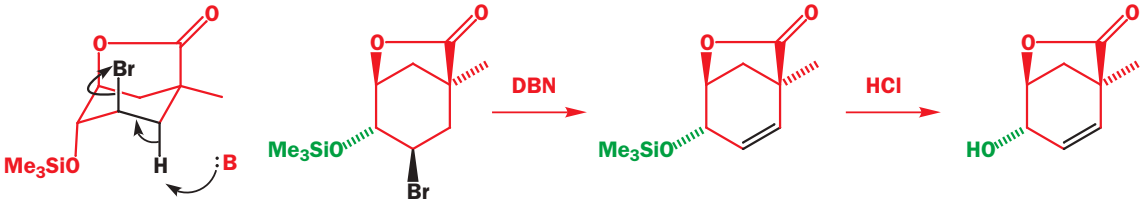
The resulting alkene has its top face blocked by the bridge so a *cis* addition reaction, such as epoxidation, will occur entirely from the bottom face.



Now the epoxide is opened with HBr to give the only possible *trans* diaxial product (Chapter 18). The role of the bridge in fixing the conformation of the ring is more important in this stereospecific reaction because the bromide ion is forced to attack from the top face. The alcohol is protected as a silyl ether.

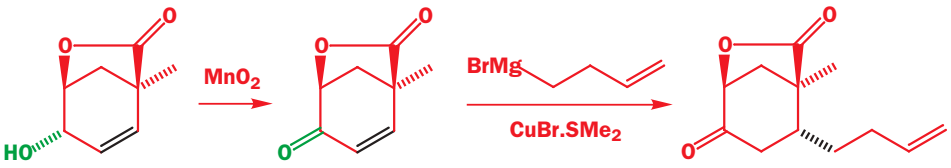


Do you see how the functional groups are being pushed round the ring? This process is extended further by a second elimination also with DBN, which this time really does have to seek out the only neighbouring axial hydrogen: there's no bridgehead to take the decision for it. Acid removes the silyl protecting group.

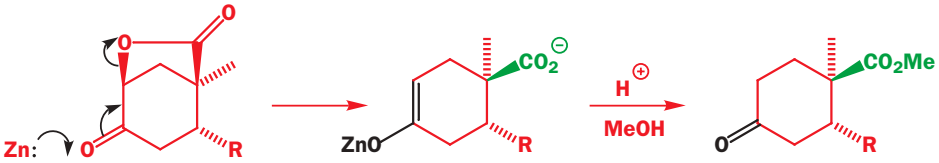


The next important reaction is a Michael addition so the alcohol must first be oxidized to a ketone. As it is an allylic alcohol, it can be oxidized by manganese dioxide. The ring is further flattened as three atoms are now trigonal. But-3-enyl Grignard reagent is next added with Cu(I)

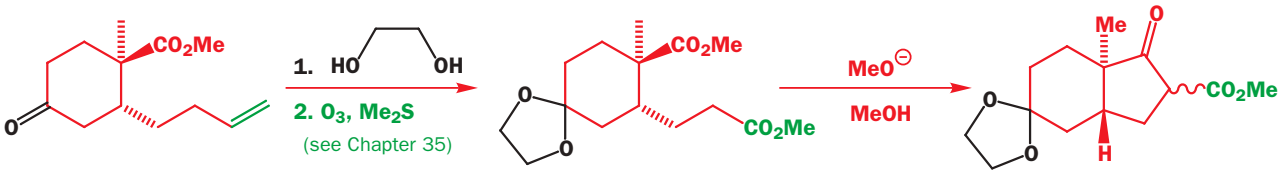
catalysis to make sure that conjugate addition occurs. Conjugate addition normally gives the axial product as we saw earlier and fortunately this is not the direction blocked by the bridge.



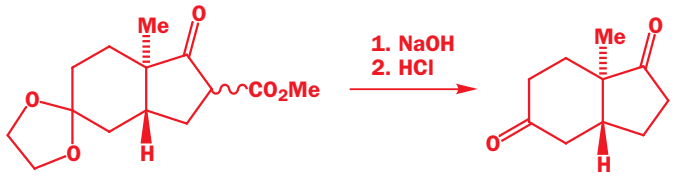
The bridge has now done its work and is removed by zinc metal reduction. This reaction removes leaving groups on the atoms next to carbonyl groups. In this case it is the axial carboxylate that is driven out by the zinc. The released carboxyl group is esterified.



The last stages are shown below. The ketone is protected, and the alkene oxidized to a carbonyl group, cleaving off one of the C atoms (you will meet this reaction—ozonolysis—in Chapter 35). The diester can be cyclized by a Claisen ester condensation. The stereogenic centres in the ring are not affected by any of these reactions so a *trans* ring junction must result from this reaction.

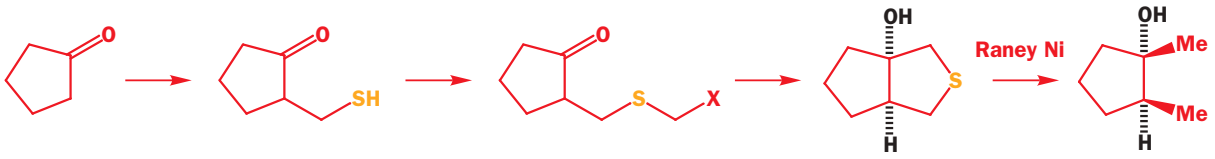


Finally, after ester hydrolysis, HCl decarboxylates the product and removes the protecting group. As we saw earlier, it is not easy to get a *trans*-fused 5/6 system. In this sequence the molecule is effectively tricked into making the *trans* ring junction by the work done with the blocking lactone bridge.



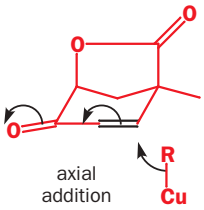
Sulfur as a tether

An even more versatile tether is a sulfur atom, which can be removed completely with Raney nickel (which reduces C–S to C–H). The sulfur atom makes the tether easy to assemble too. Here is the essence of the idea.



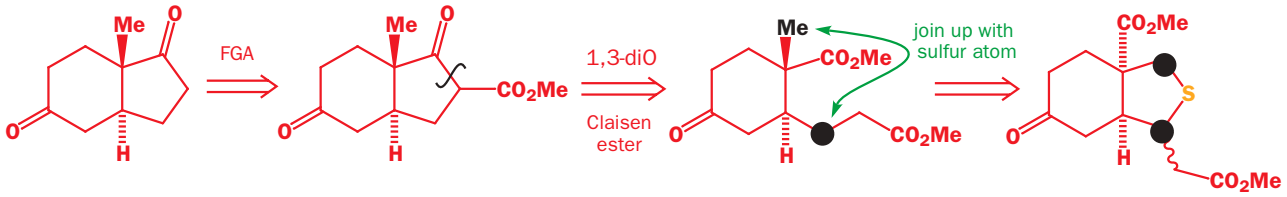
In this second synthesis of the problematic steroid *trans* ring junction, the idea is to make the five-membered ring by a Claisen ester condensation and to direct the stereochemistry by tethering the *cis* groups with a sulfur atom. We can represent this easily in disconnection terms (Chapter 31). The *cis*-carbons to be joined through sulfur are shown in black.

▶ Manganese dioxide is a reagent that oxidizes only allylic or benzylic hydroxyl groups to ketones.



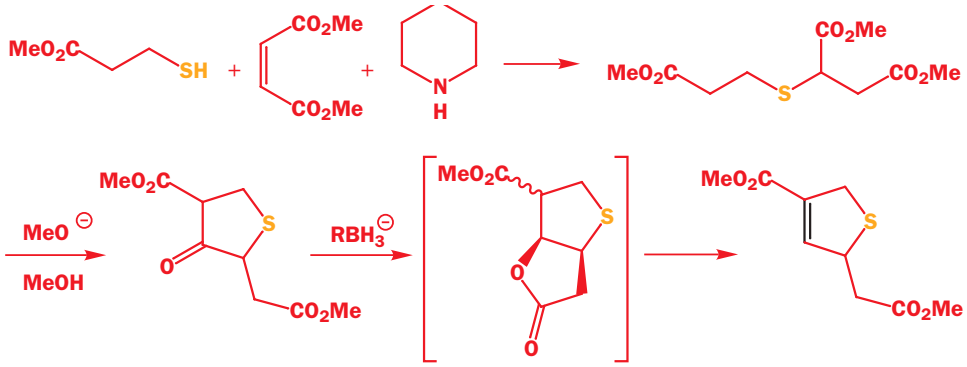
▶ This may look like a new reaction, but think back to the Reformatsky reaction (Chapter 27). Both form zinc enolates from carbonyl compounds with adjacent leaving groups.

■ You met Raney nickel in Chapter 24 and you will see more of it in Chapter 46.



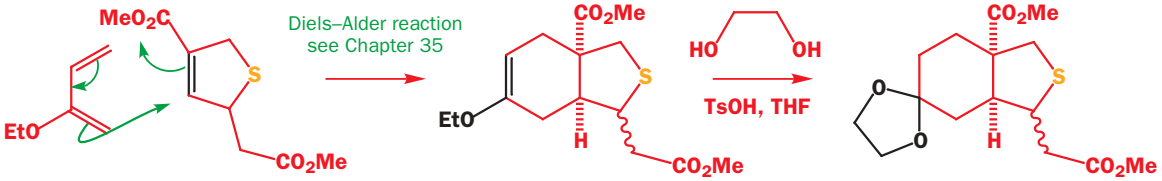
The preparation of the sulfur heterocycle uses reactions you have met before—first a five-membered ring ketone is formed, which is reduced, lactonized, and eliminated.

▶ You should be able to write mechanisms for all of the reactions in this sequence except the Diels–Alder reaction (Chapter 35). You are asked to do so in one of the problems at the end of the chapter.

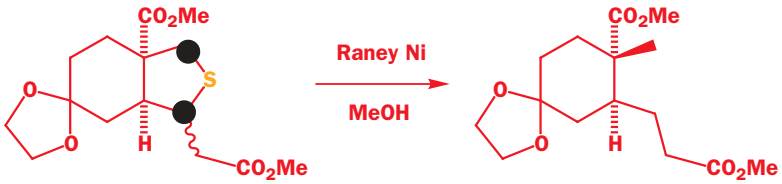


▶ The interpretation of these reactions will be one of the problems we set in Chapter 35.

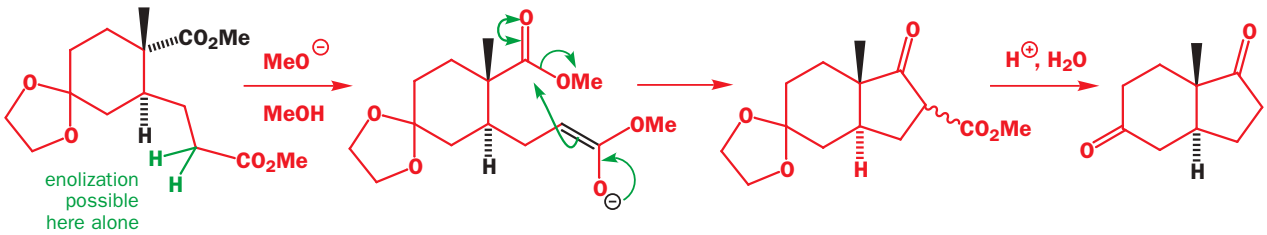
The next steps involve the Diels–Alder reaction, which you will meet in Chapter 35, so we will have no detailed discussion here, just giving the reactions, and pointing out that the product necessarily has a *cis* 6/5 ring junction.



Now the ring has done its work, the two necessary stereogenic centres are fixed, and the sulfur atom can be removed with Raney nickel. The third, undefined, stereogenic centre becomes a CH_2 group in this operation, so the lack of stereocontrol at this centre during the Diels–Alder reaction is of no consequence.



The Claisen ester condensation involves the only possible enolate attacking the only possible electrophilic carbonyl group. The stereochemistry of the ring junction cannot be changed by the reaction, and the two ester groups that started *trans* must end up *trans* in the product.

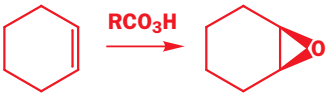


Cyclic transition states can reverse normal stereoselectivity

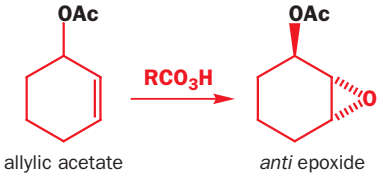
We have considered what happens when there is a ring present in the starting material, or where we encourage formation of a ring in an intermediate as a means of controlling stereochemistry. In this

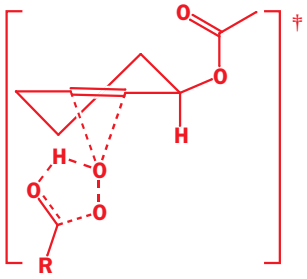
final section of this chapter we shall consider some examples where stereoselectivity arises because of a ring formed only transiently during a reaction in a cyclic transition state.

We'll start with some epoxidation reactions. Of course these *form* rings, and you have seen, in Chapter 20, epoxidations of alkenes such as cyclohexene. We said in Chapter 20 that epoxidation was stereospecific because both new C–O bonds form to the same face of the alkene.



If we block one face of the ring with a substituent—even quite a small one, such as an acetate group—epoxidation becomes stereoselective for the face *anti* to the substituent already there.

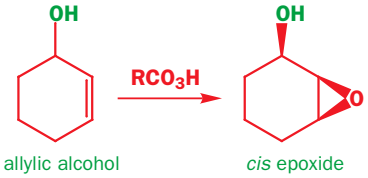


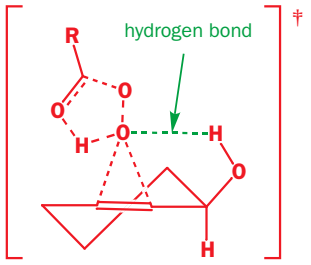


peroxy-acid approaches less hindered face of ring

■ You saw earlier the epoxidation of a lactone-bridged alkene from the less hindered face.

With one exception—when the substituent is a hydroxyl group. When an allylic alcohol is epoxidized, the peroxy-acid attacks the face of the alkene *syn* to the hydroxyl group, even when that face is more crowded. For cyclohexenol the ratio of *syn* epoxide to *anti* epoxide is 24:1 with *m*-CPBA and it rises to 50:1 with CF_3CO_3H.

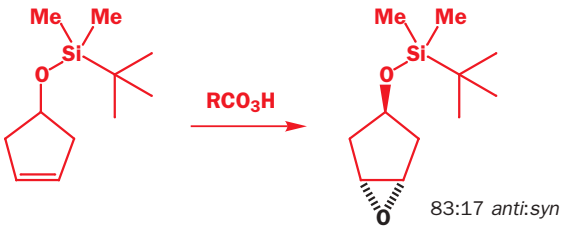




green hydrogen bond favours attack on same face as OH

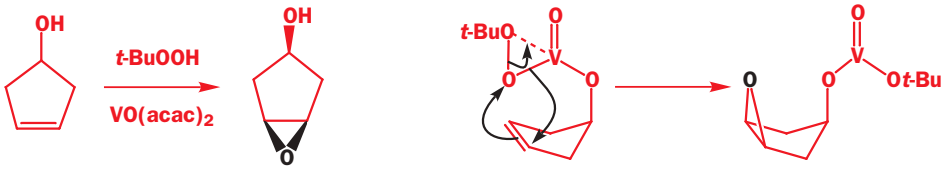
The reason is shown in the transition state: the OH group can hydrogen bond, through the H of the alcohol, to the peroxy-acid, stabilizing the transition state when the epoxidation is occurring *syn*. This hydrogen bond means that peroxy-acid epoxidations of alkenes with adjacent hydroxyl groups are much faster than epoxidations of simple alkenes, even when no stereochemistry is involved.

Peroxy-acids work for expoxidizing allylic alcohols *syn* to the OH group, but another reagent is better when the OH group is further from the alkene. 4-Hydroxycyclopentene, for example, can be converted into either diastereomer of the epoxide. If the alcohol is protected with a large group such as TBDMS (*t*-butyldimethylsilyl) it becomes a simple blocking group and the epoxide is formed on the opposite face of the alkene. The selectivity is reasonable (83:17) given that the blocking group is quite distant.



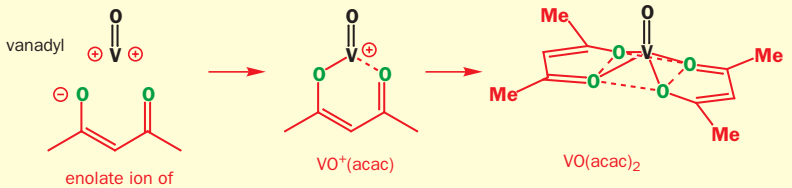
83:17 *anti*:*syn*

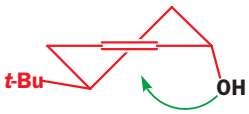
If the OH group is not blocked at all but left free, and the epoxidation reagent is the vanadium complex $VO(acac)_2$ combined with *t*-BuOOH, the *syn* epoxide is formed instead. The vanadyl group chelates reagent and alcohol and delivers the reactive oxygen atom to the same face of the alkene.



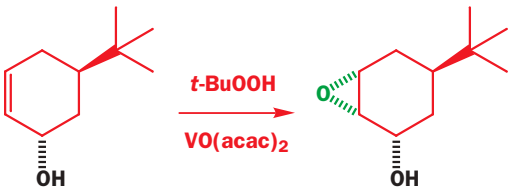
$VO(acac)_2$

Vanadyl (acac) $_2$ is a square pyramidal complex of two molecules of the enolate of 'acac' (acetyl acetone, pentan-2,4-dione) and the vanadyl (V=O) dication. It can easily accept another ligand to form an octahedral complex so there is plenty of room for the alcohol to add and for the *t*-BuOOH to displace one of the 'acac' ligands to give some complex with the essential ingredients for the reaction as shown above.



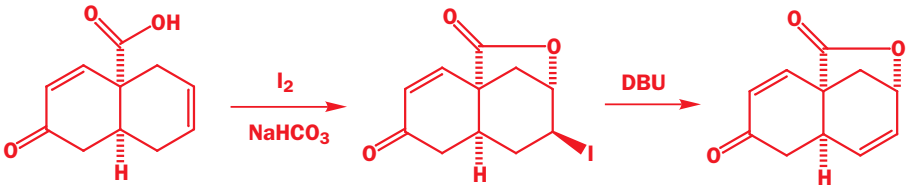


The delivery of an oxygen atom through a cyclic transition state by vanadyl complexes is also particularly effective with allylic alcohols. Here is a simple example—the green arrow shows merely the directing effect and is not a mechanism. Delivery of oxygen from OH through a VO complex is particularly effective when the OH group is pseudoaxial and the *t*-Bu group ensures this.

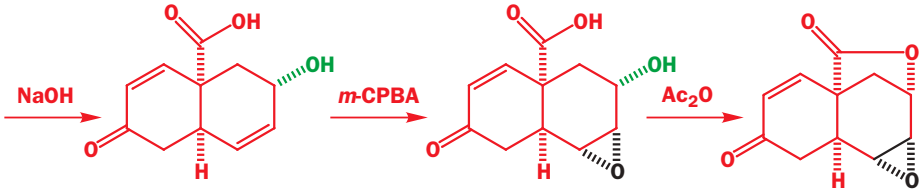


In both epoxidation examples, the stereoselectivity is due to the cyclic nature of the transition state: the fact that there is a hydrogen bond or O–metal bond 'delivering' the reagent to one face of the alkene. This is a very important concept, and we revisit it in the next chapter: cyclic transition states are the key to getting good stereoselectivity in reactions of acyclic compounds.

Before we move on, we leave you with one final example. Stereoselectivity in the epoxidation of lactone-bridged alkenes related to those we saw earlier (p. 000) can be completely reversed if the lactone is hydrolysed, revealing a hydroxyl group. In this bicyclic example, the hydroxyl group delivers the peroxy-acid from the bottom face of the alkene. First, the lactone bridge is used to introduce the alkene as before.

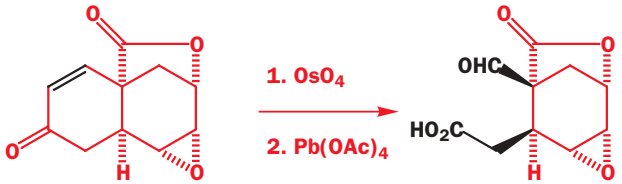


Now the critical steps—the lactone bridge is hydrolysed, the epoxide added from the bottom face by a peroxy-acid hydrogen bonded to the OH group, and the lactone bridge reinstated.



▶ You have met several methods for cleaving C=C bonds in this chapter, including this one and also ozone. These reactions will be discussed in Chapter 35.

The second ring in these compounds is actually a tether, and it enables two more functional groups to be introduced in a *cis* fashion by oxidation of the remaining alkene.



To conclude . . .

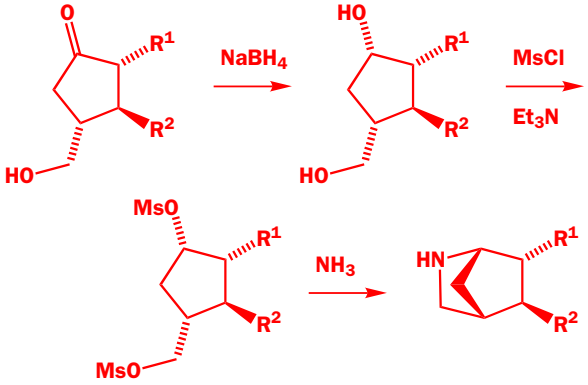
Diastereoselectivity in rings generally follows a few simple principles:

- Flattened three-, four-, or five-membered rings, especially ones with two or more trigonal carbons in the ring, are generally attacked from the less hindered face
- Flattened six-membered rings with two or more trigonal carbons in the ring (that is, which are not already a chair—so six-membered rings with one trigonal C atom don't count here) react in such a way that the product becomes an axially substituted chair
- Bicyclic compounds react on the outside face
- Reaction on the more hindered face can be encouraged by: (1) tethered nucleophiles, or (2) cyclic transition states

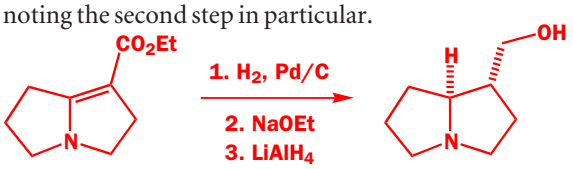
Diastereoselectivity in compounds without rings is different: it is less well controlled, because there are many more conformations available to the molecule. But even in acyclic compounds, rings can still be important, and some of the best diastereoselectivities arise when there is a ring formed temporarily in the transition state of the reaction. With or without cyclic transition states, in some cases we have good prospects of predicting which diastereoisomer will be the major reaction product, or explaining the diastereoselectivity if we already know this. That is the subject of the next chapter.

Problems

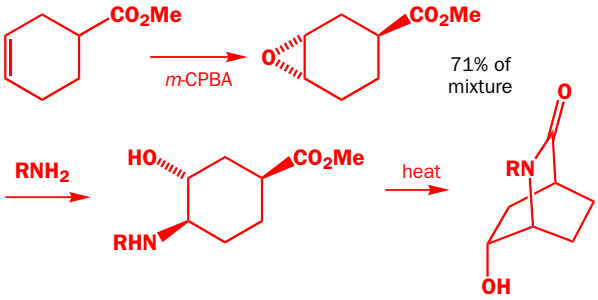
1. Comment on the control over stereochemistry achieved in this sequence.



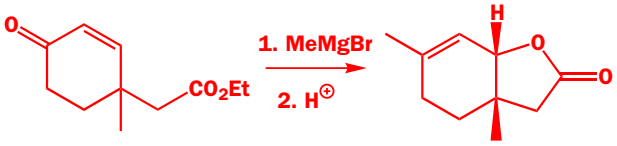
2. Explain the stereochemistry of this sequence of reactions, noting the second step in particular.



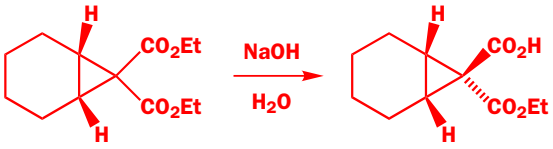
3. Explain how the stereo- and regiochemistry of these compounds are controlled. Why is the epoxidation only moderately stereoselective, and why does the amine attack where it does?



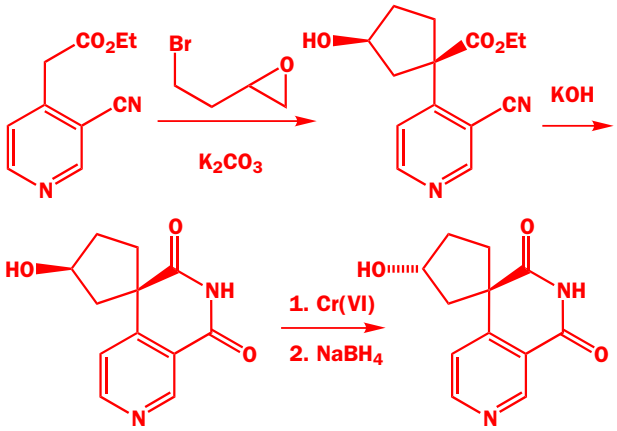
4. What controls the stereochemistry of this product? You are advised to draw a mechanism first and then consider the stereochemistry.



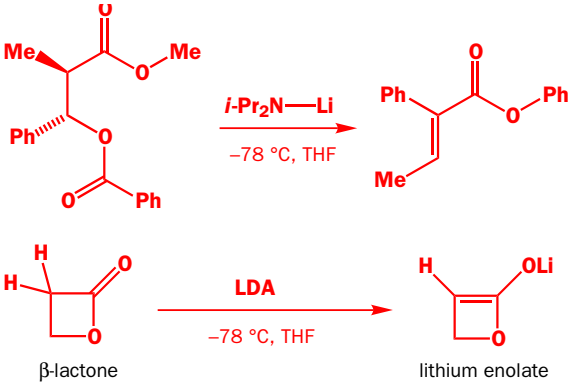
5. Why is one of these esters more reactive than the other?



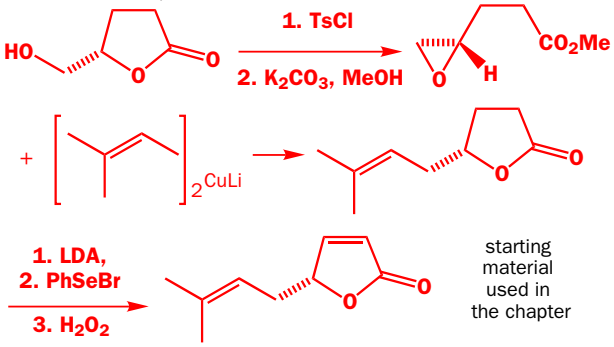
6. Explain the stereoselectivity in these reactions.



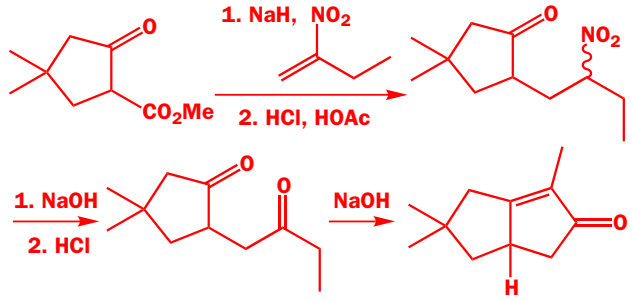
7. A problem from the chapter. Draw a mechanism for this reaction and explain why it goes so much better than the elimination on a β-lactone.



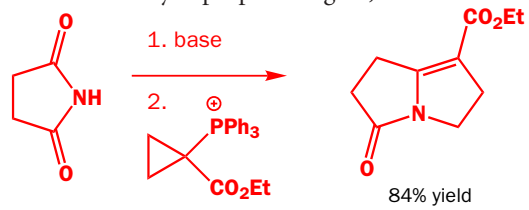
8. Another problem from the chapter. The synthesis of the starting material for this reaction is a good example of how cyclic compounds can be used in a simple way to control stereochemistry. Draw mechanisms for each reaction and explain the stereochemistry.



9. A revision problem. Suggest mechanisms for the reactions used to make this starting material used in the chapter.

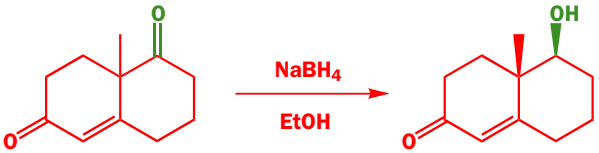


10. And another problem from the chapter. Here also draw a mechanism for the formation of the starting material. You have never seen the cyclopropane reagent, but think how it might react . . .



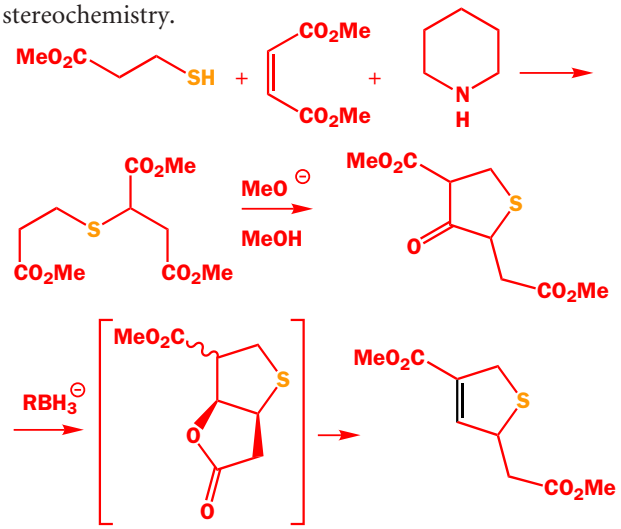
Stuck? The first step opens the three-membered ring and the second step is a well-known alkene-forming reaction . . .

11. In the chapter we introduced the selective reduction of the Wieland–Miescher ketone. The problem is: can you suggest a reason for this stereoselectivity?

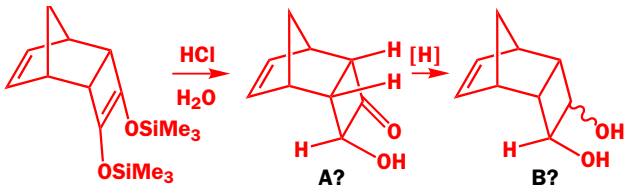


'Wieland–Miescher ketone'

12. We warned you in the chapter that this would appear as a problem: suggest mechanisms for these reactions and explain the stereochemistry.



13. Hydrolysis of a bis-silylated ene-diol gives a hydroxy-ketone A whose stereochemistry is supposed to be as shown. Reduction of A gives a diol B. The ^{13}C NMR spectrum of B has five signals: one in the 100–150 p.p.m. range, one in the 50–100 p.p.m. range, and three below 50 p.p.m. The proton NMR of the three marked hydrogens in A is given below with some irradiation data. Does this information give you confidence in the stereochemistry assigned to A? You may wish to consider the likely stereochemical result of the reduction of A.



A has δ_H 4.46 p.p.m. (1H, dd, *J* 9.0, 3.8 Hz), 3.25 p.p.m. (1H, ddd, *J* 9.0, 7.5, 4.5 Hz), and 3.48 p.p.m. (1H, ddd, *J* 7.5, 5.5, 3.8 Hz). Irradiation at 3.48 p.p.m. collapses the signal at 4.46 p.p.m. to (d, *J* 9.0 Hz) and the signal at 3.25 p.p.m. to (dd, *J* 9.0, 4.5 Hz); irradiation at 4.46 p.p.m. collapses the signal at 3.48 p.p.m. to (dd, *J* 7.5, 5.5) and the signal at 3.25 p.p.m. to (dd, *J* 7.5, 4.5).

Diastereoselectivity

34

Connections

Building on:

- Stereochemistry ch16
- Conformation ch18
- Controlling double bond stereochemistry ch31
- Determining stereochemistry by NMR ch32
- Controlling stereochemistry in cyclic compounds ch33

Arriving at:

- How to make single diastereoisomers from single geometrical isomers
- How to predict and explain the reactions of chiral carbonyl compounds
- How chelation to metal ions can change stereoselectivity
- How to predict and explain the reactions of chiral alkenes
- Stereoselectivity in the aldol reaction
- How to make *syn* aldol products
- How to make *anti* aldol products

Looking forward to:

- Saturated heterocycles ch42
- Asymmetric synthesis ch45
- Organic synthesis ch53

Looking back

You have had three chapters in a row about stereochemistry: this is the fourth, and it is time for us to bring together some ideas from earlier in the book. We aim firstly to help you grasp some important general concepts, and secondly to introduce some principles in connection with stereoselective reactions in acyclic systems. But, first, some revision.

We introduced the stereochemistry of structures in Chapter 16. We told you about two types of stereoisomers.

Enantiomers and diastereoisomers

- **Enantiomers**—stereoisomers that are mirror images of one another
- **Diastereoisomers**—stereoisomers that are not mirror images of one another

In this chapter we shall talk about how to make compounds as single diastereoisomers. Making single enantiomers is treated in Chapter 45. Chapter 33 was also about making single diastereoisomers, and we hope that, having read that chapter, you are used to thinking stereochemically.

In this chapter we shall talk about two different ways of making single diastereoisomers.

Reactions that make single diastereoisomers

- **Stereospecific reactions**—reactions where the mechanism means that the stereochemistry of the starting material determines the stereochemistry of the product and there is no choice involved
- **Stereoselective reactions**—reactions where one stereoisomer of product is formed predominantly because the reaction has a choice of pathways, and one pathway is more favourable than the other

These terms were introduced in Chapter 19 in connection with elimination reactions, and many of the reactions we mention will be familiar from earlier chapters (particularly Chapters 17–20 and 26–27).

Making single diastereoisomers using stereospecific reactions of alkenes

The essence of the definition we have just reminded you of is much easier to grasp with some familiar examples. Here are two.

- S_N2 reactions are stereospecific: they proceed with inversion so that the absolute stereochemistry of the starting material determines the absolute stereochemistry of the product

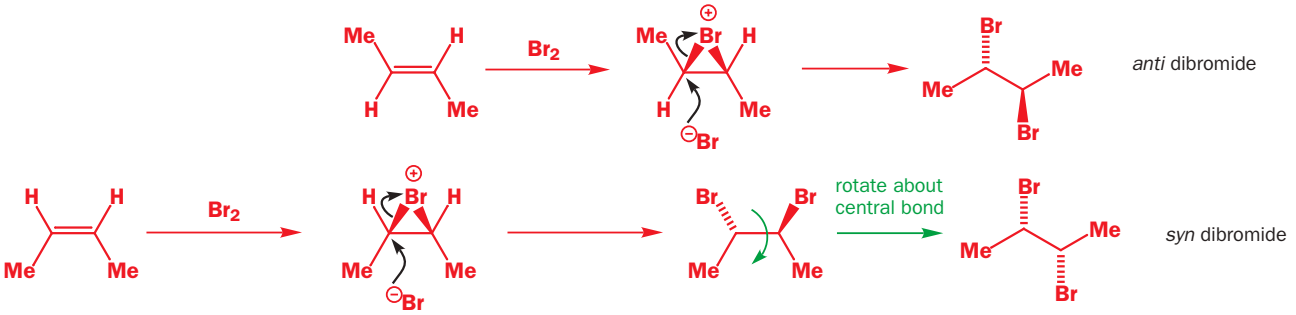
■ This is discussed in Chapter 17, p. 000.

- E2 reactions are stereospecific: they proceed through an anti-periplanar transition state, with the relative stereochemistry of the starting material determining the geometry of the product

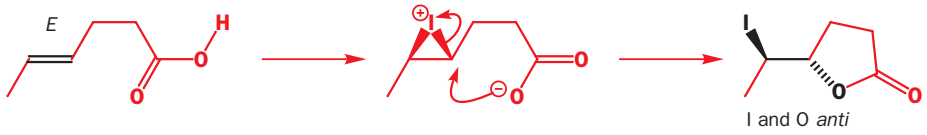
Both of these examples are very interesting because they show how, once we have some stereochemistry in a molecule, we can change the functional groups but keep the stereochemistry—this is the essence of a stereospecific reaction. In the second example, we change the bromide to a double bond, but we keep the stereochemistry (or 'stereochemical information') because the geometry of the double bond tells us which bromide we started with.

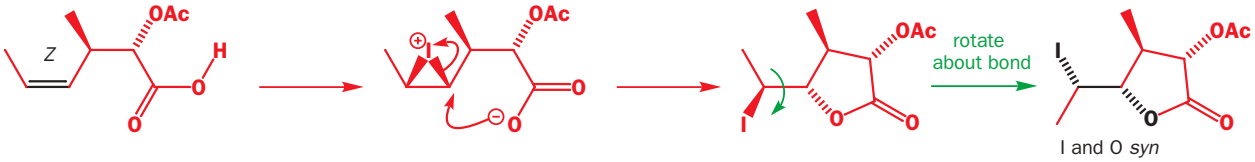
This is a good place to begin if we want to make single diastereoisomers, because we can reverse this type of reaction: instead of making a single geometry of alkene from a single diastereoisomer, we make a single diastereoisomer from a single geometry of double bond. Here is an example of this—again, one you have already met (Chapter 19). Electrophilic addition of bromine to alkenes is stereospecific and leads to *anti* addition across a double bond. So if we want the *anti* dibromide we choose to start with the *trans* double bond; if we want the *syn* dibromide we start with the *cis* double bond. The geometry of the starting material determines the relative stereochemistry of the product.

■ Chapter 31 described the methods available for controlling the geometry of double bonds.



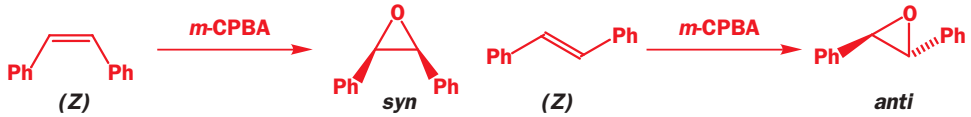
Iodolactonization has a similar mechanism; notice how in these two examples the geometry of the double bond in the starting material defines the relative stereochemistry highlighted in black in the product.



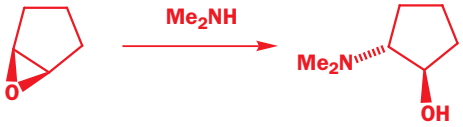


For a stereospecific alkene transformation, choose the right geometry of the starting material to get the right diastereoisomer of the product. Don't try to follow any 'rules' over this—just work through the mechanism.

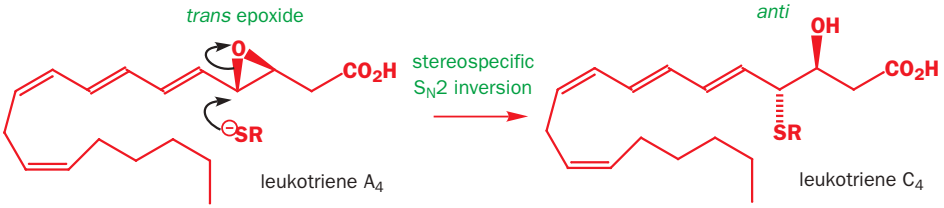
Now for some examples with epoxides. Epoxides are very important because they can be formed stereospecifically from alkenes: *cis*-alkenes give *cis* (or *syn*) -epoxides and *trans*-alkenes give *trans* (or *anti*) -epoxides.



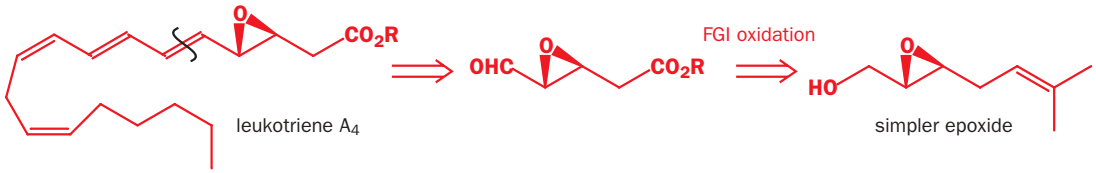
Epoxides also react stereospecifically because the ring-opening reaction is an S_N2 reaction. A single diastereoisomer of epoxide gives a single diastereoisomer of product.



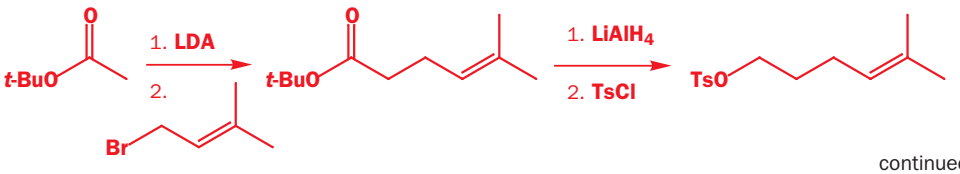
We have mentioned **leukotrienes** before: they are important molecules that regulate cell and tissue biology. Leukotriene C_4 (LTC_4) is a single diastereoisomer with an *anti* 1,2 S,O functional group relationship. In nature, this single diastereoisomer is made by an epoxide opening: since the opening is S_N2 the epoxide must start off *anti* and, indeed, the epoxide precursor is another leukotriene, LTA_4.



When Corey was making these compounds in the early 1980s he needed to be sure that the relative stereochemistry of LTC_4 would be correctly controlled, and to do this he had to make a *trans* epoxide. Disconnecting LTA_4 as shown led back to a simpler epoxide.



The *trans* allylic alcohol needed to make this compound was made using one of the methods we introduced in Chapter 31: reduction of an alkynyl alcohol with $LiAlH_4$. Here is the full synthesis: alkylation of an ester enolate with prenyl bromide gives a new ester, which itself is turned into an alkylating agent by reduction and tosylation. The alkyne is introduced as its lithium derivative with the alcohol protected as a THP acetal. Hydrolysis of the acetal with aqueous acid gives the hydroxyalkyne needed for reduction to the *E* double bond, which is then epoxidized.

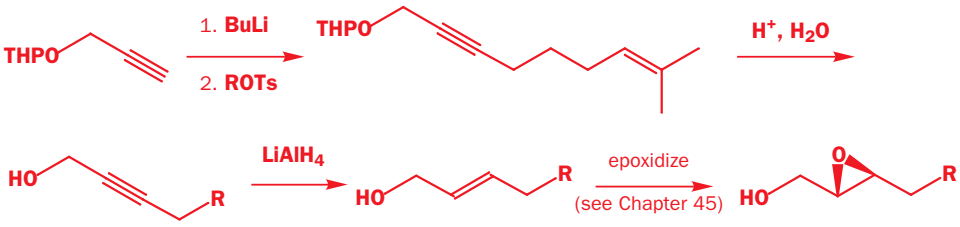


continued overleaf

There are two more stereogenic centres in the second example here and, although they do not affect the relative stereochemistry shown in black, they do affect how those two new stereogenic centres relate to the two that are already present in the starting material. We discuss how later in the chapter.

Chapter 20, p. 000.

Chapters 17 (p. 000) and 19 (p. 000).



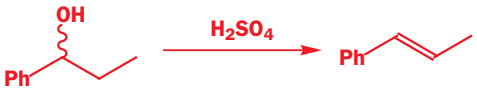
■ The epoxide was, in fact, made as a single enantiomer using the Sharpless epoxidation, which we will describe in Chapter 45.

Stereoselective reactions

For most of the rest of the chapter we shall discuss stereoselective reactions. You have already met several examples and we start with a summary of the most important methods.

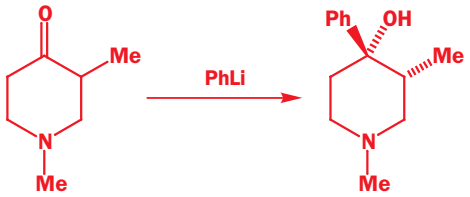
■ Chapter 18, p. 000.

- E1 reactions are stereoselective: they form predominantly the more stable alkene



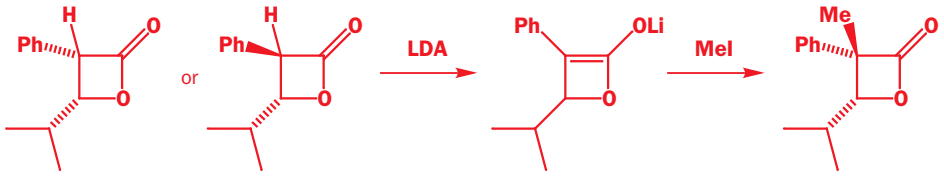
■ Chapter 33, p. 000.

- Nucleophilic attack on six-membered ring ketones is stereoselective: small nucleophiles attack axially and large ones equatorially



- Alkylation of cyclic enolates is stereoselective, with reaction taking place on the less hindered face (four- or five-membered rings) or via axial attack (six-membered rings)

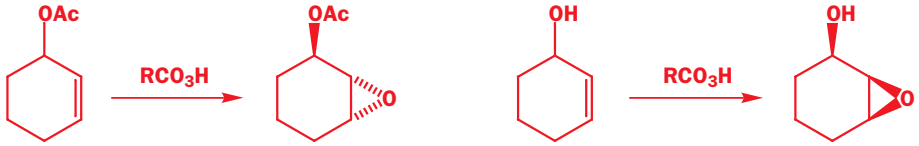
■ Chapter 33, p. 000.



▶ For a *stereoselective* reaction we can specify two different stereoisomers of the starting material and get the same product (first and third examples). In a *stereospecific* reaction, different starting material stereochemistry means different product stereochemistry.

- Epoxidation of cyclic alkenes is stereoselective, with reaction taking place on the less hindered face, or directed by hydrogen bonding to a hydroxyl group

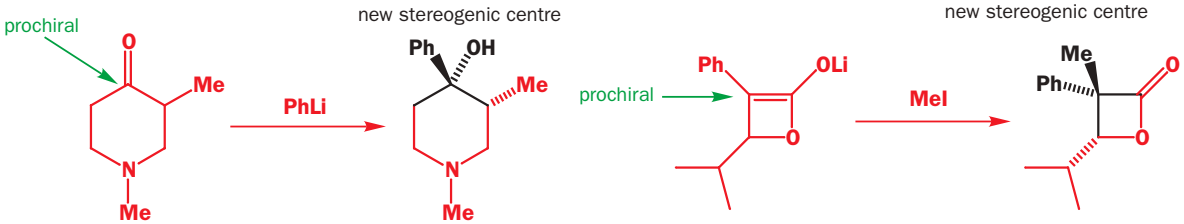
■ Chapter 33, p. 000.



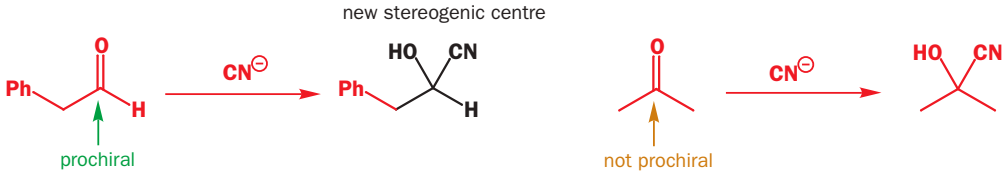
Prochirality

▶ A common misapprehension is that stereospecific means merely very stereoselective. It doesn't—the two terms describe quite different properties of the stereochemistry of a reaction.

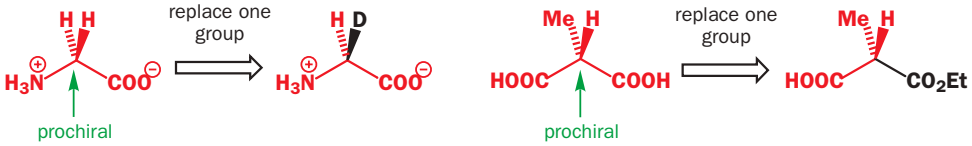
Take another look at all the reactions in the chapter so far—in particular those that give single diastereoisomers (rather than single enantiomers or geometrical isomers)—in other words, those that are **diastereoselective**. They all involve the creation of a new, tetrahedral stereogenic centre at a carbon that was planar and trigonal. This leads us to our first new definition. Trigonal carbons that aren't stereogenic (or chiral) centres but can be made into them are called **prochiral**.



At the very start of Chapter 17, we introduced stereochemistry by thinking about the reactions of two sorts of carbonyl compounds. They are shown again here: the first has a prochiral carbonyl group. The second, on the other hand, is not prochiral because no stereogenic centre is created when the compound reacts.



Tetrahedral carbon atoms can be prochiral too—if they carry two identical groups (and so are not a chiral centre) but replacement of one of them leads to a new chiral centre, then the carbon is prochiral.

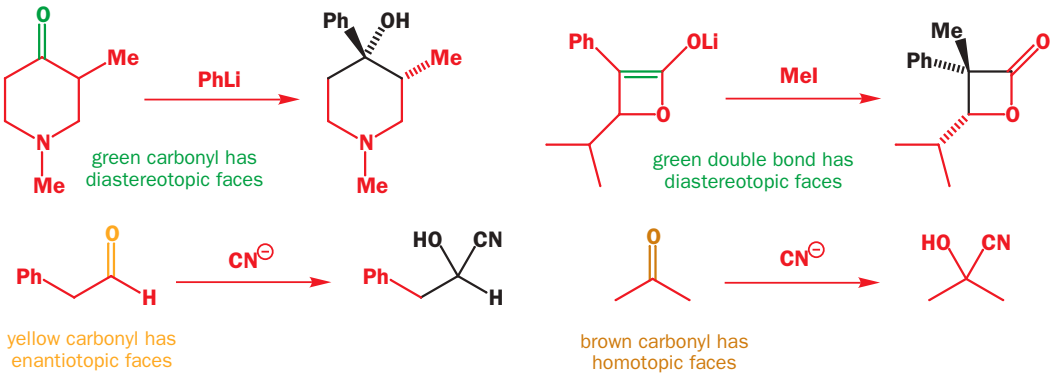


Glycine is the only α amino acid without a chiral centre, but replacing one of the two protons on the central carbon with, say, deuterium creates one: the CH_2 carbon is prochiral. Similarly, converting malonate derivative into its monoester makes a chiral centre where there was none: the central C is prochiral.

Now, does this ring any bells? It should remind you very much of the definitions in Chapter 32 of **enantiotopic** and **diastereotopic** in connection with NMR spectra. Replacing one of two enantiotopic groups with another group leads to one of two enantiomers; replacing one of two diastereotopic groups with another group leads to one of two diastereoisomers. Diastereotopic groups are chemically different; enantiotopic groups are chemically identical.

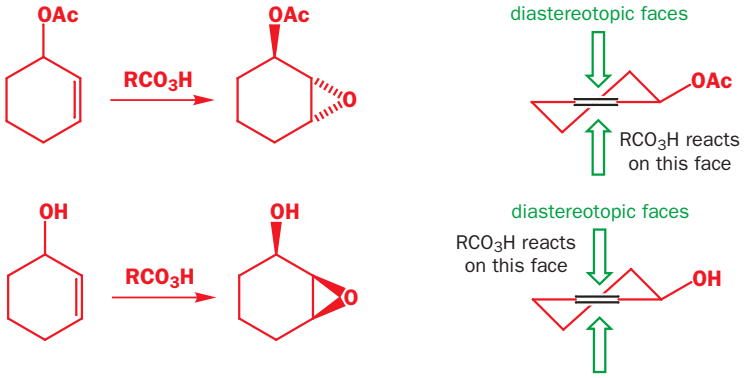
Enantiotopic and diastereotopic protons and groups are discussed in Chapter 32, p. 000.

Exactly the same things are true for the faces of a prochiral carbonyl group or double bond. If reaction on one of two faces of the prochiral group generates one of two enantiomers, the faces are enantiotopic; if the reaction generates one of two diastereoisomers, the faces are diastereotopic. We will now apply this thinking to the first few reactions in this chapter: they are shown again below. The first two examples have prochiral C=C or C=O bonds with diastereotopic faces: choosing which face of the double bond or carbonyl group to react on amounts to choosing which diastereoisomer to form. In the third example, the faces of the prochiral carbonyl group are enantiotopic: choosing which face to attack amounts to choosing which enantiomer to form. In the fourth example, the two faces of C=O are **homotopic**: an identical product is formed whichever face is attacked.



Knowing this throws some new light on the last chapter. Almost without exception, every stereoselective reaction there involved a double bond (usually C=C; sometimes C=O) with diastereotopic

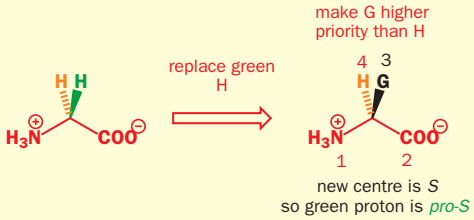
faces. The diastereotopic faces were distinguished by steric hindrance, or by a nearby hydrogen-bonding group, and so were able to react differently with an incoming reagent.

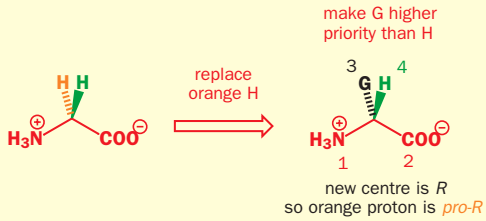


Using an *R*/*S*-type system to name prochiral faces and groups

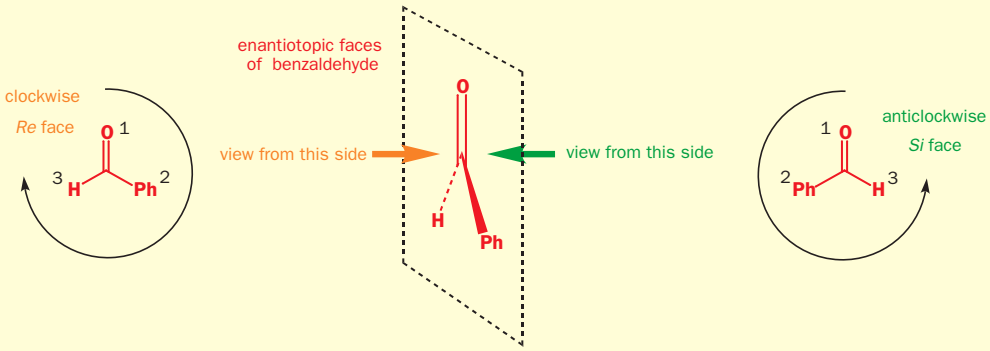
Just as stereogenic centres can be described as *R* or *S*, it is possible to assign labels to the enantiotopic groups at prochiral tetrahedral carbon atoms or the enantiotopic faces of prochiral trigonal carbon atoms. The basis of the system is the usual *R,S* system for stereogenic centres, but *pro-R* and *pro-S* are used for groups and *Re* and *Si* for faces.

Pro-R and *pro-S* can be assigned to a pair of enantiotopic groups simply by using the usual rules to assign *R* or *S* to the centre created *if* the group in question is artificially elevated to higher priority than its enantiotopic twin. We'll use G to replace H as we did in Chapter 32: just assume that G has priority immediately higher than H. The method is illustrated for glycine.



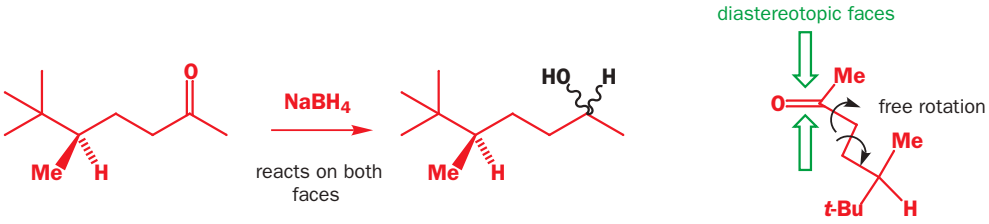


Faces of a prochiral trigonal carbon atom are assigned *Re* and *Si* by viewing the carbon from that side and counting down the groups in priority 1–3. Counting round to the right (clockwise) means the face is *Re*; counting round to the left (anticlockwise) means it's *Si*. Remember our advice from Chapter 16: think of turning a steering wheel in the direction of the numbers: does the car go to the right or the left?



Like *R* and *S*, these stereochemical terms are merely labels: they are of no consequence chemically.

Just like diastereotopic signals in an NMR spectrum, diastereotopic faces are always different in principle, but sometimes not so in practice. The very first reaction of Chapter 33 is a case in point: this C=O group has two diastereotopic faces, which, due to free rotation about single bonds, average out to about the same reactivity, so we cannot expect any reasonable level of diastereoselectivity.

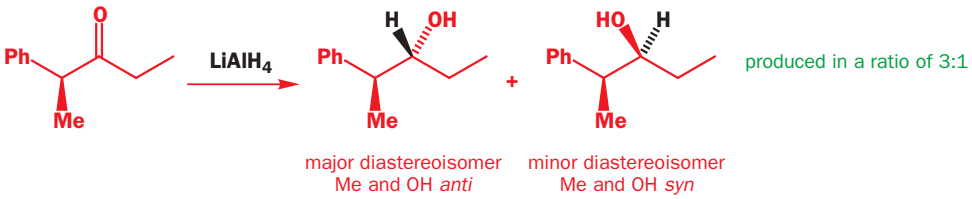


We put Chapter 33 first because in rings conformation is well defined, and this 'averaging' effect is held at bay. We are about to let it out again, but we will show you how it can be tamed to surprisingly good effect.

▶ In Chapter 32 we showed that homotopic and enantiotopic protons are identical by NMR. Similarly, homotopic faces or groups are always chemically identical. Enantiotopic faces are also chemically identical, provided that all the reagents in the reaction in question are achiral or racemic. In Chapter 45, we will consider what happens to enantiotopic faces when enantiomerically pure reagents are used.

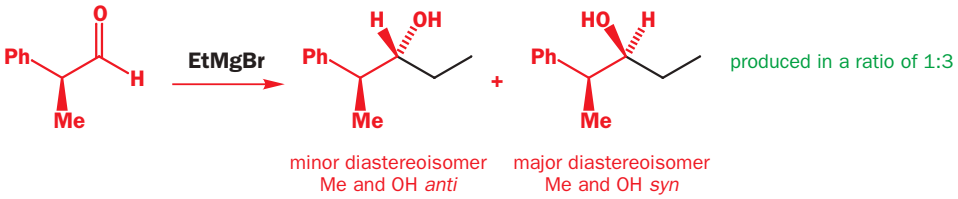
Additions to carbonyl groups can be diastereoselective even without rings

What happens if we bring the stereogenic centre closer to the carbonyl group than it was in the last example? You might expect it to have a greater influence over the carbonyl group's reactions. And it does. Here is an example.



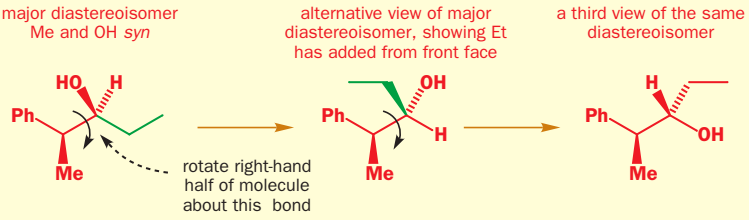
▶ We have termed the major diastereoisomer *anti* because the two substituents (Me and OH) are on opposite sides of the chain as drawn. There is no formal definition of *anti* and *syn*: they can only really be used in conjunction with a structural drawing.

There is three times as much of one of the two diastereoisomeric products as there is of the other, and the major (*anti*) diastereoisomer is the one in which the nucleophile has added to the front face of the carbonyl group as drawn here. We can make these same two diastereoisomers by addition of an organometallic to an aldehyde. For example, this Grignard reagent gives three times as much of the *syn* diastereoisomer as the *anti* diastereoisomer. The major product has changed, but the product still arises from attack on the front face of the carbonyl as shown.



Drawing diastereoisomers of acyclic molecules

If you find it hard to see that these are still the same two diastereoisomers, try mentally rotating the right-hand half of the molecule about the bond shown below. The next three structures all show the same diastereoisomer (the major product from the last reaction), but in three different conformations (we are just rotating about a bond to get from one to another).



Which is the best? A good guideline, which we suggested in Chapter 16, is to place the longest carbon chain zig-zagging across the page in the plane of the paper, and allow all the smaller substituents to extend above or below that chain. The first structure here is drawn like that. But this is only a guideline, and the second structure here is a bit more informative regarding the reaction because,when it is drawn like this, you can clearly see from which direction the ethyl group has attacked the carbonyl. Our advice would be that you first of all draw the product of any reaction in more or less the same conformation as the starting material to ensure you make no mistakes, and then rotate about a single bond to place the longest chain in the plane of the paper.

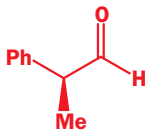
If you still have problems manipulating structures mentally—for example, if you find it hard to work out whether the substituents that aren't in the plane should be in front of or behind the page—build some models.

■ We shall draw heavily on the first part of Chapter 18 here: if you haven't read it recently, now might be a good time to refresh your memory.

These two reactions are not nearly as diastereoselective as most of the reactions of cyclic compounds you met in the last chapter. But we do now need to explain why they are diastereoselective at all, given the free rotation possible in an acyclic molecule. The key, as much with acyclic as with cyclic molecules, is **conformation**.

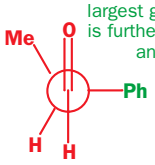
The conformation of a chiral aldehyde

What will be the conformation of the aldehyde in the margin? Using the principles we outlined in Chapter 17, we can expect it to be staggered, with no eclipsing interactions, and also with large substituents as far apart from one another as possible. A Newman projection of one of the possible conformers might look like the one shown in the margin. There are no eclipsing interactions, and the large phenyl group is held satisfactorily far away from the O and the H atoms of the aldehyde.



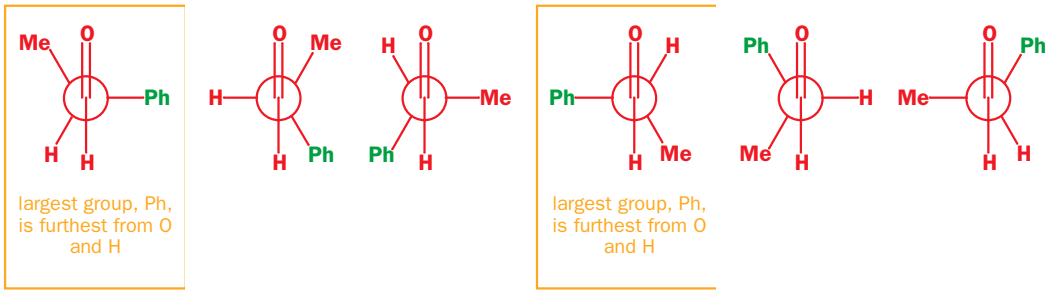
no eclipsing interactions

largest group, Ph, is furthest from O and H



Newman projection of one possible conformation

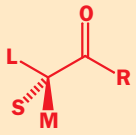
By rotating about the central bond of the aldehyde (the one represented by a circle in the Newman projection) we can suggest a series of possible conformations. Provided we move in 60° steps, none of them will have any eclipsing interactions. The full set of six conformers is shown here. Look at them for a moment, and notice how they differ.



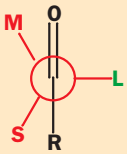
Only two of them, boxed in yellow, place the large Ph group perpendicular to the carbonyl group. These yellow boxed conformations are therefore the lowest-energy conformers and, for the purpose of the discussion that follows, they are the only ones whose reactions we need to consider.

● Lowest energy conformations of a carbonyl compound

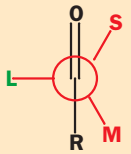
The most important conformations of a carbonyl compound with a stereogenic centre adjacent to the carbonyl group are those that place the largest group perpendicular to the carbonyl group.



most important conformations are



and

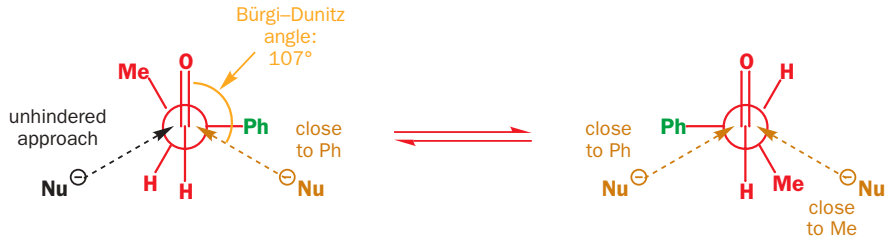


L = large group, e.g. Ph
M = medium-sized group, e.g. Me
S = small group, e.g. H

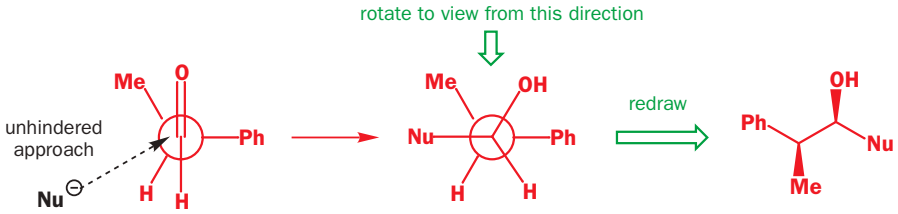
The major product arises from the most reactive conformer

■ We introduced the idea that attack on a C=O group followed this trajectory in Chapter 6.

Now that we have decided which are the important conformations, how do we know which gives the product? We need to decide which is the *most reactive*. All we need to do is to remember that any nucleophile attacking the carbonyl group will do so from the Bürgi–Dunitz angle—about 107° from the C=O bond. The attack can be from either side of C=O, and the following diagrams show the possible trajectories superimposed on the two conformations we have selected, which are in equilibrium with one another.



Not all four possible 'flight paths' for the nucleophile are equally favourable. For the three shown in brown, the nucleophile passes within 30° or so of another substituent. But, for the one shown in black, there is no substituent nearby except H to hinder attack: the conformation on the left is the most reactive one, and it reacts to give the diastereoisomer shown below.



With Nu = Et we have the right product and, more importantly, we can be pretty sure it is for the right reason: this model of the way a nucleophile attacks a carbonyl compound, called the **Felkin–Anh model**, is supported by theoretical calculations and numerous experimental results. Notice that we don't have to decide which is the lower energy of the two conformations: this is not necessary because the attack in black will occur even if the conformer on the left is the minor one in the mixture.

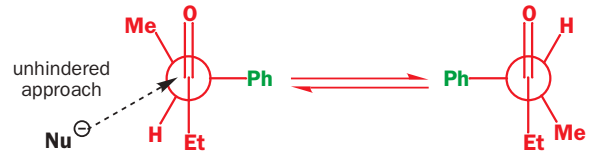
▶ Remember our guideline: draw the product in a conformation similar to that of the starting material; then redraw to put the longest chain in the plane of the paper. Here, this just means drawing the view from the top of the Newman projection—there is no need to rotate any bonds in this case.

▶ This is an example of the **Curtin–Hammett principle**, which says that it is the relative energies of the transition states that control selectivity, not the relative energies of the starting materials. It's really more of a reminder not to make a mistake than a principle.

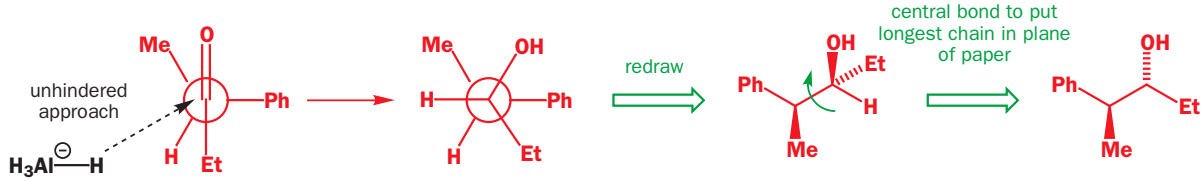
Cram's rule

You may hear 'Cram's rule' used to explain the outcome of reactions involving attack on chiral carbonyl compounds. Cram was the first to realize that these reactions could be predicted, but we now know why these compounds react in a predictable way. We will not describe Cram's rule because, although it often does predict the right product, in this case it does so for the wrong reason. Explanations and clear logical thinking are more important than rules, and you must be able to account for and predict the reactions of chiral aldehydes and ketones using the Felkin–Anh model.

The same reasoning accounts for the diastereoselectivity of the reduction on p. 000: first we need to draw the two important conformers of the ketone; the ones that have the large group (Ph) perpendicular to the C=O group.

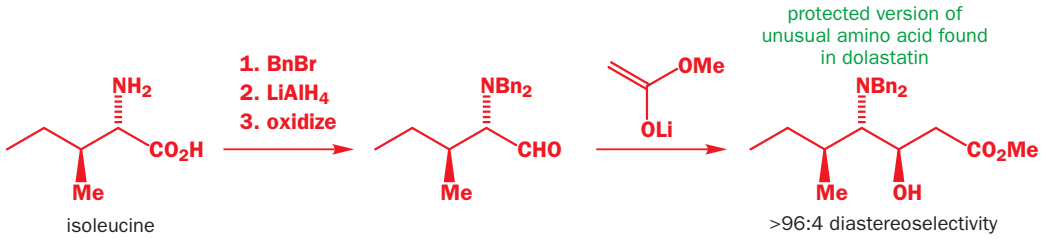


Now choose the angle of attack that is the least hindered, and draw a Newman projection of the product. Finally, redraw the Newman projection as a normal structure, preferably with the longest chain in the plane of the paper.



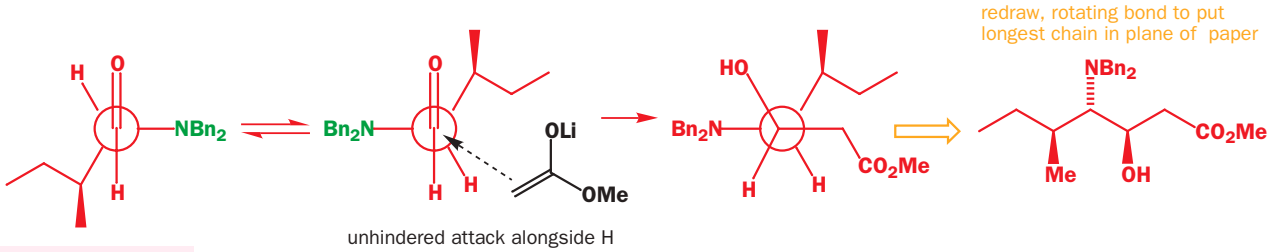
The effect of electronegative atoms

One of the most powerful anticancer agents known is dolastatin, isolated from the sea-hare *Dolabella*. Dolastatin contains an unusual amino acid, with three stereogenic centres, and chemists in Germany managed to exploit Felkin–Anh control very effectively to make it from the much more widespread amino acid isoleucine. This is the sequence of reactions.



The key step is the aldol reaction of the enolate of methyl acetate with the protected amino aldehyde. To rationalize the stereoselectivity, we first need to draw the two most important conformations of this aldehyde with the large group perpendicular to C=O. The trouble is—which do we choose as 'large': the $-NBn_2$ group or the branched alkyl group? Since we know which diastereoisomer is produced we can work backwards to find that it must be the NBn_2 group that sits perpendicular to C=O in the reactive transition state, and not alkyl.

▶ Try for yourself putting alkyl perpendicular to C=O: you will get the wrong diastereoisomer.



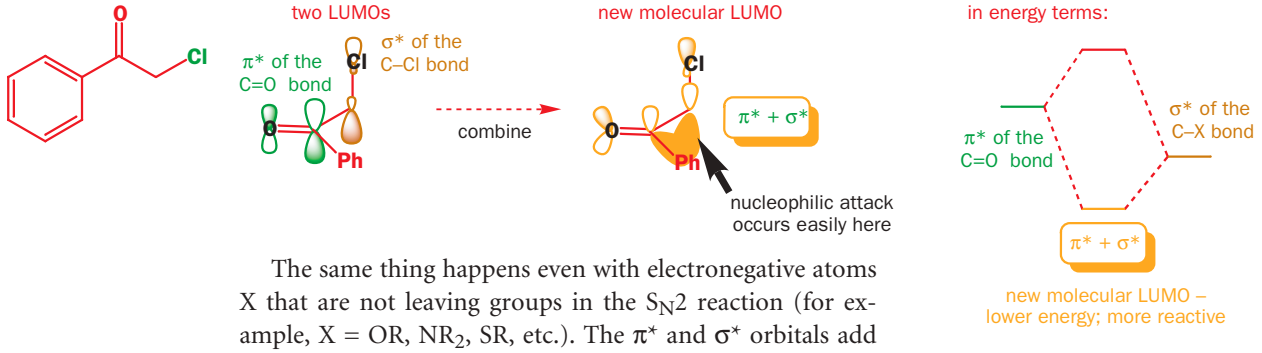
Now look at the diastereoselectivity of the reaction: it is much greater than the 3:1 we saw before—more like 20:1. This really does suggest that there is a further factor at work here, and that further factor is the electronegative N atom.

▶ When you see a selectivity given as 'greater than' something, it means that the other diastereoisomer was undetectable, but here 96:4 was the limit of detection by the method used—possibly NMR.

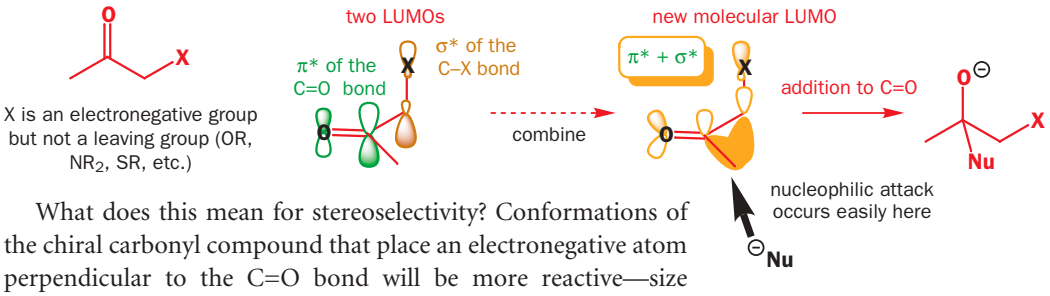
Carbonyl groups increase the reactivity of adjacent leaving groups towards nucleophilic substitution by several orders of magnitude. This was an effect that we noted in Chapter 17, where we showed that the ketone below reacts by the S_N2 mechanism 5000 times as fast as methyl chloride itself.

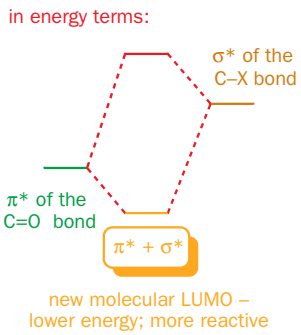
■ This is discussed on p. 000 of Chapter 17.

We explained this effect by saying that the π^* of the C=O and the σ^* of C–Cl overlap to form a new, lower-energy (and therefore more reactive) LUMO. What we did not note then, because it was not relevant, is that this overlap can only occur when the C–Cl bond is perpendicular to the C=O bond, because only then are the π^* and σ^* orbitals aligned correctly.



The same thing happens even with electronegative atoms X that are not leaving groups in the S_N2 reaction (for example, X = OR, NR_2, SR, etc.). The π^* and σ^* orbitals add together to form a new, lower-energy molecular orbital, more susceptible to nucleophilic attack. But, if X is not a leaving group, attack on this orbital will result not in nucleophilic substitution but in addition to the carbonyl group. Again, this effect will operate only when the C–X and C=O bonds are perpendicular so that the orbitals align correctly.





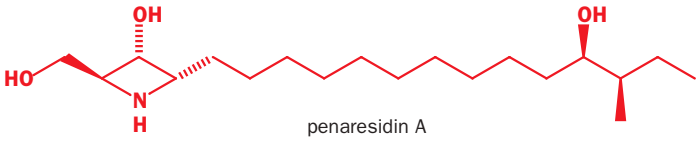
What does this mean for stereoselectivity? Conformations of the chiral carbonyl compound that place an electronegative atom perpendicular to the C=O bond will be more reactive—size doesn't matter. So, in the dolastatin amino acid example, the conformations with NBn_2 perpendicular to C=O are the only conformations we need to consider.

Using the Felkin–Anh model

To predict or explain the stereoselectivity of reactions of a carbonyl group with an adjacent stereogenic centre, use the Felkin–Anh model.

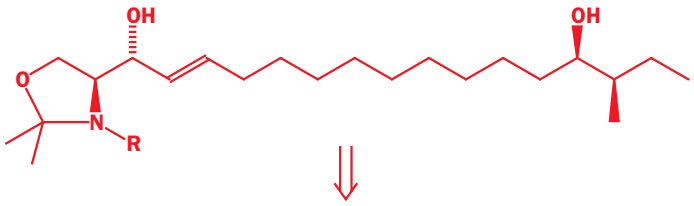
- **Draw Newman projections of the conformations of the starting material that place a large group or an electronegative group perpendicular to C=O**
- **Allow the nucleophile to attack along the least hindered trajectory, taking into account the Bürgi–Dunitz angle**
- **Draw a Newman projection of the product that arises from attack in this way**
- **Carefully flatten the Newman projection on to the page to produce a normal structure, preferably with the longest chain of C atoms in the plane of the page. Check that you have done this last step correctly: it is very easy to make mistakes here. Use a model if necessary, or do the 'flattening out' in two stages—first view the Newman projection from above or below and draw that; then rotate some of the molecule about a bond if necessary to get the long chain into the plane of the page.**

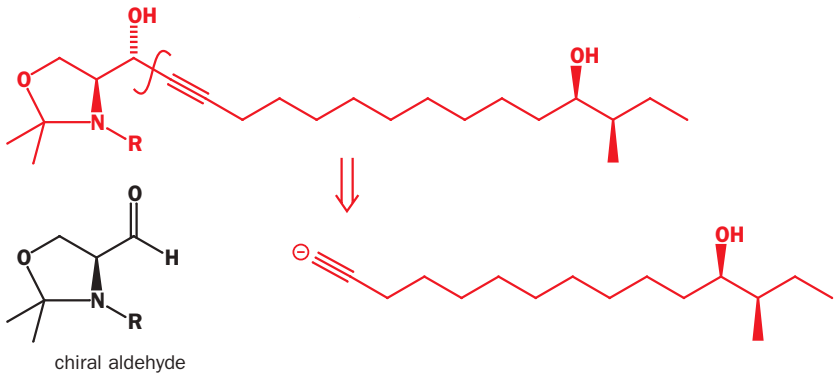
As an illustration of two sorts of diastereoselectivity, our next example is a natural product called penaresidin A. It was isolated from a Japanese sponge in 1991, and has the structure shown below



penaresidin A

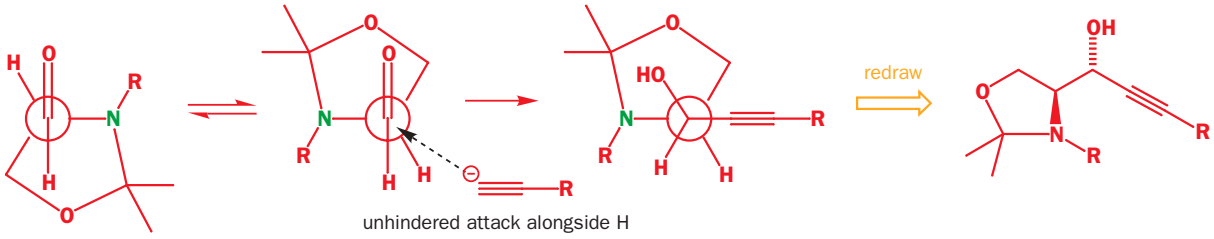
or something like this, because at the time of writing the relative stereochemistry between the two remotely related groups of chiral centres is still not known for sure. What is sure is the stereochemistry around the ring: NMR (the methods of Chapter 32) gives that. What Mori and his co-workers set out to do was to make, using unambiguous stereoselective methods, all the possible diastereoisomers of penaresidin A to discover which was the same as the natural product. It was fairly straightforward to get to the target molecule from the structure below and overleaf, so that's the compound whose synthesis we need to consider. If we imagine getting the *E*-alkene by stereoselective reduction of the alkyne, disconnection to an alkynyl anion equivalent reveals an aldehyde with a chiral centre next to the carbonyl group.



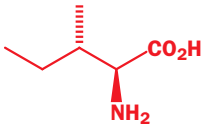


chiral aldehyde

How will this aldehyde (which can be made from the amino acid serine) react with nucleophiles such as lithiated alkynes? Consider a Felkin–Anh transition state: again, we know that the nitrogen, being electronegative, will lie perpendicular to the carbonyl group in the most reactive conformation, so we need only consider these two. The least hindered direction of attack is shown, and that indeed gives the required product.

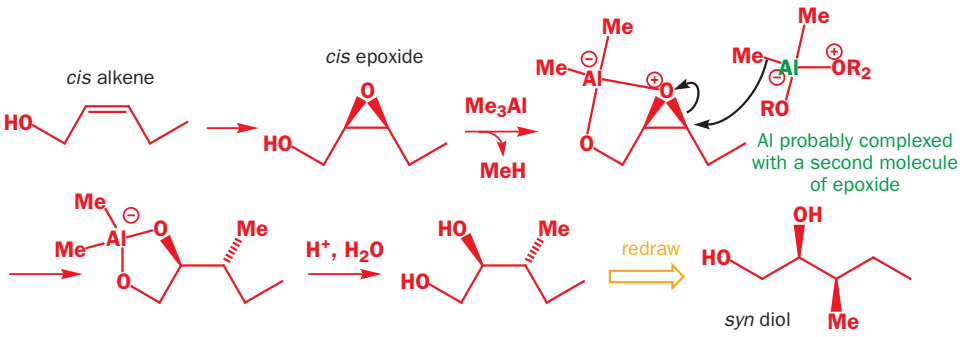


unhindered attack alongside H



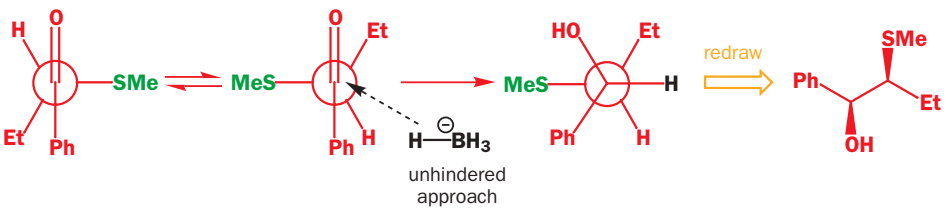
isoleucine

The other two chiral centres need to be controlled separately. The *trans* relative configuration could be obtained from another amino acid, which itself has two stereogenic centres—isoleucine. The *cis* was harder. The chemists decided to make it by starting with the *cis* diol shown, which could come from ring opening of an epoxide with an aluminium reagent. Since the ring opening goes with inversion, the epoxide needs to be *cis*, so the ultimate starting material was chosen to be a *cis* allylic alcohol. It turned out that the *cis* stereochemistry was right.



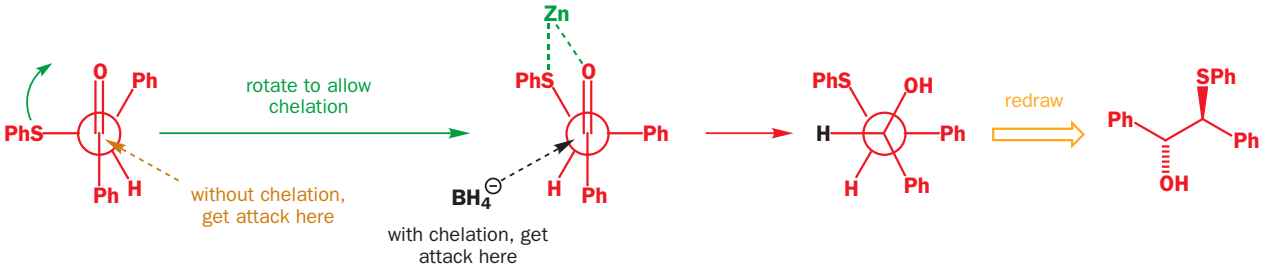
Chelation can reverse stereoselectivity

You should now be in a position to explain the outcome of this reaction without much difficulty. Sulfur is the electronegative atom, so the conformations we need to consider are the two following. Unhindered attack on the second gives the diastereoisomer shown.



But, from what we have told you so far, the next reaction would present a problem: changing the metal from sodium to zinc has reversed the stereoselectivity. Using the simple Felkin–Anh model now does not work: it gives the wrong answer.

The reason is that zinc can chelate sulfur and the carbonyl group. **Chelation** is the coordination of two heteroatoms carrying lone pairs to the same metal atom, and here it changes the conformation of the starting material. No longer does the most reactive or most populated conformation place the electronegative S atom perpendicular to C=O; instead it prefers S to lie as close to the carbonyl oxygen as possible so that Zn can bridge between S and O, like this.



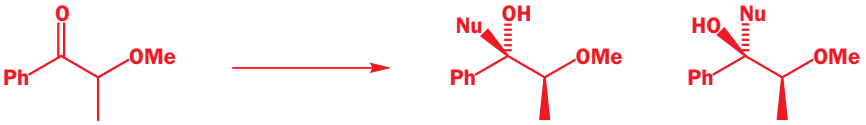
When chelation is possible, this is the conformation to consider—the one with the carbonyl O and the other chelating atom almost eclipsing one another. It is the most populated, because it is stabilized by the chelation, and it is also the most reactive, because the Lewis-acidic metal atom increases the reactivity of the carbonyl group. Attack is still along the less hindered pathway, but this now leads to the other face of the carbonyl group, and the stereochemical outcome is reversed.

Two things are needed for chelation to occur:

- a heteroatom with lone pairs available for coordination to a metal
- a metal ion that prefers to coordinate to more than one heteroatom at once. These are mainly more highly charged ions as shown in the table

Metals commonly involved in chelation	Metals not usually involved in chelation
Li^+ sometimes	Li^+ often
Mg^{2+}	Na^+
Zn^{2+}	K^+
Cu^{2+}	
Ti^{4+}	
Ce^{3+}	
Mn^{2+}	

Here is another example of a reversal in selectivity that can be explained using a nonchelated Felkin–Anh model with Na^+ and a chelated model with Mg^{2+}.

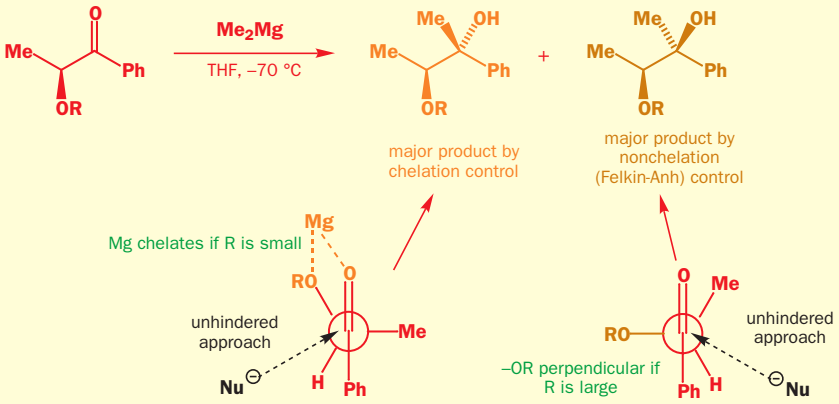


$NaBH_4$ (Nu = H)	73%	27%
Me_2Mg (Nu = Me)	1%	99%

Not only does chelation control reverse the stereoselectivity, but it gives a much higher *degree* of stereoselectivity. Stereoselectivities in chelation-controlled additions to C=O groups are typically >95:5. But this fits in nicely with the ideas we presented at the end of the last chapter: stereoselectivity is likely to be high if a cyclic transition state is involved. Chelation involves just such a transition state, so it should be no surprise that it lets us achieve much higher levels of control than the acyclic Felkin–Anh model does.

Chelation, rate, and stereoselectivity

The correlation of rate of addition with diastereoselectivity was demonstrated in a series of experiments that involved reacting Me_2Mg with protected α-hydroxy-ketones. As the protecting group was changed from a methyl ether to a trimethylsilyl ether and then through a series of increasingly bulky silyl ethers, both the rate of the reaction and the diastereoselectivity decreased. With small protecting groups, the reaction takes place through the chelated transition state—the selectivity shows this—and the rate is faster because of the activating effect of the Lewis-acidic magnesium ion. But with larger protecting groups, chelation of Mg^{2+} between the two oxygen atoms is frustrated: the rate drops off, and the selectivity becomes more what would be expected from the Felkin–Anh model.

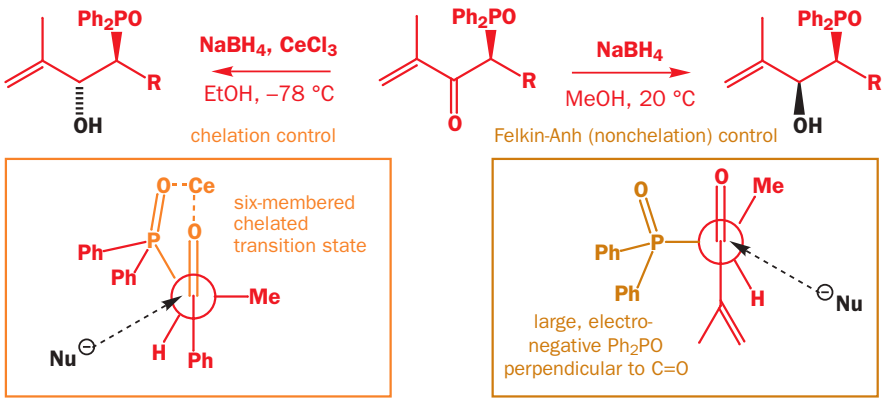


R	Ratio	Relative rate
Me	>99:1	1000
$SiMe_3$	99:1	100
$SiEt_3$	96:4	8
$SiMe_2t$-Bu	88:12	2.5
$SiPh_2t$-Bu	63:37	0.82
$Si(i\text{-}Pr)_3$	42:58	0.45

● Chelation

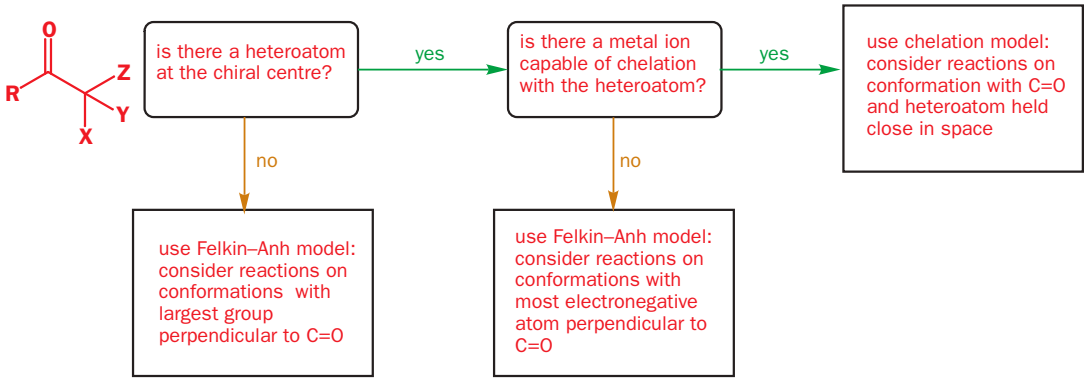
- may change the direction of diastereoselectivity
- leads to high levels of diastereoselectivity
- increases the rate of the addition reaction

Chelation is possible through six- as well as five-membered rings, and the reduction of the ketone below is a nice example of the reversal of diastereoselectivity observed when chelating Ce^{3+} ions are added to a normal sodium borohydride reduction. The products were important for making single geometrical isomers of alkenes in a modification of the Wittig reaction (Chapter 31). Notice too how the rate must change: with Ce^{3+} the reaction can be done at –78 °C.



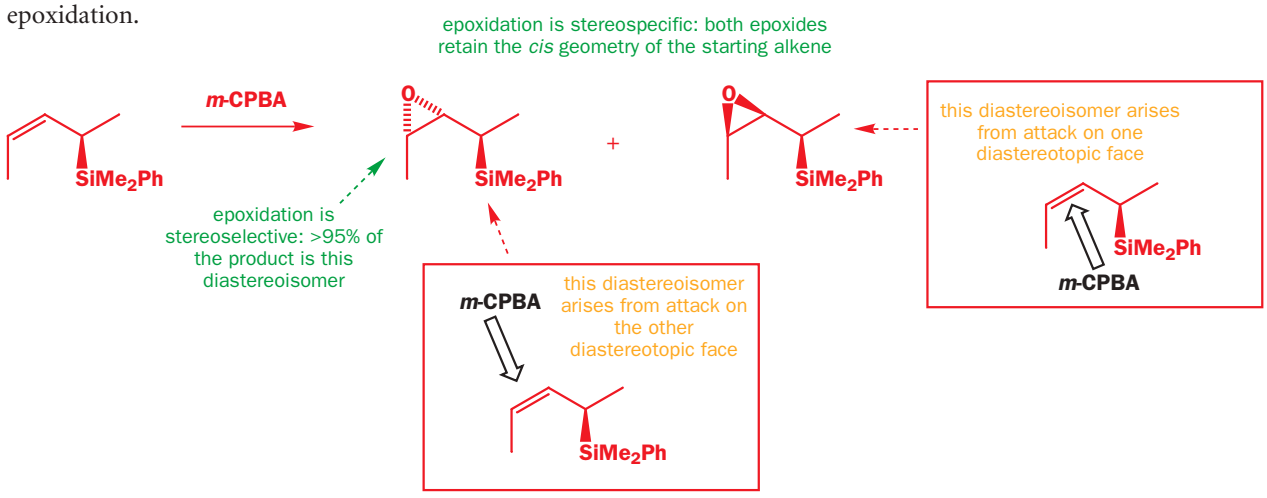
Attack on α chiral carbonyl compounds: summary

The flow chart summarizes what you should consider when you need to predict or explain the stereochemical outcome of nucleophilic attack on a chiral carbonyl compound.



Stereoselective reactions of acyclic alkenes

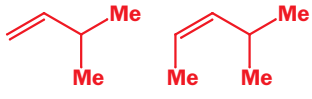
Earlier in the chapter we discussed how to make single diastereoisomers by stereospecific additions to double bonds of fixed geometry. But if the alkene also contains a chiral centre there will be a stereoselective aspect to its reactions too: its faces will be diastereotopic, and there will be two possible outcomes even if the reaction is fully stereospecific. Here is an example where the reaction is an epoxidation.



The Houk model

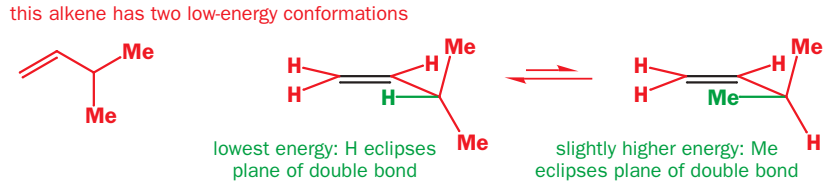
In order to explain reactions of chiral alkenes like this, we need to assess which conformations are important, and consider how they will react, just as we have done for chiral carbonyl compounds. Much of the work on alkene conformations was done by K.N. Houk using theoretical computer models, and we will summarize the most important conclusions of these studies. The theoretical studies looked at two model alkenes, shown in the margin.

■ K.N. Houk works at the University of California in Los Angeles. He has provided explanations for a number of stereochemical results by using powerful computational methods.



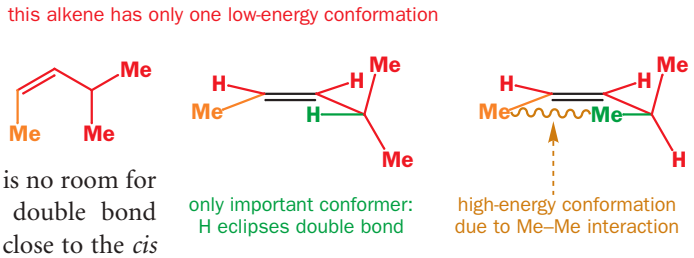
model alkene **1** model alkene **2**

The calculations found that the low-energy conformations in each case were those in which a substituent eclipses the double bond. For the simple model alkene **1**, the lowest-energy conformation is the one that has the proton in the plane of the alkene. Another low-energy conformation—only 3.1 kJ mol^{-1} higher—has one of the methyl groups eclipsing the double bond, so that when we start looking at reactions of this type of alkene, we shall have to consider both conformations.



▶ This effect—the control of conformation by a *cis* substituent—is known as **allylic strain** or $A^{1,3}$ strain. The groups involved are on carbons 1 and 3 of an allylic system.

For the model alkene **2**, with a *cis* substituent, the conformation is more predictable and the only low-energy conformer is the one with the hydrogen eclipsing the double bond. There is no room for a methyl group to eclipse the double bond because if it did it would get too close to the *cis* substituent at the other end of the double bond.



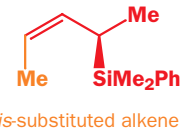
The message from the calculations is this:

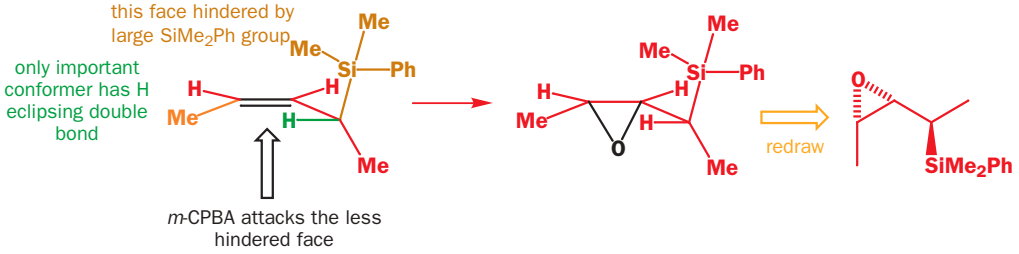
- The lowest-energy conformation of a chiral alkene will have H eclipsing the double bond
- If there is a *cis* substituent on the alkene, this will be the only important conformation; if there is no *cis* substituent, other conformations may be important too

Now we can apply the theoretical model to some real examples.

Stereoselective epoxidation

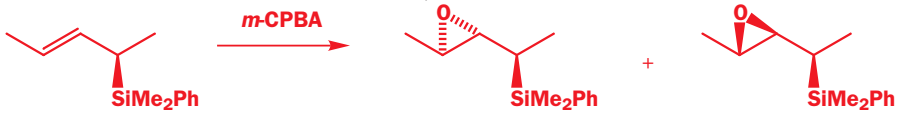
We started this section with a diastereoselective epoxidation of an alkene. The alkene was this one, and it has a substituent *cis* to the stereogenic centre. We can therefore expect it to have one important conformation, with H eclipsing the double bond. When a reagent—*m*-CPBA here—attacks this conformation, it will approach the less hindered face, and the outcome is shown.



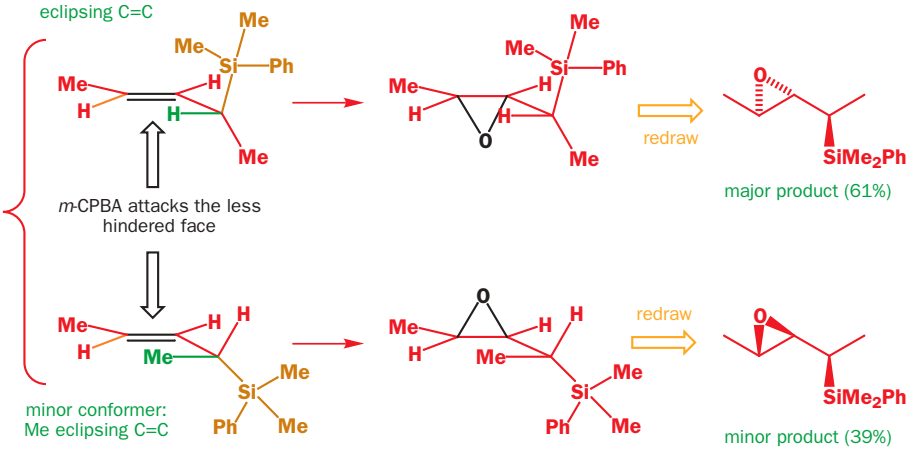


▶ Again—draw the product in the same conformation as the starting material, then flatten into the plane of the page.

Without the *cis* substituent, selectivity is much lower.



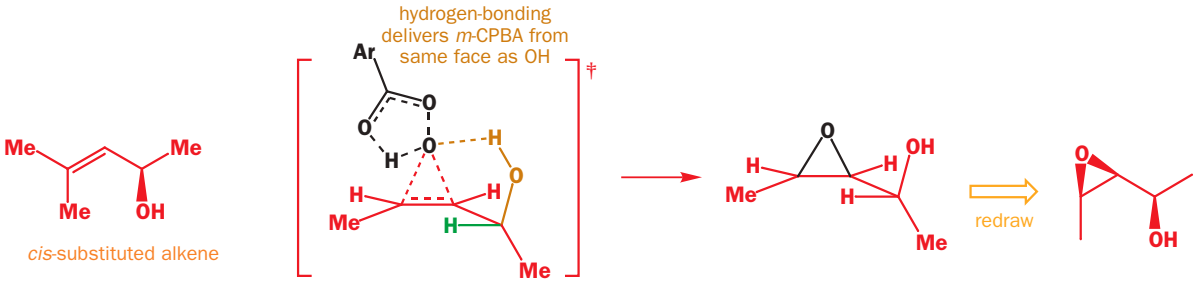
m-CPBA still attacks the less hindered face of the alkene, but with no *cis* substituent there are two low-energy conformations: one with H eclipsing the double bond, and one with Me eclipsing. Each gives a different stereochemical result, explaining the low stereoselectivity of the reaction.



You saw at the end of the last chapter that the reactions of *m*-CPBA can be directed by hydroxyl groups, and the same thing happens in the reactions of acyclic alkenes. This allylic alcohol epoxidizes to give a 95:5 ratio of diastereoisomers.

95:5 ratio of diastereoisomers

Drawing the reactive conformation explains the result. The thing that counts is the *cis* methyl group: the fact that there is a *trans* one too is irrelevant as it is just too far away from the stereogenic centre to have an effect on the conformation.

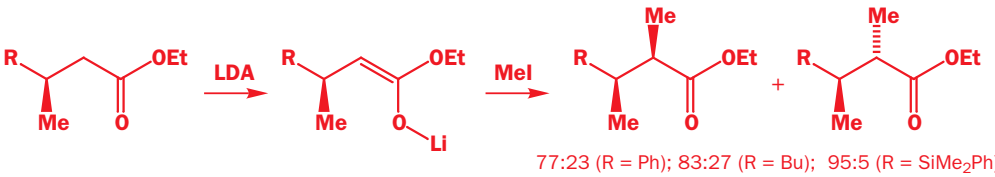


only important conformer has H eclipsing double bond

- **To explain the stereoselectivity of reactions of chiral alkenes:**
  - **Draw the conformation with H eclipsing the double bond**
  - **Allow the reagent to attack the less hindered of the two faces or, if co-ordination is possible, to be delivered to the face *syn* to the coordinating group**
  - **Draw the product in the same conformation as the starting material**
  - **Redraw the product as a normal structure with the longest chain in the plane of the paper**

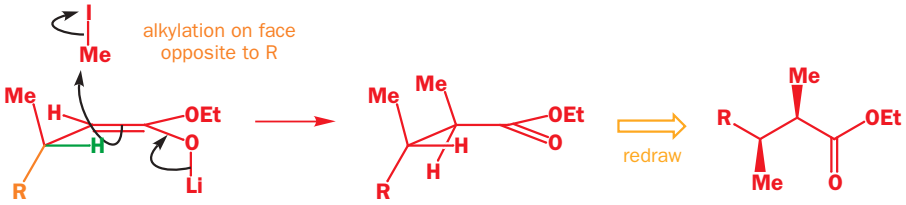
Stereoselective enolate alkylation

Chiral enolates can be made from compounds with a stereogenic centre β to a carbonyl group. Once the carbonyl is deprotonated to form the enolate, the stereogenic centre is next to the double bond and in a position to control the stereoselectivity of its reactions. The scheme below shows stereoselectivity in the reactions of some chiral enolates with methyl iodide.



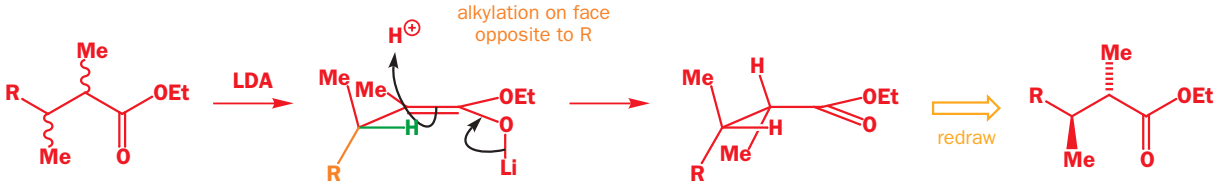
77:23 (R = Ph); 83:27 (R = Bu); 95:5 (R = $SiMe_2Ph$)

The enolate is a *cis*-substituted alkene, because either O^- or OEt must be *cis* to the stereogenic centre, so that to explain the stereoselectivity, we need consider only the conformation with H eclipsing the double bond. Notice how the diastereoselectivity increases as the group R gets bigger, because there is then more contrast between the size of Me and R. In each case, the electrophile adds to the less hindered face, opposite R.



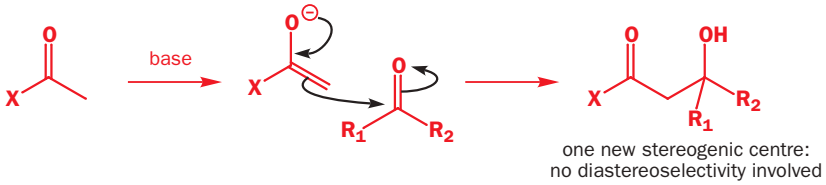
▶ The relative stereochemistry of the starting material is lost in the enolization step, so either diastereoisomer, or a mixture, can be used.

The other diastereoisomer can be made just by having the methyl group in place first and then protonating the enolate. The selectivities are lower (because a proton is small), but this does illustrate the way in which reversing the order of introduction of two groups can reverse the stereochemical outcome of the reaction.



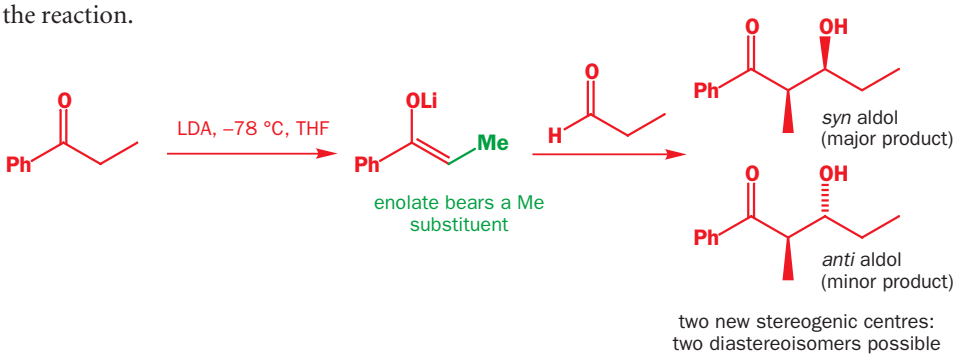
Aldol reactions can be stereoselective

In Chapter 27 you met the **aldol reaction**: reaction of an enolate with an aldehyde or a ketone. Many of the examples you saw approximated to this general pattern.



Only one new stereogenic centre is created, so there is no question of diastereoselectivity. But with substituted enolates, two new stereogenic centres are created, and we need to be able to predict which diastereoisomer will be formed. Here is an example from p. 000. We did not consider stereochemistry at that stage, but we can now reveal that the *syn* diastereoisomer is the major product of the reaction.

▶ This reaction is diastereoselective not because of stereoselective attack on one of two diastereotopic faces, but because of the way in which two prochiral reagents, each with two enantiotopic faces, come together.

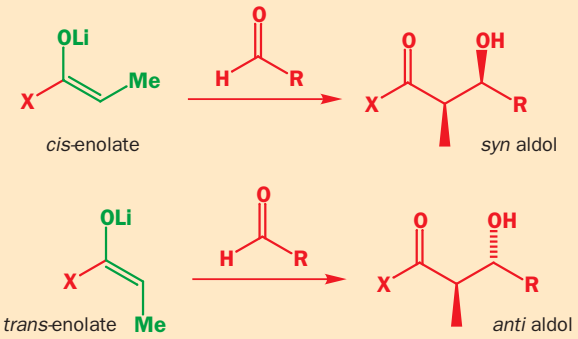


■ This is a very general rule and there are many exceptions—the enolates of some metals (Sn(II), Zr, Ti) give *syn* aldols regardless of enolate geometry. Some related reactions are discussed in Chapter 47.

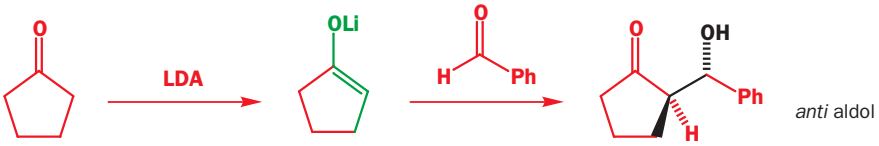
The important point about substituted enolates is that they can exist as two geometrical isomers, *cis* or *trans*. Which enolate is formed is an important factor controlling the diastereoselectivity because it turns out that, in many examples of the aldol reaction, *cis*-enolates give *syn* aldols preferentially and *trans*-enolates give *anti* aldols preferentially.

Diastereoselectivity in aldol reactions

Generally (but certainly not always!) in aldol reactions:

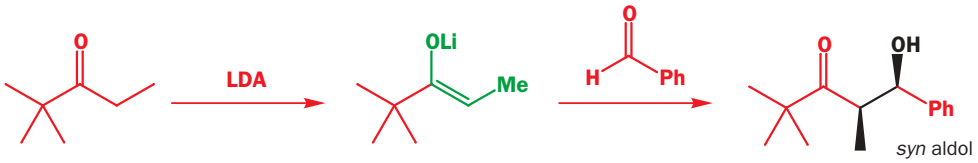


Let's start by showing some examples and demonstrating how we know this to be the case. Some enolates can only exist as *trans*-enolates because they are derived from cyclic ketones. This enolate, for example, reacts with aldehydes to give only the *anti* aldol product.



only *trans*-enolate can form

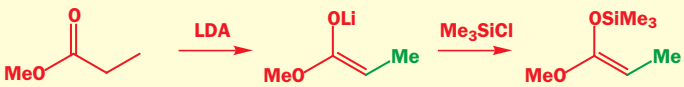
If we choose the group 'X', next to the carbonyl group, to be large, then we can be sure of getting just the *cis*-enolate. So, for example, the lithium enolate of this *t*-butyl ketone forms just as one geometrical isomer, and reacts with aldols to give only the *syn* aldol product.



cis-enolate avoids Me and *t*-Bu coming into contact

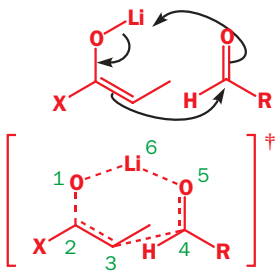
cis and *trans*, *E* and *Z*, *syn* and *anti*

Before going further, there are two points we must clarify. The first is a problem of nomenclature, and concerns the enolates of esters. Here are two closely related ester enolate equivalents, drawn with the same double bond geometry. Is it *E* or *Z*?



The answer is both! For the Li enolate, the usual rule makes OLi of lower priority than OMe, so it's *E*, while the silyl enol ether (or 'silyl ketene acetal') has OSi of higher priority than OMe, so it's *Z*. This is merely a nomenclature problem, but it would be irritating to have to reverse all our arguments for lithium enolates simply because lithium is of lower atomic number than carbon. So, for the sake of consistency, it is much better to avoid the use of *E* and *Z* with enolates and instead use *cis* and *trans*, which then always refer to the relationship between the substituent and the anionic oxygen (bearing the metal).

The other point concerns *syn* and *anti*. We said earlier that there is no precise definition of these terms: they are a useful way of distinguishing two diastereoisomers provided the structure of at least one of them is presented in diagrammatic form. For aldol products the convention is that *syn* or *anti* refers to the enolate substituent (the green Me in the last example) and the new hydroxyl group, provided the main chain is in the plane of the paper, the way we have encouraged you to draw molecules.



■ The six-membered ring transition state for the aldol reaction was proposed by Zimmerman and Traxler and is sometimes called the **Zimmerman–Traxler transition state**.

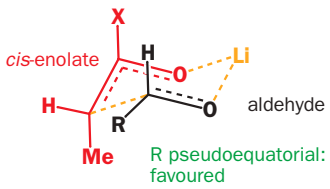
The aldol reaction has a chair-like transition state

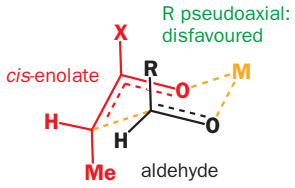
These are the experimental facts: how can we explain them? Aldol reactions are another class of stereoselective process with a cyclic transition state. During the reaction, the lithium is transferred from the enolate oxygen to the oxygen of the carbonyl electrophile. This is represented in the margin both in curly arrow terms and as a transition state structure.

A six-membered ring is involved, and we can expect this ring to adopt more or less a chair conformation. The easiest way to draw this is first to draw the chair, and then convert atoms to O or Li as necessary. Here it is.

enolate has no choice over orientation: Me must be pseudoaxial

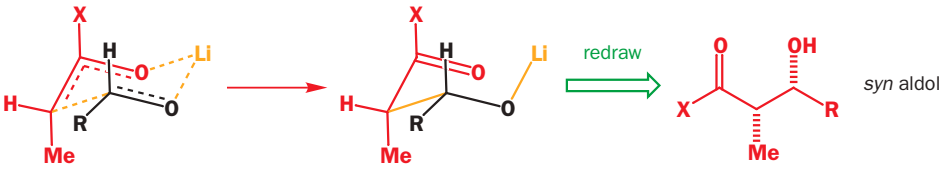
aldehyde chooses to react with R pseudoequatorial





In drawing this chair, we have one choice: do we allow the aldehyde to place R equatorial or axial? Both are possible but, as you should now expect, there are fewer steric interactions if R is equatorial. Note that the enolate doesn't have the luxury of choice. If it is to have three atoms in the six-membered ring, as it must, it can do nothing but place the methyl group pseudoaxial.

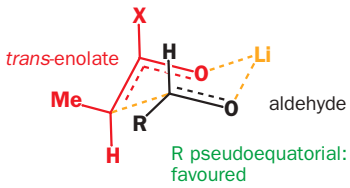
The aldol formed from the favoured transition state structure, with R pseudoequatorial, is shown below—first in the conformation of the transition state, and then flattened out on to the page, and it is *syn*.

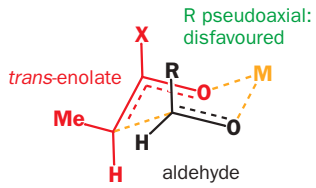


We can do the same for a *trans*-enolate. The enolate has no choice but to put its methyl substituent pseudoequatorial, but the aldehyde can choose either pseudoequatorial or pseudoaxial. Again, pseudoequatorial is better

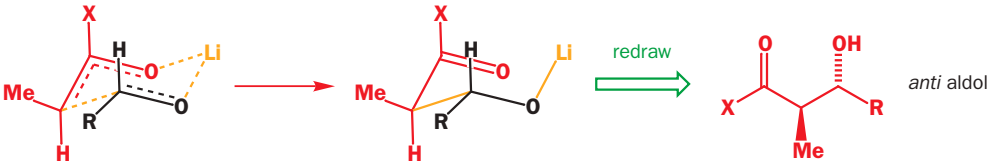
enolate has no choice over orientation: Me must be pseudoequatorial

aldehyde chooses to react with R pseudoequatorial





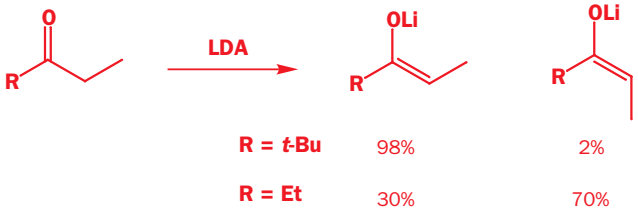
and the reaction gives the product shown—the *anti* aldol.

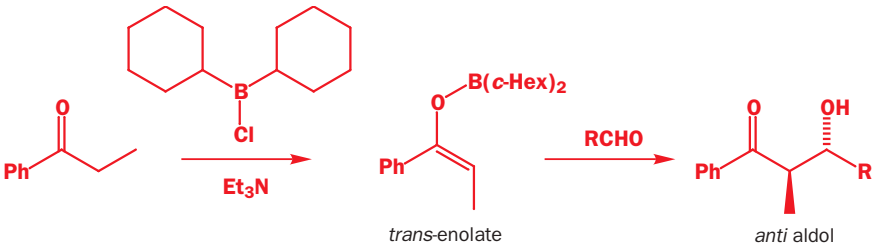


Stereoselective enolization is needed for stereoselective aldols

The cyclic transition state explains how enolate geometry controls the stereochemical outcome of the aldol reaction. But what controls the geometry of the enolate? For lithium enolates of ketones the most important factor is the size of the group that is not enolized. Large groups force the enolate to adopt the *cis* geometry; small groups allow the *trans*-enolate to form. Because we can't separate the lithium enolates, we just have to accept that the reactions of ketones with small R will be less diastereoselective.

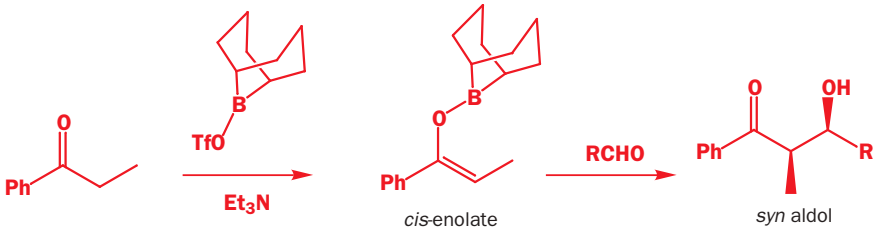
With *boron* enolates, we don't have to rely on the structure of the substrate—we choose the groups on boron—and we can get either *cis* or *trans* depending on which groups these are. Boron enolates are made by treating the ketone with an amine base (often Et_3N or *i*-$PrNEt_2$) and R_2B–X, where X^- is a good leaving group such as chloride or triflate ($CF_3SO_2^-$). With bulky groups on boron, such as two cyclohexyl groups, a *trans*-enolate forms from most ketones. The boron enolate reacts reliably with aldehydes to give *anti* aldol products through the same six-membered transition state that you saw for lithium enolates.





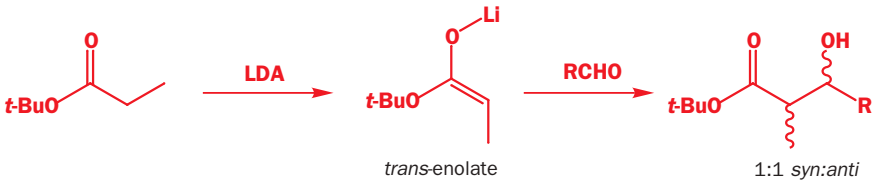
▶ In fact, geometrically defined boron enolates give the aldol products with greater stereospecificity than do lithium enolates, possibly because the B–O bonds are shorter than Li–O bonds, so the six-membered ring is 'tighter'.

With smaller B substituents, the *cis*-enolate forms selectively. Here, the boron is part of a bicyclic structure known as 9-BBN (9-borabicyclononane—you will meet this in Chapter 47). The bicyclic part may look large but, as far as the rest of the molecule is concerned, it's 'tied back' behind the boron, and the methyl group can easily lie *cis* to oxygen. The *cis*-enolate then gives *syn* aldol products. Di-*n*-butylboron triflate (Bu_2BOTf) also gives *cis*-enolates.

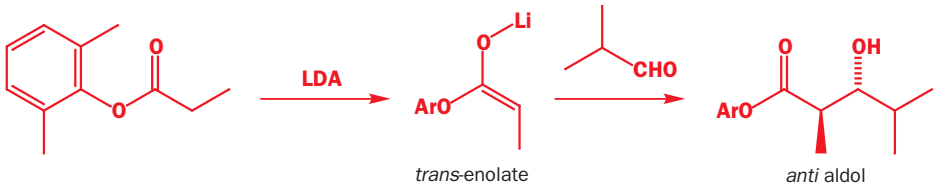


Stereoselective ester aldols

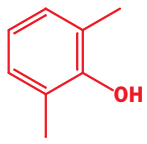
We have talked mainly about aldol reactions of ketones (as the enolate component). Esters usually form the *trans* lithium enolates quite stereoselectively. You might therefore imagine that their aldol reactions would be stereoselective for the *anti* product. Unfortunately, this is not the case, and even pure *trans*-enolate gives about a 1:1 mixture of *syn* and *anti* aldols.



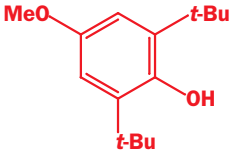
There is one important exception, and that is a class of esters of hindered phenols. The *trans*-enolates of these compounds react selectively with aldehydes to give the *anti* aldol products.



hindered phenols:

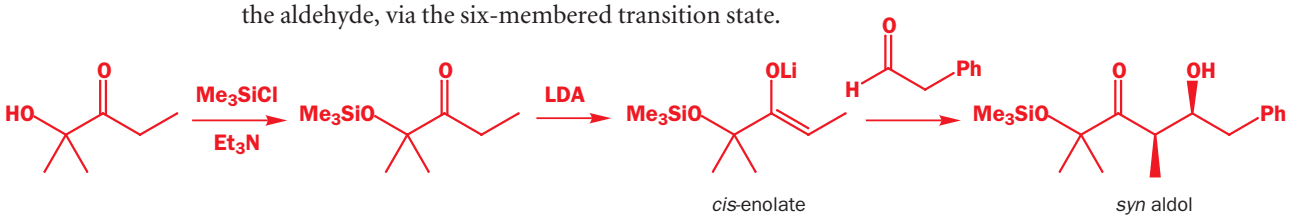


2,6-dimethylphenol

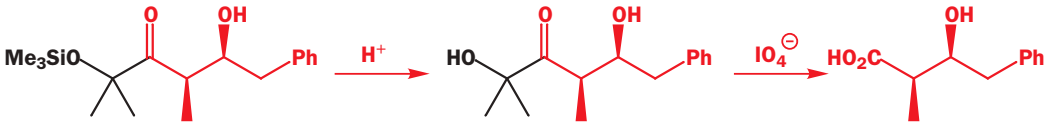


'butylated hydroxyanisole', BHA

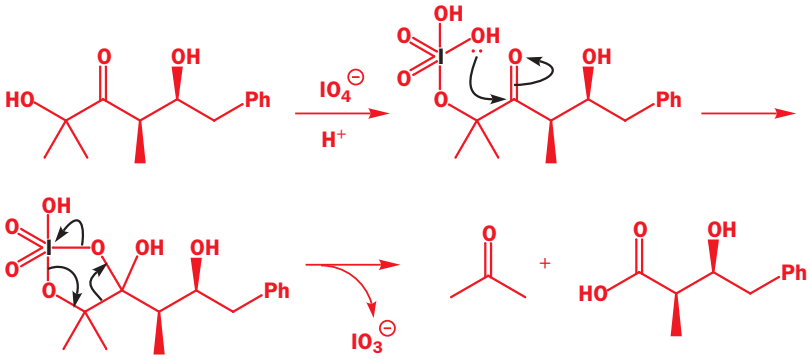
An ingenious way of getting a *syn* ester aldol product is to do the more reliable ketone *syn* aldol with a bulky group (to ensure the *cis*-enolate is formed) and then to oxidize off the bulky group. Here's what we mean. The starting material is very like the *t*-butyl ketone that you saw enolize stereoselectively above: only the *cis*-enolate can form. The enolate reacts highly *syn* selectively with the aldehyde, via the six-membered transition state.



At this point, the bulky group is no longer needed. The oxygen is deprotected in acid and, in the same step, periodate ions oxidatively cleave the C–C bond between the two oxygen substituents. The product is the acid parent of a *syn* ester aldol product.



We shall show you the mechanism of the cleavage, because it leads us nicely into the next chapter. The first step is rather like the first step of many oxidations—formation of an inorganic ester (here a periodate). The periodate can form a cyclic ester by attack on the carbonyl group. Next, we can push the arrows round the ring to reduce the iodine from I(VII) to I(V), cleave the double bond, and generate acetone and the acid.



You will see many more cyclic mechanisms in the next two chapters, including some more C–C cleavage reactions.

Summary: How to make *syn* and *anti* aldols

To make *syn* aldols of ketones:

- with a ketone RCOEt with bulky R, use lithium enolate
- use boron enolate with 9-BBN-OTf or Bu_2BOTf

To make *syn* aldols of esters:

- use a bulky 2-alkoxyketone and cleave to an acid

To make *anti* aldols of ketones:

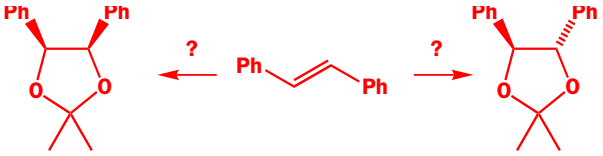
- with a cyclic ketone, use lithium enolate
- use boron enolate with dicyclohexylboron chloride

To make *anti* aldols of esters:

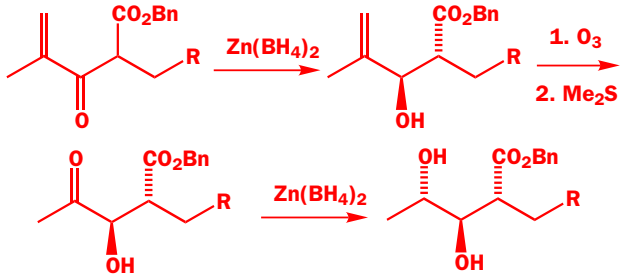
- use the ester of a hindered phenol

Problems

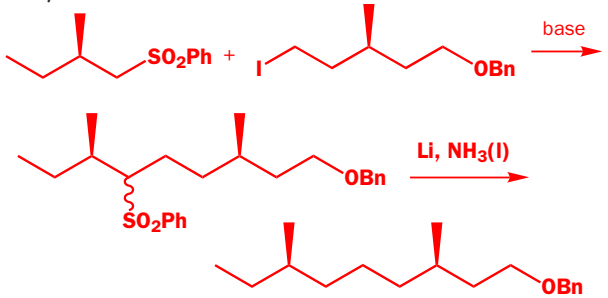
1. How would you make each diastereoisomer of this product from the same alkene?



2. Explain the stereoselectivity shown in this sequence of reactions.

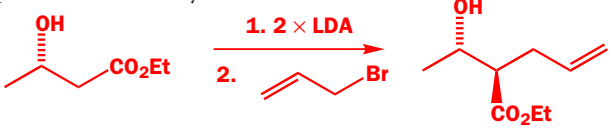


3. How is the relative stereochemistry of this product controlled? Why was this method chosen?

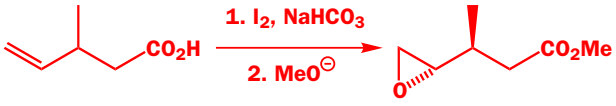


4. Explain the stereochemical control in this reaction, drawing all the intermediates.

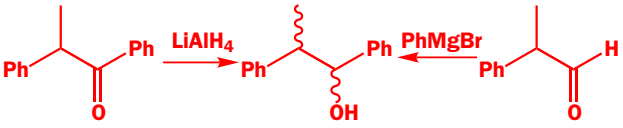
5. When this hydroxy-ester is treated with a twofold excess of LDA and then alkylated, one diastereoisomer of the product predominates. Why?



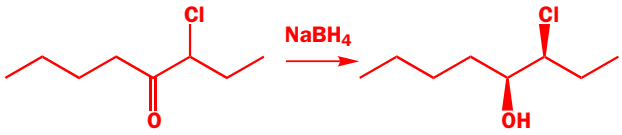
6. Explain how the stereochemistry of this epoxide is controlled.



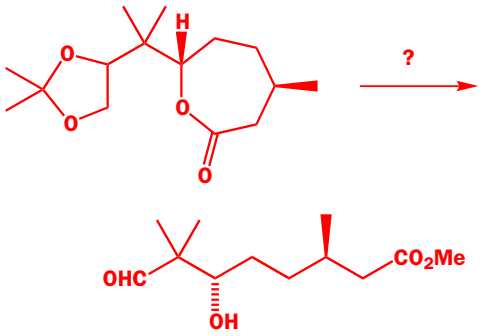
7. Explain how these two reactions give different diastereoisomers of the product.



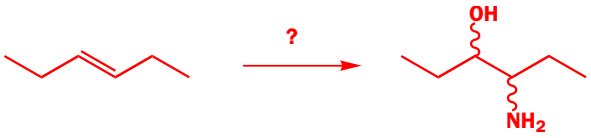
8. Explain the stereoselectivity in this reaction. What isomer of an epoxide would be produced on treatment of the product with base?



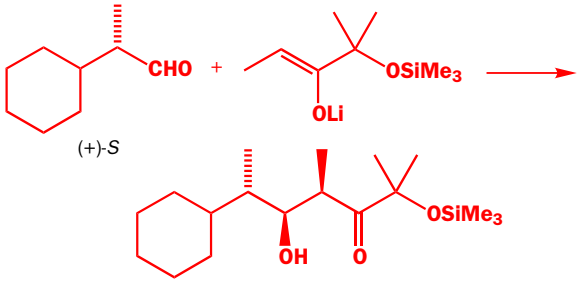
9. How could this cyclic compound be used to produce the open-chain compound with correct relative stereochemistry?



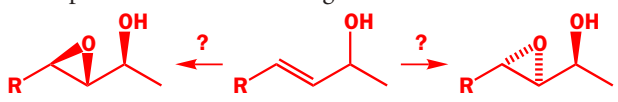
10. How would you transform this alkene stereoselectively into either of the diastereoisomers of the amino-alcohol?



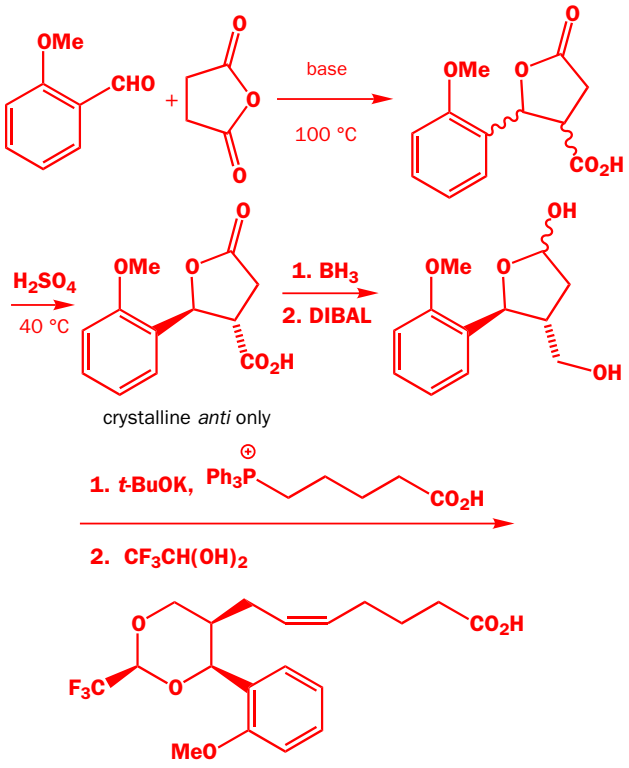
11. Explain the formation of essentially one stereoisomer in this reaction.



12. How would you attempt to transform this allylic alcohol into both diastereoisomers of the epoxide stereoselectively? You are not expected to estimate the degree of success.



13. Revision. Here is an outline of the AstraZeneca synthesis of a thromboxane analogue. Explain the reactions, giving mechanisms for each step, and explain how the stereochemistry is controlled. In what way could this be considered an example of the control of open-chain stereochemistry when all of the molecules are cyclic?



Pericyclic reactions 1: cycloadditions 35

Connections

Building on:

- Structure of molecules ch4
- Reaction mechanisms ch5
- Conjugation and delocalization ch7

Arriving at:

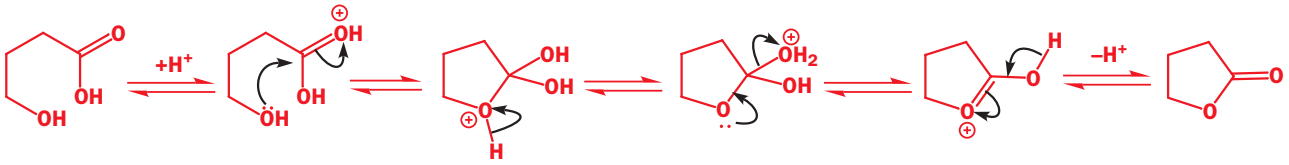
- In cycloadditions electrons move in a ring
- In cycloadditions more than one bond is formed simultaneously
- There are no intermediates in cycloadditions
- Cycloadditions are a type of pericyclic reaction
- The rules that govern cycloadditions: how to predict what will and will not work
- Photochemical reactions: reactions that need light
- Making six-membered rings by the Diels–Alder reaction
- Making four-membered rings by [2 + 2] cycloaddition
- Making five-membered rings by 1,3-dipolar cycloaddition
- Using cycloaddition to functionalize double bonds stereospecifically
- Using ozone to break C=C double bonds

Looking forward to:

- Electrocyclic reactions and sigmatropic rearrangements ch36
- Radical reactions ch39
- Aromatic heterocycles ch43–ch44
- Asymmetric synthesis ch45
- Organic synthesis ch53

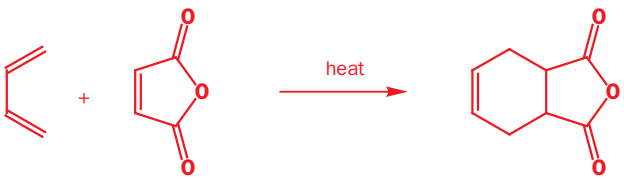
A new sort of reaction

Most organic reactions are ionic. Electrons move from an electron-rich atom towards an electron-poor atom: anions or cations are intermediates. Formation of a cyclic ester (a lactone) is an example.



The reaction involves five steps and four intermediates. The reaction is acid-catalysed and each intermediate is a cation. Electrons flow in one direction in each step—towards the positive charge. This is an ionic reaction.

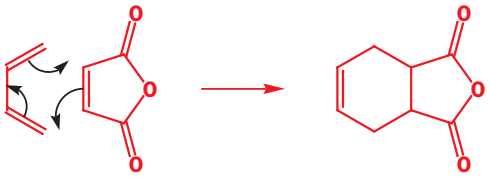
This chapter is about a totally different reaction type. Electrons move round a circle and there are no positive or negative charges on any intermediates—indeed, there are no intermediates at all. This type of reaction is called **pericyclic**. The most famous example is the **Diels–Alder reaction**.



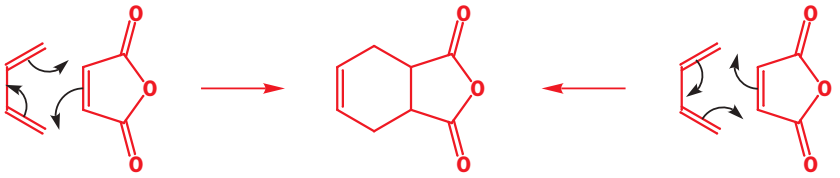
▶ In Chapter 39 you will meet a third category—radical reactions—in which one electron instead of two is on the move.

■ Otto Diels (1876–1954) and his research student Kurt Alder (1902–58) worked at the University of Kiel and discovered this reaction in 1928. They won the Nobel Prize in 1950. Diels also discovered the existence of carbon suboxide, C_2O_3 (see p. 000).

This reaction goes in a single step simply on heating. We can draw the mechanism with the electrons going round a six-membered ring.



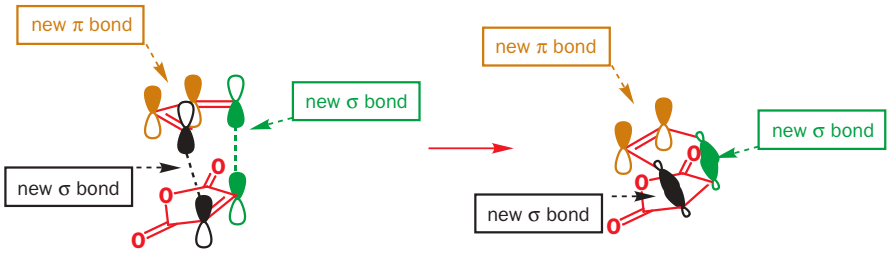
Each arrow leads directly to the next, and the last arrow connects to the first. We have drawn the electrons rotating clockwise, but it would make no difference at all if we drew the electrons rotating anticlockwise.



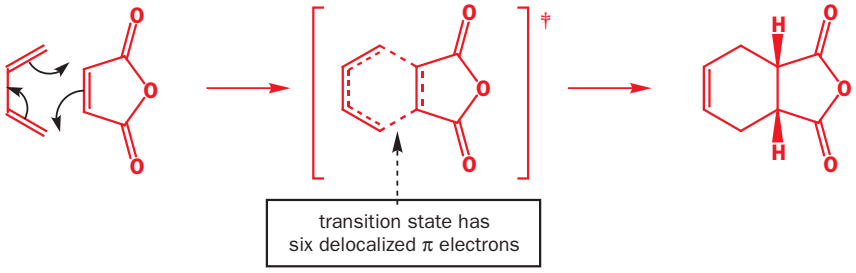
Both mechanisms are equally correct. The electrons do not really rotate at all. In reality two π bonds disappear and two σ bonds take their place by the electrons moving smoothly out of the π orbitals into the σ orbitals. Such a reaction is called a **cycloaddition**. We must spend some time working out how this could happen.

■ Cycloadditions are the first of three classes of pericyclic reactions, and the whole of this chapter will be devoted to cycloadditions. The other two—sigmatropic and electrocyclic reactions—are discussed in Chapter 36.

First, just consider the orbitals that overlap to form the new bonds. Providing the reagents approach in the right way, nothing could be simpler.



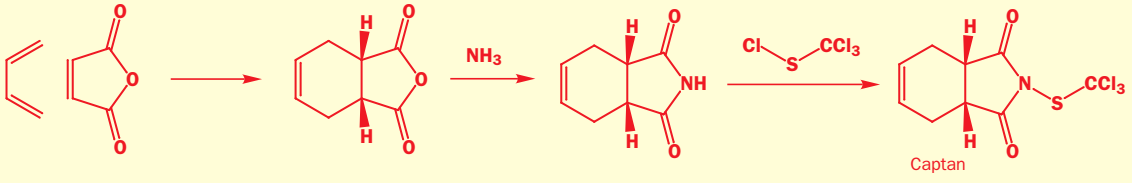
The black p orbitals are perfectly aligned to make a new σ bond as are the two green orbitals, while the two brown orbitals are exactly right for the new π bond at the back of the ring. As this is a one-step reaction there are no intermediates but there is one transition state looking something like this.



One reason that the Diels–Alder reaction goes so well is that the transition state has six delocalized π electrons and thus is aromatic in character, having some of the special stabilization of benzene. You could look at it as a benzene ring having all its π bonds but missing two σ bonds. This simple picture is fine as far as it goes, but it is incomplete. We shall return to a more detailed orbital analysis when we have described the reaction in more detail.

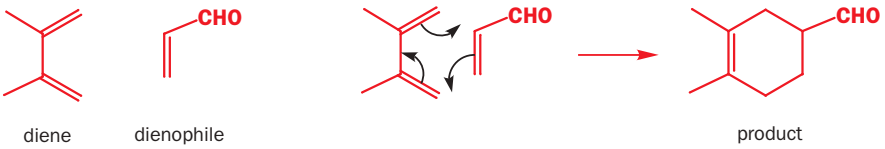
Captan

One important industrial application of the Diels–Alder reaction we have been discussing is in the synthesis of the agricultural fungicide Captan.

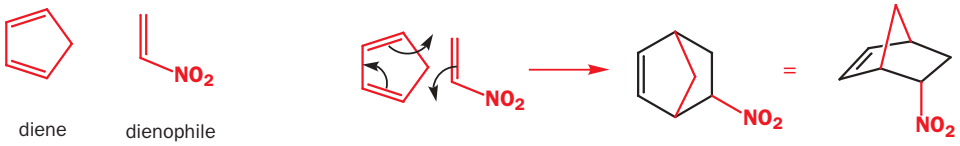


General description of the Diels–Alder reaction

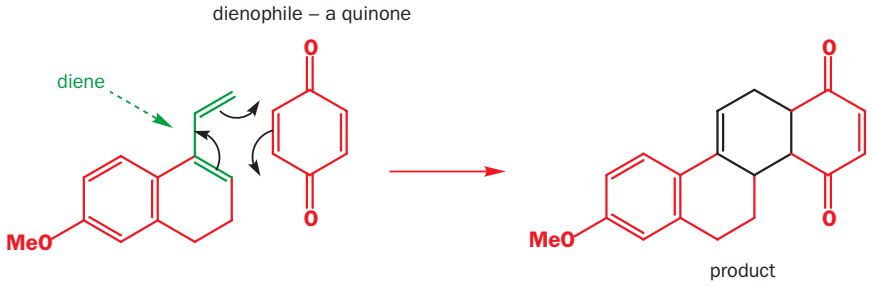
Diels–Alder reactions occur between a **conjugated diene** and an alkene, usually called the **dienophile**. Here are some examples: first an open-chain diene with a simple unsaturated aldehyde as the dienophile.



The mechanism is the same and a new six-membered ring is formed having one double bond. Now a reaction between a cyclic diene and a nitroalkene.



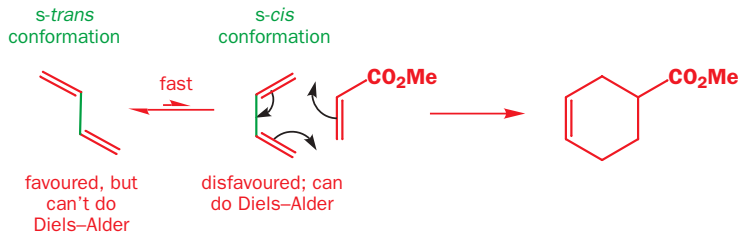
The mechanism leads clearly to the first drawing of the product but this is a cage structure and the second drawing is better. The new six-membered ring is outlined in black in both diagrams. Now a more elaborate example to show that quite complex molecules can be quickly assembled with this wonderful reaction.



The diene

The diene component in the Diels–Alder reaction can be open-chain or cyclic and it can have many different kinds of substituents. There is only one limitation: it must be able to take up the conformation shown in the mechanism. Butadiene normally prefers the **s-*trans*** conformation with the two double bonds as far away from each other as possible for steric reasons. The barrier to rotation about the central σ bond is small (about 30 kJ mol^{-1} at room temperature: see Chapter 18) and rotation to the less favourable but reactive **s-*cis*** conformation is rapid.

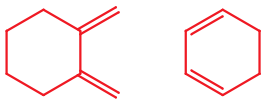
▶ The 's' in the terms 's-*cis*' and 's-*trans*' refers to a σ bond and indicates that these are con*form*ations about a single bond and not con*figur*ations about a double bond.



Cyclic dienes that are permanently in the s-*cis* conformation are exceptionally good at Diels–Alder reactions—cyclopentadiene is a classic example—but cyclic dienes that are permanently in the s-*trans* conformation and cannot adopt the s-*cis* conformation will not do the Diels–Alder reaction at all. The two ends of these dienes cannot get close enough to react with

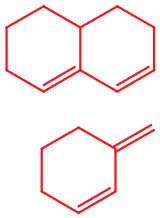
dienes permanently in the s-*cis* conformation (excellent Diels–Alder reactions)

cyclopentadiene furan



an 'exo-methylene' diene cyclohexa-1,3-diene

dienes permanently in the s-*trans* conformation (cannot do Diels–Alder reactions)



an alkene and, in any case, the product would have an impossible *trans* double bond in the new six-membered ring. (In the Diels–Alder reaction, the old σ bond in the centre of the diene becomes a π bond in the product and the conformation of that σ bond becomes the configuration of the new π bond in the product.)

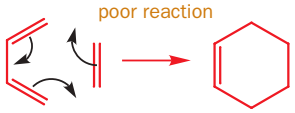
● The diene

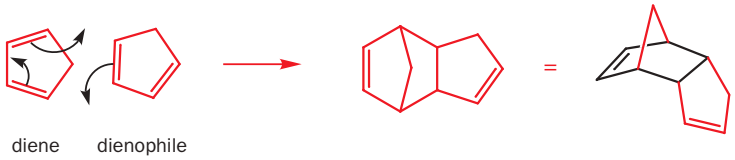
The diene must have the s-*cis* conformation.

The dienophile

The dienophiles you have seen in action so far all have one thing in common. They have an electron-withdrawing group conjugated to the alkene. This is a common though not exclusive feature of Diels–Alder dienophiles. There must be some extra conjugation—at least a phenyl group or a chlorine atom—or the cycloaddition does not occur. You will often see the reaction between butadiene and a simple alkene (even ethylene) given in books as the basic Diels–Alder reaction. This occurs in only poor yield. Attempts to combine even such a reactive diene as cyclopentadiene with a simple alkene lead instead to the dimerization of the diene. One molecule acts as the diene and the other as the dienophile to give the cage structure shown.

poor reaction

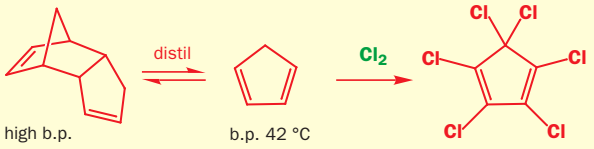




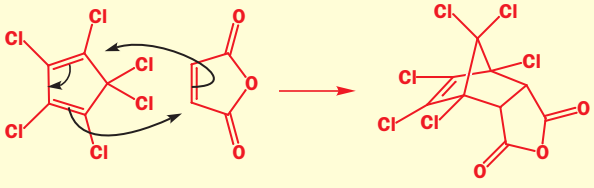
diene dienophile

Cyclopentadiene

Cyclopentadiene is formed in considerable amounts during the refining of petroleum. It exists as its dimer at room temperature but can be dissociated into the monomer on heating—the effect of the increased importance of entropy at higher temperatures (Chapter 13). It can be chlorinated to give hexachlorocyclopentadiene, and the Diels–Alder product of this diene with maleic anhydride is a flame retardant.

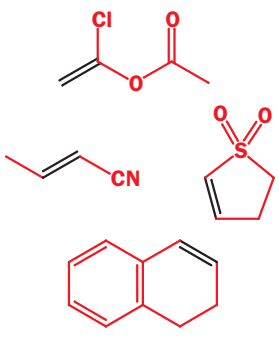


high b.p. b.p. 42 °C



flame retardant

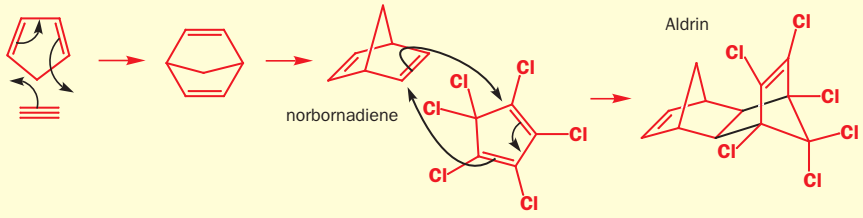
some dienophiles for the Diels–Alder reaction



Simple alkenes that do undergo the Diels-Alder reaction include conjugated carbonyl compounds, nitro compounds, nitriles, sulfones, aryl alkenes, vinyl ethers and esters, haloalkenes, and dienes. In addition to those you have seen so far, a few examples are shown in the margin. In the last example it is the isolated double bond in the right-hand ring that accepts the diene. Conjugation with the left-hand ring activates this alkene. But what exactly do we mean by 'activate' in this sense? We shall return to that question in a minute.

Dieldrin and Aldrin

In the 1950s two very effective pesticides were launched and their names were 'Dieldrin' and 'Aldrin'. As you may guess they were made by the Diels–Alder reaction. Aldrin is derived from two consecutive Diels–Alder reactions. In the first, cyclopentadiene reacts with acetylene to give a simple symmetrical cage molecule 'norbornadiene' (bicyclo[2.2.1]heptadiene). Norbornadiene is not conjugated and cannot take part in a Diels–Alder reaction as a *diene*. However, it is quite strained because of the cage and it reacts as a *dienophile* with perchlorocyclopentadiene to give Aldrin.

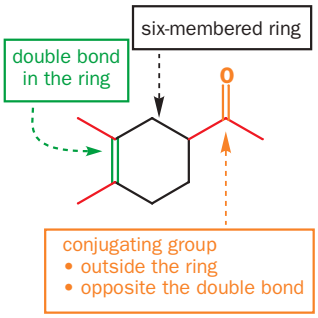


This is quite a complex product but we hope you can see how it is made up by looking at the two new bonds marked in black. Dieldrin is the epoxide of Aldrin. The use of these compounds, like that of many organochlorine compounds, was eventually banned when it was found that chlorine residues were accumulating in the fat of animals high up in the food chain such as birds of prey and humans.

The product

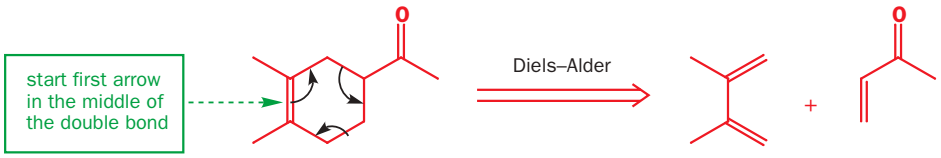
Recognizing a Diels–Alder product is straightforward. Look for the six-membered ring, the double bond inside the ring, and the conjugating group outside the ring and on the opposite side of the ring from the alkene. These three features mean that the compound is a possible Diels–Alder product.

recognizing a Diels–Alder product:

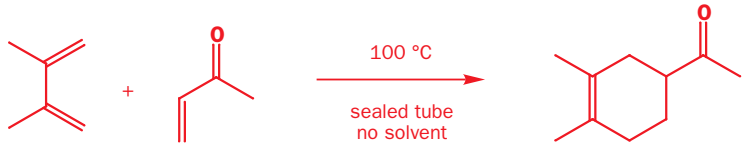


The simplest way to find the starting materials is to carry out a disconnection that is closer to a real reaction than most. Just draw the reverse Diels–Alder reaction. To do this, draw three arrows going round the cyclohexene ring starting the first arrow in the middle of the double bond. It doesn't, of course, matter which way round you go.

the disconnection is the imaginary reverse Diels–Alder reaction

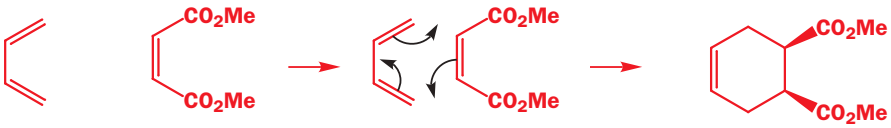


The reaction couldn't be simpler—just heat the components together without solvent or catalyst. Temperatures of around 100–150 °C are often needed and this may mean using a sealed tube if the reagents are volatile, as here.

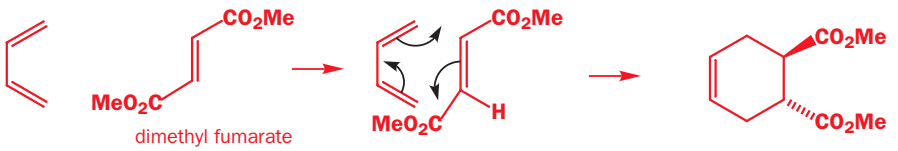


Stereochemistry

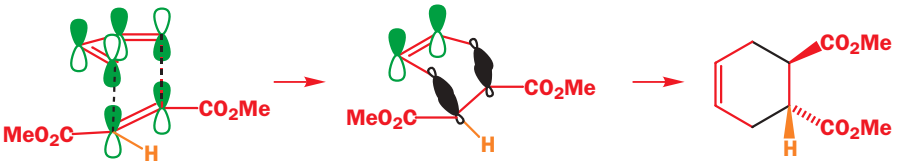
The Diels–Alder reaction is stereospecific. If there is stereochemistry in the dienophile, then it is faithfully reproduced in the product. Thus *cis* and *trans* dienophiles give different diastereoisomers of the product. Esters of maleic and fumaric acids provide a simple example.



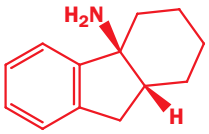
dimethyl maleate



In both cases the ester groups simply stay where they are. They are *cis* in the dienophile in the first reaction and remain *cis* in the product. They are *trans* in the dienophile in the second reaction and remain *trans* in the product. The second example may look less convincing—may we remind you that the diene actually comes down on top of the dienophile like this.

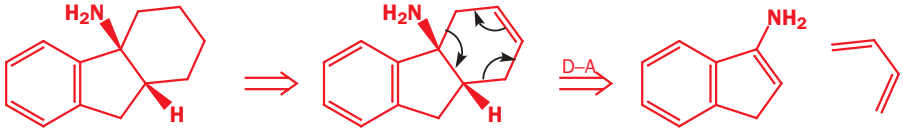


One of the CO_2Me groups is tucked under the diene in the transitions state and then, when the product molecule is flattened out in the last drawing, that CO_2Me group appears underneath the ring. The orange hydrogen atom remains *cis* to the other CO_2Me group.

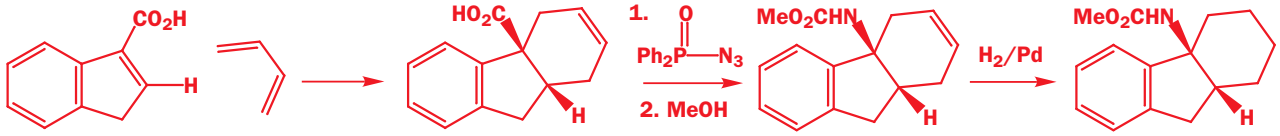


potential drugs to treat stroke

The search by the Parke–Davis company for drugs to treat strokes provided an interesting application of dienophile stereochemistry . The kinds of compound they wanted were tricylic amines. They don't look like Diels–Alder products at all. But if we insert a double bond in the right place in the six-membered ring, Diels–Alder (D–A) disconnection becomes possible.



Butadiene is a good diene, but the enamine required is not a good dienophile. An electron-withdrawing group such as a carbonyl or nitro group is preferable: either would do the job. In the event a carboxylic acid that could be converted into the amine by a rearrangement with Ph_2PON_3 (see Chapter 40) was used.

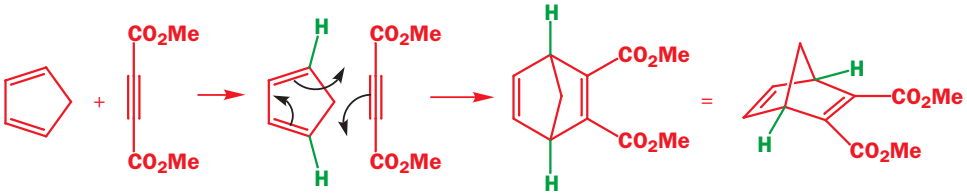


▶ You can add the Diels–Alder reaction to your mental list of reactions to consider for making a single diastereoisomer from a single geometrical isomer of an alkene: see Chapter 34.

The stereochemistry at the ring junction must be *cis* because the cyclic dienophile can have only a *cis* double bond. Hydrogenation removes the double bond in the product and shows just how useful the Diels–Alder reaction is for making saturated rings, particularly when there is some stereochemistry to be controlled.

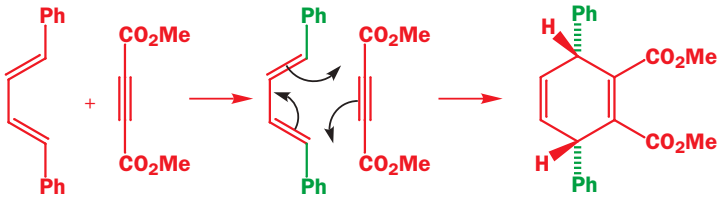
Stereochemistry of the diene

This is slightly more complicated as the diene can be *cis*, *cis*, or *cis*, *trans* (there are two of these if the diene is unsymmetrical) or *trans*, *trans*. We shall look at each case with the same dienophile, an acetylenedicarboxylate, as there is then no stereochemistry in the triple bond! Starting with *cis*, *cis*-dienes is easy if we make the diene cyclic.



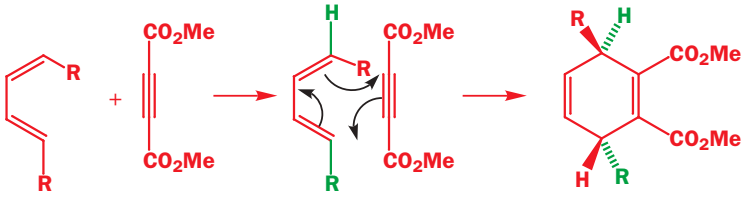
The diene has two sets of substituents—inside and outside. The inside one is the bridging CH_2 group and it has to end up on one side of the molecule (above in the last diagram) while the two green hydrogens are outside and remain so. In the final diagram they are below the new six-membered ring.

With a *trans*, *trans*-diene we simply exchange the two sets of substituents, in this example putting Ph where H was and putting H where the bridging CH_2 group was. This is the reaction.

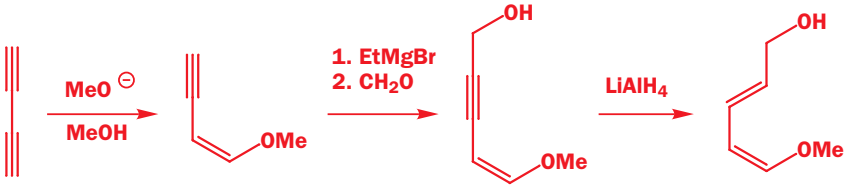


The green Ph groups end up where the hydrogens were in the first example—beneath the new six-membered ring—and the hydrogens end up above. It may seem puzzling at first that a *trans*, *trans*-diene gives a product with the two phenyls *cis*. Another way to look at these two reactions is to consider their symmetry. Both have a plane of symmetry throughout and the products must have this symmetry too because the reaction is concerned and no significant movement of substituents can occur. The black dotted line shows the plane of symmetry, which is at right angles to the paper.

The remaining case—the *cis*, *trans*-diene—is rarer than the first two, but is met sometimes. This is the unsymmetrical case and the two substituents clearly end up on opposite sides of the new six-membered ring.



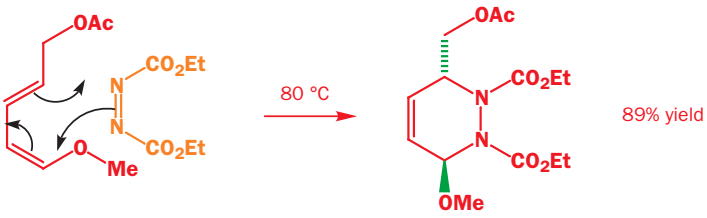
The red R group may seem to get in the way of the reaction but, of course, the dienophile is not approaching in the plane of the diene but from underneath. It is difficult to find a convincing example of this stereochemistry as there are so few known, partly because of the difficulty of making *E*,*Z*-dienes. One good approach uses two reactions you met in Chapter 31 for the control of double bond geometry. The *cis* double bond is put in first by the addition of methanol to butadiyne and the *trans* double bond then comes from $LiAlH_4$ reduction of the intermediate acetylenic alcohol.



The acetate of this alcohol is used in a Diels–Alder reaction with the interesting dienophile DEAD (diethyl azodicarboxylate—in orange).

■ The mechanism for these reactions is given on pp. 000 and 000.

■ DEAD is a key component of the Mitsunobu reaction: see p. 000.

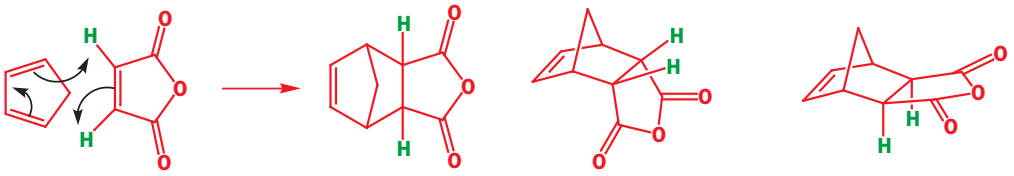


The product is formed in excellent yield and has the *trans* stereochemistry that was predicted. Do not be misled into thinking that DEAD is being shown with stereochemistry—it has none—and in the product the amide nitrogen atoms are planar and there is no stereochemistry there.

Now to the most interesting cases of all, when both the diene and the dienophile have stereochemistry.

The *endo* rule for the Diels–Alder reaction

It is probably easier to see this when both the diene and the dienophile are cyclic. All the double bonds are *cis* and the stereochemistry is clearer. In the most famous Diels–Alder reaction of all time, that between cyclopentadiene and maleic anhydride, there are two possible products that obey all the rules we have so far described.

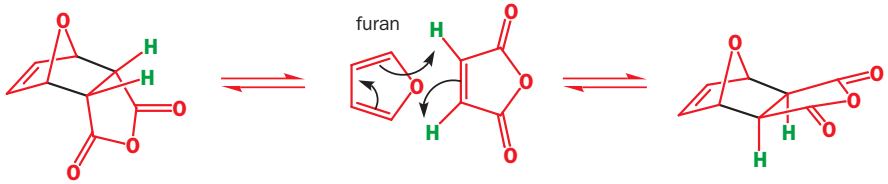


the '*endo*' adduct (formed) the '*exo*' adduct (not formed)

▶ These names arise from the relationship in space between the carbonyl groups on the dienophile and the newly formed double bond in the middle of the old diene. If these are on the same side they are called ***endo*** (inside) and if they are on opposite sides they are called ***exo*** (outside).

The two green hydrogen atoms must be *cis* in the product but there are two possible products in which these Hs are *cis*. They are called *exo* and *endo*.

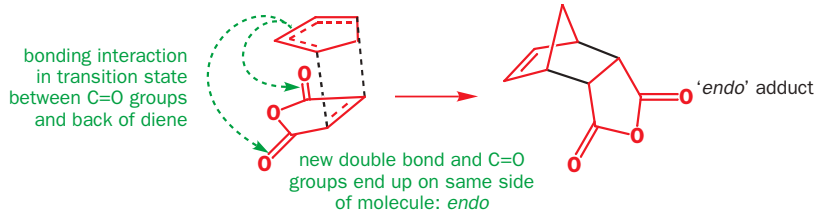
The product is, in fact, the *endo* compound. This is impressive not only because only one diastereoisomer is formed but also because it is the less stable one. How do we know this? Well, if the Diels–Alder reaction is reversible and therefore under thermodynamic control, the *exo* product is formed instead. The best known example results from the replacement of cyclopentadiene with furan in reaction with the same dienophile.



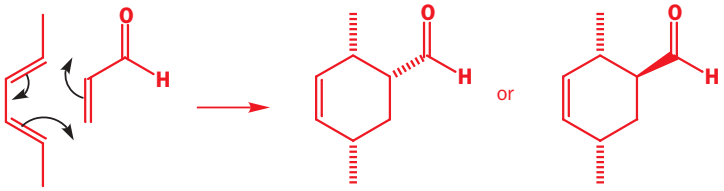
the '*endo*' adduct (less stable) the '*exo*' adduct (more stable)

Why is the *exo* product the more stable? Look again at these two structures. On the left-hand side of the molecules, there are two bridges across the ends of the new bonds (highlighted in black): a one-C-atom bridge and a two-C-atom bridge. There is less steric hindrance if the smaller (that is, the one-atom) bridge eclipses the anhydride ring.

The *endo* product is less stable than the *exo* product and yet it is preferred in irreversible Diels–Alder reactions—it must be the kinetic product of the reaction. It is preferred because there is a bonding interaction between the carbonyl groups of the dienophile and the developing π bond at the back of the diene. (The black bonds are the new σ bonds between the two reagents.)



The same result is found with noncyclic dienes and dienophiles—normally one diastereoisomer is preferred and it is the one with the carbonyl groups of the dienophile closest to the developing π bond at the back of the diene. Here is an example.

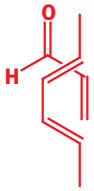


From our previous discussion we expect the two methyl groups to be *cis* to each other and the only question remaining is the stereochemistry of the aldehyde group—up or down? The aldehyde will be *endo*—but which compound is that? The easiest way to find the answer is to draw the reagents coming together in three dimensions. Here is one way to do this.

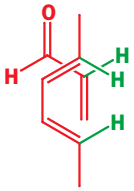
1. Draw the mechanism of the reaction and diagrams of the product to show what you are trying to decide. Put in the known stereochemistry if you wish

■ This we have just done.

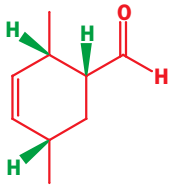
2. Draw both molecules in the plane of the paper with the diene on top and the carbonyl group of the dienophile tucked under the diene so it can be close to the developing π-bond



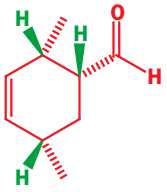
3. Now draw in all the hydrogen atoms on the carbon atoms that are going to become stereogenic centres, that is, those shown in green here



4. Draw a diagram of the product. All the substituents to the right in the previous diagram are on one side of the new molecule. That is, all the green hydrogen atoms are *cis* to each other



5. Draw a final diagram of the product with the stereochemistry of the other substituents shown too in the usual way. This is the *endo* product of the Diels–Alder reaction



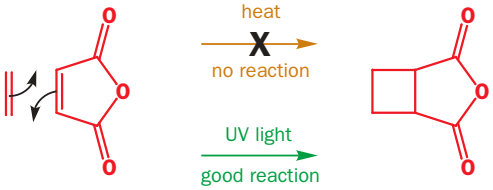
If you prefer, you may draw a three-dimensional representation of the reagents coming together, rather like the ones we have been drawing earlier in the chapter. You may indeed prefer to invent a method of your own—it does not matter which method you choose providing that you can quickly decide on the structure of the *endo* adduct in any given Diels–Alder reaction.

Time for some explanations

We have accumulated rather a lot of unexplained results.

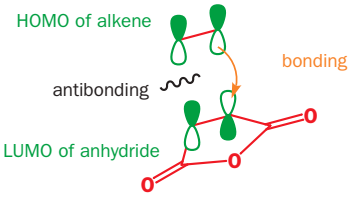
- Why does the Diels–Alder reaction work so well?
- Why must we have a conjugating group on the dienophile?
- Why is the stereochemistry of each component retained so faithfully?
- Why is the *endo* product preferred kinetically?

There is more. The simpler picture we met earlier in this chapter also fails to explain why the Diels–Alder reaction occurs simply on heating while attempted additions of simple alkenes (rather than dienes) to maleic anhydride fail on heating but succeed under irradiation with UV light.



We shall now explain all this in one section using frontier molecular orbitals. Of all the kinds of organic reactions, pericyclic ones are the most tightly controlled by orbitals, and the development of the ideas we are about to expound is one of the greatest triumphs of modern theoretical chemistry. It is a beautiful and satisfying set of ideas based on very simple principles.

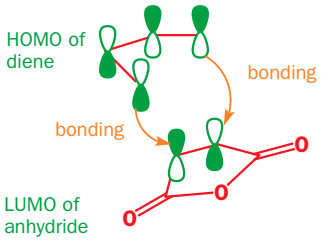
The frontier orbital description of cycloadditions



■ You may need to remind yourself about the orbitals of conjugated π systems by re-reading Chapter 7.

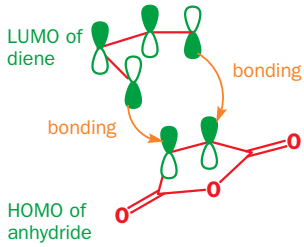
When an ionic cyclization reaction occurs, such as the lactonization at the head of this chapter, one important new bond is formed. It is enough to combine one full orbital with one empty orbital to make the new bond. But in a cycloaddition two new bonds are formed at the same time. We have to arrange for two filled p orbitals and two empty p orbitals to be available at the right place and with the right symmetry. See what happens if we draw the orbitals for the reaction above. We could try the HOMO (π) of the alkene and the LUMO (π*) of the double bond in the anhydride.

This combination is bonding at one end, but antibonding at the other so that no cycloaddition reaction occurs. It obviously doesn't help to use the other HOMO/LUMO pair as they will have the same mismatched symmetry.

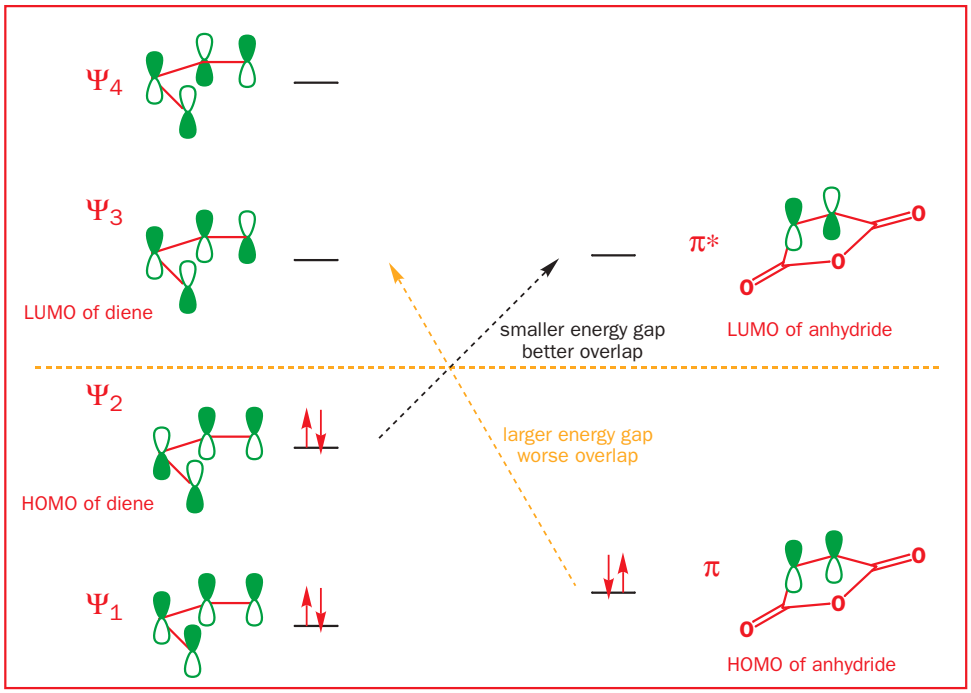


Now see what happens when we replace the alkene with a diene. We shall again use the LUMO of the electron-poor anhydride.

Now the symmetry is right because there is a node in the middle of the HOMO of the diene (the HOMO is Ψ_2 of the diene) just as there is in the LUMO of the dienophile. If we had tried the opposite arrangement, the LUMO of the diene and the HOMO of the dienophile, the symmetry would again be right.



Now the LUMO of the diene has two nodes and gives the same symmetry as the HOMO of the dienophile, which has no nodes. So either combination is excellent. In fact most Diels–Alder reactions use electron-deficient dienophiles and electron-rich dienes so we prefer the first arrangement. The electron-deficient dienophile has a low-energy LUMO and the electron-rich diene has a high-energy HOMO so that this combination gives a better overlap in the transition state. The energy levels will be like this.

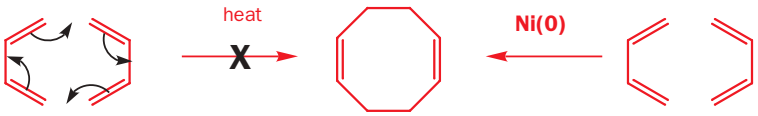


This is why we usually use dienophiles with conjugating groups for good Diels–Alder reactions. Dienes react rapidly with electrophiles because their HOMOs are relatively high in energy, but simple alkenes have relatively high-energy LUMOs and do not react well with nucleophiles. The most effective modification we can make is to lower the alkene LUMO energy by conjugating the double bond with an electron-withdrawing group such as carbonyl or nitro. These are the most common type of Diels-Alder reactions—between electron-rich dienes and electron-deficient dienophiles.

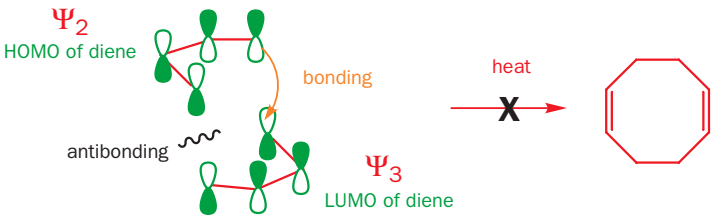
▶ A rarer type is the **reverse electron demand Diels–Alder reaction** in which the dienophile has electron-donating groups and the diene has a conjugated electron-withdrawing group. These reactions use the HOMO of the dienophile and the LUMO of the diene. This combination still has the right orbital symmetry.

Dimerizations of dienes by cycloaddition reactions

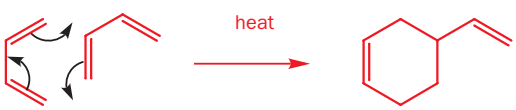
Because dienes have relatively high-energy HOMOs and low-energy LUMOs they should be able to take part in cycloadditions with themselves. And they do. What they cannot do is form an eight-membered ring in one step (though this is possible photochemically or with transition metal catalysis as we shall see later).



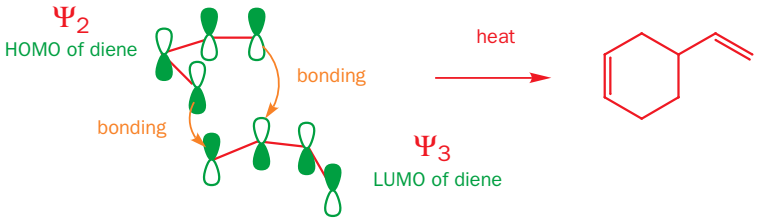
You should have expected this failure because the ends of the required orbitals must again have the wrong symmetry, just as they had when we tried the alkene dimerization.



Dienes do dimerize, but by a Diels–Alder reaction.



One molecule of the diene acts as a dienophile. Now the symmetry is correct again.



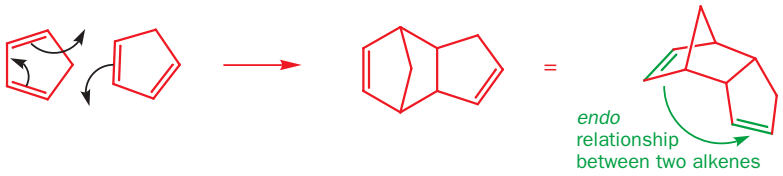
Count the number of π electrons

- The cycloadditions that *do* occur thermally, for example, the Diels–Alder reaction, have $(4n + 2\,\pi)$ electrons in their 'aromatic' transition states
- The cycloadditions that do *not* occur thermally, for example the dimerization of alkenes and of dienes, have $4n\,\pi$ electrons in their 'anti-aromatic' transition states

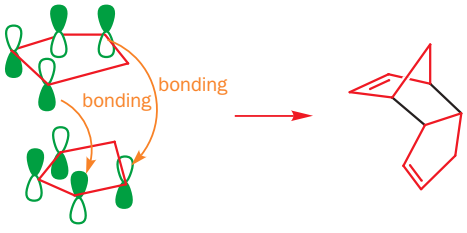
The Diels–Alder reaction in more detail

The orbital explanation for the *endo* rule in Diels–Alder reactions

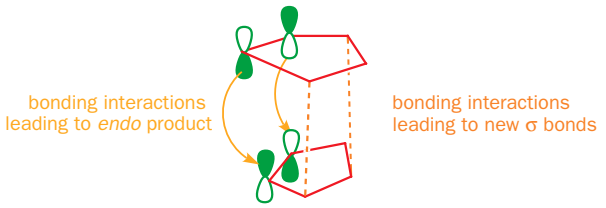
We are going to use a diene as dienophile to explain the formation of *endo* products. The diene serves as a good model for the very wide variety of dienophiles because the one thing they all have in common is a conjugating group and a second alkene is the simplest of these. To make matters even easier we shall look at the dimerization of a cyclic diene; we might almost say *the* cyclic diene—cyclopentadiene. We introduced this reaction above where we simply stated that there was a favourable electronic interaction between the conjugating group on the dienophile and the back of the diene in the *endo* product though we did not explain it at the time.



If we now draw the frontier orbitals in the two components as they come together for the reaction, we can see first of all that the symmetry is correct for bond formation.



Now we shall look at that same diagram again but replace with orange dashed lines the orbitals that are overlapping to form the new σ bonds so that we can see what is happening at the back of the diene.

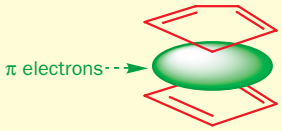


The symmetry of the orbitals is correct for a bonding interaction at the back of the diene too. This interaction does not lead to the formation of any new bonds but it leaves its imprint in the stereochemistry of the product. The *endo* product is favoured because of this favourable interaction across the space between the orbitals even though no bonds are formed.

Entropy and the *endo* rule

Another way to look at this result comes from recognizing the special entropy problem involved in cycloaddition reactions. A very precise orientation of the two molecules is required for two bonds to be formed at once. These reactions have large negative entropies of activation (Chapter 41)—order must be created at the transition state as the two components align with one another. The through-space attractive HOMO/LUMO interaction between the two molecules can lead to an initial association that can be compared to a squishy sandwich with too much mayonnaise. The cyclopentadiene rings are the slices of bread and the electrons are the filling that holds them together but still allows them to rotate until the right atoms come together for bonding.

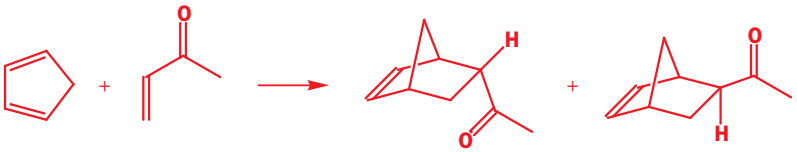
Rotation about a vertical axis through the centre of the sandwich eventually brings the right atoms together for bond formation. At that moment the backs of the rings are still stuck together by the 'mayonnaise' and the *endo* product results.



The solvent in the Diels–Alder reaction

We discussed some effects of varying the solvent in Chapter 13, and we shall now introduce a remarkable and useful special solvent effect in the Diels–Alder reaction. The reaction does not *need* a solvent and often the two reagents are just mixed together and heated. Solvents can be used but, because there are no ionic intermediates, it seems obvious that *which* solvent is unimportant—any solvent that simply dissolves both reagents will do. This is, in general, true and hydrocarbon solvents are often the best.

However, in the 1980s an extraordinary discovery was made. Water, a most unlikely solvent for most organic reactions, has a large accelerating effect on the Diels–Alder reaction. Even some water added to an organic solvent accelerates the reaction. And that is not all. The *endo* selectivity of these reactions is often superior to those in no solvent or in a hydrocarbon solvent. Here is a simple example.

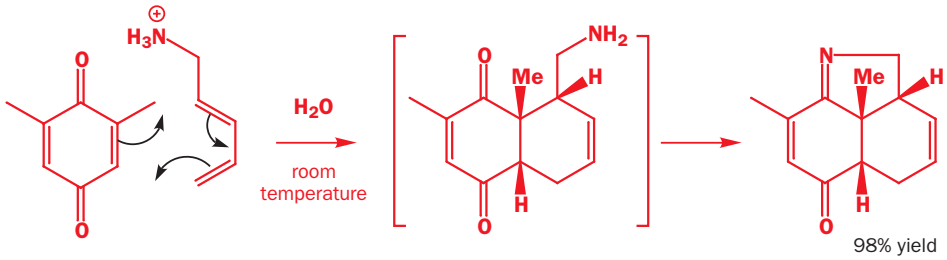


endo product *exo* product

Solvent	Relative rate	*endo*:*exo* ratio
hydrocarbon (isooctane)	1	80:20
water	700	96:4

The suggestion is that the reagents, which are not soluble in water, are clumped together in oily drops by the water and forced into close proximity. Water is not exactly a solvent—it is almost an anti-solvent!

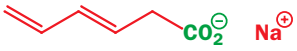
Water-soluble dienes are also used in Diels–Alder reactions in water and they too work very well. Sodium salts of carboxylic acids and protonated amines both behave well under these conditions. Presumably, the soluble tail is in the water but the diene itself is inside the oily drops with the dienophile. In this example an aminodiene reacts with a quinone dienophile.



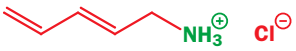
98% yield

A single regio- and stereoisomer was formed in essentially quantitative yield and the stereochemistry was easily proved by NMR using NOE (Chapter 32). Irradiation at the black methyl group in the middle of the molecule gave strong NOEs to the two green hydrogen atoms, which must therefore be on the same side of the molecule as the methyl group.

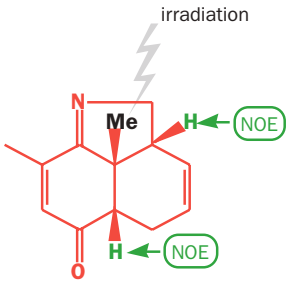
water-soluble dienes



soluble in basic solution



soluble in acidic solution

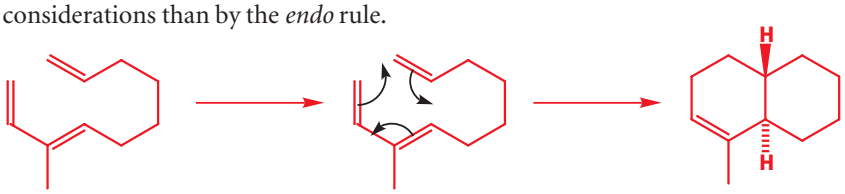


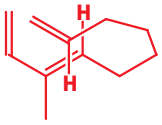
Intramolecular Diels–Alder reactions

When the diene and the dienophile are already part of the same molecule it is not so important for them to be held together by bonding interactions across space and the *exo* product is often preferred.

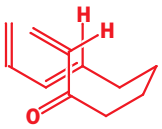
We discuss regioselectivity in Diels–Alder reactions later in the chapter (p. 000).

Indeed, it seems that intramolecular Diels–Alder reactions are governed more by normal steric considerations than by the *endo* rule.



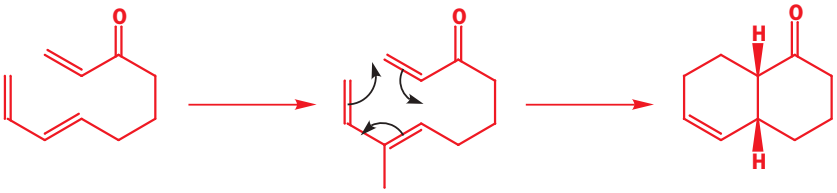


This reaction happens only because it is intramolecular. There is no conjugating group attached to the dienophile and so there are no orbitals to overlap with the back of the diene. The molecule simply folds up in the sterically most favourable way (as shown in the margin, with the linking chain adopting a chair-like conformation) and this leads to the *trans* ring junction.

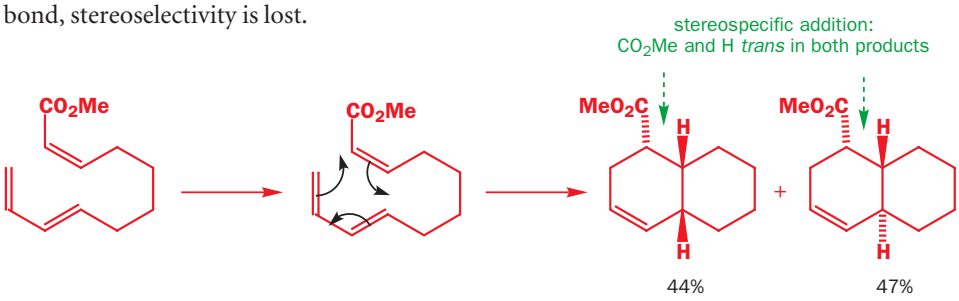


In the next example there is a carbonyl group conjugated with the dienophile. Now the less stable *cis* ring junction is formed because the molecule can fold so that the carbonyl group can enjoy a bonding overlap with the back of the diene. This time the linking chain has to adopt a boat-like conformation.

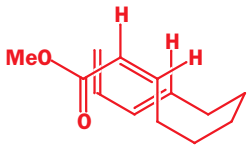
▶ If you think about the way a Diels–Alder reaction goes, the forming ring must *always* adopt a boat-like conformation. This is clear if you make a model.



If, on the other hand, we give the dienophile a conjugating group at the other end of the double bond, stereoselectivity is lost.

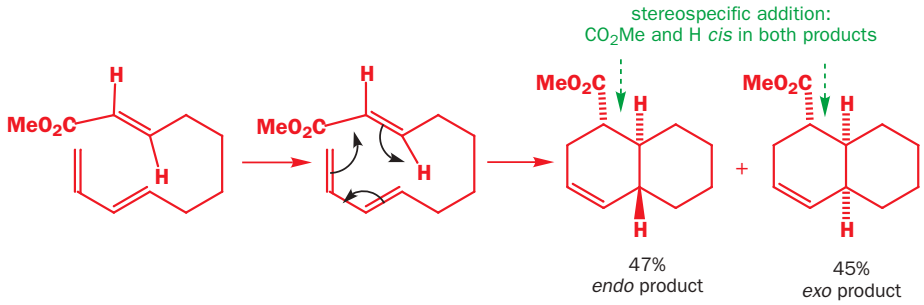


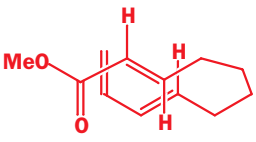
The *cis*-alkene dienophile gives stereospecific addition—in each product the CO_2Me is *cis* to the alkyl chain (and therefore *trans* to the H atom). But we get about a 50:50 mixture of *endo* and *exo* products. This does not seem to be because there is anything wrong with the transition state for *endo* addition, which leads in this case to *cis*-fused rings.



endo folding for the *cis*-alkene

Similarly, with the *trans*-alkene, two products are formed and both retain the *trans* geometry of the dienophile. But once again a nearly 50:50 mixture of *endo* and *exo* products is formed.





endo folding for the *trans*-alkene

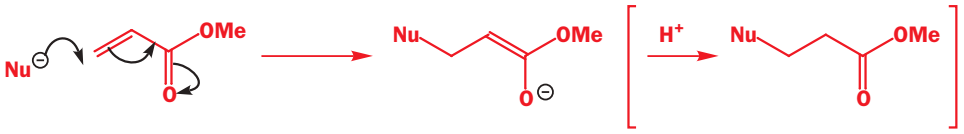
Folding the molecule so that the *endo* product would be formed does not again seem to present any problem. Presumably, either the carbonyl group of the ester is too far away from the diene to be effective or else it is simply that the advantage of the *endo* arrangement is not worth having in intramolecular Diels–Alder reactions.

Intramolecular Diels–Alder

Intramolecular Diels–Alder reactions may give the *endo* product or they may not! Be prepared for either *exo* or *endo* products or a mixture.

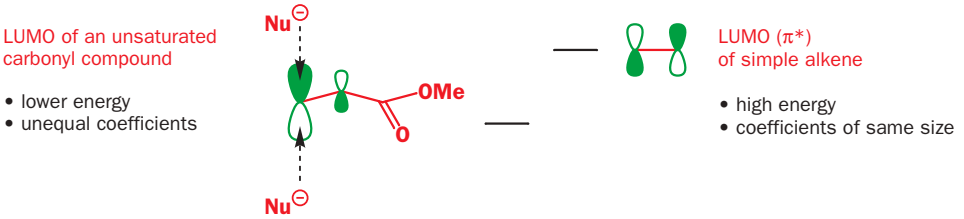
Regioselectivity in Diels–Alder reactions

The compounds that we are now calling dienophiles were the stars of Chapters 10, 23, and 29 where we called them **Michael acceptors** as they were the electrophilic partners in conjugate addition reactions. Nucleophiles always add to the β carbon atoms of these alkenes because the product is then a stable enolate. Ordinary alkenes do not react with nucleophiles.



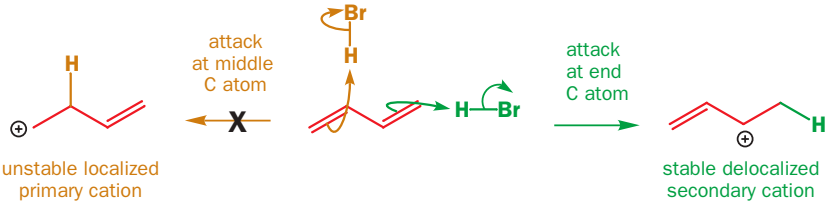
In frontier orbital terms this is because conjugation with a carbonyl group lowers the energy of the LUMO (the π* orbital of the alkene) and at the same time distorts it so that the coefficient on the β carbon atom is larger than that on the α carbon atom. Nucleophiles approach the conjugated alkene along the axis of the large p orbital of the β carbon atom.

■ This is discussed in Chapter 10.



These same features can ensure regioselective Diels–Alder reactions. The same orbital of the dienophile is used and, if the HOMO of the diene is also unsymmetrical, the regioselectivity of the reaction will be controlled by the two largest coefficients bonding together.

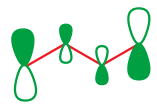
So what about distortion of the HOMO in the diene? If a diene reacts with an electrophile, the largest coefficient in the HOMO will direct the reaction. Consider the attack of HBr on a diene. We should expect attack at the ends of the diene because that gives the most stable possible cation—an allyl cation as an intermediate.



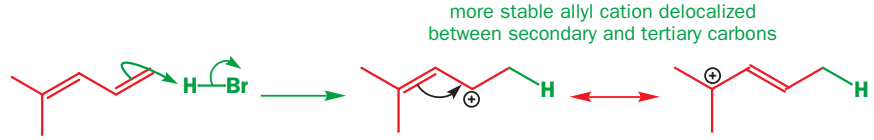
In orbital terms attack occurs at the ends of the diene because the coefficients in the HOMO are larger there. We need simply to look at the HOMO (Ψ_2) of butadiene to see this.

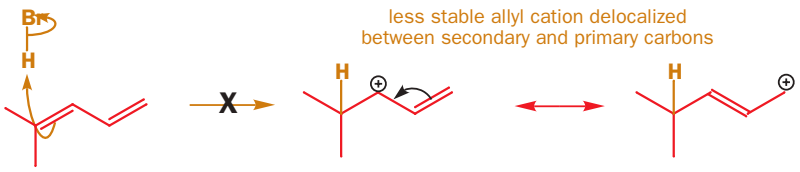
HOMO of butadiene

Ψ_2

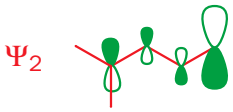


So it is not surprising that the dienes react in the Diels–Alder reaction through their end carbons. But supposing the two ends are different—which reacts now? We can again turn to the reaction with HBr as a guide. Addition of HBr to an unsymmetrical diene will give the more stable of the two possible allyl cations as the intermediate.



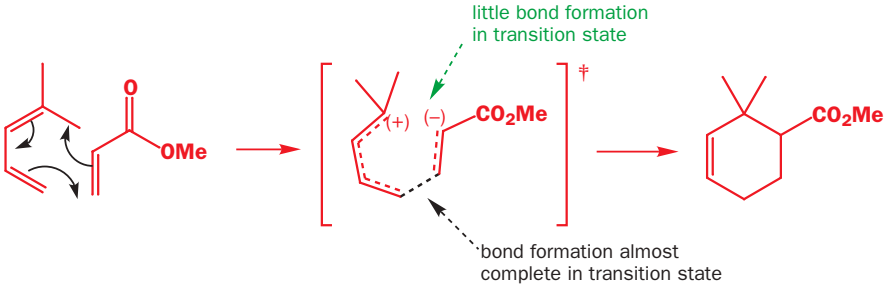


HOMO of 1,1-dimethylbutadiene

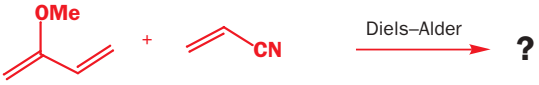


In orbital terms, this clearly means that the HOMO of the diene is distorted so that the end that reacts has the larger coefficient.

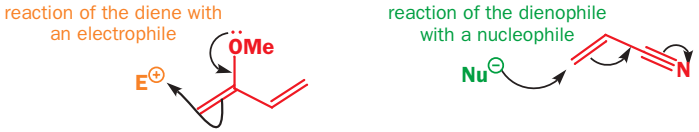
When the unsymmetrical diene and the unsymmetrical dienophile combine in a Diels–Alder reaction, the reaction itself becomes unsymmetrical. It remains concerted but, in the transition state, bond formation between the largest coefficients in each partner is more advanced and this determines the regioselectivity of the reaction.



The simplest way to decide which product will be formed is to draw an 'ionic' stepwise mechanism for the reaction to establish which end of the diene will react with which end of the dienophile. Of course this stepwise mechanism is not completely correct but it does lead to the correct orientation of the reagents and you can draw the right mechanism afterwards. As an example we shall look at a diene with a substituent in the middle. This is the reaction.

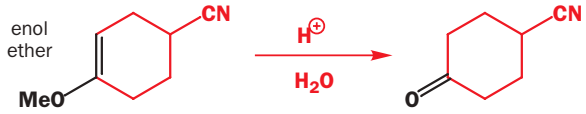


First decide where the diene will act as a nucleophile and where the diene will act as an electrophile.



Now draw the reagents in the correct orientation for these two ends to combine and draw a concerted Diels–Alder reaction.

This is an important example because an enol ether functional group is present in the product and this can be hydrolysed to a ketone in aqueous acid (see Chapter 21).

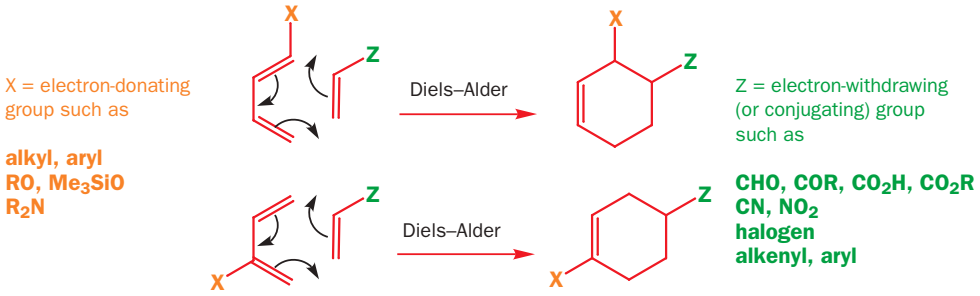


Summary of regioselectivity in Diels–Alder reactions

The important substitution patterns are: a diene with an electron-donating group (X) at one end or in the middle and a dienophile with an electron-withdrawing group (Z) at one end. These are the products formed.

▶ It is not 'cheating' to use the regioselectivity of chemical reactions to tell us about the coefficients in orbitals. Chemistry is about using experimental evidence to find out about the theoretical background and not about theory telling us what *ought* to happen. In fact, theoretical chemists have calculated the HOMO energies and coefficients of unsymmetrical dienes and they have reached the same conclusions.

■ The two circles represent the largest coefficients of the HOMO and the LUMO.



A useful mnemonic

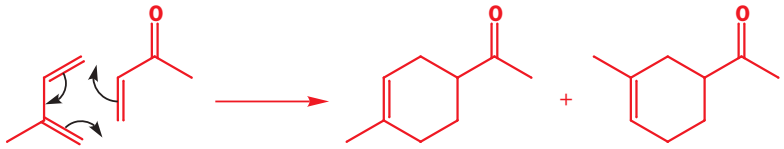
If you prefer a rule to remember, try this one.

- **The Diels–Alder reaction is a cycloaddition with an** aromatic **transition state that is *ortho* and *para* directing**

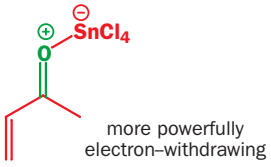
You can see that this mnemonic works if you look at the two products above: the first has the two substituents X and Z on neighbouring carbon atoms, just like *ortho* substituents on a benzene ring, while the second has X and Z on opposite sides of the ring, just like *para* substituents.

Lewis acid catalysis in Diels–Alder reactions

Where the reagents are unsymmetrical, a Lewis acid that can bind to the electron-withdrawing group of the dienophile often catalyses the reaction by lowering the LUMO of the dienophile still further. It has another important advantage: it increases the difference between the coefficients in the LUMO (a Lewis-acid complexed carbonyl group is a more powerful electron-withdrawing group) and may increase regioselectivity.



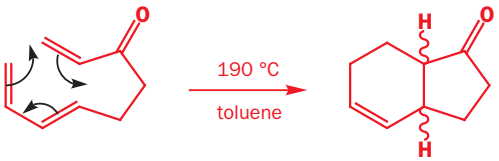
heat in toluene at 120 °C in a sealed tube	71:	:29
with $SnCl_4 \cdot 5H_2O$ at 0 °C	93:	:7



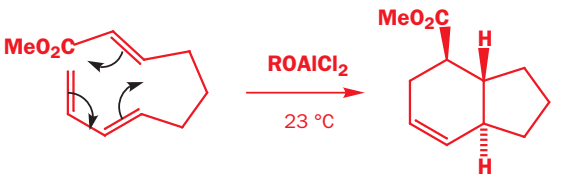
This Diels–Alder reaction is useful because it produces a substitution pattern ('*para*') common in natural terpenes (Chapter 51). But the regioselectivity introduced by one methyl group on the diene is not very great—this reaction gives a 71:29 mixture when the two compounds are heated together at 120 °C in a sealed tube. In the presence of the Lewis acid ($SnCl_4$) the reaction can be carried out at lower temperatures (below 25 °C) without a sealed tube and the regioselectivity improves to 93:7.

Regioselectivity in intramolecular Diels–Alder reactions

Just as the stereoselectivity may be compromised in intramolecular reactions, so may the regioselectivity. It may be simply impossible for the reagents to get together in the 'right' orientation. The examples below have a very short chain—just three carbon atoms—joining diene to dienophile and so the same regioselectivity is found regardless of the position of the conjugating carbonyl group.



100% yield
70:30 *cis*:*trans* mixture



only product; 72% yield

The first example has the 'right' orientation ('*ortho*') but the second has the 'wrong' orientation ('*meta*'). In real life there is no prospect of any other orientation and, as the reaction is intramolecular, it goes anyway. Notice the lower temperature required for the Lewis acid ($ROAlCl_2$)-catalysed reaction.

The Woodward–Hoffmann description of the Diels–Alder reaction

Kenichi Fukui and Roald Hoffmann won the Nobel prize in 1981 (Woodward died in 1979 and so couldn't share this prize: he had already won the Nobel prize in 1965 for his work on synthesis) for the application of orbital symmetry to pericyclic reactions. Theirs is an alternative description to the frontier orbital method we have used and you need to know a little about it. They considered a more fundamental correlation between the symmetry of all the orbitals in the starting materials and all the orbitals in the products. This is rather too complex for our consideration here, and we shall concentrate only on a summary of the conclusions—the **Woodward–Hoffmann rules**. The most important of these states:

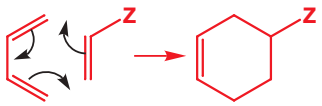
Woodeard–Hoffmann rules

In a thermal pericyclic reaction the total number of $(4q + 2)_s$ and $(4r)_a$ components must be odd.

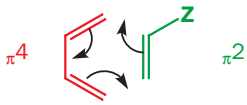
▶ You have already seen the significance of $4n$ and $4n + 2$ numbers in aromaticity.

This needs some explanation. A **component** is a bond or orbital taking part in a pericyclic reaction as a single unit. A double bond is a $_\pi 2$ component. The number 2 is the most important part of this designation and simply refers to the number of electrons. The prefix π tells us the type of electrons. A component may have any number of electrons (a diene is a $_\pi 4$ component) but may not have mixtures of π and σ electrons. Now look back at the rule. Those mysterious designations $(4q + 2)$ and $(4r)$ simply refer to the number of electrons in the component where q and r are integers. An alkene is a $_\pi 2$ component and so it is of the $(4q + 2)$ kind while a diene is a $_\pi 4$ component and so is of the $(4r)$ kind.

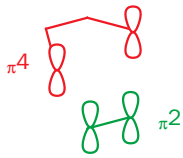
Now what about the suffixes 's' and 'a'? The suffix 's' stands for suprafacial and 'a' for antarafacial. A **suprafacial** component forms new bonds on the same face at both ends while an **antarafacial** component forms new bonds on opposite faces at both ends. See how this works for the Diels–Alder reaction. Here is the routine.



1. Draw the mechanism for the reaction (we shall choose a general one)

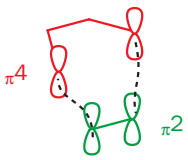


2. Choose the components. All the bonds taking part in the mechanism must be included and no others



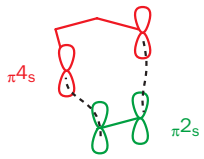
3. Make a three-dimensional drawing of the way the components come together for the reaction, putting in orbitals at the ends of the components (only!)

▶ Please note—these orbitals are just p orbitals, and do *not* make up HOMOs or LUMOs or any particular molecular orbital. Do *not* attempt to mix frontier orbital and Woodward–Hoffmann descriptions of pericyclic reactions.



4. Join up the components where new bonds are to be formed. Coloured dotted lines are often used

5. Label each component s or a depending on whether new bonds are formed on the same or on opposite sides.



6. Count the number of $(4q + 2)_s$ and $(4r)_a$ components. If the total count is odd, the reaction is allowed

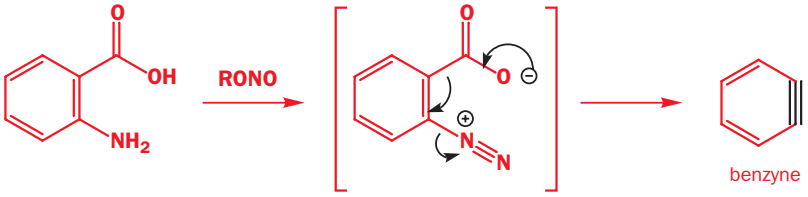
■ There is *one* $(4q + 2)_s$ component (the alkene) and *no* $(4r)_a$ components. Total = 1 so it is an allowed reaction

▶ Components of the other symmetry, that is $(4q + 2)_a$ and $(4r)_s$ components, do not count. You can have as many of these as you want!

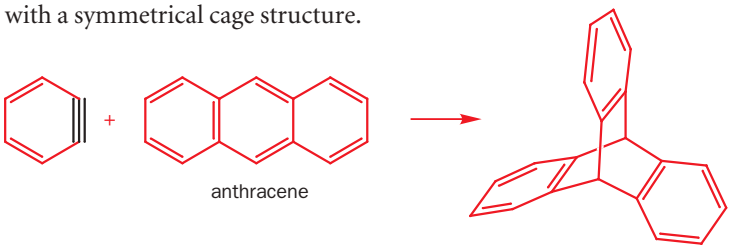
You may well feel that there is very little to be gained from the Woodward–Hoffmann treatment of the Diels–Alder reaction. It does not explain the *endo* selectivity nor the regioselectivity. However, the Woodward–Hoffmann treatment of other pericyclic reactions (particularly electrocyclic reactions, in the next chapter) is helpful. You need to know about this treatment because the Diels–Alder reaction is often described as an **all-suprafacial** [4 + 2] **cycloaddition**. Now you know what that means.

Trapping reactive intermediates by Diels–Alder reactions

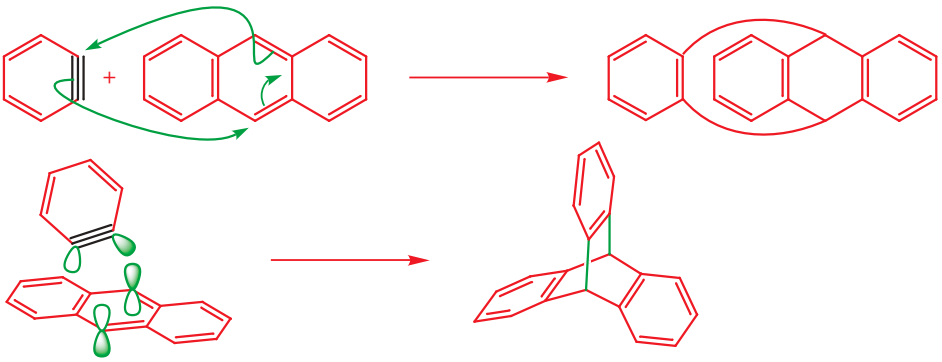
In Chapter 23 we met the remarkable intermediate benzyne and mentioned that convincing evidence for its existence was the trapping by a Diels–Alder reaction. An ideal method for generating benzyne for this purpose is the diazotization of anthranilic acid (2-aminobenzoic acid).



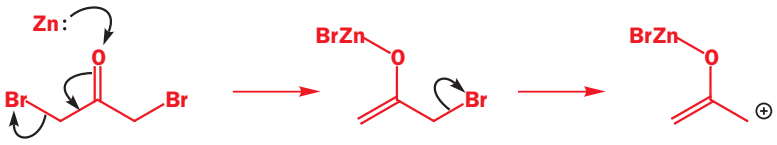
Benzyne may not look like a good dienophile but it is an unstable electrophilic molecule so it must have a low-energy LUMO (π* of the triple bond). If benzyne is generated in the presence of a diene, efficient Diels–Alder reactions take place. Anthracene gives a specially interesting product with a symmetrical cage structure.



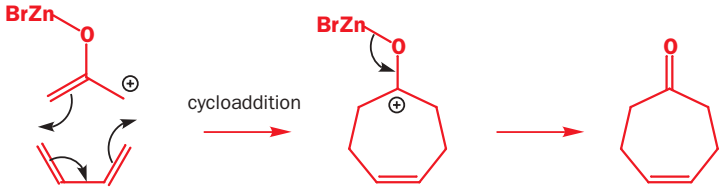
It is difficult to draw this mechanism convincingly. The two flat molecules approach each other in orthogonal planes, so that the orbitals of the localized π bond of benzyne bond with the p orbitals on the central ring of anthracene.



Another intermediate for which Diels–Alder trapping provided convincing evidence is the oxyallyl cation. This compound can be made from α,α′-dibromoketones on treatment with zinc metal. The first step is the formation of a zinc enolate (compare the Reformatsky reaction), which can be drawn in terms of the attack of zinc on oxygen or bromine. Now the other bromine can leave as an anion. It could not do so before because it was next to an electron-withdrawing carbonyl group. Now it is next to an electron-rich enolate so the cation is stabilized by conjugation.

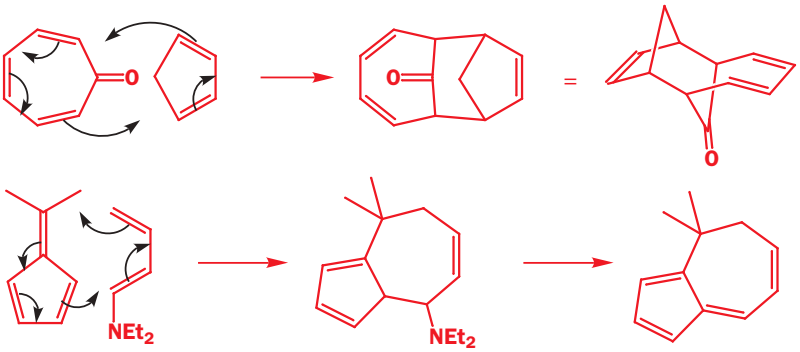


The allyl cation has three atoms but only two electrons so it can take part in cycloadditions with dienes—the total number of electrons is the required six. This is one of the few reactions that works only to produce a seven-membered ring.



Other thermal cycloadditions

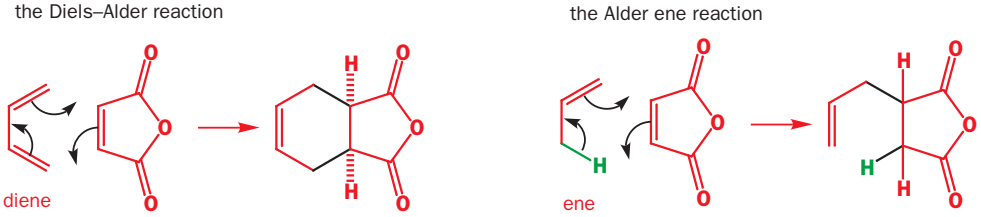
Six is not the only $(4n + 2)$ number and there are a few cycloadditions involving ten electrons. These are mostly diene + triene, that is, $_{\pi}4_s + _{\pi}6_s$ cycloadditions. Here are a couple of examples.



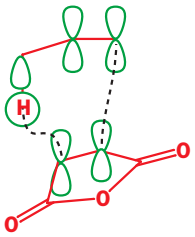
In the first case, there is an *endo* relationship between the carbonyl group and the back of the diene—this product is formed in 100% yield. In the second case Et_2NH is lost from the first product under the reaction conditions to give the hydrocarbon shown. This type of reaction is more of an oddity: by far the most important type of cycloaddition is the Diels–Alder reaction.

The Alder 'ene' reaction

The Diels–Alder reaction was originally called the 'diene reaction' so, when half of the famous team (K. Alder) discovered an analogous reaction that requires only one alkene, it was called the **Alder ene reaction** and the name has stuck. Compare here the Diels–Alder and the Alder ene reactions.

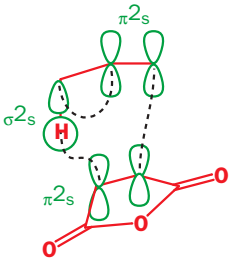


The simplest way to look at the ene reaction is to picture it as a Diels–Alder reaction in which one of the double bonds in the diene has been replaced by a C–H bond (green). The reaction does not form a new ring, the product has only one new C–C bond (shown in black on the product), and a hydrogen atom is transferred across space. Otherwise, the two reactions are remarkably similar.



The ene reaction is rather different in orbital terms. For the Woodward–Hoffmann description of the reaction we must use the two electrons of the C–H bond to replace the two electrons of the double bond in the Diels–Alder reaction, but we must make sure that all the orbitals are parallel, as shown.

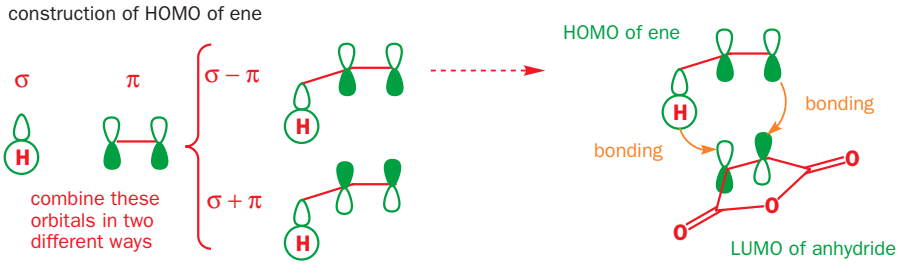
The C–H bond is parallel with the p orbitals of the ene so that the orbitals that overlap to form the new π bond are already parallel. The two molecules approach one another in parallel planes so that the orbitals that overlap to form the new σ bonds are already pointing towards each other. Because the electrons are of two types, π and σ, we must divide the ene into two components, one $_{\pi}2$ and one $_{\sigma}2$. We can then have an all-suprafacial reaction with three components.



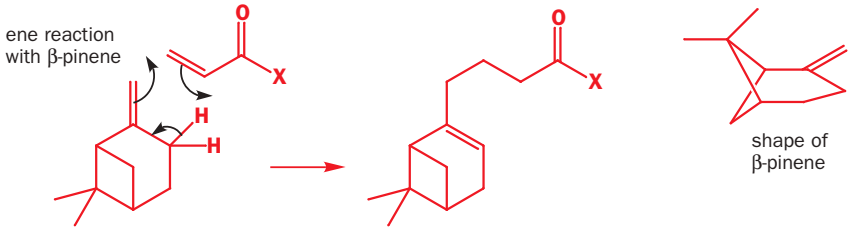
All three components are of the $(4q + 2)_s$ type so all count and the total is three—an odd number—so the reaction is allowed. We have skipped the step-by-step approach we used for the Diels–Alder reaction because the two are so similar, but you should convince yourself that you can apply it here.

▶ We discuss in more detail in Chapter 36 how to assign s or a with σ bonds. Here the σ bond reacts suprafacially because the 1s orbital of H has no nodes.

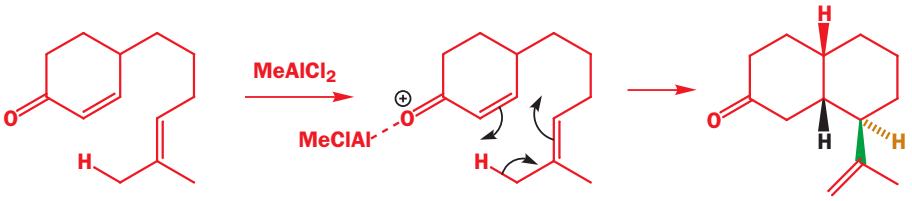
In frontier orbital terms we shall want again to use the LUMO of the anhydride so we need to construct the HOMO of the ene component. This must be the HOMO of the π bond and σ bond (C–H) combined. These two bonds can combine in a bonding way (σ + π) or in an antibonding fashion (σ – π). The second is higher in energy than the first and since there are a total of four electrons (two in the s bond and two in the π bond), it is the molecular HOMO. The HOMO of the ene is bonding at both ends with the LUMO of the anhydride and the reaction is favourable.

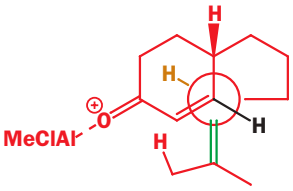


Now for some real examples. Most ene reactions with simple alkenes are with maleic anhydride. Other dienophiles—or **enophiles** as we should call them in this context—do not work very well. However, with one particular alkene, the natural terpene β-pinene from pine trees, reaction does occur with enophiles such as acrylates.



The major interaction between these two molecules is between the nucleophilic end of the exocyclic alkene and the electrophilic end of the acrylate. These atoms have the largest coefficients in the HOMO and LUMO, respectively, and, in the transition state, bond formation between these two will be more advanced than anywhere else. For most ordinary alkenes and enophiles, Lewis acid catalysis to make the enophile more electrophilic, or an intramolecular reaction (or both!), is necessary for an efficient ene reaction.

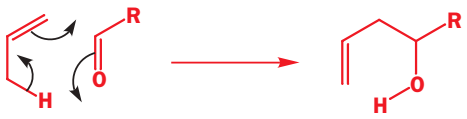




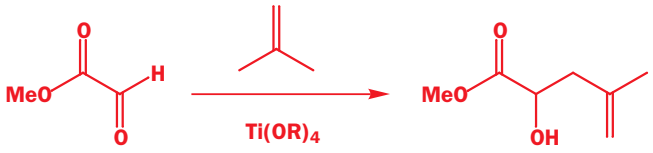
The ene is delivered to the bottom face of the enone, as its tether (Chapter 33) is too short for it to reach the top face, and a *cis* ring junction is formed. The stereochemistry of the third centre is most easily seen by a Newman projection of the reaction. In the diagram in the margin we are looking straight down the new C–C bond and the colour coding should help you to see how the stereochemistry follows.

Since the twin roles of the enophile are to be attacked at one end by a C=C double bond and at the other by a proton, a carbonyl group is actually a very good enophile. These reactions are usually called **carbonyl ene reactions**.

the carbonyl ene reaction

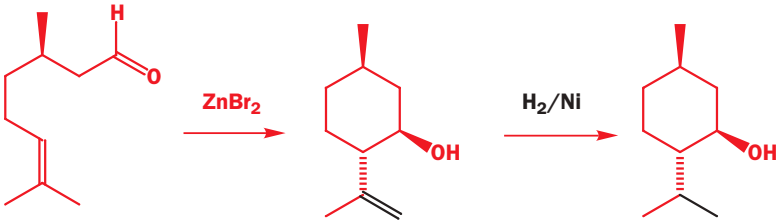


The important interaction is between the HOMO of the ene system and the LUMO of the carbonyl group—and a Lewis-acid catalyst can lower the energy of the LUMO still further. If there is a choice, the more electrophilic carbonyl group (the one with the lower LUMO) reacts.



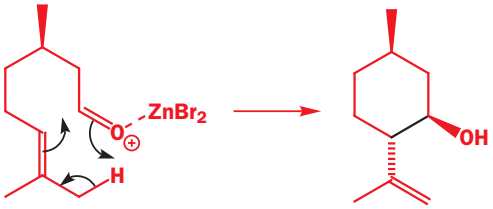
It is not obvious that an ene reaction has occurred because of the symmetry of the ene. The double bond in the product is not, in fact, in the same place as it was in the starting material.

One carbonyl ene reaction is of commercial importance as it is part of a process for the production of menthol used to give a peppermint smell and taste to many products. This is an intramolecular ene reaction on another terpene derivative.

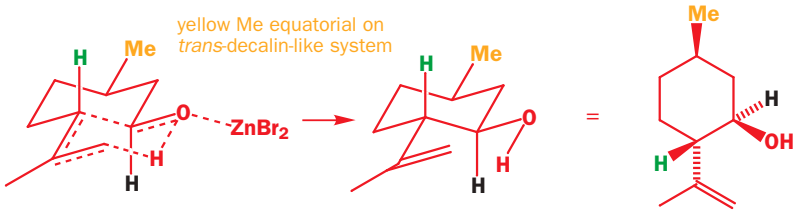


(*R*)-citronellal isopulegol (–)-menthol

It is not obvious what has happened in the first step, but the movement of the alkene and the closure of the ring with the formation of one (not two) new C–C bonds should give you the clue that this is a Lewis-acid-catalysed carbonyl ene reaction.



The stereochemistry comes from an all-chair arrangement in the conformation of the transition state. The methyl group will adopt an equatorial position in this conformation, fixing the way the other bonds are formed. Again, colour coding should make it clearer what has happened.

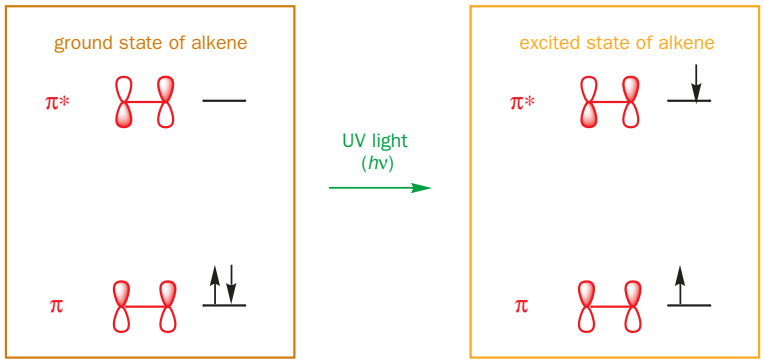


Menthol manufacture

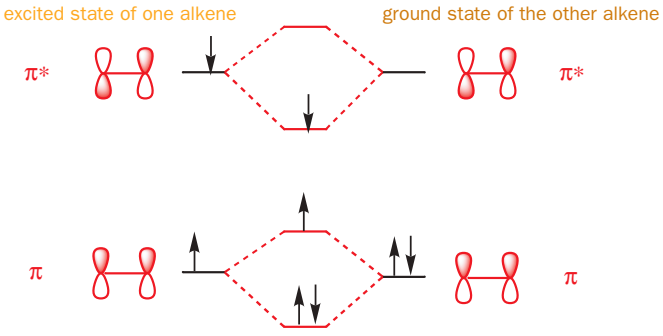
It may seem odd to you to have a chemical process to produce menthol, which would be available naturally from mint plants. This process is now responsible for about half the world's menthol production so it must make some sort of sense! The truth is that menthol *cultivation* is wasteful in good land that could produce food crops such as rice while the starting material for menthol *manufacture* is the same β-pinene we have just met. This is available in large quantities from pine trees grown on poor land for paper and furniture. The early stages of the process are discussed in Chapter 45.

Photochemical [2 + 2] cycloadditions

We shall now leave six-electron cycloadditions such as the Diels–Alder and ene reactions and move on to some four-electron cycloadditions. Clearly, four is not a $(4n + 2)$ number, but when we told you in the box on p. 000 that only cycloadditions with $(4n + 2)$ electrons are allowed we used the term 'thermally'. Cycloadditions with $4n$ electrons *are* allowed if the reaction is not thermal (that is, driven by heat energy) but **photochemical** (that is, driven by light energy). All the cycloadditions that are not allowed thermally are allowed photochemically. The problem of the incompatible symmetry in trying to add two alkenes together is avoided by converting one of them into the excited state photochemically. First, one electron is excited by the light energy from the π to the π* orbital.



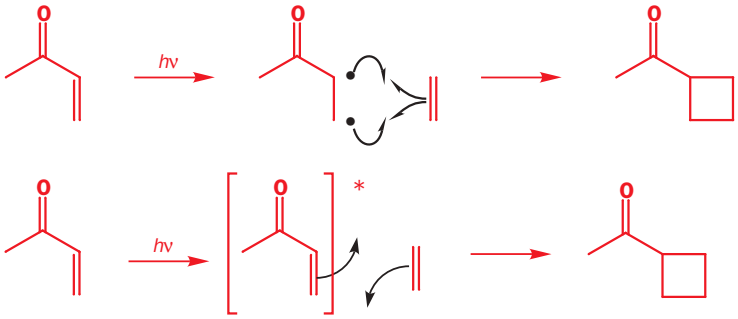
Now, combining the excited state of one alkene with the ground state of another solves the symmetry problem. Mixing the two π orbitals leads to two molecular orbitals and two electrons go down in energy while only one goes up. Mixing the two π* orbitals is as good—one electron goes down in energy and none goes up. The result is that three electrons go down in energy and only one goes up. Bonding can occur.



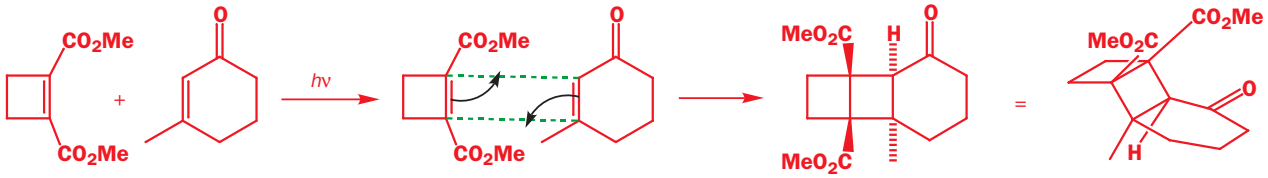
Alkenes can be dimerized photochemically in this way, but reaction between two different alkenes is more interesting. If one alkene is bonded to a conjugating group, it alone will absorb UV light and

■ In Chapter 7 we discussed why conjugated systems absorb UV light more readily than unconjugated ones do.

be excited while the other will remain in the ground state. It is difficult to draw a mechanism for these reactions as we have no simple way to represent the excited alkene. Some people draw it as a diradical (since each electron is in a different orbital); others prefer to write a concerted reaction on an excited alkene marked with an asterisk.



The reaction is stereospecific within each component but there is no *endo* rule—there is a conjugating group but no 'back of the diene'. The least hindered transition state usually results.

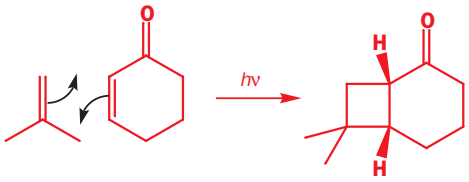


The dotted lines on the central diagram simply show the bonds being formed. The two old rings keep out of each other's way during the reaction and the conformation of the product looks reasonably unhindered.

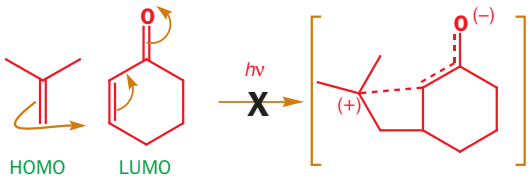
You may be wondering why the reaction works at all, given the strain in a four-membered ring: why doesn't the product just go back to the two starting materials? This reverse reaction is governed by the Woodward–Hoffmann rules, just like the forward one, and to go back again the four-membered ring products would have to absorb light. But since they have now lost their π bonds they have no low-lying empty orbitals into which light can promote electrons (see Chapter 7). The reverse photochemical reaction is simply not possible because there is no mechanism for the compounds to absorb light.

Regioselectivity in photochemical [2 + 2] cycloadditions

The observed regioselectivity is of this kind.



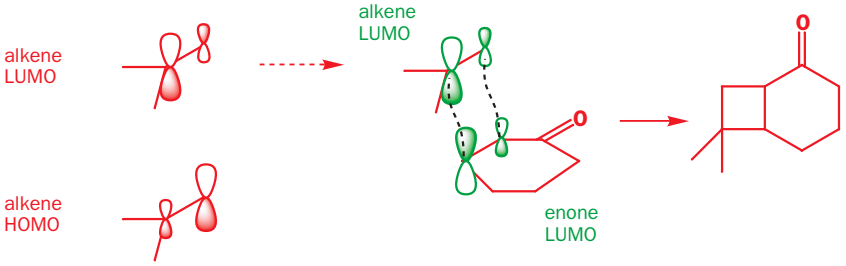
If we had combined the HOMO of the alkene with the LUMO of the enone, as we should in a thermal reaction, we would expect the opposite orientation so as to use the larger coefficients of the frontier orbitals and to maximize charge stabilization in the transition state.



But we are not doing a thermal reaction. If you look back at the orbital diagram above, you will see that it is the HOMO/HOMO and LUMO/LUMO interactions that now matter in the reactions of the excited state. The sizes of the coefficients in the LUMO of the alkene are the other way round to those in the HOMO. There is one electron in this pair of orbitals—in the LUMO of the enone in fact, as the enone has been excited by the light—so overlap between the two LUMOs (shown in the frame)

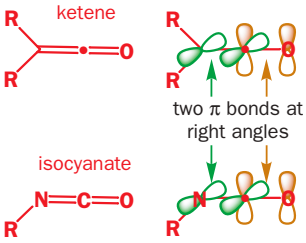
▶ It may not be immediately obvious why the sizes of the coefficients swap round, but you can think of it as we did before by considering an ionic reaction of the alkene. If we want to know about the alkene's LUMO you have to consider what *would* happen *if* you could add nucleophiles to it. Of course, with an electron-rich alkene this is a very rare reaction because the LUMO is high in energy. But some organometallic additions to unactivated alkenes are known, and they attack the more substituted end in order to locate a C–metal bond at the less substituted carbon. The LUMO has a greater coefficient at the more substituted carbon.

is bonding and leads to the observed product. The easiest way to work it out quickly is to draw the product you do *not* expect from a normal HOMO/LUMO or curly arrow controlled reaction.

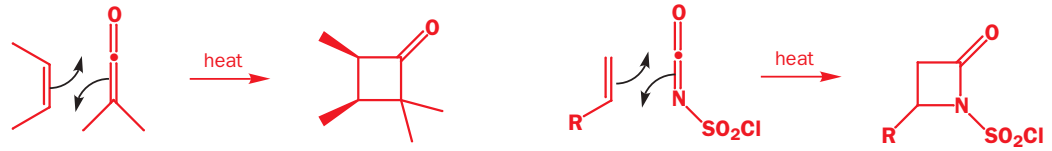


Thermal [2 + 2] cycloadditions

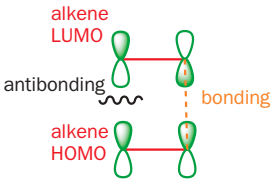
Despite what we have told you, there are some thermal [2 + 2] cycloadditions giving four-membered rings. These feature a simple alkene reacting with an electrophilic alkene of a peculiar type. It must have two double bonds to the *same* carbon atom. The most important examples are ketenes and isocyanates. The structures have two π bonds at right angles.



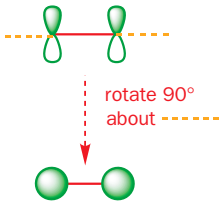
Here are typical reactions of dimethyl ketene to give a cyclobutanone and chlorosulfonyl isocyanate to give a β-lactam.



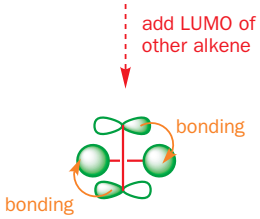
To understand why these reactions work, we need to consider a new and potentially fruitful way for two alkenes to approach each other. Thermal cycloadditions between two alkenes do not work because the HOMO/LUMO combination is antibonding at one end.



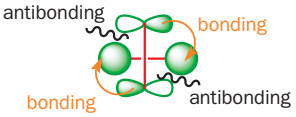
If one alkene turns at 90° to the other, there is a way in which the HOMO of one might bond at both ends to the LUMO of the other. First we turn the HOMO of one alkene so that we are looking down on the p orbitals.



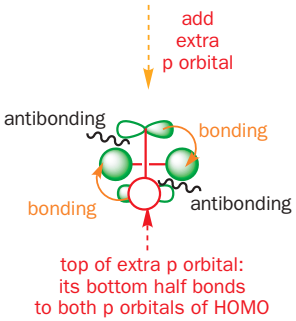
Now we add the LUMO of the other alkene on top of this HOMO and at 90° to it so that there is the possibility of bonding overlap at both ends.



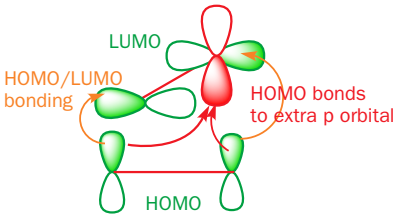
This arrangement looks quite promising until we notice that there is antibonding at the other two corners! Overall there is no net bonding.



We can tilt the balance in favour of bonding by adding a p orbital to one end of the LUMO and at a right angle to it so that both orbitals of the HOMO can bond to this extra p orbital. There are now four bonding interactions but only two antibonding. The balance is in favour of a reaction. This is also quite difficult to draw!



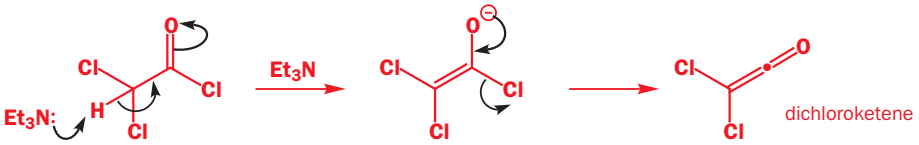
If you find this drawing difficult to understand, try a three-dimensional representation.



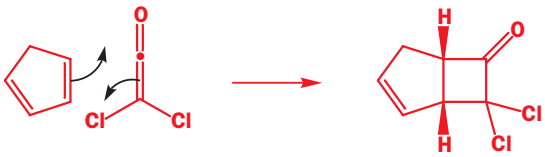
Ketenes have a central sp carbon atom with an extra π bond (the C=O) at right angles to the first alkene—perfect for thermal [2 + 2] cycloadditions. They are also electrophilic and so have suitable low-energy LUMOs.

Ketene [2 + 2] cycloadditions

Ketene itself is usually made by high-temperature pyrolysis of acetone but some ketenes are easily made in solution. The very acidic proton on dichloroacetyl chloride can be removed even with a tertiary amine and loss of chloride ion then gives dichloroketene in an E1cB elimination reaction.



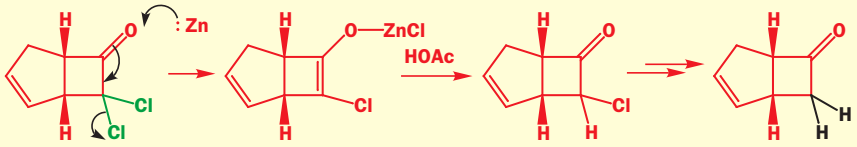
If the elimination is carried out in the presence of cyclopentadiene a very efficient regio- and stereospecific [2 + 2] cycloaddition occurs.



The most nucleophilic atom on the diene adds to the most electrophilic atom on the ketene and the *cis* geometry at the ring junction comes from the *cis* double bond of cyclopentadiene. It is impressive that even this excellent diene undergoes no Diels–Alder reaction with ketene as dienophile. The [2 + 2] cycloaddition must be much faster.

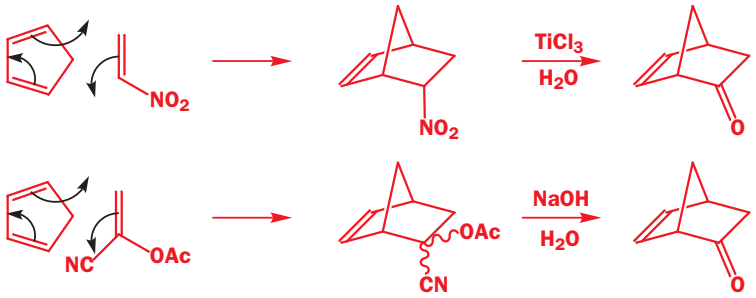
Using the products

Dichloroketene is convenient to use, but the two chlorine atoms are not usually needed in the product. Fortunately, these can be removed by zinc metal in acetic acid solution. Zinc forms a zinc enolate, which is converted into the ketone by the acid. Repetition removes both chlorine atoms. You saw the reductive formation of a zinc enolate earlier in the chapter (p. 000) and in the Reformatsky reaction (Chapter 26, p. 000).



But what do we do if we *want* the product of a ketene [4 + 2] cycloaddition? We must use a compound that is not a ketene but that can be transformed into a ketone afterwards—a **masked ketene** or

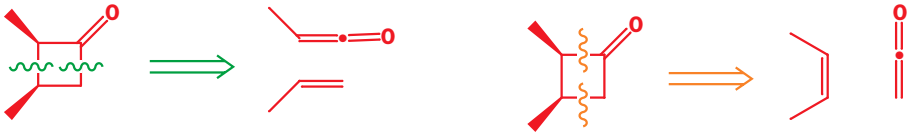
a **ketene equivalent**. The two most important types are nitroalkenes and compounds such as the 'cyanohydrin ester' in the second example.



▶ The conversion of nitro compounds to ketones by $TiCl_3$ is an alternative to the Nef reaction that you met in Chapter 29 (p. 000), and you should be able to write a mechanism for the last reaction in the scheme yourself.

Finding the starting materials for a cyclobutane synthesis

The disconnection of a four-membered ring is very simple—you just split it in half and draw the two alkenes. There may be two ways to do this.

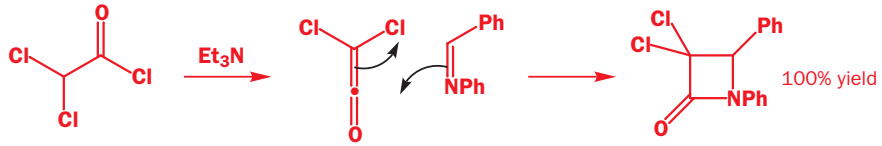


Both sets of starting materials look all right—the regiochemistry is correct for the first and doesn't matter for the second. However, we prefer the second because we can control the stereochemistry by using *cis*-butene as the alkene and we can make the reaction work better by using dichloroketene instead of ketene itself, reducing out the chlorine atoms with zinc.

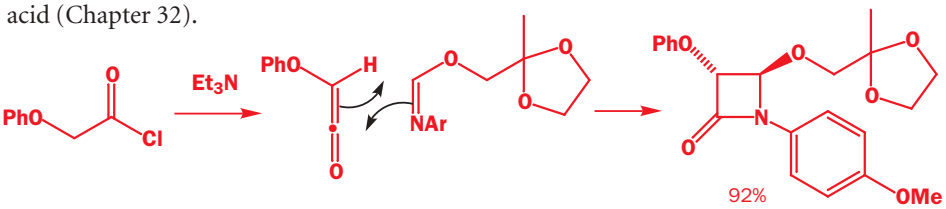
Synthesis of β-lactams by [2 + 2] cycloadditions

Now the disconnections are really different—one requires addition of a ketene to an imine and the other the addition of an isocyanate to an alkene. Isocyanates are like ketenes, but have a nitrogen atom instead of the end carbon atom. Otherwise the orbitals are the same.

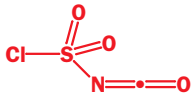
And the good news is that both work, providing we have the right substituents on nitrogen. The dichloroacetyl chloride trick works well with imines and, as you ought to expect, the more nucleophilic nitrogen atom attacks the carbonyl group of the ketene so that the regioselectivity is right to make β-lactams.



If both components have one substituent, these will end up *trans* on the four-membered ring just to keep out of each other's way. This example has more functionality and the product could be used to make β-lactams with antibiotic activity, such as analogues of the β-lactamase inhibitor, clavulanic acid (Chapter 32).



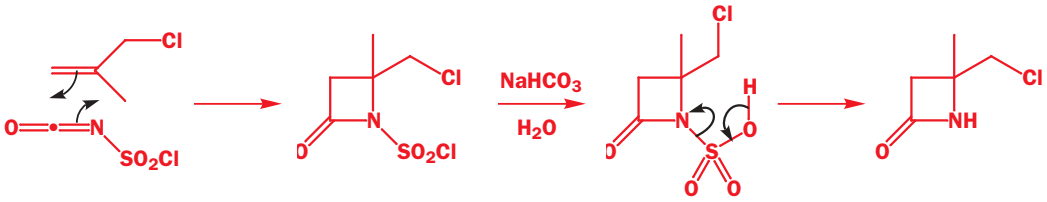
an isocyanate



chlorosulfonyl isocyanate

You will notice that in both of these examples there is an aryl substituent on the nitrogen atom of the imine. This is simply because imines are rather unstable and cannot normally be prepared with a hydrogen atom on the nitrogen. *N*-Aryl imines are quite stable (Chapter 13, p. 000).

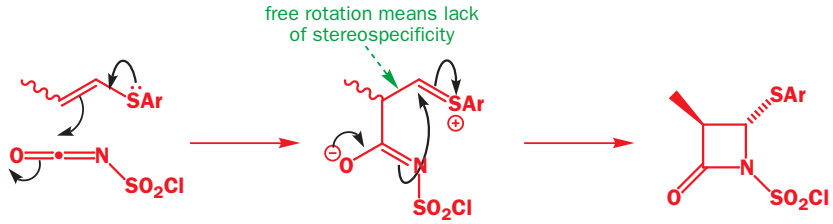
When we wish to make β-lactams by the alternative addition of an isocyanate to an alkene, a substituent on nitrogen is again required, but for quite a different reason. Because alkenes are only moderately nucleophilic, we need a strongly electron-withdrawing group on the isocyanate that can be removed after the cycloaddition, and the most popular by far is the chlorosulfonyl group. The main reason for its popularity is the commercial availability of chlorosulfonyl isocyanate. It reacts even with simple alkenes.



The alkene's HOMO interacts with the isocyanate's LUMO, and the most electrophilic atom is the carbonyl carbon so this is where the terminal carbon atom of the alkene attacks. The chlorosulfonyl group can be removed simply by hydrolysis under mild conditions via the sulfonic acid.

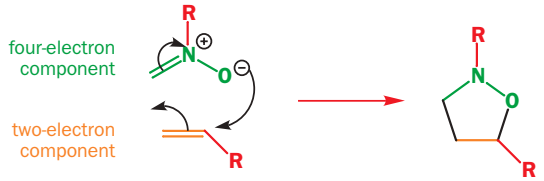
With a more electron-rich alkene—an enol ether, for example, or the following example with its sulfur analogue, a vinyl sulfide—the reaction ceases to be a concerted process and occurs stepwise. We know this must be the case in the next example because, even though the starting material is an *E*/*Z* mixture, the product has only *trans* stereochemistry: it is stereoselective rather than stereospecific, indicating the presence of an intermediate in which free rotation can take place.

▶ The lack of stereospecificity in some nonconcerted reactions is discussed in Chapter 40 in relation to carbenes.

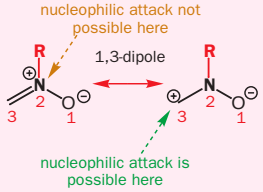


Making five-membered rings—1,3-dipolar cycloadditions

We have seen how to make four-membered rings by [2 + 2] cycloadditions and, of course, how to make six-membered rings by [4 + 2] cycloadditions. Now what about five-membered rings? It sounds at first impossible to make an odd-numbered ring in this way. However, all we need is a three-atom, four-electron 'diene' and we can do a Diels–Alder reaction. Impossible? Not at all—the molecules are called 1,3-dipoles and are good reagents for cycloadditions. Here is an example.

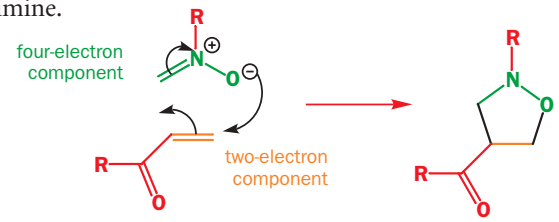


▶ The charges make it look like a 1,2-dipole, but nucleophilic attack on N^+ is impossible.



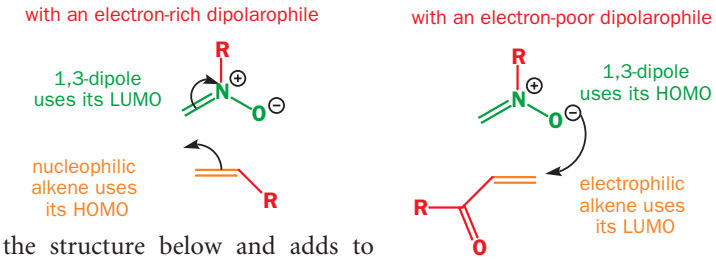
The molecule containing N and O atoms labelled 'four-electron component' is the 1,3-dipole. It has a nucleophilic end (O^-) and an electrophilic end—the end of the double bond next to the central N^+. These are 1,3-related so it is indeed a 1,3-dipole. This functional group is known as a **nitrone**. You could also think of it as the *N*-oxide of an imine.

The nitrone gets its four electrons in this way: there are two π electrons in the N=C double bond and the other two come from one of the lone pairs on the oxygen atom. The two-electron component is a simple alkene in this example. In a Diels–Alder

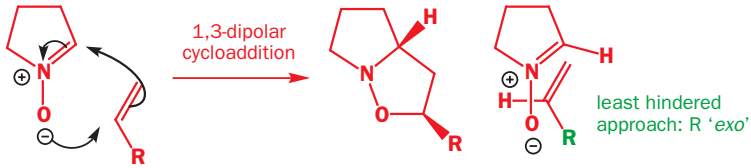


reaction it would be called the dienophile. Here it is called the **dipolarophile**. Simple alkenes (which are bad dienophiles) are good dipolarophiles and so are electron-deficient alkenes.

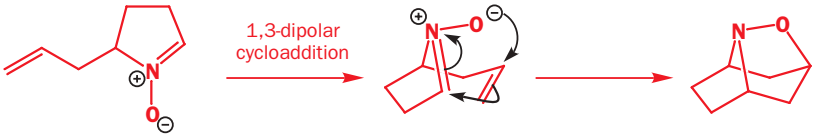
The difference between dienes and 1,3-dipoles is that dienes are nucleophilic and prefer to use their HOMOs in cycloadditions with electron-deficient dienophiles while 1,3-dipoles, as their name implies, are both electrophilic and nucleophilic. They can use either their HOMOs or their LUMOs depending on whether the dipolarophile is electron-deficient or electron-rich.



One important nitrone is a cyclic compound that has the structure below and adds to dipolarophiles (essentially any alkene!) to give two five-membered rings fused together. The stereochemistry comes from the best approach with the least steric hindrance, as shown. There is no *endo* rule in these cycloadditions as there is no conjugating group to interact across space at the back of the dipole or dipolarophile. The product shown here is the more stable *exo* product.



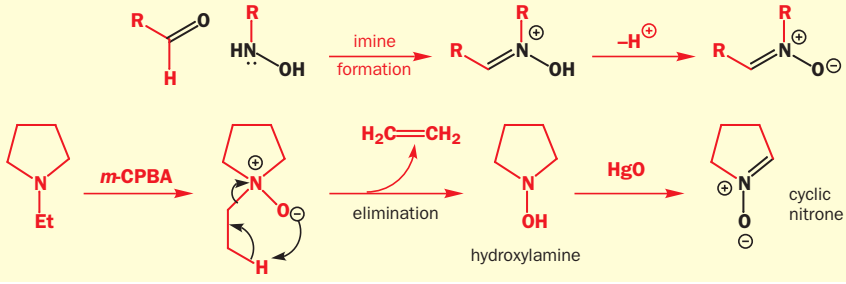
If the alkene is already joined on to the nitrone by a covalent bond so that the dipolar cycloaddition is an intramolecular reaction, one particular outcome may be dictated by the impossibility of the alternatives. Here is a simple case where an allyl group is joined to the same ring as in the previous example. The product has a beautifully symmetrical cage structure and the mechanism shows the only way in which the molecule can fold up to allow a 1,3-dipolar cycloaddition to occur.



Making nitrones

There are two important routes to nitrones: both start from hydroxylamines. Open-chain nitrones are usually made simply by imine formation between a hydroxylamine and an aldehyde.

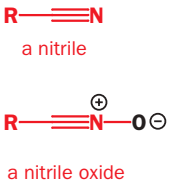
The cyclic nitrones are made from simple tertiary amines by oxidation and then cyclic elimination to give a hydroxylamine. This is oxidized again with Hg(II) to give the nitrone.



The importance of the Diels–Alder reaction is that it makes six-membered rings with control over stereochemistry. The importance of 1,3-dipolar cycloadditions is not so much in the heterocyclic products but in what can be done with them. Almost always, the first formed heterocyclic ring is broken down in some way by carefully controlled reactions. The nitrone adducts we have just seen contain a weak N–O single bond that can be selectively cleaved by reduction. Reagents such as $LiAlH_4$ or zinc metal in various solvents (acetic acid is popular) or hydrogenation over catalysts such as nickel reduce the N–O bond to give NH and OH functionality without changing the structure or stereochemistry of the rest of the molecule. From the examples above, we get these products.

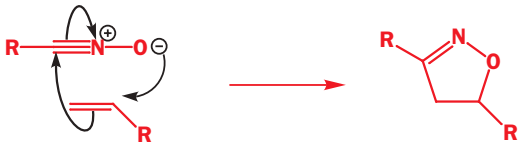
In each cycloaddition, one permanent C–C and one C–O bond (shown in orange) were made. These were retained while the N–O bond present in the original dipole was discarded. The final product is an amino-alcohol with a 1,3-relationship between the OH and NH groups.

Linear 1,3-dipoles



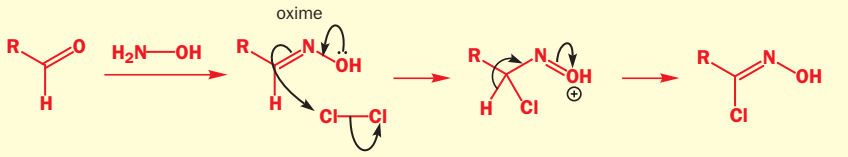
In the Diels–Alder reaction, the dienes had to have an s-*cis* conformation about the central single bond so that they were already in the shape of the product. Many useful 1,3-dipoles are actually linear and their 1,3-dipolar cycloadditions look very awkward. We shall start with the nitrile oxides, which have a triple bond where the nitrone had a double bond.

a 1,3-dipolar cycloaddition with a nitrile oxide

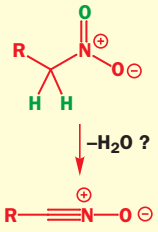


Making nitrile oxides

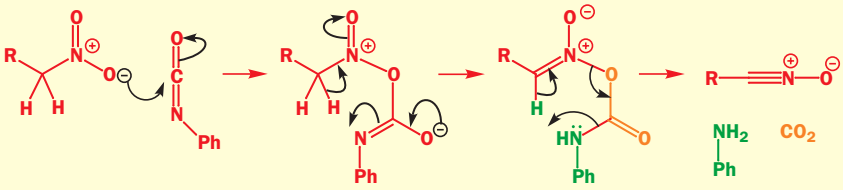
There are two important routes to these compounds, both of which feature interesting chemistry. Oximes, easily made from aldehydes with hydroxylamine (NH_2–OH), are rather enol-like and can be chlorinated on carbon.

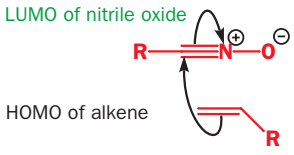


Treatment of the chloro-oxime with base (Et_3N is strong enough) leads directly to the nitrile oxide with the loss of HCl. This is an elimination of a curious kind as we cannot draw a connected chain of arrows for it. We must use two steps—removal of the OH proton and then loss of chloride. It is a γ elimination rather than the more common β elimination.



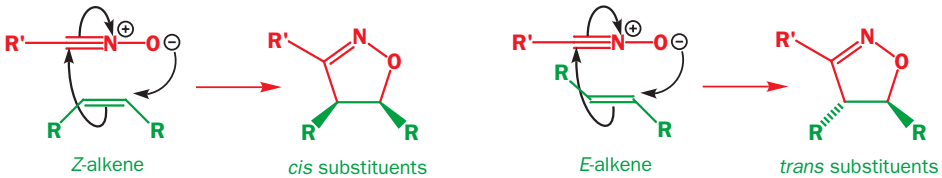
The other method starts from nitroalkanes and is a dehydration. Inspect the two molecules and you will see that the nitro compound contains H_2O more than the nitrile oxide. But how to remove the molecule of water? The reagent usually chosen is phenyl isocyanate (Ph–N=C=O), which removes the molecule of water atom by atom to give aniline ($PhNH_2$) and CO_2. This is probably the mechanism, though the last step might not be concerted as we have shown.





The dipolarophile (here a simple alkene) has to approach uncomfortably close to the central nitrogen atom for bonds to be formed. Presumably, the nitrile oxide distorts out of linearity in the transition state. As you should expect, this is a reaction between the HOMO of the alkene and the LUMO of the nitrile oxide so that the leading interaction that determines the structure of the product is the one in the margin.

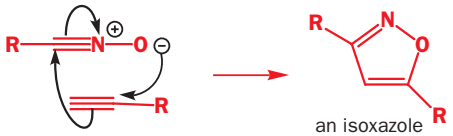
If there is stereochemistry in the alkene, it is faithfully reproduced in the heterocyclic adduct as we should expect for a concerted cycloaddition.



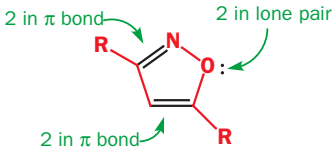
■ There is much more about making heterocycles in Chapter 44.

Both partners in nitrile oxide cycloadditions can have triple bonds—the product is then a stable aromatic heterocycle called an **isoxazole**.

cycloaddition of nitrile oxide and alkyne

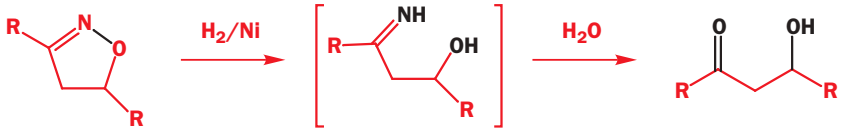


aromaticity of isoxazole - six π electrons

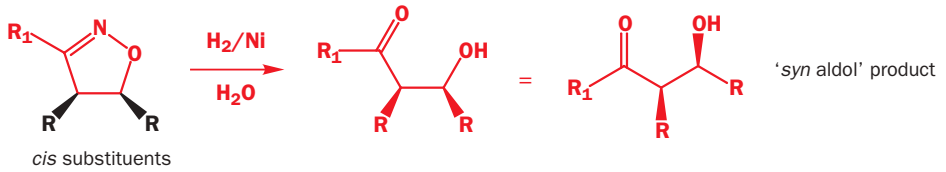


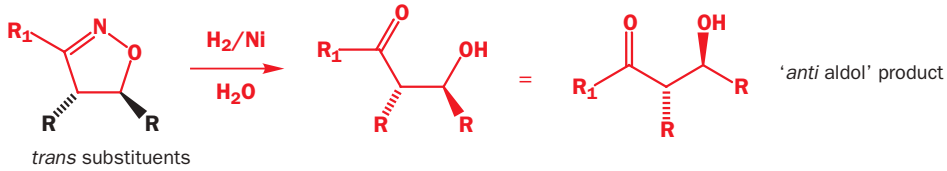
Though isoxazoles have some importance, the main interest in nitrile oxide cycloadditions lies again in the products that are formed by reduction of the N–O bond and by the C=N double bond. This produces amino-alcohols with a 1,3-relationship between the two functional groups.

The N–O bond is the weaker of the two and it is possible to reduce that and leave the C=N bond alone. This leaves an imine that usually hydrolyses during work-up.



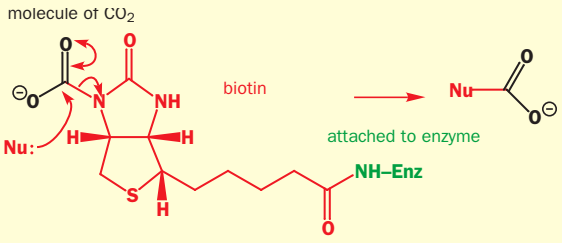
Any stereochemistry in the adduct is preserved right through this reduction and hydrolysis sequence: you might like to compare the products with the products of the stereoselective aldol reactions you saw in Chapter 34.



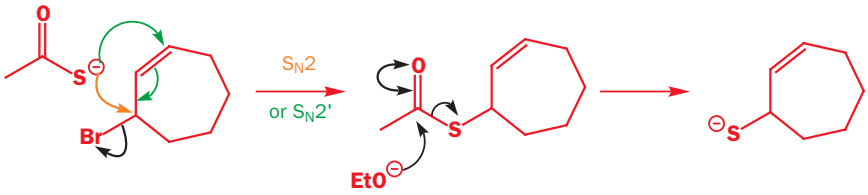


Biotin

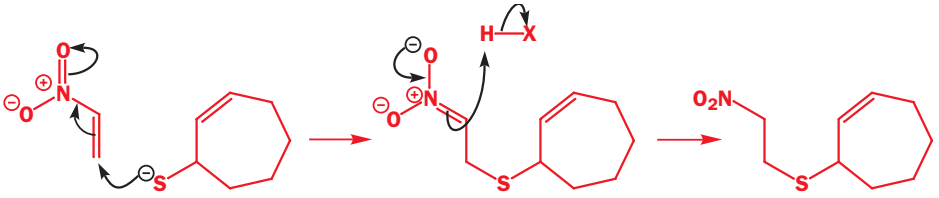
Biotin is an enzyme cofactor that activates and transports CO_2 for use as a electrophile in biochemical reactions.



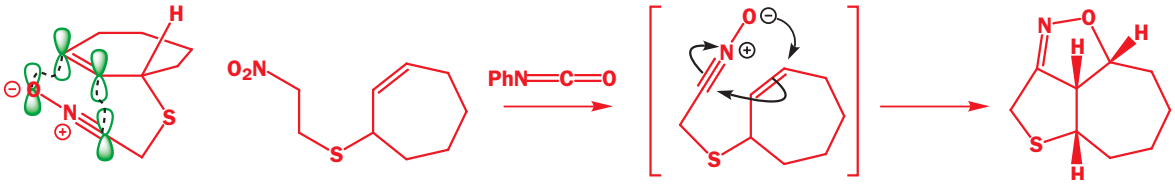
We shall end this section with a beautiful illustration of an intramolecular 1,3-dipolar cycloaddition of a nitrile oxide that was used in the synthesis of the vitamin biotin. Starting at the beginning of the synthesis will allow you to revise some reactions from earlier chapters. The starting material is a simple cyclic allylic bromide that undergoes an efficient S_N2 reaction with a sulfur nucleophile. In fact, we don't know (or care!) whether this is an S_N2 or S_N2' reaction as the product of both reactions is the same. This sort of chemistry was discussed in Chapter 23 if you need to check up on it. Notice that it is the sulfur atom that does the attack—it is the soft end of the nucleophile and better at S_N2 reactions. The next step is the hydrolysis of the ester group to reveal the thiolate anion.



This step is strictly an ester exchange rather than a hydrolysis and is discussed in Chapter 12. Next the nucleophilic thiolate anion does a conjugate addition (Chapters 10 and 23) on to a nitroalkene.

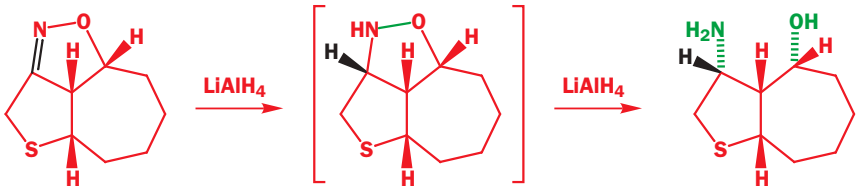


Now comes the exciting moment. The nitroalkene gives the nitrile oxide directly on dehydration with PhN=C=O and the cycloaddition occurs spontaneously in the only way it can, given the intramolecular nature of the reaction.

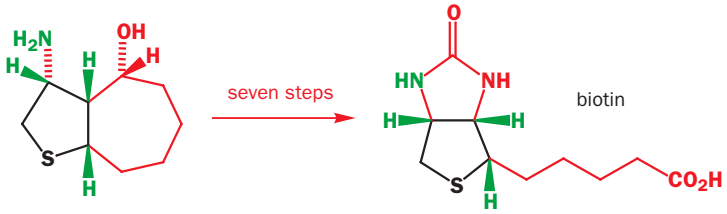


We have drawn the reaction with the nitrile oxide coming up from the underside of the seven-membered ring, pushing all the hydrogen atoms at the ring junctions upwards and making all the rings join up in a *cis* fashion.

Next the cycloadduct is reduced completely with $LiAlH_4$ so that both the N–O and C=N bonds are cleaved. This step is very stereoselective so the C=N reduction probably precedes the N–O cleavage and the hydride has to attack from the outside (top) face of the molecule. These considerations are explored more thoroughly in Chapter 33.



The sulfur-containing ring, and the stereochemistry, of biotin are already defined and, in the seven steps that follow, the most important is the breaking open of the seven-membered ring by a Beckmann rearrangement, which you will meet in Chapter 37.



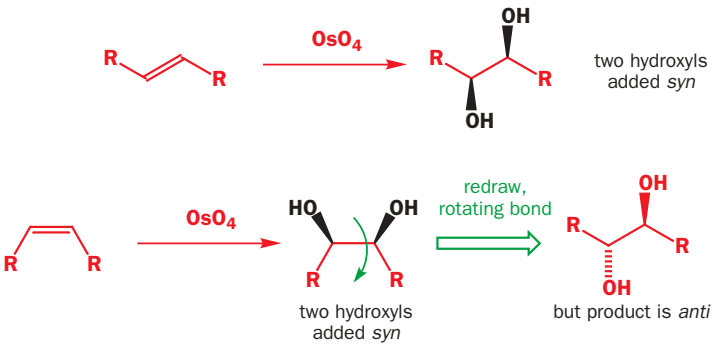
Two very important synthetic reactions: cycloaddition of alkenes with osmium tetroxide and with ozone

We shall end this chapter with two very important reactions, both of which we have alluded to earlier in the book. These reactions are very important not just because of their mechanisms, which you must

be aware of, but even more because of their usefulness in synthetic chemistry, and in that regard they are second only to the Diels–Alder reaction when considering all the reactions in this chapter. They are both oxidations—one involves osmium tetroxide (OsO_4) and one involves ozone (O_3) and they both involve cycloaddition.

OsO_4 adds two hydroxyl groups *syn* to a double bond

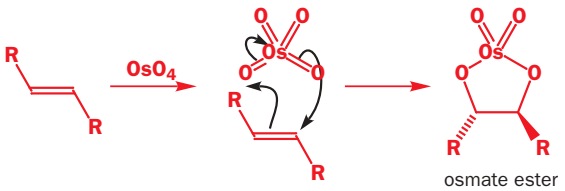
We emphasized the fact that cycloadditions, being concerted, are stereospecific with regard to the geometry of the double bond. One very important example of this is the stereospecific reaction of an alkene with OsO_4. First, we give you the result of the reaction—the overall outcome is that two hydroxyl groups are added *syn* to the double bond.



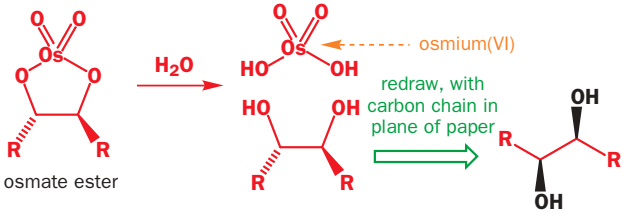
tetrahedral structure of osmium tetroxide

They add *syn* whether the double bond is *E* or *Z*, and, by redrawing the second example in a different conformation, you can see how defining the geometry of the starting material defines which diastereoisomer of the product is obtained.

Now for the mechanism. We must admit before we start that this is a reaction about which there is still some controversy, and we give you the simplest reasonable view of the mechanism. Future results may show this mechanism to be wrong, but it will certainly do to explain any result you might meet. The first step is a cycloaddition between the osmium tetroxide and the alkene. You can treat the OsO_4 like a dipole—it isn't drawn as one because osmium has plenty of orbitals to accommodate four double bonds.

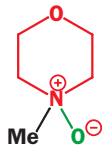


The product of the stereospecific cycloaddition is an 'osmate ester'. This isn't the required product, and the reaction is usually done in the presence of water (the usual solvent is a *t*-BuOH–water mixture), which hydrolyses the osmate ester to the diol. Because both oxygen atoms were added in one concerted step during the cycloaddition, their relative stereochemistry must remain *syn*.

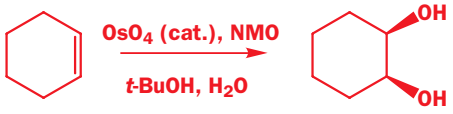


The osmium starts as Os(VIII) and ends up as Os(VI)—the reaction is, of course, an oxidation, and it's one that is very specific to C=C double bonds (as we mentioned in Chapter 24). As written, it would involve a whole equivalent of the expensive, toxic, and heavy metal osmium, but it can be made catalytic by introducing a reagent to oxidize Os(VI) back to Os(VIII). The usual reagent is *N*-methylmorpholine-*N*-oxide (NMO) or Fe(III), and typical conditions for an osmylation, or dihydroxylation, reaction are shown in the scheme alongside.

NMO =



N-methylmorpholine-*N*-oxide

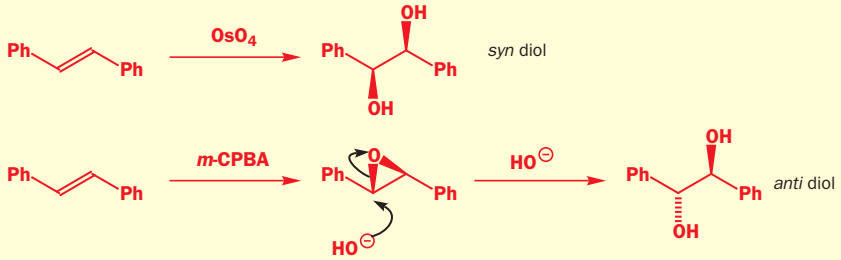


In behaviour that is typical of a 1,3-dipolar cycloaddition reaction, OsO_4 reacts almost as well with electron-poor as with electron-rich alkenes. OsO_4 simply chooses to attack the alkene HOMO

or its LUMO depending on which gives the best interaction. This is quite different from the electrophilic addition of *m*-CPBA or Br_2 to alkenes.

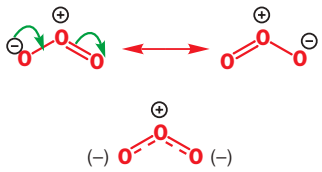
syn and *anti* addition of hydroxyl groups

It is important that you note the link between the OsO_4 reaction and the stereospecific transformations that we highlighted at the beginning of Chapter 34. In particular, you now know ways to add two hydroxyl groups both *syn* and *anti* across a double bond: the *syn* addition uses OsO_4 and the *anti* addition uses epoxidation followed by ring opening with HO^-.



A cycloaddition that destroys bonds—ozonolysis

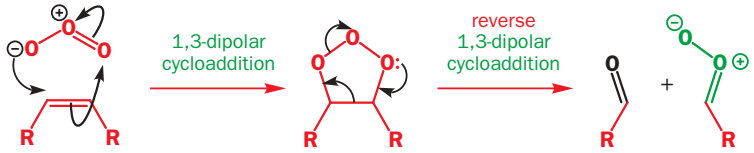
structure of ozone



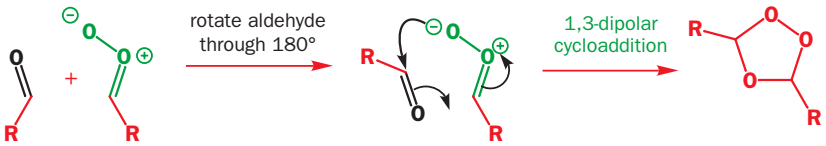
Our last type of cycloaddition is most unusual. It starts as a 1,3-dipolar cycloaddition but eventually becomes a method of cleaving π bonds in an oxidative fashion so that they end up as two carbonyl groups. The reagent is ozone, O_3.

Ozone is a symmetrical bent molecule with a central positively charged oxygen atom and two terminal oxygen atoms that share a negative charge. It is a 1,3-dipole and does typical 1,3-dipolar cycloadditions with alkenes.

The product is a very unstable compound. The O–O single bond (bond energy 140 kJ mol^{-1}) is a very weak bond—much weaker than the N–O bond (180 kJ mol^{-1}) we have been describing as weak in previous examples—and this heterocycle has two of them. It immediately decomposes—by a *reverse* 1,3-dipolar cycloaddition.

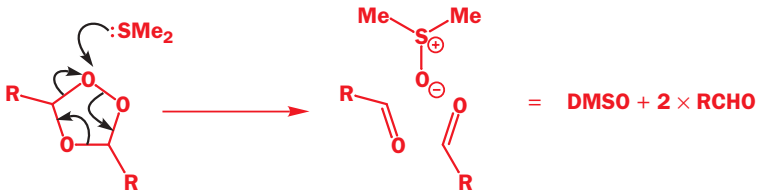


The products are a simple aldehyde on the left and a new, rather unstable looking molecule—a 1,3-dipole known as a carbonyl oxide—on the right. At least it no longer has any true O–O single bonds (the one that looks like a single bond is part of a delocalized system like the one in ozone). Being a 1,3-dipole, it now adds to the aldehyde in a third cycloaddition step. It might just add back the way it came, but it much prefers to add in the other way round with the nucleophilic oxyanion attacking the carbon atom of the carbonyl group like this.



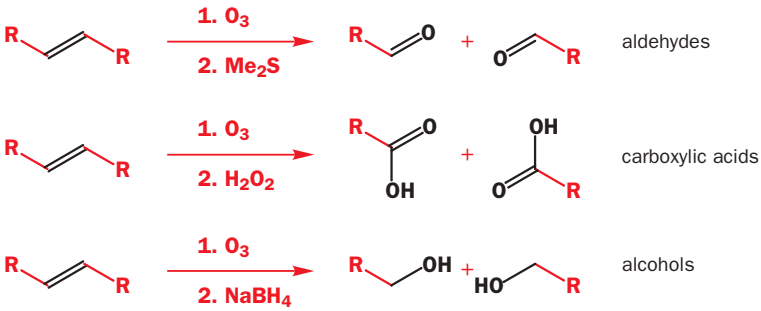
This compound—known as an **ozonide**—is the first stable product of the reaction with ozone. It is the culmination of two 1,3-dipolar cycloadditions and one reverse 1,3-dipolar cycloaddition. It is still not that stable and is quite explosive, so for the reaction to be of any use it needs decomposing. The way this is usually done is with dimethylsulfide, which attacks the ozonide to give DMSO and two molecules of aldehyde.

■ Ph_3P is also used.

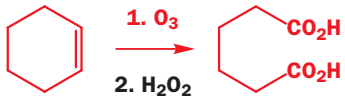


The ozonide will also react with oxidizing agents such as H_2O_2 to give carboxylic acids, or with more powerful reducing agents such as $NaBH_4$ to give alcohols. Here are the overall transformations—each cleaves a double bond—it is called an **ozonolysis**.

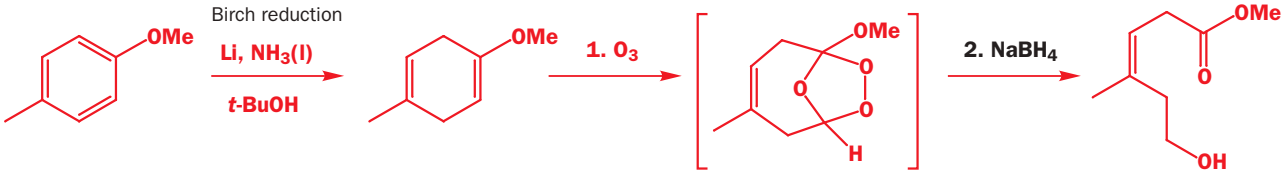
ozonolysis of alkenes to...



Ozonolysis of cyclohexenes is particularly useful as it gives 1,6-dicarbonyl compounds that are otherwise difficult to make. In the simplest case we get hexane 1,6-dioic acid (adipic acid) a monomer for nylon manufacture.

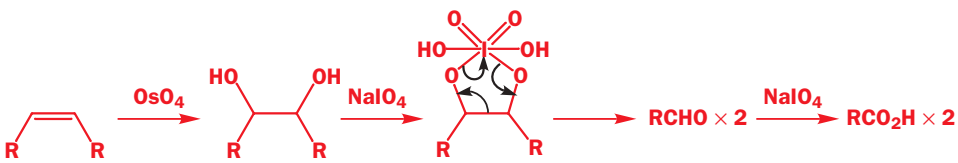


More interesting cases arise when the products of Birch reduction (Chapter 24) are treated with ozone. Here it is the electron-rich enol ether bond that is cleaved, showing that ozone is an electrophilic partner in 1,3-dipolar cycloadditions. If the ozonide is reduced, a hydroxy ester is formed whose trisubstituted bond's *Z* geometry was fixed by the ring it was part of (see Chapter 31).



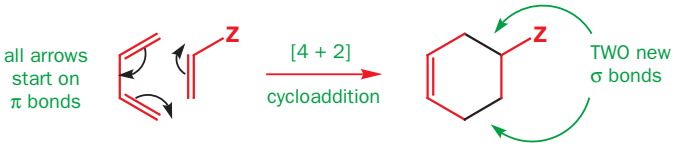
An alternative method of cleaving C=C bonds is to use OsO_4 in conjunction with $NaIO_4$. The diol product forms a periodate ester, which decomposes to give two molecules of aldehyde. These are themselves oxidized by the periodate to carboxylic acids.

■ You saw periodate being used to cleave C–C bonds in this way at the end of Chapter 34, p. 000.



Summary of cycloaddition reactions

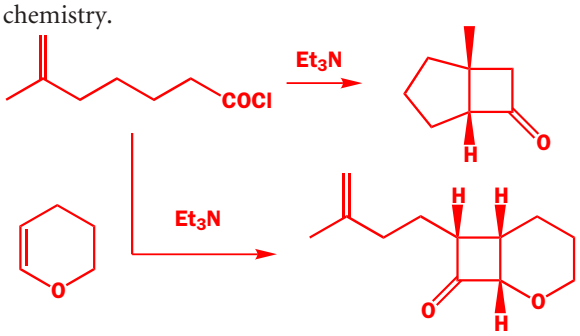
- A cycloaddition is a one-step ring-forming reaction between two conjugated π systems in which two new σ bonds are formed joining the two reagents at each end. The mechanism has one step with no intermediates, and all the arrows start on π bonds and go round in a ring.



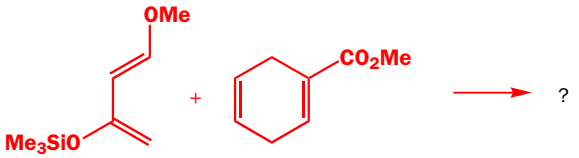
- The cycloadditions are supra-facial—they occur on one face only of each π system—and for a thermally allowed reaction there should be $4n + 2$ electrons in the mechanism, but $4n$ in a photochemical cycloaddition. These rules are dictated by orbital symmetry.
- Cycloaddition equilibria generally lie over on the right-hand side in a thermal reaction because C–C σ bonds are stronger than C–C π bonds. In a photochemical cycloaddition, the product loses its π bonds and therefore its means of absorbing energy. It is the kinetic product of the reaction even if it has a strained four-membered ring.
- The stereochemistry of each component is faithfully reproduced in the product—the reactions are stereospecific—and the relationship between their stereochemistries may be governed by orbital overlap to give an *endo* product.

Problems

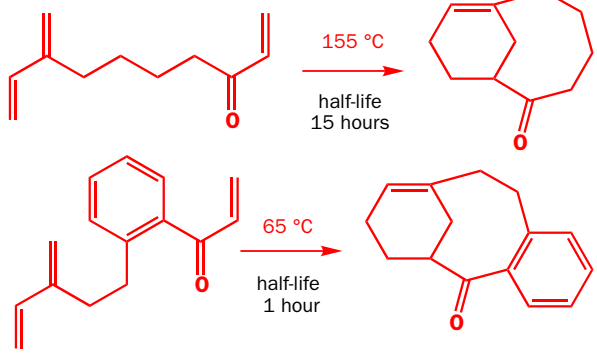
1. Give mechanisms for these reactions, explaining the stereochemistry.



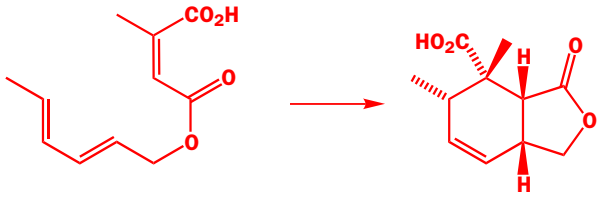
2. Predict the structure of the product of this Diels–Alder reaction.



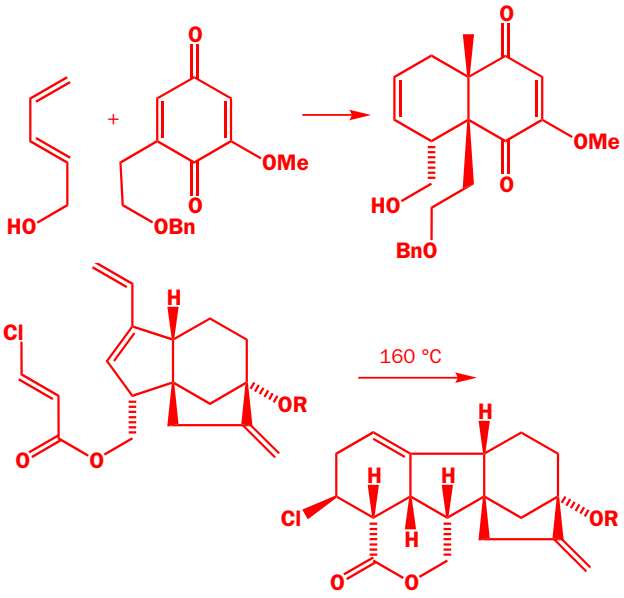
3. Comment on the difference in rate between these two reactions. It is estimated that the second goes about 10^6 times faster than the first.



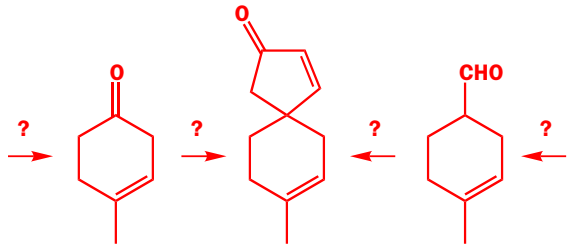
4. Justify the stereoselectivity in this intramolecular Diels–Alder reaction.



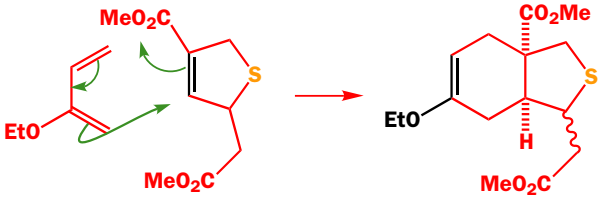
5. Explain the formation of single adducts in these reactions.



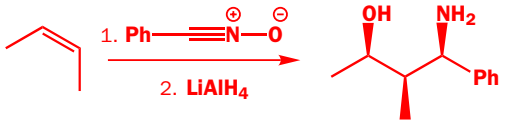
6. Revision elements. Suggest two syntheses of this spirocyclic ketone from the starting materials shown. Neither starting material is available.



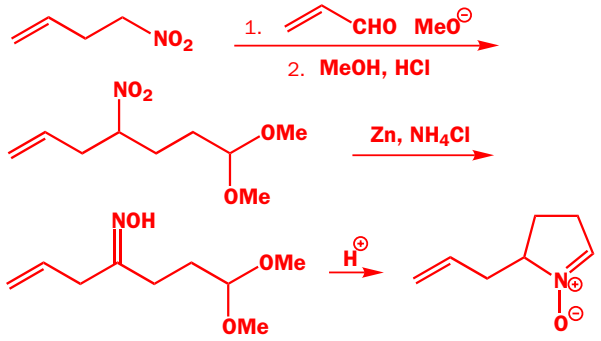
7. This reaction appeared in Chapter 33. Account for the selectivity.



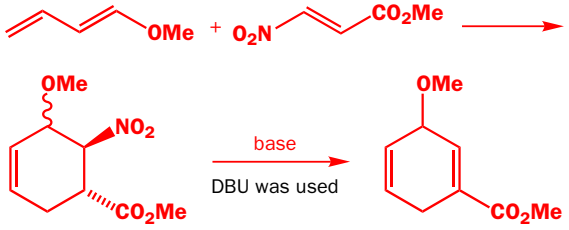
8. Draw mechanisms for these reactions and explain the stereochemistry.



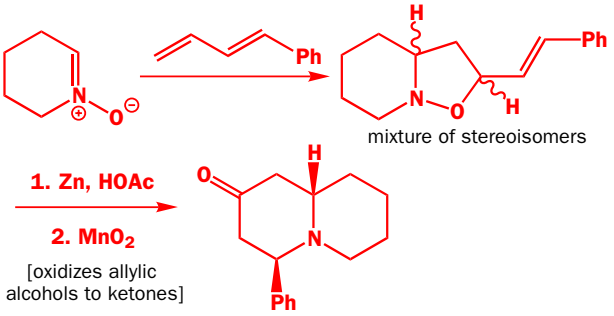
9. Revision. One of the nitrones used as an example in the chapter was prepared by this route. Explain what is happening and give details of the reactions.



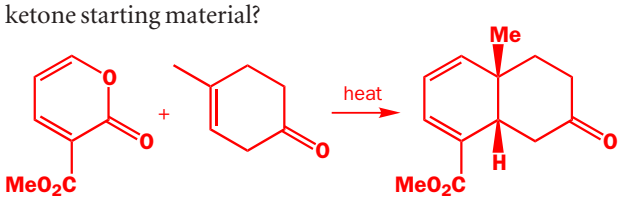
10. Explain why this Diels–Alder reaction gives total regioselectivity and stereospecificity but no stereoselectivity. What is the mechanism of the second step? What alternative route might you have considered if you wanted to make this final product and why would you reject it?



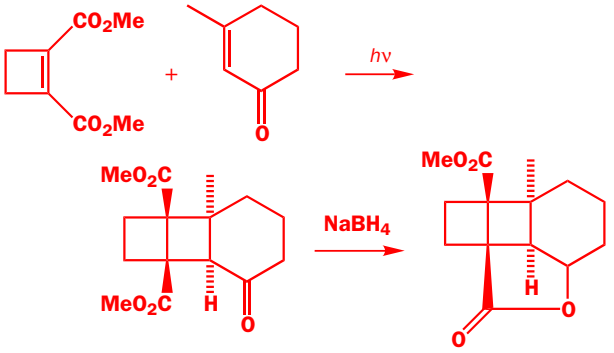
11. Give mechanisms for these reactions and explain the regio- and stereochemical control (or the lack of it!).



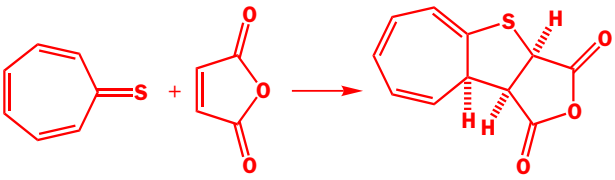
12. Suggest a mechanism for this reaction and explain the stereo- and regiochemistry. How would you prepare the unsaturated ketone starting material?



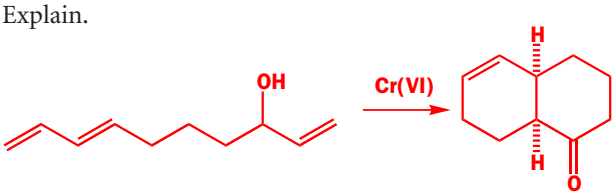
13. Photochemical cycloaddition of these two compounds is claimed to give the single diastereoisomer shown. The chemists who did this work claim that the stereochemistry of the adduct is simply proved by its conversion into a lactone on reduction. Comment on the validity of this deduction and explain the stereochemistry of the cycloaddition.



14. Thioketones, with a C=S bond, are not usually stable as we shall see in Chapter 46. However, this thioketone is quite stable and undergoes reaction with maleic anhydride to give the product shown. Comment on the stability of the starting material, the mechanism of the reaction, and the stereochemistry of the product.



15. This unsaturated alcohol is perfectly stable until it is oxidized with Cr(VI): it then immediately cyclizes to the product shown. Explain.



16. Suggest mechanisms for these reactions and comment on the stereochemistry of the first product.