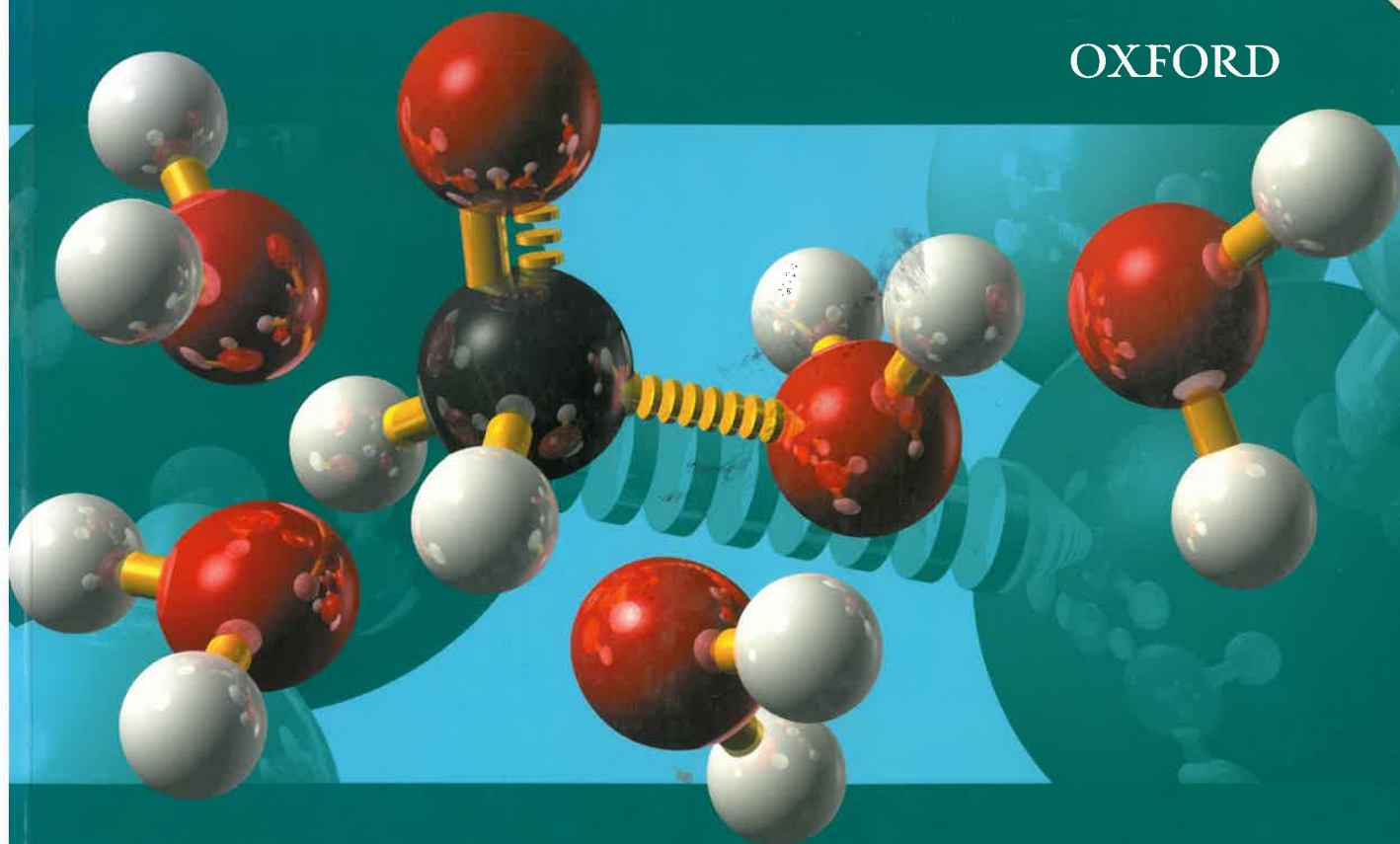


OXFORD



Clayden, Greeves, Warren
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ORGANIC CHEMISTRY

OXFORD

UNIVERSITY PRESS

Great Clarendon Street, Oxford OX2 6DP

Oxford University Press is a department of the University of Oxford
It furthers the University's objective of excellence in research, scholarship,
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Oxford New York

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Published in the United States
by Oxford University Press Inc., New York

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First published 2001

Reprinted 2001 (with corrections), 2003, 2004, 2005, 2006, 2007, 2008, 2009

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Library of Congress Cataloging in Publication Data

(Data available)

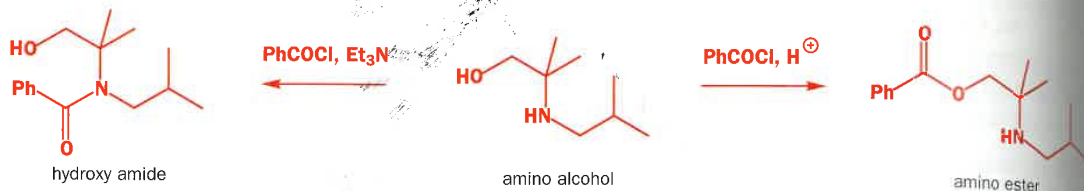
ISBN 978-0-19-850346-0

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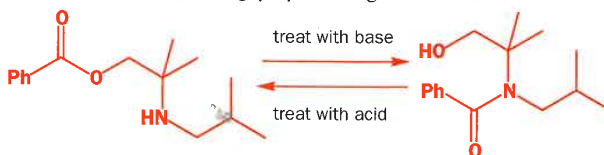
Typeset by Wyvern 21 Ltd. Bristol
Printed and bound in China by
C&C Offset Printing Co., Ltd.

One functional group may be more reactive than another for kinetic or for thermodynamic reasons

We hope that our survey of the important methods for reduction has shown you that, by choosing the right reagent, you can often react the functional group you want. The chemoselectivity you obtain is kinetic chemoselectivity—reaction at one functional group is simply faster than at another. Now look at the acylation of an amino alcohol (which is, in fact, a synthesis of the painkiller isobucaine) using benzoyl chloride under *acid* conditions. The hydroxyl group is acylated to form an ester. Yet under *basic* conditions, the selectivity is quite different, and an amide is formed.

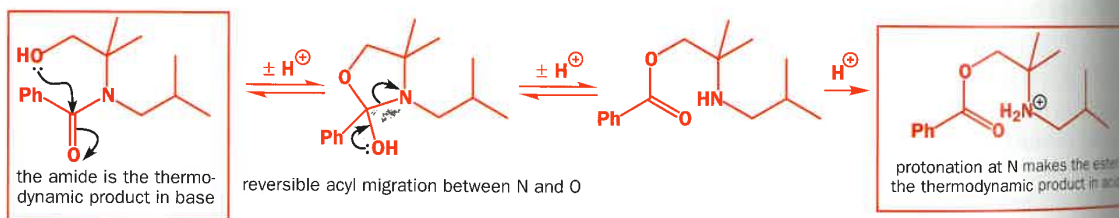


A clue to why the selectivity reverses is shown below—it is, in fact, possible to interconvert the ester and the amide simply by treating either with acid or with base.



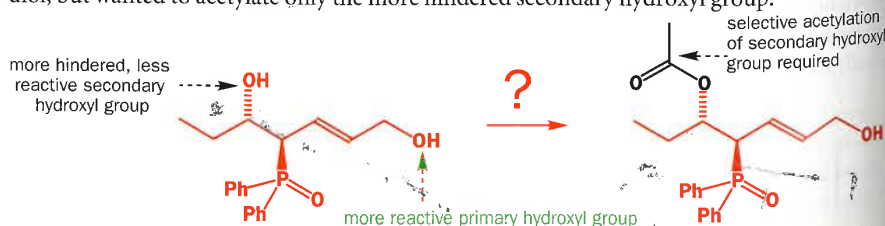
■ We first met examples of kinetic and thermodynamic control in Chapter 13.

The selectivity in these reactions is *thermodynamic* chemoselectivity. Under conditions in which the ester and amide can equilibrate, the product obtained is the more stable of the two, not necessarily the one that is formed faster. In base the more stable amide predominates, while in acid the amine is protonated, which prevents it from acting as a nucleophile and removes it from the equilibrium, giving the ester.

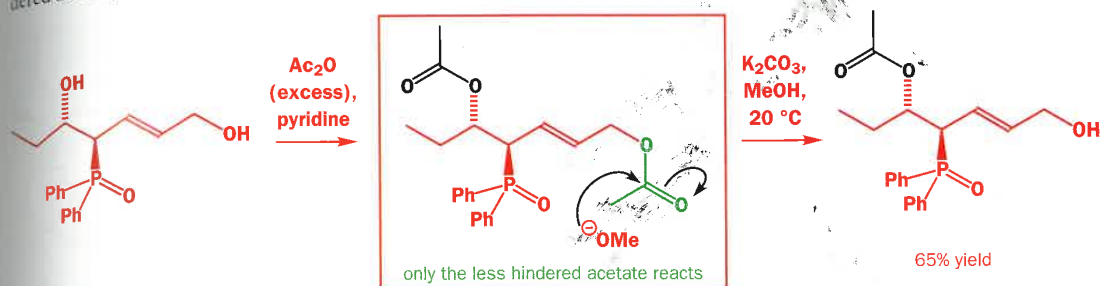


How to react the less reactive group (I)

The relative reactivity of the alcohol and amine in the example just given could be overturned by conducting a reaction under thermodynamic control. In kinetically controlled reactions, the idea that you can conduct chemoselective reactions on the more reactive of a pair of functional groups—carbonyl-based ones, for example—is straightforward. But what if you want to react the less reactive of the pair? There are two commonly used solutions. The first is illustrated by a compound needed by chemists at Cambridge to study an epoxidation reaction. They were able to make the following diol, but wanted to acetylate only the more hindered secondary hydroxyl group.



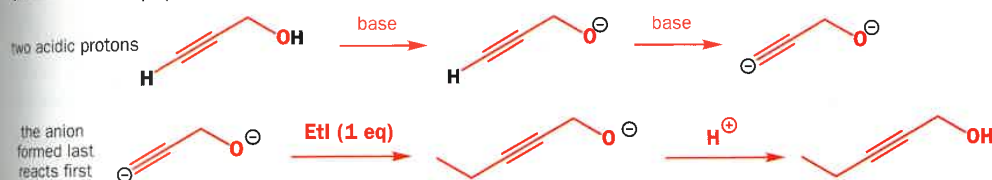
Treatment with one equivalent of an acyl chloride agent is no good because the primary hydroxyl group is more reactive; instead, the chemists acetylated both hydroxyl groups, and then treated the bis-acetate with mildly basic methanol (K_2CO_3 , MeOH, 20°C), which reacted only at the less hindered acetoxy group and gave the desired compound in 65% yield.



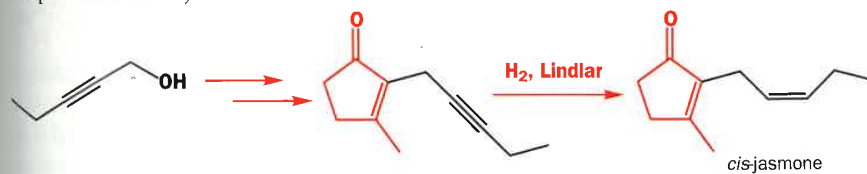
In other words, start by letting both groups react, and then go backwards but reverse the reaction at only one of the groups. Steric hindrance meant that the less favourable reaction (in other words, reaction at the less reactive group) was less readily reversed.

Chemoselectivity in the reactions of dianions

The converse of this idea is central to a useful bit of chemoselectivity that can be obtained in the reactions of dianions. 1-Propynol can be deprotonated twice by strong bases—first, at the hydroxyl group to make an alkoxide anion (the pK_a of the OH group is about 16) and, secondly, at the alkyne (pK_a of the order of 25) to make a 'dianion'. When this dianion reacts with electrophiles it always reacts at the alkynyl anion and not at the alkoxide.



This reaction is important in a synthesis of the perfumery compound *cis*-jasmone. The alkyne is the precursor to *cis*-jasmone's alkene side chain.



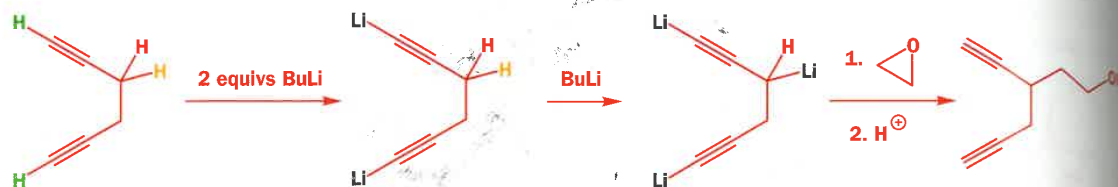
Reactivity of dianions

The anion that is formed *last* reacts *first*.

Vollhardt used this sort of chemoselectivity in his 1977 synthesis of the female sex hormone oestrone. He needed an alkyl iodide, which could be made by reacting an anion of a bis-alkyne with ethylene oxide.



Although anions can often be formed straightforwardly next to alkynes, there are two other more acidic protons (green) in the molecule that would be removed by base before the yellow proton. However, treatment with *three* equivalents of butyl lithium removes all three, and the trianion reacts with ethylene oxide at the last-formed anionic centre to give the required compound.

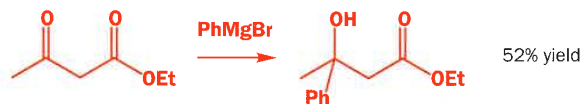


How to react the less reactive group (II): protecting groups

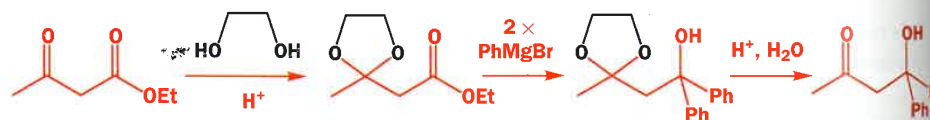
The usual way of reacting a less reactive group in the presence of a more reactive one is to use a protecting group. This tertiary alcohol, for example, could be made from a keto-ester if we could get phenylmagnesium bromide to react with the ester rather than with the ketone.



As you would expect, simply adding phenylmagnesium bromide to ethyl acetoacetate leads mainly to addition to the more electrophilic ketone.



One way of making the alcohol we want is to protect the ketone as an acetal. An acetal-protecting group (shown in black) is used.

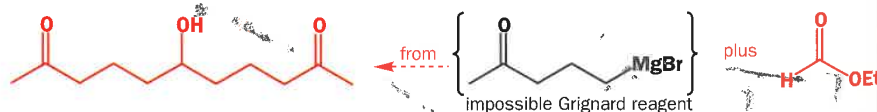


Five-membered cyclic acetals like these are known as dioxolanes. You met them first in Chapter 14 when we were discussing acetal formation and hydrolysis.

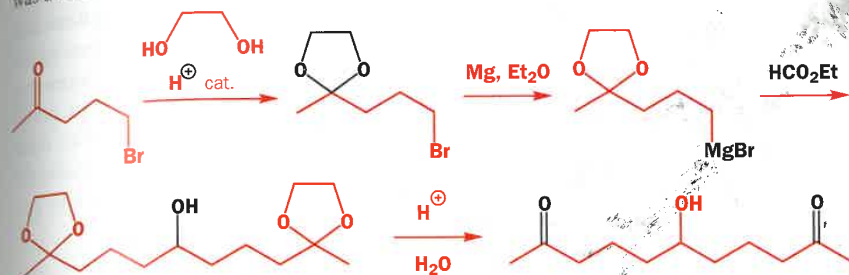
This table of protecting groups will grow, line by line, as we move through this chapter and the next.

Protecting group	Structure	Protects	From	Protection	Deprotection
acetal (dioxolane)		ketones, aldehydes	nucleophiles, bases		water, H ⁺ cat.

By protecting sensitive functional groups like ketones it becomes possible to make reagents that would otherwise be unstable. In a synthesis of the natural product porantherine, a compound based on this structure was needed.

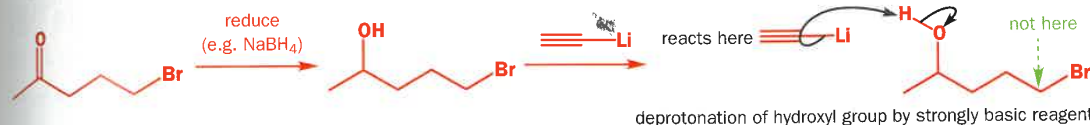


One way to make it is to add a Grignard reagent twice to ethyl formate. But, of course, a ketone-containing Grignard is an impossibility as it would self-destruct, so an acetal-protected compound was used.

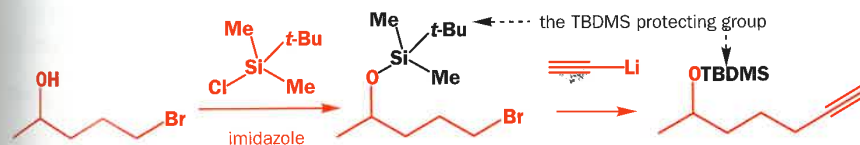
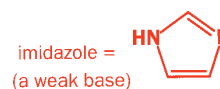


Strongly nucleophilic reagents like Grignard reagents and organolithiums are also strong bases, and may need protecting from acidic protons as well as from electrophilic carbonyl groups. Among the most troublesome are the protons of hydroxyl groups. When some American chemists wanted to make the antiviral agent Brefeldin A, they needed a simple alkynol.

A synthesis could start with the same bromoketone as the one above: reduction gives an alcohol, but alkylation of an alkynyl anion with this compound is not possible, because the anion will just deprotonate the hydroxyl group.

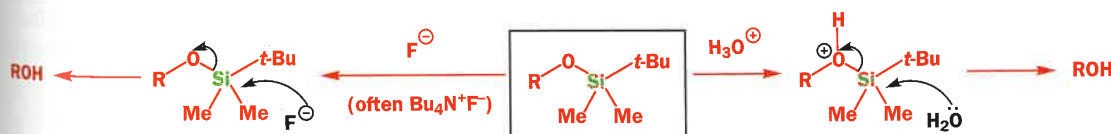


The answer is to protect the hydroxyl group, and the group chosen here was a silyl ether. Such ethers are made by reacting the alcohol with a trialkylsilyl chloride (here *t*-butyl dimethyl silyl chloride, or TBDMSCl) in the presence of a weak base, usually imidazole, which also acts as a nucleophilic catalyst (Chapter 12).



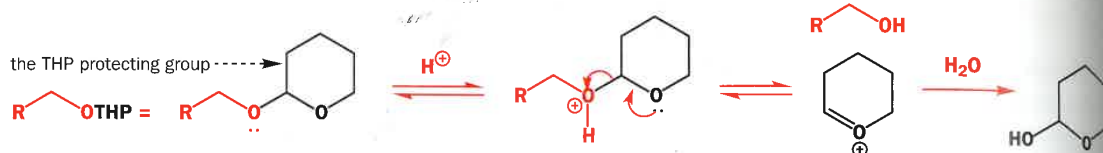
Silicon has a strong affinity for electronegative elements, particularly O, F, and Cl, so trialkylsilyl ethers are attacked by hydroxide ion, water, or fluoride ion but are more stable to carbon or nitrogen bases or nucleophiles. They are usually removed with aqueous acid or fluoride salts, particularly $\text{Bu}_4\text{N}^+\text{F}^-$ which is soluble in organic solvents. In fact, TBDMS is one member of a whole family of trialkylsilyl protecting groups and their relative stability to nucleophiles of various kinds is determined by the three alkyl groups carried by silicon. The most labile, trimethylsilyl (TMS), is removed simply on treatment with methanol, while the most stable require hydrofluoric acid.

Although not important to our discussion here, these substitution reactions are not the simple $\text{S}_\text{N}2$ reactions (Chapter 17) they might appear to be. The nucleophile adds to silicon first to form a five-valent anion which decomposes with the loss of the alcohol (Chapter 21).



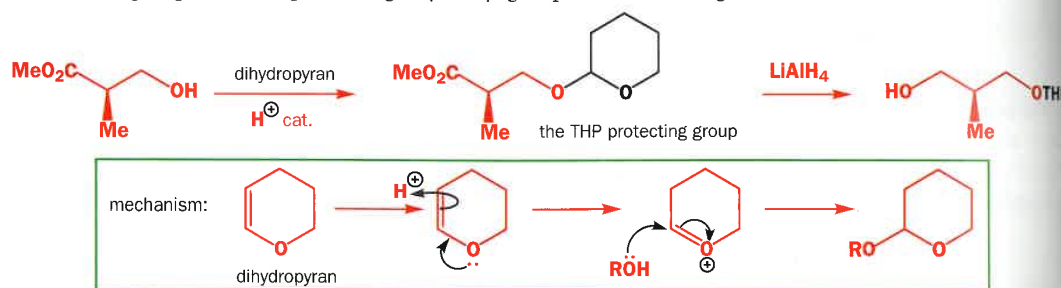
Protecting group	Structure	Protects	From	Protection	Deprotection
trialkylsilyl (R_3Si , e.g. TBDMS)	$\text{RO}-\text{SiMe}_3$ $\text{RO}-\text{SiMe}_2\text{Bu}^t$	alcohols (OH in general)	nucleophiles, C or N bases	R_3SiCl , base	H^+ , H_2O , HF

Why can't we just use a simple alkyl ether (methyl, say) to protect a hydroxyl group? There is no problem making the ether, and it will survive most reactions—but there is a problem getting an ether off again. This is always a consideration in protecting group chemistry—you want a group that is stable to the conditions of whatever reaction you are going to do (in these examples, strong bases and nucleophiles), but can then be removed under mild conditions that do not result in total decomposition of a sensitive molecule. What we need then, is an ether that has an 'Achilles' heel'—a feature that makes it susceptible to attack by some specific reagent or under specific conditions. One such group is the tetrahydropyranyl (THP) group. Although it is stable under basic conditions, as an ether would be, it is an acetal—the presence of the second oxygen atom is its 'Achilles' heel' and makes the THP protecting group susceptible to hydrolysis under acidic conditions. You could see the lone pair on the second oxygen atom as a 'safety catch' that is released only in the presence of acid.



Some chemistry of enol ethers is in Chapter 21.

Making the THP acetal has to be done in a slightly unusual way because the usual carbonyl compound plus two alcohols is inappropriate. Alcohols are protected by reacting them with an enol ether, dihydropyran, under acid catalysis. Notice the oxonium intermediate (formed by a familiar mechanism from Chapter 14)—just as in a normal acetal-forming reaction. In this example the THP group is at work preventing a hydroxyl group from interfering in the reduction of an ester.



A little further inspection will show you that the THP group here is not just stopping the OH interfering with the LiAlH_4 reduction, but is also crucial to the preservation of the chirality of this compound. The wedged bond shows you that the starting material is a single enantiomer: without a protecting group on one of the hydroxyls, they would be identical and the compound would no longer be chiral. More detailed inspection shows that the THP group also complicates the situation by introducing an extra chiral centre, and hence the potential for two diastereoisomers, which we will ignore.

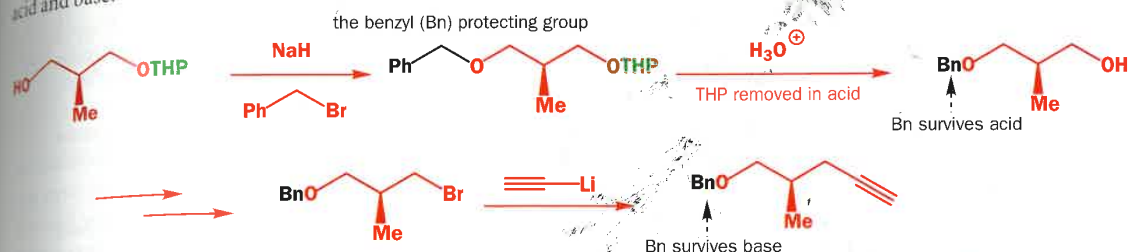
Protecting group	Structure	Protects	From	Protection	Deprotection
tetrahydropyranyl (THP)		alcohols (OH in general)	strong bases	dihydropyran and acid	H^+ , H_2O

The THP-protected compound above is an intermediate in a synthesis of the insecticide milbemycin as a single enantiomer. It needs to be converted to this alkyne—and now the *other* hydroxyl group will need protecting.



This time, though, TBDMS will not do, because the protecting group needs to withstand the acidic conditions needed to remove the THP protecting group! What is more, the protecting group needs to be able to survive acid conditions in later steps of the synthesis of the insecticide. The answer

up? There is to use a third type of hydroxyl-protecting group, a benzyl ether. Benzyl (Bn) protecting groups are put on using strong base (usually sodium hydride) plus benzyl bromide, and are stable to both strong bases and acid.



Note the abbreviation for a benzyl ether, ROCH_2Ph , is **ROBn**. Contrast this with benzoyl esters, ROCOPh , which may be abbreviated **ROBz**.

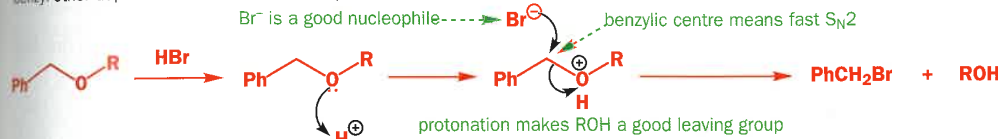
The benzyl ether's Achilles' heel is the aromatic ring and, after reading the first half of this chapter, you should be able to suggest conditions that will take it off again: hydrogenation (hydrogenolysis) over a palladium catalyst.

benzyl ether deprotection: catalytic hydrogenation



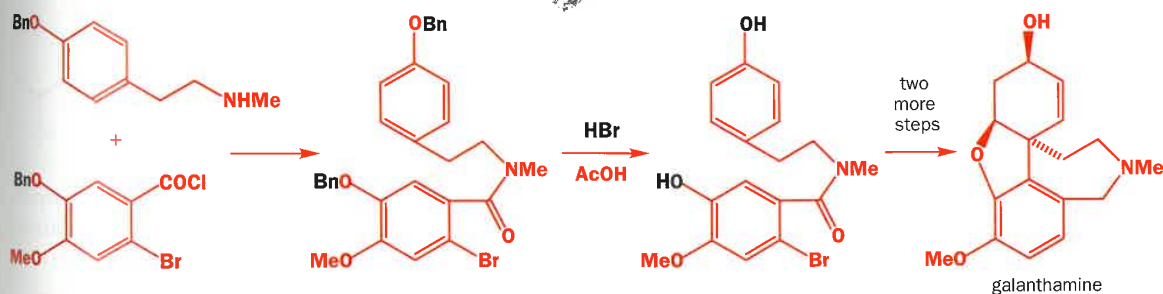
Benzyl ethers can sometimes be removed by acid, if the acid has a nucleophilic conjugate base. HBr, for example, will remove a benzyl ether because Br^- is a good enough nucleophile to displace ROH, though only at the reactive, benzylic centre.

benzyl ether deprotection: acid with nucleophilic counterion



HBr in acetic acid (just the solvent) is used to remove the benzyl ether protecting groups in this example, which forms part of a synthesis of the alkaloid galanthamine.

Alkaloids appear in Chapter 51.



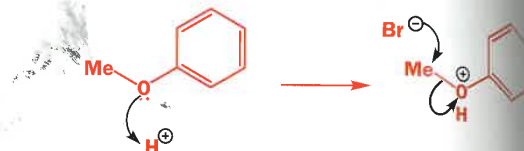
Protecting group	Structure	Protects	From	Protection	Deprotection
benzyl ether (OBn)		alcohols (OH in general)	almost everything	NaH, BnBr	H_2 , Pd/C, or HBr
methyl ether (ArOMe)		phenols (ArOH)	bases	NaH, MeI, or $(\text{MeO})_2\text{SO}_2$	BBr_3 , HBr, HI, Me_3SiI

We said earlier that simple methyl ethers are inappropriate as protecting groups for OH because they are too hard to take off again. That is usually true, but not if the OH is phenolic—ArOH is an

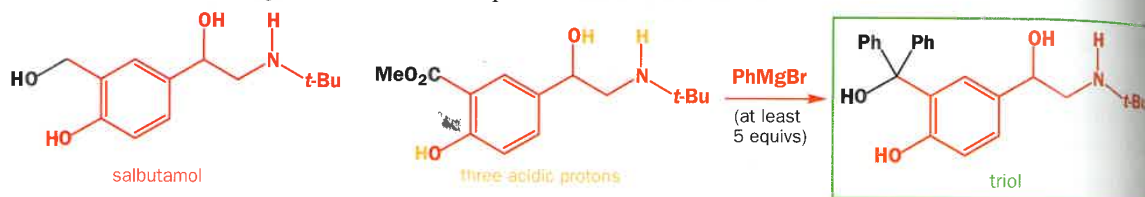
► Alternatives to HBr include BBr_3 , usually the favoured reagent, HI, and Me_3SiI . You met the reaction of phenyl ethers with BBr_3 in Chapter 17.

even better leaving group than ROH, so HBr will take off methyl groups from aryl methyl ethers. You will see an example in Chapter 25.

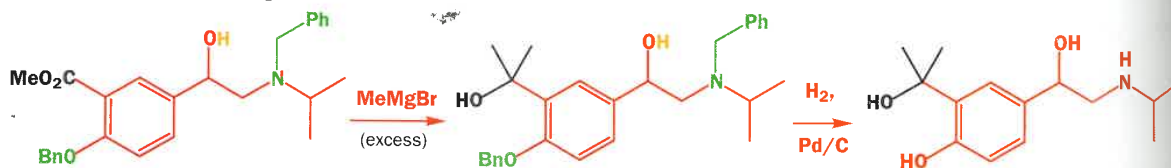
deprotection of aryl methyl ethers



Protecting groups may be useful, but they are also wasteful—both of time, because there are two extra steps to do (putting the group on and taking it off), and of material, because these steps may not go in 100% yield. Here's one way to avoid using them. During the development of the best-selling anti-asthma drug salbutamol, the triol boxed in green was needed. With large quantities of salbutamol already available, it seemed most straightforward to make the triol by adding phenylmagnesium bromide to an ester available from salbutamol. Unfortunately, the ester also contains three acidic protons, making it look as though the hydroxyl and amine groups all need protecting. But, in fact, it was possible to do the reaction just by adding a large excess of Grignard reagent enough to remove the acidic protons and to add to the ester.



This strategy is easy to try, and, providing the Grignard reagent isn't valuable (you can buy PhMgBr in bottles), is much more economical than putting on protecting groups and taking them off again. But it doesn't always work—there is no way of telling whether it will until you try the reaction in the lab. In this closely related reaction, for example, the same chemists found that they needed to protect both the phenolic hydroxyl group (but not the other, normal alcohol OH!) as a benzyl ether and the amine NH as a benzyl amine. Both protecting groups come off in one hydrogenation step.



■ This is the last appearance of the table of protecting groups in this chapter but it is extended in Chapter 25.

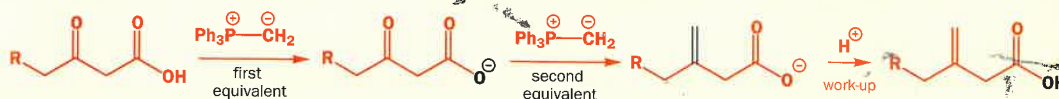
Benzyl groups are one way of protecting secondary amines against strong bases that might deprotonate them. But it is the nucleophilicity of amines that usually poses problems of chemoselectivity, rather than the acidity of their NH groups, and we come back to ways of protecting them from electrophiles when we deal with the synthesis of peptides in Chapter 25.

Bergamotene

An acidic proton posed a potential problem during E.J. Corey's synthesis of bergamotene (a component of the fragrance of Earl Grey tea). You met the Wittig reaction in Chapter 14, and phosphonium ylids are another type of basic,

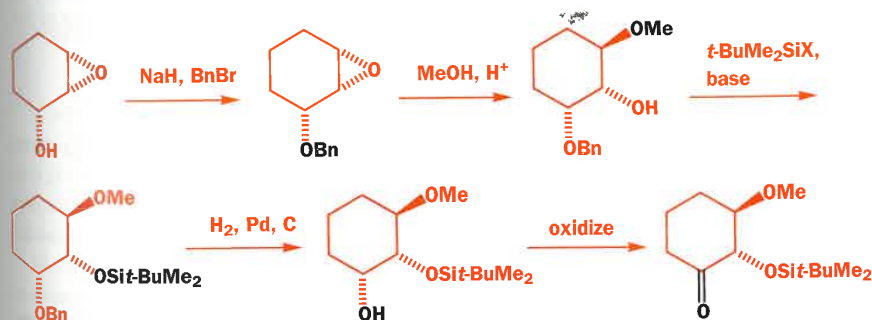
nucleophilic reagent that -OH groups often need protecting against. But, in this synthesis, a successful Wittig reaction was carried out even in the presence of a carboxylic acid, again by using an excess of the phosphonium ylid. We talk about

carboxylic acid protection in the next chapter. In fact the carboxylate anion is itself a kind of protecting group as it discourages the rather basic Wittig reagent from removing a proton to form an enolate.



Protecting group	Structure	Protects	From	Protection	Deprotection
acetal (dioxolane)		ketones, aldehydes	nucleophiles, bases		water, H ⁺ cat.
trialkylsilyl (R ₃ Si-, e.g. TBDMS)		alcohols (OH in general)	nucleophiles, C or N bases	R ₃ SiCl, base	H ⁺ , H ₂ O, or F ⁻
tetrahydropyranyl (THP)		alcohols (OH in general)	strong bases	 dihydro- pyran and acid	H ⁺ , H ₂ O
benzyl ether (OBn)		alcohols (OH in general)	almost everything	NaH, BnBr	H ₂ , Pd/C, or HBr
methyl ether (ArOMe)		phenols (ArOH)	bases	NaH, MeI, or (MeO) ₂ SO ₂	BBr ₃ , HBr, HI, Me ₃ SiI
benzyl amine (NBn)		amines	strong bases	BnBr, K ₂ CO ₃	H ₂ , Pd

We have dealt with protecting groups for C=O, OH, and NH that resist nucleophiles, acids, and base. Sometimes functional groups need protecting against oxidation, and we finish our introduction to protecting groups with an example. During a synthesis of the bacterial product rapamycin, an epoxy alcohol needed converting to a ketone through a sequence that involves selective oxidation of only one of two hydroxyl groups. The group to be oxidized is there in the starting material, so it can be protected straight away. The protecting group (Bn) needs to be acid-stable, because the next step is to open the epoxide with methanol, revealing the second hydroxyl group. This then needs protecting—TBDMS was chosen, so as to be stable to hydrogenolysis, which deprotects the hydroxyl that we want to oxidize. Finally, oxidation gives the ketone.



In this chapter we have talked about most of the steps in this sequence, except the epoxide-opening reaction (for which read Chapters 17 and 18) and the oxidation step. Which reagent would a chemist choose to oxidize the alcohol to the ketone, and why? We shall now move on to look at oxidizing agents in detail.

Oxidizing agents

We dealt in detail earlier in the chapter with reducing agents and their characteristic chemoselectivities. Oxidizing agents are equally important, and in the chapter on electrophilic addition to alkenes we told you about peracids as oxidizing agents for C=C double bonds—they give epoxides. But

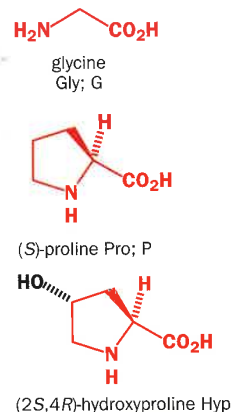
▶ In Chapter 37 you will find out that peracids also react with ketones, but that need not concern us here.

It is necessary in some situations for our blood pressure to rise (when we stand up for instance!) but too much too often is a very bad thing leading to heart attacks and strokes. Captopril is a treatment for high blood pressure called an 'ACE inhibitor' because it works by inhibiting the enzyme. It is a dipeptide mimic, having one natural amino acid and something else. The 'something else' is an SH group replacing the NH_2 group in the natural dipeptide. Captopril binds to the enzyme because it is *like* a natural dipeptide but it inhibits the enzyme because it is *not* a natural dipeptide. In particular, the SH group is a good ligand for Zn(II) . Many people are alive today because of this simple deception practised on an enzyme.

Structural proteins must be tough and flexible

In contrast with the functional enzymes, there are purely structural proteins such as collagen. Collagen is the tough protein of tendons and is present in skin, bone, and teeth. It contains large amounts of glycine (every third amino acid is glycine), proline, and hydroxyproline (again about a third of the amino acids are either Pro or Hyp).

In the enzyme above there were only three glycines and four prolines and no hydroxyproline at all. Hydroxyproline is a specialized amino acid that appears almost nowhere else and, along with proline, it establishes a very strong triply coiled structure for collagen. The glycine is necessary as there is no room in the inside of the triple coil for any larger amino acid. Functionalized amino acids are rare in collagen.



Hydroxyproline and scurvy

Hydroxyproline is a very unusual amino acid. There is no genetic codon for the insertion of Hyp into a growing protein because collagen is not made that way. The collagen molecule is first assembled with Pro where Hyp ends up. Then some proline residues are oxidized to

hydroxyproline. This oxidation requires vitamin C, and without it collagen cannot be formed. This is why vitamin C deficiency causes scurvy—the symptoms of scurvy (teeth falling out, sores, blisters) are caused by the inability to make collagen.

Proteins are enormously diverse in structure and function and we will be looking at a few of their reactions in the next chapter.

Sugars—just energy sources?

Sugars are the building blocks of carbohydrates. They used to be thought of as essential but rather dull molecules whose only functions were the admittedly useful provision of energy and cell wall construction. We have already noted that ribose plays an intimate role in DNA and RNA structure and function. More recently, biochemists have realized that carbohydrates are much more exciting. They are often found in intimate association with proteins and are involved in recognition of one protein by another and in adhesion processes.

That may not sound very exciting, but take two examples. How does a sperm recognize the egg and penetrate its wall? The sperm actually binds to a carbohydrate on the wall of the egg in what was the first event in all of our lives. Then how does a virus get inside a cell? If it fails to do so, it has no life. Viruses depend on host cells to reproduce. Here again, the recognition process involves specific carbohydrates. One of the ways in which AIDS is being tackled with some success is by a combination of the antiviral drugs we met earlier in this chapter with HIV protease inhibitor drugs, which aim to prevent recognition and penetration of cells by HIV.

We now know that many vital activities as diverse as healing, blood clotting, infection, prevention of infection, and fertilization all involve carbohydrates. Mysterious compounds such as 'sialyl Lewis-X', unknown a few years ago, are now known to be vital to our health and happiness. Far from being dull, carbohydrates are exciting molecules and our future depends on them. It is well worthwhile to spend some time exploring their structure and chemistry.

Sugars normally exist in cyclic forms with much stereochemistry

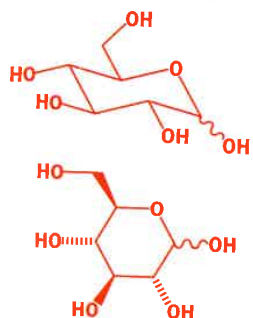
The most important sugar is glucose. It has a saturated six-membered ring containing oxygen and it is best drawn in a chair conformation with nearly all the substituents equatorial. It can also be drawn reasonably as a flat configurational diagram.

We have already met one sugar in this chapter, ribose, because it was part of the structure of nucleic acids. This sugar is a five-membered saturated oxygen heterocycle with many OH groups. Indeed, you can define a sugar as an oxygen heterocycle with every carbon atom bearing an oxygen-based functional group—usually OH, but alternatively C=O.

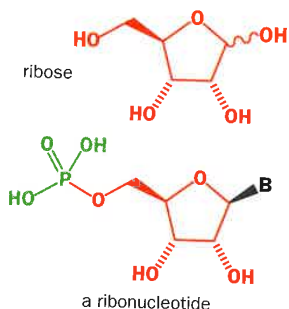
Both our drawings of glucose and ribose show a number of stereogenic centres and one centre undefined—the OH group is marked with a wavy line. This is because one centre in both sugars is a hemiacetal and therefore the molecule is in equilibrium with an open-chain hydroxy-aldehyde. For glucose, the open-chain form is this.

■ Sugars have had walk-on roles in a few other chapters, notably Chapter 16 on stereochemistry. They are discussed on pp. 146, 394, and 1220.

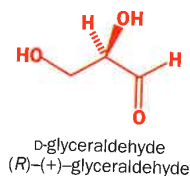
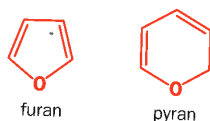
two representations of glucose



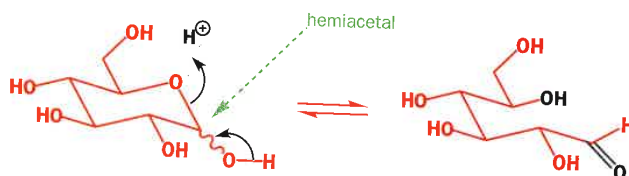
ribose



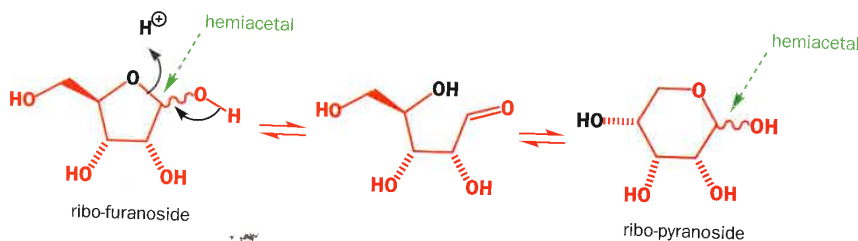
a ribonucleotide



■ Glyceraldehyde was the compound used to define the D and L designators before anyone knew what the real configurations of natural compounds were. See the discussion on p. 389 for more on this.



When the ring closes again, any of the OH groups could cyclize on to the aldehyde but there is no real competition—the six-membered ring is more stable than any of the alternatives (which could have three-, four-, five-, or seven-membered rings—check for yourself). However, with ribose there is a reasonable alternative.

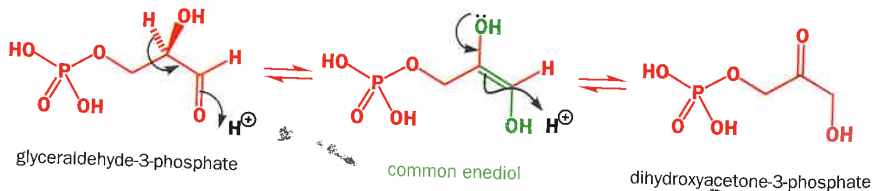


The most important sugars may exist in an open-chain form, as a five-membered oxygen heterocycle (called a furanoside after the aromatic furan) or a six-membered oxygen heterocycle (called a pyranoside after the compound pyran).

From triose to glucose requires doubling the number of carbon atoms

We will return to that in a moment, but let us start from the beginning. The simplest possible sugar is glyceraldehyde, a three-carbon sugar that cannot form a cyclic hemiacetal.

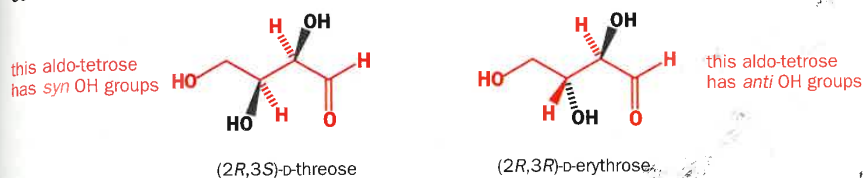
Glyceraldehyde is present in cells as its phosphate which is in equilibrium with dihydroxyacetone phosphate. This looks like a complicated rearrangement but it is actually very simple—the two compounds have a common enediol through which they interconvert.



Glyceraldehyde is an aldehyde sugar or aldose and dihydroxyacetone is a keto-sugar or ketose. That ending '-ose' just refers to a sugar. These two molecules combine to form the six-carbon sugar,

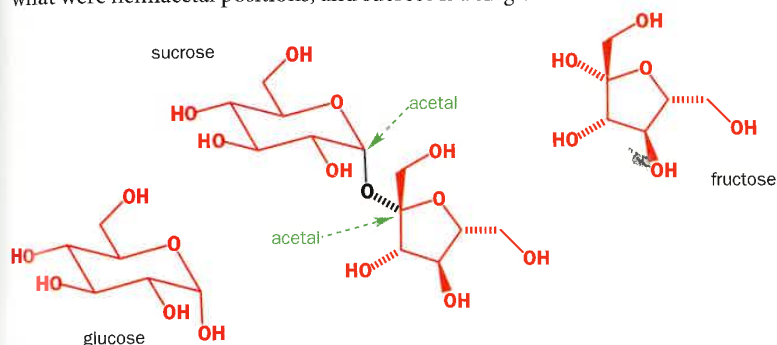
fructose, in living things and this reaction is a key step in the synthesis of organic compounds from CO_2 in plants.

When we come to the four-carbon sugars, or tetroses, two are important. They are diastereoisomers called erythrose and threose. You can see from this series that each aldose has $n - 2$ stereogenic centres in its carbon chain where n is the total number of carbon atoms in that chain.



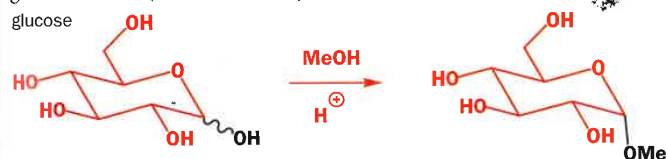
These sugars too have given their names to a stereochemical designation—'erythro-' and 'threo-' are used to describe diastereoisomers that resemble these two sugars. We do not use these rather ambiguous terms in this book, preferring more precise or vivid terms such as *R,R* or *anti* as appropriate.

We shall take a longer look at the stereochemistry and reactions of glucose and the important keto-hexose, fructose. These two are often found together in cells and are combined in the same molecule as **sucrose**—ordinary sugar. In this molecule, glucose appears as a pyranose (six-membered ring) and fructose as a furanose (five-membered ring). They are joined through an acetal at what were hemiacetal positions, and sucrose is a single diastereoisomer.

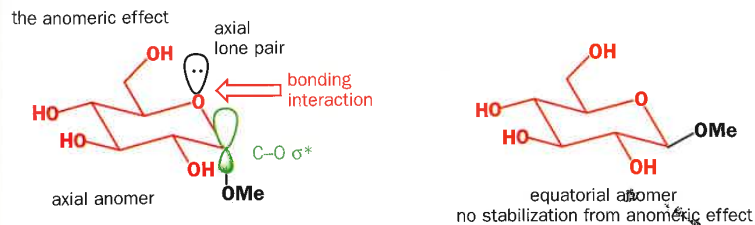


Sugars can be fixed in one shape by acetal formation

This is the simplest way to fix glucose in the pyranose form—any alcohol, methanol, for example, gives an acetal and, remarkably, the acetal has an *axial* OR group.



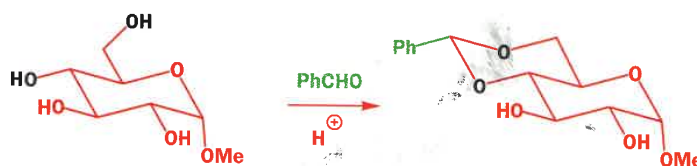
Acetal formation is under thermodynamic control (Chapter 14) so the axial compound must be the more stable. This is because of the **anomeric effect**—so called because this C atom is called the anomeric position and the acetal diastereoisomers are called anomers. The effect is a bonding interaction between the axial lone pair on the oxygen atom in the ring and the σ^* orbital of the OMe group.



The formation of acetals allows a remarkable degree of control over the chemistry of sugars. Apart from the simple glucoside acetal we have just seen, there are three important acetals worth understanding because of the way in which they illustrate stereoelectronic effects—the interplay of

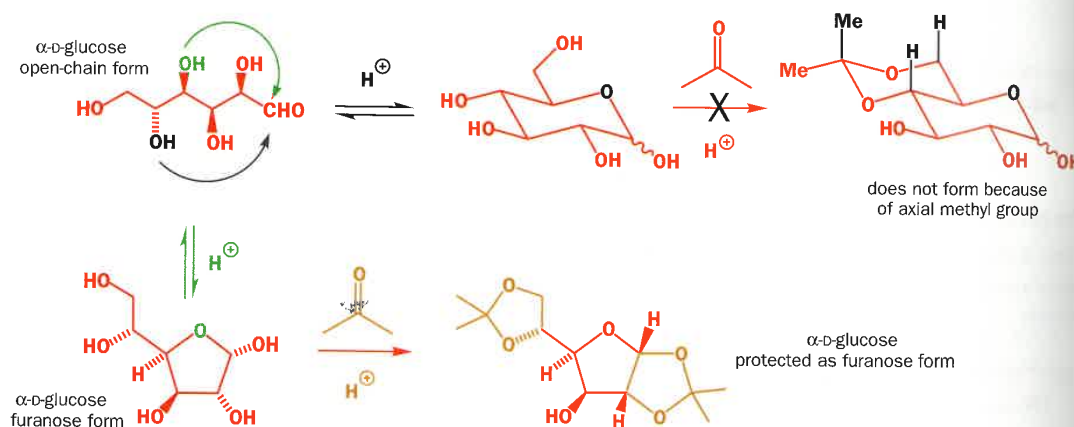
The anomeric effect was discussed in Chapter 42, and you should check that you can still write down the mechanism of acetal formation you learned in Chapter 14.

stereochemistry and mechanism. If we make an acetal from methyl glucoside, we get a single compound as a single stereoisomer.



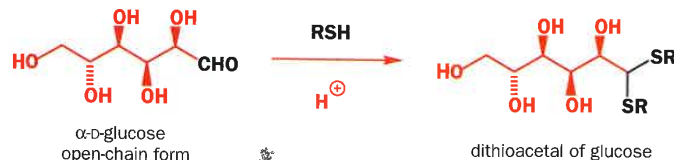
The new acetal could have been formed between any of the adjacent OH groups in the starting material but it chose the only pair (the black OH groups) to give a six-membered ring. The stereochemistry of glucose is such that the new six-membered ring is *trans*-fused on the old so that a beautifully stable all-chair bicyclic structure results, with the phenyl group in an equatorial position in the new chair acetal ring. It does not matter which OH group adds to benzaldehyde first because acetal formation is under thermodynamic control and this product is the most stable possible acetal.

Acetals formed from sugars and acetone have a quite different selectivity. For a start, cyclic acetals of acetone prefer to be five- rather than six-membered rings. In a six-membered ring, one of the acetone's methyl groups would have to be axial, so the five-membered ring is preferred. A 5/5 or 5/6 ring fusion is more stable if it is *cis*, and so acetone acetals ('acetonides') form preferentially from *cis* 1,2-diols. Glucose has no neighbouring *cis* hydroxyls in the pyranose form, but in the furanose form it can have two pairs. Formation of an acetal with acetone fixes glucose in the furanose form. This is all summarized in the scheme below.

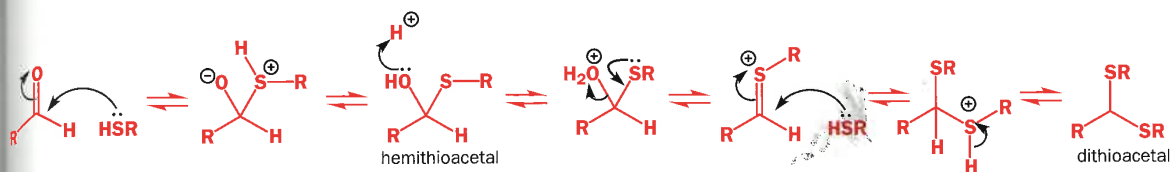


The open-chain form of glucose is in equilibrium with both pyranose and furanose forms by hemiacetal formation with the black and green OH groups, respectively. Normally, the pyranose form is preferred, but the furanose form can form a double acetal with acetone, one acetal having *cis*-fused 5/5 rings and the other being on the side chain. This is the product.

If we want to fix glucose in the open-chain form, we must make an 'acetal' of quite a different kind using a thiol (RSH) instead of an alcohol, an aldehyde, or a ketone.



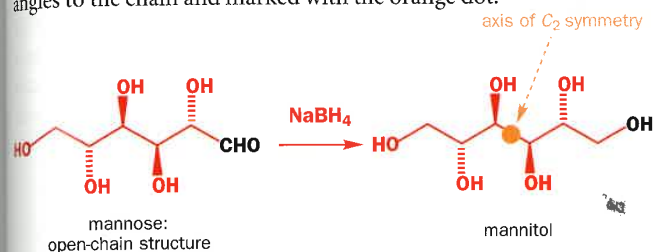
The thiol combines with the aldehyde group of the open-chain form to give a stable dithioacetal. The dithioacetal is evidently more stable than the alternative hemiacetals or monothioacetals that could be formed from the pyranose or furanose forms.



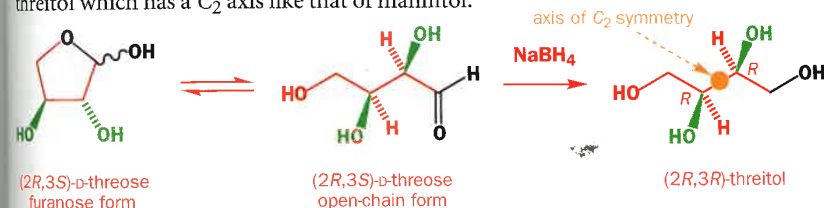
Sugar alcohols are important in food chemistry

Another reaction of the open-chain form of sugars is reduction of the aldehyde group. This leads to a series of polyols having an OH group on each carbon atom. We will use **mannose** as an example. Mannose is a diastereoisomer of glucose having one axial OH group (marked in black) and, like glucose, is in equilibrium with the open-chain form.

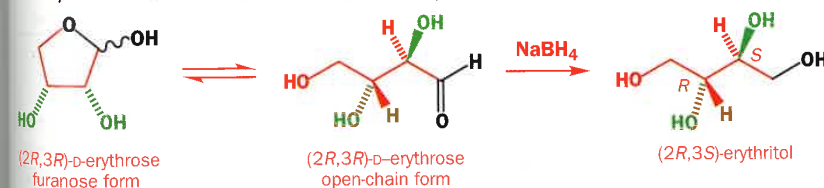
If we redraw the open-chain form in a more realistic way, and then reduce it with NaBH_4 , the product is mannitol whose symmetry is interesting. It has C_2 symmetry with the C_2 axis at right angles to the chain and marked with the orange dot.



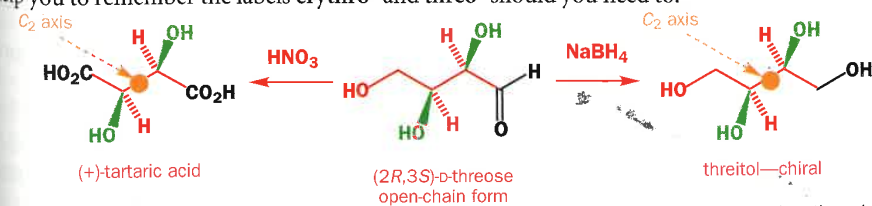
The simplification of stereochemistry results because the two ends of the sugar both now have CH_2OH groups so that the possibility of C_2 and planar symmetry arises. If we look at the two four-carbon sugars we can establish some important stereochemical correlations. Threose is reduced to threitol which has a C_2 axis like that of mannitol.



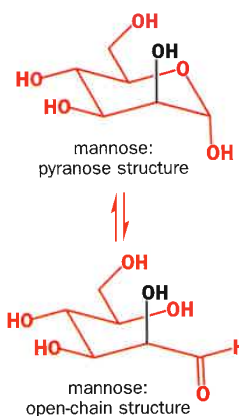
Erythrose on the other hand reduces to erythritol, which is not chiral.



The important correlation is that threose is reduced or oxidized to chiral compounds—the oxidation product is tartaric acid—while erythrose is reduced or oxidized to *meso* compounds. This may help you to remember the labels **erythro-** and **threo-** should you need to.

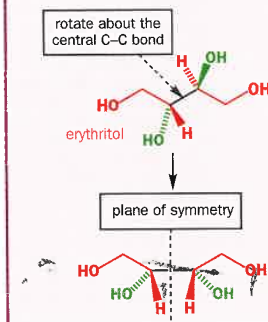


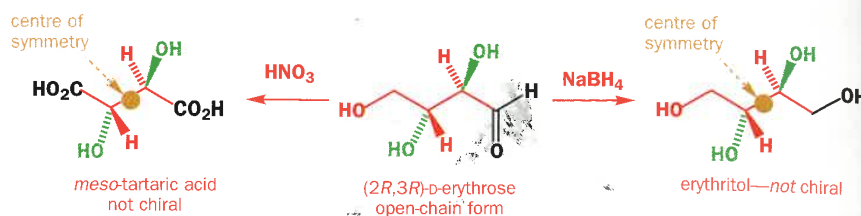
(continued overleaf)



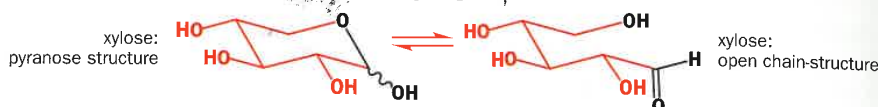
C_2 means that the axis of symmetry is twofold: rotating 180° gives the same structure.

This may not be obvious in the normal drawing (which has a centre of symmetry), but rotation around the central C—C bond clearly shows the plane of symmetry. Neither plane nor centre of symmetry may be present in a chiral molecule, but a C_2 axis is allowed (Chapter 16).

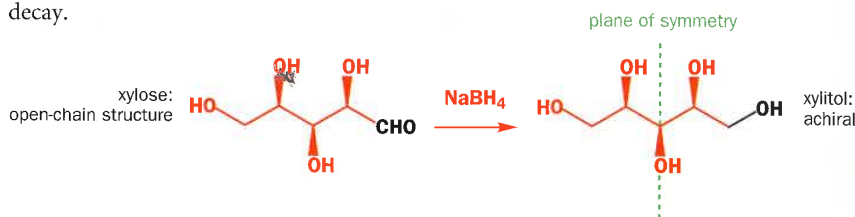




In the pentoses and hexoses there are again sugars that are reduced to *meso* alcohols and some that are reduced to C₂ symmetric alcohols. The C₅ sugar xylose has the same stereochemistry as glucose from C2 to C4 but lacks the CH₂OH group at C6.



Xylose is reduced to the *meso* alcohol xylitol. This alcohol is more or less as sweet as sugar and, as xylose (which is not sweet) can be extracted in large quantities from waste products such as sawdust or corncobs, xylitol is used as a sweetener in foods. There is an advantage in this. Though we can digest xylitol (so it is fattening), the bacteria on teeth cannot so that xylitol does not cause tooth decay.



By careful manipulation of protecting groups such as acetals and reactions such as reduction and oxidation, it is possible to transform sugars into many different organic compounds retaining the natural optical activity of the sugars themselves. As some sugars are also very cheap, they are ideal starting points for the synthesis of other compounds and are widely used in this way (Chapter 45). Sucrose and glucose are very cheap indeed—probably the cheapest optically active compounds available. Here are the relative (to glucose = 1) prices of some other cheap sugars.

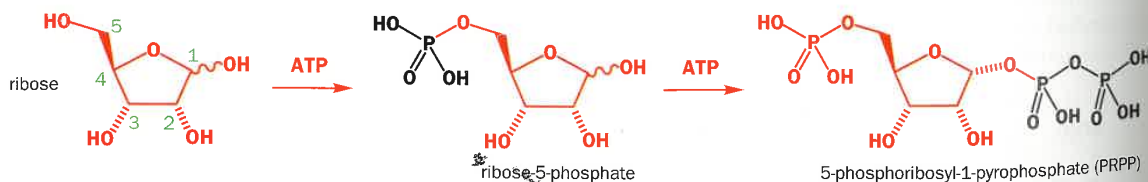
Sugar	Price ^a	Sugar	Price ^a
glucose	1	sorbitol	2
mannose	75	mannitol	4
galactose	8	dulcitol ^b	70
xylose	20	xylitol	15
ribose	100	sucrose	1

^a Prices relative to glucose = 1.

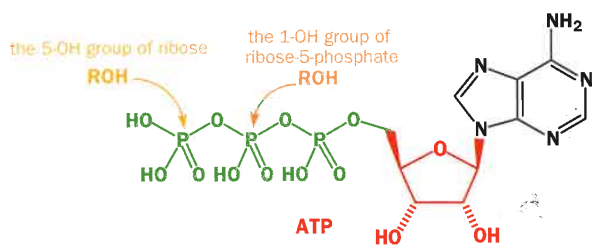
^b Dulcitol is the reduction product of galactose.

Chemistry of ribose—from sugars to nucleotides

We have said little about selective reactions of pentoses so we shall turn now to the synthesis of nucleotides such as AMP. In nature, ribose is phosphorylated on the primary alcohol to give ribose-5-phosphate. This is, of course, an enzyme-catalysed reaction but it shows straightforward chemoselectivity such as we should expect from a chemical reaction.

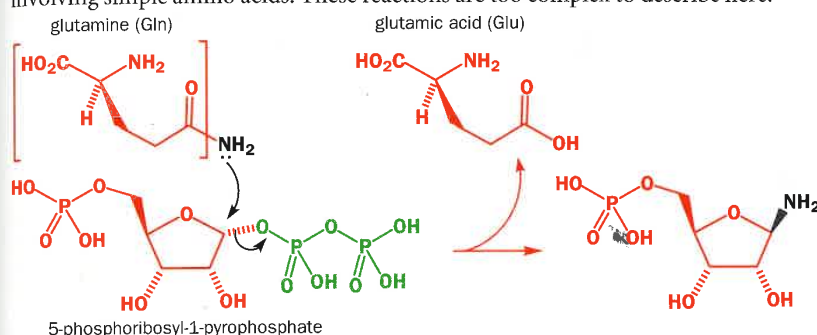


The second step is a pyrophosphorylation at the anomeric position to give PRPP. Only one diastereoisomer is produced so presumably the two anomers interconvert rapidly and only the one isomer reacts under control by the enzyme. This selectivity would be very difficult to achieve chemically.

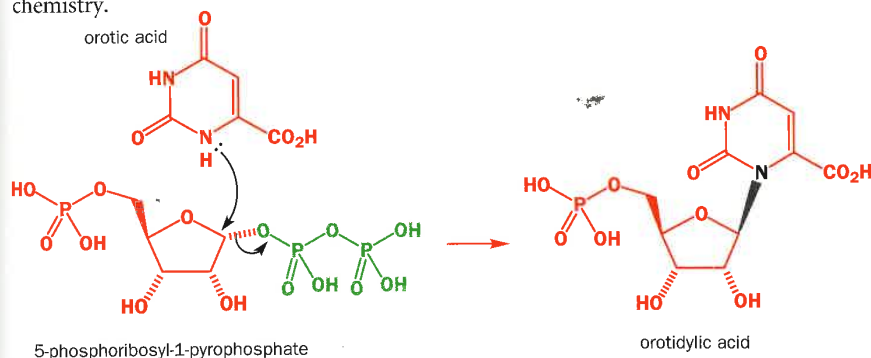


You will notice that these two reactions illustrate the flexibility with which ATP can activate biological molecules. In the first reaction, the nucleophilic OH group of ribose attacks the terminal phosphate group, but in the second the OH group must attack the middle phosphate residue. This would be impossible to control chemically.

Now the stage is set for an S_N2 reaction. The nucleophile is actually the amide group of glutamine but the amide is hydrolysed by the same enzyme in the same reaction and the result is as if a molecule of ammonia had done an S_N2 reaction displacing the pyrophosphate from the anomeric position. An NH_2 group is introduced, which is then built into the purine ring-system in a series of reactions involving simple amino acids. These reactions are too complex to describe here.



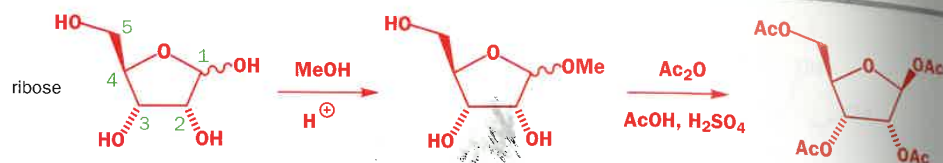
By contrast, if a pyrimidine is to be made, Nature assembles a general pyrimidine structure first and adds it in one step to the PRPP molecule, again in an S_N2 reaction using a nitrogen nucleophile. This general nucleotide, orotidylic acid, can be converted into the other pyrimidine nucleotides by simple chemistry.



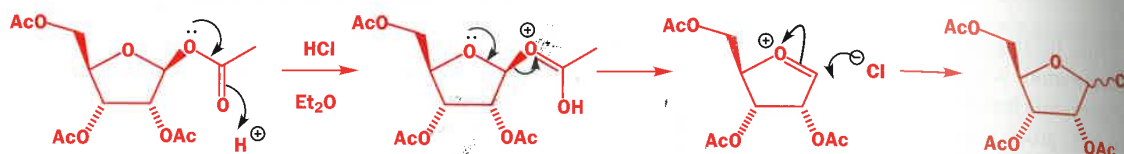
The chemical version—protection all the way

In a chemical synthesis (work that led to Alexander (Lord) Todd's Nobel prize) there are rather different problems. We cannot achieve the remarkable selectivity between the different OH groups achieved in Nature so we have to protect any OH group that is not supposed to react. We also prefer to add pre-formed purines and pyrimidines to a general electrophile derived from ribose. The first step is to form acetate esters from all the OH groups. Since ribose is rather unstable to acetylation conditions, the methyl glycoside (which is formed under very mild conditions) is used. This fixes the sugar in the furanose form. Now the tetraacetate can be made using acetic anhydride in acidic solution. All of the OH groups react by nucleophilic attack on the carbonyl group of the anhydride with retention of configuration except for the anomeric OH, which esterifies by an S_N1 mechanism. This, of course, epimerizes the anomeric centre but the crystalline diastereoisomer shown can be isolated easily.

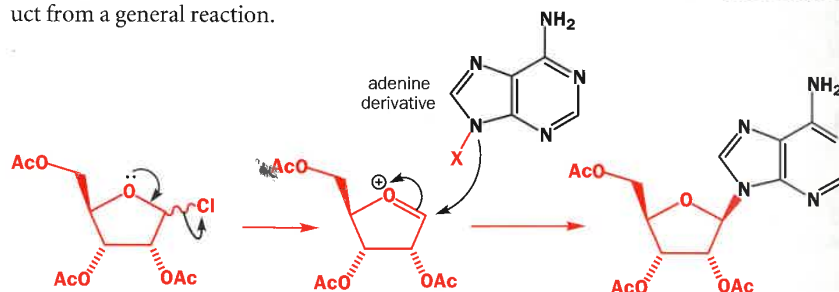
Alexander Todd (1907–97), better known as Lord Todd, was a Scot who pioneered the modern interaction between chemistry and biochemistry in his work at Frankfurt, Oxford, Edinburgh, London, CalTech, Manchester, and Cambridge. He won the Nobel prize in 1957 for his work on the synthesis of the most important coenzymes and nucleotides. This was a remarkable achievement because he had to find out how to do phosphate, ribose, and purine chemistry—none of which was known when he started, and none of which was easy as this brief excursion should show.



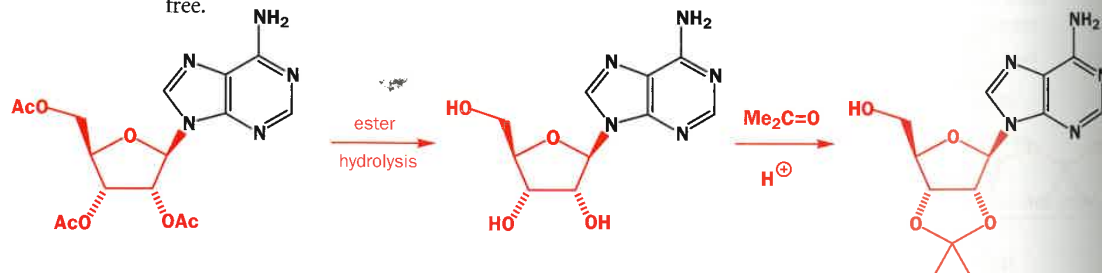
Now the anomeric centre can be activated towards nucleophilic attack by replacement of acetate by chloride. This is again an S_N1 reaction and produces a mixture of chlorides. The other esters are stable to these conditions.



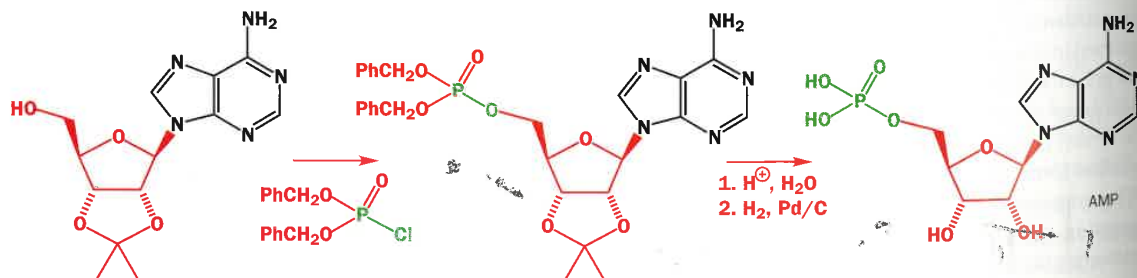
Replacement of the chlorine by the purine or pyrimidine base is sometimes quite tricky and silver or silyl derivatives are often used. Lewis acid catalysis is necessary to help the chloride ion leave in this S_N1 reaction. We shall avoid detailed technical discussion and simply draw the adenosine product from a general reaction.



Now we need to remove the acetates and put a phosphate specifically on the 5-position. The acetates can be removed with retention by ester hydrolysis and we already know how to protect the 2-OH and 3-OH groups. They are *cis* to each other so they will form an acetal with acetone leaving the 5-OH group free.



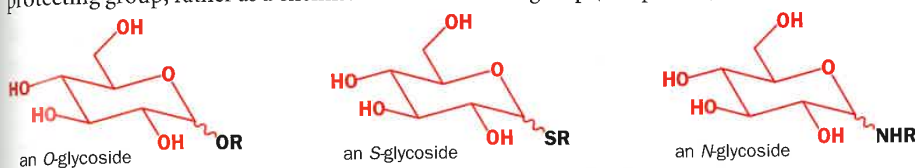
Putting on the phosphate is tricky too and more protection is necessary. This phosphorus compound with one chloride as leaving group and two benzyl esters as protecting groups proved ideal. The benzyl esters can be removed by hydrogenation (Chapter 24) and the acetal by treatment with dilute acid to give AMP.



The chemical synthesis involves a lot more selective manipulation of functional groups, particularly by protection, than is necessary in the biological synthesis. However, this synthesis paved the way to the simple syntheses of nucleotides and polynucleotides carried out routinely nowadays. The usual method is to build short runs of nucleotides and then let the enzymes copy them—a real partnership between biology and chemistry.

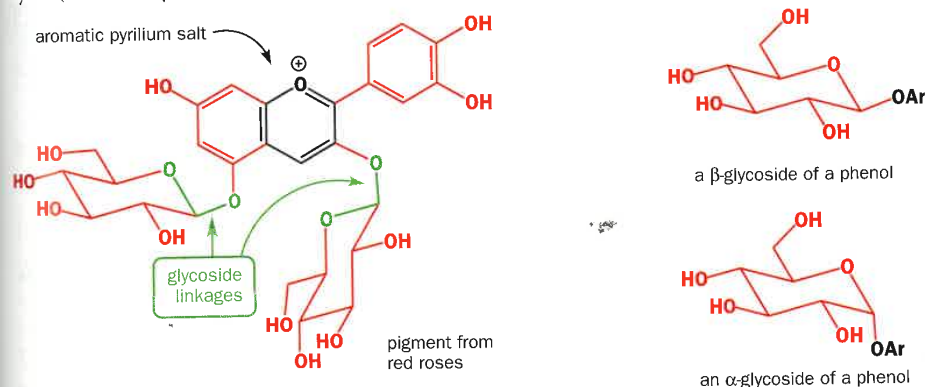
Glycosides are everywhere in nature

Many alcohols, thiols, and amines occur in nature as **glycosides**, that is as O-, S-, or N-acetals at the anomeric position of glucose. The purpose of attaching these compounds to glucose is often to improve solubility or transport across membranes—to expel a toxin from the cell, for example. Sometimes glucose is attached in order to stabilize the compound so that glucose appears as Nature's protecting group, rather as a chemist would use a THP group (Chapter 24).



O-Glycosides occur in immense variety with glucose and other sugars being joined to the OH groups of alcohols and phenols to form acetals. The stereochemistry of these compounds is usually described by the Greek letters α and β . If the OR bond is down, we have an α -glycoside; if up, a β -glycoside.

An attractive example is the pigment of red roses, which is an interesting aromatic oxygen heterocycle (an anthocyanidin). Two of the phenolic OH groups are present as β -glycosides.



The most important N-glycosides are, of course, the nucleotides and we have already described them in some detail.

We saw an example in Chapter 6 where acetone cyanohydrin is found in the cassava plant as a glucoside and suitable precautions must be taken when eating cassava to avoid poisoning by HCN.

It is easy to remember which is which. People who devise nomenclature are maliciously foolish and, just as *E* means *trans* and *Z* means *cis* (each letter has the shape of the *wrong* isomer), so α means *below* and β means *above*—each word begins with the *wrong* letter.

Protect yourself from cancer with green vegetables: S-glycosides

We will take an important series of S-glycosides for further chemical discussion in this chapter. It is clear that there are special benefits to health in eating broccoli and brussels sprouts because of their potent sulfur-containing anticancer compounds. These compounds are unstable isothiocyanates and are not, in fact, present in the plant but are released on damage by, for example, cutting or cooking when a glycosidase (an enzyme which hydrolyses glycosides) releases the sulfur compound from its glucose protection. A simple example is sinigrin.

When a glycosidase enzyme cleaves an O-glycoside, we should expect a simple general acid-catalysed first step followed by fast addition of water to the intermediate oxonium ion, essentially the same mechanism as is shown by the chemical reaction (Chapter 13).

