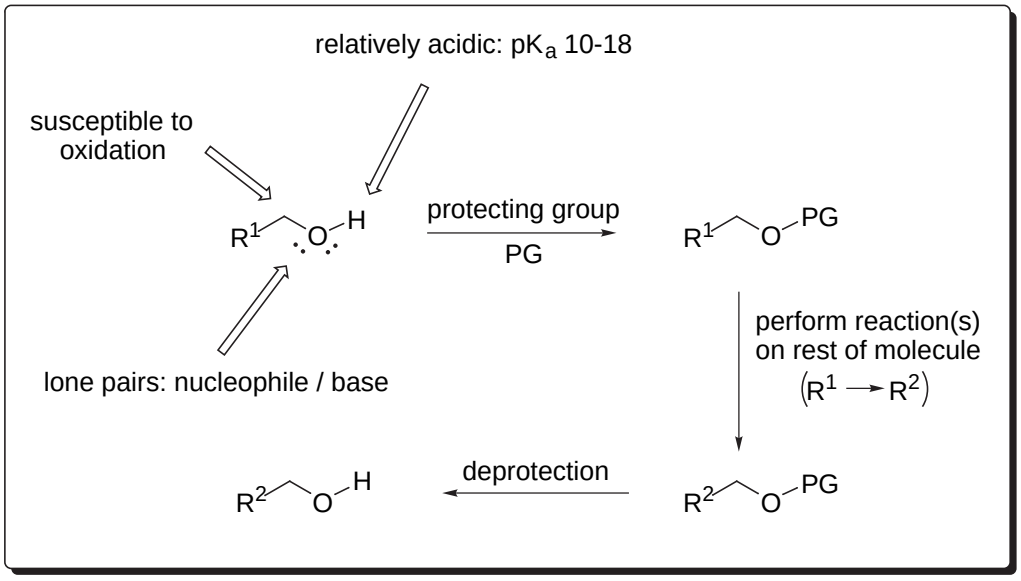
VI Protecting Groups and Orthogonal Protection Strategies

Many functional groups will interfere in reactions being carried out elsewhere in the molecule. This affects (usually detrimentally) yields and levels of regio-, chemo- and stereoselectivity. Alcohols provide a good example of such functionality (other functional groups which can be a problem include amines and carbonyl groups). However, we can minimise problems by *protecting* the alcohol. This protection strategy removes the acidic proton on the alcohol, and also reduces the nucleophilicity and basicity of the oxygen atom by steric hindrance and / or electronic effects.



VI.A Desired Properties of Protecting Groups.

- Protecting and deprotecting the alcohol introduces at least two further steps into the synthetic sequence. Therefore, these two steps must be high yielding and simple to carry out, preferably with cheap and readily available reagents.

- The protecting group should introduce minimal additional complexities into the molecule (no extra stereogenic centres) to ensure that characterisation also remains simple.

- By-products generated in the protection and deprotection steps should not affect other parts of the molecule and also be readily removed in the work-up and purification steps.

- Appropriate stability of the protecting group is crucial. This will be governed not only by the number of steps through which the protecting group has to survive, but also by the reaction conditions, work-up procedures and purification protocols required for these intermediate steps.

Selectivity

A protecting group should be introduced and removed chemo-, regio- and sometimes stereoselectively. NOT ALWAYS EASY!

Orthogonality

Many molecules contain more than one alcohol functional group (*e.g.* carbohydrates). It is often necessary to manipulate only one (or some) of these groups at a time. This is only possible by choosing a variety of protecting groups, which can be manipulated using different reaction conditions. The development of such *orthogonal protecting group strategies* makes it possible to remove one set of protecting groups, in any order, using reagents and conditions that do not affect the protecting groups in other sets.

An efficient protecting group strategy is critical for achieving the synthesis of large, complex molecules possessing a diverse range of reactive functionality. One area where protecting groups play a vital role is in the chemical synthesis of oligosaccharides. An example will illustrate the problems and outline potential solutions. We will consider the synthesis of a simple trisaccharide.

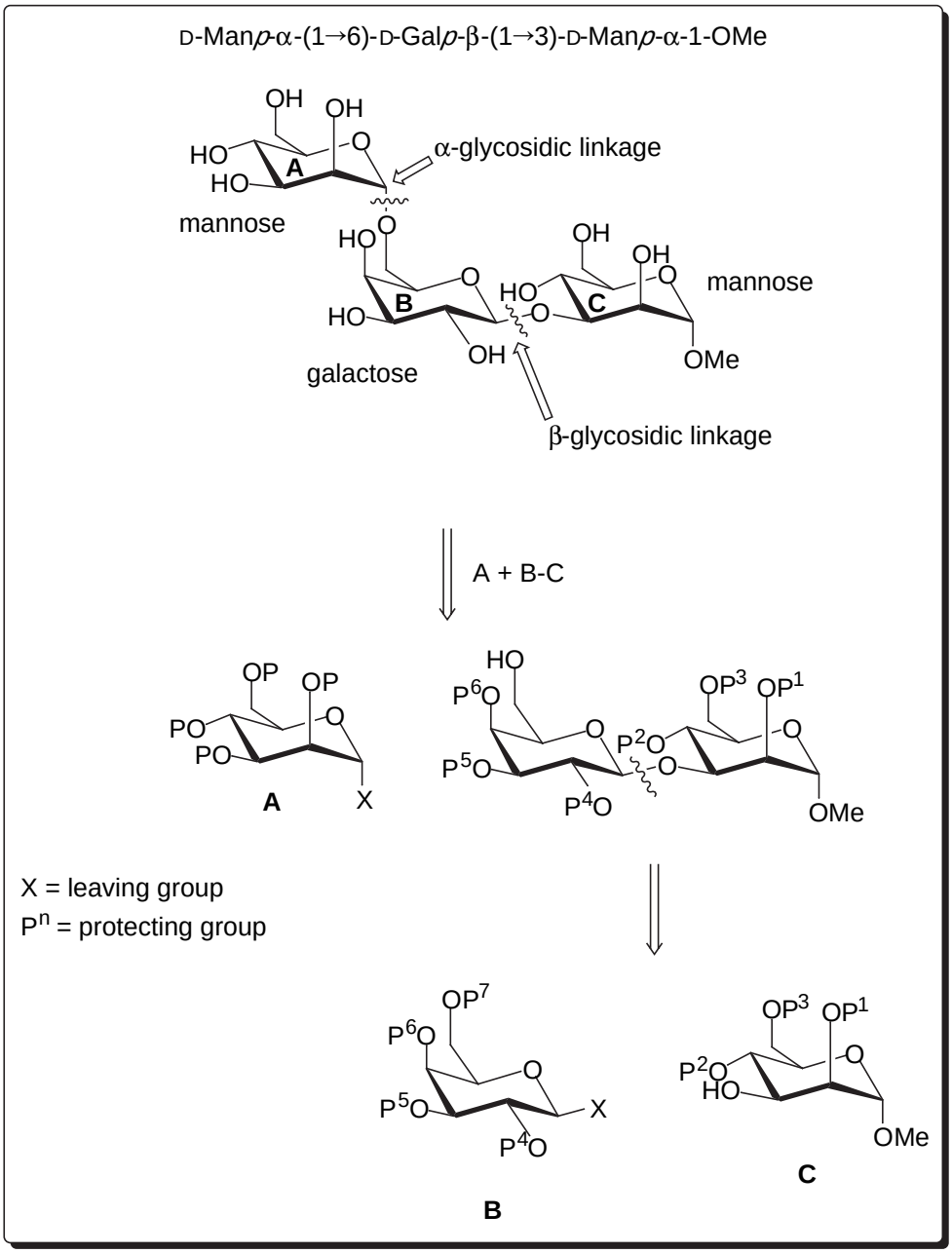
Recommended Reading

1. P. J. Kociénski, *Protecting Groups*, Thieme, Stuttgart, 1994.

2. T. W. Greene, P. G. M. Wuts, *Protective Groups in Organic Synthesis*, 2nd Ed., Wiley-Interscience, New York, 1991.

VI.B Chemical Synthesis of a Trisaccharide

Retrosynthesis:



By disconnecting at the glycosidic linkage (strategic and in this case the only sensible disconnection), the problem has been greatly simplified. We just need to prepare three monosaccharide building blocks, two derived from mannose and a third from galactose.

Consider coupling B+C:

Stereoselectivity - we require a β-glycosidic linkage

Observation - an ester protecting group at C(2) favours the formation of 1,2-*trans*-glycosides.

Can you provide a mechanistic rationale for this observation?

So an ester protecting group - an acetate will do - for P^4 in **B** will provide the desired stereoselectivity in the glycosylation.

Chemoselectivity - we want glycosylation to occur between the anomeric centre of **B** (C(1)) and the C(3)OH of the mannose derivative **C**.

We need to prepare **C** in which only C(3)OH is free and the remaining alcohols on C(2), C(4) and C(6) are protected so they cannot behave as nucleophiles.

Similarly in **B** all the alcohol groups must be protected (to avoid potential self condensation reactions) BUT, thinking ahead, after the **B**+**C** glycosylation, we need to remove the protecting group on C(6) of **B** *selectively* to allow a subsequent glycosylation between **B–C** with **A**.

We can distinguish two types of protecting groups:

1) **permanent** - this protecting group is used for functional groups which require no manipulation and just need 'masking' to prevent their interfering in intermediate steps. These protecting groups need to survive many steps (early introduction, late removal).

2) **temporary** - this protecting group, as its name suggests, is much more transient - we need to be able to instal and remove it easily and selectively WITHOUT affecting more permanent protecting groups. (*Orthogonal* Protecting Group strategy)

What types of protecting groups do we need for each alcohol group in the monosaccharides?

Below is a list of some of the more commonly encountered protecting groups used to protect alcohols. This list is by no means exhaustive but will suffice for solving our problem in the synthesis of the trisaccharide.

protecting group (PG)	method of protection	method of deprotection	comments
benzyl ether	NaH, BnBr, DMF (basic conditions) *or* $BnOC(=NH)CCl_3$, TfOH, hexane (v mildy acidic conditions)	hydrogenolysis (H_2/Pd/C)	a good permanent PG
silyl ether	R_3SiCl, imidazole, DMF (mild)	fluoride source or acid	protection of primary alcohols is generally more rapid than secondary alcohols
esters	anhydride or acid chloride, Et_3N, DMAP, CH_2Cl_2	K_2CO_3 / MeOH (mildly basic) *or* DIBALH (reductive)	useful for neighbouring group participation in glycosylations (acid stable)
benzylidene acetal	PhCHO, cat. H^+	hydrogenolysis (H_2/Pd/C) or acid	good method for protecting 1,3 diols
isopropylidene acetal	2,2-dimethoxypropane cat. H^+	acid	good method for protecting 1,2-*syn* diols

Let's consider each monosaccharide in turn

*Building block **C***

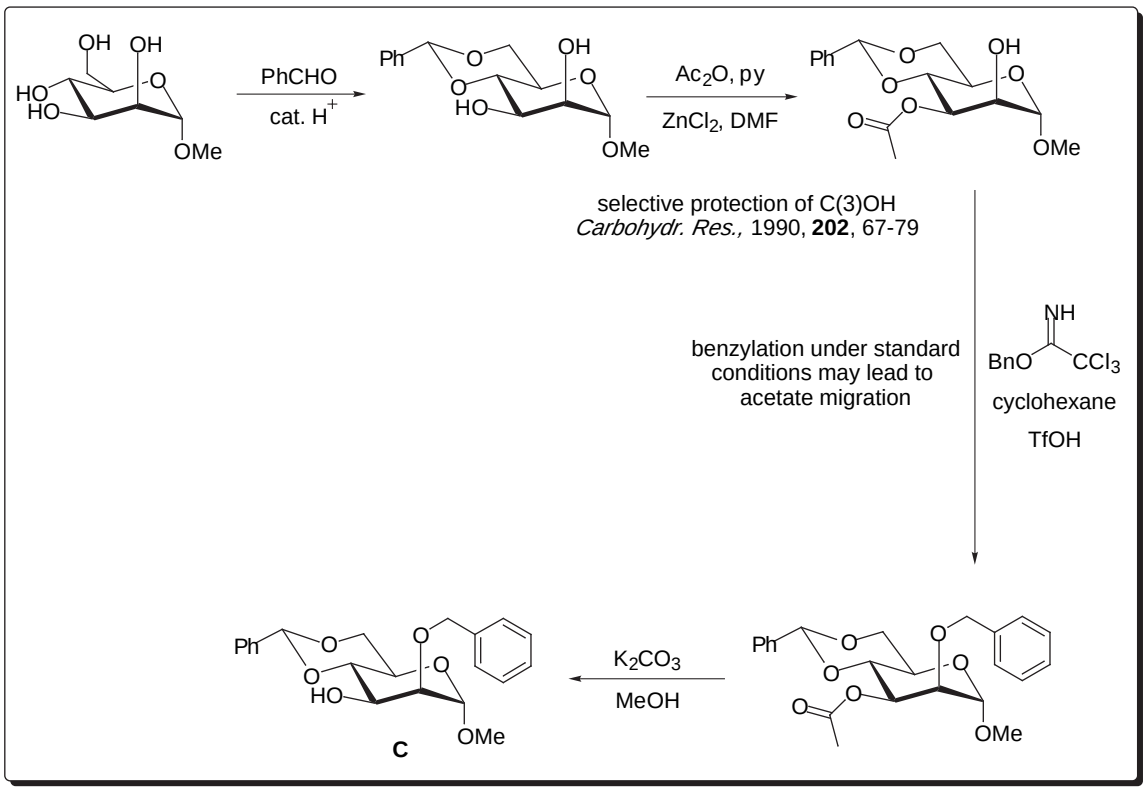
We require permanent protecting groups for C(2), C(4) and C(6).

Notes:

- A benzylidene PG could be good for protecting C(4) and C(6). *Consider the structure of the product to rationalise why this 1,3-diol is protected selectively under thermodynamic conditions.*
- We then need to differentiate C(2) and C(3). Both are secondary alcohols but one is axial and the other equatorial. Under certain conditions, it is possible to regioselectively acylate the C(3)OH in the presence of C(2)OH (see conditions in Scheme).

- However, we want to protect C(2) and have the C(3)OH free. One possibility is therefore to protect C(3) with an acetate (a temporary PG), instal a permanent PG (*e.g.* Bn) on C(2), and then deprotect C(3). This route is illustrated in the Scheme. Note that standard benzylation conditions (NaH, BnBr in DMF) would most likely lead to at least partial acetate migration from C(3)OH to C(2)OH; thus we need to employ an alternative benzylation method which is non-basic to suppress this undesirable pathway (see Scheme). (NOTE: another possibility would be to prepare the 2,3-4,6-dibenzylidene acetal of the methyl mannoside and then regioselectively open the more reactive 2,3-benzylidene acetal in a reductive fashion. This would allow us to instal the benzyl group directly on to C(2)OH.)

We now have a potential strategy for building block **C**.



*Building Block **B***

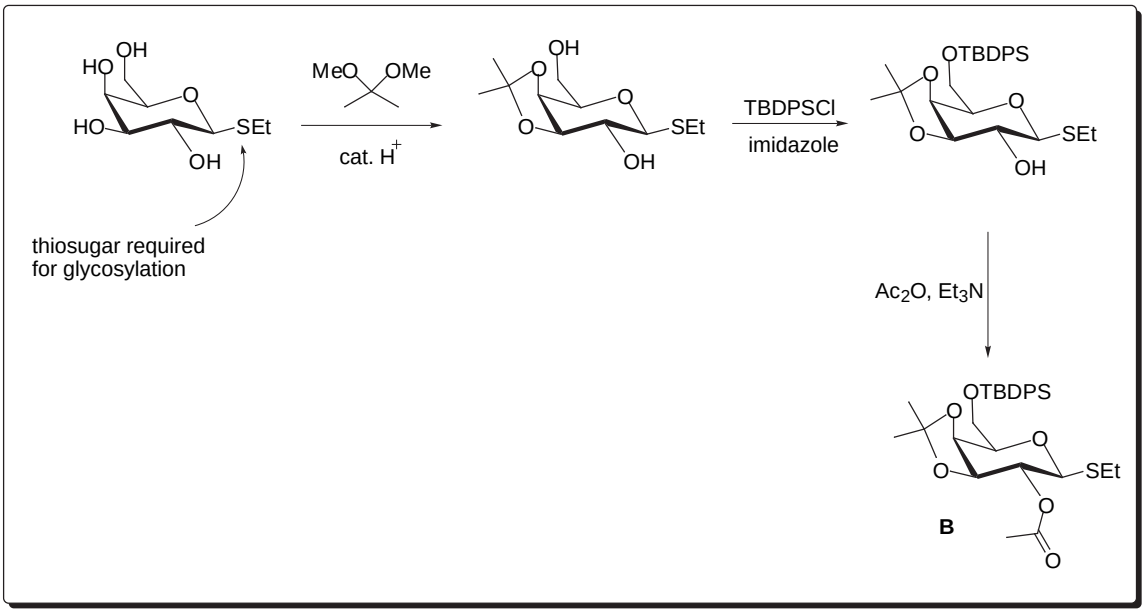
Requirements:

i) acetate PG on C(2) (to control the stereoselectivity in the glycosylation reaction)
ii) a temporary protecting group on C(6) (for the later coupling of **B**+**C** with **A**)
iii) permanent PGs on C(3) and C(4)

Notes:

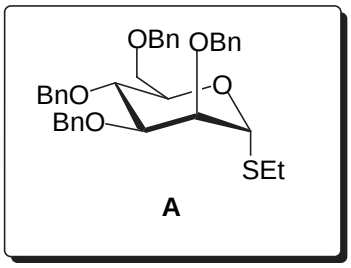
- isopropylidene acetals protect 1,2-diols and 1,3-diols. If the reaction is carried out under *thermodynamic* control, the favoured product is that from 1,2-*syn* diol protection. This therefore provides a method for protecting C(3) and C(4).
  Q? Why is the thermodynamic product of the 5-membered acetal (isopropylidene) the 1,2-protected diol whereas the thermodynamic product with a benzylidene acetal is the 1,3-protected diol? Hint: steric effects and the ring conformation of these protecting groups are important.
- the primary alcohol on C(6) is much more reactive than the other secondary alcohols. A large silyl ether protecting group can be selectively introduced on C(6). Selective deprotection with fluoride will release the alcohol later as we require.
- C(2) can then be readily acetylated.

We have now developed a protecting strategy for building block **B**.



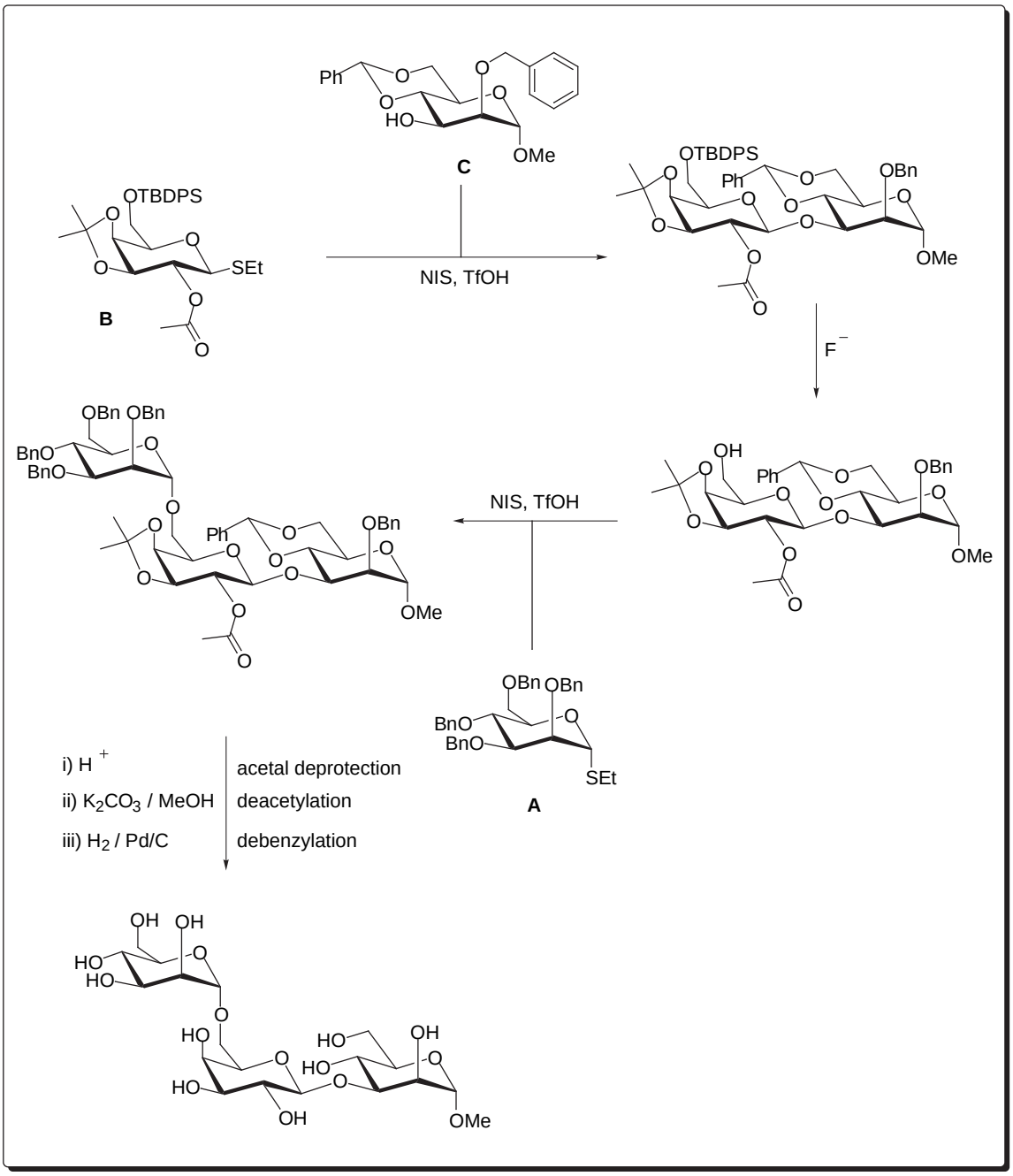
*Building block **A**.*

Very simple. Benzyl protecting groups on all alcohols and SEt group at the anomeric position. The axial orientation of the C(2) group favours formation of the desired α-glycoside.



A

We are now in a position to prepare the trisaccharide.



Summary

In this session we have developed a synthesis of a trisaccharide to illustrate some important concepts associated with protecting group strategies (orthogonality). Whilst not always the most interesting aspect of a synthesis, a poorly designed protecting group strategy has been the demise of many a total synthesis. Ignore it at your peril!