An Electrochemical Approach to Selective Oligosaccharide Synthesis

A thesis submitted for the degree of
Doctor of Philosophy (DPhil)

Robert France

St John's College

Oxford University

Trinity Term 2004

Abstract

An Electrochemical Approach to Selective Oligosaccharide Synthesis: A thesis submitted for the degree of Doctor of Philosophy (DPhil)

Robert R. France
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This thesis describes investigations into the use of electrochemical oxidation as a method for the activation of glycosyl donors, and in particular the application of this technique to the selective activation of one electrochemically active glycoside over another.

The synthesis of twenty eight electrochemically active monosaccharide donors, including thio-, seleno- and *O*-glycosides with varying protecting group patterns and anomeric substituents is described, together with the synthesis of three electrochemically active monosaccharides with the potential to act as both glycosyl donors and glycosyl acceptors.

The electrochemical analysis of these monosaccharides is reported and gives a detailed insight into the effect of various factors on the oxidation potentials of the monosaccharide donors and allows some general conclusions to be drawn. In addition the analysis of six monosaccharides by cyclic voltammetry at scan rates of up to 25 000 Vs^{-1} allows their homogenous kinetics to be outrun and formal oxidation potentials obtained.

Investigations into selective electrochemical glycosylations are reported, and the applicability of the analytical electrochemical studies to synthetic electrochemical reactions is demonstrated. Selective glycosylations are possible with selenoglycoside donors and either thio- or *O*-glycoside acceptors to give disaccharides. However the selective activation of selenoglycosides over thioglycosides is shown to be complicated by some underlying pathway for indiscriminate activation of both donor and acceptor. In contrast the use of an *O*-glycoside donor experiences no such problems. More detailed work on the underlying problems experienced with the thioglycoside acceptor was conducted, and the results are reported here.

Investigations into electrochemical activation of the disaccharides are discussed, and the thioglycoside is shown to be easily activated to give a trisaccharide. At the time of writing this is believed to be the only electrochemically mediated trisaccharide synthesis reported in the literature. The *O*-glycoside however is shown to be inactive under the electrochemical oxidation conditions employed.

Some aspects of this work have been published in the following articles:

(1) France, R. R.; Rees, N. V.; Wadhawan, J. D.; Fairbanks, A. J.; Compton, R. G.; Selective activation of glycosyl donors utilising electrochemical techniques: a study of the thermodynamic oxidation potentials of a range of chalcoglycosides, *Org. Biomol. Chem.*, **2004**, *2*, 2188-2194.

(2) France, R. R.; Compton, R. G.; Davis, B. G.; Fairbanks, A. J.; Rees, N. V.; Wadhawan, J. D., Selective electrochemical glycosylation by reactivity tuning, *Org. Biomol. Chem.*, **2004**, *2*, 2185-2202.

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Abbreviations

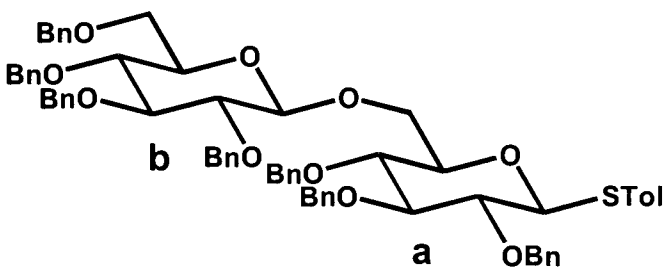
°	degrees	C	Celsius
α	alpha	*c.*	circa
α	charge transfer co-efficient	*c*,	concentration
β	beta	Calcd.	calculated
μ	micro	CI	chemical ionisation
υ	solution kinetic viscosity	COSY	correlated spectroscopy
υ	scan rate	CSA	camphor sulphonic acid
Å	Ångstrom	d	doublet
A	area	D	diffusion coefficient
A	amps	DAG	diacetone galactose
[A]	concentration of species A	DCM	dichloromethane
ABq	AB quartet	dd	doublet of doublets
Ac	acetyl	ddd	doublet of doublet of doublets
A.C.	alternating current	DEPT	distortionless enhancement through polarisation transfer
APCI	atmospheric pressure chemical ionisation	DMAP	*N*,*N*-dimethylaminopyridine
at	apparent triplet	DMF	*N*,*N*-dimethylformamide
[B]	concentration of species B	DMSO	dimethyl sulphoxide
BDA	butane diacetal	E	potential
Bn	benzyl	e^-	electron
br	broad	e.g.	*exempli gratia* (for example)
Bz	benzoyl		

$E_{1/2}$	half wave potential	I	current
E_f^0	formal potential	i.e.	*id est* (that is)
E_p	peak potential	I_p	peak current
ES	electrospray	^iPr	*iso*-propyl
ESI	electrospray ionisation	IR	infrared
Et	ethyl	*J*	coupling constant
et al	*et alia* (and co-workers)	k	rate constant
ether	diethyl ether	m	multiplet (in nmr)
F	Faraday constant	m	medium (in IR)
g	grams	M	molecular mass ion
Gal	galactose	M	molar
GalNAc	*N*-acetyl galactosamine	Man	mannose
Glu	glucose	Me	methyl
GluNAc	*N*-acetyl glucosamine	mg	milligrams
h	hour(s)	MHz	megahertz
HMBC	heteronuclear multiple-bond correlation	min	minutes(s)
		ml	millilitres
HMDS	hexamethyldisilane	mM	millimolar
HMQC	heteronuclear multiple-quantum correlation	mmol	millimoles
		m.p.	melting point
HRMS	high resolution mass spectrometry	MS	mass spectrometry
		mV	millivolts
Hz	hertz	*m/z*	mass to charge ration

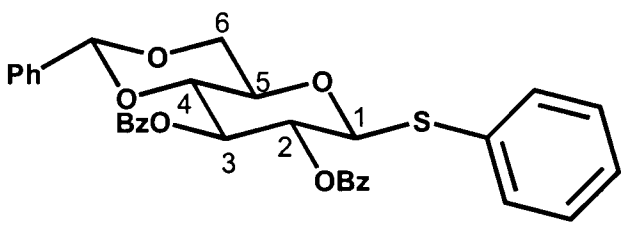
n	number of electrons	t	triplet (in nmr)
NBS	*N*-bromosuccinimide	t	time
NIS	*N*-iodosuccinimide	T	temperature
NMR	nuclear magnetic resonance	TBAP	tetrabutylammonium
nOe	nuclear Overhauser effect		perchlorate
Nu	nucleophile	Tf	trifyl (trifluoromethane-
p	*para*		sulphonyl)
[P]	generic protecting group	t.l.c.	thin layer chromatography
Ph	Phenyl	TMS	trimethylsilyl
PMP	*para*-methoxyphenyl	Tol	*para*-tolyl
ppi	pores per inch	tolyl	*para*-methylphenyl
ppm	parts per million	Trt	trityl (triphenylmethyl)
q	quartet	V	volts
R	generic organic group	w	weak
R	the universal gas constant		
R	resistance		
R_f	retention factor		
s	singlet (in nmr)		
s	strong (in IR)		
s	seconds		
S_N^2	substitution, nucleophilic,		
	bi-molecular		
t	tertiary		

A Note Concerning Nomenclature

Carbohydrates and carbohydrate derivatives are numbered according to the I.U.P.A.C. recommendations on carbohydrate nomenclature, published in 1997.[1] The two protons on C-6 are labelled H-6 and H-6', with H-6 arbitrarily assigned to the proton signal which occurs at the lower of the two chemical shift values. Where a compound is composed of more than one carbohydrate ring individual proton and carbon assignments are indicated by the use of a lower case letter, given alphabetically starting from what would be the reducing terminus. Some examples are given below.



Tolyl-2,3,4,6-tetra-*O*-benzyl-β-D-glucopyranosyl-(1→6)-2,3,4-tri-*O*-benzyl-1-thio-β-glucopyranoside



Phenyl-2,3-di-*O*-benzoyl-4,6-benzylidene-1-thio-β-D-glucopyranoside

1. McNaught, A. D. *Carbohydr. Res.*, **1997**, *297*, 1-92.

Chapter 1
General Introduction

1.1 Carbohydrates in Biology

When Emil Fischer published his pioneering work on carbohydrates in the 1880s it is hard to imagine that he could have envisaged the vast realm of science to which he had just opened the door.[1-5] It is clear however that he appreciated the importance of these compounds in nature and that the work of a synthetic organic chemist could be applied to the world of biology.[6] It is the biological relevance of carbohydrates which has always driven this field of research as chemists seek to provide compounds from which they can elucidate the functions of biological systems. Initially the role of carbohydrates in biology was thought to be confined to basic, but important, biological functions, in particular as structural components and as sources of energy.[7] Over the relatively recent past it has become clear that they perform a much more diverse array of functions, including important roles in immune response, regulating hormone activity and protein folding.[8] This has sparked a growth in the interest in the biological function of carbohydrates[9] and a consequently increased interest in their efficient synthesis.[10]

1.1.1 The metabolic and structural roles of carbohydrates[7]

Easily the most abundant carbohydrate in nature is glucose, as this simple unit is found in all biological systems in one form or another. Starch, the principal carbohydrate fuel store in plants, consists of two polymers of glucose, amylopectin **1** and amylose **2**. Amylose is a linear polymer consisting solely of α(1→4) linked glucose units, while amylopectin differs only in the presence of some α(1→6) branched chains (figure 1.1).

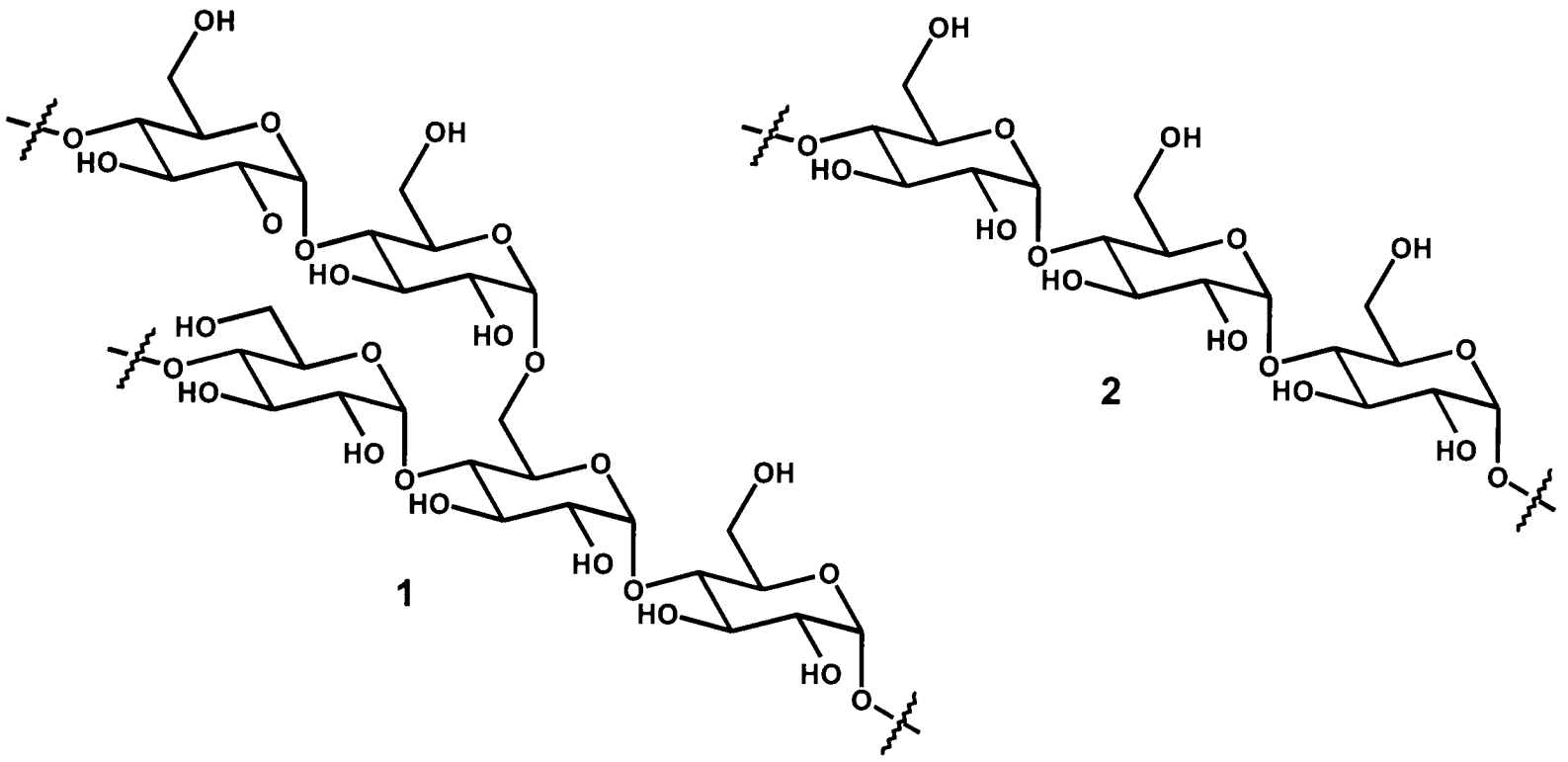


Figure 1.1: Polymeric glucose as an energy store: amylopectin **1** and amylose **2**

The primary carbohydrate energy store in animals and microbes (glycogen) differs from amylopectin **1** only in the frequency and length of the α(1→6) side chains, which are generally shorter but more frequent.

One of the main structural components of fibrous and woody plants (such as trees and grasses) is also constructed entirely from a polymer of glucose, cellulose **3**, this time β(1→4) linked (figure 1.2).

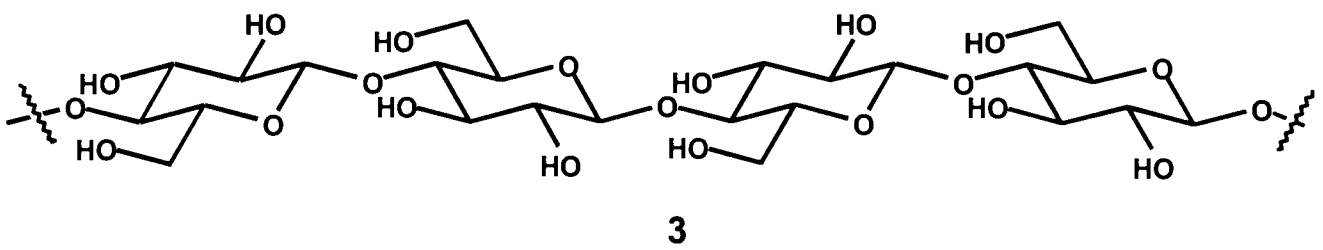
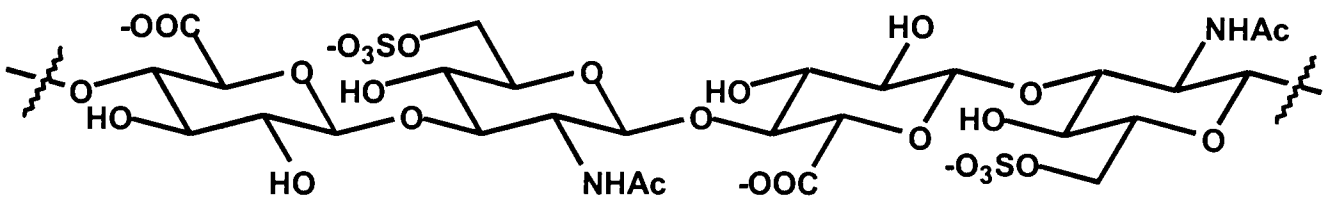


Figure 1.2: Cellulose

This would appear to be only a minor change from the α(1→4) linked polymer amylose – however that change is crucial. The β(1→4) linked cellulose polymer is able to form long

extended chains, which pack side by side held together by hydrogen bonding, to create sheets of great strength. It is this property which makes them useful as structural components. This small change has another significant implication, the enzymes responsible for the cleavage of the α(1→4) glycogen bonds in animals are unable to cleave the β(1→4) linked cellulose bonds. Consequently most animals, including humans, cannot derive any energy from this abundant source of glucose. This highlights the sensitivity of biological systems to differences in the configuration of carbohydrate systems.

The structural role of carbohydrates in nature is not limited to cellulose **3**. Other examples in plants include xylans, which are β(1→4) linked polymers of xylose, and glucomannans, which contain both mannose and glucose. Whilst higher organisms make use of cellulose and other simple carbohydrate polymers such as chitin (another β(1→4) linked polymer of a glucose derivative) they also make use of more complex carbohydrate polymers. For example glycosaminoglycans, such as chondroitin sulphate **4** and hyaluronic acid **5** are responsible for holding together the protein components of skin and connective tissue such as cartilage (figure 1.3).



4

5

Figure 1.3: Structural polysaccharides in higher organisms: chondroitin sulphate **4** and hyaluronic acid **5**

The function of these carbohydrates is closely linked to the proteins to which they are bound, although in these structural examples it is the carbohydrate which makes up the majority of the mass of the complex. However carbohydrates also play a role in many important biological functions of proteins where the carbohydrate makes up a much smaller component of the system, and it is to this that we now turn our attention.

1.1.2 Glycoproteins

The more complex functions of carbohydrates in biological systems tend to see them attached to another class of biological molecule, either lipids (to give glycolipids) or proteins (to give glycoproteins). In these cases they are no longer the polymeric species discussed above, but discrete chains of specific monosaccharides. Such chains are referred to as oligosaccharides.

Glycoproteins are implicated in roles as diverse as fertilization, immune response, viral replication, cell growth, cell-cell adhesion, degradation of blood clots and inflammation and have therefore aroused considerable interest.[9] While the proteins involved in these processes are often well known it is only recently that the role of the carbohydrates attached to them is becoming understood.[8,11,12] Any given glycoprotein will have one or more glycosylation sites, each of which may be glycosylated by one of a range of oligosaccharide chains. This gives rise to a number of compounds bearing the same protein sequence, but with different carbohydrates attached; these are known as glycoforms.

We have already seen how a small change in the glycosylation patterns in a polymer of glucose gives rise to structures with vastly different properties. It is therefore no surprise that these variations in glycosylation pattern on proteins can have a significant effect on their properties.

One well understood example is the variation in the glycosylation pattern on the surface of red blood cells, which leads directly to the determination of blood groups. The three main blood groups, A, B and O differ only in the presence or absence of one monosaccharide unit on the end of the oligosaccharide chain which is attached to a protein on the cell surface (figure 1.4).

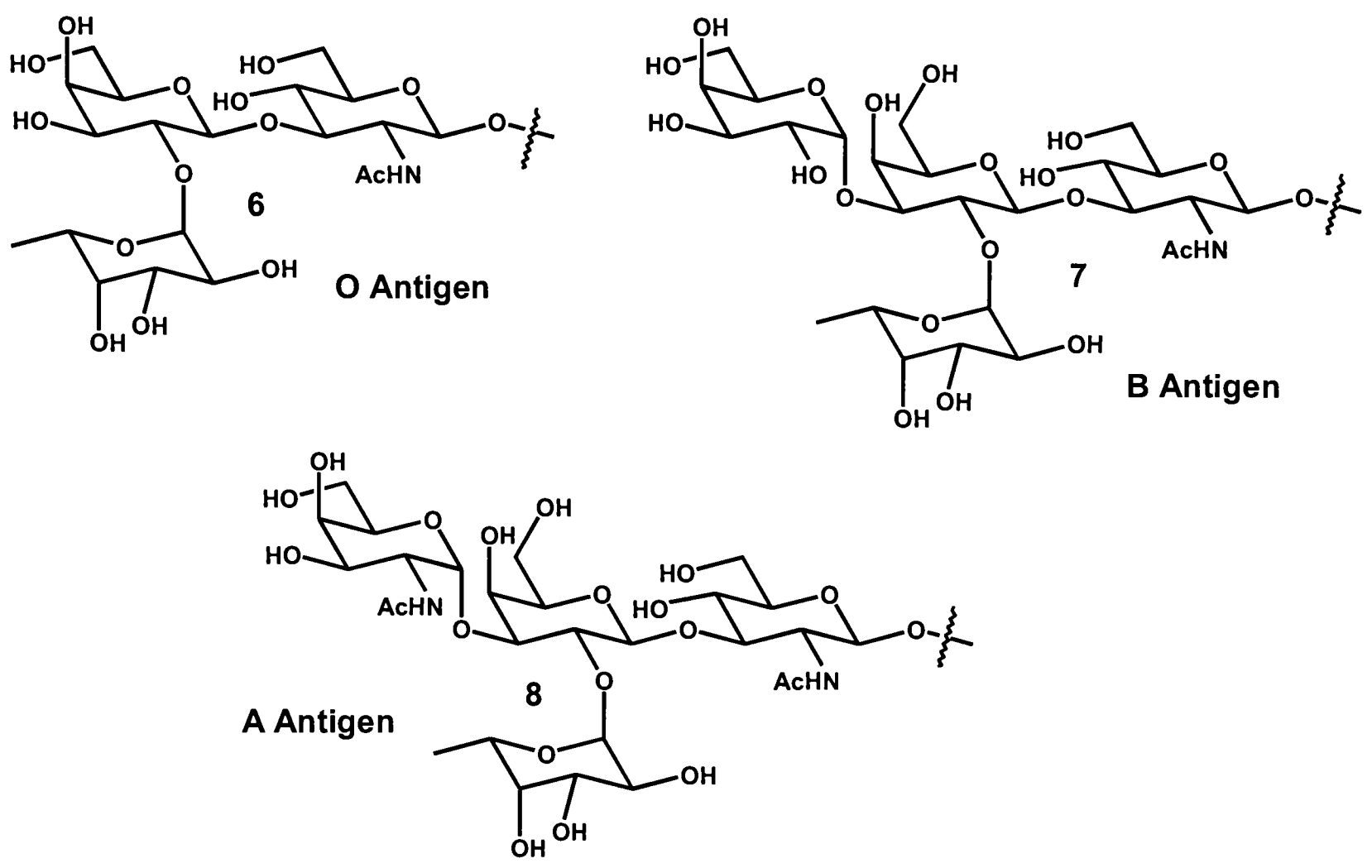


Figure 1.4: The terminal oligosaccharide residues of the three human blood antigens

This minor difference in glycoforms has a sufficient impact on immune response to have potentially fatal consequences if the wrong blood type is given in a transfusion.

Whilst this particular example has been understood for a long time it was, until recently, no simple matter to identify which carbohydrate residues were present on a given protein.

However recent advances in technology now make this information easier to obtain.[13-15] This greater understanding of which oligosaccharides are present in glycoproteins, and in what circumstances, has led to a much greater understanding of the role of protein glycosylation.[16-18]

Oligosaccharides which might be of interest, either to further probe biological systems or to develop therapeutic reagents,[19] are often difficult to obtain from natural sources. Consequently, in order to fully exploit this greater understanding of the biological role of carbohydrates, there is much demand for synthetically derived oligosaccharides.

1.2 Oligosaccharide Synthesis

1.2.1 The challenges of oligosaccharide synthesis

The standard synthesis of oligosaccharides comprises of the coupling of saccharide units together, to form the desired oligosaccharide chain (figure 1.5).

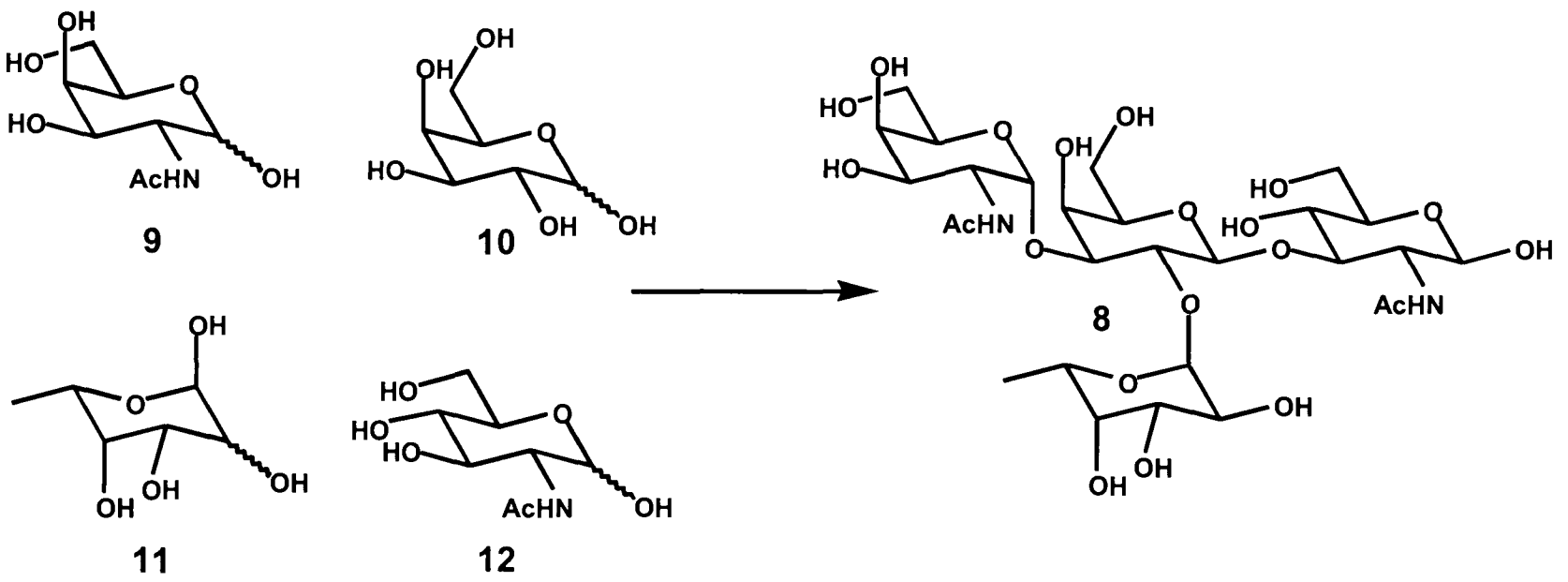


Figure 1.5: The essence of oligosaccharide synthesis

However the simplicity of this statement belies the complexity of the process. The main challenges which face the synthetic carbohydrate chemist are:

(1) Regio control

Each monosaccharide usually has a number of alcohol groups available for glycosylation (the process of connecting two saccharide units together). These are often of similar reactivity and if left unprotected usually lead to complex mixtures of products during the glycosylation step. This has led to a large area of carbohydrate chemistry dedicated to the selective protection and deprotection of glycoside alcohols, and it most cases there are now established routes to access any given position selectively.[20-23]

(2) Stereo control

One of the most challenging aspects of oligosaccharide synthesis is controlling the stereochemistry of the glycosidic bond, formed when one sugar is attached to another in a glycosylation reaction (figure 1.6).

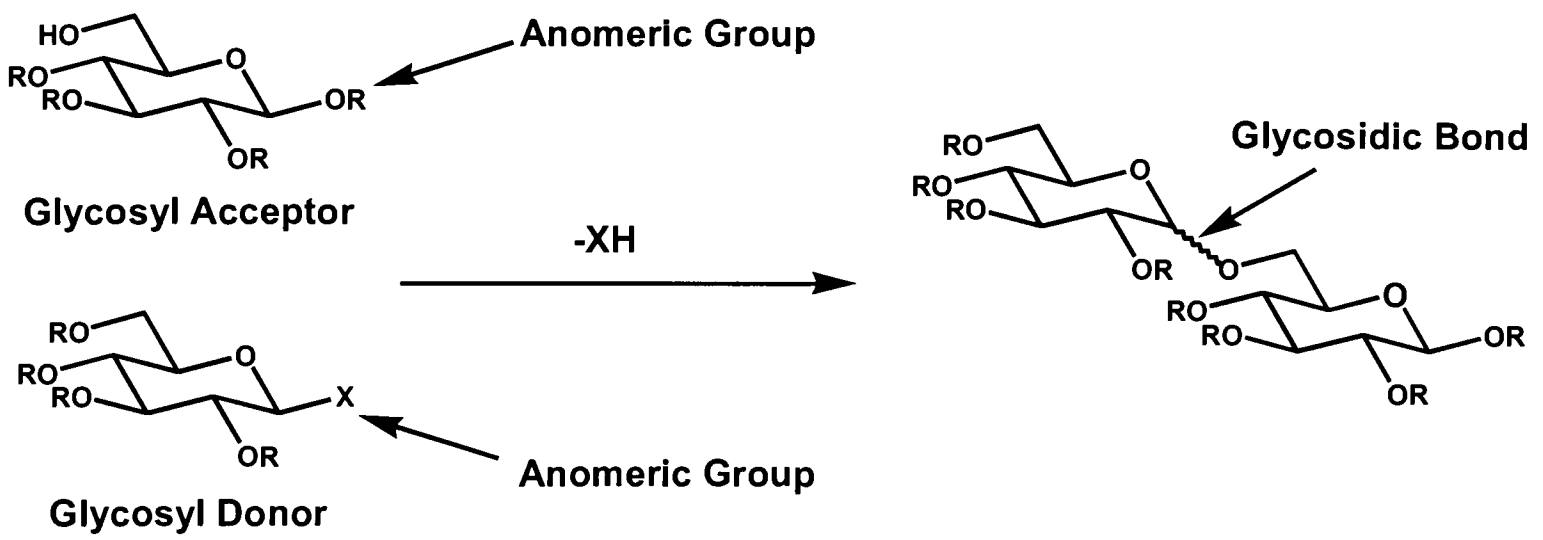
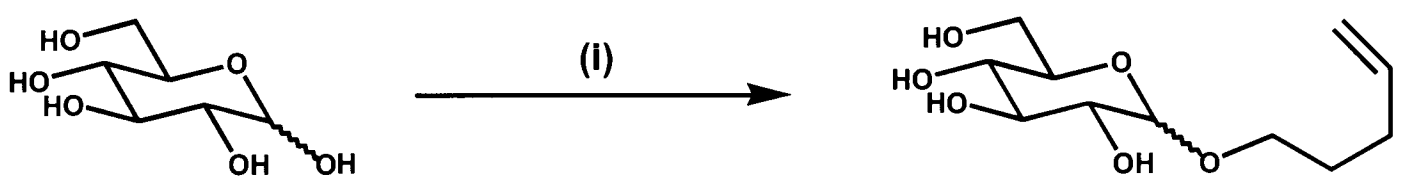


Figure 1.6: Formation of a glycosidic bond. R is a protecting group and X is a leaving group

In some cases the stereochemistry of the glycosylation can be controlled in a relatively straightforward manner. This is usually the case when the desired glycosidic bond is 1,2-*trans* in nature (i.e. β-*gluco*, or α-*manno*). In these instances use can be made of a participating group at OH-2, directing the bond formation.[24,25] The 1,2-*cis* bond presents more of a challenge and a number of techniques are in use, with none yet providing a comprehensive solution to the problem. These include S_N2 displacement of the anomeric leaving group, as in Köenigs-Knorr conditions of an insoluble silver salt activating a glycosyl halide;[26-30] intramolecular aglycon delivery, where the glycosyl acceptor is first anchored to the donor in the geometry required to give a 1,2-*cis* glycoside on glycosylation;[31-33] and formation of a 1,2-*trans* glycoside, followed by modification of the stereochemistry at C-2.[34-36]

(3) Efficiency of the glycosylation step

Such are the lengths required to achieve regio and stereo control it is essential that the crucial step, that of forming the glycosidic bond itself, should be as straightforward and high yielding as possible. This is not by any means assured, and much attention has been given to improving the efficiency of this process. The most basic glycosyl bond forming reaction is that of taking an alcohol with a free sugar, in the presence of an acid catalyst (a Fischer Glycosylation). A recent example of such a reaction by Fraser-Reid shows that this methodology still finds use today (scheme 1.1).



13 **14**

(i) pent-4-ene-1-ol, CSA, reflux, 2 days, 85%, α:β, *c.* 2:1

Scheme 1.1: A recent example of a Fischer glycosylation

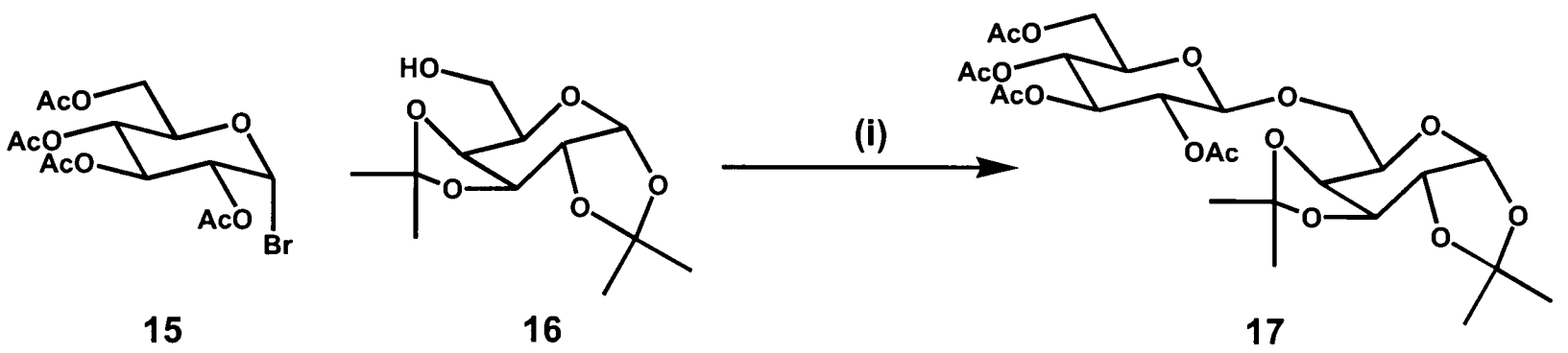
The reaction can however be inefficient, the conditions are harsh and there is a tendency to give mixtures of products. Additionally this procedure is not practical for oligosaccharides containing more than two sugar residues. Over the hundred or so years since Fisher's work a wide variety anomeric leaving groups and glycosylation strategies have been developed to improve this crucial reaction.

1.2.2 Improved anomeric leaving groups

Many anomeric leaving groups have been used in oligosaccharide synthesis over the years,[37] amongst those that have found the most widespread use are glycosyl halides, trichloroacetimidates, thioglycosides, selenoglycosides and *n*-pentenyl glycosides and these are discussed here.

1.2.2.1 Glycosyl halides

The use of anomeric halides was one of the first modifications of the glycosylation reaction, and was introduced by Köenigs and Knorr in 1901.[38] These reactions use heavy metal salts, typically of silver, to activate an anomeric chloride or bromide.[39-41] A recent example of this type of reaction uses indium (III) chloride to activate a glycosyl bromide (scheme 1.2).[42]

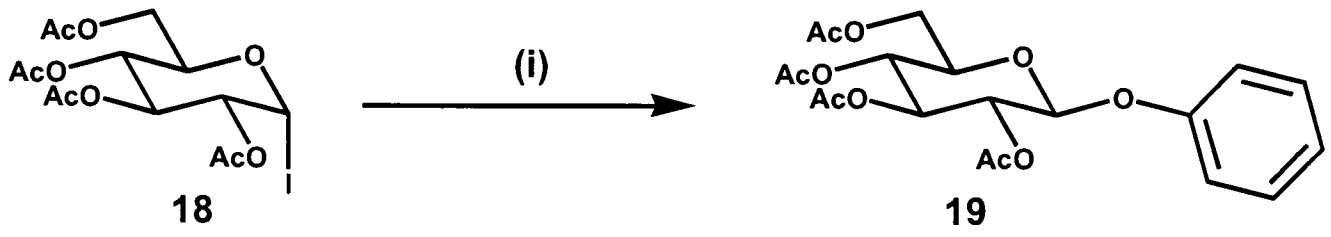


15 16 17

(i) $InCl_3$, DCM, 4 Å molecular sieves, 24 h, 78%

Scheme 1.2: Indium (III) chloride catalysed activation of a glycosyl bromide

There has also been recent interest in the use of glycosyl iodides and fluorides as glycosyl donors. Glycosyl iodides are of potential interest due to the lability of the iodide leaving group, giving the potential for S_N2 type reactions (scheme 1.3).[43,44]



18 19

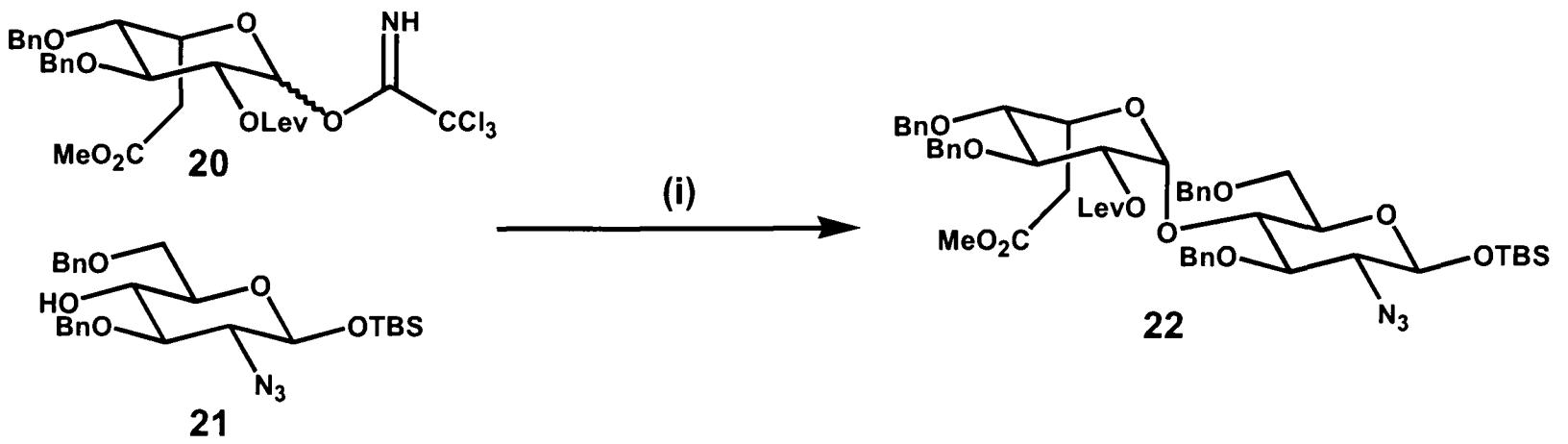
(i) phenol, $Na(CH_3)_3SiNHSi(CH_3)_3$, THF, 61%

Scheme 1.3: Nucleophilic displacement in a glycosyl iodide

On the other hand it is the stability of glycosyl fluorides under a variety of conditions (including those traditionally used to activate glycosyl halides) which has led to their widespread use in modern glycoside synthesis.[37]

1.2.2.2 Trichloroacetimidates

Acetimidates were first used as glycosyl donors by Sinaÿ in 1976,[45,46] after he had isolated them from a Köenigs-Knorr reaction.[47] However the popularity of trichloroacetimidates as glycosyl donors stems from the later work of Schmidt.[48] These donors have been widely used in oligosaccharide synthesis due to their stability and the mild conditions required for their activation.[49] Activating agents include boron trifluoride diethyl etherate,[48] trimethylsilyl triflate,[50] trichloroacetaldehyde[51] and pyridinium *p*-toluenesulphonate (PPTS).[52,53] Seeberger recently employed trichloroacetimidates as glycosyl donors in all seven glycosylation steps, in an attempted synthesis of a biologically important heparin oligosaccharide (scheme 1.4).[54]

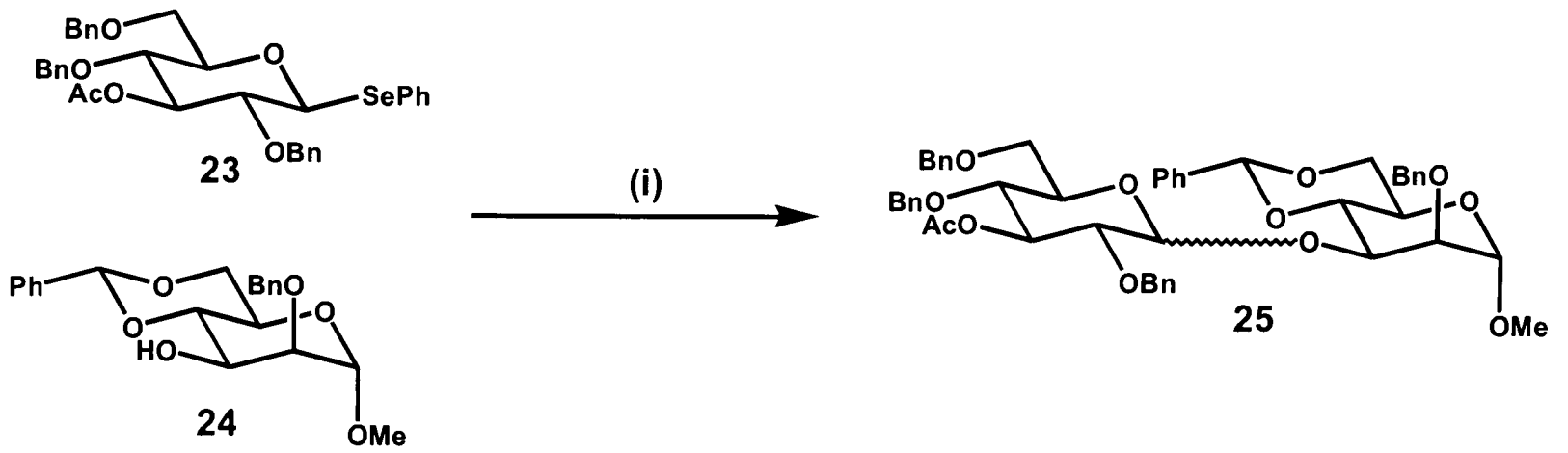


(i) TMSOTf, DCM, 74%

Scheme 1.4: The first step in Seeberger's octasaccharide synthesis

1.2.2.3 Thioglycosides and Selenoglycosides

Thioglycosides have been extensively used in oligosaccharide synthesis, and numerous different conditions are available for their activation.[10,55,56] In common with other efficient anomeric leaving groups for glycosylation they are stable to a wide range of reaction conditions, yet easily activated under mild conditions when required. In addition they are easily converted into glycosyl halides (in particular fluorides) and sulphoxides. These are both excellent leaving groups for glycosylation reactions in their own right, and give any synthesis employing thioglycosides added flexibility. Selenoglycosides are a newer addition to the armoury of glycosyl donors, having been first used by Pinto in 1991.[57] They are already finding much use in oligosaccharide synthesis, for instance in Ennis' synthesis of the Glc_3Man portion of a biologically important oligosaccharide (scheme 1.5).[58] Activation has been shown to be possible under many of the conditions applied to thioglycosides,[59-61] as well as some under which thioglycosides are not activated.[62] This gives rise to the possibility of orthogonal glycosylation strategies (*vide infra*).



(i) NIS, AgOTf, DCE:Et_2O, 1:1, 4 Å molecular sieves, 88%, α:β, 4:1

Scheme 1.5: Activation of a selenoglycoside during Ennis' synthesis of a tetrasaccharide

1.2.2.4 *n*-Pentenyl glycosides

The final anomeric leaving group to be discussed is another recent, but important, addition to the family. The *n*-pentenyl group was discovered more by chance than design by Fraser-Reid, during work on the synthesis of streptovaricin A.[63] Fraser-Reid soon realised its potential as a protecting group,[64] and soon afterwards as an anomeric leaving group.[65] It has the requisite qualities to fill this role well, being stable to most conditions used in the manipulation of carbohydrates, yet easily activated under very specific conditions – namely with an electrophilic halogen (either bromine or iodine). A number of activation systems have proven effective,[65-69] although the most efficient has been shown to be a mixture of *N*-iodosuccinimide and triethylsilyltriflate.[70,71] One of the main reasons for the use of *n*-pentenyl groups in modern chemistry is that by variation of the protecting group pattern they can be used in glycosylations where the glycosyl acceptor itself bears an anomeric leaving group, ready for further glycosylation. This concept, known as the armed/disarmed effect, is a form of selective activation and is dealt with in more detail below.

1.2.3 Selective Activation

The concept of selective activation has already been discussed briefly above. At its most basic level it is simply the process of conducting a glycosylation in which the glycosyl acceptor is itself capable of being activated as a glycosyl donor, either immediately (as in the case of the armed/disarmed approach and the orthogonal approach) or with minimal manipulation (as in the case of the latent/active approach). The concept is shown schematically below (figure 1.7).

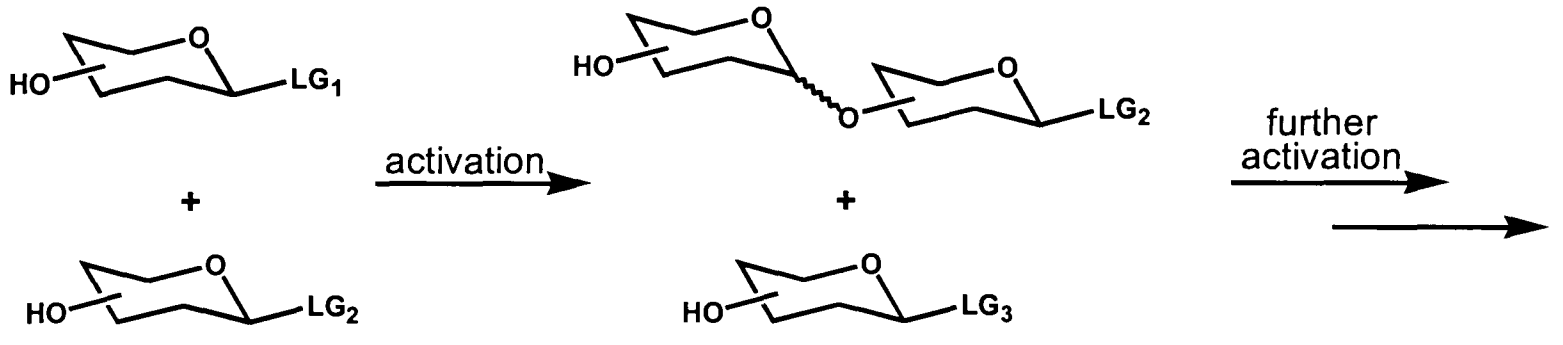
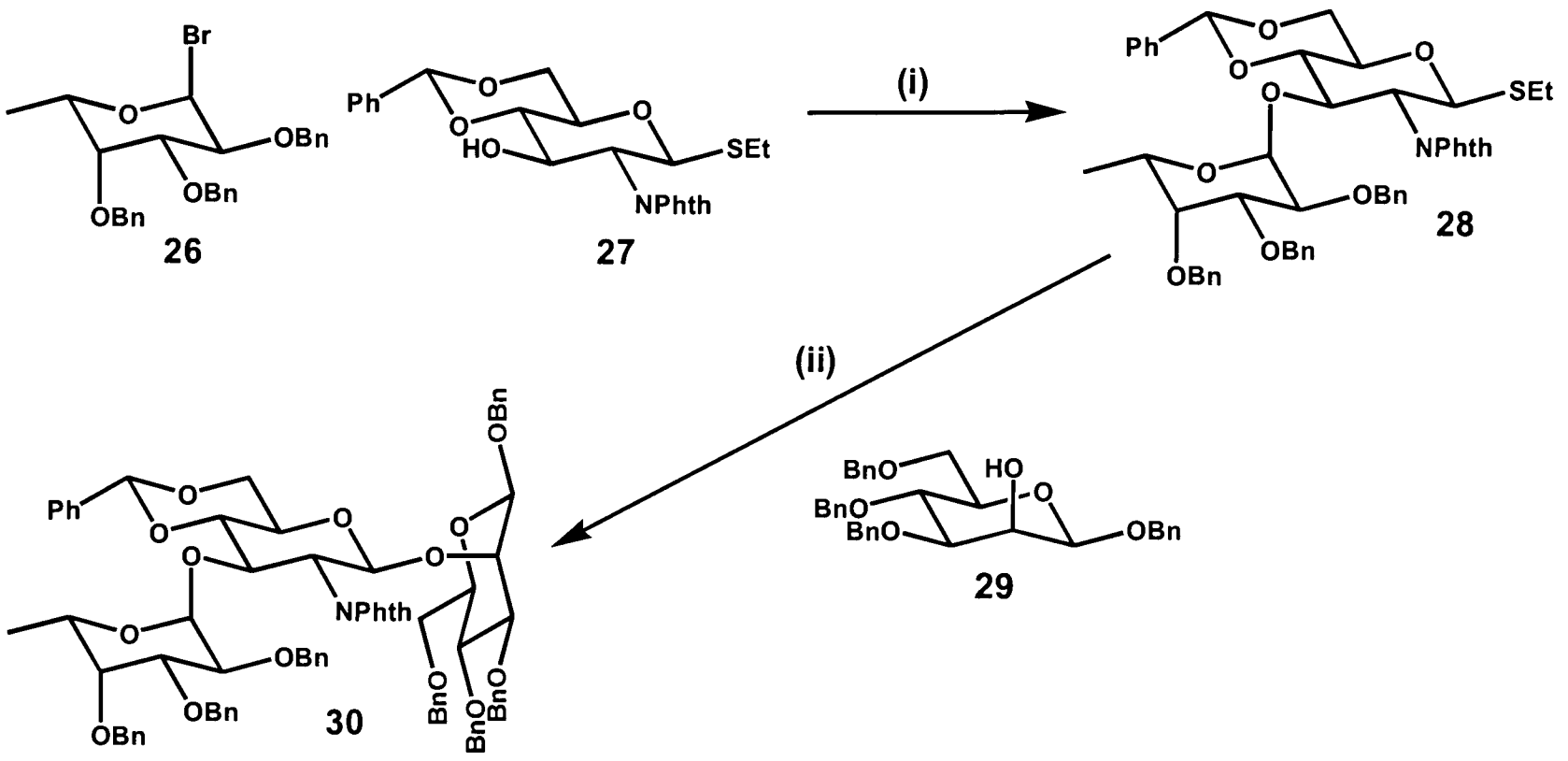


Figure 1.7: Schematic representation of a series of selective glycosylations

The driving force behind work in this area is the idea that long chain oligosaccharides could be synthesised in this way, utilising differing levels of reactivity, with the minimum of chemical manipulations between glycosylation steps.

1.2.3.1 Orthogonal Glycosylations

The selectivity in an orthogonal glycosylation comes from the use of two glycosides which can be activated under mutually exclusive conditions. In other words the conditions for the activation of one glycoside do not activate the other, and *vice versa*. Lönn demonstrated this strategy in 1985 using a glycosyl bromide and a thioglycoside (scheme 1.6).[72]

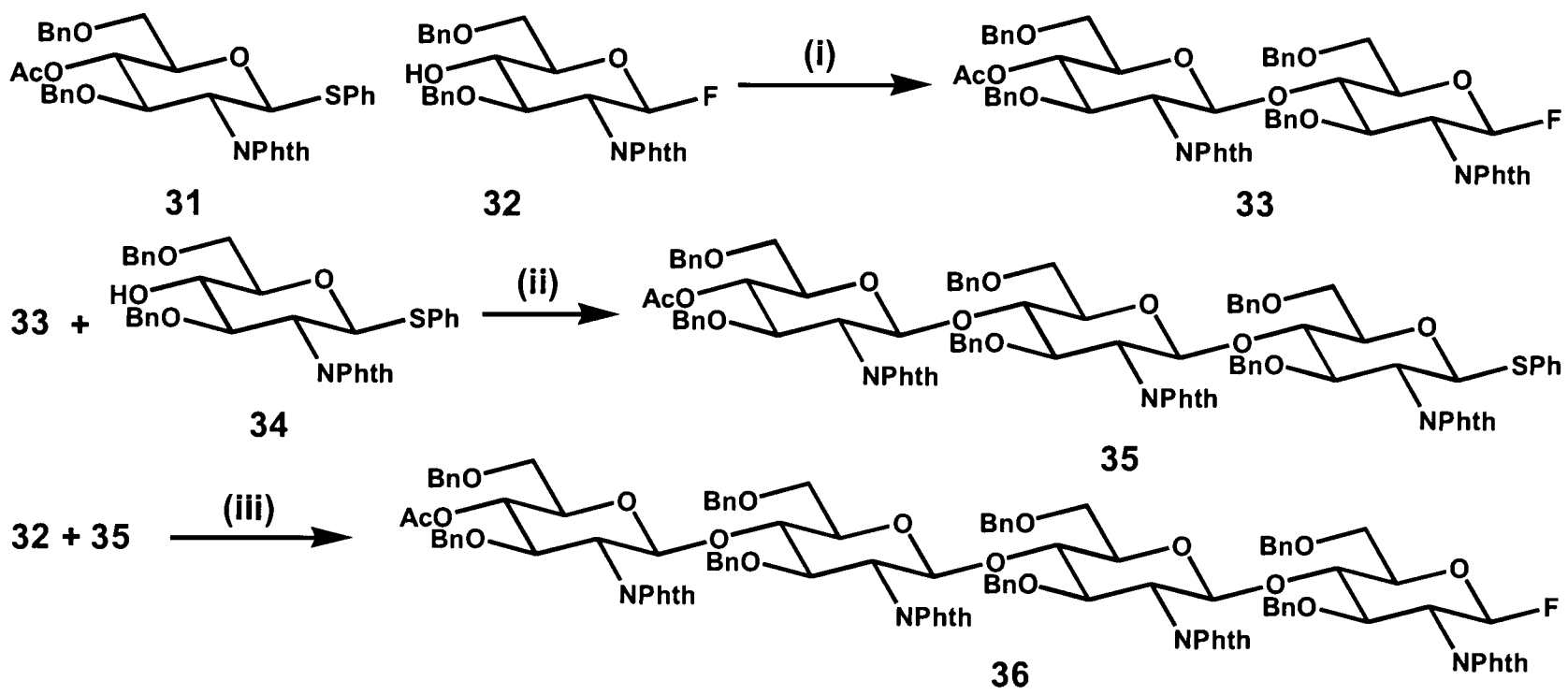


(i) activation with *n*-Bu_4NBr; (ii) activation with MeOTf

Scheme 1.6: Orthogonal activation of a glycosyl bromide, in the presence of a thioglycoside

The bromide **26** is activated first using tetrabutylammonium bromide, conditions which leave the thioglycoside **27** intact. The resultant disaccharide **28** is then activated with methyl triflate to give a trisaccharide **30**. Lönn went on to apply this methodology in the synthesis of a branched oligosaccharide.[73] Problems with *O*-methylation of acceptor **29** were observed during the activation of the thioglycoside, but the wide range of activation conditions now available make this only a minor problem. This methodology has been developed by a number of groups, showing that bromides can be selectively activated in the presence of both *n*-pentenyl-[74] and phenyl thioglycosides.[75] Pinto demonstrated that phenyl selenoglycosides can be activated using silver triflate and potassium carbonate, whilst thioglycosides are not activated under these conditions.[57,62] Nicolaou took this a stage further, activating a glycosyl fluoride in the presence of a thioglycoside using tin (II) chloride and silver perchlorate to give a disaccharide.[76,77] The disaccharide thioglycoside was then converted into a fluoride using *N*-bromosuccinimide

(NBS) and diethylaminosulphur trifluoride (DAST). The process could then be repeated to give longer chain oligosaccharides, and indeed Nicolaou prepared a pentasaccharide in this manner.[78] Further improvement came from Ogawa, who found conditions which would activate thioglycosides but not glycosyl fluorides.[79] Combining this with an improved version of Nicolaou's fluoride activation conditions he was able to demonstrate an orthogonal glycosylation strategy which requires no manipulation between iterations (scheme 1.7).



(i) NIS/AgOTf; (ii) Cp_2HfCl_2, $AgClO_4$; (iii) NIS/AgOTf

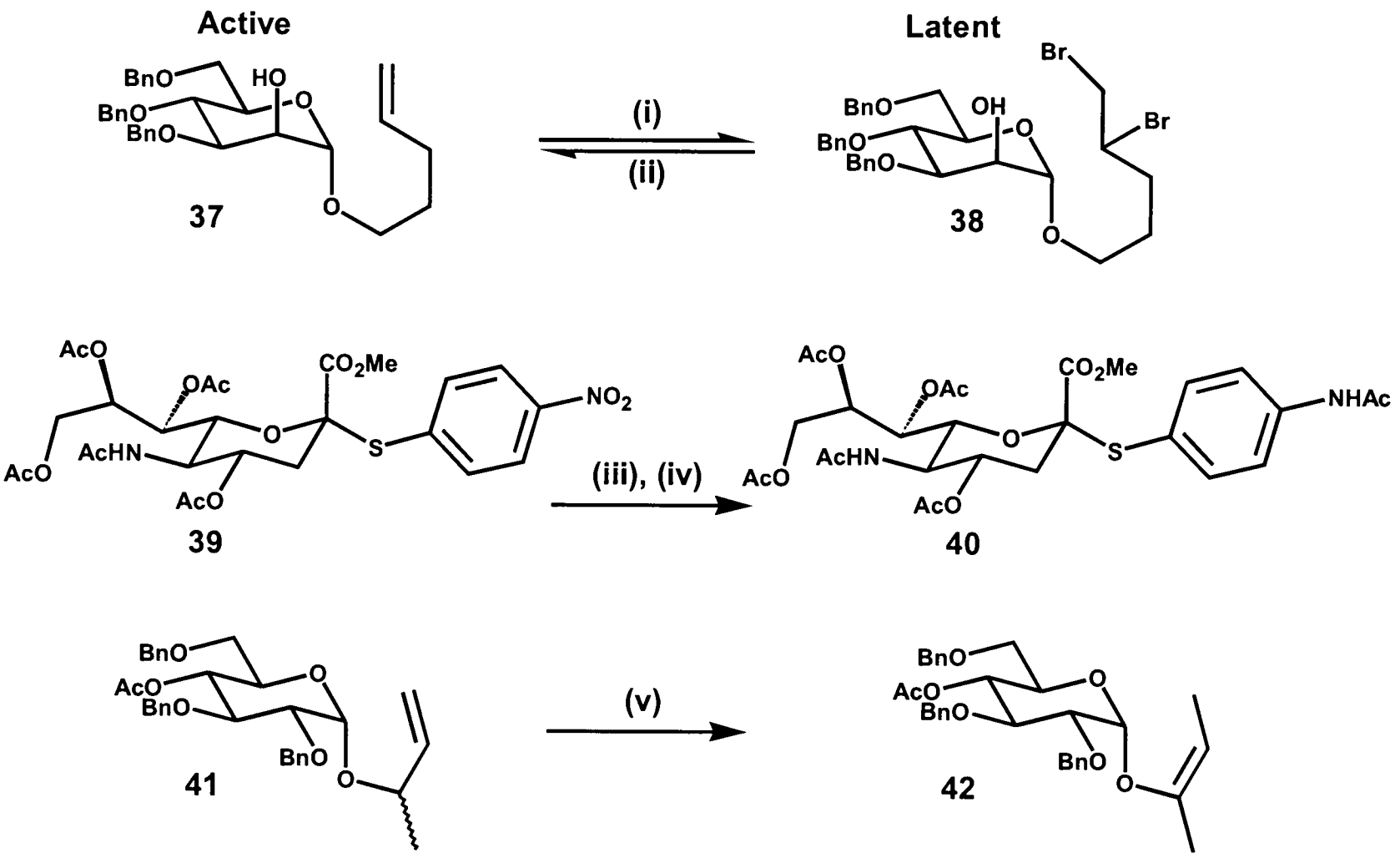
Scheme 1.7: Ogawa's iterative orthogonal glycosylation strategy

Orthogonal glycosylation has been used extensively in oligosaccharide synthesis and there are many examples in the literature.[80-84]

1.2.3.2 The latent/active approach

The latent/active approach relies on the ability to convert a glycoside bearing an anomeric group which is inert to glycosylation (the latent form) into one in which the anomeric group has been converted into a form which is amenable to glycosylation (the active form). There are three main examples in this area: Fraser-Reid's sidetracking of *n*-pentenyl glycosides into a

stable dibromo compound;[85,63] Roy's conversion of the inert *p*-nitrophenyl thioglycosides into *p*-*N*-acetylphenyl thioglycosides;[86] and Boon's conversion of substituted allyl glycosides to vinyl glycosides which can be activated by a Lewis acid. (scheme 1.8).[87]



(i) Br_2, Et_4NBr; (ii) Zn dust, Bu_4NI, EtOH; (iii) $SnCl_2$, EtOH, reflux; (iv) Ac_2O, pyridine; (v) $(Ph_3P)_3RhCl$

Scheme 1.8: Conversion of latent glycosides into active glycosides

These techniques have been used in a number of oligosaccharide syntheses, although their use has not been as widespread as the orthogonal methods described above.[88-90]

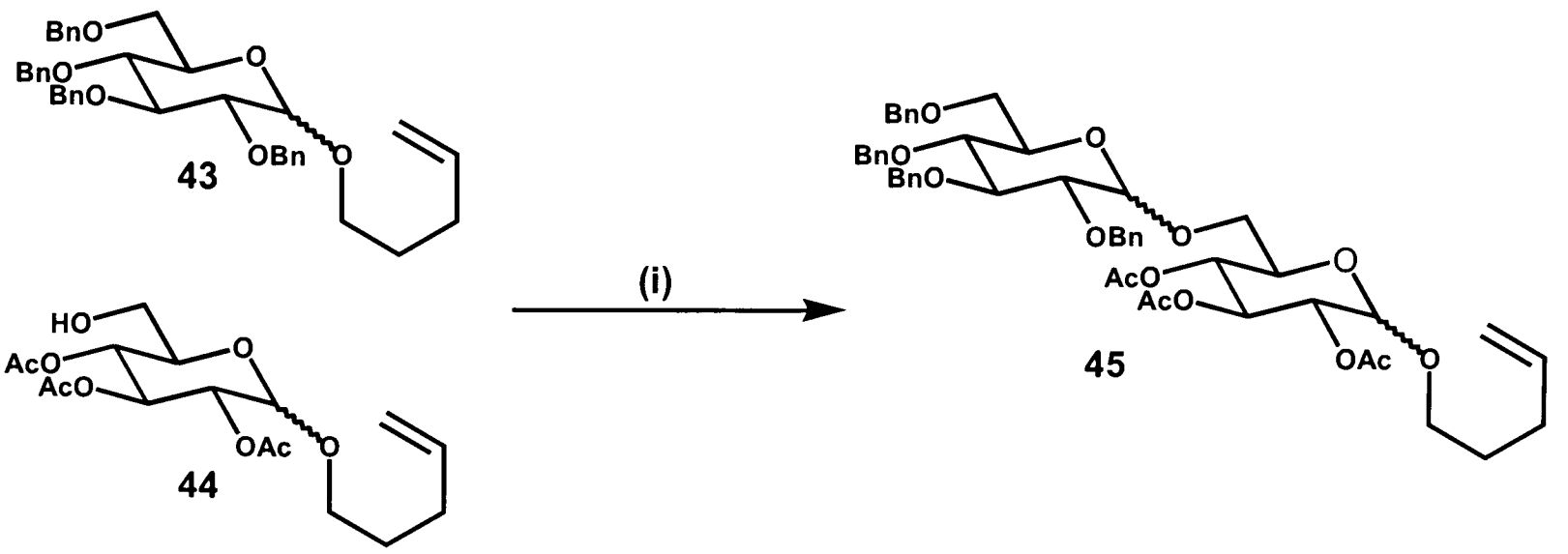
1.2.3.3 Armed/disarmed glycosides

This methodology relies on the difference in the rate at which different glycosyl donors react under a given set of activating conditions. As in the case of orthogonal glycosylations this

methodology uses a glycosyl acceptor which is capable of being activated for glycosylation. However rather then requiring a different set of conditions (or chemical manipulation) for subsequent activation, the acceptor may, in theory, be activated under the same reaction conditions as the donor. In practice the glycoside which is required to act as the donor reacts much faster than the designated acceptor – resulting exclusively in the desired glycosylation product. The resulting glycoside is then immediately available for further glycosylation under the same conditions, or often under stronger versions of the same conditions.

There are a number of factors which can affect the reactivity of glycosyl donors, but it was the effect of different protecting groups which was first noted and used in such a strategy. In his original paper on the subject[85] Fraser-Reid termed the use of different protecting group regimes to control the reactivity of a glycosyl donor as the "armed/disarmed effect". However the nature of the leaving group has also been shown to be able to contribute to the reactivity of a glycosyl donor, and this will also be discussed under this heading.

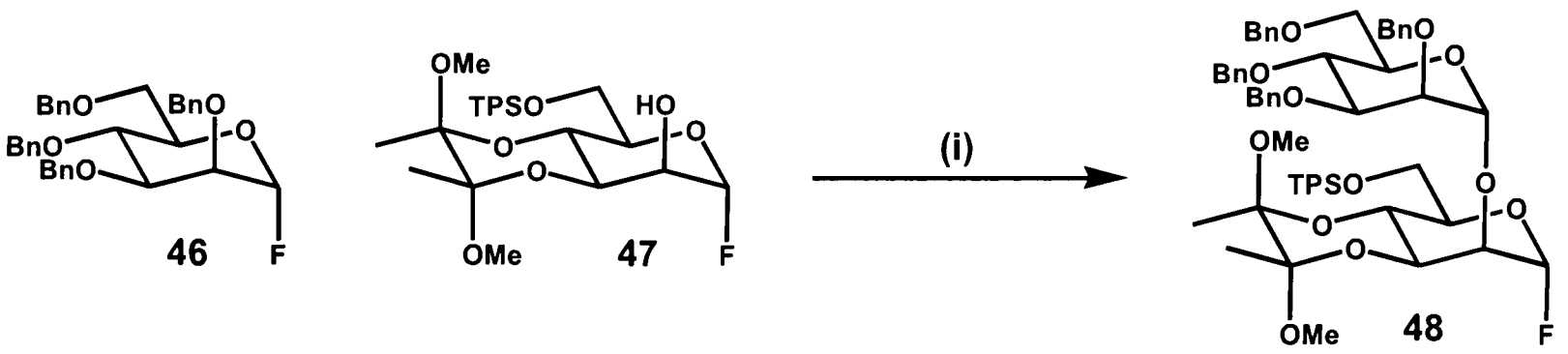
Fraser-Reid's work was based around the *n*-pentenyl system which he had recently discovered to be extremely effective in glycosylation reactions (*vide supra*). He observed that oxidative hydrolysis of an *n*-pentenyl glycoside with *N*-bromosuccinimide (NBS) was rapid if the protecting group on OH-2 was benzyl, proceeding in minutes, whilst the equivalent reaction with a benzoyl group at OH-2 required several hours. He went on to exploit this by coupling the benzylated compound **43** ("fully armed") with the acetylated compound **44** ("fully disarmed") using one equivalent of iodonium dicollidine perchlorate (IDCP) as an activator (scheme 1.9). The reaction proceeded to give disaccharide **45** in 62% yield, with none of the product which would have derived from the activation of acetyl glycoside **44** formed.



(i) IDCP, DCM, 4 Å molecular sieves, 62%

Scheme 1.9: Selective activation of an armed over a disarmed *n*-pentenyl glycoside

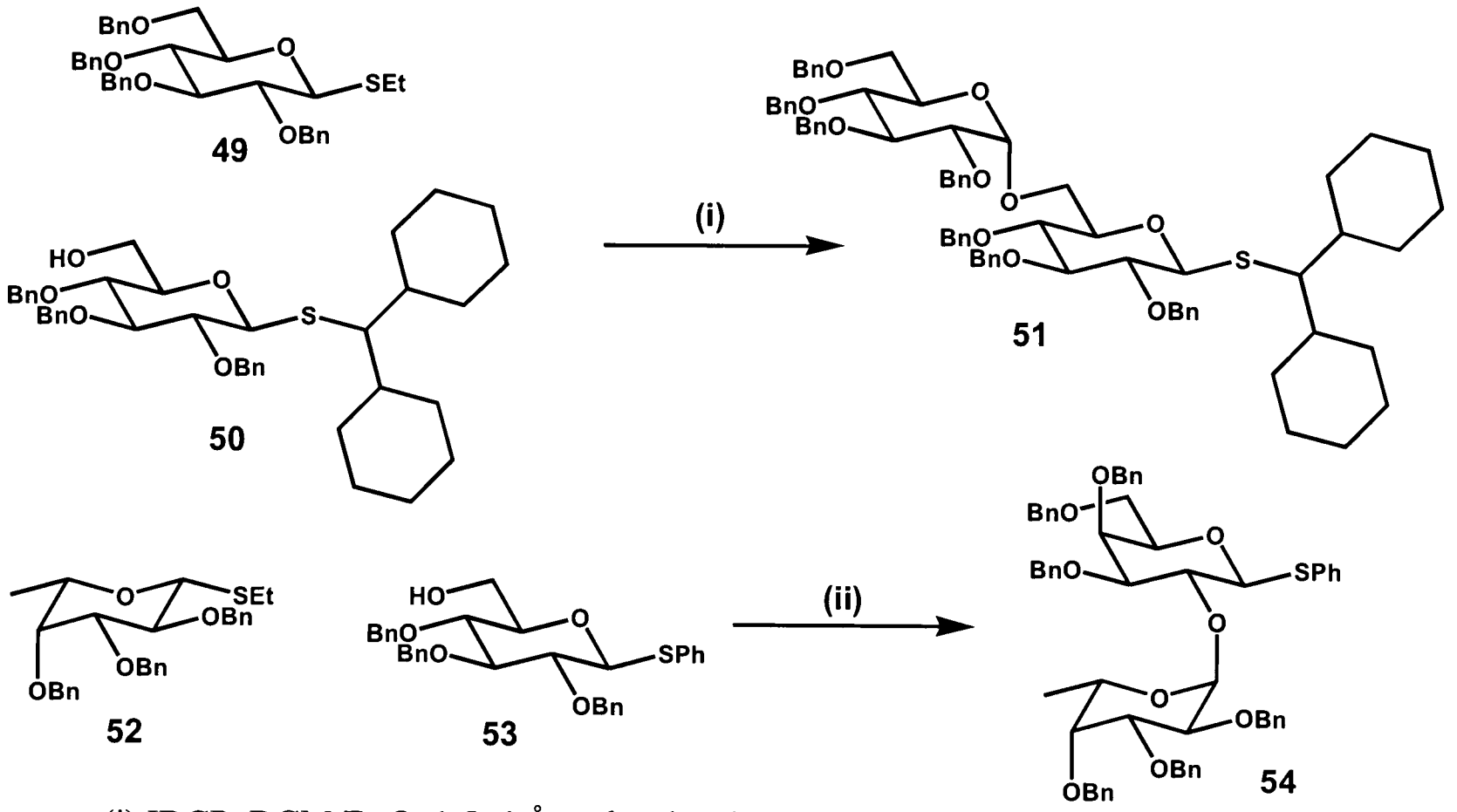
This selectivity is rationalised by considering the transition state for the reaction, in which a partial positive charge is generated at C-1. This change is destabilised by the presence of electron withdrawing groups, and consequently the activation of glycosides bearing such groups is sluggish in comparison to those bearing electron donating protecting groups. The picture is actually slightly more complex, as Fraser-Reid proposes that the activating agent can be transferred from the disarmed to the armed glycoside during the course of the reaction – further enhancing the selectivity.[85] After Fraser-Reid's work the general applicability of his findings to selective glycosylation was demonstrated in a number of systems, including thioglycosides,[91,92] selenoglycosides,[59] glycosyl fluorides[93] and glycals.[94,95] In addition the methodology has been expanded to demonstrate the deactivating effects of various cyclic protecting groups, in particular, 2,3- and 3,4-isopropylidene, 4,6-benzylidene, dispiroketal, cyclohexane-1,2-diacetal (CDA) and butane-3,4-diacetal (BDA).[96-101] A recent example of the use of cyclic protection in the chemoselective glycosylation of glycosyl fluorides is shown in scheme 1.10.[82]



(i) Cp_2HfCl_2, AgOTf, DCM, 4 Å molecular sieves, -10 °C, 85%

Scheme 1.10: Selective activation of a benzylated fluoride over a BDA protected fluoride

As has already been mentioned it is not only the alcohol protecting groups on a glycoside which can affect its ability to act as a glycosyl donor. The nature of the anomeric group can have just as much of an influence. For example ethyl thioglycosides can be activated in the presence of phenyl thioglycosides[81] or dicyclohexylmethyl thioglycosides[102] to give disaccharides in good yield (scheme 1.11).



(i) IDCP, DCM:Et_2O, 1:5, 4 Å molecular sieves, 75%; (ii) IDCP, DCM:Et_2O, 1:5, 4 Å molecular sieves, 70%.

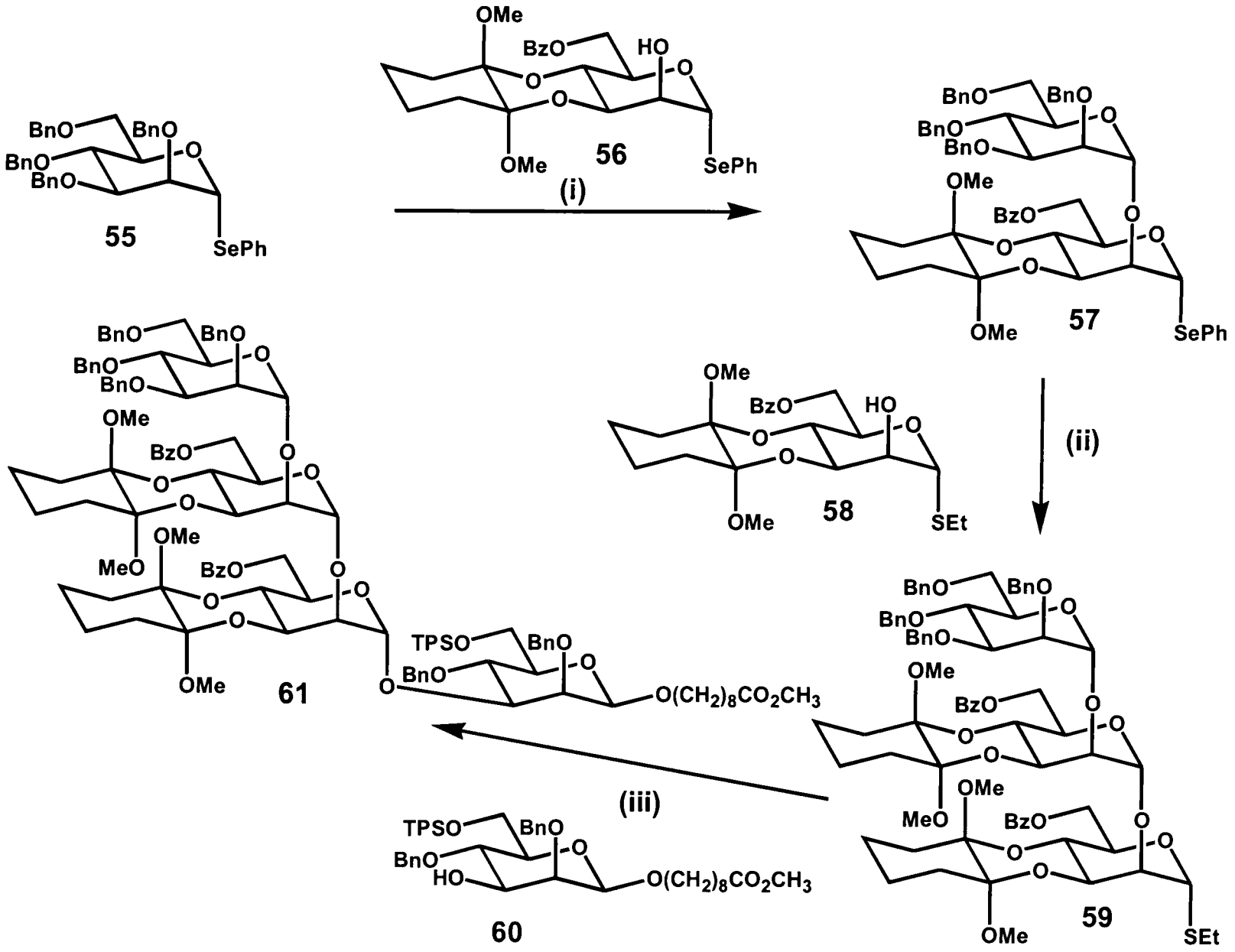
Scheme 1.11: An example of the effect of leaving group on reactivity

1.2.4 Reactivity Tuning

These selective glycosylation techniques have recently been taken a step further, with several research groups working to quantify the relative reactivity of various glycosyl donors. This enhanced understanding has since enabled the use of many more levels of selectivity in glycosylations. This concept is known as reactivity tuning, and was first elucidated by Ley and co-workers, who have also applied it in many elegant syntheses. An extremely detailed study was also conducted by Wong and co-workers, and again they have shown what a powerful tool this technique is in oligosaccharide synthesis. The work of these two groups is discussed in more detail below.

1.2.4.1 Studies by Ley and co-workers

Ley was the first to show that a detailed understanding of the concepts of selective activation could be used in the rapid assembly of complex oligosaccharides. It was in 1995 that he demonstrated the power of these techniques (scheme 1.12).[103] This synthesis uses the deactivating effect of cyclic protecting groups, and the reactivity difference between thio- and selenoglycosides, to generate a tetrasaccharide from preformed monosaccharide building blocks in three steps and an overall yield of 60%. In doing so four distinct levels of reactivity are exploited. Ley and co workers have gone on to apply this methodology to the synthesis of a number of large oligosaccharides.[104-107]



(i) NIS, TfOH, 10 min; (ii) NIS, TfOH, 3 h, (iii) Br_2, AgOTf, DCM 4 Å molecular sieves, 60%

Scheme 1.12: Ley's elegant tetrasaccharide synthesis by reactivity tuning

1.2.4.2 Studies by Wong and co-workers

Wong took this understanding of selective glycosylation a step further in 1999, using a series of competitive glycosylations and measuring the observed rate constants to quantify the relative reactivity of 50 monosaccharides.[108] These monosaccharides all bear an anomeric *S*-tolyl group, to aid the UV detection required in the HPLC analysis used, and the reactivity differences are all due to the variation in the structure and protecting group patterns of the monosaccharides. Some representative examples of the compounds analysed are shown below (figure 1.8).

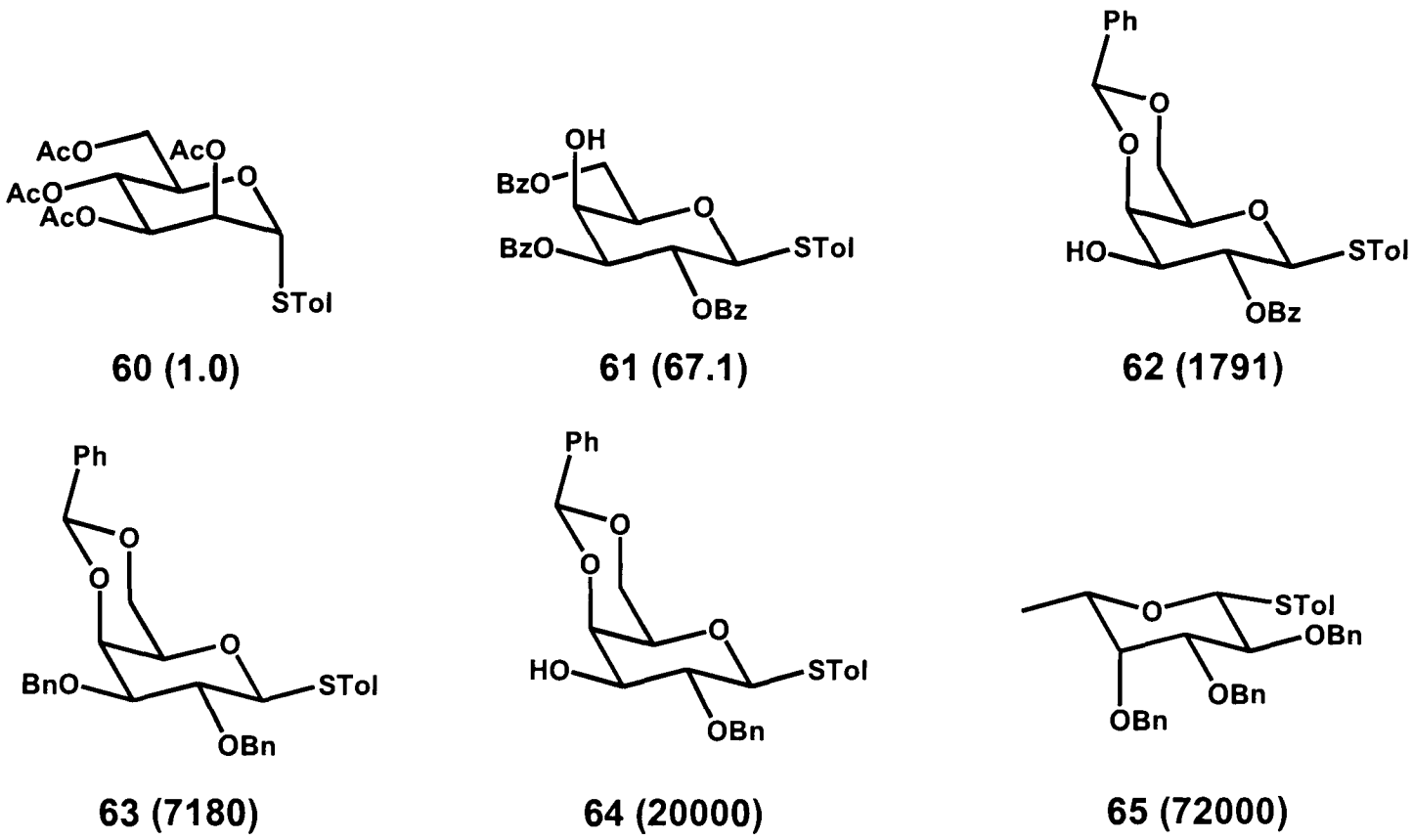
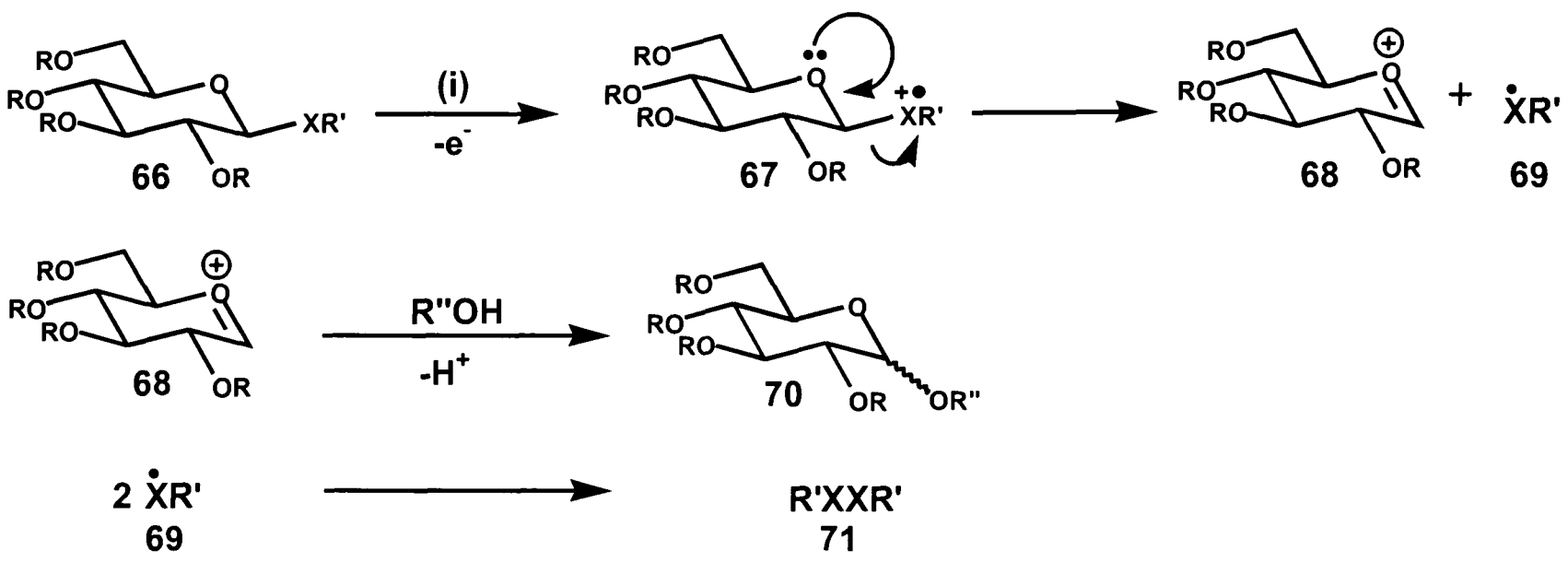


Figure 1.8: Some of Wong's 50 quantified glycosyl donors, with relative reactivity in brackets

Wong's results demonstrate the huge variation in reactivity available simply by varying protecting group patterns. The reactivities are all reported relative to the least active donor **60**. Wong has used this data to construct a computer programme, known as Optimer™, which can be used to predict which glycosyl donors are required to synthesise a given oligosaccharide. He has gone on to use this methodology to synthesise a number of biologically important oligosaccharides.[109,110] Since this original work Wong has expanded the number of glycosyl donors which he has analysed to 80, and it is interesting to note that he predicts that 300 will be required in order for the computer programme to be able to "cover the synthesis of most oligosaccharides".[110]

1.2.5 Electrochemical glycosylation

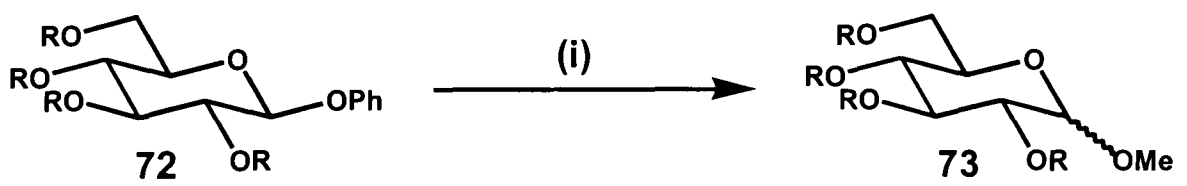
Electrochemical activation of glycosides is a relatively new area of glycosylation chemistry, and has received relatively little attention. The proposed mechanism for oxidative electrochemical glycosylation is outlined below (scheme 1.13).[111-113]



Scheme 1.13: Proposed mechanism for electrochemical activation of glycosides

A positive potential is applied to the glycoside **66**, sufficient for a one electron oxidation of the anomeric heteroatom to occur. With an appropriate leaving group the radical cation **67** formed can then under go a two electron process to form the glycosyl cation **68** and a neutral radical **69**. The glycosyl cation is then available for further reaction in exactly the same manner as in a chemical glycosylation. It is believed that the neutral radical goes on to form the dimer **71**.

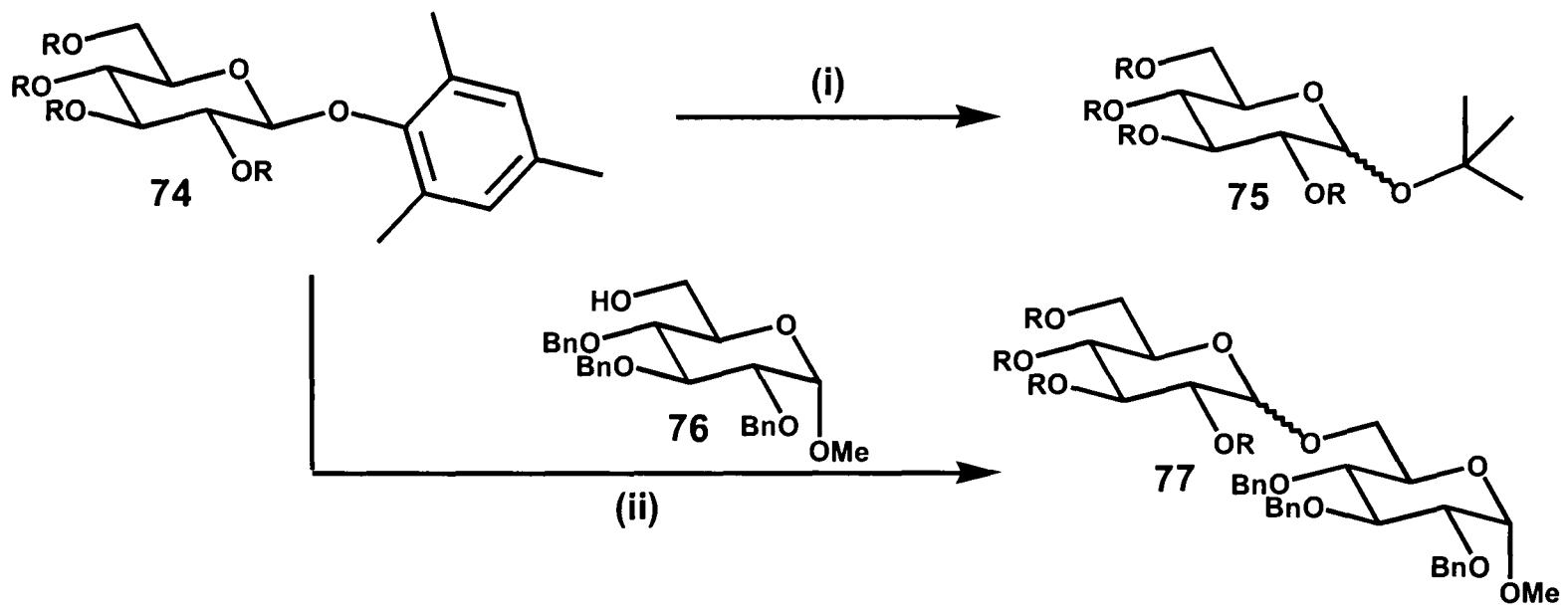
The original work in this area was reported by Noyori in 1996, when he showed that both protected and unprotected aryl *O*-glycosides could be activated by the application of a positive potential.[111] He observed that when a potential of +2.0 V was applied to unprotected, benzylated or acetylated and phenyl *O*-glycosides, in the presence of a range of simple alcohols, glycosylation products were obtained in good yields (scheme 1.14).



(i) MeOH, MeCN, $LiClO_4$, +2.0 V; R=Ac, 79%; R=Bn, 81%; R=OH, 77%

Scheme 1.14: Electrochemical activation of phenyl *O*-glycosides

In addition the equivalent 2,4,6-trimethylphenyl *O*-glycosides **73** could be successfully activated at 1.5 V and so formed glycosylation products in the presence of both simple alcohols and a monosaccharide acceptor (scheme 1.15).



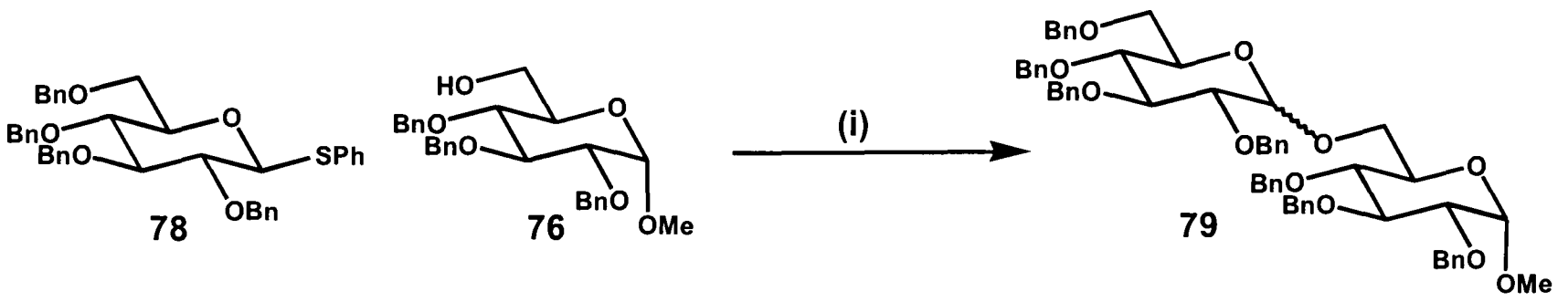
(i) $(CH_3)_3COH$, MeCN, $LiClO_4$, +1.5 V; R=Bn, 90%; R=OH, 59%;

(ii) MeCN, $LiClO_4$, +1.5 V 68%

Scheme 1.15: Electrochemical activation of 2,4,6-trimethylphenyl *O*-glycosides

These reactions were all conducted in an undivided cell using platinum as both counter and working electrodes, and silver/silver chloride as the reference electrode.

In 1990 Amatore and Sinaÿ applied this methodology to the activation of phenyl thioglycosides.[112] Their initial work, and the majority of subsequent work, was carried out at a constant current in both divided and undivided cells.[114] However they also demonstrated the activation of phenyl thioglycoside **78** at a constant potential of +1.7 V (scheme 1.16).[115]



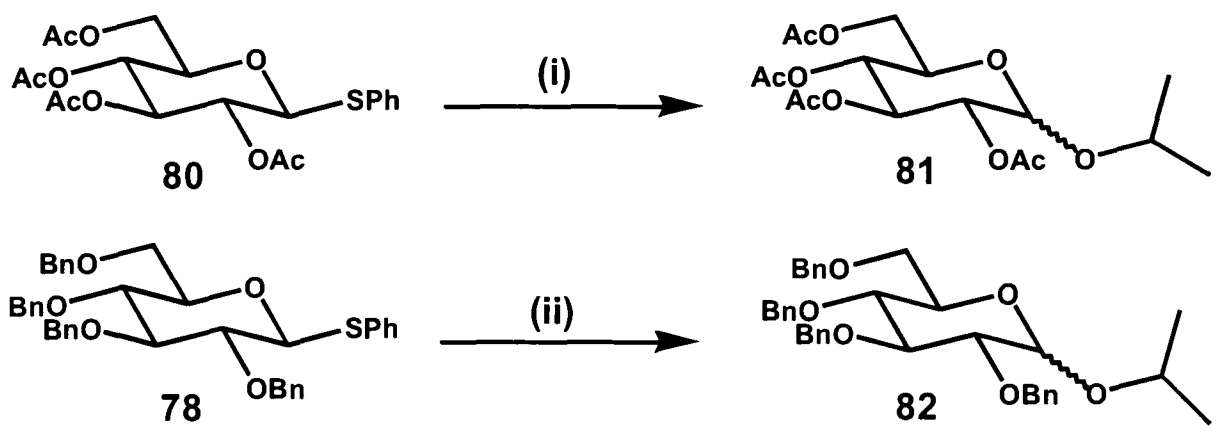
In a divided cell at constant current: (i) Bu_4NBF_4, K_2CO_3, MeCN, 50 mA, 63%

In an undivided cell at constant current: (i) $LiBF_4$, MeCN, molecular sieves, 100mA, 52%

In an undivided cell at constant potential: (i) $LiBF_4$, MeCN, molecular sieves, +1.7 V, 52%

Scheme 1.16: Amatore and Sinaÿ's electrochemical activation of *S*-glycosides

The work in a divided cell was carried out using a carbon working electrode, platinum counter electrode and standard calomel reference electrode. For their work in an undivided cell the platinum counter electrode was replaced with a nickel gauze electrode. At approximately the same time Balavoine *et al.* published some similar work – this time activating a variety of thioglycosides and two selenoglycosides at constant potentials ranging from +1.0 V to +1.7 V, depending on the nature of the glycoside (scheme 1.17).[113,116]

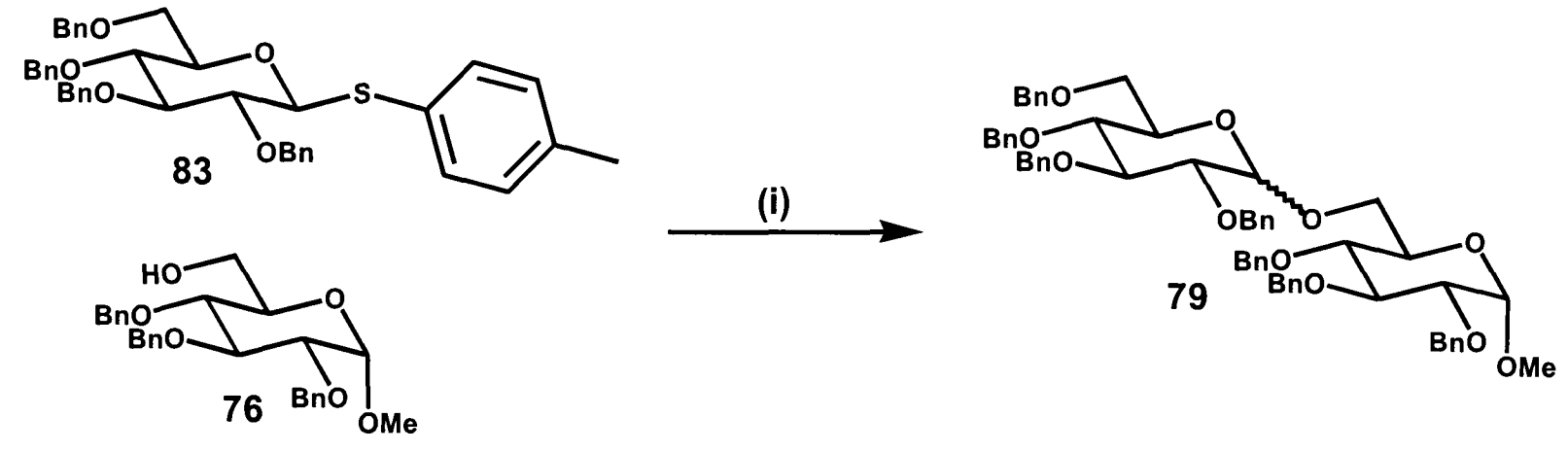


(i) $^{i}PrOH$, $LiBF_4$, MeCN, 3 Å molecular sieves, 1.67 V, 33%;

(ii) $^{i}PrOH$, $LiBF_4$, MeCN, 3 Å molecular sieves, 1.50 V, 97%

Scheme 1.17: Balavoine's electrochemical activation of *S*-glycosides

Balavoine went on to demonstrate that the methodology could be applied to the formation of a disaccharide (scheme 1.18).[117]

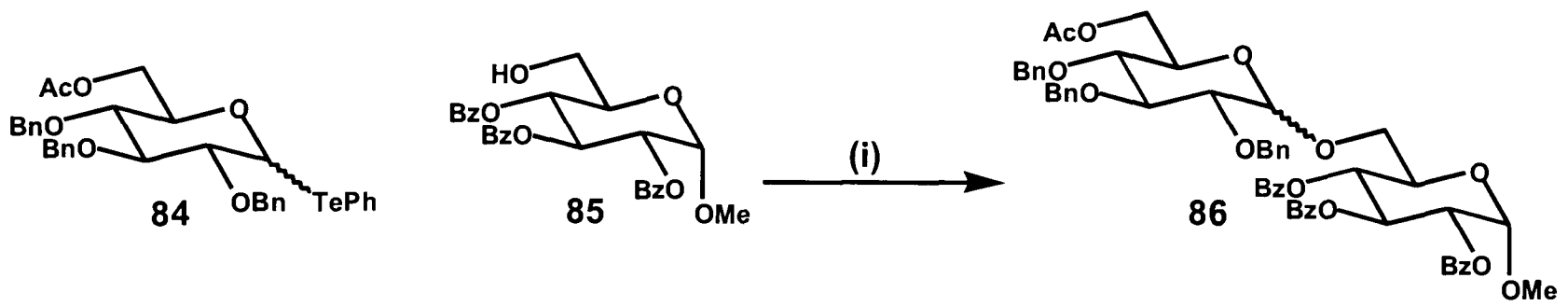


(i) $LiBF_4$, MeCN, +1.45 V 92%

Scheme 1.18: Balavoine's electrochemical disaccharide synthesis

Balavoine worked mainly with a carbon working electrode, platinum counter electrode and standard calomel reference electrode, in an undivided cell.

Most recently Yamago showed that the methodology could be applied to telluroglycosides, which underwent a glycosylation reaction at a potential of 1.1 V (scheme 1.19).[118]



(i) $LiClO_4$, MeCN, 1.1 V, 63%

Scheme 1.19 : Yamago's electrochemical activation of telluroglycosides

Reactions were carried out in a divided cell, using a carbon working electrode, platinum counter electrode and silver/silver chloride reference electrode.

1.3 Proposed research

The work on electrochemical glycosylation reported in the literature clearly demonstrates that the potential required to oxidise, and therefore activate, electrochemically active glycosyl donors varies significantly with the nature of the glycosyl donor. A number of factors can be seen to be involved, including protecting group pattern, anomeric group and monosaccharide structure. It therefore seemed that the concepts of selective activation, which have been studied in detail in relation to chemical activation (*vide supra*), might be applied to electrochemical activation. This use of a positive applied potential, instead of a traditional activating agent, would seem to have a number of advantages. The strength of the activating agent (i.e. the applied potential) can be altered on a continuous scale, offering the possibility of many levels of activation. The lack of a chemical activator removes what is often a potentially harmful reagent, and simplifies purification. Control of an applied potential is also something easily amenable to automation, one of the major goals in oligosaccharide synthesis.

This project concerns the synthesis of a range of monosaccharide donors amenable to electrochemical synthesis, the analysis of their electrochemical properties using cyclic voltammetry and finally investigations into their use in selective glycosylation reactions. Each chapter deals with one of these subjects in turn.

During the course of these studies an interesting paper applying these concepts to the activation of telluroglycosides was published by Yamago *et al*, and their results complement those presented here.[119]

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Chapter 2

Synthesis of Potentially Electrochemically Active Monosaccharides

2.1 Aims

The aim of the work described in this chapter was to synthesise a number of electrochemically active glycosides, in order to probe the range of oxidation potentials available for use in selective electrochemical glycosylations.

2.2 Scope of the study

It was necessary to limit the scope of the investigation, as the number of such compounds is large. It was decided to focus mainly on glucosides, as these compounds have been well studied under chemical activation conditions,[1,2] and in addition to synthesise a few mannosides for comparison. Within this class of compounds it was the effect of the protecting group pattern and the anomeric substituent which were chosen as the focus for the investigation, as these had been shown by Noyori,[3] Sinaÿ and Amatore,[4-6] Balavoine[7-9] and Yamago[10,11] to have a large impact in the oxidation potentials of various monosaccharides (*vida supra*).

It was therefore envisaged that compounds of the following type would be synthesised, in a systematic manner (figure 2.1)

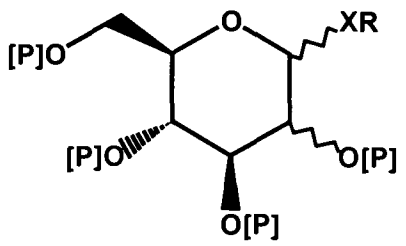


Figure 2.1: A general monosaccharide. [P] is a general protecting group, X is the anomeric heteroatom and R a general alkyl or aryl group.

The precise choice of protecting group patterns and anomeric substituents, and the underlying reasons, are discussed below.

2.2.1 Choice of Protecting Group Pattern

2.2.1.1 The armed/disarmed effect

The chief effect on oxidation potential anticipated from the protecting groups is that derived from their electron donating, or electron withdrawing natures. In the same way that this has been shown to give armed or disarmed glycosides under chemical activation conditions[12-14] this effect is also expected for electrochemical activation of a glycosyl donor. In order to investigate this effect it was decided that potential glycosyl donors bearing global benzyl protection (electron donating), global benzoyl and global acetyl protection (both electron withdrawing) would be synthesised. The benzoyl compounds also have the advantage that they are less susceptible to migration or orthoester formation, both possible complications in the synthetic work.

2.2.1.2 Constraints on the transition state – ring locking

It has been shown that protecting groups which cause torsional strain in the transition state of a glycosylation, tend to be deactivating in classical chemical glycosylation reactions.[15,16] In order to investigate whether this effect applies to electrochemical activation it was decided that a compound with the ring locking benzylidene group between the *O*-4 and *O*-6 positions would be synthesised.

2.2.2 The anomeric substituent

2.2.2.2 Heteroatom

The nature of the heteroatom has been shown to have a large effect the oxidation potential of electrochemically active glycosyl donors.[1,3] In order to probe this effect it was decided that compounds with either selenium, sulphur or oxygen at this position would be synthesised.

2.2.2.2 The R group

Variation of the group attached to the heteroatom has the potential to influence the oxidation potential of a glycosyl donor. In order to allow for controlled variation in the electronic effects of this group it was decided that compounds bearing a phenyl group, substituted at the para position with either electron withdrawing (NO_2), electron donating (OMe, Me), or unsubstituted, would be synthesised. In addition some methyl thioglycosides would be synthesised for comparison with the aromatic donors.

2.3 Summary

The combination of these factors gave a range of potential glycosyl donors as targets for the synthetic work, and these are shown below (figure 2.2)

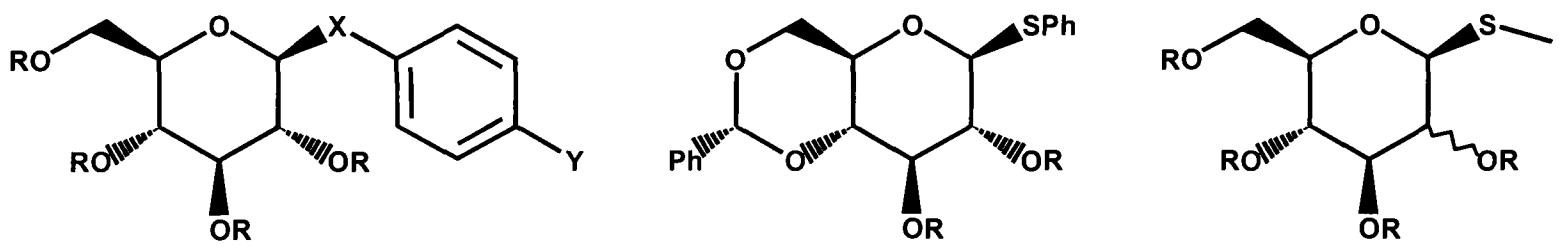


Figure 2.2: Target glycosyl donors

R=Bn, Bz or Ac; X=Se, S or O and Y=OMe, Me, H or NO_2

In addition the synthesis of a number of compounds with the potential to act as both glycosyl acceptor and as glycosyl donor were synthesised for use in the selective activation studies (figure 2.3). The syntheses are discussed here for convenience, however the choice of these compounds was only made after the electrochemical analysis, discussed in chapter 3.

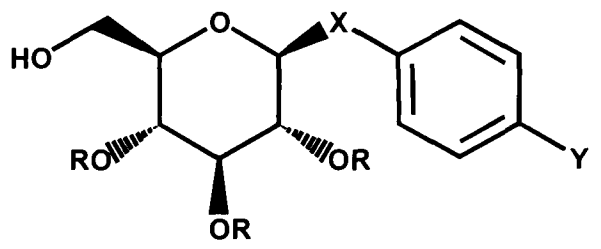


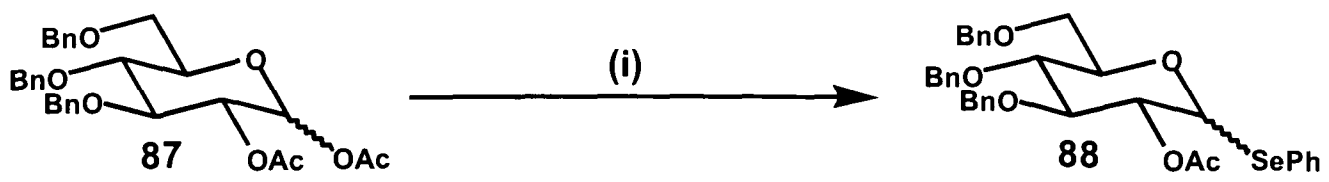
Figure 2.3: Target glycosyl donor/acceptors; R=Bn or Bz, X=S or O, Y= H or Me

The synthesis of the glycosyl donors is reported first, organised by heteroatom as it is the nature of this part of the donor which governs the synthetic route. The synthesis of the glycosyl donor/acceptors then follows.

2.3 Selenoglycosides

2.3.1 Introduction to selenoglycoside synthesis

The use of selenium in carbohydrate chemistry dates as far back as 1917 with the synthesis of selenoisotrehalose.[17] However it was not until 1991 that selenoglycosides were first used as glycosyl donors.[18] This led to increased interest in their synthesis and a range of methods are now available for their synthesis. One of the most common techniques is to react a glycoside containing an ester group (usually acetate) at the anomeric position directly with selenophenol in the presence of a Lewis acid (usually boron trifluoride diethyl etherate) to give a phenyl selenoglycoside (scheme 2.1), in an analogous manner to that frequently used for the synthesis of thioglycosides (*vide infra*).

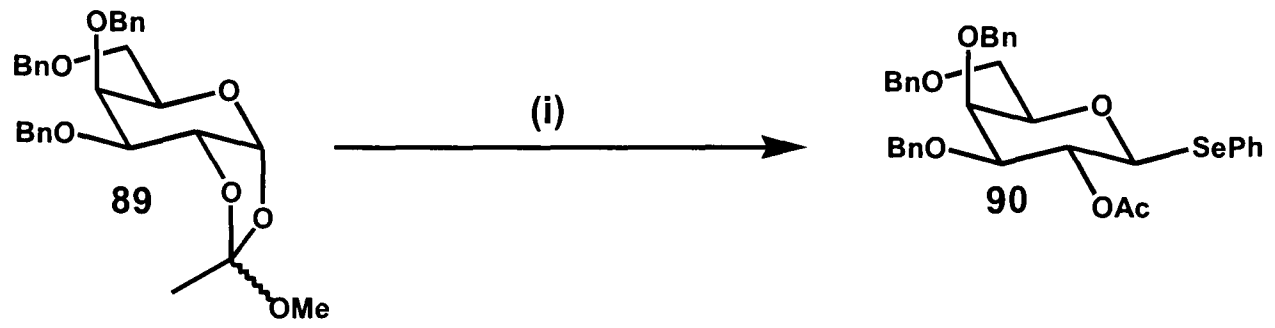


(i) PhSeH, $BF_3.Et_2O$, DCM

Scheme 2.1: Stork's Lewis acid catalysed phenyl selenoglycoside formation

Alternatively phenyltrimethylsilyl selenide in the presence of a catalytic amount of trimethylsilyl triflate has been shown to give the phenyl selenoglycoside when reacted with glucose pentaacetate over two days.[19]

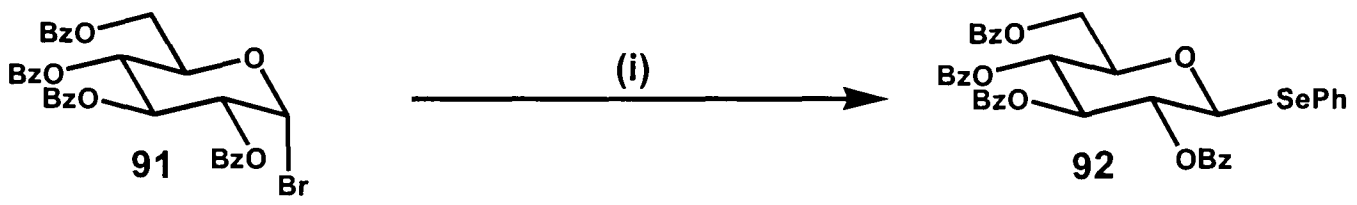
More recently Sinaÿ showed that the reaction of an orthoester with selenophenol in the presence of mercury (II) bromide as a Lewis acid catalyst gave the corresponding selenoglycoside (scheme 2.2).[20]



(i) PhSeH, $HgBr_2$, MeCN, 50 °C

Scheme 2.2: Sinaÿ's Lewis acid catalysed opening of an orthoester

Another common route to phenyl selenoglycosides is the generation of the selenophenyl anion followed by displacement of an anomeric halide. The selenophenyl anion can be generated either directly from selenophenol by the addition of a base such as potassium hydroxide[21] or by in situ reduction of diphenyldiselenide (scheme 2.3).[20,22,23] This reductive methodology has the advantage that it circumvents the need to handle the toxic and malodorous selenophenol directly (salts of selenophenol are not commercially available) and the glycosyl halide can be added directly to the reaction vessel after reduction of the diselenide.



(i) PhSeSePh, $NaBH_4$, EtOH

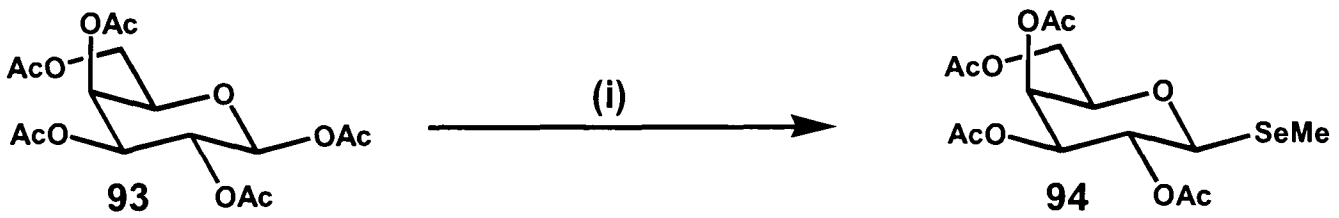
Scheme 2.3: Stick's phenyl selenoglycoside synthesis

Pinto utilised a similar methodology,[24] employing the reduction of diphenyldiselenide with hypophosphorus acid, followed by reaction of selenophenol which is generated with a peracetylated sugar in the presence of a Lewis acid (boron trifluoride diethyl etherate). However this methodology lacks the simplicity of the above diphenyldiselenide reductions, requiring manipulation of the selenide containing solution before addition of the glycoside.

Other methods of selenoglycoside synthesis include the use of selenostannanes in the presence of catalytic $Bu_2Sn(OTf)_2$ and also the opening by selenophenol of the epoxide of the Brigl anhydride. However these methods are less frequently employed.[25,26]

2.3.2 Synthesis of selenoglycosides

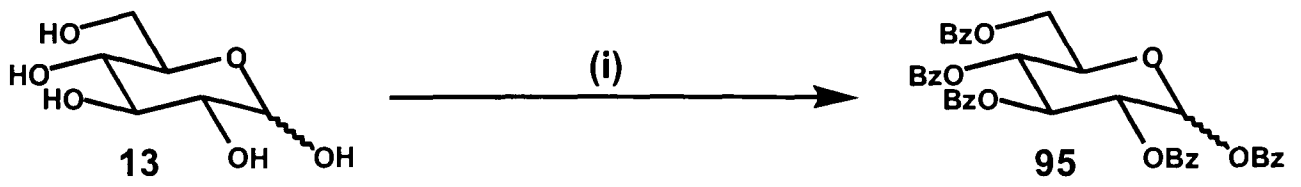
The reductive methodology of Stick *et al* seemed the most attractive. However it was envisaged that the selenoglycosides might be synthesised in one step from the peracylated glycoside by generating the glycosyl halide *in situ*, as Field has done for the formation of thioglycosides.[27] In this work, disulphides are reacted in the presence of hexamethyldisilane and iodine with peracetylated glycosides to give the corresponding β-thioglycoside directly (scheme 2.4).



(i) MeSSMe, HMDS, I_2, DCM

Scheme 2.4: Field's Iodine catalysed thioglycoside synthesis

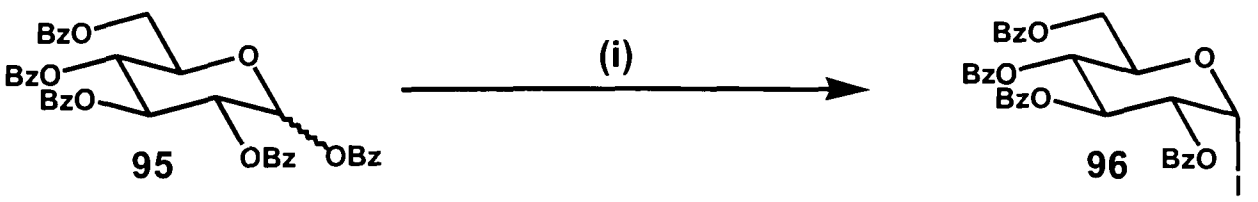
Thus reaction of glucose **13** with benzoyl chloride in pyridine gave pentabenzoyl glucose **95** in 91% yield (scheme 2.5). For a large scale reaction it was necessary to cool the reaction vessel and add the benzoyl chloride portionwise with care as the reaction was highly exothermic.



(i) BzCl, pyridine, 20 h, 91%

Scheme 2.5

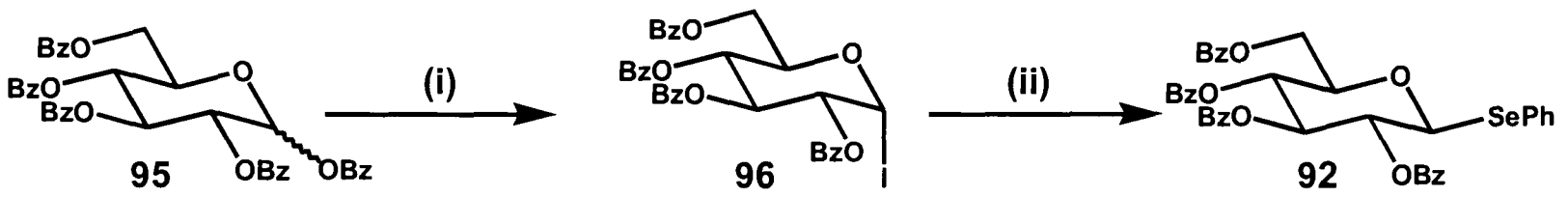
Reaction of the benzoylated compound **95** under Field's conditions,[27] using diphenyl diselenide instead of dimethyl disulphide, did not give the desired product. Instead it was only possible to isolate the α-glucosyl iodide **96** as a surprisingly stable white crystalline solid (scheme 2.6). The compound, which was fully characterised, can be easily recognised by the extremely high chemical shift of the H-1 proton (δ 6.99 ppm, $J_{1,2}$ 3.9 Hz).



(i) PhSeSePh, HMDS, I_2, DCM

Scheme 2.6

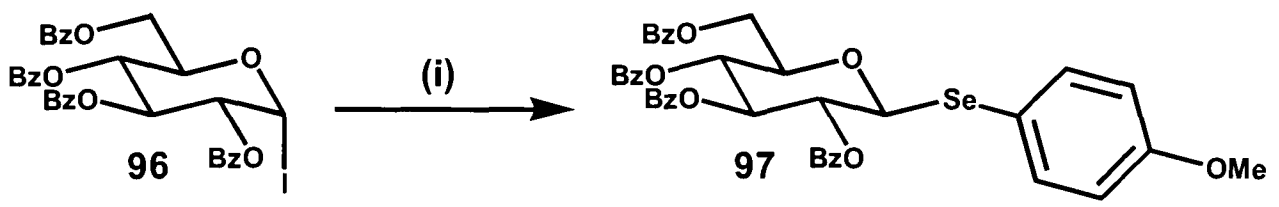
It was therefore decided to turn to the methodology employed by Stick, of reacting a glycosyl halide with the sodium salt of the diselenide, prepared *in situ* by reduction of the diselenide with sodium borohydride.[23] As the efficiency of the reaction had already been demonstrated, the iodide was synthesised using Field's conditions, simply omitting the disulphide. The glucosyl iodide **96** was isolated in 89% yield and application of Stick's procedure furnished the phenyl selenoglycoside **92** in 79% yield (scheme 2.7).



(i) HMDS, I_2, DCM, 89%; (ii) $PhSeSePh$, $NaBH_4$, EtOH, 79%

Scheme 2.7

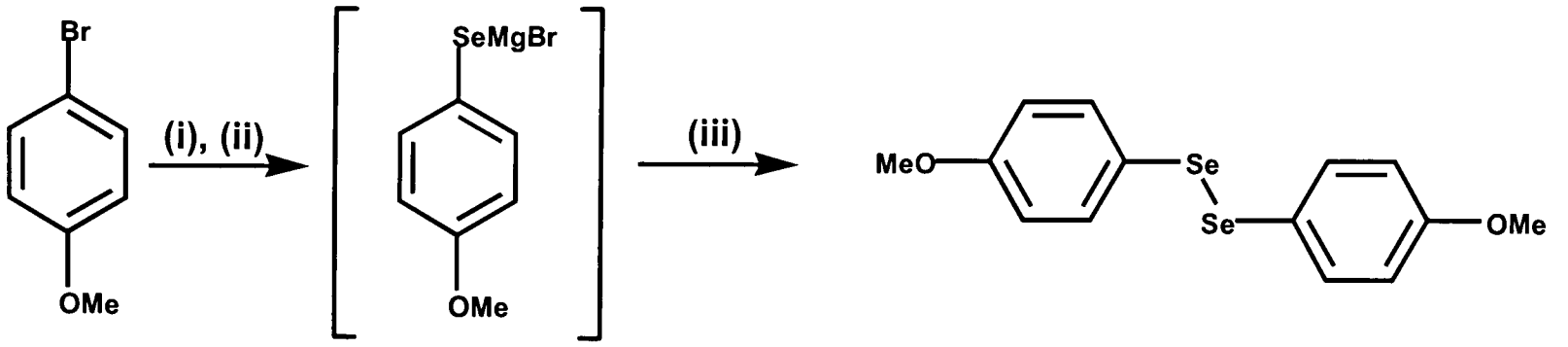
This methodology was then repeated to generate the *p*-methoxyphenyl selenoglucoside **97**, in a yield of 98% (scheme 2.8).



(i) HMDS, I_2, DCM, $MeO(C_6H_4)SeSe(C_6H_4)OMe$, 98%

Scheme 2.8

The *p*-methoxydiphenyl diselenide is not itself commercially available and instead was synthesised according to the procedure of Detty and Murray (scheme 2.9).[28] Recrystallization from cyclohexane gave a yellow crystalline solid which could be stored and used as required.

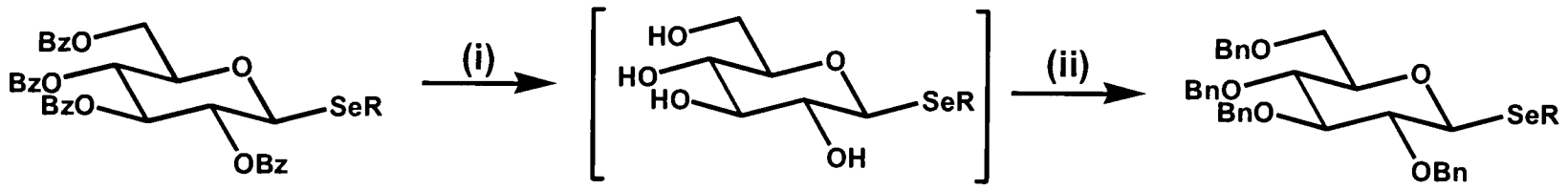


98 **99** **100**

(i) Mg, I_2, Et_2O; (ii) Se (powder); (iii) KOH, air 11% over three steps

Scheme 2.9

Deprotection of both benzoyl selenoglycosides **92** and **97** under Zemplén conditions of sodium in methanol, followed by reprotection using sodium hydride and benzyl bromide in dimethylformamide,[29] gave the fully benzylated compounds **103** and **104** in 89% and 69% yields respectively (scheme 2.10).



92 R=Ph
97 R=PhOMe

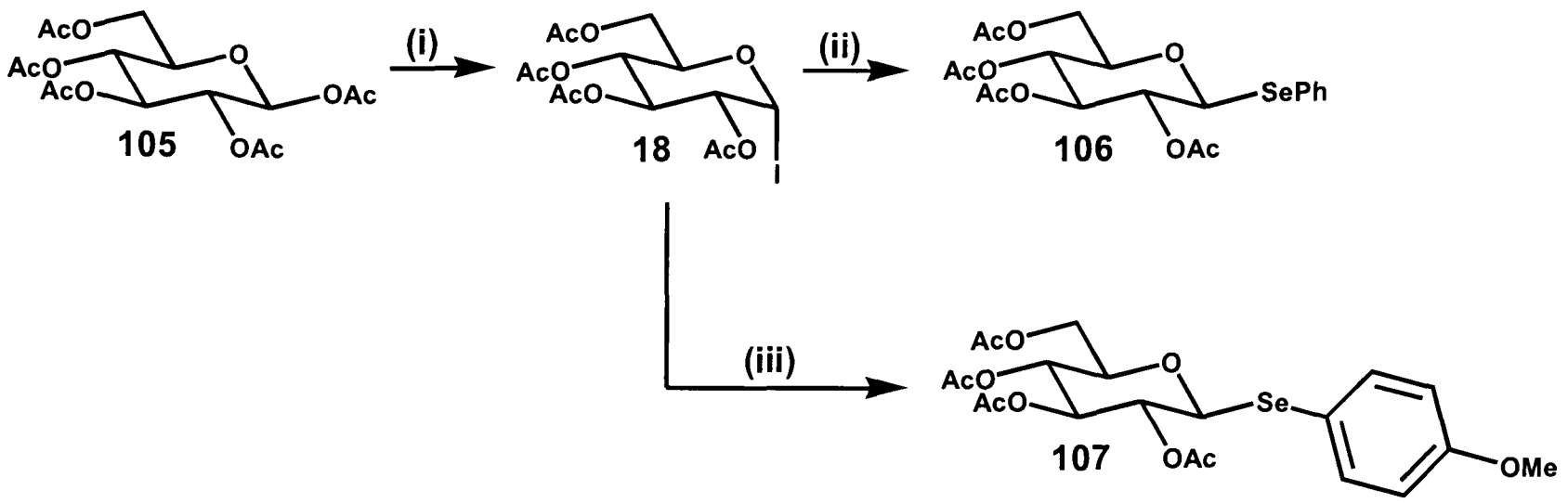
101 R=Ph
102 R=PhOMe

103 R=Ph
104 R=PhOMe

(i) NaOMe, MeOH; (ii) BnBr, NaH, DMF; R=Ph, 89%; R=PhOMe, 69%

Scheme 2.10

The analogous acetyl glucosides **106** and **107** were synthesised from the acetylated glucosyl iodide **18** following the same methodology (scheme 2.11). The lower yields are presumably due to some loss of the acetate protecting groups, removed either *via* attack by the selenium anion generated during the course of the reaction or during the work-up.



(i) HMDS, I_2, DCM, 86%; (ii) PhSeSePh, $NaBH_4$, EtOH, 45%;

(iii) $MeO(C_6H_4)SeSe(C_6H_4)OMe$, $NaBH_4$, EtOH, $CHCl_3$ 59%.

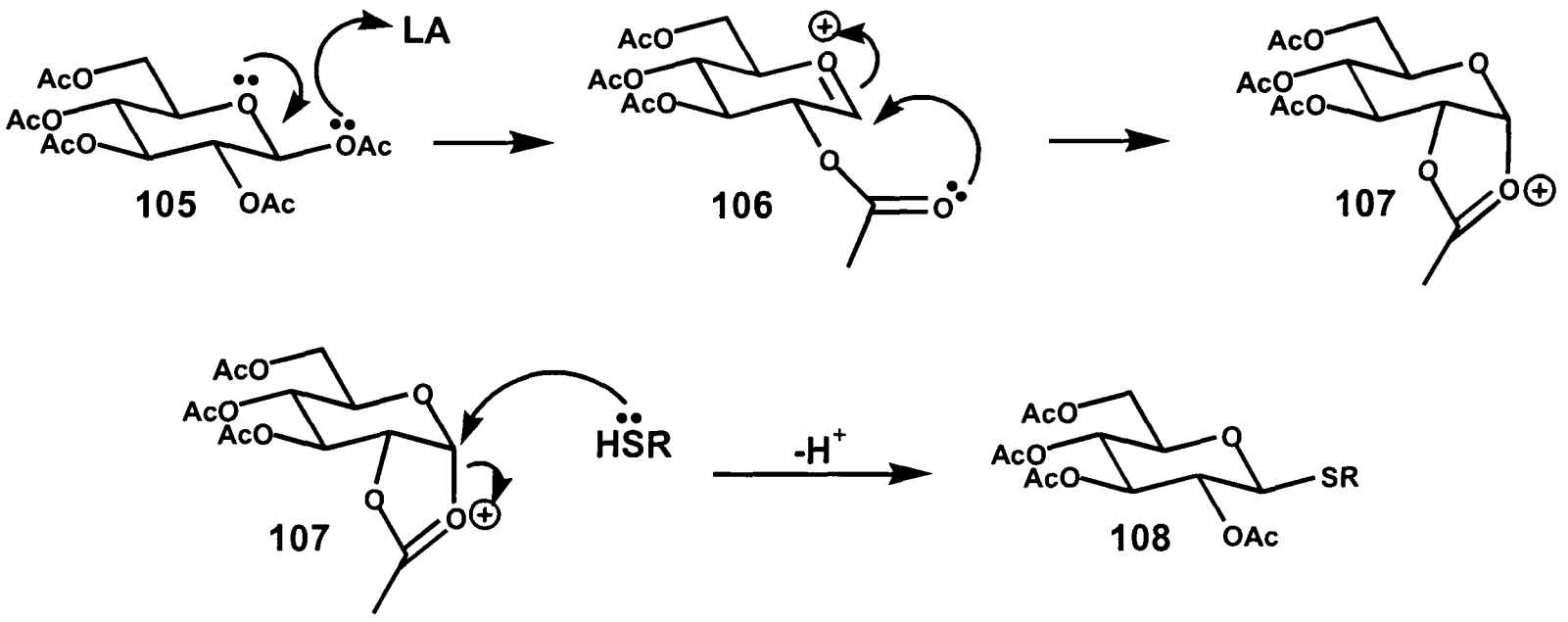
Scheme 2.11

2.4 Thioglycosides

2.4.1 Introduction to thioglycoside synthesis

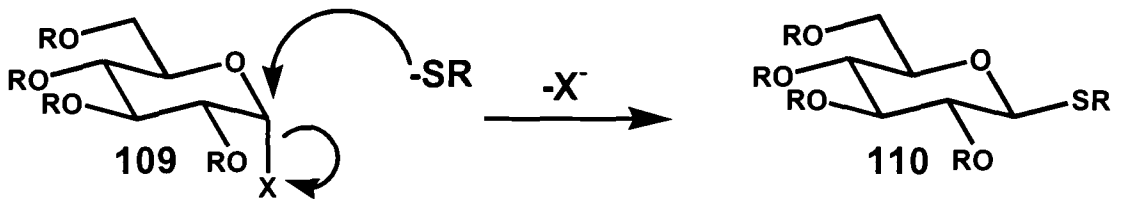
In this more established area of glycoside synthesis a wide choice of proven techniques were available. Most often an aryl thioglycoside is synthesised by a Lewis acid catalysed reaction with a peracetylated glycoside (scheme 2.12), or a glycosyl halide is reacted with the anion of an aryl thiol (scheme 2.13).

The Lewis acid catalysed route proceeds through an oxonium ion intermediate and so the stereochemistry can be controlled by the use of a participating group at C-2. In the glucosides (as shown) this favours the formation of the β-glycosides. Examples in the literature include a wide range of Lewis acids, commonly used examples are $SnCl_4$,[30-32] $ZnCl_2$,[33,34] $ZrCl_4$,[35] $FeCl_3$[36] and $BF_3.OEt_2$[37]. The efficiency and selectivity varies depending on the specific system and reaction conditions. Boron trifluoride diethyl etherate is one of the Lewis acids most often seen is use today.[38-41]



Scheme 2.12: General scheme for the Lewis acid catalysed formation of a thioglucoside

The glycosyl halide route (scheme 2.13), first used by Fischer[42] and modified by a number of others,[43-45] also continues to find much use.[46-48] This method again tends to give good β-selectivity, proceeding formally as shown above through an S_N2 type mechanism (the gluco case is shown as an example) – although it is likely that there is some assistance from the ring oxygen. This technique is less successful where R is a more basic thioalkyl anion, which can remove the acetate protecting groups.

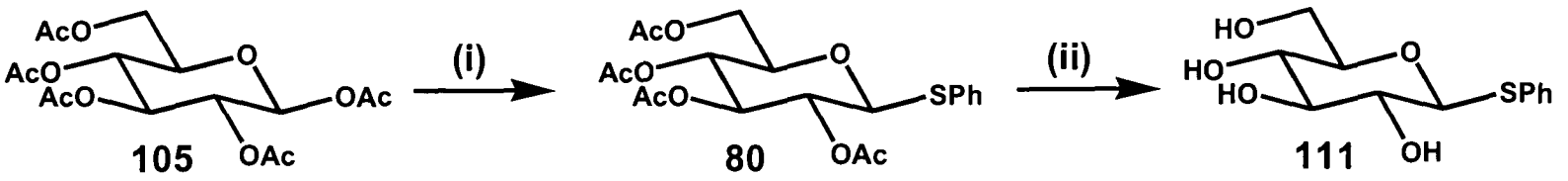


Scheme 2.13: General scheme for the formation of a thioglucoside from a glucosyl halide

These two routes, or modifications of them, provide simple access to a wide range of thio glucosides and mannosides. The choice of which route to use for any given target compound was determined principally by the availability and cost of starting materials, as well as the practical knowledge within the group, in order to synthesise the desired thioglycosides as efficiently as possible.

2.4.2 Synthesis of thioglycoside donors *via* Lewis acid catalysis

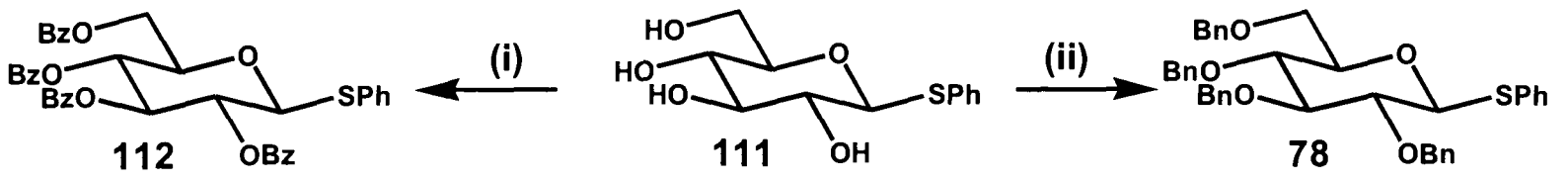
Introduction of the thiophenyl anomeric group was achieved by the reaction of commercially available pentaacetylglucose **105** with thiophenol mediated by boron trifluoride diethyl etherate in dichlormethane.[41] This gave the β-thioglycoside **80** exclusively, as expected, which was then deprotected under Zemplén conditions to give key intermediate **111** (scheme 2.14).



(i) BF_3. OEt_2, PhSH, DCM, 18 h, 78%; (ii) NaOMe, MeOH, 2 h, 99%

Scheme 2.14

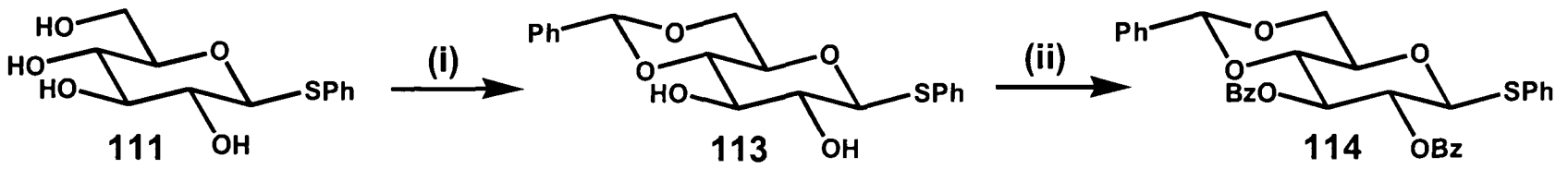
The fully deprotected thioglycoside **111** was then used to generate a range of fully protected thioglycosides, with contrasting electronic properties. Global benzylation of the tetrol using sodium hydride and benzyl bromide in dimethylformamide[29] gave benzyl glycoside **78** in 92% yield; whilst benzoylation of the tetrol using benzoyl chloride in pyridine[5] gave the benzoyl thioglycoside **112** in 96% yield (scheme 2.15).



(i) BzCl, pyridine, 18 h, 96%; (ii) BnBr, NaH, DMF, 18 h, 92%.

Scheme 2.15

A potentially torsionally deactivated thioglycoside **114** was generated by introduction of the benzylidene group over positions *O*-4 and *O*-6, and protection of the remaining free hydroxyls with electron withdrawing benzoyl groups (scheme 2.16).

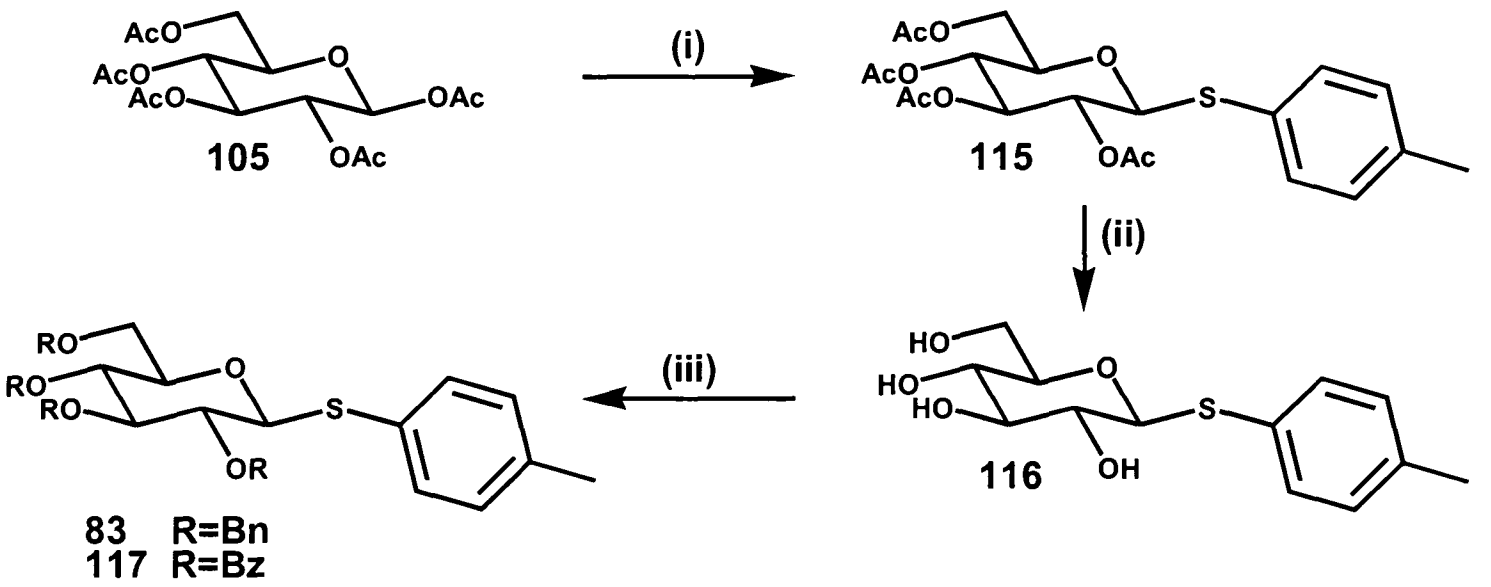


(i) $PhCH(OCH_3)_2$, CSA, DMF, 260 mbar, 60 °C, 2 h, 68%; (ii) BzCl, pyridine, 16 h, 94%.

Scheme 2.16

Benzylidenation was accomplished using benzaldehyde dimethyl acetal and catalytic camphor-10-sulphonic acid in dimethylformamide.[49] The reaction was conducted at 260 mbar and 60 °C using a rotory evaporator to remove the methanol generated during the reaction, thus driving the equilibrium in favour of the products. Benzoyl protection was once again straightforward, using the same procedure as before, to give thioglycoside **114** in 94%.

Following the same methodology a number of other thioglycoside donors were synthesised, with varying substituents on the aromatic ring of the anomeric group.

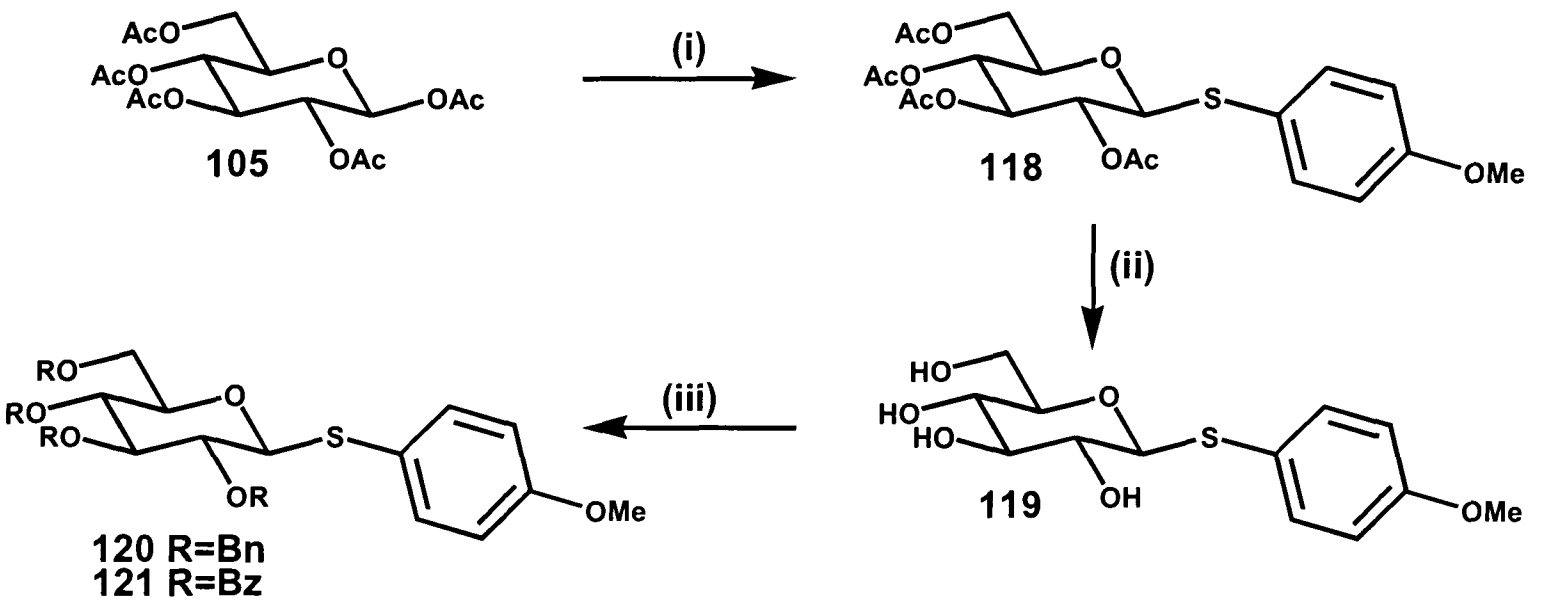


(i) *p*-thiocresol, $BF_3.OEt_2$, DCM, 16 h, 81%; (ii) NaOMe, MeOH, 1 h, 87%;

(iii) R=Bn: BnBr, NaH, DMF, 3 days, 82%; R=Bz: BzCl, pyridine, 18 h, 88%

Scheme 2.17

Thus pentaacetate **105** was reacted with thiocresol in the presence of boron trifluoride diethyl etherate to give thioglycoside **115** in 81% yield. Removal of the acetyl groups by Zemplén deacetylation afforded tetrol **116** in a yield of 87%. Protection either with benzyl bromide and sodium hydride or benzoyl chloride in pyridine gave the fully protected glycosyl donors **83** and **117** in 82% and 88% yields respectively (scheme 2.17).

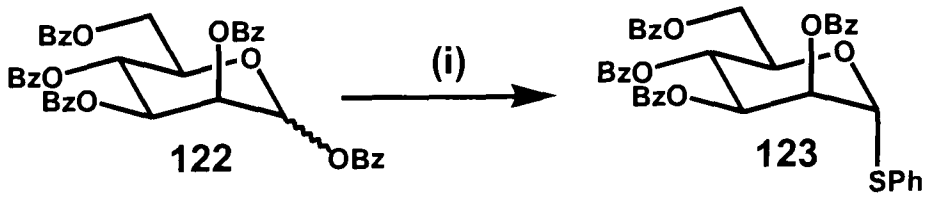


(i) *p*-methoxythiophenol, $BF_3.OEt_2$, DCM, 4 h, 91%; (ii) NaOMe, MeOH, 30 min, 83%;
(iii) R=Bn: BnBr, NaH, DMF, 16 h, 69%; R=Bz: BzCl, pyridine, 17 h, 65%

Scheme 2.18

Pentaacetate **105** was reacted with *p*-methoxythiophenol in the presence of boron trifluoride diethyl etherate to give *p*-methoxyphenyl thioglycoside **118** in 91% yield. Removal of the acetyl groups by Zemplén deacetylation then yielded tetrol **119** in a yield of 83%. Protection either with benzyl bromide and sodium hydride or benzoyl chloride in pyridine gave the fully protected glycosyl donors **120** and **121** in 69% and 65% yields respectively (scheme 2.18).

A similar procedure, this time using tin (IV) chloride,[50] was used to obtain phenyl thiomannoside **123** in a yield of 51% (scheme 2.19).

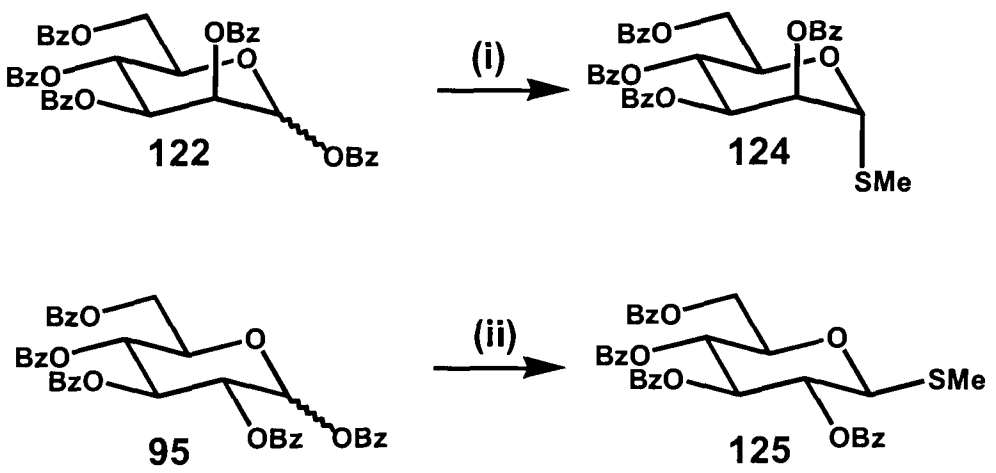


(i) $SnCl_4$, PhSH, DCM, 51% (vi) NaOMe, MeOH

Scheme 2.19

2.4.3 Synthesis of thioglycoside donors *via* glycosyl halides

The most straight forward version of this method for the synthesis of thioglycosides is that developed by Field,[27] discussed above, where it was unsuccessfully applied to the synthesis of selenoglycosides. However this methodology was developed for methyl thioglycosides, and so it was used here in the synthesis of both *gluco* and *manno* derivatives, using dimethyl disulphide. While this reagent is both highly toxic and malodorous it is preferable to the use of methyl sulphide (scheme 2.20).

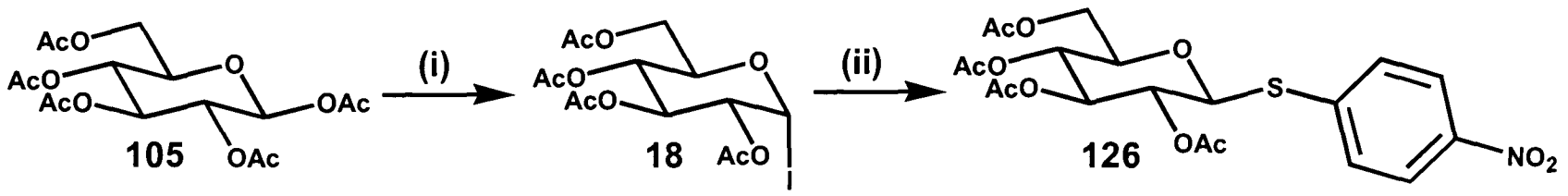


(i) HMDS, MeSSMe, I_2, DCM, 60%; (ii) HMDS, MeSSMe, I_2, DCM, 74%

Scheme 2.20

An attempt was made to apply the same methodology to the synthesis of *p*-nitrophenyl thioglycosides. However as with the selenoglycosides discussed above it was only possible to

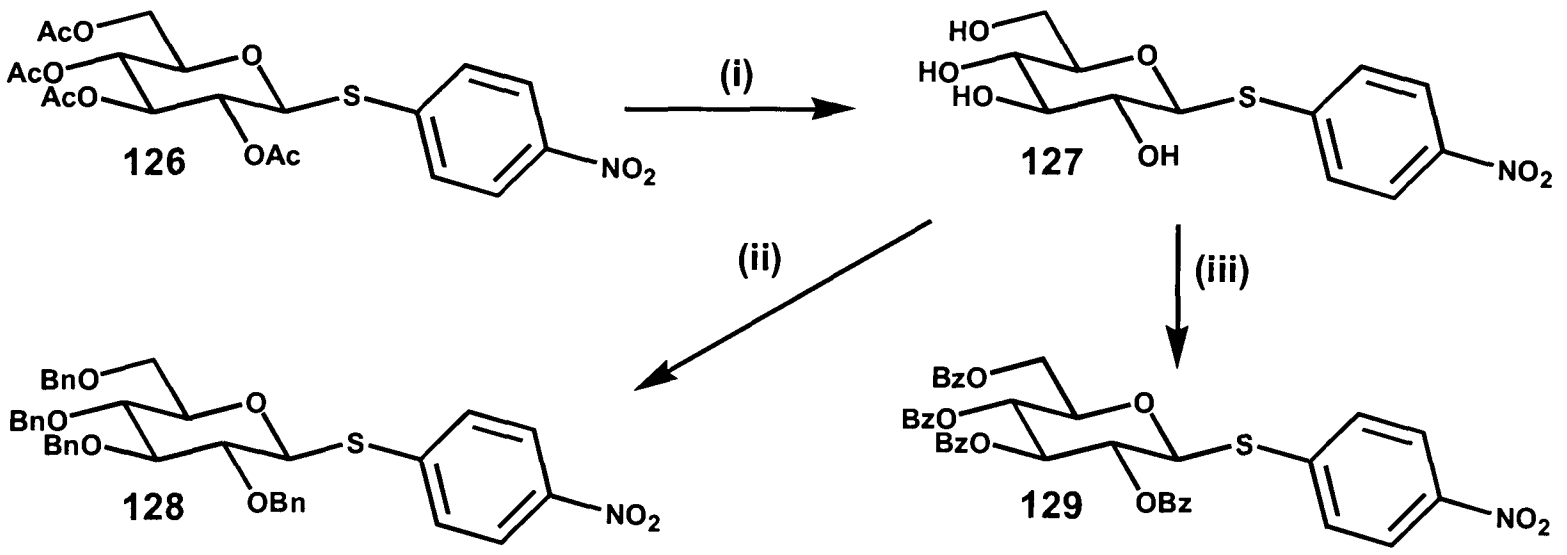
isolate the α-glycosyl iodide using this method. It was therefore necessary to conduct the reaction in a two step manner, synthesising first the α-glycosyl iodide **18** and then using the conditions of Stick to generate the thioglycoside.[23] This was chosen in preference to a Lewis acid catalysed route simply because the disulphide was available commercially at a much lower price than the thiol. Additionally the methodology had been used effectively already, in the previous work on the synthesis of selenoglycosides (scheme 2.21).



(i) HMDS, I_2, DCM, 86%; (ii) Bis(4-nitrophenyl) disulphide, $NaBH_4$, EtOH, $CHCl_3$, 4 h, 60%.

Scheme 2.21

Once again deprotection and reprotection gave both the fully armed and disarmed thioglycosides **128** and **129** for comparison with those already synthesised (scheme 2.22).



(i) NaOMe, MeOH, 30 min, 99%; (ii) BnBr, NaH, DMF, 16 h, 82%; (iii) BzCl, pyridine.

Scheme 2.22

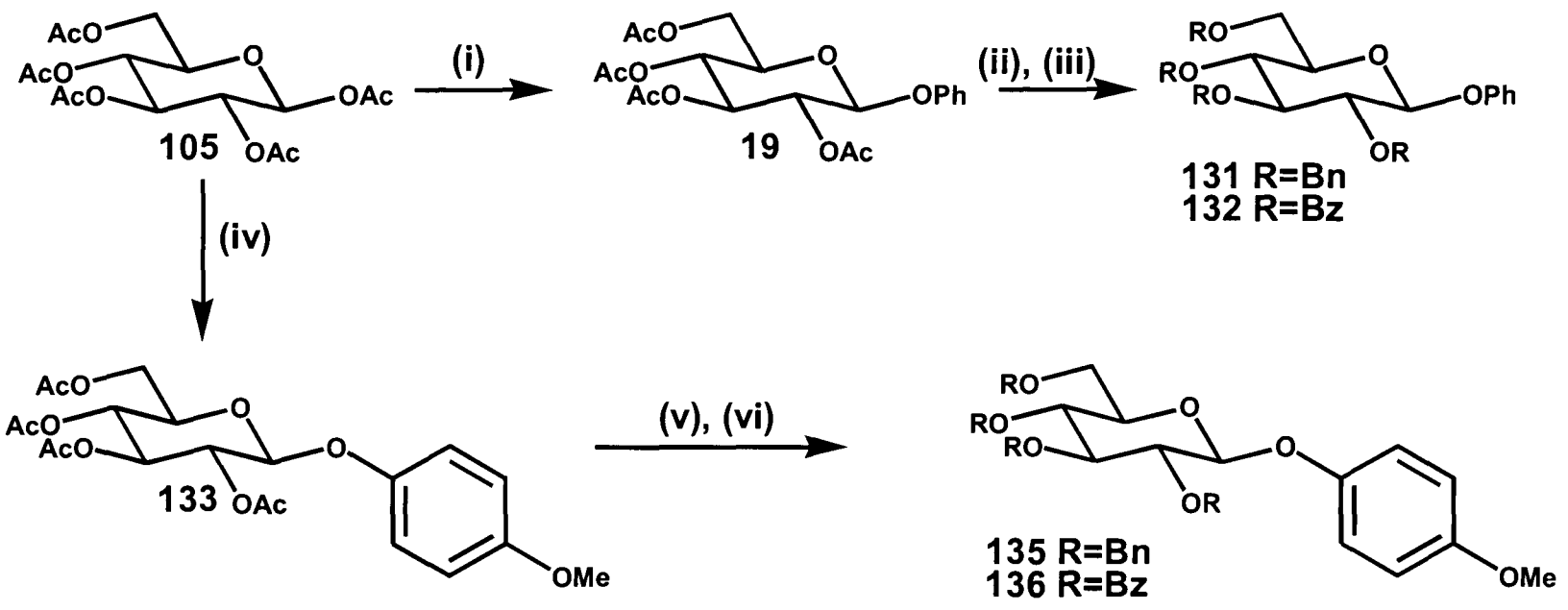
2.5 *O*-Glycosides

2.5.1 Introduction to *O*-glycoside synthesis

The synthesis of *O*-glycosides is a huge field in itself and in many ways is the final aim of all glycosylation chemistry. The scope of this project was limited to the simple synthesis of some aromatic *O*-glycosides, such as those used by Noyori in his groundbreaking work on electrochemical glycosylation.[3]

2.5.2 *O*-Glycoside synthesis

The method chosen was simply to extend the Lewis acid catalysed methodology used to provide the peracetylated sugars, which had been used to generate the thioglycoside donors. There is plenty of literature precedent in this area and the reactions caused no problems, giving the desired glycosides **19**, **131**, **132**, **133**, **135** and **136** in good yield (scheme 2.23).[51-53]



(i) PhOH, $BF_3.OEt_2$, DCM, 5 h, 95%; (ii) NaOMe, MeOH, 1 h, 92%; (iii) R=Bn: BnBr, NaH, DMF, 18 h, 85%; R=Bz: BzCl, pyridine, 17 h, 88%; (iv) 4-methoxyphenol, $BF_3.OEt_2$, DCM, 24 h, 86%; (v) NaOMe, MeOH, 1 h, 98%; (vi) R=Bn: BnBr, NaH, DMF, 16 h, 97%; R=Bz: BzCl, pyridine, 16 h, 99%.

Scheme 2.23

2.6 Synthesis of Glycosyl Acceptors

2.6.1 Introduction

In addition to the glycosyl donors discussed above, a number of monosaccharides were synthesised with the potential to act as both glycosyl donors and glycosyl acceptors. These were chosen following the electrochemical study of the donor compounds (see chapter 3), as potential glycosyl acceptors likely to have high oxidation (activation) potentials. The general retrosynthetic analysis for these compounds is shown below (figure 2.4).

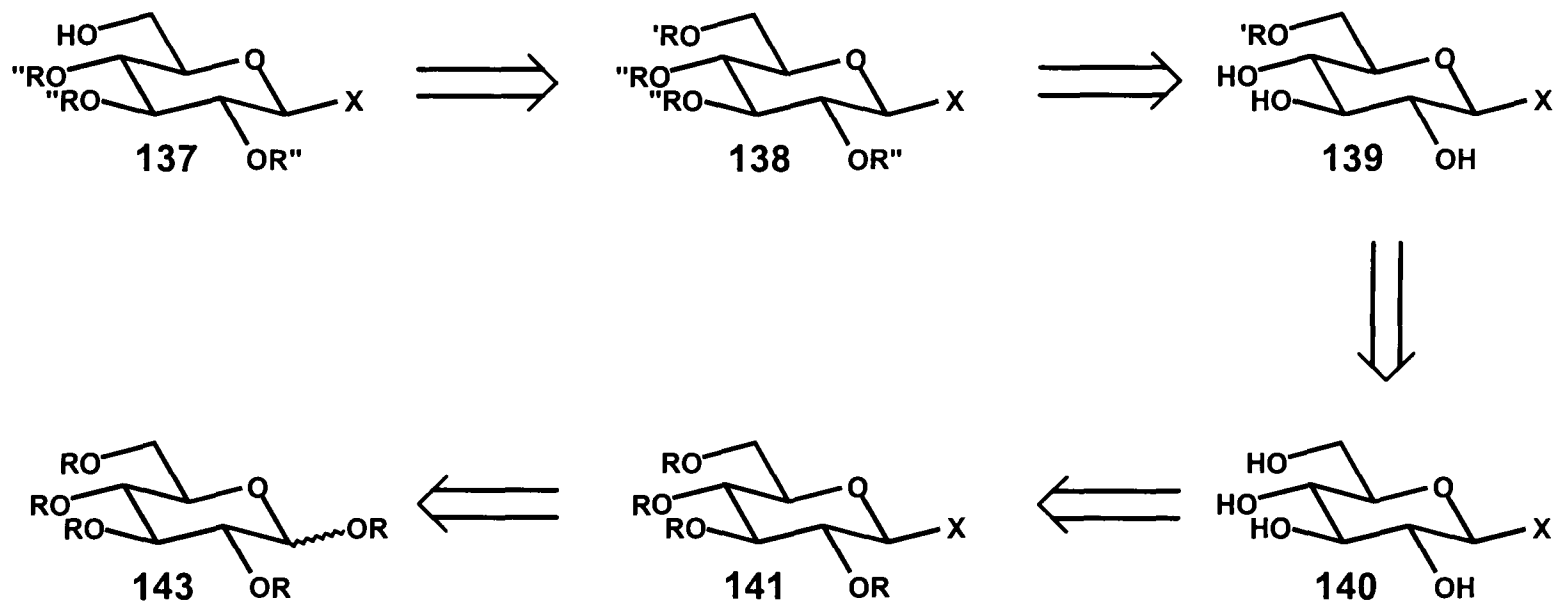


Figure 2.4: Retrosynthetic analysis of a glycoside acceptor with the OH-6 position free

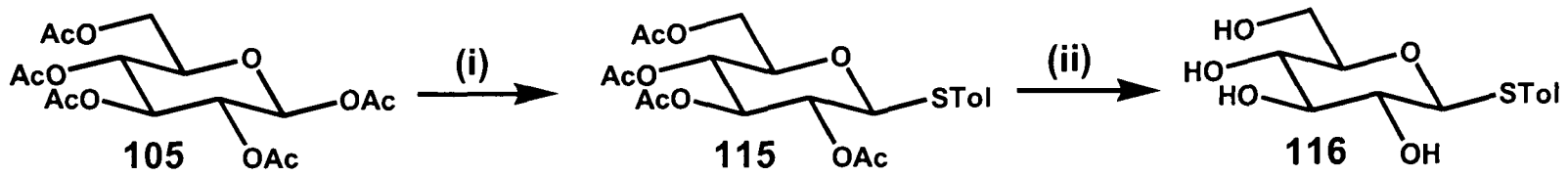
The general glycosyl acceptor **137** was chosen with the OH-6 position free for glycosylation in order to give the maximum opportunity for efficient glycosylation. In addition, as the only primary hydroxyl group present, it would be a relatively straightforward matter to differentiate this hydroxyl group from the others present by well established protecting group manipulations.

The strategy involved introduction of the desired anomeric group to give glycoside **141** as the first step, in an analogous fashion to that discussed in the synthesis of glycosyl donors. As before the stereochemistry could be controlled by the use of ester protecting groups at OH-2 (R = Ac or Bz). It was anticipated that global deprotection would then afford glycoside **140**. At this point the greater nucleophilicity of the primary hydroxyl at position *O*-6 would be used in order to selectively protect the glycoside exclusively at that position, to give compound **139**. It was envisaged that it would then be possible to introduce any protecting group desired onto the remaining free alcohol positions, with the proviso that they must be orthogonal in nature to that already present at *O*-6, to give fully protected glycoside **138**. Finally this orthogonality would be used to selectively deprotect *O*-6 to give the desired glycosyl acceptor **137**.

2.6.2 Thioglycoside acceptors

The thiotolyl group has been shown to posses similar properties to the thiophenyl substituent but has little of thiophenol's noxious odour. For this reason thiotolyl was chosen as the anomeric substituent for the thioglycoside acceptors. In addition this would allow comparison of the work with Wong's chemically activated selective glycosylations, all of which utilise thiotolyl as the anomeric leaving group. In order to maximise the scope for investigation of selective electrochemical glycosylations both the benzyl and benzoyl protected acceptors were synthesised. The synthetic path is outlined below.

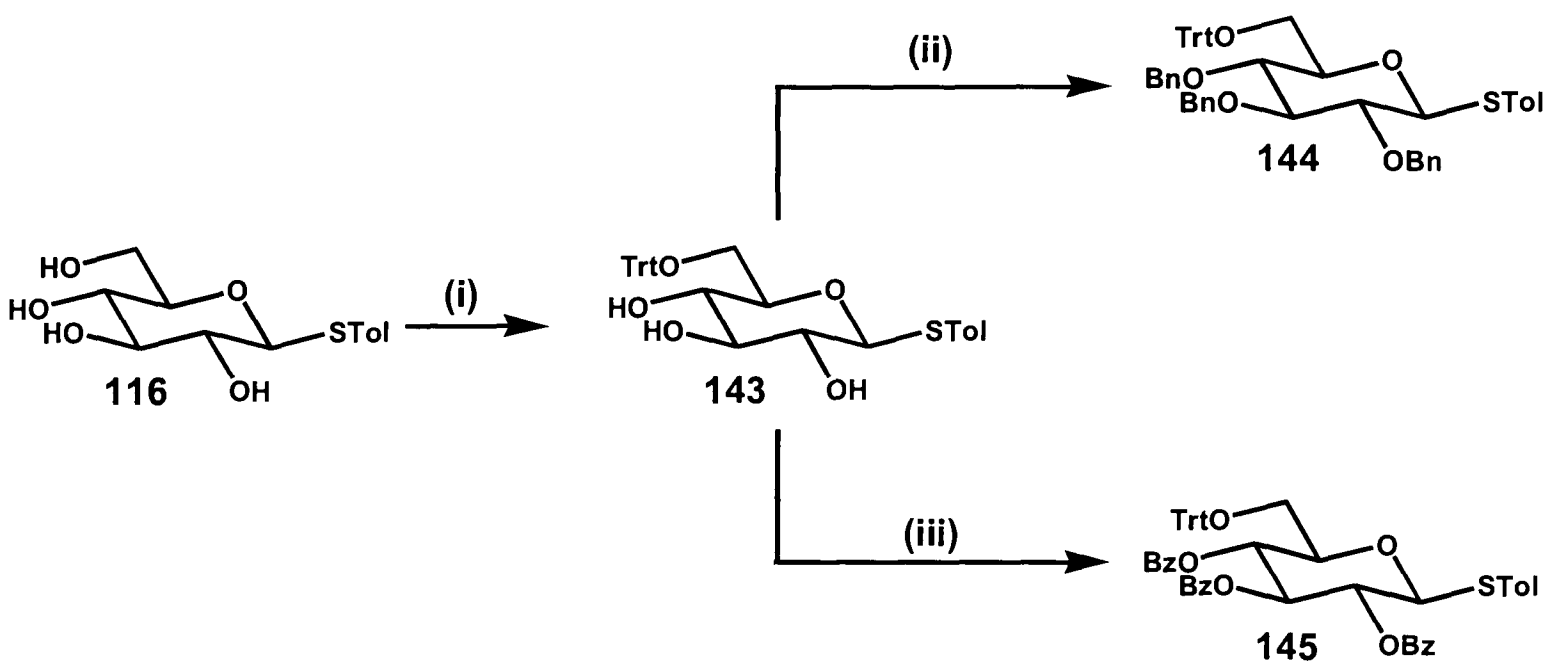
Treatment of pentaacetate **105** with thiocresol and boron trifluoride diethyl etherate gave thioglycoside **115** in 81% yield. Removal of the acetyl groups by Zemplén deacetylation then yielded the tetrol **116** in 87% yield (scheme 2.24).



(i) *p*-thiocresol, $BF_3.Et_2O$, DCM, 16 h, 81%; (ii) NaOMe, MeOH, 1 h, 87%.

Scheme 2.24

Selective protection of the *O*-6 position was achieved by treatment of the tetrol with trityl chloride and *N*,*N*-dimethylaminopyridine (DMAP) in pyridine to yield the triol. This triol was then protected both by benzylation with benzyl bromide and sodium hydride and by benzoylation with benzoyl chloride in pyridine, to afford the completely protected thioglycosides **144** (61 % over two steps) and **145** (97% over two steps) (scheme 2.25).

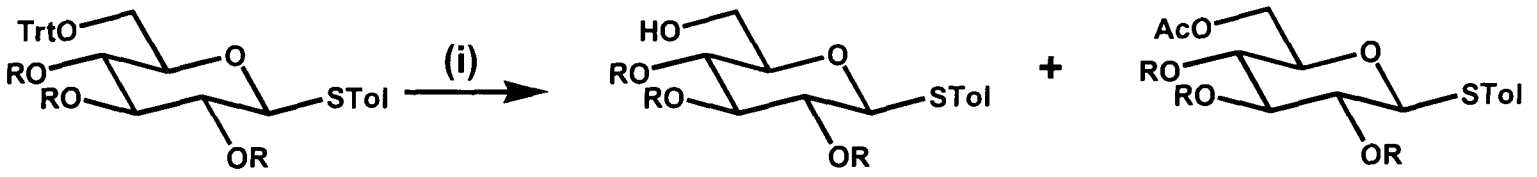


(i) TrtCl, pyridine, DMAP, 29 h; (ii) BnBr, NaH, DMF, 16 h, 61% (over two steps);
(iii) BzCl, pyridine, DMAP, 24 h, 97% (over two steps).

Scheme 2.25

Removal of the trityl group from thioglycosides **144** and **145** was achieved by refluxing in acetic acid,[54] to give the desired glycosyl acceptors **146** and **147** respectively, as well as a small amount of the 6-acetylated compounds **148** and **149**. The disarmed alcohols were easily separable by column chromatography and the side product could be minimised by the use of

aqueous acid in the deprotection steps, ultimately giving satisfactory access to both acceptors (scheme 2.26).



144 R=Bn
145 R=Bz

146 R=Bn
147 R=Bz

148 R=Bn
149 R=Bz

(i) R=Bn: AcOH:EtOH (2:1), 80 °C, 26 h, **146:** 92%, **148:** 4%;

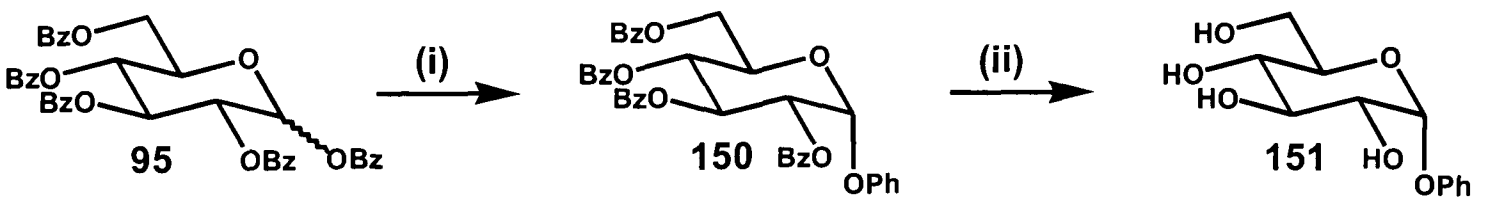
R=Bz: AcOH:EtOH (2:1), 80 °C, 24 h, **147:** 76%, **149:** 11%

Scheme 2.26

2.6.3 *O*-Glycoside acceptor

Synthesis of the *O*-glycoside acceptor **154** was conducted in a directly analogous manner and is outlined below. The *O*-phenyl anomeric group was chosen in order to give the highest anomeric oxidation potential, as indicated by the cylic voltammetric studies (chapter 3).

Glycosylation of the perbenzoylated glucose **95** with phenol and boron trifluoride diethyl etherate gave the α-*O*-glycoside **150** in 89% yield. The reaction was extremely slow and required heating at reflux for three days in order to reach completion. Presumably under these harsh conditions the addition of phenol is reversible and the phenyl α-*O*-glycoside **150** is the result of a thermodynamic equilibrium with the β-glycoside which would be expected to form kinetically *via* neighbouring group participation by the benzoyl group on *O*-2. The subsequent Zemplén deprotection proceeded smoothly to give tetrol **151** in a yield of 90% (scheme 2.27).

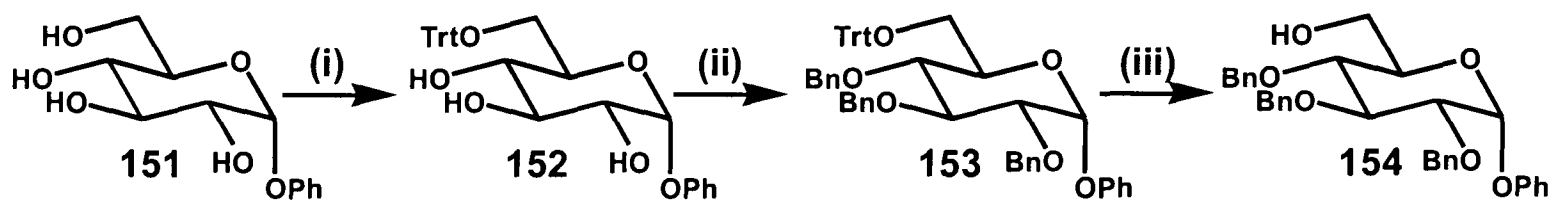


95 **150** **151**

(i) PhOH, $BF_3.OEt_2$, DCM, 50 °C, 48 h, 89%; (ii) NaOMe, MeOH, 18 h, 90%.

Scheme 2.27

Selective protection of tetrol **151** with trityl chloride and *N*,*N*-dimethylaminopyridine in pyridine in 90% yield, followed by benzylation gave the fully protected glycoside **153** in 90% yield. In this case detritylation was carried out using iron (III) chloride, a procedure that had recently been reported in the literature.[55] This avoided the problems of acetylation at the *O*-6 position, but as the reaction was less efficient overall with a yield of 65% it gave no significant benefit, over the approach used to generate thioglycosides **146** and **147**.



(i) Trt-Cl, DMAP, pyridine, 48 h, 90%; (ii) BnBr, NaH, DMF, 16 h, 90%;
(iii) $FeCl_3.6H_2O$, DCM, 48 h, 65%.

Scheme 2.28

2.7 Conclusions

In total a small library of 6 selenoglucosides, 14 thioglucosides, 2 thiomannosides and 6 *O*-glycosides with differing protecting group patterns, anomeric substituents and stereochemistry was synthesised. The next step was to investigate the relative electrochemical properties of these compounds.

In addition the synthesis of 3 glycosides with the potential to act as either glycosyl donor or acceptor was accomplished, following on from the electrochemical analysis conducted on the glycosyl donor library.

Of these compounds 16 are novel.

2.8 References

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Chapter 3

Electrochemical Analysis of Monosaccharides

3.1 Aims

The aim of the work detailed in this chapter was to investigate the electrochemical properties of the monosaccharides, the syntheses of which were discussed in chapter 2. Although electrochemical information for a few of these compounds was available before the work was begun,[1-7] and a more substantial amount became available during the course of these studies,[8] the literature data suffered from a number of problems. First the cell conditions used varied from article to article, making the data difficult to compare reliably. Secondly, and more importantly, the published work usually furnished little detail, often failing even to specify whether the oxidation potentials given are peak oxidations, half wave potentials or formal potentials. None of the papers discuss the form of the voltammetric waves or give any kinetic data. Consequently to begin the synthetic work from a position of real understanding it was necessary to survey as wide a range of monosaccharides as possible.

In addition to the analysis of these compounds at slow scan rates (20 mVs^{-1} to 2 Vs^{-1}), a few representative compounds were also studied in more detail. Specifically fast scan techniques were used to out run the kinetics of the chemical step and look at the thermodynamic oxidation potentials.

3.2 Introduction

3.2.1 Voltammetry

Voltammetry is concerned with the application of a potential across a three electrode cell. The applied potential is controlled by a potentiostat containing a waveform generator and is applied and measured across the working and reference electrodes whilst the current flows between the working and counter (or auxiliary) electrode.

In general the potential difference is monitored as a function of time and the main techniques of voltammetry can be divided into two classes, based on the way in which the system under study varies with time.

(i) Steady-state voltammetry

As the name implies in this type of voltammetric experiment, the distribution of the species involved in the reaction mechanism is constant at the applied potential (or more likely at each applied potential). Although it would, in theory, take an infinite time to reach a true steady state and there are a number of processes likely to be occurring which could perturb the equilibrium, it is usually possible to obtain a good approximation of the steady state. In a practical sense this means that the error derived from the system being at a point which only approximates to the steady state is small in comparison to other errors associated with the experimental procedure (for instance those involved in making measurements on the system). Examples of common steady state techniques are those using rotating disc[9] or channel[10] electrodes, both of which can be characterised as Hydrodynamic Voltammetric techniques.[11]

(ii) Transient voltammetry

In these techniques measurements are made to a system in which a perturbation is made to the potential at the working electrode, and the current response then measured as a function of time. As well as the variation of potential the rate at which the potential is altered (the scan rate υ) can be varied to give information about the system under consideration. Common transient techniques include cyclic, linear, square wave, pulsed and A.C. voltammetries. Detailed examples of all these techniques can be found in the book "Electrochemical Methods: Fundamentals and Applications" by Bard and Faulkner.[12]

3.2.2 Cyclic voltammetry

It is the second of these general methods, and in particular cyclic voltammetry, which is the concern of this chapter. This is a well established and understood technique, having been pioneered by Ševčík in 1948 following an increased interest in voltammetric techniques.[13] This technique has the advantage of being simple to perform and provides data which can be rapidly understood in both a qualitative and quantitative fashion.

The basis of a cyclic voltammetric experiment is that the potential is initially held at a scan rate E_1, and the potential then swept up at a given scan rate υ which, depending on the constraints of the experiment and the equipment available, can be varied from a few millivolts per second[12] to somewhere in the region of a million volts per second.[14] Upon reaching a higher potential E_2 (the exact magnitude of which is determined by experimental considerations) the direction of scan is reversed and the potential returns usually, but not necessarily, at the same scan rate to the starting potential E_1. The scan can be stopped at this point or can be allowed to continue either to less oxidising potentials or to repeat the initial sweep. It should be noted that in the

above description we have assumed that the voltammetry is conducted in a positive sense, in that the potential is swept from a lower (less oxidising) to higher (more oxidising) potential. This is because the voltammetry reported here focuses on such systems, in which oxidation is the first step. It is just as usual to conduct an experiment in the opposite sense, usually to probe reactions where reduction is the initial step. The general electrochemical process under consideration is therefore (figure 3.1):

$$A - ne^- \rightleftharpoons B$$

Figure 3.1: A simple oxidative electrochemical process.

The variation of potential with time can probably best be envisaged by reference to figure 3.2 below.

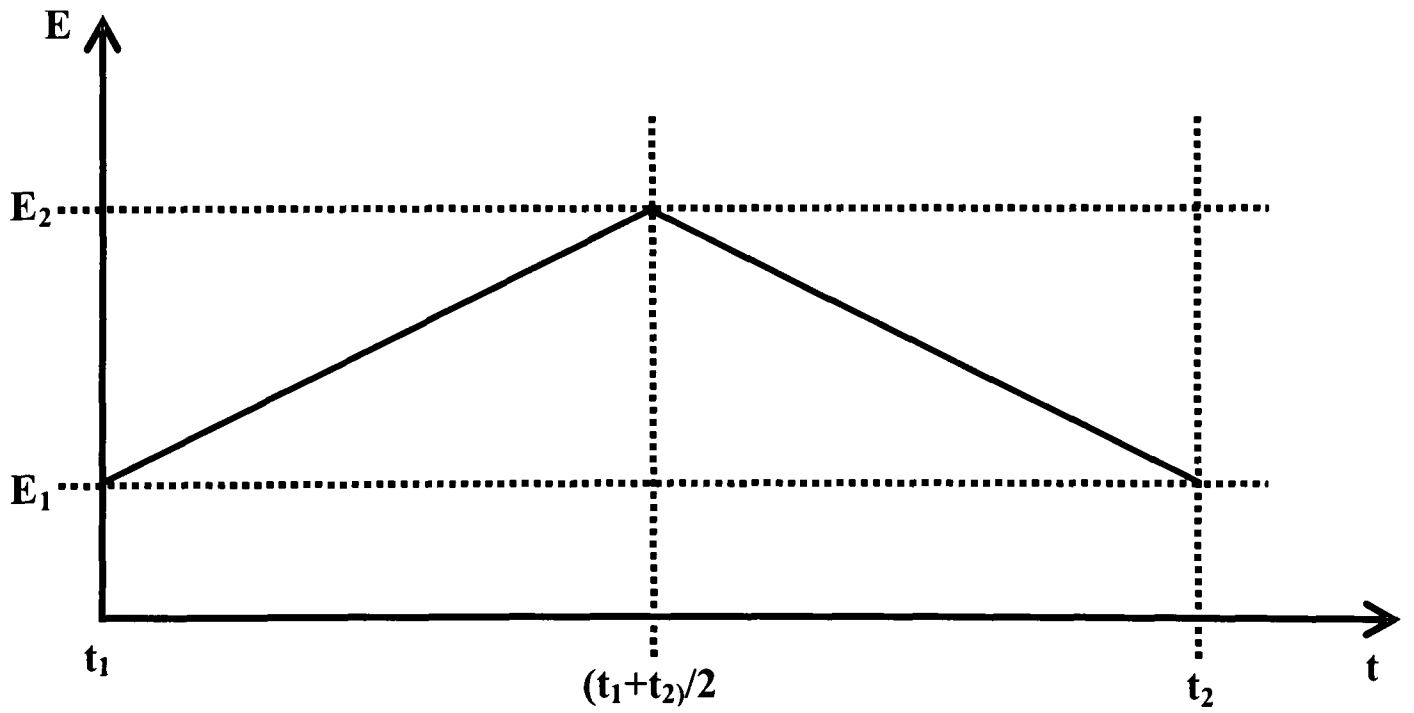


Figure 3.2: Variation of potential with time for a typical cyclic voltammetric experiment conducted at a constant scan rate. The scan rate is give by the gradient of the graph e.g. $(E_2 - E_1)/((t_1+t_2)/2)$.

The variation of current with applied potential, as described above, is plotted to give a cyclic voltammogram. There are three possible forms of this current response curve and which form is seen will depend on the kinetics of electron transfer at the working electrode.

(i) The electrochemically reversible system

In such a system the electron transfer processes (both oxidation and reduction) are fast when compared to the mass transport (in the case of cyclic voltammetry this is usually only diffusion), to the extent that the system is able to reach equilibrium within the time scale of the experiment. It is the comparison between scan rate and the electron transfer process which is important and so it is quite possible for a system to display fully reversible characteristics at higher scan rates, but one of the other forms of behaviour at lower scan rates. A characteristic voltammogram for a fully reversible system is shown below (figure 3.3).

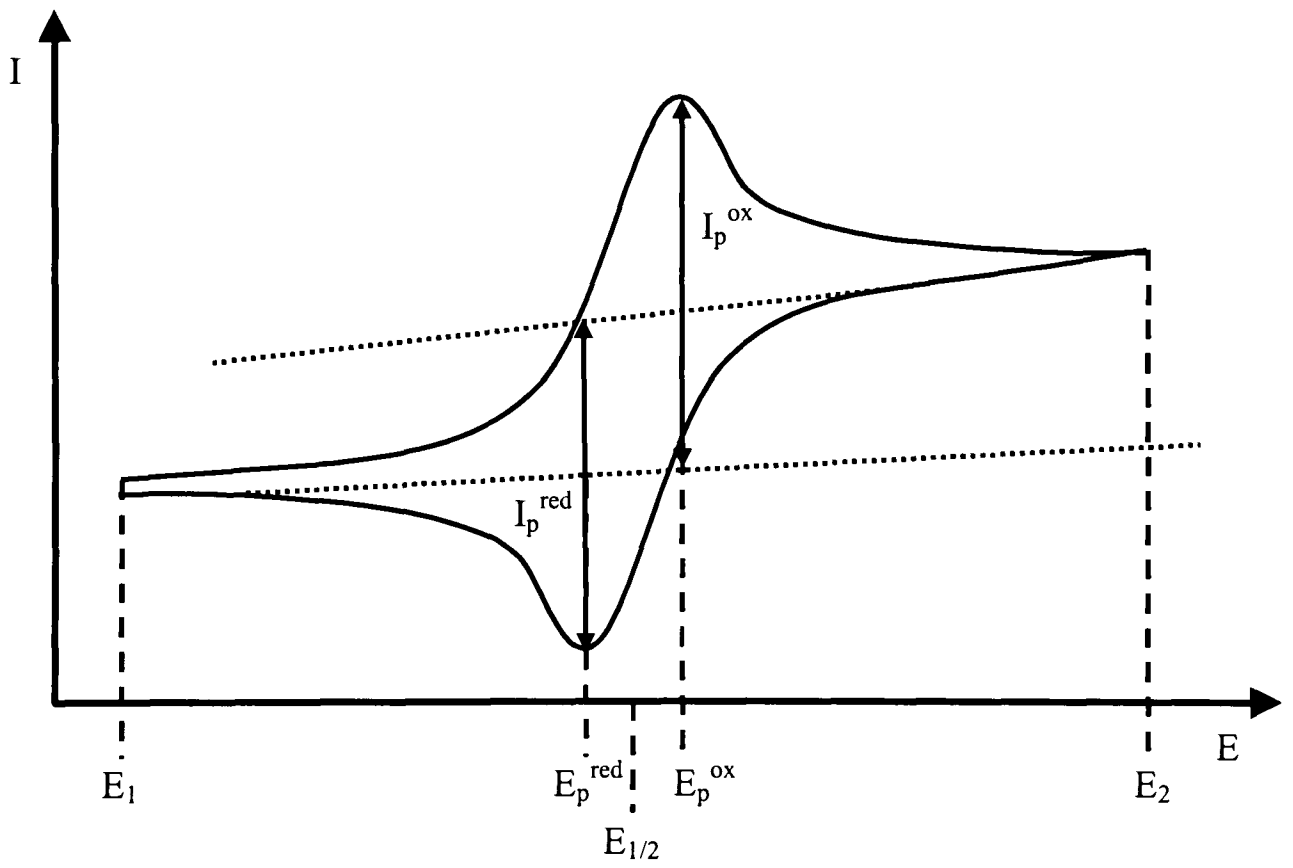


Figure 3.3: Schematic diagram of a cyclic voltammogram for an electrochemically reversible electron transfer process (in this case an oxidation).

The shape of the curve can be explained as follows, with reference to the simple electrochemical process outlined in figure 3.1. Initially the electrode potential is insufficient to oxidise A, and as the potential is increased the current increases gently in a linear fashion. Then at some point the applied potential is sufficient to oxidise species A. The concentration of A is relatively large and the electron transfer rapid, and so the current is controlled by equation (1).[15]

$$I = nFAD(\partial[A]/\partial x)_{x=0} \qquad (1)$$

where I is the current, n is the number of electrons, F is the Faraday constant, D is the diffusion coefficient, [A] is the concentration of species A and x is the perpendicular distance from the electrode surface.

It is no longer the case that $(\partial[A]/\partial x)_{x=0}$ is constant and so the current begins to rise. As the potential continues to increase $[A]_0$ falls further as A is converted into B and consequently the flux of A to the electrode surface continues to increase, as does the current. This gives rise to the section of the voltammogram where the current is steadily increasing.

Eventually however the concentration of A at the electrode surface reaches zero, as all of the species available for oxidation are consumed. (i.e. $[A]_{x=0}$). At this point there is none of compound A sufficiently close to the electrode surface for electrolysis to occur and diffusion of A from the bulk solution is necessary. This is necessarily limiting and the flux of A begins to drop, giving a resultant drop in I and consequently the characteristic maximum shown in figure 3.3 as E_p^{ox}.

The potential sweep is now reversed (position E_2). At this point the concentration of species B (the product of the oxidation process of A) at the electrode surface is large. As the potential is swept to less oxidative values B is initially not reduced; however eventually the potential reaches a point where the species B is reduced at the surface of the working electrode. Exactly as is seen in the forward, oxidative, process of A this leads to a reduction in the concentration of B at the working electrode and a concomitant increase in the flux of B to the electrode surface until the concentration of B at the electrode falls to zero. This gives rise to the back peak which shows the same asymmetric shape as the forward peak.

There are a number of characteristic properties of such a fully reversible voltammogram that it is important to note:[15]

- The peak oxidation potentials (E_p^{ox} and E_p^{red}) will be independent of scan rate.
- At 25 °C (standard conditions) the peaks will be separated by 56/n mV (where n is the number of electrons transferred during the process)
- The half wave potential ($E_{1/2}$) is the potential value at the mid point between E_p^{ox} and E_p^{red}. (i.e. $E_{1/2} = (E_p^{ox} + E_p^{red})/2$).
- $E_{1/2}$ is related to the formal wave potential by the formula:

$$E_{1/2} = E_f^0 + (RT/nF)\ln(D_A/D_B)^{1/2}$$

  In most cases $D_A \sim D_B$ and so $E_{1/2} \sim E_f^0$

- The peak currents (I_p^{ox} and I_p^{red}) in amps can be obtained from the formula:

$$I_p^{ox} = -I_p^{red} = \pm (2.69 \times 10^5) n^{3/2} A D_A^{1/2} \upsilon^{1/2} [A]_0$$

  which applies at 25 °C.

The quantities not previously defined are E_f^0, which is the formal reversible oxidation potential, R, the universal gas constant, T is the temperature, D_A is the diffusion coefficient for A, D_B is the diffusion coefficient for B, A is the area of the electrode and υ is the solution kinetic viscosity.

(ii) The fully irreversible system

This situation arises when the electrode kinetics are slow compared to the mass transport (in the case of cyclic voltammetry this is usually only diffusion). Such a system is not able to come to equilibrium at every potential and the Nernstian boundary conditions discussed above do not apply. The system can however be accurately described by the use of the kinetic boundary condition (2), which takes into account the electrode kinetics.[12]

$$D_A(\partial[A]/\partial x)_{x=0} = k[A]_{x=0} \qquad (2)$$

Inserting equation (2) into equation (1) gives:

$$I = nFA\ k[A]_{x=0} \qquad (3)$$

which gives a voltammogram of the general form shown in figure 3.4.

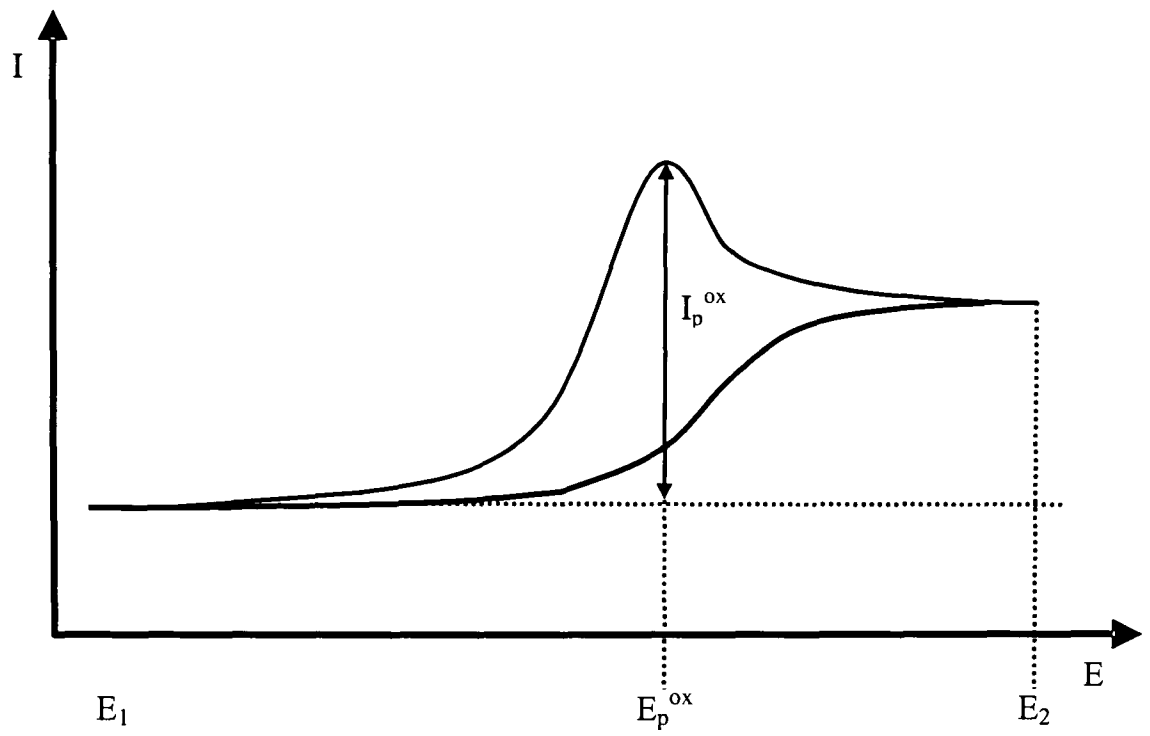


Figure 3.4: Schematic diagram of a cyclic voltammogram for an irreversible electron transfer process (in this case an oxidation).

While the forward peak has the same basic shape as in the reversible case there are a few important differences to note.

First, and most obviously, there is no longer a back peak. This is because the reverse electron transfer process is not occurring at a measurable rate under the reaction conditions.

Secondly the formula obtained for peak current in the reversible system is no longer valid and we must instead apply formula 4:[15]

$$I_p^{ox} = -(2.99 \times 10^5)n(\alpha n_a)^{1/2}AD_A^{1/2}\upsilon^{1/2}[A]_0 \qquad (4)$$

where α is the charge transfer coefficient, n_a is the number of electrons transferred *in the rate determining step* and the other quantities are as previously described.

Thirdly, the peak potential is now a function of scan rate, in marked contrast to the reversible case. As the scan rate becomes faster the peak potential moves to more positive potentials. In addition as the scan rate increases the peak broadens.

(iii) The intermediate system

It is not uncommon for electro active systems to have characteristics which fall in between the two limiting cases described above in which there are kinetic considerations for both forward and back peaks. Such systems usually display fully reversible characteristics at slow scan rates, but as the scan rate increases the kinetics are not fast enough to maintain the equilibrium.

Matsuda and Ayabe[16] proposed the following quantitative definitions of the three possible systems, based on the values of k_0 (the standard heterogeneous rate constant) and υ (the solution viscosity). These have now become generally accepted as the standard definitions of the systems.

Reversible: $k_0 \geq 0.3\upsilon^{1/2}$ cm s^{-1}

Quasi-Reversible: $0.3\upsilon^{1/2} > k_0 > (2 \times 10^{-5})\,\upsilon^{1/2}$ cm s^{-1}

Irreversible: $k_0 \leq (2 \times 10^{-5})\,\upsilon^{1/2}$ cm s^{-1}

3.3 Slow scan analysis of monosaccharides

3.3.1 Experimental conditions

The cell used for the cyclic voltammetry under slow scan conditions is shown below (figure 3.5).

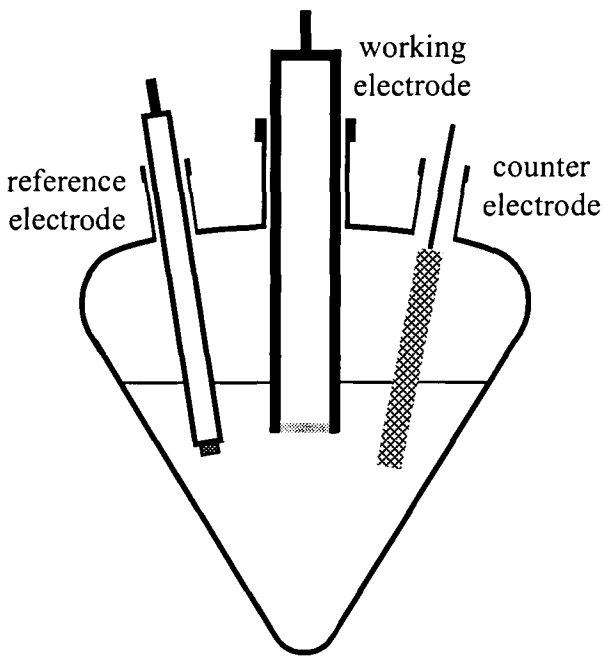


Figure 3.5: The general electrochemical cell.

The working electrode in the centre is placed close to the reference electrode in order to minimise any Ohmic drop (IR drop). This is the drop in applied potential caused by the resistance of the solution.

The counter electrode is made of an inert material, with a high surface area in order to ensure that it does not limit the current flow. For these reasons a nickel mesh counter electrode was chosen.

Initial work using both glassy carbon and platinum working electrodes showed that in some cases the platinum electrode gave poorly defined peaks. In addition there was some concern

that a platinum electrode might be poisoned during the synthetic work by the generation of selenium and sulphur species as by products of the reaction. Indeed this may well have been the reason for the poor peak definition. The majority of the work was therefore conducted using only the glassy carbon electrode. The same 5mm diameter glassy carbon electrode was employed throughout the slow scan work.

Finally a standard calomel electrode was chosen as the reference electrode. This is a well established reference electrode and the potentials derived can be easily related to that of the standard hydrogen electrode, which is defined to have a potential of 0.000V.[15] It became apparent during the work that for the synthetic studies a non-aqueous reference electrode would be needed, as rigorous exclusion of water was necessary. For this purpose a silver wire pseudo reference electrode was employed (for a more detailed discussion see Chapter 4). Reported here are the results using this system of electrodes. All of the results are given for the first scan at 100 mVs^{-1}, both for internal consistency and for ease of comparison with the literature.

In order to ensure comparable results the working electrode was thoroughly polished before each scan. The concentration of the monosaccharides was kept in the range 1.0 to 2.0 mM and the electrolyte (tetrabutylammonium perchlorate) concentration was maintained at 0.1 M. Scans were conducted in the range 0.02 Vs^{-1} to 2 Vs^{-1}.

3.3.2 Mechanistic considerations

An understanding of the mechanism involved in the process under study is necessary if the electrochemical data is to be interpreted properly. In the system under consideration the process is believed to be of the EC type, with initial electrochemical oxidation of the anomeric

heteroatom followed by a chemical step, during which the anomeric group leaves to give a glycosyl cation (figure 3.6).[4] It is this glycosyl cation formation which allows this technique to be used for synthetic glycosylation reactions and the process will be discussed in greater detail in Chapter 4.

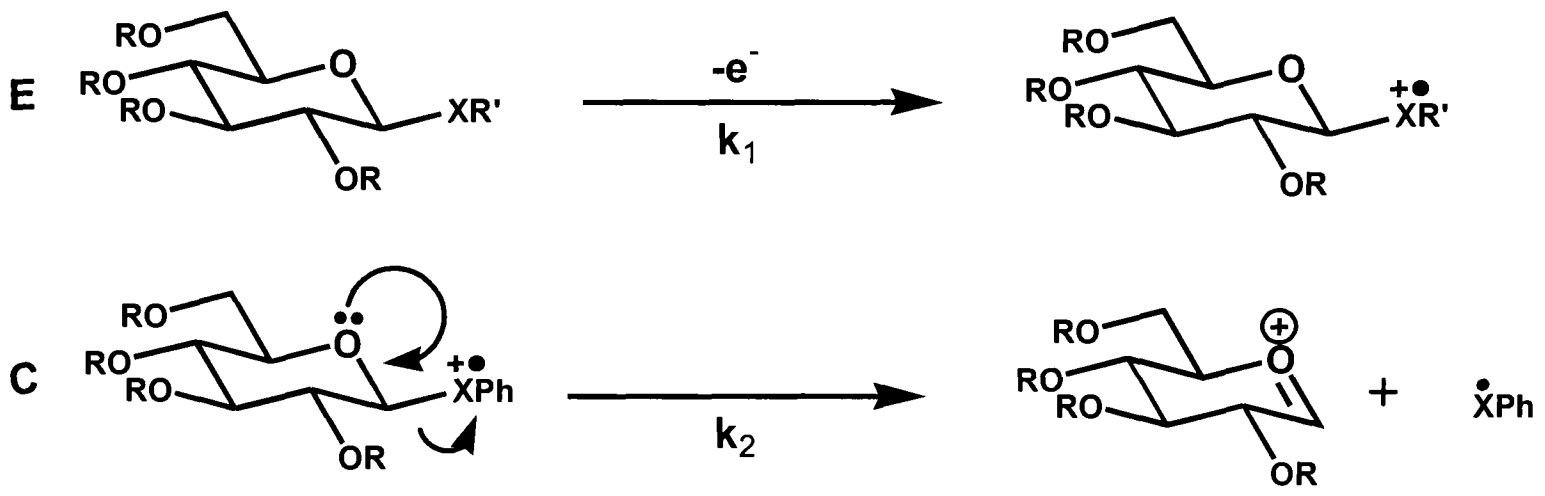


Figure 3.6: EC mechanism for the oxidation of the monosaccharides

3.3.3 The effect of protecting group pattern

In order to investigate the effect of differing protecting groups on the oxidation potential of the glycosyl donors the analysis of glycosides of the following form was conducted (figure 3.7).

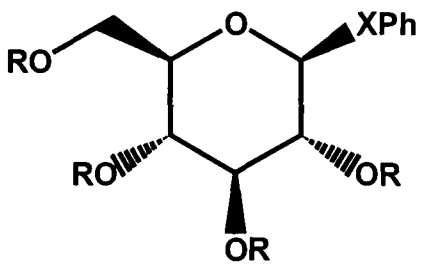


Figure 3.7: R=Bz, Bn, Ac; X=O, S, Se

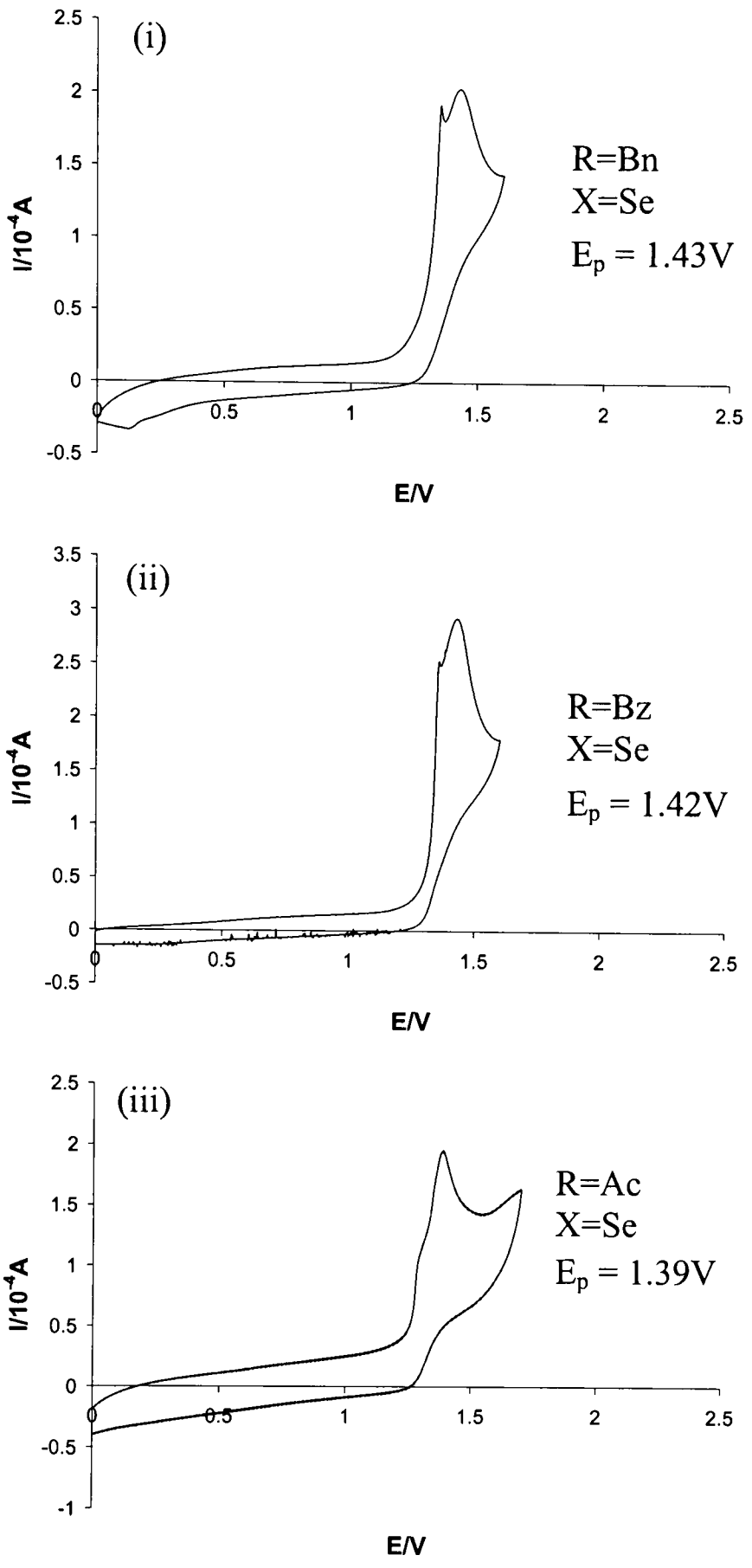


Figure 3.8: First scan voltammograms at 100 mVs^{-1} for: (i) 2.1 mM phenyl-2,3,4,6-tetra-*O*-benzyl-1-seleno-β-D-glucopyranoside; (ii) 2.1 mM phenyl-2,3,4,6-tetra-*O*-benzoyl-1-seleno-β-D-glucopyranoside; (iii) 1.3 mM phenyl-2,3,4,6-tetra-*O*-acetyl-1-seleno-β-D-glucopyranoside; all in acetonitrile with 0.1 M TBAP.

Initially compounds with selenium as the anomeric heteroatom were examined (figure 3.8). The voltammograms show no sign of a back peak and as such are indicative of a chemically irreversible oxidation process. Indeed scans at varying rate show the peak oxidation potential to be dependant on the scan rate as would be expected for an irreversible process. It can also be clearly seen that the peak oxidation potential does not vary significantly with protecting group. All three peaks show a small pre-wave, although this sharper in the case of the benzyl and benzoyl protected glycosides. This pre-wave is likely to be due to the adsorption of the glycoside onto the electrode surface, prior to oxidation. The oxidation process is however still likely to be diffusion controlled, as shown by plotting I_p against the square root of scan rate. In all three cases this gives a straight line approaching the origin (figure 3.9). (The relationship predicted for such

processes by equation (4) above, see section 3.2.2 (ii)).

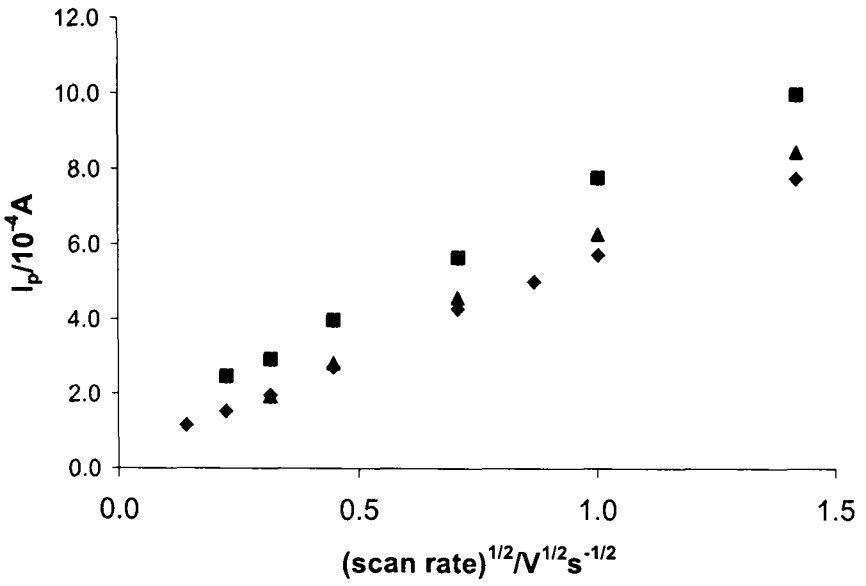
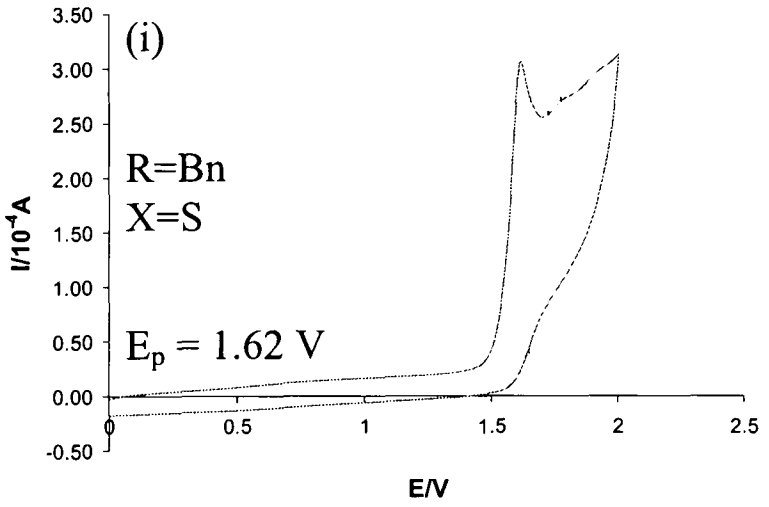
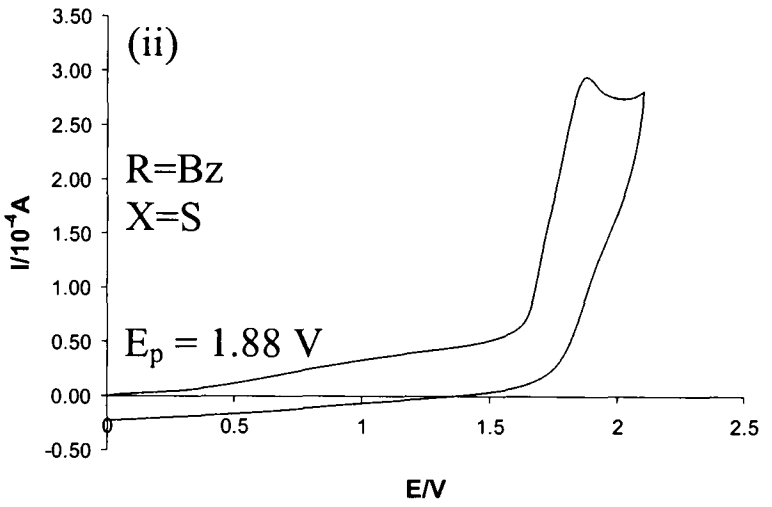


Figure 3.9: Plot of I_p vs. (scan rate)$^{1/2}$ for: (i) 2.1 mM phenyl-2,3,4,6-tetra-*O*-benzyl-1-seleno-β-D-glucopyranoside (▲); (ii) 2.1 mM phenyl-2,3,4,6-tetra-*O*-benzoyl-1-seleno-β-D-glucopyranoside (■); (iii) 1.3 mM phenyl-2,3,4,6-tetra-*O*-acetyl-1-seleno-β-D-glucopyranoside (◆); all in acetonitrile with 0.1 M TBAP

Work then moved on to look at the analogous thioglycosides (figure 3.10).





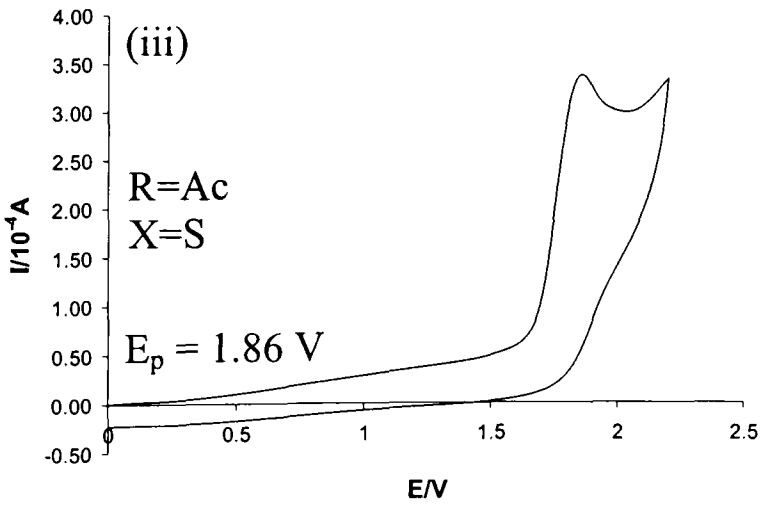


Figure 3.10: First scan voltammograms at 100 mVs^{-1} for: (i) 2.0 mM phenyl-2,3,4,6-tetra-*O*-benzyl-1-thio-β-D-glucopyranoside; (ii) 1.8 mM phenyl-2,3,4,6-tetra-*O*-benzoyl-1-thio-β-D-glucopyranoside; (iii) 2.2 mM phenyl-2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-glucopyranoside; all in acetonitrile with 0.1 M TBAP.

Once again classic irreversible voltammetry was seen, as in the case of the selenoglycosides discussed above. Also the peak oxidation potential is again dependant on scan rate and a plot of peak current against the square root of scan rate gives a linear plot approaching the origin (figure 3.11).

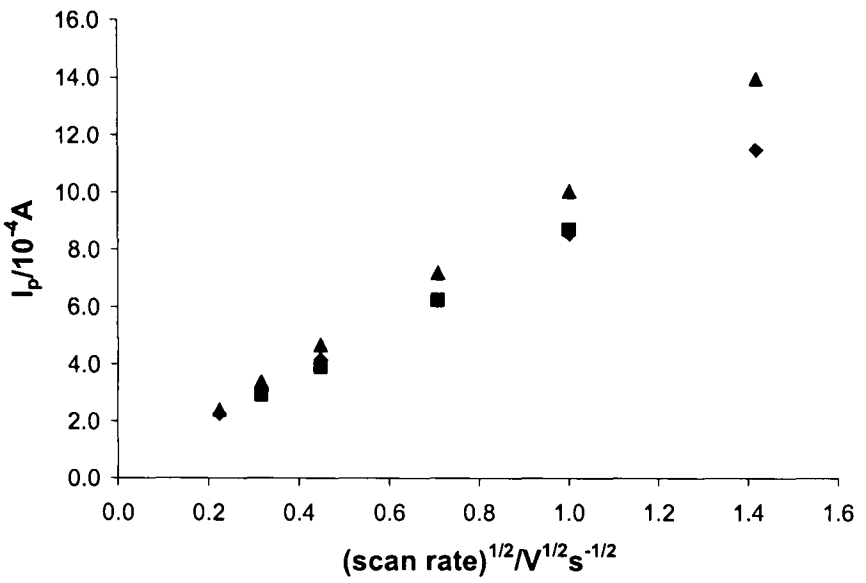


Figure 3.11: Plot of I_p vs. (scan rate)$^{1/2}$ for: (i) 2.0 mM phenyl-2,3,4,6-tetra-*O*-benzyl-1-thio-β-D-glucopyranoside (◆); (ii) 1.8 mM phenyl-2,3,4,6-tetra-*O*-benzoyl-1-thio-β-D-glucopyranoside (■); (iii) 2.2 mM phenyl-2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-glucopyranoside (▲); all in acetonitrile with 0.1 M TBAP.

In moving from selenium to sulphur the pre-wave is no longer seen and more importantly a shift in peak potential to more positive values relative to the selenium analogues is observed. Additionally it can now be seen that the protecting group pattern has an influence on the peak oxidation potential. The switch from electron donating benzyl ethers to the electron withdrawing benzoyl or acetyl esters resulted in a move to higher oxidation potential. This is presumably due to the destabilising effect of the esters on the radical cation generated by the electrochemical process in contrast to the stabilising effect of the benzyl ethers. There is no change in moving from the acetyl protection to the benzoyl protection, showing the effect is due to the ester functionality.

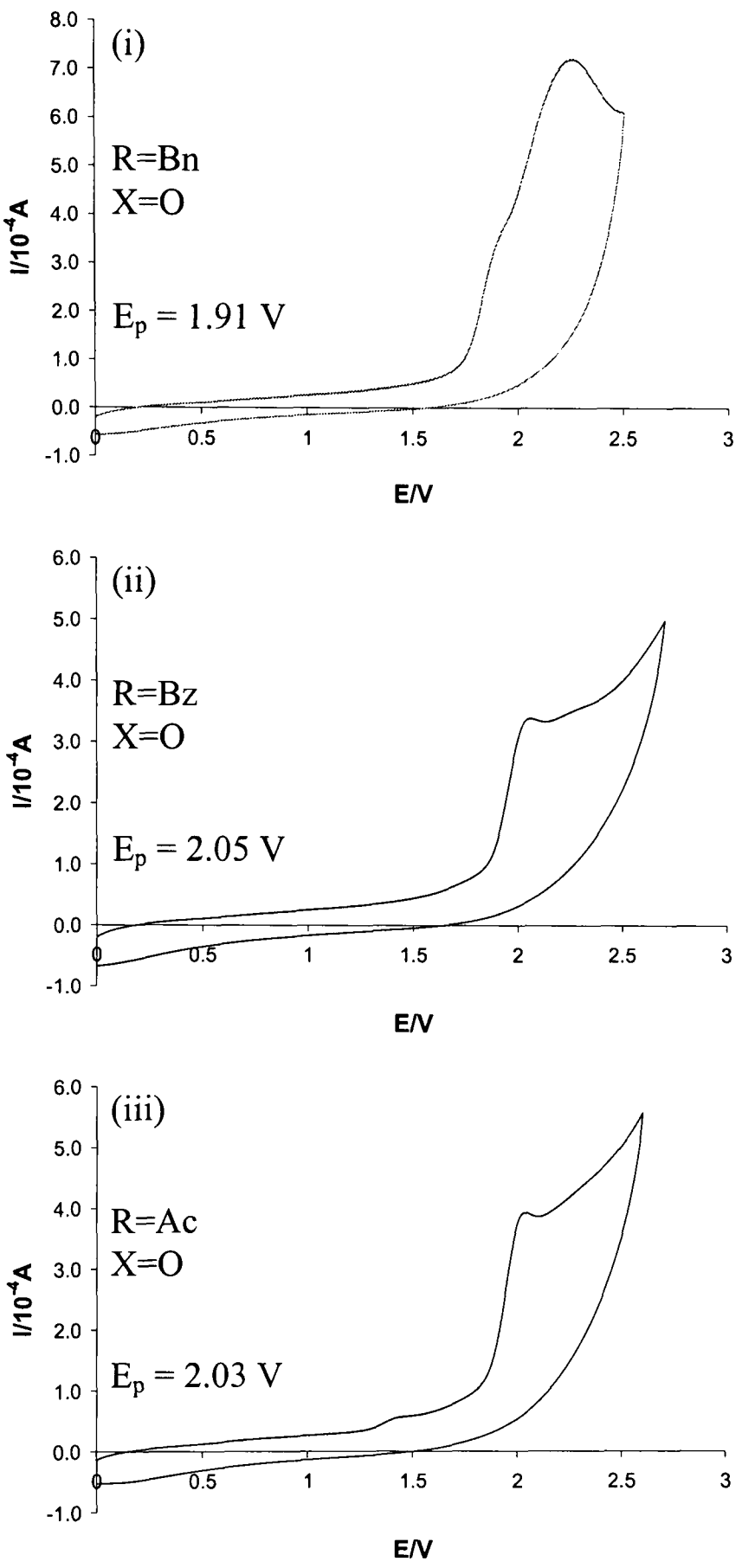


Figure 3.12: First scan voltammograms at 100 mVs^{-1} for: (i) 1.6 mM phenyl-2,3,4,6-tetra-*O*-benzyl-β-D-glucopyranoside; (ii) 1.5 mM phenyl-2,3,4,6-tetra-*O*-benzoyl-β-D-glucopyranoside; (iii) 1.5 mM phenyl-2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside; all in acetonitrile with 0.1 M TBAP.

Finally some *O*-glycosides were examined (figure 3.12). The peaks were again shifted to more positive values as we moved this time from sulphur to oxygen and again the peak potentials were found to be dependent on scan rate. The effect of the protecting groups (with the electron donating esters leading to higher oxidation potential) is not, however, so pronounced as in the case of the thioglycosides, although the pattern is the same. This is not immediately obvious, as initial examination of the benzyl protected glycoside would suggest a peak oxidation potential of about 2.3 V. The current however is too large for the anticipated one electron process, as the concentration is still comparable to the other compounds which have been analysed. In fact it would seem to be the small side peak which is associated with the oxidation of the OPh anomeric group, and this occurs at 1.9 V (although as it is not well defined it is hard

to quantify). The larger peak is probably due to the oxidation of the benzyl protecting groups. The electrochemical oxidation and cleavage of benzyl ethers has been reported in the literature.[17-19] Obviously this phenomenon would be expected to occur for both sulphur and selenium compounds which contain benzyl protection and indeed if the oxidation window is widened these peaks can be seen (figure 3.13).

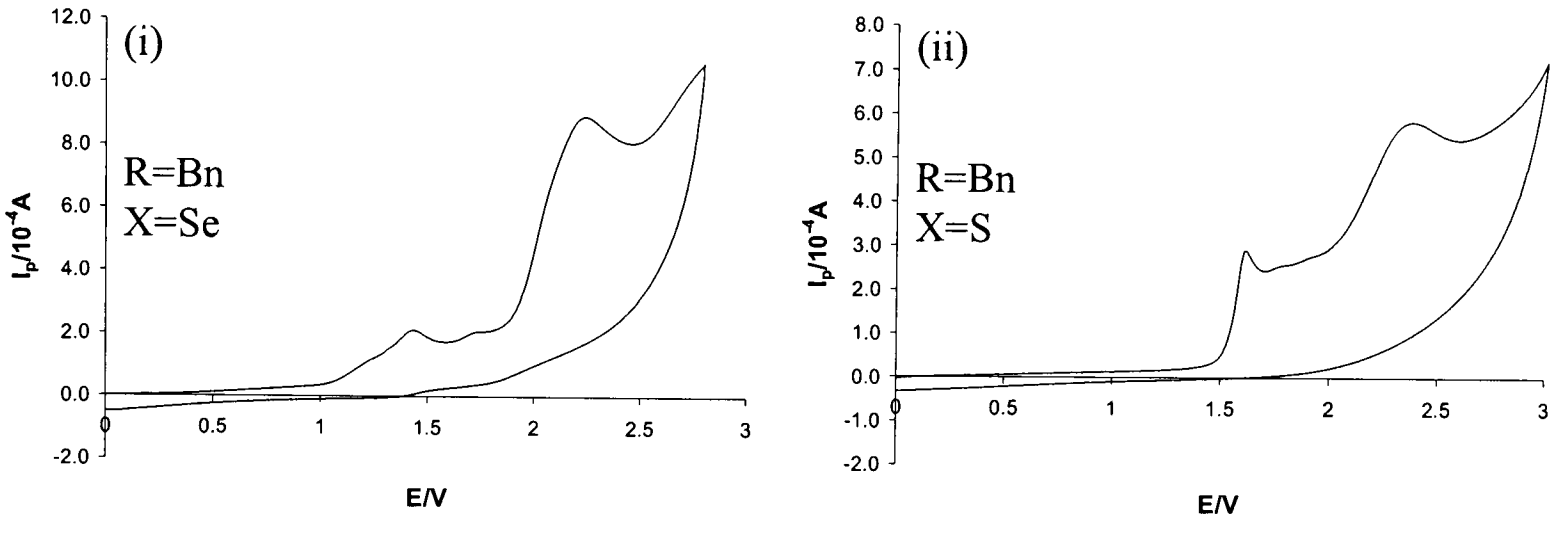


Figure 3.13: First scan voltammograms at 100 mVs^{-1} for: (i) 2.1 mM phenyl-2,3,4,6-tetra-*O*-benzyl-1-seleno-β-D-glucopyranoside; (ii) 2.0 mM phenyl-2,3,4,6-tetra-*O*-benzyl-1-thio-β-D-glucopyranoside; both in acetonitrile with 0.1 M TBAP.

These peaks are absent from the equivalent benzoyl and acetyl glycoside experiments. Noyori's original paper[1] on electrochemical glycosylation mentions the oxidation of benzyl protecting groups only in passing and under their conditions it does not appear to cause any problems with the glycosylation reactions.

Finally a plot of the peak current against the square root of scan rate is used to show that once again these compounds exhibit data which are consistent with a diffusion controlled mechanism (figure 3.14).

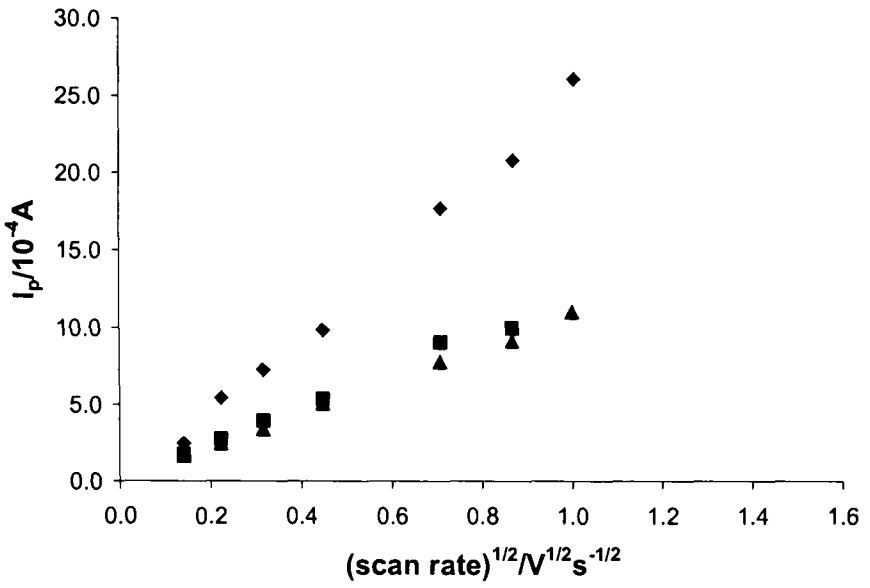


Figure 3.14: Plot of I_p vs. $(scan\ rate)^{1/2}$ for: (i) 1.6 mM phenyl-2,3,4,6-tetra-*O*-benzyl-β-D-glucopyranoside (▲); (ii) 1.5 mM phenyl-2,3,4,6-tetra-*O*-benzoyl-β-D-glucopyranoside (◆); (iii) 1.5 mM phenyl-2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside (■); all in acetonitrile with 0.1 M TBAP.

It can now be seen that under our proposed reaction conditions there does seem to be scope for selective electrochemical glycosylation, with the potential window between the most easily oxidised and least easily oxidised glycoside analysed so far being approximately 0.6 V.

3.3.4 Effect of substitution on the aryl anomeric substituent

Another method of effecting the oxidation potential of the anomeric leaving group is to add substituents to the aryl ring, which perturbs the electron distribution over the ring and hence the characteristics of the leaving as a whole. In order to investigate this glycosides of the following form were examined (figure 3.15):

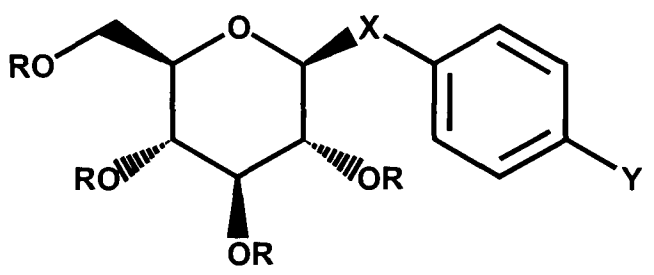


Figure 3.15: R=Bz, Bn, Ac; X=O, S, Se; Y=H, Me, OMe, NO_2

As in the examination of the variation of oxidation potential with protecting group pattern it is best to look at the trends for each heteroatom separately, as the nature of the heteroatom affects the influence of the substituents.

With selenium as the heteroatom, and benzyl protection, it can be seen that the addition of the electron donating methoxy group at the anomeric position has led to a decrease in the peak oxidation potential of approximately 0.3V, compared to the compound with no methoxy group (shown in grey for comparison) (figure 3.16).

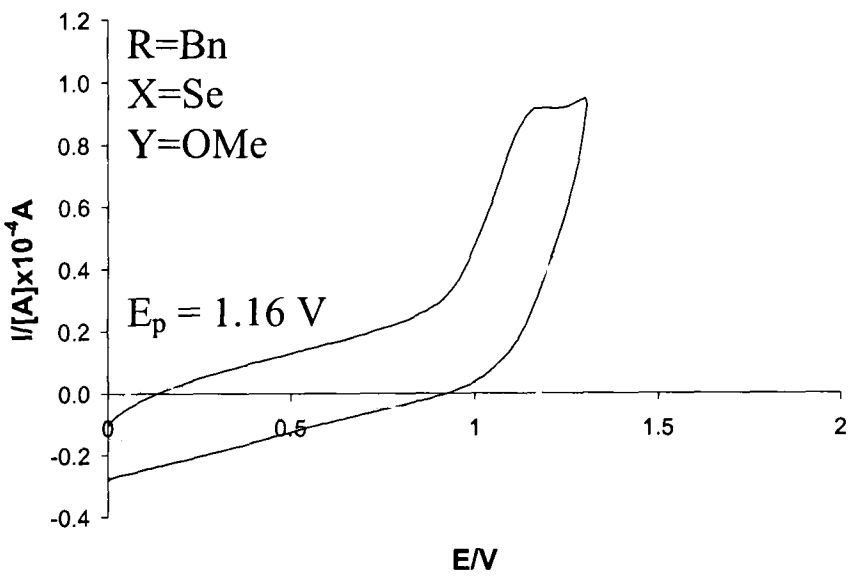


Figure 3.16: First scan voltammograms at 100 mVs^{-1} for: 1.0 mM *p*-methoxyphenyl-2,3,4,6-tetra-*O*-benzyl-1-seleno-β-D-glucopyranoside (black) and 2.1 mM phenyl-2,3,4,6-tetra-*O*-benzyl-1-seleno-β-D-glucopyranoside (grey) in acetonitrile with 0.1 M TBAP. Current is divided by concentration ([A]) for clarity.

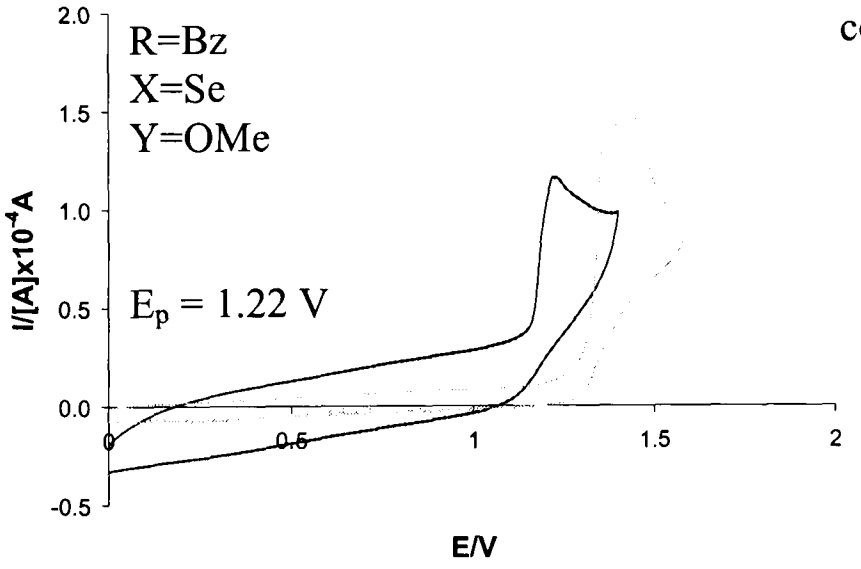


Figure 3.17: First scan voltammograms at 100 mVs^{-1} for: 0.9 mM *p*-methoxyphenyl-2,3,4,6-tetra-*O*-benzoyl-1-seleno-β-D-glucopyranoside (black) and 2.1 mM phenyl-2,3,4,6-tetra-*O*-benzoyl-1-seleno-β-D-glucopyranoside (grey) in acetonitrile with 0.1 M TBAP. Current is divided by concentration ([A]) for clarity.

When the ether protecting groups are swapped for the benzoyl ester protecting groups the drop in oxidation potential is slightly smaller compared to the compound with no methoxy group (shown in grey for comparison) (figure 3.17), at approximately 0.2 V. Interestingly this means that there is a small difference in oxidation potential (~0.05V) between the

benzyl and benzoyl substituted *p*-methoxyphenyl glycosides, with the electron withdrawing benzoyl protecting groups giving the higher peak oxidation potential as expected. This is in contrast to the unsubstituted phenyl selenoglycosides in which the protecting group pattern made no significant difference to the oxidation potential. Both of these *p*-methoxy substituted compounds show the now familiar irreversible oxidation peaks. Comparison of the peak current with the square root of scan rate shows the linear relationship characteristic of diffusion controlled oxidation (figure 3.18).

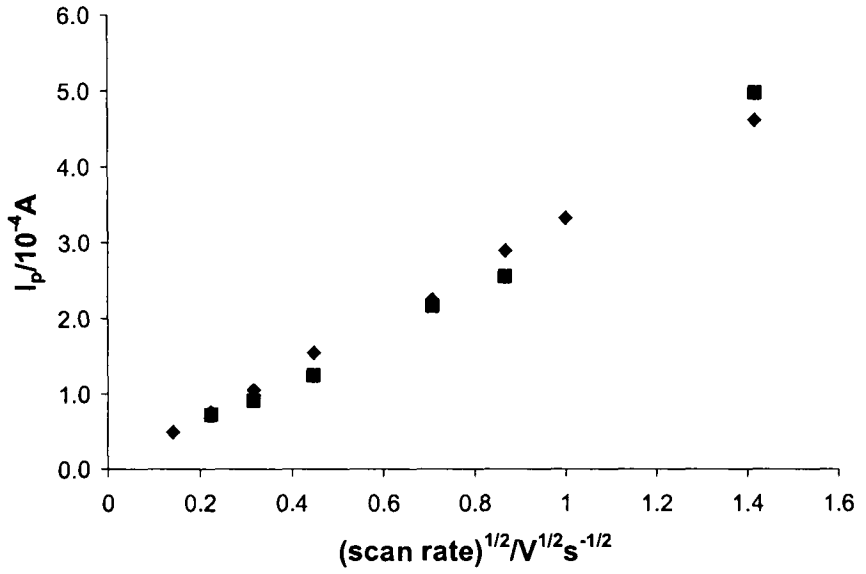


Figure 3.18: Plot of I_p vs. (scan rate)$^{1/2}$ for: 0.9 mM *p*-methoxyphenyl-2,3,4,6-tetra-*O*-benzoyl-1-seleno-β-D-glucopyranoside (▲); 1.0 mM *p*-methoxyphenyl-2,3,4,6-tetra-*O*-benzyl-1-seleno-β-D-glucopyranoside (■); both in acetonitrile with 0.1 M TBAP.

In order to examine the effect of substitution on the aryl ring in more detail compounds with sulphur at the anomeric position were examined, where a wider range of compounds had been synthesised. Initially compounds with global benzyl protection were considered (figure 3.19).

The compound with *p*-methoxy substitution shows the lowest peak oxidation potential, at 1.39 V, due to its strongly electron donating character. The *p*-methyl substitution also gives an oxidation potential lower than the unsubstituted compound, again due to its electron donating nature. The effect however is much smaller than in the case of the *p*-methoxy substitution. This can be understood in terms of the nature of the electron donation.

In the case of methyl substitution the effect is purely inductive, while in the case of the methoxy group the effect is mesomeric in origin. The methoxy group is inductively electron withdrawing, but this is offset by the more powerful electron donating mesomeric effect. Finally an electron withdrawing group was investigated. The *p*-nitro group is both inductively and mesomerically electron withdrawing and it can be seen that the oxidation potential increases dramatically compared to the unsubstituted case. In fact the oxidation peak due to the anomeric group cannot be seen as if it is present it has been swamped by the oxidation of the benzyl protecting groups.

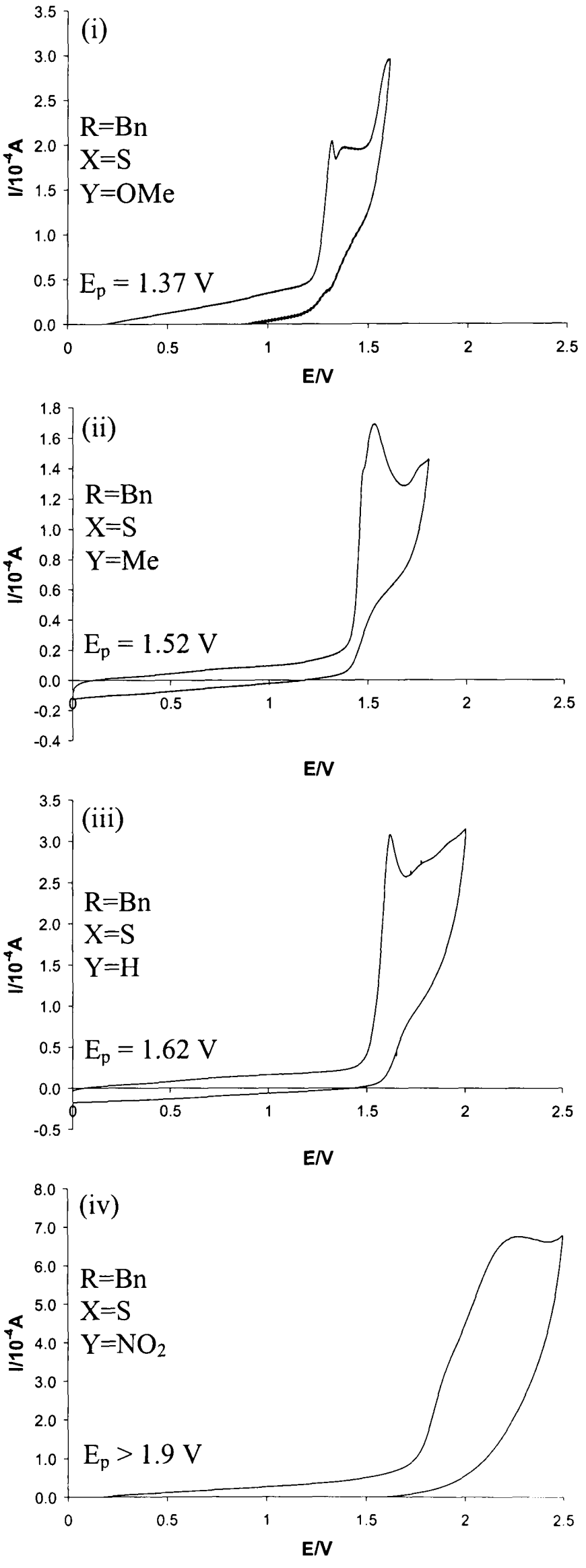
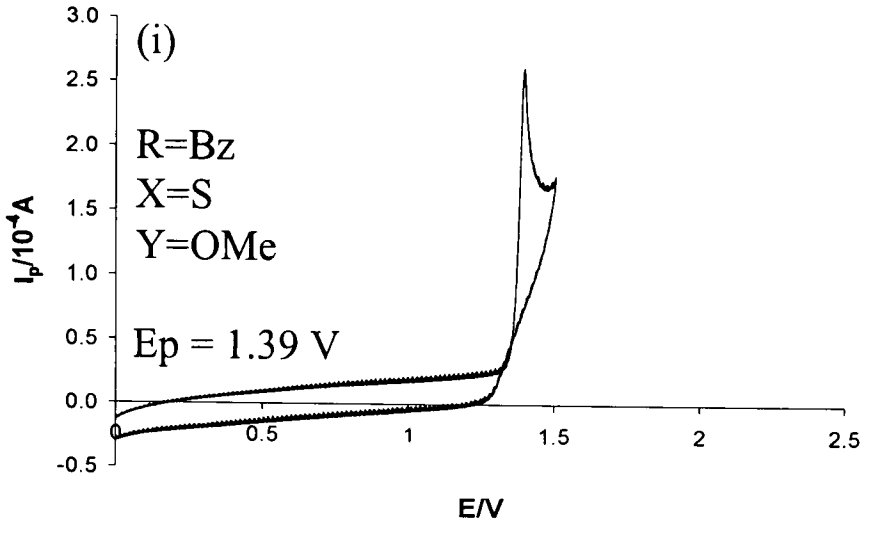
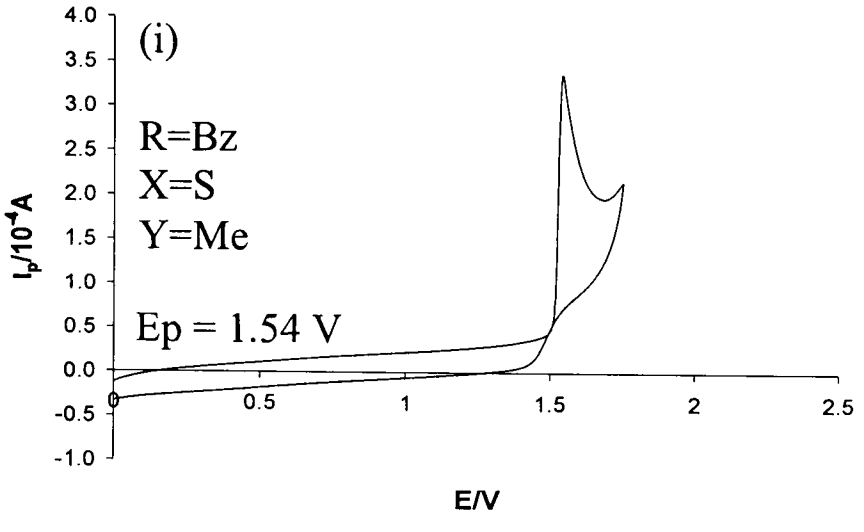
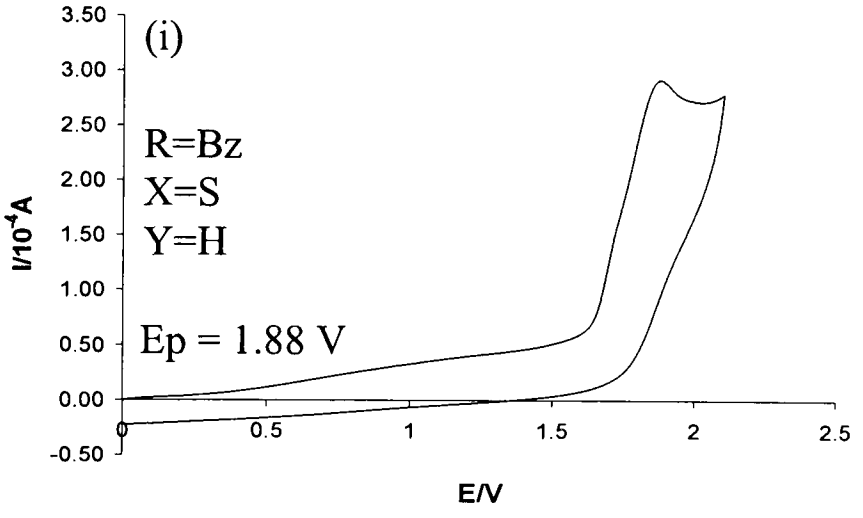


Figure 3.19 (right): First scan voltammograms at 100 mVs^{-1} for: (i) 2.1 mM *p*-methoxyphenyl-2,3,4,6-tetra-*O*-benzyl-1-thio-β-D-glucopyranoside; (ii) 1.6 mM *p*-tolyl-2,3,4,6-tetra-*O*-benzyl-1-thio-β-D-glucopyranoside; (iii) 2.0 mM phenyl-2,3,4,6-tetra-*O*-benzyl-1-thio-β-D-glucopyranoside; (iv) 1.5 mM *p*-nitro-2,3,4,6-tetra-*O*-benzyl-1-thio-β-D-glucopyranoside; all in acetonitrile with 0.1 M TBAP.







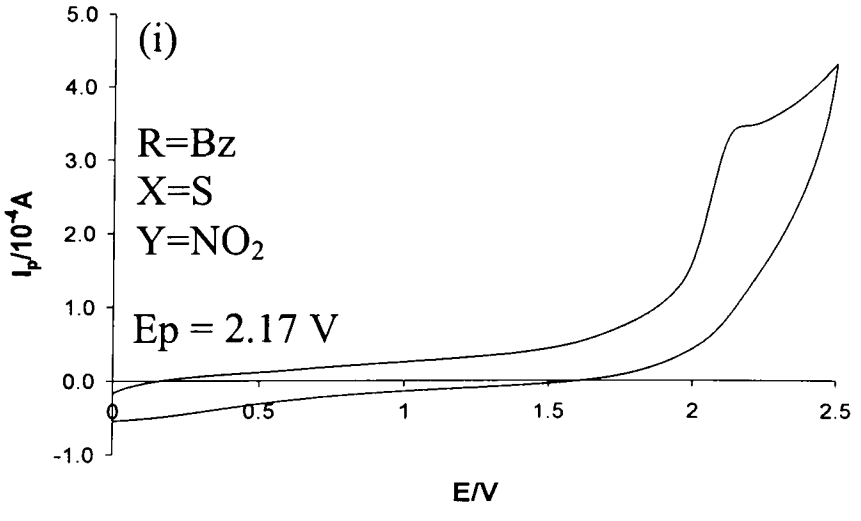


Figure 3.20 (left): First scan voltammograms at 100 mVs^{-1} for: (i) 1.7 mM *p*-methoxyphenyl-2,3,4,6-tetra-*O*-benzoyl-1-thio-β-D-glucopyranoside; (ii) 2.1 mM *p*-tolyl-2,3,4,6-tetra-*O*-benzoyl-1-thio-β-D-glucopyranoside; (iii)1.9 mM phenyl-2,3,4,6-tetra-*O*-benzoyl-1-thio-β-D-glucopyranoside; (iv) 1.5 mM *p*-nitro-2,3,4,6-tetra-*O*-benzoyl-1-thio-β-D-glucopyranoside; all in acetonitrile with 0.1 M TBAP.

Next the same series of compounds but with global benzoyl protection replacing the benzyl protection were examined (figure 3.20). The trend is the same as in the benzyl series, with the peak oxidation potentials going in the order OMe<Me<H<NO_2. What should be noted though is that substitution on the aromatic ring seems to dominate over any effect due to protecting group pattern. In the case with no substitution (i.e. X=H), the difference between the peak oxidation potential of the benzyl and benzoyl protected glycosides is 0.27 V. However when X=MeO or Me there is essentially no difference in oxidation potential. When X=NO_2 we can now see the

expected oxidation peak at 2.2 V. This cannot be compared with the equivalent benzyl protected compound as in that case the oxidation peak, if it occurred, was masked by the electrochemical activity of the benzyl protecting groups. The presence of the peak in the benzyolated compound does however imply that the benzylated analogue may undergo a similar oxidation. A number of the substituted compounds display electrochemical signals which deviated from the classical form, either by exhibiting a pre-wave (as in the case for the benzylated thioglycoside with a *p*-methoxy phenyl anomeric group); or by exhibiting an extremely sharp oxidation peak (as in the case of the benzoylated thioglycosides with *p*-methoxy- and *p*-methylphenyl glycoside anomeric groups). These signals might indicate a deviation from diffusion controlled electrochemistry. However once again it is possible to show that for all of these compounds their electrochemical properties are consistent with the diffusion controlled oxidation that would be expect by comparing the peak current with the square root of scan rate (figure 3.21).

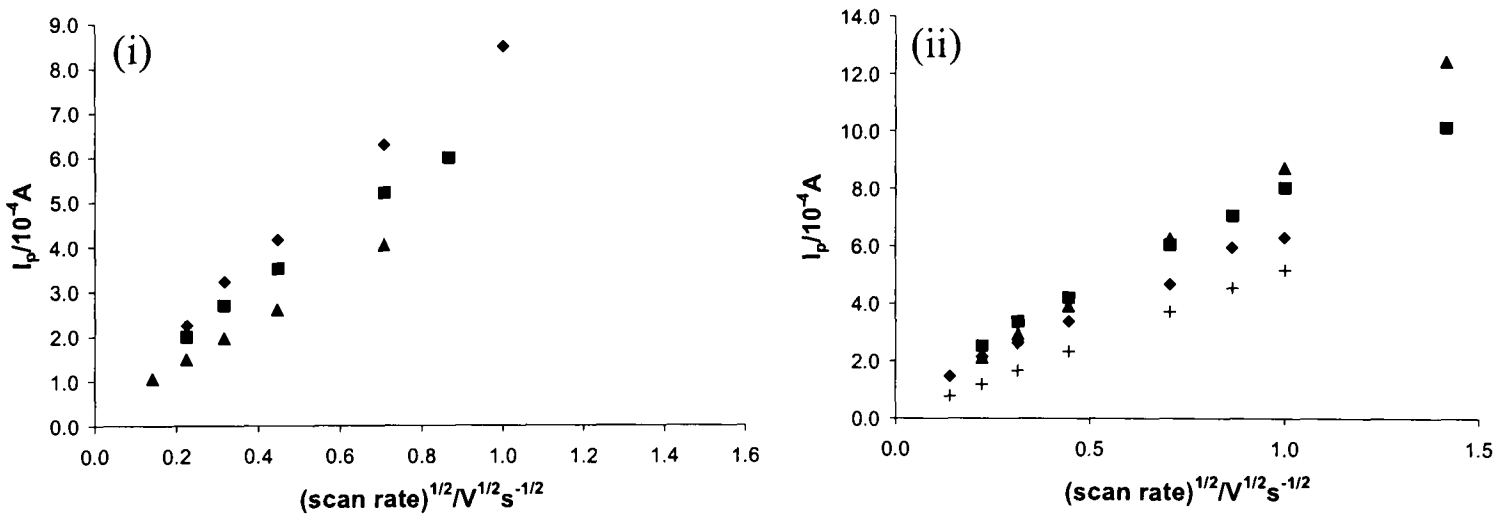


Figure 3.21: Plot of I_p vs. (scan rate)$^{1/2}$ for: (i) 2.0 mM phenyl-2,3,4,6-tetra-*O*-benzyl-1-thio-β-D-glucopyranoside (◆); 1.6 mM *p*-tolyl-2,3,4,6-tetra-*O*-benzyl-1-thio-β-D-glucopyranoside (■); 2.1 mM *p*-methoxyphenyl-2,3,4,6-tetra-*O*-benzyl-1-thio-β-D-glucopyranoside (▲); and (ii) 1.9 mM phenyl-2,3,4,6-tetra-*O*-benzoyl-1-thio-β-D-glucopyranoside (▲); 2.1 mM *p*-tolyl-2,3,4,6-tetra-*O*-benzoyl-1-thio-β-D-glucopyranoside (■); 1.7 mM *p*-methoxyphenyl-2,3,4,6-tetra-*O*-benzoyl-1-thio-β-D-glucopyranoside (◆); 1.5 mM *p*-nitrophenyl-2,3,4,6-tetra-*O*-benzoyl-1-thio-β-D-glucopyranoside (+); all in acetonitrile with 0.1 M TBAP.

Finally the effect of substitution on the *O*-glycosides was examined. Substitution on the aromatic ring, at the *para* position, with the electron donating methoxy group resulted in an extremely significant reduction in the oxidation potential of the glycoside, regardless of the protecting group pattern (the analogous unsubstituted compounds are shown in grey for comparison) (figure 3.22).

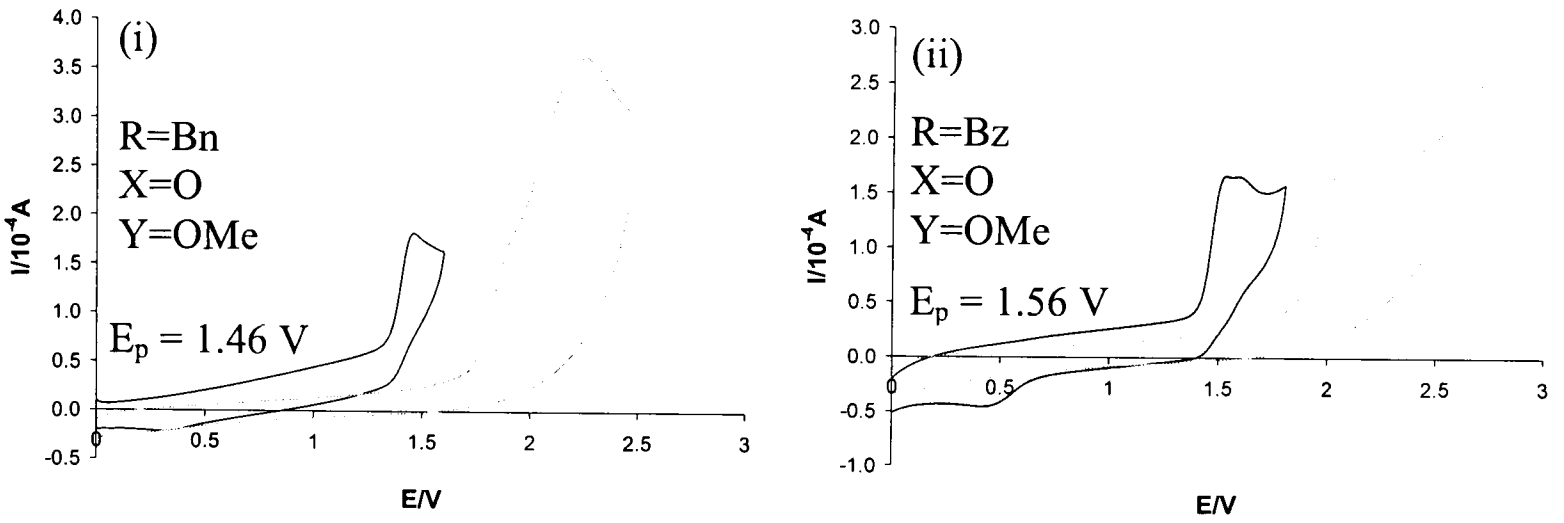


Figure 3.22: First scan voltammograms at 100 mVs^{-1} for: (i) 1.1 mM *p*-methoxyphenyl-2,3,4,6-tetra-*O*-benzyl-β-D-glucopyranoside (black) and 1.6 mM phenyl-2,3,4,6-tetra-*O*-benzyl-β-D-glucopyranoside (grey); (ii) 1.3 mM *p*-methoxyphenyl-2,3,4,6-tetra-*O*-benzoyl-β-D-glucopyranoside (black) and 1.5 mM phenyl-2,3,4,6-tetra-*O*-benzoyl-β-D-glucopyranoside (grey); both in acetonitrile with 0.1 M TBAP.

The reduction is approximately 0.4 V when the protecting groups are all benzyl and 0.5 V when the protecting groups are all benzoyl. The resulting difference in the oxidation potential of the *p*-methoxyphenyl glycosides is 0.1 V, with the benzoyl protected glycoside having the higher oxidation potential. Clearly the effect of the aromatic substitution is dominating, but in contrast to the seleno- and thioglycosides the protecting group pattern does still have some influence.

Once again when the square root of scan rate is plotted against peak current these glycosides demonstrate characteristics of an irreversible oxidation, with properties consistent with a diffusion controlled process (figure 3.23).

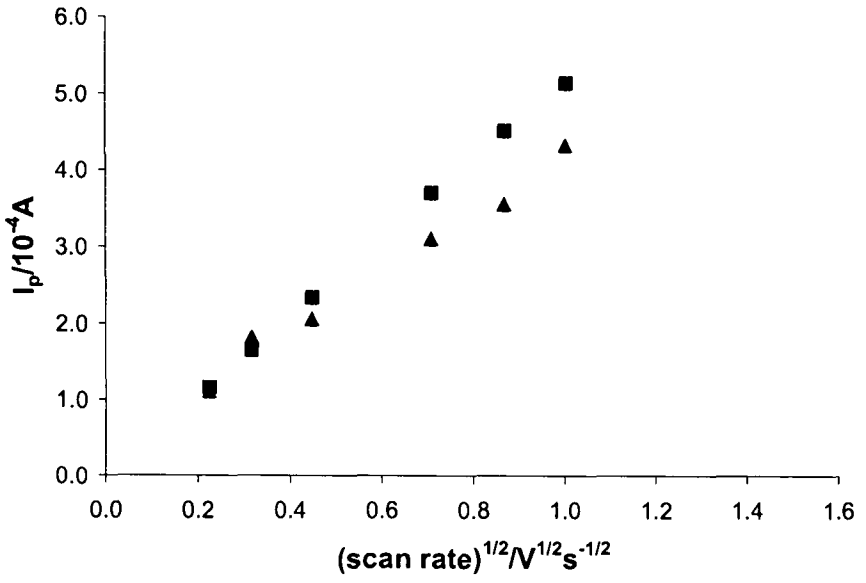


Figure 3.23: Plot of I_p vs. (scan rate)$^{1/2}$ for: 1.1 mM *p*-methoxyphenyl-2,3,4,6-tetra-*O*-benzoyl-β-D-glucopyranoside (■); 1.3 mM *p*-methoxyphenyl-2,3,4,6-tetra-*O*-benzyl-β-D-glucopyranoside (▲); both in acetonitrile with 0.1 M TBAP.

3.3.5 Effect of alternative anomeric groups

The effect of non aromatic substitution on the anomeric group was examined briefly, focusing on some common groups employed in glycosylation chemistry. Compounds were of the following form (figure 3.24).

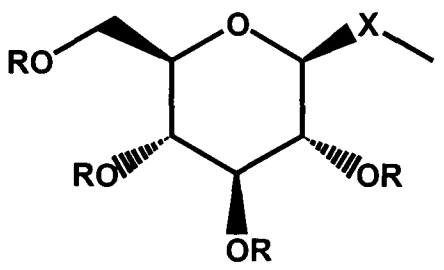


Figure 3.24: R=Bz; X=S, Se

Both compounds are electrochemically active, showing a clear irreversible peak on the forward scan (figure 3.25).

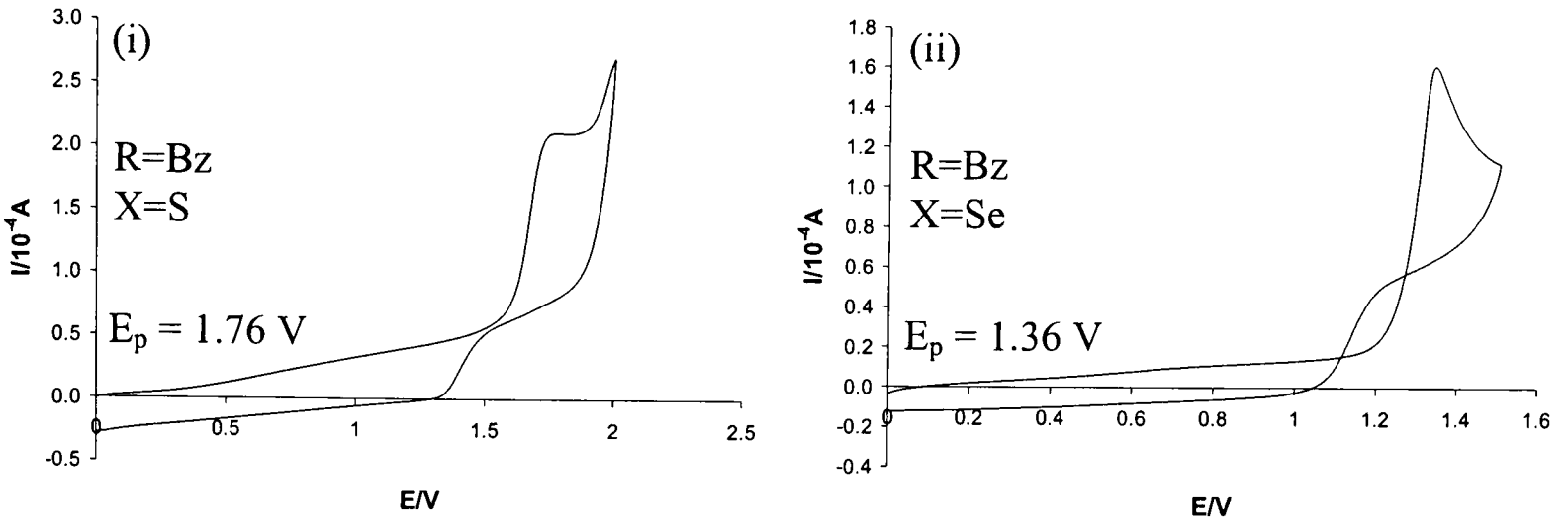


Figure 3.25: First scan voltammograms at 100 mVs^{-1} for: (i) 1.9 mM methyl-2,3,4,6-tetra-*O*-benzoyl-1-thio-β-D-glucopyranoside and (ii) 1.9 mM methyl-2,3,4,6-tetra-*O*-benzoyl-1-seleno-β-D-glucopyranoside; both in acetonitrile with 0.1 M TBAP.

As expected the thioglycoside has a higher oxidation potential (in this case by some 0.4 V) than the selenoglycoside. It can also be seen that the methyl thioglycoside is easier to oxidise, by about 0.1 V than the equivalent phenyl thioglycoside. However the methyl selenoglycoside shows almost exactly the same oxidation potential as the selenophenyl analogue. During the analysis of both of these compounds, but much more so with the selenoglycoside than the thioglycoside, an extremely noxious odour was produced. This was presumably due to the generation of free selenols or thiols respectively. Considering the small quantities of compound actually oxidised during a voltammetric scan it is of some note that the odour was appreciable. Comparison of the square root of scan rate with the peak oxidation potential is once again consistent with the diffusion controlled process that is expected (figure 3.26).

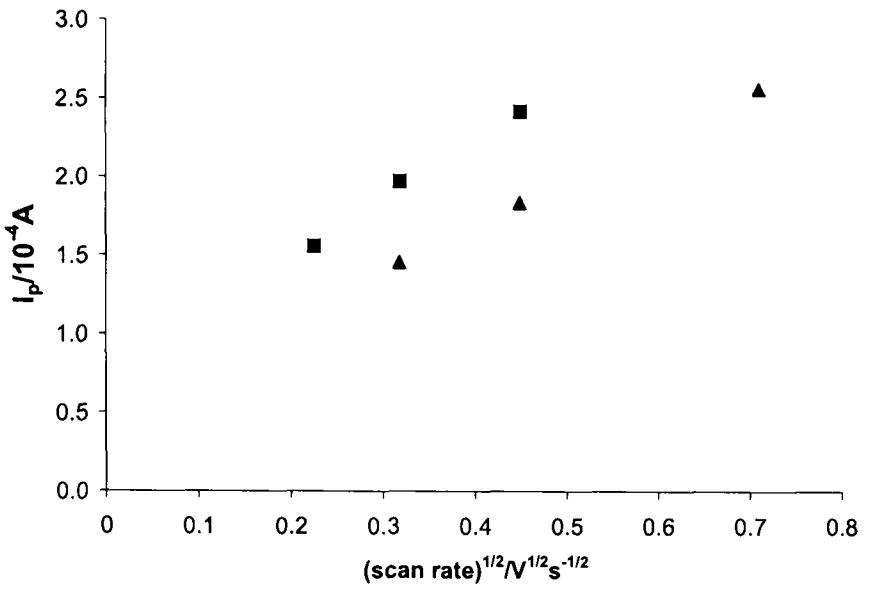
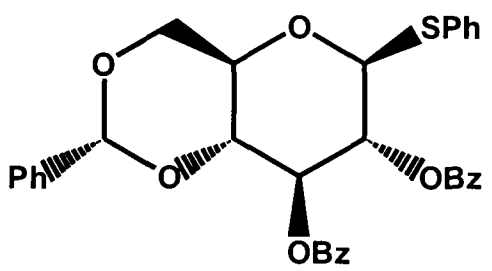


Figure 3.26: Plot of I_p vs. (scan rate)$^{1/2}$ for: 1.9 mM methyl-2,3,4,6-tetra-*O*-benzoyl-1-thio-β-D-glucopyranoside (■); 1.9 mM methyl-2,3,4,6-tetra-*O*-benzoyl-1-seleno-β-D-glucopyranoside (▲); both in acetonitrile with 0.1 M TBAP.

3.3.6 Effect of ring locking

It has been established[20] that in chemical glycosylations the use of a protecting group that restricts the conformation which the glycoside can adopt can have a deactivating effect. This results from an increase in strain during the formation of the glycosyl cation intermediate and a consequent rise in energy of that intermediate. The most common protecting group used in this way is benzylidene protection[21] across the O-4 and O-6 positions of a glucoside. In order to try to see if this effect was reflected in the electrochemical oxidation potential of such a compound the following glucoside was examined:



The irreversible oxidation occurs at almost exactly the same potential as the fully benzoylated thioglycoside, suggesting that the benzylidene group is deactivating the thioglycoside to approximately the same extent as the two electron withdrawing benzoyl groups that it has replaced (figure 3.27).

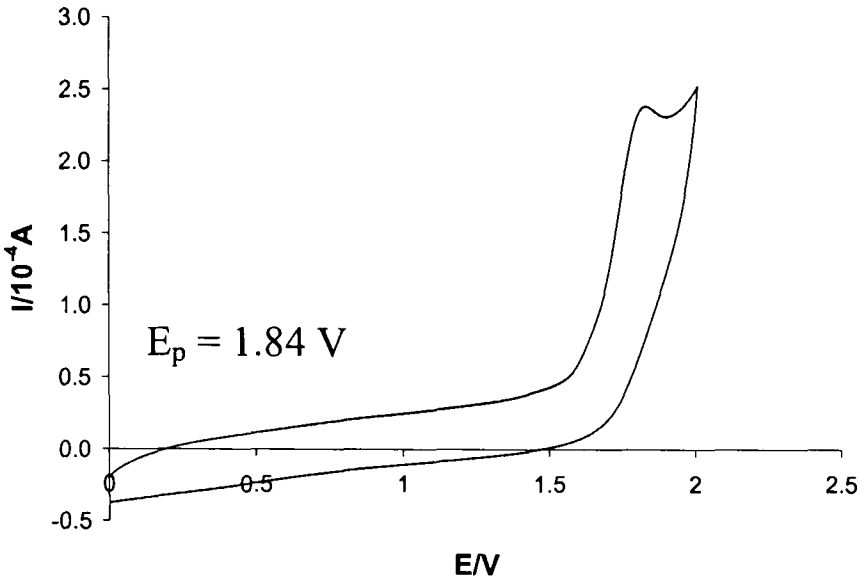


Figure 3.27: First scan voltammogram at 100 mVs^{-1} for 1.5 mM phenyl-2,3-di-*O*-benzoyl-4,6-benzylidene-1-thio-β-D-glucopyranoside in acetonitrile with 0.1 M TBAP.

Comparison of the square root of scan rate with the peak oxidation potential is consistent with a diffusion controlled mechanism (figure 3.28).

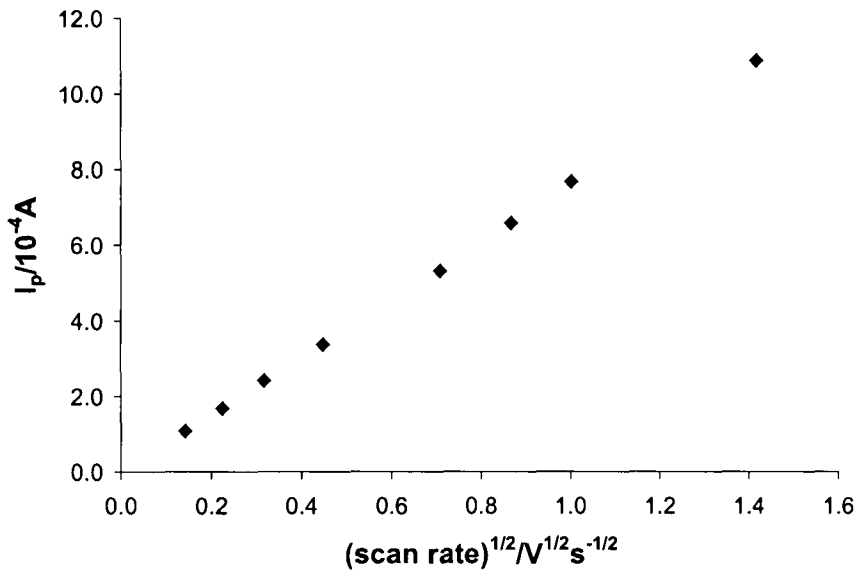


Figure 3.28: Plot of I_p vs. (scan rate)$^{1/2}$ for: 1.5 mM phenyl-2,3-di-*O*-benzoyl-4,6-benzylidene-1-thio-β-D-glucopyranoside in acetonitrile with 0.1 M TBAP.

3.3.7 Mannosides

Finally some thiomannosides were examined to give a little insight into possible variation of oxidation potential in different sugars. Two compounds were studied, the benzoylated thiophenyl mannoside and the benzoylated thiomethyl mannoside (figure 3.29).

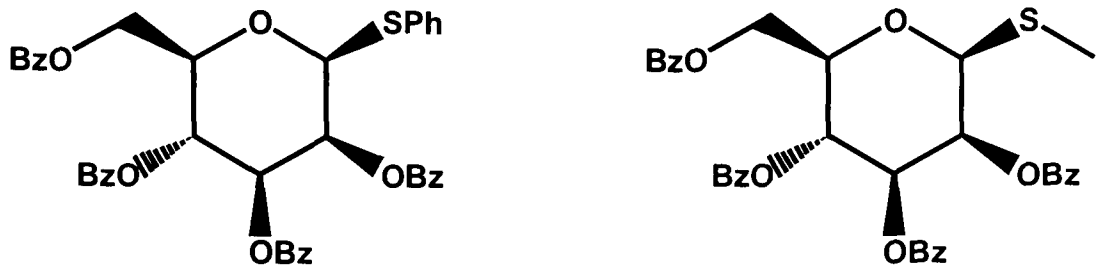


Figure 3.29

The thiophenyl mannoside gave an unusual signal, with two peaks close together just below 2 V (figure 3.30).

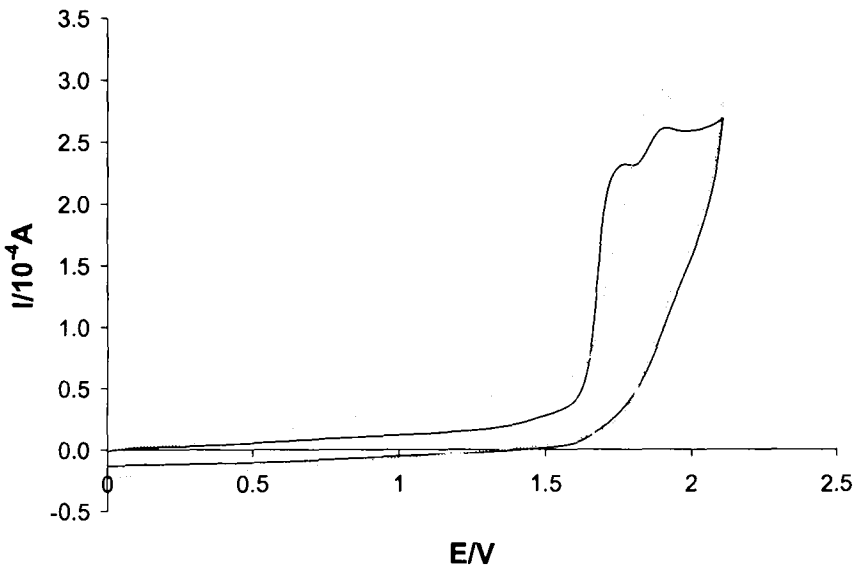


Figure 3.30: First scan voltammograms at 100 mVs^{-1} for 1.9 mM phenyl-2,3,4,6-tetra-*O*-benzoyl-1-thio-β-D-mannopyranoside (black) and 1.8 mM phenyl-2,3,4,6-tetra-*O*-benzoyl-1-thio-β-D-glucopyranoside (grey) in acetonitrile with 0.1 M TBAP.

Comparison with the analogous glucoside (shown in grey) shows that the second of these peaks is at almost the same oxidation potential as the glucoside. However it is not clear which of these signals corresponds to the oxidation of the thiophenyl anomeric group and so further analysis was not possible. The thiomethyl mannoside however shows a well defined irreversible peak at 1.52 V, significantly lower than the glucoside analogue (shown in grey for comparison) (figure 3.31). The mannoside also exhibits a much sharper peak. Plotting the peak current against the square root of the scan rate (figure 3.32) for the mannoside gives an ambiguous result. The first three points suggest a linear relationship between the two quantities, but the fourth shows significant deviation from the pattern. It is therefore not clear whether the oxidation in this case

is diffusion controlled or if the sharp oxidation peak is indicative of some adsorption at the electrode surface, which in turn affects the mass transport characteristics of the system.

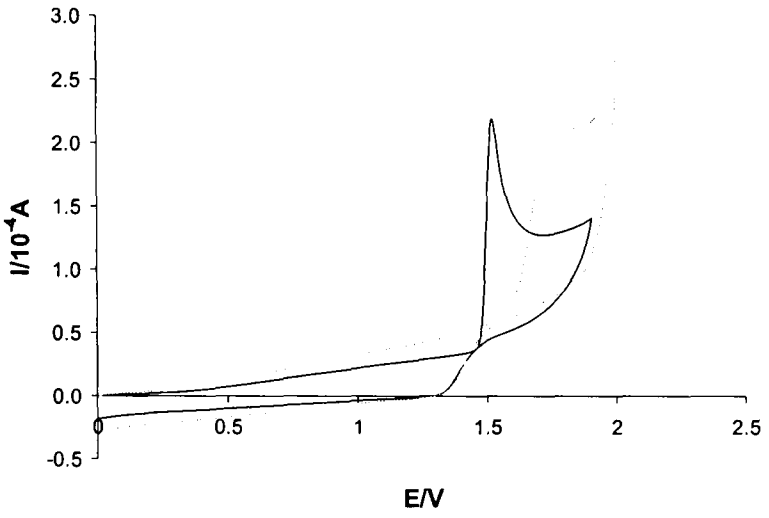


Figure 3.31: First scan voltammograms at 100 mVs^{-1} for 2.4 mM methyl-2,3,4,6-tetra-*O*-benzoyl-1-thio-β-D-mannopyranoside (black) and 1.9 mM methyl-2,3,4,6-tetra-*O*-benzoyl-1-thio-β-D-glucopyranoside (grey) in acetonitrile with 0.1 M TBAP.

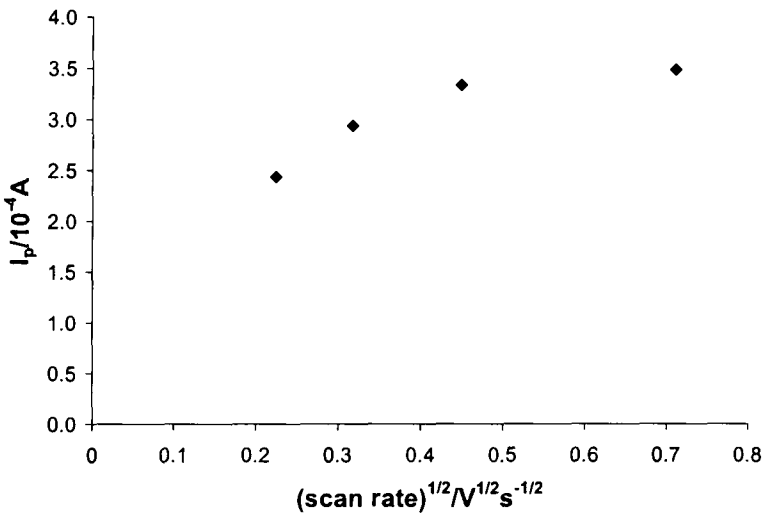
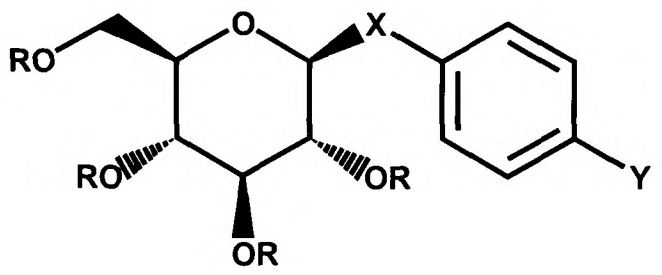


Figure 3.32: Plot of I_p vs. (scan rate)$^{1/2}$ for: 2.4 mM methyl-2,3,4,6-tetra-*O*-benzoyl-1-thio-β-D-mannopyranoside in acetonitrile with 0.1 M TBAP.

3.3.8 Summary

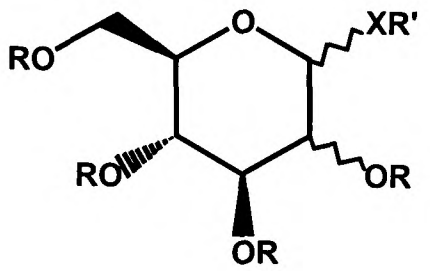
A large amount of detailed information about a range of thio-, seleno- and *O*-glycosides has been obtained, which could then be applied to synthetic systems (Chapter 4). This work revolves around an understanding of the oxidation potentials of these compounds and for ease of reference a table of peak oxidations is included here. Potentials are given both against the standard calomel reference electrode, as discussed above, as well as against the silver wire reference electrode. For reasons that will be explained in the following chapter the silver wire pseudo reference electrode was used in a majority of the synthetic work.

Table 3.1: Phenyl Glucosides



X	R	Y	Peak Oxidation Potential (E_p)/V ± 0.01 V	
			vs Ag Wire	vs Calomel
Se	Bn	OMe	1.35	1.16
Se	Bn	H	1.47	1.43
Se	Bz	OMe	1.29	1.22
Se	Bz	H	1.64	1.42
Se	Ac	H	1.44	1.39
S	Bn	OMe	1.39	1.37
S	Bn	Me	1.67	1.52
S	Bn	H	-	1.62
S	Bn	NO_2	>2.0	>1.9
S	Bz	OMe	1.51	1.39
S	Bz	Me	1.61	1.54
S	Bz	H	2.00	1.88
S	Bz	NO_2	2.18	2.17
S	PhCH, Bz*	H	1.91	1.84
S	Ac	Me	1.61	1.54
S	Ac	H	-	1.54
O	Bn	OMe	1.42	1.46
O	Bn	H	1.95	1.91
O	Bz	OMe	1.60	1.56
O	Bz	H	1.99	2.05
O	Ac	H	2.22	2.03

Table 3.2: Other Glucosides and Mannosides



X	R	R'	Glucose or Mannose	Peak Oxidation Potential (E_p)/V ± 0.01 V vs Calomel
S	Bz	Me	Glucose	1.36
Se	Bz	Me	Glucose	1.76
S	Bz	Ph	Mannose	-
S	Bz	Me	Mannose	1.52

3.3.9 Conclusions

An in depth picture of the voltammetry of a wide range of glycosides which are amenable to electrochemical glycosylations has been obtained. It has been shown that against a standard calomel electrode there is a potential window of approximately 0.9 V, with the lowest oxidation potential at 1.16 V, and the highest at 2.05 V. The trends in the oxidation potential of the glycosides have been probed and it has been shown that in general the more electron rich the glycoside the lower its oxidation potential. Of all the factors that affect this it is the nature of the heteroatom which exerts the biggest influence, followed by the nature of the subsituent directly bonded to the heteroatom. In the case of phenyl glycosides in particular dramatic changes in oxidation potential were observed when the phenyl ring was substituted with electron donating or withdrawing groups. Finally the protecting group pattern has been shown to influence the oxidation potential, if the effects of the heteroatom and other anomeric substitution are not too strong to allow the effect to be seen.

3.4 Analysis of monosaccharides by fast scan cyclic voltammetry[22]

A few representative glycosides were chosen to conduct fast scan analysis on, in order to see if it would be possible to determine their formal oxidation potentials (E_f^0). This is a purely thermodynamic property of the system, as opposed the peak potentials obtained in the previous section which are effect by factors such as mass transport to the electrode, the kinetics of electron transfer and the follow-on homogeneous kinetics. In order to infer the thermodynamic characteristics of the system it was necessary to reduce the voltammetric timescale, in order to outrun the homogenous kinetics. Six representative compounds were chosen for this work, and are shown below (figure 3.33).

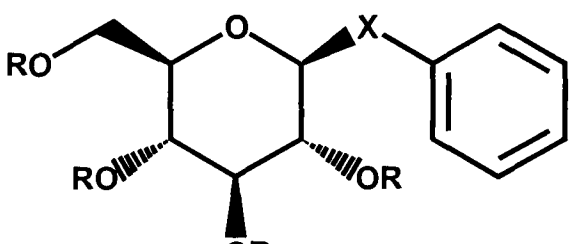


Figure 3.33: Monosaccharides for fast scan analysis. R=Bn, Bz; X=Se, S, O

Where R is benzyl or benzoyl and X is sulphur, selenium or oxygen. Once the fast scan cyclic voltammetric experiments had been conducted they were subsequently analysed using DigiSim™ software.[12]

First phenyl-2,3,4,6-tetra-*O*-benzyl-1-thio-β-D-glucopyranoside was taken as a model system and subjected to single cyclic voltage scans at scan rates in the range 0.1V to 25kV s^{-1}, using 2.5 mM, 5.5 mM and 11 mM solutions of the glycoside in DMSO with 0.25 M tetraethylammonium perchlorate (figure 3.34). The experiments were conducted using a 12.5 μm diameter platinum microdisk as the working electrode. Single voltage scans that were used as the previous slow scan work, as well as initial fast scan work, indicated that continuous

voltage sweeping led to fouling of the electrode. As an additional precaution the electrode was cleaned after each scan, and each scan repeated to ensure consistent voltammograms were obtained. Finally a background voltammogram was obtained by using a separate solution of 0.25 M tetraethyl ammonium perchlorate (TEAP) in dimethylsulphoxide with the same electrode and potentiostat set up for scan rate and ohmic compensation. These background scans were then subtracted from the previously measured voltammograms to obtain background free voltammetry for analysis. At relatively slow scan rates the voltammograms are very similar to those collected in the 20 mVs^{-1} to 2 Vs^{-1} and discussed in the previous section. However as the scan rate gets faster it was possible to see that the homogenous kinetics are being out run, and a back peak is clearly visible.

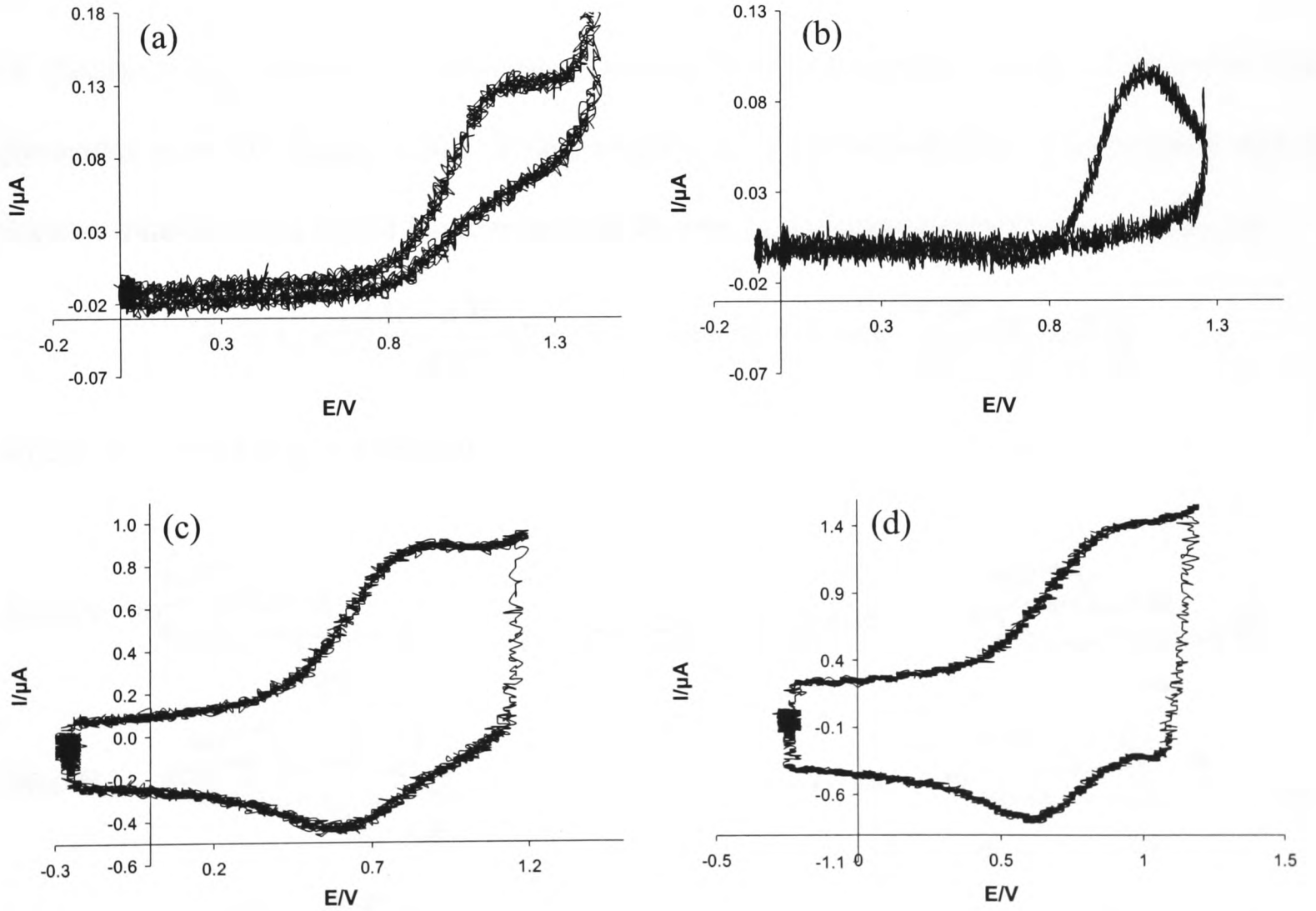


Figure 3.34: Representative single scan voltammograms for phenyl-2,3,4,6-tetra-*O*-benzyl-1-thio-β-D-glucopyranoside in DMSO with 0.25 M TEAP at: (a) 60 Vs^{-1} (2.5 mM); (b) 300 Vs^{-1} (5.5 mM); (c) 3000 Vs^{-1} (5.5 mM) and (d) 6000 Vs^{-1} (11 mM).

In order to confirm that the current-voltage response was due to diffusing rather than absorbed species a plot of peak currents against square root of scan rate was produced; the linear relationship shows this to be the case (figure 3.35).

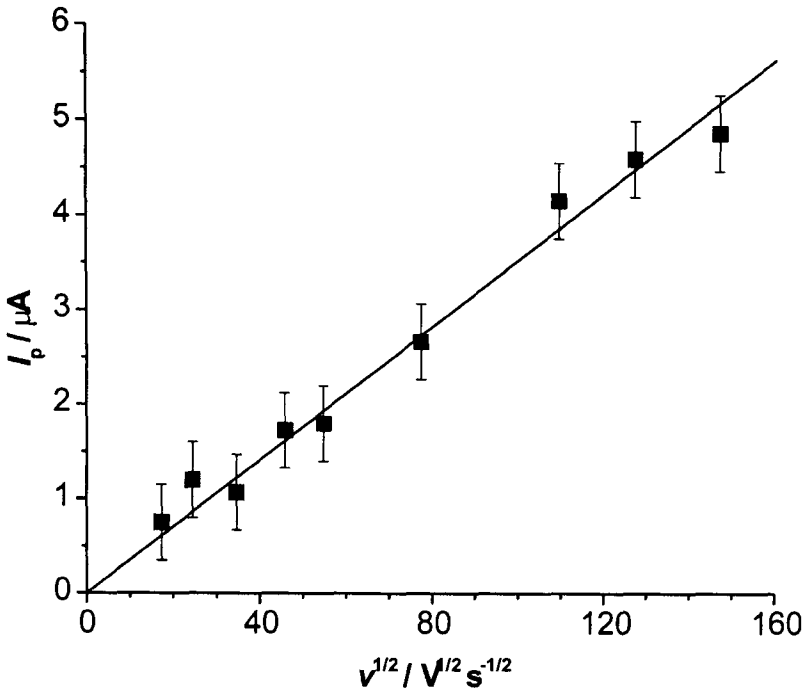


Figure 3.35: Plot of I_{peak} vs $\sqrt{v}$ for 3.0 mM phenyl-2,3,4,6-tetra-*O*-benzyl-1-thio-β-D-glucopyranoside in DMSO with 0.25 mM TEAP

As discussed previously, it is believed that the general mechanism for the oxidation of these glycosides is an EC (figure 3.36).[4] In this scheme, k_1 is the homogeneous rate constant and the electron transfer rates, k_f and k_b are related to the standard electrochemical rate constant by

$$k_f = k_0 \exp\left(\frac{(1-\alpha)F}{RT}\left(E - E_f^0\right)\right) \text{ and } k_b = k_0 \exp\left(\frac{-\alpha F}{RT}\left(E - E_f^0\right)\right)$$

where α is the transfer coefficient.[23]

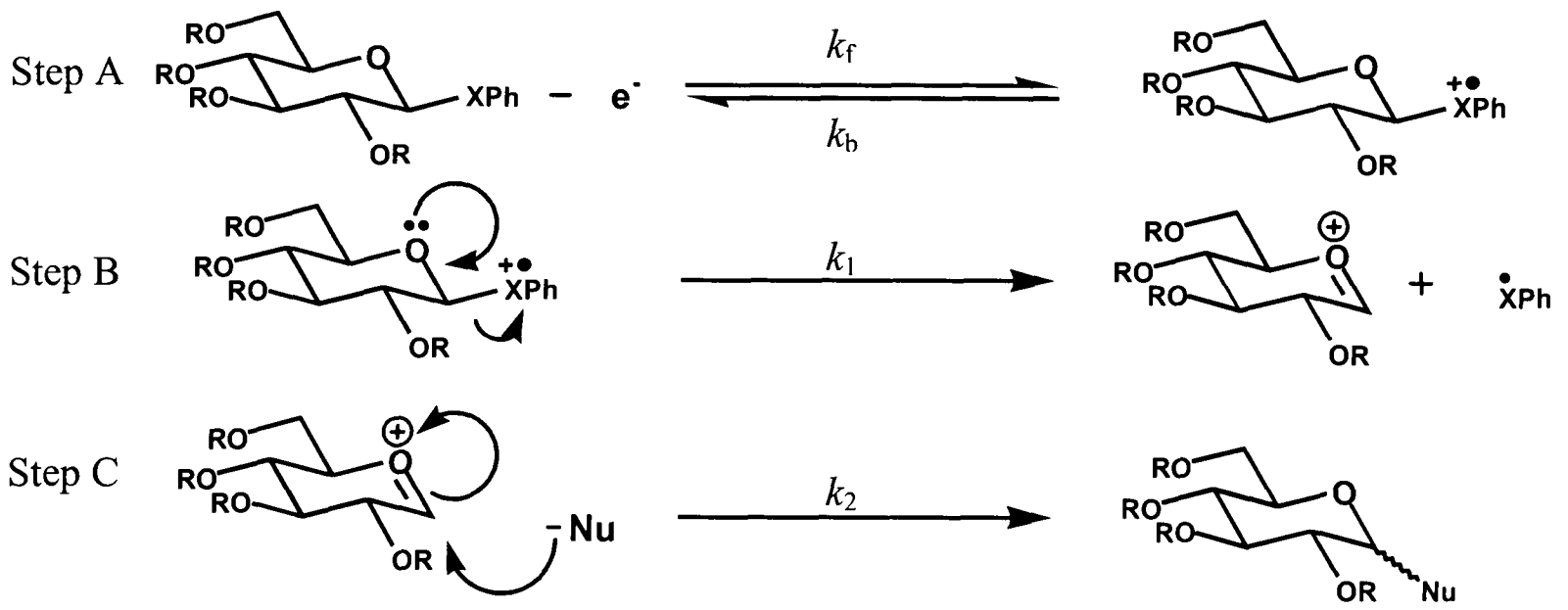


Figure 3.36: Proposed EC mechanism for the oxidation of chalcoglycosides

It is clear from this mechanism that the leaving group, which has electrochemical properties of its own, could interfere with the voltammetry. In order to confirm that this was not the case, and that therefore the EC mechanism discussed above is applicable, a simple voltammetric experiment was conducted on diphenyl disulphide (the presumed by-product of the reaction). A 6.4 mM solution of diphenyl disulphide in DMSO with 0.25 M tetraethylammonium perchlorate (TEAP) was prepared. The voltammetry was conducted using a 12.5 μm diameter platinum microdisk working electrode, a platinum mesh counter electrode and a silver wire reference electrode. A representative voltammogram is shown below, with a voltammogram of phenyl-2,3,4,6-tetra-*O*-benzyl-1-thio-β-D-glucopyranoside **78** for comparison (figure 3.37).

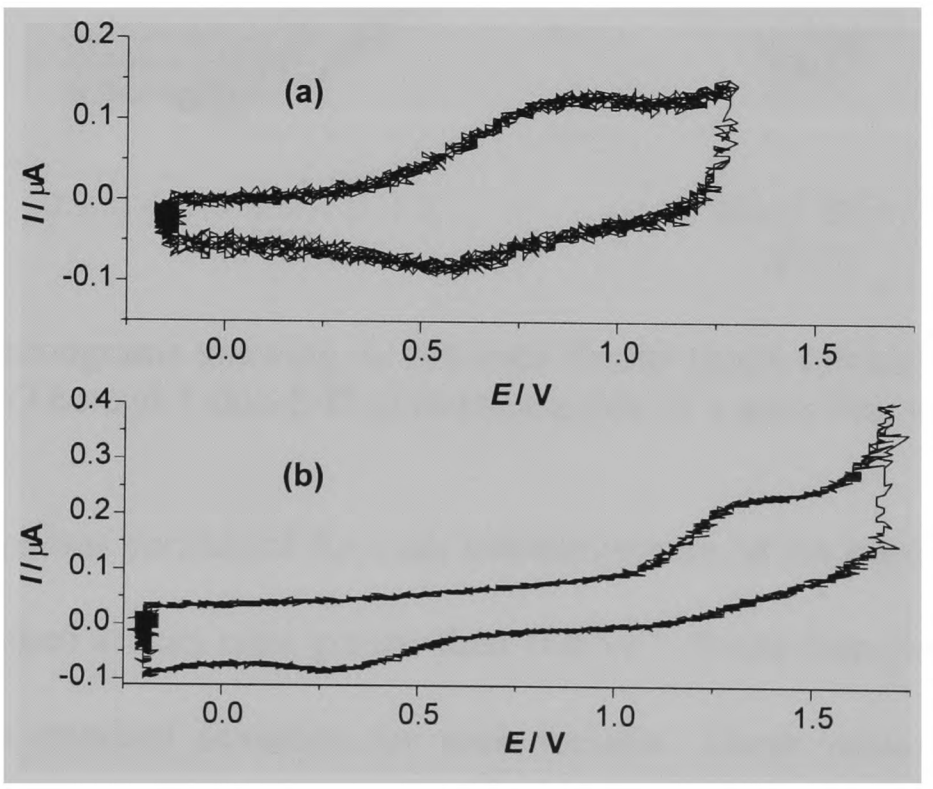


Figure 3.37: Single scan voltammograms at 1 $kVs^{-1}$for: (a) 3.0 mM phenyl-2,3,4,6-tetra-*O*-benzyl-1-thio-β-D-glucopyranoside in DMSO with 0.25 M TEAP and (b) 6.4 mM diphenyl disulphide in DMSO with 0.25 M TEAP

It can be seen that under these experimental conditions the diphenyl disulphide is oxidised at higher potentials than the thioglycoside, and so analysis for the EC mechanism is pertinent.

The theoretical comparison was conducted by comparing the experimentally obtained voltammograms of phenyl-2,3,4,6-tetra-*O*-benzyl-1-thio-β-D-glucopyranoside **78** (*vide supra*),

with simulated voltammograms obtained using the DigiSim™ programme.[24] Manual variation of the parameters E_f^0, α, k_0 and k_1 allowed us to obtain good fitting of theory to experiment (figure 3.38). Due to the short timescale of the experiments it was possible to use a linear diffusion model in the simulations rather than the convergent diffusion regime usually applied to microdisk electrodes.[25]

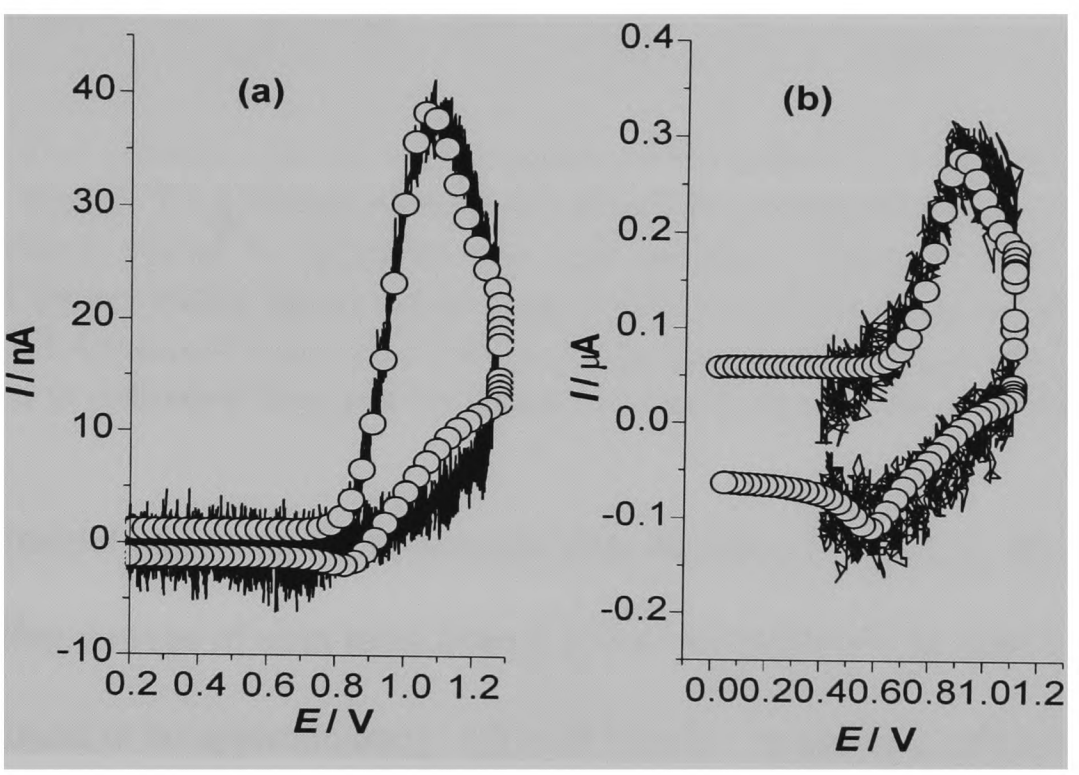


Figure 3.38: Voltammograms showing fit between theory (open circles) and experiment for phenyl-2,3,4,6-tetra-*O*-benzyl-1-thio-β-D-glucopyranoside at a scan rate of (a) 300 V s^{-1}, and (b) 2000 V s^{-1}

This fitting procedure was conducted for each voltammogram of the benzylated thioglycoside which had been obtained at scan rates greater than 100 Vs^{-1}. It was then possible to obtain both a mean value and a standard deviation for each variable. These values were then used to simulate a theoretical response for each scan rate, and these theoretical responses compared with the experimental data. Plots of the variation of both peak current ratios (anodic to cathodic) and peak potentials with scan rate were produced and show good agreement between theory and experiment (Figure 3.39).

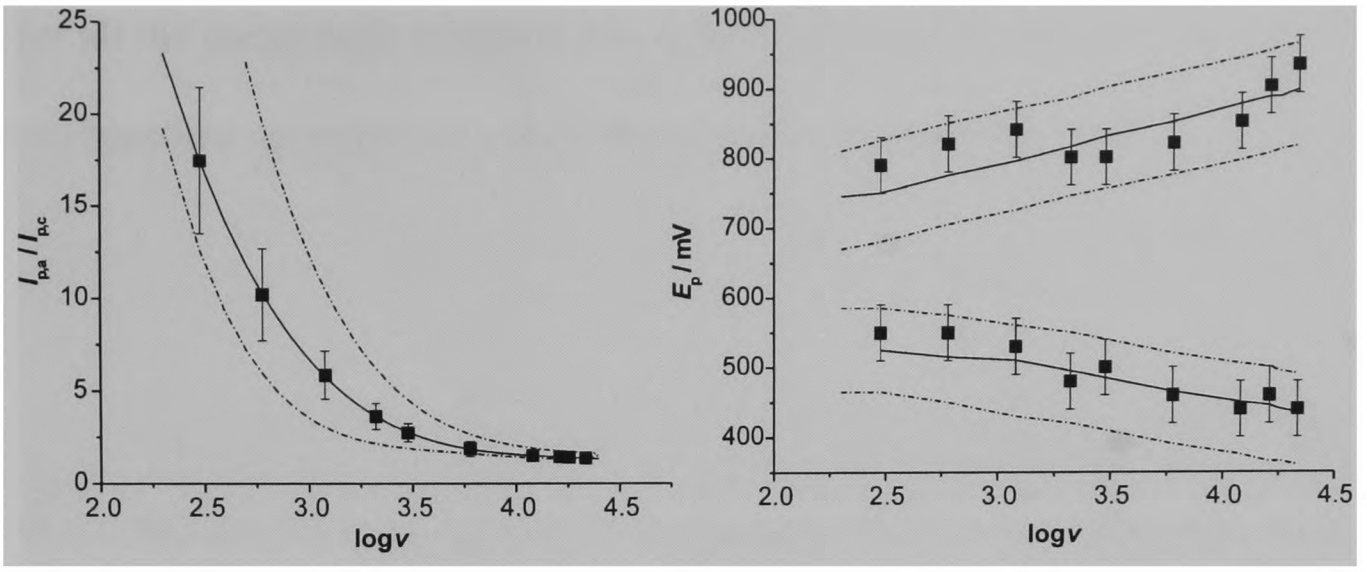


Figure 3.39: (a) Plot of theory (lines) versus experiment (squares) for ratio of peak currents vs. scan rate for phenyl-2,3,4,6-tetra-*O*-benzyl-1-thio-β-D-glucopyranoside, with the mean theoretical response is shown in unbroken line, and maximum and minimum values in broken lines; (b) Plot of theory (solid lines) versus experiment (squares) for peak potentials vs. scan rate for phenyl-2,3,4,6-tetra-*O*-benzyl-1-thio-β-D-glucopyranoside, with the mean theoretical response is shown in unbroken line, and maximum and minimum values in broken lines.

The same experimental and simulation protocols were repeated for each of the glycosides under consideration, using a range of scan rates from 0.1 V s^{-1} to 25 kV s^{-1}. In each case the diffusion coefficient was found to be approximately 1.0×10^{-5} $cm^2 s^{-1}$. In the case of the selenoglycosides it was possible able to show that there was no interference from the oxidation of diphenyl diselenide in the oxidation of the glycosides as it has a higher oxidation potential, in agreement with the literature (Figure 3.40).[26]

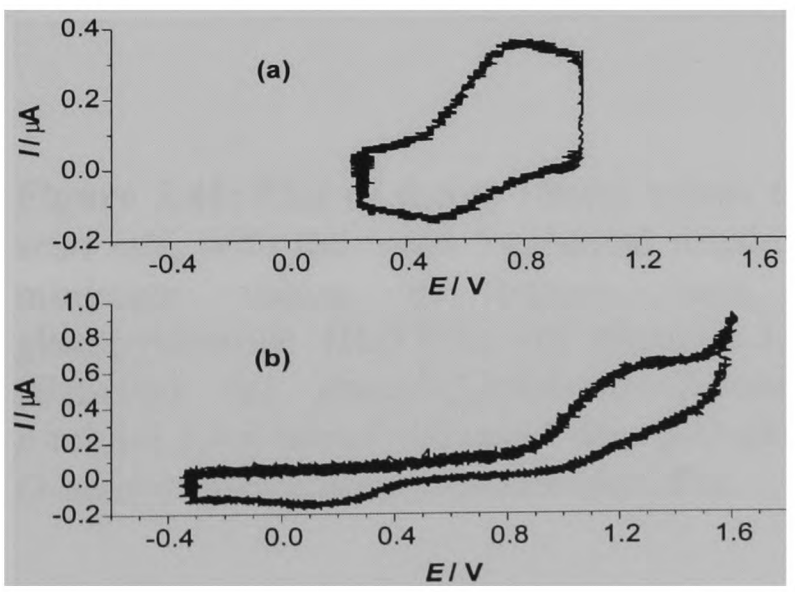


Figure 3.40: Comparison of unsubtracted voltammograms at a scan rate of 1 kV s^{-1} for: (a) 3.0 mM phenyl-2,3,4,6-tetra-*O*-benzyl-1-seleno-β-D-glucopyranoside in DMSO with 0.25 M TEAP; (b) 7.8 mM diphenyl diselenide in DMSO with 0.25 M TEAP.

The data for all the compounds analysed was collated (Table 3.3, figures 3.41 and 3.42) and in each case an excellent agreement between theory and experiment is found.

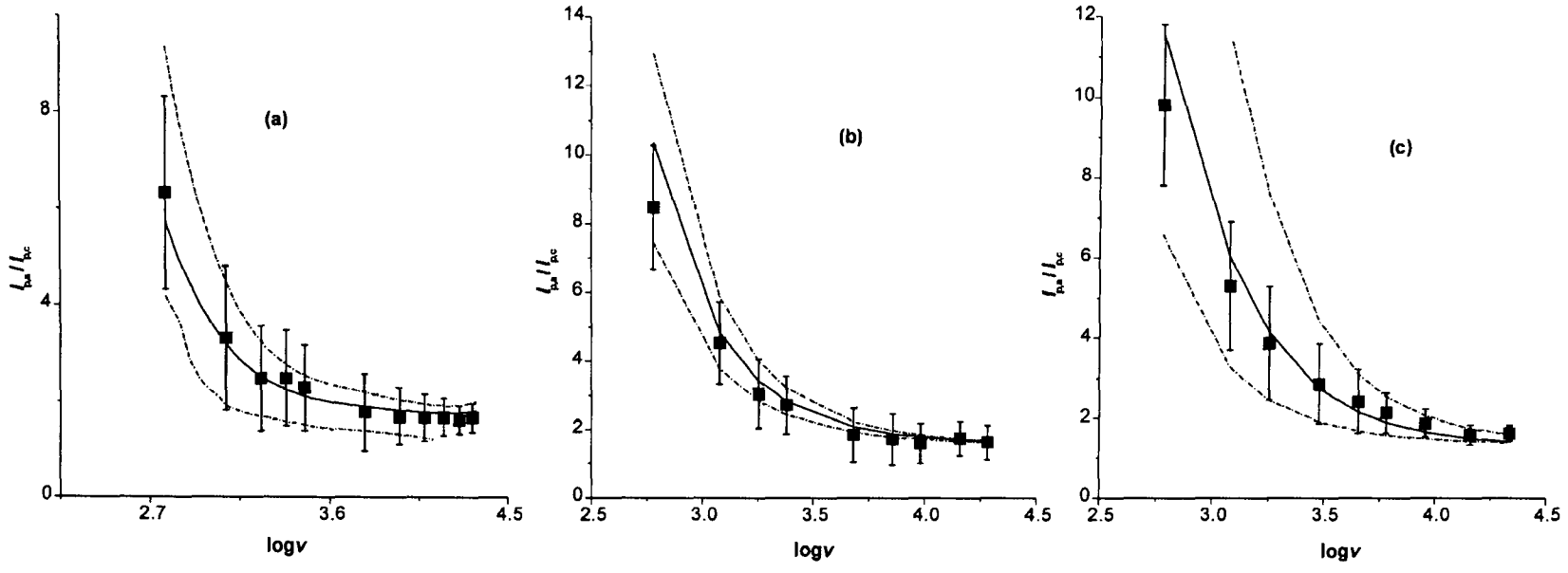


Figure 3.41: Plot of theory (lines) versus experiment (squares) for ratio of peak currents vs. scan rate, with the mean theoretical response is shown in unbroken line, and maximum and minimum values in broken lines. (a) *p*-tolyl-2,3,4,6-tetra-*O*-benzoyl-1-thio-β-D-glucopyranoside (BzSTol); (b) phenyl-2,3,4,6-tetra-*O*-benzoyl-1-seleno-β-D-glucopyranoside (BzSePh); (c) phenyl-2,3,4,6-tetra-*O*-benzyl-1-seleno-β-D-glucopyranoside (BnSePh); (d) *p*-tolyl-2,3,4,6-tetra-*O*-benzyl-1-thio-β-D-glucopyranoside (BnSTol); (e) phenyl-2,3,4,6-tetra-*O*-benzyl -β-D-glucopyranoside (BnOPh).

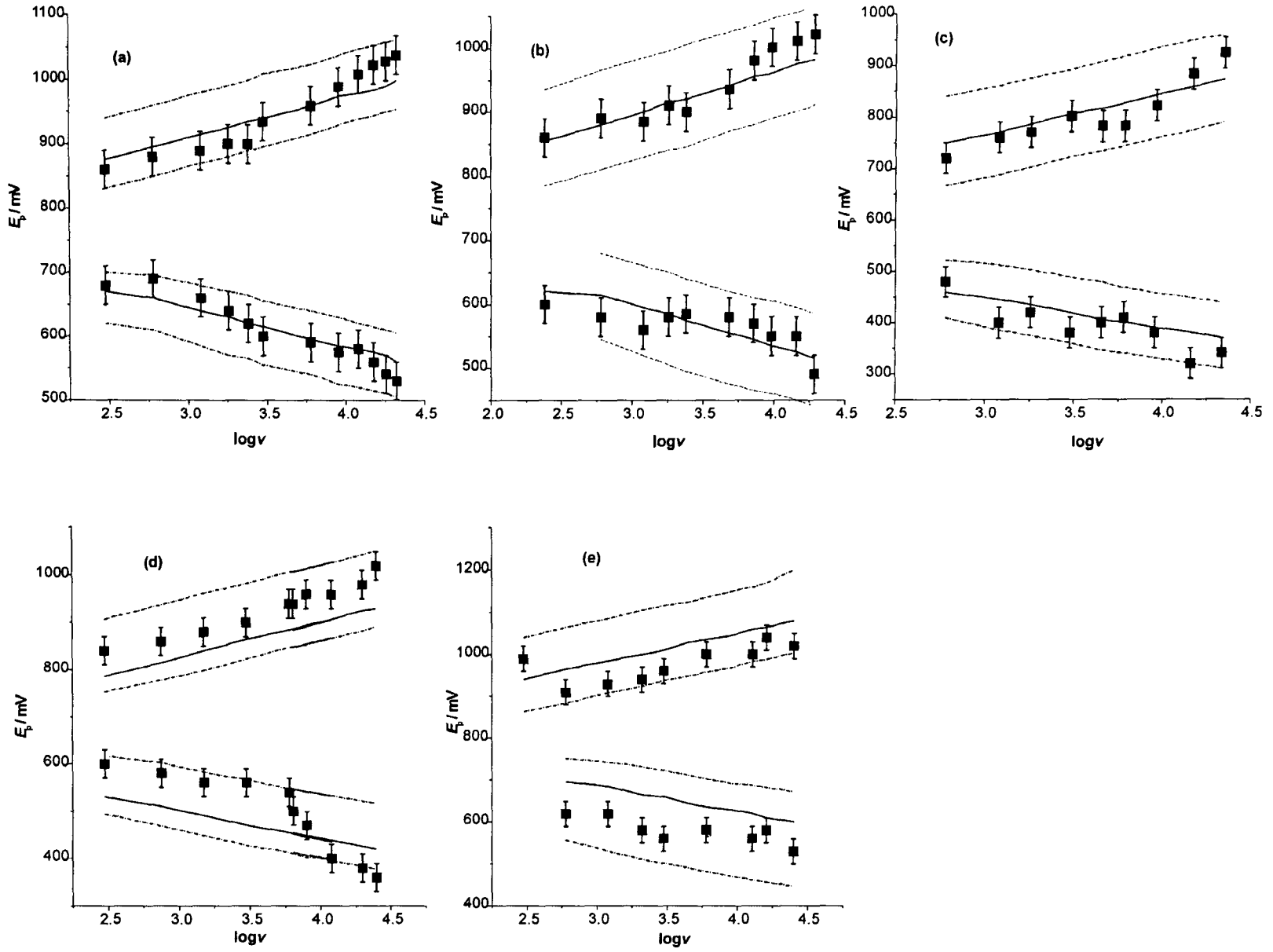


Figure 3.42: Plot of theory (solid lines) versus experiment (squares) for peak potentials vs. scan rate, with the mean theoretical response is shown in unbroken line, and maximum and minimum values in broken lines. (a) *p*-tolyl-2,3,4,6-tetra-*O*-benzoyl-1-thio-β-D-glucopyranoside (BzSTol); (b) phenyl-2,3,4,6-tetra-*O*-benzoyl-1-seleno-β-D-glucopyranoside (BzSePh); (c) phenyl-2,3,4,6-tetra-*O*-benzyl-1-seleno-β-D-glucopyranoside (BnSePh); (d) *p*-tolyl-2,3,4,6-tetra-*O*-benzyl-1-thio-β-D-glucopyranoside (BnSTol); (e) phenyl-2,3,4,6-tetra-*O*-benzyl -β-D-glucopyranoside (BnOPh).

Table 3.3: Kinetic parameters determined from simulations. k_0 and k_1 are the rate constants as shown in figure 3.36, E_f^0 is the formal oxidation potential and $E_{p,a}$ is the anodic peak potential.

Glycoside	k_0 / cm s^{-1}	k_1 / s^{-1}	E_f^0 / V (vs Ag)	$E_{p,a}$ / V (vs Ag)
BnOPh	0.05 ± 0.03	4550 ± 2730	0.785 ± 0.108	0.982 ± 0.078
BnSPh	0.06 ± 0.02	4800 ± 2910	0.617 ± 0.075	0.841 ± 0.055
BnSePh	0.04 ± 0.03	3910 ± 2190	0.570 ± 0.083	0.840 ± 0.095
BnSTol	0.04 ± 0.02	2180 ± 1100	0.663 ± 0.042	0.928 ± 0.057
BzSePh	0.05 ± 0.02	2740 ± 640	0.724 ± 0.050	0.946 ± 0.082
BzSTol	0.06 ± 0.03	2040 ± 375	0.757 ± 0.024	0.945 ± 0.082

It can be seen that there is little difference between the kinetics of the compounds, with every compound having heterogeneous rate constant for electron transfer of the order 10^{-2} cms^{-1}, and homogeneous rate constants of the order 10^{3} s^{-1}. This is not unexpected as the considerations relevant to the rate of electron transfer are obviously very similar for each compound under investigation. The rates of decomposition of the glycoside radical cation also show no significant variation, suggesting that there is little difference in the stability of the different chalco- and *O*-glycoside radical cations. What can be seen is a clear trend in the formal potentials, E_f^0, with the identity of the leaving group. This trend of OPh > STol ~ SPh > SePh, follows the carbon-chalcogenide bond energy (figure 3.43).

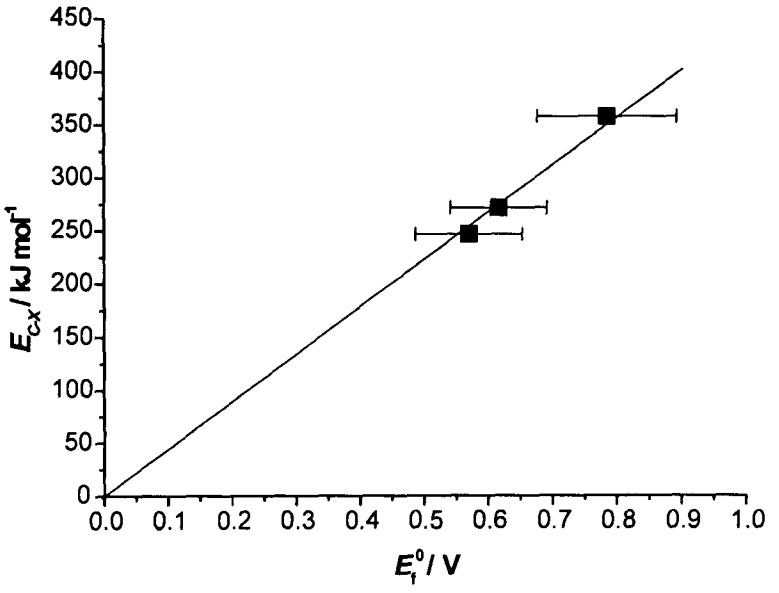


Figure 3.43: Plot of formal potential versus bond energy, formal oxidation potentials are shown for the benzylated glycosides, and the carbon-chalcogenide bond energies were obtained from the literature.[27,28]

Additionally it can be seen that the benzoylated glycosides (selenophenyl and thiotolyl) have a higher formal oxidation potential than the analogous benzylated glycosides.

3.4.1 Comparison with the slow scan work

In order to compare these results with those obtained under slow scan conditions the peak and half wave potentials obtained at 100 mVs^{-1}, and the peak and formal oxidation potentials obtained by the use of fast scan techniques and computer simulations are summarised below for the six compounds which were investigated (table 3.4).

Table 3.4

Glycoside	*$E_{1/2}$/V (at 100mVs^{-1})	*$E_{p,a}$/V (at 100 mVs^{-1})	**E_f^0 (from fast scan analysis)	**$E_{p,a}$ (from fast scan analysis)
BnSePh	1.30	1.43	0.570 ± 0.083	0.840 ± 0.095
BzSePh	1.34	1.42	0.724 ± 0.050	0.946 ± 0.082
BnSTol	1.47	1.52	0.663 ± 0.042	0.928 ± 0.057
BzSTol	1.50	1.54	0.757 ± 0.024	0.945 ± 0.082
BnSPh	1.57	1.62	0.617 ± 0.075	0.841 ± 0.055
BnOPh	1.80	1.91	0.785 ± 0.108	0.982 ± 0.078

*These potentials were obtained from the first scan at 100 mVs^{-1}, using a 5mm glassy carbon working electrode, standard calomel reference electrode and a nickel mesh counter electrode, as described in section 3.3.

** These potential were obtained from fast scan experiments, and subsequent computer modelling, using a 12.5 μm platinum microdisk, silver wire pseudo reference electrode and a platinum mesh counter electrode, as described in section 3.4.

There are a few interesting points to note. First the protecting group pattern appears to have little influence on the oxidation potentials measured at 100 mVs^{-1}, whilst at faster scan rates there is a distinct difference. For the selenoglycosides the benzoylated compound showed a formal oxidation about 0.15 V higher than the benzyl analogue, whilst at 100 mVs^{-1} the half wave potentials only differed by 0.04 V. Similarly for the tolyl thioglycosides the benzoylated compound showed a formal oxidation potential 0.09 V higher than that of the benzylated analogue, whilst at 100 mVs^{-1} the difference was only 0.03 V.

Secondly the benzylated tolyl thioglycoside showed an oxidation potential 0.1 V lower than that of the benzylated phenyl thioglycoside when the oxidation potential was measured at 100 mVs^{-1}. However, the formal oxidation potential of the benzylated tolyl thioglycoside was shown to be slightly higher (by 0.04 V) than that of the benzylated phenyl thioglycoside.

Finally for both the potentials obtained at 100 mVs^{-1} and the formal oxidation potentials the anomeric heteroatom could be seen to have a significant influence on the oxidation potential.

3.4.2 Conclusions

The thermodynamic characteristics of six representative monosaccharides have been obtained, and the data analysed. The trend shown in the formal potentials reflects that which would be expected from the chemical reactivity of the compounds.[21,29] Additionally the formal oxidation potentials of the benzylated glycosides have been shown to mirror the strength of the carbon-chalcogenide bond.

Comparison of the formal oxidation potentials with oxidation potentials obtained at slower scan rates (100 mVs^{-1}) suggests that the homogeneous follow-on kinetics of the EC mechanism not only influence the oxidation potential of the glycosides, but that they also alter the degree to which the protecting group pattern and the anomeric leaving group affect the oxidation potential.

3.5 References

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Chapter 4
Electrochemical Glycosylations

4.1 Aims

The aim of this work was to apply the electrochemical information, the detail of which was reported in the previous chapter, to the selective activation of one glycoside over another, by exploiting the observed difference in oxidation potentials. In order to do this it was first necessary to set up and optimise an electrochemical cell suitable for synthetic electrochemistry.

4.2 The synthetic cell

An electrochemical cell for the synthetic work was constructed, based on the conditions which had been employed in the cyclic voltammetry study. These conditions had in turn had been guided by the work of Balavoine and Lebineux,[1] and Sinaÿ and Amatore[2] on the electrochemical activation of thioglycosides. The cell took the form outlined in figure 4.1.

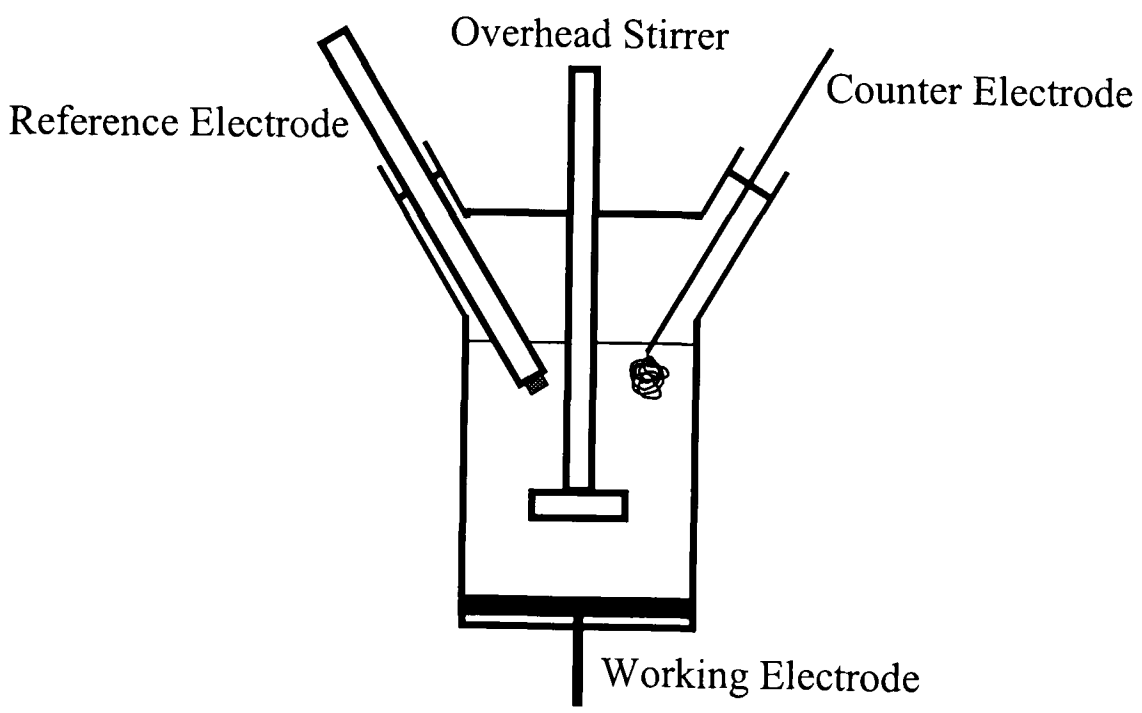
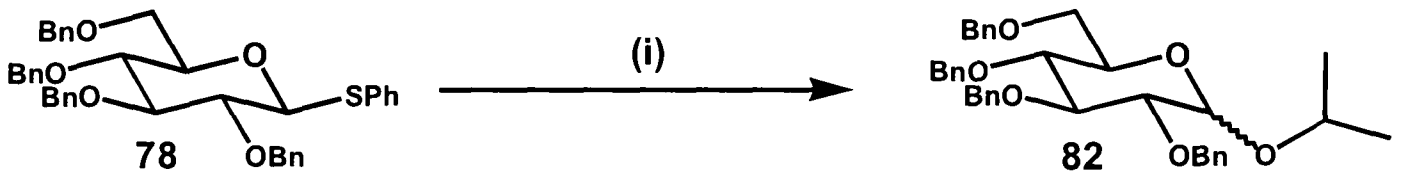


Figure 4.1: Initial cell for synthetic electrochemical glycosylations

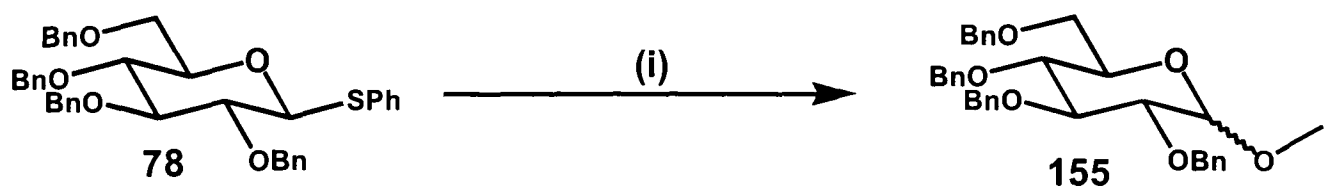
The working electrode was made from glassy carbon and was 20 mm in diameter. This was larger than that used in the cyclic voltammetry (which was 5 mm in diameter) as the cell was being used for synthetic, rather than analytical, work. As the limiting factor in the rate of reaction was likely to be the electron transfer process the greater the surface area of the working electrode the more rapidly the reaction was expected to progress.[3] The nickel counter electrode was also large, in order to prevent any current limiting effect that might otherwise occur. A standard calomel electrode was used as the reference electrode. Stirring was provided by means of an overhead motor with a stirrer attachment as shown in figure 4.1.

In order to test the cell the activation of tetrabenzyl phenyl thioglycoside **78** (which had been shown to have a peak oxidation potential of 1.62 V) was investigated. This reaction is probably the most well established synthetic electrochemical glycosylation to date, having been shown by both Balavoine[1,4] and Sinay[2,5] to work with a number of glycosyl acceptors (schemes 4.1 and 4.2) both at constant current and, more importantly, at constant potential.



(i) ^{i}PrOH, MeCN, $LiBF_4$, +1.5 V, 97%, α:β, 3:7

Scheme 4.1: Balavoine's constant potential activation of thioglycoside **78**



(i) MeOH, MeCN, $^{n}Bu_4NBF_4$, 50mA, 84%, α:β, 3:7, 1:3

Scheme 4.2: Sinaÿ and Amatore's constant current activation of thioglycoside **78**

Acetonitrile was used as solvent, in line with Balavoine's conditions[1] and previous work which had shown its utility as a solvent in single electron transfer reactions.[6,7] Lithium tetrafluoroborate was used as the electrolyte.

Under these conditions no activation of the thioglycoside was observed, using applied potentials in the range +1.5 V to +4.0 V. Similarly it was not possible to obtain any activation under constant current conditions. Balavoine *et al* used both a glassy carbon and a woven carbon working electrode for their work, more often using a woven carbon working electrode as it provided a greater surface area for reaction. It was possible to obtain some reticulated carbon, in the form of sheets, suitable for the construction of a high surface area carbon working electrode. Due to the shape and relatively large volume of the new electrode the original cell used was no longer appropriate. A new cell was therefore constructed, which allowed the use of the reticulated carbon working electrode (figure 4.2).

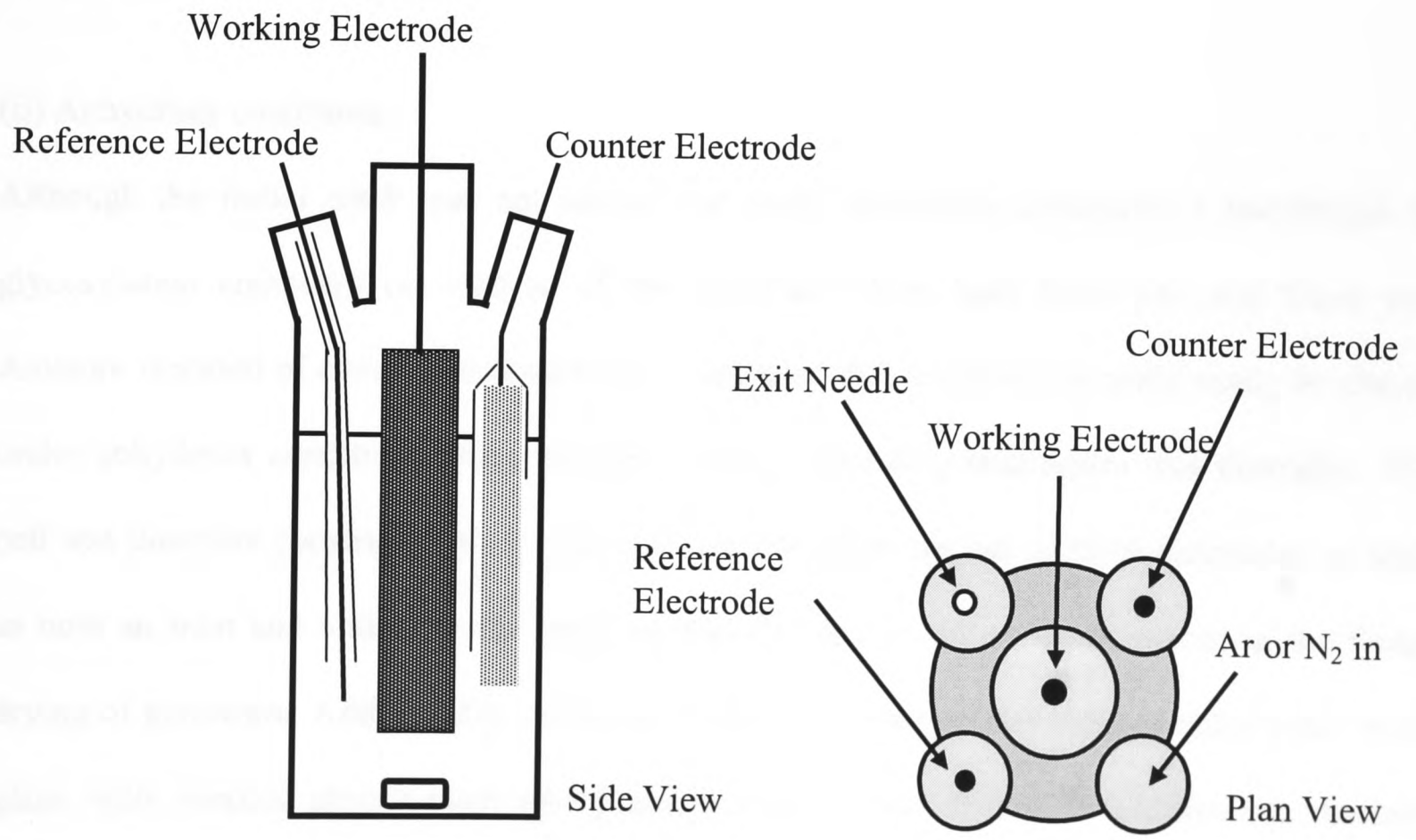


Figure 4.2: Side and plan views of the electrochemical cell, designed specifically for synthetic work with a reticulated carbon electrode

The construction of this new cell also provided the opportunity to consider a number of other design factors:

(i) Volume of the reaction

In order to utilise a large surface area electrode it is necessary for there to be a sufficient volume of solution to cover the electrode. In addition sufficient volume is required to fit both the reference and counter electrode into solution without the risk of any of the electrodes coming into contact with each other, and thereby creating a short circuit. This must be balanced against the effect of the concentration of electro active species on the current, and hence the rate of reaction. Lower concentrations lead to lower currents and hence longer reaction times.[3]

The main body of the cell which was constructed was cylindrical, with a diameter of 30 mm and a height of 65 mm. By creating a tall, thin cell the volume of solution required to fit the three electrodes was minimised.

(ii) Anhydrous conditions

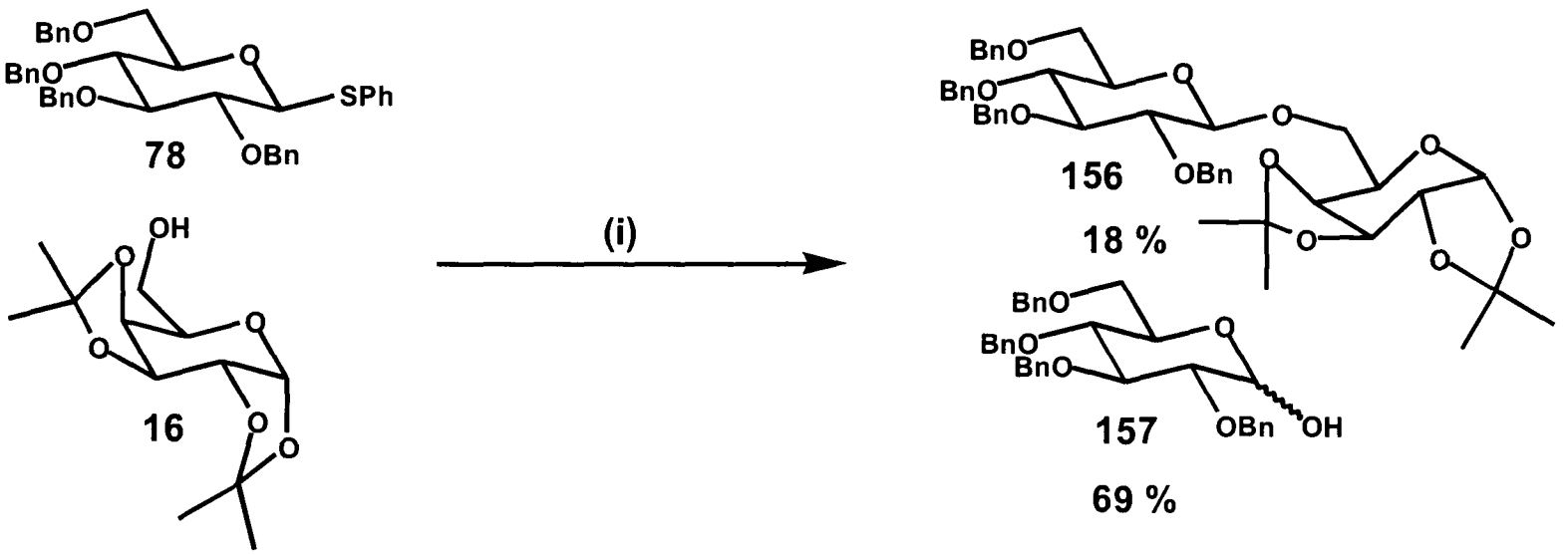
Although the initial work was not carried out under anhydrous conditions a knowledge of glycosylation chemistry (as well as of the problems which both Balavoine and Sinaÿ and Amatore reported of competitive hydrolysis) suggested that a cell which could easily be placed under anhydrous conditions using standard organic chemistry techniques was desirable. The cell was therefore constructed with sufficient joints to allow the use of three electrodes, as well as both an inlet and outlet for dry gases commonly used to purge water vapour in the flame drying of glassware. Additionally, unlike the initial cell, this one was entirely constructed from glass, with standard ground glass neck joints to permit flame drying. In addition the standard

calomel electrode used previously is aqueous, and in order to exclude this source of water a silver wire pseudo reference electrode was substituted.

(iii) Agitation of the solution

The overhead stirring employed initially was necessitated by the use of a glassy carbon working electrode as only the front face of the electrode could be presented to the solution. With the move to a reticulated carbon electrode it was possible to use a more conventional design. By giving the cell a flat base stirring could be simply achieved by the use of a magnetic flea.

With this new cell design an electrochemical activation of tetrabenzyl phenyl thioglycoside **78**, (Ep 1.62 V) was again attempted. Initial reactions at +1.7 V gave no activation of the starting material. However increasing the applied potential to +1.8 V resulted in total consumption of the phenyl thioglycoside **78** in 8 h. The major product from this reaction was not however the desired disaccharide **156** but instead tetrabenzyl glucose **157**, from the hydrolysis of the thioglycoside (scheme 4.3).

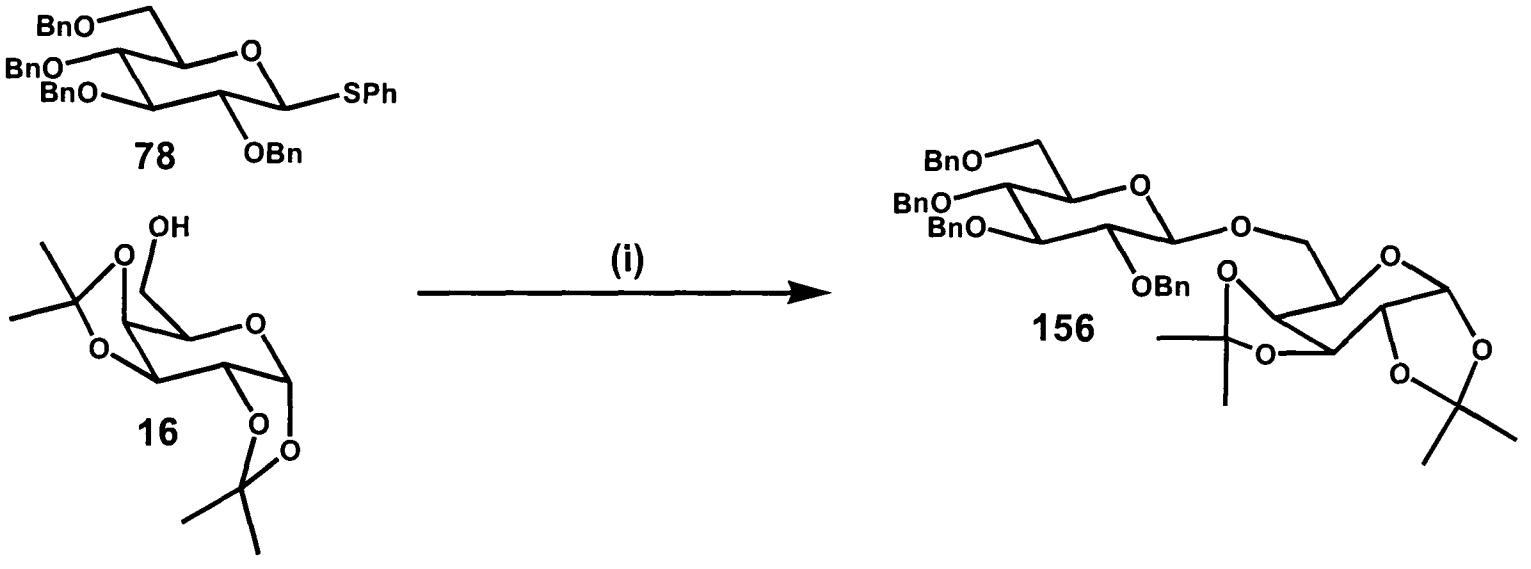


(i) MeCN, $LiBF_4$, +1.8 V, 8 h

Scheme 4.3

The fact that all of the thioglycoside appeared to have been activated was very encouraging. Attention therefore turned to ensuring anhydrous conditions, in order to minimise the

possibility of hydrolysis. Rigorous flame drying of the reaction vessel under dry nitrogen and the use of 4 Å molecular sieves, which were introduced into the reaction mixture 30 minutes before the application of a potential, resulted in the desired disaccharide product **156** in an acceptable 75% yield (scheme 4.4).



(i) MeCN, $LiBF_4$, +1.8 V, 8 h, 4 Å molecular sieves, 75%

Scheme 4.4

Increasing the potential to +2.0 V gave a more rapid reaction, with the phenyl thioglycoside consumed within 5 hours, albeit with a slightly lower yield of the disaccharide of 66%. The results are summarised below (table 4.1).

Glycosyl Acceptor	Number of Equivalents*	Applied Potential	Reaction Time	Yield of Glycosylation Product	α:β ratio
diacetone galactose **16**	2	+1.7 V	5 h	no reaction	-
diacetone galactose **16**	2	+1.8 V	8 h	75%	β only
diacetone galactose **16**	2	+2.0 V	5 h	66%	β only

* Relative to the glycosyl donor

Table 4.1: Results for glycosylation using phenyl thioglycoside **78** at varying potentials in acetonitrile with 4 Å molecular sieves and lithium tetrafluoroborate as electrolyte.

These results demonstrated that under these cell conditions phenyl thioglycoside **78** could be activated at potentials of +1.8 V, or greater, to give glycosylation products in yields of 66% and greater, with a simple carbohydrate (1,2:3,4 diacetone galactose **16**) as the glycosyl acceptor.

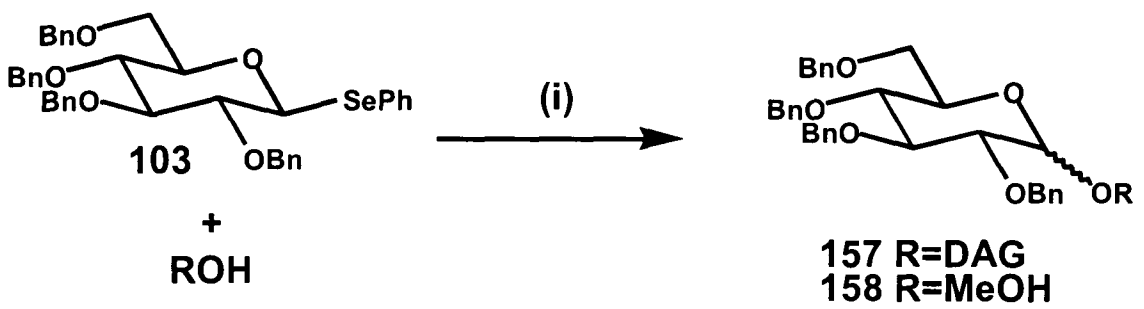
4.3 Application to electrochemical glycosylation using selenoglycoside donors

With satisfactory conditions for electrochemical glycosylation using a using a thioglycoside donor now established glycosylation of selenoglycoside donors **103** and **92** were examined (figure 4.3).



Figure 4.3: Selenoglycoside donors

Both donors showed a peak oxidation potential of approximately +1.35 V, significantly lower than that of the thioglycoside donor **78** previously discussed. This made them good candidates for a selective glycosylation with a thioglycoside acceptor. First it was necessary to ensure that they could be activated under the cell conditions, and to investigate the effect of different applied potentials on the reaction. Initially the glycosylation of benzyl glycoside **103** was studied, with either methanol or diacetone galactose **16** as the glycosyl acceptor (scheme 4.5).



(i) MeCN, $LiBF_4$, 4 Å molecular sieves, R=MeOH or DAG

Scheme 4.5

It once again proved vital to ensure rigorously anhydrous conditions in order to prevent the formation of tetrabenzyl glucose through competitive hydrolysis of the glycosyl donor. This was done by the use of a thoroughly flame dried cell and by stirring the reaction mixture with 4 Å molecular sieves for 30 minutes prior to applying a potential to the system. The reaction was conducted at a range of potentials between +1.3 V and +2.0 V and the results are presented below (table 4.2).

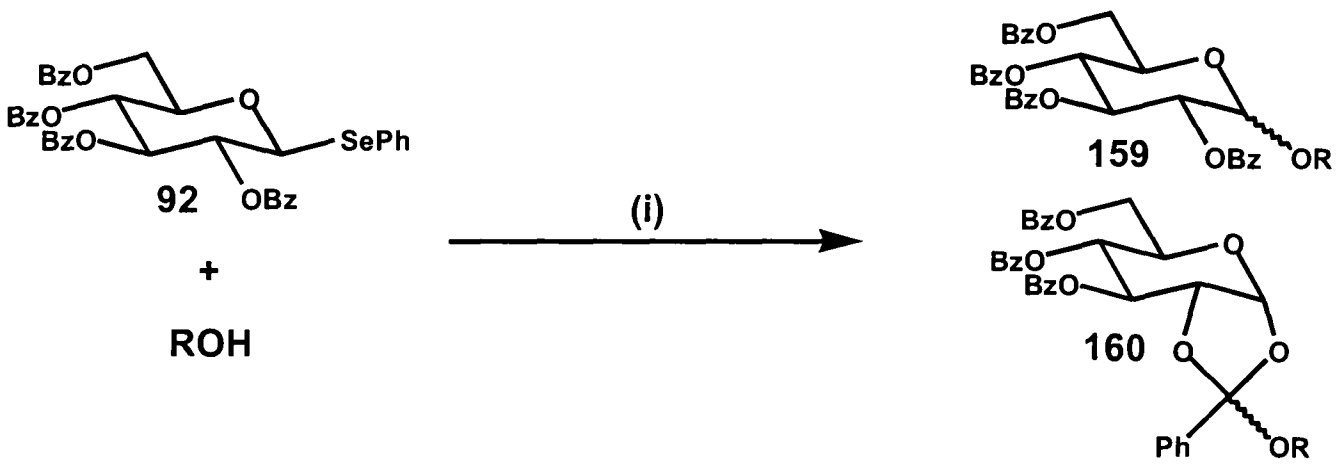
Glycosyl Acceptor	**Number of Equivalents***	**Applied Potential**	**Reaction Time**	**Yield of Glycosylation Product**	**α:β ratio**
MeOH	2	+1.3 V	5 h	no reaction	-
MeOH	2	+1.4 V	8 h	47% (84%)**	1:3
MeOH	2	+1.5 V	3 h	71%	1:4
MeOH	2	+1.7 V	8h	84%	1:6
diacetone galactose **16**	2	+1.3 V	9 h	no reaction	-
diacetone galactose **16**	3	+1.4 V	8 h	69% (91%)**	β only
diacetone galactose **16**	2	+1.5 V	8 h	85%	β only
diacetone galactose **16**	2	+1.6 V	5 h	86%	β only
diacetone galactose **16**	2	+1.7 V	3 h	85%	β only
diacetone galactose **16**	2	+1.8 V	2 h	83%	β only
diacetone galactose **16**	2	+1.9 V	2 h	85%	β only
diacetone galactose **16**	2	+2.0 V	1 h	84%	β only

* Relative to the glycosyl donor; ** Yields over recovered starting material

Table 4.2: Results for glycosylation using phenyl selenoglycoside **103** at varying potentials in acetonitrile with 4 Å molecular sieves and lithium tetrafluoroborate as electrolyte.

The results showed that the phenyl selenoglycoside **103** could be activated at potentials of +1.4 V and greater, to give glycosylation products in yields of up to 86%, when the glycosyl acceptor was diacetone galactose, or 71% when the glycosyl acceptor was methanol. The yield appeared to be independent of the applied potential (as long as that potential was sufficient to achieve activation); however activation was faster at higher potentials. The reaction was particularly sluggish at +1.4 V, with the glycosyl donor not fully activated after eight hours.

These conditions were also applied to the benzoylated selenoglycoside **92**. Although the glycosyl donor was consumed in the course of the reaction a complex mixture of products was obtained. It was not possible to identify any of the components conclusively, but it seemed likely that the mixture consisted of a mixture of ortho esters, in addition to the anticipated glycosylation products (scheme 4.6).[1]



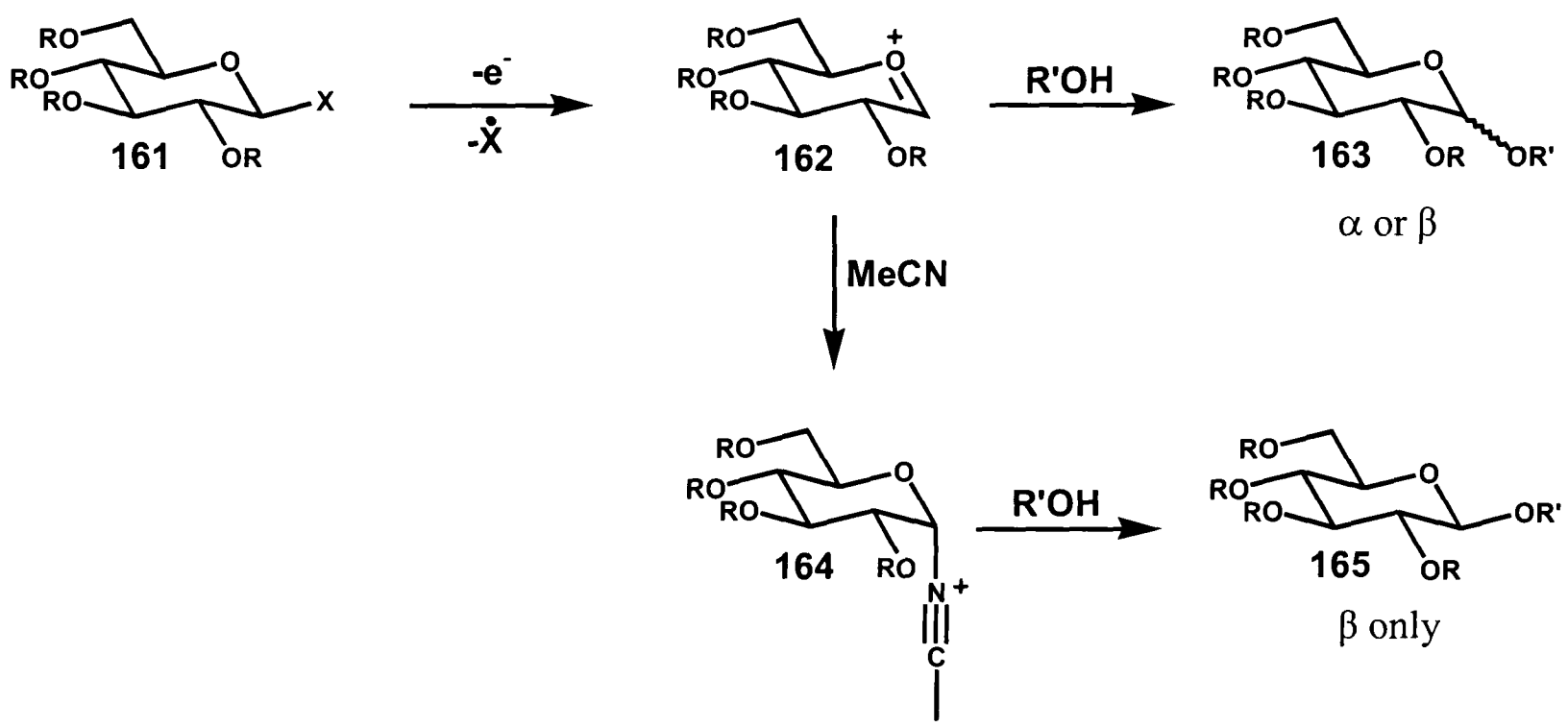
(i) MeCN, $LiBF_4$, 4 Å molecular sieves

Scheme 4.6: Proposed products from the activation of benzoylated selenoglycoside **92**

As the benzoylated selenoglycoside **92** did not show a significantly different oxidation potential to that of the benzylated equivalent **103**, and due to the high β-selectivity observed for the benzylated glycoside, there seemed little to be gained at this point by pursuing this particular avenue any further.

4.4 The origin of the β-selectivity

So far the β-selectivity observed in the successful glycosylation reactions has been allowed to pass without comment. It is however worthy of some note, as it appears to go against the known tendency of sugars which possess no participating group at *O*-2 to give predominately α-products from glycosylation reactions, due to the anomeric effect.[8] This phenomenon has been noted by others conducting electrochemical glycosylations,[9,10] and is in fact a well understood solvent effect.[11-14] The first step after activation of the glycosyl donor **161** is the formation of the glycosyl cation **162**. This cyclic oxocarbenium ion then reacts rapidly with the solvent to generate the α-acetonitrilium ion **163**. It is this species that reacts, in an S_N2 fashion, with the glycosyl acceptor to give the product from glycosylation (scheme 4.7).



Scheme 4.7: Probable solvent mediated β-glycoside formation

Where the acceptor is able to compete with the acetonitrile in the first step an α/β mixture of compounds **163** is obtained. However it appears that the low concentration of glycosyl

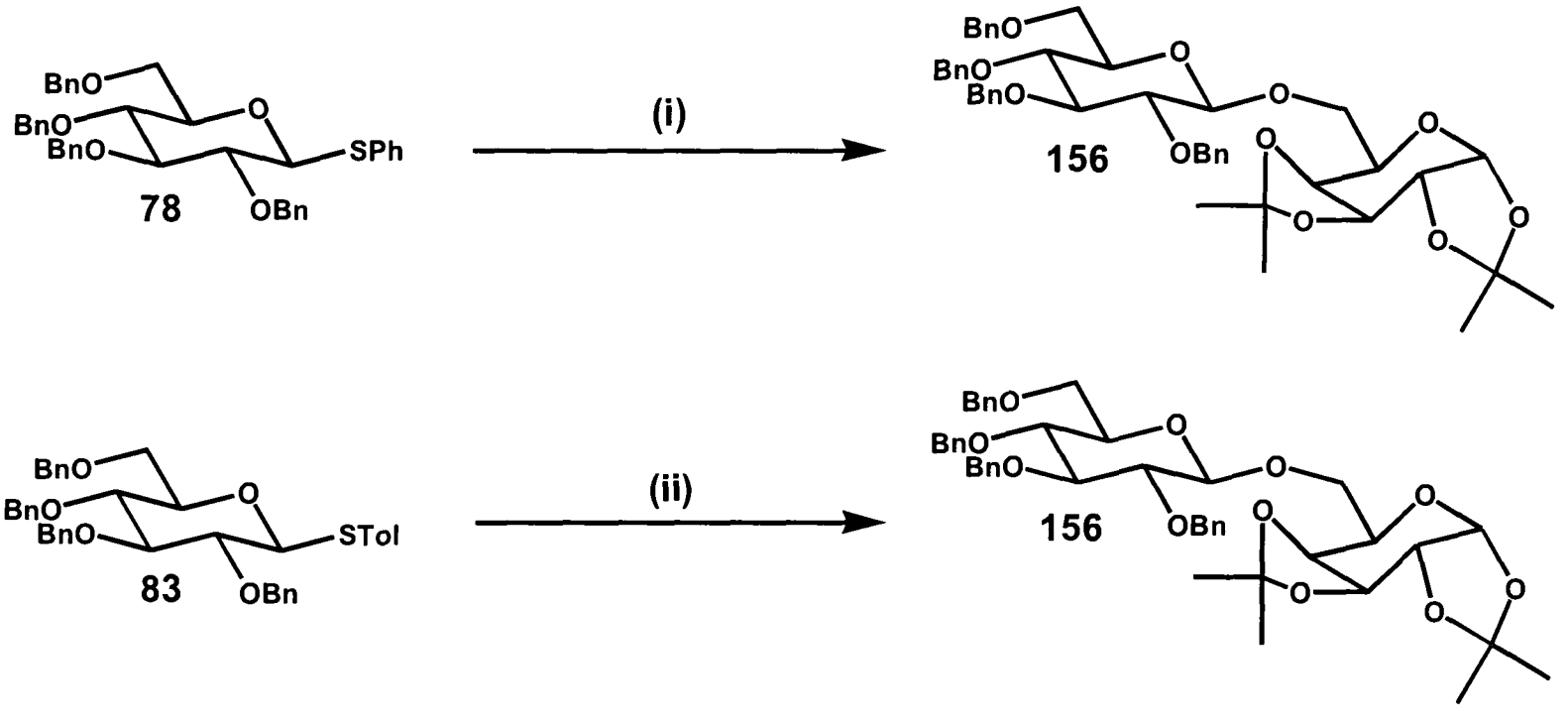
acceptors employed in the electrochemical reaction conditions used allows effective formation of an α-acetonitrilium ion such as **164** and consequently β-glycoside formation is favoured. Indeed when diacetone galactose **16** was used as the glycosyl acceptor it was only possible to isolate the β product from glycosylation.

4.5 Selective glycosylation reactions

4.5.1 Choice of system

It was now possible to move on and examine a selective glycosylation, using phenyl-2,3,4,6-tetra-*O*-benzyl-1-seleno-β-D-glucopyranoside **103** as the glycosyl donor. Tolyl-2,3,4-tri-*O*-benzyl-1-thio-β-D-glucopyranoside **146** was used as the model acceptor. This had the advantage of requiring relatively inexpensive reagents for its synthesis, whilst not requiring the use of the highly malodorous thiophenol. Although the analytical work had shown a slightly lower activation potential for this glycoside than for the thiophenyl equivalent **98** it was found that this had little practical effect under the glycosylation conditions (scheme 4.8). The electrolyte used for the activation of the glycoside **83** was tetrabutylammonium perchlorate (TBAP). It was noted at this point that a surprisingly high level of hydrolysis was being observed, compared to the initial synthetic reactions. Examination of the lithium tetrafluoroborate showed that what had initially been a free flowing white power was now starting to form clumps indicative of the incorporation of some water. This was in spite of careful handling of the reagent. It seemed likely that this was the cause of the unexpected hydrolysis and so some test reactions were conducted with tetrabutylammonium perchlorate (TBAP) as the electrolyte. The hydrolysis was significantly reduced and so subsequent

reactions were conducted using this non hydroscopic electrolyte, which has been frequently employed in the electrolysis of organic compounds in acetonitrile.[15]



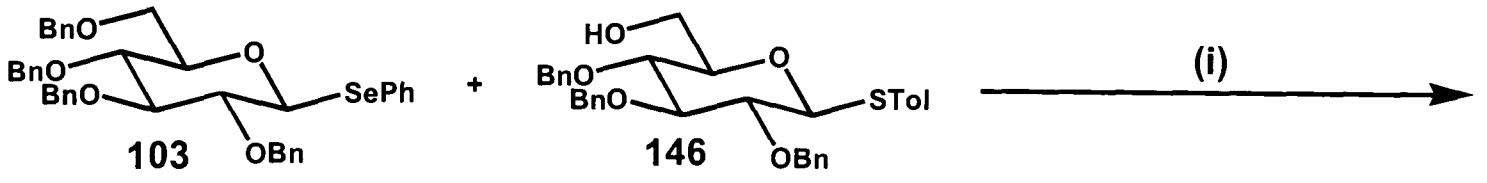
(i) MeCN, TBAP, 4 Å molecular sieves; +1.7 V, 5 h, no reaction; +1.8 V, 8 h, 75%

(ii) MeCN, TBAP , 4 Å molecular sieves; +1.7 V, 3 h 5%; +1.8 V, 5 h 81%

Scheme 4.8: Comparing the activation of phenyl thioglycoside **78** and tolyl thioglycoside **83**

4.5.2 Glycosylations

The basic reaction under consideration was therefore the selective activation of phenyl-2,3,4,6 tetra-*O*-benzyl-1-seleno-β-D-glucopyranoside **103** over tolyl-2,3,4-tri-*O*-benzyl-1-thio-β-D-glucopyranoside **146** (scheme 4.9).



Scheme 4.9: (i) MeCN, 4 Å molecular sieves, +X V, $LiBF_4$ or TBAP

Before carrying out any synthetic reactions it was first confirmed that the voltammetry of tolyl-2,3,4-tri-*O*-benzyl-β-D-glucopyranoside **146** was comparable with that of tolyl-2,3,4,6-tetra-*O*-benzyl-1-thio-β-D-glucopyranoside **83** which had been previously studied. This was done by comparison of their electrochemical properties using cyclic voltammetry, and the voltammograms against glassy carbon at 100 mVs^{-1} are shown below (figure 4.4). They show clearly that the removal of the *O*-6 benzyl group has had little or no effect on the electrochemical properties of the compound.

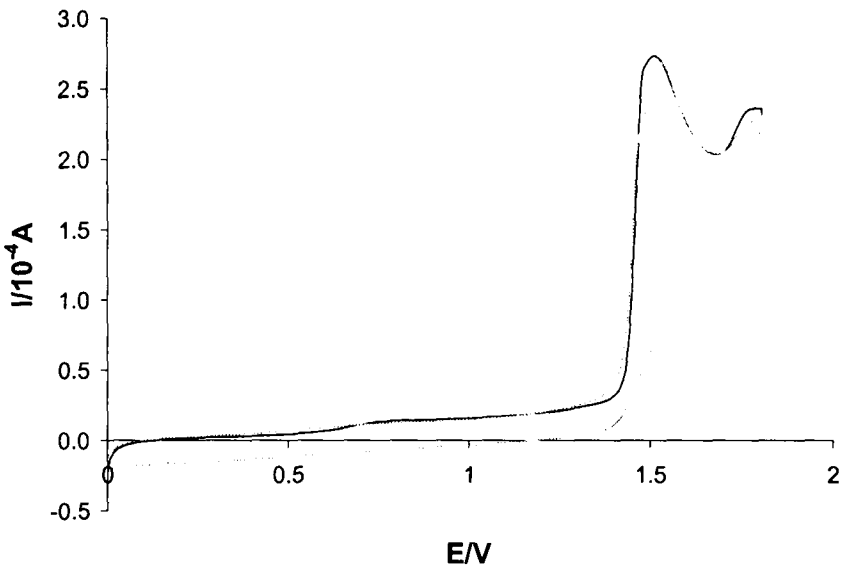
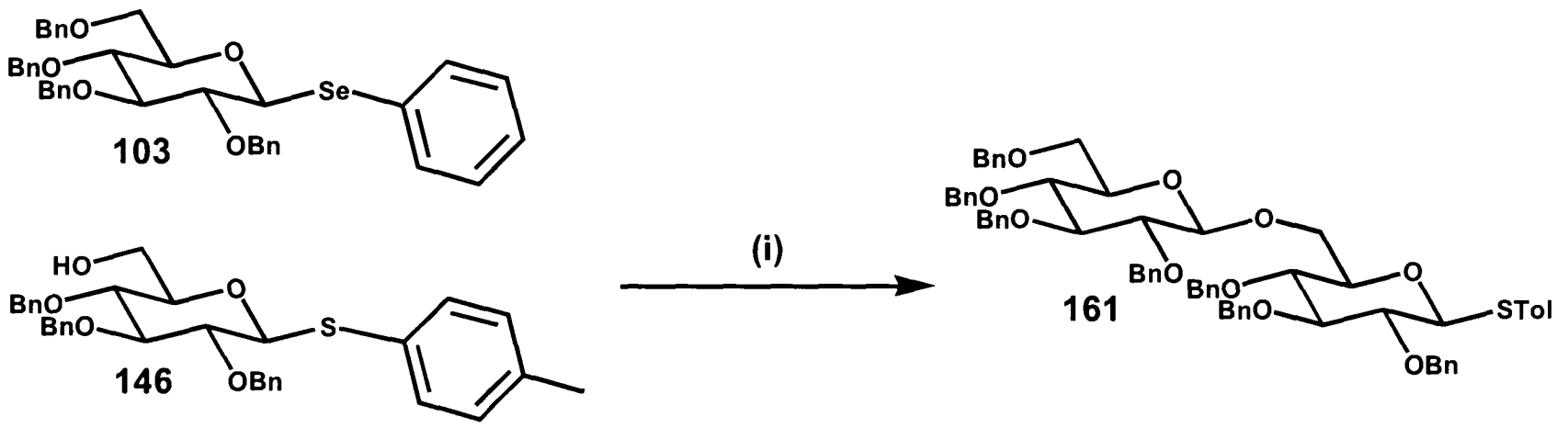


Figure 4.4: Comparison of tribenzylated thiotolyl acceptor **146** (black) with the fully benzylated tolyl thioglycoside **83** (grey)

Initial glycosylations were attempted at +1.4 V, the lowest potential at which selenoglycoside **103** had been found to be activated during the course of the study and well below the activation potential of thioglycoside **146**. Some of the desired glycosylation product was obtained, but the yields were consistently low. Longer reaction times and higher oxidation potentials did lead to total consumption of the selenoglycoside donor **103**, but only a marginal increase in the yield of the desired disaccharide **161**. At first some tetrabenzyl glucose **157** could be isolated as a side product from the reaction. Changing the electrolyte from lithium tetrafluroborate to tetrabenzylammonium perchlorate (as discussed above) eliminated this product, but did not lead

to any significant increase in the yield of glycosylation product. Despite protracted efforts it was not possible to detect any other side products from the reaction. The best result that was achieved using a potential of +1.7 V, where 35% of disaccharide **161** was isolated after 8 hours (scheme 4.10). A summary of the results for work on this reaction is presented in table 3.



(i) MeCN, TBAP, +1.7 V, 4 Å molecular sieves, 8 h, 35%

Scheme 4.10

Number of Equivalents of Acceptor*	Electrolyte	Applied Potential	Reaction Time	Yield of Glycosylation Product	α:β ratio
0.25	$LiBF_4$	+1.4 V	4 h	11%	β only
2	$LiBF_4$	+1.4 V	4 h	9% (25%)**	β only
4	$LiBF_4$	+1.4 V	8 h	12%	β only
2	$LiBF_4$	+1.5 V	8 h	16%	β only
1	$LiBF_4$	+1.6 V	6 h	18%	β only
0.5	TBAP	+1.4 V	6 h	19%	β only
1	TBAP	+1.4 V	8 h	13%	β only
2	TBAP	+1.5 V	4 h	22%	β only
10	TBAP	+1.5 V	12 h	27%	β only
2	TBAP	+1.6 V	8 h	25%	β only
1	TBAP	+1.7 V	8 h	31%	β only
2	TBAP	+1.7 V	8 h	35%	β only

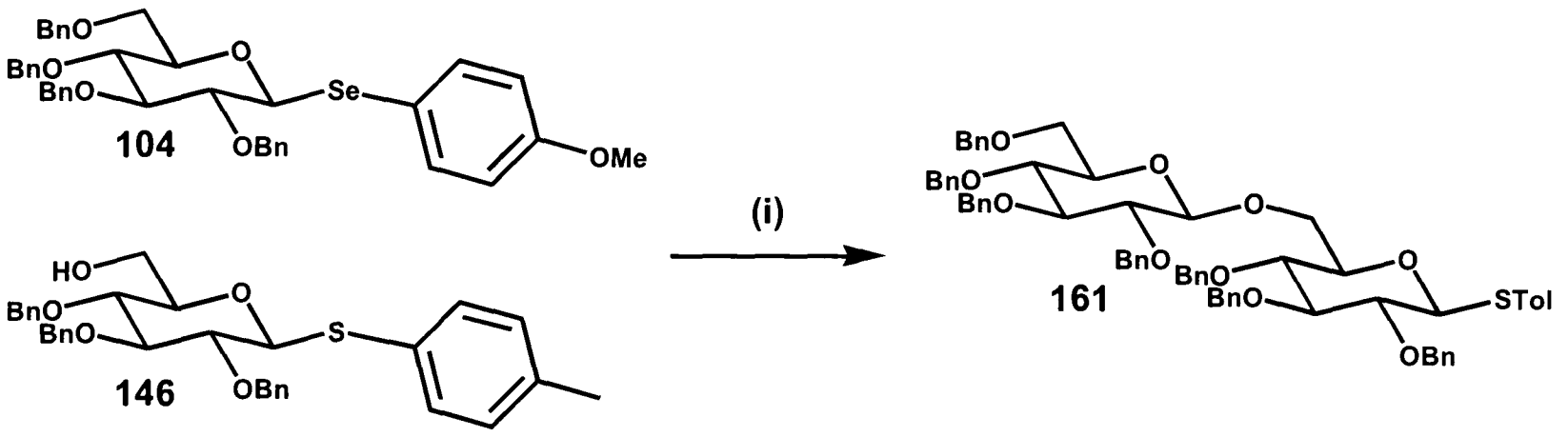
* Relative to the glycosyl donor, ** Yield over recovered starting material

Table 3: Investigations into the selective activation of selenoglycoside **103**

4.5.3 Alternative glycosyl donors

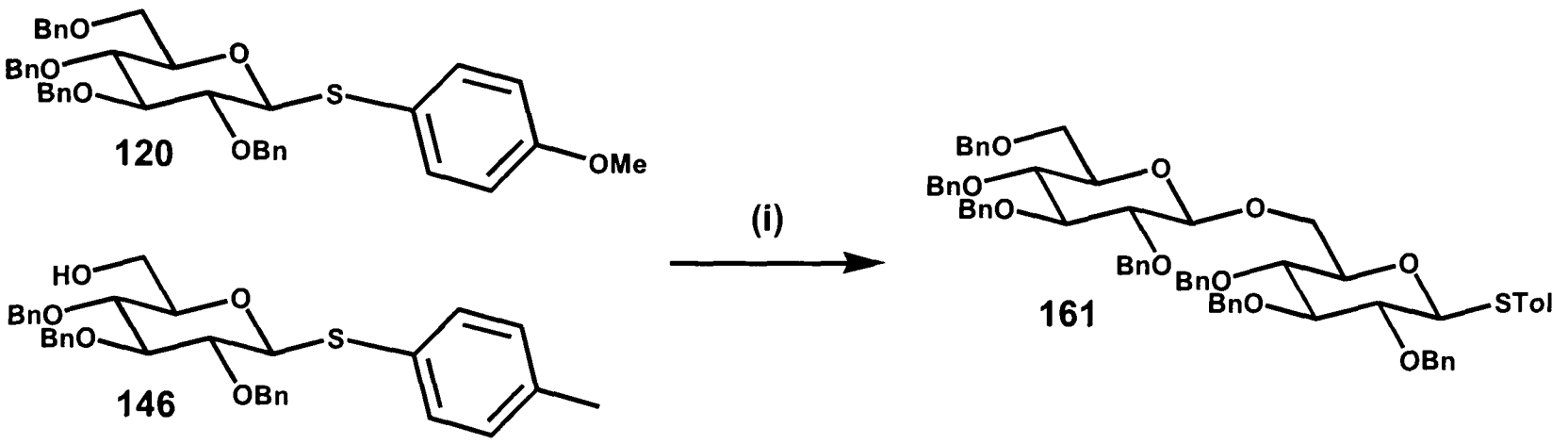
In an attempt to increase the yield of glycosylation the reaction was attempted with two glycosyl donors that had been shown to possess lower oxidation potentials than selenoglycoside **103**. *p*-Methoxyphenyl-2,3,4,6-tetra-*O*-benzyl-1-seleno-β-D-glucopyranoside **104** and *p*-methoxyphenyl-2,3,4,6-tetra-*O*-benzyl-1-thio-β-D-glucopyranoside **120** were both chosen for further study. The *p*-methoxyphenyl selenoglycoside **104** had been shown to have an oxidation potential of +1.16 V, while the *p*-methoxyphenyl thioglycoside **120** had been shown to have an oxidation potential of +1.37 V.

Glycosylation using selenoglycoside **104** was attempted at +1.3 V and +1.5 V, and using thioglycoside **120** at +1.5 V and +1.7 V. In both cases it was once again possible to obtain the β-disaccharide **161**, which is the desired product of the glycosylation reaction, but with no improvement in yield (schemes 4.11 and 4.12). Once more it was not possible to detect any by-products from the reactions which could help to explain the low yield.



(i) MeCN, TBAP, 4 Å molecular sieves; +1.3 V, 8 h, 22%; +1.5 V, 8 h, 26%.

Scheme 4.11



(i) MeCN, TBAP, 4 Å molecular sieves; +1.5 V, 8 h, 25%; +1.7 V, 8 h, 22%.

Scheme 4.12

4.5.4 An alternative glycosyl acceptor

Next the glycosyl acceptor was studied in more detail. In the analytical work the highest oxidation potentials were obtained for *O*-glycosides. The *O*-phenyl glucoside **154** therefore seemed a good candidate for use as the glycosyl acceptor, with an oxidation potential of +1.9 V (figure 4.5).

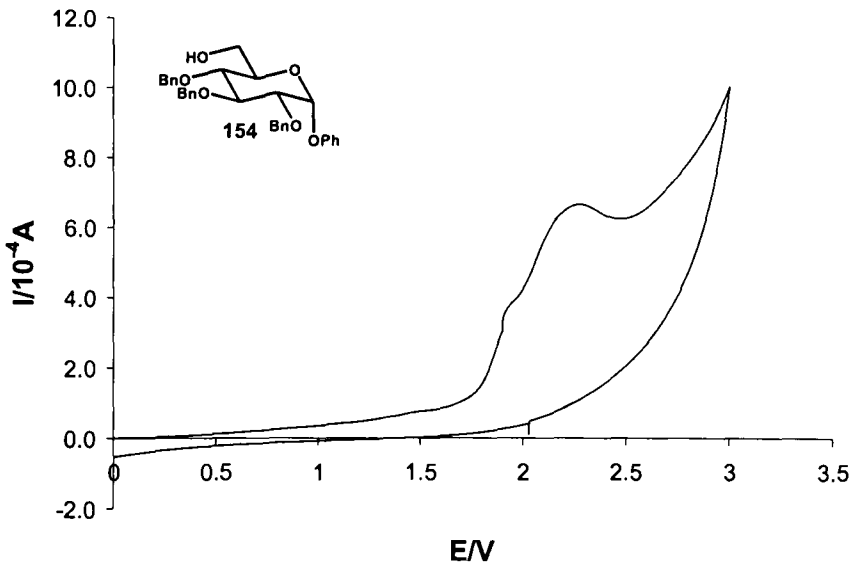
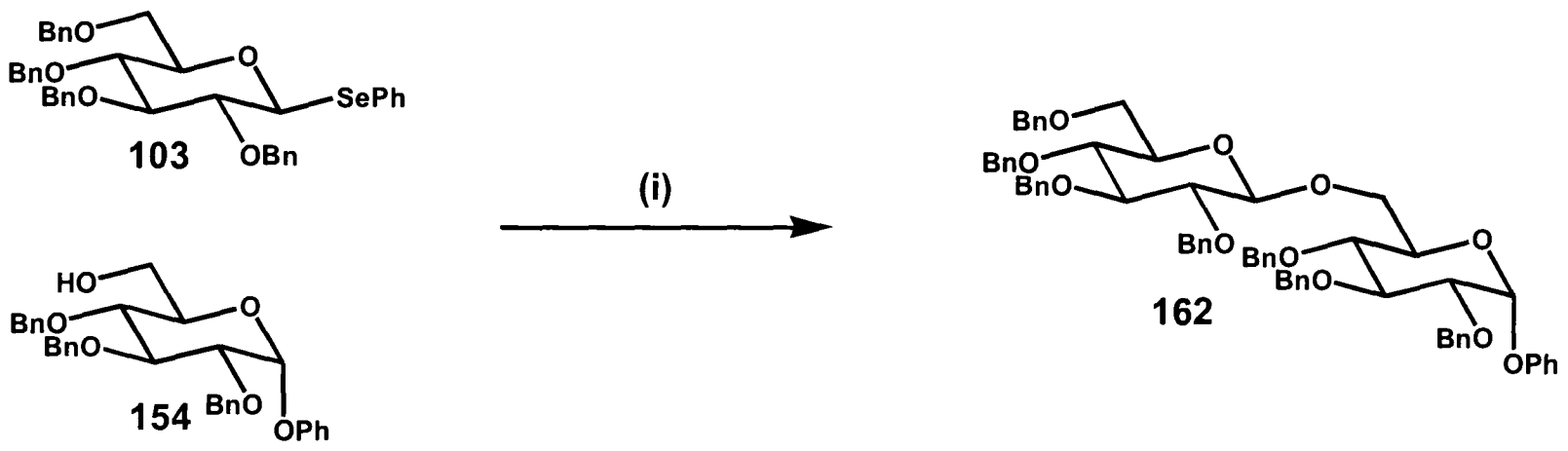


Figure 4.5: First scan voltammogram at 100 mVs^{-1} for 2.2 mM phenyl-2,3,4,-tetra-*O*-benzyl-α-D-glucopyranoside using a glassy carbon working electrode, nickel counter electrode and standard calomel reference electrode.

Application of a potential of +1.7 V to the now standard cell conditions gave a very satisfactory 79% yield of the exclusively β-disaccharide **162** (scheme 4.13). The reaction was extremely quick, with the starting material consumed in less than one hour.



(i) MeCN, TBAP, 4 Å molecular sieves, +1.7 V 1 h, 79%

Scheme 4.13

4.5.5 Further Investigations

It seemed clear that there was some unexpected process occurring during the electrolysis reaction which was responsible for the low yield observed in the selective activations where the thioglycoside **146** was being used as the glycosyl acceptor. The simple activation of the thioglycoside acceptor **146**, at the applied potential, had already been ruled out (*vide supra*, section 4.5.1); however it was possible that the disaccharide product **161** had a lower oxidation potential than the glycosyl acceptor. In order to investigate this an analysis of the oxidation potential of the disaccharide using the same voltammetric techniques as described in Chapter 3 was conducted (figure 4.6).

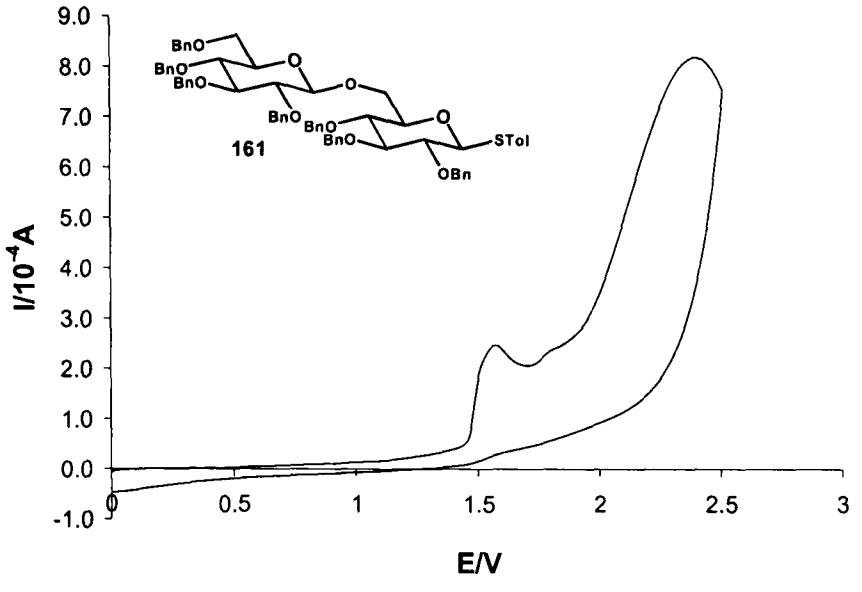


Figure 4.6: First scan voltammogram at 100 mVs^{-1} for 2.2 mM disaccharide X, using a 5mm glassy carbon working electrode, nickel mesh counter electrode and standard calomel reference electrode.

The voltammogram shows a peak oxidation potential, due to the thiotolyl anomeric group, of +1.6 V. The larger signal, with a peak oxidation potential of +2.4 V corresponds to the oxidation of the benzyl protecting groups. This signal is relatively large compared to both the oxidation of the thiotolyl group and (to a lesser extent) the previously observed oxidations of benzyl protecting groups discussed in Chapter 3. This is due to the number of functional groups associated with the oxidation process, in this case seven benzyl groups compared to one thiotolyl group. Comparison of the oxidation potential of the thiotolyl group in the disaccharide with that in the monosaccharide donor (figure 4.7) showed that the oxidation potential is almost the same. In fact it is the disaccharide which shows the slightly higher oxidation potential. This suggested that electrochemical activation of the product was not responsible for the low yield observed in the selective glycosylation reactions.

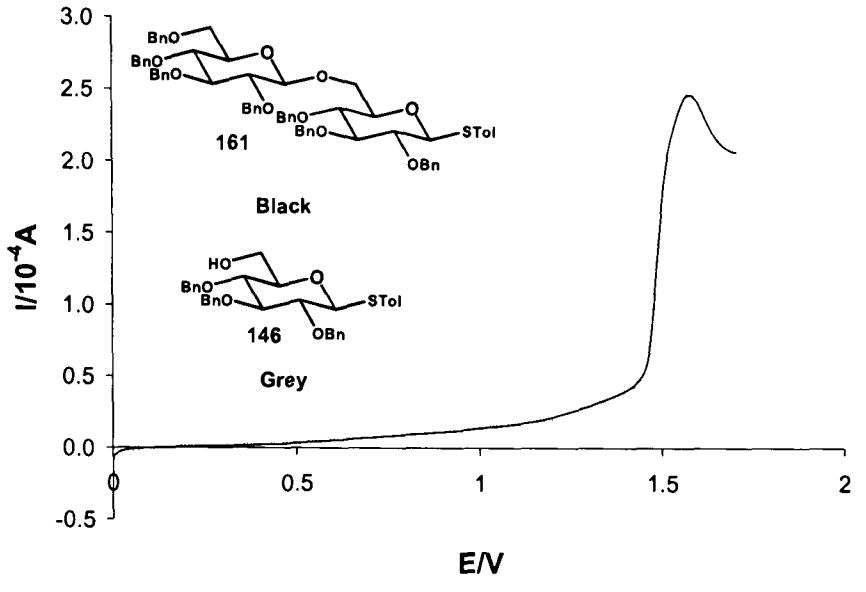
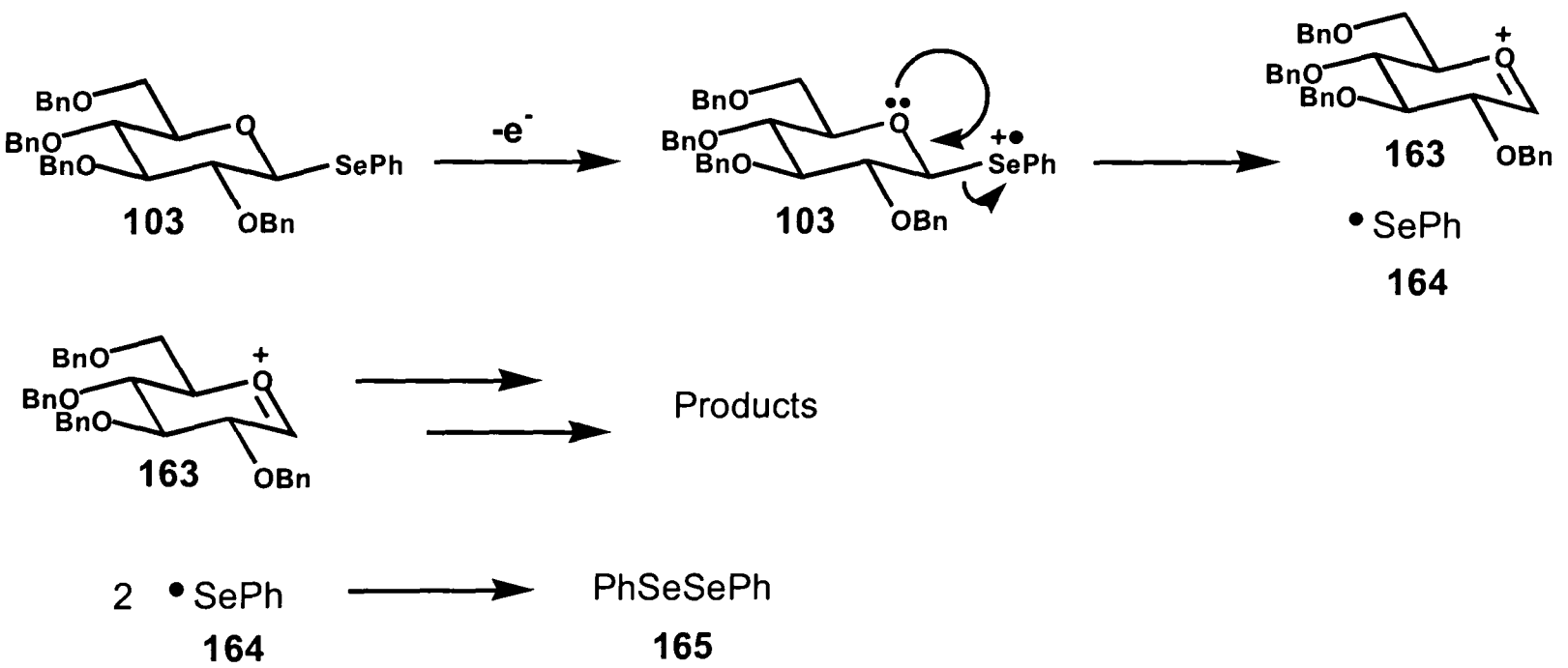


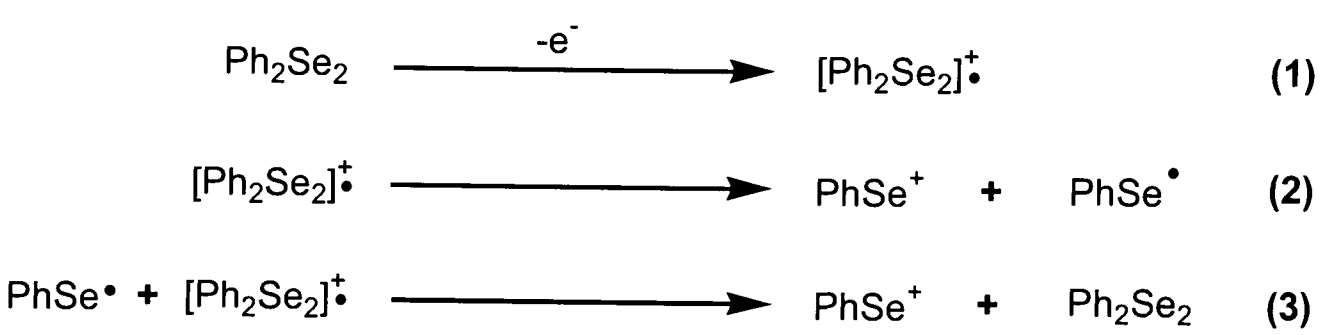
Figure 4.7: First scan voltammogram at 100 mVs^{-1} for 2.2 mM disaccharide **161** (black) and 2.2 mM thio tolyl donor **146** (grey), using a 5mm glassy carbon working electrode, nickel mesh counter electrode and standard calomel reference electrode.

Consideration was therefore given to the other known products from the reaction. The literature suggests that, in addition to the carbohydrate products of glycosylation, the anomeric leaving group forms a dimer, by radical coupling of the neutral chalco phenyl radical **164**.[9,16,10] For a majority of the selective reactions attempted up to this point this would give diphenyl diselenide **165** as the by-product of the reaction (scheme 4.14).



Scheme 4.14: Mechanism for the activation of phenyl selenoglycoside, by one electron oxidation, showing the mechanistic pathway for the formation of diphenyl diselenide.

This species has electrochemical properties of its own, and these have been well studied by Kunai *et al.*[17] They demonstrate that the cyclic voltammogram of diphenyl diselenide exhibits two irreversible anodic peaks, at +1.35 V and +1.65 V, as well as a cathodic peak at -1.25 V. Their work was conducted in acetonitrile, using a platinum working electrode. They went on to show that the initial oxidation, at +1.35 V, leads to the formation of $PhSe^+$, through a proposed mechanism shown below (scheme 4.15).

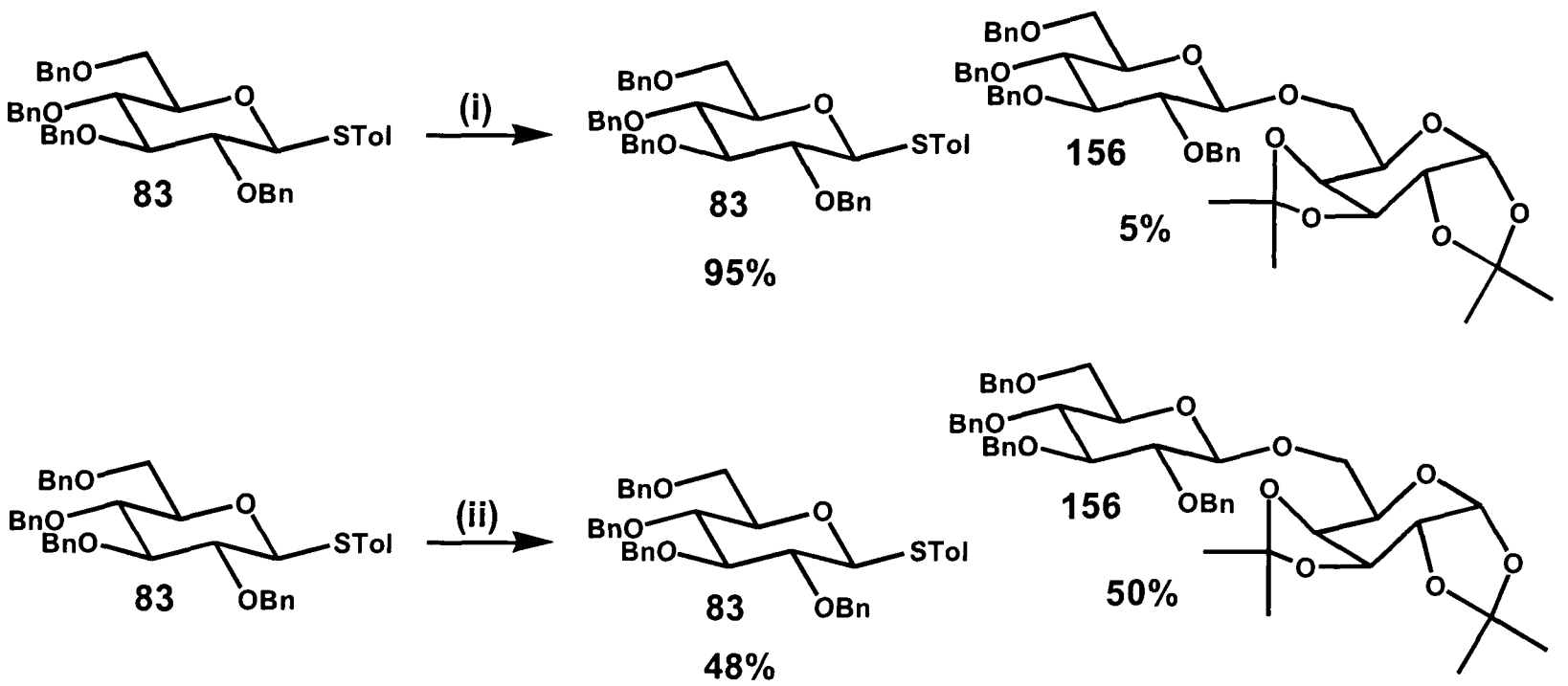


Scheme 4.15: Electrochemical oxidation of PhSeSePh, at +1.35 V as elucidated by Kunai *et al*

Step (3) was proposed following the work of Amatore and Savéant on charge-transfer and neutral radical dimerisation.[18]

Species such as $PhSe^+$ are known to be powerful activators of both seleno- and thioglycosides.[19-22] It therefore seemed possible that this species was being generated under the applied reaction conditions, and was subsequently able to activate both the thioglycoside acceptor and the disaccharide product, in addition to the selenoglycoside donor. However, despite extensive efforts, at no point was it possible to isolate or detect any carbohydrate by-products other than in those cases where hydrolysis of the glycosyl donor starting material was seen. The result of indiscriminate activation by $PhSe^+$ could well be highly polymeric saccharides, which would be difficult to isolate.

To probe this hypothesis a pair of control experiments were conducted. Activation of thioglycoside **83** was attempted at +1.7 V, both with and without diphenyl diselenide present in the starting mixture. Diacetone galactose (DAG) was used as the glycosyl acceptor and other reaction conditions were kept the same (scheme 4.16).



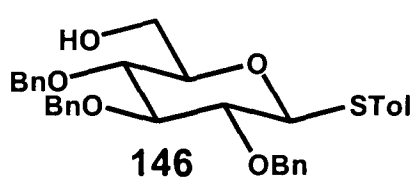
(i) MeCN, TBAP, DAG, 4 Å molecular sieves, +1.7 V, 3 h; (ii) MeCN, TBAP, DAG, **PhSeSePh,** 4 Å molecular sieves, +1.7 V, 3 h

Scheme 4.16

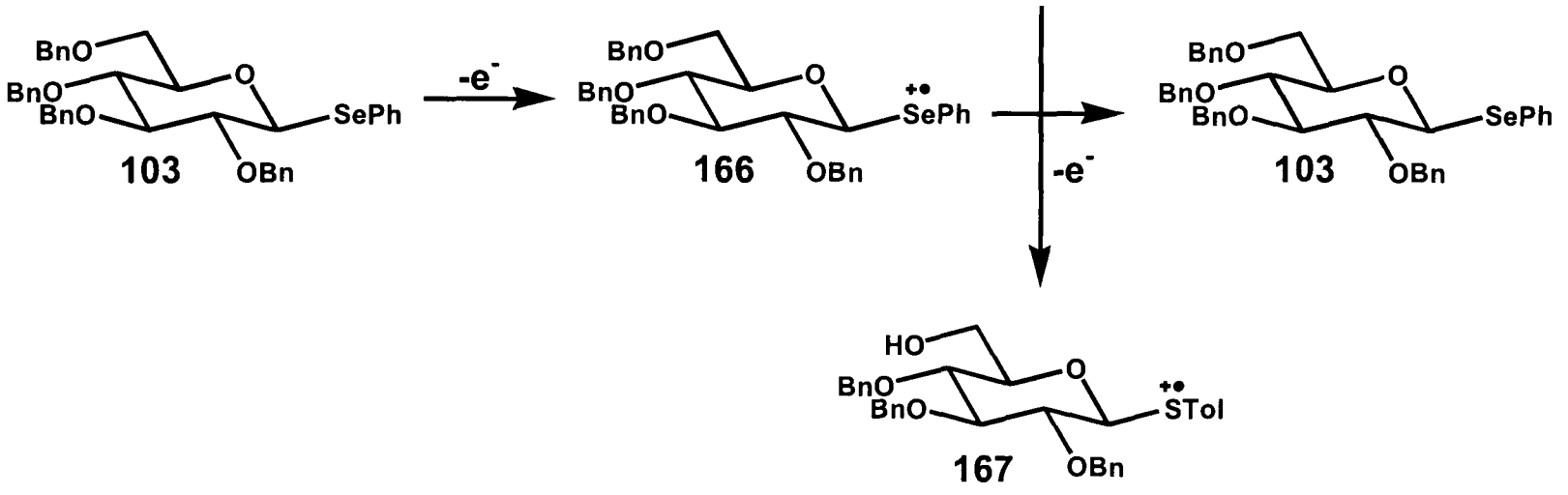
In the absence of diphenyl diselenide a small amount of activation of the thioglycoside was observed, however in the presence of diphenyl diselenide 50% of the disaccharide product formed over the same period.

This was not proof of the proposed mechanism for the loss of product, but it did indicate that some mechanism for activation other than direct electrochemical oxidation exists when diphenyl diselenide is present.

Instead of the chemical pathway of activation discussed above for activation of the thiotolyl acceptor it is also possible to envisage a single electron transfer pathway which would generate the same result. The initial step would once again be the oxidation of the glycoside with an oxidation potential lower than that applied to the system; however if this radical was sufficiently long lived single electron transfer might be able occur to any other chalcoglycoside present. For example in the attempted disaccharide synthesis described above initial oxidation of the selenoglycoside donor could be followed by single electron transfer to the thioglycoside acceptor, or disaccharide (scheme 4.17).

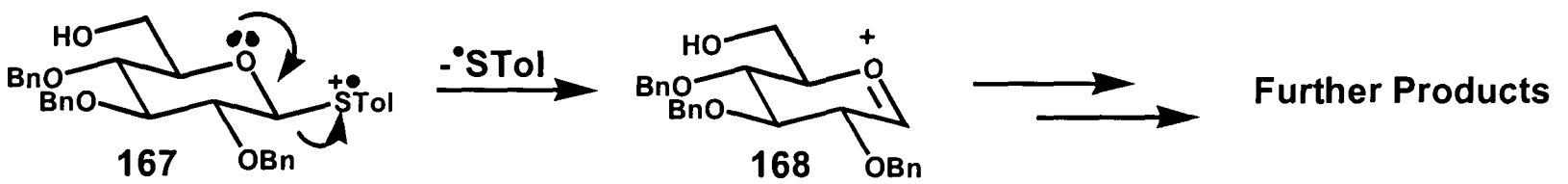


146



Scheme 4.17: Possible single electron transfer mechanism for indiscriminate activation of chalcoglycosides below their oxidation potential

It is possible to then envisage the formation of a glycosyl cation **168** from the thiotolyl radical cation **167**, in the same manner as has been previously discussed for the selenoglycoside donor (scheme 4.18). This compound would then clearly be able to go on and react to form a variety of products.



Scheme 4.18: Further reaction pathway for the thio tolyl radical cation, if formed

If this mechanism was operating, the electron transfer could of course equally well come from the selenophenyl radical cation which is generated during the electrochemical activation (see scheme 4.15 above).

Both of these mechanisms provide plausible pathways to explain the low yields in the selective glycosylation reactions, although more study would be required in order to determine if either does, in reality, operate in this system.

4.5.6 Trisaccharide Syntheses

Two electrochemically active disaccharides had thus been synthesised in sufficient yield to allow investigation of a trisaccharide synthesis. The compounds under consideration were the *O*-phenyl disaccharide **162**, and the thiotolyl disaccharide **161** with oxidation potentials of +2.03 V and +1.58 V respectively (figure 4.8).

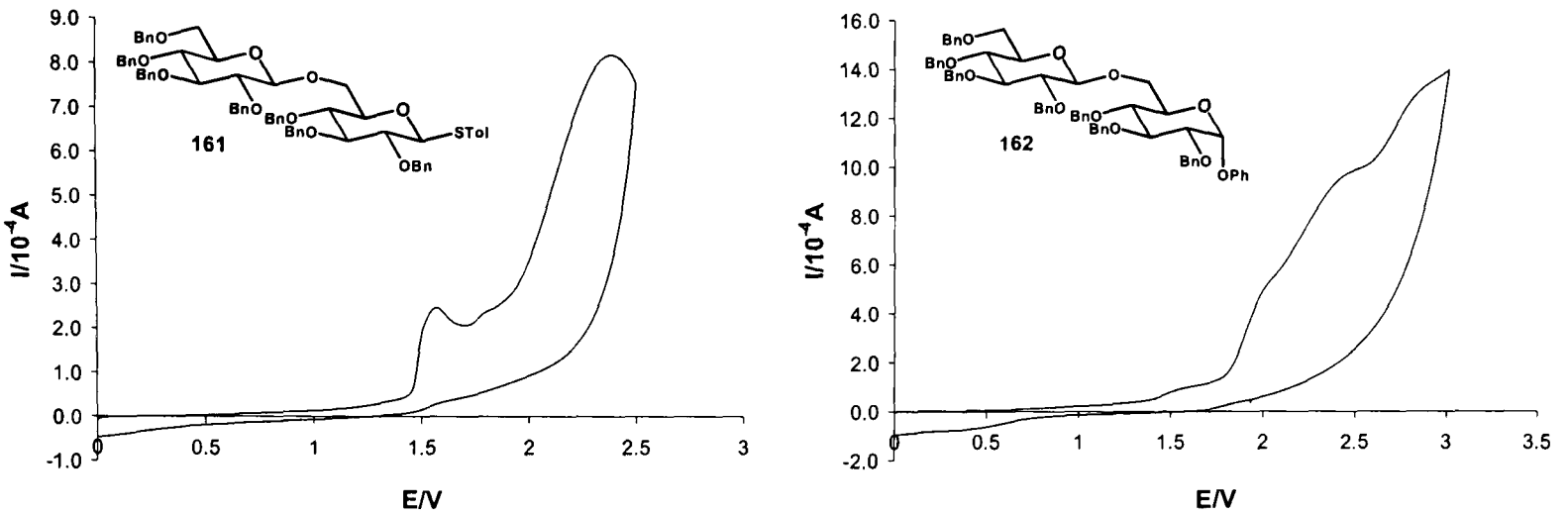
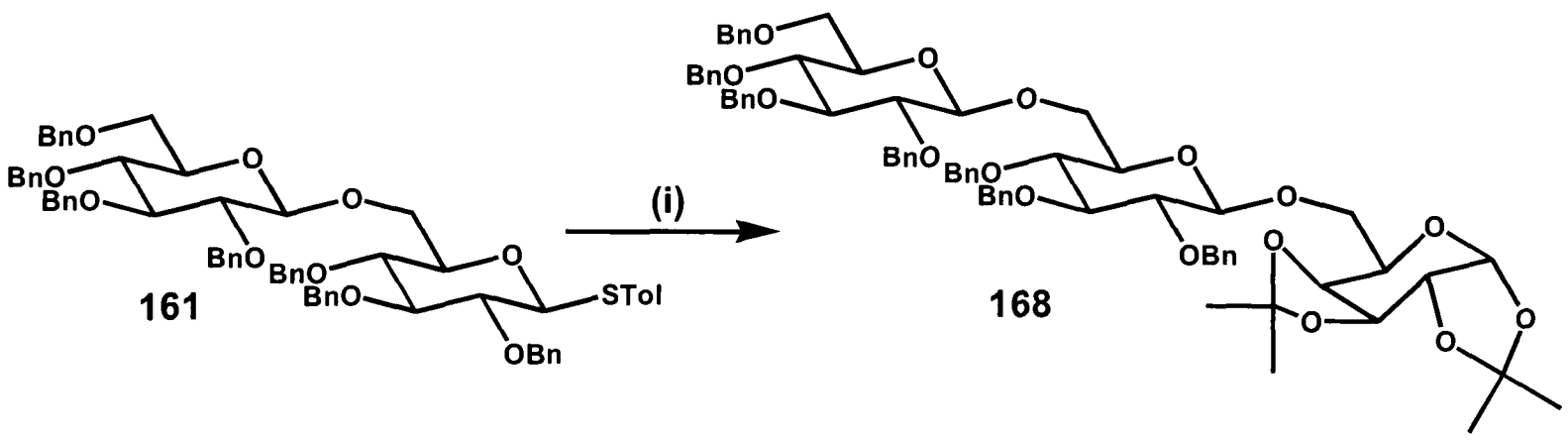


Figure 4.8: Comparison of first scan voltammograms for 2.2 mM thio tolyl disaccharide **161** and +1.8 mM *O*-phenyl disaccharide **162**, both for the first scan at 100 mVs^{-1} with a 5mm glassy carbon working electrode, nickel mesh counter electrode and calomel reference electrode.

The thiotolyl disaccharide **161** was easily activated under the standard cell conditions at +2.0 V, in the presence of diacetone galactose as the glycosyl acceptor, to give 79% of the trisaccharide (scheme 4.19). Once again only the β product was obtained from the reaction, presumably for the reasons already discussed.

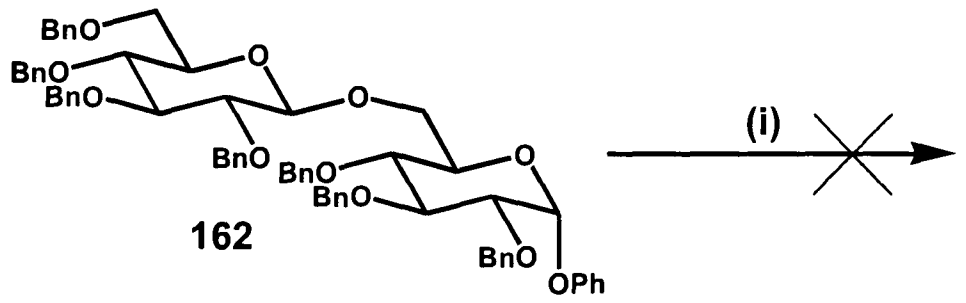


(i) MeCN, TBAP, DAG, 4 Å molecular sieves, +2.0 V, 3 h, 79%

Scheme 4.19

In the case of the *O*-phenyl disaccharide **162** activation was attempted at +2.1 V, +2.2 V, +2.3 V, +2.4 V, +2.5 V and +3.0 V. In all cases a large current was observed, but monitoring the reaction by t.l.c. showed no consumption of starting material and no new compounds being

formed. The reaction mixture did however change colour in all cases from a clear solution to a yellow or dark yellow/brown solution (scheme 4.20).



(i) MeCN, TBAP, DAG, 4 Å molecular sieves, +2.1 V → +3.0 V

Scheme 4.20

In order to confirm that there was indeed no activation the products from the reaction conducted at the highest potential (+3.0 V) were isolated and it was possible to recover 88% of the starting material, and no other carbohydrate products. The reaction was also attempted at a controlled current of 10 mA, but again no activation was observed.

4.5.7 Thioglycosides as donors

Hoping to avoid the problems which had been experienced with the selenoglycosides the possibility of activating one thioglycoside selectively in the presence of another thioglycoside of higher oxidation potential was examined. To do this a series of competition experiments were conducted, using four fully protected thioglycosides which had been shown from the analytical work to have a range of different oxidation potentials. The four thioglycosides chosen were: *p*-methoxyphenyl-2,3,4,6-tetra-*O*-benzyl-1-thio-β-D-glucopyranoside **120**, phenyl-2,3,4,6-tetra-*O*-benzyl-1-thio-β-D-glucopyranoside **78**, phenyl-2,3,4,6-tetra-*O*-benzoyl-1-thio-β-D-glucopyranoside **112** and *p*-nitrophenyl-2,3,4,6-tetra-*O*-benzyl-1-thio-β-D-

glucopyranoside **128**. These compounds showed peak oxidation potentials of +1.37 V, +1.62 V, +1.88 V and >+1.9 V respectively (figure 4.9).

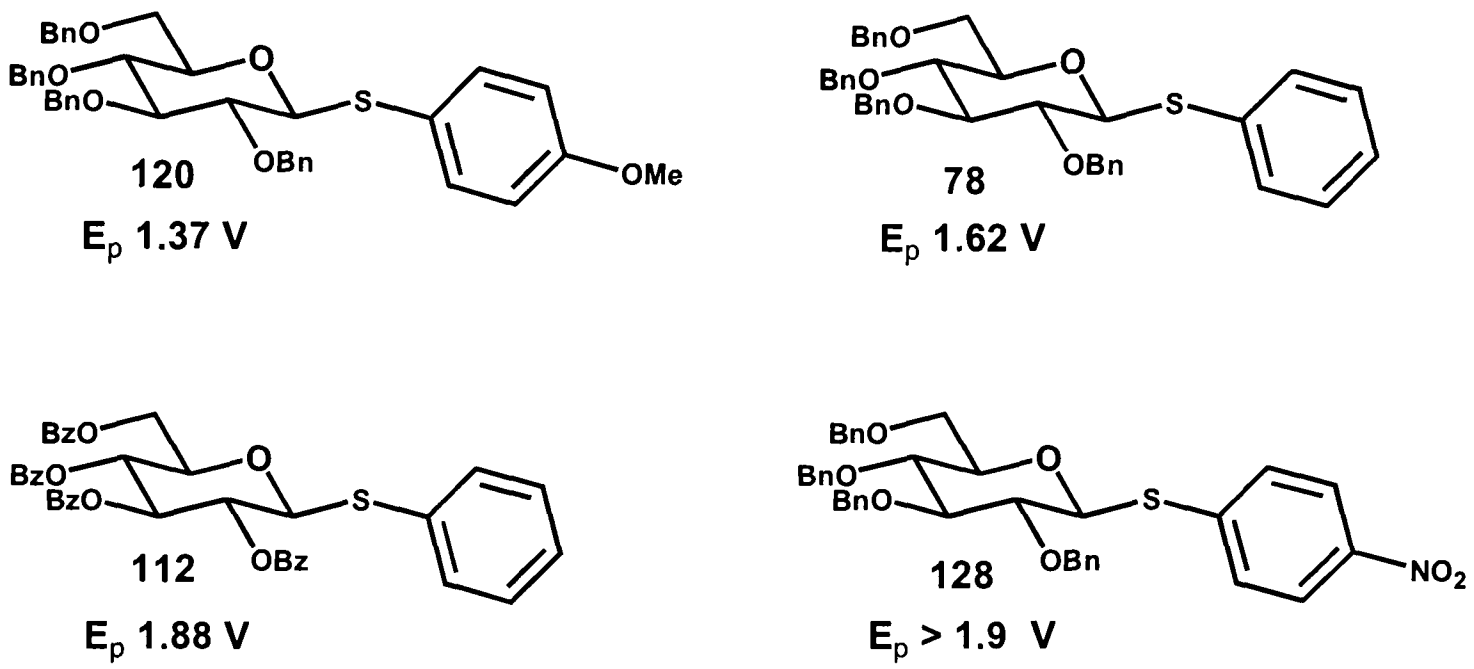
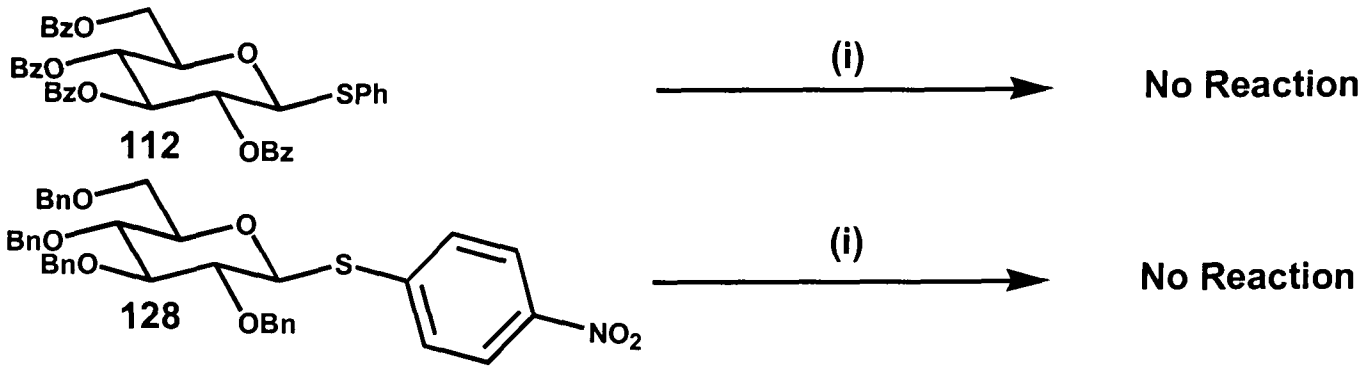


Figure 4.9: Thioglycoside donors

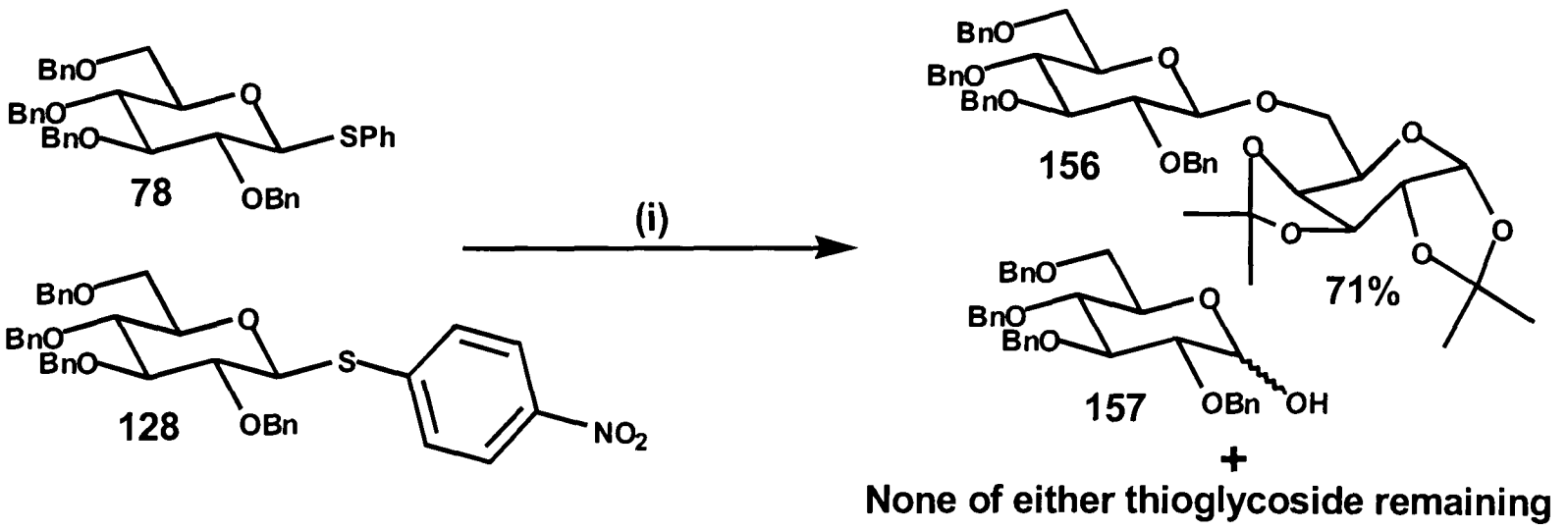
It had already been demonstrated that the benzylated phenyl thioglycoside **78** could be activated at +1.8 V, but not at +1.7 V or lower under the reaction conditions (*vide supra,* section 4.2). The analytical work (see chapter 3) suggested that neither the benzoylated phenyl thioglycoside **112** nor the benzylated *p*-nitrophenyl thioglycoside **128** would be activated at a potential of 1.8 V. It was possible to demonstrate that this was the case, with neither compound **112** or **128** showing any sign of activation after 17 hours under the standard cell conditions at +1.8 V when diacetone galactose **16** was used as the glycosyl acceptor (scheme 4.21).



(i) MeCN, TBAP, DAG, +1.8 V, 17 h

Scheme 4.21: Control experiment, showing compounds **112** and **128** were not activated at +1.8 V under the standard cell conditions.

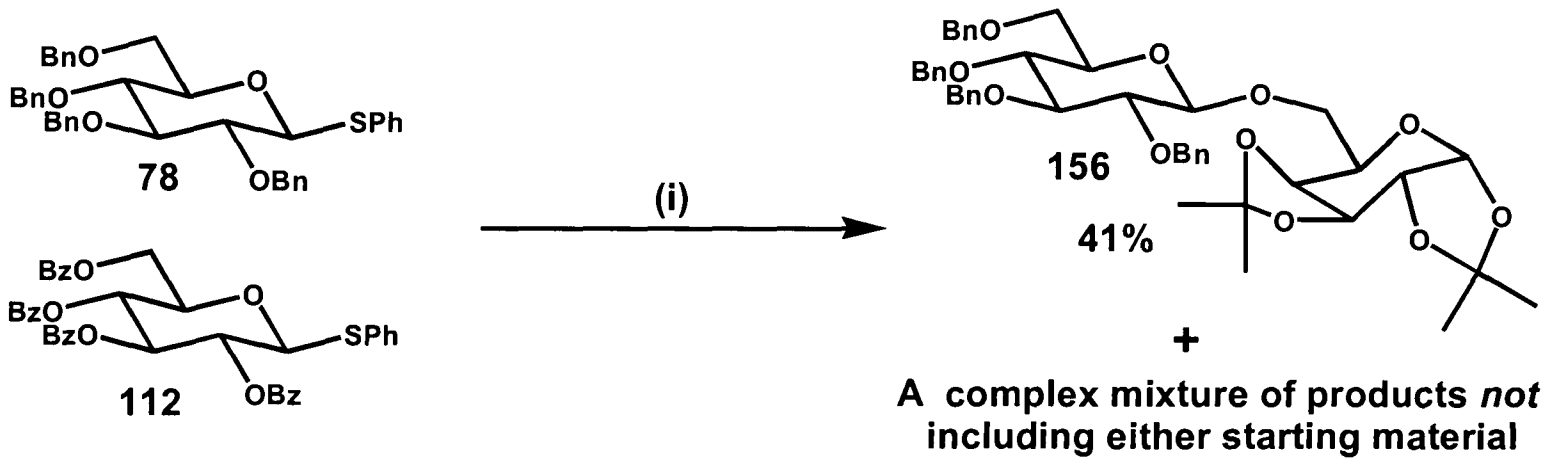
After these promising results the experiments were repeated, this time in the presence of one equivalent of benzylated phenyl thioglycoside **78**. In the reaction with the benzylated phenyl thioglycoside **78** and the benzylated *p*-nitrophenyl thioglycoside **128** it was possible to obtain some disaccharide product **156** (71% with respect to diacetone galactose, of which one equivalent was used), with t.l.c. analysis suggesting that the remainder of the reaction product consisted of tetrabenzyl glucose **157** (the product of hydrolysis), although this was not isolated. Crucially however there was none of the benzylated *p*-nitrophenyl thioglycoside **128** remaining as observed by t.l.c. analysis and none could be isolated by column chromatography (scheme 4.22).



(i) MeCN, TBAP, DAG, +1.8 V, 17 h; yield based on DAG (1 equivalent used)

Scheme 4.22

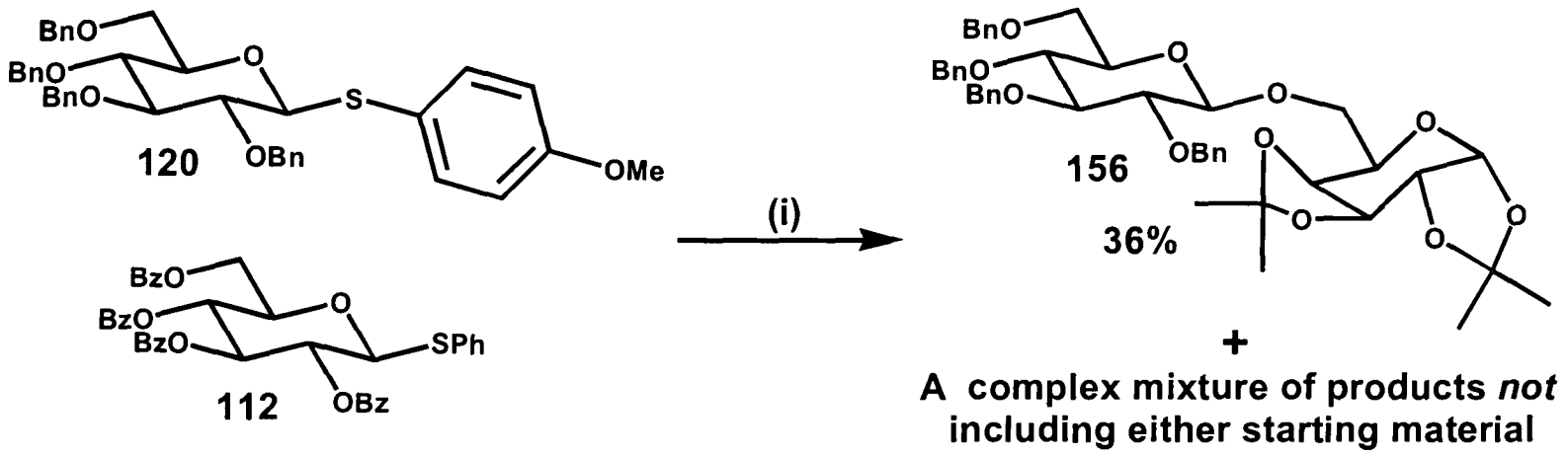
In the reaction containing benzylated phenyl thioglycoside **78** and benzoylated phenyl thioglycoside **112** t.l.c. indicated a complex mixture of products. T.l.c. analysis and subsequent purification of the reaction mixture did however show that neither starting material remained. Column chromatography was used in an attempt to isolate any remaining starting materials but, as indicated by t.l.c., none were present. As the benzylated disaccharide **156** was significantly less polar than the other products from the reaction it was again possible to isolate this product in 41% yield (scheme 4.23).



(i) MeCN, TBAP, DAG, +1.8 V, 17 h

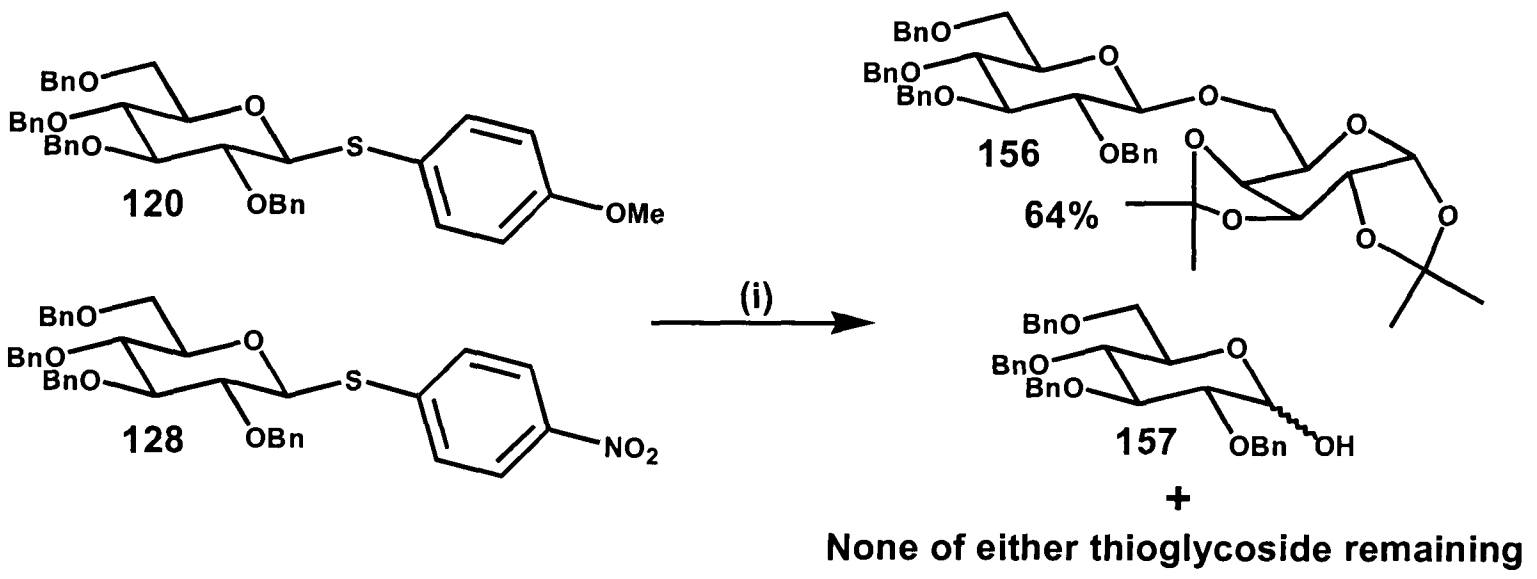
Scheme 4.23

Finally similar experiments were conducted at +1.5 V, using the *p*-methoxyphenyl thioglycoside **120** instead of the benzylated phenyl thioglycoside **78**. Even at this lower potential the results were similar, with none of either thioglycoside starting materials remaining in either case (schemes 4.24 and 4.25).



(i) MeCN, TBAP, DAG, +1.5 V, 17 h

Scheme 4.24



(i) MeCN, TBAP, DAG, +1.5 V, 17 h, yield based on DAG (1 equivalent used)

Scheme 4.25

These results further suggest that there is some mechanism operating which, under conditions which will activate one of the glycosides, serves to activate indiscriminately any other chalcoglycoside which is present, regardless of the potential required to activated that glycoside in isolation.

4.6 Conclusions

An efficient cell for electrochemical glycosylation on a synthetic scale has been constructed, and optimised conditions for glycosylation reactions using that cell have been obtained. Glycosylations using these conditions have been shown to be both rapid and high yielding as long as water is rigorously excluded from the reaction. In addition the glycosylation reactions have been shown to proceed with a high degree of β-selectivity.

The cyclic voltammetry conducted in chapter 3 has been shown to serve as a good guide to the potentials at which various seleno-, thio- and *O*-glycosides can be activated – and that at lower potentials such activation does not occur. In applying these results to a selective activation of one chalcoglycoside over another of higher oxidation potential it has been shown that there is some alternative mechanism of activation which leads indiscriminate activation of both glycosides. Nevertheless, by careful control of the reaction conditions, it was possible to obtain a disaccharide by selective activation of a selenoglycoside over a thioglycoside in modest yield. It was then demonstrated that the activation of this disaccharide at higher potential to give a trisaccharide was possible. At the time of writing this is the first electrochemically mediated trisaccharide synthesis reported in the literature.

Application of these conditions to the selective activation of thioglycosides over other thioglycosides with higher oxidation potentials gave extremely similar results to the earlier case of activation of selenoglycosides over thioglycosides. The glycosylations proceeded well, at the anticipated potentials, but attempted selective activations led to low yields and indiscriminate activation. It seems that whatever the underlying reason is it applies equally to these systems.

Use of an *O*-phenyl glycoside as acceptor overcame the problems experienced with the thioglycoside acceptors and allowed the formation of a disaccharide in much improved yield; however it was not possible to activate this to give a trisaccharide. Early work by Noyori suggests that this might be possible under alternative cell conditions.[16]

4.7 Future Work

This work provides a good basis for continued investigation in this area, with a number of different possibilities.

It is not clear what the reason for the indiscriminate activation observed during the selective reactions is. One possibility is that as an undivided cell is used processes occurring at the cathode could be affecting the reaction path. This could be investigated further by the use of a divided call, in which a porous frit is used to separate the cathodic and anodic processes. If however the problem arises due to the formation, and subsequent oxidation, of diphenyl diselenide or diphenyl disulphide (*vide supra*) the problem could be overcome by the use of *O*-glycosides as donors.

Altering the cell conditions also has the potential to affect the reaction pathway and a number of options exist for further work. The material of three electrodes (the working, counter and reference) could be varied. In particular Noyori's conditions of a platinum working electrode, platinum counter electrode and silver chloride reference electrode should allow the activation of *O*-glycosides and as such could provide rapid access to the attempted selective activation of one *O*-glycoside over another. The addition of methoxy groups to the phenyl ring of *O*-glycosides

has been shown to have a dramatic effect on the oxidation potential of the compounds, and by varying the number of methoxy groups a number of levels of electrochemical activity could be envisaged.

Other possibilities included changing the solvent, which would amongst other things give more insight into the stereocontrol seen during the synthetic reactions, and improving the mass transport to the working electrode – for instance by sonicating the reaction mixture. Alternative electrolytes could also be investigated, although care would need to be taken to avoid the reintroduction of problems with hydrolysis.

This work has demonstrated the general utility of synthetic electrochemical reactions in glycoside chemistry this could be further investigated. In particular as both acetates and benzoates can be removed under electrochemically reductive conditions the potential for electrochemical deprotection and glycosylation in one pot is opened up.

4.8 References

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Chapter 5: Experimental

5.1 General experimental

5.1.1 Electrochemical experimental

5.1.1.1 Chemical reagents and solutions

The chemicals employed in the electrochemical experiments, other than the saccharides, were purchased from commercial suppliers in the highest grade available unless otherwise stated, and were used without further purification. The reagents used were: lithium tetrafluoroborate (Aldrich, 98%), tetrabutylammonium perchlorate (TBAP, Fluka, ≥99%), tetraethylammonium perchlorate (TEAP, Fluka, ≥99%), diphenyl disulfide (Avocado Research Chemicals Ltd, ≥98%), diphenyl diselenide (Aldrich, ≥98%), dimethyl sulfoxide (DMSO, BDH "Spectrosol", ≥99.8%, stored over 5 Å molecular sieves), acetonitrile (Fischer, ≥98%, $H_2O \leq 0.01\%$) used in the cyclic voltammetric experiments and acetonitrile (Fluka, ≥99.5%, $H_2O \leq 0.01\%$, purchased over 4 Å molecular sieves in a sure/seal™ bottle) used in the potentiostatic experiments. Ultra-pure water was used for cleaning the platinum microelectrode (UHQ grade) and had a resistivity of not less than 18 MΩ cm (Elga, High Wycombe, Bucks, UK).

5.1.1.2 Instrumentation

The cyclic voltammetry was conducted using either a 12.5 μm diameter platinum microdisk electrode, constructed by sealing a platinum microwire (99.95%, Johnson Matthey plc, London, UK) into capillary soda glass according to a literature method,[1] as the working electrode with a platinum mesh counter electrode, and a silver wire (99.95%, Johnson Matthey plc, London,

UK) pseudo-reference electrode; or a 5 mm diameter glassy carbon disc electrode with a nickel mesh counter electrode and either a silver wire (99.95%, Johnson Matthey plc, London, UK) pseudo-reference electrode or a standard calomel electrode. The platinum microdisk electrode was cleaned between scans with ultra pure water and approximately 30% nitric acid, then polished using alumina lapping compounds (BDH) of decreasing size from 3 μm down to 0.25 μm on glass and soft lapping pads (Kemet Ltd, UK), finally rinsed in ultrapure water, dried carefully and stored under DMSO between each use. The electrode was regularly checked under an optical microscope to ensure that it was not recessed. The glassy carbon electrode was cleaned between scans using a succession of diamond lapping compounds of decreasing size, ending in 1.0 μm (Kemet Ltd, UK).

The potentiostatic, synthetic, reactions were conducted using a 45 PPI reticulated carbon electrode, approximately 10 mm x 10 mm x 60 mm in size as the working electrode, which was cleaned between reactions by sonication first with water, followed by acetone and finally acetonitrile; a nickel mesh counter electrode, which was cleaned between reactions by immersion in a 1M solution of nitric acid, followed by washing with water followed by acetone and finally acetonitrile; and a silver wire (99.95%, Johnson Matthey plc, London, UK) as a pseudo-reference electrode.

Experiments using the platinum microdisk working electrode were conducted using an μAutolab Type II (Eco Chemie BV, Utrecht, Netherlands) for voltammetry below 50 Vs^{-1}. For the voltammetry above this scan rate the potentiostat used was built in-house and has a scan rate of up to 3×10^4 V s^{-1} and was used with minimum filtering. This potentiostat is similar to

that described and utilised by Amatore and co-workers and is capable of achieving ohmic drop compensation by means of an internal positive feedback circuit.[2] The potential was applied with a TTi TG1304 programmable function generator (Thurlby Thandar Instruments Ltd, Huntingdon, Cambs, UK) and the current recorded with a Tektronix TDS 3032 oscilloscope (300 MHz band-pass, 2.5 GS/s). Modelling of voltammograms was carried out using DigiSim™ version 3.0 (Bioanalytical Systems Inc., West Lafayette, Indiana, USA).

Experiments using either the glassy carbon working electrode or the reticulated carbon working electrode were conducted using an Autolab PGSTAT30 (Eco Chemie BV, Utrecht, Netherlands).

5.1.2 Organic experimental

Melting points were recorded on a Kofler hot block and are uncorrected. Proton nuclear magnetic resonance (δ_H) spectra were recorded on Varian Gemini 200 (200 MHz), Bruker AC 200 (200MHz), Bruker DPX 400 (400 MHz), Bruker AV 400 (400 MHz), or Bruker AMX 500 (500 MHz) spectrometers. Proton spectra were assigned using COSY, HMBC, HMQC, DEPT sequence and/or APT sequence as necessary. Carbon nuclear magnetic resonance (δ_C) spectra were recorded on a Bruker DPX 400 (100.6 MHz) or a Bruker AMX 500 (125.75 MHz) spectrometer. Multiplicities were assigned using APT or DEPT sequence. All chemical shifts are quoted on the δ-scale using residual solvent as internal standard. Coupling constants are quoted once.

Infrared spectra were recorded on a Perkin-Elmer 150 Fourier Transform spectrophotometer or a Bruker Tensor 27 Fourier Transform spectrophotometer. Oils were analysed either as thin

films applied to sodium chloride plates (thin film) or as a solution in chloroform (chloroform). Solids were pressed into potassium bromide discs and analysed as such (KBr disk).

Low resolution mass spectra were recorded on VG Micromass 30F, or a Micromass Platform 1 using either atmospheric pressure chemical ionisation (CI) or electrospray ionisation (EI) in either the positive or the negative mode as stated. High resolution mass spectra were recorded on a Walters 2790-Micromass LCT mass spectrometer using either electrospray ionisation (ESI) or chemical ionisation (CI) as stated. M/z values are reported in Daltons and are followed by their percentage abundance in parentheses.

Optical rotations were measured on a Perkin-Elmer 241 polarimeter with a path length of 1 dm. Concentrations are given in g/100 ml. Microanalyses were performed by the microanalytical services of the Inorganic Chemistry Laboratory, South Parks Road, Oxford.

Thin layer chromatography (t.l.c.) was carried out on Merck glass backed sheets, pre-coated coated with $60F_{254}$ silica. Visualisation was achieved using a u.v. lamp (λ_{max} = 254 or 365 nm), ammonium molybdate (5% in 2M H_2SO_4) and/or sulphuric acid (5% in ethanol). Flash chromatography was carried out using Sorbsil C60 40/60 silica. Dichloromethane was dried before use either by distillation from calcium hydride (pre January 2004) or dried *via* alumina column (post January 2004).

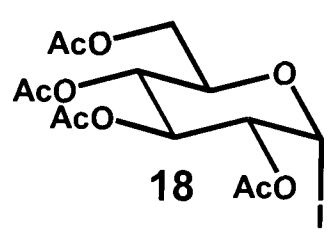
Dimethylformamide was purchased in sure/seal™ bottles either from Aldrich or Fluka, over 4 Å molecular sieves where available. Acetonitrile was purchased in 250 ml sure/seal™ bottles

from Fluka over 4 Å molecular sieves. Anhydrous methanol was purchased in sure/seal™ from Acros, over 4 Å molecular sieves.

Petrol refers to the fraction of light petroleum ether boiling in the range 40-60 °C. "Concentration in *vacuo*" refers to the removal of solvent on a rotary evaporator at an eventual pressure of *c.* 10-20 mbar with heating to 40 °C (heat was not applied in cases where the material was considered thermally sensitive). Reactions performed under an atmosphere of either argon or nitrogen gas were maintained by an inflated ballon.

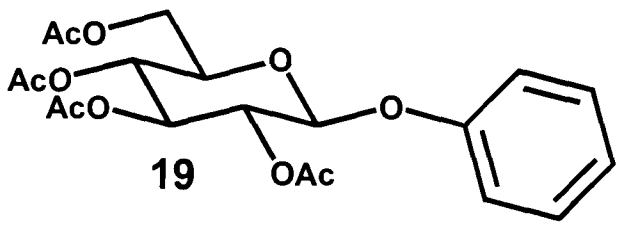
5.2 Experimental for Chapter 2

2,3,4,6-Tetra-*O*-acetyl-α-D-glucopyranosyl iodide 18



Penta-*O*-acetyl-β-D-glucopyranose **105** (10.0 g, 0.026 mol) and iodine (4.0 g, 0.031 mol) were dissolved in dichloromethane (80 ml) under argon in a flame dried flask. Hexamethyldisilazane (2.9 ml, 0.015 mol) was added and the solution stirred in the dark for 3 h, at which point t.l.c (ethyl acetat:petrol, 1:2) indicated the formation of a major product (R_f 0.3), together with a small amount of remaining starting material (R_f 0.2). The reaction mixture was diluted with dichloromethane (200 ml) and washed with sodium hydrogencarbonate (2 x 100 ml of a saturated aqueous solution) and sodium thiosulphate (2 x 100 ml of a 10% aqueous solution). The combined aqueous phases were re-extracted with dichloromethane (100 ml) and the combined organic layers washed with brine (50 ml), dried ($MgSO_4$), filtered and concentrated *in vacuo* without heating to afford 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl iodide **18** (10.1 g, 86%) as a white crystalline solid, m.p. 102-105 °C (ethyl acetate/petrol) (lit.,[3] 102-105 °C); $[\alpha]_D^{22}$ +246 (*c*, 1.0 in $CHCl_3$) (lit.,[4] $[\alpha]_D^{25}$ +230 (*c*, 1.1 in $CHCl_3$)); δ_H (400 MHz, $CDCl_3$) 2.03, 2.05, 2.09, 2.10 (4 x 3H, 4 x s, 4 x CH_3), 4.05 (1H, ddd, $J_{4,5}$ 10.3 Hz, $J_{5,6}$ 2.1 Hz, $J_{5,6'}$ 3.9 Hz, H-5), 4.11 (1H, dd, $J_{6,6'}$ 12.8 Hz, H-6), 4.20 (1H, dd, $J_{1,2}$ 4.3 Hz, $J_{2,3}$ 9.9 Hz, H-2), 4.34 (1H, dd, H-6'), 5.18 (1H, at, *J* 9.9 Hz, H-3), 5.46 (1H, at, *J* 9.5 Hz, H-4), 6.99 (1H, d, H-1).

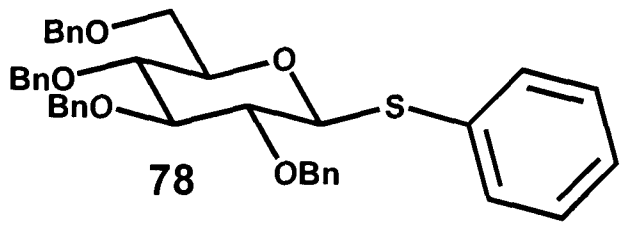
Phenyl-2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside 19



19

Penta-*O*-acetyl-β-D-glucopyranose **105** (15.0 g, 0.04 mol) and phenol (10.9 g, 0.12 mol) were dissolved in dichloromethane (100 ml) under argon in a flame dried flask and boron trifluoride diethyl etherate (14 ml, 0.10 mol) added. The mixture was stirred for 5 h, at which point t.l.c. (ethyl acetate:petrol, 1:1) indicated the formation of a major product (R_f 0.5) and the absence of starting material (R_f 0.4). Triethylamine was added dropwise to the stirred solution until effervescence ceased. The reaction mixture was then washed with water (100 ml) and the aqueous phase re-extracted with dichloromethane (100 ml). The combined organic layers were washed with brine (100 ml), dried ($MgSO_4$), filtered and concentrated *in vacuo*. Recrystallization from ethanol afforded phenyl-2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside **19** (16.1 g, 95%) as a white crystalline solid, m.p. 123-124 °C (ethanol) (lit.,[5] 127-127.5 °C); $[\alpha]_D^{20}$ -22 (*c*, 1.0 in $CHCl_3$) (lit.,[5] $[\alpha]_D^{25}$ -22 (*c*, 1.4 in $CHCl_3$)); δ_H (400 MHz, $CDCl_3$) 2.04, 2.05, 2.06, 2.08 (4 x 3H, 4 x s, 4 x CH_3), 3.86 (1H, ddd, $J_{4,5}$ 9.8 Hz, $J_{5,6}$ 2.3 Hz, $J_{5,6'}$ 5.3 Hz, H-5), 4.17 (1H, dd, $J_{6,6'}$ 12.1 Hz, H-6), 4.30 (1H, dd, H-6'), 5.09 (1H, d, $J_{1,2}$ 7.3 Hz, H-1), 5.17 (1H, at, *J* 9.3 Hz, H-4), 5.25-5.33 (2H, m, H-2, H-3), 6.99 (2H, d, *J* 8.6 Hz, ArH), 7.08 (1H, t, *J* 7.4 Hz, ArH), 7.28-7.32 (2H, m, ArH).

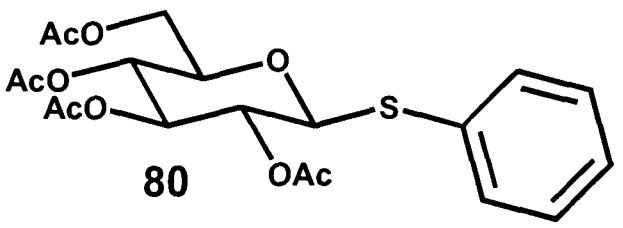
Phenyl-2,3,4,6-tetra-*O*-benzyl-1-thio-β-D-glucopyranoside 78



78

Phenyl-1-thio-β-D-glucopyranoside **111** (1.5 g, 5.52 mmol) was dissolved in *N*,*N*-dimethylformamide (20 ml) under argon in a dry flask and benzyl bromide (3.3 ml, 27.6 mmol) added. The reaction mixture was cooled to 0 °C, sodium hydride (60% dispersion in mineral oil) (795 mg, 33.1 mmol) added portionwise and the reaction allowed to warm slowly to room temperature. After 18 h t.l.c. (ethyl acetate:petrol, 1:8) showed the formation of a single product (R_f 0.3) and the absence of starting material (R_f 0). Methanol (50 ml) was added and the reaction mixture stirred for 15 min, then concentrated *in vacuo*. The residue was dissolved in ethyl acetate (100 ml), washed with brine (3 x 100 ml) and the aqueous layer re-extracted with ethyl acetate (100 ml). The combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (ethyl acetate:petrol, 1:8) to afford phenyl-2,3,4,6-tetra-*O*-benzyl-1-thio-β-D-glucopyranoside **78** (3.2 g, 92%) as a white crystalline solid, m.p. 90-91 °C (ethyl acetate/petrol) (lit.,[6] 91-92 °C); $[\alpha]_D^{22}$ +0.5 (*c*, 1.0 in $CHCl_3$) (lit.,[7] $[\alpha]_D^{20}$ +0.8 (*c*, 5.0 in $CHCl_3$)); δ_H (400 MHz, $CDCl_3$) 3.53-3.58 (1H, m, H-5), 3.55 (1H, at, *J* 9.2 Hz, H-2), 3.69 (1H, at, H-3), 3.73-3.78 (2H, m, H-4, H-6), 3.83 (1H, dd, $J_{5,6'}$ 10.9 Hz, $J_{6,6'}$ 1.9 Hz, H-6'), 4.58, 4.65 (2H, ABq, J_{AB} 12.0 Hz, PhC$\underline{H}_2$), 4.63, 4.87 (2H, ABq, J_{AB} 10.9 Hz, PhC$\underline{H}_2$), 4.71 (1H, d, $J_{1,2}$ 9.9 Hz, H-1), 4.77, 4.93 (2H, ABq, J_{AB} 10.3 Hz, PhC$\underline{H}_2$), 4.89, 4.94 (2H, ABq, J_{AB} 10.9 Hz, PhC$\underline{H}_2$), 7.22-7.65 (25H, m, ArH).

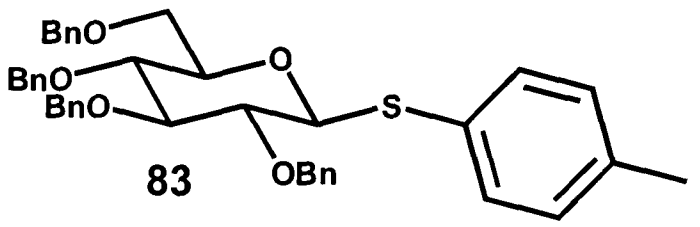
Phenyl-2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-glucopyranoside 80



80

Penta-*O*-acetyl-β-D-glucopyranose **105** (30.3 g, 0.084 mol) was dissolved in dichloromethane (200 ml) under argon in a flame dried flask. Thiophenol (12 ml, 0.12 mol) was added and the solution cooled to 0 °C. boron trifluoride diethyl etherate (30 ml, 0.24 mol) was added and the mixture stirred for 18 h, at which point t.l.c. (ethyl acetate:petrol, 1:1) indicated the formation of a major product (R_f 0.5) and the absence of starting material (R_f 0.4). The reaction mixture was diluted with dichloromethane (200 ml), washed with water (200 ml) and sodium hydrogencarbonate (2 x 200 ml of a saturated aqueous solution), dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by flash column chromatography (ethyl acetate:petrol, 1:4) to afford phenyl-2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-glucopyranoside **80** (24.6 g, 78%) as a white crystalline solid, m.p. 116-117 °C (ethanol) (lit.,[8] 117 °C); $[\alpha]_D^{21}$ -17 (*c*, 1.0 in $CHCl_3$) (lit.,[8] $[\alpha]_D^{20}$ -18 (*c*, 3.0 in $CHCl_3$)); δ_H (400 MHz, $CDCl_3$) 1.99, 2.02, 2.08, 2.09 (4 x 3H, 4 x s, 4 x CH_3), 3.73 (1H, ddd, $J_{4,5}$ 10.1 Hz, $J_{5,6}$ 2.6 Hz, $J_{5,6'}$ 5.0 Hz, H-5), 4.18 (1H, dd, $J_{6,6'}$ 12.3 Hz, H-6), 4.23 (1H, dd, H-6'), 4.71 (1H, d, $J_{1,2}$ 10.1 Hz, H-1), 4.98 (1H, at, *J* 9.7 Hz, H-2), 5.04 (1H, at, *J* 9.8 Hz, H-4), 5.23 (1H, at, *J* 9.4 Hz, H-3), 7.27-7.48 (3H, m, ArH), 7.50-7.51 (2H, m, ArH).

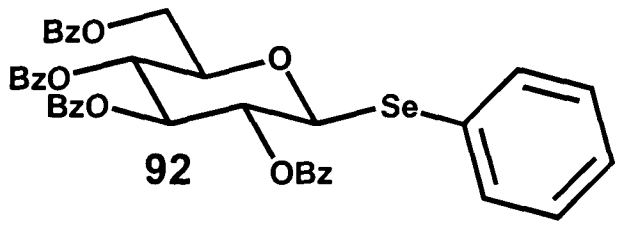
_p_-Tolyl-2,3,4,6-_O_-benzyl-1-thio-β-D-glucopyranoside 83



83

_p_-Tolyl-1-thio-β-D-glucopyranoside **115** (750 mg, 2.62 mmol) was dissolved in _N,N_-dimethylformamide (20 ml) under argon in a dry flask and benzyl bromide (1.6 ml, 13.1 mmol) added. The mixture was cooled to 0 °C and sodium hydride (60% dispersion in mineral oil) (630 mg, 15.7 mmol) added portionwise. The reaction mixture was stirred for 3 days, at which point t.l.c. (ethyl acetate:petrol, 1:8) indicated the formation of a major product (R_f 0.3) and the absence of starting material (R_f 0). Methanol (20 ml) was added and solution stirred for a further 15 min, the reaction mixture was then concentrated *in vacuo*. The residue was taken up in ethyl acetate (100 ml) and the resulting solution washed with brine (3 x 100 ml), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (ethyl acetate:petrol, 1:8) to afford _p_-tolyl-2,3,4,6-_O_-benzyl-1-thio-β-D-glucopyranoside **83** (1.4 g, 82%) as a white crystalline solid, m.p. 77-78 °C (ethanol) (lit.,[9] 80-81 °C); $[\alpha]_D^{25}$ -2 (*c*, 1.0 in $CHCl_3$) (lit.,[9] $[\alpha]_D^{21}$ +2 (*c*, 2.5 in $CHCl_3$)); δ_H (400 MHz, $CDCl_3$) 2.33 (3H, s, PhC<u>H</u>$_3$), 3.48-3.53 (2H, m, H-2, H-5), 3.66 (1H, at, *J* 9.5 Hz, H-3), 3.72 (1H, at, *J* 8.9 Hz, H-4), 3.75 (1H, dd, $J_{5,6}$ 4.8 Hz, $J_{6,6'}$ 11.0Hz, H-6), 3.81 (1H,dd, $J_{5,6'}$ 1.7 Hz, H-6'), 4.56, 4.63 (2H, ABq, J_{AB} 12.0 Hz, PhC<u>H</u>$_2$), 4.61, 4.92 (2H, ABq, J_{AB} 11.0 Hz, PhC<u>H</u>$_2$), 4.63 (1H, s, $J_{1,2}$ 10.2 Hz, H-1), 4.75, 4.85 (2H, ABq, J_{AB} 10.7 Hz, PhC<u>H</u>$_2$), 4.87, 4.90 (2H, ABq, J_{AB} 10.2 Hz, PhC<u>H</u>$_2$), 7.05-7.53 (24H, m, ArH).

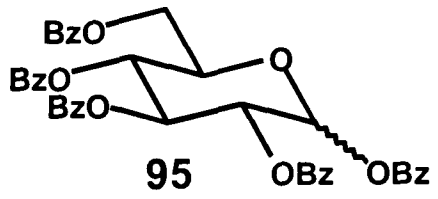
Phenyl-2,3,4,6-tetra-*O*-benzoyl-1-seleno-β-D-glucopyranoside 92



92

Diphenyl diselenide (227 mg, 0.71 mmol) was dissolved in ethanol (50 ml) and sodium borohydride (110 mg, 2.89 mmol) added portionwise. The solution was stirred for 15 min, at which point 2,3,4,6-tetra-*O*-benzoyl-α-D-glucopyranosyl iodide **96** (2.5 g, 3.54 mmol) was added and the reaction left to stir. After 18 h t.l.c. (ethyl acetate:petrol, 1:2) indicated the formation of a single product (R_f 0.4) and the absence of starting material (R_f 0.5). The reaction mixture was diluted with ethyl acetate (100 ml), washed with sodium thiosulphate (100 ml of a 10% aqueous solution) and water (100 ml), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (ethyl acetate:petrol, 1:4) to afford phenyl-2,3,4,6-tetra-*O*-benzoyl-1-seleno-β-D-glucopyranoside **92** (1.8 g, 79%) as a white crystalline solid, m.p. 170 °C (ethanol) (lit.,[10] 169.5-171 °C); $[\alpha]_D^{22}$ +21 (*c*, 1.0 in $CHCl_3$) (lit.,[10] $[\alpha]_D^{25}$ +21 (*c*, 1.0 in $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 4.13 (1H, ddd, $J_{4,5}$ 10.0 Hz, $J_{5,6}$ 6.0 Hz, $J_{5,6'}$ 2.7 Hz, H-5), 4.50 (1H, dd, $J_{6,6'}$ 12.1 Hz, H-6), 4.71 (1H, dd, H-6'), 5.08 (1H, d, $J_{1,2}$ 10.2 Hz, H-1), 5.52 (1H, at, *J* 9.7 Hz, H-2), 5.64 (1H, at, *J* 9.8 Hz, H-4), 5.95 (1H, at, *J* 9.5 Hz, H-3), 7.14-8.07 (25H, m, ArH).

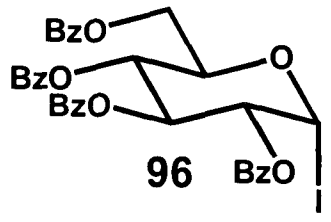
Penta-*O*-benzoyl-D-glucopyranose 95



95

D-Glucose **13** (30.0 g, 0.17 mol) was suspended in pyridine (500 ml) and the reaction mixture cooled to 0 °C. Benzoyl chloride (155 ml, 1.33 mol) was added portionwise with care and the reaction mixture allowed to warm to room temperature overnight. At this point t.l.c. (ethyl acetate:petrol, 1:3) indicated the formation of a major product (R_f 0.2) and the absence of starting material (R_f 0). The reaction mixture was diluted with dichloromethane (500 ml) and washed with hydrochloric acid (5 x 250 ml of a 0.1 M aqueous solution), sodium hydrogencarbonate (2 x 250 ml of a 10% aqueous solution), brine (2 x 250 ml), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was recrystallised from ethyl acetate/petrol to give crude penta-*O*-benzoyl-D-glucopyranose **95** (102 g, 88%) as a white crystalline solid, which was used without further purification.

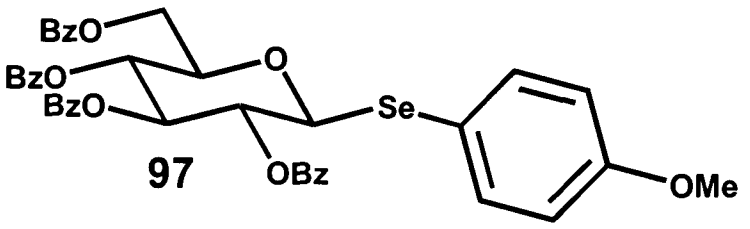
2,3,4,6-Tetra-*O*-benzoyl-α-D-glucopyranosyl iodide 96



96

Penta-*O*-benzoyl-D-glucopyranose **95** (5.0 g, 7.12 mmol) and iodine (1.1 g, 8.66 mmol) were dissolved in dichloromethane (50 ml) under argon in a flame dried flask. Hexamethyldisilazane (0.9 ml, 4.42 mmol) was added and the solution stirred in the dark for 18 h, at which point t.l.c (ethyl acetate:petrol, 1:2) indicated the formation of a major product (R_f 0.4), together with a small amount of remaining starting material (R_f 0.3). The reaction mixture was diluted with dichloromethane (200 ml) and washed with sodium thiosulphate (100 ml of a 10% aqueous solution), water (100 ml), brine (100 ml), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (ethyl acetate:petrol, 1:4) to afford 2,3,4,6-tetra-*O*-benzoyl-α-D-glucopyranosyl iodide **96** (4.5 g, 89%) as a white crystalline solid, m.p. 132-133 °C (ethyl acetate/petrol) (lit.,[4] 132-134°C); $[\alpha]_D^{22}$ +165 (*c*, 1.0 in $CHCl_3$) (lit.,[4] $[\alpha]_D^{25}$ +169 (*c*, 1.1 in $CHCl_3$)); δ_H (400 MHz, $CDCl_3$) 4.53 (1H, dd, $J_{5,6}$ 4.4 Hz, $J_{6,6'}$ 12.5 Hz, H-6), 4.70 (1H, dd, $J_{5,6'}$ 2.5 Hz, H-6'), 4.74-4.78 (1H, m, H-5), 5.36 (1H, dd, $J_{1,2}$ 4.0 Hz, $J_{2,3}$ 10.0 Hz, H-2), 5.86 (1H, at, *J* 10.1 Hz, H-4), 6.32 (1H, at, *J* 10.0 Hz, H-3), 6.90 (1H, d, H-1), 7.21-7.61 (12H, m, ArH), 7.89-8.11 (8H, m, ArH).

4-Methoxyphenyl-2,3,4,6-tetra-*O*-benzoyl-1-seleno-β-D-glucopyranoside 97

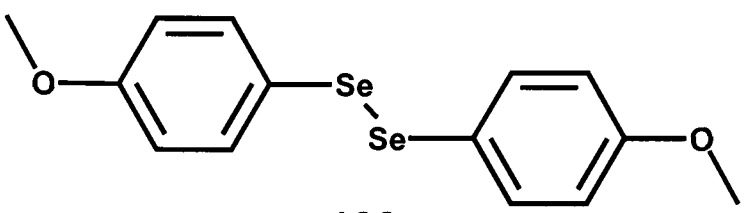


97

Bis-4-methoxyphenyl diselenide (482 mg, 1.30 mmol) was dissolved in ethanol (20 ml) and sodium borohydride (162 mg, 4.26 mmol) added portionwise. The solution was stirred for 15 min, at which point 2,3,4,6-tetra-*O*-benzoyl-α-D-glucopyranosyl iodide **96** (1.5 g, 2.12 mmol) was added and the reaction left to stir. After 2 h t.l.c. (ethyl acetate:petrol, 1:4) indicated the formation of a single product (R_f 0.1) and the absence of starting material (R_f 0.3). The reaction mixture was filtered and the residue repeatedly washed with cold petrol. Recrystallization from ethanol afforded 4-methoxyphenyl-2,3,4,6-tetra-*O*-benzoyl-1-seleno-β-D-glucopyranoside **97** (1.6 g, 98%) as a white crystalline solid, m.p. 179 °C (ethanol); $[\alpha]_D^{22}$ -7 (*c*, 1.0 in $CHCl_3$); ν_{max}(KBr disk)/cm^{-1} 1720 (C=O); δ_H (400 MHz, $CDCl_3$) 3.73 (3H, s, OCH_3), 4.15 (1H, ddd, $J_{4,5}$ 10.0 Hz, $J_{5,6}$ 5.6 Hz, $J_{5,6'}$ 2.8 Hz, H-5), 4.46 (1H, dd, $J_{6,6'}$ 12.3 Hz, H-6), 4.70 (1H, dd, H-6'), 5.14 (1H, d, $J_{1,2}$ 10.1 Hz, H-1), 5.47 (1H, at, *J* 9.7 Hz, H-2), 5.60 (1H, at, *J* 9.9 Hz, H-4), 5.80 (1H, at, *J* 9.6 Hz, H-3), 6.64-6.68 (2H, m, ArH), 7.25-7.62 (14H, m, ArH), 7.79-7.82 (2H, m, ArH), 7.89-7.91 (2H, m, ArH), 7.97-8.00 (2H, m, ArH), 8.04-8.06 (2H, m, ArH); δ_C (100.6 MHz, $CDCl_3$) 55.2 (q, OCH_3), 63.0 (t, C-6), 69.2 (d, C-4), 71.2 (d, C-2), 74.1 (d, C-3), 77.3 (d, C-5), 80.9 (d, C-1), 114.6, 128.7, 128.8, 129.3, 129.6, 133.2, 133.3, 133.5, 137.8 (9 x d, 24 x ArCH), 116.4, 128.3, 128.4, 129.7, 129.9, 160.2 (6 x s, 6 x ArC), 165.1, 165.2, 165.8, 166.0 (4 x s, 4 x C=O); *m/z* (ESI) 782 ($M(Se^{78})+NH_4^+$, 41%), 784

($M(Se^{80})+NH_4^+$, 100). (HRMS (ESI) Calcd. For $C_{41}H_{38}NO_{10}Se^{80}$ ($M+NH_4^+$) 784.1661. Found 784.1687). (Found: C, 64.29; H, 4.30. $C_{41}H_{34}O_{10}Se$ requires: C, 64.32; H, 4.48%).

Bis-4-methoxyphenyl diselenide 100

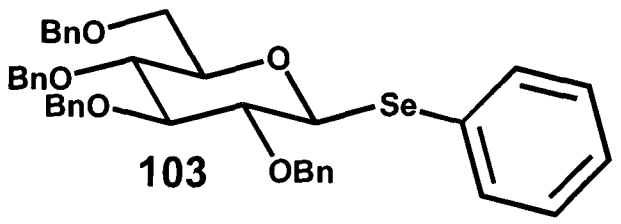


100

Magnesium turnings (611 mg, 25.5 mmol) were suspended in diethyl ether (10 ml) under argon in a flame dried three neck flask, bearing a reflux condenser and a dropping funnel; iodine (1 crystal) was added. 4-Bromoanisole (0.2 ml, 1.60 mmol) was added directly to the stirred reaction mixture. A solution of 4-bromoanisole (3.2 ml, 25.6 mmol) in diethyl ether (20 ml) was then added dropwise *via* the dropping funnel. After addition was complete the reaction mixture was refluxed for 2 h and then allowed to cool to room temperature, at which point selenium (2.0 g, 25.3 mmol) was added portionwise over 30 min. The reaction mixture was refluxed for 5 h, and then poured onto ice (200 ml). Concentrated hydrochloric acid (5 ml) was added dropwise to the stirred mixture and the ice allowed to melt. The phases were separated and the aqueous layer re-extracted with diethyl ether (100 ml). The combined organic layers were filtered through celite and added to a flame dried flask containing ethanol (100 ml) and potassium hydroxide (6 pellets). The reaction mixture was allowed to stir overnight, during which time air was pulled rapidly over the surface. The resulting residue was purified by flash column chromatography (ethyl acetate:petrol, 1:6) to afford bis-4-methoxyphenyl diselenide

100 (960 mg, 10%) as a yellow crystalline solid, m.p. 45-47 °C (cyclohexane) (lit.,[11] 46-47 °C); δ_H (400 MHz, $CDCl_3$) 3.82 (6H, s, 2 x CH_3), 6.80-6.83 (4H, m, ArH), 7.49-7.52 (4H, m, ArH).

Phenyl-2,3,4,6-tetra-*O*-benzyl-1-seleno-β-D-glucopyranoside 103

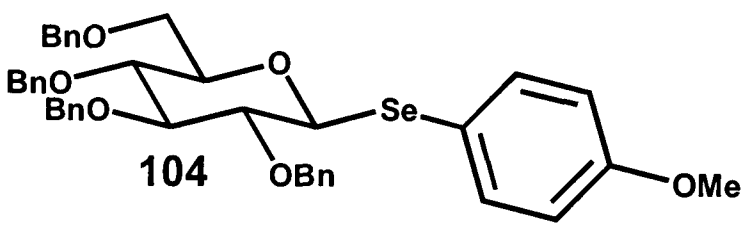


103

Phenyl-2,3,4,6-tetra-*O*-benzoyl-1-seleno-β-D-glucopyranoside **92** (1.2 g, 1.63 mmol) was dissolved in methanol (20 ml) under argon in a dry flask and a solution of sodium (114 mg, 9.35 mmol) in methanol (20 ml) was added. After 5 h t.l.c. (ethyl acetate:petrol, 1:4) showed the formation of a single product (R_f 0) and the absence of starting material (R_f 0.3). The reaction mixture was neutralised with ion exchange resin (Dowex® 50WX8), filtered and then concentrated *in vacuo*. The residue was dissolved in *N*,*N*-dimethylformamide (60 ml), the solution cooled to 0 °C and benzyl bromide (1.0 ml, 8.16 mmol) added. Sodium hydride (60% dispersion in mineral oil) (390 mg, 9.75 mmol) was added portionwise and the reaction mixture allowed to warm slowly to room temperature, with stirring. After 16 h t.l.c. (ethyl acetate:petrol, 1:8) indicated the formation of a major product (R_f 0.3) and the absence of starting material (R_f 0). The reaction mixture was diluted with ethyl acetate (100 ml) and washed with brine (3 x 100 ml). The organic phase was dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (ethyl acetate:petrol, 1:8) to afford phenyl-2,3,4,6-tetra-*O*-benzyl-1-seleno-β-D-glucopyranoside **103**

(1.0 g, 89%) as a white crystalline solid, m.p. 78-79 °C (ethanol) (lit.,[12] 79 °C); $[\alpha]_D^{22}$ –13 (*c*, 1.0 in $CHCl_3$) (lit.,[12] $[\alpha]_D^{22}$ +11 (*c*, 1.0 in CH_2Cl_2)); δ_H (400 MHz, $CDCl_3$) 3.48-3.51 (1H, m, H-5), 3.54 (1H, at, *J* 9.7 Hz, H-2), 3.65-3.73 (2H, m, H-3, H-4), 3.75 (1H, dd, $J_{5,6}$ 4.5 Hz, $J_{6,6'}$ 10.9 Hz H-6), 3.81 (1H, dd, $J_{5,6'}$ 2.1 Hz, H-6'), 4.55, 4.63 (2H, ABq, J_{AB} 11.9 Hz, PhC$\underline{H}_2$), 4.61 (1H, d, *J* 11.0 Hz, PhC$\underline{H}$H),4.74 (1H, d, *J* 10.3 Hz, PhC$\underline{H}$H), 4.83-4.92 (4H, m, 2 x PhC$\underline{H}_2$), 4.87 (1H, d, $J_{1,2}$ 9.4 Hz, H-1), 7.19-8.12 (25H, m, ArH).

4-Methoxyphenyl-2,3,4,6-tetra-*O*-benzyl-1-seleno-β-D-glucopyranoside 104

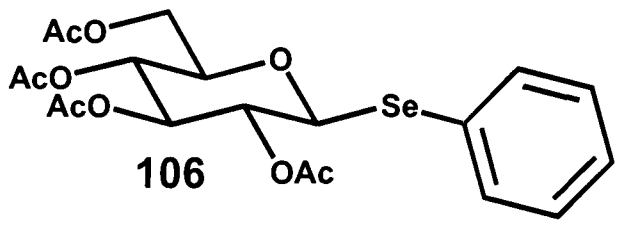


104

4-Methoxyphenyl-2,3,4,6-tetra-*O*-benzoyl-1-seleno-β-D-glucopyranoside **97** (1.4 g, 1.83 mmol) was suspended in methanol (20 ml) under argon in a dry flask and a solution of sodium (74 mg, 3.22 mmol) in methanol (10 ml) was added. After 6 h t.l.c. (ethyl acetate) showed the formation of a single product (R_f 0.1) and the absence of starting material (R_f 0.7). The reaction mixture was neutralised with ion exchange resin (Dowex® 50WX8), filtered and then concentrated *in vacuo*. The residue was dissolved in *N*,*N*-dimethylformamide (40 ml) and benzyl bromide (1.1 ml, 9.26 mmol) added. Sodium hydride (60% dispersion in mineral oil) (340 mg, 8.50 mmol) was added portionwise and the reaction mixture allowed to warm slowly to room temperature, with stirring. After 25 h t.l.c. (ethyl acetate:petrol, 1:4) indicated the formation of a major product (R_f 0.4) and the absence of starting material (R_f 0). The reaction

mixture was diluted with ethyl acetate (100 ml) and washed with brine (3 x 100 ml). The combined aqueous layers were re-extracted with ethyl acetate (100 ml) and the combined organic phases dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (ethyl acetate:petrol, 1:8) to afford 4-methoxyphenyl-2,3,4,6-tetra-*O*-benzyl-1-seleno-β-D-glucopyranoside **104** (890 mg, 69%) as a white crystalline solid, m.p. 84 °C (ethyl acetate/petrol); $[\alpha]_D^{22}$ +27 (*c*, 1.0 in $CHCl_3$); ν_{max}(KBr disk)/cm^{-1} no significant peaks; δ_H (400 MHz, $CDCl_3$) 3.45-3.50 (2H, m, H-2, H-5), 3.65, 3.69 (2 x 1H, 2 x at, *J* 9.2 Hz, *J* 8.7 Hz, H-3, H-4), 3.76 (3H, s, CH_3), 3.78-3.82 (2H, m, H-6, H-6'), 4.55, 4.62 (2H, ABq, J_{AB} 11.9 Hz, PhC$\underline{H}_2$), 4.62, 4.76 (2H, ABq, J_{AB} 9.0 Hz, PhC$\underline{H}_2$), 4.78 (1H, d, $J_{1,2}$ 9.5 Hz, H-1), 4.84 (1H, d, *J* 11.0 Hz, PhC$\underline{H}$H'), 4.88-4.92 (3H, m, PhC$\underline{H}_2$, PhCH$\underline{H}$'), 6.71-6.73 (2H, m, ArH), 7.21-7.44 (20H, m, ArH), 7.62-7.64 (2H, m, ArH); δ_C (100.6 MHz, $CDCl_3$) 55.2 (q, CH_3), 69.0 (t, C-6), 73.4, 75.1, 75.2, 75.9 (4 x t, 4 x Ph$\underline{C}H_2$), 77.8, 82.8 (2 x d, C-3, C-4), 80.0, 81.2 (2 x d, C-2, C-5), 86.8 (d, C-1), 114.6, 127.5, 127.7, 127.8, 127.9, 128.3, 128.4, 128.5, 136.9 (9 x d, 24 x ArCH), 118.0, 138.1, 138.3, 138.4, 159.8 (5 x s, 6 x ArC); *m/z* (ESI) 728 ($M(Se^{80})+NH_4^+$, 21%). (HRMS (ESI) Calcd. For $C_{41}H_{46}NO_6Se^{80}$ ($M+NH_4^+$) 728.2490. Found 728.2492). (Found: C, 69.34; H, 6.10. $C_{41}H_{42}O_6Se$ requires: C, 69.38; H, 5.96%).

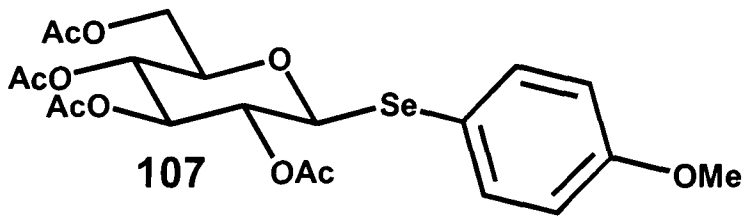
Phenyl-2,3,4,6-tetra-*O*-acetyl-1-seleno-β-D-glucopyranoside 106



106

Diphenyl diselenide (2.4 g, 7.69 mmol) was dissolved in ethanol (100 ml) and sodium borohydride (1.1 g, 28.9 mmol) added portionwise. The solution was stirred for 15 min, at which point 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl iodide **18** (6.5 g, 14.0 mmol) was added and the reaction left to stir. After 17 h t.l.c. (ethyl acetate:petrol, 1:2) indicated the formation of a single product (R_f 0.1) and the absence of starting material (R_f 0.2). Acetic acid (10 ml) was added and the reaction mixture stirred for a further 15 min, then concentrated *in vacuo*. The residue was taken up in ethyl acetate (100 ml), washed with water (100 ml), sodium hydrogencarbonate (100 ml of a saturated aqueous solution), brine (100 ml), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (ethyl acetate:petrol, 1:2) to afford phenyl-2,3,4,6-tetra-*O*-acetyl-1-seleno-β-D-glucopyranoside **106** (3.1 g, 45%) as a white crystalline solid m.p. 97-98 °C (ethanol) (lit.,[13] 99.5-100 °C); $[\alpha]_D^{20}$ -23 (*c*, 1.0 in $CHCl_3$) (lit.,[13] $[\alpha]_D^{25}$ -27 (*c*, 2.0 in $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.99, 2.02, 2.08 (4 x 3H, 3 x s, 4 x CH_3), 3.68-3.72 (1H, m, H-5), 4.19-4.20 (2H, m, H-6, H-6'), 4.89 (1H, d, $J_{1,2}$ 10.2 Hz, H-1), 5.01, 5.03 (2 x 1H, 2 x at, *J* 9.1 Hz, *J* 9.4 Hz, H-2, H-4), 5.20 (1H, at, *J* 9.3 Hz, H-3), 7.27-7.38 (3H, m, ArH), 7.60-7.62 (2H, m, ArH).

4-Methoxyphenyl-2,3,4,6-tetra-*O*-acetyl-1-seleno-β-D-glucopyranoside 107

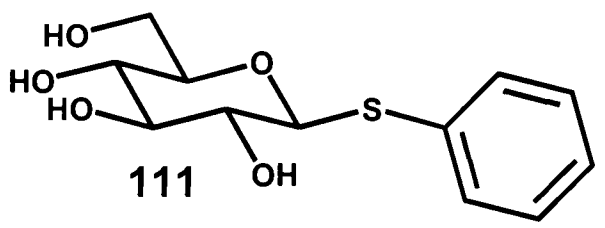


107

Bis-4-methoxyphenyl diselenide (102 mg, 0.27 mmol) was dissolved in ethanol (2 ml) and sodium borohydride (38 mg, 1.00 mmol) added portionwise. The solution was stirred for 20 min, at which point 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl iodide **18** (206 mg, 0.45 mmol) as a solution in chloroform (1 ml) was added and the reaction left to stir. After 2 h t.l.c. (ethyl acetate:petrol, 1:2) indicated the formation of a single product (R_f 0.2) and the absence of starting material (R_f 0.3). The reaction mixture was concentrated *in vacuo* and the residue taken up in ethyl acetate (20 ml) and washed with water (2 x 20 ml). The aqueous layer was re-extracted with ethyl acetate (20 ml) and the combined organic layers washed with brine (10 ml), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (ethyl acetate:petrol, 1:2) to afford 4-methoxyphenyl-2,3,4,6-tetra-*O*-acetyl-1-seleno-β-D-glucopyranoside **107** (203 mg, 59%) as a white crystalline solid, m.p. 105-106 °C (ethanol); $[\alpha]_D^{20}$ -38 (*c*, 1.0 in $CHCl_3$); ν_{max}(KBr disk)/cm^{-1} 1745 (s, C=O); δ_H (400 MHz, $CDCl_3$) 1.96, 1.99, 2.05, 2.06 (4 x 3H, 4 x s, 4 x $OCOCH_3$), 3.62-3.66 (1H, m, H-5), 3.80 (3H, s, OCH_3), 4.15-4.16 (2H, m, H-6, H-6'), 4.75 (1H, d, $J_{1,2}$ 10.1 Hz, H-1), 4.91 (1H, at, *J* 9.7 Hz, H-2), 4.96 (1H, at, *J* 9.8 Hz, H-4), 5.15 (1H, at, *J* 9.3 Hz, H-3), 6.80-6.82 (2H, m, ArH), 7.49-7.52 (2H, m, ArH); δ_C (100.6 MHz, $CDCl_3$) 20.5, 20.6, 20.7, 20.8 (4 x q, 4 x $OCO\underline{C}H_3$), 55.2 (q, OCH_3), 62.0 (t, C-6), 68.1 (d, C-4), 70.6 (d, C-2), 73.8 (d, C-3), 76.7 (d,

C-5), 80.4 (d, C-1), 114.5, 137.9 (2 x d, 4 x ArCH), 116.1, 160.3 (2 x s, 2 x ArC), 169.2, 169.3, 170.1, 170.5 (4 x s, 4 x C=O); *m/z* (ESI) 534 ($M(Se^{78})+NH_4^+$, 35%), 536 ($M(Se^{80})+NH_4^+$, 100). (HRMS (ESI) Calcd. for $C_{21}H_{30}NO_{10}Se^{80}$ ($M+NH_4^+$) 536.1035. Found 536.1026). (Found: C, 48.69; H, 5.29. $C_{21}H_{26}O_{10}Se$ requires: C, 48.75; H, 5.07%).

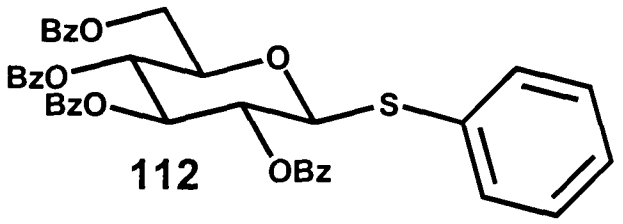
Phenyl-1-thio-β-D-glucopyranoside 111



111

Phenyl-2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-glucopyranoside **80** (5.0 g, 0.011 mol) was suspended in methanol (20 ml) in a dry flask. To this a solution of sodium (126 mg, 5.48 mmol) in methanol (30 ml) was added and the mixture stirred for 2 h, at which point t.l.c. (ethyl acetate:methanol, 1:9) indicated the formation of a major product (R_f 0.3) and the absence of starting material (R_f 0.7). Ion exchange resin (Dowex® 50WX8) was added portionwise until the solution was neutralised, at which point the reaction mixture was filtered and then concentrated *in vacuo* to afford phenyl-1-thio-β-D-glucopyranoside **111** (3.1 g, 99%) as a white crystalline solid, m.p. 131 °C (ethyl acetate) (lit.,[8] 133 °C); $[\alpha]_D^{21}$ -63 (*c*, 1.0 in MeOH) (lit.,[8] $[\alpha]_D^{19}$ -71 (*c*, 2.0 in H_2O)); δ_H (400 MHz, $CDCl_3$) 3.24 (1H, dd, $J_{1,2}$ 9.6 Hz, $J_{2,3}$ 8.8 Hz, H-2), 3.29-3.36 (2H, m, H-4, H-5), 3.41 (1H, at, *J* 8.8 Hz, H-3), 3.69 (1H, dd, $J_{5,6}$ 5.4 Hz, $J_{6,6'}$ 12.0 Hz, H-6), 3.88 (1H, dd, $J_{5,6'}$ 1.7 Hz, H-6'), 4.62 (1H, d, H-1), 7.24-7.34 (3H, m, ArH), 7.56-7.59 (2H, m, ArH).

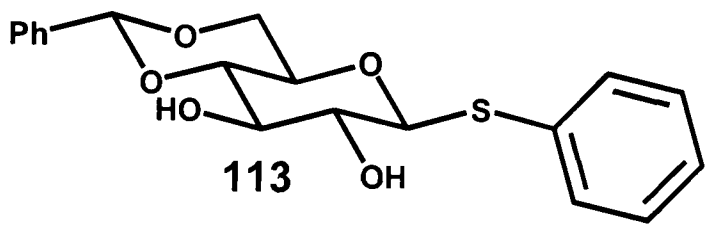
Phenyl-2,3,4,6-tetra-*O*-benzoyl-1-thio-β-D-glucopyranoside 112



112

Phenyl-1-thio-β-D-glucopyranoside **111** (958 mg, 3.33 mmol) was dissolved in pyridine (50 ml) under argon in a dry flask and benzoyl chloride (3.4 ml, 29.3 mmol) added. The mixture was stirred for 18 h, at which point t.l.c. (ethyl acetate:petrol, 1:3) indicated the formation of a major product (R_f 0.3) and the absence of starting material (R_f 0). The reaction mixture was diluted with dichloromethane (100 ml) and washed with hydrochloric acid (2 x 100 ml of a 0.1 M aqueous solution). The aqueous phase was re-extracted with dichloromethane (100 ml) and the combined organic layers washed with sodium hydrogencarbonate (2 x 100 ml of a saturated aqueous solution), brine (100 ml), dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford phenyl-2,3,4,6-tetra-*O*-benzyl-1-thio-β-D-glucopyranoside **112** (2.2 g, 96%) as a white crystalline solid, m.p. 166 °C (ethanol) (lit.,[14] 167-168 °C); $[\alpha]_D^{22}$ +35.7 (*c*, 1.0 in $CHCl_3$) (lit.,[14] $[\alpha]_D$ +34); δ_H (400 MHz, $CDCl_3$) 4.23 (1H, ddd, $J_{4,5}$ 10.0 Hz, $J_{5,6}$ 6.0 Hz, $J_{5,6'}$ 2.7 Hz, H-5), 4.51 (1H, dd, $J_{6,6'}$ 12.1 Hz, H-6), 4.71 (1H, dd, H-6'), 5.09 (1H, d, $J_{1,2}$ 10.0 Hz, H-1), 5.53 (1H, at, *J* 9.7 Hz, H-2), 5.64 (1H, at, *J* 9.7 Hz, H-4), 5.95 (1H, at, *J* 9.6 Hz, H-3), 7.14-8.07 (25 H, m, ArH), 7.87-8.09 (8H, m, ArH).

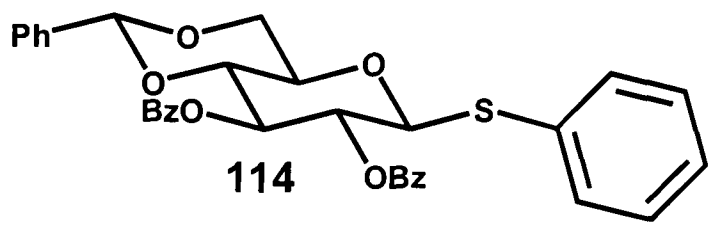
Phenyl-4,6-*O*-benzylidene-1-thio-β-D-glucopyranoside 113



113

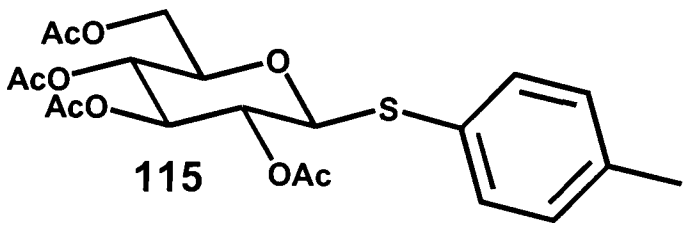
Phenyl-1-thio-β-D-glucopyranoside **111** (11.6 g, 0.04 mol) and camphor-10-sulphonic acid (1.9 g, 8.18 mmol) were dissolved in *N*,*N*-dimethylformamide (150 ml). Benzaldehyde dimethyl acetyl (12.2 ml, 0.08 mol) was added and the reaction mixture heated to 60 °C at a pressure of 200-260 mbar. After 2 h t.l.c. (ethyl acetate) indicated the formation of a major product (R_f 0.6) and the absence of starting material (R_f 0.1). The reaction mixture was concentrated *in vacuo* and recrystallization from propan-2-ol afforded phenyl-4,6-*O*-benzylidene-1-thio-β-D-glucopyranoside **113** (10.5 g, 68%) as a white crystalline solid, m.p. 184-185 °C (2-propanol) (lit.,[15] 188-188.5 °C); $[\alpha]_D^{21}$ -71 (*c*, 1.0 in MeOH) (lit.,[15] $[\alpha]_D^{25}$ -56 (*c*, 0.2 in $CHCl_3$)); δ_H (400 MHz, d6-DMSO) 3.14-3.26 (1H, m, H-2), 3.40 (1H, at, *J* 9.4 Hz, H-4), 3.49-3.57 (2H, m, H-3, H-5), 3.68 (1H, at, *J* 10.0 Hz, H-6), 4.20 (1H, dd, $J_{5,6}$ 4.9 Hz, $J_{6,6'}$ 9.9 Hz, H-6'), 4.86 (1H, d, $J_{1,2}$ 9.5 Hz, H-1), 5.47 (1H, d, $J_{3,OH}$ 5.5 Hz, OH-3), 5.59 (1H, s, PhC<u>H</u>), 5.53 (1H, d, $J_{2,OH}$ 6.3 Hz, OH-2), 7.24-7.46 (10H, m, ArH).

Phenyl-2,3-di-*O*-benzoyl-4,6-benzylidene-1-thio-β-D-glucopyranoside 114



Phenyl-4,6-*O*-benzylidene-1-thio-β-D-glucopyranoside **113** (2.1 g, 5.83 mmol) was dissolved in pyridine (50 ml) under argon in a dry flask and benzoyl chloride (2.5 ml, 21.5 mmol) added. The mixture was stirred for 16 h, at which point t.l.c. (ethyl acetate:petrol, 1:2) indicated the formation of a major product (R_f 0.5) and the absence of starting material (R_f 0.1). The reaction mixture was diluted with dichloromethane (100 ml) and washed with hydrochloric acid (2 x 100 ml of a 0.1 M aqueous solution). The aqueous phase was re-extracted with dichloromethane (100 ml) and the combined organic layers washed with sodium hydrogencarbonate (100 ml of a saturated aqueous solution), brine (100 ml), dried ($MgSO_4$), filtered and concentrated *in vacuo*. Recrystallization from ethyl acetate/petrol afforded phenyl-2,3-di-*O*-benzoyl-4,6-benzylidene-1-thio-β-D-glucopyranoside **114** (3.1 g, 94%) as a white crystalline solid, m.p. 212-213 °C (ethyl acetate/petrol) (lit.,[16] 211-212 °C); $[\alpha]_D^{21}$ +40 (*c*, 1.0 in $CHCl_3$) (lit.,[16] $[\alpha]_D^{20}$ +154 (*c*, 1.2 in $CHCl_3$)); δ_H (400 MHz, $CDCl_3$) 3.79-3.84 (1H, m, H-5), 3.92-3.99 (2H, m, H-4, H-6), 4.52 (1H, dd, $J_{5,6}$ 4.8 Hz, $J_{6,6'}$ 10.6 Hz, H-6'), 5.10 (1H, d, $J_{1,2}$ 10.3 Hz, H-1), 5.54 (1H, at, *J* 9.6 Hz, H-2), 5.60 (1H, s, PhC<u>H</u>), 5.86 (1H, at, *J* 9.5 Hz, H-3), 7.31-7.61 (16H, m, ArH), 7.98-8.04 (4H, m, ArH).

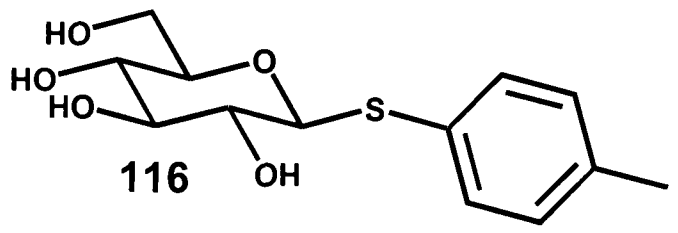
_p_-Tolyl-2,3,4,6-tetra-_O_-acetyl-1-thio-β-D-glucopyranoside 115



115

Penta-*O*-acetyl-β-D-glucopyranosose **105** (30.0 g, 0.08 mol) and *p*-thiocresol (15.2 g, 0.12 mol) were dissolved in dichloromethane (200 ml) under argon in a flame dried flask. The solution was cooled to 0 °C and boron trifluoride diethyl etherate (14 ml, 0.10 mol) added. The mixture was stirred for 16 h, at which point t.l.c. (ethyl acetate:petrol, 1:1) indicated the formation of a major product (R_f 0.5) and the absence of starting material (R_f 0.4). The reaction mixture was diluted with dichloromethane (200 ml), washed with sodium hydrogencarbonate (2 x 120 ml of a saturated aqueous solution), water (100 ml), dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by flash column chromatography to afford *p*-tolyl-2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-glucopyranoside **115** (28.2 g, 81%) as a white crystalline solid, m.p. 114-117 °C (ethyl acetate/petrol) (lit.,[17] 118 °C); $[\alpha]_D^{24}$ -18 (*c*, 1.0 in $CHCl_3$) (lit.,[17] $[\alpha]_D^{20}$ -21 (*c*, 2.0 in $CHCl_3$)); δ_H (400 MHz, $CDCl_3$) 1.99, 2.02, 2.09, 2.10 (4 x 3H, 4 x s, 4 x $COCH_3$), 2.36 (3H, s, PhC$\underline{H}_3$), 3.70 (1H, ddd, $J_{4,5}$ 10.1 Hz, $J_{5,6}$ 2.6 Hz, $J_{5,6'}$ 4.8 Hz, H-5), 4.18 (1H, dd, $J_{6,6'}$ 12.3 Hz, H-6), 4.22 (1H, dd, H-6'), 4.64 (1H, d, $J_{1,2}$ 10.1 Hz, H-1), 4.94 (1H, at, *J* 9.7 Hz, H-2), 5.03 (1H, at, *J* 9.9 Hz, H-4), 5.21 (1H, at, *J* 9.5 Hz, H-3), 7.13 (2H, d, *J* 8.1 Hz, ArH), 7.39 (2H, d, *J* 8.1 Hz, ArH).

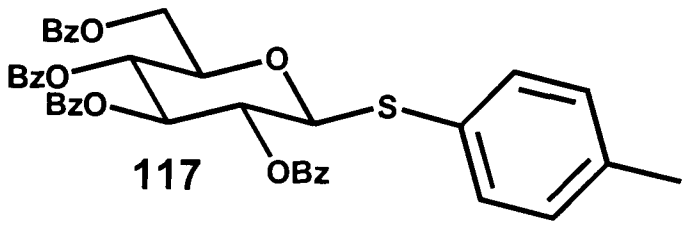
_p_-Tolyl-1-thio-β-D-glucopyranoside 116



116

_p_-Tolyl-2,3,4,6-tetra-_O_-acetyl-1-thio-β-D-glucopyranoside **115** (26.0 g, 0.057 mol) was dissolved in methanol (100 ml) under argon in a flame dried flask. To this a solution of sodium (460 mg, 0.020 mol) in methanol (100 ml) was added and the mixture stirred for 1 h, at which point t.l.c. (ethyl acetate:petrol, 1:1) indicated the formation of a major product (R_f 0) and the absence of starting material (R_f 0.5). Ion exchange resin (IR 120+) was added portionwise until the solution was neutralised, at which point the reaction mixture was concentrated _in vacuo_ to afford _p_-tolyl-1-thio-β-D-glucopyranoside **116** (14.3 g, 87%) as a white crystalline solid, m.p. 146-148 °C (ethanol/petrol) (lit.,[17] 149 °C); $[\alpha]_D^{25}$ -48 (_c_, 1.0 in MeOH) (lit.,[17] $[\alpha]_D^{20}$ -57 (_c_, 1.5 in pyridine)); δ_H (400 MHz, $CDCl_3$) 2.33 (3H, s, PhC$\underline{H}_3$), 3.19 (1H, at, _J_ 9.2 Hz, H-2), 3.26-3.33 (2H, m, H-4, H-5), 3.39 (1H, at, _J_ 8.5 Hz, H-3), 3.67 (1H, dd, $J_{5,6}$ 5.1 Hz, $J_{6,6'}$ 12.0 Hz, H-6), 3.87 (1H, dd, $J_{5,6'}$ 2.5 Hz, H-6'), 4.53 (1H, d, $J_{1,2}$ 9.7 Hz, H-1), 7.14 (2H, d, _J_ 7.9 Hz, ArH), 7.48 (2H, d, _J_ 7.9 Hz, ArH).

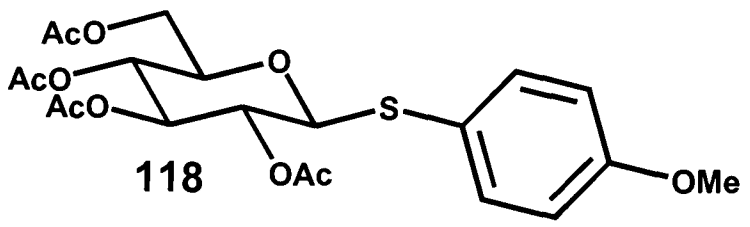
_p_-Tolyl-2,3,4,6-_O_-benzoyl-1-thio-β-D-glucopyranoside 117



117

_p_-Tolyl-1-thio-β-D-glucopyranoside **115** (1.0 g, 3.50 mmol) was dissolved in pyridine (50 ml) under argon in a flame dried flask and benzoyl chloride (3.3 ml, 28.0 mmol) added. The mixture was stirred for 18 h, at which point t.l.c. (ethyl acetate:petrol, 1:3) indicated the formation of a major product (R_f 0.3) and the absence of starting material (R_f 0). The reaction mixture was diluted with dichloromethane (100 ml) and washed with hydrochloric acid (2 x 100 ml of a 0.1 M aqueous solution). The aqueous phase was re-extracted with dichloromethane (100 ml) and the combined organic layers washed with sodium hydrogencarbonate (2 x 100 ml of a saturated aqueous solution), brine (100 ml), dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford _p_-tolyl-2,3,4,6-_O_-benzoyl-1-thio-β-D-glucopyranoside **117** (2.2 g, 88%) as a white crystalline solid, m.p. 186-188 °C (ethanol) (lit.,[9] 186-188 °C); $[\alpha]_D^{25}$ +21 (*c*, 1.0 in $CHCl_3$) (lit.,[9] $[\alpha]_D^{20}$ +23 (*c*, 1.0 in $CHCl_3$)); δ_H (400 MHz, $CDCl_3$) 2.29 (3H, s, PhC$\underline{H}_3$), 4.20 (1H, ddd, $J_{4,5}$ 9.8 Hz, $J_{5,6}$ 5.8 Hz, $J_{5,6'}$ 2.8 Hz, H-5), 4.49 (1H, dd, $J_{6,6'}$ 12.1 Hz, H-6), 4.71 (1H, dd, H-6'), 5.01 (1H, d, $J_{1,2}$ 9.7 Hz, H-1), 5.48 (1H, at, *J* 9.7 Hz, H-2), 5.62 (1H, at, *J* 9.8 Hz, H-4), 5.93 (1H, at, *J* 9.6 Hz, H-3), 6.95 (2H, d, *J* 8.0 Hz, ArH), 7.26-7.63 (14H, m, ArH), 7.81 (2H, dd, *J* 1.1 Hz, *J* 8.3 Hz, ArH), 7.91 (2H, dd, *J* 1.2 Hz, *J* 8.1 Hz, ArH), 8.00 (2H, dd, *J* 1.1 Hz, *J* 8.1 Hz, ArH), 8.07 (2H, dd, *J* 1.0 Hz, *J* 8.1 Hz, ArH).

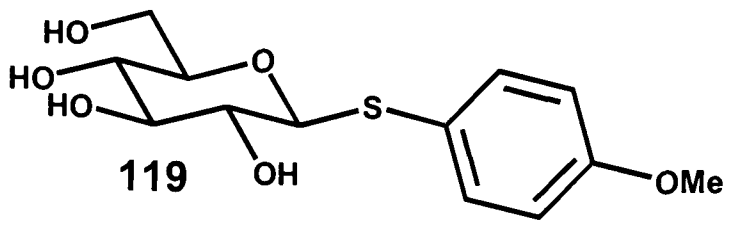
_p_-Methoxyphenyl-2,3,4,6-tetra-_O_-acetyl-1-thio-β-D-glucopyranoside 118



118

Penta-*O*-acetyl-β-D-glucopyranose **105** (1.0 g, 2.56 mmol) was dissolved in dichloromethane (20 ml) under argon in a flame dried flask. *p*-Methoxythiophenol (0.32 ml, 2.60 mmol) and then boron trifluoride diethyl etherate (0.98 ml, 7.63 mmol) were added and the reaction mixture stirred for 4 h. At this point t.l.c. (ethyl acetate:petrol, 1:1) indicated the formation of a major product (R_f 0.3) and the absence of starting material (R_f 0.2). Triethylamine was added dropwise to the reaction mixture until any effervescence ceased, and then reaction mixture was diluted with dichloromethane (20 ml), washed with water (20 ml), sodium hydrogencarbonate (20 ml of a saturated aqueous solution), brine (20 ml), dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by flash column chromatography (ethyl acetate:petrol, 1:1) to afford *p*-methoxyphenyl-2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-glucopyranoside **118** (1.1 g, 91%) as a white crystalline solid, m.p. 94-95 °C (ethanol) (lit.,[17] 101-102 °C); $[\alpha]_D^{21}$ -26 (*c*, 1.0 in $CHCl_3$) (lit.,[17] $[\alpha]_D^{20}$ -28 (*c*, 2.0 in $CHCl_3$)); δ_H (400 MHz, $CDCl_3$) 2.03, 2.05, 2.12, 2.15 (4 x 3H, 4 x s, 4 x $OCOCH_3$), 3.72 (1H, ddd, $J_{4,5}$ 10.0 Hz, $J_{5,6}$ 3.1 Hz, $J_{5,6'}$ 4.3 Hz, H-5), 3.86 (3H, s, OCH_3), 4.22 (1H, dd, $J_{6,6'}$ 12.2 Hz, H-6), 4.25 (1H, dd, H-6'), 4.60 (1H, d, $J_{1,2}$ 10.1 Hz, H-1), 4.93 (1H, dd, $J_{2,3}$ 9.6 Hz, H-2), 5.04 (1H, at, *J* 9.8 Hz, H-4), 5.24 (1H, at, *J* 9.2 Hz, H-3), 6.87-6.91 (2H, m, ArH), 7.47-7.51 (2H, m, ArH).

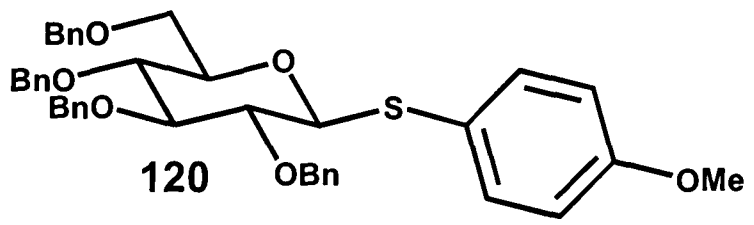
p-Methoxyphenyl-1-thio-β-D-glucopyranoside 119



119

p-Methoxyphenyl-2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-glucopyranoside **118** (500 mg, 1.06 mmol) was suspended in methanol (2.5 ml) in a dry flask. To this a solution of sodium (16 mg, 0.70 mmol) in methanol (25 ml) was added and the mixture stirred for 30 min, at which point t.l.c. (ethyl acetate:petrol, 1:2) indicated the formation of a major product (R_f 0) and the absence of starting material (R_f 0.4). Ion exchange resin (Dowex® 50WX8) was added portionwise until the solution was neutralised, at which point the reaction mixture was filtered and then concentrated *in vacuo* to afford *p*-methoxyphenyl-1-thio-β-D-glucopyranoside **119** (265 mg, 83%) as a white crystalline solid, m.p. 66-69 °C (ethyl acetate) (lit.,[17] 77 °C); $[\alpha]_D^{22}$ -37 (*c*, 1.0 in MeOH) (lit.,[17] $[\alpha]_D^{20}$ -51 (*c*, 1.0 in pyridine)); δ_H (400 MHz, MeOD) 3.14 (1H, dd, $J_{1,2}$ 9.7 Hz, $J_{2,3}$ 8.8 Hz, H-2), 3.24 (1H, at, *J* 9.8 Hz, H-4), 3.25-2.72 (1H, m, H-5), 3.37 (1H, at, *J* 8.7 Hz, H-3), 3.66 (1H, dd, $J_{5,6}$ 5.3 Hz, $J_{6,6'}$ 12.1 Hz, H-6), 3.80 (3H, s, OCH_3), 3.86 (1H, dd, $J_{5,6'}$ 1.8 Hz, H-6'), 4.41 (1H, d, H-1), 6.87-6.91 (2H, m, ArH), 7.54-7.57 (2H, m, ArH).

_p_-Methoxyphenyl-2,3,4,6-tetra-_O_-benzyl-1-thio-β-D-glucopyranoside 120



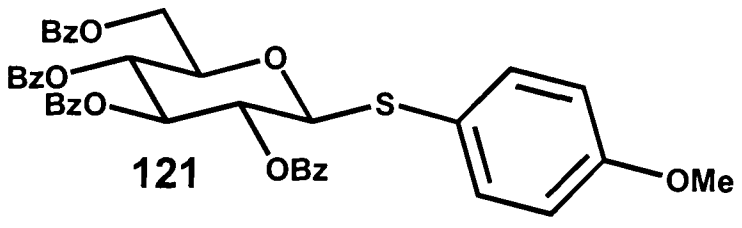
120

_p_-Methoxyphenyl-2,3,4,6-tetra-_O_-acetyl-1-thio-β-D-glucopyranoside **118** (3.0 g, 6.38 mmol) was suspended in methanol (90 ml) in a dry flask. To this a solution of sodium (14 mg, 0.61 mmol) in methanol (10 ml) was added and the mixture stirred for 1 h. Sodium (243 mg, 10.6 mmol) in methanol (10 ml) was added and the reaction mixture stirred for a further 1 h, at which point t.l.c. (ethyl acetate:petrol, 1:1) indicated the formation of a major product (R_f 0) and the absence of starting material (R_f 0.3). Ion exchange resin (Dowex® 50WX8) was added portionwise until the solution was neutralised, at which point the reaction mixture was filtered and then concentrated *in vacuo* to afford _p_-methoxyphenyl-1-thio-β-D-glucopyranoside **119** which was used without further purification.

The crude _p_-methoxyphenyl-1-thio-β-D-glucopyranoside **119** was dissolved in _N,N_-dimethylformamide (100 ml) under argon in a flame dried flask and benzyl bromide (3.7 ml, 30.1 mmol) added. The solution was cooled to 0 °C and sodium hydride (60% dispersion in mineral oil) (2.0 g, 50.0 mmol) added portionwise to the stirred solution. The reaction mixture was allowed to warm to room temperature overnight, at which point t.l.c. (ethyl acetate:petrol, 1:6) indicated the formation of a major product (R_f 0.3) and the absence of starting material (R_f 0). The reaction mixture was concentrated *in vacuo* and the residue taken

up in diethyl ether (200 ml). The organic phase was washed with water (2 x 200 ml) and the aqueous layer re-extracted with diethyl ether (100 ml). The combined organic layers were washed with brine (4 x 100 ml), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (ethyl acetate:petrol, 1:7) to afford *p*-methoxyphenyl-1-thio-β-D-glucopyranoside **120** (2.9 g, 69%) as a white crystalline solid, m.p. 82-83 °C (ethyl acetate/petrol) (lit.,[9] 79-80 °C); $[\alpha]_D^{22}$ -6 (*c*, 1.0 in $CHCl_3$) (lit.,[9] $[\alpha]_D^{20}$ -6 (*c*, 2.5 in $CHCl_3$)); δ_H (400 MHz, $CHCl_3$) 3.46 (1H, at, *J* 9.2 Hz, H-2) 3.46-3.49 (1H, m, H-5), 3.61, 3.70 (2 x 1H, 2 x at, *J* 9.0 Hz, *J* 9.3 Hz, H-3, H-4), 3.74 (1H, dd, $J_{5,6}$ 4.6 Hz, $J_{6,6'}$ 10.7 Hz, H-6), 3.77 (3H, s, OCH_3), 3.80 (1H, dd, $J_{5,6'}$ 1.7 Hz, H-6'), 4.59 (1H, d, $J_{1,2}$ 10.0 Hz, H-1), 4.55, 4.62 (2H, ABq, J_{AB} 12.0 Hz, PhC$\underline{H}_2$), 4.61, 4.83 (2H, ABq, J_{AB} 10.6 Hz, PhC$\underline{H}_2$), 4.75, 4.92 (2H, ABq, J_{AB} 10.2 Hz, PhC$\underline{H}_2$), 4.86, 4.90 (2H, ABq, J_{AB} 10.9 Hz, PhC$\underline{H}_2$), 6.74-6.77 (2H, m, ArH), 7.20-7.22 (2H, m, ArH), 7.27-7.38 (16H, m, ArH), 7.42-7.44 (2H, m, ArH), 7.53-7.57 (2H, m, ArH).

p-Methoxyphenyl-2,3,4,6-tetra-*O*-benzoyl-1-thio-β-D-glucopyranoside 121

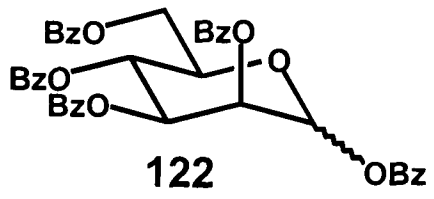


121

p-Methoxyphenyl-1-thio-β-D-glucopyranoside **119** (265 mg, 0.88 mmol) was dissolved in pyridine (10 ml) under argon in a dry flask and benzoyl chloride (0.8 ml, 7.34 mmol) added. The mixture was stirred for 17 h, at which point t.l.c. (ethyl acetate:petrol, 1:2) indicated the

formation of a major product (R_f 0.3) and the absence of starting material (R_f 0). The reaction mixture was diluted with dichloromethane (20 ml) and washed with hydrochloric acid (2 x 20 ml of a 0.1 M aqueous solution). The aqueous phase was re-extracted with dichloromethane (20 ml) and the combined organic layers washed with sodium hydrogencarbonate (2 x 20 ml of a saturated aqueous solution), brine (20 ml), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (ethyl acetate:petrol, 1:2) to afford *p*-methoxyphenyl-2,3,4,6-tetra-*O*-benzoyl-1-thio-β-D-glucopyranoside **121** (420 mg, 65%) as a white crystalline solid, m.p. 187-188 °C (ethyl acetate/petrol); $[\alpha]_D^{22}$ +6 (*c*, 1.0 in $CHCl_3$); ν_{max}(KBr disk)/cm^{-1} 1726 (s, C=O); δ_H (400 MHz, $CHCl_3$) 3.73 (3H, s, OCH_3), 4.17 (1H, ddd, $J_{4,5}$ 9.7 Hz, $J_{5,6}$ 5.7 Hz, $J_{5,6'}$ 2.9 Hz, H-5), 4.48 (1H, dd, $J_{6,6'}$ 12.2 Hz, H-6), 4.70 (1H, dd, H-6'), 4.92 (1H, d, $J_{1,2}$ 9.9 Hz, H-1), 5.43 (1H, at, *J* 9.6 Hz, H-2), 5.59 (1H, at, *J* 9.7 Hz, H-4), 5.90 (1H, at, *J* 9.5 Hz, H-3), 6.66-6.91 (2H, m, ArH), 7.25-7.62 (14H, m, ArH), 7.80 (2H, d, *J* 7.4 Hz, ArH), 7.90 (2H, d, *J* 7.7 Hz, ArH), 8.00 (2H, d, *J* 7.1 Hz, ArH), 8.05 (2H, d, *J* 7.2 Hz, ArH); δ_C (100.6 MHz, $CDCl_3$); 55.3 (q, CH_3), 63.0 (t, C-6), 69.3 (d, C-4), 70.4 (d, C-2), 74.2 (d, C-3), 76.2 (d, C-5), 86.2 (d, C-1), 114.4, 128.3, 128.4, 129.7, 129.8, 129.9, 133.2, 133.3, 133.5, 136.4 (10 x d, 24 x ArCH), 121.0, 128.7, 128.8, 129.3, 129.7, 160.3 (6 x s, 6 x ArC), 165.0, 165.2, 165.8, 166.0 (4 x s, 4 x C=O); *m/z* (ESI) 736 ($M+NH_4^+$, 100%). (HRMS (ESI) Calcd. For $C_{41}H_{38}NO_{10}S$ ($M+NH_4^+$) 736.2216. Found 736.2247). (Found: C, 68.45; H, 5.05. $C_{41}H_{34}O_{10}S$ requires: C, 68.51; H, 4.77%).

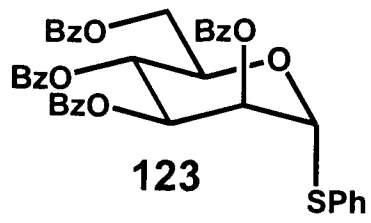
Penta-*O*-benzoyl-D-mannopyranoside 122



122

D-Mannose (30 g, 0.17 mol) was suspended in pyridine (500 ml) and the reaction mixture cooled to 0 °C. Benzoyl chloride (155 ml, 1.33 mol) was added portionwise with care and the reaction mixture allowed to warm to room temperature overnight. At this point t.l.c. (ethyl acetate:petrol, 1:3) indicated the formation of a major product (R_f 0.2) and the absence of starting material (R_f 0). The reaction mixture was diluted with dichloromethane (750 ml) and washed with hydrochloric acid (2 x 250 ml of a 0.1 M aqueous solution), sodium hydrogencarbonate (2 x 250 ml of a 10% aqueous solution), brine (250 ml), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was recrystallised from ethyl acetate/petrol to give crude penta-*O*-benzoyl-D-mannopyranosose **122** (95 g, 82%) as a white crystalline solid, which was used without further purification.

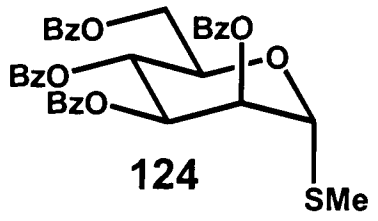
Phenyl-2,3,4,6-tetra-*O*-benzoyl-1-thio-α-D-mannopyranoside 123



123

Penta-*O*-benzoyl-D-mannopyranose **122** (4.0 g, 5.71 mmol) was dissolved in dichloromethane (200 ml) under argon in a flame dried flask. Benzenethiol (0.7 ml, 8.84 mmol) was added and the solution cooled to 0 °C. Tin (IV) chloride (0.7 ml, 5.95 mmol) was added to the stirred solution and the reaction mixture heated to 40 °C for 22 h, at which point t.l.c. (ethyl acetate:petrol, 1:2) indicated the formation of a major product (R_f 0.4) and the absence of starting material (R_f 0.3). The reaction mixture was diluted with diethyl ether (100 ml), washed with sodium hydrogencarbonate (100 ml of a saturated aqueous solution) and the aqueous layer re-extracted with diethyl ether (100 ml), washed with brine (100 ml), dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by flash column chromatography (ethyl acetate:petrol, 1:4) to afford phenyl-2,3,4,6-tetra-*O*-benzoyl-1-thio-α-D-mannopyranoside **123** (2.0 g, 51%) as an amorphous white solid; $[\alpha]_D^{22}$ +27 (*c*, 1.0 in $CHCl_3$) (lit.,[18] $[\alpha]_D^{24}$ +20 (*c*, 2.9 in $CHCl_3$)); δ_H (400 MHz, $CDCl_3$) 4.58 (1H, dd, $J_{5,6}$ 5.3 Hz, $J_{6,6'}$ 12.3 Hz, H-6), 4.69 (1H, dd, $J_{5,6'}$ 2.4 Hz, H-6'), 5.04 (1H, ddd, $J_{4,5}$ 10.0 Hz, H-5), 5.81 (1H, s, H-1), 5.89 (1H, dd, $J_{2,3}$ 3.4 Hz, $J_{3,4}$ 10.1 Hz, H-3), 6.00 (1H, dd, $J_{1,2}$ 1.6 Hz, H-2), 6.17 (1H, at, *J* 10.1 Hz, H-4), 7.24-7.63 (17H, m, ArH).

Methyl-2,3,4,6-tetra-*O*-benzoyl-1-thio-α-D-mannopyranoside 124

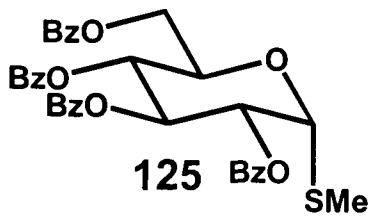


124

Penta-*O*-benzoyl-D-mannopyranose **122** (2.5 g, 3.57 mmol) was dissolved in dichloromethane (10 ml) under argon in a flame dried flask. Hexamethyldisilazane (0.37 ml, 1.82 mmol), dimethyldisulphide (0.16 ml, 1.82 mmol) and iodine (1.1 g, 4.29 mol) were added in that order and the solution stirred for 1 h. At this point t.l.c. indicated the formation of a single product (R_f .35) and complete consumption of starting material (R_f 0.25). The reaction mixture was diluted with dichloromethane (100 ml) and then washed with sodium thiosulphate (100 ml of a 10% aqueous solution), sodium hydrogencarbonate (100 ml of a saturated aqueous solution) and brine (100 ml). The organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (ethyl acetate:petrol, 1:2) to afford methyl-2,3,4,6-tetra-*O*-benzoyl-1-thio-α-D-mannopyranoside **124** (1.5 g, 74%) as a white crystalline solid; m.p. 136-137 °C (ethanol); $[\alpha]_D^{22}$ -29 (*c*, 1.0 in $CHCl_3$); ν_{max}(KBr disk)/cm^{-1} 1730 (s, C=O); δ_H (400 MHz, $CDCl_3$) 2.27 (3H, s, SCH_3), 4.55 (1H, dd, $J_{5,6}$ 4.7 Hz, $J_{6,6'}$ 12.3 Hz, H-6), 4.71 (1H, dd, $J_{5,6'}$ 2.5 Hz, H-6'), 4.82 (1H, ddd, $J_{4,5}$ 10.0 Hz, H-5), 5.48 (1H, d, $J_{1,2}$ 1.4 Hz, H-1), 5.84 (1H, dd, $J_{2,3}$ 3.2 Hz, H-2), 5.87 (1H, dd, $J_{3,4}$ 9.9 Hz, H-3), 6.16 (1H, at, H-4), 7.27-8.12 (20H, m, ArH); δ_C (100.6 MHz, $CDCl_3$) 13.9 (q, CH_3), 62.9 (t, C-6), 67.0 (d, C-4), 69.2 (d, C-5), 70.5, 71.8 (2 x d, C-2, C-3), 83.7 (d, C-1), 128.3, 128.5, 128.6, 129.7, 129.8, 133.1, 133.3, 133.5 (8 x d, 20 x ArCH), 128.9, 129.3 (2 x s, 4 x ArC), 165.3, 165.5,

166.1 (3 x s, 4 x C=O);); *m/z* (ESI) 649 ($M+Na^+$, 5%). (HRMS (ESI) Calcd. For $C_{35}H_{34}NO_9S$ ($M+NH_4^+$) 644.1954. Found 644.1944).

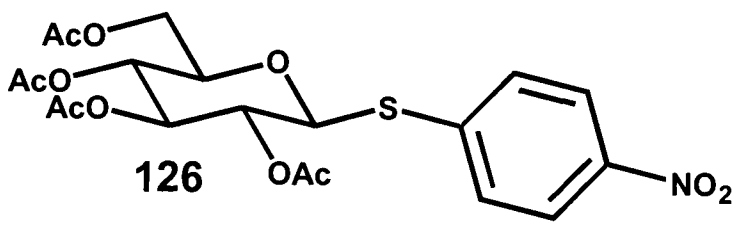
Methyl-2,3,4,6-tetra-*O*-benzoyl-1-thio-α-D-glucopyranoside 125



Penta-*O*-benzoyl-D-glucopyranose **95** (4.0 g, 5.71 mmol) was dissolved in dichloromethane (10 ml) under argon in a flame dried flask. Hexamethyldisilazane (0.60 ml, 2.91 mmol), iodine (1.75 g, 6.86 mmol) and dimethyldisulphide (0.26 ml, 2.91 mmol) were added in that order. The solution was stirred for 4 h, at which point t.l.c. (ethyl acetate: petrol, 1:3) indicated the formation of a major product (R_f 0.35) and complete consumption of starting material (R_f 0.30). The reaction mixture was diluted with ethyl acetate (100 ml) and washed with sodium thiosulphate (100 ml of a 10% aqueous solution), ammonium chloride (100 ml of a 1M aqueous solution), sodium hydrogencarbonate (100 ml of a saturated aqueous solution) and brine (100 ml). The organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (ethyl acetate:petrol 1:3) to afford 1-thiomethyl-2,3,4,6-tetra-*O*-benzoyl-α-D-glucopyranoside **125** (1.9 g, 83%) as crystalline white solid; m.p. 132 °C, $[\alpha]_D^{22}$ 105 (*c*, 1.0 in $CHCl_3$); ν_{max}(KBr disk)/cm^{-1} 1720 (s, C=O); δ_H (400 MHz, $CDCl_3$) 2.13 (3H, s, SCH_3), 4.55 (1H, dd, $J_{5,6}$ 5.5 Hz, $J_{6,6'}$ 12.4 Hz, H-6), 4.63 (1H, dd, $J_{5,6'}$ 2.8 Hz, H-6'), 4.86 (1H, ddd, $J_{4,5}$ 10.0 Hz, H-5), 5.56 (1H, dd, $J_{1,2}$ 5.7 Hz, $J_{2,3}$ 10.2

Hz, H-2), 5.71 (1H, at, *J* 9.8 Hz, H-4), 5.84 (1H, d, H-1), 6.12 (1H, at, *J* 9.9 Hz, H-3), 7.27-8.07 (20H, m, Ar); δ_C (100.6 MHz, $CDCl_3$) 11.5 (q, CH_3), 63.2 (t, C-6), 68.0 (d, C-5), 69.8 (d, C-4), 70.9 (d, C-2), 71.7 (d, C-3), 83.2 (d, C-1), 128.3, 128.4, 128.5, 129.7, 129.8, 129.9, 130.0, 133.1, 133.2, 133.4, 133.5 (11 x d, 20 x ArCH), 128.8, 128.9, 129.0, 129.1 (4 x s, 4 x ArC), 165.2, 165.3 (2 x s, 4 x C=O); *m/z* (ESI) 644 ($M+NH_4^+$, 1%) 649 ($M+Na^+$, 5). (HRMS (ESI) Calcd. For $C_{35}H_{34}NO_9S$ ($M+NH_4^+$) 644.1954. Found 644.1956).

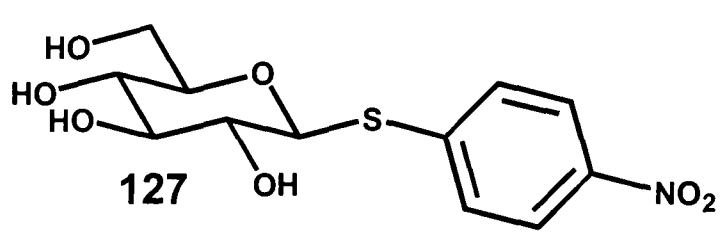
_p_-Nitrophenyl-2,3,4,6-tetra-_O_-acetyl-1-thio-β-D-glucopyranoside 126



Bis(4-nitrophenyl) disulphide (10.3 g, 0.033 mol) was suspended in ethanol (200 ml) and sodium borohydride (4.2 g, 0.11 mol) added portionwise. The resultant deep red solution was stirred for 15 min, at which point 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl iodide **18** (25.5 g, 0.056 mol) was added as a solution in chloroform (100 ml) and the reaction left to stir. After 4 h t.l.c. (ethyl acetate:petrol, 1:2) indicated the formation of a single product (R_f 0.3) and the absence of starting material (R_f 0.4). The reaction mixture was concentrated *in vacuo* and the residue taken up in dichloromethane (200 ml), washed with water (200 ml) and the aqueous phase re-extracted with dichloromethane (200 ml). The combined organic layers were washed with water (200 ml) and brine (200 ml), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (ethyl acetate:petrol, 1:2) to afford *p*-

nitrophenyl-2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-glucopyranoside **126** (16.2 g, 60%) as a white crystalline solid, m.p. 182-184 °C (ethyl acetate/petrol) (lit.,[19] 180-181 °C); $[\alpha]_D^{21}$ -33 (*c*, 1.0 in $CHCl_3$) (lit.,[20] $[\alpha]_D^{25}$ -34 (*c*, 0.8 in $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 2.00, 2.04, 2.08, 2.10 (4 x 3H, 4 x s, 4 x CH_3), 3.83 (1H, ddd, $J_{4,5}$ 10.1 Hz, $J_{5,6}$ 2.4 Hz, $J_{5,6'}$ 5.3 Hz, H-5), 4.19 (1H, dd, $J_{6,6'}$ 12.4 Hz, H-6), 4.25 (1H, dd, H-6'), 4.87 (1H, d, $J_{1,2}$ 10.1 Hz, H-1), 5.05, 5.08 (2 x 1H, 2 x at, *J* 9.7 Hz, *J* 9.9 Hz, H-2, H-4), 5.27 (1H, at, *J* 9.4 Hz, H-3), 7.59 (2H, d, *J* 9.1 Hz, ArH), 8.16 (2H, d, *J* 8.8 Hz, ArH).

_p_-Nitrophenyl-1-thio-β-D-glucopyranoside 127

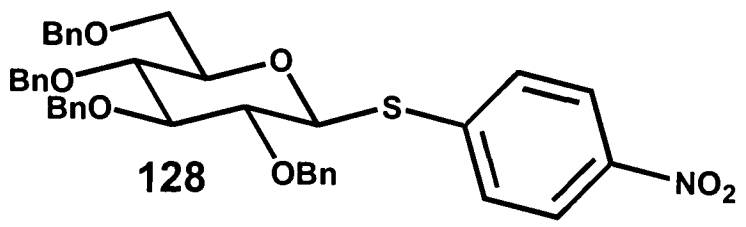


127

p-Nitrophenyl-2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-glucopyranoside **126** (10.0 g, 0.021 mol) was suspended in methanol (100 ml) under argon in a flame dried flask. To this a solution of sodium (488 mg, 0.021 mol) in methanol (100 ml) was added and the mixture stirred for 30 min, at which point t.l.c. (ethyl acetate:petrol, 1:2) indicated the formation of a major product (R_f 0) and the absence of starting material (R_f 0.3). Ion exchange resin (Dowex® 50WX8) was added portionwise until the solution was neutralised, at which point the reaction mixture was filtered and then concentrated *in vacuo* to afford *p*-nitrophenyl-1-thio-β-D-glucopyranoside **127** (6.5 g, 99%) as a white crystalline solid, m.p. 165-166 °C (ethyl acetate) (lit.,[21] 160-162 °C); $[\alpha]_D^{21}$ -121 (*c*, 1.0 in MeOH) (lit.,[21] $[\alpha]_D^{20}$ -115 (*c*, 0.7 in H_2O)); δ_H (400 MHz, $CDCl_3$) 3.33-3.40,

3.44-3.50 (2 x 2H, 2 x m, H-2, H-3, H-4, H-5), 3.70 (1H, dd, $J_{5,6}$ 6.0 Hz, $J_{6,6'}$ 12.1 Hz, H-6), 3.93 (1H, dd, $J_{5,6'}$ 2.0 Hz, H-6'), 4.88-4.91 (1H, m, H-1), 7.67 (2H, d, *J* 8.7 Hz, ArH), 8.16 (2H, *J* 8.9 Hz, ArH).

_p_-Nitrophenyl-2,3,4,6-tetra-_O_-benzyl-1-thio-β-D-glucopyranoside 128

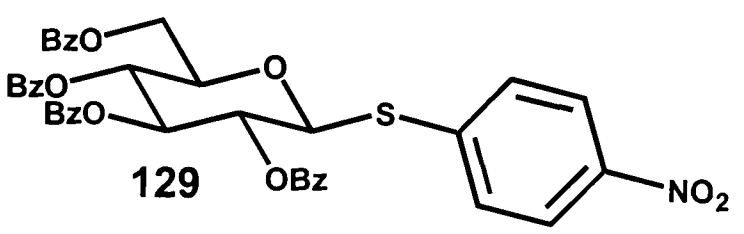


128

p-Nitrophenyl-1-thio-β-D-glucopyranoside **127** (1.0 g, 3.15 mmol) was dissolved in *N*,*N*-dimethylformamide (40 ml) under argon in a flame dried flask and benzyl bromide (1.9 ml, 16.0 mmol) added. Sodium hydride (60% dispersion in mineral oil) (862 mg, 21.55 mmol) was added portionwise and the reaction mixture stirred for 16 h, at which point t.l.c. (ethyl acetate:petrol, 1:4) indicated the formation of a major product (R_f 0.4) and the absence of starting material (R_f 0). Methanol (50 ml) was added and solution stirred for a further 15 min, the reaction mixture was then diluted with ethyl acetate (100 ml) and washed with brine (3 x 100 ml). The combined aqueous phases were re-extracted with ethyl acetate (100 ml) and the combined organic layers dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (ethyl acetate:petrol, 1:6) to afford *p*-nitrophenyl-2,3,4,6-tetra-*O*-benzyl-1-thio-β-D-glucopyranoside **128** (1.76 g, 82%) as a white crystalline solid, m.p. 127-129 °C (ethyl acetate/petrol); $[\alpha]_D^{21}$ -29 (*c*, 1.0 in $CHCl_3$); ν_{max}(KBr disk)/cm^{-1} 1341, 1515 (m, NO_2); δ_H (400 MHz, C_6D_6) 3.28-3.33 (1H, m, H-5), 3.47-3.51 (1H,

m, H-2), 3.54 (1H, dd, $J_{5,6}$ 5.0 Hz, $J_{6,6'}$ 10.6 Hz, H-6), 3.56-3.66 (3H, m, H-3, H-4, H-6'), 4.25, 4.31 (2H, ABq, J_{AB} 11.7 Hz, PhC$\underline{H}_2$), 4.54, 4.82 (2H, ABq, J_{AB} 11.3 Hz, PhC$\underline{H}_2$), 4.59 (1H, d, $J_{1,2}$ 9.7 Hz, H-1), 4.69, 4.76 (2H, ABq, J_{AB} 10.7 Hz, PhC$\underline{H}_2$), 4.83, 4.88 (2H, ABq, J_{AB} 11.4 Hz, PhC$\underline{H}_2$), 7.07-7.37 (22H, m, ArH), 7.67-7.70 (2H, m, ArH); δ_C (100.6 MHz, $CDCl_3$) 68.9 (t, C-6), 73.5, 75.2, 75.6, 75.9 (4 x t, 4 x Ph$\underline{C}H_2$), 77.7, 86.6 (2 x d, C-3, C-4), 79.2 (d, C-5), 80.7 (d, C-2), 85.8 (d, C-1), 123.9, 127.7, 127.8, 127.9, 128.0, 128.1, 128.5, 129.4 (8 x d, 24 x ArCH), 137.5, 137.8, 137.9, 138.1, 144.4, 146.1 (6 x s, 6 x ArC); *m/z* (CI) 695 ($M+NH_4^+$, 26%). (HRMS (CI) Calcd. For $C_{40}H_{43}N_2O_7S$ ($M+NH_4^+$) 695.2791. Found 695.2793). (Found: C, 71.28; H, 5.91; N, 2.09. $C_{40}H_{39}NO_7S$ requires: C, 70.88; H, 5.80; N, 2.07%).

_p_-Nitrophenyl-2,3,4,6-tetra-_O_-benzoyl-1-thio-β-D-glucopyranoside 129

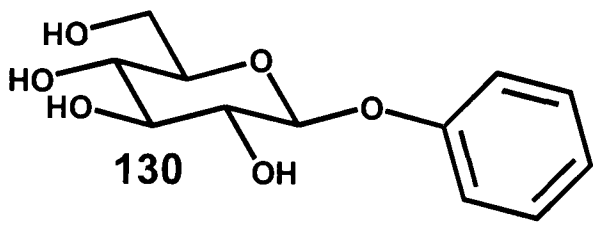


129

p-Nitrophenyl-1-thio-β-D-glucopyranoside **127** (1.0 g, 3.15 mmol) was dissolved in pyridine (50 ml) under argon in a flame dried flask and benzoyl chloride (3.0 ml, 25.9 mmol) added. The mixture was stirred for 24 h, at which point t.l.c. (ethyl acetate:petrol, 1:3) indicated the formation of a major product (R_f 0.3) and the absence of starting material (R_f 0). The reaction mixture was diluted with dichloromethane (100 ml) and washed with hydrochloric acid (2 x 100 ml of a 0.1 M aqueous solution). The aqueous phase was re-extracted with dichloromethane (100 ml) and the combined organic layers washed with sodium hydrogencarbonate (2 x 100 ml of a saturated aqueous solution), brine (100 ml), dried

($MgSO_4$), filtered and concentrated *in vacuo* to afford *p*-nitrophenyl-2,3,4,6-*O*-benzoyl-1-thio-β-D-glucopyranoside **129** (2.1 g, 91%) as a white crystalline solid, m.p. 163-164°C (ethanol); $[\alpha]_D^{24}$ -16 (*c*, 1.0 in $CHCl_3$); ν_{max}(KBr disk)/cm^{-1} 1341, 1518 (m, NO_2), 1735 (s, C=O); δ_H (400 MHz, $CDCl_3$) 4.31-4.36 (1H, m, H-5), 4.53 (1H, dd, $J_{5,6'}$ 6.5 Hz,, $J_{6,6'}$ 12.1 Hz, H-6), 4.75 (1H, dd, $J_{5,6'}$ 2.4 Hz, H-6'), 5.24 (1H, d, $J_{1,2}$ 10.0 Hz, H-1), 5.59 (1H, at, *J* 9.7 Hz, H-2), 5.67 (1H, at, *J* 9.8 Hz, H-4), 6.02 (1H, at, *J* 9.5 Hz, H-3), 7.26-7.58 (13H, m, ArH), 7.64-7.87 (11H, m, ArH); δ_C (100.6 MHz, $CDCl_3$) 63.0 (t, C-6), 69.1 (d, C-4), 70.2 (d, C-2), 73.8 (d, C-3), 76.7 (d, C-5), 84.6 (d, C-1), 123.8, 128,3, 128.5, 128.6, 129.7, 129.9, 131.0 (7 x d, 24 x ArCH), 128.7, 129.3, 141.7, 146.9 (4 x s, 6 x ArC), 165.1, 165.2, 165.7, 166.0 (4 x s, 4 x C=O); *m/z* (ESI) 756 ($M+Na^+$, 6%). (HRMS (CI) Calcd. For $C_{40}H_{35}N_2O_{11}S$ ($M+NH_4^+$) 751.1962. Found 751.1957).

Phenyl-β-D-glucopyranoside 130

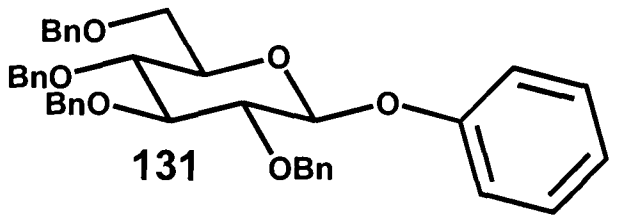


130

Phenyl-2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside **19** (7.0 g, 16.5 mmol) was suspended in methanol (90 ml) in a dry flask. To this a solution of sodium (249 mg, 10.8 mmol) in methanol (10 ml) was added and the mixture stirred for 1 h, at which point t.l.c. (ethyl acetate:petrol, 1:1) indicated the formation of a major product (R_f 0) and the absence of starting material (R_f 0.5). Ion exchange resin (Dowex® 50WX8) was added portionwise until the solution was neutralised,

at which point the reaction mixture was filtered and then concentrated *in vacuo*. Recrystallization from ethyl acetate afforded phenyl-β-D-glucopyranoside **130** (3.9 g, 92%) as a white crystalline solid, m.p. 174 °C (ethyl acetate) (lit.,[22] 176 °C); $[\alpha]_D^{22}$ -66 (*c*, 1.0 in MeOH) (lit.,[23] $[\alpha]_D^{25}$ -71 (*c*, 2.0 in H_2O)); δ_H (400 MHz, CD_3OD) 3.41-3.49 (4H, m, H-2, H-3, H-4, H-5), 3.71 (1H, dd, $J_{5,6}$ 5.1 Hz, $J_{6,6'}$ 11.8 Hz, H-6), 3.90 (1H, dd, $J_{5,6'}$ 1.7 Hz, H-6'), 4.92 (1H, d, $J_{1,2}$ 7.6 Hz, H-1), 7.01 (1H, t, *J* 7.4 Hz, ArH), 7.10 (2H, d, *J* 7.6 Hz, ArH), 7.27-7.31 (2H, m, ArH).

Phenyl-2,3,4,6-tetra-*O*-benzyl-β-D-glucopyranoside 131

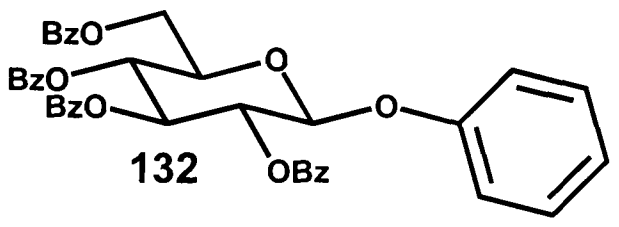


131

Phenyl-β-D-glucopyranoside **130** (1.0 g, 3.91 mmol) was dissolved in *N*,*N*-dimethylformamide (40 ml) under argon in a dry flask and benzyl bromide (2.3 ml, 19.5 mmol) added. The mixture was cooled to 0 °C and sodium hydride (60% dispersion in mineral oil) (940 mg, 23.5 mmol) added portionwise. The reaction mixture was stirred for 18 h, at which point t.l.c. (ethyl acetate:petrol, 1:8) indicated the formation of a major product (R_f 0.4) and the absence of starting material (R_f 0). Methanol (50 ml) was added and solution stirred for a further 15 min, then concentrated *in vacuo*. The residue was taken up in ethyl acetate (100 ml) and the resulting solution washed with brine (3 x 100 ml), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (ethyl acetate:petrol, 1:8) to afford

phenyl-2,3,4,6-tetra-*O*-benzyl-1-β-D-glucopyranoside **131** (2.1 g, 85%) as a white crystalline solid, m.p. 76-79 °C (ethanol) (lit.,[24] 76 °C); $[\alpha]_D^{25}$ -10 (*c*, 1.0 in $CHCl_3$) (lit.,[24] $[\alpha]_D$ -10 (*c*, 0.5 in $CHCl_3$)); δ_H (400 MHz, $CDCl_3$) 3.63-3.85 (6H, m, H-2, H-3, H-4, H-5, H-6, H-6'), 4.55-4.64 (3H, m, PhC$\underline{H}_2$, PhC$\underline{H}$H), 4.84-4.90 (3H, m, PhC$\underline{H}_2$, PhC$\underline{H}$H), 4.97-5.10 (3H, m, PhC$\underline{H}_2$, H-1), 7.02-7.40 (25H, m, ArH).

Phenyl-2,3,4,6-tetra-*O*-benzoyl-β-D-glucopyranoside 132

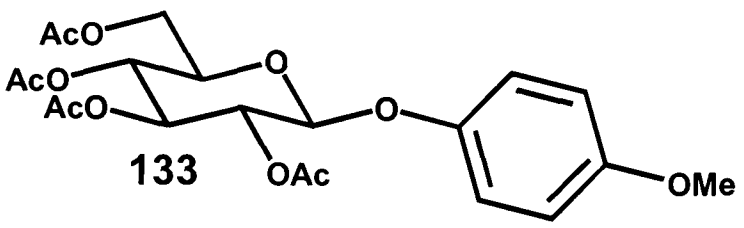


132

Phenyl-β-D-glucopyranoside **130** (1.0 g, 3.91 mmol) was dissolved in pyridine (30 ml) under argon in a dry flask and benzoyl chloride (3.6 ml, 31.2 mmol) added. The mixture was stirred for 17 h, at which point t.l.c. (ethyl acetate:petrol, 1:3) indicated the formation of a major product (R_f 0.3) and the absence of starting material (R_f 0). The reaction was diluted with dichloromethane (100 ml) and washed with hydrochloric acid (2 x 100 ml of a 0.1 M aqueous solution). The aqueous phase was re-extracted with dichloromethane (100 ml) and the combined organic layers washed with sodium hydrogencarbonate (2 x 100 ml of a saturated aqueous solution), brine (100 ml), dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford phenyl-2,3,4,6-tetra-*O*-benzoyl-β-D-glucopyranoside **132** (2.3 g, 88%) as a white crystalline solid, m.p. 174-175 °C (ethanol) (lit.,[25] 177°C); $[\alpha]_D^{25}$ +28 (*c*, 1.0 in $CHCl_3$) (lit.,[25] $[\alpha]_D^{18}$ +28 (*c*, 4.0 in $CHCl_3$)); δ_H (400 MHz, $CDCl_3$) 4.34-4.38 (1H, m, H-5), 4.55 (1H, dd, $J_{5,6}$ 6.6 Hz, $J_{6,6'}$

11.8 Hz, H-6), 4.71 (1H, dd, $J_{5,6'}$ 2.6 Hz, H-6'), 5.42 (1H, d, $J_{1,2}$ 7.8 Hz, H-1), 5.74 (1H, at, *J* 9.6 Hz, H-4), 5.84 (1H, at, *J* 8.7 Hz, H-2), 6.02 (1H, at, *J* 9.6 Hz, H-3), 7.01-8.06 (14H, m, ArH).

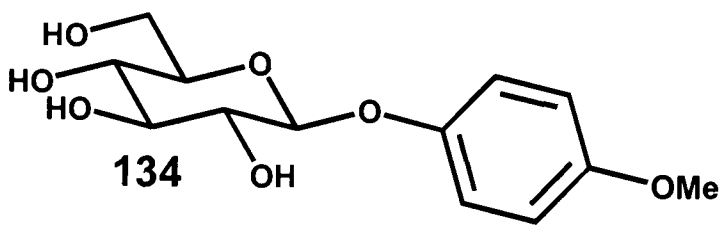
4-Methoxyphenyl-2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside 133



Penta-*O*-acetyl-β-D-glucopyranose **105** (20.3 g, 0.05 mol) and 4-methoxyphenol (13.1 g, 0.11 mol) were dissolved in dichloromethane (100 ml) under argon in a flame dried flask and boron trifluoride diethyl etherate (20 ml, 0.16 mol) added. The mixture was stirred for 24 h, at which point t.l.c. (ethyl acetate:petrol, 1:1) indicated the formation of a major product (R_f 0.3) and the absence of starting material (R_f 0.2). Triethylamine was added dropwise to the stirred solution until effervescence ceased. The reaction mixture was then diluted with dichloromethane (100 ml), washed with water (200 ml) and brine (100 ml), dried ($MgSO_4$), filtered and concentrated *in vacuo*. Recrystallization from ethanol afforded 4-methoxyphenyl-2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside **133** (20.7 g, 86%) as a white crystalline solid, m.p. 101-102 °C (ethanol) (lit.,[26] 103-104 °C); $[\alpha]_D^{20}$ -17 (*c*, 1.0 in $CHCl_3$) (lit.,[26] $[\alpha]_D^{21}$ -16 (*c*, 0.2 in $CHCl_3$)); δ_H (400 MHz, $CDCl_3$) 2.03, 2.04, 2.08, 2.08 (4 x 3H, 4 x s, 4 x $OCOCH_3$), 3.77 (3H, s, $PhOCH_3$), 3.80 (1H, ddd, $J_{4,5}$ 9.9 Hz, $J_{5,6}$ 2.3 Hz, $J_{5,6'}$ 5.1 Hz, H-5), 4.16 (1H, dd, $J_{6,6'}$ 12.1 Hz,

H-6), 4.29 (1H, dd, H-6'), 4.95 (1H, d, $J_{1,2}$ 7.0 Hz, H-1), 5.16 (1H, at, J 9.4 Hz, H-4), 5.21-5.30 (2H, m, H-2, H-3), 6.77-6.84 (2H, m, ArH), 6.93-6.97 (2H, m, ArH).

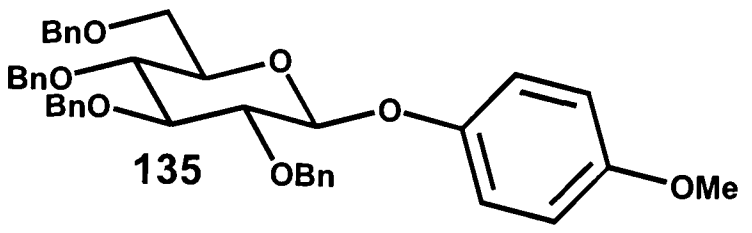
4-Methoxyphenyl-β-D-glucopyranoside 134



134

4-Methoxyphenyl-2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside **133** (6.0 g, 13.2 mmol) was suspended in methanol (50 ml) in a dry flask. To this a solution of sodium (238 mg, 10.3 mmol) in methanol (50 ml) was added and the mixture stirred for 1 h, at which point t.l.c. (ethyl acetate:petrol, 1:1) indicated the formation of a major product (R_f 0) and the absence of starting material (R_f 0.3). Ion exchange resin (Dowex® 50WX8) was added portionwise until the solution was neutralised, at which point the reaction mixture was filtered and then concentrated *in vacuo*. Recrystallization from ethyl acetate afforded 4-methoxyphenyl-β-D-glucopyranoside **134** (3.7 g, 98%) as a white crystalline solid, m.p. 175 °C (ethyl acetate) (lit.,[26] 175-177 °C); $[\alpha]_D^{22}$ -60 (*c*, 1.0 in MeOH) (lit.,[26] $[\alpha]_D^{19}$ -61 (*c*, 1.0 in water)); δ_H (400 MHz, $CDCl_3$) 3.40-3.49 (4H, m, H-2, H-3, H-4, H-5), 3.49-3.74 (1H, m, H-6), 3.76 (3H, s, OCH_3), 3.89-3.92 (1H, m, H-6'), 4.79 (1H, d, $J_{1,2}$ 7.5 Hz, H-1), 6.84-6.87 (2H, m, ArH), 7.06-7.08 (2H, m, ArH).

4-Methoxyphenyl-2,3,4,6-tetra-*O*-benzyl-β-D-glucopyranoside 135

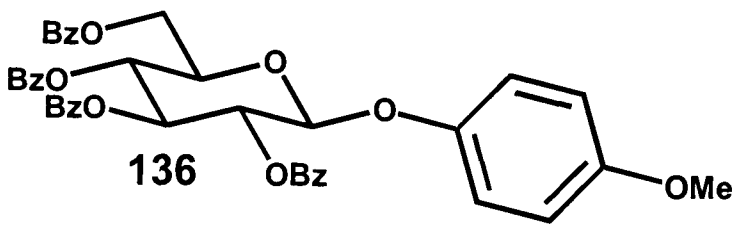


135

4-Methoxyphenyl-β-D-glucopyranoside **134** (1.0 g, 3.49 mmol) was dissolved in *N*,*N*-dimethylformamide (40 ml) under argon in a dry flask and benzyl bromide (2.2 ml, 18.5 mmol) added. The mixture was cooled to 0 °C and sodium hydride (60% dispersion in mineral oil) (930 mg, 23.3 mmol) added portionwise. The reaction mixture was stirred for 16 h, at which point t.l.c. (ethyl acetate:petrol, 1:4) indicated the formation of a major product (R_f 0.3) and the absence of starting material (R_f 0). Methanol (50 ml) was added and solution stirred for a further 30 min, the reaction mixture was then diluted with ethyl acetate (100 ml) and washed with brine (100 ml). The aqueous phase was re-extracted with ethyl acetate (100 ml) and the combined organic layers washed with brine (2 x 100 ml), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (ethyl acetate:petrol, 1:4) to afford 4-methoxyphenyl-2,3,4,6-tetra-*O*-benzyl-β-D-glucopyranoside **135** (2.2 g, 97%) as a white crystalline solid, m.p. 94-95 °C (ethyl acetate/petrol) (lit.,[24] 78 °C); $[\alpha]_D^{20}$ -5 (*c*, 1.0 in $CHCl_3$) (lit.,[24] $[\alpha]_D$ -2 (*c*, 0.5 in $CHCl_3$)); δ_H (400 MHz, $CDCl_3$) 3.59 (1H, ddd, $J_{4,5}$ 9.3 Hz, $J_{5,6}$ 3.4 Hz, $J_{5,6'}$ 5.1 Hz, H-5), 3.66-3.75 (4H, m, H-2, H-3, H-4, H-6), 3.79 (3H, s, OCH_3), 3.79-3.83 (1H, m, H-6'), 4.56, 4.62 (2H, ABq, J_{AB} 12.1 Hz, PhC$\underline{H}_2$), 4.84, 4.97 (2H, ABq, J_{AB} 10.9 Hz, PhC$\underline{H}_2$), 4.84, 5.08 (2H, ABq,

J_{AB} 10.9 Hz, PhC$\underline{H}_2$), 4.91 (1H, d, J 7.6 Hz, H-1), 4.97, 5.08 (2H, ABq, J_{AB} 10.9 Hz, PhC$\underline{H}_2$) 6.81-6.85 (2H, m, ArH), 7.04-7.08 (2H, m, ArH), 7.20-7.39 (20H, m, ArH).

4-Methoxyphenyl-2,3,4,6-tetra-*O*-benzoyl-β-D-glucopyranoside 136

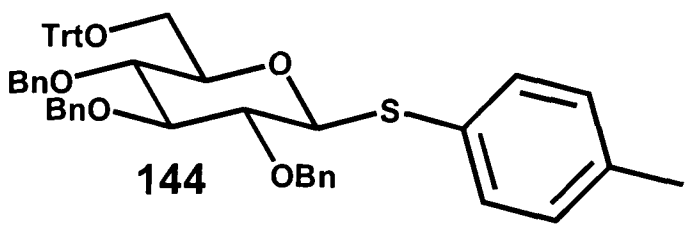


136

4-Methoxyphenyl-β-D-glucopyranoside **134** (1.0 g, 3.50 mmol) was dissolved in pyridine (50 ml) under argon in a flame dried flask and benzoyl chloride (3.3 ml, 28.4 mmol) added. The mixture was stirred for 16 h, at which point t.l.c. (ethyl acetate:petrol, 1:2) indicated the formation of a major product (R_f 0.3) and the absence of starting material (R_f 0). The reaction was diluted with dichloromethane (100 ml) and washed with hydrochloric acid (3 x 100 ml of a 0.1 M aqueous solution), sodium hydrogencarbonate (3 x 100 ml of a saturated aqueous solution), brine (100 ml), dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford 4-methoxyphenyl-2,3,4,6-tetra-*O*-benzoyl-β-D-glucopyranoside **136** (2.4 g, 99%) as a white crystalline solid, m.p. 169-170 °C (ethanol) (lit.,[27] 170-171 °C); $[\alpha]_D^{20}$ +25 (*c*, 1.0 in $CHCl_3$) (lit.,[27] $[\alpha]_D^{22}$ +28 (*c*, 1.0 in $CHCl_3$)); δ_H (400 MHz, $CDCl_3$) 3.72 (3H, s, CH_3), 4.27-4.32 (1H, m, H-5), 4.57 (1H, d, $J_{5,6}$ 6.6 Hz, $J_{6,6'}$ 12.0 Hz, H-6), 4.69 (1H, dd, $J_{5,6'}$ 3.0 Hz, H-6'), 5.28 (1H, d, $J_{1,2}$ 7.8 Hz, H-1), 5.72 (1H, at, J 9.7 Hz, H-4), 5.79(1H, dd, $J_{3,4}$ 9.6 Hz, H-2), 5.97 (1H, at, J 9.6 Hz, H-3), 6.01-6.70 (2H, m, ArH), 6.94-6.98 (2H, m, ArH), 7.27-7.60 (12H, m, ArH),

7.87 (2H, d, J 7.2 Hz, ArH), 7.94 (2H, d, J 7.2 Hz, ArH), 7.99 (2H, d, J 7.2 Hz, ArH), 8.05 (2H, d, J 7.2 Hz, ArH).

_p_-Tolyl-2,3,4-tri-_O_-benzyl-6-_O_-trityl-1-thio-β-D-glucopyranoside 144



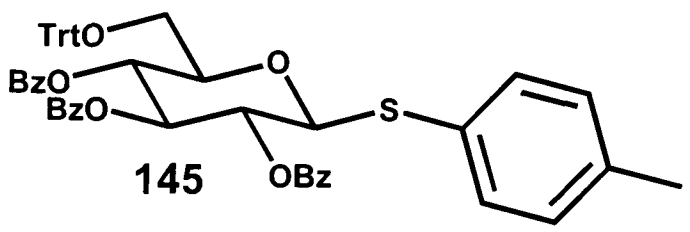
144

_p_-Tolyl-1-thio-β-D-glucopyranoside **116** (12.3 g, 0.04 mol) and triphenylmethyl chloride (13.2 g, 0.05 mol) were dissolved in pyridine (100 ml) and stirred under argon. After 24 h _N,N_-dimethylaminopyridine (500 mg, 4.67 mmol) and triphenylmethyl chloride (10.0 g, 0.04 mol) were added and the mixture stirred for a further 5 h, at which point t.l.c. (ethyl acetate) indicated the formation of a major product (R_f 0.5) and the absence of starting material (R_f 0.1). The reaction mixture was concentrated *in vacuo* and the residue taken up in dichloromethane (200 ml), washed with ammonium chloride (2 x 200 ml of a saturated aqueous solution), sodium hydrogencarbonate (2 x 200 ml of a saturated aqueous solution) and brine (200 ml). The organic layer was then dried ($MgSO_4$) and concentrated *in vacuo* to afford crude _p_-tolyl-6-_O_-trityl-1-thio-β-D-glucopyranoside **143**.

The crude residue was dissolved in _N,N_-dimethylformamide (100 ml) and benzyl bromide (27 ml, 0.23 mol) added. The solution was cooled to 0 °C and sodium hydride (60% dispersion in mineral oil) (11.0 g, 0.28 mol) was added portionwise to the stirred solution over 15 min.

The reaction mixture was allowed to warm to room temperature overnight. After 16 h t.l.c. (ethyl acetate:petrol, 1:3) indicated the formation of a major product (R_f 0.5) and the absence of starting material (R_f 0.1). Methanol (100 ml) was added and the solution stirred for 30 min, the reaction mixture was then concentrated *in vacuo* (co-evaporation with toluene, 3 x 100 ml) and the residue taken up in dichloromethane (200 ml). The resulting solution was washed with water (200 ml) and brine (3 x 100 ml), dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by flash column chromatography (ethyl acetate:petrol, 1:4) to afford *p*-tolyl-2,3,4-tri-*O*-benzyl-6-*O*-trityl-1-thio-β-D-glucopyranoside **144** (21 g, 61%) as a white crystalline solid, m.p. 144-145 °C (ethyl acetate/petrol); $[\alpha]_D^{25}$ -23 (*c*, 1.0 in $CHCl_3$); ν_{max}(KBr disk)/cm^{-1} no significant peaks; δ_H (400 MHz, $CDCl_3$) 2.36 (3H, s, PhC$\underline{H}_3$), 3.32 (1H, dd, $J_{5,6}$ 4.1 Hz, $J_{6,6'}$ 10.1 Hz, H-6), 3.37-3.50 (1H, m, H-5), 3.62 (1H, at, *J* 9.1 Hz, H-2), 3.67 (1H, dd, $J_{5,6'}$ 1.4 Hz, H-6'), 3.70 (1H, at *J* 9.0 Hz, H-3), 3.82 (1H, at, *J* 9.4 Hz, H-4), 4.37, 4.71 (2H, ABq, J_{AB} 10.4 Hz, PhC$\underline{H}_2$), 4.70 (1H, d, $J_{1,2}$ 9.6 Hz, H-1), 4.81, 4.97 (2H, ABq, J_{AB} 10.2 Hz, PhC$\underline{H}_2$), 4.86, 4.91 (2H, ABq, J_{AB} 10.8 Hz, PhC$\underline{H}_2$); δ_C (100.6 MHz, $CDCl_3$) 21.2 (s, CH_3), 62.4 (t, C-6), 75.0, 75.4, 76.0 (3 x t, 3 x Ph$\underline{C}H_2$), 77.8 (d, C-4), 78.8 (d, C-5), 80.7 (d, C-2), 86.5 (s, $\underline{C}Ph_3$), 86.8 (d, C-3), 87.7 (d, C-1), 127.0, 127.7, 127.8, 127.9, 128.0, 128.1, 128.2, 128.5, 128.8, 129.7, 129.8, 132.8 (12 x d, 34 x ArCH), 137.7, 138.2, 138.3, 143.9 (4 x s, 8 x ArC); *m/z* (ESI) 821 ($M+Na^+$, 100%). (HRMS (ESI) Calcd. For $C_{53}H_{50}O_5S$ ($M+NH_4^+$) 816.3723. Found 816.3724). (Found: C, 79.64; H, 6.31. $C_{53}H_{50}O_5S$ requires: C, 79.67; H, 6.31%).

_p_-Tolyl-2,3,4-tri-_O_-benzoyl-6-_O_-trityl-1-thio-β-D-glucopyranoside 145

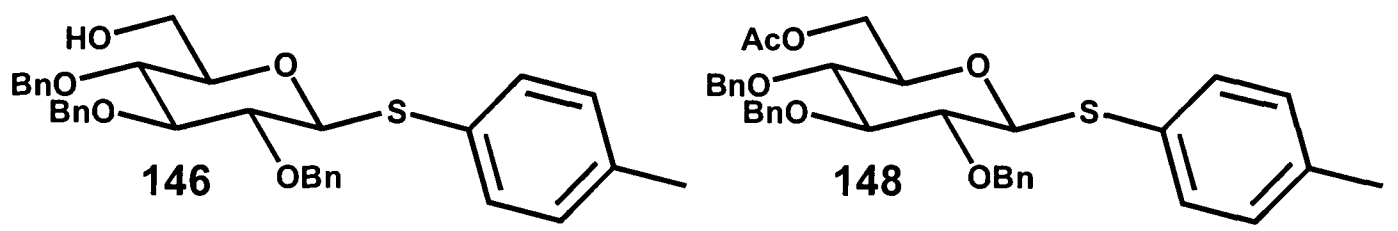


145

_p_-Tolyl-1-thio-β-D-glucopyranoside **116** (10.1 g, 0.035 mol), triphenylmethyl chloride (21.9 g, 0.079 mol) and _N,N_-dimethylaminopyridine (426 mg, 3.49 mmol) were dissolved in pyridine (100 ml) and stirred under argon in a dry flask. After 20 h t.l.c. (ethyl acetate) indicated the formation of a major product (R_f 0.5) and the absence of starting material (R_f 0.1). The reaction was cooled to 0 °C, benzoyl chloride (32.5 ml, 0.28 mol) added and the mixture stirred for 24 h, at which point t.l.c. (ethyl acetate:petrol, 1:3) indicated the formation of a major product (R_f 0.3). The reaction mixture was diluted with ethyl acetate (400 ml) and washed with hydrochloric acid (3 x 200 ml of a 1M aqueous solution). The aqueous phase was re-extracted with ethyl acetate (200 ml) and the combined organic layers washed with sodium hydrogencarbonate (3 x 200 ml of a saturated aqueous solution), brine (200 ml), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (ethyl acetate:petrol, 1:4→1:5) to afford _p_-tolyl-2,3,4-tri-_O_-benzoyl-6-_O_-trityl-1-thio-β-D-glucopyranoside **145** (28.2 g, 97%) as a white crystalline solid, m.p. 96-97 °C (ethyl acetate/petrol); $[\alpha]_D^{22}$ +8 (*c*, 1.0 in $CHCl_3$); ν_{max}(KBr disk)/cm^{-1} 1736 (s, C=O); δ_H (400 MHz, $CDCl_3$) 2.36 (3H, s, CH_3), 3.31-3.39 (2H, m, H-6, H-6'), 3.86-3.90 (1H, m, H-5), 4.98 (1H, d, $J_{1,2}$ 10.1 Hz, H-1), 5.51 (1H, at, *J* 9.9 Hz, H-2), 5.55 (1H, at, *J* 9.9 Hz, H-4), 5.78 (1H, at, *J* 9.4 Hz, H-3), 7.10-7.57 (28H, m, ArH), 7.69 (2H, d, *J* 8.1 Hz, ArH), 7.81 (2H, d, *J* 8.0 Hz,

ArH), 8.00 (2H, d, *J* 7.9 Hz, ArH); δ_C (100.6 MHz, $CDCl_3$) 21.2 (q, CH_3), 62.4 (t, C-6), 69.1 (d, C-4), 70.7 (d, C-2), 74.7 (d, C-3), 78.2 (d, C-5), 86.3 (d, C-1), 86.8 (s, $\underline{C}Ph_3$), 126.9, 127.7, 128.2, 128.4, 128.6, 129.7, 129.8, 129.9, 133.1, 133.2, 133.8 (11 x d, 34 x ArCH), 128.1, 128.9, 129.0, 129.4, 138.5, 143.6 (6 x s, 8 x ArC), 164.8, 165.1, 165.8 (3 x s, 3 x C=O); *m/z* (ESI) 858 ($M+NH_4^+$, 23%). (HRMS (ESI) Calcd. For $C_{53}H_{48}NO_8S$ ($M+NH_4^+$) 858.3101. Found 858.3098). (Found: C, 75.57; H, 5.27. $C_{53}H_{44}O_8S$ requires: C, 75.69; H, 5.27%).

_p_-Tolyl-2,3,4-tri-*O*-benzyl-1-thio-β-D-glucopyranoside 146 and _p_-Tolyl-6-*O*-acetyl-2,3,4-tri-*O*-benzyl-1-thio-β-D-glucopyranoside 148

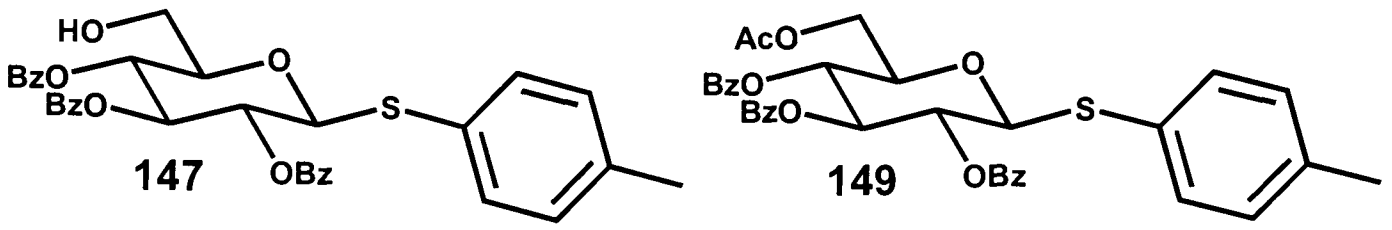


p-Tolyl-2,3,4-tri-*O*-benzyl-6-*O*-trityl-1-thio-β-D-glucopyranoside **144** (2.0 g, 2.51 mmol) was suspended in a mixture of acetic acid:ethanol (20 ml:10 ml) and refluxed at 80 °C for 26 h at which point t.l.c. (ethyl acetate:petrol, 1:4) indicated the formation of a major product (R_f 0.3) and almost complete consumption of starting material (R_f 0.6). The reaction mixture was concentrated *in vacuo* (co-evaporation with toluene) and the residue taken up in dichloromethane (200 ml), washed with sodium hydrogencarbonate (200 ml of a saturated aqueous solution), brine (200 ml), dried ($MgSO_4$) and concentrated *in vacuo* to afford *p*-tolyl-2,3,4-tri-*O*-benzyl-1-thio-β-D-glucopyranoside **146** (1.3 g, 92%) as a white crystalline solid, m.p. 97-98 °C (ethyl acetate/petrol); $[\alpha]_D^{24}$ +7 (*c*, 1.0 in $CHCl_3$); ν_{max}(KBr disk)/cm^{-1} 3411 (br, s, OH); δ_H (400 MHz, $CDCl_3$) 1.98 (1H, at, *J* 6.6 Hz, OH), 2.35 (3H, s, CH_3) 3.39 (1H, ddd,

$J_{4,5}$ 9.8 Hz, $J_{5,6}$ 5.0 Hz, $J_{6,6'}$ 10.1 Hz, H-6), 3.37-3.50 (1H, m, H-5), 3.62 (1H, at, J 9.1 Hz, H-2), 3.67 (1H, dd, $J_{5,6'}$ 2.7 Hz, H-5), 3.48 (1H, dd, $J_{1,2}$ 8.8 Hz, $J_{2,3}$ 9.5 Hz, H-2), 3.56 (1H, at, J 9.4 Hz, H-4), 3.61-3.74 (1H, m, H-6), 3.74 (1H, at, J 9.1 Hz, H-3), 3.90 (1H, ddd, $J_{5,6'}$ 2.3 Hz, $J_{6,6'}$ 11.8 Hz, $J_{6',OH}$ 5.4 Hz, H-6'), 4.67 (1H, d, H-1), 4.67, 4.88 (2H, d, ABq, J_{AB} 11.1 Hz, PhC$\underline{H}_2$), 4.79, 4.95 (2H, ABq, J_{AB} 10.3 Hz, PhC$\underline{H}_2$), 4.89, 4.94 (2H, ABq, J_{AB} 10.8 Hz, PhC$\underline{H}_2$), 7.13-7.46 (19H, m, ArH); δ_C (100.6 MHz, $CDCl_3$) 21.1 (s, CH_3), 62.1 (t, C-6), 75.1, 75.5, 75.8 (3 x t, 3 x Ph$\underline{C}H_2$), 77.6 (d, C-4), 79.2 (d, C-5), 81.1 (d, C-2), 86.6 (d, C-3), 87.8 (d, C-1), 127.8, 127.9, 128.0, 128.2, 128.5, 129.8, 132.7 (7 x d, 19 x ArCH), 129.4, 137.8, 138.0, 138.1, 138.3 (5 x s, 5 x ArC); *m/z* (ESI) 574 ($M+NH_4^+$, 100%), 579 ($M+Na^+$, 83). (HRMS (ESI) Calcd. For $C_{34}H_{36}O_5S$ ($M+NH_4^+$) 574.2627. Found 574.2628). (Found: C, 73.53; H, 6.54. $C_{34}H_{46}O_5S$ requires: C, 73.35; H, 6.52%);

and *p*-tolyl-6-*O*-acetyl-2,3,4-tri-*O*-benzyl-1-thio-β-D-glucopyranoside **148** (62 mg, 4%) as an opaque white oil; $[\alpha]_D^{20}$ +7 (*c*, 1.0 in $CHCl_3$); ν_{max}(chloroform)/cm^{-1} 1739 (s, C=O); δ_H (400 MHz, $CDCl_3$) 2.13 (3H, s, $COCH_3$), 2.42 (3H, s, CH_3), 3.57-3.65, 3.82 (1 x 3H, m, 1 x 1 H, at, J 8.4 Hz, H-2, H-3, H-4, H-5), 4.31 (1H, dd, $J_{5,6}$ 4.6 Hz, $J_{6,6'}$ 11.8 Hz, H-6), 4.77 (1H, dd, $J_{5,6'}$ 1.2 Hz, H-6'), 4.68, 4.96 (2H, ABq, J_{AB} 10.5 Hz, PhC$\underline{H}_2$), 4.70 (1H, d, $J_{1,2}$ 9.2 Hz, H-1), 4.85, 5.04 (2H, ABq, J_{AB} 10.3 Hz, PhC$\underline{H}_2$), 4.95, 5.03 (2H, ABq, J_{AB} 10.8 Hz, PhC$\underline{H}_2$), 7.18-7.50 (19H, m, ArH); δ_C (100.6 MHz, $CDCl_3$) 21.0, 21.2 (2 x q, 2 x CH_3), 63.4 (t, C-6), 75.2, 75.5, 75.9 (3 x t, 3 x Ph$\underline{C}H_2$), 76.9, 77.6, 80.9, 86.8 (4 x d, C-2, C-3, C-4, C-5), 87.8 (d, C-1), 127.3, 127.7, 127.9, 128.0, 128.1, 128.2, 128.3, 128.6, 129.5, 129.7, 132.9 (11 x d, 19 x ArCH), 137.7, 138.0, 138.1, 138.3, 147.0 (5 x s, 5 x ArC), 170.8 (s, C=O); *m/z* (ESI) 621 ($M+Na^+$, 3%). (HRMS (ESI) Calcd. For C36H38O_6NaS ($M+Na^+$) 621.2287. Found 621.2288).

p-Tolyl-2,3,4-tri-*O*-benzoyl-1-thio-β-D-glucopyranoside 147 and p-Tolyl-6-*O*-acetyl-2,3,4-tri-*O*-benzoyl-1-thio-β-D-glucopyranoside 149

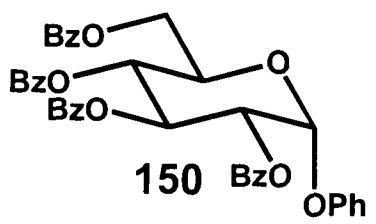


p-Tolyl-2,3,4-tri-*O*-benzoyl-6-*O*-trityl-1-thio-β-D-glucopyranoside **145** (12.0 g, 14.3 mmol) was suspended in a mixture of acetic acid:ethanol (240 ml:120 ml) and refluxed at 80 °C for 24 h, at which point t.l.c. (ethyl acetate:petrol, 1:3) indicated the formation of a major product (R_f 0.2) and the absence of starting material (R_f 0.5). The reaction mixture was allowed to cool to room temperature and then concentrated *in vacuo*. The residue was dissolved in ethyl acetate (200 ml) and washed with sodium hydrogencarbonate (2 x 100 ml of a saturated aqueous solution), water (100 ml), brine (100 ml), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (ethyl acetate:petrol, 1:4) to afford *p*-tolyl-2,3,4-tri-*O*-benzoyl-1-thio-β-D-glucopyranoside **147** (6.5 g, 76%) as a white crystalline solid, m.p. 146-147 °C (ethanol); $[\alpha]_D^{22}$ +9 (*c*, 1.0 in $CHCl_3$); ν_{max}(KBr disk)/cm^{-1} 1732, 1722 (s, C=O); δ_H (400 MHz, $CDCl_3$) 2.36 (3H, s, CH_3), 2.51 (1H, br s, OH), 3.73-3.90 (3H, m, H-5, H-6, H-6'), 5.00 (1H, d, $J_{1,2}$ 10.0 Hz, H-1), 5.44-5.49 (2H, m, H-2, H-4), 5.94 (1H, at, *J* 9.7 Hz, H-3), 7.14-7.56 (13H, m, ArH), 7.82 (2H, d, *J* 8.2 Hz, ArH), 7.94 (2H, d, *J* 7.9 Hz, ArH), 7.99 (2H, d, *J* 7.6 Hz, ArH); δ_C (100.6 MHz, $CDCl_3$) 21.2 (q, CH_3), 61.6 (t, C-6), 69.3, 70.6 (2 x d, C-2, C-4), 74.1 (d, C-3), 78.8 (d, C-5), 86.2 (d, C-1), 127.6, 128.5, 128.8, 129.2, 138.9 (5 x s, 5 x ArC), 128.3, 128.4, 128.6, 129.7, 129.8, 129.9, 133.2, 133.3, 133.7, 133.9 (10 x d, 19 x

ArCH), 165.0, 165.8, 165.9 (3 x s, 3 x C=O); *m/z* (ESI) 616 ($M+NH_4^+$, 45%), 621 ($M+Na^+$, 73), 1220 ($2M+Na^+$, 33). (HRMS (ESI) Calcd. For $C_{34}H_{34}NO_8S$ ($M+NH_4^+$) 616.2005. Found 616.2014). (Found: C, 68.41; H, 4.99. $C_{34}H_{30}O_8S$ requires: C, 68.21; H, 5.05%);

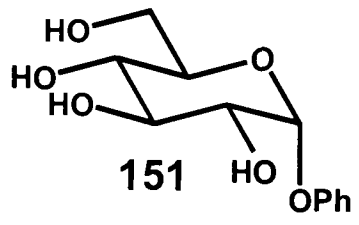
and *p*-tolyl-6-*O*-acetyl-2,3,4-tri-*O*-benzoyl-1-thio-β-D-glucopyranoside **149** (1.0 g, 11%) as crystalline white solid, m.p. 159-160 °C (ethanol); $[\alpha]_D^{20}$ +12 (*c*, 1.0 in $CHCl_3$); ν_{max}(KBr disk)/cm^{-1} 3400 (s, br, OH), 1732 (s, C=O); δ_H (400 MHz, $CDCl_3$) 2.07 (3H, s, $COCH_3$), 2.34 (3H, s, CH_3), 4.02-4.06 (1H, m, H-5), 4.32-4.33 (2H, m, H-6, H-6'), 4.97 (1H, d, $J_{1,2}$ 10.0 Hz, H-1), 5.45 (1H, at, *J* 9.7 Hz, H-2), 5.54 (1H, at, *J* 9.8 Hz, H-4), 5.87 (1H, at, *J* 9.5 Hz, H-3), 7.14 (2H, d, *J* 8.0 Hz, ArH), 7.26-7.55 (11H, m, ArH), 7.79-7.81 (2H, m, ArH), 7.90-7.92 (2H, m, ArH), 7.97-7.99 (2H, m, ArH); δ_C (100.6 MHz, $CDCl_3$) 20.7, 21.2 (2 x q, 2 x CH_3), 62.7 (t, C-6), 69.2 (d, C-4), 70.5 (d, C-2), 74.2 (d, C-3), 76.1 (d, C-5), 86.3 (d, C-1), 127.7, 128.7, 128.8, 129.2, 138.8 (5 x s, 5 x ArC), 128.3, 128.4, 129.7, 129.8, 129.9, 133.2, 133.3, 133.5, 133.9 (9 x d, 19 x ArCH), 165.0, 165.2, 165.8, 170.6 (4 x s, 4 x C=O); *m/z* (ESI) 633 ($M+Na^+$, 4%). (HRMS (ESI) Calcd. For $C_{36}H_{36}NO_9S$ ($M+NH_4^+$) 658.2111. Found 658.2115).

Phenyl-2,3,4,6-tetra-*O*-benzoyl-α-D-glucopyranoside 150



Penta-*O*-benzoyl-D-glucopyranose **95** (10.0 g, 0.014 mol) and phenol (2.7 g, 0.029 mol) were dissolved in dichloromethane (100 ml) under argon in a flame dried flask. The solution was cooled to 0 °C and boron trifluoride diethyl etherate (11.3 ml, 0.043 mol) added. The mixture was heated to 50 °C and refluxed with stirring for 48 h, at which point t.l.c. (ethyl acetate:petrol, 1:2) indicated the formation of a major product (R_f 0.5) the absence of staring material (R_f 0.4). Water (100 ml) was added and the reaction mixture stirred for a further 15 min. The reaction mixture was diluted with dichloromethane (200 ml), washed with water (100 ml), brine (150 ml), dried ($MgSO_4$) and concentrated *in vacuo* to afford phenyl-2,3,4,6-tetra-*O*-benzoyl-α-D-glucopyranoside **150** (8.4 g, 89%) as a white crystalline solid, m.p. 169-171 °C (ethyl acetate/petrol) (lit.,[28] 172-174 °C); $[\alpha]_D^{24}$ +81 (*c*, 1.0 in $CHCl_3$) (lit.,[28] $[\alpha]_D^{20}$ +84.0 (*c*, 1.0 in $CHCl_3$)); δ_H (400 MHz, $CDCl_3$) 4.51 (1H, dd, $J_{5,6}$ 6.1 Hz, $J_{6,6'}$ 12.4 Hz, H-6), 4.59 (1H, dd, $J_{5,6'}$ 2.6 Hz, H-6'), 4.65 (1H, ddd, $J_{4,5}$ 10.2 Hz, H-5), 5.54 (1H, dd, $J_{1,2}$ 3.7 Hz, $J_{2,3}$ 10.2 Hz, H-2), 5.80 (1H, at, *J* 9.9 Hz, H-4), 6.05 (1H, d, H-1), 6.46 (1H, at, *J* 9.8 Hz, H-3), 6.86-7.60 (18H, m, ArH), 7.93-8.04 (7H, m, ArH).

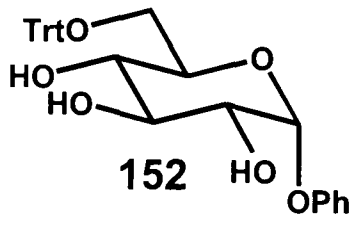
Phenyl-α-D-glucopyranoside 151



151

Phenyl-2,3,4,6-tetra-*O*-benzoyl-α-D-glucopyranoside **150** (7.8 g, 0.012 mol) was suspended in methanol (90 ml) under argon in a flame dried flask. To this a solution of sodium (44 mg, 1.91 mol) in methanol (10 ml) was added and the mixture stirred for 18 h, at which point t.l.c. (ethyl acetate:petrol, 1:2) indicated the formation of a major product (R_f 0) and the absence of starting material (R_f 0.4). Ion exchange resin (Dowex® 50WX8) was added portionwise until the solution was neutralised, at which point the reaction mixture was filtered and concentrated *in vacuo* to afford phenyl-α-D-glucopyranoside **151** (2.8 g, 90%) as a white crystalline solid, m.p. 152 °C (ethanol) (lit.,[29] 160-161 °C); $[\alpha]_D^{22}$ +184 (*c*, 1.5 in MeOH) (lit.,[29] $[\alpha]_D^{21}$ +179 (*c*, 1.25 in H_2O)); δ_H (400 MHz, $CDCl_3$) 3.45 (1H, at, *J* 9.9 Hz, H-4), 3.58 (1H, dd, $J_{1,2}$ 3.7 Hz, $J_{2,3}$ 9.8 Hz, H-2), 3.66-3.77 (3H, m, H-5, H-6, H-6'), 3.88 (1H, at, *J* 9.4 Hz, H-3), 4.49 (1H, d, H-1), 7.01 (1H, at, *J* 7.4 Hz, ArH), 7.17 (2H, d, *J* 7.7 Hz, ArH), 7.29 (2H, at, *J* 8.0 Hz, ArH).

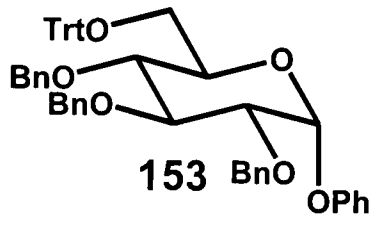
Phenyl-6-*O*-trityl-α-D-glucopyranoside 152



152

Phenyl-α-D-glucopyranoside **151** (2.0 g, 7.81 mmol), triphenylmethyl chloride (2.4 g, 8.72 mmol) and *N*,*N*-dimethylaminopyridine (486 mg, 3.98 mmol) were dissolved in pyridine (50 ml) in a dry flask under argon. After 24 h triphenylmethyl chloride (1.0 g, 3.57 mmol) was added and the reaction mixture stirred for a further 48 h, at which point t.l.c. (ethyl acetate) showed the formation of a major product (R_f 0.3) and the absence of starting material (R_f 0.1). The reaction mixture was concentrated *in vacuo* and the residue purified by flash column chromatography (ethyl acetate) to afford phenyl-6-*O*-trityl-α-D-glucopyranoside **152** (3.5 g, 90%) as a colourless oil; $[\alpha]_D^{22}$ +63 (*c*, 1.4 in $CHCl_3$); ν_{max}(KBr disk)/cm^{-1} 3413 (br, OH); δ_H (400 MHz, CD_3OD) 3.20-3.44 (3H, m, H-4, H-6, H-6'), 3.62 (1H, dd, $J_{1,2}$ 3.7 Hz, $J_{2,3}$ 9.7 Hz, H-2), 3.86 (1H, at, *J* 9.3 Hz, H-3), 3.89-3.92 (1H, m, H-5), 5.58 (1H, d, H-1), 6.98-7.62 (15H, m, ArH); δ_C (100.6 MHz, CD_3OD) 64.0 (t, C-6), 71.4 (d, C-4), 72.35, 72.40 (2 x d, C-2, C-5), 74.3 (d, C-3), 86.6 (s, $\underline{C}Ph_3$), 101.1 (d, C-1), 114.5 (1 x s, 3 x ArC), 117.4, 122.4, 126.9, 127.0, 127.6, 127.7, 128.3, 128.9, 129.0, 129.5, 129.6 (11 x d, 15 x ArCH); *m/z* (ESI) 521 ($M+Na^+$, 100%), 1019 ($2M+Na^+$, 62). (HRMS (ESI) Calcd. For $C_{31}H_{30}O_6$ (MNa^+) 521.1940. Found 521.1959).

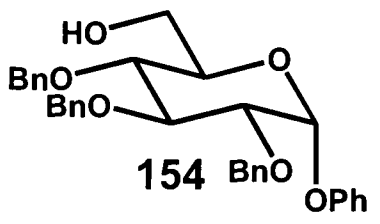
Phenyl-2,3,4-tri-*O*-benzyl-6-*O*-trityl-α-D-glucopyranoside 153



Phenyl-6-*O*-trityl-α-D-glucopyranoside **152** (3.2 g, 6.36 mmol) was dissolved in *N*,*N*-dimethylformamide (50 ml) in a flame dried flask under argon. Benzyl bromide (3 ml, 25.3 mmol) was added and the reaction mixture cooled to 0 °C, at which point sodium hydride (1.4 g, 35.3 mmol) was added portionwise and the reaction mixture then allowed to warm to room temperature overnight. After 16 h t.l.c. (ethyl acetate: petrol, 1:6) indicated the formation of a major product (R_f 0.4) and complete consumption of starting material (R_f 0). Methanol (25 ml) was added and the solution stirred for 1 h, after which time the majority of solvent was removed *in vacuo*. The resulting residue was dissolved in dichloromethane (100 ml), washed with water (2 x 100 ml) and the combined aqueous layers re-extracted with dichloromethane (100 ml). The organic phases where then combined and washed with brine (3 x 100 ml), dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by flash column chromatography (petrol then ethyl acetate:petrol, 1:8) to afford phenyl-2,3,4-tri-*O*-benzyl-6-*O*-trityl-α-D-glucopyranoside **153** (4.4 g, 90%) as a white crystalline solid, m.p. 163-164 °C (ethyl acetate/petrol); $[\alpha]_D^{24}$ +75 (*c*, 1.3 in $CHCl_3$); ν_{max}(KBr disk)/cm^{-1} no significant peaks; δ_H (400 MHz, $CDCl_3$) 3.20 (1H, dd, $J_{5,6}$ 4.6 Hz, $J_{6,6'}$ 10.0 Hz, H-6), 3.48 (1H, dd, $J_{5,6'}$ 1.8 Hz, H-6'), 3.77 (1H, at, *J* 9.5 Hz, H-4), 3.84 (1H, dd, $J_{1,2}$ 3.4 Hz, $J_{2,3}$ 9.6 Hz, H-2), 3.96-4.00 (1H, m, H-5), 4.22 (1H, at, *J* 9.3 Hz, H-3), 4.34, 4.76 (2H, ABq, J_{AB} 10.2 Hz, PhC$\underline{H}_2$), 4.79, 4.88 (2H, ABq,

J_{AB} 12.0 Hz, PhC$\underline{H}_2$), 4.91, 5.07 (2H, ABq, J_{AB} 10.6 Hz, PhC$\underline{H}_2$), 5.65 (1H, d, H-1), 6.88-7.47 (35H, m, ArH); δ_C (100.6 MHz, $CDCl_3$) 62.3 (t, C-6), 71.0 (d, C-5), 73.2, 75.2, 76.1 (3 x t, Ph$\underline{C}H_2$), 78.0 (d, C-4), 80.1 (d, C-2), 82.1 (d, C-3), 86.3 (s, $Ph_3\underline{C}$), 95.1 (d, C-1), 116.9, 122.3, 126.9, 127.7, 127.8, 127.9, 128.2, 128.5, 128.8, 129.5 (10 x d, 35 x ArCH), 137.8, 138.1, 138.7, 143.9, 156.8 (5 x s, 7 x ArC); *m/z* (ESI) 791 ($M+Na^+$, 100%), 1559 ($2M+Na^+$, 37). (HRMS (ESI) Calcd. For $C_{52}H_{48}O_6Na$ ($M+Na^+$) 791.3349. Found 791.3363).

Phenyl-2,3,4-tri-*O*-benzyl-α-D-glucopyranoside 154



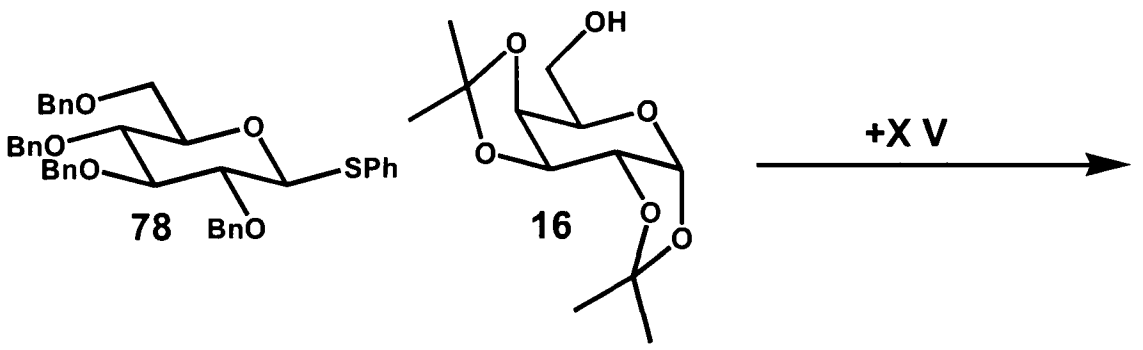
Phenyl-2,3,4-tri-*O*-benzyl-6-*O*-trityl-α-D-glucopyranoside **153** (2.0 g, 2.60 mmol) was dissolved in dichloromethane (60 ml) and iron (III) chloride (1.4 g, 5.20 mol) added. The reaction proceeded slowly, but after 48 h t.l.c. indicated the formation of a major product and only a small amount of remaining starting material. The reaction mixture was washed with water (3 x 50 ml), brine (50 ml), dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by flash column chromatography (ethyl acetate:petrol, 1:3) to afford phenyl-2,3,4-tri-*O*-benzyl-α-D-glucopyranoside **154** (896 mg, 65%) as a white crystalline solid, m.p. 72-74 °C (lit.,[30] 74-75 °C); $[\alpha]_D^{24}$ +49 (*c*, 1.0 in $CHCl_3$) (lit.,[30] +115 (*c*, 1.0 in $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 3.68-3.73, 3.81-3.85 (5H, m, H-2, H-4, H-5, H-6, H-6'), 4.27 (1H, at, *J* 9.2 Hz, H-3), 4.72, 4.85 (2H, ABq, J_{AB} 12.0 Hz, PhC$\underline{H}_2$), 4.72, 4.96 (2H, ABq, J_{AB} 11.0 Hz, PhC$\underline{H}_2$), 4.95, 5.11 (2H, ABq, J_{AB} 11.0 Hz, PhC$\underline{H}_2$), 5.46 (1H, d, $J_{1,2}$ 3.6 Hz, H-1), 7.05-7.45 (10H, m, ArH).

5.3 Experimental for Chapter 4

Typical Procedure for Electrochemical Glycosylation

The glycosyl donor (*c.* 100 mg, 0.15 mmol), glycosyl acceptor (*c.* 0.30 mmol) and tetrabutylammonium perchlorate (*c.* 855 mg, 2.50 mmol) *or* lithium tetrafluoroborate (*c.* 235 mg, 2.50 mmol) were dissolved in acetonitrile (25 ml) and transferred to a flame dried cell containing a reticulated carbon working electrode, a nickel mesh counter electrode and a silver wire pseudo reference electrode. 4 Å molecular sieves were added and the reaction mixture stirred under nitrogen for 30 min. A defined positive potential was applied and the reaction monitored by t.l.c. until no starting material remained. At this point the reaction mixture was filtered, and concentrated *in vacuo*. The residue was taken up in dichloromethane (50 ml), washed with water (50 ml) and brine (50 ml), dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was then purified by flash column chromatography (ethyl acetate:petrol).

Activation of phenyl 2,3,4,6 tetra-*O*-benzyl-1-thio-β-D-glucopyranoside 78 with 1,2:3,4-di-*O*-isopropylidene-α-galactopyranoside 16 as the glycosyl acceptor



At +1.7 V

Phenyl-2,3,4,6-tetra-*O*-benzyl-1-thio-β-D-glucopyranoside **78** (101 mg, 0.16 mmol), 1,2:3,4-di-*O*-isopropylidene-α-galactopyranoside **16** (83 mg, 0.32 mmol) and lithium tetrafluoroborate

(250 mg), in acetonitrile (25 ml) were stirred for 5 h at a potential of +1.7 V. Flash column chromatography (ethyl acetate:petrol, 1:3) gave only recovered starting material: phenyl-2,3,4,6-tetra-*O*-benzyl-1-thio-β-D-glucopyranoside **78** (95 mg, 94%) as a white crystalline solid, m.p. 90-91 °C (ethyl acetate/petrol) (lit., 91-92 °C); $[\alpha]_D^{22}$ +0.5 (*c*, 1.0 in $CHCl_3$) (lit., $[\alpha]_D^{20}$ +0.8 (*c*, 5.0 in $CHCl_3$)); δ_H (400 MHz, $CDCl_3$) 3.53-3.58 (1H, m, H-5), 3.55 (1H, at, *J* 9.2 Hz, H-2), 3.69 (1H, at, H-3), 3.73-3.78 (2H, m, H-4, H-6), 3.83 (1H, dd, $J_{5,6'}$ 10.9 Hz, $J_{6,6'}$ 1.9 Hz, H-6'), 4.58, 4.65 (2H, ABq, J_{AB} 12.0 Hz, PhC$\underline{H}_2$), 4.63, 4.87 (2H, ABq, J_{AB} 10.9 Hz, PhC$\underline{H}_2$), 4.71 (1H, d, $J_{1,2}$ 9.9 Hz, H-1), 4.77, 4.93 (2H, ABq, J_{AB} 10.3 Hz, PhC$\underline{H}_2$), 4.89, 4.94 (2H, ABq, J_{AB} 10.9 Hz, PhC$\underline{H}_2$), 7.22-7.65 (25H, m, ArH).

At +1.8 V

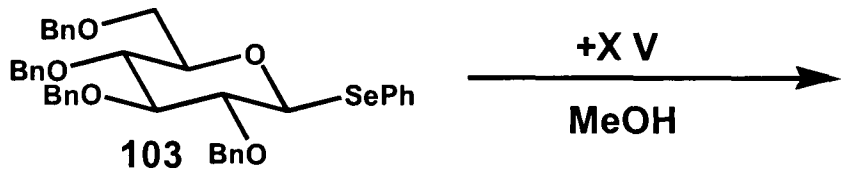
Phenyl-2,3,4,6-tetra-*O*-benzyl-1-thio-β-D-glucopyranoside **78** (106 mg, 0.17 mmol), 1,2:3,4-di-*O*-isopropylidene-α-galactopyranoside **16** (85 mg, 0.34 mmol) and lithium tetrafluoroborate (250 mg, 2.66 mmol), in acetonitrile (25 ml) were stirred for 8 h at a potential of +1.8 V. Flash column chromatography (ethyl acetate:petrol, 1:3) gave 2,3,4,6-tetra-*O*-benzyl-β-D-glucopyranosyl-(1→6)-1,2:3,4-di-*O*-isopropylidene-α-galactopyranoside **156** (98 mg, 75%) as a colourless oil; $[\alpha]_D^{22}$ –24 (*c*, 1.0 in $CHCl_3$) (lit.,[31] $[\alpha]_D^{22}$ –22 (*c*, 1.4 in $CHCl_3$)); δ_H (400 MHz, $CDCl_3$) 1.33, 1.34, 1.48, 1.52 (4 x 3H, 4 x s, 4 x CH_3), 2.11-4.06 (6H, m, H-2_b, H-3_b, H-4_b, H-5_b, H-6_b, H-$6'_b$), 4.11 (1H, ddd, $J_{4,5}$ 7.5 Hz, $J_{5,6}$ 3.4 Hz, $J_{5,6'}$ 1.8 Hz, H-5_a), 4.19 (1H, dd, $J_{6,6'}$ 10.7 Hz, H-6_a), 4.27 (1H, dd, $J_{6,6'}$ 8.0 Hz, H-$6'_a$), 4.34 (1H, $J_{1,2}$ 5.1 Hz, $J_{2,3}$ 2.4 Hz, H-2_a), 4.48 (1H, d, $J_{1,2}$ 7.7 Hz H-1_b), 4.52 (1H, d, *J* 9.8 Hz, PhC$\underline{H}$H), 4,55, 4.82 (2H, ABq, J_{AB} 11.8 Hz, PhC$\underline{H}_2$), 4.60-4.66 (3H, m, H-3_a, H-4_a, PhC$\underline{H}_2$), 4.74, 5.08 (2H, ABq, J_{AB} 11.0 Hz, PhC$\underline{H}_2$),

4.80, 4.98 (2H, ABq, J_{AB} 10.9 Hz, PhC$\underline{H}_2$), 5.59 (1H, d, $J_{1,2}$ 4.9 Hz H-1_a), 7.09-7.45 (20H, m, ArH).

At +2.0 V

Phenyl-2,3,4,6-tetra-*O*-benzyl-1-thio-β-D-glucopyranoside **78** (99 mg, 0.16 mmol), 1,2:3,4-di-*O*-isopropylidene-α-galactopyranoside **16** (81 mg, 0.31 mmol) and lithium tetrafluoroborate (250 mg, 2.66 mmol), in acetonitrile (25 ml) were stirred for 5 h at a potential of +2.0 V. Flash column chromatography (ethyl acetate:petrol, 1:3) gave 2,3,4,6-tetra-*O*-benzyl-β-D-glucopyranosyl-(1→6)-1,2:3,4-di-*O*-isopropylidene-α-galactopyranoside **156** (81 mg, 66%) as a colourless oil; data consistent with that previously described.

Activation of phenyl 2,3,4,6 tetra-*O*-benzyl-1-seleno-β-D-glucopyranoside 103 with methanol as the glycosyl acceptor.



At +1.3 V

Phenyl-2,3,4,6-tetra-*O*-benzyl-1-seleno-β-D-glucopyranoside **103** (102 mg, 0.15 mmol), anhydrous methanol (0.01 ml, 0.30 mmol) and lithium tetrafluoroborate (250 mg, 2.66 mmol), in acetonitrile (25 ml), were stirred for 6 h at a potential of +1.3 V. T.l.c. indicated that no reaction had occured.

At +1.4 V

Phenyl-2,3,4,6-tetra-*O*-benzyl-1-seleno-β-D-glucopyranoside **103** (105 mg, 0.15 mmol), anhydrous methanol (0.01 ml, 0.30 mmol) and lithium tetrafluorborate (250 mg, 2.66 mmol), in acetonitrile (25 ml), were stirred for 8 h at a potential of +1.4 V. Flash column chromatography (ethyl acetate:petrol, 1:6) gave methyl-2,3,4,6-tetra-*O*-benzyl-β-D-glucopyranoside **158** (30 mg, 36%) as a white crystalline solid, m.p. 66-67 °C (methanol) (lit.,[32] 68-69 °C); $[\alpha]_D^{24}$ +10 (*c*, 1.0 in $CHCl_3$) (lit.,[32] $[\alpha]_D^{20}$ +11 (*c*, 5.3 in dioxan)); δ_H (400 MHz, $CDCl_3$) 3.47-3.54 (2H, m, H-2, H-5), 3.63 (3H, s, Me), 3.74 (1H, dd, $J_{5,6}$ 4.8 Hz, $J_{6,6'}$ 10.8 Hz, H-6), 3.81 (1H, dd, $J_{5,6'}$ 1.9 Hz, H-6'), 4.36 (1H, d, $J_{1,2}$ 7.9 Hz, H-1), 4.58, 4.87 (2H, ABq, J_{AB} 10.6 Hz, PhC$\underline{H}_2$), 4.60, 4.67 (2H, ABq, J_{AB} 12.3 Hz, PhC$\underline{H}_2$), 4.76, 4.99 (2H, ABq, J_{AB} 10.9 Hz, PhC$\underline{H}_2$), 4.84, 4.97 (2H, ABq, J_{AB} 11.0 Hz, PhC$\underline{H}_2$), 7.19-7.41 (20H, m, ArH);

and methyl-2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranoside **157** as a colourless oil (9 mg, 11%); $[\alpha]_D^{24}$ +19 (*c*, 0.5 in $CHCl_3$) (lit.,[33] $[\alpha]_D^{20}$ +36 (*c*, 1.2 in $CHCl_3$)); δ_H (400 MHz, $CDCl_3$) 3.39 (3H, s, Me), 3.57 (1H, dd, $J_{1,2}$ 3.5 Hz, $J_{2,3}$ 9.6 Hz, H-2), 3.62-3.68 (2H, m, H-4, H-6), 3.71-3.77 (2H, m, H-5, H-6'), 3.99 (1H, at, *J* 9.2 Hz, H-3), 4.48, 4.84 (2H, ABq, J_{AB} 10.7 Hz, PhC$\underline{H}_2$), 4.49, 4.62 (2H, ABq, J_{AB} 12.4 Hz, PhC$\underline{H}_2$), 4.64 (1H, d, H-1), 4.68, 4.81 (2H, ABq, J_{AB} 12.1 Hz, PhC$\underline{H}_2$), 4.83, 4.99 (2H, ABq, J_{AB} 10.9 Hz, PhC$\underline{H}_2$), 7.12-7.38 (20H, m, ArH);

and recovered starting material: phenyl-2,3,4,6-tetra-*O*-benzyl-1-seleno-β-D-glucopyranoside **103** (46 mg, 45%) as a white crystalline solid, m.p. 90-91 °C (ethyl acetate/petrol) (lit.,[6] 91-92 °C); $[\alpha]_D^{22}$ +0.5 (*c*, 1.0 in $CHCl_3$) (lit.,[7] $[\alpha]_D^{20}$ +0.8 (*c*, 5.0 in $CHCl_3$)); δ_H (400 MHz, $CDCl_3$) 3.53-3.58 (1H, m, H-5), 3.55 (1H, at, *J* 9.2 Hz, H-2), 3.69 (1H, at, H-3), 3.73-3.78 (2H, m, H-4, H-6), 3.83 (1H, dd, $J_{5,6'}$ 10.9 Hz, $J_{6,6'}$ 1.9 Hz, H-6'), 4.58, 4.65 (2H, ABq, J_{AB} 12.0 Hz, PhC$\underline{H}_2$), 4.63, 4.87 (2H, ABq, J_{AB} 10.9 Hz, PhC$\underline{H}_2$), 4.71 (1H, d, $J_{1,2}$

9.9 Hz, H-1), 4.77, 4.93 (2H, ABq, J_{AB} 10.3 Hz, PhC$\underline{H}_2$), 4.89, 4.94 (2H, ABq, J_{AB} 10.9 Hz, PhC$\underline{H}_2$), 7.22-7.65 (25H, m, ArH).

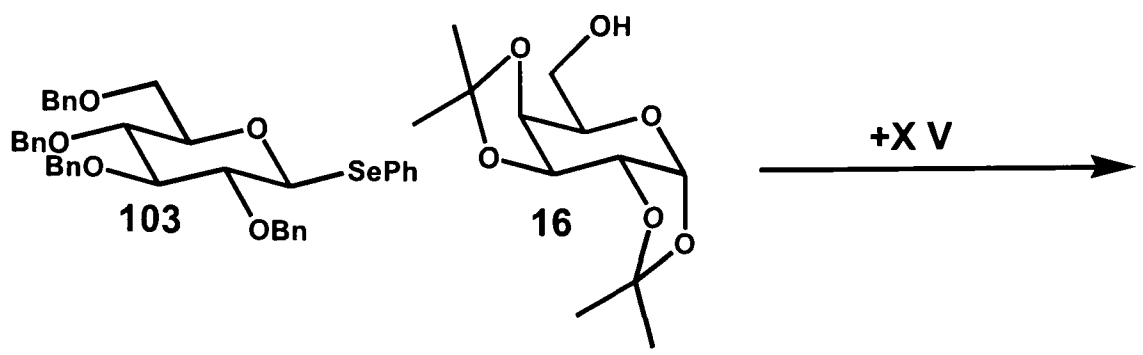
At +1.5 V with methanol

Phenyl-2,3,4,6-tetra-*O*-benzyl-1-seleno-β-D-glucopyranoside **103** (100 mg, 0.15 mmol), anhydrous methanol (0.01 ml, 0.30 mmol) and lithium tetrafluoroborate (250 mg, 2.66 mmol), in acetonitrile (25 ml), were stirred for 8 h at a potential of +1.5 V. Flash column chromatography (ethyl acetate:petrol, 1:4) gave methyl-2,3,4,6-tetra-*O*-benzyl-β-D-glucopyranoside **158** (46 mg, 56%) as a white crystalline solid; data consistent with that previously described; and methyl-2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranoside **157** (12 mg, 15%) as a colourless oil; data consistent with that previously described.

At +1.7 V with methanol

Phenyl-2,3,4,6-tetra-*O*-benzyl-1-seleno-β-D-glucopyranoside **103** (100 mg, 0.15 mmol), anhydrous methanol (0.01 ml, 0.30 mmol) and tetrabutylammonium perchlorate (850 mg, 2.49 mmol), in acetonitrile (25 ml), were stirred for 3 h at a potential of +1.7 V. Flash column chromatography (ethyl acetate:petrol, 1:6) gave methyl-2,3,4,6-tetra-*O*-benzyl-β-D-glucopyranoside **158** (58 mg, 71%) as a white crystalline solid; data consistent with that previously described; and methyl-2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranoside **157** (11 mg, 13%) as a colourless oil; data consistent with that previously described.

Activation of phenyl 2,3,4,6 tetra-*O*-benzyl-1-seleno-β-D-glucopyranoside 103 with 1,2:3,4-di-*O*-isopropylidene-α-galactopyranoside 16 as the glycosyl acceptor



At +1.3 V

Phenyl-2,3,4,6-tetra-*O*-benzyl-1-seleno-β-D-glucopyranoside **103** (105 mg, 0.15 mmol), 1,2:3,4-di-*O*-isopropylidene-α-galactopyranoside **16** (87 mg, 0.33 mmol) and lithium tetrafluoroborate (250 mg, 2.66 mmol), in acetonitrile (25 ml), were stirred for 9 h at a potential of +1.3 V. T.l.c. indicated that no reaction had occured.

At +1.4 V

Phenyl-2,3,4,6-tetra-*O*-benzyl-1-seleno-β-D-glucopyranoside **103** (101 mg, 0.15 mmol), 1,2:3,4-di-*O*-isopropylidene-α-galactopyranoside **16** (116 mg, 0.45 mmol) and lithium tetrafluoroborate (234 mg, 2.49 mmol), in acetonitrile (25 ml), were stirred for 8 h at a potential of +1.4 V. Flash column chromatography (ethyl acetate:petrol, 1:6) gave 2,3,4,6-tetra-*O*-benzyl-β-D-glucopyranosyl-(1→6)-1,2:3,4-di-*O*-isopropylidene-α-galactopyranoside **156** (80 mg, 69%) as a colourless oil; data consistent with that previously described; and recovered starting material: phenyl 2,3,4,6 tetra-*O*-benzyl-1-seleno-β-D-glucopyranoside **103** (14 mg, 14%) as a crystalline white solid; data consistent with that previously described.

At +1.5 V

Phenyl-2,3,4,6-tetra-*O*-benzyl-1-seleno-β-D-glucopyranoside **103** (100 mg, 0.15 mmol), 1,2:3,4-di-*O*-isopropylidene-α-galactopyranoside **16** (78 mg, 0.30 mmol) and lithium tetrafluoroborate (241 mg, 2.56 mmol), in acetonitrile (25 ml), were stirred for 8 h at a potential of +1.5 V. Flash column chromatography (ethyl acetate:petrol, 1:4) gave 2,3,4,6-tetra-*O*-benzyl-β-D-glucopyranosyl-(1→6)-1,2:3,4-di-*O*-isopropylidene-α-galactopyranoside **156** (98 mg, 85%) as a colourless oil; data consistent with that previously described.

At +1.6 V

Phenyl-2,3,4,6-tetra-*O*-benzyl-1-seleno-β-D-glucopyranoside **103** (104 mg, 0.15 mmol), 1,2:3,4-di-*O*-isopropylidene-α-galactopyranoside **16** (83 mg, 0.32 mmol) and lithium tetrafluoroborate (231 mg, 246 mmol), in acetonitrile (25 ml), were stirred for 5 h at a potential of +1.6 V. Flash column chromatography (ethyl acetate:petrol, 1:4) gave 2,3,4,6-tetra-*O*-benzyl-β-D-glucopyranosyl-(1→6)-1,2:3,4-di-*O*-isopropylidene-α-galactopyranoside **156** (103 mg, 86%) as a colourless oil; data consistent with that previously described.

At +1.7 V

Phenyl-2,3,4,6-tetra-*O*-benzyl-1-seleno-β-D-glucopyranoside **103** (103 mg, 0.15 mmol), 1,2:3,4-di-*O*-isopropylidene-α-galactopyranoside **16** (81 mg, 0.31 mmol) and lithium tetrafluoroborate (234 mg, 2.49 mmol), in acetonitrile (25 ml), were stirred for 3 h at a potential of +1.7 V. Flash column chromatography (ethyl acetate:petrol, 1:4) gave 2,3,4,6-tetra-*O*-benzyl-β-D-glucopyranosyl-(1→6)-1,2:3,4-di-*O*-isopropylidene-α-galactopyranoside **156** (101 mg, 85%) as a colourless oil; data consistent with that previously described.

At +1.8 V

Phenyl-2,3,4,6-tetra-*O*-benzyl-1-seleno-β-D-glucopyranoside **103** (103 mg, 0.15 mmol), 1,2:3,4-di-*O*-isopropylidene-α-galactopyranoside **16** (84 mg, 0.32 mmol) and lithium tetrafluoroborate (242 mg, 2.57 mmol), in acetonitrile (25 ml), were stirred for 2 h at a potential of +1.8 V. Flash column chromatography (ethyl acetate:petrol, 1:4) gave 2,3,4,6-tetra-*O*-benzyl-β-D-glucopyranosyl-(1→6)-1,2:3,4-di-*O*-isopropylidene-α-galactopyranoside **156** (99 mg, 83%) as a colourless oil; data consistent with that previously described.

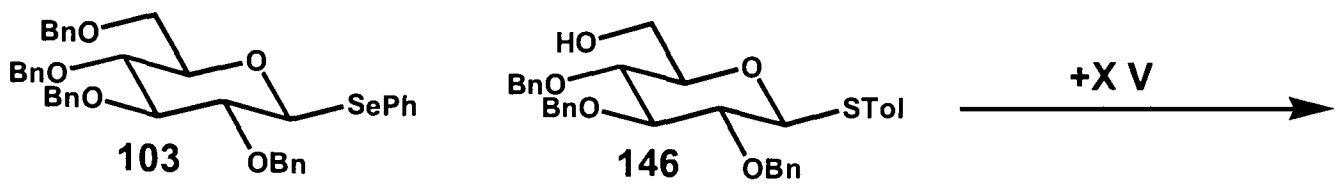
At +1.9 V

Phenyl-2,3,4,6-tetra-*O*-benzyl-1-seleno-β-D-glucopyranoside **103** (98 mg, 0.14 mmol), 1,2:3,4-di-*O*-isopropylidene-α-galactopyranoside **16** (80 mg, 0.31 mmol) and lithium tetrafluoroborate (234 mg, 2.49 mmol), in acetonitrile (25 ml), were stirred for 2 h at a potential of +1.9 V. Flash column chromatography (ethyl acetate:petrol, 1:4) gave 2,3,4,6-tetra-*O*-benzyl-β-D-glucopyranosyl-(1→6)-1,2:3,4-di-*O*-isopropylidene-α-galactopyranoside **156** (96 mg, 85%) as a colourless oil; data consistent with that previously described.

At +2.0 V

Phenyl-2,3,4,6-tetra-*O*-benzyl-1-seleno-β-D-glucopyranoside **103** (104 mg, 0.15 mmol), 1,2:3,4-di-*O*-isopropylidene-α-galactopyranoside **16** (77 mg, 0.30 mmol) and lithium tetrafluoroborate (238 mg, 2.53 mmol), in acetonitrile (25 ml), were stirred for 1 h at a potential of +2.0 V. Flash column chromatography (ethyl acetate:petrol, 1:4) gave 2,3,4,6-tetra-*O*-benzyl-β-D-glucopyranosyl-(1→6)-1,2:3,4-di-*O*-isopropylidene-α-galactopyranoside **156** (101 mg, 84%) as a colourless oil; data consistent with that previously described.

Activation of phenyl 2,3,4,6 tetra-*O*-benzyl-1-seleno-β-D-glucopyranoside 103 with tolyl-2,3,4-tri-*O*-benzyl-1-thio-β-D-glucopyranoside 146 as the glycosyl acceptor



At +1.4 V using 0.25 equivalents of the acceptor and with $LiBF_4$ as the electrolyte

Phenyl-2,3,4,6-tetra-*O*-benzyl-1-seleno-β-D-glucopyranoside **103** (400 mg, 0.59 mmol), tolyl-2,3,4-tri-*O*-benzyl-1-thio-β-D-glucopyranoside **146** (84 mg, 0.15 mmol) and lithium tetrafluoroborate (242 mg, 2.57 mmol), in acetonitrile (25 ml), were stirred for 4 h at a potential of +1.4 V. Flash column chromatography (ethyl acetate:petrol, 1:6) gave tolyl-2,3,4,6-tetra-*O*-benzyl-β-D-glucopyranosyl-(1→6)-2,3,4-tri-*O*-benzyl-1-thio-β-glucopyranoside **161** (17 mg, 11%) as a white crystalline solid, m.p. 129-131 °C (petrol/ethyl acetate); $[\alpha]_D^{22}$ +5.0 (*c*, 0.5 in $CHCl_3$); ν_{max}(KBr disk)/cm^{-1} no significant peaks; δ_H (500 MHz, $CDCl_3$) 2.30 (3H, s, Me), 3.46-3.56 (4H, m, H-2_a, H-2_b, H-4_a, H-5_b), 3.63-3.70 (4H, m, H-3_a, H-3_b, H-4_b, H-5_a), 3.73-3.81 (3H, m, H-6_a, H-6_b, H-6'$_b$), 4.24 (1H, dd, $J_{5,6'}$ 1.8 Hz, $J_{6,6'}$ 11.2 Hz, H-6'$_a$), 4.47 (1H, d, $J_{1,2}$ 7.6 Hz, H-1_b), 4.57-4.67 (4H, m, 2 x PhC$\underline{H}_2$), 4.70 (1H, d, $J_{1',2'}$ 9.8 Hz, H-1_a), 4.75-5.02 (10H, m, 5 x PhC$\underline{H}_2$), 7.06-7.52 (39H, m, ArH); δ_C (100.6 MHz, $CDCl_3$) 21.1 (q, Me), 68.6, 68.7 (2 x t, C-6_a, C-6_b), 72.5, 73.4, 74.9, 75.1, 75.5, 75.9 (6 x t, 7 x Ph$\underline{C}H_2$), 78.7, 78.9, 80.2, 80.8, 80.9, 82.2, 84.7, 86.7 (8 x d, C-2_a, C-2_b, C-3_a, C-3_b, C-4_a, C-4_b, C-5_a, C-5_b), 87.6 (d, C-1_a), 103.8 (d, C-1_b), 127.5, 127.6, 127.7, 127.8, 127.9, 128.0, 128.1, 128.2, 128.3, 128.4, 128.5, 129.7, 132.8 (13 x d, 39 x ArCH), 129.7, 137.9, 138.2, 138.9 (4 x s, 9 x ArC); *m/z* (ES^+) 1096 ($M+NH_4^+$, 24%),

1101 ($M+Na^+$, 100). (Isotope Distribution Calcd. ($M+Na^+$) 1101.46 (100%), 1102.46 (78), 1103.46 (26), 1104.47 (13). Found 1101.51 (100%), 1102.46 (70), 1103.48 (33), 1104.49 (9).

At +1.4 V using 2 equivalents of the acceptor and with $LiBF_4$ as the electrolyte

Phenyl-2,3,4,6-tetra-*O*-benzyl-1-seleno-β-D-glucopyranoside **103** (100 mg, 0.15 mmol), tolyl-2,3,4-tri-*O*-benzyl-1-thio-β-D-glucopyranoside **146** (160 mg, 0.29 mmol) and lithium tetrafluoroborate (235 mg, 2.50 mmol), in acetonitrile (25 ml), were stirred for 4 h at a potential of +1.4 V. Flash column chromatography (ethyl acetate:petrol, 1:6) gave tolyl-2,3,4,6-tetra-*O*-benzyl-β-D-glucopyranosyl-(1→6)-2,3,4-tri-*O*-benzyl-1-thio-β-glucopyranoside **161** (15 mg, 9%) as a white crystalline solid, data consistent with that previously described.

At +1.4 V using 4 equivalents of the acceptor and with $LiBF_4$ as the electrolyte

Phenyl-2,3,4,6-tetra-*O*-benzyl-1-seleno-β-D-glucopyranoside **103** (100 mg, 0.15 mmol), tolyl-2,3,4-tri-*O*-benzyl-1-thio-β-D-glucopyranoside **146** (341 mg, 0.61 mmol) and lithium tetrafluoroborate (269 mg, 2.86 mmol), in acetonitrile (25 ml), were stirred for 8 h at a potential of +1.4 V. Flash column chromatography (ethyl acetate:petrol, 1:6) gave tolyl-2,3,4,6-tetra-*O*-benzyl-β-D-glucopyranosyl-(1→6)-2,3,4-tri-*O*-benzyl-1-thio-β-glucopyranoside **161** (19 mg, 12%) as a white crystalline solid, data consistent with that previously described.

At +1.5 V using 2 equivalents of the acceptor and with $LiBF_4$ as the electrolyte

Phenyl-2,3,4,6-tetra-*O*-benzyl-1-seleno-β-D-glucopyranoside **103** (95 mg, 0.14 mmol), tolyl-2,3,4-tri-*O*-benzyl-1-thio-β-D-glucopyranoside **146** (156 mg, 0.28 mmol) and lithium tetrafluoroborate (269 mg, 2.72 mmol), in acetonitrile (25 ml), were stirred for 8 h at a potential

of +1.5 V. Flash column chromatography (ethyl acetate:petrol, 1:6) gave tolyl-2,3,4,6-tetra-*O*-benzyl-β-D-glucopyranosyl-(1→6)-2,3,4-tri-*O*-benzyl-1-thio-β-glucopyranoside **161** (24 mg, 16%) as a white crystalline solid, data consistent with that previously described.

At +1.6 V using 1 equivalent of the acceptor and with $LiBF_4$ as the electrolyte

Phenyl-2,3,4,6-tetra-*O*-benzyl-1-seleno-β-D-glucopyranoside **103** (200 mg, 0.15 mmol), tolyl-2,3,4-tri-*O*-benzyl-1-thio-β-D-glucopyranoside **146** (164 mg, 0.29 mmol) and lithium tetrafluoroborate (234 mg, 2.50 mmol), in acetonitrile (25 ml), were stirred for 6 h at a potential of +1.6 V. Flash column chromatography (ethyl acetate:petrol, 1:6) gave tolyl-2,3,4,6-tetra-*O*-benzyl-β-D-glucopyranosyl-(1→6)-2,3,4-tri-*O*-benzyl-1-thio-β-glucopyranoside **161** (57 mg, 18%) as a white crystalline solid, data consistent with that previously described.

At +1.4 V, using 0.5 equivalents of the acceptor and with TBAP as the electrolyte

Phenyl-2,3,4,6-tetra-*O*-benzyl-1-seleno-β-D-glucopyranoside **103** (100 mg, 0.15 mmol), tolyl-2,3,4-tri-*O*-benzyl-1-thio-β-D-glucopyranoside **146** (41 mg, 0.07 mmol) and tetrabutylammonium perchlorate (855 mg, 2.50 mmol), in acetonitrile (25 ml), were stirred for 6 h at a potential of +1.4 V. Flash column chromatography (ethyl acetate:petrol, 1:6) gave tolyl-2,3,4,6-tetra-*O*-benzyl-β-D-glucopyranosyl-(1→6)-2,3,4-tri-*O*-benzyl-1-thio-β-glucopyranoside **161** (15 mg, 19%) as a white crystalline solid, data consistent with that previously described.

At +1.4 V, using 1 equivalent of the acceptor and with TBAP as the electrolyte

Phenyl-2,3,4,6-tetra-*O*-benzyl-1-seleno-β-D-glucopyranoside **103** (100 mg, 0.15 mmol), tolyl-2,3,4-tri-*O*-benzyl-1-thio-β-D-glucopyranoside **146** (85 mg, 0.15 mmol) and tetrabutylammonium perchlorate (855 mg, 2.50 mmol), in acetonitrile (25 ml), were stirred for 8 h at a potential of +1.4 V. Flash column chromatography (ethyl acetate:petrol, 1:6) gave tolyl-2,3,4,6-tetra-*O*-benzyl-β-D-glucopyranosyl-(1→6)-2,3,4-tri-*O*-benzyl-1-thio-β-glucopyranoside **161** (21 mg, 13%) as a white crystalline solid, data consistent with that previously described.

At +1.5 V, using 2 equivalents of the acceptor and with TBAP as the electrolyte

Phenyl-2,3,4,6-tetra-*O*-benzyl-1-seleno-β-D-glucopyranoside **103** (97 mg, 0.14 mmol), tolyl-2,3,4-tri-*O*-benzyl-1-thio-β-D-glucopyranoside **146** (164 mg, 0.29 mmol) and tetrabutylammonium perchlorate (870 mg, 2.54 mmol), in acetonitrile (25 ml), were stirred for 6 h at a potential of +1.5 V. Flash column chromatography (ethyl acetate:petrol, 1:4) gave tolyl-2,3,4,6-tetra-*O*-benzyl-β-D-glucopyranosyl-(1→6)-2,3,4-tri-*O*-benzyl-1-thio-β-glucopyranoside **161** (34 mg, 22%) as a white crystalline solid, data consistent with that previously described.

At +1.5 V, using 10 equivalents of the acceptor and with TBAP as the electrolyte

Phenyl-2,3,4,6-tetra-*O*-benzyl-1-seleno-β-D-glucopyranoside **103** (116 mg, 0.17 mmol), tolyl-2,3,4-tri-*O*-benzyl-1-thio-β-D-glucopyranoside **146** (837 mg, 1.50 mmol) and

tetrabutylammonium perchlorate (855 mg, 2.50 mmol), in acetonitrile (25 ml), were stirred for 12 h at a potential of +1.5 V. Flash column chromatography (ethyl acetate:petrol, 1:4) gave tolyl-2,3,4,6-tetra-*O*-benzyl-β-D-glucopyranosyl-(1→6)-2,3,4-tri-*O*-benzyl-1-thio-β-glucopyranoside **161** (49 mg, 27%) as a white crystalline solid, data consistent with that previously described.

At +1.6 V, using 2 equivalents of the acceptor and with TBAP as the electrolyte

Phenyl-2,3,4,6-tetra-*O*-benzyl-1-seleno-β-D-glucopyranoside **103** (102 mg, 0.15 mmol), tolyl-2,3,4-tri-*O*-benzyl-1-thio-β-D-glucopyranoside **146** (170 mg, 0.31 mmol) and tetrabutylammonium perchlorate (842 mg, 2.46 mmol), in acetonitrile (25 ml), were stirred for 8 h at a potential of +1.6 V. Flash column chromatography (ethyl acetate:petrol, 1:6) gave tolyl-2,3,4,6-tetra-*O*-benzyl-β-D-glucopyranosyl-(1→6)-2,3,4-tri-*O*-benzyl-1-thio-β-glucopyranoside **161** (41 mg, 25%) as a white crystalline solid, data consistent with that previously described.

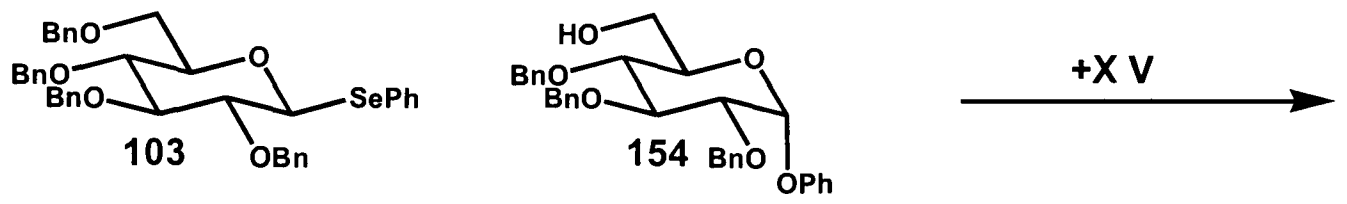
At +1.7 V, using 1 equivalen of the acceptor and with TBAP as the electrolyte

Phenyl-2,3,4,6-tetra-*O*-benzyl-1-seleno-β-D-glucopyranoside **103** (297 mg, 0.44 mmol), tolyl-2,3,4-tri-*O*-benzyl-1-thio-β-D-glucopyranoside **146** (245 mg, 0.44 mmol) and tetrabutylammonium perchlorate (870 mg, 2.54 mmol), in acetonitrile (25 ml), were stirred for 8 h at a potential of +1.7 V. Flash column chromatography (ethyl acetate:petrol, 1:6) gave tolyl-2,3,4,6-tetra-*O*-benzyl-β-D-glucopyranosyl-(1→6)-2,3,4-tri-*O*-benzyl-1-thio-β-glucopyranoside **161** (146 mg, 31%) as a white crystalline solid, data consistent with that previously described.

At +1.7 V, using 2 equivalents of the acceptor and with TBAP as the electrolyte

Phenyl-2,3,4,6-tetra-*O*-benzyl-1-seleno-β-D-glucopyranoside **103** (100 mg, 0.15 mmol), tolyl-2,3,4-tri-*O*-benzyl-1-thio-β-D-glucopyranoside **146** (167 mg, 0.30 mmol) and tetrabutylammonium perchlorate (872 mg, 2.55 mmol), in acetonitrile (25 ml), were stirred for 8 h at a potential of +1.7 V. Flash column chromatography (ethyl acetate:petrol, 1:5) gave tolyl-2,3,4,6-tetra-*O*-benzyl-β-D-glucopyranosyl-(1→6)-2,3,4-tri-*O*-benzyl-1-thio-β-glucopyranoside **161** (60 mg, 35%) as a white crystalline solid, data consistent with that previously described.

Activation of phenyl 2,3,4,6 tetra-*O*-benzyl-1-seleno-β-D-glucopyranoside 103 with phenyl-2,3,4-tri-*O*-benzyl-α-D-glucopyranoside 154 as the glycosyl acceptor

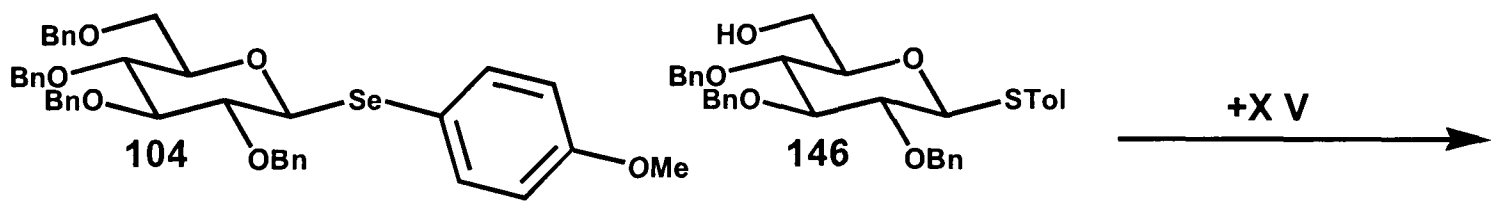


At +1.7 V

Phenyl-2,3,4,6-tetra-*O*-benzyl-1-seleno-β-D-glucopyranoside **103** (100 mg, 0.15 mmol), phenyl-2,3,4-tri-*O*-benzyl-α-D-glucopyranoside **154** (150 mg, 0.28 mmol) and tetrabutylammonium perchlorate (855 mg, 2.50 mmol), in acetonitrile (25 ml), were stirred for 1 h at a potential of +1.7 V. Flash column chromatography (ethyl acetate:petrol, 1:4) gave phenyl-2,3,4,6-tetra-*O*-benzyl-β-D-glucopyranosyl-(1→6)-2,3,4-tri-*O*-benzyl-α-glucopyranoside **162** (122 mg, 79%) as a white crystalline solid, m.p. 105-106 °C (petrol/ethyl

acetate); $[\alpha]_D^{24}$ +19 (*c*, 0.5 in $CHCl_3$); ν_{max}(KBr disk)/cm^{-1} no significant peaks; δ_H (400 MHz, $CDCl_3$) 3.41-3.44 (1H, m, H-5_b), 3.51 (1H, at, *J* 8.5 Hz, H-2_b), 3.57 (1H, at, *J* 9.1 Hz, H-4_b), 3.62-3.77 (6H, m, H-3_b, H-6_b, H-$6'_b$, H-2_a, H-4_a, H-6_a), 3.96-3.98 (1H, m, H-5_a), 4.15 (1H, dd, $J_{5,6'}$ 1.5 Hz, $J_{6,6'}$ 10.9 Hz, H-$6'_a$) 4.25 (1H, at, *J* 9.3 Hz, H-3_a), 4.31 (1H, d, $J_{1,2}$ 8.1 Hz, H-1_b), 4.32-5.08 (14H, m, PhC$\underline{H}_2$), 5.51 (1H, d, $J_{1,2}$ 3.3 Hz, H-1_a), 6.99-7.38 (40H, m, ArH); δ_C (100.6 MHz, $CDCl_3$) 68.1, 68.9 (2 x t, C-6_a, C-6_b), 70.5, 75.1, 77.6, 77.9, 79.6, 81.8, 81.9, 84.8 (8 x d, C-2_a, C-2_b, C-3°, C-3_b, C-4_a, C-4_b, C-5_a, C-5_b), 73.3, 73.4, 75.0, 75.7 (4 x d, 7 x Ph$\underline{C}H_2$), 95.4 (d, C-1_a), 103.6 (d, C-1_b), 116.9, 122.3, 127.5, 127.6, 127.7, 127.8, 127.9, 128.0, 128.3, 128.4, 128.5, 129.4 (12 x d, ArCH), 138.0, 138.1, 138.2, 138.3, 138.4, 138.5, 138.9, 156.7 (8 x s, ArC); *m/z* (ES^+) 1066.4 ($M+NH_4^+$, 100%), 1067.5 (75), 1068.5 (21), 1069.5 (6). (Found: C, 76.68; H, 6.52. $C_{67}H_{68}O_{11}$ requires C, 76.69; H, 6.53%).

Activation of *p*-methoxyphenyl-2,3,4,6-tetra-*O*-benzyl-1-seleno-β-D-glucopyranoside 104 with tolyl-2,3,4-tri-*O*-benzyl-1-thio-β-D-glucopyranoside 146 as the glycosyl acceptor



At +1.3 V

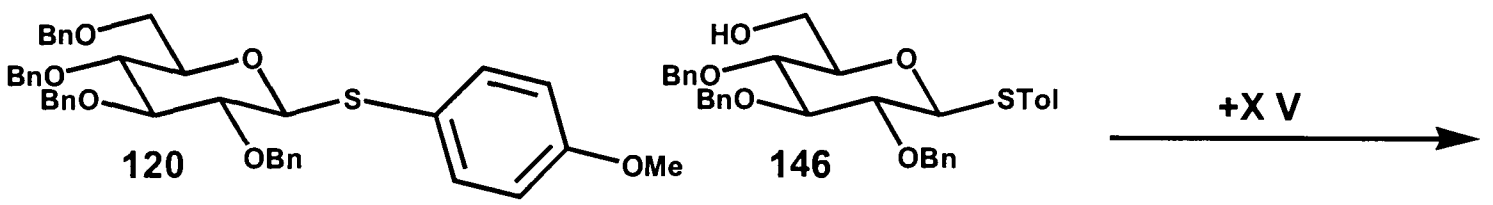
p-Methoxyphenyl-2,3,4,6-tetra-*O*-benzyl-1-seleno-β-D-glucopyranoside **104** (105 mg, 0.15 mmol), tolyl-2,3,4-tri-*O*-benzyl-1-thio-β-D-glucopyranoside **146** (85 mg, 0.33 mmol) and tetrabutylammonium perchlorate (855 mg, 2.50 mmol), in acetonitrile (25 ml), were stirred for

8 h at a potential of +1.3 V. Flash column chromatography (ethyl acetate:petrol, 1:6) gave tolyl-2,3,4,6-tetra-*O*-benzyl-β-D-glucopyranosyl-(1→6)-2,3,4-tri-*O*-benzyl-1-thio-β-glucopyranoside **161** (35 mg, 22%) as a white crystalline solid, data consistent with that previously described.

At +1.5 V

p-Methoxyphenyl-2,3,4,6-tetra-*O*-benzyl-1-seleno-β-D-glucopyranoside **104** (98 mg, 0.14 mmol), tolyl-2,3,4-tri-*O*-benzyl-1-thio-β-D-glucopyranoside **146** (90 mg, 0.35 mmol) and tetrabutylammonium perchlorate (855 mg, 2.50 mmol), in acetonitrile (25 ml), were stirred for 8 h at a potential of +1.5 V. Flash column chromatography (ethyl acetate:petrol, 1:6) gave tolyl-2,3,4,6-tetra-*O*-benzyl-β-D-glucopyranosyl-(1→6)-2,3,4-tri-*O*-benzyl-1-thio-β-glucopyranoside **161** (39 mg, 26%) as a white crystalline solid, data consistent with that previously described.

Activation of *p*-methoxyphenyl-2,3,4,6-tetra-*O*-benzyl-1-thio-β-D-glucopyranoside 120 with tolyl-2,3,4-tri-*O*-benzyl-1-thio-β-D-glucopyranoside 146 as the glycosyl acceptor



At +1.5 V

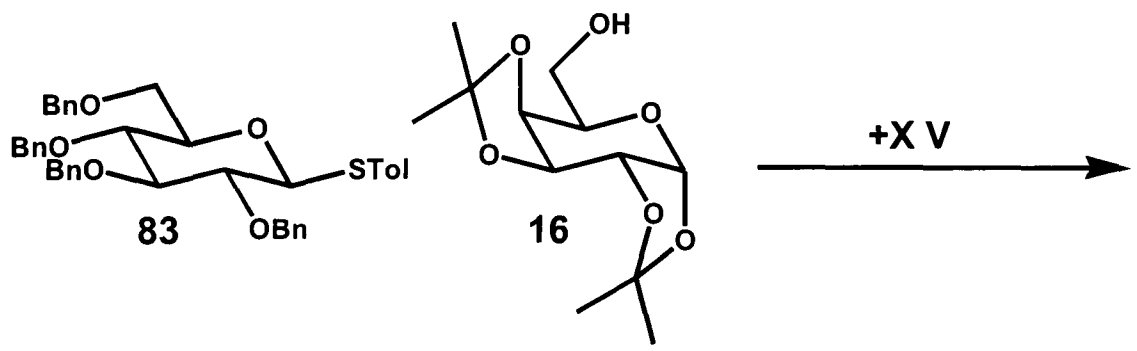
p-Methoxyphenyl-2,3,4,6-tetra-*O*-benzyl-1-thio-β-D-glucopyranoside **120** (100 mg, 0.15 mmol), tolyl-2,3,4-tri-*O*-benzyl-1-thio-β-D-glucopyranoside **146** (78 mg, 0.30 mmol) and

tetrabutylammonium perchlorate (855 mg, 2.50 mmol), in acetonitrile (25 ml), were stirred for 8 h at a potential of +1.5 V. Flash column chromatography (ethyl acetate:petrol, 1:6) gave tolyl-2,3,4,6-tetra-*O*-benzyl-β-D-glucopyranosyl-(1→6)-2,3,4-tri-*O*-benzyl-1-thio-β-glucopyranoside **161** (40 mg, 25%) as a white crystalline solid, data consistent with that previously described.

At +1.7 V

p-Methoxyphenyl-2,3,4,6-tetra-*O*-benzyl-1-seleno-β-D-glucopyranoside **120** (100 mg, 0.15 mmol), tolyl-2,3,4-tri-*O*-benzyl-1-thio-β-D-glucopyranoside **146** (85 mg, 0.33 mmol) and tetrabutylammonium perchlorate (840 mg, 2.46 mmol), in acetonitrile (25 ml), were stirred for 8 h at a potential of +1.7 V. Flash column chromatography (ethyl acetate:petrol, 1:6) gave tolyl-2,3,4,6-tetra-*O*-benzyl-β-D-glucopyranosyl-(1→6)-2,3,4-tri-*O*-benzyl-1-thio-β-glucopyranoside **161** (36 mg, 22%) as a white crystalline solid, data consistent with that previously described.

Activation of phenyl-2,3,4,6-tetra-*O*-benzyl-1-thio-β-D-glucopyranoside 83 with 1,2:3,4-di-*O*-isopropylidene-α-galactopyranoside 16 as the glycosyl acceptor



At +1.7 V

Tolyl-2,3,4,6-tetra-*O*-benzyl-1-thio-β-D-glucopyranoside **83** (100 mg, 0.15 mmol), 1,2:3,4-di-*O*-isopropylidene-α-galactopyranoside **16** (100 mg, 0.38 mmol) and tetrabutylammonium

perchlorate (855 mg, 2.5 mmol), in acetonitrile (25 ml), were stirred for 2.5 h at a potential of +1.7 V. Flash column chromatography (ethyl acetate:petrol, 1:4) gave recovered starting material: tolyl-2,3,4,6-tetra-*O*-benzyl-1-thio-β-D-glucopyranoside **83** (93 mg, 93%) as a white crystalline solid, m.p. 77-78 °C (ethanol) (lit.,[9] 80-81 °C); $[\alpha]_D^{25}$ -1.8 (*c*, 1.0 in $CHCl_3$) (lit.,[9] $[\alpha]_D^{21}$ +2 (*c*, 1.0 in $CHCl_3$)); δ_H (400 MHz, $CDCl_3$) 2.33 (3H, s, PhC$\underline{H}_3$), 3.48-3.53 (2H, m, H-2, H-5), 3.66 (1H, at, *J* 9.5 Hz, H-3), 3.72 (1H, at, *J* 8.9 Hz, H-4), 3.75 (1H, dd, $J_{5,6}$ 4.8 Hz, $J_{6,6'}$ 11.0Hz, H-6), 3.81 (1H,dd, $J_{5,6'}$ 1.7 Hz, H-6'), 4.56, 4.63 (2H, ABq, J_{AB} 12.0 Hz, PhC$\underline{H}_2$), 4.61, 4.92 (2H, ABq, J_{AB} 11.0 Hz, PhC$\underline{H}_2$), 4.63 (1H, s, $J_{1,2}$ 10.2 Hz, H-1), 4.75, 4.85 (2H, ABq, J_{AB} 10.7 Hz, PhC$\underline{H}_2$), 4.87, 4.90 (2H, ABq, J_{AB} 10.2 Hz, PhC$\underline{H}_2$), 7.05-7.53 (24H, m, ArH); and 2,3,4,6-tetra-*O*-benzyl-β-D-glucopyranosyl-(1→6)-1,2:3,4-di-*O*-isopropylidene-α-galactopyranoside **156** (6 mg, 5%).as a colourless oil; data consistent with that previously described.

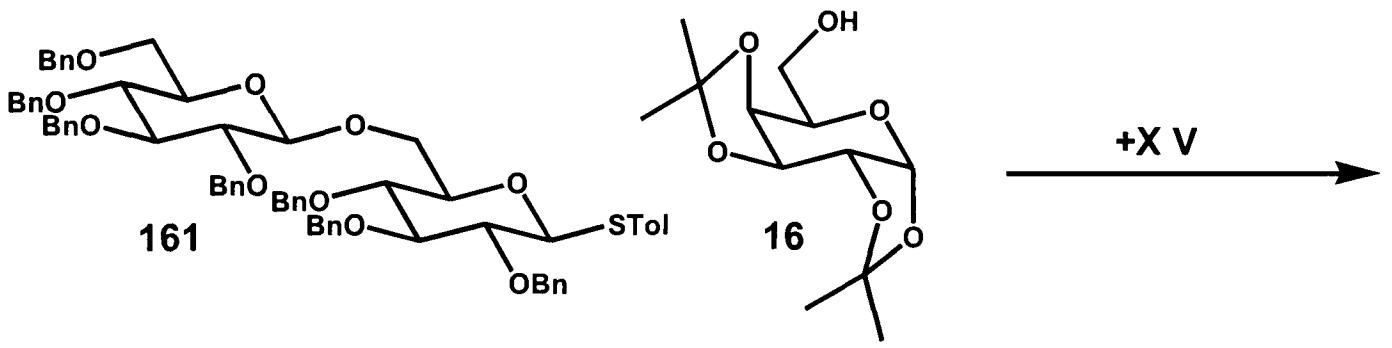
At +1.7 V in the presence of PhSeSePh

Tolyl-2,3,4,6-tetra-*O*-benzyl-1-thio-β-D-glucopyranoside **83** (105 mg, 0.16 mmol), 1,2:3,4-di-*O*-isopropylidene-α-galactopyranoside **16** (83 mg, 0.32 mmol), diphenyl diselenide (24 mg, 0.08 mmol) and tetrabutylammonium perchlorate (873 mg, 2.6 mmol), in acetonitrile (25 ml), were stirred for 2.5 h at a potential of +1.7 V. Flash column chromatography (ethyl acetate:petrol, 1:7) gave recovered starting material: phenyl 2,3,4,6 tetra-*O*-benzyl-1-thio-β-D-glucopyranoside **83** (50 mg, 48%) as a white crystalline solid; data consistent with that previously described; and 2,3,4,6-tetra-*O*-benzyl-β-D-glucopyranosyl-(1→6)-1,2:3,4-di-*O*-isopropylidene-α-galactopyranoside **156** (63 mg, 50%) as a colourless oil; data consistent with that previously described.

At +1.8 V

Tolyl-2,3,4,6-tetra-*O*-benzyl-1-thio-β-D-glucopyranoside **83** (100 mg, 0.15 mmol), 1,2:3,4-di-*O*-isopropylidene-α-galactopyranoside **16** (83 mg, 0.32 mmol) and tetrabutylammonium perchlorate (872 mg, 2.55 mmol), in acetonitrile (25 ml), were stirred for 6 h at a potential of +1.8 V. Flash column chromatography (ethyl acetate:petrol, 1:4) gave 2,3,4,6-tetra-*O*-benzyl-β-D-glucopyranosyl-(1→6)-1,2:3,4-di-*O*-isopropylidene-α-galactopyranoside **156** (98 mg, 81%) as a colourless oil; data consistent with that previously described.

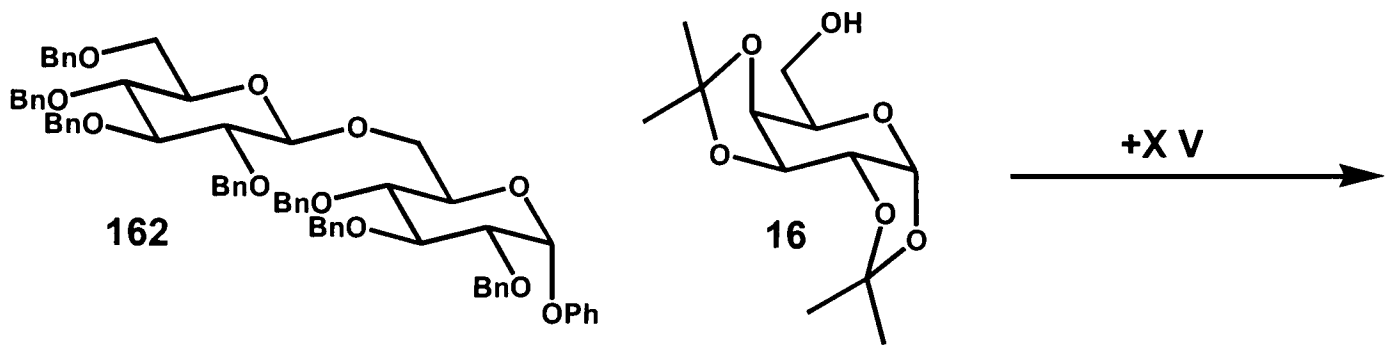
Activation of tolyl-2,3,4,6-tetra-*O*-benzyl-β-D-glucopyranosyl-(1→6)-2,3,4-tri-*O*-benzyl-1-thio-β-glucopyranoside 161 with 1,2:3,4-di-*O*-isopropylidene-α-galactopyranoside 16 as the glycosyl acceptor



Tolyl-2,3,4,6-tetra-*O*-benzyl-β-D-glucopyranosyl-(1→6)-2,3,4-tri-*O*-benzyl-1-thio-β-glucopyranoside **161** (120 mg, 0.11 mmol), 1,2:3,4-di-*O*-isopropylidene-α-galactopyranoside **16** (64 mg, 0.25 mmol) and tetrabutylammonium perchlorate (955 mg, 2.79 mmol), in acetonitrile (25 ml), were stirred for 2.5 h at a potential of +2.0 V. Flash column chromatography (ethyl acetate:petrol, 1:4) gave 2,3,4,6-tetra-*O*-benzyl-β-D-glucopyranosyl-(1→6)-2,3,4-tetra-*O*-benzyl-β-D-glucopyranosyl-(1→6)-1,2:3,4-di-*O*-isopropylidene-α-

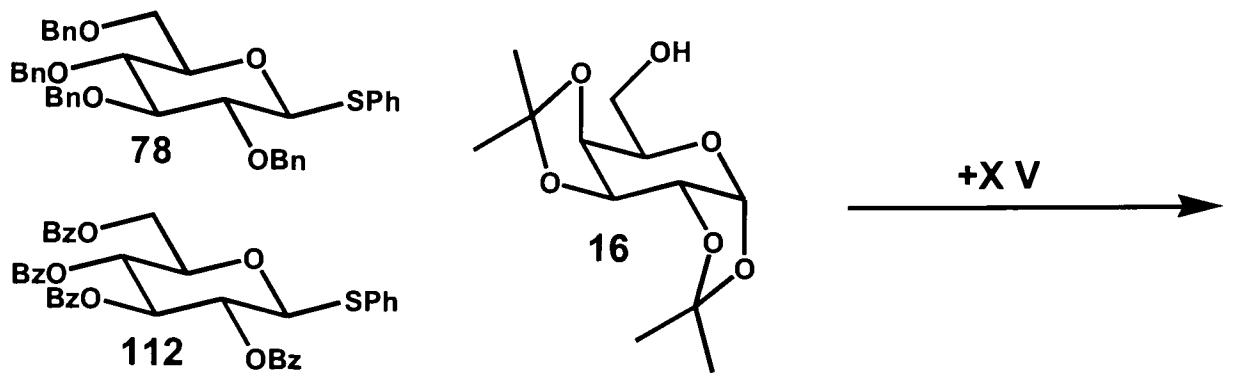
galactopyranoside **168** (107 mg, 79%) as a white crystalline solid, m.p. 137-139 °C (ethyl acetate/petrol); $[\alpha]_D^{22}$ -4.6 (*c*, 1.0 in $CHCl_3$); ν_{max}(KBr disk)/cm^{-1} no significant peaks; δ_H (500 MHz, $CDCl_3$) 1.27, 1.35, 1.43, 1.55 (4 x 3H, 4 x s, 4 x CH_3), 3.46-3.55 (4H, m, H-2_a, H-2_b, H-4_b, H-5_a), 3.58-3.61 (1H, m, H-5_b), 3.62-3.78 (7H, m, H-3_a, H-3_b, H-4_a, H-6_a, H-6_b, H6_c, H-6'$_a$), 4.04-4.08 (2H, m, H-4_c, H-5_c), 4.14 (1H, dd, $J_{5,6}$ 3.1 Hz, $J_{6,6'}$ 10.9 Hz, H-6'$_c$), 4.25 (1H, dd, $J_{5,6}$ 1.3 Hz, $J_{6,6'}$ 11.1 Hz, H-6'$_b$), 4.33 (1H, dd, $J_{1,2}$ 4.7 Hz, $J_{2,3}$ 2.5 Hz, H-2_c), 4.46 (1H, d, $J_{1,2}$ 7.9 Hz, H-1_a), 4.48 (1H, d, $J_{1,2}$ 7.6 Hz, H-1_b), 4.55-4.59 (3H, m, H-3_c, 2 x PhC<u>H</u>H'), 4.59, 4.66 (2H, ABq, J_{AB} 12.3 Hz, PhC<u>H</u>$_2$), 4.75-4.83 (5H, m, 4 x PhC<u>H</u>H', PhCH<u>H</u>'), 4.86 (1H, d, J_{AB} 11.1 Hz, PhCH<u>H</u>'), 4.96 (1H, d, J_{AB} 11.2 Hz, PhCH<u>H</u>'), 5.01 (1H, d, J_{AB} 11.0 Hz, PhCH<u>H</u>'), 5.04 (1H, d, J_{AB} 11.2 Hz, PhCH<u>H</u>'), 5.11 (1H, d, J_{AB} 11.3 Hz, PhCH<u>H</u>'), 5.59 (1H, d, $J_{1,2}$ 4.7 Hz, H-1_c), 7.21-7.48 (35H, m, ArH); δ_C (125.7 MHz, $CDCl_3$) 24.2, 24.9, 25.8, 26.0 (4 x q, 4 x CH_3), 67.3 (d, C-5_c), 68.6, 68.8, 69.8 (3 x t, C-6_a, C-6_b, C-6_c), 70.4, 70.6, 71.2 (3 x d, C-2_c, C-3_c, C-4_c), 73.4, 74.1, 74.5, 74.7, 74.9, 75.4, 75.6 (2 x d, 5 x t, C-5_a, C-5_b, 7 x Ph<u>C</u>H$_2$), 77.1, 77.7 (2 x d, C-4_a, C-4_b), 81.4, 81.8 (2 x d, C-2_a, C-2_b), 84.4, 84.7 (2 x d, C-3_a, C-3_b), 96.2 (d, C-1_c), 103.8 (d, C-1_a), 104.3 (d, C-1_b), 108.4, 109.2 (2 x s, 2 x <u>C</u>$(CH_3)_2$), 127.3, 127.4, 127.5, 127.6, 127.7, 127.8, 128.1, 128.2, 128.5 (9 x d, 35 x ArCH), 138.1, 138.4, 138.5, 138.6 (4 x s, 7 x ArC); *m/z* (ESI) 1232 ($M+NH_4^+$, 100%), 1238 ($M+Na^+$, 57). (Isotope Distribution Calcd. ($M+NH_4^+$) 1232.59 (100%), 1233.60 (84), 1234.60 (37), 1235.60 (11). Found 1232.56 (100%), 1233.56 (76), 1234.59 (25), 1235.58 (6).

Attempted activation of phenyl-2,3,4,6-tetra-*O*-benzyl-β-D-glucopyranosyl-(1→6)-2,3,4-tri-*O*-benzyl-α-glucopyranoside 162 with 1,2:3,4-di-*O*-isopropylidene-α-galactopyranoside 16 as the glycosyl acceptor



Phenyl-2,3,4,6-tetra-*O*-benzyl-β-D-glucopyranosyl-(1→6)-2,3,4-tri-*O*-benzyl-α-glucopyranoside **162** (90 mg, 0.09 mmol), 2:3,4-di-*O*-isopropylidene-α-galactopyranoside **16** (45 mg, 0.18 mmol) and tetrabutylammonium perchlorate (850 mg, 2.49 mmol), in acetonitrile (25 ml), were stirred for 3 h at a potential of +3.0 V. Flash column chromatography (ethyl acetate:petrol, 1:4) gave only recovered starting material: phenyl-2,3,4,6-tetra-*O*-benzyl-β-D-glucopyranosyl-(1→6)-2,3,4-tri-*O*-benzyl-α-glucopyranoside **162** (80 mg, 88%) as a white crystalline solid; data consistent with with that previously described.

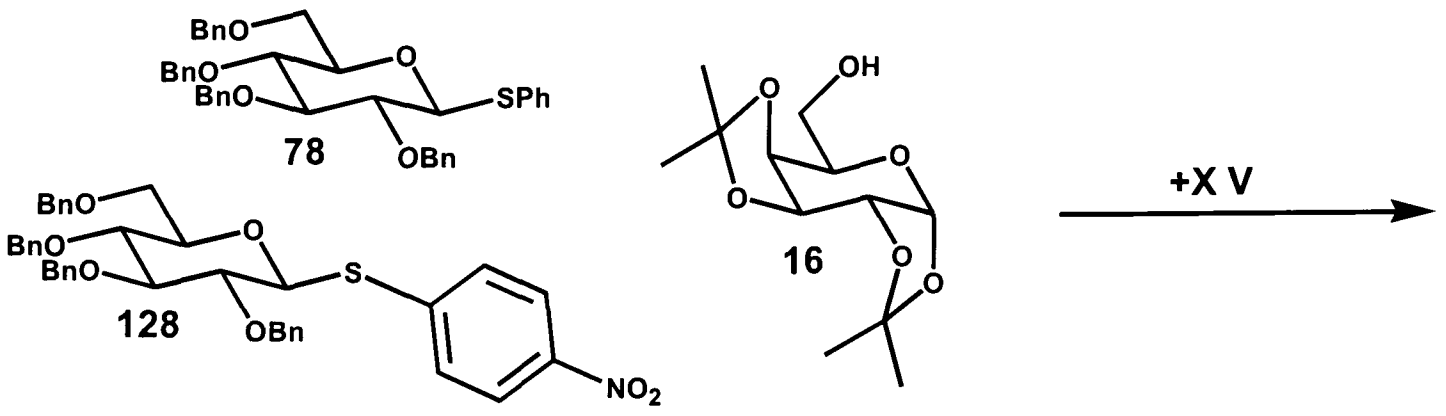
Activation of phenyl 2,3,4,6 tetra-*O*-benzyl-1-thio-β-D-glucopyranoside 78 and phenyl 2,3,4,6 tetra-*O*-benzoyl-1-thio-β-D-glucopyranoside 112 with 1,2:3,4-di-*O*-isopropylidene-α-galactopyranoside 16 as the glycosyl acceptor



At +1.8 V

Phenyl-2,3,4,6-tetra-*O*-benzyl-1-thio-β-D-glucopyranoside **78** (102 mg, 0.15 mmol), phenyl 2,3,4,6 tetra-*O*-benzoyl-1-thio-β-D-glucopyranoside **112** (110 mg, 0.16 mmol), 1,2:3,4-di-*O*-isopropylidene-α-galactopyranoside **16** (84 mg, 0.32 mmol) and tetrabutylammonium perchlorate (987 mg, 2.89 mmol), in acetonitrile (25 ml), were stirred for 17 h at a potential of +1.8 V. Flash column chromatography (ethyl acetate:petrol, 1:6) 2,3,4,6-tetra-*O*-benzyl-β-D-glucopyranosyl-(1→6)-1,2:3,4-di-*O*-isopropylidene-α-galactopyranoside **156** (104 mg, 41%) as a colourless oil; data consistent with that previously described.

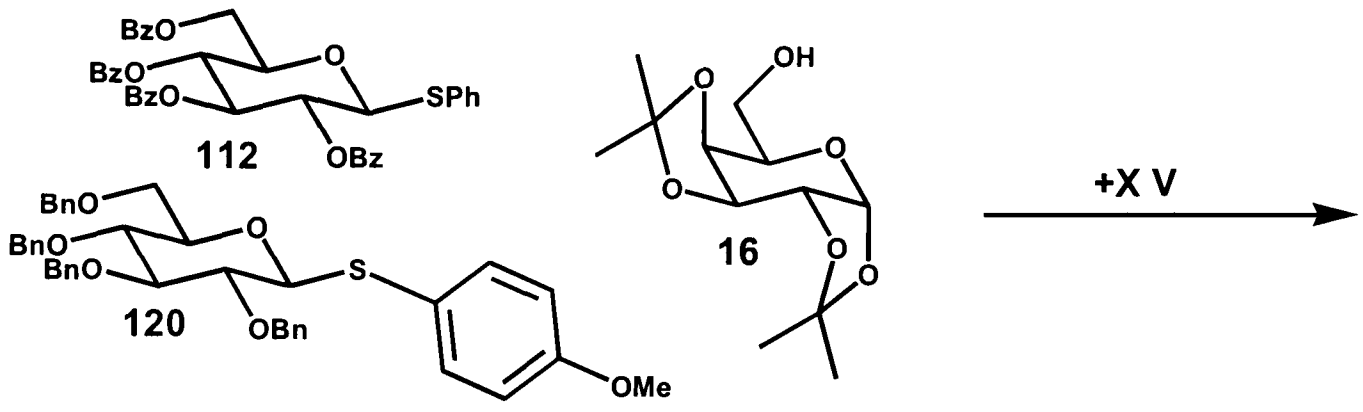
Activation of phenyl-2,3,4,6-tetra-*O*-benzyl-1-thio-β-D-glucopyranoside 78 and *p*-nitrophenyl-2,3,4,6-tetra-*O*-benzyl-1-thio-β-D-glucopyranoside 128 with 1,2:3,4-di-*O*-isopropylidene-α-galactopyranoside 16 as the glycosyl acceptor



At +1.8 V

Phenyl-2,3,4,6-tetra-*O*-benzyl-1-thio-β-D-glucopyranoside **78** (100 mg, 0.15 mmol), *p*-nitrophenyl-2,3,4,6-tetra-*O*-benzyl-1-thio-β-D-glucopyranoside **128** (101 mg, 0.15 mmol), 1,2:3,4-di-*O*-isopropylidene-α-galactopyranoside **16** (70 mg, 0.27 mmol) and tetrabutylammonium perchlorate (855 mg, 2.5 mmol), in acetonitrile (25 ml), were stirred for 17 h at a potential of +1.8 V. Flash column chromatography (ethyl acetate:petrol, 1:4) gave 2,3,4,6-tetra-*O*-benzyl-β-D-glucopyranosyl-(1→6)-1,2:3,4-di-*O*-isopropylidene-α-galactopyranoside **156** (150 mg, 71%) as a colourless oil; data consistent with that previously described.

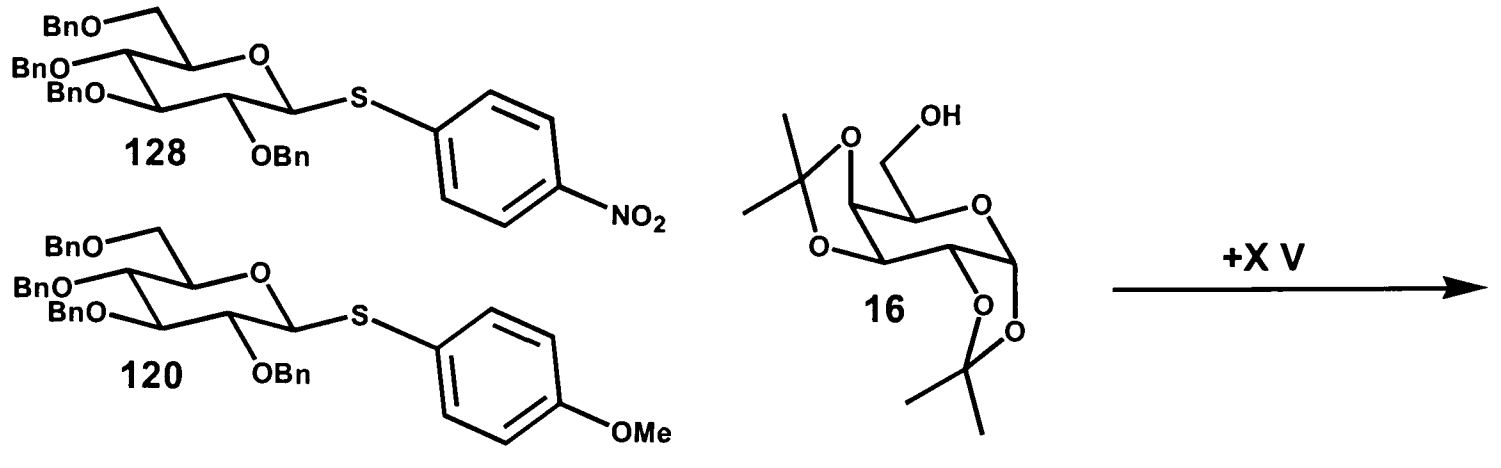
Activation of *p*-methoxyphenyl-2,3,4,6-tetra-*O*-benzyl-1-thio-β-D-glucopyranoside 120 and phenyl-2,3,4,6-tetra-*O*-benzoyl-1-thio-β-D-glucopyranoside 112 with 1,2:3,4-di-*O*-isopropylidene-α-galactopyranoside 16 as the glycosyl acceptor



At +1.5 V

p-Methoxyphenyl-2,3,4,6-tetra-*O*-benzyl-1-thio-β-D-glucopyranoside **120** (102 mg, 0.15 mmol), phenyl-2,3,4,6-tetra-*O*-benzoyl-1-thio-β-D-glucopyranoside **112** (173 mg, 0.25 mmol), 1,2:3,4-di-*O*-isopropylidene-α-galactopyranoside **16** (148 mg, 0.57 mmol) and tetrabutylammonium perchlorate (860 mg, 2.51 mmol), in acetonitrile (25 ml), were stirred for 17 h at a potential of +1.5 V. Flash column chromatography (ethyl acetate:petrol, 1:4) gave 2,3,4,6-tetra-*O*-benzyl-β-D-glucopyranosyl-(1→6)-1,2:3,4-di-*O*-isopropylidene-α-galactopyranoside **156** (43 mg, 36%) as a colourless oil; data consistent with that previously described.

Activation of *p*-methoxyphenyl-2,3,4,6-tetra-*O*-benzyl-1-thio-β-D-glucopyranoside120 and *p*-nitrophenyl-2,3,4,6-tetra-*O*-benzyl-1-thio-β-D-glucopyranoside 128 with 1,2:3,4-di-*O*-isopropylidene-α-galactopyranoside 16 as the glycosyl acceptor



At +1.5 V

p-Methoxyphenyl-2,3,4,6-tetra-*O*-benzyl-1-thio-β-D-glucopyranoside **120** (102 mg, 0.15 mmol), *p*-nitrophenyl-2,3,4,6-tetra-*O*-benzyl-1-thio-β-D-glucopyranoside **128** (100 mg, 0.15 mmol), 1,2:3,4-di-*O*-isopropylidene-α-galactopyranoside **16** (80 mg, 0.31 mmol) and tetrabutylammonium perchlorate (850 mg, 2.50 mmol), in acetonitrile (25 ml), were stirred for 17 h at a potential of +1.5 V. Flash column chromatography (ethyl acetate:petrol, 1:4) gave 2,3,4,6-tetra-*O*-benzyl-β-D-glucopyranosyl-(1→6)-1,2:3,4-di-*O*-isopropylidene-α-galactopyranoside **156** (155 mg, 64%) as a colourless oil; data consistent with that previously described.

5.4 References

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