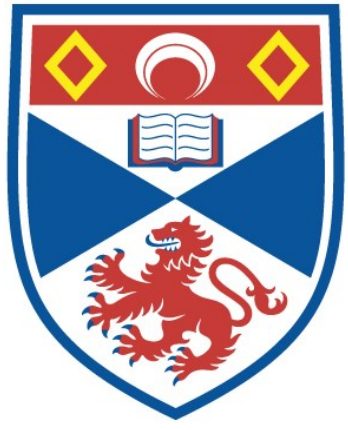
IODINE-PROMOTED ACTIVATION OF SULFUR-BASED LEAVING GROUPS IN GLYCOSYLATION REACTIONS

Steven J. Marsh

A Thesis Submitted for the Degree of PhD
at the
University of St Andrews



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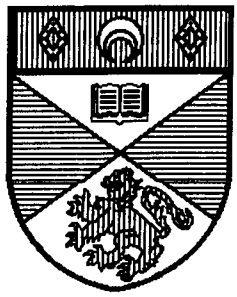

School of Chemistry
University of St Andrews

IODINE - PROMOTED ACTIVATION OF SULFUR-BASED LEAVING GROUPS IN GLYCOSYLATION REACTIONS

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September 2000

Steven J. Marsh

In 1983, my father, Tony Marsh, tried to begin an Open University course in Chemistry, but gave up when told that the disabilities he had suffered as a result of his treatment for cancer when he was 15 would prevent him from pursuing a career as a Chemist. The treatment that had saved his life finally caused a recurrence of his cancer three years later, and his death in July 1987.

Dad never had the opportunities to fulfill his talent in this subject that I have had. Shortly after his death, his brother Paul passed on to me an old Chemistry textbook which Dad had won as a prize at school. Reading this book helped to lay the foundations of my understanding of the subject, and my enthusiasm for it.

I dedicate this Thesis to Dad's memory. I think he would have been proud that I finished it.

DECLARATIONS

(i) I, Steven Jon Marsh, hereby certify that this thesis, which is approximately 42000 words in length, has been written by me, that it is the record of work carried out by me and that it has not been submitted in any previous appplication for a higher degree.

date 6/9/00 signature of candidate [redacted]

(ii) I was admitted as a research student in September 1996 and as a candidate for the degree of Doctor of Philosophy in September 1997; the higher study for which this is a record was carried out in the University of St Andrews between 1996 and 2000.

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(iii) I hereby certify that the candidate has fulfilled the conditions of the Resolution and Regulations appropriate for the degree of Doctor of Philosophy in the University of St Andrews and that the candidate is qualified to submit this thesis in application for that degree.

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ABSTRACT

Further to previous work by the Field group on the iodine-mediated activation of benzyl ether-protected ('armed') thiogalactosides, a variety of ester-protected ('disarmed') β-D-thiogalactoside derivatives containing a second sulfur atom in the aglycon were prepared and characterised, and activation of these with iodine was attempted. *O*-Ethyl *S*-(2,3,4,6-tetra-*O*-acetyl-β-D-thiogalactopyranosyl) dithiocarbonate (**26**) and *O*-isopropyl *S*-(2,3,4,6-tetra-*O*-acetyl-β-D-thiogalactopyranosyl) dithiocarbonate (**31**) were prepared and found not to undergo methanolysis in the presence of iodine, or iodine in combination with DDQ. Methylthiomethyl 2,3,4,6-tetra-*O*-acetyl-β-D-thiogalactopyranoside (**53**) and ethylthioalkyl 2,3,4,6-tetra-*O*-acetyl-β-D-thiogalactopyranosides **38-41** were prepared and found not to undergo iodine-mediated methanolysis. Of the mercaptoalkyl 2,3,4,6-tetra-*O*-acetyl-β-D-thiogalactosides **52-55**, mercaptopropyl 2,3,4,6-tetra-*O*-acetyl-β-D-thiogalactopyranoside (**53**) and mercaptobutyl 2,3,4,6-tetra-*O*-acetyl-β-D-thiogalactopyranoside (**54**) were found to glycoslate cyclohexanol, but with significant degradation observed by thin layer chromatography. Mercaptopropyl 2,3,4,6-tetra-*O*-benzoyl-β-D-thiogalactopyranoside (**64**) and mercaptobutyl 2,3,4,6-tetra-*O*-benzoyl-β-D-thiogalactopyranoside (**65**) were found to glycosylate cyclohexanol with no significant degradation. Carbohydrate acceptors methyl 2,3,4-tri-*O*-benzyl-α-D-mannopyranoside (**72**), methyl 2,3,4-tri-*O*-benzoyl-α-D-glucopyranoside (**73**), methyl 6-*O*-benzoyl-2,3-di-*O*-benzyl-β-D-galactopyranoside (**74**) and methyl 2,4,6-tri-*O*-benzoyl-β-D-galactopyranoside (**75**) were prepared. Upon attempts at iodine-mediated glycosylation of these with **64**, only the primary mannose acceptor **72** was glycosylated to a significant extent. An NMR study of the ^{1}H methylene resonances of ethylthiobutyl 2,3,4,6-tetra-*O*-acetyl-β-D-thiogalactopyranoside (**40**) showed that the remote sulfide group of this compound complexes significantly with iodine, whilst the anomeric sulfur does not.

It has also been demonstrated that 'armed' glycosyl sulfoxides can be activated with iodine or iodine monobromide. Ethyl 2,3,4,6-tetra-*O*-benzyl-α-D-thiomannopyranoside *S*-oxide (**114**) was prepared and found to give unusually high β-stereocontrol in iodine-

mediated mannosylation of acceptors **72**, **73** and **74**, as compared with excellent α-stereocontrol with acceptor **75**. Both the quantity and nucleophilicity of the glycosyl acceptors and the presence of potassium carbonate affected the speed of activation of the sulfoxides, and the anomeric stereocontrol in the products. It is proposed that reversible formation of the hypoiodites of the acceptors may be the reason for these observations.

ACKNOWLEDGEMENTS

I would like to thank the Professor Rob Field for his supervison, encouragement and patience during this project. Thanks are due to Dr Ravi Kartha (shortly to depart for the University of East Anglia) and Dr Hiroki Shimizu (now at the University of Leeds), for their patience and expert help in the laboratory. Mrs Melanja Smith and Dr Trevor Rutherford (now at University of Birmingham) have been most helpful with NMR data acquisition and processing, and I would like to extend sincere thanks to them also. I would also like to thank Mrs Sylvia Williamson for performing combustion microanalyses and Dr Catherine Botting for an amazingly efficient MALDI-TOF mass spectrometry service.

I am grateful for financial support by BBSRC and my parents during this project, and much indebted for the kind hospitality of Steve and Liz Holdsworth during the final stages of this project. I am forever indebted to my wife Maureen for her emotional support and encouragement while completing this thesis.

CONTENTS

ABBREVIATIONS USED WITHIN THE TEXT

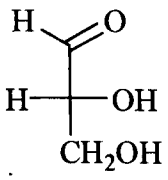
Ac	-	acetyl group, $CH_3C(O)$-
aq.	-	aqueous solution
Bn	-	benzyl group, $C_6H_5CH_2$-
Bz	-	benzoyl group, $C_6H_5C(O)$-
CAN	-	ceric ammonium nitrate
COSY	-	correlation spectroscopy
CSA	-	(1*R*)-(-)-10-camphorsulfonic acid
DCE	-	1,2-dichloroethane, $ClCH_2CH_2Cl$
DCM	-	dichloromethane, CH_2Cl_2
DMDO	-	3,3-dimethyldioxirane
DDQ	-	2,3-dichloro-5,6-dicyanobenzoquinone
DMF	-	N, N'-dimethylformamide
DMTST	-	dimethyl(methylthio)sulfonium triflate
DTBMP	-	2,3-di-*tert*-butyl-4-methylpyridine
Et	-	ethyl group, C_2H_5-
ether	-	diethyl ether, Et_2O
IDCP	-	iodonium dicollidine perchlorate
*i*Pr	-	isopropyl group, $(CH_3)_2CH$-
Me	-	methyl group, CH_3-
MSB	-	methylsulfenyl bromide
MST	-	methylsulfenyl triflate
NIS	-	*N*-iodosuccinimide
NMR	-	nuclear magnetic resonance
NOESY	-	nuclear Overhauser effect spectroscopy
Ph	-	phenyl group, C_6H_5-
PST	-	phenylsulfenyl triflate
Pv	-	pivaloyl group, $(CH_3)_3CC(O)$-
satd.	-	saturated
t.l.c.	-	thin layer chromatography
TBAHS	-	tetrabutylammonium hydrogensulfate
TBAI	-	tetrabutylammonium iodide
TBDMS-	-	*tert*-butyl dimethylsilyl group

*t*Bu	-	*tert*-butyl group, $(CH_3)_3C$-
TES-	-	triethylsilyl group
Tf-	-	trifluoromethanesulfonyl group (triflyl)
THF	-	tetrahydrofuran
TMS	-	tetramethylsilane
TMS-	-	trimethylsilyl group

1 INTRODUCTION

1.1 Oligosaccharides in biological systems

Carbohydrates are a major family of natural products that take their name from the basic chemical formula $C_x(H_2O)_y$, which many of the simplest examples possess. By convention, the term 'carbohydrate' encompasses monosaccharides, oligosaccharides, polysaccharides, and substances derived from monosaccharides by reduction of an aldehyde group, oxidation of a terminal hydroxyl to a carboxylic acid, or replacement of a hydroxyl by hydrogen, amino, thiol, or similar heteroatomic group.[1] The simplest examples are the aldoses containing three carbon atoms, namely D-glyceraldehyde **1** and L-glyceraldehyde **2**.



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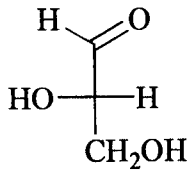

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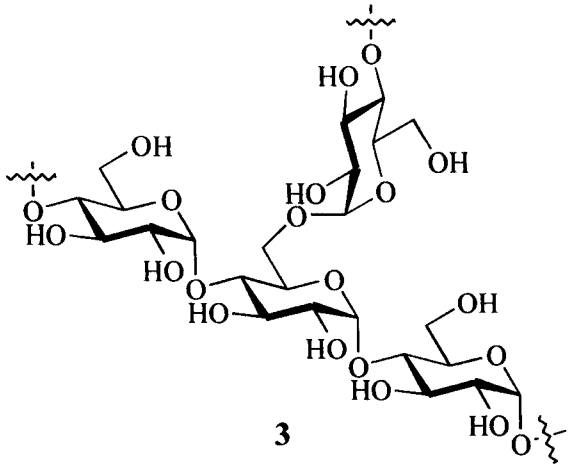
In nature, carbohydrates are generated initially by photosynthesis, and molecules such as amylopectin **3** play a vital role in the storage of energy for cellular functions. Both xylan **4**, and cellulose **5**, are of major structural importance within plants and are found particularly in their cell walls, whilst chitin **6** is present in insect and crustacean exoskeletons.[2]



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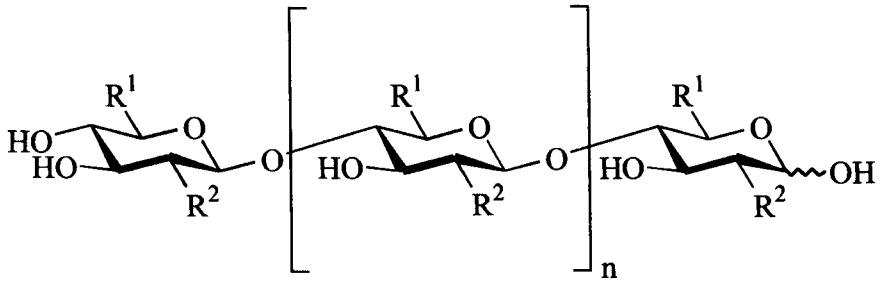


4 $R^1 = H$, $R^2 = OH$

5 $R^1 = CH_2OH$, $R^2 = OH$

6 $R^1 = CH_2OH$, $R^2 = NHAc$

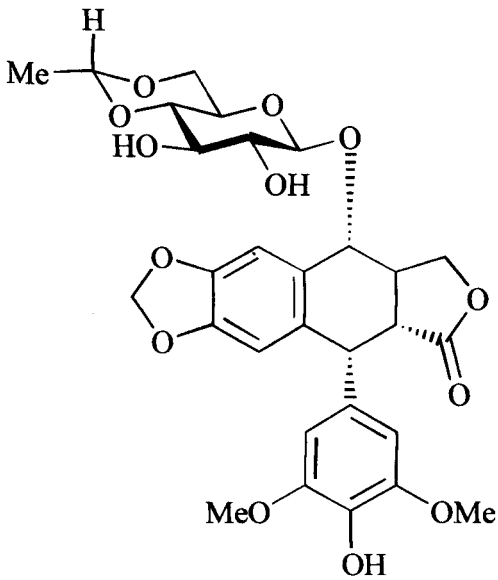
For many years these structural and energy storage roles of carbohydrates were regarded as their only real function in nature, but in recent years this perception has been challenged by the discovery that carbohydrates play key roles in many physiological processes such as cell-cell recognition and the immune response, fertilisation, embryogenesis, neuronal development, hormone activities, cell proliferation and specialisation, microbial infection, tumour metastasis and the inflammatory response.[2,3]

Complex carbohydrate structures are present on the surface of cells, as glycolipids, playing an important role in cell recognition, and thus in immune responses. Glycoproteins are proteins which incorporate carbohydrates in their structure, bound either to oxygen (*O*-linked) or nitrogen (*N*-linked) in amino acid side-chains. On the surface of proteins these may cause subtle changes in conformation of proteins which improve, or where necessary, retard their activities, or again they may have an important role in recognition, such as in blood-type determination.[4] Proteoglycans are composed of a protein and a high molecular weight polymeric carbohydrate component, known as a glycosyaminoglycan. Proteoglycans are structurally important in connective tissue, and the ability of the glycosylaminoglycans to bind to a number of proteins enables them to play a role in many functions such as blood clotting, angiogenesis and gene expression.[3]

The discovery of so many roles for glycoconjugates in biological systems has led to a belief that these may provide new targets for therapeutic intervention.[2] The potential advantages of carbohydrate-based drugs lie in their probable low toxicity and

immunogenicity compared to peptide-based molecules, and the resultant resurgence in carbohydrate chemistry has led to the development of carbohydrate-based chemotherapeutic agents for use in the treatment of conditions such as diabetes, tissue regeneration and epilepsy,[2] and as bacterial vaccines, cancer vaccines and inhibitors of pathenogenic microbes and their toxins.[5]

Carbohydrates bound to dervivatives of known biologically active compounds have also found use in moderating their activity. For example etoposide **7**, based on the powerful cytotoxin podophyllotoxin **8**, contains a β-glucose unit, and has been widely used since the mid-1980s in the treatment of small cell cancers of the lungs and testes.[6,7]



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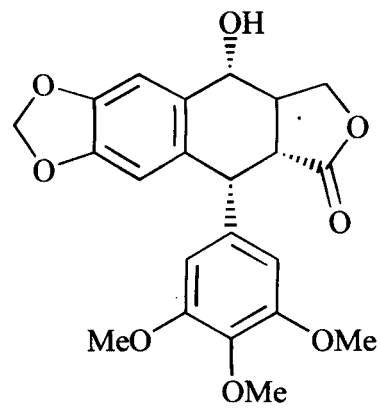

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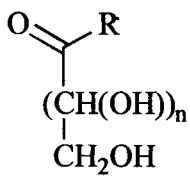
A true evaluation of the roles of carbohydrate containing materials requires an ability to produce in the laboratory not only the naturally occurring structures, but also carbohydrate-based lead compounds in the search for pharmacologically active agents, in reasonable quantities and purity. This is a major problem, as the syntheses are multi-step, expensive, often require low temperatures and harsh or toxic reagents, and synthesis yields can be very poor. There has thus been renewed activity not just in drug development based around carbohydrates, but in the methodology required to synthesise oligosaccharides. The sections that follow outline some of the key principles of

carbohydrate chemistry, as applied to the synthesis of naturally occurring oligosaccharides and glycoconjugates.

1.2 Monosaccharides[1,8]

1.2.1 Acyclic monosaccharides

The building blocks of carbohydrates are termed *monosaccharides*. Monosaccharides can be defined as the smallest units a carbohydrate can be broken down into by hydrolysis, which are still identifiable as carbohydrates. The simplest examples are based upon straight-chain carbon skeletons, possessing a single carbonyl group with all other carbon atoms monohydroxylated (Figure 1). Monosaccharides possessing an aldehyde functionality (i.e. the carbonyl group is terminal) are defined as *aldoses*, and those possessing a ketone functionality (i.e. the carbonyl group is positioned at a non-terminal position along the carbon skeleton), are defined as *ketoses*.



aldoses : R=H
ketoses : R=$(CH(OH))_nCH_2OH$

Figure 1 : Acyclic monosaccharides - general formula

Each non-terminal hydroxylated carbon atom is a stereogenic centre, which means that for any given straight-chain connectivity there will be a number of corresponding stereoisomers. By convention, where monosaccharides can be grouped in enantiomeric pairs, the enantiomers are denoted as D- or L- sugars depending upon whether or not the configuration of the first hydroxymethine group along the carbon skeleton from the terminal hydroxymethyl group matches that of D- or L-glyceraldehyde, respectively. The D-enantiomers of the aldotetroses, pentoses and hexoses are shown in Appendix 1.

1.2.2 Cyclisation of monosaccharides

The presence of a carbonyl functionality and multiple alcohol functionalities in carbon chains of more than three atoms in length gives rise to the possibility of an

intramolecular reaction to form a cyclic hemiacetal or, in the case of ketoses, a cyclic hemiketal. In general the rings so formed tend to be either five- or six-membered (Figure 2).

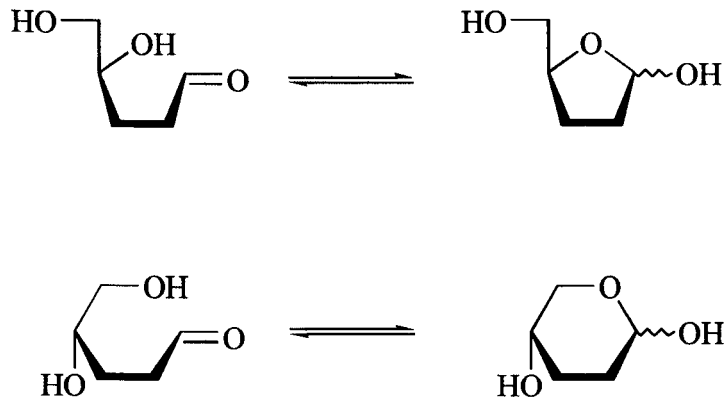


Figure 2 : Cyclisation of hydroxycarbonyl compounds

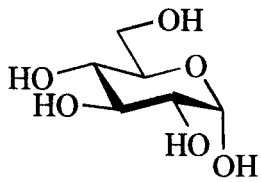
By convention, where a monosaccharide is able to cyclise to give either a five- or six-membered ring system, the two are distinguished by terming them *furanoses* or *pyranoses*, after the heterocyclic compounds furan **9** and pyran **10** respectively.

9 **10**

1.2.2.1 *Stereochemical consequences of cyclisation*

If the carbonyl group involved in cyclisation of hydroxycarbonyl compounds is prochiral, then the cyclisation reaction generates a new stereogenic centre, known as the *anomeric* centre. The two possible diastereoisomers (anomers) both retain the name of the parent monosaccharide, but since they are chemically different, they are named with the prefix α- or β-, depending on the configuration at this carbon compared to that of the highest numbered asymmetric centre in the Fischer projection of the acyclic monosaccharide. If the configurations are the same, then the prefix to be used is α-, otherwise β- is used.

When referring to D-hexopyranoses, this can be summarised by stating that the α-anomer is defined as having the substituent at the anomeric centre aligned in a *trans*-fashion with respect to the branch in the ring at C-5, e.g. α-D-glucopyranose **11**. Conversely the β-anomer is defined as having the anomeric substituent aligned in a *cis*-fashion with respect to the C-5 branch, e.g. β-D-glucopyranose **12**.



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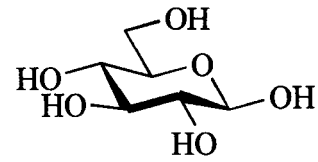

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1.2.2.2 The anomeric effect

Conformational analysis since the 1950s has shown that torsional energy plays a vital role in determining the preferred conformations of ring systems. These interactions are between the electron clouds of subtituents on adjacent atoms (typically carbon) in a chain, are repulsive, and vary with the distance between substituents, and with their size. Thus repulsions are greatest between pairs of axial substituents, and least between pairs of equatorial substituents. Axial-equatorial interactions fall somewhere between these extremes. This implies that as far as possible, the bulkiest groups attached to ring systems prefer to lie in equatorial positions.[1,8]

In pyranoid systems, however, the introduction of a ring oxygen has been shown to alter this general pattern so that electronegative groups attached to the anomeric centre prefer to lie in an axial orientation. This is known as the *anomeric effect,*[8-10] and has been often observed in compounds containing more than one heteroatom attached to the same carbon.

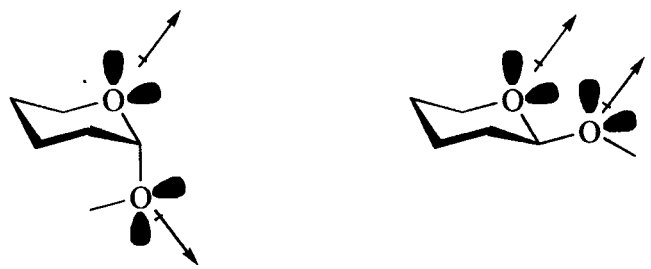
The lone pair of electrons on the ring oxygen can become delocalised into the antibonding σ*-orbital of an axial anomeric C-X bond (Figure 3). This affords some stabilisation, more particularly when the anomeric substituent is particularly

electronegative, and thus better able to draw electron density from the antibonding σ*-orbital to itself.

stabilisation no stabilisation

Figure 3 : Orbital interactions giving rise to the anomeric effect

There is also an electrostatic factor working against the formation of electronegative equatorially-substituted systems, due to increased repulsion between the lone pairs of the ring oxygen and the negative end of the C-1-X dipole compared with the axially substituted variant (Figure 4).



no repulsive interactions repulsive interactions

Figure 4 : Electrostatic interactions between dipoles contributing to the anomeric effect

The movement of electron density from the ring oxygen towards the electronegative substituent causes a further effect. The C-O bond within the ring gains some double bond character, and shortens, whilst the anomeric C-X bond lengthens. This reduces the repulsive interactions of the axial substituent with other substituents in the ring.

In hexopyranoses the C-5 substituent, a hydroxymethylene group, is preferentially oriented equatorial to the ring. Since the anomeric effect favours an axial orientation of the C-1 substituent, the consequence of this is that the α-anomer is thermodynamically favoured (Figure 5).

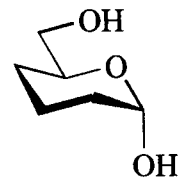


Figure 5 : α-Hexopyranoses (C-1 and C-5 substituents shown only)

1.2.3 Preferred forms of monosaccharides

For free sugars it is apparent that they can exist in either the straight-chain or cyclic forms. For cyclisation of monosaccharides of five or more carbon atoms there is also a choice between formation of a furanose or a pyranose, and within these either the α- or β- anomer can form. In general, it is more common for monosaccharides to exist in the cyclic pyranoid form. For aldohexoses which cyclise under reversible conditions (e.g. in aqueous solution), such as glucose, the different forms exist in equilibrium between the straight-chain, α- and β- pyranose, and α- and β-furanose forms, with the position of equilibrium varying with the solvent and temperature. In more polar solvents, the electrostatic effect disfavouring an equatorial orientation in pyranoses is compensated for by interactions with the solvent,[11] whilst higher temperatures tend to favour furanoses.[1]

1.3 The glycosidic bond

The carbohydrate portion(s) of glycoconjugates such as glycoproteins, glycolipids and proteoglycans are known collectively as oligosaccharides, and these are essentially composed of a sequence (straight-chain or branched) of monosaccharide units. The linkage between monosaccharide units in oligosaccharides, and between the anomeric centre of a monosaccharide unit and the protein or lipid in a glycoconjugate, is known as the glycosidic linkage, or glycosidic bond. Essentially this is an acetal- (or ketal) type functionality, derived from condensation of the hemiacetal (or hemiketal) functionality of one saccharide unit, the glycosyl donor, with a nucleophilic functionality of another, the glycosyl acceptor (Figure 6).

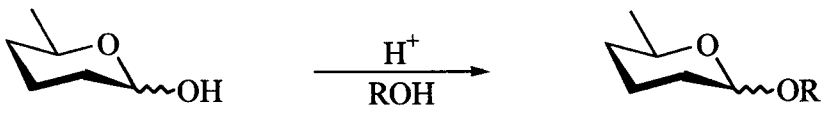


Figure 6 : Acid-catalysed reaction between a hemiacetal (or a hemiketal) and a sugar alcohol

In the case of oligosaccharides, the glycosyl acceptor will be a sugar alcohol, and in glycoconjugates the glycosyl acceptor may also be, for example, the amino side-chain of an asparagine residue of an amino acid.

Any foreign functionality attached to the anomeric centre gives rise to what is rather loosely termed a glycoside; the exact terminology used depending upon the nature of the foreign atom attached to the anomeric centre. For example, notional simple alcohol and sugar alcohol acceptors give rise to *O*-glycosides, amino acceptors give rise to *N*-glycosides, and nucleophilic sulfur acceptors give rise to *S*-glycosides (thioglycosides if the sulfur acceptor is a thiol).

1.4 Principles of oligosaccharide synthesis

1.4.1 Approaches towards the glycosylation reaction

The structure of an oligosaccharide associated with any given biological function is quite specific. The anomeric configuration, as well as the sequence of, and position of connections between monosaccharide units in any oligosaccharide is crucial in determining the role that a particular oligosaccharide can play.

In order to study the roles of carbohydrates and glycoconjugates in biological systems, we ideally need to be able to synthesise them in the laboratory. A synthon disconnection approach reveals two distinct classes of potential glycosylation reaction:

1.4.1.1 Anomeric O-alkylation

The glycosidic linkage can be disconnnected to give a negative alkoxide-type synthon at the anomeric centre of one monosaccharide, and a positive synthon at the point of

connection to the other (Figure 7). This corresponds to *O*-alkylation of a sugar hemiacetal by alkylating groups derived from a hydroxy group of a monosaccharide.

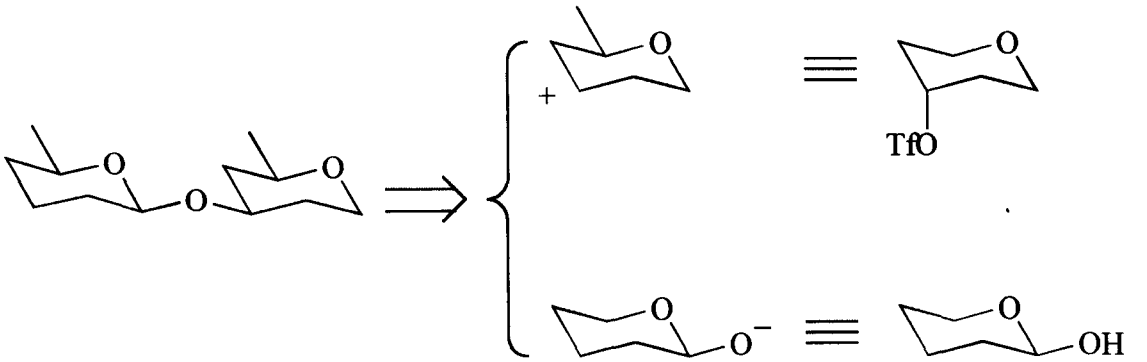


Figure 7 : Synthon disconnection of a glycosidic linkage I

Tsvetkov *et al.* have reported limited success in the formation of glycosides by these means, in polar, aprotic solvents using sugar triflates as alkylating agents.[12] One particular problem in this approach is the difficulty in obtaining a single anomer of the hemiacetal in order to gain the desired stereocontrol for the reaction.[13]

1.4.1.2 Nucleophilic attack on the anomeric centre

Reversal of the above disconnection gives a negative sugar alkoxide synthon, and a synthon which is positively charged at the anomeric centre (Figure 8). These synthons equate typically to nucleophilic attack by a sugar alcohol (glycosyl acceptor) on an anomeric centre bearing a leaving group (glycosyl donor).

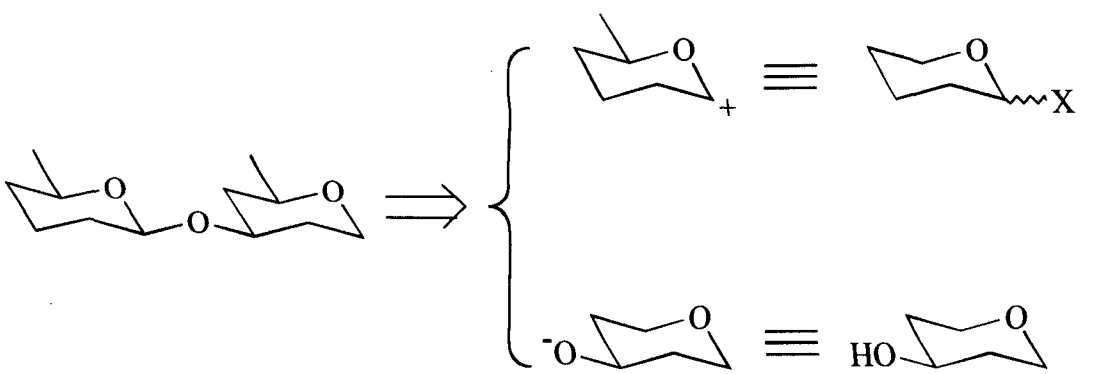


Figure 8 : Synthon disconnection of a glycosidic linkage II

In the classical Fischer synthesis,[14] simple alkyl glycosides were prepared by the reaction of the corresponding monosaccharide and an alcohol in the presence of an acid (Figure 6). Under these conditions, the leaving group at the anomeric centre is water, but many more reactions have been successfully developed utilising different leaving groups at the anomeric centre (Section 1.5). This is by far the more widely used of the two classes of coupling reaction under discussion, and is the only one which shall be considered further in this report.

1.4.2 The mechanism of glycosylation reactions

In theory, nucleophilic displacement of an anomeric leaving group in the glycosyl donor by a sugar alcohol can occur in either a stepwise (e.g. S_N1), or concerted (e.g. S_N2) fashion. In practice, however, most glycosylation reactions are believed to involve primarily a stepwise process, whereby the anomeric leaving group is firstly cleaved to generate a carbocation at the anomeric centre, which could then be partially stabilised by the ring oxygen lone pair to give an oxocarbenium ion[15] (Figure 9a). Alternatively, the monosaccharide unit could adopt a conformation whereby a lone pair of the ring oxygen is antiperiplanar to the C-1-X bond and can itself displace the leaving group to give the oxocarbenium ion directly (Figure 9b).[16]

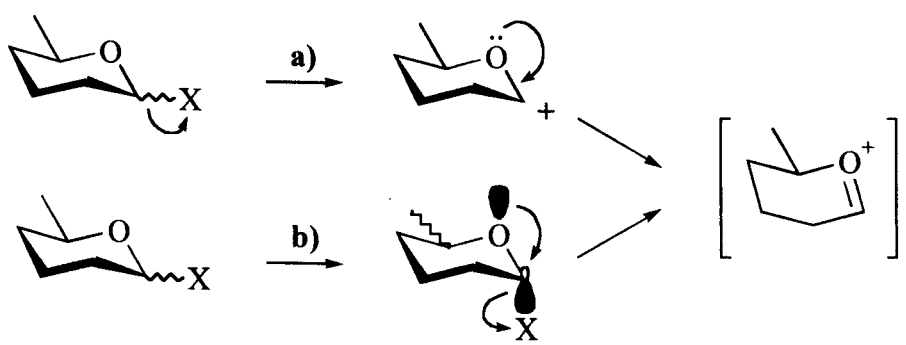


Figure 9 : Initial loss of leaving group in stepwise glycosylation reactions

Whatever the route of generation, the positively charged oxocarbenium ion is a highly reactive intermediate, and is susceptible to attack by nucleophilic sugar alcohol

acceptors from either above (Figure 10a) or below (Figure 10b) the ring to give glycosides.[15]

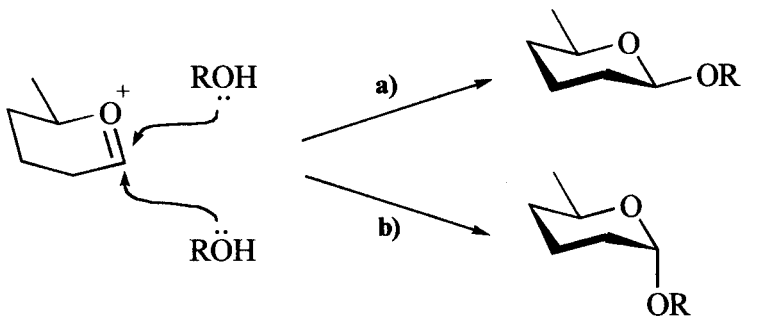


Figure 10 : Attack from above and below the face of the oxocarbenium ion intermediate

1.4.3 Regiocontrol in glycosylation reactions

1.4.3.1 The use of blocking groups

Monosaccharide units are highly functionalised, with any one glycosyl acceptor possessing several hydroxyl groups capable of reaction with the anomeric centre of a glycosyl donor to form disaccharides. Moreover, there is nothing to prevent reaction of the hydroxyl groups of one molecule of a glycosyl donor, with the anomeric centre of another. Glycosylation chemistry thus requires the extensive use of blocking, or protecting, groups to help achieve good regiocontrol in the glycosylation reactions. These must be stable under glycosylation conditions, and easily removed as required. If a monosaccharide unit is to be an acceptor for more than one glycosyl donor, then after a first glycosylation is performed the protecting group for the second site must be selectively removed (i.e. the protecting groups should be orthogonal if necessary).

Classical protecting groups used in oligosaccharide synthesis[17,18] include esters (e.g. acetate), ethers (e.g. benzyl, allyl, trityl and silyl ethers), acetals (e.g. benzylidene groups, derived from benzaldehyde) and ketals (e.g. isopropylidene groups, derived from acetone). Acetal and ketal protecting groups can be used to form a cyclic system protecting two alcohol groups at the same time. There is also a need to protect other functionalities in sugars where alcohol groups have been replaced. For example, amino sugars have an alcohol group replaced by an amine, and this can be protected by various

acylations to give, for example, acetamides, phthalimides and carbamates.[17,18] The azide group ($-N_3$) can also be used as a 'masked' amine, since it is easily reducible to an amine group.[19,20]

A secondary function of protecting groups in sugar chemistry is to improve solubility of the saccharides in organic solvents used in the glycosylations themselves, and to limit their solubility in aqueous systems.[18]

1.4.3.2 Influence of protecting groups on reactivity of glycosyl donors

The ideal leaving group for glycosylation reactions will be stable under storage conditions, and will only become activatated when the glycosyl donor is required as a glycosylating agent, by addition of a suitable promoter. Very often, as discussed in Section 1.5, these promoters are electrophilic, and activation is brought about by nucleophilic attack on the promoter by an atom within the leaving group. For example, in the Fischer synthesis[14] already discussed, the anomeric oxygen atom is the nucleophile, and hydrogen ions are effectively promoting the reaction (Figure 6). The nucleophilicity of the atom concerned (and its hardness in relation to the electrophile) will influence both the rate of activation, and the rate and stereocontrol of glycosylation. In turn, the effectiveness of the nucleophile in attacking the promoter will clearly be affected by the electron donating or withdrawing effects of protecting groups within the donor molecule, particularly those in close proximity to the anomeric centre.

Fraser-Reid *et al.*[21-24] made the observation that ether-protected glycosyl donors are generally more reactive species than the unprotected analogues. This can be attributed to the electron donating nature of ether groups, which cause an increase in electron density at the activatible atom of the leaving group. He termed such donors 'armed'.[22] Conversely, acyl protecting groups are electron withdrawing in nature, and donors containing these, particularly in positions near to the anomeric centre, showed a lower degree of lability; these were termed 'disarmed'.[22]

The differences in reactivity between 'armed' and 'disarmed' glycosyl donors suggest that varying the protecting groups can provide a means of tuning the reactivity of

glycosyl donors, so that different conditions are required for their activation. Indeed, Fraser-Reid went on to show that selective IDCP activation of C-2 benzyl ether-protected *n*-pentenyl glycoside **13** was possible in the presence of C-2 acetyl ester-protected *n*-pentenyl glycoside acceptor **14**, to generate disaccharide **15**[25] (Figure 11).

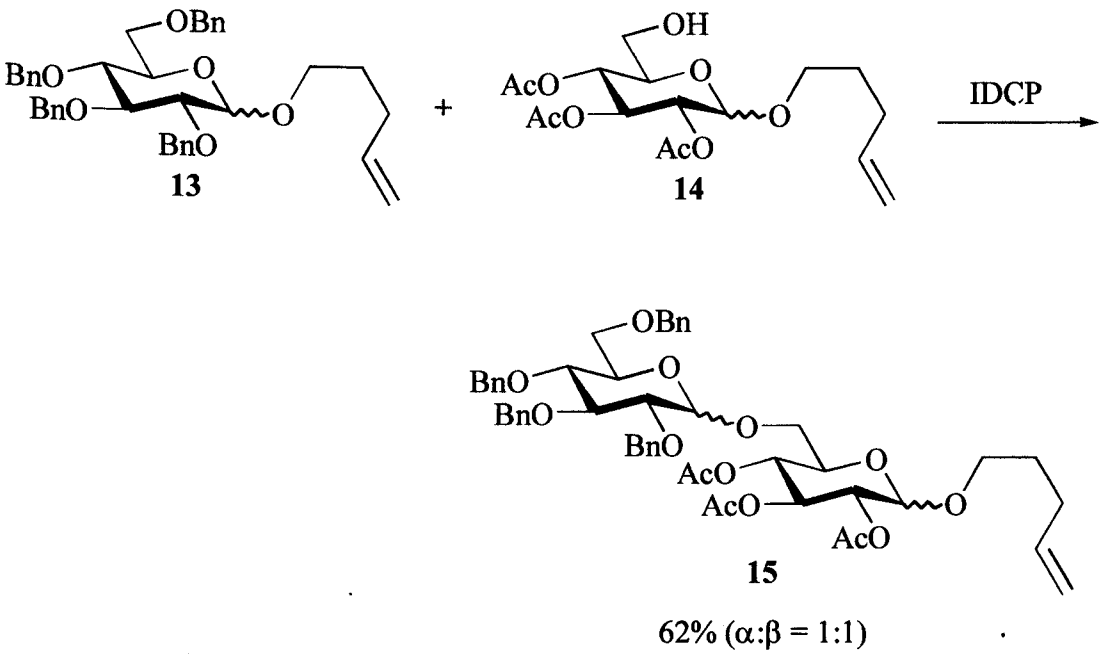
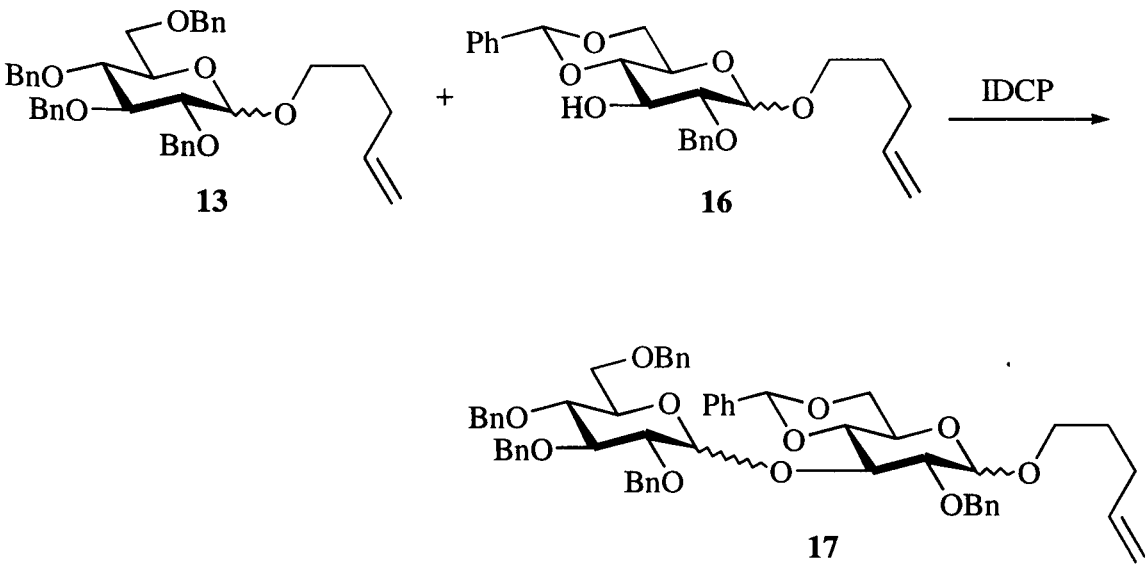


Figure 11

This concept is important in orthogonal glycoyslation strategies (Section 1.4.5), where the aim is to construct oligosaccharides from building blocks in such a way as to minimise the number of manipulations that have to be made to the oligosaccharide at each stage to prepare it for the next glycosylation.

Torsional effects also play a role in determining the reactivity of glycosyl donors. Fraser-Reid *et al.* showed that the use of cyclic acetal protecting groups has a disarming effect on *n*-pentenyl glycosyl donors.[23] The resultant bicyclic system is much more rigid than a single pyranose ring, thereby restricting access to the planar $C_5O_5^+$-C_1C_2 segment of the usual oxocarbenium ion intermediate. As a result of this, they were able to chemospecifically glycosylate[23] 4,6-benzylidene acetal-protected *n*-pentenyl glucoside **16** with *n*-pentenyl glucoside **13** to give **17** (Figure 12).



52% (α:β not quoted)

Figure 12

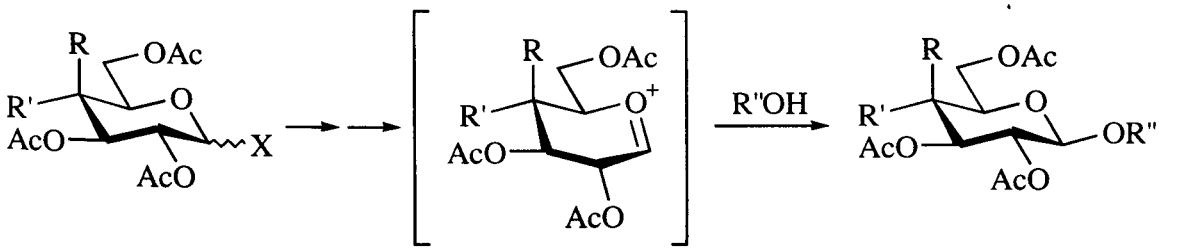
1.4.4 Anomeric stereocontrol in glycosylation reactions

Although the anomeric effect generally dictates that the thermodynamically preferred product in hexapyranoside glycosylation will be the α-anomer,[8-10] nucleophilic attack can occur from either face of the oxocarbenium ion intermediate, to give both anomers in the product.[15,26] Stereocontrol is thus not absolute, and in any case there are many examples of biologically important β-glycosides (such as the core pentasaccharide of N-linked glycoproteins, which contains both β-mannoside and β-glucoside linkages[27]) which one might wish to prepare.

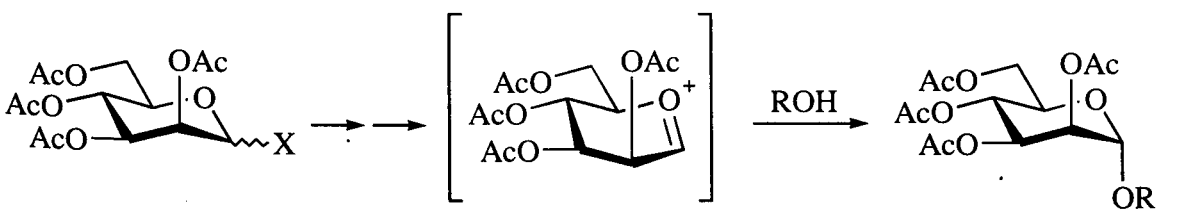
It would be desirable to be able to fully control the anomeric stereoselectivity of glycosylation reactions, according to the structure of the target oligosaccharide. There are, however, a number of factors that affect the stereochemical outcome of glycosylation reactions, including the reactivity and structure of the glycosyl donor and acceptor, the participation of protecting groups present in the glycosyl donor (as discussed in Section 1.4.4.1), the temperature and the polarity and reactivity of the solvent (as discussed in Section 1.4.4.2).

1.4.4.1 The 1,2-trans effect

In early glycosylation studies, it was noted that acylated glycosyl donors of the *gluco-* and *galacto-* series tended to give β-glycosides as products, whilst similarly protected donors from the *manno-* series gave α-glycosides.[28] In all three cases the glycosyl donor can be seen to be oriented *trans-* to the acetoxy group at C-2 (Figure 13).



a) *gluco* R = H , R' = OAc; b) *galacto* R = OAc , R' = H



c) *manno-*

Figure 13 : Acylated *galacto-*, *gluco-* and *manno-*configured glycosyl donors giving 1,2-*trans*-glycosides

This suggests that there is neighbouring group participation by the acetyl protecting group in the glycosylation reaction. It is believed[29,30] that the carbonyl oxygen of the acetoxy group attacks the anomeric centre of the oxocarbenium ion intermediate to give a bicyclic intermediate where the positive charge is now delocalised between the two oxygens of the ester protecting group. Nucleophiles can now only attack from the opposite face of the sugar ring, to give the 1,2-*trans-* product (Figure 14a), or at the acyl carbon of the ester group to give an ortho ester (Figure 14b).

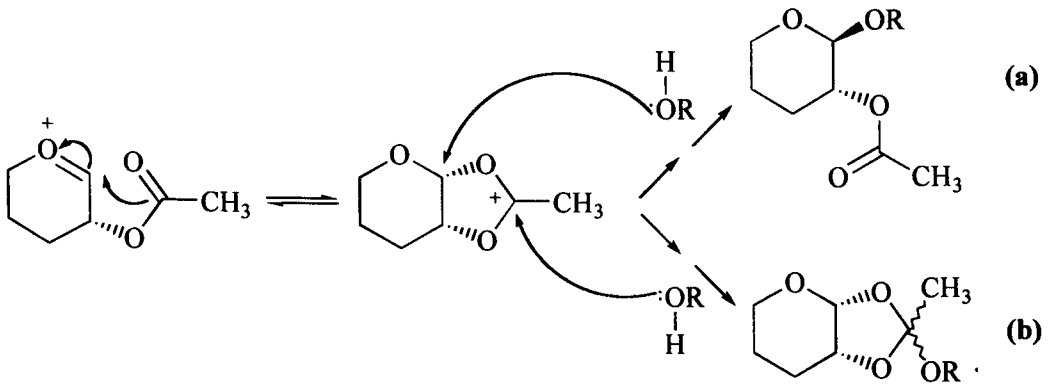


Figure 14 : Participation of C-2 *O*-acetate protecting group giving 1,2-*trans* glycosylation products or ortho esters

1.4.4.2 *Solvent effects*

Co-ordinating solvents can play a part in influencing the stereocontrol of glycosylation reactions. Attack on the anomeric centre of the oxocarbonium ion intermediate by such a solvent may allow reversible formation of a labile glycoside which is susceptible to displacement by nucleophiles, with inversion of configuration.

Thus, diethyl ether has been found to enhance α-selectivity in glycosylation reactions, presumably through formation of a β-diethyl oxonium ion (Figure 15), favoured over the corresponding α-diethyl oxonium ion due to the reverse anomeric effect,[31] whereby positively charged anomeric substituents prefer to adopt an equatorial conformation.

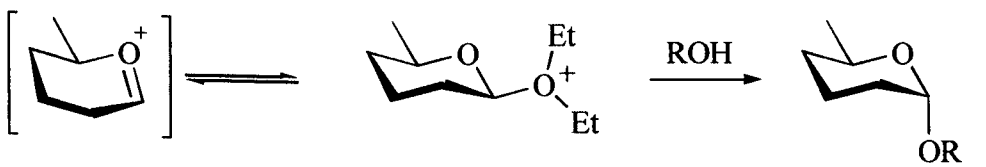


Figure 15 : Enhancement of α-selectivity during glycosylation reactions in diethyl ether

On the other hand, nitrile solvents, such as acetonitrile,[32-34] have been found applications in improving the β-stereocontrol of many glycosylation reactions. This has been shown to occur via formation of an α-nitrilium intermediate[32] (Figure 16), which undergoes S_N2 substitution reactions[35] with *O*-nucleophiles to give β-glycosides. It has been argued that formation of the α-nitrilium ion goes against the same reverse

anomeric effect mentioned above, but it is possible that interactions with the more polar solvent reduce the impact of that effect.

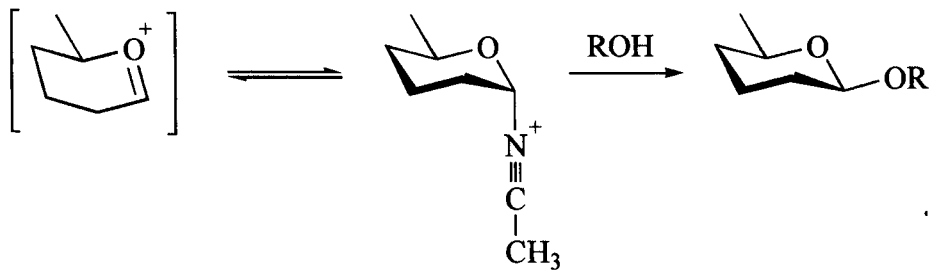


Figure 16 : Formation of α-nitrilium ion leading to enhanced β-selectivity in glycosylation products of hexopyranoses

1.4.4.3 The effect of nucleophilic species on anomeric stereocontrol

Nucleophilic species present may also influence the stereochemical outcome of the reaction, forming an adduct at the anomeric centre which, if labile, can give rise to a similar effect as seen above for co-ordinating solvents. For example, the trifluoromethanesulfonate (triflate) anion is a very poor nucleophile, but in some cases[36,37] it is believed to be capable of reacting at the anomeric centre to form an α-triflate. The triflate group not only activates the anomeric centre towards attack by nucleophiles (due to the inductive effect of the trifluoromethyl group), but the triflate anion itself is also an excellent leaving group. Consequently it is easily displaced in an S_N2 fashion by nucleophiles to give the β-glycosides.

1.4.5 Orthogonal glycosylation strategies

In any synthesis that is to be practically useful, it is necessary to attain the greatest possible yields from the fewest steps. It is thus important to select the most efficient order of performing reactions. Usually this involves performing as many of the required manipulations of building blocks (e.g. protection and addition of leaving groups) as possible before assembly, to limit the number of manipulations to be required between the key reaction steps. Ideally, the only manipulations to be performed thereafter should be simple selective deprotection steps prior to the next reaction, if required.

In oligosaccharide synthesis, there is the disadvantage that most of the coupling reactions are essentially the same, and so there is likely to be a problem with selectivity if all the glycosyl donors possess the same leaving groups. For example to form a linear trisaccharide, the glycosyl acceptor in the first reaction must be capable of becoming a glycosyl donor for the addition of the final monosaccharide unit. Clearly therefore, the conditions required for activation of the disaccharide must be different from (orthogonal to) those required for activation of the first glycosyl donor, or else the disaccharide will react with another acceptor molecule during the first glycosylation, and then this too can react further.

Orthogonal glycosylation strategies[38] involve the building-in of anomeric leaving groups into each glycosyl acceptor which are stable under conditions required for the initial coupling steps, but which can themselves be used as glycosyl donors under different conditions when required (Figure 17).

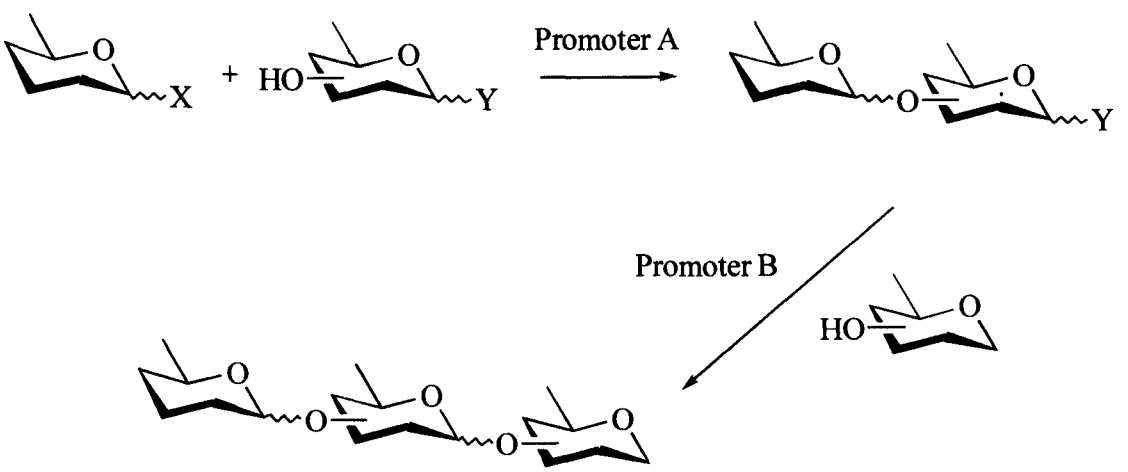


Figure 17 : Orthogonal glycosylation

Ideally, these steps might be accomplishable without intermediate isolation and purification steps. At the very least the product, once isolated, can then be used subsequently without further chemical manipulation. Ogawa *et al.* went on to show that this method could indeed be applied to the synthesis of a tetrasaccharide fragment by using alternately anomeric thioglycoside and fluoride acceptors, which can be activated under orthogonal conditions.[38] Likewise, Fraser-Reid *et al.* demonstrated that 'armed' glycosyl donors could be activated in the presence of 'disarmed' acceptors bearing the

same anomeric leaving group[25] (Figure 11, p27). Alternatively, if the two donors react at significantly different rates with the same promoter (the first one being the faster), then addition of the second acceptor should lead eventually to the trisaccharide required. If the promoters are not compatible, then a work-up would be required in between to remove the first, but the product gained will be ready to be used for the next stage without chemical manipulations.

1.5 Glycosyl donors for oligosaccharide synthesis

The classical Fischer Glycosidation reaction,[14] is the earliest of all glycosylation reactions, acetalisation (or ketalisation) of the anomeric centre occurs by reaction of a simple alcohol with a sugar hemiacetal under strongly acidic conditions. The hemiacetal hydroxyl oxygen is protonated, inducing loss of water to give the oxocarbenium ion intermediate which can then react with the alcohol acceptor to give the glycoside (Figure 18).

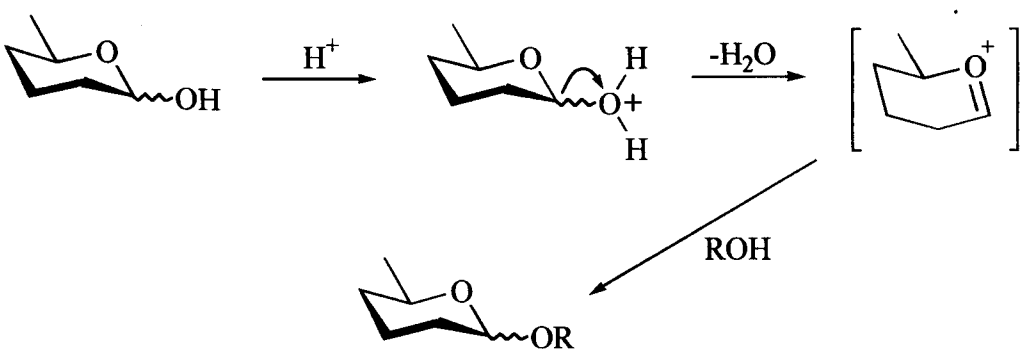


Figure 18 : Acid-promoted acetalation of sugar hemiacetals with simple alcohols

Strong acids are required for this reaction, such as hydrogen chloride, sulfonic acids or strongly acidic ion exchange resins.[26] More recently, triflic acid,[39] camphorsulfonic acid[40] and ferric chloride[41] ($FeCl_3$) have also been used.

Powerful Lewis acids such as TMS-OTf have also found use in promoting the coupling of partially protected monosaccharides with simple alcohol acceptors. Typically TMS-OTf is generated *in situ* in these reactions from a combination of zinc triflate with TMS-Cl,[42] or tin, ytterbium or lanthanum triflate with hexamethyldisiloxane.[43]

This procedure is suitable for the production of glycosides where the glycosyl acceptors are simple alcohols, although in the strongly acidic condtitions, the glycosidic linkage will be easily hydrolysed, leading to thermodynamic control in product formation. The procedure has not been put to widespread use in the synthesis of oligosaccharides, however.[26]

A wide range of glycosyl donors have been reported as being used for oligosaccharide synthesis, in the search for better yields and stereocontrol. The ideal glycosyl donor would also be easily prepared, and shelf stable until an appropriate promoter is introduced in the presence of a glycosyl acceptor.

Just as in the glycosidation reactions of hemiacetals discussed above, promoters of glycosidation reactions are typically electrophilic in nature. Most procedures rely upon an atom within a previously stable glycosyl donor becoming attracted to an electrophile, with a resultant weakening of the bond holding the leaving group attached to the anomeric centre of the glycosyl donor. The remainder of this section is devoted to a résumé of some of the most important classes of glycosyl donor reported in the literature.

1.5.1 Glycosyl halides as glycosyl donors

1.5.1.1 Glycosyl bromides and chlorides

The classical procedure to attach both simple and sugar alcohol acceptors to the anomeric centre of a carbohydrate unit is known as the Koenigs-Knorr glycosylation.[44] This involves the reaction of peracetylated glycosyl halides (X=Cl or Br) with an alcohol acceptor in the presence of an insoluble silver salt (e.g. silver carbonate), to give a glycoside (Figure 19). The reaction has been modified over the years, with the introduction of mercury promoters such as mercury cyanide,[45] and more potent, soluble, silver salts such as silver perchlorate[46] and silver triflate.[47,48]

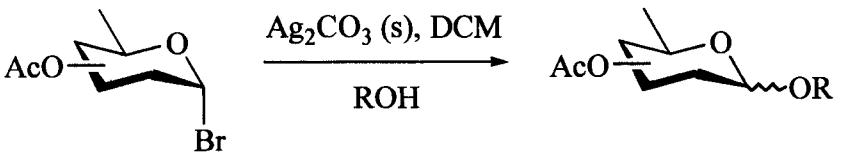


Figure 19 : Koenigs-Knorr glycosylation

The soft metal present is likely to complex with the halogen atom of the glycosyl halide, polarising the anomeric carbon-halogen bond sufficiently to induce cleavage of the bond (Figure 20). The resulting silver or mercury halide is highly insoluble in organic solvents, and so the halide ion can play no further part in the reaction.

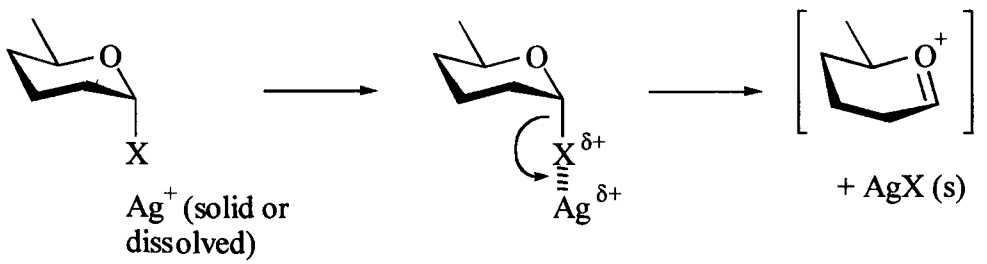


Figure 20 : Polarisation of C-X bond by silver ions

Some metal catalysts have been found to be mild enough to polarise the carbon-halogen bond just sufficiently to induce nucleophilic displacement rather than actually induce the halogen to leave.[49]

Generally, the α-bromides are not sufficiently reactive to allow direct nucleophilic displacement under neutral conditions, though some examples under mildly basic conditions have been reported.[50] Reaction of α-bromides with anionic nucleophiles can give β-glycosides, but very often these anions are sufficiently basic to induce competitive elimination reactions, to give the glycal and HBr[51] (Figure 21).

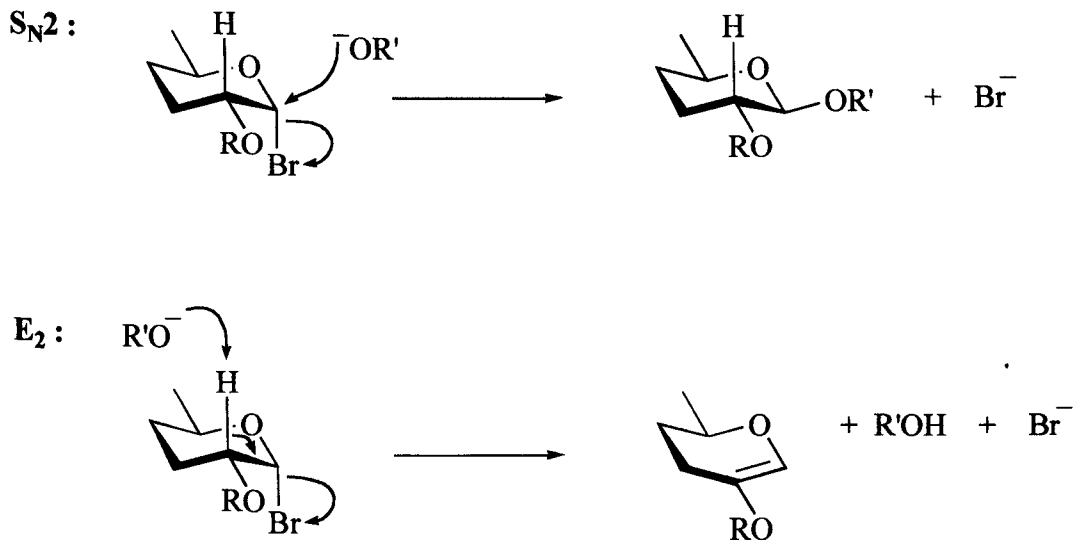


Figure 21 : Competition between nucleophilic displacement and base-assisted elimination reactions of anomeric bromides

The β-bromides are intrinsically less stable than the corresponding α-anomers due to the anomeric effect,[9,10] and are so more reactive towards nucleophiles. Epimerisation of α-bromides to the more reactive β-anomer can be accomplished *in situ* by reaction with soluble sources of bromide,[52] such as TBABr.[53,54] If no participating groups are present, then the β-bromides can be reactive enough towards nucleophiles to allow direct nucleophilic displacement, to give α-glycosides[55] (Figure 22).

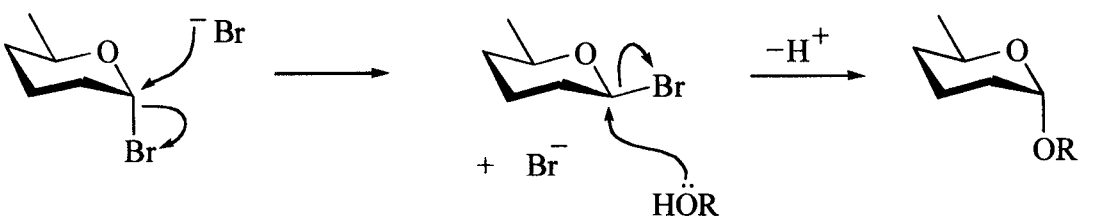


Figure 22 : *In situ* epimerisation of α-glycosyl bromides followed by S_N2 attack at the anomeric centre to give α-glycosides

If the bromine atom is *trans*-oriented with respect to a participating acyl group at C-2, then the latter can displace bromide directly to give the acetoxonium ion depicted in Figure 14. Iodine and iodine monobromide have both been used to activate glycosyl bromides towards glycosylation,[56] and there is evidence that these reactions might also proceed via epimerisation to give the β-bromide.

1.5.1.2 *Glycosyl fluorides*

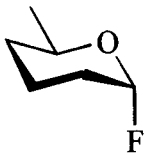


Figure 23 : Glycosyl fluorides

The use of glycosyl fluorides as glycosylating agents was first reported in 1981 by Mukaiyama *et al.*[57] They have the advantage of being more stable than the corresponding chlorides and bromides,[26] and as such are easier to handle. Activation of fluorides as glycosylating agents has been reported utilising promoters such as tin (II) chloride in combination with silver perchlorate,[57] trimethylsilyl triflate,[58] boron trifluoride etherate,[59] triflic anhydride,[60] titanium fluoride,[61] lithium perchlorate,[62] lanthanum perchlorate,[63] and a number of examples of silver compounds in combination with hafnocene[64,65] and zirconocene [64,66] complexes.

1.5.1.3 *Glycosyl iodides*

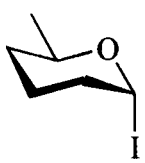


Figure 24 : Glycosyl iodides

Glycosyl iodides are more reactive towards direct nucleophilic displacement under neutral conditions than the corresponding bromides.[67,68] Typically, they have been generated *in situ* from other glycosyl donors, but recently a number of examples have, in separate pieces of work, been prepared, isolated and characterised by essentially similar reactions of anomeric acetates with TMSI[69] or with iodine and hexamethyldisilane.[70] Gervay *et al.* later reported several reactions of perbenzylated α-iodides with anionic carbon, nitrogen and oxygen nucleophiles, and some alcohols, to give various β-glycosides.[55] There were, however, problems such as a loss of stereoselectivity due to *in situ* epimerisation of the α-iodide to the more reactive β-

iodide, and elimination of HI with strongly basic nucleophiles, particularly in the *gluco-* and *galacto-* series (*cf.* Figure 21).

1.5.2 *n*-Pentenyl glycosides as glycosyl donors

Fraser-Reid *et al.*[71,72] reported the use of *n*-pentenyl groups as a protecting group for the anomeric centre which could be activated by IDCP, or NIS in combination with either triflic acid or TES-OTf. These reagents are believed to operate by addition of I^+ to the double bond of the *n*-pentenyl group to generate a cyclic iodonium ion which is attacked by the anomeric oxygen, leading to activation (Figure 25). They are also relatively simple to produce, by a Fischer glycosidation reaction[14] of pent-4-enyl alcohol with a free sugar under acidic conditions.[71]

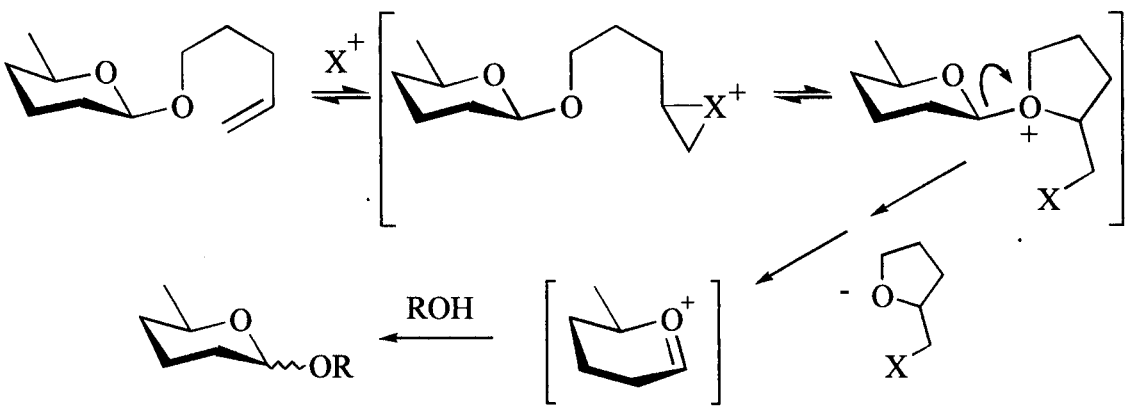


Figure 25 : Electrophilic activation of *n*-pentenyl glycosides

1.5.3 Trichloroacetimidates as glycosyl donors

Trichloroacetimidates react with alcohols in the presence of boron trifluoride etherate or trimethylsilyl triflate at low temperatures to give glycosides.[13,29] Boron trifluoride is the milder of the two reagents, and in the absence of a participating group at C-2, this can bias selectivity towards inversion of configuration in the products. This suggests mechanistically that the promoter improves the electrophilicity of the anomeric centre by co-ordinating with the trichloroacetimidate, favouring an S_N2-type displacement of the leaving group (Figure 26). The lower degree of inversion observed for TMS-OTf as a promoter suggests that activation by this means proceeds to a greater extent through cleavage of the anomeric C-O bond to generate the usual oxocarbenium intermediate.

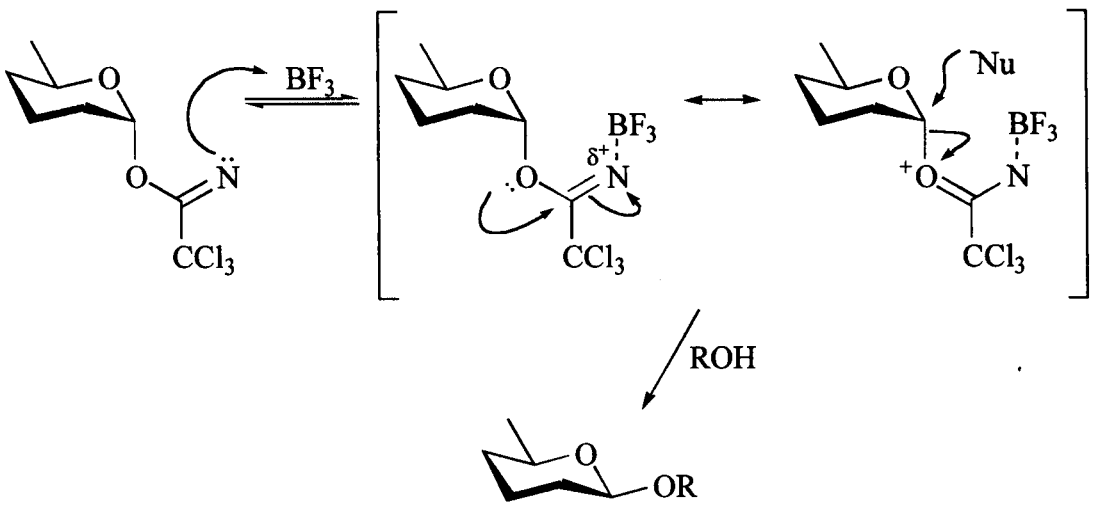


Figure 26 : Trichloroacetimidates as glycosyl donors

1.5.4 Thioglycosides as glycosyl donors[73,74]

Alkyl(aryl)thio groups appear to offer efficient temporary protection of the anomeric centre of saccharides.[73] In the first instance they were not used directly as glycosylating agents, but could be effectively converted to the classical glycosyl donors, namely glycosyl chlorides or bromides,[44] using the respective halogen[75-77] (Figure 27).

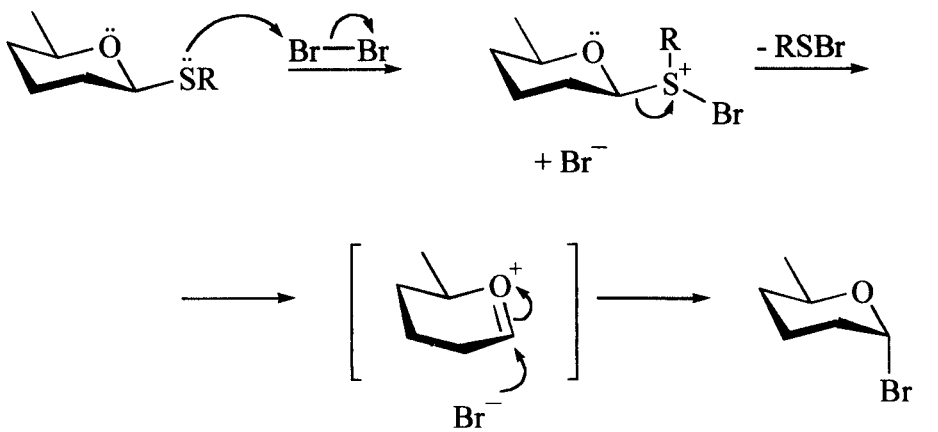


Figure 27 : Conversion of thioglycosides into glycosyl bromides

Later groups were able to convert thioglycosides into the respective glycosyl bromides *in situ* using either bromine[78] or copper (II) bromide/ tetrabutylammonium bromide,[79] in the presence of suitable halophilic promoters such as silver triflate or mercuric cyanide,

effectively allowing activation of thioglycosides in a one-pot procedure. The conversion of thioglycosides into glycosyl fluorides, using NBS-DAST,[80] has also been reported.

The indirect use of thioglycosides as glycosylating agents in this fashion led to a search for thiophilic promoters that would directly activate the thioglycoside (Figure 28).

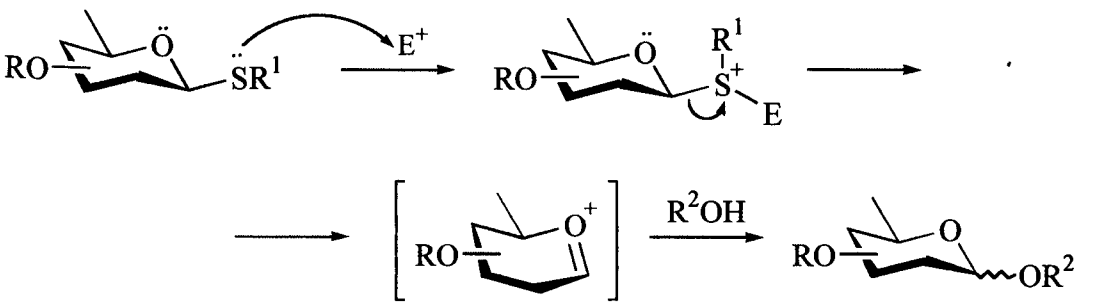


Figure 28 : Direct electrophilic activation of thioglycosides

The first direct glycosylation of a thioglycoside to give a disaccharide was achieved using mercury (II) sulfate in 1973 by Ferrier *et al.*[81] *N*-Bromosuccinimide[82] and other heavy metal salts such as copper (II) triflate,[83] phenylmercury triflate,[84] and mercury (II) chloride[85] gave limited success in production of *O*-glycosides. The highly toxic methylating agent methyl triflate was reported as an effective promoter by Lönn[86,87], but was limited in scope by its toxicity and its potential for methylating the glycosyl acceptor. If pre-mixed with dimethyl disulfide, methyl triflate reacts to form the far more reactive and thio-specific promoter dimethyl(methylthio)sulfonium triflate (DMTST)[73,88,89] (Figure 29), which functions as a source of the electrophile MeS^+.

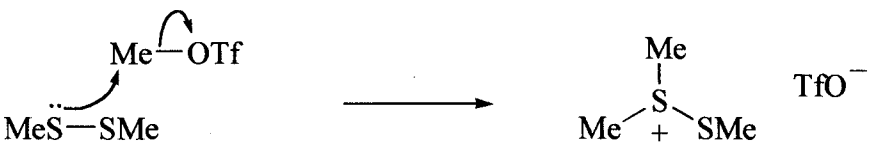


Figure 29 : Generation of DMTST

Other efficient, but less toxic, thiophilic promoters have emerged, including phenylselenyl triflate,[90,91] *N*-phenylselenyl phthalimide in conjunction with triflic acid,[92] methylsulfenyl triflate[93,94] and nitrosyl tetrafluoroborate.[95]

Iodonium dicollidine perchlorate (IDCP) appeared in the literature in 1989 as a useful source of iodonium ions for activating *n*-pentenyl glycosides[72,96], having already found application many years before in the activation of glycals[52]. Veeneman extended the use of IDCP to activation of 2-*O*-benzylated ('armed') thioglycosides,[97] but found that the corresponding 2-*O*-acylated ('disarmed') thioglycosides were not activated under these conditions. This was later rationalised as being due to the so-called disarming effect[25] of acyl protecting groups. These groups draw electron density away from the relatively easily polarisable sulfur atom of the thioglycoside, reducing its nucleophilicity, and thus retarding reaction with the iodonium ions.

N-Iodosuccinimide (NIS) was similarly found to activate 'armed' thioglycosides,[98] but was not a sufficiently powerful source of iodonium ions to activate their 'disarmed' analogs. In the presence of carboxylic acids, however, 'disarmed' thioglycosides were activated by NIS to give anomeric esters. It was proposed that this is likely to proceed by displacement of the iodonium ion from NIS by a hydrogen ion[71] to generate an iodonium carboxylate,[99] a more powerful source of iodonium ion (Figure 30).

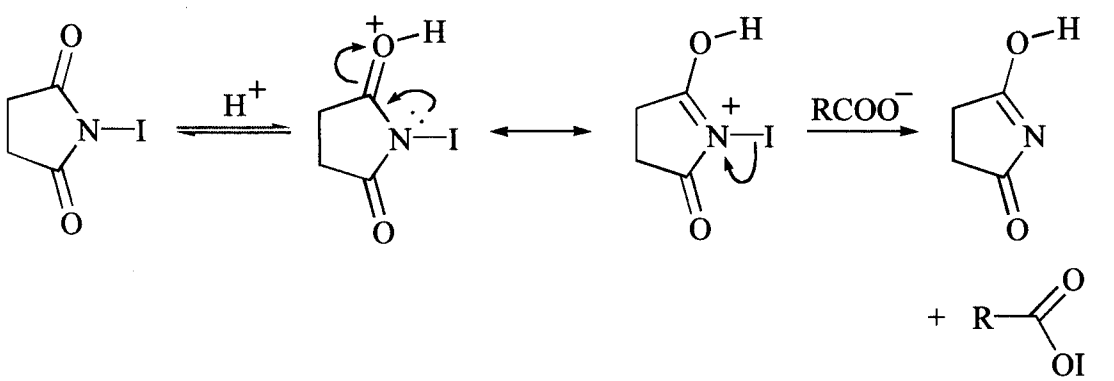


Figure 30 : Acid-assisted generation of iodonium ions from NIS

Veeneman[100] and Fraser-Reid[24,101] independently predicted that the use of NIS/triflic acid would activate 'disarmed' thioglycosides in a similar manner to NIS in conjunction with carboxylic acids. The triflate anion was already established as an excellent leaving group in glycosylation reactions,[48,102-104] and it was believed that the triflate anion would not combine with the activated glycosyl donor in the same fashion as carboxylate anions, but that glycosylation of sugar alcohol acceptors would occur in preference. This was indeed found to be the case, with even 'disarmed' thioglycoside donors

reacting within seconds in the presence of a stoichiometric amount of NIS and a catalytic amount of triflic acid (0.15 eq.). The use of a catalytic quantity of triflic acid is sufficient because hydrogen ions are liberated by the alcohol acceptor in the reaction, and are thus regenerated. Other substances shown to enhance the reactivity of NIS include TES-OTf and silver triflate.[24,101]

All of the reagents discussed for activating thioglycosides towards glycosylation have their drawbacks, being either toxic, moisture sensitive, expensive or foul-smelling. Kartha and Field showed more recently that molecular iodine could also be used as a source of iodonium ions, activating 'armed' thioglycosides efficiently at room temperature and allowing glycosylation of sugar acceptor molecules.[105] Tetrahydropyranyl derivatives have in fact long been known to be useful, iodine-cleavable[106] protecting groups for thiols,[107,108] (Figure 31).

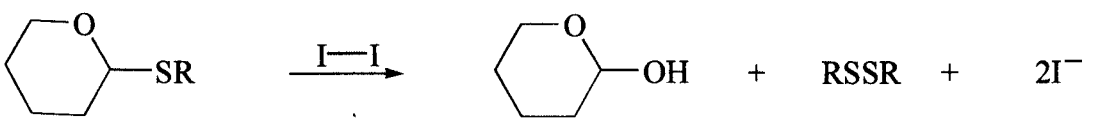


Figure 31 : Iodine-promoted removal of tetrahydropyranyl protection of thiols

Iodine was found not to activate 'disarmed' thioglycosides towards glycosylation.[109] This again can be attributed to the disarming effect of acyl protection of the hydroxyl groups in the glycosyl donor. Veeneman subsequently observed that iodine is much more effective in the activation of 'disarmed' thioglycosides when used in combination with silver triflate.[26] Presumably this is due to the formation of the powerful iodonium source IOTf *in situ*.

The interhalogen compounds of iodine with the more electronegative halogens (such as chlorine and bromine), can be reasonably expected to be a more potent source of iodonium ion, due to the intrinsic polarisation of the molecule in favour of the more electronegative halogen. During the course of this project, Kartha and Field indeed discovered that the addition of a stoichiometric amount of iodine monobromide or iodine monchloride could be used to convert even 'disarmed' thioglycosides into a glycosyl bromide or chloride, respectively.[56] They showed further that iodine

monobromide could be used to activate 'disarmed' glycosyl bromides towards glycosylation,[56] and thus that this is a suitable promoter for glycosylation reactions starting from 'disarmed' thioglycoside donors.[56]

A one electron oxidation of the sulfur atom to give a radical cation, which can then cleave to give a sulfur radical and the an oxocarbenium intermediate, provides another means of thioglycoside activation. This has been effected by electrochemical means,[110] and by use of tris (4-bromophenyl) ammoniumyl hexachloroantimonate ($TBPA^{+\bullet}$) in acetonitrile (Figure 32).[110]

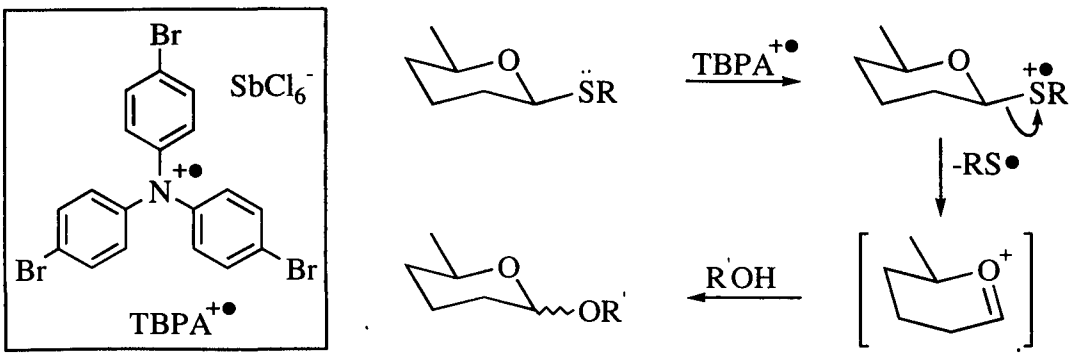


Figure 32 : One electron oxidative activation of thioglycosides

1.5.5 *S*-Glycosyl xanthates as glycosyl donors

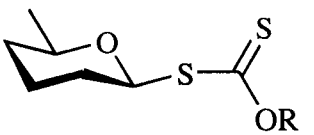


Figure 33 : *S*-Glycosyl xanthates

S-Glycosyl xanthates have been found to have use as glycosyl donors,[111] with activation by copper triflate,[110,112] DMTST,[110,113] methylsulfenyl triflate (MST),[114-116] phenylsulfenyl triflate (PST),[117] and $TBPA^{+\cdot}$.[110]

1.5.6 *S*-Glycosyl sulfoxides as glycosyl donors

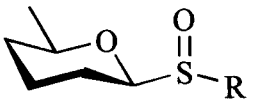


Figure 34 : *S*-Glycosyl sulfoxides

Glycosyl sulfoxides can be activated by triflation of the sulfoxide oxygen atom with triflic anhydride at low temperatures.[118,119] They have proved highly useful in glycosylation of unreactive substrates,[118] and are discussed further in Chapter 3.

1.5.7 *S*-Glycosyl sulfones as glycosyl donors

In 1988, Ley's group demonstrated that tetrahydropyranyl sulfones could be used to introduce tetrahydropyranyl protection to alcohols upon activation with magnesium bromide etherate in THF.[120] They went on to show that glycosylation of L-oleandroside acceptor **18** with the L-oleandrosyl sulfone **19** was possible under these conditions,[121] to give disaccharide **20** in 65% yield (Figure 35).

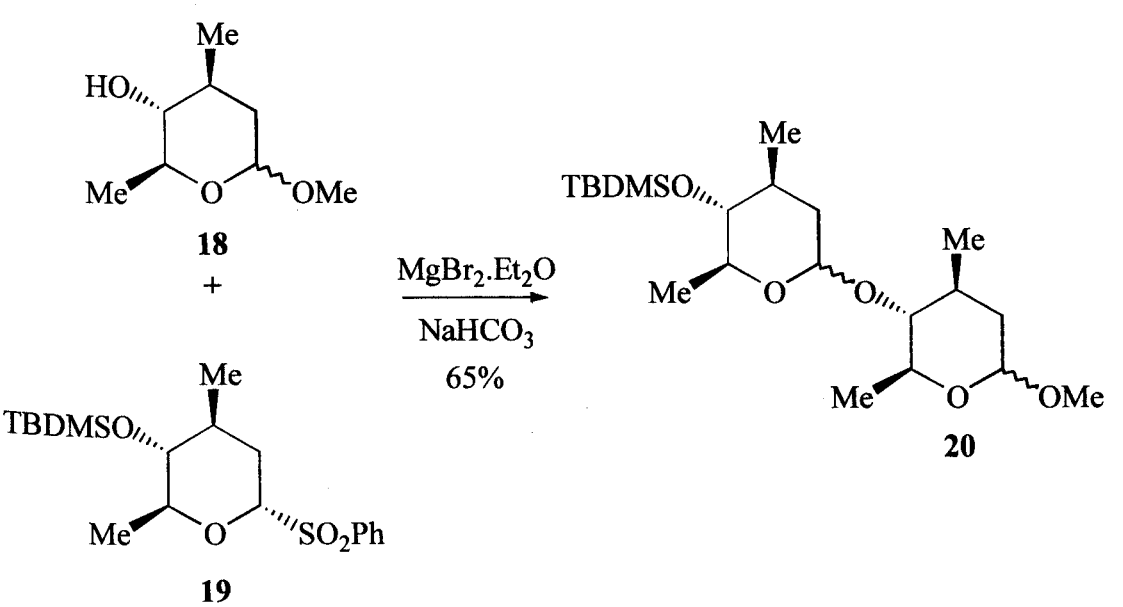


Figure 35 : Magnesium bromide etherate-promoted glycosylation using an *S*-glycosyl sulfone

A recent paper by Chang and Lowary has reported that 2-pyridyl glycosyl sulfones can also be selectively activated in the presence of thioglycosides using samarium triflate.[122]

1.5.8 Selenoglycosides as glycosyl donors

Selenium analogues of thioglycosides are readily activated by typical thiophilic promoters already discussed, such as methyl triflate, phenylselenenyl triflate, $CuBr_2/Bu_4NBr$ in conjunction with silver triflate, nitrosyl tetrafluoroborate and mercuric chloride.[123,124]

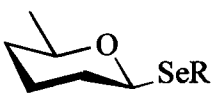


Figure 36 : Selenoglycoside donors

In addition, both 'armed' and 'disarmed' selenoglycosides can be activated with silver triflate in the presence of potassium carbonate, whilst even 'armed' thioglycosides remain unaffected by these conditions.[124,125] This demonstrates a greater intrinsic reactivity of selenoglycosides over their thioglycoside counterparts, which is important in considering orthogonal glycosylation strategies.

1.5.9 Glycals as Glycosyl donors

The olefinic bond of glycals can be activated by sources of halonium ion such as IDCP,[126,127] NBS[128] and NIS,[129] to give an intermediate cyclic halonium species which reacts with glycosyl acceptors regiospecifically at the anomeric centre (Figure 37) to give 2-haloglycosides, which can be reductively dehalogenated to give 2-deoxysugars.[130]

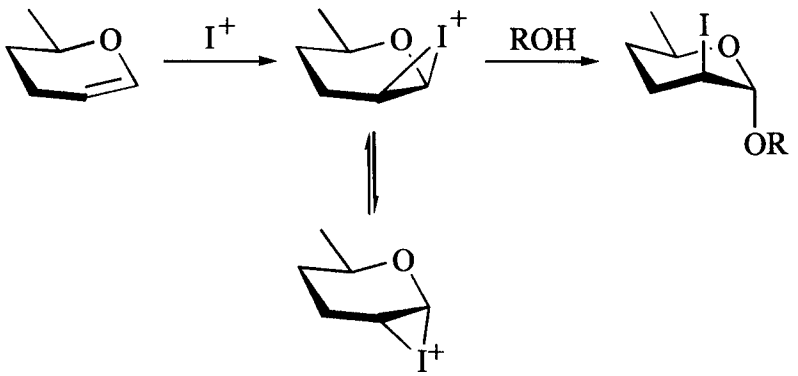


Figure 37 : Halonium ion-promoted activation of glycals

Other promoters used to activate glycals include phenylselenenyl chloride followed by reductive cleavage of selenium from the product,[131] and acids such as CSA,[132] TSOH[133] and triphenylphosphine hydrobromide.[134]

The olefinic bond of glycals can also be readily epoxidised with 3,3-dimethyldioxirane (DMDO) to give 1,2-anhydrosugars, with varying degrees of stereocontrol.[135] These can, in some instances, be further ring-opened with glycosyl acceptors (or their tributylstannyl derivatives) in the presence of zinc chloride to give glycosides [130] (Figure 38).

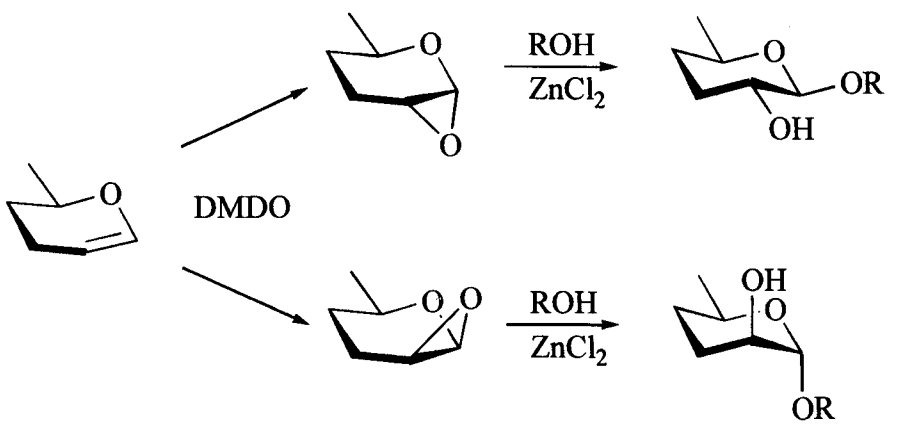


Figure 38 : Conversion of glycals to glycosides via 1,2-oxiranes

1.6 Aims and objectives of the project

The initial work of the Field group on the use of iodine in carbohydrate chemistry focussed on activation of D-galactopyranose derivatives.[105,136] Despite the reactivity of iodine towards glycosyl halides,[136] these are still intrinsically labile glycosyl donors, and as such they lack versatility in their manipulations. The ability of iodine to activate 'armed' thioglycosides[105] whilst leaving their 'disarmed' analogs relatively untouched makes it desirable to seek alternative leaving groups, sulfur-based or otherwise, which may be activatable with iodine, even in the presence of disarming protective groups, which facilitate the synthesis of 1,2-*trans* glycosides.[28]

The use of iodine monobromide as an efficient alternative to conventional means of activating 'disarmed' thioglycosides has been developed by the Field Group during the course of this project.[56] This project ran in parallel to those investigations, with the aim of investigating leaving groups that could be activated by molecular iodine, even in the case of thioglycosides diarmed[22] by the electron-withdrawing nature of hydroxyl protection employed. It was also intended to determine if iodine is capable of activating thioglycosides 'disarmed' by torsional effects.[23]

2 STUDIES ON THE IODINE-PROMOTED ACTIVATION OF FUNCTIONALISED THIOGLYCOSIDES CONTAINING A SECOND SULFUR ATOM

2.1 *Attempted activation of 'disarmed' O-alkyl S-glycosyl xanthates*

2.1.1 Introduction

Marra *et al.* indicated that in the case of α-sialylation, *S*-glycosyl xanthates are more reactive donors than the corresponding ethyl thioglycosides.[113] Moreover, 'disarmed' thioethyl glycoside **22** has been shown[114] to be relatively stable to conditions used for activation of xanthate **21** (Figure 39). Coupling of **22** and **21** gives the thioglycoside building blocks **23** and **24** in 41% and 18% yield, respectively .

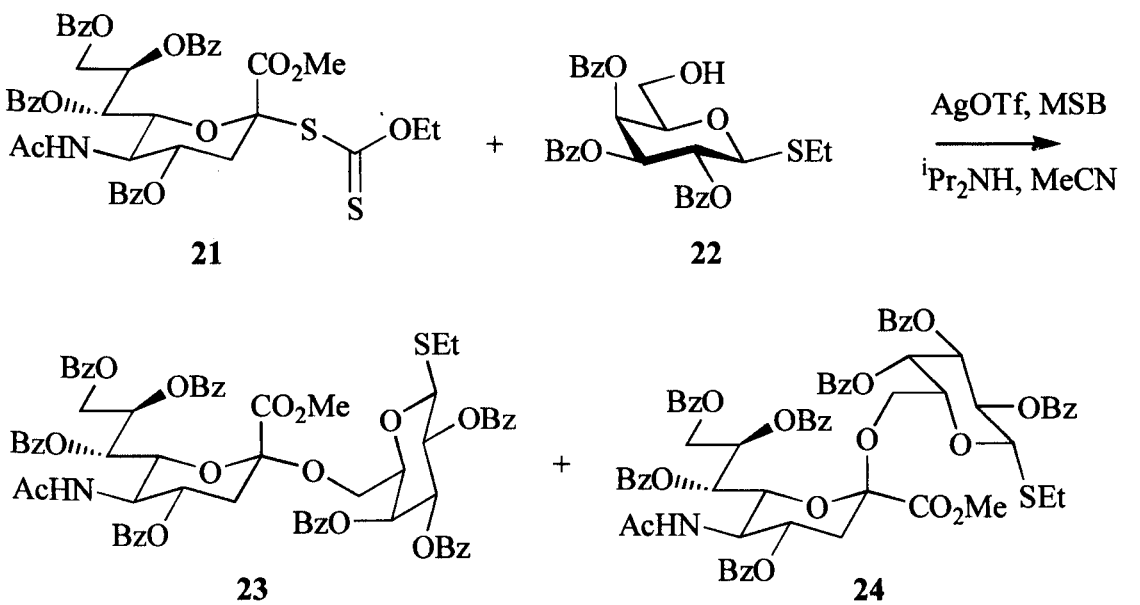


Figure 39 : Reaction of a glycosyl xanthate with a 'disarmed' thioglycoside

Mechanistically, it is likely that the thiocarbonyl sulfur is the more nucleophilic sulfur atom due the extra electron density found in the C=S double bond, and to the fact that it is more remote from the disarming acyl protecting groups. It is thus likely to be the sulfur which reacts with the electrophilic promoter. Any resultant charge on this sulfur atom can then be delocalised amongst the three heteroatoms of the xanthate group (Figure 40).

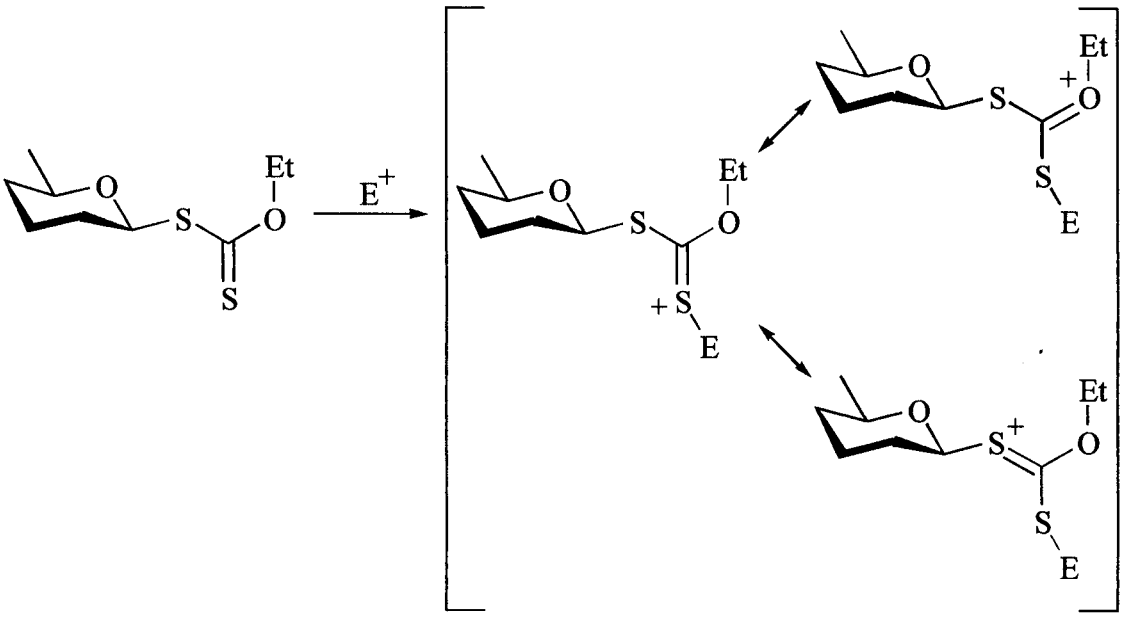


Figure 40 : Delocalisation of positive charge between heteroatoms of xanthate group

It is likely that sufficient positive character is imparted on the anomeric sulfur atom to induce cleavage of its bond to the anomeric centre, (Figure 41) and hence activation.

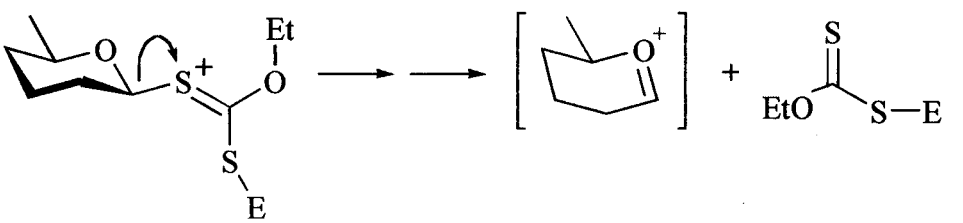


Figure 41 : Loss of xanthate leaving group to give oxocarbenium intermediate

This is essentially a similar process to that reported by Hanessian *et al.* in 1980, using remote activation of the nitrogen atom of pyridyl thioglycoside **25** by methanesulfonic acid or toluenesulfonic acid to induce cleavage of the anomeric carbon-sulfur bond[137] (Figure 42). Mercuric nitrate and silver nitrate have also been used to activate **25**.[137]

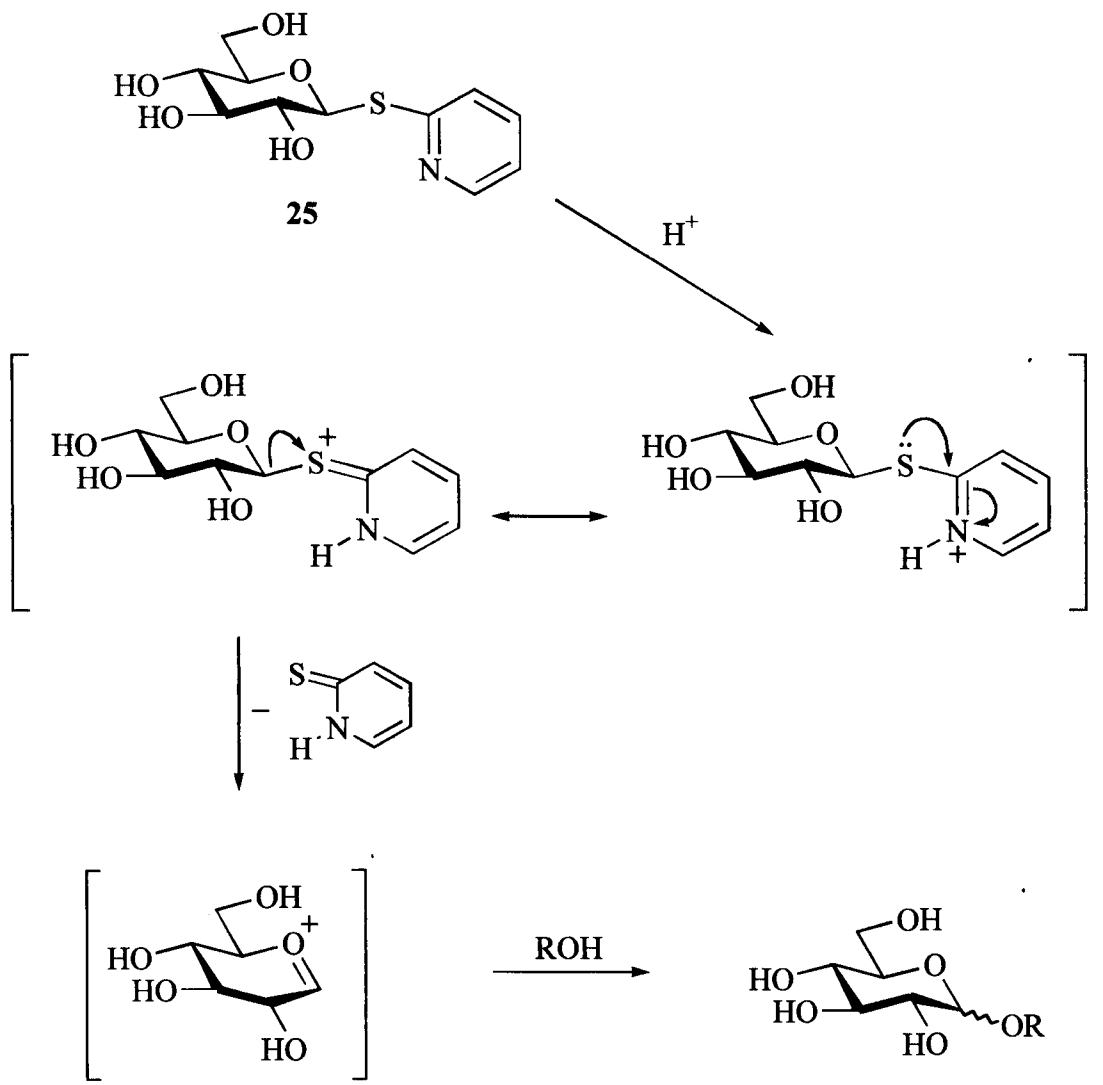


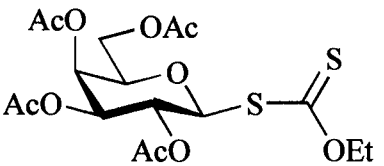
Figure 42 : Acid-promoted remote activation of pyrindyl thioglycosides

2.1.1.1 *Proposal*

It was reasoned that peracylated *S*-glycosyl xanthates may be more reactive than the corresponding thioglycosides towards activation by iodine, or iodine in combination with DDQ (DDQ has been observed to partly improve the reactivity of 'disarmed' thioglycosides as glycosyl donors when using iodine as a promoter[138]). If so, this would provide a means of extending the iodine-mediated activation of 'armed' thioglycosides to include their counterparts 'disarmed' by the presence of acyl protecting groups. This would potentially allow the 1,2-*trans* stereocontrol[28] not easily afforded by the use of benzyl ether protected thioglycosides.

2.1.2 Aims and objectives

The initial aim of this part of the project was to synthesise the 'disarmed' glycosyl xanthate **26**, and attempt glycosylation reactions with simple alcohols under typical iodine-promoted activation conditions, in both the absence and presence of DDQ.



26

2.1.3 Results and discussion

2.1.3.1 *Synthesis of O-alkyl S-glycosyl xanthates*

Tropper *et al.*[139] reported that *S*-glycosyl xanthates can be synthesised from the corresponding glycosyl bromides and potassium ethyl xanthate **28** by phase-transfer catalysis. Their two phase system comprised ethyl acetate and either 2M sodium carbonate or saturated sodium hydrogen carbonate solution, with tetrabutylammonium hydrogensulfate (TBAHS) as the phase transfer catalyst. It was reported that dichloromethane could also be used as the organic solvent,[139] but that alkylation of the xanthate ion by dichloromethane (Figure 43) means a greater excess of the potassium salt is required (3:1 as opposed to 1.5 :1) to attain a similar completion time for the reaction.

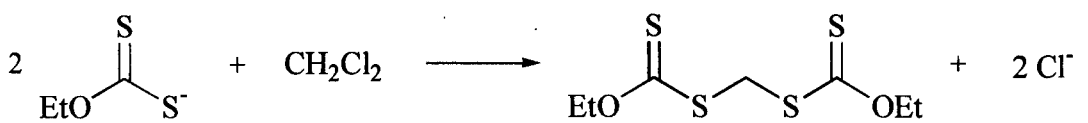


Figure 43 : Side reaction of dichloromethane with potassium ethyl xanthate

S-Galactopyranosyl xanthate **26** was thus prepared from the anomeric bromide **27** and potassium ethyl xanthate according to this phase transfer method, using ethyl acetate as the organic phase and saturated sodium hydrogen carbonate solution as the aqueous phase (Figure 44).

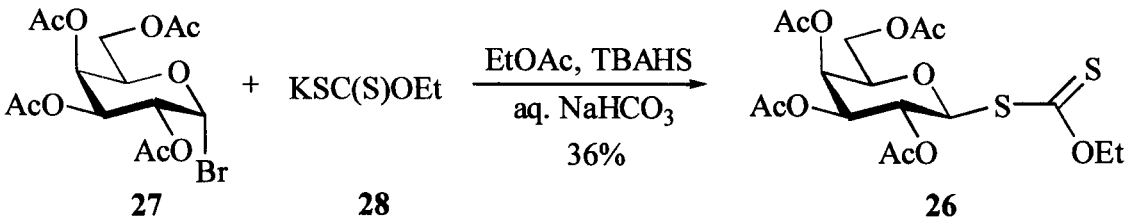


Figure 44 : *O*-Ethyl *S*-galactopyranosyl xanthate synthesis

Tropper *et al.* reported categorically that in all cases no glycosidic by-products were ever seen in the reaction mixtures, either by t.l.c., ^{1}H NMR or ^{13}C NMR.[139] This observation was not reproducible, however, and more than one glycosidic product was observed in the ^{1}H NMR spectrum of the product after purification by column chromatography using chloroform/ethyl acetate (the eluant used by Tropper *et al.*[139]) as eluant. Unsuccessful attempts to achieve separation of the products by t.l.c. were made using several ratios of chloroform/ethyl acetate as eluant. However, separation was achieved using toluene/ethyl acetate (5:1), and purification by column chromatography using this eluant allowed isolation of **26**, in 36% yield. No attempt was made to identify the spurious product, although the literature suggests that under alkaline conditions, *O*-alkyl xanthate salts can be hydrolysed to give the alcohol and carbon disulfide[140] (Figure 45).

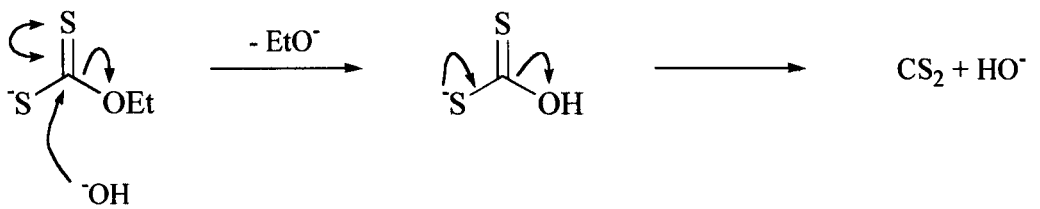
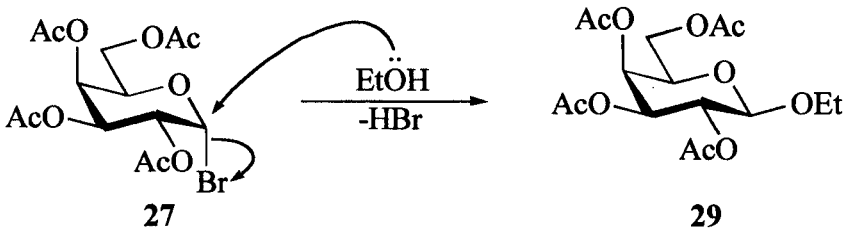


Figure 45 : Base-catalysed hydrolysis of *O*-ethyl xanthate ion

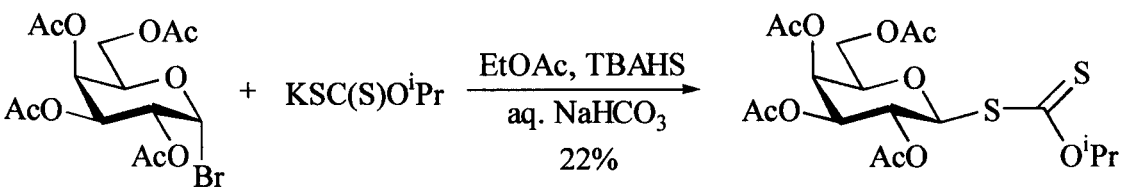
It may be that the spurious product was the ethyl glycoside, formed by displacement of bromide ions by ethanol under phase-transfer conditions (Figure 46).



27 29

Figure 46 : Possible reaction of a glycosyl bromide with ethanol under PTC conditions

Joedodibroto reported that the potassium *O*-isopropyl xanthate **30** is more stable to hydrolysis under alkaline conditions than the *O*-ethyl xanthate **28**.[140] This is a reasonable observation, as the isopropyl group would be likely to effect an increase in the electron density around the xanthate carbon atom, relative to that caused by the presence of the ethyl group, reducing its susceptibility to nucleophilic attack by hydroxide ions. It was reasoned that if hydrolysis of the xanthate group were occurring during the reaction, then use of the isopropyl analogue might lessen this effect, and give a more readily isolable glycosyl xanthate. Bromide **27** reacted with **30** under phase-transfer conditions to give isopropyl xanthate **31**. The product was purified by column chromatography, and crystallisation from dichloromethane/hexane gave *O*-isopropyl *S*-(2,3,4,6-tetra-*O*-acetyl-β-D-thiogalactopyranosyl) dithiocarbonate **(31)** in 22% unoptimized yield.



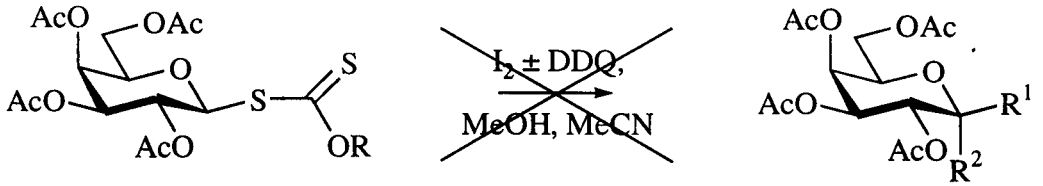
27 30 31

Figure 47 : *O*-Isopropyl *S*-galactopyranosyl xanthate synthesis

2.1.3.2 *Reaction of O-alkyl S-glycosyl xanthates with iodine, and iodine in combination with DDQ*

Glycosylation of xanthates **26** and **31** with methanol was attempted in a 2:1 mixture of acetonitrile and methanol, using iodine (2 mol. eq.), or iodine in combination with DDQ (2 mol eq. of each), as a promoter (Figure 48). In the absence of DDQ, reaction was very slow, and t.l.c. suggested that significant deprotection of the acetate groups was

occurring over a period of 48 hours. In the presence of DDQ, both **26** and **31** were observed to be consumed within 20 minutes by t.l.c.. These experiments were repeated in the presence of 3Å molecular sieves and/or powdered potassium carbonate, which both quenched the reaction.

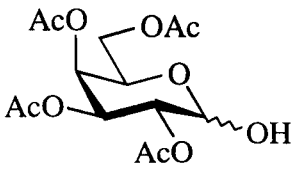


26 R = Et
31 R^1 = iPr

32 R^1 = H, R^2 = OMe
33 R^1 = OMe, R^2 = H

Figure 48 : Attempted glycosylation of *O*-alkyl xanthates with methanol in the presence of iodine or iodine in conjunction with DDQ

The product of the iodine/DDQ-promoted reactions of both **26** and **31** had the same R_f value, and co-spotting with a mixture of the expected products of methanolysis, α- and β-methyl galactopyranosides **32** and **33** (supplied by Dr K.P.R. Kartha), indicated that this product was neither of these two compounds. It was unstable to normal column chromatography, but if the silica was pre-washed with a 2% solution of triethylamine in the packing solution prior to loading of the sample, then the product could be eluted successfully. ^{1}H NMR of the chromatographed product from the attempted reaction of **31** suggested that the the *O*-alkyl group was no longer present, but confirmed that the product is neither **32** nor **33**, nor the hemiacetal **34**, which might be formed if moisture were present in the reaction mixture.



34

It is reasonable to suggest that after initial attack of iodine on the sulfur of the C=S double bond, the lone pairs of both the anomeric sulfur atom and the *O*-alkylated oxygen atom are available to stabilise the positive charge of this cation (**35**). Although sulfur is more polarisable, and less electronegative than oxygen, the disarming effects of

the acetate protecting groups in the sugar unit may limit the contribution of the anomeric sulfur atom to this stabilisation. The consequence of this may be that sufficient positive charge resides on the oxygen atom of the xanthate group to induce cleavage of the *O*-alkyl group in preference to the *S*-glysosyl group (Figure 49), to generate sulfenyl iodide **36**. This would presumably dimerise in the same manner as alkyl sulfenyl iodides,[141] to give a disulfide. We thus speculate, but could not demonstrate, that **36** or its disulfide is the labile compound produced in the reaction of with iodine and DDQ.

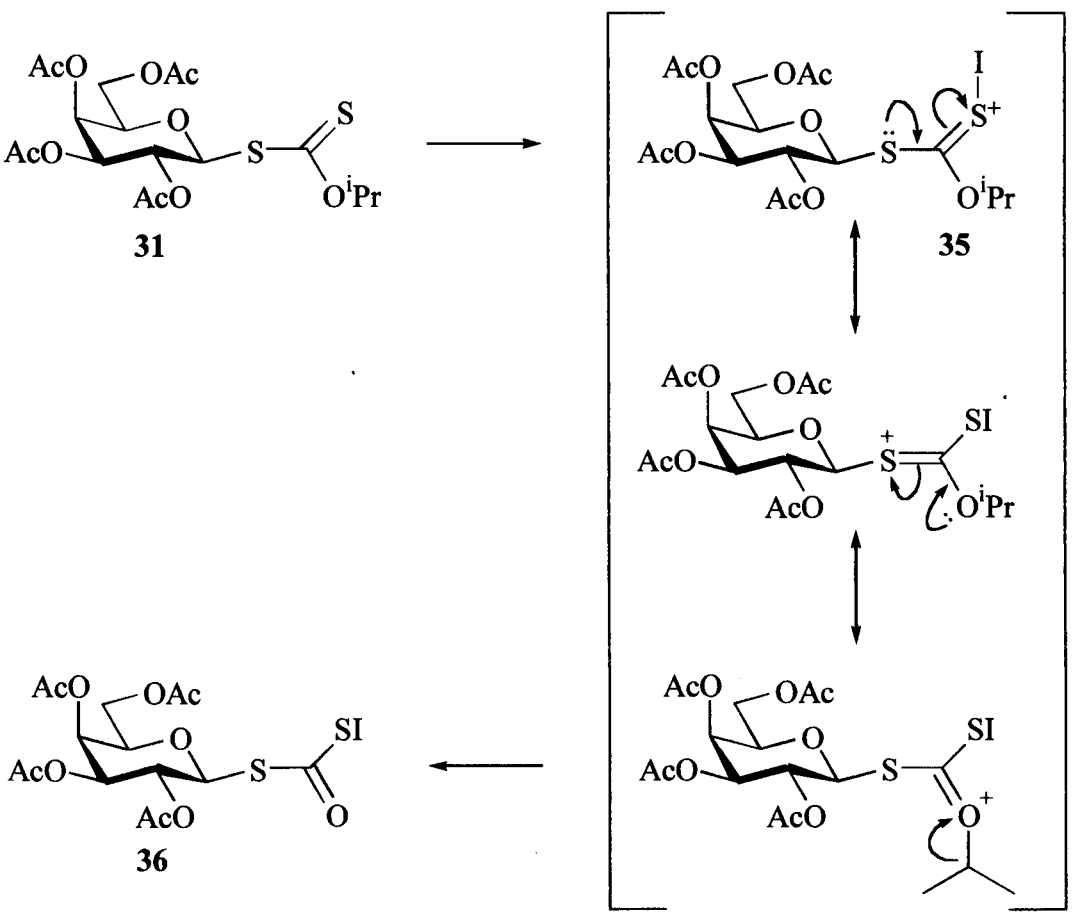


Figure 49 : Possible Reaction Between Iodine and *O*-Alkyl Xanthates

The secondary propyl cation generated could be quenched by any methanol present to generate isopropyl methyl ether. A primary ethyl cation is less likely to form than this secondary propyl cation, so in the case of the ethyl xanthate **26**, it is possible that the alcohol may directly displace the xanthate group at the carbon α- to the oxygen of the xanthate group.

2.2 *Attempted iodine-promoted activation of alkylthioalkyl thioglycosides as glycosyl donors*

2.2.1 Introduction

2.2.1.1 n-Pentenyl glycosides as glycosyl donors

Fraser Reid *et al.* first noticed the difference in reactivity between 'armed' and 'disarmed' glycosyl donors when studying the use of *n*-pentenyl glycosides as glycosyl donors.[22,40] These reagents are believed to operate by addition of I^+ to the double bond of the *n*-pentenyl group to generate a cyclic species which is attacked by the anomeric oxygen, leading to activation (Figure 50).

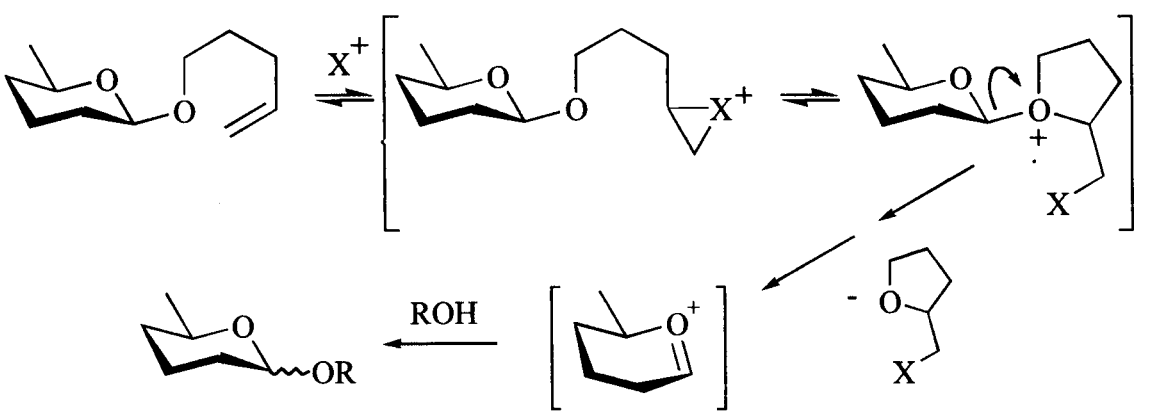


Figure 50 : Activation of *n*-pentenyl glycosides by sources of iodonium ion.

The *n*-pentenyl glycosides 'armed' by the presence of benzyl ether protection are activated by IDCP, whilst their 'disarmed' counterparts are not.[22,40] It is presumed that the relatively strongly electron-withdrawing nature of acyl protecting groups draws electron density away from the anomeric oxygen atom, reducing its nucleophilicity.[25] The 'disarmed' *n*-pentenyl glycosides thus require the more powerful iodinating agents, such as NIS in combination with either triflic acid or TESOTf, to be activated.[71]

Activation of unprotected and 'armed' thioglycosides[105] presumably proceeds *via* iodination of the anomeric sulfur atom leading to formation of an iodosulfonium ion

which cleaves to leave the usual oxocarbenium intermediate (Figure 51) and a sulfenyl iodide, which is believed to dimerise to give the corresponding disulfide.[142]

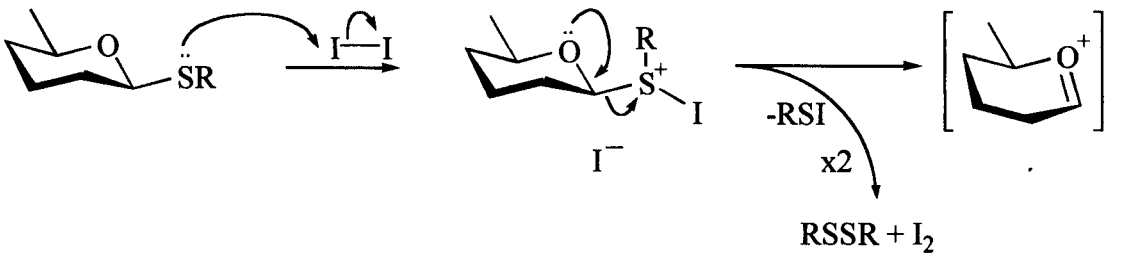


Figure 51 : Iodine-promoted activation of thioglycosides

The relative unreactivity of 'disarmed' thioglycosides towards iodine or IDCP can again be attributed to a reduction in the nucleophilicity of sulfur by the the strongly electron-withdrawing acyl protecting groups.

The activation of the anomeric oxygen in the *n*-pentenyl glycoside method is likely to be facilitated by the intramolecular nature of the alkylation step. Although activation of 'disarmed' *n*-pentenyl *O*-glycosides with IDCP, as well as 'disarmed' thioglycosides with both iodine and IDCP, has proved unsuccessful, it was considered possible that attempts to activate sulfur (as opposed to oxygen) in an intramolecular fashion might prove more effective.

Earlier attempts within the Field group to activate 'disarmed' *n*-pentenyl and allyl *S*-galactopyranosides with iodine had already proved unsuccessful,[143] so a new approach was sought. It was considered highly likely that the sulfur of a thioether may be sufficiently nucleophilic to attack iodine, forming a relatively stable iodosulfonium ion. If such a thioether moiety were linked by an appropriate spacer group to a 'disarmed' thioglycoside, it is possible that the anomeric sulfur atom could intramolecularly attack the carbon adjacent to the sulfonium ion, displacing the sulfenyl iodide. The anomeric sulfur would, in effect, be alkylated to give a cyclic sulfonium ion. Cleavage of the anomeric carbon-sulfur bond would give the reactive oxocarbonium ion, and a cyclic sulfide, which should be a good leaving group (Figure 52).

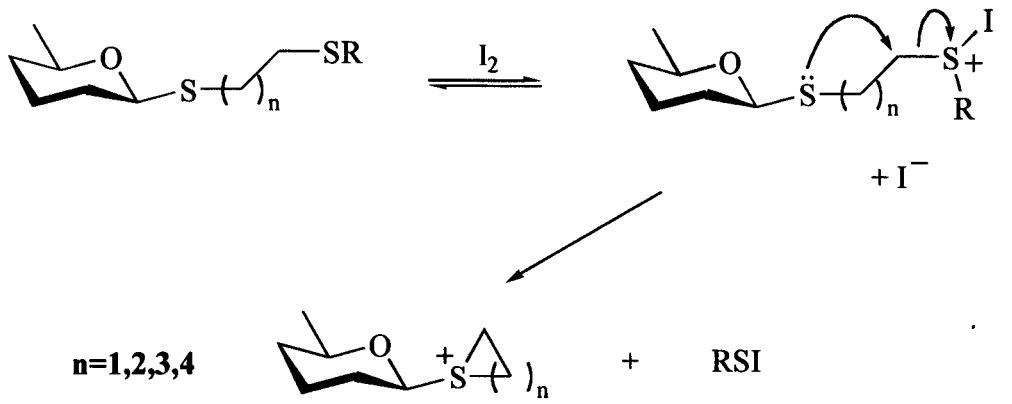


Figure 52 : Proposed remote activation of (alkylthio) alkylthioglycosides

Thus, a spacer group of two methylene units could give rise to an episulfonium ion intermediate, whilst four or five methylene units could generate tetrahydrothiophene or pentamethyl sulfide as leaving groups, respectively. The use of a single methylene group as a spacer, i. e. the creation of a dithioacetal group adjacent to the anomeric thioacetal, has the potential to allow the participation of the anomeric sulfur to occur by a different means. The lone pair of the anomeric sulfur could directly force cleavage of the remote carbon-sulfur bond, generating an *S*-glycosyl thioformaldehyde sulfonium ion, which in turn could prove to be a useful leaving group (Figure 53).

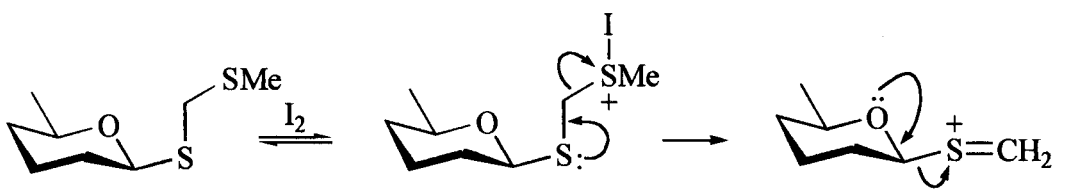
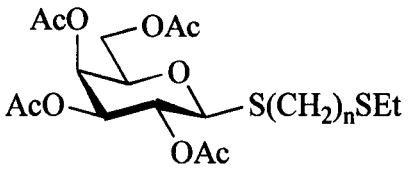


Figure 53 : Potential for generation of thioformaldehyde leaving group

2.2.2 Aims and objectives

Previous studies by the Field group on the use of iodine as a promoter in the activation of thioglycosides focussed on thioglycosides of the *galacto-* series in connection with studies on the synthesis of parasite-derived mucin glycan,[105] and it was deemed appropriate to continue to do so. The aim of this section of the project was thus to prepare and characterise the previously unknown 2,3,4,6-tetraacetylated thiogalactosides **37-41** with a variety of length of spacer group (n=1,2,3,4,5), and examine their reactivity towards alcohol acceptors in the presence of iodine.



37 n=1
38 n=2
39 n=3
40 n=4
41 n=5

2.2.3 Results and discussion

2.2.3.1 Synthesis of target compounds

Thioglycosides can be prepared by a number of different methods. The most common means are by reaction between the glycosyl peracetate and the thiol under catalysis by Lewis acids such as BF_3-etherate[144] or zinc chloride,[145] or from the peracetate and a suitable thioalkyl(aryl) trimethylsilane[146] under Lewis acid catalysis. These procedures give predominantly 1,2-*trans* thioglycosides, although small amounts of the 1,2-*cis* isomers are also observed.[74]

The use of thioalkyl(aryl) trimethylsilanes is popular, and appears to result in higher yields and less odour problems.[147] However, the procedure is generally quite slow, and requires a large excess of the expensive trimethylsilyl derivative of the thiol. During the course of this project, Kartha and Field reported a significant improvement in this reaction, by using iodine as a catalyst in acetonitrile.[148] In general the reaction was complete in less than 10 minutes. They have also demonstrated that similar syntheses can be effected by *in situ* generation of the TMS derivative from hexamethyldisilane and the corresponding disulfide.[148] In some cases they found that the use of the TMS derivative of the thiol is not necessary, and were able to effect some of these syntheses from the glycosyl pentaacetate and the free thiol in the presence of iodine.[148]

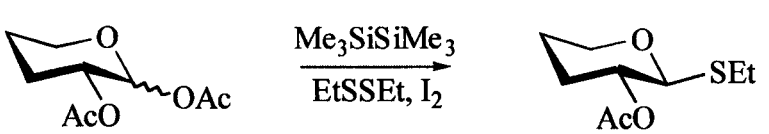


Figure 54

Other means of forming thioglycosides include alkylation of the 1-thioglycoside obtained by either selective *S*-deacetylation of the anomeric thioacetate[149] (Figure 55) or

hydrolysis of an anomeric thiouronium salt[149,150] (Figure 55), and nucleophilic displacement of an anomeric halide by a thiol under phase transfer conditions.[151]

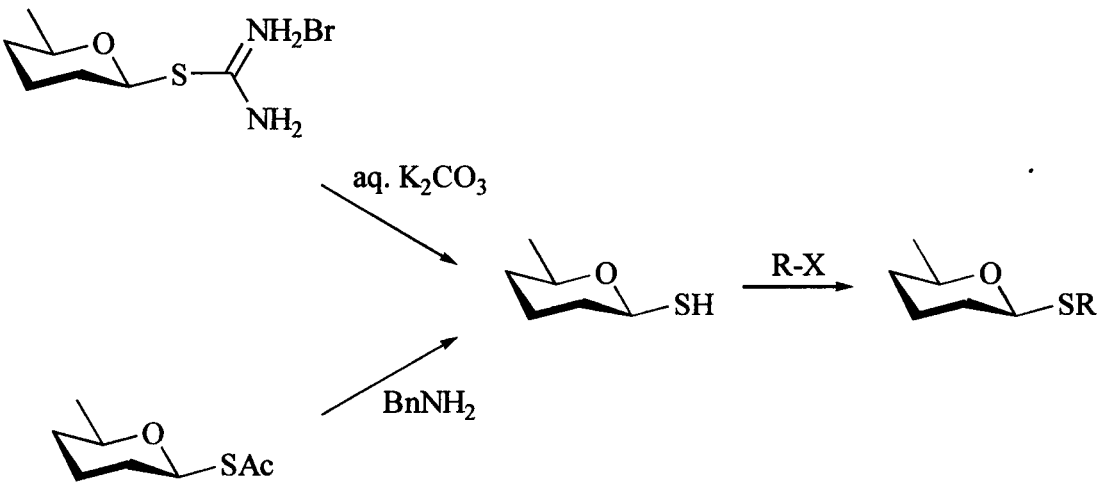
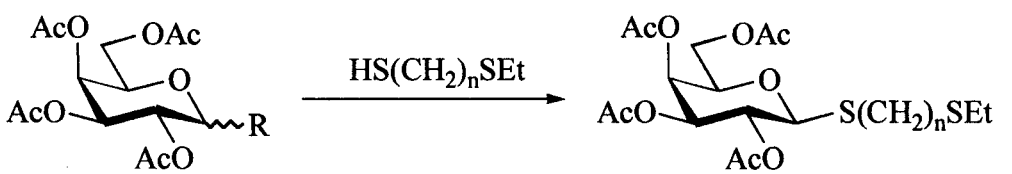


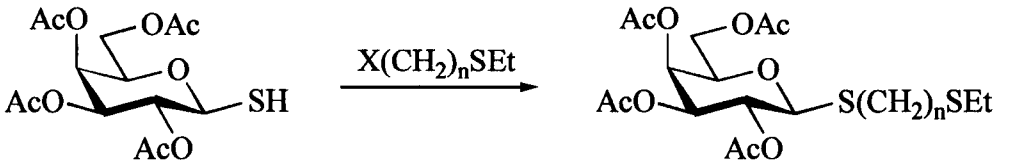
Figure 55 : Thioglycoside synthesis from anomeric thiouronium salts and thioacetates *via* the 1-thiol

Formation of simple thioglycosides can thus be seen to be relatively straightforward. The cost of preparing carbohydrate building blocks is likely to be minimised if the number of manipulations involving the carbohyrate portion of the desired product is also minimised. This means that the preferred methods of preparing the target compounds would involve either constructing the complete ethyl thioalkyl mercaptan side-chains and allowing these to react under appropriate conditions with either acetobromogalactose **27** or pentaacetylgalactose **42** (Figure 56), or constructing the corresponding ethyl thioalkyl halides, which could then be allowed to react with the 1-thioglycoside **43**, derived from selective *S*-deacetylation[149] of the anomeric thioacetate **45** (Figure 57).



27 R = Br (α) **42** R = OAc (α/β mixture)

Figure 56 : Introducing the ethyl thioalkyl mercaptan directly to the anomeric centre

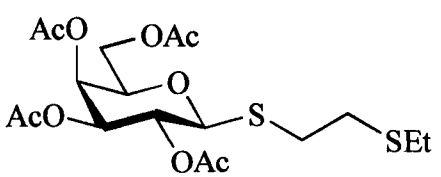


43

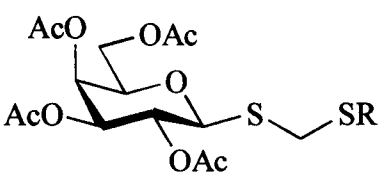
Figure 57 : The dihaloalkane approach to introducing a thioglycoside containing a remote thioether group

In the first of these two options, preparation of the mercaptans to add to the anomeric centre of the galactoside was not likely to be straightforward, and would possibly have required the separation of several strong-smelling products by distillation. This was deemed to give rise to an unacceptable risk of stench.

The second option appeared more promising. Indeed, chloroethyl ethyl sulfide (n=2) is commercially available, and it was believed that it could, in principle, be used to prepare **38** in this way. Although the analogous compound suitable for preparing **37** is not commercially available, chloromethyl methyl sulfide is, and so could be used to prepare methylthiomethyl thiogalactoside **44** instead.



38



37 R=Et **44** R=Me

This procedure required the anomeric thioacetate **45** as a starting material. This was prepared in 57% yield by refluxing of a solution of glycosyl bromide **27** in DCE in the presence of an excess of potassium thioacetate over a period of 30 hours (Figure 58-i). There was evidence, from ^{1}H NMR, of a side reaction between the thioacetate ion and DCE, analogous to that of xanthates with DCM.[152] It was believed that the phase transfer method already employed to produce glycosyl xanthates[152] could be applied here, and indeed it was found that **45** could be prepared from **27**, under PTC conditions, in 57% yield within 3 hours (Figure 58-ii). TBAI was used as the catalyst in this reaction as no TBAHS was available at the time.

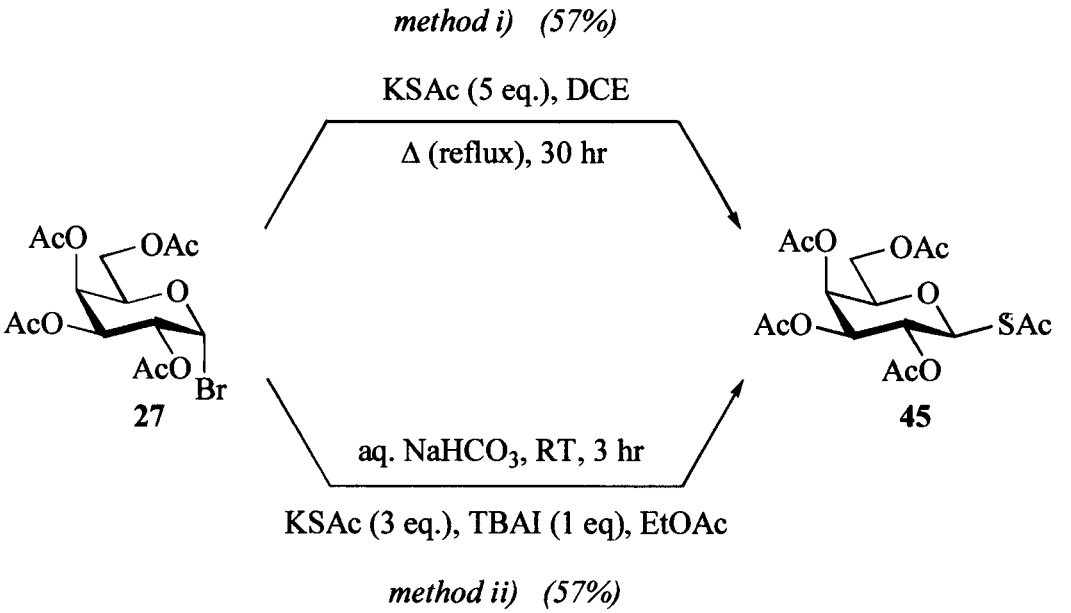


Figure 58

A qualitatively greater level of degradation of the bromide to hemiacetal, compared to those observed in similar xanthate syntheses, was observed by t.l.c.. This is likely to be as a result of attack by iodide on **27** to give the β-iodide **46** which will hydrolyse rapidly in the presence of moisture (Figure 59). TBAHS is likely to be more effective as the hydrogen sulfate ion is not likely to be a strong nucleophile, and so should not catalyse hydrolysis of the glycosyl bromide in the same way as TBAI.

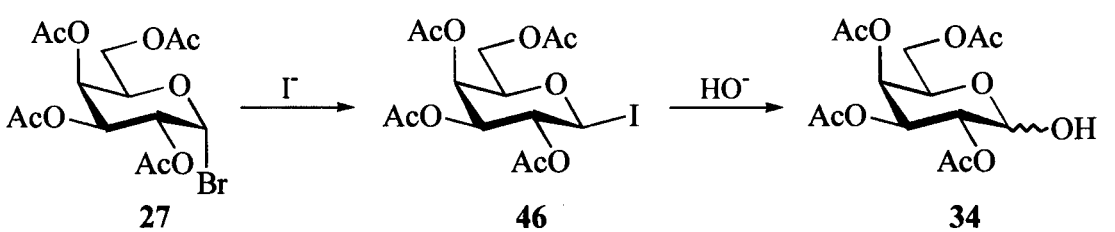
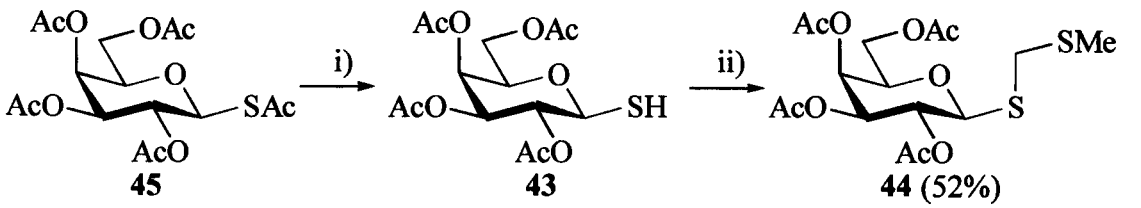


Figure 59 : Iodide-Assisted Hydrolysis of Acetobromogalactose

Preparation of **44** (Figure 60) was then effected by selective *in situ* *S*-deprotection of the anomeric thioacetate **45** with benzylamine,[149] followed by addition of chloromethyl methyl sulfide. Evidence for the structure of **44** was provided by ^{1}H and ^{13}C NMR. The product was a glassy material, from which extraction of the last traces of solvents was not possible, and confirmation of the percentage composition by elemental analysis could not be achieved.



Reagents and conditions:
i) $BnNH_2$, THF, RT; ii) $ClCH_2SMe$, Et_3N, RT.

Figure 60 : One-pot synthesis of methylthiomethyl 2,3,4,6-tetra-*O*-acetyl-β-D-thiogalactopyranoside

CI mass spectrometry of the product suspected to be **44** gave an ion of 27 units above expected molecular weight of 424, but no molecular ion. This could be explained by combination of a molecule of **44** with 2 CH_2 units under conditions of the mass spectrometry experiment, to give a structure such as **47** (Figure 61).

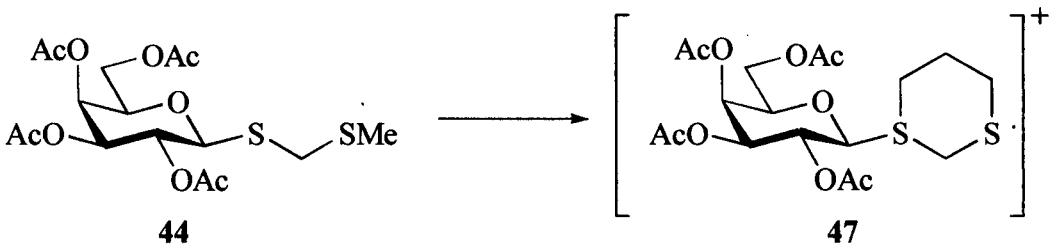


Figure 61 : Possible combination reaction to give unexpected peak in mass spectrum of 44

Attempts to adapt this synthesis for the preparation of **38** (n=2) from chloroethyl ethyl sulfide were unsuccessful. This suggests that the sulfur atom of chloromethyl methyl sulfide participates in the reaction, since sulfur has a similar electronegativity to carbon and so is not likely to activate the chlorine-bearing carbon by inductive effects. The reaction probably occurs by a stepwise process, whereby a lone pair of electrons belonging to the sulfur atom assists in the loss of a chloride ion to give a sulfenium cation which then reacts with the nucleophile (Figure 62).

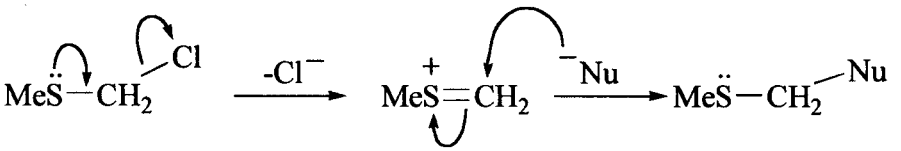


Figure 62 : The reaction of chloromethyl methyl sulfide with nucleophiles

The sulfur atom of chloroethyl ethyl sulfide is not adjacent to the chlorine-bearing carbon atom, and so cannot assist in the loss of chloride from the molecule in this way. One might expect it to be possible that intramolecular attack of sulfur on the chlorine-bearing carbon could occur, generating an episulfonium ion (Figure 63) which would be expected to be susceptible to nucleophilic attack by the anomeric thiol, but this does not appear to occur under these reaction conditions.

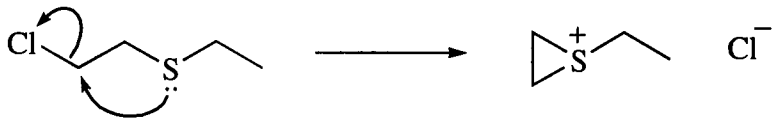


Figure 63 : Episulfonium ion formation from a β-chloro sulfide

The inability to prepare compound **38** by this route appeared to rule out the use of chlorides to prepare target compounds **38-41**. The bromoalkyl ethyl sulfides are not commercially available, and an obstacle toward their preparation was the suspicion that they might be difficult to handle due to the likelihood of intramolecular alkylation of the sulfide group to give fairly stable cyclic sulfonium ions (Figure 64).

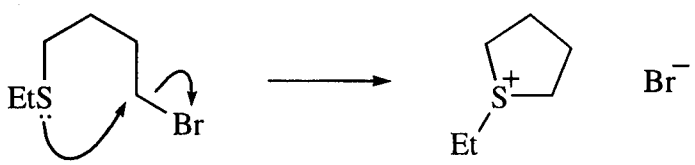


Figure 64

Possible variations on the two general strategies discussed above would involve building up the thioglycoside aglycon in two steps. Under appropriate conditions, an excess of an alkyl dithiol could be allowed to react with either **27** or **42** to give a mercaptoalkyl thioglycoside, which could then be alkylated with bromoethane to produce a remote thioether (Figure 65). This would require more manipulations of the carbohydrate portion of the molecule, but should allow facile separation of the intermediate product from unpleasant smelling thiols by column chromatography.

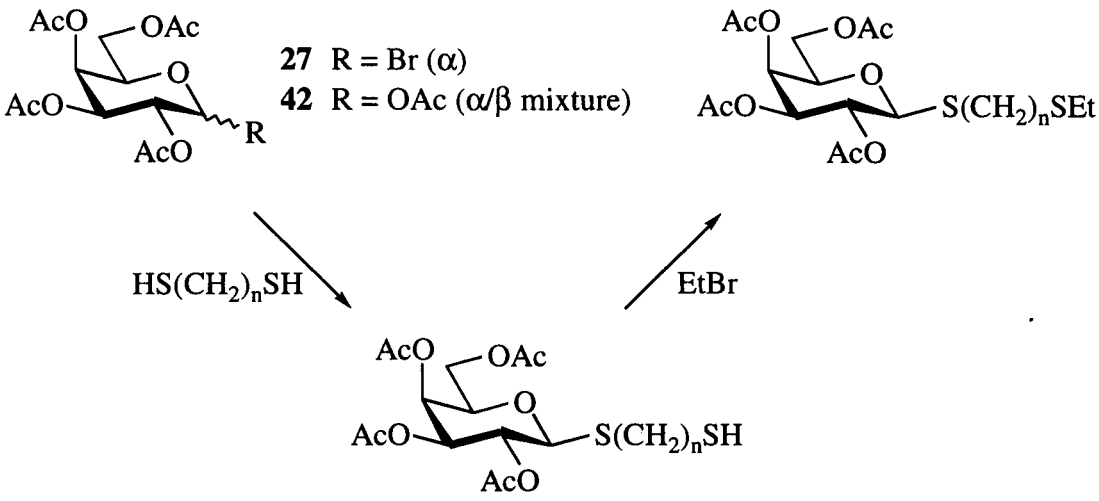


Figure 65

Alternatively, the 1-thioglycoside **43** could be alkylated with various alkyl dibromides to give haloalkyl thioglycosides. These products could then be used to alkylate ethanethiol to produce the desired compounds (Figure 66).

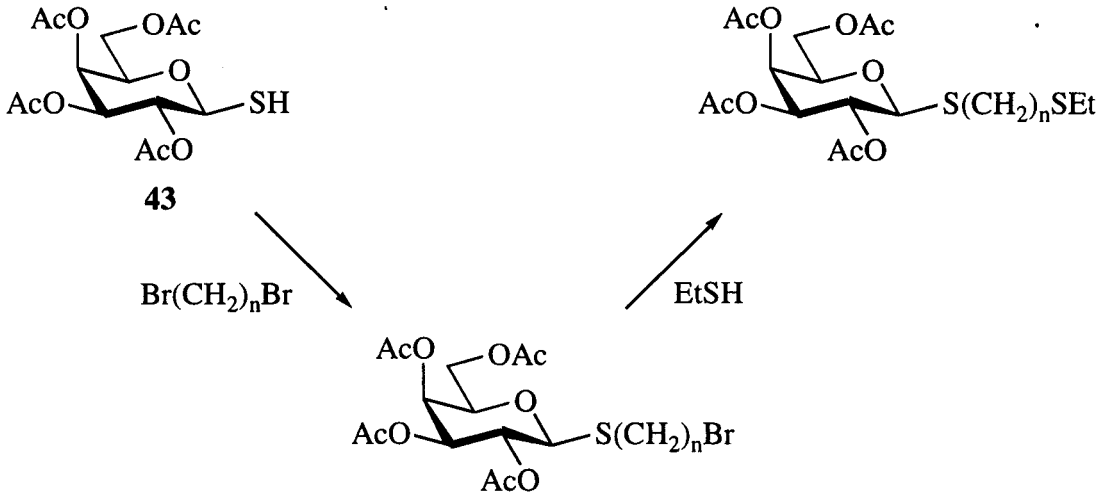
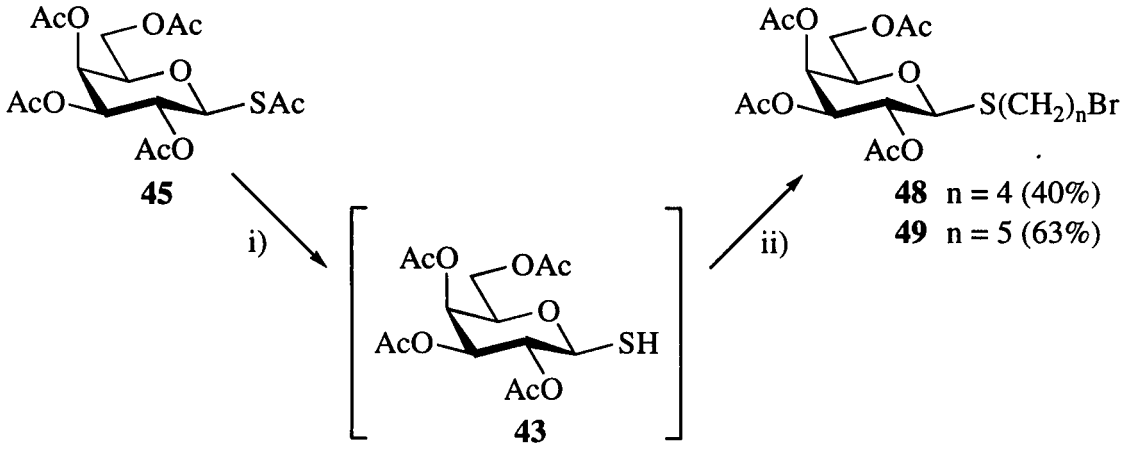


Figure 66

In order to avoid the use of the strong-smelling, yet involatile, dithiols, this latter approach was attempted. The compounds with tetramethylene (**40**) and pentamethylene (**41**) chains were expected to be the most likely to be activated by iodine in the manner described, with formation of the five or six-membered rings being the driving force for activation. In view of this, selective *S*-deacetylation of thioacetate **45** with benzylamine in dry, deoxygenated THF, in the presence of ten equivalents of 1,4-dibromobutane or

1,5-dibromopentane led to alkylation of anomeric sulfur, to form the (n-bromoalkyl) thiogalactopyranosides **48** (40%) and **49** (63%), respectively (Figure 67).



Reagents and conditions:
i) $BnNH_2$, THF, RT; ii) $Br(CH_2)_nBr$ (n=4 or n=5), Et_3N, RT.

Figure 67 : Synthesis of bromobutyl and bromopentyl thiogalactosides

The identification of these products was performed on the basis of NMR obtained, which showed the correct number of methylene groups to be present. The signal for the methylene group nearest to sulfur was spilt into two distinct resonances of one proton each, indicating the attachment of the alkyl chain to sulfur adjacent to a stereogenic (anomeric) centre.

A direct reaction of **48** with sodium ethanethiolate was attempted in DMF, with a view to preparing **40** (Figure 68). This was unsuccessful, and several decomposition products were observed by t.l.c.. It is believed possible that this may be due to deprotection of acetyl groups by the ethanethiolate ion.

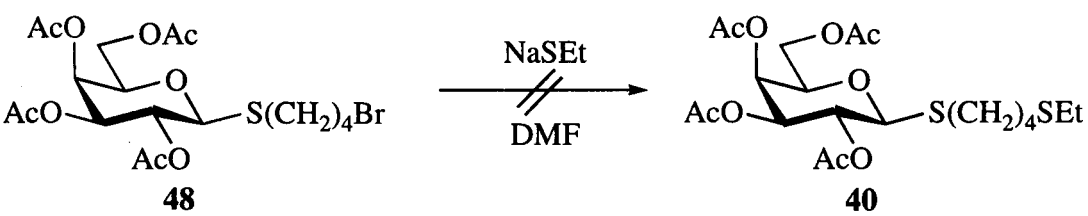


Figure 68

An attempt to synthesise **41** from **49** and NaSEt under phase transfer conditions and using TBAHS as catalyst also failed, with 83% of **49** recovered (Figure 69).

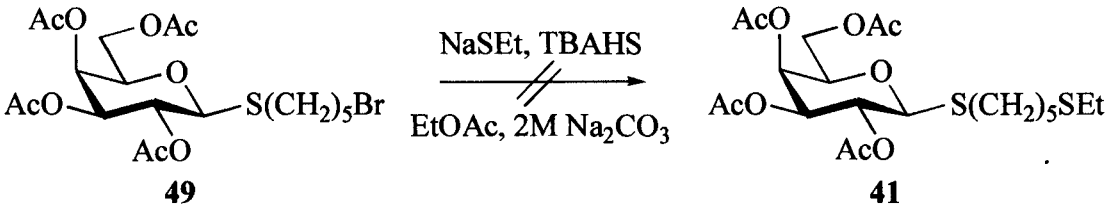


Figure 69

On storage **48** was found to decompose to give glycosyl bromide **27**. The evidence for this was gained from ^{1}H NMR data after separation from non-decomposed **48** by column chromatography. This may occur via intramolecular alkylation of the anomeric sulfur atom by the bromobutyl group, generating a cyclic sulfonium ion which is itself displaced from the anomeric centre by the liberated bromide anion, to give tetrahydrothiophene (**50**) and **27** (Figure 70). Alternatively, there may be some other, concerted, mechanism. No attempt was made to confirm tetrahydrothiophene as the other decomposition product. The occurrence of this decomposition reaction was encouraging, as it lent credibility to the initial proposal that the presence of an electrophilic centre remote from the anomeric centre would lead to cyclisation at the anomeric sulfur atom, and thus activation towards glycosylation (Figure 52).

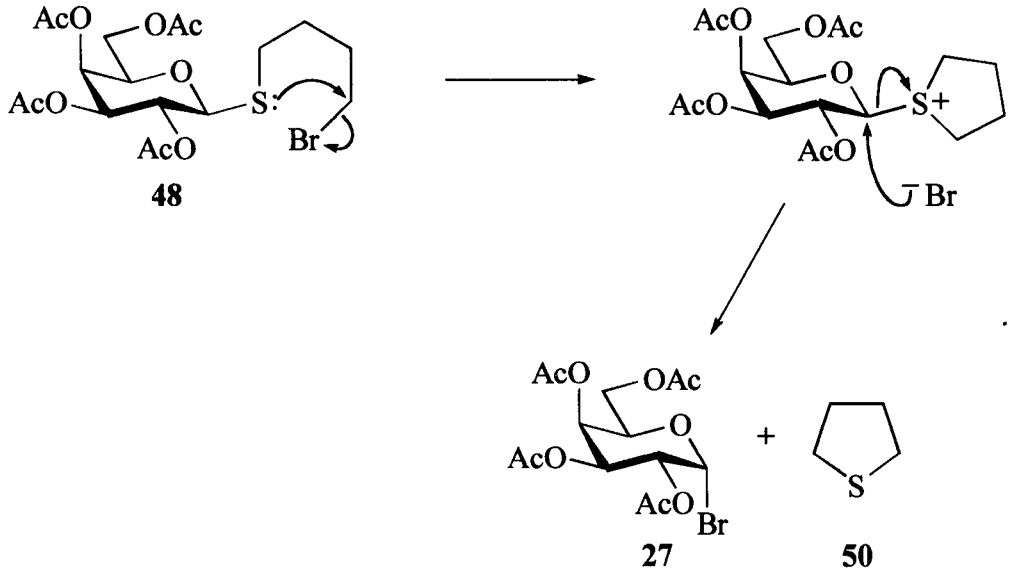


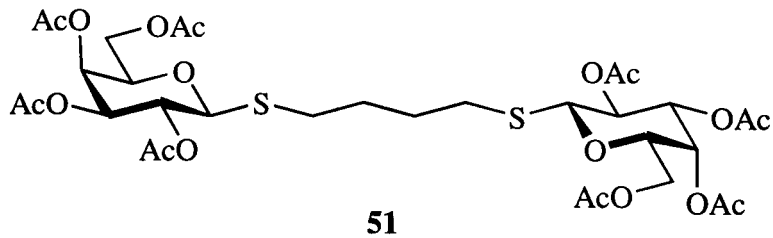
Figure 70 : Stepwise decomposition of a bromobutyl thiogalactoside

The lack of success in obtaining the target thioglycosides led to the conclusion that the odourous alkane dithiols would have to be used to prepare them. Construction of the entire thioglycoside aglycon was deemed to involve too many potential difficulties in the separation of the aglycon from side-products and starting materials, and therefore a stepwise approach was taken (Figure 65).

The usual method of introducing thiols to the anomeric centre, namely Lewis acid-promoted reactions of pentaacetate **42**, typically results in the presence of a small amount of the *cis*- (in this case α) thioglycoside in addition to the dominant *trans*- (β) thioglycoside.[74] In an attempt to ensure the stereospecificity of the preparation, the use of pentaacetate **42** was rejected in favour of a phase-transfer reaction with α-bromide **27**, which could reasonably be expected to result in S_N2 displacement of bromide to give solely the β-anomers of the products.

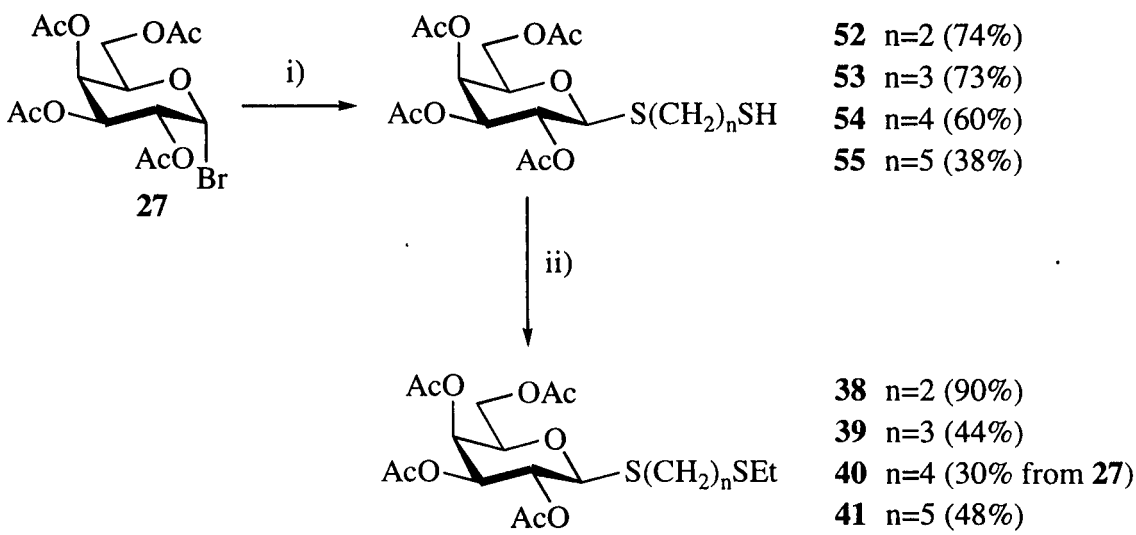
The mercaptoalkyl β-thiogalactosides **52-55** were successfully prepared by the reaction of **27** with threefold excesses of the respective alkane dithiols under PTC conditions, using ethyl acetate as the organic phase, 2M sodium carbonate solution as the aqueous phase, and TBAHS as the catalyst (Figure 71-i). The excess of dithiol was used to minimise reaction at both ends of the dimercaptal to give bridged dithioglycosides such

as **51**, and to minimise the competing hydrolysis of **27** under the basic reaction conditions (*cf.* Figure 59).



51

Conversion of **52-55** to their respective ethyl sulfides **38-41** was then achieved under similar PTC conditions, alkylating with an excess of ethyl bromide (Figure 71-ii).



Reagents and conditions:
i) $HS(CH_2)_nSH$, TBAHS, EtOAc, 2 M Na_2CO_3 RT; ii) EtBr, TBAHS, EtOAc, 2 M Na_2CO_3, RT.

Figure 71 : Syntheses of (n-ethylthioalkyl) thiogalactopyranosides

Of all of the acetylated mercaptoaalkyl thiogalactosides **38-41** and their ethyl sulfides **52-55**, only the mercaptoethyl thiogalactoside **52** was crystalline; the rest were obtained as viscous syrups. Only **52** and **53** were known compounds.[153] The composition and structure of the products was supported by ^{1}H NMR data, and high resolution mass spectrometry. Elemental analyses of these products were found to be on the limit of acceptability.

2.2.3.2 *Iodine-promoted reactions of alkylthioalkyl thiogalactosides*

Previous work on the reactivity of thioglycosides in the presence of iodine by the Field group[105,154] focussed on methanolysis in the presence of a large excess of methanol. Each of the ethylthioalkyl thiogalactosides **38-41**, and methylthiomethyl thiogalactoside **44** were thus stirred in acetonitrile with 100 mole eq. of methanol and 2 mole eq. of iodine. The result in each case was that very little, if any, glycosylation was observed, and that decomposition tended to occur if the reaction mixture was left for more than 48 hours. Repetition of these experiments in dichloromethane also gave negative results.

In an attempt to examine the proposed first step of the reaction, which is the nucleophilic attack by the thioether sulfur on molecular iodine, the attempted reaction with **40** was repeated using deuteurated methanol and acetonitrile, and studied over time by ^{1}H NMR (Figure 72).

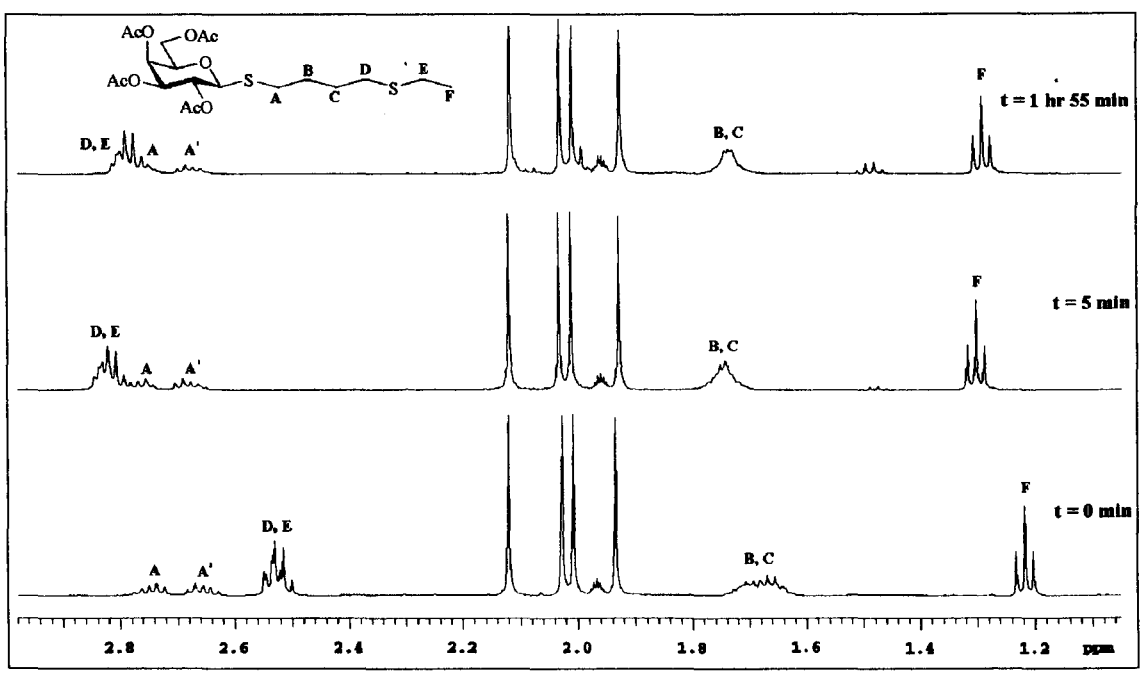


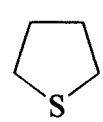
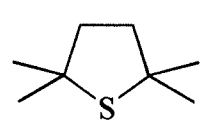
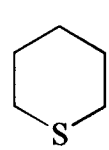
Figure 72 : ^{1}H NMR spectra showing co-ordination of a thioether by iodine

Within 5 minutes of adding the iodine to the mixture, the chemical shifts of the methylene protons either side of the thioether sulfur were observed to have shifted downfield to a considerable extent. This confirms that some interaction between iodine and the remote sulfur atom is occurring. The chemical shifts of the methylene group

nearest to the anomeric centre are not greatly affected, as would be expected given the predicted lower nucleophilicity of the anomeric sulfur atom. Whether or not the complexation of the thioether with iodine is complete or not is another matter. If the rate of exchange is faster than the NMR timescale, then the signals observed will simply be the average for each methylene group.[155]

Strom, *et al.* determined the equilibrium constants for the formation of a number of iodine-sulfide complexation from ^{1}H NMR data in 1967.[155] Amongst their results was the observation that varying the nature of groups adjacent to sulfur had a profound effect on the equilibrium constant, with more powerfully electron-releasing groups dramatically increasing the equilibrium constant (Table 1).

Table 1 : Equilibrium constants for iodine-alkyl sulfide complexes in CCl_4 at 25 °C

Sulfide	K_f (mol^{-1} dm^3)	Sulfide	K_f (mol^{-1} dm^3)
Me_2S	71.1 ± 4.8		95.8 ± 10.6
MeSEt	136.2 ± 15.8		215.9 ± 16.9
MeSPr^i	155.4 ± 11.8		
Et_2S	170.8 ± 23.3		78.4 ± 5.7
Pr_2S	168.8 ± 17.1		
$Pr^i{}_2S$	184.7 ± 14.7		136.0 ± 29.4
$Bu^t{}_2S$	159.3 ± 8.0		

(Table reproduced from data presented by Strom, *et al.*[155])

This information suggests that electron-withdrawing protecting groups, particularly at C-2, are likely to reduce the equilibrium constant for complexation of iodine with the

anomeric sulfur atom substantially. This is supported by the observation we have made that there is little downfield movement of the chemical shifts of the methylene group adjacent to the anomeric sulfur atom of **40**, and supports the view that the acyl protecting groups are reducing the nucleophilicity of sulfur.

What is apparent from our study is that although iodine-sulfur complexation is occurring at the remote sulfide, insufficent positive charge is being generated at sulfur to induce nucleophilic attack by the anomeric sulfur atom on the α-carbon of the iodosulfonium ion. This is consistent with the observations of Fraser-Reid *et al.* on the unreactivity of 'disarmed' *n*-pentenyl glycosides towards IDCP.[22,40]

2.3 Iodine-promoted reactions of mercaptoalkyl thiogalactosides

2.3.1 Introduction

2.3.1.1 Reactions of thiols with halogens[141]

Thiols react with halogens to give the sulfenyl halide and the hydrohalic acid (Equation 1). The sulfenyl halides can subsequently disproportionate, reversibly, to give the halogen and the disulfide (Equation 2). The position of equilibrium lies largely with the sulfenyl chloride in the case of chlorine, but with the disulfide in the case of iodine. Bromine lies intermediate to these two extremes, as one might expect.

$$RSH + X_2 \rightleftharpoons RSX + HX \qquad \textbf{(Equation 1)}$$

$$2RSX \rightleftharpoons RSSR + X_2 \qquad \textbf{(Equation 2)}$$

Furthermore, the sulfenyl halides are quite reactive towards nucleophiles in general (Equation 3), and have indeed been considered for a long time to be a synthetic equivalent for the sulfenyl cations themselves (Equation 4), though evidence on the existence of the free sulfenyl cations is not conclusive.

$$RSX + NuH \rightleftharpoons RSNu + HX \qquad \textbf{(Equation 3)}$$

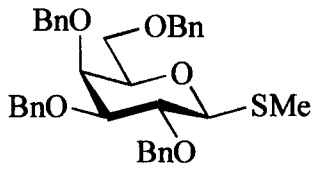
(Nu = R_2NH, HSCN, ROH, RSH, etc.)

$$RSX \rightleftharpoons RS^+ + X^- \qquad \textbf{(Equation 4)}$$

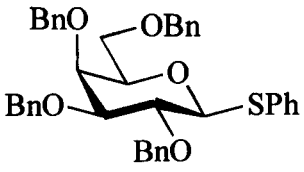
2.3.1.2 Work within the Field group on the effect of varying the thioglycoside aglycon in the iodine-promoted activation of thioglycosides

Cura[154] compared the reactivity of benzyl ether protected *S*-methyl thiogalactoside **56** and its *S*-phenyl analog **57** with iodine, and found an approximate 30 fold greater reactivity in the methyl derivative. This is in accord with previous studies on the effect

of varying the thioglycoside aglycon on the reactivity of thioglycosides, which have demonstrated than phenyl thioglycosides are less easily activated by iodonium ions than their alkyl thioglycoside counterparts.[156]



56



57

Attempts by Cura thereafter to selectively glycosylate benzylated *S*-phenyl thiogalactoside **58** acceptor with methyl thioglycoside **56** showed signs that **58** was being significantly activated over the same timescale as that taken for consumption of **56**.[157]

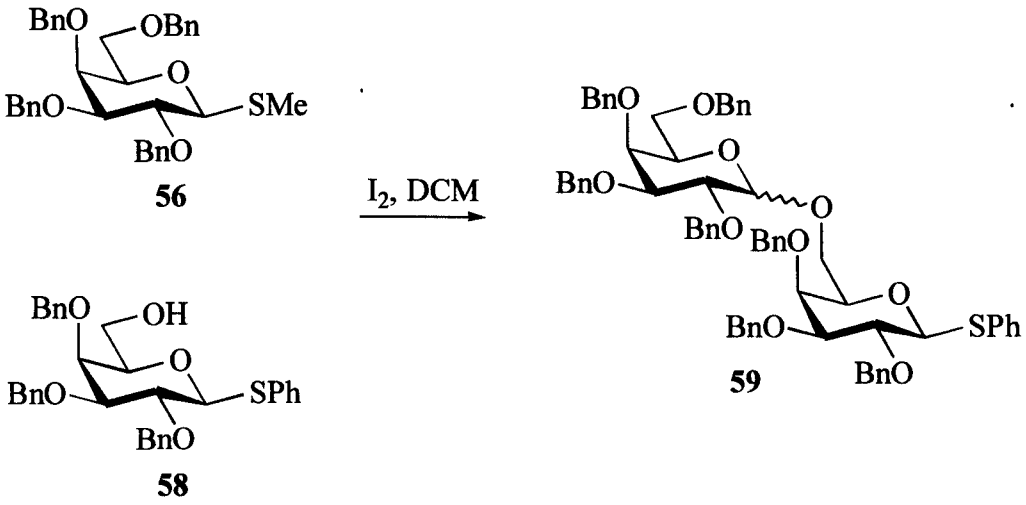


Figure 73

A possible explanation for this lies in considering the equilibrium between the sulfenyl iodide leaving group and the corresponding disulfide (Equation 2). Although the equilibrium lies in favour of the disulfide,[141] the reversible nature of the dimerisation suggests that there is always a finite concentration of methyl sulfenyl iodide present, which is capable of acting as a source of the electrophile MeS^+. Sources of MeS^+ such as dimethyl (methylthio)sulfonium triflate (DMTST) and dimethyl (methylthio)sulfonium tetraborate have already found use as efficient, thiospecific, promoters for the activation of both 'armed' and 'disarmed' thioglycosides[88,89] (Figure

74), and it is possible that MeSI generated in the activation of **56** may be activating the less reactive phenyl thioglycoside in the same manner as DMTST.

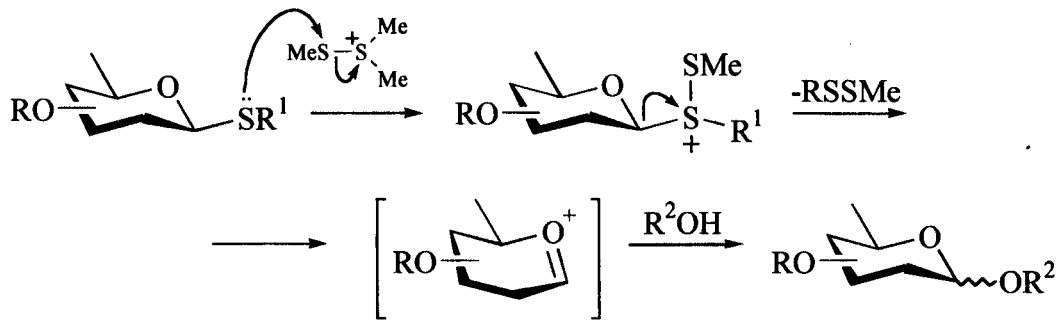


Figure 74 : Activation of thioglycosides by DMTST

2.3.1.3 *Proposal*

The preparation of the ethylthioalkyl thiogalactosides **38-41** proceeded *via* the intermediate mercaptoalkyl analogs **52-55** (Figure 71). It was reasoned that although the anomeric sulfur atom was not found to be capable of nuclephilic attack on the carbon α- to an iodosulfonium ion, iodination of the thiol-group might provide a mild, DMTST-like, equivalent for a sulfenyl cation which could be intramolecularly attacked by the anomeric sulfur to give a sulfonium-type ion (Figure 75). This in turn could eject a cyclic disulfide, allowing access to the usual intermediate, and thus glycosylation.

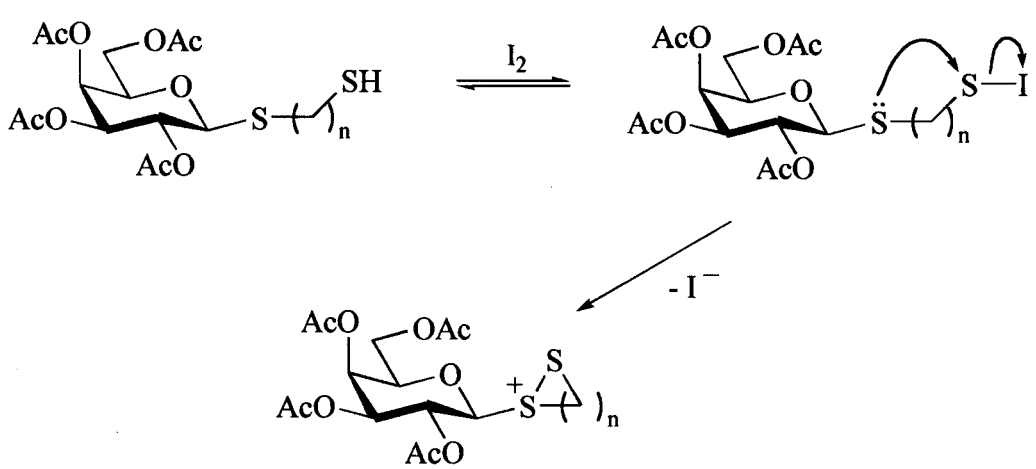
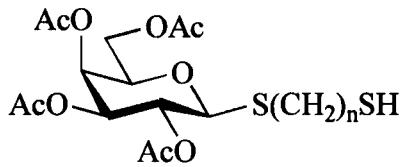


Figure 75 : Proposed iodine-promoted activation of cyclic mercaptoalkyl thiogalactosides

2.3.2 Aims and objectives

The aim of this part of the project was to examine the reactivity of the mercaptoalkyl thiogalactosides **52-55** towards iodine in the presence of suitable acceptor alcohols.



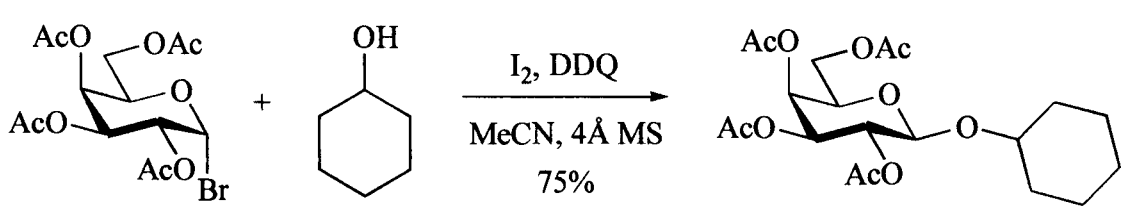
52 n=2
53 n=3
54 n=4
55 n=5

It was expected that of these four compounds, **53** and **54** would be the most likely to react, as these would give rise to cyclic disulfides containing five or six atoms.

2.3.3 Results and discussion

2.3.3.1 Reactions with cyclohexanol

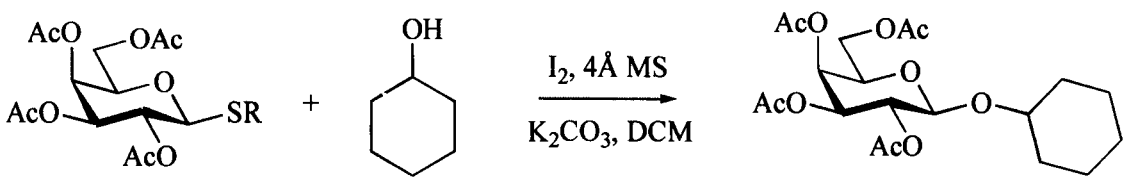
A preliminary attempt at iodine-promoted methanolysis of mercaptobutyl thiogalactoside in acetonitrile appeared, by t.l.c., to work. It was noticed that increasing the amount of methanol present from 2 to 4 mole equivalents resulted in a decrease in the rate of consumption of the acceptor. This prompted speculation that interactions between iodine and the oxygen of alcohols may reduce the effectiveness of iodine as a promoter, which we have elaborated on further in our discussion on the iodine-mediated activation of glycosyl sulfoxides (Section 3.4). Further studies were carried out using a slight excess of donor with the secondary alcohol cyclohexanol. An authentic sample of cyclohexyl glycoside **60**[158] was prepared for t.l.c. analysis by iodine/DDQ-promoted[136] reaction of bromide **27** with cyclohexanol (Figure 76).



27 **60**

Figure 76

Mercaptoalkyl thiogalactosides **52-55** were stirred with cyclohexanol (0.8 mole eq.) and iodine (2 mol eq.) in the presence of molecular sieves and potassium carbonate. In all four cases, t.l.c. of the reaction mixture after five minutes indicated that the mercaptoalkyl thioglycoside had been converted into a compound of a much lower R_f, but only in the cases of **53** and **54** did the reaction proceed further to give a substance that appeared, by t.l.c., to be **60** (Figure 77).



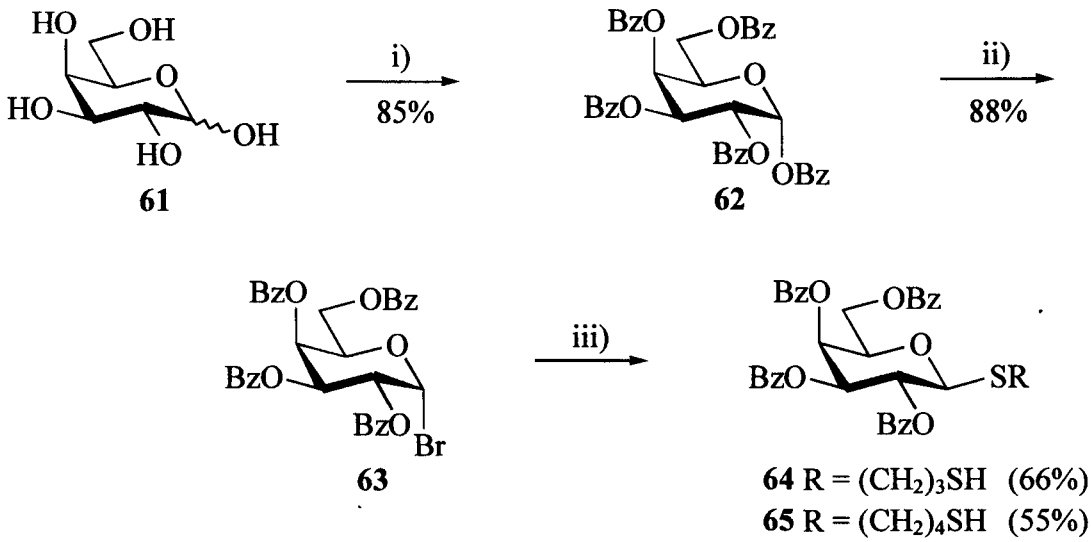
53 R = $CH_2CH_2CH_2SH$
54 R = $CH_2CH_2CH_2CH_2SH$

60

Figure 77

T.l.c. also indicated that a significant level of degradation of the acetylated sugars was occurring. Benzoyl ester protecting groups are reputed to be less labile in the presence of Lewis acids than acetyl groups,[18,159] and so benzoyl analogs **64** (n=3) and **65** (n=4) were prepared for further study. Since **52** and **55** showed no evidence of reacting to give cyclohexyl glycoside **60**, it was considered unnecessary to prepare their benzoyl analogs.

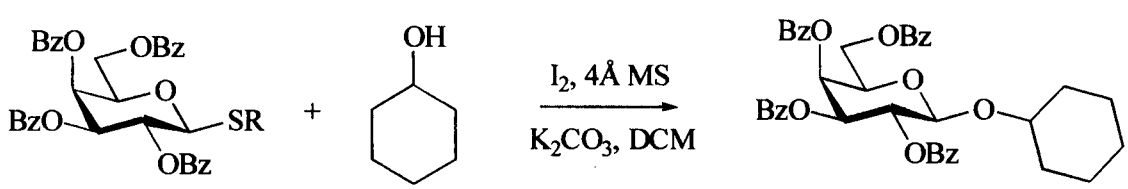
Perbenzoate **62** was prepared from galactose (**61**) by treatment with benzoyl chloride in pyridine. Reaction of with 45% HBr in acetic acid gave bromide **63**, which was then treated under phase transfer conditions with propane-1,3-dithiol to give **64**, and with butane-1,4-dithiol to give **65**, both in moderate yield (Figure 78). An authentic sample of cyclohexyl glycoside **66** was prepared, as for **60**, by iodine/DDQ-promoted reaction of bromide with cyclohexanol.



Reagents and Conditions:
i)BzCl, pyridine, 0°C; ii) 45% HBr/HOAc, DCM, 0°C; iii) $HS(CH_2)_nSH$ (n=3 or 4), TBAHS, EtOAc, 2M Na_2CO_3

Figure 78

Mercaptopropyl thiogalactoside **64** and mercaptobutyl thiogalactoside **65** were then allowed to react with cyclohexanol in the presence of iodine under the same conditions as before. Again, the initial observation by t.l.c. was that the starting thioglycosides reacted to give a substance of lower R_f, before continuing to react overnight to give cyclohexyl glycoside **66**, in 71% and 60% yield respectively (Figure 79).



64 R = $CH_2CH_2CH_2SH$
65 R = $CH_2CH_2CH_2CH_2SH$

66

Figure 79

Ethyl thioglycoside **69** was prepared (Figure 80) in order to confirm that the iodine-promoted reactions of **64** and **65** with cyclohexanol were not typical of benzoyl ester protected alkyl thiogalactosides. Reaction of galactose pentaacetate (**42**) with ethyl disulfide in the presence of HMDS and iodine[148] gave acetylated ethyl β-thiogalactoside **67** in 70% yield. Zemplén deacetylation[160] of **67** with catalytic NaOMe in MeOH,

followed by benzoylation with benzoyl chloride in pyridine, afforded **69** in 80% yield. It was found that under the iodine-mediated conditions used previously, no significant coupling between **69** and cyclohexanol to give **66** was observed by t.l.c., providing further evidence that the capability of activation of these compounds by iodine is due to the presence of the mercaptal aglycon.

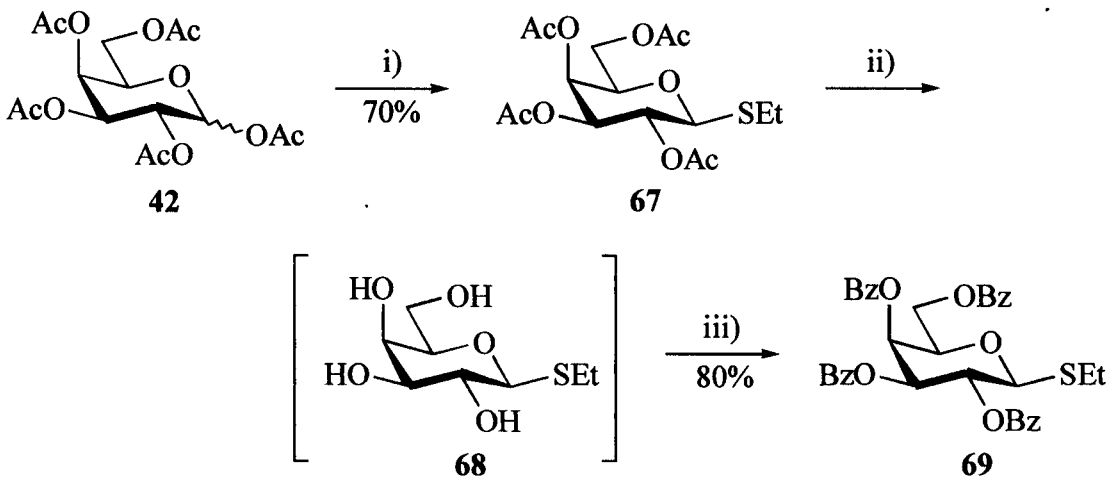


Figure 80

The intermediate compounds which moved slowly during t.l.c. were deemed likely to be the disulfides of the starting mercaptals, formed *via* formation of the corresponding sulfenyl iodides. This has already been described as a typical reaction of thiols towards iodine.[141] In support of this view, NMR (both ^{1}H and ^{13}C) and mass spectrometry (MALDI-TOF) of a sample taken from a reaction mixture initially containing **64**, and purified by column chromatography, provided evidence that the disulfide **71**, of molecular weight 1370, had been formed via sulfenyl iodide **70** (Figure 81).

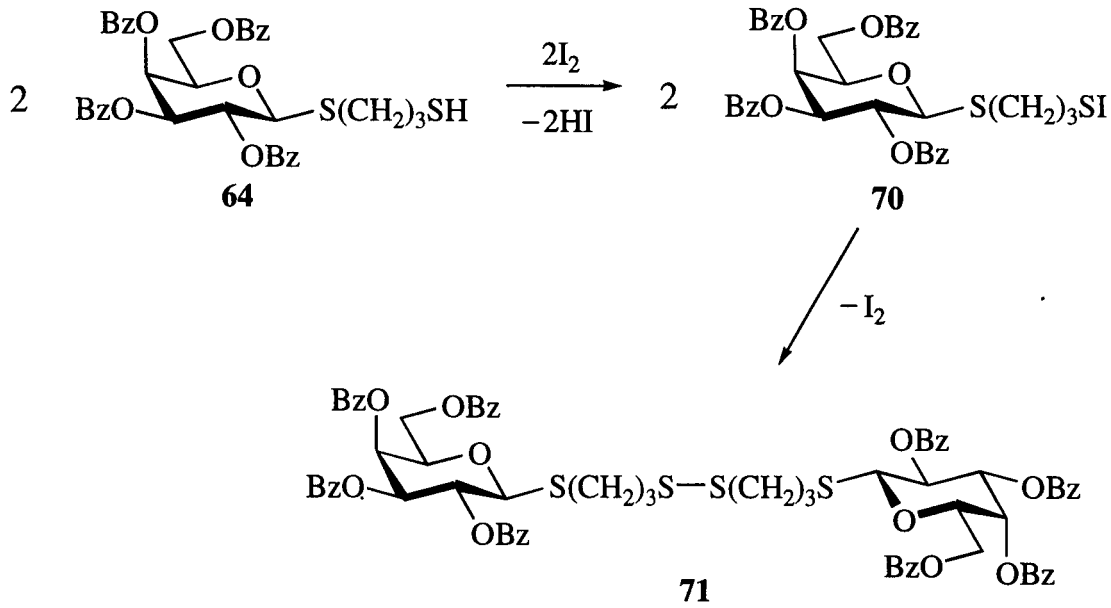


Figure 81

It was originally proposed that activation of the anomeric sulfur atom might occur by attack of the anomeric sulfur atom on the sulfur of the reversibly formed sulfenyl iodide (Figure 75). It could also be argued that iodination of either atom of the disulfide bridge of **71** would result in the formation of an iodosulfonium-type ion. The non-iodinated sulfur of the disulfide bridge could then undergo nucleophilic attack by its "own" anomeric sulfur atom, displacing sulfenyl iodide **70** as a leaving group (Figure 82).

It is not surprising that mercaptopropyl thiogalactoside **64** emerged as the most promising 'disarmed' thiogalactoside donor in this study. The slowest step in the reaction is likely to be the nucleophilic attack by the 'disarmed' anomeric sulfur on the remote sulfur to generate the disulfide linkage within the cyclic leaving group, and the formation of a five-membered ring is well known to be faster than larger rings. Additionally, the bond angles within five-membered rings are much closer to the ideal tetrahedral angle of 109 degrees, making them thermodynamically more stable than smaller rings which might, by the same logic as above, form faster.

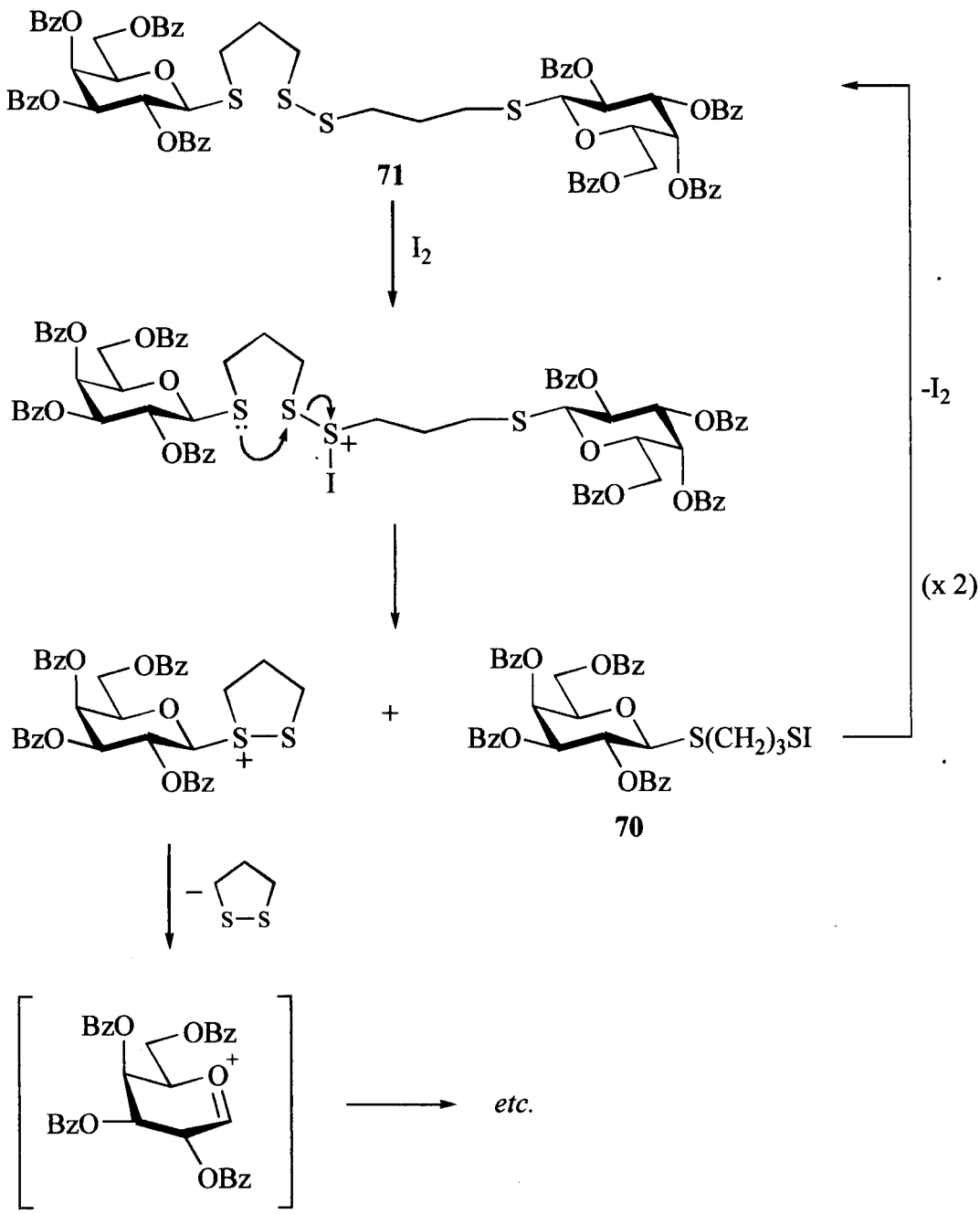
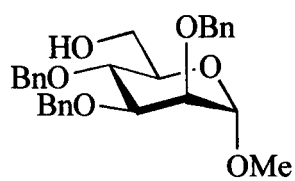


Figure 82

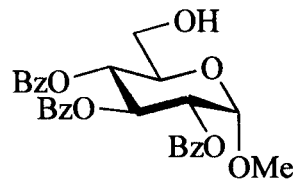
2.3.3.2 *Reactions with carbohydrate acceptors*

Having established **64** as the most promising iodine-activated donor of the 'disarmed' mercaptoalkyl thiogalactosides with the relatively simple alcohol acceptor cyclohexanol, attention turned towards reactions with carbohydrate acceptors. We thus

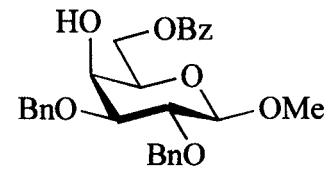
decided to prepare acceptors **72-75**, and examine their reactivity towards **64** under iodine-mediated conditions.



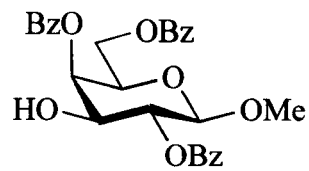
72



73



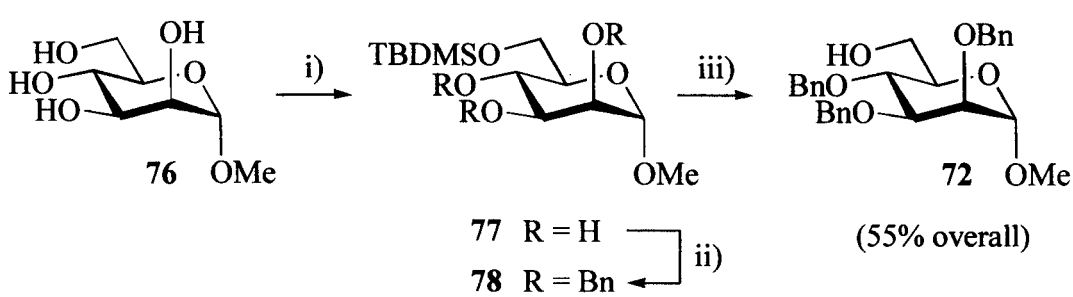
74



75

2.3.3.2.1 Preparation of carbohydrate acceptors

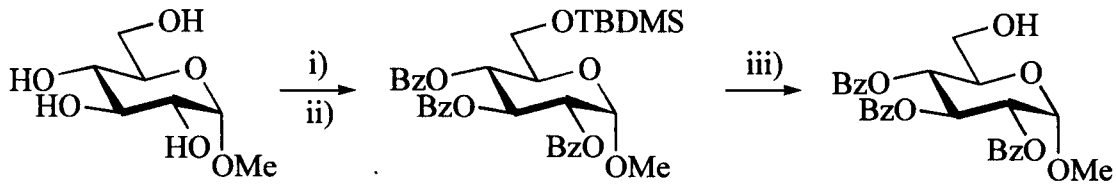
Methyl 2,3,4-tri-*O*-benzyl-α-D-mannopyranoside[161] (**72**) was synthesised from methyl α-D-mannopyranoside (**76**) in three steps (Figure 83). The primary hydroxyl group was selectively protected by reaction with tert-butyldimethylsilyl chloride[162] (TBDMS-Cl) in pyridine to give **77**. Treatment of this with sodium hydride and benzyl bromide in DMF[163] gave **78**, which was desilylated by treatment with 80% aqueous acetic acid[162] to give **72** in 55% overall yield.



Reagents and conditions:
i) TBDMS-Cl, pyridine, 0°C, 3 hr; ii) NaH, BnBr, DMF, 0°C→RT; iii) 80% aq. AcOH, RT.

Figure 83

Methyl 2,3,4-tri-*O*-benzoyl-α-D-glucopyranoside[164] (**73**) was prepared from methyl glucoside **79** by selectively protecting the primary hydroxyl group with TBDMS-Cl[162] as before, followed by benzoylation of the remaining hydroxyls with benzoyl chloride[165] in the same pot. Removal of TBDMS was again effected with 80% acetic acid[162] to give **73** in 58% overall yield (Figure 84).

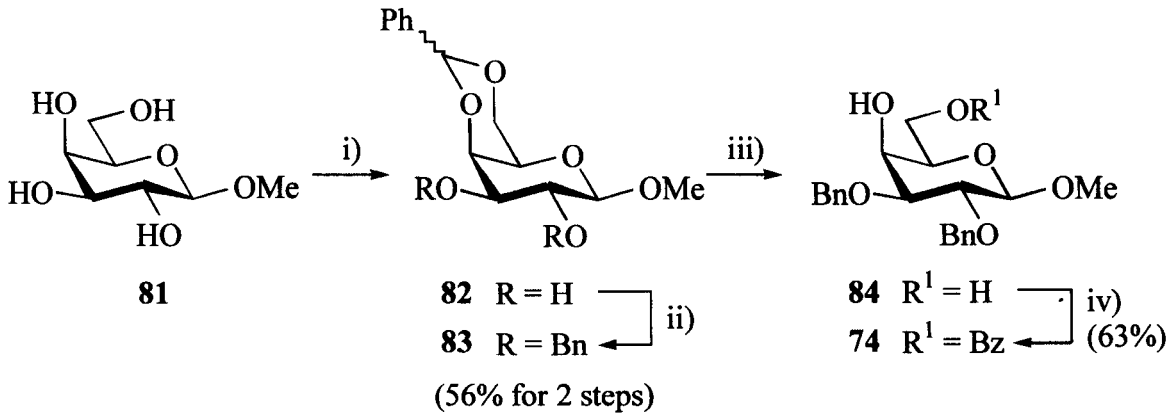


79 **80** **73** (58% overall)

Reagents and conditions:
i) TBDMS-Cl, pyridine, 0°C→RT, 3 hr; ii) BzCl, 0°C→RT, o/n; iii) 80% aq. AcOH, RT, o/n.

Figure 84

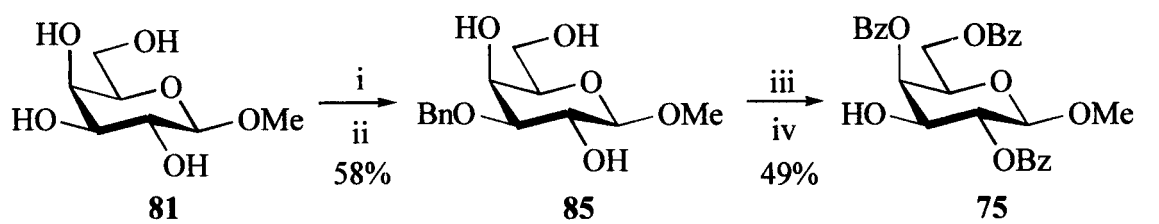
Methyl 6-*O*-benzoyl-2,3-di-*O*-benzyl-β-D-galactopyranoside[166] (**74**) was prepared in 4 steps (Figure 85). Firstly methyl galactoside **81** was treated with benzaldehyde dimethyl acetal and CSA in acetonitrile[167] to give the 4,6 benzylidene acetal **82**. This material was benzylated and purified by column chromatography to give **83**, in 56% yield over two steps. The benzylidene acetal was removed by refluxing with 80% aqueous acetic acid[168] at 80-90 °C to give **84**, and benzoyl ester protection introduced regioselectively at the 6-position by use of benzoyl cyanide[18] in pyridine/dichloromethane to give **74** in 63% yield over this second pair of steps.



Reagents and conditions:
i) $PhCH(OMe)_2$, CSA, MeCN, RT, 8.5 hr; ii) NaH, BnBr, DMF, 0°C→RT, o/n; iii) 80% aq. AcOH, 80°C, 3 hr; iv) BzCN, pyridine, 0°C, 4 hr.

Figure 85

Methyl 2,4,6-tri-*O*-benzoyl-β-D-galactpyranoside[169] (**75**) was prepared in four steps from **81** (Figure 86). Reaction of **81** in toluene with dibutyl tin oxide, followed by benzyl bromide and TBABr, in one pot,[170] gave methyl 3-*O*-benzyl-β-D-galactopyranoside (**85**). This was then benzoylated and the benzyl ether reductively removed, to give **75**.

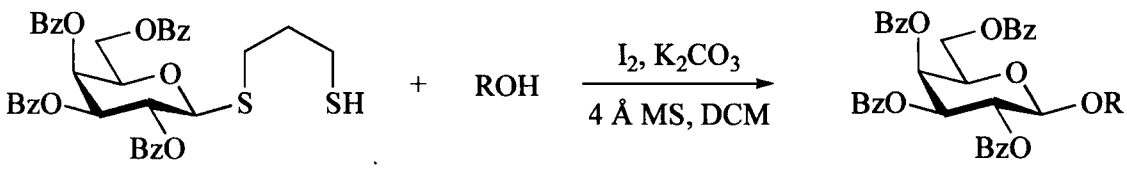


Reagents and Conditions:
i) Bu_2SnO, toluene, Δ, 10 hr; ii) BnBr, TBABr, Δ, 4 hr; iii) BzCl, pyridine; iv) H_2, $Pd(OH)_2/C$, MeOH.

Figure 86

2.3.3.2.2 Attempted iodine-promoted glycosylations of carbohydrate acceptors with the benzoylated mercaptopropyl thiogalactoside

Glycosylation of carbohydrate acceptors **72-75** (0.100 mmol) was attempted with an excess of mercaptopropyl thiogalactoside **64** (0.125 mmol), in the presence of iodine (0.25 mmol), 4A MS and potassium carbonate in dichloromethane (Figure 87).



64

Figure 87

After 24 hr there was no significant reaction of the secondary galactose acceptors **74** and **75** with the disulfide intermediate, but the primary acceptors **72** and **73** appeared to have reacted somewhat.

Benzyl ether-protected mannoside **72** reacted to give, after column chromatography, a mixture of products. In order to determine whether or not glycosylation had occurred, authentic samples of disaccharides **86** and **87** were prepared by iodine/DDQ-mediated glycosylation of **72** and **73**, respectively, with bromide **63** (Figure 88).

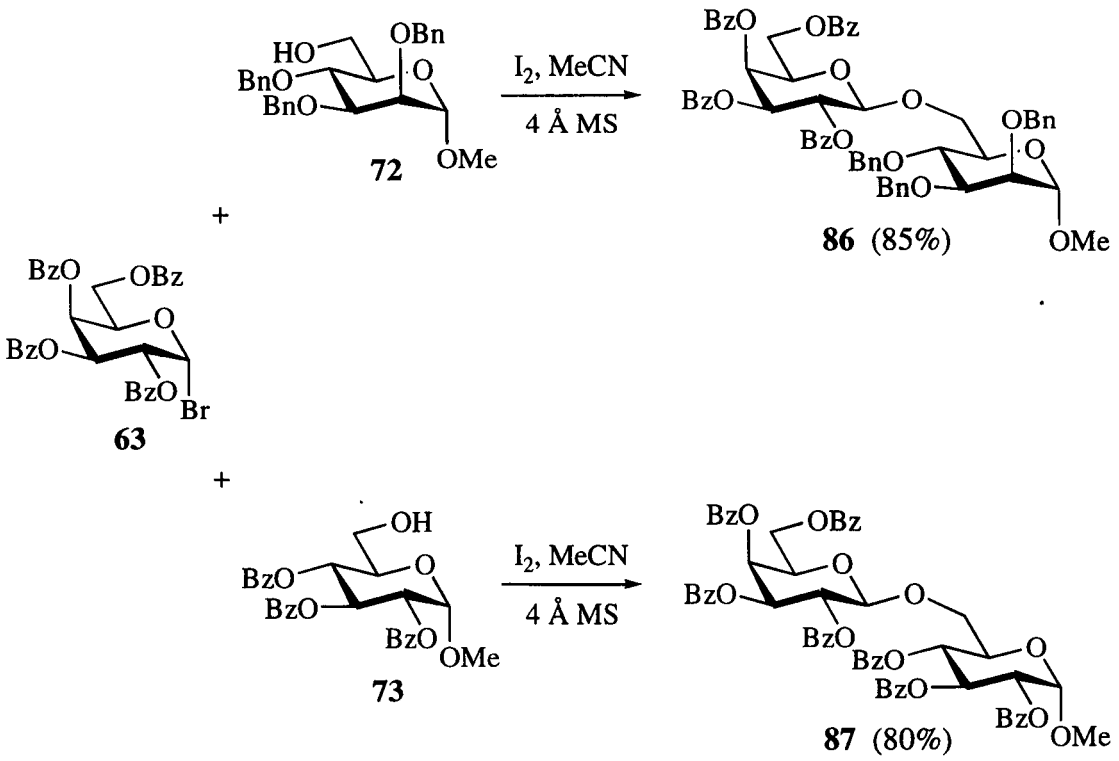
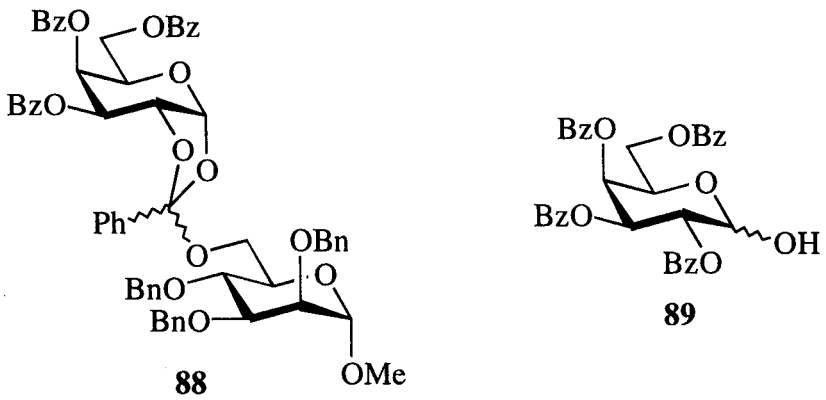


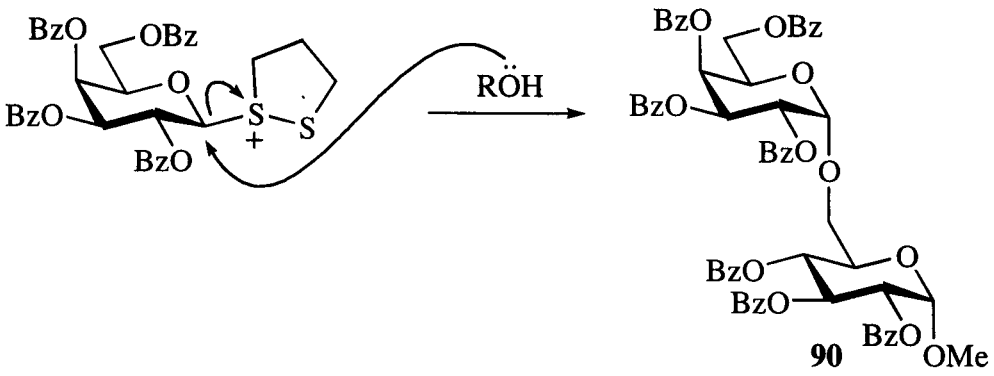
Figure 88

A comparison of the ^{1}H NMR spectrum of **86** with that of the intractable products of the attempted glycosylation of mannopyranose acceptor **72** confirmed that **86** was the major product of the reaction of **64** with **72**. There appeared to be two other sets of peaks present, but these appeared to be derived from **64** only, and were not the diastereoisomeric orthoester **88**. It is likely that the two extra sets of peaks observed are due to formation of hemiacetal **89**.



The ^{1}H NMR integral suggested that two-thirds of the material in the sample, by mole, was disaccharide **86**. Based on the assumption that the extra peaks are due to formation of hemiacetal **89**, the yield of **86** was calculated to be approximately 50%.

The benzoyl ester-protected glucopyranose acceptor **73** reacted to give a small yield of α-disaccharide **90**, presumably formed by S_N2 displacement of the activated leaving group (Figure 89).



90

Figure 89

The reactions of **72-75** with **64** were repeated in dichloromethane, in the absence of potassium carbonate, but under these conditions no consumption of any of the acceptors appeared, by t.l.c., to occur over a 24 hr period. Subsequent addition of sufficient DTBMP to neutalise only the HI produced by the initial reaction of **64** with iodine did not result in any significant reaction after 24 hr.

It is clear that glycosylation of carbohydrate acceptors with **64** is not a facile process under our conditions. We have shown that **64** can be activated by iodine, yet of the carbohydrate acceptors used, only primary acceptors **72** and **73** reacted with **64** at all.

The answer to this possibly lies in the nature of the activation process of thioglycosides. Several groups have reported that 'armed' thioglycosides epimerise at C-1 when treated with activating agents such as IDCP[171,172] or iodine[142] in the absence of carbohydrate acceptors, to give an equilibrium mixture of epimeric α- and β-thioglycosides. All three groups proposed that anomerisation occurred via recombination of the sulfenyl iodide leaving group with the oxocarbenium intermediate (*e.g.* Figure 90).

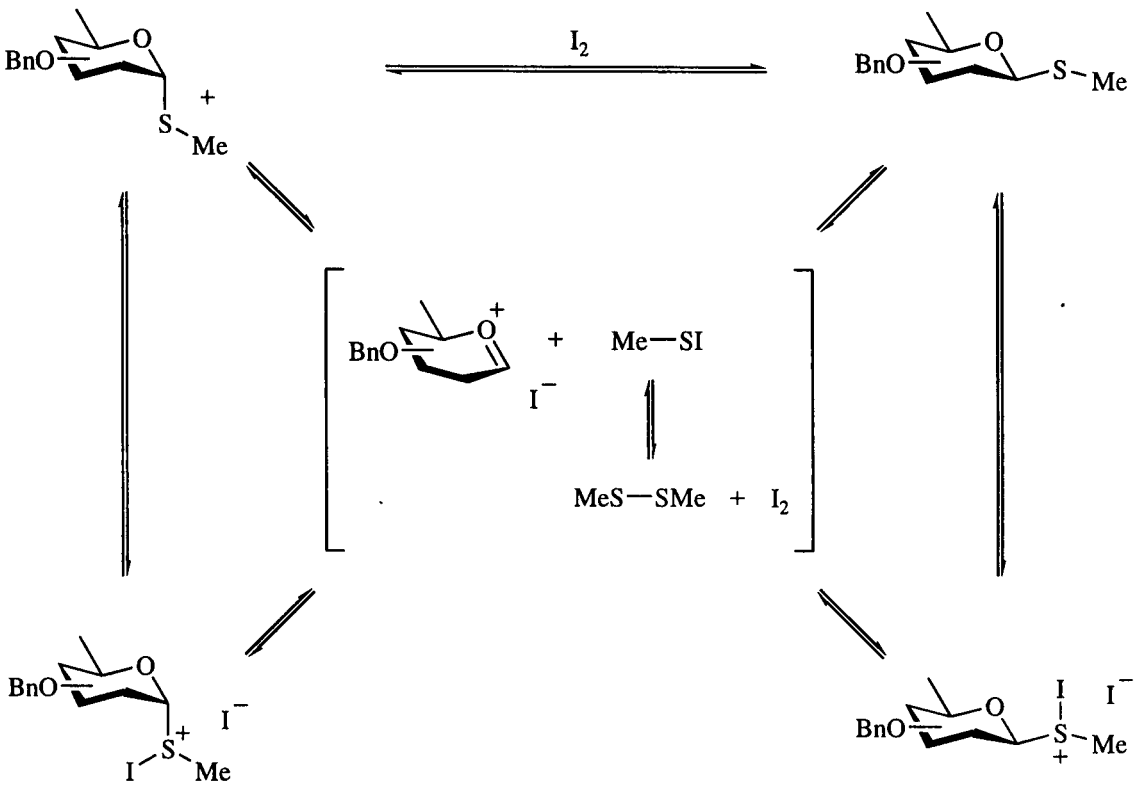


Figure 90

This is an interesting proposal, as sulfenyl iodides typically react as electrophiles rather than nucleophiles.[141] Alkyl iodides are renowned for their electrophilicity, and although sulfur is more polarisable than carbon, the electronegativities of carbon and sulfur are very similar.[173,174] It is more likely that a sulfur of the disulfide, formed by disproportionation of the sulfenyl iodide, is a better nucleophile, and able to attack the oxocarbenium ion itself (Figure 91). The presence of iodide ions may well facilitate this process by reacting with the sulfur β- to the anomeric centre, to 'deactivate' the resulting sulfonium species.

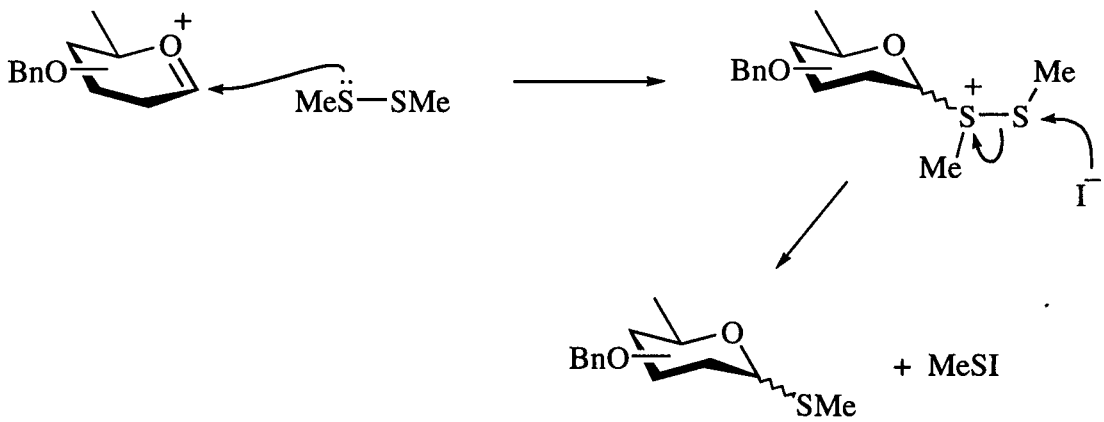


Figure 91

The iodine-promoted activation of **64** was very slow. This could be due in part to the low nucleophilicity of the anomeric sulfur atom in the cyclisation step. The sulfur atoms of the ejected 1,2-dithiane are likely to compete with the carbohydrate acceptor for the benzoylcarbonium ion, which should be highly destabilised (with respect to the oxocarbenium ion for 'armed' glycosyl donors) by the electron-withdrawing ester protecting groups. Only the most reactive acceptors would be able to compete effectively with the 1,2-dithane derivative for the benzoylcarbonium ion, which is why only the benzyl ether-protected primary acceptor **72** was able to react with this to give a disaccharide product.

3 STUDIES ON IODINE-PROMOTED ACTIVATION OF THIOMANNOSIDES AND THEIR *S*-OXIDES

3.1 Introduction

3.1.1 The problem of β-mannoside synthesis

The β-mannopyranosidic linkage is found in a variety of oligosaccharide structures, the most important class of which are the *N*-linked glycoproteins. All *N*-linked glycoproteins consist of a non-variable pentasaccharide covalently attached via an asparagine (Asn) residue to the protein portion of the molecule.[27,175] The non-variable, or "core" pentasaccharide contains a β-mannopyranosidic linkage (Figure 92).

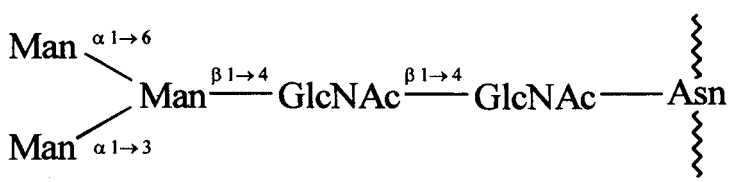


Figure 92 : The pentasaccharide core of *N*-linked glycoproteins

Other β-mannopyranoside-containing oligosaccharides reported include those found in the freshwater bivalve *Hyriopsis schlegelli*,[27] and the *O*-polysaccharides of certain gram-negative bacteria serotypes.[27,176] A polymeric β-Man-(1→2)-β-Man linkage exists in the phosphomannan-protein complex in the cell wall of *Candida albicans*,[27] and galactomannans, which are common in plants, are polymers of mannose and galactose containing Man-(1→4)-β-Man and Man-(1→4)-α-Gal linkages.[177]

The stereoselective preparation of β-mannopyranosides of interest is particularly difficult, as the anomeric effect[8-10] dictates that in the absence of significant directing effects caused by participating groups[29,30] or the solvent[32-34] in glycosylation reactions involving hexopyranosyl donors, the α-glycoside product will often be favoured over the β-anomer.

Acyl protecting groups can often assist in preparing β-glycosides where there is a 1,2-*trans*- orientation of substituents in the product, for example in the *gluco*- and *galacto*-series of sugars (Figure 93).

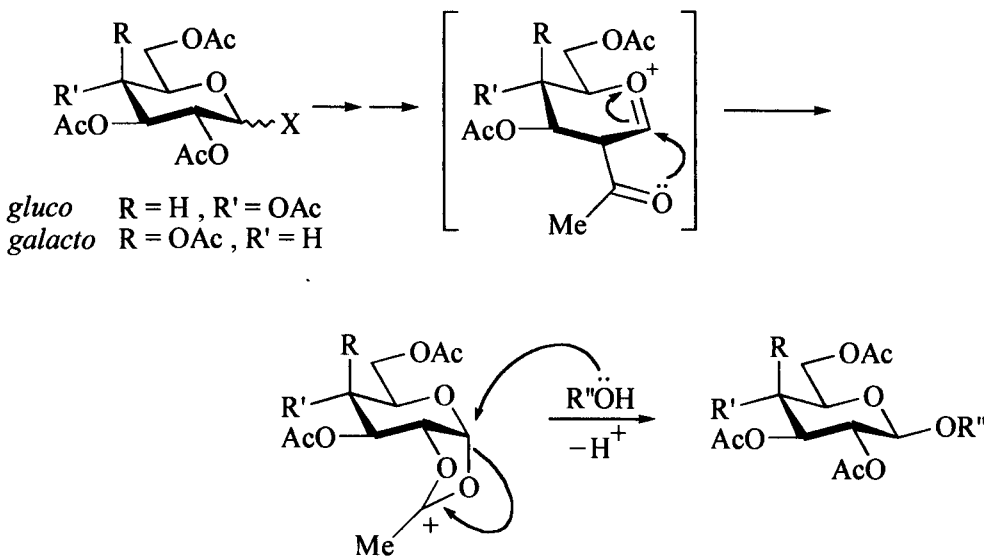


Figure 93 : Neighbouring group participation to give β-glucosides and galactosides

However, in the *manno*- series, such neighbouring group participation results in an even greater preference for α-mannosides (Figure 94).

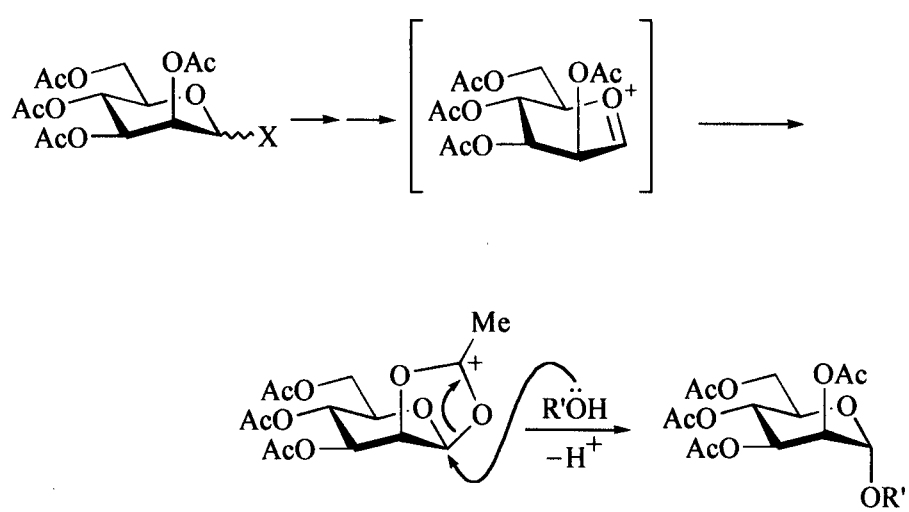


Figure 94 : Neighbouring group participation to give α-mannosides

3.1.2 Strategies employed in β-mannoside synthesis

3.1.2.1 S_N2-type displacement of α-halides

Perhaps one of the most simple method for preparing β-mannopyranosides is the modified[178] Koenigs-Knorr[44] method. The use of a mild and insoluble silver salt, such as silver silicate,[178,179] as a promoter causes polarisation of the anomeric carbon-halogen bond, rather than cleavage (Figure 95). This polarisation allows an S_N2-type displacement of bromide by nucleophiles to occur at the anomeric centre, and where an α-bromide donor is used, this leads to the formation of β-mannopyranoside linkages.

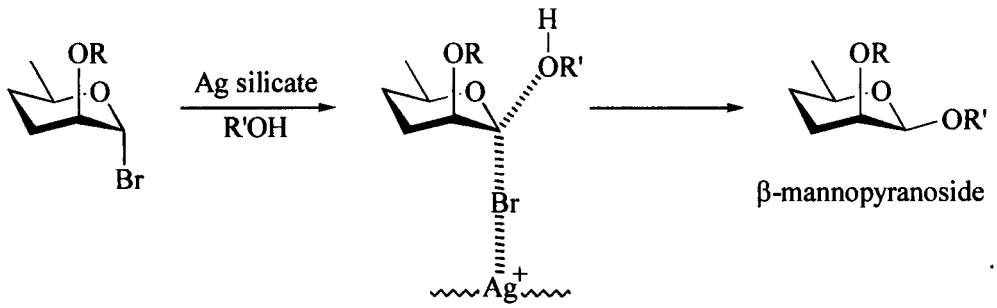


Figure 95

The combination of halide ions with the insoluble promoter will prevent *in situ* anomerisation of the glycosyl halide, which might lead to formation of unwanted α-mannopyranosides. However, the acceptor must be relatively reactive in order to be capable of directly displacing bromide at the anomeric centre.[26]

3.1.2.2 C-2 Epimerisation of β-glucopyranosides

Another common route to β-mannosides is to prepare the more accessible β-glucopyranoside analog using the aid of a C-2 participating group, and then deprotect and epimerise the C-2 position. This can be achieved by oxidation of the glucoside at C-2 to give the 2-ulose,[26] followed by reduction with sodium borohydride to give a mixture of the β-gluco- and β-manno- pyranosides (Figure 96).

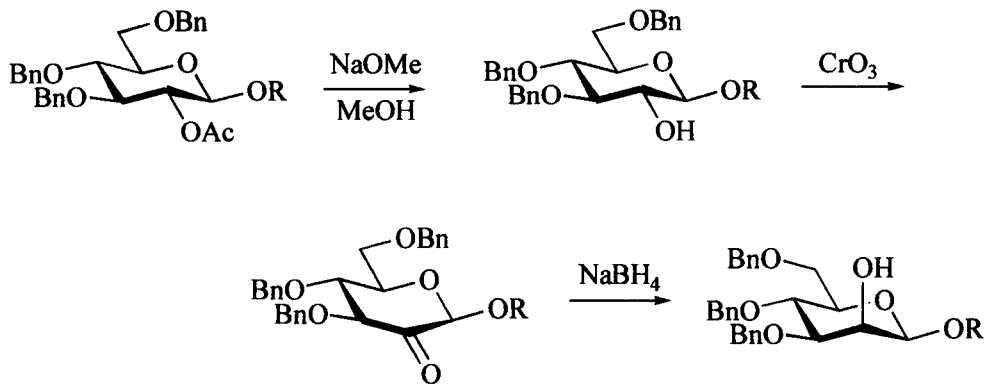


Figure 96 : C-2 oxidation-reduction of β-glucosides to give β-mannopyranosides

Alternatively the C-2 position can be triflated and subsequently inverted by an S_N2 substitution reaction with the aid of a caesium carboxylate, such as caesium acetate[180,181] (Figure 97). This is reputedly a difficult procedure due to repulsive interactions,[26] and an intramolecular epimerisation procedure has been developed to overcome this problem[182] (Figure 98).

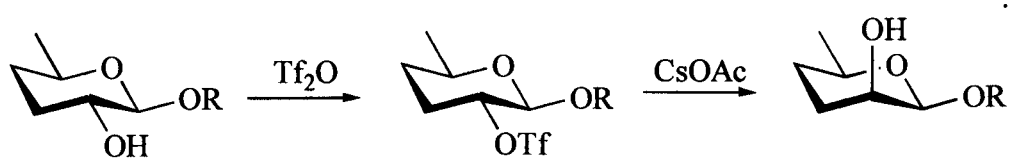


Figure 97 : Intermolecular inversion of β-glucopyranoside C-2 triflate to give a β-mannopyranoside

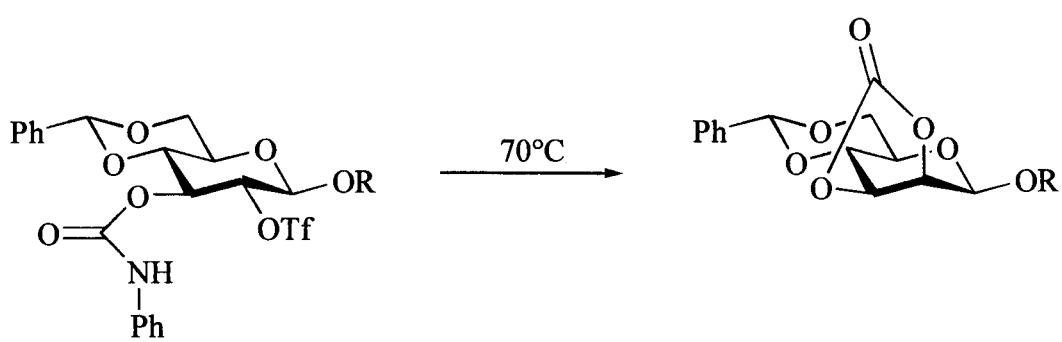


Figure 98 : Intramolecular inversion of β-glucopyranoside C-2 triflate to give a β-mannopyranoside

3.1.2.3 Intramolecular aglycon delivery

Intramolecular delivery of the aglycon (IAD) has also emerged as a useful tool for producing β-mannopyranosides. The aglycon is attached via a temporary linkage to C-2 of a mannosyl donor, immediately enhancing the possibility that any transfer of the aglycon to the anomeric centre of the donor will occur *cis*- to the C-2 substituent, generating a β-mannopyranoside. Various groups have been utilised as tethers to C-2, including isopropylidene ketals[183,184] (Figure 99), silicon acetals[185,186] (Figure 100), *p*-methoxybenzylidene acetals,[187-189] and 2-iodopropylidene acetals.[190] The latter are of particular interest since they can be generated easily from 2-*O*-allyl ether-protected donors[190] avoiding the difficulties associated with the use of the Tebbe's reagent in the generation of 2-*O*-isopropylidene ketals[183,184] from the corresponding 2-*O*-acetate.

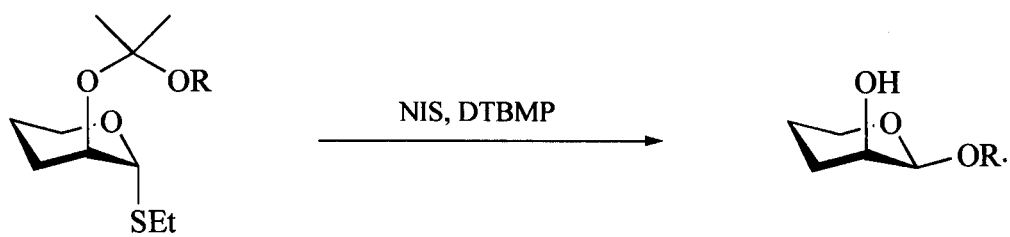


Figure 99 : Isopropylidene ketal tethers facilitating β-mannopyranoside formation

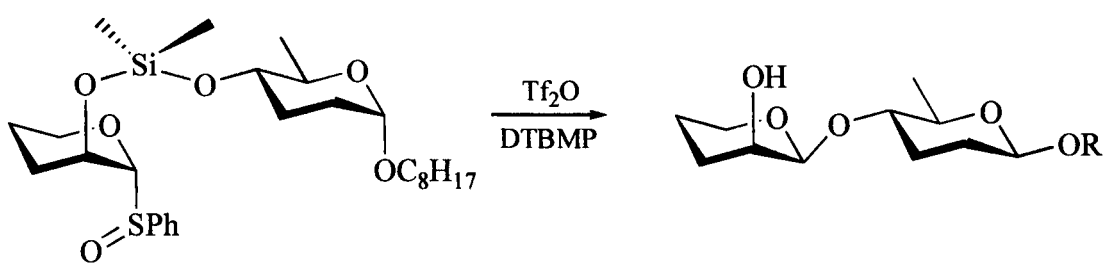


Figure 100 : Silcon acetal tethers facilitating β-mannopyranoside formation

3.1.2.4 β-Mannopyranosides via in situ generation of conformationally restrained α-mannopyranosyl triflates

Kahne *et al.* reported in 1989 that glycosyl sulfoxides were effective glycosylating agents in the glycosylation of unreactive substrates, such as the C-7 hydroxyl of deoxycholic acid derivative **91**, phenols, and silylated amide nitrogens.[118] Kahne reported a yield for the C-7 glycosylation of **91** with sulfoxide **92** in toluene of 86%[118]

(Figure 101), in comparison to earlier efforts which had required extended reaction times and had given poor yields (0-30%).[191]

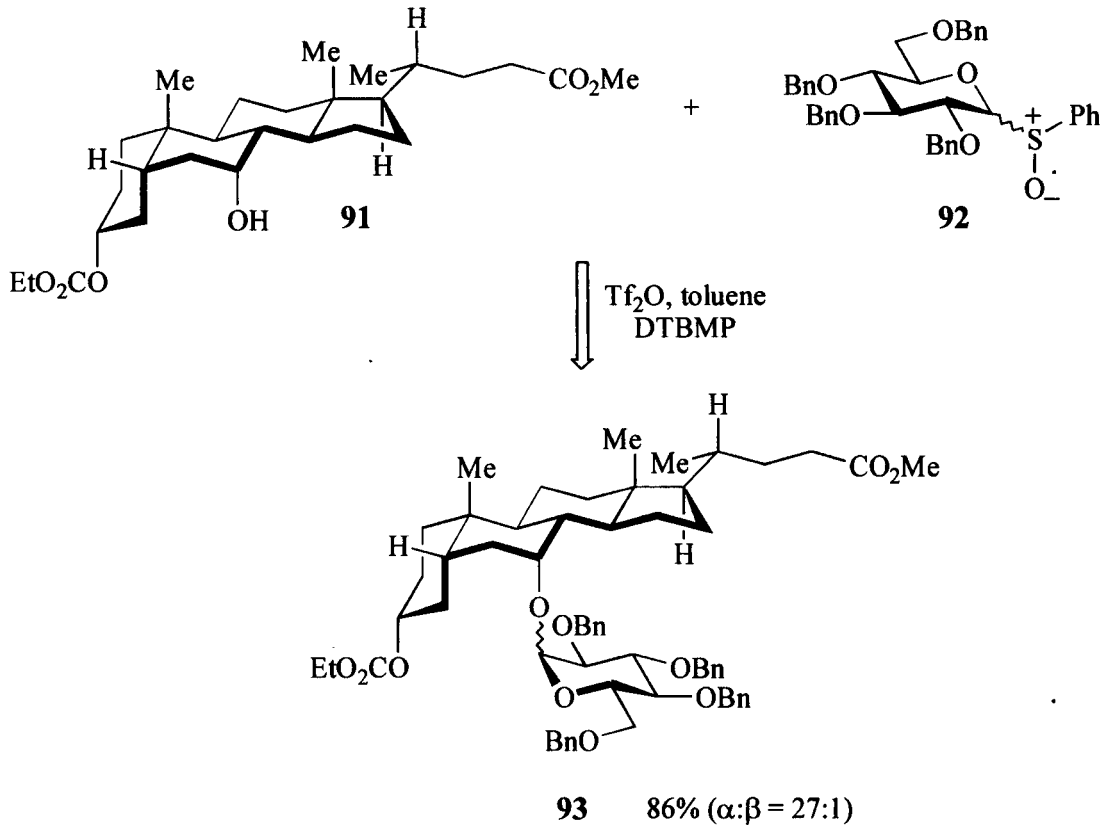


Figure 101 : Use of a glycosyl sulfoxide to glycosylate the unreactive C-7 position of deoxycholic acid

Activation of glycosyl sulfoxides occurs *via* initial triflation of the sulfoxide oxygen, to form an anomeric sulfonium ion. This leaves as phenylsulfenium triflate, to generate the usual oxocarbenium ion intermediate (Figure 102).

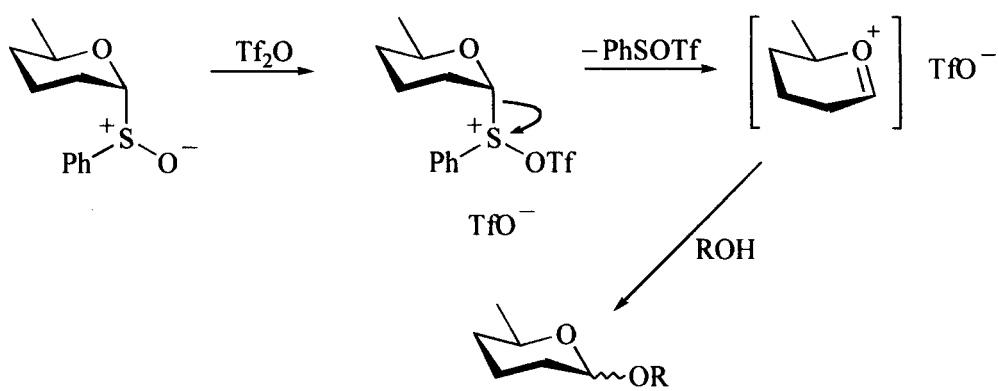


Figure 102 : The sulfoxide glycosylation method

Crich *et al.* reported that the stereochemical outcome of glycosylation reactions using 4,6-*O*-benzylidene acetal-protected mannosyl sulfoxide donors depended upon the order of addition of reactants.[36,37,192-194] In the first example that he presented, the expected α-selectivity in glycosylation product **96** was observed if the triflic anhydride promoter was added to premixed donor **94** and acceptor **95** (Figure 103-B), but enhanced β-selectivity was observed if **95** was introduced after all of **94** had been consumed by reaction with the promoter (Figure 103-A).

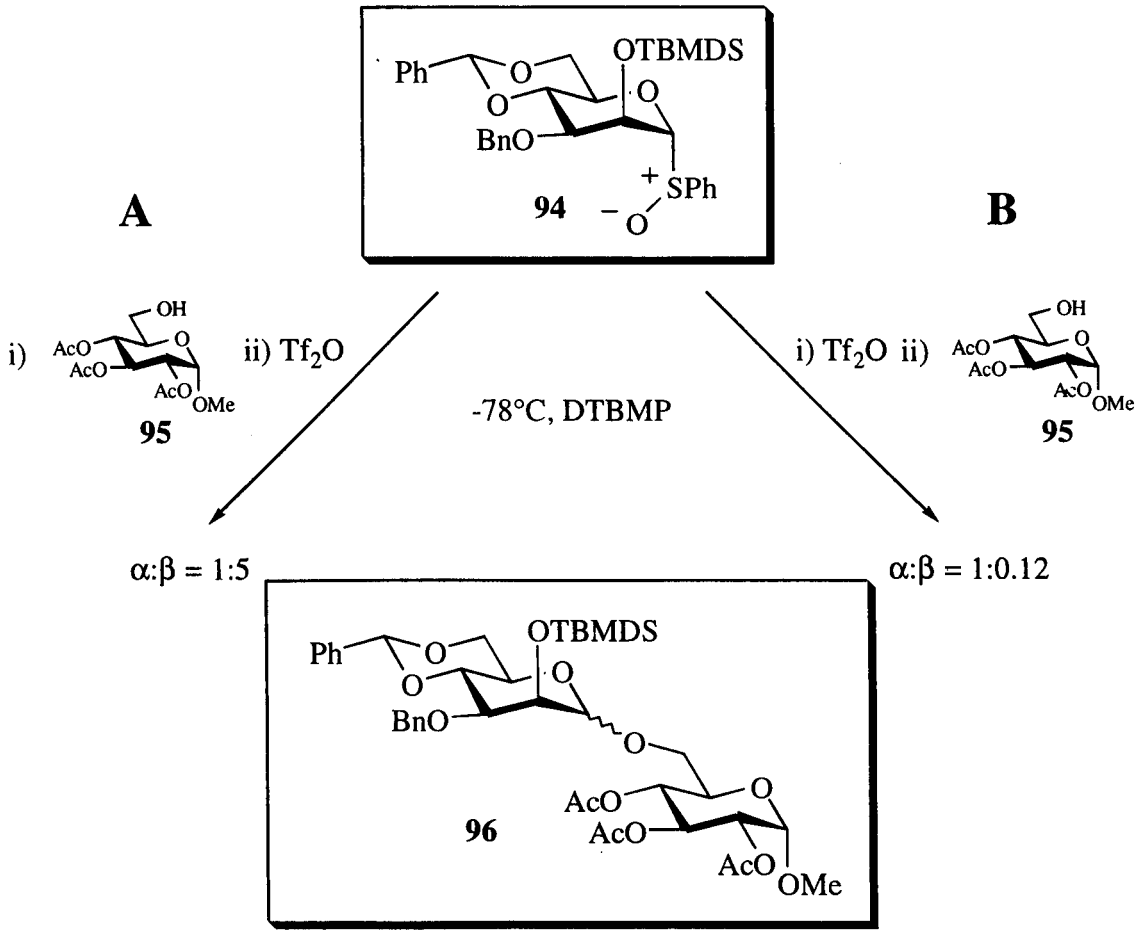


Figure 103 : The effect of the order of addition of reagents on the stereocontrol of glycosylation with torsionally-constrained mannopyranosyl sulfoxide donors

It is known that such fused bicyclic systems are generally less easily activated towards glycosylation than their single-ring analogues,[23] and it is believed that this is due to the torsional effects of the second ring. The usual case in glycosylation reactions is that the ring oxygen lone pair stabilises the cation at C-1, to give the oxocarbenium intermediate in a half-chair conformation. The minimum energy conformation for both the standard

and bicyclic oxocarbenium ion intermediates have been computed,[23] giving a C_5O_5-C_1C_2 dihedral angle of 20° in the latter case, and an ideal value of 0° in the single-ring example (Figure 104). This suggests that there is considerable strain in the pyranose ring of the bicyclic oxocarbenium intermediate.

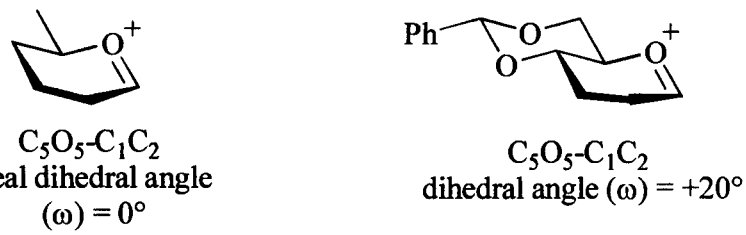


Figure 104 : The ideal dihedreal angle of the oxocarbenium ion intermediate in comparison with the calculated angle for a bicyclic analog

It was proposed by Crich that the torsional restriction in the conformation of the oxocarbenium intermediate in the bicyclic system is also responsible for his observations. The potency of triflic anhydride as a promoter in the reactions of glycosyl sulfoxides means that even in these "torsionally disarmed" examples, activation occurs readily (Figure 105).

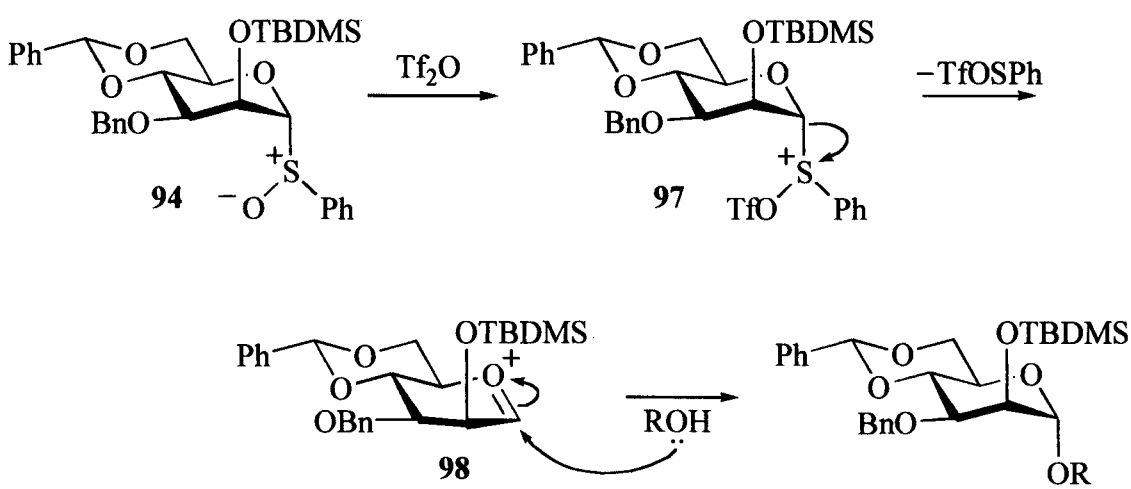


Figure 105 : Reaction of a conformationally restricted mannopyranosyl sulfoxide where glycosyl acceptor is pre-mixed with the donor prior to activation

Due to the strain within bicyclic oxocarbenium ion **98**, the latter reacts readily with any nucleophile present. When the glycosyl acceptor is present at the time of activation of the glycosyl donor, it reacts to give predominantly the α-mannopyranside, as might be

expected. The triflate anion is generally a very poor nucleophile, due to the removal of electron density away from oxygen by the strongly electronegative fluorine atoms. However, in the absence of a glycosyl acceptor, triflate is the only nucleophile available, and thus oxocarbenium intermediate **98** is intercepted by a triflate anion to form the anomeric triflate **99** (Figure 106).

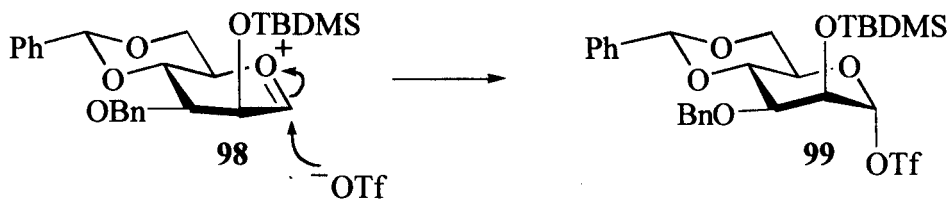


Figure 106 : Formation of a conformationally restricted mannopyranosyl triflate in the absence of a glycosyl acceptor

Under normal circumstances the anomeric triflate would be highly labile and would readily collapse back to the oxocarbenium ion, or react via S_N2 displacement of triflate. However, in this example, the strain in the oxocarbenium intermediate caused by the fused second ring means that once formed, the anomeric triflates might be expected to be stable with respect to the former. Crich was able to confirm the presence of an anomeric triflate in such a reaction mixture by ^{1}H, ^{19}F and ^{13}C NMR.[37] The excellence of triflate as a leaving group means that the subsequent introduction of the glycosyl acceptor will result in displacement of triflate by the better nucleophile, with inversion of configuration. Since α-triflate **99** is naturally favoured over its β-anomer, this will result in the formation of the β-mannopyranoside (Figure 107).

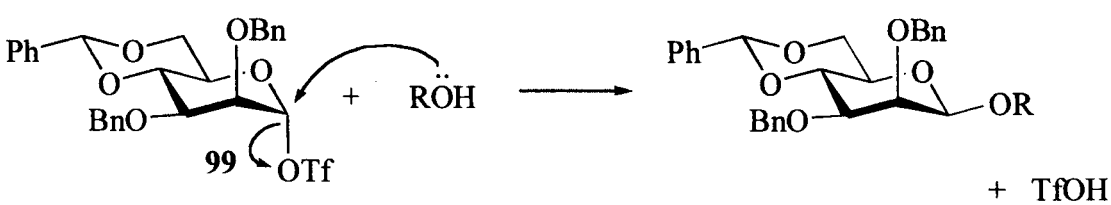


Figure 107 : S_N2 displacement of triflate at the anomeric centre of a conformationally restrained mannopyranosyl triflate

3.1.2.5 Nucleophilic displacement of anomeric iodides

Glycosyl iodides have been generated *in situ* from other glycosyl donors, and have shown greater reactivity towards nucleophilic displacement under neutral conditions than other glycosyl halides[68,195] (Figure 108).

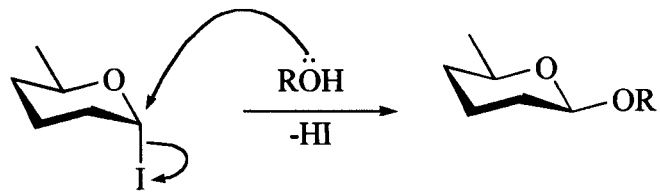


Figure 108 : Direct nucleophilic displacement of anomeric iodides

The reactivity of glycosyl iodides under neutral conditions is greatly enhanced by the addition of soluble sources of the iodide ion, such as TBAI, which facilitate *in situ* epimerisation of α-glycosyl iodides to the much more reactive β-anomers[195] (Figure 109).

Figure 109 : *In-situ* anomerisation of α-glycosyl iodides followed by nucleophilic displacement of the resultant β-iodide

Gervay *et al.* have reported the stereoselective synthesis of glycosyl iodides from anomeric acetates using trimethylsilyl iodide,[69] and Kartha and Field have reported in a similar procedure using hexamethyldisilane and iodine, essentially generating TMSI in situ.[148] Other procedures for the preparation of glycosyl iodides include the treatment of protected hemiacetals with a polymer bound triarylphosphane-iodine complex and imidazole,[196] and the reaction of glycosyl acetates or epoxides with anhydrous HI generated *in situ* by the reaction of a thiol with iodine.[197]

Subsequent work by Gervay *et al.* on reactions of glycosyl iodides with anionic nucleophiles has shown that for α-iodides of the *gluco-* and *galacto-* series, elimination is a serious problem[55], but with α-mannosyl iodides there is no such problem as there

can be no trans-diaxial arrangement of iodide and the proton at C-2, which is required for E_2-type elimination (Figure 110). As such, α-mannosyl iodides were found to react with inversion to give β-mannopyranosides.[55]

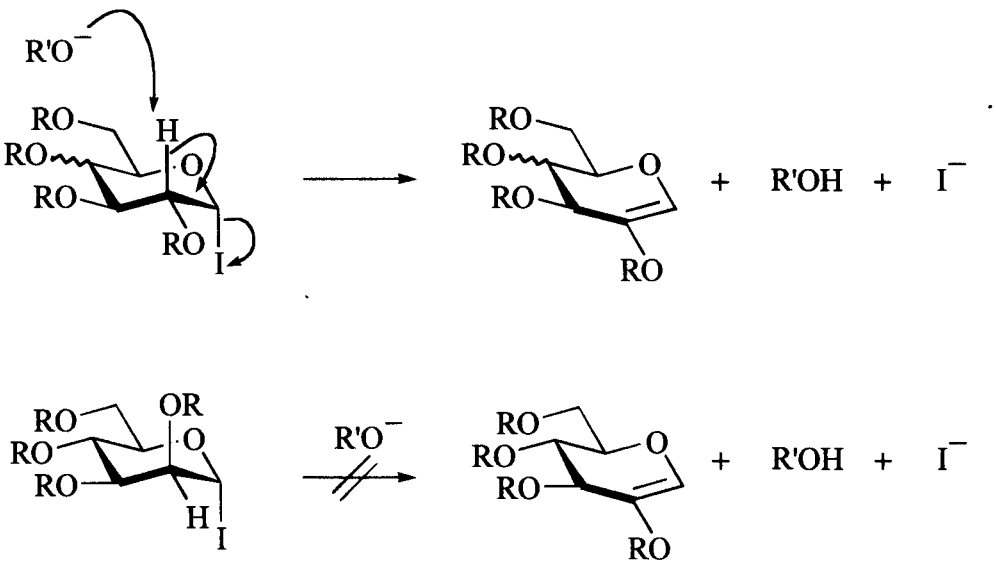


Figure 110 : Elimination during reactions of anionic nucleophiles with glycosyl iodides

3.1.3 The Pummerer rearrangement

The Pummerer methyl sulfoxide rearrangement[198,199] is believed to occur *via* a four step mechanism,[200] commencing with nucleophilic attack of the sulfoxide oxygen on acetic anhydride (Figure 111), to generate a sulfonium cation.

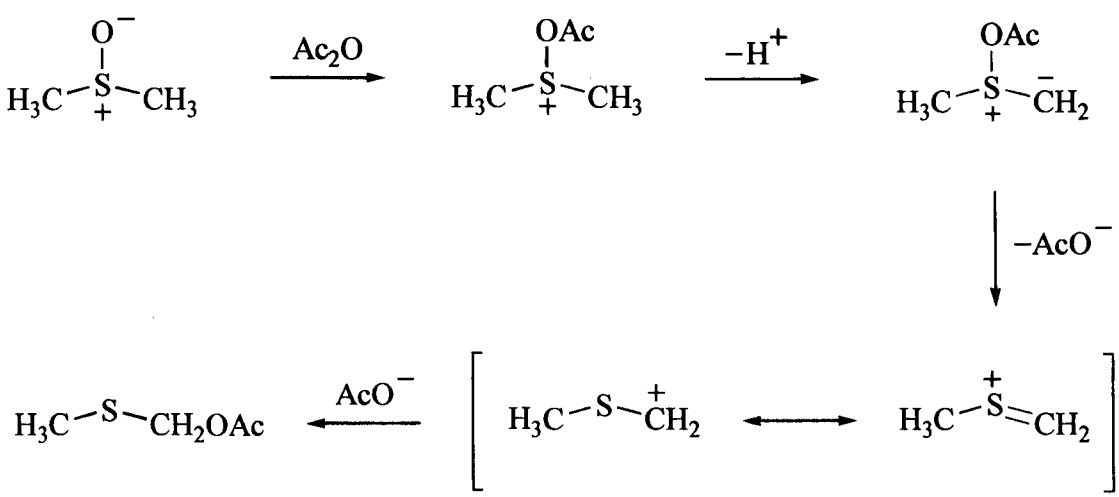


Figure 111 : The Pummerer reaction

Iodine in methanol has also previously been used to activate the sulfoxide group of **100** to generate ketal **101**[201] in a Pummerer-type reaction (Figure 112), and this prompted us to consider that iodine may also be capable of activating glycosyl sulfoxides.

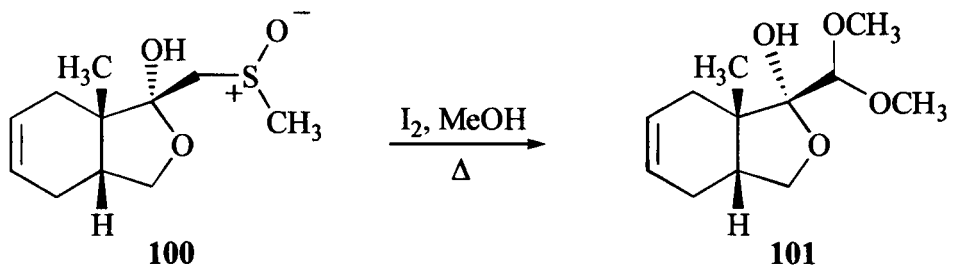


Figure 112 : Iodine/methanol-induced Pummerer rearrangement

3.2 Aims and objectives

The discovery by Crich that anomeric α-triflates can be generated *in situ* suggests that other highly labile glycosyl donors could be generated *in situ* and then reacted in a similar fashion. Of interest to the Field group was whether or not the α-iodide **103** could be generated *in situ* from a thioglycoside and iodine, and whether it might then react with nucleophiles by a direct displacement of iodide to give β-mannosides (Figure 113).

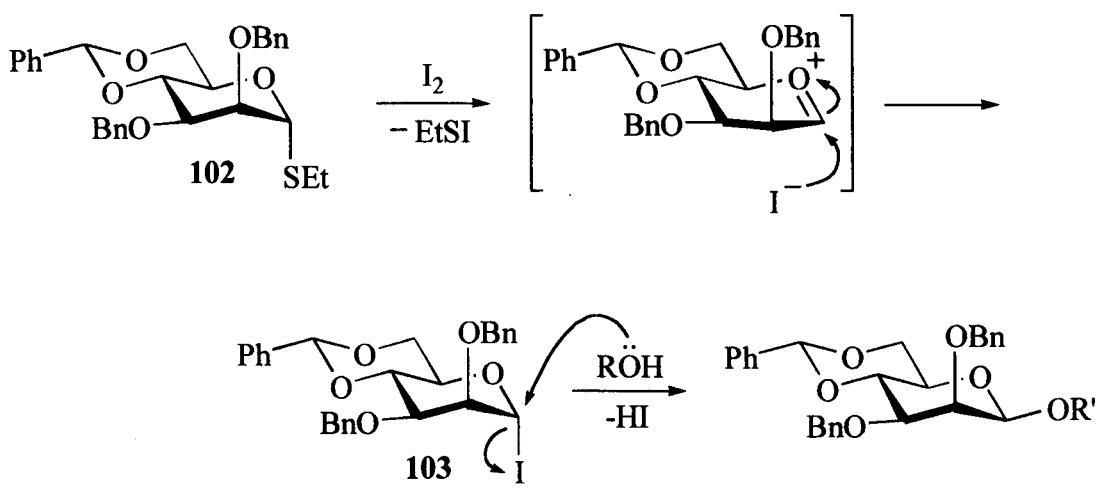
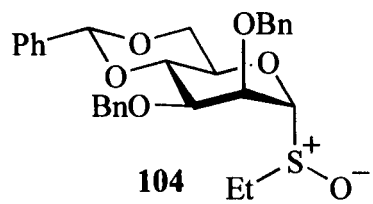


Figure 113 : Can a reactive mannosyl iodide be generated *in situ* to facilitate the formation of β-mannopyranosides?

The initial aim of this section of the project was thus to prepare the 4,6-*O*-benzylidene acetal protected α-thiomannoside **102**, and then to examine its reactivity towards methanol in the presence of iodine. If reaction occured, it was intended to examine the difference in stereoselectivity between the case where the acceptor is present throughout the reaction, and the case where it is added after activation of the glycosyl donor.

A secondary aim of this section of the project was to examine the reactivity of glycosyl sulfoxides towards iodine, and α/β-stereocontrol of any subsequent reaction. As it was already planned to prepare the conformationally restricted thiomannopyranoside **102**, we decided to attempt to convert this to the corresponding sulfoxide **104**, and examine the reactivity of this towards nucleophiles in the presence of iodine.



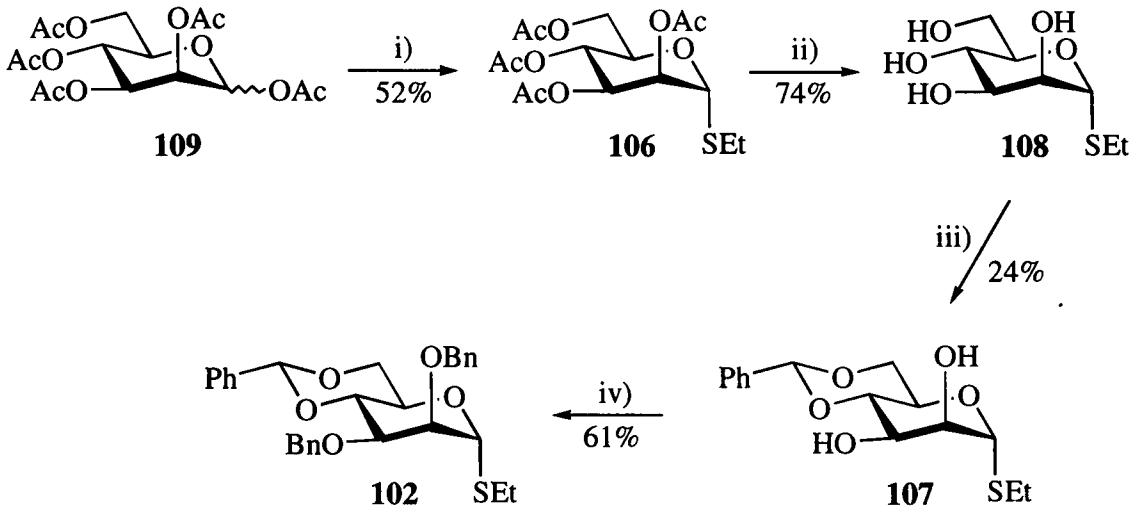
104

3.3 Results

3.3.1 Attempts to prepare β-mannopyranosides from conformationally restricted thiomannopyranoside donors

3.3.1.1 Preparation of 2,3-di-O-benzyl-4,6-O-benzylidene-α-D-thiomannopyranoside

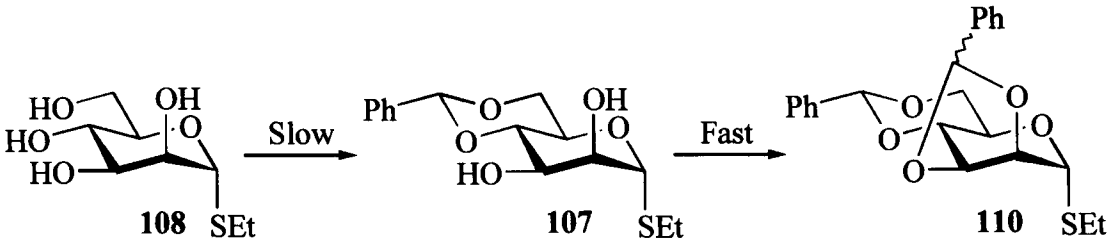
2,3-Di-*O*-benzyl-4,6-*O*-benzylidene-α-D-thiomannopyranoside[202] (**102**) was prepared from mannose pentaacetate (**109**) in four steps (Figure 114). Treatment of **109** with diethyl disulfide, iodine and HMDS in dichloromethane[148] gave a mixture of the α-thiomannoside **106** and its β-anomer **105** in a ratio of 10:1, as determined by ^{1}H NMR. Separation by column chromatography, and subsequent Zemplén deacetylation[160] of α-anomer **106** using sodium methoxide in methanol gave **108**, which crystallised from isopropanol.



Reagents and conditions:
i) Ac_2O, I_2, RT, 5 min; ii) EtSSEt, $Me_3SiSiMe_3$, I_2, DCM, 16-18°C, 2 hr; iii) NaOMe, MeOH, 2 hr; iv) $PhCH(OMe)_2$, CSA, 3Å MS, MeCN, 35°C, 18 hr; v) NaH, BnBr, DMF, RT, o/n.

Figure 114

Misra reported a procedure for introducing the 4,6-benzylidene group into α-ethyl thiomannoside **108**, in 69% yield, by stirring with benzaldehyde dimethyl acetal in acetonitrile in the presence of tosic acid.[203] In the experimental section of that paper it was reported that **108** was a "solution in acetonitrile" at room temperature. However, in our hands, even at 50°C, **108** did not appear to dissolve to any great extent. Overnight stirring using CSA as the acid resulted in formation of 4,6-benzylidene acetal **107** in poor yield, with t.l.c. indicating that a lot of starting material **108** remained unconverted. A faster eluting product was also observed. This is likely to be the 2,3;4,6-bis benzylidene acetal **110**, as positions 2 and 3 of **107** are *cis*-orientated, and thus also protectable by means of an acetal group. The uptake of the only partly soluble **108** into solution as it reacts to give the much more soluble partially protected **107** is most likely sufficiently slow to result in **107** competing with **108** to react with the benzaldehyde dimethyl acetal (Figure 115).



(poor solubility in acetonitrile)

(better solubility in acetonitrile)

Figure 115 : Sequential acetalations of ethyl α-thiomannopyranoside with benzaldehyde dimethyl acetal

Treatment of **107** with sodium hydride and benzyl bromide in DMF gave **102**. This compound had been previously reported in the literature by Garegg *et al.*,[202] but only as an intermediate before removal of the benzylidene group, and had not been characterised. Interestingly, their method of introduction of the benzylidene acetal group to **108** took only five minutes in a 1:1 mixture of formic acid and benzaldehyde, giving a yield of 49%.

3.3.1.2 Attempted iodine-promoted activation of 2,3-di-O-benzyl-4,6-O-benzylidene-α-D-thiomannopyranoside

Attempts to glycosylate methanol with thiomannoside **102** in the presence of iodine, potassium carbonate and molecular sieves failed, with t.l.c. indicating that none of **102** had been consumed (Figure 116).

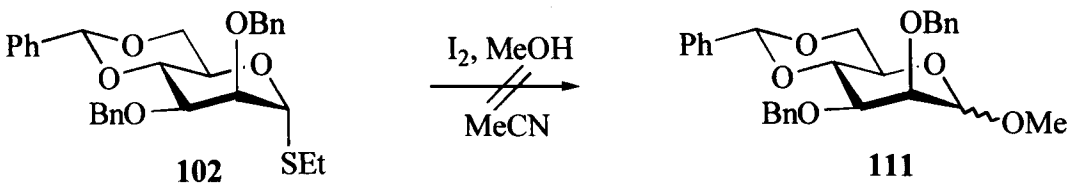


Figure 116 : Attempted iodine-promoted methanolysis of a 4,6-*O*-benzylidene acetal-protected thiomannopyranoside

This can be rationalised as being due to disarming effect of cyclic acetal protecting groups on the reactivity of glycosyl donors.[23] Iodine has already been found by the Field group to be a poor activator of 'disarmed' acylated thioglycosides,[109] and low reactivities

of conformationally 'disarmed' thioglycosides towards iodine would be consistent with this observation.

3.3.2 Iodine-promoted activation of a 4,6-benzylidene acetal-protected mannopyranosyl sulfoxide

Thiomannopyranoside **102** was converted into sulfoxide **104** by treatment with aqueous hydrogen peroxide and acetic anhydride in the presence of silica gel[204], in 85% yield (Figure 117).

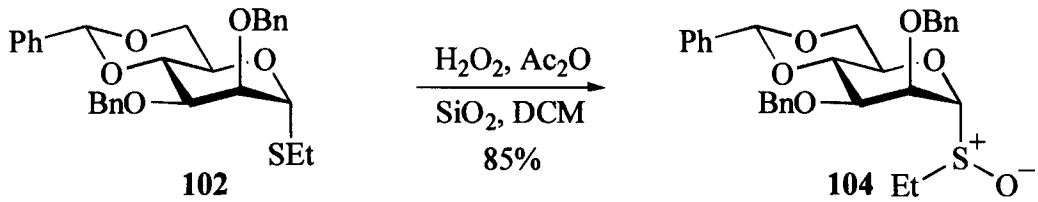


Figure 117

In a preliminary experiment, treatment of **104** with iodine (2 mol. eq.) and methanol (50 mol eq.) in acetonitrile gave no reaction in the presence of potassium carbonate. In the absence of the base, however, t.l.c. showed rapid consumption of **104** to give an intermediate product of much lower R_f, which reacted further to give products which were tentatively identified by ^{1}H NMR spectroscopy to be a mixture of anomers of methyl 2,3-di-*O*-benzyl-D-mannopyranosides (**112**), (α:β, 6:1) (Figure 118).

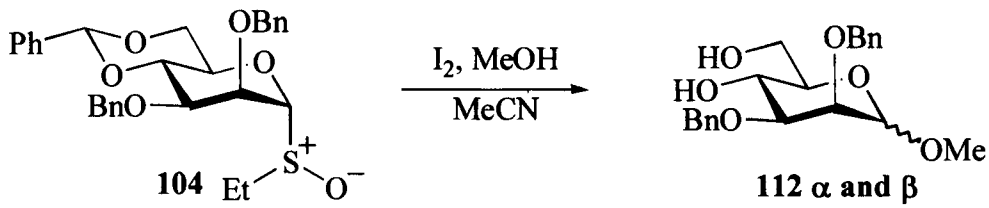


Figure 118

These preliminary experiments on the reactivity of sulfoxides in the presence of iodine were quite promising. It is possible that activation of the sulfoxide with iodine and glycosylation of methanol was occurring initially to give **111**, and that subsequently the combination of iodine and methanol, in the absence of base, was sufficiently acidic to

cleave the 4,6-*O*-benzylidene acetal to to give a mixture of partially protected mannosides **112α** and **112β** (Figure 119).

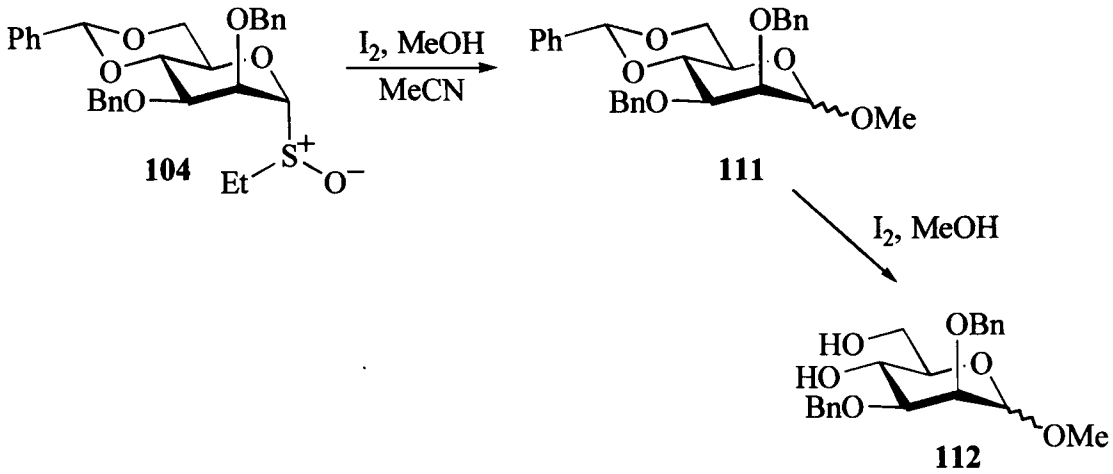


Figure 119

However, the observation by t.l.c. of intermediate products of lower R_f than either the starting materials or the final products suggested that it is more likely that cleavage of the benzylidene acetal occurred first to give the partially protected sulfoxide **113**, which was then activated by iodine, either alone or in combination with methanol, to give a mixture of partially protected mannosides **112α** and **112β** (Figure 120).

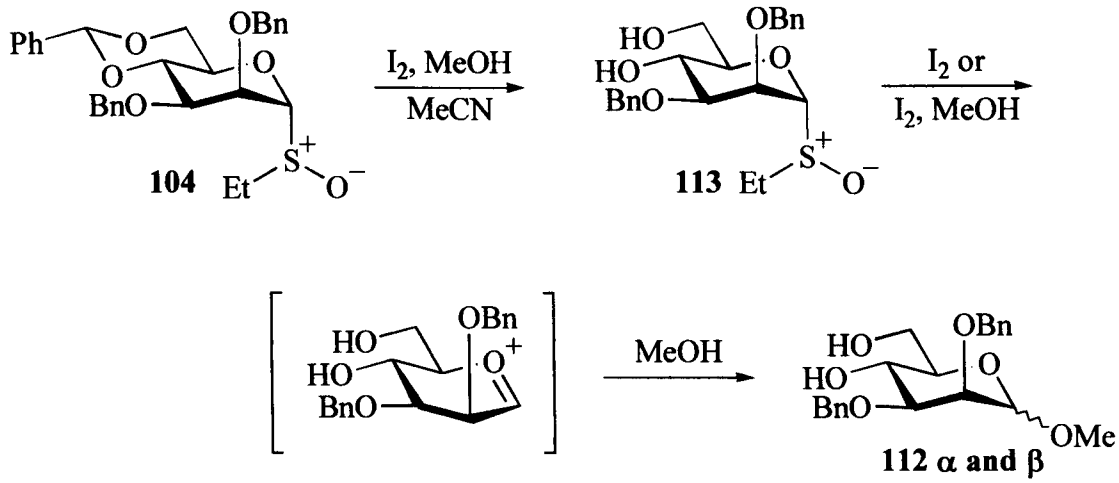


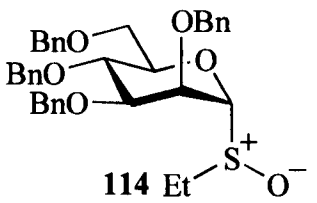
Figure 120

The unreactivity of the conformationally restricted sulfoxide **104** in the presence of base, and the lability of the benzylidene acetal protecting group in the absence of base,

suggested that further experiments on the activation of **104** with iodine were not worthwhile.

3.3.3 Iodine-promoted activation of 'armed' and 'disarmed' glycosyl sulfoxides

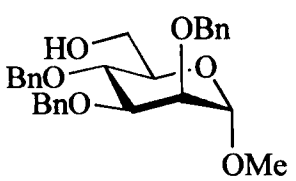
It was unclear whether or not activation of **113** occurred due to the acidity of the mixture of iodine and methanol, or due to the prior removal of the torsionally disarming 4,6-benzylidene acetal protecting group. We hypothesised that if iodine were responsible for the activation of **113**, then it should be even more capable of activating the 'armed' benzyl ether protected sulfoxide **114**.



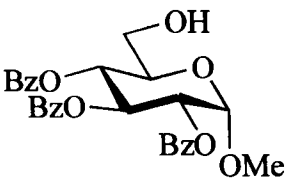
114

Previous work published by the Field group on the use of iodine to activate benzyl ether-protected galactopyranosyl thioglycosides used dichloromethane as the solvent rather than acetonitrile, in the presence of potassium carbonate.[105] The earlier work also used a slight excess of glycosyl donor over the glycosyl acceptor,[105] and because of the difficulty in accurately dispensing stoichiometric quantities of methanol in small scale reactions, we decided to move away from the use of this as the glycosyl acceptor.

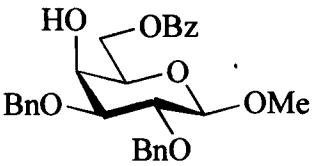
It was thus decided to synthesise sulfoxide **114**, and examine its reactivity with carbohydrate acceptors **72**, **73**, **74** and **75** (as prepared in Section 2.3.3.2) under conditions similar to the Field group's established iodine-mediated conditions,[105] in order to make a sensible comparison between the ease of activation of thioglycosides and glycosyl sulfoxides with iodine (notwithstanding the change in donor from the galactopyranosyl thioglycoside to mannopyranosyl sulfoxide).



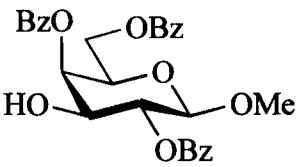
72



73



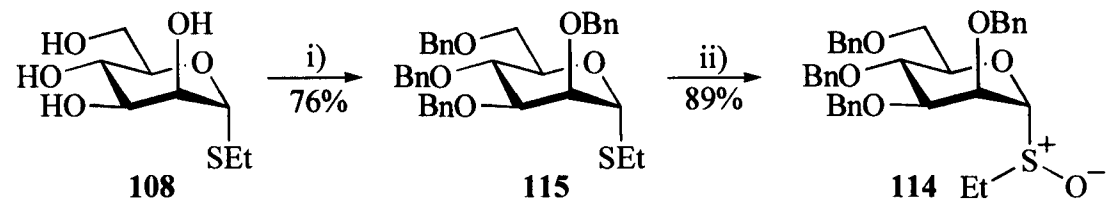
74



75

3.3.3.1 *Preparation of an 'armed' mannopyranosyl sulfoxide donor*

Ethyl 2,3,4,6-tetra-*O*-benzyl-α-D-thiomannopyranoside *S*-oxide (**114**) was prepared from ethyl α-D-thiomannopyranoside (**108**) in two steps (Figure 121).Treatment of **108** with sodium hydride and benzyl bromide in DMF gave tetrabenzylated thiomannopyranoside **115** in 76% yield. Oxidation of **115** with hydrogen peroxide and acetic anhydride in the presence of silica gel[204] then gave sulfoxide **114** in 89% yield.



108 **115** **114**

Reagents and Conditions:
i) NaH, BnBr, DMF, 0°C→RT; ii) H_2O_2, Ac_2O, SiO_2, DCM, RT.

Figure 121 : Preparation of ethyl 2,3,4,6-tetra-*O*-benzyl-α-D-mannopyranoside *S*-oxide

3.3.3.2 *Glycosylation of excess carbohydrate acceptors with the 'armed' mannopyranosyl sulfoxide*

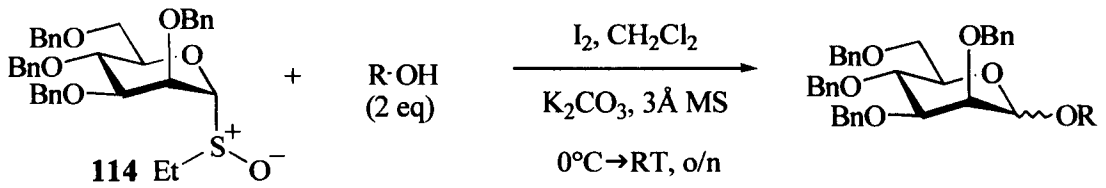
Carbohydrate acceptors **72**, **73**, **74** and **75** were glycosylated with 0.5 mol. eq. of sulfoxide **114** in the presence of iodine. The reactions were commenced at ice-bath temperature, and allowed to warm to ambient temperature overnight prior to work-up

and purification by column chromatography. In all cases the disaccharide products were isolable as a mixture of α- and β- anomers (Table 2). Assignment of the anomeric configuration of the major anomer in each case was accomplished with the aid of undecoupled ^{13}C NMR spectra (Table 3), which have been reported to show characteristic anomeric CH coupling constants of 165-175 Hz for α-hexapyranosides, compared with 155-160 Hz for β-hexapyranosides.[205]

The pattern of the yields is somewhat surprising. One might expect primary acceptors **72** and **73** to be the most reactive, followed by equatorial secondary acceptor **75**, with axial secondary acceptor **74** the least reactive. However, the best yield (55%) was obtained for disaccharide **118**, prepared from the axial 4-OH galactopyranosyl acceptor **74**, while the primary 6-OH acceptors **72** and **73** gave disaccharides **116** and **117** in 37% and 43% yields respectively. Disaccharide **119** was only prepared in 19% yield from equatorial 3-OH acceptor **75**. In addition, although the reactions were generally left overnight, it was apparent from t.l.c. that the glycosylation of 4-OH acceptor **74** with **114** was the fastest to progress.

The ^{13}C NMR data revealed slightly unusual stereocontrol in these reactions. With the exception of secondary 3-OH galactopyranosyl acceptor **75**, which produced only traces of the β-anomer of **119**, the major products were the β-mannopyranosides, in ratios of 3:1 (**116**), 2.6:1 (**117**), and 6.6:1 (**118**).

Table 2: Coupling of sugar acceptors with ethyl 2,3,4,6-tetra-*O*-benzyl-α-D-thiomannopyranoside *S*-Oxide



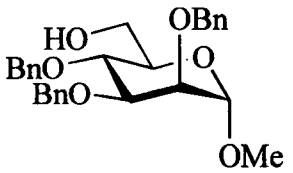
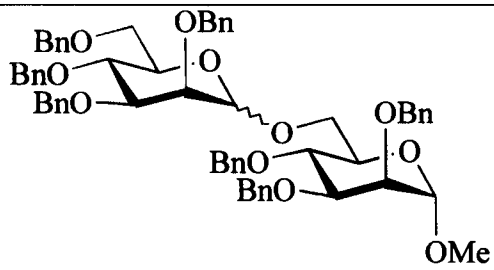
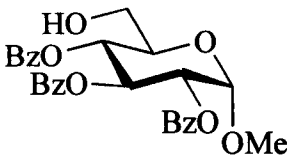
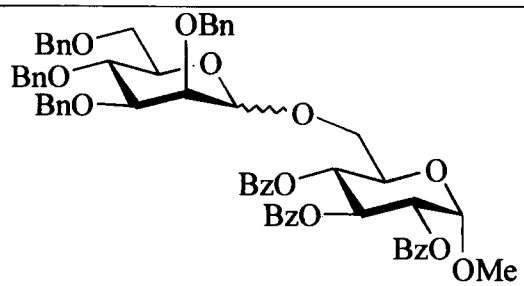
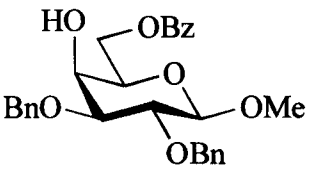
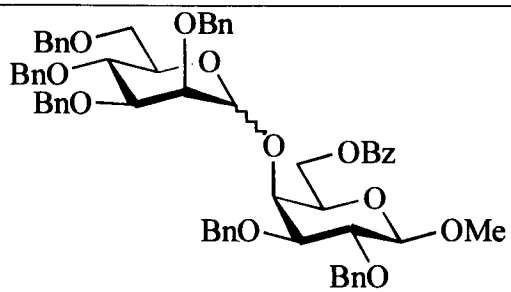
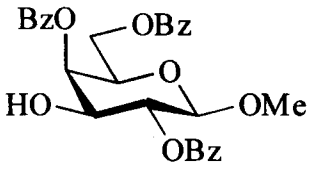
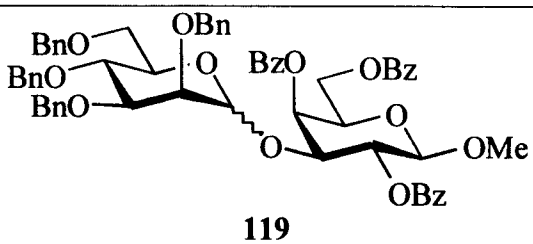
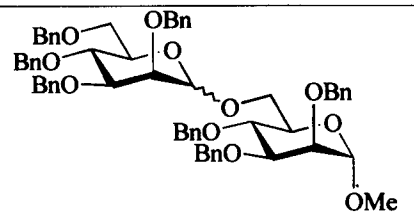
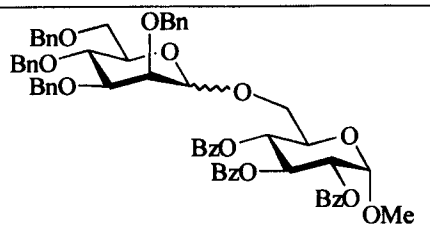
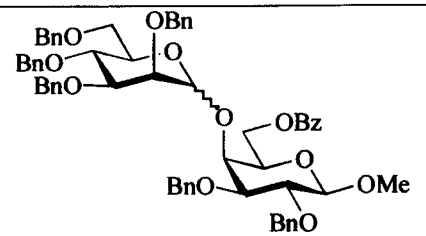
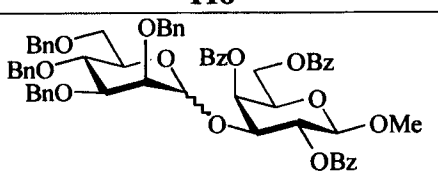
R-OH	Product	Yield	α:β
 **72**	 **116**	37%	1:3
 **73**	 **117**	43%	1:2.6
 **74**	 **118**	55%	1:6.6
 **75**	 **119**	19%	>20:1

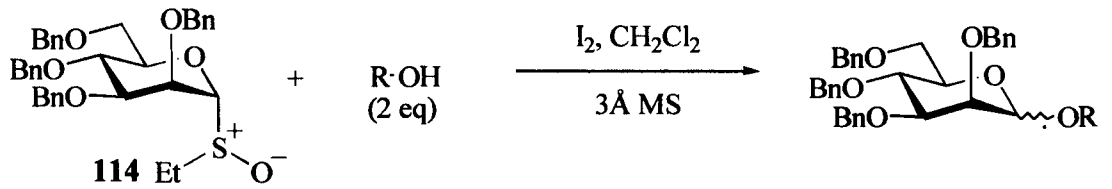
Table 3 : Anomeric ^{13}C chemical shifts and CH coupling constants of disaccharides prepared by iodine-mediated activation of an 'armed' mannopyranosyl sulfoxide

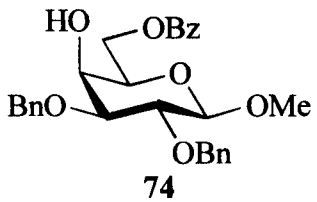
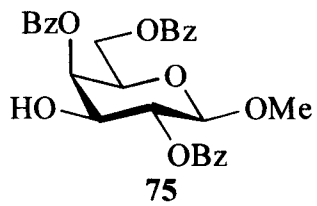
Product	α:β	$\delta_{C\text{-}1}$ (*ex* donor)		$\delta_{C\text{-}1}$ (*ex* acceptor)	
		major	minor	major	minor
 **116**	1:3	102.4 (J_{CH} 155)	98.3	99.1 (J_{CH} 166)	99.2
 **117**	1:2.6	102.5 (J_{CH} 156)	98.5	97.1 (J_{CH} 170)	97.2
 **118**	1:6.6	102.0 (J_{CH} 156)	100.7	105.1 (J_{CH} 159)	105.5
 **119**	>20:1	94.2 (J_{CH} 173)	n/a	102.7 (J_{CH} 160)	n/a

The presence of base (potassium carbonate) in the mixture suggests that it is iodine, and not acidity generated by the interaction of iodine with the acceptor, which is responsible for the activation of the glycosyl sulfoxides in these reactions. We decided to examine the effect of repeating the reaction in the absence of K_2CO_3. We selected only acceptors **74** and **75**, which gave the most extreme results in stereoselectivity and yield in our studies on the iodine-mediated activation of **114**, for further study.

It was found that in the absence of K_2CO_3, the glycosylation of 4-OH galactopyranoside acceptor **74** appeared to proceed more quickly, and was stopped after 2.5 hr (Table 4, entry ii), whereas appreciable reaction in the presence of base required an overnight reaction (Table 4, entry i). The yield was slightly lower, at 47% compared to 55% with K_2CO_3 present, and the β-stereoselectivity fell from 6.6:1 to 4:1. The glycosylation of 3-OH galactopyranoside acceptor **75** was still sluggish in the absence of K_2CO_3 (Table 4, entry iv), with a very slight increase in yield, from 19% (Table 4, entry iii) to 22%. Under the more acidic conditions, the α-stereoselectivity of the latter reaction was absolute.

Table 4: Comparison of yields for glycosylations of 4-OH acceptor (74) and 3-OH acceptor (75) with 'armed' mannopyranosyl sulfoxide (114) in the presence and absence of potassium carbonate



Entry	R-OH	Base	Temp	Time	Yield	α/β
i	 **74**	K_2CO_3	-10°C → RT	o/n	55%	1 : 6.6
ii	**74**	none	-5°C → RT	2.5 hr	47%	1 : 4
iii	 **75**	K_2CO_3	-10°C → RT	o/n	19%	>20 : 1
iv	**75**	none	-5°C → RT	o/n	22%	1 : 0

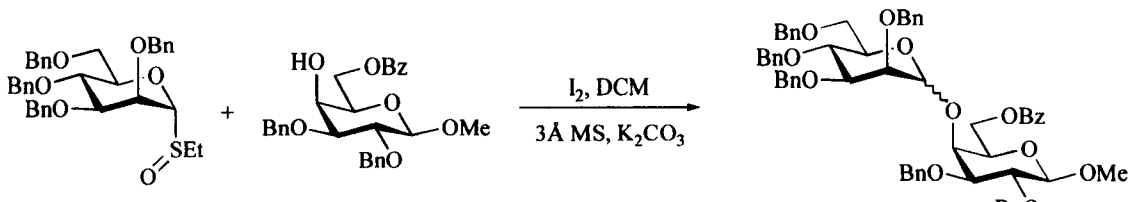
3.3.3.3 *The effect of varying the amount of acceptor on glycosylations with the 'armed' mannopyranosyl sulfoxide donor*

Having shown that iodine can be used to promote the glycosylation of sugar acceptors with the 'armed' mannopyranosyl sulfoxide, we investigated the effect of changing the relative quantities of the donor and the acceptor.

In our previous experiments, we had used 2 mole equivalents of the glycosyl acceptor for every mole of sulfoxide donor **114**. In this study, three experiments were performed in parallel for each acceptor **74** and **75**, varying only the amount of glycosyl acceptor used in the reaction. The results are outlined in Table 5 and Table 6.

In both of these sets of experiments, the major pattern observed was a much faster consumption of sulfoxide donor **114**, and an increase in the proportion of the β-anomer in the product, when the donor was in excess. The yield for the reaction of **74** and **114** to produce disaccharide **118** did not vary greatly as the amount of glycosyl acceptor was varied (Table 5), whilst for the reaction of **75** and **114** to produce disaccharide **119** the yield appears somewhat greater when an excess of donor was used (Table 6).

Table 5: Yields and product ratios for varying ratio of 4-OH Acceptor (74) to sulfoxide donor (114) in iodine-promoted glycosylation reactions



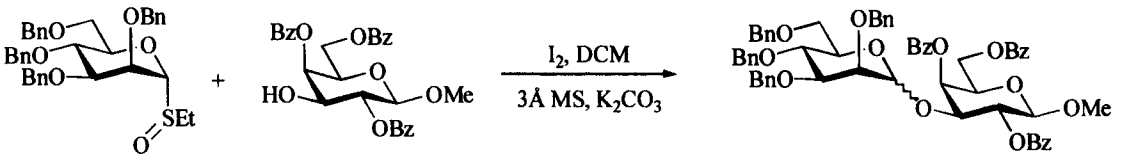
114 **74** **118**

Donor/ Acceptor	Reaction Time	Yield	α:β
2:1	3.5 hr	46%[a]	1:6.5
1:1	6 hr	36%[a]	1:6.4
1:2	18 hr	41%[b]	1:6

[a] Yield upon level of acceptor used (donor in excess or equimolar levels used)

[b] Yield based upon level of sulfoxide used (acceptor in excess)

Table 6: Yields and product ratios for varying ratio of 3-OH Acceptor (75) to sulfoxide donor (114) in iodine-promoted glycosylation reactions



114 **75** **119**

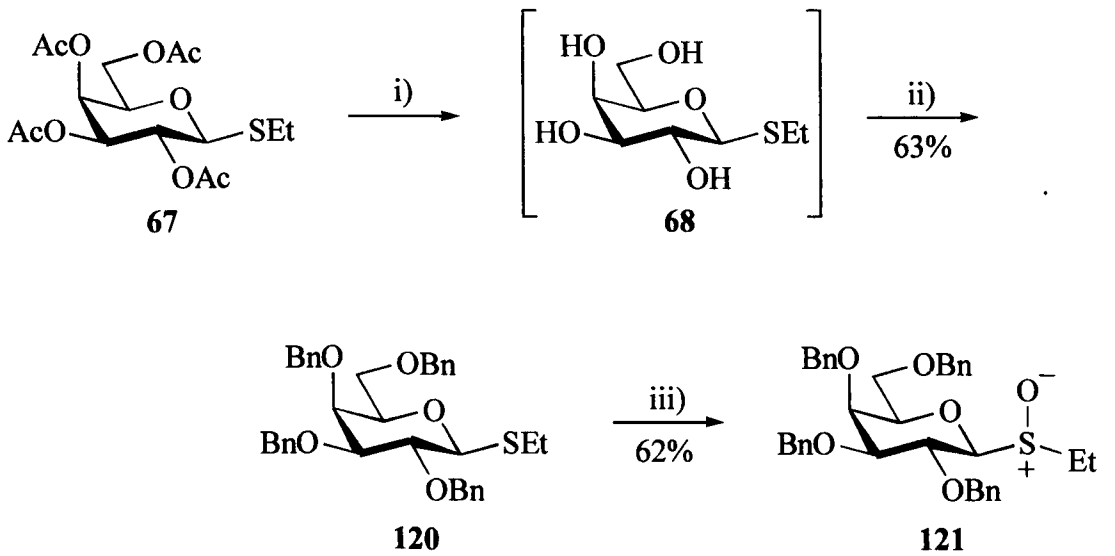
Donor/ Acceptor	Reaction Time	Yield	α:β
2:1	3.75 hr	26%[a]	7:1
1:1	7 hr	16%[a]	>25:1
1:2	20 hr	18%[b]	12.3:1

[a] Yield upon level of acceptor used (donor in excess or equimolar levels used)

[b] Yield based upon level of sulfoxide used (acceptor in excess)

3.3.3.4 *Comparision of stereochemistry of glycosylations with 'armed' mannopyranosyl and galactopyranosyl sulfoxide donors*

The unusual stereocontrol of the glycosylations of our carbohydrate acceptors with α-mannopyranosyl sulfoxide **114** prompted us to examine the analogous glycosylations of these acceptors with armed β-galactopyranosyl sulfoxide **121**. Compound **121** was prepared from acetylated ethyl thiogalactoside **67** (Figure 122) in three steps. Zemplén deprotection of **67** with sodium methoxide in methanol,[160] and subsequent benzylation with benzyl bromide and sodium hydride in DMF afforded tetra-*O*-benzyl thiogalactoside **120** in 63% yield. Oxidation of **120** with $H_2O_2/Ac_2O/SiO_2$ in dichloromethane[204] then gave **121** in 62% yield, as a 1:1 mixture of diastereomers.

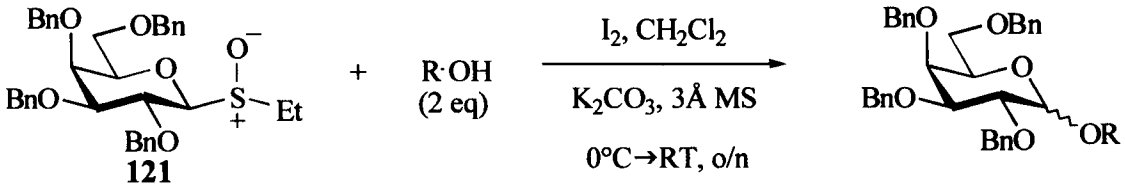


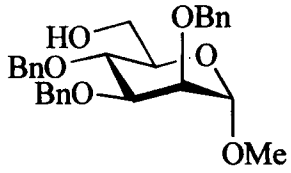
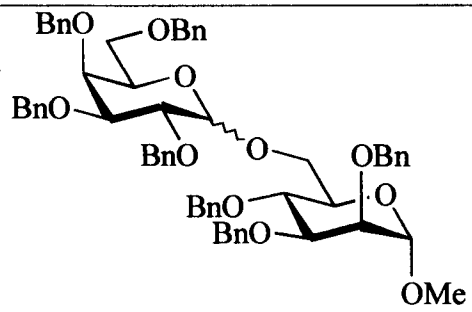
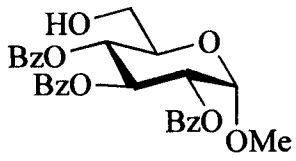
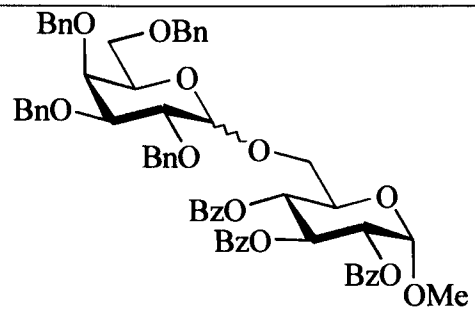
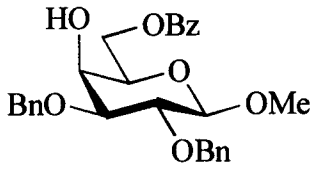
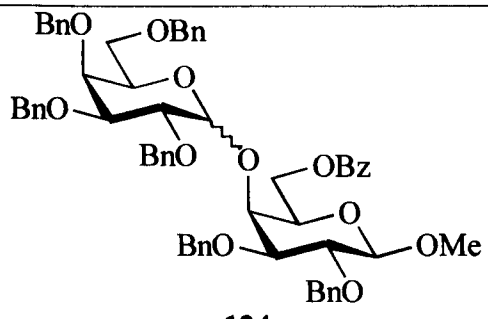
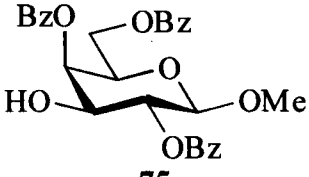
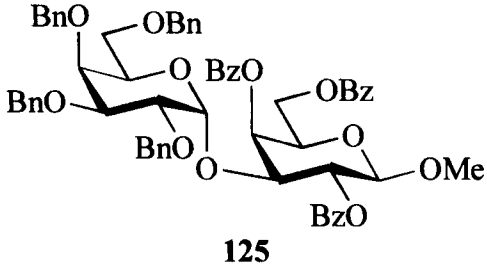
Reagents and Conditions:
i) NaOMe, MeOH; ii) BnBr, NaH, DMF; iii) H_2O_2, Ac_2O, SiO_2, DCM

Figure 122

Carbohydrate acceptors **72**, **73**, **74** and **75** were then glycosylated with galactopyranosyl sulfoxide **121** in the presence of iodine, molecular sieves and potassium carbonate under conditions as described for mannopyranosyl sulfoxide **114**. The results are summarised in Table 7.

Table 7: Coupling of sugar acceptors with ethyl 2,3,4,6-tetra-*O*-benzyl-β-D-thiogalactopyranoside *S*-Oxide



R-OH	Product	Yield	α:β
 72	 122	51%	1:1.3
 73	 123	32%	1:1
 74	 124	53%	2.3:1
 75	 125	40%	1:0

The yields, with the exception of the glycosylation of 3-OH acceptor **75**, were broadly similar to those obtained for the corresponding reactions of mannosyl sulfoxide donor **114**, with the best yield being obtained in the glycosylation of 4-OH acceptor **74** (53%). The yield obtained for glycosylation of 3-OH acceptor **75** with galactosyl donor **121** (40%) was twice that obtained for glycosylation with mannosyl donor **114** (19%).

There was a considerable improvement in the α-stereoselectivity observed in the glycosylations of **72** (1:1.3), **73** (1:1) and **74** (2.3:1), when compared to the corresponding reactions with **114**. The absolute α-stereoselectivity in the glycosylation of 3-OH acceptor **75** with **121** is very similar to that which was observed in the glycosylation of **75** with **114** (20:1), and with studies by the Field group[105] on the iodine-promoted glycosylation of 3-OH acceptors **126** and **127** with armed thiogalactoside **120** (1:0, Figure 123).

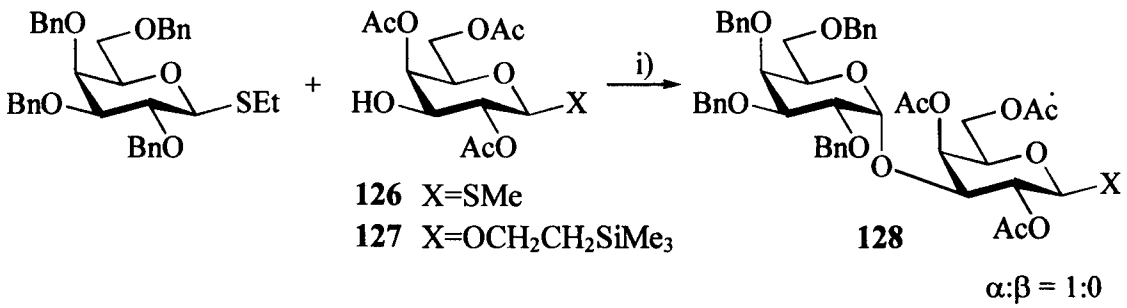
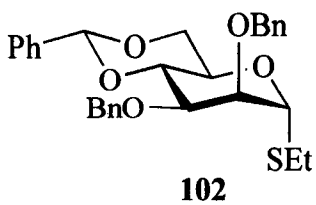


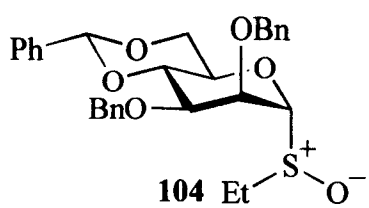
Figure 123

3.3.3.5 *Attempted glycosylation of a carbohydrate acceptor with a 'disarmed' mannopyranosyl sulfoxide*

Previous attempts to activate conformationally 'disarmed' thiomannoside **102** and its *S*-oxide **104** with iodine in the presence of potassium carbonate were unsuccessful.



102



104

It was thus considered unlikely that acetylated sulfoxide **129** would be activated with iodine either, due to the disarming effect of the acetyl protecting groups. In order to put

this to the test, acetylated mannosyl sulfoxide **129** was prepared from thiomannoside **106** by oxidation with $H_2O_2/Ac_2O/SiO_2$ in dichloromethane[204] (Figure 124).

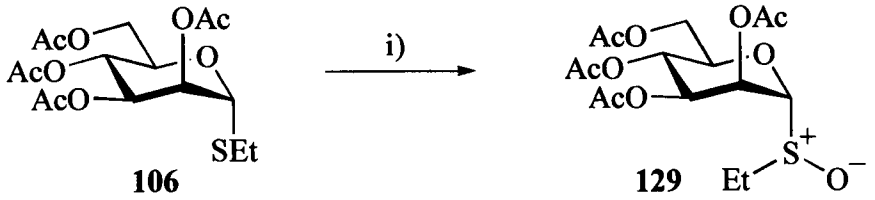


Figure 124

Since our studies on the activation of 'armed' mannosyl and galactosyl sulfoxides with iodine had shown, somewhat surprisingly, 4-OH acceptor **74** to be the most easily glycosylated of our acceptors under our conditions, we attempted to glycosylate **74** with acetylated sulfoxide **129**. In a parallel reaction, we also attempted to glycosylate **74** with 'disarmed' thiomannoside **106** (Figure 125).

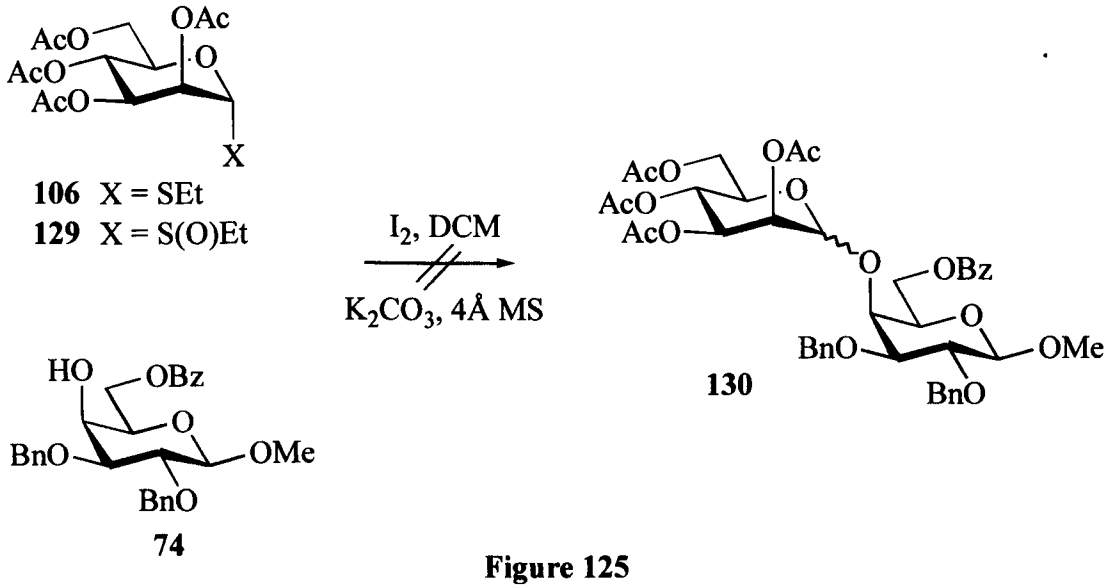


Figure 125

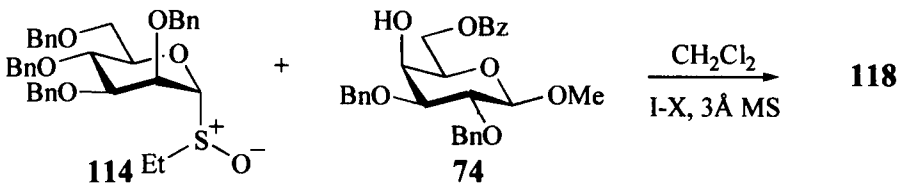
In both cases t.l.c. showed very little change in the composition of the reaction mixtures, even after 72 hours. This is in accord with our prediction, made in the light of the observed unreactivity of both **102** and **104** as glycosyl donors in the presence of iodine and potassium carbonate, that the disarming effect of the acetyl protecting groups of **129** would prevent activation of under similar conditions.

3.3.4 Iodine monobromide-promoted activation of the 'armed' mannopyranosyl sulfoxide

During the course of this project, the Field group showed that whilst iodine is limited as a promoter in that it can only activate 'armed' thioglycosides,[105,109] the more potent iodonium ion source iodine monobromide can be used to activate even 'disarmed' thioglycosides.[56] Having shown during this project that 'armed' glycosyl sulfoxides can also be activated by iodine, we rationalised that iodine monobromide may potentially be a more potent activator of glycosyl sulfoxides than iodine itself.

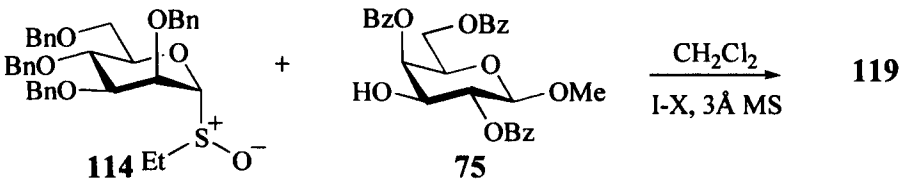
Glycosylation of **74** and **75** with 0.5 mol. eq. of sulfoxide **114** was thus attempted in the presence of iodine monobromide (0.5 mol. eq.) instead of iodine. The results show that activation did occur, and that in both cases, the yield was greater using iodine monobromide. In the case of 4-OH acceptor **74**, the reaction was significantly faster, and was stopped after 1 hour, with an improved yield of 62% (Table 8, entry iii), whilst the 3-OH acceptor **75** still reacted sluggishly, giving a yield of 37% after stirring overnight (Table 9, entry iii). The β-stereocontrol of the reaction of **74** was now reduced to 2.7:1, whilst the reaction of **75** again occurred with absolute α-stereocontrol.

Table 8 : Comparison of yields for iodine and iodine monobromide-promoted glycosylations of 4-OH Acceptor (74) with 'armed' mannopyranosyl sulfoxide (114)



Entry	I-X	Base	Temp	Time	Yield	α/β
i	I_2	K_2CO_3	-10°C → RT	o/n	55%	1 : 6.6
ii	I_2	none	-5°C → RT	2.5 hr	47%	1 : 4
iii	IBr	none	-5°C → RT	1 hr	62%	1 : 2.7

Table 9: Comparison of yields for iodine and iodine monobromide-promoted glycosylations of 3-OH Acceptor (75) with 'armed' mannopyranosyl sulfoxide (114)



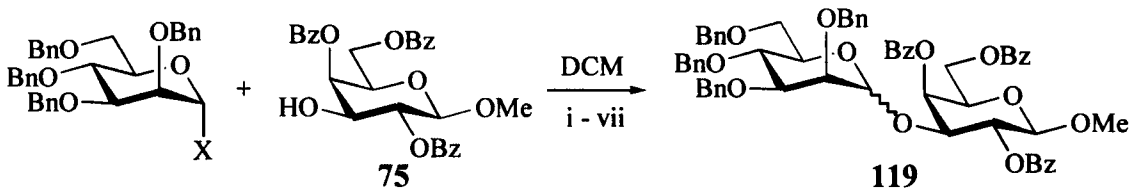
Entry	I-X	Base	Temp	Time	Yield	α/β
i	I_2	K_2CO_3	-10°C → RT	o/n	19%	>20 : 1
ii	I_2	none	-5°C → RT	o/n	22%	1 : 0
iii	IBr	none	-5°C → RT	o/n	37%	1 : 0

3.3.5 Comparative reactions of an 'armed' thiomannopyranoside and its *S*-oxide using different promoters

Glycosylations of **74** and **75** were performed under a variety of conditions (Tf_2O-promoted[118] activation of sulfoxide **114**; NIS/TfOH-promoted[98,101] activation of thioglycoside **115**; I_2-promoted[105] activation of **115**) in order to compare the yields and stereoselectivities of our reactions with the established protocols in our hands. The results of these reactions are summarized with, for the purposes of comparison, the previously discussed iodine and iodine-monobromide-promoted glycosylations of excesses of **74** and **75** with sulfoxide **114**, in Table 10 and Table 11.

The results show that glycosylation of 3-OH acceptor **75** proceeds with excellent α-stereocontrol under each set of conditions utilised. The yields for the glycosylation of **75** by means of the standard Tf_2O-promoted activation of sulfoxide **114** and NIS/TfOH-promoted activation of thioglycoside **115** were much greater than those obtained under iodine- or iodine monobromide-mediated conditions, whilst iodine-promoted activation of thioglycoside **115** gave a better yield (26%) than iodine-promoted activation of **114** (19%).

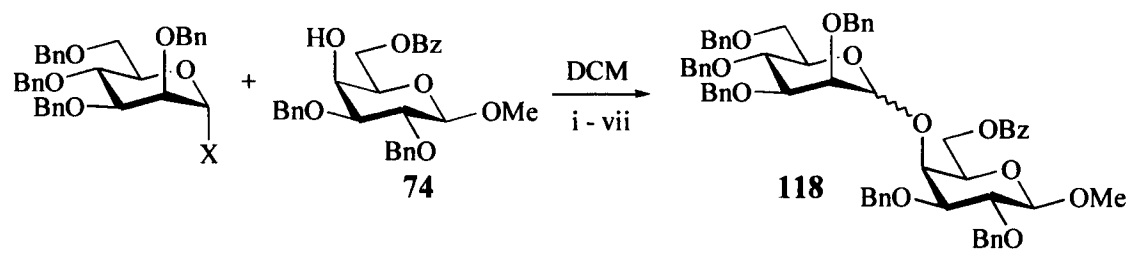
Table 10: Comparison of results for glycosylations of 3-OH Acceptor (75) with 2,3,4,6-tetra-*O*-benyl mannopyranose donors



Entry	X	Promoter	Base	Temp	Time	Yield	α/β
i	S(O)Et	Tf_2O	DTBMP	-78°C → 0°C	4 hr	69%	1 : 0
ii	S(O)Et	I_2	K_2CO_3	-10°C → RT	o/n	19%	>20 : 1
iii	S(O)Et	I_2	none	-5°C → RT	o/n	22%	1 : 0
iv	S(O)Et	IBr	none	-5°C → RT	o/n	37%	1 : 0
v	SEt	NIS/TfOH*	none	-10°C	90 min	78%	1 : 0
vi	SEt	I_2	K_2CO_3	-5°C → RT	2 days	26%	1 : 0

*Performed in 2:1 DCM/ether

Table 11: Comparison of yields for glycosylations of 4-OH Acceptor (74) with 2,3,4,6-tetra-*O*-benzylated mannopyranose donors

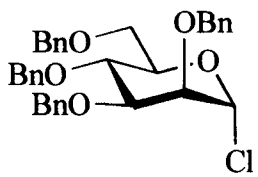


Entry	X	Promoter	Base	Temp	Time	Yield	α/β
i	S(O)Et	Tf_2O	DTBMP	-78°C → 0°C	4 hr	79%	3.1 : 1
ii	S(O)Et	I_2	K_2CO_3	-10°C → RT	o/n	55%	1 : 6.6
iii	S(O)Et	I_2	none	-5°C → RT	2.5 hr	47%	1 : 4
iv	S(O)Et	IBr	none	-5°C → RT	1 hr	62%	1 : 2.7
v	SEt	NIS/TfOH*	none	-10°C	20 min	76%	2.6 : 1
vi	SEt	I_2	K_2CO_3	-5°C → RT	o/n	67%	1 : 7

*Performed in 2:1 DCM/ether

The pattern observed in the yields for the glycosylation of 4-OH acceptor **74** is broadly similar to that observed for glycosylation of **75**, with the standard Tf_2O-promoted activation of sulfoxide **114** and NIS/TfOH-promoted activation of thioglycoside **115** both giving yields of over 75%, and iodine-promoted activation of thioglycoside **115** (67%) giving a significantly better yield than the iodine-promoted activation of **114** (55%). The most interesting observation was the difference in the stereocontrol under the different conditions. Both the NIS/TfOH- and Tf_2O- promoted procedures gave reasonable α-stereocontrol, compared to the β-stereocontrol observed under iodine- and iodine monobromide-promoted procedures.

Attempts to activate sulfoxide **114** with iodine monochloride resulted in formation of what is believed to be the benzylated α-mannopyranosyl chloride[206] **131**. The identification of this product was performed on the basis of the ^1H and ^{13}C NMR spectrum, which is in agreement with that reported in the literature,[206,207] and supported by MALDI-TOF mass spectrometry, which gave an ($M + Na^+$) peak consistent with the molecular weight of **131**.



131

3.4 Discussion

3.4.1 Iodine as a mild promoter for the activation of thioglycosides

In the activation of 'armed' thioglycosides[105] iodine can be regarded as a mild source of I^+. The mildness of the activation procedure for thioglycosides suggests a certain level of reversibility about the transfer of I^+ between sulfur and I^-. This is reinforced by the observation of Veeneman that the combination of iodine and silver triflate, the latter of which should react irreversibly with halide ions and thus remove them from any such equilibrium, is a far more potent activator of thioglycosides than iodine alone (Figure 126).[26]

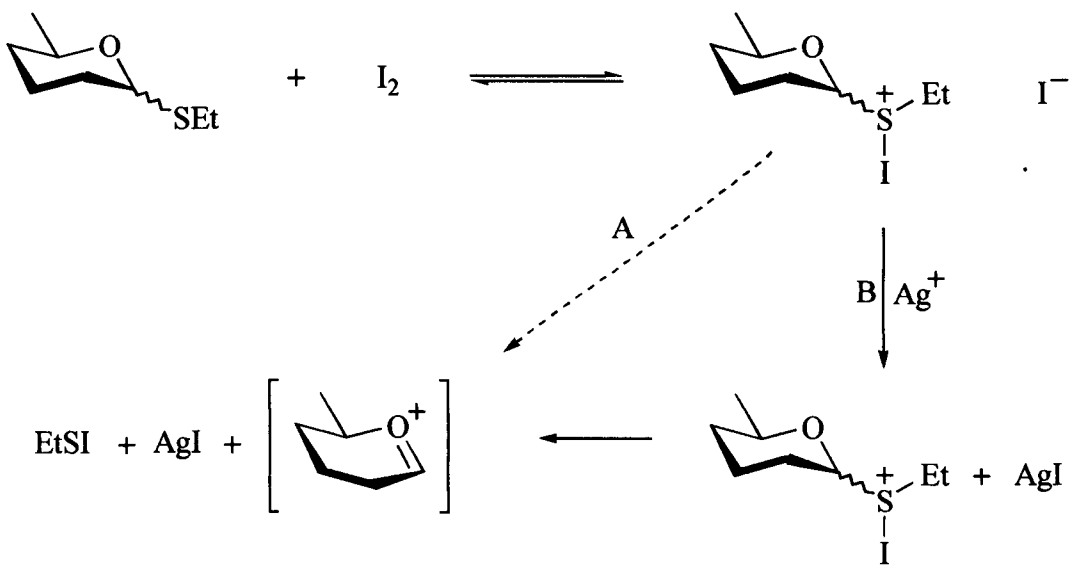


Figure 126 : Enhancement of reversible thioglycoside iodination by silver ions

3.4.2 The hypohalite reaction

The harder nature of oxygen as a nucleophile, in comparison with sulfur, suggests that any equilibrium associated with the transfer of I^+ from molecular iodine to oxygen should lie more firmly on the side of the reagents. Just as with the iodination of the anomer sulfur of thioglycosides, the use of iodine in combination with an appropriate salt of a heavy metal such as silver or mercury should prove a more potent source of I^+,

by removing I^- and thus forcing the equilibrium in the direction of the resultant hypoiodite (Figure 127).

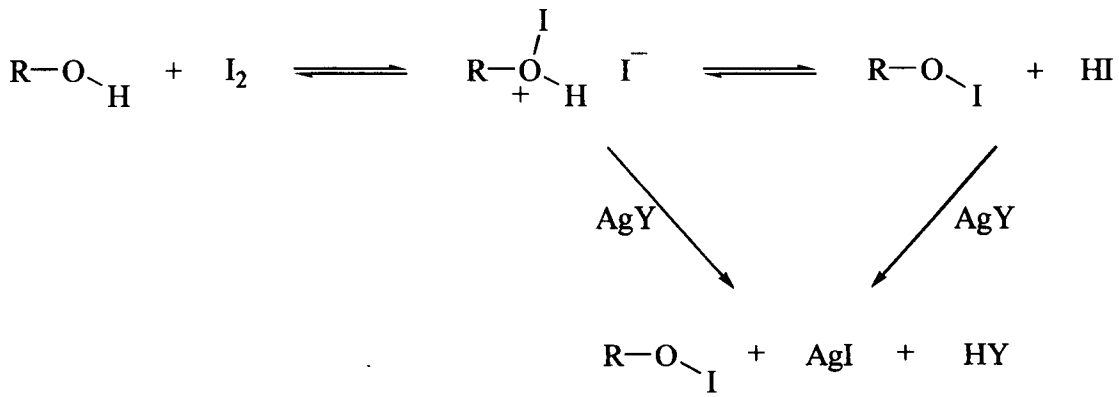


Figure 127 : Equilibria likely to be associated with the interaction of iodine with alcohols

Hypoiodites generated in this way have in fact been used extensively since the 1960s in the generation of rings within steroidal structures.[208-210] In these reactions, treatment of alcohols with sources of I^+ such as I_2/AgOAc, I_2/$Hg(OAc)_2$, I_2/$Pb(OAc)_4$, I_2/HgO and NIS,[208-210] is believed to generate alkyl hypoiodites *in situ* as reaction intermediates (Figure 128).

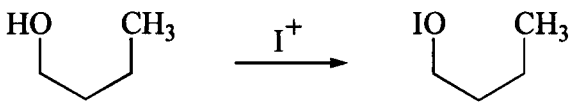


Figure 128

Subsequent homolytic cleavage of the iodine-oxygen bond at temperatures above 60°C generates a radical at oxygen, which can result in abstraction of hydrogen from a δ-carbon and transfer of an iodine atom to the δ-carbon. Intramolecular nucleophilic displacement of iodide by the hydroxyl group results in formation of a tetrahydrofuran derivative (Figure 129).

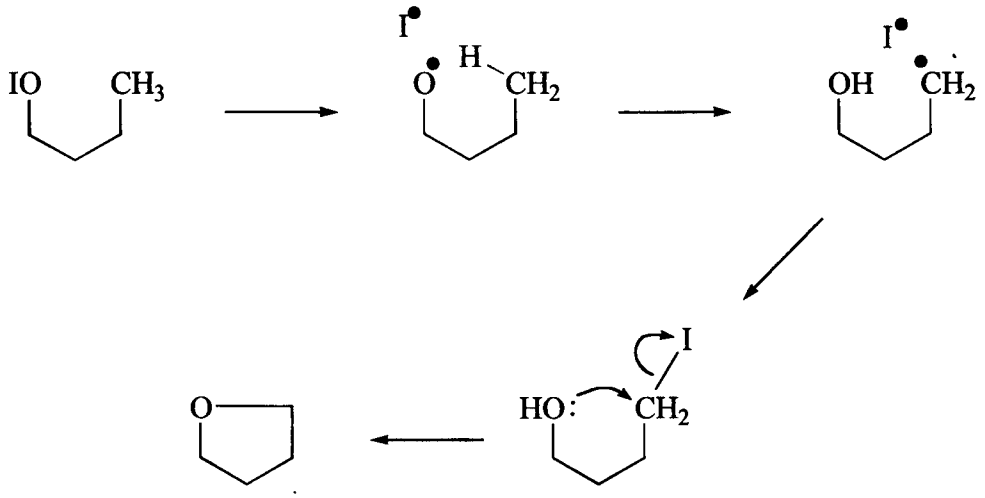


Figure 129 : Tetrahydrofuran derivative formation *via* the hypoiodite reaction

Prior to the appearance of the hypohalite reaction in the literature, the methods of choice for the generation of oxygen radicals were the photolytic cleavage of the corresponding nitrites or hypochlorites.[208] The advantage of the hypoiodite reaction over these procedures is that the hypoiodite can be generated *in situ*, whilst the corresponding hypochlorite or nitrite must be prepared from the alcohol in a separate step prior to use.[208]

3.4.3 The mechanism of activation of glycosyl sulfoxides with iodine

Clearly therefore, potent sources of I^+ can iodinate oxygen as well as sulfur nucleophiles. An ultra-violet and visible absorption study published by Musulin *et al.* in 1964 on the interaction of iodine with dimethyl sulfoxide[211] reports the formation of a characteristic absorption peak at 363 mμ resulting from the formation of I_3^-, and suggests that a peak at 297 mμ could well be due to the formation of a charge-transfer complex between the sulfoxide and iodine, referring back to a previous article by Burg which suggests that the S=O bond of DMSO has comparable donor properties to the C=O bond of acetone.[212]

It is likely therefore that the initial step in the activation of 'armed' glycosyl sulfoxides, is a reversible iodination of the sulfoxide oxygen (Figure 130). Cleavage of the anomeric carbon-sulfur bond would generate the usual oxocarbenium ion intermediate

(Figure 130, Path A), which would be free to react with the glycosyl acceptor. Alternatively, nucleophilic displacement of the iodosulfenate by the acceptor could occur, with inversion of configuration (Figure 130, Path B).

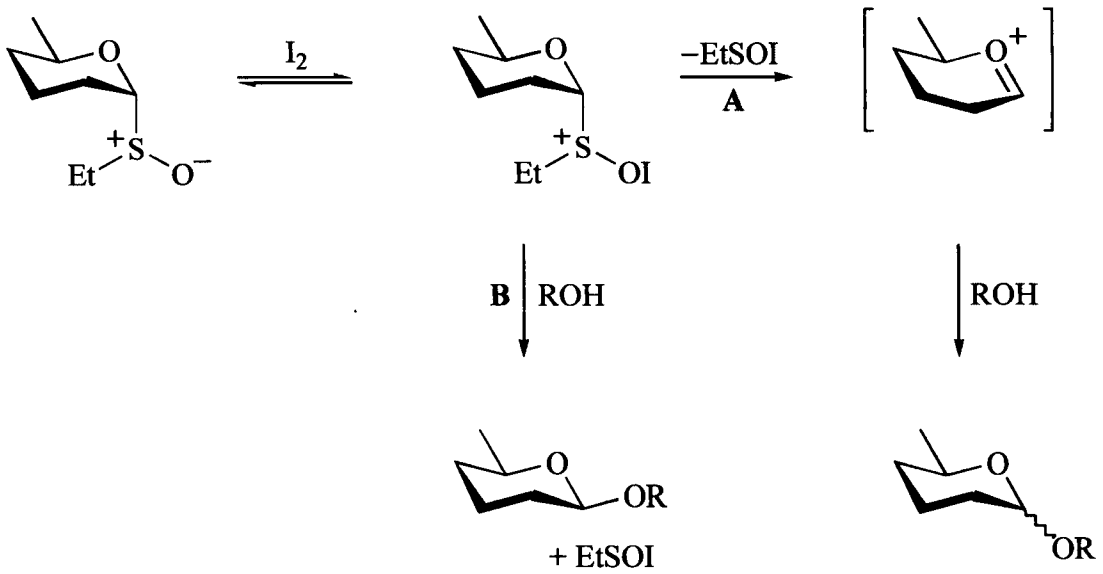


Figure 130

The activation process is likely to be complicated by the presence of the acceptor alcohol, which will also be capable of interacting with iodine. In addition to the reversible addition of iodine to the sulfoxide oxygen, there are thus two further important pre-equilibria to consider in our glycosylation system containing iodine, a glycosyl sulfoxide, and a glycosyl acceptor (Figure 131).

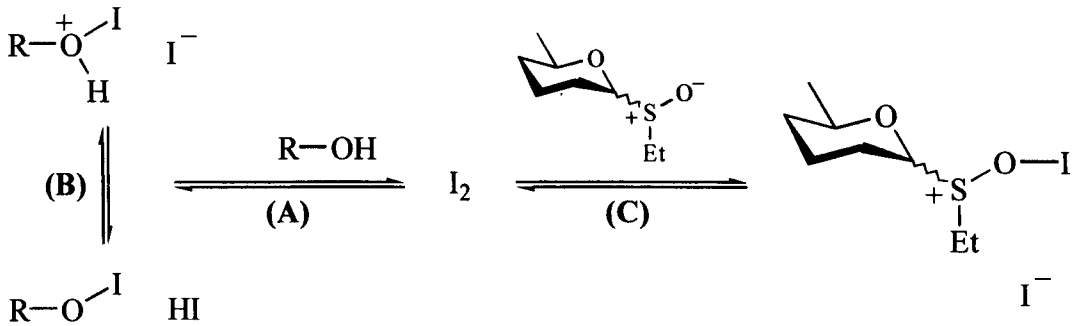


Figure 131

Iodine can reversibly donate an iodonium ion to both the acceptor alcohol, and the sulfoxide oxygen. Iodination of the acceptor should lead, reversibly, to generation of an iodoxonium ion and iodide (equilibrium A), the former of which reversibly loses H^+ to

become a hypoiodite and HI (equilibrium B). Iodination of the sulfoxide oxygen (equilibrium C), whilst reversible in itself, could eventually lead to activation of the glycosyl sulfoxide. Reaction of molecular iodine in either direction produces the iodide anion, which can accept the iodonium ion back to regenerate molecular iodine.

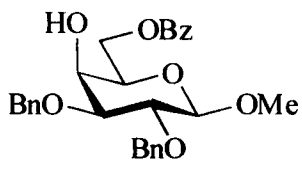
Any factor which favours equilibria A and B over equilibrium C will have a negative influence on level of I^+ available for reaction with the sulfoxide oxygen, and a commensurate negative influence on the rate of activation of the sulfoxide as a glycosyl donor. The sections that follow attempt to rationalise some of our observations in the light of this.

3.4.3.1 The effect of base on the activation of glycosyl sulfoxides

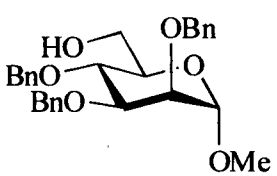
In our experiments on the activation of glycosyl sulfoxides with iodine, we found that the sulfoxide donor was consumed much faster in the absence of potassium carbonate. This suggests that HI produced reversibly in equilibrium B (Figure 131) is removed from the system by reaction with potassium carbonate, favouring hypoiodite formation and thus inhibiting sulfoxide activation.

3.4.3.2 The effect of the acceptor on the activation of glycosyl sulfoxides

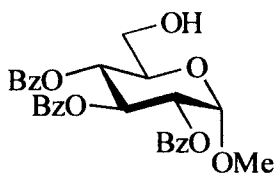
In our glycosylations of carbohydrate acceptors with 'armed' glycosyl sulfoxides (Sections 3.3.3.2 and 3.3.3.4), we were surprised by both the qualitatively faster activation and higher yields observed in the glycosylation of acceptor **74** over the theoretically more nucleophilic[213] acceptors **72**, **73** and **75**.



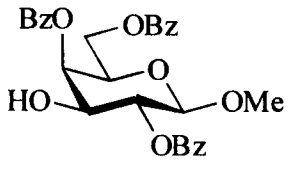
74



72



73



75

This can be explained by considering that the more nucleophilic acceptors are also more likely to compete with the sulfoxide oxygen for I^+, and thus retard the activation of the sulfoxide.

Observations with a related explanation were made during our experiment comparing the reactions of mannosyl sulfoxide with varying amounts of acceptors (Section 3.3.3.3). The experiments where only half a mole equivalent of acceptor were present in the reaction mixture proceeded much faster than those where the acceptor was in excess (Table 5 and Table 6). Again, this can be attributed to the interaction between the acceptor and iodine. It is likely that the greater levels of acceptor present caused a greater level of reaction between iodine and the acceptor, retarding activation of the glycosyl sulfoxide.

3.4.4 Stereocontrol in iodine-promoted glycosylation reactions using an 'armed' α-mannosyl sulfoxide

Glycosylation of carbohydrate acceptors **72**, **73** and **74** with mannosyl sulfoxide **114** under iodine-mediated conditions showed unexpected β-stereocontrol in the disaccharide products. A comparision of the glycosylation of 4-OH acceptor **74** with mannosyl sulfoxide **114** under iodine-mediated (α:β 1:6.5) and standard triflic anhydride-mediated conditions (3.1:1) showed a significant difference in stereocontrol. A similar difference was noted when comparing the glycosylation of **74** with thiomannoside **115** under iodine-mediated (1:7) and NIS/TfOH-mediated (2.6:1) conditions.

The reasons for these differences are likely to be complicated. It is possible that the mildness of the iodine-mediated procedure, in terms of the likely low concentration of the activated sulfoxide at any one moment in time, improves the level of nucleophilic displacement of EtSOI by the glycosyl acceptor. However, this poses a new question of why the best β-stereocontrol is obtained with what is theoretically the least nucleophilic acceptor, in **74**, when the same acceptor is glycosylated with predominantly α-stereocontrol under harsher activation conditions.

The answer to this may be connected with hypoiodite formation discussed above. The sulfur analogs to hypoiodites are the sulfenyl iodides, which are known to be electrophilic in nature while the parent thiols are nucleophilic.[141] If iodination can reduce the nucleophilic properties of sulfur, then hypoiodite formation could potentially reduce the nucleophilicity of oxygen. We have already argued that because **74** is the least nucleophilic of the acceptors glycosylated, formation of hypoiodite **132** should be less extensive than is the case with the hypoiodites derived from the more nucleophilic acceptors, allowing faster activation of the sulfoxide. In this case, a significant proportion of the acceptor will be present as alcohol **74** rather than as hypoiodite **132**. This could favour nucleophilic displacement of the activated leaving group, to generate the β-mannoside, in preference to cleavage of the leaving group to generate the oxocarbenium ion, which should lead predominantly to formation of the α-mannoside due to the anomeric effect (Figure 132).

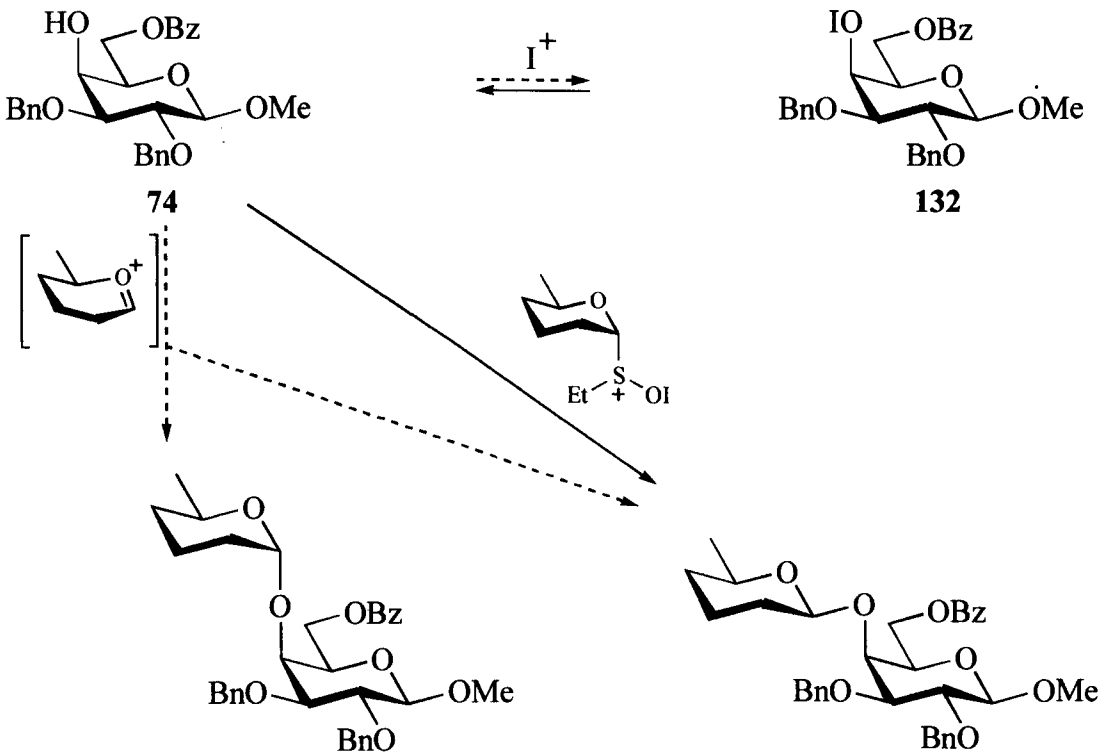


Figure 132

Again this poses another question, of why significant β-stereocontrol was observed with the primary acceptors **72** and **73**, but not the equatorial 3-OH acceptor **75**, which should be of nucleophilicity intermediate between that of the axial 4-OH acceptor **74** and

primary acceptors **72** and **73**. This can be answered by considering the relative nucleophilicities of the hypoiodite species themselves. Just as the primary alcohols should be more nucleophilic that the secondary alcohols, so primary hypoiodites such as **133**, should be more nucleophilic than secondary hypoiodites **132** and **134**. Thus the iodinated oxygen of primary hypoiodite **133** may be sufficently nucleophilic to react directly with the activated sulfoxide (Figure 133), although to a lower extent than the 4-OH group of **74**.

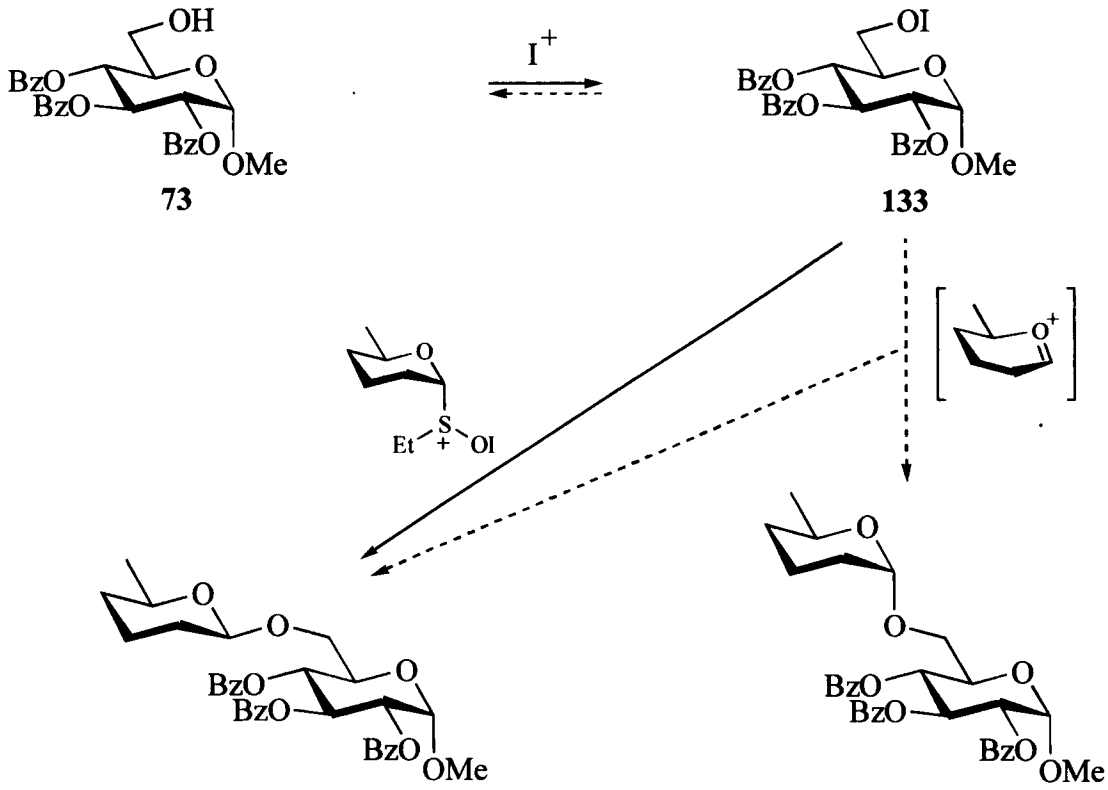


Figure 133

The equatorial secondary hypoiodite **134** (derived from **75**) may be insufficiently nucleophilic to react with the activated sulfoxide, leading to a slow rate of generation of the oxocarbenium intermediate, and a high level of α-stereoselectivity (Figure 134).

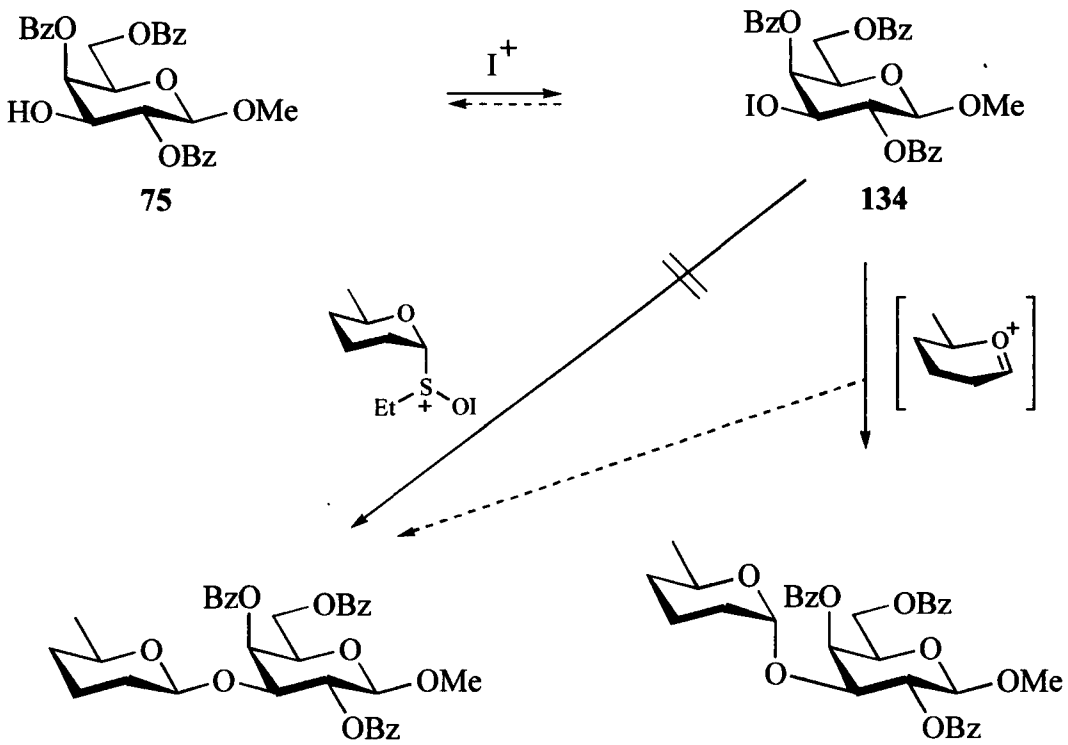


Figure 134

We observed that iodine-mediated glycosylation of **74** and **75** with **114** in the absence of potassium carbonate proceeded with an improvement in the α-stereocontrol in the products (Table 4, p112). As we have previously discussed, the presence of potassium carbonate in the reaction mixtures should neutralise hydrogen iodide generated by iodination of the carbohydrate acceptors, leading to iodination of the acceptors being favoured over iodination of the sulfoxide (Figure 131, p126). Under less basic, or even acidic, conditions it follows that iodination of the sulfoxide will become more favoured while the extra acidity will still retard the nucleophilicity of the acceptors. Activation thus occurs faster, but nucleophilic attack on the activated sulfoxide is not favoured as greatly as under basic conditions, leading to an increase in the α-stereocontrol of the reaction.

3.4.5 Stereocontrol of the glycosylation of carbohydrate acceptors with the 'armed' β-galactosyl sulfoxide

The β-orientation of **121** has certain consequences for the mechanisms that we have proposed for the glycosylation reactions of **74** and **75**. If glycosylation of **74** does

predominantly proceed with inversion of configuration, *via* nucleophilic displacement of the activated sulfoxide, then there should be a shift towards α-stereocontrol in the glycosylation of **74** with **121**. Likewise if the glycosylation of **75** proceeds mostly a highly α-stereoselective addition of **75** to the oxocarbenium ion, then there is likely to be little change in the stereocontrol with a β-oriented donor. A general consideration of course is that β-sulfoxides should be markedly less stable than their α-counterparts, and that once activated, they should cleave more easily to give a product ratio which reflects the stereocontrol of the reaction of the acceptor with the oxocarbenium intermediate.

The stereocontrol observed in the comparative glycosylations of **74** and **75** with β-galactosyl sulfoxide **121** supports this view. Glycosylation of 3-OH acceptor **75** with **121** again gave excellent α-stereocontrol, just as was obtained in the glycosylation of **75** with mannosyl sulfoxide **114**. Glycosylation of **74** with **121** gave 2.3:1 α-stereocontrol, which is a reversal of the stereocontrol observed with α-mannosyl sulfoxide **114**. This suggests that the change in the orientation of the sulfoxide donor has resulted in a change in the stereocontrol, indicating that glycosylation of **74** under our conditions proceeds, to a significant degree, *via* inversion of configuration at the anomeric centre. The presence of significant levels of the β-anomer, however, suggests that reaction of **74** with the oxocarbenium intermediate proceeds with less α-stereocontrol than that observed with **75**. This is also reflected in the glycosylation of **74** with **114** under triflic anhydride-mediated conditions. The potency of this activating system should ensure that the reaction proceeds predominantly via the oxocarbenium intermediate, yet in our hands the α-stereocontrol was 3.1:1.

Likewise there was an improvement, but of lesser magnitude than that observed with **74**, in the α-stereoselectivity of glycosylation of primary acceptors **72** (1:1.3) and **73** (1:1) with **121**. This again indicates a significant level of inversion at the anomeric centre of the glycosyl donor, but it is unclear why the proportion of β-anomer formed in these cases is so high.

3.4.6 Glycosylation reactions involving more potent iodonium ion promoters

We found (Section 3.3.4) that iodine monobromide was also more efficient than iodine as a promoter of the glycosylation of **74** and **75** with mannosyl sulfoxide **114**. There was, however, a drop in the β-stereocontrol of the glycosylation of **74** (α:β = 1:2.7), when compared to the iodine-mediated reaction in the absence of base (1:4). This may be due to the extra potency of IBr as a source of I^+, allowing faster activation of the sulfoxide and thus reducing the extent of nucleophilic substitution of the activated sulfoxide group, or due to complications associated with the presence of Br^- in the reaction mixture.

We noted that the stereocontrol of iodine-mediated glycosylations of **74** and **75** with thiomannoside **115** proceeded with similar stereocontrol to the corresponding reactions with sulfoxide **114**, which suggests that the above discussion relating to the effect of base and the quantity and nucleophilicity of the acceptors on activation of **114** also holds true to a certain extent for the iodine-mediated activation of thiomannosides. The significant improvement in the α-stereocontrol when glycosylating **74** with **115** under NIS/TfOH-mediated conditions can be attributed to the potency of the promoter as a source of I^+, leading again to a reduction in the contribution of nucleophilic displacement at the anomeric centre to the product ratio.

4 SUMMARY

4.1 *Iodine-promoted activation of 'armed' and 'disarmed' thioglycosides*

4.1.1 Conclusions

Iodine is known to be capable of activating 'armed' thioglycosides.[105] We have found that the stereocontrol of the iodine-mediated glycosylation of the unreactive 4-OH group of galactose with α-thiomannoside proceeds with excellent β-stereocontrol (Figure 135), whilst glycosylation of the 3-OH group of galactose proceeds with absolute α-stereocontrol (Figure 136).

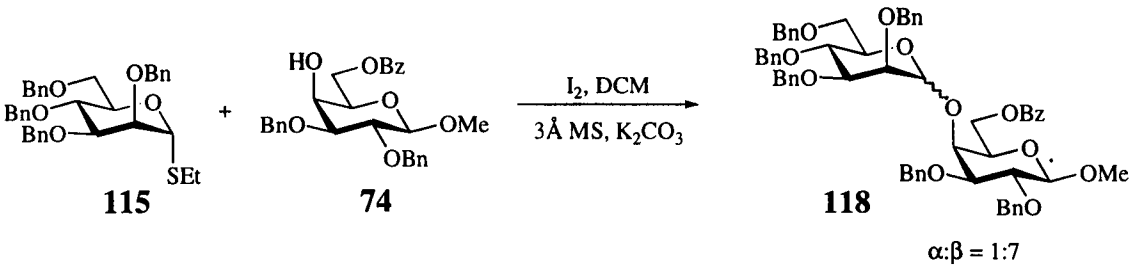


Figure 135

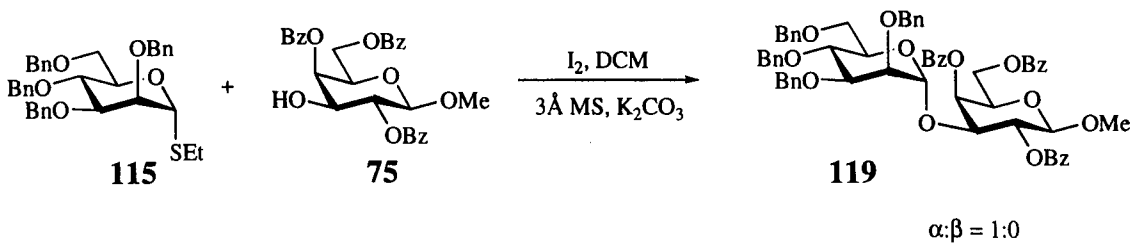
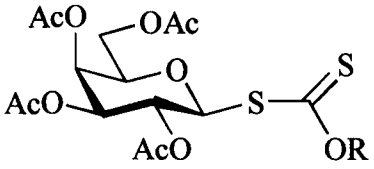
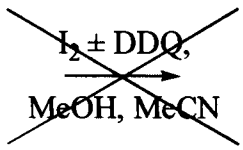
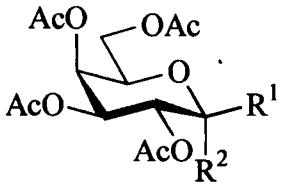


Figure 136

Activation of 'disarmed' thiogalactosides does not occur to any great extent with iodine.[109] We have shown that iodine does not promote the glycosylation of methanol with 'disarmed' glycosyl xanthates **26** and **31**.



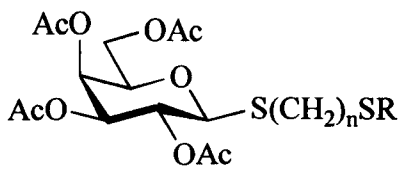




26 R = Et
31 R^1 = iPr

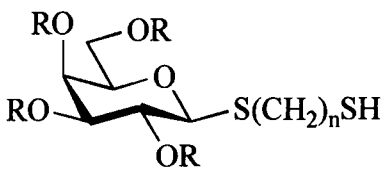
32 R^1 = H, R^2 = OMe
33 R^1 = OMe, R^2 = H

We have prepared and characterised ethylthio alkylthiogalactosides **38-41** and methylthiomethyl galactoside **44**, and shown that they are not activated by iodine. We have provided ^{1}H NMR evidence that iodine interacts significantly with the remote sulfide group of **40**, but not with the anomeric sulfur.



38 n=2, R=Et
39 n=3, R=Et
40 n=4, R=Et
41 n=5, R=Et
44 n=1, R=Me

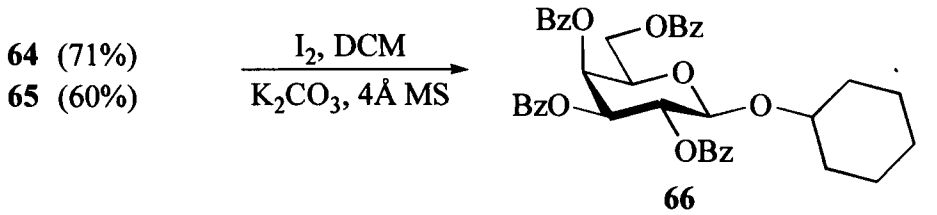
Whilst iodine did not activate 'disarmed' mercapto ethylthiogalactoside **52** and mercapto pentyl thiogalactoside **55**, mercaptopropyl thiogalactoside **53** and mercaptobutyl thiogalactoside **54** could be activated with iodine, leading to glycosylation of cyclohexanol. The reactions appeared to be accompanied by substantial deacetylation of the donors by t.l.c..



52 n=2, R=Ac
53 n=3, R=Ac
54 n=4, R=Ac
55 n=5, R=Ac

64 n=3, R=Bz
65 n=4, R=Bz

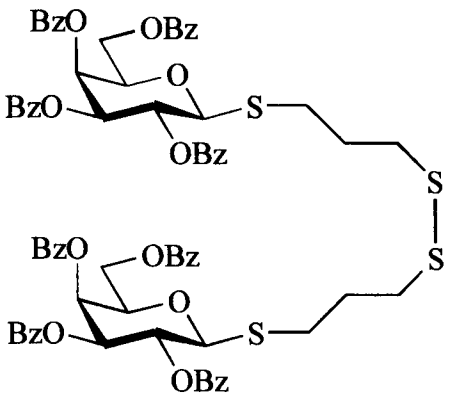
Benzoylated derivatives **64** and **65** were superior donors to **53** and **54**, glycosylating cyclohexanol to give cyclohexyl β-galactoside **66** in encouraging yields, with little debenzoylation observed (Figure 137).



66

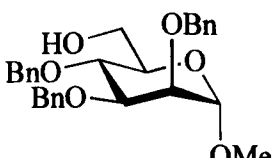
Figure 137

We demonstrated that prior to activation, mercaptal **64** was oxidised by iodine to disulfide **71**, and proposed that iodination of this species is likely to be ultimately responsible for activation.

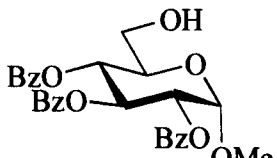


71

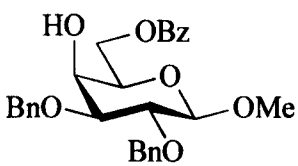
Attempts to glycosylate carbohydrate acceptors **72-75** were unsuccessful, with the exception of benzyl ether-protected primary acceptor **72** which could be glycosylated in dichloromethane, in the presence of potassium carbonate, to give disaccharide **86** in approximately 51% yield.



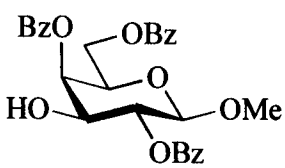
72



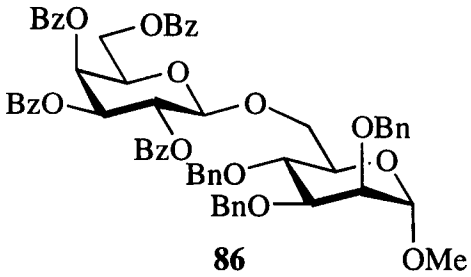
73



74

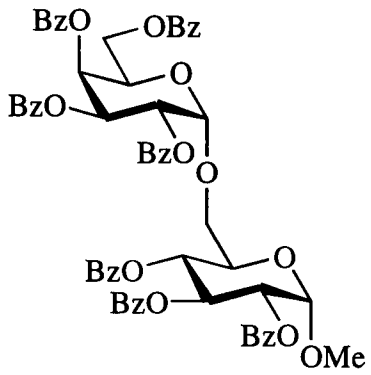


75



86

A limited reaction occurred between **73** and **64** under iodine-mediated conditions, to give α-disaccharide **90**.

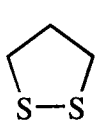


90

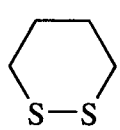
Although we have shown that 'disarmed' mercaptopropyl and mercaptobutyl thiogalactosides can be activated with iodine, it appears that only the most reactive acceptors are capable of competing effectively with the displaced cyclic disulfides for the anomeric centre of the reactive benzoyloxonium intermediate under these conditions.

4.1.2 Further work

Although we suspect that activation of mercaptals proceeds via intramolecular sulfenylation of the anomeric sulfur atom by the sulfenyl iodide of the mercaptal, we have not attempted to identify the leaving groups formed during the activation of **64** and **65**. These should be cyclic disulfides **135** and **136** respectively.



135



136

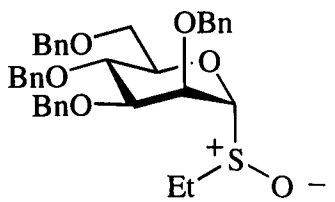
Authentic samples of these could be prepared and then gas chromatography used to test for these substances in the reaction mixtures.

The Lewis acid[214] and oxidant[215] DDQ has been shown by the Field group to enhance the potency of iodine as an activator of 'armed' thioglycosides[154] and glycosyl bromides,[136] but does not activate these donors alone.[216] The effect of DDQ on the activation of our mercaptoalkyl thiogalactosides, and their ethyl sulfides, with iodine should be investigated.

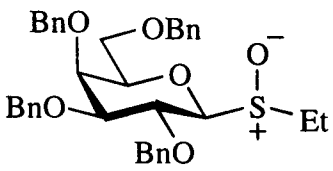
4.2 Iodine-promoted activation of glycosyl sulfoxides

4.2.1 Conclusions

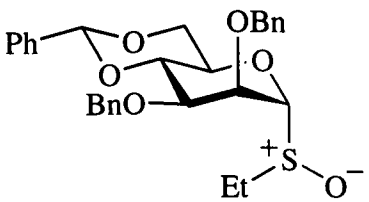
We have found that iodine is capable of activating 'armed' glycosyl sulfoxides such as **114** and **121**, and have shown that they can be used to glycosylate carbohydrate acceptors **72-75**. Under our reaction conditions, benzylidene acetal-protected and 'disarmed' sulfoxides **104** and **129** are not activated by iodine.



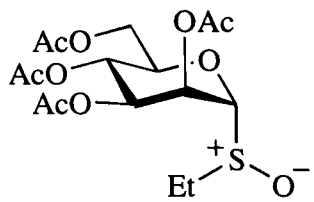
114



121



104



129

We have found that iodine-promoted activation of **104** is faster in the presence of the unreactive 4-OH galactose acceptor **74** than in the presence of primary acceptors **72** and **73**, and 3-OH galactose acceptor **75**.

We observed unusual β-stereocontrol in the iodine-promoted mannosylation of carbohydrate acceptors with **114**. In further studies on this reaction, we have established that:

1) The presence of potassium carbonate favours β-stereocontrol in these reactions.

2) The presence of an excess of the glycosyl acceptor can inhibit activation of the glycosyl sulfoxide.

We have argued, in the light of our findings, that reversible iodination of the acceptor alcohol, to generate hypoiodite species, may be the cause of both the trends in reactivity, and the anomalous stereocontrol, that we have observed. We have suggested that the iodine-promoted reaction of α-mannosyl sulfoxide **114** with alcohols may proceed by both nucleophilic displacement of the activated sulfoxide group at the anomeric centre, or *via* cleavage of ethylsulfenyl iodide to give a reactive oxocarbenium ion, and that the choice of mechanism is affected by both the ability of the alcohol functionality of the acceptor to form hypoiodites, and the nucleophilicity of the hypoiodites themselves.

A comparision of our results with those obtained under established glycosylation protocols, such as the triflic anhydride-promoted activation of glycosyl sulfoxides and NIS/TfOH-promoted activation of thioglycosides, showed the latter to give good α-stereocontrol. This shows that the product ratio observed in our reactions can be attributed to the nature of iodine as a mild source of iodonium ions.

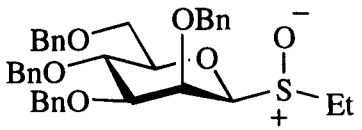
Our results suggest that glycosyl sulfoxides would be labile under the conditions of iodonium ion-mediated glycosylation procedures, and thus not suitable for use in orthogonal glycosylation strategies reliant upon the same.

4.2.2 Further work

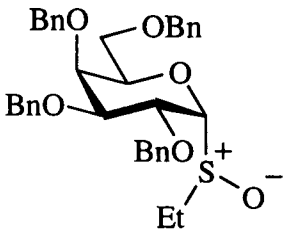
The yields in glycosylation of 'armed' sulfoxide donors, while indicating that glycosylation takes place, are not exceptional. The conditions for the glycosylation

reaction should be optimised as far as possible, examining the reaction in different solvents and at different temperatures.

In order to examine the proposal that iodine-mediated glycosylation of acceptors with glycosyl sulfoxides can proceed significantly *via* nucleophilic displacement of the activated sulfoxide group by the acceptor **137** and **138**, the anomeric epimers of glycosyl sulfoxides **114** and **121**, respectively, should be prepared and the stereocontrol of the reactions of these donors examined and compared with that obtained in this study.



137



138

The remote sulfur atom ethylthioalkyl thiogalactosides **38-41** should be more easily oxidised to the corresponding sulfoxide than the anomeric sulfur atom, bearing in mind the electron withdrawing effects of the 'diasarming' protecting groups. If oxidation of this group could be preferentially effected over the anomeric sulfur atom, then activation of the remote sulfoxide with iodine, or other electrophiles, may generate a centre electrophilic enough to induce the anomeric sulfur atom to react (Figure 138).

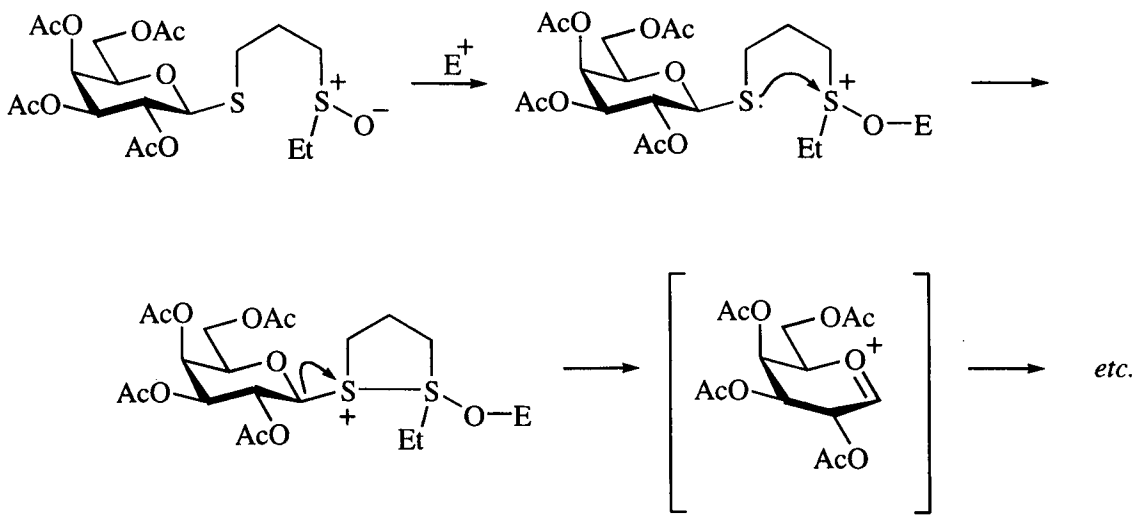


Figure 138

5 EXPERIMENTAL

5.1 Notes on characterisation

5.1.1 Nuclear magnetic resonance spectroscopy

5.1.1.1 Equipment and referencing

^{1}H NMR spectra were recorded on either a Varian Gemini 2000 spectrometer operating at 300 MHz or on a Varian NMR502 spectrometer operating at 500.3 MHz.

^{13}C NMR spectra and DEPT sequences were recorded on a Varian Gemini 2000 or Bruker Aspect 3000 spectrometer operating at 75 MHz.

^{1}H COSY spectra, and HSQC (^{1}H-^{13}C correlation) spectra, were recorded on a Varian NMR501 or NMR502 spectrometer, operating at 500.3 MHz for ^{1}H nuclei and 125.8 MHz for ^{13}C nuclei.

Spectra were referenced to either tetramethylsilane ($\delta_{H,C}$ 0), residual chloroform (δ_H 7.27, δ_C 77.23), or sodium (3-trimethylsilyl) *2,2,3,3-d*$_4$ propionate ($\delta_{H,C}$ 0).

5.1.1.2 Coupling constants and error limits

Frequently peaks that are known, from the splitting patterns, to be coupled to one another were observed to possess slightly differing coupling constants. In all cases the difference was within twice the error limit for the spectrum concerned, and thus an average of the two coupling constants is reported where the machine has reported them as non-identical.

Coupling constants (*J*) are thus given, for the most part, to the nearest half-integer value, i.e. *J* 9.89 is reported as *J* 10, *J* 4.35 is reported as *J* 4.5, and *J* 7.25 is reported as *J* 7.5.

5.1.2 Melting points

Melting points were measured using a Gallenkamp apparatus, and are uncorrected.

5.1.3 Optical rotations

Measured on either an Optical Activity AA-1000 or Perkin-Elmer 141 polarimeter at the sodium D-line, and at ambient temperature, in 5 cm or 10 cm cells. Values are given in conventional units of 10^{-1} dm^2 g^{-1}.

5.1.4 Mass spectrometry

Samples were run by the departmental mass spectroscopy service. High-resolution spectra are quoted to four decimal places. The accurately measured masses differed from the calculated masses by less than 5 ppm.

5.2 General experimental procedures

5.2.1 Sources and purification of reagents and solvents

5.2.1.1 Reagent specifications

Palladium hydroxide on carbon, used in reductive cleavage of benzyl ether protecting groups, was obtained from Aldrich, and was specified as 20% palladium (dry weight basis) with moisture content of 50%.

5.2.1.2 Drying of solvents

Solvents were dried according to literature procedures[217] and distilled under nitrogen. Methanol was dried with magnesium turnings and iodine. Acetonitrile, 1,2-dichloroethane and dichloromethane were dried by refluxing over over calcium hydride. THF and diethyl ether were dried by refluxing over sodium/benzophenone.

5.2.1.3 *Provided samples*

Samples of methyl 2,3,4,6-tetra-*O*-acetyl-α-D-galactopyranoside (**32**), methyl 2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranoside (**33**) and 2,3,4,6-tetra-*O*-acetyl-D-galactopyranose (**34**) for t.l.c. analysis were generously provided by Dr K. P. R. Kartha.

5.2.2 Thin layer chromatography

Thin layer chromatography (t.l.c.) was performed on Whatman K6F silica gel glass-backed plates (Catalogue No. 4861-820). Carbohydrate products in reaction mixtures were detected by charring, with the aid of 5% v/v solution of concentrated sulfuric acid in ethanol. During column chromatography, spraying with a 0.1% w/v solution of orcinol in 15:1:2 ethanol/water/sulfuric acid assisted in the detection of saccharide products.

5.2.3 Concentrations of aqueous solutions

Unless otherwise stated, strengths of aqueous solutions used in phase-transfer reactions and working up of experimental procedures are as follows:

NaCl (brine)	-	saturated
$NaHCO_3$	-	saturated
Na_2CO_3	-	2M
$Na_2S_2O_3$	-	15% w/w
NaS_2O_5	-	saturated
HCl	-	2M
H_2O_2	-	100 volumes

5.2.4 Column chromatography

The solid phase used was throughout this project was silica gel 60 (Fluka, 220-440mesh).

5.3 Experimental procedures

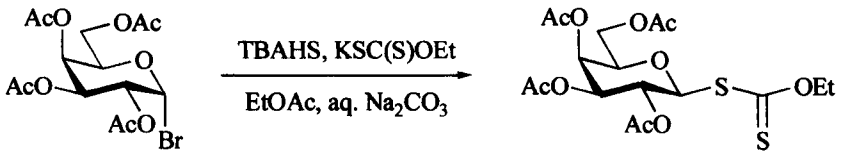
5.3.1 Preparation of glycosyl donors

2,3,4,6-Tetra-*O*-acetyl-α-D-galactopyranosyl bromide[218] (27)

42 **27**

A stirred solution of pentaacetate **42** (25.35 g, 64.9 mmol) in dichloromethane (250 ml), was cooled (ice-bath) under nitrogen. Hydrogen bromide (45% w/v solution in acetic acid, 32 ml, 178 mmol) was added dropwise. Stirring was continued overnight, during which time the temperature rose to ambient. The mixture was diluted with dilchloromethane, washed with ice cold water (x4), aqueous $NaHCO_3$ and water (x2), dried (Na_2SO_4), and concentrated *in vacuo* to give a syrup. This material was redissolved in ether and blown down with nitrogen to give bromide **27** as white powder (25.71g, 96%), m.p. 81-83°C (from ether/hexane); $[\alpha]_D^{25}$ 219.1 (c 1.1 in $CHCl_3$) {lit.,[218] m.p. 79-81°C (from ether); $[\alpha]_D^{20}$ +217 ($CHCl_3$)}; δ_H(300MHz; $CDCl_3$; Me_4Si) 2.01 (3 H, s, *Me*CO), 2.06 (3 H, s, *Me*CO), 2.12 (3 H, s, *Me*CO), 2.15 (3 H, s, *Me*CO), 4.08-4.23 (2 H, m, 6-H_A and 6-H_B), 4.49 (1 H, m, 5-*H*), 5.05 (1 H, dd, $J_{1,2}$ 4 $J_{2,3}$ 10.5, 2-*H*), 5.41 (1 H, dd, $J_{2,3}$ 10.5 $J_{3,4}$ 3.5, 3-*H*), 5.52 (1 H, dd, $J_{3,4}$ 3.5 $J_{4,5}$ 1.5, 4-*H*) and 6.70 (1 H, d, $J_{1,2}$ 4, 1-*H*); δ_C($CDCl_3$; Me_4Si) 20.6 (*Me*CO), 20.6 (*Me*CO), 20.6 (*Me*CO), 20.7 (*Me*CO), 60.9, 67.0, 67.8, 68.1, 71.1, 88.2 (*C*-1), 169.9 (*C*=O), 170.0 (*C*=O), 170.2 (*C*=O) and 170.4 (*C*=O).

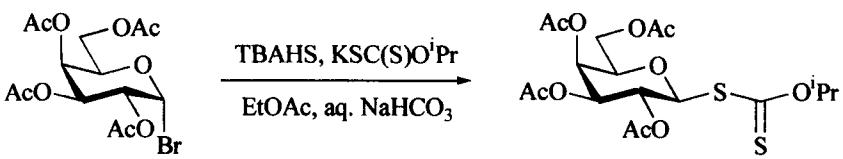
O-Ethyl S-(2,3,4,6-tetra-O-acetyl-β-D-galactopyranosyl) dithiocarbonate[219] (26)



27 **26**

To a solution of crude bromide **27** [prepared from **42** (3.90 g, 10 mmol)] in EtOAc (50 ml) was added TBAHS (3.40 g, 10 mmol), potassium *O*-ethyl dithiocarbonate **28** (1.92 g, 12 mmol), and aqueous $NaHCO_3$ (50 ml). The mixture was stirred vigorously for 45 min and then diluted with ethyl acetate. The organic phase was washed with aqueous $NaHCO_3$, water and brine, dried (Na_2SO_4), and concentrated *in vacuo*. Column chromatography of the resulting residue (EtOAc/toluene, 1:5) gave an oil, which on co-evaporation with methanol gave ethyl xanthate **26** as a white powder (1.56 g, 36% from **42**), m.p. 77-79°C (Et_2O, hexane, CH_2Cl_2); $[\alpha]_D$ 49.9 (c 0.55 in $CHCl_3$) {lit.,[219] m.p. 79-80°C; $[\alpha]_D$ 51.6 (c 1.0)}; δ_H(300 MHz; $CDCl_3$; Me_4Si) 1.44 (3 H, t, *J* 7, CH_3CH_2O), 2.00 (3 H, s, *Me*CO), 2.04 (3 H, s, *Me*CO), 2.05 (3 H, s, *Me*CO), 2.16 (3 H, s, *Me*CO), 4.03-4.18 (3 H, m, 5-*H*, 6-H_A and 6-H_B), 4.68 (2 H, q, *J* 7, CH_3CH_2O), 5.17 (1 H, dd, $J_{2,3}$ 9.5, $J_{3,4}$ 3.5, 3-*H*), 5.37 (1 H, m, 2-*H*), 5.47 (1 H, d, $J_{1,2}$ 10.5, 1-*H*) and 5.47 (1 H, m, 4-*H*); δ_C($CDCl_3$; $CHCl_3$) 13.7 (CH_3CH_2O), 20.6 (*Me*CO), 20.7 (*Me*CO), 20.7 (2 x *Me*CO) 61.5, 66.1, 67.5, 70.9, 72.1, 75.4, 76.8, 86.4 (*C*-1), 169.8 (*C*=O), 170.2 (*C*=O), 170.5 (*C*=O), 170.7 (*C*=O) and 210.5 (*C*=S).

O-Isopropyl S-(2,3,4,6-tetra-O-acetyl-β-D-galactopyranosyl) dithiocarbonate (31)



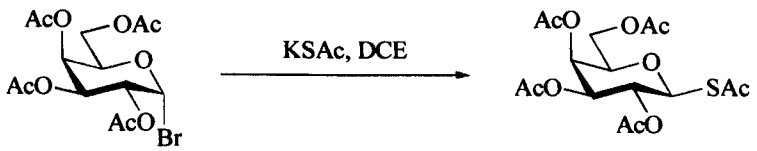
27 **31**

To a solution of crude bromide **27** [prepared from pentaacetate **42** (3.84 g, 9.8 mmol)] in EtOAc (50 ml) was added TBAHS (3.34 g, 9.8 mmol), potassium isopropyl xanthate **30** (2.06 g, 11.8 mmol), and aqueous $NaHCO_3$ (50 ml). The mixture was stirred vigorously until t.l.c. showed that all of **27** had been consumed (1 hr). The mixture was

diluted with ethyl acetate, and the organic phase washed with aqueous $NaHCO_3$, water and brine, dried (Na_2SO_4), and concentrated *in vacuo*. Column chromatography of the resulting residue (EtOAc/hexane, 3:5) gave a white powder which crystallised from CH_2Cl_2/hexane to give needles of pure *O*-isopropyl *S*-(2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyl) dithiocarbonate **31** (2.09 g, 22% from **42**), m.p. 98-99.5°C (Found: C, 46.57; H, 5.76%; $C_{18}H_{26}O_{10}S_2$ requires C, 46.34; H, 5.62%); $[\alpha]_D$ +47.0 (c 0.54 in $CHCl_3$); δ_H(500MHz; $CDCl_3$; $CDCl_3$) 1.41 (6 H, d, *J* 6.5, Me_2CH-), 1.98 (3 H, s, *Me*CO), 2.03 (3 H, s, *Me*CO), 2.04 (3 H, s, *Me*CO), 2.15 (3 H, s, *Me*CO), 4.04 (1 H, td, $J_{4,5}$ 1 $J_{5,6A}$ = $J_{5,6B}$ 6.5, 5-*H*), 4.08-4.16 (2 H, m, 6-H_A and 6-H_B), 5.15 (1 H, dd, $J_{2,3}$ 10, $J_{3,4}$ 3.5, 3-*H*), 5.35 (1 H, m, 2-*H*), 5.43 (1 H, d, $J_{1,2}$ 10.5, 1-*H*), 5.46 (1 H, dd, $J_{3,4}$ 3.5 $J_{4,5}$ 1, 4-*H*) and 5.75 (1 H, sept, *J* 6.5, Me_2C*H*-); δ_C($CDCl_3$; $CHCl_3$) 20.4, 20.5, 20.5 (double intensity), 21.0 and 21.1 (4 x *Me*CO, Me_2CH and Me_2CH), 61.3, 65.8, 67.2, 71.9, 75.0, 78.8, 85.8 (*C*-1), 169.3 (*C*=O), 170.0 (*C*=O), 170.1 (*C*=O), 170.2 (*C*=O) and 209.1 (*C*=S); *m/z* (MALDI-TOF) 489 (M + K^+), 473 (M + Na^+) and 451 (M + H^+).

2,3,4,6-Tetra-*O*-acetyl-1-*S*-acetyl-β-D-thiogalactopyranose[220] (45)

Method 1

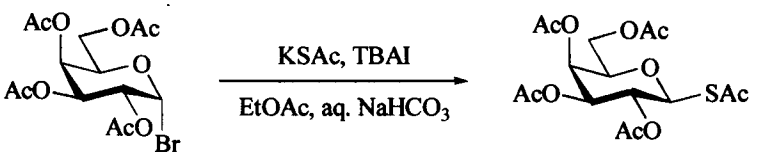


27 **45**

A solution of bromide **27** (9.00 g, 24.3 mmol) in DCE (90 ml) was refluxed, with vigorous stirring, in the presence of potassium thioacetate (12.50 g, 0.11 mol) for 30 hr. The mixture was then diluted with dichloromethane, washed with aqueous $NaHCO_3$, water and brine, dried (Na_2SO_4), and concentrated *in vacuo*. The residue was dissolved in a minimum volume of boiling ethanol, and the hot solution was stirred with activated charcoal and filtered through Celite. Thioacetate **45** crystallised on standing as off-white needles (5.10 g, 57%), m.p. 111-113°C (from EtOH); $[\alpha]_D$ +31.3 (c 1.02 in $CHCl_3$) {lit.,[220] m.p. 112-114°C; $[\alpha]_D$ +32 (c 1.25)}; δ_H($CDCl_3$; Me_4Si) 1.99 (3 H, s, *Me*CO_2),

2.04 (3 H, s, *Me*CO_2), 2.04 (3 H, s, *Me*CO_2), 2.16 (3 H, s, *Me*CO_2), 2.40 (3 H, s, *Me*COS), 4.04-4.17 (3 H, m, 5-*H*, 6-H_A and 6-H_B), 5.12 (1 H, dd, $J_{2,3}$ 9.5 $J_{3,4}$ 3.5, 3-*H*), 5.23-5.36 (2 H, m, 1-*H* and 2-*H*) and 5.46 (1 H, d, $J_{3,4}$ 3.5, 4-*H*); δ_C($CDCl_3$; Me_4Si) 20.6 (*Me*CO_2), 20.7 (*Me*CO_2), 20.7 (*Me*CO_2), 20.8 (*Me*CO_2), 31.0 (*Me*COS), 61.4, 66.5, 67.3, 72.1, 75.2, 80.7 (*C*-1), 169.9 (O*C*=O), 170.2 (O*C*=O), 170.5 (O*C*=O), 170.7 (O*C*=O) and 192.5 (S*C*=O).

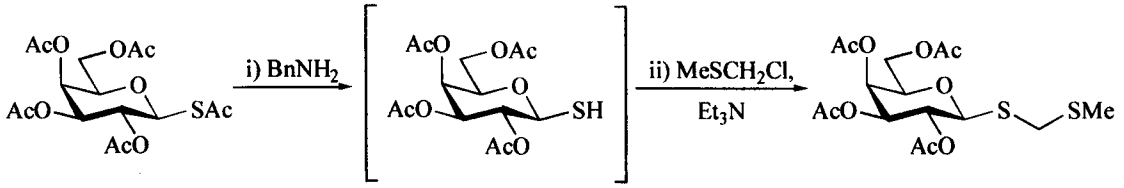
Method 2



27 **45**

To a solution of bromide **27** (15.0 g, 36.5 mmol) in ethyl acetate (170 ml) was added potassium thioacetate (20.8 g, 0.18 mol), TBAI (12.0 g, 32.5 mmol) and aqueous $NaHCO_3$ (170 ml) The mixture was stirred vigorously for 3.5 hr. The mixture was diluted with ethyl acetate and the organic phase washed with aqueous $NaHCO_3$, water and brine, dried (Na_2SO_4), and concentrated *in vacuo*. The residue was dissolved in minimum volume of boiling ethanol, and the hot solution stirred with activated charcoal before filtering through Celite. Thioacetate **45** crystallised on standing as off-white needles (8.54 g, 57%), with analytical data as stated above.

(Methylthio)methyl 2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-galactopyranoside (44)

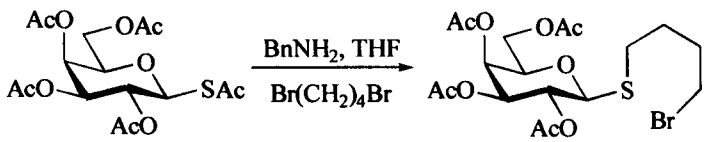


45 **44**

To a solution of thioacetate **45** (2.36 g, 5.81 mmol) in dry THF (25 ml) at room temperature under nitrogen was added benzylamine (0.76 ml, 6.96 mmol). The solution

was stirred for 1 hr 15 min. Chloromethyl methylsulfide (1.46 ml, 17.4 mmol) was added, followed by triethylamine (1.21 ml, 8.68 mmol). Stirring was continued for a further 18 hr. The mixture was diluted with dichloromethane, washed with water, aqueous HCl, water and brine, dried (Na_2SO_4) and concentrated *in vacuo*. Column chromatography of the resulting residue (EtOAc/light petroleum, 1:2) gave (methylthio)methyl 2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-galactopyranoside **44** as a syrup (1.29 g, 52%); $[\alpha]_D^{23}$ -103.0 (c 1.04 in $CHCl_3$); δ_H(300 MHz; $CDCl_3$; Me_4Si) 1.99 (3 H, s, *Me*CO), 2.05 (3 H, s, *Me*CO), 2.07 (3 H, s, *Me*CO), 2.16 (6 H, s, *Me*CO and S*Me*), 3.70 (1 H, d, *J* 13.5, SC*H*$_2$S), 3.91 (1 H, d, *J* 13.5, SC*H*$_2$S), 3.96 (1 H, m, 5-*H*), 4.08-4.18 (2 H, m, 6-H_A and 6-H_B), 4.79 (1 H, d, $J_{1,2}$ 10, 1-*H*), 5.09 (1 H, dd, $J_{2,3}$ 10 $J_{3,4}$ 3.5, 3-*H*), 5.29 (1 H, t, $J_{1,2}$ 10 $J_{2,3}$ 10, 2-*H*) and 5.45 (1 H, dd, $J_{3,4}$ 3.5 $J_{4,5}$ 1, 4-*H*); δ_C($CDCl_3$; Me_4Si) 14.6 (S*Me*), 20.6 (*Me*CO), 20.7 (2 x *Me*CO), 20.8 (*Me*CO), 35.5 (SCH$_2$S), 61.5 (*C*-6), 67.2, 67.4, 72.0, 74.6, 82.1 (*C*-1), 169.8 (*C*=O), 170.3 (*C*=O), 170.5 (*C*=O) and 170.6 (*C*=O); m/z (EI) 451 (0.5%, M + 27), 424 (1, M^+) and 331 (73, M - SCH_2SCH_3); m/z (CI) 450 (11%, M + 26), 438 (5, M + CH_2), 425 (1, M + H^+) and 331 (100, M - SCH_2SCH_3).

(4-Bromobutyl) 2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-galactopyranoside (48)



45 **48**

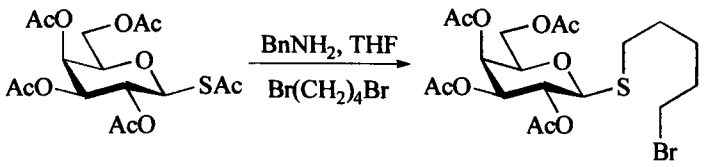
To a stirred solution of thioacetate **45** (5.00 g, 12.3 mmol) and 1,4-dibromobutane (14.7 ml, 0.12 mol) in dry, deoxygenated THF (50 ml) under argon was added benzylamine (4.0 ml, 36.6 mmol). The mixture was stirred for 90 min. Further benzylamine (2 ml, 18.3 mmol) was added, and stirring was continued for a further 19 hr, at which point t.l.c. indicated that all of **45** had been consumed. The mixture was diluted with dichloromethane, washed with water, aqueous HCl, water and brine, dried (Na_2SO_4) and concentrated *in vacuo*. Column chromatography of the resulting residue (EtOAc/toluene, 1:2) gave (4-bromobutyl) 2,3,4,6-tetra-*O*-acetyl-β-D-

thiogalactopyranoside **48** as a syrup (2.46g, 40%); δ_H(300 MHz; $CDCl_3$; $CHCl_3$) 1.79 (2 H, m, $SCH_2CH_2CH_2CH_2Br$), 1.98 (3 H, s, *Me*CO), 2.04 (3 H, s, *Me*CO), 2.07 (3 H, s, *Me*CO), 2.16 (3 H, s, *Me*CO), 1.92-2.18 (2 H, m, $SCH_2CH_2CH_2CH_2Br$), 2.64-2.82 (2 H, m, SCH_2), 3.43 (2 H, t, *J* 6.5, CH_2Br), 3.93 (1 H, t, $J_{5,6A} = J_{5,6B}$ 6.5, 5-*H*), 4.13 (2 H, m, 6-H_A and 6-H_B), 4.48 (1 H, d, $J_{1,2}$ 10, 1-*H*), 5.04 (1 H, dd, $J_{2,3}$ 10 $J_{3,4}$ 3, 3-*H*), 5.23 (1 H, m, $J_{1,2} = J_{2,3}$ 10, 2-*H*) and 5.43 (1 H, d, $J_{3,4}$ 3, 4-*H*).

Decomposition of compound 48 to give bromide 27

After a few weeks stored at room temperature the syrup was rechromatographed (EtOAc/light petroleum, 1:2) to give firstly bromide **27** as an amorphous solid (1.41 g, 70%); δ_H($CDCl_3$) identical to that of **27**; further elution reafforded **48** as a syrup (0.59 g, 24%).

(5-Bromopentyl) 2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-galactopyranoside (49)

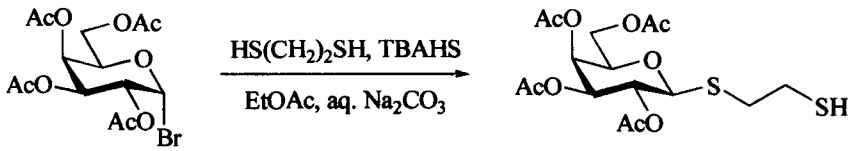


45 **49**

To a stirred solution of thioacetate **45** (2.03 g, 5.0 mmol) and 1,5-dibromopentane (6.8 ml, 49.9 mmol) in dry, deoxygenated THF (20 ml) under argon, was added benzylamine (1.54 ml, 14.1 mmol). The mixture was stirred for 90 min, at which point t.l.c. (EtOAc/hexanes, 1:2) indicated that all of **45** had been consumed, and then diluted with dichloromethane. This was washed with water, aqueous HCl, water and brine, dried (Na_2SO_4) and concentrated *in vacuo*. Column chromatography of the resulting residue (EtOAc/hexanes, 1:2) gave (5-bromopentyl) 2,3,4,6-tetra-*O*-acetyl-β-D-thiogalactopyranoside **49** as a syrup (1.60 g, 63%); δ_H(300 MHz; $CDCl_3$; $CHCl_3$) 1.53 (2 H, m, CH_2), 1.62 (2 H, m, CH_2), 1.86 (2 H, m, CH_2), 1.96 (3 H, s, *Me*CO), 2.03 (3 H, s, *Me*CO), 2.05 (3 H, s, *Me*CO), 2.14 (3 H, s, *Me*CO), 2.69 (2 H, m, SCH_2), 3.39 (2 H, t, *J* 7, CH_2Br), 3.92 (1 H, t, $J_{5,6A} = J_{5,6B}$ 6.5, 5-*H*), 4.11 (2 H, m, 6-H_A and 6-H_B), 4.46 (1

H, d, $J_{1,2}$ 10, 1-*H*), 5.02 (1 H, dd, $J_{2,3}$ 10 $J_{3,4}$ 3.5, 3-*H*), 5.21 (1 H, t, $J_{1,2}$ 10 $J_{2,3}$ 10, 2-*H*) and 5.41 (1 H, d, $J_{3,4}$ 3.5, 4-*H*).

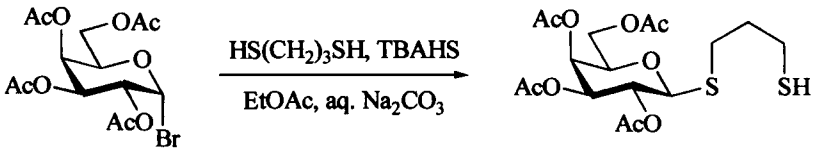
(2-Mercaptoethyl) 2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-galactopyranoside[153] (52)



27 **52**

To a solution of bromide **27** (4.11 g, 10 mmol) in ethyl acetate (50 ml) was added TBAHS (3.40 g, 10 mmol), 1,2-ethanedithiol (90% w/w, 2.75 ml, 30 mmol) and aqueous Na_2CO_3 (50 ml). The mixture was stirred vigorously, until t.l.c. (EtOAc/hexane, 1:2) indicated that until all of **27** had been consumed (45 min). The mixture was diluted with ethyl acetate, and the organic phase was retained and washed with aqueous $NaHCO_3$, water and brine, dried (Na_2SO_4), and concentrated *in vacuo*. Column chromatography of the resulting reidue (EtOAc/hexane, 1:2) afforded mercaptoethyl thiogalactoside **52** as a syrup (3.13 g, 74%), m.p. 89-90°C (from aq. MeOH); $[\alpha]_D^{22}$ -12.6 (c 1.66 in $CHCl_3$) {lit.[153] m.p. 90-91.5°C (from MeOH); $[\alpha]_D^{24}$ -10.1 (c 0.5 in $CHCl_3$)}; (Found C, 45.6; H, 5.5%. $C_{16}H_{24}O_9S_2$ requires C, 45.3; H 5.7%); δ_H(300 MHz, $CDCl_3$, $CHCl_3$) 1.99 (3 H, s, *Me*CO), 2.07 (3 H, s, *Me*CO), 2.08 (3 H, s, *Me*CO), 2.17 (3 H, s, *Me*CO), 2.70-3.05 (4 H, m, SCH_2CH_2S), 3.94 (1 H, m, 5-*H*), 4.13 (2 H, m, 6-H_A and 6-H_B), 4.52 (1 H, d, $J_{1,2}$ 10, 1-*H*), 5.05 (1 H, dd, $J_{2,3}$ 10 $J_{3,4}$ 3.5, 3-*H*), 5.24 (1 H, t, $J_{1,2}$ 10 $J_{2,3}$ 10, 2-*H*), 5.44 (1 H, dd, $J_{3,4}$ 3.5 $J_{4,5}$ 1, 4-*H*); δ_C($CDCl_3$, $CHCl_3$) 20.8 (*Me*CO), 20.9 (2 x *Me*CO), 21.0 (*Me*CO), 25.5 (CH_2S), 35.0 (CH_2S), 61.8, 67.3, 67.5, 72.0, 74.8, 84.7 (*C*-1), 169.8 (*C*=O), 170.2 (*C*=O), 170.4 (*C*=O) and 170.6 (*C*=O).

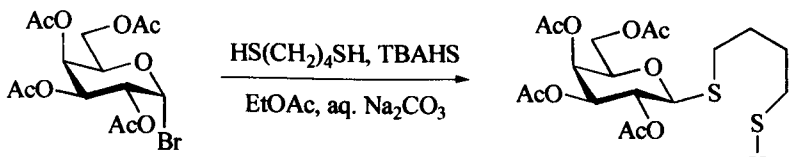
(3-Mercaptopropyl) 2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-galactopyranoside[153] (53)



27 **53**

To a solution of bromide **27** (2.00 g, 4.86 mmol) in ethyl acetate (25 ml) was added TBAHS (1.65 g, 4.86 mmol), 1,3-propanedithiol (1.50 ml, 15.0 mmol) and aqueous Na_2CO_3 (50 ml). The mixture was stirred vigorously for 3 hr, and diluted with ethyl acetate (250 ml). The organic phase was retained and washed with aqueous $NaHCO_3$, water and brine, dried (Na_2SO_4), and concentrated *in vacuo*. Column chromatography of the resulting residue (EtOAc/light petroleum, 1:4→1:2) gave mercaptopropyl thiogalactopyranoside **53** as a syrup (1.56 g, 73%); $[\alpha]_D^{23}$ -13.6 (c 2.01 in $CHCl_3$) {lit.[153] $[\alpha]_D^{23}$ -12.0 c 0.5 in $CHCl_3$)}; δ_H(300 MHz; $CDCl_3$; Me_4Si) 1.84-2.04 (2 H, m, $SCH_2CH_2CH_2S$), 1.99 (3 H, s, *Me*CO), 2.06 (3 H, s, *Me*CO), 2.07 (3 H, s, *Me*CO), 2.16 (3 H, s, *Me*CO) 2.65 (2 H, m, CH_2SH), 2.73-2.94 (2 H, m, gal-SCH_2), 3.94 (1 H, t, $J_{5,6A}$ 6.5 $J_{5,6B}$ 6.5, 5-*H*), 4.08-4.20 (2 H, m, 6-H_A and 6-H_B), 4.49 (1 H, d, $J_{1,2}$ 10, 1-*H*), 5.05 (1 H, dd, $J_{2,3}$ 10 $J_{3,4}$ 3.5, 3-*H*), 5.24 (1 H, t, $J_{1,2}$ 10 $J_{2,3}$ 10, 2-*H*) and 5.44 (1 H, dd, $J_{3,4}$ 3.5, $J_{4,5}$ 1, 4-*H*); δ_C($CDCl_3$; $CHCl_3$) 20.7 (*Me*CO), 20.8 (2 x *Me*CO), 20.9 (*Me*CO), 23.3 (CH_2), 28.6 (CH_2), 33.6 (CH_2), 61.7, 67.3, 67.5, 72.1, 74.7, 84.4 (*C*-1), 169.9 (*C*=O), 170.4 (*C*=O), 170.5 (*C*=O) and 170.7 (*C*=O).

(4-Mercaptobutyl) 2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-galactopyranoside (54)

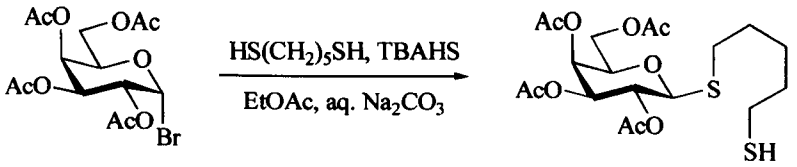


27 **54**

To a solution of bromide **27** (2.00 g, 4.86 mmol) in ethyl acetate (25 ml) was added TBAHS (1.65 g, 4.86 mmol), 1,4-butanedithiol (1.70 ml, 5.33 mmol) and aqueous Na_2CO_3 (25 ml). The mixture was stirred vigorously for 3.5 hr, at which point t.l.c.

indicated that all of **27** had been consumed. The mixture was diluted with ethyl acetate, and the organic phase was retained and washed with aqueous $NaHCO_3$, water and brine, dried (Na_2SO_4), and concentrated *in vacuo*. Column chromatography of the resulting residue (EtOAc/light petroleum, 1:2) gave (4-mercaptobutyl) 2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-galactopyranoside **54** as a syrup (1.32 g, 60%); $[\alpha]_D^{22}$ -14.5 (c 1.47 in $CHCl_3$); δ_H(300 MHz; $CDCl_3$; Me_4Si) 1.35 (1 H, t, *J* 8, CH_2SH), 1.70-1.76 (4 H, m, $SCH_2CH_2CH_2CH_2S$); 1.99 (3 H, s, *Me*CO), 2.05 (3 H, s, *Me*CO), 2.07 (3 H, s, *Me*CO), 2.16 (3 H, s, *Me*CO), 2.52-2.74 (4 H, m, 2 x SCH_2), 3.94 (1 H, t d, $J_{5,6A} = J_{5,6B}$ 6.5 $J_{4,5}$ 1), 4.08-4.20 (2 H, m, 6-H_A and 6-H_B), 4.48 (1 H, d, $J_{1,2}$ 10, 1-*H*), 5.05 (1 H, dd, $J_{2,3}$ 10 $J_{3,4}$ 3.5, 3-*H*), 5.24 (1 H, m, $J_{1,2}$ 10 $J_{2,3}$ 10, 2-*H*) and 5.44 (1 H, dd, $J_{3,4}$ 3.5 $J_{4,5}$ 1, 4-*H*); δ_C($CDCl_3$; Me_4Si) 20.6 (*Me*CO), 20.7 (2 x *Me*CO), 20.9 (*Me*CO), 24.1 (CH_2), 28.3 (CH_2), 29.4 (CH_2), 32.8 (CH_2), 61.6 (CH_2-6), 67.3, 67.4, 72.0, 74.6, 84.2 (C-1), 169.9 (*C*=O), 170.3 (*C*=O), 170.5 (*C*=O) and 170.6 (*C*=O); m/z (EI) 452 (M^+, 3%; Calculated for $C_{18}H_{28}O_9S_2$ 452.1175; Found 452.1182) and 331 (63, M – $SCH_2CH_2CH_2CH_2SH$).

(5-Mercaptopentyl) 2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-galactopyranoside (55)

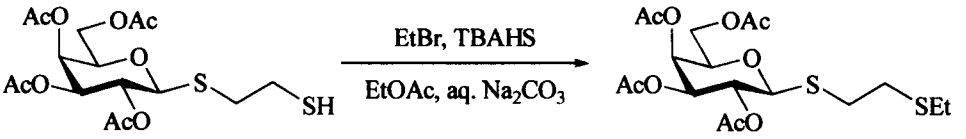


27 **55**

To a solution of bromide **27** (2.00 g, 4.86 mmol) in ethyl acetate (25 ml) was added TBAHS (1.98 g, 5.84 mmol), 1,5-pentanedithiol (2.00 ml, 14.91 mmol) and aqueous Na_2CO_3 (25 ml). The mixture was stirred vigorously for 2 hr, and then diluted with ethyl acetate. The organic phase was retained and washed with aqueous $NaHCO_3$, water and brine, dried (Na_2SO_4), and concentrated *in vacuo*. Column chromatography of the resulting residue (EtOAc/light petroleum, 1:2) gave (5-mercaptopentyl) 2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-galactopyranoside **55** as a syrup (0.86 g, 38%); $[\alpha]_D^{22}$ -15.4 (c 1.74 in $CHCl_3$); δ_H(300 MHz; $CDCl_3$; Me_4Si) 1.36 (1 H, m, CH_2SH), 1.46-1.68 (6 H, m, 3 x CH_2), 1.98 (3 H, s, *Me*CO), 2.05 (3 H, s, *Me*CO), 2.07 (3 H, s, *Me*CO), 2.16 (3 H, s, *Me*CO), 2.53 (2 H, m, CH_2SH), 2.65-2.77 (2 H, m, gal-SCH_2), 3.96 (1 H, m, 5-*H*), 4.08-

4.20 (2 H, m, 6-H_A and 6-H_B), 4.50 (1 H, d, $J_{1,2}$ 10, 1-*H*), 5.06 (1 H, dd, $J_{2,3}$ 10 $J_{3,4}$ 3.5, 3-*H*), 5.23 (1 H, t, $J_{1,2}$ 10 $J_{2,3}$ 10, 2-*H*) and 5.43 (1 H, dd, $J_{3,4}$ 3.5 $J_{4,5}$ 1, 4-*H*); δ_C ($CDCl_3$; Me_4Si) 20.6 (*Me*CO), 20.7 (2 x *Me*CO), 20.8 (*Me*CO), 24.4 (CH_2), 27.4 (CH_2), 29.1 (CH_2), 29.8 (CH_2), 33.4 (CH_2), 61.5 (CH_2-6), 67.2, 67.3, 71.9, 74.4, 84.0 (*C*-1), 169.6 (*C*=O), 170.1 (*C*=O), 170.3 (*C*=O) and 170.4 (*C*=O); m/z (EI) 466 (M^+, 3%; Calculated for $C_{19}H_{30}O_9S_2$ 466.1331; Found 466.1327) and 331 (78, M – $SCH_2CH_2CH_2CH_2CH_2SH$).

(2-*S*-Ethylthioethyl) 2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-galactopyranoside (38)

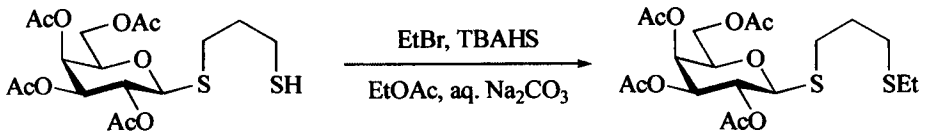


52 **38**

To a solution of mercaptan **52** (533 mg, 1.26 mmol) in ethyl acetate (6 ml) was added TBAHS (427 mg, 1.26 mmol), bromoethane (0.94 ml, 12.6 mmol) and aqueous Na_2CO_3 (6 ml). The mixture was stirred vigorously for 3 hr, at which point t.l.c. (EtOAc/hexane, 1:2) indicated that all of **52** had been consumed. The mixture was diluted with ethyl acetate, and the organic phase was retained and washed with water and brine, dried (Na_2SO_4), and concentrated *in vacuo*. Column chromatography of the resulting residue (EtOAc/hexane, 1:3→1:1) afforded (2-*S*-ethylthioethyl) 2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-galactopyranoside **38** (514 mg, 90%); $[\alpha]_D^{22}$ -15.6 (c 2.37 in $CHCl_3$); (Found C, 47.2; H, 6.2%. $C_{18}H_{28}O_9S_2$ requires C, 47.8; H 6.2%); δ_H(300 MHz; $CDCl_3$; Me_4Si) 1.28 (3 H, t, *J* 7.5, CH_3CH_2S), 1.99 (3 H, s, *Me*CO), 2.06 (3 H, s, *Me*CO), 2.07 (3 H, s, *Me*CO), 2.16 (3 H, s, *Me*CO), 2.59 (2 H, q, *J* 7.5, CH_3CH_2S), 2.75-3.02 (4 H, m, SCH_2CH_2S), 3.94 (1 H, m, 5-*H*), 4.08-4.19 (2 H, m, 6-H_A and 6-H_B), 4.53 (1 H, $J_{1,2}$ 10, 1-*H*), 5.05 (1 H, dd, $J_{2,3}$ 10 $J_{3,4}$ 3.5, 3-*H*) 5.24 (1 H, t, $J_{1,2}$ 10 $J_{2,3}$ 10, 2-*H*) and 5.44 (1 H, d, $J_{3,4}$ 3.5, 4-*H*); δ_C($CDCl_3$; $CHCl_3$) 14.9 (CH_3CH_2S), 20.7 (*Me*CO), 20.7 (2 x *Me*CO), 20.9 (*Me*CO), 26.0 (CH_2), 30.4 (CH_2), 32.2 (CH_2), 61.7, 67.3, 67.5, 72.0, 74.8, 84.4 (*C*-1), 169.9 (*C*=O), 170.4 (*C*=O), 170.5 (*C*=O) and 170.7 (*C*=O); m/z (EI) 452 (M^+, 6%; Calculated

for $C_{18}H_{28}O_9S_2$ 452.1175; Found 452.1161), 392 (32, M - SCH_2CH_2) and 331 (75, M - $SCH_2CH_2SCH_2CH_3$).

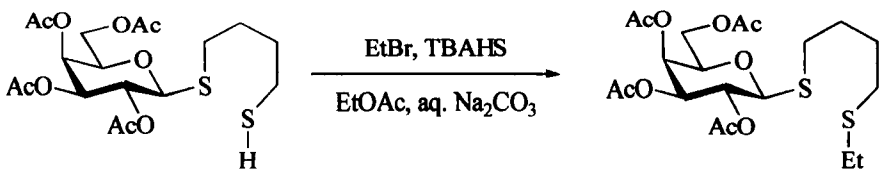
(3-*S*-Ethylthiopropyl) 2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-galactopyranoside (39)



53 **39**

To a solution of mercaptan **53** (1.50 g, 3.42 mmol) in ethyl acetate (25 ml) was added TBAHS (1.65 g, 4.86 mmol), bromoethane (3.65 ml, 48.9 mmol) and aqueous Na_2CO_3 (25 ml). The mixture was stirred vigorously for 3 hr, at which point t.l.c. (EtOAc/hexane, 1:2) indicated that all of **53** had been consumed. The mixture was diluted with ethyl acetate, and the organic phase was retained and washed with aqueous $NaHCO_3$, water and brine, dried (Na_2SO_4), and concentrated *in vacuo*. Column chromatography of the resulting residue (EtOAc/light petroleum, 1:2) gave (3-*S*-ethylthiopropyl) 2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-galactopyranoside **39** as a syrup (0.70 g, 44%); $[\alpha]_D^{22}$ -17.1 (c 1.41 in $CHCl_3$); (Found C, 48.5; H, 6.95%. $C_{19}H_{30}O_9S_2$ requires C, 48.9; H 6.5%); δ_H(300 MHz; $CDCl_3$; Me_4Si) 1.26 (3 H, t, *J* 7.5, CH_3CH_2S), 1.83-1.97 (2 H, $SCH_2CH_2CH_2S$), 1.99 (3 H, s, *Me*CO), 2.05 (3 H, s, *Me*CO), 2.07 (3 H, s, *Me*CO), 2.16 (3 H, s, *Me*CO), 2.54 (2 H, m, SCH_2CH_3), 2.72- 2.91 (2 H, m, gal-SCH_2), 3.94 (1 H, m, $J_{4,5}$ 1, 5-*H*), 4.08-4.20 (2 H, m, 6-H_A and 6-H_B), 4.50 (1 H, d, $J_{1,2}$ 10, 1-*H*), 5.05 (1 H, dd, $J_{2,3}$ 10 $J_{3,4}$ 3.5, 3-*H*), 5.24 (1 H, m, $J_{1,2}$ 10 $J_{3,4}$ 10, 2-*H*) and 5.43 (1 H, dd, $J_{3,4}$ 3.5 $J_{4,5}$ 1, 4-*H*); δ_C($CDCl_3$; Me_4Si) 14.8 (CH_3CH_2S) 20.6 (*Me*CO), 20.7 (2 x *Me*CO), 20.8 (*Me*CO), 25.9 (CH_2), 29.3 (CH_2), 29.6 (CH_2), 30.3 (CH_2), 61.5, 67.3, 72.0, 74.5, 84.4 (*C*-1), 169.7 (*C*=O), 170.2 (*C*=O), 170.3 (*C*=O) and 170.5 (*C*=O); m/z (EI) 466 (M^+, 5%; Calculated for $C_{19}H_{30}O_9S_2$ 466.1331; Found 466.1322), 331 (10, M - $SCH_2CH_2CH_2SCH_2CH_3$) and 135 (100, M – $C_6H_7O(OAc)_4$).

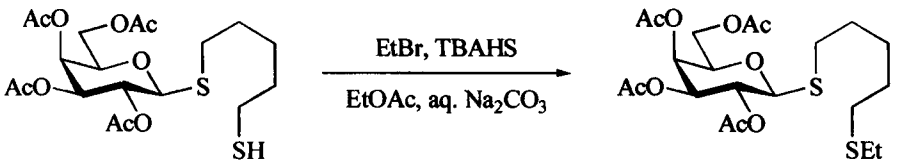
(4-*S*-Ethylthiobutyl) 2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-galactopyranoside (40)



54 **40**

To a solution of crude **54**, prepared from bromide **27** (2.00 g, 4.86 mmol), in ethyl acetate (25 ml) was added TBAHS (1.65 g, 4.86 mmol), bromoethane (3.65 ml, 48.9 mmol) and aqueous Na_2CO_3 (25 ml). This mixture was stirred for 3 hr, and then diluted with ethyl acetate. The organic phase was retained and washed with aqueous $NaHCO_3$, water and brine, dried (Na_2SO_4) and concentrated *in vacuo*. Column chromatography of the resulting residue (EtOAc/light petroleum, 2:3) gave (4-*S*-ethylthiobutyl) 2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-galactopyranoside **40** as a syrup (0.70 g, 30% from **27**); $[\alpha]_D^{22}$ -16.4 (c 0.99 in $CHCl_3$); (Found C, 49.5; H, 6.8%. $C_{20}H_{32}O_9S_2$ requires C, 50.0; H 6.7%) δ_H(300 MHz; $CDCl_3$; Me_4Si) 1.26 (3 H, t, *J* 7.5, CH_3CH_2S), 1.67-1.75 (4 H, m, $SCH_2CH_2CH_2CH_2S$), 1.99 (3 H, s, *Me*CO), 2.05 (3 H, s, *Me*CO), 2.07 (3 H, s, *Me*CO), 2.16 (3 H, s, *Me*CO), 2.50-2.57 (4 H, m, $CH_2SCH_2CH_3$), 2.66-2.76 (2 H, m, $SCH_2CH_2CH_2CH_2SEt$), 3.93 (1 H, td, $J_{5,6A} = J_{5,6B}$ 5.5 $J_{4,5}$ 1, 5-*H*), 4.08-4.20 (2 H, m, 6-H_A and 6-H_B), 4.48 (1 H, d, $J_{1,2}$ 10, 1-*H*), 5.05 (1 H, dd, $J_{2,3}$ 10 $J_{3,4}$ 3.5, 3-*H*), 5.24 (1 H, m, $J_{1,2}$ 10 $J_{2,3}$ 10, 2-*H*) and 5.43 (1 H, dd, $J_{3,4}$ 3.5 $J_{4,5}$ 1, 4-*H*); δ_C($CDCl_3$; Me_4Si) 14.8 (CH_3CH_2S), 20.6 (*Me*CO), 20.7 (2 x *Me*CO), 20.8 (*Me*CO), 25.9 (CH_2), 28.5 (CH_2), 28.7 (CH_2), 29.6 (CH_2), 31.1 (CH_2), 61.5 (*C*-6), 67.3, 67.3, 72.0, 74.5, 84.1 (*C*-1), 169.7 (*C*=O), 170.2 (*C*=O), 170.3 (*C*=O) and 170.5 (*C*=O); m/z (EI) 480 (M^+, 9%; Calculated for $C_{20}H_{32}O_9S_2$ 480.1488; Found 480.1496), 331 (20, M - $SCH_2CH_2CH_2CH_2SCH_2CH_3$) and 149 (100, M – $C_6H_7O(OAc)_4$).

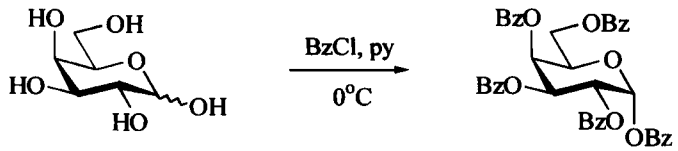
(5-*S*-Ethylthiopentyl) 2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-galactopyranoside (41)



55 **41**

To a solution of **55** (0.55 g, 1.19 mmol) in ethyl acetate (6 ml) was added TBAHS (0.40 g, 1.19 mmol), bromoethane (0.90 ml, 12.06 mmol) and aqueous Na_2CO_3 (6 ml). The mixture was stirred vigorously for 3 hours and diluted with ethyl acetate. The organic phase was retained and washed with aqueous $NaHCO_3$, water and brine, dried and concentrated *in vacuo*. Column chromatography of the resulting residue (EtOAc/light petroleum, 1:2) gave (5-*S*-ethylthiopentyl) 2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-galactopyranoside **41** as a syrup (282 mg, 48%); $[\alpha]_D^{22}$ -19.4 (c 0.82 in $CHCl_3$); (Found C, 51.05; H, 7.3. $C_{21}H_{34}O_9S_2$ requires C, 51.0; H 6.9%); δ_H(300 MHz; $CDCl_3$; Me_4Si) 1.25 (3 H, t, J 7.5, CH_3CH_2S), 1.42-1.70 (6 H, m, 3 x CH_2), 1.99 (3 H, s, *Me*CO), 2.05 (3 H, s, *Me*CO), 2.07 (3 H, s, *Me*CO), 2.16 (3 H, s, *Me*CO), 2.46-2.79 (6 H, m, 3 x SCH_2), 3.94 (1 H, td, $J_{4,5}$ 1 $J_{5,6A}$ = $J_{5,6B}$ 6.5, 5-*H*), 4.08-4.20 (2 H, m, 6-H_A and 6-H_B), 4.48 (1 H, d, $J_{1,2}$ 10, 1-*H*), 5.05 (1 H, dd, $J_{2,3}$ 10 $J_{3,4}$ 3.5, 3-*H*), 5.23 (1 H, m, $J_{1,2}$ 10 $J_{2,3}$ 10, 2-*H*) and 5.43 (1 H, dd, $J_{3,4}$ 3.5 $J_{4,5}$ 1, 4-*H*); δ_C($CDCl_3$; Me_4Si) 14.8 (CH_3CH_2S), 20.6 (*Me*CO), 20.7 (2 x *Me*CO), 20.8 (*Me*CO), 26.0 (CH_2), 28.0 (CH_2), 29.2 (CH_2), 29.3 (CH_2), 30.0 (CH_2), 31.5 (CH_2), 61.5 (*C*-6), 67.3, 67.3, 72.0, 74.5, 84.2 (*C*-1), 169.7 (*C*=O), 170.2 (*C*=O), 170.3 (*C*=O) and 170.5 (*C*=O); m/z (EI) 494 (M^+, 5%; Calculated for $C_{21}H_{34}O_9S_2$ 494.1644; Found 494.1654), 331 (26, M - $SCH_2CH_2CH_2CH_2CH_2SCH_2CH_3$) and 163 (91, M – $C_6H_7O(OAc)_4$).

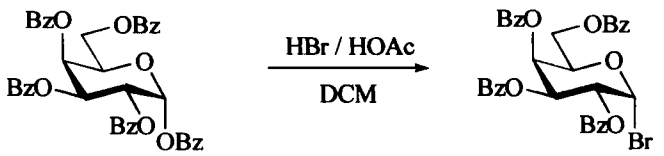
1,2,3,4,6-Penta-*O*-benzoyl-α-D-galactopyranose[221] (62)



61 **62**

A suspension of D-galactose **61** (4.62 g, 25.4 mmol) in pyridine (50 ml) was cooled to 2°C on an ice bath. Benzoyl chloride (30 ml, 258 mmol) was added slowly, keeping the temperature of the reaction mixture below 4°C. The mixture was stirred for 3 hr and then stored in a refrigerator overnight. The reaction vessel was placed in a water bath at 16°C, and methanol was added to the reaction mixture. After stirring for 1 hr, the mixture was concentrated *in vacuo* and the resulting residue dissolved in dichloromethane. This solution was washed with aqueous HCl (x2), aqueous $NaHCO_3$ and water, and concentrated *in vacuo*, co-evaporating several times with water. The resulting residue was dissolved in dichloromethane, dried (Na_2SO_4) and concentrated *in vacuo* to give α-pentabenzoate **62** as a syrup (15.3 g, 85%), m.p. 158-160°C (from EtOH); $[\alpha]_D^{21}$ +192.6 (c 2.0 in $CHCl_3$) {lit.[221] m.p. 128-129°C (from $CHCl_3$/ether); $[\alpha]_D^{29}$ +187 (c 4 in $CHCl_3$)}; δ_H(300 MHz; $CDCl_3$; Me_4Si) 4.43 (1 H, dd, $J_{5,6A}$ 7 $J_{6A,6B}$ 11.5, 6-H_A), 4.64 (1 H, dd, $J_{5,6B}$ 6,5 $J_{6A,6B}$ 11.5, 6-H_B), 4.84 (1 H, m, 5-*H*), 6.03 (1 H, dd, $J_{1,2}$ 3.5 $J_{2,3}$ 10.5, 2-*H*), 6.13 (1 H, dd, $J_{2,3}$ 10.5 $J_{3,4}$ 3.5, 3-*H*), 6.19 (1 H, d, $J_{3,4}$ 3.5, 4-*H*), 6.96 (1 H, d, $J_{1,2}$ 3.5, 1-*H*) and 7.24-8.14 (25 H, m, Ar-*H*); δ_C($CDCl_3$; $CHCl_3$) 62.0, 67.9, 68.7, 68.7, 69.7, 90.9 (*C*-1), 128.7 (*Ar*), 128.7 (*Ar*), 129.0 (*Ar*), 129.1 (*Ar*), 129.3 (*Ar*), 129.3 (*Ar*), 129.6 (*Ar*), 130.1 (*Ar*), 130.2 (*Ar*), 130.3 (*Ar*), 133.5 (*Ar*), 133.7 (*Ar*), 133.8 (*Ar*), 134.0 (*Ar*), 134.2 (*Ar*), 164.9 (*C*=O), 165.8 (*C*=O), 165.9 (*C*=O), 166.1 (*C*=O) and 166.3 (*C*=O).

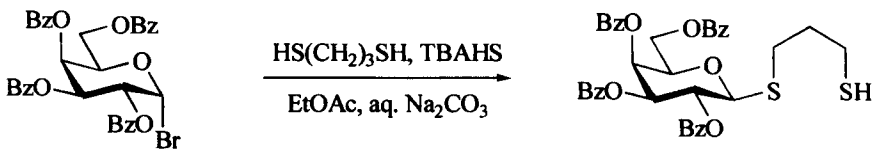
2,3,4,6-Tetra-*O*-benzoyl-α-D-galactopyranosyl bromide[222] (63)



62 **63**

A stirred solution of pentabenzoate **62** (7.46 g, 10.9 mmol) in dichloromethane (200 ml), was cooled (ice-bath) under nitrogen. Hydrogen bromide (45% w/v solution in acetic acid, 6 ml, 33.4 mmol) was added dropwise. Stirring was continued overnight, during which time the temperature rose to ambient. The mixture was diluted with dilchloromethane, washed with ice cold water (x4), aqueous $NaHCO_3$ and water (x2), dried (Na_2SO_4), and concentrated *in vacuo* to give a syrup. This was redissolved in 2:1 ether/hexane and concentrated *in vacuo* to give bromide **63** as a white foam (6.32 g, 88%); $[\alpha]_D$ +190.4 (c 1.13 in $CHCl_3$) {lit.[223] $[\alpha]_D$ +192 (c 0.5 in $CHCl_3$)}; δ_H(300 MHz; $CDCl_3$; Me_4Si) 4.47 (1 H, dd, $J_{5,6A}$ 6 $J_{6A,6B}$ 11.5, 6-H_A), 4.64 (1 H, dd, $J_{5,6B}$ 7 $J_{6A,6B}$ 11.5, 6-H_B), 4.92 (1 H, m, 5-*H*), 5.67 (1 H, dd, $J_{1,2}$ 4 $J_{2,3}$ 10.5, 2-*H*), 6.06 (1 H, dd, $J_{2,3}$ 10.5 $J_{3,4}$ 3.5, 3-*H*), 6.12 (1 H, d, $J_{3,4}$ 3.5, 4-*H*), 6.98 (1 H, d, $J_{1,2}$ 4, 1-*H*) and 7.23-8.11 (20 H, m, Ar-*H*); δ_C($CDCl_3$; $CHCl_3$) 61.9, 68.3, 68.8, 69.1, 72.0, 88.5 (*C*-1), 128.6 (*Ar*), 128.8 (*Ar*), 128.9 (*Ar*), 129.0 (*Ar*), 129.1 (*Ar*), 129.6 (*Ar*), 130.0 (*Ar*), 130.1 (*Ar*), 130.2 (*Ar*), 130.3 (*Ar*), 133.6 (*Ar*), 133.7 (*Ar*), 134.1 (*Ar*), 165.7 (*Ar*), 165.7 (*Ar*), 165.9 (*Ar*) and 166.3 (*Ar*).

(3-Mercaptopropyl) 2,3,4,6-tetra-*O*-benzoyl-1-thio-β-D-galactopyranoside (64)

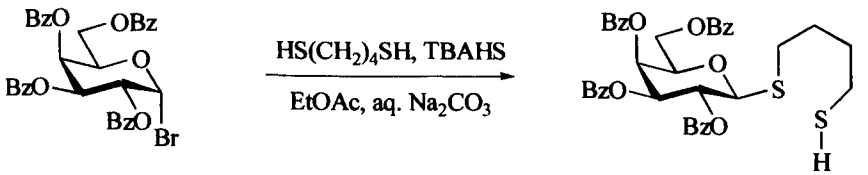


62 **64**

To a solution of bromide **62** (1.32 g, 2.00 mmol) in ethyl acetate (15 ml) was added 1,3-propanedithiol (0.60 ml, 6.0 mmol), aqueous Na_2CO_3 (15 ml), and TBAHS (679 mg, 2.00 mmol). The mixture was stirred vigorously until t.l.c. (EtOAc/hexane, 1:3)

indicated that all of **62** had been consumed (45 min), and diluted with ethyl acetate (100 ml). The organic phase was retained and washed with aqueous $NaHCO_3$, water and brine, dried (Na_2SO_4), and concentrated *in vacuo*. Column chromatography of the resulting residue (EtOAc/light petroleum, 2:9) gave (3-mercaptopropyl) 2,3,4,6-tetra-*O*-benzoyl-1-thio-β-D-galactopyranoside **64** as a white foam (0.90 g, 66%); $[\alpha]_D^{21}$ 89.8 (c 1.67 in $CHCl_3$); (Found: C, 64.55; H, 5.3. $C_{37}H_{34}O_9S_2$ requires C, 64.7; H, 5.0%); δ_H(300 MHz; $CDCl_3$; Me_4Si) 1.96 (2 H, m, $SCH_2CH_2CH_2SH$), 2.61 (2 H, m, $SCH_2CH_2CH_2SH$), 2.88 (1 H, m, $SCH_2CH_2CH_2SH$), 3.00 (1 H, m, $SCH_2CH_2CH_2SH$), 4.41 (2 H, m, 6-H_A and 6-H_B), 4.67 (1 H, m, 5-*H*), 4.86 (1 H, d, $J_{1,2}$ 10, 1-*H*) 5.65 (1 H, dd, $J_{2,3}$ 10 $J_{3,4}$ 3.5, 3-*H*) 5.85 (1 H, t, $J_{1,2}$ 10 $J_{2,3}$ 10, 2-*H*) 6.04 (1 H, d, $J_{3,4}$ 3.5, 4-*H*) and 7.2-8.1 (20 H, m, Ar-*H*); δ_C($CDCl_3$; Me_4Si) 23.3 (CH_2), 28.5 (CH_2), 33.7 (CH_2), 62.4, 68.3, 68.5, 72.8, 75.3, 84.5 (*C*-1), 128.5 (*Ar*), 128.7 (*Ar*), 128.7 (*Ar*), 128.9 (*Ar*), 129.3 (*Ar*), 129.4 (*Ar*), 129.6 (*Ar*), 130.0 (2 x *Ar*), 130.0 (*Ar*), 130.2 (*Ar*), 133.5 (2 x *Ar*), 133.6 (*Ar*), 133.9 (*Ar*), 165.6 (*C*=O), 165.8 (2 x *C*=O) and 166.3 (*C*=O); m/z (EI) 686 (M^+, 0.1%) and 579 (26, M - $SCH_2CH_2CH_2CH_2SH$).

(4-Mercaptobutyl) 2,3,4,6-tetra-*O*-benzoyl-1-thio-β-D-galactopyranoside (65)

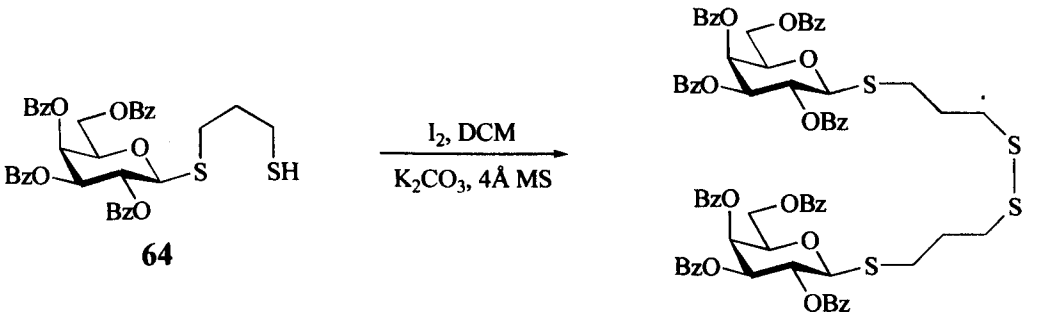


62 **65**

To a solution of bromide **62** (1.32 g, 2.00 mmol) in ethyl acetate (15 ml) was added 1,4-butanedithiol (0.72 ml, 6.0 mmol), aqueous Na_2CO_3 (15 ml), and TBAHS (679 mg, 2.00 mmol). The mixture was stirred vigorously for 75 min, at which point t.l.c. (EtOAc/hexane, 1:3) indicated that all of **62** had been consumed, and diluted with ethyl acetate (100 ml). The organic phase was retained and washed with aqueous $NaHCO_3$, water and brine, dried (Na_2SO_4), and concentrated *in vacuo*. Column chromatography of the resulting residue (EtOAc/light petroleum, 2:9) gave (4-mercaptobutyl) 2,3,4,6-tetra-*O*-benzoyl-1-thio-β-D-galactopyranoside **65** as a white foam (0.77 g, 55%), m.p. 129-133°C dec. (from ether/hexane); $[\alpha]_D^{22}$ +87.3 (c 1.01 in $CHCl_3$); (Found: C, 65.0; H,

5.45. $C_{38}H_{36}O_9S_2$ requires C, 65.1; H, 5.2%); δ_H(300 MHz; $CDCl_3$; Me_4Si) 1.62-1.82 (4 H, m, $SCH_2CH_2CH_2CH_2SH$), 2.47 (2 H, m, $SCH_2CH_2CH_2CH_2SH$), 2.72-2.92 (2 H, m, $SCH_2CH_2CH_2CH_2SH$), 4.40 (2 H, m, 6-H_A and 6-H_B), 4.67 (1 H, m, 5-*H*), 4.85 (1 H, d, $J_{1,2}$ 10, 1-*H*), 5.65 (1 H, dd, $J_{2,3}$ 10 $J_{3,4}$ 3.5, 3-*H*), 5.84 (1 H, t, $J_{1,2}$ 10 $J_{2,3}$ 10, 2-*H*), 6.03 (1 H, d, $J_{3,4}$ 3.5, 4-*H*) and 7.21-8.10 (20 H, m, Ar-*H*); δ_C($CDCl_3$; Me_4Si) 24.1 (CH_2), 28.5 (CH_2), 29.6 (CH_2), 32.9 (CH_2), 62.4, 68.3, 68.5, 72.8, 75.3, 84.4 (*C*-1), 128.5 (*Ar*), 128.6 (*Ar*), 128.7 (*Ar*), 128.9 (*Ar*), 129.0 (*Ar*), 129.3 (*Ar*), 129.4 (*Ar*), 129.6 (*Ar*), 130.0 (2 x *Ar*), 130.0 (*Ar*), 130.2 (*Ar*), 133.5 (*Ar*), 133.6 (*Ar*), 133.6 (*Ar*), 133.9 (*Ar*), 165.6 (*C*=O), 165.8 (2 x *C*=O) and 166.3 (*C*=O); m/z (EI) 700 (M^+, 0.3%) and 579 (10, M - $SCH_2CH_2CH_2CH_2CH_2SH$).

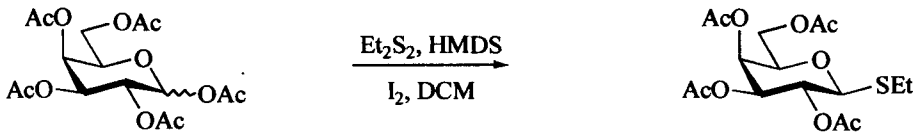
4-*S*-(2,3,4,6-Tetra-*O*-benzoyl-β-D-galactopyranosyl) thiobutyl disulfide (71)



To a solution of mercaptopropyl thiogalactoside **64** (86 mg, 0.125 mmol) in dichloromethane (2 ml), in the presence of potassium carbonate (18 mg, 0.13 mmol) and 4Å MS (50 mg) was added iodine (38 mg, 0.15 mmol). The resulting mixture was stirred at room temperature for 30 min, at which point t.l.c. (EtOAc/light petroleum, 1:2) indicated that all of **64** had been consumed. The reaction mixture was diluted with dichloromethane, washed with aqueous $Na_2S_2O_3$ and water, dried (Na_2SO_4) and concentrated *in vacuo*. Column chromatography of the resulting residue (EtOAc/light petroleum, 1:5) afforded 4-*S*-(2,3,4,6-tetra-*O*-benzoyl-β-D-galactopyranosyl) thiobutyl disulfide **71**; δ_H (300 MHz; $CDCl_3$; $CHCl_3$) 2.05 (4 H, m, $SCH_2CH_2CH_2SS$), 2.69 (4 H, m, $SCH_2CH_2CH_2SS$), 2.83 (2 H, m, $SCH_2CH_2CH_2SS$), 2.96 (2 H, m, $SCH_2CH_2CH_2SS$), 4.36-4.44 (4 H, m), 4.65 (2 H, m), 4.89 (2 H, d, $J_{1,2}$ 10, 1-*H*), 5.66 (2 H, dd, $J_{2,3}$ 10 $J_{3,4}$

3.5, 3-*H*), 5.82 (2 H, t, $J_{1,2} = J_{2,3}$ 10, 2-*H*), 6.03 (2 H, d, $J_{3,4}$ 3.5, 4-*H*) and 7.2-8.1 (40 H, m, Ar-*H*); δ_C ($CDCl_3$; $CHCl_3$) 28.6 (*C*H_2), 28.7 (*C*H_2), 36.6 (*C*H_2), 62.0, 68.0, 68.2, 72.5, 74.9, 84.2, 128.1 (*Ar*), 128.3 (*Ar*), 128.5 (*Ar*), 128.8 (*Ar*), 128.9 (*Ar*), 129.2 (*Ar*), 129.5 (*Ar*), 129.6 (*Ar*), 129.6 (*Ar*), 129.7 (*Ar*), 133.2 (2 x *Ar*), 133.3 (*Ar*), 133.5 (*Ar*), 165.2 (*C*=O), 165.3 (*C*=O) and 165.8 (*C*=O). *m/z* (MALDI-TOF) 1393 ($M + Na^+$).

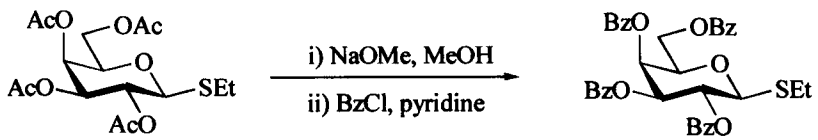
Ethyl 2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-galactopyranoside[224] (67)



42 **67**

To a solution of pentaacetate **42** (9.76g, 25.0 mmol), HMDS (2.82 ml, 13.8 mmol) and ethyl disulfide (1.70 ml, 13.8 mmol) in dichloromethane (100 ml) was added iodine (6.98 g, 27.5 mmol). The mixture was stirred for 80 min, at which point t.l.c. (EtOAc/light petroleum, 1:2) indicated that all of **42** had been consumed. The reaction mixture was shaken with aqueous $Na_2S_2O_3$ (100 ml), and extracted with dichloromethane (x3). The combined organic extracts were washed with aqueous $NaHCO_3$, water and brine, dried (Na_2SO_4) and concentrated *in vacuo*. Column chromatography of the resulting residue (EtOAc/hexane, 1:2→2:3) gave β-thioglycoside **67** (6.82 g, 70%), m.p. 72-73.5°C (from ether/hexane); $[\alpha]_D$ -6.5 (c 1.50 in $CHCl_3$) {lit.,[224] m.p. 74-75°C; $[\alpha]_D$ -8.0 (c 2.1 in $CHCl_3$)}; δ_H(300 MHz; $CDCl_3$; Me_4Si) 1.29 (3 H, t, *J* 7.5, CH_3CH_2S), 1.99 (3 H, s, *Me*CO), 2.05 (3 H, s, *Me*CO), 2.07 (3 H, s, *Me*CO), 2.16 (3 H, s, *Me*CO), 2.64-2.82 (2 H, m, CH_3CH_2S), 3.93 (1 H, m, 5-*H*), 4.08-4.20 (2 H, m, 6-H_A and 6-H_B), 4.49 (1 H, d, $J_{1,2}$ 10, 1-*H*), 5.05 (1 H, dd, $J_{2,3}$ 10 $J_{3,4}$ 3.5, 3-*H*), 5.24 (1 H, m, $J_{1,2}$ 10 $J_{2,3}$ 10, 2-*H*) and 5.43 (1 H, d, $J_{3,4}$ 3.5, 4-*H*); δ_C($CDCl_3$; Me_4Si) 14.9 (CH_3CH_2S), 20.6 (*Me*CO), 20.7 (2 x *Me*CO), 20.8 (*Me*CO), 24.4 (CH_3CH_2S), 61.5, 67.3, 67.4, 72.0, 74.5, 84.1 (*C*-1), 169.7 (*C*=O), 170.2 (*C*=O), 170.3 (*C*=O) and 170.5 (*C*=O).

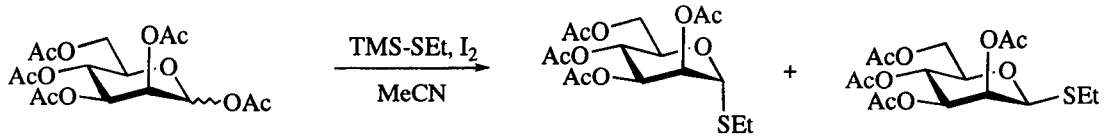
Ethyl 2,3,4,6-tetra-*O*-benzoyl-1-thio-β-D-galactopyranoside[225] (69)



67 **69**

Thiogalactoside **67** (393 mg, 1.00 mmol) was treated with sodium methoxide (25 mg, 0.46 mmol) in methanol (2 ml) for 2 hr. Amberlite IRA 200 (H^+) was added. The mixture was stirred until judged neutral to pH paper, filtered, and concentrated *in vacuo*. The residue was dissolved in pyridine (10 ml) and cooled (ice-bath). Benzoyl chloride (0.93 ml, 8.0 mmol) was added slowly to the reaction mixture as a solution in chloroform (5 ml), and the mixture was stirred overnight, with the temperature being allowed to rise to ambient. The mixture was cooled (ice-bath), and methanol (10 ml) was added. The mixture was stirred for a further 2 hr, and then concentrated *in vacuo*. The resulting residue was taken up into dichloromethane (500 ml), and the solution was washed with aqueous HCl, $NaHCO_3$, water and brine, dried (Na_2SO_4) and concentrated *in vacuo*. Column chromatography of the resulting residue (EtOAc/hexane, 1:5) gave benzoylated thiogalactoside **69** as a white foam (515 mg, 80%), m.p. 113-114°C (ether/hexane); $[\alpha]_D^{22}$ +109.4 (c 1.06 in $CHCl_3$) {lit.,[225] m.p. 101-102°C; $[\alpha]_D^{20}$ +110.2 (c 1.0)} δ_H (300 MHz; $CDCl_3$; $CHCl_3$) 1.32 (3 H, t, *J* 7.5, CH_3CH_2S), 2.74-2.94 (2 H, m, CH_3CH_2S), 4.37 (1 H, m, 5-*H*), 4.42 (1 H, dd, $J_{5,6A}$ 6.5 $J_{6A,6B}$ 10.5, 6-H_A), 4.67 (1 H, dd, $J_{5,6B}$ 6 $J_{6A,6B}$ 10.5, 6-H_B), 4.88 (1 H, d, $J_{1,2}$ 10, 1-*H*), 5.65 (1 H, dd, $J_{2,3}$ 10 $J_{3,4}$ 3.5, 3-*H*), 5.85 (1 H, t, $J_{1,2} = J_{2,3}$ 10, 2-*H*), 6.04 (1 H, dd, $J_{3,4}$ 3.5 $J_{4,5}$ 1, 4-*H*) and 7.20-8.10 (20 H, m, Ar-*H*); δ_C ($CDCl_3$; $CHCl_3$) 15.5 (CH_3CH_2S), 24.8 (CH_3CH_2S), 62.4, 68.5, 68.6, 72.9, 75.3, 84.5 (*C*-1), 128.6 (*Ar*), 128.7 (*Ar*), 129.0 (*Ar*), 129.1 (*Ar*), 129.4 (*Ar*), 129.6 (*Ar*), 129.7 (*Ar*), 130.0 (*Ar*), 130.0 (*Ar*), 130.1 (*Ar*), 130.3 (*Ar*), 133.6 (*Ar*), 133.6 (*Ar*), 133.6 (*Ar*), 133.9 (*Ar*), 165.7 (*C*=O), 165.8 (*C*=O), 165.8 (*C*=O) and 166.4 (*C*=O).

Ethyl 2,3,4,6-tetra-*O*-acetyl-1-thio-α-D-mannopyranoside[224] (106) and ethyl 2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-mannopyranoside[224] (139)



109 **106** **139**

To a stirred solution of **109** (19.6 g, 50.2 mmol) and iodine (12.74 g, 50.2 mmol) in acetonitrile (200 ml) at 18°C (water bath) under nitrogen was added (ethylthio)trimethylsilane (90%, 10.8 ml, 60.1 mmol), over 20 min. Stirring was continued for a further 10 minutes. The reaction mixture was diluted with dichloromethane, washed with aqueous $Na_2S_2O_3$, aqueous $NaHCO_3$, water and brine, dried (Na_2SO_4), and concentrated *in vacuo*. Column chromatography of the resulting residue (EtOAc/light petroleum, 1:2) gave α-thiomannoside **106** as a white powder (10.24 g, 52%), m.p. 105-6°C (from EtOH); $[\alpha]_D$ +98.0 (c 1.71 in $CHCl_3$) {lit.,[224] m.p. 107-8°C; $[\alpha]_D$ +104 (c 0.88 in $CHCl_3$)}; δ_H(500 MHz; $CDCl_3$; Me_4Si) 1.31 (3 H, t, *J* 7, CH_3CH_2S), 1.99 (3 H, s, *Me*CO), 2.05 (3 H, s, *Me*CO), 2.09 (3 H, s, *Me*CO), 2.16 (3 H, s, *Me*CO), 2.65 (2 H, m, CH_3CH_2S), 4.11 (1 H, dd, $J_{5,6A}$ 2.5, $J_{6A,6B}$ 12,* 6-H_A), 4.31 (1 H, dd, $J_{5,6B}$ 5.5, $J_{6A,6B}$ 12.5,* 6-H_B), 4.40 (1 H, m, 5-*H*), 5.27 (1 H, dd, $J_{2,3}$ 3.5† $J_{3,4}$ 9.5, 3-*H*) , 5.29 (1 H, s, 1-*H*), 5.31 (1 H, m, 4-*H*) and 5.34 (1 H, dd, $J_{1,2}$ 1 $J_{2,3}$ 3,† 2-*H*); δ_C($CDCl_3$; Me_4Si) 14.8 (CH_3CH_2S), 20.6 (*Me*CO), 20.7 (2x *Me*CO), 20.9 (*Me*CO), 25.5 (CH_3CH_2S), 62.4, 66.4, 68.9, 69.5, 71.2, 82.3 ($J_{C,H}$ 166.7, *C*-1), 169.7 (*C*=O), 169.8 (*C*=O), 170.0 (*C*=O) and 170.6 (*C*=O).

Further elution gave β-thiomannoside **139** as a white powder (0.96 g, 4.9%), m.p. 156-157°C (from EtOH); $[\alpha]_D$ -46.3 (c 1.88 in $CHCl_3$) {lit.,[224] m.p. 161-162°C; $[\alpha]_D$ -67 (c 0.67 in $CHCl_3$)}; δ_H(500 MHz; $CDCl_3$; Me_4Si) 1.31 (3 H, t, *J* 7.5, CH_3CH_2S), 1.98 (3 H, s, *Me*CO), 2.04 (3 H, s, *Me*CO), 2.08 (3 H, s, *Me*CO), 2.19 (3 H, s, *Me*CO), 2.74 (2 H,

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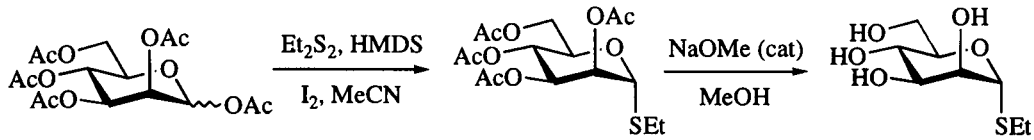
* $J_{6A,6B}$ given as 11.95 at 6-H_A and 12.55 at 6-H_B. Close enough to be within error limits (±0.60 Hz).

† $J_{2,3}$ given as 2.98 at 2-*H* and 2.99/3.58 at 3-*H*. Close enough to be within error limits (±0.60 Hz).

q, *J* 7.5, CH_3CH_2S), 3.70 (1 H, m, 5-*H*), 4.15 (1 H, dd, $J_{5,6}$ 3 $J_{6A,6B}$ 12, 6-H_A), 4.27 (1 H, dd, $J_{5,6B}$ 6 $J_{6A,6B}$ 12, 6-H_B), 4.78 (1 H, br s, 1-*H*), 5.08 (1 H, m, 3-*H*), 5.26 (1 H, m, 4-*H*), 5.51 (1 H, br d, 2-*H*); δ_C($CDCl_3$; Me_4Si) 15.0 (CH_3CH_2S), 20.6 (*Me*CO), 20.6 (*Me*CO), 20.7 (*Me*CO), 20.8 (*Me*CO), 25.9 (CH_3CH_2S), 62.9, 65.9, 70.5, 71.9, 76.5, 82.7 ($J_{C,H}$ 151.6, *C*-1), 169.6 (*C*=O), 170.0 (*C*=O), 170.2 (*C*=O) and 170.6 (*C*=O).

Ethyl α-D-thiomannopyranoside[202,224] (108)



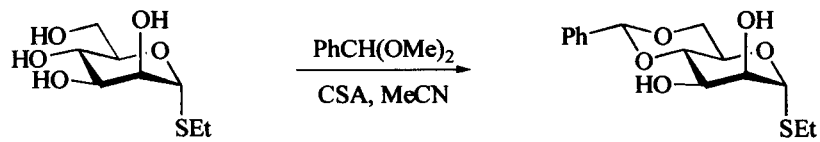
109 **106** **108**

To a stirred solution of **109** (29.63 g, 75.9 mmol), diethyl disulfide (5.14 ml, 41.7 mmol) and HMDS (8.55 ml, 41.8 mmol) in dichloromethane (300 ml) was added iodine (23.12 g, 91.1 mmol). After stirring at room temperature for 2 hr, the reaction mixture was shaken with aqueous $Na_2S_2O_3$, and extracted with dichloromethane (x3). The combined extracts were washed with aqueous $NaHCO_3$ and brine, dried (Na_2SO_4), and concentrated *in vacuo*. Crystallisation from ethanol gave a mixture of α- and β thiomannosides **106** and **139** in ratio 10:1, as determined by ^1H NMR (19.56 g, 66%). This was treated with sodium methoxide (1.40 g, 25.9 mmol) in methanol (750 ml) for 2 hr. Amberlite IRA 200 (H^+) was added. The mixture was stirred until judged neutral to pH paper, filtered, and concentrated *in vacuo*. Crystallisation of the resulting residue from isopropanol gave ethyl α-D-thiomannopyranoside* **108** (7.54 g, 74%), m.p. 125-126°C (from *i*-PrOH); $[\alpha]_D$ +202.5 (c 1.10 in H_2O); {lit., m.p. 126.5-128.5°C[202]; $[\alpha]_D^{24}$ + 217.1[226] (c 1.0 in H_2O)}; δ_H(300 MHz, D_2O, $Me_3SiCD_2CD_2COONa$) 1.29 (3 H, t, *J* 7.5, CH_3CH_2S), 2.59-2.77 (2 H, m, CH_3CH_2S), 3.68 (1 H, t, $J_{3,4}$ = $J_{4,5}$ 9.5, 4-*H*), 3.75-3.82 (2 H, m, 3-*H* and 6-H_A), 3.90 (1 H, dd, $J_{5,6B}$ 2 $J_{6A,6B}$ 12, 6-H_B), 4.01 (1 H, m, 5-*H*), 4.05

* Yield based upon 91% of material prior to treatment with NaOMe/MeOH being the α-anomer

(1 H, m, 2-*H*) and 5.33 (1 H, br s, 1-*H*); δ_C(D_2O, $Me_3SiCD_2CD_2COONa$) 17.0 (CH_3CH_2S), 27.7 (CH_3CH_2S), 63.8, 70.1, 74.1, 74.8, 76.1 and 87.3 (*C*-1).

Ethyl 4,6-*O*-benzylidene-1-thio-α-D-mannopyranoside[202] (107)



108 **107**

Compound **108** (2.97 g, 21.7 mmol) was suspended in dry acetonitrile (50 ml) and stirred with heating (oil bath at 50° C). CSA (0.27 g, 1.17 mmol). 3Å molecular sieves (3.71 g) were added, followed by benzaldehyde dimethyl acetal (2.38 ml, 15.9 mmol). The oil bath temperature was allowed to cool to 35°C, and stirring continued for 18 hours. Triethylamine (0.75 ml, 5.38 mmol) was added, and stirring continued at room temperature for a further 10 min. The mixture was diluted with acetonitrile, filtered through Celite, and concentrated *in vacuo*. Column chromatography of the resulting residue (EtOAc/light petroleum, 1:25→1:11) gave **107** (1.01 g, 24%), m.p. 169-172°C (from $CHCl_3$); $[\alpha]_D^{22}$ +161.6 (c 0.43 in $CHCl_3$) {lit.,[202] m.p. 174-175°C; $[\alpha]_D$ +167.5 (c 1.22 in $CHCl_3$)}; δ_H(500 MHz; $CDCl_3$; Me_4Si) 1.29 (3 H, t, *J* 7.5, CH_3CH_2), 2.55-2.71 (2 H, m, CH_3CH_2S), 2.75 (1 H, br s, -O*H*), 2.83 (1 H, br s, -O*H*), 3.84 (1 H, m, 6-H_A), 3.95 (1 H, m, 4-*H*), 4.04 (1 H, dd, $J_{2,3}$ 3.5 $J_{3,4}$ 10, 3-*H*), 4.11 (1 H, br d, 2-*H*), 4.20-4.25 (2 H, m, 5-*H* and 6-H_B), 5.35 (1 H, s, 1-*H*), 5.56 (1 H, s, PhC*H*O_2), 7.37-7.50 (5 H, m, Ar-*H*); δ_C($CDCl_3$; Me_4Si) 14.9, 25.1, 63.5, 68.6, 69.1, 72.4, 79.1, 84.5 (*C*-1), 102.3 ($PhCHO_2$), 126.3 (*Ar*), 128.4 (*Ar*), 129.3 (*Ar*) and 137.1 (*Ar*).

Ethyl 2,3-di-*O*-benzyl-4,6-*O*-benzylidene-1-thio-α-D-mannopyranoside[193,202*] (102)

107 **102**

To a solution of **107** (200 mg, 0.64 mmol) in DMF (2 ml) was added sodium hydride (60% w/w suspension in mineral oil, 56 mg, 1.4 mmol). This was stirred until evolution of hydrogen ceased. Benzyl bromide (175 μl, 1.47 mmol) was added to the resulting suspension, and stirring was continued overnight. The reaction mixture was diluted with dichloromethane, washed with water and brine, dried (Na_2SO_4), and concentrated *in vacuo*. Column chromatography of the resulting residue gave ethyl 2,3-di-*O*-benzyl-4,6-*O*-benzylidene-1-thio-α-D-mannopyranoside **102** as a syrup (192 mg, 61%); $[\alpha]_D$ +102.2 (c 1.09 in $CHCl_3$); (Found C, 71.1; H, 6.8%. $C_{21}H_{34}O_9S_2$ requires C, 70.7; H 6.55%); δ_H(300 and 500 MHz; $CDCl_3$; Me_4Si) 1.23 (3 H, m, CH_3CH_2S), 2.51-2.62 (2 H, m, CH_3CH_2S), 3.87-3.91 (2 H, m, 2-*H* and 6-H_A), 3.91 (1 H, dd, $J_{2,3}$ 3 $J_{3,4}$ 10, 3-*H*), 4.16-4.22 (2 H, m, 5-*H* and 6-H_B), 4.27 (1 H, m, 4-*H*), 4.62 (1 H, d, *J* 12, $PhCH_2$), 4.72 (1 H, d, *J* 12, $PhCH_2$), 4.76 (1 H, d, *J* 12, $PhCH_2$), 4.79 (1 H, d, *J* 12, $PhCH_2$), 5.29 (1 H, d, $J_{1,2}$ 1, 1-*H*), 5.63 (1 H, s, $PhCHO_2$), 7.24-7.51 (15 H, m, Ar-*H*); δ_C($CDCl_3$; Me_4Si) 14.9 (CH_3CH_2S), 25.3 (CH_3CH_2S), 64.6, 68.6 ($PhCH_2$), 73.0, 73.1 ($PhCH_2$), 76.5, 78.2, 79.3, 83.6 (*C*-1), 101.5 ($PhCHO_2$), 126.1 (*Ar*), 127.5 (*Ar*), 127.6 (*Ar*), 127.8 (*Ar*), 128.1 (*Ar*), 128.2 (*Ar*), 128.3 (*Ar*), 128.4 (*Ar*), 128.8 (*Ar*), 137.6 (*Ar*), 137.9 (*Ar*) and 138.4 (*Ar*); m/z (EI) 492 (M^+, 2.5%; Calculated for $C_{29}H_{32}O_5S$ 492.1970; Found 492.1963).

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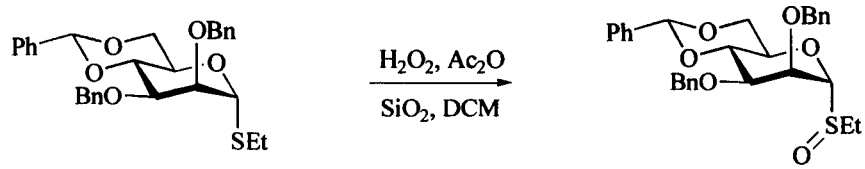
* This compound has been reported previously, but was only prepared as an intermediate to another compound. No characterisations were reported by either group cited.

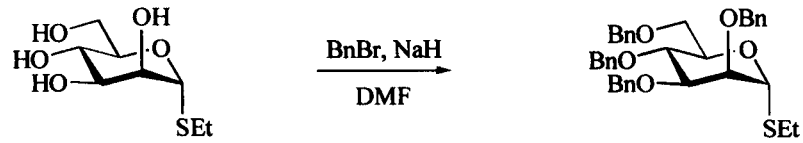
Ethyl 2,3-di-*O*-benzyl-4,6-*O*-benzylidene-1-thio-α-D-mannopyranoside *S*-oxide[194] (104)



102 **104**

To a stirred mixture of thiomannoside **102** (166 mg, 0.34 mmol), acetic anhydride (35 μl, 0.37 mmol) and 220-440 mesh silica (68 mg) in dichloromethane (1.66 ml) was added aqueous H_2O_2 (100 volumes, 46 mg). The resulting mixture was stirred for 17 hr at room temperature. A further addition of aqueous H_2O_2 was made (10 mg), and stirring was continued for a further 5 hr. The mixture was diluted with dichloromethane, washed with aqueous $Na_2S_2O_5$, aqueous $NaHCO_3$ and brine, dried (Na_2SO_4) and concentrated *in vacuo* to give sulfoxide **104** as a powder (146 mg, 85%), m.p. 106-110°C; $[\alpha]_D^{22}$ +21.2 (c 1.05 in $CHCl_3$) {lit.,[194] m.p. 110-113°C; $[\alpha]_D^{20}$ +10.4 (c 0.5)}; δ_H(300 MHz; $CDCl_3$; Me_4Si) 1.35 (3 H, t, *J* 7.5, CH_3CH_2S), 2.64 (1 H, m, CH_3CH_2S), 2.91 (1 H, m, CH_3CH_2S), 3.72 (1 H, m, 5-*H*), 3.80 (1 H, m, 6-H_B or 4-*H*), 4.12 (1 H, dd, $J_{2,3}$ 3.5 $J_{3,4}$ 10, 3-*H*), 4.20 (1 H, dd, $J_{5,6A}$ 4 $J_{6A,6B}$ 9.5, 6-H_A), 4.34 (1 H, m, 4-*H* or 6-H_B), 4.51 (1 H, m, 2-*H*), 4.61 (1 H, br s, 1-*H*), 4.68 (1 H, d, J_{AB} 12, $PhCH_2$), 4.71 (1 H, d, J_{AB} 12, $PhCH_2$), 4.79-4.87 (2 H, m, 2 x $PhCH_2$), 5.63 (1 H, s, $PhCHO_2$) and 7.25-7.50 (15 H, m, Ar-*H*); δ_C($CDCl_3$; Me_4Si) 5.9 (CH_3CH_2S), 44.1 (CH_3CH_2S), 68.3, 70.2, 73.2, 73.3, 74.2, 76.3, 78.0, 92.9 (*C*-1), 101.8 ($PhCHO_2$), 126.2 (*Ar*), 127.8 (*Ar*), 128.2 (*Ar*), 128.4 (*Ar*), 128.6 (*Ar*), 128.7 (*Ar*) 129.2 (*Ar*), 137.4 (*Ar*), 137.8 (*Ar*) and 138.3 (*Ar*).

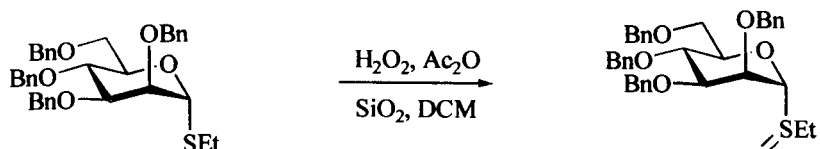
Ethyl 2,3,4,6-tetra-*O*-benzyl-1-thio-α-D-mannopyranoside[227] (115)



108 **115**

To a cooled (ice bath) solution of **108** (1.87 g, 8.34 mmol) and benzyl bromide (8 ml, 67.3 mmol) in DMF (50 ml) was added sodium hydride (60% dispersion in mineral oil, 3.00 g, 75.0 mmol). The resulting mixture was stirred overnight, with the temperature being allowed to rise to ambient. The reaction mixture was diluted with ether, washed with water and brine, dried (Na_2SO_4), and concentrated *in vacuo*. Column chromatography of the resulting residue (EtOAc/light petroleum, 15:1) gave tetrabenzylated α-thiomannoside **115** as a syrup (3.79 g, 76%); $[\alpha]_D^{21}$ +76.3 (c 2.07 in $CHCl_3$) {lit.[227] $[\alpha]_D^{22}$ +65 (c 2.1 in $CHCl_3$)}; δ_H(300 MHz, $CDCl_3$, Me_4Si) 1.24 (3 H, t, *J* 7.5, CH_3CH_2S), 2.48-2.69 (2 H, m, CH_3CH_2S), 3.71 (1 H, dd, $J_{5,6A}$ 2 $J_{6A,6B}$ 11, 6-H_A), 3.79-3.86 (3 H, m, 2-*H*, 3-*H* and 6-H_B), 4.02 (1 H, m, 4-*H*), 4.13 (1 H, m, 5-*H*), 4.51 (2 H, m, 2 x $PhCH_2$), 4.55 (1 H, m, $PhCH_2$), 4.59 (1 H, m, $PhCH_2$), 4.66 (2 H, m, 2 x $PhCH_2$), 4.73 (1 H, d, J_{AB} 12.5, $PhCH_2$), 4.88 (1 H, d, J_{AB} 11, $PhCH_2$), 5.39 (1 H, br s, 1-*H*) and 7.15-7.41 (20 H, m, Ar-*H*); δ_C($CDCl_3$, $CHCl_3$) 15.0 (CH_3CH_2S), 25.3 (CH_3CH_2S), 69.3, 72.1, 72.2, 72.2, 73.4, 75.2, 75.2, 76.6, 80.5, 82.0, 127.7 (*Ar*), 127.8 (*Ar*), 127.9 (*Ar*), 127.9 (*Ar*), 128.0 (*Ar*), 128.1 (*Ar*), 128.5 (*Ar*), 128.6 (*Ar*), 138.4 (*Ar*), 138.5 (*Ar*), 138.6 (*Ar*) and 138.8 (*Ar*).

Ethyl 2,3,4,6-tetra-*O*-benzyl-1-thio-α-D-mannopyranoside *S*-oxide[194] (114)

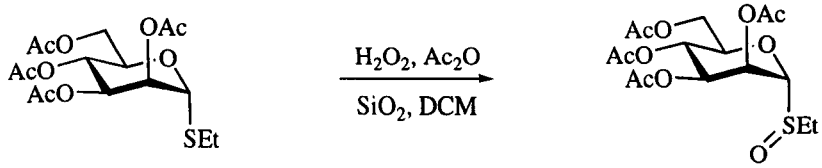


115 **114**

To a solution of **115** (2.83 g, 4.71 mmol), acetic anhydride (0.50 ml, 5.30 mmol) and 220-440 mesh silica (0.95 g) in dichloromethane (30 ml) was added 100 volumes

aqueous H_2O_2 (0.80 g). The resulting mixture was stirred in a closed vessel for 24 hr at room temperature, at which point t.l.c. (EtOAc/light petroleum, 1:1) indicated that all of **115** had been consumed. The mixture was diluted with dichloromethane, washed with aqueous $Na_2S_2O_5$, aqueous $NaHCO_3$ and brine, dried (Na_2SO_4) and concentrated *in vacuo*. Column chromatography of the resulting residue (EtOAc/light petroleum, 1:3→2:1) gave sulfoxide **114** as a syrup (2.60 g, 89%); $[\alpha]_D^{21}$ +25.3 (c 1.67 in $CHCl_3$) {lit.,[194] $[\alpha]_D^{20}$ +21.1 (c 1.3 in $CHCl_3$)}; δ_H(300 MHz; $CDCl_3$; Me_4Si) 1.34 (3 H, t, *J* 7.5, CH_3CH_2S), 2.69 (1 H, m, CH_3CH_2S=O), 2.96 (1 H, m, CH_3CH_2S=O), 3.60-3.71 (3 H), 3.97-4.06 (2 H), 4.46-4.51 (3 H), 4.56-4.67 (4 H), 4.70 (1 H, d, J_{AB} 12, PhCH_2), 4.75 (1 H, d, J_{AB} 12.5, PhCH_2) 4.88 (1 H, d, J_{AB} 11, PhCH_2) and 7.13-7.41 (20 H, m, Ar-*H*); 6.0 (CH_3CH_2S=O), 43.8 (CH_3CH_2S=O), 69.3, 71.8, 72.2, 72.9, 73.5, 73.8, 75.2, 77.7, 79.7, 91.3 (*C*-1), 127.8 (*Ar*), 127.9 (*Ar*), 127.9 (*Ar*), 128.1 (*Ar*), 128.2 (*Ar*), 128.5 (*Ar*), 128.5 (*Ar*), 137.9 (*Ar*), 138.0 (*Ar*), 138.1 (*Ar*) and 138.2 (*Ar*).

Ethyl 2,3,4,6-tetra-*O*-acetyl-1-thio-α-D-mannopyranoside *S*-oxide[204] (129)

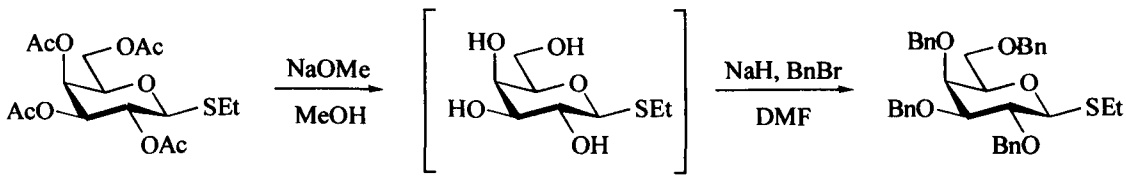


106 **129**

To a solution of **106** (392 mg, 1.00 mmol), acetic anhydride (104 μl, 1.10 mmol) and 220-440 mesh silica (200 mg) in dichloromethane (5 ml) was added aqueous H_2O_2 (121.5 mg). The resulting mixture was stirred for 22 hr at room temperature. The mixture was diluted with dichloromethane, washed with aqueous $Na_2S_2O_5$, aqueous $NaHCO_3$ and brine, dried (Na_2SO_4) and concentrated *in vacuo*. Column chromatography of the resulting residue (EtOAc/light petroleum, 1:4→3:5) gave sulfoxide **129** as a white solid (305 mg, 75%, mixture of diastereoisomers in a ratio of approximately

10:1); {lit.,[204] m.p. 134-136°C*}; δ_H(300 MHz; $CHCl_3$, Me_4Si) Major isomer: 1.38 (3 H, t, J 7.5, CH_3CH_2S), 2.02 (3 H, s, *Me*CO), 2.06 (3 H, s, *Me*CO), 2.10 (3 H, s, *Me*CO), 2.18 (3 H, s, *Me*CO), 2.78-3.05 (2 H, m, CH_3CH_2S), 4.13 (1 H, m, 5-*H*), 4.13 (1 H, m, 6-H_A), 4.28 (1 H, dd, $J_{5,6A}$ 5.5 $J_{6A,6B}$ 12.5, 6-H_B), 4.66 (1 H, d, $J_{1,2}$ 2, 1-*H*), 5.35 (1 H, m, 4-*H*), 5.59 (1 H, dd, $J_{2,3}$ 3.5 $J_{3,4}$ 10, 3-*H*) and 5.84 (1 H, dd, $J_{1,2}$ 2 $J_{2,3}$ 3.5, 2-*H*); Minor isomer: 1.38 (3 H, m, CH_3CH_2S), 2.04 (3 H, s, *Me*CO), 2.06 (*Me*CO), 2.11 (3 H, s, *Me*CO), 2.18 (*Me*CO), 2.85-3.15 (2 H, m, CH_3CH_2S), 4.30† (1 H, m, 6-H_B), 4.41 (1 H, d, $J_{1,2}$ 2.5, 1-*H*), 4.86 (1 H, m, 5-*H*), 5.36 (1 H, m, 4-*H*), 5.68 (1 H, dd, $J_{2,3}$ 3.5 $J_{3,4}$ 10, 3-*H*) and 5.77 (1 H, m, 2-*H*); δ_C($CDCl_3$, Me_4Si) Major isomer‡: 6.2 (CH_3CH_2S), 20.6 (*Me*CO), 20.7 (2 x *Me*CO), 20.9 (*Me*CO), 44.1 (CH_3CH_2S), 62.4, 65.8, 67.1, 69.0, 74.6, 90.6 (*C*-1), 169.7 (*C*=O), 169.9 (*C*=O), 169.9 (*C*=O) and 170.7 (*C*=O).

Ethyl 2,3,4,6-tetra-*O*-benzyl-1-thio-β-D-galactopyranoside[78] (120)



67 **68** **120**

To a solution of **67** (3.75 g, 9.56 mmol) in dry methanol (105 ml) was added sodium methoxide (550 mg, mmol). This was stirred at room temperature for 3.5 hr, at which point t.l.c. showed all of **67** had been consumed. Amberlite IRA120 (H^+) was added and the mixture was stirred until neutral to litmus. The liquid was filtered, and the filtrate was concentrated *in vacuo*. The resulting residue was dissolved in DMF (50 ml) and

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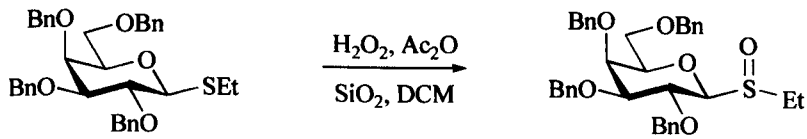
* Kakarla claims a single stereoisomer product, and as such his physical data is reported.

† The fourth acetate resonance appears to be located beneath the signal at 2.06. 6-H_A appears to be located beneath the corresponding signal for the major isomer. The integral values support this view.

‡ Minor isomer not assignable from carbon-13 spectrum.

cooled (ice bath) under nitrogen. Sodium hydride (60% w/w dispersion in mineral oil, 3.44g, 86.0 mmol) was added, and the mixture stirred until evolution of hydrogen ceased (30 min). Benzyl bromide (9.0 ml, 75.7 mmol) was added, and stirring was continued at room temperature for 8 hr. The mixture was diluted with ether, washed with water (x2) and brine, dried (Na_2SO_4) and concentrated *in vacuo*. Column chromatography of the resulting residue (EtOAc/hexane, 1:20→1:10) gave **120** (3.52 g, 63%); $[\alpha]_D^{22}$ -4.3 (c 1.07 in $CHCl_3$) {lit.[78] $[\alpha]_D^{25}$ -5.3 (c 1.4 in $CHCl_3$)}; δ_H(300 MHz; $CDCl_3$; Me_4Si) 1.29 (3 H, t, *J* 7.5, CH_3CH_2S), 2.63-2.82 (2 H, m, CH_3CH_2S), 3.53-3.62 (4 H, m, 3-*H* 5-*H* 6-H_A and 6-H_B), 3.82 (1 H, t, $J_{1,2}$ 9.5 $J_{2,3}$ 9.5, 2-*H*), 3.95 (1 H, d, $J_{3,4}$ 2.5, 4-*H*), 4.38-4.48 (3 H, m, 1-*H* and $PhCH_2$), 4.61 (1 H, d, J_{AB} 11.5, $PhCH_2$), 4.72 (2 H, s, $PHCH_2$), 4.79 (1 H, d, J_{AB} 11.5, $PhCH_2$), 4.88 (1 H, d, J_{AB} 10.5, $PhCH_2$), 4.95 (1 H, d, J_{AB} 10.5, $PhCH_2$) and 7.22-7.41 (20 H, m, Ar-*H*); δ_C($CDCl_3$; Me_4Si) 15.1 (CH_3CH_2S), 24.8 (CH_3CH_2S), 68.9, 72.8, 73.6, 73.7, 74.5, 75.8, 77.3, 78.5, 84.2, 85.4, 127.5 (*Ar*), 127.6 (*Ar*), 127.6 (*Ar*), 127.7 (*Ar*), 127.8 (*Ar*), 127.9 (*Ar*), 128.0 (*Ar*), 128.1 (*Ar*), 128.2 (*Ar*), 128.4 (*Ar*), 128.5 (*Ar*), 128.5 (*Ar*), 138.0 (*Ar*), 138.4 (*Ar*), 138.5 (*Ar*) and 138.9 (*Ar*).

Ethyl 2,3,4,6-tetra-*O*-benzyl-1-thio-β-D-galactopyranoside *S*-oxide (121)



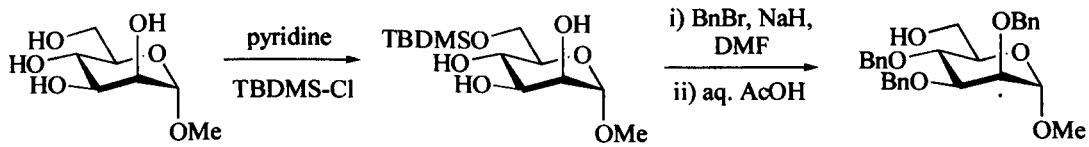
120 **121**

To a solution of **120** (1.57 g, 2.68 mmol) and acetic anhydride (0.31 ml, 3.29 mmol) in dichloromethane (13 ml) was added 220-440 mesh silica (0.91 g) and aqueous H_2O_2 (0.80 g). The mixture was stirred for 17.5 hr at room temperature. More aqueous H_2O_2 (0.21 g) was added, and stirring was continued a further 6 hr. The mixture was diluted with dichloromethane, washed with aqueous $Na_2S_2O_5$, aqueous $NaHCO_3$ and brine, dried (Na_2SO_4) and concentrated *in vacuo*. Column chromatography of the resulting residue (EtOAc/hexane, 1:2→2:1) gave sulfoxide **121** as a 1:1 mixture of diastereoisomers (1.00 g, 62%); δ_H (300 MHz; $CDCl_3$; Me_4Si) 1.18 (3 H, t, *J* 7.5, CH_3CH_2S=O), 1.22 (3 H, t *J* 7.5, CH_3CH_2S=O), 2.49 (1 H, m, CH_3CH_2S=O), 2.67 (1 H,

m, $CH_3CH_2S{=}O$), 2.87 (1 H, m, $CH_3CH_2S{=}O$), 3.04 (1 H, m, $CH_3CH_2S{=}O$), 3.50-3.70 (8 H, m), 3.77 (1 H, d, $J_{1,2}$ 9.5, 1-*H*), 3.89 (1 H, d, $J_{3,4}$ 2.5, 4-*H*), 3.92 (1 H, d; $J_{3,4}$ 1.5, 4-*H*), 4.01 (1 H, t, $J_{1,2} = J_{2,3}$ 9, 2-*H*), 4.22 (1 H, d, $J_{1,2}$ 9, 1-*H*), 4.30-4.91 (17 H, m) and 7.14-7.32 (20 H, m, Ar-*H*); δ_C ($CDCl_3$; $CHCl_3$) 7.2 ($CH_3CH_2S{=}O$), 7.5 ($CH_3CH_2S{=}O$), 40.9, 41.0, 68.3, 69.1, 72.7, 72.7, 73.1, 73.2, 73.3, 73.7, 73.8, 73.9, 74.6, 74.6, 75.1, 76.1, 77.9, 79.0, 84.1, 84.4, 89.8, 93.1, 127.8 (*Ar*), 127.9 (*Ar*), 128.0 (*Ar*), 128.0 (*Ar*), 128.1 (*Ar*), 128.2 (*Ar*), 128.4 (*Ar*), 128.5 (*Ar*), 128.5 (*Ar*), 128.6 (*Ar*), 128.7 (*Ar*), 128.7 (*Ar*), 128.8 (*Ar*), 128.9 (*Ar*), 137.9 (*Ar*), 138.0 (*Ar*), 138.1 (*Ar*), 138.2 (*Ar*), 138.2 (*Ar*), 138.3 (*Ar*), 138.7 (*Ar*) and 138.8 (*Ar*).

5.3.2 Preparation of glycosyl acceptors

Methyl 2,3,4-tri-*O*-benzyl-α-D-mannopyranoside (72)[161]



76 **72**

To a cooled (ice-bath) solution of methyl α-D-mannopyranoside **76** (1.95 g, 10.0 mmol) in pyridine (60 ml) was added *t*-butyldimethylsilyl chloride (2.27 g, 15.0 mmol). The mixture was stirred, with the temperature being allowed to rise slowly to ambient, for 3.5 hr. At this point t.l.c. (MeOH/DCM, 5:95) indicated that all of **76** had been consumed. The reaction mixture was diluted with dichloromethane, washed with aqueous HCl (x2), water (x2), aqueous $NaHCO_3$, water and brine, dried (Na_2SO_4) and concentrated *in vacuo*, co-evaporating repeatedly with toluene. The resulting residue was dissolved in DMF (25 ml), and to this was added benzyl bromide (10.7 ml, 90.0 mmol), followed, portionwise, by sodium hydride (60% w/w suspension in mineral oil, 3.60 g, 90.0 mmol). The mixture was stirred overnight, and the reaction was then quenched with methanol (100 ml). The solution was concentrated *in vacuo*, and the resulting residue was treated with 80% aqueous acetic acid (100 ml) for 20 hr. The mixture was extracted with dichloromethane, and the combined extracts were washed with water (x3), aqueous $NaHCO_3$, water and brine, dried (Na_2SO_4) and concentrated *in*

vacuo. Column chromatography of the resulting residue (EtOAc/hexane, 1:6→1:2) gave methyl tribenzyl mannoside **72** as a syrup (2.55 g, 55%); $[\alpha]_D^{12}$ +37.6 (c 1.49 in $CHCl_3$) {lit.,[161] $[\alpha]_D$ +30 (c 0.49 in $CHCl_3$)}; δ_H(300 MHz; $CDCl_3$; Me_4Si) 3.30 (3 H, s, *Me*O), 3.62 (1 H, m, 5-*H*), 3.73-3.80 (2 H, m, 2-*H* and 6-H_A), 3.84 (1 H, dd, $J_{5,6B}$ 3 $J_{6A,6B}$ 11.5, 6-H_B), 3.90 (1 H, dd, $J_{2,3}$ 3 $J_{3,4}$ 9.5), 3.97 (1 H, m, 4-*H*), 4.63-4.71 (5 H, m, 4 x PhCH_2 and 1-*H*), 4.86 (1 H, d, J_{AB} 12.5, PhCH_2), 4.94 (1 H, d, J_{AB} 11, PhCH_2) and 7.25-7.37 (20 H, m, Ar-*H*); δ_C($CDCl_3$; Me_4Si) 54.8 (*Me*O), 62.5 (*C*-6), 72.1, 72.3 (PhCH$_2$), 73.0 (PhCH$_2$), 74.8, 74.9, 75.2 (PhCH$_2$), 80.3, 99.4 (*C*-1), 127.7 (*Ar*), 127.8 (*Ar*), 127.9 (*Ar*), 128.1 (*Ar*), 128.5 (*Ar*), 138.3 (*Ar*), 138.5 (*Ar*) and 138.6 (*Ar*).

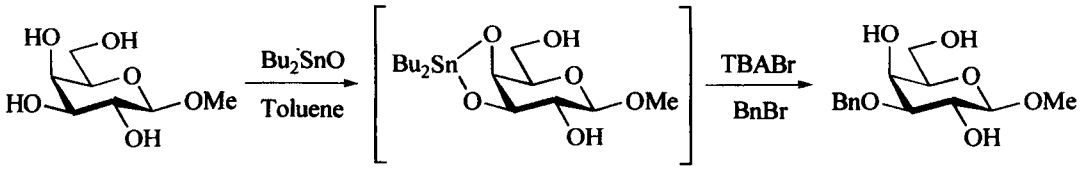
Methyl 2,3,4-tri-*O*-benzoyl-α-D-glucopyranoside[164] (73)

79 **73**

To a cooled (ice-bath) solution of methyl α-D-glucopyranoside **79** (1.94 g, 10.0 mmol) in pyridine (60 ml) was added *t*-butyldimethylsilyl chloride (2.26 g, 15.0 mmol). The mixture was stirred, with the temperature being allowed to rise slowly to ambient, over 4 hr. At this point, t.l.c. (MeOH/DCM, 5:95) indicated that all of **79** had been consumed. The mixture was cooled (ice-bath), a solution of benzoyl chloride (3.85 ml, 33.2 mmol) in chloroform (16.15 ml) was added over 5 min. Stirring was continued overnight before concentrating *in vacuo*, and then co-evaporating with toluene to give a white solid. This solid was dissolved in dichloromethane (400 ml) and washed with aqueous HCl. The organic phase was concentrated *in vacuo* and the resulting residue treated with 80% aqueous acetic acid (100 ml) for 40 hr. The mixture was extracted with dichloromethane (x3), and the combined extracts were washed with ice-cold water (x2), aqueous $NaHCO_3$, water and brine, dried (Na_2SO_4) and concentrated *in vacuo* to give methyl 2,3,4-tribenzoyl glucoside **73** as a white solid (2.90 g, 57%), m.p. 139-141°C (toluene/hexane); $[\alpha]_D^{12}$ +56.1 (c 1.05 in $CHCl_3$) {lit.,[164] m.p. 141-3°C (from C_6H_6/light petroleum); $[\alpha]_D$ +54.5 (c 2 in $CHCl_3$)}; δ_H(300 MHz; $CDCl_3$; Me_4Si) 2.70 (1 H, br, 6-O*H*), 3.47 (3 H, s, *Me*O), 3.74 (1 H, br dd, $J_{5,6A}$ 3.5 $J_{6A,6B}$ 13, 6-H_A), 3.83 (1

H, br d, $J_{6A,6B}$ 13, 6-H_B), 4.05 (1 H, m, 5-*H*), 5.26-5.32 (2 H, m, $J_{1,2}$ 3.5 $J_{2,3}$ 9.5, 1-*H* and 2-*H*), 5.51 (1 H, m, 4-*H*), 6.24 (1 H, m, 3-*H*) and 7.25-7.99 (15 H, m, Ar-*H*); δ_C ($CDCl_3$; Me_4Si) 55.8 (*Me*O), 61.2 (*C*-6), 69.7, 69.9, 70.3, 72.2, 97.3 (*C*-1), 128.5 (*Ar*), 128.7 (*Ar*), 128.7 (*Ar*), 128.8 (*Ar*), 129.3 (*Ar*), 129.4 (*Ar*), 129.9 (*Ar*), 130.1 (*Ar*), 130.2 (*Ar*), 133.4 (*Ar*), 133.6 (*Ar*), 133.9 (*Ar*), 166.1 (2 x *C*=O) and 166.7 (*C*=O).

Methyl 3-*O*-benzyl-β-D-galactopyranoside[170] (85)



81 **85**

Methyl β-D-galactoside **81** (3.88 g, 20.0 mmol) and dibutyl tin oxide (4.98 g, 20.0 mmol) were refluxed in toluene (300 ml) for 10 hr, with azeotropic removal of water. The mixture was allowed to cool to room temperature. TBABr (6.45 g, 20.0 mmol) and benzyl bromide (5.0 ml, 42.0 mmol) were added and the resulting mixture was refluxed for a further 4 hr. The solution was concentrated *in vacuo*, and the resulting residue chromatographed (EtOAc) to give **85** (3.31 g, 58%), m.p. 131-132.5°C (from *i*-PrOH); $[\alpha]_D^{23}$ +0.6 {lit.,[170] m.p. 135-137°C (from *i*-PrOH); $[\alpha]_D$ 0}; δ_H(300 MHz; D_2O; $Me_3SiCD_2CD_2COONa$) 3.51-3.65 (3 H, m, 2-*H*, 3-*H* and 5-*H*), 3.57 (3 H, s, *Me*O), 3.73 (1 H, dd, $J_{5,6A}$ 4.5 $J_{6A,6B}$ 11.75,* 6-H_A), 3.81 (1 H, dd, $J_{5,6B}$ 8† $J_{6A,6B}$ 11.75,* 6-H_B), 4.11 (1 H, d, $J_{3,4}$ 3, 4-*H*), 4.31 (1 H, d, $J_{1,2}$ 7, 1-*H*), 4.65 (1 H, d, J_{AB} 11.5,‡ PhCH_2), 4.77 (1 H, d, J_{AB} 12,‡ PhCH_2) and 7.37-7.53 (5 H, m, Ar-*H*); δ_C(D_2O;

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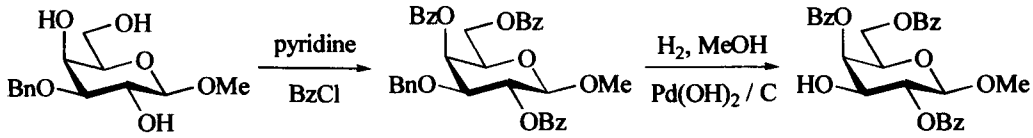
* $J_{6A,6B}$ given as 11.81 at 6-H_A and 11.82 and 11.54 at 6-H_B. Close enough to be within error limits (±0.31 Hz).

† $J_{5,6B}$ given as 7.69 and 7.97 at 6-H_B. Close enough to be within error limits (±0.31 Hz).

‡ J_{AB} given as 11.54 at 4.65 and 11.81 at 4.77. Close enough to be within error limits (±0.31 Hz).

$Me_3SiCD_2CD_2COONa$) 60.1 (*Me*O), 64.0, 68.2, 72.8, 74.1, 78.0, 83.0, 106.8 (*C*-1), 131.4 (*Ar*), 131.7 (*Ar*), 131.8 (*Ar*), and 140.4 (*Ar*).

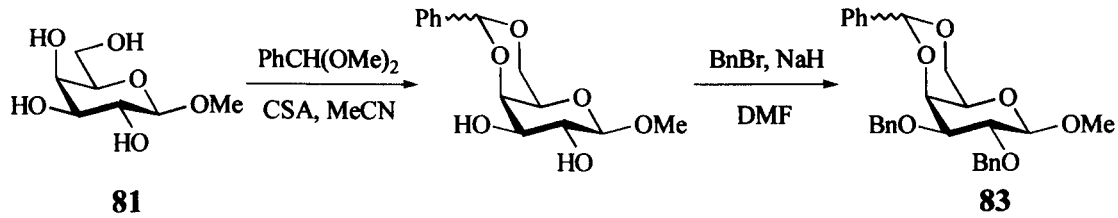
Methyl 2,4,6-tri-*O*-benzoyl-β-D-galactopyranoside[169] (75)



85 **75**

To a cooled (ice-bath) solution of **85** (3.00 g, 10.6 mmol) in pyridine (60 ml) under nitrogen was added a solution of benzoyl chloride (4.25 ml, 36.6 mmol) in chloroform (20 ml). The mixture was stirred for 11 hr, with the temperature being allowed to rise slowly to ambient. The reaction was quenched with methanol (150 ml), and the solution was concentrated *in vacuo*. The resulting residue was dissolved in dichloromethane (500 ml) and this solution was washed with aqueous HCl, water, aqueous $NaHCO_3$, water and brine, dried (Na_2SO_4) and concentrated *in vacuo* to give a crystalline material. This was suspended in methanol (300 ml), and stirred in the presence of palladium hydroxide on carbon (5.00 g) under hydrogen for 5 hr. The solution was filtered through Celite and concentrated *in vacuo* to give 2,4,6-tribenzoate **75** as a syrup (3.02 g, 57%), which precipitated from ether/hexane. $[\alpha]_D$ +4.6 (c 1.08 in $CHCl_3$) {lit.,[169] $[\alpha]_D$ +8.3 (c 1.5 in $CHCl_3$)}; δ_H(300 MHz; $CDCl_3$; $CHCl_3$) 3.57 (3 H, s, *Me*O), 4.12-4.18 (2 H, m, 3-*H* and 5-*H*), 4.43 (1 H, dd, $J_{5,6A}$ 6 $J_{6A,6B}$ 11.5, 6-H_A), 4.61 (1 H, dd, $J_{5,6B}$ 7 $J_{6A,6B}$ 11.5, 6-H_B), 4.65 (1 H, d, $J_{1,2}$ 8, 1-*H*), 5.37 (1 H, dd, $J_{1,2}$ 8 $J_{2,3}$ 10, 2-*H*), 5.78 (1 H, d, $J_{3,4}$ 3.5, 4-*H*) 7.40-7.64 (9 H, m, Ar-*H*) and 8.02-8.17 (6 H, m, Ar-*H*); δ_C($CDCl_3$; $CHCl_3$) 57.3, 62.6, 70.7, 72.1, 73.7, 102.3 (*C*-1), 128.7 (*Ar*), 128.9 (*Ar*), 129.3 (*Ar*), 129.8 (*Ar*), 129.9 (*Ar*), 130.0 (*Ar*), 130.2 (*Ar*), 130.4 (*Ar*), 133.6 (*Ar*), 133.7 (*Ar*), 133.9 (*Ar*), 166.5 (*C*=O), 166.6 (*C*=O) and 167.1 (*C*=O).

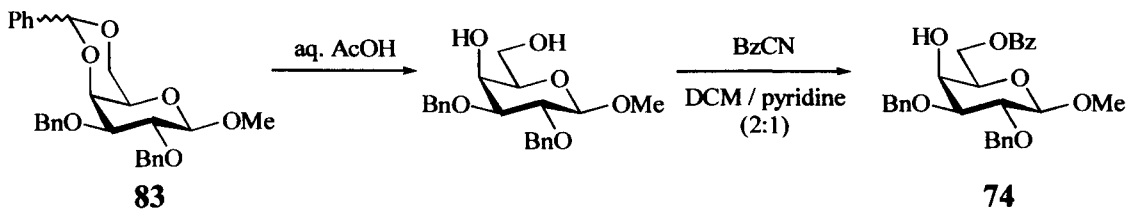
Methyl 2,3-di-*O*-benzyl-4,6-*O*-benzylidene-β-D-galactopyranoside[228] (83)



81 **83**

To a solution of methyl β-D-galactoside **81** (4.85 g, 25.0 mmol) and CSA (581 mg, 2.50 mmol) in acetonitrile (100 ml) under nitrogen was added benzaldehyde dimethyl acetal (4.50 ml, 30.0 mmol). The resulting solution was stirred for 8 hr at room temperature, at which point t.l.c. (MeOH/DCM, 5:95) showed all of **81** had been consumed. Triethylamine (1.40 ml, 10.0 mmol) was added, and stirring was continued for a further 15 min before concentrating *in vacuo*. The residue obtained was dissolved in dichloromethane, and the resulting solution was washed with water and brine, dried (Na_2SO_4), and concentrated *in vacuo*. The resulting residue was dissolved in DMF (75 ml), and cooled (ice bath) under nitrogen. Sodium hydride (60% w/w suspension in mineral oil, 6.10 g, 150 mmol) was added, portionwise, and the mixture was stirred until evolution of hydrogen ceased (15 min). Benzyl bromide (17.85 ml, 153 mmol) was added, and stirring continued at room temperature overnight. The mixture was diluted with ether, washed with water (x2) and brine, dried (Na_2SO_4) and concentrated *in vacuo*. Column chromatography of the resulting residue (EtOAc/hexane, 1:4) gave **83** (6.50 g, 56%), m.p. 120-123°C (from ether/hexane); $[\alpha]_D^{12}$ +51.6 (c 1.01 in $CHCl_3$) {lit.,[228] m.p. 116.8°C (from ether/pentane); $[\alpha]_D$ +47.6 (c 0.5 in $CHCl_3$). lit.,[166] m.p. 130-132°C (from EtOH); $[\alpha]_D$ +50 (c 7 in $CHCl_3$)}; δ_H(300 MHz; $CDCl_3$; Me_4Si) 3.32 (1 H, m, 5-*H*), 3.56 (1 H, dd, $J_{2,3}$ 9.5 $J_{3,4}$ 3.5, 3-*H*), 3.58 (3 H, s, *Me*O), 3.84 (1 H, dd, $J_{1,2}$ 7.5 $J_{2,3}$ 9.5, 2-*H*), 4.02 (1 H, dd, $J_{6A,6B}$ 12.5 $J_{5,6A}$ 2, 6-H_A), 4.11 (1 H, d, $J_{3,4}$ 3.5, 4-*H*), 4.30-4.34 (2 H, m, $J_{1,2}$ 7.5 $J_{5,6B}$ 1.5, 1-*H* and 6-H_B), 4.71-4.81 (3 H, m, PhCH_2), 4.90 (1 H, d, J_{AB} 11, PhCH_2), 5.49 (1 H, s, PhCHO_2) and 7.25-7.57 (15 H, m, Ar-*H*); δ_C($CDCl_3$; Me_4Si) 57.1 (*Me*O), 66.5, 69.3 (CH_2), 72.1 (CH_2), 74.0, 75.3 (CH_2), 78.5, 79.3, 101.4 (CHO_2), 104.8 (CHO_2), 126.6 (*Ar*), 127.6 (*Ar*), 127.7 (*Ar*), 127.8 (*Ar*), 128.1 (*Ar*), 128.2 (*Ar*), 128.3 (*Ar*), 128.4 (*Ar*), 129.0 (*Ar*), 137.9 (*Ar*), 138.5 (*Ar*) and 139.0 (*Ar*).

Methyl 6-*O*-benzoyl-2,3-di-*O*-benzyl-β-D-galactopyranoside[166] (74)

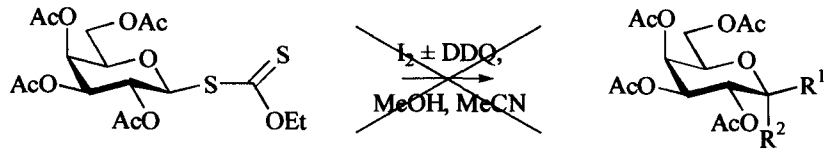


83 **74**

Compound **83** (5.40 g, 11.7 mmol) was treated with 80% v/v aqueous acetic acid (500 ml) at 75-85°C for 3 hr. At this point t.l.c. (EtOAc/hexane, 1:3) indicated that all of **83** had been consumed. The solution was concentrated *in vacuo, and co-evaporated repeatedly with toluene.* The residue obtained was dissolved in a mixture of dichloromethane (80 ml) and pyridine (40 ml), and cooled (ice bath) under nitrogen. Benzoyl cyanide (4.59 g, 35.0 mmol) was added, *and the mixture stirred for 3 hr 50 min.* Methanol was added to quench the reaction, and stirring was continued overnight. The mixture was concentrated *in vacuo* and the residue obtained dissolved *in* dichloromethane *(300 ml). This* was washed with water (x2), aqueous HCl, water, aqueous $NaHCO_3$, water and brine, dried (Na_2SO_4) and concentrated *in vacuo*. Column chromatography of the resulting residue (EtOAc/hexane, *1:3) gave* **74** *(3.53* g, *63%)*, m.p. *124-125°C* (from EtOH); $[\alpha]_D^{23}$ -2.8 (c 1.48 in $CHCl_3$) {lit.[166] m.p. 123-124°C (from aq. EtOH); $[\alpha]_D$ +1.25 ± 1 (c 2 in $CHCl_3$)} {lit.[228] m.p. 120.2°C (from ether/light petroleum); $[\alpha]_D$ -1.63 (c 0.45 in $CHCl_3$)} {lit.[229] m.p. 126°C; $[\alpha]_D$ -6}; δ_H(300 MHz; $CDCl_3$; Me_4Si) 3.53 (1 H, dd, $J_{2,3}$ 9.5 $J_{3,4}$ 3.5, 3-*H*), 3.56 (3 H, s, *Me*O), 3.65 (1 H, dd, $J_{1,2}$ 7.5 $J_{2,3}$ 9.5, 2-*H*), 3.74 (1 H, m, 5-*H*), 3.99 (1 H, d, $J_{3,4}$ 3.5, 4-*H*), 4.30 (1 H, d, $J_{1,2}$ 7.5, 1-*H*), 4.54-4.66 (2 H, m, 6-H_A and 6-H_B), 4.70 (1 H, d, J_{AB} 12, PhCH_2), 4.73 (1 H, d, J_{AB} 11, PhCH_2), 4.76 (1 H, d, J_{AB} 12, PhCH_2), 4.90 (1 H, d, J_{AB} 11, PhCH_2), 7.28-7.61 (13 H, m, Ar-*H*) and 8.03-8.06 (2 H, m, Ar-*H*); δ_C($CDCl_3$; Me_4Si) 57.0 (*Me*O), 63.5, 66.9, 72.0, 72.9, 75.2, 79.0, 80.6, 104.9 (*C*-1), 127.8 (*Ar*), 128.1 (*Ar*), 128.2 (*Ar*), 128.2 (*Ar*), 128.5 (*Ar*), 128.7 (*Ar*), 129.9 (*Ar*), 130.1 (*Ar*), 133.4 (*Ar*), 138.0 (*Ar*), 138.8 (*Ar*) and 166.6 (*C*=O).

5.3.3 Glycosylation protocols

Attempted iodine-promoted glycosylation of methanol with *O*-ethyl *S*-glycosyl xanthate



26

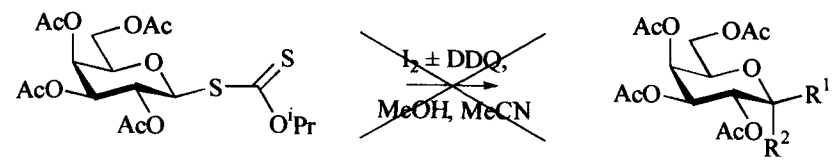
32 R^1 = H, R^2 = OMe
33 R^1 = OMe, R^2 = H

To a solution of **26** (57 mg, 0.13 mmol) in dry acetonitrile (1 ml) was added dry methanol (0.5 ml, 12.3 mmol), and iodine (63.5 mg, 0.25 mmol).The mixture was stirred and monitored by t.l.c. (EtOAc/hexane, 1:1). Over a period of 5 hours, very little change was observed. After leaving 48 hours, significant degradation was observed, t.l.c. giving several charring products.

Attempted iodine/DDQ-promoted glycosylation of methanol with *O*-ethyl *S*-glycosyl xanthate

To a solution of **26** (57 mg, 0.13 mmol) in dry acetonitrile (1 ml) was added dry methanol (0.5 ml, 12.3 mmol), DDQ (57 mg, 0.25 mmol) and iodine (64 mg, 0.25 mmol). The mixture was stirred and monitored by t.l.c. (EtOAc/hexane, 1:1). The starting material was observed to be consumed within 20 minutes, to give a single charring spot product.

Attenpted iodine and iodine/DDQ-promoted glycosylation of methanol with *O*-isopropyl *S*-glycosyl xanthate



31

32 R^1 = H, R^2 = OMe
33 R^1 = OMe, R^2 = H

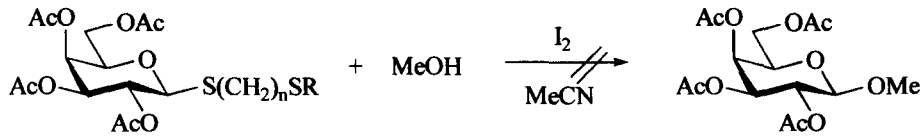
To a solution of xanthate **31** (36 mg, 76 μmol) in dry acetonitrile (1.2 ml) was added dry methanol (0.6 ml, 14.8 mmol). As appropriate, powdered 3Å molecular sieves (100 mg) or anhydrous K_2CO_3 (20 mg, 0.14 mmol) and DDQ (35 mg, 0.15 mmol) were added, followed in all cases by iodine (39 mg, 0.15 mmol). The mixture was stirred and monitored by t.l.c. (EtOAc/hexane, 1:1).

The following combinations were used:

Entry	**Additives**	**Observations**
i)	Iodine	Degradation after 48 hours
ii)	Iodine and K_2CO_3	no consumption of **31** after 48 hours
iii)	Iodine and 3Å MS	no consumption of **31** after 48 hours
iv)	Iodine and DDQ	**31** consumed within 20 min to give single charring spot by t.l.c., which co-eluted with product of similar glycosylation of **26**
v)	Iodine, DDQ and K_2CO_3	no consumption of **31** after 48 hours
vi)	Iodine, DDQ, and 3Å MS	no consumption of **31** after 48 hours

After a scale-up of reaction (iv) to 100 mg (21.4 μmol) of **31**, the mixture was diluted with dichloromethane, washed with aqueous $Na_2S_2O_3$ and water, dried and concentrated *in vacuo*. Column chromatography of the resulting residue (on silica gel-60 prewashed with 2% v/v Et_3N in eluant, EtOAc/hexane, 5:3) gave an amorphous solid (59 mg), which degraded at room temperature and subsequently gave uninterpretable NMR spectra.

Attempted iodine-promoted glycosylation of methanol with acetylated alkylthioalkyl thiogalactopyranosides

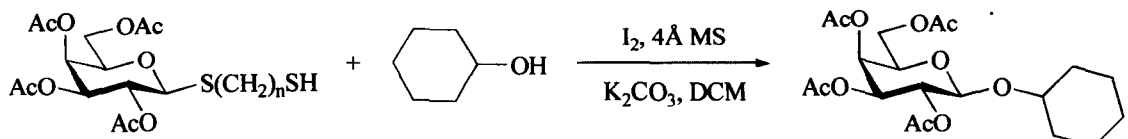


R = Me, n = 1
R = Et, n = 2,3,4 or 5

33

Iodine (64 mg, 0.25 mmol) was added to a stirred solution of the (alkylthioalkyl) 2,3,4,6-tetra-*O*-acetyl-β-D-thiogalactopyranoside (0.130 mmol) in acetonitrile (1 ml) and methanol (0.50 ml) at room temperature. The mixture was stirred for 48 hours.

Iodine-promoted glycosylation of cyclohexanol with acetylated mercaptoalkyl thiogalactoside donors

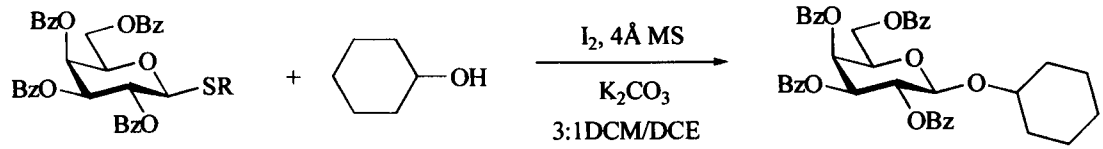


n = 2,3,4 or 5

60

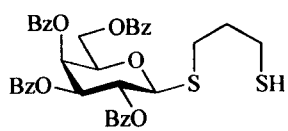
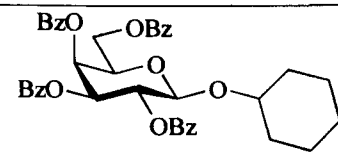
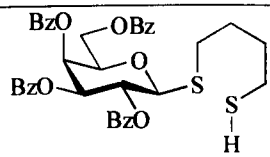
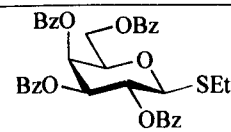
To a solution of the glycosyl donor (0.125 mmol) in DCM (1.5 ml), in the presence of 4Å MS (50 mg) and potassium carbonate (18 mg, 0.130 mmol), was added a 0.202 M solution of cyclohexanol in DCE (0.50 ml, 0.101 mmol). Iodine (64 mg, 0.252 mmol) was added, and the mixture was stirred at room temperature until the reaction, as judged by t.l.c. (EtOAc/hexane, 1:2), was complete or not successful.

Iodine-promoted glycosylation of cyclohexanol with benzoylated thiogalactoside donors

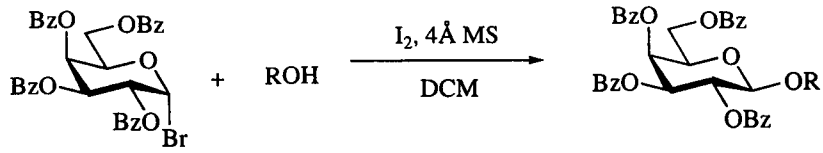


66

To a solution of the glycosyl donor (0.125 mmol) in DCM (1.5 ml), in the presence of 4Å MS (50 mg) and potassium carbonate (18 mg, 0.130 mmol), was added a 0.202 M solution of cyclohexanol in DCE (0.50 ml, 0.101 mmol). Iodine (64 mg, 0.252 mmol) was added, and the mixture was stirred at room temperature until the reaction, as judged by t.l.c. (EtOAc/hexane, 1:2), was complete or apparently not successful. The mixture was diluted with dichloromethane, filtered, washed with aqueous $Na_2S_2O_3$, dried (Na_2SO_4) and concentrated *in vacuo*. The resulting residue was purified by column chromatography (EtOAc/light petroleum, 1:4).

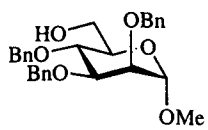
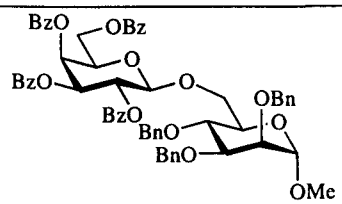
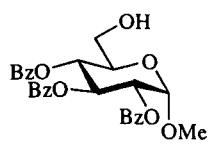
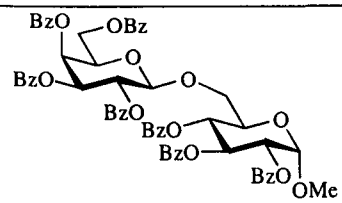
Donor	Product	Yield	α:β
 **64**	 **66**	49 mg (71%)	0:1
 **65**	**66**	41 mg (60%)	0:1
 **69**	no reaction	n/a	n/a

Iodine-promoted glycosylation of carbohydrate acceptors with benzoylbromogalactose

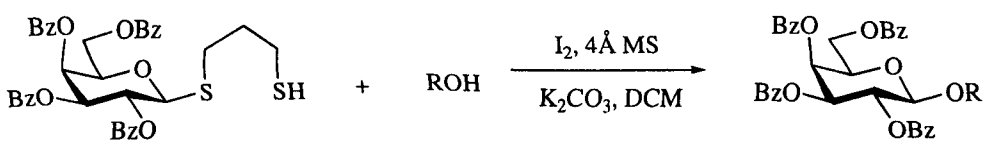


63

To a cooled (ice-bath) solution of bromide **63** (83 mg, 0.125 mmol), acceptor (0.100 mmol) and DDQ (15 mg, 0.661 mmol) in acetonitrile (2 ml) in the presence of 4Å MS (50 mg) was added iodine (64 mg, 0.252 mmol). The resulting suspension was stirred overnight. Collidine (0.20 ml) was added, and the mixture was diluted with dichloromethane, washed with aqueous $Na_2S_2O_3$, HCl, $NaHCO_3$ and water, dried (Na_2SO_4), filtered and concentrated *in vacuo*. Column chromatography of the resulting residue gave disaccharides as summarised below:

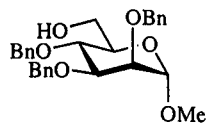
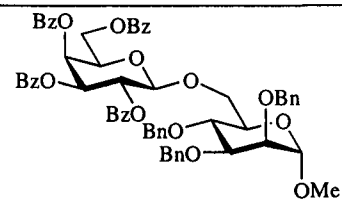
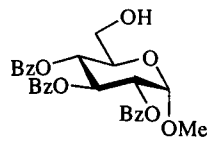
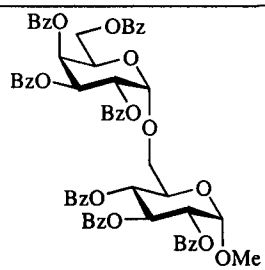
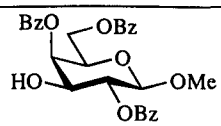
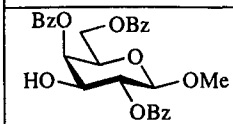
Acceptor	Product	Yield
 **72**	 **86**	89 mg (85%)
 **73**	 **87**	87 mg (80%)

Iodine-promoted glycosylations of carbohydrate acceptors with mercaptopropyl 2,3,4,6-tetra-*O*-benzoyl-β-D-thiogalactoside (64) in the presence of potassium carbonate



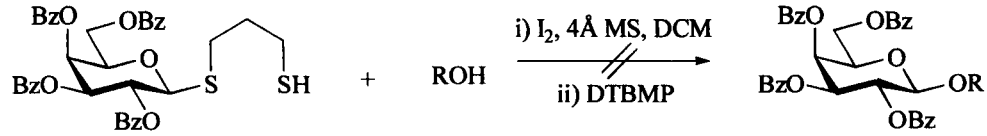
64

To a solution of mercaptopropyl thiogalactopyranoside **64** (86 mg, 0.125 mmol) and acceptor (0.100 mmol) in DCM (2 ml), in the presence of 4Å MS (50 mg) and potassium carbonate (18 mg, 0.130 mmol), was added iodine (64 mg, 0.252 mmol). The mixture was stirred at room temperature until the reaction, as judged by t.l.c. (EtOAc/hexane, 1:2), was complete or apparently not successful. The mixture was diluted with dichloromethane, filtered, washed with aqueous $Na_2S_2O_3$, dried (Na_2SO_4) and concentrated *in vacuo*. Column chromatography of the resulting residue, where reaction occurred, gave disaccharides as summarised below:

Acceptor	Product	Yield
 **72**	 **86**	53 mg* (51%)
 **73**	 **90**	12 mg (11%)
 **74**	n/a	n/a
 **75**	n/a	n/a

* 68.1 mg sample contained approximately 67 mol% **86**. NMR evidence suggested that other products present were derived from the donor, and could possibly be hemiacetal. Yield is based upon this assumption.

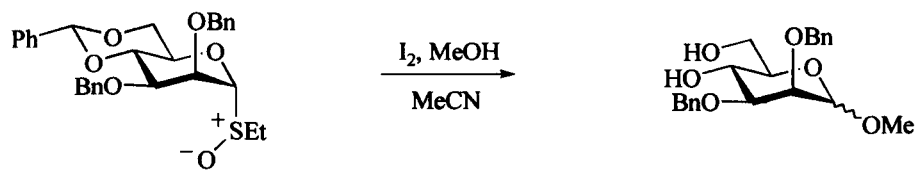
Attempted iodine-promoted glycosylations of carbohydrate acceptors with mercaptopropyl 2,3,4,6-tetra-*O*-benzoyl-β-D-thiogalactoside (64) in the absence of potassium carbonate



64

To a solution of mercaptopropyl thiogalactopyranoside **64** (163 mg, 0.237 mmol) and acceptor (0.190 mmol) in DCM (3 ml), in the presence of 4Å MS (250 mg), was added iodine (120 mg, 0.474 mmol). The mixture was stirred at room temperature for 16.5 hr. 2,6-Di-*tert*-butyl-4-methylpyridine (50 mg, 0.243 mmol) was added, and stirring continued for a further 24 hr.

Iodine-promoted glycosylation of methanol with ethyl 2,3-di-*O*-benzyl-4,6-*O*-benzylidene-1-thio-α-D-mannopyranoside *S*-oxide (104)

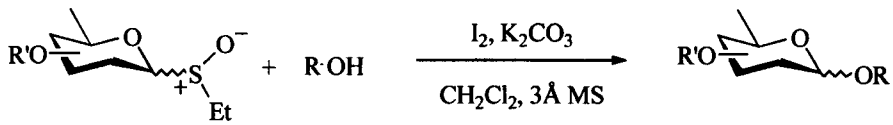


104 **112**

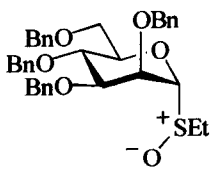
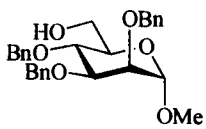
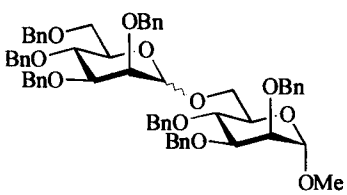
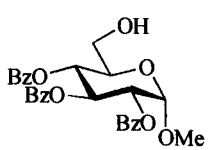
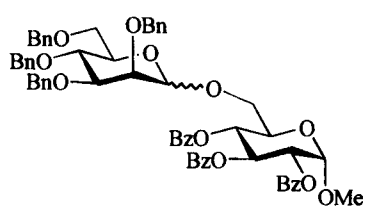
To a stirred solution of sulfoxide **104** (25 mg, 49 μmol) and methanol (100 μl, 2.47 mmol) in acetonitrile (0.4 ml) was added iodine (25 mg, 98 μmol). Stirring was maintained for 24 hr, until t.l.c. indicated that reaction had stopped. The reaction mixture was diluted with dichloromethane, washed with aqueous $Na_2S_2O_3$, aqueous $NaHCO_3$, water and brine, dried (Na_2SO_4), and concentrated *in vacuo*. Column chromatography of the resulting residue (EtOAc/light petroleum, 1:2) gave methyl 2,3-di-*O*-benzyl-D-mannopyranoside[230] **112** as a mixture of anomers (12 mg, 65%, α:β *ca.* 6:1); δ_H(300 MHz; $CHCl_3$; Me_4Si) 3.34 (*Me*O), 3.34 (*Me*O), 3.61 (1 H, m, 5-*H*), 3.70 (1 H, dd, $J_{2,3}$ 9.5 $J_{3,4}$ 3, 3-*H*), 3.80 (1 H, m, 2-*H*), 3.81 (1 H, dd, $J_{5,6A}$ 5 $J_{6A,6B}$ 11.5, 6-H_A), 3.89 (1 H, dd, $J_{5,6B}$ 3.5 $J_{6A,6B}$ 11.5, 6-H_B), 4.03 (1 H, t, $J_{3,4} = J_{4,5}$ 9.5, 4-*H*), 4.46 (1 H, d, J_{AB} 11.5, PhCH_2), 4.60 (1 H, d, J_{AB} 11.5, PhCH_2), 4.75 (1 H, br s, 1-*H*), and 7.27-7.38

(10 H, m, Ar-*H*); δ_C($CHCl_3$, Me_4Si) 55.0 (*Me*O), 63.0, 67.4, 71.7, 72.2, 73.8, 79.8, 99.5 (*C*-1), 127.8 (*Ar*), 127.9 (*Ar*), 128.0 (*Ar*), 128.0 (*Ar*), 128.5 (*Ar*) and 128.7 (*Ar*).

Iodine-promoted glycosylation of carbohydrate acceptors with glycosyl sulfoxides, in the presence of potassium carbonate.



A stirred mixture of sugar acceptor (0.25 mmol), iodine (38 mg, 0.15 mmol), anhydrous potassium carbonate (35 mg, 0.25 mmol) and 3Å molecular sieves (50 mg) in dichloromethane (1 ml) was cooled (ice/water/salt bath, -10 to -5°C) under an inert atmosphere (N_2 or Ar). A solution of glycosyl sulfoxide donor (0.125 mmol) in dichloromethane was injected over 2 to 3 min, and the mixture stirred, monitoring by t.l.c. (EtOAc/hexane, 1:2). If reaction was not complete after 2 hr, the cooling mixture was removed and the reaction allowed to warm to ambient temperature. When it became apparent that reaction was not progressing further, the reaction mixture was filtered through Celite with the aid of dichloromethane (100 ml), washed with aqueous $Na_2S_2O_3$, dried (Na_2SO_4) and concentrated *in vacuo*. Column chromatography of the resulting residue gave disaccharides as summarised below:

Donor	Acceptor	Product	Yield	α:β
 **114**	 **72**	 **116**	46 mg (37 %) (42 hr)	1:3
114	 **73**	 **117**	55 mg (43%) (27 hr)	1:2.6

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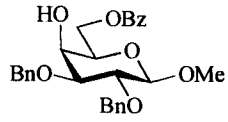
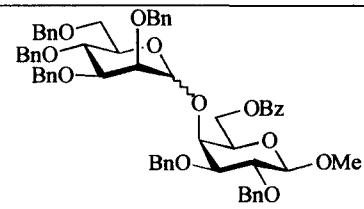
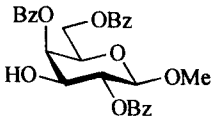
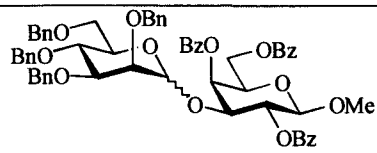
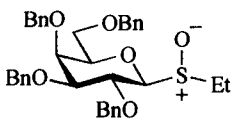
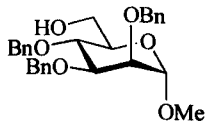
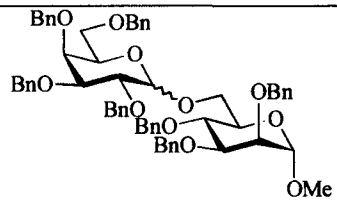
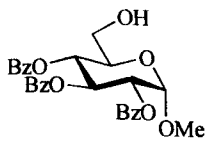
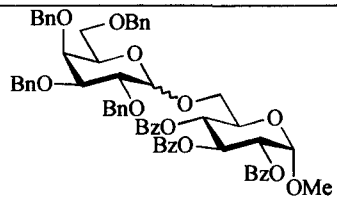
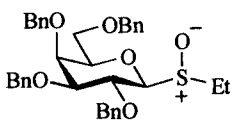
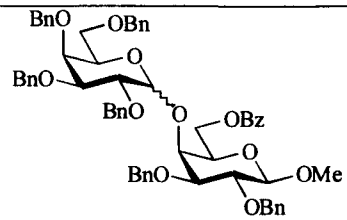
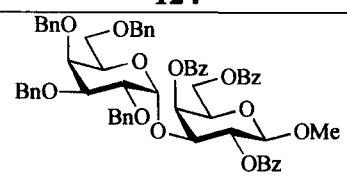
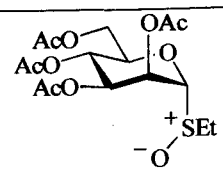
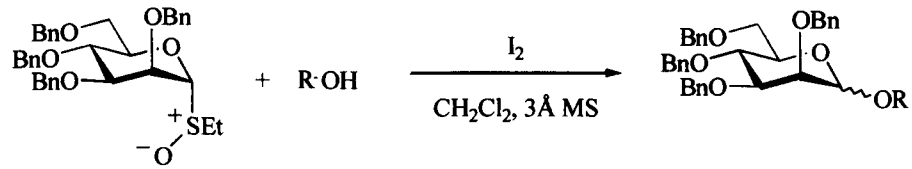
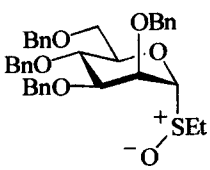
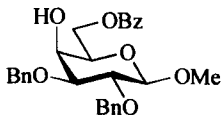
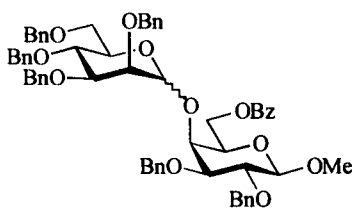
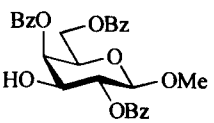
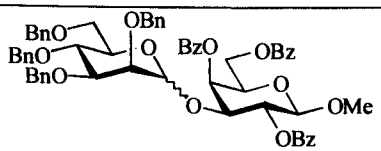
114	 **74**	 **118**	68 mg (55%) (22 hr)	1:6.6
114	 **75**	 **119**	25 mg (19%) (27 hr)	>20:1
 **121**	 **72**	 **122**	63 mg (51 %) (26 hr)	1:1.3
121	 **73**	 **123**	41 mg (32%) (22 hr)	1:1
 **121**	**74**	 **124**	66 mg (53 %) (26 hr)	2.3:1
121	**75**	 **125**	52 mg (40%) (23 hr)	1:0
 **129**	**74**	no consumption of **129** after 24 hr	n/a	n/a

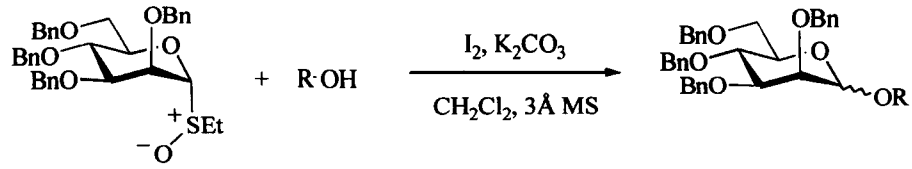
Iodine-Promoted Glycosylation of Carbohydrate Acceptors with Glycosyl Sulfoxides, in the Absence of Potassium Carbonate



A stirred mixture of sulfoxide donor (0.125 mmol), sugar acceptor (0.25 mmol) and 3Å molecular sieves (50 mg) in dichloromethane (1 ml) was cooled (ice/water/salt bath, -5 to -3°C) under an inert atmosphere (N_2 or Ar). Iodine (38 mg, 0.15 mmol) was added, and the mixture was stirred overnight (during this period, the reaction mixture was allowed to warm to ambient temperature). Collidine (0.30 ml, 2.27 mmol) was added, and resulting mixture was stirred for 1 hr, filtered through Celite with the aid of dichloromethane (100 ml), washed with aqueous $Na_2S_2O_3$, dried (Na_2SO_4) and concentrated *in vacuo*. Column chromatography of the resulting residue gave disaccharides as summarised below:

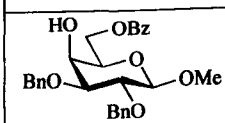
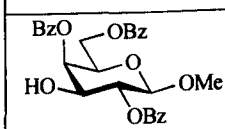
Donor	Acceptor	Product	Yield	α:β
 **114**	 **74**	 **118**	59 mg (47%)	1:4
114	 **75**	 **119**	28 mg (22%)	1:0

Comparisons of Iodine-Promoted Glycosylations of Varying Molar Equivalents of Carbohydrate Acceptors with Sulfoxide Donors



114

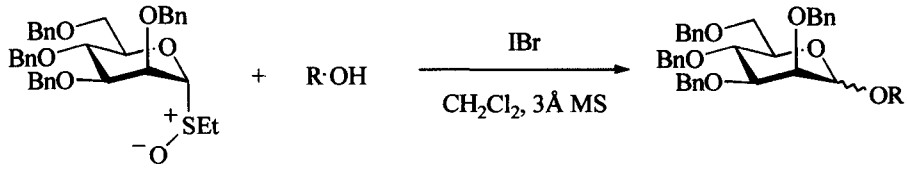
To a solution of sulfoxide **114** (75 mg, 0.125 mmol) and glycosyl acceptor **74** or **75** (0.250 mmol, 0.125 mmol or 0.063 mmol) in dichloromethane was added 3Å MS (50 mg) and potassium carbonate (35 mg, 0.253 mmol). The resulting suspension was cooled (ice bath) under nitrogen, and iodine (38 mg, 0.150 mmol) was added. The reaction mixture was stirred for approximately 1 hour at ice bath temperature. The ice bath was then removed and stirring was allowed to continue until t.l.c. (EtOAc/hexane, 1:3) indicated that the reaction was progressing no further. The mixture was diluted with dichloromethane (100 ml), filtered, washed with aqueous $Na_2S_2O_3$, dried (Na_2SO_4) and concentrated *in vacuo*. Column chromatography of the resulting residue gave disaccharides as shown below:

Acceptor	Donor/ Acceptor	Reaction Time	Yield		α:β
			weight	%	
 **74**	2:1	3.5 hr	28.8 mg	46%[a]	1:6.5
74	1:1	6 hr	45.2 mg	36%[a]	1:6.4
74	1:2	o/n	51.6 mg	41%[b]	1:6
 **75**	2:1	3.75 hr	16.5 mg	26%[a]	7:1
75	1:1	7 hr	21.7 mg	16%[a]	>25:1
75	1:2	o/n	22.6 mg	18%[b]	12.3:1

[a] Yield upon level of acceptor used (donor in excess or equimolar levels used)

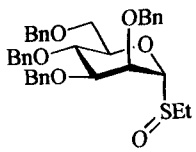
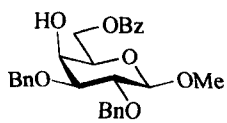
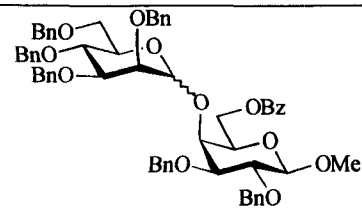
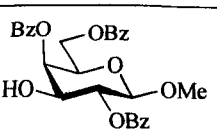
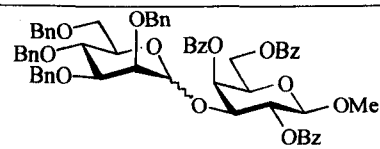
[b] Yield based upon level of sulfoxide used (acceptor in excess)

Iodine Monobromide-Promoted Glycosylation of Carbohydrate Acceptors with Glycosyl Sulfoxides

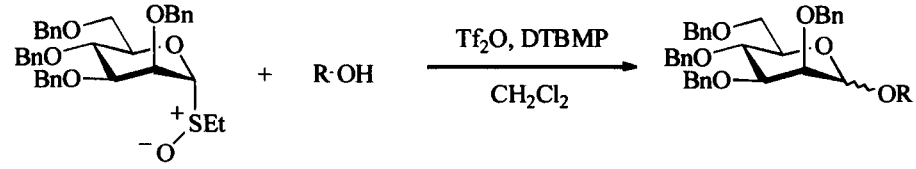


114

A stirred mixture of sulfoxide **114** (0.125 mmol), sugar acceptor (0.25 mmol) and 3Å molecular sieves (50 mg) in dichloromethane (1 ml) was cooled (ice/water/salt bath, -10 to -3°C) under an inert atmosphere (N_2 or Ar). A 1.0 M solution of iodine monobromide in dichloromethane (125 µl, 0.125 mmol) was added, and the mixture was stirred overnight (during this period, the reaction mixture was allowed to warm to ambient temperature). Collidine (0.30 ml, 2.27 mmol) was added, and resulting mixture was stirred for 1 hr, filtered through Celite with the aid of dichloromethane (100 ml), washed with aqueous $Na_2S_2O_3$, dried (Na_2SO_4) and concentrated *in vacuo*. Column chromatography of the resulting residue gave disaccharides as summarised below:

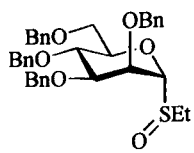
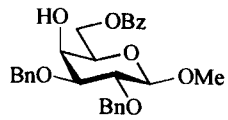
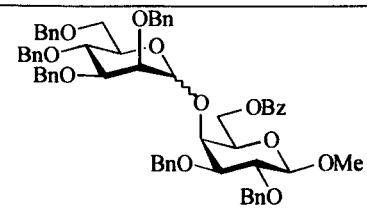
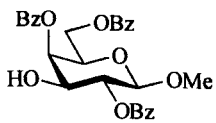
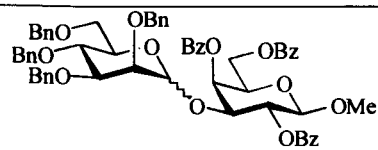
Donor	Acceptor	Product	Yield	α:β
 **114**	 **74**	 **118**	78 mg (62%)	1:2.7
114	 **75**	 **119**	48 mg (37%)	1:0

Triflic Anhydride-Promoted Glycosylations of Carbohydrate Acceptors with Sulfoxide Donors

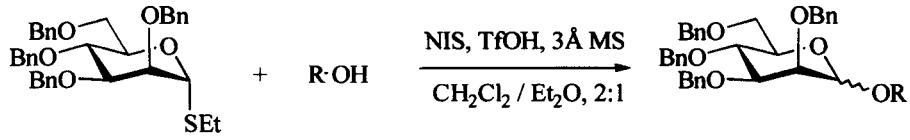


114

To a stirred solution of sulfoxide **114** (0.1 mmol) and DTBMP (41 mg, 0.2 mmol) in dichloromethane (4 ml), under nitrogen, was added a solution of glycosyl acceptor (0.2 mmol) in dichloromethane (1 ml). This was cooled to –78°C (dry ice/ethanol bath), and after 15 minutes triflic anhydride (18.6 µl, 111 µmol) was added. Stirring was continued for 1 hr before allowing to warm to 0°C over a further 1 hr 30 min. The reaction was then quenched by addition of aqueous $NaHCO_3$. The mixture was diluted with dichloromethane, washed with aqueous $NaHCO_3$ and brine, dried (Na_2SO_4) and concentrated *in vacuo*. Column chromatography of the resulting residue gave disaccharides as summarised below:

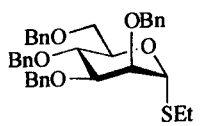
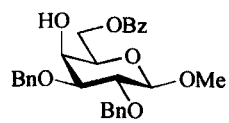
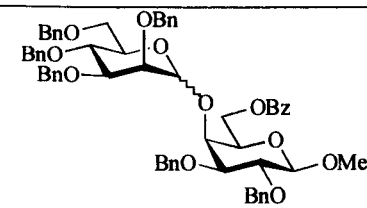
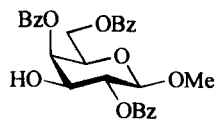
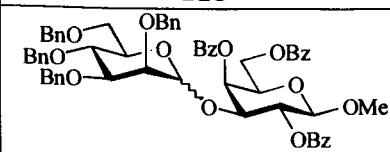
Donor	Acceptor	Product	Yield	α:β
 **114**	 **74**	 **118**	99 mg (79%)	3.1:1
114	 **75**	 **119**	89 mg (69%)	1:0

N-Iodosuccinimide/Triflic Acid-Promoted Glycosylation of Benzylated Thioglycosides

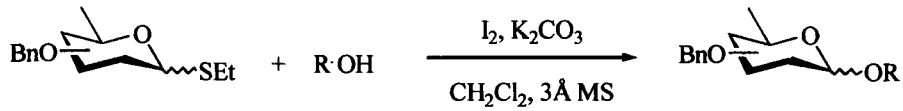


115

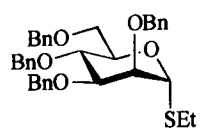
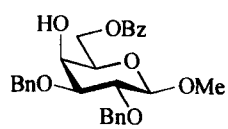
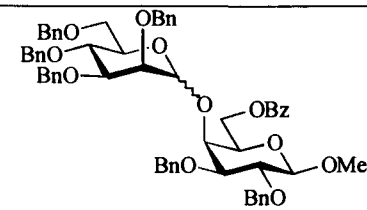
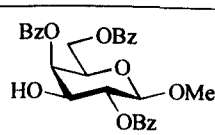
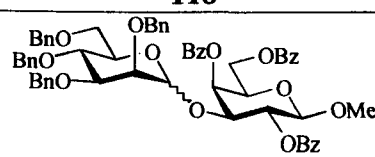
A stirred mixture of thioglycoside **115** (0.125 mmol), acceptor (0.250 mmol) and 3Å MS (50 mg) in dichloromethane (1 ml) was cooled (ice/water/salt bath, -15°C to -10°C) under nitrogen. A solution of triflic anhydride (1.36 µl, 15.4 µmol) and N-iodosuccinamide (33 mg, 0.147 mmol) in 1:1 dichloromethane/ether (2 ml) was added over 5 min. The mixture was stirred until t.l.c. (EtOAc/hexane, 1:3) indicated that all of the donor had been consumed, and then collidine (0.30 ml, 2.27 mmol) was added. The mixture was stirred for 1 hour, filtered through Celite with the aid of dichloromethane (100 ml), washed with aqueous $Na_2S_2O_3$, dried (Na_2SO_4) and concentrated *in vacuo*. Column chromatography of the resulting residue gave disaccharides as summarised below:

Donor	Acceptor	Product	Yield	α:β
 **115**	 **74**	 **118**	98 mg (76%) (20 min)	2.6:1
115	 **75**	 **119**	101 mg (78%) (90 min)	1:0

Iodine-Promoted Glycosylation of Benzylated Thioglycosides



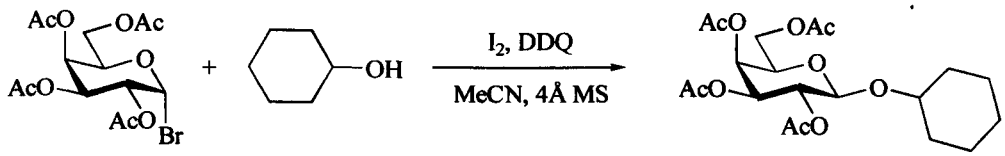
A stirred mixture of acceptor (0.25 mmol), iodine (38 mg, 0.15 mmol), anhydrous potassium carbonate (35 mg, 0.25 mmol) and 3A molecular sieves (50 mg) in dichloromethane (1 ml) was cooled (ice/water/salt bath, -5 to -10°C) under an inert atmosphere (N_2 or Ar). A solution of thioglycoside (0.125 mmol) in dichloromethane was injected over 2 to 3 min, and the mixture stirred, monitoring by t.l.c. (EtOAc/hexane, 1:2): After 2 hr, the cooling mixture was removed and the stirring was continued overnight. The reaction mixture was filtered through Celite with the aid of dichloromethane (100 ml), washed with aqueous $Na_2S_2O_3$, dried (Na_2SO_4) and concentrated *in vacuo*. Column chromatography of the resulting residue gave disaccharides as summarised below:

Donor	Acceptor	Product	Yield	α:β
 **115**	 **74**	 **118**	84 mg (67%)	1:7
115	 **75**	 ***119***	35 mg (28%)	1:0

5.3.4 Glycosylation products

Full assignment of ^{1}H NMR spectra for disaccharide products obtained from glycosylation reactions was not deemed necessary for the purposes of identifying the ratio of α- and β-anomers in the products, although in some cases many peaks were identified. In the case of disaccharides derived from mannosyl donors, assignment of the configuration of the major anomer was made based upon the anomeric $J_{C,H}$ coupling constant, obtained from undecoupled ^{13}C spectra. In the case of disaccharides derived from galactosyl donors, assignment of the configuration of the major anomer was aided, where necessary, by the use of undecoupled ^{13}C and HSQC experiments. The ratio of the two diastereomeric products formed was identified using suitable peaks derived from the glycosyl acceptor.

Cyclohexyl 2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranoside[158] (60)

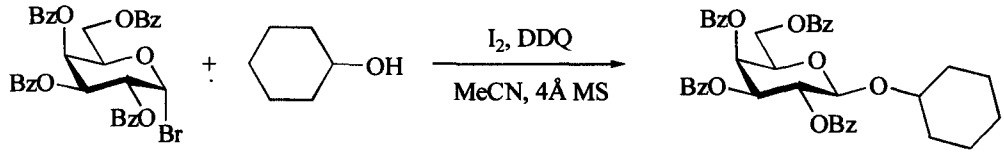


42 **60**

To a cooled (ice-bath) solution of bromide **42** (411 mg, 1.00 mmol), cyclohexanol (225 mg, 2.25 mmol), and DDQ (114 mg, 0.50 mmol) in acetonitrile (4.1 ml), in the presence of 4Å MS (411 mg), was added iodine (254 mg, 1.00 mmol). This mixture was stirred for 2 hr 45 min, at which point t.l.c. indicated that all of **42** had been consumed, and then quenched with collidine (1.00 ml). The mixture was diluted with dichloromethane (100 ml), and the resulting solution was washed successively with aqueous solutions of $Na_2S_2O_3$, HCl and $NaHCO_3$, and water, dried (Na_2SO_4) and concentrated *in vacuo*. Column chromatography of the resulting residue (EtOAc/hexane, 1:3) afforded cyclohexyl 2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranoside **60** (310 mg, 75%); $[\alpha]_D^{25}$ -9.8 (c 1.62 in $CHCl_3$) {lit.,[158] $[\alpha]_D^{20}$ -12.8 (c 0.5)}; δ_H (300 MHz; $CDCl_3$; $CHCl_3$) 1.20-1.92 (10 H, m), 1.99 (3 H, s, *Me*CO), 2.05 (3 H, s, *Me*CO), 2.05 (3 H, s, *Me*CO), 2.15 (3 H, s, *Me*CO), 3.62 (1 H, m, 1-*H*), 3.89 (1 H, m, 5-*H'*), 4.11 (1 H, dd, $J_{5,6A}$ 7 $J_{6A,6B}$ 11, 6-H_A'), 4.20 (1 H, dd, $J_{5,6B}$ 6.5 $J_{6A,6B}$ 11, 6-H_B'), 4.54 (1 H, d, $J_{1,2}$ 8, 1-*H'*), 5.02 (1 H, dd,

$J_{2,3}$ 10.5 $J_{3,4}$ 3.5, 3-*H*'), 5.19 (1 H, dd, $J_{1,2}$ 8 $J_{2,3}$ 10.5, 2-*H*') and 5.38 (1 H, dd, $J_{3,4}$ 3.5 $J_{4,5}$ 1, 4-*H*); δ_C ($CDCl_3$; $CHCl_3$) 20.7 (*Me*CO), 20.8 (*Me*CO), 20.8 (*Me*CO), 20.9 (*Me*CO), 23.7 (CH_2), 23.9 (CH_2), 25.6 (CH_2), 31.8 (CH_2), 33.4 (CH_2), 61.5, 67.3, 69.3, 70.7, 71.3, 78.4, 100.3 (*C*-1'), 169.7 (*C*=O), 170.6 (*C*=O), 170.7 (*C*=O) and 170.8 (*C*=O); *m/z* (MALDI-TOF) 453 ($M + K^+$).

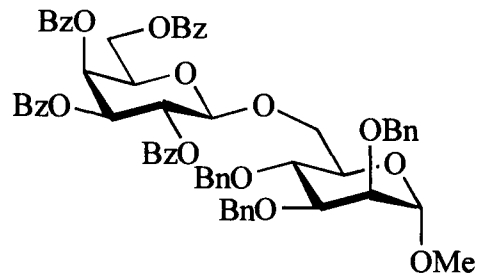
Cyclohexyl 2,3,4,6-tetra-*O*-benzoyl-β-D-galactopyranoside (66)



63 **66**

To a cooled (ice-bath) solution of bromide **63** (330 mg, 0.50 mmol), cyclohexanol (120 mg, 1.20 mmol), and DDQ (57 mg, 0.25 mmol) in acetonitrile (2.5 ml), in the presence of 4Å MS (330 mg), was added iodine (140 mg, 0.55 mmol). This mixture was stirred until t.l.c. indicated that all of **63** had been consumed (3 hr), and then quenched with collidine (0.50 ml). The mixture was diluted with ethyl acetate (100 ml), and the resulting solution was washed successively with aqueous solutions of $Na_2S_2O_3$, HCl and $NaHCO_3$, and water, dried (Na_2SO_4) and concentrated *in vacuo*. Column chromatography of the resulting residue (EtOAc/light petroleum, 1:4) afforded cyclohexyl 2,3,4,6-tetra-*O*-benzoyl-β-D-galactopyranoside **66** (239.4 mg, 71%); $[\alpha]_D^{22}$ +93.6 (c 1.13 in $CHCl_3$); (Found C, 70.5; H, 6.0. $C_{40}H_{38}O_{10}$ requires C, 70.8; H 5.6%); δ_H (300 MHz; $CDCl_3$; $CHCl_3$) 1.08-1.36 (4 H, m), 1.40-1.96 (6 H, m), 3.70 (1 H, m, 1-*H*), 4.32 (1 H, td, $J_{5,6A} = J_{5,6B}$ 6.5 $J_{4,5}$ 1, 5-*H*'), 4.44 (1 H, dd, $J_{5,6A}$ 6.5 $J_{6A,6B}$ 11, 6-H_A'), 4.69 (1 H, dd, $J_{5,6B}$ 6.5 $J_{6A,6B}$ 11, 6-H_B'), 4.92 (1 H, d, $J_{1,2}$ 8, 1-*H*'), 5.61 (1 H, dd, $J_{2,3}$ 10.5 $J_{3,4}$ 3.5, 3-*H*'), 5.79 (1 H, dd, $J_{1,2}$ 8 $J_{2,3}$ 10.5, 2-*H*'), 5.99 (1 H, dd, $J_{3,4}$ 3.5 $J_{4,5}$ 1, 4-*H*') and 7.21-8.14 (20 H, m, Ar-*H*); δ_C ($CDCl_3$; $CHCl_3$) 23.8 (CH_2), 24.0 (CH_2), 25.5 (CH_2), 31.9 (CH_2), 33.5 (CH_2), 62.3, 66.0, 68.4, 70.2, 71.4, 72.1, 79.0, 100.6 (*C*-1'), 128.6 (*Ar*), 128.6 (*Ar*), 128.7 (*Ar*), 128.9 (*Ar*), 129.2 (*Ar*), 129.4 (*Ar*), 129.8 (*Ar*), 129.9 (*Ar*), 130.1 (*Ar*), 130.1 (*Ar*), 133.4 (*Ar*), 133.5 (*Ar*), 133.5 (*Ar*), 133.8 (*Ar*), 165.6 (*C*=O), 166.0 (*C*=O), 166.1 (*C*=O) and 166.4 (*C*=O); *m/z* (MALDI-TOF) 701 ($M + Na^+$).

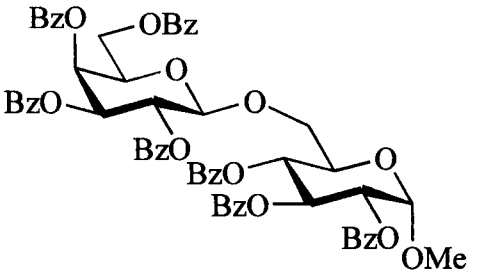
Methyl 2,3,4-tri-*O*-benzyl-6-*O*-(2,3,4,6-tetra-*O*-benzoyl-β-D-galactopyranosyl)-(1→6)-α-D-mannopyranoside (86)



86

Purification by silica gel chromatography (EtOAc/light petroleum, 1:3) afforded β-galactopyranosyl mannopyranoside **86**; $[\alpha]_D^{22}$ +66.0 (c 1.31 in $CHCl_3$); δ_H (300 MHz; $CDCl_3$; Me_4Si) 2.99 (3 H, s, *Me*O), 3.64-3.72 (2 H, m), 3.73-3.82 (3 H, m), 4.28 (1 H, m, 4-*H*), 4.30 (1 H, m, 5-*H'*), 4.40 (1 H, dd, $J_{5,6}$ 7 $J_{6A,6B}$ 11, 6-H_A'), 4.46 (1 H, d, J_{AB} 11, PhCH_2), 4.50 (1 H, d, $J_{1,2}$ 2, 1-*H*), 4.52 (2 H, s, PhCH_2), 4.65 (2 H, s, PhCH_2), 4.69 (1 H, dd, $J_{5,6B}$ 6 $J_{6A,6B}$ 11, 6-H_B'), 4.76 (1 H, d, J_{AB} 11, PhCH_2), 4.92 (1 H, d, $J_{1,2}$ 8, 1-*H'*), 5.60 (1 H, dd, $J_{2,3}$ 10.5 $J_{3,4}$ 3.5, 3-*H'*), 5.85 (1 H, dd, $J_{1,2}$ 8 $J_{2,3}$ 10.5, 2-*H'*), 5.99 (1 H, dd, $J_{3,4}$ 3.5 $J_{4,5}$ 1, 4-*H'*) and 7.19-8.12 (35 H, m, Ar-*H*); δ_C ($CDCl_3$; Me_4Si) 54.4 (*Me*O) 62.1, 68.3, 70.0, 70.0, 71.3, 71.4, 71.9, 72.1, 72.8, 74.5, 75.0, 75.2, 80.4, 89.4, 98.8 (*C*-1), 102.4 (*C*-1'), 127.7 (*Ar*), 127.7 (*Ar*), 127.8 (*Ar*), 127.9 (*Ar*), 128.1 (*Ar*), 128.4 (*Ar*), 128.5 (*Ar*), 128.5 (*Ar*), 128.5 (*Ar*), 128.7 (*Ar*), 128.8 (*Ar*), 129.0 (*Ar*), 129.3 (*Ar*), 129.7 (*Ar*), 129.8 (*Ar*), 130.0 (*Ar*), 130.3 (*Ar*), 133.2 (*Ar*), 133.4 (*Ar*), 133.7 (*Ar*), 138.5 (2 x *Ar*), 138.6 (*Ar*), 138.7 (*Ar*), 165.5 (*C*=O), 165.9 (2 x *C*=O) and 166.3 (*C*=O); *m/z* (MALDI-TOF) 1065 ($M + Na^+$).

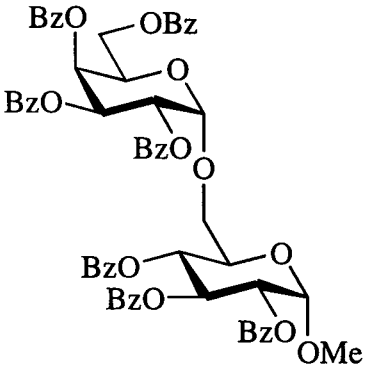
Methyl 2,3,4-tri-*O*-benzoyl-6-*O*-(2,3,4,6-tetra-*O*-benzoyl-β-D-galactopyranosyl)-(1→6)-α-D-glucopyranoside (87)



87

Purification by silica gel chromatography (EtOAc/light petroleum, 1:3) afforded β-galactopyranosyl glucopyranoside **87**; $[\alpha]_D^{22}$ +81.9 (c 1.4 in $CHCl_3$); {lit.[231] $[\alpha]_D^{20}$ +78.1 (c 1.0 in $CHCl_3$)}; δ_H (300 MHz; $CDCl_3$; $CHCl_3$) 3.11 (3 H, s, *Me*O), 3.80 (1 H, dd, $J_{5,6A}$ 7.5 $J_{6A,6B}$ 11, 6-H_A), 4.17 (1 H, dd, $J_{5,6B}$ 2 $J_{6A,6B}$ 11.5, 6-H_B), 4.26 (1 H, m, 5-*H*), 4.31 (1 H, m, 5-*H'*), 4.41 (1 H, dd, $J_{5,6A}$ 7 $J_{6A,6B}$ 11, 6-H_A'), 4.61 (1 H, dd, $J_{5,6B}$ 6.5 $J_{6A,6B}$ 11, 6-H_B'), 4.92 (1 H, d, $J_{1,2}$ 3.5 1-*H*), 4.95 (1 H, d, $J_{1,2}$ 8, 1-*H'*), 5.07 (1 H, dd, $J_{1,2}$ 3.5 $J_{2,3}$ 10.5, 2-*H*), 5.33 (1 H, m, 3-*H*), 5.63 (1 H, dd, $J_{2,3}$ 10.5 $J_{3,4}$ 3.5, 3-*H'*), 5.84 (1 H, dd, $J_{1,2}$ 2.5 $J_{2,3}$ 2-*H'*), 5.99 (1 H, dd, $J_{3,4}$ 3.5 J 4,5 1, 4-*H'*), 6.08 (1 H, t, $J_{3,4} = J_{4,5}$ 10, 3-*H*) and 7.20-8.09 (35 H, m, Ar-*H*); δ_C ($CDCl_3$; $CHCl_3$) 55.2 (*Me*O), 62.0, 68.3, 68.9, 69.4, 69.8, 70.0, 70,6, 71.6, 71.8, 72.2, 96.7 (*C*-1), 102.5 (*C*-1'), 128.5 (*Ar*), 128.6 (*Ar*), 128.7 (*Ar*), 128.7 (*Ar*), 128.8 (*Ar*), 128.9 (*Ar*), 129.1 (*Ar*), 129.3 (*Ar*), 129.4 (*Ar*), 129.5 (*Ar*), 129.7 (*Ar*), 129.7 (*Ar*), 129.9 (*Ar*), 130.1 (*Ar*), 130.1 (*Ar*), 130.2 (*Ar*), 130.3 (*Ar*), 133.3 (*Ar*), 133.5 (*Ar*), 133.6 (*Ar*), 133.6 (*Ar*), 133.6 (*Ar*), 133.8 (*Ar*), 133.8 (*Ar*), 165.7 (*C*=O), 165.8 (*C*=O), 165.9 (*C*=O), 165.9 (*C*=O), 166.0 (*C*=O), 166.0 (*C*=O) and 166.3 (*C*=O); *m/z* (MALDI-TOF) 1107 ($M + Na^+$).

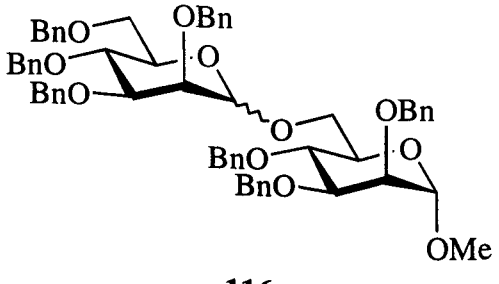
Methyl 2,3,4-tri-*O*-benzoyl-6-*O*-(2,3,4,6-tetra-*O*-benzoyl-α-D-galactopyranosyl)-(1→6)-α-D-glucopyranoside (90)



90

Purification by silica gel chromatography (EtOAc/light petroleum, 1:3) afforded α-disaccharide **90**; δ_H (300 MHz; $CDCl_3$; $CHCl_3$) 3.44 (3 H, s, *Me*O), 3.68 (1 H, dd, 6-H_A), 4.0 (1 H, dd, $J_{5,6B}$ 6 $J_{6A,6B}$ 11, 6-H_B), 4.22 (1 H, m, 5-*H*), 4.37-4.50 (2 H, m, 6-H_A' and 6-H_B'), 4.74 (1 H, m, 5-*H*'), 4.93 (1 H, dd, $J_{1,2}$ 3.5 $J_{2,3}$ 10, 2-*H*), 5.09 (1 H, d, $J_{1,2}$ 3.5, 1-*H*), 5.47 (1 H, m, 4-*H*), 5.49 (1 H, d, $J_{1,2}$ 3.5, 1-*H*'), 5.72 (1 H, m, 3-*H*'), 6.02-6.11 (3 H, m, 3-*H* 2-*H*' and 4-*H*') and 7.19-8.11 (35 H, m, Ar-*H*); δ_C ($CDCl_3$; $CHCl_3$) 55.8 (*Me*O) 56.9, 63.0, 63.6, 66.3, 66.9, 67.5, 67.9, 68.8, 69.3, 70.1, 70.7, 71.0, 72.3, 96.8, 97.0, 128.5 (*Ar*), 128.7 (*Ar*), 128.8 (*Ar*), 128.9 (*Ar*), 129.1 (*Ar*), 129.4 (*Ar*), 129.5 (*Ar*), 130.0 (*Ar*), 130.0 (*Ar*), 130.1 (*Ar*), 130.2 (*Ar*), 133.3 (*Ar*), 133.4 (*Ar*), 133.5 (*Ar*), 133.7 (*Ar*), 133.8 (*Ar*), 165.5 (*C*=O), 165.8 (*C*=O), 165.8 (*C*=O), 165.9 (*C*=O), 166.1 (*C*=O), 166.2 (*C*=O) and 166.4 (*C*=O); *m/z* (MALDI-TOF) 1107 ($M + Na^+$).

Methyl 2,3,4-tri-*O*-benzyl-6-*O*-(2,3,4,6-tetra-*O*-benzyl-D-mannopyranosyl)-(1→6)-α-D-mannopyranoside[232] (116)



116

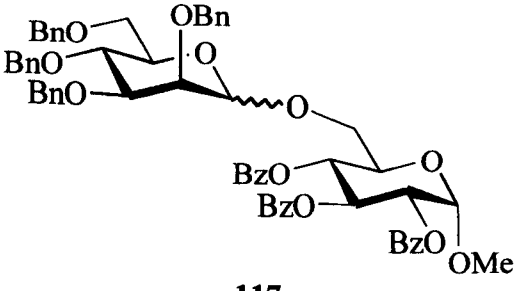
Column chromatography (EtOAc/hexane, 1:6) afforded mannosyl mannopyranoside **116** as a mixture of α- and β- anomers; *m/z* (MALDI-TOF) 1009 ($M + Na^+$).

116β: δ_H(300 MHz; $CDCl_3$, Me_4Si) 3.27 (*Me*O); δ_C($CDCl_3$; $CHCl_3$) 54.8 (*Me*O), 69.2 (*C*H_2), 69.9 (*C*H_2), 72.2 (*C*H_2), 72.9 (*C*H_2), 73.6, 73.7 (*C*H_2), 73.8 (*C*H_2), 74.7, 75.0, 75.1 (*C*H_2), 75.2, 75.4 (*C*H_2), 76.2, 77.0, 77.1 (*C*H_2), 81.8, 82.3, 99.1 (J_{CH} 166 *C*-1), 102.4 (J_{CH} 155, *C*-1'), 138.5, 138.5, 138.7, 138.8, 138.8, 138.9 and 139.2.

116α: δ_H(300 MHz; $CDCl_3$, Me_4Si) 3.24 (*Me*O); δ_C(*CDCl*$_3$; *CHCl*$_3$) 54.8 (*Me*O), 71.5, 71.6 (*C*H_2), 72.1 (*C*H_2), 72.6 (*C*H_2), 73.1 (*C*H_2), 73.5 (*C*H_2), 73.7 (*C*H_2), 74.7, 74.8, 75.2, 75.2 (*C*H_2), 77.1 (*C*H_2), 98.4 (*C*-1'), 99.2 (*C*-1), 138.6, 139.0 and 139.1.

δ_C (unassigned) 127.6 (*Ar*), 127.7 (*Ar*), 127.8 (*Ar*), 127.8 (*Ar*), 127.9 (*Ar*), 127.9 (*Ar*), 127.9 (*Ar*), 127.9 (*Ar*), 128.0 (*Ar*), 128.1 (*Ar*), 128.1 (*Ar*), 128.2 (*Ar*), 128.2 (*Ar*), 128.2 (*Ar*), 128.3 (*Ar*), 128.3 (*Ar*), 128.4 (*Ar*), 128.4 (*Ar*), 128.4 (*Ar*), 128.5 (*Ar*), 128.5 (*Ar*), 128.6 (*Ar*), 128.6 (*Ar*), 128.7 (*Ar*), 128.7 (*Ar*), 128.7 (*Ar*), 128.8 (*Ar*) and 128.8 (*Ar*).

Methyl 2,3,4-tri-*O*-benzoyl-6-*O*-(2,3,4,6-tetra-*O*-benzyl-D-mannopyranosyl)-(1→6)-α-D-glucopyranoside (117)



117

Purification by silica gel chromatography (EtOAc/hexane, 1:6) afforded mannosyl glucopyranoside **117** as a mixture of α- and β- anomers; *m/z* (MALDI-TOF) 1051 ($M + Na^+$).

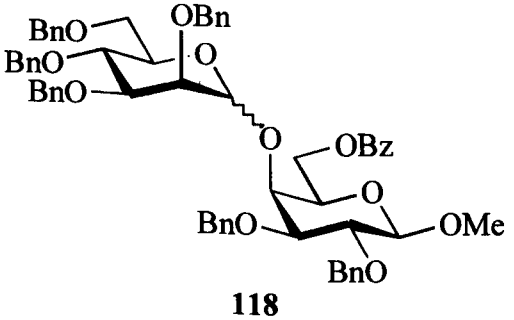
117β: δ_H(300 MHz; $CDCl_3$, Me_4Si) 3.40 (1 H, m, 5-*H*'), 3.44 (3 H, s, *Me*O), 3.50 (1 H, dd, $J_{2,3}$ 3 $J_{3,4}$ 9, 3-*H*'), 3.60-3.71 (3 H, m, 6-H_A, 6-H_A', 6-H_B'), 3.89 (1 H, t, $J_{3,4} = J_{4,5}$ 9, 4-*H*'), 4.05 (1 H, d, $J_{2,3}$ 3, 2-*H*'), 4.19 (1 H, m, 6-H_B), 4.32 (1 H, m, 5-*H*), 4.72 (1 H, d, $J_{1,2}$

5 1-*H'*), 5.25-5.29 (2 H, m, 1-*H* and 2-*H*), 6.17 (1 H, m, 3-*H*); δ_C($CDCl_3$; $CHCl_3$) 55,6 (*Me*O), 68.8, 69.1, 69.6, 69.7, 70.8, 71.6, 72.4, 73.6, 74.1, 74.3, 74.9, 75.3, 76.2, 82.4, 97.1 (J_{CH} 170, C-1) 102.5 (J_{CH} 156, C-1'), 165.8 (*C*=O), 166.1 (*C*=O) and 166.2 (*C*=O).

117α: δ_H(300 MHz; $CDCl_3$, Me_4Si) 3.39 (3 H, s, *Me*O), 3.56 (1 H, m, 2-*H'*), 3.60-3.71 (4 H, m, 3-*H'*, 6-H_A, 6-H_A', 6-H_B'), 3.87 (1 H, m, 5-*H*), 3.95 (1 H, m, 4-*H*), 4.15 (1 H, m, 5-*H*), 4.19 (1 H, m, 6-H_B), 5.17 (1 H, d, $J_{1,2}$ 3.5, 1-*H*), 5.20-5.26 (1 H, m, 2-*H*), 5.57 (1 H, m, 4-*H*) 6.12 (1 H, m, 3-*H*); δ_C($CDCl_3$; $CHCl_3$) 55.7 (*Me*O), 60.6, 66.4, 68.3, 69.2, 70.0, 72.2, 72.4, 72.4, 72.8, 73.4, 75.0, 75.0, 75.2, 81.4, 97.2 (J_{CH} 170, *C*-1), 98.5 (*C*-1'), 165.5 (*C*=O) and 166.2 (*C*=O).

δ_C (unassigned) 127.7 (*Ar*), 127.7 (*Ar*), 127.8 (*Ar*), 127.9 (*Ar*), 127.9 (*Ar*), 128.0 (*Ar*), 128.1 (*Ar*), 128.1 (*Ar*), 128.2 (*Ar*), 128.4 (*Ar*), 128.5 (*Ar*), 128.5 (*Ar*), 128.6 (*Ar*), 128.6 (*Ar*), 128.6 (*Ar*), 128.7 (*Ar*), 128.7 (*Ar*), 128.7 (*Ar*), 129.2 (*Ar*), 129.5 (*Ar*), 129.6 (*Ar*), 130.0 (*Ar*), 130.1 (*Ar*), 130.2 (*Ar*), 130.2 (*Ar*), 133.4 (*Ar*), 133.5 (*Ar*), 133.7 (*Ar*), 133.7 (*Ar*), 138.5 (*Ar*), 138.7 (*Ar*), 138.7 (*Ar*), 138.8 (*Ar*), 138.9 (*Ar*), 139.0 (*Ar*) and 139.2 (*Ar*).

Methyl 6-*O*-benzoyl-2,3-di-*O*-benzyl-4-*O*-(2,3,4,6-tetra-*O*-benzyl-D-mannopyranosyl)-(1→4)-β-D-galactopyranoside (118)



118

Purification by silica gel chromatography (EtOAc/hexane, 1:6 or EtOAc/toluene, 1:30) afforded **118** as a mixture of α- and β-anomers; *m/z* (MALDI-TOF) 1024 ($M + Na^+$).

118β: δ_H(500 MHz; $CDCl_3$; Me_4Si) 3.36 (1 H, dd, $J_{2,3}$ 3 $J_{3,4}$ 9.5, 3-*H'*), 3.36 (1 H, m, 5-*H'*), 3.52 (1 H, dd, $J_{2,3}$ 9.5 $J_{3,4}$ 3*, 3-*H*), 3.58 (3 H, s, *Me*O), 3.68-3.78 (4 H, m, 2-*H*, and 5-*H*, 6-H_A', 6-H_B'), 3.88 (1 H, m, 4-*H'*), 3.99 (1 H, d, $J_{2,3}$ 3, 2-*H'*), 4.16 (1 H, d, $J_{3,4}$ 2*, 4-*H'*), 4.29 (1 H, d, $J_{1,2}$ 7.5, 1-*H*), 4.36 (1 H, d, J_{AB} 11.5, PhCH_2), 4.48 (1 H, d, J_{AB} 11.5, PhCH_2), 4.49 (1 H, d, J_{AB} 12, PhCH_2), 4.54 (1 H, d, J_{AB} 10.5, PhCH_2), 4.58 (1 H, dd, $J_{5,6A}$ 7.5, $J_{6A,6B}$ 12, 6-H_A), 4.61 (1 H, d, J_{AB} 12,† PhCH_2), 4.62 (1 H, d, J_{AB} 12, PhCH_2), 4.70 (1 H, s, 1-*H'*), 4.70 (1 H, d, J_{AB} 11.5,† PhCH_2), 4.73 (1 H, dd, $J_{5,6B}$ 4, $J_{6A,6B}$ 12, 6-H_B), 4.77 (1 H, d, J_{AB} 11.5,† PhCH_2), 4.88 (2 H, m, PhCH_2 and PhCH_2), 4.92 (1 H, d, J_{AB} 11,† PhCH_2), 5.00 (1 H, d, J_{AB} 12.5, PhCH_2); δ_C($CDCl_3$; $CHCl_3$) 57.1 (*Me*O), 65.1 (CH_2, *C*-6), 70.0 (*C*-6'), 71.5 (CH_2), 72.6 (*C*-5), 73.1 (*C*-4 or *C*-2'), 73.3, 73.6 (CH_2), 73.7 (CH_2), 73.8 (CH_2), 75.0 (*C*-4'), 75.2 (CH_2), 75.4 (CH_2), 76.3, 79.6 (*C*-2), 81.5 (*C*-3), 82.9, 102.0 (J_{CH} 156, *C*-1'), 105.1 (J_{CH} 159, *C*-1), 127.6 (*Ar*), 127.6 (*Ar*), 127.8 (*Ar*), 127.9 (*Ar*), 127.9 (*Ar*), 128.0 (*Ar*), 128.1 (*Ar*), 128.3 (*Ar*), 128.4 (*Ar*), 128.5 (*Ar*), 128.5 (*Ar*), 128.6 (*Ar*), 128.8 (*Ar*), 130.0 (*Ar*), 133.6 (*Ar*), 128.4 (*Ar*), 138.6 (*Ar*), 138.7 (*Ar*), 138.9 (*Ar*), 139.0 (*Ar*), 139.2 (*Ar*) and 166.7 (*C*=O).

118α (selected data): δ_H 3.58 (*Me*O), 4.23 (1 H, d, $J_{1,2}$ 7.5, 1-*H*), 4.96 (1-*H'*); δ_C 57.6 (*Me*O), 62.2, 64.8, 68.6, 72.1, 72.4, 72.8, 72.8, 74.4, 74.5, 74.8, 78.8, 79.9, 80.4, 100.7 (*C*-1'), 105.5 (*C*-1), 127-140 (many *Ar*) and 166.3 (*C*=O).

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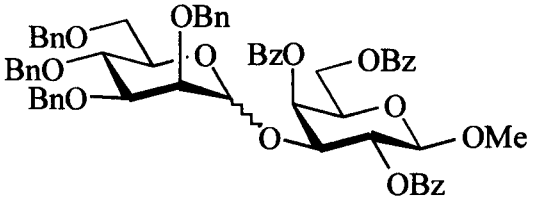
* at 3-*H* $J_{3,4}$ given as 2.86 at 4-*H* given as 2.29. Error limits ± 0.57 Hz.

† error limits ± 0.57 Hz

Methyl 2,4,6-tri-*O*-benzoyl-3-*O*-(2,3,4,6-tetra-*O*-benzyl-D-mannopyranosyl)-(1→3)-β-D-galactopyranoside (119)



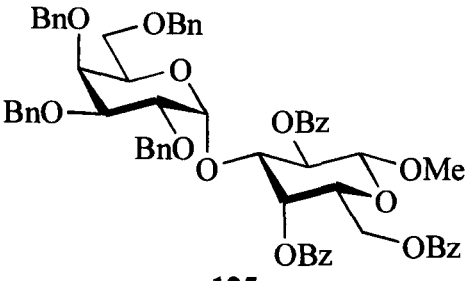
119

Purification by silica gel chromatography (EtOAc/hexane, 1:6 or EtOAc/toluene, 1:30) afforded **119** as either a mixture of α- and β-anomers, or solely the α-anomer (Found: C, 72.6; H, 6.4. $C_{62}H_{60}O_{14}$ requires C, 72.4; H, 5.9%); *m/z* (MALDI-TOF) 1051 ($M + Na^+$).

119α: δ_H(500 MHz, $CHCl_3$, Me_4Si) 3.39 (1 H, dd, $J_{2,3}$ 3.5 $J_{3,4}$ 9.5, 3-*H*'), 3.41-3.44 (2 H, m, 2-*H*' and 6-H_A'), 3.50 (1 H, dd, $J_{5,6B}$ 2 $J_{6A,6B}$ 10.5, 6-H_B'), 3.55 (3 H, s, *Me*O), 3.60 (1 H, m, 5-*H*'), 3.69 (1 H, m, 4-*H*'), 4.10 (3 H, m, 5-*H* and PhCH_2), 4.22 (1 H, d, J_{AB} 12, PhCH_2), 4.26 (1 H, dd, $J_{2,3}$ 10.5 $J_{3,4}$ 3.5, 3-*H*), 4.38 (1 H, dd, $J_{5,6A}$ 6.5 $J_{6A,6B}$ 11, 6-H_A), 4.47 (1 H, d, J_{AB} 12.5, PhCH_2), 4.55 (1 H, d, $J_{1,2}$ 8.5, 1-*H*), 4.56 (1 H, d, J_{AB} 12, PhCH_2), 4.58 (1 H, d, J_{AB} 11.5, PhCH_2), 4.61 (1 H, d, J_{AB} 12.5, PhCH_2), 4.66 (1 H, dd, $J_{5,6}$ 6.5 $J_{6A,6B}$ 11, 6-H_B), 4.73 (1 H, d, J_{AB} 12.5, PhCH_2), 5.36 (1 H, d, $J_{1,2}$ 1, 1-*H*'), 5.50 (1 H, dd, $J_{1,2}$ 8.5 $J_{2,3}$ 10, 2-*H*), 5.85 (1 H, d, $J_{3,4}$ 2.5, 4-*H*) and 6.77-8.12 (35 H, Ar-*H*); δ_C($CDCl_3$, $CHCl_3$) 57.3 (*Me*O), 62.4 (*C*-6), 66.2 (*C*-4), 69.4 (*C*-6'), 70.4 (*C*-2), 71.2 (PhCH_2), 72.0, 72.0, 72.3, 72.4, 73.5 (Ph*C*H_2), 74.2, 74.3, 74.3, 79.5 (*C*-3'), 94.2 ($J_{C,H}$ 173, *C*-1'), 102.7 ($J_{C,H}$ 160, *C*-1), 127.2 (*Ar*), 127.5 (*Ar*), 127.6 (*Ar*), 127.8 (*Ar*), 127.9 (*Ar*), 127.9 (*Ar*), 128.1 (*Ar*), 128.3 (*Ar*), 128.4 (*Ar*), 128.5 (*Ar*), 128.6 (*Ar*), 128.8 (*Ar*), 128.9 (*Ar*), 129.5 (*Ar*), 129.7 (*Ar*), 129.8 (*Ar*), 130.1 (*Ar*), 130.4 (*Ar*), 131.3 (*Ar*), 133.3 (*Ar*), 133.6 (*Ar*), 133.9 (*Ar*), 138.6 (*Ar*), 138.7 (*Ar*), 138.7 (*Ar*), 139.2 (*Ar*), 165.5 (*C*=O), 166.2 (*C*=O) and 170.2 (*C*=O).

119β: δ_H(500 MHz, $CHCl_3$, Me_4Si) 3.53 (3 H, s, *Me*O).

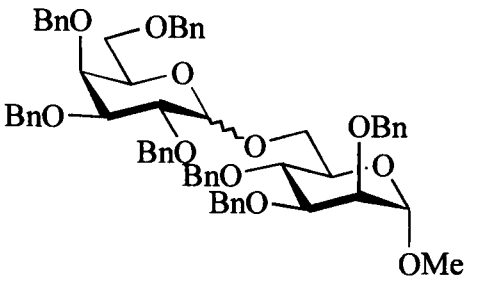
Methyl 2,4,6-tri-*O*-benzoyl-(2,3,4,6-tetra-*O*-benzyl-α-D-galactopyranosyl)-(1→3)-β-D-galactopyranoside (125)



125

Purification by silica gel chromatography (EtOAc/hexane, 1:6) afforded **125** as the α-anomer only; δ_H(300 MHz; $CDCl_3$; Me_4Si) 3.25 (1 H, dd, $J_{5,6A}$ 5.5 $J_{6A,6B}$ 9.5, 6-$H_{A'}$), 3.29 (1 H, m, 1-*H'*), 3.41 (1 H, dd, $J_{5,6B}$ 6.5 $J_{6A,6B}$ 9.5, 6-$H_{B'}$), 3.51 (1 H, dd, $J_{2,3}$ 10 $J_{3,4}$ 3.5, 3-*H'*), 3.56 (3 H, s, *Me*O), 3.91 (1 H, dd, $J_{2,3}$ 10 $J_{3,4}$ 3.5, 3-H), 3.93 (1 H, m, 5-*H* or 5-*H'*), 4.03 (1 H, m, 5-*H* or 5-*H'*), 4.22-4.54 (10 H, m, 7 x PhCH_2 1-*H* 2-*H'* and 6-H_A), 4.60 (1 H, dd, $J_{5,6A}$ 7 $J_{6A,6B}$ 10.5, 6-H_B), 4.74 (1 H, d, J_{AB} 11.5, PhCH_2), 5.28 (1 H, d, $J_{3,4}$ 3.5, 4-*H'*), 5.71 (1 H, dd, $J_{1,2}$ 8 $J_{2,3}$ 10, 2-*H*), 5.93 (1 H, d, $J_{3,4}$ 3.5, 4-*H*), 7.08-7.63 (29 H, m) and 8.04-8.13 (6 H, m); δ_C($CDCl_3$; $CHCl_3$) 57.0 (*Me*O), 62.7, 66.4, 69.6, 70.2, 71.0, 71.8, 72.5, 72.9, 73.4, 73.5, 74.6, 75.2, 75.4, 78.9, 94.5 (*C*-1'), 102.7 (*C*-1), 127.3 (*Ar*), 127.5 (*Ar*), 127.6 (*Ar*), 127.7 (*Ar*), 127.9 (*Ar*), 128.2 (*Ar*), 128.4 (*Ar*), 128.4 (*Ar*), 128.6 (*Ar*), 128.7 (*Ar*), 129.6 (*Ar*), 130.0 (*Ar*), 130.1 (*Ar*), 130.1 (*Ar*), 130.4 (*Ar*), 133.4 (*Ar*), 133.5 (*Ar*), 133.5 (*Ar*), 138.7 (*Ar*), 138.8 (*Ar*), 139.1 (*Ar*), 165.3 (*C*=O), 166.3 (*C*=O) and 166.5 (*C*=O); *m/z* (MALDI-TOF) 1051 ($M + Na^+$).

Methyl 2,3,4-tri-*O*-benzyl-6-*O*-(2,3,4,6-tetra-*O*-benzyl-D-galactopyranosyl)-(1→6)-α-D-mannopyranoside (122)



122

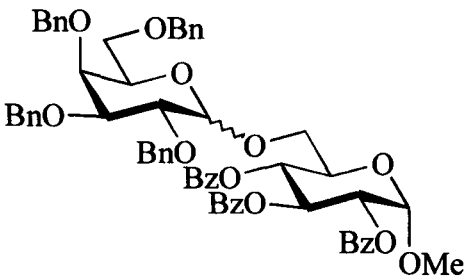
Purification by silica gel chromatography (EtOAc/hexane, 1:6 or EtOAc/toluene, 1:30) afforded **122** as a mixture of α- and β-anomers; *m/z* (MALDI-TOF) 1009 ($M + Na^+$).

122α δ_H(500 MHz; $CDCl_3$; Me_4Si) 3.13 (3 H, s, *Me*O), 4.64 (1 H, s, 1-*H*) and 5.01 (1 H, d, $J_{1,2}$ 3.5, 1-*H*'); δ_C($CDCl_3$; $CHCl_3$) 54.8 (*Me*O), 97.5 (*C*-1'), 99.1 (*C*-1)

122β δ_H(500 MHz; $CDCl_3$; Me_4Si) 3.14 (3 H, s, *Me*O), 4.31 (1 H, d, $J_{1,2}$ 8, 1-*H*') and 4.60 (1 H, s, 1-*H*); δ_C($CDCl_3$; $CHCl_3$) 54.9 (*Me*O), 99.1 (*C*-1), 104.7 (*C*-1').

δ_C (unassigned) : 66.6, 68.9, 69.0, 69.4, 71.7, 71.8, 72.3, 72.4, 72.9, 72.9, 73.0, 73.0, 73.2, 73.5, 73.5, 73.7, 73.9, 74.7, 74.9, 75.0, 75.1, 75.1, 75.2, 75.3, 75.4, 75.5, 76.9, 78.6, 79.7, 80.5, 82.4, 127.6 (*Ar*), 127.6 (*Ar*), 127.6 (*Ar*), 127.7 (*Ar*), 127.8 (*Ar*), 127.8 (*Ar*), 127.9 (*Ar*), 127.9 (*Ar*), 128.0 (*Ar*), 128.1 (*Ar*), 128.1 (*Ar*), 128.1 (*Ar*), 128.3 (*Ar*), 128.4 (*Ar*), 128.5 (*Ar*), 128.5 (*Ar*), 138.5 (*Ar*), 128.6 (*Ar*), 128.7 (*Ar*), 128.7 (*Ar*), 138.3 (*Ar*), 138.4 (*Ar*), 138.6 (*Ar*), 138.7 (*Ar*), 138.9 (*Ar*), 139.0 (*Ar*), 139.1 (*Ar*), 139.1 (*Ar*), 139.2 (*Ar*), 139.2 (*Ar*) and 139.3 (*Ar*).

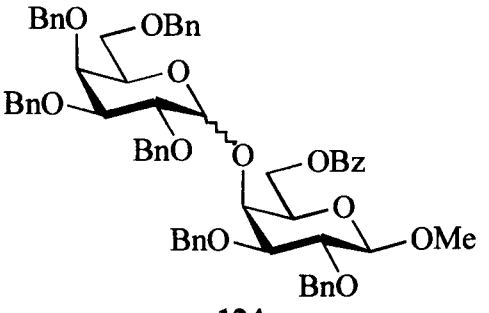
Methyl 2,3,4-tri-*O*-benzoyl-6-*O*-(2,3,4,6-tetra-*O*-benzyl-D-galactopyranosyl)-(1→6)-α-D-glucopyranoside[233] (123)



123

Purification by silica gel chromatography (EtOAc/hexane, 1:6 or EtOAc/toluene, 1:30) afforded **123** as a mixture of α- and β-anomers; δ_H(300MHz; $CDCl_3$; Me_4Si) 3.35 (s, *Me*O), 3.36 (s, *Me*O), 5.41 (t, $J_{3,4} = J_{4,5}$ 10, 4-*H*), 5.53 (t, $J_{3,4} = J_{4,5}$ 10, 4-*H*), 6.13 (t, 3-*H*) 6.15 (t, 3-*H*) and 7.10-8.00 (m, Ar-*H*); δ_C($CDCl_3$, $CHCl_3$) 55.6 (*Me*O), 55.6 (*Me*O), 66.8, 68.7, 68.8, 68.9, 69.1, 69.2, 69.5, 69.8, 70.2, 70.7, 70.9, 72.4, 73.1, 73.3, 73.4, 73.4, 73.6, 73.7, 74.7, 74.9, 75.3, 75.3, 76.6, 78.8, 79.8, 82.2, 96.9 (J_{CH} 167, C-1), 97.0 (J_{CH} 167, C-1), 98.1 (J_{CH} 169.1, C-1'), 104.5 (J_{CH} 160, C-1'), 127.7 (*Ar*), 127.8 (*Ar*), 128.0 (*Ar*), 128.0 (*Ar*), 128.1 (*Ar*), 128.2 (*Ar*), 128.4 (*Ar*), 128.5 (*Ar*), 128.5 (*Ar*), 128.6 (*Ar*), 128.7 (*Ar*), 129.2 (*Ar*), 129.4 (*Ar*), 129.4 (*Ar*), 129.4 (*Ar*), 129.6 (*Ar*), 129.6 (*Ar*), 129.9 (*Ar*), 130.1 (*Ar*), 130.2 (*Ar*), 133.3 (*Ar*), 133.6 (*Ar*), 138.2 (*Ar*), 138.4 (*Ar*), 138.8 (*Ar*), 138.8 (*Ar*), 139.1 (*Ar*), 139.2 (*Ar*), 165.7 (*C*=O), 165.9 (*C*=O), 166.1 (*C*=O), 166.1 (*C*=O), 166.2 (*C*=O) and 199.2 (*C*=O); *m/z* (MALDI-TOF) 1051 ($M + Na^+$).

Methyl 6-*O*-benzoyl-2,3-di-*O*-benzyl-4-*O*-(2,3,4,6-tetra-*O*-benzyl-D-galactopyranosyl)-(1→4)-β-D-galactopyranoside (124)



124

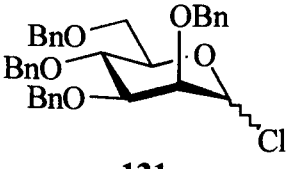
Purification by silica gel chromatography (EtOAc/hexane, 1:6 or EtOAc/toluene, 1:30) afforded **124** as a mixture of α- and β-anomers; *m/z* (MALDI-TOF) *1023.2 ($M + Na^+$)*.

124α δ_H(500 MHz; $CDCl_3$; Me_4Si) 3.49 (3 H, s, *Me*O), 4.19 (1 H, d, $J_{1,2}$ 7.5 1-*H*), 4.94 (1 H, d, $J_{1,2}$ 3.5, 1-*H'*); δ_C($CDCl_3$; $CHCl_3$) 57.4, 62.4, 68.1, 69.7, 72.4, 72.7, 73.0, 73.4, 74.2, 75.0, 75.1, 75.2, 75.9, 76.3, 79.0, 79.5, 80.8, 101.3 (J_{CH} 170, *C*-1'), 105.3 (J_{CH} 161, *C*-1), 166.4 (*C*=O)

124β δ_H(500 MHz; $CDCl_3$; Me_4Si) 3.47 (3 H, s, *Me*O), 4.19 (1 H, d, 1-*H'*), 4.20 (1 H, d, $J_{1,2}$ 7.5, 1-*H*); δ_C($CDCl_3$; $CHCl_3$) 57.2, 64.8, 69.1, 71.8, 72.5, 73.2, 73.4, 73.6, 74.2, 74.6, 75.2, 75.4, 77.4, 80.0, 80.8, 81.7, 82.2, 103.5 (*C*-1'), 105.2 (*C*-1), 166.6 (*C*=O).

δ_C (unassigned) 127.4 (*Ar*), 127.6 (*Ar*), 127.7 (*Ar*), 127.7 (*Ar*), 127.8 (*Ar*), 127.8 (*Ar*), 127.8 (*Ar*), 127.9 (*Ar*), 128.0 (*Ar*), 128.0 (*Ar*), 128.1 (*Ar*), 128.1 (*Ar*), 128.2 (*Ar*), 128.3 (*Ar*), 128.4 (*Ar*), 128.4 (*Ar*), 128.4 (*Ar*), 128.5 (*Ar*), 128.5 (*Ar*), 128.6 (*Ar*), 128.6 (*Ar*), 128.6 (*Ar*), 128.7 (*Ar*), 128.8 (*Ar*), 129.9 (*Ar*), 130.2 (*Ar*), 130.7 (*Ar*), 133.2 (*Ar*), 133.5 (*Ar*), 138.3 (*Ar*), 138.4 (*Ar*), 138.7 (*Ar*), 138.9 (*Ar*), 139.1 (*Ar*), 139.1 (*Ar*), 139.3 (*Ar*) and 139.5 (*Ar*).

2,3,4,6-Tetra-*O*-benzyl-D-mannopyranosyl chloride (131)



131

A solution of mannosyl sulfoxide **114** (75 mg, 0.125 mmol) in dichloromethane (2 ml) was stirred overnight under nitrogen, in the presence of 3 Å MS (50 mg). The mixture was cooled to -10°C (ice/water/salt bath) and a 1 M solution of iodine monochloride (135 µl, 0.135 mmol) added, dropwise. The mixture was stirred for 70 min, diluted with dichloromethane, washed with aqueous $Na_2S_2O_3$, dried (Na_2SO_4) and concentrated *in vacuo*. Column chromatography of the resulting residue afforded chloride **131** (18.4 mg, 26%); δ_H(300 MHz, $CDCl_3$, Me_4Si) 3.70 (1 H, dd, $J_{5,6A}$ 1.5 $J_{6A,6B}$ 11, 6-H_A), 3.82 (1 H, dd, $J_{5,6B}$ 4.5* $J_{6A,6B}$ 11, 6-H_B), 3.88 (1 H, m 2-*H*), 4.02 (1 H, m , 5-*H*), 4.10 (1 H, t, $J_{3,4}$ 9 $J_{4,5}$ 9.5, 4-*H*), 4.19 (1 H, dd, $J_{2,3}$ 3 $J_{3,4}$ 9, 3-H), 4.50-4.76 (7 H, m, PhCH_2), 4.90 (1 H, d, J_{AB} 11, PhCH_2), 6.11 (1 H, br s, 1-*H*) and 7.17-7.37 (20 H, Ar-*H*); δ_C($CDCl_3$, $CHCl_3$) 68.5, 72.7, 73.2, 73.6, 74.3, 74.8, 75.5, 78.1, 78.6, 91.8 (*C*-1), 127.8 (*Ar*), 127.9 (*Ar*), 128.0 (*Ar*), 128.1 (*Ar*), 128.2 (*Ar*), 128.2 (*Ar*), 128.6 (*Ar*), 128.6 (*Ar*), 128.7 (*Ar*), 128.7 (*Ar*), 137.9 (*Ar*), 138.3 (*Ar*), 138.3 (*Ar*) and 138.5 (*Ar*); *m/z* (MALDI-TOF) 581 (M + Na^+).

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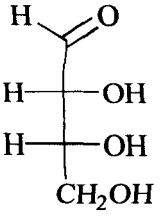
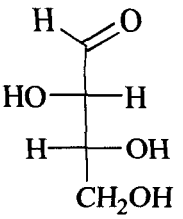
* $J_{5,6B}$ given as 4.39 and 4.18 at 6-H_B. Average taken and rounded (error limits 0.31 Hz).

APPENDIX 1:

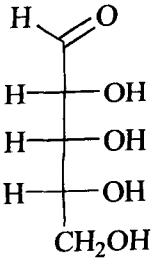


D-Erythrose

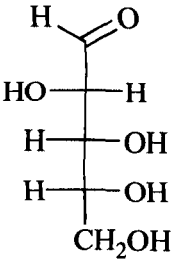


D-Threose

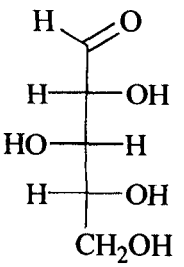
Aldotetroses



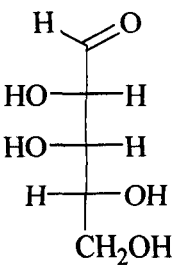
D-Ribose



D-Arabinose

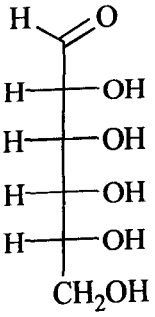


D-Xylose

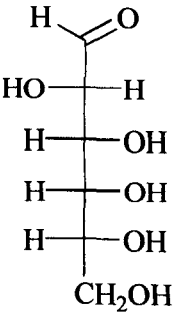


D-Lyxose

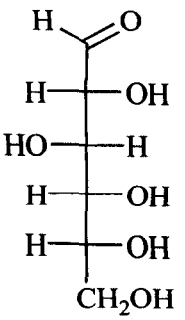
Aldopentoses



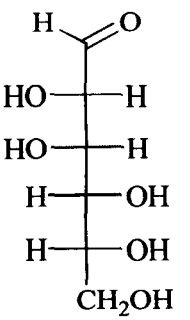
D-Allose



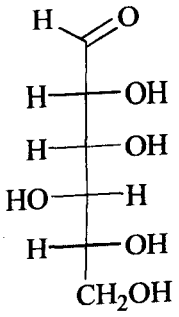
D-Altrose



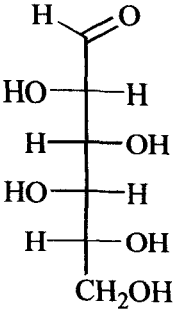
D-Glucose



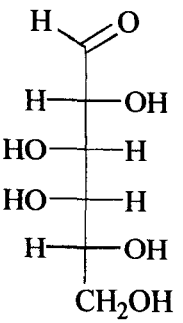
D-Mannose



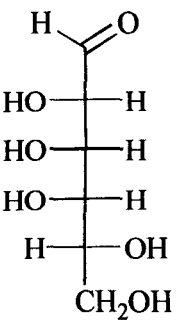
D-Gulose



D-Idose



D-Galactose



D-Talose

Aldohexoses

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