UNIVERSITY OF ALBERTA

The Synthesis of β-D-Mannopyranosides by Intramolecular Aglycon Delivery

BY

Frank W. Barresi

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NAME OF AUTHOR: **Frank W. Barresi**

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SIGNED: F.W. Barresi

PERMANENT ADDRESS:
1052 106 St.
Edmonton, Alberta, Canada T6J 6J5

DATED: JAN 21, 1994

UNIVERSITY OF ALBERTA

FACULTY OF GRADUATE STUDIES AND RESEARCH

The undersigned certify that they have read, and recommend to the Faculty of Graduate Studies and Research for acceptance, a thesis entitled **The Synthesis of β-D-Mannopyranosides by Intramolecular Aglycon Delivery** submitted by **Frank W. Barresi** in partial fulfillment of the requirements for the degree of **Doctor of Philosophy**.

Ole Hindsgaul, supervisor

D. L. J. Clive

K. R. Kopecky

G. Kotovych

B. M. Pinto

P. Sporns

DATED: Jan 20, 1994

Dedicated to my wife,

Roxanne

ABSTRACT

N-linked oligosaccharide structures are one of the most common types of biopolymer present in biological systems and are vital for life processes. The β-mannosidic linkage is present in all *N*-linked sugars as part of a consensus oligosaccharide termed the core pentasaccharide. This β-mannopyranosidic linkage has historically been the most difficult anomeric linkage to synthesize.

New methodology, termed intramolecular aglycon delivery (IAD), has been developed that provides a completely stereocontrolled synthesis of β-D-mannopyranosides. This procedure has been applied, in good yield, to several disaccharides, including octyl 3,6-di-*O*-benzyl-4-*O*-(3,4,6-tri-*O*-benzyl-β-D-mannopyranosyl)-2-deoxy-2-phthalimido-β-D-glucopyranoside, a precursor of the naturally occurring β-D-Man-(1→4)-β-D-GlcNAc linkage, found in all *N*-linked glycoproteins. The stereochemical nature of the β-mannosidic linkage has been confirmed by comparison to α-mannopyranoside standards, and the stereocontrolled reaction shown to proceed even in the presence of competing intermolecular alcohols.

The extension of this strategy to the core pentasaccharide of *N*-linked glycoproteins has revealed limitations to the methodology as developed. Nevertheless, trisaccharide portions of the core pentasaccharide containing the β-mannopyranosidic linkage could be synthesized and were compared with independently synthesized α-mannopyranosides. Future directions are discussed to improve the present methodology of IAD, in order for it to be accepted as the primary means of synthesizing this type of linkage.

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LIST OF ABBREVIATIONS

Abbreviation	Name
Ac	acetate
Ac_2O	acetic anhydride
AIBN	azoisobutyronitrile
Asn	asparagine
Bn	benzyl
Bz	benzoyl
CSA	camphorsulfonic acid
DABCO	1,4-diazabicyclo [2.2.2] octane
dH_2O	distilled water
DMF	dimethyl formamide
DMPU	dimethyltetrahydro-2-pyrimidinone
DMSO	dimethyl sulfoxide
DMTST	dimethyl(methylthio) sulfonium triflate
DMT	dimethoxytoluene
Fuc	fucose
Gal	galactose
GalNAc	*N*-acetylgalactosamine
gem	geminal
Glc	glucose
GlcNAc	*N*-acetylglucosamine
GlcUA	glucuronic acid
GPI	glycerol phosphatidyl inositol
HMDS	hexamethyldisilazane
Hunigs base	ethyldiisopropyl amine
Hz	hertz
IAD	intramolecular aglycon delivery
IDCP	iodine dicollidine perchlorate
IdoUA	idouronic acid
LAH	lithium aluminum hydride
Man	mannose
mCPBA	*m*-chloroperoxy-benzoic acid
4-Me-DTBP	2,6-di-*tert*-butyl-4-methyl- pyridine
MS	molecular sieves
NBS	*N*-bromosuccinimide
NeuAc	9-acetyl neuraminic acid, sialic acid
NIS	*N*-iodosuccinimide
NMR	nuclear magnetic resonance
PMB	*p*-methoxybenzyl
Ph	phenyl
Phth	phthalimido
PhSeOTf	phenyl selenenyl triflate
POM	4-pentenyl methylenyloxy
PPTS	pyridinyl *p*-toluenesulfonate
pyr	pyridine
RER	rough endoplasmic reticulum
R_f	retardation factor
Ser	serine
TBAF	tetrabutylammonium fluoride
$TBPA^{\cdot+}$	tris(4-bromophenyl) aminium hexachloroantimonate
Tf	trifluoromethane-sulfonyl
THF	tetrahydrofuran
Thr	threonine
tlc	thin layer chromatography
p-TSA	*p*-toluenesulfonic acid
vic	vicinal
Xyl	xylose

CHAPTER 1

Introduction:

A. The Biological Significance of Carbohydrates:

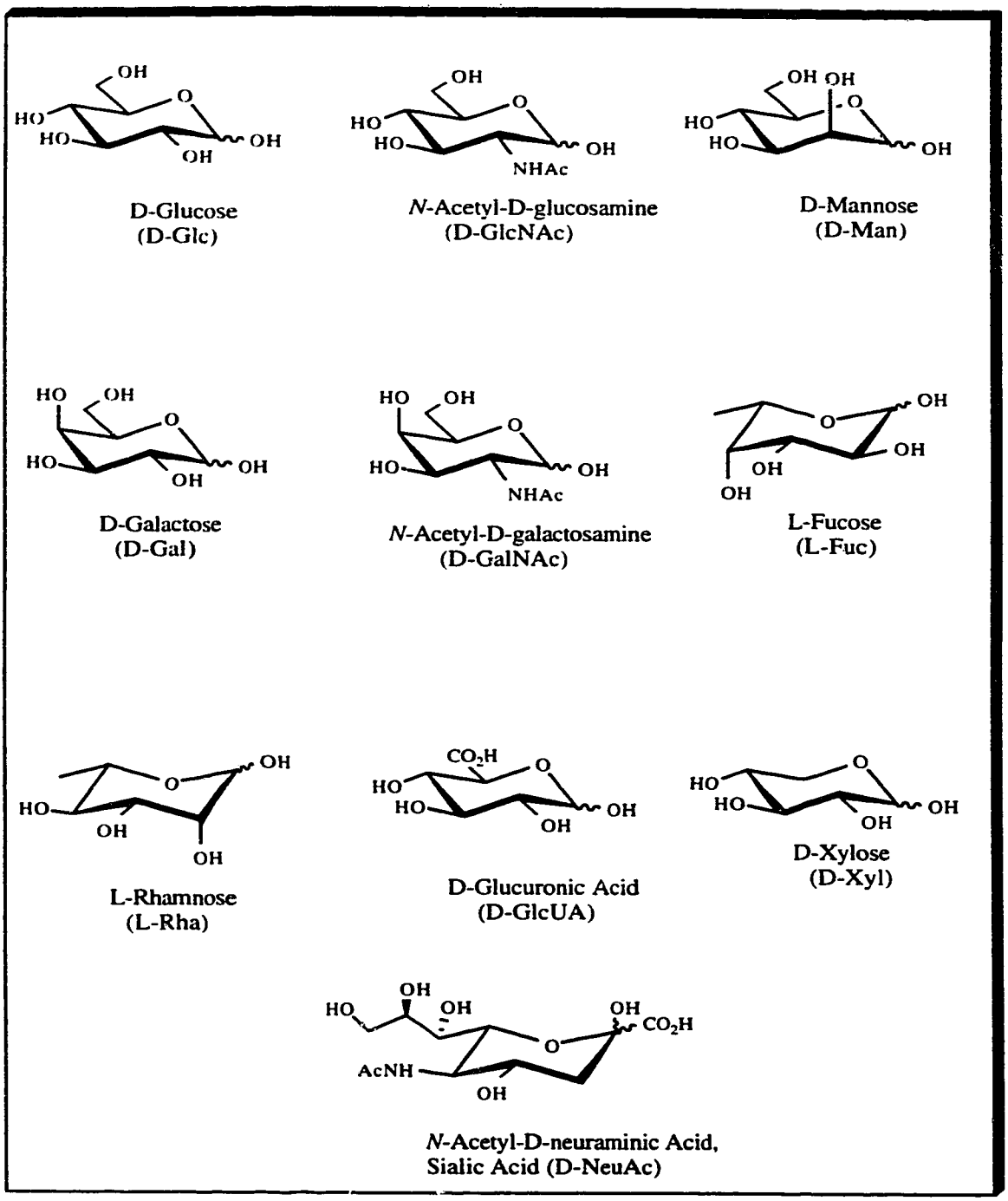
The study of the biological role of oligosaccharides has spawned a new area of research termed "glycobiology". The old concept of carbohydrates being important for energy and storage functions has been shown to be too simplistic. There has been overwhelming evidence that this class of biopolymer controls how cells communicate in their biological environment [1]. As a result, multidisciplinary research teams are exploring what has been called "one of the last great frontiers of biochemistry" [2].

The most powerful property carbohydrates display is their ability to generate extreme diversity with a small set of monosaccharide residues (Figure 1). Their polyhydroxylated surfaces allow for numerous connectivities. For example, four carbohydrate residues can be linked in over 35 000 different combinations, as opposed to four amino acid residues being linked in twenty-four combinations[3,4]. This makes oligosaccharide structures ideal candidates for "talking" to their environment[5].

The literature demonstrates that the field of glycobiology is rapidly expanding[1,3,6-12]. The following are five examples taken from eucaryotic organisms that demonstrate the diversity and importance of carbohydrate functions:

1. Carbohydrates have been implicated in embryonic development[13-15]. It has been shown that carbohydrates are vital in the compaction of embryos from the eighth to sixteenth cell stage in mice[13]. In addition, compaction can be

Figure 1: Monosaccharides Commonly Found in Nature



inhibited by treating embryonic cells with a soluble form of the same carbohydrate[15], which is a Lewis^x trisaccharide;

2. Carbohydrates are essential in the adhesion of viruses and bacteria to their hosts[1,16-18]. Numerous pathogenic organisms exploit oligosaccharides on cell surfaces to initiate recognition and binding. One particular residue that is targeted by the influenza viruses[19-21] and the parasite *Trypanosoma cruzi* [22] is sialic acid. Another example is in the binding of herpes simplex virus to the carbohydrate biopolymer heparin sulfate[23,24];

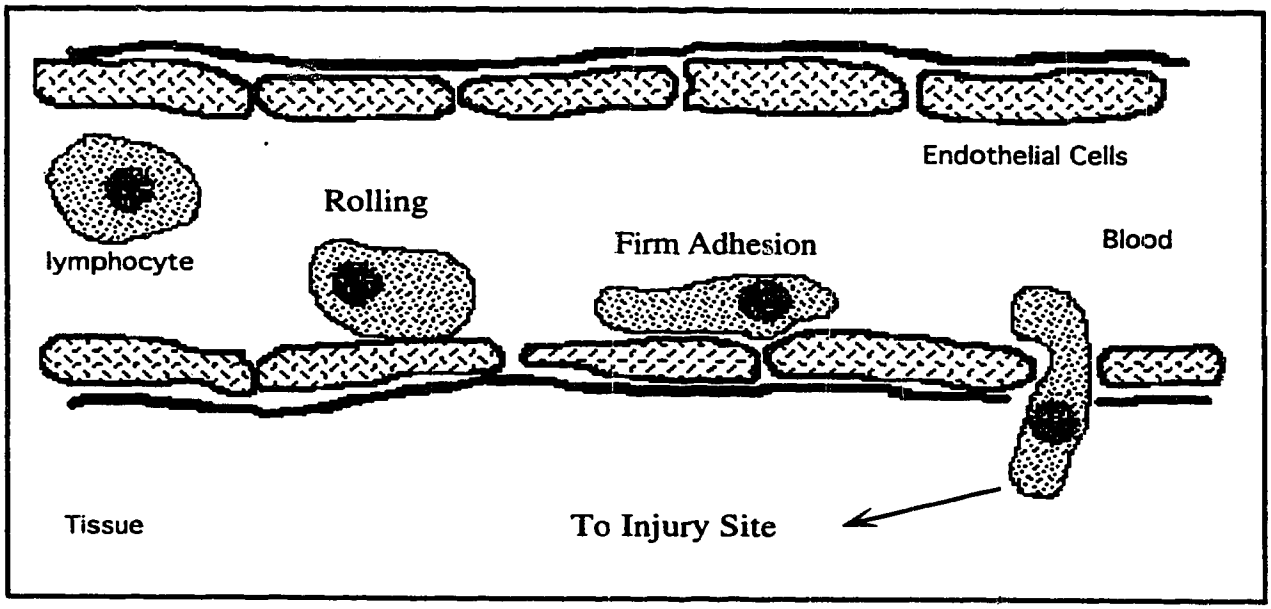
3. Fertilization studies have shown recognition of the egg by sperm is initiated by carbohydrate-protein interactions[25,26]. In particular, a galactosyltransferase on the sperm head interacts specifically with a carbohydrate containing a galactose residue in the egg coat, or zona pellucida;

4. Oligosaccharide residues are important in the modulation of protein activity. Functional diversification can be achieved by altering the number and type of oligosaccharides on the protein surface. These modifications allow for the protein to expand their functional roles and modulate their activity without having to modify their amino acid sequence. The different glycoprotein states that exist are termed "glycoforms"[27]. The glycohormone human beta chorionic gonadotropin[6,28,29] and erythropoiten[30] are examples of enzymes with glycoforms[1] and;

5. In recent years the discovery of a group of proteins referred to as selectins has gained a lot of attention[7,8,10,12]. Carbohydrates interact with selectins and are implicated in the control of the inflammation process. During an

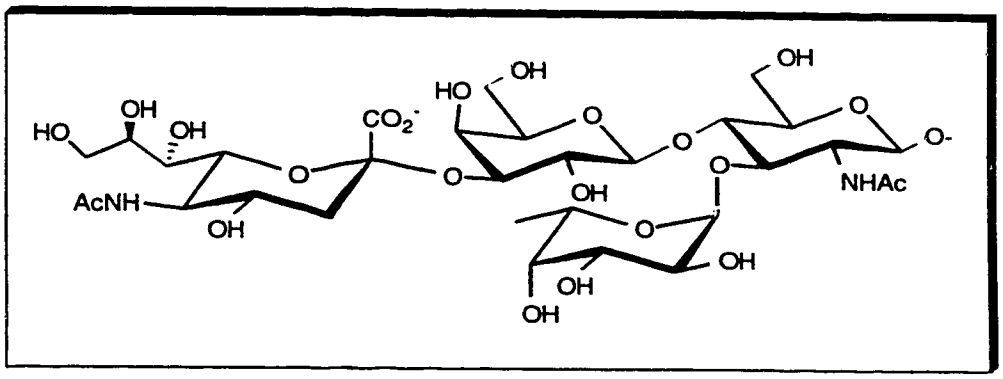
inflammatory response to injured tissue, lymphocytes pass from the blood stream through the vascular endothelium to the site of inflammation. The process occurs by a slowing down or "rolling" of the white blood cells followed by a stronger "sticking" process and eventually passage through the endothelium to the inflamed site (Figure 2)[3,4,31-33]. It is in the "rolling" stage where selectin-carbohydrate interaction occurs to initiate the process. There are three types of selectins discovered to date. They are: L-selectins[34,35], P-selectins[36,37], and E-selectins[38,39]. The L-selectins are glycoproteins found on the lymphocyte surface that bind to carbohydrates on the endothelial cells. The P and E selectins are found on the endothelial cells and interact with carbohydrates on the lymphocytes. The P-selectin is present for a longer time period than the E-selectin. Moreover, E-selectins are expressed in larger amounts and appear to be important four hours after the inflammation of injured tissue[3].

Fig. 2: Selectin Mediated Adhesion of Lymphocytes to Endothelial Cells:



Both P and E selectins interact specifically with a tetrasaccharide called Sialyl Lewis^x (Figure 3). Great effort has been expended to develop selectin inhibitors to control the inflammatory response. Such inhibitors could lead to the treatment of psoriasis, rheumatoid arthritis, and repurfusion injuries that follow heart attacks and strokes. In addition, selectins have also been identified on metastatic cancer cell lines[3], which make anti-selectin drugs potential candidates to control cancer cells from metastasizing.

Figure 3: Sialyl Lewis^x



These examples represent a fraction of the postulated carbohydrate mediated functions. One can see that the scope of this class of biopolymer is expansive and crucial for life processes. It is for these reasons that a tremendous volume of research is being directed toward understanding the role of complex carbohydrates in biological systems.

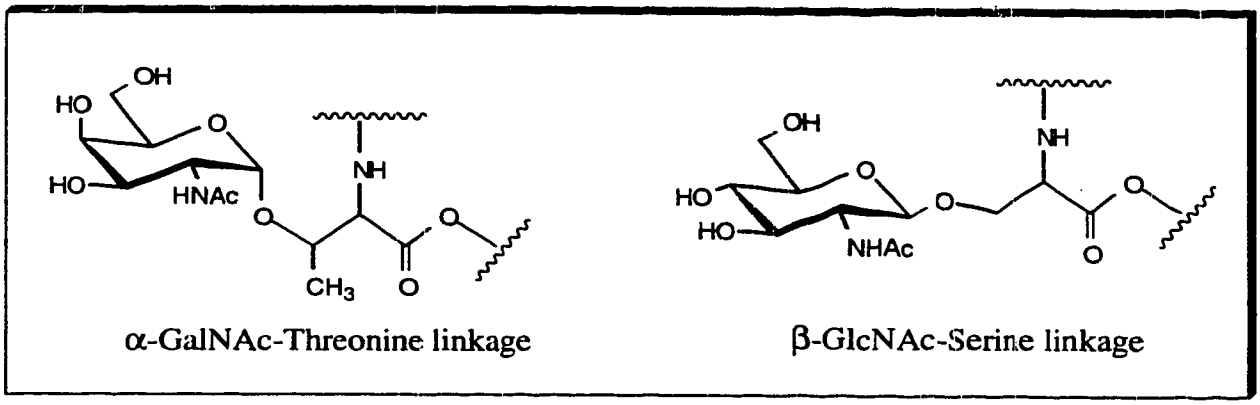
B. Biological Occurrence of Carbohydrates:

1. Classes of Complex Carbohydrates:

Complex carbohydrate structures of animal cells are divided into three major classes: glycoproteins, glycolipids, and proteoglycans. Glycoproteins are structures in

which the carbohydrate is covalently attached to a protein. There are two major subtypes of glycoproteins: *N*-linked structures, where the sugar is covalently attached to the protein via the amide nitrogen of asparagine (Figures 8-10), and *O*-linked glycoproteins, where the sugar is covalently attached to the protein via the hydroxyl of serine or threonine (Figure 4).

Figure 4: *O*-Linked Glycoproteins:

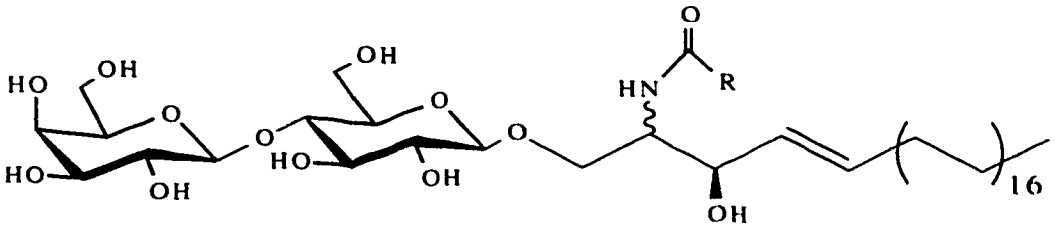


Glycolipids are structures in which the sugar is linked to a lipid structure imbedded in a cell membrane. There are two types of these structures, those that are attached to a ceramide via a β-lactosyl unit (Figure 5a)[40] and those that are attached to a phosphoroglycerol unit such as in the glycosyl phosphatidyl inositol (GPI) anchors (Figure 5b)[41-44].

The third class of oligosaccharides are referred to as the proteoglycans[45] which are long chain polymers of hundreds of carbohydrate units that can be found free in solution or lipid and protein linked. Heparin and heparan sulfate are such proteoglycans with great biological importance (Figure 6)[46-48].

Figure 5: Naturally Occurring Glycolipids:

a) Lactosyl Ceramide (R = long chain alkyl group):



b) Glycosyl Phosphatidyl Inositol (GPI) Anchor (R = long chain alkyl group):

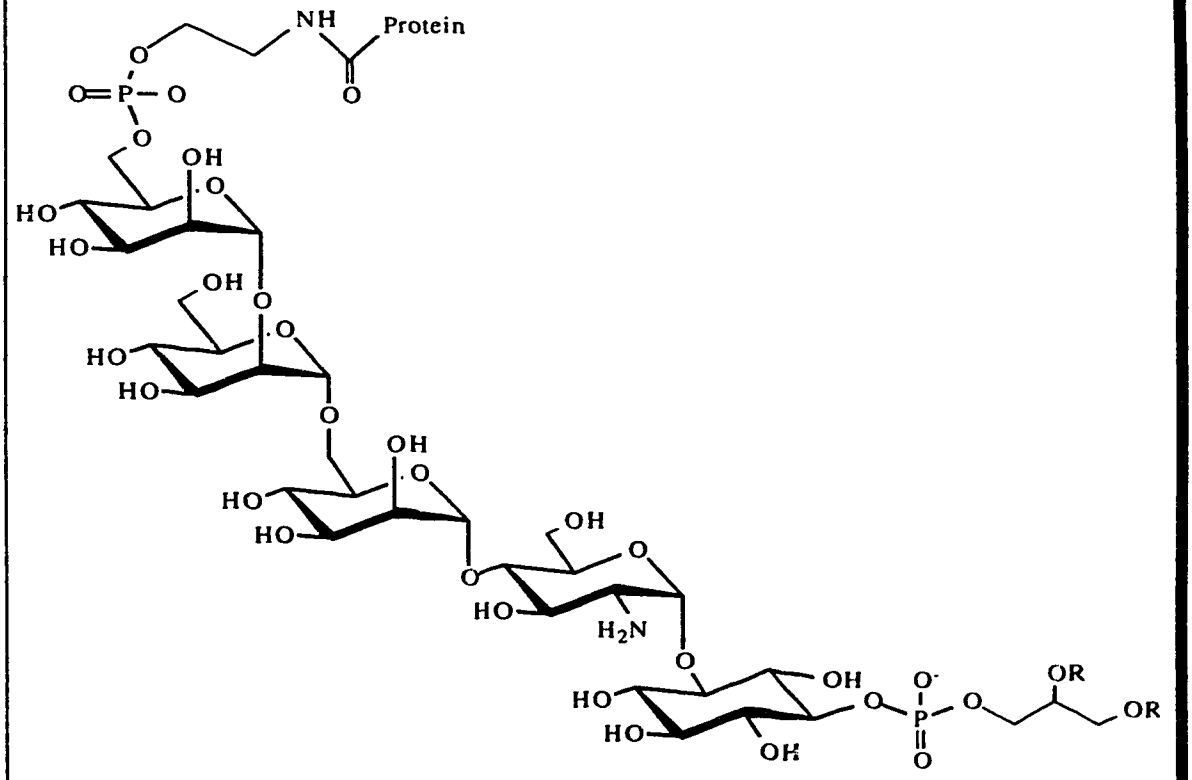
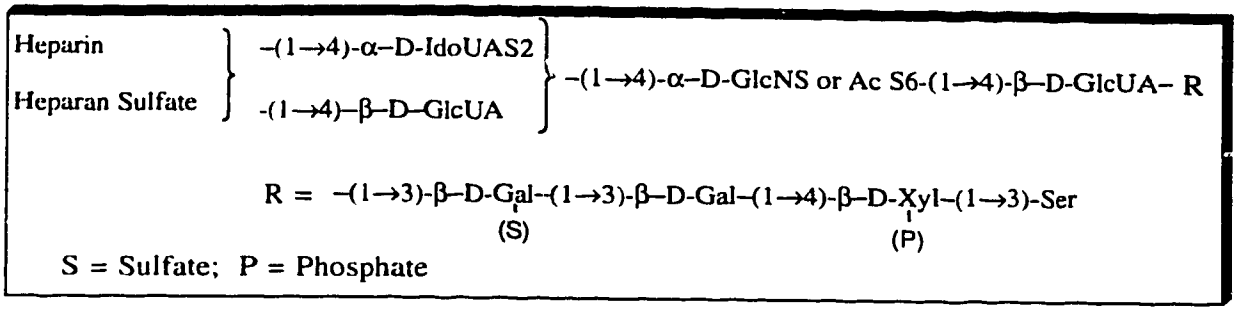


Figure 6: Proteoglycans:

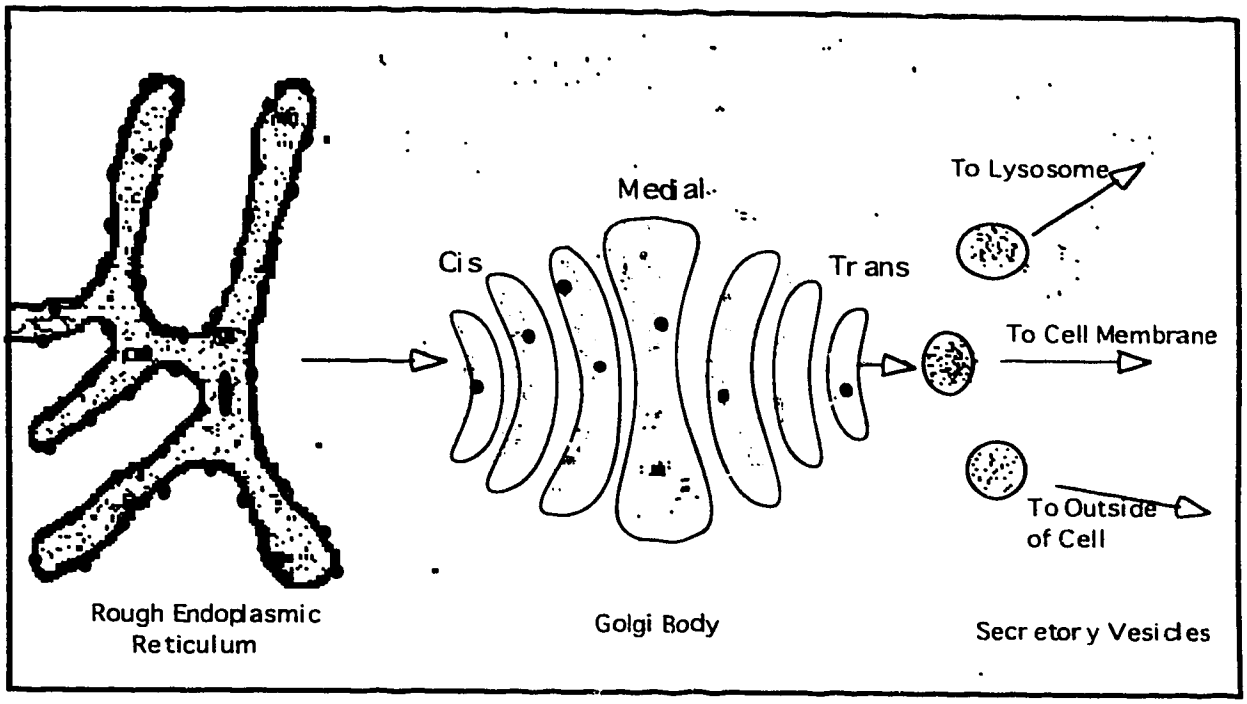


B.2. Glycosidases and Glycosyltransferases:

The manner in which complex carbohydrates are assembled involves two types of enzymes: glycosidases and glycosyltransferases. Glycosidases[49,50] are enzymes that cleave glycosidic bonds and one of their roles is to degrade carbohydrates. Another role is in the "trimming" of the oligosaccharide structures so that glycosyltransferases can recognize and further modify a given structure. Glycosidases are mainly found in the rough endoplasmic reticulum (RER), Golgi apparatus and lysozome (Figure 7).

Glycosyltransferases[5,51-56] are the second type of enzyme and are responsible for the formation of glycosidic bonds. These enzymes control the final structure of the oligosaccharide and are found primarily in the Golgi apparatus. In most instances, there is one enzyme for each carbohydrate linkage. The overall number of glycosyltransferases is estimated at over 100 (ref. 5). Twelve glycosyltransferases have been cloned to date[5] which enable the function of these enzymes to be examined more carefully, however, no crystal structures have yet been reported. There has been extensive research probing the binding and active sites of these enzymes via chemically synthesized carbohydrate analogues[57-66].

Figure 7: Organelles Involved in the Biosynthesis of Oligosaccharides:

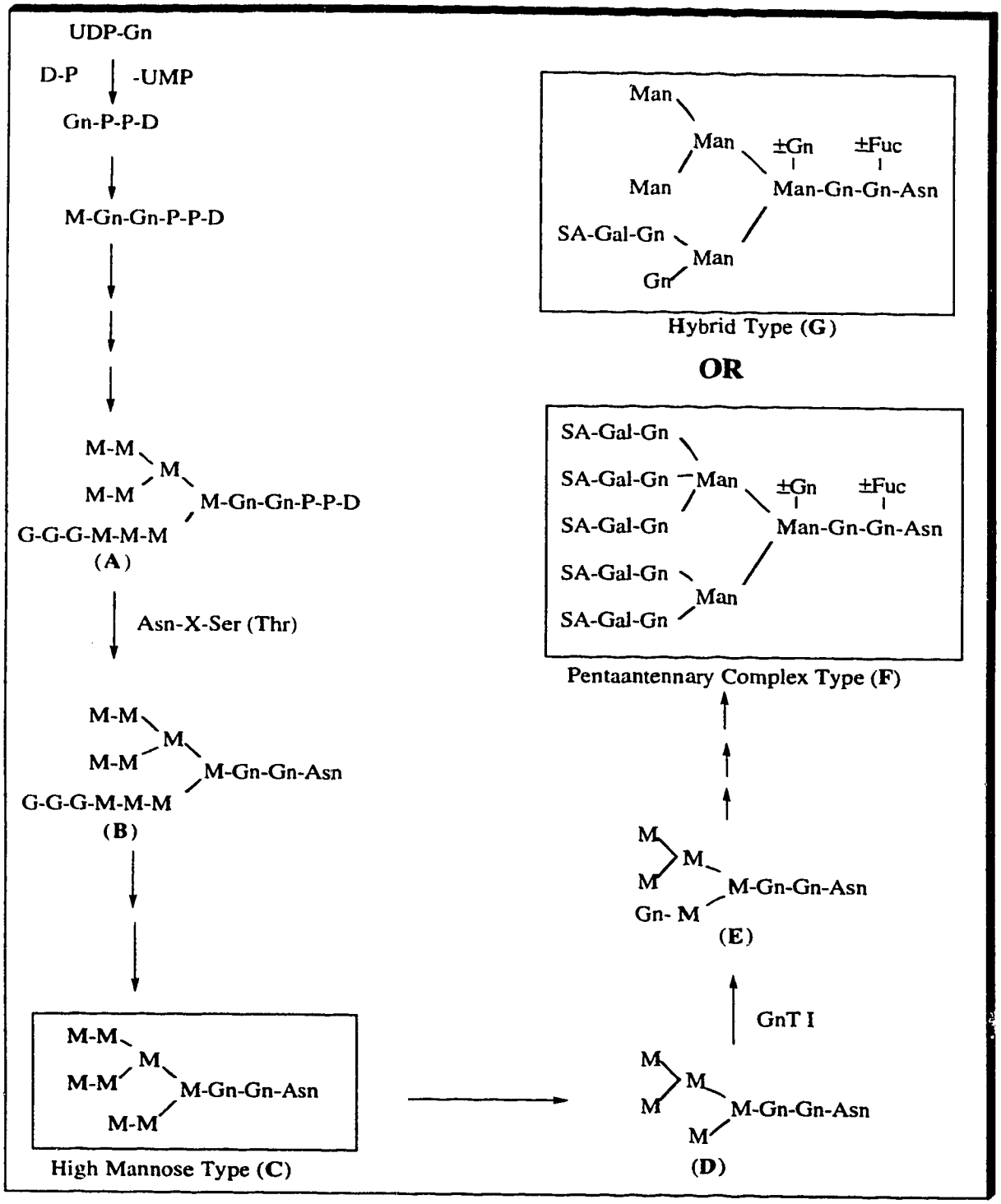


B.3. The Biosynthesis of *N* -Linked Oligosaccharides:

The most thoroughly studied of the carbohydrate classes are the glycoproteins. The *N*-linked glycoproteins show the most homogeneity. Research has been conducted to elucidate the biosynthetic pathway and enzymes involved in the synthesis of these biopolymers[5,49,53-56,67]. The biosynthesis is initiated in the rough endoplasmic reticulum and is completed in the Golgi (Figure 7). It is in the Golgi where the differentiation of the oligosaccharides is determined as the glycoproteins pass through the cis, medial and trans cisternae of this organelle.

Referring to Figure 8, the biosynthesis begins with the transfer of a GlcNAc-1-phosphate residue to the membrane lipid, dolichol pyrophosphate. This occurs in the

Figure 8: The Biosynthesis of *N*-Linked Oligosaccharides:



Abbreviations: M = Mannose; G = Glucose; Gn = *N*-Acetylglucosamine; Gal = Galactose; SA = Sialic Acid; Fuc = Fucose; D = Dolichol; P = Phosphate; Asn = Asparagine; UDP = Uridine Diphosphate; UMP = Uridine Monophosphate; GnT I = Glycosyltransferase I.

rough endoplasmic reticulum. Subsequently, glycosylation builds up a common core structure containing 3 Glc, 9 Man and 2 GlcNAc residues (structure **A**). The entire 14 residue structure is then transferred to an asparagine residue with a consensus sequence Asn-X-Ser(Thr) by oligosaccharyltransferase while the protein is still nascent or shortly after translation (structure **B**)[53]. While still in the RER, the three glucose residues and one mannose residue are removed by glycosidase enzymes (structure **C**). At this point, the remaining structure is transported in vesicles to the cis face of the Golgi apparatus. Once inside the Golgi, the glycoproteins are processed according to their final destination in the cell. For example, lysosomal proteins are phosphorylated with little further processing as opposed to plasma membrane proteins that undergo extensive modification as they pass through the medial and trans cisternae of the Golgi. One key pathway is the removal of three mannose residues by mannosidase I (structure **D**) and immediate addition of a GlcNAc residue by GnT I. This addition controls the processing of high mannose *N*-glycans to hybrid and complex *N*-glycans[5]. Further processing by a variety of glycosyltransferase and glycosidase enzymes then completes the biosynthesis of these complex structures. There are three types of oligosaccharide chains on *N*-linked glycoproteins:

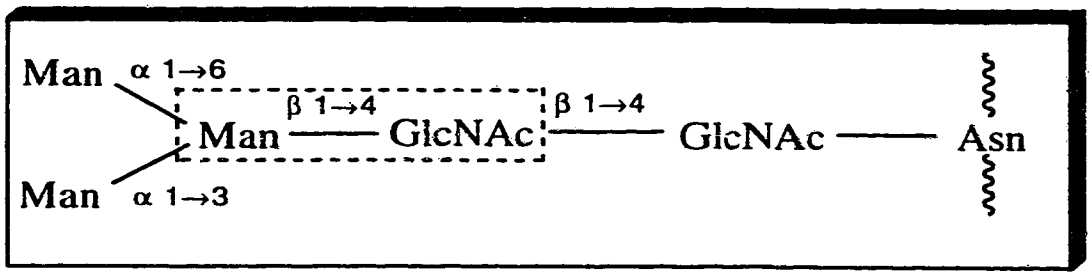
1. Complex type oligosaccharides which are the most common type and show the greatest variation in structure (Figure 8, structure **F**, and Figure 10)[68,69];

2. High mannose type oligosaccharides which show the least structural variation (Figure 8, structure **C**, and Figure 10)[68,69] and;

3. Hybrid type oligosaccharides that share characteristics of the other two sugar chains (structure **G** in Figure 8)[70,71].

Although there is a great deal of diversity within these three oligosaccharide types, there is a common structural motif in all of these structures. This is the pentasaccharide core:

Figure 9: Pentasaccharide Core of *N*-linked glycoproteins:



In this core structure there is a β-D-Man-(1→4)-β-D-GlcNAc linkage as emphasized in Figure 9. Historically this has been the most difficult linkage to synthesize chemically.

C. Chemical Synthesis of Oligosaccharides:

1. Chemically Synthesized Carbohydrates are Necessary for Biological Studies:

The chemical synthesis of oligosaccharides has presented the synthetic chemist with a challenging task. The increasing biological importance of these biopolymers in recognition events is driving a rebirth in the chemical synthesis of carbohydrates. In order to fully explore the functions of carbohydrates, methods of synthesizing sufficient amounts of these oligosaccharides is necessary. Despite great ingenuity applied in recent years to the development of new synthetic methods for stereospecific glycoside formation[57-59,72-83], problems in obtaining consistently high yielding steps remain.

C.2 Chemical Synthesis of *N*-Linked Oligosaccharides:

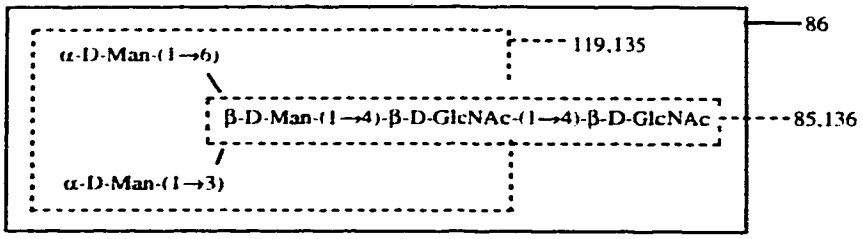
A large contribution to the field of carbohydrate chemistry has come about from the synthesis of *N*-linked oligosaccharides. Jeanloz and coworkers[84,85] were the first to construct the β-D-Man-(1→4)-β-D-GlcNAc-(1→4)–β–D-GlcNAc (Figure 10, structure **A**) trisaccharide portion of the core pentasaccharide in 1980. The majority of work in the chemical synthesis of this class of oligosaccharide comes from the laboratories of Hans Paulsen[76] and Tomoya Ogawa[81]. The core pentasaccharide was made by Paulsen et al[86] and Ogawa et al[87] (as part of a larger complex type oligosaccharide) in the early 1980's. Most of the syntheses reported on these type of oligosaccharides center around forming complex[76,81,86-97] and high mannose[76,81,97-102] type chains. Figure 10 summarizes many of the structures that have been constructed. The strategies involve the formation of the difficult β-mannosidic linkage to make a di or trisaccharide, then build up the structures from this block. The syntheses of the bisected structure **D**[88,90] are particularly noteworthy due to the complexity of the molecules. The synthesis of the entire biantennary complex type oligosaccharide (structure **C**)[89], represents what has been termed "the limits of chemical oligosaccharide synthesis"[76].

C.3 The β-Mannopyranosidic Linkage:

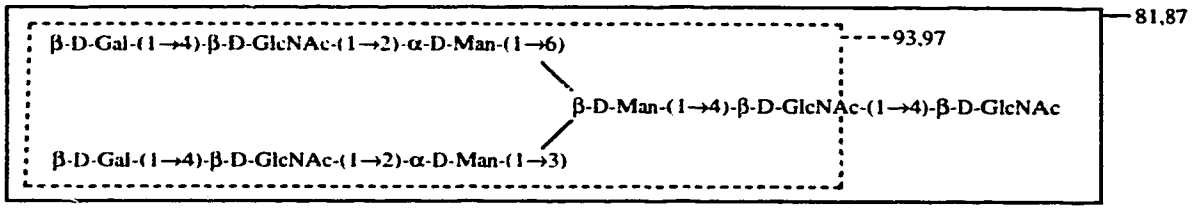
The β-mannosidic linkage is generally considered the most difficult anomeric linkage to synthesize[77]. Only the synthesis of the α-sialic acid linkage can compare in difficulty[57]. The problems with constructing this linkage are compounded by the fact that they are present in all *N*-linked oligosaccharides covalently attached to the 4-position of *N*-acetylglucosamine. The 4-position is considered to be the least reactive hydroxyl position on monosaccharides[77]. In addition, β-mannosidic linkages are also found in the cell wall of bacteria such as *Candida albicans*, which contains a β-(1→2)-linked

Figure 10: *N*-Linked Oligosaccharide Structures
(Boxed structures with reference numbers pertain to chemical syntheses)

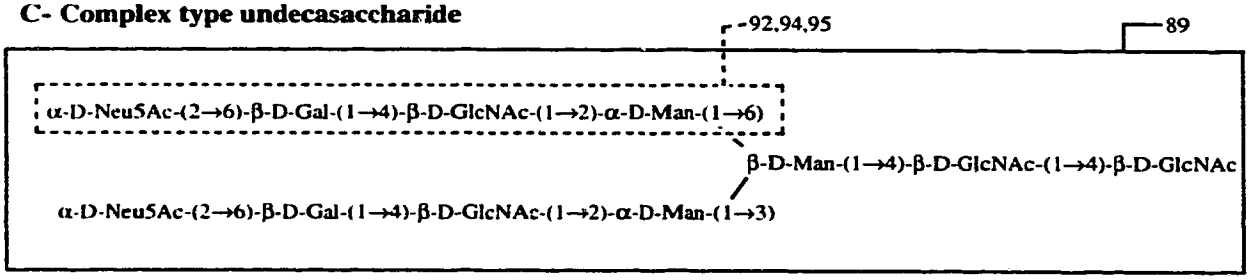
A- Core pentasaccharide



B- Complex type nonasaccharide



C- Complex type undecasaccharide



D- Bisected Complex type oligosaccharide

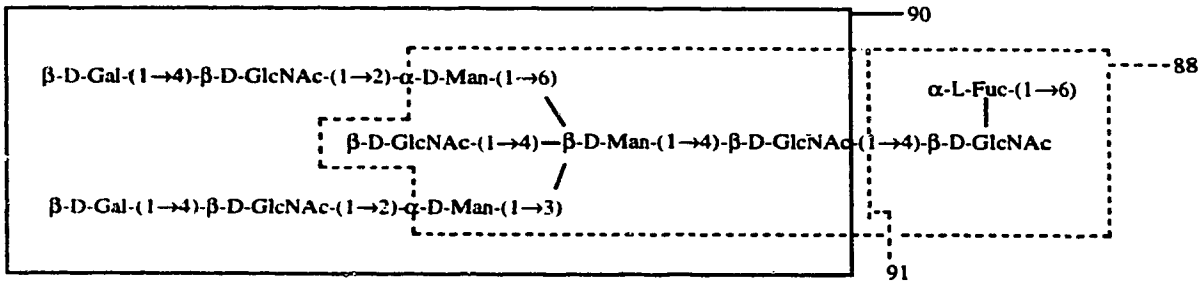
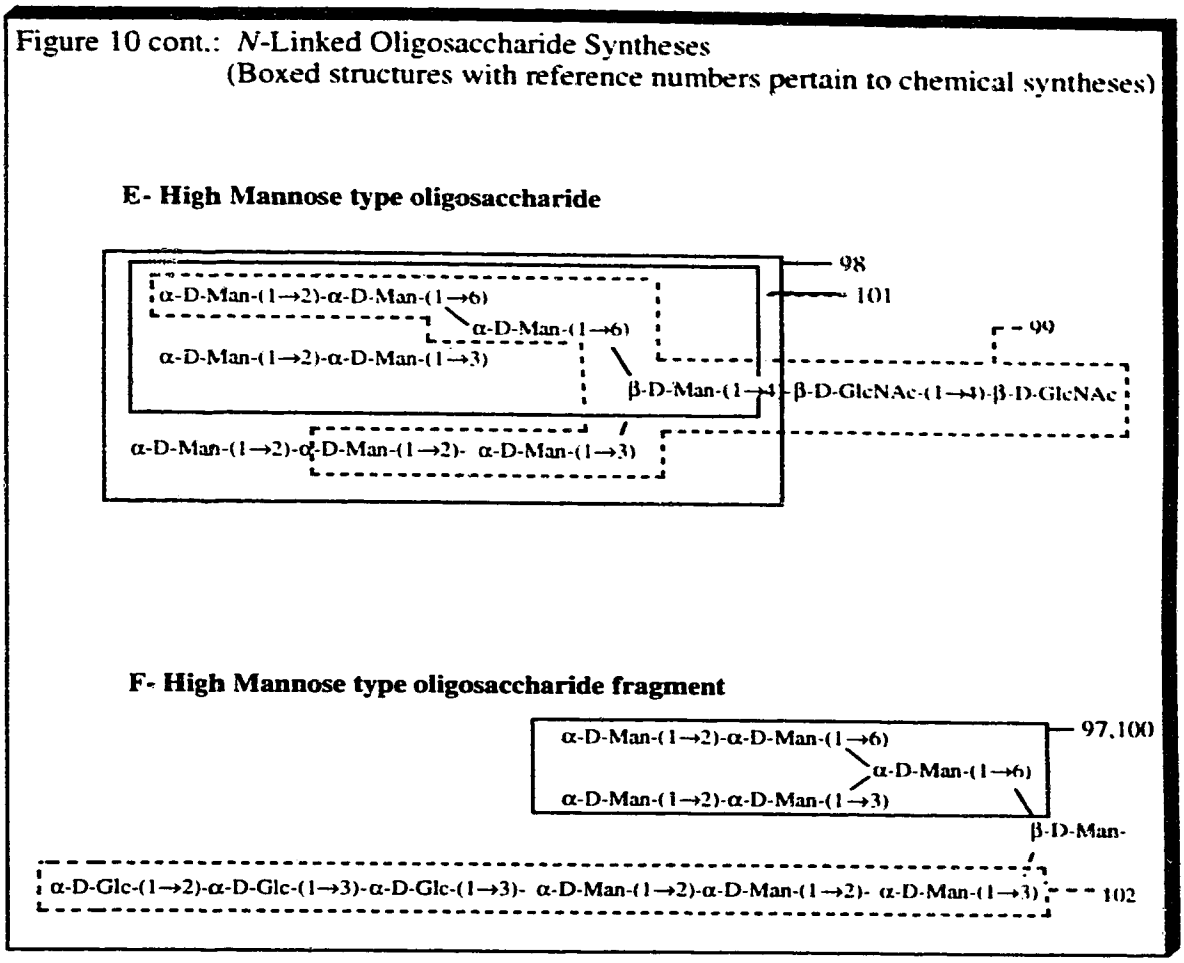


Figure 10 cont.: *N*-Linked Oligosaccharide Syntheses
(Boxed structures with reference numbers pertain to chemical syntheses)



mannooligosaccharide[103]. A β-(1-4) linkage between mannose and glucose is also present in the spermatozoa and ova of the fresh water bivalve *Hyriopsis schlegelli* [104,105].

There are two main reasons that explain why the β-mannosidic linkage is so difficult to synthesize:

1. The anomeric effect[106] stereoelectronically favors the α-mannosidic linkage. Thus any generation of an oxocarbenium ion **Z** (Figure 12) will give a predominance of α-product, in which the anomeric group is axial and;

2. Neighboring group participation via an ester (ie. an acetyl or benzoyl group) gives α-mannopyranosides. This is the method of choice to stereoselectively form 1,2-trans glycosidic linkages as is the case with β-gluco or galacto linkages. However, in mannose the 2-position is axial, thus participation from the 2-position will lead to only the α-product (Figure 11). For this reason a non-participating group such as a benzyl group must be used.

Several strategies have been developed to give β-mannosides. Most of these methods can be classified into three main groups. The first group utilizes insoluble promoters[107-109] and is an extension of the original Koenigs-Knorr[110] procedure. The second group involves an oxidation-reduction strategy to invert a β-glucoside to a β-mannoside[111-113]. The third group consists of intermolecular[114-118] and intramolecular nucleophiles[119-122] that are used to invert the 2-position of glycosides. These strategies are discussed below and cover most of the methods that have been used to make at least disaccharide linkages. Other methods such as the use of mannosidase enzymes in transmannosylations[123,124] and the use of anomeric radicals[125] have not yet been successful in giving comparable yields (>20%) of β-mannoside linked disaccharides.

C.3.i. The Use of Insoluble Promoters:

The choice of an insoluble promoter to activate a glycosyl halide (bromide or chloride) is the most often used procedure for the synthesis of β-mannosides (Figure 12). Two crucial factors must be in play in order for the reaction to give primarily the 1,2-cis configuration. The first factor is that the displacement of the glycosyl halide must occur in an S_N2 like fashion. This is because any oxocarbenium ion formation will lead to a preponderance of α-glycoside due to the anomeric effect[106]. The second factor is that the

Figure 11: Neighboring Group Participation in the Formation of α-Mannopyranosides:

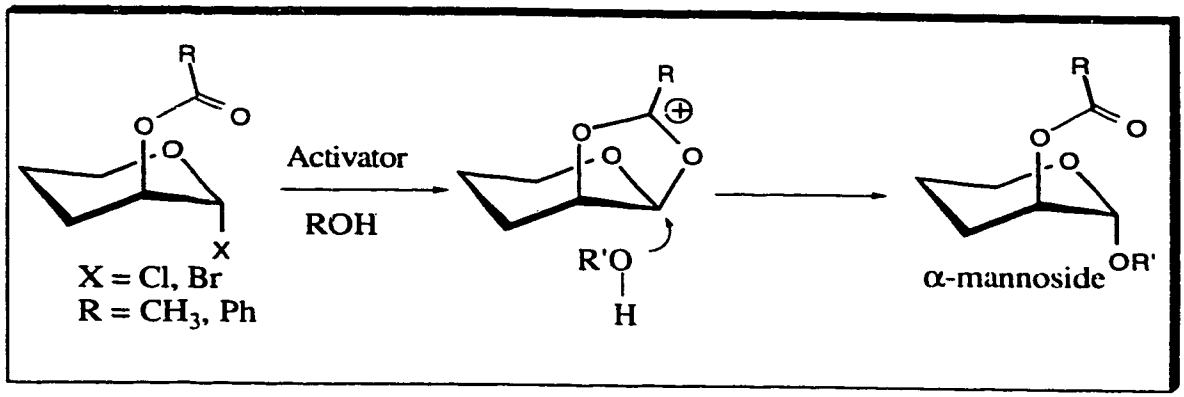
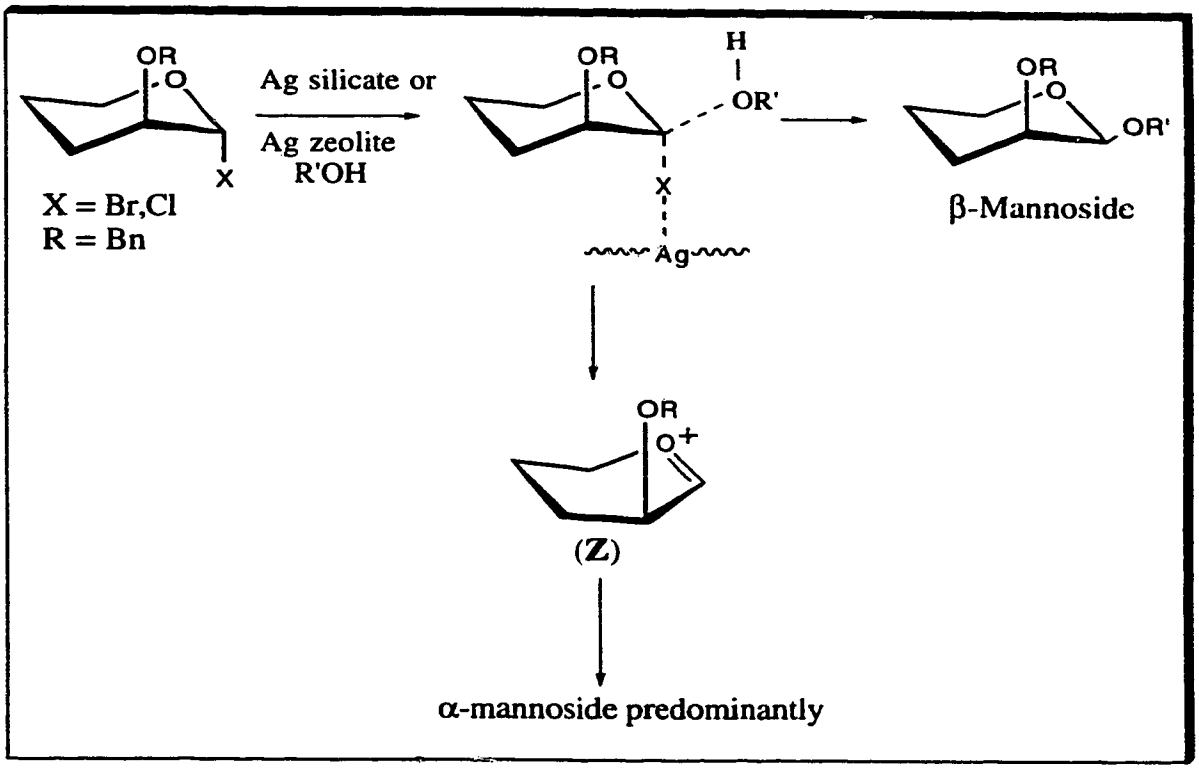


Figure 12: Insoluble Promoter Strategy for Making β-Mannopyranosides:

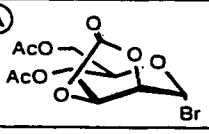
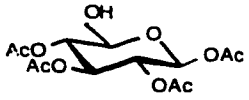
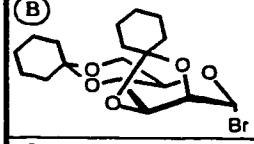
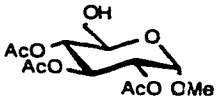
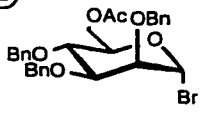
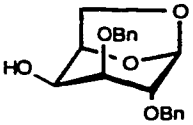
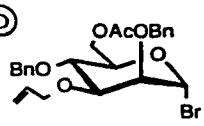
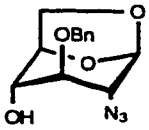
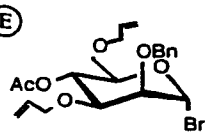
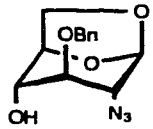
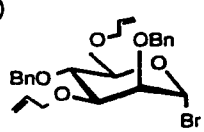
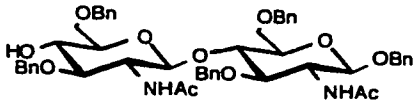
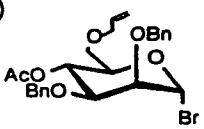
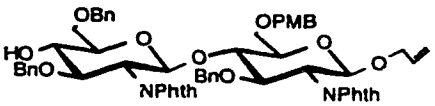
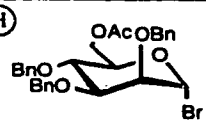
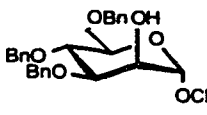


more stable α-halide must be activated in preference to the more reactive β-halide. This allows for the S_N2 displacement to give the β-glycoside. The use of an insoluble promoter is ideal for this scenario since the surface of the promoter (Figure 12) can complex to the α-anomer thereby protecting the α-side of the molecule from attack by the alcohol. The incoming nucleophile can therefore preferentially attack the activated α-halide in an S_N2 fashion to give a β-mannoside.

Despite widespread use of insoluble promoters for the formation of β-mannosides, this strategy is prone to many pitfalls. For example, the timing of the reaction, which is influenced by the reactivity of the acceptor, the donor and the promoter, must be exact to optimize a bimolecular displacement without any oxocarbenium ion formation. Therefore, reactive alcohols are the most successful as they are nucleophilic enough to attack the activated halide and thus minimize any free oxocarbenium ion formation. When unreactive secondary carbohydrate alcohols are used, more reactive promoters and donors are needed. In some instances, inconsistency with the activating ability of the silver salt promoters have caused problems. In summary, these pitfalls make this method useful only after careful optimization of each reaction system.

The first reported case of using insoluble silver salts for the formation of β-mannosides was in 1961 by Gorin and Perlin (Table 1, entry A)[126]. They utilized traditional Koenigs-Knorr[110] chemistry using silver oxide as the promoter and the linkage formed was with the highly reactive 6-position of glucose. Other uses of silver oxide[127-129] as well as promoters such as silver carbonate (Table 1, entry B)[107,130-132], silver salicylate[133], and silver tosylate[134] have been reported. In all the above examples these insoluble silver salts are only successful with highly reactive primary carbohydrate alcohols or non carbohydrate acceptors.

Table 1: Insoluble Silver Salt Promoters used in β-Mannoside Formation:

Donor	Acceptor	Promoter	Yield (%)		Reference
			α	β	
(A) 		Ag_2O	trace	45	126
(B) 		Ag_2CO_3	14	81	131
(C) 		Silver Silicate	0	81	107
(D) 		Silver Silicate	10	67	135
(E) 		Silver Silicate	11	65	91
(F) 		Silver Silicate	36	40	136
(G) 		Silver Silicate	19	48	88
(H) 		Silver Zeolite	21	50	109

The first breakthrough that enabled this procedure to be applied to less reactive alcohols came in 1981 by Paulsen and Lockoff (Table 1, entry C)[107]. They utilized the much more reactive silver silicate as an insoluble promoter that gave satisfactory yields with secondary carbohydrate alcohols. This set the stage for the elegant syntheses of the *N*-linked oligosaccharides that are described above (see section C.2 and Figure 10). For example, the reactions in entry D and E of Table 1 gave a β-mannoside yield of 67%[135] and 65%[91] respectively. Notice that in both examples the acceptor used is an anhydro sugar that locks the hydroxyl group into the axial position thus making it more reactive. Paulsen utilized this anhydro acceptor extensively in *N*-linked oligosaccharide syntheses[76,86,90,91,93,96,135]. Ogawa utilized the more direct acceptor in entry F of Table 1 to give the β-linked product in 40% yield[136]. The realization that an electron withdrawing group at the 4-position of the donor increases the amount of β-mannoside by reducing the amount of oxocarbenium ion that forms[137] is exploited in entry G to give an impressive yield of 48% β-mannoside with only 19% of α[88]. Garegg and coworkers used the promoter silver zeolite[109] to achieve similar success with secondary carbohydrate alcohols (entry H). Silver zeolite is the second most common promoter used to make β-mannosides (after Paulsen's silver silicate) and is considered less reactive[137].

An extension of the insoluble promoter strategy has been recently disclosed by Lichtenthaler and coworkers[138,139]. They utilize 2-oxo glycosyl bromide derivatives as donors to make β-selective linkages, followed by reduction of the keto functionality to give β-mannosides (Figure 13a). These glycosyl donors can be obtained in high yield (75-90%) from the treatment of 2-hydroxy glycal esters with *N*-bromosuccinimide / methanol. The fundamental aspect of this procedure is the electron withdrawing 2-keto group which limits oxocarbenium ion formation[137]. This enables an S_N2 displacement to occur at the anomeric center to give preferentially the β-isomer. Reduction of the keto group then gives a preponderance of β-mannoside.

Figure 13a: The Use of 2-Oxo Glycosyl Donors for the Synthesis of β-Mannosides: [138]

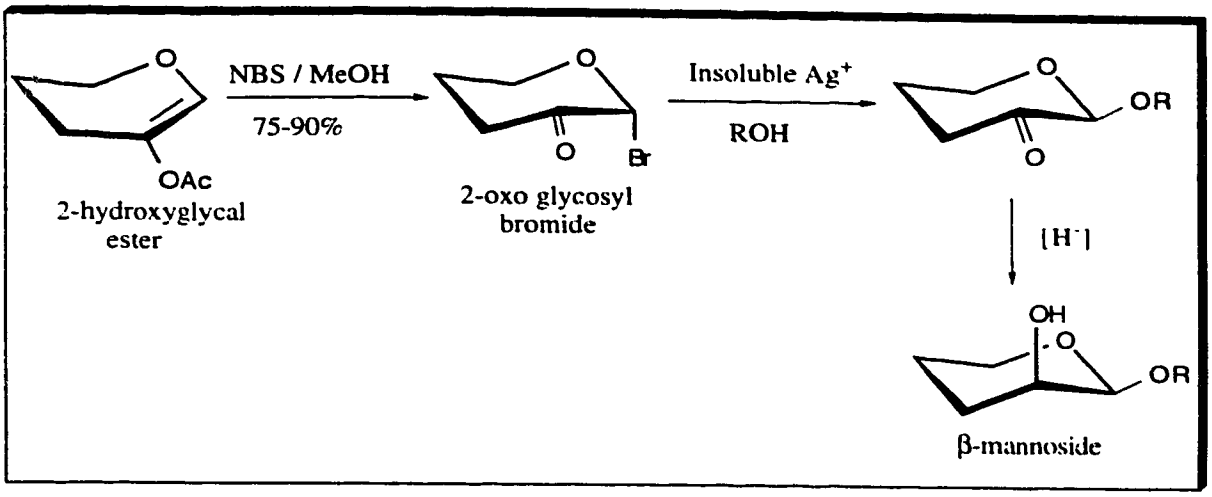
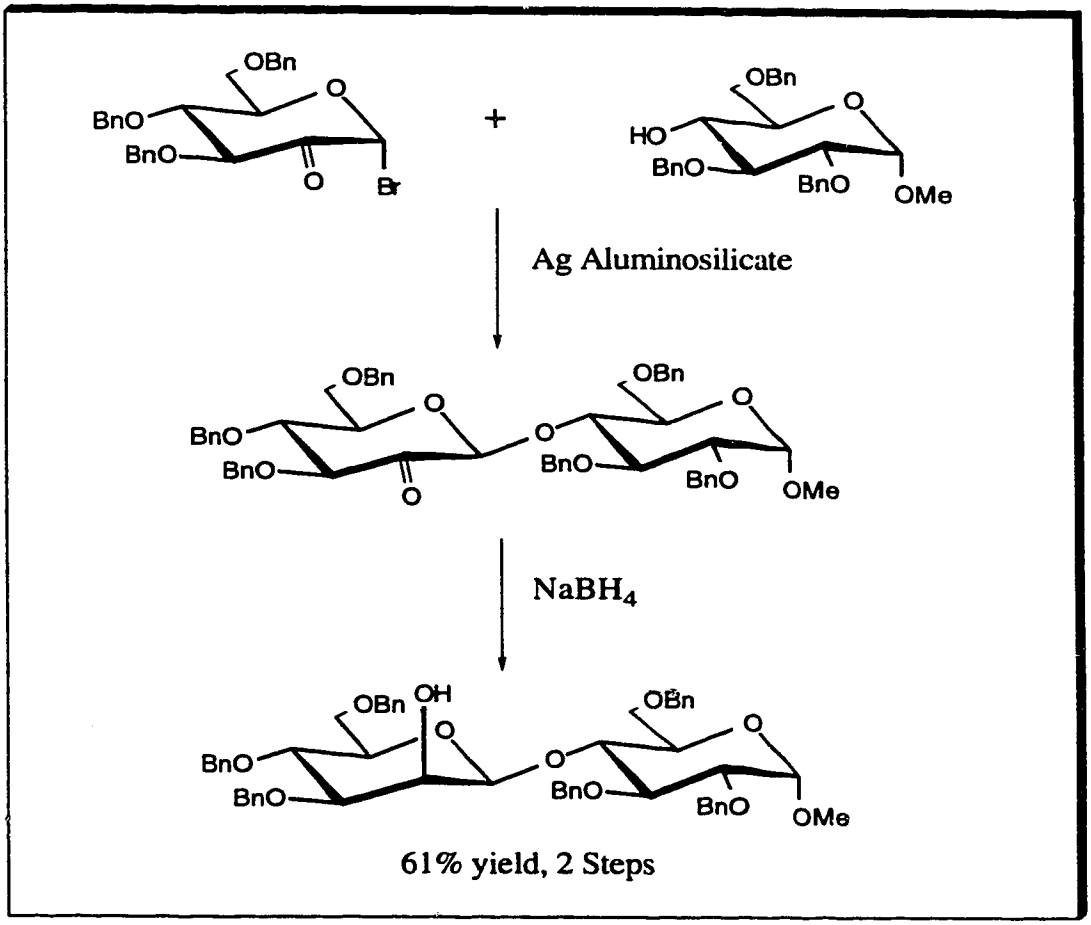


Figure 13b: The 2-Oxo Glycosyl Donor Approach in the Synthesis of a Disaccharide:[138]

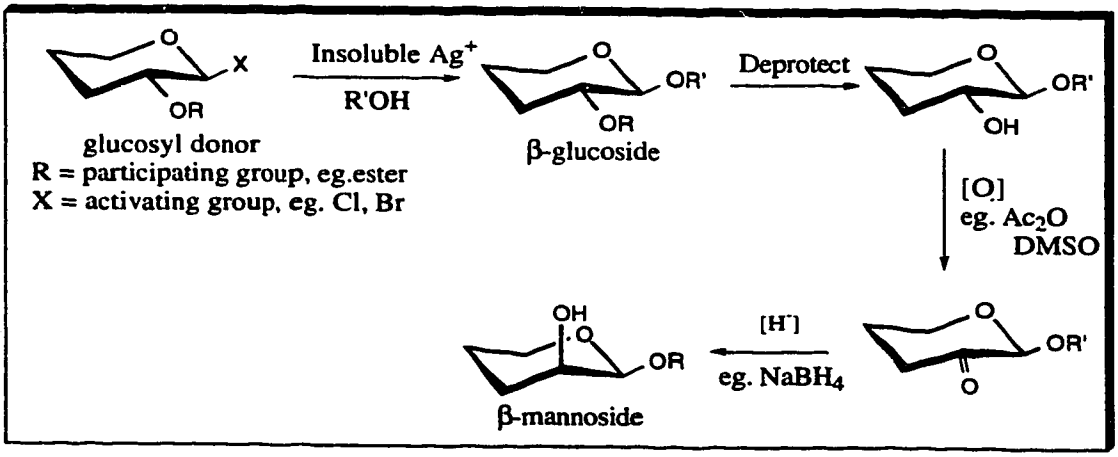


Reactions employing 2-oxo glycosyl halides have given promising results. For example, the best results to date are in the synthesis of a disaccharide component of *Hyriopsis schlegelii* [104], which was achieved in a combined yield of 61% for the glycosylation and reduction steps (Figure 13b). The use of the promoter silver aluminosilicate (Van Boeckel's Catalyst[137]) gave superior results over Paulsen's catalyst. Despite the success of this procedure, the inherent lower reactivity of the 2-oxo glycosyl bromides may prove to be a problem when applied to more complex syntheses such as *N*-linked structures.

C.3.ii. The Oxidation-Reduction Method:

The oxidation-reduction method is the second most common used strategy for the synthesis of β-mannosides. This reliable but laborious[111] procedure creates a β-glucoside and then epimerizes the 2-position by deprotection, oxidation and reduction (Figure 14). One obvious advantage is the replacement of the difficult β-mannosylation step with the relatively simpler β-glucosylation step. After deprotection and oxidation, the reduction step gives a predominance of *manno* configuration. This is because equatorial hydride attack of the 2-oxo intermediate is favored over axial hydride attack.

Figure 14: The Oxidation-Reduction Method:



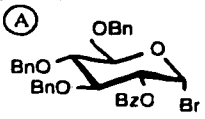
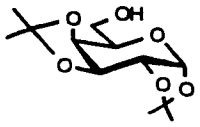
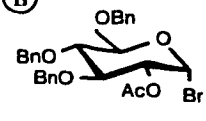
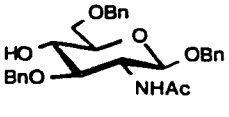
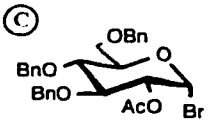
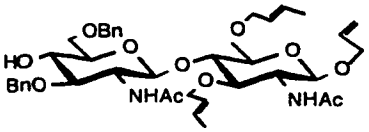
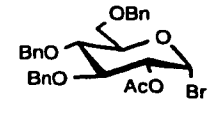
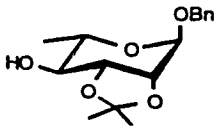
Theander[113] first demonstrated in 1958 that the stereoselective reduction of methyl β-D-arabino-hexopyranosidulose gave preferentially the *manno* configuration over the *gluco* configuration. It was not until 1972 that Lindberg and coworkers utilized this fact to synthesize β-mannosides[111] (Table 2, entry A). Jeanloz and coworkers applied this strategy to the synthesis of the β-D-Man-(1→4)-β-D-GlcNAc linkage present in the core pentasaccharide of *N*-linked glycoproteins[84,85,140] (entries B and C in Table 2). This was the first synthesis of this linkage. Kotchetkov and coworkers also used this oxidation-reduction procedure to synthesize a β–D-man-(1→4)-Rha linkage present in the *O*-specific polysaccharide of Salmonella strains (Table 2, entry D)[141,142]. Even though the use of this procedure has diminished since the advent of the silver silicate and silver zeolite insoluble promoters, there are instances[143,144] where this method is advantageous.

C.3.iii. The Use of Inter and Intramolecular Nucleophiles:

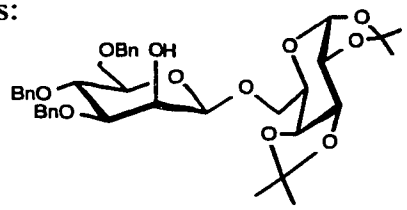
a. Intermolecular Nucleophiles:

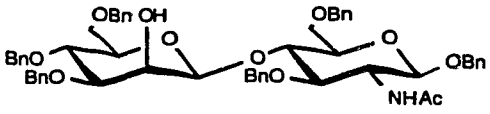
Another approach for the synthesis of β-mannosides utilizes intermolecular nucleophiles. The best results have been obtained by epimerizing the 2-position of a β-glucose residue[114,116] or both the 2- and 4-position of a β-galactose residue[115,117] to give a β-mannoside. The strategy relies upon creating a highly reactive leaving group on the position that is to be inverted and treating it with a strong nucleophile. The nucleophile causes an S_N2 displacement that epimerizes the position on the carbohydrate ring. The displacement at the 2-position with intermolecular nucleophiles is especially difficult. This has been ascribed to interactions of the nucleophile with the axially oriented lone pair of the ring oxygen[121].

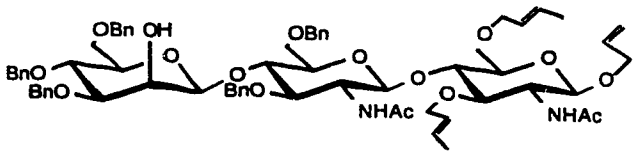
Table 2: Oxidation-Reduction Method for the Synthesis of β-Mannosides:

Donor	Acceptor	Procedure	Product	Overall Yield (% β)	Ref.
(A) 		1.$HgBr_2$ (77%) 2.NaOMe (89%) 3.Ac_2O/DMSO (79%) 4.H_2/Pt,H_2/Pd/C (90%)	A	49	111
(B) 		1.AgOTf (62%) 2.NaOMe (74%) 3.Ac_2O/DMSO (82%) 4.$NaBH_4$ (84%)	B	31	84
(C) 		1.AgOTf (44%) 2.NaOMe (98%) 3.Ac_2O/DMSO 4.$NaBH_4$ (72%)	C	31	85
(D) 		1.$Hg(CN)_2$ (80%) 2.NaOMe (80%) 3.Ac_2O/DMSO (75%) 4.$NaBH_4$ (88%)	D	42	140

Products:

A = 

B = 

C = 

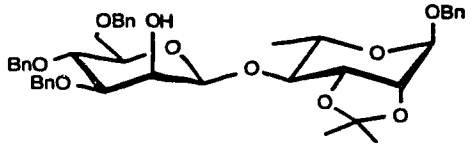
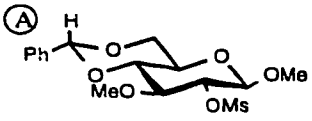
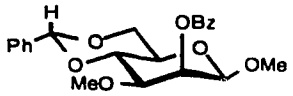
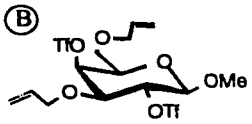
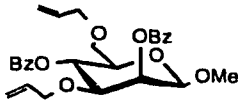
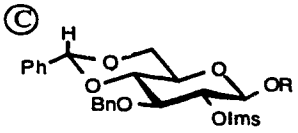
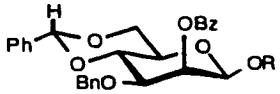
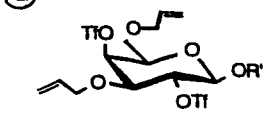
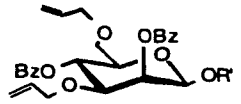
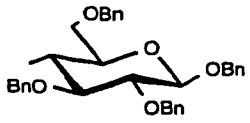
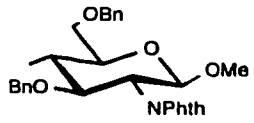
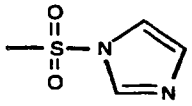
D = 

Table 3: The Use of Intermolecular Nucleophiles for the Synthesis of β-Mannosides:

Starting Material	Product	Nucleophile	Yield (%)	Reference
Ⓐ 		KOBz	62	114
Ⓑ 		Bu_4NOBz	64	115
Ⓒ 		Bu_4NOBz	90	116
Ⓓ 		Bu_4NOBz	47	117

R = 

R' = 

Ims = 

The progress of the intermolecular nucleophile method is summarized in Table 3. In entry A, Miljkovic and coworkers[114] displaced a mesylate leaving group with a benzoate to give the methyl β-mannoside in 62% yield. In entry C, David and coworkers[116] extend this concept to disaccharides, making the β-D-Man-(1→4)-β-D-Glc derivative. This disaccharide utilizes the imidazylate as a leaving group which is made from *N,N'*-sulfuryldi-imidazole which is easier to handle than the more commonly used triflic anhydride. David et al[115,117] displayed the double displacement of a galactose residue to a mannose residue in entries B and D by utilizing the highly reactive *O*-triflate leaving groups. Note that entry D represents a protected form of the β-D-Man-(1→4)-β-D-GlcNAc linkage present in *N*-linked carbohydrates. The elegance of the double inversion is exemplified by starting the reaction at room temperature (25°C) to first allow displacement of the more reactive 4-position to give the *gluco* configuration, then heating to 100°C to displace the less reactive 2-position to give the desired product.

b. Intramolecular Nucleophiles:

Kunz and Gunther have recently disclosed a novel method to create a β-mannoside linkage[119-121]. They utilize an intramolecular epimerization of the 2-position of a glucose from the neighboring 3-position (Figure 15a). This approach again replaces the difficult β-mannosylation with the easier β-glucosylation. In addition, the S_N2 displacement avoids interactions with the lone pairs of the ring oxygens which is a problem in the intermolecular displacements on the 2-position.

The strategy is outlined in Figure 15b in the synthesis of a tetrasaccharide block of the core pentasaccharide. The procedure involves making a β-glucosidic linkage with a phenylurethane on the 3-position of the glycosyl donor. The phenylurethane serves as an intramolecular nucleophile to invert the neighboring triflated 2-position. After

Figure 15a: The Synthesis of β-Mannosides by Intramolecular Inversion:[119-122]

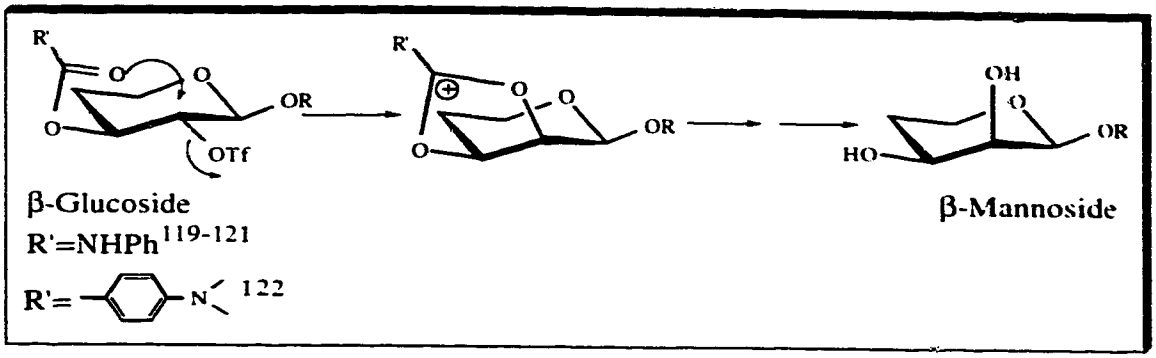
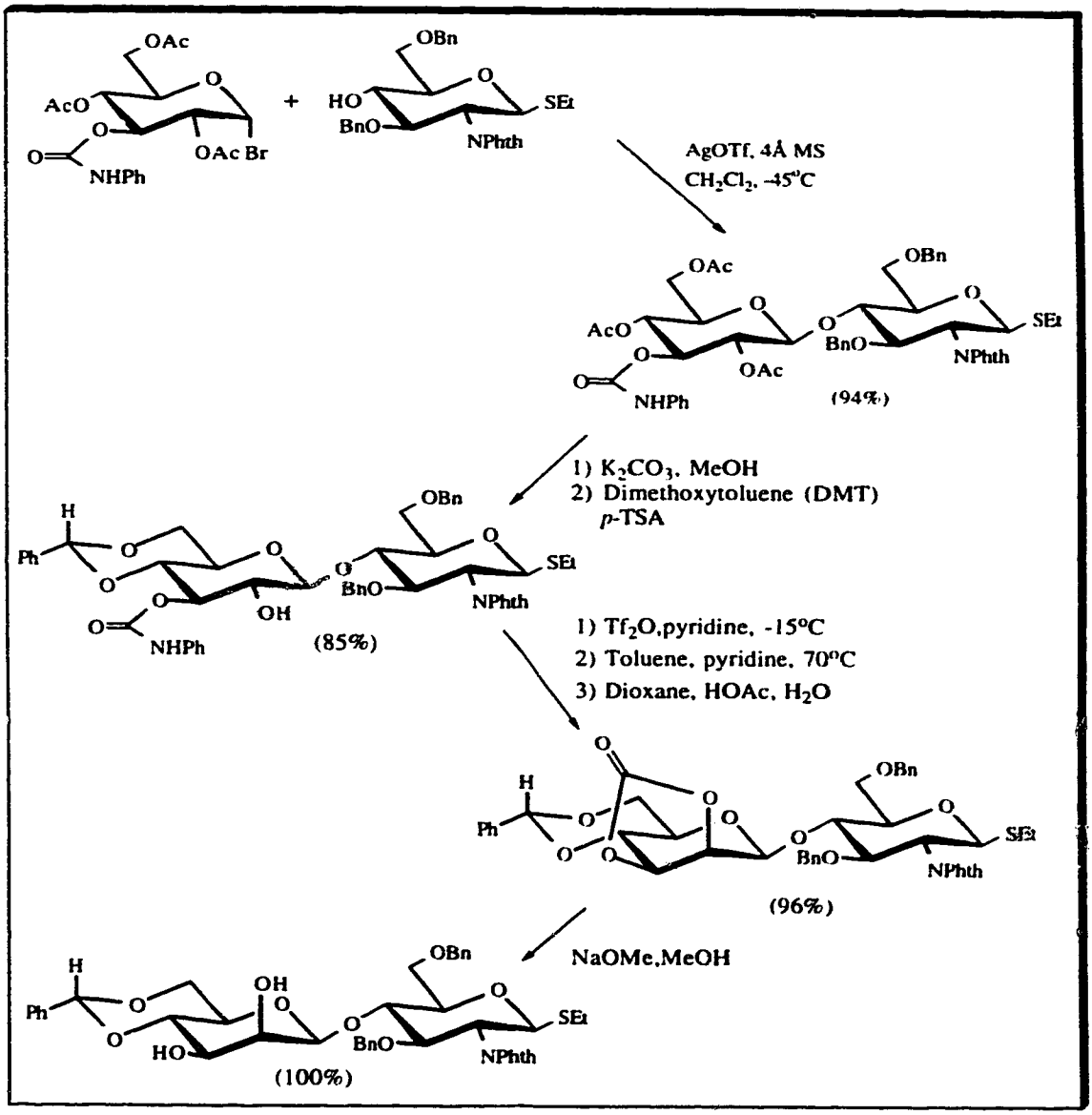


Figure 15b: Intramolecular inversion via participation from the 3-position:[119]



optimization, the overall yield for the indirect formation of the β-mannoside linkage is quite high despite the large number of steps required. One disadvantage is the necessity of the benzylidene ring in order for the displacement to occur. A similar strategy was attempted by Griffith and Hindsgaul[122] in which a *p*-*N*,*N*'-dimethylaminobenzoyl group was used at the 3-position as the intramolecular nucleophile. Ring contraction produced many side products when a 4,6-*O*-benzylidene group was not present on the glucose unit[122].

D. Summary:

The synthesis of β-mannopyranosides is extremely challenging as can be seen from the great volume of research reported in this area. Despite all this work, there still remains no definitive method to synthesize this linkage. Every time a synthesis is conducted in which a β-mannoside is present, the focus of the synthetic strategy must center on creating the β-linkage first, and building around this problematic step. The ability to devise a method that can synthesize this linkage with a more general scope would be a valuable contribution not only to carbohydrate chemistry, but to the entire field of glycobiology.

CHAPTER 2

The Synthesis of β-Mannopyranosides by Intramolecular Aglycon Delivery:

A. The Importance of Stereoselective Glycosylation Reactions:

Despite the advances in the synthesis of oligosaccharides in recent years[57-59,72-83], the field is plagued by low yielding and inconsistent glycosylation steps. One of the greatest problems with present glycosylation reactions is that they usually yield anomeric mixtures, especially when cis glycosides are synthesized. As a result, the separation of these anomers can often be difficult. Therefore, the ability to conduct reactions that yield solely one anomer is essential for the advancement of oligosaccharide synthesis.

The reactions used for the formation of 1,2-trans glycosidic linkages are the most reliable in giving high stereoselectivities. Neighboring group participation (Figure 11) is the most often used strategy although in some instances[145,146,147] this method fails. Another method for stereoselective formation of glycosidic linkages involves the opening of 1,2-anhydro sugars (Figure 16a). Classical work completed by Lemieux in the first chemical synthesis of sucrose[148,149] and maltose[150] exploited this concept. The electrophilic activation of glycals (Figure 16b) is an alternative method of generating stereocontrol which has been used by Thiem[151] in the formation of 2-deoxy sugars. More recently, Danishefsky has combined the epoxide and glycal strategies to synthesize trans linkages with complete stereoselectivity[82,83]. Danishefsky has extended this strategy to the solid phase synthesis of several oligosaccharides with trans linkages[152,153].

Figure 16a: The Use of 1,2-Anhydro Sugars in Stereocontrolled Glycoside Synthesis:

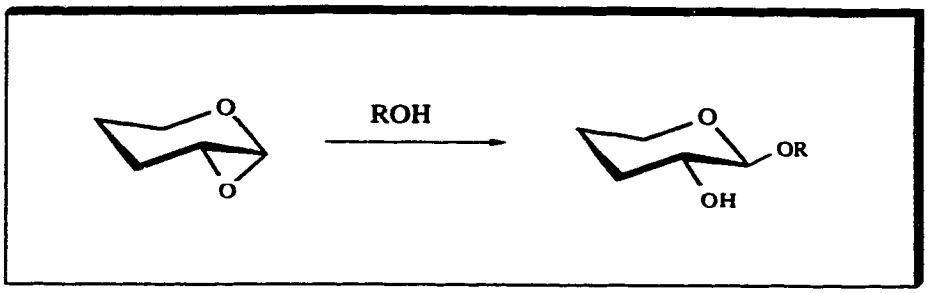
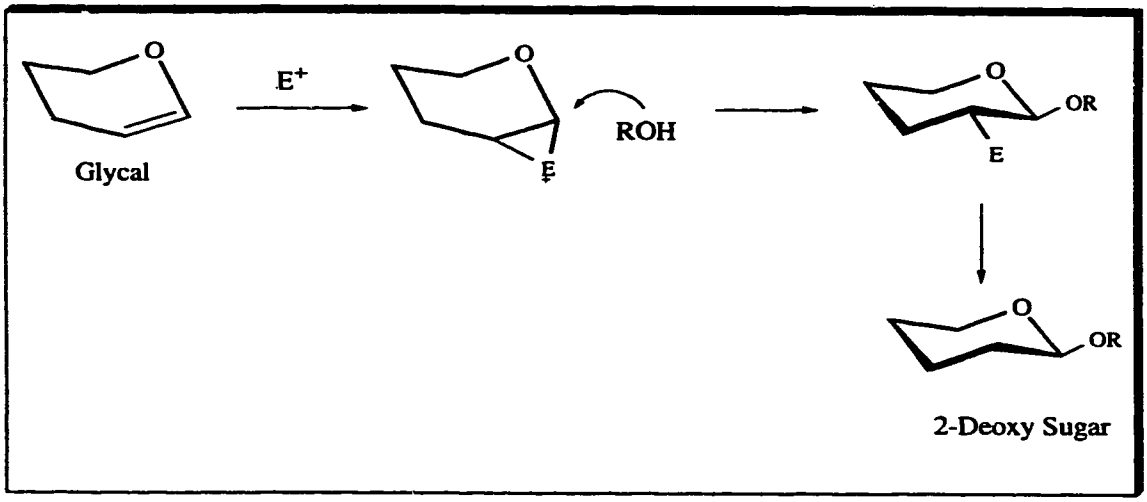


Figure 16b: The Use of 1,2-Glycals in Stereocontrolled Glycoside Synthesis:



The ability to synthesize carbohydrates via solid phase synthesis is one of the ultimate goals of carbohydrate chemistry. Solid phase synthesis would enable this class of biopolymer to be as accessible as oligonucleotides or polypeptides. With the availability of larger amounts of oligosaccharides, the progress of glycobiology would accelerate and have a tremendous biological impact. Considerable research has been conducted in developing methods for the solid phase synthesis of carbohydrates[152,154-157]. The

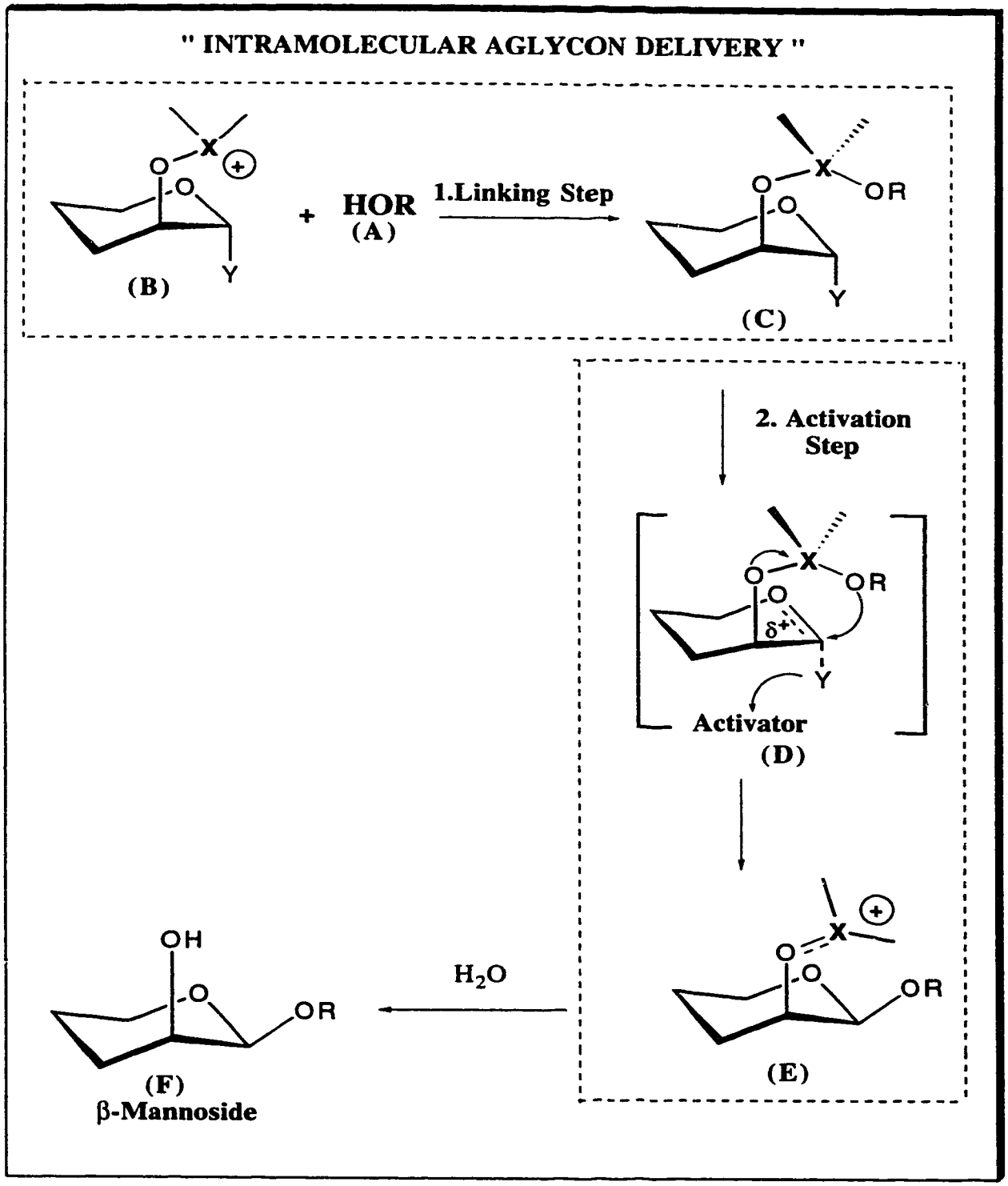
methods reported presently are for simple systems. The general view is that the synthetic methodology is not advanced enough in either yield or stereoselectivity to be successfully applied to solid phase synthesis. New methods to improve glycosylation yields and anomeric control are required.

B. General Strategy for Intramolecular Aglycon Delivery:

The ability to construct cis glycosides with complete stereocontrol would be a significant advancement for glycochemistry. It would also allow for developments in the solid phase synthesis of oligosaccharides. The intramolecular transfer of groups in a pyranose ring is a commonly observed event in carbohydrate chemistry. The migration of ester groups (especially acetates) is a well known problem that has to be carefully avoided, or used advantageously. Recently, Kunz and Gunther[119-121] have shown that a phenyl urethane group on the 3-position of glucose can undergo an intramolecular migration to invert the 2-position to give the mannose configuration (Figures 15a,b). Neighboring group participation (Figure 11) to displace an anomeric activating group is another form of intramolecular participation of groups in a carbohydrate ring.

The general strategy for intramolecular aglycon delivery (IAD) capitalized on the principle of intramolecular transfer within a pyranose ring. For D-mannose, covalent attachment of an aglycon (**A**) to the 2-position of an appropriately derivatized sugar (**B**) (Figure 17) yields the adduct **C**. Activation of the anomeric position of **C** leads to stereocontrolled intramolecular delivery proceeding through a five membered transition state (**D**) to give the cis linked intermediate **E**. Quenching of **E** with water gives β-mannoside **F**. The intramolecular nature of the reaction controls the stereochemistry, ensuring only the cis linked product is formed.

Figure 17: General Strategy for Intramolecular Aglycon Delivery from the 2-Position:



As can be seen in Figure 17, there are two critical steps involved in IAD:

1. The Linking Step: This step involves covalently attaching the aglycon to *O*-2 of the pyranose ring. In order for IAD to be successful, this first step must be a high yielding, convenient procedure that does not interfere with any other groups in the carbohydrate molecule. Ideally, no new stereogenic atoms should be created in the process or **C** will represent two molecules.

2. The Activation Step: This step involves activation of the anomeric carbon. It is essential that the anomeric substituent be stable enough to withstand earlier modification to the 2-position in step 1. Furthermore, there must also be a wide range of activation conditions available that can be used to enhance the viability of this procedure. Most importantly, activation procedures must be mild enough not to cause any destruction of the covalent linker formed in step 1 prior to stereocontrolled delivery of the aglycon to the anomeric carbon.

C. Recent Progress in Stereocontrolled Intramolecular Glycosylations:

There has been significant progress in stereocontrolled *O*-glycosylation. Our first communication in 1991[158] represented the first stereocontrolled synthesis of a complex β-mannoside and was termed intramolecular aglycon delivery. Since then, this carbon acetal strategy has been improved[159] and extended to more complex systems[160]. A report by Stork and Kim[161] in 1992 presented another intramolecular strategy for the synthesis of a β-mannoside. Bols[162-165] has extended this concept to the stereocontrolled synthesis of α-glucosides. Sinay has recently reported an intramolecular strategy for the synthesis of *C*-linked disaccharides[166,167]. In addition, Jung and Castro[168] and Sugimura and Sujino[169] have used intramolecular *N*-glycosylation to deliver a pyrimidine base in the

formation of 2-deoxyribonucleotides. This recent progress demonstrates that this concept has become an exciting, new area of research with the allure of becoming the method of choice for the synthesis of cis-linked carbohydrates.

The approach used by Stork and Kim[161] to make β-mannosides utilizes a silicon tether to covalently attach the aglycon to the 2-position of D-mannose (Figure 18). Their scheme involves the reaction of a primary alcohol with n-butyl lithium to generate an alkoxide ion. This is followed by the addition of dichlorodimethylsilane to form the chlorodimethylsiloxane compound. Reaction of this structure with the thiophenylglycoside gave the silicon tethered structure in quantitative yield. Activation of the anomeric group using Kahne's sulfoxide strategy[170] gave the β-mannoside in 68% yield. Unfortunately, this method was not successful when applied to secondary carbohydrate alcohols due to the inability in coupling the two unreactive sterically hindered alcohols in the silicon tethering step[171].

Stork and coworkers[172] have shown a similar silicon tethered strategy for the synthesis of *C*-glycosides in the *gluco*, *manno*, *ribo* and *arabino* series. The stereocontrolled formation of styryl *C*-glycosides was demonstrated by using radical mediated cyclization of a seleno glycoside with a 3-phenylethynyl group (Figure 19). In the *gluco* series, it is of special interest to note that the stereocontrolled transfer occurred from the 6- and 3-positions as well as the 2-position. Stereoselective radical cyclizations have also been shown by other researcher groups[173,174]. This is demonstrated in Figure 20, where alkenyl derivatives were utilized to form *C*-glycosides.

Figure 18: The Stereocontrolled Synthesis of β-Mannosides Using a Silicon Tether:[161]

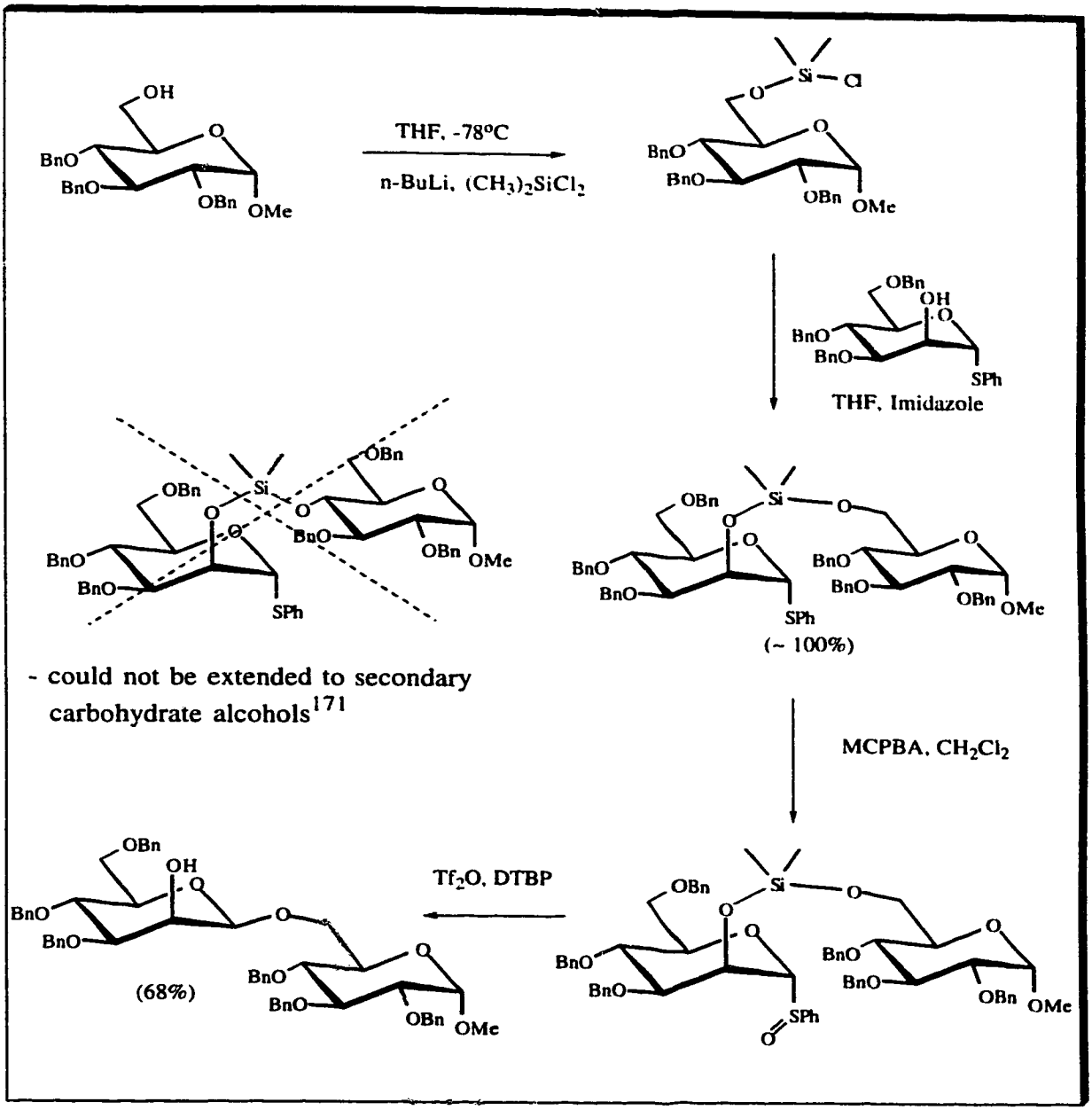


Figure 19: The Stereospecific Synthesis of *C*-Glycosides via a Temporary Silicon Connection:[172]

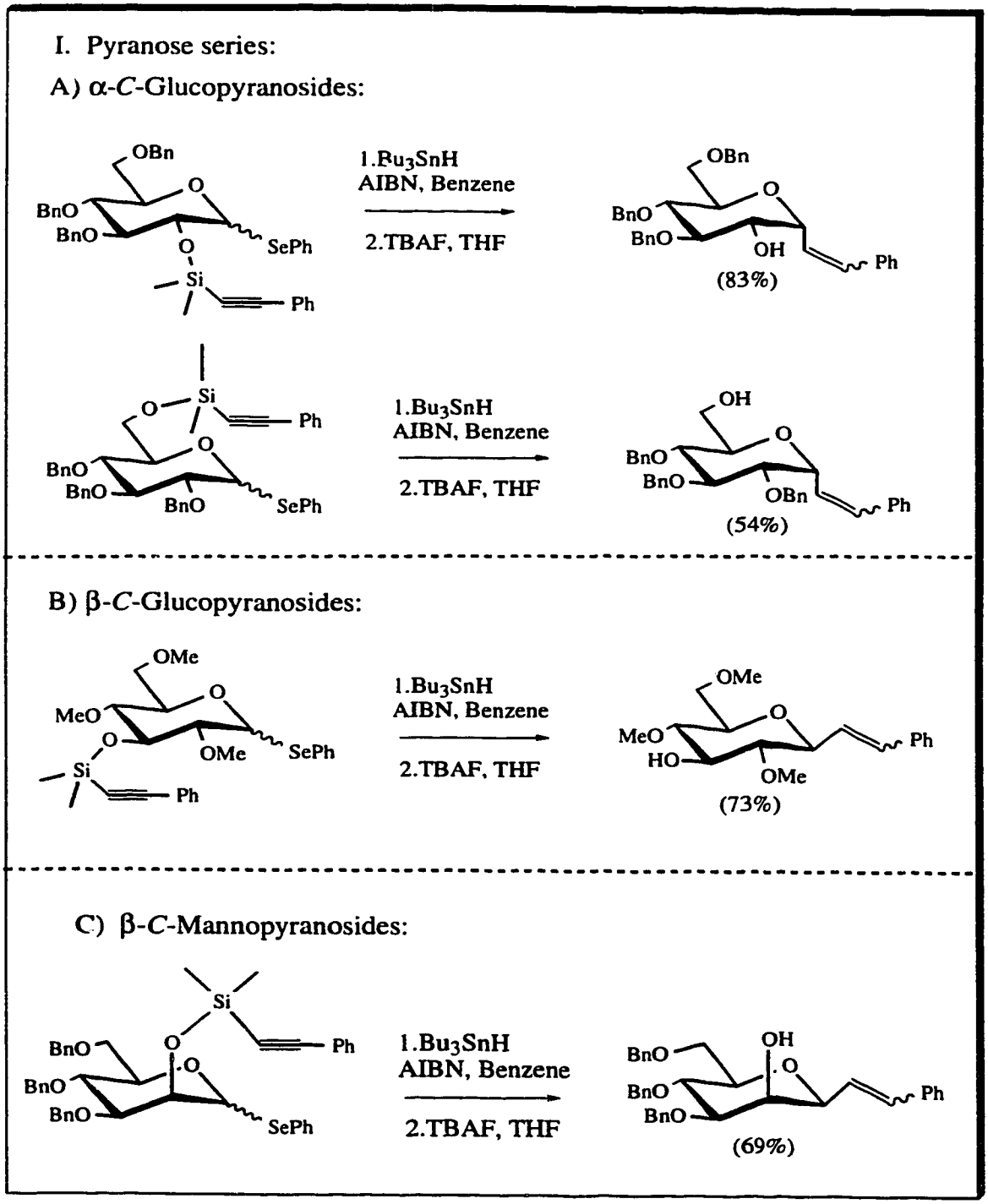
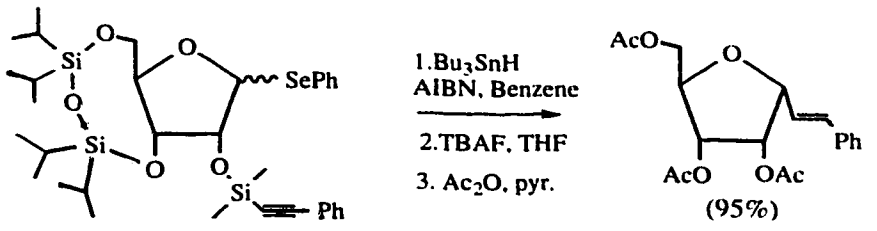
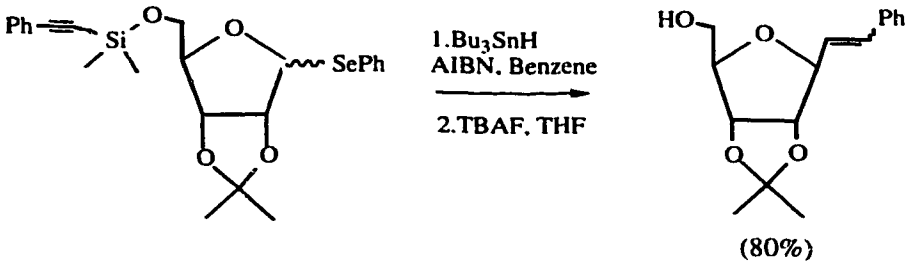


Figure 19 cont.: Stereospecific Synthesis of *C*-Glycosides via a Temporary Silicon Connection:

II. Furanose series:

A) α or β-*C*-ribofuranosides





B) β-*C*-arabinose

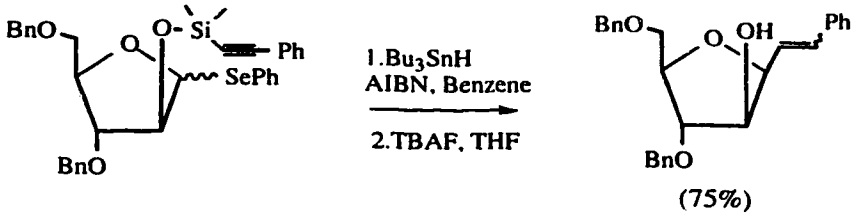
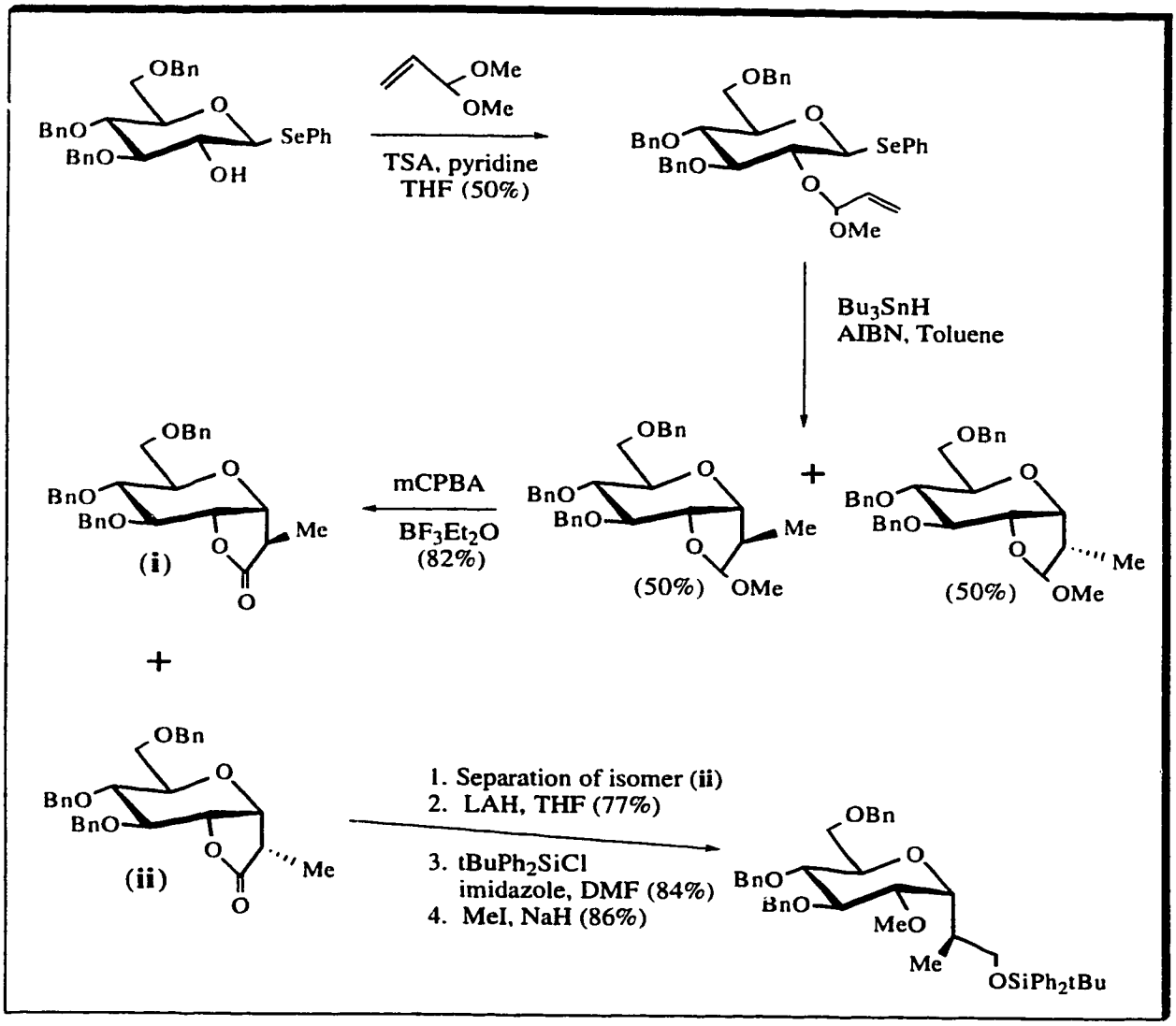
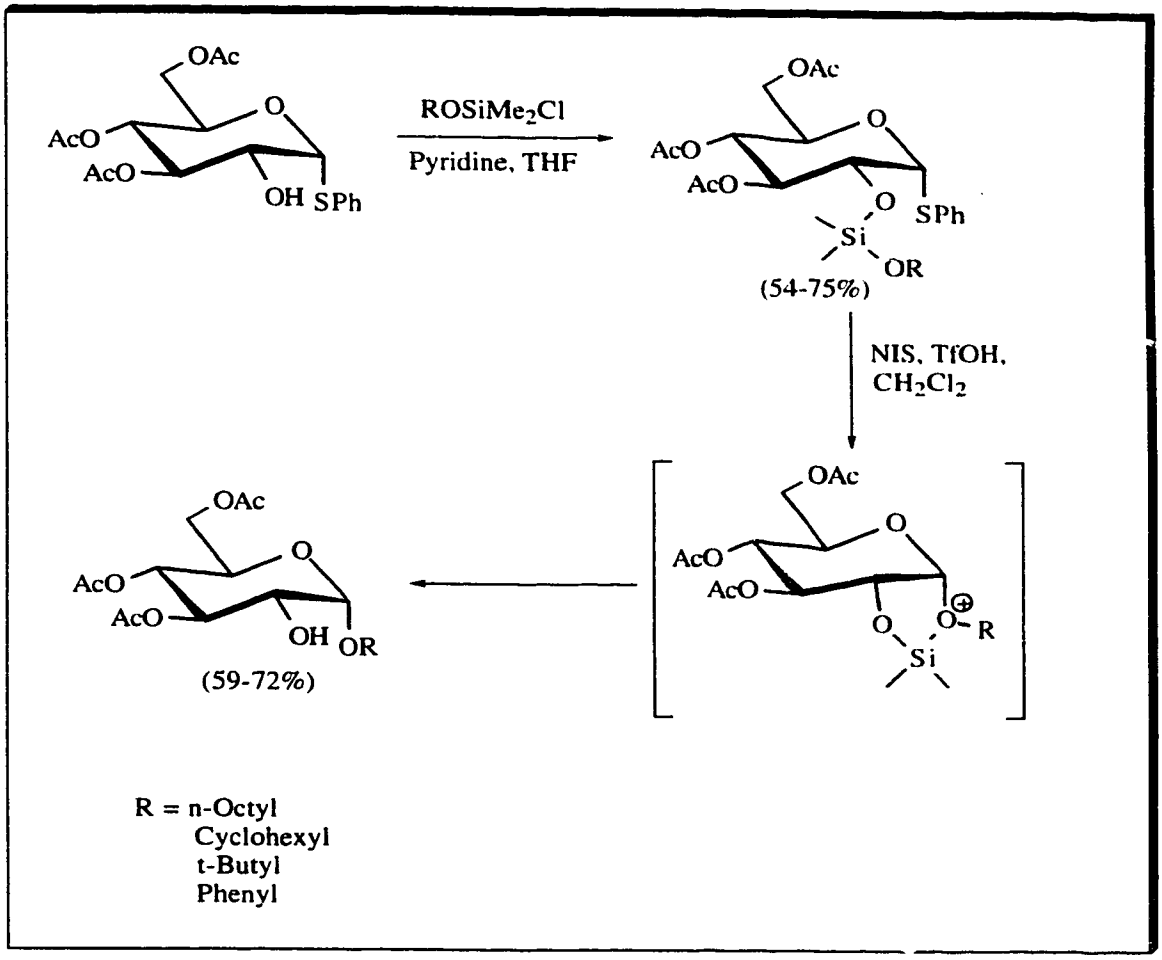


Figure 20: The Stereoselective *C*-Glycoside Formation by Radical Cyclization:[173,174]



Bols and coworkers[162-165] have reported stereocontrolled syntheses of α-glucopyranosides. Bols initially reported results on the synthesis of α-glucosides in which the aglycon is not a carbohydrate (Figure 21)[162].

Figure 21: The Stereocontrolled Synthesis of α-D-Glucopyranosides:[162,164]



Since then, he has extended this work to the synthesis of disaccharides of both the α-glucopyranose and α-galactopyranose series using secondary carbohydrate alcohols[163,165]. The strategy employed by Bols utilized a silicon tethered acetal which can be formed in high yield in a two step synthesis by reacting the sugars with dimethyl silyl dichloride (Figure 22). It is clear from this work and that of Stork and Kim that the use of silicon in the linking strategy gives superior coupling yields to the carbon acetal approach[158-160]. It does seem however, that in some cases, the silicon tether completely fails at linking highly unreactive carbohydrate alcohols[175].

Recently, use of a silyl[166] and ketal[167] tether have been demonstrated in the synthesis of *C*-linked disaccharides. Sinay and coworkers temporarily connect a seleno glucoside with a 4-exo methylene derivative (Figure 23a). This connection is then followed by anomeric radical formation which enabled the exo methylene group to cyclize, giving the methyl α-*C*-maltoside in a stereocontrolled fashion. In addition, an analogous procedure using a 2-*O*-propenyl seleno mannoside was conducted to give the ketal connected disaccharide shown in Figure 23b. This temporarily connected structure was then subjected to radical cyclization to give the α-*C*-linked disaccharide as the major product. The cyclization reaction was not completely stereocontrolled as a 10:1 mixture of α:β *C*-glycosides was obtained.

Figure 22: The Stereocontrolled Syntheses of α-D-Gluco and Galactopyranosides:[163,165]

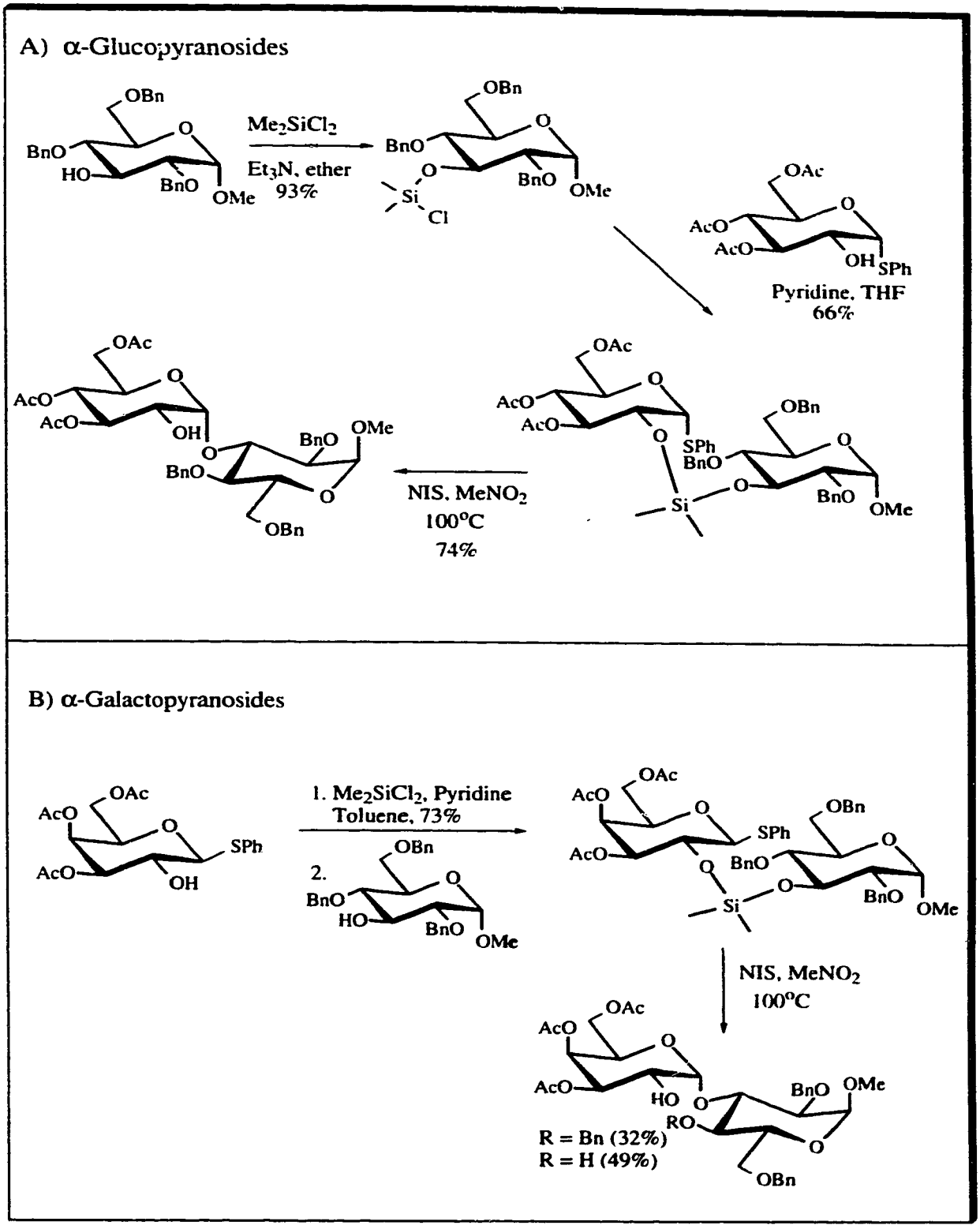
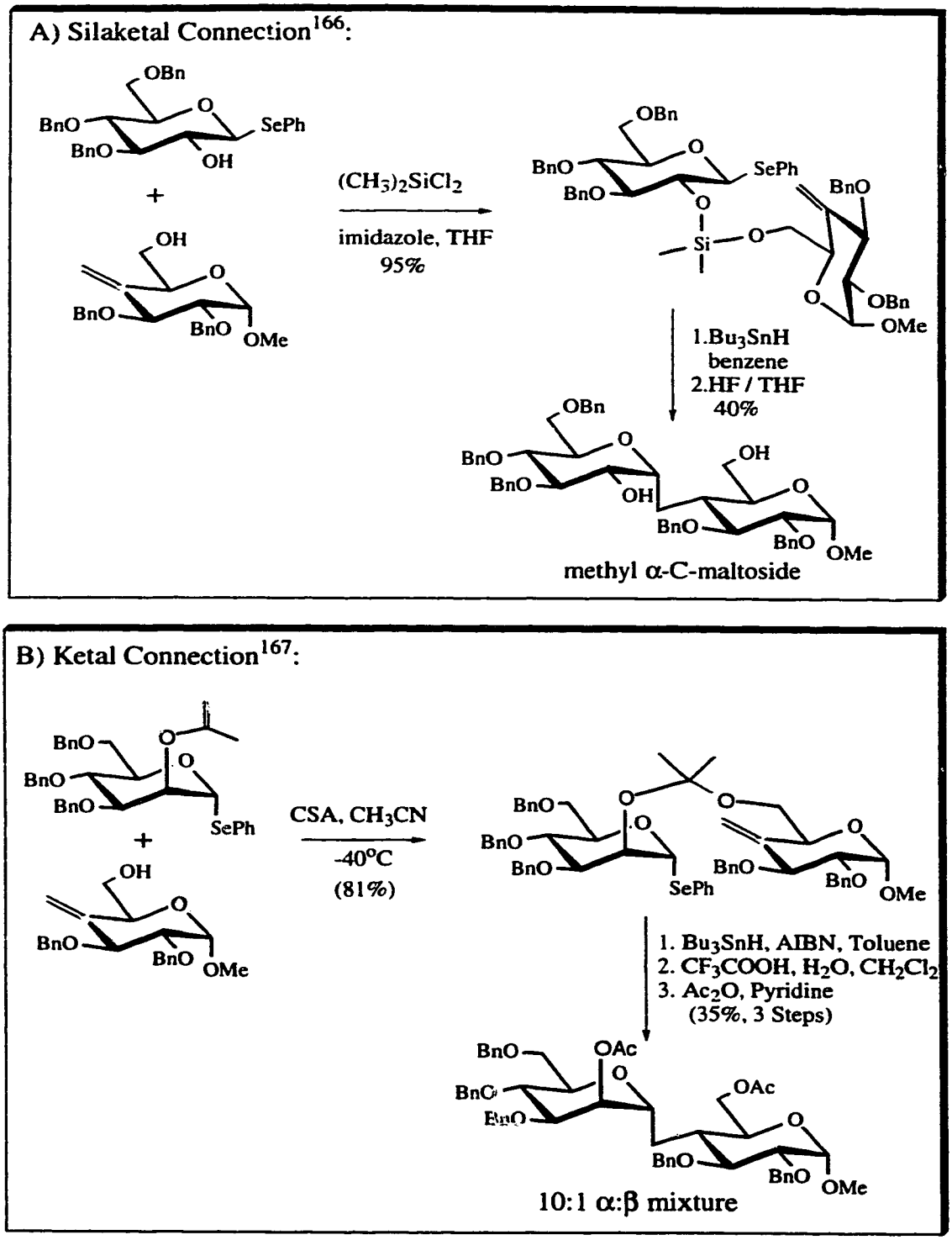
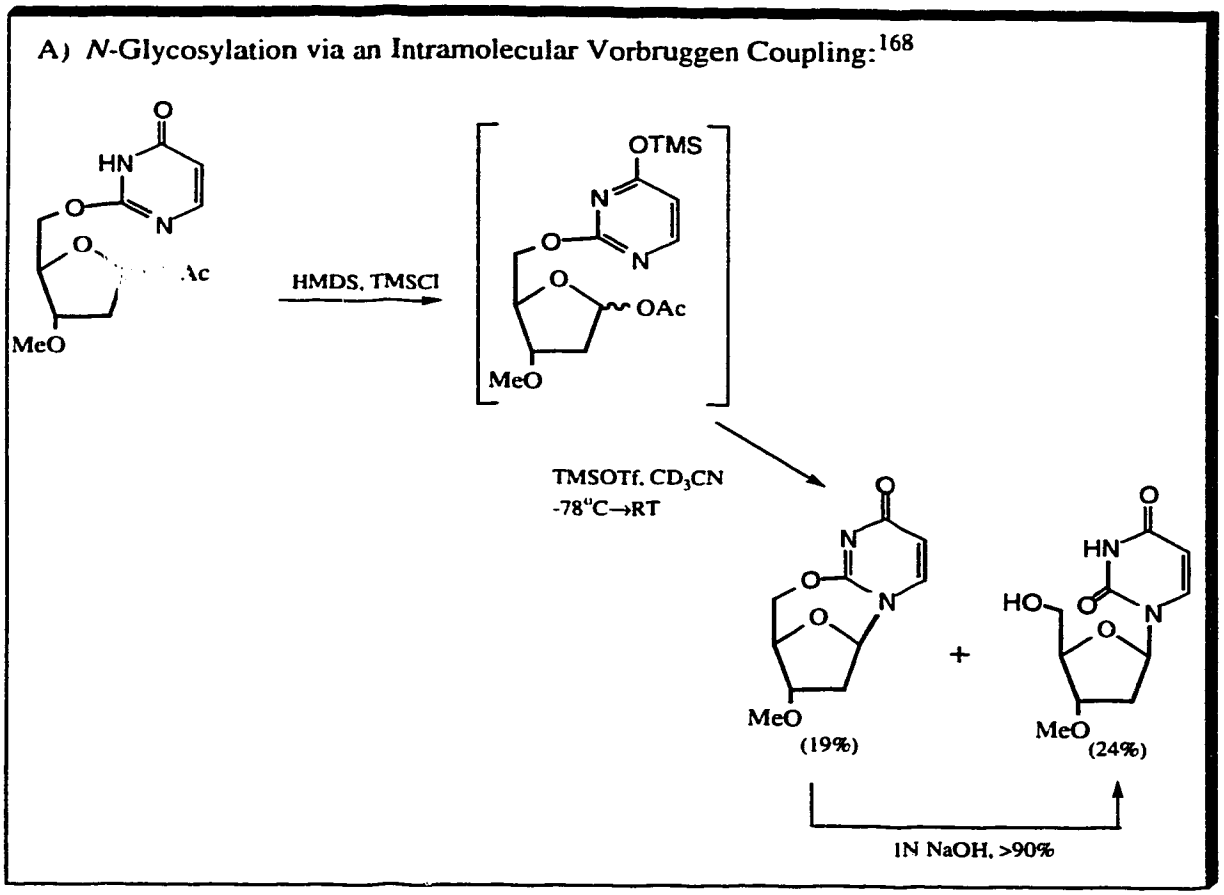


Figure 23: The Synthesis of *C*-Disaccharides Using a Temporary Connection:



The systems described to date have all been closely related. The following examples indicate that the general concept of stereocontrolled intramolecular glycosylations has wider applications. Jung and Castro use an intramolecular Vorbruggen coupling[168] to stereoselectively give a β-linked deoxyribonucleoside (Figure 24a). Sujino and Sugimura[169] covalently attach a pyrimidine base to the primary position of a 2-deoxy ribose thiophenyl glycoside and activate the thioglycoside to give the β-linked deoxyribonucleoside (Figure 24b).

Figure 24: The Stereocontrolled Synthesis of 2-Deoxyribonucleosides:

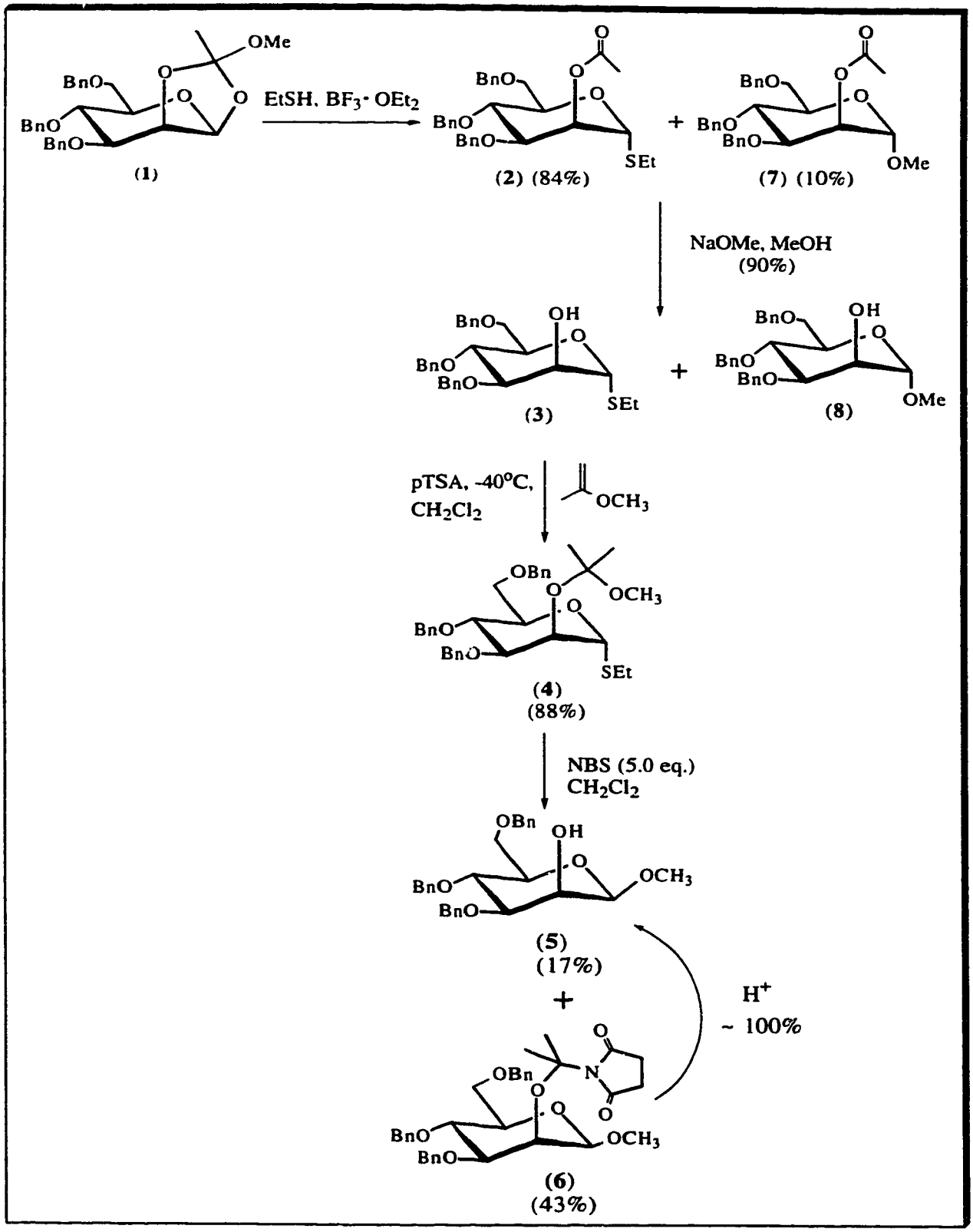


D. Development of Intramolecular Aglycon Delivery:

1. The Stereocontrolled Synthesis of Methyl β-D-Mannopyranoside:

The first breakthrough in applying IAD at the monosaccharide level came when methanol was used as the aglycon. In order to see if the general concept outlined in Figure 17 was valid, the thioglycoside **2** was synthesized from the known ortho ester **1**[176] as outlined in Figure 25. A thioglycoside enabled manipulation of the 2-position of the molecule without affecting the anomeric center. Furthermore, a wide variety of methods are available to activate the anomeric sulfur once the 2-position has been appropriately derivatized. Reaction of **3** with 2-methoxypropene under acid catalyzed conditions gave the isopropylidene acetal **4** in 88% yield. Treatment of **4** with *N*-bromosuccinimide activated the thioglycoside which allowed for intramolecular delivery of the *O*-methyl group which gave the β-mannoside **5** in an unoptimized yield of 15%. Comparison of the ^{1}H NMR spectrum of the product **5** with that of the α-mannoside **8** showed that only a β-mannoside was identified as a product from IAD. No α-mannopyranoside could be detected in the reaction mixture. The α-mannoside **8** was obtained by de-*O*-acetylation of **7** and was a by-product in the synthesis of **2**. Activation of the acetal **4** was optimized using 5.0 equivalents of NBS as shown in Figure 25. It can be noted that under these conditions 43% of succinimide adduct **6** was obtained as well as 17% of the methyl β-mannoside **5**. The overall yield of β-mannoside formation was therefore 60% because the acid hydrolysis of **6** gave a quantitative yield of **5**. Identification of the succinimide adduct further supports the intramolecular nature of this reaction. It seems that after transfer of the aglycon, the carbocation that forms on the 2-position can decompose by scavenging trace water. It can also be trapped by other nucleophiles present in the reaction mixture, such as the succinimidyl anion.

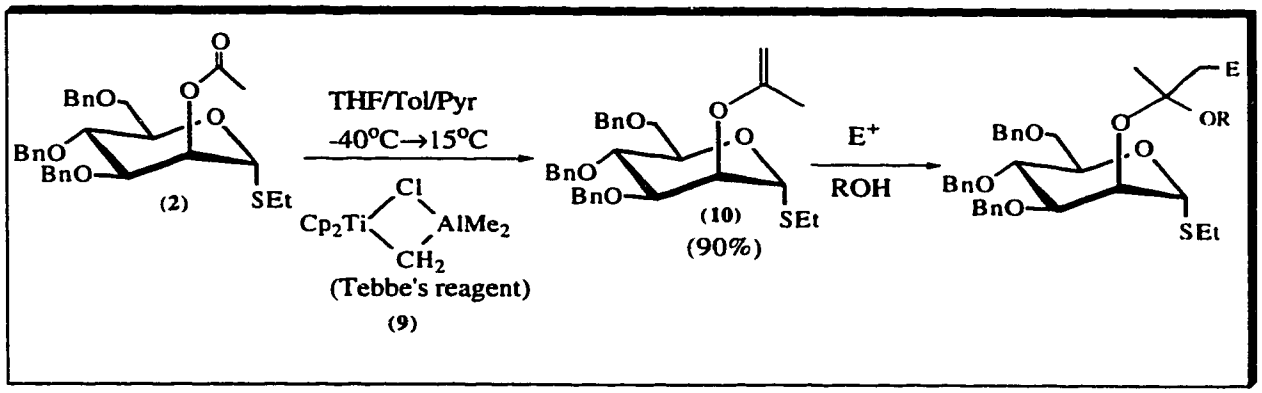
Figure 25: The Synthesis of Methyl β-D-Mannosides by Intramolecular Aglycon Delivery:



D.2. Development of the Linking Step:

The extension of IAD to more complex molecules was essential in order to test the effectiveness of this strategy. Sinay[75] had already shown that anomeric acetates could be converted to vinyl ethers which were useful in a novel glycosylation strategy. The use of Tebbe's reagent **9** has been reported frequently in the literature[177-179] and recently in carbohydrate chemistry[167,180-183]. Treatment of the thioglycoside **2** with Tebbe's reagent gave the vinyl ether **10** in as high as 90% yield but more reliably near 70% yield (Figure 26).

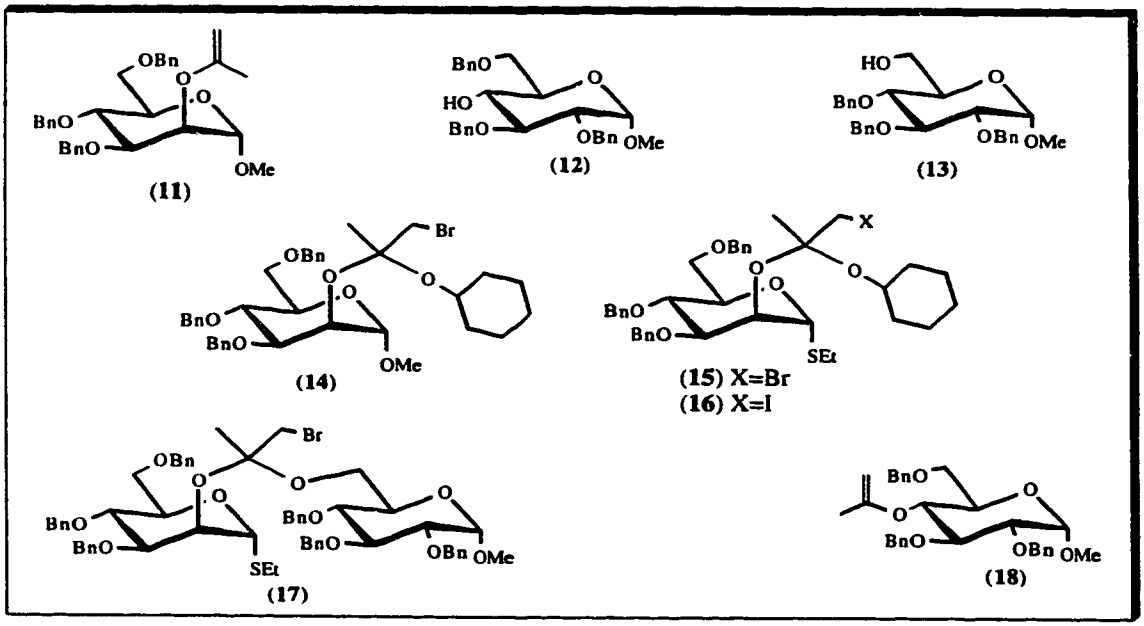
Figure 26: The Synthesis and Electrophilic Activation of the 2-*O*-Propenyl Compound (**10**):



Covalent attachment of the aglycon was then attempted by the reaction of alcohols with the 2-propenyl derivative **10**. A variety of electrophilic agents were tried which included NIS (Table 4-entries 5, 8), I_2 (entry 13), IDCP (entry 9), NBS (entries 1, 2, 4, 6), mercuric acetate (entries 10-12), mercuric sulfate (entry 3) and mercuric triflate (entry 7).

Table 4: Formation of Mixed Acetals using Various Electrophiles:

Entry	Vinyl Ether	Alcohol	Conditions	Product	Isolated Yield
1	**11**	cyclohexanol	NBS (1.2 eq.), CH_2Cl_2, 0°C	**14**	32
2	**11**	cyclohexanol	NBS (2.5 eq.), CH_2Cl_2, 0°C	**14**	20
3	**11**	cyclohexanol	$HgSO_4$, CH_2Cl_2, -40°C	–	0
4	**10**	cyclohexanol	NBS (1.2 eq.), CH_2Cl_2, -40°C	**15**	54
5	**10**	cyclohexanol	NIS (1.2 eq.), CH_2Cl_2, -40°C	**16**	79
6	**10**	**13**	NBS (1.2 eq.), CH_2Cl_2, -40°C	**17**	<10
7	**10**	**13**	HgO, Tf_2O, Hunigs base, CH_3NO_2, -15°C	–	0
8	**10**	**12**	NIS (3.0 eq.), CH_2Cl_2, -40°C	–	0
9	**10**	**12**	IDCP (1.5 eq.), CH_2Cl_2, -40°C	–	0
10	**10**	**12**	$Hg(OAc)_2$, CH_2Cl_2, -40°C	–	0
11	**10**	**12**	$Hg(OAc)_2$, DMF, -40°C	–	0
12	**10**	**12**	$Hg(OAc)_2$, THF, -40°C	–	0
13	**10**	**12**	I_2, tBuOK, THF, -40°C	–	0



NIS gave the best results, however, this reagent was effective only when used with simple alcohols such as cyclohexanol. NIS promoted coupling of primary carbohydrate alcohols gave poor isolated yields and coupling with secondary carbohydrate alcohols was not detected. A variety of acid catalysts were also tried (Table 5) such as *p*-TSA (entries 1, 2, 4, 8, 9, 14-16), CSA (entries 10-13, 17, 18), PPTS (entry 5), TfOH (entry 3), AgOTf (entry 6) and HBr (entry 7), of which *p*-TSA and CSA were the best. Table 5 summarizes the highest reaction yields (shaded entries represent the best reported yields for a particular system). Again it can be seen that high yielding reactions were obtained with simple alcohols and primary carbohydrate alcohols (entries 1, 8), but it was more difficult to couple secondary carbohydrate alcohols (entries 4, 9-18).

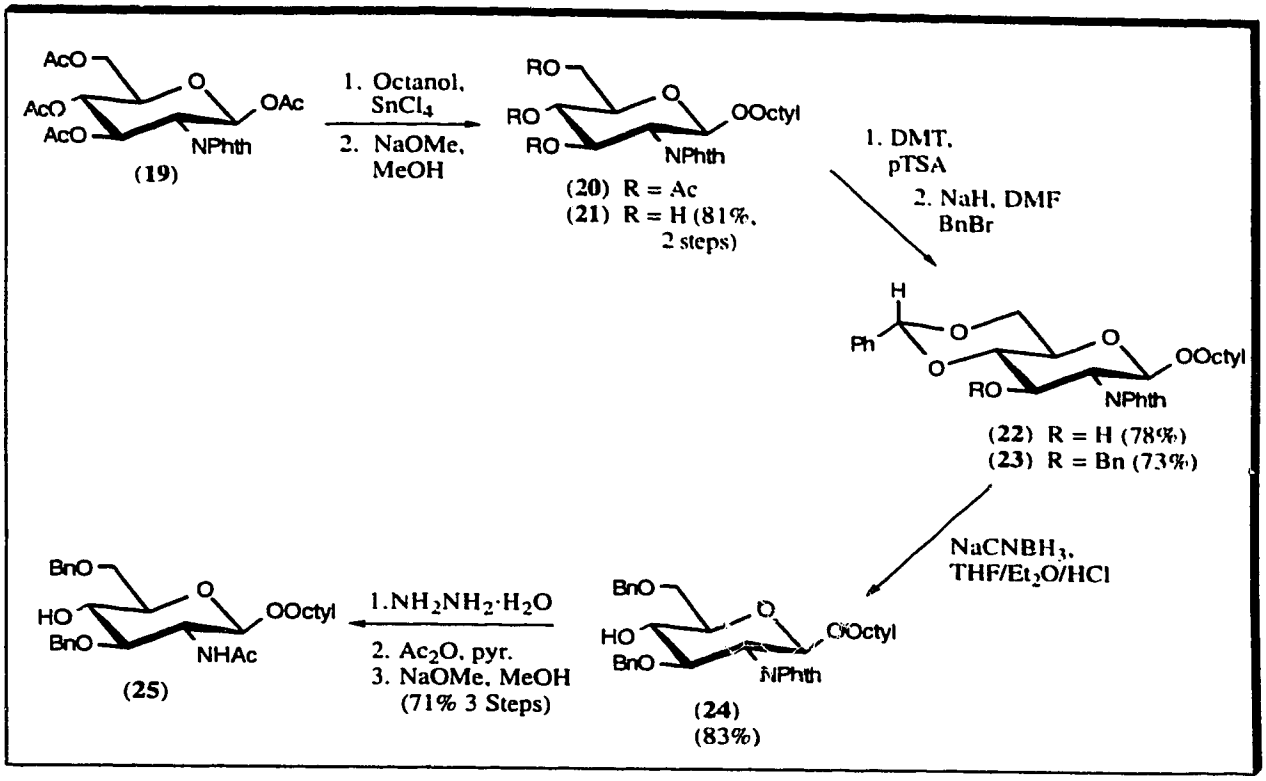
The best procedure developed used *p*-TSA or CSA. It was essential during the development of the linking strategy to use carbohydrate alcohols that were of synthetic importance. The secondary alcohol **12**[184] and the primary alcohol **13**[185] were chosen for their ease of preparation. Alcohol **12** is also considered to be an ideal acceptor to develop new glycosylation strategies because of the highly unreactive 4-position (see Table 4 for structures of **12** and **13**). The alcohol **24** was chosen as it was a precursor to the β-D-Man-(1→4)-β-D-GlcNAc linkage of *N*-linked glycoproteins. Alcohol **24** was synthesized according to Vandana et al[185] as is shown in Figure 27. One advantage of this coupling strategy was that the isopropylidene acetal that formed contained a non-stereogenic atom, which made purification and characterization easier.

A typical reaction consisted of the addition of catalytic (0.02 equiv.) *p*-TSA to a cooled (-40°C) solution of equimolar amounts of vinyl ether **10** and alcohol **13** in dry dichloromethane. The reaction was quenched by the addition of a base (e.g. triethylamine) after 10 minutes to prevent the mixed acetal **26** from forming symmetrical dimerization

Table 5: Acid Catalyzed Formation of Mixed Acetals:

Entry	Vinyl Ether	Alcohol	Conditions	Product	Isolated Yield
1	2-methoxy propene	3	*p*-TSA, CH_2Cl_2, -40°C	4	88
2	2-methoxy propene	3	*p*-TSA, CH_2Cl_2, -40°C, 4Å Ms	4	32
3	11	cyclohexanol	TfOH, CH_2Cl_2, -40°C	–	0
4	10	12	*p*-TSA, CH_2Cl_2, -40°C	29	57
5	10	12	PPTS, CH_2Cl_2, -40°C	29	14
6	10	12	AgOTf, CH_2Cl_2, -40°C	–	0
7	10	12	Et_4NBr, TfOH, CH_2Cl_2, -40°C	–	0
8	10	13	*p*-TSA, CH_2Cl_2, -40°C	26	74
9	10	24	*p*-TSA, CH_2Cl_2, -40°C	30	55
10	10	25	CSA, CH_2Cl_2, -40°C	31	15
11	10	59	CSA, CH_2Cl_2, -40°C, $CaSO_4$	70	38
12	53	12	CSA, CH_2Cl_2, -40°C	–	0
13	53	12	CSA, CH_2Cl_2, -40°C, $CaSO_4$	–	0
14	53	12	*p*-TSA, CH_2Cl_2, -40°C	–	0
15	53	13	*p*-TSA, CH_2Cl_2, -40°C	–	0
16	18	60	*p*-TSA, CH_2Cl_2, -40°C	–	0
17	65	24	CSA, CH_2Cl_2, -40°C, $CaSO_4$	66	28
18	65	59	CSA, CH_2Cl_2, -40°C, $CaSO_4$	69	9

Figure 27: The Synthesis of Alcohols (**24**) and (**25**):



products such as **27** and **28**, and simultaneously alcohols **3** and **13** (Figure 28a). Optimum coupling conditions were therefore very sensitive to structure and required great care to reproduce. Consistent yields of mixed acetal formation ranged from 55% for **30** (Figure 28b) to 74% for **26** (see Table 5, shaded entries). The coupling yield for the synthesis of **26** was similar to that reported in the literature[167]. The stability of the more hindered isopropylidene acetals was also lower; storage for greater than several hours was possible under basic conditions (solutions which contained 0.1% triethylamine).

Figure 28a: The Formation of Mixed Acetal (**26**) and Observed Side Products:

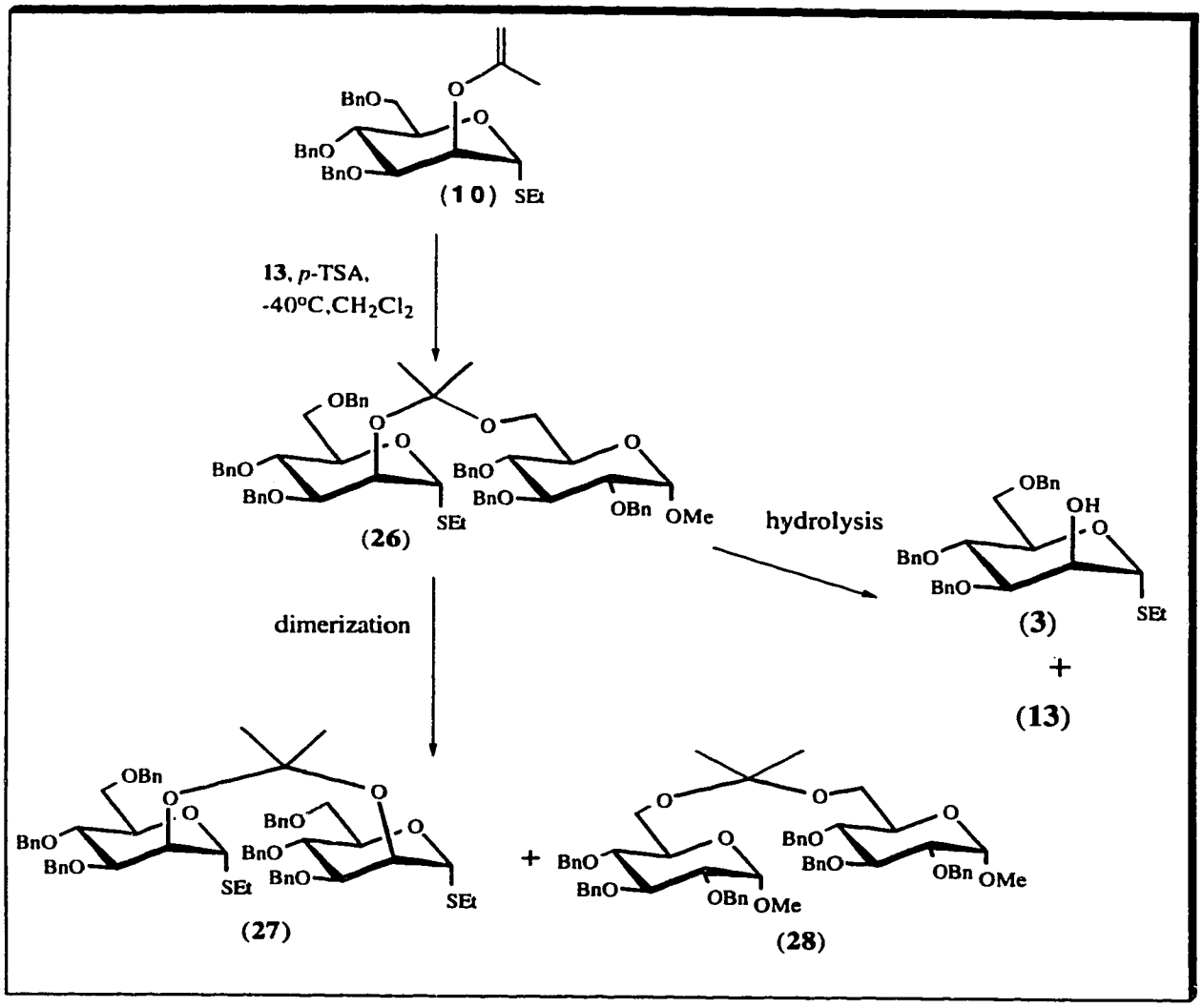
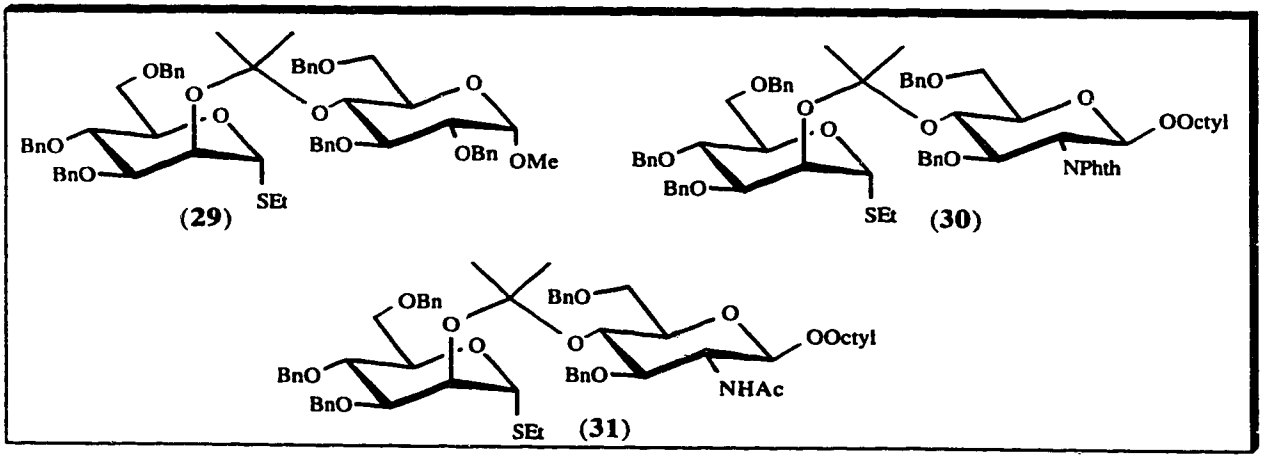


Figure 28b: Other Isopropylidene Acetals Synthesized:



D.3. Development of the Activation Step:

With sufficient quantities of isopropylidene acetals synthesized, the development of the activation step was undertaken. The majority of the methodological optimization was conducted with compound **29**, since it was an unreactive secondary carbohydrate alcohol that resembled the natural β-D-Man-(1→4)-β-D-GlcNAc system. Experimental factors that were varied included the activator, equivalents of activator, solvent and temperature. Table 6 summarizes the reaction conditions employed. With one exception, where yields are reported, no α-mannosides were observed. The exception is in entry 29 (phenyl selenenyl triflate activation). The high reactivity and acidity of PhSeOTf gave 19% of accompanying α-anomer, presumably from decomposition of the acetal before intramolecular transfer. The shaded entries 6, 14, 34, and 39 in Table 6 represented the best reported yields for the particular systems[158-160].

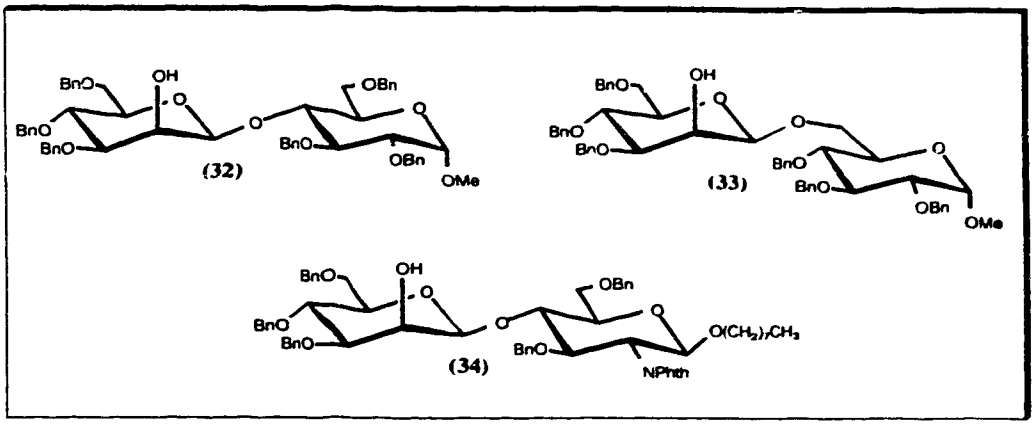
A variety of activators were examined including NIS (entries 6-15, 33-36, 39-41, 43-47), NBS (entries 1-4, 16-19, 37, 38), IDCP (entries 20-24), DMTST (entries 25-28), phenyl selenenyl triflate (entries 29, 30, 42), methyl triflate (entry 5) and $TBPA^{\cdot+}$ (entries 31, 32). With the exception of the last two, all the activators gave varied yields of β-mannosides. The best results were obtained with NIS. Several solvents were used which included dichloromethane, acetonitrile, nitromethane and DMF. The highest yields were obtained when dichloromethane was used as a solvent. Once it was determined that NIS was the activator of choice, temperature and equivalents of NIS were optimized. The optimized conditions consisted of the use of 5 equivalents of NIS in dichloromethane. The reaction was started at 0°C and allowed to warm to room temperature overnight. The addition of a hindered base such as 2,6-di-*t*-butyl-4-methyl pyridine (5 eq.) enhanced reaction yields presumably by the prevention of mixed acetal decomposition prior to

Table 6: Optimization of the Activation Step:

Entry	Acetal	Reaction Conditions Activator (equiv.), Solvent, Temperature	Product	Isolated Yield
1	4	NBS (1), CH_2Cl_2, 0°C	5	15
2	4	NBS (2), CH_2Cl_2, -40°C	5	24
3	4	NBS (3), CH_2Cl_2, -40°C	5	52
4	4	NBS (5), CH_2Cl_2, -40°C	5	60
5	4	MeOTf (1), CH_2Cl_2, -78°C	--	0
6	29	NIS (5), CH_2Cl_2, 0°C→RT	32	42
7	29	NIS (5), CH_3CN, 0°C→RT	32	28
8	29	NIS (5), DMF, 0°C→RT	32	<28
9	29	NIS (10), CH_2Cl_2, 0°C→RT	32	13
10	29	NIS (5), CH_3CN, CH_2Cl_2, 0°C→RT	--	0
11	29	NIS (5), CH_2Cl_2, -10°C→RT	32	37
12	29	NIS (5), MeOH (1), CH_2Cl_2, 0°C→RT	32	11
13	29	NIS (5), proton sponge (5), CH_2Cl_2, 0°C→RT	--	0
14	29	NIS (5), 4-Me-DTBP (5), CH_2Cl_2, 0°C→RT	32	77
15	29	NIS (5), 4-Me-DTBP (0.5), CH_2Cl_2, 0°C→RT	32	56
16	29	NBS (5), CH_2Cl_2, -40°C→RT	32	15
17	29	NBS (5), CH_2Cl_2, -15°C→RT	32	17
18	29	NBS (5), CH_3NO_2, -15°C→RT	32	13
19	29	NBS (5), CH_2Cl_2, -10°C→RT, 4Å MS	--	0
20	29	IDCP (5), CH_2Cl_2, 0°C→RT	32	11
21	29	IDCP (5), CH_3CN, CH_2Cl_2,, 0°C→RT	--	0
22	29	IDCP (3), CH_2Cl_2,, 0°C→RT	32	<11
23	29	IDCP (3), CH_3CN,, 0°C→RT	32	13
24	29	IDCP (5), CH_3CN, 0°C→RT	--	0
25	29	DMTST (2), CH_2Cl_2, -40°C	--	0
26	29	DMTST (2), 4-Me-DTBP (2), CH_2Cl_2, -40°C	32	47
27	29	DMTST (4), 4-Me-DTBP (5), CH_2Cl_2, 0°C	32	<47
28	29	DMTST (2), CH_2Cl_2, -40°C, 4Å MS	--	0
29	29	PhSeOTf (3), CH_2Cl_2, -40°C, 4Å MS	32	23
30	29	PhSeOTf (2), 4-Me-DTBP (2), CH_2Cl_2, -40°C, 4Å MS	--	0

Table 6-cont.: Optimization of the Activation Step:

Entry	Acetal	Reaction Conditions Activator (equiv.), Solvent, Temperature	Product	Isolated Yield
31	**29**	TBPA·+ (1.5), CH_2Cl_2, 0°C, 4Å MS	--	0
32	**29**	TBPA·+ (1.5), CH_3CN, 0°C, 4Å MS	--	0
33	**26**	NIS (5), CH_2Cl_2, -40°C	**33**	60
34	**26**	**NIS (5), MeOH (1), CH_2Cl_2, -5°C→RT**	**33**	61
35	**26**	NIS (5), 4-Me-DTBP (5), CH_2Cl_2, 0°C→RT	**33**	<60
36	**26**	NIS (5), 4-Me-DTBP (5), CH_2Cl_2, -40°C→RT	**33**	37
37	**26**	NBS (5), CH_2Cl_2, -40°C	**33**	60
38	**26**	NBS (5), CH_3NO_2, -15°C	**33**	46
39	**30**	**NIS (5), 4-Me-DTBP (5), CH_2Cl_2, 0°C→RT**	**34**	51
40	**30**	NIS (5), 4-Me-DTBP (5), CH_2Cl_2, 0°C→RT	--	49
41	**30**	NIS (5), CH_2Cl_2, 0°C→RT	**34**	27
42	**30**	PhSeOTf (2), CH_2Cl_2, -78°C, 4Å MS	**34**	10
43	**30**	NIS (1.5), AgOTf (0.15), CH_2Cl_2, 0°C, 4Å MS	--	0
44	**66**	NIS (5), 4-Me-DTBP (5), CH_2Cl_2, RT	**67**	27
45	**66**	NIS (5), 4-Me-DTBP (5), CH_2Cl_2, RT	**67**	28
46	**70**	NIS (5), 4-Me-DTBP (5), CH_2Cl_2, RT	**71**	27
47	**70**	NIS (5), 4-Me-DTBP (5), CH_2Cl_2, RT	**71**	22



transfer to the anomeric center. For example, the yield of **32** from **29** increased from 42% to 77% with added 4-Me-DTBP (entries 6, 14) and the yield of **34** from **30** increased from 27% to 51% with added base (entries 39,41).

E. Proof of the Stereocontrolled Nature of IAD:

In order to demonstrate the stereocontrolled nature of IAD, several approaches were taken. First, the stereochemistry of the anomeric linkage was confirmed by the gated ^{13}C NMR spectra of the β-mannosides **32, 33** and **34**. The J_{C1-H1} couplings of the β-linkage were found to be less than 160 Hz, characteristic of this type of linkage[187]. In addition, the α-mannosides **37, 39**, and **41** were synthesized separately via Helferich[188,189] coupling conditions. This was accomplished by reaction of the acceptors **12, 13**, and **24** with the bromide **35**[190] followed by de-*O*-acetylation of the 2-position (Figure 29). ^{13}C NMR spectra of the α-anomers showed the expected α-mannoside coupling constants of >170 Hz (Table 7).

With the α-mannoside reference standards synthesized, IAD reactions were monitored by tlc for the presence of α-anomers. In no instances did the R_f values of the α-mannoside standards correlate with those of any products in the reaction mixtures. Furthermore, isolation of all fractions that showed charring by tlc were collected and NMR analysis of these fractions did not show any α-glycosides. In many cases where the β-mannoside yields were low, the isolated impurities consisted of unreacted starting material and recovered aglyconic alcohols such as **12, 13,** and **24**. The benzylidene acetal **42** (Figure 30) could also be identified from many reaction mixtures. The formation of **42** indicated that free radical side reactions of the benzyl groups occurred when NIS was used as a promoter.

Figure 29: The Synthesis of Disaccharide α-Mannosides:

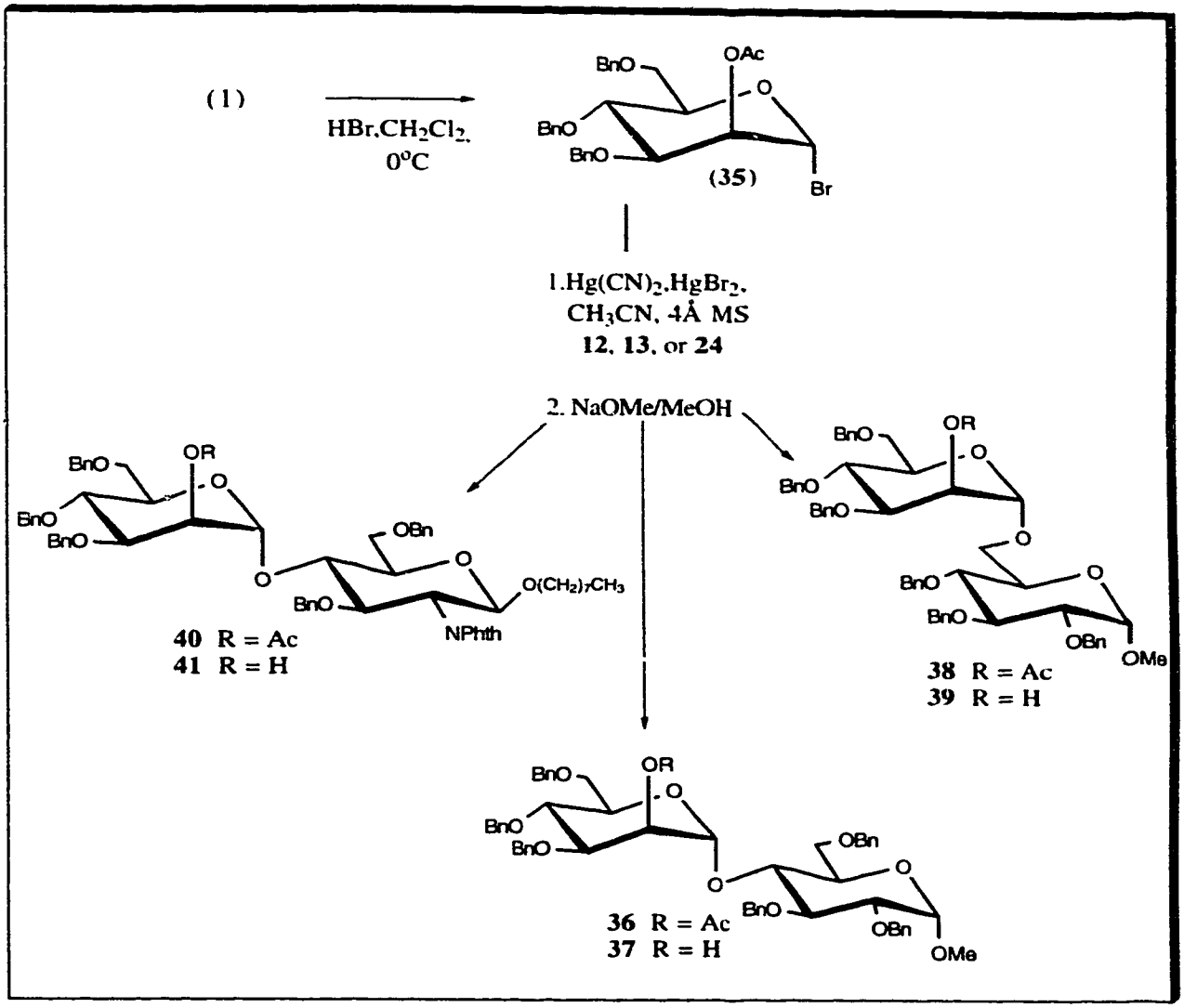
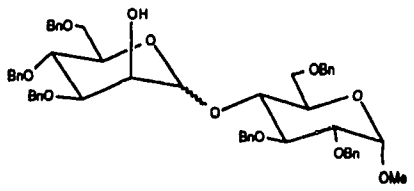
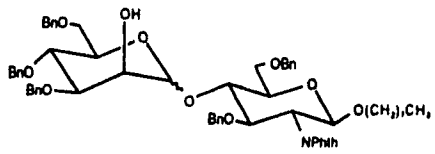
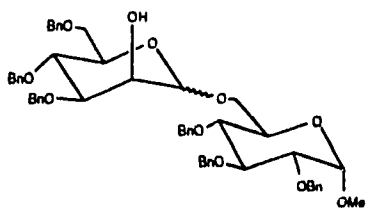
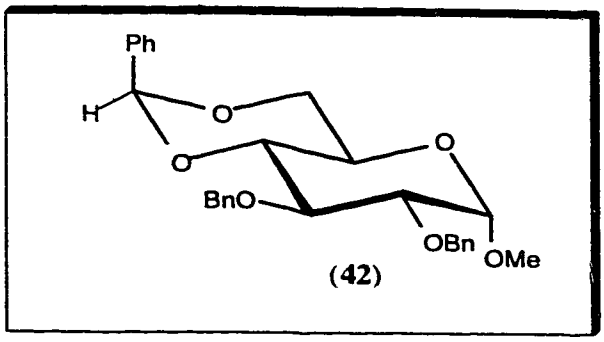


TABLE 7: NMR and Chromatographic Comparison for α- and β-Linked Disaccharide Mannopyranosides *:

Analysis						
	β (32)	α (37)	β (34)	α (41)	β (33)	α (39)
δ H-1 (300 MHz) $J_{H1', H2'}$ (ppm)	4.58 < 1Hz	5.31 1.8Hz	4.67 <1Hz	5.34 1.8Hz	4.69 <1Hz	4.89 1.2 Hz
δ ^{13}C, C-1' (75MHz) (ppm)	101.6	100.0	100.5	101.2	100.0	99.6
^{13}C $J_{C1', H1'}$ (Hz)	157	171	158	172	155	171
R_f data 1:2 EtOAc:Hexane	0.14	0.40	0.36	0.38	0.20	0.17

* NMR spectra obtained in $CDCl_3$ with Me_4Si as an internal standard.

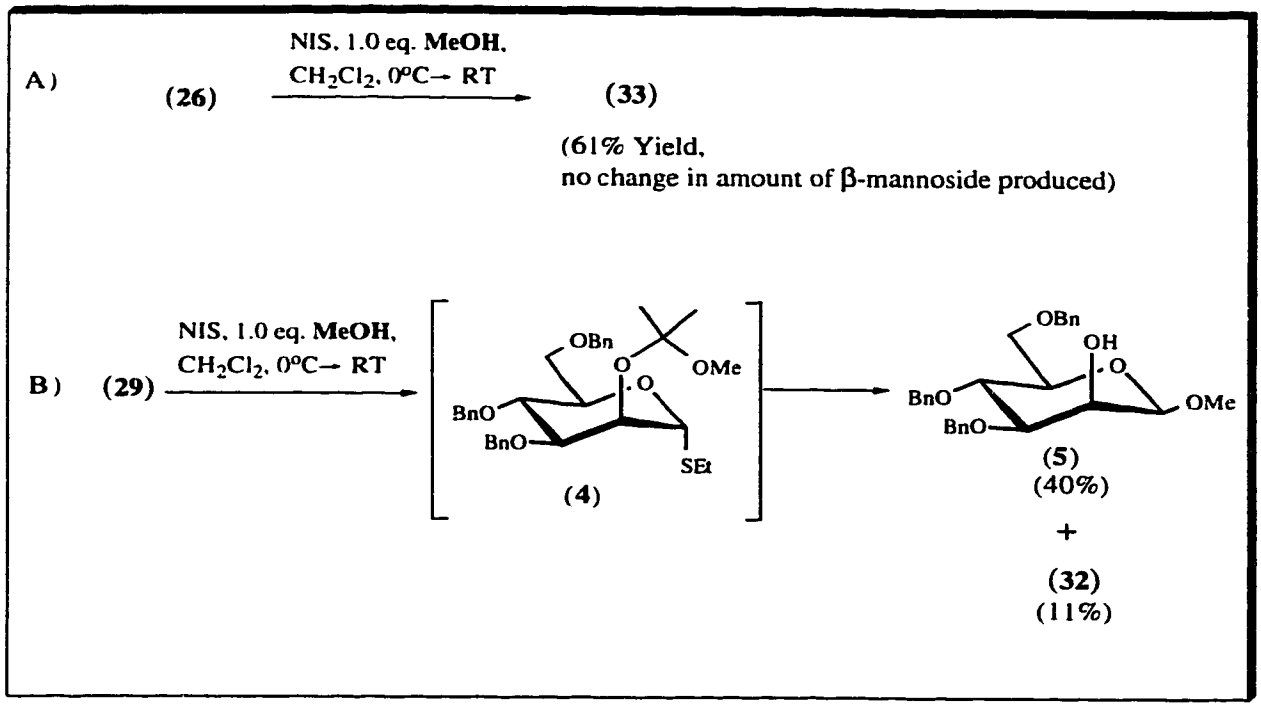
Figure 30: Benzylidene Acetal Side Product from IAD:



(42)

An experiment that supported the intramolecular nature of IAD was performed by activation of the mixed acetals **26** and **29** in the presence of methanol (Table 6, entries 12 and 34). When the acetal **26** was activated with NIS in the presence of 1.0 equivalent of methanol, the yield of the β-mannoside **33** was not affected (Figure 31a). This indicated that the intramolecular process occurred faster than the competing intermolecular reaction. This was despite the fact that the reactivity of methanol is greater than that of a primary carbohydrate alcohol. If there was any acetal decomposition prior to activation of the anomeric group, the more reactive methanol would have formed a mixture of the methyl α- and β-mannopyranosides. This observation therefore supports the reaction mechanism as outlined in Figure 17. When the same reaction was applied to the conversion of **29** to **32**, the yield of disaccharide **32** decreased to 11%. This reflects the well known lower reactivity of secondary carbohydrate alcohols (Figure 31b). In addition, 40% of the methyl β-mannoside **5** was obtained, presumably by trans-acetalization to form **4** followed by intramolecular transfer of methoxide to give **5**. The fact that no corresponding methyl α-mannoside was observed in this reaction supports the fact that a free anomeric oxocarbenium ion is not formed during IAD.

Figure 31: Intramolecular Aglycon Delivery in the Presence of Methanol:



Further evidence for the trapping of the postulated carbocation intermediate (Figure 17, E, X = C) was obtained from an initial experiment using *N*-bromosuccinimide as the activator. As described in section D.1 above (Figure 25), activation of the mixed acetal **4** yielded a mixture of the expected product **5** and the succinimide adduct **6**. This adduct shows that after transfer of the aglycon, the resultant carbocation can be trapped by nucleophiles other than water. Although these experiments do not conclusively prove that the reactions are intramolecular, the circumstantial evidence is strong.

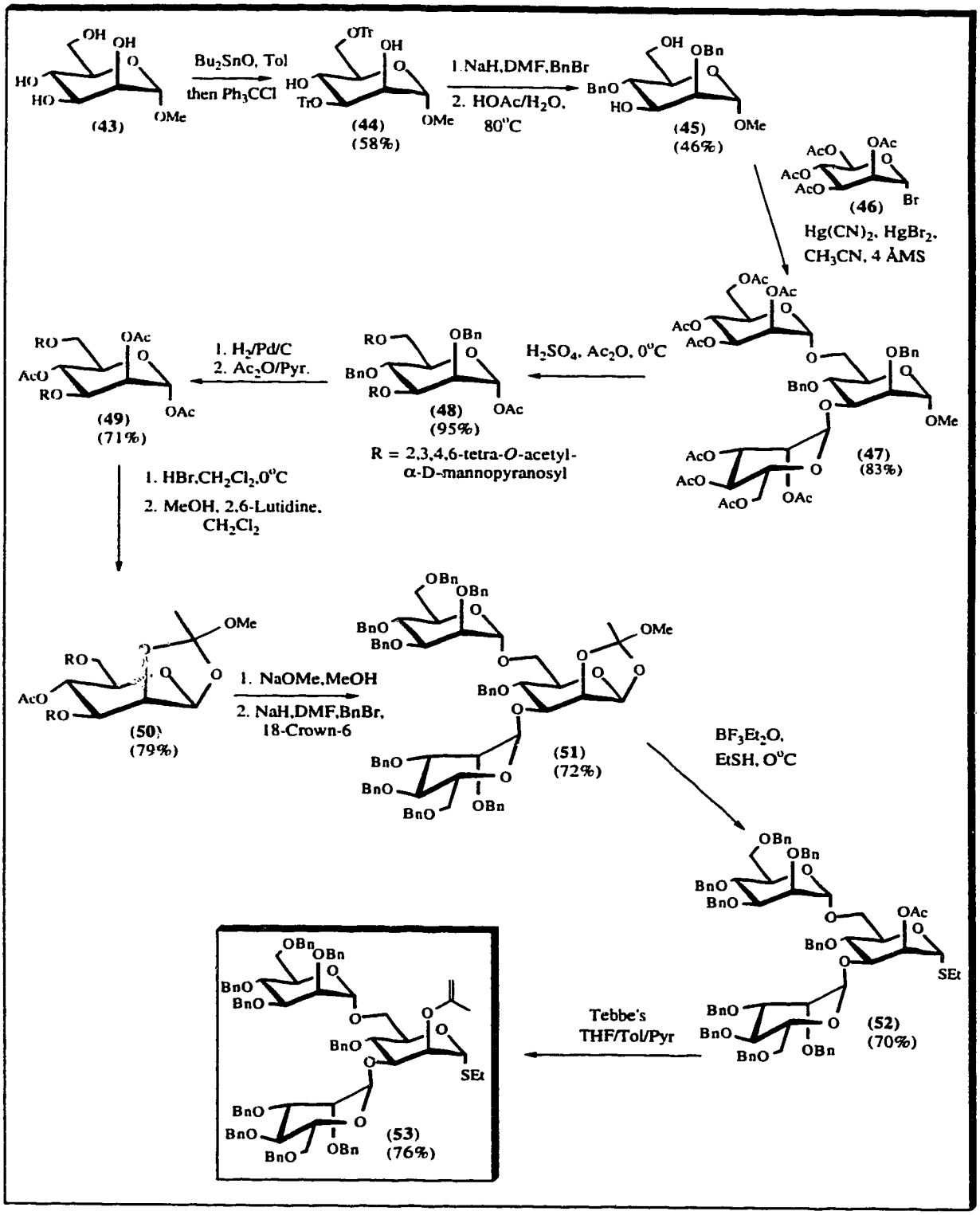
F. Extension of IAD to Complex Oligosaccharide Systems:

1. Attempted Synthesis of the Core Pentasaccharide:

Sufficient evidence and similar reported strategies[161-169] which supported the stereocontrolled nature of IAD prompted an extension of this procedure to more complex systems. In particular, the block synthesis of the core pentasaccharide of *N*-linked glycoproteins (Figure 9) was attempted. The synthetic strategy employed consisted of construction of the trisaccharide **53** and the chitobiose precursor **59**. Once these two fragments were synthesized, the coupling of them via an isopropylidene linkage would be attempted.

The synthesis of the trimannoside **53** was carried out in 13 steps in 5% overall yield from methyl α-D-mannoside (Figure 32). The methyl 2,4-di-*O*-benzyl-α-D-mannopyranoside **45** was synthesized according to Ogawa[101] in 27% yield. Helferich coupling of **45** with acetobromomannose **46**[191] gave the trimannoside derivative **47** in 83% yield. Acetolysis of **47** yielded the anomeric acetate **48** (95%) without affecting any glycosidic linkages. Removal of the benzyl groups was followed by acetylation which produced the peracetylated trimannoside **49**. Conversion to the bromide was proceeded by ortho ester formation which yielded the derivative **50** in 79% yield. Zemplen de-*O*-acetylation followed by benzylation failed to give the perbenzylated ortho ester **51**. However, de-*O*-acetylation with triethylamine, methanol and water and then benzylation was successful. With this observation it was decided to conduct a Zemplen de-*O*-acetylation of **50** followed by benzylation in the presence of 18-crown-6, and this reaction indeed proceeded smoothly to give the ortho ester **51** in 72% yield. Possible complexation of the deprotected **50** with sodium ions may have prevented benzylation of the de-*O*-acetylated structure. With the perbenzylated ortho ester **51** synthesized, conversion to the

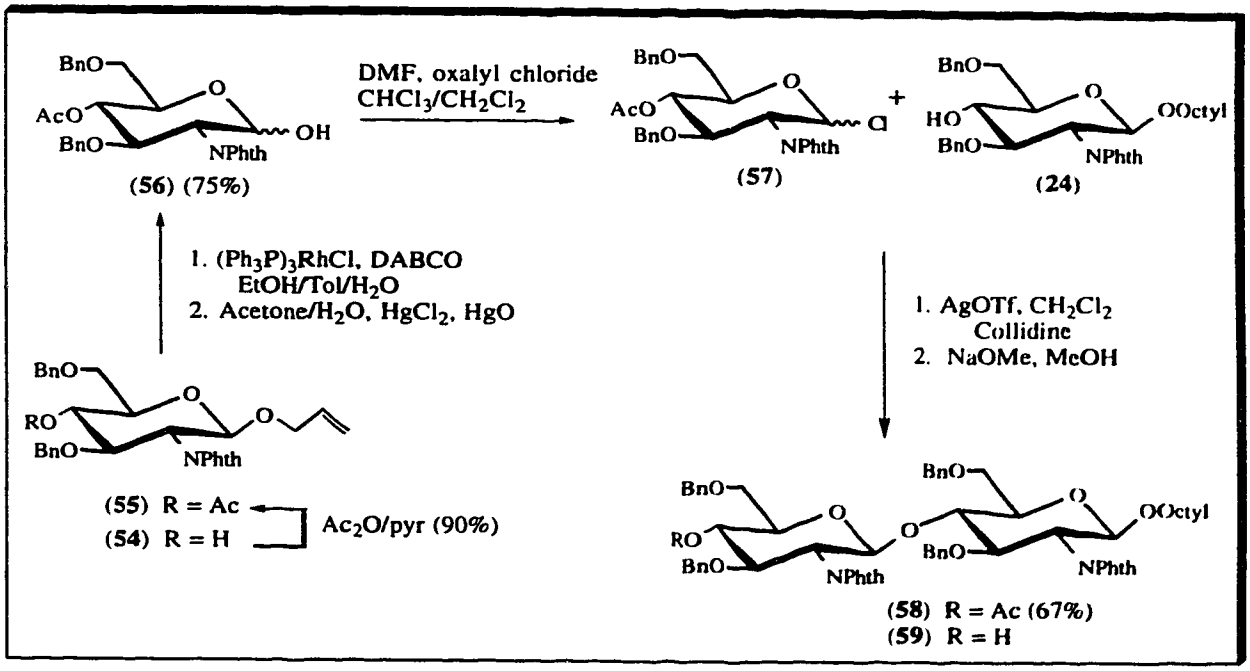
Figure 32: The Synthesis of the Trimannoside (53):



thioglycoside was conducted via a boron trifluoride etherate promoted reaction in neat ethanethiol. This reaction gave the thioglycoside **52** in 70% yield. Treatment of **53** with Tebbe's reagent produced the 2-*O*-propenyl ether **53** in 76% yield.

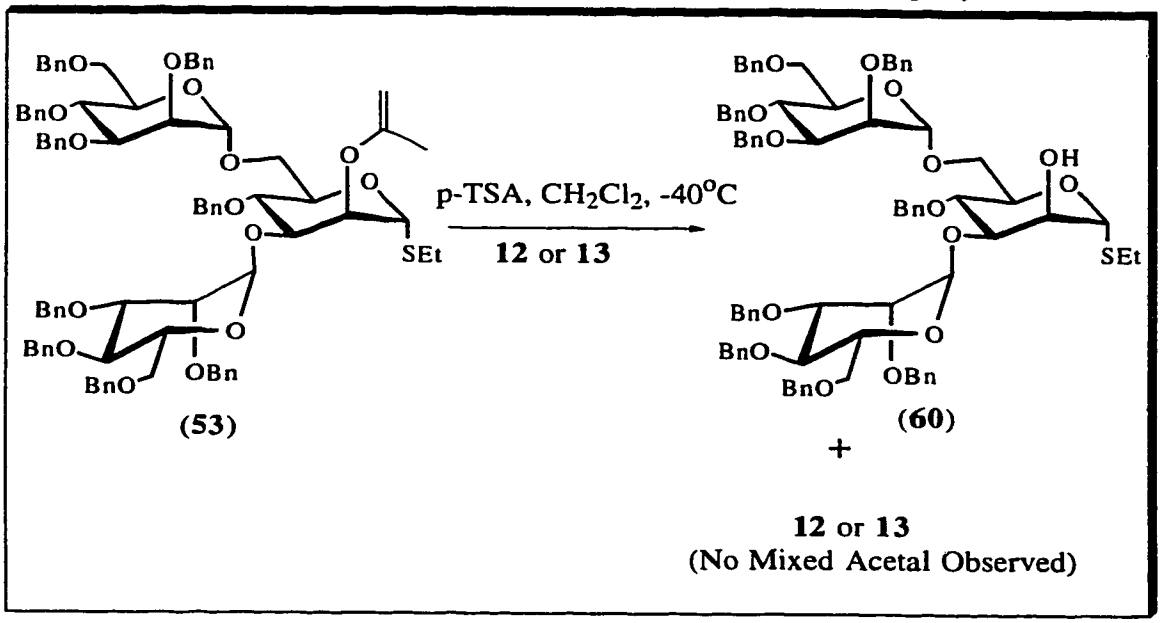
The chitobiose precursor **59** was constructed as shown in Figure 33. The acceptor **24** was synthesized as shown previously (Figure 27). The phthalimido chloride was made according to the literature[186] by acetylation of the 4-*O*-position of the allyl glycoside **54**. This was proceeded by de-*O*-allylation. The reducing sugar **56** was obtained in 75% yield from **55**. Treatment of **56** with dimethylformamide and oxalyl chloride[192] yielded the glycosyl chloride **57** as a bright yellow solid. Silver triflate promoted coupling of the crude donor **57** and the pure acceptor **24** gave the disaccharide **58** in 67% yield. The disaccharide was de-*O*-acetylated which produced the acceptor **59**.

Figure 33: The Synthesis of Chitobiose Precursor (**59**):



Coupling of the simpler alcohols **12** and **13** with **53** was attempted prior to the use of the more complex alcohol **59**. Unfortunately only slow hydrolysis of the vinyl ether which gave alcohol **60** was observed (Figure 34 and Table 5 entries 12-16). Thus acid catalyzed coupling with the chitobiose acceptor **59** was not attempted.

Figure 34: Attempted Acetalization of the Trimannoside 2-*O*-Propenyl Ether:



F.2. The Application of IAD to Tri and Tetrasaccharide Fragments of the Core Pentasaccharide:

In order to identify the reason for the failure of the linking reaction between **53** and **12** or **13**, smaller fragments of the core pentasaccharide were synthesized. The coupling reactions of **10** with **59**, **65** with **24**, and **65** with **59** were examined to better understand

the nature of the acid catalyzed mixed acetal formation. The effect of reducing the size of the vinyl ether was considered by the synthesis of the α(1→6)-linked disaccharide **65**. The removal of the 3-mannose residue in the formation of **65** would eliminate a substantial amount of steric hindrance when compared with **53**. The effect of increased alcohol complexity was examined by the coupling of **59** with the monosaccharide vinyl ether **10**. In addition, the coupling of **59** and **10** would open a reasonable route to the synthesis of the core pentasaccharide.

Synthesis of the dimannoside **65** was conducted as is shown in Figure 35. The known disaccharide **61**[193] was converted to the ortho ester **62** via the glycosyl bromide. Zemplen de-*O*-acetylation followed by benzylation gave the ortho ester **63** in 41% overall yield from **61**. No problems occurred with this step in contrast with the analogous step in the synthesis of the trimannoside **53**. Treatment of the ortho ester **63** with boron trifluoride etherate in ethanethiol gave the thioglycoside **64** (81%). Tebbe's reagent was used to convert the derivative **64** to the vinyl ether **65** in 69% yield.

When the disaccharide vinyl ether **65** was treated under acid catalyzed conditions (CSA, -40°C) in the presence of **24**, the mixed acetal **66** was isolated in 28% yield (61% based on recovered **24**, Figure 35, and Table 5, entry 17). This compound showed high instability unless stabilized by a base such as triethylamine or pyridine. The NIS / 4-Me-DTBP procedure was then used to activate the ethylthio group (Table 6, entries 44, 45). This activation was sluggish, requiring a reaction time of 70 hours at room temperature for all of **66** to be consumed. The reaction mixture showed a complex streak by tlc with the β-mannoside **67** isolated as the major product in 28% yield. The corresponding α-anomer **68** was synthesized via a different procedure (Figure 36), and was confirmed to be absent from the reaction products (Table 8). Despite the sluggish reaction and low yield of β-mannoside **66**, glycosidic bond formation proceeded in a stereocontrolled manner.

Figure 35: Synthesis of a Trisaccharide Portion of the Core Pentasaccharide by IAD :

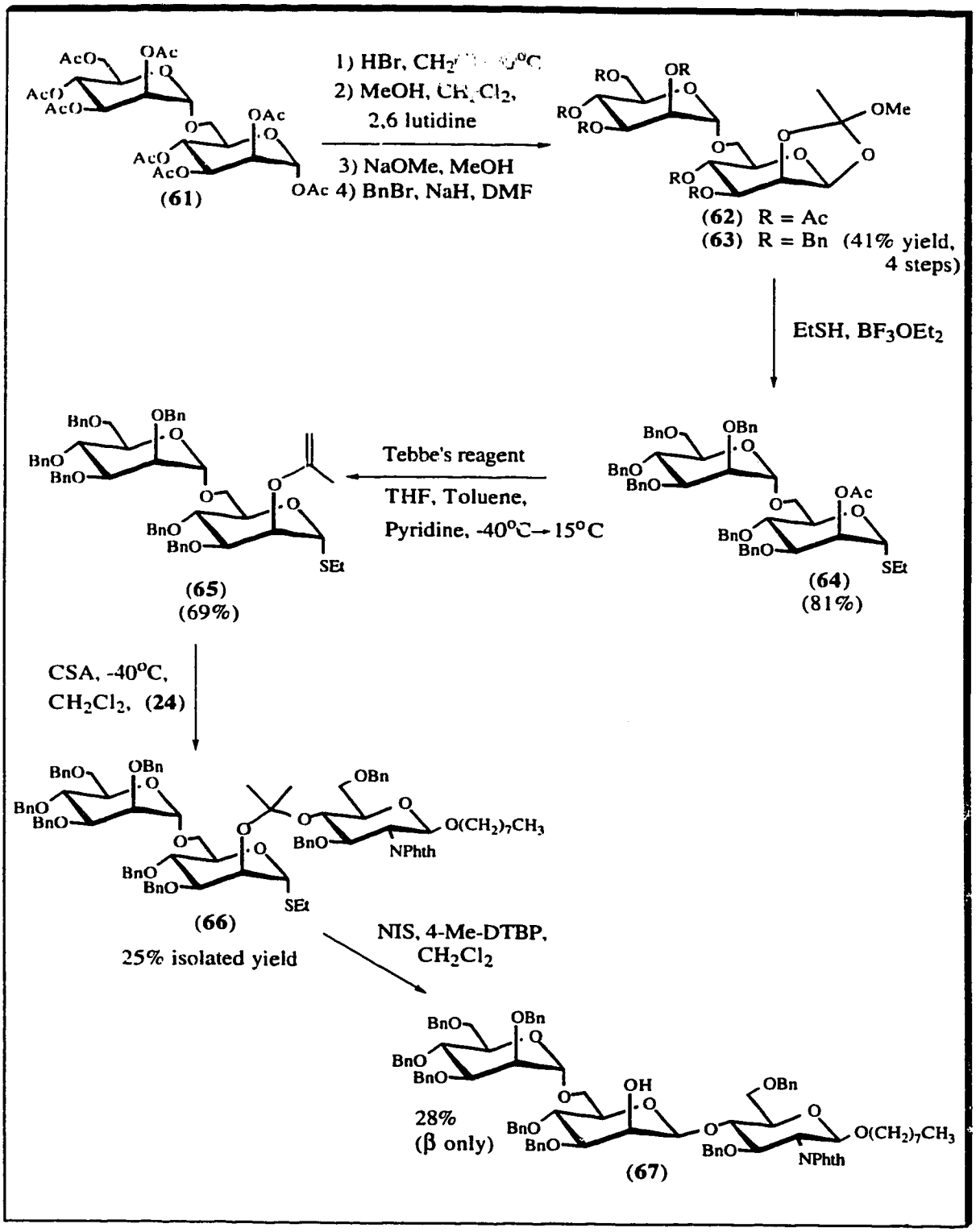
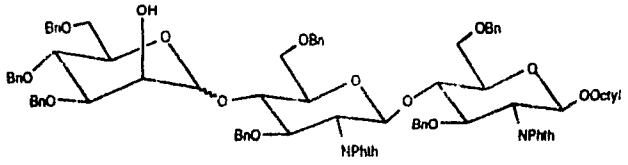
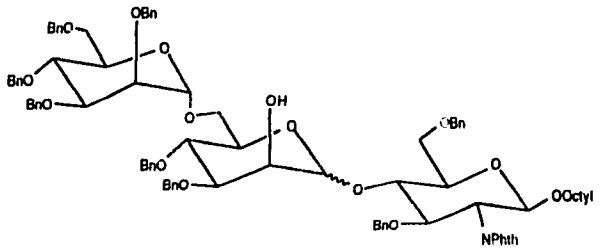
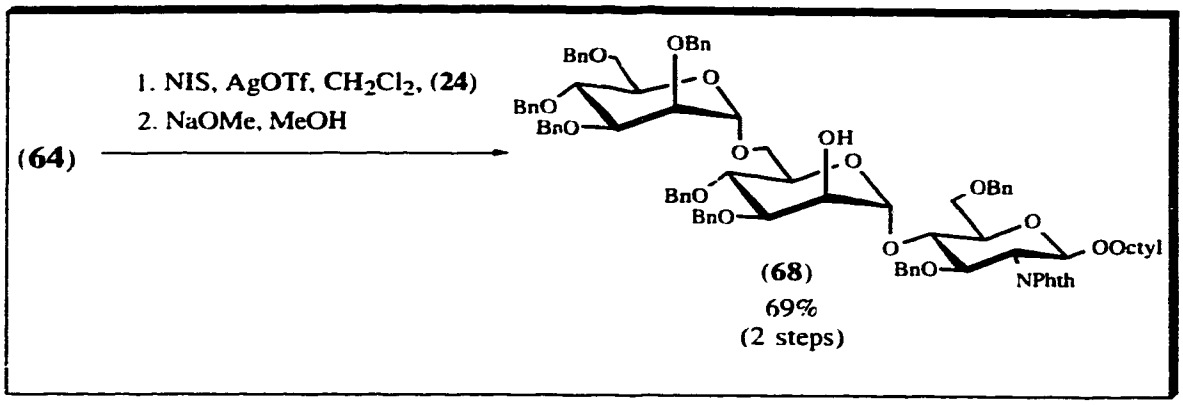


TABLE 8: NMR and Chromatographic Comparison for α- and β-Linked Trisaccharide Mannopyranosides *:

Analysis				
	β (71)	**α (72)**	**β (67)**	**α (68)**
δ H-1 (500 MHz) J H1, H2 (ppm)	4.92 (H1", H2") < 1Hz	5.36 (H1", H2") 1.3Hz	4.68 (H1', H2') <1Hz	5.27 (H1', H2') 1.2Hz
δ ^{13}C, C-1 (125MHz) (ppm)	100.3 (C-1")	100.9 (C-1")	101.0 (C-1')	101.1 (C-1')
^{13}C $J_{C1, H1'}$ (Hz)	157 (C1", H1")	170 (C1", H1")	159 (C1', H1')	173 (C1', H1')
R_f data 1:2 EtOAc:Hexane	0.27	0.27	0.34	0.50

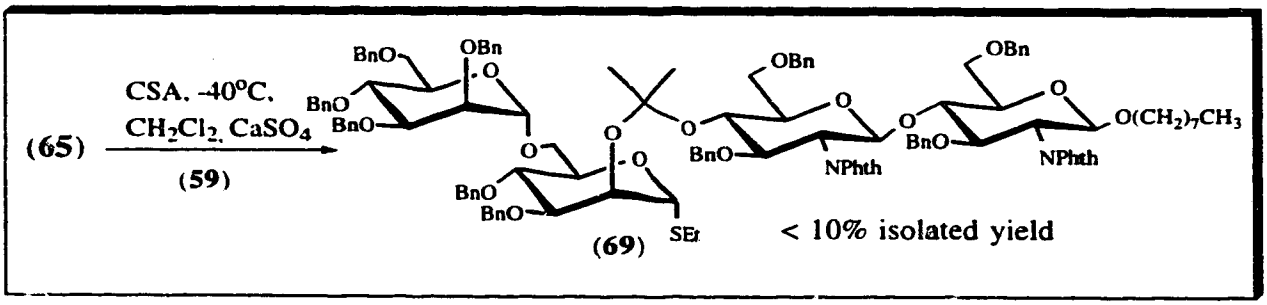
* NMR spectra obtained in $CDCl_3$ with Me_4Si as an internal standard.

Figure 36: The Synthesis of the α-Linked Trisaccharide (**68**):



Linkage of the vinyl ether **65** with the chitobiose precursor **59** was attempted to see if the procedure could make the tetrasaccharide portion of the core pentasaccharide. The coupling reaction proved to be extremely difficult. The only conditions which yielded detectable product were CSA catalysis in the presence of the drying agent calcium sulfate at -40°C (Table 5, entry 18). The desired isopropylidene acetal **69** was obtained in no greater than 9% yield after several attempts (Figure 37). The balance of the reaction products consisted of unreacted vinyl ether **65**, and alcohol **59**, as well as hydrolyzed vinyl ether. Insufficient material was obtained to attempt the activation of this mixed acetal.

Figure 37: Attempted Formation of the Tetrasaccharide Acetal (**69**) :



The effect of increased alcohol complexity, compared to **24**, was investigated by the reaction of **59** with the monosaccharide vinyl ether **10**. Acid catalyzed conditions (CSA, -40°C) yielded the trisaccharide acetal **70** in 38% isolated yield (Figure 38 and Table 5, entry 11). The reaction was virtually quantitative based on recovered starting materials. Activation of the acetal required 42 hours and a modest yield (27%) of β-mannoside **71** was isolated as the major product (Table 6, entry 46). A number of minor impurities were observed by tlc. One side-product identified was a benzylidene acetal which was formed as in the synthesis of **33** by free radical side reactions. Again, comparison with authentic α-mannoside standard **72** (Figure 39) showed no α-linked products formed from this transfer reaction (Table 8).

Figure 38: The Synthesis of the Trisaccharide (**71**) by Intramolecular Aglycon Delivery:

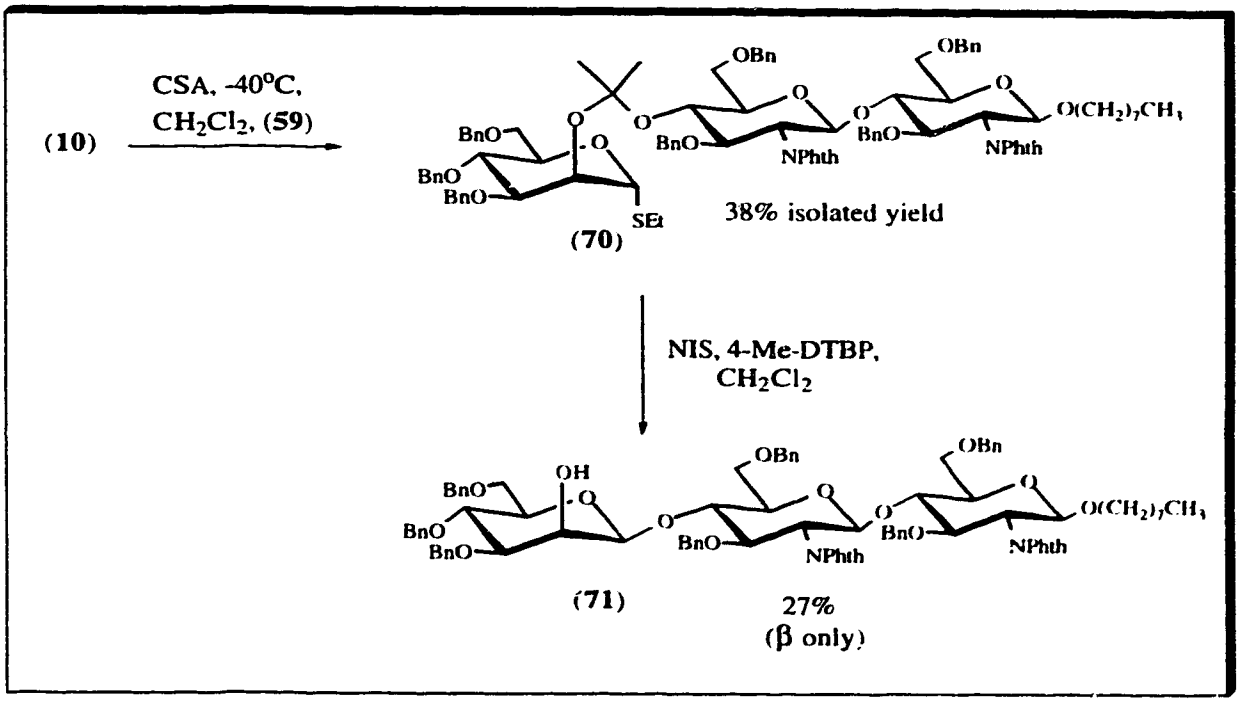
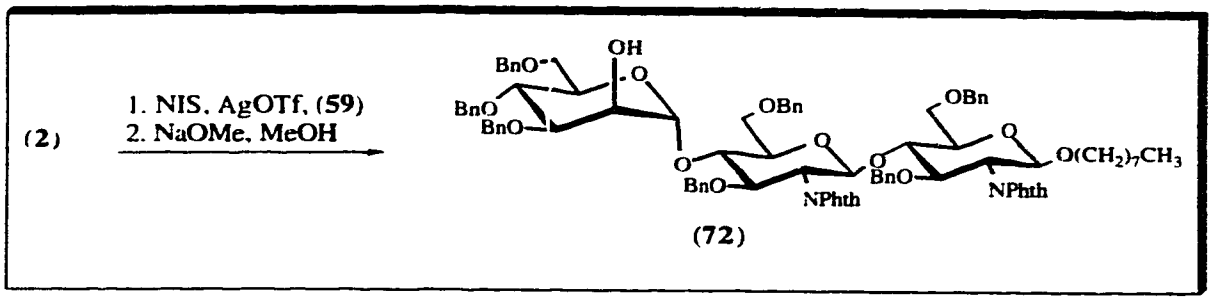


Figure 39: The Synthesis of the Trisaccharide (**72**) Containing the α-Mannosidic Linkage:



G. Limitations to the Existing Methodology of IAD:

The dramatic drop in coupling and activation yields as the complexity of the carbohydrate structures increased revealed severe limitations to the developed methodology. Even though both steps gave reduced yields, the first step was considered as the biggest problem. This was because of poor yields and the fact that the reaction was experimentally difficult to control as it depended on the isolation of a kinetic product. The second step was not considered as serious a problem to overcome. This was because of the availability of a wide variety of activating groups and conditions.

Acid catalyzed isopropylidene acetal formation was extremely sensitive to the size of the vinyl ether (Table 9). This was evident by comparison of the vinyl ethers **10**, **65** and **53**. The size of the alcohol is also important, although the effect is not as dramatic as with the vinyl ethers. There are two factors that can be considered when determining why this reaction did not work well on complex systems. The first reason is based on protonation of the 2-*O*-propenyl ether to give the carbocation (structure **B**, Figure 40). In a sterically hindered molecule, initial protonation of the vinyl ether may be

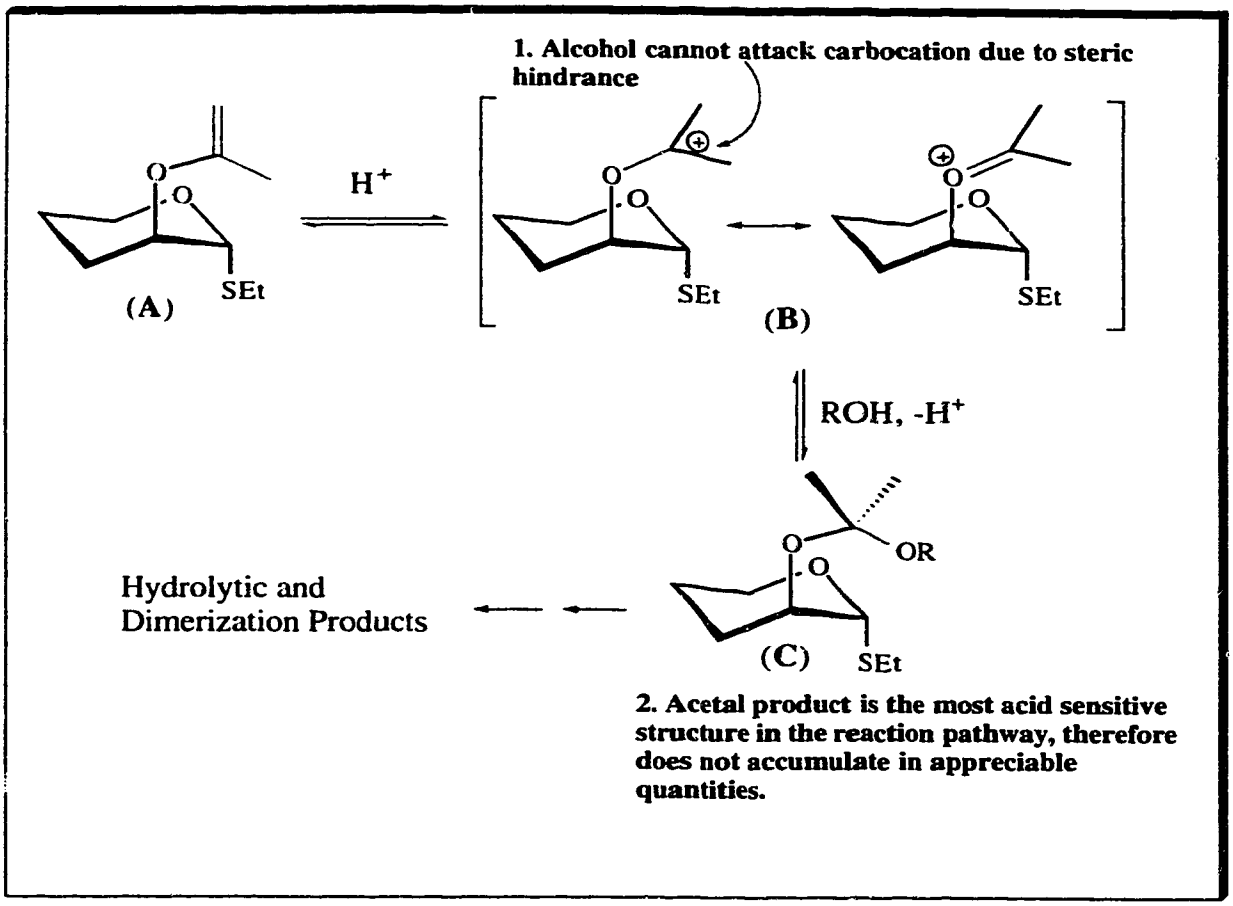
TABLE 9: Yield Comparisons for Isopropylidene Acetals:

Vinyl Ether	Alcohol	Mixed Acetal	Percent Yield
10	**13**	**26**	74
10	**12**	**29**	57
10	**24**	**30**	55
10	**59**	**70**	38
65	**24**	**66**	28
65	**59**	**69**	9
53	**12**	---	0
53	**13**	---	0

followed by a very slow attack of the alcohol as it cannot access the carbocation easily. The inability of the alcohol to attack the carbocation would allow for other reactions such as hydrolysis of the protonated vinyl ether to occur. This may have been the case when coupling reactions of the trimannoside vinyl ether **53** were attempted (Figure 34). No indication of mixed acetal formation was observed by tlc in this reaction, only slow hydrolysis of **53** to yield **60**.

The second reason to explain the poor coupling yields is that the acid sensitivity of the acetal increased with greater structural complexity. This meant that under the reaction conditions, as soon as any acetal was formed, it would protonate and be converted to more thermodynamically stable products. Such structures may have included dimerization or hydrolysis products (Figure 40). Support for this reason came from the synthesis of the mixed acetals **66** and **70**. It was noticed by tlc that these reactions had to be quenched before all the vinyl ether was consumed. This was because the amount of mixed acetal product would only reach a certain level, and then give way to side products.

Figure 40: Possible Reasons for the Failure of Acid Catalyzed Coupling of Complex Oligosaccharides:



Further support for the acid sensitivity explanation is based on the stabilities on storage of these molecules. Mixed acetals **4** and **26** were stable and did not need to be stored in basic solutions as was the case with the acetals such as **29** or **30**, which hydrolyzed if left at room temperature overnight. Structures such as **66**, **69**, and **70** showed the greatest instability, yielding complete decomposition in several hours if stored without added base. These two observations substantiated the kinetic nature of the acid catalyzed reaction. This ultimately rendered this procedure not practical for complex systems. Despite this setback, the procedure works well for simple systems such as primary carbohydrate alcohols and non carbohydrate alcohols.

The transfer yields for the formation of the β-mannosides also decreased with increased molecular complexity (Table 10, with the exception of compound **29**, where extensive optimization was performed). Analysis of the reaction times involved for the formation of the β-mannosides may explain the reduced yields. Less hindered mixed acetals such as **4** and **26** gave good yields of β-mannosides (60% for **5** and **33**) with short reaction times (2 hours). Activation of the mixed acetals **29** and **30** showed intermediate reaction times (18 hours). This reflects the increased steric repulsion of the secondary carbohydrate alcohols which may have impeded the transfer step. Extremely hindered structures such as **66** and **70** had the longest thioglycoside activation times (70 and 42 hours respectively). This indicated extreme steric repulsion was present in the activation reaction. Longer reaction times allowed for competing side reactions to occur which included the free radical formation of the benzylidene structure (Figure 30), which caused a decrease in yield.

TABLE 10: Yield and Reaction Time Comparisons for the Formation of β-Mannosides by IAD:

Mixed Acetal	β-Mannoside	Percent Yield	Time (hours)
4	**5**	60	2
26	**33**	60	2
29	**32**	77	18
30	**34**	51	18
70	**71**	27	42
66	**67**	28	70

Possible explanations to rationalize the poor transfer yields with more complex systems can be found by analysis of the possible mechanism of the delivery step. From the information collected on IAD it is expected that the transfer step is an intramolecular process that does not involve formation of a free anomeric oxocarbenium ion (as is best supported by the methanol competition experiment summarized in Figure 31). This means that the aglycon is strategically positioned to attack the anomeric position just as positive charge starts to develop at C-1. The transition state for this attack is shown in structure **D** in Figure 17. The activation reaction can be described as being composed of an initial iodination of the anomeric thiol group (k1), followed by delivery of the aglycon (k2) (Figure 41). Thus the increased reaction times with greater molecular complexity can be attributed to one of these steps. It may be that in the complex systems, the thio group is not as accessible so initial iodination (k1) is much slower. An alternative explanation is that more complex acetals may not be able to attain a reactive conformation, so that the aglycon delivery step (k2) is slowed, allowing competing side reactions to occur. This second explanation is shown in Figure 42, in which complex acetals may have rotational barriers. A mechanistic investigation using a complex acetal such as **66** or **70** is necessary to see which step (or both) is responsible. This was not conducted as efforts were concentrated on developing a more efficient IAD strategy.

Figure 41: Activation and Delivery Steps Involved in IAD:

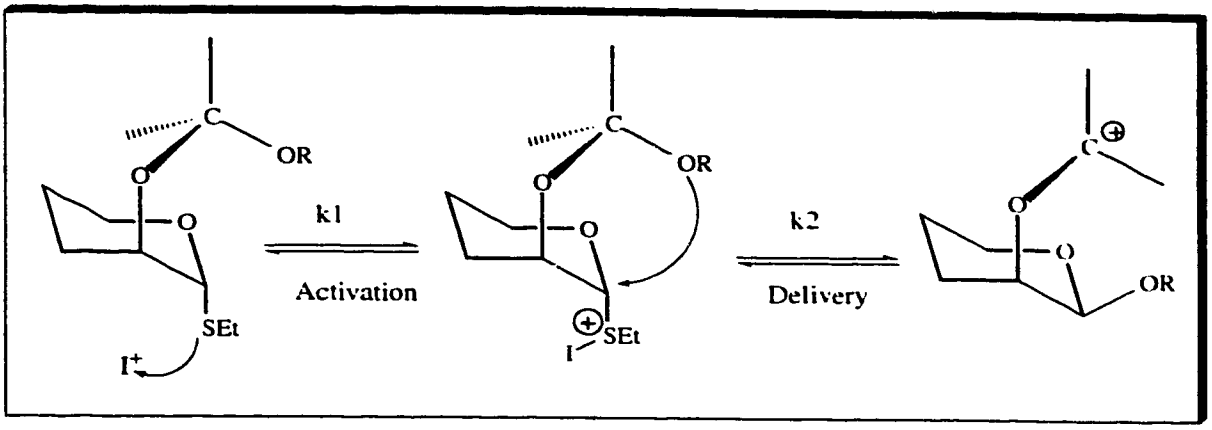
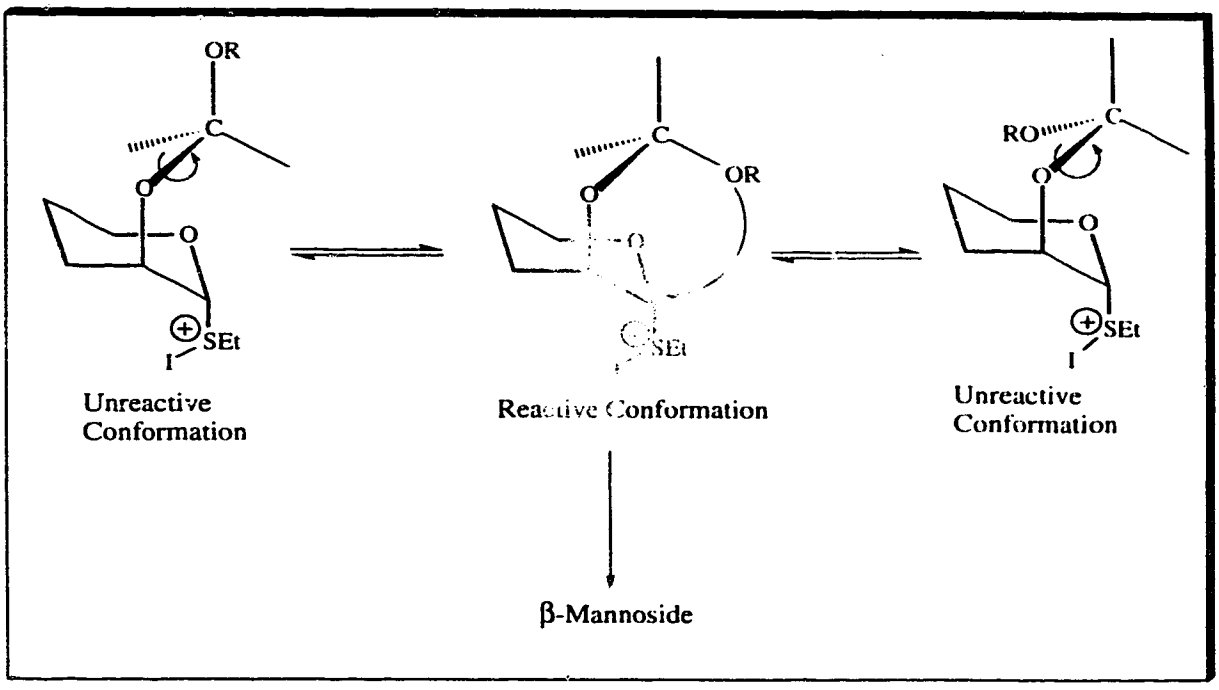


Figure 42: Hypothetical Rotation of Isopropylidene Acetals into the Reactive Conformation



CHAPTER 3

Other Strategies Examined for Intramolecular Aglycon Delivery:

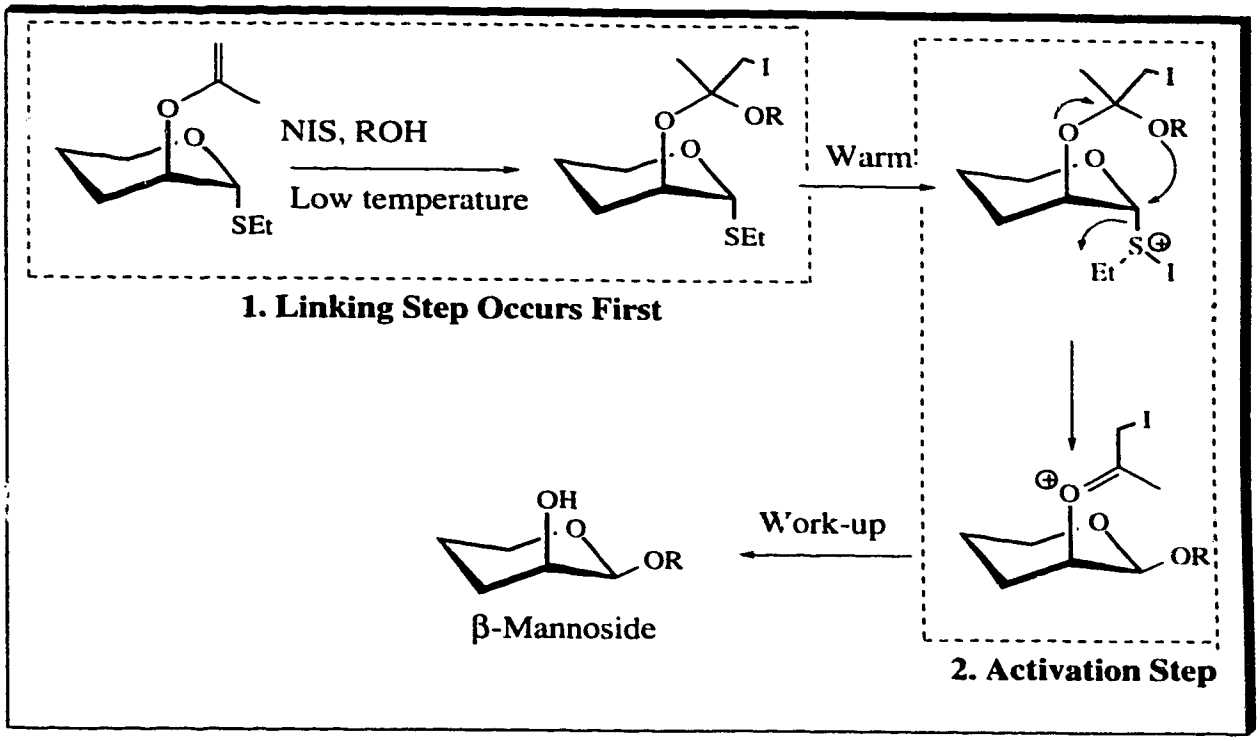
In addition to the development of the methodology outlined in Chapter Two, a variety of other strategies were examined. A "one-pot" approach was investigated to simplify the IAD procedure by combining the linking and activation steps. Several other acetal linking techniques were developed. Areas for future work are discussed, to try and extend this promising method in order for it to become accepted as the primary method for making β-mannosides.

A. "One-Pot" or *In Situ* Strategy for Synthesizing β-Mannosides:

The vinyl ether **10** was used in a "one-pot" strategy for IAD. During initial studies on the development of the coupling procedure (Table 4), it was noticed that NIS promoted electrophilic activation of the vinyl ether moiety occurred at a faster rate than the activation of the thioglycoside. This meant that a strategy could be devised to allow for *in situ* formation of the mixed acetal followed by activation of the thiol and transfer of the aglycon (Figure 43).

The reaction was predominantly tried with vinyl ether **10** and several alcohols. The results are summarized in Table 11. As can be seen from Table 11, a variety of reaction conditions were attempted with some satisfactory results. The best conditions found were based on treating equimolar amounts of vinyl ether **10** and alcohol **13** with 5 equivalents of NIS at -40°C in dichloromethane (shaded entries 6 and 16). After about 30 minutes at -40°C, the reaction was allowed to warm to room temperature overnight. These conditions allowed for initial formation of the mixed acetals (Figure 44) at low

Figure 43: General Strategy for a "One-Pot" Synthesis of β-Mannosides:



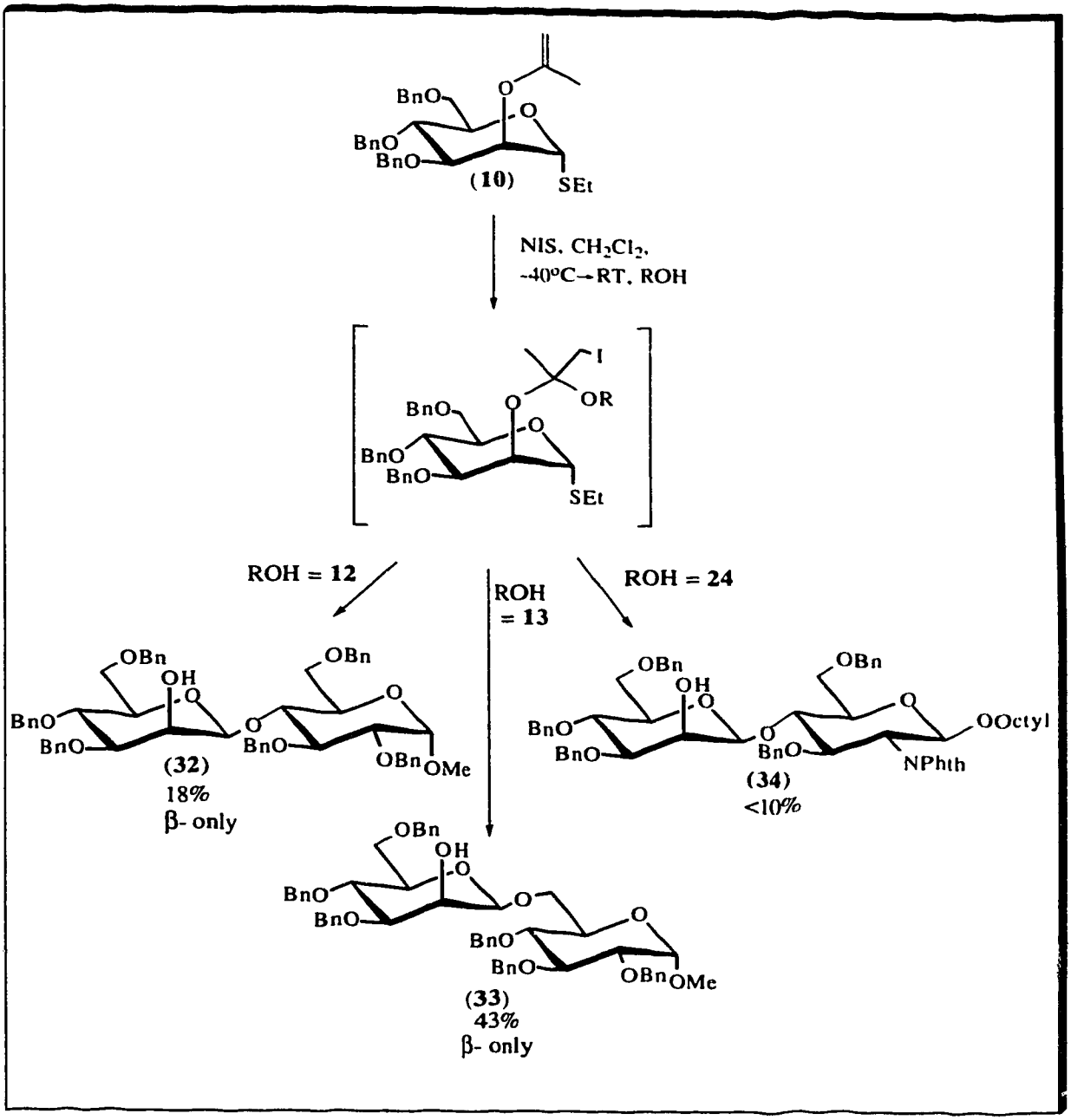
temperature without affecting the thioglycoside. Warming the system allowed for activation and delivery to occur in the previously described manner.

From the results of this one-pot approach, it is clear that the procedure was successful only for simpler alcohol systems. The isolated yields of 43% for the formation of the disaccharide **33** is actually higher than the two step approach described in Chapter Two. Moreover, it is a simpler procedure than the two step reaction. Unfortunately, the "one-pot" method does not form appreciable amounts of β-mannosides when secondary carbohydrate alcohols were used. This is because of the inability to form the

Table 11: "One-Pot" Synthesis of β-Mannosides (* indicates α,β mixture detected):

Entry	Vinyl Ether	Alcohol	Conditions	Product	Yield
1	10	13	NIS (5 eq.), CH_2Cl_2, -40°C→ RT	33	35
2	10	13	NIS (5 eq.), Hunigs base (5 eq.) CH_2Cl_2, -40°C→ RT	--	0
3	10	13	NIS (5 eq.), collidine (5 eq.) CH_2Cl_2, -40°C→ RT	--	0
4	10	13	NIS (5 eq.), CH_2Cl_2, -40°C→ RT, 4Å MS	33	<10
5	10	13	NIS (5 eq.), CH_2Cl_2, 0°C→ RT	33	7
6	**10**	**13**	**NIS (5 eq.), CH_2Cl_2, -40°C→ RT**	**33**	**43**
7	10	13	NIS (5 eq.), CH_2Cl_2, -40°C→ RT, 0.5 eq. alcohol	33	20
8	10	13	NIS (5 eq.), CH_2Cl_2, -40°C→ RT, 2.0 eq. alcohol	33	<43
9	10	13	NIS (3 eq.), CH_2Cl_2, -40°C→ RT	33	<43
10	10	13	NIS (10 eq.), CH_2Cl_2, -40°C→ RT	33	<43
11	10	13	NIS (5 eq.), Et_2O, -40°C→ RT	33	<43
12	10	13	NIS (5 eq.), Toluene, -40°C→ RT	--	0
13	10	13	NIS (5 eq.), DMF, -40°C→ RT	--	<10
14	10	13	NIS (7 eq.), 4-Me-DTBP (2 eq.), CH_2Cl_2, -40°C→ RT	33	27
15	79	3	NIS (5 eq.), CH_2Cl_2, -40°C→ RT	33	<10
16	**10**	**12**	**NIS (5 eq.), CH_2Cl_2, -40°C→ RT**	**32**	**18**
17	10	12	NIS (5 eq.), 4-Me-DTBP (5 eq.), CH_2Cl_2, -40°C→ RT	32	<10
18	10	12	DMTST (3 eq.), 4-Me-DTBP (3 eq), CH_2Cl_2, -40°C	32	19*
19	10	12	DMTST (6 eq.), 4-Me-DTBP (6 eq), CH_2Cl_2, -40°C	32	<19*
20	10	24	NIS (5 eq.), CH_2Cl_2, -40°C→ RT	34	<10
21	10	24	NIS (5 eq.), 4-Me-DTBP (5 eq.), CH_2Cl_2, -40°C→ RT	34	<10
22	10	25	NIS (5 eq.), CH_2Cl_2, -40°C→ RT	--	0
23	78	13	NIS (5 eq.), CH_2Cl_2, -40°C→ RT	33	20
24	78	13	IDCP (4 eq.), CH_2Cl_2, -40°C→RT	--	0

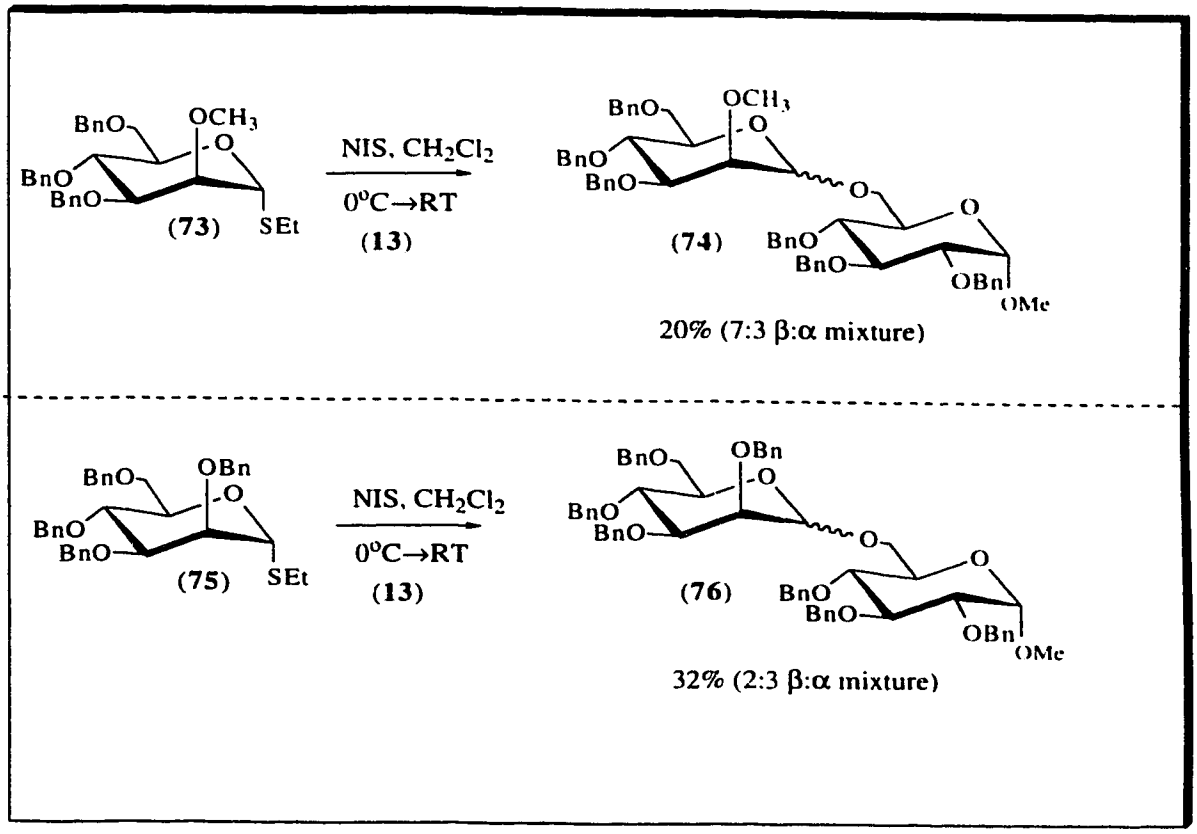
Figure 44: "One-Pot" Synthesis of Disaccharide β-Mannosides



mixed acetals in any appreciable quantity. The lack of NIS promoted mixed acetal formation was consistent with the observed results in Table 4. The data obtained from Table 4 showed that isolation of the acetals formed by NIS was attempted but was only successful when cyclohexanol or **13** were used as the alcohols.

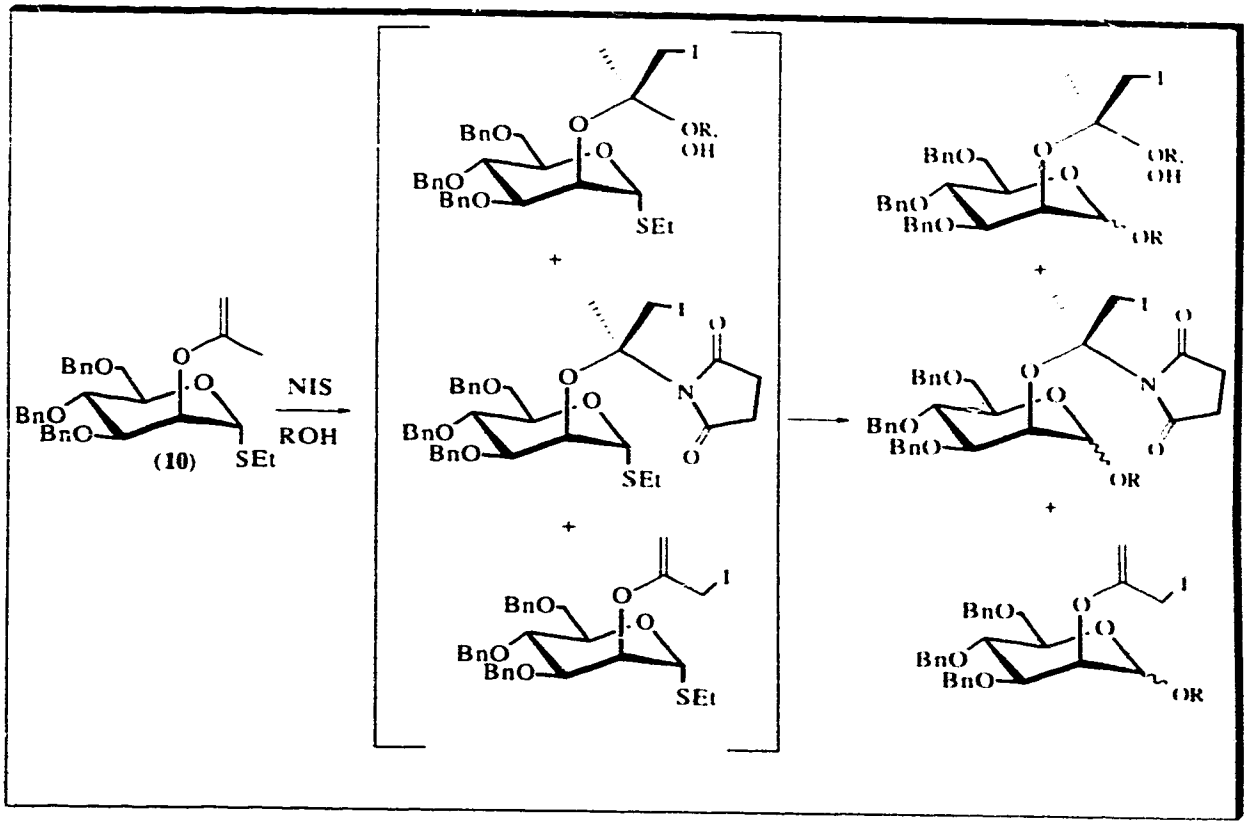
Although the *in situ* approach of IAD was not successful for more complex alcohols, optimization studies on this system revealed some important insight into the nature of this reaction. For the formation of the disaccharides **32**, **33** and **34**, the reaction seemed to show complete stereoselectivity when NIS was used as an activator, i.e. no α-mannosides were detected. This contrasts with the results in entries 18 and 19 of Table 11 where DMTST was used as a promoter and mixtures of α- and β-mannosides were detected. Since it was known that NIS activation of the vinyl ether **10** in the presence of alcohol does not give quantitative mixed acetal, there definitely was unreacted alcohol and vinyl ether present during the activation procedure. So why was there no α-mannosylation between unreacted **10** and the alcohols? One explanation was that the glycosylation yields are inherently low with NIS promoted coupling of alcohols and the thioglycoside donor **10**. Thus any formation of α-mannoside may have been too low to detect. Control reactions verified that glycosylation yields are low when NIS was used as an activator for thiomannosides in which a non-participating group was on the 2-position (Figure 45). For example, α- and β-mannoside mixtures were obtained in yields of 20% when **73** was the donor and yields of 32% when **75** was used as a donor. In addition, both of these control reactions used the highly reactive primary carbohydrate alcohol **13** as the acceptor.

Figure 45: NIS Activation of Thioglycosides with Non-Participating Groups on the 2-Position:

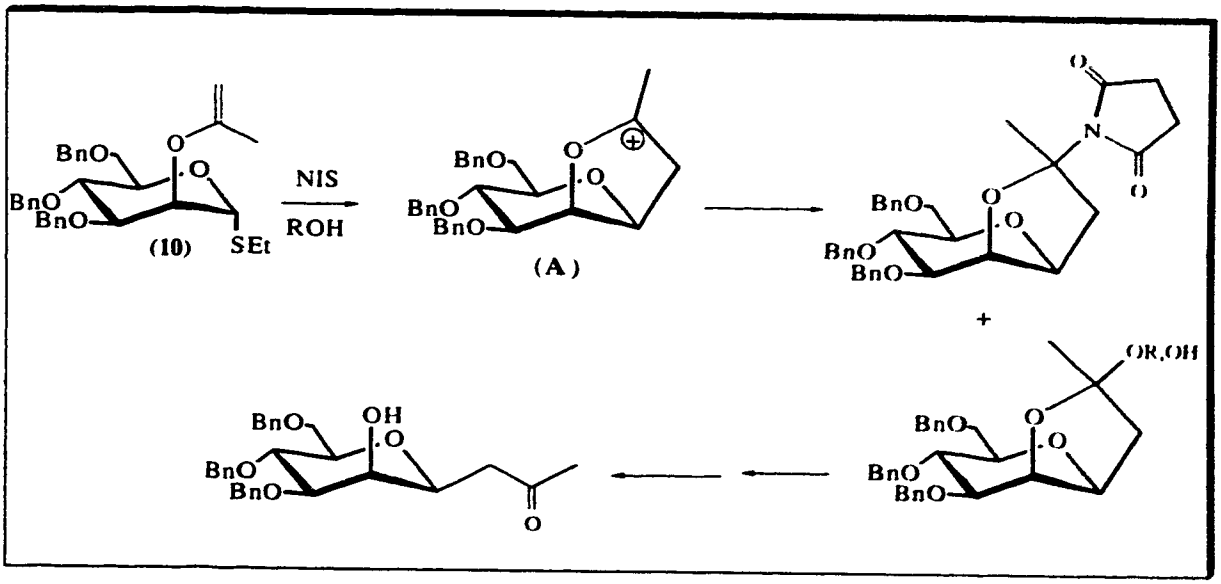


Another explanation for the stereocontrol in the "one-pot" approach was that α-mannosides may have been formed but were not identified. If the 2-position was derivatized as shown in Figure 46a, any α-mannoside formation may have been concealed. This was especially the case since emphasis was placed on observing the 2'-OH α-mannosides **37**, **39** and **41**. Several chromatographic fractions revealed the presence of complex mixtures of products by NMR and could not conclusively rule out the formation of any α-mannosides. However, such acid sensitive α-mannosides would

A) Acetal-Type Side Products:



B) *C*-Glycosyl Side Products:

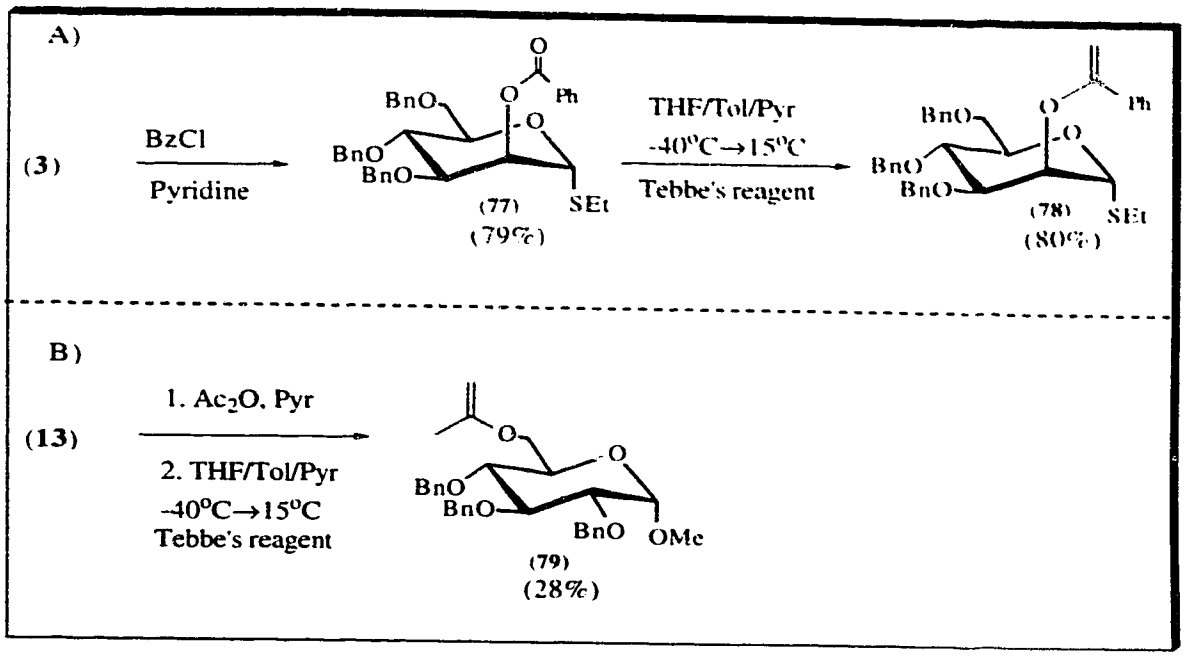


have to withstand the acidic reaction conditions as well as purification by silica gel chromatography to have remained undetected.

A third explanation to rationalize the β-selectivity is shown in Figure 46b. It could be that NIS activation of the vinyl ether **10** in the presence of an alcohol may have formed *C*-glycosyl intermediate (**A**) that effectively prevented the formation of any α-glycoside. This intermediate could have rearranged to give a number of products as demonstrated in Figure 46b. Although this is plausible, no NMR evidence was obtained to support this type of side product.

In summary, analysis of the "one-pot" strategy for IAD yielded beneficial results, even though the yields were low and the β-selectivity could not be conclusively determined. For example, the cross reactivity of NIS with bases such as collidine and Hunig's base was determined (Table 11, entries 2, 3). Furthermore, *in situ* acetalization was attempted with the vinyl ether **78**, synthesized from the 2-*O*-benzoate **77** (Figure 47a). This reaction did not give as good yields as the 2-*O*-propenyl system (Table 11, entries 23, 24) so it was not considered in the 2-step strategy. A reversed strategy which used the vinyl ether **79** and the alcohol **13** (Figure 47b) also proved to be a lower yielding approach (Table 11, entry 15). Finally, the use of different solvents (Table 11, entries 11-13) confirmed that dichloromethane gave the best results.

Figure 47: The Synthesis of Vinyl Ethers (**78**) and (**79**):



B. Other Acetal Linkages used in IAD:

Various strategies were developed that involved the use of acetals in the linkage of carbohydrates via non-anomeric positions. The acetals investigated included the use of smaller groups than the isopropylidene acetal, since the steric demand on the reaction system would be reduced. In one approach, a methylene linker was investigated because of its small size and use in the literature to covalently attach nucleoside residues[194-200]. The use of ethylidene and benzylidene acetals were also attempted as they involved less hindered secondary acetalic carbons.

B.1. Methylene Acetals:

The covalent attachment of two sugar residues through a non-anomeric position has been accomplished using a methylene acetal linker. Several approaches have been used that are based on the principles used in glycosylation procedures. For instance, one approach utilizes a sulfur activation strategy[195-200] (Figure 48a). By forming a methylthiomethyl linkage on the 3-position of the deoxy ribose moiety, activation with NIS / TfOH forms the resulting oxomethylene carbocation which is trapped by the primary alcohol in 71% yield[197]. A second approach is a modification of Fraser-Reid's pentenyl glycoside activation strategy[72,201-203] (Figure 48b). This procedure involved the synthesis of the pentenyl methoxymethyl (POM) acetal on the 3-position of the deoxy ribose moiety. Activation of the POM acetal with NIS in the presence of the primary alcohol gave the formacetal product in good yield (80%)[199]. At first glance it seems that both these strategies have the potential to cross react if applied to the thioglycoside systems used for IAD. However, the potential to fine tune the strategy so that coupling would occur first at the 2-position to form the methylene acetal and then transfer to form the β-mannoside (Figure 49) was an alluring possibility that justified further exploration.

Prior to using the POM acetal strategy for coupling two carbohydrate residues, the transfer of an octyl group was attempted. Commercially available bromomethyl octyl ether was reacted with the alcohols **3** and **81** to give the acetals shown in Figure 50. Activation of the thioglycosides **80** and **82** with NIS (5 eq.) in dichloromethane proved to be very sluggish and no β-mannosides were detected from either reaction. Despite these results, the extension of this coupling strategy to more complex systems was attempted.

Figure 48: Methylene Acetal Linker Strategies:

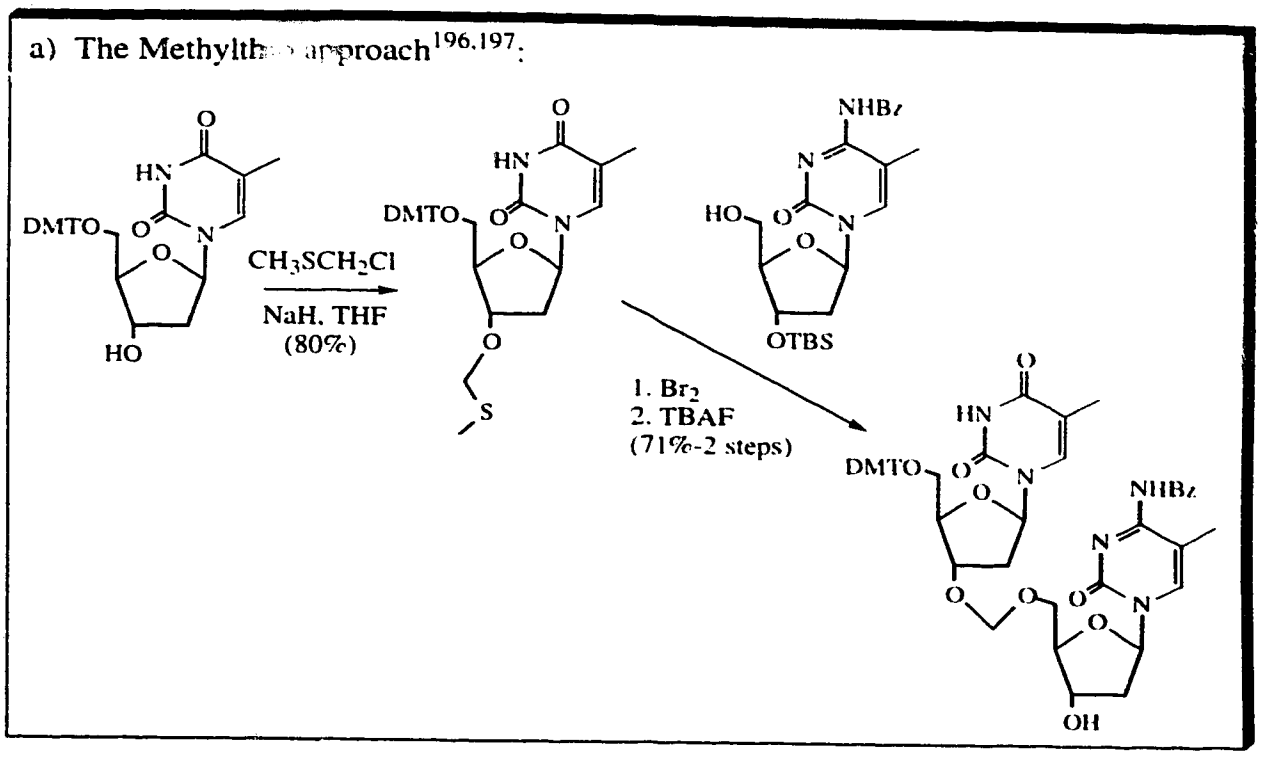


Figure 49: The Application of a Methylene Acetal Strategy to Pyranose Sugars:

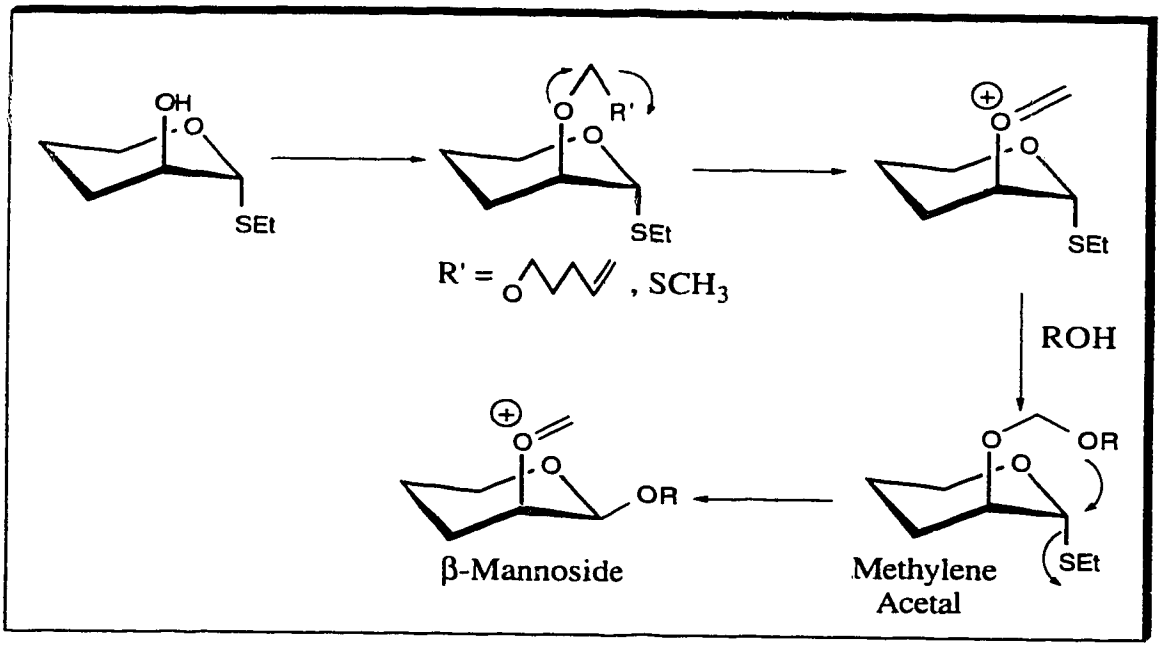
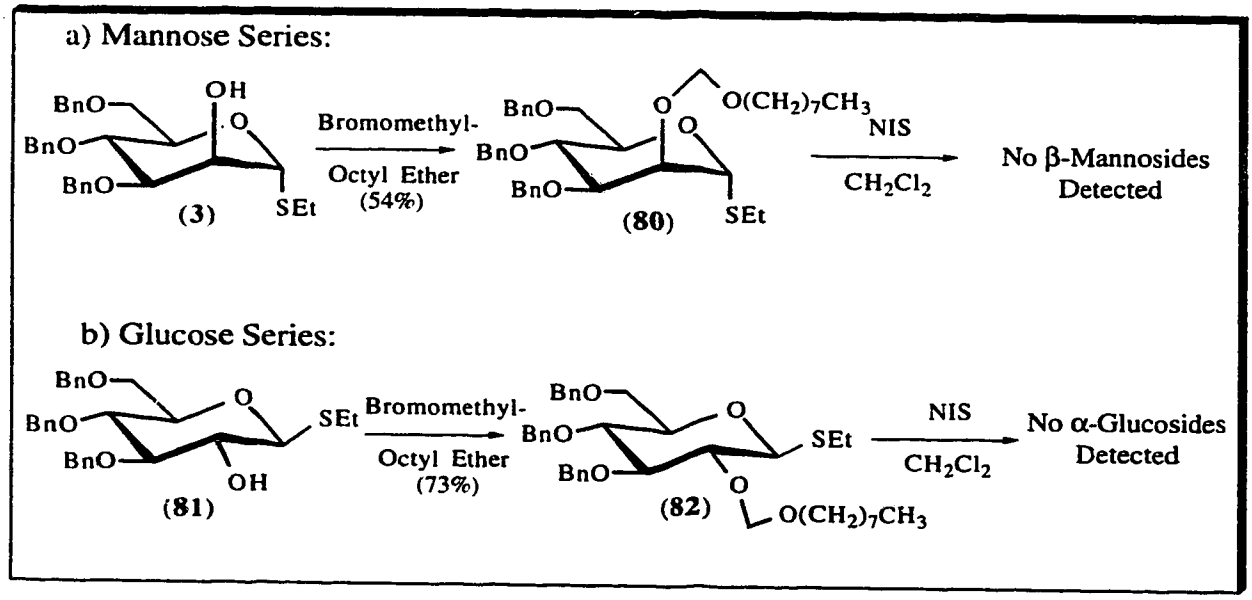


Figure 50: The Use of a Methylene Linker in IAD:



Two separate approaches were taken to test the POM acetal procedure (Figure 51 and 52). The first approach involved the reaction of POM chloride[72] with alcohol **3** to give the product **83**. The low yield for this reaction was due to premature quenching since 41% of the starting material was recovered. NIS activation (2 eq.) of **83** at 0°C in the presence of alcohol **13** yielded no product. Only the kinetic and thermodynamic benzylidene products **42** and **84** were isolated in up to 53% recovered yields (Figure 51). A second approach was attempted in which the coupling strategy was reversed (Figure 52). It was believed that this reversed strategy would be able to prevent cross reactivity of NIS with the thioglycoside. For example, the POM acetal **85** was synthesized from the alcohol **12** in 71% yield. Activation of the pentenyl group followed by the addition of the alcohols **3** or **86** turned out to be a more successful strategy. The thioglycoside **86** was synthesized from the di-acetate **91** as shown in Figure 52. It was chosen as it was a less reactive thioglycoside than the thioethyl glycoside and could potentially prevent cross reactivity with the pentenyl group. Both reactions gave low yields of product, 5% for **87** and 8% for **88**. Other products identified were the methylene acetal **89**, alcohols **3** and **12**, and the succinimide adduct **90**. These side products were consistent with those isolated in the literature[199].

Figure 51: POM Acetal Approach to Linking Pyranose Sugars:

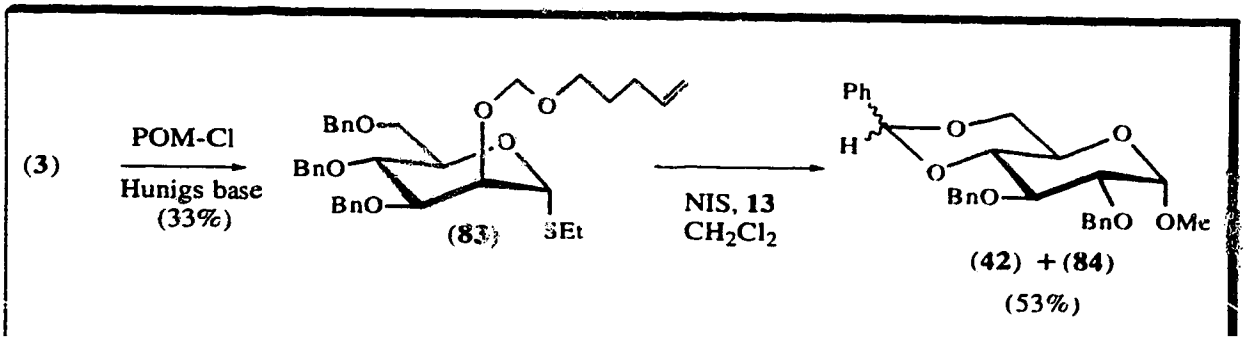
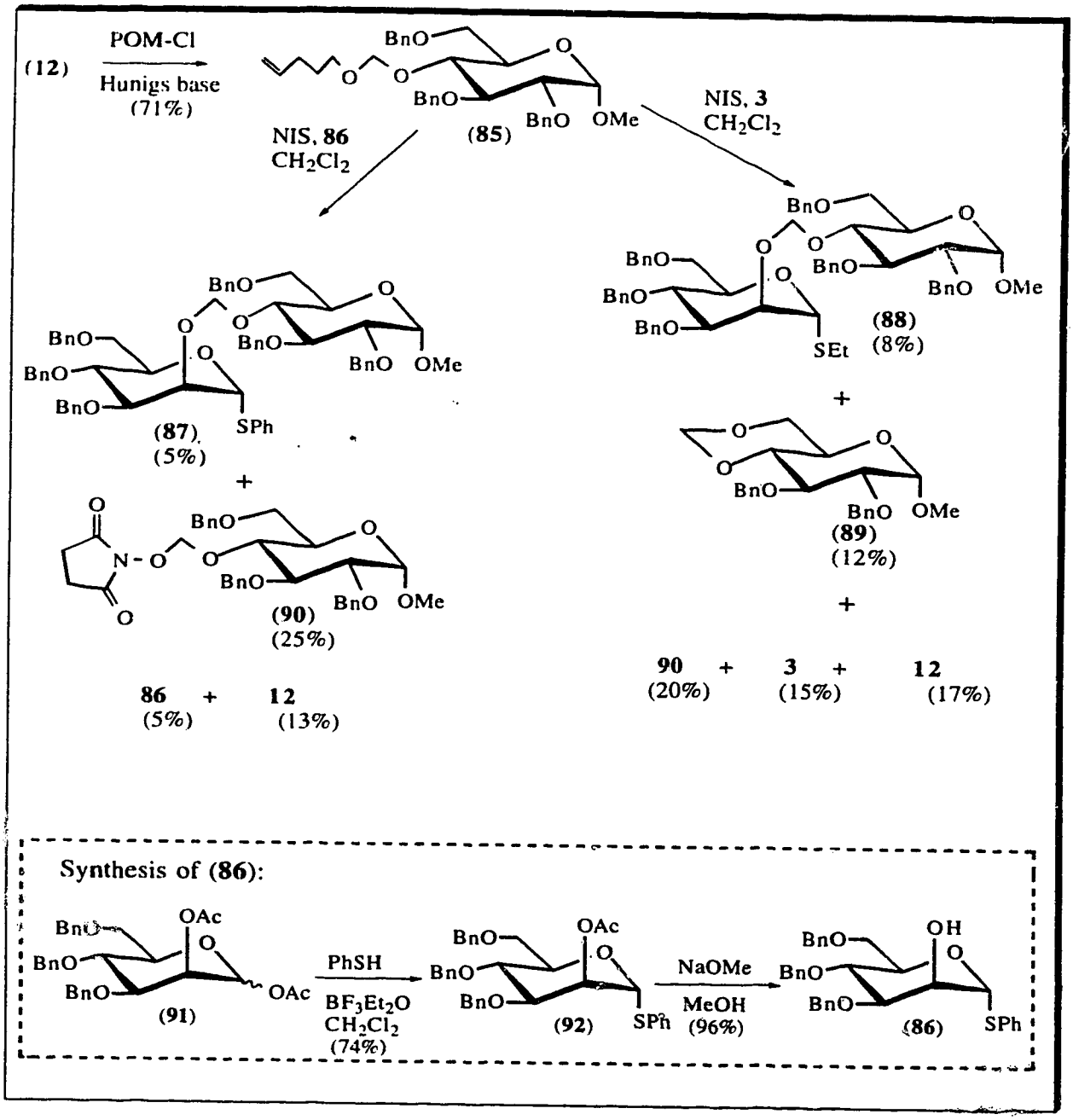


Figure 52: Reversed POM Acetal Coupling Strategy :

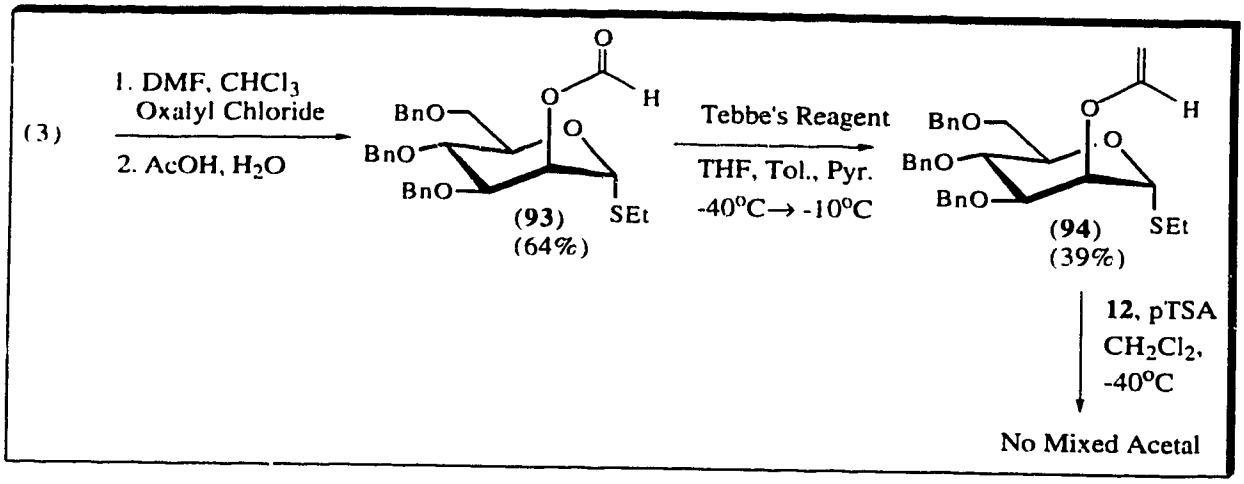


The low isolated yields from the POM acetal coupling strategy and the fact that the octyl methylene acetals **80** and **82** did not undergo IAD indicated that this was not a practical strategy for making β-mannosides. Nevertheless, important information was obtained about the sensitivity of the activation step. It is apparent that the delivery of the aglycon will not occur unless the resulting carbocation is stable enough. The slowing of this transfer steps allows for numerous side reactions to occur that ultimately cause the method to fail. In addition, valuable information on the relative reactivities of the pentenyl group versus the phenyl and ethyl thioglycosides was obtained.

B.2. Ethylidene Acetals:

Another coupling strategy involved the use of ethylidene acetals. This procedure was an extension of the isopropylidene acetal approach with the only difference being the use of a smaller linking group. As shown in Figure 53, the alcohol **3** can be converted to the formate ester[192] to give **93**. The vinyl ether **94** can then be formed by reaction with Tebbe's reagent. Acid catalyzed coupling of **94** with the alcohol **12** was slower than the isopropylidene case. In fact, no coupling was observed after two hours at -40°C. This contrasts with the 10 minute reaction times encountered when vinyl ether **10** was coupled with **12**. The long reaction time prompted a gradual increase in reaction temperature to -15°C which caused complete decomposition of **94**. The inability to form mixed acetals and the fact that a diastereomeric mixture of products would of resulted if the procedure was successful made this method unattractive and further attempts to optimize the reaction conditions were discontinued.

Figure 53: The Attempted Formation of Ethylidene Acetals:

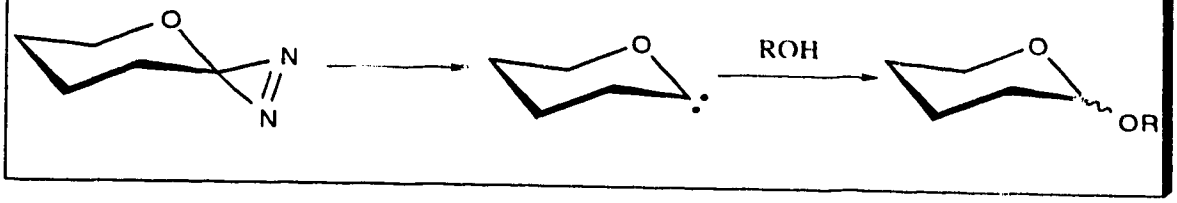


B.3. Benzylidene Acetals:

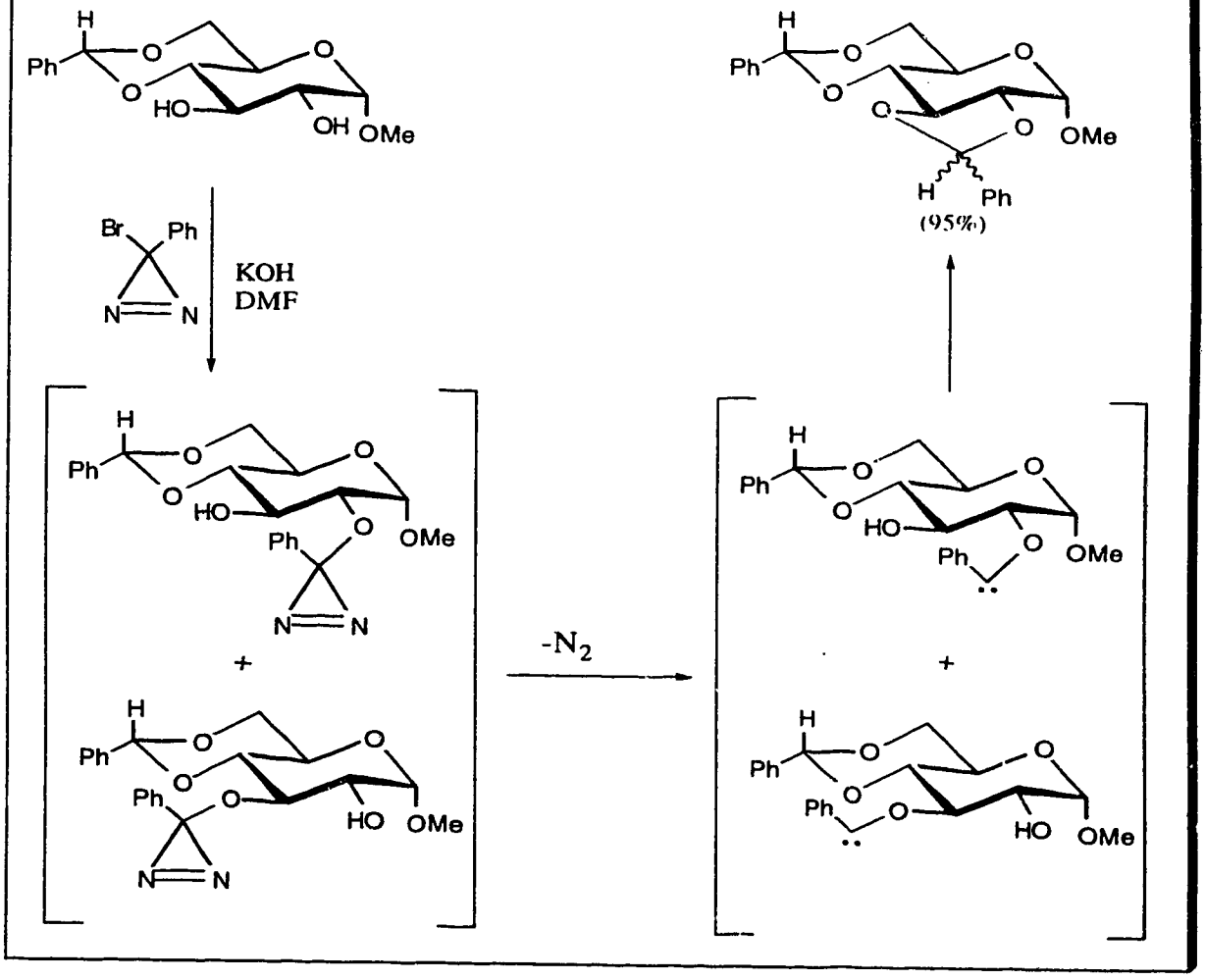
A fundamentally different approach was investigated in the use of benzylidene acetals to link two different carbohydrate residues. This approach replaced the acid catalyzed coupling described with a more reactive carbene strategy. Vasella and coworkers have used a glycosylidene carbene strategy as a new method for the construction of glycoside bonds[204]. This technique has been extended to the formation of benzylidene acetals[205]. The strategy involved the synthesis of diazirine compounds that can thermally generate a carbene which caused insertion into a hydroxyl group (Figure 54a). In Figure 54b, it was shown that a bromo diazirine can react with an alkoxide to yield an intermediate alkoxy diazirine. This highly unstable intermediate then generated a carbene which was trapped by the second hydroxyl group, in an intramolecular fashion, to form a benzylidene acetal. A progression of this strategy is postulated in Figure 55. If generation of the carbene was accomplished in the presence of another alcohol, intermolecular trapping of the carbene may occur which would yield a benzylidene linked

Figure 54: The Use of Diazirines in Carbohydrate Chemistry :

a) Glycoside Bond Formation[204]:

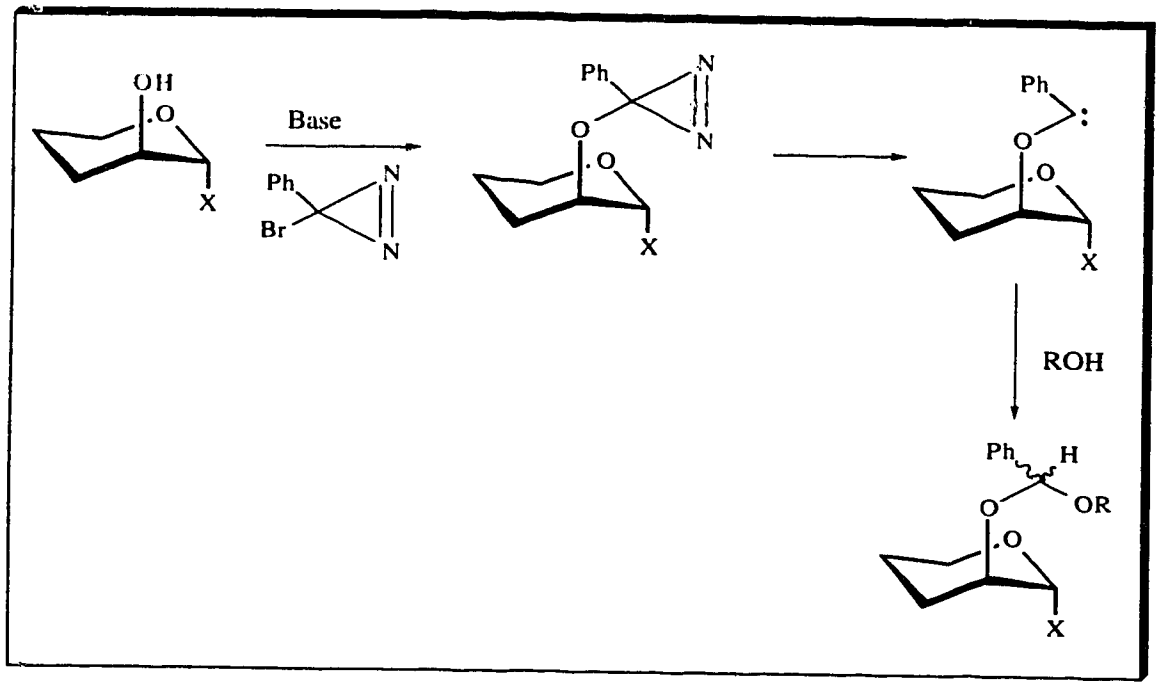


b) Benzylidenation[205]:



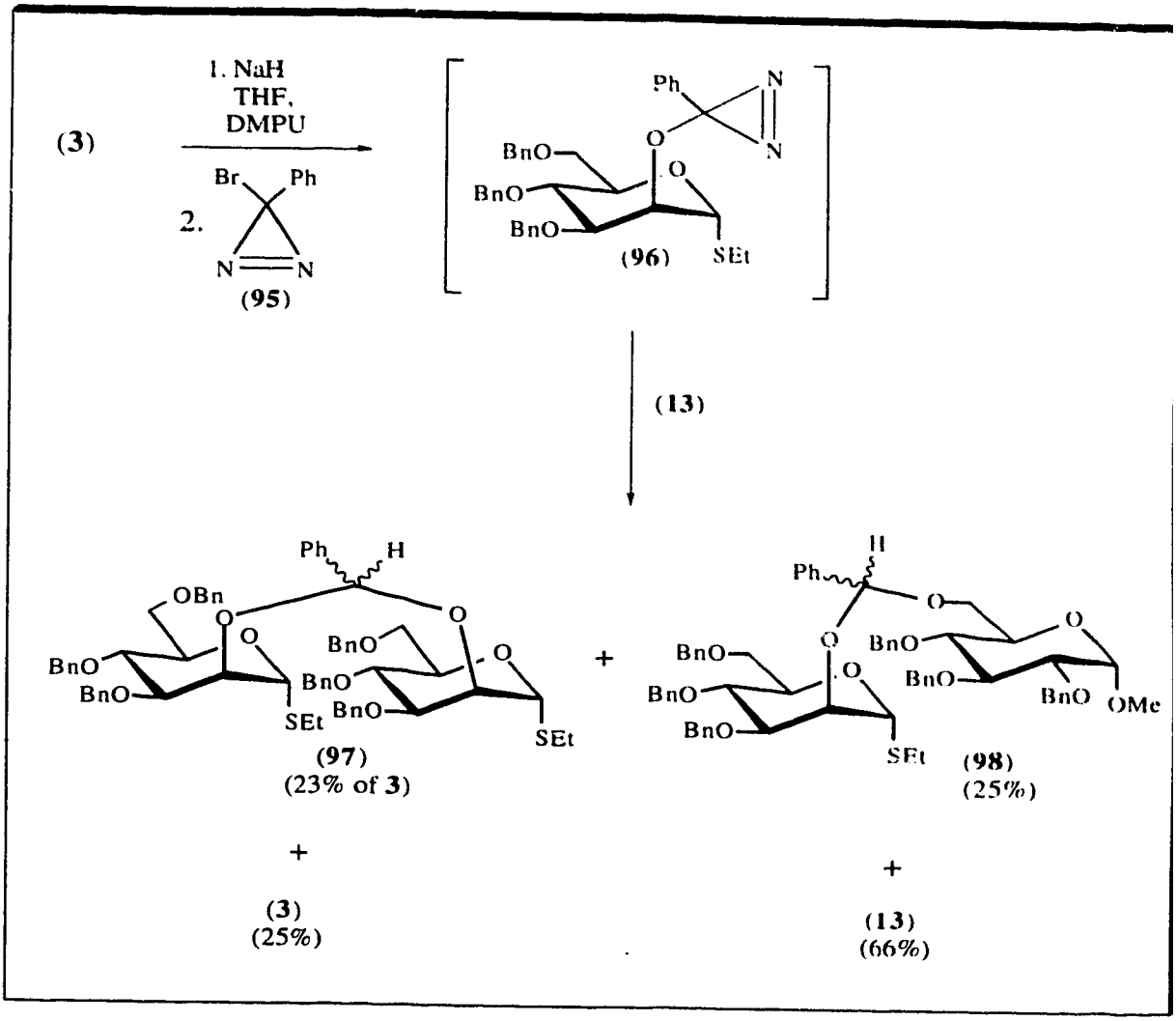
acetal. The greatest advantage of this method is that the highly reactive carbene may be able to insert into very unreactive hydroxyl groups such as those present in oligosaccharides.

Figure 55: General Strategy for Making Benzylidene Linked Acetals:



Preliminary experiments have revealed that the postulated reaction sequence does occur (Figure 56). A variety of conditions have been attempted but it was found that solvent polarity and reaction temperature were the most crucial factors to control. The best conditions developed involved the treatment of the alcohol **3** with 2 eq. of NaH in THF / DMPU. The diazirine **95**[205,206] was added and the reaction kept at -40°C for seven hours prior to the addition of **13**. This maximized the formation of the highly unstable alkoxy diazirine **96**[207-209]. Once **13** was added, the reaction was allowed to warm to room temperature overnight. The highest isolated yield of **98** was 25%. One

Figure 56: The Diazirine Approach to Making Benzylidene Acetals:



concern with this procedure is the formation of the dimer **97** that consumes 23% of th starting thioglycoside alcohol. Although the formation of **98** gives a diastereomeri mixture, one isomer is very predominant. This new coupling strategy does sho promise, but extensive optimization will be necessary for it to rival the acid catalyze technique that can typically give yields >70% when coupling involves a primary

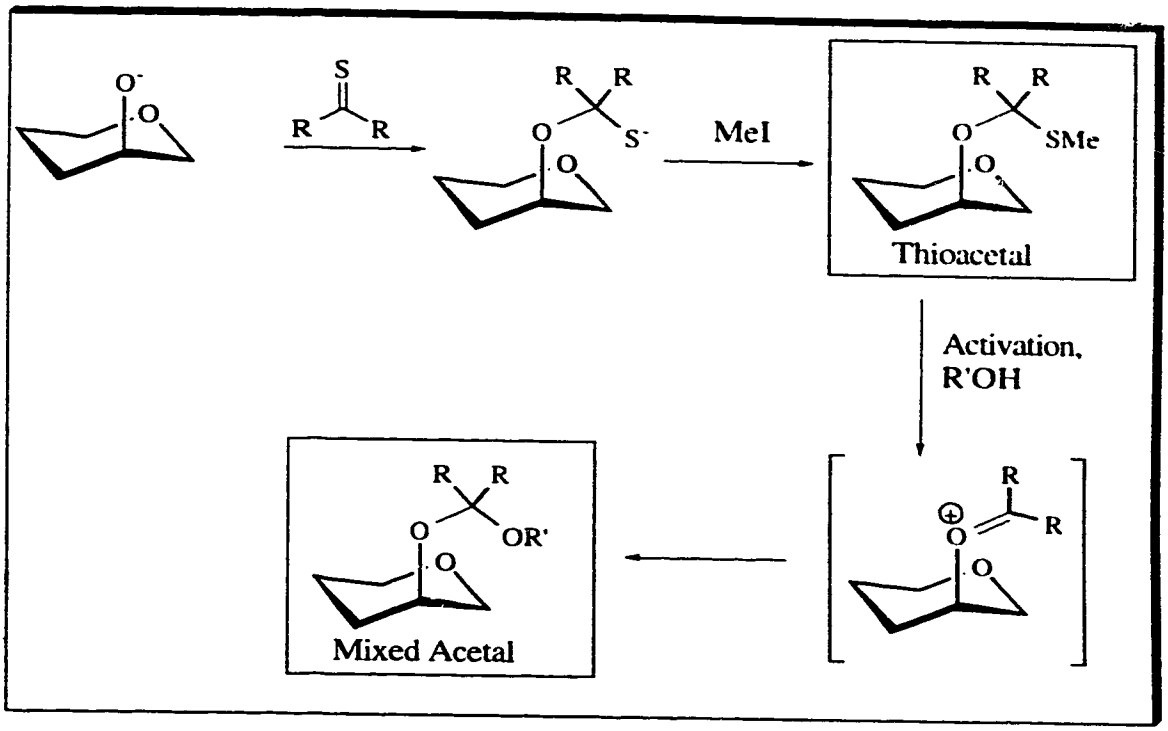
carbohydrate alcohol such as **13**. Another drawback to the method is the fact that the diazirine compounds are explosive. Since the yield of the benzylidene acetal **98** was low even for a primary alcohol, this method was not investigated further.

C. Future Work:

1. Thioacetals as Potential Linking Agents:

A different approach for the linking of carbohydrate residues through non-anomeric positions involves the use of thioacetals. The advantage of this strategy is that the thioacetal formation is a thermodynamically favored process as opposed to the kinetically driven acid catalyzed coupling presently in use. In principle, the method involves nucleophilic attack of an alkoxide on a thiocarbonyl derivative as outlined in Figure 57. This is followed by the addition of an alkylating agent such as methyl iodide to form the thioacetal as is supported in a report by Kahne[125]. Once the thioacetal is formed, activation of the thiol group in the presence of an alcohol can lead to the desired mixed acetal. Alternatively, oxidation of the thiol to the sulfoxide, followed by treatment with triflic anhydride[170] at low temperature, generates a carbocation that can be trapped by an alcohol to form the desired acetal. The carbocation formation, especially if the sulfoxide strategy is used, can be performed at low temperature (-70°C) without influencing any other groups in the system. One disadvantage to the strategy is the ease at which thioketones and thioaldehydes polymerize[210-216].

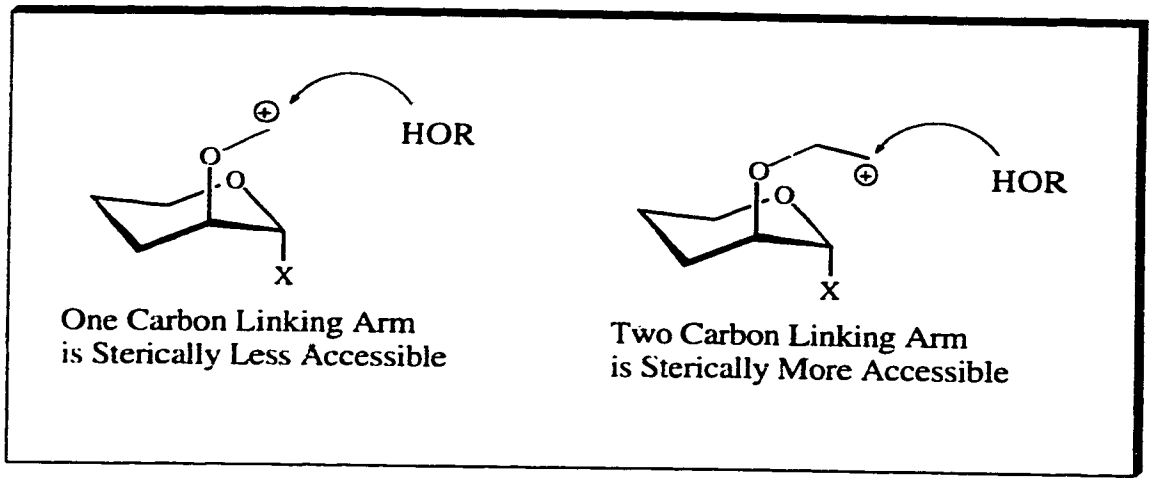
Figure 57: Thioacetals as Potential Linking Agents:



C.2. Non-Acetal Linking Strategies:

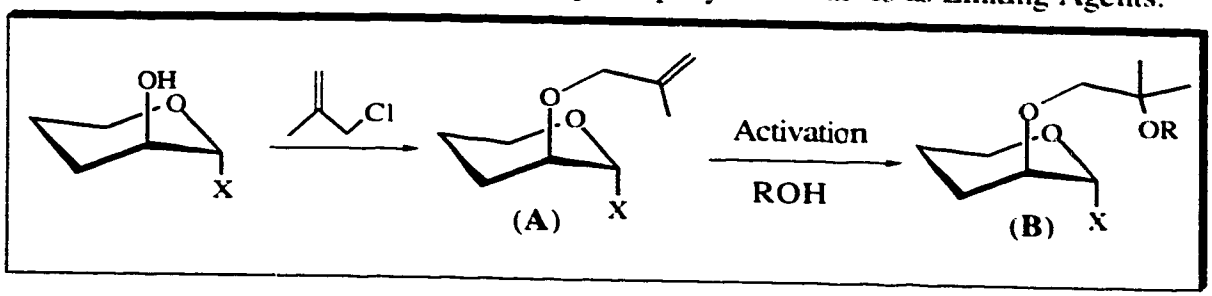
A different approach to linking carbohydrate groups together via non-acetal groups would be to use a spacer that is greater than one carbon unit. For example, extending the linking arm to two carbons would possibly alleviate the steric problems that have plagued the existing methodology (Figure 58). Two strategies are proposed as potential methods for making a two carbon linker. Moreover, several other compounds that show promise in linking carbohydrate residues are proposed.

Figure 58: The Potential Advantage of Lengthening the Linker Arm:



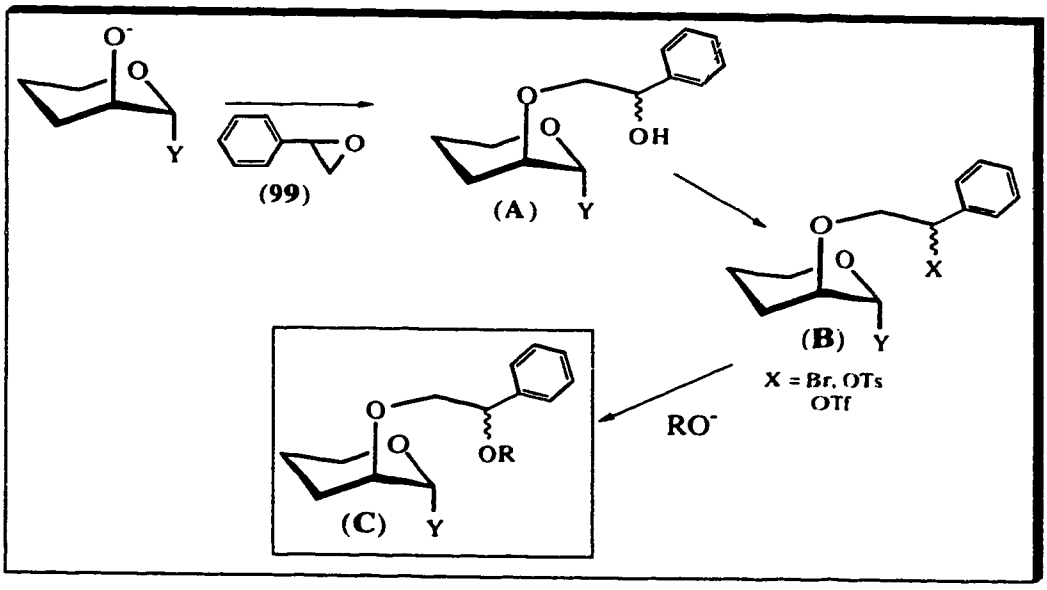
One strategy for lengthening the linker arm involves an extension of the vinyl ether strategy as outlined in Figure 59. The commercially available 2-methyl propenyl chloride might be used to covalently attach a carbohydrate residue to give a 2-methyl propenyl derivative such as **A**. Electrophilic activation of the double bond in the presence of an alcohol would allow for etherification to give the desired two carbon linked structure **B**. Although the 2-methyl propenyl derivative is analogous to the vinyl ether **10**, much more vigorous coupling conditions will be needed. This is because the chemical reactivity of the system has been dramatically altered, going from a highly reactive vinyl ether to a less reactive alkene derivative. The use of NIS / TfOH[203] or benzene selenenyl triflate[217] would be good choices as highly electrophilic activators for this system. A more stable anomeric group would be required as ethyl thioglycosides would cross react with the strong coupling conditions.

Figure 59: The Proposed Use of 2-Methyl Propenyl Derivatives as Linking Agents:



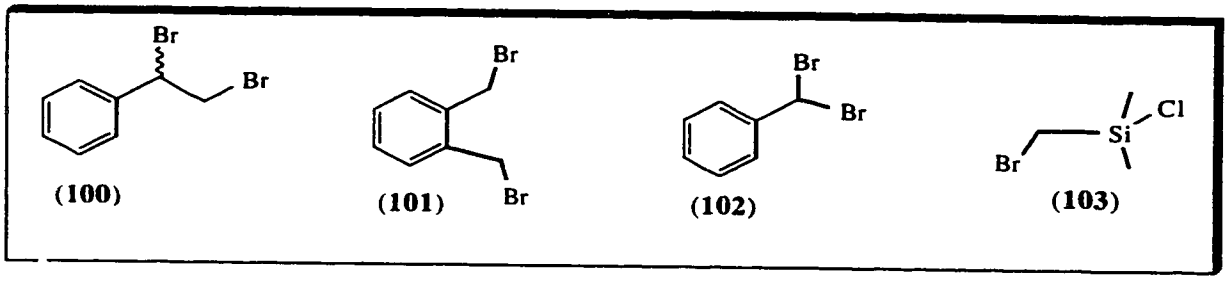
Another strategy proposed to introduce a two carbon linking arm is based on the ring opening of epoxides as shown in Figure 60. In this procedure, ring opening of an epoxide such as commercially available styrene oxide **99** by an alkoxide gives the first carbohydrate linked structure **A**. Conversion of the resulting hydroxyl group to a leaving group **B** then allows for displacement by a second alkoxide group. The resulting structure would give the required two carbon spacer **C**. Drawbacks for this method would be the formation of diastereomers by epoxide ring opening and competing elimination of HX in **B** (Figure 60) to give a conjugated double bond.

Figure 60: General Strategy for Epoxide Ring Opening:



In theory, any molecule that is derivatized with two potential leaving groups can be used to link two carbohydrate residues. For example, the 1,2-dibromoethyl benzene **100** could be used to attach a residue first through the primary position and then via the secondary position (Figure 61). The α,α'-dibromo-*o*-xylene compound **101** is another potential candidate to link two residues via non anomeric positions to give a four carbon spacer. A structure such as α,α'-dibromo toluene **102** is another possibility. The use of (bromomethyl)chlorodimethylsilane compound **103** would be an extension of the existing work of Bols[162-165] and Stork and Kim[161]. A systematic survey to evaluate such molecules is necessary to determine if any of these structures would be successful not only in linking two residues together, but also in transferring the potential aglycons in a stereocontrolled fashion.

Figure 61: Molecules with Potential to Act as Linking Agents:

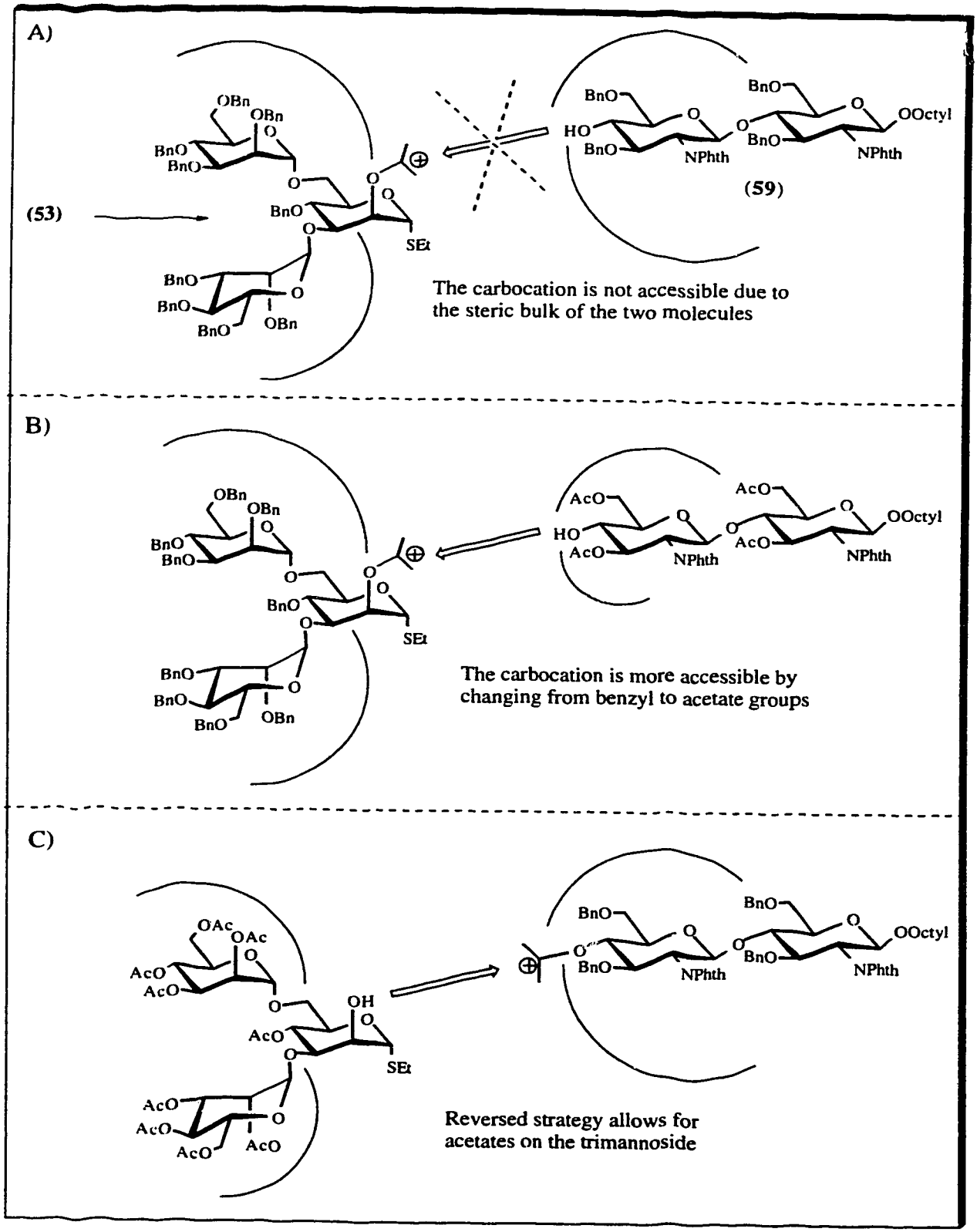


C.3. Changing Protecting Groups in the Existing Strategy:

In all the systems studied so far that have successfully undergone IAD, the main protecting group used is the benzyl group. These groups are highly hydrophobic and can enhance the steric difficulties in reaction systems. It would be of interest to see how exchanging these bulky groups for less hindered structures would influence the yields in IAD reactions. In the coupling strategy, in may be that formation of a carbocation in a

bulky structure such as **53** is buried by the nine benzyl groups on the molecule, preventing any access to the alcohol (Figure 62a). In addition, the alcohol is also protected with benzyl groups, so that these two highly lipophilic structures can not interact with each other. One possibility is to use acetates on the alcohol and see if reactivity would be enhanced (Figure 62b). Unfortunately, the use of ester protecting groups on the thioglycoside would not be compatible with the reaction of Tebbe's reagent. Reversing the strategy by having the vinyl ether on the aglyconic molecule and the thioglycoside as the alcohol would enable ester protecting groups to be used on the trimannoside (Figure 62c). These alterations to the existing strategy would help understand why IAD fails in more complex systems.

Figure 62: Protective Group Changes may Enhance IAD Reactivity:



D. Conclusion:

A two step procedure, called Intramolecular Aglycon Delivery, was developed to make β-D-mannopyranosides. In the first step, an alcohol was covalently linked to the 2-position of a mannose derivative. In the second step, the anomeric position of this mannose derivative was activated, causing the stereocontrolled delivery of the alkoxy group. In molecules as complex as disaccharide **34**, this procedure produces yields that are similar to those reported in the literature. In particular, IAD eliminates the need for separation of anomers.

When IAD was applied to the synthesis of the core pentasaccharide, the first step of the method did not yield the required isopropylidene linked acetal. Therefore alternatives to the isopropylidene acetal linker approach are necessary to make this method of practical value in the synthesis of β-D-mannopyranosides.

Other methods were investigated to replace the first step of IAD. These methods did not produce the desired result or did not improve the existing method. Further research is suggested to improve IAD to make it the method of choice for making β-D-mannopyranosides.

CHAPTER 4

Experimental:

General methods

Optical rotations were measured with a Perkin-Elmer 241 polarimeter at 22° + 2°C. Analytical thin-layer chromatography (tlc) was performed on silica gel 60-F_{254} (Merck). Tlc detection was achieved by ultra violet light visualization and by charring with sulfuric acid. All commercial reagents were used as supplied. All chromatography solvents were distilled prior to use. Column chromatography was performed using silica gel 60 (Merck 40-60 μM) or beaded silica gel 6RS-8060 (Iatrobeads) manufactured by Iatron Laboratories (Tokyo). ^{1}H-N.m.r. spectra were recorded at 360 MHz (Bruker WM-360) or 300 MHz (Bruker AM-300) or 500 MHz (Varian Unity-500) with internal $(CH_3)_4Si$ (δ 0, $CDCl_3$, CD_3OD, or D-5 pyridine). COSY spectra were obtained at 360 MHz (Bruker WM-360). ^{13}C-N.m.r. were recorded at 75.5 MHz (Bruker Am-300) or 125.7 MHz (Varian Unity-500) with internal $(CH_3)_4Si$ (δ 0, $CDCl_3$, CD_3OD, or D-5 pyridine). Only partial n.m.r. data were reported. The chemical shifts and coupling constants (as observed splittings) for ^{1}H resonances were reported as though they were first order. The assignments of ^{1}H and ^{13}C resonances were tentative. Organic solutions were concentrated under vacuum at ≤ 40°C (bath) / 12 mm Hg. All anhydrous reactions were carried out using phosphorous pentoxide (P_2O_5) dried starting materials (high vacuum ~ 50 microns) and dry solvents under argon atmosphere. Anhydrous transfers were completed with standard syringe techniques. All glassware was pre-dried overnight at 160°C. All samples submitted for elemental analysis were dried overnight under high vacuum over P_2O_5 at 56°C (refluxing acetone).

General procedure for the preparation of Tebbe's Reagent (**9**)[180]

Titanocene dichloride (0.50 g, 2 mmol, 1.0 eq.) was added to a round bottom flask and purged with argon. Trimethylaluminum (2.0 ml, 4 mmol, 2 eq., 2.0 M solution in toluene) was slowly added by syringe into the reaction flask. Prior to use, the mixture was stirred under argon atmosphere for 60 hours. The solution was a deep red color and blackened as it decomposed. Any exposure to air produced white fumes.

Ethyl 2-O-acetyl-3,4,6-tri-O-benzyl-1-thio-α–D-mannopyranoside (**2**)

The ortho ester **1**[176] (5.0 g, 9.9 mmol) was added to a round bottom flask and purged with argon. Ethanethiol (30 ml) was added to the reaction flask and the solution was cooled to 0°C. Boron trifluoride etherate (1.22 ml, 9.9 mmol) was syringed into the stirred mixture. The reaction was quenched after 15 minutes by the addition of 5 ml of distilled water (dH_2O). The ethanethiol was removed in the fumehood by blowing a stream of air over the mixture for three hours. Dichloromethane (200 ml) was added to the solution. It was then washed twice with 200 ml of dH_2O. The organic layer was dried ($MgSO_4$), filtered and concentrated which produced a pale yellow syrup. Eighteen percent (18%) ethyl acetate in hexane was used as an eluent in column chromatography of the crude reaction mixture. Purification yielded a colorless syrup **2** (4.46 g, 84%). A slower running by-product was isolated which corresponded to the methyl glycoside **7**.

2: $[\alpha]_D$ +86.8° (*c* 0.95, CH_2Cl_2). R_f 0.70 in ethyl acetate - hexane, 1:3; ^1H NMR (300 MHz, $CDCl_3$) δ: 7.30, 7.15 (m, 15H, Ph), 5.43 (dd, 1H, $J_{1,2}$ = 1.5 Hz, $J_{2,3}$ = 3.0 Hz, H-2), 5.32 (d, 1H, $J_{1,2}$ = 1.5 Hz, H-1), 4.85, 4.47 (2 x d, 2H, J_{gem} = 10.8 Hz, OCH_2Ph), 4.69 , 4.48 (2 x d, 2H, J_{gem} = 12.2 Hz, OCH_2Ph), 4.68, 4.52 (2 x d, 2H, J_{gem} = 11.1 Hz, OCH_2Ph), 4.16 (m, 1H, H-5), 3.94 (dd, 1H, $J_{3,4}$ = 9.5 Hz, $J_{4,5}$ = 9.5 Hz, H-4), 3.90 (dd, 1H, $J_{2,3}$ = 3.0 Hz, $J_{3,4}$ = 9.5 Hz, H-3), 3.84 (dd, 1H, $J_{5,6}$ = 4.0 Hz, $J_{6,6'}$ = 11.0 Hz, H-6), 3.68 (dd, 1H, $J_{5,6'}$ = 1.8 Hz, $J_{6,6'}$ = 11.0 Hz, H-6'), 2.62 (m, 2H, SCH_2CH_3), 2.15 (s, 3H, CH_3, acetate), 1.28 (t, 3H, J_{vic} = 7.5 Hz, SCH_2CH_3); ^{13}C

NMR (75.5 MHz, $CDCl_3$) δ: 170.4 ($COCH_3$), 138.4, 138.2, 137.8, 129.1-127.6 (aromatic), 82.5 (C-1), 78.6 (C-2), 76.4, 71.9, 70.6 (C-3, C-4, and C-5), 75.2, 73.4, 71.9 (3 x OCH_2Ph), 68.9 (C-6), 25.5 (SCH_2CH_3), 21.2 ($COCH_3$), 14.9 (SCH_2CH_3). Anal. calcd. for $C_{31}H_{36}O_6S$: C 69.38, H 6.76, S 5.97; found: C 68.79, H 6.82, S 6.12.

7: R_f 0.56 in ethyl acetate - hexane, 1:3; ^1H NMR (300 MHz, $CDCl_3$) δ: 5.36 (dd, 1H, $J_{1,2}$ = 1.8 Hz, $J_{2,3}$ = 3.5 Hz, H-2), 4.74 (d, 1H, $J_{1,2}$ = 1.8 Hz, H-1), 3.97 (dd, 1H, $J_{2,3}$ = 3.5 Hz, $J_{3,4}$ = 9.4 Hz, H-3), 3.88 (dd, 1H, $J_{3,4}$ = 9.4 Hz, $J_{4,5}$ = 9.4 Hz, H-4), 3.82-3.70 (m, 3H, H-5, H-6 and H-6'), 3.36 (s, 3H, OCH_3), 2.15 (s, 3H, $COCH_3$); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ: 170.52 ($COCH_3$), 98.83 (C-1), 78.21, 76.63, 71.31, 68.71 (C-2, C-3, C-4, and C-5), 54.97 (OCH_3), 21.15 ($COCH_3$).

Ethyl 3,4,6-tri-O-benzyl-1-thio-α-D-mannopyranoside (**3**)[90]

The 2-*O*-acetate **2** (1.50 g, 2.8 mmol) was dissolved in 25 ml of methanol. Catalytic sodium methoxide (10 mg) was added to the reaction mixture and it was stirred overnight at room temperature. The solution was then neutralized by the addition of Amberlite IRC-120 (H^+) resin, filtered and concentrated. The product **3** (1.37 g, 100%) was not chromatographed as the ^1H NMR did not reveal any impurities; R_f 0.45 in ethyl acetate - hexane, 1:2; ^1H NMR (300 MHz, $CDCl_3$) δ: 5.42 (d, 1H, $J_{1,2}$ = 1.2 Hz, H-1), 4.19 (m, 1H, H-5), 4.11 (dd, 1H, $J_{1,2}$ = 1.2 Hz, $J_{2,3}$ = 3.2 Hz, H-2), 3.90 (dd, 1H, $J_{3,4}$ = 9.0 Hz, $J_{4,5}$ = 9.0 Hz, H-4), 3.86 (dd, 1H, $J_{2,3}$ = 3.2 Hz, $J_{3,4}$ = 9.0 Hz, H-3), 3.82 (dd, 1H, $J_{5,6}$ = 4.5 Hz, $J_{6,6'}$ = 10.8 Hz, H-6), 3.70 (dd, 1H, $J_{5,6'}$ = 2.0 Hz, $J_{6,6'}$ = 10.8 Hz, H-6'), 2.64 (m, 2H, SCH_2CH_3), 1.30 (t, 3H, SCH_2CH_3); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ: 83.43 (C-1), 80.50, 74.62, 71.52, 69.94 (C-2, C-3, C-4, and C-5), 69.96 (C-6), 24.90 (SCH_2CH_3), 14.85 (SCH_2CH_3).

Ethyl 3,4,6-tri-O-benzyl-2-O-(methoxy isopropylidene)-1-thio-α-D-mannopyranoside (**4**)

The alcohol **3** (200 mg, 0.405 mmol) was added to a reaction flask and purged with argon. Dichloromethane (10 ml) was added followed by 0.047 ml (1.2 eq.) of dimethoxypropene. The reaction was cooled to -40°C and catalytic *p*-toluenesulfonic acid was added. After 7 minutes the reaction was quenched by the addition of triethylamine. The mixture was then concentrated and purified by using a 10% ethyl acetate in hexane solvent system that contained 0.1% triethylamine. Product **4** (201 mg, 88%) was isolated as a gummy white solid; R_f 0.57 in ethyl acetate - hexane, 1:3; ^1H NMR (360 MHz, $CDCl_3$) δ: 5.35 (d, 1H, $J_{1,2}$ = 1.5 Hz, H-1), 4.22 (dd, 1H, $J_{1,2}$ = 1.5 Hz, $J_{2,3}$ = 3.0 Hz, H-2), 4.11 (m, 1H, H-5), 3.98 (dd, 1H, $J_{3,4}$ = 9.4 Hz, $J_{4,5}$ = 9.4 Hz, H-4), 3.84 (dd, 1H, $J_{5,6}$ = 4.8 Hz, $J_{6,6'}$ = 11.0 Hz, H-6), 3.80 (dd, 1H, $J_{3,4}$ = 9.4 Hz, $J_{2,3}$ = 3.0 Hz, H-3), 3.71 (dd, 1H, $J_{5,6'}$ = 1.9 Hz, $J_{6,6'}$ = 11.0 Hz, H-6'), 3.28 (s, 3H, OCH_3), 2.60 (m, 2H, SCH_2CH_3), 1.41, 1.38 (2 x s, 6H, CH_3CCH_3'), 1.26 (t, 3H, SCH_2CH_3); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ: 101.46 (CH_3CCH_3), 84.39 (C-1), 80.05, 75.00, 72.18, 70.24 (C-2, C-3, C-4, and C-5), 69.42 (C-6), 49.62 (OCH_3), 25.0 (SCH_2CH_3), 24.94 (CH_3CCH_3), 15.17 (SCH_2CH_3); Anal. calcd. for $C_{33}H_{42}O_6S$: C 69.93, H 7.47, S 5.66; found: C 70.04, H 7.45, S 5.94.

Methyl 3,4,6-tri-O-benzyl-β-D-mannopyranoside (**5**)

The acetal **5** (50 mg, 0.0883 mmol) was added to a round bottom flask and purged with argon. Dichloromethane (3 ml) was added and the reaction cooled to -40°C. *N*-Bromosuccinimide (47.2 mg, 3 eq.) was added to the reaction mixture and stirred for 1 hour. The reaction was stopped by the addition of 1 ml of 0.5 M $Na_2S_2O_3$ solution which caused the orange reaction color to clear. Dichloromethane (10 ml) was added and the organic layer washed twice with 10 ml of dH_2O. The organic layer was dried ($MgSO_4$), filtered and concentrated. Chromatographic purification was achieved by

using 35% ethyl acetate in hexane as an eluent. The β-mannopyranoside **5** (6 mg, 15%) and the succinimide adduct **6** (20 mg, 37%) were obtained as products. Treatment of **6** with catalytic *p*-toluenesulfonic acid in dichloromethane converted it to **5** in quantitative yield.

5: R_f 0.38 in ethyl acetate - hexane, 1:1; ^{1}H NMR (360 MHz, $CDCl_3$) δ: 4.34 (d, 1H, $J_{1,2}$ < 1 Hz, H-1), 4.20 (dd, 1H, $J_{1,2}$ < 1Hz, $J_{2,3}$ = 3.2 Hz, H-2), 3.88 (dd, 1H, $J_{3,4}$ = 9.0 Hz, $J_{4,5}$ = 9.0 Hz, H-4), 3.81 (dd, 1H, $J_{5,6}$ = 2.1 Hz, $J_{6,6'}$ = 11.0 Hz, H-6'), 3.58 (dd, 1H, $J_{2,3}$ = 3.2 Hz, $J_{3,4}$ = 9.0 Hz, H-3), 3.57 (s, 3H, OCH_3), 2.39 (d, 1H, $J_{H,OH}$ = 2.4 Hz, OH).

6: R_f 0.26 in ethyl acetate - hexane, 1:2; ^{1}H NMR (360 MHz, $CDCl_3$) δ: 4.36 (dd, 1H, $J_{1,2}$ < 1 Hz, $J_{2,3}$ = 2.5 Hz, H-2), 4.22 (d, 1H, $J_{1,2}$ < 1 Hz, H-1), 3.94 (dd, 1H, $J_{3,4}$ = 9.2 Hz, $J_{4,5}$ = 9.2 Hz, H-4), 3.78 (d, 2H, $J_{5,6}$ = 3.8 Hz, H-6's), 3.47 (s, 3H, OCH_3), 3.45 (m, 2H, H-3 and H-5), 3.31 (m, 4H, CH_2CH_2, succinimide), 1.94, 1.92 (2 x s, 6H, CH_3CCH_3'); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ: 178.29 (CO), 101.43 (C-1), 89.90 (OCN), 82.17, 76.42, 75.05, 71.22 (C-2, C-3, C-4, and C-5), 69.59 (C-6), 57.09 (OCH_3), 28.56 (CH_2CH_2, succinimide), 27.49, 27.33 (CH_3CCH_3').

Methyl 3,4,6-tri-O-benzyl-α-D-mannopyranoside (**8**)[218]

The 2-*O*-acetate **7** (2.33 g, 4.6 mmol) was dissolved in 50 ml of methanol. Catalytic sodium methoxide (10 mg) was added and the reaction was stirred overnight at room temperature. The solution was then neutralized by the addition of Amberlite IRC-120 (H^+) resin, filtered and concentrated. The product **8** (2.03 g, 95%) was not chromatographed as the ^{1}H NMR did not reveal any impurities; R_f 0.30 in ethyl acetate - hexane, 1:2; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 4.69 (d, 1H, $J_{1,2}$ = 1.8 Hz, H-1), 4.03 (dd, 1H, $J_{1,2}$ = 1.8 Hz, $J_{2,3}$ = 2.8 Hz, H-2), 3.90-3.68 (m, 5H, H-3, H-4, H-5, H-6, and H-6'), 3.35 (s, 3H, OCH_3).

Ethyl 3,4,6-tri-O-benzyl-2-O-(2-propenyl)-1-thio-α-D-mannopyranoside (**10**)

The 2-*O*-acetylated thioglycoside **2** (1.3 g, 2.42 mmol) was dissolved in 12 toluene, 4 ml tetrahydrofuran, and 0.2 ml pyridine under argon atmosphere. All solve were anhydrous. The reaction mixture was cooled to -40°C. The solution color turn deep red as Tebbe's reagent **9** (4.8 ml, 1 mM in toluene, 4.8 mmol, 2 eq.) was slow added. After one hour, another 4.8 ml of Tebbe's reagent was added (2 eq.). The reacti was then gradually warmed to -10°C. After 3 hours the reaction was quenched by t addition of 0.2 ml of 1N NaOH at -10°C which caused vigorous bubbling. When t bubbling subsided (~ 5 min.), the mixture was warmed to room temperature. A furth 0.8 ml of 1N NaOH was then added. The solution was then filtered through a celite pa washed with ether until the filtrate was colorless and concentrated. Colun chromatography of the red oil using 8% ethyl acetate in hexane as an eluent yielded 1. g (90%) of a pale yellow syrup **10**; $[\alpha]_D$ + 95.6° (*c* 0.98, CH_2Cl_2); R_f 0.71 in eth acetate - hexane, 1:3; ^1H NMR (300 MHz, $CDCl_3$) δ: 7.32, 7.20 (m, 15H, aromati 5.53 (d, 1H, $J_{1,2}$ < 1.0 Hz, H-1), 4.89, 4.50 (2 x d, J_{gem} = 10.8 Hz, OC*H*$_2$Ph), 4.67, 4. (2 x d, 2H, J_{gem} = 12.1 Hz, OC*H*$_2$Ph), 4.64, 4.59 (2 x d, 2H, J_{gem} = 11.5 Hz, OC*H*$_2$P 4.40 (dd, 1H, $J_{1,2}$ < 1 Hz, $J_{2,3}$ = 3.4 Hz, H-2), 4.13 (ddd, 1H, $J_{4,5}$ = 9.2 Hz, $J_{5,6}$ = 4 Hz, $J_{5,6'}$ = 1.7 Hz, H-5), 4.02 (dd, 1H, $J_{3,4}$ = 9.2 Hz, $J_{4,5}$ = 9.2 Hz, H-4), 3.98, 3.75 (2 d, 2H, J_{gem} = 2.0 Hz, C=C*H*$_2$), 3.88 (dd, 1H, $J_{2,3}$ = 3.4 Hz, $J_{3,4}$ = 9.2 Hz, H-3), 3.8 (dd, 1H, $J_{5,6}$ = 4.4 Hz, $J_{6,6'}$ = 10.7 Hz, H-6), 3.70 (dd, 1H, $J_{5,6'}$ = 1.7 Hz, $J_{6,6'}$ = 10 Hz, H-6'), 2.60 (m, 2H, SC*H*$_2$CH$_3$), 1.59 (s, 3H, CH$_2$=CC*H*$_3$, vinyl ether), 1.26 (t, 3 J_{vic} = 7.6 Hz, SCH$_2$C*H*$_3$); ^{13}C NMR δ: 158.6 (*C*=CH$_2$), 138.7, 138.5, 138.2, 128. 127.5 (aromatic), 82.7 (C=*C*H$_2$), 80.4, 79.2 (C-1, and C-2), 74.8, 73.8, 71.8 (C-3, C- and C-5), 75.2, 73.4, 71.8 (3 x O*C*H$_2$Ph), 69.2 (C-6), 25.4 (SCH$_2$*C*H$_3$), 21 (CH$_2$=C*C*H$_3$), 15.1 (s, SCH$_2$*C*H$_3$). Anal. calcd. for $C_{32}H_{38}O_5S$: C 71.88, H 7.16, 6.00; found: C 71.88, H 7.19, S 5.83.

The 2-*O*-acetate **7** (200 mg, 0.40 mmol) was dissolved in 5 ml of dry tetrahydrofuran under argon atmosphere. The solution was then cooled to -40°C. The reaction color turned deep red as Tebbe's reagent **9** (0.40 ml, 1 mM in toluene, 0.40 mmol, 1 eq.) was slowly added. After 4.5 hours the reaction was quenched by the addition of 0.1 ml of 1N NaOH at -10°C which caused vigorous bubbling. When the bubbling had subsided (~ 5 min.), the mixture was warmed to room temperature. A further 0.5 ml of 1N NaOH was then added. The solution was filtered through a celite pad, washed with ether until the filtrate was colorless and concentrated. Column chromatography of the red oil using 7.5% ethyl acetate in hexane as an eluent yielded 108 mg (54%) of a pale yellow syrup **11**; R_f 0.66 in ethyl acetate - hexane, 1:3; ^1H NMR (300 MHz, $CDCl_3$) δ: 4.88 (d, 1H, $J_{1,2}$ = 1.5 Hz, H-1), 4.38 (dd, 1H, $J_{1,2}$ = 1.5 Hz, $J_{2,3}$ = 3 Hz, H-2), 3.96, 3.87 (2 x d, 2H, J_{gem} = 2.1 Hz, C=CH_2), 3.96 , 3.75 (2 x m, 5H, H-3, H-4, H-5, H-6, and H-6'), 3.35 (s, 3H, OCH_3), 1.88 (s, 3H, CH_2=CCH_3).

Methyl 2,3,6-tri-O-benzyl-2-O-[2-(1-bromo-2-cyclohexyloxy)-propyl]-α-D-mannopyranoside (**14**)

The vinyl ether **11** (230 mg, 0.46 mmol) was added to a round bottom flask and purged with argon. Dichloromethane (10 ml) was syringed into the reaction flask. This was followed by the addition of 0.46 ml of a 1M solution of cyclohexanol in dichloromethane (0.46 mmol, 1 equiv.). The solution was then cooled to -40°C. In one portion, NBS (97 mg, 0.55 mmol) was added. The reaction was maintained at -40°C for 75 minutes and then allowed 45 minutes to warm to room temperature. The mixture was then concentrated and chromatographed using 7% ethyl acetate in hexane as an eluent. The product **14** (101 mg, 32%) was isolated as a clear syrup and consisted of a 1:3 mixture of diastereomers; R_f 0.67 in ethyl acetate - hexane, 1:3; ^1H NMR (360 MHz, $CDCl_3$) δ: 4.57 (d, 0.75H, $J_{1,2}$ = 2 Hz, H-1), 4.09 (dd, 0.25H, $J_{1,2}$ = 2Hz, $J_{2,3}$ = 3 Hz, H-

3 and H-4), 3.63 (m, 2.25H, H-6, H-6', and OCH cyclohexyl), 3.55 (m, 1H, H-5), 3.39, 3.35 (2 x d, 1.5H, J_{gem} = 10.0 Hz, CCH_2Br), 3.27 (s, 2.25H, OCH_3), 3.26 (s, 0.75H, OCH_3, minor diastereomer), 1.80-1.05 (m, 11H, cyclohexyl), 1.53 (s, 2.25H, CH_3CCH_2Br), 1.33 (s, 0.75H, CH_3CCH_2Br, minor diastereomer); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ (major diastereomer only): 102.0 (CH_3CCH_2Br), 101.0 (C-1), 79.1, 75.2, 71.9, 70.8, 70.0 (C-2, C-3, C-4, C-5, and OCH cyclohexyl), 74.6, 73.3, 72.9 (3 x OCH_2Ph), 69.6 (C-6), 54.9 (OCH_3), 38.5 (CCH_2Br), 34.5, 34.4, 25.6, 24.3 (5 x CH_2, cyclohexyl), 22.4 (CH_3CCH_2Br).

Ethyl 2,3,6-tri-O-benzyl-2-O-[2-(1-bromo-2-cyclohexyloxy)-propyl]-1-thio-α-D-mannopyranoside (**15**)

The vinyl ether **10** (350 mg, 0.65 mmol) was added to a round bottom flask and purged with argon. Dichloromethane (10 ml) was syringed into the reaction flask. This was followed by the addition of 0.79 ml of a 1M solution of cyclohexanol in dichloromethane (0.79 mmol, 1.2 equiv.). The solution was cooled to -40°C and in one portion NBS (140 mg, 0.79 mmol, 1.2 equiv.) was added. After 20 minutes the reaction was quenched by the addition of 1 ml of a 0.5 M sodium thiosulfate solution which contained 20% by volume triethylamine. The mixture was diluted with 20 ml of dichloromethane and washed 3 x 25 ml with water. The organic layer was dried ($MgSO_4$), filtered and concentrated. Silica gel chromatography was used for purification of the reaction mixture with 7% ethyl acetate in hexane used as an eluent. Product **15** (250 mg, 54%) was obtained as a 4:1 mixture of diastereomers; R_f 0.71 in ethyl acetate - hexane, 1:3; ^1H NMR (360 MHz, $CDCl_3$) δ: 5.40 (d, 0.8H, $J_{1,2}$ = 1.3 Hz, H-1), 5.27 (d, 0.2H, $J_{1,2}$ = 1.5Hz, H-1 minor diastereomer), 4.29 (dd, 0.2H, $J_{1,2}$ = 1.5 Hz, $J_{2,3}$ = 2.8 Hz, H-2 minor diastereomer), 4.19 (dd, 0.8H, $J_{1,2}$ = 1.3 Hz, $J_{2,3}$ = 3.0 Hz, H-2), 4.12 (m, 1H, H-5), 4.00 (dd, 0.8H, $J_{3,4}$ = 9.5 Hz, $J_{4,5}$ = 9.5 Hz, H-4), 3.82 (m, 1.6H, H-6 and H-3),

3.72 (dd, 0.8H, $J_{6,6'}$ = 10.5 Hz, $J_{5,6'}$ = 2.4 Hz, H-6'), 3.50, 3.48 (2 x d, 1.6H, J_{gem} = 10.8 Hz, CH_3CCH_2Br), 2.62 (m, 2H, SCH_2CH_3), 1.85-1.16 (m, 11H, cyclohexyl), 1.57 (s, 2.4H, CH_3CCH_2Br), 1.53 (s, 0.6H, CH_3CCH_2Br, minor diastereomer), 1.28 (t, 2.4H, SCH_2CH_3), 1.27 (t, 0.6H, SCH_2CH_3, minor diastereomer); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ (major diastereomer only): 102.1 (CH_3CCH_2Br), 84.5 (C-1), 79.9, 75.2, 72.3, 71.7, 71.1 (C-2, C-3, C-4, C-5, and OCH cyclohexyl), 75.0, 73.2, 73.0 (3 x OCH_2Ph), 69.4 (C-6), 38.5 (CH_3CCH_2Br), 34.7, 34.4, 25.6, 25.3, 24.3 (5 x CH_2, cyclohexyl), 22.2 (CH_3CCH_2Br), 15.2 (SCH_2CH_3); Anal. calcd. for $C_{38}H_{49}O_6SBr$: C 63.94, H 6.92; found: C 63.56, H 6.98.

Ethyl 2,3,6-tri-O-benzyl-2-O-[2-(1-iodo-2-cyclohexyloxy)-propyl]-1-thio-α-D-mannopyranoside (**16**)

The vinyl ether **10** (50 mg, 0.094 mmol) was added to a reaction flask and purged with argon. Dichloromethane (3 ml) was syringed into the flask and 0.11 ml of a 1M solution of cyclohexanol in dichloromethane (0.11 mmol, 1.2 equiv.) was then added. The solution was cooled to -40°C and in one portion NBS (25 mg, 0.11 mmol, 1.2 equiv.) was added. After 10 minutes, the reaction was quenched by the addition of 1 ml of a 0.5 M sodium thiosulfate solution which contained 20% by volume triethylamine. The mixture was diluted with 5 ml of dichloromethane and washed with 10 ml of water. The organic layer was dried ($MgSO_4$), filtered and concentrated. Silica gel chromatography was used for the purification of the reaction mixture with 7% ethyl acetate in hexane used as an eluent. The eluent contained 0.1% triethylamine. The desired product **16** (56 mg, 79%) was obtained as a 9:1 mixture of diastereomers; R_f 0.74 in ethyl acetate - hexane, 1:3; ^1H NMR (360 MHz, $CDCl_3$) δ (major diastereomer only): 5.39 (d, 1H, $J_{1,2}$ = 1.5 Hz, H-1), 4.15 (dd, 1H, $J_{1,2}$ = 1.5 Hz, $J_{2,3}$ = 3.0 Hz, H-2), 4.12 (m, 1H, H-5), 4.02 (dd, 1H, $J_{3,4}$ = 9.5 Hz, $H_{4,5}$ = 9.5 Hz, H-4), 3.82 (dd, 1H, $J_{5,6}$ = 4.5 Hz, $J_{6,6'}$ = 11.0 Hz, H-6), 3.78 (dd, 1H, $J_{2,3}$ = 3.0 Hz, $J_{3,4}$ = 9.5Hz, H-3), 3.72 (dd, 1H, $J_{6,6'}$ = 11.0 Hz, $J_{5,6'}$ = 2.0

Hz, H-6'), 3.42, 3.32 (2 x d, 2H, J_{gem} = 10.2 Hz, CH_3CCH_2Br), 2.60 (m, 2H, SCH_2CH_3), 1.8-1.1 (m, 11H, cyclohexyl), 1.55 (s, 3H, CH_3CCH_2Br), 1.28 (t, 3H, SCH_2CH_3).

Methyl 2,3,4-tri-O-benzyl-α-D-glucopyranoside-ethyl 3',4',6'-tri-O-benzyl-1'-thio-α-D-mannopyranoside-2',6-(1-bromo-isopropylidene) acetal (**17**)

The alcohol **13** (60 mg, 0.11 mmol, 1.2 equiv.) and NBS (20 mg, 0.11 mmol) were combined in a reaction flask and purged with argon. Dichloromethane (3 ml) was syringed into the flask and the mixture was cooled to -40°C. In a separate flask, the vinyl ether **10** (50 mg, 0.094 mmol, 1.0 equiv.) was purged with argon. In 2 x 1 ml aliquots of dichloromethane, the vinyl ether was added in a dropwise fashion to the cooled solution of the alcohol and NBS. After 25 minutes, the reaction was quenched by the addition of 1 ml of 0.5 M $Na_2S_2O_3$ solution which contained 20% by volume triethylamine. The mixture was diluted with 10 ml of water and extracted 3 x 10 ml with dichloromethane. The organic layer was then dried ($MgSO_4$), filtered and concentrated. Silica gel chromatography was used to purify the mixture. The chromatography eluent was 7% ethyl acetate in hexane which contained 0.1% triethylamine. The product **17** (8 mg) was isolated in 8% yield. Tlc indicated that **3**, and unreacted **13** were present as well as two other unidentified compounds with R_f's similar to **10** . When the reaction was attempted with NIS instead of NBS no identifiable product was obtained; R_f 0.56 in ethyl acetate - hexane, 1:3; ^1H NMR (360 MHz, $CDCl_3$) δ: 5.51 (d, 1H, $J_{1,2}$ = 1 Hz, H-1'), 4.25 (m, 1H, H-2'), 4.10 (m, 1H, H-5), 4.00 (dd, 1H, $J_{3,4}$ = 9.0 Hz, $J_{4,5}$ = 9.0 Hz, H-4), 3.80 (dd, 1H, $J_{3,4}$ = 9.0 Hz, H-4'), 3.48 (dd, $J_{2,3}$ = 3.5 Hz, $J_{3,4}$ = 9.5 Hz, H-3'), 3.42 (s, 2H, CH_3CCH_2Br), 3.38 (s, 3H, OCH_3), 3.32 (dd, 1H, $J_{3,4}$ = 9.0 Hz, $J_{2,3}$ = 9.0 Hz, H-3), 2.48 (q, 2H, SCH_2CH_3), 1.57 (s, 3H, CH_3CCH_2Br), 1.26 (t, 3H, SCH_2CH_3).

Methyl 2,3,6-tri-O-benzyl-4-O-(2-propenyl)-α-D-glucopyranoside (**18**)

The alcohol **12** (500 mg, 1.08 mmol) was dissolved in 10 ml of pyridine and 1 ml of acetic anhydride was added. The reaction was stirred overnight, then diluted with 150 ml of water. The aqueous phase was extracted with 150 ml of dichloromethane. This organic layer was then washed 2 x 150 ml with 1N HCl, followed by 150 ml of water. The organic layer was then dried ($MgSO_4$), filtered and concentrated. The crude mixture was then dissolved in 9 ml toluene, 3 ml THF, and 0.1 ml pyridine (all solvent anhydrous). The mixture was cooled to -40°C and Tebbe's reagent **9** (2.2 ml, 1mM in toluene, 2.2 mmol) was syringed into the mixture. The reaction mixture was allowed to warm to room temperature and after 3 hours it was cooled to -10°C. The reaction was then quenched by the addition of 1.0 ml of 1N NaOH. The suspension was then filtered through celite and washed with ether until the filtrate was a pale yellow. The filtrate was concentrated and then purified using silica gel chromatography. The eluent was 20% ethyl acetate in hexane which contained 0.1% triethylamine. The product **18** was isolated as a yellow syrup (336 mg, 62%); R_f 0.48 in ethyl acetate - hexane, 1:3; ^1H NMR (360 MHz, $CDCl_3$) δ: 4.63 (d, 1H, $J_{1,2}$ = 3.5 Hz, H-1), 4.29, 4.04 (2 x d, 2H, J_{gem} = 2.0 Hz, $C=CH_2$), 4.25 (dd, 1H, $J_{3,4}$ = 9.5 Hz, $J_{4,5}$ = 9.5 Hz, H-4), 3.95 (dd, 1H, $J_{3,4}$ = 9.5 Hz, $J_{2,3}$ = 9.5 Hz, H-3), 3.79 (m, 1H, H-5), 3.64 (dd, 1H, $J_{5,6}$ = 2.2 Hz, $J_{6,6'}$ = 10.5 Hz, H-6), 3.56 (dd, 1H, $J_{1,2}$ = 3.5 Hz, $J_{2,3}$ = 9.5 Hz, H-2), 3.53 (dd, 1H, $J_{5,6'}$ = 4.0 Hz, $J_{6,6'}$ = 10.5 Hz, H-6'), 3.42 (s, 3H, OCH_3), 1.78 (s, 3H, $CH_3C=CH_2$).

Octyl 3,4,6-tri-O-acetyl-2-deoxy-2-phthalimido-β-D-glucopyranoside (**20**)

Under argon atmosphere, the anomeric acetate **19**[219] (5.0 g, 10.5 mmol) was dissolved in 50 ml of dry dichloromethane and cooled to 0°C. 1-Octanol (5.0 ml , 31.5 mmol, 3.0 eq.) and tin tetrachloride (2.45 ml, 21 mmol, 2.0 eq.) were consecutively syringed into the mixture. The solution was allowed to warm to room temperature and quenched after 5 hours by the addition of dH_2O (100 ml) and CH_2Cl_2 (50 ml). The

organic layer was washed by another portion of water (100 ml), dried ($MgSO_4$), filtered, and concentrated to give a tan colored syrup. A portion of this syrup was purified on silica gel (25% ethyl acetate in hexane was used as an eluent) for characterization and the balance used as crude material; $[\alpha]_D$ +21.2° (*c* 1.85, CH_2Cl_2); R_f 0.69 in ethyl acetate - hexane, 1:1; ^1H NMR (300 MHz, $CDCl_3$) δ: 7.90 - 7.70 (m, 4H, aromatic), 5.80 (dd, 1H, $J_{2,3}$ = 10.8 Hz, $J_{3,4}$ = 8.8 Hz, H-3), 5.36 (d, 1H, $J_{1,2}$ = 8.5 Hz, H-1), 5.18 (dd, 1H, $J_{3,4}$ = 8.8 Hz, $J_{4,5}$ = 10.0 Hz, H-4), 4.34 (dd, 1H, $J_{6,6'}$ = 12.2 Hz, $J_{5,6}$ = 4.6 Hz, H-6), 4.31 (dd, 1H, $J_{2,3}$ = 10.8 Hz, $J_{1,2}$ = 8.5 Hz, H-2), 4.17 (dd, 1H, $J_{6,6'}$ = 12.2 Hz, $J_{5,6'}$ = 2.3 Hz, H-6'), 3.85 (m, 2H, H-5, and OC*H*H', octyl), 3.43 (m, 1H, OCH*H'*, octyl); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ: 170.8, 170.2, 169.5 (3 x *C*OCH_3, acetates), 134.3, 131.5, 123.6 (aromatic), 98.3 (C-1), 71.9, 70.9, 69.2 (C-3, C-4, and C-5), 70.3 (C-6), 62.2 (O*C*H_2, octyl), 54.8 (C-2), 31.7, 29.3, 29.1, 25.8, 22.6 (6 x *C*H_2, octyl), 20.8, 20.7, 20.5 (3 x CH_3, acetates), 14.1 (*C*H_3, octyl); Anal. calcd. for $C_{38}H_{37}O_{10}N$: C 61.41, H 6.81, N 2.56; found: C 61.51, H 6.69, N 2.58.

Octyl 2-deoxy-2-phthalimido-β-D-glucopyranoside (**21**)

Crude **20** (10.5 mmol) was dissolved in methanol and 50 mg of sodium methoxide was added to the reaction. It was then stirred overnight (17 hours). The mixture was neutralized with Amberlite IRC-120 (H^+) resin, filtered and concentrated to give a white solid. Silica gel chromatography was used for purification with 7% methanol in dichloromethane as an eluent. Product **21** was obtained as a white solid (3.6 g, 81% from **19**); $[\alpha]_D$ -55.0° (*c* 0.20, CH_3OH); R_f 0.52 in methanol - dichloromethane, 1:9; ^1H NMR (300 MHz, CD_3OD) δ: 7.92 - 7.75 (m, 4H, aromatic), 5.14 (d, 1H, $J_{1,2}$ = 8.5 Hz, H-1), 4.25 (dd, 1H, $J_{1,2}$ = 8.5 Hz, $J_{2,3}$ = 10.7 Hz, H-2), 3.96 (dd, 1H, $J_{2,3}$ = 10.7 Hz, $J_{3,4}$ = 8.4 Hz, H-3), 3.95 - 3.70, 3.60 - 3.46 (m, 6H, H-4, H-5, H-6, H-6', O*C*H_2, octyl), 1.42 - 0.78 (m, 15H, octyl); ^{13}C NMR (75.5 MHz, CD_3OD) δ: 169.7 (CO, phthalimido), 135.5, 133.1, 124.1 (aromatic), 99.7 (C-1), 78.2, 72.6 (C-3, C-4, and C-5),

70.4 (C-6), 62.7 (OCH_2, octyl), 58.6 (C-2), 32.8, 30.3, 30.3, 30.2, 27.1, 23.6 (6 x CH_2, octyl), 14.4 (CH_3, octyl); Anal. calcd. for $C_{22}H_{31}O_7N$: C 62.69, H 7.41, N 3.32; found: C 62.02, H 7.46, N 3.27.

Octyl 4,6-O-benzylidene-2-deoxy-2-phthalimido-β-D-glucopyranoside (**22**)

The octyl glycoside **21** (3.6 g, 8.54 mmol) was dissolved in 140 ml of dichloromethane and 40 ml of dimethylformamide. Dimethoxytoluene (1.54 ml, 10.3 mmol, 1.2 eq.) and *p*-toluenesulfonic acid monohydrate (30 mg, 0.02 eq.) were added to the mixture. The mixture was then fitted with a dropping funnel which contained 4Å molecular sieves and a condenser above the dropping funnel. The solution was refluxed overnight (16 hours) and neutralized by the addition of Amberlite IR-410 (OH^-) resin. The mixture was concentrated and purified with silica gel using ethyl acetate - hexane (1:2) as an eluent. The product **22** (3.4 g, 78%) was isolated as a white foam. Further elution with 7% methanol in dichloromethane recovered 0.7 g (19%) of the starting material; $[\alpha]_D$ -30.4^o (*c* 1.0, CH_2Cl_2); R_f 0.44 in ethyl acetate - hexane, 1:2; ^1H NMR (300 MHz, $CDCl_3$) δ: 7.90 - 7.70 (m, 4H, phthalimido), 7.55 - 7.35 (m, 5H, phenyl), 5.58 (s, 1H, CH benzylidene), 5.27 (d, 1H, $J_{1,2}$ = 8.6 Hz, H-1), 4.64 (ddd, 1H, $J_{2,3}$ = 10.5 Hz, $J_{3,4}$ = 8.8 Hz, $J_{3,OH}$ = 3.6 Hz, H-3), 4.40 (dd, 1H, $J_{6,6'}$ = 10.5 Hz, $J_{5,6}$ = 4.5 Hz, H-6), 4.24 (dd, 1H, $J_{6,6'}$ = 10.5 Hz, $J_{5,6'}$ = 8.5 Hz, H-6'), 3.89 - 3.78, 3.70 - 3.57 (m, 4H, H-2, H-4, H-5, and OC*H*H' , octyl), 3.42 (m, 1H, OCH*H'*, octyl), 2.44 (d, 1H, $J_{3,OH}$ = 3.6 Hz, OH), 1.50 - 0.98 (m, 12H, octyl), 0.81 (t, 3H, J_{vic} = 7.5 Hz, CH_3, octyl); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ: 137.1, 134.1, 131.8, 129.4, 128.4, 126.4, 123.5 (aromatic), 102.0 (CH, benzylidene), 99.0 (C-1), 82.4 (C-3), 68.8, 66.2 (C-4, C-5), 70.2 (C-6), 68.8 (OCH_2, octyl), 56.7 (C-2), 31.7, 29.3, 29.1, 25.8, 22.6 (6 x CH_2, octyl), 14.1 (CH_3, octyl); Anal. calcd. for $C_{29}H_{35}O_7N$: C 68.35, H 6.92, N 2.75; found: C 68.31, H 7.08, N 2.78.

Octyl 4,6-O-benzylidene-3-O-benzyl-2-deoxy-2-phthalimido-β-D-glucopyranoside (**23**)

The alcohol **22** (3.3 g, 6.5 mmol) was dissolved in 50 ml dry dimethylformamide and sodium hydride (0.52 g, 13 mmol, 2.0 eq, 60% dispersion in oil) was added. The solution was stirred at 15°C for 30 minutes and benzyl bromide (1.5 ml, 13 mmol, 2.0 eq.) was added in one portion to the suspension. The reaction mixture was stirred overnight at ambient temperature and quenched by the addition of methanol (10 ml). The mixture was concentrated to dryness and chromatographed with 10% ethyl acetate in hexane as an eluent. A pale yellow syrup **23** (2.86 g, 73%), was obtained; $[\alpha]_D$ +23.9° (*c* 0.98, CH_2Cl_2); R_f 0.59 in ethyl acetate - hexane, 1:3; ^1H NMR (300 MHz, $CDCl_3$) δ: 7.90 - 7.60 (m, 4H, phthalimido), 7.55 - 7.30 (m, 5H, benzylidene), 7.05 - 6.80 (m, 5H, benzyl), 5.63 (s, 1H, CH, benzylidene), 5.19 (d, 1H, $J_{1,2}$ = 8.4 Hz, H-1), 4.80, 4.51 (2 x d, 2H, J_{gem} = 12.2 Hz, OC*H*$_2$Ph), 4.43 (dd, 1H, $J_{5,6}$ = 8.5 Hz, $J_{6,6'}$ = 10.4 Hz, H-6), 4.41 (dd, 1H, $J_{5,6'}$ = 4.5 Hz, $J_{6,6'}$ = 10.4 Hz, H-6'), 4.21 (dd, 1H, $J_{2,3}$ = 10.4 Hz, $J_{1,2}$ = 8.4 Hz, H-2), 3.86 (dd, 1H, $J_{2,3}$ = 10.4 Hz, $J_{3,4}$ = 10 Hz, H-3), 3.81 (dd, 1H, $J_{3,4}$ = 10 Hz, $J_{4,5}$ = 9.8 Hz, H-4), 3.77 (dt, 1H, J_{gem} = 9.9 Hz, J_{vic} = 6.8 Hz, OC*H*H', octyl), 3.64 (ddd, 1H, $J_{5,6'}$ = 4.5 Hz, $J_{5,6}$ = 8.5 Hz, $J_{4,5}$ = 9.8 Hz, H-5), 3.37 (dt, 1H, J_{gem} = 9.9 Hz, J_{vic} = 6.8 Hz, OCH*H'*, octyl), 1.43 - 0.84 (m, 12H, 6 x CH_2, octyl), 0.80 (t, 3H, J_{vic} = 7.5 Hz, CH_3, octyl); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ: 138.0, 137.4, 133.8, 131.7, 129.0, 128.3, 128.1, 127.4, 126.1, 123.3 (aromatic), 101.4 (CH, benzylidene), 99.0 (C-1), 83.2, 77.5, 66.2 (C-3, C-4, and C-5), 77.1 (O*C*H$_2$Ph), 70.1 (C-6), 66.9 (O*C*H$_2$, octyl), 55.9 (C-2), 31.7, 29.3, 29.1, 25.8, 22.6 (6 x *C*H$_2$, octyl), 14.1 (*C*H$_3$, octyl); Anal. calcd. for $C_{36}H_{41}O_7N$: C 72.10, H 6.89, N 2.34; found: C 72.28, H 6.91, N 2.35.

Octyl 3,6-di-O-benzyl-2-deoxy-2-phthalimido-β-D-glucopyranoside (**24**)

In a three neck round bottom flask, the benzylidene acetal **23** (285 mg, 4.75 mmol) was added and dissolved in 75 ml of tetrahydrofuran. The mixture was cooled to 0°C and molecular sieves (3Å), methyl orange (2mg), and sodium cyanoborohydride

(2.98 g, 47.5 mmol, 10 eq.) were consecutively added. In a separate flask, 15 ml of diethyl ether was saturated with hydrochloric acid by bubbling HCl gas through the ether at 0°C for 20 minutes. The HCl / Et_2O solution was then transferred to a dropping funnel and added in a dropwise fashion to the benzylidene acetal mixture until a strong pink color remained. The reaction was complete after 55 minutes. The suspension was filtered and poured into 250 ml of cold water (5°C). The filtrate was extracted 2 x 200 ml with dichloromethane. The organic layers were combined and washed with 250 ml of saturated sodium bicarbonate solution. The organic layer was dried ($MgSO_4$), filtered and concentrated. Twenty-two percent (22%) ethyl acetate in hexane was used as an eluent in silica gel chromatography. Product **24** (2.37 g, 83%) was obtained as a colorless syrup; $[\alpha]_D$ +14.4° (*c* 0.95, CH_2Cl_2); R_f 0.27 in ethyl acetate - hexane, 1:3; ^1H NMR (360 MHz, $CDCl_3$) δ: 7.70, 7.35, 7.10, 6.95 (m, 14H, aromatics), 5.13 (d, 1H, $J_{1,2}$ = 8.3 Hz, H-1), 4.75, 4.54 (2 x d, 2H, J_{gem} = 12.1 Hz, OC*H*$_2$Ph), 4.66, 4.58 (2 x d, 2H, J_{gem} = 11.9 Hz, OC*H*$_2$Ph), 4.23 (dd, 1H, $J_{5,6}$ = 8.0 Hz, $J_{6,6'}$ = 10.5 Hz, H-6), 4.14 (dd, 1H, $J_{5,6'}$ = 8.0 Hz, $J_{6,6'}$ = 10.5 Hz, H-6'), 3.9 - 3.7 (m, 4H, H-2, H-3, H-4, H-5), 3.65, 3.35 (2 x m, 2H, OCHH', octyl), 2.93 (d, 1H, $J_{4,\ OH}$ = 2.3 Hz, OH), 1.4 - 0.8 (m, 15H, octyl); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ: 138.3, 137.7, 133.8, 131.8, 128.6, 128.2, 127.9, 127.9, 127.4, 123.3 (aromatics), 98.4 (C-1), 78.8, 74.7, 73.5 (C-3, C-4, and C-5), 74.3, 73.9, 71.0, 69.7 (2 x OCH_2Ph, C-6, OCH_2, octyl), 55.5 (C-2), 31.7, 29.3, 29.2, 29.1, 25.6, 22.6 (6 x CH_2, octyl), 14.1 (CH_3, octyl); Anal. calcd. for $C_{36}H_{43}O_7N$: C 71.86, H 7.20, N 2.33; found C 71.78, H 7.12, N 2.38.

Octyl 2-N-acetamido-3,6-di-O-benzyl-2-deoxy-β-D-glucopyranoside (**25**)

The phthalimido derivative **24** (600 mg, 1.0 mmol) was dissolved in 30 ml of methanol. Hydrazine hydrate (0.36 ml, 7.5mmol) was syringed into the mixture which was then heated to reflux. After two hours an additional 0.36 ml of hydrazine hydrate was added (15 mmol total). The reaction mixture was refluxed for another 3 hours. The

solution was then concentrated to a white solid, cooled to 0°C, and pyridine (20 ml) was added. Acetic anhydride (2 ml) was then added and the solution stirred overnight at ambient temperature. Dichloromethane (120 ml) and water (100 ml) were added to stop the reaction. The organic layer was then separated and washed 3 x 100 ml with 1N HCl, and 1 x 100 ml with water. It was then dried ($MgSO_4$), filtered and concentrated. Thirty-five percent (35%) ethyl acetate in hexane was used as an eluent in chromatographic purification. The 4-*O*-acetylated precursor to **25** was obtained in 71% yield. The 4-*O*-acetylated precursor was dissolved in 15 ml methanol and 10 mg sodium methoxide was added. The reaction was stirred for 4.5 hours, and was neutralized by the addition of Amberlite IRC-120 (H^+) resin. The solution was then filtered and concentrated to give **25** (363 mg, 71% from **24**). NMR revealed that the compound was sufficiently pure to proceed to the next synthetic step; R_f 0.50 in ethyl acetate - hexane, 1:1; ^1H NMR (360 MHz, $CDCl_3$) δ: 5.52 (d, 1H, $J_{NH,H-2}$ = 7.5 Hz, NH), 4.90 (d, 1H, $J_{1,2}$ = 8.3 Hz, H-1), 4.08 (dd, 1H, $J_{2,3}$ = 10.2 Hz, $J_{3,4}$ = 8.3 Hz, H-3), 3.84 (m, 1H, H-2), 3.78 (m, 2H, H-6, H-6'), 3.66 (ddd, $J_{3,4}$ = 8.3 Hz, $J_{4,5}$ = 9.5 Hz, $J_{H,OH}$ = 1.8 Hz, H-4), 3.56 (m, 1H, H-5), 3.46, 3.22 (2 x m, 2H, OCH_2, octyl), 2.73 (d, 1H, $J_{H,OH}$ = 1.8 Hz, OH), 1.90 (s, 3H, N*H*Ac), 1.46 (m, 2H, OCH_2CH_2, octyl), 1.26 (m, 10H, octyl), 0.88 (t, 3H, CH_3, octyl); ^{13}C NMR (75.5 MHz, $CDCl_3$) d: 170.5 (C=O), 99.8 (C-1), 80.3, 73.8, 73.6 (C-3, C-4, C-5), 74.4, 73.8 (2 x OCH_2Ph), 70.9, 69.9 (C-6, OCH_2, octyl), 57.6 (C-2), 31.9, 29.6, 29.4, 26.0, 22.7 (6 x CH_2, octyl), 23.7 (CH_3C=O), 14.1 (CH_3, octyl).

Methyl 2,3,4-tri-O-benzyl-α-D-glucopyranoside-ethyl 3',4',6'-tri-O-benzyl-1'-thio-α-D-mannopyranoside-2',6-isopropylidene acetal (**26**)

The vinyl ether **10** (100 mg, 0.187 mmol) and the alcohol **13**[185] (87 mg, 0.187 mmol) were combined in a flask and purged with argon. Dry dichloromethane (5 ml) was added and the mixture was cooled to -40°C. Toluenesulfonic acid monohydrate (2 mg, ~0.06 eq.) was added to the flask and the reaction was carefully monitored by tlc for

the formation of the mixed acetal **26**. When tlc indicated that the product spot was maximized (10 minutes), the reaction was quenched by the addition of 2 drops of triethylamine. The reaction yields dropped dramatically when reaction times were prolonged. The reaction mixture was then concentrated and purified by column chromatography (14% ethyl acetate in hexane plus 0.1% triethylamine was used as an eluent). The mixed acetal **26** (138 mg, 74%) was isolated as a colorless syrup. The product was sufficiently stable (> 24 hrs) however, storage for long periods of time (> 2 months) was in an organic solution (dichloromethane or ethyl acetate - hexane) which contained 0.5% triethylamine. Prolonged reaction times increased the yields of vinyl ether hydrolysis product **3** and **13** as well as symmetrical acetals **27** and **28**;

26: R_f 0.50 in ethyl acetate - hexane, 1:3; ^{1}H NMR (360 MHz, $CDCl_3$) δ: 7.4-7.1 (m, 30H, aromatic), 5.48 (d, 1H, $J_{1,2}$ = 1.2 Hz, H-1'), 4.63 (d, 1H, $J_{1,2}$ = 3Hz, H-1), 4.21 (dd, 1H, $J_{1,2}$ = 1.2 Hz, $J_{2,3}$ = 3.5 Hz, H-2'), 4.11 (m, 1H, H-5'), 4.00 (dd, 1H, $J_{3,4}$ = 9.2 Hz, $J_{4,5}$ = 9.2 Hz, H-4), 3.92 (dd, 1H, $J_{3,4}$ = 9.5 Hz, $J_{4,5}$ = 9.5 Hz, H-4'), 3.86 (dd, 1H, $J_{2,3}$ = 3 Hz, $J_{3,4}$ = 9.2 Hz, H-2), 3.48 (dd, 1H, $J_{2,3}$ = 3.5 Hz, $J_{3,4}$ = 9.5 Hz, H-3'), 3.32 (s, 3H, OCH_3), 2.47 (q, 2H, J_{vic} = 7.2 Hz, SCH_2CH_3), 1.38 (s, 3H, CH_3CCH_3'), 1.36 (s, 3H, CH_3CCH_3'), 1.16 (t, 3H, J_{vic} = 7.2 Hz, SCH_2CH_3); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ: 104.08 (CH_3CCH_3), 97.92 (C-1), 84.92 (C-1'), 82.64, 80.56, 80.00, 78.92, 75.48, 72.40, 70.56 (C-2, C-3, C-4, C-5, C-2', C-3', C-4', and C-5'), 76.00, 75.12, 75.10, 73.60, 73.36, 72.56 (6 x OCH_2Ph), 69.64, 61.68 (C-6, and C-6'), 55.24 (OCH_3), 26.16, 25.80 (CH_3CCH_3), 25.56 (SCH_2CH_3), 15.00 (SCH_2CH_3); Anal. calcd. for $C_{60}H_{70}O_{11}S$: C 72.12, H 7.06, S 3.21; found: C 71.80, H 7.33, S 3.53.

27: R_f 0.57 in ethyl acetate - hexane, 1:3; ^{1}H NMR (360 MHz, $CDCl_3$) δ: 5.50 (d, 2H, $J_{1,2}$ = 1 Hz, H-1 x 2), 4.20 (dd, 2H, $J_{1,2}$ = 1 Hz, $J_{2,3}$ = 3 Hz, H-2 x 2), 4.14 (m, 2H, H-5 x 2), 3.90 (dd, 2H, $J_{3,4}$ = 9.4 Hz, $J_{4,5}$ = 9.4 Hz, H-4 x 2), 3.82 (dd, 2H, $J_{5,6}$ = 5.0 Hz, $J_{6,6'}$ = 10.8 Hz, H-6 x 2), 3.78 (dd, 2H, $J_{3,4}$ = 9.4 Hz, $J_{2,3}$ = 3.0 Hz, H-3 x 2), 3.72 (dd, 2H, $J_{5,6'}$ = 1.0 Hz, $J_{6,6'}$ = 10.8 Hz, H-6' x 2), 2.60 (m, 4H, SCH_2CH_3 x 2), 1.38

(s, 6H, CH_3, acetal), 1.22 (t, 6H, SCH_2CH_3 x 2).

28: R_f 0.33 in ethyl acetate - hexane, 1:3; ^1H NMR (360 MHz, $CDCl_3$) δ: 4.56 (d, 2H, $J_{1,2}$ = 3.5 Hz, H-1 x 2), 3.95 (dd, 2H, $J_{3,4}$ = 9.0 Hz, $J_{4,5}$ = 9.0 Hz, H-4 x 2), 3.72 (m, 4H, H-6, H-5 x 2), 3.46 (m, 6H, H-2, H-3, and H-6' x 2), 3.32 (s, 6H, OCH_3 x 2), 1.30 (s, 6H, CH_3, acetal x 2); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ: 100.01 (CH_3CCH_3), 97.74 (C-1 x 2), 82.30, 80.17, 78.08, 69.79 (C-2, C-3, C-4, and C-5 x 2), 59.92 (C-6 x 2), 54.81 (OCH_3 x 2), 24.89 (CH_3 acetal x 2). The structures of **27** and **28** were confirmed by treatment with *p*-toluenesulfonic acid for 60 minutes at room temperature in dichloromethane. The structures were converted to their respective alcohols **3** and **13** upon this treatment.

Methyl 2,3,6-tri-O-benzyl-α-D-glucopyranoside-ethyl 3',4',6'-tri-O-benzyl-1'-thio-α-D-mannopyranoside-2',4-isopropylidene acetal (**29**)

The vinyl ether **10** (374 mg, 0.699 mmol) and the alcohol **12**[184] (325 mg, 0.699 mmol) were added to a reaction flask and purged with argon. Dry dichloromethane (15 ml) was syringed into the flask. The mixture was cooled to -40°C and *p*-toluenesulfonic acid monohydrate (5 mg, 0.04 eq.) was added to the mixture. The reaction was carefully monitored by tlc for the formation of the mixed acetal product **29**. When tlc indicated that the product spot was maximized (10 min.), the reaction was quenched by the addition of 0.1 ml of triethylamine. Prolonged reaction times (> 20 min) caused a drastic reduction in yields. The mixture was concentrated and chromatographed. The chromatography solvent system was 18% ethyl acetate in hexane which contained 0.1% triethylamine. The product **29** (397 mg, 57%) was obtained as a colorless syrup. The product was unstable after prolonged periods of time (> 24 hrs.) unless it was stabilized in an organic solution (dichloromethane or ethyl acetate - hexane) which contained 0.5% triethylamine (shelf life > 2 months); R_f 0.46 in ethyl acetate - hexane, 1:3; ^1H NMR (360 MHz, $CDCl_3$) δ: 5.44 (d, 1H, $J_{1,2}$ = 1Hz, H-1'), 4.61 (d, 1H, $J_{1,2}$ = 2.5 Hz, H-1),

4.16 (dd, $J_{2,3}$ = 3.5 Hz, $J_{3,4}$ = 9.2 Hz, H-3'), 3.38 (s, 3H, OCH_3), 2.60 (m, 2H, SCH_2CH_3), 1.41 (s, 3H, CH_3CCH_3'), 1.37 (s, 3H, 1.37, CH_3CCH_3'), 1.28 (t, 3H, SCH_2CH_3); ^{13}C NMR (75.5 MHz, D-5 pyridine) δ: 105.09 (CH_3CCH_3), 97.71 (C-1), 85.07 (C-1'), 81.64, 81.57, 80.59, 75.82, 72.68, 72.42, 71.95, 71.89 (C-2, C-3, C-4, C-5, C-2', C-3', C-4' and C-5'), 75.29, 75.12, 73.46, 73.40, 72.70, 72.49 (6 x OCH_2Ph), 70.40, 70.27 (C-6, and C-6'), 54.93 (OCH_3), 26.57, 25.39 ($CH_3CCH'_3$), 25.39 (SCH_2CH_3), 15.35 (SCH_2CH_3).

Octyl 3,6-di-O-benzyl-2-deoxy-2-phthalimido-β-D-glucopyranoside-ethyl 3',4',6'-tri-O-benzyl-1'-thio-α-D-mannopyranoside-2',4-isopropylidene acetal (**30**)

The vinyl ether **10** (150 mg, 0.28 mmol) and the alcohol **24** (169 mg, 0.28 mmol) were added to a reaction flask and purged with argon. Dry dichloromethane (7 ml) was syringed into the flask and the mixture was cooled to -40°C. Toluenesulfonic acid monohydrate (3 mg, 0.06 eq.) was added to the reaction and carefully monitored by tlc until the product spot was maximized (11 minutes). Prolonged reaction times caused the product yield to drop dramatically. The reaction was quenched by the addition of five drops of triethylamine and concentrating the solution *in vacuo*. Fourteen percent (14%) ethyl acetate in hexane which contained 0.1% triethylamine was used as an eluent for chromatographic purification of the crude reaction mixture. Product **30** (175 mg) was obtained in 55% yield. The product was unstable (< 12 hrs.) unless stored in an organic solution (dichloromethane or ethyl acetate / hexane) which contained 0.5% triethylamine; R_f 0.47 in ethyl acetate - hexane, 1:3; ^1H NMR (300 MHz, D-5 pyridine) δ: 5.82 (d, 1H, $J_{1,2}$ = 1.0 Hz, H-1'), 5.62 (d, 1H, $J_{1,2}$ = 8.0 Hz, H-1), 3.93, 3.50 (2 x m, 2H, OCH_2, octyl), 2.72 (m, 2H, SCH_2CH_3), 1.64 (s, 3H, CH_3CCH_3'), 1.62 (s, 3H, CH_3CCH_3'), 1.33 (t, 3H, SCH_2CH_3); ^{13}C NMR (75.5 MHz, D-5 pyridine) δ: 105.07 (CH_3CCH_3'), 98.74 (C-1), 85.01 (C-1'), 81.08, 80.38, 77.01, 75.84, 73.97, 72.88, 72.47 (C-2', C-3', C-4', C-5', C-3, C-4, and C-5), 75.84, 75.14, 73.42, 73.42, 72.63 (5 x OCH_2Ph), 70.30, 69.58 (C-6,

and C-6'), 31.82, 29.70, 29.34, 26.15, 25.56, 22.79 (6 x CH_2, octyl, SCH_2CH_3), 27.19, 25.86 (CH_3CCH_3), 15.41 (SCH_2CH_3), 14.18 (CH_3, octyl).

Octyl 2-N-acetamido-3,6-di-O-benzyl-2-deoxy-β-D-glucopyranoside-ethyl 3',4',6'-tri-O-benzyl-1'-thio-α-D-mannopyranoside-2',4-isopropylidene acetal (**31**)

The vinyl ether **10** (42 mg, 0.078 mmol) and the alcohol **25** (40 mg, 0.078 mmol) were combined in a round bottom flask and purged with argon. Dichloromethane (5 ml) was syringed into the mixture and cooled to -40°C. Camphorsulfonic acid (0.06 ml, 0.05 M solution in dichloromethane, 0.04 equiv.), was added and the reaction monitored by tlc for the formation of **31**. After 45 minutes, the reaction was quenched by the addition of several drops of triethylamine and concentrated *in vacuo*. Fifteen percent (15%) ethyl acetate in hexane which contained 0.1% triethylamine was used as an eluent for silica gel chromatography of the reaction mixture. Product **31** was obtained as a syrup (12 mg, 15%); R_f 0.52 in ethyl acetate - hexane, 1:2; ^1H NMR (300 MHz, $CDCl_3$ with 5% added D-5 pyridine) δ: 5.39 (d, 1H, $J_{1,2}$ = 1 Hz, H-1'), 4.68 (d, 1H, $J_{1,2}$ = 4.5 Hz, H-1), 4.12 (m, 1H, H-2'), 3.37 (dt, 1H, J_{gem} = 9.0 Hz, J_{vic} = 6.5 Hz, OC*H*H', octyl), 2.60 (m, 2H, SCH_2CH_3), 1.92 (s, 3H, $COCH_3$), 1.52 (m, 2H, OCH_2CH_2, octyl), 1.41, 1.35 (2 x s, 6H, CH_3CCH_3'), 1.25 (t, 3H, SCH_2CH_3), 1.23 (m, 10H, octyl), 0.86 (t, 3H, CH_3, octyl); ^{13}C NMR (75.5 MHz, $CDCl_3$ with 5% added D-5 pyridine) δ: 169.6 (C=O), 103.9 (CH_3CCH_3'), 99.6 (C-1), 84.6 (C-1'), 79.7, 77.8, 76.3, 75.3, 72.2, 71.6, 69.4 (C-3, C-4, C-5, C-2', C-3', C-4', and C-5'), 74.9, 73.2, 72.8, 72.4, 70.8, 69.4, 69.2 (5 x CH_2Ph, C-6, C-6', and OCH_2, octyl), 51.3 (C-2), 31.8, 29.6, 29.4, 29.3, 26.1, 25.3, 22.7 (6 x CH_2, octyl and SCH_2CH_3), 26.0, 25.8 (CH_3CCH_3'), 23.5 ($COCH_3$), 15.1 (SCH_2CH_3), 14.1 (CH_3, octyl).

Methyl 2,3,6-tri-O-benzyl-4-O-(2,3,4,6-tri-O-benzyl-β-D-mannopyranosyl)-α-D-glucopyranoside (**32**)

The mixed acetal **29** (55 mg, 0.055 mmol) was added to a round bottom flask and purged with argon. Dry dichloromethane (5 ml) and 56 mg (0.0275 mmol, 5 eq.) of 2,6-di-*tert*-butyl-4-methyl-pyridine were added to the mixture and it was cooled to 0°C. In one portion, *N*-iodosuccinimide (62 mg, 5 eq.) was added and the reaction mixture was stirred overnight. The solution was allowed to warm to room temperature during the night. After 18 hours, the reaction mixture was quenched by the addition of 3 ml of 0.5 M sodium thiosulfate solution, which caused the red solution to turn colorless. Dichloromethane (10 ml) was added and the mixture washed 2 x 10 ml with dH_2O. The organic layer was dried ($MgSO_4$), filtered and concentrated to give a cloudy viscous syrup. Forty percent (40%) ethyl acetate in hexane was used as an eluent in chromatographic purification of the syrup. Product **32** (38 mg, 77%) was isolated as a clear syrup. The kinetic benzylidene acetal product **42** was isolated from the reaction mixture in small (< 20%) quantities;

32: $[\alpha]_D$ + 26.3° (*c* 0.80, CH_2Cl_2); R_f0.14 in ethyl acetate - hexane, 1:2; ^1H NMR (360 MHz, $CDCl_3$) δ: 7.40-7.16 (m, 30H, aromatic), 4.58 (d, 1H, $J_{1,2}$ = 3.7Hz, H-1), 4.44 (d, 1H, $J_{1,2}$ < 1Hz, H-1'), 4.00 (dd, 1H, $J_{2,3}$ = 9.2 Hz, $J_{3,4}$ = 9.2 Hz, H-3), 3.94 (dd, 1H, $J_{3,4}$ = 9.2 Hz, $J_{4,5}$ = 9.2 Hz, H-4), 3.94 (dd, 1H, $J_{2,3}$ = 3.0 Hz, $J_{1,2}$ < 1 Hz, H-2'), 3.83 (dd, 1H, $J_{3,4}$ = 9.5 Hz, $J_{4,5}$ = 9.5 Hz, H-4'), 3.76 (ddd, 1H, $J_{4,5}$ = 9.2 Hz, $J_{5,6}$ = 3.1 Hz, $J_{5,6'}$ = 2Hz, H-5), 3.73 (dd, 1H, $J_{5,6}$ = 3.1 Hz, $J_{6,6'}$ = 10.8 Hz, H-6a), 3.66 (dd, 1H, $J_{5,6'}$ = 2Hz, $J_{6,6'}$ = 10.8 Hz, H-6b), 3.64 (dd, 1H, $J_{5,6}$ = 1.8 Hz, $J_{6,6'}$ = 10.7 Hz, H-6'a), 3.58 (dd, 1H, $J_{5,6'}$ = 4.6 Hz, $J_{6,6'}$ = 10.7 Hz, H-6'b), 3.51 (dd, 1H, $J_{2,3}$ = 3.7 Hz, $J_{3,4}$ = 9.2 Hz, H-2), 3.37 (s, 3H, OCH_3), 3.32 (dd, 1H, $J_{2,3}$ = 3.0 Hz, $J_{3,4}$ = 9.5 Hz, H-3'), 3.24 (ddd, 1H, $J_{5,6}$ = 1.8 Hz, $J_{5,6'}$ = 4.6 Hz, $J_{4,5}$ = 9.5 Hz, H-5'), 2.53 (d, 1H, J = 3.0 Hz, OH); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ: 139.1-137.9, 128.5-127.4 (aromatic), 99.97 (d, $J_{C\text{-}1,H\text{-}1}$ = 157 Hz, C-1'), 98.26 (C-1), 81.64, 80.75, 79.66, 75.85, 75.73, 74.04,

[illegible] (C-2, C-3, C-4, C-5, C-2', C-3', C-4', and C-5'), 75.58, 75.16, 73.54, 73.47, 73.47, 71.15 (6 x OCH_2Ph), 69.11, 68.84 (C-6, and C-6'), 55.27 (OCH_3); Anal. calcd. for $C_{55}H_{60}O_{11}$: C 73.64, H 6.74; found: C 74.06, H 6.81.

42: R_f 0.59 in ethyl acetate - hexane, 1:2; ^1H NMR (360 MHz, $CDCl_3$) δ: 6.06 (s, 1H, PhC*H*), 5.81 (d, $J_{1,2}$ = 3.8 Hz, H-1), 4.13 (dd, 1H, $J_{3,4}$ = 9.0 Hz, $J_{2,3}$ = 9.0 Hz, H-3), 4.03 (m, 1H, H-5), 3.83 (dd, 1H, $J_{2,3}$ = 3.8 Hz, $J_{3,4}$ = 9.0 Hz, H-2), 3.77 (dd, 1H, $J_{5,6}$ = 2.5 Hz, $J_{6,6'}$ = 11.0 Hz, H-6), 3.62 (dd, 1H, $J_{5,6'}$ = 5.7 Hz, $J_{6,6'}$ = 11.0 Hz, H-6'), 3.42 (s, 3H, OCH_3), 3.41 (dd, 1H, $J_{3,4}$ = 9.0 Hz, $J_{4,5}$ = 9.0 Hz, H-4). The structure of this compound was confirmed by treatment with catalytic *p*-toluenesulfonic acid in dichloromethane at room temperature for one hour which converted the kinetic benzylidene product to the known thermodynamic benzylidene product[220].

Activation of Mixed Acetal (**29**) *in the presence of methanol*

The acetal **29** (75 mg, 0.075 mmol) was added to a reaction flask and purged with argon. Dry dichloromethane (5 ml) was syringed into the flask. A 0.12 ml aliquot of a freshly prepared 0.62 M solution of dry methanol in dichloromethane (0.075 mmol) was added to the reaction vessel. The mixture was cooled to 0°C and NIS (84 mg, 5 eq.) was added. The reaction was stirred overnight. The reaction was then quenched after 17 hours and treated as in the preparation of **29** without added methanol. Chromatographic isolation yielded **32** (7.5 mg, 11%) and the methyl glycoside **5** (14 mg, 40%, refer to page 105 for the characterization of **5**).

General Procedure for the "One-Pot" Synthesis of β-Mannosides **32**, **33** *and* **34**

The vinyl ether **10** (1 equiv.) and the alcohols **12**, **13** or **24** (1 equiv.) were added to a reaction vessel and purged with argon. Dichloromethane was added (~ 0.02 mmol / ml) and the solution was cooled to -40°C. NIS (5 equiv.) was added to the mixture and the reaction maintained at -40°C for 30 minutes. It was then allowed to slowly warm to

room temperature (3 hours) and stirred overnight. The red solution was quenched by the addition of 0.5 M sodium thiosulfate solution until the solution became colorless. The mixture was then diluted with dichloromethane, extracted twice with an equal volume of water, dried ($MgSO_4$), filtered and concentrated. The product alcohols were purified by silica gel chromatography.

Methyl 2,3,4-tri-O-benzyl-6-O-(3,4,6-tri-O-benzyl-β-D-mannopyranosyl)-α-D-glucopyranoside (**33**)

The mixed acetal **26** (63 mg, 0.0631 mmol) was added to a reaction flask and purged with argon. Dry dichloromethane (4 ml) was syringed into the flask and the mixture was cooled to 0°C. In one portion, *N*-iodosuccinimide (70.9 mg, 0.315 mmol, 5 eq.) was added to the flask. The reaction mixture was stirred for 2 hours and 45 minutes and quenched by the addition of 3 ml of sodium thiosulfate (0.5 M). The deep red reaction color became colorless upon quenching. Dichloromethane (10 ml) was added and the mixture was washed with 2 x 10 ml dH_2O. The organic layer was dried ($MgSO_4$), filtered and concentrated. Ethyl acetate in hexane (1:2) was used as an eluent in chromatographic purification of the crude reaction mixture. Product **33** (34 mg, 60%) was obtained as a white solid. When this reaction was carried out in the presence of 1.0 equivalent of methanol, as described for the activation of **29**, the yield of **33** was unchanged; $[\alpha]_D$ +35.2° (*c* 0.40, CH_2Cl_2), R_f 0.20 in ethyl acetate - hexane, 1:2; ^1H NMR (360 MHz, $CDCl_3$) δ: 7.35 - 7.15 (m, 30H, aromatic), 4.51 (d, 1H, $J_{1,2}$ = 3.5 Hz, H-1), 4.10 (d, 1H, $J_{1,2}$ < 0.5 Hz, H-1'), 4.09 (dd, 1H, $J_{5,6}$ = 1.5 Hz, $J_{6,6'}$ = 10.8 Hz, H-6a'), 4.00 (dd, 1H, $J_{3,4}$ = 9.5 Hz, $J_{4,5}$ = 9.5 Hz, H-4'), 3.91 (br s, 1H, H-2'), 3.82 (dd, 1H, $J_{3,4}$ = 9.5 Hz, $J_{4,5}$ = 9.5 Hz, H-4), 3.76 (ddd, 1H, $J_{4,5}$ = 9.5 Hz, $J_{5,6}$ = 1.5 Hz, $J_{5,6'}$ = 5.5 Hz, H-5'), 3.73 (dd, 1H, $J_{5,6}$ = 2.0 Hz, $J_{6,6'}$ = 10.2 Hz, H-6a), 3.66 (dd, 1H, $J_{5,6'}$ = 5.0 Hz, $J_{6,6'}$ = 10.2 Hz, H-6b), 3.56 (dd, 1H, $J_{5,6'}$ = 5.5 Hz, $J_{6,6'}$ = 10.8 Hz, H-6b'), 3.50 (dd, 1H, $J_{3,4}$ = 9.5 Hz, $J_{2,3}$ = 3.5 Hz, H-3'), 3.32 (m, 1H, H-5), 3.32 (s, 3H, OCH_3), 2.37

(br s, 1H, OH); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ: 138.8 - 138.0, 128.5 - 127.6 (aromatic), 100.00 (d, $J_{C\text{-}1,H\text{-}1}$ = 155 Hz, C-1'), 97.94 (C-1), 82.22, 81.37, 79.95, 77.65, 75.45, 74.34, 69.87, 68.33 (C-2, C-3, C-4, C-5, C-2', C-3', C-4', and C-5'), 75.76, 75.22, 74.78, 73.54, 73.41, 71.42 (6 x OCH_2Ph), 69.35, 68.18 (C-6, and C-6'), 55.20 (OCH_3); Anal. calcd. for $C_{55}H_{60}O_{11}$: C 73.64, H 6.74; found: C 73.40, H 6.79.

Octyl 3,6-di-O-benzyl-4-O-(3,4,6-tri-O-benzyl-β-D-mannopyranosyl)-2-deoxy-2-phthalimido-β-D-glucopyranoside (**34**)

Under an argon atmosphere, the mixed acetal **30** (58 mg, 0.051 mmol) was dissolved in 5 ml of dry dichloromethane. Di-*tert*-butyl-4-methyl-pyridine (52 mg, 0.255 mmol, 5 eq.) was added to the solution and it was cooled to 0°C. N-iodosuccinimide (57 mg, 0.255 mmol, 5 eq.) was added to the mixture and it was allowed to warm to room temperature overnight. The reaction was quenched after 16 hours by the addition of 3 ml of $Na_2S_2O_3$ solution (0.5 M) which caused the red reaction color to turn colorless. Dichloromethane (15 ml) was poured into the mixture and the organic layer was washed 2 x 15 ml with dH_2O. The dichloromethane layer was dried ($MgSO_4$), filtered and concentrated. Forty percent (40%) ethyl acetate in hexane was used as an eluent in the chromatographic purification of the crude reaction mixture. Product **34** (27 mg) was isolated in 51% yield; $[\alpha]_D$ +27.6°, (*c* 1.60, CH_2Cl_2); R_f 0.36 in ethyl acetate - hexane, 1:2; ^1H NMR (360 MHz, $CDCl_3$) δ: 7.8-7.55 (m, 4H, phthalimido), 7.4-6.7 (m, 25H, benzyl aromatic), 5.09 (d, 1H, $J_{1,2}$ = 8.4 Hz, H-1), 4.67 (d, 1H, $J_{1,2}$ < Hz, H-1'), 4.38 (dd, 1H, $J_{2,3}$ = 10.6 Hz, $J_{3,4}$ = 8.7 Hz, H-3), 4.16 (dd, 1H, $J_{1,2}$ = 8.4 Hz, $J_{2,3}$ = 10.6 Hz, H-2), 4.07 (dd, 1H, $J_{3,4}$ = 8.7 Hz, $J_{4,5}$ = 8.7 Hz, H-4), 4.02, (m, 1H, H-2'), 3.85 (dd, 1H, $J_{3,4}$ = 9.0 Hz, $J_{4,5}$ = 9.0 Hz, H-4'), 3.40 (dd, 1H, $J_{3,4}$ = 9.0 Hz, $J_{2,3}$ = 3.0 Hz, H-3'), 2.49 (d, 1H, $J_{H,OH}$ = 2.7 Hz, OH), 1.4-0.7 (m, 15H, octyl); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ: 167.8 (*C*=O, phthalimido), 100.48 (d, $J_{C\text{-}1,\ H\text{-}1}$ = 158 Hz, C-1'), 98.48 (C-1), 81.76, 78.48, 78.21, 75.53, 74.58, 74.05, 68.06 (C-2', C-3', C-4', C-5', C-3, C-4, and C-5), 75.11,

74.80, 73.59, 73.39, 71.35 (5 x OCH_2Ph), 69.65, 69.05 (C-6, and C-6'), 68.87 (OCH_2, octyl), 55.90 (C-2), 31.67, 29.31, 29.12, 25.84, 22.60 (6 x CH_2, octyl), 14.06 (CH_3, octyl); Anal. calcd. for $C_{63}H_{71}O_{12}N$: C 73.16, H 6.92, N 1.35; found: C 72.92, H 6.99, N 1.43.

Methyl 4-O-(2-O-acetyl-3,4,6-tri-O-benzyl-α-D-mannopyranosyl)-2,3,6-tri-O-benzyl-α-D-glucopyranoside (**36**)

The alcohol **12** (76 mg, 0.164 mmol) and crushed 4Å molecular sieves were added to a reaction vessel. Mercuric cyanide (50 mg, 0.197 mmol, 1.2 eq.) and mercuric bromide (71 mg, 0.197 mmol, 1.2 eq.) were then added and the vessel was purged with argon. Dry acetonitrile (5 ml) was syringed into the flask and the mixture was stirred for 30 minutes. In a separate flask, freshly prepared bromide **35**[190], was purged with argon. The donor **35** was added in a dropwise fashion to the reaction mixture in 2 x 1.5 ml aliquots of dry acetonitrile. After 3 hours, the reaction was filtered through a celite bed and washed with 50 ml dichloromethane. The solution was concentrated and redissolved in 20 ml CH_2Cl_2. The organic layer was washed 2 x 20 ml with saturated potassium iodide solution and 2 x 20 ml with dH_2O. The organic layer was then dried ($MgSO_4$), filtered and concentrated. Chromatography (15% ethyl acetate in hexane was used as an eluent) yielded the product **36** (63 mg, 41%) and recovered acceptor **12** (35 mg, 46%); Rf 0.59 in ethyl acetate - hexane, 1:2; ^1H NMR (360 MHz, $CDCl_3$) δ: 5.43 (dd, 1H, $J_{1,2}$ = 1 Hz, $J_{2,3}$ = 3.6 Hz, H-2'), 5.41 (d, 1H, $J_{1,2}$ = 1.5 Hz, H-1'), 4.58 (d, 1H, H-2), 3.54 (dd, 1H, $J_{2,3}$ = 3.6 Hz, $J_{3,4}$ = 9.8 Hz, H-3'), 3.38 (s, 3H, OCH_3), 1.99 (s, 3H, $COCH_3$).

Methyl 2,3,6-tri-O-benzyl-4-O-(3,4,6-tri-O-benzyl-α-D-mannopyranosyl)-α-D-glucopyranoside (**37**)

The 2-*O*-acetate **36** (60 mg, 0.0639 mmol) was dissolved in 5 ml of dry methanol and 10 mg of sodium methoxide was added to the stirred mixture. After 20 hours the

reaction was neutralized by the addition of Amberlite IRC-120 (H^+) resin. The reaction mixture was concentrated and purified by chromatography with an 18% ethyl acetate in hexane solvent system. Product **37** (51 mg, 89%) was isolated as a colorless syrup; $[\alpha]_D$ +61.7° (*c* 1.10, CH_2Cl_2); R_f 0.40 in ethyl acetate - hexane, 1:2; ^1H NMR (360 MHz, $CDCl_3$) δ: 7.45-7.15 (m, 30H, aromatic), 5.31 (d, 1H, $J_{1,2}$ = 1.8 Hz, H-1'), 4.60 (d, 1H, $J_{1,2}$ = 3.8 Hz, H-1), 3.88-3.66 (m, 12H), 3.60 (dd, 1H, $J_{5,6}$ = 3.8 Hz, $J_{6,6'}$ = 10.5 Hz, H-6a'), 3.53 (dd, 1H, $J_{1,2}$ = 3.8 Hz, $J_{2,3}$ = 9.5 Hz, H-2), 3.49 (dd, 1H, $J_{5,6'}$ = 1.5 Hz, $J_{6,6'}$ = 10.5 Hz, H-6b'), 3.38 (s, 3H, OCH_3), 2.08 (br s, 1H, OH); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ: 138.6-138.0, 128.5-127.5 (aromatic), 101.6 (d, $J_{C\text{-}1,H\text{-}1}$ = 171 Hz, C-1'), 97.8 (C-1), 81.8, 80.2, 79.9, 77.4, 74.2, 72.3, 69.8, 68.8 (C-2, C-3, C-4, C-5, C-2', C-3', C-4', and C-5'), 75.5, 75.0, 73.5, 73.3, 71.9 (6 x OCH_2Ph), 69.4, 69.0 (C-6, and C-6'), 55.3 (OCH_3); Anal. calcd. for $C_{55}H_{60}O_{11}$: C 73.64, H 6.74; found: C 72.97, H 6.76.

Methyl 6-O-(2-O-acetyl-3,4,6-tri-O-benzyl-α-D-mannopyranosyl)-2,3,4-tri-O-benzyl-α-D-glucopyranoside (**38**)

The alcohol **13** (76 mg, 0.164 mmol) and crushed 4Å molecular sieves were combined in a reaction flask. Mercuric cyanide (50 mg, 0.197 mmol, 1.2 eq.) and mercuric bromide (71 mg, 0.197 mmol, 1.2 eq.) were then added and the flask was purged with argon. Dry acetonitrile (5 ml) was syringed into the mixture and stirred for 30 minutes. In a separate flask, freshly prepared bromide **35**[190] (137 mg, 0.25 mmol, 1.5 eq.) was dissolved in 2 x 1.5 ml of acetonitrile and added in a dropwise fashion to the acceptor **13**. After 45 minutes, the reaction was filtered through a celite bed and washed with 50 ml dichloromethane. The filtrate was concentrated and redissolved in 20 ml dichloromethane. It was washed 2 x 20 ml with saturated potassium iodide solution and 2 x 20 ml with dH_2O. The organic layer was dried ($MgSO_4$), filtered and concentrated. Twelve percent (12%) ethyl acetate in hexane was used as an eluent for chromatographic purification of the crude reaction mixture. Product **38** (120 mg) was obtained in 78%

yield; R_f 0.65 in ethyl acetate - toluene, 1:2; ^1H NMR (360 MHz, $CDCl_3$) δ: 5.38 (dd, 1H, $J_{1,2}$ = 1.8 Hz, $J_{2,3}$ = 3.0 Hz, H-2'), 4.89 (d, 1H, $J_{1,2}$ = 1.8 Hz, H-1'), 4.58 (d, 1H, $J_{1,2}$ = 3.2 Hz, H-1), 3.98 (dd, 1H, $J_{2,3}$ = 9.0 Hz, $J_{3,4}$ = 9.0 Hz, H-3), 3.91 (dd, 1H, $J_{2,3}$ = 3.0 Hz, $J_{3,4}$ = 9.2 Hz, H-3'), 3.86 (dd, 1H, $J_{3,4}$ = 9.2 Hz, $J_{4,5}$ = 9.2 Hz, H-4'), 3.44 (dd, 1H, $J_{1,2}$ = 3.2 Hz, $J_{2,3}$ = 9.0 Hz, H-2), 3.42 (dd, 1H, $J_{3,4}$ = 9.0 Hz, $J_{4,5}$ = 9.0 Hz, H-4), 3.32 (s, 3H, OCH_3), 2.15 (s, 3H, $COCH_3$).

Methyl 2,3,4-tri-O-benzyl-6-O-(3,4,6-tri-O-benzyl-α-D-mannopyranosyl)-α-D-glucopyranoside (**39**)

The 2-*O*-acetate **38** (115 mg, 0.12 mmol) was dissolved in 5 ml of dry methanol and 10 mg of sodium methoxide was added. The mixture was stirred for 20 hours and neutralized by the addition of Amberlite IRC-120 (H^+) resin. The solution was filtered, concentrated and purified by silica gel chromatography. The chromatography eluent was 30% ethyl acetate in hexane. The product **39** (83 mg, 76%) was obtained along with the accompanying β isomer (2 mg, 2%); $[\alpha]_D$ +74.4° (*c* 2.55, CH_2Cl_2); R_f 0.17 in ethyl acetate - hexane, 1:2; ^1H NMR (360 MHz, $CDCl_3$) δ: 7.40 - 7.10 (m, 30H, aromatic), 5.02 - 4.40 (m, 12H, 6 x OCH_2Ph), 4.96 (d, 1H, $J_{1,2}$ = 1.5 Hz, H-1'), 4.60 (d, 1H, $J_{1,2}$ = 3.7 Hz, H-1), 4.03 (dd, 1H, $J_{1,2}$ = 1.5 Hz, $J_{2,3}$ = 3 Hz, H-2'), 3.99 (dd, 1H, $J_{3,4}$ = 9.4 Hz, $J_{4,5}$ = 9.4 Hz, H-3), 3.85 (dd, 1H, $J_{5,6}$ = 4.5 Hz, $J_{6,6'}$ = 10 Hz, H-6a), 3.83 (m, 1H, H-3'), 3.82 (dd, 1H, $J_{5,6'}$ = 3.5 Hz, $J_{6,6'}$ = 10 Hz, H-6b), 3.70 (m, 3H, H-5, H-4', and H-5'), 3.62 (dd, 1H, $J_{5,6}$ = 4.0 Hz, $J_{6,6'}$ = 11.0 Hz, H-6a'), 3.55 (dd, 1H, $J_{5,6'}$ = 2.0 Hz, $J_{6,6'}$ = 11.0 Hz, H-6b'), 3.50 (dd, 1H, $J_{2,3}$ = 3.7 Hz, $J_{3,4}$ = 9.8 Hz, H-2), 3.45 (dd, 1H, $J_{4,5}$ = 9.4 Hz, $J_{3,4}$ = 9.4 Hz, H-4), 3.33 (s, 3H, OCH_3), 2.40 (br s, 1H, OH); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ: 138.85 - 137.85, 128.55 - 127.58 (aromatic), 99.57 (d, $J_{C-1, H-1}$ = 175 Hz, C-1'), 97.88 (C-1), 82.17, 80.09, 79.74, 77.74, 74.22, 71.21, 69.84, 68.26 (C-2, C-3, C-4, C-5, C-2', C-3', C-4', and C-5'), 75.82, 75.05, 74.96, 73.41, 73.29, 71.92 (6 x OCH_2Ph), 69.84, 65.92 (C-6 and C-6'), 55.14 (OCH_3); Anal. calcd. for $C_{55}H_{60}O_{11}$: C 73.64, H

6.74; found: C 73.57, H 6.82.

Octyl 4-O-(2-O-acetyl-3,4,6-tri-O-benzyl-α-D-mannopyranosyl)-3,6-di-O-benzyl-2-deoxy-2-phthalimido-β-D-glucopyranoside (**40**)

The acceptor **24** (91 mg, 0.166 mmol) and crushed 4Å molecular sieves were mixed in a reaction vessel. Mercuric cyanide (50 mg, 0.20 mmol, 1.2 eq.) and mercuric bromide (72 mg, 0.20 mmol, 1.2 eq.) were then added to the vessel and the mixture purged with argon. Dry acetonitrile (5 ml) was syringed into the mixture and it was stirred for 30 minutes. Freshly prepared bromide **35** (138 mg, 0.25 mmol, 1.5 eq.) was dissolved in 2 x 1 ml acetonitrile and added in a dropwise fashion to the reaction. The mixture was stirred for 2 hours, filtered through a celite pad, washed with dichloromethane (30 ml) and concentrated. Fresh dichloromethane (25 ml) was added and washed 2 x 25 ml with saturated potassium iodide solution and 1 x 25 ml with distilled water. The organic layer was dried ($MgSO_4$), filtered and concentrated. Fifteen percent (15%) ethyl acetate in hexane was used as an eluent in the chromatographic purification of the crude mixture. Product **40** (71 mg, 40%) and acceptor **24** (37 mg, 40%) were isolated; R_f 0.62 in ethyl acetate - hexane, 1:3; ^1H NMR (360 MHz, $CDCl_3$) δ: 5.54 (m, 1H, H-2'), 5.42 (d, 1H, $J_{1,2}$ = 1.6 Hz, H-1'), 5.10 (d, 1H, $J_{1,2}$ = 8.4 Hz, H-1), 4.22 (dd, 1H, $J_{1,2}$ = 8.4 Hz, $J_{2,3}$ = 10.6 Hz, H-2), 3.66, 3.38 (2 x m, 2H, OCH_2, octyl), 2.04 (s, 3H, $COCH_3$).

Octyl 3,6-di-O-benzyl-4-O-(3,4,6-tri-O-benzyl-α-D-mannopyranosyl)-2-deoxy-2-phthalimido-β-D-glucopyranoside (**41**)

The 2-*O*-acetate **40** (65 mg, 0.0604 mmol) was dissolved in 5 ml of dry methanol and 3 mg of sodium methoxide was added. The reaction was stirred for 14 hours and neutralized by the addition of Amberlite IRC-120 (H^+) resin, filtered and concentrated. The resultant syrup was purified by column chromatography. The chromatography

eluent used was 20% ethyl acetate in hexane. Product **41** (55 mg) was obtained in 88% yield; $[\alpha]_D$ +44.6°, (*c* 1.05, CH_2Cl_2); R_f 0.38 in ethyl acetate - hexane, 1:2; ^1H NMR (360 MHz, $CDCl_3$) δ: 7.8-7.6 (m, 4H, phthalimido), 7.4-7.1, 7.05-6.75 (m, 25H, benzyl aromatics), 5.34 (d, 1H, $J_{1,2}$ = 1.8 Hz, H-1'), 5.08 (d, 1H, $J_{1,2}$ = 8.5 Hz, H-1), 4.19 (dd, 1H, $J_{1,2}$ = 8.5 Hz, $J_{2,3}$ = 10.7 Hz, H-2), 3.96 (m, 1H, H-2'), 3.7, 3.35 (2 x m, 2H, OCH_2, octyl), 2.20 (d, 1H, $J_{H,OH}$ = 2.8 Hz, OH), 1.4-0.7 (m, 15H, octyl); ^{13}C (75.5 MHz, $CDCl_3$) δ: 101.23 (d, $J_{C-1,H-1}$ = 172 Hz, C-1'), 98.10 (C-1), 80.94, 79.89, 78.11, 74.90, 74.21, 72.35, 69.02 (C-2', C-3', C-4', C-5', C-3, C-4, and C-5), 75.07, 74.62, 73.50, 73.38, 72.11 (5 x OCH_2Ph), 69.60, 69.60 (C-6, and C-6'), 68.90 (OCH_2, octyl), 55.81 (C-2), 31.66, 29.29, 29.13, 25.84, 22.60 (6 x CH_2, octyl), 14.06 (CH_3, octyl); Anal. calcd. for $C_{63}H_{71}O_{12}N$: C 73.16; H 6.92, N 1.35; found: C 72.80, H 6.92, N 1.40.

Methyl 3,6-di-O-trityl-α-D-mannopyranoside (**44**) [221]

Methyl α-D-mannopyranoside **43** (25 g, 0.13 mol) and toluene (400 ml) were combined in a 1 litre flask. Bis(tributyltin) oxide (99 ml, 0.20 mol) was poured into the reaction slurry and it was refluxed with continuos removal of water until all of **43** was dissolved (7 hours). The solution was then cooled to 55°C and trityl chloride (108 g, 0.39 mol) was added in one portion. The reaction was quenched after 17 hours at 55°C by pouring it into a solution of 122 g potassium fluoride and 100 ml water. The quenched reaction was stirred for two hours and filtered. The filtrate was washed with 300 ml water and the organic layer was removed, dried ($MgSO_4$), filtered and concentrated. The crude product **44** was recrystallized with ethyl acetate and hexane which yielded pink crystals (57.5 g, 66%) ; $[\alpha]_D$ +48.7° (c 0.95, CH_2Cl_2); R_f 0.51 in ethyl acetate - hexane, 1:3; ^1H NMR (360 MHz, $CDCl_3$) δ: 5.48 (d, 1H, $J_{1,2}$ = 2.0 Hz, H-1), 3.92 (ddd, 1H, $J_{3,4}$ = 9.0 Hz, $J_{4,5}$ = 8.8 Hz, $J_{H,OH}$ = 2.8 Hz, H-4), 3.89 (dd, 1H, $J_{3,4}$ = 9.0 Hz, $J_{2,3}$ = 3.2 Hz, H-3), 3.58 (m, 1H, H-5), 3.37 (m, 2H, H-6, and H-6'), 3.25 (s, 3H, OCH_3), 2.75 (m, 1H, H-2), 2.22 (d, 1H, $J_{H,OH}$ = 3.4 Hz, OH), 1.94 (d, 1H,

$J_{4,OH}$ = 2.8 Hz, OH); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ: 100.32 (C-1), 87.42, 87.00 (2 x CPh_3), 74.74, 71.16, 69.11, 68.31 (C-2, C-3, C-4, and C-5), 64.87 (C-6), 54.70 (OCH_3); Anal. calcd. for $C_{45}H_{42}O_6$: C 79.62, H 6.24; found: C 79.45, H 6.35.

Methyl 2,4-di-O-benzyl-α-D-mannopyranoside (**45**)[97, 222]

Sodium hydride (3.5 g, 0.088 mmol) was added to a reaction vessel followed by 125 ml of dimethylformamide. The suspension was stirred for 30 minutes. In a separate flask, the di-*O*-tritylated methyl mannoside **44** (15 g, 0.022 mol) was dissolved in 50 ml of DMF and added in a dropwise fashion to the NaH / DMF suspension. After a further 30 minutes, benzyl bromide (9.2 ml, 0.077 mmol) was mixed with 75 ml of DMF and slowly added to the cooled (5° C) suspension. The solution was stirred overnight (16 hours) and quenched by the addition of 300 ml water. Ethyl acetate (300 ml) was added and the organic layer was separated and washed with water (2 x 350 ml). The organic layer was dried ($MgSO_4$), filtered and concentrated to a golden brown oil (20 g) which was dissolved in 150 ml of 80% acetic acid / water and heated to 60°C. After 20 hours, the reaction mixture was cooled and filtered to remove a pink solid. The filtrate was neutralized with 250 ml saturated sodium bicarbonate solution and extracted 2 x 250 ml with ethyl acetate. The combined organic layers were washed with water (400 ml), dried ($MgSO_4$), filtered and concentrated. Purification by column chromatography (ethyl acetate in hexane (1:2) was used as eluent) gave 3.9 g of product **45** (46%) as a viscous oil; $[\alpha]_D$ +22.3° (c 1.05, CH_2Cl_2); Rf 0.42 in ethyl acetate - hexane, 1:1; ^1H NMR (300 MHz, $CDCl_3$) δ: 7.35 (m, 10H, benzyl aromatics), 4.90, 4.65 (2 x d, 2H, J_{gem} = 11.0 Hz, CH_2Ph), 4.72, 4.59 (2 x d, J_{gem} = 11.8 Hz, CH_2Ph), 4.75 (d, 1H, $J_{1,2}$ = 1.5 Hz, H-1), 3.98 (m, 1H, H-5), 3.86 (dd, 1H, $J_{5,6}$ = 3.0 Hz, $J_{6,6'}$ = 11.5 Hz, H-6), 3.77 (dd, 1H, $J_{5,6'}$ = 4.2 Hz, $J_{6,6'}$ = 11.5 Hz, H-6'), 3.73 (dd, 1H, $J_{1,2}$ = 1.5 Hz, $J_{2,3}$ = 3.5 Hz, H-2), 3.68 (dd, 1H, $J_{3,4}$ = 9.2 Hz, $J_{4,5}$ = 9.2 Hz, H-4), 3.59 (ddd, 1H, $J_{3,4}$ = 9.2 Hz, $J_{2,3}$ = 3.5 Hz, $J_{H,OH}$ = 5.5 Hz, H-3), 3.32 (s, 3H, OCH_3), 2.05 (d, 1H, $J_{H,OH}$ = 5.5 Hz, OH); ^{13}C

NMR (75.5 MHz, $CDCl_3$) δ: 98.27 (C-1), 78.44, 76.64, 71.77, 71.22 (C-2, C-3, C-4, and C-5), 74.91, 73.16 (2 x CH_2Ph), 62.39 (C-6), 54.90 (OCH_3); Anal. calcd. for $C_{21}H_{26}O_6$: C 67.36, H 7.00; found: C 67.31, H 7.07.

Methyl 2,4-di-O-benzyl-3,6-di-O-(2,3,4,6-tetra-O-acetyl-α-D-mannopyranosyl)-α-D-mannopyranoside (**47**)

The diol **45** (2.0 g, 5.35 mmol) and 4Å molecular sieves were added to a round bottom flask. Mercuric cyanide (4.1 g, 16.1 mmol) and mercuric bromide (5.8 g, 16.1 mmol) were then added to the flask and it was purged with argon. Dry acetonitrile (100 ml) was added and the mixture was stirred and cooled to 0°C. Acetobromomannose **46**[191] (11.5 g, 28 mmol, 5.2 eq.) was dissolved in 100 ml acetonitrile and added to the reaction mixture over a 10 minute period. After 2.5 hours, the mixture was filtered and washed with dichloromethane (50 ml). The filtrate was concentrated to a brown foam which was dissolved in 250 ml of CH_2Cl_2. It was then washed 2 x 250 ml with saturated potassium iodide solution, 250 ml with saturated sodium bicarbonate solution, 250 ml with water and 250 ml with brine. The organic layer was dried ($MgSO_4$), filtered and concentrated. Sixty percent (60%) ethyl acetate in hexane was used as the solvent system for chromatographic purification of the crude mixture. Product **47** was obtained as white crystals (5.86 g, 83%); $[\alpha]_D$ +73.20 (c 1.15, CH_2Cl_2); R_f 0.51 in ethyl acetate - hexane, 7:3; ^1H NMR (360 MHz, $CDCl_3$) δ: 5.13, 4.90, 4.74 (3 x d, 3H, $J_{1,2}$ = 1.5 Hz, H-1, H-1' and H-1''), 3.35 (s, 3H, OCH_3), 2.14, 2.06, 2.06, 2.05, 2.04, 2.04, 2.00, 1.98 (8 x s, 24H, $COCH_3$); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ: 170.69, 170.57, 169.87, 169.76, 169.65 (8 x s, $COCH_3$), 99.37, 98.06, 97.39 (C-1, C-1', and C-1''), 78.48. 77.30, 75.23, 72.32, 69.63, 69.56, 69.00, 69.00, 68.89, 68.55, 66.30, 66.25 (C-2,2',2'', C-3,3',3'', C-4,4',4'', and C-5,5',5''), 75.08, 72.26, 66.65, 62.53, 62.40 (C-6, C-6', C-6'', and 2 x CH_2Ph), 54.77 (OCH_3), 20.88, 20.72, 20.67, 20.55 (8 x $COCH_3$); Anal. calcd. for $C_{49}H_{62}O_{24}$: C 56.86, H 6.04; found: C 56.48, H 5.96.

1-O-Acetyl-2,4-di-O-benzyl-3,6-di-O-(2,3,4,6-tetra-O-acetyl-α-D-mannopyranosyl)-α-D-mannopyranose (**48**)

The trisaccharide **47** (3.9 g, 3.77 mmol) was dissolved in 195 ml acetic anhydride and cooled to 0°C. Sulfuric acid (0.2 ml) was added to 19.8 ml of acetic anhydride and was poured into the reaction mixture (0.1% H_2SO_4, v / v). The reaction mixture was stirred at 0°C for 25 minutes and was then quenched by the addition into a solution of sodium bicarbonate (300 ml). The mixture was stirred for one additional hour to destroy excess acetic anhydride. Dichloromethane (300 ml) was added to the reaction and the organic layer was separated. This layer was washed with 2 x 300 ml $NaHCO_3$ solution and 300 ml with brine. The organic layer was then dried ($MgSO_4$), filtered and concentrated to give a white foam **48** (3.8 g, 95%). A portion of this was purified (45% ethyl acetate in hexane solvent system) for characterization; $[\alpha]_D$ +69.9° (c 1.70, CH_2Cl_2); R_f 0.63 in ethyl acetate - hexane, 7:3; ^1H NMR (360 MHz, $CDCl_3$) δ: 6.23 (d, 1H, $J_{1,2}$ = 2.0 Hz, H-1), 5.13, 4.89 (2 x d, 2H, H-1', H-1"), 2.14, 2.09, 2.08, 2.06, 2.04, 2.04, 2.02, 2.00, 1.98 (9 x s, 27H, $COCH_3$); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ: 170.62, 170.35, 169.71, 169.64, 169.56, 168.83 (9 x $COCH_3$), 99.77, 97.85 (C-1', and C-1"), 90.55 (C-1), 79.31, 75.90, 74.01, 73.88, 69.55, 69.47, 69.01, 68.95, 68.87, 68.47, 66.15, 66.02 (C-2,2',2", C-3,3',3", C-4,4',4", and C-5,5',5"), 75.31, 71.66, 66.54, 62.44, 62.32 (C-6,6',6" and 2 x CH_2Ph), 20.96, 20.86, 20.70, 20.60 (9 x $COCH_3$); Anal. calcd. for $C_{50}H_{62}O_{25}$: C 56.49, H 5.88; found: C 55.77, H 5.74.

1,2,4-Tri-O-acetyl-3,6-di-O-(2,3,4,6-tetra-O-acetyl-α-D-mannopyranosyl)-α-D-mannopyranose (**49**)

The di-benzylated trimannoside **48** (1.09 g, 1.03 mmol) was added to a flask and purged with argon. Palladium on charcoal (10%, 1 g) was added to the flask. Ethanol (100 ml, 95%) and glacial acetic acid (1 ml) were then added to the vessel. The suspension was stirred overnight under a hydrogen atmosphere and then filtered through

a celite pad. The clear solution was concentrated to a foam and re-dissolved in 100 ml of pyridine. Acetic anhydride (20 ml) was added and the reaction mixture stirred overnight. Water (50 ml) was poured into the mixture to destroy excess acetic anhydride followed by 300 ml of dichloromethane. The organic layer was washed 4 x 300 ml with 1N HCl, 300 ml with bicarbonate solution and 300 ml with water. The organic layer was dried ($MgSO_4$), filtered and concentrated. Sixty five percent (65%) ethyl acetate in hexane was used as an eluent in chromatographic purification of the crude mixture. Product **49** (0.71 g, 71%) was isolated as a white foam; $[\alpha]_D$ +53.7° (c 1.20, CH_2Cl_2); R_f 0.57 in ethyl acetate - hexane (7:3); ^1H NMR (360 MHz, $CDCl_3$) δ: 6.06 (d, 1H, $J_{1,2}$ = 2.0 Hz, H-1), 5.06, 4.81 (2 x d, 2H, H-1' and H-1"), 3.76 (dd, 1H, $J_{5,6}$ = 5.5 Hz, $J_{6,6'}$ = 11.0 Hz, H-6), 3.68 (dd, 1H, $J_{5,6'}$ = 3.0 Hz, $J_{6,6'}$ = 11.0 Hz, H-6'), 2.24, 2.16, 2.14, 2.12, 2.12, 2.09, 2.08, 2.06, 2.00, 1.98 (11 x s, $COCH_3$); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ: 170.68, 170.54, 170.23, 170.03, 169.86, 169.78, 169.59, 167.96 (11 x $COCH_3$), 99.20, 97.61 (C-1' and C-1"), 90.50 (C-1), 74.78, 71.61, 69.96, 69.96, 69.59, 69.36, 69.11, 68.60, 68.24, 67.97, 65.92, 65.92 (C-2,2',2", C-3,3',3", C-4,4',4', and C-5,5',5"), 66.94, 62.45, 62.45 (C-6,6',6"), 20.77 - 20.66 (11 x $COCH_3$); Anal. calcd. for $C_{40}H_{54}O_{27}$: C 49.69, H 5.63; found: C 49.71, H 5.60.

4-O-Acetyl-3,6-di-O-(2,3,4,6-tetra-O-acetyl-α-D-mannopyranosyl)-1,2-methoxyethylidene-β-D-mannopyranoside (**50**)

The per-acetate **49** (1.52 g, 1.57 mmol) was added to a reaction vessel and purged with argon. Dichloromethane (60 ml) was added to the vessel and the solution was cooled to 0°C. Hydrobromic acid gas was bubbled through the mixture for 3.5 hours. The reaction was concentrated and co-evaporated with toluene. The crude bromide was re-dissolved in dichloromethane (60 ml). 2,6-lutidine (0.42 ml, 2.3 eq.) and methanol (0.15 ml, 2.3 eq.) were syringed into the solution and stirred overnight. The reaction was diluted with dichloromethane (100 ml) and quenched by the addition into 200 ml of

sodium bicarbonate solution. The organic layer was washed with 200 ml water, dried ($MgSO_4$), filtered and concentrated. The foam was recrystallized from ethyl acetate and hexane which gave a white crystalline product **50** (1.16 g, 79%); $[\alpha]_D$ +36.3° (c 0.30, CH_2Cl_2); R_f 0.48 in ethyl acetate - hexane, 7:3; ^1H NMR (360 MHz, $CDCl_3$) δ: 5.83 (d, 1H, $J_{1,2}$ = 3.0 Hz, H-1), 5.33, 5.31 (2 x dd, 2H, H-3' and H-3"), 5.24 (dd, 1H, $H_{1,2}$ = 1.6 Hz, $J_{2,3}$ = 3.0 Hz, H-2"), 5.17 (dd, 1H, $J_{3,4}$ = 9.8 Hz, $J_{4,5}$ = 9.8 Hz, H-4), 5.14 (dd, 1H, $J_{1,2}$ = 1.8 Hz, $J_{2,3}$ = 3 Hz, H-2'), 4.98 (d, 1H, $J_{1,2}$ = 1.8 Hz, H-1'), 4.78 (d, 1H, $J_{1,2}$ = 1.6 Hz, H-1"), 4.59 (dd, 1H, $J_{2,3}$ = 3.5 Hz, $J_{1,2}$ = 3.0 Hz, H-2), 3.86 (dd, 1H, $J_{2,3}$ = 3.5 Hz, $J_{3,4}$ = 9.8 Hz, H-3), 3.79 (dd, 1H, $J_{5,6}$ = 6.4 Hz, $J_{5,6'}$ = 10.6 Hz, H-6), 3.63 (m, 1H, H-5), 3.57 (dd, $J_{5,6'}$ = 3.0 Hz, $J_{6,6'}$ = 10.6 Hz, H-6'), 3.30 (s, 3H, OCH_3), 2.17, 2.16, 2.15, 2.11, 2.10, 2.06, 2.05, 2.00, 1.99 (9 x s, 27H, $COCH_3$), 1.73 (s, 3H, $OCOCH_3$); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ: 170.71 - 169.65 (9 x $COCH_3$), 124.25 ($OCOCH_3$), 99.69 (C-1), 97.72, 97.58 (C-1' and C-1"), 78.85, 72.48, 69.77, 69.41, 69.35, 69.17, 68.85, 68.58, 66.93, 65.95, 65.85 (C-2,2',2", C-3,3',3", C-4,4',4", and C-5,5',5"), 67.77 (C-6), 62.29, 62.22 (C-6' and C-6"), 50.24 (OCH_3), 23.72 ($OCCH_3$), 20.92 - 20.65 ($COCH_3$); Anal. calcd. for $C_{39}H_{54}O_{26}$: C 49.89, H 5.80; found: C 49.79, H 6.04.

4-O-benzyl-3,6-di-O-(2,3,4,6-tetra-O-benzyl-α-D-mannopyranosyl)-1,2-methoxyethylidene-β-D-mannopyranoside (**51**)

The acetylated ortho ester **50** (974 mg, 1.04 mmol) was dissolved in 20 ml of methanol and catalytic sodium methoxide (5 mg) was added to the reaction. The solution was stirred overnight and concentrated, without neutralization, to a white foam. In a separate flask, sodium hydride (1.25 g, 31.2 mmol) and dimethylformamide (50 ml) were combined and stirred for 30 minutes. The crude mixture was dissolved in 3 x 5 ml DMF and transferred to the NaH / DMF suspension. In one portion, 18-crown-6 (1.37 g, 5.2 mmol) was then added to the reaction flask. After the mixture was stirred for 30 minutes, benzyl bromide (3.7 ml, 31.2 mmol) was dissolved in 10 ml DMF and added in a

organic layer was dried ($MgSO_4$), filtered and concentrated. Thirty percent (30%) ethyl acetate in hexane which contained 0.1% triethylamine was used as an eluent for chromatographic purification of the crude mixture. Product **51** (1.03 g, 72%) was obtained as a colorless syrup; $[\alpha]_D$ +27.6° (c 0.55, CH_2Cl_2); R_f 0.37 in ethyl acetate - hexane, 2:3; ^1H NMR (360 MHz, $CDCl_3$) δ: 5.24 (d, 1H, $J_{1,2}$ = 2.5 Hz, H-1), 5.16 (d, 1H, $J_{1,2}$ = 1.6 Hz, H-1'), 4.96 (d, 1H, $J_{1,2}$ = 1.7 Hz, H-1"), 3.20 (s, 3H, OCH_3), 1.62 (s, 3H, $OCCH_3$); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ: 124.10 ($OCOCH_3$), 101.17, 98.67, 97.48 (C-1, C-1', and C-1"), 80.45, 80.23, 79.63, 79.30, 75.61, 75.05, 74.50, 73.51, 72.76, 72.27 (C-2,2',2", C-3,3',3", C-4,4',4", and C-5,5',5"), 75.12, 73.60, 73.31, 72.72, 72.61, 72.42, 71.82 (9 x CH_2Ph), 69.52, 69.12, 66.41 (C-6, C-6', and C-6"), 49.74 (OCH_3), 25.13 ($OCCH_3$); Anal. calcd. for $C_{84}H_{90}O_{17}$: C 73.56, H 6.61; found: C 73.40, H 6.78.

Ethyl 2-O-acetyl-4-O-benzyl-3,6-di-O-(2,3,4,6-tetra-O-benzyl-α-D-mannopyranosyl)-1-thio-α-D-mannopyranoside (**52**)

The ortho ester **51** (460 mg, 0.335 mmol) was added to a round bottom flask and purged with argon. Ethanethiol (10 ml) was added to the flask and the solution was cooled to 0°C. Boron trifluoride etherate (0.041 ml, 0.335 mmol) was syringed into the stirred mixture. The reaction was quenched after six minutes by the addition of water. The ethanethiol was removed in the fumehood by warming the solution to 40°C. A stream of air was then blown over the mixture for several hours to ensure complete removal of all the thiol. Dichloromethane (50 ml) was added to the solution and it was washed with water (40 ml). The organic layer was separated, dried ($MgSO_4$), filtered and concentrated. Twenty percent (20%) ethyl acetate in hexane was used as an eluent

H-1), 5.16 (d, 1H, $J_{1,2}$ = 1.6 Hz, H-1'), 5.00 (d, 1H, $J_{1,2}$ = 1.4 Hz, H-1"), 2.55 (m, 2H, SCH_2CH_3), 2.00 (s, 3H, $COCH_3$), 1.22 (t, 3H, SCH_2CH_3); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ: 170.03 ($COCH_3$), 100.39, 98.18 (C-1' and C-1"), 81.98 (C-1), 79.89, 79.95, 78.39, 75.34, 74.90, 74.88, 74.06, 73.03, 72.00, 71.71, 71.55, 70.73 (C-2,2',2", C-3,3',3", C-4,4',4", and C-5,5',5"), 75.12, 73.45, 73.27, 72.57, 72.45, 72.36, 72.08, 71.89 , 70.78 (9 x CH_2Ph), 69.16, 68.86, 66.07 (C-6, C-6', and C-6"), 25.53 (SCH_2CH_3), 21.11 ($COCH_3$), 14.95 (SCH_2CH_3); Anal. calcd. for $C_{85}H_{92}O_{16}S$: C 72.83, H 6.62, S 2.29; found: C 72.79, H 6.68, S 2.54.

Ethyl 4-O-benzyl-3,6-di-O-(2,3,4,6-tetra-O-benzyl-α-D-mannopyranosyl)-2-O-(2-propenyl)-1-thio-α-D-mannopyranoside (**53**)

The 2-*O*-acetate **52** (209 mg, 0.149 mmol) was added to a reaction vessel and purged with argon. Toluene (10 ml), tetrahydrofuran (3.3 ml) and pyridine (0.1 ml) were consecutively added to the solution and it was cooled to -40°C. Freshly prepared Tebbe's reagent (0.60 ml, 0.60 mmol) was slowly syringed into the mixture. After 70 minutes, the reaction temperature had reached -10°C and it was quenched by the addition of 1 ml of 1N NaOH. The deep red mixture was filtered through a celite pad and washed with ether (100 ml). The filtrate was dried ($MgSO_4$), filtered and concentrated to give an orange oil. Column chromatography was used to purify the oil (18 % ethyl acetate in hexane was used as an eluent) which gave 186 mg (89%) of a viscous, clear syrup; R_f 0.72 in ethyl acetate - hexane, 1:2; ^1H NMR (360 MHz, $CDCl_3$) δ: 5.46 (d, $J_{1,2}$ = 1Hz, H-1), 5.13 (d, $J_{1,2}$ = 1.8 Hz, H-1'), 5.01 (d, 1H, $J_{1,2}$ = 1.6 Hz, H-1"), 2.50 (m, 2H, SCH_2CH_3), 1.76 (s, 3H, $CH_2=CCH_3$), 1.18 (t, 3H, SCH_2CH_3); ^{13}C NMR (75.5 MHz, $CDCl_3$ + 10% D-5 pyridine) δ: 157.23 ($C=CH_2$), 100.28, 97.82 (C-1', and C-1"), 83.28

68.61, 65.72 (C-6, C-6', and C-6"), 24.91 (SCH_2CH_3), 20.97 ($CH_3C=CH_2$), 14.72 (SCH_2CH_3).

Attempted acetalization of the trisaccharide **53**

The vinyl ether **53** (182 mg, 0.13 mmol) and the alcohol **12** (72.5 mg, 1.2 eq.) were added to a reaction flask. Calcium sulfate (1 g) was then added and the flask purged with argon. Dichloromethane was added to the stirred reaction mixture and it was cooled to -40°C. After 30 minutes, camphorsulfonic acid (0.08 eq.) was added. The reaction was stirred at -40°C for 4 hours and quenched by the addition of triethylamine. Unreacted vinyl ether **53** was recovered (84 mg, 46%). In addition, 62 mg of **12** and 78 mg of hydrolyzed vinyl ether **60** were recovered.

60: R_f 0.59 in ethyl acetate - hexane, 1:2; ^1H NMR (360 MHz, $CDCl_3$) δ: 5.05, 5.00, 4.96 (H-1, H-1', and H-1"), 3.36 (s, 1H, OH), 2.50 (m, 2H, SCH_2CH_3); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ: 99.50, 98.13 (C-1', and C-1"), 84.67 (C-1), 83.31, 79.94, 79.68, 75.51, 75.41, 74.65, 73.82, 72.21, 71.78, 71.44, 70.75 (C-2, C-3, C-4, C-5, C-2', C-3', C-4', C-5', C-2", C-3", C-4", and C-5"), 69.93, 69.24, 66.23 (C-6, C-6', and C-6"), 25.05 (SCH_2CH_3), 14.99 (SCH_2CH_3).

Allyl 4-O-acetyl-3,6-di-O-benzyl-2-deoxy-2-phthalimido-β-D-glucopyranoside (**55**)

The alcohol **54**[186] (1.65 g, 3.12 mmol) was dissolved in 50 ml of pyridine. Acetic anhydride (10 ml) was added to the reaction and it was stirred overnight at ambient temperature. Dichloromethane (200 ml) was added to the mixture. The organic layer was washed 2 x 200 ml with saturated sodium bicarbonate solution and 1 x 200 ml with saturated sodium chloride solution. The organic layer was dried ($MgSO_4$), filtered

$[\alpha]_D$ +66.3° (*c* 0.80, CH_2Cl_2); R_f 0.46 in ethyl acetate - hexane, 1:2; ^1H NMR (300 MHz, $CDCl_3$) δ: 7.80 - 7.60 (m, 4H, phthalimido), 7.40 - 7.25, 7.05 - 6.85 (m, 10H, benzyl), 5.68 (dddd, 1H, J_{trans} = 17.3 Hz, J_{cis} = 10.6 Hz, J_{vic} = 6.4 Hz, $J_{vic'}$ = 5.2 Hz, $OCH_2CH{=}CH_2$), 5.19 (d, 1H, $J_{1,2}$ = 8. 5 Hz, H-1), 5.12 (dd, 1H, $J_{3,4}$ = 9.0 Hz, $J_{4,5}$ = 9.2 Hz, H-4), 5.10, 5.01 (2 x dddd, 2H, $OCH_2CH{=}CHH'$), 4.60, 4.32 (2 x d, 2H, J_{gem} = 12.0 Hz, OCH_2Ph), 4.56 (s, 2H, OCH_2Ph), 4.44 (dd, 1H, $J_{2,3}$ = 10.6 Hz, $J_{3,4}$ = 9.0 Hz, H-3), 4.31 (dd, 1H, $J_{2,3}$ = 10.6 Hz, $J_{1,2}$ = 8.5 Hz, H-2), 4.25, 4.01 (dddd, 2H, $OCH_2CH{=}CH_2$), 3.75 (dt, 1H, $J_{4,5}$ = 9.2 Hz, $J_{5,6}$ = 4.6 Hz, H-5), 3.62 (d, 2H, $J_{5,6}$ = 4.6 Hz, H-6), 1.96 (s, 3H, $COCH_3$); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ: 169.68 ($COCH_3$), 138.01, 137.76, 128.4 - 127.5 (benzyl aromatic), 133.7,131.68, 123.37 (phthalimido), 133.58 ($OCH_2CH{=}CH_2$), 117.49 ($OCH_2CH{=}CH_2$), 97.32 (C-1), 77.06, 73.56, 72.63 (C-3, C-4, and C-5), 55.50 (C-2), 73.82, 73.67 (2 x OCH_2Ph), 69.84 (C-6, and OCH_2, octyl), 20.93 ($COCH_3$); Anal. calcd. for $C_{33}H_{33}O_8N$: C 69.34, H 5.82, N 2.45; found: C 68.88, H 5.95, N 2.49.

4-O-Acetyl-3,6-di-O-benzyl-2-deoxy-2-phthalimido-α,β-D-glucopyranose (**56**)

The allyl glycoside **55** (1.61 g, 2.82 mmol) was dissolved in 110 ml of a 7:3:1 mixture of ethanol, toluene, and water. 1,4-Diazabicyclo[2.2.2]octane (DABCO, 142 mg, 1.27 mmol, 0.45 eq.) was first added to the reaction mixture followed by tris(triphenylphosphine)rhodium(I) chloride (Wilkinson's catalyst, 391 mg, 0.42 mmol, 0.15 eq.). The mixture was refluxed for 44 hours, cooled and concentrated to a black solution. This solution was dissolved in 50 ml of acetone. Mercuric oxide (15 mg, 0.005 eq.) was first added to the black solution, followed by 50 ml of a 9:1 mixture of acetone - water which contained 3.8 g (14.1 mmol, 5 eq.) of dissolved mercuric chloride. After 12

washed 3 x 200 ml with a saturated potassium iodide solution and 2 x 200 ml with dH_2O. The organic layer was then dried ($MgSO_4$), filtered and concentrated. Ethyl acetate - hexane (1:2) was used as an eluent for chromatographic purification of the crude reaction mixture. Product **56** was isolated (1.12 g, 75%) as a 85:15 mixture of β:α anomers; R_f 0.14 in ethyl acetate - hexane, 1:2; ^1H NMR, β anomer only, (360 MHz, $CDCl_3$) δ : 7.80 - 7.60 (m, 4H, phthalimido), 7.40 - 7.25, 7.05 - 6.90 (m, 10H, benzyl aromatic), 5.38 (dd, 1H, $J_{1,2}$ = 8.2 Hz, $J_{1,OH}$ = 6 Hz, H-1β), 5.17 (dd, 1H, $J_{3,4}$ = 9.0 Hz, $J_{4,5}$ = 9.8 Hz, H-4), 4.63, 4.36 (2 x d, 2H, J_{gem} = 12.3 Hz, OCH_2Ph), 4.58 (s, 2H, OCH_2Ph), 4.52 (dd, 1H, $J_{1,2}$ = 8.2 Hz, $J_{2,3}$ = 10.6 Hz, H-2), 4.20 (dd, 1H, $J_{2,3}$ = 10.6 Hz, $J_{3,4}$ = 9.0 Hz, H-3), 3.82 (m, 1H, H-5), 3.60 (m, 2H, H-6), 2.92 (d, 1H, $J_{H,OH}$ = 6 Hz, OH), 1.93 (s, 3H, CH_3, acetate); ^{13}C NMR, β anomer only, (75.5 MHz, $CDCl_3$) δ: 169.65 (CO, acetate), 133.95, 131.62, 123.42 (phthalimido), 137.72, 128.4 - 127.3 (benzyl aromatics), 92.94 (C-1), 76.78, 73.57, 72.28 (C-3, C-4, and C-5), 57.18 (C-2), 73.90, 73.69 (2 x OCH_2Ph), 69.38 (C-6); Anal. calcd. for $C_{30}H_{29}O_8N$: C 67.79, H 5.50, N 2.64; found: C 67.54, H 5.64, N 2.51.

4-O-Acetyl-3,6-di-O-benzyl-2-deoxy-2-phthalimido-α,β-D-glucopyranosyl chloride (**57**)

The reducing sugar **56** (600 mg, 1.13 mmol) was dissolved in dry dichloromethane (10 ml) under argon atmosphere. In a separate flask, Vilsmeier reagent was prepared by the addition of 0.84 ml (10.8 mmol) of dimethylformamide (DMF) to 8.2 ml of chloroform. Oxalyl chloride (0.94 ml, 10.8 mmol) was syringed into the DMF / chloroform solution which formed a deep yellow color. The Vilsmeier reagent was stirred for 15 minutes and it had a concentration of 1.08 mmol / ml. In one portion, the Vilsmeier solution (5.2 ml, 5.6 mmol, 5 eq.) was added to the reducing sugar **56** and

was washed with 2 x 100 ml of dH_2O. The organic layer was dried ($MgSO_4$), filtered and concentrated to give 620 mg of a bright yellow solid **57**; R_f 0.55 (α), 0.45 (β) in ethyl acetate - hexane, 1:2. ^1H NMR (360 MHz, $CDCl_3$) δ: 6.22 (d, 0.45H, $J_{1,2}$ = 3.8 Hz, H-1α), 5.99 (m, 0.55H, $J_{1,2}$ = 9.2 Hz, H-1β), 5.43 (dd, 0.45H, $J_{2,3}$ = 11.0 Hz, $J_{3,4}$ = 9.0 Hz, H-3α), 5.31 (dd, 0.45H, $J_{3,4}$ = 9.0 Hz, $J_{4,5}$ = 9.0 Hz, H-4α), 5.21 (m, 0.55H, H-4β), 4.64 (dd, 0.45H, $J_{1,2}$ = 3.8 Hz, $J_{2,3}$ = 11.0 Hz, H-2α), 4.43 (m, 1.1H, H-3β, and H-2β), 4.33 (m, 0.45H, H-5α), 3.85 (m, 0.55H, H-5β), 3.62 (m, 2H, H-6α, H-6β, H-6'α, and H-6'β), 1.94 (s, 1.65H, $COCH_3$, β), 1.90 (s, 1.35H, $COCH_3$, α); ^{13}C NMR, α only, (75.5 MHz, $CDCl_3$) δ: 169.74 ($COCH_3$), 92.76 (C-1), 74.20, 73.90 (2 x OCH_2Ph), 73.86, 72.67, 72.16 (C-3, C-4, and C-5), 57.54 (C-2), 68.49 (C-6), 21.06 ($COCH_3$).

Octyl 4-O-(4-O-acetyl-3,6-di-O-benzyl-2-deoxy-2-phthalimido-β-D-glucopyranosyl)-3,6-di-O-benzyl-2-deoxy-2-phthalimido-β-D-glucopyranoside (**58**)

The octyl glycoside acceptor **24** (340 mg, 0.565 mmol), 4Å molecular sieves and silver triflate (363 mg, 1.41 mmol, 2.5 eq.) were added to a reaction vessel and purged with argon. Dry dichloromethane (6 ml) and sym-collidine (0.1 ml, 0.85 mmol, 1.5 eq.) were added to the vessel and the reaction mixture was stirred for 30 minutes. The mixture was cooled to -15°C. The chloride **57** (620 mg, 1.13 mmol, 2 eq.) was dissolved in 2 x 2 ml of dichloromethane and added in a dropwise fashion to the acceptor. A white color was observed during the chloride addition (AgCl). The reaction mixture was stirred at room temperature for 60 hours and then it was diluted with 75 ml of dichloromethane. The organic layer was filtered, washed with 75 ml dH_2O, 75 ml 1N HCl, 75 ml saturated sodium bicarbonate and 75 ml with brine. The organic layer was then dried ($MgSO_4$),

an eluent for chromatographic purification of the crude reaction mixture. Purification yielded the disaccharide **58** (423 mg, 67%) and the recovered acceptor **24** (70 mg, 21%); R_f 0.63 in ethyl acetate - toluene, 1:3; ^1H NMR (500 MHz, $CDCl_3$) δ: 5.33 (d, 1H, $J_{1,2}$ = 8.4 Hz, H-1'), 5.15 (dd, 1H, $J_{3,4}$ = 9.0 Hz, $J_{4,5}$ = 9.0 Hz, H-4'), 4.93 (d, 1H, $J_{1,2}$ = 8.1 Hz, H-1), 1.91 (s, 3H, $COCH_3$); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ: 169.67 ($COCH_3$,), 98.18, 97.21 (C-1, and C-1'), 76.93, 76.93, 76.40, 74.61, 73.45, 72.74 (C-3, C-4, C-5, C-3', C-4', and C-5'), 74.43, 73.92, 73.60, 72.74 (4 x OCH_2Ph), 69.49, 69.40 (C-6, and C-6'), 68.23 (OCH_2, octyl), 56.32, 55.79 (C-2, and C-2'), 31.64, 29.24, 29.12, 25.80, 22.58 (6 x CH_2, octyl), 20.93 ($COCH_3$), 14.04 (CH_3, octyl).

Octyl 3,6-di-O-benzyl-4-O-(3,6-di-O-benzyl-2-deoxy-2-phthalimido-β-D-glucopyranosyl)-2-deoxy-2-phthalimido-β-D-glucopyranoside (**59**)

The disaccharide **58** (423 mg, 0.38 mmol) was dissolved in 10 ml of dry methanol and 5 mg of sodium methoxide was added to the flask. The reaction mixture was stirred overnight and then it was neutralized with Amberlite IRC-120 (H^+) resin. The mixture was filtered to remove the Amberlite resin and concentrated. Fifteen percent (15%) ethyl acetate in toluene was used as an eluent for chromatographic purification of the reaction mixture. Product **59** (282 mg, 69%) was obtained as a colorless syrup; $[\alpha]_D$ -12.6° (*c* 0.70, CH_2Cl_2); R_f 0.50 in ethyl acetate - toluene, 1:3; ^1H NMR (360 MHz, $CDCl_3$) δ: 7.9 - 7.5 (m, 8H, 2 x phthalimido), 7.4 - 6.8 (m, 20H, benzyl aromatics), 5.30 (d, 1H, $J_{1,2}$ = 8.1 Hz, H-1'), 4.92 (d, 1H, $J_{1,2}$ = 7.8 Hz, H-1), 4.25 (dd, 1H, $J_{2,3}$ = 10.5 Hz, $J_{3,4}$ = 8.5 Hz, H-3'), 4.2 (m, 4H, H-2, H-3, H-4, and H-2'), 3.82 (ddd, 1H, $J_{3,4}$ = 8.5 Hz, $J_{4,5}$ = 8.5 Hz, $J_{H,OH}$ = 1.9 Hz, H-4'), 3.65, 3.23 (2 x m, 2H, OCHH', octyl), 3.09 (d, 1H, $J_{H,OH}$ = 1.9 Hz, OH), 2.3 - 0.7 (m, 15H, octyl); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ: 167.72 (C=O, phthalimido), 98.18, 97.08 (C-1, and C-1'), 78.41, 76.88, 75.94, 75.52,

OCH_2Ph), 71.06, 69.42 (C-6, and C-6'), 68.31 (OCH_2, octyl), 56.18, 55.78 (C-2, and C-2'), 31.65, 29.24, 29.11, 25.81, 22.59 (6 x CH_2, octyl), 14.05 (CH_3, octyl); Anal. calcd. for $C_{64}H_{68}O_{13}N_2$: C 71.61, H 6.39, N 2.62; found: C 71.68, H 6.32, N 2.56.

3,4-Di-O-acetyl-6-O-(2,3,4,6-tetra-O-acetyl-α-D-mannopyranosyl)-1,2-methoxyethylidene)-β-D-mannopyranoside (**62**)

The per acetate **61**[193] (4.0 g, 5.9 mmol) was dissolved in dichloromethane and cooled to 0°C. Hydrobromic acid gas was passed through a $CaSO_4$ drying tube and bubbled through the dichloromethane solution for 30 minutes. The solution was concentrated *in vacuo*, co-evaporated twice with toluene and dried under high vacuum for 2 hours to give a golden foam. The foam was dissolved in dichloromethane (150 ml) and 2,6-lutidine (1.8 ml, 14.7 mmol, 2.5 eq.) was syringed into the mixture. Methanol (0.6 ml, 14.7 mmol, 2.5 eq.) was added to the reaction mixture and it was stirred for 60 hours. Dichloromethane (100 ml) was added to the mixture and the organic layer was washed with 250 ml of saturated sodium bicarbonate solution and 3 x 250 ml with dH_2O. The organic layer was dried ($MgSO_4$), filtered and concentrated to give 4.0 g of a crude foam (~ 100%). A portion of this foam was purified for characterization. The solvent system used for chromatographic purification was ethyl acetate in hexane (1:1). Purification yielded a white solid **62**; $[\alpha]_D$ +47.8° (*c* 0.80, CH_2Cl_2; R_f 0.52 in ethyl acetate - hexane, 7:3; ^1H NMR (360 MHz, $CDCl_3$) δ: 5.52 (d, 1H, $J_{1,2}$ = 2.8 Hz, H-1), 5.30 (m, 2H, H-2', and H-4'), 5.24 (m, 1H, H-3'), 5.23 (dd, 1H, $J_{4,5}$ = 9 Hz, $J_{3,4}$ = 9.8 Hz, H-4), 5.15 (dd, 1H, $J_{3,4}$ = 9.8 Hz, $J_{2,3}$ = 3.8 Hz, H-3), 4.80 (d, 1H, $J_{1,2}$ = 1.7 Hz, H-1'), 4.62 (dd, 1H, $J_{1,2}$ = 2.8 Hz, $J_{2,3}$ = 3.8 Hz, H-2), 4.33 (dd, 1H, $J_{5,6}$ = 5.0 Hz, $J_{6,6'}$ = 12.6 Hz, H-6b), 4.06 (m, 2H, H-5' and H-6b'), 3.79 (dd, 1H, $J_{5,6}$ = 5.8 Hz, $J_{6,6'}$ = 10.2 Hz, H-6a), 3.69 (ddd, 1H, $J_{5,6}$ = 5.8 Hz, $J_{5,6'}$ = 3.0 Hz, $J_{4,5}$ = 9 Hz, H-5), 3.60 (dd, 1H, $J_{5,6'}$ = 3.0 Hz, $J_{6,6'}$ = 10.2 Hz, H-6b), 3.28 (s, 3H, OCH_3), 2.15, 2.13, 2.10, 2.08, 2.06, 1.99 (6 x s,

18H, COC*H*3), 1.72 (s, 3H, C*H*3COCH3, ortho ester); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ: 170.66, 170.37, 169.98, 169.76, 169.69 (6 x *C*OCH3), 124.34 (CH_3COCH_3, ortho ester), 97.78 (C-1), 97.46 (C-1'), 76.32, 72.22, 70.51, 69.35, 69.09, 68.63, 66.41, 65.94 (C-2, C-3, C-4, C-5, C-2', C-3', C-4', and C-5'), 67.60 (C-6'), 62.30 (C-6), 50.05 (OCH_3), 24.17 (*C*H3COCH3, ortho ester), 20.88 - 20.68 (CO*C*H3); Anal. calcd. for $C_{27}H_{38}O_{18}$: C 49.85, H 5.89; found: C 49.58, H 5.85.

3,4-Di-O-benzyl-6-O-(2,3,4,6-tetra-O-benzyl-α-D-mannopyranosyl)-1,2-(methoxyethylidene)-α-D-mannopyranoside (**63**)

The crude per acetylated ortho ester **62** (4.0 g, 5.9 mmol) was dissolved in 150 ml of dry methanol and 30 mg of sodium methoxide was added to the flask. The reaction mixture was stirred overnight. The mixture was concentrated *in vacuo* and dried under high vacuum which gave a white foam (2.6 g, ~ 100%) . A portion of this foam (2.0 g, 4.5 mmol) was dissolved in 80 ml of dry dimethylformamide (DMF) and added to a dropping funnel. In a separate flask, sodium hydride (3.0 g, 75 mmol, 60% dispersion in oil) was mixed with 120 ml DMF and stirred for 30 minutes. The suspension was cooled to 0°C. The ortho ester was added in a dropwise fashion to the DMF / NaH suspension over a 15 minute period. After the suspension was stirred at 0°C for 30 minutes, a thick gelatinous mixture was formed. Benzyl bromide (8.9 ml, 75 mmol) was diluted with DMF (20 ml) and added in a dropwise fashion to the reaction mixture over a 10 minute period. The solution became less viscous and was allowed to warm to room temperature overnight. The reaction was quenched by the addition of methanol (50 ml) and concentrated under reduced pressure to a total volume of 150 ml. Dichloromethane (150 ml) was then added to the mixture. This mixture was washed 2 x 300 ml with dH_2O and then with 300 ml of a saturated solution of sodium chloride. The organic layer was dried ($MgSO_4$), filtered and concentrated. Purification by column chromatography (28% ethyl acetate in hexane which contained 0.1% triethylamine was used as an eluent) produced a

colorless syrup **63** (2.26 g, 41% from **61**); $[\alpha]_D$ +24.4° (*c* 0.95, CH_2Cl_2); R_f 0.30 in ethyl acetate - hexane, 2:3; ^1H NMR (360 MHz, $CDCl_3$) δ: 7.45 - 7.12 (m, 30H, aromatic), 5.33 (d, 1H, $J_{1,2}$ = 2.4 Hz, H-1), 5.00 (d, 1H, $J_{1,2}$ = 1.8 Hz, H-1'), 4.92, 4.49 (2 x d, 2H, J_{gem} = 11.0 Hz, OC*H*$_2$Ph), 4.89, 4.55 (2 x d, 2H, J_{gem} = 11.2 Hz, OC*H*$_2$Ph), 4.79 (s, 2H, OC*H*$_2$Ph), 4.72 (s, 2H, OC*H*$_2$Ph), 4.62, 4.43 (2 x d, 2H, J_{gem} = 12.2 Hz, OC*H*$_2$Ph), 4.62, 4.61 (2 x d, 2H, J_{gem} = 11.5 Hz, OC*H*$_2$Ph), 4.40 (dd, 1H, $J_{1,2}$ = 2.4 Hz, $J_{2,3}$ = 3.8 Hz, H-2), 4.02 (dd, 1H, $J_{3,4}$ = 9.2 Hz, $J_{4,5}$ = 9.2 Hz, H-4'), 3.95 (dd, 1H, $J_{5,6}$ = 4.0 Hz, $J_{6,6'}$ = 11.4 Hz, H-6a'), 3.89 (dd, 1H, $J_{2,3}$ = 3.0 Hz, $J_{3,4}$ = 9.4 Hz, H-3'), 3.83 (dd, 1H, $J_{3,4}$ = 9.2 Hz, $J_{4,5}$ = 9.2 Hz, H-4), 3.82 (dd, 1H, $J_{1,2}$ = 1.8 Hz, $J_{2,3}$ = 3.0 Hz, H-2'), 3.73 (dd, 1H, $J_{2,3}$ = 3.8 Hz, $J_{3,4}$ = 9.2 Hz, H-3), 3.73 (m, 1H, H-5), 3.68 (m, 2H, H-6a, and H-6'b), 3.61 (dd, 1H, $J_{5,6}$ = 1.6 Hz, $J_{6,6'}$ = 10.8 Hz, H-6a') 35 (m, 1H, H-5'), 3.28 (s, 3H, OCH_3), 1.69 (s, 3H, *C*H_3COCH$_3$); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 138.7 - 137.8, 128.9 - 127.4 (aromatics), 123.95 (CH$_3$*C*OCH$_3$, ortho ester), 98.61 (C-1), 97.53 (C-1'), 79.88, 79.37, 77.14, 74.81, 74.68, 73.90, 73.35, 72.21 (6 x O*C*H$_2$Ph, C-6, and C-6'), 75.19, 74.98, 73.31, 72.62, 72.28, 71.95, 69.19, 66.34 (C-2, C-3, C-4, C-5, C-2', C-3', C-4', and C-5'), 49.73 (OCH_3), 24.71 (*C*H$_3$COCH$_3$, ortho ester); Anal. calcd. for $C_{57}H_{62}O_{12}$: C 72.90, H 6.65; found: C 73.17, H 6.79.

Ethyl 2-O-acetyl-3,4-di-O-benzyl-6-O-(2,3,4,6-tetra-O-benzyl-α-D-mannopyranosyl)-1-thio-α-D-mannopyranoside (**64**)

The ortho ester **63** (1.26 g, 1.34 mmol) was added to a reaction flask and purged with argon. Ethanethiol (15 ml) was added to the flask and the solution was cooled to 0°C. Boron trifluoride etherate (0.17 ml, 1.34 mmol) was syringed into the stirred mixture. The reaction was quenched after 10 minutes by the addition of dH_2O (10 ml). In the fumehood, the ethanethiol was removed by blowing a stream of air over the mixture for 2 hours. Dichloromethane (100 ml) was added and the mixture was washed 2 x 100 ml with distilled water. The organic layer was dried ($MgSO_4$), filtered and

concentrated to give a pale yellow syrup. The oil was chromatographed (15% ethyl acetate in hexane was used as an eluent) which gave a colorless syrup **64** (1.06 g, 81%); $[\alpha]_D$ +64.9° (*c* 1.50, CH_2Cl_2), R_f 0.59 in ethyl acetate - hexane, 1:2. ^1H NMR (300 MHz, $CDCl_3$) δ: 7.40 - 7.10 (m, 30 H, aromatics), 5.42 (dd, 1H, $J_{1,2}$ = 1.5 Hz, $J_{2,3}$ = 3.2 Hz, H-2), 5.22 (d, 1H, $J_{1,2}$ = 1.3 Hz, H-1'), 5.03 (d, 1H, $J_{1,2}$ = 1.5 Hz, H-1), 4.86, 4.45 (2 x d, 2H, J_{gem} = 12 Hz, OC*H*$_2$Ph), 4.86, 4.47 (2 x d, 2H, J_{gem} = 11.0 Hz, OC*H*$_2$Ph), 4.76, 4.71 (2 x d, 2H, J_{gem} = 12 Hz, OC*H*$_2$Ph), 4.66, 4.49 (2 x d, 2H, J_{gem} = 10.8 Hz, OC*H*$_2$Ph), 4.63, 4.56 (2 x d, 2H, J_{gem} = 12.2 Hz, OC*H*$_2$Ph), 4.63, 4.44 (2 x d, 2H, J_{gem} = 10.4 Hz, OC*H*$_2$Ph), 4.13 (m, 1H, H-5), 4.01 (dd, 1H, $J_{3,4}$ = 9.5 Hz, $J_{4,5}$ = 9.5 Hz, H-4), 3.91 (dd, 1H, $J_{5,6}$ = 4.8 Hz, $J_{6,6'}$ = 11.0 Hz, H-6a'), 3.89 (m, 4H, H-2, H-3, H-2', and H-3'), 3.75 (dd, 1H, $J_{4,5}$ = 9.2 Hz, $J_{3,4}$ = 9.2 Hz, H-4'), 3.74 (m, 1H, H-5'), 3.68 (dd, 1H, $J_{5,6}$ = 4.8 Hz, $J_{6,6'}$ = 10.8 Hz, H-6a), 3.66 (dd, 1H, $J_{5,6'}$ = 1.7 Hz, $J_{6,6'}$ = 11.0 Hz, H-6b'), 3.60 (dd, 1H, $J_{5,6'}$ = 1.7 Hz, $J_{6,6'}$ = 10.8 Hz, H-6b), 2.55 (m, 2H, J_{vic} = 7.8 Hz, SC*H*$_2$CH$_3$), 2.06 (s, 3H, COC*H*$_3$), 1.21 (t, 3H, J_{vic} = 7.5 Hz, SCH$_2$C*H*$_3$); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ: 138.73 - 137.66, 128.44 - 127.45 (aromatic), 98.09 (C-1'), 82.28 (C-1), 79.85, 78.74, 74.89, 74.89, 74.55, 71.98, 71.46, 70.48 (C-2, C-3, C-4, C-5, C-2', C-3', C-4', and C-5'), 75.06, 75.06, 73.30, 72.55, 71.88, 71.88 (6 x OCH$_2$Ph), 69.20, 66.13 (C-6 and C-6'), 25.41 (SCH$_2$*C*H$_3$), 21.10 (CO*C*H$_3$), 14.94 (SCH$_2$*C*H$_3$); Anal. calcd. for $C_{58}H_{64}O_{11}S$: C 71.88, H 6.66, S 3.31; found: C 71.90, H 6.69, S 3.23.

Ethyl 3,4-di-O-benzyl-6-O-(2,3,4,6-tetra-O-benzyl-α-D-mannopyranosyl)-2-O-(2-propenyl)-1-thio-α-D-mannopyranoside (**65**)

The thioglycoside **64** (583 mg, 0.60 mmol) was added to a round bottom flask and purged with argon. Dry toluene (9 ml), tetrahydrofuran (3 ml) and pyridine (0.1 ml) were consecutively syringed into the flask and the mixture was cooled to -40°C. Tebbe's reagent (1.20 ml, 1.2 mmol, 2.0 eq.) was slowly syringed into the mixture. The reaction color became deep red. The solution was allowed to slowly warm to -10°C and after 2.5

hours it was quenched by the addition of 0.1 ml of 1M NaOH (vigorous methane evolution). After the gas evolution subsided, the mixture was warmed to room temperature and a further 0.5 ml of 1M NaOH was added. The deep red mixture was filtered through a celite bed which removed aluminum salts (orange). The celite bed was washed with ether until only a faint orange color was observed entering the filtrate. The clear red filtrate was concentrated under reduced pressure and was purified by column chromatography. The chromatography eluent used was 15% ethyl acetate in hexane which contained 0.1% triethylamine. A clear syrup was obtained **65** (402 mg, 69%); R_f 0.57 in ethyl acetate - hexane, 1:3. ^1H NMR (300 MHz, $CDCl_3$ + 2% D-5 pyridine) δ: 7.40 - 7.10 (m, 30H, aromatic), 5.46 (d, 1H, $J_{1,2}$ = 1Hz, H-1'), 5.05 (d, 1H, $J_{1,2}$ = 1Hz, H-1), 4.89, 4.47 (2 x d, 2H, J_{gem} = 10.8 Hz, OCH_2Ph), 4.87, 4.45 (2 x d, 2H, J_{gem} = 11.0 Hz, OCH_2Ph), 4.75, 4.70 (2 x d, 2H, J_{gem} = 12.0 Hz, OCH_2Ph), 4.63, 4.56 (2 x d, 2H, J_{gem} = 12 Hz, OCH_2Ph), 4.63, 4.44 (2 x d, 2H, J_{gem} = 11.5 Hz, OCH_2Ph), 4.40 (d, 1H, J_{gem} = 2.0 Hz, C=C*H*H'), 4.09 (m, 1H, H-5), 4.01 (d, $J_{4,5}$ = 9.0 Hz, $J_{3,4}$ = 9.0 Hz, H-4), 3.76 (d, 1H, J_{gem} = 2.0 Hz, C=CH*H'*), 3.74 (m, 1H, H-5'), 2.53 (m, 2H, SCH_2CH_3), 2.31 (s, 3H, $CH_3C=CH_2$), 1.20 (t, 3H, SCH_2CH_3); ^{13}C NMR (75.5 MHz, D-5 pyridine) δ: 158.73 (*C*=CH2), 139.58 - 138.84, 129.27 - 127.69 (aromatics), 98.44 (C-1'), 83.37 (C=CH_2), 80.84 (C-1), 80.26, 75.93, 75.45, 75.31, 74.34, 72.62, 72.01 (C-2, C-3, C-4, C-5, C-2', C-3', C-4', and C-5'), 75.31, 75.18, 73.38, 73.02, 71.69, 71.58 (6 x OCH_2Ph), 69.94, 66.75 (C-6 and C-6'), 25.39 (SCH_2CH_3), 21.31 ($CH_3C=CH_2$), 15.18 (SCH_2CH_3).

Octyl 3,6-di-O-benzyl-2-deoxy-2-phthalimido-β-D-glucopyranoside-ethyl 3',4'-di-O-benzyl-6'-O-(2'',3'',4'',6''-tetra-O-benzyl-α-D-mannopyranosyl)-1'-thio-α-D-mannopyranoside-2',4-isopropylidene acetal (**66**)

The vinyl ether **65** (88 mg, 0.091 mmol) and the alcohol **24** (66 mg, 0.109 mmol,

1.2 eq.) were added to a reaction vessel. The vessel was then purged with argon. Dry dichloromethane (7 ml) was added to the mixture and it was cooled to -40°C. In a separate flask, a 0.05 mM solution of camphorsulfonic acid was prepared by dissolving 23.3 mg of acid in 2 ml of dry dichloromethane. A 0.18 ml aliquot of the acid mixture (0.009 mmol, 0.1 eq.) was syringed into the vessel which contained **24** and **65**. The reaction was carefully monitored by tlc for product formation (60 minutes) and was quenched by the addition of 0.05 ml of triethylamine. The mixture was concentrated and purified by silica gel chromatography. Seventeen percent (17%) ethyl acetate in hexane which contained 0.1% triethylamine was used as an eluent for chromatographic purification of the crude reaction mixture. The mixed acetal **66** (35 mg, 25%) was obtained as a colorless, viscous syrup. In addition, vinyl ether **65** (28 mg) and alcohol **24** (44 mg) were recovered. The product was unstable (< 12 hours at room temp.) unless it was stored in an organic solution which contained 0.5% triethylamine; R_f 0.72 in ethyl acetate - hexane, 1:2; ^1H NMR (360 MHz, $CDCl_3$ + 2% D-5 pyridine) δ: 5.35 (d, 1H, $J_{1,2}$ = 1 Hz, H-1_M), 5.10 (d, 1H, $J_{1,2}$ = 7.4 Hz, H-1_{Gn}), 5.03 (d, 1H, $J_{1,2}$ = 1 Hz, H-$1'_M$), 2.56 (m, 2H, SCH_2CH_3), 1.42 (s, 3H, CH_3CCH_3'), 1.37 (s, 3H, CH_3CCH_3'), 1.30 (t, 3H, J_{vic} = 7.0 Hz, SCH_2CH_3), 1.3 - 0.75 (m, 15H, octyl); ^{13}C NMR (75.5 MHz, $CDCl_3$ + 2% D-5 pyridine) δ: 104.79 (OCO, acetal), 98.08, 97.76 (C-1_{Gn}, C-$1'_M$), 84.67 (C-1_M), 79.84, 79.83, 76.20, 75.06, 75.04, 74.92, 74.64, 73.14, 71.91, 71.61, 71.41 (C-2_M, C-3_M, C-4_M, C-5_M, C-2'M, C-3'M, C-4'M, C-5_M, C-3_{Gn}, C-4_{Gn}, and C-5_{Gn}), 75.15, 74.85, 74.76, 74.72, 73.17, 73.01, 72.62, 72.49, 72.62, 72.49, 71.61, 69.43, 69.01 (8 x OCH_2Ph, C-6_M, C-6'M, C-6_{Gn}, and OCH_2, octyl), 56.49 (C-2_{Gn}), 31.55, 29.23, 29.04, 29.00, 25.74, 25.22, 22.48 (6 x CH_2, octyl, SCH_2CH_3), 26.36, 25.81 (2 x CH_3, acetal), 15.21 (SCH_2CH_3), 13.94 (CH_3, octyl).

Octyl 3,6-di-O-benzyl-4-O-[3,4-di-O-benzyl-6-O-(2,3,4,6-tetra-O-benzyl-α-D-mannopyranosyl)-β-D-mannopyranosyl]-2-deoxy-2-phthalimido-β-D-glucopyranoside (**67**)

The mixed acetal **66** (35 mg, 0.0223 mmol) was purged with argon in a round bottom flask. Dry dichloromethane (6 ml) was syringed into the flask and was then followed by the addition of 1.1 ml of a 0.10 mM solution of 4-Me-DTBP (0.112 mmol, 5.0 eq.). *N*-iodosuccinimide (25 mg, 0.112 mmol, 5.0 eq.) was added to the reaction and the mixture was stirred overnight. After 18 hours, the reaction was not complete so another 25 mg (10 eq. total) of NIS was added to the mixture. The reaction mixture was stirred an additional 52 hours (70 hours total). It was quenched by the addition of 2 ml of 0.5 M sodium thiosulfate. Dichloromethane (10 ml) was then added and the solution was washed 2 x 10 ml with dH_2O, dried ($MgSO_4$), filtered and concentrated. Twenty-five percent (25%) ethyl acetate in hexane was used as an eluent for chromatographic purification of the crude reaction mixture. The trisaccharide **67** (9 mg, 28%) was isolated as a viscous syrup; R_f 0.37 in ethyl acetate - hexane, 1:2; ^1H NMR (360MHz, $CDCl_3$) δ: 7.7 - 7.5 (m, 4H, phthalimido), 6.95, 6.70 (m, 40H, benzyl aromatics), 5.07 (d, $J_{1,2}$ = 8.3 Hz, H -1), 4.96 (d, 1H, $J_{1,2}$ = 1.5 Hz, H-1"), 4.68 (d, 1H, $J_{1,2}$ < 1Hz, H-1'), 4.30 (m, 2H, H-3, H-3'), 4.12 (dd, $J_{1,2}$ = 8.5 Hz, $J_{2,3}$ = 10.5 Hz, H-2), 4.05 (m, 1H, H-2'), 3.70 (m, 1H, H-2"), 3.39 (dd, 1H, $J_{2,3}$ = 3.2 Hz, $J_{3,4}$ = 9.0 Hz, H-3'), 3.36 (m, 1H, OC*H*H', octyl), 2.48 (d, 1H, $J_{H,OH}$ = 2.5 Hz, OH), 1.4 - 0.75 (m, 15H, octyl); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ: 100.99 (d, $J_{C1,H1}$ = 159 Hz, C-1'), 98.44, 98.42 (C-1, C-1"), 81.82, 79.68, 78.69, 78.27, 74.88, 74.85, 74.71, 74.48, 73.54, 72.15, 67.64 (C-3, C-4, C-5, C-2', C-3', C-4', C-5', C-2", C-3", C-4", and C-5"), 76.19, 75.03, 74.78, 74.73, 73.62, 73.28, 72.46, 71.59, 71.25, 69.69, 69.20, 68.87 (8 x OCH_2Ph, C-6, C-6', C-6", and OCH_2, octyl), 55.90 (C-2), 31.68, 29.31, 29.16, 29.13, 25.85, 22.62 (6 x CH_2, octyl), 14.08 (CH_3, octyl).

The thioglycoside **64** (58 mg, 0.0599 mmol) and the acceptor **24** (54 mg, 0.0898 mmol, 1.5 eq.) were added to a reaction flask. This was followed by the addition of crushed 4Å molecular sieves (400 mg) and the reaction flask was then purged with argon. Dry dichloromethane (8 ml) was added to the mixture and it was stirred for 30 minutes. The reaction mixture was cooled to 0°C. N-iodosuccinimide (15 mg, 0.0659 mmol, 1.1 eq.) was first added to the cooled solution, followed by a catalytic amount of silver triflate (2 mg, 0.1 eq.). After two minutes, a deep red color was observed in the solution and the reaction was complete by t = 4 minutes. The mixture was filtered and dichloromethane (10 ml) was added to the filtrate. The solution was washed with 10 ml of 0.5 M $Na_2S_2O_3$ solution and with 10 ml of saturated sodium bicarbonate solution. The organic layer was dried ($MgSO_4$), filtered, concentrated and re-dissolved in 10 ml of dry methanol. Sodium methoxide (3 mg) was added to the solution and it was stirred overnight. The reaction was neutralized with Amberlite IRC-120 (H^+) resin, filtered and concentrated. Iatrobead column chromatography was used for purification of the crude reaction mixture. The chromatography eluent used was 8% ethyl acetate in toluene. The trisaccharide **68** (61 mg, 69%) was obtained as a colorless syrup; $[\alpha]_D$ +39.9° (*c* 1.55, CH_2Cl_2); R_f 0.50 in ethyl acetate - hexane, 1:2; ^1H NMR (500 MHz, $CDCl_3$) δ: 5.26 (d, 1H, $J_{1,2}$ = 1.5 Hz, H-1'), 5.07 (d, 1H, $J_{1,2}$ = 8.7 Hz, H-1), 5.02 (d, 1H, $J_{1,2}$ = 1Hz, H-1''), 4.36 (dd, 1H, $J_{2,3}$ = 10.7 Hz, $J_{3,4}$ = 8.9 Hz, H-3), 4.20 (dd, 1H, $J_{1,2}$ = 8.7 Hz, $J_{2,3}$ = 10.7 Hz, H-2), 3.96 (m, 1H, H-2'), 3.75 (m, 1H, H-2''), 3.34 (dt, 1H, J_{vic} = 7.0 Hz, J_{gem} = 9.8 Hz, OCHH', octyl), 2.08 (s, 1H, OH), 1.4 - 0.8 (m, 15H, octyl); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ: 101.08 (d, J_{C1-H1} = 173 Hz, C-1'), 98.95 (C-1''), 98.07 (C-1), 80.82, 79.89, 79.46, 78.01, 74.86, 74.77, 74.70, 73.66, 72.12, 72.01, 68.81 (C-3, C-4, C-5, C-2', C-3', C-4', C-5', C-2'', C-3'', C-4'', and C-5''), 74.99, 74.99, 74.62, 73.39, 73.29, 72.35,

Octyl 3,6-di-O-benzyl-4-O-(3',6'-di-O-benzyl-2'-deoxy-2'-phthalimido-β-D-glucopyranosyl)-2-deoxy-2-phthalimido-β-D-glucopyranoside-ethyl 3'',4''-di-O-benzyl-6''-O-(2''',3''',4''',6'''-tetra-O-benzyl-α-D-mannopyranosyl)-α-D-mannopyranoside-2'',4''-isopropylidene acetal (**69**)

The vinyl ether **65** (100 mg, 0.103 mmol, 1.2 eq.), the alcohol **59** (90 mg, 0.0842 mmol, 1.0 eq.) and 500 mg of crushed $CaSO_4$ were added to a reaction vessel. The vessel was purged with argon. Dry dichloromethane (7 ml) was added and the mixture stirred for 30 minutes before it was cooled to -40°C. A 0.05 mM solution of camphorsulfonic acid was prepared by the addition of 2 ml of dry dichloromethane to 23.3 mg of acid under an argon atmosphere. A 0.2 ml aliquot of this acidic solution (0.01 mmol, 0.11 eq.) was syringed into the cooled solution which contained the vinyl ether and alcohol. A further 2 x 0.2 ml (total eq. of acid added = 0.33) of acid was added to the reaction mixture that maximized the amount of mixed acetal as observed by tlc. The reaction was quenched after 2 hours by the addition of 0.1 ml of triethylamine, warmed to room temperature and filtered. The filtrate was concentrated and chromatographed. Seventeen percent (17%) ethyl acetate in hexane which contained 0.1% triethylamine was used as an eluent for chromatographic purification. The mixed acetal product **69** (18 mg, 8%) was obtained as well as recovered vinyl ether **65** (32 mg) and recovered alcohol **59** (53 mg). The product **69** was unstable unless it was stored in a solution which contained 0.5% triethylamine; R_f 0.50 in ethyl acetate - hexane, 1:2; ^1H NMR (360 MHz, $CDCl_3$ + 2% D-5 pyridine) δ: 5.40 (d, 1H, $J_{1,2}$ = 1Hz, H-1_M), 5.32 (d, 1H, $J_{1,2}$ = 7.5 Hz, H-1_{Gn}), 5.08 (d, 1H, $J_{1,2}$ = 1 Hz, H-$1_{M'}$), 4.92 (d, 1H, $J_{1,2}$ = 7.8 Hz, H-$1_{Gn'}$), 2.58 (m, 2H, SCH_2CH3), 1.43 (s, 3H, CH_3CCH_3', acetal), 1.40 (s, 3H, CH_3CCH_3', acetal), 1.26 (t,

($C\text{-}1_M$), 80.55, 79.94, 79.87, 76.98, 76.29, 76.25, 75.15, 75.06, 74.78, 74.67, 73.03, 71.99, 71.58, 71.45 ($C\text{-}2_M$, $C\text{-}3_M$, $C\text{-}4_M$, $C\text{-}5_M$, $C\text{-}2'_M$, $C\text{-}3'_M$, $C\text{-}4'_M$, $C\text{-}5'_M$, $C\text{-}3_{Gn}$, $C\text{-}4_{Gn}$, $C\text{-}5_{Gn}$, $C\text{-}3'_{Gn}$, $C\text{-}4'_{Gn}$, and $C\text{-}5'_{Gn}$), 75.21, 75.00, 74.82, 74.45, 73.32, 73.30, 73.07, 72.71, 72.56, 71.76 (10 x OCH_2Ph), 69.37, 69.13, 68.51, 68.32 ($C\text{-}6_{Gn}$, $C\text{-}6'_{Gn}$, $C\text{-}6_M$, and $C\text{-}6'_M$), 66.41 (OCH_2, octyl), 57.27, 55.78 ($C\text{-}2_{Gn}$, and $C\text{-}2'_{Gn}$), 31.66, 29.25, 29.10, 25.81, 22.60 (6 x CH_2, octyl), 25.33 (SCH_2CH_3), 26.44, 25.9 (2 x CH_3, acetal), 15.38 (SCH_2CH_3), 14.06 (CH_3, octyl).

Octyl 3,6-di-O-benzyl-4-O-(3',6'-di-O-benzyl-2'-deoxy-2'-phthalimido-β-D-glucopyranosyl)-2-deoxy-2-phthalimido-β-D-glucopyranoside-ethyl 3",4",6"-tri-O-benzyl-1"-thio-α-D-mannopyranoside-2",4'-isopropylidene acetal (**70**)

The vinyl ether **10** (137 mg, 0.256 mmol, 2.0 eq.) and the alcohol **59** (138 mg, 0.129 mmol, 1.0 eq.) were added to a round bottom flask and purged with argon. Dry dichloromethane (8 ml) was syringed into the mixture and it was cooled to -40°C. A 0.05 mmol solution of camphorsulfonic acid in dichloromethane was prepared and 0.25 ml of this solution (0.1 eq.) was syringed into the cooled reaction mixture. The reaction was carefully monitored by tlc for product formation and quenched after 60 minutes by the addition of several drops of triethylamine. Prolonged reaction times caused a reduction in product yield. The mixture was concentrated and purified by silica gel chromatography which used 17% ethyl acetate in hexane which contained 0.1% triethylamine as an eluent. Product **70** (78 mg, 38%) was obtained as well as recovered vinyl ether **10** (93 mg) and recovered alcohol **59** (82 mg). The mixed acetal was unstable unless it was stored under basic conditions such as in a dichloromethane solution which contained 0.5% triethylamine; R_f 0.53 in ethyl acetate - hexane, 1:2; ^1H NMR (500 MHz, $CDCl_3$ + 2% D-5 pyridine) δ: 5.43 (s, 1H, $J_{1,2}$ = 1.0 Hz, H-1M), 5.32 (d, 1H, $J_{1,2}$

1.42 (s, 3H, CH_3CCH_3'), 1.29 (t, 3H, SCH_2CH_3), 1.15 - 0.84 (m, 15H, octyl); ^{13}C NMR (125.7 MHz, $CDCl_3$ + 2% D-5 pyridine) δ: 104.76 (OCO, acetal), 98.05, 96.94 ($C\text{-}1_{Gn}$, and C-1'Gn), 84.54 ($C\text{-}1_M$), 80.34, 79.73, 76.34, 76.31, 75.28, 74.65, 73.30, 72.12, 71.72 ($C\text{-}3_{Gn}$, $C\text{-}4_{Gn}$, $C\text{-}5_{Gn}$, C-3'Gn, C-4'Gn, C-5'Gn, $C\text{-}2_M$, $C\text{-}3_M$, $C\text{-}4_M$, and $C\text{-}5_M$), 75.31, 74.89, 74.39, 73.20, 73.01, 72.66, 72.43 (7 x OCH_2Ph), 69.50, 69.26, 68.82, 68.29 ($C\text{-}6_{Gn}$, C-6'Gn, $C\text{-}6_M$, and OCH_2, octyl), 57.15 - 55.73 ($C\text{-}2_{Gn}$, C-2'Gn).

Octyl 3,6-di-O-benzyl-4-O-[3,6-di-O-benzyl-4-O-(3,4,6-tri-O-benzyl-β-D-mannopyranosyl)-2-deoxy-2-phthalimido-β-D-glucopyranosyl]-2-deoxy-2-phthalimido-β-D-glucopyranoside (**71**)

The mixed acetal **70** (24 mg, 0.015 mmol) was added to a flask and purged with argon. Dry dichloromethane (3 ml) was syringed into the flask followed by 1.5 ml of a 0.05 mM solution of 2,6-di-*tert*-butyl-4-methyl-pyridine (4-Me-DTBP, 0.075 mmol, 5 eq., prepared by dissolving 51 mg of 4-Me-DTBP in 5 ml dry dichloromethane under argon atmosphere in the presence of 4Å molecular sieves). N-iodosuccinimide (17 mg, 0.075 mmol, 5 eq.) was added to the reaction and it was stirred for 42 hours. The reaction was quenched by the addition of 2 ml of 0.5 M sodium thiosulfate solution. This caused the deep red reaction color to turn colorless. Dichloromethane (10 ml) was added to the reaction and the organic layer was washed 2 x 10 ml with dH_2O, dried ($MgSO_4$), filtered and concentrated. Twenty-five percent (25%) ethyl acetate in hexane was used as an eluent for chromatographic purification of the crude reaction mixture. Trisaccharide **71** (6 mg) was isolated as a viscous syrup; Rf 0.27 in ethyl acetate - hexane, 1:2; ^1H NMR (500 MHz, $CDCl_3$) δ: 7.9 - 7.5 (m, 8H, phthalimido), 7.35 - 7.1, 7.0 - 6.9, 6.85 - 6.70 (m, 35H, benzyl aromatics), 5.27 (d, 1H, $J_{1,2}$ = 8.4 Hz, H-1'), 4.92 (d, 1H, $J_{1,2}$ = 8.6 Hz, H-1), 4.65 (d, 1H, $J_{1,2}$ < 0.5 Hz, H-1''), 4.40 (dd, 1H, $J_{2,3}$ = 10.8 Hz, $J_{3,4}$ = 8.6 Hz,

Hz, H-4), 3.60 (dd, 1H, $J_{3,4}$ = 9.0 Hz, $J_{4,5}$ = 9.0 Hz, H-4"), 3.39 (dd, 1H, $J_{2,3}$ = 3.0 Hz, $J_{3,4}$ = 9.0 Hz, H-3"), 3.36 (dt, 1H, J_{gem} = 9.9 Hz, J_{vic} = 6.3 Hz, OC*H*H', octyl), 3.22 (dt, 1H, J_{gem} = 9.9 Hz, J_{vic} = 6.3 Hz, OCH*H*', octyl), 2.43 (br s, 1H, OH), 1.35 - 0.75 (m, 15H, octyl); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ: 100.35 (d, $J_{C-1, H-1}$ = 157 Hz, C-1"), 98.12, 97.00 (C-1, and C-1'), 81.75, 78.51, 77.91, 75.72, 75.41, 74.52, 74.48, 74.01, 68.10 (C-3, C-4, C-5, C-3', C-4', C-5', C-2", C-3", C-4", and C-5"), 75.06, 74.83, 74.29, 73.33, 73.24, 72.59, 71.35 (7 x O*C*H_2Ph), 69.34, 68.90, 68.10, 68.01 (C-6, C-6', C-6", and OCH_2, octyl), 56.47, 55.75 (C-2, and C-2'), 31.59, 29.15, 29.12, 29.06, 25.74, 22.53 (6 x CH_2, octyl), 14.05 (CH_3, octyl).

Octyl 3,6-di-O-benzyl-4-O-[3,6-di-O-benzyl-4-O-(3,4,6-tri-O-benzyl-α-D-mannopyranosyl)-2-deoxy-2-phthalimido-β-D-glucopyranosyl]-2-deoxy-2-phthalimido-β-D-glucopyranoside (**72**)

The thioglycoside **2** (58 mg, 0.108 mmol, 2.0 eq.), acceptor **59** (58 mg, 0.054 mmol) and crushed 4Å molecular sieves were added to a round bottom flask and purged with argon. Dry dichloromethane (7 ml) was added and the mixture stirred for 30 minutes and cooled to 0°C. N-iodosuccinimide (24 mg, 0.108 mmol, 2.0 eq.), followed by catalytic silver triflate (0.011 mmol, 0.2 eq.) were consecutively added to the mixture. A characteristic burst of red color was observed within two minutes of the addition of the silver triflate. The reaction was filtered after 30 minutes and dichloromethane (10 ml) was added to the filtrate. The filtrate was washed with 10 ml of 0.5 M sodium thiosulfate solution and then with 10 ml of saturated sodium bicarbonate solution. The organic layer was dried ($MgSO_4$), filtered and concentrated. The residue was dissolved in 10 ml of methanol and 5 mg of sodium methoxide was added to it. The reaction mixture was stirred overnight and neutralized with Amberlite IRC-120 (H^+) resin. The filtered

column chromatography. Product 72 (40 mg, 49%) was isolated as well as some unreacted acetylated compound (13 mg, 16%); $[\alpha]_D$ +24.8° (*c* 1.20, CH_2Cl_2); R_f 0.49 in ethyl acetate - toluene, 1:3; ^1H NMR (500 MHz, $CDCl_3$) δ: 7.8 - 7.5 (m, 8H, phthalimido), 7.35 - 7.05, 7.0 - 6.7 (m, 35H, benzyl aromatics), 5.35 (d, 1H, $J_{1,2}$ = 1.3 Hz, H-1"), 5.26 (d, 1H, $J_{1,2}$ = 8.4 Hz, H-1'), 4.91 (d, 1H, $J_{1,2}$ = 8.2 Hz, H-1), 4.38 (dd, 1H, $J_{2,3}$ = 10.6 Hz, $J_{3,4}$ = 8.5 Hz, H-3'), 4.23 (dd, 1H, $J_{2,3}$ = 10.6 Hz, $J_{1,2}$ = 8.4 Hz, H-2'), 4.20 - 4.08 (m, 3H, H-2, H-3, H-4), 3.98 (dd, 1H, $J_{1,2}$ = 1.3 Hz, $J_{2,3}$ = 3.0 Hz, H-2"), 3.96 (dd, $J_{3,4}$ = 8.5 Hz, $J_{4,5}$ = 9 Hz, H-4'), 3.90 (d, 1H, $J_{3,4}$ = 9.0 Hz, $J_{4,5}$ = 9.0 Hz, H-4"), 3.81 (dd, $J_{3,4}$ = 9.0 Hz, $J_{2,3}$ = 3.0 Hz, H-3"), 3.81 (m, 1H, H-5"), 3.74 (dd, 1H, $J_{5,6}$ = 1.5 Hz, $J_{6,6'}$ = 11.0 Hz, H-6'a), 3.69 (dd, 1H, $J_{5,6}$ = 3.6 Hz, $J_{6,6'}$ = 10.8 Hz, H-6"a), 3.64 (dd, 1H, $J_{5,6'}$ = 3.5 Hz, $J_{6,6'}$ = 11.0 Hz, H-6'b), 3.64 (dt, 1H, J_{vic} = 6.6 Hz, J_{gem} = 9.8 Hz, OC*H*H', octyl), 3.56 (dd, 1H, $J_{5,6}$ = 1.2 Hz, $J_{6,6'}$ = 10.8 Hz, H-6"b), , 3.52 (dd, $J_{5,6}$ = 1.0 Hz, $J_{6,6'}$ = 11.0 Hz, H-6a), 3.41 (dd, 1H, $J_{5,6'}$ = 3.8 Hz, $J_{6,6'}$ = 11.0 Hz, H-6b), 3.32 (m, 1H, H-5'), 3.28 (m, 1H, H-5), 3.22 (dt, 1H, J_{vic} = 9.8 Hz, J_{gem} = 6.6 Hz, OCH*H*', octyl), 2.21 (br s, 1H, OH), 1.4 - 0.7 (m, 15H, octyl); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ: 100.91 (d, $J_{C\text{-}1,H\text{-}1}$ = 170 Hz, C-1"), 98.16, 96.81 (C-1, C-1'), 80.76, 79.91, 77.36, 75.92, 74.94, 74.60, 74.19, 72.20, 69.03 (C-3, C-4, C-5, C-3', C-4', C-5', C-2", C-3", C-4", and C-5"), 56.50, 55.76 (C-2, and C-2'), 75.10, 74.65, 74.35, 73.51, 73.17, 72.72, 72.07 (7 x O*C*H_2Ph), 69.36, 68.80, 68.29 (C-6, C-6', and C-6"), 68.54 (OCH_2, octyl), 31.63, 29.21, 29.11, 29.08, 25.79, 22.57 (6 x CH_2, octyl), 14.04 (CH_3, octyl); Anal. calcd. for $C_{91}H_{96}O_{18}N_2$: C 72.58, H 6.43, N 1.87; found: C 72.28, H 6.45, N 1.84.

The 2-*O*-acetate **2** (500 mg, 0.93 mmol) was dissolved in 10 ml of methanol and 10 mg of sodium methoxide was added. The mixture was stirred for 3.5 hours and concentrated to dryness. The residue was dissolved in 5 ml of DMF which was added in a dropwise fashion to a suspension of NaH (95 mg, 60% dispersion in oil, 2.4 mmol) and DMF (10 ml). After 30 minutes, methyl iodide (0.064 ml, 1 mmol) was syringed into the mixture and the reaction was quenched after 1.5 hours by the addition of methanol (10 ml). The mixture was concentrated and 150 ml of water added to it. The aqueous layer was extracted 3 x 50 ml with dichloromethane and the combined organics washed with another 200 ml of water. The organic layer was dried (Na_2SO_4), filtered and concentrated. The mixture was purified by silica gel chromatography (10% ethyl acetate in hexane was used as an eluent). Pure **73** was isolated in 50% yield (239 mg); R_f 0.77 in ethyl acetate - hexane, 1:2; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 5.43 (d, 1H, $J_{1,2}$ = 1.3 Hz, H-1), 4.11 (ddd, 1H, $J_{4,5}$ = 9.3 Hz, $J_{5,6}$ = 3.0 Hz, $J_{5,6'}$ = 2.0 Hz, H-5), 3.92 (dd, 1H, $J_{3,4}$ = 9.3 Hz, $J_{4,5}$ = 9.3 Hz, H-4), 3.83 (dd, 1H, $J_{5,6}$ = 3.0 Hz, $J_{6,6'}$ = 11.0 Hz, H-6), 3.78 (dd, 1H, $J_{2,3}$ = 3.0 Hz, $J_{3,4}$ = 9.3 Hz, H-3), 3.68 (dd, 1H, $J_{5,6'}$ = 2.0 Hz, $J_{6,6'}$ = 11.0 Hz, H-6'), 3.56 (dd, 1H, $J_{1,2}$ = 1.3 Hz, $J_{2,3}$ = 3.0 Hz, H-2), 2.62 (m, 2H, SCH_2CH_3), 1.28 (t, 3H, SCH_2CH_3).

Methyl 2,3,4-tri-O-benzyl-6-O-(3,4,6-tri-O-benzyl-2-O-methyl-α,β-D-mannopyranosyl)-α-D-glucopyranoside (**74**)

The thioglycoside **73** (60 mg, 0.12 mmol) and the acceptor **13** (55 mg, 0.12 mmol) were added to a reaction vessel and purged with argon. Dichloromethane (3 ml) was added and the mixture cooled to 0°C. NIS (132 mg, 0.59 mmol) was added to the reaction and the mixture was stirred overnight at room temperature. The reaction was quenched by the addition of 0.5 M $Na_2S_2O_3$ and then diluted with a further 10 ml of water. The aqueous layer was extracted twice with 10 ml of dichloromethane, dried

chromatography (15% ethyl acetate in hexane was used as an eluent). The α -disaccharide product **74α** was isolated first (7mg, 7%) followed by the **74β** product (16 mg, 15%). The acceptor **13** was also recovered (24 mg, 44%);

74α: R_f 0.61 in ethyl acetate - hexane, 1:2; ^1H NMR (360 MHz, $CDCl_3$) δ 5.23 (d, 1H, $J_{1,2}$ = 2 Hz, H-1'), 4.61 (d, 1H, $J_{1,2}$ = 3.5 Hz, H-1), 3.49 (dd, 1H, $J_{1,2}$ = 3.5 Hz, $J_{2,3}$ = 9.5 Hz, H-2), 3.44, 3.41 (2 x s, 6H, 2 x OCH_3).

74β: R_f 0.44 in ethyl acetate - hexane, 1:2; ^1H NMR (360 MHz, $CDCl_3$) δ: 4.55 (d, 1H, $J_{1,2}$ = 4 Hz, H-1), 4.18 (d, 1H, $J_{1,2}$ = 1H, H-1'), 4.00 (dd, 1H, $J_{3,4}$ = 9.5 Hz, $J_{4,5}$ = 9.5 Hz, H-2'), 3.79 (m, 1H, H-5'), 3.48 (dd, 1H, $J_{2,3}$ = 3.8 Hz, $J_{3,4}$ = 9.7 Hz, H-3'), 3.59, 3.33 (2 x s, 6H, 2 x OCH_3); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ: 101.5 (d, $J_{C\text{-}1,H\text{-}1}$ = 154 Hz, C-1'), 97.8 (C-1), 82.2, 81.9, 80.0, 78.1, 78.0, 75.9, 75.1, 69.9 (C-2, C-3, C-4, C-5, C-2', C-3', C-4', and C-5'), 75.9, 75.2, 74.9, 73.6, 73.4, 72.0 (6 x CH_2Ph), 69.8, 68.6 (C-6 and C-6'), 61.7, 55.0 (2 x OCH_3).

Ethyl 2,3,4,6-tetra-O-benzyl-1-thio-α-D-mannopyranoside (**75**)[223]

The alcohol **3** (350 mg, 0.71 mmol) and sodium hydride (57 mg, 60% dispersion in oil, 1.42 mmol) were added to a round bottom flask. DMF (20 ml) was syringed into the mixture and stirred at 0°C for 30 minutes. Benzyl bromide (0.17 ml, 1.42 mmol) was added and the reaction mixture stirred overnight at room temperature. The reaction was quenched by the addition of methanol (5 ml) and concentrated. The viscous oil was then chromatographed (10% ethyl acetate in hexane was used as an eluent). Product **75** (368 mg, 89%) was obtained as a clear syrup; R_f 0.69 in ethyl acetate - hexane, 1:3; ^1H NMR (360 MHz, $CDCl_3$) δ: 5.42 (d, 1H, $J_{1,2}$ = 1.3 Hz, H-1), 4.90, 4.52 (2 x d, 2H, J_{gem} = 10.8 Hz, OC*HH*'Ph), 4.75, 4.68 (2 x d, 2H, J_{gem} = 12.2 Hz, OC*HH*'Ph), 4.68, 4.52 (2 x d, 2H, J_{gem} = 11 Hz, OC*HH*'Ph), 4.60, 4.56 (2 x d, 2H, J_{gem} = 12.0 Hz, OC*HH*'Ph), 4.16 (m, 1H, H-5), 4.03 (dd, 1H, $J_{3,4}$ = 9.5 Hz, $J_{4,5}$ = 9.5 Hz, H-4), 3.86 (m, 2H, H-2 and H-3),

3.85 (dd, 1H, $J_{5,6}$ = 4.7 Hz, $J_{6,6'}$ = 10.5 Hz, H-6), 3.73 (dd, 1H, $J_{5,6'}$ = 2.0 Hz, $J_{6,6'}$ = 10.5 Hz, H-6'), 2.61 (m, 2H, SCH_2CH_3), 1.25 (t, 3H, SCH_2CH_3).

Methyl 2,3,4-tri-O-benzyl-6-O-(2,3,4,6-tetra-O-benzyl-α,β-D-mannopyranosyl)-α-D-glucopyranoside (**76**)

The thioglycoside **75** (50 mg, 0.085 mmol) and the acceptor **13** (40 mg, 0.085 mmol) were combined in a reaction vessel and purged with argon. Dichloromethane (5 ml) was added and the solution cooled to 0°C. In one portion, NIS (96 mg, 0.425 mmol) was added and the reaction was allowed to warm to room temperature and stirred overnight. After 20 hours, the mixture was quenched by the addition of 2 ml of 0.5 M $Na_2S_2O_3$ The solution was diluted with 15 ml of water and extracted twice with 15 ml of dichloromethane. The combined organic layers were then dried ($MgSO_4$), filtered and concentrated. Twenty-five percent (25%) ethyl acetate in hexane was used as an eluent for chromatographic purification of the reaction mixture. Product **76** (27 mg, 32% yield) was obtained as a colorless syrup. NMR analysis of **76** gave a complex mixture in which determination of the anomers was difficult. The sample was therefore purged with argon and 3 mg of 5% Pd / C was added to the vessel. Dry methanol (2.5 ml) was carefully added to the reaction vessel and the mixture was stirred overnight under a hydrogen atmosphere. The reaction mixture was filtered through celite and concentrated to give 9 mg of a white solid; R_f of **76** 0.55 in ethyl acetate - hexane, 1:2; ^1H NMR of deblocked **76** (300 MHz, D_2O) δ: 4.88 (d, 0.6H, $J_{1,2}$ = 1.7 Hz, H-1'α), 4.80, 4.81 (2 x d, 1H, $J_{1,2}$ = 3.8 Hz, H-1α, H-1β), 4.68 (d, 0.4H, $J_{1,2}$ < 1 Hz, H-1'β), 3.40 (2 x s, 3H, 2 x OCH_3); ^{13}C NMR (75.5 MHz, D_2O) δ: 100.4 (d, $J_{C1,H1}$ = 161 Hz, C-1'β), 99.3 (d, $J_{C1,H1}$ = 170 Hz, C-1'α), 99.2 (d, $J_{C1,H1}$ = 170 Hz, C-1α), 99.1 (d, $J_{C1,H1}$ = 170 Hz, C-1β), 55.0, 54.9 (2 x OCH_3).

Ethyl 2-O-benzoyl-3,4,6-tri-O-benzyl-1-thio-α-D-mannopyranoside (**77**)

The alcohol **3** (500 mg, 1.01 mmol) was dissolved in 5 ml of pyridine. Benzoyl chloride (0.18 ml, 1.5 mmol) was syringed into the mixture and stirred overnight. The reaction was quenched by the addition of 30 ml of 1N HCl. Dichloromethane (30 ml) was then poured into the reaction and the organic layer separated. The organic layer was washed with 1N HCl (2 x 30 ml), with saturated sodium bicarbonate solution (50 ml), and with water (50 ml). The organic layer was dried ($MgSO_4$), filtered and concentrated. Silica gel chromatography (10% ethyl acetate in hexane was used as an eluent) gave the product **77** in 79% yield (478 mg); $[\alpha]_D$ +48.2° (*c* 1.4, CH_2Cl_2); R_f 0.74 in ethyl acetate - hexane, 1:3; ^1H NMR (360 MHz, $CDCl_3$) δ: 5.58 (dd, 1H, $J_{1,2}$ = 1.6 Hz, $J_{2,3}$ = 2.9 Hz, H-2), 5.44 (d, 1H, $J_{1,2}$ = 1.6 Hz, H-1), 4.22 (m, 1H, H-5), 4.13 (dd, 1H, $J_{3,4}$ = 9.3 Hz, $J_{4,5}$ = 9.5 Hz, H-4), 4.02 (dd, 1H, $J_{2,3}$ = 2.9 Hz, $J_{3,4}$ = 9.3 Hz, H-3), 3.83 (dd, 1H, $J_{5,6}$ = 3.6 Hz, $J_{6,6'}$ = 11.0 Hz, H-6), 3.76 (dd, 1H, $J_{5,6'}$ = 1.7 Hz, $J_{6,6'}$ = 11.0 Hz, H-6'), 2.65 (m, 2H, SCH_2CH_3), 1.29 (t, 3H, SCH_2CH_3); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ: 165.7 (C=O), 82.62 (C-2), 78.7 (C-1), 74.5, 72.0, 70.9 (C-3, C-4, and C-5), 75.2, 73.4, 71.6 (3 x OCH_2Ph), 69.0 (C-6), 25.7 (SCH_2CH_3), 15.0 (SCH_2CH_3); Anal. calcd. for $C_{36}H_{38}O_6S$: C 72.22, H 6.40, S 5.35; found: C 71.81, H 6.47, S 5.18.

Ethyl 3,4,6-tri-O-benzyl-2-O-(1-phenylethenyl)-1-thio-α-D-mannopyranoside (**78**)

The 2-*O*-benzoate **77** (400 mg, 0.67 mmol) was added to a reaction vessel and purged with argon. Toluene (9 ml), tetrahydrofuran (3 ml) and pyridine (0.1 ml) were sequentially syringed into the flask and it was cooled to -40°C. Tebbe's reagent **9** (2.0 ml, 2.0 mmol) was added and the mixture was stirred for 4 hours. The mixture was allowed to reach -10°C. The reaction was then quenched by the addition of 0.5 ml of 1N NaOH in a dropwise fashion. The suspension was filtered through a celite bed, washed with ether until the filtrate was a pale orange color and concentrated. Purification by silica gel chromatography (5% ethyl acetate in hexane which contained 0.1%

triethylamine was used as an eluent) gave a syrup **78** (320 mg, 80%); R_f 0.74 in ethyl acetate - hexane, 1:3; ^1H NMR (360 MHz, $CDCl_3$) δ: 5.61 (d, 1H, $J_{1,2}$ = 1.2 Hz, H-1), 4.75, 4.56 (2 x d, 2H, J_{gem} = 3.0 Hz, C=C*HH'*), 4.20 (dd, 1H, $J_{3,4}$ = 9.5 Hz, $J_{4,5}$ = 9.5 Hz, H-4), 4.18 (dd, 1H, $J_{2,3}$ = 3.2 Hz, $J_{3,4}$ = 9.5 Hz, H-3), 4.14 (dd, 1H, $J_{1,2}$ = 1.2 Hz, $J_{2,3}$ = 3.2 Hz, H-2), 4.00 (m, 1H, H-5), 3.86 (dd, 1H, $J_{5,6}$ = 3.6 Hz, $J_{6,6'}$ = 10.8 Hz, H-6), 3.75 (dd, 1H, $J_{5,6'}$ = 1.5 Hz, $J_{6,6'}$ = 10.8 Hz, H-6'), 2.62 (m, 2H, S*CH*$_2$CH$_3$), 1.26 (t, 3H, SCH$_2$*CH*$_3$); ^{13}C NMR (75.5 MHz, D-5 pyridine) δ: 159.1 (*C*=CH$_2$), 84.9 (C=*C*H$_2$), 80.9, 80.0 (C-1 and C-2), 75.5, 75.2, 72.7 (C-3, C-4, and C-5), 75.3, 73.5, 71.8 (3 x O*C*H$_2$Ph), 69.9 (C-6), 25.6 (S*C*H$_2$CH$_3$), 15.2 (SCH$_2$*C*H$_3$).

Methyl 2,3,4-tri-O-benzyl-2-O-(2-propenyl)-α-D-glucopyranoside (**79**)

The alcohol **13** (500 mg, 1.08 mmol) was dissolved in pyridine (10 ml) and acetic anhydride (1 ml) was added to the solution. The reaction mixture was stirred overnight and quenched by the addition of water (100 ml). The mixture was stirred for 1 hour and then the aqueous layer was extracted with dichloromethane (100 ml). The organic layer was then washed 3 x 100 ml with 1N HCl, dried ($MgSO_4$), filtered and concentrated to an amorphous yellow solid. This solid was then treated with Tebbe's reagent as in the preparation of **78**. After work-up, the syrup was purified by chromatography. Ten percent (10%) ethyl acetate in hexane which contained 0.1 % triethylamine was used as an eluent for chromatographic purification. The product was isolated in a yield of 29% (158 mg); R_f 0.80 in ethyl acetate - hexane, 1:2; ^1H NMR (360 MHz, $CDCl_3$) δ: 4.62 (d, 1H, $J_{1,2}$ = 3.7 Hz, H-1), 4.00 (dd, 1H, $J_{2,3}$ = 9.6 Hz, $J_{3,4}$ = 9.2 Hz, H-3), 3.91-3.79 (m, 5H, H-5, H-6, H-6', and C=C*HH'*), 3.65 (dd, 1H, $J_{3,4}$ = 9.2 Hz, $J_{4,5}$ = 9.2 Hz, H-4), 3.55 (dd, 1H, $J_{1,2}$ = 3.7 Hz, $J_{2,3}$ = 9.6 Hz, H-2), 3.37 (s, 3H, OCH_3), 1.82 (C*H*$_3$C=CH$_2$); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ: 159.5 (*C*=CH$_2$), 98.3 (C-1) 82.1, 80.0, 77.6, 69.0 (C-2, C-3, C-4, and C-5), 82.0 (C=*C*H$_2$), 75.9, 75.2, 73.5 (3 x O*C*H$_2$Ph), 65.8 (C-6), 55.2 (OCH_3), 20.9 (*C*H$_3$C=CH$_2$).

Ethyl 3,4,6-tri-O-benzyl-2-O-(octyloxymethyl)-1-thio-α-D-mannopyranoside (**80**)

The alcohol **3** (150 mg, 0.30 mmol) was dissolved in dichloromethane (10 ml). Hunig's base (0.26 ml, 1.52 mmol) and bromomethyl octyl ether (0.3 ml, 1.52 mmol). were sequentially syringed into the solution. The mixture was stirred for 75 hours and quenched with methanol (1 ml). The reaction was concentrated and purified by chromatography (5% ethyl acetate in hexane was used as an eluent). A viscous yellow oil **80** was obtained (103 mg, 54%); R_f 0.66 in ethyl acetate - hexane, 1:3; ^{1}H NMR (360 MHz, $CDCl_3$) δ: 5.40 (d, 1H, $J_{1,2}$ = 1.3 Hz, H-1), 4.83, 4.78 (2 x d, 2H, J_{gem} = 6.8 Hz, OC*HH'*OOctyl), 4.14 (m, 1H, H-5), 4.09 (dd, $J_{1,2}$ = 1.3 Hz, $J_{2,3}$ = 3.2 Hz, H-2), 3.94 (dd, 1H, $J_{3,4}$ = 9.3 Hz, $J_{4,5}$ = 9.3 Hz, H-4), 3.84 (dd, 1H, $J_{2,3}$ = 3.2 Hz, $J_{3,4}$ = 9.3 Hz, H-3), 3.80 (dd, 1H, $J_{5,6}$ = 4.8 Hz, $J_{6,6'}$ = 11.0 Hz, H-6), 3.68 (dd, 1H, $J_{5,6'}$ = 2.0 Hz, $J_{6,6'}$ = 11.0 Hz, H-6'), 3.58 (2 x m, 2H, OC*HH'*, octyl), 2.60 (m, 2H, SC*H*$_2$CH$_3$), 1.52, 1.24 (2 x m, 12H, octyl), 1.23 (t, 3H, SCH$_2$C*H*$_3$), 0.85 (t, 3H, CH_3, octyl); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ: 95.1 (O*C*H$_2$OOctyl), 83.1(C-1), 80.1 (C-2), 75.1, 74.8, 72.0 (C-3, C-4, and C-5), 75.2, 73.3, 72.2 (3 x O*C*H$_2$Ph), 69.2, 68.4 (C-6 and O*C*H$_2$, octyl), 31.9, 29.7, 29.5, 29.3, 26.3, 25.4, 22.7 (6 x CH_2, octyl and S*C*H$_2$CH$_3$), 15.0, 14.2 (CH_3, octyl and SCH$_2$*C*H$_3$).

Ethyl 3,4,6-tri-O-benzyl-2-O-(octyloxymethyl)-1-thio-β-D-glucopyranoside (**82**)

The alcohol **81**[143] (50 mg, 0.101 mmol) was dissolved in dichloromethane (3 ml). Hunig's base (0.088 ml, 0.505 mmol) and bromomethyl octyl ether (0.06 ml, 3.0 eq) were sequentially syringed into the mixture. After 47 hours, the reaction was quenched by the addition of methanol (0.5 ml) and concentrated *in vacuo*. Five percent (5%) ethyl acetate in hexane was used as an eluent for chromatographic purification of the reaction mixture. Product **82** was isolated in 73% yield (47 mg); R_f 0.73 in ethyl acetate - hexane, 1:3; ^{1}H NMR (360 MHz, $CDCl_3$) δ: 4.96, 4.83 (2 x d, 2H, J_{gem} = 6.2 Hz, OC*HH'*OOctyl), 4.39

(d, 1H, $J_{1,2}$ = 9.2 Hz, H-1), 3.75 (dd, 1H, $J_{5,6}$ = 2 Hz, $J_{6,6'}$ = 10.2 Hz, H-6), 3.66 (dd, 1H, $J_{5,6'}$ = 4.4 Hz, $J_{6,6'}$ = 10.2 Hz, H-6'), 3.72-3.46 (m, 6H, H-2, H-3, H-4, H-5, and OC*HH'*, octyl), 2.74 (m, 2H, SCH_2CH_3), 1.4, 1.22 (m, 12H, 6 x CH_2, octyl), 1.30 (t, 3H, SCH_2CH_3), 0.86 (t, 3H, CH_3, octyl); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ: 96.9 (O*C*HH'OOctyl), 86.8 (C-1), 84.8 (C-2), 79.3, 78.2, 77.8 (C-3, C-4, and C-5), 75.5, 75.0, 73.5 (3 x OCH_2Ph), 69.6, 69.1 (C-6 and O*C*HH', octyl), 31.9, 29.6, 29.5, 29.3, 26.1, 24.5, 22.7 (6 x CH_2, octyl and SCH_2CH_3), 15.0, 14.1 (SCH_2CH_3 and CH_3 octyl).

*Attempted Activation of Methylene Acetals **80** and **82**:*

The acetals **80** (63 mg, 0.099 mmol) or **82** (42 mg, 0.062 mmol) were dissolved in dichloromethane (6 and 4 ml respectively) and treated with 5 equivalents of NIS. After the reactions were stirred overnight, they were quenched by the addition of a sodium thiosulfate solution (0.5 M). Both reactions were worked-up in the manner described for the preparation of **32**. Silica gel chromatography was used for purification with 25% ethyl acetate in hexane as the solvent system for elution. Several fractions were obtained that were shown to be complex mixtures by ^1H NMR. In both cases, the desired octyl glycosides were not observed.

Ethyl 3,4,6-tri-O-benzyl-2-O-(4-pentenyloxymethyl)-1-thio-α-D-mannopyranoside (**83**)

The alcohol **3** (197 mg, 0.40 mmol) was dissolved in dichloromethane (15 ml). Hunig's base (0.28 ml, 1.94 mmol) and 4-pentenylmethoxy chloride[72] (POM-Cl, 0.071 ml, 0.98 mmol) were syringed into the flask and the mixture was stirred for 48 hours. The reaction mixture was concentrated *in vacuo* and purified by chromatography. Ten percent (10%) ethyl acetate in hexane was used as the solvent system for chromatographic purification of the reaction mixture. The product **83** was isolated in 33% yield (79 mg) with 80 mg of recovered **3**; $[\alpha]_D$ +94.7° (*c* 0.45, CH_2Cl_2); R_f 0.72 in ethyl acetate - hexane, 1:3; ^1H NMR (360 MHz, $CDCl_3$) δ: 5.78 (dddd, 1H,

CH_2=C*H*-), 5.40 (d, 1H, $J_{1,2}$ = 1.5 Hz, H-1), 5.00, 4.92 (2 x m, 2H, C*H*$_2$=CH), 4.84, 4.79 (2 x d, 2H, J_{gem} = 7.0 Hz, OC*HH'*Opentenyl), 4.12 (m, 1H, H-5), 4.09 (dd, 1H, $J_{1,2}$ = 1.5 Hz, $J_{2,3}$ = 3.2 Hz, H-2), 3.94 (dd, 1H, $J_{3,4}$ = 9.5 Hz, $J_{4,5}$ = 9.5 Hz, H-4), 3.85 (dd, 1H, $J_{2,3}$ = 3.2 Hz, $J_{3,4}$ = 9.5 Hz, H-3), 3.80 (dd, $J_{5,6}$ = 5.0 Hz, $J_{6,6'}$ = 10.8 Hz, H-6), 3.69 (dd, 1H, $J_{5,6'}$ = 2.0 Hz, $J_{6,6'}$ = 10.8 Hz, H-6'), 3.60 (2 x m, 2H, OC*HH'*, pentenyl), 2.70 (m, 2H, SC*H*$_2$CH$_3$), 2.06 (m, 2H, $OCH_2CH_2CH_2CH=CH_2$), 1.64 (m, 2H, $OCH_2CH_2CH_2CH=CH_2$), 1.25 (t, 3H, SCH_2CH_3); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ: 138.2 (CH_2=*C*H-), 114.8 (*C*H$_2$=CH-), 95.1 (OCHH'O), 83.1 (C-1), 80.1 (C-2), 75.2, 74.9, 72.2 (C-3, C-4, and C-5), 73.4, 72.2, 69.2, 67.7 (3 x O*C*H$_2$Ph, C-6, and O*C*H$_2$, pentenyl), 30.3, 28.9 ($OCH_2CH_2CH_2CH=CH_2$), 25.4 (SCH_2CH_3), 15.0 (SCH_2CH_3); Anal. calcd. for $C_{35}H_{44}O_6S$: C 70.92, H 7.48, S 5.41; found: C 70.92, H 7.41, S 5.23.

Attempted Acetalization of ***83****:*

The acetal **83** (55 mg, 0.093 mmol) and the alcohol **13** (43 mg, 0.093 mmol) were added to a reaction flask and purged with argon. Dichloromethane (7 ml) was added to the mixture followed by NIS (84 mg, 0.37 mmol). The mixture was stirred for seven hours and then quenched by the addition of 2 ml of 0.5M $Na_2S_2O_3$. The reaction mixture showed a complex smear of products by tlc of which the benzylidene structures **42** and **84** could be identified as major products (23 mg, 53% of **13**).

Methyl 2,3,6-tri-O-benzyl-4-O-(4-pentenyloxymethyl)-α-D-mannopyranoside (**85**)

The alcohol **12** (300 mg, 0.645 mmol) was dissolved in 15 ml of dichloromethane and 0.9 ml (5.2 mmol) of Hunig's base was syringed into the mixture. 4-pentenylmethoxy chloride[72] (0.12 ml, 1.29 mmol) was added to the reaction vessel and the mixture stirred overnight. After one night, an additional 0.12 ml of POM-Cl was added and the mixture was stirred a second night. A further 0.24 ml of POM-Cl (8 eq. total) and 0.45 ml of Hunig's base (12 eq. total) was added the third day and the solution

runny oil. Twenty percent (20%) ethyl acetate in hexane was used as an eluent for chromatographic purification of the oil. Product **85** (256 mg, 71%) was isolated as a clear syrup; $[\alpha]_D$ +103.3° (*c* 0.40, CH_2Cl_2); R_f 0.62 in ethyl acetate - hexane, 1:2; ^1H NMR ($CDCl_3$, 360 Hz) δ: 5.73 (dddd, 1H, CH_2=C*H*-), 4.94 (m, 2H, C*H*$_2$=CH-), 4.79, 4.69 (2 x d, 2H, J_{gem} = 6.2 Hz, OC*H*$_2$Opentenyl), 4.61 (d, 1H, $J_{1,2}$ = 3.8 Hz, H-1), 3.88 (dd, 1H, $J_{2,3}$ = 9.0 Hz, $J_{3,4}$ = 9.0 Hz, H-3), 3.84 (m, 1H, H-5), 3.71 (dd, 1H, $J_{5,6}$ = 2.0 Hz, $J_{6,6'}$ = 10.5 Hz, H-6), 3.64 (dd, 1H, $J_{5,6'}$ = 4.7 Hz, $J_{6,6'}$ = 10.5 Hz, H-6'), 3.56 (dd, 1H, $J_{3,4}$ = 9.0 Hz, $J_{4,5}$ = 9.0 Hz, H-4), 3.50 (dd, 1H, $J_{1,2}$ = 3.8 Hz, $J_{2,3}$ = 9.0 Hz, H-2), 3.44, 3.36 (2 x m, 2H, OC*HH'*, pentenyl), 3.38 (s, 3H, OCH_3), 2.00 (m, 2H, OCH_2CH_2C*H*$_2$CH=), 1.55 (m, 2H, OCH_2C*H*$_2CH_2CH$=); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ: 138.1 (C*H*$_2$=*C*H-), 114.8 (*C*H$_2$=CH-), 98.0 (C-1), 97.3 (O*C*H$_2$Opentenyl), 81.7, 79.9, 76.1, 70.0 (C-2, C-3, C-4, and C-5), 75.6, 73.5, 73.3 (3 x O*C*H$_2$Ph), 69.2, 68.5 (C-6 and O*C*H$_2$, pentenyl), 55.2 (OCH_3), 30.2 ($OCH_2CH_2CH_2CH$=), 28.8 (OCH_2*C*H$_2CH_2CH$=); Anal. calcd. for $C_{34}H_{42}O_7$: C 72.57, H 7.52; found: C 72.32, H 7.74.

Phenyl 2-O-acetyl-3,4,6-tri-O-benzyl-1-thio-α-,β-D-mannopyranoside (**92**)

The di-acetate **91**[143] (550 mg, 1.03 mmol) was dissolved in dichloromethane (10 ml). Benzenethiol (0.21 ml, 2.06 mmol) was syringed into the mixture followed by boron trifluoride etherate (0.19 ml, 1.55 mmol). After two hours, the reaction was quenched by the addition of triethylamine (0.25 ml). The solution was concentrated *in vacuo* and purified by silica gel chromatography (15% ethyl acetate in hexane was used as the chromatography eluent). Product **92** was isolated in 74% yield (443 mg) as a 2:1 α:β mixture of anomers; R_f 0.55 (both anomers) in ethyl acetate - hexane, 1:3; ^1H NMR

0.33H, $J_{1,2}$ = 1.0 Hz, H-1β), 4.32 (m, 0.66H, H-5α), 3.98 (dd, 0.66H, $J_{3,4}$ = 9.2 Hz, $J_{4,5}$ = 9.2 Hz, H-4α), 3.67 (dd, 0.33H, $J_{2,3}$ = 3.5 Hz, $J_{3,4}$ = 9.5 Hz, H-3β), 3.54 (m, 0.33H, H-5β), 2.22 (s, 1H, OCH_3β), 2.14 (s, 2H, OCH_3α); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ: 170.5, 170.3 (*C*=O, α,β), 86.3 (C-1α), 85.4 (C-1β), 81.6, 79.9, 74.2, 70.2 (C-2, C-3, C-4, and C-5, β anomer), 78.6, 74.6, 73.4, 70.4 (C-2, C-3, C-4, and C-5, α anomer), 69.6 (C-6β), 68.9 (C-6α), 21.1, 20.9 ($COCH_3$, α, β); Anal. calcd. for $C_{35}H_{36}O_6S$: C 71.89, H 6.21, S 5.48; found: C 71.94, H 6.24, S 5.82.

Phenyl 3,4,6-tri-O-benzyl-1-thio-α-D-mannopyranoside (**86**)

The anomeric mixture **92** (425 mg, 0.73 mmol) was dissolved in methanol (10 ml) and sodium methoxide (20 mg) was added to the solution. After overnight, the solution was neutralized by the addition of Amberlite IRC-120 (H^+) resin, filtered and concentrated. Twenty percent (20%) ethyl acetate in hexane was used as an eluent for chromatographic purification of the reaction mixture. Product **86** (330 mg, 83%) as well as **92** (71 mg) were recovered; $[\alpha]_D$ +20.6° (*c* 2.50, CH_2Cl_2); R_f 0.36 in ethyl acetate - hexane, 1:3; ^1H NMR (360 MHz, $CDCl_3$) δ: 5.62 (d, 1H, $J_{1,2}$ = 1.4 Hz, H-1), 4.29 (m, 1H, H-5), 4.24 (dd, 1H, $J_{1,2}$ = 1.4 Hz, $J_{2,3}$ = 2.8 Hz, H-2), 3.94 (dd, 1H, $J_{3,4}$ = 9.2 Hz, $J_{4,5}$ = 9.2 Hz, H-4), 3.88 (dd, 1H, $J_{3,4}$ = 9.2 Hz, $J_{2,3}$ = 2.8 Hz, H-3), 3.80 (dd, 1H, $J_{5,6}$ = 4.5 Hz, $J_{6,6'}$ = 10.6 Hz, H-6), 3.68 (dd, 1H, $J_{5,6'}$ = 1.8 Hz, $J_{6,6'}$ = 10.6 Hz, H-6'), 2.64 (d, 1H, $J_{H,OH}$ = 2.5 Hz, OH); ^{13}C NMR (75.5 MHz, $CDCl_3$), δ: 87.4 (C-1), 80.3, 74.6, 72.3, 69.9 (C-2, C-3, C-4, and C-5), 75.2, 73.4, 72.2 (3 x OCH_2Ph), 68.9 (C-6); Anal. calcd. for $C_{33}H_{34}O_5S$: C 73.04, H 6.32, S 6.32; found: C 72.79, H 6.47, S 6.80.

The methylene acetal **85** (50 mg, 0.089 mmol) and the alcohol **86** (48 mg, 0.089 mmol) were added to a reaction flask and purged with argon. Dichloromethane (8 ml) was syringed into the flask followed by the addition of NIS (40 mg, 0.178 mmol). After 52 hours, the mixture was quenched by the addition of 2 ml of 0.5 M $Na_2S_2O_3$ and diluted with 20 ml of water. The aqueous layer was extracted 2 x 20 ml with dichloromethane and the organic layer dried ($MgSO_4$), filtered and concentrated. Fifteen percent (15%) ethyl acetate in hexane which contained 0.1% triethylamine was used as an eluent for chromatographic purification of the reaction mixture. A number of compounds were isolated which included the product **87** (4 mg, 5%), the alcohol **86** (2.5 mg, 5%), the alcohol **12** (5.4 mg, 13%), and the succinimide adduct **90** (13 mg, 25%).

87: R_f 0.60 in ethyl acetate - hexane, 1:2; ^1H NMR (360 MHz, $CDCl_3$) δ: 5.67 (d, 1H, $J_{1,2}$ = 1.4 Hz, H-1'), 4.28 (m, 1H, H-5'), 4.14 (dd, 1H, $J_{1,2}$ = 1.4 Hz, $J_{2,3}$ = 3.0 Hz, H-2'), 3.80 (dd, 1H, $J_{2,3}$ = 3.0 Hz, $J_{3,4}$ = 9.5 Hz, H-3'), 3.46 (dd, 1H, $J_{1,2}$ = 3.8 Hz, $J_{2,3}$ = 9.6 Hz, H-2), 3.25 (s, 3H, OCH_3).

90: R_f 0.21 in ethyl acetate - hexane, 1:2; ^1H NMR (360 MHz, $CDCl_3$) δ: 4.99, 4.73 (2 x d, 2H, J_{gem} = 11.5 Hz, OC*HH*Ph), 4.96 (s, 2H, OCH_2N), 4.78, 4.62 (2 x d, 2H, J_{gem} = 12.0 Hz, OC*HH*Ph), 4.58 (d, 1H, $J_{1,2}$ = 3.8 Hz, H-1), 4.63, 4.56 (2 x d, 2H, J_{gem} = 12.0 Hz, OC*HH*Ph), 3.85 (dd, 1H, $J_{3,4}$ = 9.2 Hz, $J_{2,3}$ = 9.2 Hz, H-3), 3.76 (dd, 1H, $J_{6,6'}$ = 11.0 Hz, $J_{5,6}$ = 3.4 Hz, H-6), 3.72 (dd, 1H, $J_{3,4}$ = 9.2 Hz, $J_{4,5}$ = 9.2 Hz, H-4), 3.66 (m, 1H, H-5), 3.61 (dd, 1H, $J_{6,6'}$ = 11.0 Hz, $J_{5,6'}$ = 1.7 Hz, H-6'), 3.54 (dd, 1H, $J_{1,2}$ = 3.8 Hz, $J_{2,3}$ = 9.2 Hz, H-2), 3.34 (s, 3H, OCH_3), 2.26 (m, 4H, 2 x CH_2, succinimide); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ: 176.9 (C=O, succinimide), 98.1 (C-1), 81.0, 80.2, 76.9, 70.1 (C-2, C-3, C-4, and C-5), 75.4, 73.8, 73.5 (3 x OCH_2Ph), 68.5 (C-6), 68.5 (OCH_2N), 55.3 (OCH_3), 28.0 (2 x CH_2, succinimide).

The methylene acetal **85** (50 mg, 0.089 mmol) and the alcohol **3** (44 mg, 0.089 mmol) were added to a round bottom flask and purged with argon. Dichloromethane (8 ml) was syringed into the flask followed by the addition of NIS (40 mg, 0.178 mmol). After 27 hours, the mixture was quenched by the addition of 2 ml of 0.5 M $Na_2S_2O_3$ and worked-up as in the preparation of **87**. Twelve percent (12%) ethyl acetate in hexane which contained 0.1% triethylamine was used as an eluent for chromatographic purification of the reaction mixture. A number of compounds were isolated, including the product **88** (7 mg, 8%), the alcohol **3** (7.5 mg, 15%), the alcohol **12** (7.5 mg, 17%), the methylene acetal **89** (6 mg, 12%), and the succinimide adduct **90** (11 mg, 20%).

88: R_f 0.61 in ethyl acetate - hexane, 1:2; ^1H NMR (360 MHz, $CDCl_3$) δ: 5.44 (d, 1H, $J_{1,2}$ = 1.5 Hz, H-1'), 4.99, 4.93 (2 x d, 2H, J_{gem} = 5.5 Hz, OCHH'O), 4.59 (d, 1H, $J_{1,2}$ = 4.0 Hz, H-1), 4.12 (m, 1H, H-5'), 3.98 (dd, 1H, $J_{1,2}$ = 1.5 Hz, $J_{2,3}$ = 4.0 Hz, H-2'), 3.48 (dd, 1H, $J_{1,2}$ = 3.5 Hz, $J_{2,3}$ = 9.6 Hz, H-2), 3.38 (OCH_3), 2.57 (m, 2H, SCH_2CH_3), 1.24 (t, 3H, SCH_2CH_3.

89: R_f 0.65 in ethyl acetate - hexane, 1:2; ^1H NMR (360 MHz, $CDCl_3$) δ: 5.07, 4.59 (2 x d, 2H, J_{gem} = 6.2 Hz, OCHH'O), 4.86, 4.80 (2 x d, 2H, J_{gem} = 11.2 Hz, OC*HH'*Ph), 4.80, 4.64 (2 x d, 2H, J_{gem} = 12.0 Hz, OC*HH'*Ph), 4.54 (d, 1H, $J_{1,2}$ = 3.6 Hz, H-1), 4.11 (dd, 1H, $J_{5,6}$ = 4.8 Hz, $J_{6,6'}$ = 10.2 Hz, H-6), 3.95 (dd, 1H, $J_{2,3}$ = 9.2 Hz, $J_{3,4}$ = 9.2 Hz, H-3). 3.71 (ddd, $J_{4,5}$ = 9.5 Hz, $J_{5,6}$ = 4.8 Hz, $J_{5,6'}$ = 1 Hz, H-5), 3.49 (dd, 1H, $J_{1,2}$ = 3.6 Hz, $J_{2,3}$ = 9.2 Hz, H-2), 3.42 (dd, 1H, $J_{5,6}$ = 1 Hz, $J_{6,6'}$ = 10.2 Hz, H-6'), 3.37 (s, 3H, OCH_3), 3.30 (dd, 1H, $J_{3,4}$ = 9.2 Hz, $J_{4,5}$ = 9.5 Hz, H-4); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ: 99.2 (C-1), 93.8 (OCH_2O), 82.1, 79.4, 78.6, 62.5 (C-2, C-3, C-4, and C-5), 75.3, 73.8 (2 x OCH_2Ph), 68.9 (C-6), 55.4 (OCH_3).

The alcohol **3** (250 mg, 0.51 mmol) was introduced into a round bottom flask, purged with argon and dissolved in dichloromethane (5 ml). In a separate flask, oxalyl chloride (0.2 ml, 2.3 mmol) was syringed into 1.9 ml of chloroform. DMF (0.18 ml, 2.3 mmol) was then added in a dropwise fashion to the oxalyl chloride solution with vigorous bubble evolution. An adduct of concentration 1 mmol / ml was formed. After 30 minutes, 2 ml of this solution (2 mmol, 4 equiv.) was syringed into the flask which contained **3**. The mixture became deep yellow and was stirred for 2 hours. The reaction was quenched by the addition of 10 ml of a 1:1 acetic acid / water solution and stirred an additional 2 hours. The mixture was then diluted with 100 ml of dichloromethane. The organic layer was washed with 100 ml of water and 100 ml of saturated sodium bicarbonate solution. The organic layer was then dried ($MgSO_4$), filtered and concentrated. Purification by column chromatography (15% ethyl acetate in hexane was used as an eluent) yielded the product **93** (170 mg, 64%); R_f 0.70 in ethyl acetate - hexane, 1:2; ^1H NMR (360 MHz, $CDCl_3$) δ: 8.17 (s, 1H, *H*CO), 5.53 (dd, 1H, $J_{1,2}$ = 1.3 Hz, $J_{2,3}$ = 2 Hz, H-2), 5.32 (d, 1H, $J_{1,2}$ = 1.3 Hz, H-1), 4.14 (m, 1H, H-5), 3.95 (dd, $J_{3,4}$ = 9.5 Hz, $J_{4,5}$ = 9.5 Hz, H-4), 3.92 (dd, 1H, $J_{3,4}$ = 9.5 Hz, $J_{2,3}$ = 2 Hz, H-3), 3.82 (dd, 1H, $J_{5,6}$ = 4.2 Hz, $J_{6,6'}$ = 11.0 Hz, H-6), 3.66 (dd, 1H, $J_{5,6'}$ = 2.0 Hz, $J_{6,6'}$ = 11.0 Hz, H-6'), 2.62 (m, 2H, SCH_2CH_3), 1.27 (t, 3H, SCH_2CH_3).

Ethyl 3,4,6-tri-O-benzyl-2-O-ethenyl-1-thio-α-D-mannopyranoside (**94**)

The 2-*O*-formate **93** (160 mg, 0.036 mmol) was purged with argon and dissolved in 6 ml of toluene, 2 ml of tetrahydrofuran and 0.1 ml of pyridine (solvents anhydrous). The mixture was cooled to -40°C and Tebbe's reagent **9** (0.92 ml, 0.92 mmol) was added in a dropwise fashion. After 90 minutes, the solution was quenched and worked-up as for the preparation of **10**. Silica gel chromatography with 8% ethyl acetate in hexane which contained 0.1% triethylamine as the solvent system was used to purify the reaction

as viscous, clear syrups; R_f 0.66 in ethyl acetate - hexane, 1:3; 6.41 (dd, 1H, J_{cis} = 6.8 Hz, J_{trans} = 14.4 Hz, CHH'=C*H*-), 5.45 (d, 1H, $J_{1,2}$ = 1.3 Hz, H-1), 4.28 (dd, J_{gem} = 2.0 Hz, J_{trans} = 14.4 Hz, CH*H'*=CH-), 4.21 (dd, 1H, $J_{1,2}$ = 1.3 Hz, $J_{2,3}$ = 3.4 Hz, H-2), 4.15 (m, 1H, H-5), 4.11 (dd, J_{gem} = 2.0 Hz, J_{cis} = 6.8 Hz, C*H*H'=CH-), 4.00 (dd, 1H, $J_{3,4}$ = 9.2 Hz, $J_{4,5}$ = 9.2 Hz, H-4), 3.89 (dd, 1H, $J_{2,3}$ = 3.4 Hz, $J_{3,4}$ = 9.2 Hz, H-3), 3.83 (dd, 1H, $J_{5,6}$ = 4.6 Hz, $J_{6,6'}$ = 11.0 Hz, H-6), 3.69 (dd, 1H, $J_{5,6'}$ = 2.0 Hz, $J_{6,6'}$ = 11.0 Hz, H-6'), 2.62 (m, 2H, SCH_2CH_3), 1.25 (t, 3H, SCH_2CH_3).

*Attempted Mixed Acetal Formation with **94**:*

The vinyl ether **94** (29 mg, 0.056 mmol) and the alcohol **12** (26 mg, 0.056 mol) were added to a reaction vessel and purged with argon. Dichloromethane (3 ml) was syringed into the flask and it was cooled to -40°C. Toluenesulfonic acid (0.05 equiv.) was added in one portion and the reaction monitored by tlc for the formation of any mixed acetals. After 2 hours at -40°C, the reaction was slowly increased to -15°C at which time all the vinyl ether was converted to hydrolysis product **3**.

Methyl 2,3,6-tri-O-benzyl-α-D-glucopyranoside-ethyl 3',4',6'-tri-O-benzyl-1'-thio-α-D-mannopyranoside-2',4-benzylidene acetal (**98**)

The alcohol **3** (40 mg, 0.081 mmol) and sodium hydride (6.5 mg, 0.162 mmol) were added to a reaction flask and purged with argon. Dry THF (1.8 ml) and DMPU (0.2 ml) were syringed into the mixture. The solution was stirred for 30 minutes and it was cooled to -40°C. The diazirine **95** (0.24 ml of a 33% solution in hexane (w / w), 0.404 mmol) was added in a dropwise fashion to the reaction mixture. The solution was stirred for 5 hours at -40°C prior to the addition of **13** (38 mg, 0.081 mmol). The mixture was then stirred overnight and allowed to warm to room temperature. The mixture was concentrated *in vacuo* and purified by chromatography with 13% ethyl acetate in hexane

yield (21 mg). The dimer **97** (10 mg, 23% of **3**), as well as **3** (10 mg, 25%), and **13** (25 mg, 66%) were also isolated. Treatment of **98** in dichloromethane with excess *p*-toluenesulfonic acid yielded the alcohols **3** and **13**. Treatment of **97** with excess acid gave the alcohol **3**.

97: R_f 0.75 in ethyl acetate - hexane, 1:2; ^{1}H NMR (360 MHz, $CDCl_3$) δ: 5.74 (s, 1H, PhC*H*), 5.06 (d, 2H, $J_{1,2}$ = 1.2 Hz, H-1, H-1'), 2.62 (m, 2H, SC*H*$_2$CH$_3$), 2.42 (m, 2H, SCH$_2$·CH$_3$·), 1.22 (t, 3H, SCH$_2$C*H*$_3$), 1.07 (t, 3H, SCH$_2$·C*H*$_3$·).

98: R_f 0.66 in ethyl acetate - hexane, 1:2; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 5.91 (s, 1H, PhC*H*), 5.52 (d, 1H, $J_{1,2}$ = 1.5 Hz, H-1'), 4.69 (d, 1H, $J_{1,2}$ = 3.5 Hz, H-1), 4.46 (dd, 1H, $J_{1,2}$ = 1.5 Hz, $J_{2,3}$ = 4.5 Hz, H-2'), 4.23 (m, 1H, H-5'), 4.13 (dd, 1H, $J_{3,4}$ = 9.5 Hz, $J_{4,5}$ = 9.5 Hz, H-4'), 4.04 (dd, 1H, $J_{2,3}$ = 9.5 Hz, $J_{3,4}$ = 9.5 Hz, H-3), 3.96 (dd, 1H, $J_{2,3}$ = 3.5 Hz, $J_{3,4}$ = 9.5 Hz, H-2), 3.83 (m, 1H, H-5), 3.65 (dd, 1H, $J_{2,3}$ = 4.5 Hz, $J_{3,4}$ = 9.5 Hz, H-3') 3.46 (s, 3H, OCH$_3$), 2.60 (m, 2H, SC*H*$_2$CH$_3$), 1.28 (t, 3H, SCH$_2$C*H*$_3$); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ: 102.9 (Ph*C*H), 97.9 (C-1), 84.1, 82.1, 80.6, 80.0, 78.4, 75.1, 74.2, 72.2, 70.3 (C-1', C-2', C-3', C-4', C-5', C-2, C-3, C-4, and C-5), 75.7, 75.0, 75.0, 73.4, 73.3, 72.0 (6 x Ph*C*H$_2$), 69.3, 63.6 (C-6 and C-6'), 55.1 (OCH$_3$), 25.3 (S*C*H$_2$CH$_3$), 15.1 (SCH$_2$*C*H$_3$).

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