SYNTHESIS OF SEGMENTS OF THE REPEATING UNIT OF THE C-POLYSACCHARIDE OF *STREPTOCOCCUS PNEUMONIAE*

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To my parents, my wife Aiqin, my daughter Xu and my son Chianfu

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List of Abbreviations and Symbols Used

Å	Ångström
$[\alpha]^D$	specific rotation, observed rotation measured by using the D line of a sodium lamp
aa	*anti anti*
AAT	2-acetamido-4-amino-2,4,6-trideoxy-D-galactose
Ac	acetyl
agp	*anti gauche plus*
AIBN	azobisisobutyronitrile
All	allyl
Bn	benzyl
bp	boiling point
bs	broad singlet
Bu	butyl
Bz	benzoyl
c	concentration in gram per milliliter
CAN	ceric ammonium nitrate
Cbz	benzyloxycarbonyl
CNE	cyanylethyl
COSY	correlated spectroscopy
d	doublet
D1	relaxation delay time
D8	mixing time

dd	doublet of doublet
ddd	doublet of doublet of doublet
DEAD	diethyl azodicarboxylate
DFT	density functional theory
DIPEA	diisopropylethylamine
DMAP	4-dimethylaminopyridine
DMF	*N,N*-dimethylformamide
DMSO	dimethyl sulfoxide
DMTST	dimethyl(methylthio)sulfonium trifluoromethanesulfonate
DNA	deoyxribose nucleic acid
DPFGSE	double pulsed field gradient spin echo
DPPA	diphenylphosphoryl azide
DTBMP	2,6-di-*tert*-butyl-4-methylpyridine
ea	*exo anti*
egm	*exo gauche minus*
egp	*exo gauche plus*
EI	electron ionization
eq	equivalent
esd	estimated standard deviation
ESI	electrospray ionization
Et	ethyl
eV	electron volt(s)
g	gram(s)

GIAO	gauge invariant atomic orbital
h	hour(s)
HETCOR	heteronuclear correlated spectroscopy
HMQC	heteronuclear multiple quantum coherence
HSPm	*meta* phenyl proton of the phenyl group connecting a sulfur atom in glycosyl sulfoxides
HSPo	*ortho* phenyl proton of the phenyl group connecting a sulfur atom in glycosyl sulfoxides
HSPp	*para* phenyl proton of the phenyl group connecting a sulfur atom in glycosyl sulfoxides
HSQC	heteronuclear single quantum coherence
Hz	Hertz
I	the nucleus at which the enhancement is measured in nOe experiment
iBu	isobutyl
J	coupling constant
kcal	kilocalories
lit.	literature
m	multiplet
M	molarity
*m*CPBA	*meta*-chloroperoxybenzoic acid
Me	methyl
MHz	megaHertz
min	minute(s)
mL	milliliter(s)

μL	microliter(s)
mmol	millimole(s)
mol	mole(s)
mp	melting point
mol. siev.	molecular sieves
MPa	megaPascal
MS	mass spectra
NBS	*N*-bromosuccinimide
NIS	*N*-iodosuccinimide
NMR	nuclear magnetic resonance
nOe	nuclear Overhauser effect
NOESY	nuclear Overhauser effect spectroscopy
°C	degree Celsius
ORTEP	Oak Ridge thermal ellipsoid plot
PC	phosphorylcholine
PDCA	pyridinium dichromate-acetic anhydride
Ph	phenyl
pMBn	*para*-methoxybenzyl
pMPh	*para*-methoxyphenyl
ppm	parts per million
Py	pyridine
q	quartet
r	internuclear distance

Ref	reference
Rf	retention factor for migration distance of a substance on TLC
rt	Room temperature
s	singlet
S	the nucleus which is satuated in nOe experiments
σ	standard deviation
t	triplet
T1	nonselective longitudinal relaxation time
Tf	trifluoromethanesulfonyl group
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	tetramethylsilane
TMSOTf	trimethylsilyl triflate
Tr	trityl, triphenylmethyl
UV	ultraviolet
V	unit cell volume of single crystal
V	volt
ZPVE	zero point vibrational energy
δ	chemical shifts in parts per million from TMS

Abstract

The C-polysaccharide is an antigen common to all known *Streptococcus pneumoniae* bacteria. The repeating unit in the C-polysaccharide is a pentasaccharide, which consists of the following sugars in order: two *N*-acetyl-D-galactopyranoses (**A** & **B**), ribitol phosphate (**C**), D-glucopyranose (**D**), and 2-acetamido-4-amino-2,4,6-trideoxy-D-galactopyranose (**E**), and with phosphorylcholine attached to C-6 of the **A** and **B** units (Figure 1.2). Successful syntheses of derivatives of the rare sugar **E** were developed. Many unsuccessful attempts were made to form the **DE** unit by two different strategies. Derivatives of the AB disaccharide were synthesized that had the required α-linkage between unit **A** and **B** and also a linker arm β-linked to **B**. Use of solvent participation and careful control of reaction temperature allowed formation of the desired anomeric configurations with excellent stereoselectivity. It was found that phosphorylcholine units could be added regioselectively at both O-6s of the mostly unprotected AB-linker arm dimer. An improved synthetic route was developed to prepare an expensive reagent, D-galactal from D-galactose. The configurations and conformations of glycosyl sulfoxides were studied by X-ray crystallography, nOe experiments and DFT calculations. The evidence presented in this thesis shows that the most stable configurations of glycosyl sulfoxides are those that can adopt conformations with the aglycon *exo* and the lone pair on sulfur *anti* to the C1-O5 bond, because of the n→σ* overlap possible in this orientation. For D-sugars, these are the S_S configurations of the α-anomers. For glycosyl sulfoxides of α-anomers having the kinetically favored R_S configurations, the *anti* conformations were found to be comparable in stability to the *exo* conformations, a surprising conclusion in view of literature assumptions. The calculations suggest that the *anti* conformation is stabilized by overlap of a p-type lone pair on the sulfoxide sulfur atom with the C1-O5 σ* orbital.

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There are no words that can express the thanks I owe to my parents, my wife, my daughter, my son, my sister and my brother. Without their consistent love, support and patience, I would not have been able to finish this thesis.

Chapter 1 Introduction

1.1 Synthetic studies of the repeating unit of the C-polysaccharide of *Streptococcus pneumoniae*

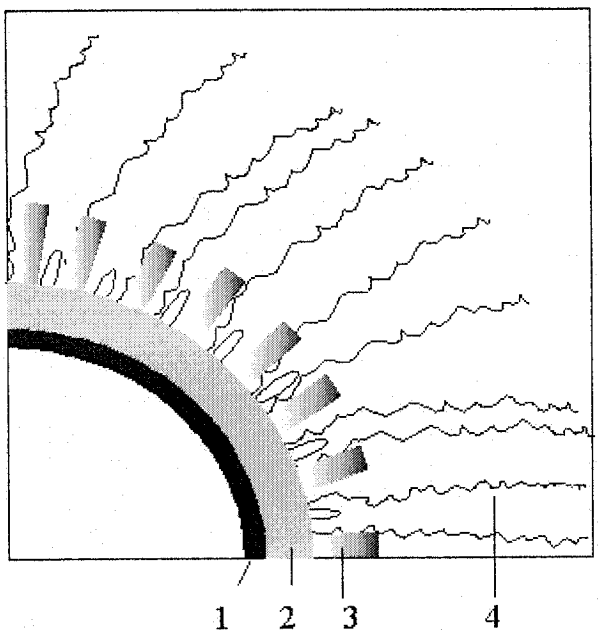
1.1.1 General

Streptococcus pneumoniae, a diplococcus Gram-positive bacterium which was independently described in 1881 by Pasteur and Sternberg, is responsible for invasive diseases such as pneumonia, meningitis, bacteremia, and septicemia, as well as for noninvasive diseases such as pharyngitis, conjunctivitis and otitis media in human beings.[1,2] For more than 100 years, this family of bacteria has persisted in being a major causative agent of the above mentioned serious human diseases, especially community-acquired pneumonia.

Streptococcus pneumoniae is known to have at least 90 serotypes,[3] each of which has a different capsular polysaccharide extending from the cell wall. The structures of most, but not all, of these capsular polysaccharides are known.[4] The 90 serotypes have different local concentrations in different parts of the world.[2,5-7] Also extending from the peptidoglycan of the cell wall is the C-polysaccharide, which is thought to have the same or similar structures[8] in all 90 *Streptococcus pneumoniae* serotypes. The same polysaccharide is also present in the cell wall of *Streptococcus Mitis* biovar 1 strain SK137.[9] This polysaccharide has antigenic properties[8-10] and thus is an attractive candidate for vaccine preparation.

1.1.2 Structure of the *Streptococcus pneumoniae* cell surface

Figure 1.1[11] shows a schematic structure of the cell surface of *Streptococcus pneumoniae*. Surrounding the pneumococcus bacterial cell is the capsule, which consists of a covalently attached polysaccharide (a capsular polysaccharide) as mentioned above.



1. Plasma membrane (9nm).
2. Peptidoglycan layer of the cell wall (20nm).
3. Cell wall polysaccharide and proteins (20 to 30 nm). The cell wall polysaccharide is located on both the outer and inner surfaces of isolated cell walls.
4. Capsule polysaccharide (200 to 400 nm).

Figure 1.1 A schematic structure of the cell surface of *Streptococcus pneumoniae*[11]

The capsule is the thickest layer and mostly conceals the inner structures in pneumococci.[12] The differential ability of serotypes to survive in the bloodstream and possibly to cause invasive disease is determined by the thickness of the capsule and the chemical structure of the capsular polysaccharide.[11] The cell wall consists of a triple-layered peptidoglycan backbone that anchors the capsular polysaccharide, the C-polysaccharide, and also proteins. The chemical compositions of the polysaccharides on the cell surface of *Streptococcus pneumoniae* will be described in detail in the following sections.

1.1.3 The capsular polysaccharides

The chemical composition of the capsular polysaccharide determines its specific serological type, of which there are now 90 types known.[3] These different serotypes were divided into 46 groups, numbered 1 to 48 (26 and 30 are not used). The serotype distribution varies with geographical region,[5-7] and the presence of the different serotypes has been found to vary with age.[6] The capsular polysaccharides of *Streptococcus pneumoniae* bacteria are usually regular, periodic polymers with diverse structures that contain, in several instances, comparatively rare monosaccharides. Extensive studies on the structures of the polysaccharides have been carried out, particularly starting from the time of the development of the pneumococcal polysaccharide-based vaccine[4] and these studies are continuing to appear.[13-15] The oligosaccharides that constitute the repeating units of these polysaccharides provide demanding challenges in terms of oligosaccharide synthesis. Advances in glycoside synthesis and in the ancillary techniques of chromatographic separation, high field NMR spectroscopy and mass spectrometry have allowed rational synthesis of such oligosaccharides to be planned and successfully completed. Much work has been done on pneumococcal capsular polysaccharides, both on structural elucidation[16-19] and on oligosaccharide synthesis.[20-32] The structures of pneumococcal capsular polysaccharides and the available syntheses before 1998 have been summarized by Kamerling.[4]

1.1.4 Cell wall and cell membrane polysaccharides

The pneumococcal cell wall is typical of a Gram-positive microorganism, which is relatively thick and homogeneous. It is constructed from three layers of cross-linked peptidoglycan chains with the common C-polysaccharide and the individual capsular

polysaccharide covalently attached.[33] The peptidoglycan is an enormous polymer composed of many identical carbohydrate subunits crosslinked through short peptides. The basic carbohydrate-containing polymer subunit is a disaccharide, 2-acetamido-2-deoxy-β-D-glucopyranosyl-(164)-2-acetamido-3-*O*-[(S)-1-carboxyethyl]-2-deoxy-β-D-glucopyranosyl (164), which contains the monosaccharides commonly termed, *N*-acetyl-D-glucosamine and *N*-acetylmuramic acid, respectively, and is repeated many times. The carbohydrate portion differs from chitin, the major constituent of the shells of crustaceans, in having lactic acid side chains ether-linked to *O*-3 of alternate glucosamines and from cellulose, the major constituent of plant cell walls, by, in addition, having 2-acetamide substituents rather than 2-hydroxy substituents. *N*-acetylmuramic acid forms an amide bond from the carboxyl group of its lactic acid side chain to the amino group of L-alanine, which is usually linked to D-isoglutamine and then L-lysine. Variation occurs thereafter, though D-alanine is commonly present, often in dimeric units. Chains of linked peptidoglycan subunits are joined by cross-links between the peptides.

The C-polysaccharide is uniformly distributed on both the inside and the outside of the cell walls.[12,34] It is also covalently bonded to a lipid moiety in the plasmic membrane through a phosphodiester linkage,[35,36] to give the F antigen. The C-polysaccharide was first described as a somatic antigen (fraction "C") of the pneumococcus in 1930.[37] Structural studies[38-42] showed that the polysaccharide was composed of a repeating unit containing residues of 2-acetamido-2-deoxy-α-D-galactopyranose, 2-acetamido-2-deoxy-β-D-galactopyranose, ribitol phosphate, β-D-glucopyranose, 2-acetamido-4-amino-2,4,6-trideoxy-α-D-galactopyranose, and

phosphorylcholine. The O-1 of 2-acetamido-4-amino-2,4,6-trideoxy-α-D-galactopyranose connected the O-4 of a 2-acetamido-2-deoxy-α-D-galactopyranose in the next repeating unit. With the development of modern NMR techniques, the structure of the C-polysaccharide was almost completely elucidated.[9,36,43-45] The sequence of the carbohydrate residues, most of their absolute configurations, the positions of the *N*-acetyl groups, the locations of phosphorylcholine substituents and other phosphorus linkage sites were clearly identified. Figure 1.2 shows the structure of the C-polysaccharide.[44] The configuration of the ribitol phosphate was shown to be D, As reported in this laboratory earlier.[46]

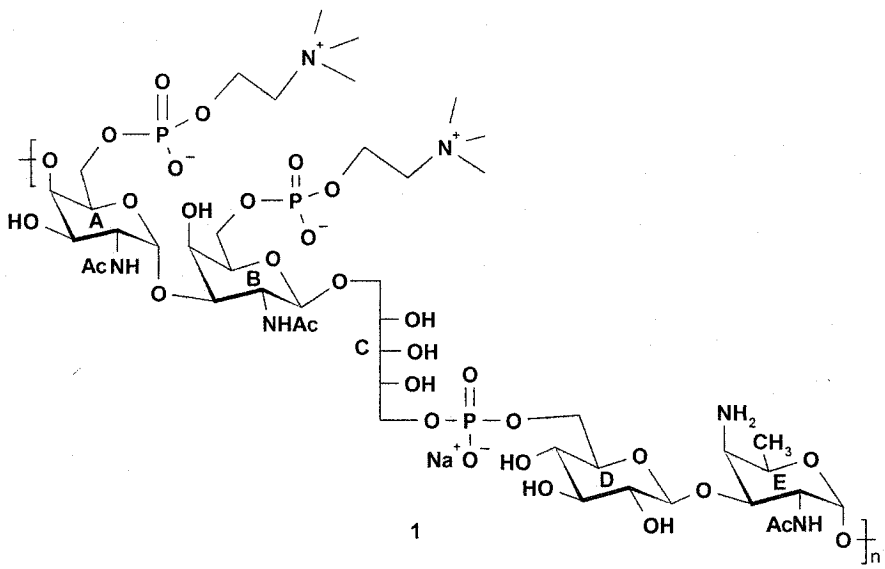


Figure 1.2 The structure of the C-polysaccharide of *Streptococcus pneumoniae*[43]

Recently, it has become apparent that there is some variability in the structures of the C-polysaccharides from different serotypes.[8] Jennings et al. originally proposed from very careful work on C-polysaccharide from serotype 1 that the structure was as shown in Figure 1.3.[42] Later, from more modern NMR measurements but much less detailed

chemical studies on the C-polysaccharide from serotype R36A, this group considered that they had corrected the structure to be that shown in Figure 1.2.[43]

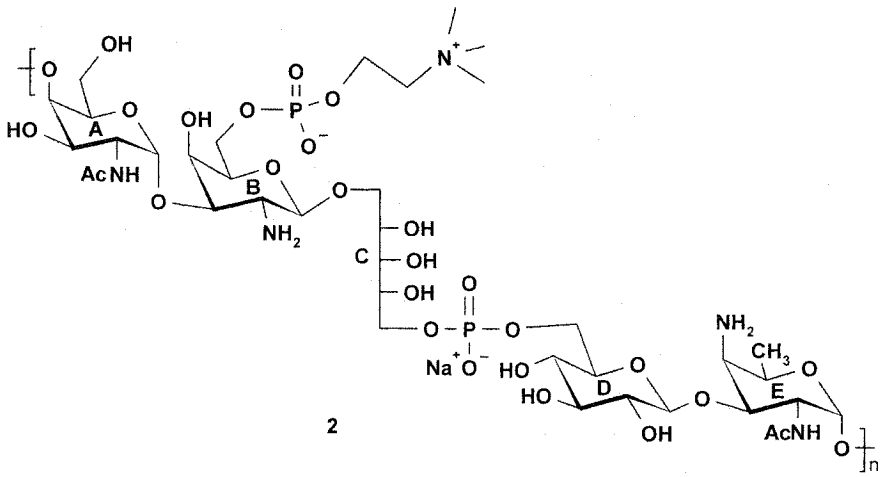


Figure 1.3 The first complete structure of the repeating unit of the C-polysaccharide[42]

At about the same time, Fischer et al obtained the same structure for C-polysaccharide from stain R6.[44] An outline of the differences between the Danish and American serotype nomenclature is contained in the review by Kamerling;[4] serotype R36A is a noncapsulated rough mutant that is considered by Karlsson et al[8] to be derived from serotype 2 and R6 is derived from strain R36A.[35] However, Karlsson et al examined C-polysaccharides from several serotypes. They showed that the C-polysaccharide from a different rough mutant from serotype 2, strain CSR SCS2 had the structure shown in Figure 1.4. This structure was also found in the C-polysaccharide from serotype 18A (Danish nomenclature) but serotypes 32F and 32A contained the bisphosphorylcholine form pictured in Figure 1.2.[8]

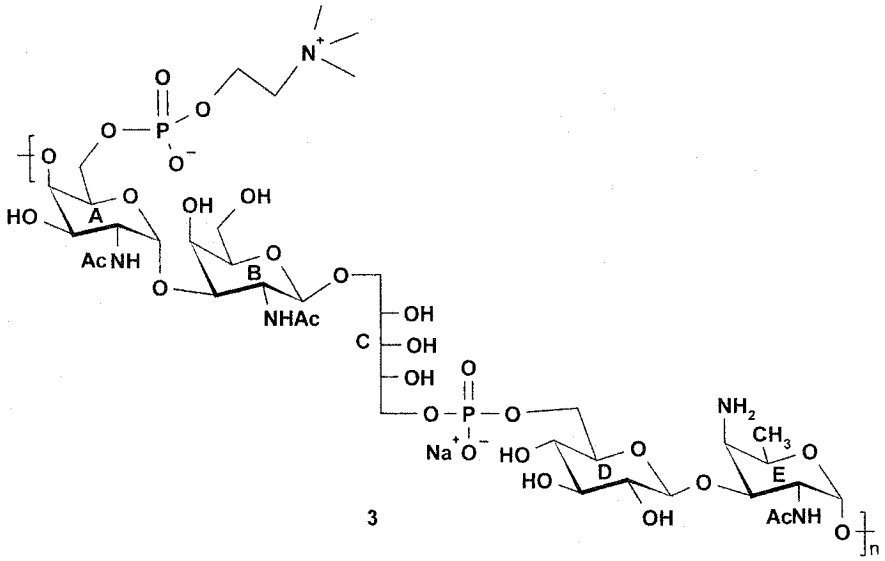


Figure 1.4 The third complete structure for the C-polysaccharide repeating unit[8]

It was noted earlier that *Streptococcus mitis* also contains the C-polysaccharide with the normal bisphosphorylcholine structure.[9] More detailed examination of the C-polysaccharides from a number of *Streptococcus mitis* serotypes has shown that a few contain a modified structure where the phosphorylcholine units are converted into phosphorylethanolamine units.[45]

1.1.5 Vaccines against *Streptococcus pneumoniae*

The first pneumococcal vaccine proposed by Wright in 1914[47,48] was a whole-cell killed bacteria vaccine and this approach to a vaccine was pursued by Lister.[49] The introduction of sulfonamides in the late 1930s and of penicillin in 1945 dramatically changed the prognosis of pneumococcal infections. In the meantime, knowledge about the capsules of *Streptococcus pneumoniae* and its many serotypes was acquired.[50,51] The emergence of antibiotic-resistant strains of pneumococcus[52,53] has made this family of bacteria a very severe health problem again. This led to the introduction of increasingly

more sophisticated vaccines based on the polysaccharides present in the cell capsules of *Streptococcus pneumoniae.*

Like other encapsulated bacteria, the pneumococcus relies on its polysaccharide surface capsule to evade the host's phagocytic defenses. Induction of anti-capsular antibodies by active or passive immunization has long been known to protect against disease by enhancing phagocytosis of the bacteria.[54] However, the development of a vaccine with adequate coverage of pneumococci is complicated by the existence of various distinct pneumococcal capsular polysaccharide serotypes.[3] This obstacle was partially overcome with the introduction of a polyvalent pneumococcal vaccine i.e., one that contains capsular polysaccharide from more than one serotype. In 1977, a vaccine containing the purified capsular polysaccharides of 14 of the most prevalent serotypes was licensed,[55] this vaccine provided coverage against about 80% of invasive pneumococcal isolates in the United States. With the introduction of the 23-valent pneumococcal polysaccharide (PS-23) vaccine (serotypes 1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19A, 19F, 20, 22F, 23F, 33F) in 1983, coverage was increased to almost 90% of the infections caused by *Streptococcus pneumoniae* in the United States.[1] The six serotypes (6B, 9V, 14, 19A, 19F, and 23F) that most frequently cause invasive drug-resistant pneumococcal infection in the United States are represented in the 23-valent vaccine. Preparation of these vaccines poses formidable challenges, because a certain number of separate vaccines must be manufactured, controlled, and combined in appropriate concentrations.

The T-cell-independent response generated by the polysaccharide vaccine results in limited immunogenicity and effectiveness in several important populations. Older

adults and persons with chronic illness or immunodeficiency may not respond after they receive PS-23 vaccine. Children less than two years of age do not fully develop the T-cell-independent response. The PS-23 vaccine is poorly immunogenic for important serotypes in this group, so that the PS-23 vaccine has not been recommended for use among children less than 2 years of age who show the highest incidence of invasive pneumococcal infections (Figure 1.5). The immunologic response to serotype 6A and 14 is decreased in children aged 2-5 years.[56] Furthermore, polysaccharide vaccines do not induce T-cell memory and hence reimmunization is required.[57] Considering these limitations of this type of vaccine, efforts have been made to prepare better alternatives based on polysaccharide or oligosaccharide conjugates, having proteins as the carrier.[58]

In the last few years, vaccines have been marketed in which depolymerized polysaccharide is conjugated to protein.[59,60] The polysaccharide fragments are conjugated to proteins such as a non-toxic toxin (CRM_{197}), a detoxified toxin (diphtheria or tetanus), or an outer membrane protein complex from *Neisseria meningitidis*.[59,61,62] Other proteins are under consideration.[59,63] The current conjugated vaccine is seven-valent (4, 6B, 9V, 14, 18C, 19F, and 23F) which limits coverage to 75 % of the cases in developed countries.[59] A test of this seven-valent conjugated vaccine on 37,868 children in California indicates that it is much more effective in preventing invasive pneumococcal disease as well as acute otitis media and pneumonia in children than the PS-23 vaccine.[64] Another test on 22 infection-prone non-responders to the PS-23 vaccine in Germany showed that the conjugate vaccine is more immunogenic,[65] providing additional support for the use of the new vaccine. The seven-valent conjugated vaccine is also more effective against otitis media but shifts the serotype population towards those

not in the seven-valent vaccine.[66] An 11-valent conjugated vaccine is still under testing. Its serotype combination would give 83, 79, 75 and 72 % serotype coverage in North America, Oceania, Europe and Latin America, respectively.[5] Table 1.1 shows pneumococcal conjugated vaccines licensed or in development in the United States.[56]

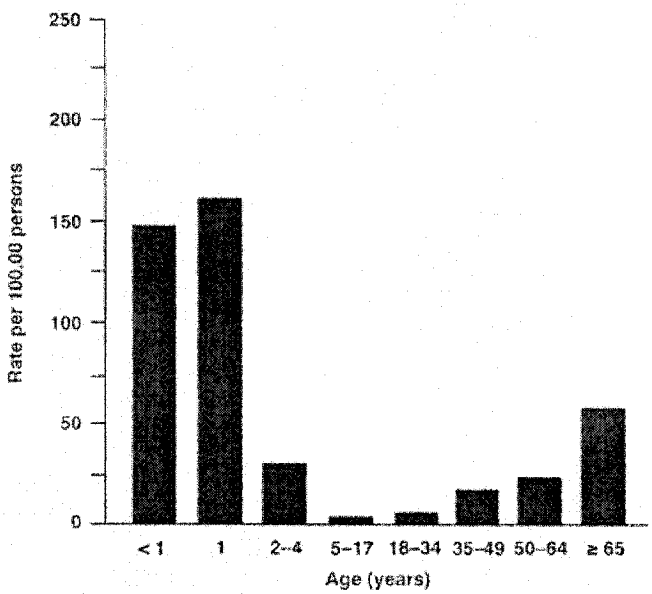


Figure 1.5 Incidence of invasive pneumococcal disease in the United States, by age, 2000[56]

Table 1.1 Pneumococcal conjugate vaccines licensed or in development in the United States

Conjugated vaccines	Manufacturer	Status
Seven-valent (4, 6B, 9V, 14, 18C, 19F, 23F)		
Pnc-CRM7 (polysaccharides conjugated to CRM_{197} protein)	Wyeth Vaccines (Pearl River, New York)	Licensed
Pnc-OMP (polysaccharides conjugated to outer membrane protein of *Neisseria meningitidis* group B)[a]	Merck & Co. (Whitehouse Station, New Jersey)	Phase III (otitis media endpoint)
Nine-valent (seven-valent plus 1, and 5)		
Pnc-CRM9 (polysaccharides conjugated to CRM_{197} protein)	Wyeth Vaccines	Phase III (invasive disease and pneumonia endpoints)
11-valent (nine-valent plus 3, and 7F)		
Pnc-D/T (polysaccharides conjugated to diphtheria toxoid and tetanus protein)[b]	Aventis Pasteur (Lyon, France)	Phase III (pneumonia endpoint)
Polysaccharides conjugated to protein D of non-typable *Haemophilus influenzae*	GlaxoSmithKline (Uxbridge, Middlesex, United Kingdom)	Phase II/III (otitis media endpoint)
Pnc-CRM11 (polysaccharides conjugated to CRM_{197} protein)	Wyeth Vaccines	Preclinical

a. This product is not being developed further by Merck & Co.

b. This product is not being developed further by Aventis Pasteur in part because of lower-than-expected immunogenicity of concomitantly administered cellular pertussis vaccine.

Because of the serotype problem, alternative approaches to pneumococcal vaccines are also being considered. The C-polysaccharide, a common antigen to all the known types of *Streptococcus pneumoniae*,[34,67] is an attractive candidate. Interestingly, a closely similar polysaccharide has been recently found in *Streptococcus mitis*.[9] Immunization with noncapsular antigens that might induce protection against all serotypes would be advantageous either instead of or as a complement to, capsular polysaccharide-based vaccines.[58] Such a vaccine could enhance protective efficacy of type-specific conjugate vaccines and extend protection to strains not included in the vaccine. In addition, although concealed by capsular polysaccharides in the log phase of growth of pneumococci, the C-polysaccharide is found to be exposed on decaying cells. It is therefore possible that a host infected by pneumococci can benefit from antibodies to these antigens, because they may facilitate the clearance of potentially harmful disintegrated bacterial residues such as the peptidoglycan. Studies showed that anti-C-polysaccharide antibody may contribute to the removal of pneumococci with no or partially disintegrated capsules during the course of pneumococcal infections, thereby diminishing inflammatory reactions.[68] It has been reported that non-type-specific antibodies could protect mice against pneumococcal infections.[58] On the other hand, it was also reported that mice were not protected against pneumococcal infections by passive immunization with polyclonal rabbit antiserum to C-polysaccharide.[69] Intensive research efforts are being conducted to clarify this situation.[60,61,63,70]

The C-polysaccharide was found to be a contaminant in most preparations of capsular polysaccharides and methods have not been found to remove it completely.[71] Capsular polysaccharides were found to be strongly attached to the cell walls of different

types of pneumococci and they persisted even after enzymatic disintegration of cell walls.[72] It is usually very difficult to isolate large polar molecules like those from biological specimens in very high purity, which makes it difficult to accurately evaluate the immunoefficacy of different parts of the cell. To understand the structure-activity of the natural antigen, the availability of the pure polysaccharide or the oligosaccharide of the repeating unit or analogues would be helpful. Chemical synthesis in this regard is a necessary alternative to provide pure research substances. Development of a reasonable way to synthesize the compound could be the most economical way to obtain it.

In order to clarify the confusion about the immunoefficacy of the C-polysaccharide and possibly to develop a commercially effective vaccine, an effort was made here to synthesize the repeating unit of the C-polysaccharide.

1.2 Methodology of oligosaccharide synthesis

Synthetic carbohydrate chemistry has expended enormously in the last 20 years with the recognition that carbohydrates and particularly oligosaccharides linked to proteins and lipids are important for biological recognition. Since the introduction of the Koenigs-Knorr method in 1901,[73] much effort has been made to try to synthesize oligosaccharides stereoselectively, regioselectively, and in high yields. As seen in Figure 1.6, in order to form an oligosaccharide, the key steps involve linking two carbohydrate units through formation of acetal linkages. The anomeric carbon C-1 of one completely protected carbohydrate (glycosyl donor **4**) is coupled with a free hydroxyl group at C-4 from another appropriately protected carbohydrate (glycosyl acceptor **5**) or at C-4' in the glycosyl acceptor **7**. A well-designed synthetic procedure has to be planned in order to get the desired coupling in a high yield and to avoid obtaining a complex mixture. Figure

1.6 describes the synthesis of a fully protected β-D-glucopyranosyl-containing oligosaccharide. L in glycosyl donor **4** stands for a leaving group, which usually needs to be activated during the coupling of the glycosyl donor with the acceptor. R_1, R_2 ... R_8 indicate the protecting groups that can be deprotected for further coupling reactions to afford the designed oligosaccharide.

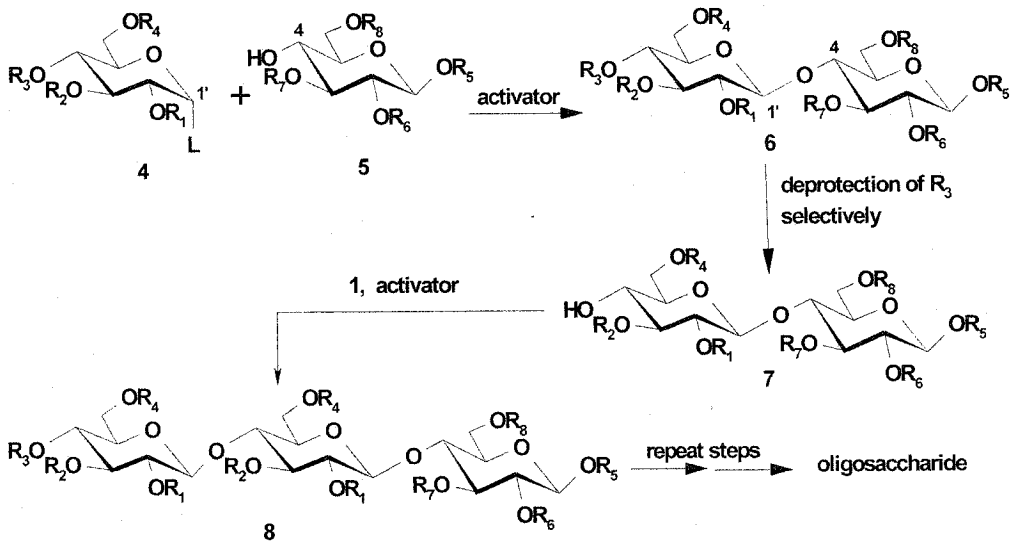


Figure 1.6 A schematic description of synthesis of a homooligosaccharide

1.2.1 Protection and deprotection in oligosaccharide synthesis

Carbohydrates are multifunctional compounds. In order to accomplish an unambiguous coupling of a desired hydroxyl group, all other potentially competing functional groups of the same reactivity have to be protected before the coupling reaction is performed. This includes groups on both the glycosyl donor and the glycosyl acceptor. In addition, if further glycosylations have to be performed subsequently on other hydroxyl groups, these positions have to be protected differentialy and in a manner that will allow facile deprotection without influencing the other protecting groups. A detailed

discussion of protection and deprotection can be found in reviews of protecting groups in oligosaccharide synthesis.[74,75]

1.2.2 Glycosyl donors in glycosidic reactions

Over the past several years, methods for the synthesis of oligosaccharides have advanced tremendously. The applications of different types of glycosyl donors and methods for their activation can be found in the literature.[76-87] Figure 1.7 shows some types of the most commonly used glycosyl donors.

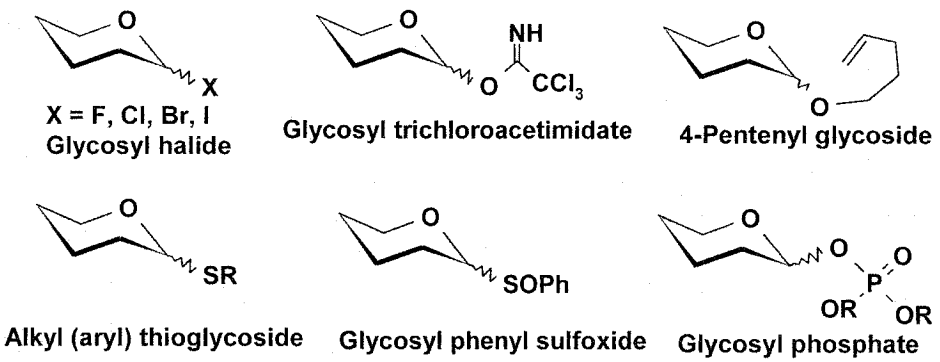


Figure 1.7 Some types of most commonly used glycosyl donors

1.2.2.1 Glycosyl halides

For over 100 years, the Keonigs-Knorr method[73] has been the most popular method and modifications of it are still being developed. In this classical method acetylated glycosyl chlorides or bromides are converted in the presence of silver catalysts, such as silver carbonate, into glycosides. Tetrabutylammonium bromide was introduced by Lemieux and coworkers as a catalyst to produce α-D-linked disaccharides.[88] Many other types of activators were also introduced and these are described in the literature.[85] The selectivity of a coupling reaction can be modulated by the choice of activators. A successful synthesis using a glycosyl fluoride as a glycosyl

donor gave a 95 % yield of a stereoselectively coupled oligosaccharide product.[89] The use of glycosyl iodides has also been advocated recently.[90-92]

1.2.2.2 Thioglycosides and phenyl sulfoxides

Thioglycosides are another useful type of glycosyl donor. The decisive contribution which led to the successful development of the thioglycoside method was made by Lönn.[93] He activated thioglycosides by using methyl triflate, which methylates sulphur to form an intermediate sulfonium ion which leaves readily during an oligosaccharide synthesis. Thioglycosides are stable in many chemical environments and are widely used in oligosaccharide synthesis. However methyl triflate is volatile and extremely toxic. Fugedi and Garegg first employed dimethyl(methylthio)sulfonium trifluoromethanesulfonate (DMTST) as the thiophilic promoter to show an excellent result.[94,95] After then, a whole range of other promoters were discovered, which were able to activate the thioglycoside group and which are well suited for oligosaccharide synthesis. These include nitrosyl tetrafluoroborate,[96] phenylselenyl triflate,[97] alkylsulfenyl triflate,[95] NIS-trifluoroacetic acid,[98] phenylsulfenyl triflate[99] and 1-benzenesulfinyl piperidine/triflic anhydride.[100] They can also be activated by various heavy metals,[85] NBS.[101]

Further improvement in thioglycoside methodology were introduced in 1989, when glycosylation of hindered alcohols and derivatives of phenol was studied.[102] As shown in Figure 1.8, phenyl sulfoxides were used as the glycosyl donors.

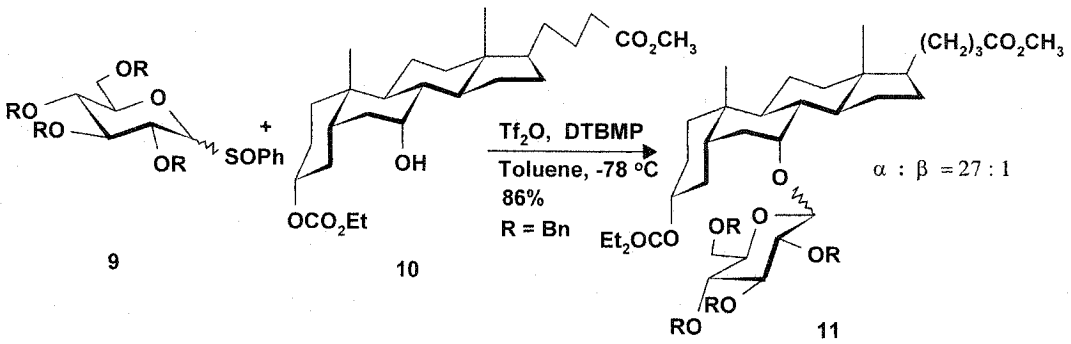


Figure 1.8 Glycosylations with glycosyl sulfoxides

These glycosylation reactions can be carried out at low temperatures, and it is also worth noting that the reactions work well regardless of the electron-releasing or electron-withdrawing properties of the sugar protecting groups. Protecting groups influence the stereochemistry of glycosidation. For instance, when a pivaloyl group is at the C-2 position, a β-linkage is formed stereoselectively; but with a benzyl group at the C-2 position, an α-linkage product is formed predominantly. It is thought that the β-directive effect of esters and amides is due to the neighbouring group participation effect. In the absence of participating groups at the C-2 position, the thermodynamic preference for α-anomers dictated by the anomeric effect dominates. Kinetic factors probably also favour α-anomers. Recently, with this methodology, the blood group antigens Le^a, Le^b, and Le^x were successfully synthesized by glycosyl sulfoxides, with the yield of the glycosylation steps ranging from 65% to 86%.[103] Due to their high reactivity, glycosyl phenyl sulfoxides were used successfully for the glycosylation reactions on the solid phase. In the past several years, the sulfoxide glycosidation reaction has been used to prepare oligosaccharides and other glycoconjugates both in solution and on the solid phase.[104-106] A major use has been for the preparation of β-mannoside derivatives, a particularly

important glycosidic linkage because it forms part of the core of all *N*-linked oligosaccharides.[107-111]

1.2.2.3 Other glycosyl donors

There are a number of other mild and efficient methods for the activation of glycosyl centres. Among the most commonly used leaving groups are trichloroacetimidates,[79,112-114] phosphates,[115-118] and 4-pentenyl groups.[119] Thus, methods are available that provide access to various kinds of glycosidic linkages.[120] However, it should be noted that each linkage is different.

1.2.2.4 Armed/disarmed glycosyl donors

Fraser-Reid and coworkers[84,121,122] introduced the concept of armed/disarmed glycosyl donors defined by the nature of the protecting group at the *O*-2 position of the glycosyl donors. (Figure 1.9)

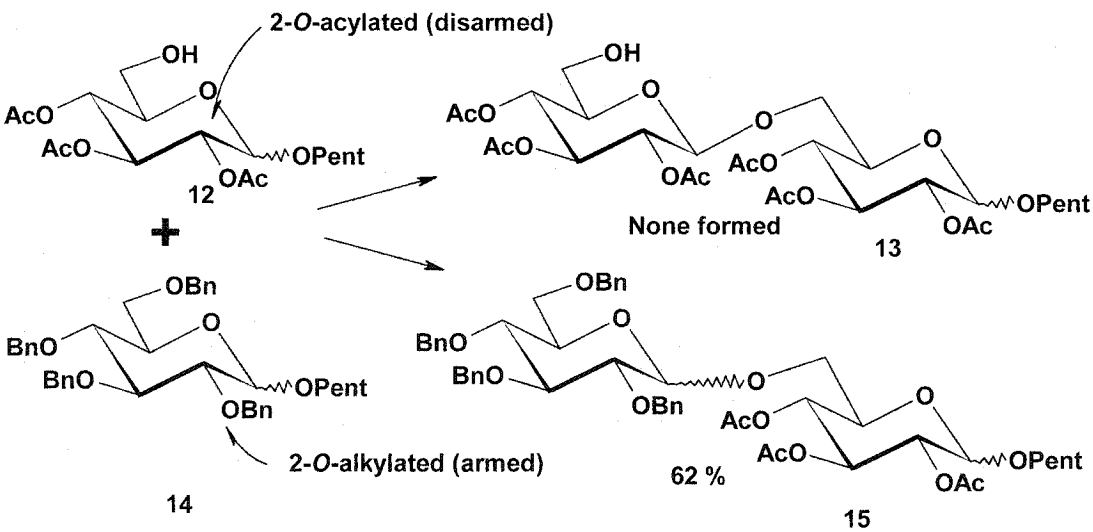
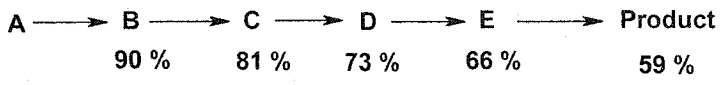


Figure 1.9 An example of reaction results of armed/disarmed glycosyl donors

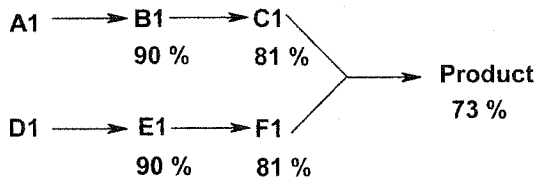
Disarmed donors are 2-*O*-acylated glycosyl donors and armed donors are 2-*O*-alkylated glycosyl donors. Protecting groups influence the stereochemistry of glycosidation. A β-linkage is formed selectively from 2-*O*-acylated glycosyl donors because of neighbouring group participation. The disadvantages of using 2-*O*-acylated glycosyl donors are that they react more slowly than 2-*O*-alkylated donors and that orthoester byproducts are often obtained. In the absence of a participating group, the thermodynamic preference for α-anomers dictated by the anomeric effect dominates when 2-*O*-alkylated donors are used. In order to get a β-linkage stereoselectively, solvent and temperature effects must be considered. Those effects (solvent and temperature) will be discussed in detail in sections 2.6, 3.5 and 3.6.

1.2.3 The formation of glycosidic linkages: linear and convergent synthesis

Synthetic routes to obtain target compounds can be classified as linear or convergent. There are several difficulties with linear syntheses. The yields from the initial starting material in linear routes drop off rapidly even with high yields at each step because a completely linear synthesis has many more consecutive steps than a convergent synthesis. Figure 1.10 shows a yield comparison of five-stage syntheses via convergent and linear routes. Another disadvantage is that, if a synthesis has one low yielding step, the overall yield will be lower to the same extent. In addition, one step that does not work as conceived can stop a linear synthesis. Thus, convergent routes will be considered first. However, sometimes a linear synthetic route has to be adopted in order to obtain the target molecule.



Yields of 90% at each step in a 5-stage linear synthesis

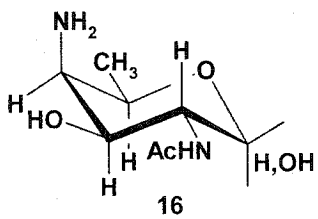


Yields of 90% at each step in a 5-stage convergent synthesis

Figure 1.10 The yields at each step in linear/convergent synthesis methods

1.3 The synthesis of methyl 2-acetamido-4-azido-2,4,6-trideoxy-α-D-galactopyranoside

The rare sugar, 2-acetamido-4-amino-2,4,6-trideoxy-D-galactopyranose (AAT) (**16**) (Figure 1.11), is present in a small number of bacterial polysaccharides. It is present in the Gram-negative bacteria, *Shigella sonnei*,[123] and in the Gram-positive bacteriae *Streptococcus pneumoniae*,[124] *Streptococcus mitis*,[9] and *Bacteroides fragilis*.[125] In *Streptococcus pneumoniae*, it is one of three sugars constituting the repeating unit of the capsular polysaccharide of serotype 1[126] and is one of five sugars in the repeating unit of the C-polysaccharide, which is common to all 90 serotypes.[4,8] Because of the importance of this latter bacterium, this project is aimed at *Streptococcus pneumoniae* and particularly at the C-polysaccharide.



16

Figure 1.11 2-Acetamido-4-amino-2,4,6-trideoxy-D-galactopyranose (AAT)

The pentasaccharide repeating unit of the C-polysaccharide contains a number of unique features. In addition to the rare sugar **16**, it contains two α-linkages and one or two phosphorylcholine units and thus presents a formidable synthetic challenge. In my MSc thesis, the development of a short synthesis of the acetamide of **16** and some derivatives was described, preliminary work towards preparation of the pentasaccharide. Some work aimed at preparation of the disaccharide portions of the C-polysaccharide repeating unit in which the derivatives of **16** are glycosyl acceptors and protected glucopyranosyl are glycosyl donors will be discussed in the thesis in chapter 2.

Previous syntheses of derivatives of **16** are described as following. Methyl 2-acetamido-4-azido-2,4,6-trideoxy-α-D-galactopyranoside was synthesized in 6 steps with an overall yield of 18 % starting from methyl 2-acetamido-4,6-benzylidene-α-D-glucopyranoside by the Lönn group.[127] This starting material (**17**) is three steps removed from a commercially available starting material, D-glucosamine hydrochloride (Figure 1.12).

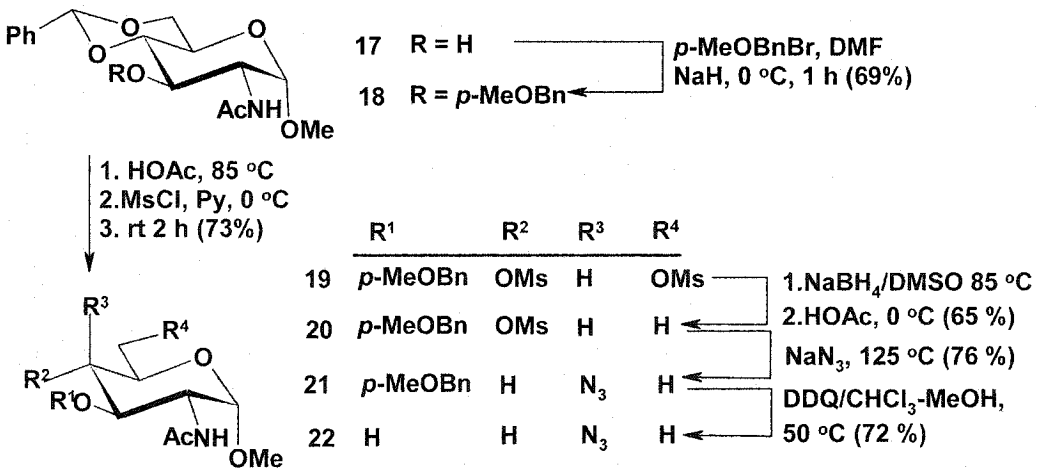


Figure 1.12 Lönn's method for the preparation of methyl 2-acetamido-4-azido-2,4,6-trideoxy-α-D-galactopyranoside[127]

Medgyes *et al.*[123] used 11 steps to obtain 2-acetamido-4-azido-2,4,6-trideoxy-β-D-glucopyranoside starting from ethyl 3-*O*-acetyl-2-deoxy-4,6-*O*-isopropylidene-2-phthalimido-1-thio-β-D-glucopyranoside in 11 % yield. This latter compound is itself nine steps from D-glucosamine hydrochloride.

Van Boom's group[128] prepared benzyl 2,4-diacetamido-2,4,6-trideoxy-D-galactopyranoside from 1,6-anhydro-2,3-*O*-(4-methoxybenzylidene)-β-D-mannopyranose in 12 steps with an overall yield of 4 %. The starting material for this synthesis is also not easily accessible.

None of these syntheses appeared to be suitable for the large scale preparation needed to obtain a pentasaccharide in an economical manner. It was therefore necessary to find an efficient and short method from a readily available cheap starting material. The route selected was related to that used in the syntheses of Lönn[127] and Medgyes,[123] but a considerable number of improvements were made and a number of difficulties were overcome.

In my MSc thesis, the shortest and highest yielding synthesis route to methyl 2-acetamido-4-azido-2,4,6-trideoxy-α-D-galactopyranoside (**30**) was achieved. From the readily available starting material, D-glucosamine hydrochloride (**23**), compound **22** was obtained in seven steps in an overall yield of 38 % (Figure 1.13).[129]

Compound **30** was expected to be a glycosyl acceptor or the precursor of another glycosyl acceptor that could act as glycosyl acceptors at their O-3 positions.

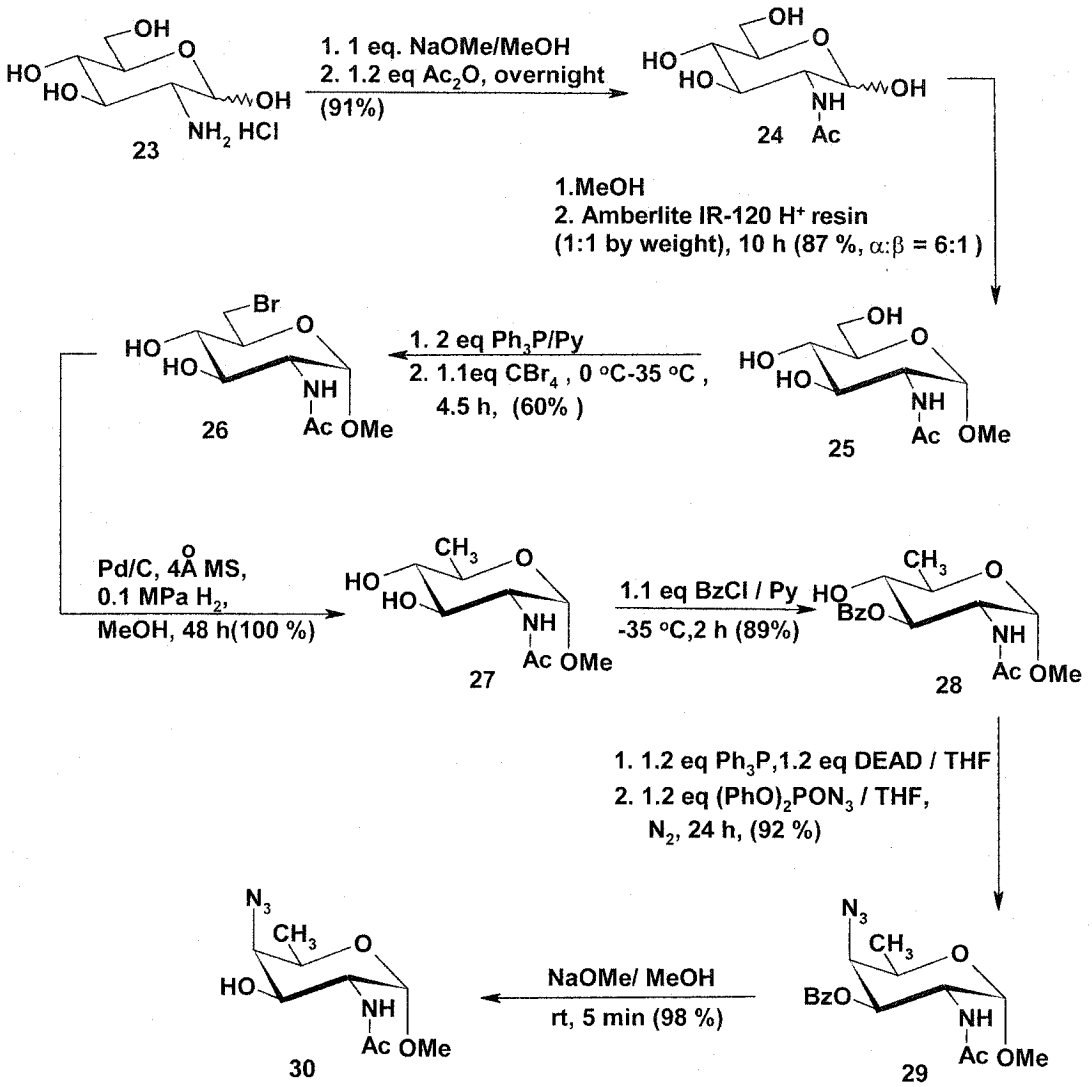


Figure 1.13 Preparation of methyl 2-acetamido-4-azido-2,4,6-trideoxy-α-D-galactopyranoside **30**

1.4 Retrosynthetic study of the pentasaccharide repeating unit of C-polysaccharide

The last stage of the retrosynthetic scheme for the synthesis of a completely protected pentasaccharide (**31**) is shown in Figure 1.14. An allyl protecting group was selected for the anomeric position of sugar **E** fragment in order to provide a linker arm to form a glycoconjugate of the pentasaccharide to protein.[130] Compound **31** can be

prepared by coupling of the disaccharide glycosyl donor **32** and the trisaccharide glycosyl acceptor **33** with a suitable activator.[3,66-69]

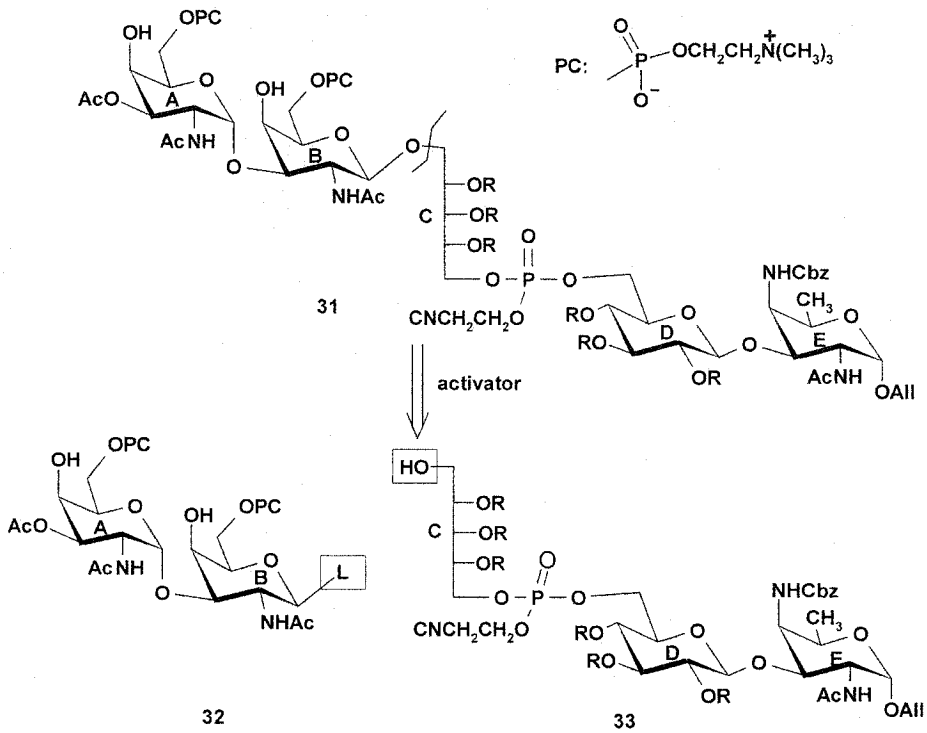


Figure 1.14 The retrosynthetic analysis of pentasaccharide **31**

Compound **32** can be obtained by glycosidation of synthons **34** and **35**, followed by reduction to remove 4,6-*O*-benzylidene acetals and reduce azides to amines, regioselective acetylation of the amine, and regioselective introduction of phosphorylcholine at the 6- positions of **A** and **B** (Figure 1.15). Synthons **34** and **35** can be prepared from tri-*O*-acetyl-D-galactal.

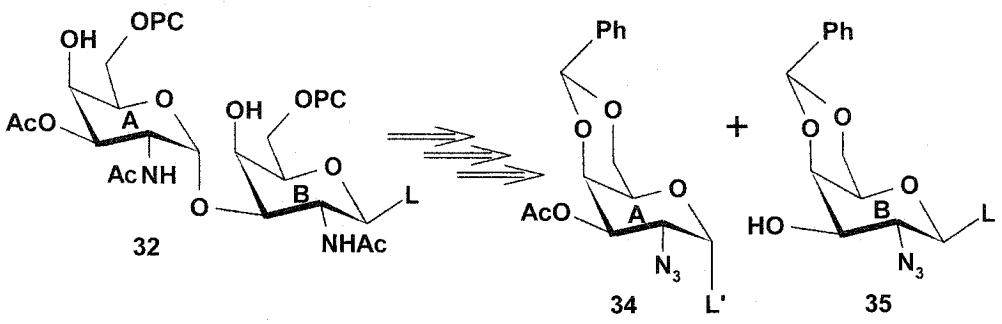


Figure 1.15 The retrosynthetic analysis of the disaccharide donor **32**

Retrosynthetic analysis of acceptor **33** gives two synthons: **36** and **37**. Compound **37** can be obtained from synthons **38** and **39** (Figure 1.16). Compound **36** has been prepared previously in this laboratory.[46]

Compound **30,** a precursor compound of acceptor **39,** was prepared from glucosamine hydrochloride in my MSc work[129] (Figure 1.13).

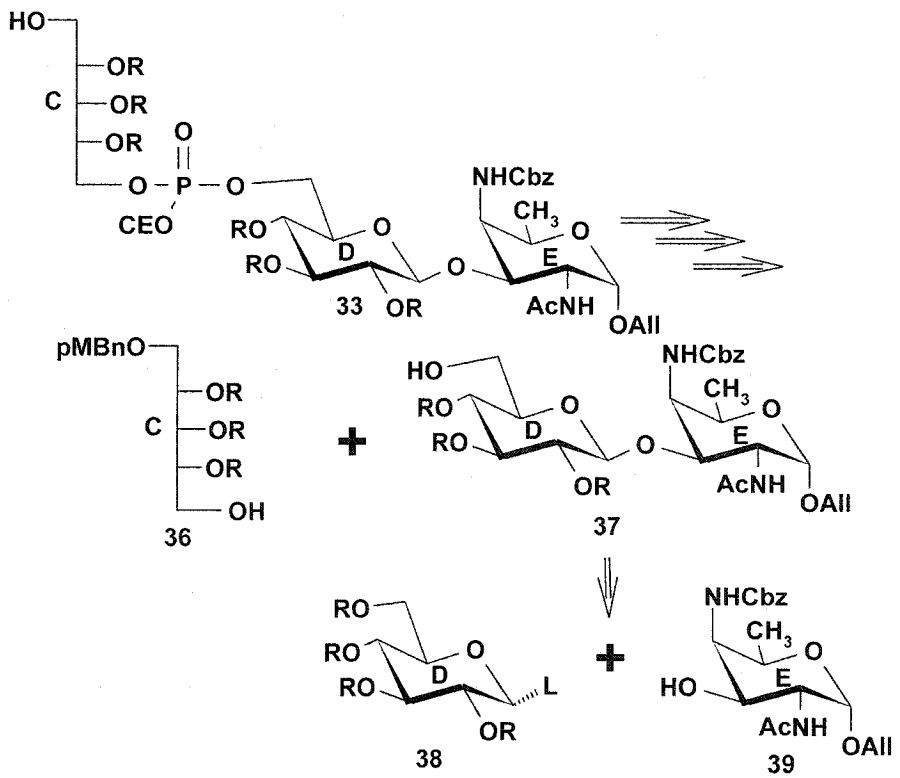
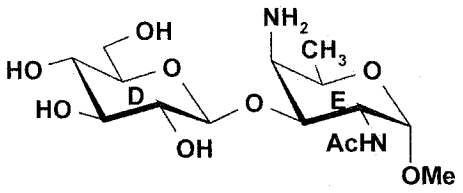


Figure 1.16 The retrosynthetic analysis of the trisaccharide acceptor **33**

Chapter 2 Attempts to synthesize methyl 2-acetamido-4-amino-3-*O*-(β-D-glucopyranosyl)-2,4,6-trideoxy--α-D-galactopyranoside

This chapter describes some attempts to obtain the model disaccharide of the pentasaccharide repeating unit of the C-polysaccharide: methyl 2-acetamido-4-amino-3-*O*-(β-D-glucopyranosyl)-2,4,6-trideoxy-α-D-galactopyranoside (**40**) (Figure 2.1)



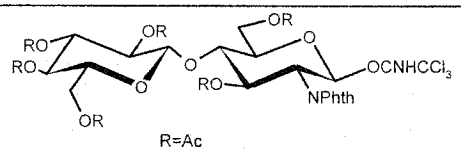
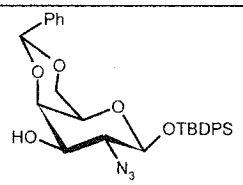
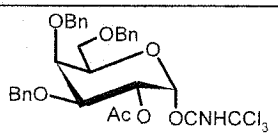
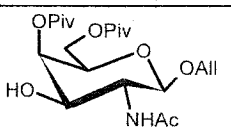
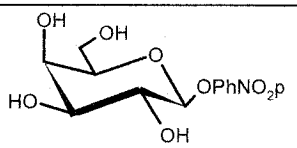
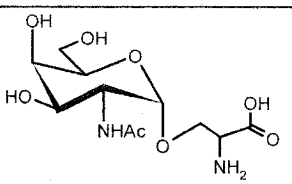
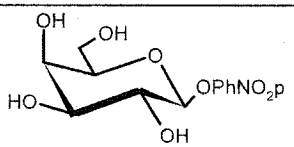
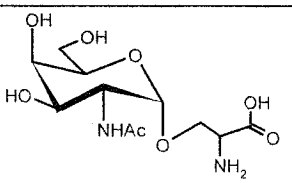
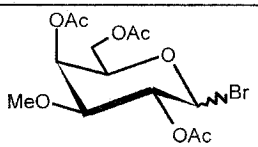
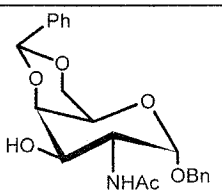
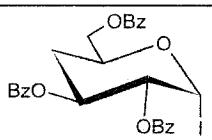
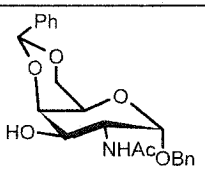
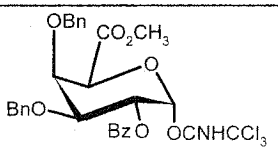
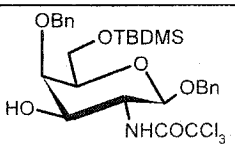
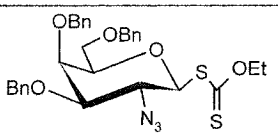
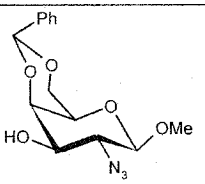
40

Figure 2.1 Methyl 2-acetamido-4-amino-3-*O*-(β-D-glucopyranosyl)-2,4,6-trideoxy-α-D-galactopyranoside (**40**), a DE disaccharide derivative from the C-polysaccharide

Building the linkage between the **D** and **E** synthons proved to be very difficult. Although some methods have been reported for the glycosidation at O-3 of glycosyl acceptors having one nitrogen atom at the C-2 position of galactopyranose derivatives (Table 2.1), only one reference has mentioned a coupling reaction involving a glycopyranose acceptor having nitrogen atoms at both C-2 and C-4 positions: Smid et al[131] reported the preparation of a tetrasaccharide by using NIS/triflic acid to promote the coupling reaction between a thioethyl donor (**41**) and methyl 2-acetamido-2-deoxy-3,6-di-*O*-benzyl-4-*O*-(2-acetamido-4-(benzyloxylcarbonyl)-2,4,6-trideoxy-α-D-galactopyranosyl)-α-D-galactopyranoside (**42**) (Figure 2.2).

In the section following, the syntheses of the required monosaccharide components will be discussed first, that is the preparation of glycosyl acceptors and glycosyl donors. Then, attempts at assembly of the disaccharide will be discussed.

Table 2.1 Reported glycosidation reactions at O-3 of glycosyl acceptors having a nitrogen atom at the C-2 position of galactopyranose derivatives

Entry	Donor	Acceptor
1.[132] $BF_3{\cdot}Et_2O$, AW-300 mol. siev., -20 °C, 84 % (β)		
2.[133] $BF_3{\cdot}Et_2O$, 4Å mol. siev., 52 % (β)		
3.[134] β-1,3-D-galactosidase, 3 h, DMF/water, 37 °C, pH 6.0, 68 % (β)		
4.[135] β-galactosidase, 48 h, 37 °C, pH 4.3, 22 % (β)		
5.[136] a. AgOTf, rt 16 h; b. 70 % HOAc, 2 h, 90 °C 77 % (β)		
6.[137] $Hg(CN)_2$, 5 h 10 °C, 72 % (β)		
7.[138] TMSOTf, 4Å mol. siev., CH_2Cl_2, 30 min, 62 % (β)		
8.[81] $Cu(OTf)_2$, 4Å mol. siev., CH_2Cl_2, 20 h, 85 % (α)		

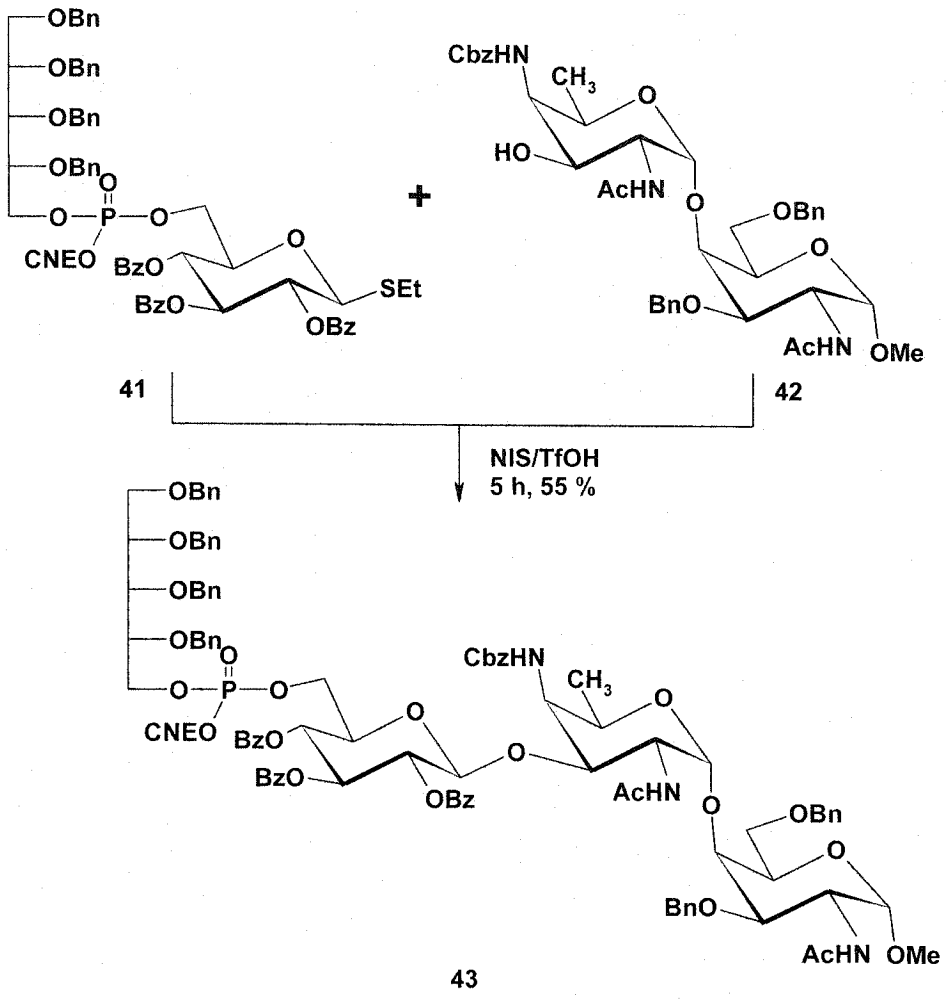


Figure 2.2 Preparation of a tetrasaccharide by using NIS/triflic acid to promote the coupling between thioethyl donor **41** and an acceptor **42**[31]

2.1 Preparation of glycosyl acceptors

The preparation of methyl 2-acetamido-4-azido-2,4,6-trideoxy-α-D-galactopyranoside (**30**) was described in section 1.3 (Figure 1.13). Different glycosyl acceptors were prepared as alternatives to compound **30** by reduction of the azido group. The simplest acceptor, methyl 2,4-diacetamido-2,4,6-trideoxy-α-D-galactopyranoside (**44**), was produced by catalytic hydrogenation (10 % Pd/C), acetylation and de-*O*-benzoylation by a one-pot reaction in a yield of 75 %. A by-product, methyl 2-

acetamido-4-benzamido-2,4,6-trideoxy-α-D-galactopyranoside (**45**) was also obtained (Figure 2.3). This by-product probably formed after the hydrogenation step: after the azide group had been reduced to an amino group, an intramolecular benzoyl group migration could occur to give the benzamide, which was more stable than the benzoate. Rearrangement of esters that are *cis* to alcohol groups on pyranose sugars occurs readily under mildly basic conditions.[139] In order to avoid the intramolecular migration, the benzoyl group was removed first. Compound **44** can be obtained by de-benzoylation with sodium methoxide in methanol, hydrogenation in ethanol with 10 % palladium-on-charcoal and acetylation from compound **29** in an overall yield of 67 %. Unfortunately, the solubility of compound **44** in glycosidation solvents was so poor that it could not be further used in the glycosidation reaction as a glycosyl acceptor.

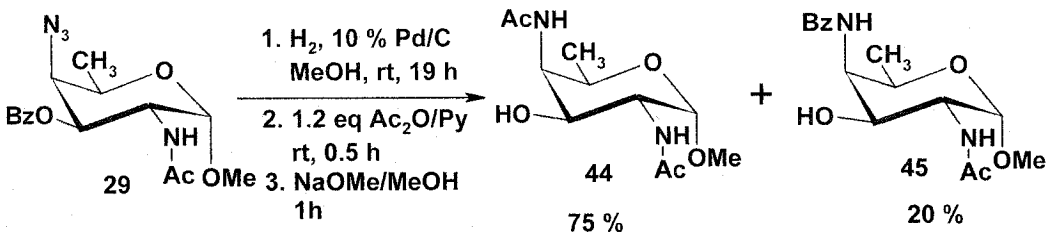


Figure 2.3 The synthesis of methyl 2,4-diacetamido-2,4,6-trideoxy-α-D-galactopyranoside **44**

Many reagents have been used to reduce an azide to an amino group, such as hydrogen sulfide,[140,141] zinc borohydride,[142] and borohydride exchange resin-nickel acetate.[143] Thioacetic acid converts azide groups to acetamido groups.[144] The azido group of compound **30** was reduced by catalytic hydrogenation (10 % Pd/C in ethanol) to afford methyl 2-acetamido-4-amino-2,4,6-trideoxy-α-D-galactopyranoside (**46**). A second amino protecting group (benzyloxycarbonyl) was introduced in order to differentiate the 4-amino group from the 2-acetamido group.

Benzyloxycarbonyl (Cbz) protection of amino groups was reported by Bergmann and Zervas[145] in 1931 and their paper is generally regarded as a milestone in the development of modern peptide synthesis. Benzyloxylcarbonyl chloride has also been used in carbohydrate synthesis to give a temporary Cbz protecting group for a secondary amino group.[131,146] The reaction normally is performed with a weak base in a mixed solvent containing water and an organic solvent that is both miscible in water and dissolves the reactants. The frequently adopted reaction systems include $NaHCO_3$ / THF / H_2O, $NaHCO_3$ / dioxane / H_2O, $NaHCO_3$ / acetone / H_2O, $NaHCO_3$ / Et_2O / H_2O, K_2CO_3 / dioxane / H_2O, Et_3N / Et_2O, etc.

Methyl 2-acetamido-4-(benzyloxylcarbonyl)amino-2,4,6-trideoxy-α-D-galacto-pyranoside (**47**) was obtained in a yield of 77 % from compound **46**. However, only methyl 2-acetamido-3-*O*-benzyloxycarbonyl-4-(benzyloxycarbonyl)amino-2,4,6-tridoxy-α-D-galactopyranoside (**48**) was obtained if more benzyloxycarbonyl chloride and sodium bicarbonate were used in the solvent THF/water 3:4 (v/v) (Figure 2.4).

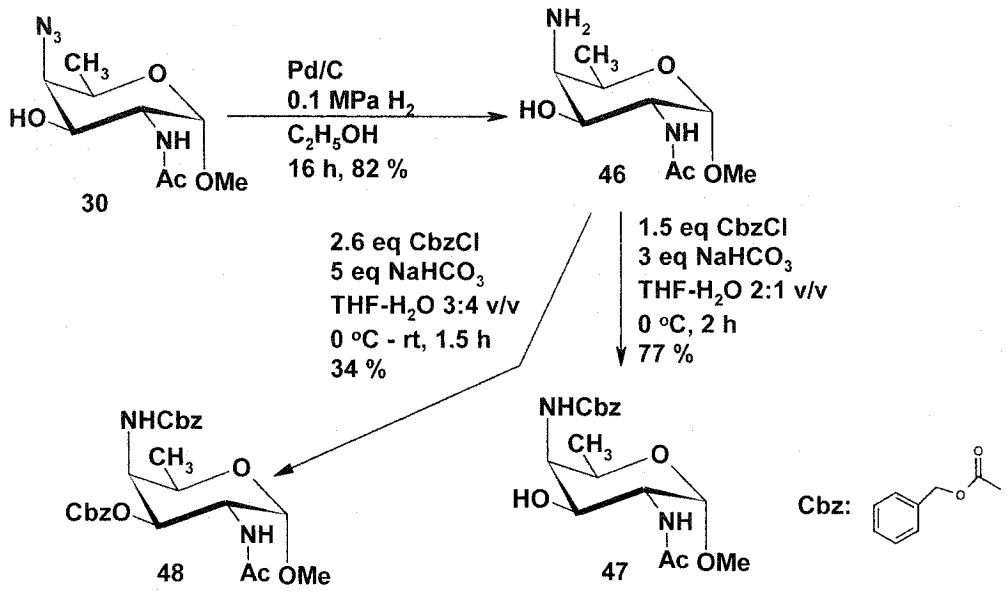


Figure 2.4 The synthesis of the glycosyl acceptor methyl 2-acetamido-4-(benzyloxycarbonyl)amino-2,4,6-trideoxy-α-D-galactopyranoside (**47**)

Mildly basic and nucleophilic reagents do not affect the Cbz group at room temperature. The typical cleavage conditions are hydrogen bromide/acetic acid.[132] This reaction proceeds by an S_N2 mechanism. Trimethylsilyl iodide,[147] aqueous lithium hydroxide,[148] and catalytic hydrogenolysis[131] can also be used to remove the Cbz group.

Alternative syntheses were evaluated that introduced the 4-amino group at the disaccharide stage. Methyl 2-acetamido-4,6-*O*-benzylidene-2-deoxy-α-D-glucopyranoside (**49**) was prepared to be the glycosyl acceptor for this purpose in an excellent yield.[149]

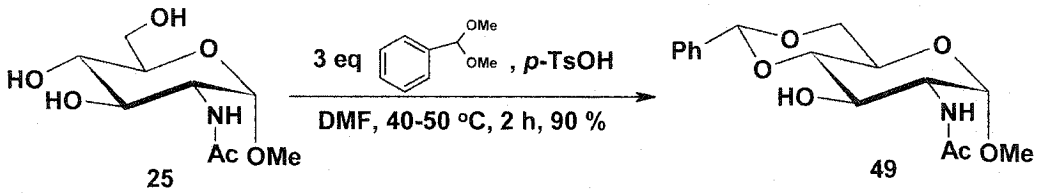


Figure 2.5 The synthesis of methyl 2-acetamido-4,6-*O*-benzylidene-2-deoxy-α-D-glucopyranoside (**49**)

2.2 Preparation of glycosyl donors

Glycosyl donors can be classified in two types:[84,121,122] disarmed glycosyl donors are 2-*O*-acylated and armed glycosyl donors are 2-*O*-alkylated. Figure 2.6 shows examples of both types of glycosyl donors. Protecting groups at the O-2 position influence the stereochemistry of glycosidation. 2-*O*-Acylated glycosyl donors form *trans*-anomeric linkages stereoselectively because of neighbouring group participation. The disadvantages of using 2-*O*-acylated glycosyl donors are that they react more slowly than 2-*O*-alkylated donors and that orthoester byproducts are sometimes obtained. In the absence of a neighbouring participating group at the C-2 position, the anomeric effect will cause the thermodynamically stable α-anomers to be the major products. In order to obtain the β-linkage product stereoselectively for pyranose sugars, solvent and temperature effects need to be considered.

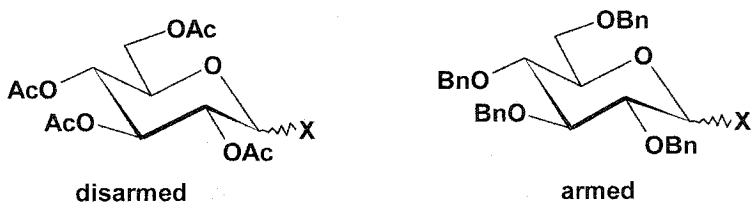


Figure 2.6 Examples of disarmed and armed glycosyl donors

2.2.1 Preparation of disarmed glycosyl donors 51, 52, 54, 55, and 57

Phenyl 2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-glucopyranoside **51** and phenyl 2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-glucopyranoside(S)-oxide **52** were prepared according to literature methods (Figure 2.7).[102,104]

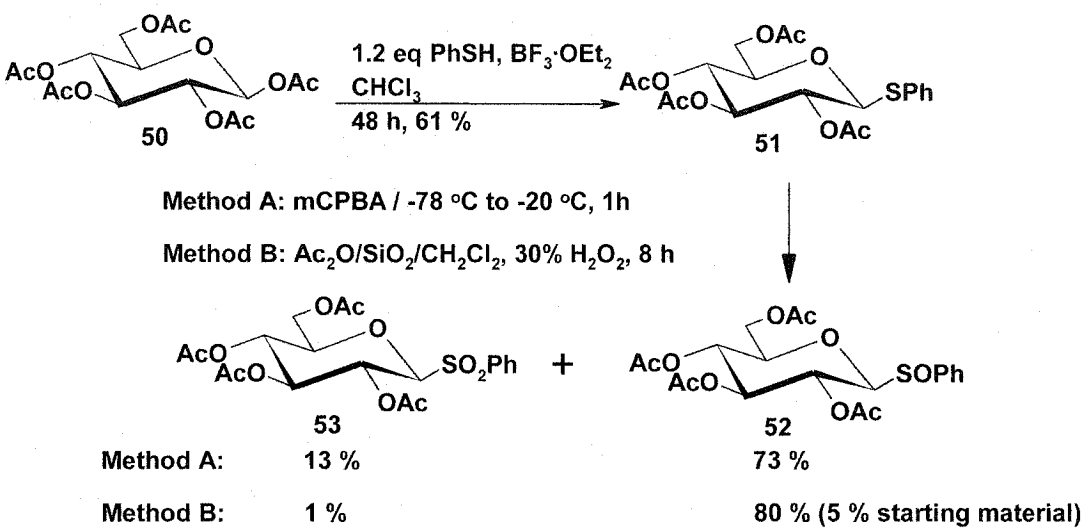


Figure 2.7 Preparation of phenyl 2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-glucopyranoside (**51**) and phenyl 2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-glucopyranoside (*S*)-oxide (**52**) glycosyl donors

Two methods were used to make phenyl 2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-glucopyranoside (*S*)-oxide (**52**). Method A is the most frequently used method, which requires low temperature and occurs rapidly. Kakarla *et al.*[150] reported a method to perform the oxidation by hydrogen peroxide with silica gel and acetic anhydride in 1996. The advantages of this method were that the reaction was carried out at room temperature and less sulfone by-product (**53**) was obtained. Here, an 80 % yield of compound **52** was obtained under these conditions. The advantage of using a sulfoxide donor is that the

extremely mild conditions utilized in glycosylation reactions allow trityl and other sensitive protecting groups to be used for temporary protection.[151]

Thioalkyl glycosides are also used as glycosyl donors. Derivatives of thioethyl glycosides have been shown to be effective glycosyl donors toward carbohydrate acceptors under the agency of NIS/triflic acid,[131,152,153] or NIS/silver triflate,[154] among others.

Ethyl 2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-glucopyranoside (**54**) (Figure 2.8) was prepared from compound **50** as in the literature.[104]

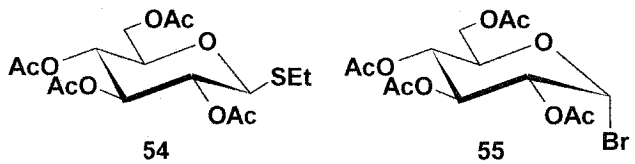


Figure 2.8 Preparation of ethyl 2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-glucopyranoside (**54**) and 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide (**55**)

Acetylated glycosyl bromides can be converted into glycosides in the presence of silver catalysts.[73] Silver triflate is often used as a soluble glycosidation promoter at low temperature.[155-158] 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide (**55**) (Figure 2.8) was prepared according to a literature method.[159]

Glycosyl trichloroacetimidates can be used as glycosyl donors to build glycosidic linkages with promoters such as trimethylsilyl triflate,[79,112-114,138,160-163] or boron trifluoride etherate.[164] Acetylated trichloroacetimidates were prepared according to published methods.[165,166]

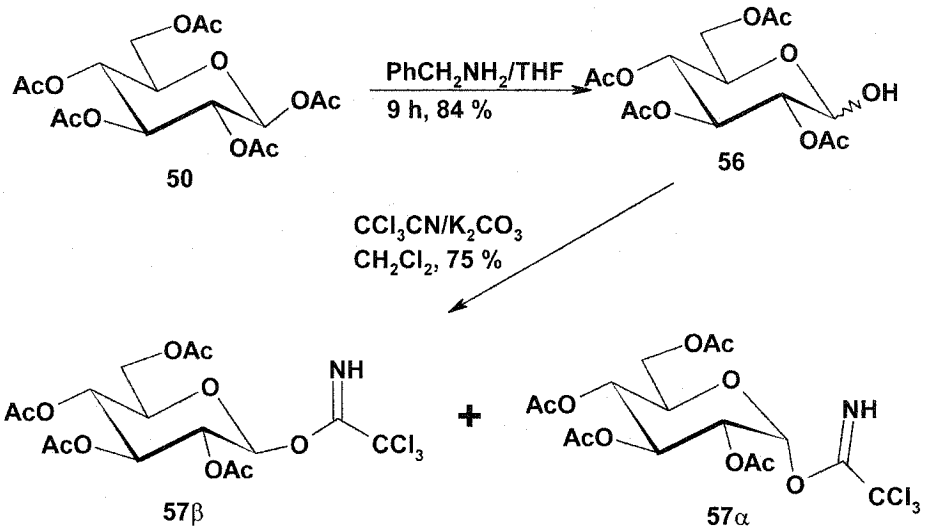


Figure 2.9 Preparation of 2,3,4,6-tetra-*O*-acetyl-1-*O*-α/β-D-glucopyranosyl trichloroacetimidate (**57**α and **57**β)[130,131]

The reaction shown in Figure 2.9 gave a syrupy anomeric mixture. Pure anomers were obtained by flash column chromatography on silica gel. The β-anomer was colorless crystals, while the α-anomer was a syrup. If the reaction was stopped in 3 h, the kinetically controlled product, the β-anomer **57**β, was the major product. Under thermodynamic control obtained by allowing the reaction to proceed for 72 h, the α-anomer **57**α became the dominant product (Figure 2.9).

2.2.2 Preparation of armed glycosyl donors: 59 and 61

The readily accessible phenyl 2,3,4,6-tetra-*O*-benzyl-1-thio-β-D-glucopyranoside (**59**) has proven to be an excellent glycosyl donor, leading to good yields with high stereoselectivities in glycosidic coupling reactions.[99,167] Compound **59** was prepared from compound **51** in two steps with an overall yield of 72.0 %. Compound **59** afforded compound **61**, a trichloroacetimidate donor, in two steps[168] (Figure 2.10).

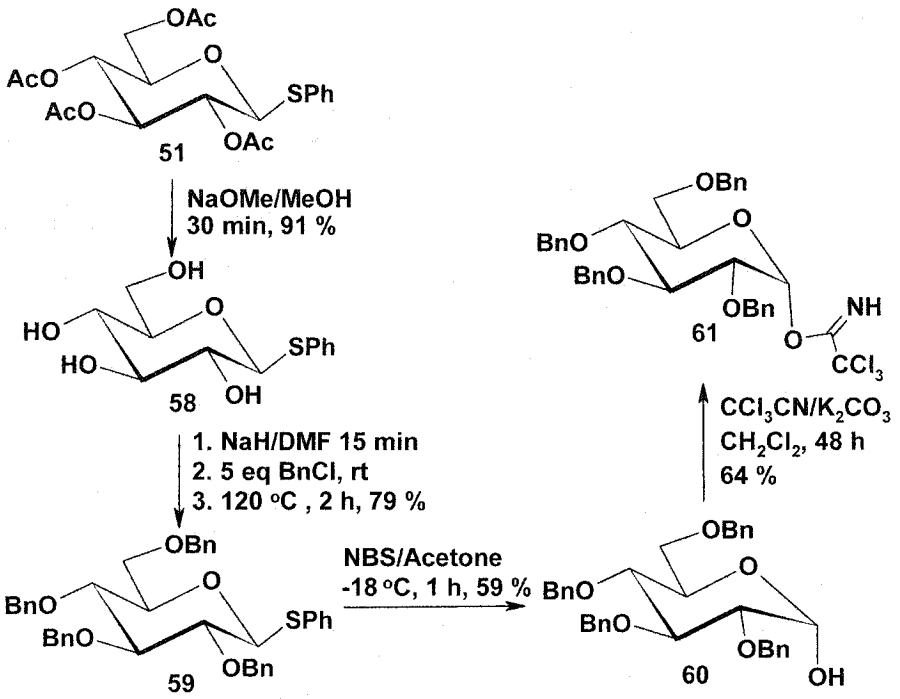


Figure 2.10 Preparation of phenyl 2,3,4,6-tetra-*O*-benzyl-1-thio-β-D-glucopyranoside (**59**) and 2,3,4,6-tetra-*O*-benzyl-1-*O*-α-D-glucopyranosyl trichloroacetimidate (**61**)

2.2.3 Preparation of a glycosyl donor with two different protecting groups: 63

Phenyl 2,3,4-tri-*O*-acetyl-6-*O*-trityl-1-thio-β-D-glucopyranoside (**63**) was prepared from phenyl 1-thio-β-D-glucopyranoside (**58**) in two steps. This compound has two different protecting groups: a trityl group at O-6 and acetyl groups at the O-2, O-3 and O-4 positions. De-*O*-tritylation of **63** with 30 % hydrogen bromide in acetic acid at room temperature as previously reported[169-171] gave compound **64** instantly in an 80 % yield (Figure 2.11).

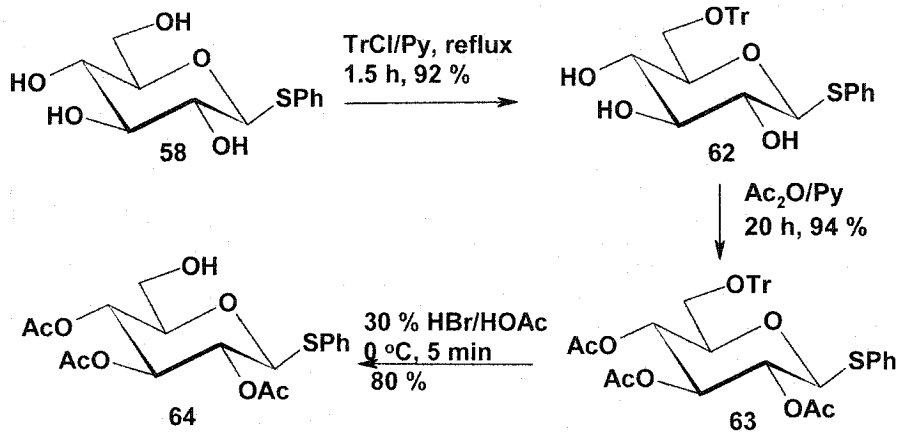


Figure 2.11 Preparation of phenyl 2,3,4-tri-*O*-acetyl-6-*O*-trityl-1-thio- β -D-glucopyranoside (**63**)

2.3 Regioselective debenzylation of the 6-*O*-benzyl group

This section describes preliminary work to investigate the feasibility of selective 6-*O*-debenzylation of glucopyranoside in order to build a 1→6-linked oligosaccharide via an alternative pathway. Compound **65** was obtained but the yield was lower than that reported by Yang *et al.*[172] The lower yield may have been due to the difficulty of obtaining dry zinc chloride in small particle sizes (Figure 2.12).

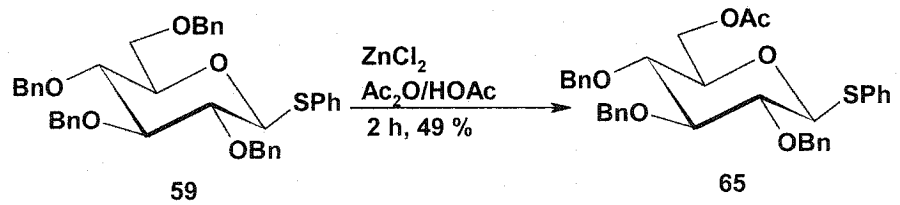


Figure 2.12 The selective 6-*O*-debenzylation of phenyl 2,3,4,6-tetra-*O*-benzyl-1-thio-β-D-glucopyranoside (**59**)

2.4 Attempts to synthesize disaccharides containing the β-D-glucopyranosyl-(1→3)-α-D-galactopyranosyl linkage (the DE unit)

Linear and convergent approaches were tried to achieve the target β(1→3)-linked DE-dimer (Figure 2.1). In the linear route, before modifications of the disaccharide to obtain the desired target compound, the β(1→3) glycosidic linkage was formed first; on the other hand, in the convergent approach suitable synthons (glycosyl donor and glycosyl acceptor) were prepared, then glycosidation was attempted to obtain the desired disaccharide.

Glycosyl donors and acceptors that have been prepared are listed in Figure 2.13 and Figure 2.14 separately.

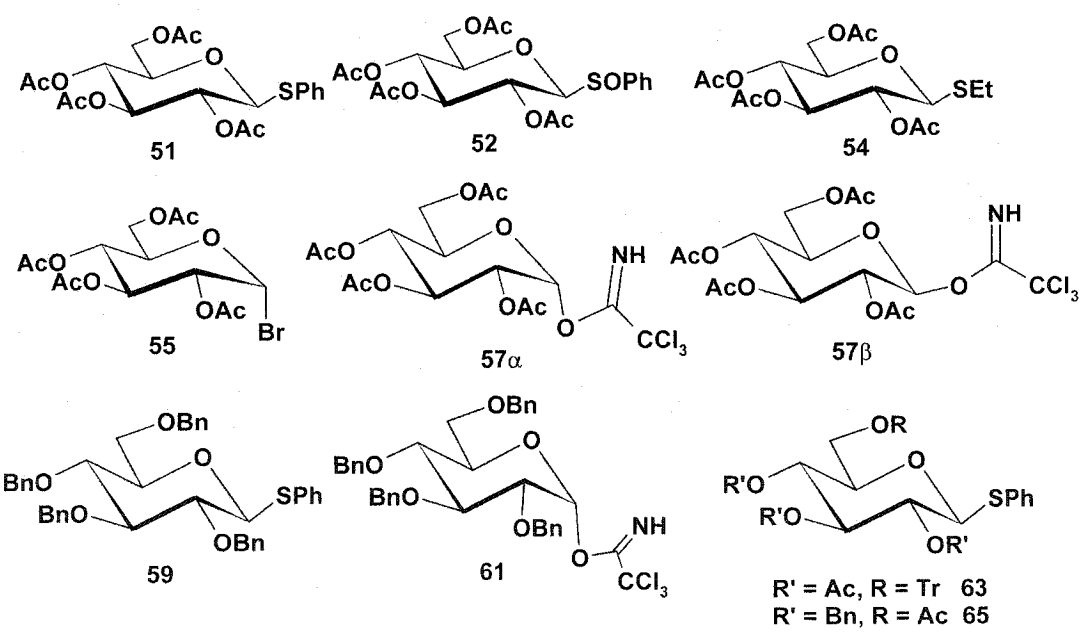


Figure 2.13 Glycosyl donors

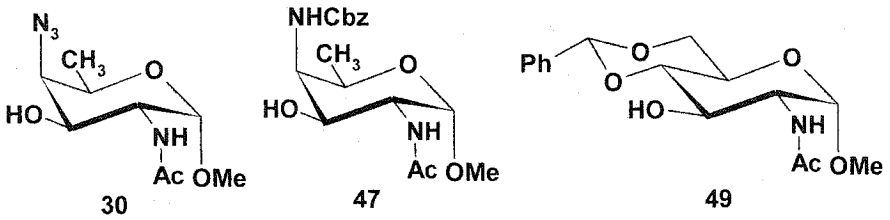


Figure 2.14 Glycosyl acceptors

2.5 Attempted preparation via a convergent route

The overall yield is a concern in the preparation of the β(1→3)-linked DE-dimer via a linear route. If the yield in one step in the route is lower, the overall yield will drop. Therefore, efforts to obtain the target β(1→3)-linked DE-dimer were made first via a convergent route.

Azide compound **30** (Figure 1.13) was prepared to act as the glycosyl acceptor. If compound **30** could couple with a glycosyl donor, the disaccharide **67**, a precursor of the target disaccharide **40,** would be obtained (Figure 2.15). Unfortunately, a number of glycosidation reactions were tested for the azido acceptor **30** but no disaccharide was ever obtained. In all reactions, the donor was activated successfully and disappeared as monitored by TLC, but no disaccharide was formed and the acceptor azide **30** was recovered totally. Donors that were tested with different activators were thiophenyl glycosides (**51** and **59**) activated by NIS/AgOTf or NIS/TfOH, thiophenyl sulfoxide (**52**) activated by NIS/AgOTf or DTBMP/TMSOTf, bromide (**55**) activated by AgOTf, and trichloroacetimidate (**57**α, **57**β and **61**) activated by (TMSOTf). Although a huge effort was put into investigations of glycosidation conditions, such as reaction temperature (from -78 °C to room temperature), the sequence of addition of reactants and promoters, the reaction time and the ratio of donor/acceptor/promoter, compound **67** was not formed.

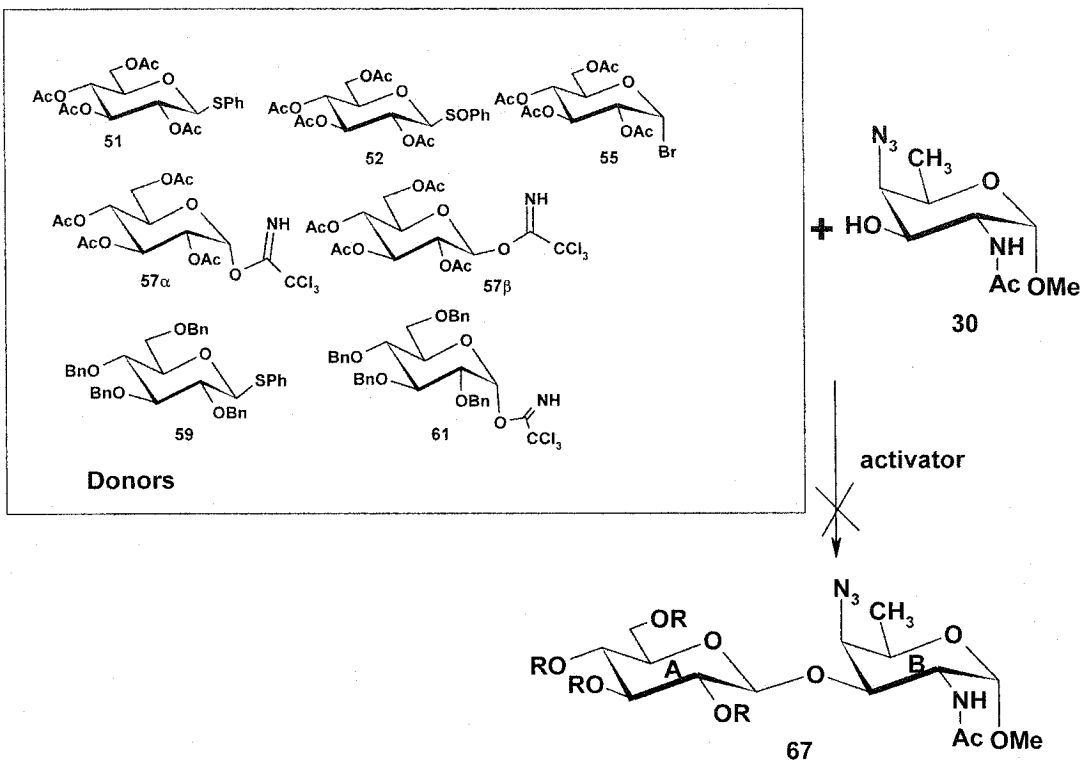


Figure 2.15 Attempts of glycosidation with methyl 2-acetamido-4-azido-2,4,6-trideoxy-α-D-galactopyranoside (**30**)

Because of the reported formation of a tetrasaccharide[131] (Figure 2.2) by formation of a similar glycosidic bond, compound **47** and ethylthio glycoside (**54**) were reacted as glycosyl acceptor and glycosyl donor, respectively (Figure 2.16). No disaccharide was obtained after promotion by NIS/AgOTf or NIS/TfOH. Donors **61**, **63** and **65** also gave the same negative result: the donor disappeared completely from TLC, but no disaccharide formed and the acceptor was recovered.

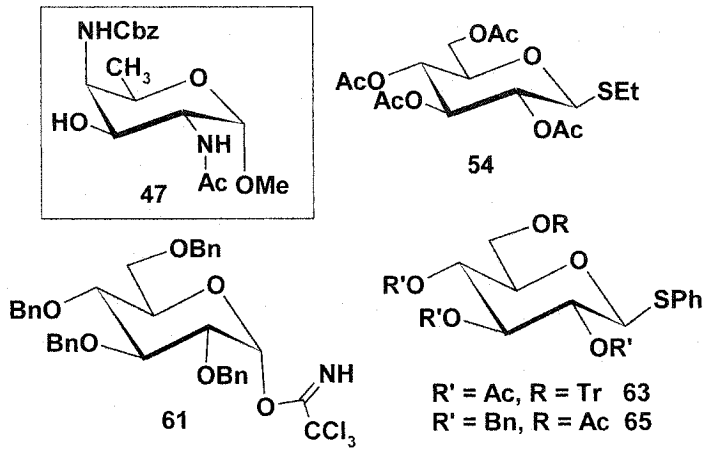


Figure 2.16 Glycosyl acceptor **47** and donors **54**, **61**, **63**, and **65**

The 3-OH group of an α-D-galactopyranoside, which has two nitrogen atoms at the 2- and 4- positions, proved to be very inert to glycosidation reactions. Thus far, conditions have not been established to use either compound **30** or compound **47** as glycosyl acceptors to form the target disaccharide **40**.

2.6 Attempted preparation via a linear route

After the convergent method using azide derivatives **30** or benzyloxycarbonyl derivative **47** as glycosyl acceptors had been shown to have serious difficulties, a linear route was tested in order to achieve the target disaccharide **40** (Figure 2.17).

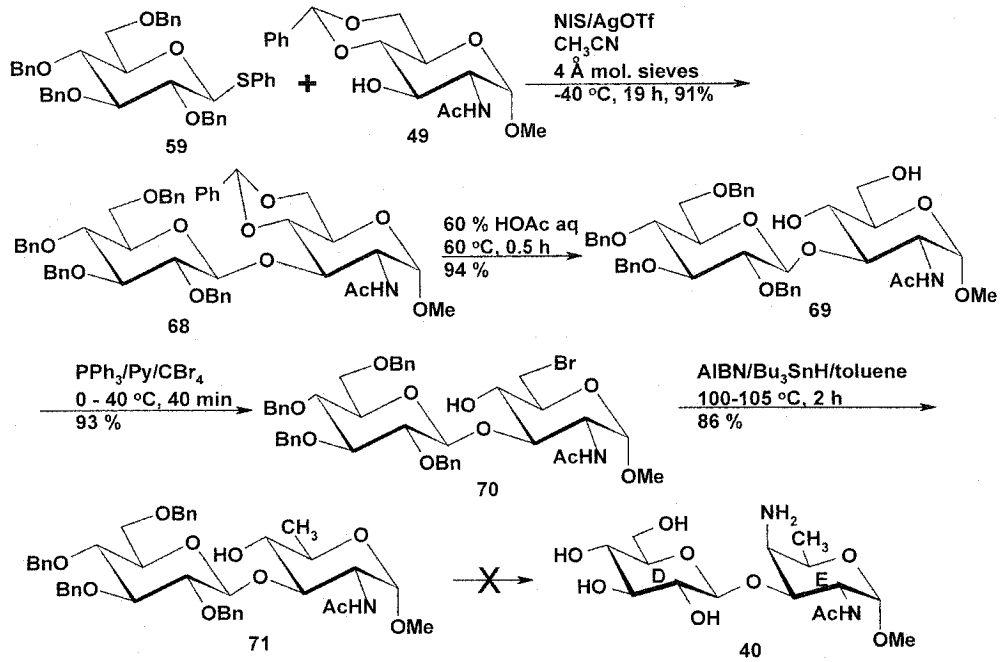


Figure 2.17 Attempted preparation of target disaccharide methyl 2-acetamido-4-amino-2,4,6-trideoxy-3-*O*-(β-D-glucopyranosyl)-α-D-galactopyranoside (**40**) via a linear route

The glycosyl donor phenyl 2,3,4,6-tetra-*O*-benzyl-1-thio-β-D-glucopyranoside (**59**), activated by NIS/AgOTf, was coupled with acceptor methyl 2-acetamido-4,6-*O*-benzylidene-2-deoxy-α-D-glucopyranoside (**49**) to afford the β(1→3)-linked disaccharide **68** in an excellent yield of 91 % as outlined in Figure 2.17. The 2-*O*-benzyl group is not a neighbouring participating protection group, so solvent participation[81,148] and a low reaction temperature were used in order to reduce the formation of undesired thermodynamically favourable anomeric product: the α(1→3)-linked disaccharide **68**α.

Acetonitrile was found to be a good solvent to obtain the β-linked disaccharide **68** diastereoselectively. Temperature was also found to be an important factor on the β-anomer stereoselectivity. At 0 °C, the glycosidation reaction completed in 2.5 h and the α:β ratio was 1:3 according to the ^{1}H NMR spectrum. The similar Rf values of the two

anomers precluded separation by flash column chromatography on silica gel. Pure anomers were obtained by recrystallization from ethanol: the first crop was the β-anomer and the second crop was the α-anomer.

A specific jacketed dropping funnel (Figure 2.18) was designed to pre-cool the solution of NIS and silver triflate in acetonitrile to -40 °C before it was added dropwise to the reaction mixture contained in a jacketed two-necked round bottom flask at -40 °C. Under these conditions, the β-anomer product was obtained with very high stereoselectivity. The H-1 signal at 5.44 ppm (J 4.0 Hz) of the α-anomer **68**α could not be detected in the ^{1}H NMR spectrum (Bruker AC-250) of the crude reaction mixture after the reaction had finished. Use of a normal dropping funnel to add the room temperature solution of NIS/AgOTf to the reaction mixture at -40 °C gave an α/β ratio of products of 1:9.

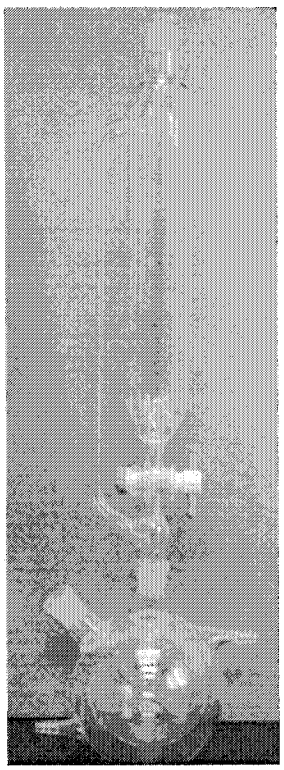


Figure 2.18 The special jacketed dropping funnel and two-necked round bottomed flask used in low temperature reactions

Solvent participation in glycosylation reactions has been discussed extensively.[81,173] Schmidt and his co-workers used trichloroacetimidates as glycosyl donors to stereoselectively obtain β-*O*-glycosides in acetonitrile.[174,175] Recently, Hashimoto and his co-workers used 2-azido-2-deoxy-D-glycosyl diphenyl phosphates as

glycosyl donors stereoselectively to construct 1,2-trans-β-glycosidic linkages.[176] This group found in this paper and in one earlier report with different glycosyl phosphates[177] that lowering the temperature markedly increased stereoselectivity as has been found here. Diphenyl phosphates were activated by TMSOTf in propionitrile at -78 °C and products were obtained with high β-selectivity. The β-selectivity has been attributed to the formation of the kinetically favored α-nitrilium ions.[176,178,179] Here, the thiophenyl leaving group is activated by a promoter and the oxocarbenium ion is formed, which then reacts with either the hydroxyl group of the glycosyl acceptor or the nitrogen of acetonitrile. At low temperatures, the predominant reaction is that of the acetonitrile because it is the reaction solvent. The formation of the α-nitrilium ion is controlled by the anomeric effect. In the next step, the α-nitrilium ion intermediate reacts with the glycosyl acceptor **49** on the β-face and forms the desired β-linked disaccharide **68** (Figure 2.19).

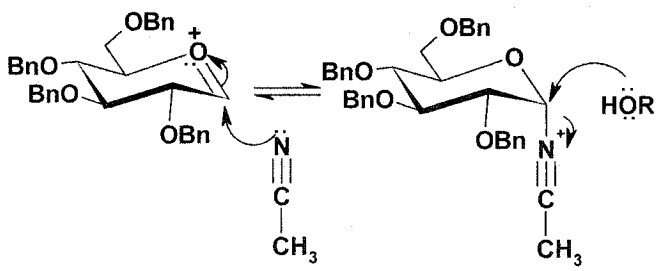


Figure 2.19 Acetonitrile participation in the glycosidation reaction gave the β-anomeric product

Butyronitrile has a lower melting point (mp -91 °C) than acetonitrile does. It was evaluated as a reaction solvent in order to decrease the reaction temperature further to get better β stereoselectivity. However the poor solubility of acceptor **49** in butyronitrile

made its use impossible. Use of an acetonitrile-dichloromethane mixed solvent system which has a lower freezing point also failed because of the very poor solubility of **49** in it.

De-*O*-benzylidenation was carried at 60 °C with 60 % acetic acid-water to give disaccharide **69** in an excellent yield (94 %) in half an hour.

The replacement of the primary hydroxyl group by a bromine atom proceeded faster for disaccharide **69** than it had for the monosaccharide analog **25** (see figure 1.13, 60 % yield) and also proceeded in a much higher yield (93 %) to give the disaccharide bromide **70** (figure 2.17). Presumably reaction of the monosaccharide was complicated by the presence of the 3- and 4- hydroxyl groups.

The conditions used for reduction of the bromide in the monosaccharide **26** (H_2/Pd-C) could not be used for the debromination of disaccharide **70** because the benzyl groups would have been reduced at the same time. However, it was found that the bromide **70** could be reduced by tributyltin hydride in the presence of azobisisobutyrodinitrile (AIBN) to afford disaccharide **71** in a yield of 86 %.

The Mitsunobu reaction, the route used to introduce the nitrogen atom at C-4 in monosaccharide **28** (Figure 1.13), did not work to convert 4-OH to 4-azido group for the disaccharide **71**. The hydroxyl group in **71** also did not react with triflic anhydride in order to form a good leaving group for the S_N2 reaction to introduce a nitrogen atom. Oxidation of **71** was expected to produce a ketone, then oxime formation/reduction or reductive amination could serve to achieve the target disaccharide **40**. However, **71** could not be oxidized using pyridinium dichromate-acetic anhydride (PDCA),[180] pyridinium dichromate-acetic acid,[181] the Swern oxidation procedure,[182] and the Dess-

Martin periodinane oxidant.[183,184] Monosaccharide **28** was oxidized to its corresponding ketone **72** readily (Figure 2.20).

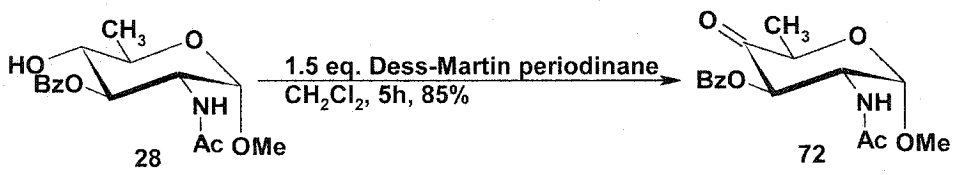


Figure 2.20 Oxidation of monosaccharide

Probably the steric hindrance imposed by the O-3 linked glucosyl unit or the hydrogen bonding of the 4-hydroxyl group makes the C-4 hydroxyl group very inert. The ^{1}H NMR spectrum shows evidence of the presence of intramolecular hydrogen bonding in compound **71**: a clear doublet was observed for the hydroxyl proton at 4.61 ppm with a coupling constant of 1.6 Hz (Figure 2.21). The relationship of the size of H-C-O-H J values to torsional angles has been shown to follow a Karplus-type equation,[74,185] as it does with other H-C-X-H units. Observation of a value other than the rotationally averaged value (~7 Hz) implies specific hydrogen bonding.

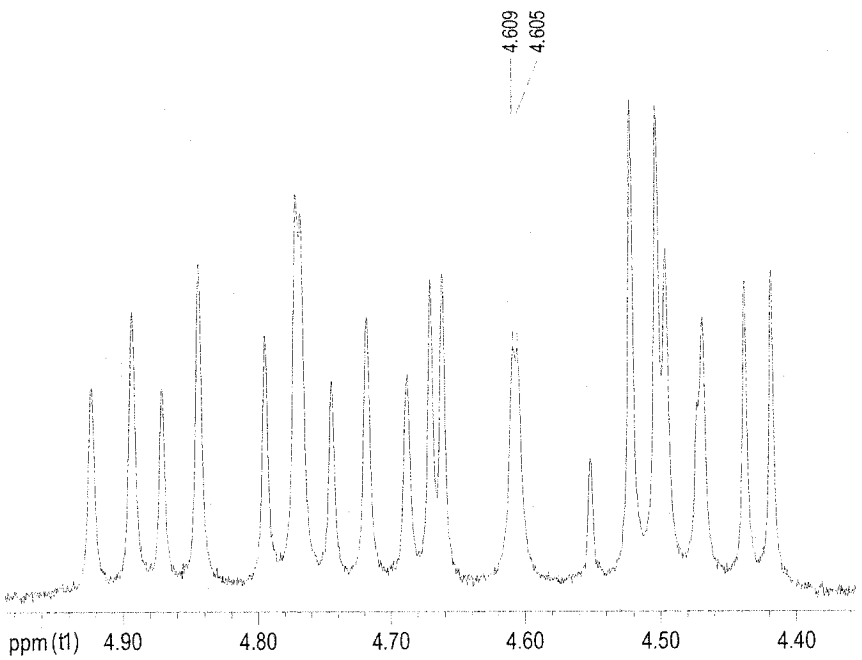


Figure 2.21 Part of the 400 MHz ^{1}H NMR spectrum of disaccharide methyl 2-acetamido-2,6-dideoxy-3-*O*-(2,3,4,6-tetra-*O*-benzyl-β-D-glucopyranosyl)-α-D-glucopyranoside (**71**). The labeled doublet is the hydroxyl proton signal.

Thus, the linear route to achieve the target disaccharide **40** stopped at compound **71.**

Future work (Chapter 5) contains two suggested methods to overcome this synthetic problem, one is a way to avoid the difficulty, and the other is another approach to the formation of the linkage.

Chapter 3 Synthesis of derivatives of disaccharides containing the α-D-galactopyranosyl-(1→3)-β-D-galactopyranosyl linkage (the AB unit)

This chapter describes the synthesis of derivatives of disaccharide containing the α-D-galactopyranosyl-(1→3)-β-D-galactopyranosyl linkage (the AB unit) (Figure 3.1)

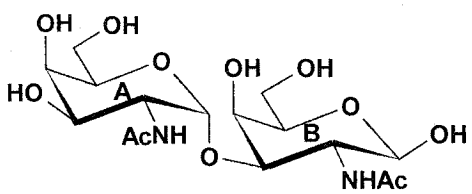


Figure 3.1 The α-D-galactopyranosyl-(1→3)-β-D-galactopyranosyl disaccharide from the pentasaccharide repeating unit of the C-polysaccharide of *Streptococcus pneumoniae*

According to the retrosynthetic analysis (Figure 1.15), the glycosyl donors and the glycosyl acceptors used in the glycosidation reaction can be prepared from tri-*O*-acetyl-D-galactal. In the chapter following, the preparation of D-galactal will be discussed first, then the preparations of glycosyl donors and glycosyl acceptors, finally the syntheses of the derivatives of disaccharides containing the α-D-galactopyranosyl-(1→3)-β-D-galactopyranosyl linkage will be discussed.

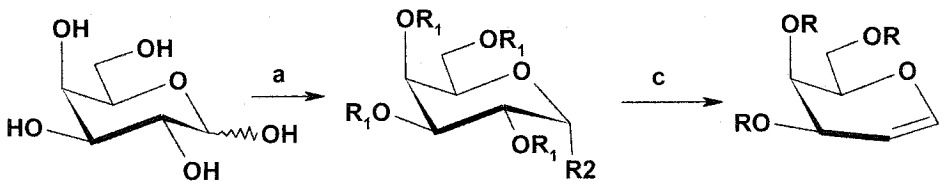
3.1 An improved method for the preparation of D-galactal

D-Galactal (77) has been widely used as a starting material in syntheses of oligosaccharides, C-glycosides, glycopeptides, glycolipids and other types of compounds.[186-191] D-galactal is available commercially but is too expensive (the price is between 130 CAN $ and 194 CAN $ per gram) to be used as a starting material. Table 3.1 lists 2004 prices from some sources.

Table 3.1 List prices of D-galactal from some sources, July 2004

Company	Price (CAN $/g)
Sigma-Aldrich Canada Ltd., ON, Canada	174
Toronto Research Chemicals Inc., ON, Canada	194
TCI America, OR, USA	143
MP Biomedicals Co., CA, USA	130

In this thesis, an improved synthetic route was developed to obtain compound **77** on a multigram scale (Figure 3.2). Numerous syntheses have been published[187,192] but it is thought that the procedure outlined in the following reaction is superior on a large scale.



a. Ac_2O/Py, 14 h.
b. 1) $PBr_3/H_2O/CH_2Cl_2$, 4h; 2) K_2CO_3.
c. Zinc dust/1-methylimidazole/EtOAc, refluxing, 1 h; 80 % for three steps.
d. $NaOCH_3/CH_3OH$, 1h, 96 %

Figure 3.2 An improved synthetic route to prepare D-galactal (**77**)

Acetylation of D-galactose (**73**) is invariably carried out using acetic anhydride as the reagent and employing catalysts such as pyridine,[188,193] sodium acetate,[194,195,195] or

perchloric acid.[186] Pyridine, which acts as both the nucleophilic catalyst and the solvent, is the most widely used catalyst. D-Galactopyranose pentaacetate (**74**) was obtained in a quantitative yield after D-galactose was stirred with acetic anhydride in dry pyridine for 14 h at room temperature in a water-free atmosphere. The α-anomer was the predominant product, and crystallization from ethanol gave the pure anomer with physical constants matching those in the literature. Elaborate conditions, such as adding DMAP at 0 °C under an argon atmosphere,[193] are unnecessary. After workup, a solution of **74** in dichloromethane was used in the next step without further purification.

The critical improved step in the synthesis of D-galactal was step 2, the conversion of the galactopyranosyl pentaacetate **74** to the corresponding bromide **75**. There are a few methods that can be used to convert a pentaacetate to a bromide.[186,193,196] Most researchers now use a large excess of hydrogen bromide in acetic acid for this step.[186-188,193] In our hands (see also Maier's report[193]), the product of the hydrogen bromide method could not be stored for any period of time without decomposing, even if organic solution of the product was washed with saturated sodium bicarbonate aqueous solutions. Lemieux's red phosphorus/bromine method[197] which was used to make tetra-*O*-acetyl-α-D-glucopyranosyl bromide is rather inconvenient on a large scale since it uses highly noxious bromine and solid red phosphorus which is awkward to handle.

Treatment with phosphorus tribromide/water was found to be an excellent condition to convert pentaacetate **74** to bromide **75**. Neutralization by anhydrous potassium carbonate afforded the product as a pale yellow syrup, which was stable for up to two weeks when stored in a desiccator. Only a slight excess (1.2 eq) of phosphorus tribromide was used rather than the normal conditions of 6 to 10 eq of hydrogen bromide in acetic acid. Phosphorus tribromide is much less costly for this reaction (Can

$64.4/mol for 500 g of 97% PBr_3 from Aldrich) in comparison with HBr in acetic acid (Can $39.1/mol for 2L of 30% from Aldrich: 6 eq needed cost Can $235/mol of starting material). The use of only a slight excess of PBr_3 (1.2 eq) makes the procedure cheaper, more efficient, and much more environmentally friendly. Compound **75** was used in the next step without further purification. The purity of the crude **75** can be seen from its ^{1}H-NMR spectrum recorded on a 400 MHz NMR spectrometer (Figure 3.3). The replacement of the doublet at 6.38 ppm from the H-1 of the α anomer of **74** with the doublet at 6.63 ppm (H-1 of **75**) showed the end of the reaction, and the coupling constant of $J_{1,2}$ (2.6 Hz) confirmed that bromo group was oriented in the α configuration. Column chromatography of the crude compound **75** on silica gel gave the pure substance as a colorless syrup.

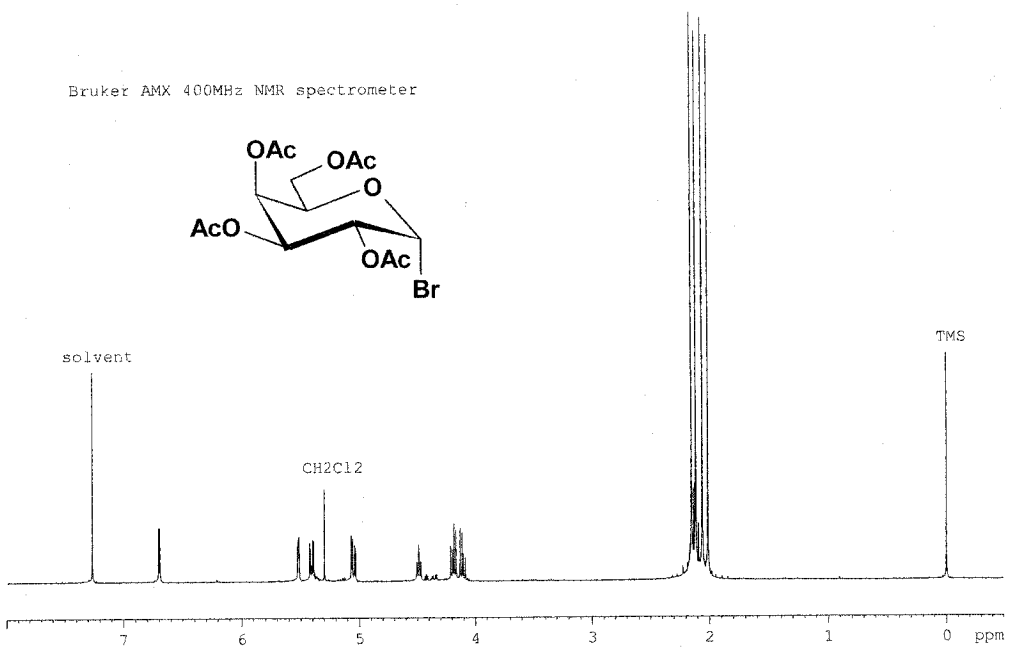


Figure 3.3 400 MHz ^{1}H-NMR spectrum of crude 2,3,4,6-tetra-*O*-acetyl-α-D-galactopyranosyl bromide (**75**) in $CDCl_3$

Both anomeric forms of compound **74** yield compound **75** in the α configuration. The strong electron-withdrawing property of bromine results in such a large anomeric effect that the α configuration was obtained even though a *cis* *O*-acetyl group, a neighboring participating group, is present at the C-2 position. The proposed mechanism is illustrated in Figure 3.4. Presumably, any equatorial β-bromide anomer that forms is converted to the thermodynamically stable α-anomer under the reaction conditions. Hydrogen bromide gas was generated during the reaction. Phosphorus tribromide reacted with water vigorously; water had to be added dropwise into a cooled solution of compound **74** and phosphorus tribromide in dichloromethane (ice bath) to moderate the reaction, then the reaction temperature was brought to room temperature to complete the reaction in 4 h.

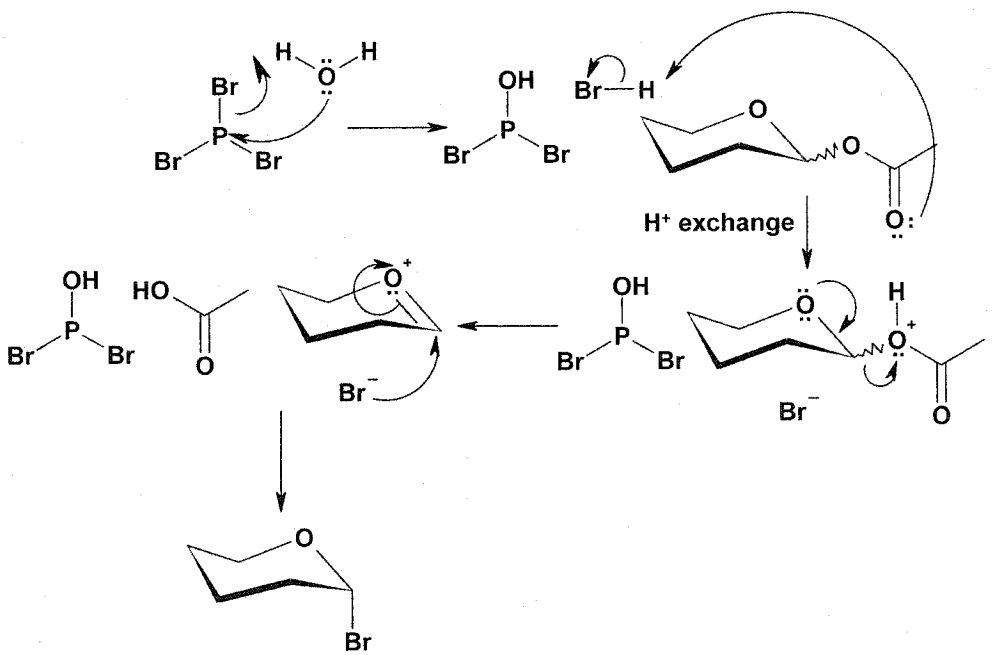


Figure 3.4 The proposed mechanism of bromination with phosphorus tribromide/water

Compound **75** was reduced to **76** by zinc dust in ethyl acetate catalyzed by 1-methylimidazole. The sequence in which the reagents were added affected the result of the reduction of bromide: if 1-methylimidazole was added to a refluxing suspension of bromide and zinc dust in ethyl acetate,[186] 1,2,3,4,6-penta-*O*-acetyl-β-D-galactopyranose (**78**) was the major product (56 %). It is necessary to use freshly activated zinc dust and ethyl acetate that was freshly distilled from calcium hydride in order to avoid the formation of byproduct **78**. Tri-*O*-acetyl-D-galactal (**76**) was obtained by adding a solution of bromide (**75**) in dry ethyl acetate to a refluxing suspension of zinc dust and 1-methylimidazole in dry ethyl acetate. When Shafizadeh's method[192] was tried to reduce compound **75**, which employs zinc dust and 3 % aqueous platinic chloride in 50 % acetic acid, the reaction yield was lower. This may be because the crude bromide syrup was used instead of powdered **75**. Deacetylation with sodium methoxide in methanol gave D-galactal (**77**) in 95.3 % yield.[192]

In conclusion, preparation of D-galactal **77,** by acetylation, bromination, reduction and deacetylation of D-galactose **73**, gave an excellent overall yield (77 %).

3.2 The preparation of the linker arm 6-phthalimido-1-hexanol

6-Phthalimido-1-hexanol (**83**) was prepared from 1,6-hexanediol (**79**) (Figure 3.5).

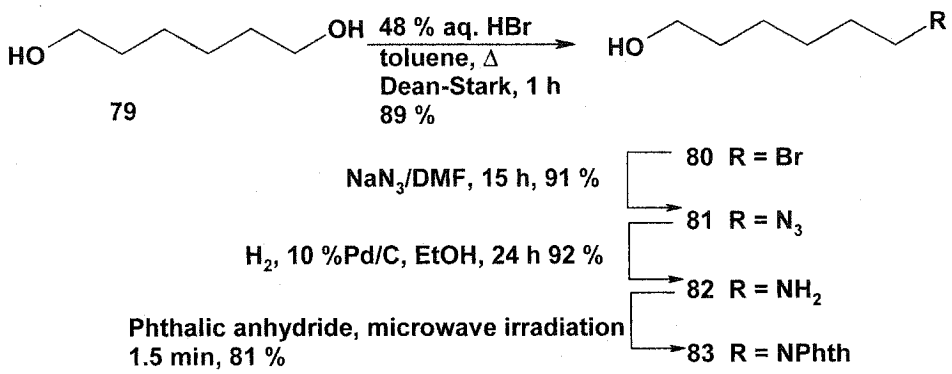


Figure 3.5 Preparation of 6-azido-1-hexanol (**81**) and 6-phthalimido-1-hexanol (**83**)

The mono bromide (**80**) was obtained from 1,6-hexanediol and aqueous hydrogen bromide[198-200] refluxing for 1 h. After workup, a crude product was obtained that had triplets at 3.62 ppm (CH_2OH) and 3.42 ppm ($BrCH_2$) in its 250 MHz ^1H NMR spectrum (Figure 3.5), indicating that the molecule is unsymmetrical. In agreement, the ^{13}C NMR spectrum contained six signals representing the six carbons which have their own distinct environment. The ccompound rude **80** was pure enough for the next reaction.

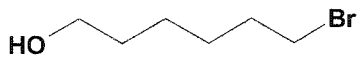


Figure 3.6 ^1H-NMR spectrum of the crude bromide **80** in $CDCl_3$

The bromide **80** was converted to azide **81** by reaction with sodium azide in dry DMF. Hydrogenation of **81** yielded amine **82**.

Vidal et al[201] reported that compound **82** could be converted into its phthalimide by reaction with phthalic anhydride under microwave irradiation. The microwave-induced reaction requires that compound **82** be a solid. Compound **82** has a low melting point (53 - 56 °C). In order to obtain **82** in solid form, DMF had to be removed completely from azide **81** before hydrogenation. This purification was done using a short silica gel column and eluting with hexanes until the DMF was removed, then with ethyl acetate.

Compound **83** was made by this literature procedure.[201] However, instead of using a special microwave generating device, a commercial microwave oven was used to perform the microwave-induced reaction for the synthesis of the phthalimido compound **83.** The reaction finished in 1.5 min and in good yield (81 %).

3.3 The preparation of two anomers: phenyl 2-azido-2-deoxy-1-thio-α-D-galactopyranoside (86) and phenyl 2-azido-2-deoxy-1-thio-β-D-galactopyranoside (87)

Two anomers, phenyl 2-azido-2-deoxy-1-thio-α-D-galactopyranoside (**86**) and phenyl 2-azido-2-deoxy-1-thio-β-D-galactopyranoside (**87**), were obtained with a ratio of 1:1 from tri-*O*-acetyl-D-galactal (Figure 3.7).

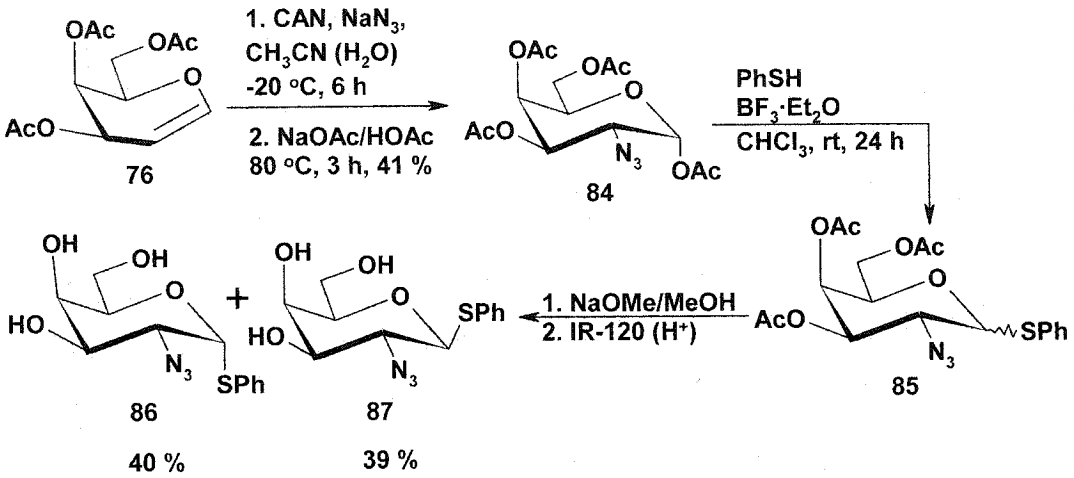


Figure 3.7 The preparation of phenyl 2-azido-2-deoxy-1-thio-α/β-D-galactopyranoside (**86** and **87**)

3,4,6-Tri-*O*-acetyl-2-azido-2-deoxy-D-galactopyranosyl nitrate **88** was prepared by Lemieux's method.[202] It was essential to grind and dry the mixture of ceric ammonium nitrate and sodium azide in order to get a good yield. The reaction finished in 6 h at -20 °C and an extension of the reaction time to 48 h did not improve the reaction yield. The crude product was a yellow oil containing a mixture of 2-azido-1-nitrate addition products of compound **88**, 3,4,6-tri-*O*-acetyl-2-azido-2-deoxy-α-D-talopyranosyl nitrate (**89**) and *N*-acetyl 3,4,6-tri-*O*-acetyl-2-azido-2-deoxy-α-D-galactopyranosylamine (**90**) (Figure 3.8).[202] The only workup required was to wash the ether-diluted mixture with water until the organic layer was colorless. The purification was done after the acetylation step. Sometimes, the yellow organic layer could not be washed to colorless by water in the workup stage. In this case, column chromatography had to be conducted before acetylation. The fast moving fractions from this column with an eluent system of ethyl acetate and hexanes (1:1 v/v, Rf 0.65) contained **88.** Treatment of compound **88**

with sodium acetate in acetic acid gave 1,3,4,6-tetra-*O*-acetyl-2-azido-2-deoxy-α-D-galactopyranose (**84**).[202] The overall yield of the two steps from **76** to **84** was 41 %.

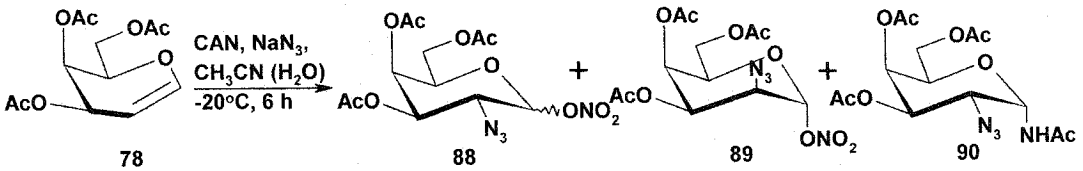


Figure 3.8 The azidonitration of tri-*O*-acetyl-D-galactal

Compound **84** was reacted with benzenethiol and freshly distilled boron trifluoride etherate in chloroform to give phenyl 3,4,6-tri-*O*-acetyl-2-azido-2-deoxy-1-thio-D-galactopyranoside (**85**) as a 1:1 mixture of its α- and β-anomers as reported previously.[203] Both anomers had the same Rf value and could not be separated by flash column chromatography on silica gel. Before deacetylation was performed, it was necessary to run a short column. Excess benzenethiol was removed by eluting ethyl acetate : hexanes (1:5), then compound **85** was eluted with ethyl acetate : hexanes (1:1).

Compound **85** was deacetylated by sodium methoxide to give a mixture of two anomers: phenyl 2-azido-2-deoxy-1-thio-α-D-galactopyranoside (**86**) and phenyl 2-azido-2-deoxy-1-thio-β-D-galactopyranoside (**87**). Compounds **86** and **87** had different Rf values, 0.34 and 0.26 in ethyl acetate : hexanes (10:1, v/v) respectively, and they were separated by flash column chromatography. Both anomers, **86** and **87**, were used as precursors of glycosyl donors and glycosyl acceptors in the disaccharide synthesis.

3.4 Preparation of glycosyl donors and acceptors with O-4 and O-6 protected

Benzylidene acetals are frequently used to protect two hydroxyl groups simultaneously in carbohydrate synthesis. If the hydroxyl groups are at the 4- and 6-

positions, benzylidene acetals provide extremely versatile protection because conditions have been developed to selectively deprotect O-4[204,205] or O-6[206] or both.

The benzaldehyde dimethyl acetal approach[149] gave a good yield in the preparation of compound **49** (Figure 2.5), but did not give the expected 4,6-*O*-benzylidene product here. The excess reagent continued to react with the hydroxyl group at O-4 position and formed compound **91** (Figure 3.9).

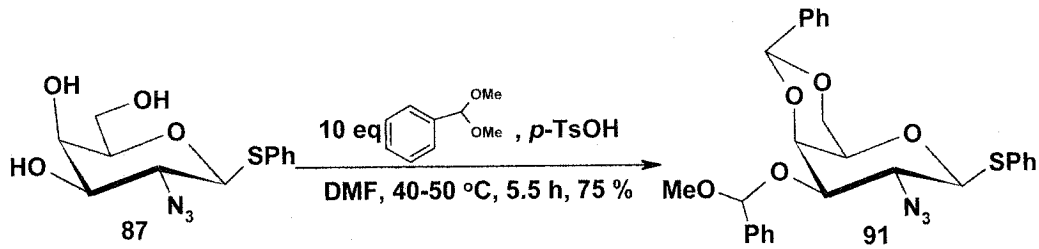


Figure 3.9 Phenyl 2-azido-2-deoxy-1-thio-β-D-galactopyranoside (**87**) reacted with excess benzaldehyde dimethyl acetal to form phenyl 2-azido-4,6-*O*-benzylidene-2-deoxy-3-*O*-(methoxyphenylmethyl)-1-thio-α-D-galactopyranoside (**91**)

It was found that the conditions recently introduced by Muiguia for the formation of ketals from insoluble polyols[207] could be used for the formation of the desired compound here. Benzaldehyde was refluxed with compound **87** in a mixed solvent (DMF : benzene 3:2) with *p*-toluenesulfonic acid as catalyst using a Dean-Stark apparatus to remove water to form the 4,6-*O*-benzylidene product in a high yield. Phenyl 2-azido-4,6-*O*-benzylidene-2-deoxy-1-thio-α-D-galactopyranoside (**92**) and phenyl 2-azido-4,6-*O*-benylidene-2-deoxy-1-thio-β-D-galactopyranoside (**93**) were obtained in yields of 91 % and 89 %, respectively, from compounds **86** and **87**. When a mixture of compounds **86** and **87** was used as the starting material, a mixture of compounds **92** and **93** was obtained. Column chromatography could be used to separate the anomers at this stage as well. Acetylation of compound **92** and **93** gave the corresponding 3-*O*-acetyl products:

phenyl 3-*O*-acetyl-2-azido-4,6-*O*-benylidene-2-deoxy-1-thio-α-D-galactopyranoside (**94**) and phenyl 3-*O*-acetyl-2-azido-4,6-*O*-benylidene-2-deoxy-1-thio-β-D-galactopyranoside (**95**) (Figure 3.10).

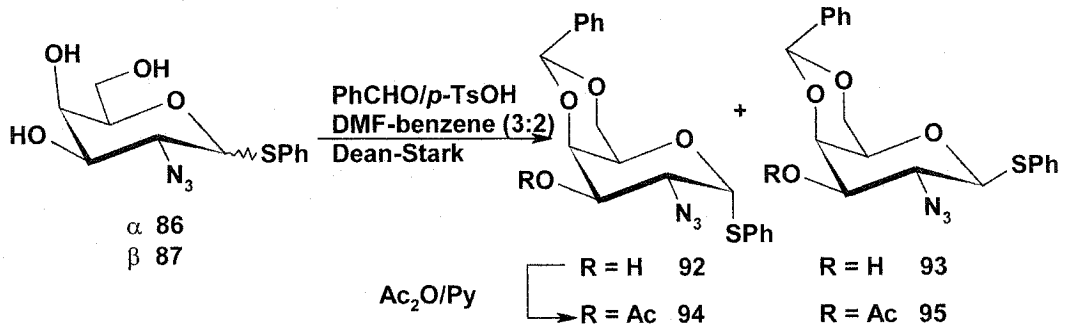


Figure 3.10 Preparation of compounds phenyl 2-azido-4,6-*O*-benzylidene-2-deoxy-1-thio-α-D-galactopyranoside (**92**), phenyl 2-azido-4,6-*O*-benzylidene-2-deoxy-1-thio-β-D-galactopyranoside (**93**), phenyl 3-*O*-acetyl-2-azido-4,6-*O*-benzylidene-2-deoxy-1-thio-α-D-galactopyranoside (**94**) and phenyl 3-*O*-acetyl-2-azido-4,6-*O*-benzylidene-2-deoxy-1-thio-β-D-galactopyranoside (**95**)

Compound **92** was reported by Nifantiev et al in 2002.[208] However, this group only assigned one hydrogen signal in the ^{1}H NMR spectrum, that of H-1. Because the ^{1}H NMR spectrum was not assigned completely, several carbon signals (C3, C5 and C6) were assigned incorrectly in the ^{13}C NMR spectrum.

A similar reaction of compound **86** with anisaldehyde yielded the 4,6-*O*-*p*-methoxybenzylidene analogue **98** which was acetylated to give the 3-*O*-acetyl derivative **99** (Figure 3.12).

Oxidation of thioglycosides **94** and **99** with *m*-chloroperoxybenzoic acid in dichloromethane at –76 °C yielded two isomeric sulfoxides for the 4,6-*O*-benzylidene derivative (**96R**, **96S**) and for the 4,6-*O*-*p*-methoxybenzylidene derivative (**100R** and **100S**). The preferences for the oxidation to yield the $(R)_S$ isomer was much less than

noted for *gluco*[209] and *manno*[107,158] analogues, being 3/1 for compound **96** and 7/2 for compound **100** (Figure 3.11 and 3.12).

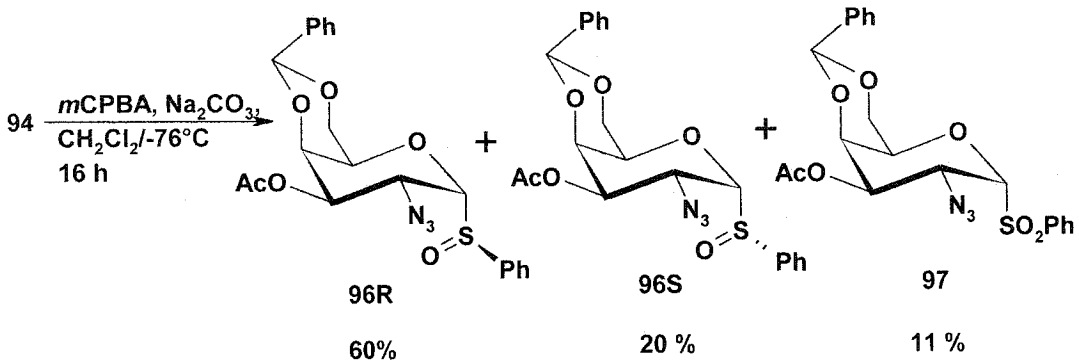


Figure 3.11 Oxidation of phenyl 3-*O*-acetyl-2-azido-4,6-*O*-benzylidene-2-deoxy-α-D-galactopyranoside (**94**)

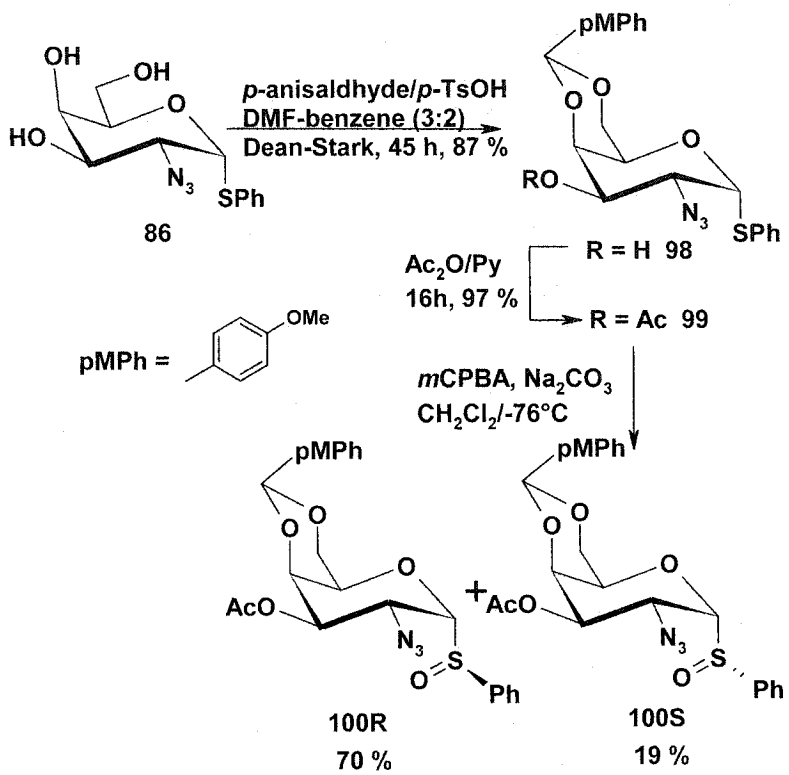


Figure 3.12 Preparation of phenyl 2-azido-2-deoxy-4,6-*O*-(*p*-methoxybenzylidene)-1-thio-α-D-galactopyranoside (**98**), phenyl 3-*O*-acetyl-2-azido-2-deoxy-4,6-*O*-(*p*-methoxybenzylidene)-1-thio-α-D-galactopyranoside (**99**), phenyl 3-*O*-acetyl-2-azido-2-deoxy-4,6-*O*-(*p*-methoxybenzylidene)-1-thio-α-D-galactopyranoside(*R*)s-oxide **(100R)** and phenyl 3-*O*-acetyl-2-azido-2-deoxy-4,6-*O*-(*p*-methoxybenzylidene)-1-thio-α-D-galactopyranoside(*S*)s-oxide (**100S**)

3.5 Attachment of the linker arm to the glycosyl acceptor

6-Phthalimidohexanyl 3-*O*-acetyl-2-azido-2-deoxy-4,6-*O*-(*p*-methoxybenzylidene-2-deoxy-β-D-galactopyranoside (**101**) was obtained by the reaction of compound **99** with an excess amount of compound **83** at -40 °C to -30 °C for 18 h (Figure 3.13). Compound **101** can serve as the glycosyl acceptor with the linker arm at the anomeric carbon after removal of the 3-*O*-acetyl group.

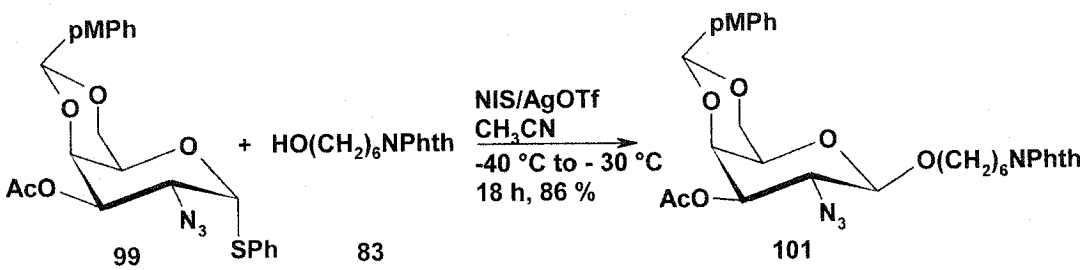


Figure 3.13 Preparation of 6-phthalimidohexanyl 3-*O*-acetyl-2-azido-2-deoxy-4,6-*O*-(*p*-methoxybenzylidene)-β-D-galactopyranoside (**101**)

The overall synthetic strategy was designed to produce the diphosphorylcholine derivative and both monophosphorylcholine derivatives, that is, derivatives with phosphorylcholine units on ring **A**, ring **B** or both rings **A** and **B** (Figures 1.2, 1.3 and 1.4). In order to do this, it was necessary to prepare compounds with linker arms attached to both the 4,6-*O*-benzylidene and 4,6-*O*-*p*-methoxybenzylidene acetals of 2-azido-2-deoxy-D-galactopyranose. It was thought that compound **102** could be prepared directly from the reaction of compound **92** and **83**. A potential complication was the presence of the free hydroxyl group on **92** which could yield a disaccharide if it reacted with its own activated glycosyl center. However, it was thought that the primary hydroxyl group of **83** would be much more reactive than the secondary hydroxyl group of **92**, and an excess amount of **83** was used to increase the probability of the reaction between **83** and activated **92**. As predicted, the reaction of compound **92** and **83** activated by *N*-iodosuccinimide and silver triflate yielded compound **102** in an excellent yield (93 %). The reaction may have followed an S_N2 mechanism to yield **102** with inversion of the configuration of the original thioglycoside **92.** When the β-anomer (**93**) was used at – 40 °C or at room temperature, compound **102** was not obtained, even though the β-product was still expected based on solvent participation by acetonitrile.

The reaction temperature also affected the stereoselectivity of the reaction. When the reaction of **92** and **83** was carried out at room temperature, the yield of 6-phthalimidohexanyl 2-azido-4,6-*O*-benzylidene-2-deoxy-β-D-galactopyranoside (**102**) was very poor (3 %).

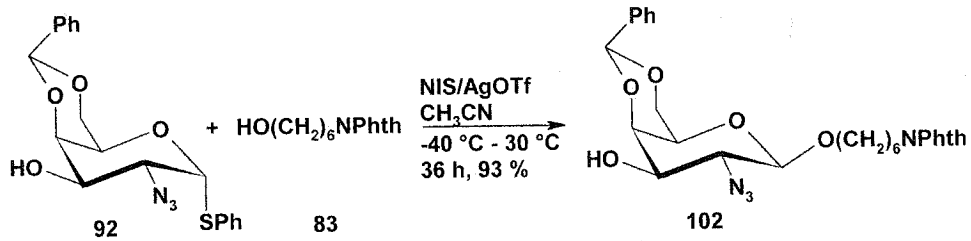


Figure 3.14 Preparation of 6-phthalimidohexanyl 2-azido-4,6-*O*-benzylidene-2-deoxy-β-D-galactopyranoside (**102**)

3.6 Disaccharide syntheses

Glycosyl sulfoxides can be used as glycosyl donors under promotion with trifluoromethanesulfonic anhydride.[210,211] The structures and conformations of this type of glycosyl donor will be discussed in greater detail in chapter 4. Disaccharide **103** was prepared as shown in Figure 3.15. When acceptor **92**, which has an α-configuration, was used, phenyl 2-azido-3-*O*-(2'-azido-2'-deoxy-3'-*O*-acetyl-4',6'-*O*-benzylidene-α-D-galactopyranosyl)- 4,6-*O*-benzylidene-2-deoxy-1-thio-α-D-galactopyranoside (**104**) was obtained in a yield of 62 %.

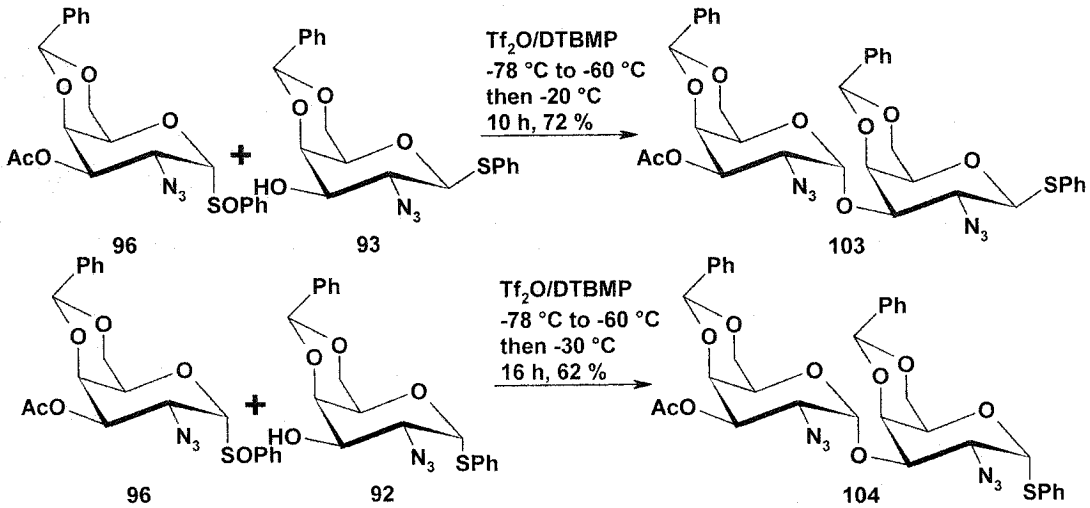


Figure 3.15 Preparation of disaccharides phenyl 3-*O*-(3'-*O*-acetyl-2'-azido-4',6'-*O*-benzylidene-2'-deoxy-α-D-galactopyranosyl)-2-azido-4,6-*O*-benzylidene-2-deoxy-1-thio-β-D-galactopyranoside (**103**) and phenyl 3-*O*-(3'-*O*-acetyl-2'-azido-4',6'-*O*-benzylidene-2'-deoxy-α-D-galactopyranosyl)-2-azido-4,6-*O*-benzylidene-2-deoxy-1-thio-α-D-galactopyranoside (**104**)

Thioacetic acid[144] was used to reduce the azide group of disaccharide **103** to yield disaccharide **105** (Figure 3.16). Reduction occurred with concomitant acetylation to form acetamides at C-2 of both galactopyranoside units. In the ^{1}H NMR spectrum of the product, two doublets appeared at 5.78 and 5.65 ppm. From the COSY spectrum These signals were assigned to the two NH groups by means of the cross peaks between the NH and H-2 protons (Figure 3.17).

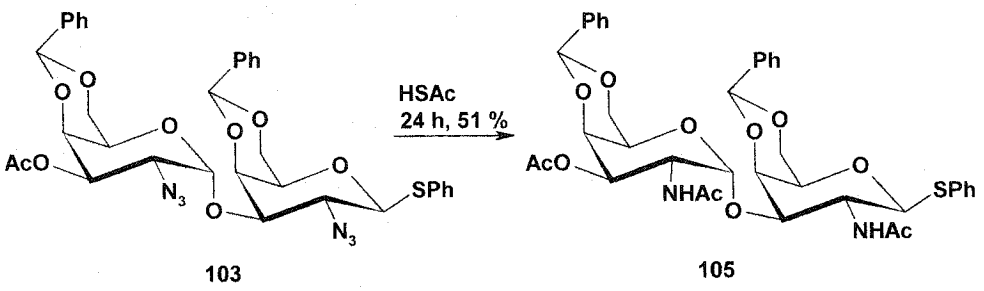


Figure 3.16 Reduction of azido groups in compound **103** to form the disaccharide phenyl 2-acetamido-3-*O*-(2'-acetamido-3'-*O*-acetyl-4',6'-*O*-benzylidene-2'-deoxy-α-D-galactopyranosyl)-4,6-*O*-benzylidene-1-thio-α-D-galactopyranoside (**105**)

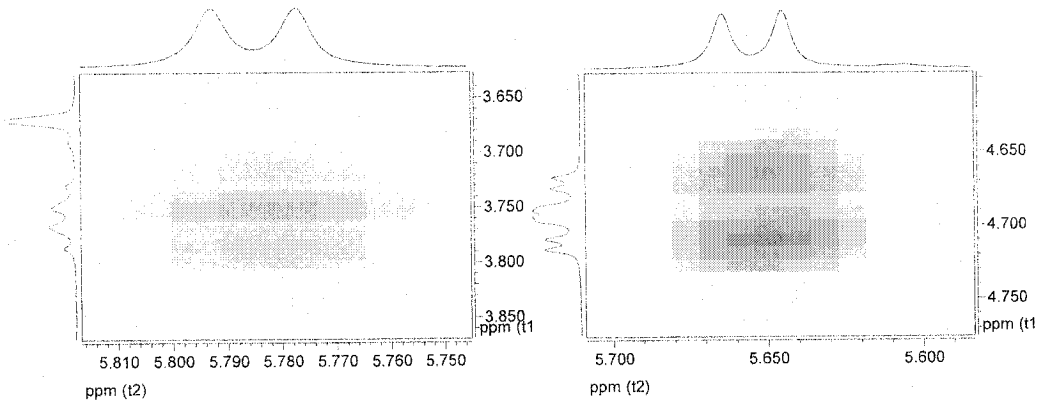


Figure 3.17 Crosspeaks of NH/H-2 (left) and NH'/H-2' (right) in the COSY spectrum of compound **105**

Compound **106** was obtained by two methods (Figure 3.18). In method A, thioglycoside **95** was activated by NIS/AgOTf at – 40 °C and reacted with glycosyl acceptor **102** to give the disaccharide 6-phthalimidohexanyl 3-*O*-(3'-*O*-acetyl-2'-azido-4',6'-*O*-benzylidene-2'-deoxy-α-D-galactopyranosyl)-2-azido-4,6-*O*-benzylidene-2-deoxy-β-D-galactopyranoside (**106**) in a yield of 45 %. The β-anomer **106β** was formed in a yield of 24 %, perhaps because of solvent participation. If the reaction was conducted in a mixed solvent of dichloromethane and acetonitrile (1:1) at -60 °C (24 h), then at -40 °C (12 h), **106β** became the major product: the ratio of **106** and **106β** was 1:30. The effects of solvent participation and temperature on the stereoselectivity of

glycosidation reactions were observed again! In method B, disaccharide **104** had a thiophenyl leaving group. It reacted with linker arm derivative **83** on activation with NIS/AgOTf to yield disaccharide **106** in a yield of 50 %. Method A gave a lower yield than method B did because the side effect of the solvent participation. However, the glycosyl acceptor **102** was made from the α-anomer **86** and the glycosyl donor **95** was a derivative of the β-anomer **87**. Method A satisfied the designed synthetic strategy: making full use of both anomers of phenyl 2-azido-2-deoxy-1-thio-D-galactopyranoside in the disaccharide synthesis.

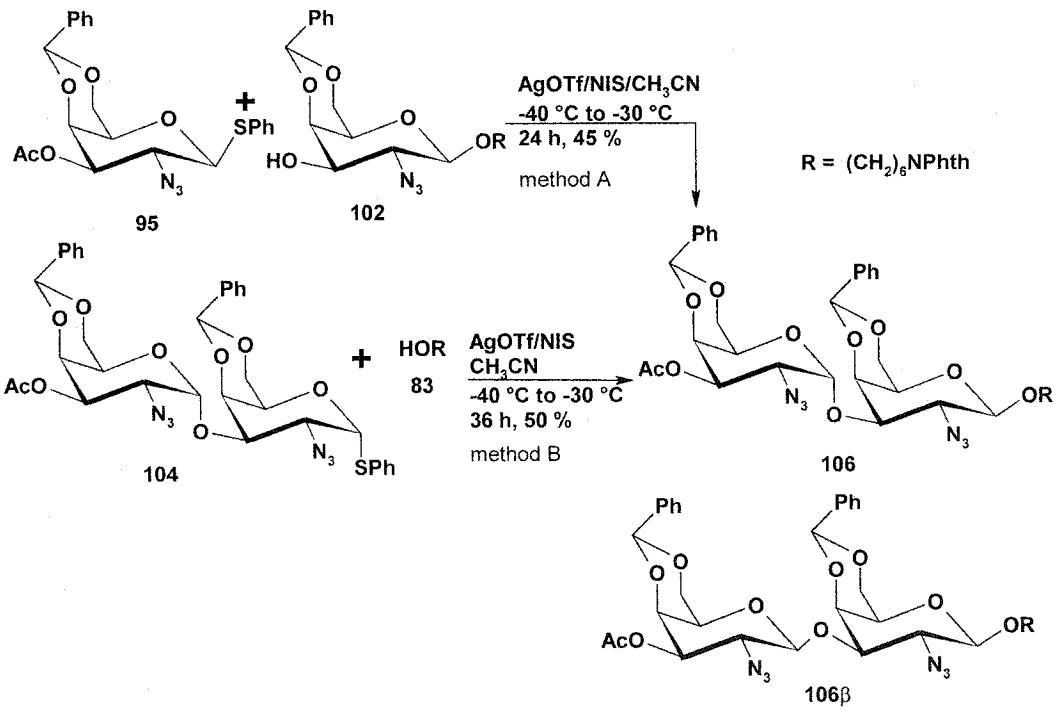


Figure 3.18 Preparation of the disaccharide with the linker arm: 6-phthalimidohexanyl 3-*O*-(3'-*O*-acetyl-2'-azido-2'-deoxy-4',6'-*O*-benzylidene-α-D-galactopyranosyl)-2-azido-4,6-*O*-benzylidene-2-deoxy-β-D-galactopyranoside (**106**)

Aqueous acetic acid (60 %) hydrolyzed the 4,6-*O*-benzylidene acetals from compound **106** to yield compound **107**. However, the reaction yield was extremely low

(4.3 %). Even though mild conditions were used, the two glycosidic linkage were mostly hydrolyzed (Figure 3.19).

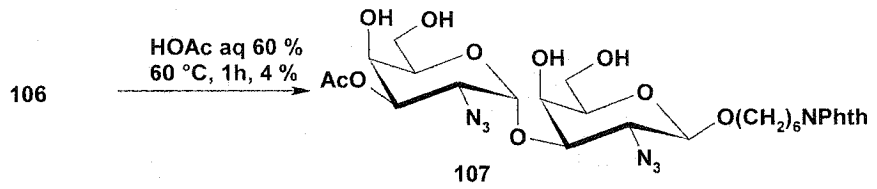


Figure 3.19 Preparation of disaccharide 6-phthalimidohexanyl 3-*O*-(3'-*O*-acetyl-2'-azido-2'-deoxy-α-D-galactopyranosyl)- 2-azido-2-deoxy-β-D-galactopyranoside (**107**)

An alternative route was adopted because of the poor yield. Compound **109** was prepared from compound **106** by hydrogenation and acetylation (Figure 3.20). The hydrogenation reaction was conducted in a mixed solvent (ethanol : chloroform, 1:1, v/v) and finished in 24 h. However, the standard reagent, acetic anhydride in methanol did not give the desired acetylated product **109**. The glycosidic linkages of this type of disaccharide appear to be extremely acid sensitive, since even treatment with a low concentration of a weak acid such as acetic acid resulted in cleavage. The extremely low yield in the hydrolysis of compound **106** (Figure 3.19) is also attributed to this sensitivity to acid.

A solution to this problem that has not been fully completed was obtained by buffering during the acetylation. Addition of sodium acetate (4 eq) and acetic anhydride (4 eq) to the product of a new hydrogenation reaction in methanol gave the desired product as measured by the ESI mass spectrum of the product. This spectrum contained two major peaks at *m/z* 718.4 and 806.3. The first is at the molecular mass (+ Na) of the expected product, the second is at the molecular mass (+ Na) of the product of the di-*N*-acetate of the azide-reduced mono-*O*-benzylidene derivative. Apparently reduction of the benzylidene rings had not been completely accomplished.

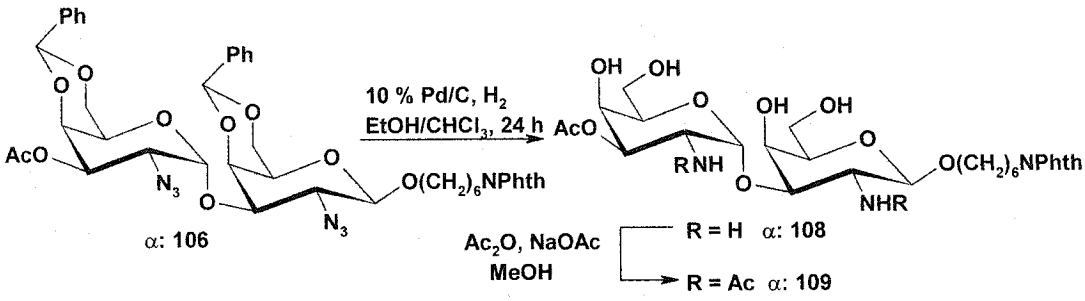


Figure 3.20 Deprotection, reduction and regioselective *N*-acetylation of compound **106**

3.7 Introduction of phosphorylcholine groups at O-6 of the disaccharide

3.7.1 Methods for the introduction of phosphorylcholine

Phosphorylcholine groups are important bioactive constituents of the teichoic acid and lipoteichoic acid of the surface of *Streptococcus pneumoniae*.[212]

Several procedures for the introduction of the phosphorylcholine moiety from corresponding alcohols have been described in the literature. Different types of phosphorus compounds were used as the source of the phosphorus atom which will be summarized in the following sections.

3.7.1.1 Use of 2-bromoethylphosphodichloridate as the phosphorus source

This method, first reported by Hirt and Berchtold in 1958,[213] led to poor yields[214] and many by-products, which made purification difficult.[215] However, Y. Nishida[216] successfully applied this reagent to introduce phosphorylcholine at O-6 of glucopyranosides in a reasonable yield (Figure 3.21).

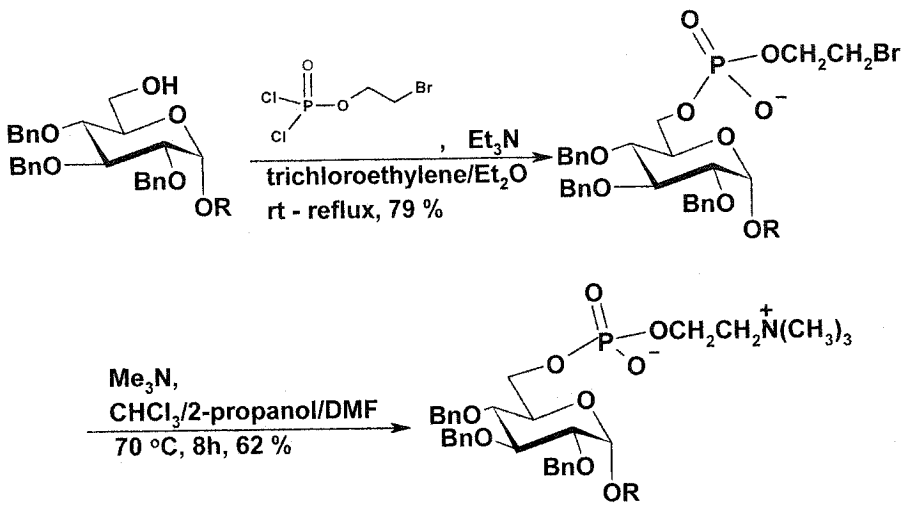


Figure 3.21 Introduction of phosphorus using 2-bromoethylphosphodichloridate as the phosphorus source

3.7.1.2 Use of 2-chloro-l,3,2-dioxaphospholane-2-one as the phosphorus source

In this method, an alcohol is reacted with 1 eq of 2-chloro-2-oxo-l,3,2-dioxaphospholane in benzene using 1 eq triethylamine as the catalyst to form the cyclic phosphotriester. The ring of the ethylene-bridged phosphate diester portion of the molecule is opened by anhydrous trimethylamine in acetonitrile at 60-65 °C for 24-48 h. Chandrakumar and Hajdu[217] reported the use of this method in 1982 to stereospecifically synthesize the enzyme-inhibitor 2-sn-deoxy-2-amidophosphatidylcholine. Guivisdalsky and Bittman[218] used this method in 1986 for the synthesis of unnatural, cytotoxic ether-linked phospholipids. F.M. Menger et al[219] used this method to obtain macrocyclic phospholipids containing 32 - 44 ring atoms in 1993 (Figure 3.22). This approach has not only been successfully applied in the above coupling of glycerols to the phosphate moiety, but also has been used to prepare some kinds of amphoteric glycolipid analogues containing a phosphorylcholine residue recently.[220,221] However, 2-chloro-2-oxo-l,3,2-

dioxaphospholane was observed to be unreactive with sterically hindered alcohols.[222,223]

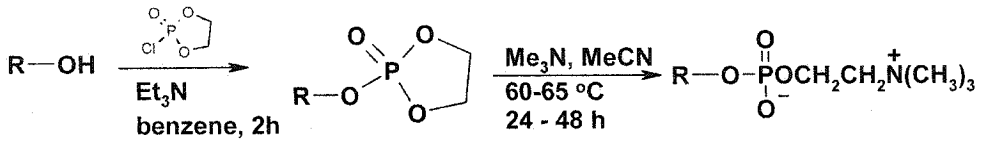


Figure 3.22 Introduction of phosphorus using 2-chloro-1,3,2-dioxaphospholane-2-one as the phosphorus source

3.7.1.3 Use of phosphorus oxychloride as the phosphorus source

Magolda and Johnson reported a method to synthesize alkyl phosphorylcholines from phosphorus oxychloride via a two-pot, three-step process in 1985.[222] The overall yield from the requisite alcohol was 35 – 50 %. (Figure 3.23)

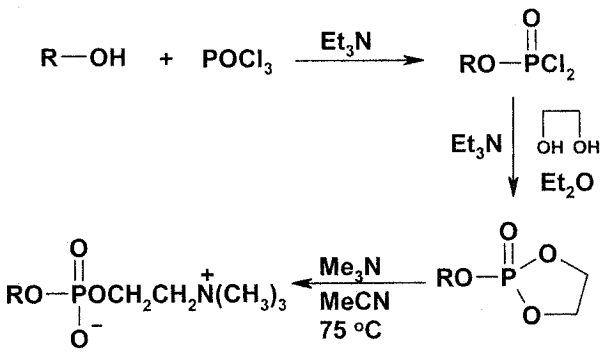


Figure 3.23 Introduction of phosphorus using phosphorus oxychloride as the phosphorus source

3.7.1.4 Use of 2-chloro-1,3,2-dioxaphospholane as the phosphorus source

In 1994, Bittman's group introduced a simple one-pot method involving five sequential reactions (phosphitylation, P(III) oxidation, ring opening, hydrolysis, and amination) in three operations to obtain antitumor alkyl phosphorylcholines[224] (Figure 3.24). Since then, this group has applied this method to introduce phosphorylcholine into different glycerol derivatives.[225-229] Nitrogen dioxide was also reported as an oxidant to

oxidize the phosphite at the oxidation step.[230]

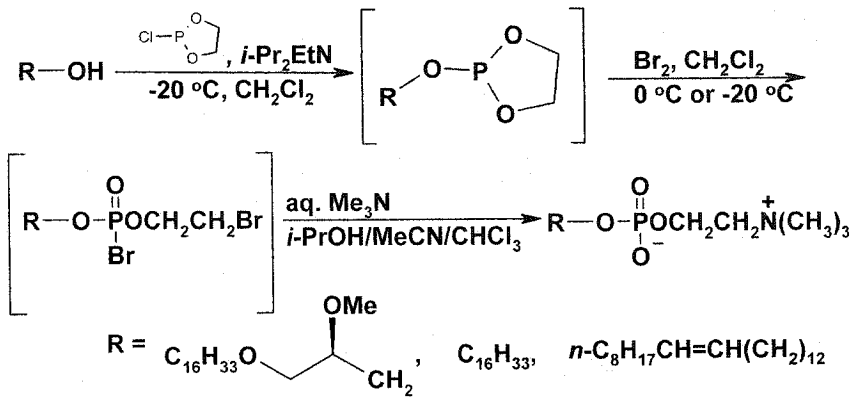


Figure 3.24 Introduction of phosphorus using 2-chloro-1,3,2-dioxaphospholane[224] as the phosphorus source

3.7.1.5 Use 2-cyanoethyl-*N,N,N',N'*-tetraisopropylphosphoramidite as the phosphorus source

As shown in Figure 3.25, Noshida et al[214] also used a standard phosphitylation reagent, 2-cyanoethyl-*N,N*-diisopropylphosphoramidite, to introduce the phosphorus atom for making phosphoryl derivatives in 1999. Choline was introduced in the same pot also using 1H-tetrazole as the base. Oxidization *in situ* by silver (II) dipicolinate and removal of the cyanoethyl group in aqueous ammonia in methanol gave the product.

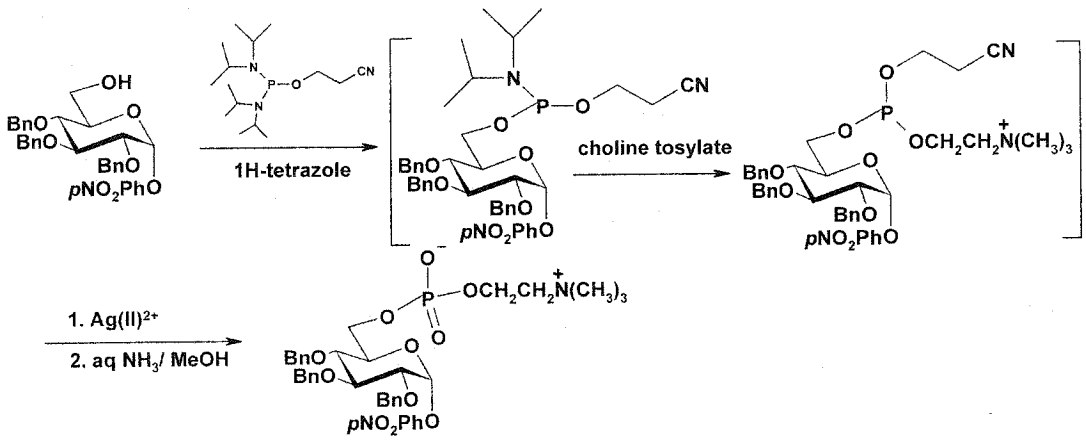


Figure 3.25 Introduction of phosphorus using 2-cyanoethyl-*N,N*-diisopropylphosphoramidite as the phosphorus source

3.7.1.6 Purification of phosphorylcholine

Normally, crude phosphorylcholine compounds have been desalted by passing through a mixed bed ion-exchange resin column (such as TMD-8,[224,227] Rexyn I-300,[215] or Sephadex LH20[220]), then purified by column chromatography on silica gel. Direct application to a silica gel column [219] could fail to elute product due to the zwitterionic properties of phosphorylcholine compounds. Dowex MR-3 (H-OH) mixed bed ion exchange resin was used here.

3.7.2 Regioselective introduction of phosphorylcholine at O-6 of methyl 2-acetamido-2-deoxy-α-D-glucopyranoside

The monosaccharide, methyl 2-acetamido-2-deoxy-α-D-glucopyranoside (**25**), was tested as a model compound for the introduction of phosphorylcholine. Compound **25** has three free hydroxyl groups and an acetamido group at C-2. Following Bittman's method,[224] methyl 2-acetamido-2-deoxy-6-*O*-phosphorylcholine-α-D-glucopyranoside (**112**) was obtained. Because compound **25** has poor solubility in dichloromethane, chloroform and tetrahydrofuran, pyridine was used as the reaction solvent. This one-pot reaction had good regioselectivity for the primary hydroxyl group (Figure 3.26). The ^{1}H NMR spectrum could not be interpreted because of very extensive overlap. ESI mass spectrometry has been used extensively to determine the location of sulfate groups on sulfated carbohydrates.[231-236] Low energy collision induced dissociation in MS/MS experiments is particularly informative. An ESI MS/MS experiment established the location of the group. Figure 3.27 proposes possible fragmentation pathways. Figure 3.28 gives a possible mechanism for fragment formation. The presence of a fragment at 226 (m/z) in this spectrum indicated that the phosphorylcholine was linked to the O-6

position. Only a structure having the phosphoryl choline unit attached to O-6 can lose 14 Da (CH_2) from the ion that results from eliminating $HOPO_2R$ (m/z 240).

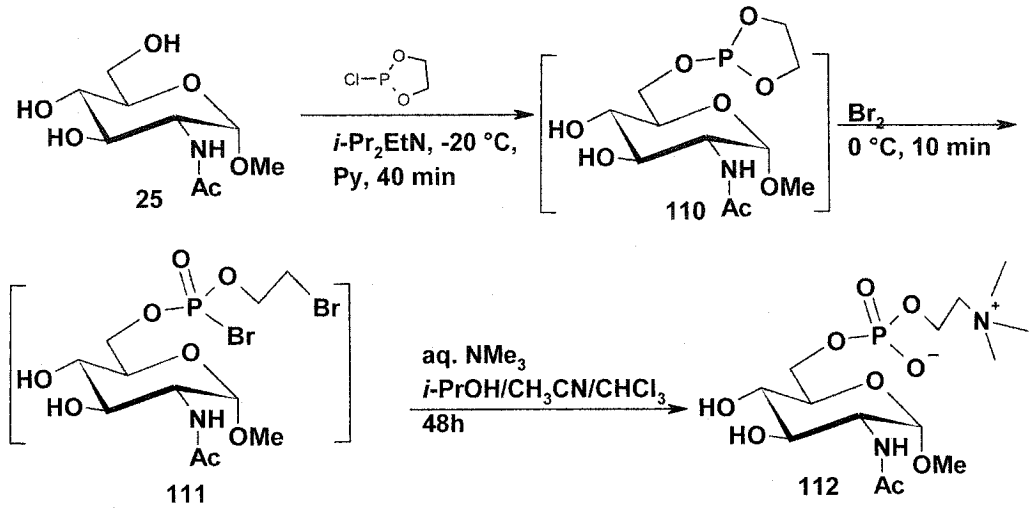


Figure 3.26 Preparation of methyl 2-acetamido-2-deoxy-6-*O*-phosphorylcholine-α-D-glucopyranoside (**112**)

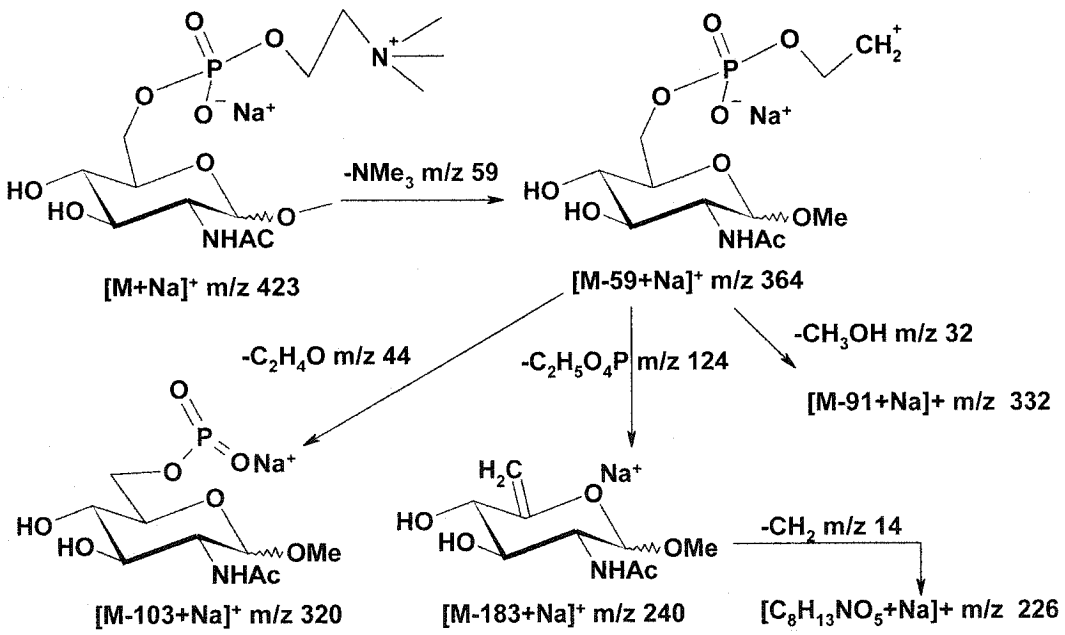


Figure 3.27 Proposed fragmentation pathways of $[M+Na]^+$ for compound **112**

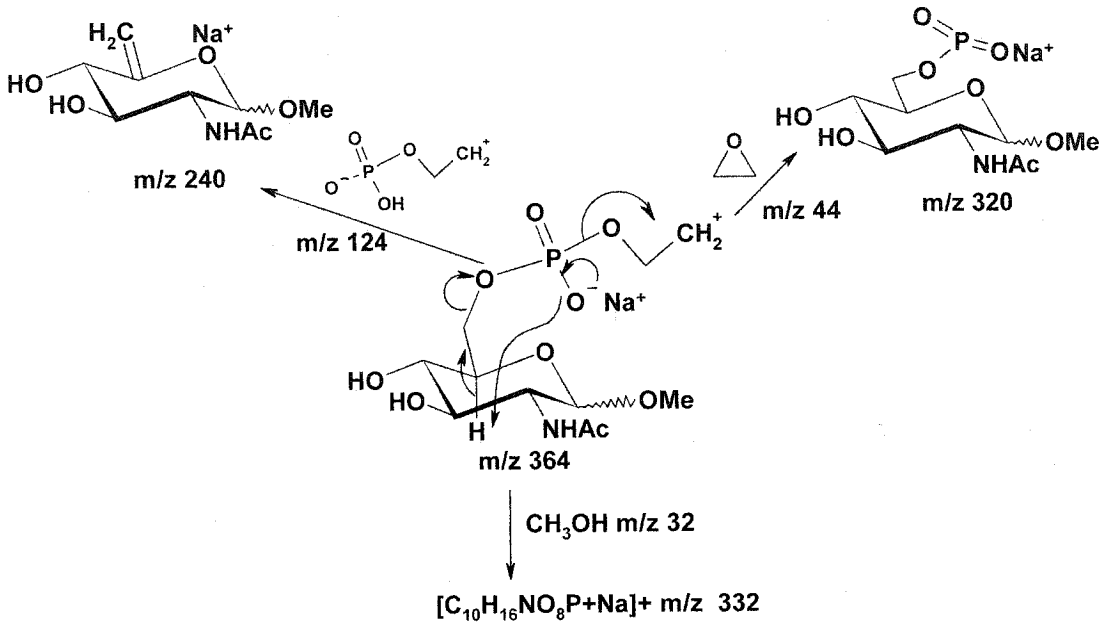


Figure 3.28 Possible mechanism for the formation of ions at m/z 332, 320 and 240 from the precursor ion [M-NMe_3+Na]+ at m/z 364

3.7.3 Regioselective introduction of phosphorylcholine at O-6 positions of the disaccharide

Exposure of the disaccharide **107** to Bittman's conditions gave compound **113**. Pyridine was used as the solvent and also as a base in the first step of the reaction. In the ^{31}P NMR spectrum, there were two peaks at 0.30 and 0.08 ppm, indicating that two phosphorylcholine groups had been introduced into the molecule. The locations of the phosphorylcholine units were established from the chemical shifts of C-6 and C-6', at 67.4 and 64.4 ppm, compared to chemical shifts of 62.9 and 62.3 ppm for the analogous carbon atoms in the spectrum of the precursor, compound **107**. These signals as well as those of C-5' and the two choline OCH_2 signals appeared as doublets because of coupling to ^{31}P. Jansson and coworkers[8,45] and Jennings and coworkers[43] reported chemical shifts

of 64.4 to 65.3 for C-6 of phosphorylcholine-substitituted GalNAc in the C-polysaccharide variants.

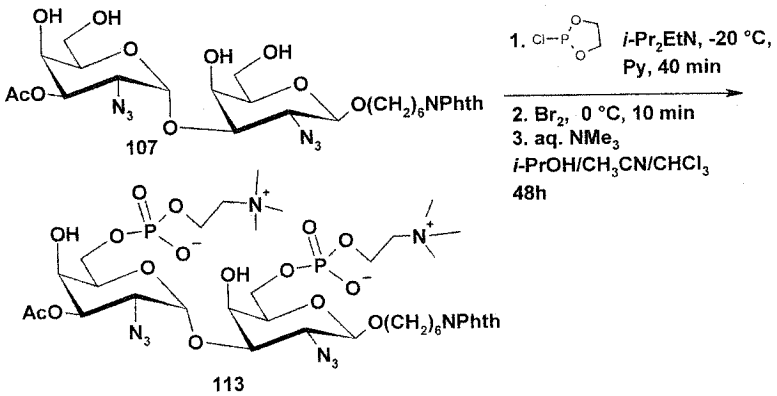


Figure 3.29 Preparation of 6-phthalimidohexanyl 2-azido-2-deoxy-3-*O*-(3'-*O*-acetyl-2'-azido-2'-deoxy-6'-*O*-phosphorylcholine-α-D-galactopyranosyl)-6-*O*-phosphorylcholine-β-D-galactopyranoside (**113**)

Chapter 4 Configuration and conformation of glycosyl sulfoxides

One of the most important techniques for the formation of glycosides employs glycosyl sulfoxides activated by electrophiles as leaving groups.[102] This method has been used to form glycosides that have widely varying structures for both the glycosyl donors and aglycons.[103,104,108,111,151,158,237-244] The activated sulfoxide is sufficiently reactive that reactions in solution can be conducted at -78 °C and it can also be used in solid phase reactions.[245] The configuration of the sulfoxide does not influence the stereochemistry of glycosylation reactions but does affect the rate of glycosylation reactions[246] and the rates of competing elimination and hydrolysis reactions.[247,248] The stabilities of the different sulfoxide diastereomers are inherently linked to the conformations that they adopt. It has been assumed that these conformations are influenced primarily by the exoanomeric effect with contributions from dipole-dipole repulsion between C-O and S-O dipoles[249] and $n \rightarrow \sigma^*$ donation from the sulfur lone pair into the C-O *anti* bonding orbital.[250] The results herein will show that the exoanomeric effect is much less dominant in controlling the conformations of glycosyl sulfoxides than of glycosyl sulfides or of normal glycosides and that dipole-dipole repulsion is not important.

Crich and coworkers have observed that oxidation of axial thioglycosides on pyranoside rings gave one stereoisomer predominantly, the $(R)_S$ isomer for α-D-pyranosides.[249,251] Stereoselectivity is particularly high if the pyranoside rings are made rigid by fusion to 4,6-*O*-benzylidene acetals.[107,252] This group[249] and others[253] observed that oxidation of equatorial sulfoxides was unselective. Khiar and coworkers also found that oxidation of O2-protected equatorial thioglycosides was normally unselective but

observed that oxidation of O2-unprotected equatorial thioglycosides is highly diastereoselective.[247,250] A few O2-substituted equatorial thioglycosides were found to exhibit highly selective oxidations also; peresters of β-thiophenyl or β-ethyl 2-tetrachlorophthalimido-2-deoxy-D-glucopyranosides gave diasteromeric ratios *R*s:*S*s> 9:1.[247]

Assignment of configuration of the product sulfoxides has been based on results from X-ray crystallography,[246,247,249,251,254,255] augmented by empirical rules developed from NMR measurements[250] and from the use of chiral shift reagents.[255,256] Khiar proposed two methods for making assignments directly based on NMR results.[250] For ethyl sulfoxides, the methylene protons of the ethyl group are diastereotopic. For equatorial sulfoxides of D-pyranosides, the chemical shift differences between the ^{1}H NMR signals of these diastereotopic protons is considerably larger for the R_S isomer than the S_S isomer.[247,250] This observation has been rationalized in terms of the assumption that the major conformation present for the R_S sulfoxides is that in which the ethyl group adopts the *exo* orientation,[250] which agreed with results from semiempirical (AM1) calculations.[255] This conformation of the R_S sulfoxides has the sulfoxide sulfur lone pair *anti* to the C1-O5 bond, aligned so that n→σ* overlap can occur (see Figures 4.1 and 4.2).

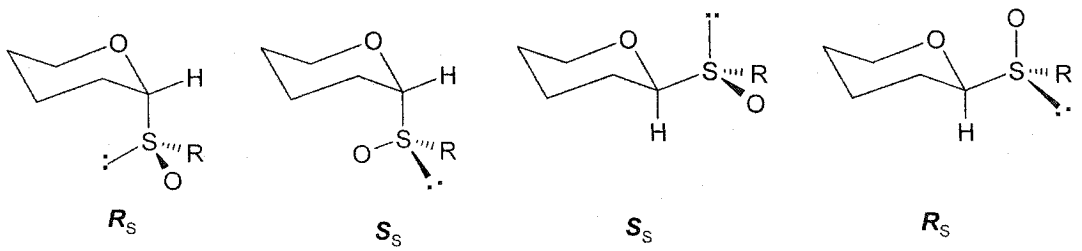


Figure 4.1 *Exo* conformations of the glycosyl sulfoxides of D-sugars in $^4C_1$ chair conformations

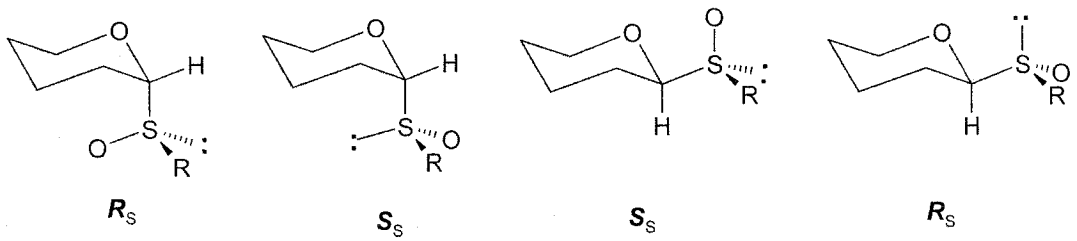


Figure 4.2 *Anti* conformations of the glycosyl sulfoxides of D-sugars in $^4C_1$ chair conformations.

The second NMR method for making assignments was based on the ^{13}C NMR chemical shifts of anomeric carbons; those for R_S sulfoxides of equatorial D-pyranosides are more shielded by >2 ppm for both aryl and alkyl sulfoxides.[247,250] For axial sulfoxides of D-pyranosides, the minor S_S isomer exhibits the more shielded anomeric carbon and the larger chemical shift difference between the diastereotopic protons of ethyl sulfoxides.[247] The larger shielding was attributed to the n→σ* overlap mentioned above.[250] If it is assumed that the contribution of conformers with the aglycon gauche to both the ring oxygen and C2 are negligible, this arrangement only occurs in the *exo* conformation of the equatorial R_S sulfoxide of D-sugars and in the *exo* conformation of the minor S_S isomer of axial sulfoxides (see Figures 4.1 and 4.2).

In contrast, Crich and coworkers have identified S-O C1-O5 dipole repulsion as being very important in determining the conformations of axial sulfoxides.[249] For α-D-pyranosides, the major R_S sulfoxide has the S-O group *anti* to the ring C1-O5 bond if the conformation adopted is that favored by the exoanomeric effect. They have interpreted equilibration results on glycosyl allyl sulfoxides in terms of the importance of dipole-dipole repulsion.[249] The Crich group has observed several exceptions to the tendency for the methylene protons of ethyl sulfoxides to have larger chemical shift differences in particular diastereomers.[249]

Most of the conclusions about sulfoxide conformation and configuration have been based on X-ray crystallography,[247,249,251,254,255] supported by AM1 calculations.[255] With one exception,[249] the ten glycosyl sulfoxides previously studied adopted conformations in the solid state with the sulfoxide alkyl or aryl group in the exoanomeric conformation. Both 96R and 100R adopt an *anti* conformation. In addition, NMR studies have been performed in which NOE buildup rates have been used to determine the preferred conformations of these apparently anomalous sulfoxides in solution. Extensive molecular orbital calculations using density functional theory at the B3LYP/6-311+(d,p) level have now provided improved understanding of the factors which determine the relative stabilities of the conformations of the two sulfoxide configurations. These calculations suggest that the oxidation of a glycosyl sulfide to a glycosyl sulfoxide results in a change of the normal preference of glycosides to adopt *exo* conformations (exoanomeric effect[257]) into a preference for *anti* conformations or for mixtures of the two types of conformations.

4.1 Crystal structures of phenyl 3-*O*-acetyl-2-azido-4,6-*O*-benzylidene-2-deoxy-1-thio-α-D-galactopyranoside (94), phenyl 3-*O*-acetyl-2-azido-4,6-*O*-benzylidene-2-deoxy-1-thio-α-D-galactopyranoside $(R)_S$-oxide (96R), and $(S)_S$-oxide (96S) and phenyl 3-*O*-acetyl-2-azido-4,6-*O*-(*p*-methoxybenzylidene)- 2-deoxy-1-thio-α-D-galactopyranoside $(R)_S$-oxide (100R)

X-ray crystal structure determinations were performed on compounds **94**, **96R**, **96S**, and **100R**. The phenyl thioglycoside **94** adopted the *exo* conformation (Figure 4.3). A compilation of all 22 structures previously published that contain axial thioglycosides was assembled from the Cambridge Data File and data from this compilation is listed in Table 4.1. In all previous 22 structures as well as in the one determined here, the conformation adopted was *exo*.

Table 4.1 Thioglycosides with axial S atoms

Entry	Type of Aglycone	Ring size, Chair Conf	Anomeric conf.	Tor. angle (°) O5-C1-S-C	Code
1	Primary alkyl	6, $^4C_1$	*exo*	67.6	BIFPIP[258]
2	Sugar (sec)	6, $^4C_1$	*exo*	89.0	CIBYAN[259]
3	Primary alkyl	6, $^1C_4$	*exo*	-66.1	DEVWOQ[260]
4	Phenyl	6, $^4C_1$	*exo*	63.4	DEZYAI[261]
5	Secondary alkyl	6, $^1C_4$	*exo*	-52.3	DUMHAU[262]
6	Primary alkyl	6, $^4C_1$	*exo*	63.7	GUNTEO[263]
7	Secondary alkyl	6, $^4C_1$	*exo*	64.4	IFAKOP[264]
8	Secondary alkyl	6, $^4C_1$	*exo*	-62.6	IKAKUV[264]
9	Carbimine alkyl	6, $^4C_1$	*exo*	54.9	KUHNEG[265]
10	Primary alkyl	6, $^1C_4$	*exo*	-51.3	NAFYOI[266]
11	Primary alkyl	6, $^4C_1$	*exo*	46.6	PUYRIK[267]
12	Secondary alkyl	6, $^4C_1$	*exo*	67.0	QIBKAN[268]
13	Methyl	6, $^4C_1$	*exo*	54.0-61.9	SUPBIO[268]
14	Primary alkyl	6, $^4C_1$	*exo*	53.1	VERMEK[269]

15	Primary alkyl	6, $^4C_1$	*exo*	62.8	VODQOU[270]
16	Primary alkyl	6, $^4C_1$	*exo*	58.8	VODQUA[270]
17	Primary alkyl	6, $^4C_1$	*exo*	56.2	VODRAH[270]
18	Primary alkyl	6, $^4C_1$	*exo*	74.9	VODREL[270]
19	Primary alkyl	6, $^4C_1$	*exo*	66.2	VODRIP[270]
20	Phenyl	6, $^4C_1$	*exo*	73.7	WACJAL[271]
21	Secondary alkyl	6, $^1C_4$	*exo*	-64.0	XAYHEK[272]
22	Phenyl	6, $^1C_4$	*exo*	-38.3	WUNQIF[273]
23	Phenyl	6, $^4C_1$	*exo*	60.0	**94**

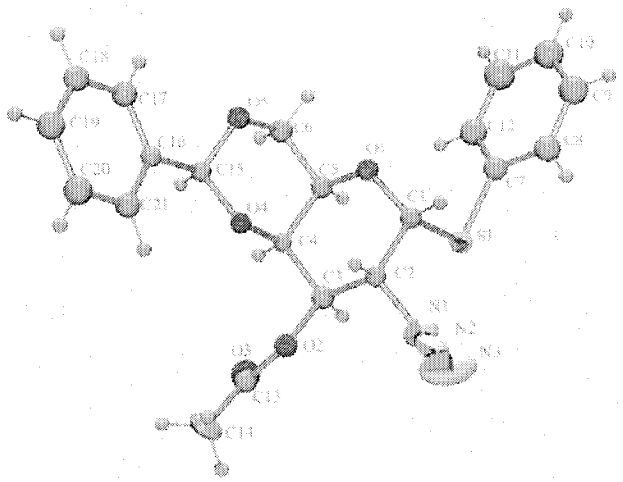


Figure 4.3 ORTEP diagram of phenyl 3-*O*-acetyl-2-azido-4,6-*O*-benzylidene-2-deoxy-1-thio-α-D-galactopyranoside (**94**) with the numbering system

The X-ray crystal structure determinations of the kinetically favored sulfoxides **96R** (Figure 4.4) and **100R** (Figure 4.5) show that both adopt *anti* conformations, different from the *exo* conformations present in the four previous determinations of axial glycosyl sulfoxides: two $(R)_S$ ethyl 1-thio-α-D-mannopyranoside S-oxides adopted *exo* conformations[251] and two ethyl 1-thio-β-D-galactofuranoside S-oxides with the sulfur atom in pseudoaxial positions, also adopt *exo*-like conformations.[246] ORTEP diagrams for **96R** and **100R** are shown in Figures 4.4 and 4.5. The minor diastereomer, **96S**,

adopts the *exo* conformation in the solid state. Its ORTEP diagram is shown in Figure 4.6.

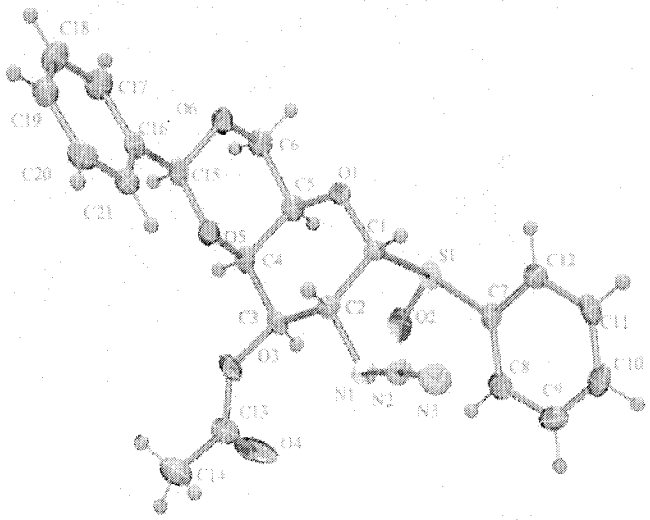


Figure 4.4 ORTEP diagram of phenyl 3-*O*-acetyl-2-azido-4,6-*O*-benzylidene-2-deoxy 1-thio-α-D-galactopyranoside (*R*)s-oxide (**96R**) with the numbering system

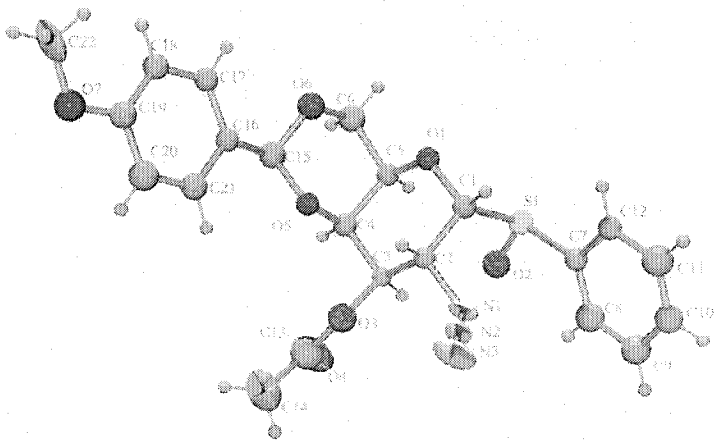


Figure 4.5 ORTEP diagram of phenyl 3-*O*-acetyl-2-azido-2-deoxy-4,6-*O*-(*p*-methoxybenzylidene)-1-thio-α-D-galactopyranoside (*R*)s-oxide (**100R**) with the numbering system

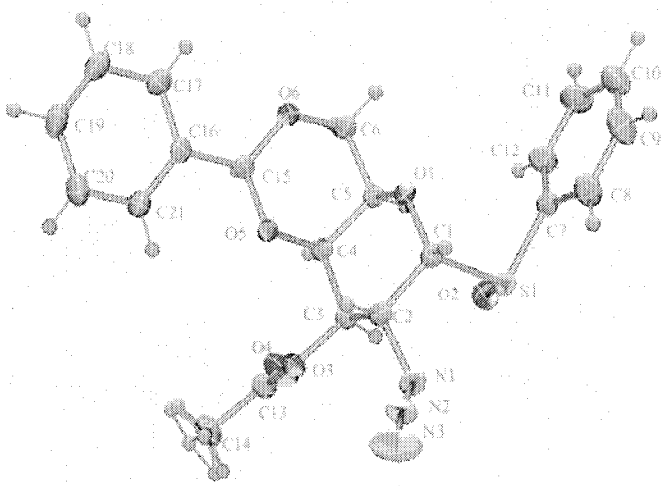


Figure 4.6 ORTEP diagram of phenyl 3-*O*-acetyl-2-azido-4,6-*O*-benzylidene-2-deoxy-1-thio-α-D-galactopyranoside (*S*)s-oxide (**96S**) with the numbering system

The ORTEP diagrams (Figure 4.3 to 4.6) of crystal structures and the puckering parameters[274-276] (Table 4.2) confirmed that the pyranose ring in these compounds adopted the $^4C_1$ chair conformation. The configuration of the sulfur chiral centre is *S* for **96S**, *R* for **96R** and **100R**.

Table 4.2 The ring puckering parameters

Compound	Q (Å)	θ (°)	Φ(°)	Note
94	0.529	4.09	23.48	very similar to a C-Form
96R	0.532	1.25	221.64	a C-Form
96S	0.516	0.91	206.5	a C form
100R	0.570	4.73	161.58	very similar to a C-Form
6-membered rings[276] :		C : Chair θ = 0. H : Half-Chair θ = 50.8; Φ = k × 60 + 30 E : Envelope θ = 54.7; Φ = k × 60 S : Screw-Boat θ = 67.5; Φ = k × 60 + 30 B : Boat θ = 90.0; Φ = k × 60 T : Twist-Boat θ = 90.0; Φ = k × 60 + 30		

4.1.1 Torsion angles

The geometries about the anomeric centre deviate from perfect staggering to different extents in these four X-ray structure determinations. The torsion angles are shown in Figure 4.7. In the crystal of the parent sulfide **94**, the quaternary phenyl carbon atom is perfectly staggered between the ring O and H1. In the crystals of the two sulfoxides that adopt *anti* conformations, **96R** and **100R**, the quaternary phenyl carbon atom is much further away from C2 than expected for a staggered conformation, having C2-C1-S-C7 torsion angles of 80.6(3)° and 75(1)°, for **96R** and **100R**, respectively. In contrast, in the crystal of the sulfoxide that adopts an *exo* conformation, **96S**, the quaternary phenyl carbon atom is closer to the ring oxygen (O1-C1-S-C7 torsion angle 48.0(2)°) than expected for a staggered conformation (60°).

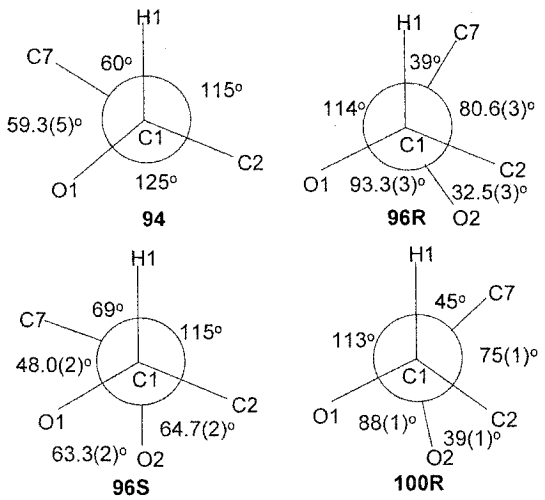


Figure 4.7 Newman projections viewing along C1 to S with C1 in front indicating torsion angles about the anomeric centres. Uncertainties are not provided for torsion atoms to the hydrogen atoms or for torsion angles calculated for bond angles using the program PLATON.[277]

Figure 4.8 shows Newman projections of compounds **94**, **96R**, **96S** and **100R** viewing along the C2 to N1 bond with C2 in front. For **94**, **96S**, and **96R**, H2 and N2 are

in *gauche minus* conformation (see later discussion in section 4.2.1), the torsion angles of H2-C2-N1-N2 are 10°, 11° and 48° respectively; while for compound **100R**, H2 and N2 is in *gauche plus* conformation, the torsion angle of H2-C2-N1-N2 is -3°.

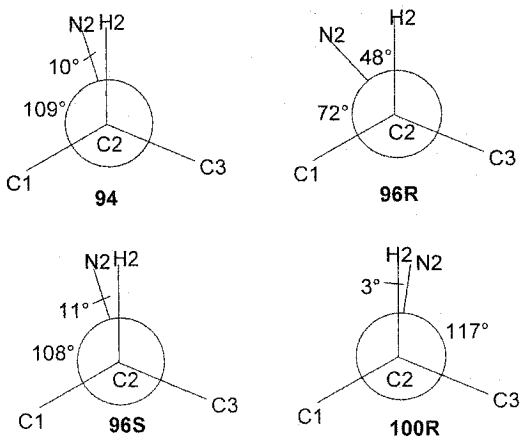


Figure 4.8 Newman projections of compounds **94**, **96R**, **96S** and **100R** viewing along C2 to N1 bond with C2 in front.

The acetyl group at C3 and C4 are in the *gauche minus* conformation except for **96R**, in which the acetyl group and C4 is in the *gauche plus* conformation (almost in a *syn* conformation 5°). Newman projections are shown in Figure 4.9.

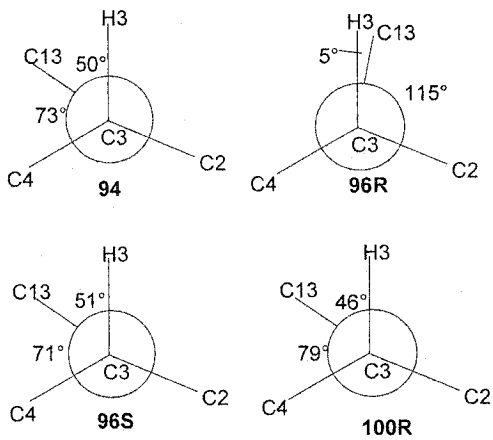


Figure 4.9 Newman projections of compounds **94**, **96R**, **96S** and **100R** viewing along C3 to O3 (O2 for **94**) bond with C3 in front

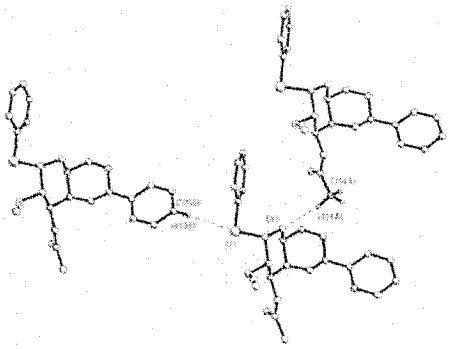
4.1.2 Hydrogen bonds and other short intermolecular contacts

No classic hydrogen bonds exist. Table 4.3 shows the short intermolecular contacts (C-H...Acceptor interactions) of **94, 96R**, **96S** and **100R**. Figure 4.10 shows these intermolecular contacts in details.

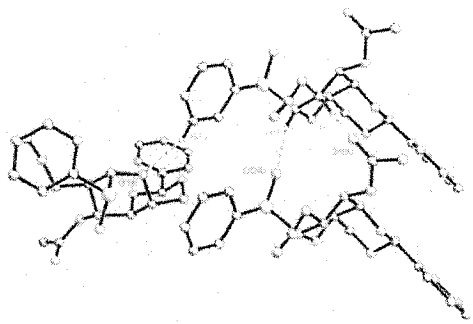
Table 4.3 Hydrogen bonds and other short intermolecular contacts [Å and °]

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
94				
C19-H19...S1[a]	0.95	2.85	3.689	148.3
C140-H14A...O1[b]	0.98	2.54	3.447	153.0
96R				
C2-H2...O4[c]	0.95	2.38	3.193	143.0
C11-H15...O1[d]	0.95	2.49	3.343	150.0
96S				
C19-H19···S1[a]	0.93	2.74	3.646	165.0
C14-H14B···O1[e]	0.96	2.51	3.419	159.0
C14-H14D···O6[e]	0.96	2.35	3.305	178.0
C15-H15···O2[f]	0.98	2.38	3.199	141.0
100R				
C1-H1...O2[c]	1.00	2.21	3.055(18)	140.8
C11-H11...O1[g]	0.95	2.40	3.290(16)	155.6

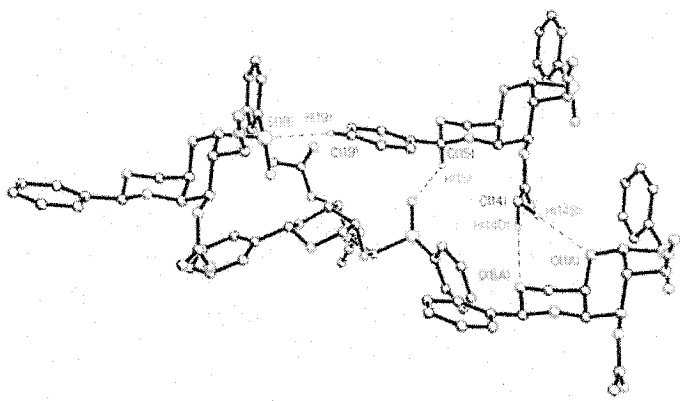
Symmetry transformations used to generate equivalent atoms:
a x,-1+y,z ; b -1+x,y,z; c x,y,-1+z; d -1/2+x,1/2-y,-z;
e 1+x,y,z; f 1-x,-1/2+y,-z; g -1/2+x, 3/2-y, 1-z.



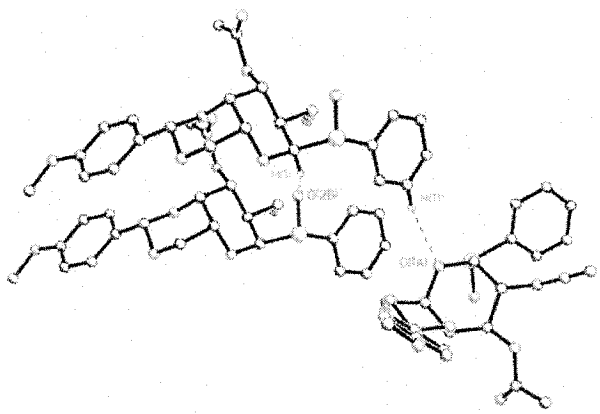
94



96R



96S



100R

Figure 4.10 Intermolecular contacts in compounds **94**, **96R**, **96S** and **100R**

4.2 Theoretical calculations of glycosyl sulfoxides and sulfides

Geometry optimizations are performed to locate minima on potential energy surfaces so that equilibrium conformer structures in molecular systems can be predicted.

A potential energy surface can be represented by Figure 4.11. These surfaces specify the way in which the energy of a molecular system varies with small changes in its structure. In this way, a potential energy surface is a mathematical relationship linking to the molecular structure and the resultant energy. For larger systems, the surface has as many dimensions as there are degrees of freedom within the molecule. The potential energy surface illustration considers only two of the degrees of freedom within the molecule, and plots the energy above the plane defined by them, creating a surface. Each point represents a particular molecular structure, with the height of the surface at that point corresponding to the energy of that structure.

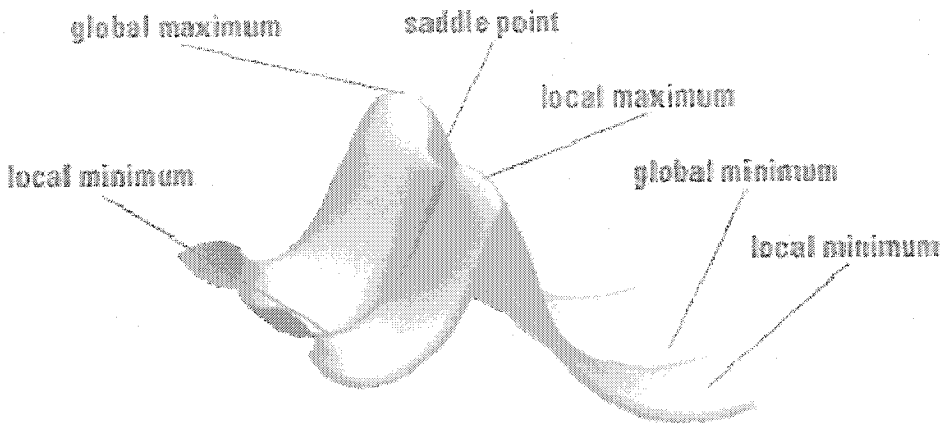


Figure 4.11 A potential energy surface

A minimum is a point at the bottom of a potential valley, from which motion in any direction leads to a higher energy. A local minimum corresponds to the lowest point in some limited region of the potential surface; a global minimum corresponds to the lowest

energy point anywhere on the potential surface. Different minima correspond to different conformations of the molecule under investigation. Similarly, we have local maxima and a global maximum. Between maxima, a saddle point exists corresponding to a transition state structure. In figure 4.11, the potential energy surface contains three minima: two of them are local minima, and one is the global minimum.

At both minima and saddle points, the first derivative of the energy, known as the gradient, is zero. A point on the potential energy surface where the forces are zero is called a stationary point. A successful geometry optimization locates a stationary point which is usually the closest minimum (or saddle point) to the geometry from which the minimization started.

There are several possibilities as to the nature of geometry optimization results: the global minimum may be found, a local minimum but not the global minimum may be found, or a saddle point is located. A geometry optimization alone can not tell the nature of the stationary point that it finds. In order to characterize a stationary point, it is necessary to perform a frequency calculation on the optimized geometry.

Frequency calculations can distinguish between minima and saddle points and verify whether the structure is fully optimized. The frequency calculation will give a variety of results: frequencies, intensities, the associated normal modes, the structure's zero point energy, and various thermochemical properties. If any of the frequency values are less than zero, these frequencies are known as imaginary frequencies. The number of imaginary frequencies indicates the sort of stationary point to which the given molecular structure corresponds. By definition, a structure which has n imaginary frequencies is an nth order saddle point. Thus, the minimum will have zero imaginary frequencies, and an

ordinary transition structure will have one imaginary frequency since it is a first order saddle point.

A conformational search can distinguish a local minimum from the global minimum. There are a variety of conformational search tools that can help with this task. Conformational searches are usually conducted by molecular mechanics methods, and empirical force fields are used for this purpose.

4.2.1 Nomenclatures of conformers

The nomenclature of conformers used in this thesis included three parts:

Nxy

The first part (N) is a number representing the compound number;

The second part (x) is a letter (a or e) which defined the position of the phenyl or methyl group attached on sulfur: "a" means *anti* to the oxygen (O5) in the sugar ring, the torsion angle of O5-C1-S-C7 is smaller than -120 ° or greater than 120 °; "e" means *exo* to the oxygen (O5) in the sugar ring, the torsion angle of O5-C1-S-C7 is between -120 ° and 120 °. Newman projections (viewing along C1-S bond with C1 in front) illustrate them in Figure 4.12.

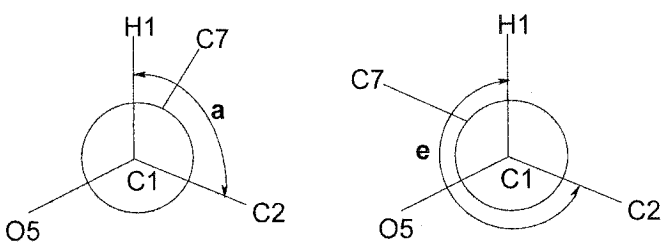


Figure 4.12 Illustration of nomenclature of conformers relating O5 and phenyl ring

The third part (y) is one or two letters (a, gp or gm) which defines the position of the azido group: "a" means N2 atom at azido group *anti* to H2 atom, the torsion angle of H2-C2-N1-N2 was smaller than -120° or greater than 120°; "gp" means N2 atom at azido group *gauche* with a *plus* angle to H2 atom, the torsion angle of H2-C2-N1-N2 is between 0 ° and 120 °; "gm" means N2 atom at azido group *gauche* with a *minus* angle to H2 atom, the torsion angle of H2-C2-N1-N2 is between -120° and 0°. Newman projections (viewing along C2-N1 bond with C2 in front) illustrate those situations in Figure 4.13.

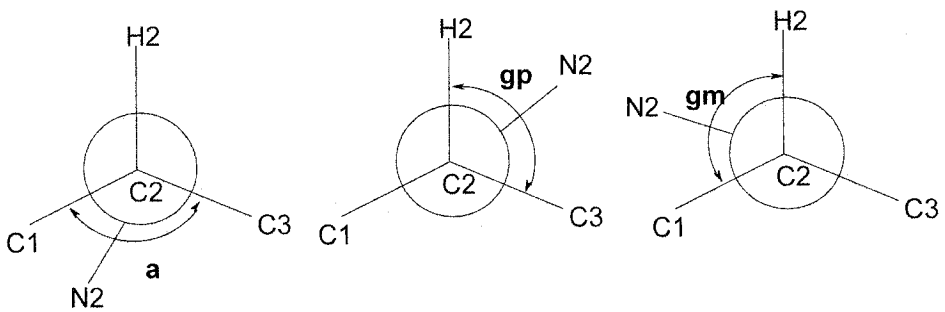


Figure 4.13 Illustration of nomenclature of conformers relating azido and H2

4.2.2 Calculation results

Quantum mechanical calculations were performed with density functional theory as implemented in Gaussian 03[278] with Becke's three parameter exchange functional and Lee–Yang–Parr correlation function.[279,280] The X-ray structures provided the initial geometries for one rotamer of the thiophenyl glycoside and its sulfoxides. The initial geometries for the second staggered rotamer were generated by rotating about the C1-S bond using tools in the program GaussView. The third staggered rotamer, with the aglycon *gauche* to both C2 and the ring oxygen, was used as a starting point for geometry minimization. Initial geometries for the SMe analog and its sulfoxides were obtained

from the minimized thiophenyl conformers by replacing the phenyl group with a methyl group. Full geometry optimizations were carried out at the B3LYP/6–31G(d) level of theory on **94**, **96R**, **96S** and their SMe analogs (**114, 115R** and **115S**). Frequency calculations confirmed that all structures identified as conformers were minima on the potential energy surface. Similar levels of theory have successfully predicted sulfoxide properties.[281-283] Single point energy calculations were performed for all conformers at the B3LYP/6–311G+(d,p) level of theory. ^{13}C NMR chemical shifts with respect to TMS were calculated by gauge invariant atomic orbital (GIAO) method[284,285] at the B3LYP/6-311+G(d,p) level.

Rotamer geometries and energies as functions of two torsion angles were evaluated: the glycosidic torsion angle O5-C1-S-C and the torsion angle to the azide group, H2-C2-N1-N2. All other torsion angles were allowed to rotate freely to minimum energy values. *Anti* conformations of **94** about the C1-S bond were not minima on this potential energy surface; initial geometries obtained from a variety of strategies always rotated smoothly back to the *exo* conformer on minimization. The *anti* conformer of the methyl analogue **114** was a minimum, 2.30 kcal mol^{-1} less stable than the *exo* conformer at the B3LYP/6–31G(d) + ZPVE level and 1.70 kcal mol^{-1} less at the B3LYP/6–311G+(d,p) + ZPVE level. Initial geometries for the two additional rotamers about the C2-N1 bond were obtained by starting from the minimized geometry for each C1-S rotamer and rotating about this bond using GaussView. Several of these C-N1 rotamers minimized to previously minimized structures but two sets of *exo* and *anti* minima were obtained for **96R** and **115R**, and one set of two for the *exo* conformer of **94**. Only one azide rotamer was found for each of the *exo* and *anti* conformers of **96S** and **115S**.

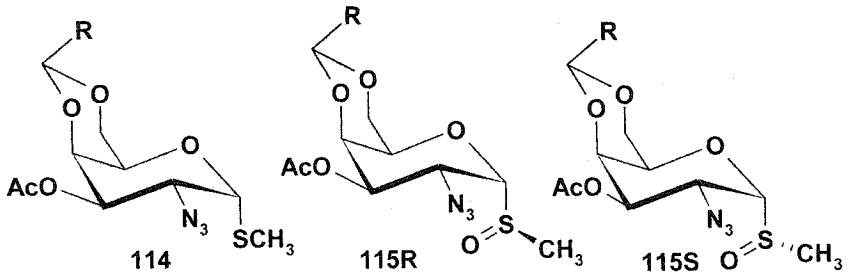
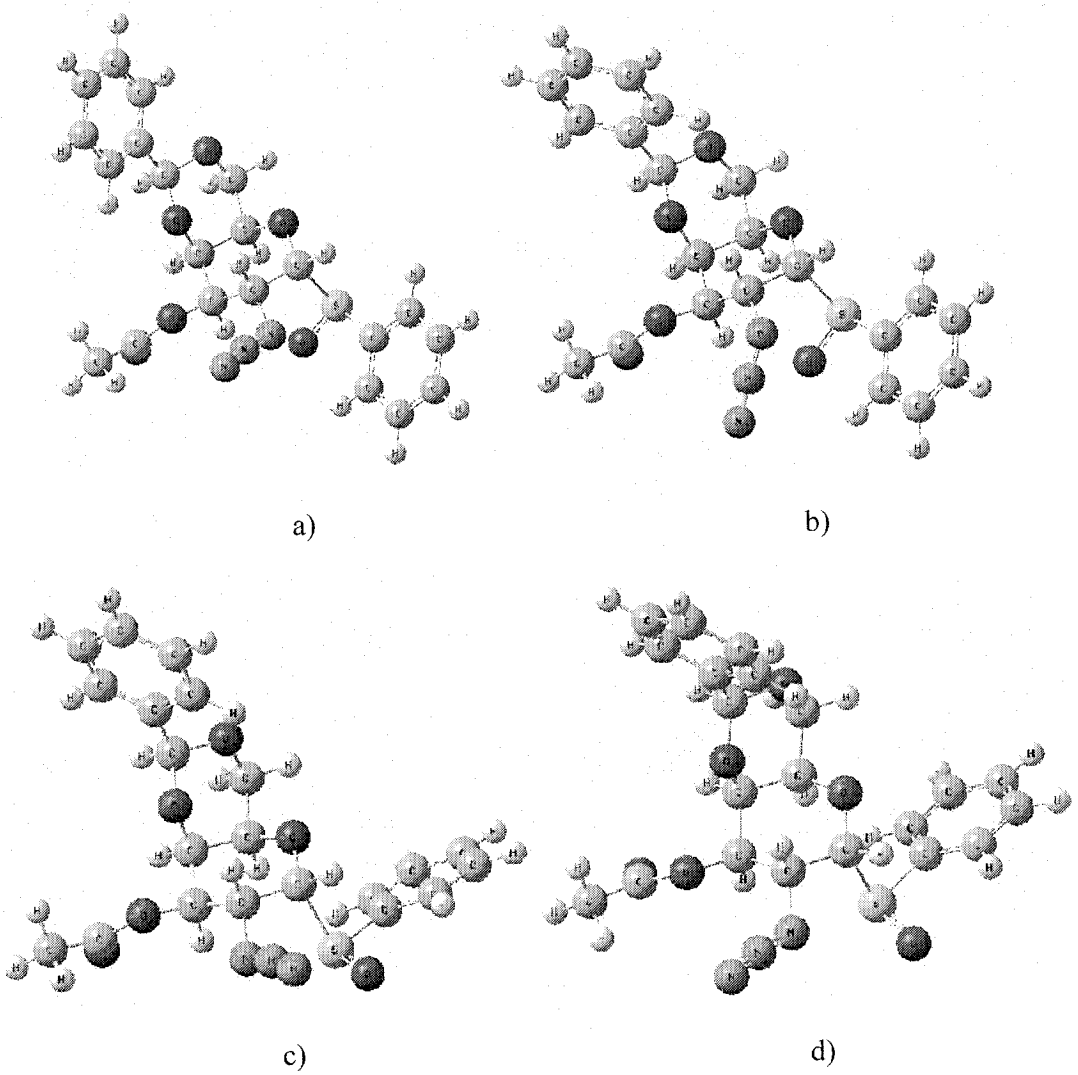


Figure 4.14 Structures of compounds **114**, **115R**, **115S** (methyl compounds)

The conformers obtained for **96R** are illustrated in Figure 4.15. These are named according to the nomenclature described above (section 4.2.1). Conformer stabilities are listed in Table 4.4.



a) b)

c) d)

Figure 4.15 Diagrams indicating the minimum energy conformations calculated for **96R**. a) **96Ragp** b) **96Raga** c) **96Regm** d) **96Regp**

Table 4.4 Calculated conformational energies (kcal/mol) and dipole moments (Debye)

Conformer	†a ΔE	†b ΔE	†a ΔE +ZPVE	†b ΔE +ZPVE	‡a ΔE +ZPVE	‡b ΔE +ZPVE	‡Dipole Moment
94egp	0.0	0.0	0.0	0.0	0.0	0.0	1.84
94ea	1.21	1.21	1.28	1.28	1.08	1.08	1.96
114egp	0.0	0.0	0.0	0.0	0.0	0.0	2.24
114agp	2.30	2.30	2.33	2.33	1.70	1.70	0.57
96Ragp	2.03	0.0	2.00	0.0	2.25	0.0	2.54
96Raa	3.04	1.01	3.08	1.07	3.08	0.83	3.31
96Regm	5.36	3.33	5.12	3.12	4.27	2.02	5.55
96Regp	5.97	3.94	5.63	3.62	5.18	2.92	5.73
115Ragp	2.36	0.0	2.42	0.0	2.61	0.0	2.54
115Raa	3.47	1.11	3.58	1.16	3.67	1.05	3.17
115Regm	5.62	3.26	5.29	2.86	4.04	1.42	5.64
115Regp	6.08	3.72	5.62	3.35	5.16	2.54	5.75
96Segp	0.0	0.0	0.0	0.0	0.0	0.0	3.49
96Sagp	1.39	1.39	1.41	1.41	1.08	1.08	2.62
115Segp	0.0	0.0	0.0	0.0	0.0	0.0	3.33
115Sagp	2.45	2.45	2.46	2.46	1.96	1.96	2.99

[a] Relative to the most stable conformer of all diastereomers of this compound. [b] Relative to the most stable conformer of this diastereomer. † Calculated using the 6-31G(d) basis set. ‡ Calculated using the 6-311G+(d,p) basis set.

For the conformers arising because of rotation about the C2-N1 bond (azide conformers), the *gauche plus* (**gp**) conformer is usually calculated to be the most stable and the *anti* the least stable. The former conformer is always a minimum on the potential energy surface. In the three cases where the latter conformation is a minimum (**94**, **96R**, **115R**), it is less stable than the **gp** conformer by 1.0 ± 0.2 kcal mol^{-1}. The *gauche minus* (**gm**) conformer was calculated to be a minimum only for **Re** sulfoxide conformers, **96Re** and **115Re**, but in those two cases, it was calculated to be more stable than the **gp** conformer by 0.7 and 0.9 kcal mol^{-1}, respectively. The azides in the crystal structures of **94** (**e**) and **96R** (**a**) are present in **gm** conformations, while those in **96S** (**e**) and **100R** (**a**) are present in **gp** conformations, consistent with small energy differences between the latter two conformations and probably small barriers between these two minima. The absence of *anti* conformations in crystal structures are consistent with the larger energetic destabilization differences calculated for the ***anti*** conformations with respect to the **gp** conformations. H2-C2-N1-N2 torsion angles were calculated to be small but significant, having absolute values of 38-46° in all **gp** and **gm** conformers. In the three C-N *anti* conformers, the H2-C2-N1-N2 torsion angles were between 127 and 147° with the N close to being eclipsed with C3.

The relative energies calculated for the anomeric conformers of these axial glycosyl sulfoxides (Table 4.4) were unexpected in view of all previous discussion.[247,249,255] The *anti* conformers of the kinetically favored R_S sulfoxides were calculated to be more stable than the *exo* conformers by 2.0 and 1.4 kcal mol^{-1} at the B3LYP/6–311G+(d,p) + ZPVE level, for the phenyl- and methylsulfinyl glycosides, respectively. For the minor sulfoxides, the S_S diastereomers, the *exo* conformer is

calculated to be more stable by 1.1 kcal mol^{-1} for the phenyl glycoside and 2.0 kcal mol^{-1} for the methyl glycoside.

The interesting variations in geometry from perfect staggering around the C1-S bond observed in the X-ray results were evident here for all conformers (Figure 4.16). In particular, the quaternary phenyl carbon atom in the *anti* conformer of **96R** (gp) is calculated to be about as far away from C2 as observed in the crystal, having a C2-C1-S-C7 torsion angle of 81°. In the methyl analogue, this angle is calculated to be slightly smaller, 76°. The *exo* conformers of **96R** are calculated to deviate more from perfect staggering in the unexpected direction than observed in the X-ray structure of **96S**; the O5-C1-S-C7 angle was calculated to be 31° in the most stable gp conformer. In the two previously determined X-ray structures of α-D-mannopyranosyl ethyl sulfoxides, the comparable angles observed were larger, 50.7 to 56.8°.[251]

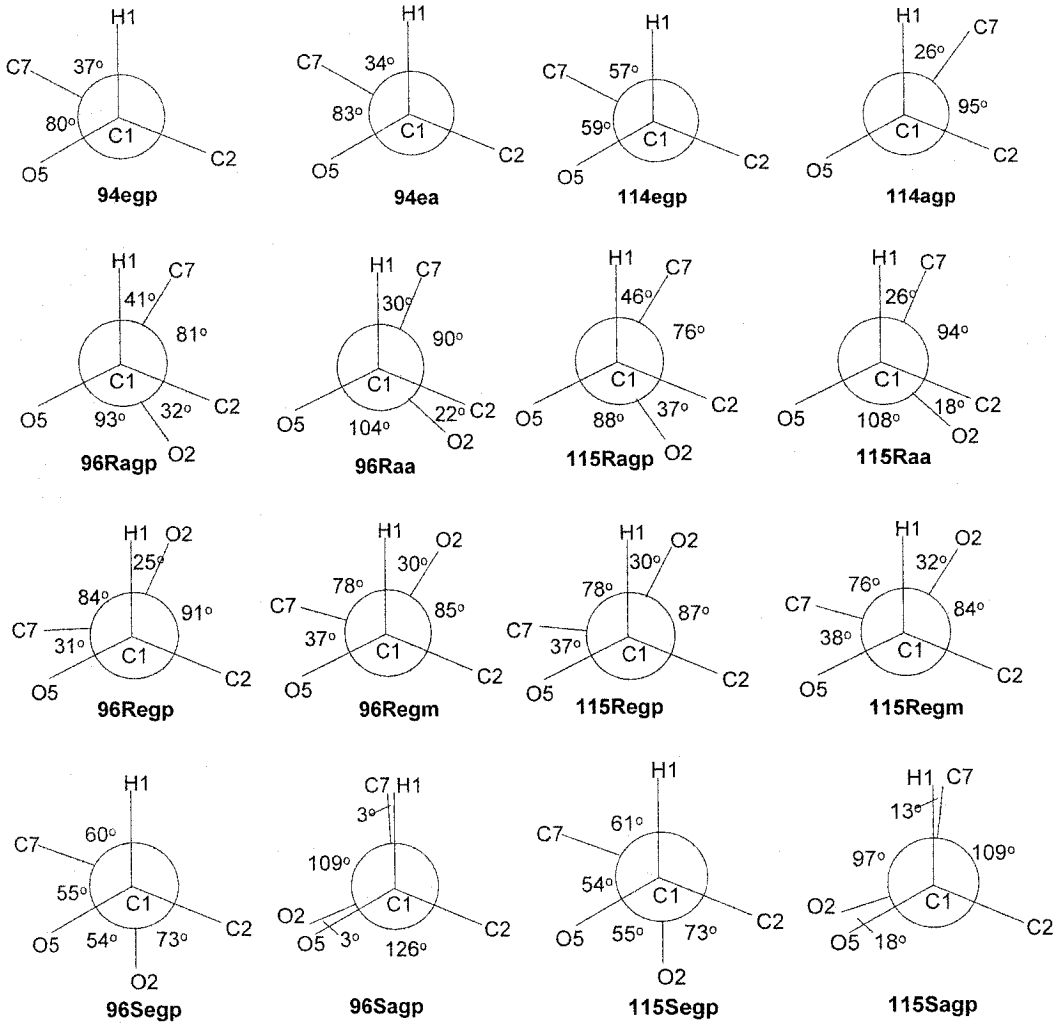


Figure 4.16 Newman projections from C1 to S showing torsion angles about the anomeric centre calculated for the various conformers of compounds **94**, **114**, **96R**, **115R**, **96S**, and **115S**.

In view of the distance determinations obtained from nOe measurements (vide infra) and the difference between calculated and X-ray geometries mentioned earlier, the variations in energy as a function of two different torsion angles were evaluated for compound **96R**. Rotation about the axis of the glycosyl phenyl ring was evaluated first. The torsion angle C1-S-C7-C8 was held constant at fixed values in 10° intervals from the

value found at the minimum for the conformer **96Regp**. Figure 4.17 shows how the energy and the internuclear distances vary as a function of this angle. The energy change as a function of torsion angle is fairly symmetrical about the minima indicating that the measured nOe should represent the minimum well. Then the torsion angle O5-C1-S-C7 was held constant at values ranging in 5 to 10° increments about the value found at the minimum for the conformer **96Regp**. Figure 4.18 shows how the energy and the internuclear distances vary as a function of this angle. For torsion angles beyond 90°, the energy decreased in a non-symmetric way because the azide conformation minimized from the **gm** arrangement most stable in **96Re** to the **gp** most stable for **96Ra**. The variation in energy is not symmetric about this angle, being much flatter towards values of the torsion angle larger than that of the minimum. Hence, the nOe observed for this conformer would yield an O5-C1-S-C7 torsion angle significantly larger than that present in the geometry of the minimum.

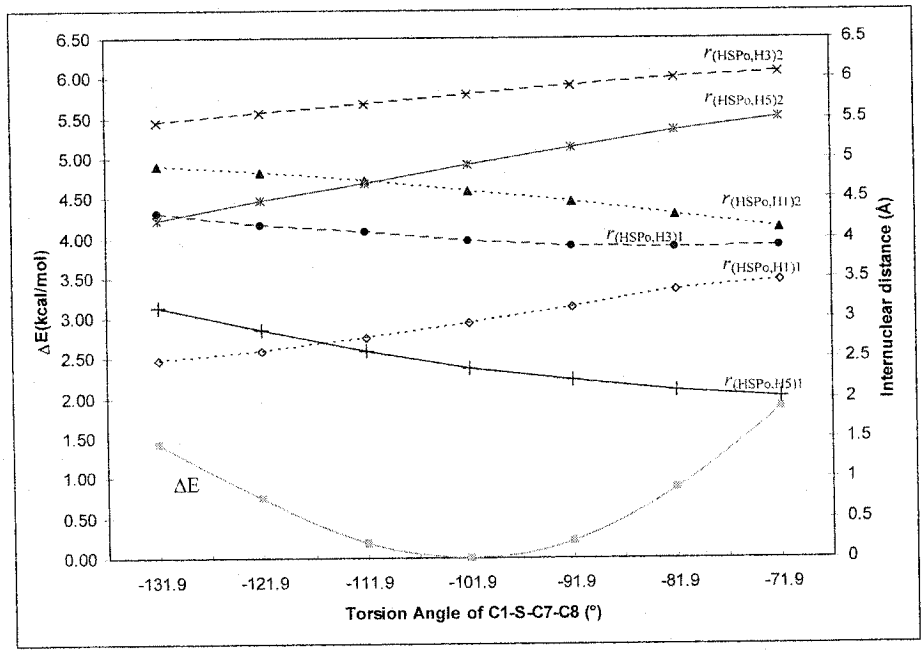


Figure 4.17 Variation in energy and internuclear distances calculated using B3LYP6-31G(d) as a function of C1-S-C7-C8 torsion angle. Top: internuclear distances. Bottom: energies

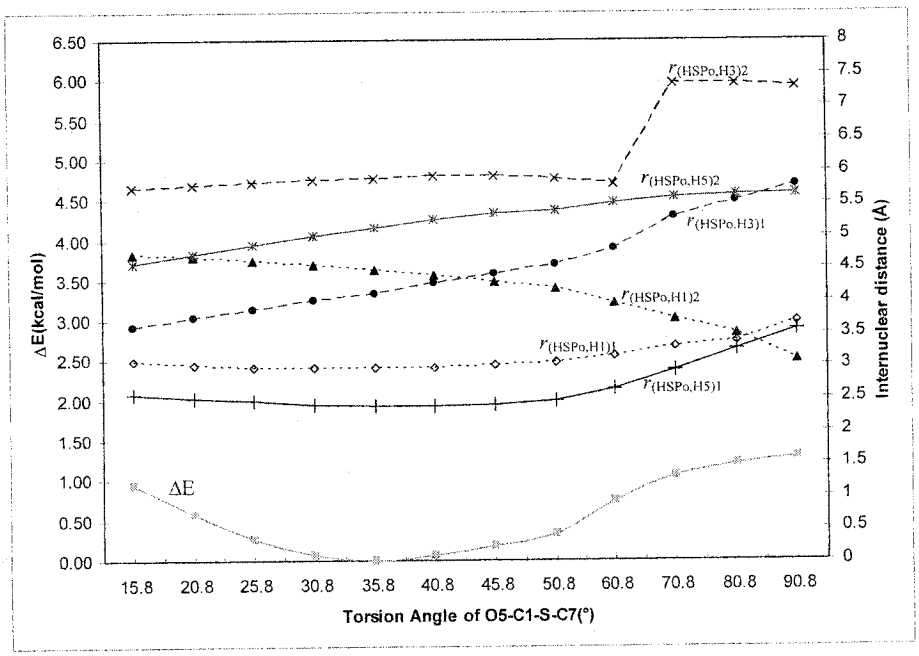


Figure 4.18 Variation in energy and internuclear distances calculated using B3LYP6-31G(d) as a function of O5-C1-S-C7 torsion angle. Top: internuclear distances. Bottom: energies

4.3 NMR studies of phenyl sulfoxides 96R, 96S, 100R and their precursor thiophenyl galactopyranoside 94

When one resonance in an NMR spectrum is perturbed by saturation or inversion, the net intensities of other resonance in the spectrum may change. This phenomenon is called the nuclear Overhauser effect (nOe). It is important that the resonances that change their intensities are due to spins close in space to those directly affected by the perturbation. It occurs because adjacent nuclei cause the relaxation of the nucleus under consideration and altering the populations of the energy levels of the adjacent nuclei affects relaxation pathways. Since these interactions are related by an r^{-6} dependence, nOe can be used to estimate internuclear distance. In contrast to other NMR experiments, in which spins are connected through bonds, the nuclear Overhauser effects connect nuclei through space. This effect is fundamentally different as exchange between the nuclei does not involve scalar coupling. Instead, the direct magnetic interaction (no electrons in between) between dipoles is involved, which usually does not have an observable effect in solution (in contrast to solid state!). The nOe provides an indirect pathway to obtain information of this dipolar interaction, which in turn can be correlated with internuclear distances and molecular motion. Other methods for obtaining these parameters are not available for solutions, making the nOe an extremely useful and important phenomenon.

The conformation adopted in solution was investigated by measuring initial NOE buildup rates using both selective 1D NOE measurements with the double pulsed field gradient spin echo (DPFGSE) sequence[286] and 2D NOESY experiments using a variety of mixing times.

Kinetic nOe experiments can be divided into two types: truncated driven nOe and transient nOe experiments. 1D gradient nOe[281,282] is a type of transient nOe experiment. Such experiments do not give as large a nOe enhancement as steady state experiments. Their advantage over steady state experiments arises from the fact that gradient nOe experiments are not difference experiments. The absence of subtraction artifacts means that much smaller nOes can be reliably measured in gradient experiments. Gradient nOe experiments can give good quality data rapidly and experiments can be continued at will to improve signal/noise ratio, and to obtain the nOe buildup curve.

The initial rate approximation means that the initial rate of enhancement buildup in any kinetic nOe experiment can be approximated as linear. At later times, this linear build-up curve falls off. In a transient system, any relaxation and any cross relaxation lead to population changes, and therefore affect in principle the cross-relaxation rate again. As the Solomon equation is only valid for the initial buildup rate of the nOe, the nOe has to be obtained at several mixing times and the buildup curve constructed. As long as the mixing time is in the linear range of the buildup curve, the nOe can be used to measure internuclear distance. The internuclear distance relies on the sixth root of nOe intensities, so that even quite large errors in intensity measurements have a relatively small effect on the derived internuclear distance; small errors of reference distance have little effect due to an equivalent fractional error in the calculated distance based on the reference distance. The most commonly used reference distance are those between methylene protons (r = 1.75 – 1.80 Å) and those between *ortho* aromatic protons (r ≅ 2.8 Å).[287] The initial rates are directly proportional to the internuclear distances (r_{IS}) and were calibrated using a known reference internuclear distance (r_{ref}) as follows:

$$r_{IS} = r_{ref}\left(\frac{nOe_{ref}}{nOe_{IS}}\right)^{1/6} \quad \text{.....Equation 4.1}$$

The distance between *ortho* phenyl protons (HSPo) and meta phenyl protons (HSPm)($r_{HSPo,HSPm}$ = 2.8 Å)[287] was used as a reference distance to calculate internuclear distances.

4.3.1 T1 relaxation time measurements

The relaxation delay times (D1) of different nuclei were determined by T1 relaxation time measurement experiments with inversion recovery. The ***t1ir*** pulse program in Bruker Avance 500 MHz NMR spectrometer was used to acquire data, the ***proc_t1*** program was used to process data. T1 relaxation times were measured for compounds **94** and **96R**. Figure 4.19 shows an example of the T1 measurement results, those for **96R**. Table 4.5 shows the T1 relaxation time measurements for different nuclei in compounds **94** and **96R** in acetone-d_6.

Table 4.5 T1 relaxation time results for **94** and **96R**

Nuclear	**94**		**96R**	
	T1 (sec)	σ^a (sec)	T1 (sec)	σ^a (sec)
H-SPo	3.966	0.004	3.400	0.005
H-1	3.146	0.003	2.652	0.006
H-2	3.112	0.002	3.121	0.005
H-3	2.939	0.012	2.790	0.012
H-4	1.420	0.012	1.331	0.015
H-5	1.686	0.005	1.531	0.004
H-6a	0.747	0.018	0.705	0.021
H-6b	0.960	0.008	0.979	0.008

[a]Standard deviations.

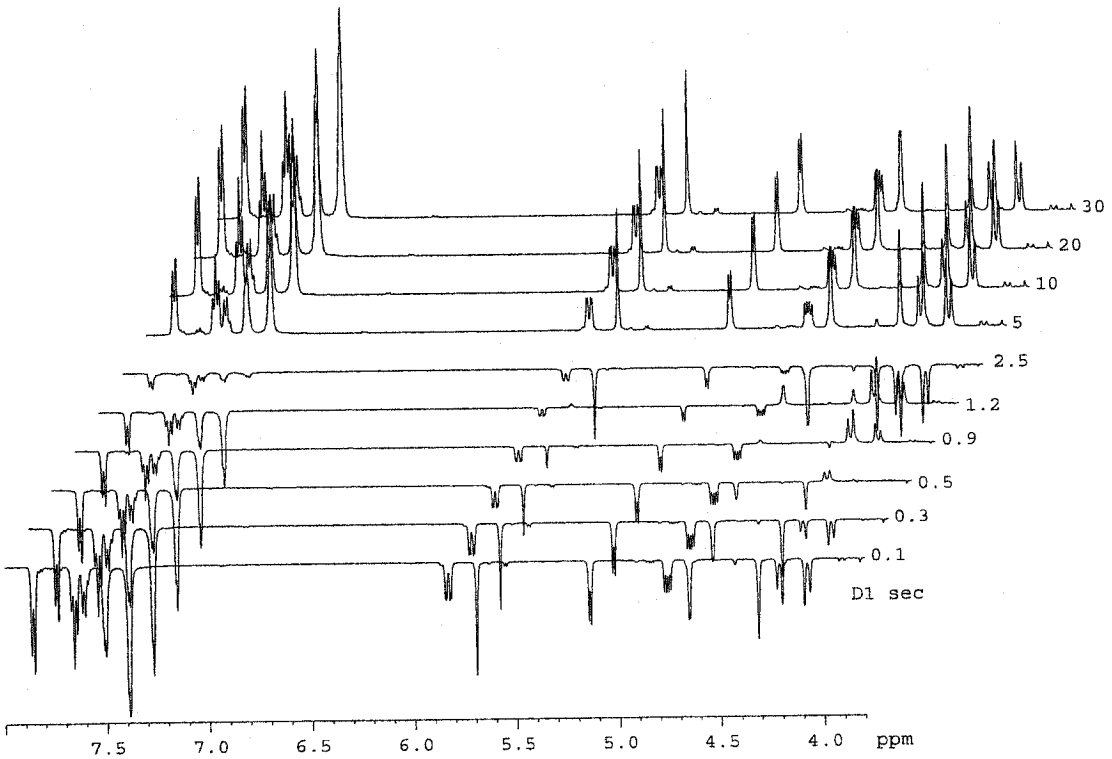


Figure 4.19 T1 relaxation time measurements for **96R** (D1 is the delay time, the inversion recovery pulse program is ***t1ir***)

4.3.1.1 Buildup curves

The ***selnogp*** pulse sequence was used for nOe experiments on the Bruker Avance 500 MHz NMR spectrometer. Irradiation of HSPo of compound **96R** at different mixing times (0.3, 0.9, 1.25, 1.5, 1.75, and 2.25 sec) gave nOe spectra as shown in Figure 4.20. Similar spectra were obtained after irradiation of HSPo of compound **96S** at different mixing times (0.5, 0.75, 1, 1.25, 1.5, 1.75, 2, 2.25, 2.5, and 3 sec) (Figure 4.21), and of compound **94** at different mixing times (0.3, 0.5, 0.75, 0.9, 1, 1.1, 1.25) (Figure 4.22).

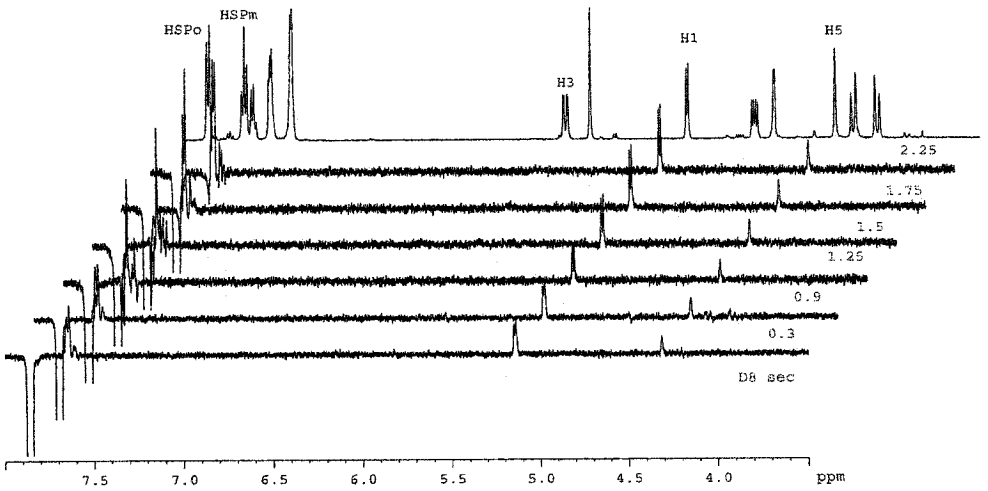


Figure 4.20 NOe spectra of **96R** (Irradiation HSPo, D1=10 sec, D8 is labeled on spectra)

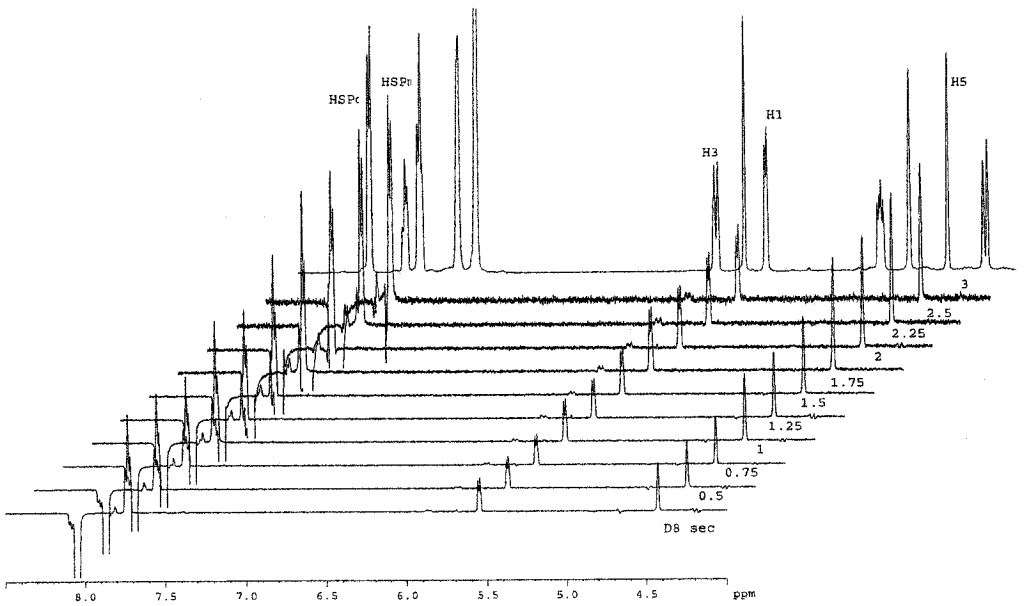


Figure 4.21 NOe spectra of **96S** (Irradiation HSPo, D1=10 sec, D8 is labeled on spectra)

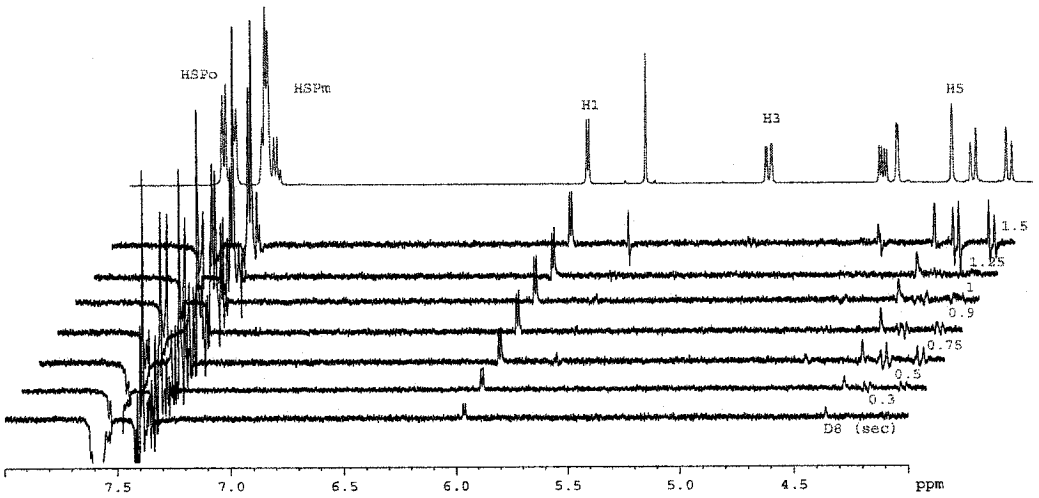


Figure 4.22 NOe spectra of **94** (Irradiation HSPo, D1=10 sec, D8 is labeled on spectra)

Buildup curves of compounds **94**, **96R** and **96S** were obtained (Figures 4.23, 4.24 and 4.25)

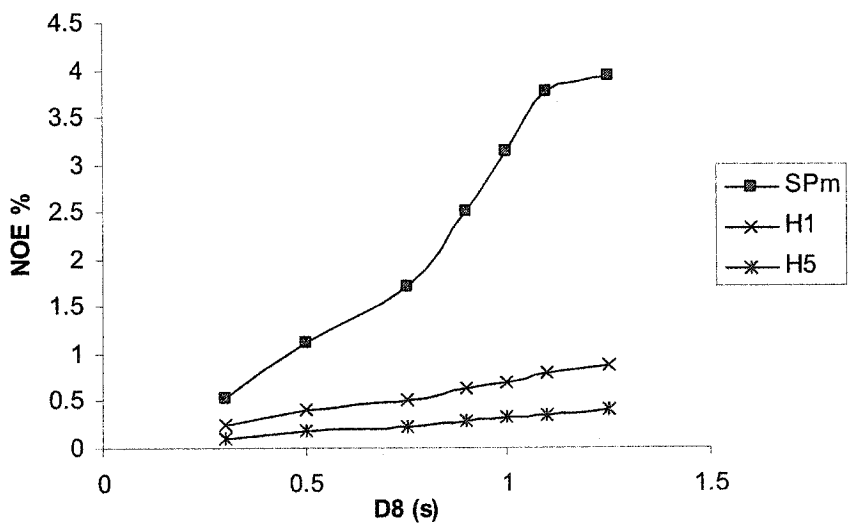


Figure 4.23 Buildup curve of **94** after irradiation of HSPo at D1=10 sec

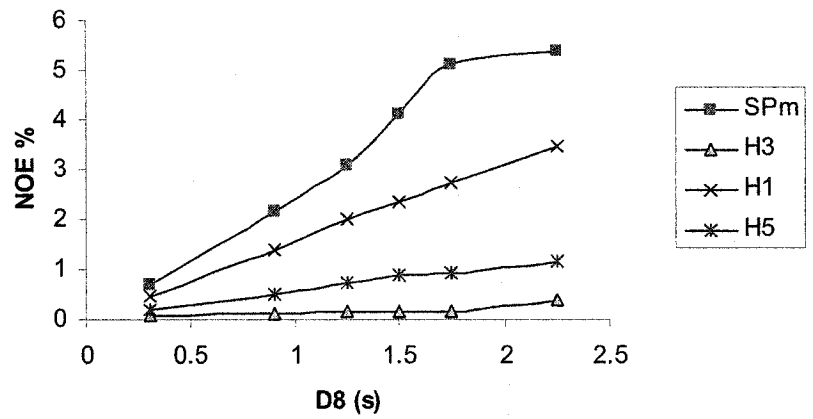


Figure 4.24 Buildup curve of **96R** after irradiation of HSPo at D1=10 sec

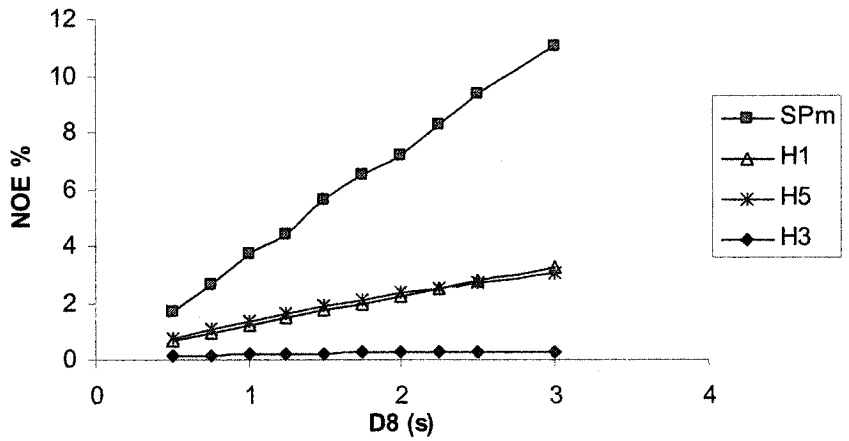


Figure 4.25 Buildup curve of **96S** after irradiation of HSPo at D1=10 sec

4.3.2 Internuclear distances measured by nOe results

After buildup curves are obtained, internuclear distances can be calculated according to the equation 4.1. The results are given in Table 4.6 along with the results obtained by the previous methods.

Table 4.6 Comparison of results obtained by different methods

Compound	Method		Internuclear Distance (Å)			Relative Energy (kcal mol^{-1})
			$r_{(HSPo,H1)}$	$r_{(HSPo,H3)}$	$r_{(HSPo,H5)}$	
94	nOe		3.0	no[a]	3.4	na[b]
	DFT	**egp**	2.64	5.09	3.40	0.00
		ea	2.64	5.59	3.46	1.08
	X-Ray (**egm**)		2.84	4.78	2.67	na[b]
96R	nOe		3.0	4.7	3.6	na[b]
	DFT	**agp**	2.55	3.84	5.15	0.00
		aa	2.51	4.17	5.11	0.83
		egm	2.96	4.12	2.38	2.02
		egp	2.93	3.96	2.38	2.92
	X-Ray (**agm**)		2.68	3.92	5.26	na[b]
100R	X-Ray (**agp**)		2.53	3.86	5.07	na[b]
96S	nOe		3.4	4.6	3.3	na[b]
	DFT	**egp**	2.64	4.66	2.87	0.00
		agp	3.02	4.76	4.45	1.08
	X-Ray (**egp**)		2.95	4.58	2.55	na[b]

[a] Not observed. [b] Not applicable.

For the parent compound **94**, the nOe results fit the geometry calculated for the *exo* conformer well. The distances from HSPo obtained to H1 and to H5 are within 0.4 Å of those calculated and no nOe was observed for the interaction with H3, as expected. However, the H5-HSPo distance obtained from the nOe measurement was much longer than that measured from the X-ray results. As discussed above, the potential surface is fairly flat with respect to changes in the O5-C1-S-C7 torsion angle from the 80° value calculated for the gas phase. Crystal packing presumably causes this value to be altered from that calculated for the minimum to the 59° value observed in the solid. The average

of all 22 O5-C1-S-C7 torsion angles from the crystal structures in the Cambridge data file (Table 3.2) was 61.5°.

For the R_S sulfoxide, the distances obtained from the nOe measurements do not match the pattern obtained from the X-ray results or from the geometries calculated for the two lowest energy minima, the global minimum, the **96Ragp** conformer and the other *anti* conformer **96Raa**. In both *anti* conformers, the HSPo H5 distance is calculated by DFT is > 5 Å, too long to give an nOe. However, one was observed and the distance calculated from it was 3.6 Å. For both *exo* conformers, the HSPo H5 distances are calculated by DFT to be 2.38 Å, much shorter than the distance obtained from the nOe. The HSPo H1 distance, obtained from the nOe, was 3.05 Å. The DFT calculated values average 2.95 Å in the two *exo* conformers and 2.53 Å in the two *anti* conformers. These results indicate that a mixture of the *exo* and *anti* conformers is present in solution. The lack of accuracy in the nOe results precludes more precise conclusions than this.

Although the DFT calculations indicate that the most stable *anti* conformer is more stable than the most stable *exo* conformer by 2.0 kcal mol^{-1} in the gas phase, the *exo* conformer is calculated to have a much larger dipole moment, 5.55 D versus 2.54 D. Thus, a shift in conformer populations on changing to a more polar environment is anticipated. 1D nOes were measured for **96R** in dichloromethane-d_2 and acetonitrile-d_3 at one short mixing time (1.25 s) and these results as well as those obtained from buildup curves in acetone-d_6 are shown in Table 4.4. The uncertainties in the nOes are too great to provide additional support for the idea that a more polar solvent stabilizes the *exo* conformers.

Table 4.7 NOe for **96R** as a function of solvent

Solvent	nOe (%) (on irradiation of H-SPo)		Distances (Å)	
	H-1	H-5	$r_{(HSPo,H1)}$	$r_{(HSPo,H5)}$
CD_2Cl_2 (8.9†)	2.24	0.62	2.81	3.48
$(CD_3)_2CO$ (20.7†)	2.04	0.75	3.05	3.62
CD_3CN (37.5†)	1.94	0.87	A	a

[a] Could not be obtained because of overlap of the reference signals (HSPm and HSPp)

† dielectric constant of solvent without deuterium atoms.

4.4 Discussion

The DFT calculations indicate that axial glycosyl sulfides favor the *exo* anomeric conformers over *anti* conformers by substantial amounts, 1.7 kcal mol^{-1} for the methyl thioglycoside. The fact that all 23 X-ray structure determinations on axial glycosyl sulfides have observed that *exo* conformations are present in the solid state (Table 3.2) confirms these calculated results.

The inherent conformational preference is calculated to shift from being in favor of the *exo* conformer for the parent methyl sulfide (**114egp**) by 1.7 kcal mol^{-1} to being in favor of the *anti* conformer for the R_S sulfoxide (**115Ragp**) by 1.4 kcal mol^{-1}, a change of 3.1 kcal mol^{-1} (3.7 kcal mol^{-1} for the phenyl glycoside if it is assumed that the sulfide preference is the same as for the methyl glycoside). The S_S sulfoxides (**96S** and **115S**) have about the same preferences as the parent sulfides.

Of the two diastereomers of compounds **96** and **115**, the most stable conformer of the minor diastereomers **96S** and **115S** are calculated to be more stable than that of the major diastereomers by 2.3 and 2.6 kcal mol^{-1}, respectively. This result strongly supports the conclusion that the stereoselectivity of oxidation is kinetically controlled and results

from the preferred *exo* conformation of the sulfide.[249,251] Crich and coworkers equilibrated the two sulfoxide diastereomers of allyl 2,3,4-tri-*O*-benzoyl-1-thio-α-D-xylopyranoside oxide (**116**) and allyl 2,3-di-*O*-benzyl-4,6-*O*-benzylidene-1-thio-α-D-mannopyranoside oxide (**117**) in both benzene-d_6 and methanol-d_4 at 60 °C. The former compound is most analogous to those studied here because in its $^4C_1$ conformation, it bears an equatorial substituent at C2. For **116**, the S_S diastereomer was favored by 2:1 in benzene but the other diastereomer was favored by 2.5 to 1 in methanol. These results massively underestimate the preference for this orientation of the S_S diastereomer because the R_S diastereomer ring inverts completely (as determined from $^3J_{H,H}$ values) to the $^1C_4$ chair. To compare relative stabilities of particular conformers of the S_S and R_S diastereomers, the same ring conformations must be employed. If the conformational preference for $^1C_4$ over $^4C_1$ is estimated at > 9/1, the equilibration results for **116** correspond to ΔG° values of >1.9 and > 0.8 kcal mol^{-1} at 60 °C in benzene and methanol, respectively, in favor of the S_S diastereomer in the $^4C_1$ conformation. The value in benzene is in the same range as that calculated by DFT methods here, even though the C2 substituent is very different. Since the S_S diastereomers are calculated to have somewhat larger dipole moments (3.3 versus 2.5 D for **115**, 3.5 versus 2.5 D for **96**), the decreased preference for this diastereomer in methanol is unexpected and may be due to specific solvation of the R_S diastereomer. For compound **117**, the preferences for the R_S diastereomer are 0.7 and 0.6 mol^{-1} at 60 °C in benzene and methanol, respectively. It is clear that the C2 configuration has a large effect on diastereomer stability.

It remains to consider why the relative stabilities of the conformations of these sulfoxides are quite different than expected based on conventional[249] conformational

arguments. The most stable conformer of **96S**, **96Sepg** is perfectly arranged (see Figure 4.16) for n→σ* donation from the sulfur lone pair into the σ* orbital for the ring O-C1 bond. This conformer is calculated to have the shortest C1-S bonds of all conformers of **96** (Figure 4.26), consistent with this overlap. Thus, the *exo* arrangement of the aglycon plus the n→σ* overlap explains the greater stability of this conformer of the kinetically disfavored diastereomer.

The greater stability of the *anti* conformers of **96R** than the *exo* conformers is rather surprising. In view of the well established preference of glycosides and thioglycosides for *exo* anomeric conformations, having the aglycon in the *exo* orientation must be an energetically favorable arrangement. Thus, some other effect must either stabilize the *anti* conformers or destabilize the *exo* conformers. As noted above, the *anti* conformers appear to minimize steric interactions with C2 and its substituents by having C2-C1-S-C7 torsion angles that are considerably greater than staggered. It is interesting that the C7-S-O units in the *anti* conformers are close to being eclipsed with the H1-C1-C2 unit (Figure 4.26). If they were eclipsed, the lone pair on the sulfur atom would be perfectly aligned to overlap with the σ* orbital for the C1-O bond, if the lone pair was in a p orbital. The C1-S bond in the most stable **96Ra** conformer, **96Ragp**, is almost as short as the corresponding bond in **96Sepg**, the global minimum, where n→σ* overlap is accepted, consistent with an extra interaction in **96Ragp**. All of the other conformers have C1-S bond lengths that are 0.02 to 0.05 Å longer (Figure 4.26). In view of the

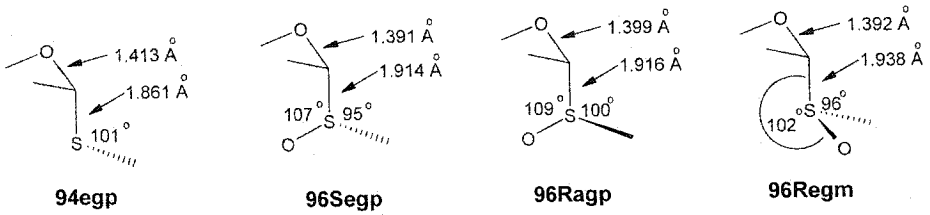


Figure 4.26 Calculated structural features

previous discussion,[249,251] which emphasized the importance of C-O S-O dipole repulsion, it is notable that none of the *exo* conformers have O-C1-S-O torsion angles close to 180°, the value that would maximize dipole dipole repulsion. The O5-C1-S-O torsion angles calculated for **96Regp**, **96Regm**, **100Regp**, and **100Regm** are 139.3, 144.4, 145.0 and 146.2°, respectively. In the calculated results, the *exo* conformers appear to decrease the O-C1-S-C7 torsion angle to avoid having the O-C1 bond *anti* to the S-O bond. It should be noted that the results pictured in Figure 4.18 show that the potential energy surface is relatively flat as the O5-C1-S-C7 torsion angle is made larger, which also makes the O5-C1-S-O torsion angle closer to 180°. If dipole-dipole repulsion were very important, the geometry of the minimum would be one that maximized this effect, not the opposite as calculated. Thus, it appears that dipole-dipole repulsion is not a significant stabilizing factor for glycosyl sulfoxides. The most likely cause of the extra stability of the *anti* conformers is overlap of the p-type lone pair on the sulfur atom in the close to eclipsed orientation with the C1-O5 antibonding orbital. There has been no previous instance where $n \rightarrow \sigma^*$ overlap has been invoked as a stabilizing factor with sulfoxides where the lone pair has to be a p-type lone pair.

4.5 Calculations of ^{13}C NMR spectra of conformers of 96R and 96S

The 13C NMR chemical shifts of the anomeric carbons are of interest because of their suggested use for assignment of sulfoxide configuration.[250] The ^{13}C NMR spectra

of the four minima of **96R** and two minima of **96S** were calculated by using the B3LYP density function. The Gauge invariant atomic orbital (GIAO) method was used for the shielding calculations using the 6-311+G(d,p) basis set. TMS was used as the reference for chemical shifts. The experimental data used were the values measured in $CDCl_3$.

When the calculated ^{13}C NMR chemical shifts with respect to TMS were plotted against the experimental data, a good fit was obtained. All the root mean square deviations are greater than 0.99 (Figures 4.27 and 4.28), so there is not a large overall difference to allow identification of populated experimental conformations by comparison of experimental and calculated chemical shifts. The slopes of the lines are all about 0.95, thus the calculated values are larger and the differences increase with chemical shift. Examination of Figure 4.27 shows that the anomeric carbons are calculated less accurately than the other carbons. These values were of particular interest in view of their use as prediction of sulfoxide configuration.[250] A much larger value was observed for **96R**, 96.4 ppm, than for **96S**, 92.5 ppm. The values calculated were 106.1 and 105.7 ppm for C1 of **96Segp** and **96Sagp**, and 108.9, 112.6, 114.8 and 114.8 for the four **96R** conformers, **96Ragp**, **96Raa**, **96Regp** and **96Regm**, respectively. If the populated conformers are considered, the calculated values are 106.1 ppm for **96Segp** and 108.9 and 114.8 ppm for **96Ragp** and **96Regp**. The calculated difference between **96Regp** and **96Ragp** is 2.8 ppm, less than the 3.9 ppm observed. Inclusion of some contribution from **96R** would increase this difference to the size of experimentally observed difference. Thus, the tentative conclusion drawn is the same as that drawn from the nOe experiments, solution of **96R** contains a mixture of both *exo* and *anti* conformers. Table 4.8 shows the results of the calculations.

Table 4.8 Comparison of calculated and experimental (in $CDCl_3$) ^{13}C NMR chemical shifts (ppm)

carbon	$\delta_{calc.}$				$\delta_{expt.}$	$\delta_{calc.}$		$\delta_{expt.}$
	96Ragp	**96Raa**	**96Regp**	**96Regm**	**96R**	**96Segp**	**96Sagp**	**96S**
C-1	108.9	112.6	114.8	114.8	**96.4**	106.1	105.7	**92.5**
C-2	66.1	63.1	63.2	63.4	**58.0**	64.5	64.3	**57.3**
C-3	76.8	73.6	79.9	75.9	**70.4**	78.5	79.6	**71.2**
C-4	77.9	78.1	77.0	77.3	**72.8**	77.9	78.2	**73.0**
C-5	74.5	73.9	72.2	72.7	**67.7**	75.2	72.9	**68.8**
C-6	73.8	73.9	72.9	72.8	**69.0**	73.1	73.6	**68.7**
C-B*	104.8	110.2	108.9	109.1	**100.9**	108.7	105.5	**100.7**
CO	178.7	179.3	179.7	179.8	**173.0**	178.7	179.1	**170.0**
$CHCH_3$	23.7	23.5	23.5	23.1	**21.1**	23.7	23.5	**21.0**

*Benzylidene acetal carbon

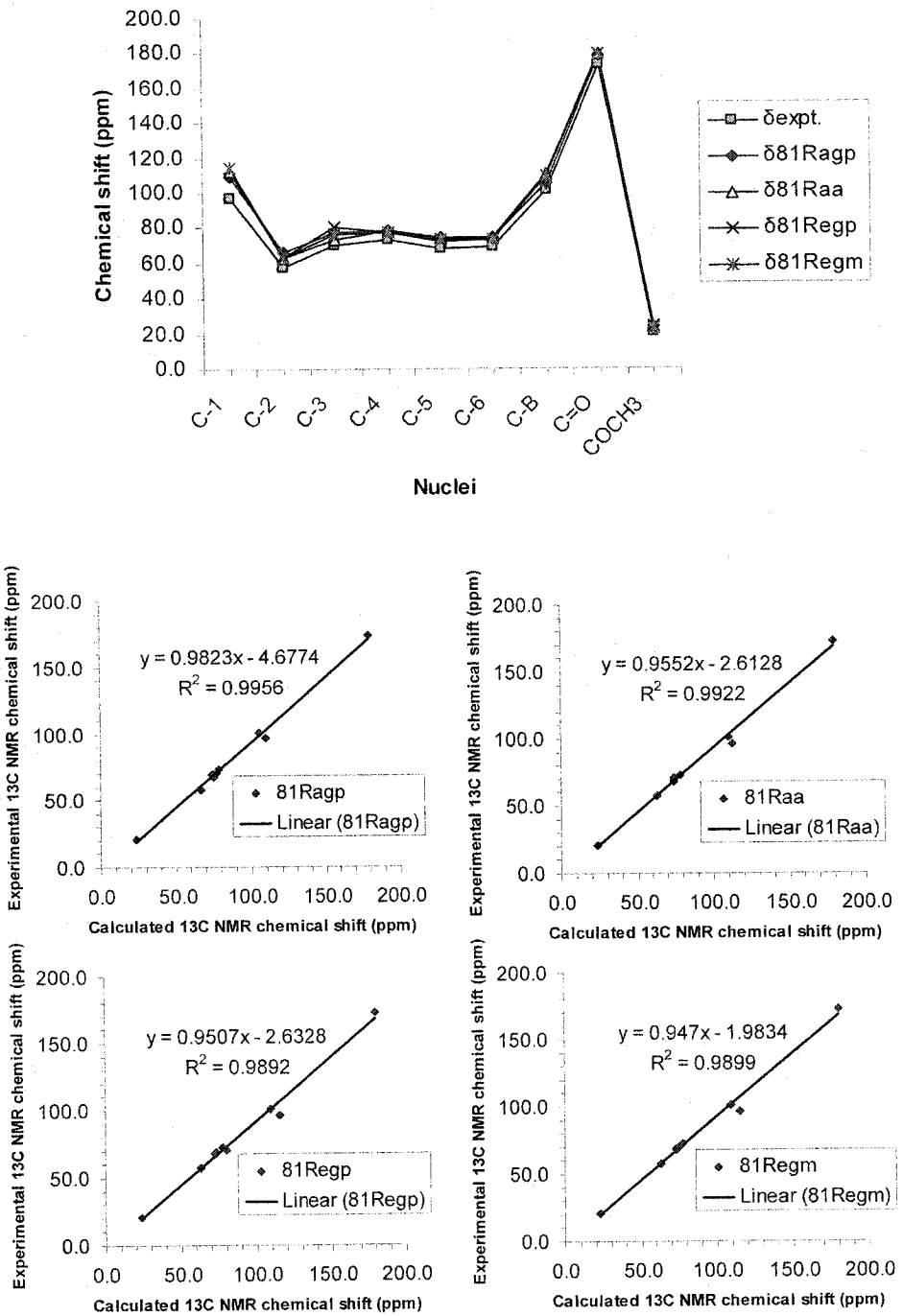


Figure 4.27 Comparison of calculated (**96Ragp, 96Raa, 96Regp** and **96Segm**) and experimental (**96R**) ^{13}C NMR chemical shifts of selected carbons

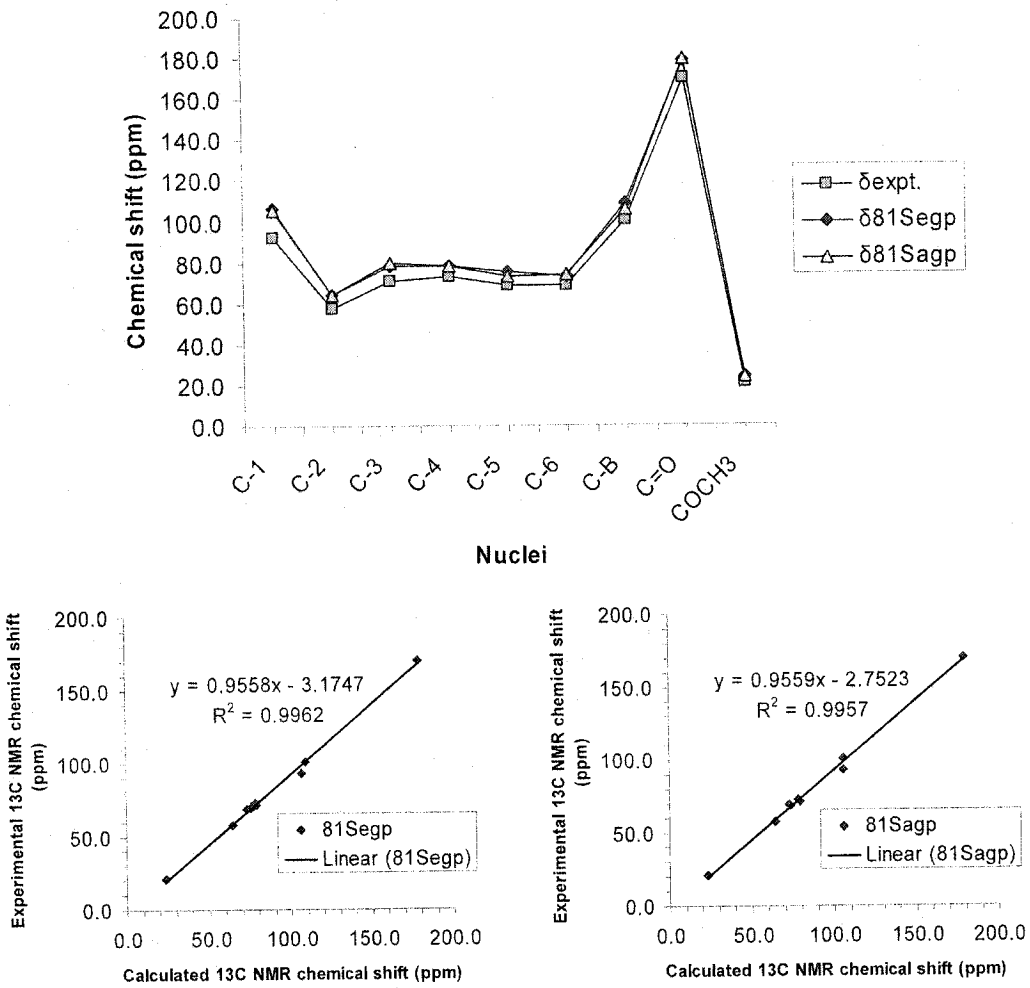


Figure 4.28 Comparison of calculated (**96Segp** and **96Sagp**) and experimental (**96S**) ^{13}C NMR chemical shifts of selected carbons

Chapter 5 Conclusions and future work

5.1 Conclusions

Three derivatives of the rare sugar 2-acetamido-4-amino-2,4,6-trideoxy-α-D-galactopyranose (ATT), methyl 2-acetamido-4-azido-2,4,6-trideoxy-α-D-galactopyranoside (**22**), methyl 2,4-diacetamido-2,4,6-trideoxy-α-D-galactopyranoside (**27**), and methyl 2-acetamido-4-(benzyloxycarbonyl)amino-2,4,6-trideoxy-α-D-galactopyranoside (**30**), have been prepared as glycosyl acceptors for the purpose of preparation of the model disaccharide **23** via a convergent route. A number of glycosyl donors were prepared and tested in glycosidation reactions with these donors, including bromide **37**, sulfide **33**, **36** and **40**, sulfoxide **34** and trichloroacetimidate **38** and **42**. The conditions of the glycosidation reactions investigated were reaction temperature, reaction time, activator structure and reagent addition sequence. However, coupling with these different types of glycosyl donors did not occur under any of these combinations. It is concluded that the 3-hydroxyl groups of compounds **22** and **30** are inactive as glycosyl acceptors in glycosidation reactions. The poor solubility of compound **27** in glycosidation solvents prevented its evaluation as a glycosyl acceptor.

Disaccharide **71** was obtained from the glycosyl donor phenyl 2,3,4,6-tetra-*O*-benzyl-1-thio-β-D-glucopyranoside **59** and glycosyl acceptor methyl 2-acetamido-4,6-*O*-benzylidene-2-deoxy-α-D-glucopyranoside **49** through the formation of the glycosidic linkage, the hydrolysis of the benzylidene acetal, regioselective bromination at O-6, and the reduction of the bromide (Figure 2.17). It was found that formation of the glycosidic bond occurred with the best stereoselectivity at the lowest possible temperature in the

participating solvent, acetonitrile. Each step gave an excellent yield. However, access to the 4-hydroxyl group at compound **71** was found to be hindered by the glycosyl group attached at O-3 or by hydrogen bonding, or by both effects. As a result, conversion of O-4 into a nitrogen-containing substituent along with a configuration inversion could not be achieved.

The Mitsunobu and oxidation reactions gave good results for the monosaccharide model compounds, but the 4-hydroxyl group of disaccharide **71** could not be converted to the corresponding functional group by either method.

An economic, convenient, efficient and environmentally friendly synthetic route was developed to prepare an expensive reagent, D-galactal from a commercially available starting material: D-galactose. The route consists of four steps and gives an excellent overall yield of 77 %. The key improvement is in the second step: the conversion of the galactopyranosyl pentaacetate to the corresponding bromide using phosphorus tribromide. In comparison with the normal reagent, hydrogen bromide in acetic acid, bromination was performed using a lesser amount of the cheaper reagent phosphorus tribromide and water. Hence, this step is more economical, more efficient and more environmentally friendly. At the same time, the reaction yields a relatively stable bromide product which is stable for up to two weeks when stored in a desiccator unlike the product of the HBr reaction which must be used immediately to avoid decomposition. Each step in the four step process occurs in an excellent yield and no cumbersome purification procedures are needed.

This thesis applied a microwave-induced reaction by a commercial microwave oven to prepare the linker arm precursor, 6-phthalimido-1-hexanol, in 1.5 min with a high

yield. In carbohydrate synthesis, the phthalimido group is a frequently used protecting group to protect nitrogen atoms. This successful application of a commercial microwave oven opens a faster and easier alternative way to protect amino groups of carbohydrates by a phthalimido group. This procedure requires that the carbohydrate be a solid with a low melting point. This method had been developed using an expensive laboratory microwave system but it is shown here that the cheaper alternative also works well.

Synthesis of the target disaccharide α-D-galactopyranosyl-(1→3)-β-D-galactopyranose (the AB unit) requires that both an α-linkage and a β-linkage be formed stereoselectively. Phenyl 2-azido-2-deoxy-1-thio-D-galactopyranoside was prepared as a 1:1 ratio of α and β anomers. A well designed synthetic route was designed to employ both anomers to form the target disaccharide: the α-anomer served as a precursor of glycosyl acceptor and the β-anomer served as a precursor of the glycosyl donor during the glycosidation reaction. As a result, although the preparation of phenyl 2-azido-2-deoxy-1-thio-D-galactopyranoside occurred with no anomeric stereoselectivity, both parts of this anomeric mixture were used efficiently.

The glycosidic linkages in the disaccharide α-D-galactopyranosyl-(1→3)-β-D-galactopyranoside are very acid sensitive. Decomposition of disaccharides **106** and **108** was observed in weakly acidic environments. Acidic conditions should be avoided during the modification of such types of disaccharides.

It was found that lowering the reaction temperature made solvent participation by acetonitrile highly successful in controlling the stereoselectivity of formation of the desired β-glycosidic bonds of disaccharide **68**, of the linkerarm-containing glycosyl acceptor **102**, and of the precursor of glycosyl acceptor **101**.

It was discovered that the two phosphoryl linkages can be incorporated regioselectively in a single step at the two primary oxygen atoms of the disaccharides. Compound **113** was prepared with phosphorylcholine at both O-6 positions of the disaccharide AB unit. After reduction and acetylation, the azido group can be converted to the acetamido group.

Single crystals of compound 3-*O*-acetyl-2-azido-2-deoxy-4,6-*O*-benzylidene-1-thio-α-D-galactopyranoside (**94**), phenyl 3-*O*-acetyl-2-azido-4,6-*O*-benzylidene-2-deoxy-1-thio-α-D-galactopyranoside (R)$_S$-oxide (**96R**), and (S)$_S$-oxide (**96S**) and phenyl 3-*O*-acetyl-2-azido-2-deoxy-4,6-*O*-(*p*-methoxybenzylidene)-1-thio-α-D-galactopyranoside (R)$_S$-oxide (**100R**) were prepared and their X-ray structures were measured.

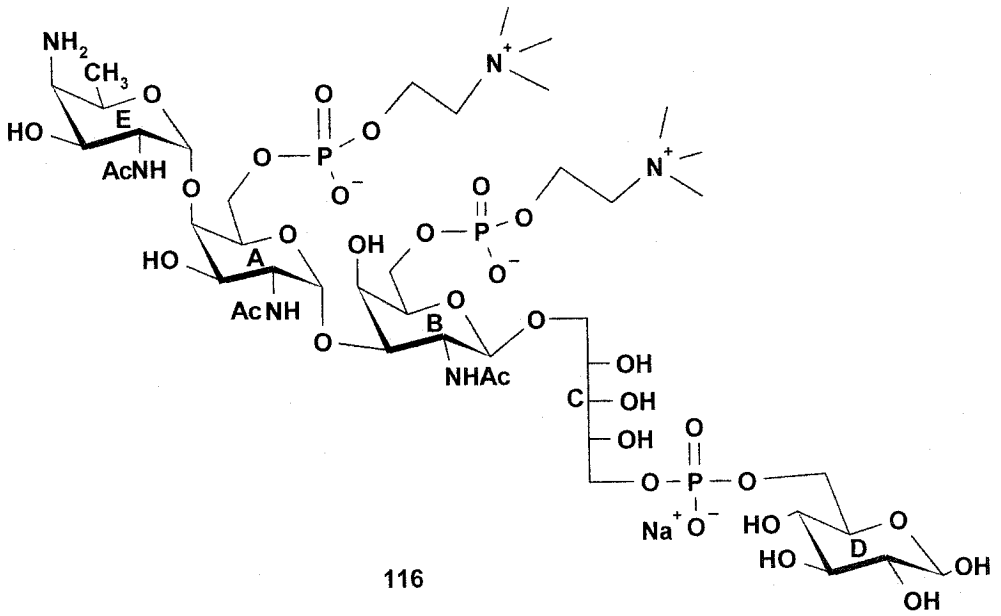
The conformations and configurations of glycosyl sulfoxides were studied by X-ray crystallography, DFT calculations and nOe experiments. In the solid state, sulfoxides with *R* configurations at the sulfur atom (**96R** and **100R**) adopt *anti* conformations, while sulfoxides with an *S* configuration at the sulfur atom (**96S**) and the parent sulfide **94** adopt *exo* conformations. In solution, the nOe effect between H3 and HSPo is much weaker than that between H5 and HSPo. Based on the calculated structures of the possible conformers, this result indicates that there is some population of the *exo* conformers present in solution, unlike in the solid state. Minimum energy geometries of **94**, **98R**, **98S** and their corresponding methyl analogous **114**, **115R** and **115S** were calculated by DFT methods (B3LYP/6-13G(d)//B3LYP/6-311+G(d,p)) in Gaussian 03. For thioglycoside **94,** two minima were obtained differing in their azide orientations and both have *exo* conformations. For the S_S-sulfoxides **98S**, two minima were obtained of which one is *exo*. The *exo* minimum has a lower energy than the *anti* one. Theoretical

calculations, X-ray data and nOe observations all indicate that *exo* conformations are adopted by the thiophenyl glycoside **94** and the S_S-sulfoxide **98S**. For the R_S-sulfoxide **98R**, four minima were obtained: two *anti* and two *exo*. The *anti* minima are calculated to be more stable than the *exo* minima. This agrees with the result for the solid but the nOe observations from either 1D or 2D nOe experiments from solution suggest that some population of the exo conformer is present. This conformer is calculated to have a much larger dipole moment and it might be expected that the solution phase would favor it in comparison with the gas phase. Calculations were also performed on the methyl analogues of the phenyl glycosides and similar results were obtained. NMR chemical shifts of minima of **98R** and **98S** were also calculated by DFT method.

The evidence presented in this thesis shows that the most stable configurations of glycosyl sulfoxides are those that can adopt conformations with the aglycone *exo* and the lone pair on sulfur *anti* to the C1-O5 bond, because of the n→σ* overlap possible in this orientation. For D-sugars, these are the S_S configurations of the α-anomers and the R_S configurations of the β-anomers. For the kinetically favoured R_S α-sulfoxides, the anti conformers are calculated to be most stable, in contrast to literature assumptions. For these anti conformers, the C2-C1-S-C torsional angle is much larger than eclipsed and the C1-S bond is as short as it is when n→σ* overlap is present. These observations indicated the n→σ* overlap was also present for this conformer, which is only possible if the sulfoxide lone pair is a p-type lone pair. Equilibration studies by Crich and coworkers[249] can be interpreted as supporting the conclusions drawn here for glycosyl sulfoxides when the substituents at C2 are in equatorial orientations but indicate that the configuration at C2 has a major effect on glycosyl sulfoxide conformer stability.

5.2 Future work

Based on the results drawn from this thesis and the previous work in this laboratory,[46] the following pentasaccharide **116** (Figure 5.2) will be a more practical target pentasaccharide as the repeating unit of the C-polysaccharide. This target compound would require the formation of an α-linkage between ring **E** and ring **A**. Choice of this target would avoid the difficulty of formation of the DE glycosidic linkage observed in this thesis but would retain the full repeating unit.



116

Figure 5.1 A new target pentasaccharide of the repeating unit of the C-polysaccharide

Methyl 2-acetamido-3-*O*-benzoyl-2,6-dideoxy-α-D-*xylo*-hexoyranoside-4-ulose (**72**) was synthesized in this thesis. De-*O*-benzoylation of compound **72** would free the 3-hydroxyl group and form methyl 2-acetamido-2,6-dideoxy-α-D-*xylo*-hexoyranoside-4-ulose (**117**). Compound **117** would probably serve as glycosyl acceptor toward the glucopyranosyl donors made in this thesis since it was shown that methyl 2-acetamido-

4,6-*O*-benzylidene-2-deoxy-α-D-glucopyranoside does. After the desired disaccharide is obtained, reductive amination should convert the ketone to the amine. It is well known that reduction of ketones and imines on pyranosides occurs to yield axial hydroxyl and amino groups, respectively. If reductive amination was employed, the current strategy to prepare the C-polysaccharide repeating unit (see Figure 1.2) could be retained.

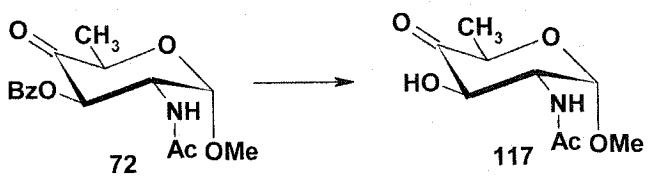


Figure 5.2 De-*O*-benzoylation of methyl 2-acetamido-3-*O*-benzoyl-2,6-dideoxy-α-D-xylo-hexopyranoside-4-ulose (**72**)

Phosphorylcholine could be selectively introduced into either unit **A** or unit **B** if disaccharide **119** was prepared. Deacetylation of compound **101** would form compound **118**, which now has a free 3-hydroxyl group and compound **118** can serve as the glycosyl acceptor and react with either compound **95** or compound **96** to form the disaccharide **119**. The reactivity difference between the 4,6-*O*-benzylidene acetal and 4,6-*O*-*p*-methoxybenzylidene acetal makes it possible to perform regioselective deprotection. As a result, the phosphorylcholine group could be put on the 6-O position of either ring **A** or ring **B**. It is highly desirable to have these two monophosphorylcholine derivatives and the diphosphorylcholine derivatives available to test the immunological implications of the different types of C-polysaccharides identified recently.[42,43]

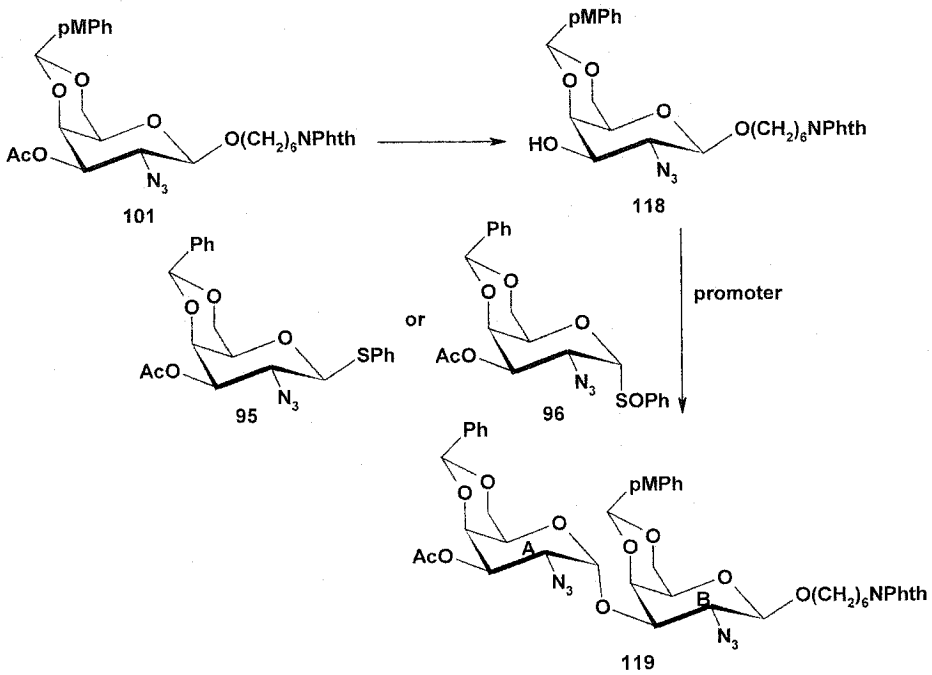


Figure 5.3 Preparation of a disaccharide with different protecting groups at ring **A** and **B**

Chapter 6 Experimental

6.1 General Procedures

6.1.1 Instruments

Melting points were determined with a Fisher-Johns melting point apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded at 300 K in 5 mm NMR tubes on Bruker NMR spectrometers (AC-250, AMX-400, or Avance 500) operating at 250.13, 400.13 or 500.13 MHz for ^{1}H NMR and 62.9, 100.08 or 125.77 MHz for ^{13}C NMR, respectively, on solutions in chloroform-*d*, unless otherwise indicated. Chemical shifts are given in parts per million (ppm)(+/-0.01 ppm) relative to that of tetramethylsilane (TMS) (0.00 ppm) in the case of the ^{1}H NMR spectra or phosphoric acid (0.00 ppm) in the case of the ^{31}P NMR, and to the central line of chloroform-*d* (δ 77.16) or acetone-d_6 (δ 29.92) for the ^{13}C NMR spectra. All assignments were confirmed by COSY, HETCOR, HMQC, HSQC or HMBC experiments.

Exact masses of ions obtained from electron ionization (EI) (70 eV) were recorded on a CEC 21-110B mass spectrometer. Electrospray mass spectra were recorded on a Fisons Quattro mass spectrometer with a Quattro source (cone voltage: 55 V, flow rate: 5 μL /min, complexing agent: potassium acetate, solvent: 75:25 v/v acetonitrile / water) or on a ThermoFinnigan LCQ Duo mass spectrometer (4.5 kv, flow rate 20 μL/min, solvent: methanol). The electrospray exact masses were measured on ions from positive ion mode electrospray ionization on a Micromass ZabSpec Hybrid Sector-TOF mass spectrometer. The liquid carrier (MeOH) was infused into the electrospray source

by means of a Harvard syringe pump at a flow rate of 10 :L/min.

Reaction temperature below -10 °C was maintained with a Neslab Cryocool CC-100 chiller. Optical rotations were determined with a Rudolph Instruments Digipol 781 automatic polarimeter. Microwave-induced reactions were conducted in a commercial microwave oven Beaumark model MM802 1.2 kw.

Elemental analyses were performed by the Canadian Microanalytical Service, Delta, BC, Canada.

6.1.2 Purifications

TLC was performed on aluminium-backed plates bearing 200 um silica gel 60 F_{254} (Merck or Silicycle). Compounds were visualized quenching of fluorescence by UV light (254 nm) where applicable and/or were located by spraying with or dipping into a solution of 2% cerium sulfate in 1M sulfuric acid followed by heating on a hot plate until color developed. Compounds were purified on silica gel (TLC standard grade, 230-400 mesh) by flash chromatography using specified eluents. The ratios of the solvents used in TLC and column chromatography are volume ratios.

6.1.3 Pre-purifications of some chemicals

Acetonitrile, dichloromethane, ethyl acetate, pyridine, and triethylamine were dried by refluxing over calcium hydride followed by distillation and were stored over molecular sieves (4 Å).

Benzyl chloride was initially dried with anhydrous magnesium sulfate, then refluxed over calcium hydride and finally fractionally distilled at reduced pressure, collecting the middle fraction.

Toluene and 1,2-dichloroethane were refluxed over phosphorus oxide for 3 h,

distilled and then stored over molecular sieves (4 Å).

Amberlite IR-120 (H^+) resin was washed with a 10 % hydrochloric acid solution and distilled water, and then dried *in vacuo* at 50 °C overnight. Dowex mixed bed MR-3 (H^+/OH^-) resin was washed with distilled water and methanol before use.

Triphenylchloromethane (trityl chloride) was purified by recrystallization from 15:1 (v/v) hexanes-acetyl chloride. Carbon tetrabromide was heated with an aqueous sodium carbonate solution (1 %) for 2 h. Steam distillation then gave a colorless solid that was recrystallized from ethanol to give colorless crystals. They were dried *in vacuo* for 2 days and stored to avoid light. *N*-Iodosuccinimide was recrystallized from dioxane-carbon tetrachloride, dried *in vacuo* overnight and stored to avoid light. Zinc dust was stirred in aqueous hydrochloride (10 %) for 2 min, filtered, washed with water, acetone and diethyl ether, and dried *in vacuo* overnight. Ceric ammonium nitrate and sodium azide were ground to powder and dried *in vacuo* for two days. Boron trifluoride diethyl etherate was distilled before use.

6.2 Methyl 2,4-diacetamido-2,4,6-trideoxy-α-D-galactopyranoside (44) and methyl 2-acetamido-4-benzamido-2,4,6-trideoxy-α-D-galactopyranoside (45)

A suspension of methyl 2-acetamido-4-azido-3-*O*-benzoyl-2,4,6-trideoxy-α-D-galactopyranoside **29** (49.9 mg, 0.14mmol) and 10% Pd/C (74.8 mg, Degussa) in dry methanol (5 mL) was stirred under hydrogen at atmospheric pressure. After the disappearance of **29** (19 h) on TLC (ethyl acetate : hexanes 3:1), the catalyst was removed by filtration through a bed of Celite. The solid was washed with methanol (3 × 5 mL). Concentration of the filtrate yielded a colorless solid, that was dissolved in pyridine (2 mL) and acetic anhydride (20 μL, 0.21 mmol, 1.5 eq). The reaction mixture

was stirred at room temperature until the amino compound had disappeared on TLC (chloroform : methanol 8:1) (0.5 h). The reaction mixture was quenched with methanol (5 mL), and evaporated to give the diacetamide as a syrup. This syrup was dissolved in methanol (4 mL) and sodium methoxide was added (0.8 mL, 30 mg sodium in 6 mL methanol). After being stirred at rt for 1 h, the reaction mixture was neutralized with Amberlite IR-120 (H^+), filtered and concentrated to a yellow syrup. The syrup was purified by flash column chromatography (ethyl acetate : methanol 6:1) to give two compounds. Compound **44** was a colorless solid: 33.8 mg (74 %); Rf 0.20 (ethyl acetate : methanol 6:1); mp 213-215 °C; ^{1}H NMR δ 6.10 (d, 1H, $J_{NH,4}$ 7.8 Hz, NH-4), 5.82 (d, 1H, $J_{NH,2}$ = 9.4 Hz, NH-2), 4.69 (d, 1H, $J_{1,2}$ = 4.1 Hz, H-1), 4.31 (m, 1H, H-4), 4.13 - 4.07 (m, 2H, H-2, H-5), 3.92 (dd, 1H, $J_{2,3}$ = 10.8 Hz, $J_{3,4}$ = 4.0 Hz, H-3), 3.35 (s, 3H, OCH_3), 2.12, 2.04 (2s, 6H, 2 × $COCH_3$), 1.17 (d, 3H, $J_{5,6}$ = 6.6 Hz, H-6); ^{13}C NMR (D_2O) δ 178.4, 177.3 (2 × C=O), 101.0 (C-1), 69.7 (C-3), 68.0 (C-5), 58.0 (OCH_3), 56.2 (C-4), 52.9 (C-2), 24.7 (2 × $COCH_3$), 18.31 (C-6).

HRMS (EI) calcd for $[C_{11}H_{20}N_2O_5\text{-}CH_3OH]^+$: 228.1110, found: *m/z* 228.1110.

Compound **45** was a colorless syrup: 9.0 mg (21 %); Rf 0.50 (ethyl acetate : methanol 6:1); ^{1}H NMR δ 7.85 - 7.42 (m, 5H, PhH), 6.69 (d, $J_{NH,4}$ = 7.4 Hz, NH-4), 6.01 (bs, 1H, NH-2), 4.75 (d, 1H, $J_{1,2}$ = 3.7 Hz, H-1), 4.51 (m, 1H, H-4), 4.16 - 3.98 (m, 3H, H-2, H-3, H-5), 3.36 (s, 3H, OCH_3), 1.96 (s, 3H, $COCH_3$), 1.22 (d, 3H, $J_{5,6}$ = 5.5 Hz, H-6); ^{13}C NMR δ 171.4, 169.9 (2 × C=O), 133.9, 131.9, 128.6, 127.3 (Ph), 98.5 (C-1), 69.4 (C-3), 64.8 (C-5), 55.5 (OCH_3), 54.4 (C-4), 51.0 (C-2), 23.3 ($COCH_3$), 16.9 (C-6).

6.3 Methyl 2-acetamido-4-amino-2,4,6-trideoxy-α-D-galactopyranoside (46)

A solution of methyl 2-acetamido-4-azido-2,4,6-trideoxy-α-D-glucopyranoside (**30**) (89.5 mg, 0.37 mmol) in dry ethanol (1.5 mL) was stirred with 10 % palladium-on-charcoal (0.24 g) under hydrogen at rt for 16 h. The reaction was filtered through a bed of Celite. The solid was washed with ethanol (3 × 2 mL) and the filtrate was concentrated to a colorless residue. The residue was purified by flash column chromatography (dichloromethane : methanol 4:1) to give the title compound **46** as a colorless solid: 65.2 mg (81.5 %); Rf 0.21 (dichloromethane : methanol 4:1); mp 194.5 - 196.0 °C; $[\alpha]_D$ +159.4° (*c* 1.2, C_2H_5OH); ^1H NMR δ 6.99 (d, 1H, $J_{2,NH}$ = 8.5 Hz, NH), 4.65 (d, 1H, $J_{1,2}$ = 3.8 Hz, H-1), 4.08 (ddd, 1H, $J_{2,3}$ = 10.8 Hz, H-2), 3.97 (qd, 1H, $J_{5,6}$ = 6.6 Hz, $J_{4,5}$ = 1.8 Hz, H-5), 3.73 (dd, 1H, $J_{3,4}$ = 4.2 Hz, H-3), 3.35 (s, 3H, OCH_3), 2.96 (dd, 1H, H-4), 2.05 (s, 3H, $COCH_3$), 1.25 (d, 3H, H-6); ^{13}C NMR δ 171.7 (C=O), 98.5 (C-1), 69.7 (C-3), 65.4 (C-5), 55.2 (OCH_3), 54.8 (C-4), 50.5 (C-2), 23.4 ($COCH_3$), 16.8 (C-6).

EIMS calcd for $[C_9H_{18}N_2O_4\text{-}OCH_3]^+$: 187.1083, found: *m/z* 187.0878; (ESI), calcd for $[C_9H_{18}N_2O_4+K]^+$: 257.2, found: *m/z* 257.5.

6.4 Methyl 2-acetamido-4-(benzyloxylcarbonyl)amino-2,4,6-trideoxy-α-D-galactopyranoside (47)

Benzyl chloroformate (64 μL, 0.45 mmol, 1.5 eq) was added to a solution of compound **46** (65.2 mg, 0.30 mmol) and sodium bicarbonate (75.6 mg, 0.90 mmol, 3.0 eq) in 2:1 (v/v) tetrahydrofuran-water (1.5 mL) dropwise at 0 °C. The mixture was stirred at 0 °C for 2 h. The resulting two-phase mixture was diluted with ethyl acetate (3 mL) and extracted with ethyl acetate (3 × 3 mL). The combined organic layers were

concentrated *in vacuo* and purified by flash column chromatography (dichloromethane : methanol 20:1) give title compound **47** as a colorless solid: 81.1 mg (76.7 %); Rf 0.20 (dichloromethane : methanol 20:1); mp 62.5 - 64.5 °C; $[\alpha]_D$ +87.0° (*c* 0.7, $CHCl_3$); ^1H NMR δ 7.36 (s, 5H, PhH), 5.79 (d, 1H, $J_{2,NH}$ = 8.7 Hz, NHAc), 5.30 (d, 1H, $J_{4,NH}$ = 9.8 Hz, NHCbz), 5.17, 5.09 (2d, 2H, J = 12.2 Hz, CH_2Ph), 4.63 (d, 1H, $J_{1,2}$ = 3.7 Hz, H-1), 4.12 - 4.02 (m, 3H, H-2, H-4, H-5), 3.86 (m, 1H, H-3), 3.34 (s, 3H, OCH_3), 3.22 (d, 1H, $J_{3,OH}$ = 6.1 Hz, OH), 2.01 (s, 3H, $COCH_3$), 1.18 (d, 3H, $J_{5,6}$ = 6.4 Hz, H-6); ^{13}C NMR δ 170.1 (C=O), 154.8 (C=O from NHCbz), 133.1, 129.0, 128.6, 128.2 (Ph), 98.4 (C-1), 69.8 (C-3), 67.3 (CH_2Ph), 64.9 (C-5), 65.6 (C-4), 55.3 (OCH_3), 50.9 (C-2), 23.4 ($COCH_3$), 16.6 (C-6).

6.5 Methyl 2-acetamido-3-*O*-benzyloxylcarbonyl-4-(benzyloxylcarbonyl)amino-2,4,6-trideoxy-α-D-galactopyranoside (48)

Compound **46** (106.5 mg, 0.49 mmol) was dried *in vacuo* and then dissolved in tetrahydrofuran-water (7 mL, 3:4 v/v). Addition of sodium bicarbonate (205.8 mg, 2.44 mmol, 5.0 eq) to the clear solution gave a milky mixture. Benzyl chloroformate (180 μL, 1.27 mmol, 2.6 eq) was added to the mixture dropwise at 0 °C. The mixture was stirred at 0 °C for 0.5 h and then at rt for 1 h. The resulting two-phase mixture was extracted with ethyl acetate (3 × 10 mL). The combined organic layers were concentrated *in vacuo* and the residue was purified by flash column chromatography (ethyl acetate : hexanes 2:1) to give the title compound **48** as a colorless solid: 81.0 mg (34.2 %); Rf 0.21 (ethyl acetate : hexanes 2:1); mp 120.0 - 123.0 °C; $[\alpha]_D$ +98.8° (*c* 0.5, $CHCl_3$); ^1H NMR (acetone-d_6) δ 7.42 - 7.26 (m, 10H, PhH), 7.00 (d, 1H, $J_{2,NH}$ = 8.5 Hz, NHAc), 6.77 (d, 1H, $J_{4,NH}$ = 10.0 Hz, NHCbz), 5.17, 5.10 (2d, 2H, J = 12.3 Hz, NHCOOCH_2Ph), 5.08 (s,

2H, OCOOCH_2Ph), 4.89 (dd, 1H, $J_{2,3}$ = 11.8 Hz, $J_{3,4}$ = 4.2 Hz, H-3), 4.64 (d, 1H, $J_{1,2}$ = 3.7 Hz, H-1), 4.41 (ddd, 1H, H-2), 4.30 (ddd, 1H, $J_{4,5}$ = 1.8 Hz, H-4), 4.08 (qd, 1H, $J_{5,6}$ = 6.5 Hz, H-5), 3.34 (s, 3H, OCH_3), 1.83 (s, 3H, $COCH_3$), 1.18 (d, 3H, H-6); ^{13}C NMR δ 170.2 (C=O, NHAc), 157.0 (C=O, OCbz), 154.9 (C=O, NHCbz), 136.4, 135.2 (q Ph), 128.41, 128.39, 128.37, 128.2, 127.9, 127.4 (Ph), 98.3 (C-1), 73.46 (C-3), 69.8, 66.8 (2 × CH_2Ph), 64.5 (C-5), 55.3 (OCH_3), 52.7 (C-4), 48.0 (C-2), 23.0 ($COCH_3$), 16.4 (C-6).

MS (ESI) calcd for $[C_{25}H_{30}N_2O_8+K]^+$: 525.3, found: *m/z* 525.0.

6.6 Methyl 2-acetamido-4,6-*O*-benzylidene-2-deoxy-α-D-glucopyranoside (49)

A solution of methyl 2-acetamido-2-deoxy-α-D-glucopyranoside **(25)** (1.42 g, 6.04 mmol), benzaldehyde dimethyl acetal (2.7 mL, 18.12 mmol, 3.0 eq) and *p*-toluenesulfonic acid (0.14 g) in dry DMF (15 mL) was rotated in a water bath at 40-50 °C for 2 h. Concentration *in vacuo* gave a brown residue which became colorless after washing with an aqueous sodium bicarbonate solution (150 mL, 5 %). The solid was filtered, washed with water (50 mL), and recrystallized from ethanol to afford the title compound **49** as a colorless solid: 1.75 g (89.6 %); mp 253.5 - 260.0 °C; $[\alpha]_D$ +7.0° (*c* 0.9, $CHCl_3$); ^{1}H NMR (DMSO-d_6, 400 MHz) δ 7.88 (d, $J_{2,NH}$ = 8.0 Hz, NHAc), 7.47 - 7.37 (m, 5H, PhH), 5.61 (s, 1H, C*H*Ph), 5.13 (d, 1H, $J_{3,OH}$ = 5.7 Hz, 3-OH), 4.62 (d, 1H, $J_{1,2}$ = 3.7 Hz, H-1), 4.17 (dd, 1H, $J_{5,6a}$ = 4.8 Hz, $J_{6a,6b}$ = 10.9 Hz, H-6a), 3.85 (ddd, 1H, $J_{2,3}$ = 10.3 Hz, H-2), 3.74 (dd, 1H, $J_{5,6b}$ = 9.3 Hz, H-6b), 3.63 (ddd, 1H, $J_{4,5}$ = 9.9 Hz, H-5), 3.62 (dd, 1H, $J_{3,4}$ = 8.6 Hz, H-3), 3.51(dd, 1H, H-4), 3.30 (s, 3H, OCH_3), 1.99 (s, 3H, $COCH_3$); ^{13}C NMR (DMSO-d_6) δ 169.5 (C=O), 137.8, 128.9, 128.1, 128.4 (Ph), 101.0 (C-1), 98.8 (*C*HPh), 82.1 (C-3), 68.1 (C-5), 67.5 (C-4), 62.5 (C-6), 55.8 (OCH_3), 54.2 (C-2), 22.7 ($COCH_3$).

6.7 Phenyl 2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-glucopyranoside (51)

1,2,3,4,6-Penta-*O*-acetyl-β-D-glucopyranose **50** (66.91 g, 0.17 mol) was dissolved in chloroform (400 mL). Benzenethiol (21 mL, 0.21 mol, 1.2 eq) was slowly added from a dropping funnel to the solution followed by freshly distilled boron trifluoride etherate (100 mL, 0.86 mol, 5 eq). The mixture was stirred for 48 h at rt. The clear reddish solution was washed with saturated sodium bicarbonate solution (2 × 150 mL) and water (3 × 100 mL). The combined aqueous layers were washed with chloroform (2 × 100 mL), and the organic layers were combined and dried over anhydrous magnesium sulfate. The mixture was filtered, and the filtrate was concentrated to a yellow residue. Recrystallization from ethanol gave the title compound (**51**) as colorless needles: 46.38 g (61.4 %); mp 115.0 - 115.5 °C (lit.[288] 117 - 118 °C); $[\alpha]_D$ -15.2° (*c* 1.1, $CHCl_3$) (lit.[288] -16°); ^{1}H NMR δ 7.31 (m, 5H, PhH), 5.23 (dd, 1H, $J_{2,3}$ = 9.2 Hz, $J_{3,4}$ 9.3 Hz, H-3), 5.04 (dd, 1H, $J_{4,5}$ 10.1 Hz, H-4), 4.98 (dd, 1H, $J_{1,2}$ 10.1 Hz, H-2), 4.71 (d, 1H, H-1), 4.20 (dd, 2H, $J_{5,6a}$ 4.9 = Hz, $J_{5,6b}$ = 3.0 Hz, 2 × H-6), 3.73 (m, 1H, H-5), 2.09, 2.08, 2.02, 1.99 (4s, 12H, 4 × $COCH_3$); ^{13}C NMR δ 170.6, 170.2, 169.4, 169.3 (4 × C=O), 133.1, 131.6, 128.9, 128.4 (Ph), 85.8 (C-1), 75.8 (C-5), 74.0 (C-3), 69.9 (C-2), 68.2 (C-4), 62.2 (C-6), 20.8 (2C), 20.6 (2C4).

6.8 Phenyl 2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-glucopyranoside (*RS*)$_S$-oxide (52)

Compound **51** (1.06 g, 2.41 mmol) was dissolved in dichloromethane (180 mL). A solution of *m*-chloroperoxybenzoic acid (0.52 g, 2.56 mmol, 1.1 eq, 85%) in dichloromethane (10 mL) was added dropwise to the solution at -78 °C. The reaction mixture was stirred at -78 °C for 0.5 h, then at -20 °C for 0.5 h. The reaction was quenched with a saturated sodium bicarbonate (200 mL) solution. The resulting solution

was extracted with chloroform (2 × 100 mL), and the organic layers were combined, dried (anhydrous magnesium sulfate) and filtered. The filtrate was concentrated to a yellow residue. Recrystallization from ethanol gave the title compound (**52**) as colorless needles: 0.80 g (72.7 %); mp 54.0 - 55.0 °C (lit.[150] 54 -56 °C); ^{1}H NMR δ 7.71 - 7.52 (m, 10H, PhH), 5.38 - 5.21 (m, 4H, 2 × H-2, 2 × H-3), 5.04 - 4.93 (m, 2H, 2 × H-4), 4.45, 4.29 (2d, 2H, $J_{1,2}$ = 9.8 Hz, $J_{1',2'}$ = 9.8 Hz, 2 × H-1), 4.19 - 4.00 (m, 4H, 2 × H-6), 3.59 - 3.75 (m, 2H, 2 × H-5), 2.07 - 1.90 (4s, 24H, 8 × $COCH_3$); ^{13}C NMR δ 170.4, 170.1, 169.4, 169.3, 169.2, 169.0 (8 × C=O), 139.0, 138.7, 131.7, 128.9, 125.7 (Ph), 92.3, 89.9 (2 × C-1), 76.6, 76.3 (2 × C-5), 73.8, 73.6 (2 × C-2), 2 × 67.7, 2 × 67.4(2 × C-3, 2 × C-4), 61.7, 61.3 (2 × C-6), 2 × 20.63, 3 × 20.59, 3 × 20.55 (8 × $COCH_3$).

6.9 Ethyl 2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-glucopyranoside (54)

A solution of compound **50** (5.01 g, 12.8 mmol) in dry dichloromethane (60 mL) was treated with ethanethiol (97 %, 1.2 mL, 15.4 mmol, 1.2 eq) at 0 °C. After the clear colorless mixture had been stirred for 15 min, boron trifluoride etherate (3.2 mL, 30.8 mmol, 2.4 eq) was added dropwise. The mixture was stirred at rt for 2 h until TLC (ethyl acetate-hexane, 1:1) showed completion of the reaction. The reaction was diluted with dichloromethane (60 mL) and washed successively with aqueous sodium thiosulfate solution (25 %, 2 × 30 mL), saturated sodium bicarbonate (25 mL) and distilled water (25 mL). It was then dried (anhydrous sodium sulfate) and concentrated to an orange syrup. The syrup was purified by a short silica gel column using 1:1 (v/v) ethyl acetate-hexanes as eluent to give the title compound as colorless needles: 4.76 g (94.5 %); mp 78.5 - 80.0 °C (lit.[289] 78 - 79 °C); $[\alpha]_D$ -19.4° (*c* 0.9, $CHCl_3$) (lit.[290] -24.4°); ^{1}H NMR δ 5.19 (dd, 1H, $J_{2,3}$ = 9.2 Hz, $J_{3,4}$ = 9.3 Hz, H-3), 5.09 (dd, 1H, $J_{4,5}$ = 9.8 Hz, H-4), 5.04 (dd, 1H, $J_{1,2}$ = 9.9

Hz, H-2), 4.50 (d, 1H, H-1), 4.25 (dd, 1H, $J_{5,6a}$ = 4.9 Hz, $J_{6a,6b}$ = 12.4 Hz, H-6a), 4.14 (dd, 1H, $J_{5,6b}$ = 2.6 Hz, H-6b), 3.71 (ddd, 1H, H-5), 2.80 - 2.59 (m, 2H, SCH_2), 2.08, 2.06, 2.03, 2.01 (4s, 12H, 4 × $COCH_3$), 1.28 (t, 3H, J = 6.5 Hz, J = 7.4 Hz, SCH_2CH_3); ^{13}C NMR δ 170.6, 169.4 (4 × C=O), 83.5 (C-1), 75.9 (C-5), 73.9 (C-3), 69.8 (C-2), 68.3 (C-4), 62.1 (C-6), 24.1 (SCH_2), 20.7, 20.6, 2 × 20.5 (4 × $COCH_3$), 14.8 (SCH_2CH_3).

HRMS (ESI), calcd for $[C_{35}H_{36}O_6S+Na]^+$: 607.213, found: *m/z* 607.214.

6.10 2,3,4,6-Tetra-*O*-acetyl-α-D-glucopyranosyl bromide (55)

A mixture of compound **50** (20.02 g, 51.3 mmol) and hydrogen bromide in glacial acetic (30 %, 30 mL) was stirred at rt for 1 h. The pink reaction mixture was diluted with dichloromethane (300 mL) and poured into ice water (300 mL). The dichloromethane solution was separated and washed successively with distilled water (2 × 200 mL), saturated sodium bicarbonate (2 × 200 mL) and distilled water (2 × 100 mL). It was dried over anhydrous sodium sulfate, filtered and concentrated to give a pale yellow syrup. The syrup was crystallized from ethyl acetate-hexanes to give the title compound as colorless needles: 20.01 g (94.9 %); mp 78.0 - 82.0 °C (lit.[291] 86 - 88 °C); $[\alpha]_D$ 196.0° (*c* 2.0, $CHCl_3$) (lit.[291] 140.8°, *c* 1, CH_2Cl_2).

6.11 2,3,4,6-Tetra-*O*-acetyl-1-*O*-α-D-glucopyranosyl trichloroacetimidate (57α) and 2,3,4,6-tetra-*O*-acetyl-1-*O*-β-D-glucopyranosyl trichloroacetimidate (57β)

Both title compounds were prepared from compound **56** following literature procedures.[130,131] Compound **57α** was a colorless syrup. $[\alpha]_D$ +98.0° (*c* 1.0, $CHCl_3$) (lit.[292] +103°); ^1H NMR δ 8.74 (s, 1H, NH), 6.56 (d, 1H, $J_{1,2}$ = 3.7 Hz, H-1), 5.57 (dd, 1H, $J_{2,3}$ = 9.7 Hz, $J_{3,4}$ = 10.0 Hz, H-3), 5.19 (dd, 1H, $J_{4,5}$ = 9.3 Hz, H-4), 5.14 (dd, 1H, H-2), 4.21 (dd, 1H, $J_{5,6a}$ = 4.1 Hz, $J_{6a,6b}$ = 11.8 Hz, H-6a), 4.14 (ddd, 1H, $J_{5,6b'}$ = 1.53 Hz, H-5),

4.05 (dd, 1H, H-6b), 2.00, 1.98, 1.96, 1.94 (4s, 4 × $COCH_3$); ^{13}C NMR δ 170.3, 169.8, 169.6, 169.3 (4 × C=O), 160.5 (C=NH), 92.7 (C-1), 90.5 (CCl_3), 69.8 (C-5), 69.7 (C-3), 69.5 (C-2), 67.6 (C-4), 61.2 (C-6), 20.5, 20.4, 2 × 20.2 (4 × $COCH_3$).

Compound **57β** was obtained as colorless needles: mp 153.0 - 155.0 °C (lit.[165] 154 - 155 °C); $[\alpha]_D$ +5° (*c* 1, $CHCl_3$) (lit.[165] +8.3°); ^1H NMR δ 8.72 (s, 1H, NH), 5.87 (d, 1H, $J_{1,2}$ = 7.6 Hz, H-1), 5.57 (dd, 1H, $J_{2,3}$ = 9.7 Hz, $J_{3,4}$ = 10.0 Hz, H-3), 5.19 (dd, 1H, $J_{4,5}$ = 9.3 Hz, H-4), 5.14 (dd, 1H, H-2), 4.21 (dd, 1H, $J_{5,6a}$ = 4.4 Hz, $J_{6a,6b}$ = 12.5 Hz, H-6a), 4.16 (dd, 1H, $J_{5,6b}$ = 2.3 Hz, H-6b), 3.91 (ddd, 1H, H-5), 2.09, 2.04, 2.03, 2.02 (4s, 4 × $COCH_3$); ^{13}C NMR δ 170.4, 170.0, 169.2, 168.8 (4 × C=O), 160.6 (C=NH), 95.3 (C-1), 88.6 (CCl_3), 72.5 (C-5), 72.4 (C-3), 70.0 (C-2), 67.7 (C-4), 61.3 (C-6), 20.7, 20.6, 20.5, 20.4 (4 × $COCH_3$).

6.12 Phenyl 1-thio-β-D-glucopyranoside (58)

A suspension of compound **51** (10.00 g, 22.7 mmol) in dry methanol (100 mL) was treated with sodium methoxide (1.0 g sodium in 50 mL dry methanol). The suspension became clear after being stirred for 30 min. TLC (methanol-chloroform, 1:1) showed completed disappearance of starting material. The reaction mixture was then neutralized by IR-120 (H^+) resin, filtered, and concentrated to give the title compound **58** as a colorless solid. Recrystallization from ethyl acetate gave colorless needles: 5.62 g (90.7 %); mp 130.5 - 133.0 °C (lit.[293] 132 - 133.5 °C); ^1H NMR (400 MHz, D_2O) δ: 7.60 - 7.39 (m, 5H, PhH), 4.79 (d, 1H, $J_{1,2}$ = 9.9 Hz, H-1), 3.88 (dd, 1H, $J_{5,6}$ = 2.2 Hz, $J_{6a,6b}$ = 12.5 Hz, H-6a), 3.71 (dd, 1H, $J_{5,6b}$ = 5.7 Hz, H-6b), 3.52 (dd, 1H, $J_{2,3}$ = 8.9 Hz, $J_{3,4}$ = 8.8 Hz, H-3), 3.47 (ddd, 1H, $J_{4,5}$ = 9.6 Hz, H-5), 3.04 (dd, 1H, H-2), 3.35(dd, 1H, H-4); ^{13}C NMR

(D_2O) δ 134.8, 134.4, 132.1, 130.9 (Ph), 90.0 (C-1), 82.6 (C-4), 80.0 (C-3), 74.5 (C-2), 72.1 (C-5), 63.5 (C-6).

6.13 Phenyl 2,3,4,6-tetra-*O*-benzyl-1-thio-β-D-glucopyranoside (59)

Sodium hydride (0.75 g, 31.2 mmol, 4 eq) was added to a solution of **58** (2.13 g, 7.8 mmol) in dry DMF (25 mL) with vigorous stirring. After mixture had been stirred for 15 min, benzyl bromide (4.8 mL, 41.7 mmol, 5.3 eq) was added dropwise at rt. After being stirred for 2 h at 120 °C, the brown reaction mixture was cooled to rt, then poured into ice water (200 g). When ethanol (40 mL) was added to the stirred milky mixture, a brown solid separated. Filtration and recrystallization from ethanol gave the title compound **59** as colorless needles: 3.94 g (79.4 %); mp 86 - 88 °C (lit.[293] 84 - 85 °C); $[\alpha]_D$ +5.0° (*c* 1, $CHCl_3$) (lit.[293] +10°); ^{1}H NMR δ 7.68 - 7.13 (m, 25H, PhH), 4.90, 4.83 (2d, 2H, J = 10.9 Hz, C*H*$_2$Ph), 4.88, 4.72 (2d, 2H, J = 11.3 Hz, C*H*$_2$Ph), 4.82, 4.59 (2d, 2H, J = 11.9 Hz, C*H*$_2$Ph), 4.61, 4.53 (2d, 2H, J = 12.0 Hz, C*H*$_2$Ph), 4.66 (d, 1H, $J_{1,2}$ = 9.8 Hz, H-1), 3.81-3.47 (m, 6H, H-2, H-3, H-4, H-5, 2 × H-6); ^{13}C NMR δ 138.4, 138.3, 138.0, 133.8 , 132.0, 128.9, 128.4, 128.3, 128.2, 128.0, 127.8, 127.8, 127.7, 127.6, 127.5, 127.4 (Ph), 87.4 (C-1), 86.7, 80.8, 79.1, 77.8 (C-2, C-3, C-4, C-5), 75.8, 75.4, 75.0, 73.4 (4 × *C*H$_2$Ph), 69.0 (C-6).

6.14 2,3,4,6-Tetra-*O*-benzyl-α-D-glucopyranose (60)

N-Bromosuccinimide (89.3 mg, 0.50 mmol, 1.6 eq) was added to a solution of compound **59** (200.0 mg, 0.32 mmol) in dry acetone (8 mL) at -18 °C. After 50 min at -18 °C the reaction was quenched by adding a saturated aqueous sodium bicarbonate solution (10 mL) and a colorless precipitate was obtained. When ethyl acetate (20 mL) was added, the precipitate dissolved. The organic layer was separated and the aqueous

phase was extracted with ethyl acetate (3 × 5 mL). The combined organic layers were washed with brine (2 × 5 mL), dried over anhydrous sodium sulfate, and concentrated to give a colorless residue. Recrystallization from chloroform-hexane gave the title compound **60** as colorless needles: 100.1 mg (58.5 %); mp 153 - 155 °C (lit.[294] 153 - 155 °C); $[\alpha]_D$ +20.1° (*c* 1, $CHCl_3$) (lit.[294] +20.9°).

6.15 2,3,4,6-Tetra-*O*-benzyl-α-D-glucopyranosyl trichloroacetimidate (61)

Compound **60** (100.1 mg, 0.19 mmol) was dissolved in dry dichloromethane (1 mL), and trichloroacetonitrile (200 μL, 2.00 mmol, 10.5 eq) and potassium carbonate (272 mg, 1.97 mmol, 10.4 eq) were added to the solution. The mixture was stirred for 48 h, diluted with dichloromethane (10 mL), filtered and concentrated to give the title compound **61** as a colorless solid: 81.1 mg (64.0 %); mp 70.0 - 72.0 °C (lit.[295] 72 - 73 °C); $[\alpha]_D$ +21.9° (*c* 1, $CHCl_3$) (lit.[295] +22°); ^{1}H NMR δ 8.58 (s, 1H, NH), 7.31 - 7.13 (m, 20H, PhH), 6.52 (d, 1H, $J_{1,2}$ = 3.4 Hz, H-1), 4.96, 4.82 (2d, 2H, J = 10.8 Hz, CH_2Ph), 4.85, 4.52 (2d, 2H, J = 10.6, CH_2Ph), 4.75, 4.67 (2d, 2H, J = 11.7 Hz, CH_2Ph), 4.61, 4.46 (2d, 2H, J = 12.1 Hz, CH_2Ph), 4.05 (t, 1H, $J_{2,3} = J_{3,4}$ = 9.3 Hz, H-3), 3.99 (ddd, 1H, $J_{4,5}$ = 9.0 Hz, $J_{5,6a}$ = 2.0 Hz, $J_{5,6b}$ = 4.7 Hz, H-5), 3.79 (dd, 1H, H-4), 3.77 (dd, 1H, H-2), 3.78 (dd, 1H, $J_{6a,6b}$ = 11.0 Hz, H-6a), 3.66 (dd, 1H, H-6b); ^{13}C NMR δ 161.3 (C=O), 138.6, 138.1, 138.0, 137.8, 128.4, 128.4, 128.1, 128.0, 127.9, 127.8, 127.7, 127.6, 127.6 (Ph), 94.4 (C-1), 91.3 (CCl3), 81.4 (C-3), 79.4 (C-2), 76.8 (C-4), 73.1 (C-5), 75.6, 75.3, 73.5, 72.9 (4 × CH_2Ph), 68.0 (C-6).

6.16 Phenyl 6-*O*-trityl-1-thio-β-D-glucopyranoside (62)

The solution of compound **58** (5.51 g, 20.2 mmol) and trityl chloride (10.12 g, 36.3 mmol, 1.8 eq) in dry pyridine (100 mL) was refluxed for 1.5 h. The reaction mixture was

poured into ice-water (200 mL). The yellow suspension was extracted with dichloromethane (3 × 100 mL). The combined organic layers were washed with a saturated aqueous sodium bicarbonate solution (50 mL) and distilled water (50 mL), dried over anhydrous sodium sulfate and concentrated to a yellow syrup. The syrup was purified by flash column chromatography (chloroform : methanol 5:1) to give title compound **62** as a colorless solid: 9.50 g (92.0 %); mp 110.0 – 112.5 °C; Rf 0.25 (chloroform : methanol 5:1); ^{1}H NMR δ 8.58 - 7.21 (m, 20H, PhH), 4.50 (d, 1H, $J_{1,2}$ = 9.5 Hz, H-1), 4.52 - 3.29 (m, 6H, H-2, H-3, H-4, H-5, 2 × H-6); ^{13}C NMR δ 149.7, 143.8, 136.2, 132.7, 132.1, 129.0, 128.6, 127.9, 127.1, 123.8 (Ph), 87.7 (C-1), 86.9 (CPh$_3$), 77.0, 76.5, 71.7, 70.8, 63.6 (C-2, C-3, C-4, C-5, C-6).

6.17 Phenyl 2,3,4-tri-*O*-acetyl-6-*O*-trityl-1-thio-β-D-glucopyranoside (63)

Acetic anhydride (0.4 mL, 2.12 mmol, 8.5 eq) was added to a solution of compound **62** (0.13 g, 0.25 mmol) in dry pyridine (5 mL). The reaction mixture was stirred for 20 h, poured into ice-water (20 mL). The mixture was extracted with dichloromethane (4 × 5 mL). The combined organic layers were washed with saturated sodium bicarbonate (2 × 5 mL) and distilled water (5 mL), dried over anhydrous magnesium sulfate and concentrated to a syrup. The syrup was purified by flash column chromatography (chloroform) to give title compound **63** as a colorless solid: 0.15 g (93.8 %); Rf 0.23 (chloroform); mp 185 - 187 °C; ^{1}H NMR δ 7.61 - 7.15 (m, 20H, PhH), 5.19 (dd, 1H, $J_{2,3}$ = 9.2 Hz, $J_{3,4}$ = 12.2 Hz, H-3), 5.10 (dd, 1H, $J_{4,5}$ = 10.7 Hz, H-4), 5.06 (dd, 1H, H-2), 4.72 (d, 1H, $J_{1,2}$ = 9.7 Hz, H-1), 3.57 (ddd, 1H, $J_{5,6a}$ = 1.8 Hz, $J_{5,6b}$ = 5.0 Hz, H-5), 3.28 (dd, 1H, $J_{6a,6b}$ = 10.5 Hz, H-6a), 3.13 (dd, 1H, H-6b), 2.09, 1.97, 1.70 (3s, 9H, 3 × $COCH_3$); ^{13}C NMR δ 170.2, 169.3, 168.9 (3 × C=O), 143.5, 133.2, 131.8, 129.0, 128.6,

128.3, 128.2, 127.8, 127.0, 125.3 (Ph), 86.6 (C-1), 86.9 (CPh_3), 77.5 (C-5), 74.3 (C-3), 70.1 (C-2), 68.3 (C-4), 61.9 (C-6), 20.9, 20.7, 20.4(3 × $COCH_3$).

6.18 Phenyl 2,3,4-tri-*O*-acetyl-1-thio-β-D-glucopyranoside (64)

30 % hydrogen bromide in acetic acid (50 μL) was added to a solution of compound **63** (140.0 mg, 0.22 mmol) in acetic acid (2 mL) at 0 °C. The mixture was stirred for 5 min at 0 °C, filtered to remove colorless precipitates, and the filtrate was concentrated to a yellow solid. The solid was purified by flash column chromatography (chloroform : methanol 90:1) to give title compound **64** as a colorless solid: 70.0 mg (80.4 %); Rf 0.21 (chloroform : methanol 90:1); mp 121-123 °C; $[\alpha]_D$ -10.0° (*c* 0.5, $CHCl_3$) (lit.[296] -8.04°); ^1H NMR δ 7.61 - 7.15 (m, 5H, PhH), 5.27 (dd, 1H, $J_{2,3}$ = 9.3 Hz, $J_{3,4}$ = 9.4 Hz, H-3), 5.10 (dd, 1H, $J_{4,5}$ = 7.8 Hz, H-4), 5.06 (dd, 1H, $J_{1,2}$ = 10.0 Hz, H-2), 4.72 (d, 1H, H-1), 3.57 - 3.54 (m, 3H, H-5, 2 × H-6), 3.45 (br, 1H, 6-OH), 2.09, 1.97, 1.70 (3s, 9H, 3 × $COCH_3$); ^{13}C NMR δ 170.2, 169.9, 168.2 (3 × C=O), 146.8 , 132.8, 129.1, 128.4, 127.9, 127.2 (Ph), 85.6 (C-1), 78.2 (C-5), 73.8 (C-3), 70.1 (C-2), 68.4 (C-4), 61.4 (C-6), 20.7, 2 × 20.6 (3 × $COCH_3$).

6.19 Phenyl 6-*O*-acetyl-2,3,4-tri-*O*-benzyl-1-thio-β-D-glucopyranoside (65)

A solution of zinc chloride (108.0 mg, 0.79 mmol, 7.2 eq) in acetic anhydride-acetic acid (2:1 v/v, 1 mL) was added to a solution of compound **59** (66.8 mg, 0.11 mmol) in acetic anhydride-acetic acid (1 mL, 2:1 v/v). The reaction mixture was stirred for 2 h, diluted with dichloromethane (5 mL), poured into water (10 mL), and extracted with dichloromethane (2 × 5 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered and concentrated to give a brown syrup. The syrup was purified by flash column chromatography (ethyl acetate : hexanes 1:15) to recover

starting material (12.0 mg) and the title compound (**65**) as a colorless solid: 30.1 mg (49.0 %); Rf 0.23 (ethyl acetate : hexanes 1:15); mp 67.0 - 69.5 °C (lit.[297] 69.5 - 70.5); $[\alpha]_D$ +16.6° (*c* 0.9, +$CHCl_3$) (lit.[297] 10°); ^{1}H NMR δ 7.58 - 7.24 (m, 20H, PhH), 4.93, 4.84 (2d, 2H, J = 10.8 Hz, C*H*$_2$Ph), 4.92, 4.74 (2d, 2H, J = 10.2 Hz, C*H*$_2$Ph), 4.86, 4.58 (2d, 2H, J = 10.8 Hz, C*H*$_2$Ph), 4.66 (d, 1H, $J_{1,2}$ = 9.8 Hz, H-1), 4.37 (dd, 1H, $J_{5,6}$ = 2.1 Hz, $J_{6a,6b}$ = 11.4 Hz, H-6a), 3.13 (dd, 1H, $J_{5,6b}$ = 4.7 Hz, H-6b), 3.74 (t, 1H, $J_{3,4}$ = $J_{4,5}$ = 8.8 Hz, H-4), 3.59-3.50 (m, 3H, H-2, H-3, H-5), 2.05 (s, 3H, $COCH_3$); ^{13}C NMR δ 170.7 (C=O), 138.2, 137.9, 137.6, 132.1, 128.9, 128.5, 128.5, 128.2, 128.1, 127.8 (Ph), 87.5 (C-1), 86.7 (C-4), 80.9 (C-3), 77.5 (C-2), 76.9 (C-5,), 75.9, 75.5, 75.1 (3 × CH_2Ph), 63.3 (C-6), 20.9 ($COCH_3$).

6.20 Methyl 2-acetamido-4,6-*O*-benzylidene-2-deoxy -3-*O*-(2',3',4',6'-tetra-*O*-benzyl-β-D-glucopyranosyl)-α-D-glucopyranoside (68) and methyl 2-acetamido-4,6-*O*-benzylidene-2-deoxy-3-*O*-(2',3',4',6'-tetra-*O*-benzyl-α-D-glucopyranosyl)-α-D-glucopyranoside (68α)

A mixture of phenyl 2,3,4,6-tetra-*O*-benzyl-1-thio-β-D-glucopyranoside **59** (1.63 g, 2.58 mmol, 1.3 eq), methyl 2-acetamido-4,6-*O*-benzylidene-2-deoxy-α-D-glucopyranoside (**49**) (0.66 g, 2.04 mmol) and freshly activated 4Å molecular sieves (0.50 g) in dried acetonitrile (150 mL) was stirred at rt for 2 h then cooled to -40 °C. A solution of NIS (0.98 g, 4.37 mmol, 2.1 eq) and silver triflate (1.05 g, 4.08 mmol, 2.0 eq) in dry acetonitrile (20 mL) at -40 °C was added and the reaction mixture was stirred at -40 °C for 48 h. The reaction was quenched by adding pyridine (10 mL). The reaction mixture was filtered and concentrated to a yellow residue which was purified by flash column chromatography (ethyl acetate : hexanes 1:1) to give a colorless solid.

Recrystallization from ethanol-chloroform yielded colorless needles of compound **68**: yield 1.41 g (81.5 %); Rf 0.60 (ethyl acetate : hexanes 2:1); mp 182 - 183.5 °C; $[\alpha]_D$ +75.7° (*c* 1.3, $CHCl_3$); ^1H NMR (400 MHz) δ 7.30 - 7.12 (m, 25H, PhH), 5.87 (d, 1H, $J_{2,NH}$ = 8.6 Hz, NH), 5.46 (s, 1H, C*H*Ph), 4.82, 4.79 (2d, 2H, J = 11.8 Hz, CH_2Ph), 4.79, 4.72 (2d, 2H, J = 11.1 Hz, CH_2Ph), 4.77 (d, 1H, $J_{1,2}$ = 3.6 Hz, H-1), 4.74, 4.48 (2d, 2H, J = 10.9 Hz, CH_2Ph), 4.68 (d, 1H, $J_{1',2'}$ = 7.4 Hz, H-1'), 4.50, 4.46 (2d, 2H, J = 11.8 Hz, CH_2Ph), 4.33 (ddd, 1H, $J_{2,3}$ = 10.2 Hz, H-2), 4.24 (dd, 1H, $J_{5,6a}$ = 2.8 Hz, $J_{6a,6b}$ = 10.9 Hz, H-6a), 4.23 (dd, 1H, $J_{3,4}$ = 10.2 Hz, H-3), 3.83 (m, 1H, H-5), 3.78 (dd, 1H, $J_{4,5}$ = 9.3 Hz, H-4), 3.78 (dd, 1H, $J_{5,6b}$ = 10.0 Hz, H-6b), 3.56 (dd, 1H, $J_{3',4'}$ = 11.6 Hz, $J_{4',5'}$ = 8.8 Hz, H-4'), 3.61 (dd, 1H, $J_{2',3'}$ = 8.4 Hz, H-3'), 3.50 (dd, 1H, $J_{5',6a'}$ = 2.1 Hz, $J_{6a',6b'}$ = 10.7 Hz, H-6a'), 3.44 (dd, 1H, H-2'), 3.43 (dd, 1H, $J_{5',6b'}$ = 5.3 Hz, H-6b'), 3.36 (s, 3H, OCH_3), 3.23 (ddd, 1H, H-5), 1.67 (s, 3H, $COCH_3$); ^{13}C NMR δ 169.9 (C=O), 138.5, 138.0, 137.3, 129.1, 128.3, 128.2, 128.0, 127.0, 127.5, 127.3, 126.2 (Ph), 101.7 (*C*HPh), 101.7 (C-1'), 98.8 (C-1), 84.8 (C-4'), 82.5 (C-2'), 81.0 (C-4), 77.8 (C-3'), 75.3, 74.9, 73.4, 74.2 (4 × CH_2Ph), 74.6 (C-5'), 74.2 (C-3), 69.0 (C-6), 68.9 (C-6'), 62.6 (C-5), 55.2 (OCH_3), 53.2 (C-2), 22.9 ($COCH_3$).

HRMS (ESI NaOAc) calcd for $[C_{50}H_{55}NO_{11}+Na]^+$: 868.3672, found: *m/z* 868.3627.

Recrystallization of the residue resulting from concentration of the mother liquor from ethanol-chloroform yielded colorless needles of compound **68**α, 0.16 g (9.2 %); Rf 0.60 (ethyl acetate : hexanes 2:1); mp 142.0 - 143.0 °C; $[\alpha]_D$ +71.2° (*c* 1.0, $CHCl_3$); ^1H NMR (400 MHz) δ 7.35 - 6.87 (m, 25H, PhH), 6.16 (d, 1H, $J_{2,NH}$ = 9.2 Hz, NH), 5.44 (d, 1H, $J_{1',2'}$ = 4.0 Hz, H-1'), 5.41 (s, 1H, C*H*Ph), 4.93, 4.70 (2d, 2H, J = 10.8 Hz, CH_2Ph), 4.83, 4.45 (2d, 2H, J = 10.9 Hz, CH_2Ph), 4.69 (d, 1H, $J_{1,2}$ = 3.5 Hz, H-1), 4.60, 4.48 (2d,

2H, J = 11.7 Hz, C*H*$_2$Ph), 4.52, 4.25 (2d, 2H, J = 12.8 Hz, C*H*$_2$Ph), 4.40 (ddd, 1H, $J_{2,3}$ = 10.6 Hz, H-2), 4.24 - 4.40 (m, 2H, H-4', H-6a'), 4.15 (ddd, 1H, $J_{4,5}$ = 10.3 Hz, $J_{5,6a}$ = 0.9 Hz, $J_{5,6b}$ = 8.5 Hz, H-5), 3.88 (t, 1H, $J_{2',3'}$ = $J_{3',4'}$ = 9.9 Hz, H-3'), 3.86 (dd, 1H, $J_{3,4}$ = 9.0 Hz, H-3), 3.83 (m, 1H, H-5'), 3.81 (dd, 1H, $J_{6a,6b}$ = 9.9 Hz, H-6a), 3.72 (t, 1H, $J_{5',6b'}$ = $J_{6a',6b'}$ = 10.1 Hz, H-6b'), 3.44 (dd, 1H, H-6b), 3.40 (dd, 1H, H-2'), 3.32 (s, 3H, OCH_3), 3.20 (dd, 1H, H-4), 1.85 (s, 3H, $COCH_3$); ^{13}C NMR δ 170.2 (C=O), 138.4, 137.9, 137.7, 137.2, 129.4, 128.5, 128.4, 128.3, 128.0, 127.9, 127.6, 127.4, 127.3, 127.2, 126.5 (Ph), 102.3 (*C*HPh), 99.1 (C-1), 96.2 (C-1'), 83.0 (C-5'), 81.8 (C-3'), 78.6 (C-2'), 77.9 (C-4), 75.8, 74.6, 74.1, 70.8 (4 × *C*H$_2$Ph), 72.2 (C-4'), 70.4 (C-6), 70.3 (C-5), 69.2 (C-6'), 62.6 (C-3), 55.3 (O*C*H$_3$), 52.1 (C-2), 22.0 (CO*C*H$_3$).

HRMS (ESI KOAc) calcd for $[C_{50}H_{55}NO_{11}+K]^+$: 884.475, found: *m/z* 884.343.

6.21 Methyl 2-acetamido-2-deoxy-3-*O*-(2',3',4',6'-tetra-*O*-benzyl-β-D-glucopyranosyl)-α-D-glucopyranoside (69)

Water (12 mL) was added to a swirled solution of **68** (0.37 g, 0.44 mmol) in acetic acid (18 mL) at 60 °C. The solution was stirred at 60 °C for 0.5 h. The mixture was concentrated with co-distillation of water (2 × 50 mL) to remove acetic acid, and then dried by azeotropic concentration with ethanol (50 mL) and toluene (2 × 50 mL). Recrystallization from ethanol-chloroform yielded compound **69** as colorless needles: 0.31 g (93.9 %); Rf 0.55 (ethyl acetate : hexanes 2:1); mp 192.0 - 193.0 °C; $[\alpha]_D$ 73.7° (*c* 0.8, $CHCl_3$); ^{1}H NMR (400 MHz) δ 7.33 - 7.14 (m, 20H, PhH), 5.65 (d, 1H, $J_{2,NH}$ = 8.8 Hz), 4.91, 4.71 (2d, 2H, J = 12.0 Hz, C*H*$_2$Ph), 4.85, 4.76 (2d, 2H, J = 10.9 Hz, C*H*$_2$Ph), 4.78, 4.46 (2d, 2H, J = 11.1 Hz, C*H*$_2$Ph), 4.73 (d, 1H, $J_{1,2}$ = 3.3 Hz, H-1), 4.49 (2d, 2H, J = 12.1 Hz, C*H*$_2$Ph), 4.44 (d, 1H, $J_{1',2'}$ = 7.9 Hz, H-1'), 4.29 (ddd, 1H, H-2), 3.91 – 3.49 (m,

11H, H-3, H-4, H-5, 2 × H-6, H-2', H-3', H-4', H-5', 2 × H-6'), 3.31 (s, 3H, OCH_3), 1.58 (s, 3H, $COCH_3$); ^{13}C NMR δ 170.3 (C=O), 138.4, 138.1, 137.5, 137.4, 128.5, 128.4, 128.3, 128.1, 128.0, 127.9, 127.7, 127.6, 127.4, 127.0 (Ph), 103.9 (C-1'), 98.1 (C-1), 75.8, 75.1, 74.5, 73.6 (4 × CH_2Ph), 84.7, 83.5, 81.6, 77.7, 74.5, 71.5, 69.1 (C-3, C-4, C-5, C-2', C-3', C-4', C-5'), 68.9, 63.1 (C-6, C-6'), 54.5 (OCH_3), 52.1 (C-2), 23.0 ($COCH_3$).

HRMS (ESI, NaOAc) calcd for $[C_{43}H_{51}NO_{11}+Na]^+$: 780.3359, found: *m/z* 780.3366.

6.22 Methyl 2-acetamido-6-bromo-2,6-dideoxy-3-*O*-(2',3',4',6'-tetra-*O*-benzyl-β-D-glucopyranosyl)-α-D-glucopyranoside (70)

Carbon tetrabromide (0.14 g, 0.42 mmol, 1.2 eq) was added to the colorless solution of **69** (266.1 mg, 0.35 mmol) and triphenylphosphine (177.6 mg, 0.68 mmol, 1.9 eq) in dry pyridine (12 mL) at 0 °C. The mixture was stirred for 40 min at 35-40 °C until the starting material was no longer detectable by TLC (ethyl acetate : hexanes 3:1). The pink mixture solution was evaporated and the yellow residue was purified by flash column chromatography (ethyl acetate : hexanes 1:10) to give the title compound **70** as a colorless solid: 268.2 mg (93.0 %); Rf 0.20 (ethyl acetate : hexanes 1:10); mp 222.5 - 223.0 °C; $[\alpha]_D$ +60.8° (*c* 0.1, $CHCl_3$); ^1H NMR (400 MHz) δ 7.30-7.15 (m, 20H, PhH), 5.52 (d, 1H, $J_{2,NH}$ = 9.1 Hz, NH), 4.99, 4.69 (2d, 2H, J = 11.9 Hz, CH_2Ph), 4.85, 4.75 (2d, 2H, J = 11.0 Hz, CH_2Ph), 4.78, 4.48 (2d, 2H, J = 11.0 Hz, CH_2Ph), 4.77 (d, 1H, $J_{4,OH}$ = 2.2 Hz, 4-OH), 4.74 (d, 1H, $J_{1,2}$ = 3.3 Hz, H-1), 4.51, 4.47 (2d, 2H, J = 11.7 Hz, CH_2Ph), 4.43 (d, 1H, $J_{1',2'}$ = 7.9 Hz, H-1'), 4.29 (m, 1H, H-2), 3.70 – 3.42 (m, 11H, H-3, H-4, H-5, 2 × H-6, H-2', H-3', H-4', H-5', 2 × H-6'), 3.36 (s, 3H, OCH_3), 1.55 (s, 3H, $COCH_3$); ^{13}C NMR δ 128.8, 128.5, 128.4, 128.3, 128.3, 128.1, 128.1, 128.0, 127.9, 127.8, 127.7, 127.4,

127.1 (Ph), 104.0 (C-1'), 98.1 (C-1), 75.8, 75.1, 74.5, 73.7 (4 × CH_2Ph), 84.7, 83.4, 81.6, 77.8, 74.3, 71.5, 70.9, 69.1 (C-3, C-4, C-5, C-2', C-3',C-4',C-5', C-6'), 55.1 (OCH_3), 51.9 (C-2), 33.4 (C-6), 22.9 ($COCH_3$).

HRMS (ESI, NaOAc) calcd for $[C_{43}H_{50}BrNO_{10}+Na]^+$: 842.2515, found: *m/z* 842.2516.

Anal. calcd for $C_{43}H_{50}BrNO_{10}$: C,62.98; H, 6.15; N, 1.71 %. Found C,63.03; H, 5.87; N, 2.07 %.

6.23 Methyl 2-acetamido-2,6-dideoxy-3-*O*-(2,3,4,6-tetra-*O*-benzyl-β-D-glucopyranosyl)-α-D-glucopyranoside (71)

A white suspension of **70** (51.4 mg, 0.063 mmol), AIBN (10 mg) and tributyltin hydride (150 μL) in dry toluene (5 mL) was heated to 100 to 105 °C for 2 h. The clear mixture was evaporated and the yellow residue was purified by column chromatography using 1.5:1 (v/v) ethyl acetate-hexane to give the title compound **71** as a colorless solid: 39.8 mg (85.8 %); Rf 0.20 (ethyl acetate : hexanes 3:1); mp 200.5 - 202.5 °C; $[\alpha]_D$ +108.6° (*c* 0.6, $CHCl_3$); ^{1}H NMR (400 MHz) δ 7.30-7.16 (m, 20H, PhH), 5.54 (d, 1H, $J_{2,NH}$ = 9.2 Hz, NH), 4.90, 4.70 (2d, 2H, J = 11.8 Hz, CH_2Ph), 4.85, 4.75 (2d, 2H, J = 10.7 Hz, CH_2Ph), 4.78, 4.48 (2d, 2H, J = 10.9 Hz, CH_2Ph), 4.67(d, 1H, $J_{1,2}$ = 3.5 Hz, H-1), 4.61 (d, 1H, $J_{4,OH}$ = 1.6 Hz, 4-OH), 4.53, 4.48 (2d, 2H, J = 11.8 Hz, CH_2Ph), 4.43 (d, 1H, $J_{1',2'}$ = 7.7 Hz, H-1'), 4.26 (ddd, 1H, $J_{1,2}$ = 3.5 Hz, $J_{2,3}$ = 9.1 Hz, H-2), 3.75 - 3.45 (m, 9H, H-3, H-4, H-5, H-2', H-3', H-4', H-5', 2 × H-6'), 3.32 (s, 3H, OCH_3), 1.56 (s, 3H, $COCH_3$), 1.56 (d, 3H, $J_{5,6}$ = 6.1Hz, CHCH_3); ^{13}C NMR δ 170.2 (C=O), 138.5, 138.2, 137.7, 137.5, 128.5, 128.3, 128.3, 128.3, 128.0,128.0, 127.9, 127.7, 127.6, 127.3, 127.1 (Ph), 104.1 (C-1'), 98.1 (C-1), 75.8, 75.0, 74.6, 73.6 (4 × CH_2Ph), 84.7, 83.5, 81.6, 77.7,

74.3, 71.5, 69.1, 69.0 (C-3, C-4, C-5, C-2', C-3', C-4', C-5', C-6'), 54.8 (OCH_3), 52.3 (C-2), 23.0 ($COCH_3$), 17.8 (C-6).

HRMS (ESI, NaOAc), calcd for $[C_{43}H_{51}NO_{10}+Na]^+$: 764.3410, found: *m/z* 764.3440.

6.24 Methyl 2-acetamido-3-*O*-benzoyl-2,6-dideoxy-α-D-*xylo*-hexopyranoside-4-ulose (72)

A solution of Dess-Martin periodinane (130.0 mg, 0.31 mmol) in dichloromethane (5 mL) was added to a solution of methyl 2-acetamido-3-*O*-benzoyl-2,6-dideoxy-α-D-glucopyranoside **28** (66.5 mg, 0.21 mmol) dichloromethane (5 mL). The clear colorless mixture was stirred at rt for 5 h, poured into a saturated aqueous sodium bicarbonate solution (30 mL) containing sodium thiosulfate (0.5 g). The obtained mixture was extracted with dichloromethane (3 × 5 mL). The combined organic layers were washed with brine (3 mL) and distilled water (3 mL), dried over anhydrous sodium sulfate, filtered, and concentrated to yield a colorless syrup. The syrup was purified by column chromatography using 15:1 (v/v) chloroform-methanol to give the title compound **72** as a colorless syrup: 56.3 mg (85.2 %); Rf 0.58 (chloroform : methanol 8:1); ^{1}H NMR δ 8.31 - 7.42 (m, 5H, PhH), 6.18 (d, 1H, $J_{2,NH}$ = 9.3 Hz, NH), 5.70 (d, 1H, $J_{2,3}$ = 10.9 Hz, H-3), 4.90 (d, 1H, $J_{1,2}$ = 3.4 Hz, H-1), 4.85 (ddd, 1H, H-2), 4.39 (q, 1H, $J_{5,6}$ = 5.7 Hz, H-5), 3.52 (s, 3H, OCH_3), 1.95 (s, 3H, $COCH_3$), 1.36 (d, 3H, H-6); ^{13}C NMR δ 197.9 (C-4), 169.9 (*C*OCH3), 169.3 (*C*OPh), 133.7, 130.2, 128.7, 128.6 (Ph), 98.6 (C-1), 75.2 (C-3), 69.9 (C-5), 56.2 (OCH3), 54.0 (C-2), 20.4 ($COCH_3$), 13.9 (C-6).

6.25 1,2,3,4,6-Penta-*O*-acetyl-α-D-galactopyranoside (74)

Acetic anhydride (90 mL, 99 %) was added to a suspension of D-galactopyranose

(**73**) (15.02 g, 0.083 mol) in dry pyridine (140 mL). The reaction mixture was stirred for 14 h at rt. The clear colorless reaction mixture was treated with distilled water (100 mL) to destroy the excess acetic anhydride, concentrated *in vacuo* to give a colorless syrup. The syrup was added to distilled water (100 mL) and extracted with dichloromethane (3 × 100 mL). The combined dichloromethane layers were washed with saturated sodium bicarbonate (3 × 50 mL) and distilled water (3 × 50 mL), dried over anhydrous sodium sulfate, filtered, and the filter cake was washed with dichloromethane (2 × 50 mL). The obtained clear colorless solution was used in the next step reaction without further purification.

A colorless syrup was obtained after the removal of solvent. A pure colorless powder of the title compound could be obtained after crystallization of the syrup from ethanol-water. Rf 0.65 (ethyl acetate : hexanes 1:1); mp 94.5 - 96.0 °C (lit.[298] 95.5 °C); $[\alpha]_D$ +152.0° (*c* 0.8, $CHCl_3$) (lit.[298] +106.7 °); ^{1}H NMR δ 6.38 (d, 1H, $J_{1,2}$ = 2.6 Hz, H-1), 5.50 (m, 1H, H-4), 5.37 - 5.31 (m, 2H, H-2, H-3), 4.36 (m, 1H, $J_{4,5}$ = 1.4 Hz, H-5), 4.10, 4.06 (m, 2H, $J_{6a,6b}$ = 10.0 Hz, $J_{5,6a}$ = 6.6 Hz, $J_{5,6b}$ = 6.7 Hz, H-6a, H-6b), 2 × 2.16, 2.04, 2.02, 2.01 (4s, 15H, 5 × $COCH_3$); ^{13}C NMR[299] δ 170.4, 2 × 170.1, 169.9, 168.9 (5 × *C*OCH_3), 89.7 (C-1), 68.8 (C-5), 67.4, 67.3(C-2, C-3), 66.4(C-4), 61.2 (C-6), 2 × 20.9, 2 × 20.7, 20.6 (5 × CO*C*H_3).

6.26 2,3,4,6-Tetra-*O*-acetyl-α-D-galactopyranosyl bromide (75)

Phosphorus tribromide (10 mL, 0.10 mol) was added to a solution of the crude **74** in dichloromethane (400 mL). Water (4 mL, 0.22 mol) was added to the clear colorless solution dropwise at 0 °C. The obtained yellow milky solution was stirred for 4 h at rt to give a two phase solution. After removal of the bottom yellow layer by a separatory

funnel, the organic layer was neutralized with potassium carbonate (100 g) under a vigorous mechanical stirring, filtered through a bed of Celite. The solid was washed with dichloromethane (2 × 100 mL). The combined colorless organic layers were concentrated to the title compound **75** as a pale yellow syrup (31.46 g, 95.6 % in two steps). The bromide was used in the next step reaction without further purification.

A pure colorless syrup of title compound could be obtained by flash column chromatography (ethyl acetate : hexanes 1 : 3). Rf 0.65 (ethyl acetate : hexanes 1:1); ^{1}H NMR δ 6.63 (d, 1H, $J_{1,2}$ = 3.9 Hz, H-1), 5.43 (dd, 1H, $J_{3,4}$ = 3.3 Hz, $J_{4,5}$ = 1.2 Hz, H-4), 5.32 (dd, 1H, $J_{2,3}$ = 10.6 Hz, H-3), 4.96 (dd, 1H, H-2), 4.41 (ddd, 1H, $J_{5,6a}$ = $J_{5,6b}$ = 6.4 Hz, H-5), 4.15 - 3.99 (m, 2H, $J_{6a,6b}$ = 11.4 Hz, H-6a, H-6b), 2.07, 2.03, 1.98, 1.93 (4s, 12H, 4 × $COCH_3$); ^{13}C NMR δ 170.3, 170.0, 169.9, 169.7 (4 × C=O), 88.2 (C-1), 71.1 (C-5), 68.0 (C-3), 67.8 (C-2), 67.0 (C-4), 60.8 (C-6), 20.7, 20.6, 20.6, 20.6 (4 × $COCH_3$).

6.27 3,4,6-Tri-*O*-acetyl-D-galactal (76)

A solution of above compound **75** (31.46 g, 0.077 mmol) in dry ethyl acetate (100 mL) was added dropwise to a refluxing suspension of zinc dust (30.20 g, 0.46 mol) and 1-methylimidazole (6.2 mL) in dry ethyl acetate (310 mL) with a vigorous mechanical stirring. The reaction mixture was refluxed for 1 h under an Argon atomosphere, cooled to rt and filtered through a bed of Celite. The solid was washed with ethyl acetate (3 × 100 mL). The green-yellow solution was washed with saturated sodium bicarbonate aqueous solution (2 ×100 mL) and distilled water (3 × 100 mL), dried over sodium sulfate anhydrous, filtered and concentrated to yield the title compound **76** as a yellow syrup. The syrup was purified by flash column chromatography (ethyl acetate : hexanes 1:3) to give a colorless syrup; 18.16 g (80.3 %); Rf 0.20 (ethyl acetate : hexanes 1:3);

$[\alpha]_D$ -15° (*c* 1.5, $CHCl_3$) (lit[192]-16.5°); ^1H NMR δ 6.47 (dd, 1H, $J_{1,2}$ = 6.3 Hz, $J_{1,3}$ = 1.7 Hz, H-1), 5.56 (m, 1H, H-3), 5.43 (dt, 1H, $J_{2,4}$ = 1.4 Hz, $J_{3,4}$ = 1.4 Hz, $J_{4,5}$ = 4.5 Hz, H-4), 4.73 (ddd, 1H, $J_{2,3}$ = 2.6 Hz, H-2), 4.40 (m, 3H, $J_{5,6a}$ = 6.5 Hz, $J_{5,6b}$ = 6.1 Hz, $J_{6a,6b}$ = 11.1 Hz, H-5, H-6a, H-6b), 2.13, 2.09, 2.03(3s, 9H, 3 × $COCH_3$); ^{13}C NMR δ 170.6, 170.3, 170.1 (3 × C=O), 145.4 (C-1), 98.9 (C-2), 72.8 (C-5), 63.9 (C-3), 63.8 (C-4), 61.9 (C-6), 20.81, 20.78, 20.7 (3 × $COCH_3$).

MS (ESI, *m/z*) calcd for $[C_{12}H_{16}O_7+Na]^+$: 295.1, found: 295.0.

1,2,3,4,6-penta-*O*-acetyl-β-D-galactose (**78**) was obtained as a by-product after the column chromatography as colorless crystals: yield 1.25 g; Rf 0.18 (ethyl acetate : hexanes 1:3); mp 140-141 °C (lit.[300] mp 142 °C); ^1H NMR δ 5.70 (d, 1H, $J_{1,2}$ = 8.3 Hz, H-1), 5.43 (dd, 1H, $J_{3,4}$ = 3.4 Hz, $J_{4,5}$ = 0.8 Hz, H-4), 5.33 (dd, 1H, $J_{2,3}$ = 11.4 Hz, H-2), 5.08 (dd, 1H, H-3), 4.16, 4.13 (m, 2H, $J_{6a,6b}$ = 10.0 Hz, $J_{5,6a}$ $J_{5,6b}$ = 5.0 Hz, H-6, H-6'), 4.05 (m, 1H, H-5), 2.17, 2 × 2.12, 2.05, 2.00 (4s, 15H, 5 × C=O); ^{13}C NMR δ 170.3, 170.1, 170.0, 169.4, 169.0 (5 × $COCH_3$), 92.2 (C-1), 71.7 (C-5), 70.9 (C-3), 67.9 (C-2), 66.8 (C-4), 61.0 (C-6), 20.8, 2 × 20.64, 20.62, 20.5 (5 × $COCH_3$).

6.28 D-Galactal (77)

Following Shafizadeh's method,[192] treatment of compound **76** (3.22 g, 11.8 mmol) with sodium methoxide in methanol gave D-galactal (1.65 g, 11.3 mmol, 95.8 %) as a colorless solid. mp 93 - 97 °C (lit.[192] 104 °C); [α] -10° (*c* 1.0, CH_3OH) (lit[192] +5°).

6.29 6-Bromo-1-hexanol (80)

Following a literature method[200], a toluene (100 mL) solution of 1,6-hexanediol (**79**) (9.28 g, 78.5 mmol) and aqueous hydrogen bromide (48 %, *d* 1.490, 12 mL, 106.1 mmol, 1.4 eq) were refluxed for 1 h with a Dean-Stark apparatus. This procedure gave

the title compound **80** (12.65 g, 89.0 %).

6.30 6-Azido-1-hexanol (81)

A suspension of 6-bromo-1-hexanol (12.65 g, 69.9 mmol) and sodium azide (5.45 g, 83.8 mmol, 1.2 eq) in dry DMF (100 mL) was stirred for 15 h. The reaction suspension was concentrated and dichloromethane (150 mL) was added to the residue. The resulting solution was washed with distilled water (3 × 30 mL), dried with anhydrous sodium sulfate, filtered and concentrated to a pale yellow syrup. Purification by a short silica gel column (hexanes then ethyl acetate) to remove the DMF and gave the title compound **81** as a colorless syrup: 9.09 g, (90.9 %); Rf: 0.33 (ethyl acetate : hexanes 1:4); ^{1}H NMR δ 3.61 (t, 2H, J = 6.7 Hz, 2 × H-1), 3.27 (t, 2H, J = 7.3 Hz, 2 × H-6), 2.62 (bs, 1H, OH), 1.59 (m, 4H, 2 × H-2, 2 × H-5), 1.39 (m, 4H, 2 × H-3, 2 × H-4); ^{13}C NMR δ 62.5 (C-1), 51.4 (C-6), 32.5 (C-5), 28.8 (C-2), 26.5 (C-4), 25.4 (C-3).

6.31 6-Amino-1-hexanol (82)

A solution of **81** (1.06 g, 7.40 mmol) in ethanol (8 mL) was stirred with 10 % palladium-on-charcoal (0.17 g, Degussa) under atmosphere hydrogen at rt for 24 h. The reaction mixture was filtered through a bed of Celite and the filtrate was concentrated to the title compound **82** as a colorless solid: 0.80 g (92.2 %); mp 53-56 °C (lit[201] 56-58 °C); ^{1}H NMR δ 3.57 (t, 2H, J 6.6 Hz, 2 × H-1), 3.39 (s, 1H, OH), 2.78 (s, 2H, NH_2), 2.68 (t, 2H, J = 7.0 Hz, 2 × H-6), 1.59-1.52 (m, 2H, 2 × H-2), 1.50-1.44 (m, 2H, 2 × H-5), 1.40-1.34 (m, 4H, 2 × H-3, 2 × H-4); ^{13}C NMR δ 62.1 (C-1), 41.9 (C-6), 33.3 (C-5), 32.8 (C-2), 26.7 (C-3), 25.7 (C-4).

6.32 6-Phthalimido-1-hexanol (83)

A mixture of **82** (0.72 g, 6.14 mmol) and phthalic anhydride (0.91 g, 6.14 mmol) in

an Erlenmeyer flask (25 mL) was irradiated by microwave for 1.5 min in a commercial microwave oven. The obtained slightly yellow liquid was cooled to rt. Purification by flash column chromatography (ethyl acetate : hexanes 1:2) gave a colorless liquid. Crystallization from ethyl acetate-hexanes (2 mL, 1:1) at 0 °C gave the title compound **83** as colorless crystals: 1.23 g (81.0 %); Rf: 0.18 (ethyl acetate : hexanes 1:2); mp 42-44 °C (lit[201] 46-48 °C); ^{1}H NMR δ 7.87-7.70 (m, 4H, PhH), 3.68 (t, 2H, J = 7.2 Hz, 2 × H-6), 3.63 (t, 2H, J = 6.6 Hz, 2 × H-1), 2.56 (bs, 1H, OH), 2.04-1.68 (m, 2H, 2 × H-5), 1.67-1.55 (m, 2H, 2 × H-2), 1.46-1.36 (m, 4H, 2 × H-3, 2 × H-4); ^{13}C NMR δ 168.6 (2 × C=O), 134.0, 132.2, 123.3 (Ph), 62.7 (C-1), 38.0 (C-6), 32.6 (C-2), 28.6 (C-5), 26.6 (C-4), 25.3 (C-3).

6.33 1,3,4,6-Tetra-*O*-acetyl-2-azido-2-deoxy-α-D-galactopyranose (84)

A solution of **76** (18.16 g, 66.7 mmol) in dry acetonitrile (700 mL) was added to a mixture of finely ground ceric ammonium nitrate (109.68 g, 200.1 mmol, 3.0 eq) and sodium azide (6.50 g, 100.0 mmol, 1.5 eq) at -20 °C with a vigorous stirring under an argon atmosphere. The mixture was stirred for 6 h, diluted with cooled diethyl ether (600 mL), washed with cooled distilled water until both phases became colorless, dried over anhydrous sodium sulfate, filtered and concentrated to 3,4,6-tri-*O*-acetyl-2-azido-2-deoxy-D-galactopyranosyl nitrate **88** as a yellow oil.

A solution of above compound **88** in glacial acetic acid (150 mL) was treated with anhydrous sodium acetate (10.94 g, 133.4 mmol). The mixture was stirred at 80 °C for 3 h. The mixture was cooled to rt and poured into distilled water (150 mL). The clear yellow solution was evaporated *in vacuo* to give a yellow syrup. The syrup was treated with chloroform (200 mL), washed with ice-cooled distilled water (50 mL), a saturated

aqueous sodium bicarbonate solution (3 × 50 mL) and distilled water (3 × 50 mL), dried over anhydrous sodium sulfate, filtered and concentrated to a yellow syrup. Purification by flash column chromatography (ethyl acetate : hexanes 1:3) gave the title compound **84** as a colorless solid: 10.07 g (40.5 %); Rf 0.63 (ethyl acetate : hexanes 1:1); mp: 113 – 115 °C (lit[202] 114 – 115 °C); $[\alpha]_D$ +92.5° (*c* 1, $CHCl_3$) (lit[202] +91.7°); ^{1}H NMR δ 6.32 (d, 1H, $J_{1,2}$ = 3.7 Hz, H-1), 5.48 (dd 1H, $J_{3,4}$ = 3.2 Hz, $J_{4,5}$ = 1.1 Hz, H-4), 5.32 (dd, 1H, $J_{2,3}$ = 11.0 Hz, H-3), 4.28 (t, 1H, H-5), 4.09 (m, 2H, 2 × H-6), 3.93 (dd, 1H, H-2), 2.18, 2.17, 2.08, 2.04 (4s, 12H, 4 × $COCH_3$); ^{13}C NMR δ 170.3, 170.0, 169.9, 168.7 (4 × C=O), 90.4 (C-1), 68.8 (C-3), 68.7 (C-5), 66.9 (C-4), 61.1 (C-6), 56.9 (C-2), 20.9, 20.7, 2 × 20.6 (4 × $COCH_3$).

6.34 Phenyl 3,4,6-tri-*O*-acetyl-2-azido-2-deoxy-1-thio-D-galactopyranoside (85)

Benzenethiol (14 mL, 136.0 mmol, 5 eq) was added to a solution of 1,3,4,6-tetra-*O*-acetyl-2-azido-2-deoxy-α-D-galactopyranoside **84** (10.07 g, 27.0 mmol) in chloroform (175 mL) at 0 °C. Freshly distilled boron trifluoride diethyl etherate (19 mL, 151.3 mmol, 5.6 eq) was added dropwise to the colorless clear solution. The reaction mixture was stirred at rt for 24 h. The clear orange solution was washed with an aqueous sodium thiosulfate solution (5 %, 2 × 50 mL), a saturated aqueous sodium bicarbonate solution (3 × 30 mL) and distilled water (3 × 30 mL), dried over anhydrous sodium sulfate, filtered and concentrated to a yellow liquid. The liquid was passed a short silica gel column (ethyl acetate : hexanes 1:5, then 1:1) to give the crude title compound **85** as a yellow residue which was used in the next reaction without further purification.

6.35 Phenyl 2-azido-2-deoxy-1-thio-α-D-galactopyranoside (86) and phenyl 2-azido-2-deoxy-1-thio-β-D-galactopyranoside (87)

A solution of sodium methoxide in methanol (100 mL, 1.2 M) was added in a solution of the crude thiophenyl 1,3,4,6-tetra-*O*-acetyl-2-azido-2-deoxy-D-galactopyranose **85** in methanol (100 mL). The basic solution was stirred for 1 h, neutralized by Amberlite IR-120 (H^+), filtered and concentrated to give a yellow syrup.

Pure α and β isomers were obtained by flash column chromatography (ethyl acetate : hexanes 10:1) followed by recrystallization from ethanol-hexanes.

Phenyl 2-azido-2-deoxy-1-thio-α-D-galactopyranoside (**86**) was obtained as colorless needles: 3.21 g (40.0 %); Rf: 0.34 (ethyl acetate : hexanes 10:1); mp 130.0 - 133.0 °C; $[\alpha]_D$ +252.2° (*c* 1.3, C_2H_5OH); ^1H NMR (acetone-d_6) δ 7.58 - 7.29 (m, 5H, PhH), 5.67 (d, 1H, $J_{1,2}$ = 5.4 Hz, H-1), 4.47 (d, 1H, $J_{3,OH}$ = 7.1 Hz, OH-3), 4.31 (t, 1H, H-5), 4.17 (dd, 1H, $J_{2,3}$ = 10.5 Hz, H-2), 4.15 (d, 1H, $J_{4,OH}$ = 3.7 Hz, OH-4), 4.09 (ddd, 1H, $J_{3,4}$ = 3.4 Hz, $J_{4,5}$ = 1.3 Hz, H-4), 3.84 (ddd, 1H, H-3), 3.79 - 3.69 (m, 3H, 2 × H-6, OH-6); ^{13}C NMR (acetone-d_6) δ 135.4, 133.1, 129.9, 128.2 (Ph), 88.8 (C-1), 73.2 (C-5), 71.1 (C-3), 70.0 (C-4), 62.1 (C-6), 62.0 (C-2).

HRMS (EI, *m/z*) calcd for $[C_{12}H_{15}N_3O_4S]^+$: 297.0783, found: *m/z* 297.0793.

Phenyl 2-azido-2-deoxy-1-thio-β-D-galactopyranoside (**87**) was obtained as colorless needles: 3.09 g (38.5 %); Rf: 0.26 (ethyl acetate : hexanes 10:1); mp: 149.0 - 149.5 °C; $[\alpha]_D$ +24.0° (*c* 0.3, C_2H_5OH); ^1H NMR (acetone-d_6) δ 7.58 - 7.29 (m, 5H, PhH), 4.60 (d, 1H, $J_{1,2}$ = 10.0 Hz, H-1), 4.53 (d, 1H, $J_{3,OH}$ = 7.3 Hz, OH-3), 4.05 (d, 1H, $J_{4,OH}$ = 4.1 Hz, OH-4), 3.98 (dd, 1H, $J_{3,4}$ = 3.2 Hz, $J_{4,5}$ was less than 1 Hz, H-4), 3.90 (dd, 1H, $J_{6a,OH}$ = 6.8 Hz, $J_{6b,OH}$ = 6.6 Hz, OH-6), 3.79 (m, 2H, H-6a and H-6b), 3.68 (ddd, 1H, $J_{2,3}$

= 10.5 Hz, H -3), 3.65 (dd, 1H, $J_{5,6a}$ = 6.6 Hz, $J_{5,6b}$ = 3.9 Hz, H-5), 3.57 (dd, 1H, H-2); ^{13}C NMR (acetone-d_6) δ 134.3, 132.5, 129.8, 128.3 (Ph), 86.8 (C-1), 80.1 (C-5), 74.9 (C-3), 69.3 (C-4), 64.2 (C-2), 62.2 (C-6).

HRMS (EI, *m/z*) calcd for $[C_{12}H_{15}N_3O_4S]^+$: 297.0783, found: *m/z* 297.0794.

6.36 Phenyl 2-azido-4,6-*O*-benzylidene-2-deoxy-3-*O*-(methoxyphenylmethyl)-1-thio-β-D-galactopyranoside (91)

Following the same procedure as methyl 2-acetamido-4,6-*O*-benzylidene-2-deoxy-α-D-glucopyranoside (**49**), compound **87** (1.80 g, 6.0 mmol) in DMF (20 mL) was treated with *p*-toluenesulfonic acid (20 mg) and benzaldehyde dimethyl acetal (9.1 mL, 60.0 mmol, 10.0 eq) at 40-50 °C for 7.5 h. After purification by flash column chromatography (ethyl acetate : hexanes 1:5), the title compound was obtained as colorless solid. Recrystallization from ethanol-chloroform yielded the title compound **91** as colorless needles: 2.28 g (75.2 %); Rf 0.21(ethyl acetate : hexanes 1:5); mp 132.5 - 135.5 °C ; $[\alpha]_D$ -8.5° (*c* 0.7, $CHCl_3$); ^1H NMR δ 7.35 - 7.19 (m, 15H, PhH), 5.70, 5.43 (2s, 2H, 2 × C*H*Ph), 4.36 (d, 1H, $J_{1,2}$ = 9.8 Hz, H-1), 4.36 (dd, 1H, $J_{5,6a}$ = 1.5 Hz, H-6a), 4.17 (d, 1H, $J_{3,4}$ = 3.2 Hz, H-4), 4.16 (dd, 1H, $J_{5,6b}$ = 1.5 Hz, $J_{6a,6b}$ = 12.4 Hz, H-6b), 3.79 (t, 1H, $J_{2,3}$ = 9.9 Hz, H-2), 3.64 (dd, 1H, H-3), 3.40 (s, 4H, H-5, OCH_3); ^{13}C NMR δ 137.8, 137.2, 134.3, 130.4, 129.2, 129.1, 129.0, 128.5, 128.5, 128.4, 127.1, 126.5 (Ph), 101.6, 101.1 (2 × *C*HPh), 85.4 (C-1), 75.1 (C-3), 73.2 (C-4), 69.9 (C-5), 69.5 (C-6), 59.7 (C-2), 53.6 (OCH_3).

HRMS (EI, *m/z*) calcd for $[C_{27}H_{27}N_3O_5S]^+$: 505.1671, found: 505.1651.

6.37 Phenyl 2-azido-4,6-*O*-benzylidene-2-deoxy-1-thio-α-D-galactopyranoside (92)

A solution of **86** (2.98 g, 10.0 mmol), *p*-toluenesulfonic acid (0.10 g) and

benzaldehyde (5 mL, 50.0 mmol, 5eq) in DMF-benzene (100 mL, 3:2 v/v) was refluxed using a Dean-Stark apparatus for 15 h. After TLC showed a completed disappearance of the starting material (ethyl acetate, Rf 0.45), the reaction mixture was cooled to rt, neutralized with anhydrous potassium carbonate (1.00 g), filtered and concentrated to an orange syrup. The orange syrup was purified by flash column chromatography (ethyl acetate : hexanes 1:3), then crystallized from ethanol-hexanes to give the title compound **92** as colorless needles: 3.50 g (90.9 %); Rf: 0.35 (ethyl acetate : hexanes 1:3); mp 114.5-115.5 °C; $[\alpha]_D$ 157.7° (*c* 0.8, $CHCl_3$) (lit.[208] +134.9°); ^{1}H NMR δ 7.48 - 7.28 (m, 10H, PhH), 5.76 (d, 1H, $J_{1,2}$ = 5.3 Hz, H-1), 5.62 (s, 1H, C*H*Ph), 4.34 (dd, 1H, $J_{3,4}$ = 3.4 Hz, $J_{4,5}$ = 0.8 Hz, H-4), 4.27 (bs, 1H, H-5), 4.26 (dd, 1H, $J_{5,6a}$ = 1.6 Hz, $J_{6a,6b}$ = 12.5 Hz, H-6a), 4.21 (dd, 1H, $J_{2,3}$ = 10.5 Hz, H-2), 4.16 (dd, 1H, $J_{5,6b}$ = 1.5 Hz, H-6b), 4.03 (ddd, 1H, $J_{3,OH}$ = 10.4 Hz, H-3), 2.54 (d, 1H, 3-OH); ^{13}C NMR δ 137.3, 137.7, 131.2, 129.4, 129.2, 128.4, 127.4, 126.3 (Ph), 100.3 (*C*HPh), 87.3 (C-1), 75.2 (C-4), 69.5 (C-3), 69.1 (C-6), 63.7 (C-5), 61.2 (C-2).

HRMS (EI, *m/z*) calcd for $[C_{19}H_{19}N_3O_4S]^+$: 385.1096, found: 385.1107.

6.38 Phenyl 2-azido-2-deoxy-4,6-*O*-benzylidene-1-thio-β-D-galactopyranoside (93)

Following the same procedure for as **92**, compound **87** (3.21 g, 10.8 mmol) gave **93** as colorless needles; 3.70 g (88.9 %); Rf: 0.4 (ethyl acetate : hexanes 1:1); mp 79.0-80.0 °C; $[\alpha]_D$ -23.0° (*c* 0.5, $CHCl_3$); ^{1}H NMR (500 MHz) δ 7.79-7.33 (m, 10H, PhH), 5.58 (s, 1H, C*H*Ph), 4.47 (d, 1H, $J_{1,2}$ = 9.8 Hz, H-1), 4.46 (dd, 1H, $J_{5,6a}$ = 1.2 Hz, $J_{6a,6b}$ = 12.5 Hz, H-6a), 4.24 (d, 1H, $J_{3,4}$ = 3.5 Hz, 1H, H-4), 4.09 (dd, 1H, $J_{5,6b}$ = 1.4 Hz, H-6b), 3.70 (ddd, 1H, $J_{2,3}$ = 9.7 Hz, $J_{OH,3}$ = 9.8 Hz, H-3), 3.58 (dd, 1H, H-2), 3.57 (bs, 1H, H-5), 2.55 (d, 1H, 3-OH); ^{1}H NMR (acetone-d_6, 500 MHz) δ 7.74-7.31 (m, 10H, Ph), 5.68 (s,

C*H*Ph), 4.68 (d, 1H, $J_{1,2}$ = 9.9 Hz, H-1), 4.58 (d, 1H, $J_{OH,3}$ = 8.8 Hz, 3-OH), 4.33 (d, 1H, $J_{3,4}$ = 2.7 Hz, 1H, H-4), 4.27 (dd, 1H, $J_{5,6a}$ = 1.4 Hz, $J_{6a,6b}$ = 12.2 Hz, H-6a), 4.18 (dd, 1H, $J_{5,6b}$ = 1.6 Hz, H-6b), 3.81 (ddd, 1H, $J_{2,3}$ = 9.7 Hz, H-3), 3.79 (bs, 1H, H-5), 3.69 (d, 1H, H-2); ^{13}C NMR δ 139.1, 134.3, 132.5, 129.5, 129.0, 128.5, 128.3, 126.5 (Ph), 101.4 (*C*HPh), 85.1 (C-1), 74.5 (C-4), 73.3 (C-3), 69.9 (C-5), 69.3 (C-6), 62.2 (C-2); ^{13}C NMR (acetone-d_6) δ 139.0, 133.1, 132.1, 129.0, 128.8, 128.0, 127.9, 126.7 (Ph), 100.9 (*C*HPh), 84.9 (C-1), 75.5 (C-4), 73.0 (C-3), 70.1 (C-5), 69.1 (C-6), 62.5 (C-2).

HRMS (EI, *m/z*) calcd for $[C_{19}H_{19}N_3O_4S]^+$: 385.1096, found: 385.1088.

6.39 Phenyl 3-*O*-acetyl-2-azido-4,6-*O*-benzylidene-2-deoxy-1-thio-α-D-galactopyranoside (94)

Acetic anhydride (1.5 mL, 97 %, 15.0 mmol, 5eq) was added to the solution of compound **92** (1.15 g, 2.98 mmol) in dry pyridine (10 mL). The reaction mixture was stirred at rt for 24 h, concentrated *in vacuo* to give a colorless syrup. The syrup was dissolved in chloroform (15 mL). The solution was washed with a saturated aqueous sodium bicarbonate solution (3 mL) and distilled water (3 mL), dried over anhydrous sodium sulfate, filtered and concentrated to a colorless syrup. The syrup was crystallized from diethyl ether to give a colorless solid. Recrystallization from ethanol-chloroform yielded the title compound **94** as colorless needles: 1.20 g (94.3 %); mp: 154.5 - 155.5 °C; $[\alpha]_D$ +198.9° (*c* 0.6, $CHCl_3$); ^{1}H NMR δ 7.50-7.24 (m, 10H, PhH), 5.81 (d, 1H, $J_{1,2}$ = 5.3 Hz, H-1), 5.56 (s, 1H, C*H*Ph), 5.13 (dd, 1H, $J_{2,3}$ = 11.0 Hz, $J_{3,4}$ = 3.4 Hz, H-3), 4.57 (dd, 1H, H-2), 4.53 (d, 1H, H-4), 4.26 (bs, 1H, H-5), 4.22 (dd, 1H, $J_{5,6a}$ = 1.4 Hz, $J_{6a,6b}$ = 12.6 Hz, H-6a), 4.09 (dd, 1H, $J_{5,6b}$ = 1.7 Hz, H-6b), 2.16 (s, 3H, $COCH_3$); ^{13}C NMR δ 170.4 (C=O), 137.4, 133.4, 131.3, 129.2, 128.3, 127.5, 126.2 (Ph), 100.8 (*C*HPh), 87.2

(C-1), 76.7 (C-4), 73.1 (C-3), 71.4 (C-6), 63.4 (C-5), 57.8 (C-2), 21.0 ($COCH_3$); ^{13}C NMR (acetone-d_6) δ 170.6 (C=O), 139.5, 134.5, 132.9, 130.1, 129.7, 128.9, 128.5, 127.3 (Ph), 101.4 (*C*HPh), 88.3 (C-1), 74.2 (C-4), 71.5 (C-3), 69.6 (C-6), 64.7 (C-5), 59.0 (C-2), 20.8 ($COCH_3$).

HRMS (EI, *m/z*) calcd for $[C_{21}H_{21}N_3O_5S]^+$: 427.1202, found: *m/z* 427.1202.

Single crystal of **94** was obtained by recrystallization from ethanol-chloroform-toluene. An X-ray crystal structure was obtained.

6.40 Phenyl 3-*O*-acetyl-2-azido-4,6-*O*-benzylidene-2-deoxy-1-thio-β-D-galactopyranoside (95)

Following the same procedure as for **94**, compound **93** (1.05 g, 2.72 mmol) gave compound **95** as a colorless syrup: 0.99 g (85.3 %); Rf 0.18 (ethyl acetate : hexanes 1:4); $[\alpha]_D$ +4.3° (*c* 0.6, $CHCl_3$); ^1H NMR δ 7.42-7.29 (m, 10H, Ph), 5.54 (s, 1H, C*H*Ph), 4.87 (dd, 1H, $J_{2,3}$ = 10.3 Hz, $J_{3,4}$ = 3.3 Hz, H-3), 4.55 (d, 1H, $J_{1,2}$ = 9.9 Hz, H-1), 4.43, 4.06 (2dd, 2H, AB part of ABX pattern, $J_{5,6a}$ $J_{5,6b}$ = 1.5 Hz, $J_{6a,6b}$ = 12.5 Hz, H-6a, H-6b), 4.39 (d, 1H, H-4), 3.91 (dd, 1H, H-2), 3.61 (bs, 1H, H-5), 2.15 (s, 3H, $COCH_3$); ^{13}C NMR δ 170.3 (C=O), 137.6, 134.3, 130.2, 129.2, 129.0, 128.5, 128.2, 126.4 (Ph), 100.9 (*C*HPh), 85.3 (C-1), 74.0 (C-3), 72.6 (C-4), 69.6, (C-5), 69.2 (C-6), 58.3 (C-2), 20.9 ($COCH_3$).

HRMS (EI, *m/z*) calcd for $[C_{21}H_{21}N_3O_5S]^{+\cdot}$: 427.1202, found: *m/z* 427.1210.

6.41 Phenyl 3-*O*-acetyl-2-azido-4,6-*O*-benzylidene-2-deoxy-1-thio-α-D-galactopyranoside (R)$_S$-oxide (96R), phenyl 3-*O*-acetyl-2-azido-4,6-*O*-benzylidene-2-deoxy-1-thio-α-D-galactopyranoside (S)$_S$-oxide (96S) and phenyl 2-azido-4,6-*O*-benzylidene-2-deoxy-1-sulfonyl-α-D-galactopyranoside (97)

A solution of *m*-chloroperoxybenzoic acid (0.23 g, 77 %, 1.03 mmol, 1.1 eq) in

dichloromethane (2 mL) was added to a mixture of phenyl 3-*O*-acetyl-2-azido-4,6-*O*-benzylidene-2-deoxy-1-thio-α-D-galactopyranoside **94** (0.40 g, 0.94 mmol) and sodium bicarbonate (0.10 g, 1.19 mmol, 1.3 eq) in dichloromethane (8 mL) at -76 °C. The reaction mixture was stirred -76 °C for 16 h and then the temperature was allowed to rise to rt. The reaction mixture was diluted with dichloromethane (10 mL), and the resulting solution was washed with an aqueous sodium thiosulfate solution (20 %, 5 mL), a saturated aqueous sodium bicarbonate solution (5 mL) and distilled water (5 mL), dried over anhydrous sodium sulfate, filtered and concentrated to a colorless solid. Purification by flash column chromatography (ethyl acetate : hexanes 1:2) gave three compounds. All three compounds were crystallized from ethanol-hexanes to yield colorless needles.

Compound **96R**: 247.5 mg (59.6 %); Rf 0.20 (ethyl acetate : hexanes 1:2); mp 191.5-192.5 °C; $[\alpha]_D$ +4.6° (*c* 0.4, $CHCl_3$); ^{1}H NMR (500 MHz) δ 7.54 (m, 2H, *o*-SPhH), 7.45 (m, 3H, *p*-SPhH and *m*-SPhH), 7.36 (m, 5H, *o*-CH*PhH*, *m*-CH*PhH* and *p*-CH*PhH*), 5.78 (dd, 1H, $J_{2,3}$ = 10.8 Hz, $J_{3,4}$ = 3.4 Hz, H-3), 5.53 (s, 1H, C*H*Ph), 4.95 (s, 1H, $J_{1,2}$ = 5.7 Hz, H-1), 4.65 (dd, 1H, H-2), 4.62 (d, 1H, H-4), 4.11 (bs, 1H, H-5), 4.14 (dd, 1H, $J_{5,6b}$ = 1.5 Hz, H-6b), 4.02 (dd, 1H, $J_{5,6a}$ = 2.2 Hz, $J_{6a,6b}$ = 12.3 Hz, H-6a), 2.16 (s, 3H, $COCH_3$); ^{1}H NMR (acetone-d_6, 500 MHz) δ 7.86 (d, 2H, *o*-SPhH), 7.65 (t, 2H, *m*-SPhH), 7.60 (t, 2H, *p*-SPhH), 7.51 (m, 2H, *o*-CH*PhH*), 7.39 (m, 3H, *m*-CH*PhH* and *p*-CH*PhH*), 5.85 (dd, 1H, $J_{2,3}$ = 11.0 Hz, $J_{3,4}$ = 3.5 Hz, H-3), 5.69 (s, 1H, C*H*Ph), 5.15 (d, 1H, $J_{1,2}$ = 6.6 Hz, H-1), 4.78 (dd, 1H, H-2), 4.66 (d, 1H, H-4), 4.32 (bs, 1H, H-5), 4.21 (dd, 1H, $J_{5,6a}$ = 1.5 Hz, $J_{6a,6b}$ = 12.7 Hz, H-a), 4.09 (dd, 1H, $J_{5,6b}$ = 1.5 Hz, H-6b), 2.12 (s, 3H, $COCH_3$); ^{1}H NMR (CD_2Cl_2, 500 MHz) δ 7.77 (m, 2H, *o*-SPhH), 7.63 (m, 2H, *m*-SPhH), 7.61 (t, 2H, *p*-SPhH), 7.50 (m, 2H, *o*-CH*PhH*), 7.43 (m, 3H, *m*-CH*PhH* and *p*-CH*PhH*), 5.86 (dd,

1H, $J_{2,3}$ = 10.8 Hz, $J_{3,4}$ = 3.5 Hz, H-3), 5.58 (s, 1H, C*H*Ph), 5.01 (d, 1H, $J_{1,2}$ = 5.6 Hz, H-1), 4.67 (dd, 1H, H-2), 4.61 (d, 1H, H-4), 4.20 (bs, 1H, H-5), 4.15 (dd, 1H, $J_{5,6a}$ = 1.6 Hz, $J_{6a,6b}$ = 12.8 Hz, H-6a), 4.07 (dd, 1H, $J_{5,6b}$ = 1.6 Hz, H-6b), 2.19 (s, 3H, $COCH_3$); ^{1}H NMR (CD_3CN, 500 MHz) δ 7.80 (m, 2H, *o*-SPhH), 7.63 (m, 3H, *m*-SPhH and *p*-SPhH), 7.48 (m, 2H, *o*-CH*PhH*), 7.42 (m, 3H, *m*-CH*PhH* and *p*-CH*PhH*), 5.78 (dd, 1H, $J_{2,3}$ = 11.0 Hz, $J_{3,4}$ = 3.4 Hz, H-3), 5.61 (s, 1H, C*H*Ph), 5.07 (d, 1H, $J_{1,2}$ = 5.6 Hz, H-1), 4.70 (dd, 1H, H-2), 4.54 (d, 1H, H-4), 4.14 (bs, 1H, H-5), 4.05 (dd, 1H, $J_{5,6a}$ = 1.4 Hz, $J_{6a,6b}$ = 12.9 Hz, H-6a), 3.95 (dd, 1H, $J_{5,6b}$ = 1.4 Hz, H-6b), 2.17 (s, 3H, $COCH_3$); ^{13}C NMR δ 170.3 (C=O), 141.4, 137.2, 131.5, 129.4, 129.3, 128.4, 126.2, 125.0 (Ph), 100.9 (*C*HPh), 96.4 (C-1), 72.8 (C-4), 70.4 (C-3), 69.0 (C-6), 67.7 (C-5), 58.0 (C-2), 21.1 ($COCH_3$).

HRMS (EI, *m/z*) calcd for $[C_{21}H_{21}N_3O_6S\text{-}N_2]^+$: 415.1089, found: 415.1096.

Single crystals of **96R** were obtained by recrystallization from ethanol-chloroform and an X-ray structure was obtained.

Compound **96S**: 82.1 mg (19.8 %); Rf: 0.45 (ethyl acetate : hexanes 1:2); mp 197.5-198.5 °C; $[\alpha]_D$ +367.7° (*c* 0.6, $CHCl_3$); ^{1}H NMR (500 MHz) δ 7.63 (d, 2H, *o*-SPhH), 7.55 (t, 1H, *p*-SPhH), 7.52 (t, 2H, *m*-SPhH), 7.43 (m, 2H, *o*-CH*PhH*), 7.35 (m, 3H, *m*-CH*PhH* and *p*-CH*PhH*), 5.94 (dd, 1H, $J_{2,3}$ = 10.9 Hz, $J_{3,4}$ = 3.3 Hz, H-3), 5.49 (s, 1H, C*H*Ph), 4.90 (s, 1H, H-5), 4.76 (dd, 1H, $J_{1,2}$ = 6.6 Hz, H-2), 4.61 (d, 1H, H-4), 4.56 (d, 1H, H-1), 4.01 (dd, 1H, $J_{5,6b}$ = 1.4 Hz, $J_{6a,6b}$ = 12.9 Hz, H-6b), 3.90 (dd, 1H, $J_{5,6a}$ = 1.3 Hz, H-6a), 2.12 (s, 3H, $COCH_3$); NMR (acetone-d_6, 500 MHz) δ 7.78 (d, 2H, *o*-SPhH), 7.67 (t, 2H, *m*-SPhH), 7.62 (t, 2H, *p*-SPhH), 7.48 (m, 2H, *o*-CH*PhH*), 7.37 (t, 3H, *m*-CH*PhH* and *p*-CH*PhH*), 6.02 (m, 1H, H-3), 5.64 (s, 1H, C*H*Ph), 4.92 – 4.89 (m, 3H, H-1, H-2, H-5), 4.63 (d, 1H, $J_{3,4}$ = 2.5 Hz, H-4), 4.07, (dd, 1H, $J_{5,6b}$ = 1.3 Hz, $J_{6a,6b}$ = 12.8 Hz,

H-6b), 3.85 (dd, 1H, $J_{5,6a}$ = 1.4 Hz, H-6a), 2.12 (s, 3H $COCH_3$); ^{13}C NMR δ 170.0 (C=O), 140.5, 137.3, 131.1, 129.2, 129.1, 128.2, 126.0, 124.7 (Ph), 100.7 (*C*HPh), 92.5 (C-1), 73.0 (C-4), 71.2 (C-3), 68.8 (C-5), 68.7 (C-6), 57.3 (C-2), 21.0 ($COCH_3$); ^{13}C NMR (acetone-d_6) δ 169.6 (C=O), 141.4, 138.7, 130.9, 129.8, 128.8, 128.0, 126.4, 125.0 (Ph), 100.4 (*C*HPh), 92.4 (C-1), 73.2(C-4), 70.4 (C-3), 69.1 (C-5), 68.4 (C-6), 58.2 (C-2), 20.1 ($COCH_3$).

MS (ESI, *m/z*) calcd for $[C_{21}H_{21}N_3O_6S+Na]^+$: 466.0, found: 466.0; HRMS (EI, *m/z*) calcd for $[C_{21}H_{21}N_3O_6S-C_6H_5OS]^+$: 318.1090, found: 318.1098.

Single crystals of **96S** were obtained by recrystallization from ethanol-chloroform and an X-ray structure was obtained.

Compound **97**: 46.8 mg (10.8 %); Rf: 0.42 (ethyl acetate : hexanes 1:2); mp 183.0-184.0 °C; $[\alpha]_D$ +131.4 ° (*c* 0.4, $CHCl_3$); ^1H NMR (acetone-d_6, 500 MHz) δ 8.04 (d, 2H, *o*-SPhH), 7.82 (t, 1H, *p*-SPhH), 7.73 (t, 2H, *m*-SPhH), 7.41 (d, 2H, J = 7.1 Hz, *o*-CH*PhH*), 6.92 (d, 2H, *m*-CH*PhH*), 5.85 (dd, 1H, $J_{2,3}$ = 11.3 Hz, $J_{3,4}$ = 3.4 Hz, H-3), 5.63 (s, 1H, C*H*Ph), 5.55 (d, 1H, $J_{1,2}$ = 6.0 Hz, H-1), 4.83 (dd, 1H, H-2), 4.64 (bs, 1H, H-4), 4.41 (bs, 1H, H-5), 4.16 (d, 1H, $J_{6a,6b}$ = 12.4 Hz, H-6a), 3.89 (d, 1H, H-6b), 3.82 (s, 3H, OCH_3), 2.83 (s, 3H, $COCH_3$); ^1H NMR (500 MHz) δ 7.92 (d, 2H, *o*-SPhH), 7.68 (t, 1H, *p*-SPhH), 7.58 (t, 2H, *m*-SPhH), 7.44 -7.35 (m, 4H, CH*PhH*), 5.87 (dd, 1H, $J_{2,3}$ = 11.1 Hz, $J_{3,4}$ = 3.4 Hz, H-3), 5.52 (s, 1H, C*H*Ph), 5.13 (d, 1H, $J_{1,2}$ = 6.3 Hz, H-1), 4.66 (dd, 1H, H-2), 4.64 (bs, 1H, H-4), 4.35 (bs, 1H, H-5), 4.06 (d, 1H, $J_{5,6a}$ = 1.3 Hz, $J_{6a,6b}$ = 12.8 Hz, H-6a), 3.99 (d, 1H, $J_{5,6b}$ = 1.2 Hz, H-6b), 3.82 (s, 3H, OCH_3), 2.17 (s, 3H, $COCH_3$); ^{13}C NMR δ 170.1 (C=O), 138.8, 137.3, 134.4, 129.4, 128.9, 128.4, 126.1 (Ph), 100.9 (*C*HPh), 89.9 (C-1), 72.7 (C-4), 69.9 (C-3), 68.9 (C-6), 67.1 (C-5), 56.3 (C-2), 21.1 ($COCH_3$).

MS (ESI, *m/z*) calcd for $[C_{21}H_{21}N_3O_7S+Na]^+$: 482.0, found: 482.0; HRMS (EI, *m/z*) calcd for $[C_{21}H_{21}N_3O_7S\text{-}C_6H_5O_2S]^+$: 318.1090, found: 318.1092.

Single crystals of **97** were obtained by recrystallization from ethanol-chloroform.

6.42 Phenyl 2-azido-2-deoxy-4,6-*O*-(*p*-methoxybenzylidene)-1-thio-α-D-galactopyranoside (98)

A solution of phenyl 2-azido-2-deoxy-1-thio-α-D-galactopyranoside (**86**) (0.97 g, 3.26 mmol), *p*-anisaldehyde (3.2 mL), and *p*-toluenesulfonic acid (80.0 mg) in DMF-benzene (65 mL, 3:2 v/v) was refluxed for 45 h with a Dean-Stark apparatus. After TLC showed a completed disappearance of the starting material (ethyl acetate, Rf 0.45), the reaction mixture was cooled to rt, neutralized with anhydrous potassium carbonate (1.00 g), filtered and concentrated to yield a brown syrup. Purification by flash column chromatography (ethyl acetate : hexanes 1:3) gave a colorless solid. Recrystallization from ethanol-hexanes yielded the title compound **98** as colorless needles: 1.18 g (87.1 %); Rf 0.43 (ethyl acetate : hexanes 1:2); mp 133.5 - 134.0 °C; $[\alpha]_D$ +89.1° (*c* 0.5, $CHCl_3$); ^{1}H NMR δ 7.48 - 7.26 (m, 8H, PhH), 6.91 (d, 1H, PhH), 5.76 (d, 1H, $J_{1,2}$ = 5.3 Hz, H-1), 5.58 (s, 1H, C*H*Ph), 4.32 (bd, 1H, $J_{3,4}$ = 3.5 Hz, $J_{4,5}$ was less than 1 Hz, H-4), 4.26 (bs, 1H, H-5), 4.24 (bd, 1H, $J_{5,6a}$ was less than 1 Hz, H-6a), 4.20 (dd, 1H, $J_{2,3}$ = 10.6 Hz, H-2), 4.12 (dd, 1H, $J_{5,6b}$ = 1.5 Hz, $J_{6a,6b}$ = 12.3 Hz, H-6b), 4.03 (ddd, 1H, $J_{3,OH}$ = 10.4 Hz, H-3), 3.80 (s, 3H, OCH_3), 2.55 (d, 1H, 3-OH); ^{13}C NMR δ 160.5, 133.7, 131.2, 129.7, 129.2, 127.7, 127.5, 113.7 (Ph), 101.4 (*C*HPh), 87.3 (C-1), 75.1 (C-4), 69.6 (C-3), 69.2 (C-6), 63.7 (C-5), 61.5 (C-2), 55.4 (OCH_3).

6.43 Phenyl 3-*O*-acetyl-2-azido-2-deoxy-4,6-*O*-(*p*-methoxylbenzylidene)-1-thio-α-D-galactopyranoside (99)

Acetic anhydride (2 mL, 97 %, 20.0 mmol) was added to the solution of phenyl 2-azido-2-deoxy-4,6-*O*-(*p*-methoxylbenzylidene)-1-thio-α-D-galactopyranoside **98** (1.18 g, 2.84 mmol) in dry pyridine (10 mL). The reaction mixture was stirred at rt for 16 h, concentrated *in vacuo* to an orange syrup. The syrup was converted into a yellow solid residue by azeotropic distillation with toluene (3 × 4 mL) to a yellow solid residue. Recrystallization from ethanol yield the title compound **99** as colorless needles: 1.26 g (96.8 %); Rf 0.33 (ethyl acetate : hexanes 1 : 3); mp: 138.5 - 140.0 °C; $[\alpha]_D$ +206.2° (*c* 0.6, $CHCl_3$); ^{1}H NMR δ 7.50 - 6.88 (m, 9H, PhH), 5.80 (d, 1H, $J_{1,2}$ = 5.5 Hz, H-1), 5.51 (s, 1H, C*H*Ph), 5.12 (dd, 1H, $J_{2,3}$ = 11.0 Hz, $J_{3,4}$ = 3.1 Hz, H-3), 4.57(dd, 1H, H-2), 4.50 (d, 1H, H-4), 4.24 (bs, 1H, H-5), 4.20 (dd, 1H, $J_{5,6a}$ = 1.4 Hz, $J_{6a,6b}$ = 12.8 Hz, H-6a), 4.07 (dd, 1H, $J_{5,6b}$ = 1.5 Hz, H-6b), 3.81 (s, 3H, OCH_3), 2.16 (s, 3H, $COCH_3$); ^{13}C NMR δ 170.3 (C=O), 160.2, 133.4, 131.3, 130.0, 129.1, 127.5, 113.6 (Ph), 100.9 (*C*HPh), 87.3 (C-1), 73.2 (C-4), 71.4 (C-3), 69.1 (C-6), 63.4 (C-5), 57.9 (C-2), 55.3 (OCH_3), 20.9 ($COCH_3$).

HRMS (EI, *m/z*) calcd for $[C_{22}H_{23}N_3O_6S]^+$: 457.1307, found: 457.1325.

6.44 Phenyl 3-*O*-acetyl-2-azido-2-deoxy-4,6-*O*-(*p*-methoxylbenzylidene)-1-thio-α-D-galactopyranoside (*R*)$_S$-oxide (100R) and phenyl 3-*O*-acetyl-2-azido-2-deoxy-4,6-*O*-(*p*-methoxylbenzylidene)-1-thio-α-D-galactopyranoside (*S*)$_S$-oxide (100S)

Following the same procedure as for **96R** and **96S**, **100R** and **100S** were obtained from compound **99** (0.30 g), sodium bicarbonate (0.07) and *m*-chloroperoxybenzoic acid (0.13 g).

Compound **100R** was crystallized from ethanol-chloroform to give colorless needles: 217.3 mg (70.1 %); Rf 0.17 (ethyl acetate : hexanes 1:2); mp: 161.5 – 163.0 °C; $[\alpha]_D$ +44.4° (*c* 0.3, $CHCl_3$); ^{1}H NMR δ 7.71 - 6.89 (m, 9H, PhH), 5.76 (dd, 1H, $J_{2,3}$ = 11.0 Hz, $J_{3,4}$ = 3.7 Hz, H-3), 5.48 (s, 1H, C*H*Ph), 4.95 (d, 1H, $J_{1,2}$ = 5.5 Hz, H-1), 4.64 (dd, 1H, H-2), 4.60 (bd, 1H, $J_{4,5}$ was less than 1 Hz, H-4), 4.08 (bs, 1H, H-5), 4.10, 3.98 (m, 2H, $J_{5,6a}$ = 1.2 Hz, $J_{5,6b}$ = 2.4 Hz, $J_{6a,6b}$ = 12.5 Hz, H-6a, H-6b), 3.80 (s, 3H, OCH_3), 2.16 (s, 3H, $COCH_3$); ^{13}C NMR δ 170.4 (C=O), 160.4, 141.4, 129.8 131.6, 129.4, 127.6, 125.0, 113.8 (Ph), 101.0 (*C*HPh), 96.5 (C-1), 72.8 (C-4), 70.5 (C-3), 69.0 (C-6), 67.7 (C-5), 58.0 (C-2), 55.5 (OCH_3), 21.1 ($COCH_3$).

HRMS (EI, *m/z*) calcd for $[C_{22}H_{23}N_3O_7S\text{-}C_6H_5OS]^+$: 348.1195, found: 348.1188.

Single crystals of **100R** were obtained by recrystallization from ethanol-chloroform and an X-ray structure was obtained.

Compound **100S** was crystallized from ethanol-chloroform to give colorless needles: 55.9 mg (18.6 %); Rf 0.30 (ethyl acetate : hexanes 1:2); mp 224.0 – 224.5 °C; $[\alpha]_D$ +153.8° (*c* 0.3, $CHCl_3$); ^{1}H NMR δ 7.65 – 7.54 (m, 5H, PhH), 7.36, 6.87 (2d, 4H, PhH), 5.86 (dd, 1H, $J_{2,3}$ = 11.0 Hz, $J_{3,4}$ = 3.4 Hz, H-3), 5.47 (s, 1H, C*H*Ph), 5.14 (d, 1H, $J_{1,2}$ = 6.3 Hz, H-1), 4.65 (dd, 1H, H-2), 4.61 (bd, 1H, $J_{4,5}$ was less than 1 Hz, H-4), 4.43 (bs, 1H, H-5), 4.02, 3.98 (m, 2H, $J_{5,6a}$ = 1.5 Hz, $J_{5,6b}$ = 1.6 Hz, $J_{6a,6b}$ = 12.8 Hz, H-6a, H-6b), 3.79 (s, 3H, OCH_3), 2.16 (s, 3H, $COCH_3$); ^{13}C NMR δ 170.3 (C=O), 160.4, 138.7, 134.4, 129.8, 129.4, 128.9, 127.6, 113.8 (Ph), 100.9 (*C*HPh), 89.9 (C-1), 72.7 (C-4), 69.9 (C-3), 68.8 (C-6), 67.1 (C-5), 56.2 (C-2), 55.5 (OCH_3), 21.1 ($COCH_3$).

Single crystals of **100S** were obtained by recrystallization from ethanol-chloroform.

6.45 6-Phthalimidohexanyl 3-*O*-acetyl-2-azido-2-deoxy-4,6-*O*-(*p*-methoxybenzylidene)-β-D-galactopyranoside (101)

A suspension of compound **99** (104.0 mg, 0.24 mmol), compound **83** (178.1 mg, 0.72 mmol, 3 eq) and freshly activated 4Å molecular sieves (0.20 g) in dry acetonitrile (2 mL) was stirred 1 h in rt. A solution of NIS (95 %, 67.5 mg, 0.30 mmol, 1.3 eq) in acetonitrile (2 mL) was added at -40 °C, followed by adding a solution of silver triflate (78.0 mg, 0.18 mmol, 1.4 eq) in acetonitrile (1 mL). After 1 h at -40 °C, the temperature of the reaction mixture was allowed to rise to -30°C and the solution was stirred at that temperature for 36 h. The reaction was quenched by pyridine (1 mL), then diluted with dichloromethane (10 mL) and the resulting rt solution was filtered through a bed of Celite, then concentrated to a yellow residue. The title compound **101** was obtained by flash column chromatography (ethyl acetate : hexanes 1:1) as a colorless syrup: 114.0 mg (85.9 %); Rf 0.35 (ethyl acetate : hexanes 1:1); $[\alpha]_D$ -19.3° (*c* 1.0, $CHCl_3$); ^1H NMR δ 7.83, 7.69 (2m, 4H, PhthH), 7.42, 6.88 (2d, 4H, PhH), 5.45 (s, 1H, C*H*Ph), 4.68 (dd. 1H, $J_{2,3}$ = 10.8 Hz, $J_{3,4}$ = 3.4 Hz, H-3), 4.34 (d, 1H, $J_{1,2}$ = 8.0 Hz, H-1), 4.29, 4.01 (2d, 2H, $J_{6a,6b}$ = 12.7 Hz, H-6a, H-6b), 4.28 (d, 1H, H-4), 3.96, 3.52 (2m, 2H, OCH_2), 3.87 (dd, 1H, H-2), 3.80 (s, 3H, OCH_3), 3.68 (t, 2H, J = 7.3 Hz, NCH_2), 3.42 (bs, 1H, H-5), 2.13 (s, 3H, $COCH_3$), 1.72-1.40 (m, 8H, 4 × CH_2); ^{13}C NMR δ 170.5, 168.4 (3 × C=O), 160.2, 133.8, 132.2, 130.2, 127.6, 123.2, 113.6 (Ph), 102.2 (C-1), 100.9 (*C*HPh), 72.7 (C-4), 72.2(C-3), 70.0 (OCH_2), 68.9 (C-6), 66.3 (C-5), 60.4 (C-2), 55.3 (OCH_3), 38.0 (NCH_2), 29.3, 28.5, 26.6, 25.5 (4 × CH_2), 21.4 ($COCH_3$).

MS (ESI, *m/z*) calcd for $[C_{30}H_{34}N_4O_9+Na]^+$: 617.2, found: 617.4.

6.46 6-Phthalimidohexanyl 2-azido-4,6-*O*-benzylidene-2-deoxy-β-D-galactopyranoside (102)

A suspension of compound **92** (0.41 g, 1.06 mmol), **83** (0.52 g, 2.12 mmol, 2 eq) and freshly activated 4Å molecular sieves (0.50 g) in dry acetonitrile (5 mL) was stirred 1 h in rt. A solution of NIS (95 %, 0.38 g, 1.59 mmol, 1.5 eq) in acetonitrile (2 mL) was added at -40 °C, followed by adding a solution of silver triflate (0.41 g, 1.59 mmol, 1.5 eq) in acetonitrile (0.5 mL). After 24 h at -40 °C, the temperature of the reaction mixture was allowed to -30°C and was maintained at that temperature while it was stirred for 12 h. The reaction was quenched by pyridine (1 mL). The yellow suspension was filtered through a bed of Celite at rt and concentrated to a yellow syrup. The title compound **102** was obtained by flash column chromatography (ethyl acetate : hexanes 1:1.5) as a colorless syrup: 0.51 g (92.7 %); Rf 0.15 (ethyl acetate : hexanes 1:1.5); $[\alpha]_D$ -10.8° (*c* 0.7, $CHCl_3$); ^{1}H NMR δ 7.83, 7.70 (2m, 4H, PhthH), 7.50, 7.37 (2m, 5H, PhH), 5.56 (s, 1H, C*H*Ph), 4.33, 4.07 (2dd, 2H, $J_{5,6a} = J_{5,6b} = 1.5$ Hz, $J_{6a,6b} = 12.5$ Hz, H-6a, H-6b), 4.27 (d, 1H, $J_{1,2} = 7.9$ Hz, H-1), 4.17 (d, 1H, $J_{3,4} = 3.6$ Hz, H-4), 3.97, 3.52 (2m, 2H, OCH_2), 3.68 (t, 2H, J = 7.2 Hz, NCH_2), 3.61 (dd, 1H, $J_{2,3} = 10.2$ Hz, H-2), 3.54 (dd. 1H, H-3), 3.43 (bs, 1H, H-5), 2.55 (d, 1H, $J_{3,OH} = 9.5$ Hz, OH), 1.72-1.69 (m, 8H, 4 × CH_2); ^{13}C NMR δ 2 × 168.5 (2 × C=O), 137.3, 133.8, 132.2, 129.3, 128.3, 126.4, 123.2 (Ph), 102.1 (C-1), 101.5 (*C*HPh), 74.6 (C-4), 71.5 (C-3), 70.0 (OCH_2), 69.1 (C-6), 66.6 (C-5), 64.2 (C-2), 38.0 (NCH_2), 29.3, 28.5, 26.6, 25.5 (4×CH_2).

MS (ESI, *m/z*) calcd for $[C_{27}H_{30}N_4O_7+Na]^+$: 545.2, found: 545.1.

6.47 Phenyl 3-*O*-(3'-*O*-acetyl-2'-azido-4',6'-*O*-benzylidene-2'-deoxy-α-D-galactopyranosyl)-2-azido-4,6-*O*-benzylidene-2-deoxy-1-thio-β-D-galactopyranoside (103)

Triflic anhydride (100 μL, 0.59 mmol, 2.5 eq) in dichloromethane (0.5 mL) was added to a solution of **96** (101.8 mg, 0.23 mmol) and DTBMP (90.3 mg, 0.44 mmol 1.9 eq) in dichloromethane (3 mL) at -78 °C. The reaction was brought to -60 °C and stirred for 10 min, then compound **93** (113.5 mg, 0.29 mmol, 1.3 eq) in dichloromethane (2 mL) was added. The reaction was stirred for 10 h at -20 °C. A saturated aqueous sodium bicarbonate solution (1 mL) was added to quench the reaction. The reaction mixture was poured into distilled water (10 mL). The resulting mixture was extracted with dichloromethane (3 × 5 mL), and the combined organic layers were washed with a saturated aqueous sodium bicarbonate solution (3 ml) and distilled water (3 mL), dried over anhydrous sodium sulfate, filtered and concentrated to a colorless syrup. The syrup was purified by flash column chromatography to give the title compound **103** as a colorless syrup: 121.5 mg (75.2 %); Rf 0.38 (ethyl acetate : hexane 2:3); $[\alpha]_D$ +185.2° (*c* 0.5, $CHCl_3$); ^1H NMR δ 7.70 - 7.19 (m, 15H, PhH), 5.56, 5.53 (2s, 2H, 2 × C*H*Ph), 5.31 (dd, 1H, $J_{2',3'}$ = 11.0 Hz, $J_{3',4'}$ = 3.2 Hz, H-3'), 5.29 (d, 1H, $J_{1',2'}$ = 3.6 Hz, H-1'), 4.51 (d, 1H, H-4'), 4.45 (d, 1H, $J_{1,2}$ = 9.8 Hz, H-1), 4.40 (d, 1H, $J_{6a,6b}$ = 12.2 Hz, H-6a), 4.31 (d, 1H, $J_{3,4}$ = 2.6 Hz, H-4), 4.25 (d, 1H, $J_{6a',6b'}$ = 12.5 Hz, H-6a'), 4.07 (d, 1H, H-6b'), 4.04 (d, 1H, H-6b), 3.95(bs, 1H, H-5'), 3.93 (dd, 1H, H-2'), 3.83 (t, 1H, $J_{2,3}$ = 9.9 Hz, H-2), 3.71 (dd, 1H, H-3), 3.46 (bs, 1H, H-5), 2.10 (s, 3H, $COCH_3$); ^{13}C NMR δ 170.2 (C=O), 137.5, 133.8. 130.3, 129.1, 129.1, 129.0, 128.4, 128.2, 128.1, 126.2, 126.1 (Ph), 100.8, 100.7 (2 × *C*HPh), 95.1 (C1'), 85.6 (C-1), 76.5(C-3), 73.3 (C-4'), 70.6 (C-4), 69.8 (C-5), 69.3 (C-

6), 69.1 (C-6'), 69.0 (C-3'),63.3 (C-5'), 59.8 (C-2), 56.6 (C-2'), 20.9 ($COCH_3$).

6.48 Phenyl 3-*O*-(3'-*O*-acetyl-2'-azido-4',6'-*O*-benzylidene-2'-deoxy-α-D-galactopyranosyl)-2-azido-4,6-*O*-benzylidene-2-deoxy-1-thio-α-D-galactopyranoside (104)

A suspension of compound **96** (172.8 mg, 0.39 mmol, 1.5 eq) and freshly activated 4Å molecular sieves (0.21 g) in dichloromethane (5 mL) was stirred at rt for 30 min, then cooled to -78 °C. Triflic anhydride (70 μL, 0.42 mmol, 1.6 eq) was added, then a solution of compound **92** (101.4 mg, 0.26 mmol) and DTBMP (178.0 mg, 0.87 mmol, 3.3 eq) was added to the suspension dropwise at –60 °C. After 20 min at -60 °C, the reaction mixture was stirred at -30 °C for 16 h. At 0 °C, the reaction mixture was filtered through a bed of Celite into a flask containing a saturated aqueous sodium bicarbonate solution (5 mL). The aqueous layer was separated and extracted with dichloromethane (3 × 5 mL). The combined organic layers were washed with a saturated aqueous sodium bicarbonate solution (4 mL) and distilled water (4 mL), dried over anhydrous sodium sulfate, filtered, and concentrated to a yellow syrup. The syrup was purified by flash column chromatography (ethyl acetate : hexanes 1:2) to give the title compound **104** as a colorless syrup: 113.5 mg (62.1 %); Rf 0.49 (ethyl acetate : hexanes 2:3); $[\alpha]_D$ +159.8° (*c* 0.5, chloroform); ^{1}H NMR δ 7.57 - 7.27 (m, 15H, PhH), 5.80 (d, 1H, $J_{1,2}$ = 5.3 Hz, H-1), 5.64, 5.57 (2s, 2H, 2 × C*H*Ph), 5.44 (dd, 1H, $J_{2',3'}$ = 11.0 Hz, $J_{3',4'}$ = 3.1 Hz, H-3'), 5.41 (d, 1H, $J_{1',2'}$ = 5.3 Hz, H-1'), 4.57 (d, 1H, $J_{3,4}$ = 3.1 Hz, H-4), 4.55 (dd, 1H, $J_{2,3}$ = 11.0 Hz, H-2), 4.50 (d, 1H, H-4'), 4.34 (dd, 1H, $J_{5,6a}$ = 1.5 Hz, $J_{6a,6b}$ = 12.8 Hz, H-6a), 4.28 (dd, 1H, $J_{5',6a'}$ = 1.7 Hz, $J_{6a',6b'}$ = 12.8 Hz, H-6a'), 4.22 (bs, 1H, H-5'), 4.16 (dd, 1H, $J_{5,6b}$ = 1.3 Hz, H-6b), 4.14 (dd, 1H, $J_{5',6b'}$ = 1.7 Hz, H-6b'), 4.10 (dd, 1H, H-3), 4.22 (bs, 1H, H-5), 3.96

(dd, 1H, H-2'), 2.14 (s, 3H, $COCH_3$); ^{13}C NMR δ 170.25 (C=O), 137.51, 137.23, 133.34 131.22, 129.21, 129.15, 128.98, 128.26, 128.15, 127.58, 126.13, 125.95 (Ph), 100.81 (2 × *C*HPh), 94.42 (C-1'), 87.16 (C-1), 73.46 (C-4), 72.58 (C-5), 70.96 (C-4'), 69.34 (C-6), 69.20 (C-6'), 68.83 (C-3'), 63.57 (C-5'), 63.38 (C-3), 59.35 (C-2), 56.51 (C-2'), 20.94 ($COCH_3$)

6.49 Phenyl 2-acetamido-3-*O*-(2'-acetamido-3'-*O*-acetyl-4',6'-*O*-benzylidene-2'-deoxy-α-D-galactopyranosyl)-4,6-*O*-benzylidene-2-deoxy-1-thio-β-D-galactopyranoside (105)

A solution of compound **103** (113.0 mg, 0.16 mmol) in thioacetic acid (1 mL) was stirred at rt for 24 h. A yellow syrup was obtained after removal of solvent. The syrup was purified by flash column chromatography (ethyl acetate : hexanes =1:3 then ethyl acetate) to give the title compound **105** as a colorless syrup: 60.1 mg (51.1 %); Rf 0.21 (ethyl acetate); $[\alpha]_D$ +114.2° (*c* 0.3, CH_3Cl_3); ^1H NMR δ 7.65 - 7.28 (m, 15H, PhH), 5.78 (d, 1H, $J_{2,NH}$ = 7.8 Hz, NH), 5.65 (d, 1H, $J_{2',NH'}$ = 9.6 Hz, NH'), 5.49, 5.39 (2s, 2H, 2 × C*H*Ph), 5.25 (d, 1H, $J_{1,2}$ = 10.1 Hz, H-1), 5.10 (d, 1H, $J_{1',2'}$ = 3.6 Hz, H-1'), 5.31 (dd, 1H, $J_{2',3'}$ = 11.2 Hz, $J_{3',4'}$ = 3.2 Hz, H-3'), 4.69 (dd, 1H, H-2'), 4.50 (dd, 1H, $J_{2,3}$ = 10.3 Hz, $J_{3,4}$ = 2.6 Hz, H-3), 4.31 (d, 1H, $J_{6a,6b}$ = 12.4 Hz, H-6a), 4.26 (d, 1H, H-4'), 4.22 (d, 1H, $J_{6a',6b'}$ = 12.1 Hz, H-6a'), 4.21 (d, 1H, H-4), 3.98 (d, 1H, H-6b'), 3.96 (d, 1H, H-6b), 3.75 (dd, 1H, H-2), 3.67(s, 1H, H-5'), 3.54 (s, 1H, H-5), 2.03, 1.99, 1.98 (3s, 9H, 3 × $COCH_3$); ^{13}C NMR δ 170.4, 170.4, 170.1 (3 × C=O), 137.7, 137.4, 133.5, 131.2, 129.4, 129.1, 128.3, 128.2, 126.5, 126.3 (Ph), 101.1, 100.9 (2 × *C*HPh), 93.9 (C-1'), 83.7 (C-1), 73.5 (C-4'), 72.4 (C-3), 70.8 (C-4), 69.6 (C-5), 69.5 (C-6), 69.4 (C-3'),69.1 (C-6'), 63.2 (C-5'), 51.1 (C-2), 46.8 (C-2'), 23.6, 22.5, 21.0 (3 × $COCH_3$).

6.50 6-Phthalimidohexanyl 3-*O*-(3'-*O*-acetyl-2'-azido-4',6'-*O*-benzylidene-2'-deoxy-α-D-galactopyranosyl)-2-azido-4,6-*O*-benzylidene-2-deoxy-β-D-galactopyranoside (106) and 6-phthalimidohexanyl 3-*O*-(3'-*O*-acetyl-2'-azido-4',6'-*O*-benzylidene-2'-deoxy-β-D-galactopyranosyl)-2-azido-4,6-*O*-benzylidene-2-deoxy-β-D-galactopyranoside (106β)

Method A: A suspension of **95** (0.30 g, 0.70 mmol, 1.4 eq), **102** (0.26 g, 0.50 mmol) and freshly activated 4Å molecular sieves (0.30 g) in dry acetonitrile (5 mL) was stirred for 1 h in rt. NIS (95 %, 0.19 g, 0.86 mmol, 1.7 eq) in acetonitrile (2 mL) was added at -40 °C, followed by silver triflate (99 %, 0.22 g, 0.86 mmol, 1.7 eq) in acetonitrile (1 mL). After 1 h at -40 °C, the temperature of the reaction mixture was allowed to -30 °C and it was stirred for 48 h at that temperature. The reaction was quenched by adding pyridine (1 mL) at -30 °C. The reaction mixture was diluted with dichloromethane (10 mL) and the resulting rt reaction mixture was filtered through a bed of Celite and concentrated to a yellow syrup. Flash column chromatography (ethyl acetate : hexanes 1:1) yielded the title compound **106** as a colorless syrup: 0.19 g (45.2 %); Rf 0.40 (ethyl acetate : hexanes 1:1); $[\alpha]_D$ +31.5° (*c* 0.5, $CHCl_3$); ^{1}H NMR δ 7.89, 7.71 (2m, 4H, PhthH), 7.58 - 7.31 (m, 10H, PhH), 5.63, 5.89 (2s, 2H, 2 × C*H*Ph), 5.43 (dd, 1H, $J_{2',3'}$ = 11.1 Hz, $J_{3'4'}$ = 3.3 Hz, H-3'), 5.34 (d, 1H, $J_{1'2'}$ = 3.4 Hz, H-1'), 4.55 (d, 1H, H-4'), 4.31 (d, 1H, $J_{1,2}$ = 8.2 Hz, H-1), 4.29 (d, 1H, H-4), 4.36, 4.08 (2dd, 2H, $J_{6a,6b}$ = 11.1 Hz, 2 × H-6), 4.36, 4.08 (2dd, 2H, $J_{6'a,6'b}$ = 12.4 Hz, 2 × H-6'), 4.11 (bs, 1H, H-5'), 3.97, 3.51 (2m, 2H, OCH_2), 3.94 (dd, 1H, H-2'), 3.87 (dd, 1H, $J_{2,3}$ = 10.5 Hz, H-2), 3.69 (t, 2H, J = 7.1 Hz, NCH_2), 3.63 (dd, 1H, H-3), 3.39 (bs, 1H, H-5), 2.13 (s, 3H, $COCH_3$), 1.81-1.37 (m, 8H, 4×CH_2); ^{13}C NMR δ 170.3, 168.5 (3 × C=O), 137.4, 133.8, 132.2, 129.1,

128.9, 128.2, 128.1, 126.1, 123.2 (Ph), 102.3 (C-1), 101.0, 100.8 (2 × *C*HPh), 94.9 (C-1'), 74.2 (C-3), 73.4 (C-4'), 70.8 (C-4), 69.9 (OCH_2), 69.2, 69.2 (C-6, C-6'), 69.1 (C-3'), 66.4 (C-5), 63.1 (C-5'), 61.4 (C-2 '), 56.6 (C-2), 38.0 (NCH_2), 29.3, 28.5, 26.6, 25.5 (4 × CH_2), 20.9 ($COCH_3$).

MS (ESI, *m/z*) calcd for $[C_{42}H_{45}N_7O_{12}+Na]^+$: 862.3, found: 862.3.

Compound **106β** was a colorless syrup: 0.10 g (23.8 %); Rf 0.18 (ethyl acetate : hexanes 1:1); $[\alpha]_D$ +105.5° (*c* 0.5, $CHCl_3$); ^1H NMR δ 7.84, 7.70 (2m, 4H, PhthH), 7.58 - 7.31 (m, 10H, PhH), 5.59, 5.53 (2s, 2H, 2 × C*H*Ph), 4.81 (d, 1H, $J_{1'2'}$ = 8.0 Hz, H-1'), 4.78 (dd. 1H, $J_{2',3'}$ = 10.8 Hz, $J_{3'4'}$ = 3.3 Hz, H-3'), 4.36 (d, 1H, H-4), 4.32 (d, 1H, $J_{1,2}$ = 8.0 Hz, H-1), 4.32 (d, 1H, H-4'), 4.28, 4.04 (2dd, 2H, $J_{6a,6b}$ = 10.6 Hz, 2 × H-6), 4.32, 4.07 (2dd, 2H, $J_{6'a,6'b}$ = 10.8 Hz, 2 × H-6'), 4.00 (dd, 1H, H-2'), 4.00, 3.54 (2m, 2H, OCH_2), 3.94 (dd, 1H, $J_{2,3}$ = 10.5 Hz, H-2), 3.70 (t, 2H, J = 7.2 Hz, NCH_2), 3.62 (dd, 1H, H-3), 3.48 (bs, 1H, H-5'), 3.37 (bs, 1H, H-5), 2.16 (s, 3H, $COCH_3$), 1.74-1.38 (m, 8H, 4 × CH_2); ^{13}C NMR δ 170.4, 2 × 168.3 (3 × C=O), 137.7, 137.5, 133.8, 132.0, 129.0, 128.6, 128.2, 128.0, 126.23, 126.16, 123.1 (Ph), 102.8 (C-1'), 102.4 (C-1), 100.7, 100.6 (2 × *C*HPh), 77.3 (C-3), 75.1 (C-4), 72.4 (C-4'), 71.8 (C-3'), 69.8 (OCH_2), 2 x 68.9 (C-6, C-6'), 66.5 (C-5), 66.2 (C-5'), 62.5 (C-2), 60.1 (C-2'), 37.8 (NCH_2), 29.2, 28.4, 26.5, 25.4 (4 × CH_2), 20.8 ($COCH_3$).

MS (ESI, *m/z*) calcd for $[C_{42}H_{45}N_7O_{12}+Na]^+$: 862.3, found: 862.4.

Method B: following the same procedure as method A, compound **104** (50.2 mg, 0.071 mmol) reacted with compound **83** (30.5 mg, 0.12 mmol, 1.7 eq), NIS (95 %, 24.3 mg, 0.11 mmol, 1.5 eq) and silver triflate (99 %, 28.1 mg, 0.11 mmol, 1.5 eq) in acetonitrile at – 40 °C for 36 h yielded the title compound **106** (29.6 mg, 49.6 %).

6.51 6-Phthalimidohexanyl 3-*O*-(3'-*O*-acetyl-2'-azido-2'-deoxy-α-D-galactopyranosyl)-2-azido-2-deoxy-β-D-galactopyranoside (107)

A solution of **106** (300.0 mg, 0.35 mmol) in aqueous acetic acid solution (5 mL, 60 %) was heated at 60 °C for 1 h. Removal of solvent gave a colorless syrup. Purification by flash column chromatography (ethyl acetate) gave a colorless syrup: 10.1 mg (4.3 %); Rf 0.28 (ethyl acetate); $[\alpha]_D$ +42.3° (*c* 0.5, $CHCl_3$); ^1H NMR δ 7.89, 7.76 (2m, 4H, PhthH), 5.04 (d, 1H, $J_{1',2'}$ = 3.1 Hz, H-1'), 4.54 (dd, 1H, OH), 4.34 (t, 1H, OH), 4.32 (d, 1H, $J_{1,2}$ = 8.0 Hz, H-1), 4.18 (m, 1H, H-2'), 4.06 – 3.96 (m, 5H), 3.90 (dd, 1H, $J_{2,3}$ = 11.8 Hz, $J_{3,4}$ = 4.8 Hz, H-3), 3.84 (dd, 1H, OH). 3.72 (t, 2H, J = 7.2 Hz, NCH_2), 3.65 (dd, 2H), 3.58 (m, 1H, H-2), 3.53 – 3.49 (m, 3H), 2.13 (s, 3H, $COCH_3$), 1.76-1.40 (m, 8H, 4×CH_2); ^{13}C NMR δ 171.5, 2 × 168.5 (3 × C=O), 133.9, 133.2, 123.2 (Ph), 102.4 (C-1), 94.7 (C-1'), 76.9 (C-5), 74.0 (C-3), 70.1 (C-4'), 69.4, 2 × 68.9 (C-4, OCH_2, C-5'), 65.1 (C-3'), 62.9, 62.3 (C-6, C-6'), 61.8 (C-2'), 61.0 (C-2), 37.9 (NCH_2), 29.3, 28.5, 26.5, 25.5 (4 × CH_2), 20.9 ($COCH_3$).

MS (ESI, *m/z*) calcd for $[C_{28}H_{37}N_7O_{12}+Na]^+$: 686.2, found: 686.2.

6.52 6-Phthalimidohexanyl 3-*O*-(3'-*O*-acetyl-2'-amino-2'-deoxy-α-D-galactopyranosyl)-2-amino-2-deoxy-β-D-galactopyranoside (108)

A solution of compound **106** (100.1 mg, 0.12 mmol) in ethanol-chloroform (6 mL, 1:1 v/v) was stirred with 10 % palladium-on-charcoal (0.10 g) under hydrogen at rt for 12 h, additional palladium-on-charcoal (0.10 g) was added and the black suspension was stirred under hydrogen at rt for 12 h. TLC shown the complete disappearance of compound **106** (ethyl acetate : hexanes 1:1, Rf 0.40). The reaction mixture was filtered through a bed of Celite. The solid was washed with methanol (3 × 2 mL) and the

combined filtrates were concentrated to the title compound as a colorless syrup. The crude product was used to in the next step without further purification. Rf 0.41 (ethyl acetate : methanol : water 5:1:0.4); $[\alpha]_D$ +42.3° (*c* 0.5, CH_3OH); ^1H NMR δ 7.41 – 7.25 (m, 4H, PhthH), 5.37 (bs, 1H), 4.77 – 4.62 (m), 4.37 – 3.50 (m), 3.35 (bs, 1H), 3.17 (m, 1H), 2.20 (s, 3H, $COCH_3$), 1.70-1.39 (m, 8H, 4 × CH_2); ^{13}C NMR (CD_3OD-$CDCl_3$ 1:1) δ 179.5, 2 × 170.2 (3 × C=O), 133.3, 129.2, 128.2, 127.9 (Ph), 103.0 (C-1), 98.8 (C-1'), 77.3 (C-5, obscured by $CDCl_3$), 74.8 (C-3), 71.5, 69.5, 69.3, 67.4, 63.8, 61.4, 60.4, 56.9, 53.5, 37.2 (NCH_2), 29.1, 28.0, 26.0, 24.8 (4 × CH_2), 17.1 ($COCH_3$).

MS (ESI, *m/z*) calcd for $[C_{28}H_{41}N_3O_{12}+H]^+$: 612.3, found: 612.1.

6.53 Methyl 2-acetamido-2-deoxy-6-*O*-phosphorocholine-α-D-glucopyranoside (112)

A solution of methyl 2-acetamido-2-deoxy-α-D-glucopyranoside (**25**) (245.7 mg, 1.0 mmol) in dry pyridine (5 mL) was added diisopropyl ethyl amine (0.5 mL) and ethylene chlorophosphite (140 μL, 1.5 mmol) at -20 °C. Bromine (150 μL) was added at 0 °C after the mixture was stirred for 40 min. The mixture was stirred for 10 min at 0 °C, concentrated to give a brown syrup. The syrup was dissolved in a mixed solvent of acetonitrile-isopropanol-chloroform (5:5:3, 2mL). An aqueous trimethylamine solution (40 %, 2 mL) was added to the mixture. The resulting mixture was stirred at rt for 48 h, then concentrated to a brown syrup. The syrup was passed through a Dowex MR-3 (H-OH) mixed bed ion exchange resin column (10 g, eluent: methanol then water). The fractions containing the crude product were combined and concentrated to a brown syrup.

MS (ESI, *m/z*) calcd for $[C_{14}H_{29}N_2O_9P+Na]^+$: 423.2, found: 423.1

6.54 6-Phthalimidohexanyl 3-*O*-(3'-*O*-acetyl-2'-azido-2-deoxy-6'-*O*-phosphorylcholine-α-D-galactopyranosyl)-2-azido-2-deoxy-6-*O*-phosphorylcholine-β-D-galactopyranoside (113)

A solution of compound **107** (10.0 mg, 0.015 mmol) in dry pyridine (0.5 mL) was added diisopropylethylamine (10 μL) and ethylene chlorophosphite (5 μL, 0.054 mmol) at -20 °C. Bromine (10 μL) was added at 0 °C after the mixture had been stirred for 40 min at -20 °C. The mixture was stirred for 10 min then concentrated to a brown syrup. The syrup was dissolved in a mixed solvent of acetonitrile-isopropanol-chloroform (5:5:3, 2mL). An aqueous trimethylamine solution (40 %, 2 mL) was added to the mixture. The resulting mixture was stirred at rt for 48 h and concentrated to a brown syrup. The syrup was passed through a Dowex MR-3 (H-OH) mixed bed ion exchange resin column (2 g, eluent: methanol then water). The fractions containing the crude product were combined and concentrated to give a brown syrup. Purification by TLC (Rf 0.45, ethyl acetate : methanol : water 5:1:0.4) gave a colorless syrup: 2.5 mg (16.7 %); ^{1}H NMR (CD_3OD-$CDCl_3$ 1:1) δ 7.90-7.76 (m, 4H, PhthH), 4.68 (d, 1H, $J_{1'2'}$ = 3.6 Hz, H-1'), 4.29 (d, 1H, $J_{1,2}$ = 8.0 Hz, H-1), 4.37 - 3.49 (m), 3.23, 3.24 (2s, 18H, 6 × NCH_3), 2.10 (s, 3H, $COCH_3$), 1.76-1.40 (m, 8H, 4 × CH_2); ^{13}C NMR (CD_3OD-$CDCl_3$ 1:1) δ 172.4, 2 × 168.6 (3 × C=O), 134.0, 132.3, 123.3 (Ph), 102.7 (C-1), 98.6 (C-1'), 77.3 (C-5, obscured by $CDCl_3$), 74.2 (C-3), 71.4 (d, $^{3}J_{C,P}$ = 7 Hz, C-5'), 71.1, 70.2, 70.0 (C-4', OCH_2, C-4), 67.4 (d, $^{2}J_{C,P}$ = 6 Hz, C-6 or C-6'), 66.5 (C-3'), 64.4 (d, $^{2}J_{C,P}$ = 5 Hz, C-6 or C-6'), 62.4, 62.0 (C-2, C-2'), 59.2, 59.0 (2d, $^{2}J_{C,P}$ = 5 Hz, 2 × OCH_2), 57.9, 57.5, 56.7, 55.9, 55.0, 54.1 (6 × NCH_3), 38.0 (NCH_2), 29.3, 28.5, 26.6, 25.4 (4 × CH_2), 21.0 ($COCH_3$); ^{31}P NMR (CD_3OD-$CDCl_3$ 1:1) δ 0.30, 0.08.

MS (ESI, *m/z*) calcd for $[C_{38}H_{61}N_9O_{18}P_2+Na]^+$: 1016.4, found: 1016.6.

Appendices

A.1 Gaussian output files for geometry optimization calculations

A.1.1 Phenyl 3-*O*-acetyl-2-azido-4,6-*O*-benzylidene-2-deoxy-1-thio-α-D-galactopyranoside: phenyl *exo*, azido *anti* (94ea)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2.9418187676|O,-1.3701516023,0.1013788922,-0.2947799714|O,0.6049994478
,-0.6763939919,1.7720881207|O,-1.6081484028,-1.202218337,2.3067114879|
O,2.7679157647,-0.3152172931,0.0946922869|O,3.2752122806,-2.4245332119
,-0.5587248067|N,1.6924560208,1.8699970129,-1.4511532889|N,2.441854991
4,1.3957340602,-2.3112039997|N,3.191764966,1.104463337,-3.1211983658|C
,-0.57505501,0.8372986768,-1.1981688399|C,0.8743129577,0.9426129925,-0
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C,-1.8416092925,-1.8093855988,1.0428811957|C,-0.2577857971,-1.31749005
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167,-0.1271537898,4.4179557763|C,1.3401664875,0.3974415198,5.697654636
8|C,0.3039704008,0.3517397992,6.6317771561|C,-0.9202422273,-0.21926467
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1023,0.9149303184,-3.5781014959|C,-3.2764206829,0.9946587512,-2.819944
0178|C,-4.4232743057,1.5597492169,-3.3800630268|C,-4.4172663479,2.0164
920806,-4.6990297782|C,-3.2495622129,1.9182582613,-5.457966079|C,-2.08
99035438,1.3803597277,-4.8997962794|C,3.6057810642,-1.3797882367,-0.04
41814628|C,4.9688171482,-1.058919118,0.5145195882|H,-1.0174674588,1.83
35475451,-1.2445542059|H,0.7873316951,1.4121186623,0.3280221356|H,1.52
5460955,-1.0048717733,-1.4032407022|H,0.8722287667,-2.3040487456,0.512
7111287|H,-1.0074190221,-1.8336324754,-0.9525591296|H,-2.8879436933,-1
.619965432,0.7933243371|H,-1.6796236261,-2.898424905,1.1023157408|H,0.
0079589882,-2.3938491683,2.7120971397|H,1.9543983529,-0.0845843673,3.6
852445344|H,2.2941093077,0.8454038267,5.9633331489|H,0.448857957,0.760
7878669,7.6282202021|H,-1.7332102244,-0.2536843856,6.999781026|H,-2.06
14605191,-1.1789151882,4.7200733197|H,-3.2920325504,0.6183132146,-1.80
24171957|H,-5.3291784744,1.6285176345,-2.7834441946|H,-5.3161263965,2.
4457687388,-5.1327181239|H,-3.2332286042,2.2760111589,-6.4839983621|H,
-1.1745918709,1.3294873672,-5.4822991738|H,5.4220282925,-0.2449002734,
-0.0612646552|H,5.600813228,-1.945641778,0.459310718|H,4.8834920444,-0
.7189642648,1.551266228||Version=x86-Win32-G03RevB.05|State=1-A|HF=-17
51.3613749|RMSD=8.367e-009|RMSF=4.740e-006|Dipole=-0.5056058,-0.191145
5,0.5633219|PG=C01 [X(C21H21N3O5S1)]||@
```


A.1.2 Phenyl 3-*O*-acetyl-2-azido-4,6-*O*-benzylidene-2-deoxy-1-thio-α-D-galactopyranoside: phenyl *exo*, azido *gauche plus* (94egp)


```
1|1|UNPC-UNK|FOpt|RB3LYP|6-31G(d)|C21H21N3O5S1|PCUSER|12-Apr-2004|0||#
 OPT FREQ=NORAMAN RB3LYP/6-31G(D)||T2-9: thiophenyl galactopyranoside
N3 gauche between C3 and H2 opt freq||0,1|S,-1.3884173396,-0.336429218
1,-2.7837833485|O,-1.3815549566,-0.3281170137,-0.024937864|O,1.1765784
119,-0.3994460242,1.4531008871|O,-0.6133145762,-1.3916852019,2.5810236
```

148|O,2.6526520172,0.3365473114,-0.7400087512|O,3.5766001568,-1.585964
7607,-1.5026269856|N,0.6847481056,1.8518009205,-2.1757266375|N,1.62345
4733,2.6429422664,-2.0265317681|N,2.4520966875,3.4276099579,-2.0367764
561|C,-1.0769611636,0.4820174076,-1.1415984667|C,0.3788837402,0.983608
7777,-1.0266281737|C,1.3363084337,-0.2093556845,-0.9236288462|C,0.9295
891414,-1.1114484828,0.2438091679|C,-0.5604298217,-1.4868467629,0.1438
305083|C,-0.9927487532,-2.1579724863,1.4455207663|C,0.7734930794,-1.13
65932964,2.5947131375|C,1.1330018777,-0.3596037927,3.8407865607|C,2.21
88207336,0.522277931,3.8341575885|C,2.5781237341,1.2001942809,4.999541
7877|C,1.8589254105,0.9998929591,6.1789629615|C,0.775760971,0.11916474
48,6.1874096026|C,0.4135767348,-0.5597428539,5.0237405497|C,-3.1641431
258,-0.1423931795,-2.9387860151|C,-4.0450864876,-0.2773829637,-1.85657
83248|C,-5.4185828547,-0.1316132183,-2.0594355676|C,-5.9258287715,0.11
55513877,-3.3358664951|C,-5.0480399923,0.2313848539,-4.4154754814|C,-3
.6721360196,0.1150532619,-4.2199011855|C,3.7038356334,-0.4538016542,-1
.0947675924|C,5.0055892485,0.2812713356,-0.8982916747|H,-1.7624955314,
1.3292116254,-1.0866473301|H,0.4379715468,1.5460952937,-0.0872996902|H
,1.3245989691,-0.7973474329,-1.8465116991|H,1.533773283,-2.0310430427,
0.2199896306|H,-0.7138962112,-2.1757251837,-0.6991927022|H,-2.08023753
48,-2.2531250274,1.4815556516|H,-0.5442064299,-3.1642317969,1.49210025
9|H,1.3053624901,-2.1092461253,2.5700568757|H,2.768127273,0.6820942184
,2.9126265098|H,3.4193965634,1.8881658449,4.9843467271|H,2.1396378116,
1.5286868263,7.0860346105|H,0.2081368551,-0.0380578575,7.1007804082|H,
-0.4340017966,-1.2366772978,5.0239972203|H,-3.6590172729,-0.4934260249
,-0.8661837591|H,-6.0944828311,-0.2268308866,-1.2135145934|H,-6.996623
4079,0.2177640342,-3.4885593895|H,-5.4317360128,0.4300460889,-5.412681
6228|H,-2.9890262886,0.2345694063,-5.0559034245|H,4.9750736684,1.24823
48022,-1.4098992678|H,5.8267190626,-0.3257395906,-1.2806161943|H,5.160
1076289,0.4803277252,0.1678033348||Version=x86-Win32-G03RevB.05|State=
1-A|HF=-1751.3632981|RMSD=4.135e-009|RMSF=5.684e-006|Dipole=-0.2883041
,-0.36985,0.5865245|PG=C01 [X(C21H21N3O5S1)]||@

A.1.3 Phenyl 3-*O*-acetyl-2-azido-4,6-*O*-benzylidene-2-deoxy-1-thio-α-D-galactopyranoside ($(R)_S$-oxide: phenyl *anti*, azido *anti* (96Raa)

1|1|UNPC-UNK|FOpt|RB3LYP|6-31G(d)|C21H21N3O6S1|PCUSER|20-Sep-2004|0||#
P OPT=CALCFC RB3LYP/6-31G(D) GEOM=CONNECTIVITY||T210R-aa opt redo||0,1
|C,2.8163396724,2.4695212228,-3.1322534844|C,2.8146879863,2.4702179075
,-1.7390783779|C,4.0059953022,2.472338711,-1.0094468391|C,5.2206931808
,2.4305130571,-1.6944409124|C,5.236658171,2.4093867985,-3.0915788542|C
,4.0376441634,2.433667144,-3.8070677798|S,1.2172081634,2.6364042036,-0
.8823751527|C,1.1901073527,0.953023472,0.0388853492|O,0.6034822686,1.1
414611736,1.2933896986|C,-0.8170111713,1.3540960439,1.2938018082|C,-1.
560788872,0.2134345756,0.5819515676|C,-0.9990761103,-0.0105678541,-0.8
24763185|C,0.5196674181,-0.1949445446,-0.7516975257|C,-1.2546323983,1.
3933494565,2.755731028|O,-1.1608980036,0.1121494561,3.3624668311|C,-1.
8925660556,-0.8690487883,2.6563253565|O,-1.4185766985,-0.9974858789,1.
3214583105|N,1.2159675844,-0.4049051568,-2.0314266799|N,0.6054970343,-
0.1852762207,-3.0814647753|N,0.1795091814,-0.0431700924,-4.130199641|O
,-1.5124528355,-1.213962733,-1.4265100097|C,-2.7898922685,-1.172771085
2,-1.89063157|C,-3.1508820001,-2.4761288406,-2.5582975863|C,-1.7232469
853,-2.1955127861,3.3481673016|C,-0.4375150328,-2.6728372458,3.6282958
765|C,-0.2723275764,-3.9087929439,4.2495338364|C,-1.3890293887,-4.6763
283079,4.5939467938|C,-2.6714004767,-4.202748229,4.316168563|C,-2.8365
444922,-2.9634267649,3.69402387|O,0.1264664629,2.6306967728,-1.9444934
95|O,-3.5126369833,-0.208462081,-1.7755406303|H,2.2422454656,0.7169361

278,0.2156420807|H,0.7059471789,-1.0990701008,-0.1612743861|H,-1.26077
00776,0.8481216889,-1.4475854691|H,-2.6240103372,0.4804263887,0.500934
541|H,-1.0552627914,2.3122613649,0.8088598983|H,-0.6069549266,2.059612
5585,3.3300939173|H,-2.2892315621,1.7710748996,2.8057166002|H,-2.95638
63558,-0.5692893833,2.6180378065|H,0.421478696,-2.0653181848,3.3618024
606|H,0.7273253246,-4.2754797438,4.4670475746|H,-1.2579822965,-5.64000
55452,5.0791081107|H,-3.5426060946,-4.7944651952,4.5838523022|H,-3.835
9712645,-2.5932708354,3.4773624553|H,3.9932392024,2.5116145889,0.07765
21045|H,6.1534096203,2.4225461464,-1.1372668014|H,6.1848069066,2.38330
23025,-3.6213716763|H,4.0517065718,2.4255756856,-4.893486315|H,1.86955
33597,2.4940547407,-3.6634686945|H,-2.9659411391,-3.3131034004,-1.8778
991135|H,-2.5208831581,-2.6244368554,-3.4419298122|H,-4.2002157375,-2.
4539138861,-2.8538045245||Version=x86-Win32-G03RevB.05|State=1-A|HF=-1
826.530602|RMSD=8.963e-009|RMSF=1.036e-006|Dipole=0.8546612,-0.4842411
,0.8106087|PG=C01 [X(C21H21N3O6S1)]||@

A.1.4 Phenyl 3-*O*-acetyl-2-azido-4,6-*O*-benzylidene-2-deoxy-1-thio-α-D-galactopyranoside ($(R)_S$-oxide: phenyl *anti*, azido *gauche plus* (96Ragp)

1|1|UNPC-UNK|FOpt|RB3LYP|6-31G(d)|C21H21N3O6S1|PCUSER|26-Jan-2004|0||#
P B3LYP/6-31G* GUESS=READ GEOM=CHECK OPT=RCFC||T2-10 X-ray Structure f
requency||0,1|S,-2.6691933575,-1.3285776288,-1.0541590948|O,-0.1257482
815,-1.8855092566,-0.3766908438|O,2.0915940336,0.059793529,-0.34065447
32|O,2.7298295583,-2.1328390749,-0.8348818731|O,0.423241251,2.23370177
53,-0.316683862|O,0.5965908408,2.9719912784,-2.4516405459|O,-2.6530583
228,-0.1958530532,-2.068536631|N,-1.8923476251,1.0820434391,0.93535143
6|N,-1.6417169635,2.0757488933,1.6247356356|N,-1.5661388733,3.00727347
63,2.2797116213|C,-1.1824453083,-1.1262808033,0.1376951699|C,-0.735163
8385,0.3151613069,0.445871603|C,-0.0792535277,0.9656476708,-0.77831815
86|C,1.0427365933,0.0710257367,-1.3071916616|C,0.5304938439,-1.3591471
517,-1.543526391|C,1.717863984,-2.2782555629,-1.8216638328|C,3.1568304
272,-0.7932003017,-0.7213829977|C,4.2592177786,-0.6983410717,0.3091246
688|C,4.4561704917,0.4904764292,1.0199580297|C,5.5034270691,0.59436817
2,1.9357666255|C,6.36242734,-0.4857542002,2.1461857907|C,6.1677126866,
-1.6723340108,1.4371157316|C,5.1214108434,-1.7793356407,0.5203453052|C
,-4.0417723294,-1.0284051554,0.1027851193|C,-4.3428303013,-1.972434950
3,1.0866169607|C,-5.4527810567,-1.7659857348,1.9071116835|C,-6.2599292
155,-0.6408309812,1.7221357776|C,-5.9603387602,0.2803937738,0.71521967
69|C,-4.8475065231,0.0888754388,-0.1037419734|C,0.6957104417,3.1730726
451,-1.2627398936|C,1.1375120454,4.4615333941,-0.6137519894|H,-1.50927
33144,-1.6229105198,1.0555793792|H,0.0296148926,0.2333194378,1.2294780
404|H,-0.8196730755,1.125581229,-1.5642986348|H,1.4133325927,0.4787410
675,-2.2588889207|H,-0.1562696969,-1.3662963304,-2.4010385927|H,1.4029
635055,-3.3237599002,-1.7954224448|H,2.1169558816,-2.0488087664,-2.823
4111925|H,3.516701081,-0.4586534554,-1.7152115152|H,3.7788760883,1.322
8534458,0.8615493085|H,5.6459639944,1.5196905797,2.4878343682|H,7.1779
24759,-0.4036873388,2.8599427617|H,6.8296003865,-2.5190092817,1.599084
1597|H,4.9612230816,-2.7028511786,-0.0254406865|H,-3.7286664694,-2.861
6000923,1.2123614391|H,-5.6918576631,-2.4883999741,2.6826616603|H,-7.1
280410071,-0.487623426,2.3572589838|H,-6.594486118,1.1504027226,0.5679
12562|H,-4.58609992,0.7865318906,-0.8932432203|H,0.4077045159,4.777362
5623,0.1381314757|H,1.2535190598,5.2311185933,-1.3774660258|H,2.091956
6375,4.3080045332,-0.0984038717||Version=x86-Win32-G98RevA.9|HF=-1826.
5322037|RMSD=6.541e-009|RMSF=3.221e-006|Dipole=0.0515182,-0.5402589,0.
7950962|PG=C01 [X(C21H21N3O6S1)]||@

A.1.5 Phenyl 3-*O*-acetyl-2-azido-4,6-*O*-benzylidene-2-deoxy-1-thio-α-D-galactopyranoside ($(R)_S$-oxide: phenyl *exo*, azido *gauche minus* (96Regm)

1|1|UNPC-UNK|FOpt|RB3LYP|6-31G(d)|C21H21N3O6S1|PCUSER|15-Feb-2004|0||#
P RB3LYP/6-31G(D) OPT||T210R-exo rotate N3 45 clockwise||0,1|S,2.13759
53315,-1.784835941,1.5693125001|O,1.1800101031,0.188922008,-0.22737994
5|O,-1.6539883559,0.6208874611,-0.8764507546|O,-0.1554807179,1.4851871
7,-2.4504370761|O,-2.5512607424,-1.2612928735,0.9600540587|O,-2.929695
8828,-3.1356261133,-0.2538064644|O,2.5386713919,-1.4656234711,2.998257
9836|N,-0.4824612001,-1.1581162146,2.8387678232|N,-0.2158782983,-0.502
2997004,3.8546119082|N,-0.0113904561,-0.0177005215,4.8648849373|C,1.07
04675691,-0.238977361,1.0923020524|C,-0.3955161122,-0.4398664959,1.555
578268|C,-1.1817768196,-1.257549565,0.5334440917|C,-1.0329950091,-0.66
0671784,-0.8636044564|C,0.4509954701,-0.5309218014,-1.2269368538|C,0.5
784020392,0.2713416508,-2.5196989648|C,-1.5155470172,1.2738176535,-2.1
345387845|C,-2.2119955263,2.6060217363,-2.0538393615|C,-1.6670404879,3
.6289170106,-1.2690342394|C,-2.319276183,4.8562311037,-1.1722465159|C,
-3.5195539469,5.0694745717,-1.8566037753|C,-4.0644777066,4.0516561432,
-2.6395875779|C,-3.4100109421,2.8219623024,-2.7371951086|C,3.567769422
3,-1.3759161161,0.5227502494|C,3.7085611699,-1.9666972916,-0.733875006
|C,4.834605813,-1.6720307454,-1.5048291335|C,5.8141534955,-0.809092775
5,-1.0077438454|C,5.6767739147,-0.2477991254,0.2647595266|C,4.55297602
23,-0.5348467547,1.0395348836|C,-3.3266985946,-2.2798486914,0.50674913
95|C,-4.7168877335,-2.1831132274,1.0827839064|H,1.5674114415,0.5120682
625,1.7158190089|H,-0.8578398721,0.5527676567,1.6237001862|H,-0.814158
9425,-2.2888273905,0.5135238441|H,-1.5215813159,-1.3255410788,-1.59165
53527|H,0.8881582566,-1.5298707752,-1.3696684273|H,1.621235338,0.54416
55571,-2.6954179968|H,0.2231221514,-0.349260051,-3.3592801499|H,-1.971
8351414,0.6295126241,-2.9092421581|H,-0.7307287839,3.4547002868,-0.748
5539042|H,-1.8920318945,5.6488961509,-0.5638881371|H,-4.026241699,6.02
78972684,-1.7803082803|H,-4.995700134,4.2133404992,-3.1756952319|H,-3.
8336207853,2.028207005,-3.348347168|H,2.9600463866,-2.6646766469,-1.10
23051076|H,4.9543180623,-2.127061053,-2.4843173969|H,6.6932310631,-0.5
867889462,-1.6064205987|H,6.4494083154,0.408841816,0.6554577774|H,4.43
37521149,-0.1402796866,2.0445216834|H,-5.1546121892,-1.2081461723,0.84
59389785|H,-4.6733030862,-2.2655735545,2.173830133|H,-5.3360642978,-2.
9823577338,0.6745422317||Version=x86-Win32-G98RevA.9|HF=-1826.5269018|
RMSD=5.275e-009|RMSF=1.793e-006|Dipole=-0.3150769,0.5260901,-1.9771906
|PG=C01 [X(C21H21N3O6S1)]||@

A.1.6 Phenyl 3-*O*-acetyl-2-azido-4,6-*O*-benzylidene-2-deoxy-1-thio-α-D-galactopyranoside ($(R)_S$-oxide: phenyl *exo*, azido *gauche plus* (96Regp)

1|1|UNPC-UNK|FOpt|RB3LYP|6-31G(d)|C21H21N3O6S1|PCUSER|13-Jan-2004|0||#
 B3LYP/6-31G* OPT=RCFC GUESS=READ GEOM=CHECK||T2-10 minima #1 frequenc
y||0,1|S,-3.103621046,0.9975888766,0.39937419 27|O,-0.9701902872,-0.879
5445505,0.3089971435|O,1.8148137975,-0.194671692,-0.4139145549|O,1.274
7872384,-2.4579440198,-0.646778957|O,1.2778800181,2.5342499424,-0.5041
732292|O,1.0226109857,2.9868215031,-2.708370201 7|O,-3.7054805133,1.461
3633546,1.7091783168|N,-0.8466231461,2.6432445906,1.4033399872|N,-0.04
02241638,3.4610854742,1.856868621|N,0.5819917307,4.2999710415,2.316131
3933|C,-1.3699815303,0.2982555838,0.93864877|C,-0.2852753902,1.3912441
367,0.8714295659|C,0.2114327093,1.5756988476,-0.5659528086|C,0.6713748
613,0.2399086244,-1.1429020182|C,-0.4601835947,-0.7908754177,-1.025939
9996|C,0.0892340768,-2.1719794882,-1.3749049358|C,2.2706716308,-1.4764

598549,-0.8374364985|C,3.4808980259,-1.8387293678,-0.0184835725|C,3.33
15779436,-2.1756081833,1.3318675101|C,4.4512483541,-2.4850429995,2.101
1400245|C,5.7261446408,-2.458371365,1.5282862149|C,5.8774504177,-2.123
3893134,0.1825404971|C,4.7550414304,-1.8144751695,-0.5885866564|C,-3.8
636415094,-0.6129169917,0.0178555791|C,-3.9862555117,-1.0309175428,-1.
3079376282|C,-4.6183071576,-2.2448105061,-1.5872167239|C,-5.1362972106
,-3.0167316503,-0.5450639309|C,-5.0369995323,-2.5716976282,0.776497699
4|C,-4.4058207048,-1.361706707,1.0624964941|C,1.5793253741,3.197945197
5,-1.6542883928|C,2.6820381545,4.1965804114,-1.4118906008|H,-1.5987898
713,0.0517400911,1.9800175912|H,0.5606078463,1.0478484093,1.4790950987
|H,-0.589182724,1.9756131587,-1.1967824509|H,0.9267483508,0.3696553011
,-2.2055777556|H,-1.2705060155,-0.5335163904,-1.7225231195|H,-0.635657
6835,-2.9455812392,-1.113000373|H,0.2825600268,-2.2135214458,-2.459828
1065|H,2.5182147877,-1.4147956944,-1.9136838467|H,2.3364132184,-2.2012
576836,1.7641865474|H,4.3312219319,-2.748543765,3.1485680791|H,6.59800
11689,-2.7007310108,2.1301510079|H,6.865934302,-2.1042286548,-0.268275
3568|H,4.8720688729,-1.5541342909,-1.6381341509|H,-3.6128866205,-0.408
4236304,-2.1182815713|H,-4.7204320593,-2.5779675794,-2.6164896533|H,-5
.6337782755,-3.9575309109,-0.7642950033|H,-5.4583507561,-3.165842315,1
.5828931764|H,-4.3465932089,-0.9740517374,2.0754519301|H,3.5967409031,
3.6715685945,-1.1162734981|H,2.4105421402,4.8658744511,-0.5894801164|H
,2.8616266758,4.7685765735,-2.3225651963||Version=x86-Win32-G98RevA.11
.2|HF=-1826.5259247|RMSD=9.927e-009|RMSF=1.846e-006|Dipole=0.9387529,-
1.4974191,-1.2074263|PG=C01 [X(C21H21N3O6S1)]||@

A.1.7 Phenyl 3-*O*-acetyl-2-azido-4,6-*O*-benzylidene-2-deoxy-1-thio-α-D-galactopyranoside (S)$_S$-oxide: phenyl *exo*, azido *gauche plus* (96Sagp)

1|1|UNPC-UNK|FOpt|RB3LYP|6-31G(d)|C21H21N3O6S1|PCUSER|01-Feb-2004|0||#
 OPT RB3LYP/6-31G(D)||T210_S||0,1|S,-1.0016746437,-0.4542585142,-2.857
9618689|O,-1.4879215605,-0.4214049649,-0.1411481694|O,0.6848731048,-0.
6946175567,1.8559004415|O,-1.4177067471,-1.4011363911,2.5922812487|O,2
.6892510853,-0.3153452755,-0.0269846663|O,3.4354592141,-2.3800085971,-
0.5872108708|O,-1.8641659152,-1.6859259964,-2.63508014|N,1.2193058867,
1.3688065301,-1.8733977435|N,2.2597312521,1.9977128439,-1.6445151204|N
,3.2095698754,2.6249869402,-1.5761545525|C,-0.844568819,0.368660483,-1
.0745628227|C,0.6287036047,0.637800611,-0.7330315001|C,1.3589260728,-0
.6731122131,-0.4366841051|C,0.609849785,-1.4465831254,0.6477552422|C,-
0.855313251,-1.6608644442,0.2340316333|C,-1.6383010118,-2.19264691,1.4
304919136|C,-0.0486294195,-1.3083560466,2.9055826142|C,0.131544362,-0.
5004300557,4.1707459627|C,1.3239474625,0.1957088129,4.3969418719|C,1.5
096723569,0.900395064,5.586538262|C,0.5084393745,0.9123802708,6.559327
1691|C,-0.681419949,0.2176169757,6.3354870474|C,-0.870377214,-0.487833
7308,5.1466344799|C,-2.0806227112,0.8204327379,-3.5817673126|C,-3.4272
235221,0.5101676945,-3.7596340002|C,-4.2655751757,1.4543966268,-4.3549
888912|C,-3.7539257515,2.6865712827,-4.7681903788|C,-2.3987463258,2.97
95681478,-4.5915521991|C,-1.5493351167,2.0425702179,-4.0013739687|C,3.
6568300858,-1.2648087475,-0.174501067|C,4.9975581247,-0.7200003167,0.2
483880332|H,-1.393248147,1.309350809,-1.1394621581|H,0.652480008,1.252
6746743,0.1745621005|H,1.421857135,-1.2957541599,-1.3348937573|H,1.084
2330197,-2.4300124951,0.7860938655|H,-0.9203527175,-2.3659535502,-0.60
0864036|H,-2.7097304784,-2.1573114199,1.2243337043|H,-1.3418594412,-3.
2382630497,1.6145443585|H,0.3510949335,-2.3346027514,3.0335356458|H,2.
0952080565,0.1919468586,3.6340254066|H,2.4367997782,1.4430021493,5.751
8739455|H,0.6540141805,1.4615486929,7.4858393163|H,-1.4672649451,0.226
5394556,7.0861753677|H,-1.7971864694,-1.0208391097,4.9646818362|H,-3.7

895273149,-0.4606113874,-3.4343952322|H,-5.3186456513,1.2270148565,-4.4975371819|H,-4.4093055095,3.4177765993,-5.2334658143|H,-2.0005888792,3.9360222114,-4.9194070208|H,-0.4935676379,2.2590233524,-3.8625889058|H,5.2162752429,0.2063025374,-0.2921988955|H,5.7699222521,-1.4641979622,0.0525425329|H,4.9790265639,-0.4783540409,1.3165760883||Version=x86-Win32-G98RevA.9|HF=-1826.5332163|RMSD=1.709e-009|RMSF=1.619e-006|Dipole=0.2154364,0.8255787,0.4836142|PG=C01 [X(C21H21N3O6S1)]||@

A.1.8 Phenyl 3-*O*-acetyl-2-azido -4,6-*O*-benzylidene-2-deoxy -1-thio-α-D-galactopyranoside (*S*)$_S$-oxide: phenyl *exo-staggered*, azido *gauche plus* (96Segp)

1|1|UNPC-UNK|FOpt|RB3LYP|6-31G(d)|C21H21N3O6S1|PCUSER|01-Feb-2004|0||# OPT RB3LYP/6-31G(D)||T210_S1||0,1|S,-1.2821165858,-0.4519675934,-2.8986866757|O,-1.2892602592,-0.3310457536,-0.1241058965|O,1.173860613,0.0070809967,1.4808237676|O,-0.6126326349,-0.9613179336,2.6358942673|O,2.7511340249,0.5151934956,-0.7332296878|O,3.8328431045,-1.4594386914,-0.9830408932|O,-0.5290777672,-1.7761470397,-2.8388277882|N,0.740577691,1.6741687988,-2.4518537084|N,1.6809627697,2.4770815281,-2.4637967747|N,2.5033982002,3.2510310443,-2.6221699909|C,-0.9634201339,0.4394397928,-1.2354280482|C,0.4758066523,0.9836517699,-1.1755652332|C,1.4789992889,-0.1386083596,-0.8878614995|C,1.0585048711,-0.8896165856,0.3761713852|C,-0.3848002219,-1.3960167929,0.2434881706|C,-0.8580723076,-1.9051577994,1.6005314419|C,0.7450660534,-0.5840092049,2.7022740298|C,0.9175717014,0.4310263055,3.8015581535|C,0.0723116242,1.5452975416,3.8569022319|C,0.2413114387,2.5006845919,4.8568488151|C,1.2556766342,2.3507186407,5.8071105621|C,2.0991643698,1.2408832508,5.7546432168|C,1.9286996726,0.2831203591,4.7526389951|C,-3.0332060499,-0.816176322,-2.5632952001|C,-3.3977315543,-2.1281260778,-2.2710605433|C,-4.7457494555,-2.4292277463,-2.0683276908|C,-5.7114776143,-1.4250011011,-2.1628634493|C,-5.3343213855,-0.1153785361,-2.4724228454|C,-3.9905897869,0.1935311168,-2.6847221435|C,3.8654754542,-0.2607049957,-0.8221053901|C,5.1065535733,0.5851837112,-0.6831452151|H,-1.6697511795,1.2755636741,-1.2633490649|H,0.5174466533,1.6903569362,-0.337688322|H,1.5258147783,-0.8447790491,-1.7206788601|H,1.7234164008,-1.753356001,0.5212489192|H,-0.4320512596,-2.1921384911,-0.5046924292|H,-1.9363896158,-2.0789254144,1.5869694922|H,-0.3463136604,-2.8572061608,1.8185530463|H,1.3637445463,-1.4822916176,2.8865852067|H,-0.7174400541,1.646310572,3.1193179441|H,-0.4186812894,3.3631839787,4.8978564399|H,1.3853536207,3.0966117373,6.5868893668|H,2.887262502,1.1178654512,6.4926071207|H,2.5849432461,-0.583311188,4.7119951447|H,-2.6260590643,-2.8905877378,-2.2236941931|H,-5.0424909874,-3.4493513964,-1.8397596294|H,-6.7599247868,-1.6632625245,-2.0065284119|H,-6.0869703054,0.6635420529,-2.5580553933|H,-3.6973147136,1.2077239121,-2.9472204839|H,5.1346482581,1.0375158793,0.3140375934|H,5.0913393729,1.4020474904,-1.4115864291|H,5.9891386901,-0.0376821533,-0.8314055441||Version=x86-Win32-G98RevA.11.2|HF=-1826.5354297|RMSD=6.626e-009|RMSF=9.063e-006|Dipole=-0.9331404,0.4289059,0.913834|PG=C01 [X(C21H21N3O6S1)]||@

A.1.9 Methyl 3-*O*-acetyl-2-azido-4,6-*O*-benzylidene-2-deoxy-1-thio-α-D-galactopyranoside: methyl *anti*, azido *gauche plus* (114agp)

1|1|UNPC-UNK|FOpt|RB3LYP|6-31G(d)|C16H19N3O5S1|PCUSER|29-May-2004|0||#P OPT FREQ RB3LYP/6-31G(D) GEOM=CONNECTIVITY||thiomethyl: Me Anti O1; N3 syn H2; opt and freq||0,1|S,-1.9306297053,-0.4420750302,-3.49270837

02|O,-2.1642250953,-0.438155393,-0.7844593626|O,0.2100697939,-0.459049
3988,0.9773213633|O,-1.659126869,-1.5448771165,1.8638408156|O,1.899266
0962,0.3948304881,-1.0167100334|O,2.973689475,-1.4842159732,-1.6854871
54|N,0.0328799362,1.8617637468,-2.6465326287|N,0.9346845494,2.67160515
98,-2.4022945367|N,1.7422295675,3.4737355023,-2.3199473276|C,-1.766345
8013,0.4078520052,-1.8344368854|C,-0.3546789339,0.9627394602,-1.542202
2676|C,0.6322344773,-0.1926978662,-1.3603613032|C,0.1324628136,-1.1430
533151,-0.2704517836|C,-1.3219507098,-1.5677648225,-0.5512073054|C,-1.
8768627566,-2.2917850656,0.6743883634|C,-0.294236572,-1.2424689307,2.0
452416013|C,-0.1114639081,-0.4880175613,3.3427550578|C,0.9484280006,0.
4128721391,3.491012366|C,1.1431875754,1.0722883395,4.7050379061|C,0.28
40276619,0.8347583767,5.7793222368|C,-0.773393197,-0.0648487055,5.6332
582928|C,-0.9710324893,-0.7255991204,4.4205086236|C,-2.554101843,0.947
491284,-4.5053897022|C,3.0110243623,-0.3544194594,-1.2532955568|C,4.25
45563154,0.4203795901,-0.8954806088|H,-2.4805300084,1.2346799461,-1.84
42011153|H,-0.4162010823,1.5174609425,-0.5978916382|H,0.7394125831,-0.
7477694492,-2.2964192083|H,0.7714778191,-2.0386550471,-0.2474003022|H,
-1.3525694172,-2.2460540346,-1.4178788341|H,-2.9569685152,-2.420845762
6,0.5783104963|H,-1.4005792924,-3.2834254871,0.7488156068|H,0.27340971
71,-2.1949048316,2.0596466057|H,1.6066632555,0.6023097558,2.6498797682
|H,1.9655280359,1.7751695738,4.8099958836|H,0.4364590987,1.3493411714,
6.7244126724|H,-1.4493901361,-0.2510113732,6.4636651701|H,-1.797986762
8,-1.4169966312,4.2998602754|H,4.2594995981,1.3865539935,-1.4096930713
|H,5.1358628034,-0.1600611167,-1.1698592417|H,4.2667726639,0.623377839
4,0.18088302|H,-3.4854023848,1.3465515052,-4.0922585466|H,-2.757799828
,0.5368115375,-5.4977482572|H,-1.8046584138,1.7363181472,-4.5856031501
||Version=x86-Win32-G03RevB.05|State=1-A|HF=-1559.6249639|RMSD=5.175e-
009|RMSF=3.061e-006|Dipole=-0.0919754,-0.0001128,0.2669754|PG=C01 [X(C
16H19N3O5S1)]||@

A.1.10 Methyl 3-*O*-acetyl-2-azido-4,6-*O*-benzylidene-2-deoxy-1-thio-α-D-galactopyranoside: methyl *exo*, azido *gauche plus* (114egp)

1|1|UNPC-UNK|FOpt|RB3LYP|6-31G(d)|C16H19N3O5S1|PCUSER|30-May-2004|0||#
P OPT FREQ=NORAMAN RB3LYP/6-31G(D) GEOM=CONNECTIVITY||thiomethyl :CH3
exo; N3 gauche C3 and H2: egp||0,1|S,-2.2020396254,-0.209105654,-3.355
9391465|O,-2.1936074299,-0.3095382838,-0.612380795|O,0.3389456001,-0.3
855307234,0.9006236311|O,-1.459652259,-1.4172251068,1.9784066057|O,1.8
521848461,0.3914000067,-1.261567903|O,2.7932753083,-1.5251109001,-2.01
8652202|N,-0.1108840426,1.907071624,-2.714457663|N,0.8363176271,2.6890
388271,-2.5740349015|N,1.6708226249,3.467416757,-2.5893639282|C,-1.874
7423115,0.5457828414,-1.6891518905|C,-0.4175850074,1.0379141377,-1.564
6895863|C,0.5389627291,-0.1559519062,-1.4707071712|C,0.1207017819,-1.0
789469229,-0.3252054109|C,-1.3637854225,-1.4637188996,-0.4590159922|C,
-1.8129489363,-2.164499152,0.8217537696|C,-0.076372675,-1.1478172335,2
.0208026568|C,0.2533753858,-0.3888292653,3.2862008075|C,1.3474198812,0
.4823793732,3.319683916|C,1.6797632185,1.1453622469,4.5014216038|C,0.9
249440931,0.9408694409,5.6577461777|C,-0.1663433313,0.07091698,5.62630
13802|C,-0.5014921634,-0.5933068476,4.4460304995|C,-3.9886578978,-0.52
69175259,-3.1276835554|C,2.9103598985,-0.3945917499,-1.6028633014|C,4.
2072272436,0.3424069966,-1.3813020255|H,-2.5508367276,1.3978326368,-1.
5836413211|H,-0.3529614568,1.5985550433,-0.6247283562|H,0.5376011498,-
0.7275163392,-2.4029517202|H,0.7336154184,-1.9925364043,-0.3527936218|
H,-1.4929707585,-2.1351161046,-1.3198150122|H,-2.9003075234,-2.2673727
403,0.8374342269|H,-1.3572889666,-3.1680479041,0.8573573445|H,0.466313
8605,-2.1142952453,1.9883217363|H,1.9243248852,0.6463916329,2.41584997

51|H,2.5276896648,1.8251050927,4.5171639813|H,1.18448854,1.4581011555,
6.5777055325|H,-0.7615496031,-0.089434121,6.5214177178|H,-1.3550617711
,-1.2618220956,4.4152217617|H,4.1895961365,1.3038788485,-1.9039790275|
H,5.0374692757,-0.2680903782,-1.7374787483|H,4.3351764534,0.553218187,
-0.3140204391|H,-4.1658836054,-1.112436223,-2.223014689|H,-4.323953365
3,-1.094191513,-3.9992801508|H,-4.5507485105,0.4105014569,-3.076113358
8||Version=x86-Win32-G03RevB.05|State=1-A|HF=-1559.6278622|RMSD=3.820e
-009|RMSF=2.749e-006|Dipole=-0.3768723,-0.5324332,0.6399749|PG=C01 [X(
C16H19N3O5S1)]||@

A.1.11 Methyl 3-*O*-acetyl-2-azido-4,6-*O*-benzylidene-2-deoxy-1-thio-α-D-galactopyranoside (*S*)$_S$-oxide: methyl *anti*, azido *gauche plus* (115Sagp)

1|1|UNPC-UNK|FOpt|RB3LYP|6-31G(d)|C16H19N3O6S1|PCUSER|29-Mar-2004|0||#
P OPT=CALCFC FREQ=NORAMAN RB3LYP/6-31G(D)||Methyl Sulfoxide S: Me Anti
; N3 gauche opt freq||0,1|S,-2.1146896932,-0.456166467,-3.1542510207|O
,-2.096267491,-0.3566635903,-0.413107008|O,0.4313294991,-0.3301810593,
1.1094332308|O,-1.373373674,-1.3039566789,2.2315138204|O,1.9639838743,
0.3002258407,-1.1144574723|O,2.8650597717,-1.6570866758,-1.8145611423|
O,-3.0486520415,-1.5918413012,-2.7869215707|N,-0.0559202938,1.71179814
76,-2.6646148594|N,0.9247661762,2.4659623744,-2.6661673093|N,1.7829872
924,3.2040545613,-2.8031908615|C,-1.7606383845,0.4700545496,-1.4732553
595|C,-0.3033213609,0.9520648168,-1.4201175296|C,0.6420029244,-0.24213
71503,-1.2701128736|C,0.223355943,-1.0966853826,-0.0729950371|C,-1.256
5036072,-1.5013155256,-0.1950195957|C,-1.713529938,-2.1252153435,1.120
4350412|C,0.005684362,-1.0271699827,2.2720757371|C,0.3235956661,-0.189
3410663,3.489803314|C,1.4598542268,0.627230518,3.5005040099|C,1.782664
3053,1.3652823807,4.6392644429|C,0.9753577619,1.2911915154,5.775953168
9|C,-0.1577903062,0.4763099564,5.7673178681|C,-0.4832991342,-0.2634551
096,4.6297508087|C,-3.1211357705,0.8893798989,-3.888006858|C,3.0065896
652,-0.5139430176,-1.4451665015|C,4.316363229,0.21434787,-1.2804630714
|H,-2.4428247247,1.3226101234,-1.434538404|H,-0.1876313327,1.596789213
4,-0.5407966479|H,0.6193760374,-0.8636419843,-2.1703544185|H,0.8406110
116,-2.0075071333,-0.0456003806|H,-1.3978202673,-2.2192282235,-1.01204
62659|H,-2.7999564746,-2.2309789628,1.1274635164|H,-1.2536086715,-3.12
172364,1.2221695452|H,0.5550532779,-1.989803606,2.3016775436|H,2.07762
14021,0.6908580727,2.6108893624|H,2.6640254779,2.0012960813,4.63716763
24|H,1.2272428201,1.8667520431,6.6628018736|H,-0.7933204623,0.41729030
72,6.6469630874|H,-1.3677585095,-0.8907962782,4.6162720151|H,4.31063671
78,1.1372403142,-1.8692845075|H,5.1340337453,-0.4321882498,-1.60001934
14|H,4.4548601134,0.497176636,-0.2315145936|H,-3.9815537687,1.09117309
44,-3.2431114742|H,-3.466106802,0.5405201548,-4.8643581537|H,-2.492813
7241,1.7765540805,-4.0029570954||Version=x86-Win32-G03RevB.05|State=1-
A|HF=-1634.7974549|RMSD=6.852e-009|RMSF=9.755e-007|Dipole=0.6299613,0.
8066869,0.3371563|PG=C01 [X(C16H19N3O6S1)]||@

A.1.12 Methyl 3-*O*-acetyl-2-azido-4,6-*O*-benzylidene-2-deoxy-1-thio-α-D-galactopyranoside (*S*)$_S$-oxide: methyl *exo*, azido *gauche plus* (115Segp)

1|1|UNPC-UNK|FOpt|RB3LYP|6-31G(d)|C16H19N3O6S1|PCUSER|27-Mar-2004|0||#
P OPT=CALCFC FREQ=NORAMAN RB3LYP/6-31G(D)||Methyl Sulfoxide: Me Exo; N
3 gauche opt freq||0,1|S,-2.096450503,-0.2746748889,-3.2789523979|O,-2
.0959975908,-0.2671873341,-0.5094905732|O,0.3804739923,-0.2750444819,1
.0976374745|O,-1.5009548795,-1.1028393457,2.2115193802|O,2.0156793914,
0.1489680615,-1.0982982915|O,2.8698009513,-1.9221594592,-1.4337949154|

O,-1.4855729124,-1.6701317274,-3.2873861052|N,0.1494105877,1.59823833,
-2.75873779|N,1.1736691953,2.2907789581,-2.7399841415|N,2.0773743015,2
.9744044666,-2.8682527423|C,-1.6823251816,0.5097055529,-1.5945127018|C
,-0.1918357355,0.8880151888,-1.5118362058|C,0.6785431395,-0.3510060263
,-1.2765902009|C,0.1743901532,-1.1049048574,-0.045669972|C,-1.31433765
64,-1.4455107699,-0.1988024181|C,-1.8396886272,-1.9667648382,1.1341482
73|C,-0.1108077664,-0.871888961,2.2923462967|C,0.1622081698,0.06889304
9,3.4362199198|C,-0.5619643446,1.2620078538,3.5419787281|C,-0.29956318
5,2.1476036671,4.5850462765|C,0.6883593638,1.8486048967,5.5279766992|C
,1.411697715,0.6602432879,5.4248301951|C,1.1474130847,-0.2276009626,4.
3797707044|C,-3.8834237486,-0.4695036629,-2.9122393972|C,3.0364110105,
-0.7420922969,-1.2253318783|C,4.3645015823,-0.0459399864,-1.0614104221
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87,-0.644684531|H,0.6449171725,-1.0204744997,-2.1397364422|H,0.7415300
514,-2.0408827085,0.0614289934|H,-1.447842591,-2.1915889279,-0.9877150
219|H,-2.9302602272,-2.0315138698,1.1194514723|H,-1.4275493203,-2.9752
449827,1.3037772204|H,0.4097753273,-1.8372886298,2.4351517412|H,-1.332
3593706,1.4785663393,2.8087716245|H,-0.8658712867,3.0717074257,4.66558
4839|H,0.8907955414,2.5401397892,6.3416239726|H,2.1786361289,0.4219449
097,6.1568159852|H,1.7098580105,-1.1549909537,4.2991218769|H,4.4428523
678,0.3667277706,-0.0498304267|H,4.4414797846,0.7914283382,-1.76218049
36|H,5.171768272,-0.7583849059,-1.2336446139|H,-4.0172598436,-0.937036
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36,0.5672399,0.9042628|PG=C01 [X(C16H19N3O6S1)]||@

A.1.13 TMS

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P OPT FREQ RB3LYP/6-311+G(D,P) GEOM=CONNECTIVITY||TMS NMR||0,1|C,0.898
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22,-0.1391593238,-2.0817454988|H,-1.5875248808,-1.6068860905,-1.122771
4333|H,-2.4350008469,-0.138735678,-0.643664334|C,1.1977843813,1.037440
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)]||@

A.2 Tables of X-Ray crystallography results of phenyl 3-*O*-acetyl-2-azido -4,6-*O*-benzylidene-2-deoxy-1-thio-α-D-galactopyranoside (94), phenyl 3-*O*-acetyl-2-azido-4,6-*O*-benzylidene-2-deoxy-1-thio-α-D-galactopyranoside $(R)_S$-oxide (96R), phenyl 3-*O*-acetyl-2-azido-4,6-*O*-benzylidene-2-deoxy-1-thio-α-D-galactopyranoside $(S)_S$-oxide (96S), and phenyl 3-*O*-acetyl-2-azido-2-deoxy-4,6-*O*-(*p*-methoxybenzylidene)-1-thio-α-D-galactopyranoside $(R)_S$-oxide (100R)

Table A.1 Crystal data and details of the structure determination of compounds **94**, **96R**, **96S** and **100R**

Parameter	**94**	**96R**	**96S**	**100R**
Formula	$C_{21}H_{21}N_3O_5S$	$C_{21}H_{21}N_3O_6S$	$C_{21}H_{21}N_3O_6S$	$C_{22}H_{22}N_3O_7S$
Formula weight	427.47	443.47	443.47	473.50
Crystal System	Monoclinic	Orthorhombic	Monoclinic	Orthorhombic
Space group	$P2_1$, #4	$P2_12_12_1$ #19	$P2_1$, #4	$P2_12_12_1$ #19
Unit cell dimensions	*a* 8.712(3) Å	*a* 12.370(4) Å	*a* 8.715(1) Å	*a* 12.26(1) Å
	b 13.316(3) Å	*b* 31.24(2) Å	*b* 13.2848(9) Å	*b* 33.81(1) Å
	c 9.414(3) Å	*c* 5.494(1) Å	*c* 9.674(1) Å	*c* 5.42(1) Å
	$\alpha = 90$ °		$\alpha = 90$ °	
	$\beta = 112.28(2)$ °		$\beta = 112.792(9)$ °	
	$\gamma = 90$ °		$\gamma = 90$ °	
Volume	1010.5(6) $Å^3$	2123.1(16) $Å^3$	1032.5(2) $Å^3$	2246(4) $Å^3$
Z	2	4	2	4
Density (calculated)[Mg/m^3]	1.405	1.387	1.426	1.400
μ(MoKα) [mm^{-1}]	0.199	0.196	0.201	0.193
F(000)	448	928	464	992
Crystal size [mm^3]	0.14 x 0.17 x 0.25	0.18 x 0.23 x 0.47	0.28 x 0.22 x 0.20	0.06 x 0.11 x 0.27
Temperature [K]	173	143	296	296
Radiation [Å]	0.71070	0.71070	0.71070	0.71070
Theta Min-Max [°]	2.5, 30.1	2.6, 30.0	2.5, 30.1	2.9, 25.0
Dataset	0<=h<=12	0<=h<=17	0<=h<=12	0<=h<=13
	0<=k<=18	0<=k<=43	0<=k<=18	0<=k<=40

	-13<=l<=12	0<=l<=7	-13<=l<=12	0<=l<=6
Tot., Unq. Data, R(int)	3263, 3078, 0.074	3598, 3563, 0.530	3352, 3162, 0.018	2183, 2152, 0.000
Observed data [I > 2.0 σ(I)]	1002	1697	2467	530
Nref, Npar	1002, 145	1697, 280	3162, 280	530, 163
R, wR2, S	0.0436, 0.0490, 0.90	0.0430, 0.0480, 1.13	0.0292, 0.0827, 1.03	0.0513, 0.1208, 0.97
Max. and Av. Shift / Error	0.00, 0.00	0.00, 0.00	0.00, 0.00	0.00, 95.79
Flack x	0.05(17)	-0.01(18)	0.04(7)	0.1(5)
Largest diff. peak and hole [e/Å^3]	0.346, -0.518	0.46, -0.28	0.295, -0.185	0.373, -0.535

Table A.2 Non-hydrogen atomic coordinates and equivalent isotropic displacement parameters ($Å^2$) for compound **94**

Atom	x	y	z	U(eq)	Atom	x	y	z	U(eq)
S1	0.4499(3)	-0.05540	0.2109(3)	0.0277(6)	C7	0.4490(10)	0.0723(7)	0.1310(10)	0.022(2)
O1	0.5648(7)	0.1373(5)	0.2299(7)	0.0220(10)	C8	0.2760(10)	0.1177(7)	0.0790(10)	0.020(2)
O2	0.3698(6)	0.3077(5)	0.2654(6)	0.0200(10)	C9	0.2340(10)	0.1482(7)	0.2160(10)	0.026(2)
O3	0.6541(7)	0.3298(5)	0.3931(7)	0.0240(10)	C10	0.3700(10)	0.2095(7)	0.3293(9)	0.018(2)
O4	0.0811(7)	0.2056(5)	0.1502(7)	0.0250(10)	C11	0.5390(10)	0.1612(7)	0.3670(10)	0.024(2)
O5	0.0397(8)	0.1888(6)	0.3692(8)	0.041(2)	C12	0.6760(10)	0.2329(7)	0.4590(10)	0.027(2)
N1	0.1470(10)	0.0474(7)	-0.0193(9)	0.039(3)	C13	0.4980(10)	0.3692(7)	0.3710(10)	0.020(2)
N2	0.0820(10)	0.0700(8)	-0.1570(10)	0.040(3)	C14	0.4800(10)	0.4734(6)	0.3060(10)	0.020(2)
N3	0.0140(10)	0.0820(10)	-0.2830(10)	0.077(5)	C15	0.3270(10)	0.5103(7)	0.2120(10)	0.028(2)
C1	0.6590(10)	-0.0837(7)	0.2400(10)	0.029(2)	C16	0.3140(10)	0.6072(8)	0.1540(10)	0.035(3)
C2	0.7810(10)	-0.0753(8)	0.3810(10)	0.037(3)	C17	0.4520(10)	0.6674(8)	0.1940(10)	0.033(2)
C3	0.9470(10)	-0.0957(9)	0.4020(10)	0.050(3)	C18	0.6030(10)	0.6308(8)	0.2900(10)	0.029(2)
C4	0.9830(10)	-0.1254(9)	0.2770(10)	0.043(3)	C19	0.6180(10)	0.5360(8)	0.3460(10)	0.030(2)
C5	0.8590(10)	-0.1347(9)	0.1350(10)	0.042(3)	C20	-0.0030(10)	0.2243(8)	0.2430(10)	0.026(2)
C6	0.6970(10)	-0.1162(8)	0.1160(10)	0.034(2)	C21	-0.1480(10)	0.2900(9)	0.1650(10)	0.040(4)

U(eq) 1/3 of the trace of the orthogonalized U Tensor

Table A.3 Non-hydrogen atomic coordinates and equivalent isotropic displacement parameters ($Å^2$) for compound **96R**

Atom	x	y	z	U(eq)	Atom	x	y	z	U(eq)
S1	0.69900(10)	0.79292(4)	0.9893(3)	0.0251(3)	C7	0.3036(4)	0.8827(2)	0.7470(10)	0.0253(14)
O1	0.5209(3)	0.81490(10)	0.7502(7)	0.0230(12)	C8	0.2549(4)	0.9076(2)	0.5370(10)	0.0230(16)
O2	0.4108(3)	0.89680(10)	0.7840(7)	0.0243(12)	C9	0.3138(4)	0.9395(2)	0.4170(10)	0.0253(17)
O3	0.2989(3)	0.83850(10)	0.6891(7)	0.0277(12)	C10	0.2673(5)	0.9618(2)	0.2270(10)	0.0307(17)
O4	0.5714(3)	0.93800(10)	1.0074(8)	0.0280(12)	C11	0.1616(5)	0.9536(2)	0.1540(10)	0.0297(17)
O5	0.6596(4)	0.94260(10)	1.3607(8)	0.0533(16)	C12	0.1025(4)	0.9217(2)	0.2760(10)	0.0337(19)
O6	0.6969(3)	0.81420(10)	1.2316(7)	0.0360(12)	C13	0.1490(5)	0.8988(2)	0.4630(10)	0.0333(19)
N1	0.7529(4)	0.89000(10)	0.8439(8)	0.0247(14)	C14	0.8351(4)	0.7951(2)	0.8798(9)	0.0210(14)
N2	0.8116(4)	0.88790(10)	0.6610(9)	0.0270(14)	C15	0.8615(4)	0.7717(2)	0.6730(10)	0.0253(17)
N3	0.8752(4)	0.8873(2)	0.5140(10)	0.0397(17)	C16	0.9697(5)	0.7705(2)	0.5980(10)	0.0280(17)
C1	0.6310(4)	0.8276(2)	0.7643(9)	0.0180(12)	C17	1.0482(4)	0.7919(2)	0.7280(10)	0.0323(17)
C2	0.6397(4)	0.8762(2)	0.8003(9)	0.0190(16)	C18	1.0202(5)	0.8145(2)	0.9360(10)	0.0350(19)
C3	0.5720(4)	0.89190(10)	1.0130(10)	0.0217(14)	C19	0.9135(4)	0.8162(2)	1.0130(10)	0.0293(17)
C4	0.4578(4)	0.87600(10)	0.9890(10)	0.0230(16)	C20	0.6188(5)	0.9597(2)	1.1910(10)	0.0293(17)
C5	0.4549(4)	0.8276(2)	0.9509(9)	0.0247(17)	C21	0.6142(5)	1.0064(2)	1.1480(10)	0.042(2)
C6	0.3409(5)	0.8137(2)	0.8860(10)	0.0303(17)					

U(eq) 1/3 of the trace of the orthogonalized U Tensor

Table A.4 Non-hydrogen atomic coordinates and equivalent isotropic displacement parameters ($Å^2$) for compound **96S**

Atom	x	y	z	U(eq)	Atom	x	y	z	U(eq)
S1	0.44690(6)	0.83039(4)	0.65808(6)	0.0247(1)	C7	0.6653(3)	0.85151(15)	0.7162(2)	0.0248(6)
O1	0.57267(18)	0.63710(11)	0.71956(18)	0.0243(4)	C8	0.7227(3)	0.8759(2)	0.6051(3)	0.0371(8)
O2	0.4044(2)	0.83696(15)	0.79419(19)	0.0329(5)	C9	0.8914(4)	0.8913(3)	0.6442(3)	0.0443(9)
O3	0.08287(18)	0.56674(13)	0.64017(17)	0.0258(4)	C10	1.0010(3)	0.8859(2)	0.7945(3)	0.0408(8)
O4	0.0467(2)	0.5851(2)	0.8565(2)	0.0465(7)	C11	0.9402(3)	0.8653(2)	0.9035(3)	0.0414(8)
O5	0.37283(18)	0.46607(11)	0.75958(17)	0.0223(4)	C12	0.7714(3)	0.8474(2)	0.8648(3)	0.0325(7)
O6	0.65805(19)	0.44512(12)	0.88528(18)	0.0256(4)	C13	0.0020(3)	0.55034(19)	0.7328(3)	0.0292(7)
N1	0.1502(3)	0.71946(16)	0.4651(2)	0.0325(5)	C14	-0.1449(3)	0.4835(2)	0.6588(3)	0.0379(8)
N2	0.0852(3)	0.6947(2)	0.3320(2)	0.0353(6)	C15	0.5005(3)	0.40788(17)	0.8666(2)	0.0237(6)
N3	0.0147(4)	0.6826(3)	0.2082(3)	0.0653(12)	C16	0.4835(3)	0.30050(17)	0.8121(2)	0.0244(6)
C1	0.4508(3)	0.69486(16)	0.6103(2)	0.0223(6)	C17	0.6218(3)	0.23724(19)	0.8546(3)	0.0306(7)
C2	0.2760(3)	0.64835(17)	0.5641(2)	0.0238(5)	C18	0.6050(3)	0.13785(19)	0.8055(3)	0.0337(7)
C3	0.2339(2)	0.62504(16)	0.6994(2)	0.0225(6)	C19	0.4504(4)	0.1019(2)	0.7145(3)	0.0386(8)
C4	0.3737(3)	0.56571(17)	0.8167(2)	0.0224(5)	C20	0.3117(3)	0.1630(2)	0.6732(3)	0.0381(8)
C5	0.5420(3)	0.61559(16)	0.8531(2)	0.0232(5)	C21	0.3281(3)	0.26209(19)	0.7238(3)	0.0322(7)
C6	0.6804(3)	0.54450(18)	0.9476(3)	0.0272(6)					

U(eq) 1/3 of the trace of the orthogonalized U Tensor

Table A.5 Non-hydrogen atomic coordinates and equivalent isotropic displacement parameters ($Å^2$) for compound **100R**

Atom	x	y	z	U(eq)	Atom	x	y	z	U(eq)
S1	0.76770	0.20650	0.50760	0.0350	C7	0.63590	0.20930	0.37170	0.0290
O1	0.95560	0.18890	0.28690	0.0290	C8	0.55010	0.19010	0.48420	0.0460
O2	0.76240	0.17990	0.72320	0.0440	C9	0.44430	0.19270	0.40070	0.0470
O3	0.86300	0.07310	0.32930	0.0440	C10	0.42950	0.21620	0.19840	0.0420
O4	0.88860	0.04790	0.70480	0.0814	C11	0.50960	0.23590	0.08410	0.0500
O5	1.04910	0.11070	0.23520	0.0280	C12	0.61690	0.23350	0.17070	0.0300
O6	1.17710	0.16060	0.24800	0.0400	C13	0.87720	0.04240	0.48420	0.0570
O7	1.38830	0.03770	-0.49790	0.0480	C14	0.87240	0.00310	0.34470	0.0809
N1	0.70560	0.12920	0.22200	0.0380	C15	1.16400	0.11880	0.25580	0.0380
N2	0.67060	0.11290	0.03710	0.0439	C16	1.21710	0.10090	0.04120	0.0290
N3	0.63600	0.09770	-0.12310	0.0674	C17	1.30940	0.11780	-0.07860	0.0300
C1	0.84160	0.18100	0.26020	0.0300	C18	1.36610	0.09740	-0.26090	0.0330
C2	0.82420	0.13720	0.21670	0.0250	C19	1.33320	0.05930	-0.33530	0.0360
C3	0.87440	0.11310	0.42900	0.0210	C20	1.24450	0.04220	-0.21810	0.0460
C4	0.99460	0.12210	0.44760	0.0310	C21	1.18860	0.06230	-0.03970	0.0370
C5	1.00800	0.16740	0.47730	0.0280	C22	1.47330	0.05630	-0.63600	0.0620
C6	1.13100	0.17870	0.46180	0.0400					

U(eq) 1/3 of the trace of the orthogonalized U Tensor

A.3 NMR spectra

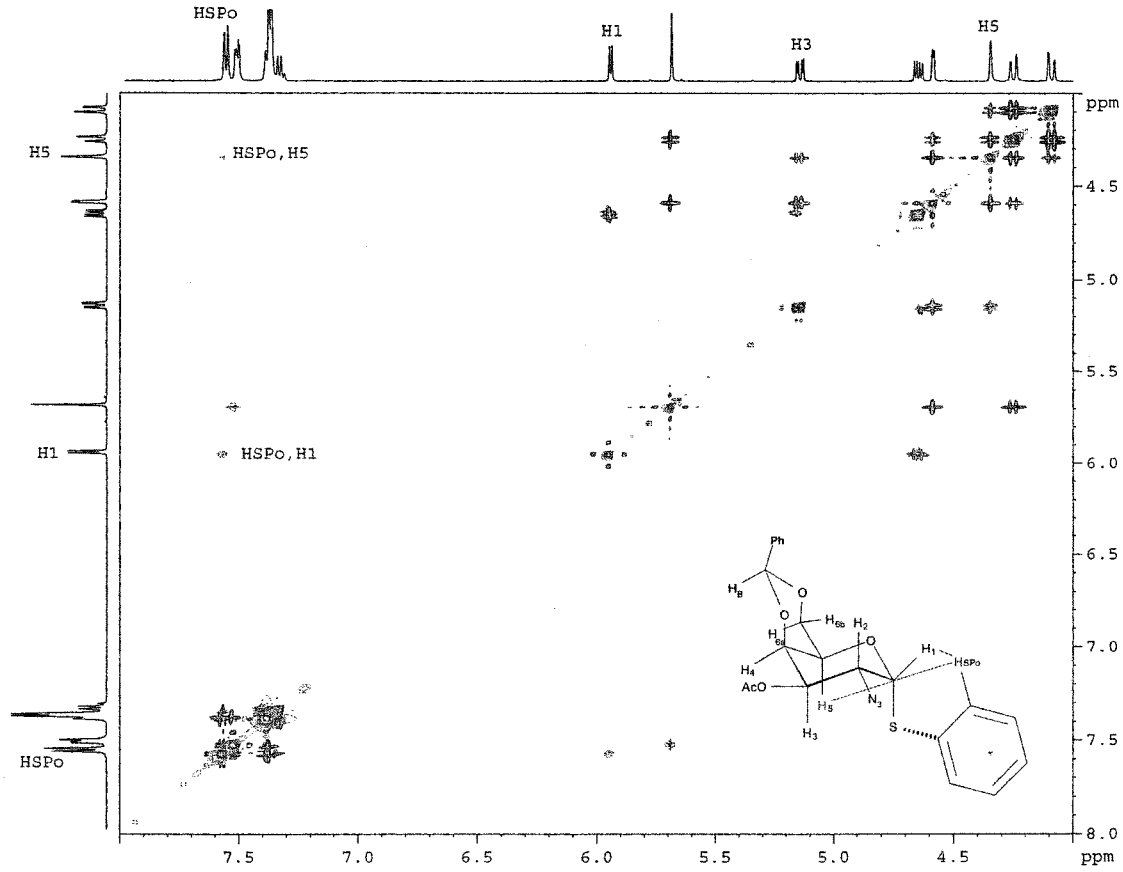

Figure A.1 NOESY spectrum of compound **94** recorded at relaxation delay (D1) = 1 sec with a mixing time (D8) of 0.3, 0.5, 0.7, 1, 1.5 sec in acetone-d_6. The best result obtained at D8 = 1 sec

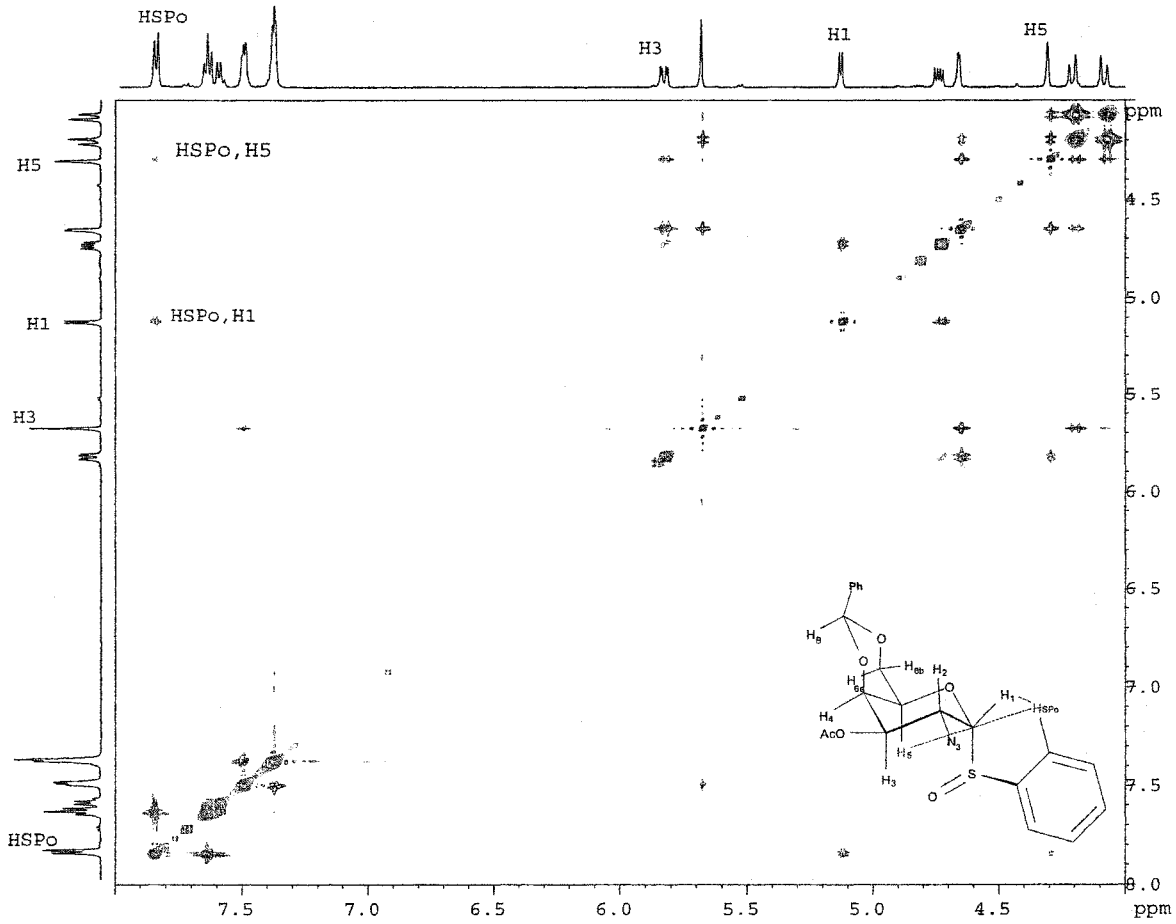

Figure A.2 NOESY spectrum of compound **96R** recorded at relaxation delay (D1) = 2.5 sec with a mixing time (D8) of 0.5, 0.7, 0.9, 1.1, 1.3 sec in acetone-d_6. The best result obtained at D8 = 0.9 sec.

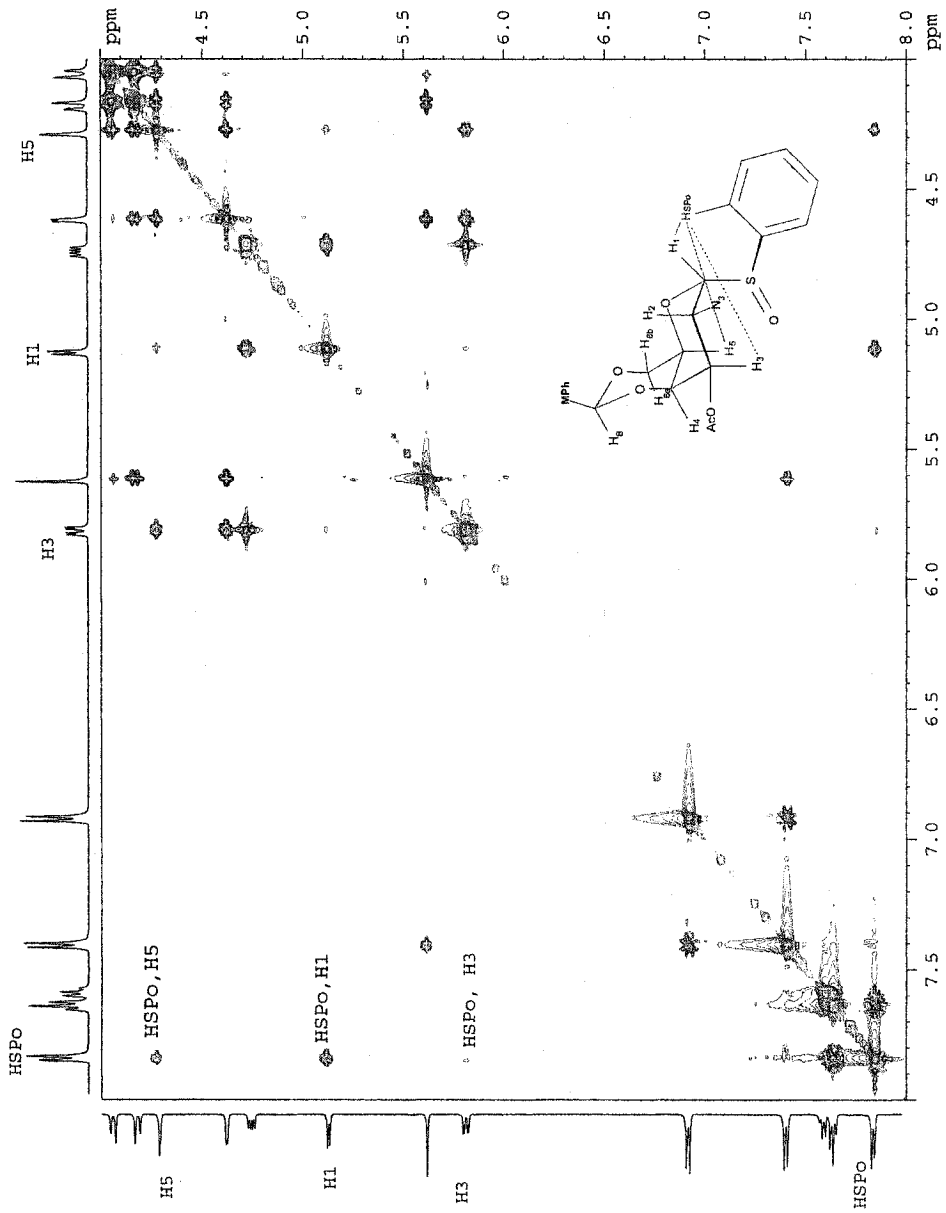

Figure A.3 NOESY spectrum of compound **100R** recorded at relaxation delay (D1) = 1 sec with different mixing times (D8) of 0.3, 0.5, 0.7, 1, 1.5 sec in acetone-d_6. The best result obtained at D8 = 1 sec.

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