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PREPARATION OF RARE SUGARS & ADVANCED DERIVATIVES FROM COMPLEX CARBOHYDRATES & CARBOHYDRATE POLYMERS

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Changyou Yuan

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PREPARATION OF RARE SUGARS & ADVANCED DERIVATIVES FROM COMPLEX CARBOHYDRATES & CARBOHYDRATE POLYMERS

By

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ABSTRACT

PREPARATION OF RARE SUGARS & ADVANCED DERIVATIVES FROM COMPLEX CARBOHYDRATES & CARBOHYDRATE POLYMERS

By

Changyou Yuan

Carbohydrates have the potential as the ultimate raw materials for highly functionalized, optically pure chemicals which were extensively used in pharmaceutical, agrichemical and biotech industry. However, these high potentials of carbohydrates remain nearly untouched due to the complex structure and often redundant hydroxyl groups of carbohydrates. The aim of this work is to develop strategies to overcome these difficulties and transform complex carbohydrates to advanced derivatives.

A protocol for the transformation of glycosides to anhydroalditols was established using Me-D-glucoside as the model compound (Chapter 2). Transformation of the free hydroxyl groups to allyl ether followed by reductive cleavage of the glycosidic bond using triethylsilane gave the protected 1,5-anhydroglucitol. Cleavage of the allyl ether bond was achieved by employing $PdCl_2/CuCl_2$ catalytic system. This Protection-Reduction-Deprotection protocol was successfully used in the transformation of complex carbohydrates, such as cellulose, starch and levan, to the corresponding anhydroalditols. The anhydroalditol, 1,5-anhydro-D-glucitol, was transformed to its 6-phosphate, and 2, 3-deoxy derivatives in Chapter 3.

The carbohydrate derivated (S)-2-hydroxyl-butyrolactone and (S)-2-hydroxyl-tetrahydrofuran were transformed to their iodo derivatives in Chapter 4. By controlling the neighboring group effect, the mono and diiodo derivatives were selectively formed.

Chapter 5 presents an efficient route to prepare cyclic nitrone from D-ribose. Optically pure iminosugar and isoxazolidines were prepared from the nitrone through stereoselective addition reactions and cycloaddition reactions.

ACKNOWLEDEMENTS

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Chapter 1

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Abstract

Carbohydrates hold the promise as the general raw materials to substitute fossil raw materials. They are renewable and available in large volume. However, the structural differences between carbohydrates and fossil based raw materials make the development of carbohydrate based chemistry challenging. At first, the structural features of carbohydrates available in large quantity are reviewed. These include polysaccharides, such as cyclodextrins and maltodextrins, monosaccharides and disaccharide, such as sucrose, lactose, maltose, fructose and xylose. In the last several decades, carbohydrates have been used extensively in the preparation of naturally occurring and medicinally important compounds. Recently, progresses have been made in the transformation of carbohydrates to general chiral 3 and 4 carbon synthons. These more general synthons have been used directly and more widely in the synthesis of medicinally important targets.

1.1 Introduction: Availability and structural features of commodity carbohydrates.

From the beginning of the industrial revolution, more and more fossil resources- coal, oil, and natural gas, have been used to provide us energy. Fossil resources have also been used as raw materials to support our more and more luxury lives, from electricity and gasoline to bulk, intermediate and fine chemicals. One big disadvantage of fossil resources is that they are not renewable and we are near the peak of the fossil material production. For petroleum this will be around 2008, for natural gas around 2020 and for coal in a few decades[1]. With the depletion of the fossil raw materials, the development of a chemical industry based on renewable resources becomes inevitable and urgent[1,2].

Biomass had been used as the major raw materials before the industrial revolution It is expected that in the next few decades, or even in the next few years, the use of biomass as raw materials for chemical industry will become economically viable with the ever increasing prices of fossil materials, it is estimated that the oil price will reach $182 per barrel within the decade[3].

The widely available biomass is composed of carbohydrates, amino acids and lipids. Among them, the most important class is carbohydrates in term of volume production, which account for roughly 75% of the annually renewable biomass of about 200 billion tons. However, majority of the carbohydrate biomass decays and only a minor fraction (ca. 4 %) is used by human beings[4].

The majority of the annually renewable carbohydrate biomass is polysaccharides, these include cellulose, starch, chitin, inulin, xylan, etc[5]. Derived from these polysaccharides are some oligosaccharides, such as cyclodextrins and maltodextrins. Monosaccharides and disaccharides, such as sucrose, lactose, fructose, maltose and xylose, are also available in bulk.

1.1.1 Polysaccharides: cellulose, starch, chitin and inulin.

Cellulose is the most abundant form of living terrestrial biomass, it is found in higher plants as the principle component of cell walls in the form of microfibrils (2-20 nm diameter and 100 - 40 000 nm long)[6]. It is a linear polymer of about 2,000-14,000 β-(1-->4)-D-glucopyranose units in $^4C_1$ conformation (Fig. 1.1 a). The usage of cellulose largely takes advantage of its ability to hold water. Uses include anticaking agents, emulsifiers, stabilizers, dispersing agents, thickeners, and gelling agents.

Chitin, the second most abundant polysaccharide in nature, can be found in the covering layer of insects, crabs, and shrimps and in the cell walls of many fungi. Each year, at least 10 gigatons of chitin are synthesized and degraded in the biosphere. Chitin mainly consists of partially deacetylated aminosugar N-acetylglucosamine through β-(1→4)-linkage, the same as cellulose (Fig 1.1 d)[7]. The mostly deacetylated form of chitin is called chitosan. It is used for waste water clearing, for cosmetics and for medical and veterinary applications.

Another abundant polysaccharide is starch; it is a major carbohydrate reserve in fruits, seeds, and tubers of plant[8]. 2850 million tones of starch is produced annually by photosynthesis. Corn is the largest source of starch; the other important sources include wheat, potato, tapioca and rice. Starch exists in the form of amylose (normally 20-30%) and amylopectin (normally 70-80%). Both amylose and amylopectin consist of polymers of α-D-glucose units in the $^4C_1$ conformation (Fig 1.1 a & b). In amylose, these units are linked in the form of α -(1-->4)- linkage, with the ring oxygen atoms all on the same side (Fig 1.1 b), whereas in amylopectin about one residue in every twenty units is linked in the form of α-(1-->6)- linkage to form branch-points (Fig 1.1 c). The ratio of amylose to amylopectin and the α-(1-->6)-branch-points in amylopectin depend on the source of the starch, for example, amylomaizes contain over 50% amylose whereas 'waxy' maize has almost none (~3%). Starch is an important plant product; it is used as the major food resources for human beings throughout the history. Even today, starch still provides 80 % of man's daily calorie intake in areas such as the Far East and Africa[8]. With the excess production of starch, the non-food usage of starch increased during the last century. Like cellulose, the majority usage of starch depends on its ability to hold water, such as thickener, water binder, emulsion stabilizer and gelling agent.

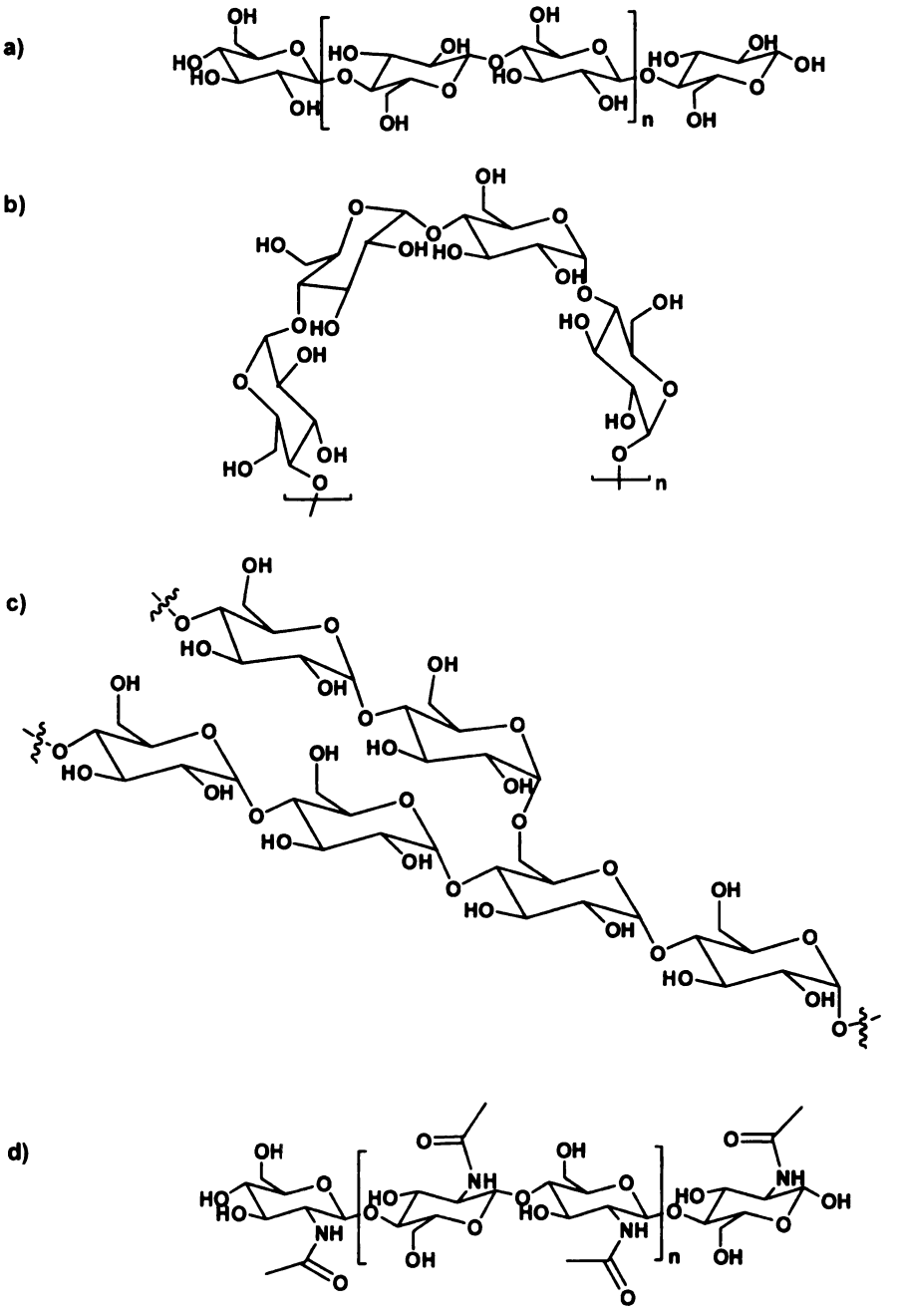


Figure 1.1 Representative partial structures of complex carbohydrates. (a) cellulose; (b) amylose; (c) amylopectin; (d) chitin.

Inulin, or fructose oligosaccharides, is present as plant carbohydrate storage[9]. High concentration of inulin can be found in dandelion, wild yam, Jerusalem artichokes, and chicory. Industrially, chicory has been used for the extraction of inulin.

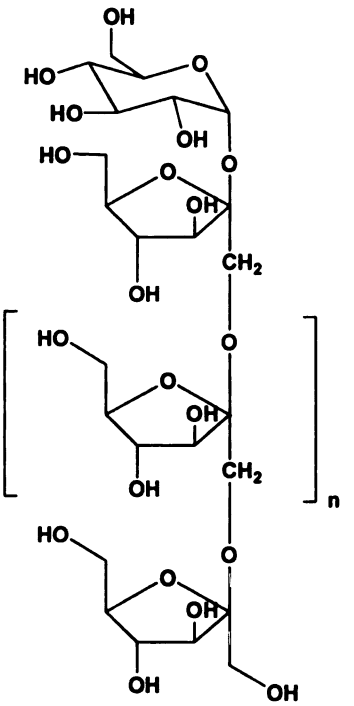


Figure 1.2 Representative partial structure of complex carbohydrate inulin

Inulin is a polydisperse β-(2-->1) fructan. The fructose units are linked through β-(2-->1) linkage, a glucose molecule typically resides at the end of each fructose chain and is linked by an α–(1→2) bond. The chain lengths of these fructans range from 2 to 60 units, with an average DP of ~10[10]. The unique β–(2→1) bonds in inulin make it cannot be digested in the upper gastrointestinal tract as a typical carbohydrate and are responsible for its reduced caloric value and dietary fiber effects[9]. The uptake of inulin does not lead to a rise in serum glucose level or stimulate insulin secretion. Therefore, inulin has been

used to replace fat or sugar to reduce the calories of foods, such as dairy products, baked foods, etc.

1.1.2 Oligosaccharides: cyclodextrins, maltodextrins

Recently, some oligosaccharides, such as cyclodextrins, maltodextrins, have been produced on an industrial scale[11].

Cyclodextrins are a family of three cyclic oligosaccharides composed of α-1,4- linked glucogan units. The α, β, γ, cyclodextrin has 6, 7, 8 glucopyranose units respectively. In the 1970, cyclodextrins are only available as a rare fine chemical. Now, cyclodextrins are produced from partial hydrolysis of starch using the enzymes cyclodextrin gluconotransferases by choosing the type of the microorganism used, α or β cyclodextrin can be selectively produced[12]. Many factories are producing cyclodextrins at over 1000 tons/year scale. The usage of cyclodextrins largely depends on their ability to form host-guest complexes with hydrophobic molecules. They have been used for drug release,[13] for environmental protection, food industry, cosmetics and personal care items, etc.[14].

a) b)

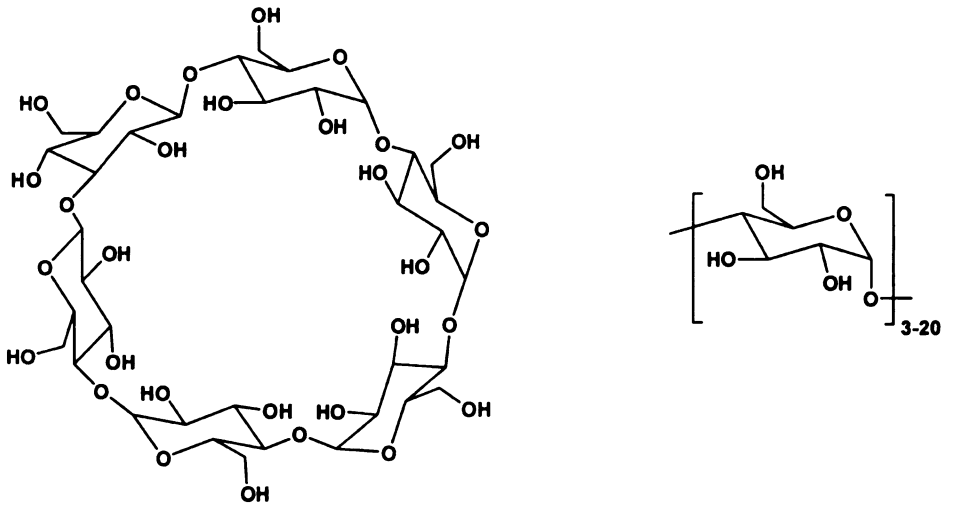


Figure 1.3 Structure of α-cyclodextrin (a) and maltodextrins (b).

Maltodextrins are also produced from partial hydrolysis of starch using acid or enzyme[15, 16]. Unlike cyclodextrins, maltodextrins are linear α-1,4- linked glucogan units, with the chain length from 3 to 20 and average chain length 7. Maltodextrins are moderately sweet polysaccharides and are used as food additive. They are also used as coating agents in pharmaceutical industries and as water soluble glues among other uses[17].

1.1.3 Monosaccharides and disaccharides: sucrose, lactose, maltose, fructose, xylose

Sucrose, the table sugar, can be obtained from supermarkets in crystalline form in very high purity (>99%). It is the world's single most abundant naturally occurring organic compound. In 2004, 144 million tons of sucrose was produced in the world[18]. Sucrose is a major carbohydrate reserve and energy resource in plants. Industrially, sucrose is extracted from sugar cane (20 % by weight) and sugar beet (15 % by weight). The

structure of sucrose is shown in Figure 1.4 a. It is a non-reducing disaccharide, composed of one D-glucose and one-D-fructose unit linked through their anomeric carbon atoms by α, β-1→2-glycosidic bond. About 95 % of the sucrose produced is used in the food industry as a sweetener.

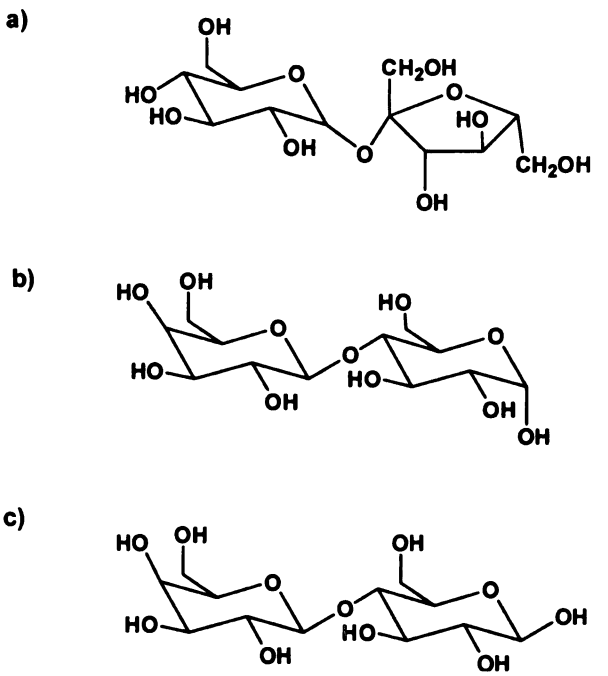


Figure 1.4 Structure of disaccharides (a) sucrose; (b) α-lactose; (c) β-lactose

Lactose, also called milk sugar, is a unique carbohydrate only found in mammalian milk[19]. Lactose is obtained from whey, the by-product in the production of cheese, quark and casein. It is a disaccharide composed of one glucose and one galactose unit through β-(1→4) linkage by aldehyde group of D-galactose. Lactose exists in α and β isomeric forms, with difference in configuration of the hydroxyl moiety at C-1 of the glucose unit. Lactose is largely used in the food industry; it is also used in the pharmaceutical industry, infant nutrition and fermentation.

Naturally, the disaccharide maltose (Fig. 1.5 a) is present in germinating grain. Industrially, maltose is produced from the hydrolysis of starch[12, 20]. The two D-glucose units in maltose are linked through (1→4)-α linkage. The glucose unit at the reducing end has the β configuration. The major usage of maltose is as a food sweetner in its reduced form maltitol.

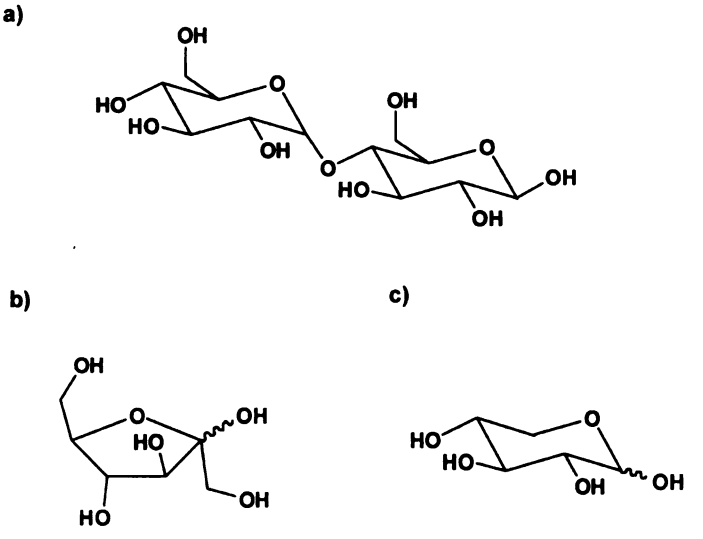


Figure 1.5 Structure of (a) maltose; (b) fructose; and (c) xylose.

Fructose (Fig. 1.5 b) is a monosaccharide which can be found in many foods such as honey, tree fruits, berries, and beets, sweet potatoes etc.[21]. It is one of the three most important blood sugars along with glucose and galactose. Fructose has been consumed by human beings for thousands of years at the amount of 16-20 grams per day. With the westernization of the diets, that number has increased significantly to 85-100 grams per day, mainly coming from the additives to foods and drinks in the form of high fructose corn syrup.. About 16 billion pounds of high fructose corn syrup was consumed each year

in the United States. The increased uptake of fructose has caused problems in human health, such as obesity, diabetes, etc.[22, 23].

Xylose (Fig. 1.5 c) is the most abundant pentose; it can be easily obtained from wood, straw-derived xylan[24]. Xylose is used in dyeing and tanning and also for diabetic diets.

Besides the polysaccharides, oligosaccharides, disaccharides and monosaccharides discussed above, some other carbohydrates, such as isomaltoluse, L-sorbose, and carbohydrate derivatives, such as D-sorbitol, D-xylitol, D-gluconic acid are also available in large quantities and with the prices comparable to the common fossil based solvents, such as methanol, toluene. Table 1.1 listed the annual production and price of some common sugars, sugar derivatives and common solvents.

Table 1.1 Annual world production and prices of some commodity carbohydrates, carbohydrate derivatives and common solvents.

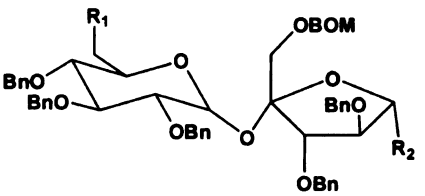
		World production (metric ton / year)	Price ($/kg)
Carbohydrates[a]	Starch	2,729,000,000	0.34
	Sucrose	144,000,000	0.22
	glucose	304,073	0.43
	Lactose	181,031	0.58
	D-Fructose	91,863	0.69
Carbohydrate derivates[b]	D-Sorbitol	650,000	1.80
	D-Xylitol	30,000	5.00
	D-Gluconic acid	60,000	1.40
Solvents[b]	Acetone	3,200,000	0.55
	Methanol	25,000,000	0.15
	Toluene	6,500,000	0.25

[a] Edited based on data from United States Department of Agriculture Foreign Agricultural Service, for the year 2005. http://www.fas.usda.gov

[b] Values are for the year 2003. Adapted from Table 1 in Lichtenthaler, F. W. *Carbohydrates as Raw Materials for the Chemical Industry. Green Chemistry Series No. 1.* Tundo, P. Ed., 3rd Ed., **2004,** pp.105-127.

1.2 Progress in utilization of carbohydrates as general raw materials for organic synthesis

In the last several decades, progress have been made in the usage of carbohydrates as starting materials for organic synthesis and several reviews are available on this subject. The chemistry for the transformations performed at the terminal positions of sucrose (C-1' and/or C-6 and/or C-6') is reviewed by Jarosz[25]. This review focus on the preparation of sucrose derivatives, such as amines, uronic acids, crown ether analogues, from the selectively protected sucrose 2,2',3,3',4-Penta-*O*-benzyl sucrose. Some of those derivatives were shown in Figure 1.6.



1: R_1 = $CH_2OTBDPS$, R_2 = CH_2NH_2

2: R_1 = CH_2NH_2, R_2 = $CH_2OTBDPS$

3: R_1 = R_2= CH_2NH_2

4: R_1 = $CH_2OTBDPS$, R_2 = COOH

5: R_1 = COOH, R_2 = $CH_2OTBDPS$

6: R_1 = R_2 = COOH

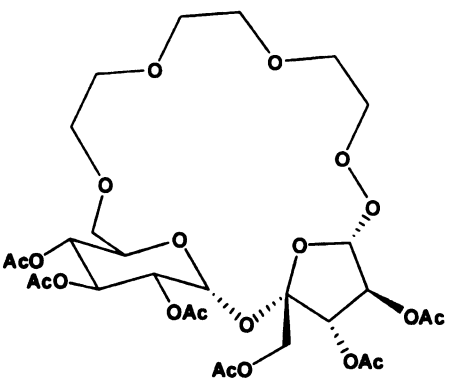


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Figure 1.6 Sucrose derivatives of amines, uronic acids and crown ether analogues

Isomaltulose, a disaccharide produced as the precursor to the sweetener isomalt®, is available in large quantities and its chemistry has been reviewed by Lichtenthaler[18]. Under acidic conditions, dehydration of the fructose portion of isomaltulose afforded 5-

(α-D-glucosyl)-oxymethyl-furfural (α-GMF). From α-GMF, a variety of compounds have been made (Figure 1.7)

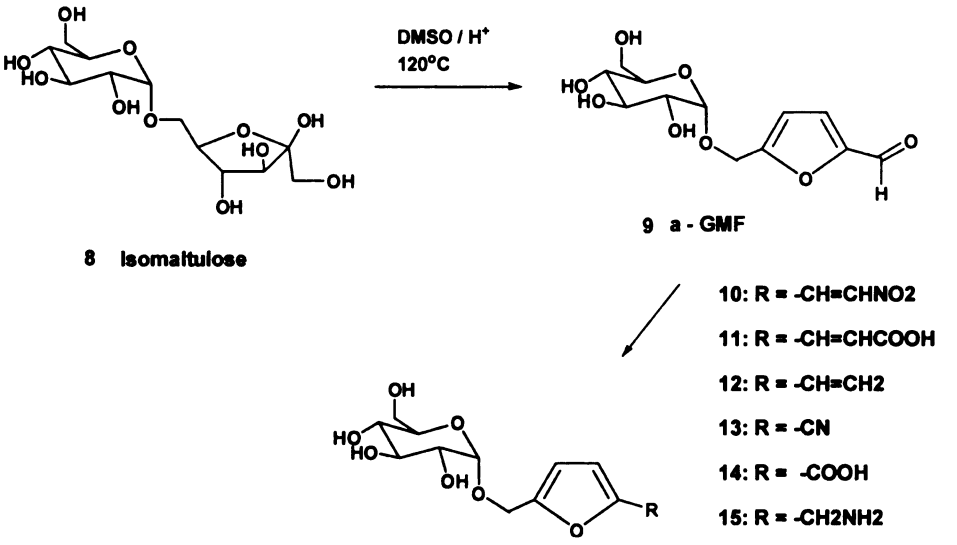


Figure 1.7 Isomaltulose derivatives

The application of D-glucose as a starting material in organic synthesis has also been reviewed[4, 5, 18, 26]. The commonly used intermediates in the transformation of glucose to its derivatives are glucosides, glucals, hydroxyl glucals, glycosyl bromides, 2-oxoglycosyl bromides, enolone bromides, etc. (Fig. 1.8). The transformations of these intermediates have been demonstrated[26].

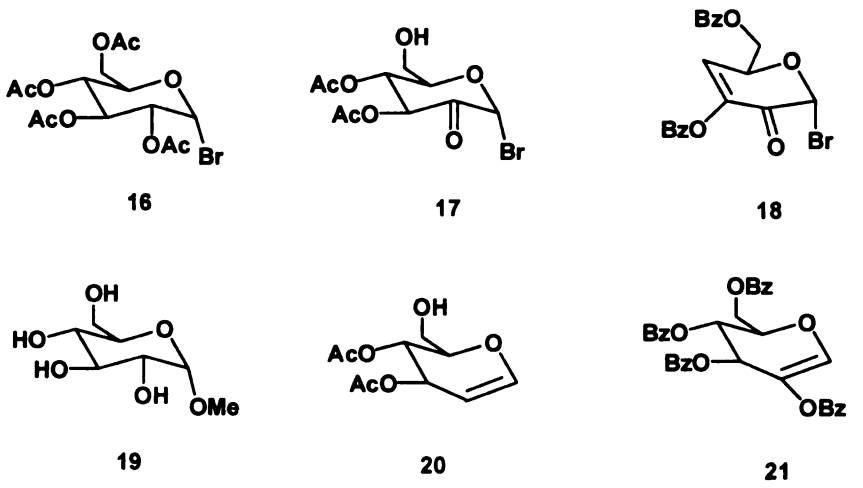


Figure 1.8 Glucose derivatives glucosides, glucals, glycosyl bromides and enolone bromides

Carbohydrates were also often used in natural product synthesis. In the preparation of natural products, clinically important compounds, complex oligosaccharides and carbohydrate-based peptidomimetics, carbohydrate starting materials were extensively used in Nicolaou's group[27]. Some representative structures were shown in Fig. 1.9

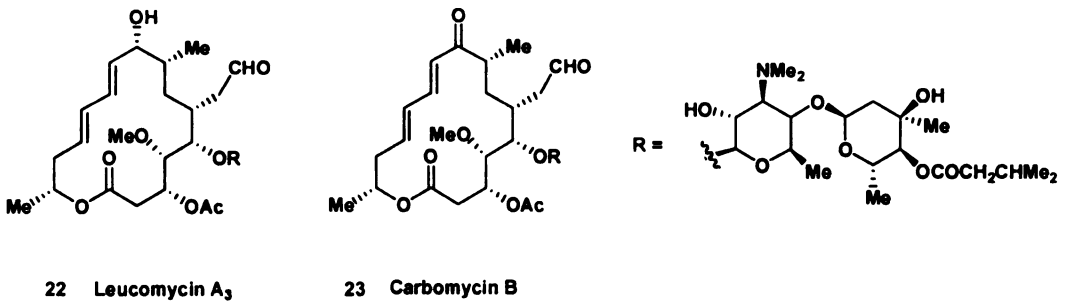


Figure 1.9 Application of carbohydrates in natural products

Leucomycin A_3 **22** and carbomycin B **23** are two clinically important 16-membered ring macrolide antibiotics. They were prepared starting from D-glucose.

The carbohydrates used in the above discussed applications are usually very specific, that is, the carbohydrates used have to be highly modified based on each synthetic targets. For this reason, the application of carbohydrates in organic synthesis is still limited compared to their potential. It is expected that if the more general synthons, such as 3, 4, or 5 carbon compounds with one or two stereocenters could be derived from carbohydrates, the carbohydrate based chemistry will be strong enough to challenge the position of fossil oil based chemistry. Here, the progress in the preparation of general raw materials for organic synthesis is reviewed.

1.2.1 General difficulties in the transformation of carbohydrates to organic synthons

The transition from fossil based production to biomass carbohydrates based production is hampered by several factors. Fossil raw materials based chemicals are still more affordable at present and the technology for this transformation is well developed. Structurally, carbohydrates are very different from the commonly used fossil based chemicals. The commonly used industrial-scale fossil based raw materials are lipophilic low molecular weight products and their derivatives with functional groups, such as –OH, COOH, C=C, C=O added (Figure 1.10). Compared to these compounds, carbohydrates are hydrophilic, have much higher molecular weight, are overly functionalized with hydroxyl groups and lack the C=C, C=O functional groups which are advantageous for chemical transformations. In the last decade, intense efforts have been made for the development of chemistries and technologies to obtain general raw organic materials from carbohydrates.

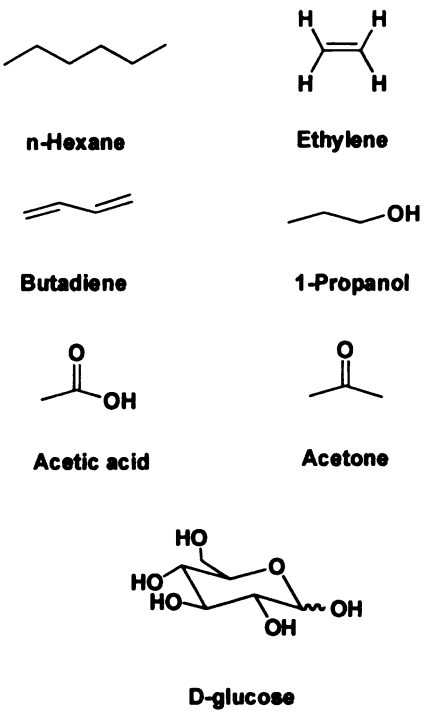


Figure 1.10 Structure of some important basic chemicals and D-glucose

1.2.2 Successes in the preparation of general synthons from carbohydrates

Recently, 4-linked aldohexoses, such as lactose, maltose starch, maltodextrins, have been used in the preparation of 3,4-dihydroxybutyric acid and its lactone[28-30]. Under basic conditions, the reducing end of the aldohexoses **24** is isomerized to ketose **25**, base catalyzed β-elimination of the 4-alkoxy substituent gave the α-diketone **27** (Figure 1.11). Oxidative cleavage of the diketone formed the dihydroxy butyric acid **28** and glycolic acid **29,** cyclization of the dihydroxy acid gave the lactone **30**. The chiral center in the lactone obtained come from C-5 of the D-aldohexoses and thus has (S) configuration. Similarly, the (R)-isomer **36** has been obtained from pentose (Figure 1.12).

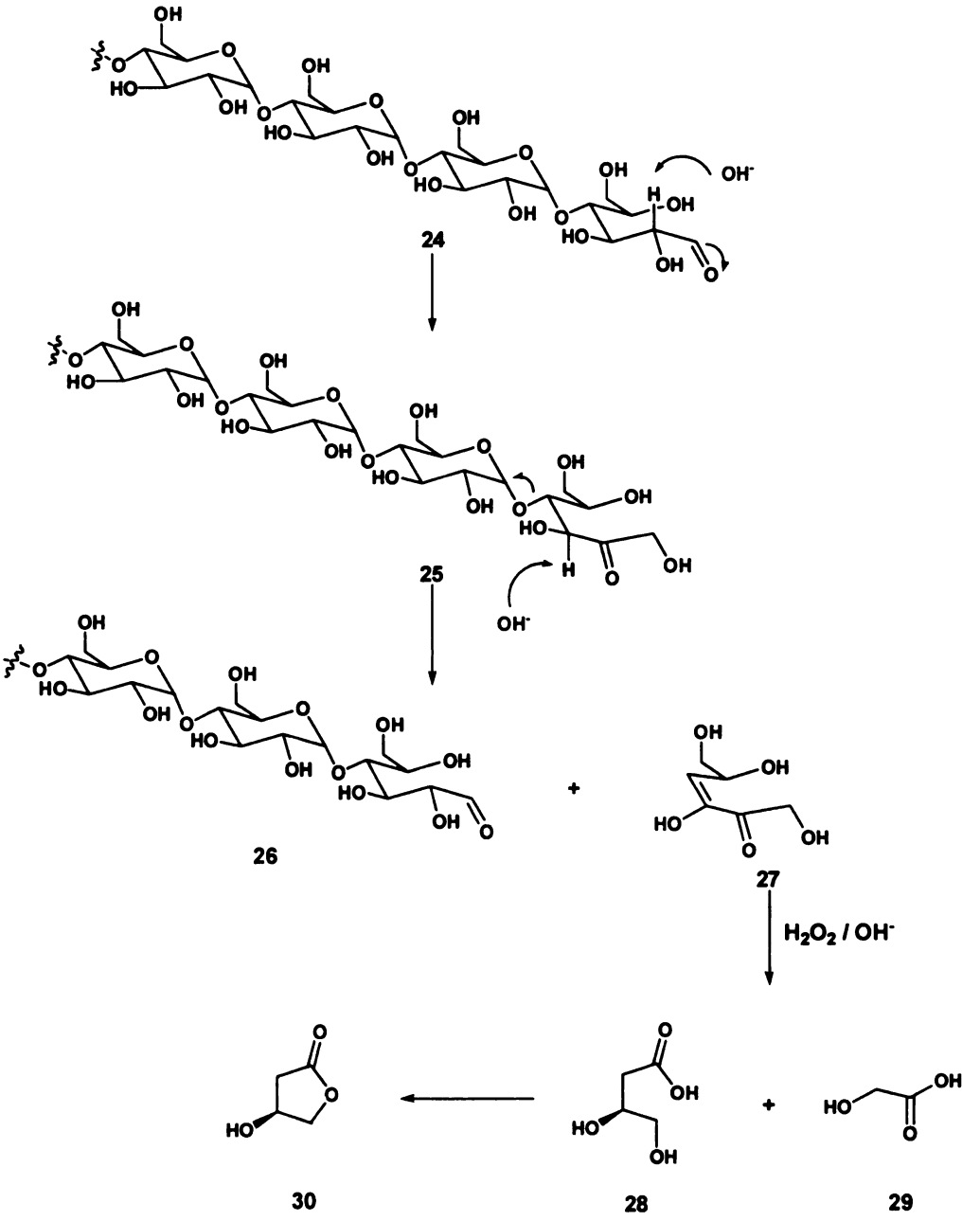


Figure 1.11 Transformation of starch to (S)-3-hydroxy-butyrolactone

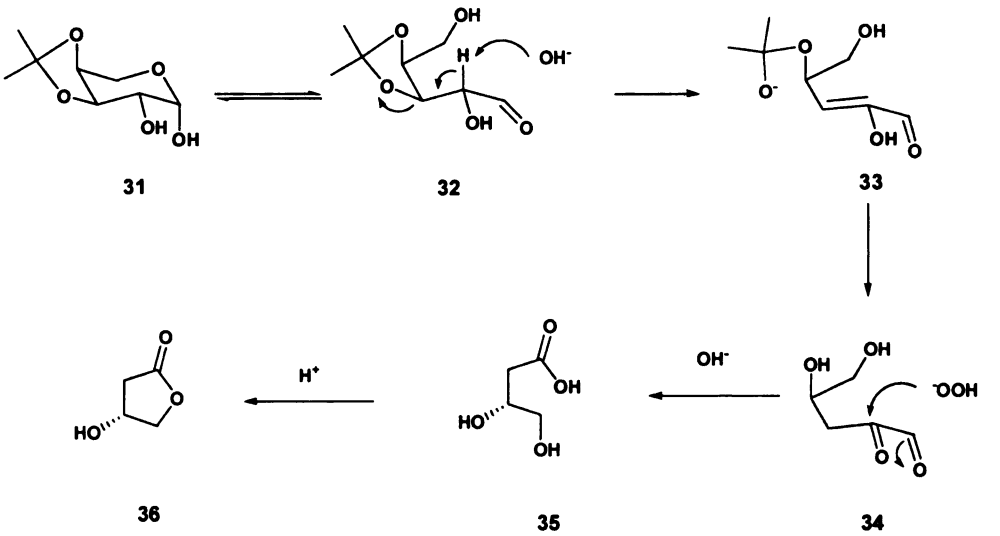


Figure 1.12 Transformation of L-arabinose to (R)-3-hydroxy-butyrolactone

One of the oldest yet still widely used methods for the production of chiral 3-carbon synthons from carbohydrate is through the oxidative cleavage of protected monosaccharide[31]. Oxidation of 1,2-5,6-di-O-isopropylidene-D-mannitol **38** with periodate or lead tetra-acetate gave the protected D-glyceraldehyde **39**. Although satisfactory yields were obtained on small scales, the toxicity and high cost of the reagents prevents the application of this method on industrial scale.

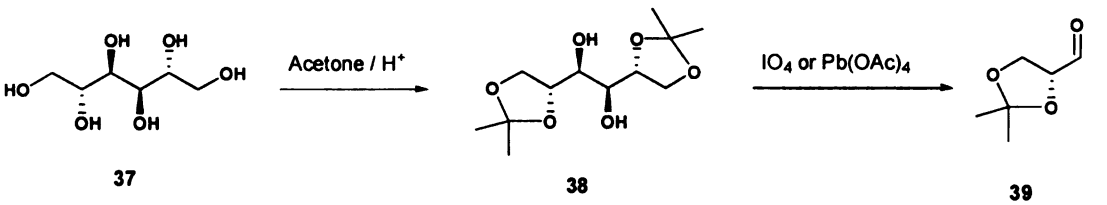


Figure 1.13 Preparation of 2,3-O-isopropylidene-D-glyceraldehyde from D-mannitol

Recently, a more benign method was developed for the oxidation step. Using sodium hypochlorite as the oxidation reagent and ruthenium chloride as the catalyst, 1,2-5,6-di-O-isopropylidene-D-mannitol **38** was oxidized to isopropylidene-D-glyceric acid **39**.[32]

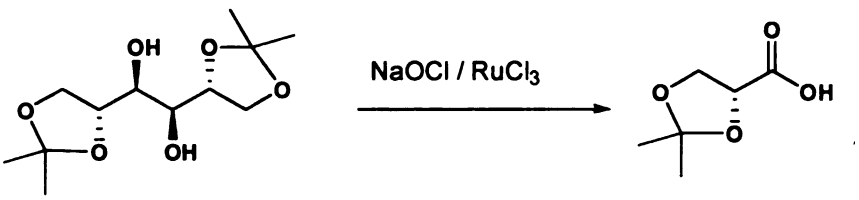


Figure 1.14 Oxidation of 1,2-5,6-di-O-isopropylidene-D-mannitol with Sodium hypochlorite/Ruthenium chloride

To obtain the L-isomer of glyceraldehydes, L-ascorbic acid, which is widely available, was used[33]. Oxidation of the protected L-ascorbic acid **40** with hydrogen peroxide gave 3,4-isopropylidene-D-erythronic acid **41** which was further oxidized by NaOCl to afford 2,3-isopropylidene-L-glyceraldehyde **42**.

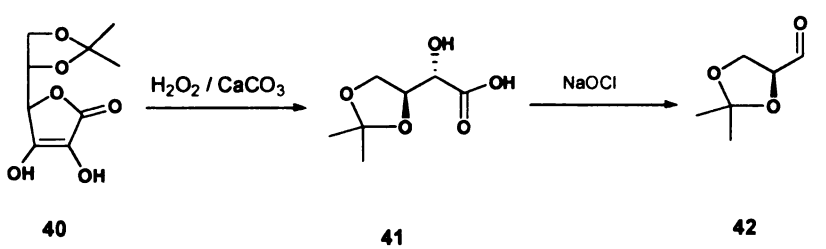


Figure 1.15 2,3-O-isopropylidene-L-glyceraldehyde from L-ascorbic acid

1.3 Some medicinally important synthesis targets from carbohydrates and carbohydrate derived synthons.

Carbohydrates and carbohydrate derived 3 or 4 carbon synthons have been used extensively in natural product synthesis, in the preparation of medicinally important targets[34-36].

1.3.1 From 3 or 4 carbon synthons

The development of new antibiotics is always urgent and challenging with the emergence of multi-drug resistant organism. Linezolid, marketed by Pharmacia and UpJohn, is the newest antibiotic available for the treatment of infections caused by vancomycin-resistant *Enterococcus faecium,* hospital acquired *pneumonia* and methicillin-resistant *Staphylococcus aureus*[37, 38]. Chiral 3-carbon synthons are widely used in the preparation of linezolid and its derivatives[39-43].

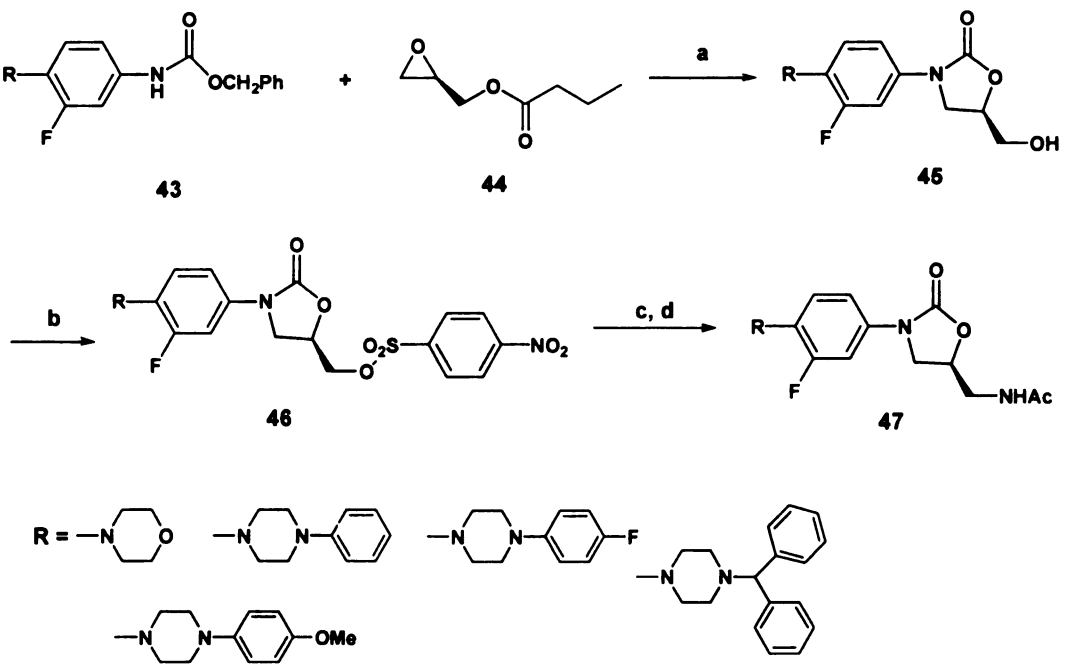


Figure 1.16 Preparation of Linezolid derivatives from (R)-glycidyl butyrate.

(a) n-BuLi/hexane; (b) 4-Nitrobenzenesulfonyl chloride/Et_3N;

(c) NH_3/CH_3OH; (d) Ac_2O

Figure 1.16 lists one recent example for the preparation of Linezolid and its derivatives from of 3-carbon synthon[44]. Deprotonation of the carbamate **43** with n-BuLi followed by

addition of (R)-glycidyl butyrate **44** give the (5R)-(hydroxy methyl)-2-oxazolidinone **45**, which is converted to the final Linezolid and its derivatives **47** in two more simple steps.

(L)-Carnitine is a small molecule which was identified more than 100 years ago[45]. It can be found in all animals, in bacteria and in some plants. It is present in all cells and body fluids of human being[46]. (L)-carnitine is involved in the transfer of fatty acids into mitochondria. Mitochondria are potentially attractive targets of DNA damaging agents[47-51]. In cancer cells, the amount of mitochondria and the expression of carnitine transporter increased which makes the mimics of (L)-carnitine potential antitumor agents[52-53]. The carnitine derivatives can be easily prepared from the 4-carbon synthons as shown in Figure 1.17[54].

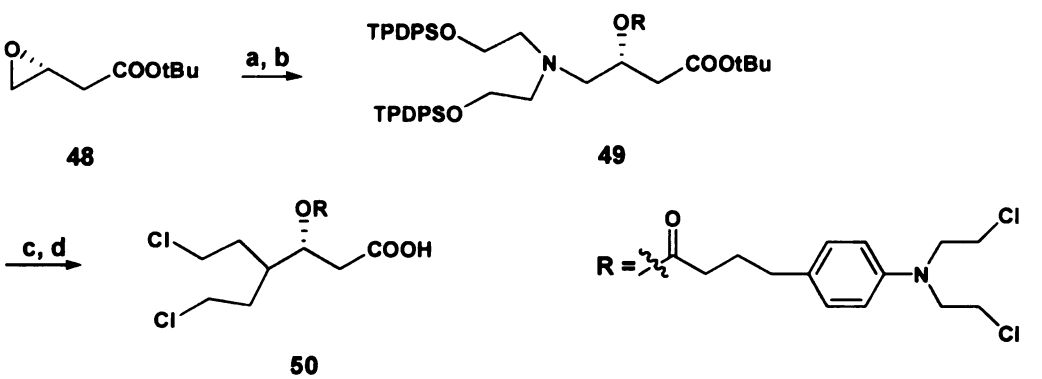
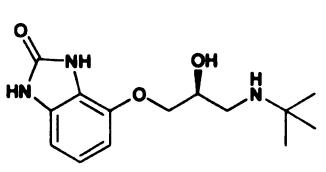


Figure 1.17 Preparation of (L)-carnitine derivatives. (a) bis-silylated amine, SiO_2, 50 %; (b) Chloroambucil, Et_3N, 52 %; (c) (i) TBAF/THF/imidazole; (ii) p-tosyl chloride, DMAP, Et_3N, 23 %, 2 steps; (d) TFA, 87%.

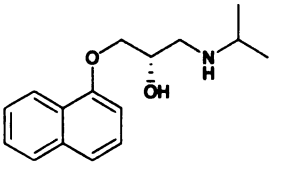
Ring opening of the chiral epoxide **48** by bis(tert-butyldiphenylsilyloxyethyl)amine followed by acylation using chloroambucil give the γ-amino β-hydroxyester derivative

49. The free acid 50 is obtained after deprotection of **49** followed by transforming the hydroxyl groups to chlorides.

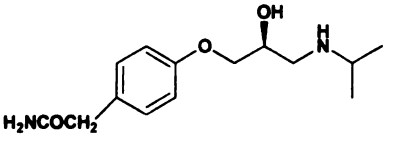
Some other medicinally important compounds derived from 3 and 4 carbon synthons are listed in Figure 1.18.



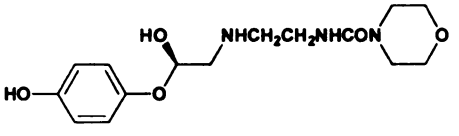
51
beta-3 Adrenergic receptor antagonist for obesity, diabetes



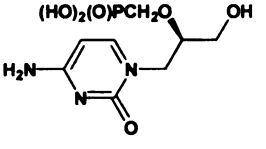
52
(S)-Propranolol



53
(S)-Atenolol



54
Xamoterol
beta-1-Adrenoceptor partial agonist



55
Cidofovir
Antiviral agent

Figure 1.18 Some of the medicinally important compounds derived from chiral 3-carbon synthons.

1.3.2 Iminosugar derivatives

Imino-sugars, or aza sugars, are a class of sugar mimics with the ring oxygen substituted with nitrogen atom. They are important inhibitors for glycosidase and glycotransferase which are involved in many important biological processes, such as intestinal digestion, glycoprotein post-translation, glycoconjugate catabolism, and etc.[55-57]. They are potential drug candidates to treat diabetes, viral disease, lysosomal storage disease, cancer, and

etc.[58-62] Because of the structural similarity between imino-sugars and carbohydrates, carbohydrates are often used for the preparation of imino-sugars[63-65].

Figure 1.19 lists some of the important imino-sugars. Deoxynojirimycin **56** is a potent α-glucosidase inhibitor[66]. Its derivative, N-hydroxylethyl-deoxynojirimycin **57**, is a potent α–glucosidases inhibitor with higher in vivo efficacy and has been approved for the treatment of type II diabetes (Miglitol)[67]. N-butyl-Deoxynojirimycin **58** (Zavesca) recently has been approved for the treatment of a glycosphingolipid lysosomal storage disease, type I Gaucher disease[68].

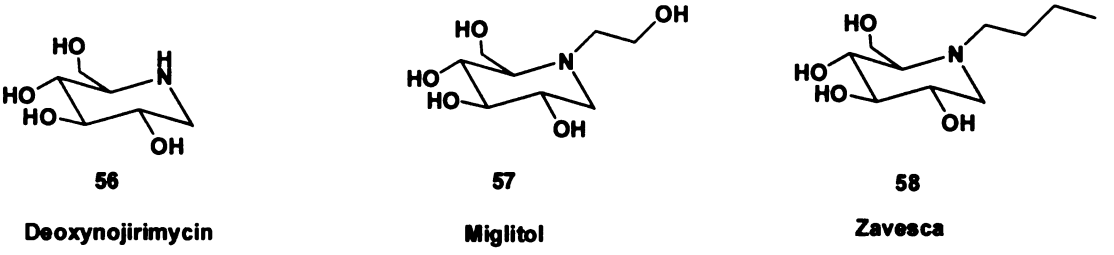


Figure 1.19 Important iminosugars

Many methods with different starting materials have been used in the preparation of imino-sugars. The obvious structural similarities between iminosugars and carbohydrates make carbohydrates the ideal starting point. Besides carbohydrates, other chiral pool materials, such as amino acids, tartaric acids have also been used[69]. Imino-sugars have also been synthesized from achiral precursors, such as olefins, through Sharpless asymmetric epoxidation and dihydrolylaiton[70]. This subject has been extensively reviewed recently[70-72].

1.3.3 Furan/pyran derivatives

Functionalized tetrahydrofuran and tetrahydropyran are common components of naturally occurring and synthetic bioactive compounds[73, 74].

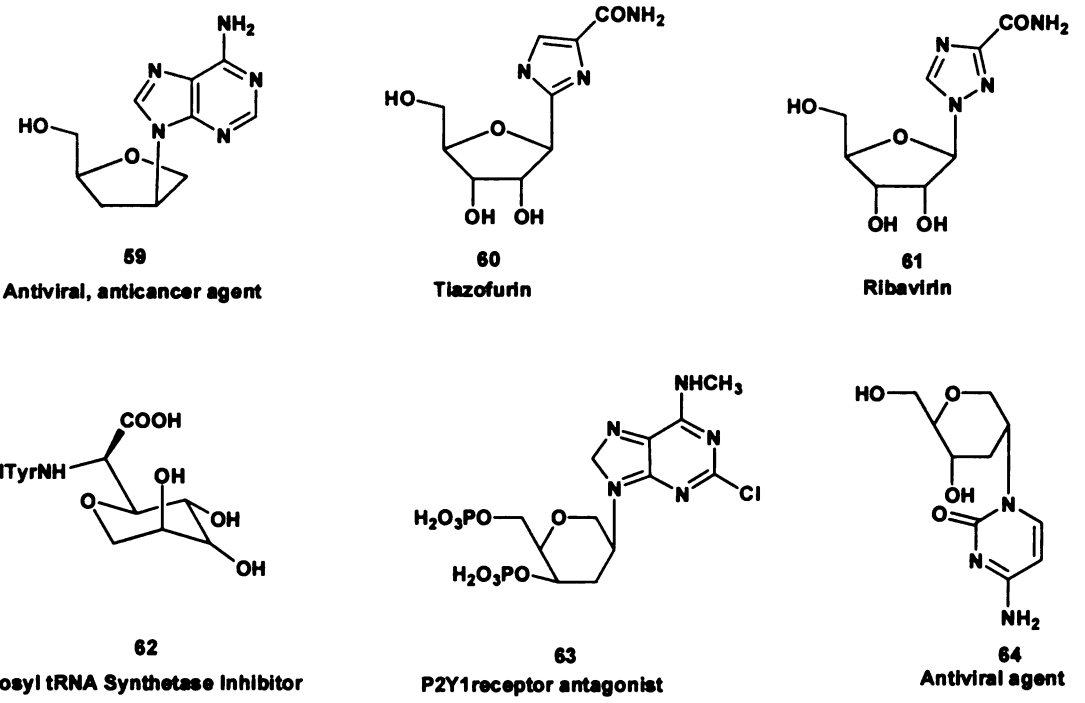


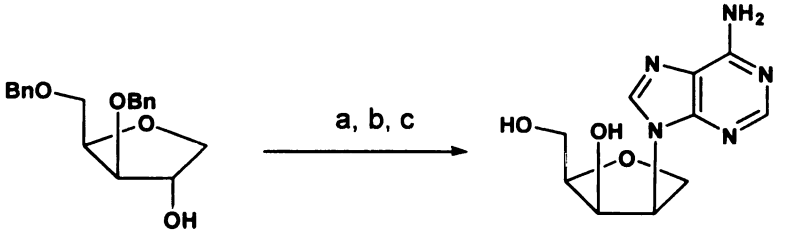
Figure 1.20 Medicinally important furan and pyran derivatives

Figure 1.20 lists some of the medicinally important furan and pyran derivatives. Compounds **59, 60, 61** are nucleoside analogues, in these analogues, the sugar part of the nucleosides have been modified to resist hydrolysis and enzyme degradation of the nucleosides. Isonucleosides, such as (S,S)-iso-ddA **59** and its enantiomer (R,R)-iso-ddA, have shown activities against viruses and tumor cells[75,76].

Tiazofurin [2-(β-D-ribofuranosyl)thiazole-4-carboxamide, compound **60**], the commercialized drug used for treatment of cancers, is a C-nucleoside which has significant activities against human lymphoid[77], lung tumors[78], and ovarian cancers[79]. It

also has activities against chronic myeloid leukemia in blast crisis[80]. Compound **62** is a C-pyranosyl peptide which shown Tyrosyl tRNA synthetaswe inhibition properties[81]. The six-membered ring anhydrohexitol bisphosphate analogue of adenosine-3′,5′–bisphosphates (compound **63**) is an antagonist of P2Y1 receptors[82]. Compound **64,** 1,5-anhydro-2,3-dideoxy-D-ribohexitolnucleoside, is a moderate but selective antiviral agent against Herpes simplex type 1 and 2[82].

Carbohydrates and anhydroalditols are often used in the preparation of these furan and pyran derivatives[83]. Figure 1.21 shows a very efficient route for the preparation of isonucleoside from 1,4-anhydro-D-xylitol[84].



65 **66**

Figure 1.21 Preparation of isonucleoside from 1,4-anhydro-D-xylitol. (a) Tosyl chloride, Pyr, 98 %; (b) Adenine, 18-c-6, K_2CO_3, DMF, 58 %; (c). 10 % Pd/C, H_2, 93 %.

Tosylation of compound **65** followed by reaction with adenine in the presence of 18-crown-6 and K_2CO_3 give the protected isonucleoside. Reductive debenzylation provides isonucleoside **66**.

1.4 Conclusion

Carbohydrates have been used extensively in the preparation of naturally occurring and medicinally important compounds. In most of these applications, their usages are largely case dependent – the carbohydrates have to be modified based on each synthetic target. Recently, progress have been made in the transformation of carbohydrates to general chiral 3 and 4 carbon synthons, which have been used directly and more widely in the synthesis of these medicinally important targets. However, the potential of the annually renewable biomass carbohydrates is far from being fully explored. Compared to their large scale availability and structural richness in stereochemistry and functionality, the usage of carbohydrates as raw materials for both research and industry is still at the very beginning. A surge in the usage of carbohydrates as green and renewable raw materials is expected with the depletion of the non-renewable fossil resources.

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Chapter 2

Transformation of Commodity Carbohydrates to High Value Chemical Intermediates by Reductive Cleavage

Abstract

In this chapter, a practical process for the preparation of anhydroalditols from commercially available carbohydrates was developed. Using methyl-D-glucopyranoside as the model compound, a protocol for reductive cleavage of glycosidic linkage was established. Protecting the hydroxyl groups with allyl groups, the glycosidic bond was effectively cleaved with $Et_3SiH/BF_3{\bullet}OEt_2$. The allyl ether groups were cleaved with the $PdCl_2$-$CuCl_2$-Activated-Carbon system. This protocol was successfully applied to sucrose, cellulose, starch and leven. From these commodity complex carbohydrates, the valuable anhydroalditols, 1,5-anhydro-D-glucitol, 2,5-anhydro-D-mannitol and 2,5-anhydro-D-glucitol were obtained in high yields and purity. The transformation was neat and clean, no column separation was needed for the preparation of 1,5-anhydro-D-glucitol from cellulose and starch. The catalytic cleavage of the allyl ether with the $PdCl_2$-$CuCl_2$-Activated-Carbon system makes these transformations more practical economically

2.1 Introduction

2.1.1 Availability and structural features of commodity carbohydrates

The raw materials used in human history were substantially renewable until the begging of last century. The discovery of coal tar based materials followed by fossil gas and oil took the lead as the raw materials in the past 100 years, and the usage of renewable feedstock dropped to very modest levels. The limits of a chemical industry overly relying on fossil raw materials are very clear as they are depleting and are irreplaceable. With the predicted ending of cheap oil period in the near future (2040), the development of biomass based chemistry is necessary and urgent[1, 2].

The widely available biomasses are carbohydrates, amino acids and lipids. The most important class of them in terms of volume produced is *carbohydrates*, as they represent roughly 75% of the annually renewable biomass of about 200 billion tons. Of these, only a minor fraction (ca. 4%) is used by human beings, the rest decays and recycles along natural pathways[3]. The bulk of the annually renewable carbohydrate biomass are polysaccharides, these include cellulose, starch, inulin, xylan, chitin, etc. Their non-food utilization is confined to textile, paper, and coating industries, either as such or in the form of simple esters and ethers[4].

These complex carbohydrates are composed of repeating units of monosaccharides, and the repeating units are usually five or six member-carbon-rings with one heteroatom in the ring and multiple chiral hydroxyl groups attached to the ring (Figure 2.1)[5].

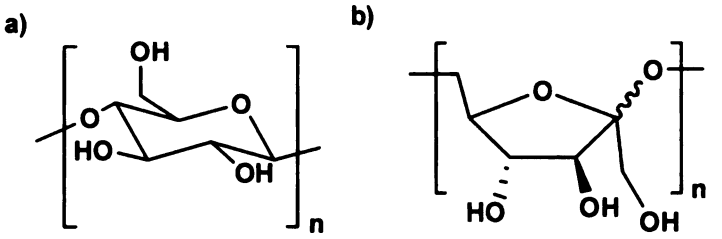


Figure 2.1 Repeating units in complex carbohydrates. (a) cellulose; (b) levan

The repeating units, if correctly modified, are ideal starting materials for the preparation of enantiopure building blocks, high-value-added special chemicals intermediates, and will find wide application in pharmaceutical, agrochemical, and fine chemical industry. To make the transformation of complex carbohydrates into desired products practical, the reagents used should be simple, inexpensive, non-toxic or low-toxic, the separation procedures during work-up should also be simple. However, such kind of chemistry is not as developed as the one for fossil based raw materials. This originates from the structural differences between carbohydrates and fossil based raw materials. In carbohydrates, the multiple hydroxyl groups make them barely soluble in most organic solvents; the carbon skeleton is over functionalized compared to the target molecules; the functional groups are only hydroxyl groups, no C=C or C=O functionality available for further modification[6, 7].

In this chapter, a new process was developed for the transformation of commodity carbohydrates, such as sucrose, cellulose, starch and levan, into anhydroalditols. After protecting the hydroxyl groups of complex carbohydrates with allyl ether, the glycosidic linkages were cleaved through silane reduction. The free anhydroalditols were obtained through $PdCl_2$ catalyzed deprotection of the allyl groups.

2.1.2 Organosilane reduction

Gilman found that diphenylsilane can reduce certain diaryl-type ketones to the corresponding hydrocarbon derivatives at relatively high temperatures[8]. In the 1970's, Doyle and co-workers published a serial of papers on the silane reductions in acidic media[9-14]. In these papers, they reported more practical methods for the reduction of aldehydes and ketones. Trialkylsilanes reduce aldehydes and ketones in alcoholic acidic media to ethers[9-11]. Thus, in methanol, using 97 % sulfuric acid as catalyst, benzaldehyde was reduced to benzyl methyl ether by triethylsilane in 87 % yield. When trifluoroacetic acid or trichloroacetic acid was used, benzyl methyl ether was obtained in 87 or 85% respectively.

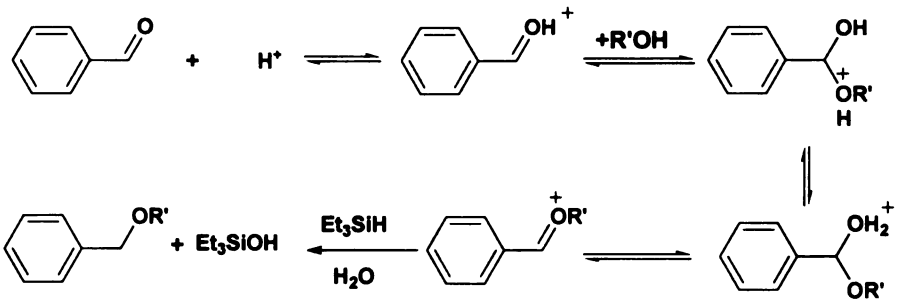


Figure 2.2 Reduction of aldehydes using triethylsilane

Lewis acids, such as $AlCl_3$, $ZnCl_2$, $SnCl_4$, and BF_3 can also be used to activate the carbon center in the reduction of aldehydes and ketones by organosilanes[16-20]. Among the Lewis acids used, BF_3 gives the best results. In the presence of boron trifluoride etherate, aldehydes and ketones are rapidly reduced by triethylsilane at room temperature to borate esters and symmetrical ethers[21]. Triethylsilyl fluoride is the oxidation product. The discovery that acids can catalyze the transfer of hydrides from silicon to carbon makes

the ambient temperature organosilane reduction of carbonyl groups possible, which accelerated the application of silane reduction in organic chemistry.

In the early 80's, Gray introduced the organosilane reduction method to the structural determination of polysaccharides[23] (Figure 2.3). Reductive cleavage of the permethylated cyclohexaamylose with triethylsilane in the presence of either boron trifluoride etherate or trimethylsilyl trifluoromethanesulfonate, followed by acetylation of the newly formed hydroxyl group, gave the methyl-acetyl derivatives of 1,5-anhydro-D-glucitol. The linkage position can be determined through the analysis of the derivatives **2** obtained.

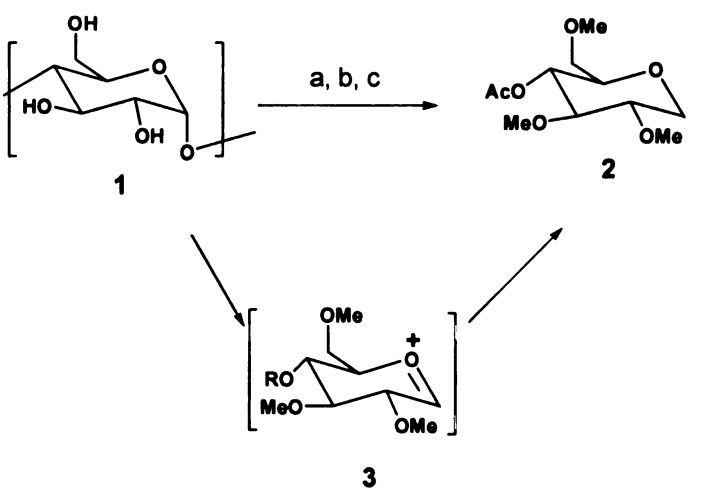


Figure 2.3 Reductive cleavage of polysaccharide by triethylsilane. (a) methylation; (b) reductive cleavage; (c) acetylation.

Later on, this method was extensively used to analysis the structure of polysaccharides[24-28], for example, the structure of the *O*-specific polysaccharide from the lipopolysaccharide fraction of the phytopathogenic bacterium *Xanthomonas fragariae*[28].

The reductive cleavage of glycosidic linkage is a powerful method for the analysis of fully methylated polysaccharides. However, these methods require large amounts of reducing agent and Lewis acid (often over 50 molar equivalents)[23] and are only applicable to methylated sugars in micro to milligram amounts. Much work has to be done in applying this type of chemistry on the synthetic scale. Among the questions to be answered are:

(1) What influence does the nature of the protecting group in the 2 position of the *aldo* sugar have on the rate and yield of the reaction?

(2) What influence does the stereochemistry of the 2-position have on the rate and yield.

(3) What influence does ring size have?

(4) What protecting groups are compatible with the reaction conditions?

(5) Is it possible to get a combination of catalyst and reductant that gives synthetically useful results in a reasonable time?

(7) What carbohydrate polymers or other commodity carbohydrate feedstock can this chemistry be applied to?

2.2 Results

2.2.1 Establishing the protocol for triethylsilane cleavage of the glycosidic linkage.

The reduction of methyl 2,3,4,6-tetra-O-acetyl-α-D-glucopyranoside was processed with 5 equiv of Et_3SiH and 5 equiv of $BF_3{\bullet}OEt_2$ under N_2 atmosphere (Table 2.1). No reduction product was observed when the reaction was run at r.t. with H_2SO_4, CF_3COOH, or CF_3SO_3H as catalyst. Elevation the temperature did not give any reduction product either. After workup (MeOH/HCl), the observed products were only the hydrolyzed starting material.

Table 2.1 Reduction of methyl-2,3,4,6-tetra-O-acetyl-α-D-glucopyranoside.*

Entry	Solvent	Acid	Temp.	Time	Product
1	CH_2Cl_2	H_2SO_4	r.t.	10hr	glucose
2	CH_2Cl_2	CF_3COOH	r.t	10hr	
3	CH_2Cl_2	CF_3SO_3H	r.t.	10hr	
4	CH_2Cl_2	CF_3COOH	r.t	3days	
5	CH_2Cl_2	CF_3COOH	reflux	10hr	
6	$ClCH_2CH_2Cl$	CF_3COOH	60°C	10hr	

* Reaction conditions: 5 equiv Et_3SiH, 5 equiv $BF_3 \bullet OEt_2$, N_2 atmosphere.

When methyl 2,3,4,6-tetra-O-benzyl-α-D-glucopyranoside **4** was treated with triethylsilane (30 equiv), TMSOTf (30 equiv), and $BF_3 \cdot OEt_2$ (10 equiv) in dichloromethane at r.t. for 24 h, the product obtained after workup is methyl α-D-glucopyranoside **5**.

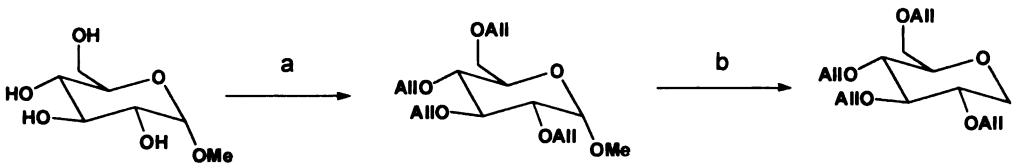
4 **5**

Figure 2.4 Reaction of methyl 2,3,4,6-tetra-O-acetyl-α-D-glucopyranoside with Et_3SiH

Allyl group was then chosen as protecting group. Treatment of methyl α-D-glucopyranoside **5** in DMSO with NaOH followed by allyl bromide gave the desired product methyl 2,3,4,6-tetra-O-allyl-α-D-glucopyranoside **6** in 85 % yield.

Treatment of **6** with triethylsilane (30 equiv), TMSOTf (30 equiv), and $BF_3 \cdot OEt_2$ (10

equiv) in dichloromethane at r.t for 24 h gave the desired product 1,5-anhydro-2,3,4,6-tetra-O-allyl-D-glucitol **7** in ~90% yield. Using 2 equiv of triethylsilane, 3 equiv of trifluoroborane-etherate and catalytic amount of trifluoromethanesulfonic acid, **6** was reduced to **7** in 91 % yield. NMR shown the product was very pure (>99 %) and no further purification was needed.

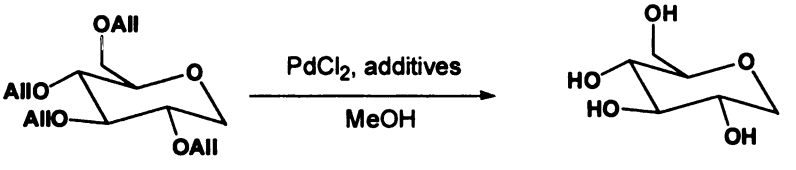


5 6 7

Figure 2.5 Reduction of methyl 2,3,4,6-tetra-O-allyl-α-D-glucopyranoside with Et_3SiH (a) Allyl Bromide, DMSO/NaOH, 24 h, 85 %; (b) Et_3SiH/BF_3OEt_2, CF_3SO_3H, CH_2Cl_2, 0°C-r.t, 6 h, 91 %.

2.2.2 Practical and economic Palladium chloride catalyzed de-allylation of 1,5-anhydro-2,3,4,6-tetra-O-allyl-D-glucitol.

By refluxing allyl ether **7** in methanol in the presence of palladium(II) chloride for 12 h, the deprotected 1,5-anhydro-D-glucitol (**8**) was obtained in almost quantitative yield.



7 8

Figure 2.6 Deallylation of 1,5-anhydro-2,3,4,6-tetra-O-allyl-D-glucitol with $PdCl_2$

Using $CuCl_2$ as a co-catalyst and activated carbon as an additive, a real catalytic protocol

for the cleavage of allyl ether was developed. As shown in table 2.2, when $CuCl_2$ was used as a co-catalyst, the product was obtained in 91% with only 1 mol % of $PdCl_2$ (entry 3). The reaction runs smoothly at 0.1 gram scale. However, when the reaction was carried out on a 1.0 gram scale, only 15% of the fully de-allyllated product was obtained. When activated carbon was added to facilitate the distribution of the solid catalyst $PdCl_2$, the reaction can be performed on up to a 5.0 gram scale to yield the desired product in around 90% yield.

Table 2.2 Deprotection of 2,3,4,6-tetra-O-allyl-D-1,5-anhydro-glucitol

Entry	Allyl-glucitol (gram)	conditions		$PdCl_2$ (mol %)	Yield (%)
		$CuCl_2 \cdot 2H_2O$	Activated carbon		
1	0.1	none	none	80	93
2	0.1	none	none	4	10
3	0.1	1 eq	none	1	91
4	1.0	1 eq	none	1	15
5	1.0	1 eq	0.5 gram	1	90
6	3.0	1eq	3.0 gram	1	91
7	5.0	1 eq	5.0 gram	1	90

2.2.3 Application of the Allylation-Reduction-De-allylation protocol to other mono, disaccharides and complex carbohydrates.

Methyl D-mannopyranoside

Under the same conditions as for the reduction of methyl 2,3,4,6-tetra-O-allyl-α-D-glucopyranoside, methyl 2,3,4,6-tetra-O-allyl-α-D-mannopyranoside **10** was reduced to 1,5-anhydro-2,3,4,6-tetra-O-allyl-D-mannitol **11** in 90 % yield (Figure 2.15).

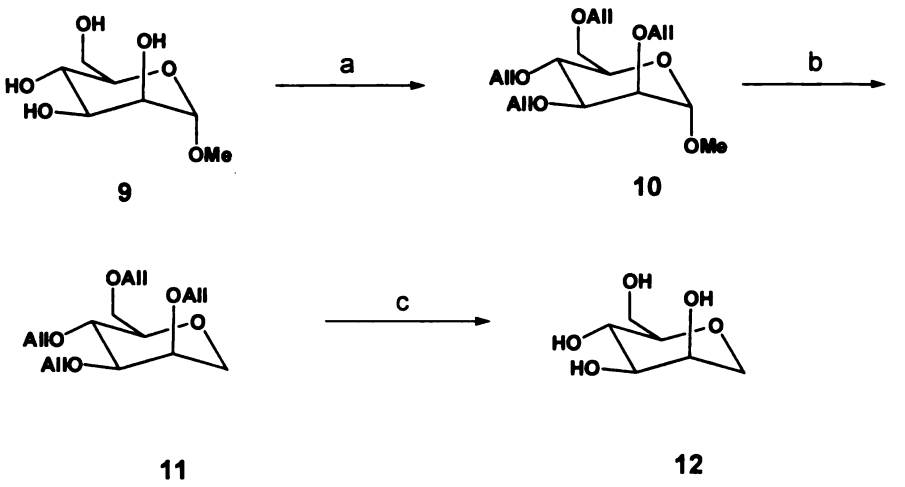


Figure 2.7 Reductive cleavage of methyl 2,3,4,6-tetra-O-allyl-D-mannopyranoside (a) Allyl Bromide, DMSO/NaOH, 24 h, 85 %; (b) Et_3SiH/BF_3OEt_2, CF_3SO_3H, CH_2Cl_2, 0°C, 5 min, 90 %; (c) $PdCl_2/CuCl_2$, activated carbon, MeOH, refulx, 12 h, 90 %.

After refluxing 1,5-anhydro-tetra-O-allyl-D-mannitol **11** in methanol for 12 h with 1 mol % of $PdCl_2$, 1,5-anhydro-D-mannitol **12** was obtained in 91 % yield.

Methyl D-ribofuranoside

Methyl-D-riboside **13** (mixture of α/β anomers, ration 1/9) was first protected with allyl groups. The reduction of methyl 2,3,5-tri-O-allyl-D-riboside **14** under the same conditions as for the reduction of methyl-D-glucoside derivative was done within 3 minutes at 0°C and gave the reduced product **15** in 91 % yield.

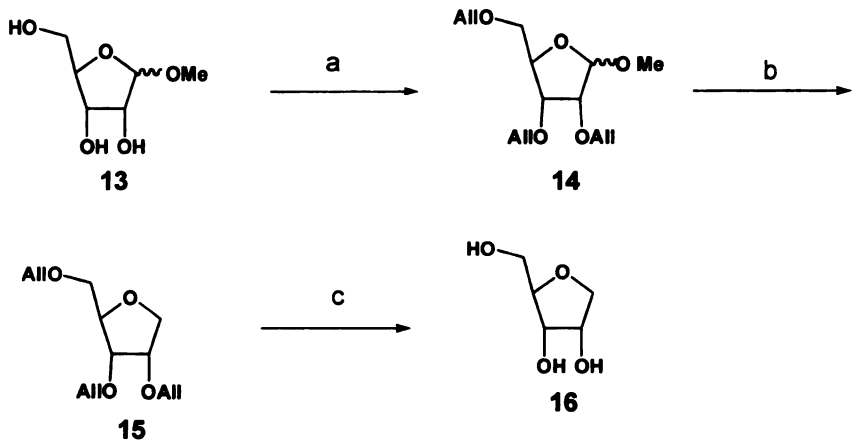


Figure 2.8 Reductive cleavage of methyl 2,3,5-tri-O-allyl-D-ribofuranosides (a) Allyl Bromide, DMSO/NaOH, 24 h, 87 %; (b) Et_3SiH/BF_3OEt_2, CF_3SO_3H, CH_2Cl_2, 0°C, 3 min, 91 %; (c) $PdCl_2/CuCl_2$, activated carbon, MeOH, refulx, 12 h, 85 %.

Sucrose

Octa-O-allyl-sucrose **18** was prepared through allylation of sucrose **17** with allyl bromide and sodium hydride in DMF in 68 % yield. The reduction of **18** was done in 8 h, the D-glucopyranosyl group gave rise to a single anhydroalditol, namely, 1,5-anhydro-2,3,4,6-tetra-O-allyl-D-glucitol **7** (45 %), and the D-fructofuranosyl group gave two anhydroalditols, identified as 2,5-anhydro-1,3,4,6-tetra-O-allyl-D-mannitol **22** (39 %) and 2,5-anhydro-1,3,4,6-tetra- O-allyl -D-glucitol **21** (7 %).

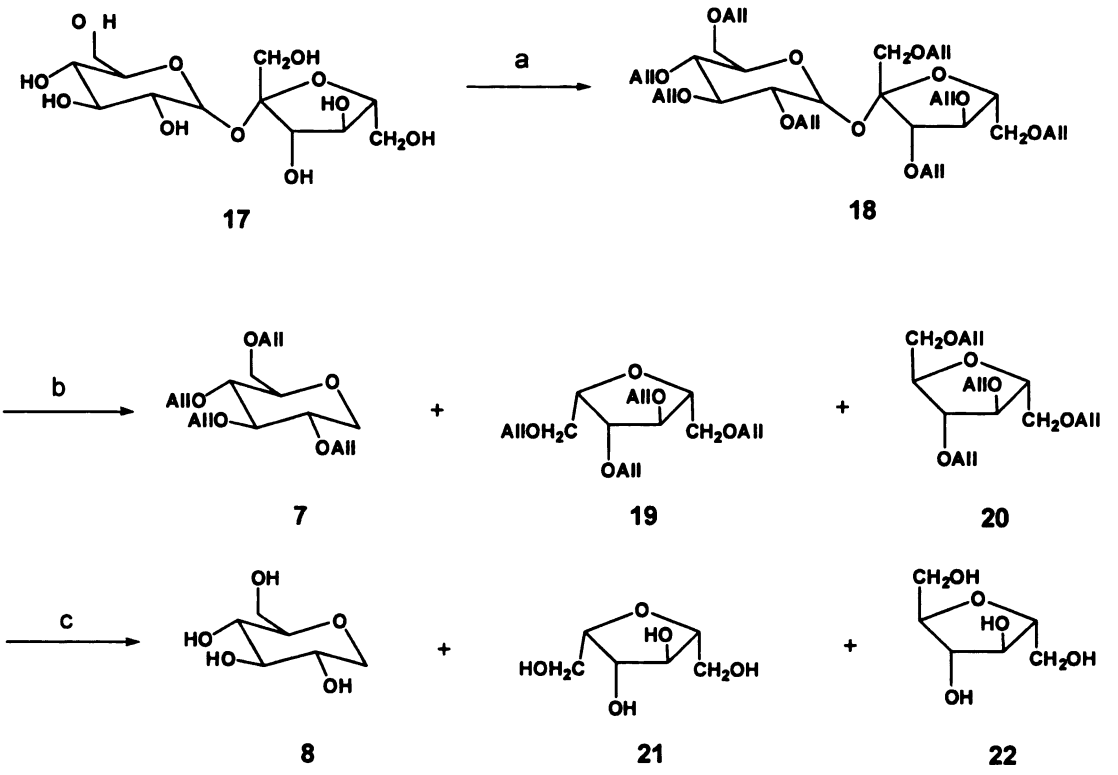
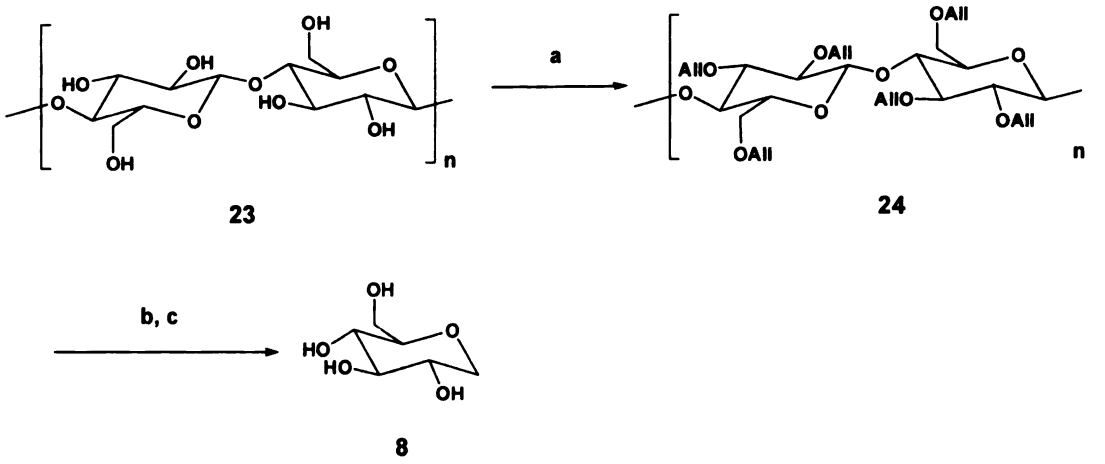


Figure 2.9 Reductive cleavage of Octa-O-allyl-sucrose. (a) Allyl Bromide, DMSO/NaOH, 24 h, 68 %; (b) Et_3SiH/BF_3OEt_2, CF_3SO_3H, CH_2Cl_2, 0°C, 8 h, 91 %;(c) $PdCl_2/CuCl_2$, activated carbon, MeOH, refulx, 12 h, 85 %.

Cellulose

For the preparation of tri-O-allyl-polysaccharides, the polysaccharides were first dissolved in hot DMSO (65°C), followed by addition of powered NaOH and then allyl bromide. In this way, tri-O-allyl-cellulose **24** was obtained in 85 % yield while tri-O-allyl-starch **26** and tri-O-allyl-levan **28** were obtained in 80 % and 78 % respectively.



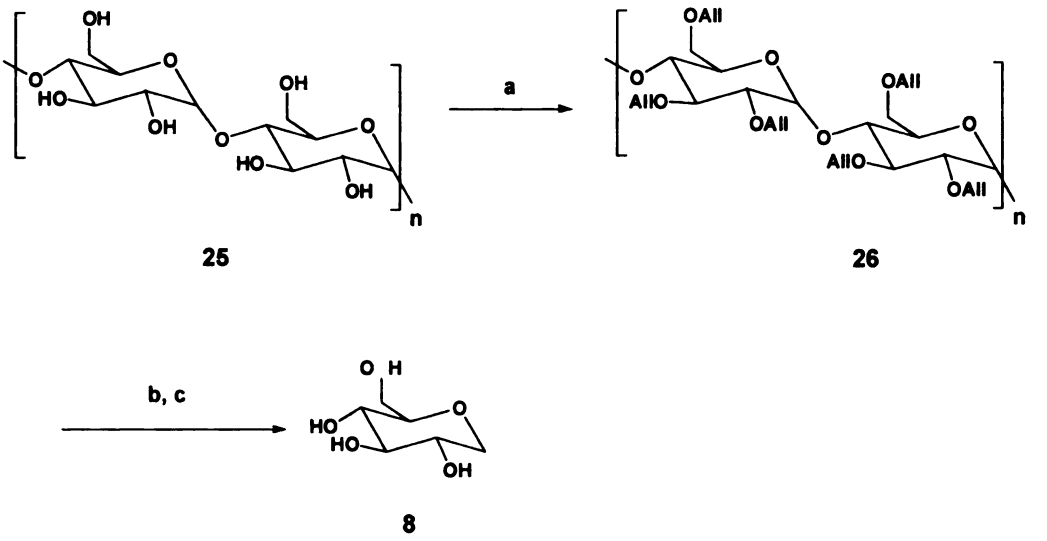
23 24 8

Figure 2.10 Reductive cleavage of tri-O-allyl-cellulose. (a) Allyl Bromide, DMSO/NaOH, 24 h, 85 %; (b) Et_3SiH/BF_3OEt_2, CF_3SO_3H, CH_2Cl_2, 0°C-r.t, 24 h; (c) $PdCl_2/CuCl_2$, activated carbon, MeOH, refulx, 66 %, 2 steps.

Under similar conditions as for the reduction of methyl tetra-O-allyl-glucoside, tri-O-allyl-cellulose **24** was reduced, however, the reaction time was much longer, and it took 24 hours for the reaction to be completely done. After de-allylation, 1,5-anhydro-D-glucitol was obtained as the single product, and the yield for the two steps (reduction and de-protection) is 66%.

Starch

The reduction of tri-O-allyl-starch **26** was done in 24 hours, de-allylation of the mixture gave 1,5-anhydro-D-glucitol as the single product in 69 % yield.



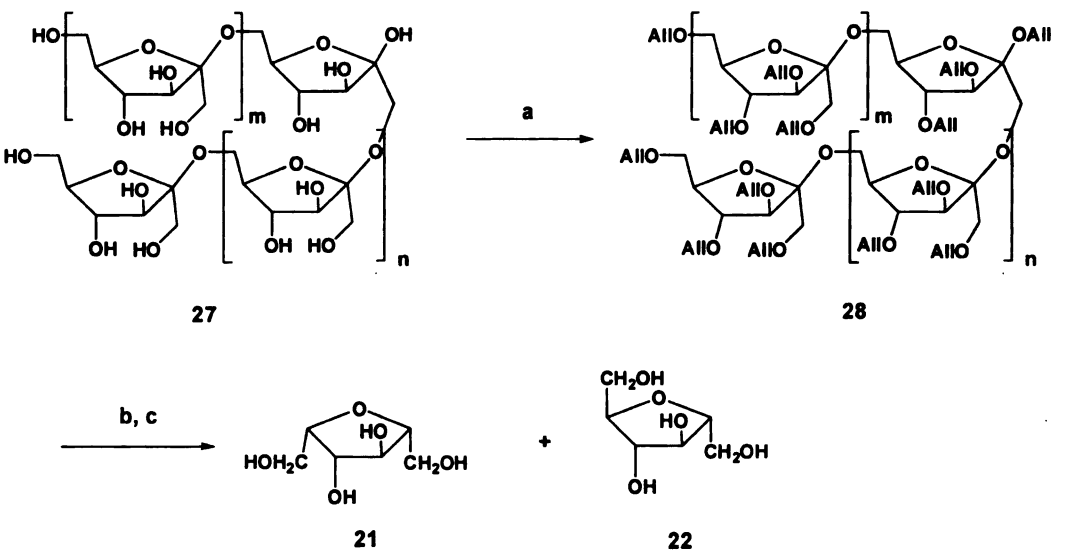
25 26

8

Figure 2.11 Reductive cleavage of tri-O-allyl-starch (a) Allyl Bromide, DMSO/NaOH, 24 h, 80 %; (b) Et_3SiH/BF_3OEt_2, CF_3SO_3H, CH_2Cl_2, 0°C-r.t, 24 h; (c) $PdCl_2/CuCl_2$, activated carbon, MeOH, reflux, 69 %, 2 steps.

Levan

Using the same sequence as for reduction of tri-O-allyl-cellulose, reduction of tri-O-allyl-levan gave 2,5-anhydro-D-mannitol **22** and 2,5-anhydro-D-glucitol **21** as the two products in the ratio of 5 to 1 and in 65 % yield after the reduction and de-protection steps.



27 28 21 22

Figure 2.12 Reductive cleavage of tri-O-allyl-levan (a) Allyl Bromide, DMSO/NaOH, 24 h, 78 %; (b) Et_3SiH/BF_3OEt_2, CF_3SO_3H, CH_2Cl_2, 0°C-r.t, 16 h; (c) $PdCl_2/CuCl_2$, activated carbon, MeOH, reflux, 65 %, 2 steps.

2.3 Discussion

2.3.1 Establishing the protocol for triethylsilane cleavage of the glycosidic linkage.

To avoid the decomposition and rearrangement of carbohydrates under acidic conditions, the free hydroxyl groups must be protected. To find the suitable protecting group for carbohydrates, especially the complex carbohydrates, such as cellulose, starch, levan, several factors must be considered. First, what kind of solvent should be used? Carbohydrates are not soluble in solvents with low dielectric constants, such as toluene, dichloromethane. The best solvent for carbohydrates is water, but water is not a good solvent for the protection of complex carbohydrates for several reasons. The first reason is that the hydroxyl group of water will compete with the hydroxyl groups of carbohydrates which make some reactions, e.g., acetylation of carbohydrates, impossible to be run in water. The second reason is that once the majority of the hydroxyl groups are

protected, the product tends to precipitate from water due to the hydrophobic properties of the protecting groups and thus makes it impossible for the protection of all the hydroxyl groups. The solvents with high dielectric constants, such as DMSO, DMF, can solve or partially solve the complex carbohydrates, and the protected carbohydrates are also soluble in them. However, one possible problem still exists: the partially protected carbohydrate chains tend to fold which makes some of the free hydroxyl groups are buried in the coil and hard to be functionalized. Using DMSO, DMSO/H_2O and DMF, satisfactory results were obtained for both the monosaccharides and polysaccharides.

Second, what kind of protecting group should be used? The installation and removal of the protecting group should be friendly and no harsh reaction conditions or toxic reagents should be used, also, costly reagents should be avoided. The protecting groups must survive the reduction process: since acid is used so no acid labile functional group should be used and no functional groups which are easily reduced by triethylsilane should be used either. The stereo and electronic effects of the installed functional groups on the reduction process are also crucial: the intermediate formed in the reduction process is oxocarbenium ion, electron withdrawing group at 2-position will retard or stop the formation of the oxocarbenium ion while electron giving groups will facilitate the process. Sterically demanding groups will make the access of the oxocarbenium ion by triethylsilane difficult, thus retard the reduction process.

Methyl group is the best choice if no deprotection was needed for the reduced products. Methyl ethers are easy to install, stable to acid and silane, slightly electron giving, and relatively small in size. Indeed, methyl group was the mostly used protecting group in the

analysis of complex carbohydrates by the silane reduction method[23-26]. However, the harsh conditions used in the cleavage of methyl ether bonds make it not a suitable choice since our purpose is to prepare the unprotected anhydroalditols.

Acetyl groups are easy to install and remove, relatively small in size and it is one of the least costly protecting groups. One possible problem is that it is an electron withdrawing group, and participation of 2-acetyl group to the reduction process is also possible through formation of the dioxonium ion with C-1. However, similar reactions with saccharides containing propanoate groups at C-2 had been used with $Me_3SiOSO_2CF_3$ as the catalyst[25].

Thus acetyl groups were chosen as the protecting groups for evaluation of the reductive cleavage process. To simplify the reaction process, methyl α-D-glucopyranoside was chosen as a model compound. However, no reduction product was obtained from methyl 2,3,4,6-tetra-O-acetyl-α-D-glucopyranoside, the only product after workup was the hydrolyzed starting material, glucose (Table 2.2, Figure 2.13).

A possible reaction pathway was shown in Figure 2.13. Once the carbocation **31** was formed, the acetyl group from C-2 apparently stabilized it and formed the dioxonium ion **32**, thus making the hydride transfer to the anomeric carbon disfavored, so that no reduction product was formed.

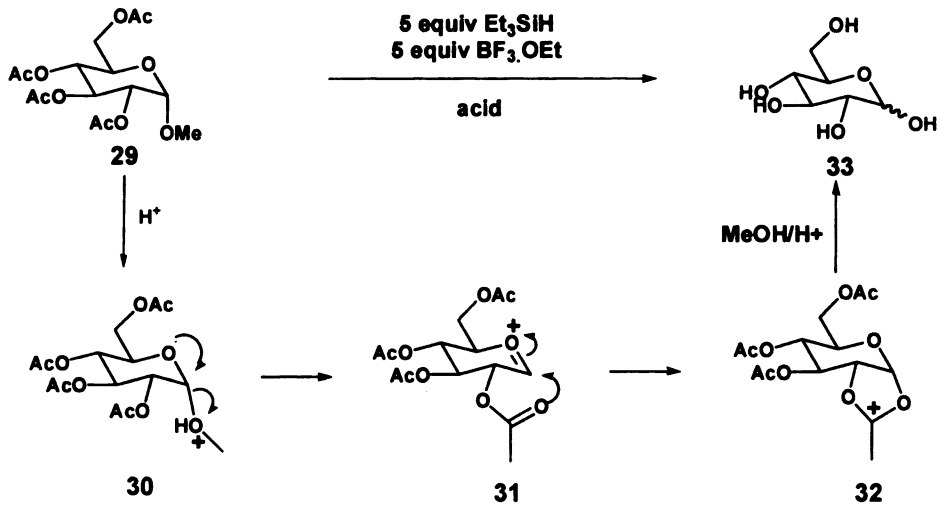


Figure 2.13 Mechanism for reaction of methyl 2,3,4,6-tetra-O-acetyl-α-D-glucopyranoside with Et_3SiH

Benzyl group will not participate in the reduction process; one possible problem is that under the action of hydride, the benzyl ether bond may be cleaved. However, if the cleavage of the glycosidic bond is faster than that of the benzyl ether bond, the cleavage of the benzyl ether bond will not be a problem.

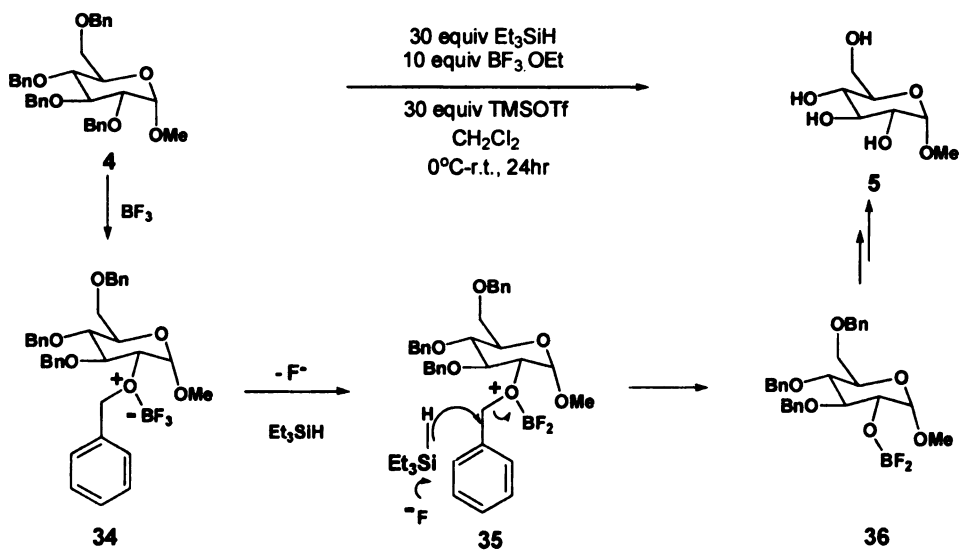


Figure 2.14 Mechanism for reaction of methyl 2,3,4,6-tetra-O-acetyl-α-D-glucopyranoside with Et_3SiH

No reduction of the glycosidic bond was observed even with excess Et_3SiH (30 equiv) used. Instead, cleavage of the benzyl ether bond was observed. After workup, the product obtained was methyl α-D-glucoside **5**. A mechanism was proposed in Figure 2.8. Coordination of BF_3 with the benzyl ether oxygen formed complex **34**; transfer of hydride from Et_3SiH to the benzylic carbon gave the partially deprotected **36**. Continued reductive cleavage of the benzyl ether bonds gave the deprotected **5**.

So, an alterative protecting group which will not participate during the reduction process and is more stable under acidic reductive conditions than benzyl ether is needed. And this protecting group should be easy to cleave. Allyl group seems to meet all the requirements for the reductive cleavage reaction: allyl ether is stable under acidic conditions; it will not participate in the reduction process as ester does, allyl group is relatively small in size, and the allylic hydrogens are also less reactive compared to benzylic hydrogens. The installation of allyl ether is relatively easy, and many methods have been reported for the cleavage of allyl ether. Allyl group was then chosen as the protecting group for the reductive cleavage reaction.

For the formation of allyl ether, several methods are available. The most obvious and widely used method is through the reaction of alkali metal alkoxides with allyl halides. The reaction is best when carried out in polar solvent, such as DMF[29]. This method is good for the universal protection of all the hydroxyl groups in a certain compound. Another extensively used method for the formation of allyl ether is the tin method[30-32]. The hydroxyl groups are first converted to tributylstannyl ethers or, in the case of diols, to dibutylstannylidene acetals and then alkylation of the alkoxy-tin derivatives give the

ally ether. An advantage of this method is that functional groups, such as azido groups, O-TBDMS groups and acetamido groups can be tolerated[33, 34]. This method is mostly used when partial of the hydroxyl groups need to be protected selectively[35-37]. The third widely used method is through palladium catalyzed decarboxylative rearrangement of mixed allyl alkyl carbonates. Alkyl allyl carbonates undergo decarboxylative rearrangement when heated at 50-70 °C in the presence of palladium catalysts[38]. The alcohols were first converted to allyl carbonates, and then palladium catalyzed extrusion of CO_2 give the allyl ether. This method has been successfully applied to base sensitive substrates, such as carbonate or 1,1,3,3-tetraisopropyldisiloxane-1,3-diyl (TIPS) derivatives of carbohydrates[38, 39]. Alcohols can also be converted to allyl ethers through their barium salts[40-42], or using the trichloracetamidate method[43, 44].

For the preparation of methyl 2,3,4,6-tetra-O-allyl-α-D-glucopyranoside **6**, the most practical and economic method is through the Williamson synthesis. Using this method, methyl 2,3,4,6-tetra-O-allyl-α-D-glucopyranoside **6** was obtained in 85 % yield (Figure 2.9). The reduction of **6** gave the desired product **7** in high yield. At first, conditions used in the reductive cleavage of methyl protected carbohydrates were used[23, 24]. With 30 equiv Et_3SiH, 30 equiv TMSOTf, and 10 equiv $BF_3{\cdot}OEt_2$, the reaction was done within 24 h at r.t., the desired product 1,5-anhydro-2,3,4,6-tetra-O-allyl-D-glucitol was obtained in 90% yield.

Although these conditions work well for the reduction, the high equivalents of triethylsilane and TMSOTf used prevent the practical usage of these conditions for the preparation of 1,5-anhydro-D-glucitol in gram scale. Fortunately, we found that by using

catalytic amount of trifluoromethanesulfonic acid in dichloromethane, even without the expensive TMSOTf, a very good yield of the desired product can be obtained with much less triethylsilane and $BF_3{\cdot}OEt_2$ used. Using only 2 equiv of triethylsilane, 3 equiv of trifluoroborane-etherate and catalytic amount of trifluoromethanesulfonic acid, the desired product was obtained in 91% isolated yield. Furthermore, NMR shown the product was very pure (>99 %) and no further purification was needed.

The proposed mechanism is shown in Figure 2.15. Coordination of boron trifluoride to the glycosidic oxygen forms the complex **37**. At the assistance of the lone pair electrons from the ring oxygen, the glycosidic linkage is cleaved with the formation of the ring oxocarbenium ion and boron fluoride methanolate. The boron fluoride methanolate ion decomposes to form fluoride and difluoromethoxylborane. At the assistance of fluoride, hydride transfers from triethylsilane to C-1 of **39** forms the reduced anhydroglucitol **7** and fluorotriethylsilane.

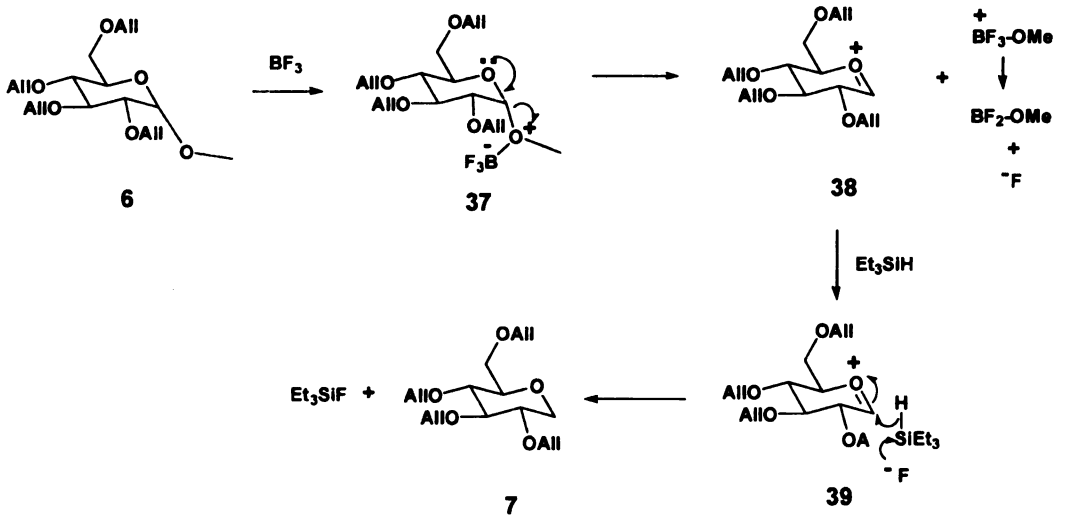


Figure 2.15 Mechanism for reaction of methyl 2,3,4,6-tetra-O-allyl-α-D-glucopyranoside with Et_3SiH

2.3.2 Palladium chloride catalyzed de-allylation of 1,5-anhydro-2,3,4,6-tetra-O-allyl-D-glucitol.

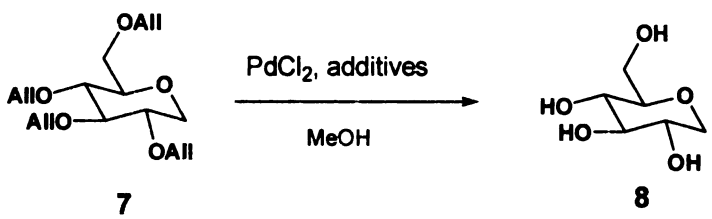
Many methods have been reported for the cleavage of allyl ether bond, most of them involve prior isomerization of the allyl ether, either base[45-47] or transition metal catalysed,[48-50] to labile prop-1-enyl ethers which may then be cleaved under generally mild conditions.

Several literature methods were evaluated for the cleavage of the allyl ether. These included TMSCl/NaI[51], $NaBH_4/I_2$[52], NBS and light[53] and DDQ[54]. No satisfactory results were obtained either because the yield was too low (TMSCl/NaI, $NaBH_4/I_2$, <5 %) or the recovery of the product was too problematic (NBS/light or DDQ).

Recently, palladium complexes have been used for the direct cleavage of allyl ether. $PdCl_2(PhCN)_2$, used in stoichiometric amount, allows direct cleavage of allyl phenyl ethers to phenols in 85-95%yield[55]. Another powerful and selective method for cleavage of allyl ethers has found extensive use in carbohydrate chemistry[56-63]. In this method, the substrate is reacted with equimolar (or often excess) amounts of $PdCl_2$ in aqueous acetic acid and in the presence of sodium acetate at temperatures ranging from 25°C to 70°C. The free alcohol is obtained directly. Although the above mentioned palladium mediated cleavage of allyl ether gave high yield of the deprotected product, stoichiometric amount of palladium usually is required. Kusama and co-workers devised a catalytic method for the deprotection of allyl glycosides[64]. Heating allyl glycosides in acetic acid in the presence of palladium tetrakis(triphenylphosphine) afforded the deprotected product. The amount of catalyst required is rather high (ca. 30 mol %).

For the deprotection of 1,5-anhydro-2,3,4,6-tetra-O-allyl-D-glucitol, which has 4 allyl groups, 1.2 equivalent of palladium will be needed even 30 mol % of palladium per allyl group is used. Further more, the reported palladium based catalytic direct deprotection of allyl ether can only be used to cleave allyl ether as allyl glycosides[64, 65]. Thus, a more efficient, more general catalytic protocol must be developed for the deprotection of 1,5-anhydro-2,3,4,6-tetra-O-allyl-D-glucitol.

We found that by refluxing the allyl ether solution in methanol in the presence of $PdCl_2$ for 12 h, the de-protected 1,5-anhydro-glucitol could be obtained in almost quantitative yield. In this case, catalytic amount of palladium (II) chloride (0.8 equiv or 0.2 equiv per allyl group) was used (entry 1, Table 2.2). When 0.04 equiv of $PdCl_2$ was used, however, only 10 % of the product was obtained (entry 2, Table 2.2). The large amount of catalyst needed makes the development of a more efficient catalytic protocol necessary to make this reductive cleavage method practically viable.



7 8

Figure 2.6 Deallylation of 1,5-anhydro-2,3,4,6-tetra-O-allyl-D-glucitol with $PdCl_2$

One possible reason for the low efficiency of the palladium(II) chloride was that part of Pd(II) was reduced to Pd(0) and thus lost the catalytic property. $CuCl_2$ has the ability to oxidize Pd(0) to Pd(II) and it is expected that by using $CuCl_2$ as a co-catalyst, the Pd(0) will be recycled and thus only a very lower loading of $PdCl_2$ was needed. Indeed, when 1

equiv of $CuCl_2$ was used, with only 0.01 equiv of $PdCl_2$, the product was obtained in very high yield (91 %) (entry 3, Table 2.2).

The reaction runs smoothly at 0.1 gram scale with the $PdCl_2$-$CuCl_2$ catalytic system, however, when the reaction was carried out on a 1.0 gram scale, only 15% of the fully de-allyllated product was obtained (entry 3, Table 2.2). The possible reason was that at larger scale, as the volume of the solvent increased, the rate of the biphasic reaction decrease since $PdCl_2$ is not soluble in MeOH. A better disperse of the solid catalyst in the reaction system should be able to solve this problem. We were happy to find that with an equal amount of activated carbon used along with the substrate, the reaction can be performed on 5.0 gram scale without decreasing in yield (entry 7, Table 2.2).

Although some palladium based catalysts for the deallylation of allyl ether have been developed, the mechanism is still not very clear[65-69]. A mechanism, based on *anti-Markovnikov* hydroxypalladation followed by β-alkoxy elemination, was proposed for cleavage of the allyl ether (Figure 2.16)[70].

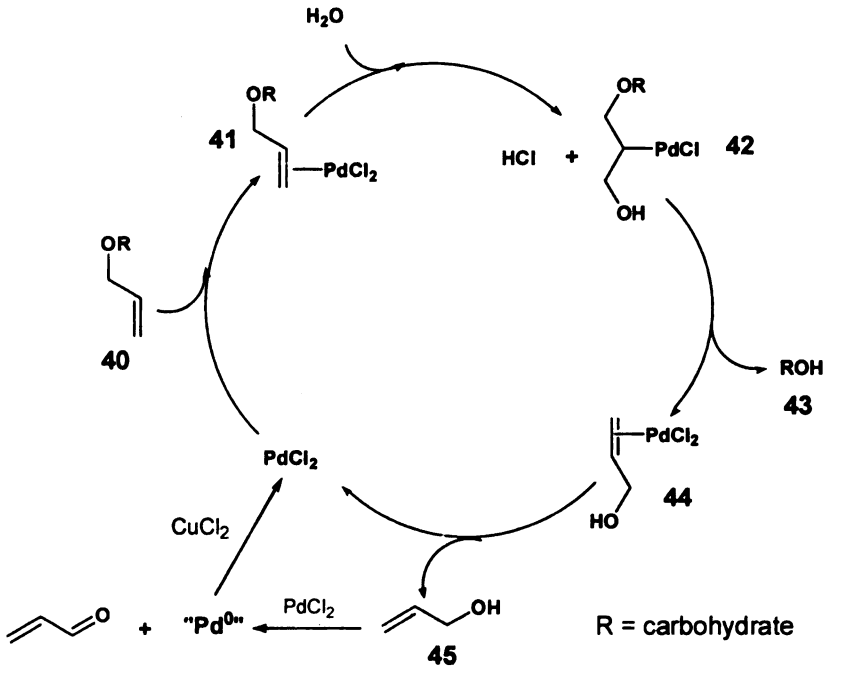


Figure 2.16 Proposed mechanism for catalytic cleavage of allyl ether

Coordination of allyl-ether **40** with $PdCl_2$ followed by attacking the terminal carbon of the olefin by H_2O gives the intermediate **42**, which loses ROH **43** (the free carbohydrate) and gives the allyl alcohol complex **44**. Dissociation of $PdCl_2$ with **44** gives free $PdCl_2$ and finishes the catalytic cycle. The allyl alcohol formed in the process would reduce palladium(II) to palladium(0) with formation of oxidized by-products such as acrolein[71]. Pd(0) can be oxidized back to Pd(II) by $CuCl_2$

2.3.3 Application of the Allylation-Reduction-De-allylation protocol to other mono, disaccharides and complex carbohydrates.

Once the *Allylation-Reduction-De-allylation* protocol was established, it was tested on the reduction of other glycosides and complex carbohydrates. It turns out that this protocol is very general; it can be used on other monosaccharides, such as mannose,

ribose, and disaccharide, such as sucrose, and on polysaccharides, such as starch, cellulose and levan.

Methyl D-Mannopyranoside

The stereochemistry at C-2 of aldohexapyranose has a great effect on the reactivity of C-1. In this case, methyl α-D-mannopyranoside was chosen to study the C-2 stereochemistry effect on the reductive-cleavage of the glycosidic linkage. For the reductive cleavage of the glycosidic linkage in methyl 2,3,4,6-tetra-O-allyl-α-D-mannopyranoside, the reaction was much faster than that of methyl 2,3,4,6-tetra-O-allyl-α-D-glucopyranoside, the reaction was done within 5 minutes at 0°C with 90 % yield (Figure 2.7). The only difference between the glucopyranoside derivatives and mannopyranoside derivatives is the stereochemistry at C-2: the hydroxyl (allyl ether for protected glycosides) group is equatorial for glucopyranoside while it is axial for mannopyranoside. It took 6 hours for the reduction to complete for glucopyranoside while only 5 minutes for mannopyranoside. What caused the big difference in the reaction rates between glucopyranoside and mannopyranoside derivatives?

For the reduction of methyl 2,3,4,6-tetra-O-allyl-D-glucopyranoside and methyl 2,3,4,6-tetra-O-allyl-D-mannopyranoside, the mechanisms are the same (Figure 2.17): coordination of BF_3 with the glycosidic oxygen forms the BF_3 – glycoside complexes **37** and **50**, cleavage of the glycosidic bond forms the oxycarbenium ions **38** and **51**, reduction of the oxycarbenium ion give the anhydroalditol derivatives **7** and **11**. In this process, the rate determining step is the formation of the oxycarbenium ions **38** and **51**, the same as in the hydrolysis of alkyl glycopyranosides[72,73].

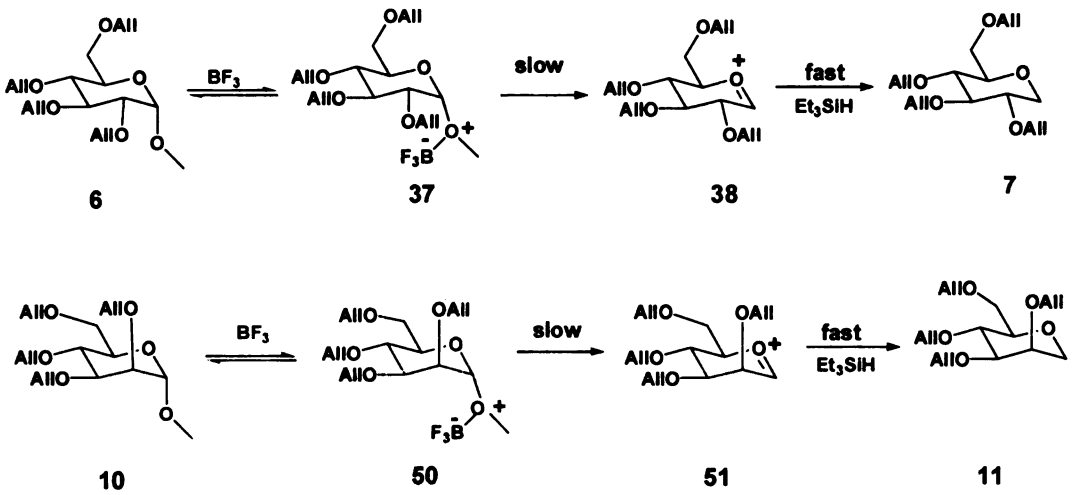


Figure 2.17 Mechanism for reduction of methyl α-D-glucoside and methyl α-D-mannoside.

It has been known for many years that stereoisomeric glycosides hydrolyze with increasing rate depending on the number of axial hydroxyl groups[74].

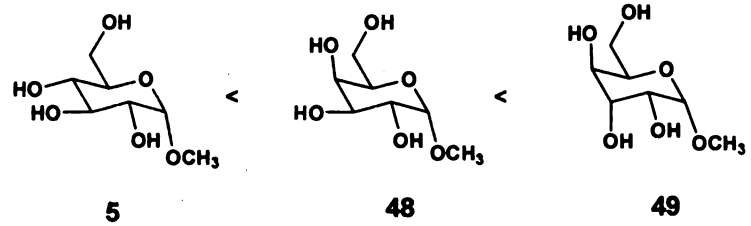


Figure 2.18 Relative acid-catalysed hydrolysis rates of glucoside, galactoside and guloside.

An explanation for the hydrolysis rate difference between different glycopyranosides was based on the relief of steric strain. On the basis of available data and some assumptions on pyranoside reactant-state conformations and the mechanism of hydrolysis, Edward gave an explanation to this phenomenon[75-78]. The rationale as to why guloside **49** reacts faster than galactoside **48**, which again reacts faster than glucoside **5** (Figure 2.18), was

based on the easiness for the relief of steric strain. Axial substituents would ease the rotation around the C2-C3 and C4-C5 bonds and thereby facilitate the transformation from reactant into intermediate, which possess a more flattened half-chair conformation.

For the reduction of glycopyranoside derivatives, the rate determining step is also the formation of the oxocarbenium ion (Figure 2.17), the same rational can be used to explain the rate difference between glucopyranoside and mannopyranoside: the C-2 axial substitute in mannopyranoside eases the rotation around the C2-C3 and C4-C5 bonds and thereby facilitate the transformation from reactant into intermediate, which accounts for the big rate difference.

The stereochemistry at C-1 of methyl 2,3,4,6-tetra-O-allyl-D-mannopyranoside does not affect the reaction rate much in the reduction process. No difference was observed for the α and β anomers. The de-allylation was also successful with the *$PdCl_2$-$CuCl_2$-Activated-Carbon* system. After refluxing 1,5-anhydro-tetra-O-allyl-D-mannitol in methanol for 12 h with 1 mol % of $PdCl_2$, 1 equiv $CuCl_2$ and activated carbon, 1,5-anhydro-D-mannitol was obtained in 91 % yield.

Methyl D-ribofuranoside

With the successful application of this reductive cleavage protocol on methyl D-mannopyranoside, the reductive cleavage of pentosides with this protocol should pose no problem. Ribosides were chosen as substrates to test this method. The reduction of methyl 2,3,5-tri-O-allyl-D-ribofuranoside (mixture of α/β anomers, ration 1/9) under the same conditions as for the reduction of methyl D-glucopyranoside derivative was done

within 3 minutes at 0°C and the product was obtained in 91% isolated yield.

In furanose, the ring carbon atoms are distorted from the tetrahedron structure and the substituents are eclipsed to each other. Thus, the furanose ring is highly strained. This strain is partially released when the oxocarbenium ion is formed. Compared to furanose, the pyranose ring is more flexible and the strains in pyranose were released through pucker of the ring. The structural difference between furanose and pyranose is the reason for the rate difference in the acid catalyzed hydrolysis of furanose and pyranose. For example, methyl α-D-mannofuranoside hydrolyzed 150 times faster than methyl α-D-mannopyranoside[79]. The same reason can be used to explain the rate difference in the triethylsilane reduction of methyl D-ribofuranoside and methyl D-glucopyranoside. In the silane reduction reactions, the rate determining step is also the formation of the oxocarbenium ion, as in the acid catalyzed hydrolysis of glycosides. The faster rate in the formation of the furan-oxocarbenium ion makes the reduction of methyl D-ribofuranoside faster than methyl D-glucopyranoside.

2.3.4 Preparation of 1,5-anhydro-D-glucitol, 2,5-anhydro-D-glucitol and 2,5-anhydro-D-mannitol from sucrose.

Next, the disaccharide, sucrose, was used as the substrate for the reduction. Based on the results for reduction of monosaccharides, anhydroalditols are the expected products via the formation and reduction of oxocarbenium ions. The D-glucopyranosyl group was expected to give rise to a single product, namely, 1,5-anhydro-2,3,4,6-tetra-O-allyl-D-glucitol The D-fructofuranosyl group can, however, give rise to two anhydroalditols, namely, 2,5-anhydro-1,3,4,6-tetra-O-allyl-D-mannitol and 2,5-anhydro-1,3,4,6-tetra-O-

allyl-D-glucitol. Compounds 2 and 3 are the result of net overall retention and inversion, respectively, of the stereochemistry at C-2 in the D-fructofuranosyl group.

As expected, three products were obtained: 1, 5-anhydro-2,3,4,6-tetra-O-allyl-D-glucitol from the D-glucopyranosyl part of sucrose, 2,5-anhydro-1,3,4,6-tetra-O-allyl-D-mannitol and 2,5-anhydro-1,3,4,6-tetra-O-allyl-D-glucitol from the D-fructofuranosyl moiety of sucrose (Figure 2.21).

A possible reaction pathway was shown in Figure 2.29. Coordination of trifluoroborane to the glycosidic oxygen forms the oxonium intermediate **52**, which breaks down to form the glucopyranosyl derived oxocarbenium ion **38** and fructosyl derived oxocarbenium ion **53**. Similar to the triethylsilane reduction of methyl glucopyranosides, transfer of hydride from triethylsilane to this oxocarbenium ion gives the allyl protected 1,5-anhydro-D-glucitol **7.**

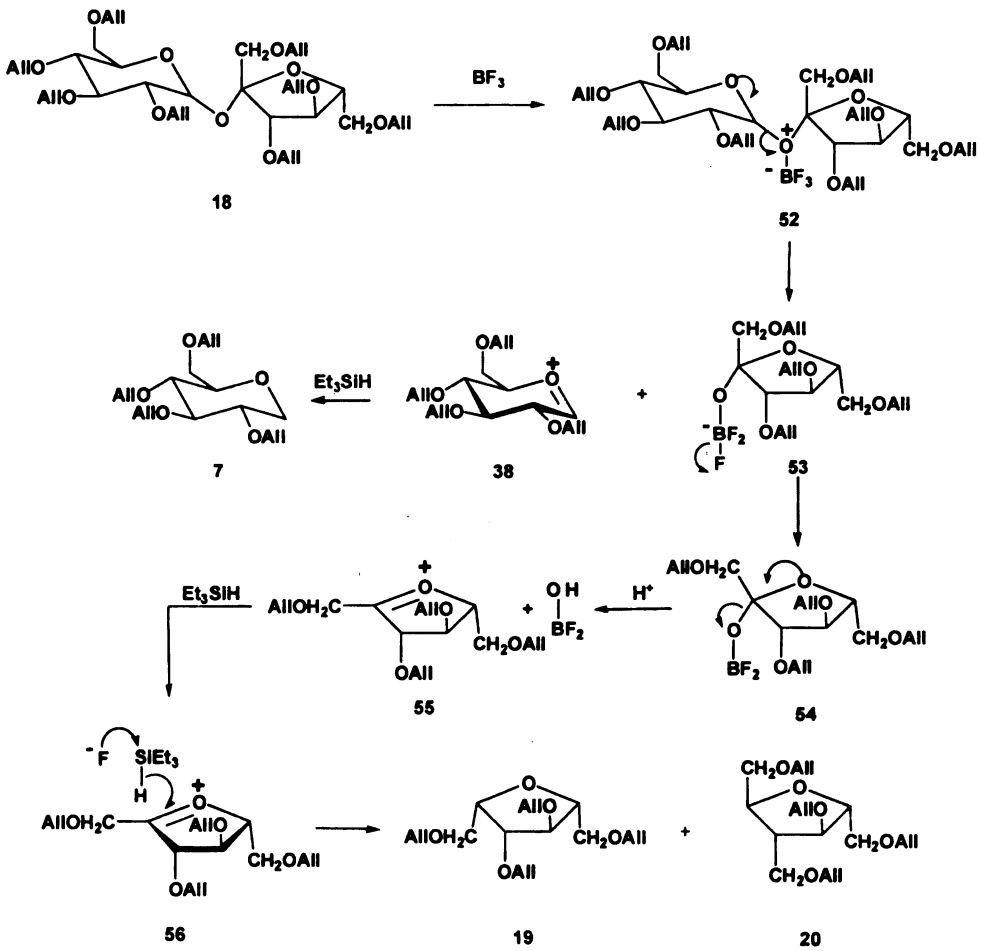


Figure 2.19 Mechanism for reductive cleavage of Octa-O-allyl-sucrose

Reduction of the oxocarbenium intermediate **55** gave products 19 and 20. The symmetrical 2,5-anhydro-D-mannitol derivatives **20** was formed as the major product (39 %) while the 2,5-anhydro-D-glucitol derivative **19**, was obtained in 7 %.

Cellulose

The preparation of valuable chemicals from commodity carbohydrates, such as cellulose, starch, levan, etc., has very high economic potentials and is a great challenge for synthetic chemistry. The real test for the *Allylation-Reduction-De-allylation* proctol is

whether it can be used for the preparation of anhydroalditols from these commodity carbohydrates. Using this protocol, 1,5-anhydro-D-glucitol, 2,5-anhydro-D-glucitol and 2,5-anhydro-D-mannitol were prepared from complex carbohydrates, such as cellulose, starch and levan.

The appropriate solvents for the allylation of polysaccharides should be able to dissolve or at least partially dissolve the polysaccharides and should also be able to solve the final products. Two polar, non-protonic solvents, DMSO and DMF, were chosen as the reaction solvents. When DMSO was used as solvent, the polysaccharides were first dissolved in hot DMSO (65°C), followed by addition of powered NaOH and then allyl bromide, the reaction was done in 10 h at 80°C. In this way, tri-O-allyl-cellulose was obtained in 85 % yield while tri-O-allyl-starch and tri-O-allyl-levan were obtained in 80 % and 78 % respectively (Figure 2.10). With DMF as solvent, NaH was used as the base, and the reaction was done in 24 h at r.t. A slightly higher yields were obtained with DMF as solvent (tri-O-allyl-cellulose, 92%, tri-O-allyl-starch, 85 %, tri-O-allyl-levan 85 %).

For the reduction of these tri-O-allyl-polysaccharides, because all the hydroxyl groups are protected, no ring contraction or rearrangement should occur during the reduction process, and therefore, the only expected products are 1,5-anhydro-glucitol (from cellulose, starch), 2,5-anhydro-D-mannitol and 2,5-anhydro-D-glucitol (from levan).

Under similar conditions as for the reduction of methyl tetra-O-allyl-glucoside, tri-O-allyl-cellulose was reduced, however, the reaction time was much longer, it took 24 hours for the reaction to be completely done. ^{13}C NMR analysis of the final product shown that

the anomeric carbon signals were totally disappeared. However, it also shown that the product was a complex mixture of several compounds.. It is known that for the acetylation and alkylation of polysacchrides, it is hard to get the homogeneously functionalized products. Although no hydroxyl group signal (3100 cm^{-1}) was detected by IR, it is still possible that part of the hydroxyl groups are un-allylated and the product obtained contain 1,5-anhydro-D-glucitol derivatives with different degree of allylation. If only 1,5-anhydro-D-glucitol derivatives present in the mixture, 1,5-anhydro-D-glucitol would be obtained as the single product after de-allylation. Indeed, after de-allylation, 1,5-anhydro-D-glucitol was obtained as the single product, and the yield for the two steps (reduction and de-protection) is 66% (Figure 2.10).

From tri-O-allyl-starch, 69 % of 1,5-anhydro-D-glucitol was obtained as the single product after the reduction-deprotection process (Figure 2.11).

Levan is a D-fructan of high molecular weight that is comprised of a (2–6)-linked D-fructofuranose backbone which is branched at some of the O-l atoms. As for the reduction of sucrose, the expected products from the fructofuranosyl units are 2,5-anhydro-D-mannitol and 2,5-anhydro-D-glucitol. The same reaction sequences as for the reduction of tri-O-allyl-cellulose gave the two expected product 2,5-anhydro-D-mannitol and 2,5-anhydro-D-glucitol in the ratio of 5 to 1 and in 65 % yield after the reduction and de-protection steps (Figure 2.12).

Table 2.3 listed the overall yields for the transformation of those commodity carbohydrates to the corresponding anhydroalditols.

Table 2.3 Transformation of glycosides to anhydroalditols.

Commodity carbohydrates	Anhydroalditols	Yield (%)
Me-α-D-glucopyranoside	1,5-anhydro-D-glucitol	69.7
Me-α/β-D-mannopyranoside	1,5-anhydro-D-mannitol	70.5
Me-α/β-D-ribofuranosideide	1,4-anhydro-D-ribitol	72.9
Sucrose	1,5-anhydro-D-glucitol	38.3
	2,5-anhydro-D-mannitol	33.1
	2,5-anhydro-D-glucitol	6.0
Cellulose	1,5-anhydro-D-glucitol	56.1
Starch	1,5-anhydro-D-glucitol	55.2
Levan	2,5-anhydro-D-mannitol	42.3
	2,5-anhydro-D-glucitol	8.5

2.4 Conclusion

The commercially viable transformation of commodity carbohydrates to high value added small chiral molecules and intermediates are imperative both environmentally and economically with the depleting of the fossil raw materials. An practical protocol for the preparation of anhydroalditols from commercially available carbohydrates was developed. The Allylation-Reduction-De-Allylation process transformed sucrose, cellulose, starch and levan to 1,5-anhydro-D-glucitol, 2,5-anhydro-D-mannitol and 2,5-anhydro-D-

glucitol in high yields and purity. The transformation was neat and clean, no column separation was needed for the preparation of 1,5-anhydro-D-glucitol from cellulose and starch. The catalytic cleavage of the allyl ether with the $PdCl_2$-$CuCl_2$-Activated-Carbon system makes these transformations more practical economically.

2.5 Experimental

General procedures: ^{1}H, ^{13}C NMR spectra were recorded at 500, 125, MHz, respectively, with a Varian instrument at 293 K. The chemical shifts are given in ppm using $CDCl_3$ residue as reference (δ7.24 ppm) for ^{1}H and relative to the central $CDCl_3$ resonance (δ= 77.00 ppm) for ^{13}C NMR unless otherwise specified. ^{1}H and ^{13}C are assigned on the basis of 2D ^{1}H COSY and ^{1}H-^{13}C chemical-shift correlated experiments. Melting points were determined on a Fisher-Johns melting point apparatus (uncorrected). Optical rotations were measured on a Jasco P1010 polarimeter at 20°C. IR spectra (wave numbers in cm^{-1}) were recorded on a FT IR Nicolet 740 spectrometer in $CHCl_3$ solutions or KBr pellets. All chemicals were purchased from Aldrich Chemical Co. and used without further purification.

Methyl-2,3,4,6-tetra-*O*-allyl-α-D-glucopyranoside (6)

To a stirred solution of methyl-α-D-glucopyranoside (1.94g, 10mmol) in DMSO (50ml), was added powered NaOH (2.72 g, 68 mmol). After stirring at r.t. for 30 min, allyl bromide (68 mmol) was drop-wise added during a 30 min periond. Stirring was continued for 24 h at r.t., the reaction mixture was then poured into ice-water (100ml) and the stirring was continued for another 30 min. The mixture was extracted with Ethyl ether(3x50ml), dried over anhydrous Na_2SO_4, concentrated under reduced pressure, and the product was purified by column chromatography on silica gel. The product methyl-2,3,4,6-tetra-allyl-α-D-glucopyranoside **6** was obtained as a colorless oil (3.0 g, 85 %). $[\alpha]_D^{20}$ +94.0 (c 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 3.34 (s, 3H, OCH_3), 3.35 (dd, J = 3.4, 9.0 Hz, H-2), 3.40 (m, 1H, H-4), 3.57-3.60 (m, 3 H, H-5, H-6a, H-6b), 3.65 (t, J = 9.5 Hz, 1H,

H-3), 3.91-4.33 (m, 8H, 4 CH_2 O-allyl), 4.70 (d, J = 3.4, 1H, H-1), 5.06-5.24 (m, 8H, 4 CH_2 vinyl), 5.78-5.97 (m, 4H, 4 CH vinyl); ^{13}C NMR($CDCl_3$): δ 54.9 (OCH_3), 68.3 (C-6), 69.8, 72.3, 72.4, 73.7 (4 CH_2 O-allyl), 74.1, 77.2, 79.2, 81.3, 98.2 (C-1), 116.2, 116.5, 117.0, 117.4 (4 CH_2 vinyl), 134.4, 134.7, 134.8, 135.2 (4 CH vinyl); IR υ_{max} ($CHCl_3$) (cm^{-1}) 3080, 2982, 2910, 2844, 1645, 1460, 1422, 1384, 1351, 1200, 1150, 1083, 1052, 980, 920.

1,5-anhydro-2,3,4,6-tetra-*O*-allyl-D-glucitol (7)

To a solution of methyl-2,3,4,6-tetra-*O*-allyl-α–D-glucopyranoside(2.83 g, 8.0 mmol) in CH_2Cl_2(40 ml) at 0°C, were added Et_3SiH(2.68 ml, 16 mmol), BF_3OEt_2(3.48 ml, 24 mmol), and CF_3SO_3H(50 υl), and the reaction mixture was stirred at room temperature for 12 h. The reaction was then quenched with saturated aqueous $NaHCO_3$(50 ml) and extracted with CH_2Cl_2(3 x 50 ml). The combined dichloromethane extracts were washed with water and brine, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The product 1,5-anhydro-2,3,4,6-tetra-*O*-allyl-D-glucitol **7** was obtained as colorless oil (2.36 g, 91 %): $[\alpha]_D^{20}$ +58.7 (c 1, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 3.07 (dd, J=-10.3Hz, 11.0Hz, 1H, H-1-b), 3.23 (m, 1H, H-5), 3.28-3.31 (m, 2H, H3, H4), 3.35 (m, 1H, H-2), 3.60 (dd, J=2.0Hz, 10.5Hz, 1H, H-6a), 3.94 (m, 1H, H-1a), 3.97-4.08 (m, 5H, CH_2 O-allyl), 4.23-4.30 (m, 3H, CH_2 O-allyl), 5.08-5.26 (m, 8H, CH_2 vinyl), 5.76-5.96 (m, 4H, CH vinyl); ^{13}C NMR($CDCl_3$): δ 67.8(C-1), 68.7 (C-6), 71.7, 72.1, 73.5, 73.8 (4 CH_2-allyl), 77.2 (C-3 or C-4), 77.6 (C-3 or C-4), 79.0 (C-5), 85.5 (C-2), 115.9, 116.2, 116.6, 116.8 (4 CH_2 vinyl), 134.3, 134.6, 134.7, 135.1 (4 CH vinyl); υ_{max} ($CHCl_3$) 3083, 3008, 2924, 2867, 1672, 1462, 1423, 1350, 1243, 1151, 1087, 997, 933 cm^{-1}.

1,5-anhydro-D-glucitol (8)

(a) With $PdCl_2$ only as the catalyst: To a solution of 1,5-anhydro-2,3,4,6-tetra-O-allyl-D-glucitol(0.1 g, 0.31 mmol) in methanol(7 ml) was added $PdCl_2$(38.5 mg, 0.22 mmol), and the reaction mixture was stirred at 60°C for 8 h. After remove the solid and the solvent, the product 1,5-anhydro-D-glucitol **8** was obtained quantitatively (45 mg, 100 %).

(b) With $PdCl_2$-$CuCl_2$ catalyst system: To a solution of 1,5-anhydro-2,3,4,6-tetra-O-allyl-D-glucitol (0.1 g, 0.31 mmol) in methanol (7 ml) was added $PdCl_2$ (38.5mg, 0.22 mmol), and $CuCl_2$ (0.54 mg, 0.0031 mmol), the reaction mixture was stirred at 60°C for 8 h. After remove the solid and the solvent, 1,5-anhydro-D-glucitol **8** was in 91 % yield.

(c) With $PdCl_2$-$CuCl_2$-Activated Carbon catalyst system: To a solution of 1,5-anhydro-2,3,4,6-tetra-O-allyl-D-glucitol(5.0 g, 15.5 mmol) in methanol(350 ml) was added $PdCl_2$(27.0 mg, 0.155mmol), and $CuCl_2$ (2.1 g, 15.5 mmol), the reaction mixture was stirred at 60°C for 8 h. After remove the solid and the solvent, ,5-anhydro-D-glucitol **8** was in 90 % yield.

The crude 1,5-anhydro-D-glucitol was crystallized from EtOH: mp 142-143 °C; $[\alpha]_D^{20}$ +40.5 (c 1, H_2O); ^1H NMR (D_2O): 3.83(dd, 1H, J=11.2Hz, 2.6Hz, H-1'), 3.73(dd, 1H, J=13.7Hz, 1.0Hz, H-6), 3.53(ddd, 1H, J= 12.5, 4.2, 1.6, H-6'), 3.43(m, 1H, H-2), 3.28(m, 1H, H-3), 3.21(m, 2H, H-4, 5), 3.12(dd, 1H, J1=J2=11.0, H-1-b); ^{13}C NMR: 60.1(C-6), 68.0(C-1), 68.5(C-2), 68.8(C-4), 76.6(C-3), 79.4(C-5).

1,3,4,6-Tetra-O-acetyl-2,5-anhydro-D-glucitol.

The 1,5-anhydro-D-glucitol product obtained was acetylated using Ac_2O/Pyr for further structural identification.

^1H NMR ($CDCl_3$): δ 2.08, 2.10, 2.11, 2.12 (fours, 12 H, OAc), 4.06 (ddd, **1** H, H-2), 4.22-4.40 (complex, 4 H, H-1,1',6,6'), 5.00 (dd, J = 1.5, J = 3.5, 4.8, 6.3 Hz, 1 H, H-5), 4.16 (ddd, J = 3.7, 6.4, 11.3 Hz, 3.5 Hz, 1 H, H-4), 5.32 (dd, J = 1.5, 3.7 Hz, 1 H, H-3).

The Allylation, reduction and deprotection of other monosaccharides are the same as the ones for glucoside, except that the reaction time varied.

Methyl 2,3,4,6-tetra-*O*-allyl-α-D-mannopyranoside (10)

The same procedure as for the preparation of methyl 2,3,4,6-tetra-*O*-allyl-α-D-mannopyranoside gave methyl 2,3,4,6-tetra-*O*-allyl-α-D-mannopyranoside **10** as a colorless oil (87 %): ^1H NMR(500 M Hz, CD_3Cl): δ 3.25 (s, OMe), 3.53-3.56 (m, 1H, H-5), 3.57-3.59 (m, 4H, H-2, H-4, H-6a, H-6b), 3.91-4.08 (m, 8H, 4 CH_2 O-allyl), 4.26 (dd, J = 5.7, 11.4 Hz, 1H, H-3), 4.63 (s, 1H, H-1), 5.02-5.23 (m, 8H, 4 CH_2 vinyl), 5,78-5.88 (m, 4H, 4 CH vinyl); ^{13}C NMR (125M Hz, $CDCl_3$) δ 54.5 (OMe), 69.2 (C-6), 70.9, 71.2, 71.8, 72.2 (4 CH_2 O-allyl), 73.7, 74.5, 74.6, 79.3, 98.9 (C-1), 116.3, 116.4, 116.6, 117.2 (4 CH_2 vinyl), 134.7, 134.8, 134.9, 135.0 (4 CH vinyl).

1,5-anhydro-2,3,4,6-tetra-*O*-allyl-D-mannitol (11)

The product was obtained as colorless oil (2.36g, 91 %): ^1H NMR ($CDCl_3$): 3.29 (dd, J = 12.8, 1.1 Hz, 1H, H-1b), 3.32 (ddd, J = 9.5, 6.3, 2.0 Hz, 1H, H-5), 3.40 (dd, J = 9.3 Hz, 1H, H-3), 3.57(t, J = 9.7 Hz, 1H, H-4), 3.61(dd, J = 10.5, 6.3 Hz, 1H, H-6b); 3.70(dd,

J=10.5 Hz, 2.0 Hz, 1H, H-6a); 3.71(m, 1H, H-2); 3.98-4.06(m, 6H, H-1a, CH_2 O-allyl); 4.14-4.19(m, 2H, CH_2 O-allyl), 4.34(m, 1H, CH_2 O-allyl), 5.10-5.18(m, 4H, CH_2 vinyl), 5.20-5.30(m, 4H, CH_2 vinyl), 5.85-5.96(m, 4H, 4 CH vinly); ^{13}C NMR($CDCl_3$): 67.1(C-1), 69.8(C-6), 70.6, 70.7, 72.5 (3 carbon, 3 CH_2 O-allyl), 72.7 (C-2), 74.1 (CH_2 O-allyl), 75.2(C-4), 79.6 (C-5), 82.3 (C-3), 116.6, 116.9, 117.2, 117.5 (4 CH_2 vinyl), 134.8, 134.9, 135.0, 135.1 (4 CH_2 vinyl); υ_{max} ($CHCl_3$) cm^{-1} 3080, 3010, 2928, 2865, 1674, 1459, 1424, 1355, 1244, 1157, 1087, 995, 930 cm^{-1}.

1,5-Anhydro-D-mannitol (12)

To a solution of 1,5-anhydro-2,3,4,6-tetra-O-allyl-D-mannitol (1.0 g, 3.1 mmol) in methanol(70 ml) was added $PdCl_2$(6.0 mg, 0.031 mmol), and $CuCl_2$ (0.42 g, 3.1 mmol), the reaction mixture was stirred at 60°C for 8 h. After remove the solid and the solvent, 1,5-anhydro-D-mannitol **9** was in 92 % yield (0.47 g): mp 154-155 °C; $[\alpha]_D^{20}$ - 50.5 (c 1, H_2O); ^1H NMR (D_2O): δ 3.86 (br s, 1H), 3.80 (dd, J = 12.5, 1.5 Hz, 1H), 3.77 (dd, J = 12.5, 2.5, Hz, 1H), 3.57 (dd, J = 12.5, 6.4 Hz, 1H), 3.55-3.48 (m, 2 H), 3.46 (d, J = 9.5 Hz, 1H), 3.18 (ddd, J = 9.5, 6.5, 2.5 Hz, 1H); ^{13}C NMR (D_2O): δ 82.21, 75.20, 71.48, 70.69, 68.93, 62.85.

1,5-anhydro-2,3,4,6-tetra-O-acetyl-D-mannitol.

^1H NMR ($CDCl_3$): 2.01, 2.05, 2.11, 2.17 (4 s, 12 H, OAc), 3.59 (ddd, H-la), 4.07 (dd, *J* = 2.1, 13.2 Hz, 1 H, H-le), 4.14 (dd, *J* = 2.4, *J* = 2.4, 5.4, 9.9 Hz, 1 H, H-5), 3.67 (dd, *J* = 1.3, 13.2 Hz, 1 H, 12.3 Hz, 1 H, H-6), 4.24 (dd, *J* = 5.4, 12.3 Hz, 1 H, H-6), 5.06 (dd, *J* = 3.5, 10.0 Hz, 1 H, H-3), 5.28 (t, *J* = 10.0 Hz, 1 H, H-4), 5.32 (complex, 1 H, H-2).

For methyl D-ribofuranosides, a α/β mixture was used as the starting material for reduction. The tri-O-allyl products were partially separated, and methyl 2,3,5-tri-*O*-allyl-β-D-ribofuranoside was obtained while the α anomer was obtained as its mixture with the β anomer.

Me-2,3,5-tri-*O*-allyl-α-D-ribofuranoside.

^{13}C NMR ($CDCl_3$): δ 55.0 (OMe), 70.0 (C-5), 71.2, 71.3, 71.5 (3 CH_2 O-allyl), 75.2(C-), 77.9 (C-), 81.6 (C-), 102.0 (C-1), 116.7, 117.1, 117.3 (3 CH_2 vinyl), 134.3, 134.4, 134.7 (3 CH vinyl).

Me-2,3,5-tri-*O*-allyl-β-D-ribofuranoside

^{1}H-NMR δ 3.26 (s, 3H, OMe), 3.42 (dd, J = 5.9, 10.8 Hz, 1H, H-5a), 3.50 (dd, J = 4.0, 10.7 Hz, 1H, H-5b), 3.72 (d, J = 4.7 Hz, 1H, H-2), 3.86 (dd, J = 4.5, 7.5 Hz, 1H, H-3), 3.95-4.00 (m, 4H, 2 CH_2 O-allyl), 4.03-4.06 (m, 2 H, CH_2 O-allyl), 4.12 (ddd, J = 4.3, 6.0, 10.7 Hz, 1H, H-4), 4.79 (s, 1H, H-1), 5.05-5.24(m, 6H, 3 CH_2 vinyl), 5.74-5.89(m, 3H, (3 CH vinyl); ^{13}C NMR($CDCl_3$): δ 54.7 (OMe), 71.2 (3 carbon, 3 CH_2 O-allyl), 71.9 (C-5), 78.1, 79.5, 80.1, 106.1 (C-1), 116.5, 117.1, 117.2 (3 CH_2 vinyl), 134.1, 134.2, 134.5(3 CH vinyl).

1,4-anhydro-2,3,5-tri-*O*-allyl-D-ribitol (15)

Reduction of pure methyl-2,3,5-tri-*O*-allyl-β-D-ribofuranoside and a mixture of α/β anomers gave the same product 1,4-anhydro-2,3,5-tri-*O*-allyl-D-ribitol **15** as a

colorless oil in 90 % yield: ^{1}H-NMR δ 3.44 (dd, J = 4.4, 10.8 Hz, 1H, H-5a), 3.54 (dd, J = 3.5, 10.7 Hz, 1H, H-5b), 3.81 (t, J = 5.6 Hz, 2H, H-), 3.92-4.03 (m, 8H, 3 CH_2 O-allyl), 4.08 (m, 1H, H-5), 5.08-5.26(m, 6H, 3 CH_2 vinyl), 5.78-5.91(m, 3H, 3 CH vinyl); ^{13}C NMR($CDCl_3$): δ 69.9, 70.4, 70.8, 71.1, 72.2, 76.4, 78.1, 80.1, 116.7, 117.1, 117.2 (3 CH_2 vinyl), 134.3, 134.4, 134.4(3 CH vinyl).

1,4-anhydro-D-ribitol (16)

De-allylation of 1,4-anhydro-2,3,5-tri-*O*-allyl-D-ribitol gave 1,4-anhydro-D-ribitol **16** in 89 % yield: mp 101-102 °C ; $[\alpha]_D^{20}$ +63.0; ^{1}H-NMR (D_2O) δ 3.45 (m, 2 H, H-5, H-5'), 3,63 (m 3 H), 3.89 (m, 2 H), 4.09 (m, 1 H); ^{13}C NMR (D_2O) δ 61.5, 71.2, 71.7, 72.4, 81.7.

1,4-anhydro-2,3,5-Tri-O-acetyl-D-ribitol.

^{1}H NMR ($CDCl_3$): δ 2.08, 2.09, 2.10(3 s, 9 H, OAc), 3.87 (dd, *J* = 3.9, 10.3 Hz, 1 H, H-la), 4.12 (dd, *J* = 5.0, 11.3 Hz, 1 H, H-5), 4.16 (complex, 1 H, H-4), 4.23 (dd, *J* = 5.2, 10.3 Hz, 1 H, H-lb), 4.33 (complex, 1 H, H-5'), 5.13 (complex, 1 H, H-3), 5.37 (dt, *J* = 3.9, 5.3 Hz, 1 H, H-2); ^{13}C NMR($CDCl_3$): δ 19.9, 20.0, 20.0 (3 Me from Ac), 61.0, 61.2 (C-1 and C-5), 67.4(C-2), 68.5, 68.6 (C-3 and C-4), 169.0, 169.2, 169.6(3 Ac)

Octa-O-allyl-sucrose (18)

In a 250 ml round bottom flash was added NaH (60 % in mineral oil, 6.7 g, 140 mmol), after washing with hexanes (3 x 20 ml), DMSO (150 ml) was added, followed by addition of a solution of sucrose (3.0 g, 8.77 mmol)I in DMSO (30 ml). Water bath was used to control the temperature of the reaction mixture below 45°C. After stirring for 1 h,

allyl bromide (9.2 ml, 105 mmol) was drop wised added over 30 min period, with water bath to control the temperature below 50°C. After stirring at 45°C for 12 h, the reaction mixture was poured into cold water, and extracted with diethyl ether (4 x 70 ml). The combined organic layer was washed with water (3 x 100 ml), brine (3 x 100ml) and then dried over anhydrous sodium sulfate. After filtration and removal of the solvent under reduced pressure, a colorless oil (5.9 g) was obtained. NMR shown the product was the desired octa-O-allylsucrose with > 96 % purity (85 % yield). Small amount the raw product was further purified by flash column (Hexanes/Ethyl Acetate: 1/9) for characterization purpose. $[\alpha]_D^{20}$ + 58.0° (c 1.00, EtOAc); ^{1}H-NMR δ 3.25 (dd, J = 3.9, 9.7 Hz, 1H, H-2), 3.34 (dd, J = 6.4, 9.1 Hz, 1H, H-4), 3.41 (s, 1H, H-lb'), 3.52-3.62 (m, 6 H, H-3, H-6a, H-6b, H-l'a, H-6'a, H-6'b), 3.87 (m, 1H, H-5'), 3.91-3.96(m, 5 H, H-5, 2 CH_2 O-allyl), 3.98 (m, 2 H, CH_2 O-allyl), 4.00(m, 3 H, H-4', CH_2 O-allyl), 4.04-4.06(m, 4 H, 2 CH_2 O-allyl), 4.11-4.18(m, 4 H, 2 CH_2 O-allyl), 4.22-4.30(m, 1H, H-3'), 5.14-5.30 and 4.98-5.13 (m, 16H, CH_2 vinyl), 5.49(d, J = 3.8 Hz, 1H, H-1), 5.74-5.94 (m, 8H, CH_2 vinyl); ^{13}C NMR($CDCl_3$): δ 68.4 (C-6), 70.2 (C-5), 70.6 (C-1'), 71.2 (CH_2-3' O-allyl), 71.5 (CH_2-4' O-allyl), 71.5 (CH_2-2 O-allyl), 71.9 (C-6'), 71.9 (CH_2-6' O-allyl), 72.2 (CH_2-6 O-allyl), 72.2 (CH_2-1' O-allyl), 73.5 (CH_2-4 O-allyl), 73.9 (CH_2-3 O-allyl), 76.9 (C-4), 79.2 (C-2), 79.4 (C-5'), 81.1 (C-3), 82.2 (C-4'), 83.3 (C-3'), 89.9 (C-1), 104.3 (C-2'), 116.0, 116.2, 116.2, 116.5, 116.5, 116.6, 116.7, 116.8, (8 CH_2 vinyl), 134.4, 134.5, 134.6 (3 carbon), 134.8, 135.0, 135.4, (8 CH vinyl).

Reduction of Octa-O-allyl-sucorse

To a solution of Octa-O-allyl-sucrose **18** (3.31 g, 5.0 mmol) in CH_2Cl_2 (40 ml) at 0°C, were added Et_3SiH (3.35 ml, 20 mmol), BF_3OEt_2 (4.35 ml, 30 mmol), and CF_3SO_3H (60

υl), and the reaction mixture was stirred at room temperature for 12 h. The reaction was then quenched with saturated aqueous $NaHCO_3$ (50 ml) and extracted with CH_2Cl_2 (3 x 50 ml). The combined dichloromethane extracts were washed with water and brine, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. Flash column chromatography gave three products **7**, **19** and **20**.

1,5-anhydro-2,3,4,6-tetra-*O*-allyl-D-glucitol (7): 45 % yield, gave the same spectra data as the product from reduction of methyl 2,3,4,6-tetra-*O*-allyl-α-D-glucopyranoside.

2,5-anhydro-1,3,4,6-tetra-*O*-allyl D-mannitol 20: 39% yield, $[\alpha]_D^{20}$ + 26.4° (c 1.00, $CHCl_3$); ^{1}H-NMR δ 3.48 (dd, J = 4.3, 5.8 Hz, 4H, H-1a, H-1b, H-6a, H-6b), 3.88 (dd, J = 1.4, 2.5 Hz, 2H, H-3, H-4), 3.95-3.99 (m, 8H, 4 CH_2 O-allyl), 4.03-4.06 (m, 2H, H-2, H-5), 5.08-5.12 (m, 4H, CH_2 vinly), 5.18-5.24 (m, 4H, CH_2 vinly), 5.78-5.86 (m, 4H, CH vinly); ^{13}C NMR($CDCl_3$): δ 70.0 (2 carbon, C-1, C-6), 70.5 (2 carbon, CH_2 O-allyl), 72.1 (2 carbon, CH_2 O-allyl), 81.4 (2 carbon, C-2, C-5), 84.6 (2 carbon, C-3, C-4), 116.7 (2 carbon, 2 CH_2 vinyl), 116.8 (2 carbon, 2 CH_2 vinyl), 134.2 (2 carbon, 2 CH vinyl), 134.5 (2 carbon, 2 CH_2 vinyl); Anal. Calcd for C18H28O5: C, 66.64; H, 8.70. Found: C, 66.56; H, 8.62.

2,5-anhydro-D-mannitol (22): $[\alpha]_D^{20}$ +52.2 ° (c 1.00, H_2O); M.p. 100-102 ° C; ^{1}H NMR (D_2O): δ 3.68 (dd, J1 = J2 = 5.6 Hz, 2H, H-1b, H-6b), 3.78 (dd, J = 3.1, 12.4 Hz,

2H, H-1a, H-6a), 3.90(m, 2H, H-2, H-5), 4.05(m, 2H, H-3, H-4); ^{13}C NMR($CDCl_3$): δ 61.3 (2 carbon, C-1, C-6), 76.6 (2 carbon, C-3, C-4), 82.4 (2 carbon, C-2, C-5).

1,3,4,6-Tetra-O-acetyl-2,5-anhydro-D-mannitol: $[\alpha]_D^{20}$ + 26.5 ° (c 1.00, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 2.11 (s, 12 H, 4 OAc), 4.25 (s, 6 H, H-1a,1H-1b, H-2, H-5, H-6a, H-6b), 5.16 (ss, 2 H, H-3, H-4); ^{13}C NMR($CDCl_3$): δ 21.2 (4 carbon, CH_3 OAc), 63.4 (2 carbon, C-1, C-6), 78.5 (2 carbon, C-3, C-4), 81.4 (2 carbon, C-2, C-5), 170.3 and 171.0 (2 carbon, C=O Ac).

2,5-anhydro-1,3,4,6-tetra-*O*-allyl D-glucitol (19) 7 % yield,

^1H-NMR δ 3.46 (m, 4 H, H-1a, H-1b, H-6a, H-6b), 3.90 (m, 2H, H-3, H-4), 3.93-3.99 (m, 8H, 4 CH_2 O-allyl), 4.00-4.05 (m, 2H, H-2, H-5), 5.07-5.12 (m, 4H, CH_2 vinly), 5.19-5.25 (m, 4H, CH_2 vinly), 5.79-5.86 (m, 4H, CH vinly); ^{13}C-NMR δ 70.2(C-1 or C-6), 70.4 (C-1 or C-6), 70.5, 70.9, 72.0, 72.9 (4 CH_2 O allyl), 75.3, 79.0, 83.1, 83.7, 116.1, 116.6, 116.7, 117.0 (4 CH_2 vinyl), 134.4, 134.7, 134.9, 135.3 (4 CH vinyl).

2,5-Anhydro-D-glucitol (21)

^1H NMR (D_2O): δ 3.68 (dd, J = 12.1, 6.0 Hz, 1H, H-1), 3.73 (dd, J = 7.0, 11.8 Hz, 1H, H-6), 3.77 (dd, J = 3.8, 12.1 Hz, 1H, H-1'), 3.82 (dd, J = 4.3, 11.8 Hz, 1H, H6'), 3.84 (ddd, J = 3.7, 4.3, 6.0 Hz, 1H, H-2), 4.01 (dd, J = 2.4, 4.3 Hz, 1H, H-3), 4.12 (dt, J = 4.4, 7.0 Hz, 1H, H-5), 4.17 (dd, J = 2.5, 4.3 Hz, 1H, H-4); ^{13}C-NMR(D_2O): δ 60.7, 62.3 (C-1, C-6), 77.5, 78.6, 81.5, 85.2 (C-2, C-3, C-4, C-5).

General method for the preparation of tri-O-allyl-polysaccharides:

Unprotected polysaccharide(1.0 gram) was dissolved in DMSO (50ml) at 60 °C, NaH (60 % in mineral oil, 5.84g, 122 mmol, 5 mol/mol hydroxlyl group) was added to this after washing with hexanes (3 x 20 ml). After stirring at r.t for 1 h under nitrogen atmosphere, allyl bromide (10.7 ml, 122 mmol) was drop wised added over 30 min period, with water bath to control the temperature below 50°C. After stirring at r.t. for 12 h, the reaction mixture was poured into cold water, and extracted with chloroform (4 x 50 ml). The combined organic layer was washed with water (3 x 100 ml), brine (3 x 100ml) and then dried over anhydrous sodium sulfate. After filtration and removal of the solvent under reduced pressure, the tri-O-allyl-polysaccharides were obtained as a syrup.

General method for the reduction of tri-O-allyl-polysaccharides:

The methods for the reduction of tri-O-allyl-polysaccharides are the same as for monosaccharides, except longer times (24 h) were needed for the reduction to complete.

Tri-*O*-allyl-cellulose (24)

85 % yield for allylation: ^{1}H NMR ($CDCl_3$): δ 3.14 (br, 1H), 3.54 (br, 1H), 3.84-4.00 (br, 2H), 4.12 (br,1H), 4.16-4.30 (br, 1H), 4.49-4.64 (br, 8H, 4 CH_2 O-allyl), 4.93-5.27 (br, 9H, H-1, 4 CH_2 vinyl), 5.66-5.93 (br, 4H, 4 CH vinyl); ^{13}C NMR($CDCl_3$): δ 69.2 (br, C-6), 73.3 (br, C-5), 75.2-76.0 (br, CH_2 O-allyl), 76.1 (br, C-3), 82.3 (br, C-2), 84.2 (br, C-4), 102.9 (br, C-1), 116.3-117.0 (br, CH_2 vinyl), 134.9-135.5 (br, CH vinyl);

Reduction-deprotection steps gave 1,5-anhydro-D-glucitol in 66 % for 2 steps.

Tri-*O*-allyl-starch (26)

85 % yield for allylation: : ^{1}H NMR ($CDCl_3$): δ 3.32 (br, 1H), 3.55 (br, 1H), 3.65 (br, 1H), 3.85-4.28 (br, 12 H, H-1, 4 CH_2 O-allyl), 5.00-5.23 (br, 8H, 4 CH_2 vinyl), 5.60-5.85 (br, 4H, 4 CH vinyl); ^{13}C NMR($CDCl_3$): δ 68.2(br, C-6), 70.0(br, C-5), 72.0-72.4 (br, 4 CH_2 O-allyl), 73.1 (br, C-3), 79.5 (br, C-4), 81.4 (br, C-2), 116.2-117.0 (br, CH_2 vinyl), 134.7-135.8 (br, CH vinyl);

Reduction-deprotection steps gave 1,5-anhydro-D-glucitol in 65 % for 2 steps.

Tri-*O*-allyl-levan (28)

78 % yield for allylation: ^{1}H NMR ($CDCl_3$): δ 3.42-3.58 (m, 2H, H-6a, H-6b), 3.79-3.94(m, 2H, H-3, H-4), 4.02-4.44(m, 11H, H-1a, H-1b, H-5, 4 CH_2 O-allyl), 5.18-5.55(m, 8H, CH_2 vinyl), 5.84-6.12(m, 4H, CH vinyl); ^{13}C NMR($CDCl_3$): δ 62.2(br, C-6), 71.0(br), 71.1(br), 72.2(br), 72.3(br, 4 CH_2 O-allyl), 72.3(br, C-5), 78.0(br, C-1), 82.1(br, C-4), 83.9(br, C-3), 103.8(br, C-2), 116.4(2 CH_2 vinyl), 116.7(2 carbon CH_2 vinyl), 134.5, 134.7, 134.8, 135.0(4 CH vinyl).

Reduction-deprotection gave 2,5-anhydro-D-mannitol (54.2 %), 2,5-anhydro-D-glucitol (10.8 %).

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Chapter 3

Advanced Derivatives of 1, 5-Anhydro-D-Glucitol

Abstract

Anhydroalditols and their derivatives are considered metabolically inert for lacking the C1 hydroxyl group. The glucose 6-phophate analogue 1,5-Anhydro-D-glucitol 6-phosphate is widely used as a hexokinase inhibitor in the study of enzyme mechanisms and as a probe to study carbohydrate metabolic pathways. Recently, deoxy anhydroalditols have been used in the construction of biologically important molecules, such as anhydrohexitol nucleosides, which showed activities against herpes simplex virus, Sialyl Lewis^x analogues as potent E-selectin inhibitors. They have also been used in the preparation of catalysts for enantioselective cyanation of ketones. With the easily available anhydroalditols through the reductive cleavage of complex carbohydrates, these anhydroalditols and deoxy anhydroalditols can be easily prepared. From 1,5-anhydro-D-glucitol, 1,5-Anhydro-D-glucitol–6-phosphate was prepared from 1,5-anhydro-D-glucitol in two steps in over 60 % yield. The important deoxy-anhydrohexitols, which are components of E-selectin inhibitors, scaffolds of anhydrohexitol nucleosides and chiral catalysts, were also prepared from 1,5-anhydro-D-glucitol efficiently.

3.1 Introduction

3.1.1 Glycolysis and 1,5-anhydro-D-glucitol-6-phosphate

Glycolysis is a catabolic pathway in the cytoplasm that is found in almost all organisms- irrespective of whether they live aerobically or anaerobically[1]. During glycolysis, glucose is oxidized to either lactate or pyruvate. Figure 3.1 lists the substrates and enzymes for the first several steps of glycolysis and the corresponding anhydrosugars as the substrate analogues. The first step of glycolysis is the ATP-dependent phosphorylation of glucose to form glucose 6-phosphate catalyzed by the isoenzymes known as hexokinases. The phosphorylation of glucose accomplishes two goals: First, nonionic glucose was converted into glucose 6-phosphate (G6P), an anion that is trapped in the cell, since cells lack transport systems for phosphorylated sugars. Second, the otherwise biologically inert glucose becomes activated into a labile form capable of being further metabolized.

The second reaction of glycolysis is an isomerization, in which G6P is converted to fructose 6-phosphate (F6P). The enzyme catalyzing this reaction is glucose 6-phosphate isomerase. The reaction is freely reversible at normal cellular concentrations of the two hexose phosphates and thus catalyzes this interconversion during glycolytic carbon flow and during gluconeogenesis.

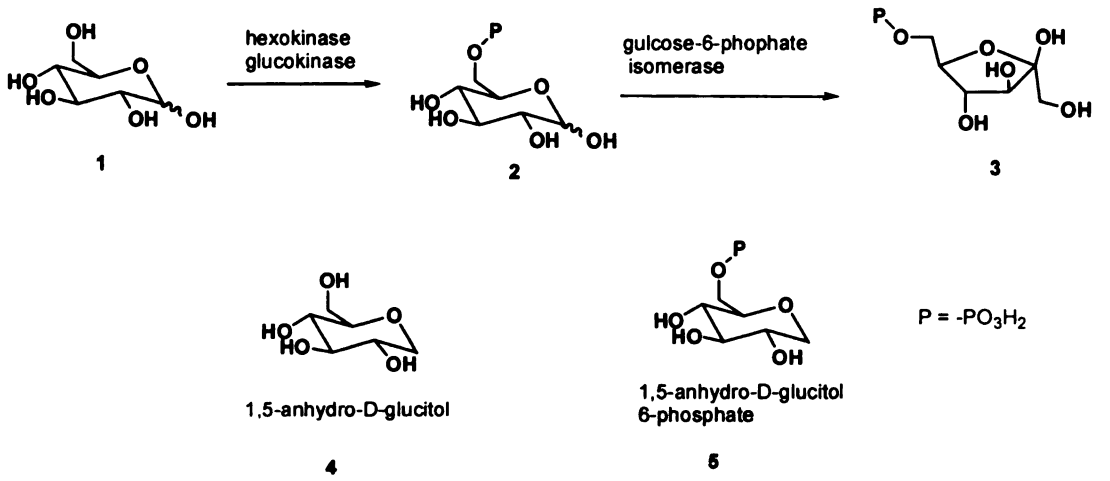


Figure 3.1 Anhydrosugars as substrate analogues in carbohydrate glycolysis.

Substrate analogues are useful tools in the study of enzyme catalyzed reaction mechanisms. Such analogues could help in the identification of the active substrate conformation or configuration or in the stabilization of reaction intermediates. Thus changes of the substrates during the enzyme catalyzed reactions could be identified at molecular level. Some sugar metabolizing enzymes have been studied using this method[2-4].

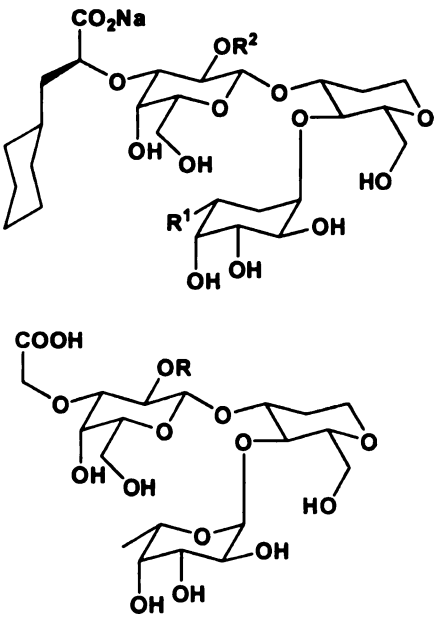
1,5-Anhydro-D-glucitol **4** and 1,5-anhydro-D-glucitol 6-phosphate **5** are the analogue of D-glucose **1** and D-glucose-6-phosphate **2**. Because **4** and **5** lack a hydroxyl group at the C1 position of the pyranose ring, they are considered to be metabolically inert. 1,5-Anhydro-D-glucitol 6-phosphate **5** is widely used as a hexokinase inhibitor in the study of enzyme mechanisms and as a probe to study carbohydrate metabolic pathways[5-10].

3.1.2 Deoxy anhydroalditols: application in construction of biologically important molecules and chiral catalysts

Deoxysugars are carbohydrates in which one or more of the normally occurring oxygen atoms are deleted (i.e., replaced by hydrogen atoms) or replaced by any other heteroatom or heteroatomic group, such as sulfur (thiosugars), halogen, nitrogen (aminosugars) or NO_x (nitro- and nitrososugars)[11].

Many of those naturally occurring deoxysugars have been shown to serve as ligands for cell-cell interactions or as targets for toxins, antibodies, and microorganisms[12-16]. The replacement of one or more hydroxyl groups in these sugars by various functionalities generally induces fundamental changes in the chemical properties of the resulting monosaccharides and, therefore, has a direct bearing on the wide range of their biological activities[17]. Deoxysugars are also frequently found in the secondary metabolites of microorganisms and plants, such as cardioglycosides, antibiotics, and anticancer agents[18]. These sugar residues play crucial roles in conferring optimal biological activity for many natural products. Their removal often results in the loss of all biological activity of the parent compounds[19].

Recently, another class of deoxysugars, the deoxy 1-deoxy sugars, or deoxy anhydrosugars, has been used in the construction of molecules which have important biological functions[20-23].



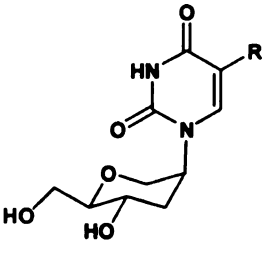
Sialy Lewis^x
relative IC_{50} (**E-Sel**) = 1.0

6 R^1 = Me R^2 = H IC_{50} = 0.020
7 R^1 = H R^2 = H IC_{50} = 0.305
8 R^1 = Me R^2 = Bz IC_{50} = 0.010
9 R^1 = H R^2 = Bz IC_{50} = 0.090

10 R = H IC_{50} > 5
11 R = Bz IC_{50} = 0.290

Figure 3.2 Sialyl Lewis^x analogues as potent E-selectin inhibitors.

Sialyl Lewis^x is a tetrasaccharide which is a weak E-selectin inhibitor (K_D = 1060 uM), it is a lead structure in the identification of simplified but more-potent selectin antagonists[20-22]. Thoma and co-workers prepared the simplified Sialyl Lewis^x analogues **6-11**, which contain a 1,5-anhydro-2-deoxy-D-glucitol building block (Figure 3.2)[20,22]. The much simplified trisaccharides showed enhanced inhibitory properties against E-selectin. The most potent compound is **8**, which is 100-fold more potent than Sialyl Lewis^x in the binding assay and has an IC_{50} value of 1-2 υM in a cell-based in vitro flow assay.



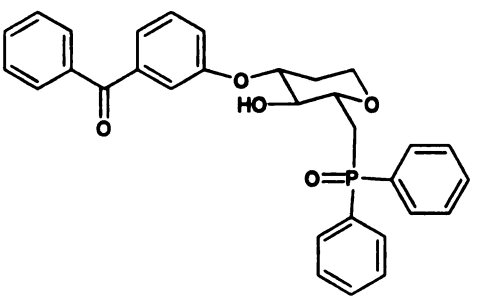
12 R = I
13 R = Cl
14 R = CF3
15 R = –CH=CH2

16 R =
17 R = –C≡CH
18 R = –C≡C–CH3

Figure 3.3 Anhydrohexitol Nucleosides

Recently, a series of anhydrohexitol nucleosides (compounds **12-18,** Figure 3.3) are prepared and tested against herpes simplex virus (HSV)[23]. The trifluoromethyl, vinyl, and propynyl analogues **14**, **15** and **18** showed potent activity against HSV. The selectivity index for **15** is large than 16000 against HSV-1 and larger than 1000 against HSV-2.

The deoxy anhydroalditols have also been used as scaffold for the construction of catalyst for enantioselective cyanosilylation of ketones. High yields and ee's were obtained for aryl ketones (Figure 3. 4)[24,25].



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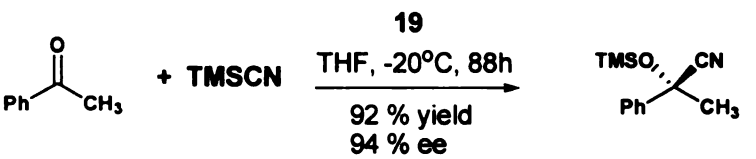


Figure 3.4 Deoxy anhydroalditols based chiral catalysts

Although these anhydroalditols derivatives have been used extensively, no general route is available for their preparation. With the easily available anhydroalditols through our reduction method as discussed in chapter 2, these anhydroalditols derivatives can be easily prepared.

3.2 Preparation of 1,5-anhydro-D-glucitol-6-phosphate

With 1,5-anhydro-D-glucitol in hand, 1,5-Anhydro-D-glucitol 6-phosphate was easily prepared in several steps (Figure 3.5).

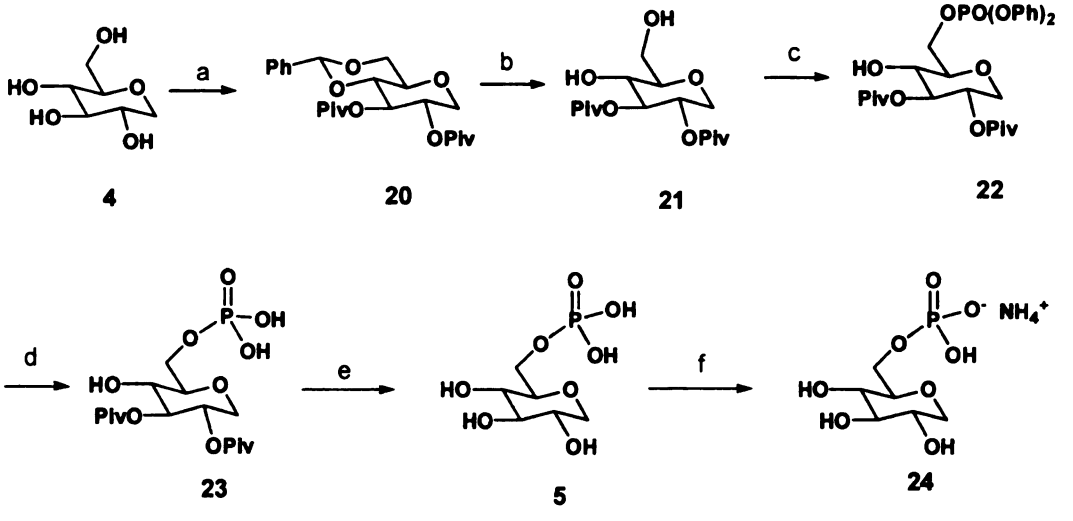
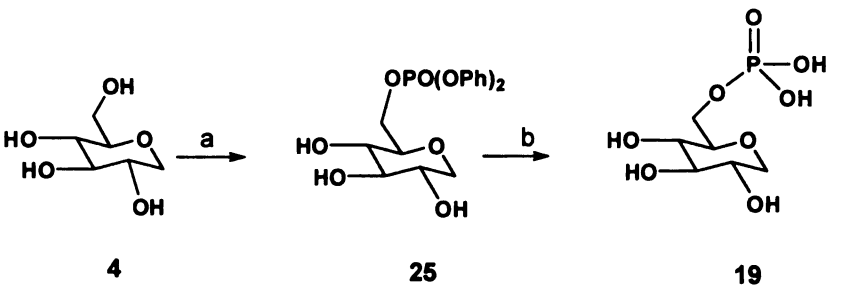


Figure 3.5 Preparation of 1,5-Anhydro-D-glucitol 6-phosphate

(a) 1). $PhCH(OMe)_2$, p-TsOH, DMF; 2). PivCOCl, Pyr, 83 %, 2 steps; (b). EtOH-H_2O-CF_3COOH, 85%; (c). $(PhO)_2POCl$/Pyr, 62%; (d). H_2, PtO_2, MeOH, 100%; (e). NaOMe, MeOH, 83%; (f). NH_3, 100%.

The 4,6-hydroxy groups were first protected with benzylidene by treatment of 1,5-anhydro-D-glucitol **4** with benzaldehyde dimethyl acetal in DMF. The 2 and 3 hydroxy groups were then protected with pivolyl groups to afford the fully protected 1,5-anhydro-D-glucitol derivative **20**. Treatment of **20** with EtOH-H_2O-CF_3COOH (60:8:1) gave compound **21** with 4, 6 hydroxyl groups freed. Phosphorylation of **21** using $(PhO)_2P(O)Cl$ in pyridine was selective among the primary and secondary hydroxyl groups and gave the protected phosphate ester **22**. The final product **19** was obtained

from **22** by first removing the Ph group using H_2/PtO_2 and then removing the pivolayl group using NaOMe/MeOH. Because **19** is a strong acid, it was converted to its ammonia salt **24** by treatment with ammonia.



4 **25** **19**

Figure 3.6 Preparation of 1,5-Anhydro-D-glucitol 6-phosphate using the direct phosphorylation method. (a) $(PhO)_2POCl/Pyr$; (b) H_2, PtO_2, MeOH.

Because $(PhO)_2P(O)$ is a sterically demanding reagent, it is expected that under controlled conditions, the selective mono-functionalization of **4** is possible. Thus, the direct transformation of **4** to **25** was attempted (Figure 3.6). Treatment of **4** with 1 equivalent of $(PhO)_2P(O)Cl$ in pyridine gave the protected 6-phosphate **25** in 60 % isolated yield. Deprotection of **25** using H_2/PtO_2 gave **19** directly in quantitative yield. Compared to the method in figure 3.5, this method is more straightforward, and 1,5-anhydro-D-glucitol-6-phosphate **19** was prepared in two steps in 60 % overall yield from 1,5-anhydro-D-glucitol **4**.

3.3 Preparation of Deoxysugars from 1, 5 –anhydro-D-glucitol

3.3.1 Formation of 2,3-anhydro derivatives of 1,5-anhydro-D-glucitol

The 2,3-anhydro derivatives **27** and **28** can be easily prepared from **26** since the 2, 3 hydroxyl groups are anti to each other. Transforming one of the hydroxyl groups to a good leaving group followed by an intramolecular attack from the other free hydroxyl group will form the 2,3-anhydro derivaties[26-29].

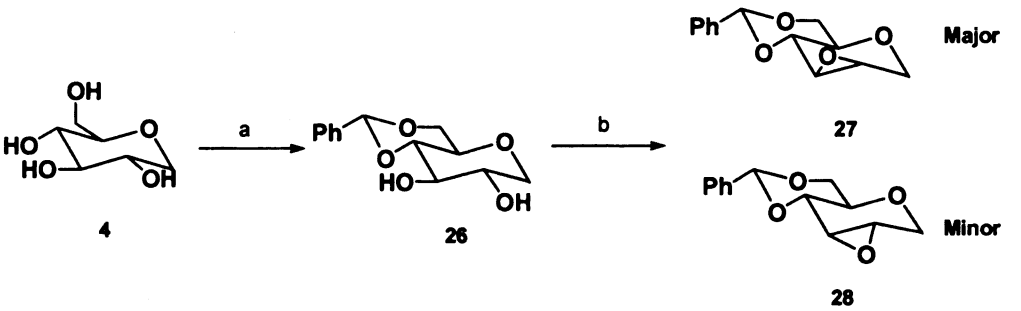


Figure 3.7 Preparation of 4,6-benzylidene-2,3-epoxide derivatives of 1,5-anhydro-D-glucitol (a) $PhCH(OMe)_2$, pTsOH, DMF, r.t. 12 h, 82 %; (b.) Ph_3P, DIAD, THF, 60°C, 12 h, 72 %, **27**/**28** 2.1/1

Reaction of **4** with benzaldehyde dimethyl acetal in DMF with catalytic amount of *p*-TsOH gave 4,6-O-benzylidene protected derivative **26** in 82 % yield. Treatment of 26 under Mitsunobu conditions (Ph_3P, DIAD) at room temperature for 24 hour gave no product. Raising the reaction temperature to 60°C, the reaction was done in 12 hour. Compound **27** with *manno* configuration was formed as the major product in 48.8 % and compound **28** with *allo* configuration was formed as the minor product in 23.2 % (Figure 3.7).

The mechanism for formation of **27** and **28** is shown in figure 3.8. Formation of the triphenylphosphonium intermediate **29** followed by intramolecular attach by 3-OH gave **27**, while formation of the triphenylphosphonium intermediate **30** at 3-OH followed by intramolecular attach by 2-OH gave **28**. In intermediate **30**, there is a very severe steric

interaction between the triphenylphosphonium ion and the 4,6-O-benzylidene ring, while in **29**, this steric interaction is greatly reduced.

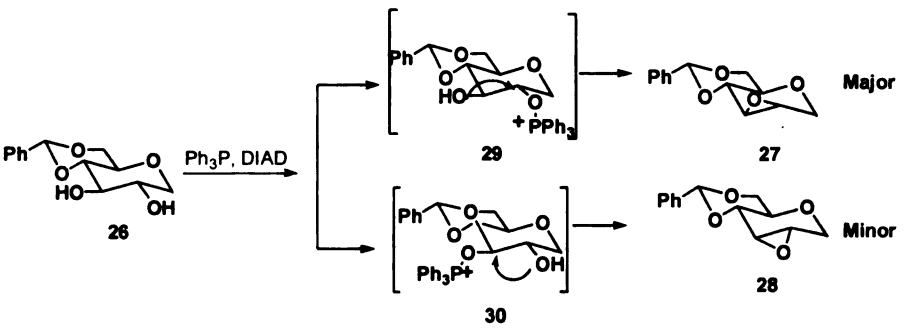


Figure 3.8 Mechanism for the formation of 2,3-anhydro derivatives under Mitsunobu conditions.

(p-Tolylsulfonyl)imidazole (ImTs) has also been used in the construction of 1,2 anhydro sugars from 1,2 diols in carbohydrates. With ImTs, the separation of the products from the reaction mixture is easier compared to Ph_3P/DIAD[30-33]. For substrate **26**, another advantage using ImTs is that formation of epoxides **27** and **28** can be controlled by the reaction conditions. If ImTs was added immediately after adding NaH (2.2 equivalent), a mixture of **27** and **28** was obtained in 67 % yield (**27**/**28** 3/1). While if **26** was treated with NaH (2.2 equivalent) for 2 hour and then adding ImTs, only **27** was obtained and the yield is very high (86 %).

The different results came from the formation of either monoalkoxide or dialkoxide derivative of **26**. After adding NaH, the C-2 or C-3 monoalkoxide (**31** or **32**) was formed at first. If adding ImTs at this time, a mixture of C-2 or C-3 tosylate was formed and thus the final products were obtained as mixture of **27** and **28**. However, if adding ImTs after the dialkoxide **33** was formed, the formation of C-2 or C-3 tosylate was controlled by the

steric effect, and the more sterically favored C-2 tosylate was formed. Once the C-2 tosylate was formed, it immediately transformed to product **27** since the C-3 alkoxide is already formed.

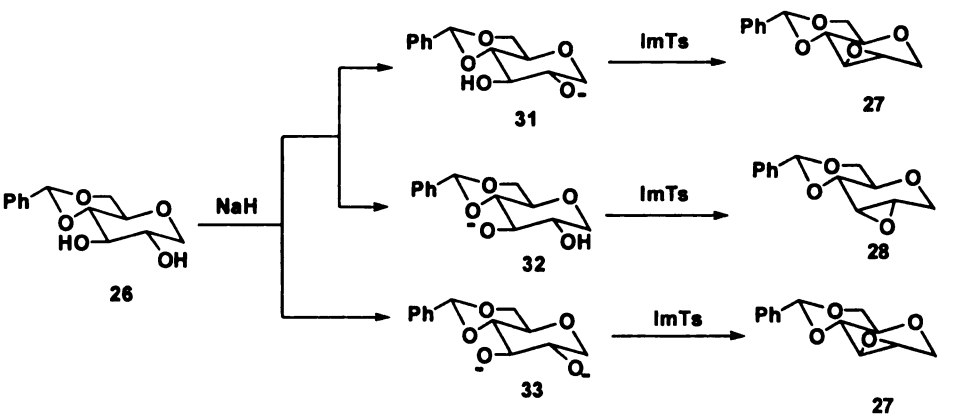


Figure 3.9 Formation of 2,3-anhydro derivatives using NaH/ImTs.

3.3.2 Preparation of deoxyanhydrohexitols

From the 4,6-O-benzylidene-2,3-anhydro derivatives, the 2 or 3 deoxy derivatives **34** and **35** were prepared. Reduction of **27** with LAH gave compound 4,6-O-benzylidene-3-deoxy-1,5-anhydro-D-mannitol **34** exclusively in 96 % yield with the delivery of the hydride to the axial position.

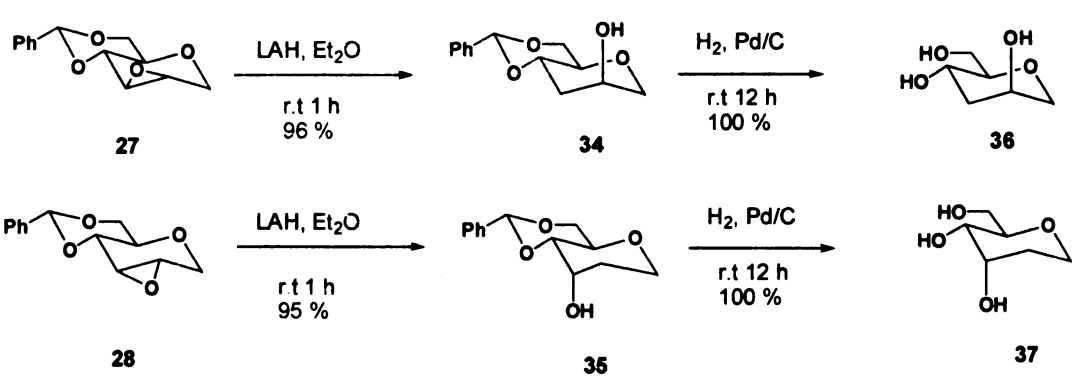


Figure 3.10 LAH reduction of 2,3-anhydro derivatives to form deoxy anhydrohexitols

Similarly, 1,5-anhydro-4,6-O-benzylidene-2-deoxy-D-allitol **35** was prepared in 95 % yield from 28 (Figure 3. 10). Deprotection of the protecting group in **34** and **35** gave the free deoxy anhydrohexitols **36** and **37** in quantitative yield.

3.4 Conclusion

Important anhydroalditol derivatives were prepared efficiently from the anhydroalditols.

1,5-Anhydro-D-glucitol –6-phosphate, the inert analogue of D-glucose-6-phosphate, was prepared from 1,5-anhydro-D-glucitol in two steps in over 60 % yield. The important deoxy-anhydrohexitols, which are components of E-selectin inhibitors, scaffolds of anhydrohexitol nucleosides and chiral catalysts, were also prepared from 1,5-anhydro-D-glucitol efficiently.

3.5 Experimental

General Procedures

^1H, ^{13}C NMR spectra were recorded at 500, 125, 121 MHz, respectively, with a Varian instrument at 293 K. The chemical shifts are given in ppm using $CDCl_3$ residue as reference (δ7.24p) for ^1H and relative to the central $CDCl_3$ resonance (δ= 77.00p) for ^{13}C NMR unless otherwise specified. ^{31}P NMR chemical shifts are given in ppm with H_3PO_4 as an external reference. ^1H and ^{13}C are assigned on the basis of 2D ^1H COSY and ^1H-^{13}C chemical-shift correlated experiments. Melting points were determined on a melting point apparatus (uncorrected). Optical rotations were measured on a Jasco P1010 polarimeter at 20°C. IR spectra (wave numbers in cm^{-1}) were recorded on a FT IR Nicolet 740 spectrometer in $CHCl_3$ solutions or KBr pellets. All chemicals were purchased from Aldrich Chemical Co. and used without further purification.

1,5-Anhydro-2,3-dipivolyl-4,6-O-benzylidene-D-glucitol (20)

To a solution of 1,5-anhydro-glucitol **4** (0.984g, 6.0mmol) in anhydrous DMF, were added benzaldehyde dimethyl acetal(1.65ml, 12.0mmol), sulfuric acid(98%, 45ul). The mixture was stirred overnight under N_2 atmosphere. After adding anhydrous pyridine (1.0ml) and stirring for 10 minutes, methanol was removed under reduced pressure. The mixture was cooled to 0°C, then anhydrous pyridine (9.7ml, 120mmol), and pivaloyl chloride (2.22ml, 60mmol) were added. After stirring at room temperature for 24hr, water and chloroform were added, the organic layer was separated, and the aqueous layer was dried over anhydrous Na_2SO_4. After remove the solvent, the residue was crystallized from Hexane-Ethyl acetate to give **20** (2.1g, 83%): $[\alpha]_D^{20}$ +19.2 (c 1, $CHCl_3$); ^1H NMR

(500 MHz, $CDCl_3$): δ 1.14(s, 9H, tBu); 1.16(s, 9H, tBu), 3.36(dd, 1H, J1=J2=10.7 Hz, H-1-b), 3.47(dd, 1H, J=9.7 Hz, 4.9 Hz, H-6-b); 3.65(dd, 1H, J1=J2=9.7 Hz, H-4), 3.69(dd, 1H, J1=J2=10.4 Hz, H-6-a), 4.09(dd, 1H, J=8.4 Hz, 5.9 Hz, H-1-a), 4.33(dd, 1H, J=7.7 Hz, 5.0 Hz, H-5), 5.03(ddd, 1H, J1=J2=8.2Hz, J3=5.6Hz, H-2), 5.35(dd, 1H, J=9.7Hz, 9.7Hz, H-3), 5.50(s, 1H, PhC*H*O), 7.40(m, 5H, H-arom); ^{13}C NMR: 27.1, 38.8, 67.5(C-1), 68.6(C-5), 69.3(C-2), 71.3(C-4), 71.9(C-3), 79.1(C-6), 101.0, 125.8, 1289.1, 128.8, 136.9, 177.2,177.4; υ_{max} (KBr) 3072, 2973, 2935, 2873, 1731, 1602, 1585, 1481, 1454, 1284, 1168, 1101, 709. Anal. Calcd for C23H32O7: C, 65.70; H, 7.67. Found: C, 65.50; H, 7.49

1,5-Anhydro-2,3-dipivolyl-D-glucitol (21)

A solution of **20** (1.68g, 4.0mmol) in EtOH-H_2O-CF_3COOH (60:8:1, 50ml) was stirred at room temperature for 24hr. The mixture was concentrated. Column chromatography of the residue on silica gel using EtOAC-Hexane 1:1 as eluant afforded the desired product 1,5-anhydro-2,3-dipivolyl-glucitol **21** (1.11g, 85%): mp 84-85°C; $[\alpha]_D^{20}$ +49.3 (c 1, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$): δ 1.13(s, 9H); 1.17(s, 9H), 3.26(dd, J=10.5 Hz, 1H, H-1-a), 3.33(ddd, J1=J2=9.6 Hz, J3=4.5 Hz, 1H, H-5), 3.65(dd, J1=J2=9.0 Hz, 1H, H-1-4), 3.78(dd, J=4.5 Hz, 12.0 Hz, 1H, H-6-b), 3.90(dd, J=3.0 Hz, 12.0 Hz, 1H, H-6-a), 4.05(dd, J=5.4 Hz, 10.8 Hz, 1H, H-1-b), 4.94(ddd, J1=J2=11.4 Hz, J3=5.7, 1H, H-2), 5.04(dd, J1=J2=9.6Hz, 1H, H-3); ^{13}C: 27.1, 38.8, 39.0, 62.2, 66.8, 68.8, 69.9, 76.6, 80.4; υ_{max} (KBr) 3380, 2976, 2973, 2873, 1739, 1286, 1174, 1153; Anal. Calcd for C16H28O7: C, 57.82; H, 8.49. Found: C, 67.30; H, 8.10.

1,5-Anhydro-2,3-dipivolyl-6-diphenylphosphate-D-glucitol (22)

To a solution of **21** (0.664g, 2.0mmol) in CH_2Cl_2, pyridine (0.9ml) and diphenylchlorophosphate (0.62ml, 3.0mmol) were added at 0°C. After stirring at room temperature for 1.5hr, water and CH_2Cl_2 were added. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2. The combined organic layer was washed with 1M HCl, saturated $NaHCO_3$, and water, then dried over anhydrous Na_2SO_4. After remove the solvent under reduced pressure and purify by column chromatography on silica gel using CH_2Cl_2-CH_3OH(13:1) as an eluant afforded the product **22** (0.701g, 62%): mp 75-76 °C; $[\alpha]_D^{20}$ +12.3 (c 1, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$): δ 1.11(s, 9H, tBu); 1.14(s, 9H. tBu), 3.18(dd, J1=J2=10.2 Hz, 1H, H-1-b), 3.37(m, 2H, H-4,5), 3.97(dd, J1=10.8 Hz, J2=J3=5.4 Hz, 1H, H-1-a), 4.42(dd, J1=J2=11.7 Hz, 1H, H-6-b), 4.50(ddd, J1 =J2 =9.8 Hz, J3, 5 =3.5 Hz, H-6-a), 4.76(ddd, J1=10.2 Hz, J2=J3=5.7 Hz, 1H, H-2), 5.06(dd, J=9.3Hz, 1H, H-3), 7.25(m, 10H, H-arom); ^{13}C NMR ($CDCl_3$): δ 26.9, 38.5, 38.6, 66.4(C-1), 67.4(C-6), 67.9(C-5), 68.5(C-2), 75.0(C-3), 78.9(C-4), 120.1, 125.6, 129.0, 150.1, 177.1, 178.1; ^{31}P NMR ($CDCl_3$): δ -9.77; υ_{max} (KBr) 3399, 2971, 2873, 1735, 1590, 1487, 1280, 1184, 1166, 1056, 962, 773, 690; Anal. Calcd for C28H37O10P: C, 59.57; H, 6.61. Found: C, 59.27; H, 6.10.

1,5-Anhydro-2,3-dipivolyl-6-phosphate-D-glucitol (23)

To a solution of **22** (0.564g, 1.0mmol) in methanol, PtO_2 (0.113g, 0.50mmol) was added. After stirring vigorously at room temperature under H_2 atmosphere for 6 hr, the solid was removed by filtration. The product **23** was obtained after removing the solvent under reduced pressure as syrup (0.412g, 100%): ^1H NMR (500 MHz, $CDCl_3$): δ 1.03(s, 9H,

tBu); 1.08(s, 9H, tBu), 3.30(dd, J1=J2=10.2 Hz, 1H, H-1b), 3.45(m, 1H, H-5), 3.67(dd, J1=J2=9.8 Hz, 1H, H-4), 4.03(dd, J1=J2=11.0 Hz, 6.1 Hz, 1H, H-6b), 4.20(m, 2H, H-1a, H-6a), 4.88(ddd, J1=9.0 Hz, J2=J3=6.1 Hz, 1H, H-2), 5.16(dd, J1=J2=9.8Hz, 1H, H-3); ^{13}C NMR: δ 26.8, 38.5, 38.6, 65.3, 66.3, 68.0, 68.8, 75.1, 79.0, 177.4, 178.2; ^{31}P NMR (CD_3CN): δ 1.97

1,5-Anhydro-D-glucitol-6-phosphate (5)

To a solution of **23** (0.247 g, 0.60 mmol) in methanol, 95% powered NaOMe (65.0 mg, 1.2 mmol) was added. After stirring at 40°C for 10 hr, the solution was passed through a cation ion-exchange resin to remove the salt. Removal of the solvent gave the free acid **5** as a syrup (0.123 g, 83 %). $[\alpha]_D^{20}$ +29.5 (c 1, D_2O); ^1H NMR(D_2O): δ 2.85(dd, J1=J2=9.5 Hz, 1H, H-1-b); 3.02(m, 2H, H-1-a, H-5), 3.04(m, 1H, H-4; 3.16(m, 1H, H-3), 3.53(dd, J1=5.7 Hz, J2=11.0 Hz, 1H, H-2), 3.69(ddd, J1=9.0 Hz, J2=J3=4.5 Hz, 1H, H-6-b), 3.80(ddd, J1=9.0Hz, J2=7.1Hz, J3=3.9 Hz, 1H, H-6-a); ^{13}C NMR(D_2O): δ 65.2, 68.8, 69.9, 69.1, 77.2, 78.5; ^{31}P NMR (D_2O): 0.96; υ_{max} (KBr) 3382, 2925, 2898, 1203, 1097, 1051;

1,5-Anhydro-D-glucitol-6-phosphate monoammonium salt (24)

In the preparation of **5**, the elute from cation ion-exchange was condensation to about 2 ml, ammonia (0.5 M in 1,4-dioxane, 10ml) was then added to the solution. After stirring at room temperature for 1hr, the product was precipitated as white solid. Filtration gave **24** in quantitative yield: m.p. 105-107°C; ^1H NMR(D_2O): δ 3.10(t, J=10.9Hz, H-1-b), 3.20(m, 1H, H-2), 3.27(d, J=9.0Hz, H-3 or H-4), 3.33(d, J=9.3Hz, H-3 or H-4), 3.42(m,

1H, H-5), 3.76-3.81(m, 3H, H-6-a, H-6-b, H-1-a); ^{13}C NMR(D_2O): δ 63.8 (C-6), 67.9(C-1), 68.1(C-3 or C-4), 68.3(C-3 or C-4), 76.3(C-2), 77.9(C-5); ^{31}P NMR (D_2O): 4.30; υ_{max} (KBr) 3411, 3222, 2919, 2867, 1631, 1459, 1097, 1054.

1,5-anhydro-D-Glucitol-6-diphenolphosphate (25)

To a solution of **4** (0.328g, 2.0 mmol) in dry pyridine (5ml) at 0°C diphenylchlorophosphate (0.43 ml, 2.1 mmol) was drop-wise added. After stirring at 0°C for 1.5 h and then 0.5 h at room temperature, MeOH (2.0ml) was added to quench the reaction. Removal of the solvent followed by flash chromatography (10:1 $CHCl_3$: MeOH) afford **25** as a crystal (0.46g, 60%): mp 113-114°C; $[\alpha]_D^{20}$ +22.1 (c 1, CH_3OH); ^1H NMR(DMSO): δ 2.99(t, J=9.6Hz, H-1-b), 3.06(t, J=8.8Hz, H-1-a), 3.12(t, J=8.8Hz, H-4), 3.22-3.30(m, 2H, H3 and H5), 3.71(dd, J1=10.8Hz, J2=4.9Hz, 1H, H-2), 4.24(m, 1H, H-6-b), 4.47(m, 1H, H-6-a), 4.96(d, J=3.6Hz, 1H, OH), 5.02(sb, 1H, OH), 5.20(d, J=4.9Hz, 1H, OH), 7.24(m, 5H, H-arom), 7.42(m, 4H, H-arom); ^{13}C NMR(DMSO): δ 64.7(C-6), 65.2(3 C, C-1, C-2, C-3), 73.6(C-4), 74.4(C-5), 115.7(C-arom), 121.3(C-arom), 125.8(C-arom), 145.7(C-arom); ^{31}P NMR (DMSO): -10.65; υ_{max} (KBr) 3382, 3282, 3066, 2971, 2904, 2877, 2852, 1590, 1488, 1454, 1390, 1253, 1224, 1190, 1101, 1083, 1043, 943, 771, 688, 520 cm^{-1} ; Anal. Calcd for C18H21O8P: C, 54.55; H, 5.34. Found: C, 54.21; H, 5.12.

Formation of epoxides 27, 28 from 4,6-O-benzylidene-1,5-anhydro-D-glucitol:

NaH-ImTs method:

In a 100ml flask, Sodium hydride (50% in mineral oil, 0.525 g, 10.5 mmol) was washed free of oil with hexane, anhydrous DMF (20 ml) was added followed by addition of 4,6-O-benzyliden-1,5-anhydro-D-glucitol (**26**) (1.01g, 4.0 mmol). After stirring at r.t. under N_2 for 0.5 h, ImTs (1.16 g, 5.24 mmol, in 5 ml DMF) was added. The reaction mixture was let to stir for another 4 h at r.t., and then EtOAc (30 ml) and brine (30 ml) was added. After separation, the aqueous phase was extracted with EtOAc (2x30ml), the combined organic phase washed with water (30ml), brine(30ml), and dried over anhydrous $MgSO_4$. Evaporation of the solvent under reduced pressure gave a syrup. Flash column (Hexane/EtOAc 5/1) gave **27** (0.337 g, 46.5 %) and 28 (0.160 g, 22.1 %).

1,5:2,3-Dianhydro-4,6-O-benzylidene-D-mannitol (27)

$[\alpha]_D^{20}$ -19.32 (c 1, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 3.40(m, 1H, H-2); 3.54 (d, J = 4.4 Hz, 1H, H-3), 3.63 (td, J = 10.3, 1.5 Hz, 1H, H-6'), 3.72 (ddd, J = 9.8, 4.9, 1.5 Hz, 1H, H-5), 4.00 (d, J = 9.8 Hz, H-4), 4.06 (m, 2H, H-1, H-1'), 4.21 (dd, *J* = 10.3, 4.8Hz, 1H, H-6), 5.57 (s, 1H, PhC*H*), 7.36 (m, 3H, Ph-H), 7.50 (m, 2H, Ph-H); ^{13}C NMR (125 M Hz, $CDCl_3$) δ 51.0 (C-2); 53.1 (C-3), 64.4 (C-1 or C-5), 64.5 (C-1 or C-5), 68.8 (C-6), 78.1 (C-4), 102.5 (Ph*C*H), 126.2, 128.2, 129.1, 137.1; Anal. Calcd for C13H14O4: C, 66.66; H, 6.02. Found: C, 66.54; H, 6.10.

1,5:2,3-Dianhydro-4,6-O-benzylidene-D-Allitol (28)

$[\alpha]_D^{20}$ -4.22 (c 1, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 3.14 (td, J = 9.8, 4.7Hz, 1H, H-5), 3.19(dd, J = 4.0, 1.2 Hz, 1H, H-2), 3.48(d, J = 4.0Hz, 1H, H-3), 3.66 (d, J = 10.0Hz, 1H, H-4), 3.68 (t, J = 10.3Hz, 1H, H-6), 3.91 (dd, J = 13.7, 1.3 Hz, 1H, H-1'), 4.21 (d, J =

13.7 Hz, 1H, H-1), 4.27 (dd, *J* = 10.5, 4.6Hz, 1H, H-6), 5.56 (s, 1H, PhC*H*), 7.38 (m, 3H, Ph-H), 7.50 (m, 2H, Ph-H); ^{13}C NMR (125M Hz, $CDCl_3$) δ 49.8 (C-2), 53.3 (C-3), 65.2 (C-1), 69.2 (C-5), 69.3 (C-6), 75.3 (C-4), 102.1 (PhCH), 126.0, 128.2,129.1, 137.0; Anal. Calcd for C13H14O4: C, 66.66; H, 6.02. Found: C, 66.40; H, 5.92.

1,5-Anhydro-3-deoxy-4,6-O-benzylidene-D-arabino-hexitol (34)

To a stirred solution of **27** (0.117 g, 0.5 mmol) in Et_2O (5 ml) was added LAH (37 mg, 1.0 mmol). After stirring under nitrogen atmosphere for 4 h, ethanol (1 ml) was added. Stirring was continued for another 30 min. Filtration followed by removal of the solvent gave the crude product as a syrup. Column chromatography (CH_2Cl_2:MeOH 30:1) gave the pure 34 (113 mg, 96 %); $[\alpha]_D^{20}$ -30 (c 1, $CHCl_3$); m.p 101-103°C; ^1H NMR (500 MHz, $CDCl_3$) δ 7.34-7.51 (m, 5 H, Ar-H), 5.56 (s, 1H, PhCH), 4.31-4.27 (m, 1H), 3.98-3.95 (m, 1 H), 3.89-3.83 (m, 1H), 3.70 (t, J = 10.2 Hz, 1H), 3.57-3.52 (m, 1H), 3.42 (t, J = 10.2 Hz, 1H), 3.40-3.31 (m, 1H), 2.65 (br s, 1H, OH), 2.03-1.98 (m, 1H), 1.84-1.75 (m, 1H); 137.3, 129.2, 128.3, 126.2, 101.9, 83.9, 71.1, 69.5, 68.8, 66.3, 33.2; Anal. Calcd for C13H16O4: C, 66.09, H, 6.83. Found C: 66.01; H, 6.89.

1,5-Anhydro-2-deoxy-4,6-O-benzylidene-D-ribo-hexitol (35)

Using the same procedure as for the preparation of **34** from **27, 35** was obtained from **28** in 95 %. $[\alpha]_D^{20}$ - 23.7 (c 1, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 1.86 (ddd, J = 3.1, 11.8, 13.0 Hz, 1H, H-2), 2.12 (br s, 1H, OH), 2.33 (m, 1H, H-2'), 3.42 (ddd, J = 5.0, 9.2, 10.1 Hz, 1H, H-6), 3.71 (dd, J = 1.5, 2.4 Hz, 1H), 3.81 (t, J = 10.3 Hz, 1H), 3.96 (ddd, J = 1.7, 2.1, 12.4 Hz, 1H), 4.04 (ddd, J = 4.6, 9.2, 11.9 Hz, 1H), 4.14 (br s, 1H), 4.33 (dd, J =

4.9, 10.4 Hz, 1H, H-4), 5.63 (s, 1H), 7.38-7.54 (m, 5H, Ar-H); ^{13}C NMR (125M Hz, $CDCl_3$) δ 35.6, 67.0, 69.0, 72.5, 74.2, 74.3, 101.9, 126.1, 128.3, 129.0, 137.4; Anal. Calcd for C13H16O4: C, 66.09, H, 6.83. Found C: 66.05; H, 6.78.

1,5-Anhydro-2-deoxy-D-ribo-hexitol (37)

A solution of **35** (100 mg, 0.42 mmol) in methanol (3 ml) with Pd/C (10 %, 40 mg) was stirred under hydrogen atmosphere over night. After filtration through celite, the solvent was removed under vacuum. Water (1 ml) was added to the flask and the solution was washed with toluene (2 x 1 ml). Removal of the solvent gave **37** in quantitative yield (62 mg, 100 %); ^{1}H NMR (500 MHz, D_2O) δ 3.97-3.95 (m, 1H), 3.79 (dd, J = 2.4, 12.2 Hz, 1H), 3.72 (td, J = 2.1, 12.2 Hz, 1H), 3.68 (dddd, J = 0.5, 4.8, 6.8, 9.6 Hz, 1H), 3.56 (dd, J = 6.8, 12.2 Hz, 1H), 3.48 (dd, J = 0.5, 12.5 Hz, 1H), 3.17 (ddd, J = 2.2, 6.9, 9.6 Hz, 1H), 2.09 (m, 1H), 1.59 (ddd, J = 3.2, 11.4, 14.6 Hz, 1H); ^{13}C NMR (125M Hz, $CDCl_3$) δ 82.2, 71.0, 66.3, 62.5, 61.5, 37.5; Anal. Calcd for C6H12O4: C, 48.64, H, 8.16. Found C: 48.52; H, 8.09.

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Chapter 4

Iodo Derivatives of Advanced Carbohydrate Intermediates

Abstract

Using hydriodic acid as an economic and general reagent, the general 4-carbon synthons derived from carbohydrates, (S)-3-hydroxy-butyrolactone and (S)-3-hydroxy-tetrahydrofuran, were successfully transformed to the acyclic iodo derivatives. From (S)-3-hydroxy-tetrahydrofuran, all the mono and diiodo derivatives were prepared selectively by taking advantage of the electron withdrawing property of the 3-hydroxy group and controlling the neighboring group effect of the 3-acetyl group. The application of these iodo derivatives was demonstrated in the preparation (S)-3-hydroxyl cylopentane, (S)-3-hydroxyl tetrahydrothiphene and (S)-3-hydroxyl-pyrolidien derivatives.

4.1 Introduction

Organic halides, especially organic iodides, are important intermediates in organic synthesis; they are often involved in the formation of C-C bond via radical[1] or ionic reactions[2]. They are also important indispensable intermediates in substitution reactions, rearrangement reaction and elimination reactions[3,4,5]. Iodides are the most reactive among halides; therefore, many methods have been developed for the preparation of organic iodides[6,7,8]. The most used method is converting the corresponding alcohol to the iodides, and a number of methods for this transformation have been reported. The classical method is through a two-step procedure – the alcohol is first converted to the tosylate and then a S_N2 substitution with iodide ion gives the organic iodide[9]. Recently, many new methods have been reported, such as BF_3-Et_2O/KI[10], P_4/I_2[11], Cl_2SO-DMF/KI[12], MgI_2[13], Me_3SiCl/NaI[14], Ph_3P/I_2[15], Ph_3P/DDQ/$R_4N^+I^-$ [16].

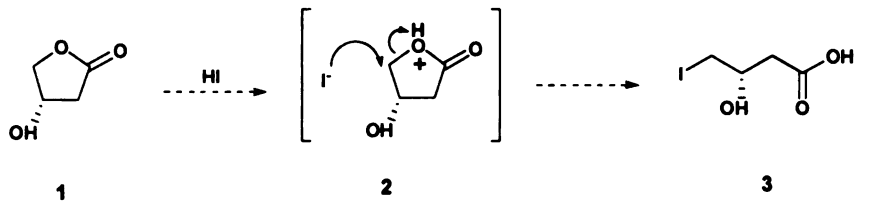
The reported methods suffer from one or the other problems. Using BF_3-Et_2O/KI, Only allylic or benzylic alcohols can be used as substrates[10]. Other methods involve the usage of expensive reagents ($PdCl_2/Et_3SiH$)[17], give low yields (I_2/petroleum ether)[18], need long reaction time (Cl_2SO-DMF/KI)[8], and require tedious workup procedures (Ph_3P/DDQ/$R_4N^+I^-$)[16].

Using hydriodic acid as an economic and general reagent, we successfully transformed the general 4-carbon synthons derived from carbohydrates, (S)-3-hydroxy-butyrolactone and (S)-3-hydroxy-tetrahydrofuran[19,20], to the acyclic iodo derivatives. The application of

these iodide derivatives was demonstrated in the preparation of the S and N containing heterocycles.

4.2 Preparation of iodo derivatives from (S)-3-hydroxy-butyrolactone

The ring-opening reaction of (S)-3-hydroxy-butyrolactone **1** with HI seemed to be very straight forward: under acidic conditions, iodide attacks C-4 position to give the acyclic 4-iodo product **3** (Figure 4.1).



1 2 3

Figure 4.1 Proposed reaction of (S)-3-hydroxy-butyrolactone with HI

Reaction of (S)-3-hydroxy-butyrolactone **1** with HI was very slow when the reaction was run in water. No reaction product was observed after treating compound **1** with 5 equivalent of HI in water for 24 h.

To accelerate the reaction, the free hydroxyl group was acetylated. It is known that acyl groups can participate in reactions involving carbocations through formation of 1,3-dioxonium ions and thus stabilize the carbocation formed[21,22]. For acetylated compound **1**, with the assistance of the acetyl group, under acidic conditions, the ring opening reaction of **1** would be much faster.

To avoid the hydrolysis of the acetate, the reaction was run in AcOH/Ac_2O. The results are shown in Table 4.1 (Figure 4.2)

Table 4.1 Ring-opening reactions of (S)-3-hydroxy-butyrolactone with HI* in AcOH/Ac_2O

Entry	Ac_2O (%)**	Time (h)	Iodo Product **4** (%)
1	50	20	0
2	50	44	< 1
3	50	68	1.9
4	5	20	21.5
5	5	44	35.0
6	5	68	40.0

* 5 equiv HI **Ac_2O concentration in AcOH

No product was observed after treating (S)-3-hydroxyl-butyrolactone **1** with 5 equiv HI in acetic acid containing 50 % Ac_2O. Even after 68 h, only 1.9 % of the desired product **4** was observed. The yield of **4** increased with the decreased concentration of Ac_2O. With only 5 % Ac_2O in acetic acid solution, 21.5 % of **4** was formed after 20 h, after 68 h, 40 % of **4** was formed.

The increased yield of product **4** with the decreased concentration of acetic anhydride is related to the dissociation of HI in the solution. HI is a weaker acid in acetic anhydride than in acetic acid. With the increasing concentration of acetic anhydride, less free iodide and proton is available and thus the rate for the ring-opening reaction of **5** decreased. It is

expected then that with no Ac_2O in the reaction system, the iodide product should be formed much faster.

Table 4.2 listed the results for ring-opening reactions of (S)-2-hydroxyl-butyrolactone **1** with HI in AcOH without Ac_2O.

Table 4.2 Ring-opening reactions of (S)-3-hydroxyl-butyrolactone with HI in AcOH

Entry	Temp (°C)	Time (h)	Iodo product **4** (%)
1	25	0.5	16.5
2	25	6	58.1
3	25	22	61.5
4	25	48	10

The reaction rate was highly accelerated without Ac_2O. After only 0.5 h, 16.5 % of the desired iodide product **4** was formed, 61.5 % of **4** was formed after 22 h.

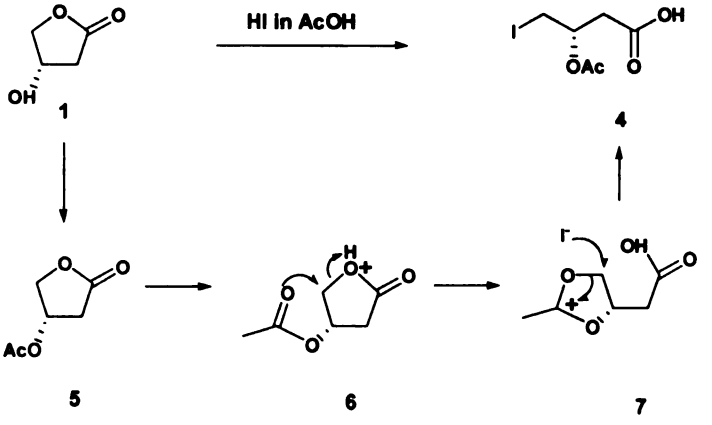


Figure 4.2 Neighboring acetyl group assisted ring opening reaction of (S)-2-hydroxy-butyrolactone with HI

However, the yield of the iodide product cannot be further improved by simply prolonging the reaction time. Product **4** was obtained in only 10 % yield after stirring the reaction solution at room temperature for 48 h (Figure 4.3). Two new products were formed. The but-3-enoic acid **9** was formed in 5 % and 3-iodo butanoic acid **8** was formed in 85 % yield. Compound **8** is optically inactive.

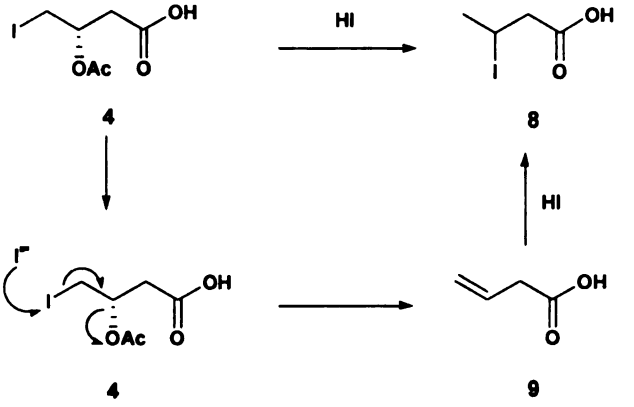


Figure 4.3 Formation of optically inactive 4-iodide butanoic acid

It is known that iodide can reduce organic iodo compounds[23]. In this case, once the 4-iodo product **4** was formed, the free iodide in the reaction system attacks the primary iodide. Elimination of the 3-acetate group gave the olefin **9** (Figure 4.3). Addition of HI to **9** formed the secondary iodo compound 3-iodo butanoic acid **8**. The optical activity was lost in the elimination step. Without excess iodide ion in the system, the byproducts would be greatly diminished. Thus, when the reaction was run with only 1 equivalent of HI for every equivalent of lactone, no elimination product **8** or **9** was observed.

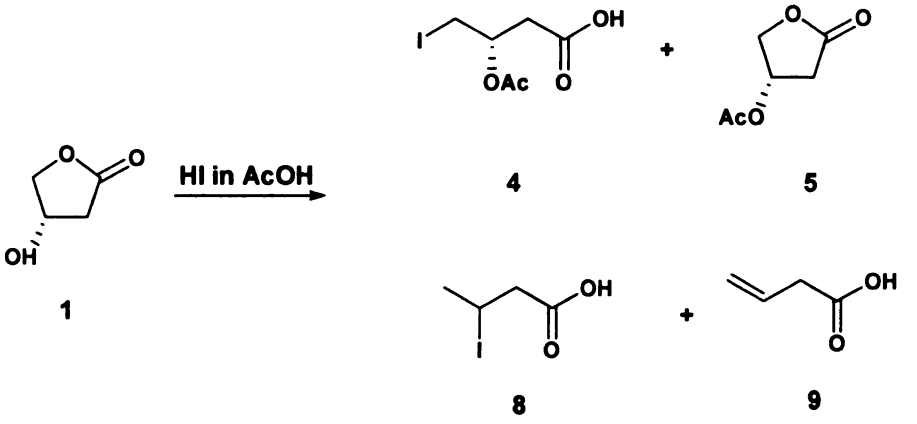


Figure 4.4 Reaction of (S)-3-hydroxy-butyrolactone with HI in acetic acid at various temperatures

Table 4.3 Reaction of (S)-3-hydroxy-butyrolactone with HI in acetic acid*

Entry	Temp (°C)	Time (h)	Products (%)			
			1	**4**	**5**	**8 + 9**
1	4	12	6	20	74	0
2	4	36	4.2	59.5	34.1	2.2
3	30	4	0	2.4	97.6	0
4	30	6	0	70.6	29.4	0
5	30	12	0	81.0	16.4	2.6
6	30	22	0	90.5	4.7	4.8
7	40	6	0	70.6	22.0	7.4
8	40	22	0	73.5	15.1	11.4
9	60	6	0	89.5	0	10.5
10	60	22	0	47.6	0	52.4

* 1 equivalent of HI used.

At lower temperature (4°C), the desired iodo product **4** was formed in about 60 % after 36 h (Table 4.3, entry 2), along with 34 % of the cyclic lactones (**1** + **5**), and small amount (2.2 %) of the elimination products (Table 4.3, entry 2). At higher temperature

(30, 40, and 60 °C), product **4** was formed in more than 70 % yield after 6 h (Table 4.3, entry 4, 7, 9). However, substantial amount of elimination products were formed when the reaction was run at 40 °C and 60°C, especially with longer reaction time (Table 4.3, entry 8, 10). The best results were obtained when the reaction was run at 30°C for 22 h. The desired iodo product **4** was obtained in 90.5 % yield with a fraction of elimination products (4.8 %) and acelyted starting lactone (4.5 %) left (Table 4.3, entry 6). The optical purity of compound **4** was greater than 98 % determined by optical rotation.

4.3 Preparation of iodo derivatives by ring opening of (S)-3-hydroxyl-tetrahydrofuran with HI

After successful preparation of (S)-3-acetoxy-4-iodobutanoic acid **4** through the ring opening reaction of (S)-3-hydroxy-butyrolactone with HI, (S)-3-hydroxyl-tetrahydrofuran was used as the substrate for the ring opening reaction with HI. Unlike the lactone **1**, which can only cleave the C4-O bond in the ring opening reactions and thus can only get the 4-iodo product, the cyclic ether **10** has 2 possible sites for iodination and thus 3 iodo products can be obtained: the monoiodo products **11**, **12** and the diiodo product **13**.

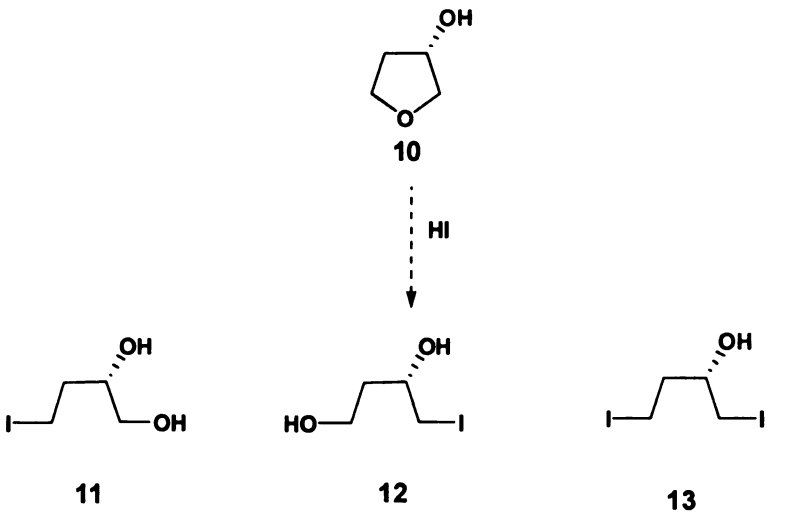


Figure 4.5 Possible iodo products from ring opening reaction of (S)-3-hydroxy-tetrahydrofuran with HI

Water as solvent

When water was used as solvent, the mono iodide product **11** was obtained. However, the yields varied if the reaction was run in an open flask. Two factors can affect the yield in this reaction: light and oxygen. Light can catalyze the formation of iodine from HI; oxygen can oxidize HI to iodine.[24] Table 4.4 listed the light and oxygen effects on the ring opening reaction of (S)-3-hydroxyl- tetrahydrofuran **10** with HI.

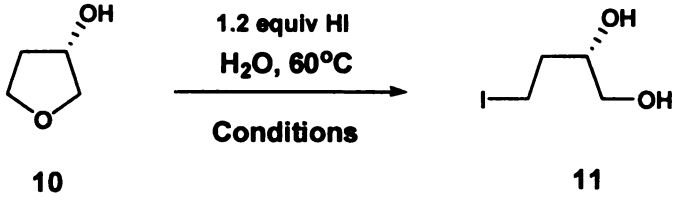


Figure 4.6 Ring opening reaction of (S)-3-hydroxy- tetrahydrofuran with HI in water

Table 4.4 Light and oxygen effects on the ring opening reaction of (S)-3-hydroxyl- tetrahydrofuran with HI

Entry	conditions	Yield (%)		
		1.5 h	3 h	6 h
1	-	35.5	43.5	25
2	hv	44.1	40.2	15.6
3	O_2	93.5	68.0	18.6
4	hv + O_2	95.2	78.1	13.0

These results indicate that light and oxygen can accelerate the reaction. Without light or oxygen, the highest yield obtained was 43 %, with light slightly higher yield was obtained, while with oxygen, 93 % of the iodide compound was obtained in 1.5 h. The effects of light and oxygen were additive: with both light and oxygen, 95 % of the iodo product was obtained. It is noted that during the first 1.5 h of the reaction process, the color of the reaction solution (which came from HI_3) increased in the order of

Without light/oxygen < light < oxygen < light and oxygen

the same order as for the formation of the iodide compound. It has been reported that iodine can catalyze the ring opening polymerization of THF[25], a similar iodine catalyzed ring opening iodination of (S)-3-hydroxy- tetrahydrofuran was proposed in Figure 4.7.

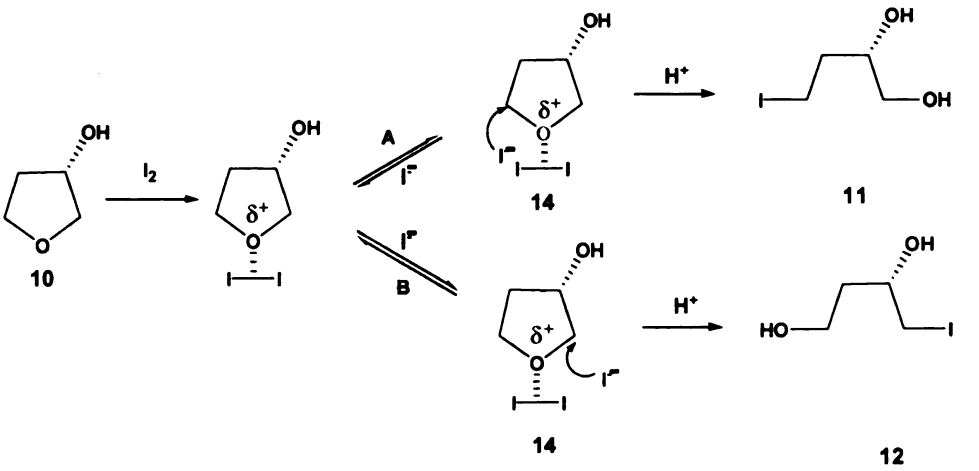


Figure 4.7 Mechanism for iodine catalyzed ring opening iodination of (S)-3-hydroxy- tetrahydrofuran

Reaction of HI with oxygen forms iodine, light can catalyze this process. Coordination of iodine with the ring oxygen forms the iodine complex. Iodide can attack the complex in two possible pathways: from path A iodide attacks C-5 to form the 4-iodo 1,2 diol product **11**, from path B iodide attacks C-2 to form the 4-iodo 1,3-diol product **12**. The exclusive formation of 1,2 diol product **11** is understandable as the electron withdrawing 2-hydroxyl group makes C2 of **14** less reactive toward the nucleophile iodide compared to C5 of **14**, and thus the cleavage of C5-O bond is much easier than that of C2-O bond.

Acetic acid as solvent

If the HI mediated ring opening iodination of (S)-3-hydroxy- tetrahydrofuran was run in acetic acid, it is expected that the acetyl group at C-3 position would participate in the ring opening process to form the five membered 1,3-dioxolanium followed by iodide attacking C-1 to form the 4-iodo 1,3-diol derivative **16** as shown in Figure 4.8.

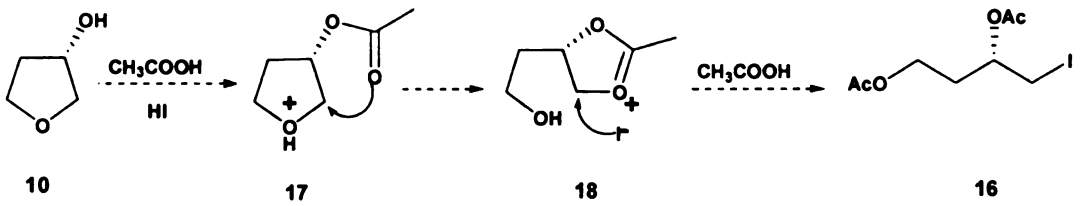


Figure 4.8 Proposed reaction of (S)-3-hydroxyl- tetrahydrofuran and HI in Acetic acid

When 2 equiv of HI was used, the diiodo product **20** was obtained in 90 % with 10 % of acetylated starting material **19** left, while no expected mono iodide product was formed. Reducing the amount of HI to 1 equiv, still, only diiodo product 20 was obtained, even though 55 % of 19 remained in the reaction system.

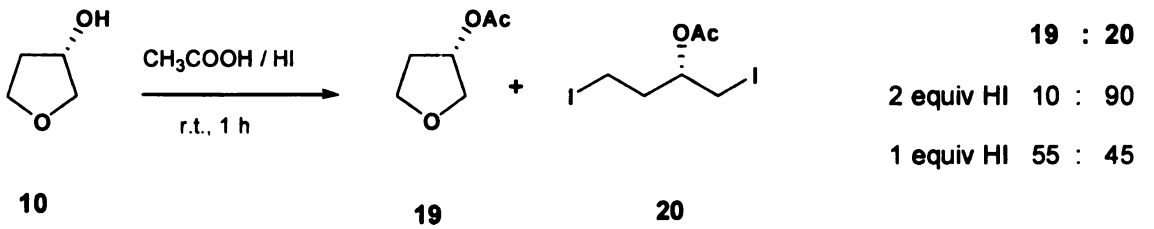


Figure 4.9 Reaction of (S)-3-hydroxy- tetrahydrofuran and HI in Acetic acid

The formation of only diiodo product indicated that the monoiodo intermediate was very reactive. Once it was formed, it quickly transformed to the diiodo product. A mechanism based on this observation is shown in Figure 4.10.

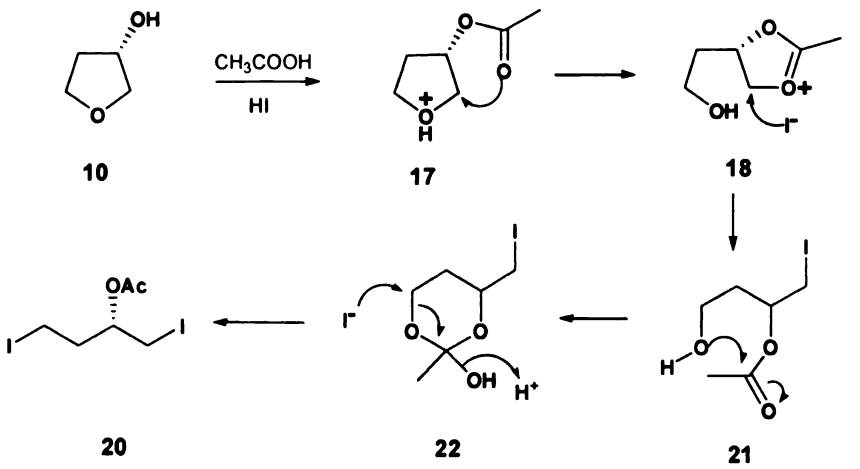


Figure 4.10 Mechanism for reaction of (S)-3-hydroxy- tetrahydrofuran and HI in Acetic acid

Once the monoiodo compound **21** was formed, the 4-hydroxyl group attacks the acetyl carbonyl carbon to form the six-membered orthoester intermediate **22,** iodide attacked C-4 to cleave the orthoester and give the diiodo product **20**. In this process, the rate determining step is the formation of the 1,3-dioxolanium **18** from **17**. To form **18**, a highly strained fused bicyclic ring transition state must be formed. Once **18** was formed, it was quickly transformed to **20** through **21** and **22.**

If no participation group exists, the opening of the THF ring is expected to be slower and the monoiodo product should be formed predominately. Indeed, treating THF with 2 equiv HI in acetic acid at room temperature for 3 hour gave 64 % monoiodo product 4-iodo butyl acetate **24** with 36 % THF remaining, no diiodo product was observed (Figure 4.11).

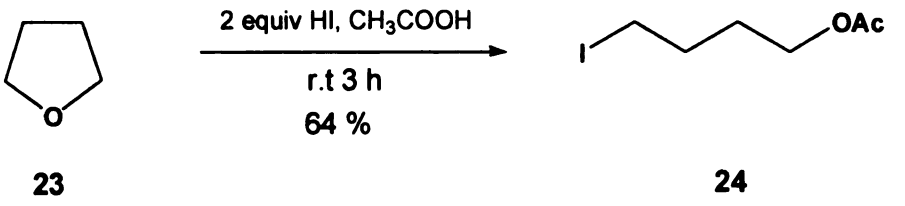


Figure 4.11 Reaction of tetrahydrofuran and HI in Acetic acid

Trifluoroacetic acid (TFA) as solvent

If the reaction of (S)-3-hydroxy-tetrahydrofuran **10** with HI was run in a non-participation solvent, such as TFA, the monoiodo product should be formed exclusively without the formation of the diiodo product. Also, without participation in the opening of the THF ring, the 1,2-diol derivative should be obtained because the position of the electron withdrawing hydroxyl group.

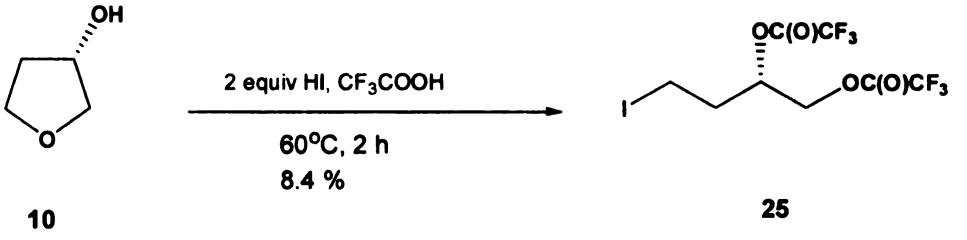


Figure 4.12 Reaction of (S)-3-hydroxy-tetrahydrofuran and HI in trifluoroacetic acid

Reaction of (S)-3-hydroxy-tetrahydrofuran **10** with 2 equiv HI at room temperature for 5 hour gave 3.2 % of the expected 4-iodo-1,2-diol derivative **25** without formation of the 1,3 diol or diiodide product (Figure 4.12). However, the reactions in TFA were very slow. After 64 h at room temperature, only 12 % of the product **25** was obtained. Raising

the reaction temperature to 60 °C did not give satisfactory results either. Product **25** was obtained in 4.7 % and 6.8 % after 2 and 5 hour respectively.

Acetic Acid/Acetic Anhydride as solvent

If extra acetic anhydride existed in the reaction system with acetic acid as solvent, then once the ring was opened, the free hydroxyl group will be acetylated and thus the monoiodo 1,2 diol product should be obtained.

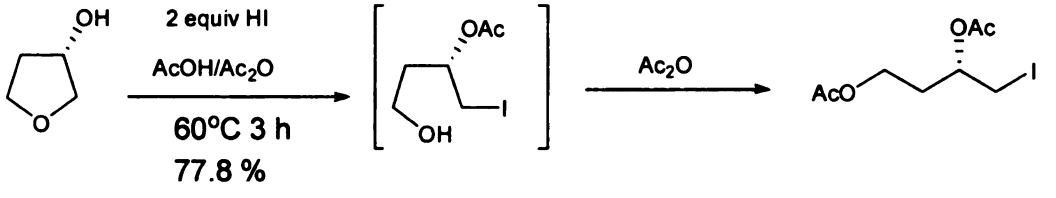


Figure 4.13 Reaction of (S)-3-hydroxy-tetrahydrofuran and HI in acetic acid/acetic anhydride

Reaction of (S)-3-hydroxy-tetrahydrofuran **10** with 2 equiv HI and 5 equiv Ac_2O in AcOH at 60°C for 3 h gave 77.8 % of the expected 4-iodo-1,3 diol derivative **16** without formation of the 1,2 diol or diiodo product (Figure 4.13). As discussed in Chapter 4.2, the existence of Ac_2O in the reaction system lowered the reaction rate (without Ac_2O, 90 % of the diiodo product was obtained at room temperature for 1 hour, Figure 4.9).

The results for the reaction of (S)-3-hydroxy-tetrahydrofuran with HI under different conditions are shown in Figure 4.14. The regio selectivity is realized by taking advantage

of the electron withdrawing property of the 3-hydroxy group and controlling the neighboring group effect of the 3-acetyl group.

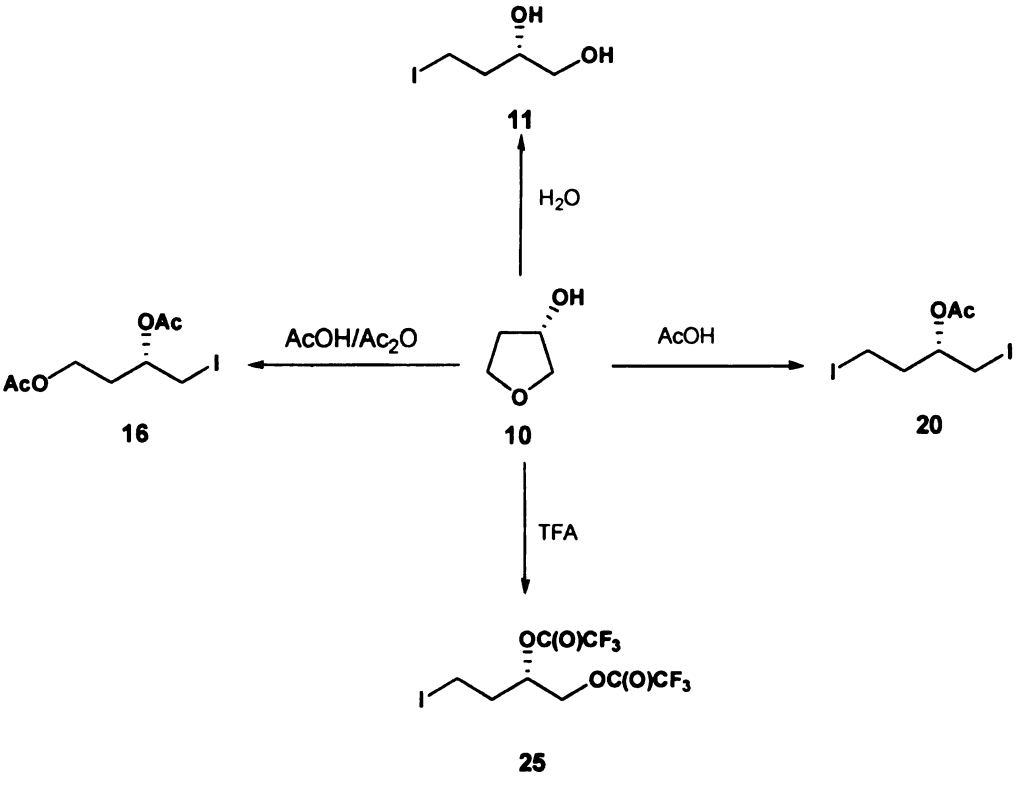


Figure 4.14 Reaction of (S)-3-hydroxy - tetrahydrofuran and HI under various conditions

4.4 Reactions of 1,5-anhydro-2,3,4,6-tetra-O-acetyl-D-glucitol with HI

Under similar conditions as for the reaction of (S)-3-hydroxy-tetrahydrofuran with HI in acetic acid, the reaction of the tetrahydropyran derivative 1,5-anhydro-2,3,4,6-tetra-O-acetyl-D-glucitol **27** should give the open chained 6-iodo product **30** as proposed in Figure 4.15. Protonation of the ring oxygen followed by 6-acetyl group assisted cleavage of the ring C5-O bond should give the open chained dioxonium ion **29**, which should be opened by iodide at C-6 to give the iodo product **30.**

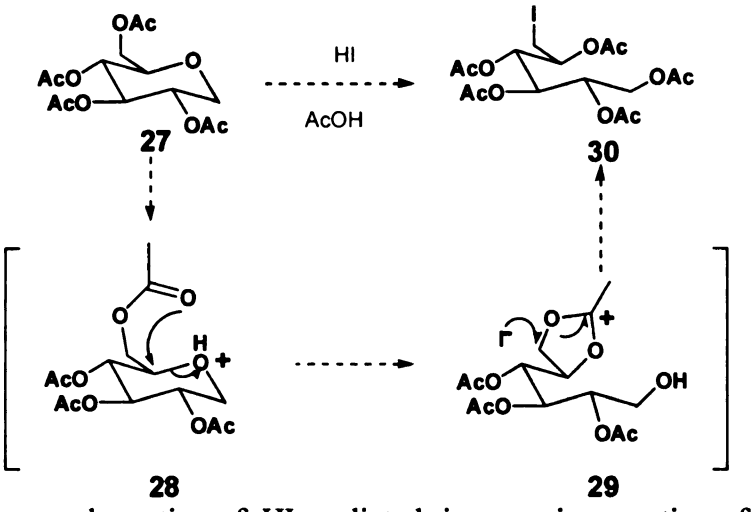


Figure 4.15 Proposed reaction of HI mediated ring opening reaction of 1,5-anhydro-2,3,4,6-tetra-O-acetyl-D-glucitol

The results for reaction of 1,5-anhydro-2,3,4,6-tetra-O-acetyl-D-glucitol with HI are listed in table 4.5 (Figure 4.16).

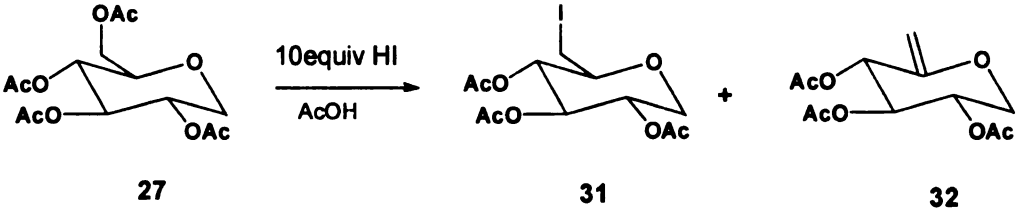


Figure 4.16 Reaction of 1,5-anhydro-2,3,4,6-tetra-O-acetyl-D-glucitol

Table 4.5 Reaction of 1,5-anhydro-2,3,4,6-tetra-O-acetyl-D-glucitol

Entry	Temp (°C)	Time (h)	Product(s)
1	25	18	**27** (95 %)
2	55	18	**27** (95%)
3	95	18	**27** (30 %) **31** (30 %) **32** (10 %)
4	110	7	Decomposed

At lower temperature (25 °C, 55 °C) after 18 h (Table 4.5, entry 1, 2), no product is obtained while 95 % of the starting **27** is recovered. Raising the temperature to 95 °C for

18 h, the cyclic 6-iodo product **31** was obtained in 30 % yield along with 10 % olefin product **32**. **27** is recovered in ~30% and no open chained iodo product was observed. At higher temperature (110 °C), no significant amount of any product or starting material can be isolated.

It is known that the cleavage of tetrahydropyran (THP) is much slower than that of THF, as the six-membered cyclic THP is more stable than the five-membered cyclic THF. As for 1,5-anhydro-2,3,4,6-tetra-O-acetyl-D-glucitol, the 4 electron withdrawing groups make the THP ring more electron deficient and harder to be cleaved. Under the conditions used, no ring-cleavage product can be formed.

4.5 The application of iodide products in the preparation of advanced derivatives

The chiral iodide products prepared can easily be converted to other heteroatom containing compounds, such as S, N heterocyclic compounds and carbocyclic compounds.

Refluxing 1,4-diiodo-2-butanol-acetate **20** with sodium sulfide in ethanol for 5 h gave (S)-3-hydroxy-tetrahydrothiophene **33** in quantitative yield. The optical purity of **33** is higher than 99 %.[26]

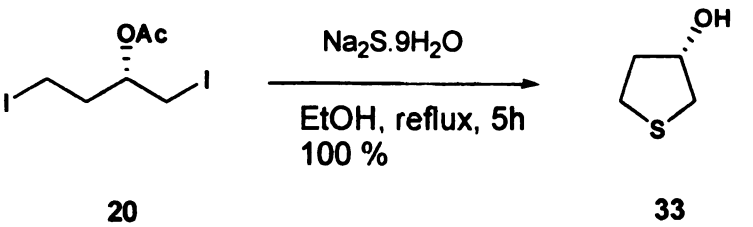
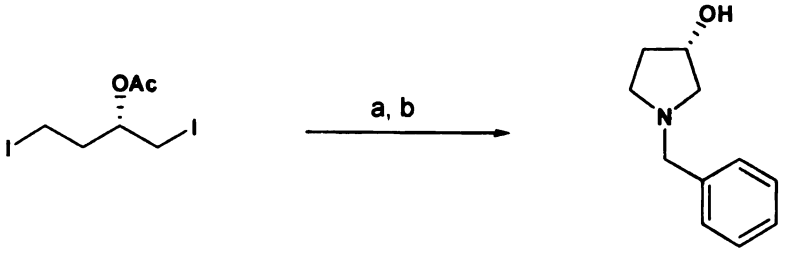


Figure 4.17 Preparation of (S)-3-hydroxy-tetrahydrothiophene

Reaction of the diiodo compound with benzyl amine in toluene at the existence of potassium carbonate for 5 h under reflux followed by hydrolysis of the acetyl gave the desired (S)-1-benzyl-3-hydroxy-pyrolidine **34** in 60 % over 2 steps. The optical purity of 31 is larger than 99 %.[27]



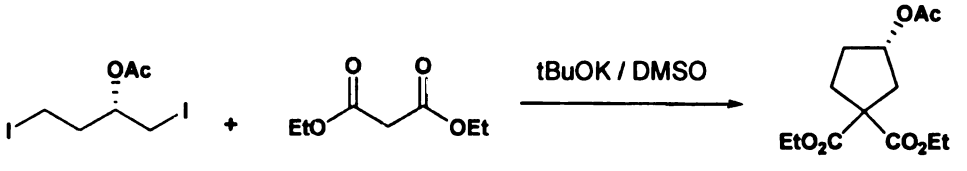
20 **34**

Figure 4.18 Preparation of (S)-1-benzyl-3-hydroxy-pyrolidine

Reaction conditions: a). $BnBH_2$, K_2CO_3, Toluene, reflux, 5 h;

b) K_2CO_3, H_2O 2 steps, 60 %.

Compound **20** is also a good intermediate for the construction of carbocyclic compounds. Reaction of **20** with diethyl malonate in the presence of *t*-butoxyl potassium gave the chiral cyclopentane derivative **35** in 65 % yield.



20 **35**

Figure 4.19 Preparation of (S)-diethyl-3-acetoxycyclopentane-1,1-dicarboxylate

4.6 Conclusion

Using HI as an economic and general iodide source, the important 4-carbon iodide synthons, (S)-3-hydroxy-4-iodo-butanoic acid, (S)-4-iodo-1,3-butanediol, (S)-4-iodo-1,2-butanediol, (S)-1,4-diiodo-2-butanol and their acetylated derivatives are prepared. The usefulness of the iodide synthons were demonstrated through the preparation of the heterocyclic compounds (S)-3-hydroxy-tetrahydrothiophene and (S)-1-benzyl-3-hydroxy-pyrolidine and also the carbocyclic compound (S)-diethyl-3-acetoxycyclopentane-1,1-dicarboxylate.

4.7 Experimental

General procedures: ^{1}H, ^{13}C NMR spectra were recorded at 500, 125, MHz, respectively, with a Varian instrument at 293 K. The chemical shifts are given in ppm using $CDCl_3$ residue as reference (δ 7.24 p) for ^{1}H and relative to the central $CDCl_3$ resonance (δ= 77.00p) for ^{13}C NMR unless otherwise specified. Optical rotations were measured on a Jasco P1010 polarimeter at 20°C. IR spectra (wave numbers in cm^{-1}) were recorded on a FT IR Nicolet 740 spectrometer in $CHCl_3$ solutions or KBr pellets. All chemicals were purchased from Aldrich Chemical Co. and used without further purification.

The HI in acetic acid, acetic acid/acetic anhydride, trifluoroacetic acid solution was prepared as needed. For the preparation of HI in acetic acid solution, 47 % HI in H_2O (6.16 g) was cooled to 0°C with ice-bath, Ac_2O (17.16 ml) was added drop-wised with the control of the solution temperature no higher than 40°C. Stirring was continued for another 30 min at r.t. after the addition was done, the solution prepared contain 11 % HI. For the preparation of HI in acetic acid/acetic anhydride, trifluoroacetic acid, the same protocol is followed with the addition of the amount of anhydrides needed.

For HI mediated reactions, the progress of the reaction was monitored with ^{1}H and ^{13}C No-Deuterium NMR. The signal monitored for the ring opening reaction of (S)-3-hydroxy-butyrolactone is H-3 and C-4. For (S)-3- hydroxy-tetrahydrofuran, the signal monitored are H-3 and C-1 or C-4 (whichever is iodinated).

(S)-3-acetoxy-butyrolactone (5)

To a stirred solution of Ac_2O (4.7 ml) in dry pyridine (15 ml) at r.t was added (S)-3-hydroxy-butyrolactone (1.02 g, 10mmol). After stirring at r.t overnight, most of the solvent was removed under high vacuum, diethyl ether (50 ml) was added and washed successively with cold water, saturated aqueous $NaHCO_3$, and brine (30 ml each) and dried over anhydrous Na_2SO_4. Removal of the solvent gave compound **5** as a colorless oil (1.32 g, 94 %). $[\alpha]^{20}_D$ -45.5 (c 1, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 2.03 (s, 3H, CH_3 Ac), 2.48-2.54(m, 1H, H-2a), 2.82(dd, J = 6.7, 18.4 Hz, 1H, H-2b), 4.27-4.30(m, 1H, H-4a), 4.45 (dd, J = 5.0, 11.1 Hz, 1H, H-4b), 5.36 (m, 1H, H-3); ^{13}C NMR($CDCl_3$): δ 20.5, 34.2 (C-2), 69.6 (C-3), 72.7 (C-4), 170.0, 174.5.

Reaction of (S)-3-hydroxy-butyrolactone 1 with HI:

H_2O as solvent:

(S)-3-hydroxy-butyrolactone (0.102 g, 1 mmol) was added to a solution of HI in H_2O (47%, 1.36 g), after stirring at r.t for 24 h, no reaction product was observed from NMR.

AcOH, AcOH/Ac_2O as solvent:

(S)-3-hydroxy-butyrolactone (0.102 g, 1 mmol) was added to a solution of HI in AcOH with excess Ac_2O (50 %, 5 % or 0 %), the samples were stirred at the desired temperature, and were tested using NMR for the formation of products at the time listed in table 4.1, 4.2.

For workup: after removing most of AcOH under vacuum, EtOAc (20 ml) was added followed by addition of saturated aqueous $NaHCO_3$, after separation, the aqueous layer was extracted with EtOAc(2 x 20 ml), the combined organic layer was washed with brine (20 ml) and dried over anhydrous Na_2SO_4. Removal of the solvent gave a colorless oil. Column chromatography (if needed) gave **3-acetoxy-4-iodo-butyric acid 3:** ^1H NMR ($CDCl_3$): δ 2.04(s, 3H, CH_3 Ac), 2.76(dd, J = 6.7, 7.0 Hz, 2H, H-2), 3.34 (dd, J = 4.5, 11.0 Hz, 1H, H-4a), 3.39 (dd, J = 5.2, 11.0 Hz, 1H, H-4b), 4.99(m, 1H, H-3); 13 C NMR($CDCl_3$): δ 6.8 (C-4), 20.8, 38.6 (C-2), 68.3 (C-3), 170.1, 175.6.

Ethyl 3-(S)-hydroxy-4-iodo-butyrate

For the preparation of Ethyl 3-(S)-acetoxyl-4-iodo-butyrate, ethanol (30ml) was added to the condensed reaction solution (~2 ml) of (S)-3-hydroxy-butyrolactone (0.102 g) with HI in acetic acid along with 2 drops of concentrated sulfuric acid. After stirring at r.t. for 12 h, the reaction solution was concentrated, EtOAc (20 ml) and saturated aqueous $NaHCO_3$ (20 ml) was added, after separation, the aqueous layer was extracted with EtOAc(20 ml), the combined aqueous layer was washed with brine (20 ml), dried over anhydrous Na_2SO_4 and condensed. Column chromatography gave **Ethyl (S)-3-hydroxy-4-iodo-butyrate** as a colorless oil (0.21 g, 81 %), $[\alpha]^{20}_D$ -9.7 (c 1, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 1.16 (t, J = 7.2 Hz, 3 H, CH_3 O ethyl), 2.47 (dd, J = 4.2, 16.6 Hz, 1 H), 2.58 (dd, J = 4.1, 16.5 Hz, 1H), 3.20-3.36 (m, 2H,), 3.86-4.00 (m, 1H, H-3), 4.05 (q, J = 7.0 Hz, 2 H, OCH_2); ^{13}C NMR($CDCl_3$): δ 12.0 (C-4), 13.8 (CH_3 O-ethyl), 40.7 (C-2), 60.8 (CH_2 O-ethyl), 67.3 (C-3), 171.4 (C=O).

(S)-3-Tetrahydrofuryl-acetate (19)

$[\alpha]^{20}_D$ -16.75 (c 1, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 1.89 (m, 1H, H-4), 1.95 (s, 3H, $COCH_3$), 2.06 (m, 1H, H-4'), 3.69-3.83 (m, 4H, H-2, H-5), 5.17 (m, 1H, H-3); ^{13}C NMR($CDCl_3$): δ 20.8 ($COCH_3$), 32.4 (C-4), 66.7 (C-5), 72.8 (C-2), 74.5 (C-3), 170.5 ($COCH_3$).

4-Iodo-(S)-2-hydroxy-butan-1-ol (11)[29]

General method for the reaction of (S)-3-hydroxy-tetrahydrofuran with HI in water: (S)-3-hydroxy-tetrahydrofuran (0.088 g, 1 mmol) was added to a solution of HI in water (47 %, 0.33 g, 1.2 mmol) at 60°C, under the conditions listed as in table 4.4 (for the conditions with no light, no oxygen, the reactions were run in a deep-dark colored flask under argon atmosphere; for the conditions with light only, the reactions were run in a ordinary flash under argon atmosphere; for the conditions with both light and oxygen, the reactions were run with ordinary flask and air was bubbled to the reaction solution through the process.).

For workup:

Sodium thiosulfate (~ 0.05 g) was added to the stirred solution until the Iodine color disappear, then brine (10 ml) was added, the mixture was extracted with THF (4 x 15 ml), the organic layers were combined, dried and condensed to give a colorless oil, column chromatography gave the pure product **11**. $[\alpha]^{20}_D$ ^1H NMR ($CDCl_3$): δ 1.81-1.88 (m, 1H, H-3), 1.93-2.00(m, 1H, H-3'), 3.23-3.32 (m, 2H, H-1, H-1'), 3.46 (dd, J = 6.6, 11.6 Hz, 1H, H-4), 3.56 (dd, J = 3.8, 11.6 Hz, 1H, H-4'), 3.76 (m, 1H, H-2); ^{13}C NMR($CDCl_3$): δ 1.28 (C-4), 34.0 (C-3), 63.0 (C-1), 69.7 (C-2).

(S)-4-(2-iodoethyl)-2,2-dimethyl- 1,3-Dioxolane

A solution of 4-Iodo-(S)-2-hydroxy-butan-1-ol (0.216 g, 1mmol) in acetone with catalytic amount of concentrated sulfuric acid was stirred at r.t for 5 h and then solid sodium bicarbonate (0.5 g) was added and stirring was continued for 1 h. After filtration, concentration, the residue was dissolved in diethyl ether and washed successively with saturated aqueous sodium bicarbonate, water and brine. Evaporation of the solvent gave the product as a colorless oil (0.235 g, 92 %).$[\alpha]^{20}_{D}$ (c 1, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 1.35 (s, 3H, CH_3), 1.40 (s, 3H, CH_3), 2.01-2.14 (m, 2H, H-), 3.15-3.30 (m, 2H, H-), 3.55 (dd, J = 6.2, 7.9 Hz, 1H, H-), 4.07 (dd, J = 6.2, 7.9 Hz, 1H, H-), 4.14-4.19 (m, 1H, H-); ^{13}C NMR ($CDCl_3$): δ 1.51 (C-4), 25.5, 27.0, 37.8, 68.7, 75.7

1, 4–diiodo-(S)-2-butanol-acetate (20)[29]

To a stirred solution of HI in water (47 %, 3.1 g, 11.4 mmol) under ice-water bath was added drop-wised acetic anhydride (8.6 ml). After stirring another 10min, the ice-water bath was removed and (S)-hydroxytetrahydrofuran (0.50 g, 5.7 mmol) was added. After stirring at r.t. for 1 h, the reaction solution was cooled to r.t. and then concentrated to about 3 ml under vacuum at r.t. Diethyl ether and saturated aqueous $NaHCO_3$ (30 ml each) were added to the reaction solution. After separation, the aqueous layer was extracted with EtOAc, the combined organic layer was washed with 5 % aqueous sodium thiosulfate, brine and dried over anhydrous Na_2SO_4. Removal of the solvent gave **20** a colorless oil (1.88 g, 90 %).$[\alpha]^{20}_{D}$ -35.9 (c 1, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 4.56(m, 1H, H-2), 3.23(dd, 1H, J=10.7 Hz, 5.3 Hz, H-1a), 3.13(dd, 1H, J= 10.7 Hz, 4.8 Hz, H-1b),

2.94-3.04(m, 2H, H-4), 2.03-2.10(m, 2H, H-3), 1.92(s, 3H, CH_3CO); ^{13}C NMR ($CDCl_3$): δ -0.20 (C-4), 7.53 (C-1), 20.77 (CH_3CO), 37.41(C-3), 71.42(C-2), 169.1 (CH_3CO); Anal. Calcd for C6H10I2O2: C, 19.59; H, 2.74. Found: C, 19.69; H, 2.62.

Trifluoroacetic acid as solvent for the reaction of (S)-3-hydroxy-tetrahydrofuran with HI:

To a stirred solution of HI in water (47 %, 1.55 g, 5.7 mmol) under ice-water bath was added drop-wised trifluoroacetic anhydride (6.3 ml). After stirring another 10 min, the ice-water bath was removed and (S)-hydroxytetrahydrofuran (0.50 g, 5.7 mmol) was added. After stirring at 60°C for 2 h, NMR shown 8.4 % of 4-Iodo-1,2-butanediol – di-trifluoroacetate was formed. The reaction solution was cooled to r.t. and then concentrated to about 3 ml under vacuum at r.t, brine (10 ml) was added, followed by addition of solid sodium thiosulfate until the Iodine color disappear, the mixture was then extracted with THF (4 x 15 ml), the combined organic layer was dried, condensed. 82 % (0.41 g) of the starting (S)-2-hydroxy-tetrahydrofuran was recovered through column chromatography, 4-Iodo-(S)-2-hydroxy-butan-1-ol **11** was obtained as the hydrolyzed product (67.5 mg, 5 %), which gave the same spectra as the product from reaction in water.

(S)-4-Iodo-1,3-butanediol–diacetate (16)[29]

To a stirred solution of HI in water (47 %, 1.55 g, 5.7 mmol) under ice-water bath was added drop-wised acetic anhydride (9.1 ml). After stirring another 10min, the ice-water bath was removed and (S)-hydroxytetrahydrofuran (0.50 g, 5.7 mmol) was added. After

stirring at 60°C for 3 h, the reaction solution was cooled to r.t. and then concentrated to about 3 ml under vacuum at r.t. Diethyl ether and saturated aqueous $NaHCO_3$ (30 ml each) were added to the reaction solution. After separation, the aqueous layer was extracted with diethyl ether, the combined organic layer was washed with cold 5 % aqueous sodium thiosulfate, brine and dried over anhydrous Na_2SO_4. Removal of the solvent gave **16** as a colorless oil (1.32 g, 77.8 %): ^{1}H NMR ($CDCl_3$): δ 4.42-4.51 (m, 1H, H-3), 4.11 (t, J = 6.2 Hz, 1H), 3.22-3.43 (m, 2H), 2.13-2.2.25 (m, 2H), 2.09, 2.03 (2 s, 3H each, 2 OAc); ^{13}C NMR ($CDCl_3$): δ 171.7, 171.0, 69.4, 60.3,34.8, 21.1, 21.0, 7.8.

Reactions of 2,3,4,6-tetra-O-Acetyl-1.5-Anhydro-D-glucitol (27) with HI

A solution of HI in AcOH (11 % w/w, 23.3 g, 20 mmol) containing compound **27** (0.664 g, 2.0 mmol) was stirred at 95°C for 18 h. After removing the solvent under vacuum, EtOAc and saturated aqueous $NaHCO_3$ (30 ml each) were added to the reaction solution. After separation, the aqueous layer was extracted with EtOAc (2 x 30 ml), the combined organic layer was washed with, brine and dried over anhydrous Na_2SO_4. Removal of the solvent followed by column chromatography gave compound **27** (30 %), **31** (30 %) and **32** (10 %).

1,5-anhydro-6-deoxy-6-iodo-D-glucitol (31)

^{1}H NMR ($CDCl_3$): δ 5.18 (t, J = 9.4 Hz, 1H), 4.98 (ddd, J = 5.8, 9.6, 10.6 Hz, 1H, H-), 4.86 (t, J = 9.3 Hz, 1H), 4,16 (dd, J = 5.7, 10.3 Hz, 1H), 3.36-3.26 (m, 3H, H-6, H-6', H-1), 3.10 (dd, J = 7.6, 11.7 Hz, 1H, H-1'), 2.04, 2.01, 2.00 (s, 3 H each, 3 OAc); ^{13}C NMR($CDCl_3$): δ 170.18, 169.60, 169.35 (3 OAc), 77.27, 73.16, 72.22, 68.94, 66.56, 20.62, 20.59, 20.59 (3 OAc), 3.55 (C-6).

2,6-anhydro-1-deoxy-3,4,5-tri-O-acetate-L-xylo-Hex-1-enitol (32)

$[\alpha]^{20}_{D}$ + 9.00 (c 1 $CHCl_3$); ^1H NMR ($CDCl_3$): δ 2.12, 2.10, 2.09 (3 s, 9 H, 3 x OAc), 3.45 (dd, J = 8.3, 11.5 Hz, 1H, H-6), 4.07 (dd, J = 4.9, 11.5 Hz, 1H, H-6'), 4.35 (t, J = 1.5 Hz, 1H, H-1), 4.60 (t, J = 1.5 Hz, 1H, H-1'), 4.93 (m, 1H, H-5), 4.99 (t, J = 7.8 Hz, 1H, H-4), 5.47 (d, J = 7.8 Hz, 1H, H-3); ^{13}C NMR($CDCl_3$): δ 20.3, 20.3, 20.6 (3 Carbon, 3 CH_3), 66.7 (C-6), 68.5 (2 Carbon) 72.0 (C-3, 4, 5), 95.4 (C-2), 153.5 (C-1), 168.9, 169.4, 169.4 (3 x OAc).

(S)-3-Hydroxy-tetrahydrothiophene (33)[30, 31]

To a stirred solution of 1, 4-diiodo-2-butanol- acetate (0.368 g, 1.0 mmol) in ethanol (6.0 ml) was added Sodium sulfide nonahydrate (0.360 g, 1.5 mmol). After stirring under reflux for 5 h, EtOAc (20 ml) was added. After filtration and condensation, **33** was obtained as colorless oil (1.04g, 100%) $[\alpha]^{20}_{D}$ -14.1 (c 1 $CHCl_3$); ^1H NMR ($CDCl_3$): δ 1.75-1.84 (m, 1H, H-4a), 2.07-2.14 (m, 1H, H-4b), 2.13 (s, 1H, C(3) OH), 2.76-2.98 (m, 4H, 2 H-2, 2 H-5), 4.56(m, 1H, H-3); ^{13}C NMR($CDCl_3$): δ 28.1 (C-5), 37.9 (C-4), 39.7 (C-2), 74.4 (C-3).

1-Benzyl-3-(S)-hydroxypyrrolidine(34)[32,33]

To a mixture of benzylamine (0.54 g, 5.0 mmol) and potassium carbonate (1.4 g, 10.0 mmol) in acetonitrile (30 mL) was added 1,4-diiodo-(S)-2-butanol-acetate (1.84 g, 5.0 mmol). After refluxing for 12 h, the solvent was removed under vacuum, water (2.0 g) and ethanol (10 ml) were added. The solution was then stirred under reflux for1 h. After

removing the solvent, water and ethyl acetate (30 mL each) were added to the residue. After separation and extracting the aqueous layer with ethyl acetate (2 x 30 mL), the organic layers were combined, dried over $MgSO_4$ and concentrated under vacuum. Purification using column chromatography on silica gel gave **34** as a colorless oil (0.53 g, 60 %); $[\alpha]^{20}_D$ -3.6 (c 1 $CHCl_3$); ^1H NMR ($CDCl_3$): δ 1.62-1.77 (m, 1H), 2.07-2.35 (m, 2 H), 2.50 (br, 1H), 2.52 (dd, J = 5.1, 10.0 Hz, 1H), 2.65 (dd, J = 2.2, 10.0 Hz, 1H), 2.82 (ddd, J = 4.1, 8.3, 8.3 Hz, 1H), 3.60 (s, 2H), 4.31 (m, 1H), 7.29 (m, 5H); ^{13}C NMR($CDCl_3$): δ 35.0 (C-4), 52.6 (C-5), 60.3 (C-2), 63.1 (Ph*C*H_2), 70.7 (C-3), 127.0, 128.1, 128.8, 138.6.

3-Acetoxy-cyclopentane-1,1-dicarbohylic acid diethyl ester (35)

To a mixture of dimethyl malonate (0.66 g, 5.0 mmol) and $KOBu^t$ in DMSO (15 ml) was added a solution of 1,4-diiodo-(S)-2-butanol-acetate (1.84 g, 5.0 mmol) in DMSO(5 ml). After stirring at r.t. for 48 h, brine and ethyl acetate (30 ml each) were added to the residue. After separation and extracting the aqueous layer with ethyl acetate (2 x 30 mL), the organic layers were combined, dried over $MgSO_4$ and concentrated under vacuum. Purification using column chromatography on silica gel gave 3-Acetoxy-cyclopentane-1,1-dicarbohylic acid diethyl ester **35** as a colorless oil (0.88 g, 65 %); $[\alpha]^{20}_D$ -2.26 (c 1 $CHCl_3$); ^1H NMR ($CDCl_3$): δ 1.07-1.15 (m, 6 H, 2 OCH_2CH_3), 1.66-1.72 (m, 1H, H-5), 1.84 (s, 3H, OAc), 1.92 (dd, J = 1.1, 22.1 Hz, 1H, H-4), 2.03 (dddd, J = 4.8, 8.3, 13.4 Hz, 1H, H-4'), 2.23 (m, 1H, H-2), 2.30 (dt, J = 8.3, 13.4 Hz, 1H, H-5'), 2.44 (dd, J = 6.1, 14.9 Hz, 1H, H- 2'), 4.01-4.07 (m, 4H, 2 OCH_2CH_3), 5.00-5.04 (m, 1H, H-3); ^{13}C NMR($CDCl_3$): δ 13.67, 13.71 (2 OCH_2CH_3), 20.78 (OAc-CH_3), 31.58 (C-4 or C-5),

31.63 (C-4 or C-5), 39.88 (C-2), 58.77 (C-1), 61.14, 61.28 (2 O*CH*$_2$CH$_3$), 75.33 (C-3), 170.13, 171.16, 171.59 (3 CH$_3$*C*O).

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Chapter 5

Preparation of Ribose Derived Nitrone and its Application in the Preparation of Iminosugars

Abstract

Starting from D-ribose, a six-membered cyclic nitrone was prepared in 3 steps. The nucleophilic reaction and 1,3-dipolar cycloaddition reaction of the nitrone prepared were explored. Employing nitromethane as the nucleophile, a 2-aminomethyl-3,4,5-piperidinetriol derivative was prepared without using the toxic TMSCN reagent. Isoxazolidines were prepared by the 1,3-dipolar cycloaddition of the nitrone with allyl alcohol and vinyl ethyl ether. Spiro-isoxazolidines were also prepared by employing carbohydrate derived alkenes. The cycloaddition reactions of nitrone and carbohydrate derived alkenes are highly regio and diastereoselective, only one product was obtained from each alkene.

5.1 Introduction

5.1.1 Iminosuars as glycosidases inhibitors

Glycosidases catalyze the hydrolysis of glycosidic bonds in carbohydrates, glycoproteins and glycolipids[1, 2]. Glycosidases are involved in the biosynthesis of the oligosaccharide chains and quality control mechanisms in the endoplasmic reticulum of the N-linked glycoproteins. Inhibition of these glycosidases can have profound effects on quality control, maturation, transport, and secretion of glycoproteins and can alter cell-cell or cell-virus recognition processes[2, 3].

In 1966 nojirimycin was discovered as the first glucose analog with the nitrogen atom in place of the ring oxygen (iminosugars)[4]. Nojirimycin was first described as an antibiotic produced by *Streptomyces roseochromogenes* R-468 and *S. lavendulae* SF-425 and was shown to be a potent inhibitor of α- and β-glucosidases from various sources[5]. Since then, over 100 iminosugars have been isolated from plants and microorganisms and many of those natural occurring glycosidase inhibitors and their derivatives or analogues have been synthesized[6-9].

In recent years, the biological activities of these iminosugars have been extended to the inhibition of glycosyltransferases[10, 11], of nucleosidase[12, 13] and glycogenphosphorylases[14], and of sugar nucleotide mutase[15, 16]. These remarkable properties of iminosugar give tremendous opportunities in the development of iminosugar based medicines for a wide range of diseases, such as diabetes[17, 18], viral infections[19, 20], and tumor metastasis[21, 22].

The strong therapeutic potential of iminosugars has generated a huge interest in their synthesis and structural modification and has stimulated many groups to develop short and stereoselective routes for their synthesis. Many recent syntheses use readily available and inexpensive chiral-pool starting materials such as carbohydrates[23-25], amino acids[26-28], and tartaric acids[29, 30]. Sharpless asymmetric epoxidation and dihydroxylation reactions have found successful applications in the chiral synthesis of azasugars[31-33].

5.1.2 Application of nitrones in the preparation of iminosugars and aza-C-glycosides.

For the preparation of the iminosugars and aza-C-glycosides from carbohydrates[23-25], usually, the nitrogen functionalities were installed at very late stage of the synthesis and thus make the preparation of libraries of nitrogen containing carbohydrate mimics very tedious. If the nitrogen functionality can be introduced at the early stage, or carbohydrate derivated synthons containing nitrogen functionality can be prepared, the preparation of the iminosugar libraries will be much easier. Recently, carbohydrate derivated nitrones have been used as the nitrogen containing chiral starting materials for the preparation of iminosugars[34-38].

The carbohydrate derivated nitrones can be classified into two categories based on the position of the nitrone functionality: the acyclic nitrones and the cyclic nitrones (Figure 5.1).

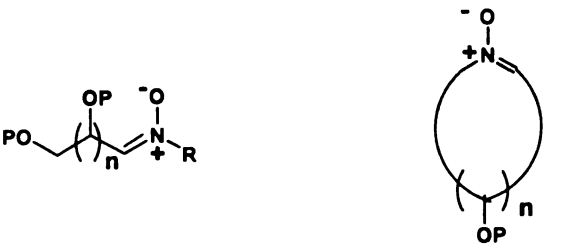
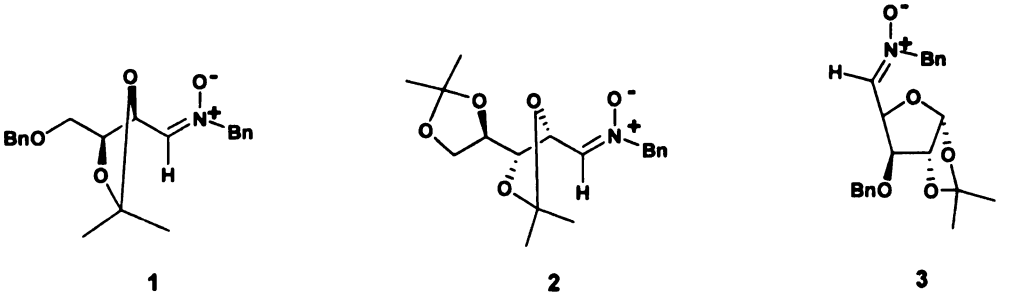


Figure 5.1 General structure of carbohydrate based acyclic and cyclic nitrones.

The acyclic nitrones can be prepared very efficiently by condensation of the carbonyl groups, usually aldehydes, with hydroxyl amines[39]. Figure 5.2 list some of the acyclic nitrones.



1 2 3

Figure 5.2 Carbohydrate based acyclic nitrones.

For the preparation of cyclic nitrones, usually, the protected carbohydrates are first condensed with protected hydroxylamines to form the protected oximes. Transforming one of the hydroxyl groups to a good leaving group followed by deprotection of the oxime give the cyclic nitrones (Figure 5.3 I).

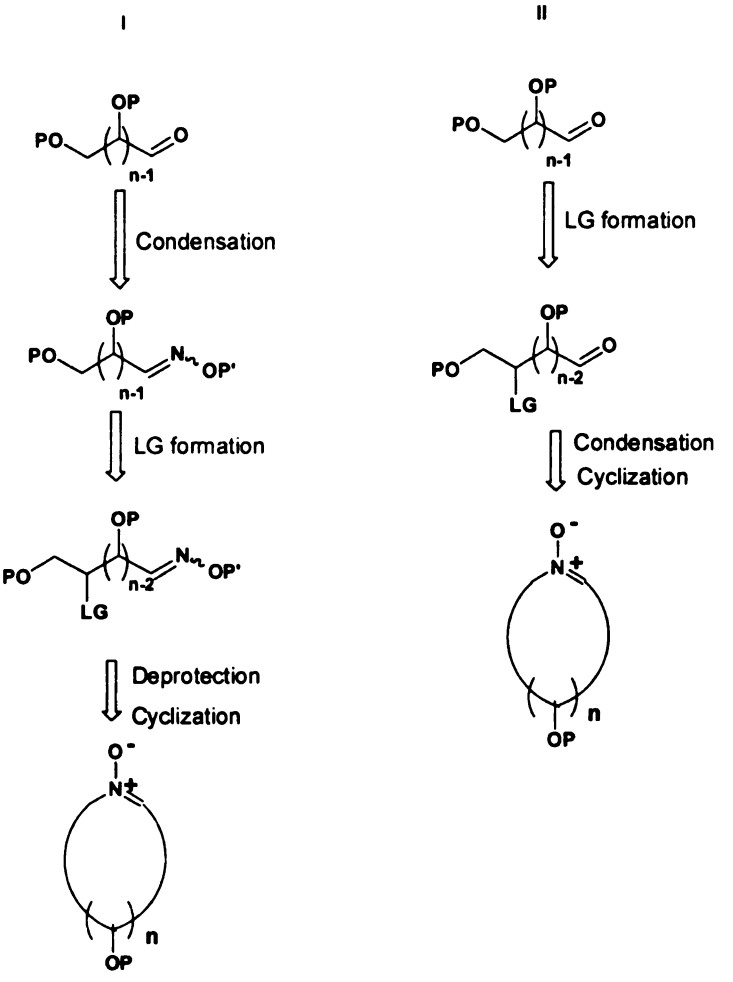


Figure 5.3 Strategies for the preparation of cyclic nitrones.

Recently, Goti et al reported the preparation of the cyclic nitrone **8** from L-xylose (Figure 5.4)[40].

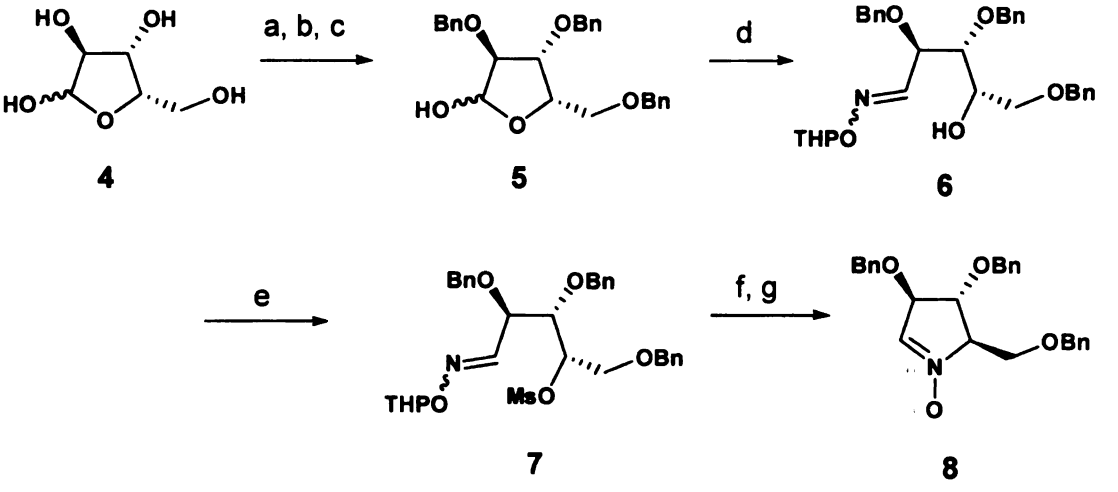


Figure 5.4 Preparation of cyclic nitrone from L-xylose (a) MeOH/H_2SO_4, anhydr. Na_2SO_4, rt, 21 h; (b) BnCl/KOH, Na_2SO_4, reflux, 8 h; (c) 6N HCl, CH_3COOH, 60–70°C (50% over three steps); (d) NH_2OTHP, no solvent, rt, 6 d, 100%; (e) MsCl, TEA, CH_2Cl_2, rt, 24 h, 50%; (f)DOWEX 50W X8, MeOH, rt, 24 h, 96%; (g) 0.1 M NaOH, dioxane, 0°C, 2 h, 55%.

From these acyclic and cyclic nitrones, a variety of iminosugar derivatives have been prepared through the addition reaction and 1,3-dipolar cycloaddition reactions. For recent developments in the nucleophilic addition reactions of chiral nitrones, Merino's review is a good resource[41]. In another review, the application of 1,3-dipolar cycloaddition reactions of nitrones in the construction of carbohydrate mimics were discussed[42].

Although progresses have been made in the preparation of carbohydrate derived nitrones, these processes are not very efficient, especially for the preparation of cyclic nitrones. Usually, the expensive $THPONH_2$[43] or $TBDPSONH_2$[44] is needed or the oxime intermediates formed have to be protected[45].

In this chapter, a different method was used for the preparation of cyclic nitrone. In this approach, the good leaving group is installed at first. The following one-pot condensation-cyclization reaction gives the cyclic nitrone directly. No protected hydroxylamines or extra steps to protect-deprotect the oxime is needed (Figure 5.3 II).

In the addition reactions of nitrones, for the introduction of the aminomethyl group, TMSCN as a nucleophile gave good results[46, 47]. However, the high toxicity of TMSCN prohibits its practical application. For the cycloaddition reactions of nitrones, usually, the alkenes used were not derivated from carbohydrates. In the rare cases where the alkenes were derivated from carbohydrates, the olefin functionalities are usually not connected to the carbohydrate ring[48].

Here, our efforts for the development of a more efficient and economic method for the preparation of carbohydrate derived nitrone and its application in the addition and cycloaddition reactions involving carbohydrate derived alkenes are discussed.

5.2 An efficient route for the preparation of cyclic nitrone from ribose.

Reaction of D-ribose with acetone using concentrated H_2SO_4 as the catalyst gives 2,3-O-isopropylidene-D-ribofuranose in quantitative yield. Reaction of 2,3-O-isopropylidene-D-ribofuranose with tosyl chloride in pyridine at 0°C affords 5-O-tosyl-2,3-O-isopropylidene-D-ribofuranose **10** in 78 %. **10** is unstable at room temperature and is

used directly in the next step without further purification. (At -17 °C, tosylate **10** can be stored for several weeks without obvious change).

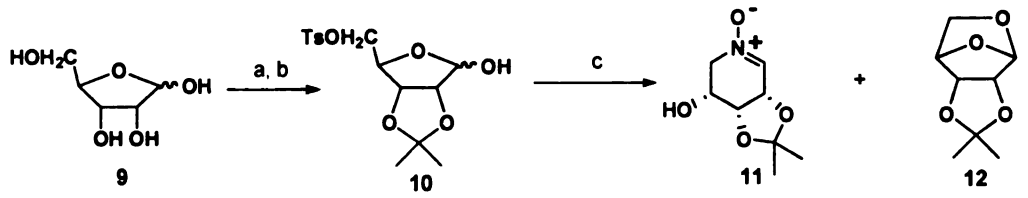


Figure 5.5 Preparation of nitrone using tosylate as substrate. (a) acetone, conc. H_2SO_4, quantitative; (b) tosyl chloride, pyridine, 78 %; (c) $H_2NOH.HCl$, base, various yields.

For the condensation-cyclization step, various bases and solvents are used. The results are listed in Table 5.1.

Table 5.1 Preparation of nitrone using tosylate as substrate.

Entry	Base	Solvent	Time (h)	Yield (%)
1	$NaHCO_3$	MeOH	24	6
2	$NaHCO_3$	MeOH/H_2O	12	11
3	$NaHCO_3$	i-PrOH	30	5
4	$NaHCO_3$	i-PrOH/ H_2O	12	~7
5	$NaHCO_3$	EtOH	24	~ 5
6	$NaHCO_3$	EtOH/H_2O	12	~ 6
7	Pyridine	MeOH	24	-
8	Et_3N	MeOH	24	12
9	Et_3N	EtOH	24	15

* Reactions are run at room temperature, TLC are used to monitor the reactions.

The base used is crucial to this reaction. If pyridine is used, no nitrone **11** can be formed. Changing the base to $NaHCO_3$, nitrone **11** is formed in various solvent. The best result is obtained in MeOH/ H_2O with 11 % of nitrone **11** formed (Table 5.1, entry 2). A better result was obtained by using Et_3N as the base and ethanol as solvent (15 %, Table 5.1, entry 9). For all the reaction conditions listed in table 5.1, except entry 7, along with the nitrone, a small amount of the 2,3-O-isopropyliden-1,4-anhydro-D-ribopyranose was formed (4-10 % yield). The other components obtained were complex mixture of compounds. The possible products from the reaction of tosylate **10** with hydroxylamine under basic conditions are shown in Figure **5.6.** No further efforts are made to separate and characterize these compounds except **11** and **12**.

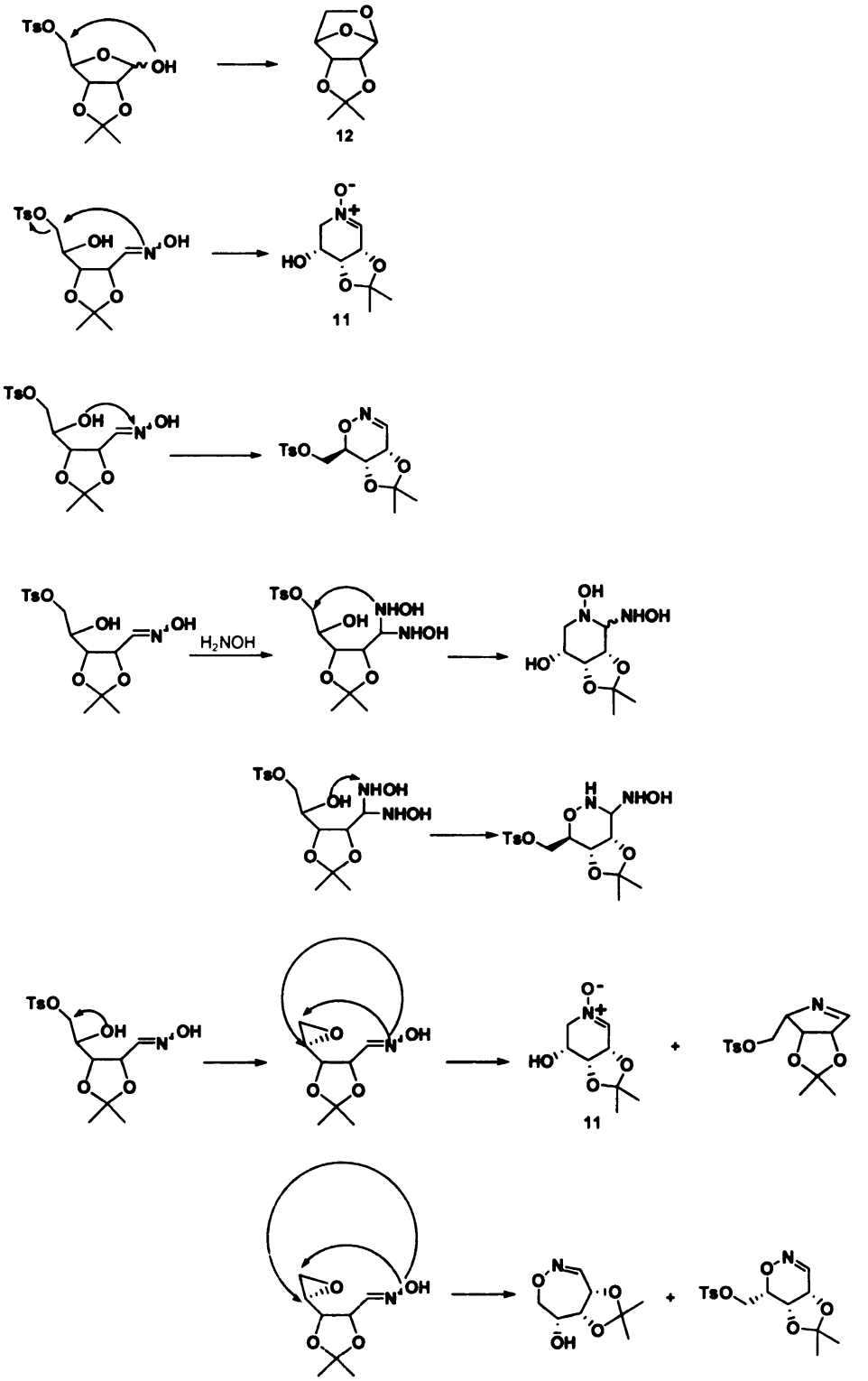
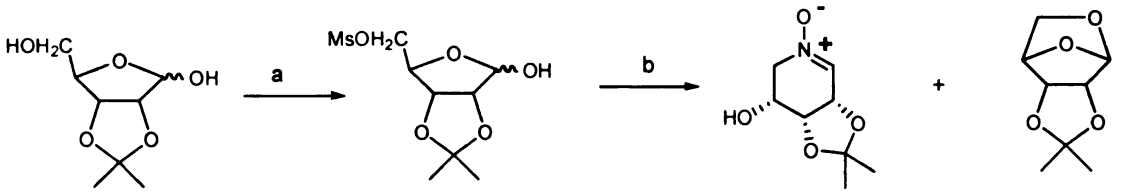


Figure 5.6 Possible products from reaction of tosylate **10** with hydroxylamine under basic conditions

Fortunately, much better results are obtained by switching tosylate **10** to mesylate **14** (Figure 5.7, Table 5.2).



13 **14** **11** **12**

Figure 5.7 Preparation of nitrone using tosylate as substrate.

(a) Mesyl chloride, pyridine, 75 %; (b) $H_2NOH.HCl$.

Table 5.2 Preparation of nitrone using mesylate as substrate.

Entry	Base	Solvent	Time (h)	Yield (%)
1	$NaHCO_3$	MeOH	24	14
2	$NaHCO_3$	MeOH/H_2O	12	18
3	$NaHCO_3$	EtOH	24	15
4	$NaHCO_3$	EtOH/H_2O	12	22
5	Et_3N	MeOH	24	25
6	Et_3N	EtOH	24	62

* Reactions are run at room temperature. TLC is used to monitor the reaction.

The best result is obtained with Et_3N as the base and EtOH as solvent (62 %, entry 6, Table 5.2). Although the yield is still not very high, considering the short steps and the cheap reagents used, this is still a practical route for the preparation of nitrone from D-ribose.

5.3 Steroeselective addition of nitromethane to the chiral nitrone.

To search for a substitute of TMSCN as the reagent for the introduction of an aminomethyl group to the nitrone, nitromethane is chosen since it is much less toxic compared to TMSCN and also it has been used extensively for Michael Reactions,[49-52] Henry Reacitons[53, 54].

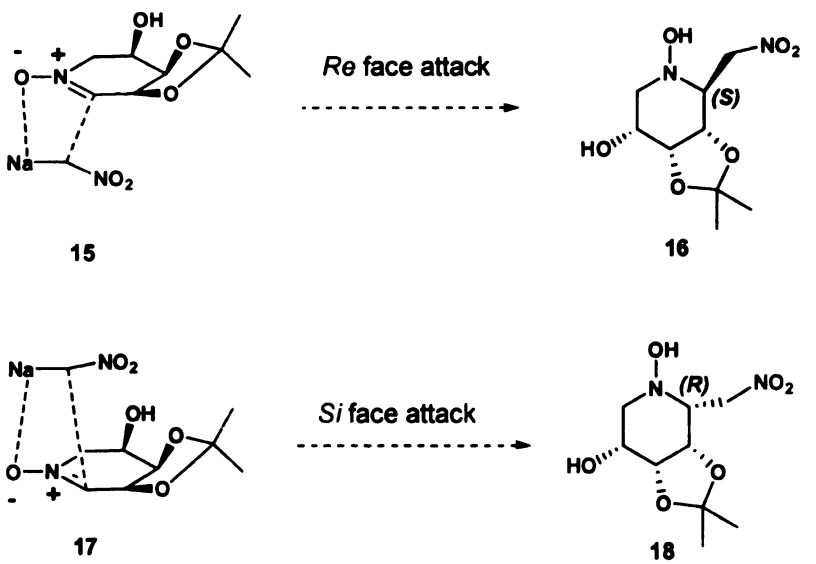


Figure 5.8 Possible products from addition of nitromethane to nitrone

Two possible transition states were shown in figure 5.8 for the nucleophilic addition of nitromethane to nitrone. Addition of nitromethane from the *Re* face (TS **15**) of the nitrone will give the S product **16** while addition of nitromethane from the *Si* face (TS **17**) of the nitrone will give the R product **18.** In TS **15,** the incoming nitromethane is anti to the isopropylidene group, while in TS **17**, it is syn to the isopropylidene group. The strong steric interaction between the nitromethane group and the isopropylidene in TS **17** will prohibit the *Si* face approach and thus it is expected that only the *Re* face attack will happen and only the S product **16** can be obtained.

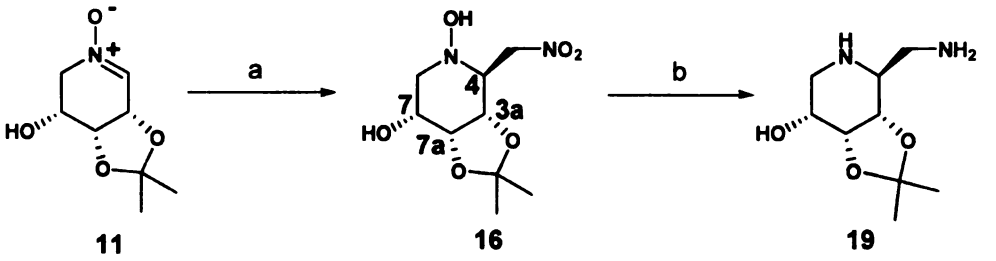


Figure 5.9 Addition of nitromethane to nitrone. (a) $MeNO_2$, MeONa, MeOH, r.t, 12 h, 82 %; (b) H_2, Pd/C (10 %), MeOH, 100 %.

The reaction of nitrone **11** with nitromethane is very efficient. Using MeONa as the base, with 2 equivalent of $MeNO_2$, the reaction is completed in 12 h with a high yield (82 %). NMR showed only one product is formed. The stereochemistry of the nitro compound was confirmed by the NOE. No NOE is observed between H3a and H4, which suggests that they are anti to each other as in structure **16.** Treatment of the nitro compound **16** with H_2 using Pd/C as catalyst give the reduced product **19** in quantitative yield (Figure 5.9).

5.4 Cyclization reactions of the ribose derived nitrone with non-carbohydrate based alkenes

For the 1,3-dipolar cycloadditions of nitrones to akenes, usually, the 5-substituted isoxazolidines are obtained from mono-substituted and 1,1-disubstituted alkenes with electron-donating and moderate electron-withdrawing groups[55, 56]. For olefins with strong electron-withdrawing groups, the 4-substituted isoxazolidines are formed[57,58]. If 1,2-disubstituted alkenes are used, mixtures of regioisomers are often formed. Usually, the isomer with the less electron rich substituent at 4-position is formed as the major product[59-61].

To control the stereochemistry outcome of the 1,3-dipolarcycloaddtion, many methods have been developed, for example, Lewis acids activation of the dipolarophiles, using chiral auxiliaries, employing enantioselective catalysts (metal or organo-catalysts), etc[62, 63]. For chiral nitrones, the steric hindrance plays an important role in control the approaching of the alkenes toward the nitrones, which makes it possible to achieve high regio and stereo control for cycloaddition reactions of chiral nitrones without the assistance of Lewis acids, chiral auxiliaries or catalysts[63].

A model for the cycloaddition of the chiral nitrone **11** with allyl alcohol is shown in figure 5.10. As in the nucleophilic addition reactions of the chiral nitrone (Figure 5.8), allyl alcohol can only approach nitrone **11** from the *Re* face to form the anti product. In figure 5.10, only the transition states with *Re* attack of the alkenes to the nitrone are shown.

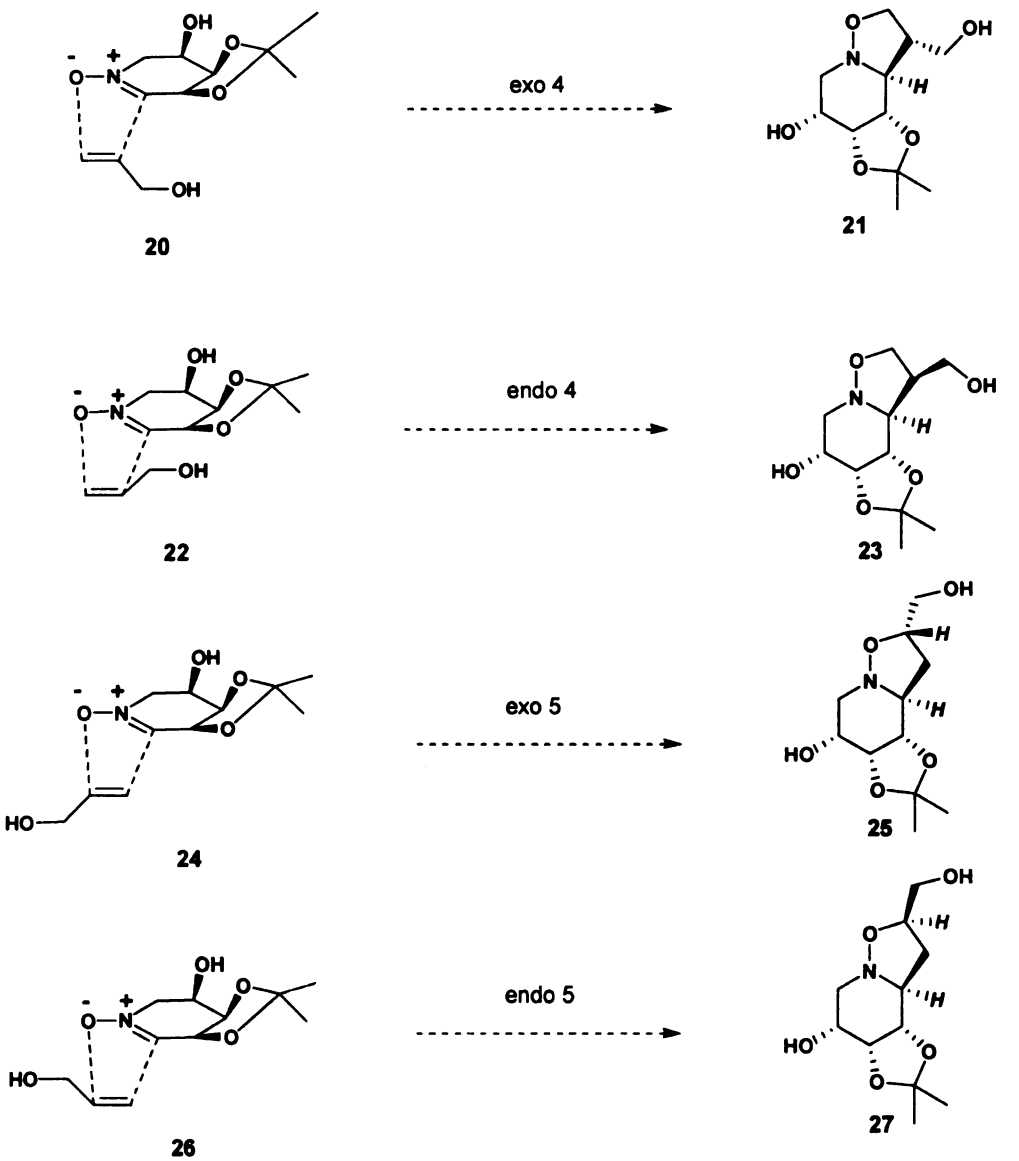


Figure 5.10 Possible products from cyclization of nitrone with allyl alcohol

There are 4 possible products from the 1,3-dipolar cycloaddition of nitrone toward allyl alcohol: the exo-4 (4 substituted isoxazolidines **21**), endo-4 (**23**), exo-5 (5 substituted isoxazolidines **25**) and endo-5 (**27**). Since no strong electron withdrawing group present in allyl alcohol, the cycloaddition reaction should show high region-selectivity with only the 5 substituted isoxazolidines **25**, **27** formed. As for **25** and **27**, the exo-5 product **25** is expected to be formed as the major product for steric reason. It is reported that for the

cycloaddition of 6-member-ring nitrone, 3-(*tert*-butyldiphenylsilyl)oxy-1-piperidine-1-oxide with allyl alcohol, a 90:10 exo/endo-selectivity, 74:26 diastereofacial selectivity was observed[64]. For the cycloaddition of 5-member-ring nitrone, 3-(*tert*-butyldimethylsilyl)oxy-1-pyrroline-1-oxide with allyl alcohol, a 85:15 exo/endo-selectivity, 82:18 diastereofacial selectivity was observed in the favorite formation of the exo product[65].

Refluxing nitrone **11** with allyl alcohol in toluene for 4 h give the cycloaddition products in 92 % yield (Figure 5.11). The reaction is highly regio-selective as no endo-4 or exo-4 product **21** or **23** is observed. For the two exo-5 and endo-5 products **25** and **27**, **25** is formed as the major product (89:11). The stereochemistry was confirmed by NOESY1D. No NOE between H-2 and H-3a is observed for the major product **25** while a 13 % NOE is observed between H-2 and H-3a in the minor product **27**.

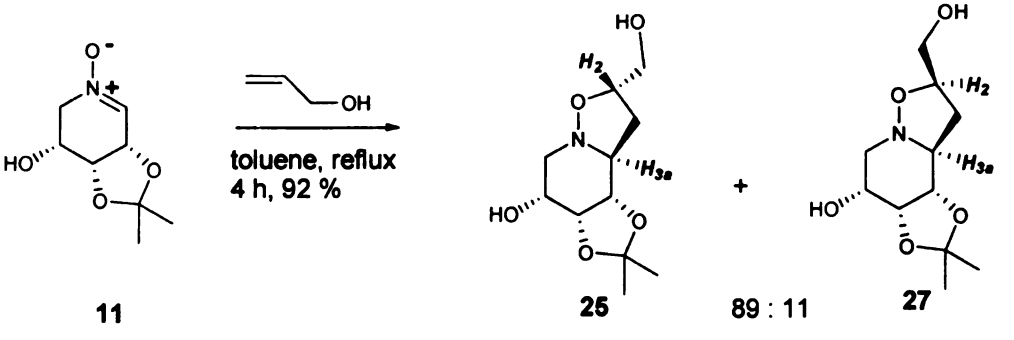


Figure 5.11 Cycloaddition of nitrone with allyl alcohol

Next, the cycloaddition of nitrone **11** with vinyl ethyl ether is studied. Similarly, no syn product should be formed as the vinyl ethyl ether can only attack the nitrone from the *Si* face. Vinyl ether type alkenes always give the 5-substituted isoxazolidines in

cycloaddition reaction with nitrones[66-68]. So the expected products are only the exo-5 and the endo-5 products **29** and **31** (Figure 5.12).

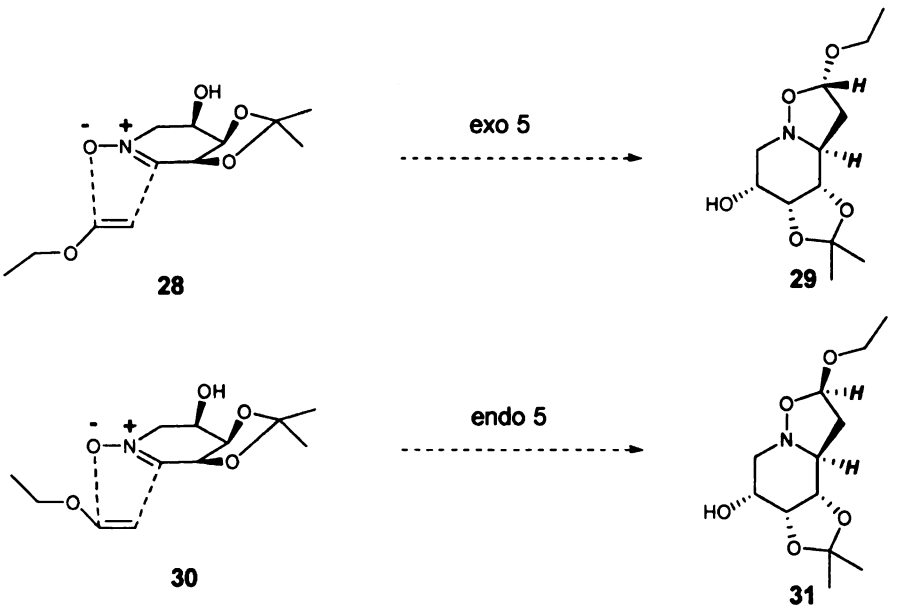


Figure 5.12 Products from cycloaddition of nitrone with vinyl ethyl ether

Heating a mixture of nitrone **11** and vinyl ethyl ether in chloroform at 62°C in a sealed flask for 4 h give the cycloaddition products in 94 % yield (Figure 5.13). As expected, no endo-4 or exo-4 product is observed. For the two exo-5 and endo-5 products, exo-5 is formed as the major product (68:32). The stereochemistry is confirmed by NOESY1D. No NOE between H-2 and H-3a is observed for the major product while 11 % NOE was observed between H-2 and H-3a in the minor product.

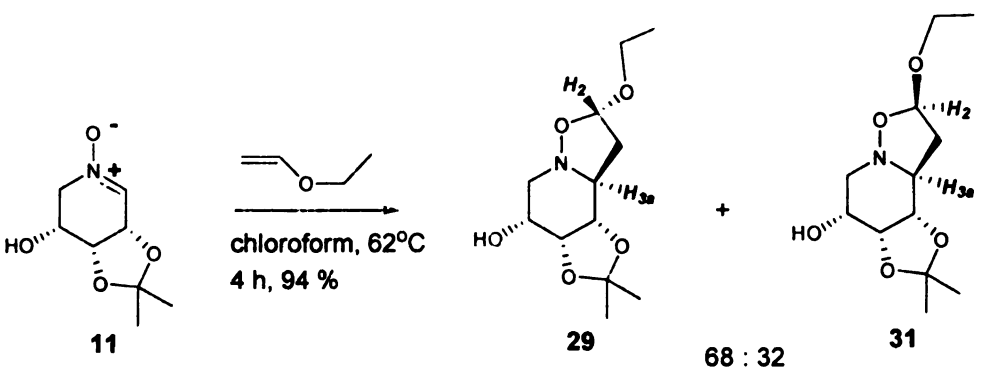


Figure 5.13 Reaction of nitrone with vinyl ethyl ether

5.5 Cycloaddition reactions of the ribose derived nitrone with carbohydrate based alkenes

After the successful cycloaddition reactions of the nitrone with non-carbohydrate based alkenes, the carbohydrate based alkenes are used in the 1,3-dipolar cycloaddition reactions. Alkenes **34** and **37**, derived from methyl-D-glucopyranoside and 1,5-anhydro-D-glucitol, are used.

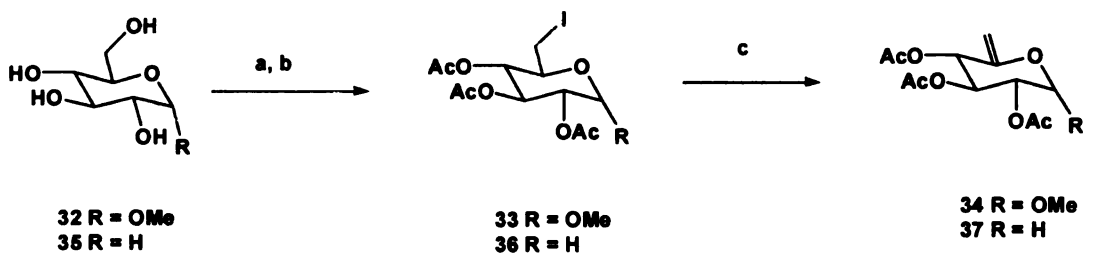


Figure 5.14 Preparation of carbohydrate derived alkenes. (a) Ph_3P/I_2, imidazole, toluene, 70°C, 3 h; (b). Ac_2O/pyridine, r.t, 12 h, 2 steps, 68 % for **33**, 65 % for **36**. (c) DBU, DMF, 75°C, 3 h, 75 % for **34**, 76 % for **37**.

Conversion of the primary hydroxyl groups to iodides followed by elimination of HI under strong basic conditions give the carbohydrate derived alkenes **34** and **37** in modest yields (~52 %, Figure 5.14).

As discussed above, alkenes only approach the nitrone **11** from the Si face. For the vinyl ether type alkenes, the 5-substituted isoxazolidines are formed with modest to high exo/endo selectivity. Similar results are expected for the 1,3-dipolar cycloaddition of the carbohydrate derived vinyl ether type alkenes **34** and **37**. However, higher exo/endo selectivity is expected since the chiral alkenes **34** and **37** are used.

Refluxing nitrone **11** and alkene **34** in toluene for 12 h give only one product in a very high yield (96 %, Figure 5.15). No NOE was observed between H3' and H3α, which suggests the structure of the product is the spiro-isoxazolidine **39**. The high diastereoselectivity is not surprising when the two possible transition states **38** and **40** are considered. In the two transition states, the one with fewer groups which are endo to the nitrone ring and at the same time syn to the isopropylidene group will be favored. In transition state **38,** the 3- and 4-acetyl groups are endo to the nitrone ring while only 3-acetyl group is syn to the isopropylidene group. In transition state **40**, only the 1-methoxyl group is endo to nitrone the nitrone ring and at the same time syn to the isopropylidene group. Although both the 3-acetyl group in **38** and 1-methoxyl group in **40** are at β position to the alkene, the shorter C-O bond makes the 1-methoxyl group in **40** more sterically hindered than the 3-acetyl group in **38**. From the sterically favored transition state **38**, the product **39** is formed exclusively.

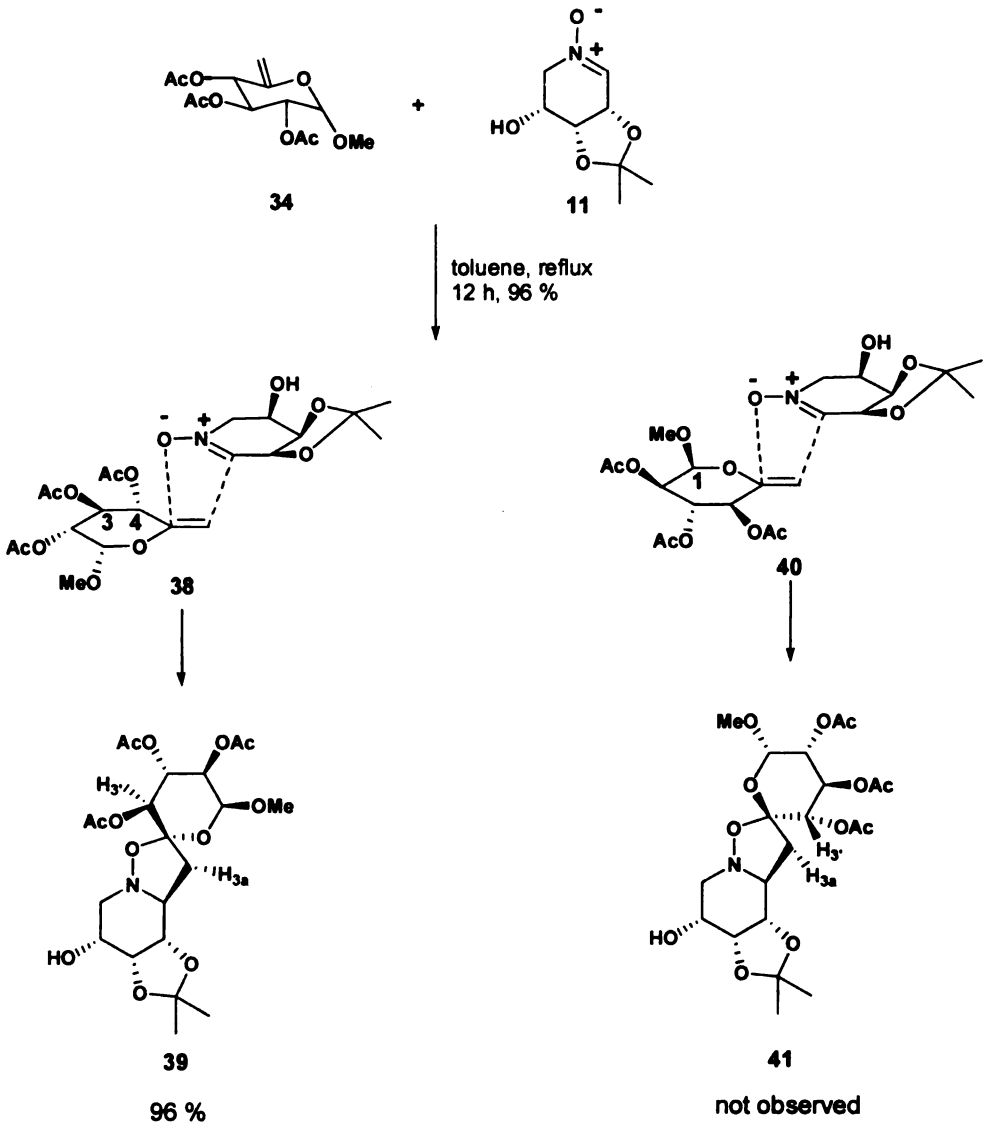


Figure 5.15 Cycloaddition of nitrone with carbohydrate derived alkene I

From the above analysis, if the 1-methoxyl group was removed, as shown in figure 5.16, transition state **44** should be favored and the product **45** should be formed as the major product.

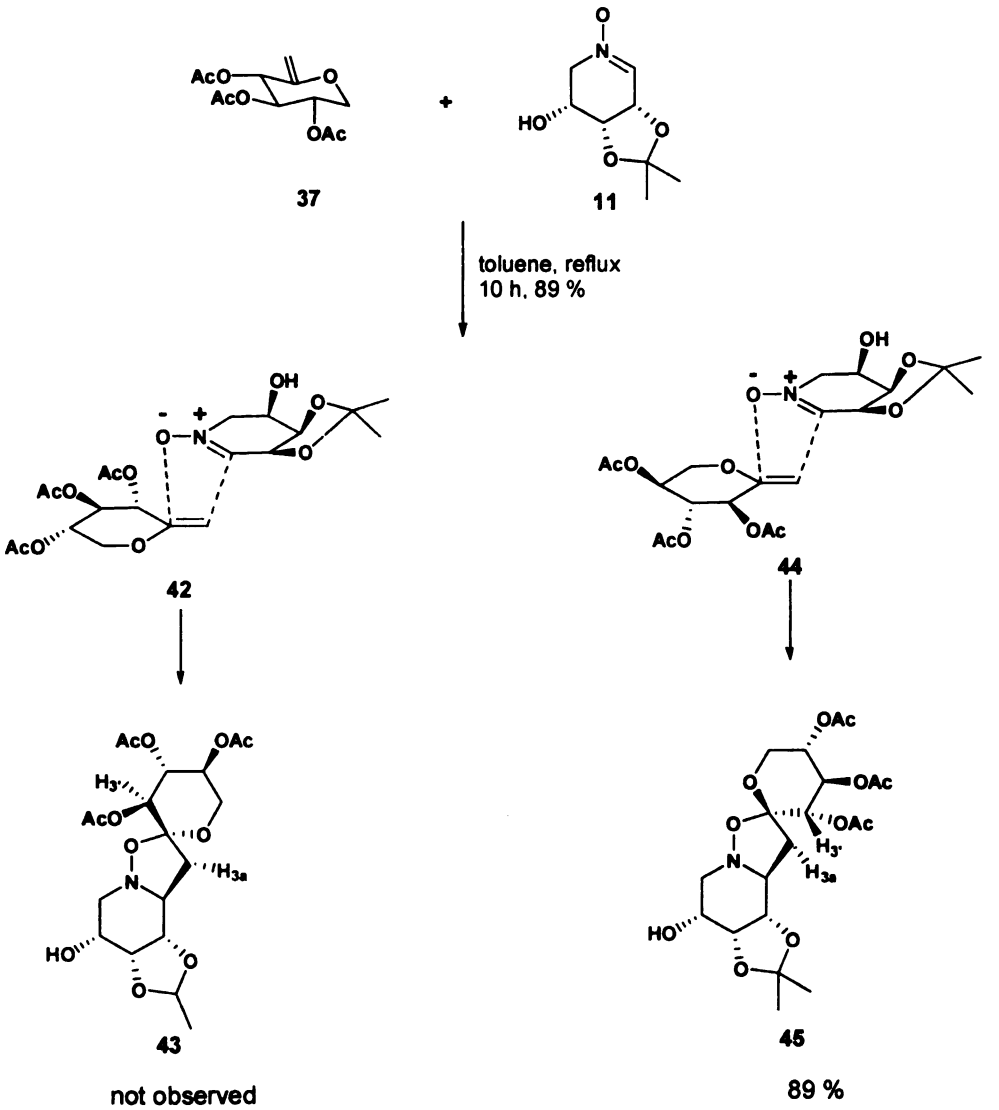


Figure 5.16 Cycloaddition of nitrone with carbohydrate derived alkene II

Only one product was obtained by the cycloaddition reaction of nitrone **11** and alkene **37** (89 %, Figure 5.16). A high NOE between H3' and H3α was observed (NOE: H3α, H3β 30 %, H3α, H3' 15 %), which means the structure is the spiro-isoxazolidine **45** from transition state **44**.

5.6 Conclusion

Start from D-ribose, a six-membered cyclic nitrone was prepared in 3 steps. The nucleophilic reaction and 1,3-dipolar cycloaddition reaction of the nitrone prepared were explored. Employing nitromethane as the nucleophile, a 2-aminomethyl-3,4,5-piperidinetriol derivative was prepared without using the toxic TMSCN reagent. Isoxazolidines and spiro-isoxazolidines were prepared by the 1,3-dipolar cycloaddition of the nitrone with achiral and chiral alkenes. For the chiral carbohydrate derived alkenes, the cycloaddition reaction is highly diastereoselective, only one product was obtained from each alkene.

5.7 Experimental

General procedures: ^{1}H, ^{13}C NMR spectra were recorded at 500, 125, MHz, respectively, with a Varian instrument at 293 K. The chemical shifts are given in ppm using $CDCl_3$ residue as reference (δ 7.24 ppm) for ^{1}H and relative to the central $CDCl_3$ resonance (δ= 77.00 ppm) for ^{13}C NMR unless otherwise specified. ^{1}H and ^{13}C are assigned on the basis of 2D ^{1}H COSY and ^{1}H-^{13}C chemical-shift correlated experiments. For the 1,3 cyclization products, all the NMR were done at 100°C with DMSO-d6 as solvent. Melting points were determined on a Fisher-Johns melting point apparatus (uncorrected). Optical rotations were measured on a Jasco P1010 polarimeter at 20°C. IR spectra (wave numbers in cm^{-1}) were recorded on a FT IR Nicolet 740 spectrometer in $CHCl_3$ solutions or KBr pellets. All chemicals were purchased from Aldrich Chemical Co. and used without further purification.

2,3-O-isopropylidene-D-ribofuranose (13)

In a 250 ml flask containing 100 ml acetone, D-Ribose (10.0 gram, 66.6 mmol) was added followed by the addition of conc. H_2SO_4 (1.0 ml). After stirring at r.t. for 4 h, NaHCO3 (4.0 gram) was added. Stirring was continued until the pH of the solution is 7. Filtration followed by removal of the solvent gave the product **13** as a syrup (12.6 g, 100 %). The product was used without further purification. ^{1}H NMR ($CDCl_3$): 5.43(s, 1H, H-1); 4.59(d, J=5.9 Hz, 1H, H-2); 4.85(d, J = 5.9 Hz, 1H, H-3), (br, 1H, H-4), 3.81-3.66 (m, 2H, H-5, H-5'); 1.58(s, 3H, CH_3); 1.41 (s, 3H, ^{1}H NMR ($CDCl_3$): 5.43(s, 1H, H-1); 4.59(d, J=5.9 Hz, 1H, H-2); 4.85(d, J = 5.9 Hz, 1H, H-3), (br, 1H, H-4), 3.81-3.66 (m, 2H, H-5, H-5'); 1.58(s, 3H, CH_3); 1.41 (s, 3H, CH_3); CH_3); ^{13}C NMR($CDCl_3$): 112.06 (

$C(CH_3)_2$); 103.07(C-1); 87.82 (C-4); 86.89 (C-2); 81.68 (C-3); 63.65 (C-5); 24.74, 26.28 (2 $C(CH_3)_2$);

2,3-O-isopropylidene-5-O-Tosyl-D-ribofuranose (10)

To a stirred solution of 2,3-O-isopropylidene-D-ribofuranose **13** (6.3 g, 33.3 mmol) in pyridine (100 ml) at 0°C was added Tosyl chloride (6.35 g, 33.3 mmol) in 3 portions at 30 minutes apart. The reaction solution was warmed to r.t gradually and stirred for another 12 h. Ethanol (5 ml) was added to quench the reaction. After removal of the pyridine, the remaining syrup was partitioned between $CHCl_3$ and saturated aqueous $NaHCO_3$ (60 ml each). The aqueous phase was extracted with $CHCl_3$ (30 ml) once and the combined organic phases were washed with water, brine, dried over $MgSO_4$ and condensed to gave **10** as a syrup (8.9 g, 78 %). The product **10** is not stable at r.t and it is used directly for the next step without further purification. A small amount of the product was purified through column chromatography for characterization purpose. m.p. 94-95 (lit 92.5-94)[69] ^1H NMR ($CDCl_3$): δ 7.73 (d, J = 18.2 Hz, 2H), 7.30 (d, J = 18.2 Hz, 2H), 5.36 (d, J = 2.6 Hz, 1H, H-1), 4.58 (dd, J = 0.9, 5.8 Hz, 1H, H-3), 4.51 (d, J = 5.9 Hz, 1H, H-2), 4.25 (m, 1H, H-4), 4.02-4.06 (m, 2H, H-5, H-5'), 3.69 (br s, 1H, OH), 2.39 (s, ArCH_3), 1.39, 1.23 (s, 2 $C(CH_3)$; ^{13}C NMR($CDCl_3$): δ 145.07, 132.37, 129.95, 127.84, 112.52, 102.82, 85.44, 83.55, 81.41, 69.87, 26.17, 24.65, 21.50.

2,3-O-Isopropylidene-5-O-methanesulfonyl-β-D-ribofuranose (14)

To a stirred solution of 2,3-O-isopropylidene-D-ribose **13** (5.0 g, 26.3 mmol) in pyridine (50 ml) at 10℃ was drop-wise added methanesulfonyl chloride (3.10 g, 26.3 mmol). The reaction mixture was gradually warmed to r.t and stirring was continued for another 4 h.

Ethanol (5 ml) was added to quench the reaction. After removal of the pyridine under vacuum, CH_2Cl_2 (30 ml) and water (30 ml) were added. After extraction the aqueous phase with CH_2Cl_2 (30 ml), the organic phases were combined, washed with cold 3 M HCl (20 ml), saturated aqueous $NaHCO_3$, and dried over $MgSO_4$. Removal of the solvent gave **14** as a white solid (5.4 g, 76.6 %). Part of the product was recrystalized from CH_2Cl_2/Et_2O for characterization purpose. M.p. 112-113°C (lit 112-114)[70] ^1H NMR (CD_3CN): δ 5.35 (s, 1H, H-1), 4.68 (d, J = 5.9 Hz, 1H, H-3), 4.55 (d, J = 5.9 Hz, 1H, H-2), 4.18-4.27 (m, 3H, H-4, H-6, H-6'), 3.09 (s, $MeSO_2$), 1.49, 1.34 (s, 2 C(CH_3); ^{13}C NMR(CD_3CN): δ 112.18, 102.74, 85.93, 83.46, 81.58, 71.13, 37.01, 26.10, 24.44.

(3aS, 7R, 7aR)-3a, 6, 7, 7a-tetrahydro-2, 2-dimethyl-5-oxide-1, 3-Dioxolo [4, 5-c] pyridin-7-ol (11)

Method 1: From 2,3-O-isopropylidene-5-O-Tosyl-D-ribofuranose

To 5 ml water was added $NaHCO_3$ (1.26 g, 15 mmol) and $H_2NOH.HCl$ (1.04 g, 15 mmol), the mixture was stirred until no bubble come out. This solution was then transferred to a flask containing a solution of 2,3-O-isopropylidene-5-O-Tosyl-D-ribofuranose (1.03 g, 3 mmol) in methanol (15 ml). After stirring at r.t. for 24 h, the solution was then condensed under vacuum with the bath temperature at no higher than 25°C to a syrup. Column chromatography of this syrup gave the desired nitrone **11** in 24 % yield.

Method 2: From 2,3-O-Isopropylidene-5-O-methanesulfonyl-β-D-ribofuranose

To 5 ml water was added $NaHCO_3$ (1.26 g, 15 mmol) and $H_2NOH.HCl$ (1.04 g, 15 mmol), the mixture was stirred until no bubble come out. This solution was then transferred to a flask containing a solution of 2,3-O-isopropylidene-5-O-methanesulfonyl-D-ribofuranose (0.805 g, 3 mmol) in methanol (15 ml). After stirring at r.t. for 24 h, the solution was then condensed under vacuum with the bath temperature at no higher than 25°C to a syrup. Column chromatography of this syrup gave the desired nitrone **11** in 30 % yield.

Method 3: From 2,3-O-Isopropylidene-5-O-methanesulfonyl-β-D-ribofuranose with Et_3N as base

To 10 ml ethanol was added Et_3N (1.52 g, 15 mmol) and $H_2NOH.HCl$ (1.04 g, 15 mmol), the mixture was stirred until the entire solid dissolved. This solution was then transferred to a flask containing a solution of 2,3-O-isopropylidene-5-O-methanesulfonyl-β–D-ribofuranose (1.03 g, 3 mmol) in ethanol (15 ml). After stirring at r.t. for 24 h, the solution was then condensed under vacuum with the bath temperature at no higher than 25°C to a syrup. Column chromatography (Hexane/EtOAc/EtOH 1:1:0 to 0:1:1) of this syrup gave the desired nitrone in **11** 62 % yield.

$[\alpha]^{20}_D$ -148.75 (c 1 $CHCl_3$); ^1H NMR ($CDCl_3$): 1.41 (s, 3H,), 1.44 (s, 3H), 2.15 (s, 1H, OH), 3.88 (dd, J = 4.8, 14.3 Hz, 1H, H-6a), 3.96 (ddt, J = 1.5, 11.3, 14.3 Hz, 1H, H-6b), 4.14 (ddd, J = 3.1, 4.8, 9.2 Hz, 1H, H-7), 4.50 (dd, J = 3.0, 6.4 Hz, 1H, H-7a), 4.85 (dd, J = 3.5, 6.4 Hz, 1H, H-3a), 7.05 (dd, J = 1.8, 3.5 Hz, 1H, H-4); ^{13}C NMR ($CDCl_3$): 134.3 (C-4), 110.9, 72.2, 70.6, 64.1, 58.1 (C-6), 26.8, 25.4. Calculated for C8H13NO4 C, 51.33, H, 7.00, N, 7.48; Found C 51.30, H, 6.94, N, 7.50.

1,5-anhydro-2,3-O-(1-methylethylidene)- β-D-Ribofuranose (12)[70]

$[\alpha]^{20}_D$ -72 (c 1 $CHCl_3$); ^1H NMR ($CDCl_3$): δ 5.43 (s, 1H, H-1), 4.69 (d, J = 3.7 Hz, 1H, H-4), 4.27 (d, J = 5.5 Hz, 1H, H-2), 3.42 (dd, J = 3.8, 7.2 Hz, 1H, H-5a), 3.30 (d, J = 7.2 Hz, 1H, H-5b), 1.46, 1.29 (2 s, 3 H each, $C(Me)_2$); ^{13}C NMR ($CDCl_3$): 112.0, 99.7 (C-1), 81.1 (C-2), 79.3 (C-3), 77.4 (C-4), 63.0 (C-5), 25.8, 25.1 (CMe_2).

(3aS, 4S, 7R, 7aR)-2,2-Dimethyl-4-nitromethyl-tetrahydro-[1,3]dioxolo[4,5-c]pyridine-5,7-diol (16)

To a stirred solution of nitrone **11** (46.7 mg, 0.25 mmol) in methanol (2.0 ml) was added nitromethane (61 mg, 1.0 mmol) and MeONa (13.0 mg, 0.25 mmol). After stirring at r.t for 8 h, the reaction mixture was cooled to 0°C and 3 N HCl was added to adjust the solution pH to 7. After condensation, ethyl acetate and water (10 ml each) were added to the flash. The aqueous layer was separated and extracted with ethyl acetate twice (2 x 10 ml). The combined organic extracts were washed with water, brine, dried over $MgSO_4$. Condensation followed by column chromatography (chloroform : methanol 25 : 1) gave **16** as a white solid (50.8 mg, 82 %). $[\alpha]^{20}_D$ -3.52 (c 1 $CHCl_3$); ^1H NMR (DMSO): δ 7.87 (br s, 1H, N-OH), 4.63 (dd, J = 7.7, 13.0 Hz, 1H, CH_2NO_2), 4.56 (dd, J = 3.6, 13.0 Hz, 1H, CH_2NO_2), 4.32 (t, J = 4.2 Hz, 1H, H-7a), 4.09 (ddd, J = 3.9, 5.0, 11.3 Hz, 1H, H-7), 4.01 (dd, J = 4.5, 9.1 Hz, 1H, H-3a), 3.23 (ddd, J = 3.5, 7.7, 11.2 Hz, 1H, H-4), 3.08 (dd, J = 5.1, 11.3 Hz, 1H, H-6), 2.73 (t, J = 11.3 Hz, 1H, H-6'), 1.50, 1.34 (2 s, 3 H each, CMe_2); ^{13}C NMR(DMSO): δ 108.59, 75.47, 74.73, 72.77, 64.10, 61.95, 57.70, 27.37, 25.68; NOESY1D: no NOE observed between H-4 and H-3a;

(3aS, 4S, 7R, 7aR)-4-Aminomethyl-2,2-dimethyl-hexahydro-[1,3]dioxolo[4,5-c]pyridine-7-ol (19)

To a solution of **16** (0.128 g, 0.5 mmol) in methanol (5 ml) was added Pd/C (10 %, 40 mg), the solution was stirred under H_2 atmosphere (1 atm) for 8 h. Filtration of the solution through celite followed by removal of the solvent gave the hydrogenated product **19** in quantitative yield (0.101 g, 100 %).

$[\alpha]^{20}_D$ (c 1 $CHCl_3$); ^1H NMR (DMSO): δ 4.61 (dd, J = 4.6, 11.3 Hz, 1H), 4.34 (t, J = 4.2 Hz, 1H), 4.27 (t, J = 4.2 Hz, 1H), 4.07 (ddd, J = 4.2, 4.9, 11.3 Hz, 1H), 4.00 (dd, J = 4.6, 9.4 Hz, 1H), 3.81-3.84 (m, 1H), 3.67-3.74 (m, 1H), 3.06-3.12 (m 1H), 3.03 (dd, J = 5.5, 9.8 Hz, 1H), 2.90-2.98 (m, 1H), 2.77 (dd, J = 6.5, 11.5 Hz, 1H), 1.47, 1.33 (2 s, 3 H each, 2 CMe_2); ^{13}C NMR(DMSO): δ 74.83, 74.40, 62.37, 57.75, 57.77, 53.50, 27.49, 25.80.

Cycloaddition of nitrone (11) with allyl alcohol:

To a solution of nitrone (93.5 mg, 0.5 mmol) in toluene (5.0 ml) was added allyl alcohol (145 mg, 2.5 mmol). The reaction mixture was stirred under reflux for 6 h. Removal of the solvent gave a syrup (112 mg, 92 %, 89 : 11 by NMR), which is a diastereomeric mixture of the cyclization products and can not be separated by column chromatography. Crystallization from chloroform gave the 2S anomer **25** as white crystals (75 mg, 61 %). Upon standing at –17°C for 48 h, the 2R anomer **27** was obtained as a crystal from the mother liquid (14 mg, 11 %).

(2S, 3aS, 4S, 5R, 6R) 2-methanol-4,5-O-isopropylidene-6-hydroxyl-hexahydro-2H-Isoxazolo [2,3a] pyridine (25)

^{1}H NMR (DMSO): δ 4.28-4.42 (br, 2 H, 2 OH), 4.23 (t, J = 4.3 Hz, 1H, H-5), 3.98-4.03 (m, 3 H, H-2, H-4, H-6), 3.40-3.42 (m, 2 H, C*H*$_2$OH), 3.16 (dd, J = 4.9, 10.1 Hz, 1H, H-7), 2.65-2.72 (m, 2 H, H-3a, H-7), 2.08-2.14 (m, 1H, H-3), 1.98 (ddd, J = 8.4, 11.2, 18.0 Hz, 1H, H-3'), 1.45, 1.32 (2 s, 3 H each, 2 CMe$_2$); ^{13}C NMR (DMSO): δ 108.02, 76.63, 75.81, 74.59, 63.88, 63.70, 62.61, 53.95, 34.91, 27.13, 25.36; Calculated for C11H19NO5 C, 53.87, H, 7.81, N, 5.71; Found C 53.60, H, 7.65, N, 5.86.

(2R, 3aS, 4S, 5R, 6R) 2-methanol-4,5-O-isopropylidene-6-hydroxyl-hexahydro-2H-Isoxazolo [2,3a] pyridine (27)

^{1}H NMR (DMSO): δ 4.49 (d, J = 2.1 Hz, 1H, C-6 OH), 4.27 (t, J = 5.5 Hz, 1H, CH$_2$*OH*), 4.23 (t, J = 4.2 Hz, 1H, H-5), 3.98-4.02 (m, 3 H, H-2, H-4, H-6), 3.37-3.43 (m, 2 H, *CH*$_2$OH), 3.16 (dd, J = 5.7, 10.2 Hz, 1H, H-7), 2.65-2.71 (m, 2H, H-3a, H-7'), 2.12 (ddd, J = 4.9, 7.0, 16.8 Hz, 1H, H-3), 1.98 (ddd, J = 8.5, 8.5, 16.8 Hz, 1H, H-3'), 1.46, 1.32 (2 s, 3 H each, 2 CMe$_2$); ^{13}C NMR (DMSO): δ 76.59, 75.78, 74.59, 63.87, 63.62, 62.57, 53.95, 34.88, 27.13, 25.36; NOESY1D: no NOE observed between H-2 and H-3a; Calculated for C11H19NO5 C, 53.87, H, 7.81, N, 5.71; Found C 53.89, H, 7.88, N, 5.79.

Cycloaddition of Nitrone 11 with Vinyl ethyl ether

To a solution of nitrone **11** (93.5 mg, 0.5 mmol) in chloroform (5.0 ml) was added ethyl vinyl ether (180 mg, 2.5 mmol). After sealing the flask, the reaction mixture was stirred at 62°C 4 h. Removal of the solvent gave a syrup, which is a diastereomeric mixture of the cyclization products (121.8 mg, 94 %). The diastereomeric mixture was separated by

column chromatography gave the pure 2R anomer **29** (58.3 mg, 45 %) and the 2S anomer **31** (40.1 mg, 31 %)

(2S, 3aS, 4S, 5R, 6R) 2-ethoxy-4,5-O-isopropylidene-6-hydroxyl-hexahydro-2H-Isoxazolo [2,3a] pyridine (29)

$[\alpha]^{20}_D$ + 57.53 (c 1 $CHCl_3$); ^{1}H NMR (DMSO): δ 5.10 (t, J = 4.3 Hz, 1H, H-2), 4.26 (t, J = 4.8 Hz, 1H, H-5), 4.05 (t, J = 6.1 Hz, 1H, H-4), 3.99 (dt, J = 3.9, 9.9 Hz, 1H, H-6), 3.56-3.66 (m, 1H, OCH_2CH_3), 3.38-3.49 (m, 1H, OCH_2CH_3), 3.06-3.17 (m, 2 H, H-3a, H-7), 2.94 (dd, J = 9.9, 11.1 Hz, 1H, H-7'), 2.16-2.20 (m, 2 H, H-3, H-3'), 1.44, 1.31 (s, 3 H each, , 2 $C(CH_3)_2$), 1.12 (t, J = 7.0 Hz, 3H, OCH_2CH_3); ^{13}C NMR (DMSO): δ 107.91 ($C(CH_3)_2$), 99.86(C-2), 75.56, 74.15, 62.07 , 61.68, 60.33, 52.33, 40.29 (C-3), 26.72, 25.00 (2 $C(CH_3)_2$), 14.31; NOESY1D: no NOE observed between H-2 and H-3a; Calcd. for C21H31NO4 489.1846, found 489.1846; Calculated for C12H21NO5 C, 55.58, H, 8.16, N, 5.40; Found C 55.70, H, 8.12, N, 5.10.

(2R, 3aS, 4S, 5R, 6R) 2-ethoxy-4,5-O-isopropylidene-6-hydroxyl-hexahydro-2H-Isoxazolo [2,3a] pyridine (31)

$[\alpha]^{20}_D$ -105.56 (c 1 CHCl3); ^{1}H NMR (DMSO): δ 5.11 (t, J = 3.1 Hz, 1 H, H-2), 4.24 (t, J = 3.9 Hz, 1H, H-5), 4.04 (t, J = 5.4 Hz, 1H, H-4), 3.99 (m, 1H, H-6), 3.57-3.72 (m, 1H, OCH_2CH_3), 3.40-3.53 (m, 1H, OCH_2CH_3), 3.25 (dd, J = 5.1, 9.4 Hz, 1H, H-7), 2.53-2.65 (m, 2 H, H3a, H-7'), 2.17-2.21 (m, 1H, H-3), 1.79-1.86 (m, 1H, H-3'), 1.45, 1.32 (2 s, 3 H each, 2 CMe_2), 1.13 (t, J = 6.9 Hz, 3H, OCH_2CH_3); 108.09, 100.70, 75.24, 74.71, 65.15, 64.33, 62.22, 54.99, 40.38, 27.24, 25.38, 14.27; NOESY1D: 11 % NOE observed

between H-2 and H-3a; Calculated for C12H21NO5 C, 55.58, H, 8.16, N, 5.40; Found C 55.68, H, 8.19, N, 5.49.

1,5-anhydro-2,3,4-tri-O-acetyl-6-deoxy-6-iodo-D-glucitol (36)

To a solution of toluene (25 ml) containing triphenylphosphine (3.05 g, 12.0 mmol), iodine (2.98 g, 12.0 mmol) and imidazole (2.45 g, 36.0 mmol) were added 1,5-anhydro-D-glucitol (1.64 g, 10 mmol). The reaction mixture was stirred at 70[illegible] for 3 h and then cooled to r.t. After adding water (30 ml), the mixture was stirred vigorously for 30 min. After separation, the toluene phase was extracted with water (3 x 20 ml). The combined water extracts were condensed and dried under high vacuum. Pyridine (40 ml) was added to dissolve the residue, followed by the addition of acetic anhydride (20 ml). The mixture was stirred at r.t. for 12 h. After concentration of the reaction mixture, EtOAc (50 ml) and aqueous saturated $NaHCO_3$ (50 ml) were added to the flask. The aqueous phase was separated and extracted with EtOAc (30 ml) once. The combined organic phase was washed with water, brine, and dried over $MgSO_4$. Column chromatography gave the iodo product **36** (2.60 g, 65 %). ^1H NMR ($CDCl_3$): δ 5.18 (t, J = 9.4 Hz, 1H), 4.98 (ddd, J = 5.8, 9.6, 10.6 Hz, 1H, H-), 4.86 (t, J = 9.3 Hz, 1H), 4,16 (dd, J = 5.7, 10.3 Hz, 1H), 3.36-3.26 (m, 3H, H-6, H-6', H-1), 3.10 (dd, J = 7.6, 11.7 Hz, 1H, H-1'), 2.04, 2.01, 2.00 (s, 3 H each, 3 OAc); ^{13}C NMR($CDCl_3$): δ 170.18, 169.60, 169.35 (3 OAc), 77.27, 73.16, 72.22, 68.94, 66.56, 20.62, 20.59, 20.59 (3 OAc), 3.55 (C-6).

Methyl-6-deoxy-6-iodo-2,3,4-tri-O-acetyl-a-D-glucopyranoside (33)

Methyl-6-deoxy-6-iodo-2,3,4-tri-O-acetyl-a-D-glucopyranoside was prepared from methyl-a-D-glucopyranoside using the same sequences as for the preparation of 1,5-

anhydro-2,3,4-tri-O-acetyl-6-deoxy-6-iodo-D-glucitol (68 %). $[\alpha]^{20}_D$ + 113.5 (c 1 $CHCl_3$); ^1H NMR ($CDCl_3$): δ 5.45 (dd, J = 9.4, 10.0 Hz, 1H, H-3), 4.94 (d, J = 3.7 Hz, 1H, H-1), 4.87 (dd, J = 3.7, 10.1 Hz, 1H, H-2), 4.86 (t, J = 10.1 Hz, 1H, H-4), 3.77 (ddd, J = 2.4, 9.5, 8.3 Hz, 1H, H-5), 3.46 (s, 3H, OMe), 3.28 (dd, J = 2.4, 10.9 Hz, 1H, H-6), 3.12 (dd, J = 8.3, 10.9 Hz, 1H, H-6'), 2.05, 2.03, 1.98 (s, 3 H each, 3 OAc); ^{13}C NMR($CDCl_3$): δ 170.1, 170.0, 169.6 (3 OAc), 96.69 (C-1), 72.45, 70.89, 69.65, 68.62, 55.74, 20.69, 20.67, 20.64 (3 OAc), 3.59 (C-6).

2,6-anhydro-1-deoxy-3,4,5-tri-O-acetate-L-xylo-Hex-1-enitol (37)

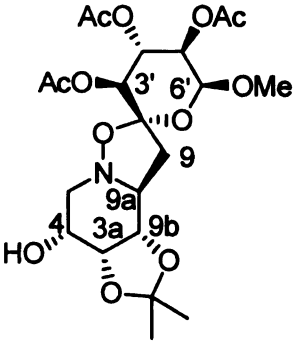
To a solution of 1,5-anhydro-2,3,4-tri-O-acetyl-6-deoxy-6-iodo-D-glucitol (2.0 g, 5.0 mmol) in anhydrous DMF (20 ml) was added DBU (4.8 ml, 30 mmol) and the mixture was stirred at 75°C for 3 h. After cooling to r.t, water and ethyl acetate (30 ml each) were added to the reaction mixture. The aqueous layer was separated and extracted with ethyl acetate twice (2 x 20 ml). The combined organic extracts were washed with saturated aqueous $NaHCO_3$, water, brine, dried over $MgSO_4$. Condensation followed by column chromatography (ethyl acetate: hexane 1 : 5) gave **37** as a white solid (1.03 g, 76 %). $[\alpha]^{20}_D$ + 9.00 (c 1 $CHCl_3$); ^1H NMR ($CDCl_3$): δ 5.47 (d, J = 7.8 Hz, 1H, H-3), 4.99 (t, J = 7.8 Hz, 1H, H-4), 4.93 (m, 1H, H-5), 4.60 (t, J = 1.5 Hz, 1H, H-1'), 4.35 (t, J = 1.5 Hz, 1H, H-1), 4.07 (dd, J = 4.9, 11.5 Hz, 1H, H-6'), 3.45 (dd, J = 8.3, 11.5 Hz, 1H, H-6), 2.12, 2.10, 2.09 (3 s, 9 H, 3 x OAc), ^{13}C NMR($CDCl_3$): δ 168.9, 169.4, 169.4 (3 x OAc), 153.5 (C-1), 95.4 (C-2), 72.0 68.5 (2 Carbon) (C-3, 4, 5), 66.7 (C-6), 20.3, 20.3, 20.6 (3 Carbon, 3 CH_3).

Methyl 2,3,4 tri-O-acetyl 6-deoxy-α–D-xylohex-5-enopyranoside (34)

Methyl 2,3,4 tri-O-acetyl 6-deoxy-α–D-xylohex-5-enopyranoside was prepared from Methyl-6-deoxy-6-iodo-2,3,4-tri-O-acetyl-α-D-glucopyranoside using the same sequences as for the preparation of 2,6-anhydro-1-deoxy-3,4,5-tri-O-acetate-L-xylo-Hex-1-enitol (75 %). $[\alpha]^{20}_D$ (c 1 $CHCl_3$); ^1H NMR ($CDCl_3$): δ 5.42-5.48 (m, 2H, H-6, H-1), 4.95-4.98 (m, 2H, H-6', H-3), 4.76 (t, J = 1.8 Hz, 1H, H-4), 4.58 (t, J = 1.8 Hz, 1H, H-2), 3.42 (s, 3 H, OMe), 2.09, 2.05, 2.00 (3 s, 3 OAc); ^{13}C NMR($CDCl_3$): δ 170.1, 169.8, 169.5 (3 OAc), 97.74, 97.46, 70.63, 69.68, 69.37, 55.53 (OMe), 20.67, 20.66, 20.64 (3 OAc).

(3aR, 3'S, 4R, 4'R, 5'R, 6'S, 9aS, 9bS)-4-hydroxy-6'-methoxy-2,2-dimethyldecahydrospiro[1,3-dioxolo[4,5-*c*]isoxazolo[2,3-*a*]pyridine-8,2'-pyran]-3',4',5'-triyl triacetate (39)

A solution of toluene (10.0ml) containing nitrone (93.5 mg, 0.5 mmol) and methyl 6-deoxy-a-D-xylo-hex-5-enopyranoside (151 mg, 0.5 mmol) was stirred under reflux for 12 h. Removal of the solvent followed by column chromatography gave the cyclization product **39** (235 mg, 96 %).



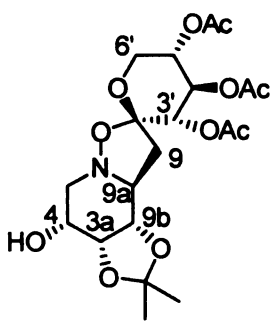
39

$[\alpha]^{20}_D$ +37.41 (c 1 CHCl3); ^1H NMR (DMSO): δ 8.12 (s, 1H, OH), 5.17 (t, J = 8.1 Hz, 1H, H-4), 4.99 (d, J = 3.5 Hz, 1H, H-2), 4.98(d, J = 8.0 Hz, 1H, H-5,), 4.94 (dd, J = 3.5, 8.2 Hz, 1H, H-3), 4.30(dd, J = 4.4, 5.4 Hz, 1H, H12), 4.26 (t, J = 5.9 Hz, 1H, H-11), 3.92 (dt, J = 4.4, 10.0 Hz, 1H, H-13), 3.43 (s, 3H, OMe), 3.31 (m, 1H, H-9), 3.12 (dd, J = 4.2, 11.5 Hz, 1H, H-14), 2.90 (t, J = 10.8 Hz, 1H, H-14), 2.60 (dd, J = 6.2, 12.8 Hz, 1H, H-10), 2.23 (dd, J = 10.7, 12.8 Hz, 1H, H-10'), 2.05, 2.01, 2.00 (s, 3 OAc), 1.46, 1.32 (s, 2 Me); ^{13}C NMR (DMSO): δ 168.56, 168.17, 167.82 (3 OAc),

108.04, 104.49 (C-6), 95.98 (C-2), 78.30, 74.71, 73.88, 69.22, 68.65, 67.82, 62.60, 61.28, 55.49, 53.51, 40.21(C-10), 26.57, 24.78, 19.44, 19.38, 19.38; NOESY1D: NOE H10 – H10' 25 %, H10 – H5' < 1 %; HRFABMS; Calcd. for C21H31NO4 489.1846, found 489.1846; Calculated for C21H31NO12 C, 51.53, H, 6.38, N, 2.86; Found C 51.50, H, 6.44, N, 3.10.

(3aR, 3'S, 4R, 4'R, 5'R, 9aS, 9bS)-4-hydroxy-2,2-dimethyldecahydrospiro[1,3-dioxolo[4,5-*c*]isoxazolo[2,3-*a*]pyridine-8,2'-pyran]-3',4',5'-triyl triacetate (39)

To a stirred solution of nitrone (93.5 mg, 0.5 mmol) in toluene (5.0 ml) was added 2,6-anhydro-1-deoxy-3,4,5-tri-O-acetate-L-xylo-Hex-1-enitol (163 mg, 0.6 mmol). The reaction mixture was stirred under reflux for 10 h. Removal of the solvent followed by column chromatography gave the cyclization product as a single diastereomer **45** (204 mg, 89 %).



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$[\alpha]^{20}_D$ -122.20 (c 1 $CHCl_3$); ^1H NMR ($CDCl_3$): δ 5.13 (t, J = 9.8Hz, 1H, H-4), 5.02 (dd, J = 1.0, 10.2 Hz, 1H, H-5), 4.87-4.95(m, 1H, H-3), 4.22 (t, J = 4.3 Hz, 1H, H-12), 4.05 (dd, J = 4.9, 8.3 Hz, 1H, H-11), 4.02 (t, J = 4.9 Hz, 1H, H-3, 2H), 3.81 (dd, J = 6.1, 11.0 Hz, 1H, H-2), 3.65 (t, J = 10.9 Hz, 1H, H-2'), 3.34 (dd, J = 5.2, 9.0 Hz, 1H, H-14), 2.96 (br s, 1H), 2.69 (t, J = 9.5 Hz, 1H, H-14'), 2.54-2.62 (m, 1H, H-9), 2.40 (dd, J = 6.6, 13.0 Hz, 1H, H-10), 2.08 (dd, J = 10.3, 13.0 Hz, 1H, H-10'), 2.03, 1.97, 1.95 (3 OAc), 1.30, 1.42 (s, 3 H each, 2 CH3); ^{13}C NMR(DMSO): δ 168.75, 168.61, 168.55 (3 OAc), 108.28, 103.57, 78.50, 74.78, 74.75, 70.34, 68.23, 65.99, 64.31, 56.63, 55.22; 42.11, 27.25. 25.38, 19.53, 19.47, 19.44; NOESY1D: NOE

H3 – H3' 30 %, H3 – H5' 15 %. Calculated for C20H29NO11 C, 52.28, H, 6.36, N, 3.05; Found C 52.20, H, 6.42, N, 3.26.

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