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Novel Methods for the Synthesis of Septanose Sugars/Extended Ring Systems from Hexose Sugars

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Novel Methods for the Synthesis of Septanose Sugars/Extended Ring Systems from Hexose Sugars

A Dissertation

*In the
Department of Chemistry and Biochemistry submitted to the faculty of the
Graduate School of Arts and Science in partial fulfillment of the requirements for
the*

degree of

Doctor of Philosophy

In Chemistry

at

Seton Hall University


by

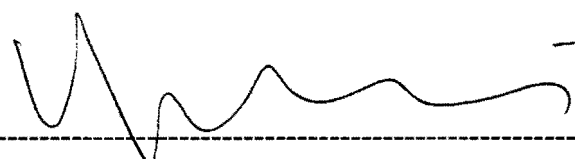
Nada Khan

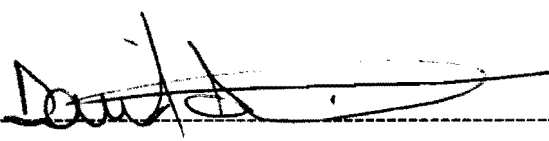
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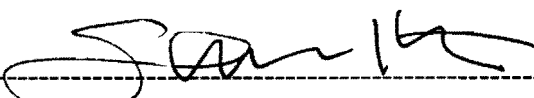
We certify that we have read this thesis and that in our opinion it is adequate in scientific scope and quality as a dissertation for the degree of Doctor of Philosophy.

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Last, but surely not least, I am very grateful to my husband Faraz Khan whose love and support was 24/7 with me over the past years.

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Abbreviations

C.E. = Common Era or Christ Era

DCM = Dichloromethane

DIPEA = Diisopropylethylamine

DMDO = Dimethyldioxirane

DMF = Dimethylformamide

DMSO = Dimethylsulfoxide

NMR = Nuclear magnetic resonance

RT = Room temperature

RXN = Reaction

TBAF = tetra-n-butylammonium fluoride

TBDMSCl = *tert*-butyldimethylsilyl chloride

TBSCl = *tert*-butylsilyl chloride

TEA = Trimethylamine

TESCl = Triethylsilyl chloride

TEBAC = *tert*-Butyl acetate

THF = Tetrahydrofuran

TMSCl = Trimethylsilyl chloride

Dedicated to:

My Dear Husband, without whom this effort would have been worth nothing...and whose love and support was constantly with me throughout my studies.

Abstract

Nada Khan

Seton Hall University

Dr. Cecilia H. Marzabadi, Advisor

New methodologies to synthesize septanoses and extended ring systems are described using different divergent routes. Septanoses are the ring extended analogs of pyranose sugars. They are rare in nature presumably because of ring strain. Septanose sugars have many high energy conformations. Out of 28, only four conformations are low energy conformations. A major part of our research focuses on the synthesis of a stable septanose ring. Our inspiration for this project arose as we know that some septanose derivatives, such as those that bind concanavalin A, are glycosidase inhibitors, and have been used to define new types of protein-carbohydrate interactions. More conformations can allow more ways for the sugar to bind.

The syntheses described are all accomplished by: ring opening of the hexose sugars, stereoselective introduction of a carbon atom to the open chain; and recyclization of the homologated structure to the septanose sugar. The starting material for these sequences is 2,3,4,6-tetra-O-benzyl-D-glucopyranose. In one scheme, the cyclic sugar was subjected to homologation of a carbon by a Wittig reaction, followed by oxidation of the resulting secondary alcohol then hydroboration/oxidation of the newly introduced alkene. Similarly, epoxidation of a sugar aldehyde was followed by concurrent intramolecular ring opening of the epoxide in basic conditions, to yield a

septanose. Likewise, in a third route we first reduced the starting sugar with NaBH_4 to give the acyclic diol. Both alcohol groups of the diol were converted into dicarbonyl groups and the dicarbonyl intermediate was then treated with thiourea to yield an extended ring compound having N and S atoms in the ring system.

Chapter 1

An Introduction to Carbohydrates

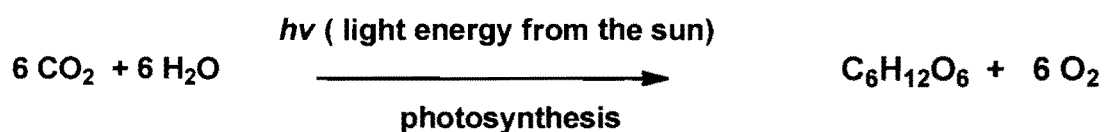
1.1. Introduction

Carbohydrates are the main source of energy in almost all organisms.¹ They are the most abundant of the four major classes of biomolecules on the earth. We cannot underestimate their roles in living organisms such as in energy transport and as being structural components of plants and arthropods. They are intermediates in the biosynthesis of fats and proteins.² A carbohydrate is the term derived from the French word “hydrate de carbone” meaning hydrates of carbon. They also are called saccharides, derived from the Greek term “sakcharon” meaning sugar.³ Carbohydrates are naturally occurring molecules which are made up of carbon, hydrogen and oxygen. That is why they are called hydrates of carbon with the general formula $C_n(H_2O)_n$.

Chemically, carbohydrates can be defined as simple organic compounds that are polyhydroxylated aldehydes or ketones. They must have at least three hydroxyl groups attached to the carbon backbone. We will discuss the structure and classification of the carbohydrates in detail in section 1.3 of this chapter.

When we talk about carbohydrate chemistry, it is against etiquette not to mention glucose, the most common and popular member of this class. Glucose plays an important role in biological processes.⁴ Glucose is used as source for storage of energy such as in form of glycogen in animals and starch in plants. It plays a key role in the

existence and in the evolution of the life on the earth as they are directly linked between the energy of the sun and the chemical energy. For instance, glucose is produced during the process of photosynthesis. Photosynthesis is the process in which light energy from the sun is converted into chemical energy by combining carbon dioxide gas (CO₂) with water (H₂O) to form carbohydrates (C₆H₁₂O₆) and molecular oxygen (O₂) as shown in **Scheme 1.1**.



Scheme 1.1

Glucose is the body's primary source of energy. Our body catabolizes one glucose molecule into two equivalents of pyruvate by the process called glycolysis (Figure 1.1). Glycolysis is a series of ten enzyme-catalyzed reactions which involves ten intermediate compounds.⁵ The intermediates provide entry points to glycolysis. For example, monosaccharides like fructose, glucose, and galactose can be converted to one of these intermediates.

Figure 1.1. Glycolysis process.

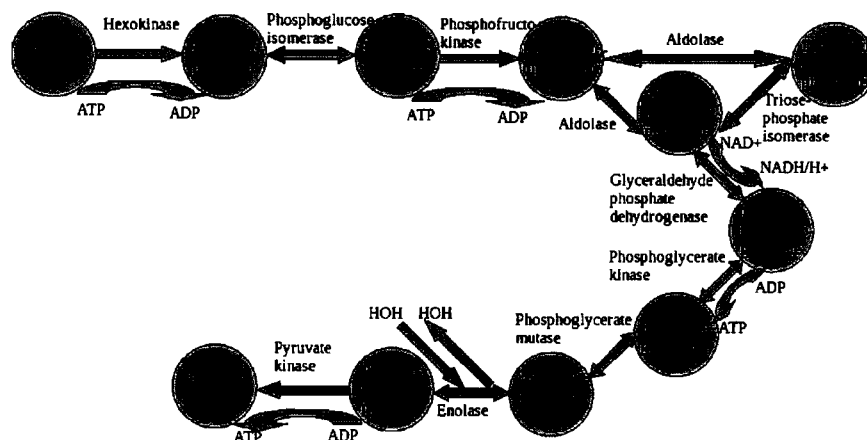


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Although, carbohydrates are considered as the sweetest molecules on the earth, they have a sour side too; which is their complexity. This complexity is due to the structure and chemistry of these molecules based on numerous hydroxyl groups. Specifically, hydroxyl groups are challenging for the organic synthetic chemists to work with due to issues related to solubility and chemical reactivity. As these hydroxyl groups are polar in nature, it is very hard to dissolve these molecules with organic solvents.⁶ The necessity of protecting groups to protect these hydroxyl groups then arises for chemo- and stereoselective reactions. The most common protecting groups are acetyl or benzoyl esters and silyl or benzyl ethers⁷ which opens the doors for diverse reaction conditions for synthesizing new target compounds.

1.2. Historical perspective of carbohydrates

Since ancient times, carbohydrates like cellulose, starch, and sucrose have been very well-known as they had great cultural influences by providing the societies clothing, food, and shelter. For example, in 4000, B.C., the outer bark of the plant *Cyperus Papyrus* was used to make papyrus,⁸ a material used for writing purposes. Starch was used by early humans as a part of their diet in vegetables and grains as well as to stiffen their clothes.

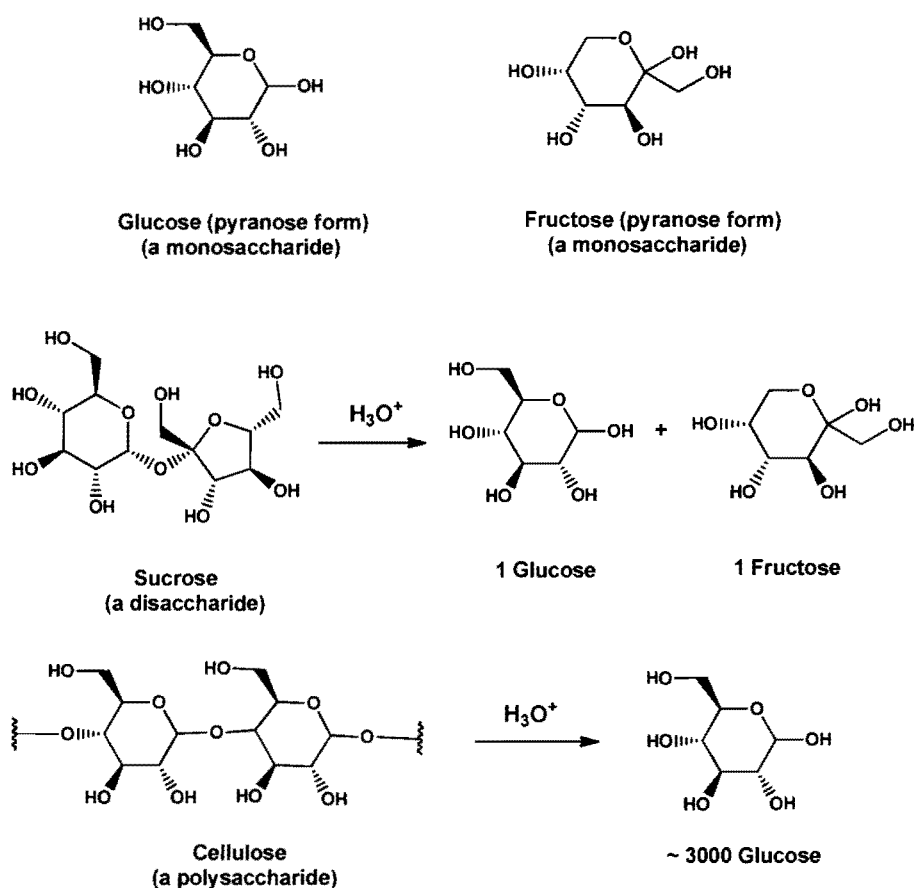
In 975 C.E. an Arabian pharmacologist described the treatment of starch with saliva to produce a poultice for the treatment of wounds.⁹ He named that poultice as “artificial honey”. Another ancient source for carbohydrates was sugar cane out of which sucrose was extracted. In 1792 a carbohydrate was found in honey which was not sucrose. Then in 1802, the same carbohydrate was found in grapes. Later, in 1811, it was discovered that acid hydrolysis of starch produced a carbohydrate which was same as the sugar found in grapes (and honey). Also, in 1820 research showed that urine of diabetics contains the same sugar.¹⁰

Finally, in 1838 this sugar was named as glucose. A well-known German Chemist August Kekule later changed the name to dextrose. In 1881, another sugar was isolated from honey initially named Levulose. But later in 1890, the German Chemist Emil Fisher (Kekule's former student) renamed it fructose and changed the name of dextrose to glucose again.¹¹

1.3. Classification

Carbohydrates are generally classified on the basis of their carbohydrate unit as either simple or complex. Simple carbohydrates, in their monomer form, are called **monosaccharides** (e.g. glucose and fructose that cannot be converted into smaller sugars by hydrolysis). Complex carbohydrates are made of two or more simple sugars linked together. Sucrose is a **disaccharide** made up of one glucose linked to a fructose molecule. Similarly, cellulose is a **polysaccharide** made up of several thousand glucose units linked together by a glycosidic bond. These polysaccharides are broken down into their monosaccharides units by enzyme-catalyzed hydrolysis.¹² Some examples of mono-, di-, and polysaccharides are shown in Figure 1.2.

Figure 1.2. Examples of mono, di and polysaccharides.



Monosaccharides are further subdivided as either **aldoses** or **ketoses**. The suffix **-ose** indicates a carbohydrate while prefixes *aldo-* and *keto-* stands for the kind of carbonyl group present, whether aldehyde or ketone.

All ketoses and aldoses are further subdivided on the basis of number of carbon atoms in the chain by putting a numerical term *tri-*, *tetra-*, *penta-*, *hexa-*, and so on, between *aldo-* and **-ose** in the name as shown in Figure 1.3 and 1.4.

Figure 1.3. Classification of aldoses.¹³

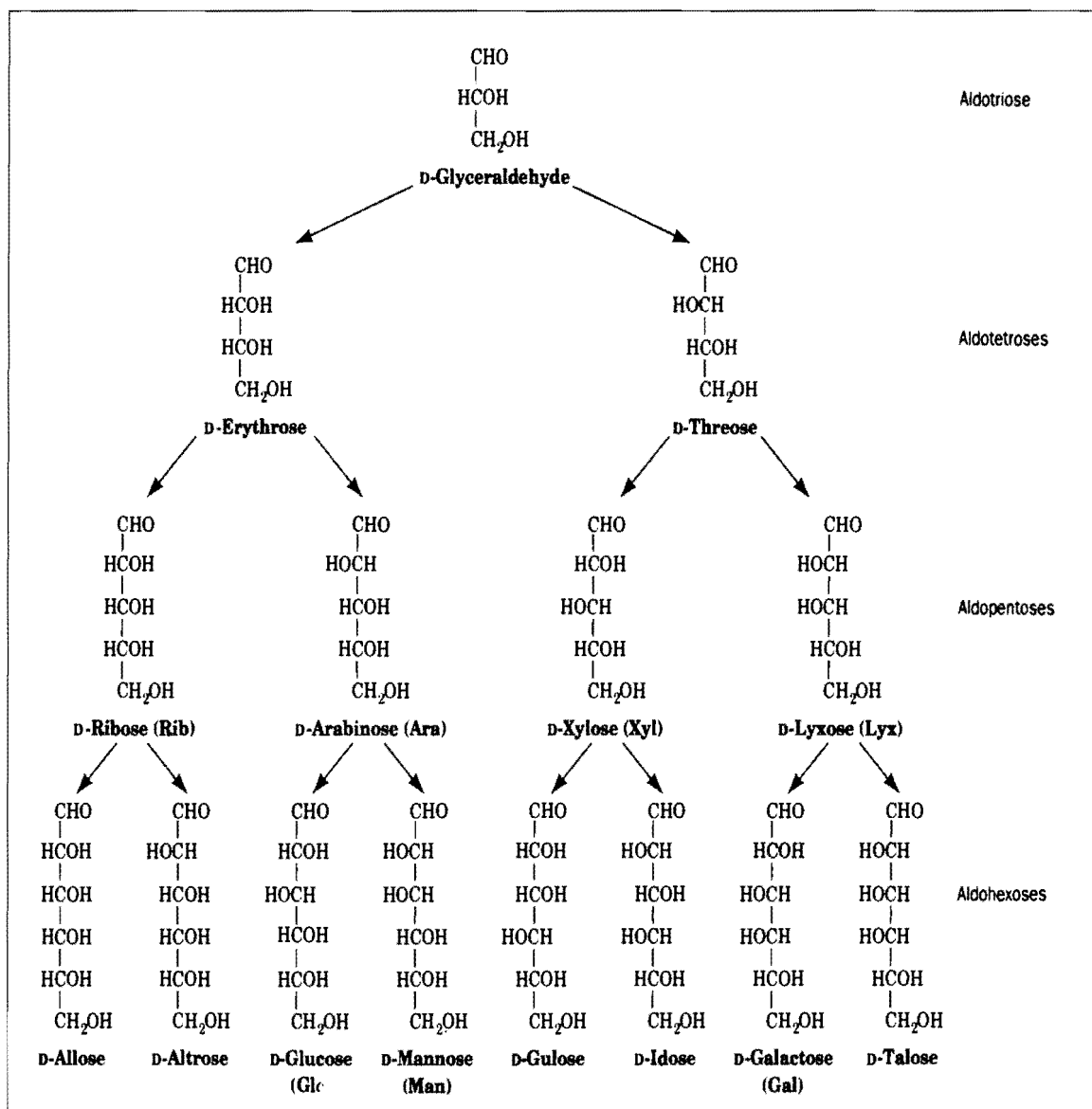


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Figure 1.4. Classification of ketoses.¹³

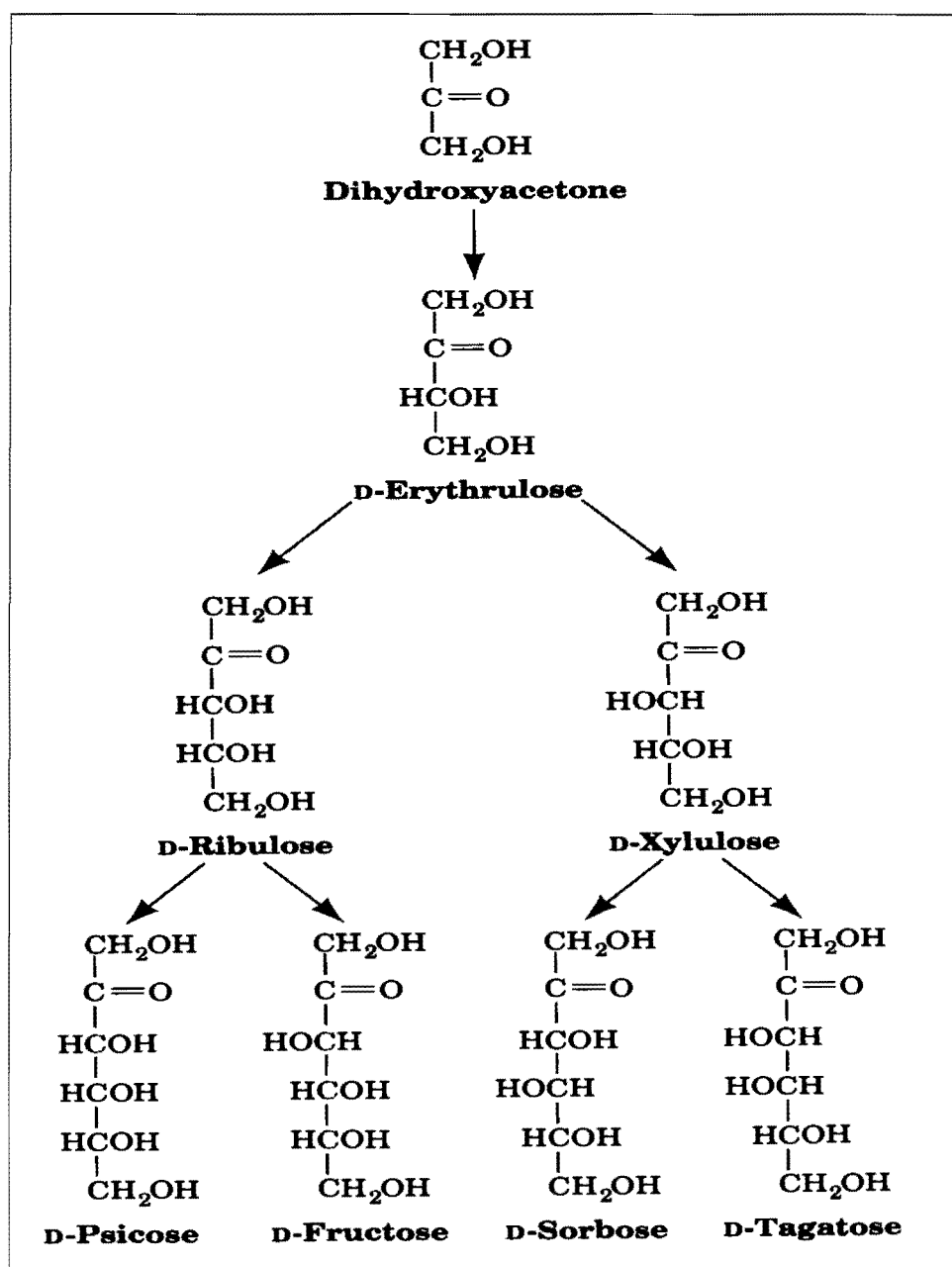
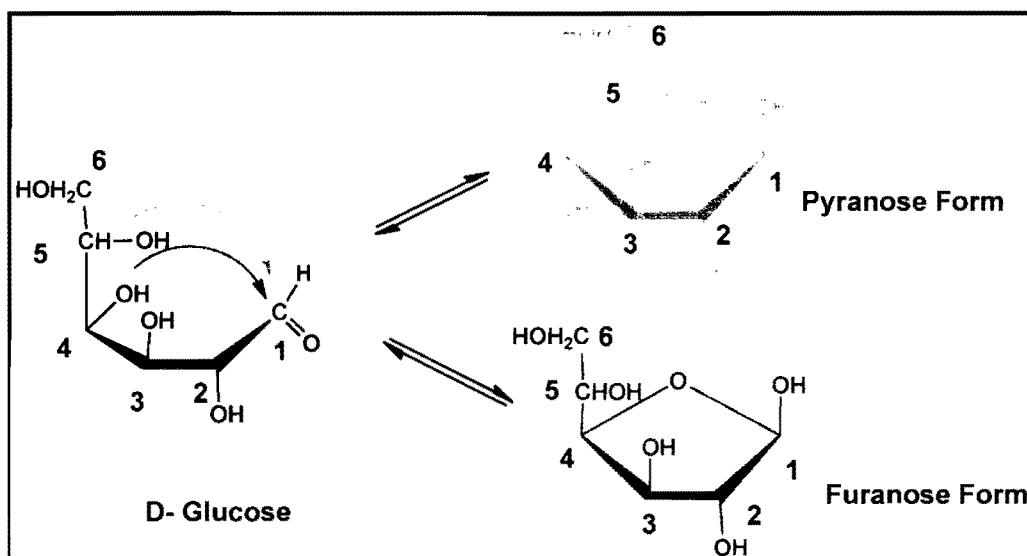


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1.5. Furanose and pyranose forms

In solution, the open-chain form of glucose exists in equilibrium with different cyclic isomers.¹⁴ The cyclic forms occur because of a nucleophilic addition reaction between the hydroxyl group of C-4 or C-5 and the carbonyl functionality at C-1. Either hemi-acetals or hemi-ketals form depending on the type of sugar (i.e. aldose or ketose). If the C-4 hydroxy closes the ring then the cyclic form of the glucose is known as the furanose form, after the 5-membered ring cyclic ether furan while if C-5 hydroxy cyclizes, then the ring formed is called pyranose form, after the six-membered ring cyclic ether pyran, as shown in the Figure 1.5.

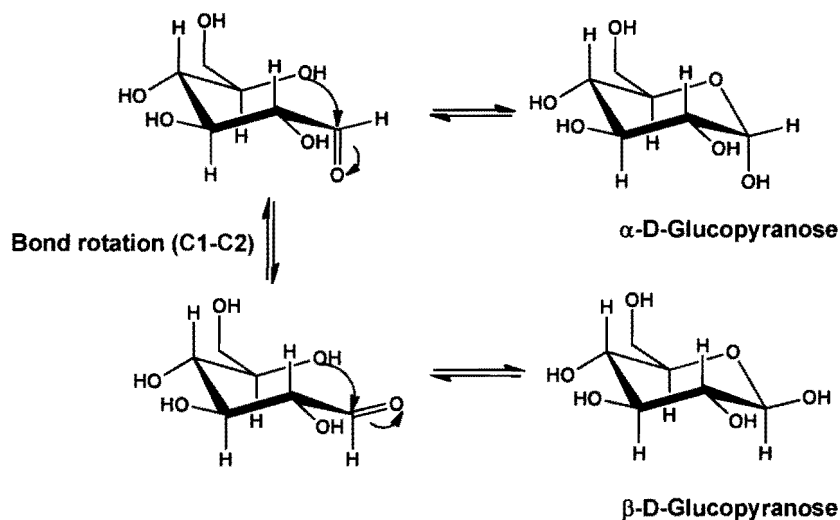
Figure 1.5. Pyranose and furanose forms of glucose.



In aqueous solution, more than 99% of glucose molecules exist in the pyranose form while the open chain form of glucose is limited to about 0.25%.¹⁵ The furanose form also exists in almost negligible quantity. When we refer to term glucose, this usually refers to the cyclic forms.

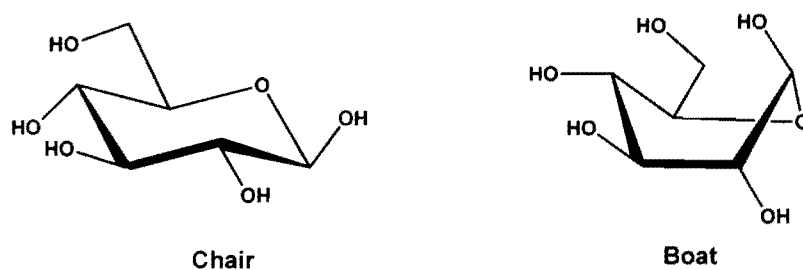
Out of the two, the pyranose form is more stable than the furanose form because of attaining six membered ring structure.¹⁶ The pyranose and furanose forms are further subdivided on the basis of how they cyclize. During the cyclization, the anomeric carbon (the hemiacetal carbon atom originating from the carbonyl oxygen) becomes a stereogenic center with 2 possible configurations (α or β) depending on the way they cyclize. The resulting isomers are called anomers and this property is called mutarotation. Mutarotation is the change in optical rotation that occurs by epimerization at the anomeric center. That means, it is the change in the equilibrium between two epimers, when the corresponding stereocenters interconvert. Cyclic sugars show mutarotation as α and β anomeric forms interconvert in the solution. In aqueous solution, D-glucose exists as a mixture of 36% α form and 64% β form (>99% of cyclic form exists as a pyranose). The β form is favored because all of the hydroxyl groups are in equatorial position, while in minor α anomer, one hydroxyl group is forced into the axial position which causes high energy in the molecule and makes it less stable. The equilibrium occurs via the ring opening of the cyclic sugar at the anomeric center with the acyclic form as the intermediate. The α and β anomers form because of the C1-C2 bond rotation of the acyclic sugar and the subsequent ring closure to the pyranose form (Figure 1.6).

Figure 1.6. Anomers of D-glucose.



The most stable conformations of the six-membered ring form of glucose are the (i) chair conformations and the (ii) boat conformations. In these conformations, the ring is bent so that the bond lengths and angles are close to those ideal values (109.5° for sp^3 carbon) which have less strain energy than a flat ring with 120° angles. Out of the two, the chair conformation is more stable than the boat conformation. The boat conformation has the steric as well as torsional strain¹⁷ and is approximately 17 kJ/mol (4 kcal/mol) less stable than the chair conformation.

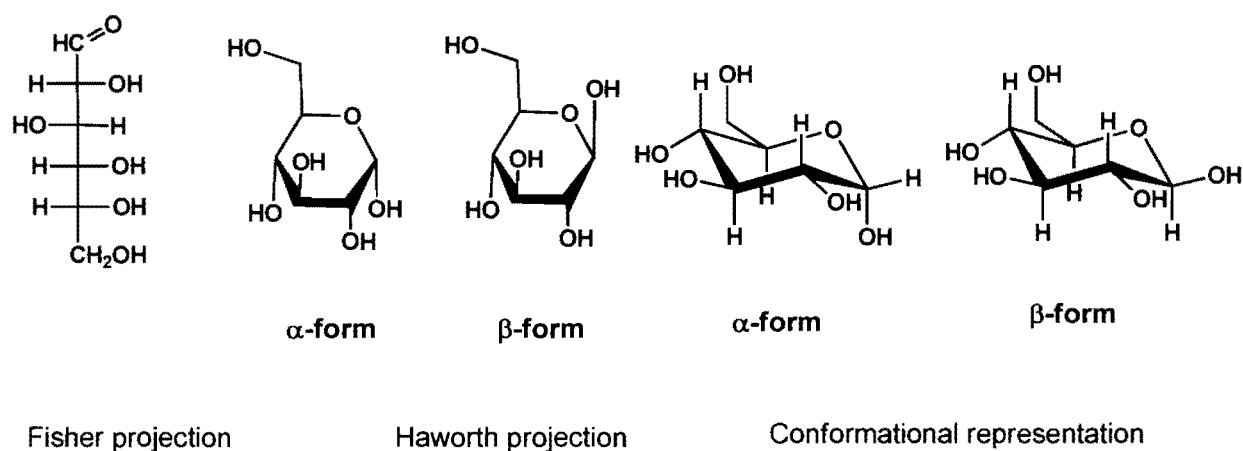
Figure 1.7. Examples of chair and boat conformations of glucose.



The structures of monosaccharides are usually represented in three forms (Figure 1.8):

- 1) Fisher projection: straight chain representation,
- 2) Haworth projection: simple ring in perspective, and
- 3) Conformational representation: chair and boat configurations.

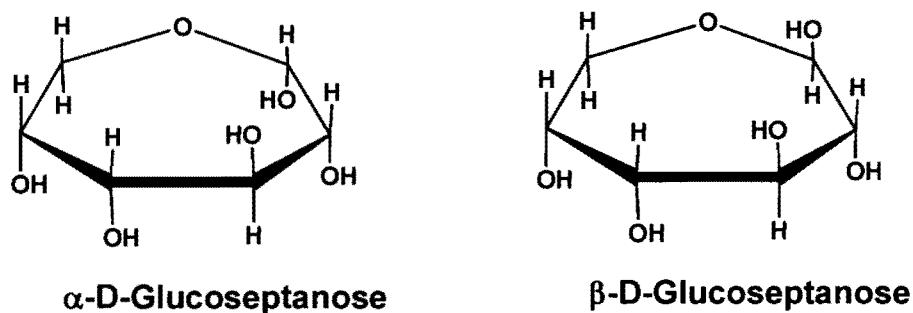
Figure 1.8. Structural representations of D-glucose.



1.5. Septanose form

As discussed in section 1.4, aqueous solutions of aldoses contain complex mixtures. Detailed studies show that the equilibrium mixture of hexose sugars consists at least six forms: two pyranoses, two furanoses, an aldehyde isomer, and a hydrate of the aldehyde form.¹⁸ In addition to these, two other cyclic isomers can exist that are named as septanoses, based on a 7-membered ring carbohydrate.¹⁹ Like pyranoses and furanoses, septanoses differ by the configuration at the anomeric center as shown in Figure 1.9.

Figure-1.9. Structure of glucoseptanose.



Studies on septanoses are limited as they are very unstable.¹⁹ Such structures were isolated only for D-idose. According to the ^{13}C NMR data a solution of D-idose at 37°C contains 1.6% of a mixture of septanose anomers.²⁰

1.6. Biological activity of carbohydrates

Carbohydrate derivatives can be potent therapeutic agents.²¹ For a long time, the biological importance of carbohydrates was underestimated by the pharmaceutical and academic societies. They used to be thought of as dull molecules whose only functions were providing energy and in cell wall construction.²² Recent studies validate their significance in medicinal chemistry programs, such that biochemists are presently exploring the role of carbohydrates in proteins binding and activity in a hot area of research coined glycobiology.²³

In the early ages, people found the cures for their illnesses by chewing the herbs, roots, barks etc. of plants. Some of these remedies were successful but the real knowledge of the actual constituents of those herbs was unknown.²⁴ With advances in research capabilities, scientists became able to identify the constituent compounds found in the plants. For example, by the middle of the sixteenth century, people used the extract of cinchona bark for chills and fevers. Later in 1820, the active constituent of the cinchona bark was isolated and was found to be quinine, an antimalarial drug.²⁵ Another remedy was an extract of fox glove plant was used for the treatment of congestive heart failure (dropsy) in 1785. The active constituents of this plant were found to be secondary glycosides digitoxin (Figure 1.10) and digoxin (Figure 1.11) from *Digitalis purpurea* and *Digitalis lanata* (fox glove plants).²⁶ The latter are in clinical use for congestive heart failure and are manufactured by the extract of fox glove plants²⁵.

Figure 1.10. Structure of Digitoxin.

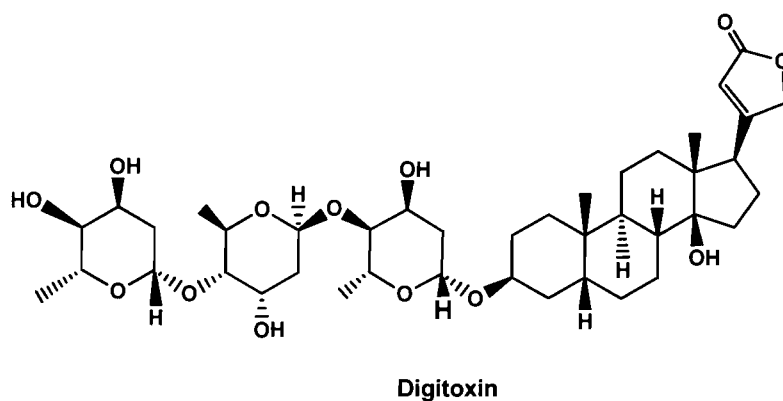
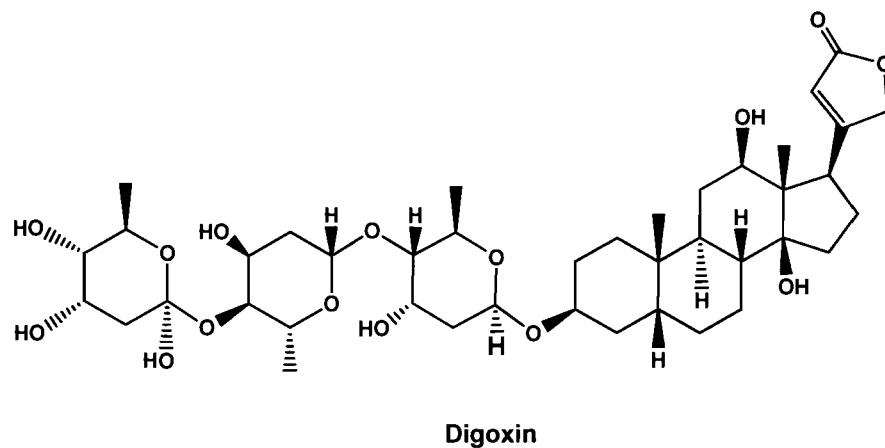


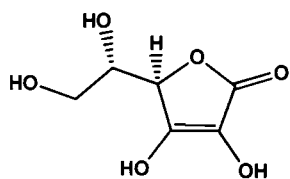
Figure 1.11. Structure of Digoxin.



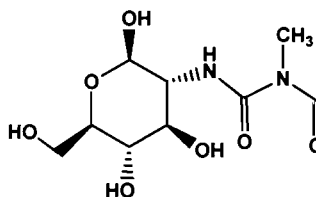
Today, many carbohydrate derivatives play a significant role in drug design and development²⁵. For example, monosaccharides such as ascorbic acid own a broad spectrum of bio-activity and applications in medicine.²⁷ Another name for this molecule is vitamin C which is present in citrus fruits. But a deficiency of vitamin C causes the disease scurvy which can be treated by ascorbic acid. Among monosaccharides, two

amino sugars are antibiotics that are well-known. Streptozotocin²⁸ and Prumycin,²⁹ they both have anti-tumor activity. Streptozotocin is a naturally occurring compound which is toxic to the insulin- producing beta cell of the pancreas in mammals and potentially implicated in diabetes. This drug is potent to treat cancers of the Langerhans.²¹ Another simple sugar with antiepileptic activity is known as Topiramate.³⁰ The anticonvulsant properties of Topiramate were discovered through biological screening. Structures of these drugs are shown in Figure 1.12.

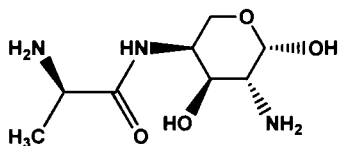
Figure 1.12. Monosaccharides as therapeutics.



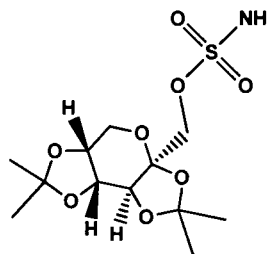
Ascorbic acid



Streptozotocin



Prumycin

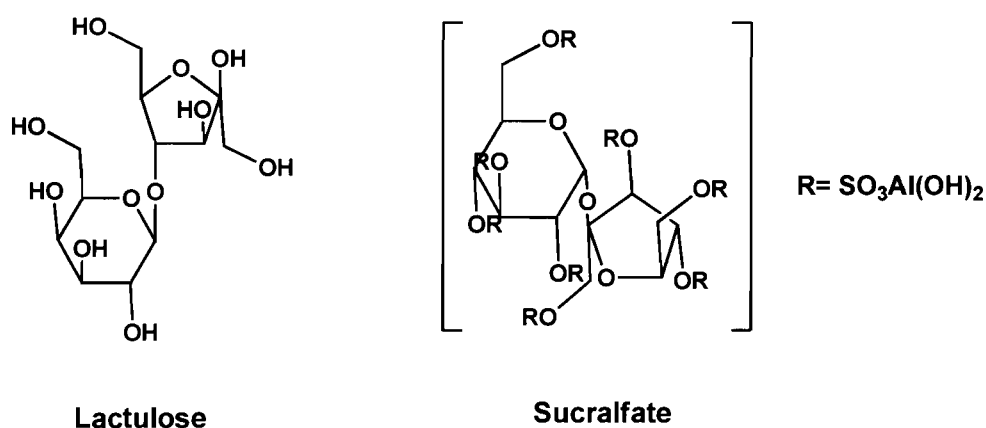


Topiramate

Among disaccharides the very well-known and the first therapeutic which is still in clinical use is Lactulose.³¹ Lactulose is used for the treatment of hepatic coma. It is also used to treat constipation and for regulating ammonia concentrations in the blood. It is

synthesized commercially by the isomerization of lactose.³² It consists of two monosaccharide units, fructose and galactose. Another classical example of this class of sugars is Sucralfate – an aluminum hydroxide complex of sucrose sulfate.²¹ This drug is currently being used in the therapy of duodenal ulcers (Figure 1.13).

Figure 1.13. Disaccharides as therapeutics.



1.7. Summary

Carbohydrates are the most abundant and common biomolecules in nature. They are the major source of energy in living organisms. Carbohydrate derivatives are actively involved in fertilization, immune system development and in the treatment of diseases. Glucose is a biologically- significant monosaccharide involved in metabolic and energetic pathways. Glycoconjugates, in which the carbohydrate moiety is covalently linked with other chemical species, also have very important roles in biology

(e.g. glycoproteins, glycopeptides, peptidoglycans, and glycolipids). All organisms depend on carbohydrates and glycoconjugates to maintain their life.

In short, carbohydrates play vast and diverse roles in biological systems. Because this was not previously recognized, medicinal and pharmaceutical applications have not been fully pursued. Now, synthetic medicinal chemists have made major contributions towards novel target compounds as a variety of carbohydrate derivatives are serving as potent therapeutics. Both simple and complex carbohydrates are playing roles in treating human diseases like diabetes, cancer and infections.

Chapter 2

Septanoses

2.1. Introduction

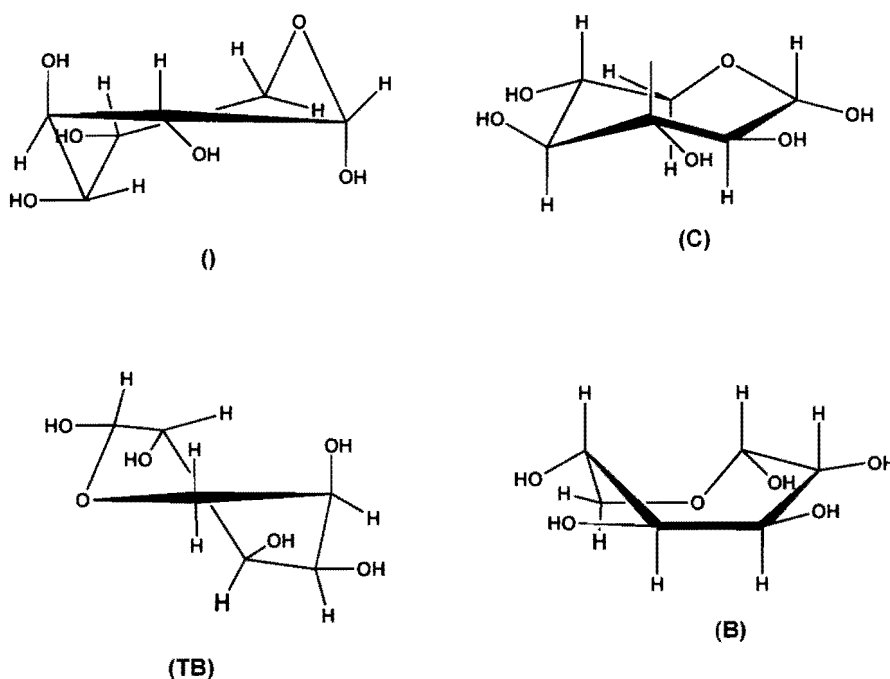
Seven-membered ring sugars (septanoses) are uncommon in nature as the thermodynamic preference is for five- and six-membered furanose and pyranose rings.¹⁶ Since general methods of carbohydrate synthesis favor furanose and pyranose isomers over their seven-membered ring structures, this area of research has remained largely unexplored.

Our inspiration for the synthesis of septanose carbohydrates is based on the development of glycosidase inhibitors. Septanoses may represent good candidates for glycosidase inhibition because of its many conformations.³³ In the key biological process where a carbohydrate moiety binds a lectin (a carbohydrate-binding protein)³⁴, the conformational preferences of septanose carbohydrate may enhance the protein-carbohydrate interaction.

2.2. Conformations

Because of ring strain, septanose sugars do not exist in great abundance naturally. There are 28 conformations available to the septanose.³⁵ In general; seven membered ring systems show four low energy conformations. These are: (i) twist-chair (TC), (ii) chair (C), (iii) twist-boat (TB), and (iv) boat (B). Among the four, the twist chair is the most stable by 4kcal/mol.³⁵

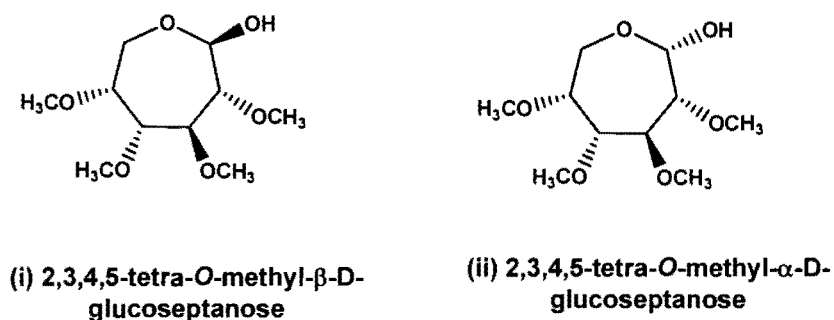
Figure 2.1. Conformations of glucoseptanose..



It is known that none of the unprotected aldo-hexoses exist as septanoses in aqueous solution to any great extent.³⁶ However, if the hydroxyl groups at positions C4

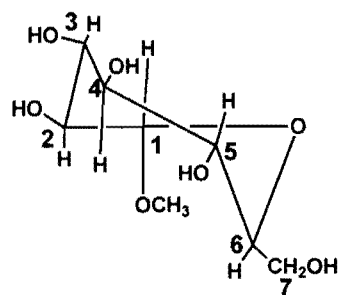
and C5 are substituted to prevent the formation of pyranoses and furanoses, like in 2,3,4,5-tetra-O-methyl-D-glucose, then septanose sugars may be formed as shown in Figure 2.2.

Figure 2.2. Structure of septanose.

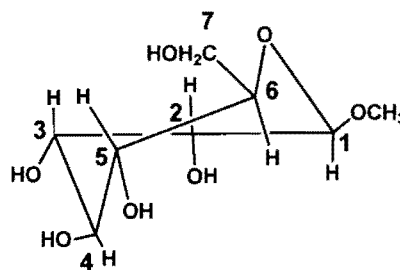


Septanoses exhibit 14 unique low energy TC conformations. The most stable conformers are shown in Figure 2.3.³⁷ For these conformers three atoms define a molecular plane and the remaining atoms lie above or below the plane. In the case of $^{3,4}\text{TC}_{5,6}$, for example, molecular oxygen, C1 and C2 are coplanar with each other while C3 and C4 are above the plane and C5 and C6 are below the plane. An axis of pseudosymmetry is centered on C1 of the $^{3,4}\text{TC}_{5,6}$ conformation. The same applies for $^{6,0}\text{TC}_{4,5}$ conformer. The atoms or substituents at this position are called isoclinal because they have the same steric environment on the top of the ring as well as the bottom of the ring³⁷ as shown in Figure 2.3.

Figure 2.3. Twist chair conformation of glucoseptanose.



3,4TC_{5,6}

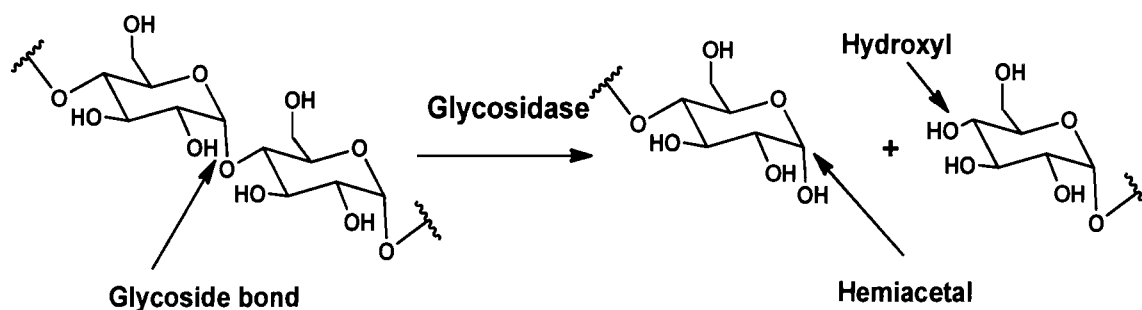


6,0TC_{4,5}

2.3. Septanoses as Glycosidase inhibitors

Complex carbohydrates are formed by the linkage of monosaccharides. Two residues of monosaccharides join together by a glycosidic bond. A glycosidic bond is defined as a bond between anomeric hydroxyl group of the sugar residue and a hydroxyl of another sugar or some other compound, with a removal of a water molecule. A glycosidic bond is therefore a bond formed by the condensation of two monosaccharides and removal of one water molecule. The enzymes required to break glycosidic bonds are called hydrolases (glycosidase) i.e. enzymes requiring water and catalyze glycosidic bond hydrolysis (Figure 2.4.).

Figure 2.4. Hydrolysis of a glycosidic bond.



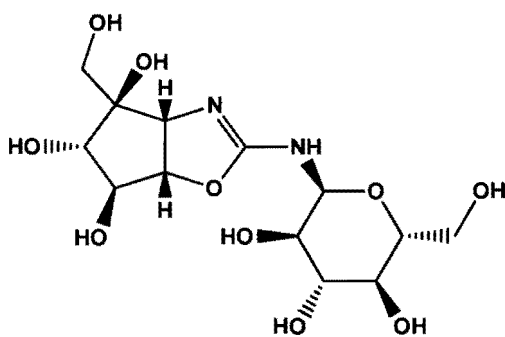
Glycosidases are involved in a broad range of biological and pathological processes. They have a variety of uses, for example, in the degradation of plant material like cellulose to the monosaccharide glucose. In the food industry, there is a glycosidase called invertase which is used to manufacture invert sugar and amylase and to break down starch into table sugar.³⁸ In the paper and pulp industry, xylanases are used for removing hemicellulose from paper pulp.³⁹ Glycosidases are also actively involved in the process of digestion, in the biosynthesis of oligosaccharides, and in quality control processes of the endoplasmic reticulum (ER), such as ER-associated degradation of glycoproteins and catabolism of glycoconjugates.⁴⁰

Although the role of these enzymes is very important for maintaining life but there are some disorders in which enzyme inhibition is desired for therapeutic applications. Glycosidase inhibitors are currently of great interest as potential therapeutic agents for anti-viral,⁴¹ anti-proliferative⁴² or anti-diabetic treatments.⁴³ Almost 40 years ago, the classic glycosidase inhibitor nojirimycin was discovered from the culture broth of *Streptomyces* species.⁴⁴ After that hundreds of glycosidase

inhibitors were isolated from different plants and many were synthesized on the same template. Glycosidase inhibitors are a widespread class of molecules that are used as agrochemicals as well as potent therapeutics.⁴⁵

Agrochemicals refer to a broad range of pesticides including insecticides, herbicides and fungicides.⁴⁵ One of the very well-known classes of these enzymes which serves as glycosidase inhibitors are the Trehalase inhibitors.⁴⁶ They inhibit the enzyme Trehalase which hydrolyses a sugar known as trehalose. Trehalose is a blood sugar in insects and a major storage sugar in fungi and yeast. Therefore these inhibitors serve as potent insecticides or fungicides. One of the very common trehalase inhibitors is known as Trehazolin⁴⁷ as shown in Figure 2.5.

Figure 2.5 Structure of Trehazolin.

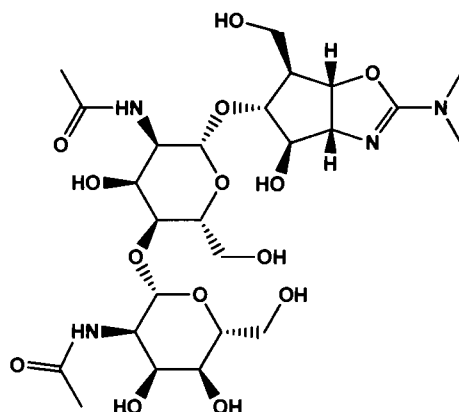


Trehazolin

Other inhibitors are chitinase inhibitors⁴⁸ with strong inhibitory activity towards chitinases which is the key enzyme for the ecdysis for the insects. Studies show that

these inhibitors have disruptive effects on biosynthesis of chitin. Allosamidin⁴⁹ is a classic example of this type of inhibitor (Figure 2.6).

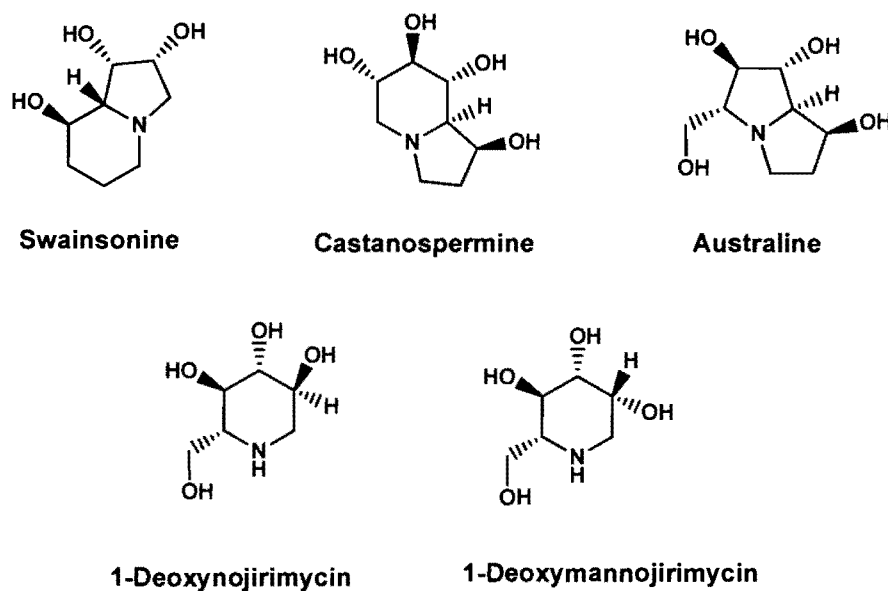
Figure 2.6. Structure of Allosamidin.



Allosamidin

As mentioned earlier, nojirimycin is a potent glycosidase inhibitor⁴⁴. It was discovered as the first glucose analog with the oxygen ring atom replaced with a nitrogen atom. This feature classifies this kind of therapeutics as aza-sugars. Aza-sugars have a broad spectrum of activity, including potent glycosidase inhibition.⁵⁰ This class of compounds contains poly-(hydroxypiperdines) and poly-(hydroxypyrrolidines) in their structures. This class of analogues serves as specific glycosidase inhibitors, as potential antidiabetic⁵¹ and anti-tumor agents.⁵² Figure 2.7 shows a few actively potent aza-sugars. Swainsosine and Castanospermine belong to the class of indolizidine alkaloids and are used in chemotherapy²¹. 1-Deoxynojirimycin and 1-Deoxymannojirimycin are derivatives of Nojirimycin.

Figure 2.7. Structures of Aza-sugar glycosidase inhibitors.



Previously, it was mentioned that the lectin (a carbohydrate binding protein) of jack bean known as concanavalin A binds septanose carbohydrates. The monosaccharide ligands that binds to concanavalin A are β -septanosides that also act as a glycosidase inhibitors.⁵³ They act as substrates for *Agrobacterium* sp. β -glucosidase.⁵⁴ The ability of concanavalin A to bind a seven membered ring monosaccharide has been investigated by isothermal titration and saturation transfer difference NMR spectroscopy.⁵⁴

2.4. Synthetic approaches to septanoses in the literature

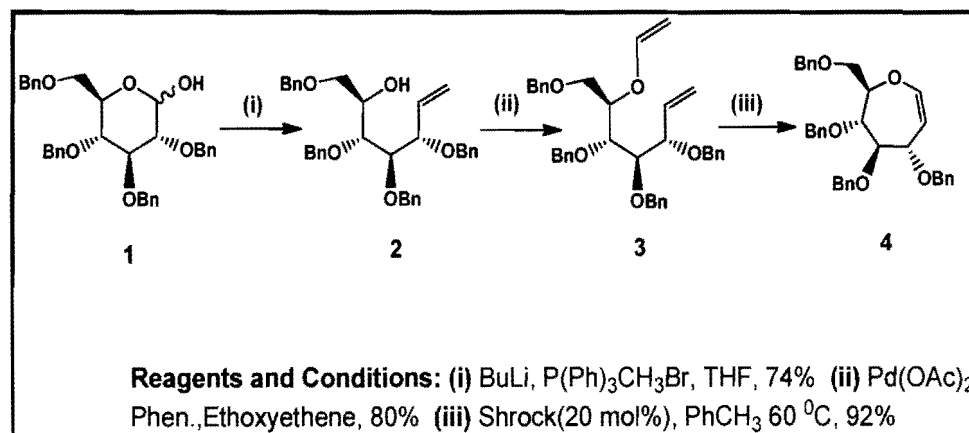
In the literature, much work has been done to synthesize five or six membered heterocycles. Only within the past ten years have scientists begun working on the synthesis of septanoses. They have been prepared from reducing sugars by the Baeyer-Villiger oxidation of inositols, by condensation of dialdehydes with active methylene compounds, by pyridinium chloride mediated ring opening of a protected gluco pyranosides and by the Bayer-Fischer reaction of sugar dialdehydes.⁵⁵ In addition, Hoberg also has mentioned variety of methods to synthesize seven-membered oxacycles in his review article.⁵⁶

More recently, Peczu and his research group began synthesizing septanose derivatives. They reported the synthesis of oxepines using a ring-closing metathesis (RCM) approach starting from tetra-O-benzyl-D-glucose.⁵⁷

2.4.1. RCM approach starting from tetra-O-benzyl-D-glucose:

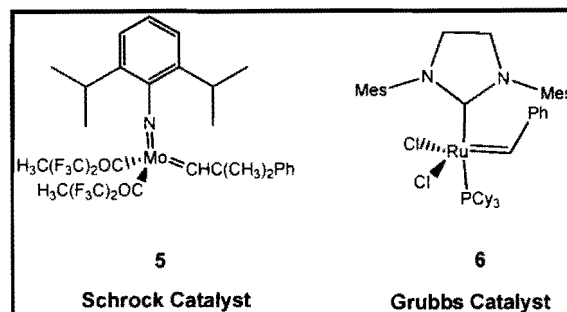
RCM (ring closing metathesis) is a method for the cyclization of dienes using organometallic catalysts like the Shrock **5** or Grubbs **6** reagents (Figure 2.8). In this three-step methodology, Peczu and his group reported the synthesis of tetra-O-benzyl oxepine **4** in 92% yield. The sequence of reactions started with commercially-available 2,3,4,6-tetra-O-benzyl-D-glucopyranose **1** which was subjected to Wittig olefination to prepare **2**. Compound **2** was converted to the vinyl ether **3**, a precursor for RCM by

treating with ethoxyethane, using Pd (II) in the presence of phenanthroline. Compound **3** was heated in toluene in the presence of the RCM catalyst (Shrock or Grubbs). They reported that no product formation was observed when using the Grubbs catalyst while the Shrock catalyst converted the diene **3** into tetra-O-benzyl oxepine **4**. (**Scheme 2.1**)



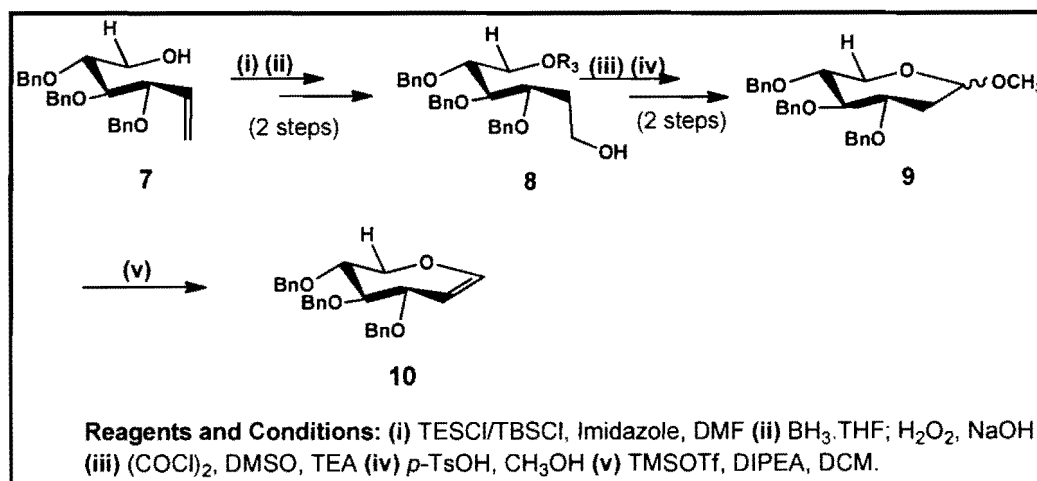
Scheme 2.1

Figure 2.8. Structures of Shrock and Grubbs catalyst.



2.4.2. Cyclization-elimination route to septanose glycols:

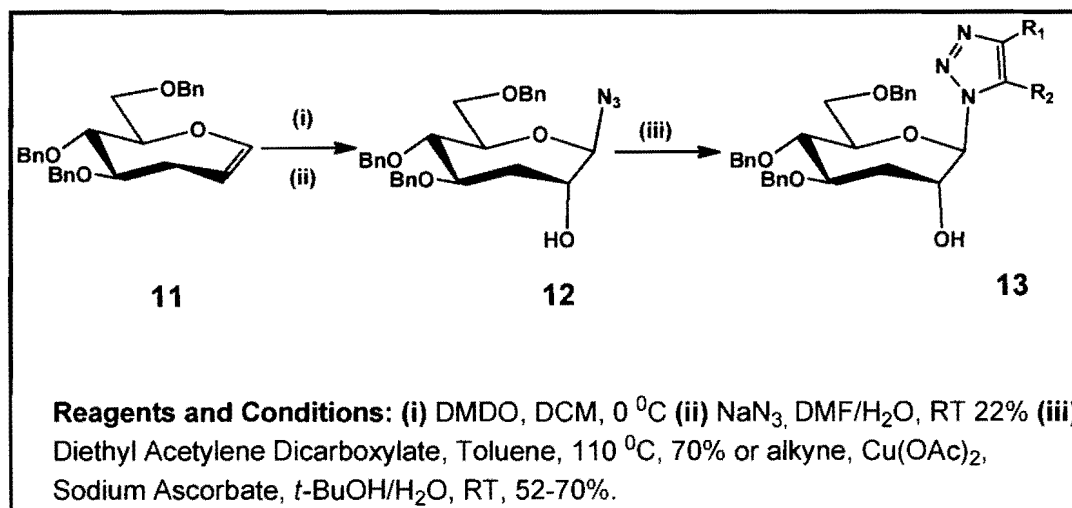
In 2004, Peczuh and his group also reported a five-step synthesis of oxepines from hept-1-enitols (**Scheme 2.2**) using an oxidation-reduction sequence.⁵⁸ The known hept-1-enitol **7** was transformed into compound **8** in two steps by first protecting the hydroxyl group as its triethylsilyl ether and then by hydroboration-oxidation of the olefin. The resulting hydroxyl of **8**, was subjected to Swern oxidation and submitted to acetalization conditions by using *p*-toluenesulfonic acid (*p*-TsOH) in methanol. They reported the deprotection of the silyl ether and cyclization/acetal formation to occur in one pot to form **9**. Subsequently, elimination of methanol provided oxepine **10**.



Scheme 2.2

2.4.3. Synthesis of septanosyl-1,2,3-triazoles:

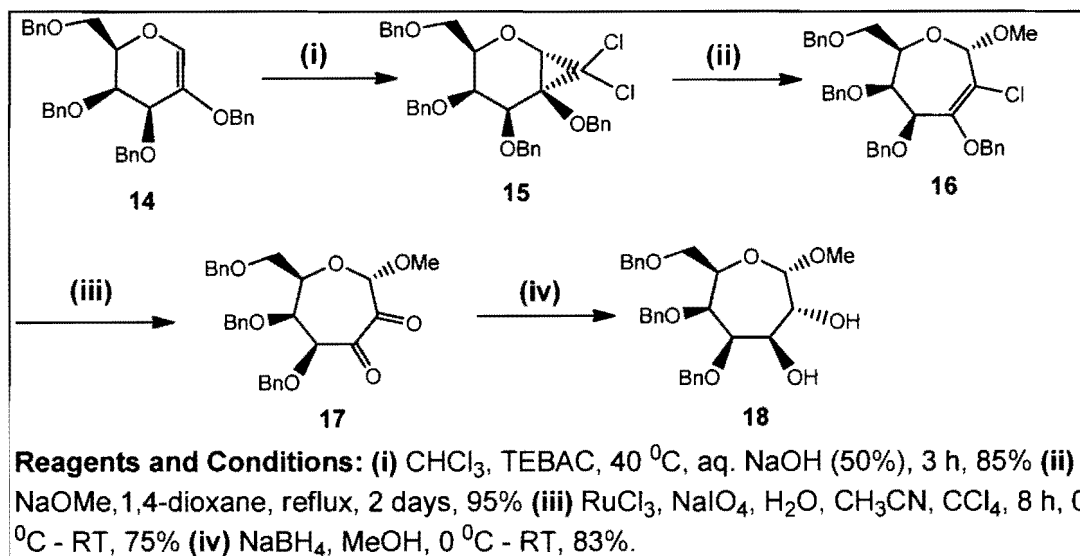
In 2007, Peczuh reported the synthesis of a septanose N-glycoside. In this synthesis, oxepine **11** was converted to septanosyl-1, 2,3 -triazoles **13** (**Scheme-2.3**).⁵⁹ Epoxidation of compound **11** using DMDO provided a 1,2-anhydroseptanose which was not isolated and was carried to the next step by treating with tetrabutylammonium azide in DCM to form **12**. Finally, triazole **13** was made by Huisgen dipolar cycloaddition of **12** with diethyl acetylene dicarboxylate in refluxing toluene (**Scheme 2.3**). The other derivatives of triazoles were also synthesized and each of the triazoles was evaluated for activity against glycosidases such as α - glucosidase, β -glucosidase, α -galactosidase, β -galactosidase α -mannosidase, and β -mannosidase.



Scheme 2.3

2.4.4. Cyclopropanation/ring expansion route to septanose carbohydrates:

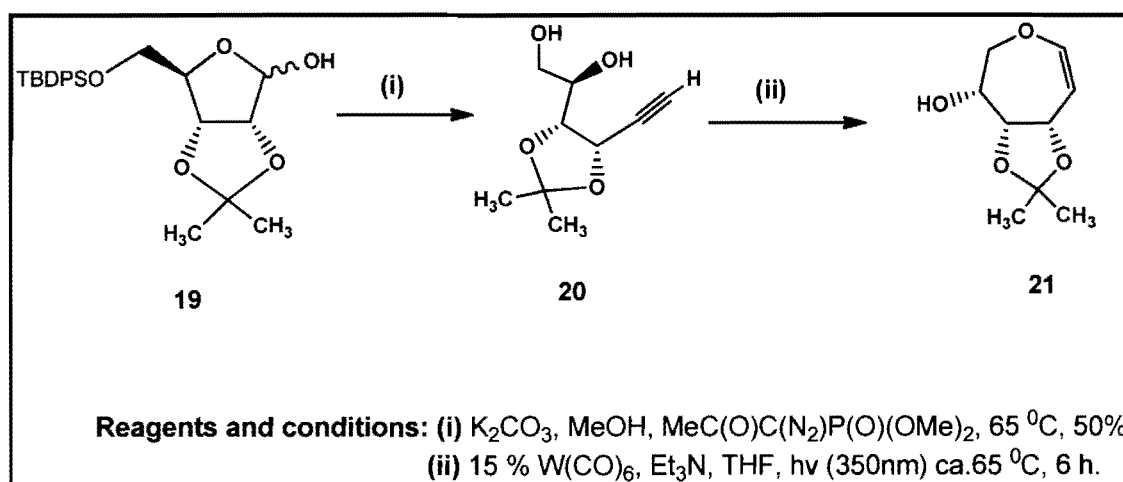
In 2007, another new route to synthesize septanoside derivatives from hydroxygalactal was reported by Jayaraman.⁶⁰ In this synthesis, they started the sequence with the vinyl ether synthon **14** and the cyclopropanation of **14** with TEBAC in the presence of chloroform yielded cyclopropanated dichloro adduct **15**. The ring was expanded by treating the cyclopropanated adduct with sodium methoxide and dioxane to generate oxepine **16**. The RuO₄-mediated oxidation was conducted to obtain a diketo derivative **17**. The NaBH₄ reduction to this diketo derivative led to the formation of a diol which was basically the septanose **18** (Scheme 2.4).



Scheme 2.4

2.4.6. McDonald's *endo*-Selective Alkynol Cycloisomerization:

In 2004, McDonald and his research group reported the three step synthesis of a septanose⁶¹ starting from known ribofuranose acetonide **19**. An alkynyl alcohol **20** was formed by using a diazophosphonate reagent for homologation. The loss of a *tert*-butyldiphenylsilyl group was reported. Tungsten-catalysed cycloisomerization of **20** gave oxepine **21** in 68% yield (**Scheme 2.5**). They also reported the importance of isopropylidene protection, as this group tethers the terminal alkyne and diol functional groups in close proximity for the heterocyclization reaction.

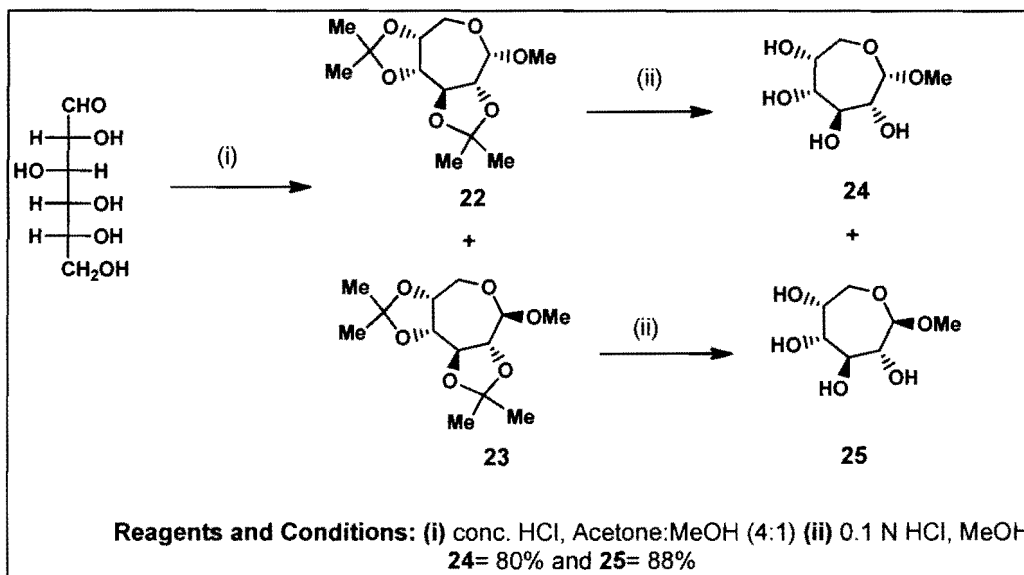


Scheme 2.5

2.4.7. Steven's Septanose Synthesis:

In this synthesis, Steven and his research group synthesized a septanose starting from D-glucose.⁶² Treatment of D-glucose with a mixture of hydrochloric acid in

acetone and methanol yielded D-glucoseptanoside **22** and **23** in 45% yield after eight days reaction. Compounds **22** and **23** were treated with milder acidic conditions which resulted in acetonide cleavage to yield unprotected alpha and beta methyl glycosides **24** and **25** in 80% and 88% respectively (**Scheme 2.6**).



Scheme 2.6

2.5. Summary

Septanoses are seven membered ring sugars which because of their ring strain rarely occur in nature. Conformational studies are ongoing in order to attain greater knowledge concerning their stability. There is evidence in the literature for the recognition of a naturally occurring septanose by concanavalin A. This evidence has led us to develop synthetic steps to prepare septanose derivatives. The newly prepared

septanoses are expected to be good ligands for glycosidases due to their enhanced conformational flexibility relative to 6-membered ring sugars.

Several research groups have synthesized septanoses in different ways. Conformational studies on septanoses are limited but they show potential in assessing biological activities. There is much to explore for organic and bioorganic chemists regarding the nature of septanose-protein interactions and the developments of the analogues that can serve as tools for glycobiology.

Chapter 3

Extended Ring Systems

3.1. Introduction

The term “extended ring system” covers a broad range of compounds such as macrocyclic compounds (e.g. crown ethers, Figure 3.1) or compounds having macrolide rings (e.g. Erythromycin A, Figure 3.2) or Spinosad (Figure 3.3). Here, we have to narrow down the window for this term. To remain concise, in this chapter, we will discuss members of the classes of compounds that have seven- or eight-membered ring systems, specifically heterocycles.

Figure 3.1. Common structures of crown ethers.

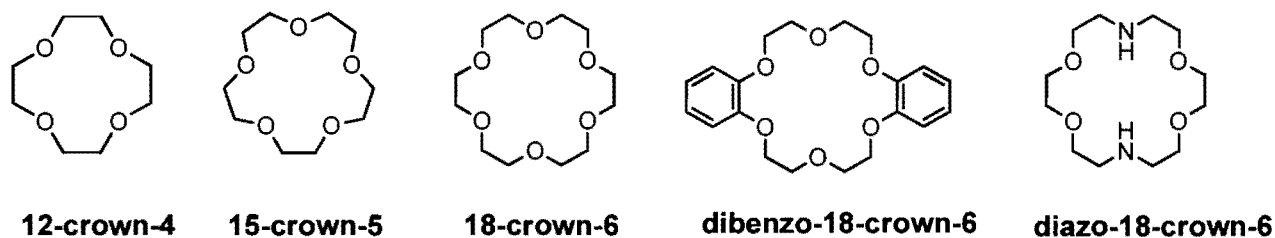
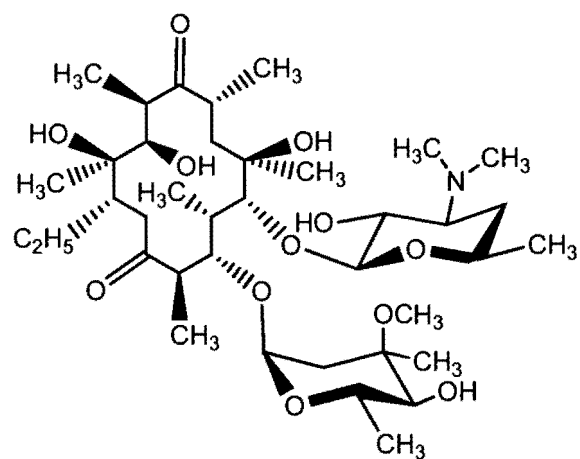
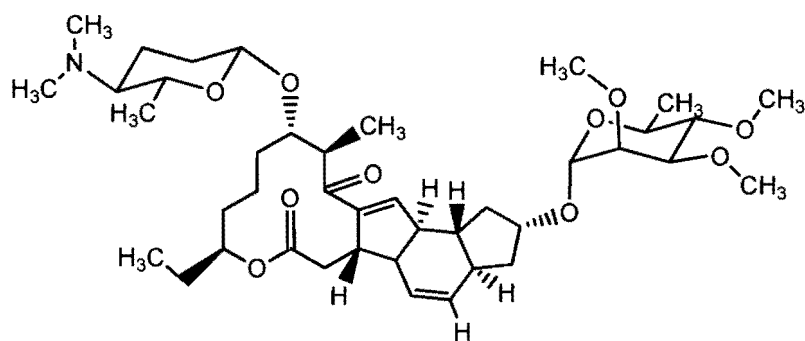


Figure 3.2. Structure of Erythromycin A.



Erythromycin A

Figure 3.3. Structure of Spinosad.



Spinosad A

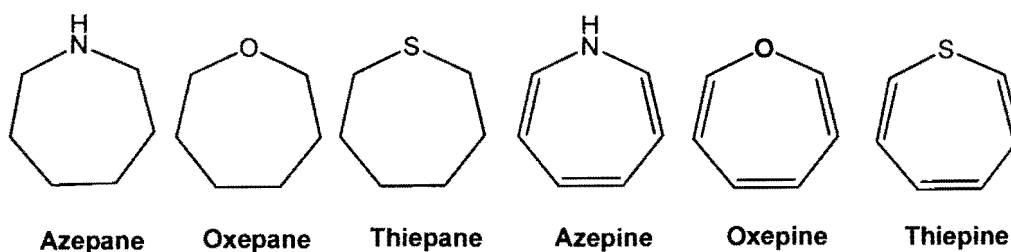
3.2. Heterocyclic compounds

If we further narrow down the extended ring systems, we highlight seven or eight membered heterocycles. Heterocycles are the cyclic compounds in organic chemistry in which at least one carbon atom of the cycle is generally replaced by oxygen, nitrogen or sulfur. These heterocycles are classified on the basis of:

- 1- The number of atoms in the ring
- 2- Saturated or unsaturated ring
- 3- Type of atom/atoms replaced by the carbon atom.

For seven membered heterocycles, the suffixes *-panes* (for saturated) and *-pines* (for unsaturated) are used. If one of the carbon atoms of the ring is replaced by an oxygen atom, then it will be an oxapane or oxapine depending on the degree of unsaturation. While, if a carbon atom is replaced by a nitrogen atom, it will be an azapane or azapine. Similarly, a prefix *thia-* will be used for a heterocycle in which a carbon is replaced by a sulfur atom. (e.g. thiapane or thiapene).

Figure 3.4. Structures of seven membered heterocycles.



But not always is just one carbon atom of the cycle replaced with the other atoms. When two oxygen, nitrogen or sulfur atoms are present in the ring, the prefix *dioxi-*, *diaze-*, and *dithia-* will be used. Sometimes, carbon atoms of the cycle are replaced by two different types of atoms. For example, a seven membered heterocycle having sulfur and a nitrogen atom present in the cycle will be called thiazapane/thiazapine (suffix thia for sulfur and aza for nitrogen).

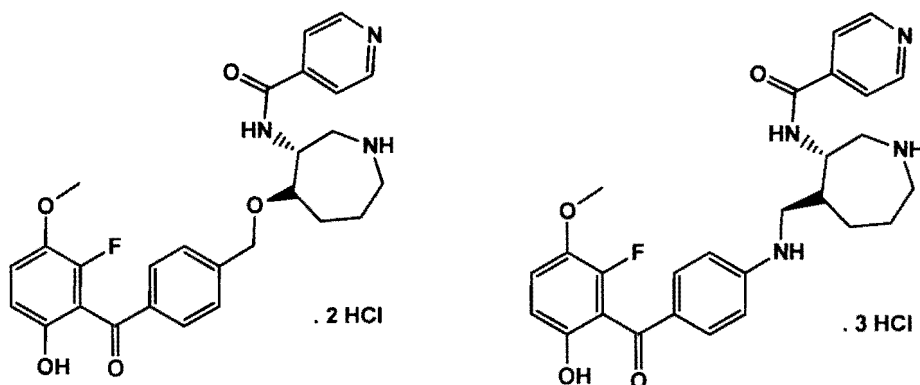
Figure 3.5. Structure of thiazepanes.



Azepane, thiepane and thiazepane derivatives are gaining much attention in medicinal chemistry and pharmaceuticals because of their biological activities

In 2004, new azepane derivatives were synthesized and found to serve as protein kinase B (PKB) inhibitors.⁶³ These derivatives were also potent inhibitors of PKB *in vitro* and in various tumor cell lines. In this research paper they also mentioned that the derivatives possessed anti-cell proliferation properties and induced apoptosis.

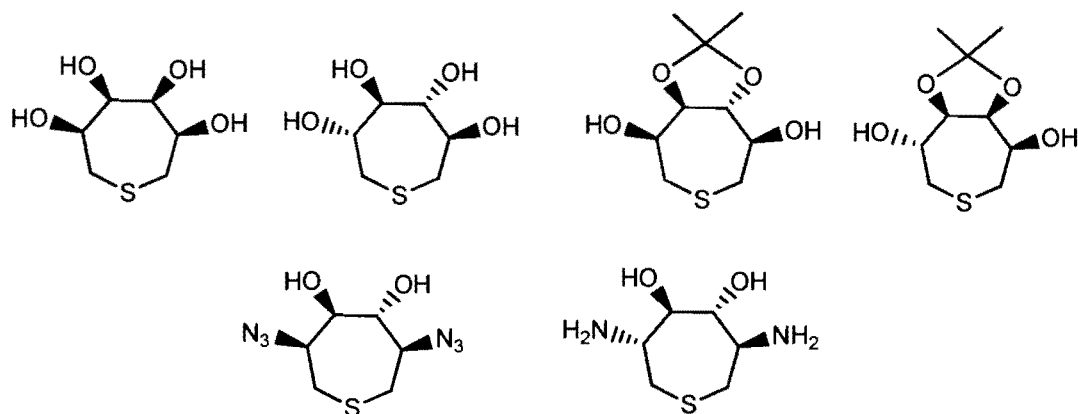
Figure 3.6. New Azepane derivatives.



In 2008, substituted 2-oxo-azepane derivatives were found to be potent and orally active γ -secretase inhibitors.⁶⁴ γ -secretase is a main proteolytic enzyme involved in Alzheimer's disease. The most well-known substrate of γ -secretase is amyloid precursor protein. Alzheimer's disease is a disease caused when amyloid is deposited in the brain in extracellular plaques and intracellularly in neurofibriles. The amyloid plaques are composed of A β peptides, whose production and deposition is the ultimate cause of Alzheimer's disease.

Some thiepane derivatives were also synthesized and evaluated as glycosidase inhibitors in 2002.⁶⁵ From the readily available thiepanes, enantiomerically pure 3,6-diazido and 3,6-diamino-4,5-dihydroxythiepanes were synthesized and were found to be potent glycosidase inhibitors.

Figure 3.7. Structures of thiepane derivatives used as glycosidase inhibitors.

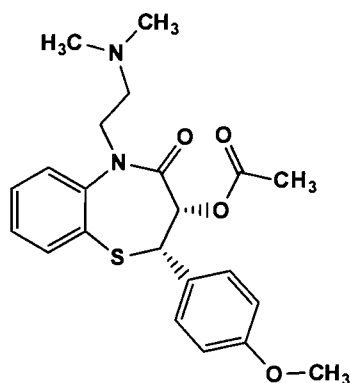


Besides azepanes, thiazepanes and diazepanes, there is another class of heterocycles worth mentioning known as the benzothiazepines. These molecules are discussed in detail in the next section.

3.3. Benzothiazepines and their biological activity

Benzothiazepines are compounds consisting of a thiazepene ring fused with a benzene ring structure. Benzothiazepines are considered as calcium channel blockers in medicinal chemistry.⁶⁶ Their activity is an intermediate class between phenylalkylamines and dihydropyridines. Benzothiazepines have both cardiac depressant and vasodilator activities.⁶⁷ Therefore they are able to reduce arterial pressure without producing the same degree of cardiac stimulation caused by dihydropyridines. The main representative of this class is Diltiazem (Figure 3.8).

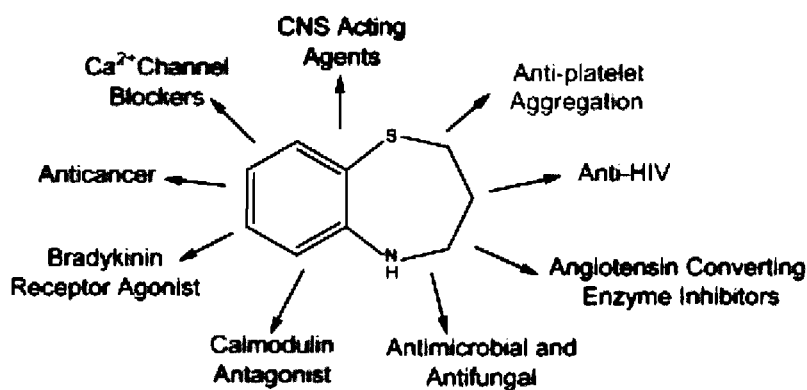
Figure 3.8. Structure of Diltiazem.



Diltiazem

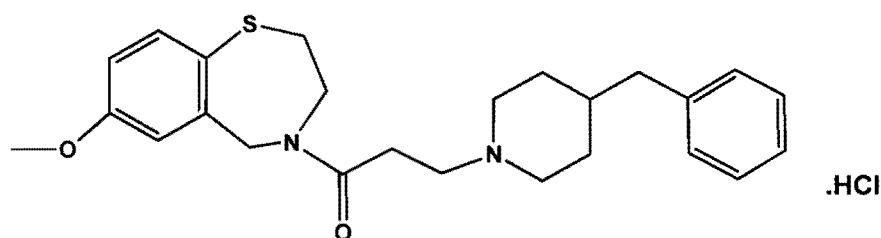
Diltiazem is a drug which is used to treat high blood pressure, angina pectoris and some kinds of arrhythmia. The biological activity of benzothiazepines is not only limited to calcium channel blockers but also some analogues serve as potent tranquilizers,⁶⁸ antidepressants,⁶⁹ CNS stimulants,⁷⁰ antihypertensives,⁷¹ and antiulcer⁷² drugs. A graphical diagram summarizes these properties in Figure 3.9.

Figure 3.9. Benzothiazepine as therapeutic agent.



Besides these, another potent action of this class was as antiarrhythmic drugs.⁷³ K201 (Figure 3.10) is a novel 1,4 benzothiazepine drug with cardioprotective and antiarrhythmic properties.⁷⁴ This drug also possesses natriuretic, diuretic, and vasodialating properties which may support the role of this drug in the treatment of heart failure.

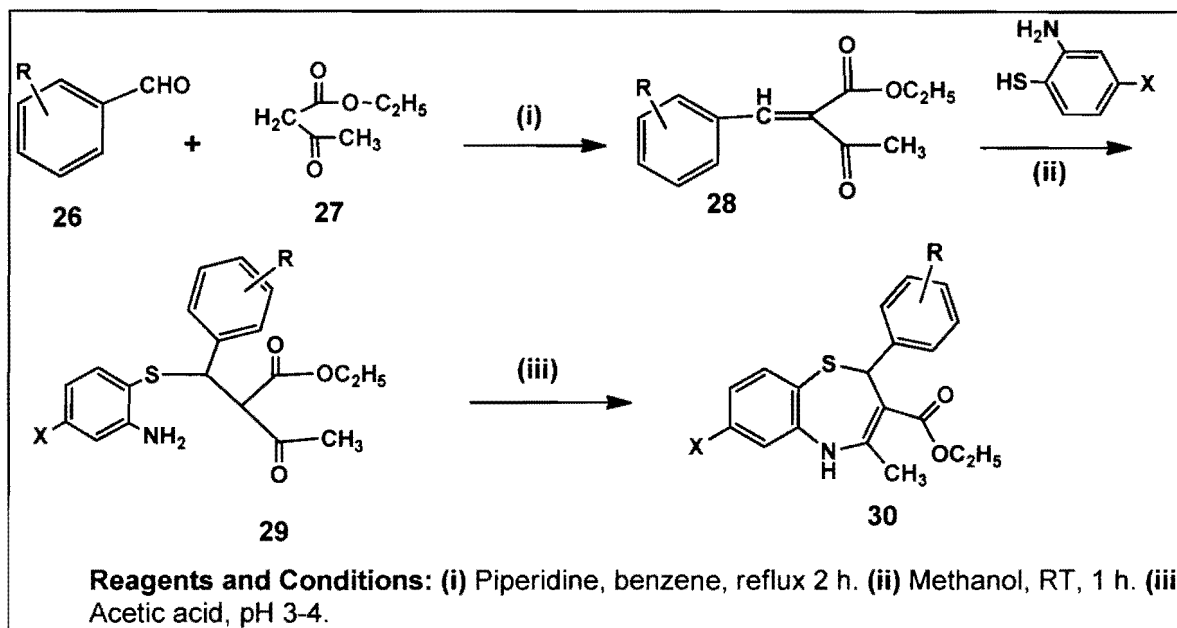
Figure 3.10. Structure of K201 drug.



3.3. Synthetic approaches to Benzothiazepines in the literature

In the literature there has been much work reported on the synthesis of benzothiazapine therapeutics. In 2009, the first 1,5 benzothiezapine derivatives were synthesized^{72, 75} in three steps by Knoevenagel condensation of aldehydes with 2,4-ketoester **27** in anhydrous benzene in the presence of piperidine to yield compound **28**. Then Michael addition of **28** with o-aminothiophenol in the presence of methanol gave ketoester derivative **29**. Finally compound **29** was cyclized by dehydration in acetic acid/methanol to provide derivatives of compound **30** (**Scheme 3.1**). In this paper,

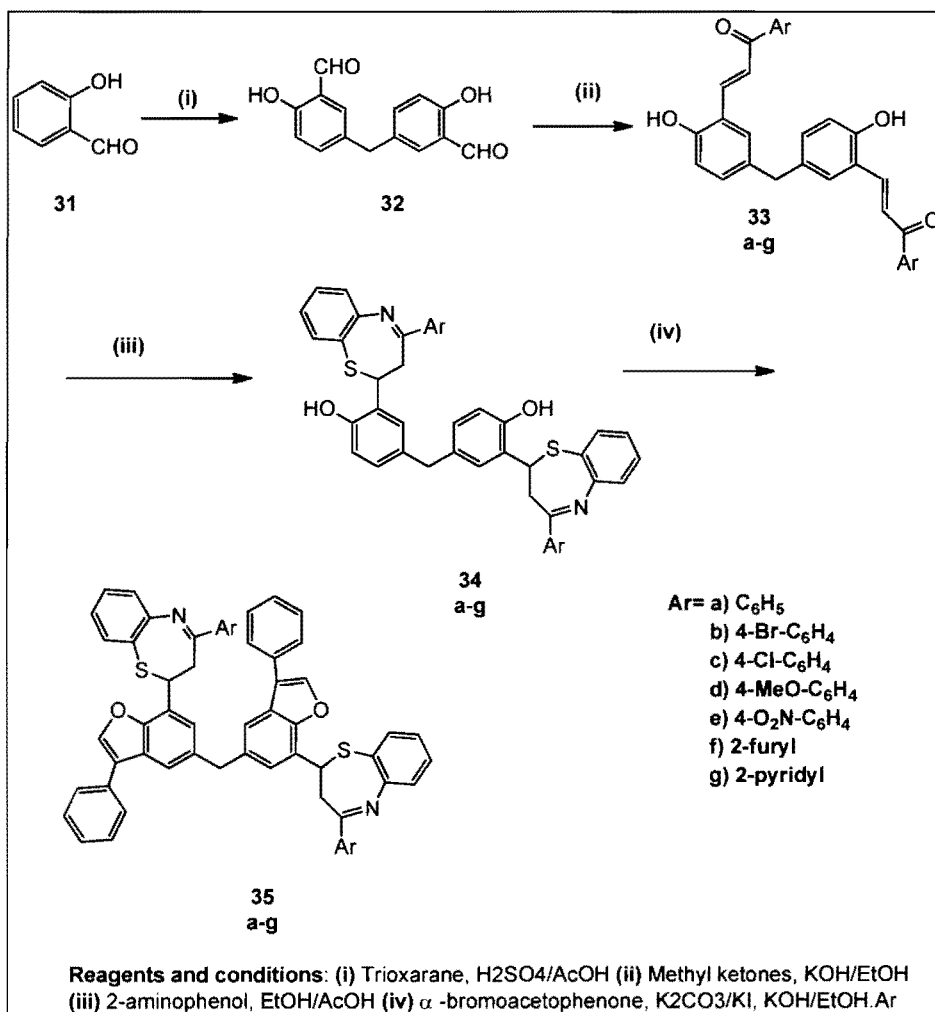
derivatives were synthesized with X as H or a Cl group while R was varied as *p*-NO₂, *o*-NO₂, *p*-Cl, *o*-Cl, *p*-CH₃, *p*-OH, H, *p*-OCH₃, *p*-F, and 2,4-dichloro groups.



Scheme 3.1

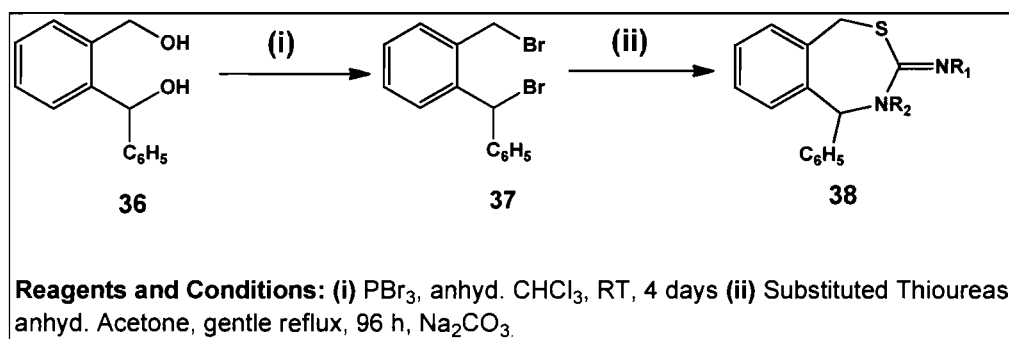
A series of novel methylene-bis-benzofuranyl-[1,5]-benzothiazepines were synthesized in 2008 and found to be biologically active against Gram-positive and Gram-negative bacteria and fungi.⁷⁴ These derivatives were prepared by the reaction of salicylaldehyde **31** with trioxane in presence of a mixture of acetic acid and conc. sulfuric acid to generate 5-(3-formyl-4-hydroxybenzyl)-2-hydroxybenzaldehyde **32**. The condensation of **32** with methyl ketones afforded methylene-bis-chalcones **33**. The series of **33** was reacted with 2-aminothiophenol to get **34** in good yield which later were converted into bioactive **35** on condensation with alpha-bromoacetophenone, in

the presence of anhydrous K_2CO_3 /dry acetone and catalytic amount of KI, followed by cyclization in ethanolic KOH (**Scheme 3.2**).



Scheme 3.2

We were also inspired by a synthetic method found in literature for 1- and 5- Aryl-2,4-benzothiazepines done in 1977.⁷⁵ A series of benzothiazepines were synthesized in two steps starting from 2-hydroxymethylbenzhydrol **36**. Compound **36** was brominated by treating with PBr_3 to yield dibromo intermediate **37**. The dibromo intermediate was then cyclized by treating with substituted thioureas to yield a benzothiazepine derivative **38** (**Scheme 3.3**). Inspired by this methodology, our ultimate goal was to synthesize a seven or eight membered ring sugar by treating an acyclic dibromo derivative of our starting sugar with compounds like thiourea.



Scheme 3.3

3.4. Summary

Extended ring systems in organic chemistry are a wide range of compounds with medicinal and biological importance. Most of the compounds are naturally occurring. Many serve as therapeutic agents. In particular, extended ring systems having seven or eight membered rings such as: sesquiterpene lactones, cyclooctanoids, azepanes, thiazepanes and benzothiazepines.

Our key interest is in the benzodiazepine class. We were interested to know if a thiazepine could also be active if a carbohydrate moiety replaces the benzene ring? To answer our question we developed a novel synthetic route to achieve our target thiazepene molecule which is discussed in Chapter 4.

Chapter 4

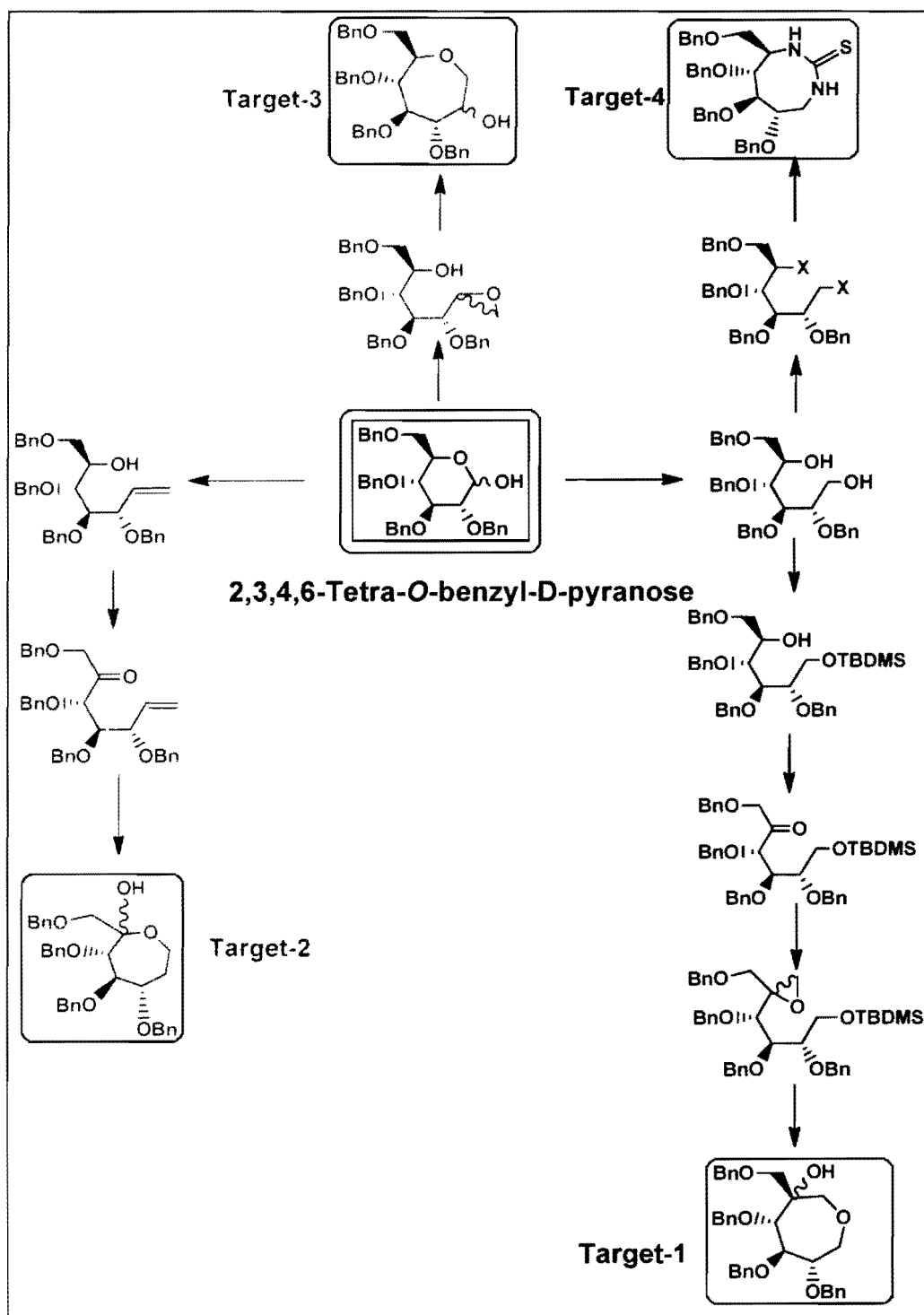
Novel Reactions and Syntheses of Septanoses/Extended Ring Systems

4.1. Introduction

The growing interest in septanose and septanoside sugars made us focus our efforts on doing synthesis in this area and to develop a convenient method for homologation of six membered ring sugars to serve as precursors for cyclic septanoses. Therefore the initial goal for our project was to develop a new methodology for the synthesis of septanoses using the ring opening of hexose sugars followed by the homologation of the acyclic sugar using a sulfur ylide, and subsequent recyclization of the chain-extended compound to the seven membered ring. We planned to start with a commercially-available hexose sugar, 2,3,4,6-tetra-O-benzyl-D-glucopyranose. Four divergent pathways were developed to generate four different target molecules. A summary of these pathways is shown in Figure 4.1.

4.2. Research Pathways

Figure 4.1. Research Pathways.



4.3. Research strategy

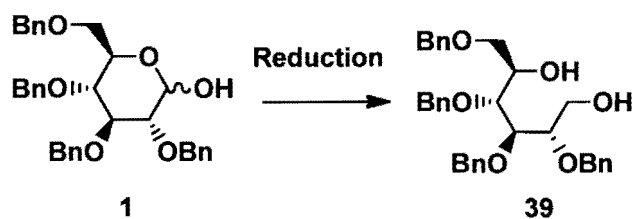
We have synthesized septanoses and large ring systems. This has been accomplished by:

- **Ring opening** of a hexose sugar.
- Stereoselective **homologation** of a carbon atom
- **Cyclization** to the septanose sugar.

Ring Opening:

This methodology was designed to initiate the sequences with ring opening of the hexose sugar. Ring opening could be achieved in two ways:

1- By the reduction of the starting hexose sugar 2,3,4,6-tetra-O-benzyl-D-glucopyranose to yield a diol (**Scheme 4.1**); or



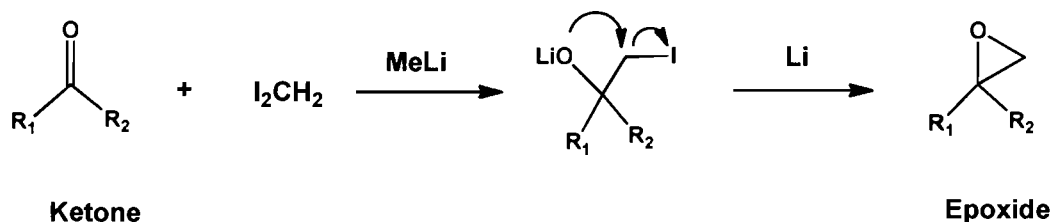
Scheme 4.1

2- By subjecting the starting sugar to a Wittig olefination reaction to yield a homologated (unsaturated) intermediate. In this step ring opening and homologation can be carried out in one step process (**Scheme 4.2**).



Another convenient epoxidation reagent we used was diiodomethylithium. The mechanism of this epoxidation reaction is different from that of the sulfur ylides as shown in Figure 4.3.

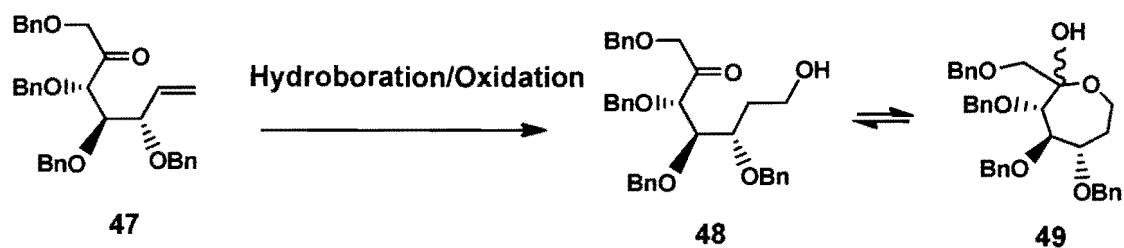
Figure 4.3. Mechanism of iodomethylithium epoxidation.



Cyclization:

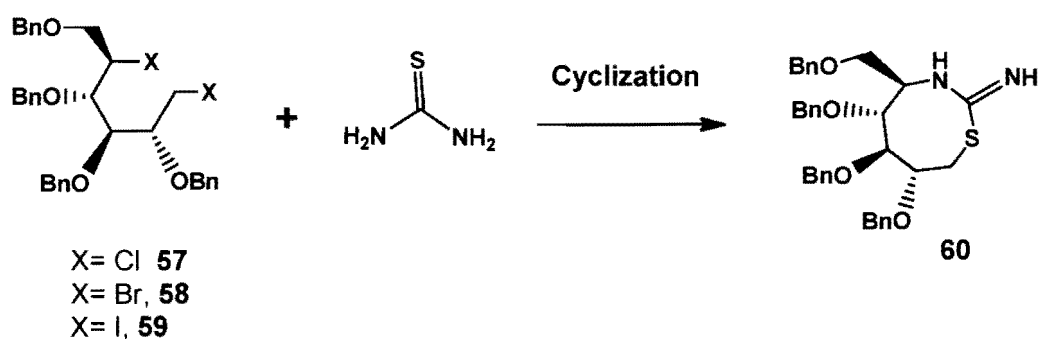
Cyclization is the step in which we close the ring of the homologated sugar as a septanose. For this step, we planned two ways:

1- By subjecting the Wittig product to a Hydroboration/Oxidation Reaction and then the intramolecular cyclization of the resulting hydroxyl sugar with the ketone can give a septanose with a hemiacetal. (**Scheme 4.3**), or



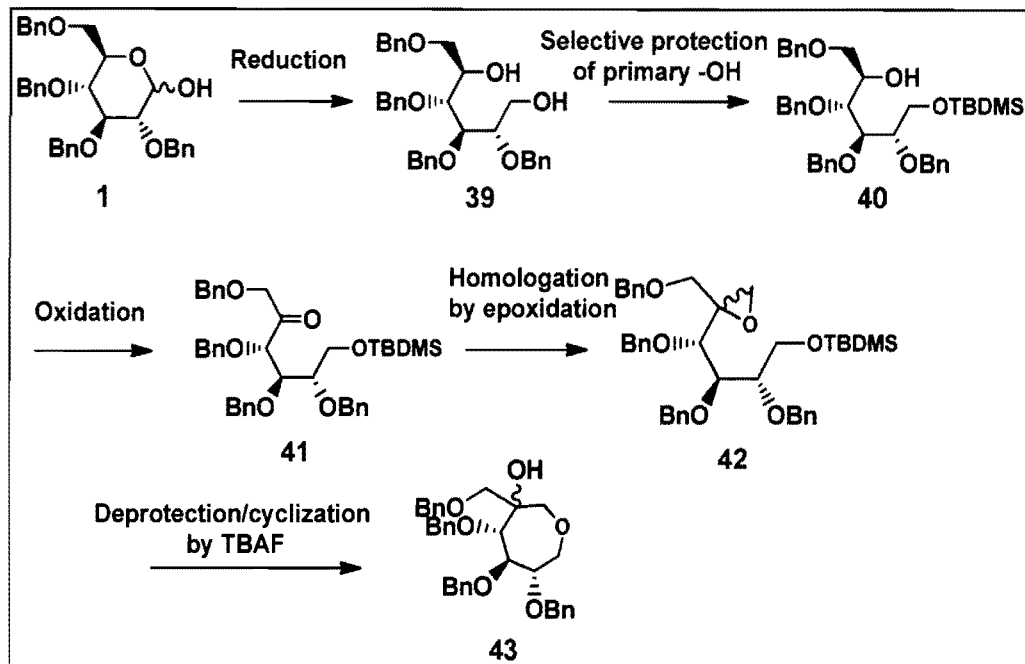
Scheme 4.3

2- By treating the dihalocompounds with reagents like thiourea to form a cyclized product. In this process homologation and cyclization is one-step process.



Scheme 4.4

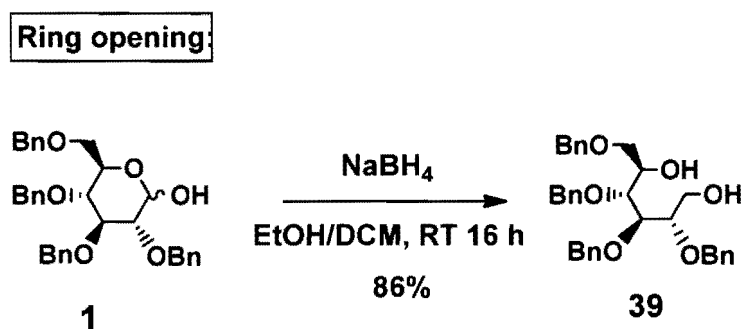
Pathway-1 designed scheme:



Scheme 4.5

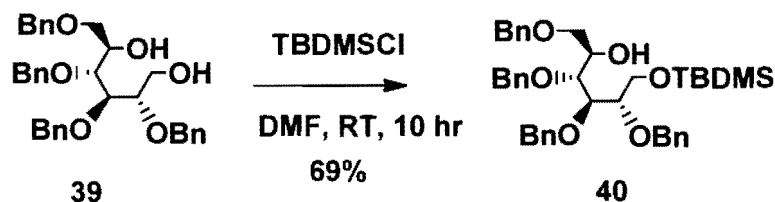
Pathway-1 was designed in a way that the pyranose sugar **1** will undergo reduction as a ring opening step and will yield a diol **39**. The primary alcohol of the diol **39** would then be selectively protected as silyl ether **40** so that the secondary alcohol could be made a precursor for the epoxidation reaction. Therefore, **40** would be subjected to Swern oxidation to yield **41** which would then be homologated by epoxidation with a sulfur ylide to provide epoxide **42**. Finally, the deprotection of the silylated hydroxyl of **42** by TBAF could generate an alkoxide nucleophile, which consequently will attack the less hindered carbon of the epoxide forcing intramolecular cyclization to yield **43** as a septanose (**Scheme 4.5**).

In this route, the ring opening step is favored by the reduction of 2,3,4,6-tetra-O-benzyl-D-glucopyranose **1**. Using literature methodology,⁷⁷ 2,3,4,6-tetra-O-benzyl-D-glucitol **39** was synthesized successfully from **1** by treatment with NaBH₄ in a mixture of EtOH and DCM in 86% yield (**Scheme 4.6**). Impurities were removed by flash chromatography (SiO₂).



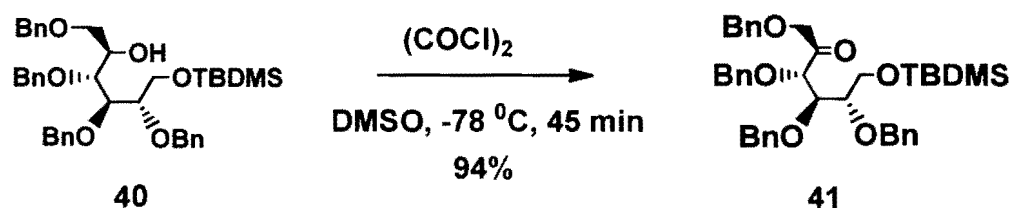
Scheme 4.6

The glucitol **39**, then underwent selective silylation of the more reactive primary alcohol, using TBDMSCl as the silylating reagent, in the presence of imidazole as a base and DMF as a solvent to produce **40** in 69% yield (**Scheme 4.7**).⁷⁸ The crude product was purified by column chromatography.



Scheme 4.7

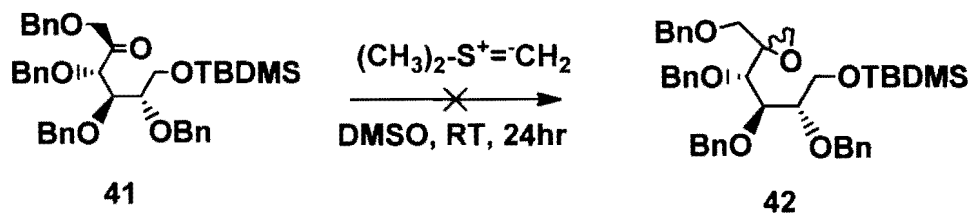
Compound **40** was then subjected to Swern oxidation according to the literature methodology⁷⁹ to synthesize a ketone **41** in 94 % yield (**Scheme 4.8**).



Scheme 4.8

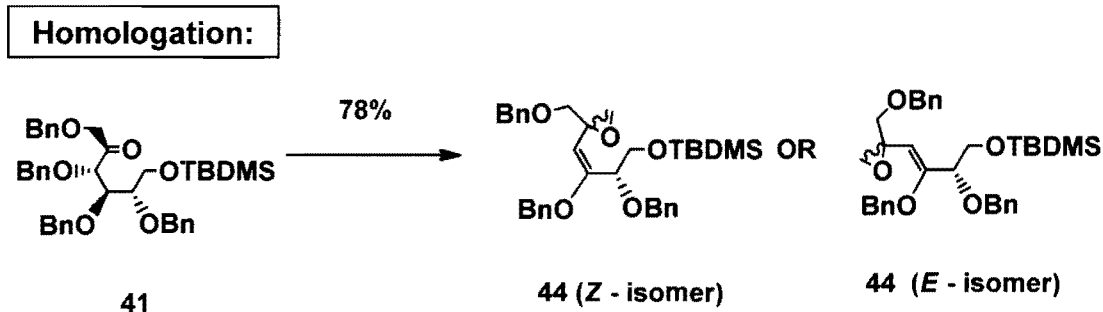
The epoxidation of the carbonyl group was next attempt using a sulfur ylide as an epoxidation reagent to give **42** (**Scheme 4.9**).

Homologation:



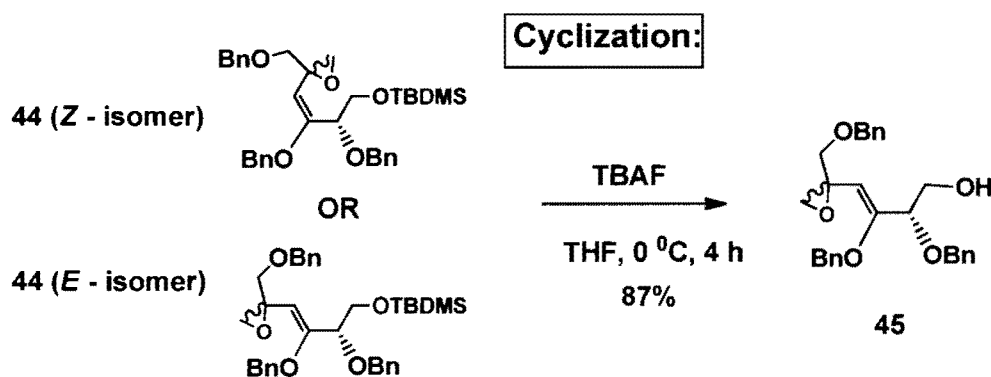
Scheme 4.9

Unfortunately compound **42** was not obtained following this route. Instead, epoxidation of the carbonyl functionality also occurred with elimination of benzyl alcohol to yield *E/Z* **44** in 78%. The reason for the elimination reaction was the basicity of the sulfur ylide.



Scheme 4.10

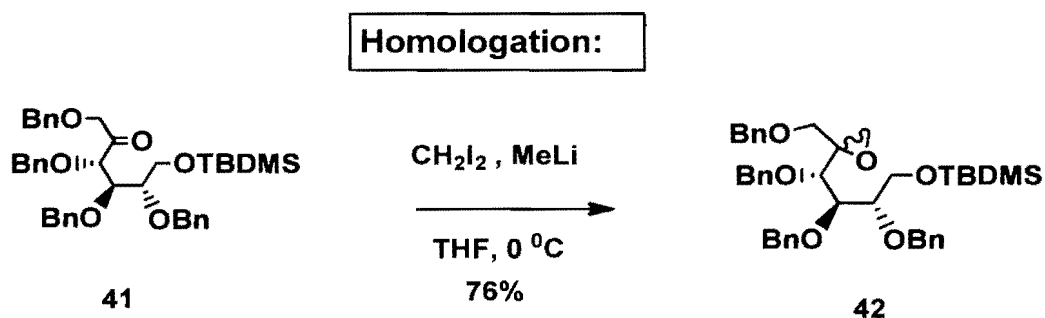
Here, the stereochemistry of alkene **44** is worth mentioning. Since the allyl epoxide may still be prone to cyclization in its *Z*-isomer form, we proceeded to the deprotection of the alcohol and subsequent cyclization to afford the septanose. Here, the stereochemistry of the alkene **44** did not allow the cyclization to occur presumably because the alkene existed in the *E*-conformer. Deprotection of compound **44** using TBAF gave an epoxy alcohol **45** in 85 % yield (**Scheme 4.11**).



Scheme 4.11

NOESY NMR was used to confirm the formation of *E*-conformer of **44**. The results were not conclusive to confirm the formation of *E*-conformer as the alkene proton does not have any neighboring proton in the structure.

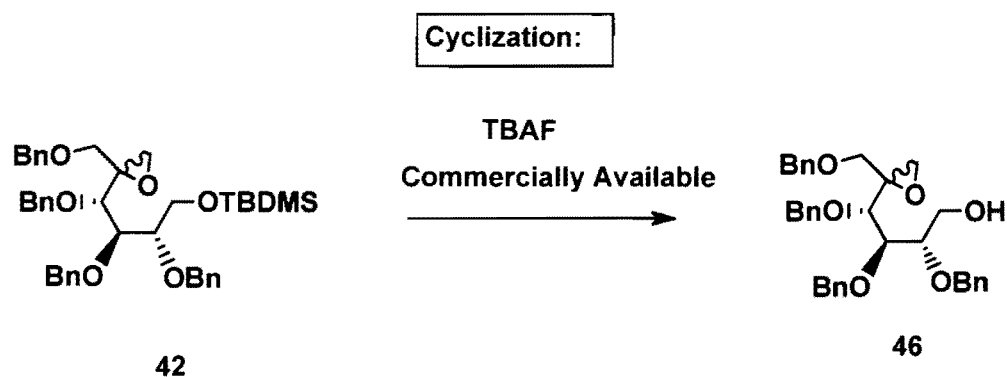
We did not get the desired cyclized septanose; therefore, we changed the epoxidation method. In this case, we used diiodomethylithium as an epoxidation reagent to avoid the elimination reaction.⁸⁰ An epoxide **42** was achieved in 76% yield without the loss of a benzyl alcohol group (**Scheme 4.12**).



Scheme 4.12

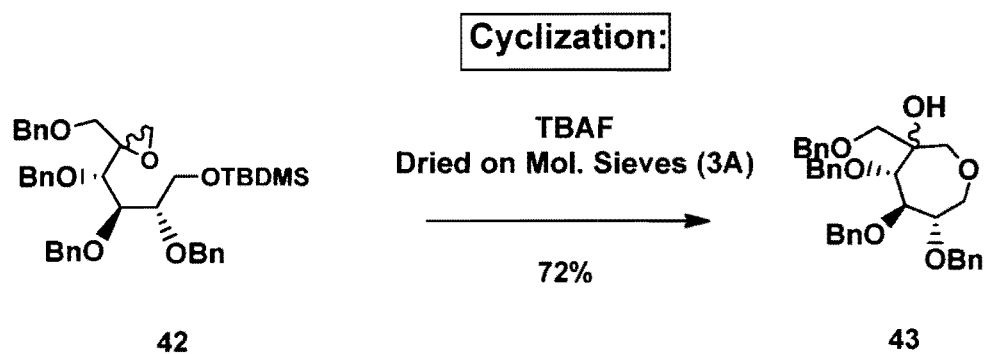
Cyclization was carried out by the deprotection of the alcohol by using TBAF to afford **43** as a septanose (**Scheme 4.14**). The problem encountered during the deprotection step was the presence of moisture in the commercially-available TBAF. We came to know this by examination of the literature which says that the commercially-available TBAF contains almost 5% H₂O.⁸¹ When the deprotection was carried out with commercially available TBAF, product **42** did not cyclize; instead it gave an epoxy-alcohol **46** due to quenching of the alkoxide with water (**Scheme 4.13**). Since, we

instead wanted an intramolecular cyclization to occur keeping the reaction environment anhydrous became a high priority.



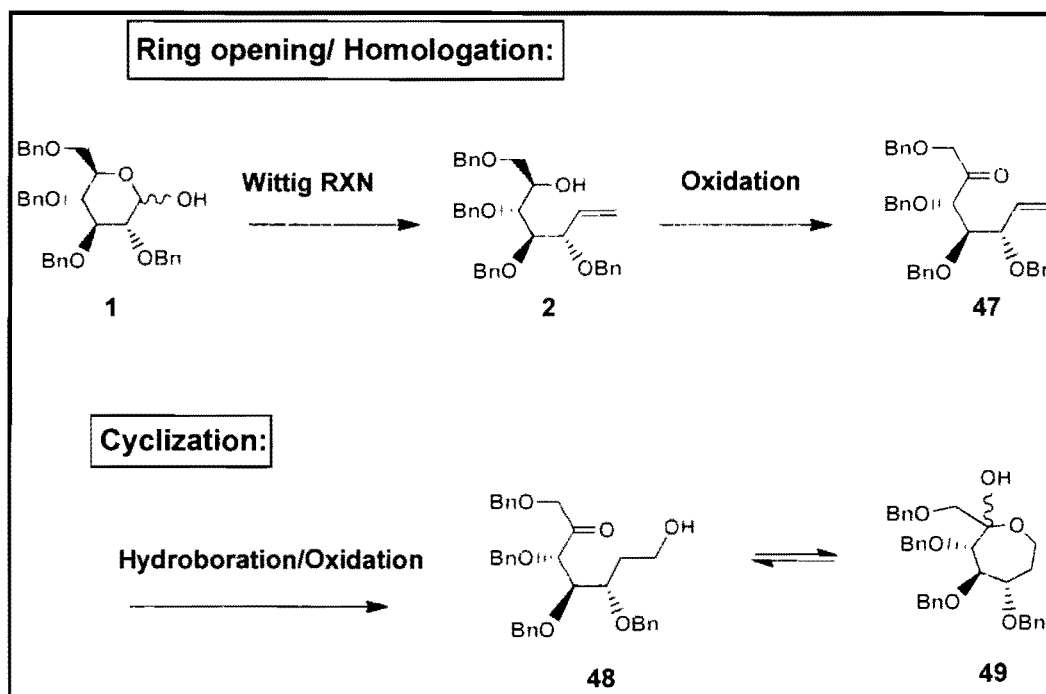
Scheme 4.13

Therefore, we dried commercially-available TBAF over molecular sieves (3A) overnight and conducted the reaction in a totally anhydrous environment to prepare the cyclic seven membered ring sugar **43**.



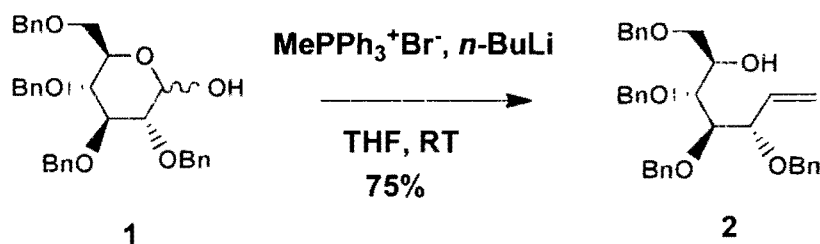
Scheme 4.14

Pathway-2 designed as:



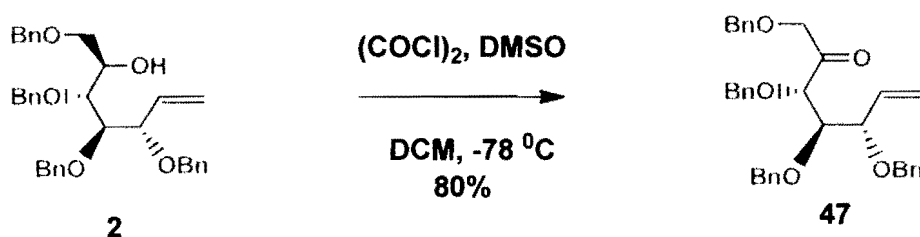
Scheme 4.15

In Pathway 2, **ring opening** and the **homologation** was carried out in a one-step reaction by subjecting the starting sugar **1** to a Wittig reaction, using literature methodology,⁸² yielding an acyclic extended chain sugar **2** in 75% yield (**Scheme 4.16**).



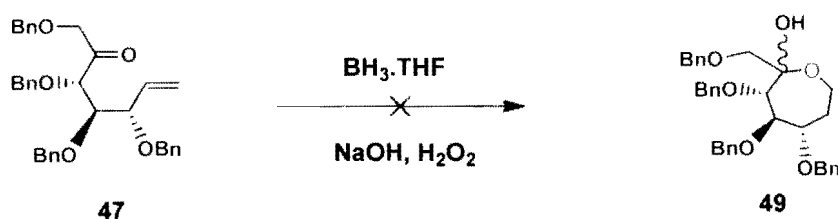
Scheme 4.16

The oxidation of the hydroxyl group of **2** was done by a Swern oxidation which yielded compound **47** in 80% yield (**Scheme 4.17**).

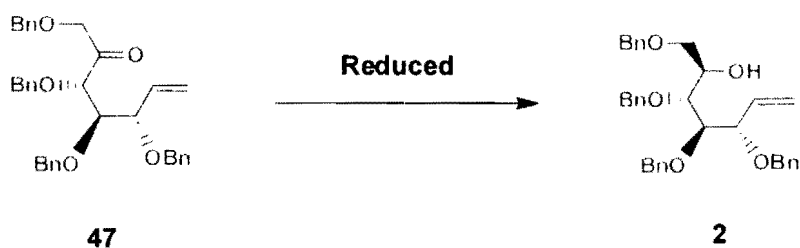


Scheme 4.17

The alkene moiety of compound **47** was subjected to a hydroboration/oxidation reaction by using $\text{BH}_3\cdot\text{THF}$ (**Scheme 4.18**). The drawback of using this reagent was, instead of hydroborating the alkene moiety, it reduced the the ketone to the alcohol **2** (**Scheme 4.18**).



Scheme 4.18

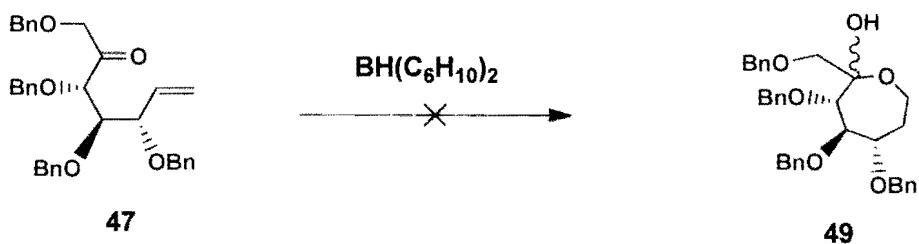


Scheme 4.19

Dicyclohexyl borane was next attempted because it is a specific reagent for the selective hydroboration/oxidation of the alkene moiety without reducing the carbonyl group if present in the molecule.⁸³ Not all bulky borane reagents have that property. Dicyclohexyl borane is not commercially available due to its poor stability. Therefore, it is synthesized either *in-situ* or separately. We tried both ways of synthesizing the borane reagent and then subjected the alkene to hydroboration/oxidation. The results of two trials are summarized in Table 4.1.

Table 4.1. Trials of Dicyclohexylborane reductions.

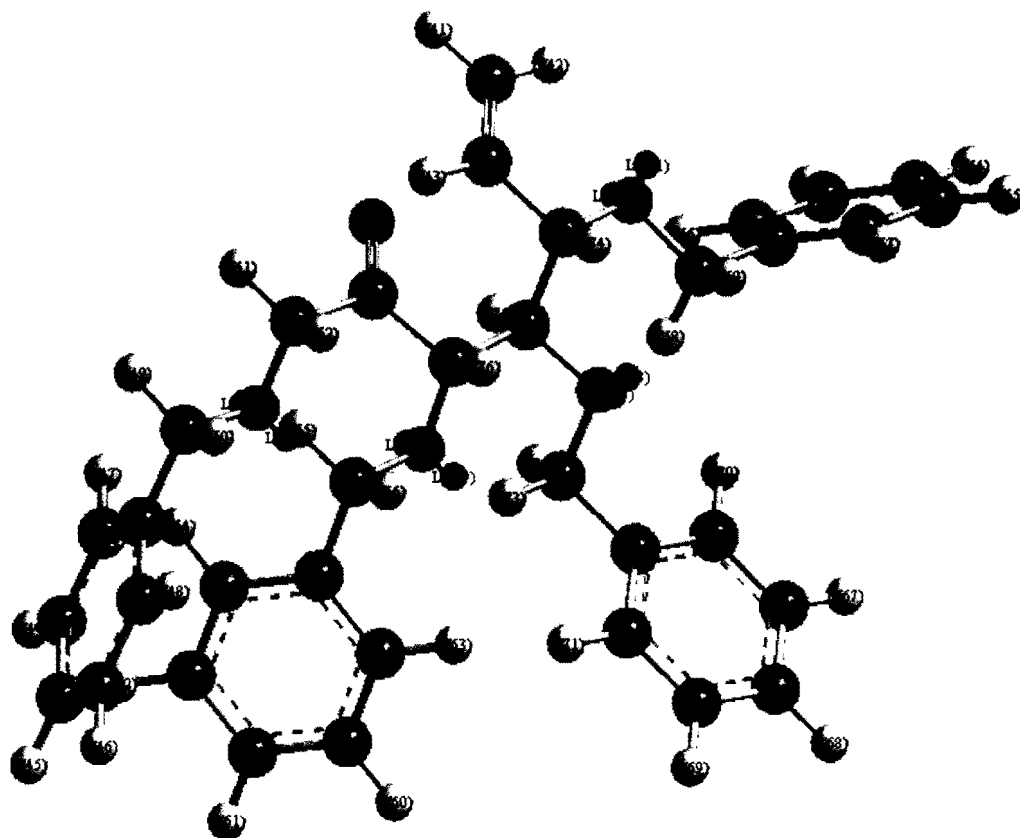
Trial	Borane reagent	Synthesized <i>in-situ</i>	Synthesized separately	Reaction
1	BH(C ₆ H ₁₀) ₂	✓		No rxn
2	BH(C ₆ H ₁₀) ₂		✓	No rxn



Scheme 4.20

After several trials of hydroboration/oxidation reactions with different conditions in which **47** was unaffected, we decided to do molecular modeling of the compound to look at the conformation of the molecule. Using Chem 3-D software we used MM2 calculations to minimize the energy of the structure (Figure 4.3). From the minimized structure obtained we came to know that alkene and carbonyl moieties are close to each other and perhaps bulky reagents like dicyclohexyl borane are not able to react because of steric hindrance between the two groups. While, with the use of non-bulky reagents, the carbonyl functionality was first reduced. Another option would have been to protect the carbonyl first and then perform the hydroboration/oxidation reactions.

Figure 4.3. Molecular modeling of compound 47.



In the model of **47** (Figure 4.3), carbon and oxygen atoms of the carbonyl group are labeled as C(1) and O(6) respectively. While, the carbon and hydrogen atoms of alkene (-CH=CH₂) are labeled as C(5), C(31), H(41), H(42) and (H43). To see the specific atom causing hindrance in two functional groups, measurements were calculated to generate all atoms with close contacts. The results are listed in Table 4.2.

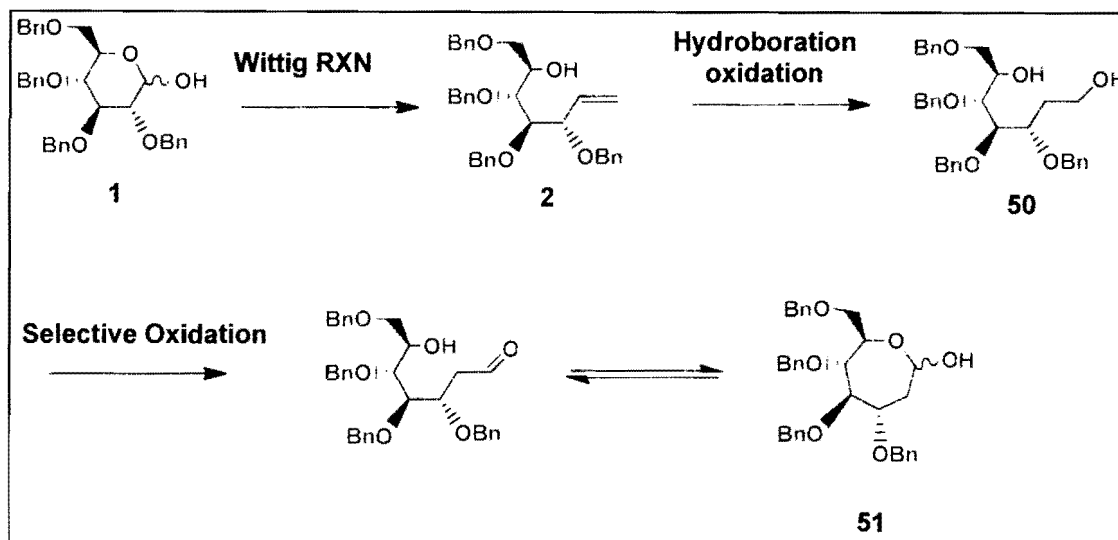
Table 4.2. Molecular modeling simulation results.

	Atoms in close contacts	Actual distance between atoms (^o /A)	Calculated (^o /A)
1	C(1) – H(43)	1.8521	1.9
2	C(1) – C(5)	2.5218	2.5
3	O(6) – H(43)	1.3762	1.4
4	O(6) – C(5)	1.8934	1.9
5	O(6) – C(31)	2.6620	2.7

On the basis of the calculated values, it is concluded that distance between the hydrogen atom of alkene H(43) and the oxygen atom of ketone O(6) is the least (1.4 ^o/A) among all which is the reason of steric hindrance.

Failure to achieve the desired compound led us to two more divergent pathways; pathway **2A** and pathway **2B**.

Pathway 2A:



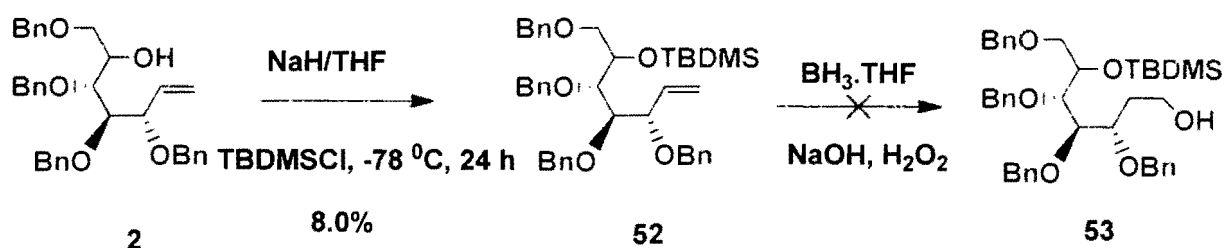
Scheme 4.21

In this pathway, compound **2** was synthesized as reported in pathway 2. To compound **2** was carried out hydroboration oxidation reaction to achieve a diol **50** (**Scheme 4.21**) so that primary alcohol of the resulting diol would have been subjected to selective oxidation consequently cyclize intramolecularly to yield **51**.

The hydroboration oxidation reaction was monitored by thin layer chromatography which showed that starting material **2** remained unchanged and was recovered as it is.



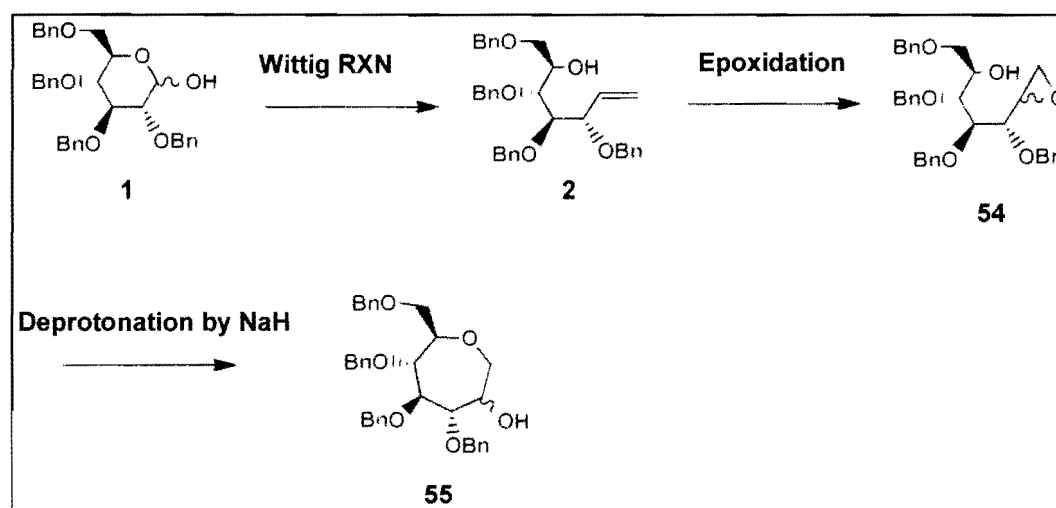
The alternative route was the protection of the alcohol group, but we did not encourage that idea as the protecting group would give steric hindrance to the alkene functionality of the compound, like in compound **47**. To strengthen our idea, we tried to protect the alcohol moiety of compound **2** with silyl ether. The yield of the silylated product **52** was extremely low (8%)(**Scheme 4.23**). Compound **52** was subjected to hydroboration oxidation reaction on small scale. The reaction was monitored by thin layer chromatography which showed that reaction did not work and the starting material remained intact.



Scheme 4.23

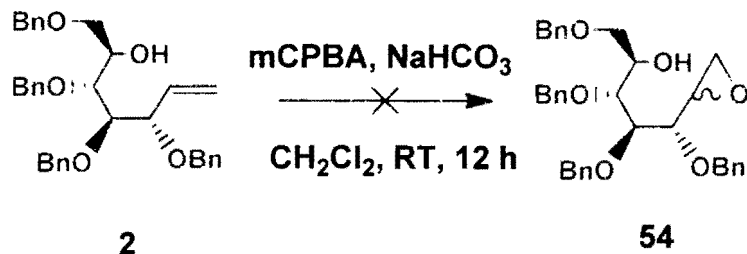
The divergent pathway 2B was then followed.

Pathway 2B:



Scheme 4.24

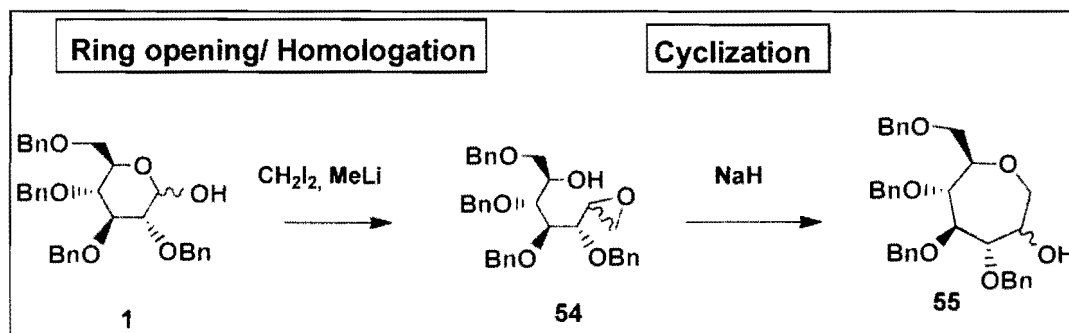
In this pathway, the alkene functionality of **2** was expected to convert to epoxide **54** (Scheme 4.24). The deprotonation of alcohol of **54** using sodium hydride as a base was rationalized to yield a cyclic septanose **55** by the attack of alkoxide to the less hindered carbon of the epoxide.



Scheme 4.25

Compound **2** was subjected to an epoxidation reaction using mCPBA reagent but reaction did not work and compound **2** was recovered and confirmed by NMR.

Pathway-3 designed scheme:

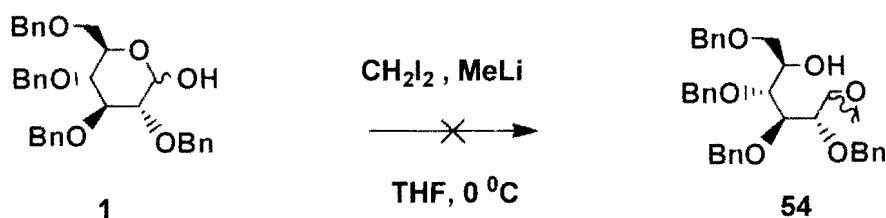


Scheme 4.26

This pathway was designed with the alternative epoxidation reagent iodomethyl lithium which successfully worked with silylated carbonyl compound **41** in pathway-1. To minimize the number of steps of the reaction we planned to make the epoxide from the carbonyl moiety of the starting sugar **1**. In this pathway, ring-opening and homologation would be a one step process. Later, **54** could be treated with a base

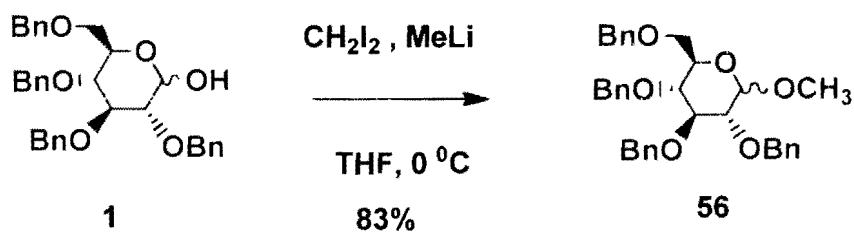
such as NaH which could abstract the proton of the secondary hydroxyl group and generate a nucleophile for attack onto the less hindered carbon of the epoxide, resulting in cyclization to **55**.

Unfortunately, when we treated the starting sugar with the epoxidation reagent, instead of epoxidation of the aldehyde group, the anomeric hydroxyl group was methylated (**Scheme 4.28**). Here, iodomethyl lithium worked by inserting between the oxygen and hydrogen atoms of the anomeric hydroxyl group.



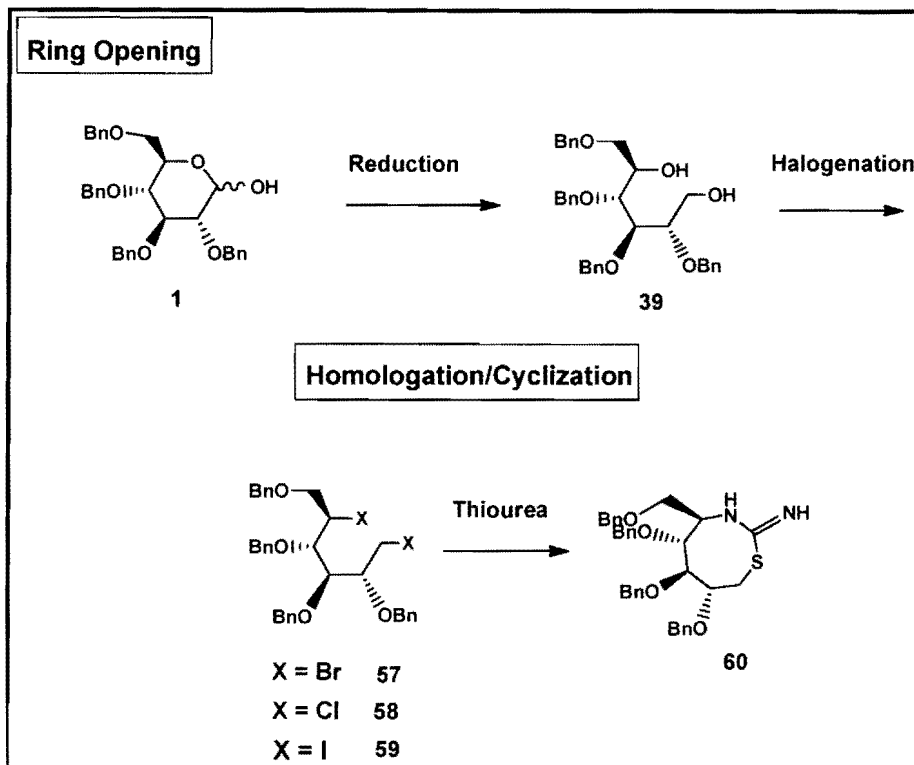
Scheme 4.27

The resulting compound **56** is a commercially available compound and data analysis (MS, NMR ^1H and ^{13}C DEPT) confirmed the formation of β -isomer of **56**. We did not achieve our target molecule **54** but came up with a new method of preparing the methyl glycoside **56**.



Scheme 4.28

Pathway- 4 designed scheme:

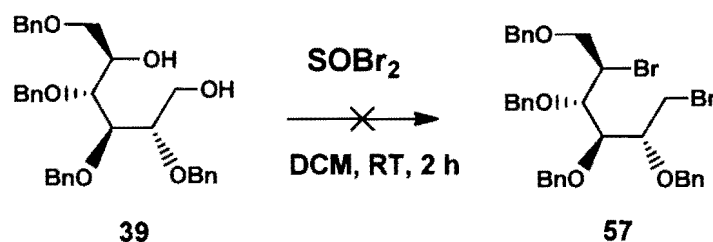


Scheme 4.29

This pathway was designed to synthesize a target molecule with a thiazepine template. As previously mentioned we wanted to see the effects replacing the benzene moiety of a benzothiazepine with a sugar moiety. For this purpose, we designed a pathway in which ring opening was carried out by reduction of **1** as we did before. The diol **39** would then be converted to the dihalo compound. Initially we wanted to brominate the diol because later the bromo groups could serve as good leaving groups in the cyclization reaction with thiourea.

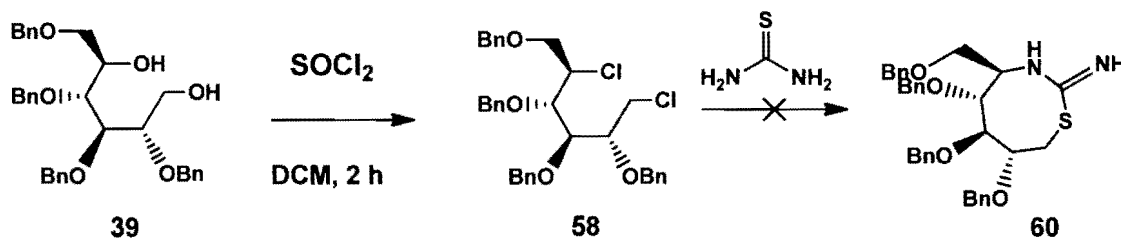
Using a literature procedure,⁸⁵ thionylbromide was used as a bromination reagent and was reacted with diol **39** (**Scheme 4.30**). Unfortunately, the reaction was

not successful and product **57** was not obtained. Alternate conditions (Table 4.3) were tried but product **57** did not form. Benzyl alcohol was consistently isolated as a reaction by-product suggesting elimination was occurring from our material.



Scheme 4.30

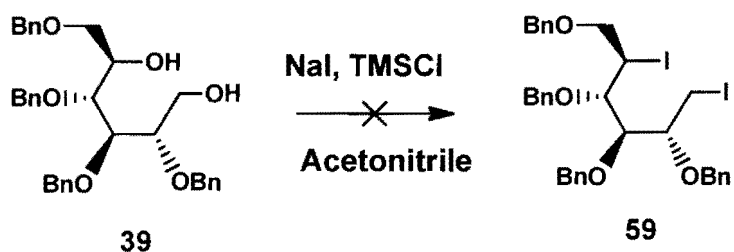
After the failure of **Scheme 4.30** we switched the halogenation reagent to thionyl chloride. After different trials we were able to achieve **58**. However, no reaction occurred with **58** was treated with thiourea. We concluded that the chloro groups were stable to the thiourea displacement conditions, most likely due to the weak nucleophilicity of thiourea.



Scheme 4.31

The last attempt we made for the dihalo intermediate was to use an iodination reaction. Using a literature procedure,⁸⁶ we tried to synthesize diiodo intermediate **59**.

Again, instead of the desired diiodo compound, benzyl alcohol was the major byproduct isolated.



Scheme 4.32

Table 4.3. Summary of halogenation reactions.

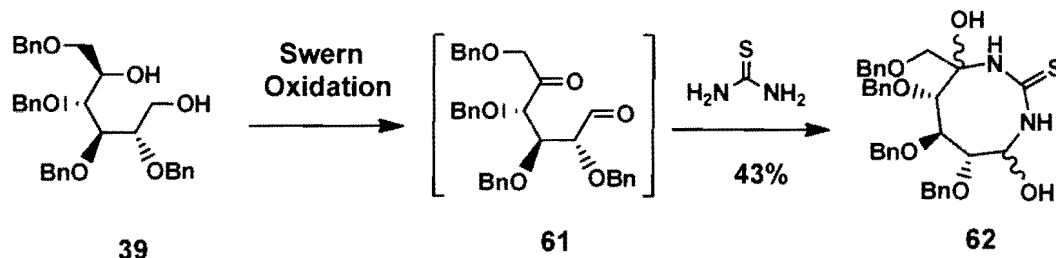
Reagent	RXN Temp. °C	RXN Time h	Quenching Temp. °C	Product 57, 58, 59	Product 60	By-product
SOBr ₂	RT	2	RT	ND	-	BnOH
	0	2	RT	ND	-	BnOH
PBr ₃	RT	5	0	ND	-	BnOH
SOCl ₂	RT	1	RT	ND	-	
	RT	2	RT	ND	-	
	50	1	RT	D	-	
	RT	4	0	53	No RXN	
NaI	RT	5	RT	ND	-	BnOH

ND = Not Detected

D = Decomposed

After the failure of the halogenation reactions, an alternative intermediate was planned for the reaction with thiourea. From the failure of the halogenation reaction it was concluded that halo-groups which are supposed to be good leaving groups were not amenable to the cyclization conditions with thiourea. Therefore, we thought of making a dicarbonyl intermediate that could serve as a source of a good electrophile for the thiourea. In the literature we found evidence for the reactions of urea with carbonyl groups to give imines.⁸⁷

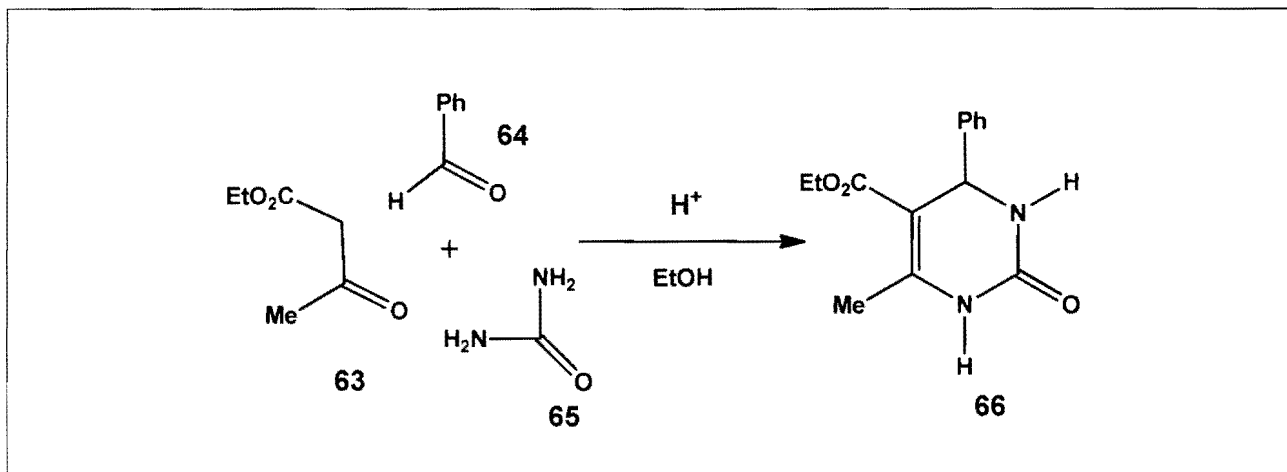
Keeping all these points in mind, we planned a one pot synthesis of a di-carbonyl compound **61** as an intermediate starting from diol **39** (**Scheme 4.33**). According to the literature this compound is unstable and prone to hydrolysis. The di-carbonyl compound **61** was made as an intermediate *in-situ* by Swern oxidation of compound **39**. After the completion of the reaction, thiourea was added directly to the di-carbonyl compound **61**. To our astonishment, we observed a spot on TLC plate which turned yellow in PdCl₂ dip (an indication of the presence of sulfur in the molecule).⁸⁸ When we worked-up the reaction we are able to isolate the product as a white solid. It was noticed that when thiourea was added in the reaction mixture at room temperature, the % yield of the overall reaction was low (27%) while when thiourea was added at -78 °C, the yield was increased up to 58%. Later, MS, NMR (H¹ and C¹³), IR confirmed that the new compound was indeed our desired target molecule **62**.



Scheme 4.33

As we have mentioned before, there is no evidence in the literature for this kind of reaction, but our further study of the literature led us to a similar kind of reaction, called the Bignelli reaction. The Bignelli reaction is an acid catalyzed 3-component cyclization reaction, in which a urea, a β -ketoester and an aldehyde cyclize together to yield dihydropyrimidone.⁸⁹

Figure 4.4. Bignelli reaction.



4.5. Summary

For this project we designed multi-step synthetic pathways to synthesize a stable septanose and a heterocycle based upon a benzothiazepine structure. We developed 4 divergent routes for these pathways out of which we were able to achieve pathway-1 and pathway-4 successfully. Pathway-1 was made successful by altering the epoxidation reagent while pathway-4 was made successful by changing the dihalo intermediates with dicarbonyl compounds. Halogenation reactions failed with the use of brominating reagents like phosphorus tribromide and thionylbromide and the byproduct of those reactions was benzyl alcohol. Halogenation reactions worked with thionyl chloride to yield the dichloro intermediate but the final cyclized product could not be formed presumably because chloro-groups are not as good leaving groups as bromo-groups.

In consequence, because the halogenation reactions did not work, carbonyl electrophiles were tried in the reactions with thiourea and yielded a cyclized eight-membered ring product.

Chapter 5

Summary

5.1. Conclusions

Carbohydrates are versatile synthetic precursors. Our main goal of this project was to synthesize a stable septanose sugar starting from a hexose sugar. There are syntheses reported in the literature for septanoses but no known homologation methods using classic epoxidation reagents, the sulfur ylides.

Halogenation reactions failed with the use of brominating reagents like phosphorus tribromide and thionylbromide and the by-product of those reactions was benzyl alcohol. Halogenation reactions worked with thionyl chloride to yield the dichloro intermediate but the final cyclized product could not be formed in the reaction with thiourea. It could also be concluded that thiourea is not a very good nucleophile for this reaction.

The new methodology we have developed includes a new way to epoxidize the sugars as well as to cyclize the dicarbonyl intermediate with urea or thiourea. The heterocycles obtained could serve as new therapeutics. Because of the versatility in the structure of sugar molecules a number of derivatives can be synthesized using this new methodology.

5.2. Experimental

5.2.1. General methods:

All reactions were carried out under nitrogen in oven-dried glassware unless otherwise mentioned. For moisture sensitive reactions, anhydrous solvents were used and reagents were added to the reaction mixtures through syringes. All reactions were monitored by thin layer chromatography (TLC). Column chromatography was carried out by using Silitech 32-63 D (230-400 mesh) silica gel. ^1H and ^{13}C NMR spectra were recorded on a 500 MHz Varian Inova spectrometer in chloroform- d or acetone- d_6 as solvent using tetramethylsilane as an internal standard. Infrared spectra were recorded on a Nicolet FT-IR. Mass spectral analyses were performed at the University of Illinois-Champaign-Urbana using electrospray ionization (ESI).

5.2.2. (2R,3R,4R,5S)-1,3,4,5-tetrakis(benzyloxy)hept-6-en-2-ol (2)

To a suspension of Ph_3MePBr (7.93 g, 22.20 mmol) in THF (50 mL) at $-20\text{ }^\circ\text{C}$, was added dropwise 1.6 M BuLi in hexane (15 mL). The mixture was stirred at $-20\text{ }^\circ\text{C}$ for 15 min, at RT for 1 h, and then cooled again to $-20\text{ }^\circ\text{C}$. To this was added dropwise a solution of **1** (3.0 g, 5.55 mmol) in THF (15 mL). The mixture was stirred at $-20\text{ }^\circ\text{C}$ for 15 min and RT for 6 h, acetone (30 mL) was added and the mixture was stirred at RT for 30 min. Et_2O (100 mL) was added and the precipitate of Ph_3PO was removed by filtration through Celite. The filter was rinsed with Et_2O and the combined filtrate and the washings were washed with aq sat. NaHCO_3 (50 mL), then brine (50 mL), dried over

Na₂SO₄, filtered and concentrated at reduced pressure. The residue was purified by flash chromatography (Hexanes-EtOAc, 4:1) to afford **2** (2.20 g, 76%) as a colorless oil. ¹H and ¹³C NMR data for this compound were consistent with literature values.⁹⁰

5.2.3. 2,3,4,6-tetrakis(benzyloxy)hexane-1,5-diol (**39**):

Commercially-available 2,3,4,6-tetra-O-benzyl-D-glucopyranose (9.0 g, 16.65 mmol) **1** was taken in an oven-dried, 1000 mL round bottom flask. EtOH/DCM (1:1) (140 mL) was added and the solution was stirred for 15 min at room temperature. NaBH₄ (3.0 g, 79.3 mmol) was added as a single portion and the reaction was stirred for 16 h at room temperature. After the completion of the reaction, 2M HCl (30 mL) was added to the reaction mixture and it was stirred for an additional 5 min. The organic layer was extracted in dichloromethane (2 x 20 mL). The organic layers were combined and dried over Na₂SO₄. The solvent was evaporated under reduced pressure to afford crude compound that was purified by flash chromatography (Hexanes/EtOAc, 3:1) to yield **39** (8.4 g, 93.4%) as a colorless oil.

¹H and ¹³C NMR data for this compound were consistent with literature values.⁷⁷

5.2.4. 1,3,4,5-tetrakis(benzyloxy)-6-((tert-butyldimethylsilyl)oxy)hexan-2-ol (**40**):

To a well-stirred solution of **39** (3.0 g, 5.52 mmol) in DMF (anhydrous, 20 mL) was added imidazole (0.4 g, 7.17 mmol) and the temperature was brought to 0°C. The reaction was stirred for 20 min at 0°C and TBDMSCl (0.91 g, 6.0 mmol) was added. The reaction mixture was brought to RT and stirred for an additional 24 h. After the completion of the reaction, water (20 mL) was added and the aqueous layer was

extracted with CH_2Cl_2 (3 x 20 mL). The combined organic layers were dried over Na_2SO_4 , decanted and concentrated under reduced pressure. The residue was purified by flash chromatography (Hexanes/EtOAc, 3:1) to afford **40** (2.0 g, 66.6%) as a colorless oil.

^1H and ^{13}C NMR data was consistent with literature values.⁹¹

5.2.5. 1,3,4,5-tetrakis(benzyloxy)-6-((tert-butyldimethylsilyl)oxy)hexan-2-one (41):

To the solution of oxalyl chloride (0.6 mL, 6.80 mmol) in CH_2Cl_2 (20 mL) was added a solution of DMSO (1.0 mL, 13.70 mmol) in CH_2Cl_2 (5 mL) via dropping funnel at $-78\text{ }^\circ\text{C}$. The reaction mixture was stirred for 5 min and then a solution of **40** (4.0 g, 62.0 mmol) in CH_2Cl_2 (5 mL) was added. It was stirred for an additional 15 minutes and TEA (triethylamine) (4.3 mL) was added. Water (25 mL) was added and the aqueous layer was extracted with CH_2Cl_2 (3 X 20 mL). The combined organic layers were dried over Na_2SO_4 and the solvent was removed under reduced pressure. The residue was purified by flash chromatography (Hexanes/EtOAc, 4:1) to afford **41** (3.1 g, 79%) as a colorless viscous compound.

^1H and ^{13}C NMR data was consistent with literature values.⁹²

5.2.6. tert-butyldimethyl((2S,3R,4S)-2,3,4-tris(benzyloxy)-4-(2-((benzyloxy)methyl)oxiran-2-yl)butoxy)silane (42):

To the solution of **41** (2.5 mmol) and diiodomethane (0.3 mL, 3.75 mmol) in THF (10 mL) was added dropwise methyllithium (3.4 mL of 1.5 M solution in diethyl ether, 5 mmol) over 5 min and under nitrogen at $0\text{ }^\circ\text{C}$ for 30 min. The mixture was stirred for one

additional hour at room temperature. The resulting mixture was poured on ice and extracted with DCM (3 x 10 mL). The combined organic layers were dried over Na₂SO₄, filtered and the solvent was removed under reduced pressure to yield **42** as colorless oil in 56% yield. Compound **42** was used for the next step without purification.

5.2.7. (2S,Z)-2,3-bis(benzyloxy)-4-(2-((benzyloxy)methyl)oxiran-2-yl)but-3-en-1-ol (43).

A solution of **42** (30.0 mg, 0.053 mmol) and THF (2 mL) was cooled to 0 °C and TBAF (18 mg) (commercially available TBAF was made anhydrous by adding 3A molecular sieves) was added. The mixture was allowed to stir for 45 minutes. After the completion of the reaction, cold water (25 mL) was added and it was extracted in CH₂Cl₂ (3 x 5 mL). The combined organic layers were dried over Na₂SO₄ and the solvent was removed under reduced pressure. The residue was purified by flash chromatography (Hexanes/EtOAc, 3:1) to afford **43** (0.021 mg, 72%) as a colorless oil.

¹H NMR (500 MHz, CDCl₃): δ = 7.36 - 7.26 (m, 20 H), 4.69 - 4.60 (m, 2 H), 4.59 - 4.50 (m, 8 H, CH₂Ph), 3.91 - 3.85 (m, 2H), 3.82 - 3.72 (m, 3 H), 3.65 - 3.60 (m, 2H).

¹³C NMR (500 MHz, CDCl₃): δ = 139.0, 138.0, 137.3, 136.0, 128.6-128.7 (20 C), 85.1, 82.2, 81.8, 81.1, 77.5, 74.5, 74.0, 73.3, 73.2, 72.4, 72.3, 72.2, 72.1, 71.5, 70.5, 69.2, 61.1, 61.6, 59.1, 58.0, 48.8, 46.6. HRMS calcd for C₃₅H₃₈O₆ [M+Na]⁺: 577.2566, found 577.2568.

5.2.8. *tert*-butyldimethyl((2*S*,3*R*,4*S*)-2,3,4-tris(benzyloxy)-4-(2-((benzyloxy)methyl)oxiran-2-yl)butoxy)silane (**44**)

NaH (60% dispersion in mineral oil) (87 mg, 3.66 mmol) was taken in a reaction flask and washed with hexanes. To the flask, DMSO (5 mL) was added and the reaction was stirred for 25 min. Trimethylsulfonium iodide (0.6 g, 2.88 mmol) was then added to the reaction flask and the mixture was refluxed for 30 min. then cooled to room temperature. A solution of **41** (1.6 g, 2.44 mmol) dissolved in DMSO (5 mL) was added to the reaction mixture and it was stirred for 1 h. After the completion of the reaction, cold water (25 mL) was added and it was extracted in CH₂Cl₂ (3 x 10 mL). The combined organic layers were dried over Na₂SO₄ and the solvent was removed under reduced pressure. The residue was purified by flash chromatography (Hexanes/EtOAc, 3:1) to afford **44** (1.05 g, 64%) as a colorless oil.

¹H NMR (500 MHz, CDCl₃): δ = 7.38-7.26 (m, 15 H), 5.15 (dd, *J* = 5.5, 4.0 Hz, 1H), 4.85-4.35 (m, 6H, 3 CH₂Ph), 3.84 (d, *J* = 10 Hz, 1H), 3.78-3.65 (m, 2H), 3.58-3.51 (m, 2H), 2.98-2.84 (m, 2H), 0.9 (s, 9H, CH₃Si-), 0.01 (s, 6H, CH₂Si-).

¹³C NMR (500 MHz, CDCl₃): δ = 139.0, 138.0, 137.3, 128.6-128.7 (15 C), 113.6, 74.3, 73.9, 73.6, 70.7, 70.3, 66.3, 57.8, 51.0, 26.1, 18.60. HRMS calcd for C₃₄H₄₄O₅Si [M+Na]⁺: 583.6, found 583.2.

5.2.9. (4*S*,5*R*,6*S*)-4,5,6-tris(benzyloxy)-3-((benzyloxy)methyl)oxepan-3-ol (**45**)

A solution of **44** (20.0 mg, 0.03 mmol) in THF (4 mL) was stirred 0 °C for 15 minutes. TBAF in THF (0.04 mmol, 0.04 mL) was added and the mixture was warmed to room temperature and stirred an additional 45 minutes. After the completion of the reaction,

cold water (25 mL) was added and it was extracted with CH₂Cl₂ (3 x 5 mL). The combined organic layers were dried over Na₂SO₄ and the solvent was removed under reduced pressure. The residue was purified by flash chromatography (Hexanes/EtOAc, 4:1) to afford **45** (11.3 mg, 68%) as a colorless oil.

¹H NMR (500 MHz, CDCl₃): δ = 7.38-7.26 (m, 15 H), 5.15 (dd, *J* = 5.5, 4.0 Hz, 1H), 4.85-4.35 (m, 6H, 3 CH₂Ph), 3.84 (d, *J* = 10 Hz, 1H), 3.78-3.65 (m, 2H), 3.68-3.61 (m, 2H), 3.46 (s, 1H, OH), 2.98-2.84 (m, 2H).

¹³C NMR (500 MHz, CDCl₃): δ = 139.0, 138.0, 137.3, 128.6-128.7 (15 C), 113.6, 74.3, 73.9, 73.6, 71.2, 70.7, 70.3, 66.3, 57.8, 51.0. HRMS calcd for C₂₈H₃₀O₅Si [M+Na]⁺: 469.2093, found 469.1993.

5.2.10. (2S,3R,4S)-2,3,4-tris(benzyloxy)-4-(2-((benzyloxy)methyl)oxiran-2-yl)butan-1-ol (46)

A solution of **42** (50.0 mg, 0.074 mmol) in THF (10 mL) was stirred at 0 °C for 15 min. TBAF (0.07 mmol, 0.07 mL) was added and the reaction was warmed to room temperature and was stirred for an additional 1 h. After completion of the reaction, cold water (50 mL) was added and it was extracted in CH₂Cl₂ (3 x 10 mL). The combined organic layers were dried over Na₂SO₄ and the solvent was removed under reduced pressure. The residue was purified by flash chromatography (Hexanes/EtOAc, 4:1) to afford **46** (29 mg, 73%) as a colorless oil.

¹H NMR (500 MHz, acetone) δ = 7.36 - 7.27 (m, 20 H), 4.75 - 4.07 (m, 10 H), 4.83 - 4.76 (m, 2H), 3.99 (m, 1H), 3.74 (m 1H), 3.65 (m, 1 H), 2.93 (d, *J*=5.61 Hz, 1 H), 2.82 (s, 1 H), 2.79 (d, *J*=5.61 Hz, 1 H).

HRMS calcd for $C_{35}H_{38}O_6$ $[M+H]^+$: 555.2741, found 555.2741.

5.2.11 (3S,4R,5S)-1,3,4,5-tetrakis(benzyloxy)hept-6-en-2-one (47)

To a suspension of Dess-Martin periodinane (183 mg, 0.43 mmol) in CH_2Cl_2 (5 mL) was added a solution of **2** (80 mg, 0.14 mmol) in CH_2Cl_2 (2 mL) at RT and the mixture was stirred for 30 min. Et_2O (20 mL) and 10% aq $Na_2S_2O_3$ solution (10 mL) were added and the mixture was stirred for 10 min. The phases were separated and the aqueous phase was extracted with Et_2O (2 x 10 mL). The combined organic phases were washed with sat. aq $NaHCO_3$ (15 mL), brine (15 mL), dried over Na_2SO_4 , filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (Hexane- $EtOAc$, 4:1) to afford **47** (70 mg, 91%) as a colorless oil.

1H NMR (500 MHz, $CDCl_3$): δ = 7.33 - 7.23 (m, 20 H), 5.79 (ddd, J =17.24, 10.40, 7.87 Hz, 1 H), 5.34 - 5.29 (m, 2 H), 4.44 - 4.34 (m, 8 H), 4.22 (d, J =8.85 Hz, 1 H), 4.82 - 4.76 (m, 2 H), 3.92 (dd, J =6.77, 3.48 Hz, 1 H), 3.62 (m, 1H).

^{13}C NMR (500 MHz, $CDCl_3$): δ = 206.7, 138.5, 138.4, 138.3, 138.1, 129.3 – 127.5 (20 C), 118.9, 81.5, 81.3, 78.5, 74.7, 73.3, 73.2, 71.3, 70.7, 70.4. MS calcd for $C_{35}H_{36}O_5$ $[M+Na]^+$: 559.0, found 559.2.

5.2.12. (2R,3R,4S,5R)-3,4,5-tris(benzyloxy)-2-((benzyloxy)methyl)-6-methoxytetrahydro-2H-pyran (56)

To the solution of **1** (2.5 mmol) and diiodomethane (0.3 mL, 3.75 mmol) in dry THF (10 mL) at $0^\circ C$ was added dropwise methyllithium (3.4 mL of 1.5 M solution in diethyl ether, 5 mmol) over 5 min. The mixture was warmed to room temperature and was stirred for one additional hour. The resulting mixture was poured on ice and extracted

with DCM (3 x 10 mL). The combined organic layers were dried over Na₂SO₄, filtered, and the solvent was removed under reduced pressure to yield **56** in 56% yield.

¹H and ¹³C NMR data was consistent with literature values.¹⁰¹

5.2.13. (5S,6R,7R)-5,6,7-tris(benzyloxy)-4-((benzyloxy)methyl)-4,8-dihydroxy-1,3-diazocane-2-thione (62)

To a solution of oxalyl chloride (0.6 mL, 6.80 mmol) in CH₂Cl₂ (10 mL) was added a solution of DMSO (1.0 mL, 13.70 mmol) in CH₂Cl₂ (5 mL) via dropping funnel at -78 °C. The reaction mixture was stirred for 5 min and then a solution of **39** (0.6 g, 1.10 mmol) in CH₂Cl₂ (5 mL) was added. It was stirred for an additional 15 min and TEA (triethylamine) (2.3 mL) was added and it was stirred for another 20 minutes. Then the mixture was warmed to -60 °C and thiourea (0.15 g, 1.84 mmol) was added. The reaction mixture was slowly warmed to RT and was stirred for 24 h. Water (15 mL) was added and the aqueous layer was extracted with CH₂Cl₂ (3 X 10 mL). The combined organic layers were dried over Na₂SO₄ and the solvent was removed under reduced pressure. The residue was purified by flash chromatography (Hexanes/EtOAc, 4:1) to afford **62** as white solid (0.26 g, 43%).

¹H NMR (500 MHz, CDCl₃): δ = 7.36 - 7.26 (m, 20 H), 4.90 (d, 2 H), 4.80- 4.47, 8 H), 3.57 (d, *J*=9.33 Hz, 2 H), 3.48 (s, 2 H), 3.41 (d, *J*=9.94 Hz, 2 H), 3.37 - 3.28 (m, 2 H).

¹³C NMR (500 MHz, CDCl₃): δ = 184.6, 138.2, 137.9, 137.3, 137.0, 128.8-127.8 (20 C), 97.45, 81.9, 79.8, 79.7, 78.3, 75.8, 75.6, 75.4, 73.7, 71.3. HRMS calcd for C₃₅H₃₈N₂O₆S [M+H]⁺: 615.2529, found 615.2524.

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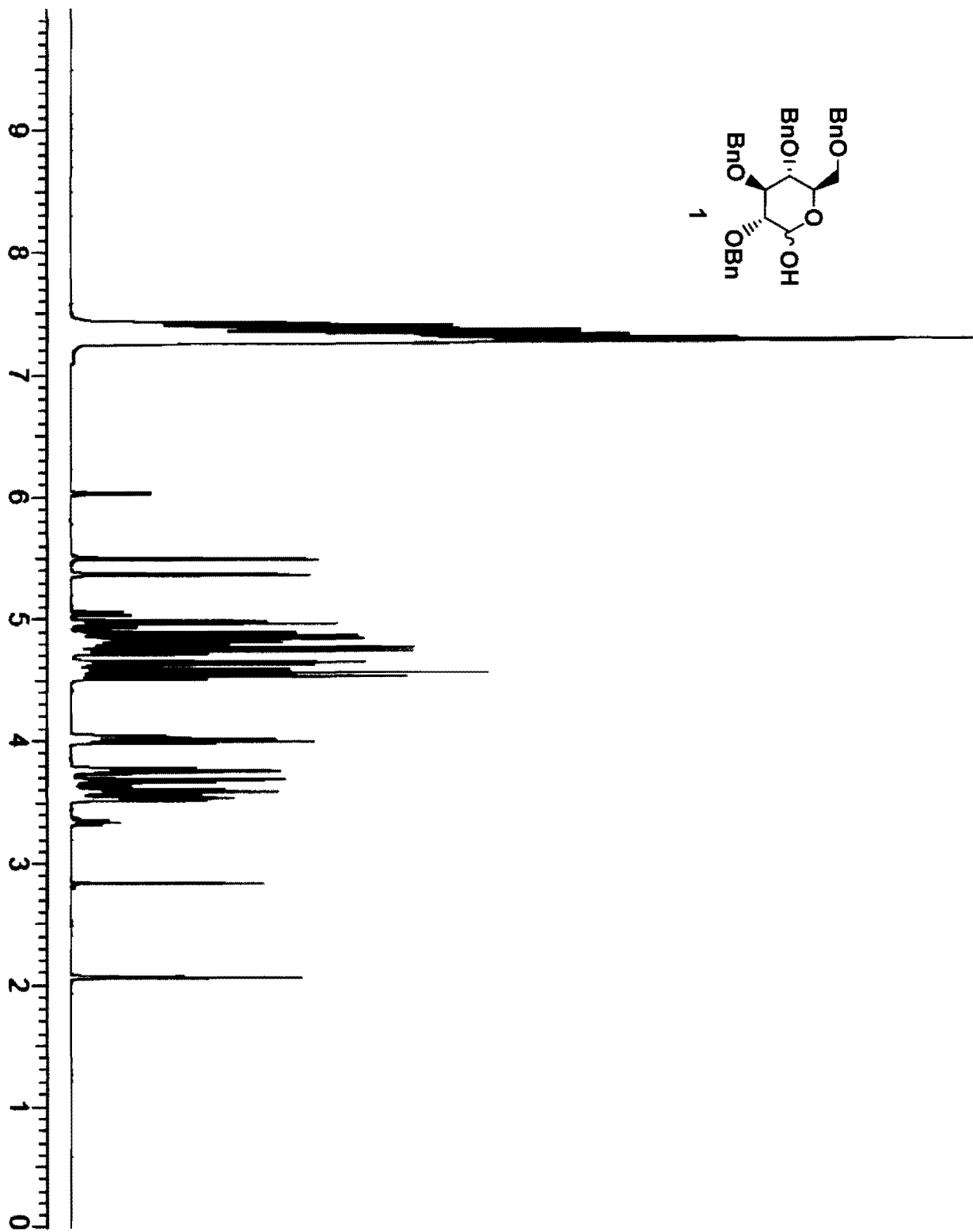
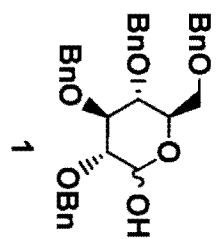
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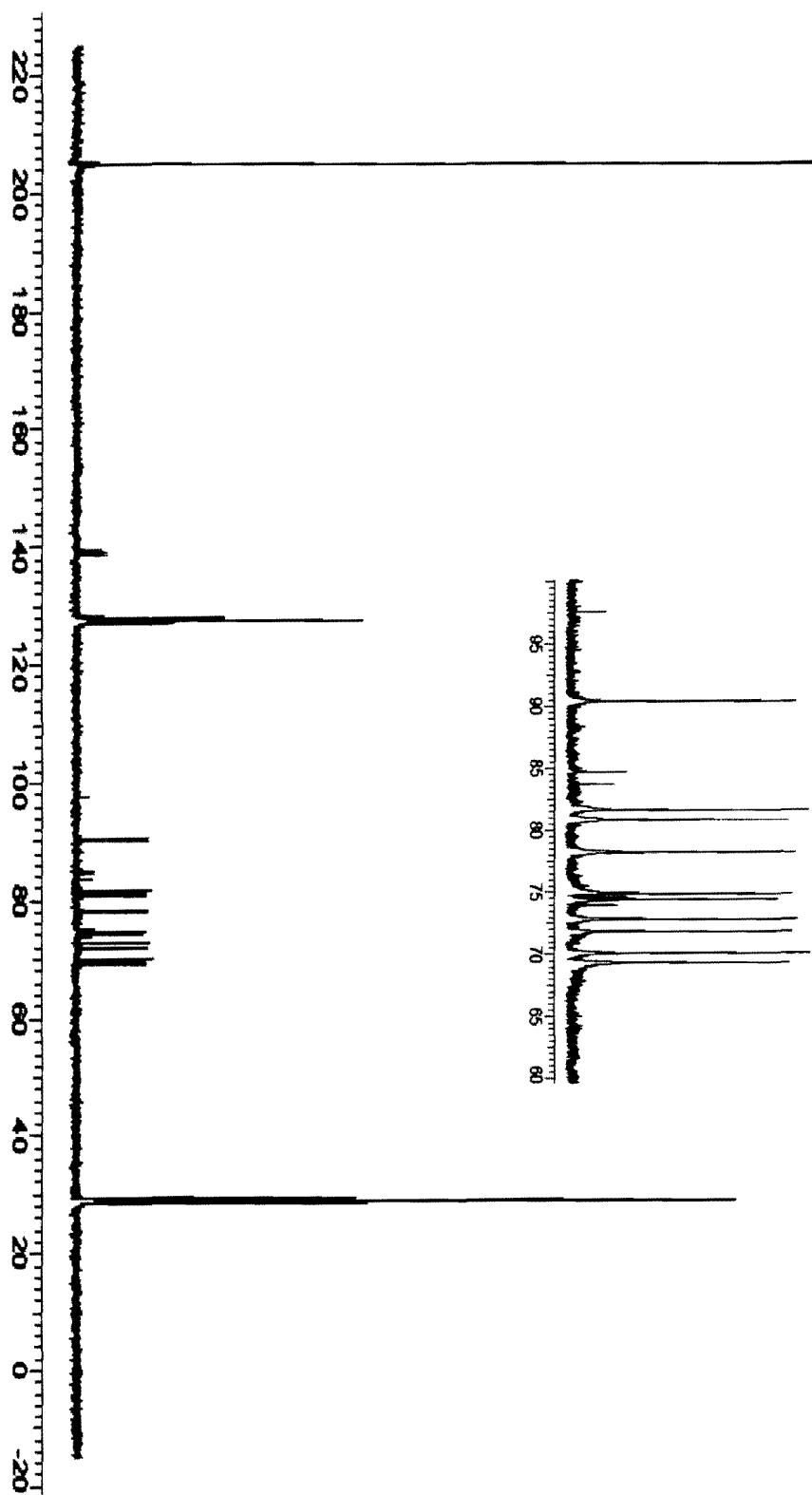
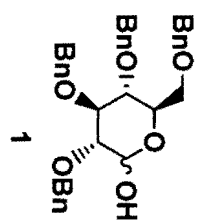
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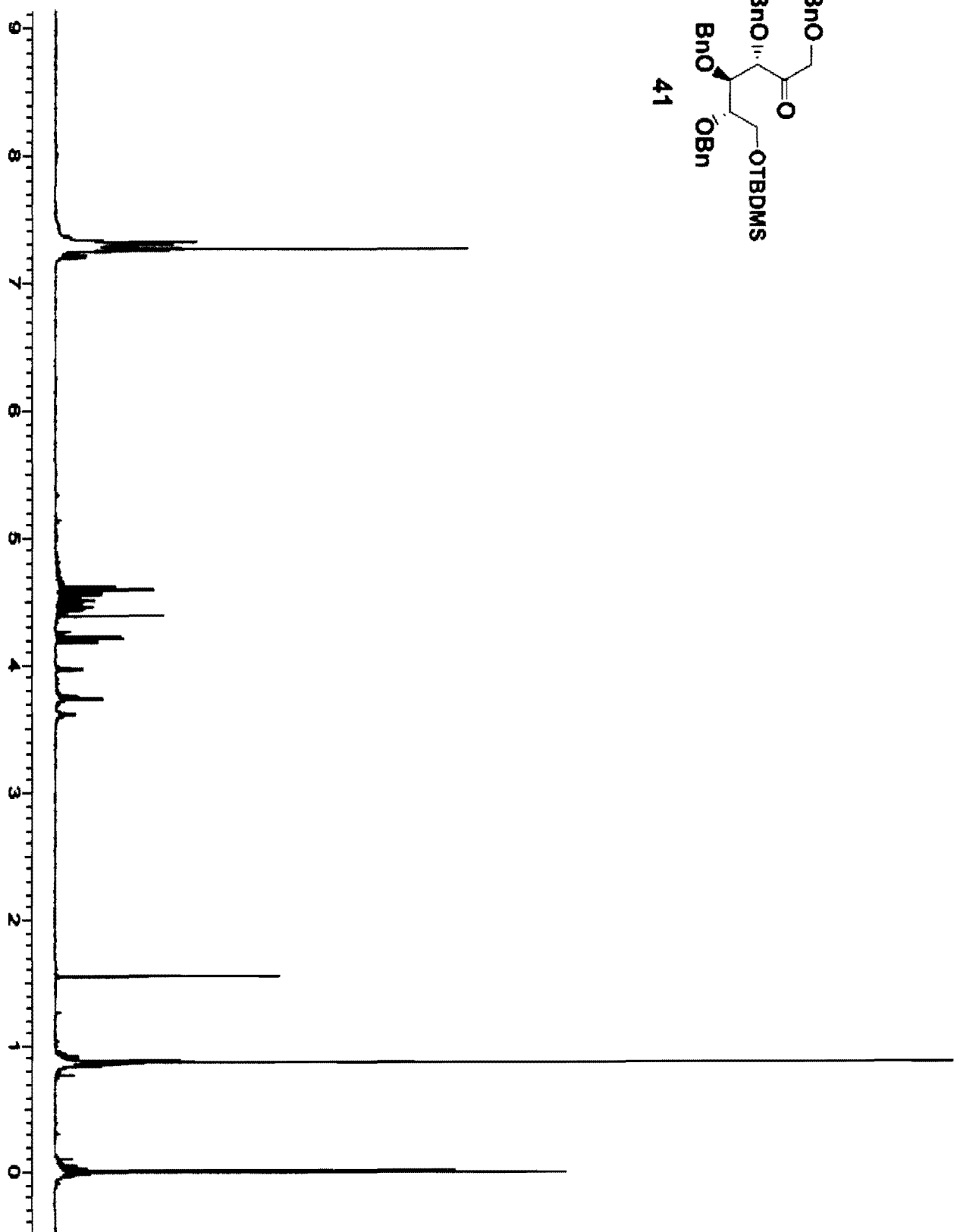
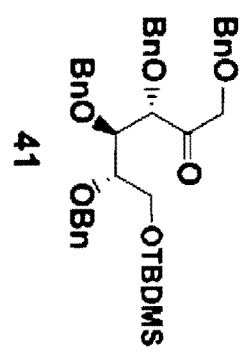
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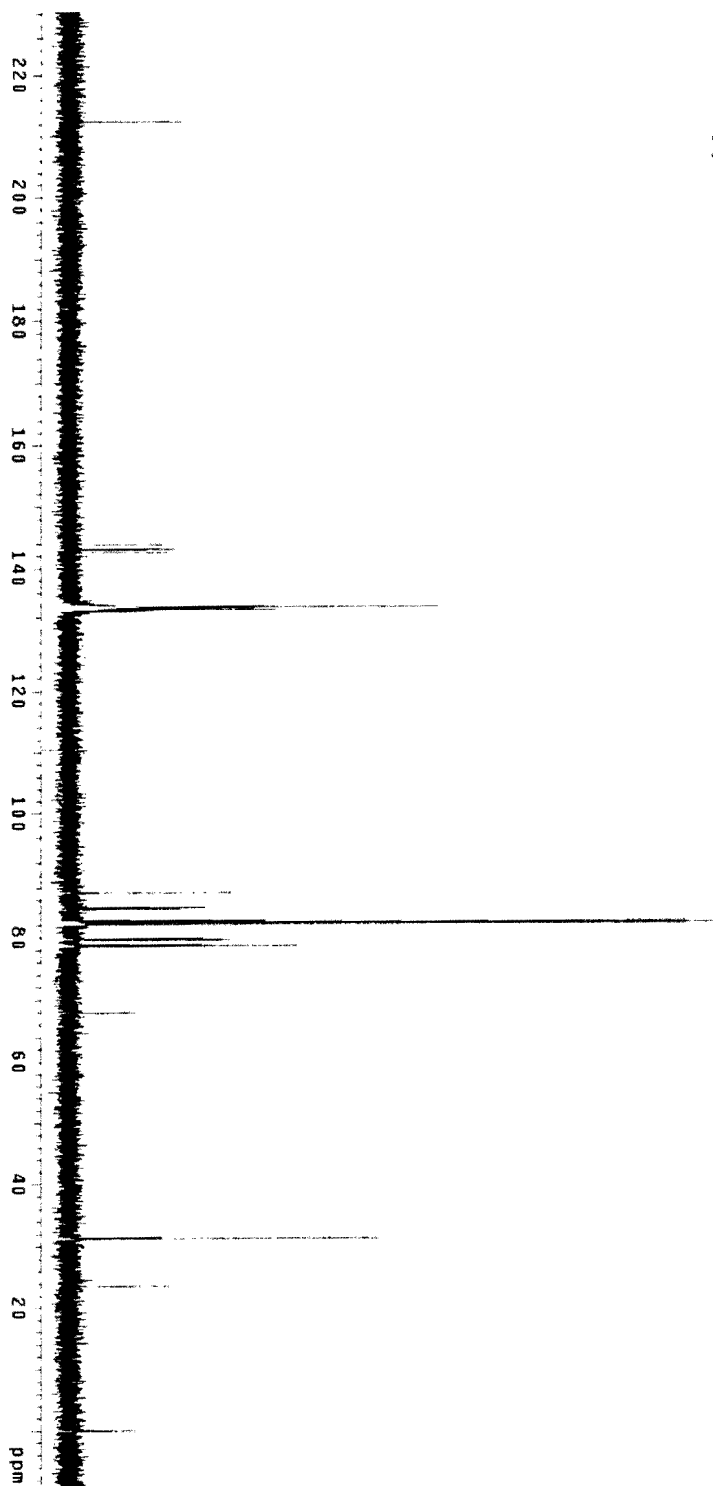
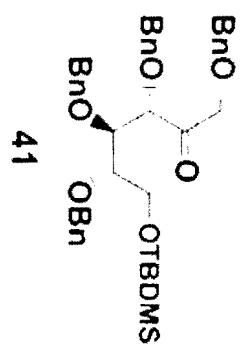
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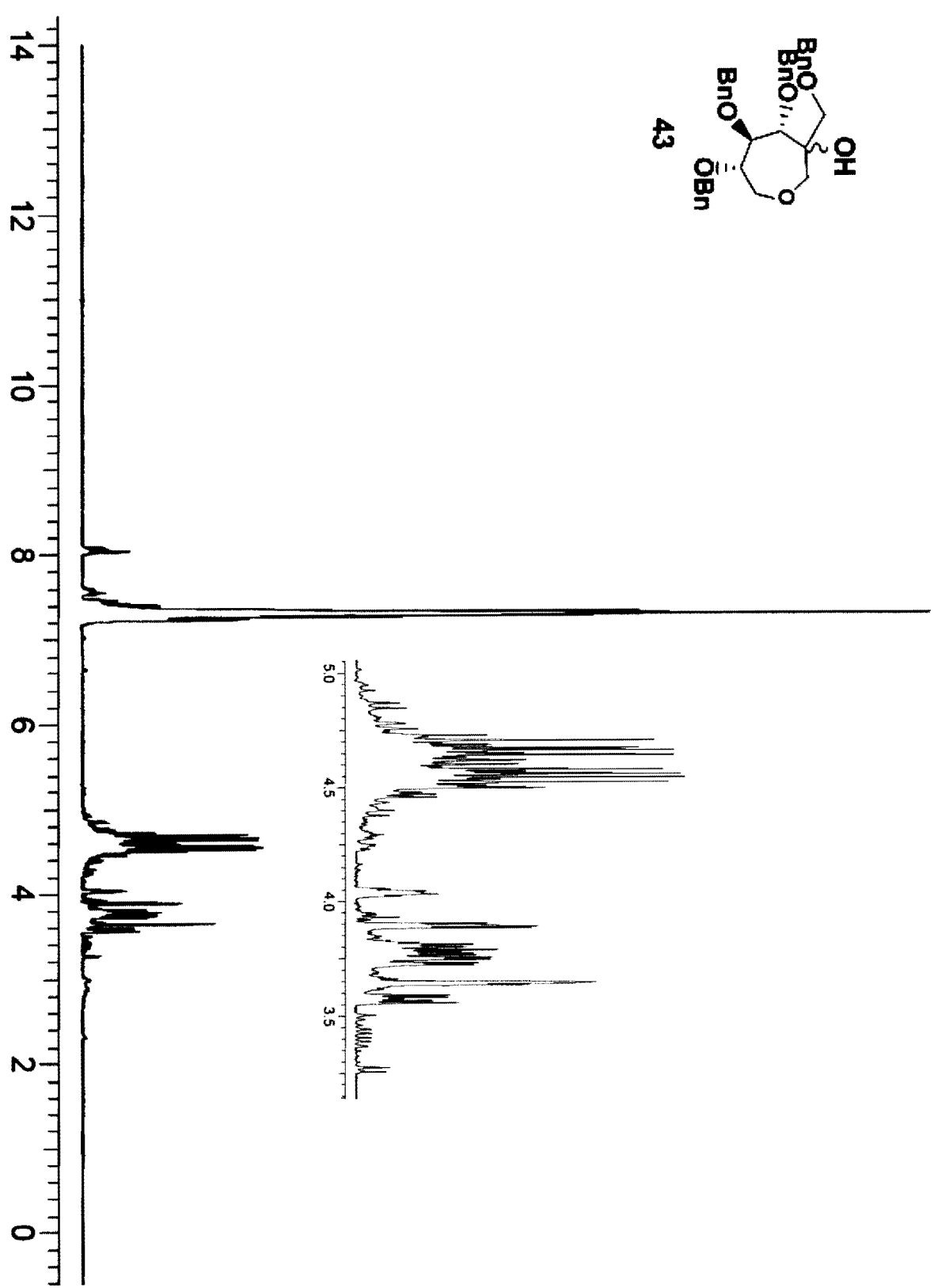
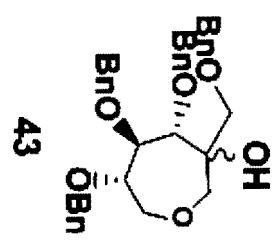
5.4. Appendix (NMR spectra)

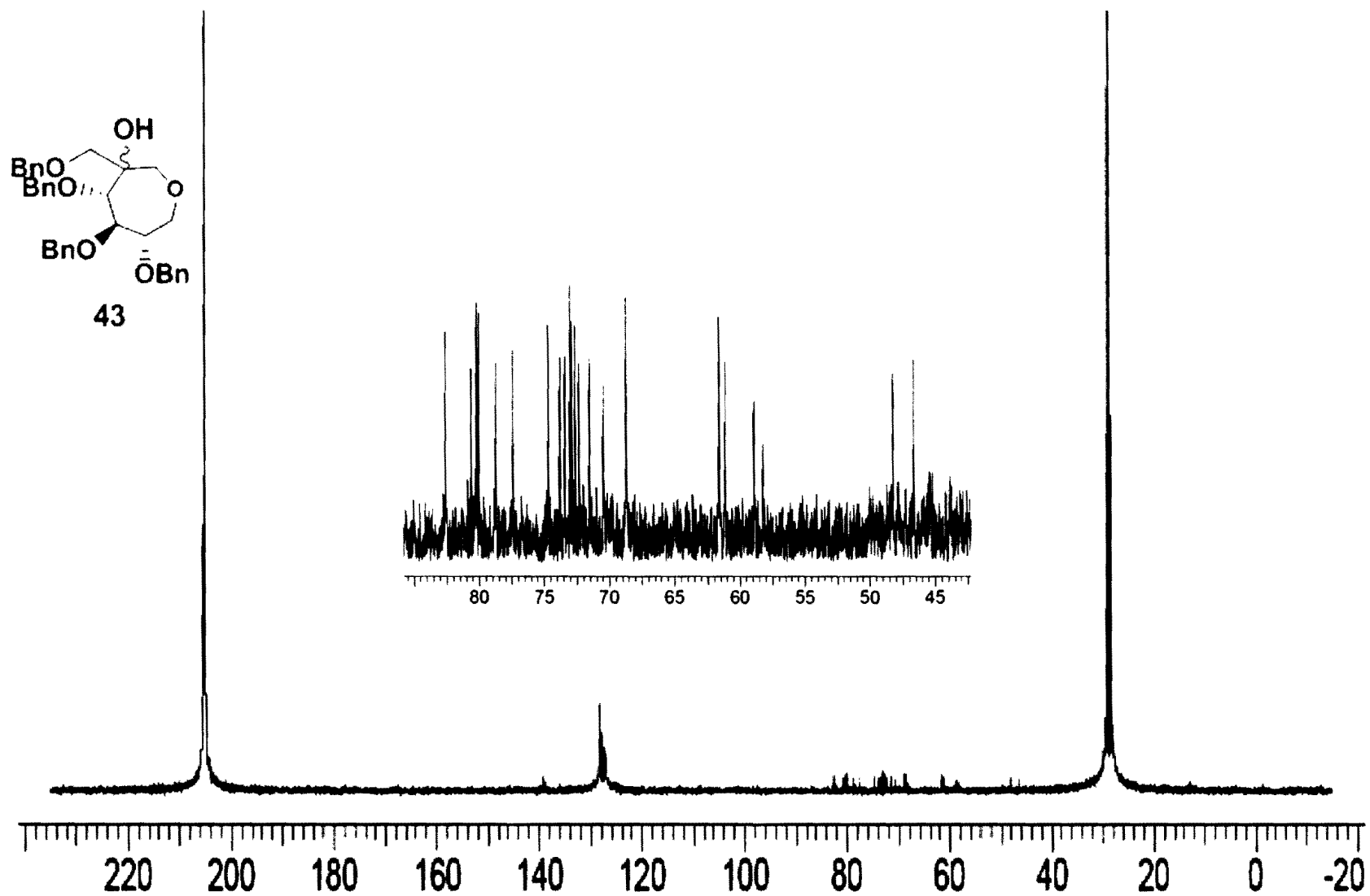




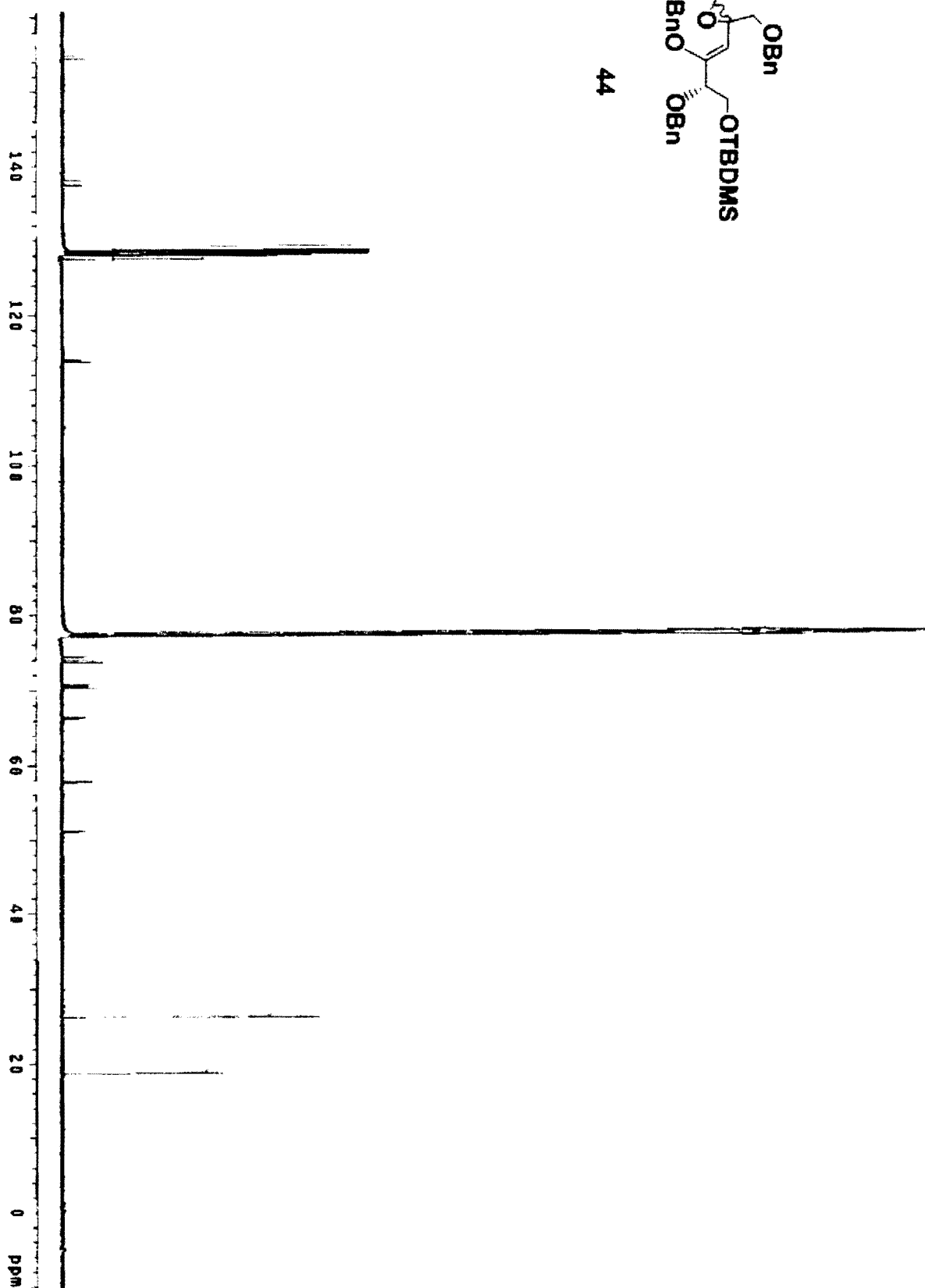
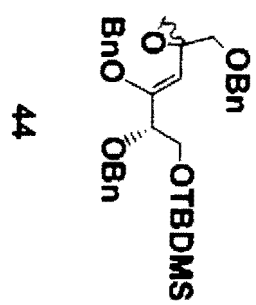


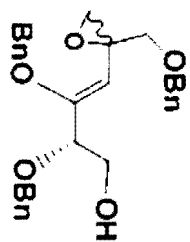




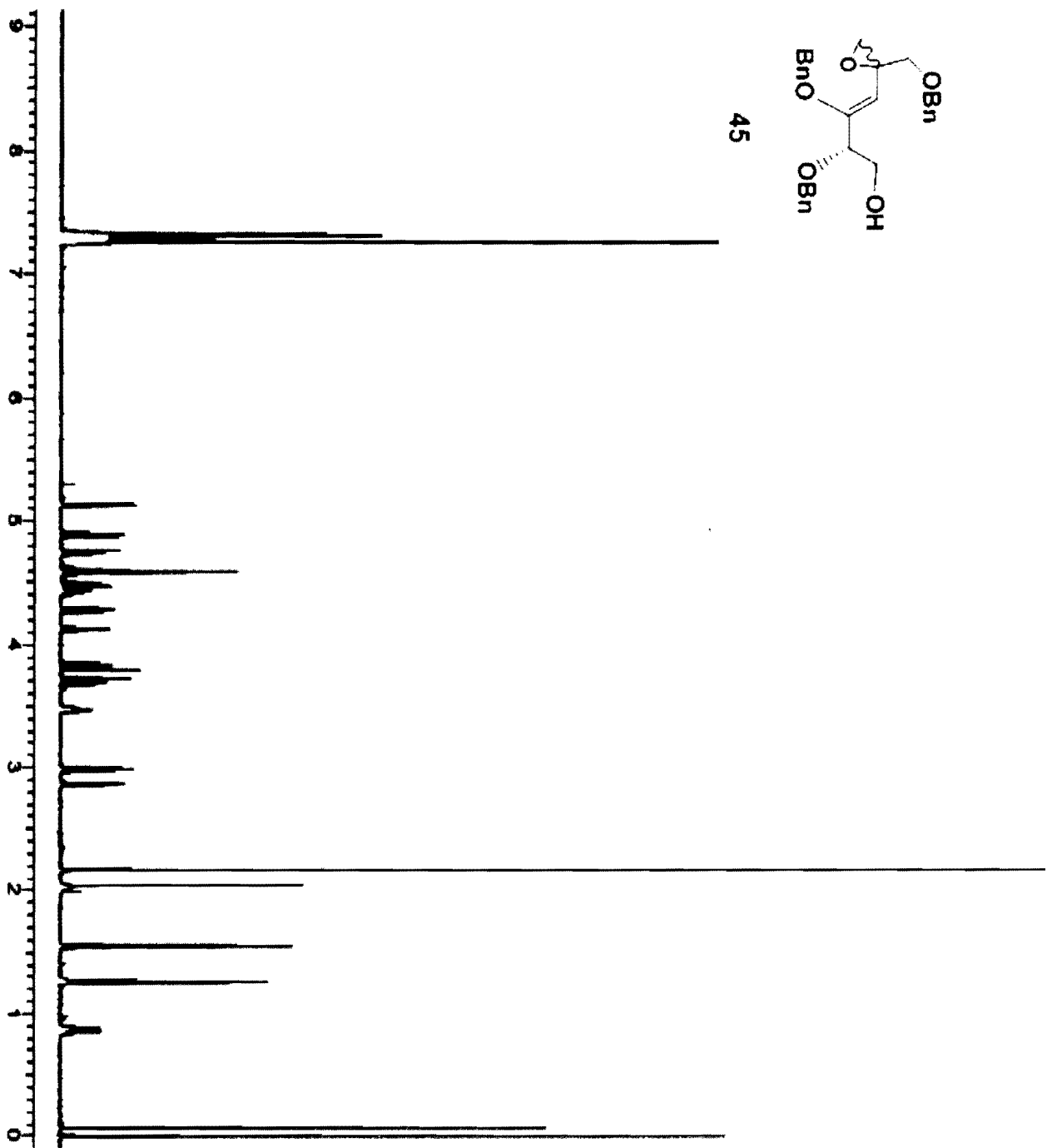


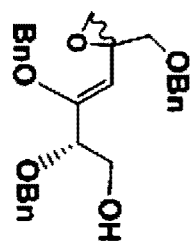






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