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Synthesis of Pyranobenzopyrans

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Synthesis of Pyranobenzopyrans

By

Sumiea B. Eltayeb

Submitted in partial fulfillment of the requirements for the Degree

Doctor of Philosophy

Department of Chemistry and Biochemistry

Seton Hall University

May 2017

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

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Abstract

Synthesis of Pyranobenzopyrans

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Carbohydrates and their derivatives are involved in a wide array of biological processes and are crucial for the survival of living entities. As a result, sugar-based compounds have become attractive scaffolds for drug design. In addition, pyranobenzopyran derivatives have shown promise in the treatment of numerous health conditions such as anticoagulants, antifungal, and anti-inflammatory agents. They have also shown important properties as antibiotics (anti-AIDS agents) and antitumor drugs.

The main point of our research was to determine and develop a synthetic method for the preparation of pyranobenzopyrans and carbohydrate fused heterocyclic compounds. This was accomplished via a [4+2] cycloaddition reaction to generate the oxygen-containing six-membered ring by the addition of the imine *o*-hydroxybenzaldehyde and its derivatives to glucals in organic solvent under catalysis by scandium triflate. The conventional method and microwave reactor method were initially used to achieve this goal, but no reaction was observed. The failure of these reactions may be due to the sugar protecting group such as the acetyl ester. Acetyl could deactivate electronically, where benzyl and

butyldimethylsilyl ethers created steric hindrance and inhibited the reaction. Then new methodology was developed and an ionic liquid was used as a solvent to dissolve the D-glucal and the other reactants. A series of pyranobenzopyrans have been prepared via Lewis Acid catalyzed cycloaddition reactions of D-glucal and *o*-hydroxybenzaldehyde and its derivatives in room temperature imidazolium ion-based ionic liquid solvents. Different *o*-hydroxybenzaldehyde derivatives were tested to study the effect of the substituents in the rate of the reaction. Four products were obtained in poor to moderate yields. Because 2-hydroxy-5-nitrobenzaldehyde, 2-hydroxy-5-methylbenzaldehyde and 2,5-dihydroxybenzaldehyde were insoluble in the ionic liquids, no product was obtained from their reaction with D-glucal. Danishefsky's Diene, 1-methoxy-3-trimethylsiloxy-1,3-butadiene, was also reacted in ionic liquid and the product 2,5,8a-dihydroxy-1(hydroxymethyl)-1,4a,5,6,7,8a-hexahydro-8H-isochromenone was obtained in moderate yield. In these reactions, the glycal itself was found to serve as a diene with another molecule of glycal as the dienophile to form an interesting sugar dimer. All the structures prepared were confirmed by NMR and elemental analyses.

Chapter 1

Introduction

1.1. Carbohydrates

1.1.1. General Structure and Properties of carbohydrates

The term carbohydrates was originally derived in the nineteenth century from the French term (hydrate de carbon) for the family of the compounds possessing the empirical formula $C_n(H_2O)_n$.¹ Carbohydrates are a unique family of poly functional molecules; they exist as monosaccharide building blocks that are linked together in almost limitless ways to form oligosaccharides and polysaccharides.²

Monosaccharides are polyhydroxy -aldehydes or ketones. The most common types of structures are aldoses (Figure 1.1) and consist of linear carbon chains with an aldehyde (CHO) group at C-1 and varying number of carbon atoms that are secondary alcohols (CHOH), and a primary alcohol (CH₂OH) at the terminal end. Ketoses (Figure 1.2) have a primary alcohol at both ends and have a ketone carbonyl (C=O) within the chain at C-2.²

Figure 1.1. Aldoses General Structure.

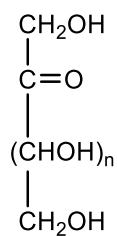
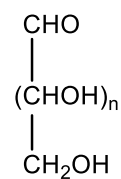
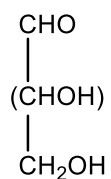


Figure 1.2. Ketoses General Structure.

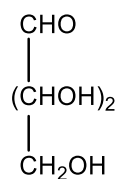


The simplest example of an aldose is glyceraldehyde that consists of three carbons. Higher sugars containing four carbons are known as tetroses, five carbons pentoses, and six carbons hexoses (Figure 1.3).

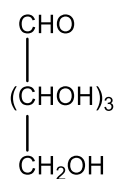
Figure 1.3 Example of Aldoses.



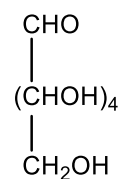
Glyceraldehyde



Tetrose

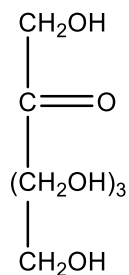


Pentose

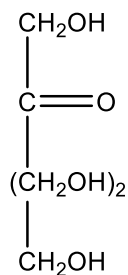


Hexose

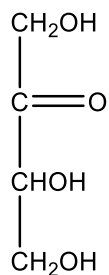
Figure 1.4. Example of Ketoses



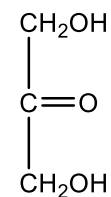
Dihydroxyacetone



Ketotetrose



Ketopentose



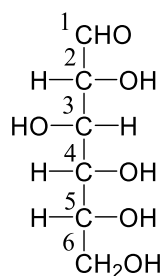
Ketohexose

Each of the carbon atoms that are secondary alcohols have four different groups attached and are stereogenic (or chiral) centers, giving rise to stereoisomers. Although the stereoisomeric diversity is often times problematic and the chemistry of carbohydrates present numerous challenges, their widespread presence in biological systems makes them attractive targets for continued research, especially in the field of therapeutics.³ In addition, carbohydrate products are utilized in food, clothing, and the agrochemical industry.⁴ The importance of carbohydrates to living things can hardly be overemphasized. The energy stores of most animals and plants are both carbohydrate and lipid in nature; carbohydrates are generally available as an immediate energy source, Glucose, the prevalent uncombined, or free, sugar circulating in the blood of higher animals, is essential to cell function. The proper regulation of glucose metabolism is of paramount importance to survival.³

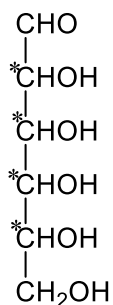
1.1.2 The Structure and Properties of Glucose.

The structure and properties of glucose will be considered in greater detail than those of the other monosaccharides. Glucose is an aldohexose, which means the structure has a six-carbon sugar with a terminal aldehyde group. From the formula $C_6H_{12}O_6$ sixteen possible configurational isomers are known- some occur naturally and the others have been synthesized. This problem of identifying glucose as a particular one of the sixteen possibilities was solved by Emil Fischer during the latter part of the nineteenth century, and he was awarded the Nobel Prize in chemistry in 1902.⁴ Fischer established the fundamental

groundwork that provides the basis of the structure of the enantiomer of natural glucose shown in the projections of the formula **1** and formula **2**.



1



2

The great difficulties of working with carbohydrates, are: their considerable solubility in water, their instability to strong oxidizing agents and acidic or basic reagents, their reluctance to crystallize, and their tendency to decompose rather than give sharp melting points.⁴

1.1.3. Ring Structure of Monosaccharides

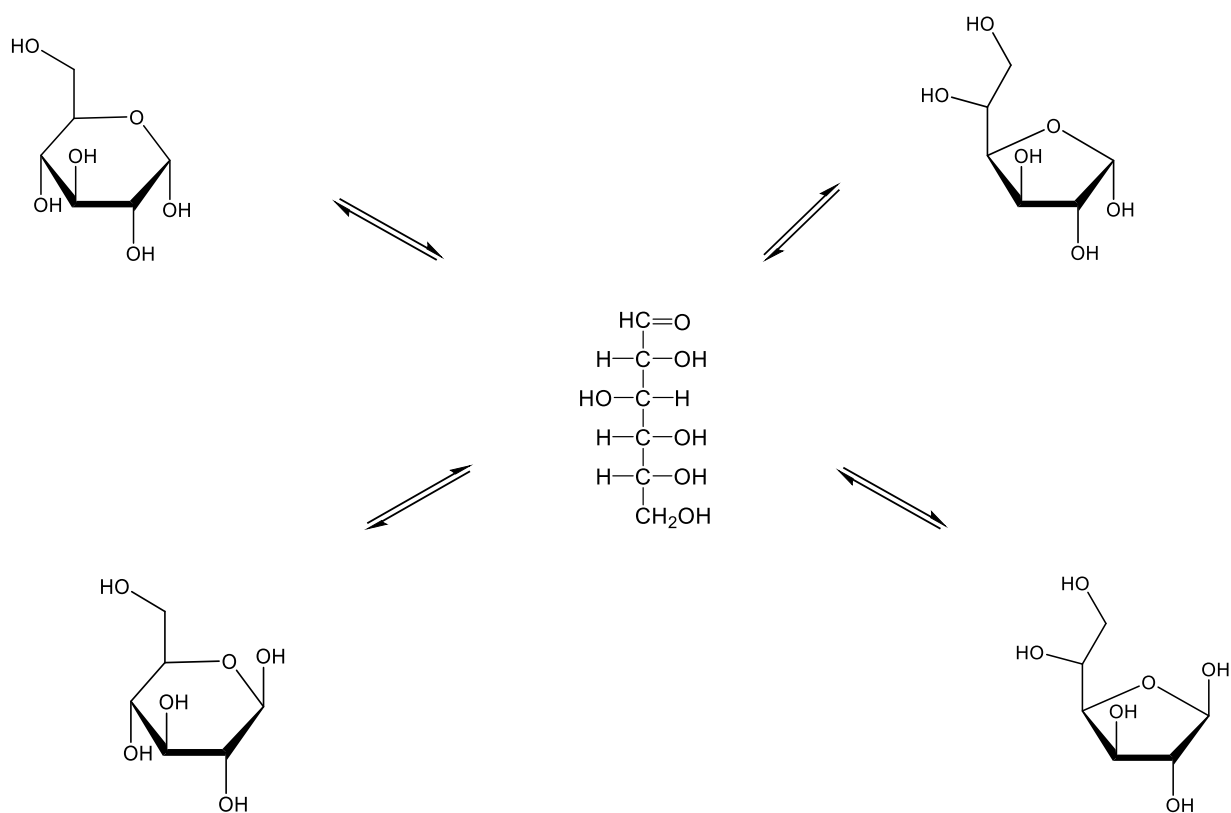
Any given mixture of an aldehyde and alcohol is in equilibrium with a hemiacetal, a process which forms a new stereogenic center. Since carbohydrates have both carbonyl and hydroxyl functions they are capable of forming intramolecular hemiacetals, known as lactols.² The cyclic form occurs because of 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.

1.1.4. Six-Membered Cyclic Pyranoses and Five-Membered Cyclic Furanoses.

Pyranoses and furanoses forms are further subdivided on the basis of how they

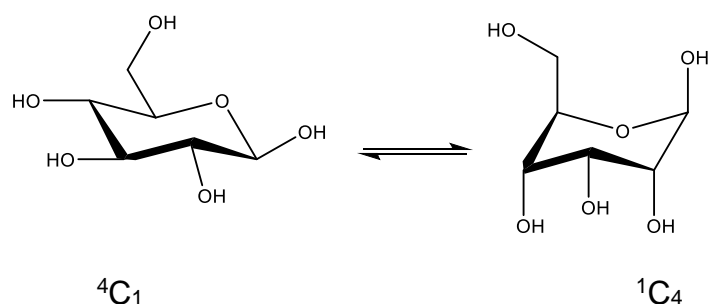
cyclize. During the cyclization, the anomeric carbon (the hemiacetal carbon atom originating from the carbonyl oxygen) becomes a stereogenic center with two possible configurations α or β . (figure 1.5) depending on the way they cyclize. The resulting isomers are called anomers and the interconversion of the anomers in solution 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 anomers, when the corresponding stereocenters interconvert. Cyclic sugars show mutarotation as α and β anomeric forms interconvert. In aqueous solution, D-glucose exists as a mixture of 38% α and 62% β (Figure 1.6). The β is favored because all of the hydroxyl groups are in equatorial position on the ring, while in α anomer, one hydroxyl group is forced into the axial position which causes higher energy in the molecule and makes it less stable.²

Figure 1.5. Configuration of the Hydroxyl Group at the Anomeric Carbon



Another equilibrium process that is characteristic of sugars is conformational interconversion of the cyclic ring, where the six-membered ring can undergo an equilibrium between different chair conformations. For glucopyranose, the ${}^4\text{C}_1$ conformation is preferred because all the hydroxyl group substituents are in the equatorial position while ${}^1\text{C}_4$ conformation has all the hydroxyl groups in the axial position.

Figure 1.6. Conformational Conversion of the Cyclic ring



1.1.5. The Biological Importance of Sugars.

Carbohydrates are one of most abundant biomolecules on the Earth and they are involved in many essential biological processes: they act as an energy source, in biological signaling and recognition mechanisms and as basic structural building blocks controlling the architecture of nature. For example, sugars are integral parts of DNA, RNA, starch, cellulose and chitin (insect and lobster shells). D-glucose is central to several biochemical pathways. For example, it is the major fuel of most organisms and occupies an essential position in both anabolic and catabolic reactions. Glucose is the product of photosynthesis carried out by plants whereby energy from sunlight is converted into chemical bonds (Scheme 1).⁶



Glucose is a building unit for many disaccharides, for example sucrose (commonly known as table sugar) consists of glucose and fructose. Starch is a polymer of glucose units, consisting of a mixture of amylose (linear) and amylopectin (branched), is used in plants for energy storage. It is found in the

tuber, roots, fruits and seeds of plants. Glycogen is a highly branched, high molecular weight polymer of D-glucose that is the mammalian counterpart to starch. It serves as an abundant energy storage form of carbohydrates, and occurs widely in nature.² Sugars can also play important roles in other biological activities such as signals communication both within and between cells.¹ The correct carbohydrate structures on cell surfaces are also necessary for the fertilization of eggs by sperm and for development of embryos.¹ Many carbohydrates in the cell are covalently bound to proteins or lipids that are coated on the surface of the cells where they act as recognition molecules for viruses, and other pathogens.⁷

Complex carbohydrates are chains of monosaccharides, often called glycans. The carbohydrates attached to proteins are known as glycoproteins, whereas the ones conjugated to the lipids are glycolipids. Glycans are involved in a variety of biological processes including protein folding and signaling events. Unlike DNA and proteins, however, monosaccharides, may be linked to one or more other monosaccharides, such that they form a branched tree structure.⁶

1.1.6. Carbohydrate-Based Drugs.

A relatively untapped source of new chemical entities of drugs comes from the area of functional carbohydrates. All cell surfaces are coated with complex carbohydrates which extend much further out from the cell than the protein layer. These intricate molecules act as recognition molecules, not just for other cells, but also for pathogens that must identify and bind specific cell types for successful infection. On the cell surface, they form layers known as glycocalyx

ranging from 10 to 100 nm in thickness and thus extending much further out from the cell surface than proteins.⁷

These O- and N-glycans are present in many different molecular forms including glycoproteins, proteoglycans, glycolipids, and glycosphosphatidylinositol-linked proteins. Their broad diversity originates from their assembly from monosaccharide building blocks, which can be linked with others at various positions on their pyranose/furanose rings. In addition, branched structures are formed because each ring can establish several linkages.⁸ Finally, the density of structural information is further increased by the possibility of α - and β -isomers at the anomeric center. These chemical characteristics bestow carbohydrates with optimal properties that are desired for recognizing molecules. Certain proteins (called lectins) have evolved three-dimensional domains (called carbohydrate-recognition domains CRD) that can bind specific carbohydrate structures and thus decode this information.⁸ Cell surface carbohydrates involved in specific cell- to- cell recognition exhibit biological phenomena like cell adhesion, cell activation, inflammatory migration, neurite outgrowth, and cancer metastasis.¹ Pathogens including viruses, bacteria, and even parasites infect their host cells by recognizing and binding to specific carbohydrates and cell surfaces. Perhaps the most popular examples are the influenza viruses, which are designated by viral coat proteins hemagglutinin (H) and neuraminidase (N). Both of these viral proteins, in fact, bind specific carbohydrate sequences on the host cell surfaces. Antibodies that recognize carbohydrates and promote disease are identified as therapeutic targets in autoimmune disease.⁹ “The identification of functional

carbohydrate epitopes and their corresponding specific carbohydrate-binding proteins as new targets for drug development is emerging at a rapid rate due to concerted worldwide efforts to organize and support technologies for elucidating the human “glycome”.⁹ While carbohydrates act as excellent recognition molecules on cell surfaces, many of their intrinsic properties make them poor choices for small molecule drugs.¹⁰ In many cases the binding affinities of monovalent carbohydrates are in the millimolar to micromolar range and are therefore relatively weak and usually not adequate to compete with multivalent interactions. The general hydrophilic nature of carbohydrates and their higher density of hydroxyl groups work against the lipophilicity required for passive absorption through the intestine.⁸

1.1.7. The Application and the Categories of Carbohydrate Drugs.

The pharmacokinetic properties of absorption, distribution, biotransformation and excretion are important areas of focus in the field of drug discovery. This is, especially true when dealing with sugar-based compounds.¹⁰ The ability to generate structure activity relationship (SAR) data while balancing stability, solubility, molecular weight, lipophilicity and metabolism is extremely important in the “hit to lead” process. Although high throughput methodology and combinatorial libraries hold many advantages for drug discovery, natural product modification has the potential to provide improved structures for drug discovery and to provide improved structural diversity. Often, sugar-based compounds have enhanced activity against specific targets.³

A few dozen FDA-approved prescription drugs contain carbohydrate moieties as part of their structures. These drugs can be divided into five categories, listed below:

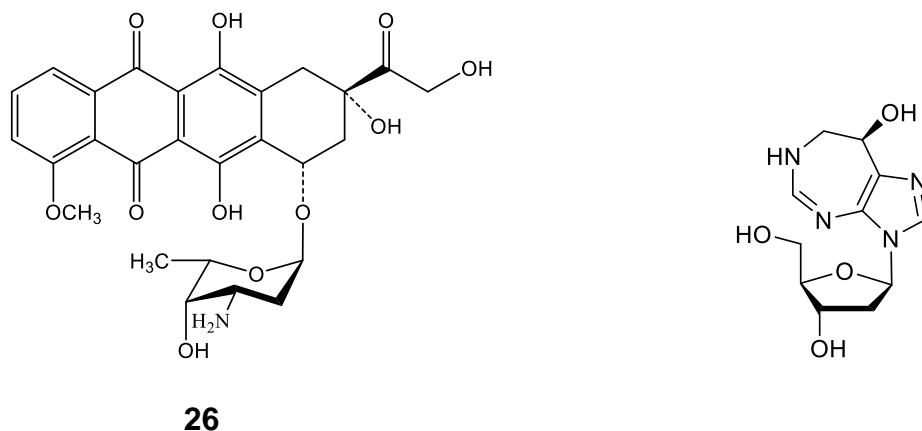
- 1- Monosaccharide Conjugates.
- 2- Disaccharides and their Conjugates.
- 3- Trisaccharides and their Conjugates.
- 4- Oligosaccharides and Polysaccharides
- 5- Macrolides

1.1.7.1. Monosaccharide Conjugates

Monosaccharide Conjugates can be divided into four groups:

1) Anthracycline antibiotics **26** and agents, 2) Nucleotides and nucleosides and their analogs (for example an antitumor drug, 3) polyenes and the forth group of monosaccharide drugs that contains a number of assorted compounds such as Pentostatin **27**, that inhibits RNA and DNA Synthesis by being a direct inhibitor of enzymes adenosine deaminase and ribonucleotide reductase, particularly in cells of the lymphoid system).^{12,13}

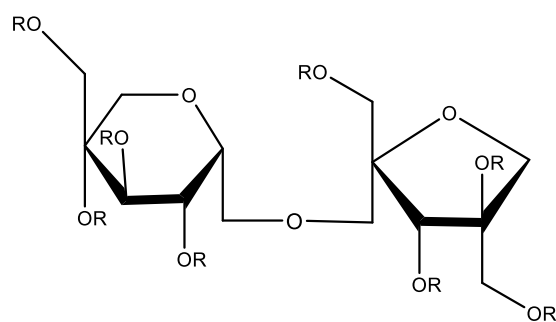
Figure 1.7. Monosaccharide Conjugates



1.1.7.2. Disaccharides and their Conjugates.

The next subcategory of prescription carbohydrate drugs is disaccharides and their conjugates. A good example of these is sucralfate **28**, which is a β -D-fructofuranosyl- α -D-glucopyranoside basic aluminum sucrose sulfate complex. It accelerates healing of duodenal ulcers, in part by inhibiting pepsin activity in gastric juice. A synthetic colonic acidifier Lactulose **29**, (Figure 1.8) 4-O- β -D-galactosyl-D-fructose, promotes laxation.¹²

Figure 1.8. Disaccharides and their Conjugates.

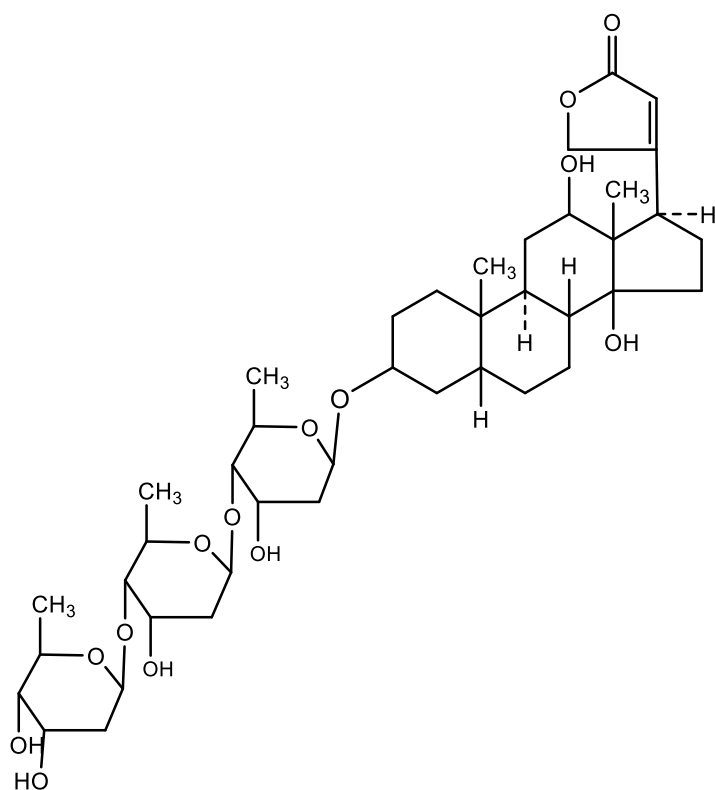


29

1.1.7.3. Trisaccharides and their Conjugates

The third category, trisaccharides and their conjugates, is represented by two prescription drugs; an antibacterial aminoglycoside antibiotic of microbial origin, Tobramycin, and a cardiac glycoside, Digoxin **30**. The latter drug belongs to a closely related group of drugs of plant origin that contains a sugar and a cardenolide; the sugar part consists of O-2,6-dideoxy- β -D-ribo-hexapyranosyl-(1->4)-O-2,6-dideoxy-beta-D-ribo-hexapyranosyl-(1->4)-2 ... -. ¹³

Figure 1.9. Trisaccharides and their Conjugates.



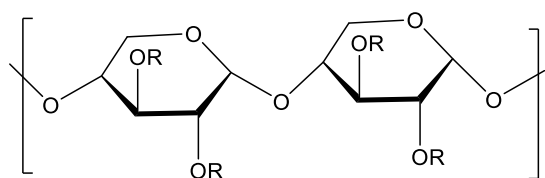
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1.1.7.4. Oligosaccharides and Polysaccharides.

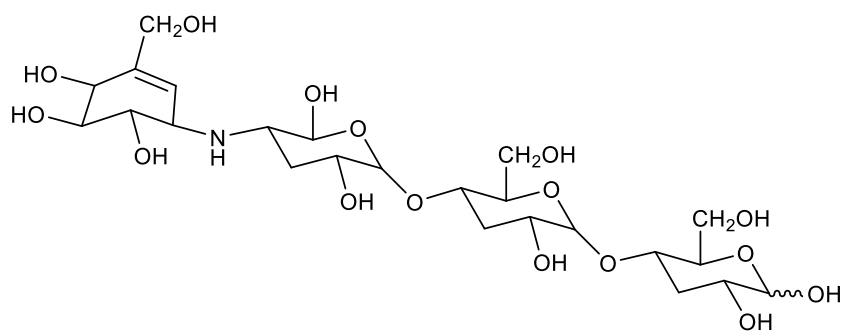
Oligosaccharides are saccharide polymer containing a small number typically two to ten of simple sugars (monosaccharides). and polysaccharides are complex carbohydrates consist of more than ten of monosaccharides. The main monosaccharides in their building blocks are glucose, fructose and galactose,² also known as simple carbohydrates. Prescription drugs made of oligosaccharides and polysaccharides include two principal groups, heparin and heparin-like saccharides. Heparin is a heterogeneous group of glycosaminoglycans, straight-

chain anionic mucopolysaccharides that have anticoagulant activity. Pentosan **31** polysulfate is a semi-synthetic sulfated heparin-like oligomer. Composed of β -D-xylopyranose residues, it shows anticoagulant and fibrinolytic effects.¹² The complex oligosaccharides, can be represented by acarbose **32**. This compound derives from a microbial origin. It inhibits α -glucosidase and delays the digestion of ingested carbohydrates, making the drug beneficial for the management of type 2 diabetes mellitus.¹²

Figure 1.10. Oligosaccharides and Polysaccharides.



31

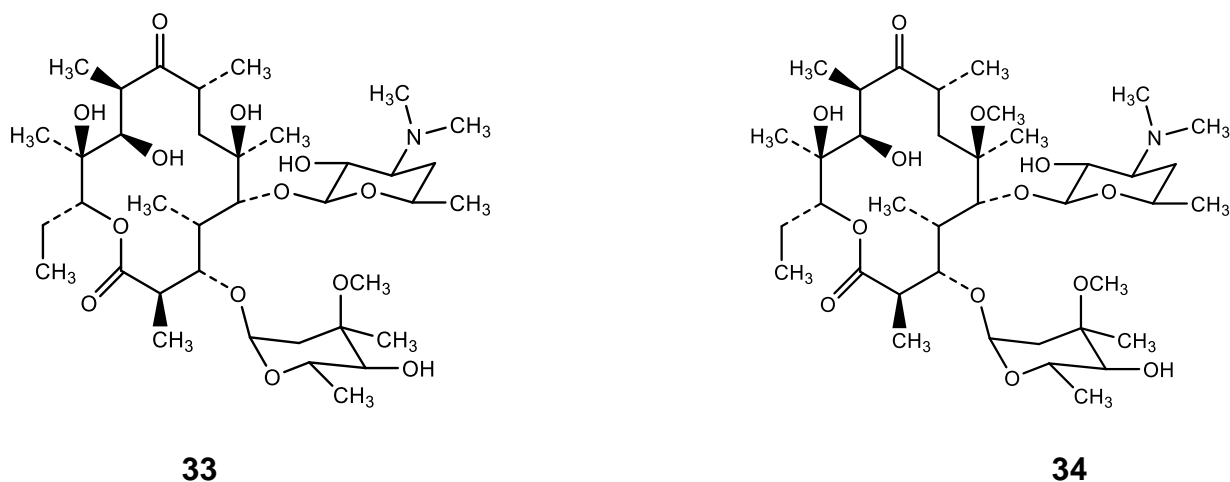


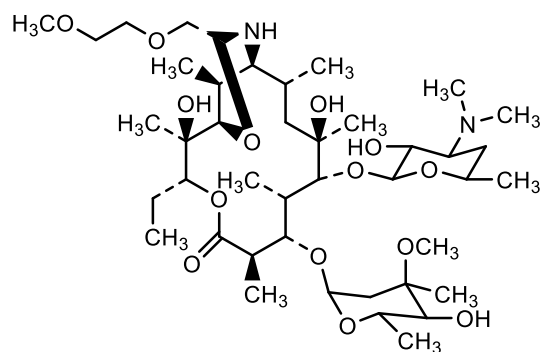
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1.1.6.5. Macrolides.

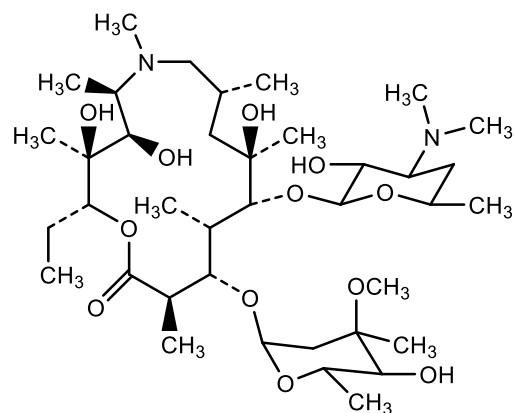
The final subcategory of prescription carbohydrate drugs is represented by macrolide group of antibiotics. Erythromycin **33**, is of microbial origin; it appears to inhibit protein synthesis in susceptible organisms by binding to ribosomal subunits and thereby inhibiting translocation of aminoacyl transfer-RNA. The other three Clarithromycin **34**, Dirithromycin **35**, and Azithromycin **36** are semi-synthetic macrolide antibiotics derived of Erythromycin. Dirithromycin is a pro-drug that is transformed during intestinal absorption into an anti-bacterial active form, Erythromycylamine. Clarithromycin is 6-O-methylerythromycin. Azithromycin is *N*-methyl-11-aza-10-deoxo-10-dihydroerythromycin".^{12,13}

Figure 1.11 Macrolides





35



36

1.1.6.6. Summary.

Carbohydrates are the most abundant molecules in natural products. The word carbohydrate is derived from the observation that simple sugars are hydrates of the element carbon. Carbohydrates are main energy source for mammals, the major constituents of the shells of insects, and the supporting tissue of plants. Carbohydrate chemistry has been a topic of interest and carbohydrate derivatives are attractive for drug design because of their unique structure and biological activity. Cell surface carbohydrates are involved in recognition, fertilization, signal transduction, Multiple stereocenters and numerous hydroxyl functional groups make carbohydrates a diverse class of structurally unique compounds. Glucose is biologically-significant monosaccharide involved in metabolic and energetic pathways. A large number of carbohydrates and carbohydrates derivatives are used as therapeutics. Understanding the bioactive conformation of sugars and carbohydrates-protein interactions, allows for the rational design of small drug-

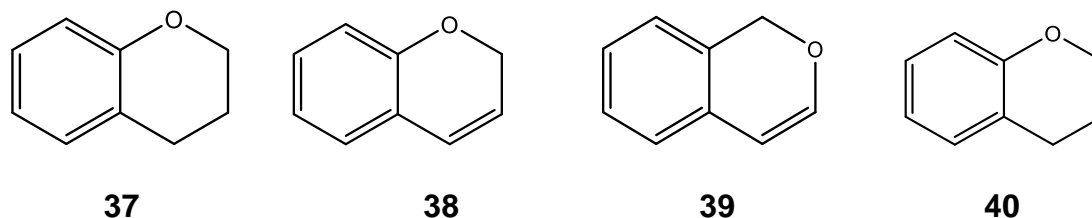
like molecules with increased affinity, stability, and bioavailability. In addition to therapeutics, carbohydrates are important in the paper and textile industries. As the result of the prevalent importance of carbohydrates, there is a significant future for basic research involving carbohydrates.

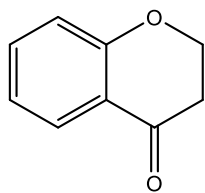
1.2. Benzopyrans.

1.2.1. General structure and properties of benzopyrans.

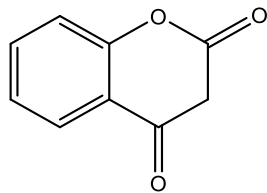
The chemistry of heterocyclic compounds is one of the most complex branches of organic chemistry. It is equally interesting for its theoretical implications, for the diversity of its synthetic procedures,¹⁴ and for the physiological and industrial significance of heterocyclic compounds. Among all heterocyclic compounds, oxygen heterocycles are special because of their wide occurrence in nature and broad pharmaceutical significance. Benzopyrans appear as an important structural components in various natural products, and mainly consist of a benzene ring fused to a pyran ring.¹⁵ Benzopyrans can be classified according to their various levels of saturation and oxidation, namely , chromane **37**, 2H-chromene **38**, 1H-isochromene **39**, 4H-chromene] **40**, 4- chromanone **41**, 2,4-chromanedione **42**, and chromone **43**

Figure 1.12. Examples of Different Levels of Saturation and Oxidation of Chromanes

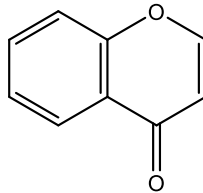




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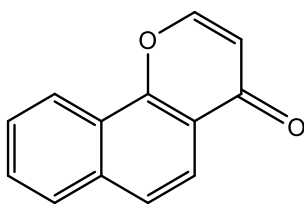


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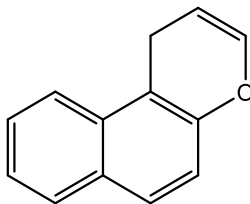


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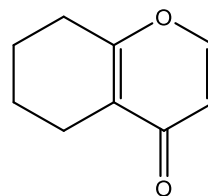
In addition to functional derivatives of these ring systems, compounds in which a benzene or other carbocyclic ring is fused to the benzene ring for example, benzochromones **44**, naphthopyrans **45**, reduced chromones **46** and spiro compounds **47** are also common in nature.¹⁴



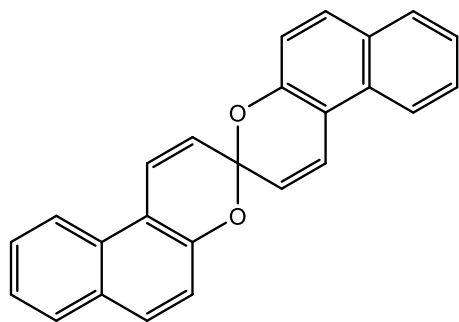
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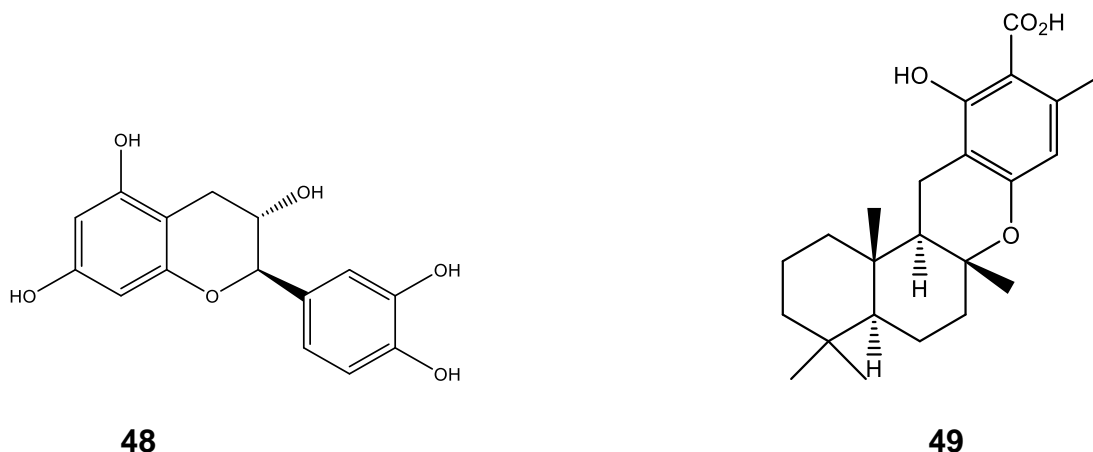


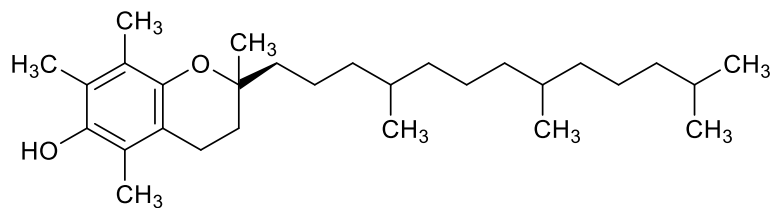
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1.2.2. Benzopyran Biological Activities.

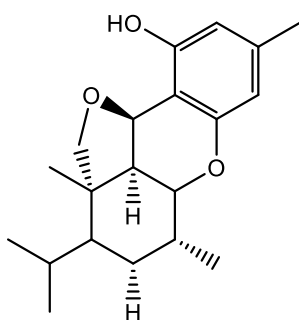
Benzopyrans (Chromenes) are one of the privileged medicinal pharmacophores that appear as important structural components in natural compounds and have generated great attention because of their interesting biological activity.¹⁵ It is a heterocyclic ring system consisting of a benzene ring fused to a pyran ring. Chromenes constitute the basic backbone of various types of polyphenols and widely found in natural alkaloids, tocopherols, flavonoids, and anthocyanins.¹⁶ It is known that certain natural and synthetic chromene derivatives possess important biological activities such as: antitumor (Catechin) **48**, antibacterial (Hongoqercin) **49**, antivasular,¹⁷ antiviral, antimicrobial,¹⁸ antioxidant,¹⁹ (Tocopherol) **50**, as TNF- α inhibitors,²⁰ antifungal, (Siccanin) **51**.²¹ anticoagulant, antispasmodic,²² estrogenic,²² antiviral,²³ anti-helminthic,²⁴ anticancer,²⁴ anti-HIV (Calanolide A) **52**,²⁵ antitubercular,²⁶ anti-inflammatory,²⁷ herbicidal, analgesic and as anticonvulsants.²⁸ A key feature is that the lipophilic nature of the benzopyran derivatives helps them to cross the cell membrane easily.^{29, 30}

Figure 1.13. Examples of biologically active compounds.

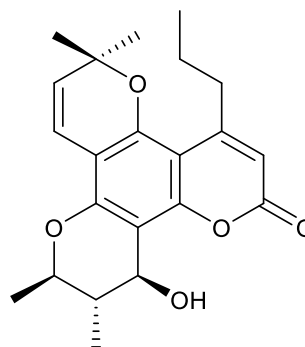




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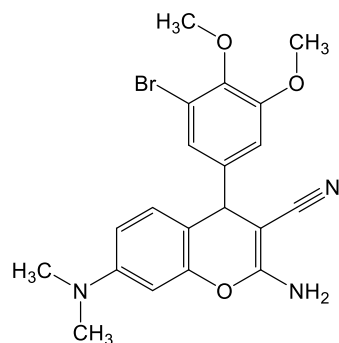
12.2.31. Anticancer Activity Of Chromenes.

Cancer constitutes the second main mortality cause in the world.³¹ Cancer is a disease characterized by the uncontrolled growth of abnormal cells. It is documented that the most cytotoxic anticancer agents induce apoptosis which is programmed cell death. Chromene derivatives are an attractive template for the identification of potential anticancer agents.³² In recent years, there has been much interest in this class of compounds and their potential utility as anti-cancer drugs. Many natural compounds contain chromene moieties that have been reported with anticancer activity. These compounds are isolated from plants, fish, etc. Some of the examples of natural anticancer compounds include tephrosin,³³ (lung

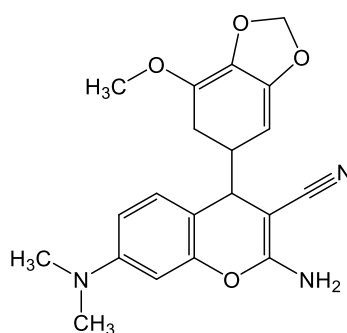
cancer) calanone,^{34,35} (leukemia and cervical carcinoma) and acronycine³⁶ (lung, colon and ovary cancer). The potential pro-apoptotic chemotherapeutic agents target tubulin, bind to the different sites of tubulin and inhibit tubulin polymerization.³⁷ This has led to the discovery of new structural classes of compounds capable of binding to the colchicine site of tubulin. The drugs under this category that binds to the colchicine binding site of tubulin resulting in the deformation of the α , β - dimer structure that prevents the tubulin from assembling into microtubules leading to apoptotic cell death. ^{38,39} Substituted 4-aryl-4Hchromene compounds belongs to a novel class of microtubule inhibitors and a systematic change in the substitution of 4-aryl group increases the anticancer activity of the compound.^{40,41} Examples of compounds coming from this category are 2-amino-4-(3-bromo-4,5-dimethoxyphenyl)-7-(dimethylamino)-4H-chromene-3-carbonitrile **53** and 2-amino-7-(dimethylamino)-4-(7-methoxy-1,3-benzodioxol-5 **54**. In the above compounds, 2-amino-4-(3-bromo-4,5-dimethoxyphenyl)-4H-chromene-3-carbonitrile **53** induces caspase-mediated apoptosis in tumor cells and is more potent than the commonly prescribed anticancer alkaloids. Furthermore, this compound treats drug-resistant cancers and also possesses vascular targeting activity.⁴² to developed this type of compound, combretastatin A-4 which is a phosphate prodrug (CA-4P), was used as a lead compound because of its simple structure and, potent cytotoxic and vascular disrupting activity.^{23, 37} Bcl-2 protein binding compounds also provide lead compounds for the development of potential anticancer agents. Substituted 4H-chromene compounds bind to Bcl-2 protein (β cell lymphoma) and induce apoptosis in tumor cells.²⁰ Ethyl 2-Amino-6-

Bromo-4-(1-Cyano-2- Ethoxy-2-Oxoethyl)-4H-Chromene-3-Carboxylate (HA14-1) **55** is an antagonist for antiapoptotic Bcl-2 proteins and has been used to overcome drug resistance in cancer.³⁸

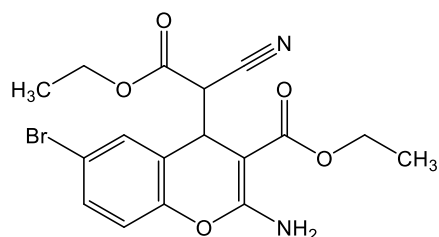
Figure 1.14. Examples of Microtubule Inhibitors.



53



54



55

The SAR studies of the chromene nucleus found that the 4-aryl moiety, 3-cyano group and 2-amino group are all essential for cytotoxic activity.^{24,40} The replacement of the 2-amino group with the oxo group gives the same activity and helps in the synthesis by removing the chiral center.⁴³ Substituting the seven position with an electron donating group enhances the potency of the compound while an electron withdrawing group in that position decreases the activity.

1.2.4.3. Summary.

Benzopyran is one of the privileged scaffolds that appears as an important structural component in various natural products and also possesses useful photochemical properties. The derivatives of the benzopyran moiety can be capable of interacting with a variety of cellular targets which leads to their wide ranging biological activities such as antitumor, antihepatotoxic, antioxidant, anti-inflammatory, diuretic, anticoagulant, antispasmodic, estrogenic, antiviral, antifungal, antimicrobial, anti-helminthic, hypothermic, vasodilatory, anti-HIV, antitubercular, herbicidal, anticonvulsant and analgesic activities. The potency of these clinically useful pharmacophores in the treatment of cancer and inflammation and other activities encouraged us to develop ways to synthesize these significant compounds.

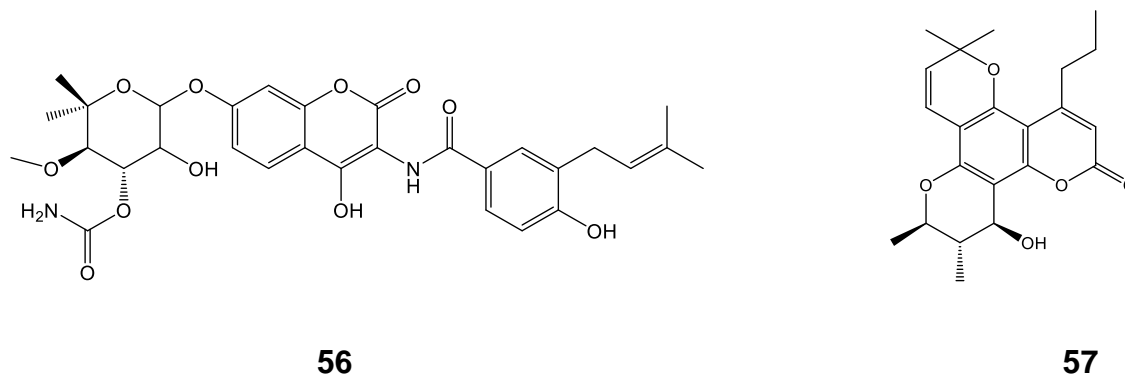
Chapter 2

Pyranobenzopyrans

2.1. Overview and Historical Perspective

Coumarin derivatives (pyranobenzopyrans) have revealed promising biological activity with interesting potential therapeutic applications⁴⁴ besides their traditional use as anticoagulants,⁴⁵ antifungal,⁴⁶ anti-inflammatory agents.⁴⁷ They have also shown important property as antibiotics (novobiocin) **56**,⁴⁸ anti-AIDS agents (calanolides) **57**.⁴⁷ and antitumor drugs.^{49,50}

Figure 2.0. Examples of Coumarin bioactive compounds.



The biological activities of pyranobenzopyrans and their derivatives has made their synthesis very important. Although numerous prescription medicines are available for the treatment of human disease, medicinal chemist are continuously searching for compound with improved efficacy.

2.2. Synthetic Approaches to Pyranobenzopyrans and their Derivatives in Literature

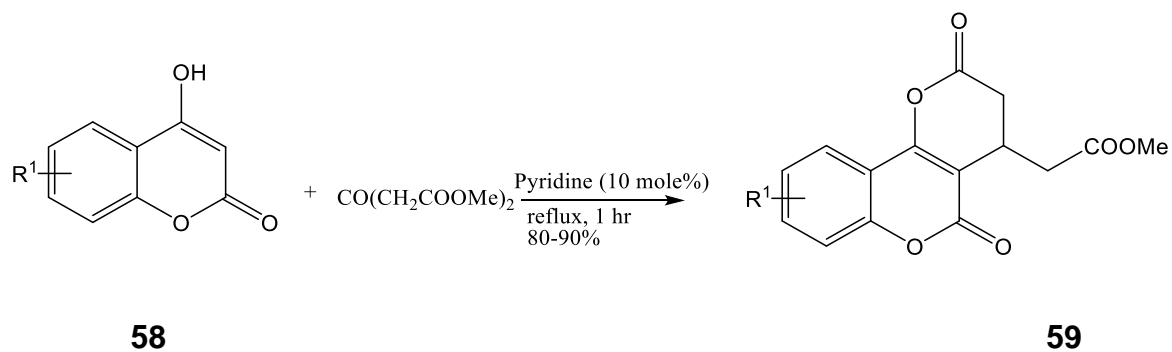
2H-1-Benzopyrans (2H-chromenees) and 3,4-dihydro-2H-1-benzopyrans (chromanees) have proven to be very important due to the biological activity of naturally occurring representatives.⁵¹ 4-Aminobenzopyrans and their derivatives show a wide range of biological activities.⁵² Particularly, fused tetrahydropyranobenzopyran derivatives are frequently found in naturally occurring bioactive molecules. In 1999, Miyazaki and co-workers reported a *p*-toluenesulfonic acid-catalyzed intramolecular [4+2] cycloaddition. Reaction of *o*-quinonemethides for the synthesis of angularly trans-fused pyranobenzopyrans.⁵³ The aza-Diels–Alder reaction of *o*-hydroxybenzaldimines with 3,4-dihydro-2H-pyran (DHP) and 2,3-dihydrofuran (DHF) is a convenient protocol for the synthesis of fused pyranobenzopyrans and furanobenzopyrans.^{54,55} Several protic acids and Lewis acids have been used to catalyze this reaction, such as LiBF₄,⁵⁶ PPh₃-HClO₄,⁵⁷ and Bi(OTf)₃.⁵⁸ Although these methods are available, new, efficient, selective, and facile protocols are still in strong demand. In the literature, much work has been done in this field, we report some examples.

2.2.1. Facile, Solvent-free, One-Pot Synthesis of Pyranobenzopyrans and their Derivatives

In May 2011, Sirisha and her group have developed a sequential one-pot reaction for the synthesis of variety of substituted pyranobenzopyrans by condensation of hydroxyl coumarins in a facile one-pot procedure with active methylene esters under solventless conditions. The product underwent further

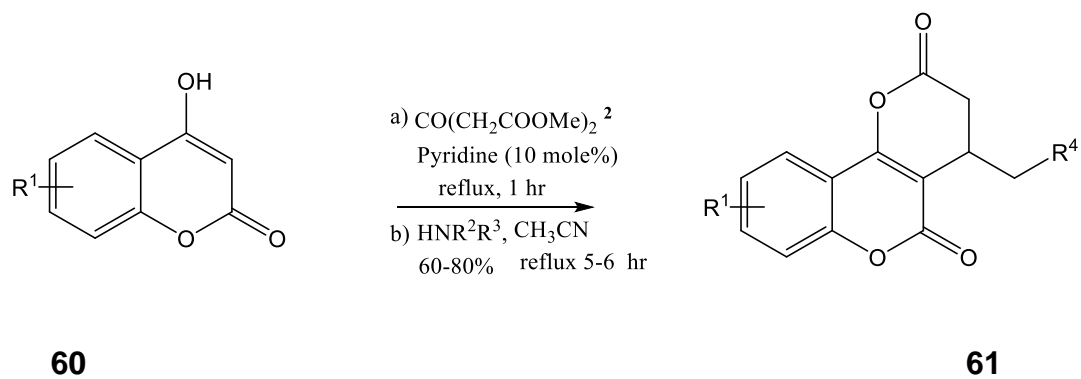
condensation and cyclization reactions to form novel heterocycles.⁵⁹ (Schemes 2.0), (Schemes 2.1), (Schemes 2.2)

Scheme 2.0. One-pot Synthesis of Pyranobenzopyrans.



R¹ = 7-H, 7-OH, 6-Me

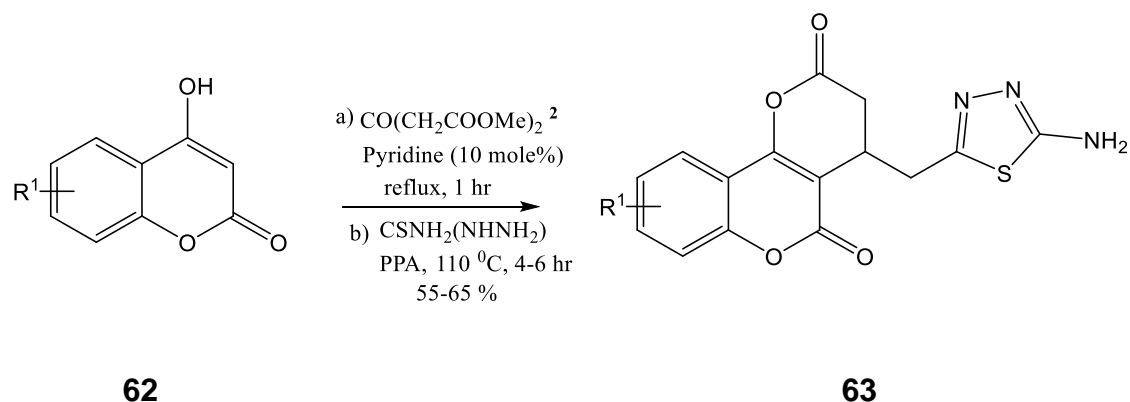
Scheme 2.1. One-pot Synthesis of Amide Substituted Pyranobenzopyran.



R¹ = H, Me

R⁴ = CONR₂R₃

Scheme 2.2. Efficient, Synthetic Protocol for Thia-Diazole.



$\text{R}^1 = 7\text{-H}, 7\text{-OH}, 6\text{-Me}$

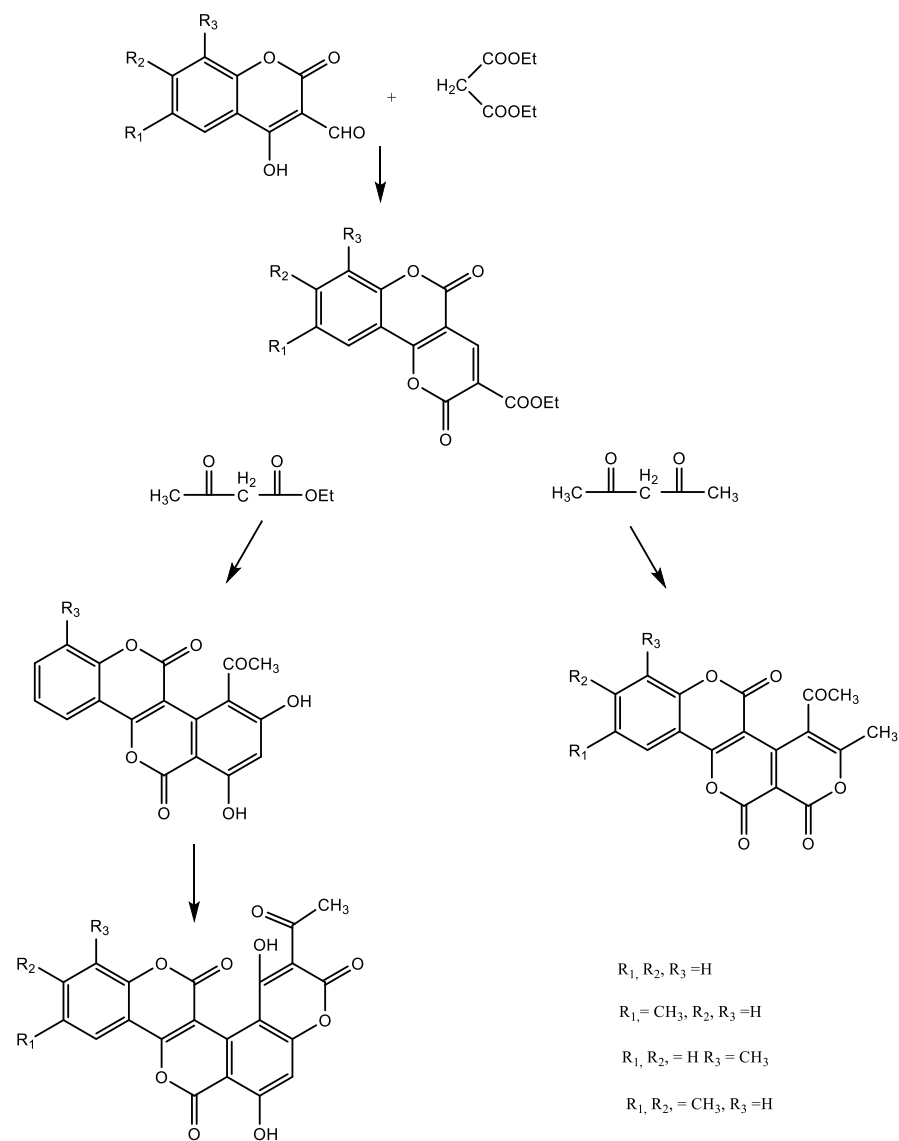
$\text{R}^4 = \text{CONR}_2\text{R}_3$

2.2.2. Synthesis of Pyranobenzopyran Derivatives as Potent Antibacterial Agents

Mulwad and his group reported the synthesis of pyranobenzopyran derivatives as a potent antibacterial agents by using 3-formyl-4-hydroxy-2 H (1)-benzopyran-2-ones (**1a-d**) in reactions with diethyl malonate in the presence of piperidine to give ethyl-2 H,5 H-2,5-dioxopyrano[3,2- c] benzopyran-3-oate **2a-d**.. Michael addition of (**2a-d**) with ethyl acetoacetate gives ethyl 2,4-dihydroxy-5H, 12 H - 5, 12-dioxo [2] benzo pyrano [4,3-c] [1] benzopyran- 1-oate (**3a-d**). on Pechmann condensation with ethyl acetoacetate gives 2-acetyl-1,6-dihydroxy-3 H, 7H,14 H-3,7,14-trioxo-pyrano [2 / ,3 / ,5,6] [2] benzo pyrano [3,2- c] benzopyran (**4a-d**). Michael addition followed by cyclization of acetylacetone with ethyl-2 H, 5H-2,5-dioxo-pyrano[3,2-c] benzopyran-3-oate (**2a-d**) in the presence of sodium methoxide in boiling

methanol afforded 1-acetyl-2-methyl-4H, 5 H,12 H, 4,5,12-trioxo-dipyranobenzopyran.⁶⁰
(Scheme 2.3).

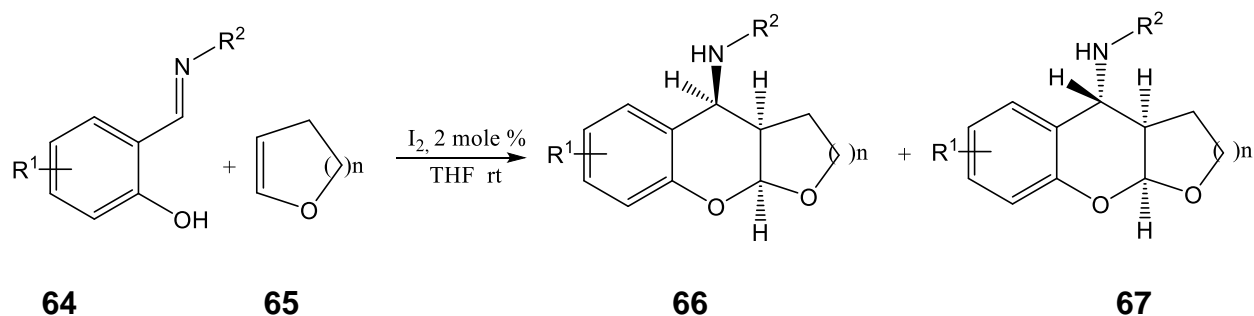
Scheme 2.3. 1-acetyl-2-methyl-4H, 5 H,12 H, 4,5,12-trioxo-dipyranobenzopyran



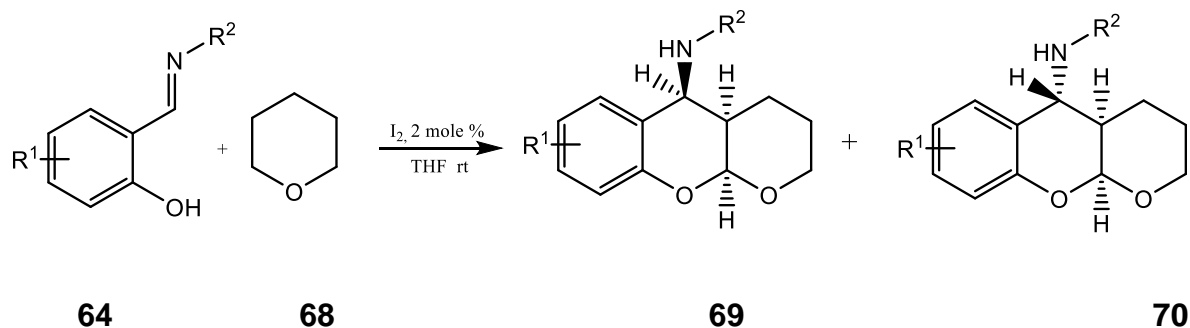
2.2.3. Molecular Iodine-catalyzed Diastereoselective Synthesis of *cis*-Fused Pyranobenzopyrans and Furanobenzopyrans.

Recently, molecular iodine has received considerable attention as an inexpensive and readily available catalyst for various organic transformations due to its moderate Lewis acidity and water tolerance. Jun Wang, and his group in May 2008 described a diastereoselective synthesis of *cis*-fused pyranobenzopyrans and furanobenzopyrans via a molecular iodine-catalyzed reaction of *o*-hydroxybenzaldimines with 3,4-dihydro-2H-pyran and 2,3-dihydrofuran at ambient temperature. Using this method, 2-butoxy-4-N-arylaminobenzopyrans were also synthesized from *o*-hydroxybenzaldehyde and *n*-butyl vinyl ether. The notable features of the procedure include mild and metal-free reaction conditions, operational simplicity, using a catalytic amount of molecular iodine (2 mol %), short reaction time, and good yields.⁶¹ (Scheme 2.4), (Scheme 2.5),

Scheme 2.4. Synthesis of Furanobenzopyrans.



Scheme 2.5. Synthesis of Pyranobenzopyrans.

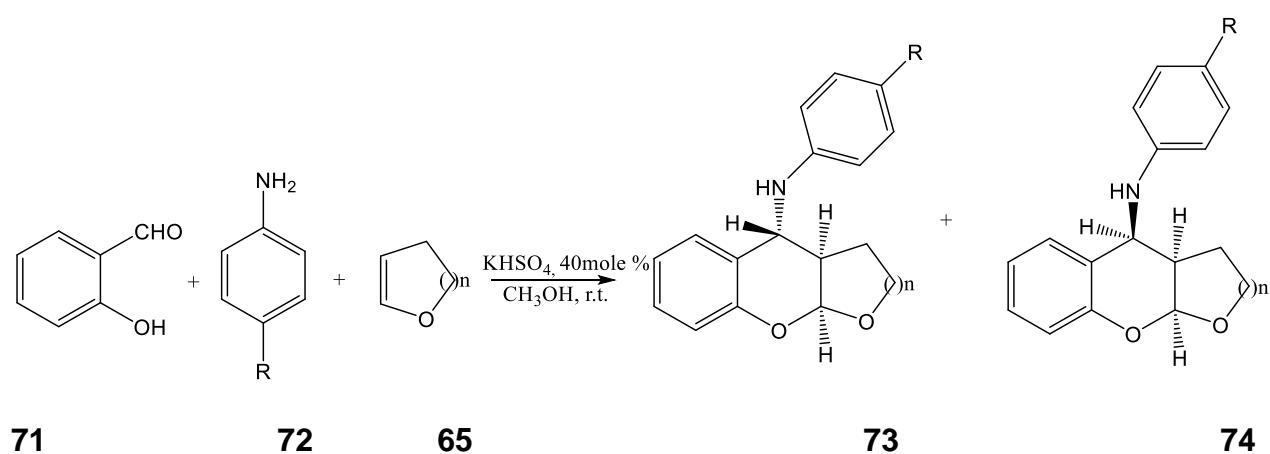


2.2.4. Diastereoselective, One-Pot Synthesis of Pyranobenzopyran, Furanobenzopyrans and Tetrahydroquinolines Derivatives.

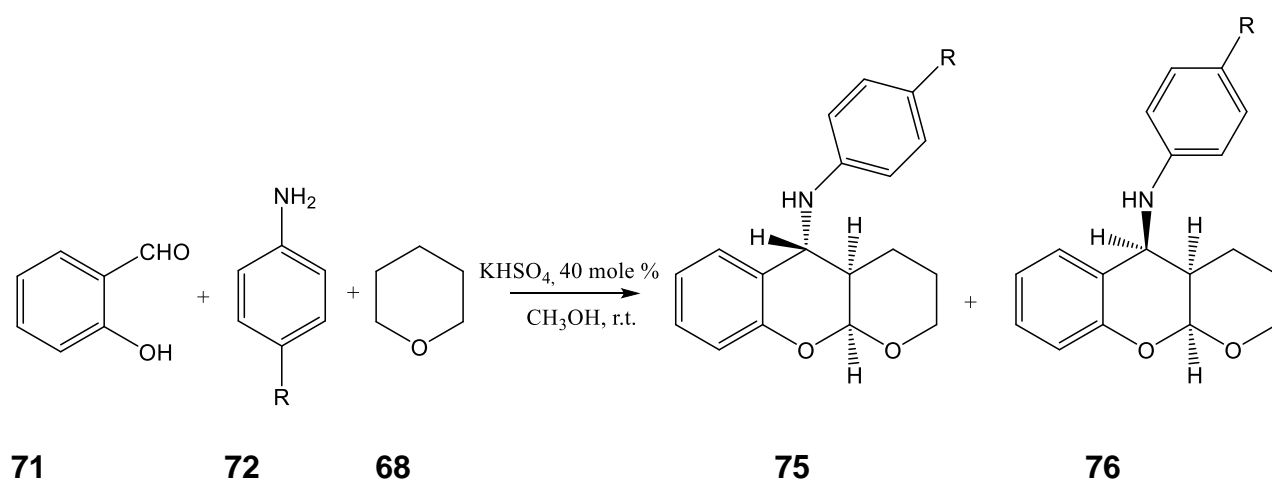
The classical Diels-Alder reaction, a [4+2] cycloaddition of diene and dienophile to generate a six membered carbocyclic system in modified form can be used to generate nitrogen or oxygen containing six membered rings. In February 2004, Senthil Kumar and his group reported a one-pot procedure which is useful when the diene is unstable and difficult to purify either by distillation or chromatography. Lewis acids such as lanthanide triflates, were found to catalyze this reaction, however most of these reactions suffer from various disadvantages such as, more than a stoichiometric amount of catalyst is needed due to strong coordination of it with the heteroatoms, longer reaction times, higher costs and use of only aprotic solvents under anhydrous conditions. Also, these reactions cannot be performed in one pot because the amine and water that are present during the formation of imine can decompose or deactivate the Lewis acids.

However the use of KHSO_4 as a catalyst is inexpensive, mild, and does not require the maintenance of anhydrous conditions. Treatment of salicylaldehyde, amine, and dihydropyran in the presence of KHSO_4 in methanol at room temperature gave an inseparable mixture of linearly *cis*-fused pyranochromanees with higher diastereoselectivity.⁶² (Scheme 2.6).

Scheme 2.6. One-Pot Synthesis of Furanobenzopyrans.



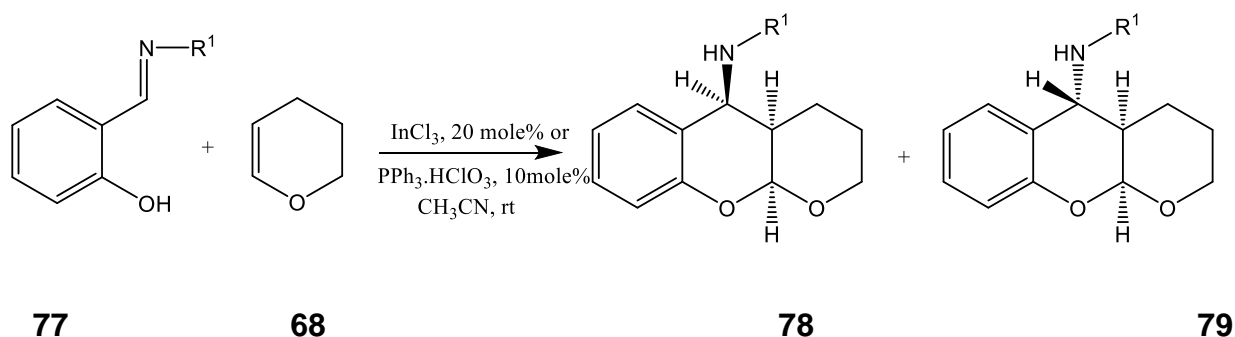
Scheme 2.7. One-Pot Synthesis of Pyranobenzopyran



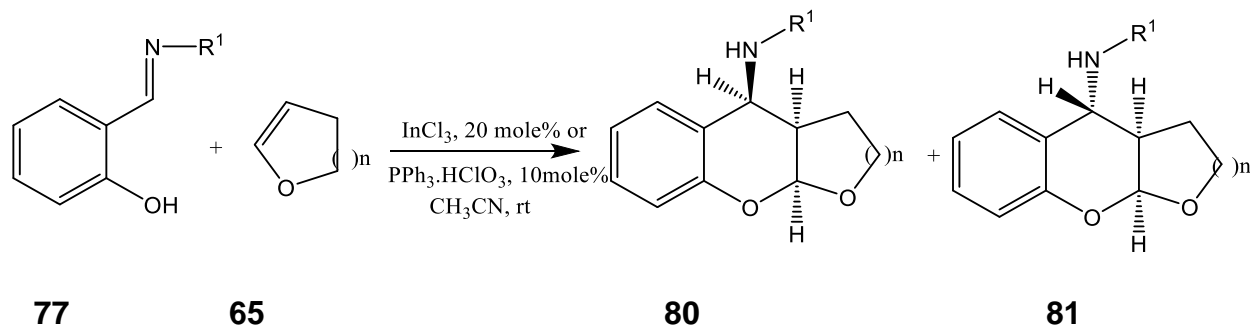
2.2.5. Diastereoselective Synthesis of *cis*-fused Pyrano- and Furanobenzopyrans Catalyzed by Indium Trichloride or Triphenylphosphonium Perchlorate

In October 2002, Marimuthu Anniyappan and his research group reported the application of Indium trichloride and triphenylphosphonium perchlorate to be effective catalysts for the cyclization of *o*-hydroxyaldimines with 3,4-dihydro-2H-pyran and 2,3-dihydrofuran at ambient temperatures to afford novel pyrano- and furanobenzopyrans and their derivatives (Schemes 2.8 and 2.9). One pot syntheses of pyrano- and furanobenzopyrans from *o*-hydroxybenzaldehyde, aromatic amines and an enol ether under identical conditions was reported for the first time (Scheme 2.10). Similarly, various substituted salicylaldehydes reacted well to give the corresponding *cis*-fused pyranobenzopyrans in good yields.⁶²

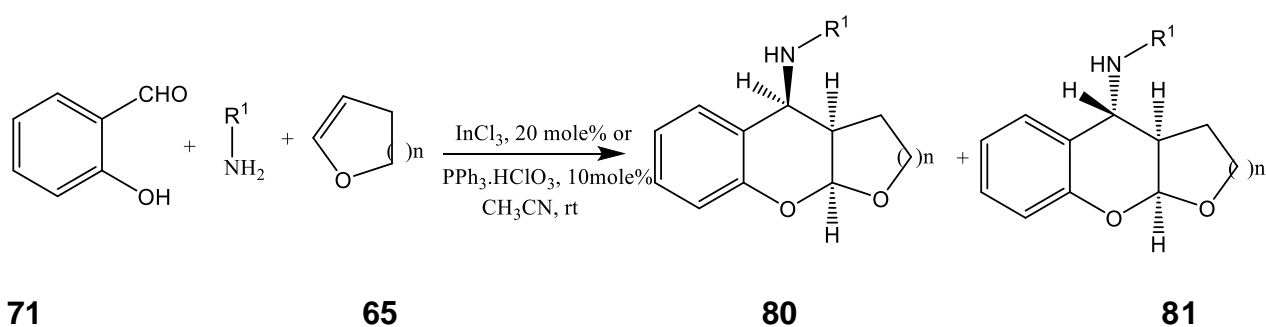
Scheme 2.8. Synthesis of Pyranobenzopyrans Using Indium Trichloride and Triphenyl Phosphonium Perchlorate



Scheme 2.9. Synthesis of Furanobenzopyrans Using Indium Trichloride and Triphenyl Phosphonium Perchlorate.



Scheme 2.10. One pot Syntheses of Furanobenzopyrans Using Indium Trichloride and Triphenylphosphonium Perchlorate.

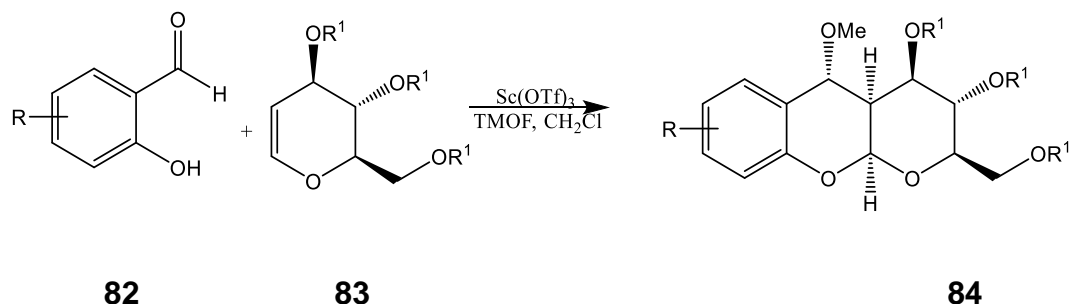


2.2.6. $\text{Sc}(\text{OTf})_3$ Catalyzed Synthesis of Pyrano[3,2-b]-1-Benzopyrans from D-glycals

In this report, Yadav and his research group had describe a new and efficient method for the synthesis of fused pyranobenzopyrans from o-hydroxybenzaldehydes and glycals using a catalytic amount of scandium triflate. Thus treatment of o-hydroxybenzaldehyde with 3,4,6-tri-O-methyl-D-glucal and trimethyl orthoformate (TMOF) in the presence of 3 mol% of $\text{Sc}(\text{OTf})_3$ in dichloromethane at ambient temperature resulted in the formation of the *cis*-fused

pyrano[3,2-b]benzopyran in 80% yield (Scheme 2.11). Similarly, several salicylaldehydes reacted well to give the corresponding *cis*-annelated acetals in excellent yields. In all cases, the reactions proceeded smoothly at ambient temperature with high selectivity. Only one diastereomer was obtained in each reaction, the structure of which was established with the help of various NMR experiments like double quantum filtered correlation spectroscopy, nuclear Overhauser effect spectroscopy and selective homonuclear decoupling studies.⁶³

Scheme 2.11. Synthesis of pyrano[3,2-b]-1-benzopyrans from D-glycals

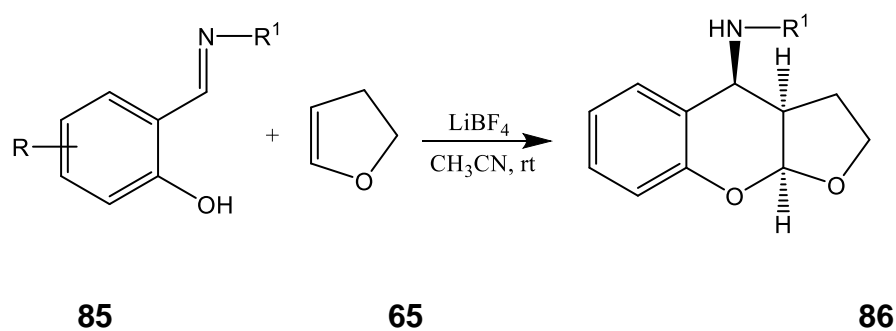


2.2.7. LiBF₄-Catalyzed Formation of Fused Pyrano- and Furanobenzopyrans

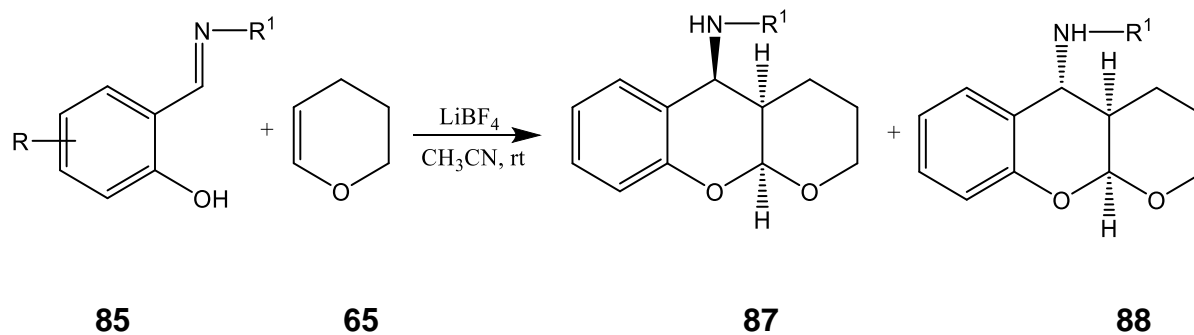
In this report, Yadav and his group described a new and highly efficient protocol for the synthesis of fused pyrano- and furanochromanes (Scheme 2.12), (Scheme 2.13), using a catalytic amount of LiBF₄ in acetonitrile. The treatment of the Schiff base of salicylaldehyde with 2,3-dihydrofuran in the presence of lithium tetrafluoroborate at ambient temperature afforded the *cis*-fused furanochromane in 90% yield. Similarly, several *o*-hydroxybenzaldimines (formed *in situ* from 3 *o*-hydroxybenzaldehydes and anilines in the presence of anhydrous Na₂SO₄ in

acetonitrile) reacted well to give the corresponding *cis*-fused acetals in excellent yields. The reactions proceed smoothly at ambient temperatures with high diastereoselectivity.⁶⁴ In all reactions, the product was obtained as a single isomer, the structure of which was confirmed by detailed ¹H-NMR and NOESY experiments.

Scheme 2.12. Synthesis of Furanobenzopyrans Using a Catalytic Amount of LiBF₄.



Scheme 2.13. Synthesis of Pyranobenzopyrans Using a Catalytic Amount of LiBF₄

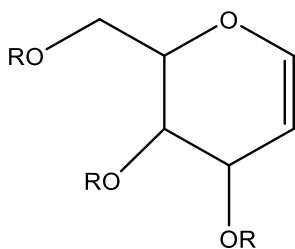


2.3. Glycals in Heterocyclic Organic Synthesis.

Glycals are cyclic vinyl ether derivatives of sugars that contain a double bond between carbon atoms 1 and 2 of the ring. These 1,2 unsaturated sugars **89** are either commercially-available or easily prepared from 1-halogeno sugars.

Manipulations of this double bond have been the focal point of many syntheses that use glycals as starting materials. Addition reactions have been employed in the preparation of carbohydrate-based compounds, including fused heterocycles. A survey of the current scientific strategies may prove useful when applied to sugars with double bonds at other position of the molecule.⁶⁵

Figure 2.1. 1, 2- Unsaturated Sugars (glycals)



89

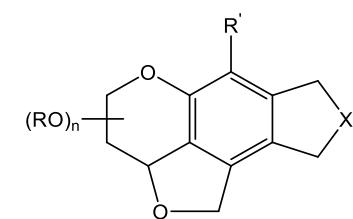
2.3.1. Hybrids of Sugars and Aromatics: A Pd-Catalyzed Modular Approach to Chromanes and Isochromanes.

Markus Leibeling and his group reported the synthesis of chromanes and isochromanes using carbohydrates as starting materials. They report the full details of this highly efficient procedure to access chromanes and isochromanes by utilizing an appropriately substituted 2-bromoglycal as the starting material of a domino reaction (Scheme 2.14).⁶⁶ Their method allowed for the easy

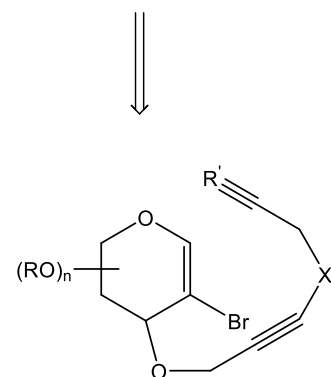
introduction of defined stereocenters on the pyran unit. For the creation of the benzene moiety an intramolecular Pd-catalyzed reaction was used that employs a diyne chain attached to the pyran core. Such a procedure allows the synthesis of heavily functionalized chromane and isochromane derivatives that are difficult to obtain by other routes. The target molecules may be regarded as hybrids between carbohydrates and an aromatic compound.

Scheme 2.14. Synthesis of chromanes and isochromanes

Chromane

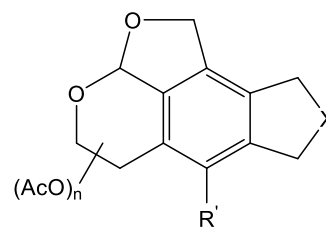


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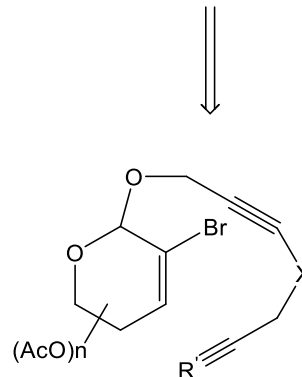


91

Isochromane



90

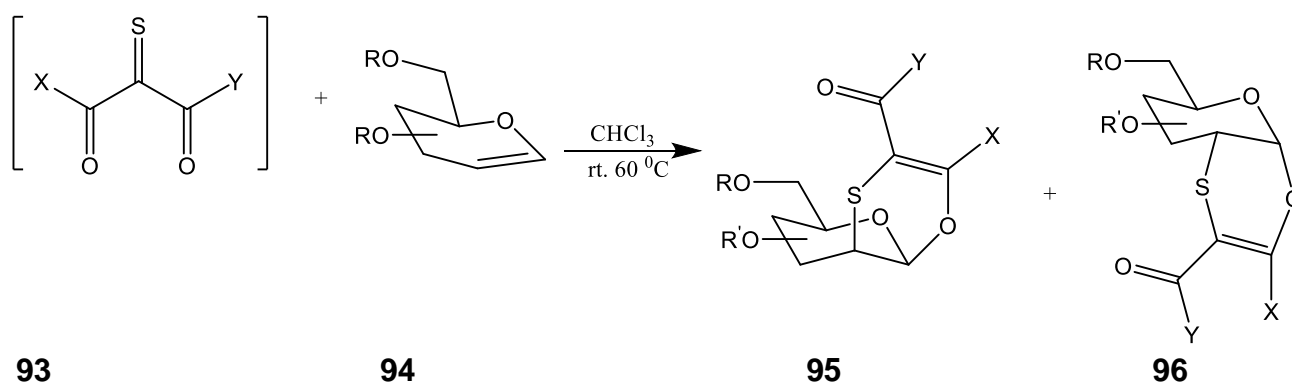


92

2.2.2. The hetero Diels-Alder approach to carbohydrate-containing molecular scaffolds

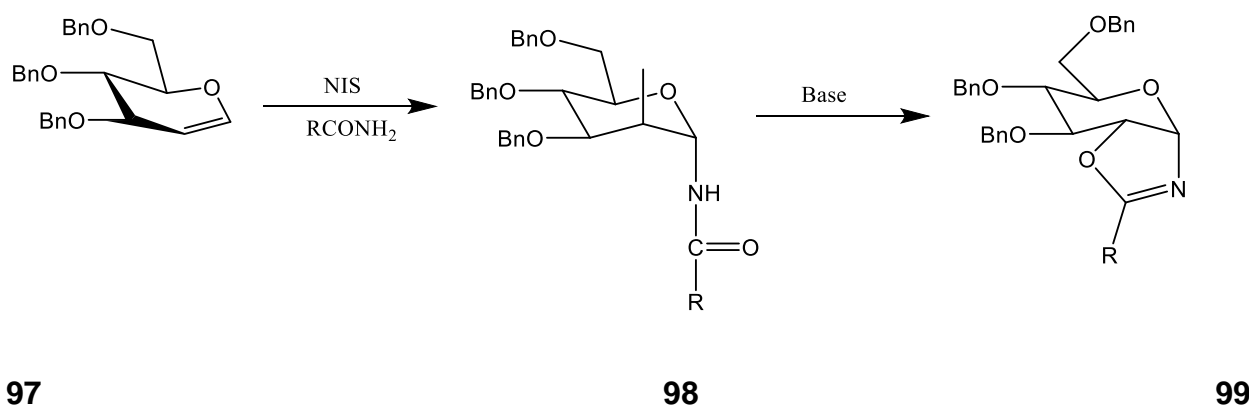
Martina Cacciarini and her group at the University of Florence used a strategy that relies on a totally stereoselective hetero Diels-Alder reaction. It is an inverse electron-demand [4+2] cycloaddition between α,α' -dioxo-thiones, α -oxo- α' -iminothiones or ortho-thioquinones as electron-poor heterodienes and unprotected or differently protected glycals as electron-rich dienophiles.⁶⁷ (Scheme 2.14).

Scheme 2.16. Carbohydrate-Containing Molecular Scaffolding.



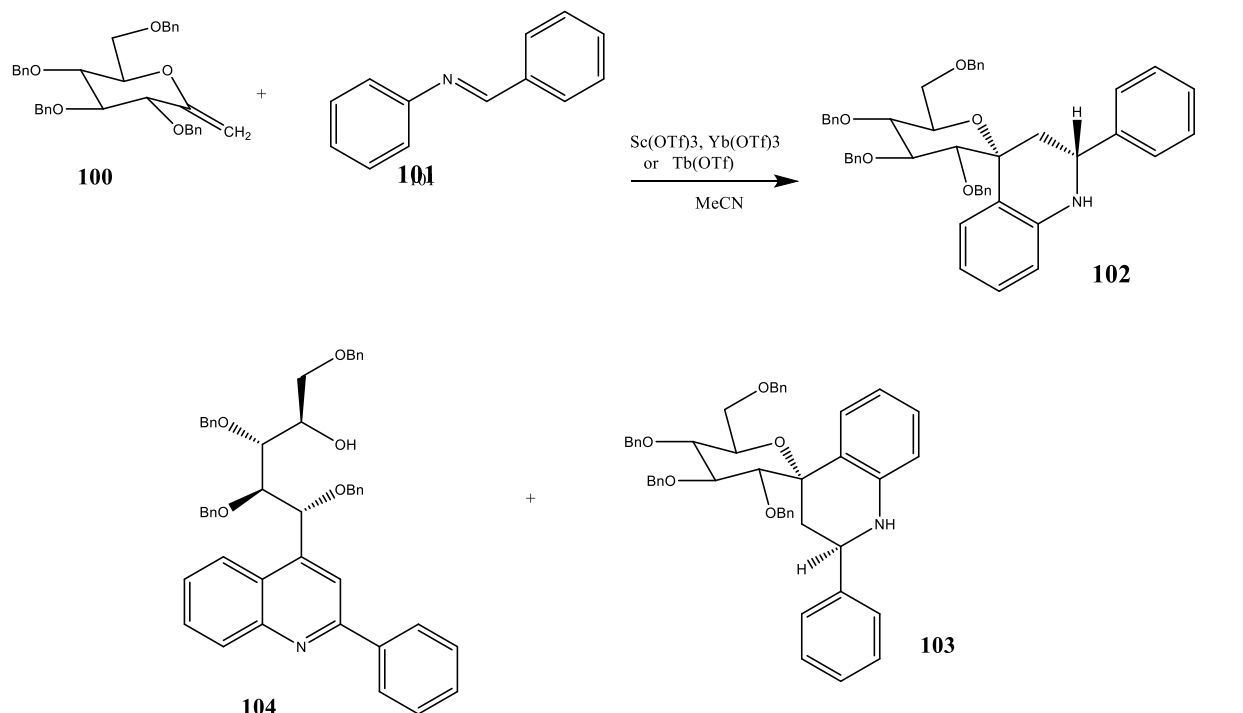
The research group of Professor Marzabadi became interested in developing a general method for the synthesis of carbohydrate-based oxazolines accessed from 2-iodo-glycosylamides.⁶⁸ Glycosylamides were prepared by reaction of different protected glycals with N-iodosuccinimide and alkyl and aryl amides. Mixtures of diastereomers were obtained from these reactions. These were then cyclized in the presence of base to produce the heterocycle. Assignment of the product stereochemistry was made by analyzing the vicinal coupling constants in the product's NMR spectra (Scheme 2.16)

Scheme 2.17. Synthesis of Glycosylamides.



Professor Marzabadi has also focused in the preparation of C-linked, quinoline derivatives from glycals. They developed and expanded the scope of a facile, one-pot method based upon Povarov reaction to prepare novel C-glycosylated quinolines. The reaction proceeded through the stereoselective formation of sugar-spiroannellated tetrahydroquinoline intermediates⁶⁹. These compounds are subsequently oxidized and undergo sugar ring opening to form the fully aromatized quinolines (Scheme 2.18).

Scheme 2.18. Synthesis of Spiroanellated Tetrahydroquinoline



2.4 Summary

Pyranobenzopyrans and their derivatives are oxygen heterocyclic compounds that structurally consist of a pyran ring fused to chromane or chromene and/or their derivative. The synthesis of pyranobenzopyrans and their derivatives has been a subject of great importance in the field of organic chemistry because of the biological activity of naturally-occurring representatives.

In our survey of the literature, many research groups synthesized pyranobenzopyrans and their derivatives in different ways by using a variety of starting materials, but there is only one report on the synthesis of pyranobenzopyrans from using unsaturated carbohydrates (glycals) in place of

3,4-dihydro-2H-pyran. This reaction was reported by Yadav and his colleagues. We report additional studies directed at the synthesis of these molecules.

Chapter 3

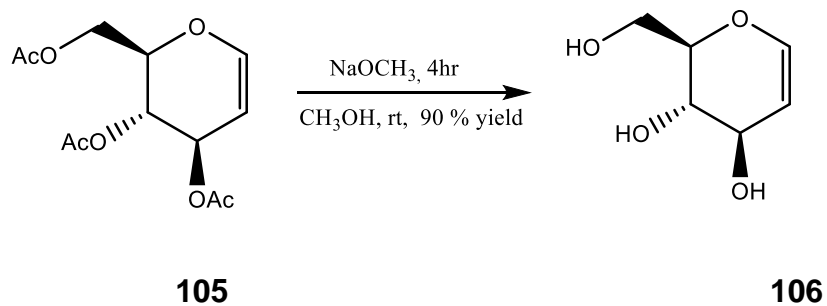
The Synthesis of Carbohydrate-Fused Benzopyrans

3. Results

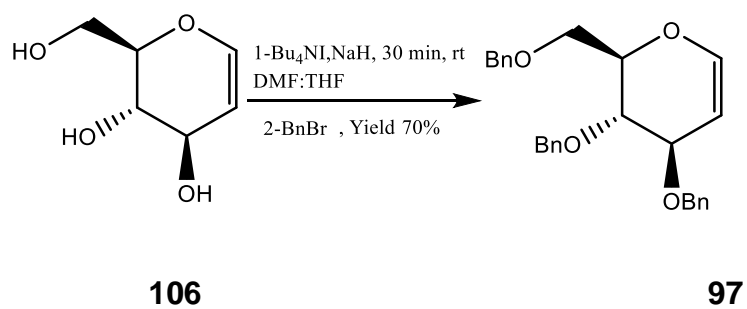
3.1. Synthesis of the Starting Materials.

Due to the growing interest in carbohydrate drugs and the importance of the pyranobenzopyran moiety, as mentioned before, we focused our efforts on doing synthesis in this area and in the development of convenient methods for doing this chemistry using glycals as precursors. We first needed to prepare the starting materials from which we would conduct our research. The synthesis was begun with the ester hydrolysis of commercially-available tri-O-acetyl-D-glucal **105** to produce D-glucal **106** (Scheme 3.0).⁷⁰ This material is used as a starting material for preparation of tri-O-benzyl-D-glucal **97** and *tris*-O-*t*-butyl-dimethylsilyl-D-glucal **107** using published literature procedures⁷¹ (scheme 3.1) and (Scheme 3.2). The idea behind the use of the different protecting groups was to study the effect of the protecting group on stereoselectivity and the two different groups activate the double bond to cycloaddition during the synthesis of pyranobenzopyran. The imine **108** was also prepared using known literature procedures. The synthetic procedure involved a room temperature reaction between 2-hydroxybenzaldehyde and aniline. (Scheme 3.4).

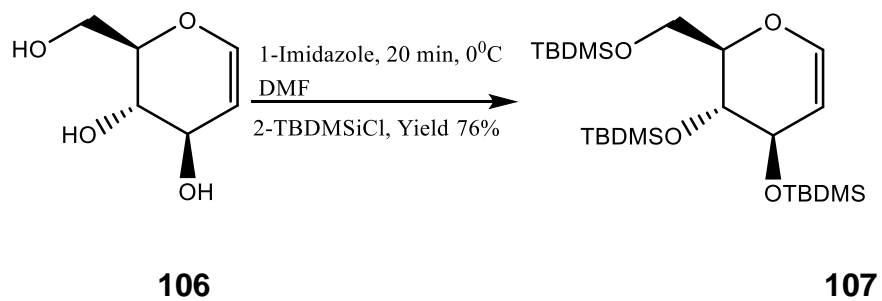
Scheme 3.0 De-O-acetylation of D-Glucal



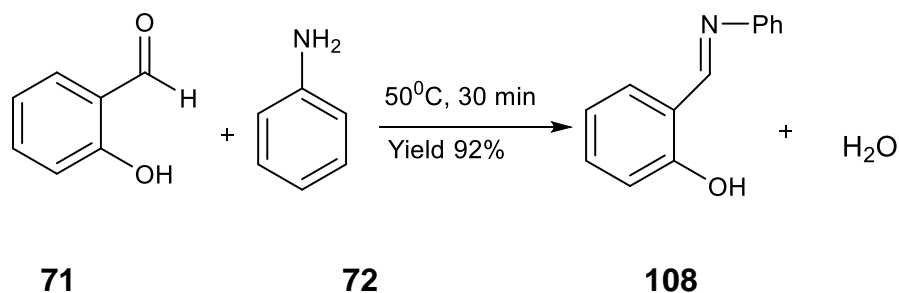
Scheme 3.1. Benzylation



Scheme 3.2. Silylation



Scheme 3.3. Synthesis of the Imine



3.2. Catalyst Screening

In order to investigate conditions for the cycloaddition reaction between the glucal and benzaniline, we screened several rare earth metal triflates as Lewis acid catalysts (Table 3.0). Based on our literature survey,⁶⁸ we chose to study Sc(OTf)₃, InCl₃, Yb(OTf)₃, PdCl₂ and TESOTf as they had shown effectiveness in other similar reactions.

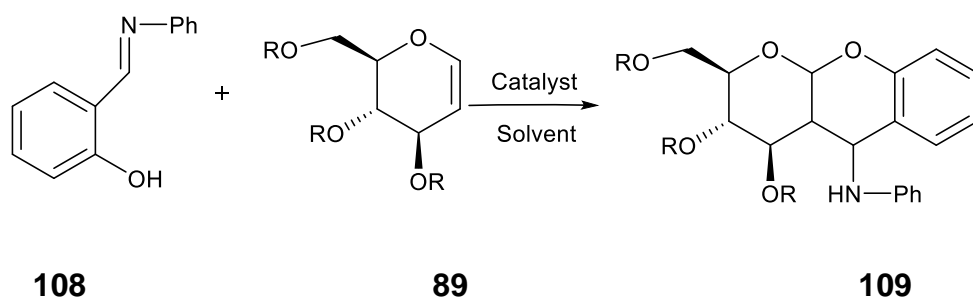
3.3. General Synthetic Procedure.

Despite the multitude of publications covering the synthesis of pyranobenzopyrans, we focused our work on using a less common method for synthesis. Our reactions utilize an inverse electron-demand Diels-Alder reaction. This is a [4 + 2] cycloaddition of a diene and a dienophile to generate a six-membered heterocyclic system;⁶³ in our case an oxygen containing six-membered ring system. We tried three different methods for carrying out these reactions using glycals **106** as both the dienophile and **the heterodiene**. **The different methods used are listed below as are the different conditions** of temperature, catalyst, reaction time and solvent (See Tables. 3.1, 3.2, 3.10 and 3.11).

3.3.1. The Conventional Cycloaddition Methods.

In this method, we used a known procedure from the literature in which a variety of protected glucals: tri-*O*-acetyl-D-glucal **105**, tri-*O*-benzyl-D-glucal **97** and tris-*O*-*tert*-butyldimethylsilyl-D-glucal **107** (scheme 3.4)⁷³ were reacted with imine **108** in the presence of a catalyst in organic solvent. The effects of the alcohol protecting group, solvents and catalysts on the reactions rates, the product yields, and the product stereoselectivities of the addition reaction were studied (Table 3.1). The choice of the solvents used was based upon the substrates and catalysts being readily soluble in dichloromethane and acetonitrile. The reactions were conducted under nitrogen and a range of temperatures were applied.

Scheme 3.4. Conventional Methods.



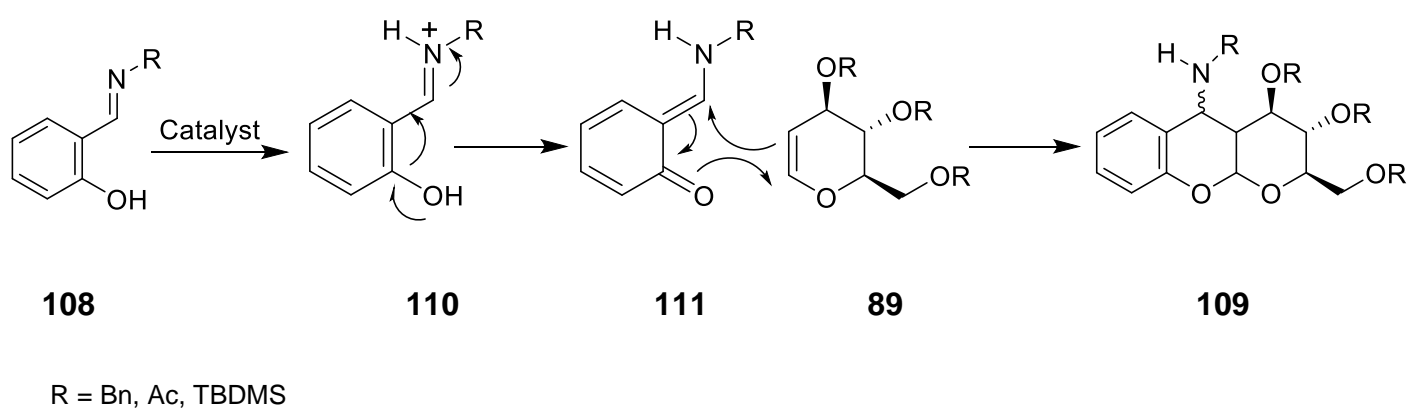
R = Bn, Ac, TBDMS, Solvent = CH₃CN, CH₂Cl₂, Catalyst = Sc(OTf)₃, InCl₃, Yb(OTf)₃, PdCl₃ and TESOTf

3. 3.1.1. Reaction Mechanism

The postulated reaction mechanism for the synthesis of pyranobenzopyrans is as follows (Scheme 3.5): first, the Lewis acid catalyst complexes to the nitrogen of the imine **109** resulting in the formation of the iminium ion intermediate **110** in

which the nitrogen atom bears a positive charge. The resulting *o*-quinonemethide acts as an oxadiene **111**. The electrons from the activated alkene react with the unsaturated sugar to create a bond that couples the two compounds together to give the pyranobenzopyran **112**.

Scheme .3.5. Reaction Mechanism for the Synthesis of Pyranobenzopyrans



From our observations, the reactions of tri-*O*-acetyl-D-glycal **105** took a long time and did not progress with different solvents and different catalysts even after 7 days (Table 1). That is most likely due to the deactivating nature of the electron withdrawing acetate groups in compound **105**. In the cycloaddition reaction, electrons of the π -system of the sugar must be available for bonding to occur, therefore; having electron withdrawing protecting groups will decrease the electron density of the double bond and slow down the reaction. On the other hand, with tri-*O*-benzyl-D-glucal **97**, the benzyl group is electron donating and we postulated that the reaction would work better. However, the same results were obtained

with this protecting group when the reactions were conducted at room temperature. When the experiments were conducted at 60 and 80 °C, we observed a gradual color change from yellow to brown. The progress of the reaction was checked by TLC (90:10 hexane/ethyl acetate) and a mixture of products were observed along with a large amount of unreacted starting material. These results can be explained by the effect of the benzyl and silyl protecting groups that causes steric-hindrance for the reaction and hinders its progress, where acetyl glucal has electron withdrawing nature will decrease the electron density of the double bond and hence slow down the rate of the reaction.

3.3.1.2. Summary.

The synthesis of pyranbenzopyrans using the conventional method was unsuccessful. That may be due to many factors including: the effect of the size and the nature of the protecting groups that can block or electronically deactivate the glycal double bond in the Diels-Alder reaction.

Table 3.1. The Conventional Methods and conditions

Dienophile	Temp °C	Time	Catalyst	Solvent
Tri-O-acetyl-D-glucal	25	7 days	Sc(OTf) ₃	CH ₃ CN
	25	7 days	InCl ₃	CH ₂ Cl ₂
<i>Tris-O-tert-butyl</i> dimethylsilyl-D-glucal	25	7 days	Sc(OTf) ₃	CH ₃ CN
	25	7 days	InCl ₃	CH ₂ Cl ₂
Tri-O-benzyl-D-glucal	25	7 days	Sc(OTf) ₃	CH ₃ CN
	25	7 days	InCl ₃	CH ₂ Cl ₂
	25	7 days	PdCl ₂	CH ₃ CN
	25	7 days	Yb(OTf) ₃	CH ₃ CN
	25	4 days	TESOTf	CH ₃ CN
	60	18 hr	Sc(OTf) ₃	CH ₃ CN
	60	18 hr	TESOTf	CH ₃ CN
	80	18 hr	Sc(OTf) ₃	CH ₃ CN

3.3.2. The Microwave Reactor.

Our failure in obtaining pyranobenzopyrans using the conventional synthetic method led us to think about other possible procedures. Because the Diels-Alder reaction requires higher energy to take place,⁷⁴ we chose microwave activation as a non-conventional energy source. Microwave energy has become a very popular and useful technology in organic chemistry. The conventional heating techniques such as a hot plate, oil bath, heated jackets and sand baths, are rather slow and a temperature gradient can develop within the sample. In addition, local overheating may lead to decomposition of reactants as well as the products. On the other hand, microwave radiation passes through the walls of the reaction vessel and heats only the reactant and solvent. The heating effect utilized in microwave-assisted organic transformations is due to dielectrical polarization, although conduction losses can also be important particularly at higher temperatures.⁷² Only dipolar and interfacial polarization are important factors in heating effects associated with microwave irradiation, the use of polar components facilitates the absorption of microwave energy and consequently the conversion into heat and with the use of a sealed vessel it was possible to increase the temperature and eventually the pressure and the reaction rates.⁷⁵ The short reaction times and expanded reaction range offered by microwave assisted organic syntheses are suited to the increased demand of the chemical industry. "It is nearly a Herculean effort to give a complete overview where microwave heating has been applied to heat up chemical reactions."⁷⁶⁻⁸⁶

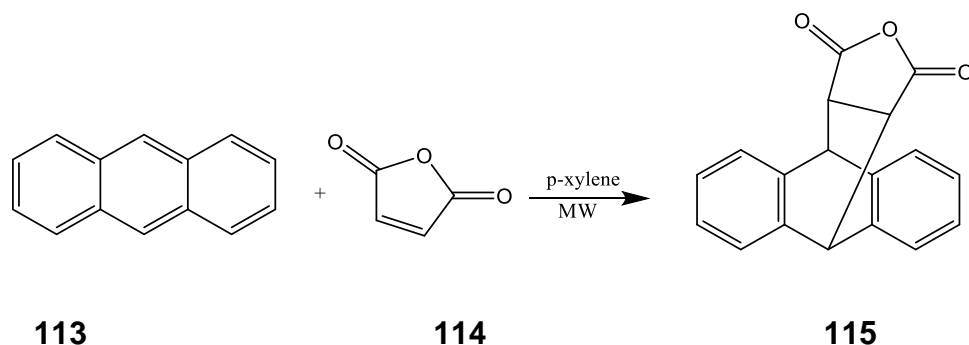
“Even below room temperature microwave irradiation is used to run reactions in combination with simultaneous cooling.”^{87, 88}

3.3.2.1. The Background of the Microwave Technology.

Diels-Alder Reactions

In 1986 several Diels-Alder reactions were investigated in the microwave oven. For example, the reaction of anthracene **113** with maleic **114** anhydride provided the required product yield in 89% in 5 minutes.⁸⁹ (Scheme 3.6).

Scheme 3.6. Diels-Alder Reaction of Anthracene with Maleic Anhydride.

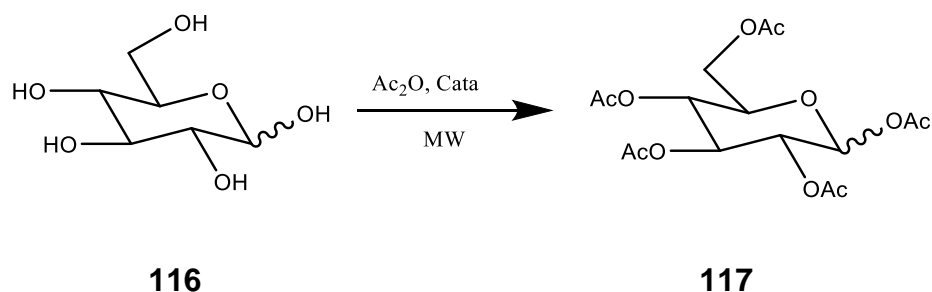


In our survey of the literature the use of microwave energy in carbohydrate chemistry is very limited, we reviewed the application of microwave reactors in carbohydrate chemistry; below are some examples:

Peracetylation

Peracetylation **117** of D-glucose **116** to give the penta-O-acetyl derivative with a small excess of acetic anhydride under catalysis with either anhydrous potassium or sodium acetate was carried out and the reaction reached completion within 15 minutes in the microwave reactor.⁹⁰ (Scheme 3.7)

Scheme 3.7 Peracetylation

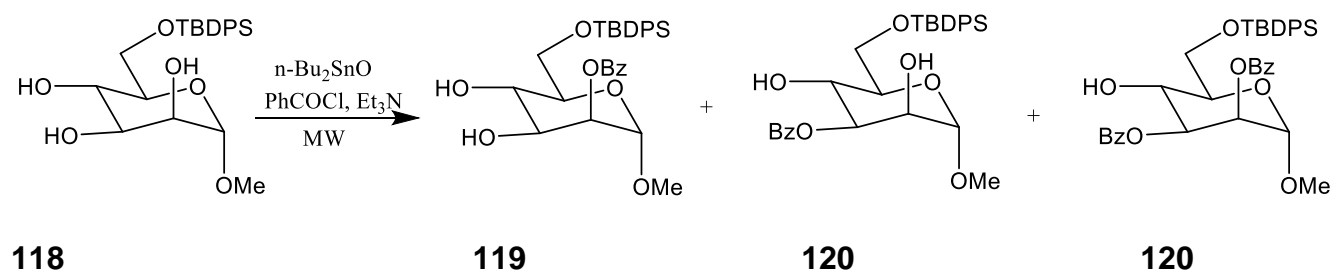


Catalyst = anhydrous potassium or sodium acetate

Benzoylation.

In order to verify the possibility of modulating the selectivity in microwave-promoted protection of hydroxyl functionalities, Herradòn et al.⁹¹ studied the influences of both the solvent and the power output of the oven on the selectivity of dibutylstannylene acetal-mediated benzoylation of methyl α -D-mannopyranoside **118** with PhCOCl, n-Bu₂SnO and Et₃N, the resulting compounds **119**, **120** and **120** shown in (Scheme 3.8) “verify the possibility of modulating the selectivity in microwave-promoted production of hydroxyl functionalities.”⁹¹

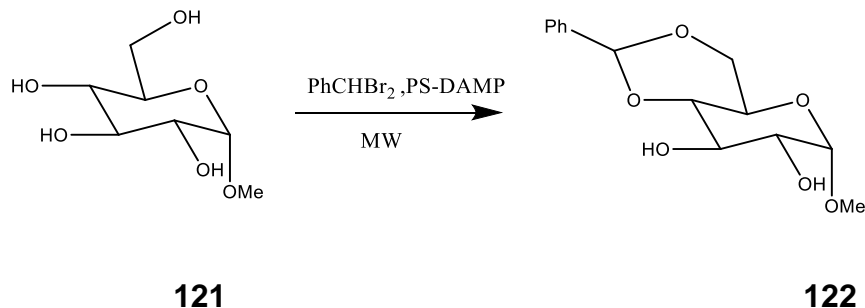
Scheme 3.8. Benzoylation



Acetal Formation.

This method, was modified by Oscarson when he treated α -D-glucopyranoside **121** with benzal bromide and N-(methylpolystyrene-4-(methylamino)pyridine in acetonitrile to form 4,6-O-benzylidene derivative **122** at 170°C for 5 min to yield 83% of the product (Scheme 3.10).⁹²

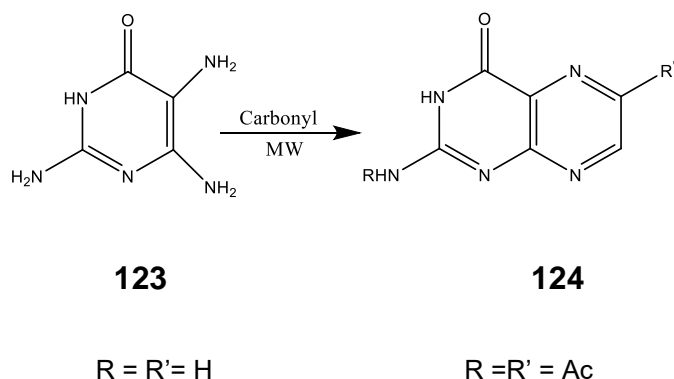
Scheme 3.9. Acetal Formation.



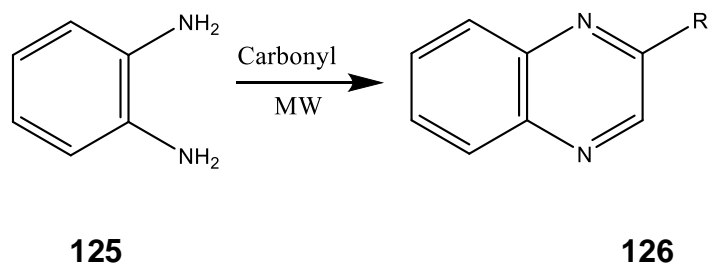
Pterins.

Isay condensed pyrimidine diamine **123** with aldohexoses, to afford pterins with a sugar substituent (Scheme 3.10) under microwave irradiation (300 W) for 270 sec. Interestingly, the desired, isomerically free, 6-substituted sugar derivatives were synthesized in moderate to good yields, whereas mixtures of two isomers are generally obtained using conventional Isay type condensations.⁹³ When benzene diamine, was used, quinoxaline **124** was obtained. (Scheme 3.11).

Scheme 3.10. Synthesis of Pterins.



Scheme 3.11. Synthesis of Quinoxaline

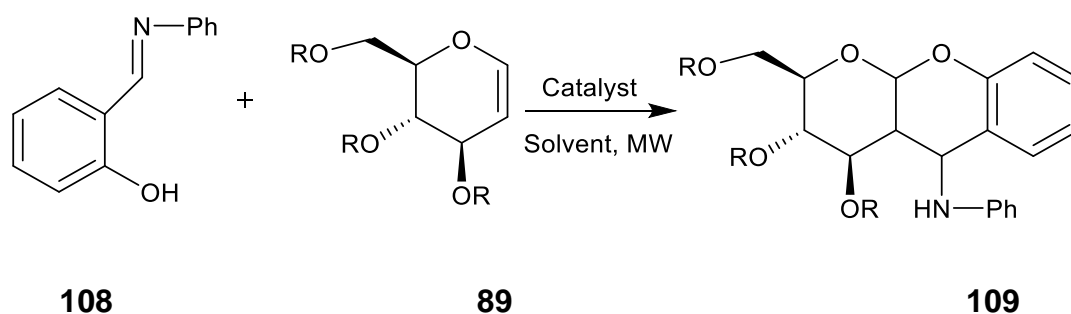


3.3.2.2. Microwave Reaction Results

The variety of applications of microwave technology in carbohydrate chemistry especially in the field of synthesis and the high yields obtained in short reaction times, encouraged us to use microwave irradiation in synthesis of pyranobenzopyrans. Since the conventional methods failed to produce our target molecules, we used the same procedure that we applied in the conventional method to see if there would be an improvement, (Scheme 3.12) The only

difference was the total volume of the reactant mixture used was 7 mL and that was based on the microwave tube volume. Different solvents and different conditions were used also (Table 2). The temperature and the pressure were adjusted according to the boiling point of the solvent. Solvents play an important role in organic synthesis and microwave heating, therefore the choice of the solvent can be a crucial factor in the outcome of a reaction in microwave reactor. One of the important characteristics of the solvent is its polarity. With microwave heating, this becomes a more significant component, as microwaves directly couple with molecules that are present in the reaction mixture. This interaction leads a rapid rise in temperature and faster reaction rates.

Scheme 3.12. Synthesis of Pyranobenzopyrans Using a Microwave.



R = Bn, Ac, TBDMS

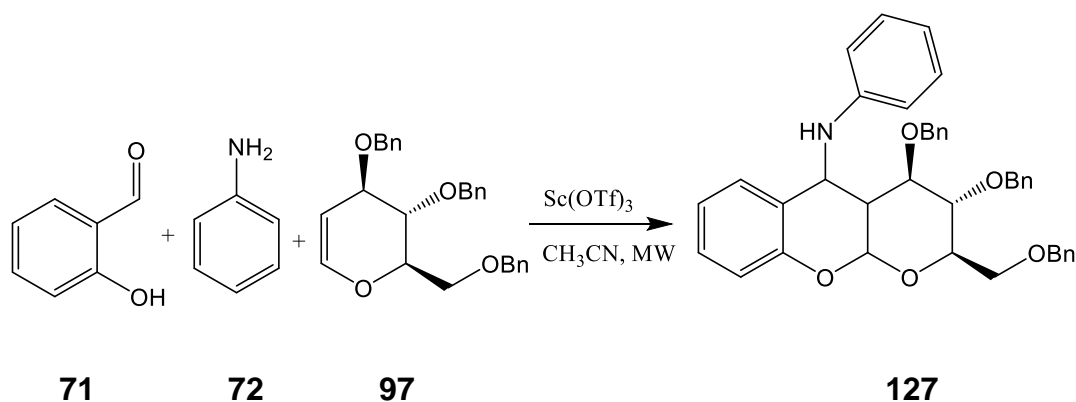
Table 3.2. Microwave conditions

Dienophile	Solvent	catalyst	Temp °C	Pressure Bar	Power W	Time min
Tri-O-acetyl-D-glucal	DCM	TESOTF	65	6	300	20
	DCM	Sc(OTf) ₃	65	6	300	20
	Acetonitrile	TESOTF	82	10	300	20
	Acetonitrile	Sc(OTf) ₃	82	10	300	20
Tri-O-benzyl-D-glucal	Acetonitrile	TESOTF	82	10	300	20
	Acetonitrile	Sc(OTf) ₃	82	10	300	20
	Acetonitrile	TESOTF	82	10	300	20
	Acetonitrile	Sc(OTf) ₃	82	10	300	20
<i>Tris-O-tert-butyl</i> dimethylsilyl-D-glucal	Acetonitrile	TESOTF	82	10	300	20
	Acetonitrile	Sc(OTf) ₃	82	10	300	20

The results in (Table 3.2) show the different conditions that we used for the microwave reactor. We used dichloromethane and acetonitrile as solvents because all the reactants are soluble in them. The boiling point of dichloromethane is very low (40 °C) and the maximum temperature we could apply for the reaction was 65 °C.⁸⁴ The time was increased gradually from 5 minutes to 20 minutes and the progress of the reaction was checked by TLC every two minutes. The reaction color gradually changed from yellow to brown and when the time reached 20 minute the color had turned black, and when we checked by TLC decomposition of the imine was observed. The use of

acetonitrile as a solvent with tri-*O*-acetyl-D-glucal and *tris-O-tert-butyl*dimethylsilyl-D-glucal did not enhance the conversion and with an increase in the reaction time and/or the the reaction temperature decomposition of the imine was observed. When acetonitrile was used as a solvent with tri-*O*-benzyl-D-glucal at a temperature of 82 °C for 16 minutes, only a small amount of product formation was observed by TLC. This was a mixture of products that were difficult to be isolated and identify, with an increase in time and/or temperature, the products and starting imine were shown to have decomposed. Because we were unsuccessful in producing our target molecule using this method, we thought about a one pot synthesis, in which the production of fresh imine in the microwave reactor may help the reaction to move forward and lead to the formation of the target product (Scheme 3.14). The reaction was setup by mixing tri-*O*-benzy-D-glucal **97**, *o*-hydroxybenzaldehyde **71**, and aniline **72**, in acetonitrile was catalyzed by scandium triflate (5 mole %). Different temperature ranges and times were applied. Unfortunately the TLC showed only the starting material, after 18 minutes and this method was abandoned.

Scheme 3.13. The Microwave Reactor in One Pot Synthesis.



3.3.2.3.Summary

We hypothesized that since microwaves are powerful, reliable energy sources in which the microwaves couple directly with molecules that are present in the reaction mixture, that this rapid rise in temperature may promote our reaction towards the formation of the required product and thereby increase the yield.

Unfortunately no reaction took place with the various microwave conditions.

The reasons for failure to react may be due to the presence of large protecting groups as previously discussed or to the effect of their electron withdrawing nature. Although many attempt to synthesize this molecule were made by using the microwave reactor, unfortunately we were unsuccessful. Then we decided to try non-traditional solvents, the ionic liquids. These solvents possess many good chemical and physical properties and it was our hope that they would enable the synthesis of our target molecules.

3.3.3.The Use of Ionic Liquids as Solvent in the Synthesis of Pyranobenzopyran

3.3.3.1. Ionic Liquids- an Overview.

Ionic liquids (ILs) are organic salts that are liquid at ambient temperature. They consist of organic cations such as: imidazolium, pyridinium, sulfonium, phosphonium, etc. (Figure 3.0) and organic or inorganic anions (Figure 3.1).⁹⁴ Ionic liquids have emerged as a new class of solvents that can be used as an alternative to environmentally- volatile organic solvents. They are practical alternatives, due to their unique combination of low volatility, low melting point, chemical stability, high conductivity, wide electrochemical window, and their ability to dissolve organic and inorganic solutes and gases.⁹⁵⁻⁹⁹

Figure 3.0. The Most Common Ionic Liquid Cations.

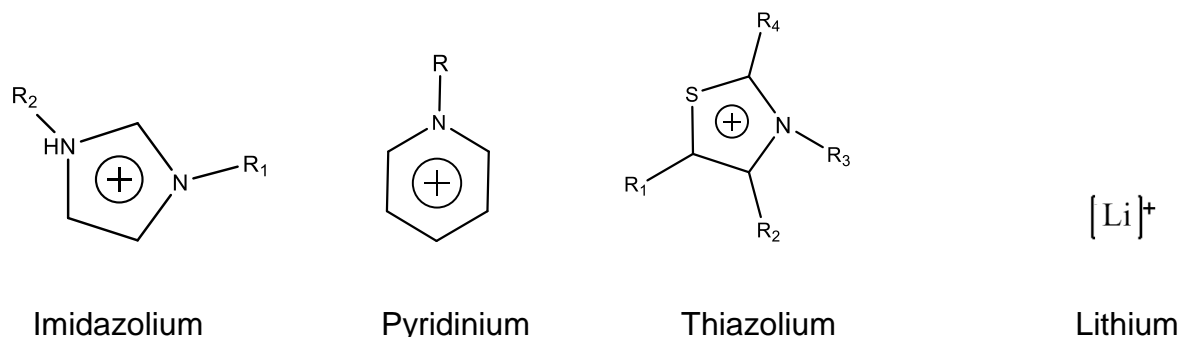


Figure 3.1. The Most Common Anions



Ionic liquids are not easily crystallized and remain liquids through a wide range of temperatures. They are not often involved in the processes of solvolysis and solvation, usually associated with traditional aqueous and organic solvents, and can also be designed to solubilize either polar or non-polar molecules. Hence, ionic liquids are attracting attention as potential replacements for the conventional, volatile, environmentally harmful organic solvents.

The particular importance of the ionic liquids: ability to Design Specific Physical and Chemical Properties.

Arguably the most useful property of the ionic liquids is the ability to 'design' or 'tune' a set of specific desirable physical and chemical properties through the simple adjustment of the side chains of the cation (R groups) (Figure 2) and / or the appropriate selection of the anion (Figure 3.0).¹⁰⁰ The range of physical and chemical properties available with ionic liquids is considerably wider than those

of commonly used organic solvents. Thus, an appropriate “Task Specific Ionic Liquid (TSIL)”¹⁰⁰ can be designed with the precise physical and chemical properties desired by the end user.;

Low or Near Zero Vapor Pressure.

ionic liquids are salts, and hence, have a very low or a nearly zero vapor pressure. Because of this property very little ionic liquid is lost into the environment through evaporation, even when ILs are used at elevated temperatures as solvents and /or as catalysts;¹⁰⁰

Low Melting Points.

Most of the room temperature ionic liquids have a very low melting point, enabling them to be liquids at or below room temperature. This low melting point can be attributed to the asymmetric nature of the ions making up these salts. This asymmetry prevents the compact packing of the ions. The ionic liquid, 1-ethyl, 3-methyl imidazolium tetrachloroaluminate for example has a melting point of 9 °C;¹⁰¹

Water Miscibility.

Some ionic liquids are water miscible and some are not. This property can be switched on and off according to the process requirements by modifying the cationic structure of the ionic liquids or by changing its anion. The anion chosen plays a prominent role in ionic liquid water miscibility. $[\text{PF}_6]^-$, $(\text{CF}_3\text{SO}_2)_2\text{N}^-$ are example of water immiscible anions, where $[\text{CH}_3\text{COO}]^-$, $[\text{CF}_3\text{COO}]^-$, $[\text{NO}_3]^-$, $[\text{CH}_3\text{CH}_2\text{SO}_3]^-$, Br^- , I^- , and Cl^- are water miscible anions;¹⁰¹

Recoverability and Reusability.

Since the miscibility properties differ significantly based on ionic liquid structure, the products of reactions can often be recovered from ionic liquids by means of extraction. Supercritical CO₂, water or organic solvents can be used to recover products and enable the recycling of the ionic liquid for subsequent reactions;.

Large Liquid Range and Thermal Stability.

Ionic liquids have a very large liquids range, and they are very stable with respect to elevated temperatures. For example, 1-ethyl-3-methyl imidazolium bis(trifluoromethylsulfonyl) imide has a liquid range of 471 degrees, with a melting point 15 °C and a decomposition temperature at 455 °C.¹⁰² This property makes RTILs useful for reactions that need to be maintained at either low or high temperatures.

Air and Moisture Stable Ionic Liquids.

One of the major drawbacks which hinders the use of chloroaluminate ionic liquids is their sensitivity to air and moisture. The development of ionic liquids that are air and moisture stable has provided renewed interest in ionic liquid chemistry. The concept of ionic liquids received a substantial boost by the Wilkes group when they described in 1992 the synthesis of ionic liquids with significantly enhanced stability against hydrolysis;^{103,105}

Acid-Base Properties and Water Interactions.

While simple salts such as KCl can be thought of as the product of an electron transfer between elements, organic salts can be traced to a proton transfer between an acid and base. Cations such as emim⁺ and n-bupy⁺ result from the

alkylation of the bases emim⁺ and py⁺. Anions such as [NO₃]⁻, [AlCl₄]⁻ and [PF₆]⁻ derive from Lewis acid base reactions. It is also possible for Lewis neutral ions to add further Lewis acids to form acidic ions, e.g., [Al₂Cl₇]⁻. As a result we can obtain Lewis basic, neutral or acidic ionic liquids, exemplified by the well-researched haloaluminates. In addition we can make protic acidic liquids which are simultaneously of any Lewis aspect,¹⁰⁶ and relate the proton chemistry in ionic liquids to proton chemistry in water. The acidic protons in ionic liquids are bonded to bases such as pyridine and ethylimidazole are not labile,¹⁰⁷ These bases do not behave in line with their pK_b's in water; bases in ionic liquids appear to act in accordance with their gas phase proton affinities (1-methylimidazole > pyridine > ammonia).¹⁰⁸ The complicating factor is solvation in water. One can, however, obtain Hammett acidity data for some systems which make fair chemical sense;¹⁰⁹

Densities.

The density range of ionic liquids is 1.1 to 1.6 g/cm⁻³, and it mainly depends on the type of cation and anion used in the IL. The density of the ionic liquids depends on the bulkiness of the organic cation, with an increase of the bulkiness of the cation the density is decreased. This allows the chemist to adjust the density as required for a specific synthesis (Table 3. 3).¹¹⁰

Table 3.3. Densities of Imidazolium Ionic Liquids.

	Ionic Liquid	Density(g/cm ⁻³)
1	[bmim]BF ₄	1.320
2	[bmim]PF ₆	1.38
3	[emim]PF ₆	1.426
4	[emim]Br	1.575
5	[emim]EtSO ₄	1.240

Viscosity.

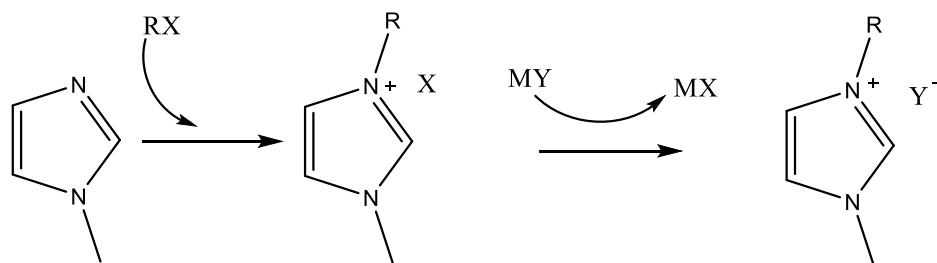
The viscosity of an ionic liquid is essentially determined by its tendency to form hydrogen bonds and by the strength of its Van der Waals forces.¹¹⁰ Comparison of the viscosity of different hydrophobic ionic liquids with [bmim]⁺ ions emphasizes the interplay between Van der Waals interactions and hydrogen bonding as the structure of the cation influences the viscosity. Low viscosities are usually obtained with [emim]⁺ ion in which a mobile side chain is combined with a low molar mass. Longer or fluorinated alkyl chains result in higher viscosities because of stronger Van der Waals interactions.¹¹¹

3.3.2. Synthesis of Ionic Liquids

The story of ionic liquids is generally regarded as beginning with the first report of the preparation of ethylammonium nitrate in 1914. This species was formed by the addition of concentrated nitric acid to ethylamine, after which water was removed by distillation to give the pure salt, which was liquid at room temperature. The protonation of suitable starting materials (generally amines and

phosphines) still represents the simplest method for the formation of such materials, but unfortunately it can only be used for a small range of useful salts. The possibility of decomposition through deprotonation has severely limited the use of such salts, and so more complex methods are generally required. Probably the most widely used salt of this type is pyridinium hydrochloride. Thus, most ionic liquids are formed from cations that do not contain acidic protons. The majority of ionic liquid chemistry based on nitrogen-containing heterocycles focuses on the use of 1-alkyl-3-methylimidazolium and N-alkylpyridinium cations. 1-Alkyl-3-methylimidazolium hexafluorophosphate (AMImPF₆), 1-alkyl-3-methylimidazolium tetrafluoroborate (AMImBF₄), N-alkylpyridinium tetrafluoroborate (APyBF₄) and N-alkylpyridinium hexafluorophosphate (APyPF₆) are typically ionic liquids used as solvent or catalysts. There are two basic methods for the preparation of these ionic liquids: metathesis of a halide salt (Finkelstein step) with silver, group 1 metal or ammonium salt of the desired anion and acid–base neutralization reactions. Either way, there is a need to prepare the imidazolium or pyridinium halides via alkylation (Menschutkin step) using a large molar excess of haloalkane (10–400%) for as long as 72 h at refluxing condition, and then RTILs are prepared with variable yields and much longer reaction times. The most common method uses stoichiometric amounts of 1-methylimidazole or pyridine, alkylhalides and the potassium, sodium or ammonium salt of hexafluorophosphate or tetrafluoroborate in one-pot under solvent-free condition.¹¹² (Scheme 3.14).

Scheme 3.14. Synthesis of Imidazolium Ionic Liquid



3.3.3. Ionic Liquids as Solvents:

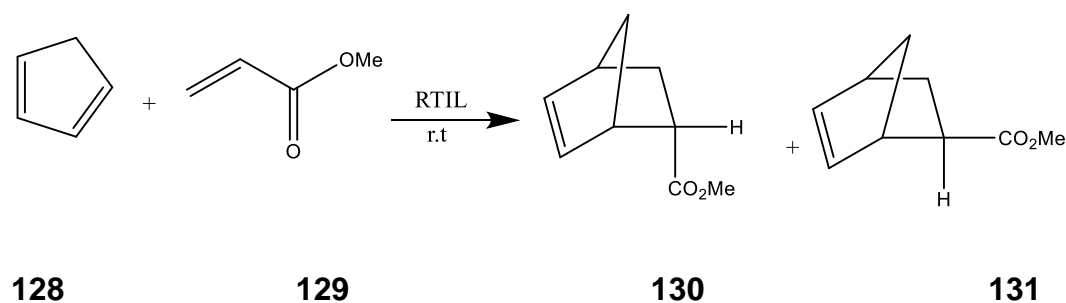
In recent years, environmentally-friendly reaction processes have been extensively studied from the standpoint of green chemistry. For example, oxidation reactions with air, or reactions in water, supercritical fluids, and fluorosolvents are reported. Most recently, ionic liquids have gained much attention as green reaction solvents for organic synthesis. As seen above, ionic liquids are salts, consisting of cations such as imidazolium, pyridinium, quaternary ammonium and quaternary phosphonium, and anions such as halogen, triflate, tetrafluoroborate and hexafluorophosphate, which exist in the liquid state at relatively low temperatures. Their characteristic features include almost no vapor pressure, non-flammability, non-combustibility, high thermal stability, relatively low viscosity, wide temperature ranges for being liquids, and high ionic conductivity. When an ionic liquid is used as a reaction solvent, the solute is solvated by ions only, where the reaction proceeds under quite different conditions as compared to using water or the regular organic solvents. Hence, they are expected to exhibit unconventional reactivity, and their applications in a variety of organic reactions

are being explored. Furthermore, some ionic liquids have a very low solubility in water and polar organic solvents. Utilization of this property enables recovery and reuse of ionic liquids, after extracting the product with an organic solvent. That can help to reduce the waste of traditional solvents which are rarely reused. Moreover, ionic liquids have attracted much attention as safe solvents, due to their low volatility. The following are some reaction examples using ionic liquids.¹¹³

Diels-Alder Reaction.

The Diels-Alder reaction between cyclopentadiene and the methyl acrylate ester has been reported. In the Diels-Alder reaction using 1-ethyl-3-methylimidazolium chloride/chloroaluminate [emimCl/(AlCl₃)X], the *endo* / *exo* ratio of the products varies largely, depending on the ratio of emimCl/ (AlCl₃)X. The amount of *endo* form increases four-fold with the acidic emimCl/(AlCl₃)X, compared to that of the basic emimCl/(AlCl₃)X.^{114,115} When the same reaction is carried out with 1-butyl-3-methylimidazolium tetrafluoroborate (bmimBF₄) there was similar reactivity to Lewis basic emimCl/(AlCl₃)X.

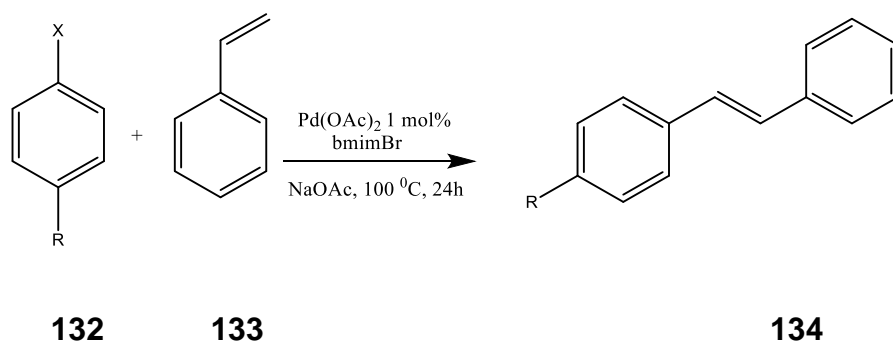
Scheme 3.15. Diel-Alder Reaction.



Heck Reaction.

In the Heck reaction using palladium catalysts, polar solvents such as DMF and acetonitrile are usually employed, and aryl iodides are normally used as substrates. In cases where the less expensive but less reactive aryl bromides or chlorides are employed, it is necessary to use more active catalysts or add phosphine ligands in order to retain the catalytic activity. By utilizing 1-butyl-3-methylimidazolium bromide (bmimBr) as a solvent, aryl bromides react with styrene to afford stilbenes in high yields without adding a phosphine ligand.¹¹⁶

Scheme 3.16. Heck Reaction

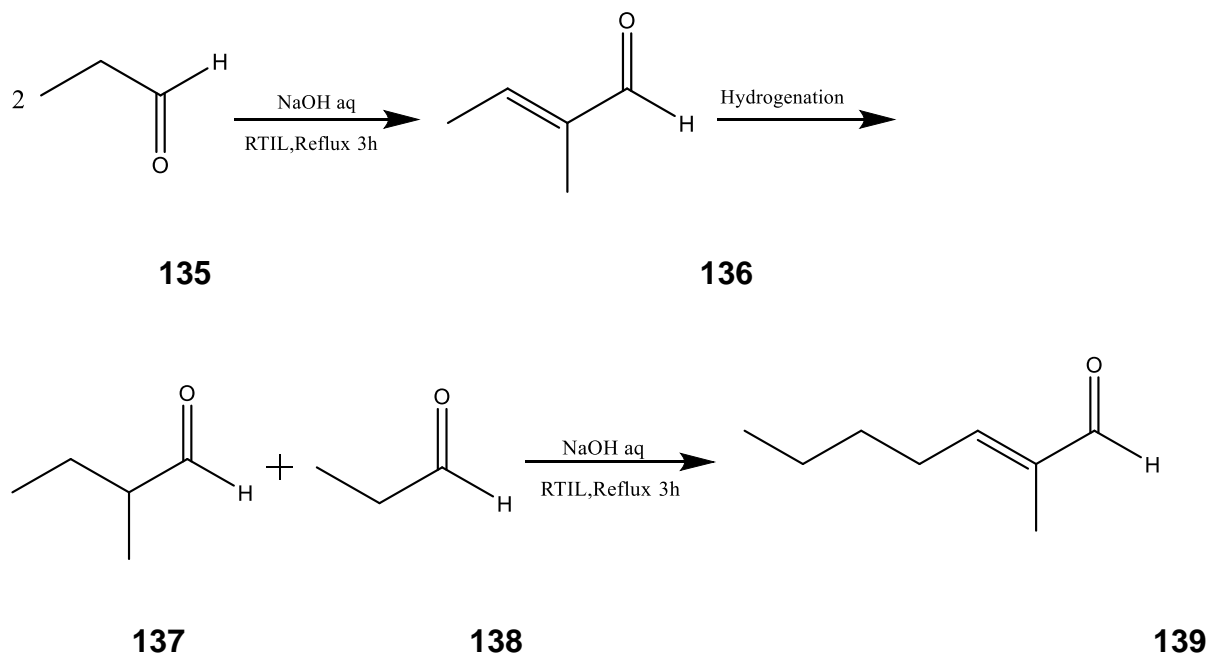


Aldol Condensation Reaction

The Aldol Condensation reaction using ionic liquids has also been reported. In the reaction for obtaining 2,4-dimethylhept-2-enal **134** from propanal via two Aldol condensations, the conversion values of the ionic liquid phase is comparable to a water medium in the Aldol I reaction. However, the product selectivity is reduced, as can be seen (Scheme 3.17) below. This is due to a side reaction proceeding from the high solubility of product **136** toward the ionic liquid. In contrast, in the Aldol II reaction, as compared with the reaction in water, the product selectivity

in ionic liquids are increased. This is because the hydrogenated product of **136** is difficult to dissolve in water but is easy in ionic liquids.¹¹⁷

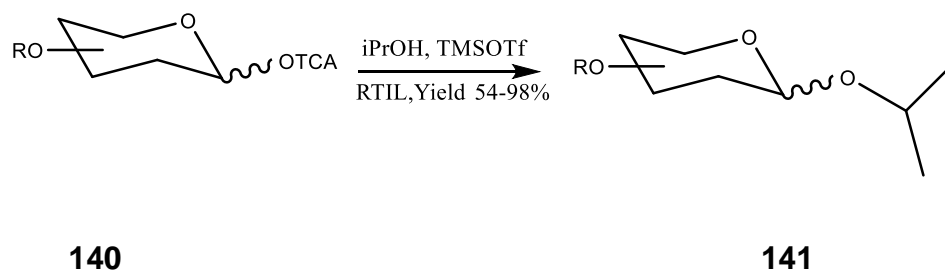
Scheme 3.17. Aldol Condensation Reaction



Synthesis of Isopropyl glycosides

In another study, trichloroacetamidate donors (TCA) were used in glycosylation reactions in $[\text{bmIm}][\text{PF}_6]$ and $[\text{emIm}][\text{OTf}]$ with monosaccharide derivatives.¹¹⁸ (Scheme 3.18).

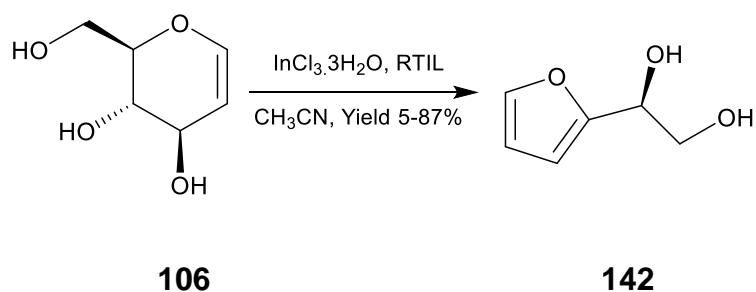
Scheme 3.18. Synthesis of Isopropyl Glycosides



Synthesis of Furan Diol

2-(D-glycero-1,2-dihydroxyethyl) furan **142** is a potential chiral building block used as an intermediate in the organic synthesis of biologically significant products.^{119,120} Monosaccharides are extremely acid-labile and under hydrolytic conditions lead to furans. Thus, in 1966, the first transformation of D-glucal **106** to optically active furan diol was reported, using $\text{H}_2\text{O}/\text{HOAc}$ at 170°C .^{121,122} RTILs in this transformation were used as catalyst promoters with 10% $\text{InCl}_3 \cdot 3\text{H}_2\text{O}$ as the catalyst and acetonitrile as the solvent at room temperature. (Scheme 3.19)

Scheme 3.19. Synthesis of Furan Diol.

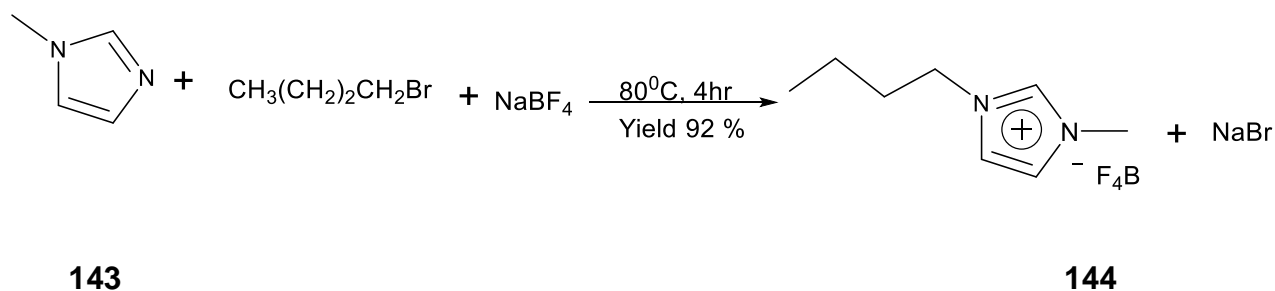


3.3.4. The Synthesis of Pyranobenzopyran Using Ionic Liquids

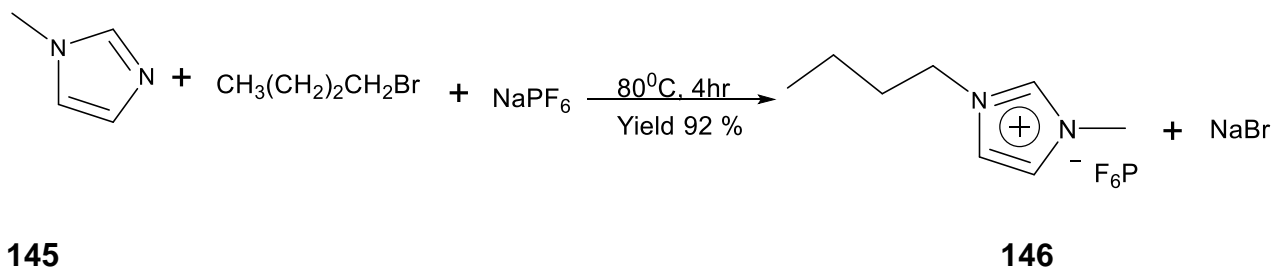
The application of ionic liquids in a variety of reactions and their success in obtaining the required product in good yields encouraged us to think about the use of ionic liquids as solvent in the synthesis of pyranobenzopyrans. Three different ionic liquids were used, 1-butyl-3-methylimidazolium tetrafluoroborate, 1-butyl-3-methylimidazolium hexafluorophosphate and 1-ethyl-3-methylimidazolium ethylsulfate, to study the effect of the different anions and alkyl chain lengths on the imidazolium ion in the yield of the products. The choice of imidazolium ionic liquids was due to their reported physical properties and suitability for the reactants. The ionic liquids based on the [bmim]⁺ have low melting points, for example The [bmim]PF₆ salt has a melting point of 58-60 °C while the [bmim]BF₄⁻ and the [emim]EtSO₃⁻ salts have melting points of 15 and -20 °C, respectively.¹⁰² These ionic liquids have low viscosities, are air and moisture stable and are easily and cheaply synthesized. They can also dissolve a wide range of organic and inorganic compounds which make them applicable in organic synthesis. These properties have opened up the avenue of using them as potential replacement solvents. At present, the most widely used ionic liquids are the species based on 1-methylimidazole. Examples of this group of ionic liquids are [bmim]PF₆ and [bmim]BF₄ which are widely used in synthesis. They are neutral stoichiometric compounds and they are stable to both air and moisture. Also, they are easily synthesized without great expense. They have low densities, viscosities, and they are liquids below room temperature.¹⁰²⁻¹⁰⁵ Two of our ionic liquids were synthesized in lab 1-butyl-3-methylimidazolium

tetrafluoroborate **144** (Scheme 3.20) and 1-butyl-3-methylimidazolium hexafluorophosphate (Scheme 3.21), using known procedures from the literature.¹²³ The yields obtained for both of them were 92%.

Scheme 3.20. Synthesis of 1-Butyl-3-methylimidazolium Tetrafluoroborate

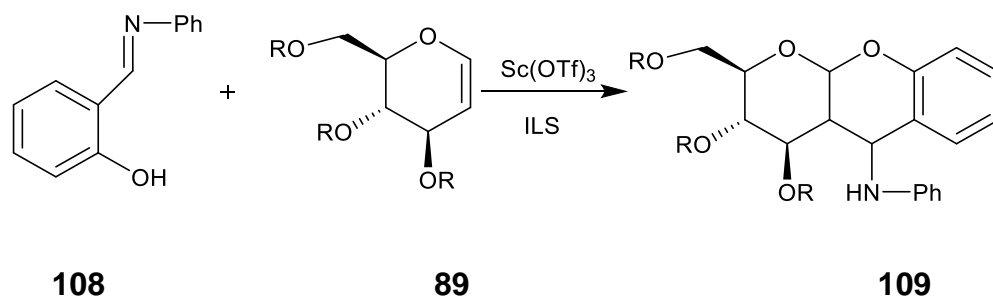


Scheme 3.21. Synthesis of 1-Butyl-3-methylimidazolium Hexafluorophosphate



Cycloaddition reactions were carried out using the previously described method, in which the protected D-glucals were added to the *o*-hydroxybenzalimines in an ionic liquid solvent (ILS) and catalyzed with scandium triflate at room temperature. (Scheme 3.22).

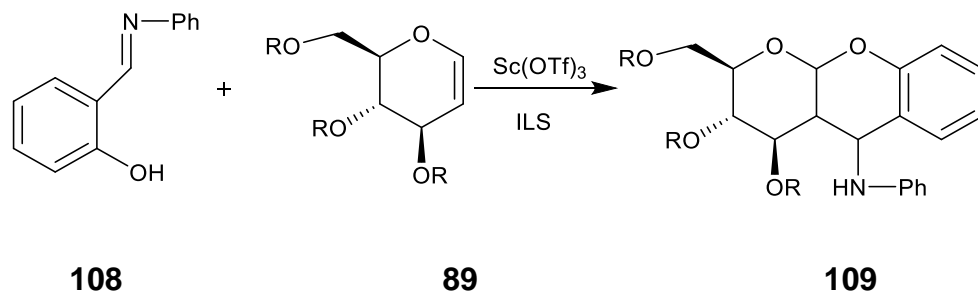
Scheme 3.22. Synthesis of Pyranobenzopyran Using Ionic Liquids.



OR = Acetyl, Silyl, Benzyl ILS = 1-butyl-3-methylimidazolium tetrafluoroborate, 1-butyl-3-methylimidazolium hexafluorophosphate, 1-ethyl-3-methylimidazolium ethylsulfate

Tri-*O*-acetyl and tri-*O*-benzyl D-glucal were insoluble in the ionic liquids whereas the *tris-O-tert*-butyldimethylsilylglucal give a very sticky mixture which was difficult to stir. No reaction was observed to take place with this sugar nor was product obtained. The reason for the failure of these reactions was likely the higher polarity and viscosity of the ionic liquid. With this in mind, we decided to use D-glucal due to its inherent polarity. (Scheme 3.23).

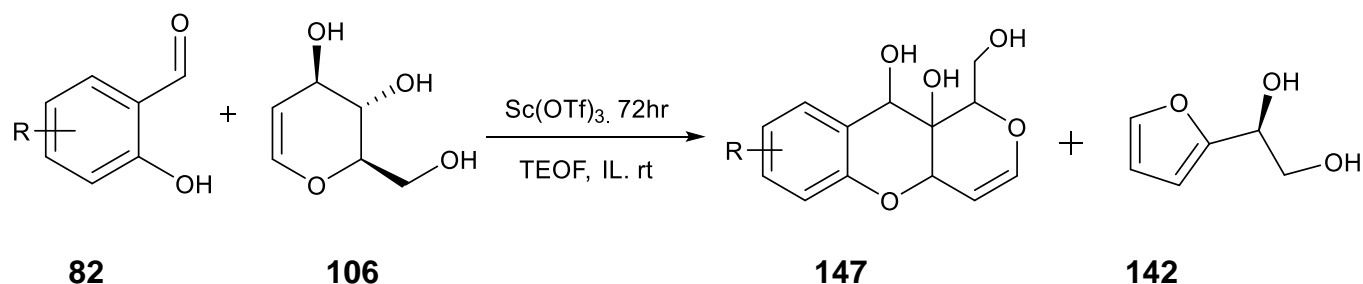
Scheme 3.23 Synthesis of Pyranobenzopyran Using D-glucal in Ionic Liquids



R = Bn, Ac, TBDMS

The D-glucal dissolved well in both 1-butyl-3-methylimidazolium tetrafluoroborate and 1-ethyl-3-methylimidazolium ethylsulfate ionic liquids, as did all the other components of the reaction, to give homogenous mixtures with a brown color. Though the mixtures were stirred for 48 hours the TLC using mixture of (4:1 hexane/EtOAc, acetate) did not show the formation of any product. If the reaction was stirred longer, decomposition of the imine to the aniline and *o*-hydroxybenzaldehyde was observed. We concluded that our procedure was not suitable for the conversion of D-glucal, and we decided to try another literature procedure for the synthesis of pyranobenzopyrans.⁶³ First, we stirred a mixture of *o*-hydroxybenzaldehyde, triethyl orthoformate and Sc(OTf)₃ for 20 min and then added it to the solution of the D-glucal in ionic liquid (Scheme 3. 24). The reaction was stirred for 72 h, and the reaction completion was monitored by thin layer chromatography. Many spots were observed on the TLC. The two major spots were isolated using column chromatography and were identified as chromene derivative **147** and furan diol **142**. The structures of those molecule and all of the other products formed were determined from 1D and 2D, ¹H and ¹³C NMR experiments.

Scheme 3.24. Addition Reactions of D-glucal and *o*-Hydroxybenzaldehydes

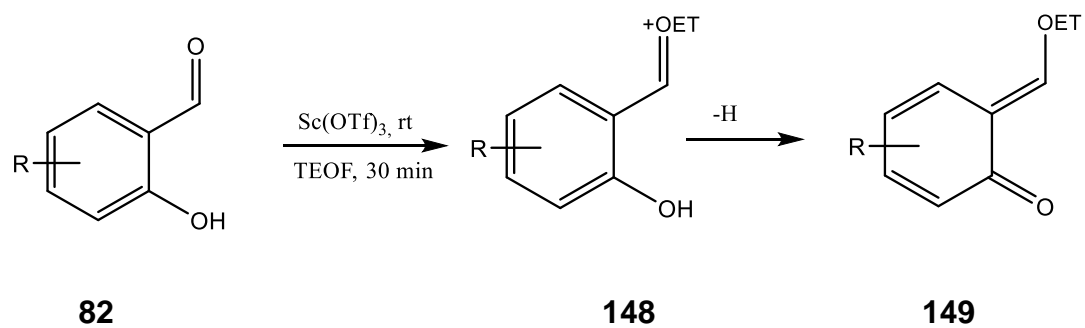


R = H, Cl, Br, OMe, NO₂, OH, Me

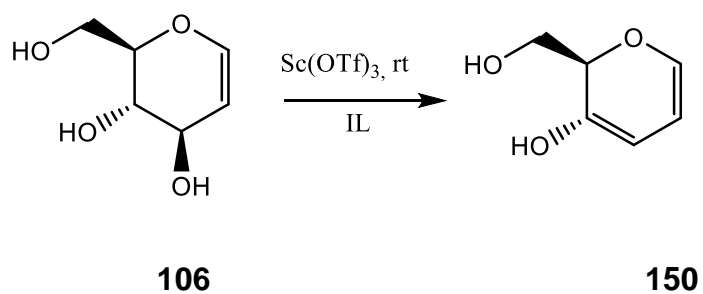
The Proposed Mechanism of the Reaction

The reaction of 2-hydroxybenzaldehyde with triethyl orthoformate probably proceeds through the intermediate formation of **148** and then the formation of the oxa-diene **149**, (step1). In the other hand the stirring of the D-glucal with $\text{Sc}(\text{otf})_3$ in the ionic liquid lead to the formation of the D-glucal diene **150**, (step2). The addition of the sugar diene **150** that react as dienophile to the oxa-diene in a [4+2] cycloaddition to generate the oxygen-containing six member ring **147**, and furan diol as major by-product .

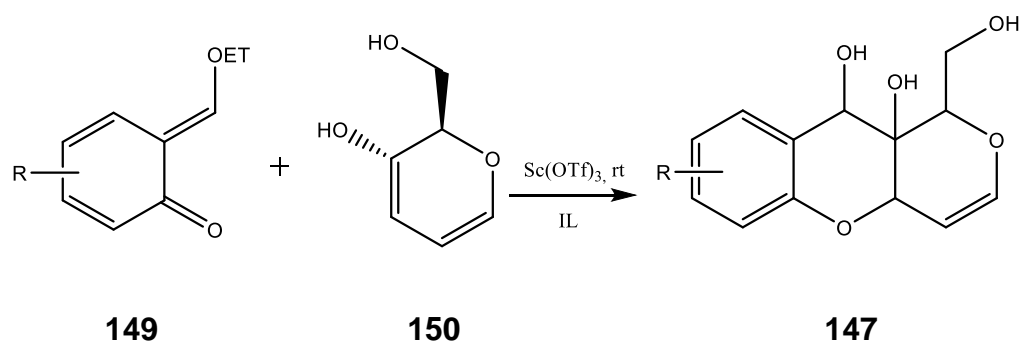
Step1 Formation of Oxa Diene



Step2 Formation of the D-glucal Diene



Step 3 The Cycloaddition Reaction

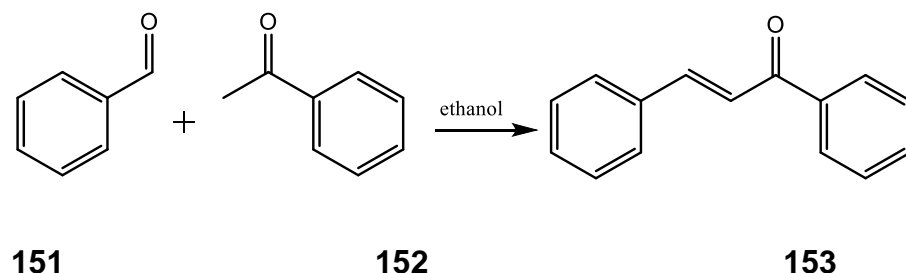


Reaction Optimization

In order to study the effect of substituent on the synthesis of pyranobenzopyrans several salicylaldehyde derivatives **82a-82g**

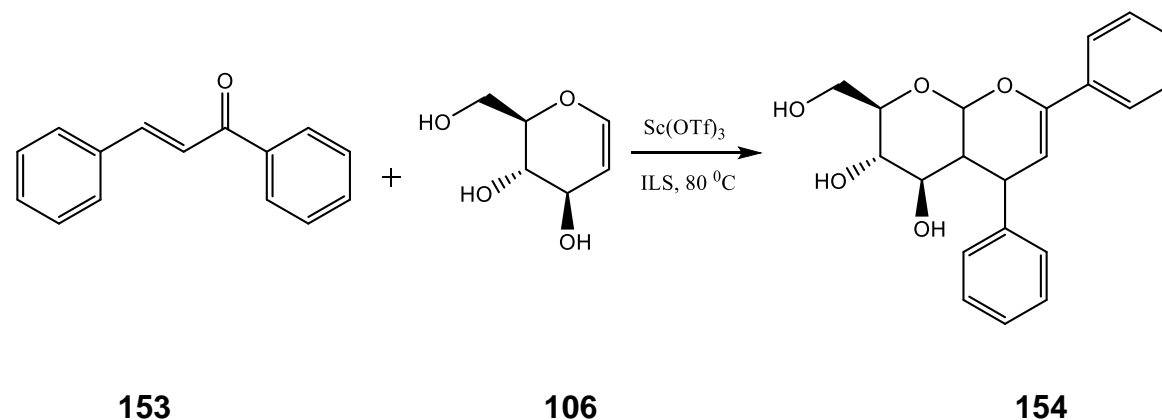
were reacted with glucal **106**. Unfortunately most of the salicylaldehyde derivatives have moderate to zero solubility in the ionic liquids which leads to a reduction of the yield of the major products and an increase in the yield of by-products. The yields for the products **147a-147d** ranged from 36% to 79%. With all of the soluble salicylaldehyde derivatives and glucal addition reactions, furan by-product **142** was also obtained (39-58%). Acetonitrile was added as co-solvent in the reaction to improve the solubility of ionic liquid insoluble salicylaldehyde derivatives such as 2-hydroxy-5-nitrobenzaldehyde, 2-hydroxy-5-methylbenzaldehyde and 2,5-dihydroxybenzaldehyde. 2-Hydroxy-5-nitrobenzaldehyde was completely dissolved in the mixture of the ionic liquid with acetonitrile, whereas 2-hydroxy-5-methylbenzaldehyde and 2,5-dihydroxybenzaldehyde were partially dissolved but no product was formed after stirring for 72 hours at room temperature. Our success in the synthesis using ionic liquids encouraged us to try different dienes, *E*-chalcone **153**, was first prepared as the starting material using the known literature procedure.¹²⁴ (Scheme 3.25). A representative experimental procedure for this involved a room temperature reaction between benzaldehyde **151**, acetophenone **152** and a saturated sodium hydroxide solution in 95% ethanol.

Scheme 3.25. Synthesis of *E*-Chalcone



Once the *E*-chalcone **153** was synthesized we added it to D-glucal **106** in ionic liquid in the presence of scandium triflate (Scheme 3.26). The *E*-chalcone **153** was insoluble in the ionic liquid in both conditions, at room temperature, or when it was heated to 80 °C.

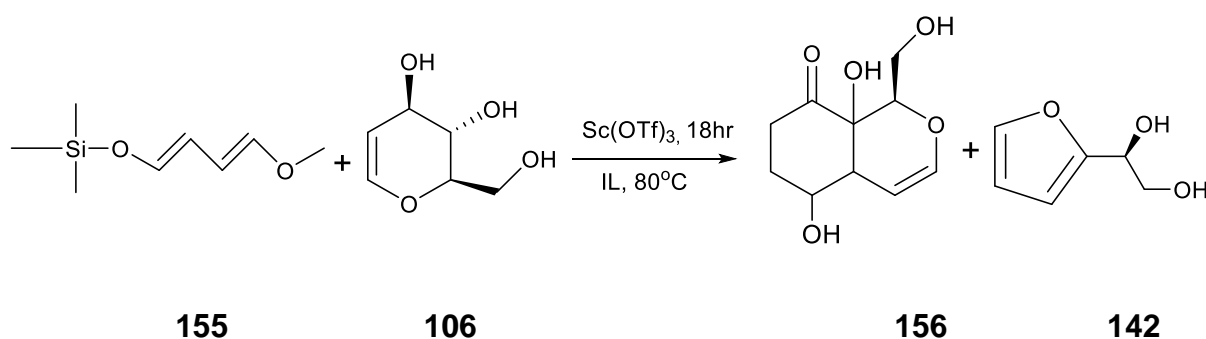
Scheme 3.26. The Reaction Between D-glucal with *E*-Chalcone.



D-glucal **106** and 1-methoxy-3-trimethylsiloxy-1,3-butadiene **155** was also reacted in ionic liquid solvent in the presence of Sc(OTf)₃. The electron donating nature of this diene is known to confer higher reactivity and orientational specificity in its reaction with unsymmetrical dienophiles.¹²⁵ We first conducted this reaction at room temperature but it took a long time (72 hours) and a low yield (56%) was

obtained for the main product Then we heated the reaction to 80 °C for 12 hours to optimize for the product. The resulting molecule, 2-5,8a-dihydroxy-1(hydroxymethyl)-1, 4a, 5, 6, 7,8a-hexahydro-8H-isochromeneone **156** was obtained in 76 % yield (Scheme 3.27). Upon our successes in this reaction we used the microwave reactor to provide heat and shorten the reaction time, the reaction mixture was heated for a range of time from 2 to 10 minutes at 80 °C R = Bn, Ac, TBDMS had occurred.

Scheme 3.27 Reaction of Danishefsky's Diene with D-Glucal



In general, we assumed the [4+2] cycloaddition reaction would take place between the diene and the unsaturated carbons in D-glucal but the ^1H NMR and ^{13}C NMR showed the glucal double bonds were still present around 6 ppm in all the predicted structures. The tables below summarize the ^1H and ^{13}C data and illustrate the assigned structures **147_a**-**147_d**, **156**. Then we believed that the reaction occurred via the initial formation of a sugar diene that reacts as a dienophile where the other reactants in a [4+2] cycloaddition to generate the oxygen-containing six-membered ring. The fact that D-glucal **106** could participate as both the diene or as the dienophile in these ionic liquid mediated reactions was evidenced by the formation of the glucal dimer **157** (Scheme 3.27). The

formation of furan diol **142** can also be accounted for via an acid catalyzed elimination such as that leading to intermediate **157** or a similar ring opened analog.

Scheme 3.28. Dimerization of D-Glucal.

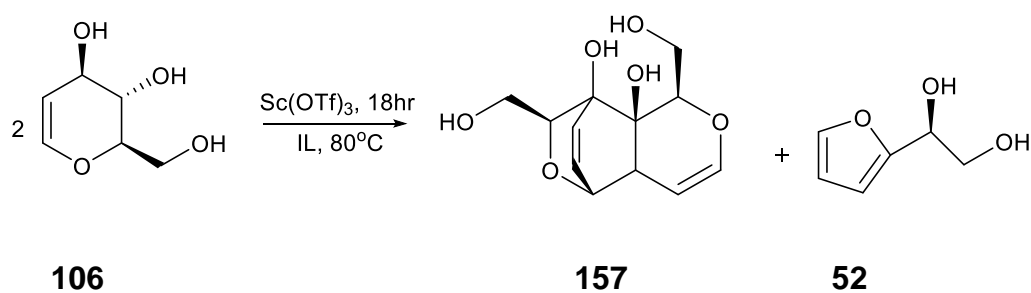
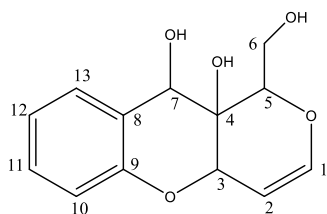


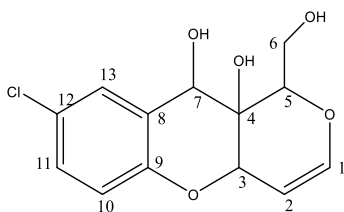
Table 3.4. 1-(hydroxymethyl)-1H,10H-pyrano[4,3-b]chromene-10,10a(4aH)-diol (9a)

147_a



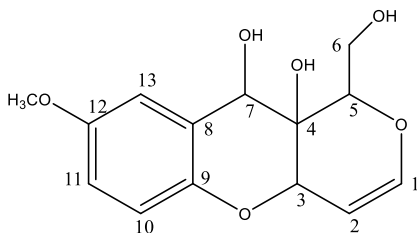
Atom label	¹ H Chemical Shift (ppm)	¹³ C Chemical Shift (ppm)
1	6.34	144.02
2	4.74	106.23
3	4.38	81.97
4	4.77	100.30
5	4.25	69.58
6, 6'	3.94-3.81	66.72
7	5.96	68.98
8		128.77
9		130.93
10	7.43	116.87
11	6.90	128.77
12	6.87	120.10
13	7.22	130.93

Table 3.5. 12-chloro-1-(hydroxymethyl)-1H, 10H-pyrano[4,3-b]chromene-10,10a(4aH)-diol **147b**



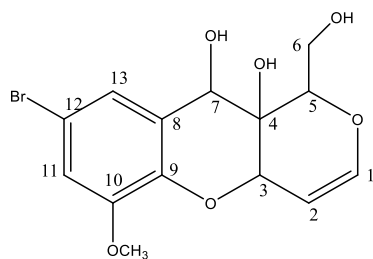
Atom label	¹ H Chemical Shift (ppm)	¹³ C Chemical Shift (ppm)
1	6.35	143.11
2	4.47	105.34
3	4.42	81.04
4		97.72
5	4.29	68.60
6, 6'	3.91	55.8
7	5.93	68.06
8		117.60
9		129.71
10	6.88	127.43
11	7.22	129.47
12		127.43
13	7.42	129.47

Table 3.6.14-(hydroxymethyl)-12-methoxy-1H,10H- pyrano[4,3-b]chromene-10,
10a(4aH)-diol **147c**



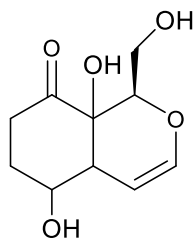
Atom label	¹ H Chemical Shift (ppm)	¹³ C Chemical Shift (ppm)
1	6.35	144.03
2	4.74	106.15
3	4.41	81.90
4		99.96
5	4.35	69.53
6, 6'	3.90-3.80	66.72
7	5.90	68.93
8		124.88
9		153.78
10	6.80	116.49
11	6.80	117.64
12		113.71
13	6.99	149.50
14	3.72	

Table 3.7. 12-bromo-1-(hydroxymethyl)-6 methoxy-1H, 10-H-pyrano[4,3-b]c10, 10a
(4aH)-diol **147d**



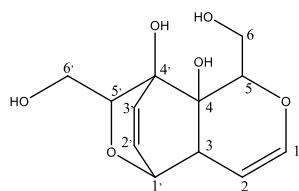
Atom label	¹ H Chemical Shift (ppm)	¹³ C Chemical Shift (ppm)
1	6.38	
2	4.76	110.94
3	4.25	81.89
4		97.38
5	3.84	69.62
6, 6'	3.84	66.73
7	5.99	68.95
8		126.51
9		144.03
10		144.03
11	7.25	115.65
12		149.31
13	7.11	122.72
14	3.89	56.86

Table 3.8. 1a-dihydroxy-7-(hydroxymethyl)-1, 4 a, 5, 6, 7, 8a-hexahydro-1H-
isochromene-1-one **156**



Atom label	¹ H Chemical Shift (ppm)	¹³ C Chemical Shift (ppm)
1	6.29	144.16
2	4.75	103.83
3	4.39	80.47
4		98.95
5	4.20	68.05
6, 6'	3.60	66.66
7		68.34
8, 8'	2.13	31.21
9	2.81	48.28
10	5.06	204.1

Table 3.9. D-Glucal Dimer **157**



Atom label	¹ H Chemical Shift (ppm)	¹³ C Chemical Shift (ppm)
1	6.28	143.36
1'	3.36	79.20
2	4.56	104.70
2'	5.06	104.90
3	3.10	69.60
3'	4.83	143.25
4		68.92
4'		79.44
5	3.60	79.94
5'	3.60	79.70
6 _a , 6 _b	3.98, 3.70	68.85
6' _a , 6' _b	3.57	60.84

3.3.4. Summary

In this research, we examined three imidazolium-based ionic liquids as solvents in cycloaddition reactions. The choice of these ionic liquids is based on their features such as ease of modifications, stability under acidic conditions.¹²⁶ 1-butyl-3-methylimidazolium tetrafluoroborate (Table 3.10) and 1-ethyl-3-methylimidazolium ethylsulfate ionic liquid (Table 3.11), readily solubilized D-glucal **106**, o-hydroxybenzaldehyde and its derivatives, triethyl orthoformate and $\text{Sc}(\text{OTf})_3$ whereas the ionic liquid 1-butyl-3-methylimidazolium hexafluorophosphate was very poor at solubilizing those reagents. The difference in these three RTILs and their solubilizing ability for D-glucal **106** is a good example of the tunable properties of ionic liquids. In general, we observed the yields from 1-ethyl-3-methylimidazolium ethylsulfate were much better due to the higher solubility of D-glucal than in the other solvents. In this medium, the difference in the viscosity of the IL determines its reaction rates with D-glucal. The reactant particles diffuse faster in less viscous solvents and can collide at a higher frequency per unit time. Thus the reaction rates decrease rapidly with the increase of solvent viscosity. The viscosity of 1-ethyl-3-methylimidazolium ethylsulfate is 122 mpa where the viscosity for 1-butyl-3-methylimidazolium tetrafluoroborate is 135 mpa.¹²⁷

Table 3.10. The Result Obtained Using the 1-butyl-3-methylimidazolium
Tetrafluoroborate Ionic Liquid Solvent

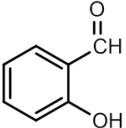
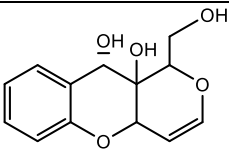
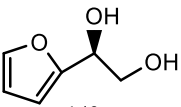
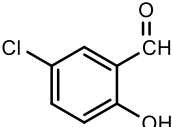
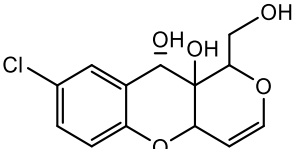
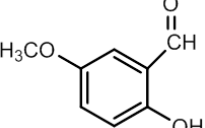
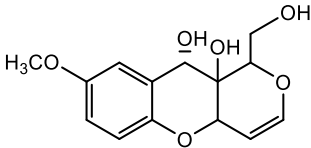
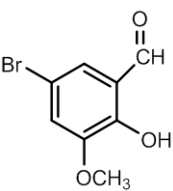
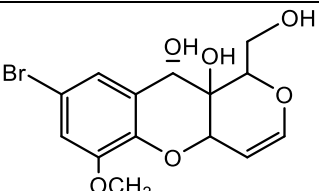
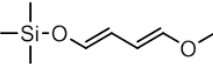
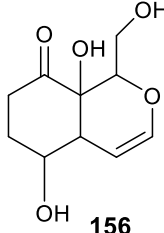
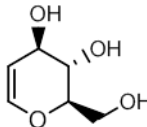
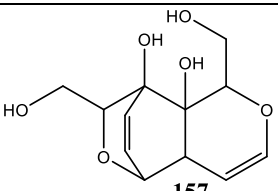
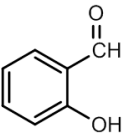
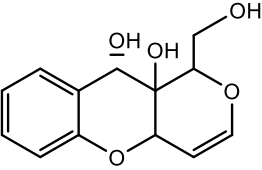
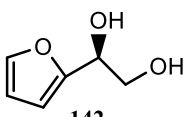
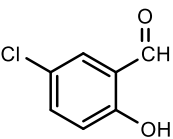
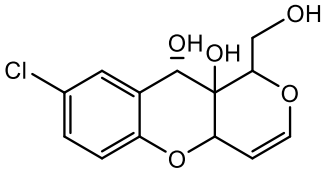
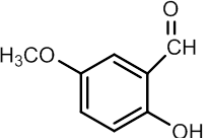
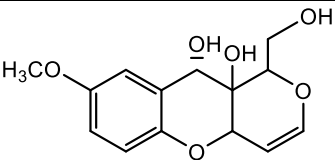
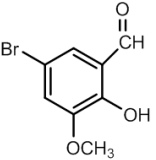
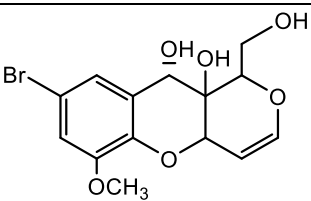
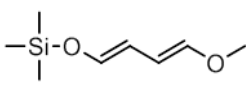
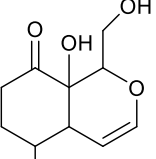
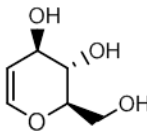
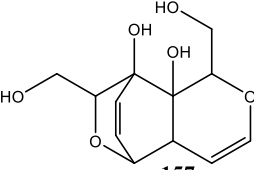
Entry	Diene	Product	% Yield	By-product	% Yield
1-		 147a	51	 142	29
2-		 147b	57	"	41
3-		 147c	53	"	32
4-		 147d	36	"	53
5-		 156	61	"	23
6-		 157	32	"	53

Table 3.11. Cycloaddition Reactions with 1-ethyl-3-methylimidazolium ethylsulfate Ionic Liquid

Entry	Diene	Product	% Yield	By-product	% Yield
1-		 147a	73	 142	22
2-		 147b	78	"	18
3-		 147c	72	"	21
4-		 147d	58	"	37
5-		 156	76	"	17
6-		 157	32	"	53

Summary

The reaction of carbohydrates in organic solvents typically requires protection of the hydroxyl groups as non-polar-moieties to enhance their solubility. Later, a subsequent deprotection step is carried out to remove the protecting groups. In this part of our research we have been able to synthesize a series of pyranobenzopyrans **147_a**-**147_d** in modest yields. Furan diol **142** was isolated as the major byproduct from these reactions. Lewis acid-catalyzed cycloaddition reactions of D-glucal **106** with different dienes were carried out in room temperature ionic liquids. The products obtained from these reactions are shown in Table 3.10.

Chapter 4

Conclusion

4.1. Summary

The goal of this project was to develop a method for the synthesis of pyranobenzopyrans and carbohydrate-fused heterocyclic compounds. This was accomplished via a [4+2] cycloaddition reaction to generate the oxygen-containing six-membered ring by the addition of the imine **64**; *o*-hydroxybenzalimine and its derivatives to glucals in organic solvent under catalysis by scandium triflate. The conventional method and microwave reactor method were initially used to achieve this goal, but no reaction was observed in both cases. The failure of this reaction under these cases may be due to the sugar protecting groups such as acetyl, benzyl and *t*-butyldimethylsilyl that made steric hindrance and inhibited the reaction. Then new methodology was developed and an ionic liquid was used as solvent to dissolve the D-glucal and the other reactants. A series of pyranobenzopyrans have been prepared via Lewis Acid catalyzed cycloaddition reactions of D-glucal and *o*-hydroxybenzaldehyde and its derivatives in room temperature imidazolium ion-based ionic liquid solvents. Different *o*-hydroxybenzaldehyde derivatives **82a-82g** were tested to study the effect of the substituents on the rate of the reaction. Four products were obtained **147a-147d** in poor to moderate yields. Because 2-hydroxy-5-nitrobenzaldehyde, 2-hydroxy-5-methylbenzaldehyde and 2,5-dihydroxybenzaldehyde

were insoluble in the ionic liquids, no product was obtained from their reaction with D-glucal. Danishefsky's Diene, and 1-methoxy-3-trimethylsiloxy-1, 3-butadiene **155**, were also reacted in ionic liquids and the product 2-5,8a-dihydroxy-1(hydroxymethyl)-1,4a, 5, 6, 7,8a-hexahydro-8H-isochromeneone **156** was obtained in moderate yield. In these reactions, the glycal itself was found to serve as a diene with another molecule of glycal as the dienophile to form an interesting sugar dimer.

In conclusion, we successfully synthesized pyranbenzopyran derivatives and their structures were confirmed by using 1-D ^1H and 2-D ^1H and ^{13}C NMR

4.2. Experimental Section

General methods: Proton nuclear magnetic resonance (^1H NMR) spectra were recorded on a Varian Inova (500 MHz) spectrometer. NMR samples were dissolved in d_6 -acetone, d_1 -chloroform or d_6 -DMSO and chemical shifts were reported in ppm relative to the residual non-deuterated solvent (acetone methyl group at 2.05 ppm) or to the methyl protons on tetramethylsilane (TMS, 0.00 ppm). ^1H NMR data are reported as follows: chemical shift, integration, multiplicity (s = singlet; d = doublet; dd = doublet of doublet; ddd = doublet of doublet of doublets; m = multiplet), coupling constant, and assignment. ^{13}C NMR were recorded on the same instrument (125 MHz). The ^{13}C chemical shift were reported relative to the references at 29.84, 77.23 and 39.51 ppm, respectively. All the NMR experiments were run at room temperature (25°C) and assignments were done by using gCOSY and gHMQC. The mass spectra were obtained at the University of Illinois (Champaign-Urbana). Both the higher resolution and the low resolution

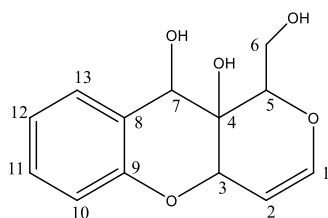
mass spectra were obtained by ESI (electron spray ionization). Melting points (mp) were measured on a Mel-Temp melting point apparatus (Laboratory Devices, Inc., USA). The optical rotations were recorded on automatic polarimeter (Rudolph Instruments, New Jersey USA). Reactions were monitored by thin-layer chromatography (TLC) on 0.25 mm silica gel coated aluminum sheets 60 F254 (Analtech). Silica gel (particle size 40–63 Å, 230–400 mesh) (Silicycle) was used for flash column chromatography. Preparative thin-layer chromatographic separations were carried out on 2000 mm silica gel coated glass plates 60 F254 (Analtech). All the reactions were carried out in oven-dried glassware under nitrogen. D-glucal was prepared from commercially-available 3, 4, 6-tri-O-acetyl-D-glucal (Aldrich Chemical Co.). The ionic liquids were prepared using 1-methylimidazole, 1-bromobutane, sodium tetrafluoroborate or sodium hexafluorophosphate at 80 °C. All the starting materials and reagents were obtained from Alfa Aesar and Sigma Aldrich Chemical Companies.

4.2.1. Representative Experimental Procedures

3.2.1. 1-(hydroxymethyl)-1H,10H-pyrano[4,3-b]chromene-10, 10a(4aH)-diol (147a).

A mixture of o-hydroxybenzaldehyde **8a** (287 µL, 2.7 mmol), triethyl orthoformate (558 µL, 2.7 mmol) and scandium triflate (66 mg) was stirred in 5 mL of 1-butyl-3-methylimidazolium tetrafluoroborate or 1-ethyl-3-methylimidazolium ethylsulfate for 20 min then (400 mg, 2.7 mmol) D-glucal **106** was added to the mixture. The resulting mixture was stirred at ambient temperature until complete conversion was indicated by TLC. The reaction mixture was quenched with water (20 mL) and extracted with ethyl acetate (3 x 10 mL); the combined organic extracts were dried over anhydrous sodium sulfate, and concentrated *in vacuo*. The crude

product was purified by column chromatography using mixture of (98:2 CHCl₃/CH₃OH) followed by repurification on a 2000 μ m silica gel thin layer chromatography plate. All subsequent reported yields were from reactions conducted in 1-butyl-3-methylimidazolium tetrafluoroborate. NMR assignments refer to the following ring positions:



The final product **147a** was a white powder (0.376 g, 1.38 mmol, 51%): mp 118 °C: R_f (98:2 CHCl₃/CH₃OH): 0.36; [α]_D 21° + 8.6 (c 0.75, CHCl₃); ¹H NMR (500 MHz, d₆ acetone) δ 7.22 (m, 2H, H-13, H-10, Ar), 7.09 (m, 2H, H-11, H-14 Ar), 6.34 (dd, 1H, J_{1,2} = 6.0, J_{1,3} = 1.5 Hz, H-1), 5.96 (s, 1H, H-7), 4.74 (dd, 1H, J_{2,1} = 6.0 Hz, J_{2,3} = 1.5 Hz, H-2), 4.38 (ddd, 1H, J = 6.5 Hz, J_{3,2} = 2.0 Hz, J_{3,1} = 1.5 Hz, H-3), 4.25 (dd, 1H, J_{5,6} = 10.0 Hz, J_{5,6'} = 5.0 Hz, H-5), 3.94-3.81 (m, 2H, H-6, H-6'); ¹³C NMR (125 MHz, d₆ acetone) δ 144.02 (C-1), 130.93 (2C) (C-13, C-9), 128.77 (2C) (C-11, C-8), 120.10 (C-12), 116.87 (C-10), 106.23 (C-2), 100.30 (C-4), 81.97 (C-3), 69.58 (C-5), 68.98 (C-7), 66.72 (C-6). HRMS (ESI): Calcd. for C₁₃H₁₄O₅ for (M+Na)⁺ 273.0741. Found 273.0739. Compound **142** (0.100 g, 0.78 mmol, 29%) was also isolated as a colorless oil: R_f (98:2 CHCl₃/CH₃OH): 0.48. The ¹H NMR (500 MHz, CDCl₃) was in good agreement with previously reported data for this compound. ¹³C NMR (125 MHz, d₆-acetone) 153.59 (C1), 141.55 (C4), 110.18 (C2), 106.42 (C3), 63.06 (C1'),

42.43 (C2'); HRMS (ESI): Calcd for $C_6H_8O_3$ for $(M + H)^+$ 128.04735. Found 128.04773.

3.2.2. 8-chloro-1-(hydroxymethyl)-1H, 10H-pyrano[4,3-b]chromene-10,10a(4aH)-diol (147b).

The title compound was obtained as white powder (0.473 g, 1.5 mmol, 57%) : mp 71 °C: R_f (98:2 CHCl₃/CH₃OH): 0.38; $[\alpha]_D^{22}$ - 9.7 (c 0.75, CHCl₃); ¹H NMR (500 MHz, d₆ acetone) δ 7.42 (d, 1H, J_{1,11} = 1.5 Hz, H-13, Ar), 7.22 (dd, 1H, J_{11,10} = 6.5 Hz, J_{11,13} = 2.5 Hz, H-11, Ar), 6.88 (d, 1H, J_{10,11} = 9.0 Hz, H-10, Ar), 6.35 (d, 1H, J_{1,2} = 6.0 Hz, H-1), 5.93 (s, 1H, H-7), 4.74 (dd, 1H, J_{2,1} = 6.0 Hz, J_{2,3} = 1.5 Hz, H-2), 4.42 (brs, 2H, H-3, OH), 4.29 (dd, 1H, J_{5,6} = 10.0 Hz, J_{5,6'} = 5.0 Hz, H-5), 3.91 (m, 2H, H-6, H-6'); ¹³C NMR (125 MHz, d₆ acetone) δ 154.47 (C-12), 143.11 (C-1), 129.71 (2C) (C-13, C-9), 127.43 (2C) (C-11, C-12), 105.34 (C-2), 97.72 (C-4), 81.04 (C-3), 68.60 (C-5), 68.06 (C-7), 55.80 (C-6); HRMS (ESI): Calcd. for $C_{13}H_{14}O_5$ for $(M+Na)^+$ 307.0352. Found 307.0349. Elution also afforded **142** (0.142 g, 1.11 mmol, 41%).

3.2.3. 1-(hydroxymethyl)-8-methoxy-1H, 10H- pyrano[4,3-b]chromene-10, 10a(4aH)-diol (147c).

The title compound was obtained as white powder (0.434 g, 1.43 mmol, 53%) : mp 87 °C: R_f (98:2 CHCl₃/CH₃OH): 0.40; $[\alpha]_D^{21}$ + 8.9 (c 0.75, CHCl₃); ¹H NMR (d₆ acetone) δ 7.66 (brs, 1H, OH), 6.99 (d, 1H, J_{13,11} = 2.0 Hz, H-13, Ar), 6.80 (m, 2H, H-10,11, Ar), 6.35 (d, 1H, J_{1,2} = 4.5 Hz, H-1), 5.90 (s, 1H, H-7), 4.74 (dd, 1H, J_{2,1} = 5.0 Hz, J_{2,3} = 1.5 Hz, H-2), 4.45 (brs, 1H, OH), 4.41 (dd, 1H, J_{3,2} = 6.0 Hz, J_{3,1} = 2.0 Hz, H-3), 4.35 (dd, 1H, J_{5,6} = 10.0, J_{5,6'} = 5 Hz, H-5), 3.90- 3.80 (m, 2H, H-6, H-6'), 3.72 (s, 3H, H-

14); ^{13}C NMR (d6 acetone) δ 153.78 (C-9), 149.50 (C-13), 144.03, (C-1) 124.88 (C-8), 117.64 (C-11), 116.49 (C-10), 113.71 (C-13), 106.15 (C-2), 99.96 (C-4), 81.90 (C-3), 69.53 (C-5), 68.93 (C-7), 66.72 (C-6), 55.98 (C-14); HRMS (ESI): Calcd. for $\text{C}_{14}\text{H}_{16}\text{O}_6$ for $(\text{M}+\text{Na})^+$ 303.0839. Found 303.0845. Furan diol **142** was also obtained (0.110 g, 0.87 mmol, 32%).

3.2.4. 8-bromo-1-(hydroxymethyl)-6 methoxy-1H, 10H-pyrano[4,3-b]c10, 10a

(4aH)-diol 147_d The title product was obtained as white powder (0.349 g, 0.97 mmol, 36 %); mp 92 °C; Rf (98:2 CHCl_3 / CH_3OH): 0.42; $[\alpha]_{\text{D}}^{22} + 12.4$ (c 0.75, CHCl_3); ^1H NMR (d6 acetone) δ 7.25 (d, 1H, $J_{11,13} = 2.5$ Hz, H-11 Ar), 7.11 (d, 1H, $J_{13,11} = 2.5$ Hz, H-13 Ar), 6.38 (dd, 1H, $J_{1,2} = 6.0$ Hz, $J_{1,3} = 1.5$ Hz, H-1), 5.99 (s, 1H, H-7), 4.76 (dd, $J_{2,1} = 6.0$ Hz, $J_{2,3} = 1.2$ Hz, H-2), 4.25 (dd, 1H, $J_{3,2} = 1.5$ Hz, $J_{3,1} = 1.2$ Hz, H-3), 3.89 (s, 3H, H-14), 3.84 (m, 3H, H-5, 6, 6'); ^{13}C NMR (d6 acetone) δ 149.31 (C-12), 144.48 (C-1), 144.03 (2C)(C-9, C-10), 126.51 (C-8), 122.72 (C-13), 115.65 (C-11), 110.94 (C-12), 106.22 (C-2), 97.38 (C-4), 81.89 (C-3), 69.62 (C-5) 68.95 (C-7), 66.73 (C-6), 56.86 (C-14). HRMS (ESI): Calcd for $\text{C}_{14}\text{H}_{15}\text{O}_6$ for $(\text{M}+\text{H})^+$ 359.0115. Found 359.0130. Compound **142** was also isolated (0.183 g, 1.43 mmol, 53%).

3.3. 8a-dihydroxy-1-(hydroxymethyl)-1, 4 a, 5, 6, 7, 8a-hexahydro-8H-isochromene-8-one (156).

A mixture of D-glucal **106** (400 mg, 2.7 mmol), 1-methoxy-3-trimethylsiloxy-1 3-butadiene **155** (517 mg 3.0 mmol) and scandium triflate (66 mg) in 1-butyl-3-ethylimidazolium tetrafluoroborate (5 mL) was stirred overnight at 80 °C. After completion of the reaction, as indicated by TLC using mixture of 98:2 ($\text{CHCl}_3/\text{CH}_3\text{OH}$), the reaction mixture was quenched by addition of water (20 mL)

and extracted with ethyl acetate (3 x 10 mL). The combined organic layers were dried over anhydrous sodium sulfate, and the resulting product was purified by column chromatography using mixture of 98:2 (CHCl₃/CH₃OH) followed by a second purification on a 2000 μ m thin layer SiO₂ chromatography plate and the pure product was concentrated *in vacuo*. The final product **156** was white powder (0.354 g, 1.6 mmol, 61%) : mp 95 °C; R_f (98:2 CH₃OH/CHCl₃): 0.32; [α] D₂₁ + 36.2 (c 0.80 ,CHCl₃); ¹H NMR (500 MHz,CDCl₃) δ 6.15 (dd,1H, J_{1,2} = 6.5, J_{1,3} = 2.0 Hz, H-1), 4.92 (dd, 1H, OH), 4.60 (dd,1H, J_{2,1} = 6.0, J_{2,3} = 2.5 Hz, H-2), 4.24 (ddd, 1H, J_{3,7} = 5.5, J_{3,2} = 2.5 Hz, J_{3,1} = 1.2 Hz, H-3), 4.05 (dd, 1H, J_{5,6} = 10.0, J_{5,6a} = 5.5 Hz, H-5), 3.60 (m, 1H, H-7), 3.50 (m, 2H, H-6, H-6a), 2.67 (dd, 2H, J = 5.00 Hz, H-9, H-9a), 2.13 (m, 2H, H-8, H-8a). ¹³C NMR (125 MHz, CDCl₃) 204.1 (C-10), 144.16 (C-1), 103.83 (C-2), 98.95 (C-4), 80.47 (C-3), 68.34 (C-7), 68.05 (C-5), 66.66 (C-6), 48.28 (C-9), 31.21 (C-8). HRMS (ESI): Calcd for C₁₀H₁₄O₅ for (M+H⁺) 215.0917. Found 215.0919; Prior elution also gave **142** (0.08 g, 0.62 mmol, 23%).

3.4. D-Glucal Dimer (**157**).

A mixture of D-glucal **106** (400 mg, 2.7 mmol) and scandium triflate (66 mg) was stirred in of 1-butyl-3-methylimidazolium tetrafluoroborate (5 mL) overnight at 80 °C. The crude product was purified by column chromatography (92:8 CHCl₃/CH₃OH) to afford product **157** as a white solid (0.221 g, 0.86 mmol, 32 %) : mp 78 °C: R_f (92:8 CHCl₃ /CH₃OH): 0.29; ¹H NMR (d₆ DMSO) δ 6.28 (dd, 1H, J_{1,2} = 6.0 Hz, J_{1,3} = 1.5 Hz, H-1), 5.06 (brd, 1H, J_{2'}, 3' = 4.5 Hz, H-2'), 4.83 (brd, 1H, J_{3'}, 2' = 4.5 Hz, H-3'), 4.56 (m, 2H, H-2, H-4'), 3.98 (brs, 1H, H-6a), 3.70 (brs, 1H, H-6b), 3.57 (d, 2H, J_{6'a,6'b} = 10.5 Hz, H-6'a, H-6'b), 3.36 (brs, 1H, H-5), 3.10 (m, 1H, H-5'); ¹³C NMR

(CDCl₃) δ = 143.36 (C-1), 143.25 (C-3'), 104.90 (2C) (C-2, C-2'), 79.94 (C-5), 79.70 (C-5'), 79.44 (C-4'), 79.20 (C-1') 69.60 (C-3), 68.92 (C-4), 68.85 (C-6), 60.84 (C-6')

LRMS (ES⁺): Calcd C₁₂H₁₆O₆ for (M+Na)⁺ 256.08. Found 256.09. Compound **142** was also obtained (0.183 g, 1.43 mmol, 53%).

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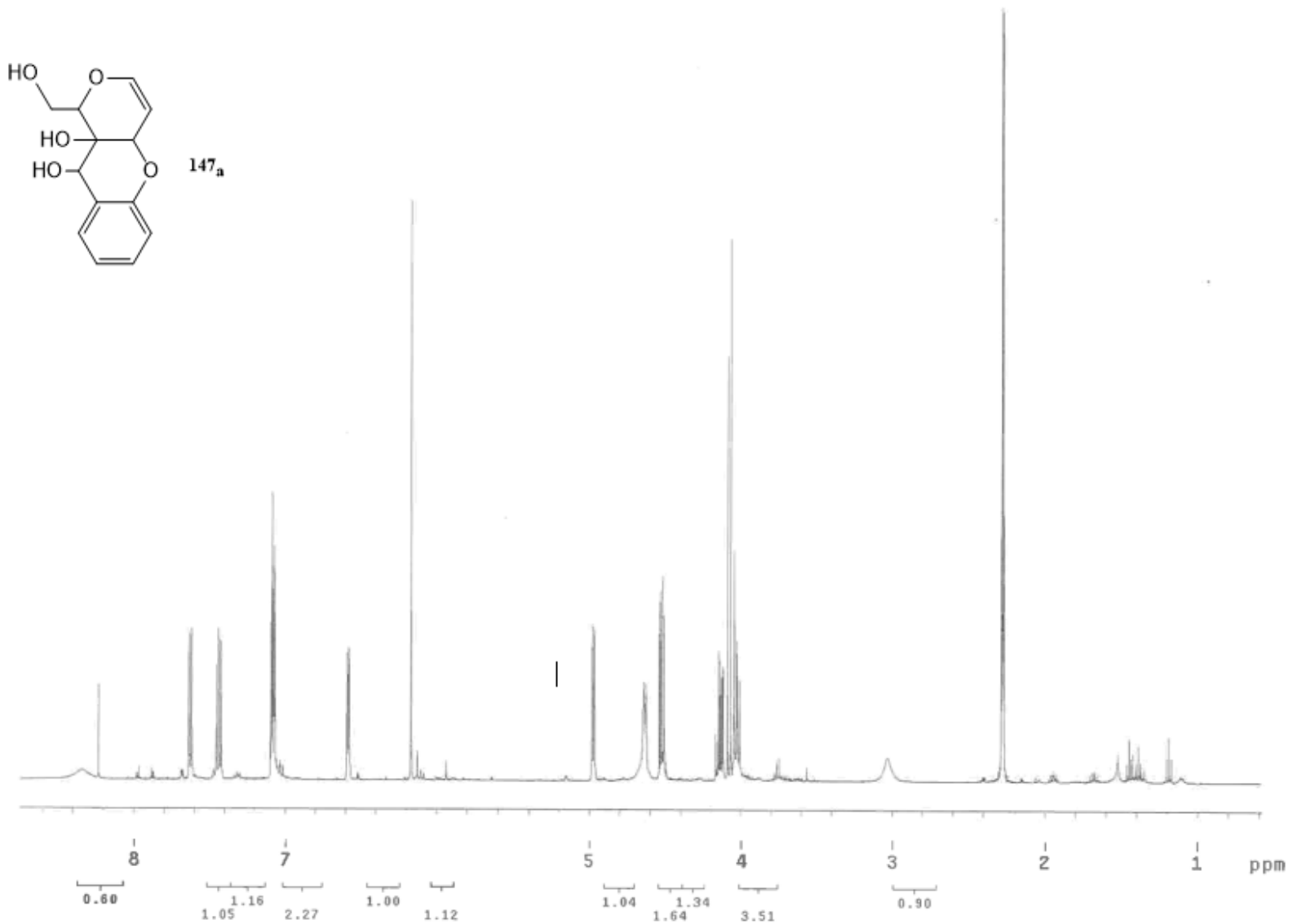
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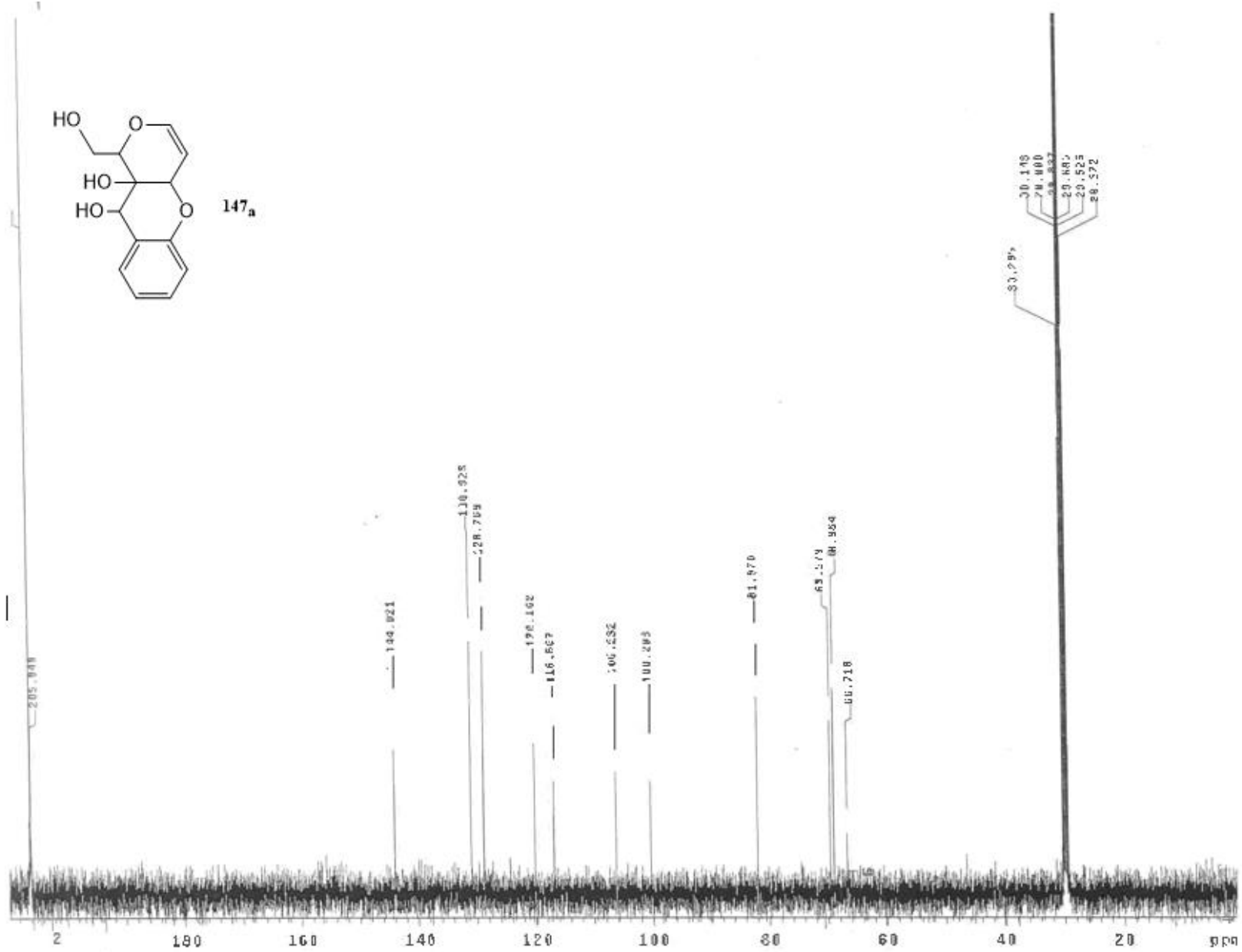
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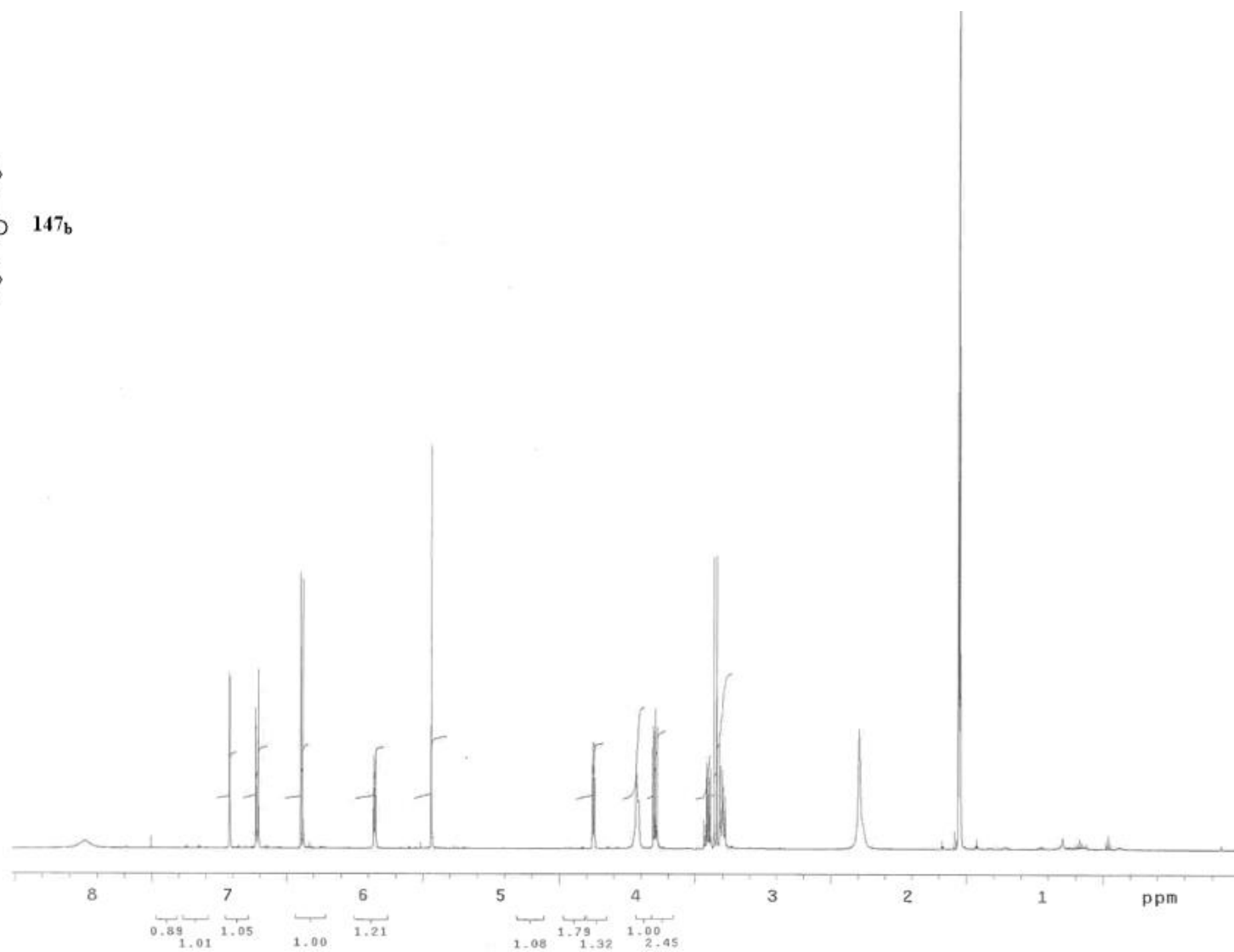
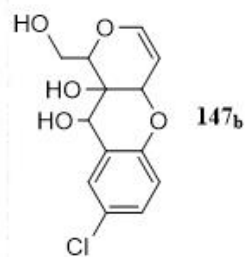
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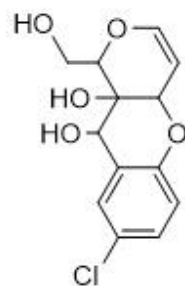
4.3. Appendix

^1H and ^{13}C NMR Spectra of the produced compounds

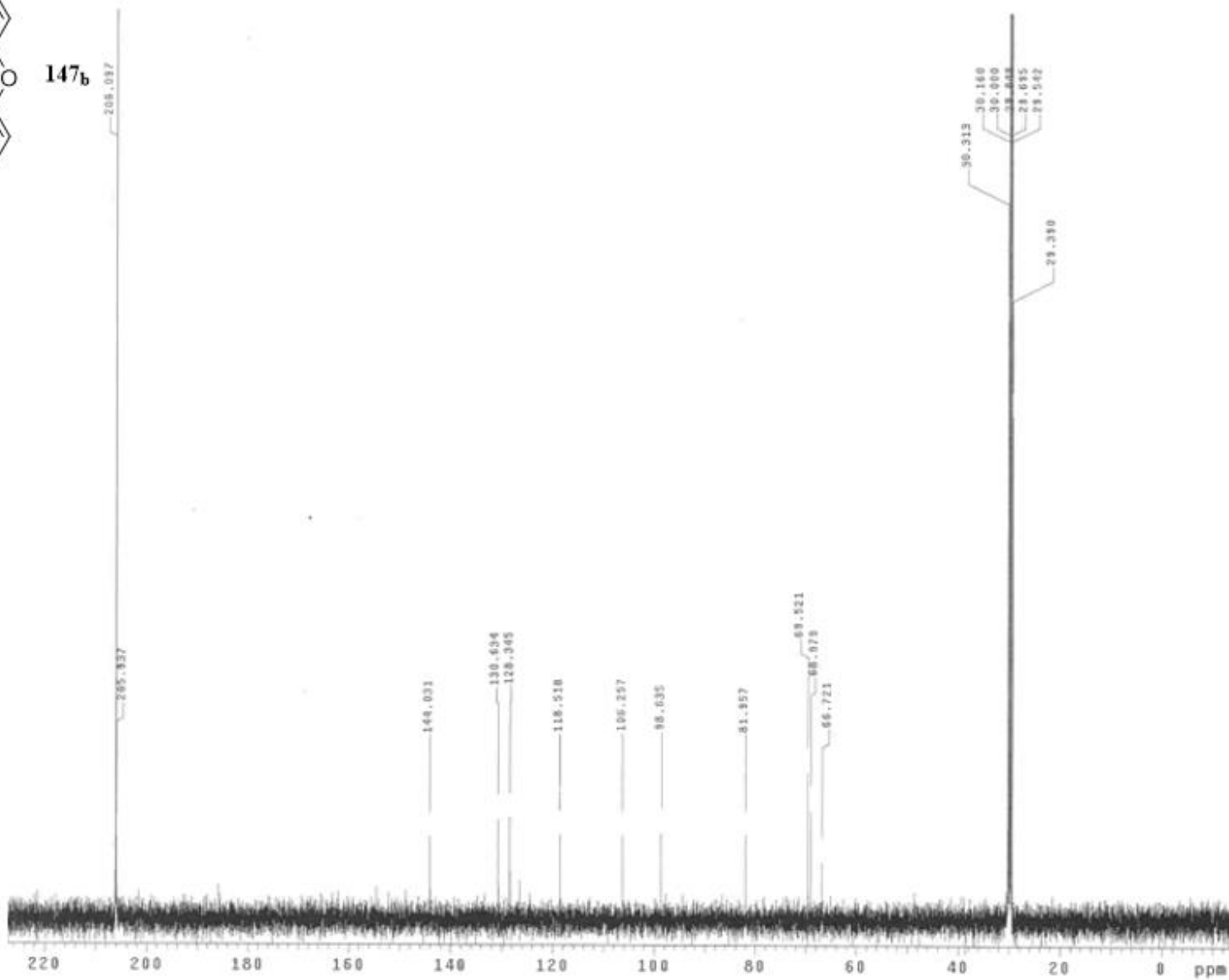


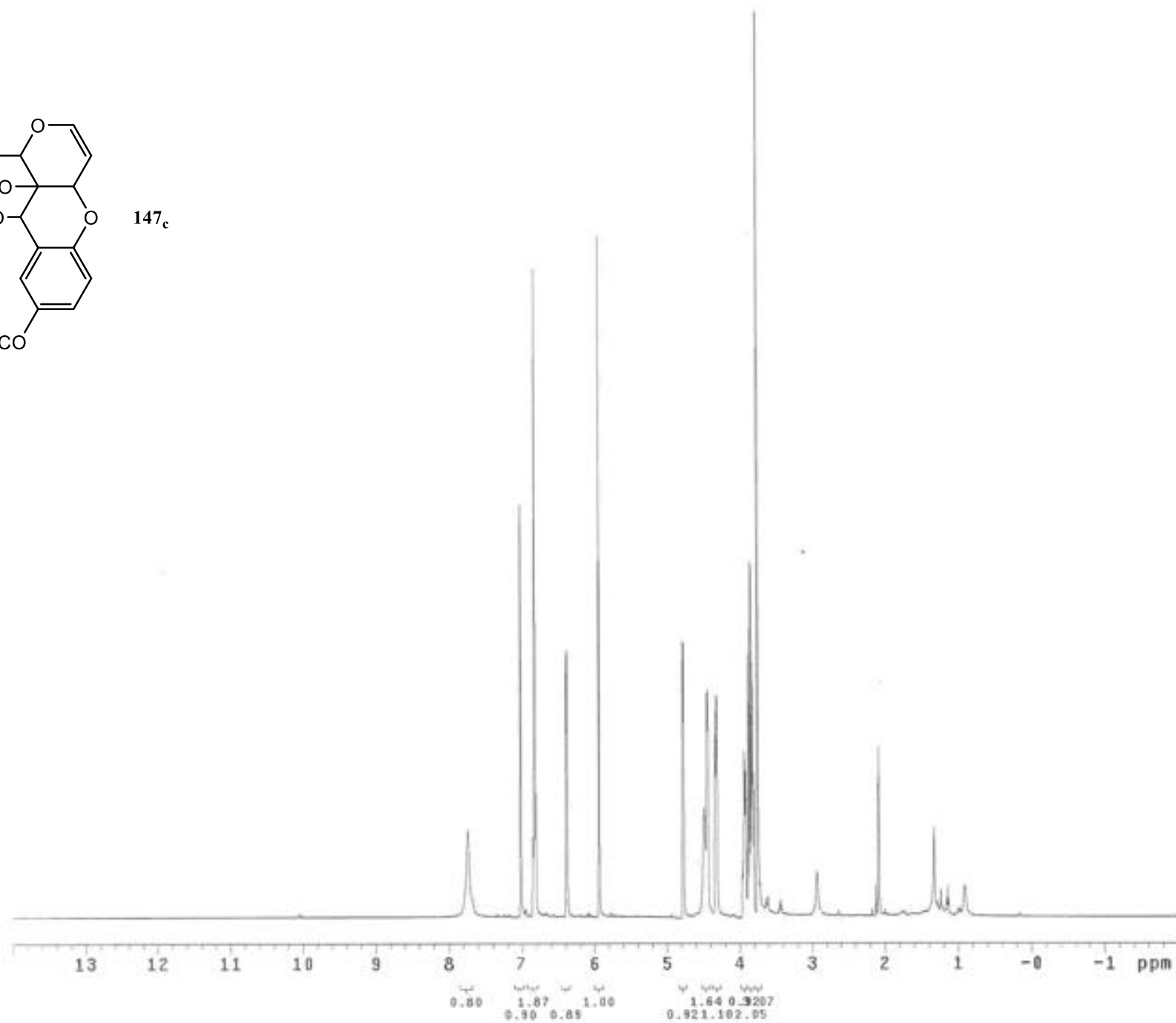
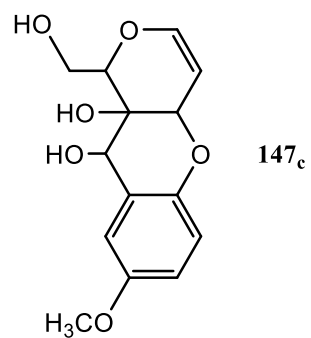


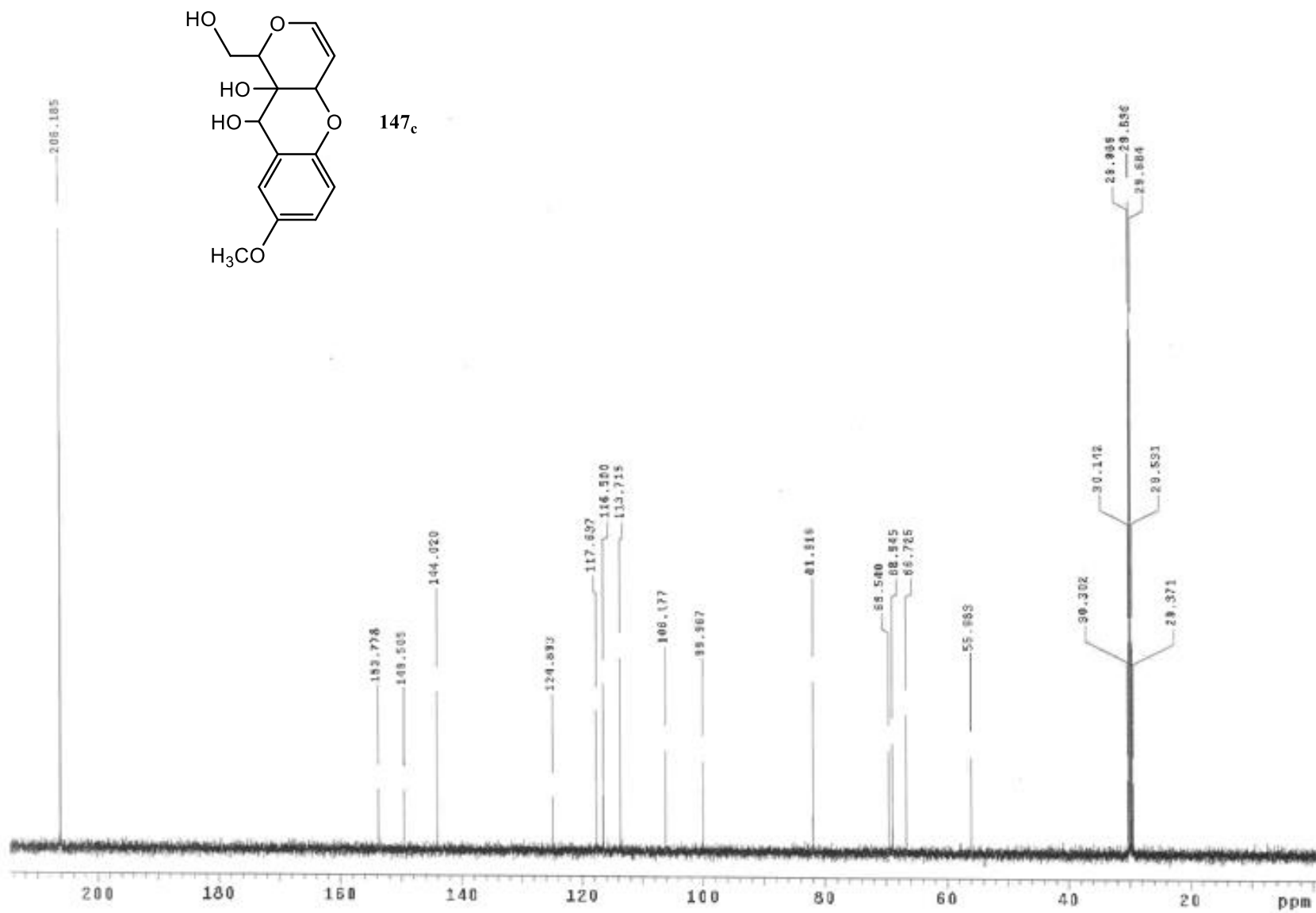


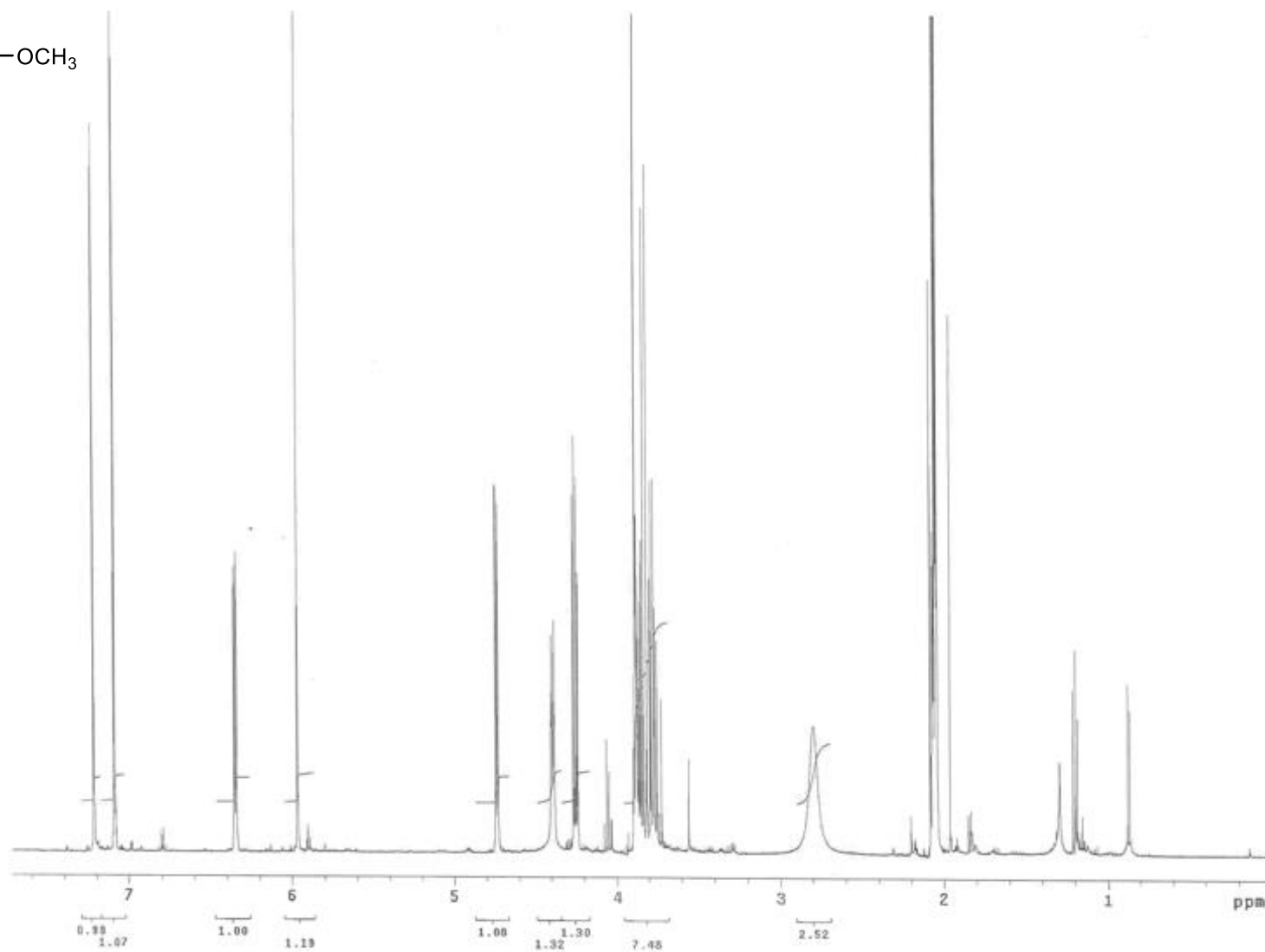
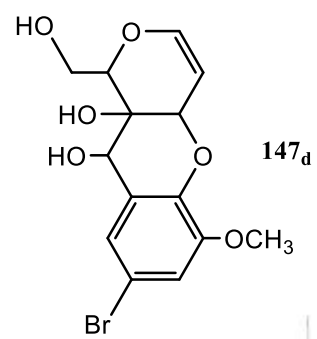


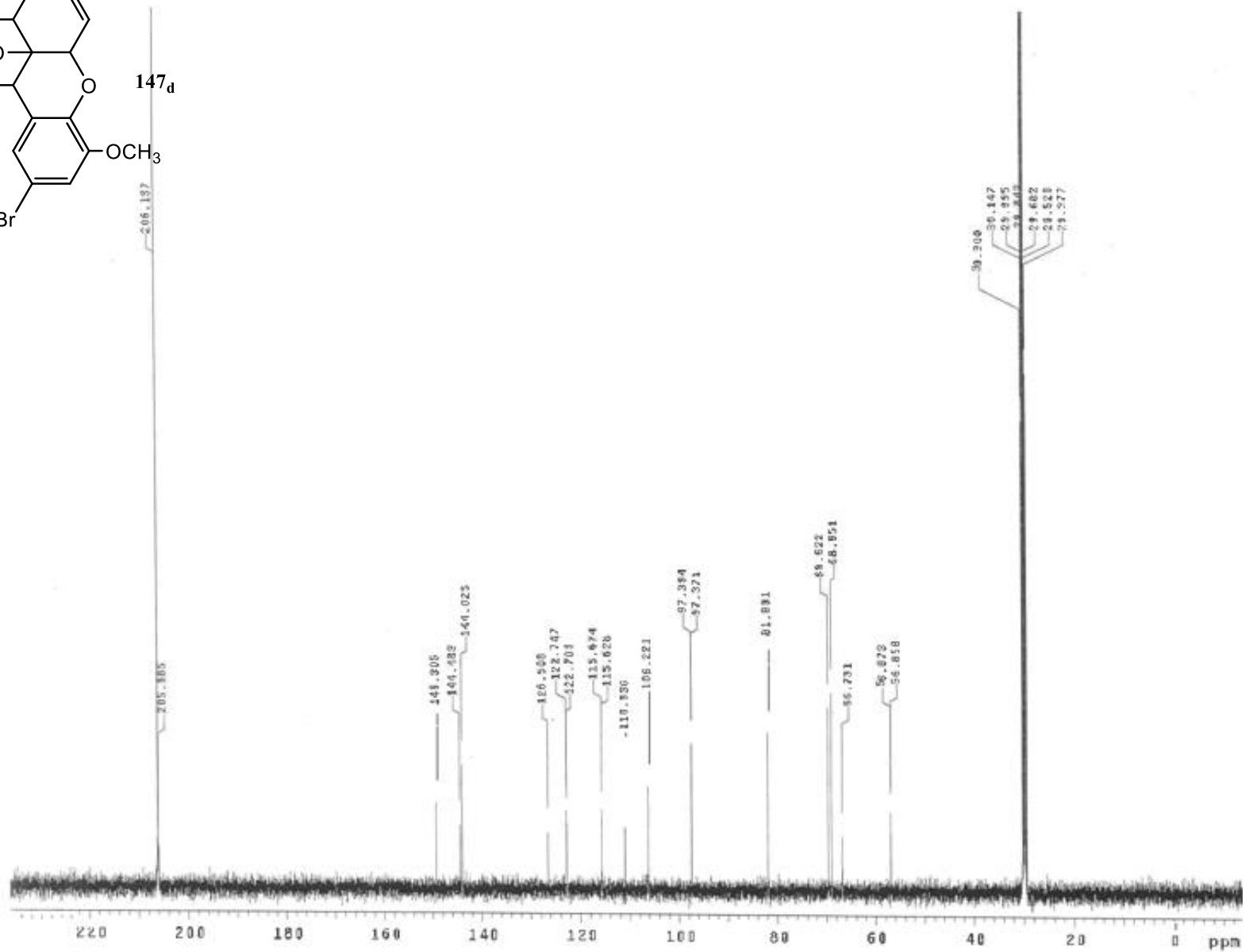
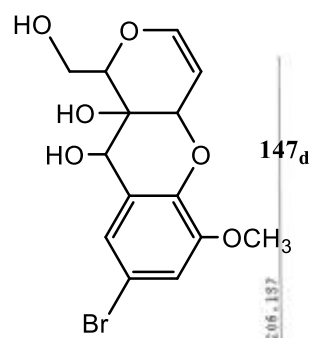
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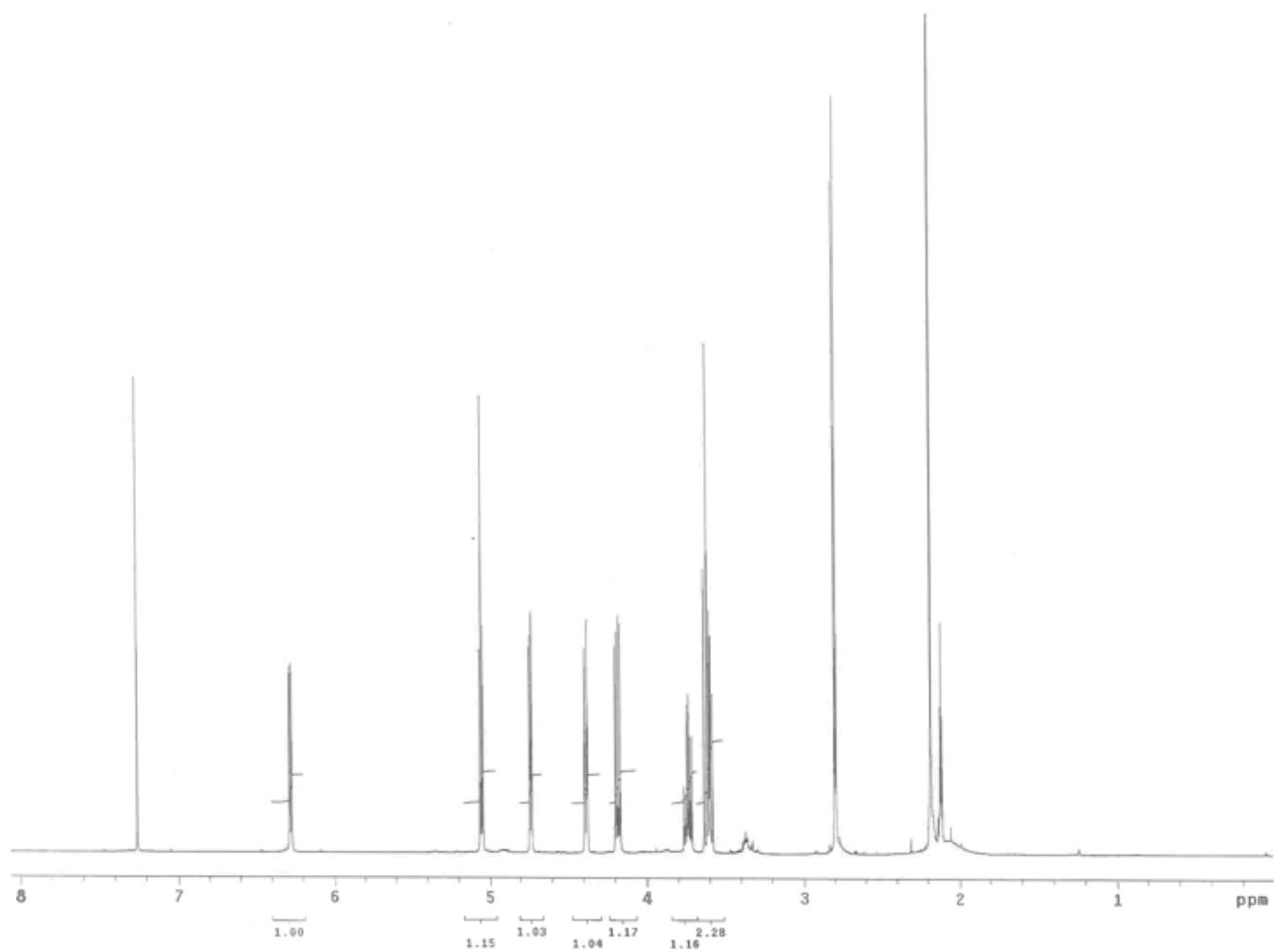
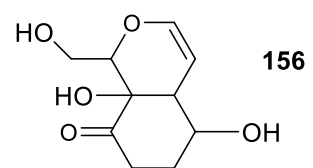


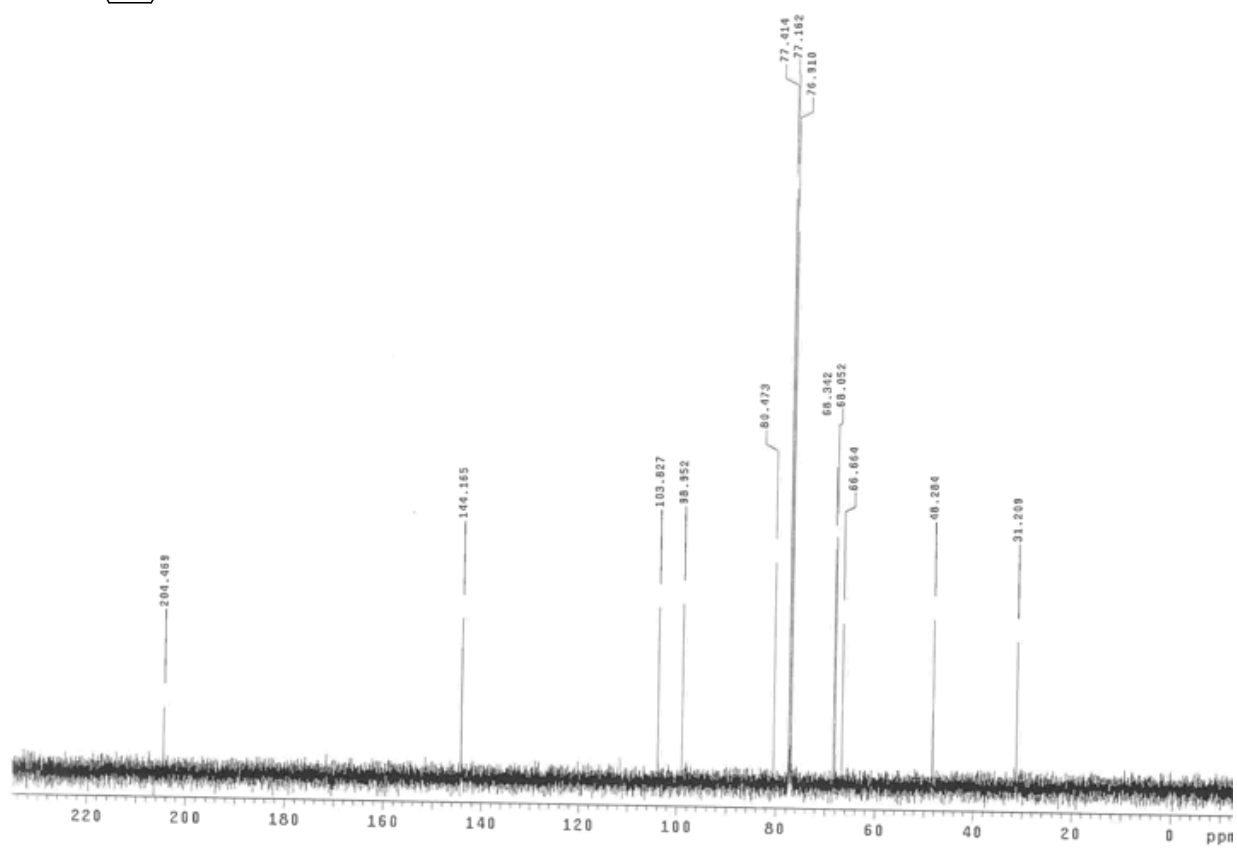
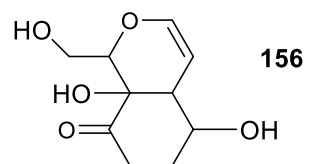


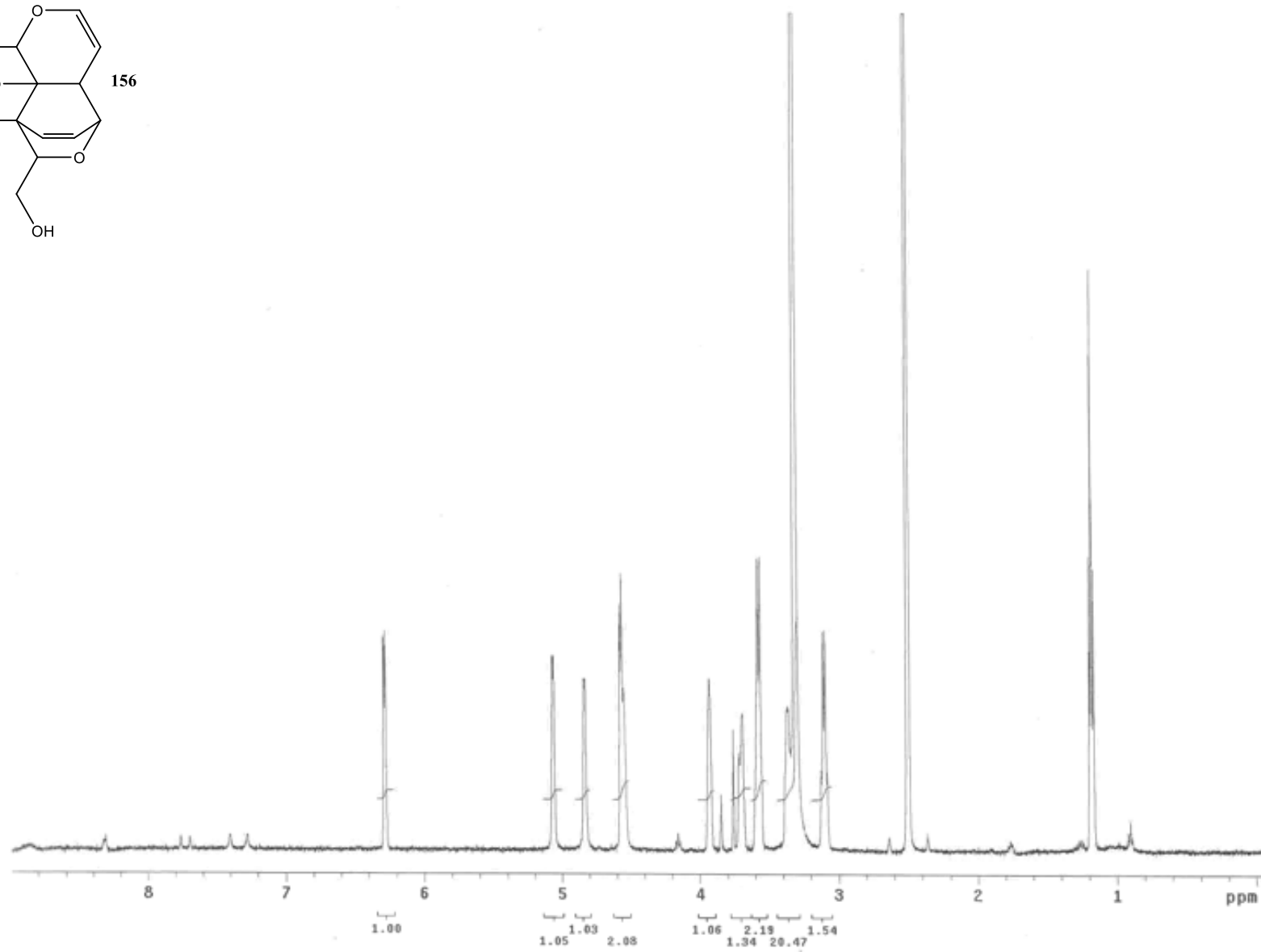
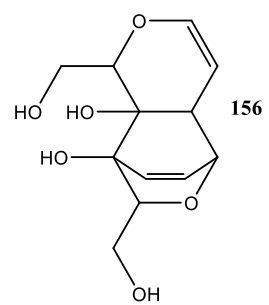


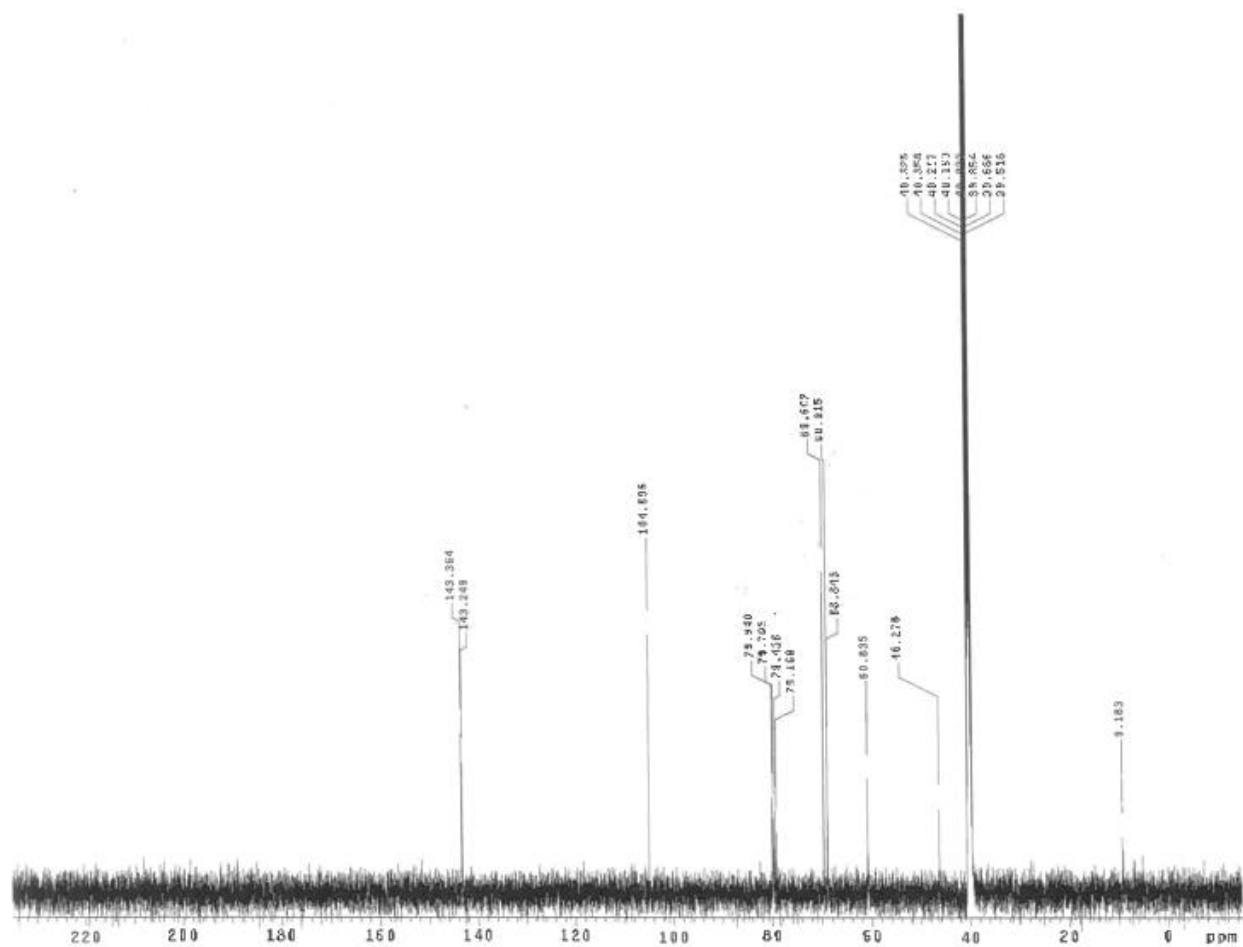
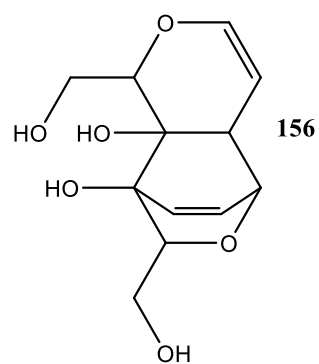


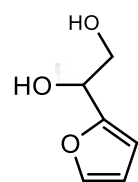




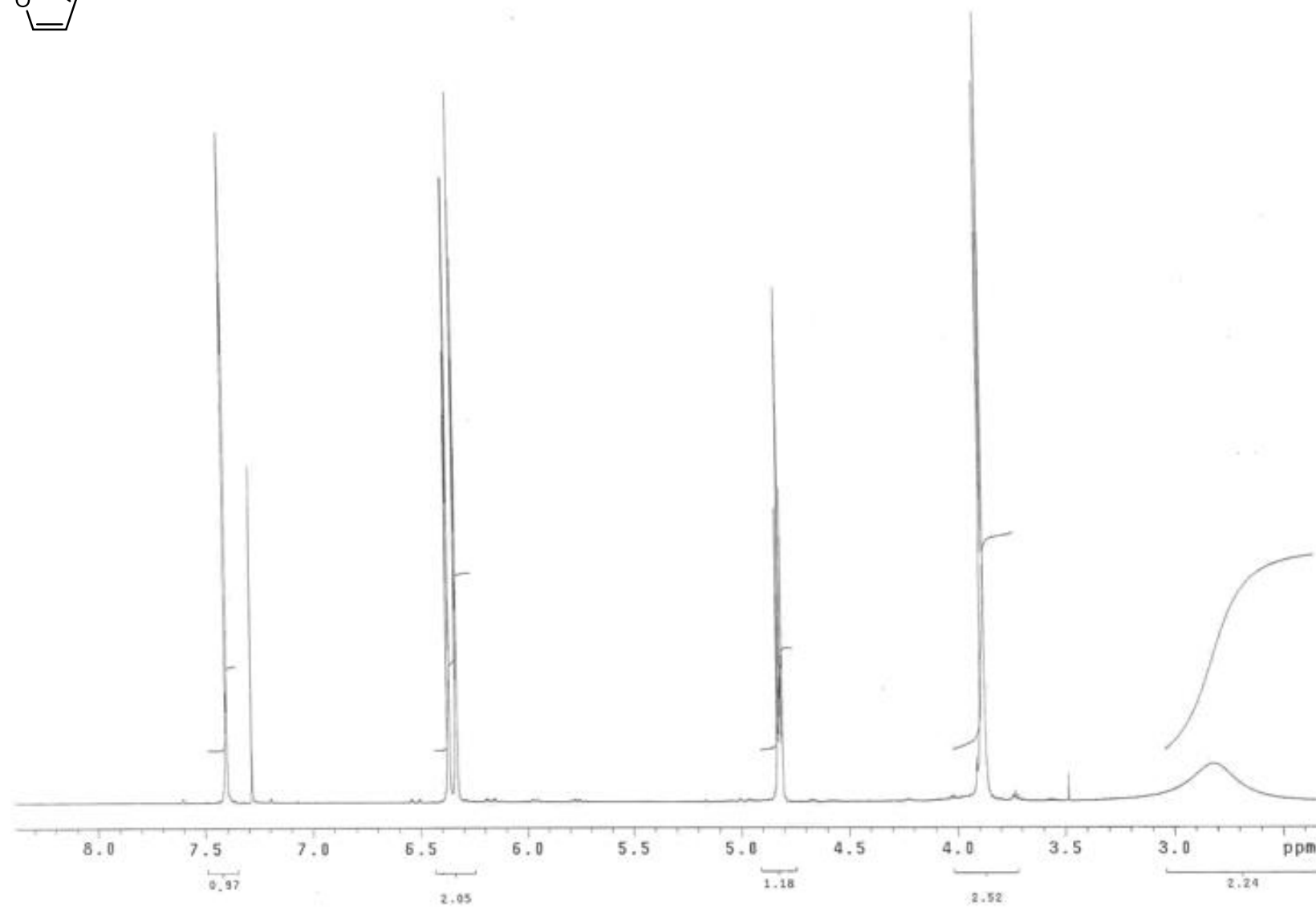


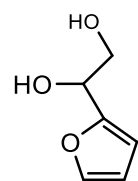






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