

GLYCALS AND THEIR DERIVATIVES



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Glycals and their Derivatives

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Glycals and their Derivatives

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FOREWORD

Carbohydrates are fascinating molecules that constitute an important class of naturally occurring compounds. They are most abundant in nature, biocompatible with minimal toxicity, and structurally diverse. Because of their key role in almost all biological processes, for example, cellular interaction, intercellular adhesion, signal transduction, inflammation, immune response, metastasis, fertilization, transport, modulation of protein function, cell surface recognition, and many more, there is an increased demand of carbohydrate-based molecules for their complete chemical, biochemical, and pharmacological investigations. For a long time, they have been explored as essential components in multiple vaccines and pharmaceuticals.

Among various carbohydrate entities, glycals (unsaturated sugars) and their derivatives particularly exhibit promising biological activities, ranging from antimicrobial to anticancer effects. The book “**Glycals and their Derivatives**” is timely, appropriate, and relies on carbohydrate-derived unsaturated sugars in drug discovery and development. The chapters in this book deliberate the practical utilities of a wide spectrum of diverse glycosides and 2-*C*-branched sugars by exploring their structural insights. This book provides a comprehensive overview of the different synthetic strategies for synthesizing crucial sugar analogs such as glycohybrids and glycoconjugates derived from glycals, offering a new avenue of understanding to the reader regarding glycoscience, glycobiology, and glycotecology. The chemistry of glycals and their derivatives encompasses a vast array of reactions and transformations. Their reactivity is largely governed by the presence of the electron-rich double bond, which renders them susceptible to various electrophilic additions and cycloadditions. This reactivity is harnessed in the synthesis of diverse carbohydrate structures, including oligosaccharides and *O*-, *N*-, *S*-, and *C*-glycosides, which are pivotal in numerous biological functions and have profound implications for drug design and development.

This book, “*Glycals and their Derivatives*”, also delves into the pharmacological profiles, selectivity, and metabolic stability of the intended sugar derivatives by exploring their post-modifications. Overall, this book has made a fantastic effort to acquaint the reader with the scope and emerging applications of carbohydrate-derived unsaturated sugars. I heartily congratulate the editors, Dr. Nazar Hussain and Dr. Atul Kumar, on making an eccentric and fruitful effort with this forthcoming valuable book, which certainly is a promising tool for synthetic glycochemists and glycobiologists.

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PREFACE

In the vast landscape of organic chemistry, the pursuit of novel molecules and functional groups has been a driving force behind groundbreaking discoveries and technological advancements. Among these, glycols (unsaturated sugars) and their derivatives stand as remarkable entities, captivating the interest of chemists across diverse fields. These cyclic enolic ethers are recognized as versatile chiral building blocks and are employed as starting materials for the total synthesis of various biologically active molecules. They have been extensively utilized in numerous glycosylation reactions, especially for the synthesis of deoxy sugars, Ferrier products, oligosaccharides synthesis, and cross-coupling reactions in the synthesis of C2-branched sugars. Originating from carbohydrates, the fundamental building blocks of life, glycols offer a fascinating intersection of biology and chemistry, promising avenues for both basic research and practical applications.

The unique reactivity of glycols lies in the presence of endocyclic and exocyclic double bonds, which offer multiple avenues for their transformation into various biologically important building blocks. In the realm of medicinal chemistry, glycols and their derivatives exhibit promising biological activities, ranging from antimicrobial and antiviral properties to anticancer effects. Structural modifications enable fine-tuning of their pharmacological profiles, enhancing potency, selectivity, and metabolic stability. Additionally, glycols have emerged as potential therapeutic agents for the treatment of diseases such as diabetes and inflammation, owing to their interactions with carbohydrate-processing enzymes and receptors.

The proposed book, "Glycols and their Derivatives", presents an exceptional compilation of cutting-edge research on carbohydrate-derived unsaturated sugars. It embodies the most recent scientific breakthroughs in organic and medicinal chemistry, offering an in-depth examination of glycols and their extensive derivatives. With its abundance of insights and discoveries, this book is positioned to become an essential reference for professionals, students, researchers, and academics involved in the dynamic realms of drug discovery and development.

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CHAPTER 1**Introduction to Glycals****Bindu Tiwari¹, Mittali Maheshwari¹, Altaf Hussain², Ram Pratap Pandey¹ and Nazar Hussain^{1,*}**¹ Department of Medicinal Chemistry, Institute of Medical Sciences, Banaras Hindu University, Varanasi-221005, India² Government Degree College, Budhal, J&K Higher Education Department, Jammu and Kashmir-185233, India

Abstract: Glycals are 1,2-unsaturated sugars having a C=C bond between C-1 and C-2 of the pyranose or furanose moieties of the carbohydrate scaffold. The presence of a C=C bond leads to enhanced reactivity. They are used as chiral building blocks in the synthesis of various natural products and medicinally significant molecules. There are numerous methods for the synthesis of exo-glycals and endo-glycals, such as glycosidations, reagent-based methods, and electrochemical methods. Glycals have shown their versatility and applicability in chemical synthesis in many ways *e.g.*, epoxidation, cycloaddition, and formation of various glycosides like *C*-glycosides, *O*-glycosides, *N*-glycosides. They have also been employed in the synthesis of many biologically relevant natural products as starting materials.

Keywords: Exo-glycals, Furonoid glycals, Glycals, Reactivity, Synthesis.

INTRODUCTION

Carbohydrates are polyhydroxy aldehydes or ketones. They are firstly produced by plants and form a very large group of naturally occurring products. Carbohydrates are primarily used as biosynthetic precursors and structural elements in all living organisms. They exist as organic molecules in nature; some are used as energy suppliers and some as storage vehicles. They exist in simple forms as monosaccharides and disaccharides. They also exist as more complex glycosides like glycolipids, glycoproteins, peptidoglycans, proteoglycans, nucleic acids, and poly and lipopolysaccharides [1, 2]. Emil Fischer (1852-1990) (Fig. 1) is regarded as the father of carbohydrate chemistry. He was one of the pioneering scientists in the area of organic chemistry.

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Fig. (1). Emil Fischer.

Glycals are a class of carbohydrate derivatives that play a significant role in organic and medicinal chemistry. The term “glycals” is derived from combining “glycosides” and “alcohol”, reflecting the structural feature of these compounds. Glycals are essential carbohydrates that contain a C=C double bond between C-1 and C-2 of the carbohydrate scaffold [3]. Glycals are versatile intermediates in the synthesis of complex carbohydrates and have found applications in medicinal chemistry, natural product synthesis, and many other areas of chemical science. They found their versatility and applicability in carbohydrate chemistry because of their stable transformations as well as unsaturation present at C-1 and C-2 positions [4]. They are unsaturated sugars that contain a double bond at the anomeric position, as shown in Fig. (2). The IUPAC name of the most common glycal is 1, 2-dideoxy-hex-1-eno-pyranose.

‘Glycal’ is a general term for all 1,2-unsaturated sugars, while the glycals of specific sugars have their own name from which they are derived *e.g.*, glucal from glucose, galactal from galactose, xylal from xylose, and so on (Fig. 3).

Depending on the electronic nature and size of the substituents, as well as the presence of the ring oxygen atom, glycals can adopt either 5H_4 or 4H_5 conformation, as shown in Fig. (4).

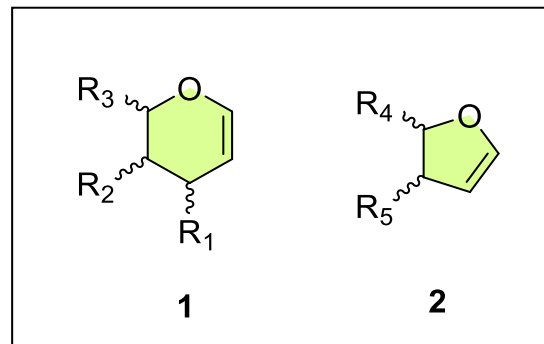


Fig. (2). General structure of pyranose and furanose glycols.

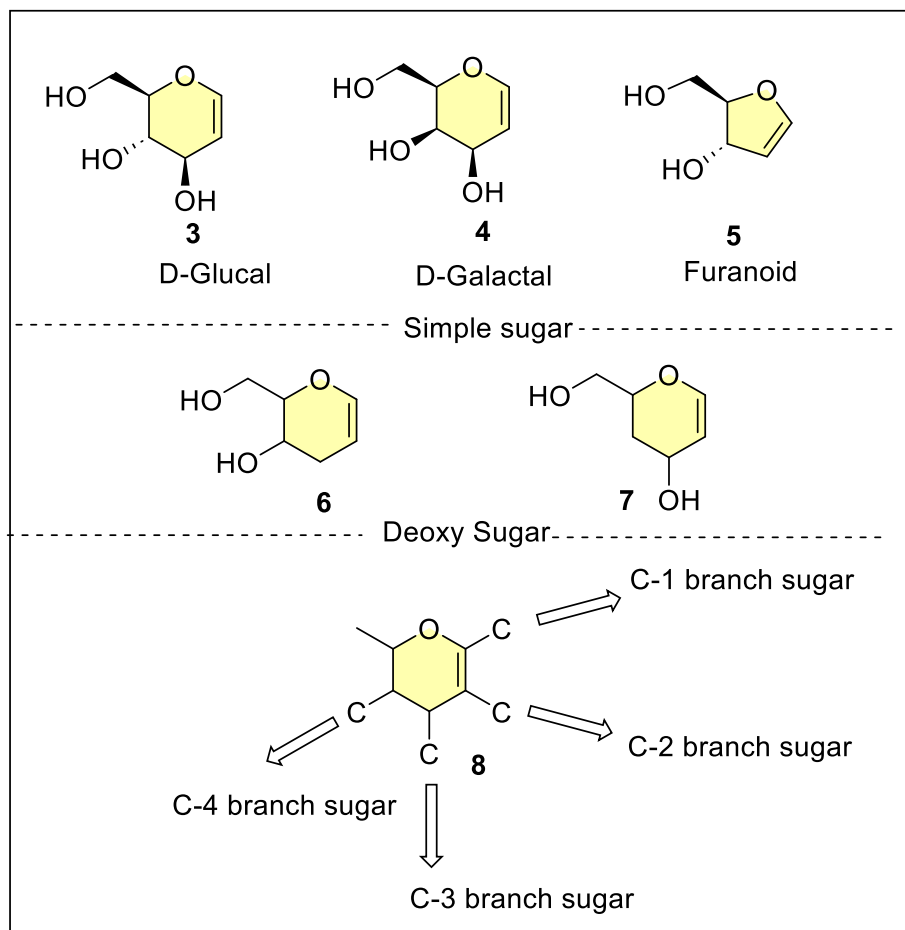


Fig. (3). Examples of some glycols.

Recent Advances in the Synthesis of *O*- and *S*-Glycosides from Glycols

Mittali Maheshwari¹, Bindu Tiwari¹, Manish Kumar Sharma¹ and Nazar Hussain^{1,*}

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Abstract: Approximately 20 to 30 percent of all natural drugs are glycosylated, and the attached carbohydrate unit is pivotal for their biological activity. *O*- and *S*-glycosides constitute a significant portion of various biologically potent molecules and natural products. The synthesis of *O*- and *S*-glycosides holds immense importance due to several medicinal benefits. This chapter explores several methodologies for accessing *O*- and *S*-glycosides and the subsequent utilization of these glycosides for oligosaccharide generation. Specific pathways involved in *O*- and *S*-glycosides synthesis are discussed, along with detailed consideration of factors influencing the stereoselectivity of the desired products.

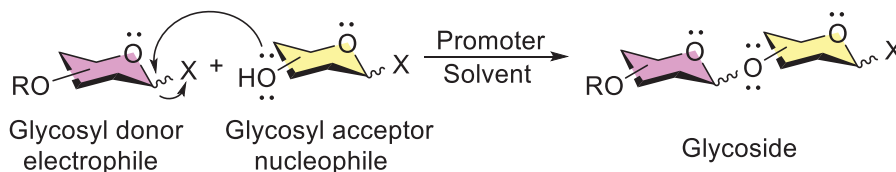
Keywords: Acceptors, Glycosyl donors, Glycols, Oligosaccharides, *O*-glycosides, *S*-glycosides, Stereoisomers.

INTRODUCTION TO *O*-GLYCOSIDES

When one carbohydrate unit is attached to an aglycone or another carbohydrate unit to generate a linkage, it is called a glycosidic linkage [1], and the process is referred to as glycosylation. This linkage can be facilitated through *O*-, *N*-, *S*-, or *C*-glycosidic bonds. *O*-glycosylation involves the coupling of a glycosyl donor with glycosyl acceptors in the presence of promoters and solvent, as depicted in (Scheme 1) [2]. *O*-glycosides are commonly found in plants [3]. Glycosyl amines or nucleosides contain *N*-glycosides. Glucosinolates or thioglycosides comprise *S*-glycosides. *C*-glycosides are stable glycosides and resistant to hydrolysis due to the existence of a covalent bond between glycone and acceptors [4, 5]. In this process, the glycone acts as the donor molecule, offering its anomeric position, while the aglycone serves as the acceptor molecule. The resulting glycosidic bond

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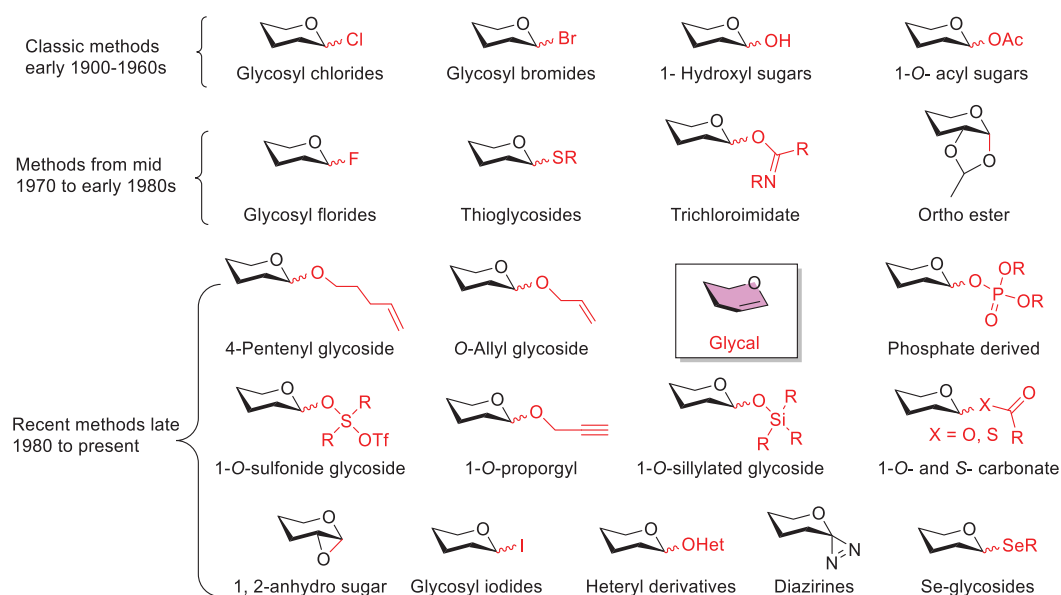
can manifest as either an α - or β -diastereoisomer, known as α - or β -glycosides, respectively. β -linked *O*-glycosides are prevalent in plant glycosides [6].



Scheme 1. General strategy for the synthesis of *O*-glycosides.

Various novel glycosyl donors have been developed and utilized in the glycosylation process [7 - 10]. (Scheme 2) illustrates some of the reported glycosyl donors. In earlier times, glycosyl chlorides/ bromides [11] and 1-*O*-hydroxyl sugars [12] were used as donor molecules for creating the glycosidic linkage. Subsequently, during the medieval period, glycosyl fluorides [13], thioglycosides [14], and trichloroimidate [15] were synthesized for the glycosylation purpose. In recent years, a variety of donors have been introduced and employed for the production of *O*-glycosides. Among these, glycals stand out as significant donor molecules [16]. Glycals are derivatives of monosaccharides with an endocyclic double bond at the C1/C2 position, serving as versatile building blocks in the assembly of natural products and biologically active molecules [17]. Essentially highly substituted cyclic vinylic enol ethers, glycals exhibit distinct reactivity at the C1 and C2 positions due to the conjugation of the ring oxygen with the double bond [18]. Recent advancements in glycals and their transformation into diverse biologically active molecules have broadened their application in modern organic synthesis. Since their initial discovery and synthesis by Fischer and Zach in 1913, glycals have been extensively utilized as pivotal precursors for synthesizing numerous biologically significant molecules [19]. The extensive transformation of glycals into various biologically active molecules and natural products stems from their unsaturation and facile conversion into diverse derivatives and precursors for further derivatization [20].

Numerous strategies have been proposed for the glycosylation of glycals with various nucleophiles, leading to the formation of *O*-glycosides [21 - 23]. In this chapter, we will discuss the various approaches employed to activate donors effectively for the synthesis of *O*-glycosides and apply these protocols in achieving high yields in oligosaccharide synthesis. Our focus primarily lies in the methodologies introduced since 2017.



Scheme 2. Different donor molecules used for glycosylation.

HISTORICAL ASPECTS

In the late 19th century, Michael [24] and Fischer [25] presented the chemical synthesis of the first *O*-glycosides, namely *p*-methoxyphenyl β -D-glucopyranoside and methyl α -D-glucopyranoside, respectively. Subsequently, Koenigs and Knorr [11] proposed modified and controlled protocols for *O*-glycoside synthesis. Over time, various methodologies have been developed, advancing mechanistic pathways and enhancing control over the stereochemistry of the desired products. Glycosylation can yield two different anomeric stereoisomers: 1,2 *cis*- and 1,2 *trans*-isomers. Lemieux *et al.* [26] and Ness [27] emphasized the significance of the protecting group at the C2 position of glycosyl donors on product stereochemistry. Fraser-Reid *et al.* [28] introduced the concept of armed and disarmed approaches, where an ether linkage at the C2 position (armed donor) results in 1,2 *cis*-glycosides, while an ester bond (disarmed donor) yields 1,2 *trans*-products.

To optimize glycosylation conditions, various modified approaches have been developed [29]. One-pot glycosylation has gained popularity, incorporating numerous advancements and novel reaction conditions [30 - 32]. Computational chemistry and kinetic studies have contributed to elucidating the mechanism of glycosylation. Despite efforts in this branch of carbohydrate chemistry, mastering the mechanism remains a challenge.

CHAPTER 3

Recent Advances in the Synthesis of C-Glycosides Using Glycals and their Derivatives

Manish Kumar Sharma¹, Anand Kumar Pandey¹, Ram Pratap Pandey¹ and Nazar Hussain^{1,*}

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Abstract: A glycoside is recognized as a C-glycoside when the anomeric carbon of a sugar moiety is linked to an aglycone or another carbohydrate, creating a new C-C bond. Recently, C-glycosides have been recognized as a privileged class of carbohydrates owing to their extensive application in medicinal chemistry and drug discovery. These glycosides have played a vital role in designing various drug candidates owing to their stability towards acidic or enzymatic degradation. This chapter deals with the recent advances in the synthesis of privileged C-glycosides, including 2-deoxy-C-glycosides, using glycals and their derivatives.

Keywords: C-glycosides, Cross-coupling reactions, Directing groups, Drug discovery, Ferrier rearrangement, Glycals, Glycoconjugates, Glycosylation, Natural products, Photoredox catalysis, Transition metal catalysis.

C-glycosides are an important class of carbohydrate derivatives where a carbohydrate unit is directly connected to an aglycone or another carbohydrate, creating a new C-C bond [1 - 4]. Recently, C-glycosides have been recognized as an important carbohydrate mimetic due to their extensive application in medicinal chemistry and drug discovery programs [5]. They are known to exhibit high chemical and metabolic stability as compared to O-glycosides. The recent advancements in the synthesis of C-glycosides have reignited the interest of synthetic chemists by substituting the enzymatically labile glycosidic oxygen with a carbon center. Furthermore, the stability of C-glycosides toward acidic or enzymatic degradation has played a pivotal role in the designing of biological probes and pharmaceutical compounds. For example, a number of SGLT-2 inhibitors, such as canagliflozin, dapagliflozin, and empagliflozin, have been explored successfully against type II diabetes [6 - 8]. Pro-XylaneTM, a C-alkyl

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glycoside, has been explored as a popular skin anti-aging agent. The *C*-analogs of KRN7000 and blood group H-antigen are known to exhibit various biological activities, including anticancer activity, as depicted in Fig. (1) [9 - 11].

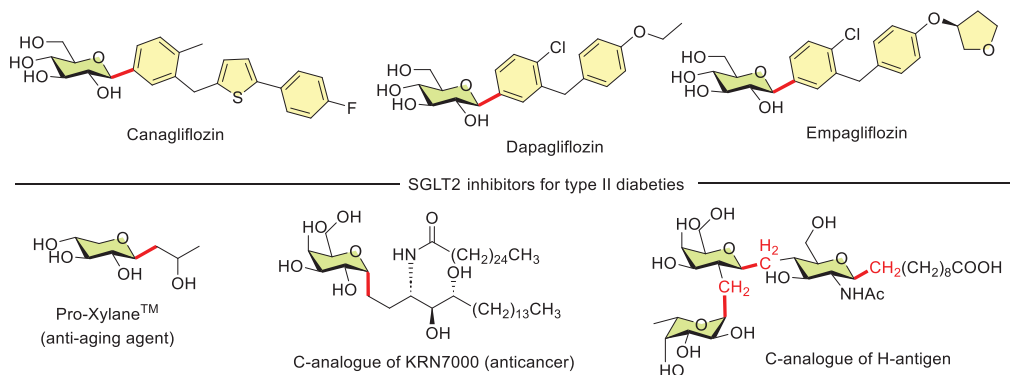


Fig. (1). Selected examples of metabolically stable *C*-glycoside drugs.

Moreover, aryl *C*-glycosides are widely distributed in several bioactive natural products and popular drug candidates. The natural products derived from aryl *C*-glycosides have particularly attracted a great deal of attention due to their potential bioactivity ranging from anti-inflammatory to anticancer, as depicted in Fig. (2). On the other hand, 2-Deoxy- β -*C*-glycosides embody an important class of carbohydrate derivatives and are widely distributed in various bioactive motifs *e.g.*, saptomycin B and vieomycinone B₂ methyl ester (Fig. 2).

In this regard, the research group of Keisuke Suzuki has demonstrated the synthetic challenges of aryl *C*-glycoside natural products in their preparation [5, 12]. The authors covered two aspects in this review: (i) synthetic approaches and their application for the total synthesis of aryl *C*-glycoside natural products and (ii) synthetic strategies that favor the glycosylation of arenes utilizing three different types of reactions, *viz.*, cross-coupling reactions, glycosyl anions, and electrophilic sugar derivatives. A number of glycosyl donors such as glycals, 1,2-anhydro sugars, sugar lactols and lactones, glycosyl phosphates/imidates, methyl glycosides, glycosyl acetates, chalcogenoglycosides/sulfoxides/sulfones, glycosyl halides, and other glycal derivatives are archetypally used in the *C*-glycosylation reactions, as illustrated in Fig. (3).

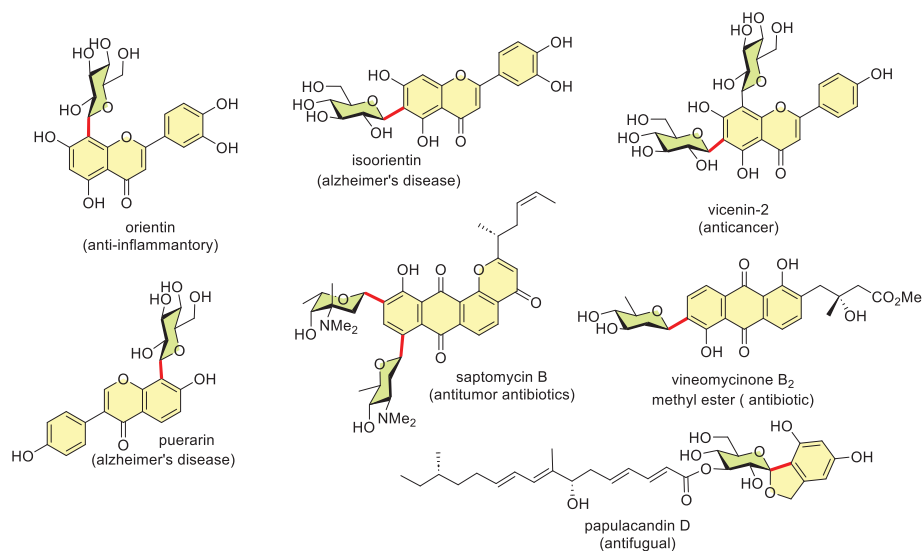


Fig. (2). Some selected examples of biologically active aryl C-glycoside natural products.

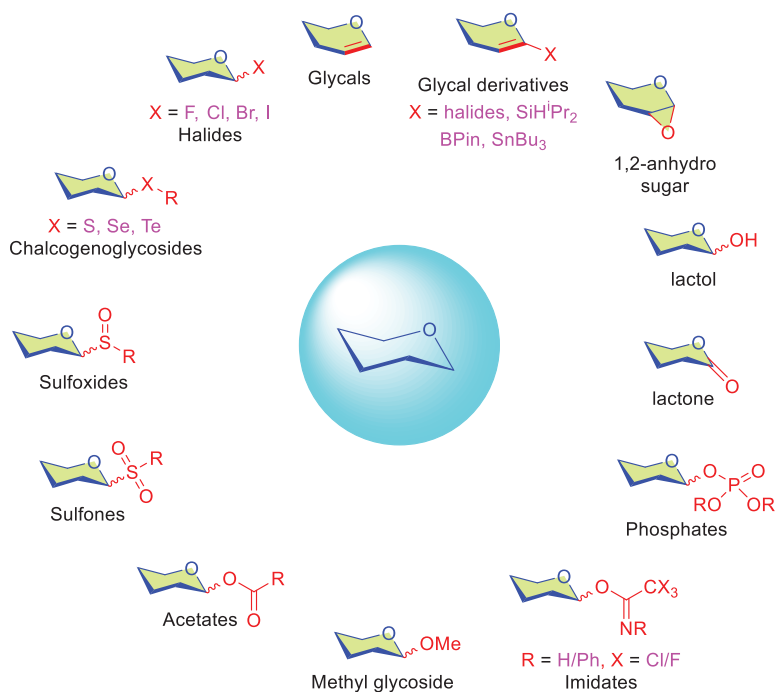


Fig. (3). Various glycosyl donors employed in the synthesis of C-glycosides.

Exploring the C-2 Position of Glycals: Structural Insights and Synthetic Applications

Ram Pratap Pandey¹, Manish Kumar Sharma¹, Anand Kumar Pandey¹, Altaf Hussain² and Nazar Hussain^{1,*}

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Abstract: The chemistry of glycals and their derivatives has emerged as a hot topic in carbohydrate chemistry owing to their incredible applications in biological and medicinal chemistry. Annulated and C-2-branched sugars derived from glycal moiety and its derivative have received immense attention. Herein, we have incorporated the current advancement in the synthesis of 2-C-branched sugars and annulated sugars derived from glycals, 2-haloglycals, and 2-nitroglycals using various synthetic strategies, including C-H activation, 1,2-annulation, and cyclopropanation.

Keywords: C-H activation, Cyclopropanation, Glycals, Glycosides, 1,2-Annulation, 2-Haloglycals.

INTRODUCTION

Glycals are a class of carbohydrates distinguished by a cyclic structure that includes an oxygen atom and an unsaturated alkene bond between the 1-C and 2-C positions of the pyranose or furanose ring. These compounds are crucial in modern organic synthesis and mimic structural elements found in biologically active molecules. The first glycal was discovered and synthesized by Fischer and Zach in 1913 [1]. The double bond within the ring enables various reactions, including addition, cycloaddition, substitution, cross-coupling, 1,2-annulation, rearrangements, and occasionally ring opening, as illustrated in Fig. (1) [2]. The oxygen atom in the ring enhances conjugation and promotes the trapping of nucleophiles at the C-1 position and electrophiles at the C-2 position.

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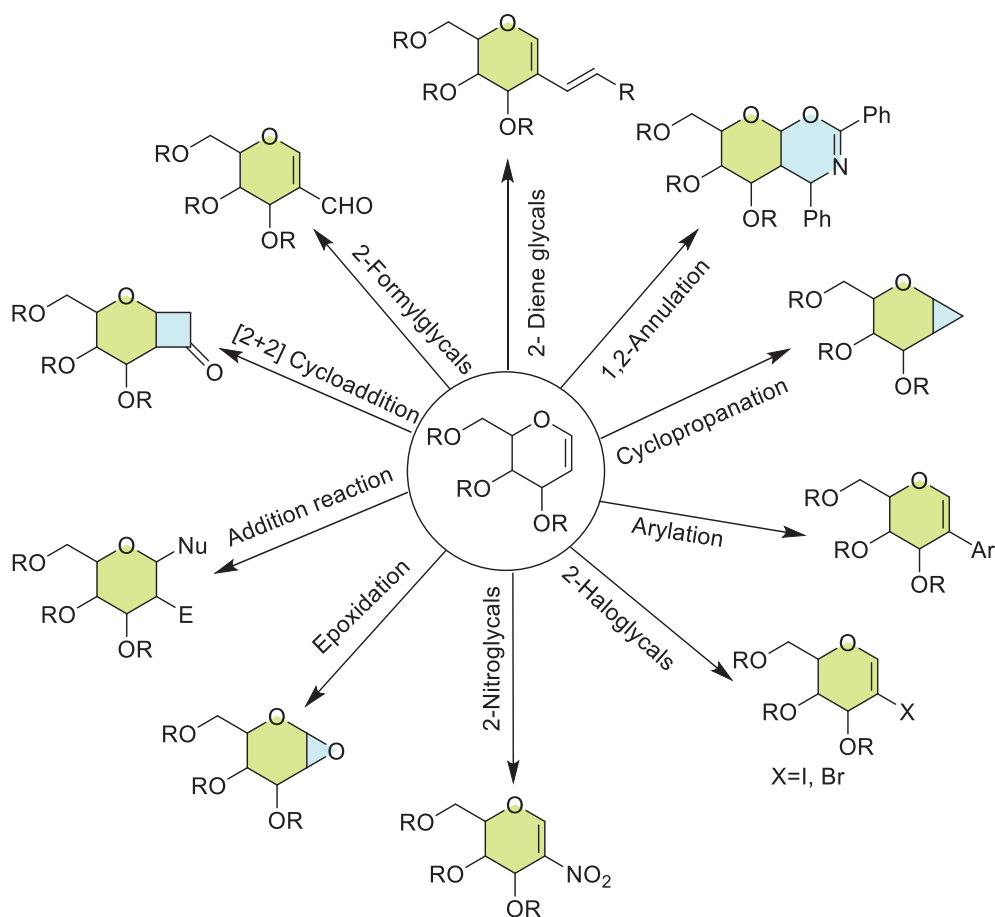


Fig. (1). Typical reactivity of glycols.

The most studied transformations of glycols involve a rearrangement known as Ferrier rearrangement, in which the double bond is usually shifted from the carbon atom 1 and 2 position to the ring's 2 and 3 positions, usually under acidic conditions. The C-2 position of glycol is nucleophilic, which allows various electrophilic attacks to generate 2-C-branched sugars [3]. The presence of a double bond inside the ring makes the glycols prone to epoxidation, hydroxylation, hydrogenation, ozonolysis, *etc.* [4]. As a result, the glycols can be further employed in different types of glycosylation reactions, 1,2-annulation reactions and C-2 branched synthesis [5, 6]. In the recent past, a large number of efforts have been made for reactions at the C-2 position of glycols. 2-C-branching and 1,2-annulation reactions are particularly appealing because they allow the

manipulation of the anomeric center. Often, C-2-branched sugars can be further transformed into 1,2-annulated sugars, which serve as valuable precursors for synthesizing a variety of biologically relevant compounds. The development of these molecules aids in creating novel synthetic methods to assemble these small molecules into chiral building blocks for complex compounds.

Over the past decades, the reaction at the C2 position of glycol can offer a cluster of C2 functionalized products with enormous advantages. The C2 functionalized glycols are widely distributed in numerous natural molecules and biologically active motifs, as outlined in Fig. (2) [7].

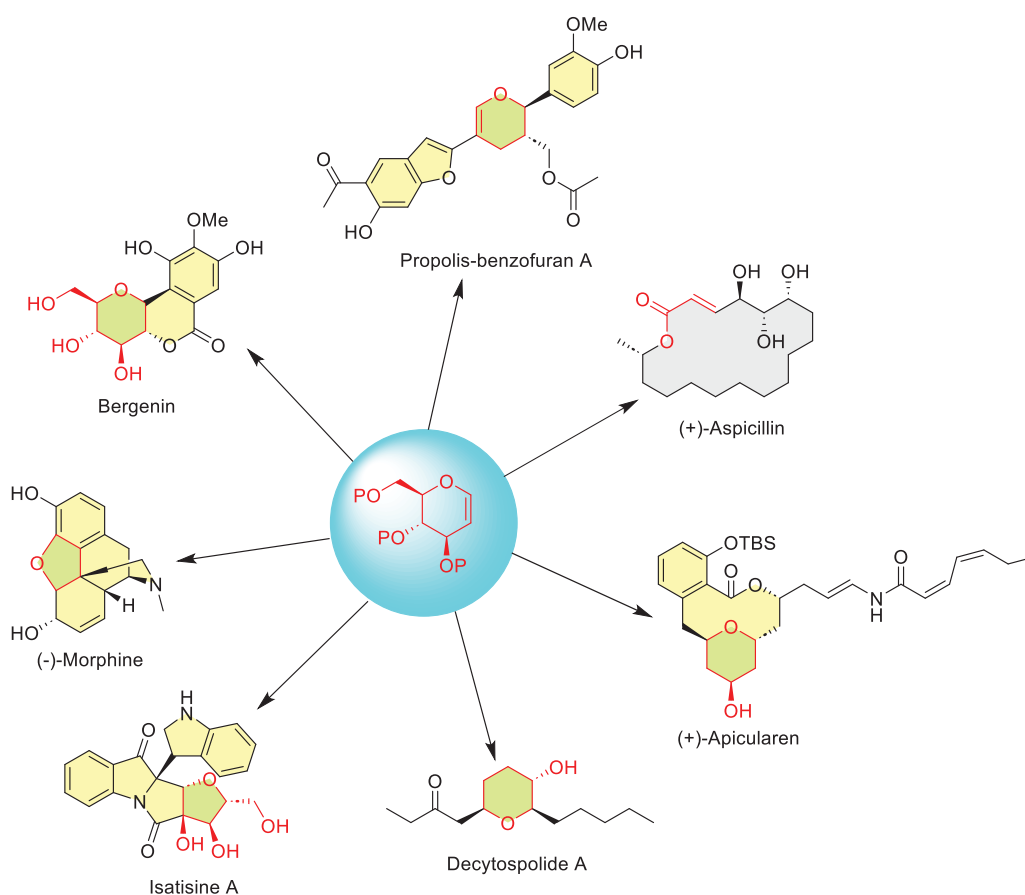


Fig. (2). Glycol-derived natural products.

2-Haloglycols

2-haloglycols have been identified as important building blocks for the further functionalization at the C-2 position of glycols to access C-2-branched sugars and

CHAPTER 5**Total Synthesis of Natural Products and Medicinally Important Molecules from Glycals****Norein Sakander¹ and Qazi Naveed Ahmed^{2,*}**¹ *Natural Products and Medicinal Chemistry Division, CSIR-Indian Institute of Integrative Medicine, Canal Road, Jammu-180001, India*² *Academy of Scientific and Innovative Research (AcSIR), Ghaziabad-201002, India*

Abstract: Glycals have been widely used as a versatile building block for the synthesis of C-glycosides and branched sugars and the total synthesis of natural products and biologically active molecules. The versatility of glycals is due to their easy availability and the presence of a ring oxygen connected to a double bond. The inherent chirality of glycals also makes them valuable for the synthesis of various natural products and pharmaceuticals. This chapter provides a detailed overview of the progress made in synthesizing natural products and important molecules derived from glycals.

Keywords: Bradyrhizose, Carbohydrates, Catalysis, Cycloaddition, Drugs, Diospongin, Epoxide, Glycals, Glycosides, Glucopyranoside, Hemicetal, Natural products, Reblastatin, Synthron, Stereoselectivity, Total synthesis, Tricyclic flavonoid, Takai olefination, Yamaguchi esterification, α,β -unsaturated ketones.

INTRODUCTION

The field of organic chemistry encompasses a complex and highly rewarding area known as the total synthesis of natural products and medicinally vital scaffolds derived from glycals [1]. Sugar enol ethers, which serve as versatile building blocks, provide an exceptional foundation for the creation of intricate structures present in natural compounds and substances of pharmaceutical significance. This synthetic approach entails utilizing the distinctive reactivity and structural characteristics of glycals, which are derivatives of carbohydrates that possess a double bond between two carbon atoms in a ring structure [2]. By capitalizing on their inherent flexibility, tolerance towards functional groups, and ability to control stereochemistry, chemists undertake complex routes to create elaborate molecular structures. The importance of total synthesis resides in its ability to co-

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mpletely replicate, within a controlled laboratory environment, natural molecules that possess a diverse array of biological effects and therapeutic possibilities. Through the utilization of glycals as initial substances, scientists navigate through strategic chemical conversions, such as glycosylation, stereoselective reactions, and manipulation of functional groups, to construct intricate frameworks of natural products [3]. The synthesis of these compounds not only allows for a more profound comprehension of their structures and biological functions but also provides opportunities for the creation of innovative medicinal agents. By synthesizing natural products and medically important molecules from glycals, researchers strive to uncover fresh avenues for drug discovery and therapeutic advancements, potentially addressing unmet medical requirements and improving human well-being [1]. The dynamic interplay between organic synthesis and medicinal chemistry is exemplified by the synergy between the intricate chemistry of glycals and the pursuit of unlocking the therapeutic potential of natural compounds. This synergy has led to groundbreaking discoveries in the realm of drug development and molecular design.

Additionally, glycals have been widely employed as the starting material for the creation of 1,2-annulated sugars [4] and additionally for the synthesis of a broad spectrum of natural products, as depicted in Fig. (1) [5]. Glycals and their derivatives are used not only to synthesize natural products but also to produce SGLT-2 inhibitors like dapagliflozin, canagliflozin, and empagliflozin [6]. Glycals are now more useful as a building block in organic synthesis due to the production of these naturally occurring or artificially created therapeutically relevant compounds. In the literature, a few review articles showed the importance of glycals in the transformation to natural products and biologically relevant molecules [3a, 3h]. Here, we provide a summary of the use of glycals in the overall synthesis of natural products and scaffolds with medical significance.

Synthesis of Diospongin A

The bioactive steroid Diospongin A was obtained from marine sponges that are members of the *Diospongia* genus. It is a simple 2,4,6-tri substituted pyran natural product isolated from the rhizomes of *Dioscorea spongiosa* exhibiting potent anti-osteoporotic activity [7]. A significant advancement in organic chemistry has been made with the effective synthesis of diospongin A. This is a significant accomplishment because this natural substance has a complex and fascinating structure. Diospongin A was synthesized entirely from tri-*O*-acetyl-D-glucal through a complex series of processes. Tri-*O*-acetyl-D-glucal **1** is first transformed into α,β -unsaturated ketone **2** over three steps, which is then subjected to the Michael addition of phenyl lithium that is catalyzed by Cu to yield diastereomeric ketones **3** and **3a** in a 1:1.2 ratio. The stereoselective keto

reduction of compound **3** is achieved using L-selectride followed by MOM-protection using MOM chloride in the presence of DIPEA in DCM, giving **4**. *Ent*-diospongine **7** is produced in good yields by dehydroxylation using Im_2CS , AIBN, and Bu_3SnH in toluene, followed by side chain expansion over 4 steps, as illustrated in (Scheme 1) [8].

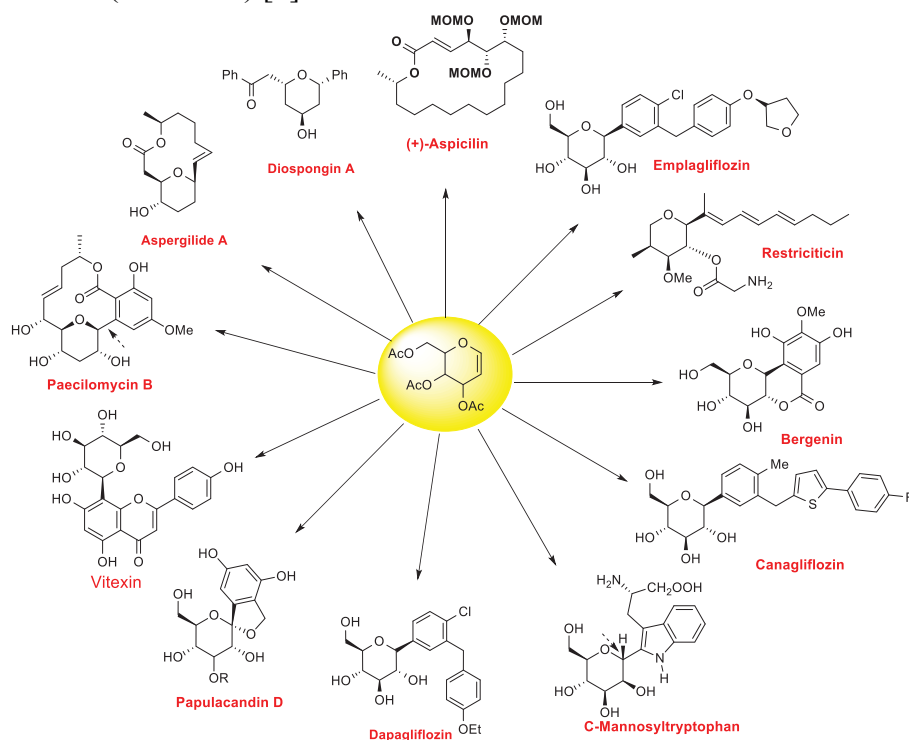
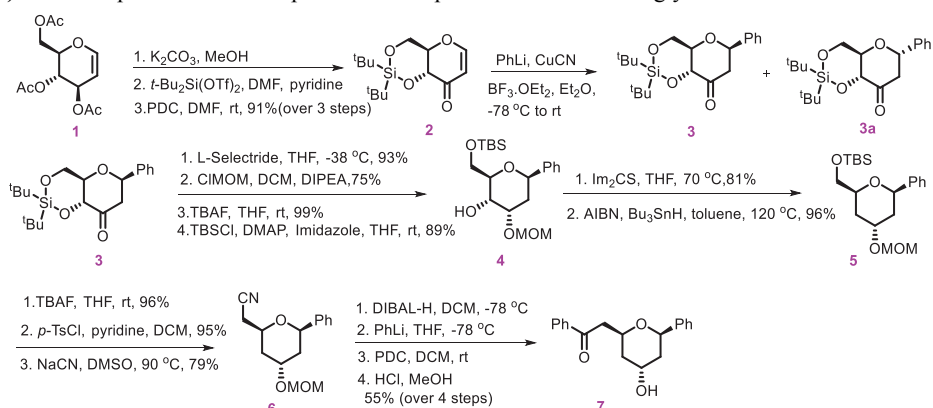


Fig. (1). A few representative examples of natural products derived from glycols.



Scheme 1. Synthesis of Diospongine A.

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