Handbook of Chemical Glycosylation

Advances in Stereoselectivity and
Therapeutic Relevance

Edited by
Alexei V. Demchenko

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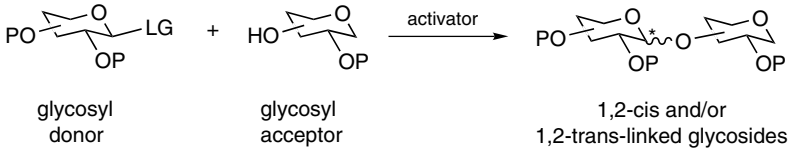
Contents

Preface

Carbohydrates are the most abundant biomolecules on Earth. Although information about these fascinating natural compounds is not yet complete, we have already learned about some crucial aspects of the carbohydrate involvement in damaging cellular processes such as bacterial and viral infections, development and growth of tumors, metastasis, septic shock that are directly associated with deadly diseases of the twenty-first century, such as AIDS, cancer, meningitis and septicemia. The tremendous medicinal potential of glycostructures has already been acknowledged by the development of synthetic carbohydrate-based vaccines and therapeutics. The elucidation of the mechanisms of carbohydrate involvement in disease progression would be further improved if we could rely on the detailed knowledge of the structure, conformation and properties of the carbohydrate molecules. Therefore, the development of effective methods for the isolation and synthesis of complex carbohydrates has become critical for the field of glycosciences. Although significant improvements of the glycoside and oligosaccharide synthesis have already emerged, a variety of synthetic targets containing challenging glycosidic linkages cannot yet be directly accessed.

A vast majority of biologically and therapeutically active carbohydrates exist as polysaccharides (cellulose, chitin, starch, glycogen) or complex glycoconjugates (glycolipids, glycopeptides, glycoproteins) in which monosaccharide units are joined via glycosidic bonds. This linkage is formed by a glycosylation reaction, most commonly a promoter-assisted nucleophilic displacement of the leaving group (LG) of the glycosyl donor with the hydroxyl moiety of the glycosyl acceptor. Other functional groups on both the donor and the acceptor are temporarily masked with protecting groups (P). These reactions are most commonly performed in the presence of an activator: promoter or catalyst. As the new glycosidic linkage creates a chirality center, particular care has to be taken with regard to the stereoselectivity. Although in the natural environment specificity and selectivity of an enzyme ensure the stereoselectivity of glycosylation, synthesis of synthetic carbohydrate faces a major challenge in comparison to the synthesis of other natural biopolymers, that is proteins and nucleic acids.



Although mechanistic studies of the glycosylation reaction are scarce, certain conventions have already been established. Pioneering mechanistic work of Lemieux was enriched by recent studies by Bols, Boons, Crich, Gin, Kochetkov, Schmidt, Whitfield and others. 1,2-*trans* Glycosides are often stereoselectively obtained with the assistance of the 2-acyl neighboring participating group. In case of ether-type nonparticipating substituents, the glycosylation proceeds with poorer stereocontrol that results in mixtures of diastereomers, which makes the synthesis of 1,2-*cis* glycosides a notable challenge.

Since the first attempts at the turn of the twentieth century, enormous progress has been made in the area of the chemical *O*-glycoside synthesis. However, it is only in the past two–three decades that the scientific world has witnessed a dramatic improvement in the methods used for glycosylation. Recently, an abundance of glycosyl donors that can be synthesized under mild reaction conditions and that are sufficiently stable toward purification, modification and storage have been developed. Convergent synthetic strategies enabling convenient and expeditious assembly of oligosaccharides from properly protected building blocks with the minimum synthetic steps have also become available.

As it stands, many of the recent developments in the area of chemical glycosylation still remain compromised when applied to the stereoselective synthesis of difficult glycosidic linkages. These special cases include the synthesis of 1,2-*cis* glycosides, especially β-mannosides and *cis*-furanosides, 2-amino-2-deoxyglycosides, 2-deoxyglycosides and α-sialosides. In spite of the considerable progress and the extensive effort in this field, no universal method for the synthesis of targets containing these types of linkages has yet emerged. Therefore, these difficult cases will be discussed individually.

This book summarizes the recent advances in the area of chemical glycosylation and provides updated information regarding the current standing in the field of synthetic carbohydrate chemistry. An expansive array of methods and strategies available to a modern synthetic carbohydrate chemist is discussed. The first chapter (Chapter 1) discusses major principles of chemical glycosylation, reaction mechanisms, survey methods for glycosylation and factors influencing the reaction outcome, as well as describes the strategies for expeditious synthesis of oligosaccharide. Each subsequent chapter discusses a certain class of glycosyl donors. Methodologies developed to date are classified and discussed based on the type of the anomeric leaving group: halogens (Chapter 2), oxygen-based derivatives (Chapter 3) and sulfur/selenium-based derivatives (Chapter 4). Bicyclic compounds, 1,2-dehydro derivatives, miscellaneous glycosyl donors and indirect synthetic methods are discussed in Chapter 5. Each chapter will discuss the following aspects of a particular methodology or approach, wherever it is applicable:

(1) Introduction (relevant to this class of glycosyl donors/methods)
(2) Synthesis of glycosyl donor
(3) Glycosylation (major activators/promoters, particulars of the reaction mechanism, examples of both 1,2-*cis* and 1,2-*trans* glycosylations)
(4) Application to target/total synthesis (oligosaccharides, glycoconjugates, natural products)
(5) Special topics (synthesis of β-mannosides, furanosides, sialosides, glycosides of aminosugars and deoxysugars, if applicable)
(6) Conclusions and future directions
(7) Typical experimental procedures
(8) References.

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January, 2008

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1
General Aspects of the Glycosidic Bond Formation

Alexei V. Demchenko

1.1
Introduction

Since the first attempts at the turn of the twentieth century, enormous progress has been made in the area of the chemical synthesis of *O*-glycosides. However, it was only in the past two decades that the scientific world had witnessed a dramatic improvement the methods used for chemical glycosylation. The development of new classes of glycosyl donors has not only allowed accessing novel types of glycosidic linkages but also led to the discovery of rapid and convergent strategies for expeditious oligosaccharide synthesis. This chapter summarizes major principles of the glycosidic bond formation and strategies to obtain certain classes of compounds, ranging from glycosides of uncommon sugars to complex oligosaccharide sequences.

1.2
Major Types of *O*-Glycosidic Linkages

There are two major types of *O*-glycosides, which are, depending on nomenclature, most commonly defined as α- and β-, or 1,2-*cis* and 1,2-*trans* glycosides. The 1,2-*cis* glycosyl residues, α-glycosides for D-glucose, D-galactose, L-fucose, D-xylose or β-glycosides for D-mannose, L-arabinose, as well as their 1,2-*trans* counterparts (β-glycosides for D-glucose, D-galactose, α-glycosides for D-mannose, etc.), are equally important components in a variety of natural compounds. Representative examples of common glycosides are shown in Figure 1.1. Some other types of glycosides, in particular 2-deoxyglycosides and sialosides, can be defined neither as 1,2-*cis* nor as 1,2-*trans* derivatives, yet are important targets because of their common occurrence as components of many classes of natural glycostructures.

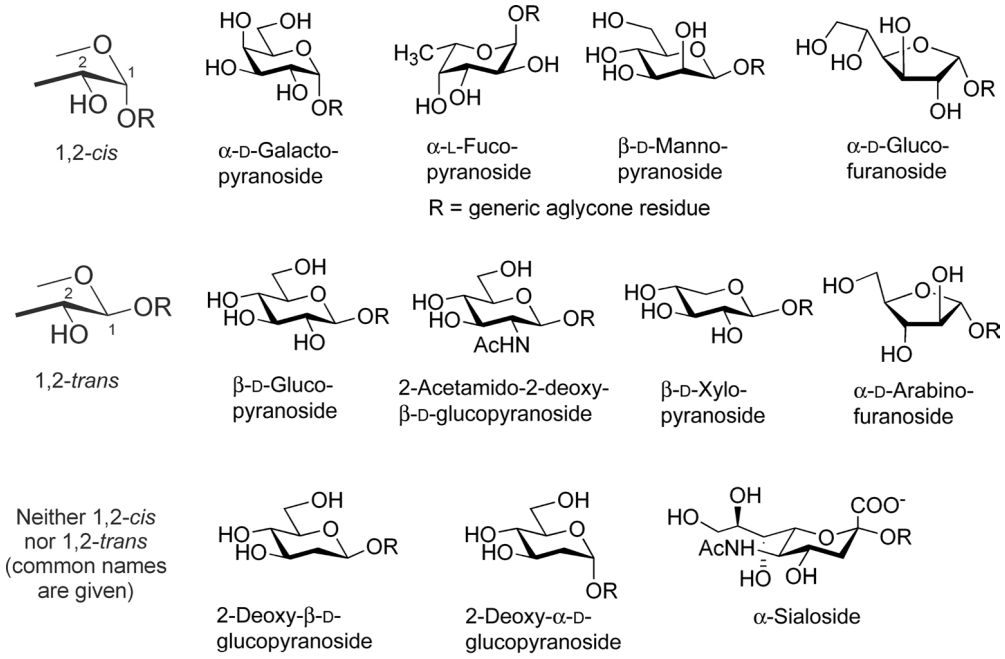


Figure 1.1 Common examples of *O*-glycosides.

1.3
Historical Development: Classes of Glycosyl Donors

The first reactions performed by Michael (synthesis of aryl glycosides from glycosyl halides) [1] and Fischer (synthesis of alkyl glycosides from hemiacetals) [2] at the end of the nineteenth century showed the complexity of the glycosylation process. The discovery of the first controlled, general glycosylation procedure involving the nucleophilic displacement of chlorine or bromine at the anomeric center is credited to Koenigs and Knorr [3]. The glycosylations were performed in the presence of Ag_2CO_3, which primarily acted as an acid (HCl or HBr) scavenger. At that early stage, glycosylations of poorly nucleophilic acceptors such as sugar hydroxyls were sluggish and inefficient; hence, even the synthesis of disaccharides represented a notable challenge. The first attempts to solve this problem gave rise to the development of new catalytic systems that were thought to be actively involved in the glycosylation process [4]. Thus, Zemplen and Gerecs [5] and, subsequently, Helferich and Wedermeyer [6] assumed that the complexation of the anomeric bromides or chlorides with more reactive, heavy-metal-based catalysts would significantly improve their leaving-group ability. This approach that has become a valuable expansion of the classic Koenigs–Knorr method made it possible to replace Ag_2CO_3 or Ag_2O by more active mercury(II) salt catalysts. The early attempts

to improve the glycosylation process have revealed the necessity to find a delicate balance between the reactivity and stereoselectivity [7,8]. Indeed, it was noted that faster reactions often result in a decreased stereoselectivity. At around the same time, the first attempts to involve other classes of anomeric leaving groups (LGs) resulted in the investigation of peracetates as glycosyl donors [9].

Seminal work of Lemieux [10] and Fletcher and coworkers [11,12] has led to the appreciation that the reactivity of the glycosyl halides and the stereoselectivity of glycosylation are directly correlated to the nature of the protecting groups, especially at the neighboring C-2 position. From early days, it has been acknowledged that peracylated halides often allow stereoselective formation of 1,2-*trans* glycosides. Later, this phenomenon was rationalized by the so-called participatory effect of the neighboring acyl substituent at C-2. Although occasionally substantial amounts of 1,2-*cis* glycosides were obtained even with 2-acylated glycosyl donors, the purposeful 1,2-*cis* glycosylations were best achieved with a nonparticipating ether group at C-2, such as methyl or benzyl. Further search for suitable promoters for the activation of glycosyl halides led to the discovery of Ag-silicate that proved to be very efficient for direct β-mannosylation, as these reactions often proceed via a concerted S_N2 mechanism [13,14].

For many decades classic methods, in which anomeric bromides, chlorides, acetates or hemiacetals were used as glycosyl donors, had been the only procedure for the synthesis of a variety of synthetic targets ranging from simple glycosides to relatively complex oligosaccharides (Figure 1.2). Deeper understanding of the reaction mechanism, driving forces and principles of glycosylation have stimulated the development of other methods for glycosylation, with the main effort focusing on the development of new anomeric leaving groups [15,16]. During the 1970s to early 1980s, a few new classes of glycosyl donors were developed. The following compounds are only the most representative examples of the first wave of the leaving-group development: thioglycosides by Ferrier *et al.* [17], Nicolaou *et al.* [18], Garegg *et al.* [19] and others [20]; cyanoethylidene and orthoester derivatives by Kochetkov and coworkers [21,22]; *O*-imidates by Sinay and coworkers [23] and Schmidt and Michel [24]; thioimidates including *S*-benzothiazolyl derivatives by Mukaiyama *et al.* [25]; thiopyridyl derivatives by Hanessian *et al.* [26] and Woodward *et al.* [27] and glycosyl fluorides by Mukaiyama *et al.* [28] (Figure 1.2). Many glycosyl donors introduced during that period gave rise to excellent complimentary glycosylation methodologies. Arguably, trichloroacetimidates [29,30], thioglycosides [31–33] and fluorides [34,35] have become the most common glycosyl donors nowadays.

A new wave of methods arose in the end of the 1980s, among which were glycosyl donors such as glycosyl acyl/carbonates [36–38], thiocyanates [39], diazirines [40], xanthates [41], glycals [42,43], phosphites [44,45], sulfoxides [46], sulfones [47], selenium glycosides [48], alkenyl glycosides [49–51] and heteroaryl glycosides [52] (Figure 1.2). These developments were followed by a variety of more recent methodologies and improvements, among which are glycosyl iodides [53], phosphates [54], Te-glycosides [55], sulfonylcarbamates [56], disulfides [57], 2-(hydroxycarbonyl) benzyl glycosides [58] and novel thio- [59,60] and *O*-imidates [61,62] (Figure 1.2). In

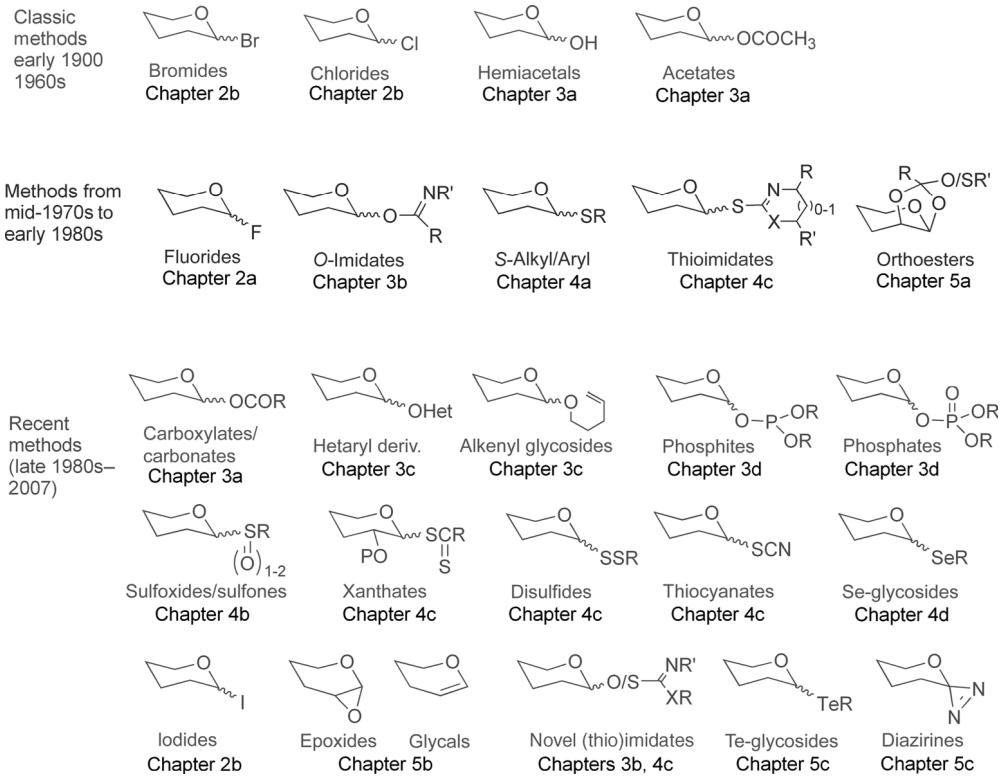
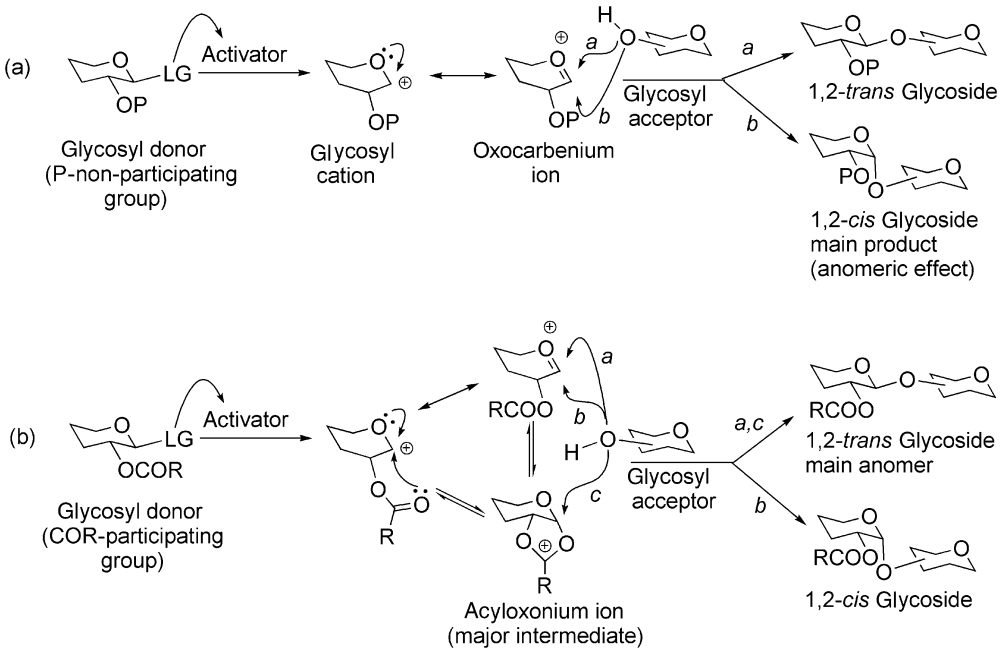


Figure 1.2 Survey of glycosyl donors.

addition, a variety of new recent methodologies bring the use of classic glycosyl donors such as hemiacetals to entirely different level of flexibility and usefulness [63]. These innovative concepts will be discussed in the subsequent chapters dealing with particular classes of clycosyl donors..

1.4 General Reaction Mechanism

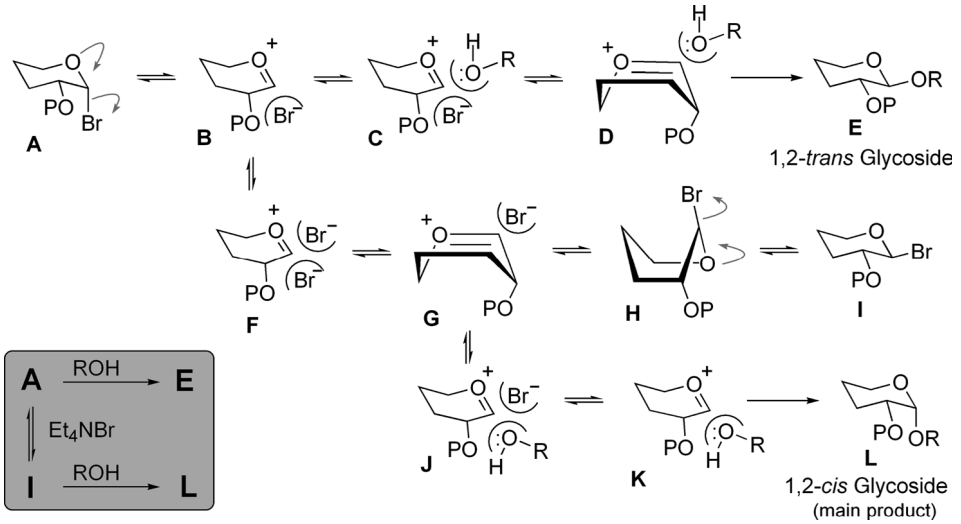
Detailed glycosylation mechanism has not been elucidated as yet; therefore, speculations and diagrams presented herein are a commonly accepted prototype of the glycosylation mechanism. Most commonly, the glycosylation reaction involves nucleophilic displacement at the anomeric center. As the reaction takes place at the secondary carbon atom with the use of weak nucleophiles (sugar acceptors), it often follows a unimolecular S_N1 mechanism. Glycosyl donors bearing a nonparticipating and a participating group will be discussed separately (Scheme 1.1a and b, respectively). In most cases, an activator (promoter or catalyst) assisted departure of the anomeric leaving group results in the formation of the glycosyl cation. The only



Scheme 1.1

possibility to intramolecularly stabilize glycosyl cation formed from the glycosyl donor bearing a non-participating group is by resonance from O-5 that results in oxocarbenium ion (Scheme 1.1a). The most commonly applied nonparticipating groups are benzyl (OBn) for neutral sugars and azide (N_3) for 2-amino-2-deoxy sugars; however, other moieties have also been occasionally used. The anomeric carbon of either resonance contributors is sp^2 hybridized; hence, the nucleophilic attack would be almost equally possible from either the top (*trans*, β- for the D-gluco series) or the bottom face (*cis*, α-) of the ring. Even though the α-product is thermodynamically favored because of the so-called anomeric effect (discussed in the subsequent section) [64], a substantial amount of the kinetic β-linked product is often obtained owing to the irreversible character of glycosylation of complex aglycones. Various factors such as temperature, protecting groups, conformation, solvent, promoter, steric hindrance or leaving groups may influence the glycosylation outcome (discussed below) [65,66].

1,2-*trans* Glycosidic linkage can be stereoselectively formed with the use of anchimeric assistance of a neighboring participating group, generally an acyl moiety such as *O*-acetyl (Ac), *O*-benzoyl (Bz), 2-phthalimido (NPhth) and so on [67–69]. These glycosylations proceed primarily via a bicyclic intermediate, the acyloxonium ion (Scheme 1.1b), formed as a result of the activator-assisted departure of the leaving group followed by the intramolecular stabilization of the glycosyl cation. In this case, the attack of a nucleophile (alcohol, glycosyl acceptor) is only possible from the top face of the ring (pathway c), therefore allowing stereoselective formation of a 1,2-*trans* glycoside. Occasionally, substantial amounts of 1,2-*cis*-linked products are also



Scheme 1.2

formed, most often when unreactive alcohols are used as the substrates and/or poorly nucleophilic participatory substituents are present at C-2. In these cases, glycosylation assumingly proceeds via oxocarbenium ion, via pathways a and b (Scheme 1.1b), resulting in the formation of 1,2-*trans* and 1,2-*cis* glycosides, respectively, or most commonly mixtures thereof.

Seminal work by Lemieux on the halide-ion-catalyzed glycosidation reaction involved extensive theoretical studies that gave rise to a more detailed understanding of the reaction mechanism [70]. Thus, it was postulated that a rapid equilibrium could be established between a relatively stable α-halide **A** and its far more reactive β-counterpart **I** by the addition of tetraalkylammonium bromide (Et_4NBr, Scheme 1.2). In this case, a glycosyl acceptor (ROH) would preferentially react with the more reactive glycosyl donor (**I**) in an S_N2 fashion, possibly via the tight ion-pair complex **K**, providing the α-glycoside **L**. It is likely that the energy barrier for a nucleophilic substitution **I** → **L** (formation of the α-glycoside) is marginally lower than that for the reaction **A** → **E** (formation of a β-glycoside). If the difference in the energy barrier were sufficient, it should be possible to direct the reaction toward the exclusive formation of α-anomers.

Therefore, to obtain complete stereoselectivity, the entire glycosylation process has to be performed in a highly controlled manner. In this particular case, the control is achieved by the use of extremely mild catalyst (R_4NBr), although very reactive substrates and prolonged reaction at times are required.

Other common approaches to control the stereoselectivity of glycosylation will be discussed in the subsequent sections. In addition to the apparent complexity of the glycosidation process, there are other competing processes that cannot be disregarded. These reactions often cause the compromised yields of the glycosylation products and further complicate the studies of the reaction mechanism.