1.1 Carbohydrates

Carbohydrates are one of the most abundant classes of organic molecules present in nature and it exists as glycosides, glycoconjugates or polysaccharides [1]. Carbohydrates are primarily known as energy provider for living organism rather than biomolecule. However, the recent developments in glycochemistry and glycobiology revealed the fundamental roles of carbohydrates in development and recognition of living cells and organisms [2]. Carbohydrates are the structural component of the cell walls of many bacteria that mediate intercellular communication in different forms [3]. Structurally, carbohydrates are poly-hydroxy compounds with unique structural features.

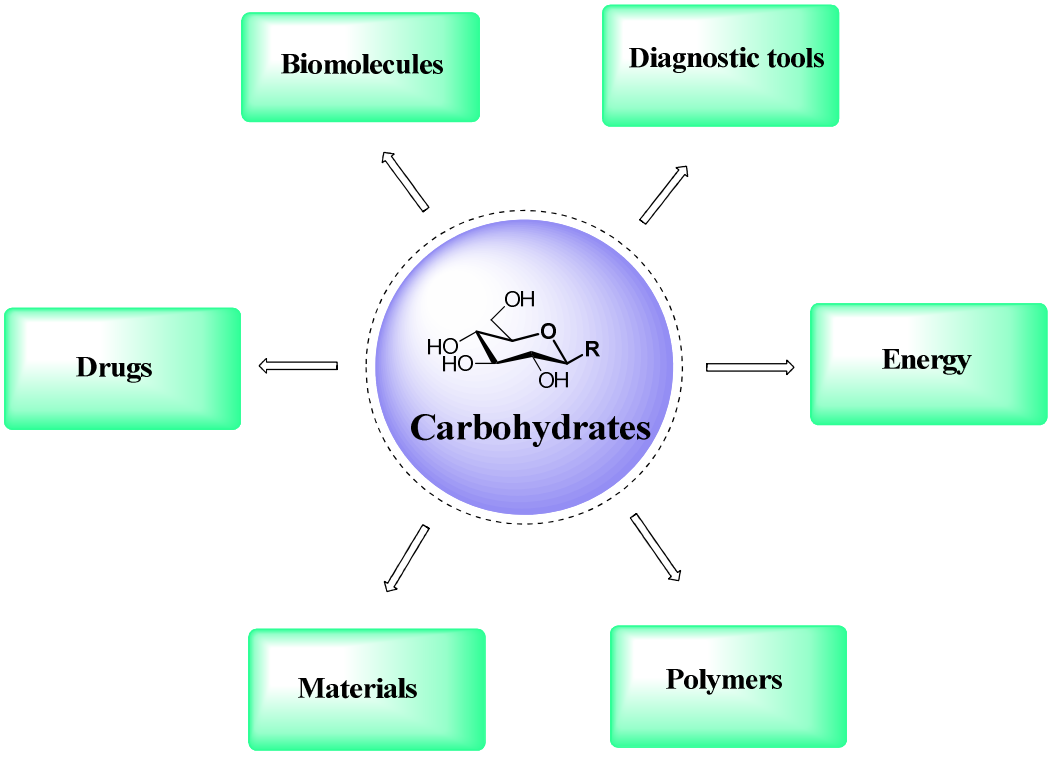


Figure 1.1 Applications of carbohydrates in different fields

Unlike proteins and nucleic acids which are linear biopolymers, carbohydrate structures are more complex and often branched leading to larger diversity [4]. Hence, carbohydrates continue to be central focus in different research areas including chemistry, biology, materials and polymer sciences (**Figure 1.1**) [5]. Moreover, recently many research groups focused on the development of carbohydrate based drugs, diagnostic tools, vaccines, biomedical devices, etc. (**Figure 1.2**) [6].

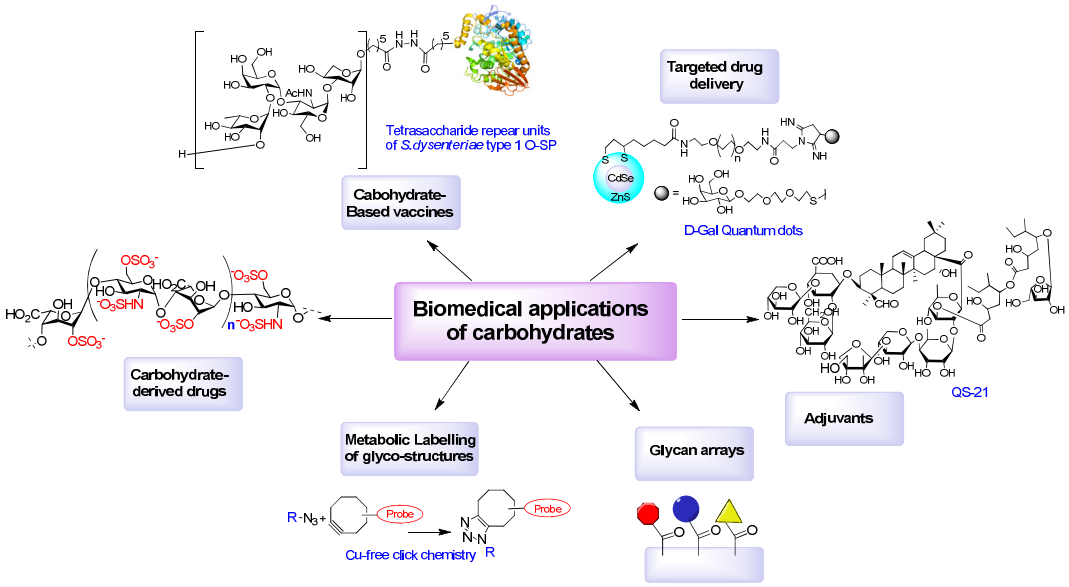


Figure 1.2 Biological relevance of carbohydrates

1.2 Classification of carbohydrates

Carbohydrates are primarily classified as monosaccharides, disaccharides, oligosaccharides and polysaccharides based on the number carbohydrate units attached through glycosidic bonds. Monosaccharides are single sugar unit which act as the building blocks of disaccharides, oligosaccharides and polysaccharides (**Figure 1.3**).

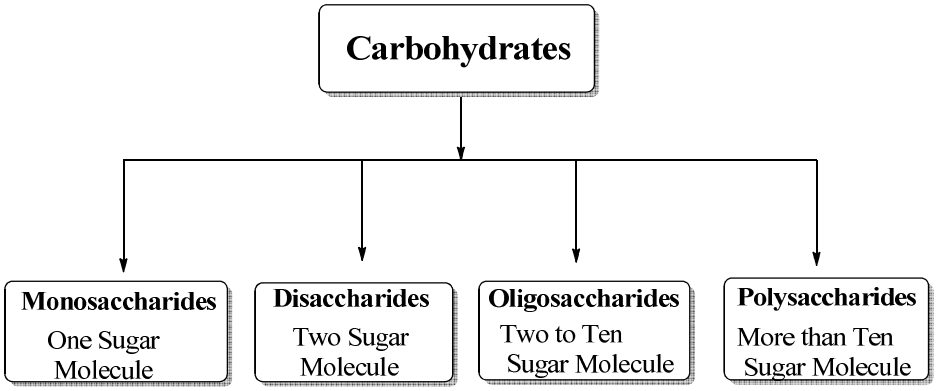


Figure 1.3 Primary classification of carbohydrates

Besides that, carbohydrates are also further classified as *O*-glycosides, *N*-glycoside, *S*-glycosides and *C*-glycosides based on the anomeric linkages (**Figure 1.4**). A brief introduction to all these glycosides is given below; however, as per the focus of current thesis, more emphasis has been given to the synthetic approaches involved in the preparation of aryl-*C*-glycosides.

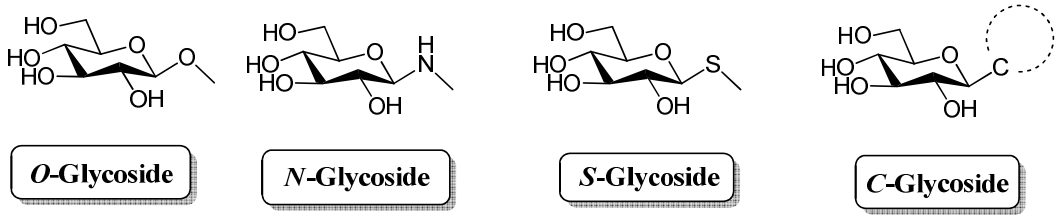


Figure 1.4 Classification of glycosides

1.3 *O*-Glycosides

O-Glycosides are those having direct *C*-*O* linkage between anomeric carbon of a sugar and glycan or aglycon molecule. Among the different types of glycosides, *O*-glycosides are most commonly present in nature. Many natural carbohydrate polymers including starch, cellulose, glycogen, etc., are *O*-glycosides (**Figure 1.5**). Glycoconjugates such as glycolipids and glycoproteins that are found in living organism are mostly *O*-

glycosides which participate in various biological processes including cell-growth and differentiation, bacterial and viral infections, immunological response, inflammation, etc., [2, 7]. Moreover, a wide range of natural products including antibiotics and anticancer agents possess carbohydrate units attached via *O*-glycosidic bond [8]. The chemistry of *O*-glycosides receives continuous attention over many decades due to its broad applications in the area of drug discovery and chemical biology [9].

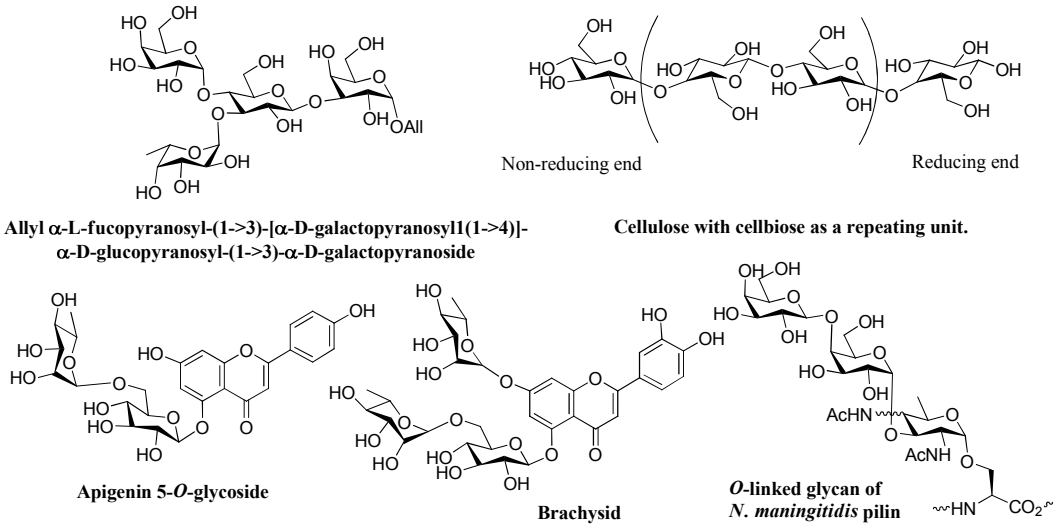
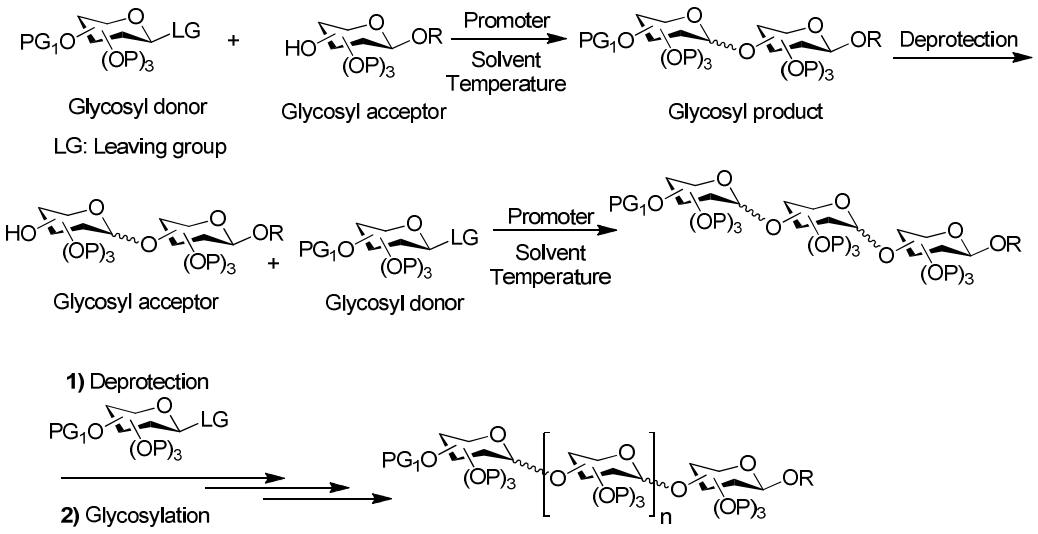


Figure 1.5 Structures of some important *O*-glycosides

1.3.1. Synthesis of *O*-glycosides

Structurally well defined oligosaccharides played a crucial role in our recent understanding of functions of carbohydrates in biology. *O*-Glycosides can be obtained from natural sources by isolation in very small quantities, however often as heterogeneous-glycan mixtures. Chemical synthesis or enzymatic synthesis or by the combination of both, i.e. chemo-enzymatic synthesis are the alternative process for

glycan synthesis. Among these methods, synthesis of oligosaccharides through chemical methods considered to be most promising. Because, chemical methods are scalable that helps in preparing glycans in required amounts in high purity that are suitable for the biochemical studies. In chemical synthesis, *O*-glycosides are prepared through glycosylation process which involves the activation of glycosyl donors (i.e. sugar molecule with leaving group) followed by coupling with hydroxyl group of acceptors (i.e. it can be glycan or aglycon) [10]. The traditional synthesis of *O*-glycosides relies on the stepwise preparation as shown in **Scheme 1.1** [11].



Scheme 1.1 Stepwise preparation of oligosaccharides

However, many new methods and approaches have been recently developed for achieving highly regio-and stereo-selective formation of *O*-glycosides. Among others, programmable one-pot synthesis and automated solid phase synthesis received extensive attention in the last decade. These new methods significantly reduce the labor and time requirement as demanded in typical stepwise synthesis. Nevertheless, the other

important aspect of *O*-glycoside synthesis is creation of desired stereocenters (i.e. α/β) at the anomeric carbon, which is mainly based on the selection of acceptors, donors, protecting groups, solvents, activators, etc.

1.3.2. Programmable one-pot oligosaccharide synthesis

The programmable one-pot reaction approach is basically conducting multiple sequential glycosylation in a same reaction flask [12]. This approach was developed by Prof. Chi-Huey Wong and primarily relies upon using a reactivity profile of sugar building blocks that facilitates automated oligosaccharide synthesis in a simple manner. For instance, types of protecting groups and leaving groups in the molecules can dictate the reactivity of any building blocks. A computer program called OptiMer has been developed to determine the reactivity of set of building blocks. Based on the reactivity profile, building blocks are added to one-pot flask in a sequence where most reactive at first while least reactive at the last. By this way, the order of formation of glycosidic bond is controlled. In general, thioglycoside building blocks were employed as donors and several tedious isolation protocols are eliminated during the complex oligosaccharide synthesis. In 2018, the OptiMer software was upgraded as Auto-CHO44 that expands the scope of programmable synthesis (**Figure 1.6**). Using this approach, recently syntheses of complex glycosaminoglycan (GAGs) derivatives were demonstrated (**Scheme 1.2**) [13].

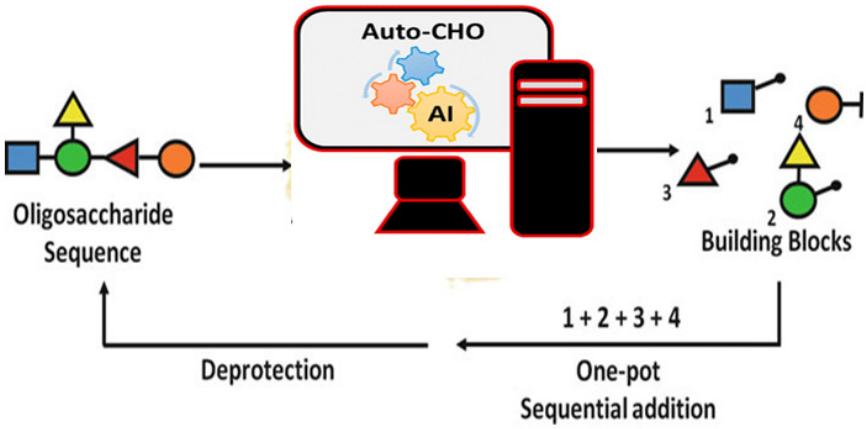
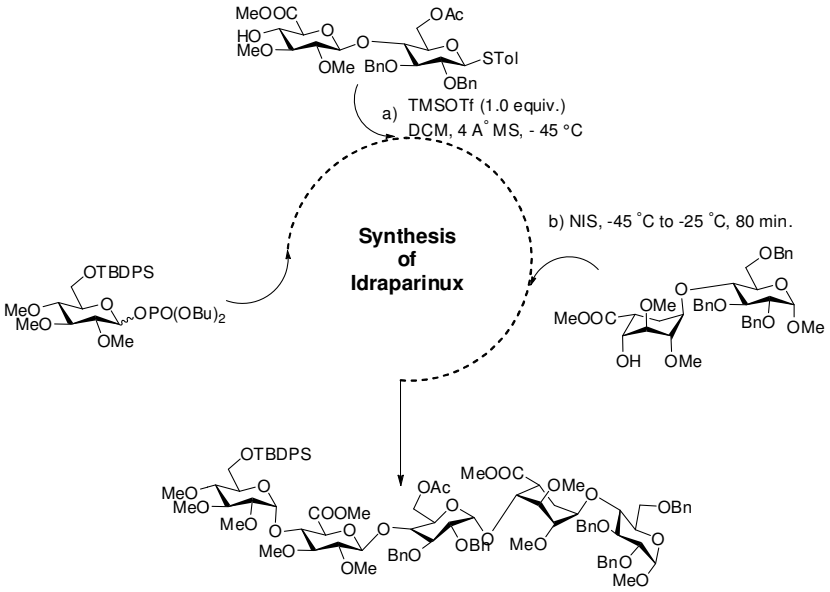


Figure 1.6 Programmable one-pot oligosaccharide synthesis



Scheme 1.2 One-pot synthesis of protected idraparinux

1.3.3. Automated solid phase synthesis of *O*-glycosides

Automated solid phase synthesis is one of the high-speed methods developed for oligosaccharide assembly **(Figure 1.7)** [14]. This method was developed by Prof. Peter

H. Seeberger, which is highly attractive and promising. The automation assembly of oligosaccharides was initially accomplished by modified peptide synthesizer [15].

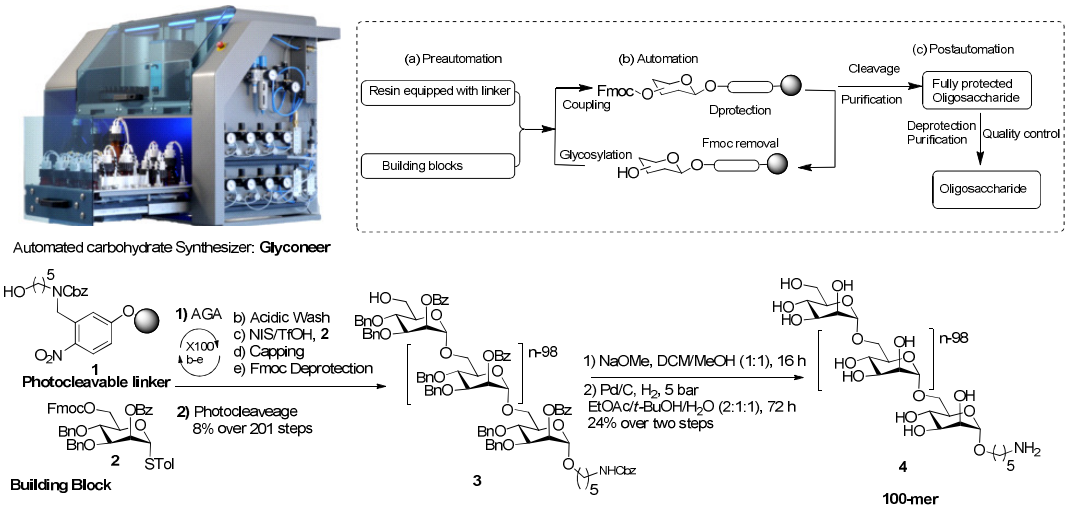


Figure 1.7 Automated synthesis of oligosaccharides

Merrifield resin was used as a solid support due to its favorable swelling properties in organic solvents. The design of the linker to connect the sugar and the solid support play key role in this technique. For the automated synthesis, olefin-type linker (that can be cleaved using Grubb's catalyst), ester linker (cleaved by saponification reaction) and photocleavable linker (cleaved by light) have been developed by Seeberger group. Glycosylimidates, thioglycosides and glycosylphosphates donors have been frequently used in the automation process with suitable activators (e.g. TMSOTf, NIS/TfOH, etc.,) while Fmoc and Lev groups were used as the temporary protecting groups. Recently, Seeberger group demonstrated the synthesis 100-mer and 150-mer using prototype automated synthesizer called glyconeer [16].

1.3.4. Other strategies

Besides, there are many attractive strategies have been recently developed for *O*-glycoside synthesis [17]. Notably, HPLC-based automated polymer-supported synthesis [18], fluorous tag-supported synthesis [19], surface-tethered iterative synthesis [20] and solution phase-based automated synthesis using electrochemical activation of thioglycosides [21] have emerged as new and attractive strategies for *O*-glycosides synthesis.

1.4 *N*-Glycosides

N-glycosides represent an important class of carbohydrates that possess diverse applications in biology [4].

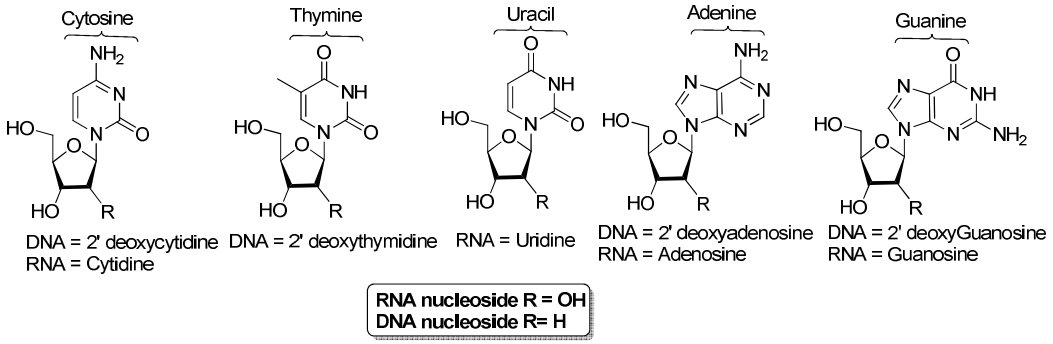


Figure 1.8 Structure of nucleosides

N-glycosides are those having *C–N–C* linkage between anomeric carbon of a sugar and aglycon moiety. Among others, nucleosides are the most important *N*-glycosides since they are fundamental components of deoxyribonucleic acid (DNA) and ribonucleic acid (RNA) (**Figure 1.8**).

Many carbohydrates that are present in cell walls usually attached to proteins through the nitrogen atom of amino acid asparagine. These *N*-glycosides, also known as *N*-glycoproteins, are essential in biological systems that involved in immune response, cell growth and recognition, and viral replication [7, 22]. On the other hand, a large range of drugs and bio-active molecules including antibacterial, antiviral, and anticancer agents are the derivatives of *N*-glycosides **Figure 1.9** [9b, 23].

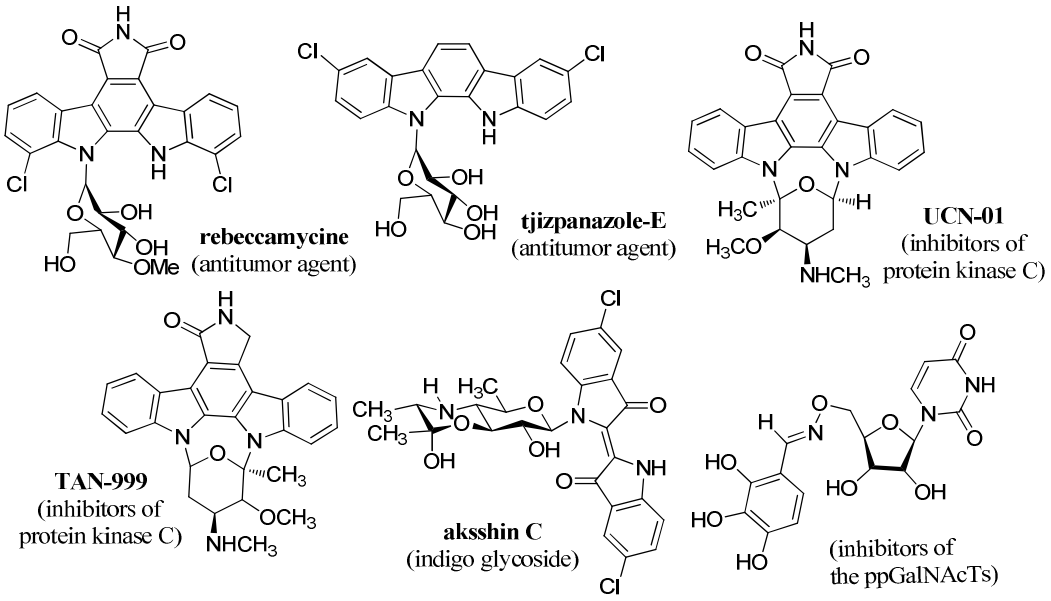
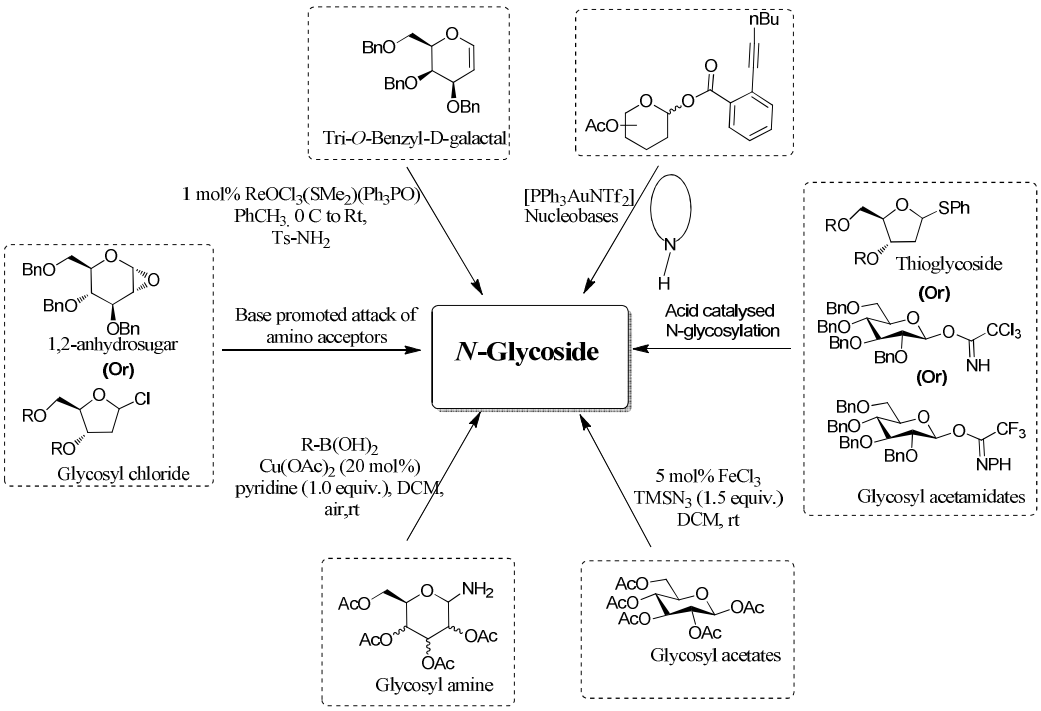


Figure 1.9 Structures of some important *N*-glycosides

1.4.1. Synthesis of *N*-glycosides

The synthesis of *N*-glycoside have been reported by a different variety of methods including base catalyzed glycosylation of glycosyl halide and ring opening of 1,2-anhydrosugars with nucleophilic amine acceptors [24]. On the other hand, activation of

glycosyl acetamidates, thioglycosides, and glycosyl acetates with suitable amine acceptors provides the desired *N*-glycosides (**Scheme1.3**) [25].



Scheme 1.3 Preparation methods of *N*- glycosides

Further, *N*-glycosylation of 2-deoxythioriboside donors with modified nucleobases, to afford *N*-2-deoxyribosides, was recently developed [26]. *N*-phenyltrifluoroimidates are also used for *N*-glycosylation with asparagines attached peptides in the presence of TMSOTf [27]. Gold (I)-catalyzed, an efficient method for *N*-glycosylation of glycosyl *ortho*-alkynyl benzoates with different purines and pyrimidines was reported (**Scheme 1.3**) [28]. *N*-Glycosylation of protected glycals were achieved by Re(V) catalyst [29]. Alternative to these methods, *N*-arylation of 1-aminoglycosides was reported with different arylboronic acids through Chan-Lam-Evans coupling reaction [30].

1.5 *S*-Glycosides

S-Glycosides, also called as thioglycosides, are generated when anomeric carbon of a sugar is attached to glycan or aglycon, through a sulfur atom, establishing *C–S–C* linkage. *S*-Glycosides are rarely found in nature while most of the compounds belonging to glucosinolates family, i.e. *O*-sulfated thiohydroximates of 1-thio-β-D-glucopyranosides [31].

More than hundred glucosinolates have been isolated and characterized from different plant species including *Arabidopsis thaliana*, *Barbarea vulgaris*, *Isatis tinctoria, etc.* Afrostyraxthioside A (**2**), raphanuside (**3**), and lincomycin A (**4**) are few other examples of naturally occurring *S*-glycosides (**Figure 1.10**).

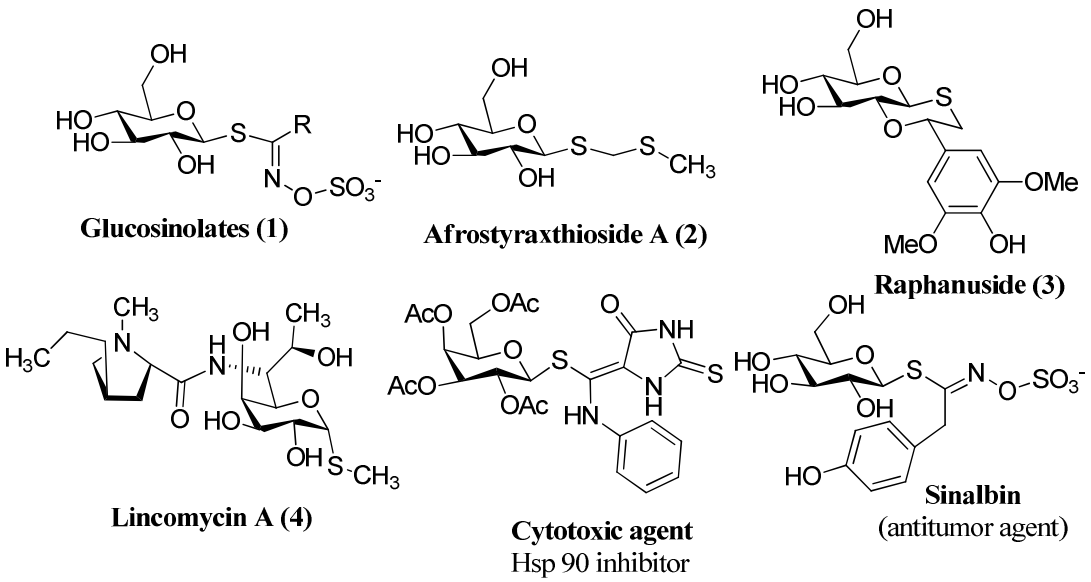
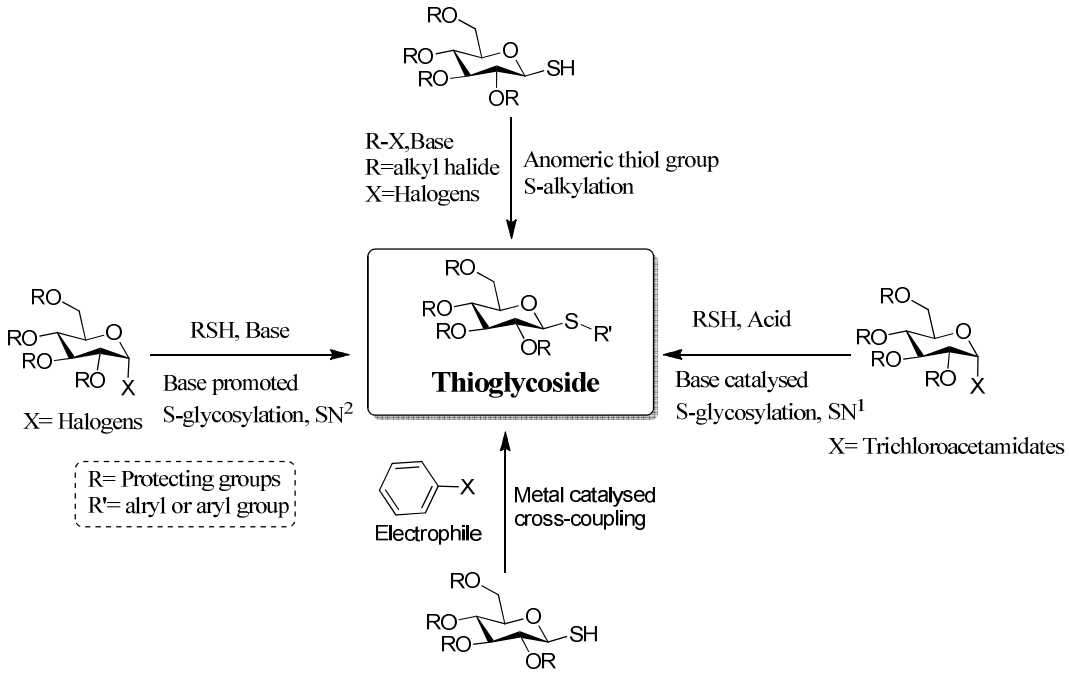


Figure 1.10 Examples of some natural *S*-glycosides

On the other hand, S-glycosides (i.e. thioglycosides) are frequently used in glycosylation reactions as donors in the synthesis of *O*-glycosides [11]. Although, many new types of glycosyl donors arrived in carbohydrate synthesis, thioglycosides remain as one of the most stable donors [10a]. Thioglycosides are usually activated by *N*-iodosuccinimide (NIS) in the presence of acids/Lewis acids and used in the preparation of large number of biologically relevant oligosaccharides. In particular, thioglycosides are used in programmable one-pot sequential glycosylation methods [12a, 13, 32]. In fact, thioacetal function can act not only glycosyl donors but also as anomeric protecting group which can be cleaved to hemi-acetal in the presence of *N*-bromosuccinimide (NBS)/acetone-water mixture. Thioglycosides display good stability under different reaction conditions and offer good temporary protection to the anomeric center.

1.5.1. Synthesis of *S*-glycosides

Thioglycosides are usually prepared from glycosyl halides or glycosyl acetates and thio-acceptors (sugar or non-sugar) via glycosylation reactions [31b]. Alternatively, transition metal catalyzed functionalization of 1-thiosugars with different aryl and heteroaryl compounds received great attention in recent years [33]. Aryl and heteroaryl halides as well as arylboronic acids have been used in the cross coupling reactions (**Scheme 1.4**).



Scheme 1.4 Different methods for synthesis of thioglycosides

1.6 *C*-Glycosides

C-Glycosides are generated when anomeric carbon of a sugar component is attached to glycan or aglycon through C–C linkage. After the *O*-glycosides, *C*-glycosides are more predominant in nature [4, 34]. *C*-Glycosides have attracted much attention due to their effectiveness as therapeutic agents [35]. In general, *C*-glycosides are resistant to enzymatic or chemical hydrolysis since the anomeric acetal functional group has been transformed from to stable ether functionality. Hence, *C*-glycosides have become usual choices for the generation of artificial analogs of the *O*-glycosides as potential therapeutic agents. Structurally, *C*-glycosides can be constituted with alkyl or aromatic aglycon moieties, called as alkyl-*C*-glycosides or aryl-*C*-glycosides, respectively, while

the sugar part can be pyranose or furanose. *In this context, aryl-C-glycosides are more predominant in nature and they display a number of biological activities including anti-diabetic, anti-oxidant, anti-bacterial, anti-viral, anti-inflammatory, anti-cancer, etc.*

1.7 Aryl-*C*-Glycosides

Aryl-*C*-glycoside structural motifs are widespread in nature and embedded in plenty of biologically active natural products [8b, 35-36]. Due to biological and medicinal significance, the preparation of aryl *C*-glycosides received tremendous interest in synthetic organic chemistry. Naturally occurring aryl-*C*-glycosides exist predominantly in two types, namely, 2-hydroxy-β-aryl-*C*-glycosides and 2-deoxy-β-aryl-*C*-glycosides. In the past decade, many excellent reviews, books and book chapters have been published in the area of *C*-glycoside synthesis [34, 37]. Moreover, recently three excellent reviews were also published on the synthesis of *C*-glycosides and related natural products [36a, 36b, 38].

The majority of the aryl-*C*-glycosides are two types:

i) 2-Hydroxy-aryl-*C*-glycosides

ii) 2-Deoxy aryl-*C*-glycosides

1.8 2-Hydroxy-β-Aryl-*C*-Glycosides

Several natural products including bergenin, mangiferin, papulacandin and aspalathin possesses 2-hydroxy-aryl-*C*-glycoside units (**Figure 1.11**). For instance, bergenin is a natural product isolated from different plants and used as one of main ingredients in herbal and ayurvedic medicines [39].

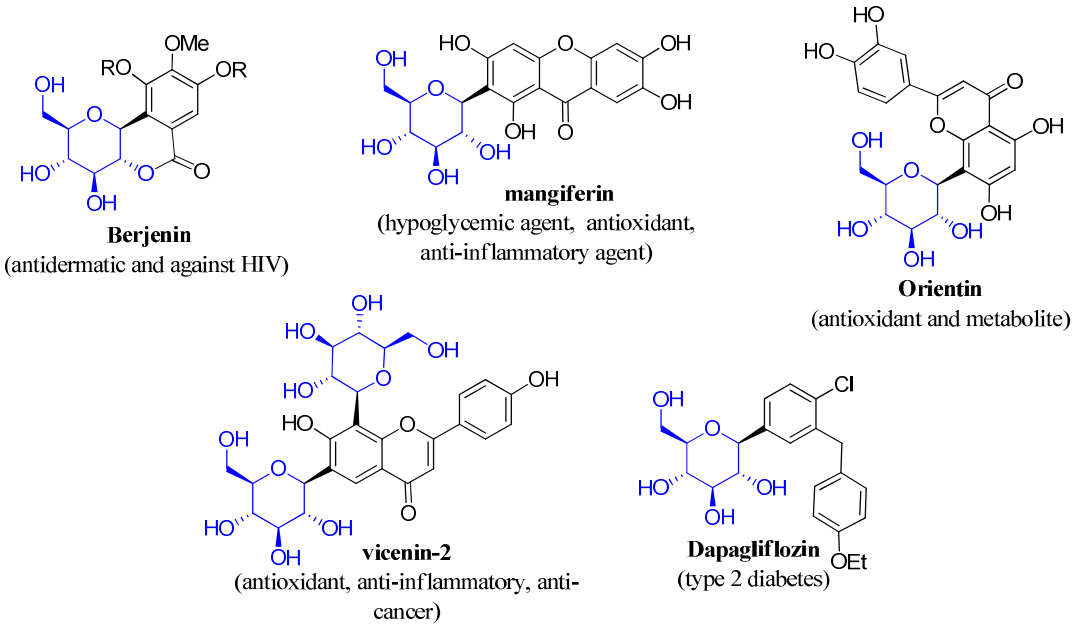


Figure 1.11 Biologically important 2-hydroxy-β-aryl-*C*-glycosides

Bergenin displays antiviral, antifungal and antidiabetic properties. Similarly, mangiferin is a bioactive compound isolated from the mango tree with potent antioxidant, antidiabetic, and neuroprotective activities [40]. Besides the natural products, many synthetic antidiabetic drugs i.e. sodium-glucose co-transporter inhibitors (SGLT-1 and -2) such as canagliflozin, dapagliflozin, empagliflozin etc., are 2-hydroxy-β-aryl-*C*-glycosides (**Figure 1.12**) [38, 41]. The most common methods of 2-hydroxy-β-aryl-*C*-glycosides preparation are discussed below:

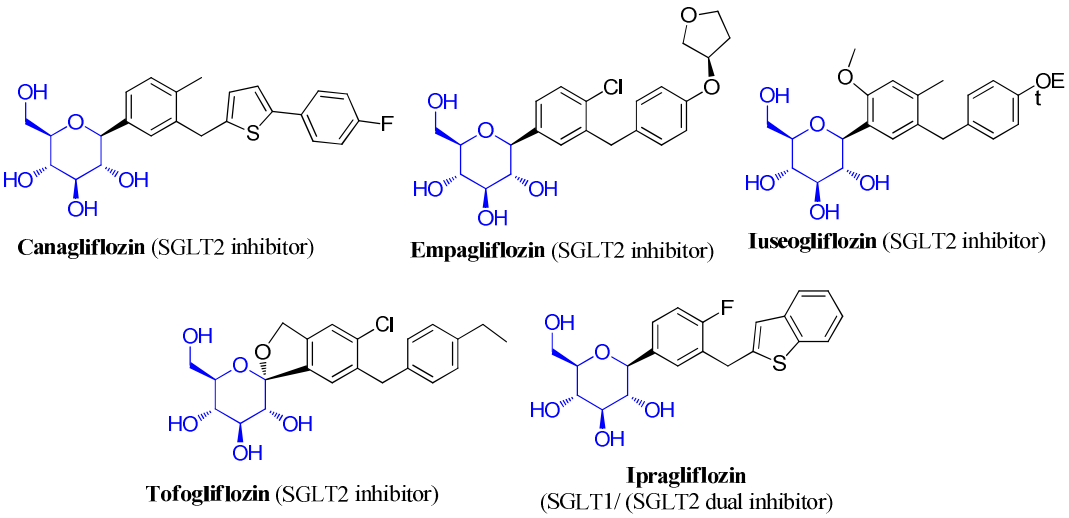
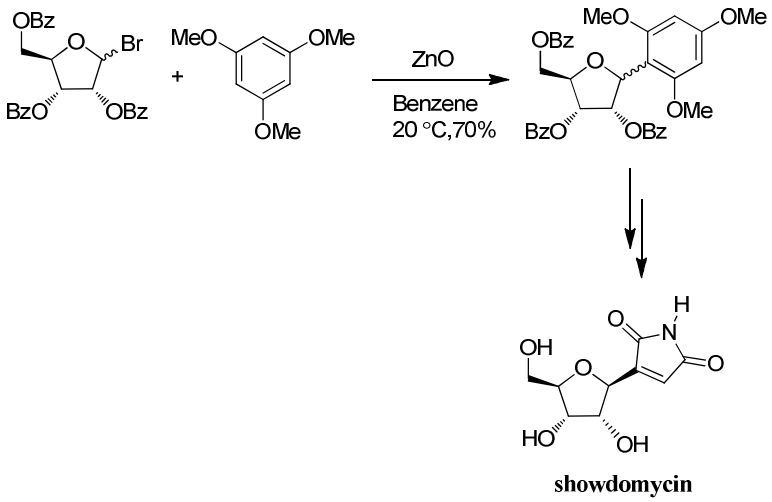


Figure 1.12 Structures of inhibitors of sodium-glucose co-transporter (SGLT1 and 2)

1.8.1. Friedel-Crafts reaction

Initial examples of synthesis of 2-hydroxy-β-aryl-*C*-glycosides are based on Friedel-Crafts alkylation approach in which glycosyl donor is activated to facilitate the electrophilic attack by an aromatic ring.

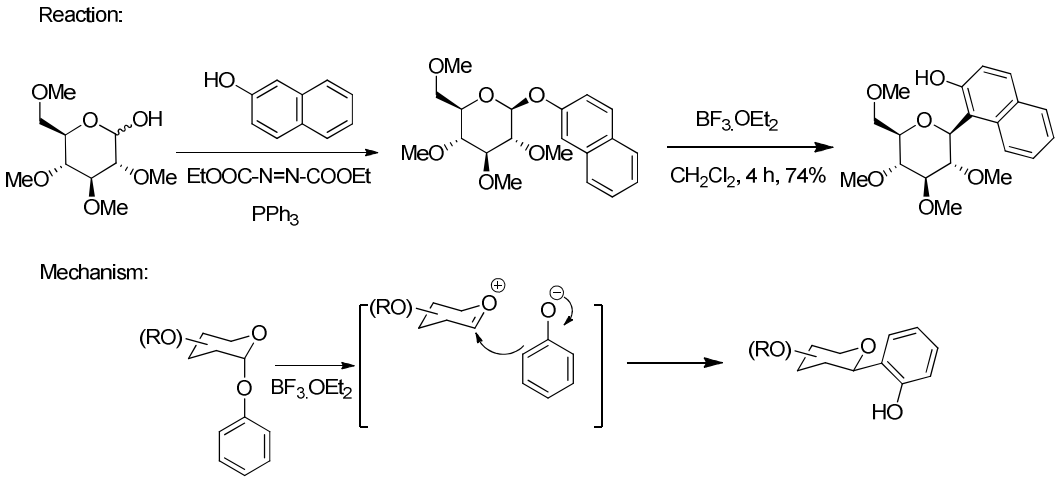


Scheme 1.5 Showdomycin preparation using Friedel-Crafts approach

Typically, these reactions proceed well with electron-rich aromatic compounds. Glycosyl halides, acetates, trichloroacetimidates, etc., have been used as the donors while $BF_3.OEt_2$, $AlCl_3$, ZnO, $SnCl_4$ and AgOTf were used as activators in the Friedel-Crafts approach. One example of preparation of natural product showdomycin, a nucleoside antibiotic, through Friedel-Crafts reaction is shown in the **Scheme 1.5** [42].

1.8.2. *O→C* Glycoside rearrangement reaction (Fries-type reaction)

In close line with Friedel-Crafts approach, *O→C* glycoside rearrangement reactions (i.e. Fries-type reaction) are used for the preparation of 2-hydroxy-β-aryl-*C*-glycosides. For instance, β-naphthol-*O*-glycoside obtained by the Mitsunobu reaction, was transformed into *C*-glycoside in the presence of $BF_3 \cdot OEt_2$ (**Scheme 1.6**) [43].



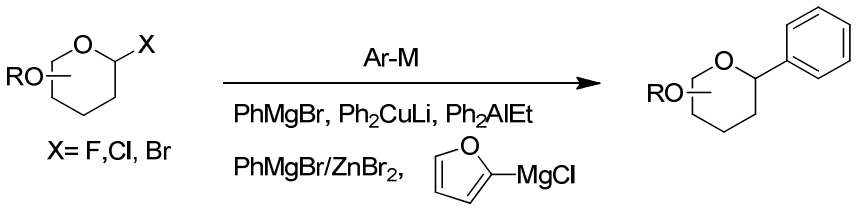
Scheme 1.6 *O→C* Glycoside rearrangement reaction

As per the proposed mechanism, phenol glycoside is activated by $BF_3 \cdot OEt_2$ to generate an oxocarbenium and phenoxide intermediates. Subsequently, the phenoxide ion undergoes electrophilic substitution (irreversible Friedel-Crafts reaction) with oxocarbenium, preferably at the *ortho*-position to provide the aryl *C*-glycosides. Mostly

it was observed that at low temperatures *O*-glycoside are stable while in higher temperatures *O*-glycoside dissociates to form more stable *C*-glycosides.

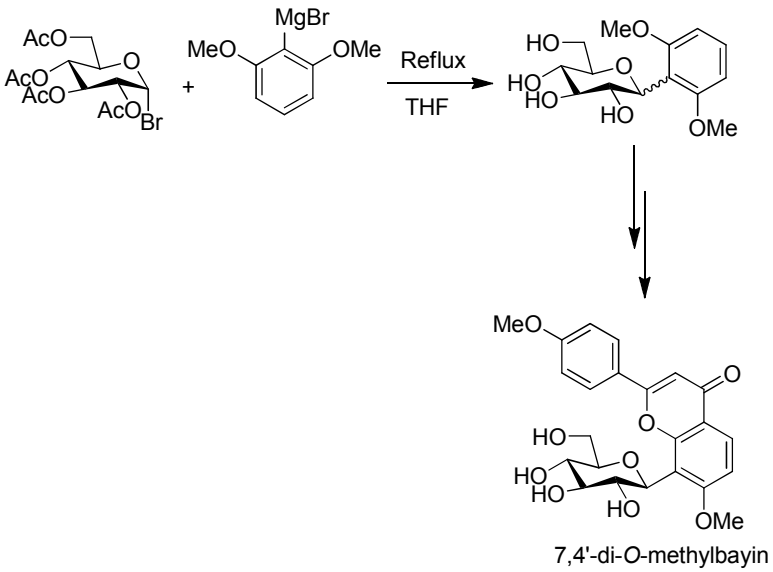
1.8.3. Coupling of organometallic reagents with glycosyl halides

One of the most frequent methods for preparing aryl-*C*-glycosides involve coupling of aromatic nucleophile including Grignard reagents, aryllithium compounds, Gilman reagents, aryl zinc reagents, etc., with glycosyl halides (**Scheme 1.7**).

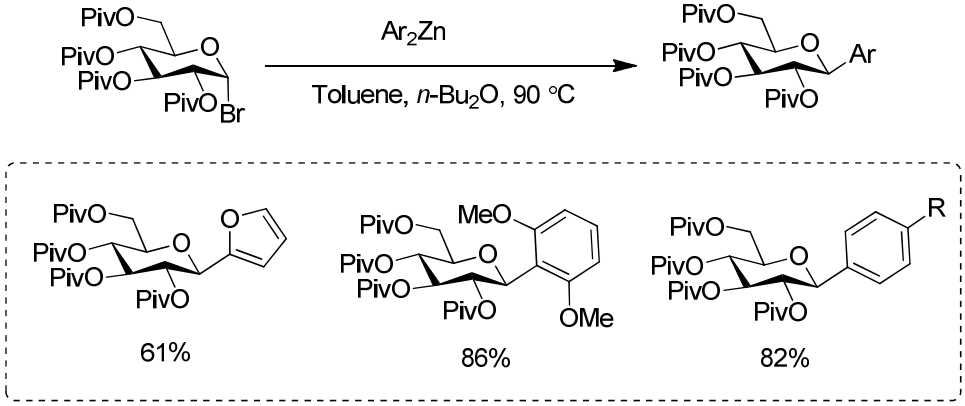


Scheme 1.7 Coupling of glycosyl halide with organometallic reagents

This approach proceeds through S_N2 type of displacement reaction. If acetate groups are used as protecting group, we need to use large excess of organometallic reagent that provides fully deprotected aryl-*C*-glycosides. This approach has been used in the preparation of intermediates for many natural products. For instance, the flavanoide *C*-glycoside, 7,4'-di-*O*-methylbayin has been synthesized using this approach (**Scheme 1.8**) [44]. Similar to Grignard reagents, aryl zinc reagents (Negishi cross-coupling) were also efficiently used in the *C*-glycosylation reaction (**Scheme 1.9**) [45].



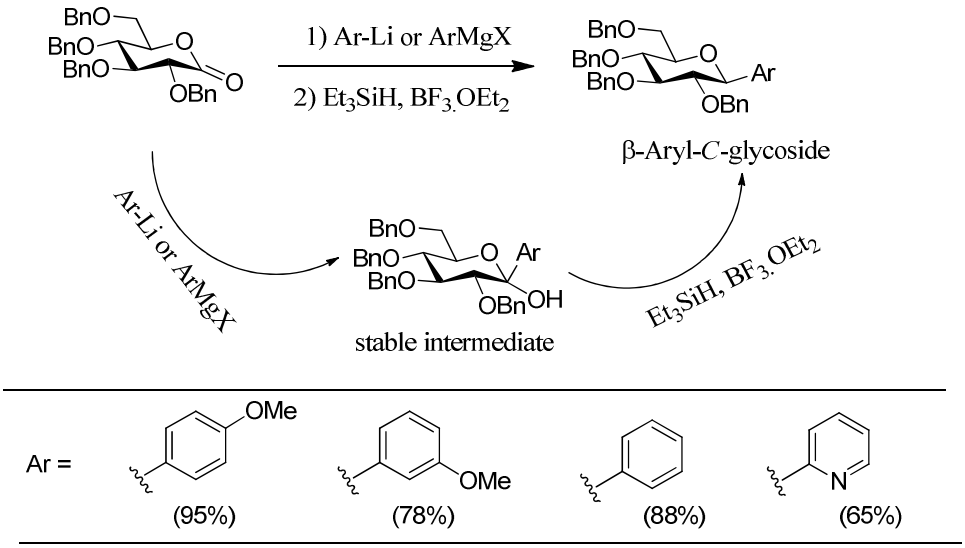
Scheme 1.8 Synthesis of 7,4'-di-*O*-methylbayin



Scheme 1.9 *C*-Glycosylation of arylzinc reagents with glucosyl bromide

1.8.4 Nucleophilic addition of organometallic reagents with glycosyl lactones

Among the different key methods of aryl-*C*-glycosides preparation, addition of organometallic reagents (e.g. RLi or RMgX) to sugar-derived lactones is most frequently used in natural product synthesis.



Scheme 1.10 Sugar-derived lactone in aryl *C*-glycoside synthesis

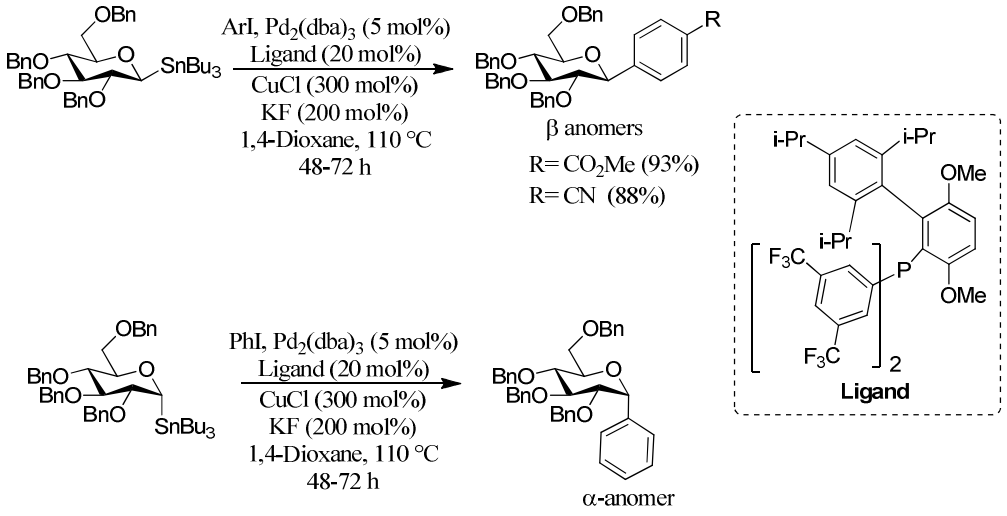
This reaction provides ketol derivatives which are subjected to the hydride reduction. This approach is highly stereoselective where hydride ion is delivered from the α-side and provides β-aryl-*C*-glycosides (**Scheme 1.10**) [46].

1.8.5 Other methods for the synthesis of 2-hydroxy aryl-*C*-glycosides

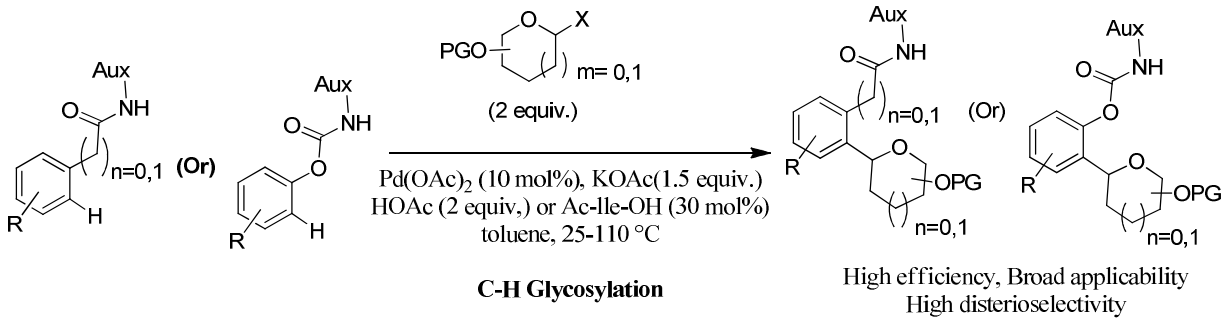
Besides above methods, some other more interesting methods have been developed recently. Walczak and co-workers reported the palladium catalyzed cross-coupling of stable sp^3-hybridized anomeric glycosyl stannanes with aryl halides (**Scheme 1.11**) [47]. Retentive stereochemistry of the products was obtained with respect to stereochemistry of glycosyl stannanes in excellent yields.

Wang *et al.* reported a simple and efficient strategy for the stereoselective preparation of aryl-*C*-glycosides via palladium-catalysed *ortho*-CH functionalization of arenes with

glycosyl halide donors [48]. The method is compatible to a wide range of auxiliary groups, aryl and heteroaryl substrates, and glycosyl halide donors (**Scheme 1.12**).



Scheme 1.11 Cross-coupling reactions of anomeric stannanes with aryl halides



Scheme 1.12 *Ortho* C–H functionalization of arenes with different glycosyl chlorides

1.9 2-Deoxy-β-Aryl-*C*-Glycosides

Similar to 2-hydroxy-β-aryl-*C*-glycosides, many natural products including angucyclines (e. g. landomycin, marmycin, urdamycinones), kidamycin, altromycins and pluramycin possess 2-deoxy-β-aryl-*C*-glycoside units (**Figure 1.13**) [37].

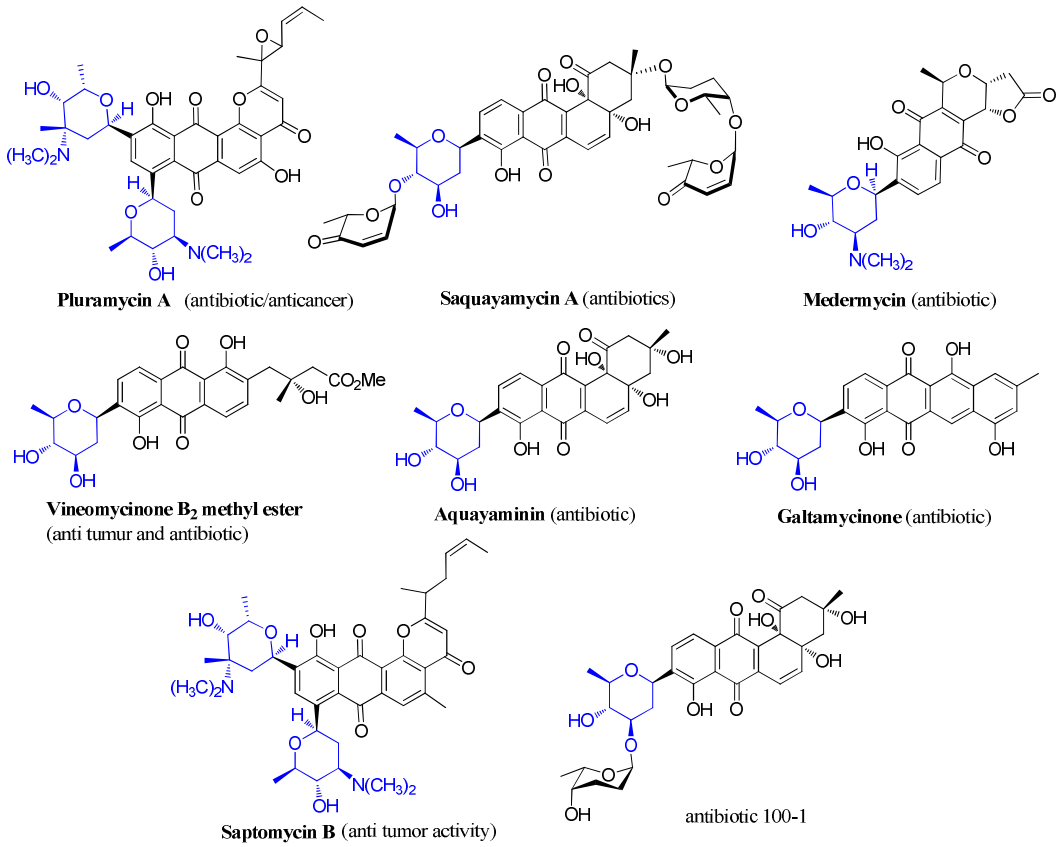


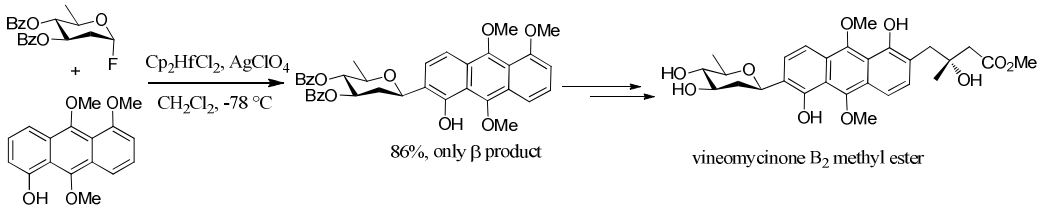
Figure 1.13 Structure of biologically important 2-deoxy-β-aryl-*C*-glycoside

Angucycline is group of polycyclic aromatic natural products bearing 2-deoxy aryl-*C*-glycoside units [36d]. Angucycline family shows various biological activities including anticancer and antibacterial activities. Landomycin is the first discovered compound in angucycline family. Similarly, kidamycinis the secondary metabolites of soil Streptomyces with high antibacterial potentials [49]. Pluramycin A is an antibiotic and

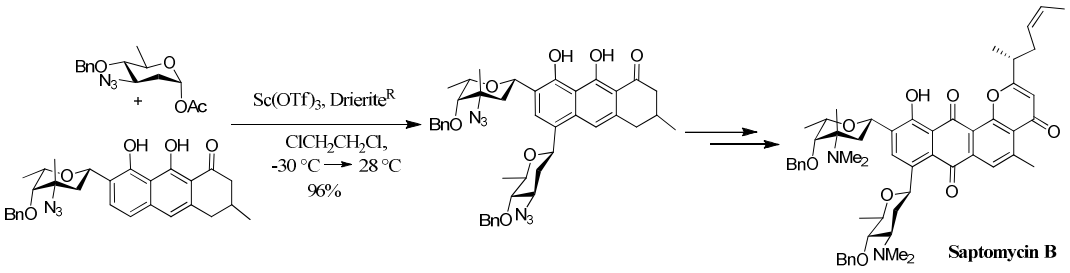
anticancer compound that inhibits nucleic acid biosynthesis [50]. Synthesis of 2-deoxy-β-aryl-*C*-glycosides has been achieved in numerous ways. In particular, synthesis of 2-deoxy-aryl-*C*-glycosides has been achieved from glycals and non-glycal substrates. The most common methods of 2-deoxy aryl-*C*-glycosides preparation are discussed below:

1.9.1 Synthesis of 2-deoxy-aryl-*C*-glycosides from non-glycal Substrates:

Fries-type reaction, i.e. *O*→*C* glycoside rearrangement is one of the initial approaches used in the preparation of 2-deoxy-β-aryl-*C*-glycosides. Early examples of the *O*→*C* glycoside rearrangements involved the use of glycosyl halides, in particular glycosyl fluorides, to achieve these transformations. However, later many catalysts including Cp_2HfCl_2-$AgClO_4$, TMSOTf/$AgClO_4$ and $Sc(OTf)_3$ have been developed for the *O*→*C* glycoside rearrangement reactions that allowed the use of glycosyl acetates as donors. Using this approach, various 2-deoxy aryl-*C*-glycosides have been synthesized. Interestingly, this approach provides β-selectivity in *C*-glycosidic bond formation. For instance, using this approrach total synthesis of vineomycinone B_2 as well as saptomycin B were acheived as shown in **Scheme 1.13** and **Scheme 1.14** [51].

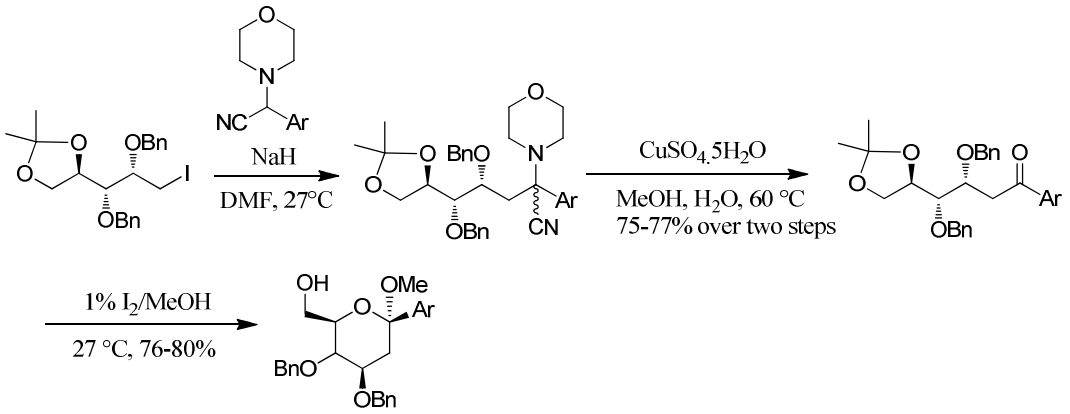


Scheme 1.13 Synthesis of vineomycinone B_2 methyl ester



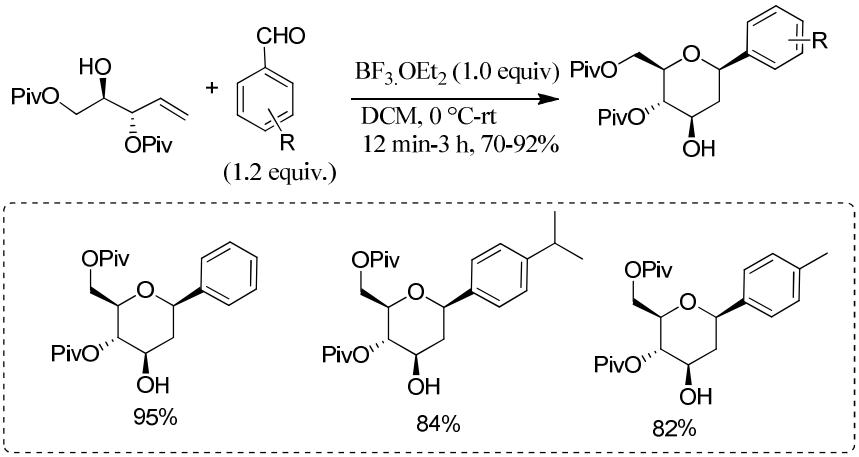
Scheme 1.14 Synthesis of Saptomycin B

The synthesis of 2-deoxy aryl-*C*-glycosides was also demonstrated using umpolung strategy [52]. In this notable method, sugar derived halide was reacted with α-aminonitriles and subsequently converted in to ketone. Cleavage of the isopropylidene group in the molecule provide the hemiketal and that was converted in to methyl glycoside in acidic methanol stereoselectively to afford 2-deoxy aryl-*C*-glycosides (**Scheme 1.15**).



Scheme 1.15 Synthesis of 2-deoxy aryl-*C*-glycosides by umpolung strategy

Further, synthesis of 2-deoxy-β-aryl-*C*-glycosides was demonstrated via Prins cyclization from pivaloyl protected allylic alcohol and different aryl/alkyl aldehydes [53]. The method provides high yields and excellent stereoselectivity (**Scheme 1.16**).



Scheme 1.16 Stereoselective synthesis of 2-deoxy β-aryl-*C*-glycosides by Prins cyclization

1.9.2 Synthesis of 2-deoxy-aryl-*C*-glycosides from glycal substrates:

On the other hand, 2-deoxy aryl-*C*-glycosides can be synthesized from *C*-1 functionalized glycals as well as from nude glycals. These approaches delivered mainly three different types of 2-deoxy-aryl-*C*-glycosides. Namely,

a) 2-Deoxy 1,2-unsaturated aryl-*C*-glycosides,

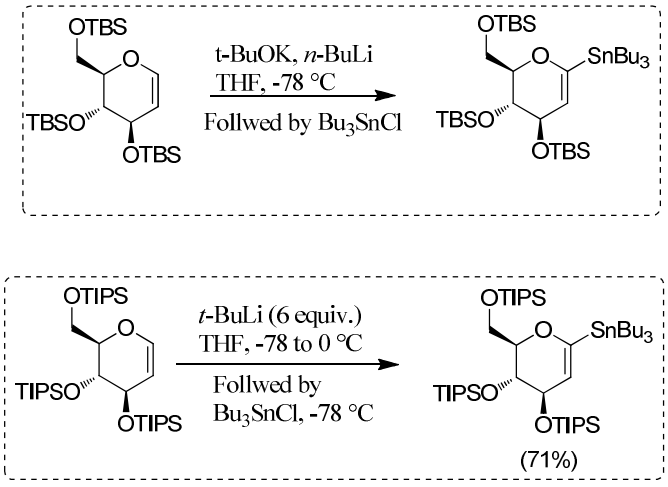
b) 2-Deoxy-2,3-unsaturared aryl-*C*-glycosides.

c) 2,3-Deoxy-2,3-unsaturared aryl-*C*-glycosides,

1.9.2.1. 2-Deoxy 1,2-unsaturated aryl-*C*-glycosides from *C*-1 functionalized glycals

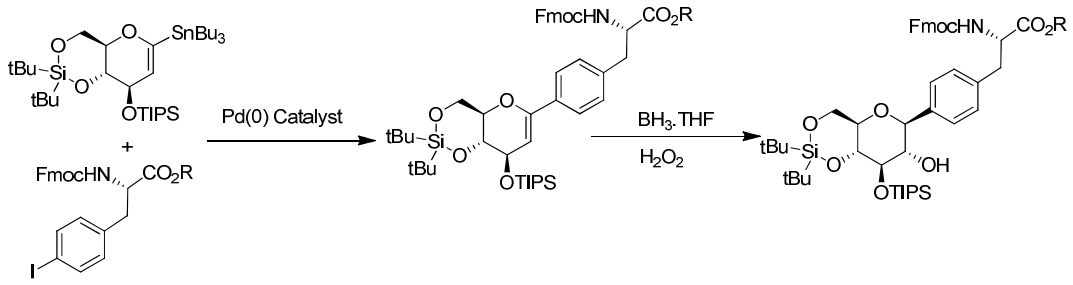
2-Deoxy 1,2-unsaturated aryl-*C*-glycosides are highly useful precursors for the preparation of both 2-deoxy β-aryl-*C*-glycosides and 2-hydroxy β-aryl-*C*-glycosides. The *C*-1-metalated glycals are versatile building blocks frequently used in the preparation of *C*-glycosyl arenes with a 1,2-unsaturation [54]. In this context, C-1-

lithiated glycal is the main precursor to achieve *C*-1-metalated glycals. *C*-1-Lithiated glycals are usually obtained from silyl protected glycals using *t*BuLi and transmetalated to stable stannylglycals (**Schehme 1.17**) [54-55].

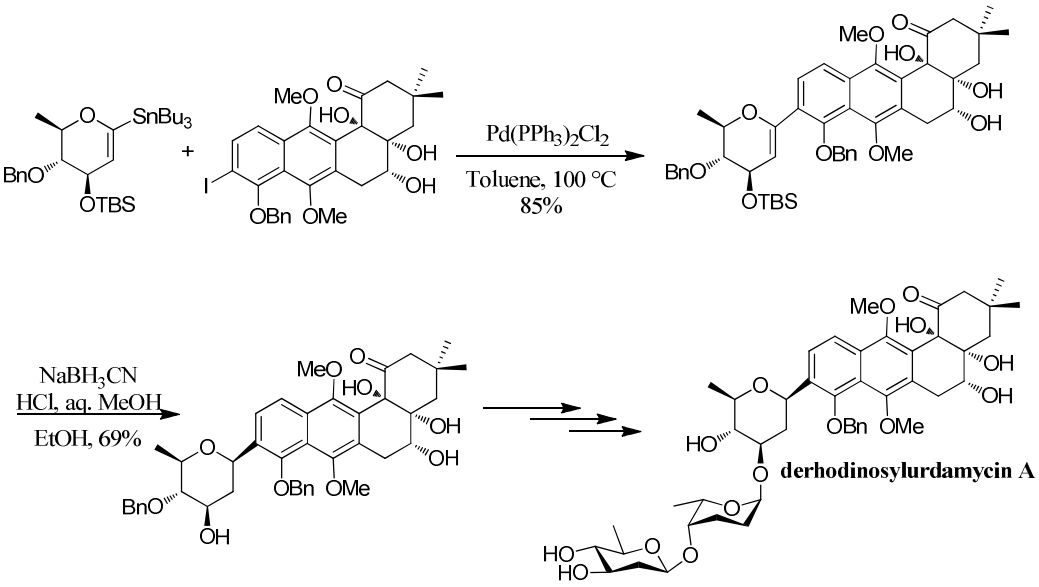


Scheme 1.17 Synthesis of stannyl glycals

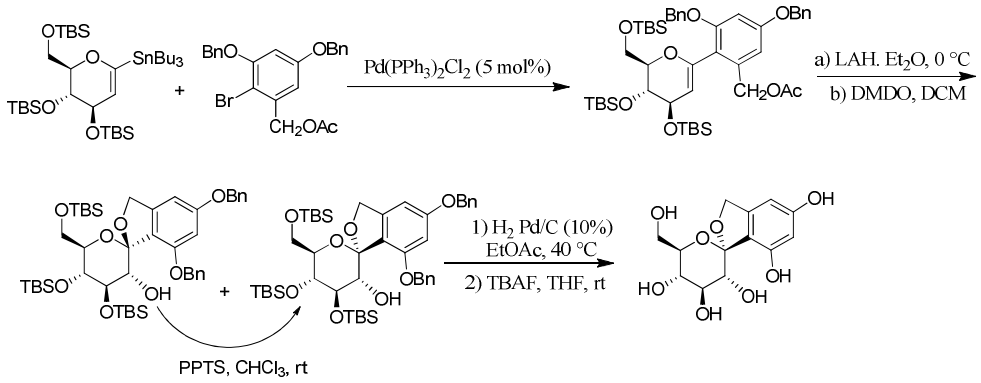
Stannyl glycals are one of the most explored *C*-1-metalated glycals in cross coupling reactions for the preparation of natural products bearing 2-deoxy β-aryl-*C*-glycosides and 2-hydroxy β-aryl-*C*-glycosides as shown in the **Schemes 1.18**, **1.19** and **1.20** [56].



Scheme 1.18 Synthesis of *C*-glycosylated phenylalanine

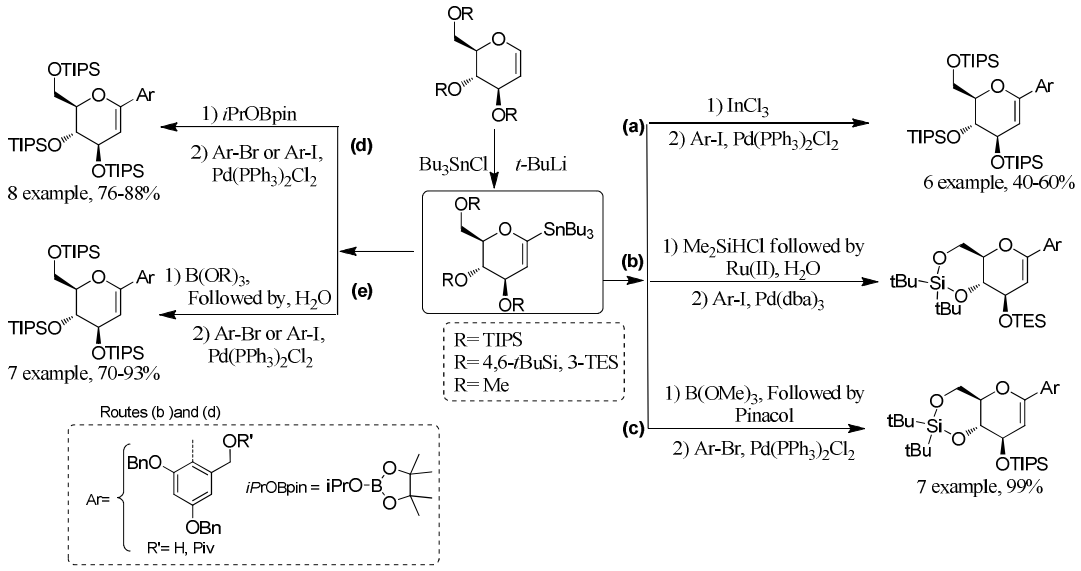


Scheme 1.19 Synthesis of derhodinosylurdamycin A



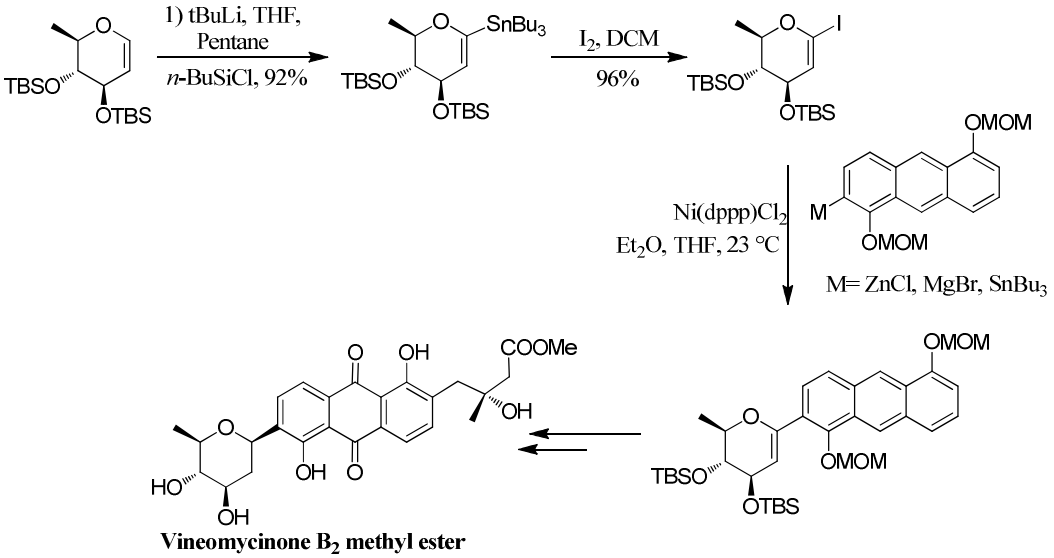
Scheme 1.20 Synthesis of papulacandin core

On the other hand, *C*-1-lithiated glycals were also transmetalated to indium, sillyl, zinc and boron derivatives *in situ* and subjected to cross-coupling reactions with aromatic halides under palladium catalysis to afford the 1,2-unsaturated aryl *C*-glycosides (**Scheme 1.21**) [38].



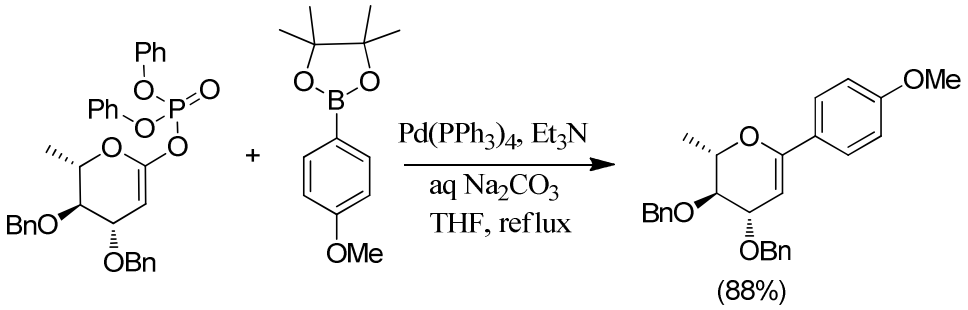
Scheme 1.21 *C*-1-Metelated glycals in coupling reactions

Reverse-polarity approaches, i.e. cross-coupling of glycal iodide or phosphate with aryl metal compounds, has also been reported. Total synthesis of vineomycinone B_2 has been attempted using this approach (**Scheme 1.22**) [57].



Scheme 1.22 Synthesis of vineomycin B_2 methyl ester through stannyl glycal

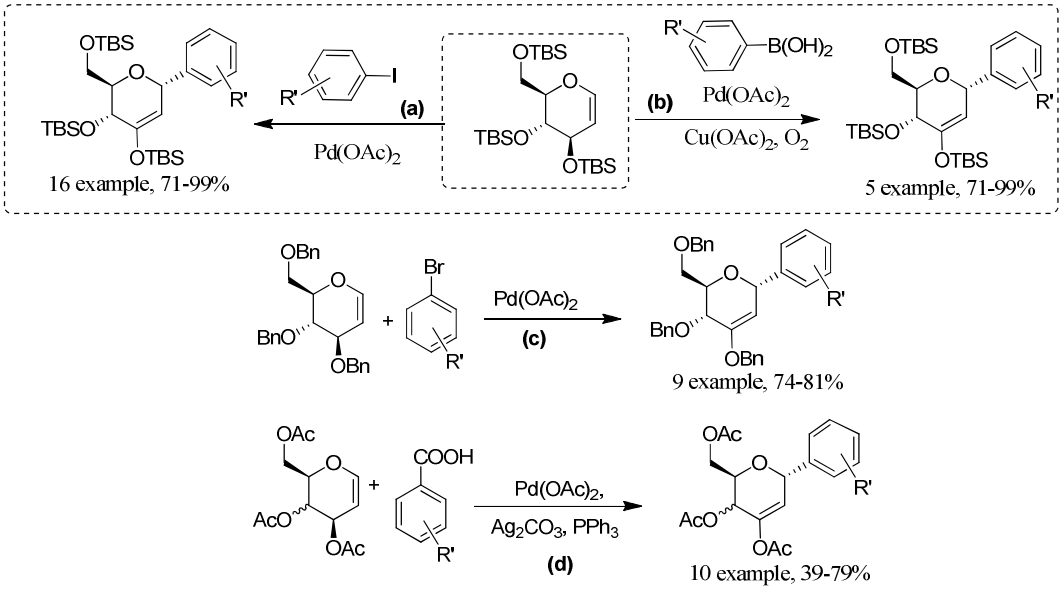
Similar to glycal iodides, glycal phosphates were readily prepared from the corresponding lactones and used in the cross-coupling reaction with arylboronate esters to achieve 2-deoxy 1,2-unsaturated aryl-*C*-glycosides (**Scheme 1.23**) [58].



Scheme 1.23 Coupling of glycosyl phosphate with arylboronate

1.9.2.2. 2-Deoxy-2,3-unsaturared aryl-*C*-glycosides from nude glycals

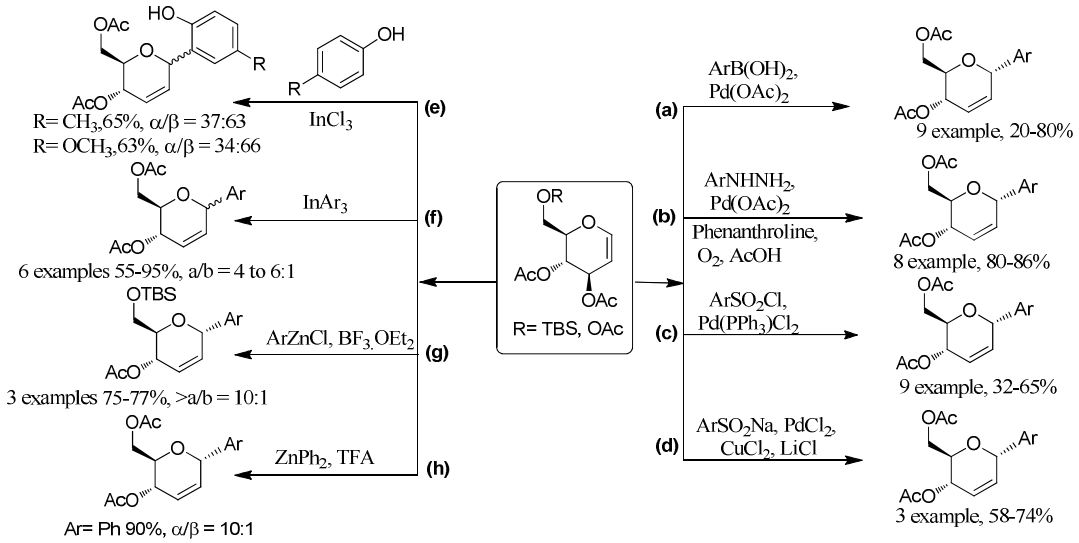
Several methodologies involving palladium catalyzed *C*-glycosylation by nude glycals has been reported (**Scheme 1.24**) [36a, 36b, 38]. These methods provide 2-deoxy-2,3-unsaturared aryl-*C*-glycosides in good yields. For, instance, palladium acetate catalyzed oxidative Heck-type *C*-glycosylations of TBS and benzyl protected glycals with arylboronic acids, aryl bromides and aryl iodides provide 2-deoxy-2,3-unsaturared aryl-*C*-glycosides. In a similar fashion, decarboxylative Pd-catalyzed cross-coupling of wide range of protected glycals with different arylboronic acids were reported recently. *All these methodologies provide α-selective aryl-C-glycosyl compounds.*



Scheme 1.24 Synthesis of 2-deoxy-2,3-unsaturared aryl-*C*-glycosides

1.9.2.3. 2,3-Deoxy-2,3-unsaturared aryl-*C*-glycosides from nude glycals

2,3-Unsaturated aryl *C*-glycosides were usually synthesized from *O*-peracetylated glycals (**Scheme 1.25**) [36a, 36b, 38]. For instance, reaction of glycals with phenols in the presence of $InCl_3$ (Ferrier type *O*→*C* rearrangement), triarylorganoindium compounds, arylzinc-chlorides and diarylzinc compounds lead to the formation of 2,3-deoxy-2,3-unsaturared aryl-*C*-glycosides. Alternatively, palladium catalyzed Heck-type coupling of arylboronic acids, aryl hydrazines, arenesulfonyl chlorides, arylsulfinates with glucal acetate also leads to the formation of 2,3-unsaturared aryl-*C*-glycosides. *Most of these reactions provide the α-anomers of aryl-C-glycosides.*



Scheme 1.25 Synthesis of 2,3-deoxy-2,3-unsaturared aryl-*C*-glycosides

1.10 Summary and Focus of the Thesis

Carbohydrates are important biomolecules and they involved in many biological functions in living organism. Recent understanding of functions of carbohydrates leads to the development of various carbohydrates based therapeutic tools including drugs, vaccines, biomedical devices, bio-materials, etc. In general, carbohydrates exist as oligosaccharides, polysaccharides and glycoconjugates (such as glycolipids and glycoproteins) in biological system. Besides that carbohydrate motifs are found to be attached to various natural products, predominantly through *O*-linkage (called as *O*-glycosides) or *C*-linkage (called as *C*-glycosides). In this context, aryl-*C*-glycosides are ubiquitous structural motifs embedded in many bioactive natural products. In view point of their therapeutic potential as antioxidant, antibiotic, anti-diabetic, anticancer activities, etc., aryl-*C*-glycosides received continuous attention in both chemistry and

biology over many decades. In particular, synthetic organic chemists have developed numerous protocols for the preparation of many naturally occurring aryl-*C*-glycosides and their synthetic derivatives. Indeed, these studies helped directly to develop the anti-diabetic drugs such as canagliflozin, dapagliflozin, empagliflozin, ertugliflozin, etc. This recent findings encouraged researchers to develop modern synthetic routes for achieving aryl-*C*-glycosides with cost-effective manner.

2-Deoxy-β-*C*-aryl glycosides are belonging to a subclass of *C*-glycosides have been found as part of a many bioactive natural products. In this aspect, development of new and efficient synthetic routes for the preparation of 2-deoxy-β-*C*-aryl glycosides is an important topic. Among the different routes of 2-deoxy-aryl-*C*-glycosides preparation, coupling of nude glycals with various aryl donors such as arylboronic acids, arylhydrazines, aryl carboxylic acids, arylzinc reagents, aryl halides, aryl triflates, etc., considered to be not only simple, but also efficient and economic. However, unfortunately this approach provides *α*-selective 2-dexoxy aryl-*C*-glycosides while naturally occurring 2-dexoxy aryl-*C*-glycosides exist in β-configuration. In addition, most of these coupling methods require i) inert and anhydrous reaction conditions, ii) high reaction temperature, iii) additives or ligands, iv) longer reaction time, etc. Therefore, the development of simple and practical methods for the formation of highly regio- and stereoselective aryl-glycosidic bond still remains as an important challenge in synthetic carbohydrate chemistry.

Considering these drawbacks of exiting methods, the thesis was focused on the development of new synthetic routes for achieving both α and β anomers of 2-deoxy-aryl-C-glycosides in efficient manner under mild conditions.

In this context, the major objectives of the present thesis are,

- To develop a palladium catalyzed stereo-selective methods for the synthesis of 2-deoxy-*α*-aryl-*C*-glycosides and 2-deoxy-*β*-aryl-*C*-glycosides using arenediazonium salts under mild reaction condition.
- To explore the utility of enones derived from glycals in the palladium catalyzed synthesis of 2-deoxy-*α*-aryl-*C*-glycosides and 2-deoxy-*β*-aryl-*C*-glycosides with arylboronic acids under mild reaction condition.

The aforementioned projects have been well-planned and executed systematically in the last five years at IIT (BHU). The outcomes of the project have been divided in to **six chapters** including introduction and summary.

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