Minireview

Chemistry of xylopyranosides

Karin Thorsheim a, Anna Siegbahn a, Richard E. Johnsson a, Henrik Stålbrand b, Sophie Manner a, Göran Widmalm c, Ulf Ellervik a,*

a Centre for Analysis and Synthesis, Centre for Chemistry and Chemical Engineering, Lund University, P.O. Box 124, SE-221 00 Lund, Sweden
b Centre for Molecular Protein Science, Centre for Chemistry and Chemical Engineering, Lund University, P.O. Box 124, SE-221 00 Lund, Sweden
c Department of Organic Chemistry, Arrhenius Laboratory, Stockholm University, SE-106 91 Stockholm, Sweden

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ABSTRACT

Xylose is one of the few monosaccharidic building blocks that are used by mammalian cells. In comparison with other monosaccharides, xylose is rather unusual and, so far, only found in two different mammalian structures, i.e. in the Notch receptor and as the linker between protein and glycosaminoglycan (GAG) chains in proteoglycans. Interestingly, simple soluble xylopyranosides can not only initiate the biosynthesis of soluble GAG chains but also function as inhibitors of important enzymes in the biosynthesis of proteoglycans. Furthermore, xylose is a major constituent of hemicellulosic xylans and thus one of the most abundant carbohydrates on Earth. Altogether, this has spurred a strong interest in xylose chemistry. The scope of this review is to describe synthesis of xylopyranosyl donors, as well as protective group chemistry, modifications, and conformational analysis of xylose.

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1. Introduction

Being a major constituent of xylans, a group of hemicelluloses, xylose is one of the most abundant carbohydrates on Earth. The name xylose (Greek ξυλον, xylon meaning wood) originates from the isolation of the sugar from wood by Koch in 1886, and xylose is also known as wood sugar. Xylose is a pentose and can thus form both pentofuranosides and pentopyranosides, with the latter being the most common configurations (Fig. 1). Hydrogenation, or microbiological fermentation, of xylose gives the sugar alcohol xylitol (birch sugar), which is also found in many natural sources, such as birch sap. Xylitol is considerably sweeter than xylose, and is used as a sweetener.

Apart from plant origins, xylose is also found in important mammalian cell surface structures, such as proteoglycans. Due to the biological importance of xylose, it has attracted a great deal of research interest. The development of methods for synthesis of xylopyranosyl donors, acceptors, and analogs of d-xylopyranosides are summarized in this review.

1.1. Xylosides in plants

1.1.1. Xylan and xyloglucan

Plant xylans, in the form of hemicellulose, are among the most abundant renewable bioresources available. Hemicelluloses are plant cell-wall heteroglycans built up by a β-linked glycan backbone, of e.g. xylose, mannose, galactose, and/or glucose. β-Mannans are the dominant hemicelluloses in softwoods and β-xylans are dominant in hardwoods and grasses. In general, the xylan backbone is substituted to different degrees by sugar residues and/or other components (Fig. 2). Hardwoods contain up to 35% of O-acetyl-4-O-methyl-glucuronoxylan. Acetylation occurs at C2 and C3 and it is worth mentioning that acetyl migration may occur in vitro. In grasses and softwoods the xylan backbone is substituted with L-arabinofuranoside units in addition to methylglucuronic acid. The xylan content in grasses is similar or higher than that in hardwood, while softwood contains less (up to 15%). The primary cell-walls of many plants contain xyloglucan, which has a β-glucan backbone that is substituted by xylose units, and the xyloglucan structure varies with species and tissue. Xyloses in xyloglucan may be further substituted, e.g. by galactose or arabinofuranoside residues. A further common modification is a fucose unit carried by some galactoses.
Xylans are synthesized in the Golgi-apparatus, and some of the glycosyl transferases (e.g., UDP-xylose as substrate) and other proteins that are involved have been identified. Xylans may furthermore be modified by plant encoded glycoside hydrolases (e.g., endoxylanase or exo-β-xylosidase) which may act outside the Golgi. These processes are, however, not well understood in plants. Recently, an Arabidopsis protein capable of catalyzing xylan acetylation was identified.

1.1.2. Biocconversion of plant xylans and xylosides

Plant xylans and other hemicelluloses are major renewable resources for chemical or microbial conversion to value added products (biofuels, materials, biochemicals) within biorefinery strategies. Following biomass pretreatment and/or extraction, e.g., from hardwoods or agricultural crops such as cereals, xylan can be hydrolyzed by microbial enzymes (glycoside hydrolases) into oligo- or mono-saccharides. Xylooligosaccharides produced from e.g., wheat, other cereals, or hardwood xylan, have potential applications as prebiotics since they can stimulate human gut Bifidobacteria. Xylose is a valuable feedstock for production of biofuels, biochemicals, and also xyitol for which microbial production is being investigated as an alternative to the established chemical production route. Baker’s yeast, Saccharomyces cerevisiae, is unable to ferment xylose and several strategies for fermentation of xylose to ethanol have been developed, such as the use of other microbes and genetic engineering of yeasts.

The main xylan backbone hydrolyzing glycoside hydrolases are endo-1,4-β-xylanase that hydrolyzes xylosidic bonds internally in the backbone and exo-β-xylanase that hydrolyzes terminal non-reducing xylose units. Other glycoside hydrolases and esterases hydrolyze the various substitutions. Glycoside hydrolases are classified in families and clans based on protein sequence similarities (see further the CAZY database). The classification of carbohydrate esterases and auxiliary activities (e.g., polysaccharide oxidases) and carbohydrate-binding protein modules are also displayed in the CAZY database. The main families containing endoxylanases are GH10 and GH11. Enzymes from both families catalyze hydrolysis by retaining the anomeric configuration. Two main catalytic residues are involved, an acid/base and a nucleophile.

Retaining glycoside hydrolases may catalyze kinetically controlled transglycosylation, which has been shown for several xylanases including the synthesis of tertiary alkyl β-xylosides. In transglycosylation reactions, the enzyme-glycosyl intermediate of the retaining reaction is disrupted by an acceptor molecule, rather than a water molecule, as is the case in hydrolysis. Thus, this results in the formation of a new glycosidic bond. Potential hydrolysis of the reaction product may be overcome by the use of the glycansynthase approach for synthesis of glycosides. Glycosynthases are retaining glycoside hydrolases where the nucleophile has been substituted to a non-functional amino acid, thus rendering them hydrolytically incapable. By use of a glycosyl fluoride as a donor, the glycosyl unit can be transferred to an acceptor molecule resulting in the synthesis of a new glycosidic bond as shown e.g. for a Cellulomonas fiinixylanase. Xylanolytic enzymes also have other applications in the food, feed, and pulp industries mainly as catalysts for xylan hydrolysis.

1.1.3. Other plant xylosides

Nectar, i.e., the incentive for pollinators, is usually composed of the carbohydrates, glucose, fructose, and sucrose, in various amounts. Interestingly, xylose has been found in high concentrations, up to 39%, in nectar from two genera of Proteaceae, found in southern Africa and Australia. Some of these plants are pollinated by rock mice (Aethomys namaquensis). This is surprising since xylose is considerably less sweet than sucrose, and cannot be metabolized by non-ruminant animals, such as rodents. Instead these animals rely on bacteria for conversion of xylose. Insects and birds show strong adversity toward xylose.

In a screening of plants from the Amazon rain forest, an O3-substituted xyloside (1, Fig. 3) was found in Maieta guianensis.

1.2. Xylosides in mammalian cells

Xylose is an unusual carbohydrate in mammalian cells and so far only found as the linker between the protein and the glycosaminoglycan chains of some proteoglycans, and in the Notch receptor. UDP-xylose, i.e., the activated building block used in mammalian cells, is synthesized from UDP-glucose. Xylose from dietary sources is not used in the biosynthesis.

1.2.1. Biosynthesis of UDP-xylose

Mammalian cells use a rather small number of monosaccharidic building blocks, activated as nucleoside phosphates (NDP, often UDP) and only a few NDP-sugars are used in eukaryotic cells. Xylose is formed from UDP-glucose in two steps (Scheme 1). UDP-glucose is first oxidized by the enzyme UDP-glucose-6-dehydrogenase (UDGH) to form UDP-glucuronic acid (UDP-GlcA) and then decarboxylated by UDP-xylose synthase 1 (UXS1) to form UDP-xylose.

In 2012, Nieditzky and co-workers expressed, crystallized, and characterized a truncated version of human UXS1 (hUXS1) in Escherichia coli. A detailed catalytic mechanism was proposed, using molecular dynamics simulations of the ternary Michaelis complex, mutagenesis experiments, and deuterium incorporation (Scheme 2). These experiments suggest that UDP-GlcA adopts the B0.3 boat conformation. The 1C4→B0.3 transition is needed to align the catalytic groups for the NAD-dependent oxidation, and is believed to be the rate determining step. The transportation of UDP-xylose across Golgi membranes is mediated by the UDP-xylose transporter SLC35B4.

1.2.2. Glycosaminoglycans and proteoglycans

Proteoglycans (PGs) are large macromolecules that consist of a core protein decorated by large, negatively charged, carbohydrate chains called glycosaminoglycans (GAGs). These GAGs are linear polysaccharides built of repeating disaccharide units consisting of one amino sugar and one uronic acid. There are four different classes of GAGs defined by the kind of disaccharide unit they are composed of: hyaluronate (HA), chondroitin sulfate/dermatan sulfate (CS/DS), heparin/heparan sulfate (HS), and keratan sulfate (KS). The PGs are found on the cell surface as well as in the extracellular matrix where they have important roles in the regulation of growth factor signaling, inflammation, angiogenesis, and cell–cell interaction. PG and GAG thus play important roles in cancer, and mutations in genes encoding for enzymes involved in thebiosynthesis of

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1. www.cazy.org
PG/GAG may result in genetic disorders, such as the Ehler–Danlos syndrome. The biosynthesis of CS/DS and HS is initiated by xylosylation of a serine residue in the PG protein. The xylosylation of the core protein is performed by a xylosyltransferase, of which two isoforms have been found (XylT-I and XylT-II), using UDP-Xyl as substrate. After xylosylation, two galactose residues are added stepwise to the xylosylated protein by two different galactosyltransferases, GalT-I (β4GalT7) and GalT-II (β3GalT6). Finally, GlcA is added by glucuronyltransferase 1 (GlcAT-I). The tetrasaccharide linker (GlcA(β1-3)Gal(β1-3)Gal(β1-4)Xylβ, Fig. 4) is a branching point for the synthesis of CS/DS and HS, respectively, and the growing chain is later on modified by epimerization and sulfation reactions, resulting in extensive structural diversity.

The GAG chain formation is regulated by modifications in various positions of the linker region. For example, a transient phosphorylation at O2 of the xylose residue has been seen in CS/DS and HS biosynthesis. The enzyme FAM20B has been identified as a kinase that phosphorylate xylose in the linker, while the dephosphorylation is performed by 2-phosphoxylose phosphatase (XYLP, Fig. 4). Today, all known enzymes involved in the biosynthesis of the tetrasccharide linker have been cloned.

Interestingly, exogenously added xylopyranosides, i.e. without core protein, can serve as initiators of the synthesis of GAG chains. In 1969, Helting and Rodén observed that simple xylosides were galactosylated in a cell free system. They showed that D-xylose, methyl β-D-xylopyranoside, and L-serine β-D-xylopyranoside served as acceptors for galactose transfer from UDP-Gal (Fig. 5). A few years later, Okayama et al. made a similar study in which p-nitrophenyl β-D-xylopyranoside was identified as a more efficient substrate. Okayama and co-workers also showed that β-D-xylosides can act as artificial initiators of GAG (CS) synthesis in embryonic chicken cartilage, and that the priming of CS synthesis was much determined by the nature of the aglycon.

A therapeutic strategy is to target key enzymes in the GAG biosynthesis. Some β-D-xylosides serve as substrates for GalT-I/β4GalT7 and thereby initiate GAG chain formation, and at the same time act as inhibitors of the enzyme GalT-I/β4GalT7. This dual function of the xylosides could be exploited for the development of new therapeutic strategies.
time prevent GAG elongation on core proteins forming PGs. Mani and co-workers have shown that treatment with 2-(6-hydroxynaphthyl) β-β-xylopyranoside 5 (Fig. 5) selectively inhibits the growth of tumor cells in vitro as well as in vivo, reducing the average tumor load in severe combined immunodeficient (SCID) mice by up to 97%. Furthermore, xylosides where the 4-OH has been replaced with e.g. a fluorine atom have been synthesized, and are reported to efficiently inhibit PG/GAG formation. Over the years, several hundred xylose derivatives have been synthesized and tested to explore cellular uptake, priming of GAG chains, and inhibition of biosynthetically important enzymes. Xylosides have been synthesized with variation in: the aglycon size and hydrophilicity, the distance between the carbohydrate and the aglycon, and the anomeric configuration. Furthermore, C-xylosides and N-xylosides, phosphorylated xylosides, and peracylated xylosides have been synthesized. Moreover, analogs modified in the xylose residue have been investigated, such as epimers, ethers, ketones, halogens, amines, and deoxy compounds. Kuberen and co-workers have synthesized a large library of xylosides using click-chemistry, containing a triazole ring linked to the xylose residue. Naphthyl β-L-xylopyranosides does not prime GAG chains. In order to study cellular effects, several Chinese hamster ovary (CHO) cell lines, with defect GAG biosynthesis, have been developed: e.g. pgsA-745 cells lack the enzyme XylT2, pgsB-761 cells are defective in β4GalT7, and have been reported to efficiently inhibit PG/GAG formation.

1.4. Concluding remarks

Despite the fact that xylose is a rather unusual carbohydrate in mammalian cells, it has several important functions, especially being the linker between protein and GAG chains in proteoglycans. Simple soluble xylosides can not only work as inhibitors of important enzymes in the biosynthesis of proteoglycans, but also initiate the biosynthesis of soluble GAG chains. This has spurred a strong interest in xylose chemistry, as indicated in the following sections of this review.

2. Xylosyl donors

Numerous methods for xylosylation have been developed over the years, to achieve the required chemo-, regio-, and stereoselectivity. These are multistep procedures that often involve manipulating protective groups and activation of the anomic carbon to form glycosyl donors that are suitable for glycosylation reactions. The formation of a xylosidic linkage can occur either through an Sn2 type mechanism, usually under basic conditions with xylosyl halides, or through an Sn1 type mechanism under acidic conditions. The stereochemical outcome of Lewis acid-promoted xylosylations is directed by several factors, such as the anomic effect, which generally directs the aglycon to the thermodynamically preferred axial orientation. However, participating groups, e.g. esters, at C2 can interact with the intermediate oxocarbonium ion to form a cyclic acyloxonium ion. The acyloxonium ion is subsequently opened by the acceptor in an Sn2 manner which results in a 1,2-trans xylosidic bond, hence β-β-xylosides are fairly easy to synthesize by standard methods, whereas α-β-xylosides can be formed by anomerization of the kinetic β-products. Below, syntheses of the most common xyosyl donors are described with examples of how they are used in glycosylation reactions.

2.1. Unprotected α-xylose as donor

Treatment of unprotected and unactivated xylose with an alcohol in the presence of acid in the Fischer glycosylation forms furanosides and pyranosides in α,β-mixtures depending on the nature of the generated glycosides as well as the reaction conditions. This method is still used for simple alcohols, and it can be used for temporary protection of the anomic hydroxyl group. As an example, benzyl α-β-xylopyranoside can be produced from α-xylose and HCl-saturated benzyl alcohol in 31% (Table 1, Entry 1). Modified Fischer glycosylation procedures have been used in the synthesis of xylosides, e.g. methyl and allyl α-xylopyranosides (Entries 2, 3, and 9 for methyl and 4, 5, and 10 for allyl).

In 2007, Damez et al. investigated how the α,β-ratio was affected by the acid source. α-Xylopyranosides were formed using Amberlite IR 120 and acetyl chloride, whereas β-xylopyranosides were the major products when pTSA was employed (Entries 6–8).
Microwave-assisted glycosylation reactions catalyzed by Montmorillonite K10, an inexpensive, stable, and reusable catalyst, have been reported. Primary alcohols were used generating d-xylopyranosides in good yields with clear α-selectivity (Entry 9).

The advantages with this method are short reaction times and easy removal of the catalyst by filtration. Sulfonated biomass carbonaceous material, consisting of flexible polycyclic carbon sheets that bear phenolic hydroxyl, carboxylic acid, and sulfonic acid groups, is an inexpensive, stable, and environmentally benign catalyst that has been used in glycosylation reactions.

Treating d-xylose with allyl alcohol in the presence of this catalyst generated allyl d-xylopyranoside in 90% as an α,β-mixture of 7:3 (Entry 10).

Methods to synthesize O-aryl xylosides have been developed and the first example of stereoselective O-aryl glycosylation using unprotected xylose was reported in 1994, where d-xylose was reacted with N,N'-thionyldiimidazole (SO(Im)2) and phenoxide ions in a one-pot procedure (Entry 11). In this protocol, the phenoxide ion acts as a nucleophile that attacks the intermediate cyclic sulfite, stereoselectively generating β-d-xylopyranosides in moderate yields. 2,4-Dinitrophenyl β-d-xylopyranoside has been synthesized in 20% yield with high stereoselectivity by treating d-xylose with 1-fluoro-2,4-dinitrobenzene in a saturated NaHCO3 solution of H2O–EtOH (Entry 12).

In 2004, Krausz and co-workers reported the use of Lewis acids in glycosylation reactions with unprotected carbohydrates, including d-xylose, and nucleosides where FeCl3 in acetonitrile proved to be the most efficient catalyst, generating the product in an 1.8:1 α,β-mixture (Entry 13). Sc(OTf)3 can also be used as a catalyst where the yield and α-selectivity were improved when the reaction was performed in the ionic liquid 1-butyl-3-methylimidazolium trifluoromethansulfonate (Entry 14).

The fact that the reaction goes through an oxocarbenium ion that could be stabilized by the ionic liquid could explain the observed increase in yields, which were more pronounced for other unprotected monosaccharides. The use of Brønsted acid ionic liquid (BAIL) as catalyst in glycosylation reactions without any Lewis acid catalyst has been reported quite recently, where aminotetrazoles and alkyltetrazoles were evaluated.

Glycosylation of d-xylose with octanol gave the d-xylopyranoside in good yield with α-selectivity (Entry 15). Mahrwald and co-workers developed a new method for direct glycosylation of unprotected carbohydrates under mild conditions using Ti(OtBu)4 and d-mandelic acid in the presence of LiBr. When acetonitrile was added, iso-propyl d-xylopyranoside was formed almost exclusively over the furanoside in 66% yield, in a 29:63 α,β-mixture (Entry 16). Further development of this methodology using catalytic amounts of PPh3 and CBr4 as well as LiClO4 as an additive.

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**Table 1**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reagents</th>
<th>R</th>
<th>Solvent</th>
<th>Yield</th>
<th>Ratio (α:β)</th>
<th>Ref</th>
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<td>1</td>
<td>HCl</td>
<td>Bn</td>
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<td>31% α&lt;sup&gt;a&lt;/sup&gt;</td>
<td>–</td>
<td>104</td>
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<td>2</td>
<td>Amberlite IRA-120</td>
<td>Me</td>
<td></td>
<td>49%&lt;sup&gt;b&lt;/sup&gt;</td>
<td>1:2</td>
<td>105</td>
</tr>
<tr>
<td>3</td>
<td>Dowex-50 X-8H&lt;sup&gt;+&lt;/sup&gt;</td>
<td>Me</td>
<td></td>
<td>76%</td>
<td>1:0.81</td>
<td>106</td>
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<tr>
<td>4</td>
<td>Dowex-50W H&lt;sup&gt;+&lt;/sup&gt;</td>
<td>Allyl</td>
<td></td>
<td>46%&lt;sup&gt;c&lt;/sup&gt;</td>
<td>1:0.5</td>
<td>107</td>
</tr>
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<td>5</td>
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<td>Allyl</td>
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<td>11</td>
<td>LiH, SO(Im)&lt;sub&gt;2&lt;/sub&gt;</td>
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<td>DMF</td>
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<td></td>
<td>H&lt;sub&gt;2&lt;/sub&gt;O/EtOH</td>
<td>20%</td>
<td>0:1</td>
<td>113</td>
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<tr>
<td>13</td>
<td>FeCl&lt;sub&gt;3&lt;/sub&gt;</td>
<td></td>
<td>MeCN</td>
<td>20%&lt;sup&gt;d&lt;/sup&gt;</td>
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<td>14</td>
<td>Sc(OTf)&lt;sub&gt;3&lt;/sub&gt;</td>
<td>n-C&lt;sub&gt;8&lt;/sub&gt;H&lt;sub&gt;17&lt;/sub&gt;</td>
<td>[BMIM][OTf]</td>
<td>78%</td>
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<td>15</td>
<td>D-Mandelic acid, Ti(OtBu)&lt;sub&gt;4&lt;/sub&gt;, LiBr</td>
<td>iPr</td>
<td>H&lt;sub&gt;2&lt;/sub&gt;O, BAIL</td>
<td>72%&lt;sup&gt;e&lt;/sup&gt;</td>
<td>1:0.52</td>
<td>116</td>
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<td>16</td>
<td>PPh&lt;sub&gt;3&lt;/sub&gt;, CBr&lt;sub&gt;4&lt;/sub&gt;, LiClO&lt;sub&gt;4&lt;/sub&gt;</td>
<td>iPr</td>
<td>MeCN</td>
<td>66%&lt;sup&gt;e&lt;/sup&gt;</td>
<td>1:2.2</td>
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<td>17</td>
<td>n-C&lt;sub&gt;8&lt;/sub&gt;H&lt;sub&gt;17&lt;/sub&gt;</td>
<td>H&lt;sub&gt;2&lt;/sub&gt;O, BAIL</td>
<td>72%&lt;sup&gt;e&lt;/sup&gt;</td>
<td>1:0.52</td>
<td>116</td>
<td></td>
</tr>
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</table>

<sup>a</sup> Only anomer isolated after recrystallization.
<sup>b</sup> Pure β-anomer obtained in 26% yield after recrystallization.
<sup>c</sup> Yield after acetylation/deacetylation.
<sup>d</sup> Contains 5% furanosides.
<sup>e</sup> Contains 6% furanosides.
All reactions retained the forming the desired xyloside with free Selective removal of an anomeric allyl group, Similar methods have been used on oligoxylosides such as peracetylated xylooligosaccharides, using benzylamine or Hüning’s base/NaOMe, forming the desired xylose with free amine hydroxyl group in good to excellent yields. The anomeric acetates can also be reacted with different tin-reagents to give 1-O-tin derivatives, which subsequently are hydrolyzed (Entries 5–7). Bases, such as NaOMe, usually give global deacetylation of peracetylated sugars. However, 2 equivalents of NaOMe in THF resulted in regioselective 1-O-deacetylation in 70% yield (Entry 8). Similarly, (NH₄)₂CO₃ in DMF gave anomeric deprotection in 63% (Entry 9), whereas treatment with alumina gave 55% conversion to the 1-O product (Entry 10). A number of acidic methods have also been used, where Lewis acid lanthanide triflates gave anomeric deacetylation in very good yields (Entries 11–14). Regioselective deacetylation using HClO₄—SiO₂ and copper(II) acetate dihydrate removed the anomeric acetate in excellent and moderate yield, respectively (Entries 15 and 16).

Apart from anomeric acetates, several other protective groups can be removed regioselectively. Anomeric benzyl group has been removed under acidic conditions as well as by hydrogenation (Table 3, Entries 1–3). Per-O-methylated d-xylene can be treated with TFA (aq.) or 2M HCl-dioxane to selectively remove the anomeric O-methyl in moderate yields (Entries 4 and 5). Hydrolisis of the anomeric methyl group in the presence of benzyl protective groups using 1M H₂SO₄ in dioxane–H₂O generated the corresponding hemiacetal in 71%, starting from d-xylene (Entry 6). Furthermore, permethacrylated xylose was selectively deprotected at the anomeric position in 36% yield by treatment with benzylamine in THF (Entry 7). Selective removal of an anomeric allyl group, in the presence of p-methoxybenzyl (PMB) protective groups, using catalytic amount of PdCl₂ in MeOH generated the desired product in excellent yield (Entry 8). An anomeric 2-methoxyethyl group was selectively removed in the presence of allyl, benzyl, and acetate groups in 51–80% yield by brief treatment with TiCl₄ in CH₂Cl₂ to form the intermediate anomic chloride that was hydrolyzed during silica chromatography.

### 2.3. Peracetylated xylose as donor

Tetra-O-acetyl-d-xylopyranose can be, as described later on, used to form other xylosyl donors: however, peracetylated xylose can also be used directly in glycosylation reactions. Acetylation of xylose is most commonly performed with a large excess of Ac₂O in the presence of a catalyst. Using NaOAc or KOAc as the catalyst at high temperatures generated the β-anomer in high stereoselectivity (Table 4, Entries 1 and 2), whereas reaction with Py or DMAP/Py formed the α-anomer in excellent yield (Entries 3 and

### Table 2

Selective anomeric deacetylation of peracetylated D-xylose

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reagents</th>
<th>Solvent</th>
<th>Yield</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Etylenediamine, AcOH</td>
<td>THF</td>
<td>&gt;95%&lt;sup&gt;a&lt;/sup&gt;</td>
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</tr>
<tr>
<td>2</td>
<td>Hydrazine acetate</td>
<td>DMF</td>
<td>81%</td>
<td>122</td>
</tr>
<tr>
<td>3</td>
<td>Imidazole</td>
<td>MeOH</td>
<td>72%</td>
<td>123</td>
</tr>
<tr>
<td>4</td>
<td>Polymer-bound BnNH₂</td>
<td>THF</td>
<td>96%</td>
<td>124</td>
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<tr>
<td>5</td>
<td>(Bu₅Sn)₂O</td>
<td>Toluene</td>
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<td>6</td>
<td>Bu₂SnOMe</td>
<td>DCE</td>
<td>76%</td>
<td>126</td>
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<tr>
<td>7</td>
<td>Bu₂SnO</td>
<td>MeOH</td>
<td>58%</td>
<td>127</td>
</tr>
<tr>
<td>8</td>
<td>NaOMe</td>
<td>THF</td>
<td>70%&lt;sup&gt;b&lt;/sup&gt;</td>
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</tr>
<tr>
<td>9</td>
<td>(NH₄)₂CO₃</td>
<td>DMF</td>
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<td>129</td>
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<tr>
<td>10</td>
<td>Al₂O₃</td>
<td>MeOH</td>
<td>55%&lt;sup&gt;c&lt;/sup&gt;</td>
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</tr>
<tr>
<td>11</td>
<td>Yb(OTf)&lt;sub&gt;3&lt;/sub&gt;</td>
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<tr>
<td>12</td>
<td>Eu(OTf)&lt;sub&gt;3&lt;/sub&gt;</td>
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<tr>
<td>13</td>
<td>Sm(OTf)&lt;sub&gt;3&lt;/sub&gt;</td>
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<td>14</td>
<td>Nb(OTf)&lt;sub&gt;3&lt;/sub&gt;</td>
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<td>15</td>
<td>HClO₄—SiO₂</td>
<td>MeCN</td>
<td>90%</td>
<td>132</td>
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<tr>
<td>16</td>
<td>Cu(OAc)&lt;sub&gt;2&lt;/sub&gt;·2H₂O</td>
<td>MeOH/H₂O</td>
<td>58%</td>
<td>133</td>
</tr>
</tbody>
</table>

<sup>a</sup> Estimated by TLC analysis.  
<sup>b</sup> 14% of the starting material was recovered.  
<sup>c</sup> Conversion.

Table 3

Regioselective removal of anomeric protective group

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>R₁</th>
<th>R₂</th>
<th>R₃</th>
<th>Reagents</th>
<th>Solvent</th>
<th>Yield</th>
<th>Ref</th>
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<tr>
<td>1</td>
<td>α-Bn</td>
<td>Bn</td>
<td>Bn</td>
<td>Bn</td>
<td>HCl</td>
<td>MeCN</td>
<td>85%</td>
<td>136</td>
</tr>
<tr>
<td>2</td>
<td>α-Bn</td>
<td>Allyl</td>
<td>Allyl</td>
<td>Bn</td>
<td>HCl</td>
<td>AcOH</td>
<td>91%</td>
<td>137</td>
</tr>
<tr>
<td>3</td>
<td>α-Bn</td>
<td>MBz</td>
<td>TES</td>
<td>TES</td>
<td>Pd/C, H₂, Et₃N</td>
<td>TMEDA</td>
<td>76%</td>
<td>104</td>
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<tr>
<td>4</td>
<td>Me</td>
<td>Me</td>
<td>Me</td>
<td>Me</td>
<td>TFA</td>
<td>H₂O</td>
<td>65%</td>
<td>138</td>
</tr>
<tr>
<td>5</td>
<td>Me</td>
<td>Me</td>
<td>Me</td>
<td>Me</td>
<td>2M HCl</td>
<td>Dioxane</td>
<td>60%&lt;sup&gt;a&lt;/sup&gt;</td>
<td>139</td>
</tr>
<tr>
<td>6</td>
<td>Me</td>
<td>Bn</td>
<td>Bn</td>
<td>Bn</td>
<td>1M H₂SO₄</td>
<td>Dioxane</td>
<td>71%&lt;sup&gt;a&lt;/sup&gt;</td>
<td>140</td>
</tr>
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<td>α-Acr</td>
<td>Acr</td>
<td>Acr</td>
<td>Acr</td>
<td>BnNH₂</td>
<td>THF</td>
<td>36%</td>
<td>141</td>
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<tr>
<td>8</td>
<td>α-All</td>
<td>PMB</td>
<td>PMB</td>
<td>PMB</td>
<td>PdCl₂</td>
<td>MeOH</td>
<td>90%</td>
<td>108</td>
</tr>
</tbody>
</table>

<sup>a</sup> Yield over several steps from d-xyllose.

in acetonitrile generated iso-propyl d-xylopyranoside in 99% yield with low stereoselectivity (Entry 17). Transglycosylation reactions, catalyzed by enzymes, have been investigated as well as reverse hydrolysis. Transglycosylation with methyl β-d-xylopyranoside and a variety of alcohols using Trichoderma reesei β-d-xylosidase showed that primary alcohols are good substrates, secondary alcohols can be used, whereas tertiary alcohols proved to be poor substrates. All reactions retained the β-configuration. Reverse hydrolysis, where d-xylene was treated with the same enzyme in the presence of an alcohol, produced β-d-xylopyranosides with short primary and secondary alcohols. The yields for the transglycosylation were generally higher, compared to the more time-consuming (6 days) reverse hydrolysis procedure. An Aspergillus β-d-xylosidase has been shown to catalyze transglycosylation to produce p-nitrophenyl β-d-xyloterminosaccharides using p-nitrophényl β-d-xylopyranoside as both donor and acceptor.

### 2.2. Removal of anomeric protective groups

The anomeric hydroxyl group can be selectively protected, as described above, but also selectively deprotected. A common starting point for selective deprotection at the anomeric position is 1,2,3,4-tetra-O-acetyl-β-d-xylopyranose, where the anomeric acetate can be easily removed in high yields using amines (Table 2, Entries 1–4). Similar methods have been used on oligoxyloligosides such as peracetylated xylooligosaccharides, using benzylamine or Hüning’s base/NaOMe, forming the desired xylose with free amine hydroxyl group in good to excellent yields. The anomeric acetates can also be reacted with different tin-reagents to give 1-O-tin derivatives, which subsequently are hydrolyzed (Entries 5–7). Bases, such as NaOMe, usually give global deacetylation of peracetylated sugars. However, 2 equivalents of NaOMe in THF resulted in regioselective 1-O-deacetylation in 70% yield (Entry 8). Similarly, (NH₄)₂CO₃ in DMF gave anomeric deprotection in 63% (Entry 9), whereas treatment with alumina gave 55% conversion to the 1-O product (Entry 10). A number of acidic methods have also been used, where Lewis acid lanthanide triflates gave anomeric deacetylation in very good yields (Entries 11–14). Regioselective deacetylation using HClO₄—SiO₂ and copper(II) acetate dihydrate removed the anomeric acetate in excellent and moderate yield, respectively (Entries 15 and 16).

Apart from anomeric acetates, several other protective groups can be removed regioselectively. Anomeric benzyl group has been removed under acidic conditions as well as by hydrogenation (Table 3, Entries 1–3). Per-O-methylated d-xylene can be treated with TFA (aq.) or 2M HCl-dioxane to selectively remove the anomeric O-methyl in moderate yields (Entries 4 and 5). Hydrolisis of the anomeric methyl group in the presence of benzyl protective groups using 1M H₂SO₄ in dioxane–H₂O generated the corresponding hemiacetal in 71%, starting from d-xylene (Entry 6). Furthermore, permethacrylated xylose was selectively deprotected at the anomeric position in 36% yield by treatment with benzylamine in THF (Entry 7). Selective removal of an anomeric allyl group, in the presence of p-methoxybenzyl (PMB) protective groups, using catalytic amount of PdCl₂ in MeOH generated the desired product in excellent yield (Entry 8). An anomeric 2-methoxyethyl group was selectively removed in the presence of allyl, benzyl, and acetate groups in 51–80% yield by brief treatment with TiCl₄ in CH₂Cl₂ to form the intermediate anomic chloride that was hydrolyzed during silica chromatography.

### 2.3. Peracetylated xylose as donor

Tetra-O-acetyl-d-xylopyranose can be, as described later on, used to form other xylosyl donors: however, peracetylated xylose can also be used directly in glycosylation reactions. Acetylation of xylose is most commonly performed with a large excess of Ac₂O in the presence of a catalyst. Using NaOAc or KOAc as the catalyst at high temperatures generated the β-anomer in high stereoselectivity (Table 4, Entries 1 and 2), whereas reaction with Py or DMAP/Py formed the α-anomer in excellent yields (Entries 3 and
4), 145, 146 Lewis acids such as FeCl₃, 147 Montmorillonite K-10, 148 H-beta zeolite, 149 I₂, 150 Ce(OTf)₃, 151 Sm(OTf)₃, FeCl₃, 152 TMSOTf, 153 TMSOTf, 154 H₂SO₄—SiO₂, 155 sulfonic acid functionalized nano γ-Al₂O₃, 156 and InCl₃ under microwave irradiation in acetonitrile. 157 In combination with Ac₂O (Entries 5–15) formed peracetylated xylose as α,β-mixtures where the α-anomer was the major product. Peracetylated β-d-xylose is a cheap and effective donor that is usually activated with BF₃·OEt₂, generating β-d-xylosides in good stereoselectivity and yields, sometimes at low temperature. 160, 161 Other Lewis acids, e.g. TMSOTf and Sc(OTf)₃, 162 have also been used.

2.4. Xylosyl trichloroacetimidates

Trichloroacetimidate donors can be activated at low temperatures by a catalytic amount of Lewis acid and is thus the method of choice for sensitive or complicated targets. This is especially true for the trichloroacetimidate, the anomeric position needs to be unpro- tected. In 1984, Schmidt and co-workers synthesized xylosyl trichloroacetimidate 9 by treating 2,3,4-tri-O-benzyl-d-xylopyranose 8 with trichloroacetimidate and NaH (Scheme 3), generating a 6:1 α,β-mixture. 165 A slight modification of this procedure is to perform the reaction in CH₂Cl₂. 166 The kinetic product, i.e. the β-anomer, is formed if a weak base such as K₂CO₃ is used. 166 Using DBU as base might give poor stereoselectivity. However, in some cases the α-anomer can be formed as the major product in high yield. 166, 167

The trichloroacetimidate method usually gives excellent yields for β-xylosides. In the glycosylation reaction, BF₃·Et₂O is commonly used in the presence of 4 Å molecular sieves in CH₂Cl₂, often at low temperatures, e.g. in oligosaccharide synthesis. 168, 169 TMSOTf in Et₂O, at low temperatures, can also be used to activate the trichloroacetimidate donor, sometimes with the α-anomer as the major product. 166

2.5. Xylosyl halides

Halides have played an important role in the history of carbohydrate chemistry, especially by the Koenigs-Knorr reaction for synthesis of 1,2-transglycosides, such as β-xylosides. One major problem with the Koenigs-Knorr method is the environmentally malnig use of toxic metal salts such as Ag₂CO₃, Ag₂O, AgOTf, HgBr₂, or HgCN₂. 13 H₂SO₄—SiO₂, 1,2-Cisglycosides, i.e. α-xylosides can be formed by the halide catalysis method introduced by Lemieux. In this method, an α-bromide is used as donor, activated by tetraethylammonium bromide. These methods are commonly used with chlorides and bromides. The very stable fluorides have also been used with a range of promoters, as well as the very reactive iodides. Syntheses of suitable xylosyl halide donors are described below.

2.5.1. Xylosyl fluorides

The first method developed to introduce a fluoride in the anomeric position involved distillation of HF, formed from KHF₂, to a receiving flask containing the peracetylated xylose, which gave the anomeric fluoride 13 in 34% (Scheme 4). 170 This method also works well with other protective groups, such as benzyl, 171 methyl and benzoyl, 172 and for anomeric benzoates, to give the α-fluoro anomeric 173 Fluoride 13 has also been formed from 12 by using HF in pyridine, in 92% yield. 171 In a one-pot reaction, methyl β-d-xylopyranoside was converted to the peracetylated xylosyl fluoride 13 in 98% yield using HF and Ac₂O in a special HF solvolysis apparatus. 172, 173 To introduce an anomeric fluoride in β-position, d-xylose 18 was directly converted to fully protected β-d-xylopyranosyl fluoride 19 in 60% yield by reaction with 8 equivalents of N,N-diethyl-α,α-difluoro-(m-methylbenzyl)amine (DFMBA). 174, 175 In a halogen exchange reaction, an anomeric bromide was exchanged for a fluoride using triethylamine trihydrofluoride in CH₃CN generating 13 in 95% yield. 176

Xylosyl fluorides can be used in glycosylation reactions, catalyzed by BF₃·Et₂O. As an example, 15 reacts with alcohols and silyl ethers, where Et₃N needs to be added to trap HF. 172 Disaccharides have been synthesized in good to excellent yields, although with
An anomeric mixture of (d) TiCl₄, CHCl₃, 80%; SnCl₄, (f) In(OTf)₃, BzBr, 60%. Glycosylation reactions with Xylosyl chlorides can react with alcohols in (c) SnCl₄, SOCl₂, C H₂Cl₂, 100%; (e) MoO₂Cl₂, or In addition, PCl₅, Interestingly, or SnCl₄ (f) PCl₅, B F₃·Et₂O, CH₂Cl₂, 88%; (b) BiOCl, (h) or by treatment with HBr—AcOH in CH₂Cl₂ or In(OTf)₃, BzCl, 75%. Several methods for Themethod workswell with (g) PCl₅, MeCN, 88%; Xylosyl fluorides have and as for the chloride, unprotected FeCl₃, Et₂O, BiOCl, a method that is also suit- (3) in combination with BF₃·Et₂O in CH₂Cl₂ or PCl₅ in acetonitrile yiel ded (i) In(OTf)₃, BzCl, 75% 190. poor stereoselectivity, by using 15 as donor in the presence of SnCl₄, AgClO₄, and 4 Å molecular sieves. 179. An anomeric mixture of 15 showed, on the other hand, good α-selectivity in the presence of Cp₂ZrCl₂, AgClO₄, and 4 Å molecular sieves. 180. Xylosyl fluorides have also been employed as donors using the glycosynthase technology in the synthesis of xylo-oligosaccharides. Withers and co-workers introduced a new class of mutant glycosidases, called glycosynthases, which are hydrolytically incompetent enzymes that efficiently, stereo-, and regioselectively catalyze glycosidic bond formation. 24,181–183.

2.5.2. Xylosyl chlorides

2,3,4-Tri-O-acetyl-α-d-xylopyranosyl chloride 21 has been prepared from peracetylated d-xylose 12β in high yields with SOCl₂ in combination with ZnCl₂, 184 BiOCl, 185 or SnCl₂ 186 (Scheme 5). Using TiCl₄ in CHCl₃ formed 21 from 12β, 187 a method that is also suitable for 1,2,3,4-tetra-O-levulinoyl-α-d-xylopyranose. 191 Interestingly, when SOCl₂ is used in the presence of AcOH in CH₂Cl₂, the corre- 22 sponding β-anomer 22 is produced in 82% yield. 188 In addition, PCl₅ in combination with BF₃·Et₂O in CH₂Cl₂ or PCl₃ in acetonitrile yielded 22 in excellent yields. 189 Unprotected d-xylose can be converted in a one-pot reaction to 21 and 23 in 75% by reaction with In(OTf)₃ and AcCl or BzCl. 190 Xylosyl chlorides can react with alcohols in a Koenigs–Knorr glycosylation reaction. 191

2.5.3. Xylosyl bromides

Peracetylated α-d-xylopyranosyl bromide 20 has been synthesized from peracetylated α- and β-d-xylopyranose, or mixtures thereof, in high yields in the presence of HBr in AcOH, 150,192 Et₂O, 193 or CH₂Cl₂, 182 or by treatment with HBr—AcOH in CH₂Cl₂ 184 (Scheme 6). The latter method has proved to work well on perivaloylated 196 and perlevulinated 198 d-xylopyranose yielding the corresponding α-d-xylopyranosyl bromides in 68% and 88% yield, respectively. 1-O-Acetyl-2,3,4-tri-O-benzyl-d-xylopyranose can react with TMSBr in CH₂Cl₂ to yield the perbenzylated d-xylopyranosyl bromide. 197 Bromide 20 can also be synthesized from d-xylose 18 and HBr in Ac₂O (Scheme 6), 195 and as for the chloride, unprotected 18 has been converted in a one-pot reaction to the perbenzoylated α-d- xylopyranosyl bromide 24 in 60% by reaction with In(OTf)₃ and benzyl bromide. 190

The Koenigs–Knorr and Lemieux protocols are commonly used for glycosylation reactions with bromide donors. Michael glycosylation, which is an aromatic O-glycosylation between gly- cosyl halides and arylo alcohols under basic conditions with inversion at the anomeric center, can be performed using 20198 and this re- action can also be performed under phase-transfer conditions with Bu₄NBr as catalyst. 200,199 Xylosyl bromides 20 and 24 have been used in the formation of β-O-(9-fluorenyl)-d-xylopyranose. 205

2.6. Thioxylosides

Thioglycosides are relatively stable carbohydrate derivatives, which make them suitable when the remaining hydroxyl groups need to be modified or protected. Thioxylosides are usually produced either from the anomeric halide or from the peracetylated compound, but several other methods have been used, as shown below. The synthesis of phenyl 1-thio-β-d-xylopyranoside 26 was published by Purves in 1929, where the bromide 20 was gener- ated and directly treated with potassium thiophenolate (Scheme 7). 200 Using a similar method, Zinner et al. synthesized methyl, ethyl, n-propyl, and benzyl thioxylosides in good yields from 20 and the potassium salt of the corresponding thiol. 208 Several methods for the synthesis of 1-thio-β-thioglycosides from peracetylated xylose 12β have been developed. In 1976, Ferrier and Furneaux introduced the method that is most used today, i.e. to treat 12β with a thiol in CHCl₃ using BF₃·OEt₂ as catalyst (Scheme 8). 207 The method works well with other Lewis acids, such as ZrCl₄, 208,210 SnCl₄, 211 FeCl₃, 212 MoO₃, 213 and Fe₂. 214 Thioxylosides can also be synthesized from an acetyl

![Scheme 5](image)

**Scheme 5.** Reagents and conditions: (a) ZnCl₂, SOCl₂, benzene, 81%; (b) BiOCl, SOCl₂, CH₂Cl₂, 92%; (c) SnCl₄, SOCl₂, CH₂Cl₂, 100%; (d) TiCl₄, CHCl₃, 80%; (e) SOCl₂, AcOH, 82%; (f) PCl₅, BF₃·Et₂O, CH₂Cl₂, 88%; (g) PCl₅, MeCN, 88%; (h) In(OTf)₃, BzCl, 75% 190.

![Scheme 6](image)

**Scheme 6.** Reagents and conditions: (a) 12α or 12β, HBr, AcOH, 77% from 12α, 81% from 12β; 188 (b) 12α, HBr, Et₂O, 193 (c) 12β, HBr, CH₂Cl₂; 182 (d) 12, HBr, AcOH, CH₂Cl₂; 194 (e) HBr, Ac₂O, 196 (f) In(OTf)₃, BzBr, 60%; 196.

![Scheme 7](image)

**Scheme 7.** Reagents and conditions: (a) Ac₂O, I₂ (cat), then I₂, HMDS. 150

![Scheme 8](image)

**Scheme 8.** Reagents and conditions: (a) PhSH, KOH, CHCl₃, 80%; (b) PhSH, BF₃·OEt₂, CHCl₃, 50%. 207
In addition, or from xylosyl bromide Xylosyl phosphite (g) (TMS)2S, TMSOTf, CH2Cl2, 0°C. (c) NIS, TFA, CH2Cl2, 0°C; or by NIS and TMSOTf and in studies of anomeric radical reactions by or with SO(Im)2 and LiN3 in DMF. (d) ZnCl2, CH2Cl2, This 150

Xylosyl azides can be used in, e.g. 1,3-dipolar or deactivated It is also possible to synthesize thioxylosides from (f) DMDO, CH2Cl2, 0°C, Another method is to use xylal that can be oxi-

or with MeOTf Thio-orthoesters, (43) has been oxidized by KF/mCPBA or mCPBA to give the corresponding sulfoxides, such as 44, in excellent yield. The sulf- oxides can be used as donors in Kuhne’s glycosylation reaction.

2.7. Miscellaneous

α-d-Xylopyranosyl phosphinic acid 40 (Fig. 8) has been synthesized from d-xylose, phosphinic acid, and propylene oxide in dioxane in 85% yield.229 Xylosyl phosphite 41 has been synthesized by treating a partly protected xylose with dimethyl N,N-diethylylphosphoramidite in the presence of 1H-tetrazole in CH2Cl2.108 41 was directly reacted with an alcohol in a ZnCl2/AgClO4-promoted glycosylation to give the products as α,β-mixtures in 70–76%. Phosphorylation of d-xylose using Na3P3O9·6H2O in aqueous solution (pH 12), generated the β-triphosphate 42 in 42% yield.230

D-xylose can undergo stereoselective azidation to form β-d-xylopyranosyl azide 43 (Fig. 8) in high yields by treatment with PPh3, NCS, and LiN3 in DMF,211 or with SO(Im)2 and LiN3 in DMF.232 This compound can also be synthesized from peracylated d-xylose, TMSN3, and SnCl4 in CH2Cl2, followed by deacylation using standard Zemplén conditions,233 or from xylal bromide 20 using NaN3 in acetonitrile.234 Xylosyl azides can be used in, e.g. 1,3-dipolar cyclodadditions.

Thioxylosides have been oxidized by KF/mCPBA or mCPBA to give the corresponding sulfoxides, such as 44, in excellent yield. The sulfoxides can be used as donors in Kuhne’s glycosylation reaction.

In order to perform regioselective reactions, the hydroxyl groups of carbohydrates usually need to be protected. In the case of xylose, all three hydroxyl groups are equatorial, and similar in reactivity. Hence, protective group strategies are important when using xylosides, and the most common ones are described below.

3. Protective groups

When it comes to choosing a donor for a specific glycosylation reaction, several aspects need to be considered, such as whether α- or β-selectivity is desired, if manipulations of the other hydroxyl groups in the xylose moiety of the donor are needed prior to glycosylation, and the kind of acceptor that is to be used. Even though α-xylosides are thermodynamically more stable than β-xylosides, many glycosylation reactions generate trans-xylosidic linkages due to neighboring group participation. Peracylated xylose is an easily accessible, and commercially available, donor that gives good β-selectivity, and would be the donor of choice if a straightforward glycosylation reaction is possible. However, if α-selectivity is desired, the Lemieux protocol using xylosyl chlorides or bromides is preferred. If either the donor and/or the acceptor are sensitive to strong Lewis acids or harsh conditions, trichloroacetimidates can be used since the activation can be performed at low temperatures with catalytic amount of Lewis acid. On the other hand, if many manipulations of the donor, including protection/deprotection of the other hydroxyl groups, are required before the glycosylation reaction, thioxylosides are a good alternative due to its robustness.

3. Protective groups

In order to perform regioselective reactions, the hydroxyl groups of carbohydrates usually need to be protected. In the case of xylose, all three hydroxyl groups are equatorial, and similar in reactivity. Hence, protective group strategies are important when using xylosides, and the most common ones are described below.

Fig. 8. Various xylosides. PG = protective group.
3.1. Esters

3.1.1. Acetates

In 1962, Garegg investigated partial acetylation of saccharides, including benzyl 4-O-methyl-β-D-xylopyranoside, using different reagents (Table 5, Entries 1 – 5). The best selectivity for 2-OH was seen with Ac₂O and NaOAc whereas Ac₂O and HClO₄ gave the 3-OAc product. Treatment of unprotected D-xylose with Ac₂O and NaOAc resulted in full acetylation (27%) as well as a mixture of tri-acetate products in 29% yield, of which 1,2,4-tri-O-acetyl-β-D-xylopyranose was isolated in 7% yield.

When methyl β-D-xylopyranoside was acetylated with Ac₂O in pyridine, each one of the three monoacetylated products was isolated in 13–16% yield (Entry 6). Using MoCl₅ as a catalyst together with Ac₂O generated the 3-OAc as the major product for many carbohydrates. However, methyl β-D-xylopyranoside yielded a complicated mixture of mono-, di-, and triacetylated products (Entry 7). Enzymatic catalysis has also been explored, where regioselective acetylation of 4-OH was accomplished with Pseudomonas fluorescens lipase (PFL) and Candida cylindracea lipase (CCL) using vinyl acetate as the acetylating reagent (Entries 8 and 9).

Acetylating methyl α-D-xylopyranoside using CCL in EtOAc generated the 2-OAc product almost exclusively, however, in low yield (Entry 10).

Investigations of monoacetylation of octyl β-D-xylopyranoside with Pseudomonas cepacia lipase (lipase PS) in different solvents showed that more hydrophobic solvent resulted in higher propensity for acetylation of position 2, whereas the 4-OAc was the major product when more polar solvents, such as acetonitrile, were used (Entries 11 and 12). This tendency has been observed in other solvents as well.

Lipase PS has also been used to form diacetates and when treating methyl β-D-xylopyranoside, the 3,4-diacetate product was obtained in 85% yield (Table 6, Entry 1). As for monoacetylation, the aglycon and solvent play crucial roles for the selectivity, which was seen with e.g. octyl (Entries 2 and 3) or 4-nitrophenyl as aglycon. The specific enzyme does also affect the regioselectivity of the acetylation, as exemplified with Novozyme 435 (immobilized C. antarctica lipase) and lipase PS (Entries 4 and 5).

Regioselective deacetylation using enzymes has also been used as a method for generation of partly acetylated xylosides. Enzymes such as porcine liver esterase (PLE), Novozym 435, lipase PS, and PEG-modified CCL gave deacetylation in position 4 of 2,3,4-tri-O-acetyl protected xylosides with excellent regioselectivity and high yields. Regioselective deacetylation of position 3 has been reported with Novozyme 435 as well as rabbit serum esterase, which also selectively removes pivaloyl groups in positions 3 and 4 in the presence of acetates.

3.1.2. Chloroacetates

A chloroacetyl protective group can be regioselectively introduced at 4-OH by reaction with Bu₂SnO followed by stoichiometric amounts of chloroacetyl chloride (Scheme 10).

3.1.3. Benzoates

A common method for regioselective benzoylation is the use of BzCl in dry pyridine, often at low temperatures (Table 7). For α-D-xylopyranosides, monobenzoylation gives good selectivity for either 2-OH (Entries 1 and 10) or 3-OH (Entry 14), whereas β-D-xylopyranosides generally show low regioselectivity (Entry 5). The

### Table 5

<table>
<thead>
<tr>
<th>Entry</th>
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<td>2-OAc</td>
<td>3-OAc</td>
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<td>Ac₂O, NaOAc</td>
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<td>33%</td>
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<td>2</td>
<td></td>
<td>Ac₂O, Py</td>
<td>45%</td>
<td>26%</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td>AcCl, Py</td>
<td>27%</td>
<td>24%</td>
</tr>
<tr>
<td>4</td>
<td></td>
<td>Ac₂O, Py, HCl</td>
<td>29%</td>
<td>29%</td>
</tr>
<tr>
<td>5</td>
<td></td>
<td>Ac₂O, HClO₄</td>
<td>25%</td>
<td>75%</td>
</tr>
<tr>
<td>6</td>
<td></td>
<td>Ac₂O, MoCl₅</td>
<td>24%</td>
<td>29%</td>
</tr>
<tr>
<td>7</td>
<td></td>
<td>PFL, vinyl acetate</td>
<td>29%</td>
<td>1%</td>
</tr>
<tr>
<td>8</td>
<td></td>
<td>CCL, vinyl acetate</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>9</td>
<td></td>
<td>CCL, EtOAc</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>10</td>
<td></td>
<td>Lipase PS, vinyl acetate, hexane</td>
<td>81%</td>
<td>6%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Lipase PS, vinyl acetate, MeCN</td>
<td>35%</td>
<td>5%</td>
</tr>
</tbody>
</table>

### Table 6

<table>
<thead>
<tr>
<th>Entry</th>
<th>Starting material</th>
<th>Reagents</th>
<th>Product ratio</th>
<th>Total yield</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>2,3-OAc</td>
<td>2,4-OAc</td>
</tr>
<tr>
<td>1</td>
<td></td>
<td>Lipase PS, vinyl acetate, MeCN</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td>Lipase PS, vinyl acetate, MeCN</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td>Lipase PS, vinyl acetate, hexane</td>
<td>22%</td>
<td>7%</td>
</tr>
<tr>
<td>4</td>
<td></td>
<td>Novozym 435, vinyl acetate</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>5</td>
<td></td>
<td>Lipase PS, vinyl acetate</td>
<td>100%</td>
<td>–</td>
</tr>
</tbody>
</table>
2,4-dibenzocate derivatives are often the major product using 2 equivalents of BzCl (Entries 2, 6, 11, and 15). However, the 3,4-dibenzozylated product of N-acetyl-N-aryl-β-d-xylorynosamines was obtained using this method.\textsuperscript{266} 1,2,4-tri-O-benzoyl-α-d-xyloryside, obtained in 32%, was the major product when treating unprotected xylose with 3.1 equivalents of BzCl in pyridine.\textsuperscript{261}

The use of Bu\textsubscript{2}SnO and (Bu\textsubscript{3}Sn)\textsubscript{2}O in regioselective benzyolation of xyloses has been investigated.\textsuperscript{255,257} For α-d-xyloryanosides, the 2- and 4-O-benzoyl products are often obtained, with 2-OBz products as the major product (Entries 3, 4, and 12). In contrast, the methyl β-anomer is usually regioselectively monobenzyolated at the 4-OH (Entries 7 and 9). Excellent selectivity is obtained when using 2 equivalents of BzCl, generating the 2,4-di-O-benzoyl product for the α-anomer and the 3,4-di-O-benzoyl product for the β-anomer (Entries 8 and 13). The Bu\textsubscript{2}SnO method also proved efficient when monobenzyolation thymine β-d-xylorypanoside, and the 4-O-benzoyl product was obtained in 79%.\textsuperscript{262}

Benzoylation with benzoic anhydride in the presence of copper(II) trifluoracetate gave regioselective monobenzyolation of methyl and benzyl β-d-xylorynosides in the 4-OH position in 86% and 87% yield, respectively.\textsuperscript{263} Methyl α-d-xylorypanoside, on the other hand, generated a 1:1 mixture of 2-OBz and 4-OBz products together with some di- and tri-O-benzoylated derivatives.

### 3.1.4. 4-Methoxybenzoxates

In addition to benzoyl protective groups, 4-methoxybenzoates have been used. Treating benzyl α-d-xylorypanoside with 4-methoxybenzoyl chloride in dry pyridine generated regioselective benzyolation of the 2-OH.\textsuperscript{194} On the other hand, the 3-OH was protected when phenyl 1-thio-β-d-xylorypanoside was reacted with 4-methoxybenzoic acid in the presence of DCC and DMAP.\textsuperscript{264}

### Table 7

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>eq BzCl</th>
<th>Reagents/conditions</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2-Bz 3-Bz 4-Bz 2,3-Bz 2,4-Bz 3,4-Bz 2,3,4-Bz</td>
</tr>
<tr>
<td>1</td>
<td>α-Me</td>
<td>1</td>
<td>Py, 0 °C</td>
<td>56%</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td>2</td>
<td>Py, –40 °C</td>
<td>–</td>
</tr>
<tr>
<td>3</td>
<td>1.1</td>
<td>Bu\textsubscript{2}SnO</td>
<td>52%\textsuperscript{a}</td>
<td>–</td>
</tr>
<tr>
<td>4</td>
<td>1.5</td>
<td>(Bu\textsubscript{3}Sn)\textsubscript{2}O</td>
<td>41%\textsuperscript{a}</td>
<td>–</td>
</tr>
<tr>
<td>5</td>
<td>β-Me</td>
<td>1</td>
<td>Py, –40 °C</td>
<td>26%</td>
</tr>
<tr>
<td>6</td>
<td>2</td>
<td>Py, –40 °C</td>
<td>23%</td>
<td>4%</td>
</tr>
<tr>
<td>7</td>
<td>1</td>
<td>Bu\textsubscript{2}SnO</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>8</td>
<td>2</td>
<td>Bu\textsubscript{2}SnO</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>9</td>
<td>1.5</td>
<td>(Bu\textsubscript{3}Sn)\textsubscript{2}O</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>10</td>
<td>α-Bn</td>
<td>1</td>
<td>Py, –30 °C</td>
<td>59%</td>
</tr>
<tr>
<td>11</td>
<td>2.2</td>
<td>Py, –30 °C</td>
<td>9%</td>
<td>–</td>
</tr>
<tr>
<td>12</td>
<td>1</td>
<td>Bu\textsubscript{2}SnO</td>
<td>44%</td>
<td>–</td>
</tr>
<tr>
<td>13</td>
<td>2</td>
<td>Bu\textsubscript{2}SnO</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>14</td>
<td>α-All</td>
<td>1</td>
<td>Py, rt</td>
<td>–</td>
</tr>
<tr>
<td>15</td>
<td>2.2</td>
<td>Py, rt</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

\textsuperscript{a} Unseparable mixture.
\textsuperscript{b} Unseparable mixture.

### 3.1.5. Pivaloates

Rosenberg et al. selectively pivaloylated 2-OH of allyl α-d-xyloryside 46 in 53% yield by treatment with pivaloyl chloride in pyridine at –40 °C in their synthesis of agonists for the myo-inositol receptor (Scheme 11).\textsuperscript{108} Other protective group manipulation made it possible to exchange the pivaloate to a benzyl group later in the synthesis.

Pivaloylation of methyl β-d-xylorypanoside with one equiv-alent PvCl in pyridine gave the 3-pivaloylester in 20% and the 4-pivaloylester in 22%.\textsuperscript{249} When three equivalents were used, the 2,4-pivaloated product was obtained in 25% and the 3,4-pivaloated product in 26% yield. Hydrolysis of the dipivaloates with rabbit serum esterase generated monopivaloates.

### 3.1.6. Carbamates

Regioselective protection of the 3-OH of some xylopyranosides as phenylcarbamate by the use of phenyl isocyanate in the presence of zinc naphthalenate has been reported by Nishino et al.\textsuperscript{265} The 3-O-phenylcarbamoyl derivatives were formed as the major products (53–64%), alongside the 2-O-phenylcarbamoyl (10–18%) as well as the 4-O-phenylcarbamoyl (8–9%).

### 3.1.7. Sulfonates

Chalk and Ball investigated the reactivity of the hydroxyls of xylose by mesylation of methyl xylopyranosides (Table 8).\textsuperscript{266} The order of reactivity of the α-anomer was determined to be O2 > O4 > O3, whereas the order for the corresponding β-anomer was O4 > O3 > O2. This trend had been indicated previously.\textsuperscript{267} Tosylation of methyl and benzyl α-d-xylorypanoside using TsCl in dry pyridine showed the same selectivity as for the mesylation, where the 2-O-tosyl was the major product for monotosylation and 2,4-di-O-tosyl was formed as the major product when using 2 equivalents of TsCl.\textsuperscript{268,269} The reaction with methyl β-d-xylorypanoside

![Scheme 10. Reagents and conditions: (a) Bu\textsubscript{2}SnO, MeOH, reflux, then CICH\textsubscript{2}COCl, CH\textsubscript{2}Cl\textsubscript{2}.\textsuperscript{250}](image)

![Scheme 11. Reagents and conditions: (a) PvCl, pyridine, –40 °C.\textsuperscript{108}](image)
was on the other hand much less regioselective and 2,4-, 4-, and 2,3-O-tosylated products were isolated in 34%, 31%, and 20% yield, respectively, when sulfonated with 2 equivalents of TsCl. Alternatively, tosyl protective groups can be introduced by reaction with Bu₂SnO in combination with TsCl. When methyl α-d-xylopyranoside was first treated with Bu₂SnO followed by TsCl and DMAP, the 4-O-tosylated compound was the major product (Table 9). Under the same conditions, the β-anomer gave a quantitative conversion to the 4-O-tosylated product. When using only catalytic amounts of Bu₂SnO together with TsCl and Et₃N, the regioselectivity was reversed for methyl α-d-xylopyranoside.

3.1.8. Phenylborate esters

Ferrier et al. developed a method involving a 2,4-cyclic borate ester as a transient protective group. Methyl α- and β-d-xylopyranosides were treated with phenylboronic acid to form 2,4-phenyl boronates where the xylose moiety gets locked in a 1C₄ conformation. The 3-OH could then be selectively acetylated, benzoylated, or methylated. Methyl 2,4-di-O-methyl-d-xylopyranoside could also be synthesized using this procedure, by reacting the free 3-OH with phenyl isocyanate forming a transient carbamate, which after removal of the phenyl boronate and methylation could be cleaved off.

3.1.9. Orthoesters

Orthoesters can be used as protective groups of 1- and 2-OH while modifications are done at other positions. The orthoester can then be opened to form a 1,2-trans-glycoside. This approach allows for orthogonal protection of the hydroxyl groups. α-Xylosyl bromides that contain an ester protective group at C2, such as acetate, benzoate, or pivaloate, are reacted with a base and an alcohol or thiol to form a bicyclic orthoester over O1 and O2 (Scheme 12). Instead of reacting the orthoester with an alcohol to form a β-xyloside, treatment with acid generates a tricyclic orthoester also involving O4, where position 3 can be selectively modified.

3.2. Ethers

3.2.1. Methyl ethers

Regioselective monomethylation of methyl α-d-xylopyranoside was achieved by Tsuda and co-workers using Bu₂SnO and methyl iodide. A monomethylated mixture was obtained in 65% yield, composed of the 2-O-Me and the 4-O-Me derivatives in a ratio of 57:43. In the same study, methoxymethyl chloride was used as alkylating agent as well. This resulted in a yield of 89% of monoalkylated products of methyl α-d-xylopyranoside, composed of all three isomers with the 2-O-MOM analog as the major product, which also was the case when alkylating the β-anomer.

3.2.2. Benzyl ethers

The direct benzylation of methyl α-d-xylopyranoside generated the 2,4-di-O-benzyl derivative in 70% yield using NaH and BnCl (Scheme 13). Under similar conditions, the β-anomer yielded 54 in 53% as the major product. 2,4-Di-O-benzylated xylopyranoside was also the major product, obtained in 66% yield, when 2-naphthyl β-d-xylopyranoside was directly benzylated with BnBr under phase-transfer conditions.

Table 8

<table>
<thead>
<tr>
<th>Entry</th>
<th>α/β</th>
<th>Eq MsCl</th>
<th>Yield 2-Ms</th>
<th>3-Ms</th>
<th>4-Ms</th>
<th>2,3-Ms</th>
<th>2,4-Ms</th>
<th>3,4-Ms</th>
<th>2,3,4-Ms</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>α</td>
<td>1</td>
<td>35%</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>2</td>
<td>α</td>
<td>2</td>
<td>4%</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>3</td>
<td>β</td>
<td>1</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>38%</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>4</td>
<td>β</td>
<td>2</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>10%</td>
<td>–</td>
<td>–</td>
<td>44%</td>
</tr>
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</table>

Table 9

<table>
<thead>
<tr>
<th>Entry</th>
<th>α/β</th>
<th>Method</th>
<th>Yield 2-Ts</th>
<th>3-Ts</th>
<th>4-Ts</th>
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<tbody>
<tr>
<td>1</td>
<td>α</td>
<td>A</td>
<td>32%</td>
<td>–</td>
<td>52%</td>
</tr>
<tr>
<td>2</td>
<td>α</td>
<td>B</td>
<td>54%</td>
<td>–</td>
<td>16%</td>
</tr>
<tr>
<td>3</td>
<td>β</td>
<td>A</td>
<td>–</td>
<td>–</td>
<td>100%</td>
</tr>
<tr>
<td>4</td>
<td>β</td>
<td>B</td>
<td>4%</td>
<td>–</td>
<td>36%</td>
</tr>
</tbody>
</table>

a Method A: Bu₂SnO, MeOH, then TsCl, DMAP, dioxane. Method B: Bu₂SnO (cat), TsCl, Et₃N, dioxane.
Regioselective monobenzylation can be performed, as for monomethylation, using Bu₂SnO followed by the addition of BnBr. The reaction with 49 yielded a mixture of the monobenzylated products where the 2-O-benzyl derivative was the major one. For 2, the benzylation generated the 4-O-benzyl analog as the only product in 70% yield. When the solvent was changed from dioxane to DMF, a 1:1 mixture of 2-O and 4-O-benzylation products was found. Using a similar procedure, allyl α-d-xylorosane formed the 2-O-benzyl derivative in 40% yield, whereas the corresponding β-anomer could not be benzylated using the same method. Instead, it was treated with one equivalent of BnBr and NaH to give allyl 2-O-benzyl-β-d-xylorosane in 20% yield.

3.2.3. Allyl ethers
Methyl α-d-xylorosane was monoallylated with allyl bromide by Tsuda and co-workers using the Bu₂SnO procedure. The 2-O-allyl derivative was the major product obtained in 47% yield followed by the 4-O-allyl derivative in 23% yield.

3.2.4. Silylethers
Regioselective silylation of β-d-xylorosanes with TBDPSCI in the presence of base often generates the 4-O-TBDPS derivatives as the major product followed by the 2-O-silylated compound (Scheme 14). Treating methyl β-d-xylorosane 2 with TBDMScI in the presence of imidazole generated the 2-, 3-, and 4-O-TBDMS products in 1:2:2 ratio in 71% total yield. However, TBDMS-H in combination with PdCl₂ formed the 3-O-silylated product 60 in 57% yield as the major product (Scheme 14). TBDMSOTf has also been used as a silylating agent in the presence of base. Due to steric effects, pent-4-enyl 2-O-benzoyl-β-d-xylorosane gave the 4-O-silylated derivative in 83% yield. A 4-O-PMB protected β-d-xylorosane was regioselectively silylated in excellent yield at O3 when the reaction was performed in THF, and at O2 when using CH₂Cl₂ as solvent. Silyl ethers have also been introduced using TiPDSCI, where the α-anomer was protected as the 2,3-cyclic silyl derivative in 79% and the β-anomer was protected as the 3,4-cyclic silyl ether in 74%. The formation of an epoxide between C2 and C3 has been a way to selectively protect, modify, or react 4-OH. Starting from d-arabinose, the 2,3-epoxide can be generated in several steps, which later on can be opened to form the xyloside by nucleophilic attack by either hydroxide to generate a diol, or by an alkoxide to yield a derivative with free 2-OH.

3.3. Acetals
3.3.1. Isopropylidene acetals
Isopropylidene acetals are often used when 2-OH or 4-OH is to be modified and the remaining hydroxyl groups need to be protected. 2-Methoxy propene is the most commonly used reagent in the presence of a strong acid such as TFA, CSA, pTSA, or HCl in DMF. However, 2,2-dimethoxypropane can also be used. For xylopyranosides, the 2,3-O-isopropylidene derivatives are the major products (Scheme 15).

![Scheme 15](image)


3.3.2. Cyclohexyldiene acetals
Koto and co-workers has also investigated the use of cyclohexyldiene acetals. Treatment of methyl or benzyl α-d-xylorosane with 1,1-dimethoxycyclohexane and pTSA in DMF gave the 2,3-acetals as the major products.

3.3.3. Diacetics
The butane-2,3-diacetal (BDA) was introduced in xylose chemistry by Jenkins and Potter by the reaction of allyl α-d-xylorosane with 2,2,3,3-tetramethoxybutane, which generated a mixture of the 2,3- and 3,4-acetal in 1:1 ratio in 93% yield. Later on, selectivity for the 3,4-BDA product was achieved using both 2,2,3,3-tetramethoxybutane and butane-2,3-dione (Scheme 16). Xylofuranosan can be used to install different protective groups and then later on, the furanosides have been converted to the xylopyranosides.

3.4. Miscellaneous

3.5. Concluding remarks
The general reactivity trend for α-xylorosides is O2 > O4 > O3 and for β-xylorosides O4 > O3 > O2, as observed in many reactions. When it comes to β-d-xylorosanes, excellent regioselective protection of 4-OH is often obtained by using Bu₂SnO, and benzoate, chloroacetate, tosylate, benzyl, and triethylsilyl groups, among others, have been introduced in this way. α-d-Xylorosanes, on the other hand, do not always show as high regioselectivity with this method.

![Scheme 16](image)
but the major products are often xylosides protected at 2-OH. Using stannylene acetics, diprotection can also be obtained, with protection of positions 2 and 4 of α-xylosides, whereas β-xylosides reacts at 3- and 4-OH. An alternative method is the use of cyclic acetics, where propylidene acetics generate 2,3-O-protected xylosides in high yields and BDA-acetics can be used for protection of positions 3 and 4. Enzymatic reactions can be used to regioselectively introduce e.g. acetates, and enzymatic deacetylation in particular shows high selectivity producing xylosides with a free 4-OH.

4. Modifications

Functional group manipulations are common in organic synthesis. Below, a few examples are given for each modification. In many cases, a new sugar is obtained, e.g. when performing an epimerization (Table 10).

4.1. Oxidations

Enzymes have been used for oxidation, e.g. d-xylose was oxidized to d-xylonic acid 70 by the action of xylose dehydrogenase from Pseudomonas fragi 302−304 or glucose oxidase from Aspergillus niger 305 (Fig. 9). Pyranose oxidase, isolated from mycelium extracts of the fungi basidiomycota, oxidized D-xylose at C2 to D-xylosone 72.306−308 Using pyranose dehydrogenase from Agaricus bisporus, oxidation occurred successively at C2 and C3 generating 2,3-diketo-d-xylose 73.309 Oxidation of methyl α- and β-d-xylalysides formed the 4-keto products 76 and 77 when using the acetic acid bacterium Acetobacter suboxydans 293,310 or when the xylosides were treated with bromine in the presence of NaBO2.312

2,3,4-Tri-O-protected pyranosylamines were oxidized at the anomeric position by treatment with Ac2O/DMSO,313 PCC,138,311 or TPAP/NMO114 to form the corresponding δ-lactones 71. Oxidizing d-xylopyranose using cupric acetate generated 72 in 50−55% yield.315 Methyl α- and β-d-xylals are oxidized at C3 with Ac2O/DMSO in the presence of phenylboronic acid, which formed 74 and 75.316 Interestingly, using (Bu3Sn)2O followed by brominolysis, the β-anomer generated 75, whereas the corresponding α-xyloside formed the 4-keto derivative 76.317,318 It has also been shown that it is possible to oxidize partly protected xylosides at C2, C3, and C4 by performing a Swern oxidation519,320 or by oxidation with Dess−Martin periodinane.48,321

4.2. Reductions

4.2.1. Xylal synthesis

Xylals, i.e. 1,2-unsaturated xyosyl derivatives, are most often synthesized from peracetylated xyosyl bromide 78 using e.g. Zn/AgO,322 Zn/Ag-graphite,323 Zn/CuSO4,324,325 Zn/NaH2PO4,326 Zn/β-cyclodextrin,327 (Cp2TiCl)2,328 or [Cr(EDTA)]2−329 as reagents (Scheme 17). 1-Thioxylosides have also been transformed to the corresponding xylals using [Cr(EDTA)]2−330 or Li-naphthalenide.332 A ferrier rearrangement of xylals generates a 2,3-unsaturated derivative, often as an anomeric mixture. The xylal is thus reacted with an alcohol and a catalyst, such as BF3·Et2O,333,334 PdCl2,335 SnCl4,336 TMSOTf,337 CAN,338 I2,337 and zeolite338 (Scheme 17).

4.2.2. Deoxygenation

Tsuda and co-workers investigated the use of stannylene intermediates in the regioselective deoxygenation of carbohydrates. Treatment of methyl α- and β-d-xylalosides with Bu3SnO and phenoxythiocarbonyl chloride generated the 4-thionocarbonate derivative 86 exclusively for the β-anomer, whereas a 1:1 mixture of 82 and 83 was obtained for the α-anomer (Scheme 18).339,340 Acetylation followed by reduction with Bu3SnH formed the corresponding deoxy derivatives 84, 85, and 87 in excellent yields. Alternatively, xylosyanides have been deoxygenated by the use of xanthate intermediates that were reacted with Bu3SnH and AIBN in a Barton McCombie radical deoxygenation. This has been performed with, e.g. naphthyl β-d-xylosyanides that have been deoxygenated at positions 2, 3, and 4 using this methodology.36

Treatment of peracetylated α-d-xyosyl bromide 20 directly with Bu3SnH and AIBN produced the 2-deoxy compound 88 in 81% yield (Scheme 19).341 This reaction proceeds through a xylosyl radical,

### Table 10

<table>
<thead>
<tr>
<th>Position</th>
<th>Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>d-Lyxlxose</td>
</tr>
<tr>
<td>3</td>
<td>d-Ribose</td>
</tr>
<tr>
<td>4</td>
<td>l-Arabinose</td>
</tr>
</tbody>
</table>

### Scheme 17.

Reagents and conditions: (a) Zn/Ag-graphite, THF, −20 °C; (b) Bu3SnO, MeOH, 70%; (c) Zn/AgO, THF, −20 °C; (d) Bu3SnH, AIBN, toluene, 100 °C.

### Scheme 18.

Reagents and conditions: (a) Bu3SnO, MeOH, reflux; (b) PhOCSiCl, dioxane; (c) Ac2O, pyridine; (d) Bu3SnH, AIBN, toluene, 100 °C.
Microwave irradiation accelerated the 2,3-A ring-closing however, inversion at other positions Sureshan and co-workers utilized Sulfo-Performing a Mitsunobu in this way, lyxosides, ribosides, and ara-

protected methyl β-

of Et3N and reduction to form the corresponding riboside Martin periodinane, followed by epimerization at C3 by the action

generated the 4-oxo derivative utilized the esteric strain in trans

oxidation followed by reduction has been used to invert a hy-
droxyl group. Tsuda and coworkers reduced 3- and 4-oxo derivatives 75 and 76 (Fig. 9) with NaBH4, which in the case of 75 only gener-
ated the corresponding xylose whereas 76 formed a mixture of xylose and arabinoside 90 (Fig. 10). Catalytic hydrogenation of 75 over Pt in AcOH gave the riboside 89 as the major product. Manner et al. reduced isopropylidene-protected 2- and 4-oxo xylosides with NaBH4 and formed the corresponding lyxose and arabinoside as major products.

Although the epimerized xylose analogs are commercially available, it is sometimes more convenient to form these glycosides from the corresponding xylosides and several strategies are available for epimerization of the hydroxyl groups of xylose. When β-xylose was treated with molybdc acid in an aqueous solution, epimerization at C2 to form lyxose in equilibrium was observed. However, xylose was the major component. Microwave irradiation accelerated the reaction and also further shifted the equilibrium toward xylose. The Mitsunobu reaction can be used to invert the stereochemistry of alcohols and when performed with methyl β-D-xylopyranoside, epimerization occurred solely at C3 forming lyxoside whereas arabinoside as major products.

4.3. Epimerizations

Another method for epimerization is the transformation of the hydroxyl group into a better leaving group followed by an Sn2 reaction. Sulfonates are commonly used in such procedures where fully mesylated or tosylated xylosides have been epimerized selectively at C4 (Scheme 21). However, inversion at other positions has also been reported using partly protected xylosides. Sulfo-

formed by halogen abstraction, followed by a cis-migration of the acetate and finally the rearranged radical is trapped by tin hydride. When investigating the formation of branched furanosides formed by LiAlH4 reduction of monosulfonates, Tsuda et al. also obtained deoxyglycosides. Reacting 4-O-tosylated methyl α- and β-D-xylopyranosides with LiAlH4 produced the 4-deoxy products in 25% and 41%, respectively.

Starting from the corresponding L-xylopyranose would generate the enantiomer 104, which has been synthesized from methyl α-D-glucopyranoside 103. Compound 103 was regioselectively iodinated at C6, followed by benzoylation, sonication with zinc, and treatment with vinyl magnesium bromide before the ring-closing metathesis was performed that yielded (+)-conduritol F derivative 104.

4.4.2. 5-Thio-β-D-xylopyranosides

The synthesis of 5-thiopentoses often requires the displacement of the primary hydroxyl group at C5 of furanosides by a nucleophilic sulfur reagent. 5-Thio-β-D-xylopyranosides can be formed from fully acetylated 107, which was synthesized from d-xylose. In several steps, 18 was converted to 5-O-tosyl derivative 105, where the tosyl group was displaced by BzSK to form 106 (Scheme 24). This furanoside was then transformed to peracetylated 5-thio-β-D-xylopyranose 107 in 36% overall yield by treatment with NaOMe followed by acetylation and acetolysis. Alternatively, instead of introducing a tosyl group at C5, 108 was reacted with thionyl chloride and oxidized to a 3,5-O-cyclic sulfate that was opened by AcSK that generated 109 (Fig. 11). 5-Thio-β-D-xylopyranose 107 was obtained in an overall yield of 56% by following the same procedure as for 106.

Using another procedure, yet methodologically similar, Lalot et al. started from d-xyloono-1,4-lactone 110 that was converted to the C5 bromide 111 (Scheme 25).355 Displacement of the bromide with AcSK followed by reduction of the lactone functionality generated lactol 112, which formed 5-thio-β-D-xylopyranose 113 after saponification with NaOMe in 42% overall yield in just 5 steps from 110.

4.4.3. 5-Amino-5-deoxy-β-D-xylopyranosides

Strategies that are similar to those used for synthesis of 5-thio-xylosides have also been applied to the formation of 5-amino-5-deoxy-β-D-xylopyranoses, i.e. the use of xylofuranoses where the 5-OH is replaced in these cases with an amine, azide, or amide derivative. Garcia-Moreno et al. synthesized 5-deoxy-5-(3-phenylureido)-α-D-xylopyranose 116 and analogs starting from azide 114, which was obtained from tosyl derivative 105 (Scheme 26).356 Exchanging protective groups and performing an aza-Wittig-type reaction followed by the addition of water generated 115, which formed 116 upon reaction with NaOMe. Tosyl derivative 105 was also transformed to bromide 117 (Fig. 12) in high yield, which was treated with amines to generate e.g. 118, or with aminealcohols to yield e.g. 119 and 120.357,358 α-Anomer 119 is formed 20 times faster than β-anomer 120 when 117 is treated with 3-amine-1-propanol, although 120 is more stable and is the major product.

Martinez-Castro et al. synthesized alkoxyaminoxylopyranose 124, starting from mono-O-isopropylidene-D-glucofuranose 121 that formed 122 via oxidative degradation of the side chain (Scheme 27).359 This aldehyde was then reacted with O-benzylhydroxylamine to generate an oxime that was reduced to form 123, which yielded 5-amino-5-deoxy-α-D-xylopyranose 124 when treated with acidic resins.

4.5. C-xylosides

In C-xylosides, the exo-anomeric oxygen has been exchanged for a methylene group. Several methods have been developed starting from unprotected \( \text{d-xylose} \). Sowden et al. formed \( \text{\beta-d-xylopyranosyl nitromethane} \) in two steps from \( \text{d-xylose} \), via base-catalyzed addition of nitromethane (Scheme 28).\(^{360}\) When reacting \( \text{d-xylose} \) and 1,3-dimethyl barbituric acid, applying Knoevenagel conditions, sodium \( \text{\beta-d-xylopyranosylbarbiturate} \) was obtained,\(^{361}\) and when using pentane-2,4-dione under similar conditions, keto C-pyranoside was synthesized in 96 % yield.\(^{362}\) Compound 127 was also synthesized from D-xylose via the Horner–Wadsworth–Emmons reaction, using \( \beta \)-keto phosphonates, in 57 % yield (\( \alpha: \beta \) 7:93).\(^{363}\)

Xylosyl donors have also been used in the synthesis of C-xylosides. Peracetylated xylosyl bromide was converted to \( \text{128} \) by treatment with \( \text{Hg(CN)2} \), and reaction between trichloroacetimidate and silyl enol ethers, catalyzed by \( \text{ZnCl2} \), generated \( \text{129} \) and \( \text{130} \) as \( \alpha, \beta \)-mixtures (Scheme 29).\(^{364}\) Although controlling the stereochemistry in Lewis acid-promoted xylosylation reactions can be problematic, Shie and co-workers obtained \( \beta \)-selectivity exclusively in their \( \text{Sc(OTf)3} \)-promoted synthesis of di-C-\( \beta-d \)-xylopyranosolphloroacetophenone.\(^{365}\)

Depending on the restricted conformation of the substrate, Tamura et al. could control the stereoselectivity in \( \text{BF3·OEt2} \)-promoted C-glycosylation of xylosyl fluorides with allytrimethylsilane (Scheme 30), where \( \text{C1-restricted} \) \( \text{134} \) gave excellent \( \alpha \)-selectivity and \( \text{136} \) gave \( \beta \)-specificity.\(^{366}\)

Using the same strategy, high \( \alpha \)- and \( \beta \)-selectivity was obtained in a radical C-glycosylation reaction using 1-phenylseleno-D-xylopyranosides that was treated with allyltributyltin and AIBN followed by deprotection and benzoylation to form the desired perbenzoylated C-xyloside (Table 11).\(^{228}\)

In the glycosyl radical addition between peracetylated xyloside bromide and vinyl phosphonates, C-glycosyl phosphate ester was formed as an \( \alpha, \beta \)-mixture (Scheme 31).\(^{368}\)

Zhong et al. reported an oxidation–olefination–coupling sequence for installation of the C-glycosidic bond. Conversion of \( \delta \)-lactone into olefin, using Petasis’ reagent, was followed by coupling with the corresponding aryl triflate via a Suzuki–Miyaura cross-coupling reaction to form \( \text{141} \) (Scheme 32), exclusively with \( \beta \)-conformation.\(^{369}\) Using another approach, López et al. treated \( \delta \)-lactone with \( \text{BnLi} \) to form \( \text{143} \), which was converted to the monophenyl thioketal that was subsequently reduced to generate \( \text{144} \) in a total yield of 29% from \( \text{142} \) (Scheme 32).\(^{313}\)
Instead of starting from D-xylose, Ellervik and co-workers used a position inversion-strategy, i.e. position 1 of a glucoside becomes position 5 of a xyloside. Starting from 145, C-xyloside 146 was formed via anomeric bromination and reduction (Scheme 33). Next, the acetates were exchanged for benzyl groups followed by selective deprotection and oxidation of the primary alcohol to give aldehyde 147. This aldehyde was then coupled with 2-bromo-naphthalene with subsequent benzylic reduction of the formed hydroxyl group generating 148.

Table 11  
Radical C-allylation of conformationally restricted selenoxylosides \(^{228}\)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Product ratio (α:β)</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td>1:0.18</td>
<td>73%</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td>1:0.1</td>
<td>69%</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td>1:99</td>
<td>61%</td>
</tr>
<tr>
<td>4</td>
<td></td>
<td>1:99</td>
<td>26%</td>
</tr>
</tbody>
</table>

5. Conformational analysis  
D-Xylose exists as a pyranoid ring in water solution in a relative ratio of 4:6 between the α- and β-anomeric forms, respectively.\(^{360}\) Based on NMR \(^3J_HH\) coupling constants of the non-exchangeable protons, both forms populate the \(^1C_1\) chair conformation to a very large extent or exclusively. For example, \(^3J_{H3,H4} = 10.5\) Hz, in agreement with an antiperiplanar arrangement between the protons, and the values of \(^3J_{H4,H5} = 5.5\) Hz, \(^3J_{H3,H4} = 9.0\) Hz, and \(^3J_{H2,H3} = 9.4\) Hz are consistent with the \(^4C_1\) conformation. Deviations of these coupling constants due to structural or substituent effects can, separately or together, reveal a change in the conformational equilibrium toward e.g. the \(^1C_4\) chair conformation. In the case of methyl β-D-xylopyranoside 2 (Fig. 13), the use of \(^3J_{H1,H2} = 7.8\) Hz for the \(^4C_1\) conformation and deviations therefrom toward a lower value of the coupling constant will be diagnostic of a conformational change. If the aglycon is made larger and in particular more hydrophobic, compared to the methyl group in 2, such as a 2-naphthyl group as in 67, the solubility in water decreases significantly. Thus, methanol was chosen for NMR studies and subsequent conformational analysis of 67.\(^{86}\)

At this point, it is pertinent to consider not only the \(^1C_4\) chair as an alternative to the \(^4C_1\) conformation, but also the other 36 possible canonical conformations of a pyranose ring, namely six boat (B), six skew (S) or twistboat, twelve halfchair (H), and twelve envelope (E) conformations.\(^{370}\) Upon mono-O-methylation of 67, the \(^4C_1\) chair was still present to >90%, the remaining one being the \(^2S_0\) skew conformation populated to <10%.\(^{86}\) These results are in line with the detailed computational studies carried out on β-D-xylose showing that the lowest Gibbs free energy barrier is the one to the \(^2S_0\) skew conformation.\(^{271}\) Furthermore, interconversions between local energy minima between skew conformations for the itinerary along the equator of the sphere describing the Cremer–Pople puckering parameters occur more readily (lower barrier) than to the \(^2C_4\) and \(^1C_4\) chair conformations.

Derivatives of D-xylose were made early on both at the hydroxyl groups around the pyranose ring and at the anomeric position. Per-O-acylation of the D-xylopyranosyl halides facilitated investigation of conformational preferences in organic solvents, often chloroform-d, by 1H NMR spectroscopy. The conformational equilibria of tri-O-acetyl-α-D-xylopyranosyl bromide 20 (Fig. 14) and the corresponding chloride were at 31 °C shifted far toward the \(^3C_1\) chair form (>98%),\(^{372}\) However, the β-anomeric form of the chloride 22\(^{273}\) favored instead the \(^1C_4\) chair to ~80% and to an even larger...
A similar behavior was observed for the corresponding per-O-benzoylated chloro derivative 149, populating the $C_1$ chair to ~98%. A similar behavior was deduced for fluoride 150. For these types of structures, various contributions to the observed equilibria were noted. In particular, the importance of the anomic effect in orienting the halogen substituents of different sizes in 1,3-syn-diaxial orientations has to be considered, as well as the geometrical arrangements disfavoring or favoring dipolar interactions, as described by Jeans’ formula.

For the per-O-benzoylated β-d-xylopyranosyl halides in the crystalline state, the distortions from an ideal $C_1$ conformation toward the $C_4$ conformation were found to differing extent. For example, in tri-O-benzylid-β-d-xylopyranosyl bromide 151 (Fig. 14), the van der Waals repulsion between the 1-bromon and O3 atoms leads to a substantial flattening of the pyranose ring at C2 as deduced from the torsion angles O5–C1–C2–C3 and C1–C2–C3–C4 being ~37° and 38°, respectively, as well as the Br–C1–C2–O2 torsion of ~138° deviating substantially from an antiperiplanar orientation. Subsequently, the α- and β-anomeric forms of mono-, di-, and tri-O-acetylated methyl β-d-xylopyranosides were studied at 18 °C in chloroform-d. Irrespective of the substitution patterns of the α-linked methyl glycosides, the $C_4$ chair conformation was exclusively populated. In contrast, for all substitution combinations, the methyl β-d-xylopyranosides contained a component of the $C_3$ conformation, i.e., between 14% and 43%. The largest extent of this conformation was present for the derivatives that had a non-substituted hydroxyl group at position 3, e.g. methyl 2,4-di-O-acetyl-β-d-xylopyranoside 152, and it was suggested that the reason for this was due to an O1–H–O3 hydrogen bond.

Infrared (IR) spectroscopy was used to characterize xylose derivatives in carbon tetrachloride. In a later study, methyl or benzyl mono- and di-O-substituted β-d-xylopyranosides were substituted by methyl, benzyl, or acetyl groups. An IR spectrum of a free hydroxyl group of a secondary alcohol shows an absorption band at 3626 cm$^{-1}$, which represents a $V_{\text{max}}$ value. In the spectra of the partially substituted β-d-xylopyranosides, additional peaks are observed at lower wave numbers reporting on 5-membered rings with $\Delta\nu_{\text{O-H}} = 7–43$ cm$^{-1}$ ($\nu_1$) such as O2–H–O3 or O3–H–O4, 6-membered rings with $\Delta\nu_{\text{O-H}} = 71–106$ cm$^{-1}$ ($\nu_1$) with O1–H–O3 or O2–H–O4, and 7-membered rings with $\Delta\nu_{\text{O-H}} = 134–147$ cm$^{-1}$ ($\nu_1$) such as the band from C3 = O–H–O4 at 3491 cm$^{-1}$ in methyl 2,3-di-O-acetyl-β-d-xylopyranoside 153 (Fig. 14). When the substituent is present in position 3, the $C_4$ conformation is exclusively (methyl or benzyl group) or predominantly (acetyl group) populated. In contrast, when this position is unsubstituted and the other positions are substituted, the $C_4$ chair occurs to various extents. There are, however, some notable differences, e.g., with respect to the substituents, where methyl 2,4-di-O-acetyl-β-d-xylopyranoside 152 occurs in the $C_1$ chair to ~90%, and the acetylated compound methyl 2,4-di-O-methyl-β-d-xylopyranoside 154 exclusively populates the $C_4$ conformation. Furthermore, the aglycon also affects the conformation, where methyl xyloside 54 populates the $C_1$ conformation to ~50%, benzyl xyloside 155 results in exclusive population of the $C_1$ chair. Thus, seemingly subtle differences between structures may result in significant changes in the conformational equilibria between the $C_1$ and $C_4$ chair conformations of partially or fully substituted β-d-xylopyranosides.

For N-(2,3,4-tri-O-acetyl-α-d-xylopyranosyl)imidazole 156 in chloroform-d solution, a conformational equilibrium exists between the $C_4$ (35%) and $C_1$ (65%) chair forms. Upon protonation, the equilibrium with a cationic aglycon is shifted to ~95% of the $C_1$ conformation (Scheme 34).

For the corresponding per-O-benzoylated and per-O-acetylated analogs, substantial conformational shifts to the $C_4$ chair were also observed upon protonation. It was concluded that the $C_4$ conformation was favored due to stable antiparallel arrangements of dipoles of the ring substituents as well as a decrease of steric interactions. It may be noted that lyxopyranosyl derivative 157 (Fig. 15), having an axial substituent at C2 in the $C_4$ conformation (present to ~95%), was not conformationally affected upon protonation of the imidazole ring. For N-(β-d-xylopyranosyl)imidazole 158, which adopts the $C_1$ chair in D$_2$O solution, protonation to give the cationic form did not reveal any conformational changes from the $C_4$ ring form. However, α-anomer 159 exists in a dynamic conformational equilibrium ($C_4$: $C_1$ ~4–6), which is shifted to ~3:7 upon protonation. In organic solvents, the α-anomeric form shows increased population of the $C_1$ chair, which is further favored when the aglycon is protonated. The preferred conformations of the protonated forms were also investigated in the gas phase by infrared laser multiphoton dissociation (IRMPD) spectroscopy where the $\alpha$- and $\beta$-anomeric forms of the N-imidazole derivatives display the $C_1$ and $C_4$ conformations, respectively, thereby revealing the relative strengths of the internal non-covalent interactions. Additional spectroscopic and computational studies of α-xylose and xylopyranosides in the gas phase have revealed structural details such as arrangements of intramolecular hydrogen bond networks.

Tong-like derivatives are made by substituting methyl β-d-xylopyranoside by pyrenecarbonyl groups at O2 and O4. Compared to the methyl 2,4-di-O-pyrenecarbonyl-β-d-xylopyranoside 160, which in chloroform-d is populated to ~90% in the $C_1$ chair (Scheme 35), the 3-O-allyl derivative exists to ~80% in this inverted chair conformation. The large extent of this chair conformer, analyzed by $^1$H NMR spectroscopy, was proposed to be due to favorable stacking interactions between the two pyrenecarbonyl groups, in comparison to the 2,4-di-O-acetyl derivative having the $C_4$ conformation populated to ~40% in the same solvent, employing also NMR spectroscopy in the analysis. The presence of a hydrogen bond O1–H–O3 in the former pyrenecarbonyl derivative...
was supported by an absorption band at 3530 cm\(^{-1}\) in the IR spectrum. In the polar solvents methanol-\(d_4\) and DMSO-\(d_6\), the \(^{1}\text{C}_4\) conformation was less populated, to \(-60\%\) and \(-20\%\), respectively, i.e., the higher the dielectric constant of the solvent, the higher the content of the \(^{3}\text{C}_4\) conformation. These findings were confirmed in more recent computational studies on methyl 2,4-di-O-acetyl-\(^{1}\beta\)-d-xylopyranoside 152.\(^{397,388}\)

Modifications of the xylose residue with respect to substituents and stereochemistry around the pyranose ring have been made for a number of 2-naphthyl \(^{1}\beta\)-d-xylopyranosides.\(^{86,88,389,390}\) These include \(O\)-methyl derivatives, deoxygenations, fluorine bioisosteres, and \(C\)-alkylation with methyl or ethyl groups. The alterations performed by change of stereochemistry, compared to the \(^1\beta\)-d-xylopyranosyl configuration, result for the inversion of configuration at \(C2\) in the \(^1\beta\)-d-lyxo-configuration, at \(C3\) in the \(^1\beta\)-d-ribo-configuration, and at \(C4\) in the \(^1\alpha\)-l-arabinono-configuration. For the 2-, 3-, and 4-fluoro bioisosteres of 67, the \(^1\text{C}_4\) chair conformation is the major one in polar solvents, but the \(^2\text{S}_0\) skew conformation is populated to some extent (5\%–16\%). For the nonpolar solvents such as toluene and benzene, the \(^1\text{C}_4\) chair conformation is also populated significantly, close to 20\% in 67.\(^{389}\) Interestingly, it is not present in 2-fluoro-4-deoxy analog 161 (Fig. 16) in chloroform-\(d\), whereas in 3-fluoro-4-deoxy compound 162, it occurs to a small extent (5\%). Most notably, the \(^1\text{C}_4\) chair conformation is populated to \(-25\%\) in 4-fluoro-4-deoxy compound 163, and the presence of this conformation was further supported by a \(^{1}J_{\beta3H}\) coupling constant of 2.0 Hz. The latter finding corroborates the interpretation that 67 does indeed populate the \(^1\text{C}_4\) chair conformation was present to only a few percent. The 3-\(C\)-methyl-substituted derivatives show a complex dynamic equilibrium with at least three populated ring conformations and in methanol-\(d_4\) at 37 °C, the \(^3\text{C}_4\) conformation is more favored for the \(\beta\)-configured derivative 165, compared to the \(\alpha\)-xylo-configured derivative 166. Conversely, in chloroform-\(d\), the \(^1\text{C}_4\) chair format is favored to a larger extent for the latter compound compared to the former. Most interestingly, the \(^{13}J_{\text{CM}N} = \) 6.5 Hz, which is consistent with an antiperiplanar arrangement and consequently this conformation is stabilized by an intramolecular O1\(\rightarrow\)HO3 hydrogen bond besides O4\(\rightarrow\)HO2 (Fig. 17), the latter being analogous to the one deduced by the 4-fluoro-4-deoxy derivative 163.

Introduction of bulky silyl groups at positions 3 and 4 with hydroxyl groups oriented in a trans-relationship in glucopyranosides leads, due to mutual steric repulsion, to a conformational change from the \(^3\text{C}_4\) to the \(^1\text{C}_4\) chair conformation.\(^{296}\) In the synthesis of oligosaccharides, suitably protected phenyl 1-seleno- and 1-thio-\(^1\beta\)-d-xylopyranosides are valuable as donors and introduction of trisopropylsilyl (TIPS) groups give the corresponding trikis-\(O\)-silyl derivatives in high yield.\(^{292}\) These superaromated donors, 167 and 168 (Fig. 18), in the \(^3\text{C}_4\) conformation, are thus staged for efficient glycosylation reactions. The protective group strategy for radical \(\text{C}\)-glycosylation reactions of xylopyranoses\(^{228}\) utilized the fact that \(^1\text{C}_4\)-restricted substrates, such as BDA-protected 169, afforded the corresponding \(\alpha\)-products whereas the \(^1\text{C}_4\)-restricted substrates, such as the above described 1-seleno-TIPS derivative 167, selectively gave the \(\beta\)-products, as described in Section 4.4.4.

Conformational changes were observed for the \(\beta\)-xylopyranose residue in the synthesis of a saponin from Solanum indicum L., containing a trisaccharide moiety, viz., \(\beta\)-d-Xylp(1\(\rightarrow\)3)[\(\alpha\)-L-Rhap(1\(\rightarrow\)2)]-\(\beta\)-d-Galp, linked to diosgenin as the aglycon.\(^{303}\) The...
trichloracetimidate donor 38 (Fig. 18) was present in the \( ^4 \)C\(_1\) conformation, but upon glycosylation the resulting 2,3,4-tri-O-benzoyl-\( \beta \)-D-xylopyranosyl group changed to the \( ^4 \)C\(_1\) conformation, being part of the fully protected compound. Subsequent deprotection to the target saponin restored the \( ^4 \)C\(_1\) chair, underscoring the flexible character of xylose.

Oxidation of S-allyl 2,3,4,6-tetra-O-benzoyl-1-thio-\( \beta \)-D-xylopyranoside 169 (Fig. 19), which exists not only in the \( ^4 \)C\(_1\) chair conformation but also in the presumed \( ^4 \)C\(_1\) conformation, by mCPBA at \(-78^\circ\text{C}\) leads to the diastereomeric sulfoxides S-allyl 2,3,4,6-tetra-O-benzoyl-1-thio-\( \beta \)-D-xylopyranoside (R)s-oxide 170 and (S)s-oxide 171, both of which exist predominantly as the \( ^4 \)C\(_1\) chairs.\(^{235}\) However, oxidation of S-allyl 2,3,4,6-tetra-O-benzoyl-1-thio-\( \alpha \)-D-xylopyranoside 172 leads with high selectivity to the S-allyl 2,3,4,6-tetra-O-benzoyl-1-thio-\( \alpha \)-D-xylopyranoside (R)s-oxide 173. For a 1-thio-\( \alpha \)-D-xylopyranoside in the \( ^4 \)C\(_1\) chair conformation, and the exo-anomeric effect prevailing with the aglyconic group having a gauche relationship to the ring oxygen, the pro-\( \Lambda \) lone pair is exposed to the solvent and consequently this is where the oxidation takes place whereas the pro-S lone pair is shielded under the ring. The resulting (R)s-oxide will then have the S-O and C1-O5 dipoles aligned in a favorable antiparallel fashion. The ring conformation changes from the \( ^4 \)C\(_1\) to the \( ^4 \)C\(_1\) chair (choloroform-\( d \) at ambient temperature), where the conformational preferences of the exo-cyclic sulfoxide are governed by the presence or absence of steric interactions between the aglycon and lone pair on the sulfur atom, as well as the arrangement of dipoles.

Rates of hydrolysis and of glycosylation reactions were studied for xylose analogs based on a 2-oxacyclo[2.2.2]octane framework in which the ring conformation becomes locked by a \(-\text{CH}_2\text{CH}_2-\) bridge between the C2 and C5 atoms in alkyl xylopyranoside derivatives.\(^{194}\) Compound 174 (Fig. 20) adopts a \( ^4 \)B conformation and is hydrolyzed \(-10^4\) times faster than methyl \( \alpha \)-D-xylopyranoside, and compound 175 adopts a \( ^4 \)S conformation and is hydrolyzed \(-10^2\) times faster than methyl \( \beta \)-D-xylopyranoside. When locked, S-phenyl xyloviolides were used as donors in glycosylation reactions with methanol as acceptor, they reacted \(-10^2\) times faster than the conformationally flexible S-phenyl xyloviolides. The high reactivity of the locked analogs can be related to ground state destabilization in which the donor substrate is forced into a geometry closer to the transition state of the reaction, where the oxacarbenium ion should have the C5, O5, C1, and C2 atoms approximately coplanar.

### 6. Concluding remarks

Despite being an inexpensive and simple carbohydrate, \( \alpha \)-xylose poses special problems concerning the synthesis of analogs. The three hydroxyl groups are all equatorial in the \( ^4 \)C\(_1\) conformation and of similar reactivity. Furthermore, pentopyranosides often show a much higher conformational flexibility, compared to hexopyranosides such as glucose. In this review article we have summarized detailed procedures for the synthesis of xylopyranosyl donors, protective group chemistry, and modifications of xylose, as well as conformational analysis of xylose. With this information at hand it should be possible to efficiently synthesize xylose-containing compounds and analogs thereof to address important questions in both mammalian systems and plant biology.

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### References


Fig. 19. Xylosyl thiols and sulfoxides.

Fig. 20. Conformationally restricted xylosides.


