Chemistry of xylopyranosides

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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 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.

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 (Figure 1). Hydrogenation, or microbial fermentation,[1] 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.

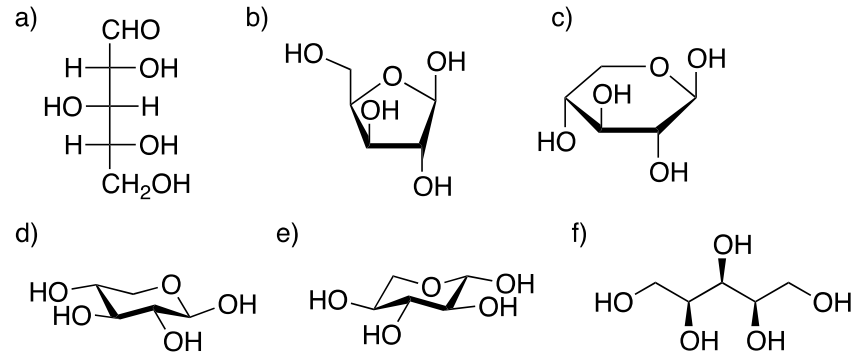


Figure 1. (a) D-xylose (58-86-6), open form. (b) β-D-xylofuranose, Haworth projection. (c) β-D-xylopyranose, Haworth projection. (d) β-D-xylopyranose, chair conformation. (e) β-L-xylopyranose, chair conformation. (f) Xylitol (87-99-0)

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.[2-3] 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 (Figure 2). Hardwoods contain up to 35% of *O*-acetyl-4-*O*-methyl-glucuronoxylan.[4] Acetylation occurs at C2 and C3 and it is worth mentioning that acetyl migration may occur in vitro.[5] In grasses and softwoods the xylan backbone is substituted with L-arabinofuranoside units in addition to methylglucuronic acid.[6] In grasses, arabinoses may be esterified by phenolic compounds (*p*-coumaric acid and ferulic acid). The xylan content in

grasses is similar or higher than that in hardwood, while softwood contains less (up to 15%).[6] The primary cell-walls of many plants contain xyloglucan, which has a β-glucan backbone that is substituted by xylose units,[3] 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.

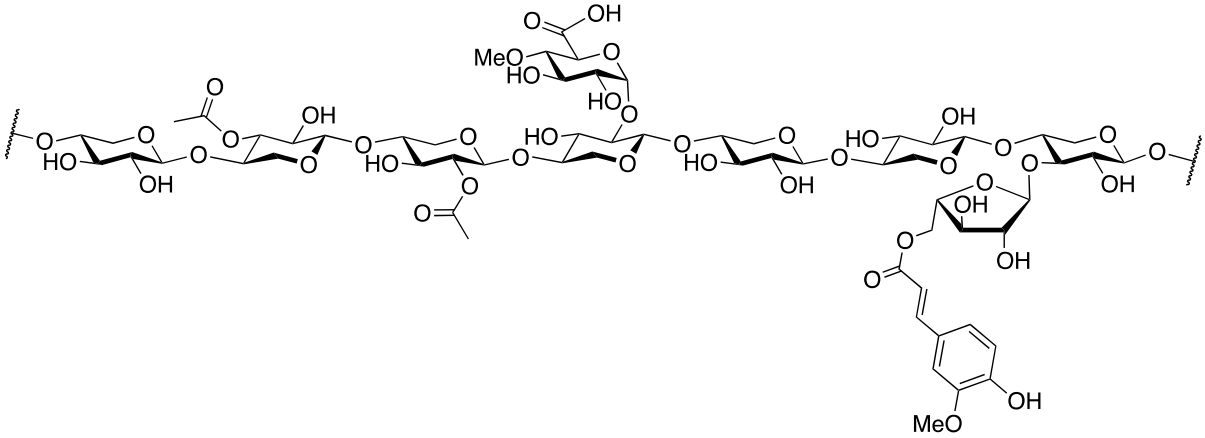


Figure 2. Part of a hypothetical plant xylan.

Xylans are synthesized in the Golgi-apparatus,[3, 7] and some of the glycosyl transferases (e.g. using 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.[7] These processes are, however, not well understood *in planta*. Recently, an Arabidopsis protein capable of catalyzing xylan acetylation was identified.[8]

1.1.2 Bioconversion 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.[9] 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 monosaccharides. Xylooligosaccharides produced from e.g. wheat, other cereals, or hardwood xylan, have potential applications as prebiotics since they can stimulate human gut Bifidobacteria.[10-13] Xylose is a valuable feedstock for production of biofuels, biochemicals, and also xylitol for which microbial production is being investigated as an alternative to the established chemical production route.[14-15] 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.[16]

The main xylan backbone hydrolyzing glycoside hydrolases are endo-1,4-β-xylanase that hydrolyzes xylosidic bonds internally in the backbone and exo-β-xylosidase that hydrolyzes terminal non-reducing xylose units.[17] Other glycoside hydrolases and esterases hydrolyzes the various substitutions.[18] Glycoside hydrolases are classified in families and clans based on protein sequence similarities (see further the CAZy database[1]).[19] 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.[17] Enzymes from both families catalyze hydrolysis by retaining the anomeric configuration.[20] Two main catalytic residues are involved, an acid/base and a nucleophile.

Retaining glycoside hydrolases may catalyze kinetically controlled transglycosylation,[21] which has been shown for several xylanases including the synthesis of tertiary alkyl β-xylosides.[22] 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 glycosynthase 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.[23] 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 fimi* xylanase.[24] Xylanolytic enzymes also have other applications in the food, feed, and pulp industries mainly as catalysts for xylan hydrolysis.[25-26]

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.[27] Some of these plants are pollinated by rock mice (*Aethomyces namaquensis*). This is surprising since xylose is considerably less sweet[28] than sucrose, and cannot be

[1] www.cazy.org

metabolized by non-ruminant animals, such as rodents. Instead these animals rely on bacteria for conversion of xylose.[29] Insects and birds show strong adversity towards xylose.[30]

In a screening of plants from the Amazon rain forest, an O3-substituted xyloside (**1**, Figure 3) was found in *Maieta guianensis*.[31]

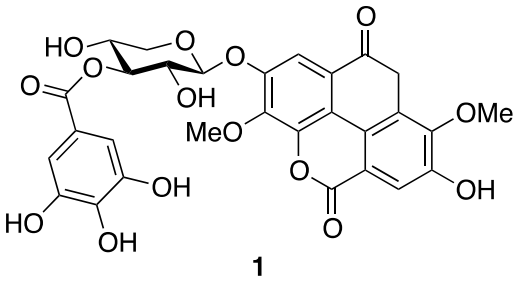


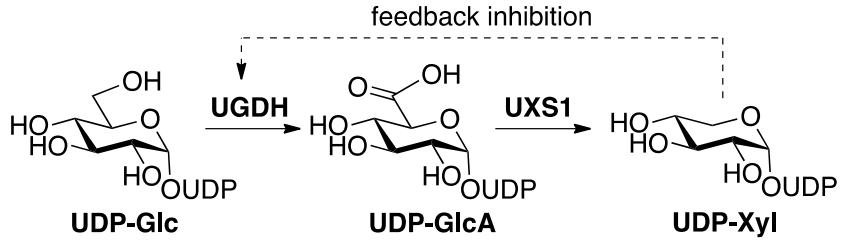
Figure 3. Structure of a natural xyloside from *Maieta guianensis*.

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

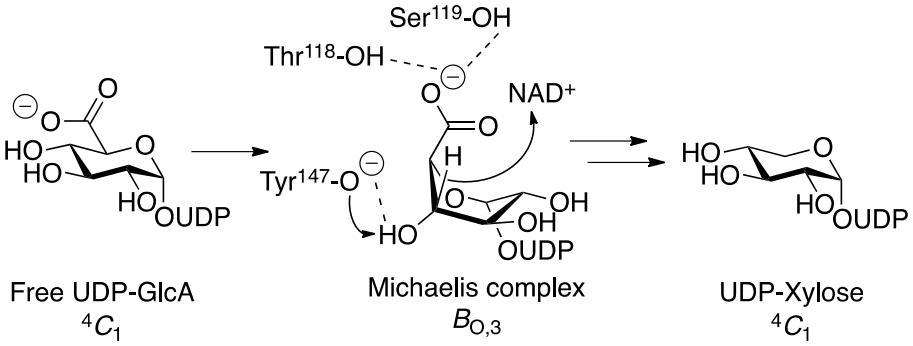
Mammalian cells use a rather small number of monosaccharidic building blocks, activated as nucleoside phosphates (NDP, often UDP) and only a few NDP-sugars are used in eukaryotic cells. Xylose is formed from UDP-glucose in two steps (Scheme 1). UDP-glucose is first oxidized by the enzyme UDP-glucose-6-dehydrogenase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



Scheme 1. Biosynthesis of UDP-xylose.

In 2012, Nidetzky and co-workers expressed, crystallized, and characterized a truncated version of human UXS1 (hUXS1) in *E. coli*.[32] A detailed catalytic mechanism was

proposed, using molecular dynamics simulations of the ternary Michaelis complex, mutagenesis experiments, and deuterium incorporation (Scheme 2). These experiments suggests that UDP-GlcA adopts the $B_{O,3}$ boat conformation. The $^{1}C_{4} \rightarrow B_{O,3}$ 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.[33]



Scheme 2. Proposed catalytic mechanism of hUXS1 in which NAD^{+} acts as an acceptor for the hydride transfer, resulting in oxidation at C4.

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 aminosugar and one uronic acid.[34] 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.[35-37] PG and GAG thus play important roles in cancer,[38] and mutations in genes encoding for enzymes involved in the biosynthesis of PG/GAG may result in genetic disorders,[39] such as the *Ehler-Danlos syndrome*.[40]

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.[41-42] After xylosylation, two galactose residues are added stepwise to the xylosylated protein by two different galactosyltransferases, GalT-I (β4GalT7[43]) and GalT-II (β3GalT6[44]). Finally, GlcA

is added by glucuronyltransferase 1 (GlcAT-I[45]). The tetrasaccharide linker (GlcA(β1-3)Gal(β1-3)Gal(β1-4)Xylβ, Figure 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.

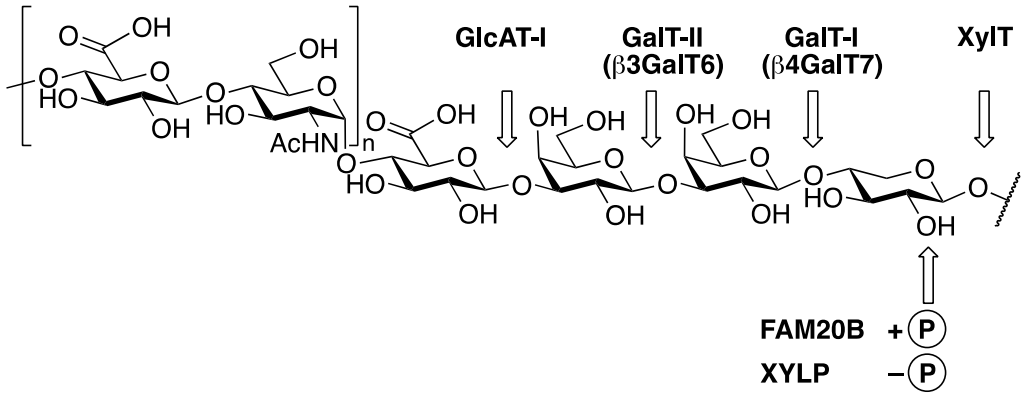


Figure 4. General structure for glycosaminoglycan (GAG) chains. The GAG chains are connected to the protein by a linker tetrasaccharide, GlcA(β1-3)Gal(β1-3)Gal(β1-4)Xylβ.

The GAG chain formation is regulated by modifications in various positions of the linker region.[46-49] For example, a transient phosphorylation at O2 of the xylose residue has been seen in CS/DS and HS biosynthesis[50] The enzyme FAM20B has been identified as a kinase that phosphorylate xylose in the linker,[51] while the dephosphorylation is performed by 2-phosphoxylose phosphatase (XYLP, Figure 4).[52-53] Today, all known enzymes involved in the biosynthesis of the tetrasaccharide linker have been cloned.[54]

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.[55] They showed that D-xylose, methyl β-D-xylopyranoside **2**, and L-serine β-D-xylopyranoside **3** served as acceptors for galactose transfer from UDP-Gal (Figure 5). A few years later, Okayama et al. made a similar study in which *p*-nitrophenyl β-D-xylopyranoside **4** was identified as a more efficient substrate.[56] 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.[57]

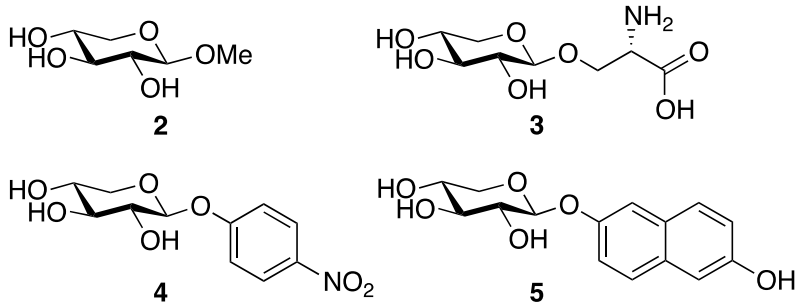


Figure 5. Examples of GAG primers.

A therapeutic strategy is to target key enzymes in the GAG biosynthesis.[58] Some β-D-xylosides serve as substrates for GalT-I/β4GalT7 and thereby initiate GAG chain formation, and at the same time prevent GAG elongation on core proteins forming PGs. Mani and co-workers have shown that treatment with 2-(6-hydroxynaphthyl) β-D-xylopyranoside **5** (Figure 5) selectively inhibit 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%.[59-60] 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.[61-62]

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,[57, 63-70] the distance between the carbohydrate and the aglycon,[63, 69, 71-72] and the anomeric configuration.[57, 72-78] Furthermore, *C*-xylosides,[66, 77, 79] *S*-xylosides,[57, 63, 66, 76-77, 80] *N*-xylosides,[66] phosphorylated xylosides,[81] and peracylated xylosides[82-83] have been synthesized. Moreover, analogs modified in the xylose residue have been investigated, such as epimers, ethers, ketones, halogens, amines, and deoxy compounds.[61-62, 84-88] Kuberan and co-workers have synthesized a large library of xylosides using click-chemistry, containing a triazole ring linked to the xylose residue.[69, 72, 89-90] Naphthyl β-L-xylopyranoside does not prime GAG chains.[91] In order to study cellular effects, several Chinese hamster ovary (CHO) cell lines, with defect GAG biosynthesis have been developed: pgsA-745 cells lack the enzyme XylT2, pgsA-761 cells are defective in β4GalT7, and pgsI-208 cells are deficient in UXS1.[92] In conclusion: very few modifications are tolerated in the sugar residue of β-D-xylosides to maintain GAG priming ability. However, some of these analogs function as efficient inhibitors of the GAG biosynthesis.

1.2.3 The Notch receptor

The cell surface receptor Notch is vital for intercellular signaling during development and adult homeostasis. Dysregulated Notch signaling can lead to developmental disorders and has been linked to cancer, which has initiated a strong interest in Notch regulation as a therapeutic target.[93] The Notch receptor is a membrane protein with 29-36 epidermal growth factor (EGF) domains located in the extracellular parts. These EGF repeats are often *O*-glycosylated with fucose, glucose, or *N*-acetylglucosamine glycans. The *O*-glucose sites on EGF10-15 seem to positively regulate Notch signaling. Interestingly these *O*-glucose residues can be xylosylated twice to form a Xyl(α1-3)Xyl(α1-3)Glc trisaccharide (Figure 6).[94] The first xylose residue is added by glucoside xylosyltransferase (GXYLT1 and GXYLT2)[95] and the second one by xyloside xylosyltransferase (XXYLT1).[96] The xylosylation seems to down-regulate Notch signaling.[97]

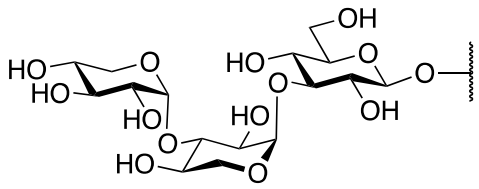
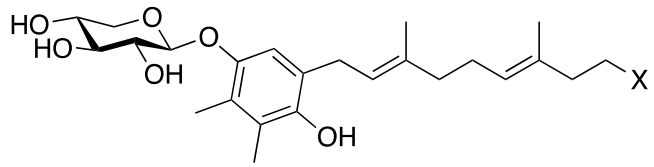


Figure 6. Xyl(α1-3)Xyl(α1-3)Glc, the trisaccharide glycan decorating mammalian Notch.

1.3 Xylosides of other origin

Some allergic reactions are induced by the binding of IgE antibodies to certain glycoproteins. The allergenicity is often caused by typical nonmammalian structures, which incorporate, for example, (α1-3)-fucosylation or (β1-2)-xylosylation.[98] Pollen exposure can lead to development of these carbohydrate-recognizing IgE, which can cross-react with glycoproteins from other plants, molluscs, and insects, all carrying (β1-2)-xylosylated glycans.[99]

Female gametes of the green flagellate Chlamydomonas strains use the xylosylated pheromones lurlenic acid **6** and lurlenol **7** (Figure 7) to attract male gametes.[100-101]



6 X = COOH
7 X = CH_2OH

Figure 7. Lurlenic acid **6** and lurlenol **7**.

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 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 anomeric carbon to form glycosyl donors that are suitable for glycosylation reactions. The formation of a xylosidic linkage can occur either through an S_N2 type mechanism, usually under basic conditions with xylosyl halides, or through an S_N1 type mechanism under acidic conditions. The stereochemical outcome of Lewis acid-promoted xylosylations is directed by several factors, such as the anomeric 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 oxocarbenium ion to form a cyclic acyloxonium ion. The acyloxonium ion is subsequently opened by the acceptor in an S_N2 manner which results in a 1,2-*trans* xylosidic bond, hence β-D-xylosides are fairly easy to synthesize by standard methods, whereas α-D-xylosides can be formed by anomerization of the kinetic β-products. Below, syntheses of the most common xylosyl donors are described with examples of how they are used in glycosylation reactions.

2.1 Unprotected D-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 anomeric hydroxyl group.[102-103] As an example, benzyl α-D-xylopyranoside can be produced from D-xylose and HCl-saturated benzyl alcohol in 31% (Table 1, Entry 1).[104] Modified Fischer glycosylation procedures have been used in the synthesis of xylosides, e.g. methyl and allyl D-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 *p*TSA was employed (Entries 6-8).[105] Microwave-assisted glycosylation reactions catalyzed by Montmorillonite K10, an inexpensive, stable, and reusable catalyst, have been reported.[106] 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.[107] 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).

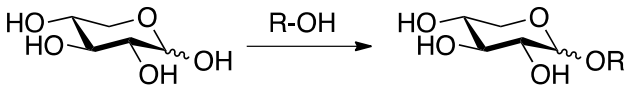
Methods to synthesize *O*-aryl xylosides have been developed and the first example of stereoselective *O*-aryl glycosylation using unprotected xylose was reported in 1994, where D-xylose was reacted with *N*,*N*'-thionyldiimidazole ($SO(Im)_2$) and phenoxide ions in a one-pot procedure (Entry 11).[108] In this protocol, the phenoxide ion act 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 $NaHCO_3$ solution of H_2O-EtOH (Entry 12).[109]

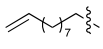
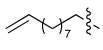
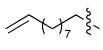
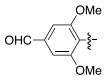
In 2004, Krausz and co-workers reported the use of Lewis acids in glycosylation reactions with unprotected carbohydrates, including D-xylose, and nucleosides where $FeCl_3$ in acetonitrile proved to be the most efficient catalyst, generating the product in an 1.8:1 α,β-mixture (Entry 13).[110] $Sc(OTf)_3$ 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-

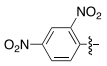
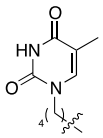
methylimidazolium trifluoromethansulfonate (Entry 14).[111] The fact that the reaction goes through an oxocarbenium ion that could be stabilized by the ionic liquid, could explain the observed increase in yields, which were more pronounced for other unprotected monosaccharides. The use of Brønsted acid ionic liquid (BAIL) as catalyst in glycosylation reactions without any Lewis acid catalyst has been reported quite recently, where aminotetrazoles and alkyltetrazoles were evaluated.[112] 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(O*t*Bu)$_4$ and D-mandelic acid in the presence of LiBr.[113] 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 PPh_3 and CBr_4 as well as $LiClO_4$ as an additive in acetonitrile, generated *iso*-propyl D-xylopyranoside in 99% yield with low stereoselectivity (Entry 17).[114]

Table 1. Glycosylation of unprotected D-xylose.



Entry	Reagents	R	Solvent	Yield	Ratio (α:β)	Ref
1	HCl	Bn		31% α[a]	-	[104]
2	Amberlite IRA-120	Me		49%[b]	1:2	[115]
3	Dowex-50 X-8H$^+$	Me		76%	1:0.81	[116]
4	Dowex-50W H$^+$	Allyl		46%[c]	1:0.5	[117]
5	HCl	Allyl		41% α[a]	-	[118]
6	Amberlite IR 120			45%	1:0.67	[105]
7	AcCl			71%	1:0.43	[105]
8	*p*TSA		THF	81%	1:1.3	[105]
9	Montmorillonite K-10	Me		87%	1:0.07	[106]
10	Biomass carbonaceous solid acid	Allyl		90%	1:0.43	[107]
11	LiH, SO(Im)$_2$		DMF	50%	0:1	[108]

12	$NaHCO_3$		H_2O/EtOH	20%	0:1	[109]
13	$FeCl_3$		MeCN	20%[d]	1:0.56	[110]
14	$Sc(OTf)_3$	*n*-C_8H_{17}	[BMIM][OTf]	78%	1:0.52	[111]
15		*n*-C_8H_{17}	H_2O, BAIL	72%[e]	1:0.52	[112]
16	D-Mandelic acid, $Ti(OtBu)_4$, LiBr	*i*Pr	MeCN	66%[e]	1:2.2	[113]
17	PPh_3, CBr_4, $LiClO_4$	*i*Pr	MeCN	99%	1:0.82	[114]

[a]Only anomer isolated after recrystallization. [b]Pure β-anomer obtained in 26% yield after recrystallization. [c]Yield after acetylation/deacetylation. [d]Contains 5% furanosides. [e]Contains 6% furanosides.

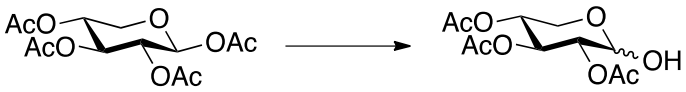
Transglycosylation reactions, catalyzed by enzymes, have been investigated as well as reverse hydrolysis. Transxylosylation with methyl β-D-xylopyranoside and a variety of alcohols using *Trichoderma reesei* β-D-xylosidase showed that primary alcohols are good substrates, secondary alcohols can be used, whereas tertiary alcohols proved to be poor substrates.[119] All reactions retained the β-configuration. Reverse hydrolysis, where D-xylose 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 transxylosylation 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-xylooligosaccharides using *p*-nitrophenyl β-D-xylopyranoside as both donor and acceptor.[120]

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).[121-124] Similar methods have been used on oligoxylosides such as peracetylated xylobiose and xylotriose, using benzylamine[125]

or Hünig's base/NH_4OAc,[126] forming the desired xyloside with free anomeric 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).[127-129] 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).[130] Similarly, $(NH_4)_2CO_3$ in DMF gave anomeric deprotection in 63% (Entry 9),[131] whereas treatment with alumina gave 55% conversion to the 1-OH product (Entry 10).[132] A number of acidic methods have also been used, where Lewis acidic lanthanide triflates gave anomeric deacetylation in very good yields (Entries 11-14).[133] Regioselective deacetylation using $HClO_4$-SiO_2[134] and copper(II) acetate dihydrate[135] removed the anomeric acetate in excellent and moderate yield, respectively (Entries 15 and 16).

Table 2. Selective anomeric deacetylation of peracetylated D-xylose.



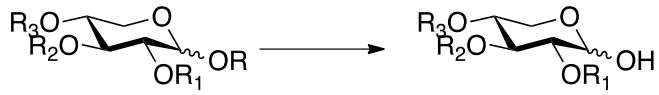
Entry	Reagents	Solvent	Yield	Ref
1	Etylenediamine, AcOH	THF	>95% [a]	121
2	Hydrazine acetate	DMF	81%	122
3	Imidazole	MeOH	72%	123
4	Polymer-bound $BnNH_2$	THF	96%	124
5	$(Bu_3Sn)_2O$	Toluene	80%	127
6	Bu_3SnOMe	DCE	76%	128
7	Bu_2SnO	MeOH	58%	129
8	NaOMe	THF	70% [b]	130
9	$(NH_4)_2CO_3$	DMF	63%	131
10	Al_2O_3	MeOH	55% [c]	132
11	$Yb(OTf)_3$	MeOH	85%	133
12	$Eu(OTf)_3$	MeOH	81%	133
13	$Sm(OTf)_3$	MeOH	85%	133
14	$Nb(OTf)_3$	MeOH	81%	133

15	$HClO_4$-SiO_2	MeCN	90%	[134]
16	$Cu(OAc)_2 \cdot 2H_2O$	MeOH/H_2O	58%	[135]

[a]Estimated by TLC analysis. [b]14% of the starting material was recovered. [c]Conversion.

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).[104, 136-137] Per-*O*-methylated D-xylose can be treated with TFA (aq.) or 2M HCl-dioxane to selectively remove the anomeric *O*-methyl in moderate yields (Entries 4 and 5).[138-139] Hydrolysis of the anomeric methyl group in the presence of benzyl protective groups using 1M H_2SO_4 in dioxane-H_2O generated the corresponding hemiacetal in 71%, starting from D-xylose (Entry 6).[140] Further more, permethacrylated xylose was selectively deprotected at the anomeric position in 36% yield by treatment with benzylamine in THF (Entry 7).[141] Selective removal of an anomeric allyl group, in the presence of *p*-methoxybenzyl (PMB) protective groups, using catalytic amount of $PdCl_2$ in MeOH generated the desired product in excellent yield (Entry 8).[118] 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 $TiCl_4$ in CH_2Cl_2 to form the intermediate anomeric chloride that was hydrolyzed during silica chromatography.[142]

Table 3. Regioselective removal of anomeric protective group.



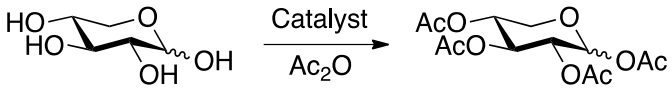
Entry	R	R_1	R_2	R_3	Reagents	Solvent	Yield	Ref
1	α-Bn	Bn	Bn	Bn	HCl	MeCN	85%	[136]
2	α-Bn	Allyl	Allyl	Bn	HCl	AcOH	91%	[137]
3	α-Bn	MBz	TES	TES	Pd/C, H_2, Et_3N	EtOAc	76%	[104]
4	Me	Me	Me	Me	TFA	H_2O	65%	[138]
5	Me	Me	Me	Me	2M HCl	Dioxane	60%[a]	[139]
6	Me	Bn	Bn	Bn	1M H_2SO_4	Dioxane H_2O	71%[a]	[140]
7	α-Acr	Acr	Acr	Acr	$BnNH_2$	THF	36%	[141]
8	α-All	PMB	PMB	PMB	$PdCl_2$	MeOH	90%	[118]

[a]Yield over several steps from D-xylose.

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 Ac_2O 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),[143-146] whereas reaction with Py or DMAP/Py formed the α-anomer in excellent yields (Entries 3 and 4).[147-148] Lewis acids such as $FeCl_3$,[149] Montmorillonite K-10,[150] H-beta zeolite,[151] I_2,[152] $Ce(OTf)_3$,[153] $La(OTf)_3$,[154] $Sm(OTf)_3$,[155] $Fe_2(SO_4)_3{\cdot}xH_2O$,[156] H_2SO_4-SiO_2,[157] sulfonic acid functionalized nano γ-Al_2O_3,[158] and $InCl_3$ under microwave irradiation in acetonitrile,[159] in combination with Ac_2O (Entries 5-15) formed peracetylated xylose as α,β-mixtures where the α-anomer was the major product.

Table 4. Acetylation of D-xylose by Ac_2O and different catalysts.



Entry	Catalyst	Yield	Ratio (α:β)	Ref
1	NaOAc, 100 °C	97%	0:1	145
2	KOAc, 140 °C	50%	1:33	146
3	Py	95%	1:0	147
4	DMAP, Py	94%	1:0	148
5	$FeCl_3$	77%	1:0.26	149
6	Montmorillonite K-10	76%[a]	1:0.53	150
7	H-beta zeolite	74%[a]	1:0.31	151
8	I_2	93%	1:0.25	152
9	$Ce(OTf)_3$	93%	1:0.25	153
10	$La(OTf)_3$	98%	1:0.20	154
11	$Sm(OTf)_3$	98%	1:0.20	155
12	$Fe_2(SO_4)_3{\cdot}xH_2O$	91%	1:0.17	156
13	H_2SO_4-SiO_2	96%	1:0.71	157
14	SO_3H functionalized nano γ-Al_2O_3, 50 °C	95%	1:0.30	158

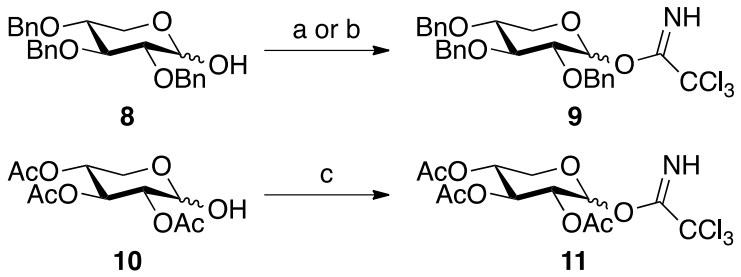
15	$InCl_3$ in MeCN, MW (720 W)	95%	1:0.11	[159]

[a]Not isolated, determined by ^1H NMR.

Peracetylated β-D-xylose is a cheap and effective donor that is usually activated with $BF_3{\cdot}OEt_2$, generating β-D-xylosides in good stereoselectivity and yields, sometimes at low temperature.[160-161] Other Lewis acids, e.g. TMSOTf[162-163] and $Sc(OTf)_3$[164], 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. In order to install the trichloroacetimidate, the anomeric position needs to be unprotected. In 1984, Schmidt and co-workers synthesized xylosyl trichloroacetimidate **9** by treating 2,3,4-tri-*O*-benzyl-D-xylopyranose **8** with trichloroacetonitrile and NaH (Scheme 3), generating a 6:1 α,β-mixture.[165] A slight modification of this procedure is to perform the reaction in CH_2Cl_2.[139] The kinetic product, i.e. the β-anomer, is formed if a weak base such as K_2CO_3 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.[104, 167]



8 **9** **10** **11**

Scheme 3. Reagents and conditions: (a) Cl_3CCN, NaH, 53% **9α**, 9% **9β**;[165] (b) Cl_3CCN, K_2CO_3, CH_2Cl_2, 55% **9β**;[166] (c) Cl_3CCN, DBU, DCE, 82% **11α**, 16% **11β**.[167]

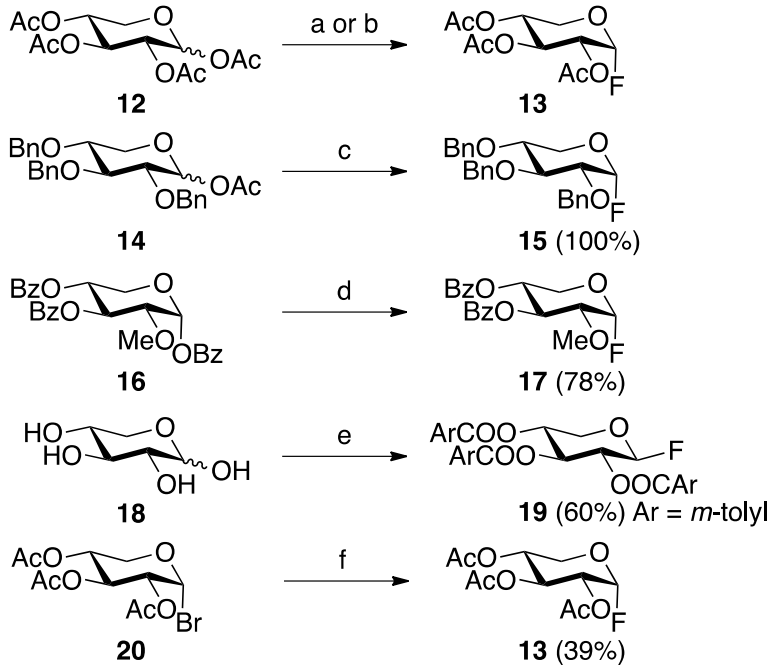
The trichloroacetimidate method usually gives excellent yields for β-xylosides. In the glycosylation reaction, $BF_3{\cdot}Et_2O$ is commonly used in the presence of 4 Å molecular sieves in CH_2Cl_2, often at low temperatures, e.g. in oligosaccharide synthesis.[168-169] TMSOTf in Et_2O, at low temperatures, 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-*trans*glycosides, such as β-xylosides. One major problem with the Koenigs-Knorr method is the environmentally malign use of toxic metal salts such as Ag_2CO_3, Ag_2O, AgOTf, $HgBr_2$, or $HgCN_2$. 1,2-*Cis*glycosides, 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 tetraalkylammonium 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 KHF_2, to a receiving flask containing the peracetylated xyloside, 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 anomer.[172] Fluoride **13** has also been formed from **12** by using HF in pyridine, in 92% yield.[173] In a one-pot reaction, methyl β-D-xylopyranoside was converted to the peracetylated xylosyl fluoride **13** in 98% yield using HF and Ac_2O in a special HF solvolysis apparatus.[174-175] 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).[176-177] In a halogen exchange reaction, an anomeric bromide was exchanged for a fluoride using triethylamine trihydrofluoride in CCl_4 generating **13** in 39% yield.[178]



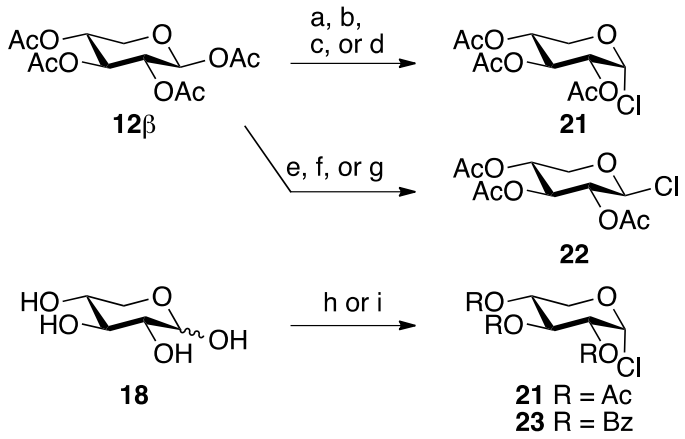
Scheme 4. Reagents and conditions: (a) HF (l), 34%;[170] (b) 70% HF-Py, -20 °C, 92%;[173] (c) HF (l), CH_2Cl_2, -70 °C;[171] (d) HF (l);[172] (e) DFMBA;[176-177] (f) $Et_3N{\cdot}3HF$, CCl_4, reflux.[178]

Xylosyl fluorides can be used in glycosylation reactions, catalyzed by $BF_3{\cdot}Et_2O$. As an example, **15** reacts with alcohols and silyl ethers, where Et_3N needs to be added to trap HF.[171] Disaccharides have been synthesized in good to excellent yields, although with poor stereoselectivity, by using **15** as donor in the presence of $SnCl_2$, $AgClO_4$, and 4 Å molecular sieves.[179] An anomeric mixture of **15** showed, on the other hand, good α-selectivity in the presence of Cp_2ZrCl_2, $AgClO_4$, 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 using $SOCl_2$ in combination with $ZnCl_2$,[184] BiOCl,[185] or $SnCl_4$[186] (Scheme 5). Using $TiCl_4$ in $CHCl_3$ formed **21** from **12β**,[187] a method that is also suitable for 1,2,3,4-tetra-*O*-levulinoyl-α-D-xylopyranose.[188] Interestingly, when $SOCl_2$ is used in the presence of AcOH in CH_2Cl_2, the corresponding β-anomer **22** is produced in 82% yield.[189] In

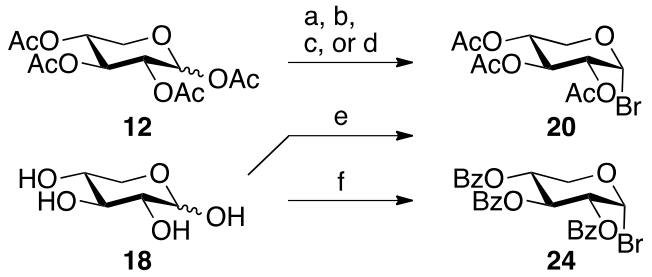
addition, PCl_5 in combination with $BF_3{\cdot}Et_2O$ in CH_2Cl_2 or PCl_5 in acetonitrile yielded **22** in excellent yields.[190] Unprotected D-xylose can be converted in a one-pot reaction to **21** and **23** in 75% by reaction with $In(OTf)_3$ and AcCl or BzCl.[191] Xylosyl chlorides can react with alcohols in a Koenigs-Knorr glycosylation reaction.[188]



Scheme 5. Reagents and conditions: (a) $ZnCl_2$, $SOCl_2$, benzene, 81%;[184] (b) BiOCl, $SOCl_2$, CH_2Cl_2, 92%;[185] (c) $SnCl_4$, $SOCl_2$, CH_2Cl_2, 100%;[186] (d) $TiCl_4$, $CHCl_3$, 80%;[187] (e) $SOCl_2$, AcOH, 82%;[189] (f) PCl_5, $BF_3{\cdot}Et_2O$, CH_2Cl_2, 88%;[190] (g) PCl_5, MeCN, 88%;[190] (h) $In(OTf)_3$, AcCl, 75% **21**;[191] (i) $In(OTf)_3$, BzCl, 75% **23**.[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,[144, 192] Et_2O,[193] or CH_2Cl_2,[162] or by treatment with HBr-AcOH in CH_2Cl_2[194] (Scheme 6). The latter method has proved to work well on perpivaloylated[195] and perlevulinated[188] 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 CH_2Cl_2 to yield the perbenzylated D-xylopyranosyl bromide.[196] Bromide **20** can also be synthesized from D-xylose **18** and HBr in Ac_2O (Scheme 6),[197] 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 benzoyl bromide.[191]

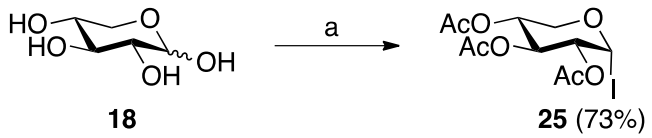


Scheme 6. Reagents and conditions: (a) **12α** or **12β**, HBr, AcOH, 77% from **12α**, 81% from **12β**;[144] (b) **12α**, HBr, Et_2O;[193] (c) **12β**, HBr, CH_2Cl_2;[162] (d) **12**, HBr, AcOH, CH_2Cl_2;[194] (e) HBr, Ac_2O;[197] (f) $In(OTf)_3$, BzBr, 60%.[191]

The Koenigs-Knorr and Lemieux protocols are commonly used for glycosylation reactions with bromide donors. Michael glycosylation, which is an aromatic O-glycosylation between glycosyl halides and aryl alcohols under basic conditions with inversion at the anomeric center, can be performed using **20**[198] and this reaction can also be performed under phase-transfer conditions with Bu_4NBr as catalyst.[161, 199] Xylosyl bromides **20** and **24** have been used in the formation of β-D-xylopyranosyl esters in moderate to excellent yields by reaction with a carboxylic acid in the presence of base.[200-202] Glycosylation reactions with **20** and **24** have also been reported by treatment with I_2, DDQ, and 4 Å molecular sieves,[203] or by heating **20** with the acceptor in DMF.[204]

2.5.4 Xylosyl iodides

In a one-pot reaction, **18** was converted to 2,3,4-tri-*O*-acetyl-α-D-xylopyranosyl iodide **25** in 73% yield using Ac_2O with I_2 as catalyst followed by an excess of I_2 and hexamethyldisilazane (HMDS).[152] The intermediate xylosyl iodide, activated by TMSI in CH_2Cl_2 in the presence of base, has been used in the synthesis of β-*O*-(9-fluorenyl)-D-xylopyranose.[205]

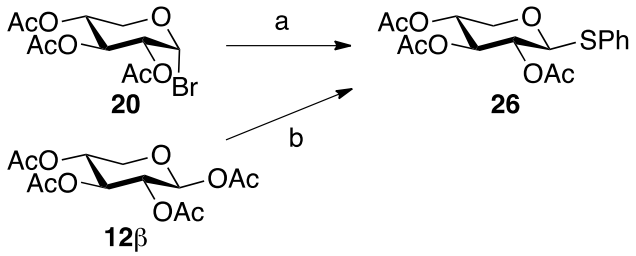


Scheme 7. Reagents and conditions: (a) Ac_2O, I_2 (cat), then I_2, HMDS.[152]

2.6 Thioxylosides

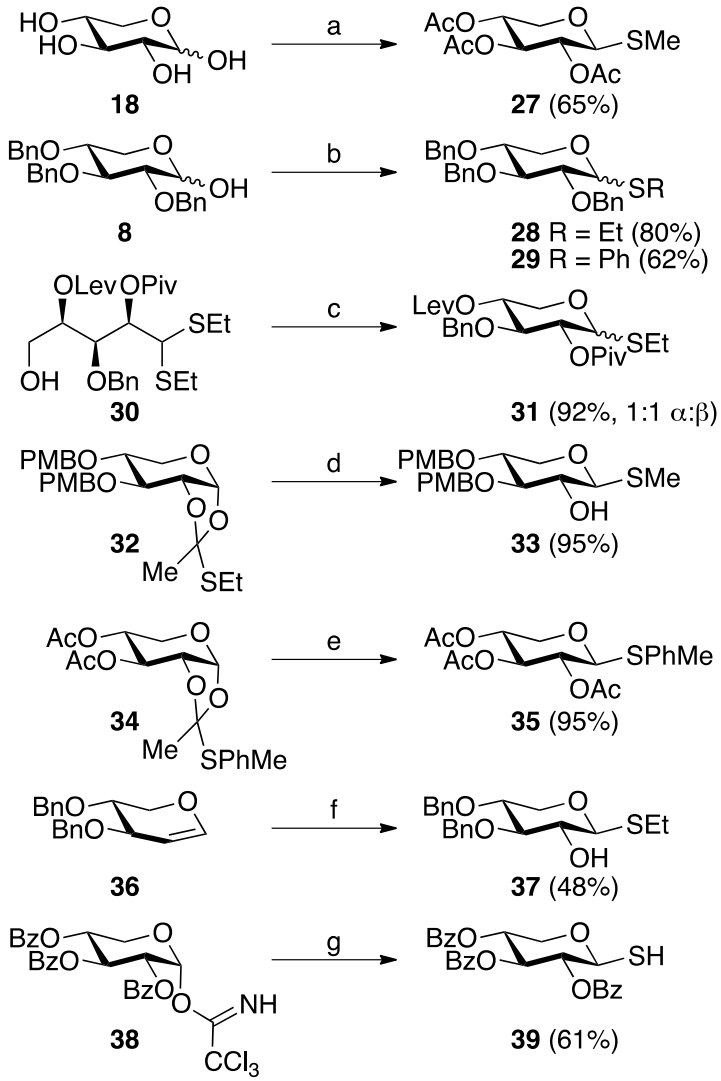
Thioglycosides are relatively stable carbohydrate derivatives, which make them suitable when the remaining hydroxyl groups need to be modified or protected. Thioxylosides are usually

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 generated and directly treated with potassium thiophenolate (Scheme 8).[206] 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.[207] Several methods for the synthesis of 1-thio-β-xylosides 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 $CHCl_3$ using $BF_3{\cdot}OEt_2$ as catalyst (Scheme 8).[208] The method works well with other Lewis acids, such as $ZrCl_4$,[209-210] $SnCl_4$,[211] $FeCl_3$,[212] MoO_2Cl_2,[213] or FeI_3[214]. Thioxylosides can also be synthesized from an acetyl donor and TMSSMe with $BF_3{\cdot}OEt_2$[215] or TMSOTf[216] as catalysts in moderate yields, or TMSSPh in combination with $SnCl_4$[217]. In addition, Bu_3SnSMe in DCE has been used in the presence of $SnCl_4$ to give desired product as a 1:1.7 α,β-mixture in 90% yield.[218]



Scheme 8. Reagents and conditions: (a) PhSH, KOH, $CHCl_3$, 80%;[206] (b) PhSH, $BF_3{\cdot}OEt_2$, $CHCl_3$, 56%.[208]

Thioxyloside **27** has been synthesized in a one-pot procedure from D-xylose in 65% yield via iodide **25** that was reacted with MeSSMe (Scheme 9).[152] It is also possible to synthesize thioxylosides from xylopyranoses such as **8** by treatment with a thiol and concentrated HCl over 3 days, which goes via an open dithioacetal.[219] Dithioacetals can be ring-closed to form a thioxyloside by reaction with NIS and TFA, usually as an α,β-mixture.[220] Thio-orthoesters, such as **32** and **34**, has also been used to give thioxylosides with good stereoselectivity by treatment with $ZnCl_2$[221] or deactivated Raney nickel[222]. Another method is to use xylal that can be oxidized to form an epoxide, and subsequently opened by EtSH in the presence of catalytic amount of TFAA.[223] α-D-Xylopyranosyl trichloroacetimidates can be converted to the corresponding β-thioxylopyranose by the action of $(TMS)_2S$ and TMSOTf in CH_2Cl_2.[224]



Scheme 9. Reagents and conditions: (a) Ac_2O, I_2 (cat), then I_2, HMDS, then MeSSMe;[152] (b) RSH, HCl, benzene;[219] (c) NIS, TFA, CH_2Cl_2, 0 °C;[220] (d) $ZnCl_2$, CH_2Cl_2, -60 °C, then NaOMe, MeOH;[221] (e) Deactivated Raney nickel, toluene;[222] (f) DMDO, CH_2Cl_2, 0 °C, then EtSH, TFAA, CH_2Cl_2, 0 °C;[223] (g) $(TMS)_2S$, TMSOTf, CH_2Cl_2, 0 °C.[224]

Thioxyloside donors have been used, e.g. in the synthesis of disaccharides, by treatment with AgOTf and PhSeCl[215] or with MeOTf[218] giving good β-selectivity. Glycosylation reactions with thioxylosides can also be promoted by NBS in acetonitrile,[225] or by NIS and TMSOTf in CH_2Cl_2/acetonitrile.[226]

In addition to thioxylosides, a few selenoxyloside have been synthesized using similar methods, e.g. in Nicolaou's total synthesis of everninomicin,[227] and in studies of anomeric radical reactions by Abe et al.[228]

2.7 Miscellaneous

α-D-Xylopyranosyl phosphinic acid **40** (Figure 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*-diethylphosphoramidite in the presence of 1*H*-tetrazole in CH_2Cl_2.[118] **41** was directly reacted with an alcohol in a $ZnCl_2/AgClO_4$-promoted glycosylation to give the products as α,β-mixtures in 70-76%. Phosphorylation of D-xylose using $Na_3P_3O_9{\cdot}6H_2O$ 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** (Figure 8) in high yields by treatment with PPh_3, NCS, and LiN_3 in DMF,[231] or with $SO(Im)_2$ and LiN_3 in DMF.[232] This compound can also be synthesized from peracetylated D-xylose, $TMSN_3$, and $SnCl_4$ in CH_2Cl_2, followed by deacetylation using standard Zemplén conditions,[69] or from xylosyl bromide **20** using NaN_3 in acetonitrile.[233] Xylosyl azides can be used in, e.g. 1,3-dipolar cycloadditions.

Thioxylosides have been oxidized by KF/*m*CPBA or *m*CPBA to give the corresponding sulfoxides, such as **44**, in excellent yield. The sulfoxides can be used as donors in Kahne's glycosylation reaction.[234-235]

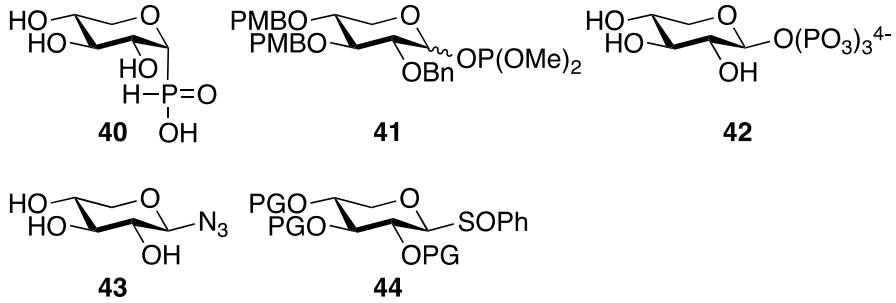


Figure 8. Various xylosides. PG = protective group.

2.8 Concluding remarks

When it comes to choosing a donor for a specific glycosylation reaction, several aspects needs 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 is 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 generates *trans*-xylosidic linkages due to

neighboring group participation. Peracetylated 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, trichloroacetimidate donors 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.

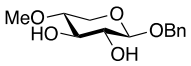
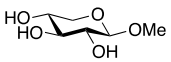
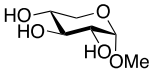
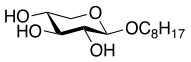
3.1 Esters

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).[236] The best selectivity for 2-OH was seen with Ac_2O and NaOAc whereas Ac_2O and $HClO_4$ gave the 3-OAc product. Treatment of unprotected D-xylose with Ac_2O 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.[237] When methyl β-D-xylopyranoside was acetylated with Ac_2O in pyridine, each one of the three monoacetylated products were isolated in 13-16% yield (Entry 6).[238] Using $MoCl_5$ as a catalyst together with Ac_2O 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).[239] Acetylating methyl α-D-xylopyranoside using CCL in EtOAc, generated the 2-OAc product almost exclusively, however, in low yield (Entry 10).[240] Investigations of monoacetylation of octyl β-D-xylopyranoside with

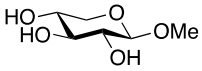
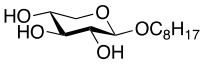
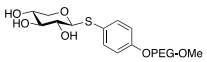
Pseudomonas cepacia lipase (lipase PS) in different solvents showed that more hydrophobic solvent, resulted in higher propensity for acetylation of position 2, whereas the 4-OAc was the major product when more polar solvents, such as acetonitrile, were used (Entries 11 and 12).[241] This tendency has been observed in other solvents as well.[242-243]

Table 5. Regioselective monoacetylation of some xylosides.

Entry	Starting material	Reagents	Product ratio				Total yield	Ref
			2-OAc	3-OAc	4-OAc	Multi		
1		Ac_2O, NaOAc	67%	33%	-	-	-	[236]
2		Ac_2O, Py	45%	26%	-	28%	-	[236]
3		AcCl, Py	27%	24%	-	49%	-	[236]
4		Ac_2O, Py, HCl	29%	29%	-	43%	-	[236]
5		Ac_2O, $HClO_4$	25%	75%	-	-	-	[236]
6		Ac_2O, Py	24%	29%	25%	22%	55%	[238]
7		Ac_2O, $MoCl_5$	29%	1%	21%	49%	100%	[238]
8		PFL, vinyl acetate	-	-	100%	-	65%	[239]
9		CCL, vinyl acetate	-	-	100%	-	59%	[239]
10		CCL, EtOAc	97%	3%	-	-	39%	[240]
11		Lipase PS, vinyl acetate, hexane	83%	6%	11%	-	53%	[241]
12		Lipase PS, vinyl acetate, MeCN	35%	5%	60%	-	42%	[241]

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).[241] As for monoacetylation, the aglycon and solvent plays crucial roles for the selectivity, which was seen with e.g. octyl (Entries 2 and 3)[241] or 4-nitrophenyl[243] as aglycon. The specific enzyme does also affect the regioselectivity of the acetylation, as exemplified with Novozyme 435 (immobilized *Candida antartica* lipase) and lipase PS (Entries 4 and 5).[242]

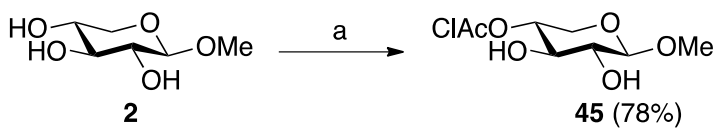
Table 6. Regioselective diacetylation of some xylosides.

Entry	Starting material	Reagents	Product ratio			Total yield	Ref
			2,3-OAc	2,4-OAc	3,4-OAc		
1		Lipase PS, vinyl acetate, MeCN	-	-	100%	85%	[241]
2		Lipase PS, vinyl acetate, MeCN	-	44%	56%	-	[241]
3		Lipase PS, vinyl acetate, hexane		22%	78%	-	[241]
4		Novozym 435, vinyl acetate	-	-	100%	85%	[242]
5		Lipase PS, vinyl acetate	100%	-	-	40%	[242]

Regioselective deacetylation using enzymes has also been used as a method for generation of partly acetylated xylosides. Enzymes such as porcine liver esterase (PLE),[244] Novozym 435,[245] lipase PS,[137, 239, 246-247] and PEG-modified CCL[248] 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 Novozym 435[242] as well as rabbit serum esterase,[249] which also selectively removes pivaloyl groups in position 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 Bu_2SnO followed by stoichiometric amounts of chloroacetyl chloride (Scheme 10).[250] This method has been proven successful for many β-D-xylopyranosides.[188, 251-254]



2 **45** (78%)

Scheme 10. Reagents and conditions: (a) Bu_2SnO, MeOH, reflux, then $ClCH_2COCl$, CH_2Cl_2.[250]

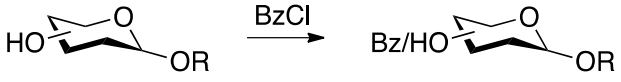
3.1.3 Benzoates

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 2,4-dibenzoate derivatives are often the major product using 2 equivalents of BzCl (Entries 2, 6, 11, and 15). However, the 3,4-dibenzoylated product of *N*-acetyl-*N*-aryl-β-D-xylopyranosylamines was obtained using this method.[255] 1,2,4-tri-*O*-benzoyl-α-D-xyloside, obtained in 32%, was the major product when treating unprotected xylose with 3.1 equivalents of BzCl in pyridine.[256]

The use of Bu_2SnO and $(Bu_3Sn)_2O$ in regioselective benzoylation of xylosides has been investigated.[257-258] For α-D-xylopyranosides, 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 monobenzoylated 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_2SnO method also proved efficient when monobenzoylating thymine β-D-xylopyranoside, and the 4-*O*-benzoyl product was obtained in 79%.[259]

Benzoylation with benzoic anhydride in presence of copper(II) trifluoroacetate gave regioselective monobenzoylation of methyl and benzyl β-D-xylopyranosides in the 4-OH position in 86% and 87% yield, respectively.[260] Methyl α-D-xylopyranoside, 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.

Table 7. Regioselective benzoylation of some xylosides with benzoyl chloride.



Entry	R	eq BzCl	Reagents/ conditions	Yield							Ref
				2-Bz	3-Bz	4-Bz	2,3-Bz	2,4-Bz	3,4-Bz	2,3,4-Bz	
1	α-Me	1	Py, 0 °C	56%	-	-	20%[a]	15%[a]	-	-	[257]

2		2	Py, -40 °C	-	5%	-	39%	45%	-	11%	[261]
3		1.1	Bu_2SnO	52%[a]	-	30%[a]	-	-	-	-	[257]
4		1.5	$(Bu_3Sn)_2O$	41%[a]	-	31%[a]	-	-	-	-	[257]
5	β-Me	1	Py, -40 °C	26%	25%	20%	13%[a]	8%	6%[a]	2%	[261]
6		2	Py, -40 °C	2%[a]	4%	2%[a]	37%[b]	22%	16%[b]	17%	[261]
7		1	Bu_2SnO	-	-	93%	-	-	-	-	[258]
8		2	Bu_2SnO	-	-	-	-	-	80%	-	[258]
9		1.5	$(Bu_3Sn)_2O$	-	-	43%	-	26%[a]	20%[a]	-	[257]
10	α-Bn	1.1	Py, -30 °C	59%	-	-	-	-	-	-	[262]
11		2.2	Py, -30 °C	9%	-	-	27%	45%	-	15%	[262]
12		1	Bu_2SnO	44%	-	29%	-	14%	-	-	[258]
13		2	Bu_2SnO	-	-	-	-	90%	-	-	[258]
14	α-All	1	Py, rt	-	75%	-	-	-	-	-	[263]
15		2.2	Py, rt	-	-	-	20%	45%	-	25%	[263]

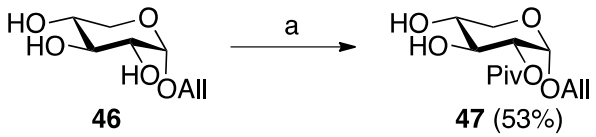
[a]Unseparable mixture. [b]Unseparable mixture.

3.1.4 4-Methoxybenzoates

In addition to benzoyl protective groups, 4-methoxybenzoates have been used. Treating benzyl α-D-xylopyranoside with 4-methoxybenzoyl chloride in dry pyridine generated regioselective benzoylation of the 2-OH.[104] On the other hand, the 3-OH was protected when phenyl 1-thio-β-D-xylopyranoside was reacted with 4-methoxybenzoic acid in the presence of DCC and DMAP.[264]

3.1.5 Pivaloates

Rosenberg et al. selectively pivaloylated 2-OH of allyl α-D-xylose **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).[118] Other protective group manipulation made it possible to exchange the pivaloate to a benzyl group later in the synthesis.



46 **47** (53%)

Scheme 11. Reagents and conditions: (a) PvCl, pyridine, -40 °C.[118]

Pivaloylation of methyl β-D-xylopyranoside with one equivalent PvCl in pyridine gave the 3-pivaloylester in 20% and the 4-pivaloylester in 22%.[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.

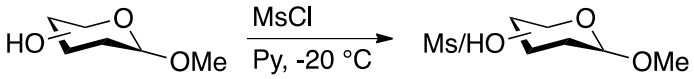
3.1.6 Carbamates

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.[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).[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.[267]

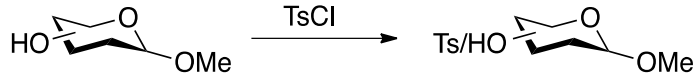
Table 8. Mesylation of methyl α- and β-D-xylopyranoside.[266]



Entry	α/β	eq MsCl	Yield						
			2-Ms	3-Ms	4-Ms	2,3-Ms	2,4-Ms	3,4-Ms	2,3,4-Ms
1	α	1	35%	-	-	-	-	-	-
2	α	2	4%	-	-	3%	57%	-	9%
3	β	1	-	-	38%	-	-	-	-
4	β	2	-	-	10%	-	-	44%	6%

Tosylation of methyl and benzyl α-D-xylopyranoside 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.[266, 268-269] The reaction with methyl β-D-xylopyranoside 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.[269] Alternatively, tosyl protective groups can be introduced by reaction with Bu_2SnO in combination with TsCl. When methyl α-D-xylopyranoside was first treated with Bu_2SnO followed by TsCl and DMAP, the 4-*O*-tosylated compound was the major product (Table 9).[270] The β-anomer gave a quantitative conversion to the 4-*O*-tosylated product. When using only catalytic amounts of Bu_2SnO together with TsCl and Et_3N, the regioselectivity was reversed for methyl α-D-xylopyranoside.[271]

Table 9. Tosylation of methyl α- and β-D-xylopyranoside.[270-271]



Entry	α/β	Method[a]	Yield		
			2-Ts	3-Ts	4-Ts
1	α	A	32%	-	52%
2	α	B	54%	-	16%
3	β	A	-	-	100%
4	β	B	4%	-	36%

[a]Method A: Bu_2SnO, MeOH, then TsCl, DMAP, dioxane.[270] Method B: Bu_2SnO (cat), TsCl, Et_3N, dioxane.[271]

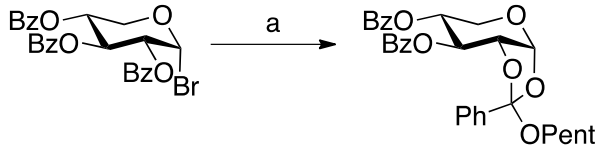
In a study of nucleophilic substitution reactions of pyranose polytosylates, McGeary and co-workers formed the 2,3-di-*O*-tosyl derivative of methyl α-D-xylopyranoside, by initial per-*O*-tosylation of methyl β-L-arabinopyranoside and then displacement of the 4-tosylate by treatment with $NaNO_2$.[115] The corresponding methyl 2,3-di-*O*-tosyl-β-D-xyloside has been synthesized by a slightly longer procedure using a similar approach starting from methyl β-D-xylopyranoside.[272]

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 $^1C_4$ conformation.[273] 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).[142, 216, 274-280] 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.



24 **48** (87%)

Scheme 12. Reagents and conditions: (a) Pent-4-enyl-1-ol, lutidine. Pent = pent-4-enyl.[277]

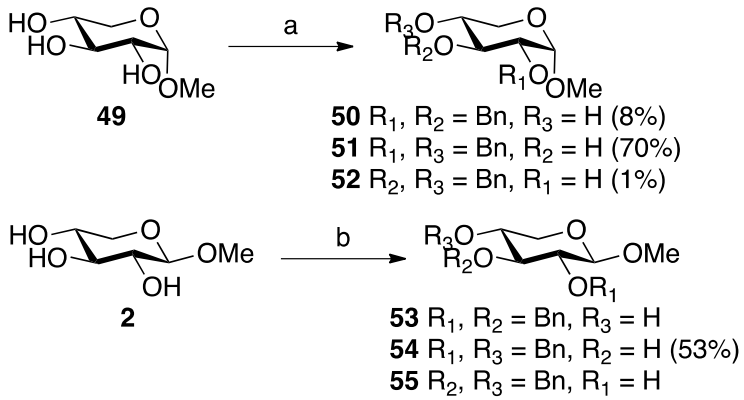
3.2 Ethers

3.2.1 Methyl ethers

Regioselective monomethylation of methyl α-D-xylopyranoside was achieved by Tsuda and co-workers using Bu_2SnO and methyl iodide.[281] 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 **49** generated the 2,4-di-*O*-benzyl derivative **51** in 70% yield using NaH and BnCl (Scheme 13).[282] Under similar conditions, the β-anomer **2** yielded **54** in 53% as the major product.[283] 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.[86]



Scheme 13. Reagents and conditions: (a) BnCl, NaH, 100 °C;[282] (b) BnCl, LiOH, DMSO, 130 °C, 37% **53**+**55**.[283]

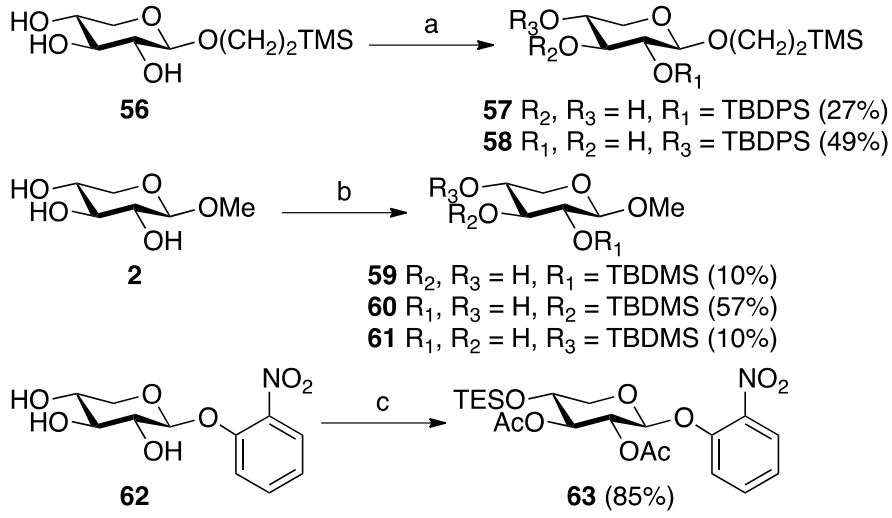
Regioselective monobenzylation can be performed, as for monomethylation, using Bu_2SnO followed by the addition of BnBr. The reaction with **49** yielded a mixture of the monobenzylated products where the 2-*O*-benzyl derivative was the major one.[281] For **2**, the benzylation generated the 4-*O*-benzyl 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*-benzylated products was found. Using a similar procedure, allyl α-D-xylopyranoside formed the 2-*O*-benzyl derivative in 40% yield, whereas the corresponding β-anomer could not be benzylated using the same method.[117] Instead, it was treated with one equivalent of BnBr and NaH to give allyl 2-*O*-benzyl-β-D-xylopyranoside in 20% yield.

3.2.3 Allyl ethers

Methyl α-D-xylopyranoside was monoallylated with allyl bromide by Tsuda and co-workers using the Bu_2SnO procedure.[281] 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 Silyl ethers

Regioselective silylation of β-D-xylopyranosides with TBDPSCl 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).[86, 284] Treating methyl β-D-xylopyranoside **2** with TBDMSCl 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 $PdCl_2$ formed the 3-*O*-silylated product **60** in 57% yield as the major product (Scheme 14).[285] 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-xylopyranoside gave the 4-*O*-silylated derivative in 83% yield.[277] A 4-*O*-PMB protected β-D-xylopyranoside was regioselectively silylated in excellent yield at O3 when the reaction was performed in THF, and at O2 when using CH_2Cl_2 as solvent.[137] Silyl ethers have also been introduced by the action of tin acetals. Aryl β-D-xylopyranosides were treated with Bu_2SnO followed by TESCl to regioselectively protect 4-OH in good yields (Scheme 14).[168] Disilylation of methyl D-xylopyranosides has been obtained using $TiPDSCl_2$ 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%.[286]

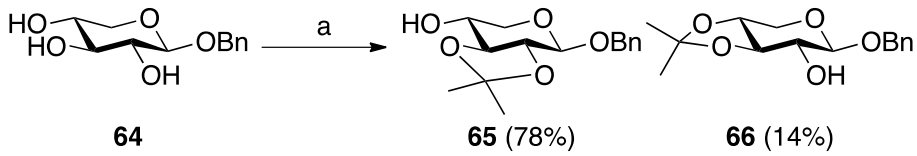


Scheme 14. Reagents and conditions: (a) TBDPSCl, Et_3N, DMAP, $CHCl_3$;[284] (b) TBDMSH, $PdCl_2$, DMA;[285] (c) (i) Bu_2SnO, benzene, toluene, reflux, (ii) TESCl, 0 °C, (iii) Ac_2O, Py.[168]

3.3 Acetals

3.3.1 Isopropylidene acetals

Isopropylidene acetals are often used when 2-OH or 4-OH are 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, *p*TSA, 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).[137, 163, 258, 282, 287-292]



64 **65** (78%) **66** (14%)

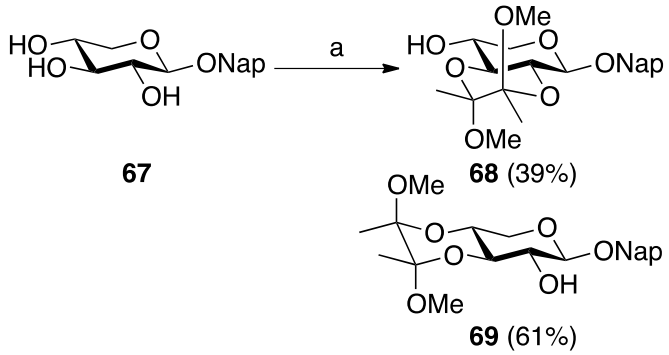
Scheme 15. Reagents and conditions: (a) 2-Methoxy propene, CSA, DMF, 60 °C.[289]

3.3.2 Cyclohexylidene acetals

Koto and co-workers has also investigated the use of cyclohexylidene acetals.[282-283] Treatment of methyl or benzyl α-D-xylopyranoside with 1,1-dimethoxycyclohexane and *p*TSA in DMF gave the 2,3-acetals as the major products.

3.3.3 Diacetals

The butane-2,3-diacetal (BDA) was introduced in xylose chemistry by Jenkins and Potter by the reaction of allyl α-D-xylopyranoside 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.[293] 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).[86, 252, 294-295]



67 **68** (39%) **69** (61%)

Scheme 16. Reagents and conditions: (a) 2,2,3,3-Tetramethoxybutane, $BF_3 \cdot Et_2O$, MeCN. Nap = 2-naphthyl.[86]

3.4 Miscellaneous

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.[218, 296-298] Xylal has been used to form an epoxide between C1 and C2. Protection of 3- and 4-OH in the xylal was then followed by epoxidation and ring opening by the action of an alcohol to form a xyloside with a free 2-OH.[299-300]

Xylofuranosides can be used to install different protective groups and then later on, the furanosides have been converted to the xylopyranosides.[220, 301]

3.5 Concluding remarks

The general reactivity trend for α-xylosides is O2 > O4 > O3 and for β-xylosides O4 > O3 > O2, as observed in many reactions. When it comes to β-D-xylopyranosides, excellent regioselective protection of 4-OH is often obtained by using Bu_2SnO, and benzoate, chloroacetate, tosylate, benzyl, and triethylsilyl groups, amongst others, have been introduced in this way. α-D-Xylopyranosides, on the other hand, do not always show as high regioselectivity with this method, but the major products are often protected 2-OH xylosides. Using stannylene acetals, 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 acetals, where isopropylidene acetals generate 2,3-*O*-protected xylosides in high yields and BDA-acetals 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).

Table 10. Name of the epimerized D-xylose analogs.

Position	Name
2	D-Lyxose

3	D-Ribose
4	L-Arabinose

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] (Figure 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-xylopyranosides formed the 4-keto products **76** and **77** when using the acetic acid bacterium *Acetobacter suboxydans*[310-311] or when the xylosides were treated with bromine in the presence of $NaBO_2$.[312]

2,3,4-Tri-*O*-protected xylopyranoses were oxidized at the anomeric position by treatment with Ac_2O/DMSO,[137] PCC,[138, 313] or TPAP/NMO[314] to form the corresponding δ-lactones **71**. Oxidizing D-xylose using cupric acetate generated **72** in 50-55% yield.[315] Methyl α- and β-D-xylopyranosides were oxidized at C3 with Ac_2O/DMSO in the presence of phenylboronic acid, which formed **74** and **75**.[316] Interestingly, using $(Bu_3Sn)_2O$ 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 oxidation[319-320] or by oxidation with Dess-Martin periodinane[88, 321].

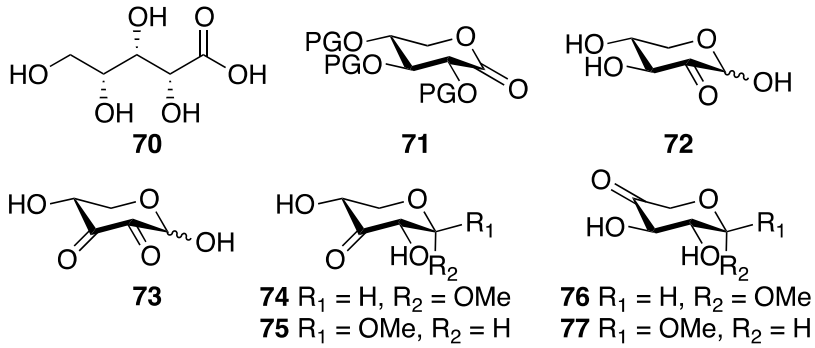
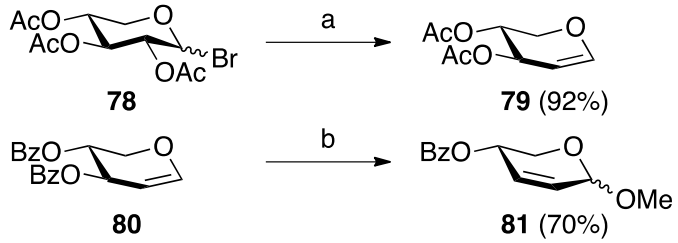


Figure 9. Oxidation products. PG = protective group.

4.2 Reductions

4.2.1 Xylal synthesis

Xylals, i.e. 1,2-unsaturated xylose derivatives, are most often synthesized from peracetylated xylosyl bromide **78** using e.g. Zn/AcOH,[322] Zn/Ag-graphite,[323] Zn/$CuSO_4$,[324-325] Zn/NaH_2PO_4,[326] Zn/β-cyclodextrin,[327] $(Cp_2TiCl)_2$,[328] or $[Cr^{II}(EDTA)]^{2-}$[329] as reagents (Scheme 17). 1-Thioxylosides have also been transformed to the corresponding xylals using $[Cr^{II}(EDTA)]^{2-}$ [330] or Li-naphthalenide[331]. 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 $BF_3{\cdot}Et_2O$,[332] $PdCl_2$,[333] $SnCl_4$,[334] TMSOTf,[335] CAN,[336] I_2,[337] and zeolite[338] (Scheme 17).



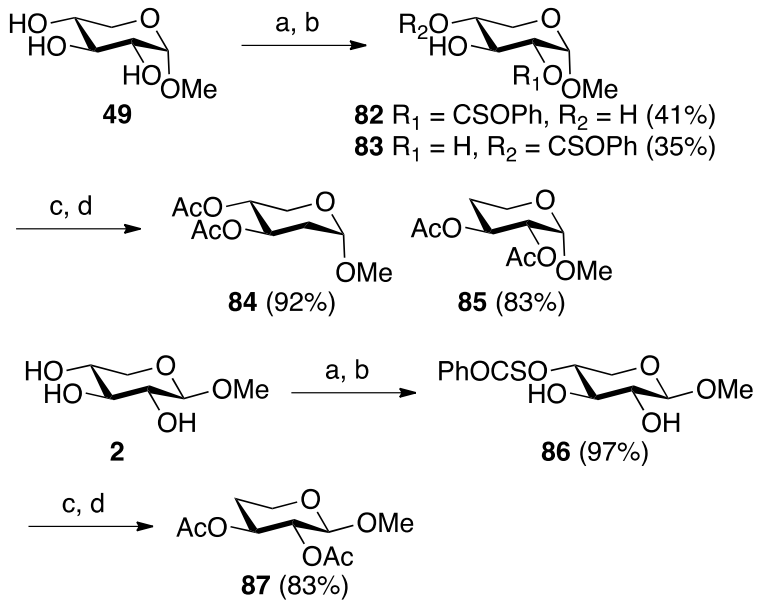
78 **79** (92%)

80 **81** (70%)

Scheme 17. Reagents and conditions: (a) Zn/Ag-graphite, THF, -20 °C;[323] (b) $BF_3{\cdot}Et_2O$, MeOH, CH_2Cl_2, 70%.[332]

4.2.2 Deoxygenation

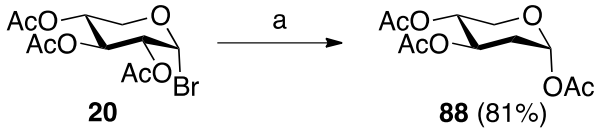
Tsuda and co-workers investigated the use of stannylene intermediates in the regioselective deoxygenation of carbohydrates. Treatment of methyl α- and β-D-xylopyranosides with Bu_2SnO and phenoxythiocarbonyl chloride generated the 4-thionocarbonate derivative **86** exclusively for the β-anomer, whereas a 1:1 mixture of **82** and **83** was obtained for the α-anomer (Scheme 18).[339-340] Acetylation followed by reduction with Bu_3SnH formed the corresponding deoxy derivatives **84**, **85**, and **87** in excellent yields.



Scheme 18. Reagents and conditions: (a) Bu_2SnO, MeOH, reflux; (b) PhOCSCl, dioxane; (c) Ac_2O, pyridine; (d) Bu_3SnH, AIBN, toluene, 100 °C.[339]

Alternatively, xylopyranosides have been deoxygenated by the use of xanthate intermediates that were reacted with Bu_3SnH and AIBN in a Barton McCombie radical deoxygenation. This has been performed with, e.g. naphthyl β-D-xylopyranosides that have been deoxygenated at position 2, 3, and 4 using this methodology.[86]

Treatment of peracetylated α-D-xylosyl bromide **20** directly with Bu_3SnH and AIBN produced the 2-deoxy compound **88** in 81% yield (Scheme 19).[341] This reaction proceeds through a xylosyl radical, formed by halogen abstraction, followed by a *cis*-migration of the acetate and finally the rearranged radical is trapped by tin hydride.

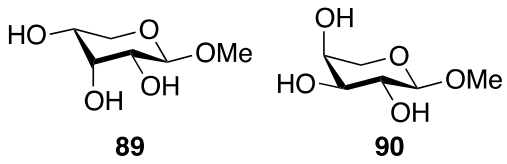


Scheme 19. Reagents and conditions: (a) Bu_3SnH, AIBN, benzene.[341]

When investigating the formation of branched furanosides formed by $LiAlH_4$ reduction of monosulfonates, Tsuda et al. also obtained deoxyglycosides. Reacting 4-*O*-tosylated methyl α- and β-D-xylopyranosides with $LiAlH_4$ produced the 4-deoxy products in 25% and 41%, respectively.[342]

4.3 Epimerizations

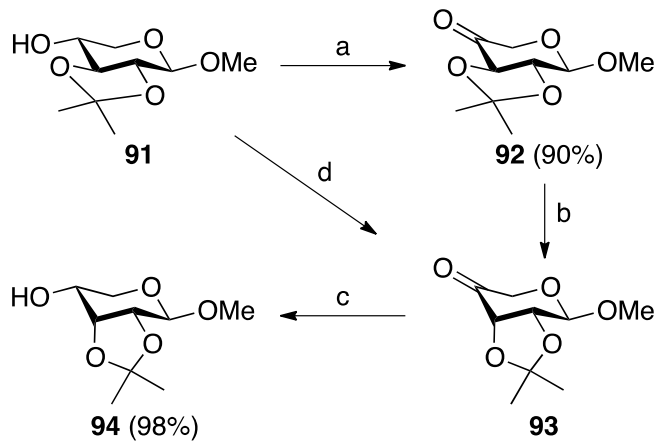
Although the epimerized xylose analogs are commercially available, it is sometimes more convenient to form these glycosides from the corresponding xylosides and several strategies are available for epimerization of the hydroxyl groups of xylose. When D-xylose was treated with molybdic acid in an aqueous solution, epimerization at C2 to form lyxose in equilibrium was observed. However, xylose was the major component.[343] Microwave irradiation accelerated the reaction and also further shifted the equilibrium towards xylose.[344] 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 **89** (Figure 10) in 20% yield.[345]



89 **90**

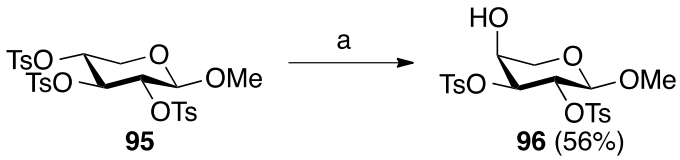
Figure 10. Methyl β-D-ribopyranoside **89** and methyl α-L-arabinopyranoside **90**.

Oxidation followed by reduction has been used to invert a hydroxyl group. Tsuda and coworkers reduced 3- and 4-oxo derivatives **75** and **76** (Figure 9) with $NaBH_4$, which in the case of **75** only generated the corresponding xyloside whereas **76** formed a mixture of xyloside and arabinoside **90** (Figure 10). Catalytic hydrogenation of **75** over Pt in AcOH gave the riboside **89** as the major product.[317-318] Manner et al. reduced isopropylidene-protected 2- and 4-oxo xylosides with $NaBH_4$ and formed the corresponding lyxoside and arabinoside as major products.[320] Sureshan and co-workers utilized the steric strain in *trans*-ketals positioned adjacent to a carbonyl to epimerize to a *cis*-ketal via an enolate.[321] 2,3-*O*-isopropylidene-protected methyl β-D-xylopyranoside **91** was oxidized with Dess-Martin periodinane, followed by epimerization at C3 by the action of Et_3N and reduction to form the corresponding riboside **94** in high yield (Scheme 20). Swern oxidation, where Et_3N was used as the base, generated the 4-oxo derivative **93** epimerized at C3, in one step. In a comprehensive study, isopropylidene-protected xylosides were oxidized using Swern conditions followed by in situ reduction. When the more hindered base, Hünig's base, was used instead of Et_3N, no isomerization occurred.[320] In this way, lyxosides, ribosides, and arabinosides can be formed from xylosides.



Scheme 20. Reagents and conditions: (a) Dess-Martin periodinane, CH_2Cl_2; (b) Et_3N, CH_2Cl_2, 84%; (c) $NaBH_4$, MeOH, 0 °C; (d) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, 82%.[321]

Another method for epimerization is the transformation of the hydroxyl group into a better leaving group followed by an S_N2 reaction. Sulfonates are commonly used in such procedures where fully mesylated or tosylated xylosides have been epimerized selectively at C4 (Scheme 21).[115, 346] However, inversion at other positions have also been reported using partly protected xylosides.[86] Sulfonates were reacted with either $NaNO_2$ or quaternary nitrite salt to form the epimerized alcohol directly, or alternatively, esters were produced by reaction with acetate or benzoate that later on can be hydrolyzed.[86, 115]



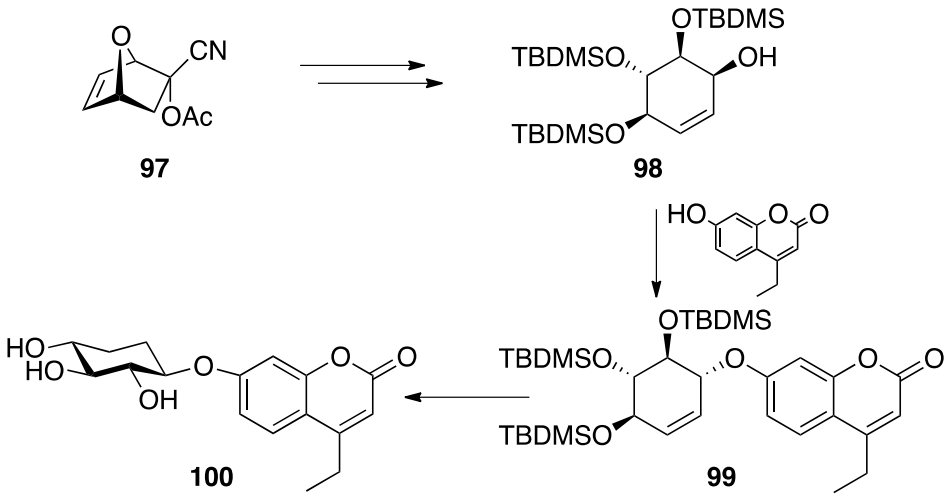
Scheme 21. Reagents and conditions: (a) $NaNO_2$, DMF, 130 °C.[115]

4.4 Other analogs

4.4.1 5a-Carba-β-D-xylopyranosides

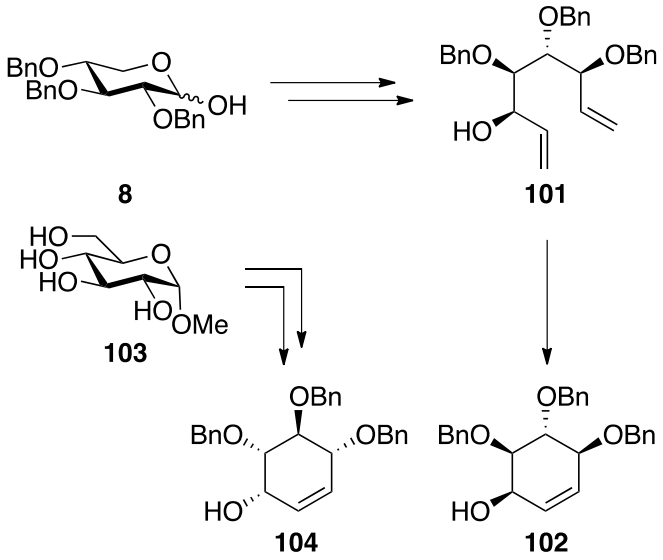
There are several ways of synthesizing carbasugars, i.e. carbohydrate analogs in which the endocyclic oxygen atom has been replaced by a methylene group. 5a-Carba-β-D-xylopyranosides can be synthesized using several different routes of which (+)-conduritol F derivatives are common precursors. Vogel and co-workers initiated their synthesis of 5a-carba-β-D-xylopyranoside **100** from the Diels-Alder adduct **97**, which was converted to the conduritol F derivative **98** in several steps (Scheme 22).[347] Performing a Mitsunobu reaction

with **98** and 4-ethylumbelliferone generated **99** with the desired stereochemistry after which hydrogenation and desilylation yielded **100**.



Scheme 22. Synthetic route to 5a-carba-β-D-xylopyranoside **100**.

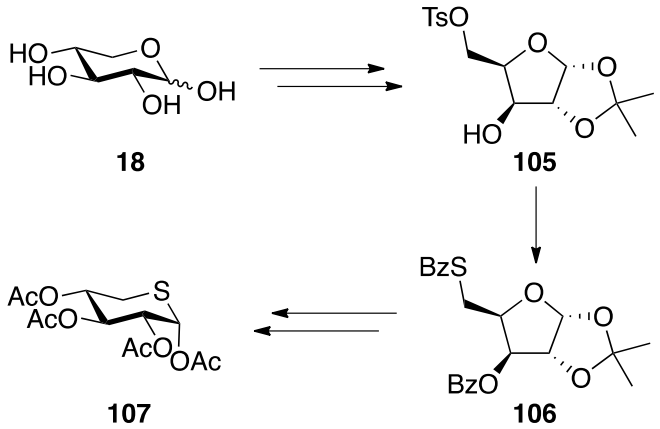
d'Alarcao and co-workers have synthesized conduritol F derivatives starting from 2,3,4-tri-*O*-benzyl-D-xylopyranose **8**. In a reaction sequence including a Wittig reaction, Swern oxidation, and Grignard reaction with vinyl magnesium bromide, alcohol **101** was obtained together with its epimer (Scheme 23).[348-351] A ring-closing metathesis was then performed to yield (-)-conduritol F derivative **102**. 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**.[352-353]



Scheme 23. Synthetic route to (-)-conduritol F derivative **102** from 2,3,4-tri-*O*-benzyl-D-xylopyranose **8** and (+)-conduritol F derivative **104** from methyl α-D-glucopyranoside **103**.

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 furanoses 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.[354] 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** (Figure 11). 5-Thio-β-D-xylopyranose **107** was obtained in an overall yield of 56% by following the same procedure as for **106**.



Scheme 24. Synthetic route to 5-thio-β-D-xylopyranose **107**.

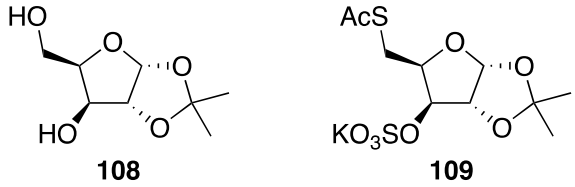
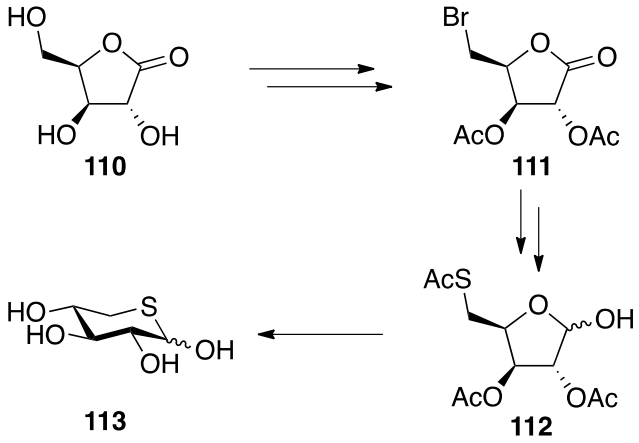


Figure 11. Synthetic intermediates in the synthesis of 5-thio-β-D-xylopyranose **107**.

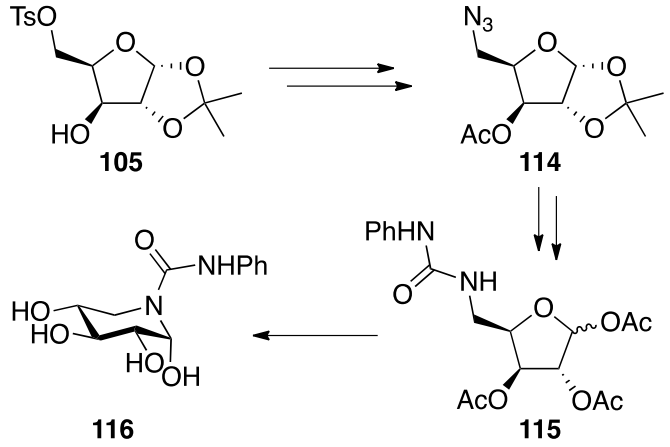
Using another procedure, yet methodologically similar, Lalot et al. started from D-xylono-1,4-lactone **110** that was converted to the C5 bromide **111** (Scheme 25).[355] Displacement of the bromide with AcSK followed by reduction of the lactone functionality generated lactol **112**, which formed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



Scheme 25. Synthetic route to 5-thio-β-D-xylopyranose **113**.

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 applies 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** also was transformed to bromide **117** (Figure 12) in high yield, which was treated with amines to generate e.g. **118**, or with aminoalcohols 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-amino-1-propanol, although **120** is more stable and is the major product.



Scheme 26. Synthetic route to 5-deoxy-5-(3-phenylureido)-α-D-xylopyranose **116**.

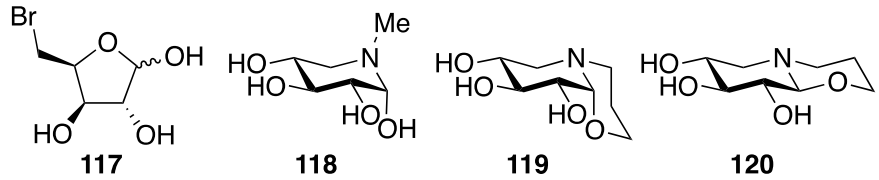
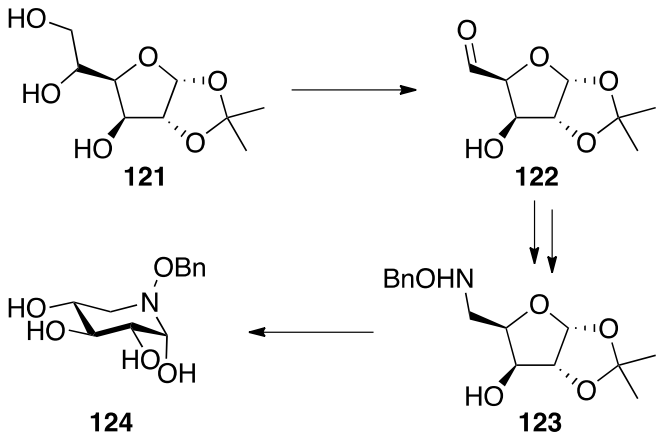


Figure 12. 5-Amino-5-deoxy-β-D-xylopyranoses synthesized from xylofuranose **117**.

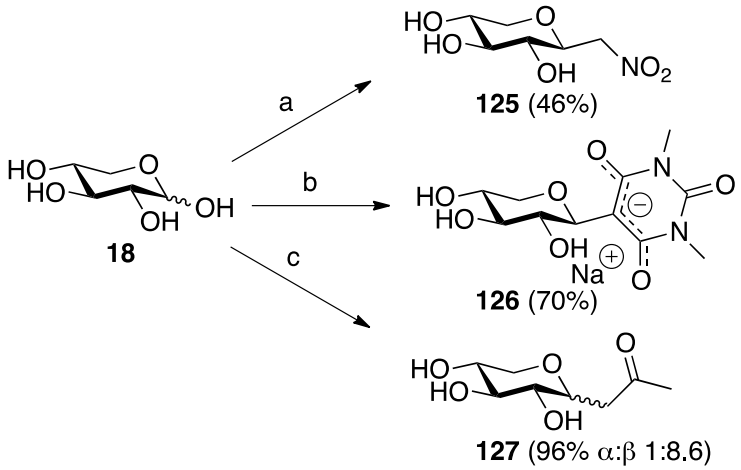
Martinez-Castro et al. synthesized alkoxyaminoxylopyranose **124**, starting from mono-*O*-isopropylidene-D-glucofuranose **121** that formed **122** via oxidative degradation of the side chain (Scheme 27).[359] This aldehyde was then reacted with *O*-benzylhydroxylamine to generate an oxime that was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



Scheme 27. Synthetic route to 5-deoxy-5-amino-α-D-xylopyranose **124**.

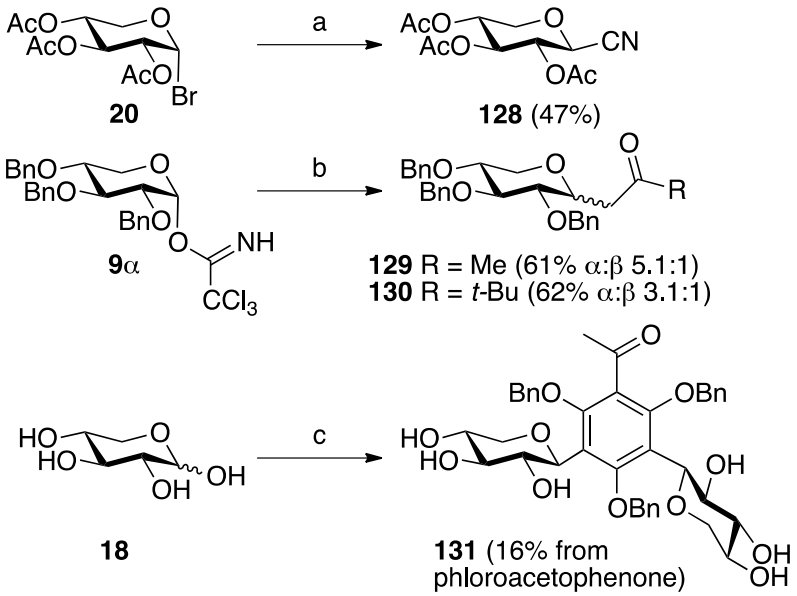
4.4.4 C-xylosides

In *C*-xylosides, the *exo*-anomeric oxygen has been exchanged for a methylene group. Several methods have been developed starting from unprotected D-xylose. Sowden et al. formed β-D-xylopyranosyl nitromethane **125** in two steps from D-xylose, via base-catalyzed addition of nitromethane (Scheme 28).[360] When reacting D-xylose and 1,3-dimethyl barbituric acid, applying Knoevenagel conditions, sodium β-D-xylopyranosylbarbiturate **126** was obtained,[361] and when using pentane-2,4-dione under similar conditions, keto *C*-pyranoside **127** was synthesized in 96 % yield.[362] Compound **127** was also synthesized from D-xylose via the Horner-Wadsworth-Emmons reaction, using β-keto phosphonates, in 57 % yield (α:β 7:93).[363]



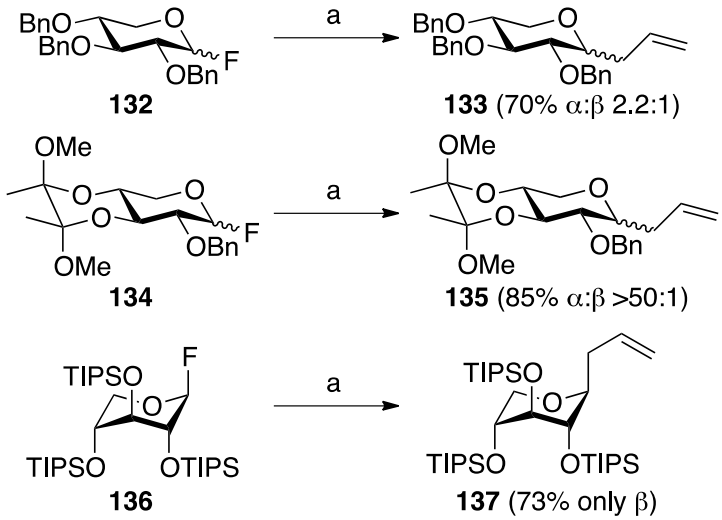
Scheme 28. Reagents and conditions: (a) $MeNO_2$, NaOMe, MeOH, then H_2O, reflux;[360] (b) 1,3-Dimethylbarbituric acid, Na_2CO_3, H_2O, 80 °C;[361] (c) Pentane-2,4-dione, Na_2CO_3, H_2O, 90 °C.[362]

Xylosyl donors have also been used in the synthesis of *C*-xylosides. Peracetylated xylosyl bromide **20** was converted to **128** by treatment with $Hg(CN)_2$,[364] and reaction between trichloroacetimidate **9α** and silyl enol ethers, catalyzed by $ZnCl_2$, generated **129** and **130** as α,β-mixtures (Scheme 29).[365] Although controlling the stereochemistry in Lewis acid-promoted xylosylation reactions can be problematic, Shie and co-workers obtained β-selectivity exclusively in their $Sc(OTf)_3$-promoted synthesis of di-*C*-β-D-xylopyranosylphloroacetophenone **131**.[366]



Scheme 29. Reagents and conditions: (a) $Hg(CN)_2$, MeCN;[364] (b) Silyl enol ethers, $ZnCl_2$, CH_2Cl_2;[365] (c) Phloroacetophenone, $Sc(OTf)_3$, EtOH, reflux, then BnBr, K_2CO_3, DMF.[366]

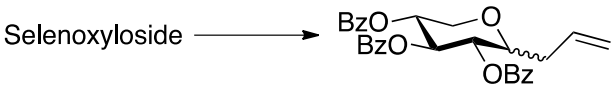
Depending on the restricted conformation of the substrate, Tamura et al. could control the stereoselectivity in $BF_3{\cdot}OEt_2$-promoted *C*-glycosylation of xylosyl fluorides with allyltrimethylsilane (Scheme 30), where $^4C_1$-restricted **134** gave excellent α-selectivity and $^1C_4$-restricted **136** gave β-specificity.[367]

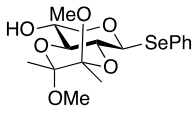
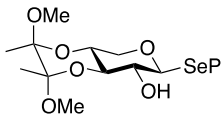
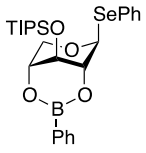
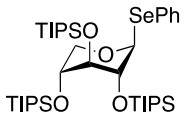


Scheme 30. Reagents and conditions: (a) Allyltrimethylsilane, $BF_3{\cdot}OEt_2$, 4Å MS, CH_2Cl_2.[367]

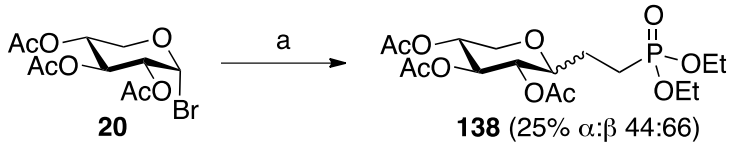
Using the same strategy, high α- and β-selectivity was obtained in a radical *C*-glycosylation reaction using 1-phenylseleno-D-xylopyranosides that was treated with allyltributyltin and AIBN followed by deprotection and benzoylation to form the desired perbenzoylated *C*-xyloside (Table 11).[228]

Table 11. Radical *C*-allylation of conformationally restricted selenoxylosides.[228]



Entry	Substrate	Product ratio (α:β)	Yield
1		1:0.18	73%
2		1:0.1	69%
3		1:99	61%
4		1:99	26%

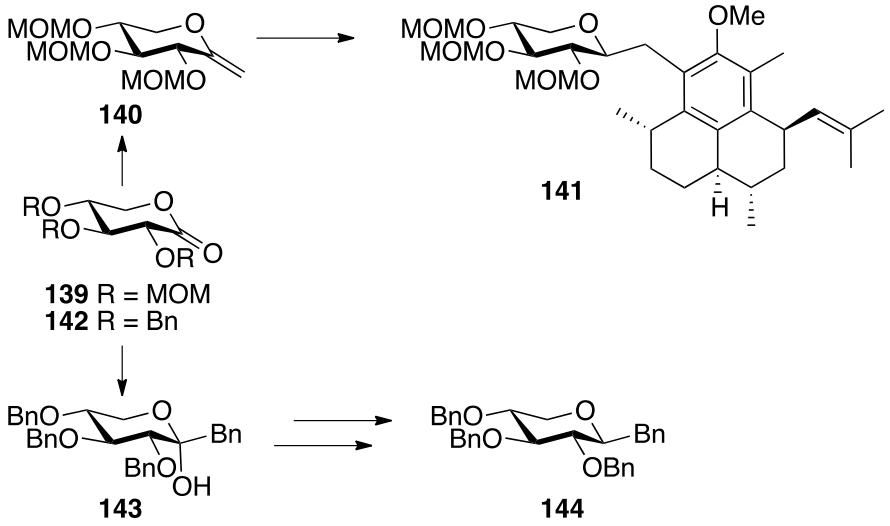
In the glycosyl radical addition between peracetylated xyloside bromide **20** and vinyl phosphonates, *C*-glycosyl phosphonate ester **138** was formed as an α,β-mixture (Scheme 31).[368]



20 **138** (25% α:β 44:66)

Scheme 31. Reagents and conditions: (a) Diethyl vinylphosphonate, Bu_3SnH, Et_2O, light, reflux.[368]

Zhong et al. reported an oxidation-olefination-coupling sequence for installation of the *C*-glycosidic bond. Conversion of δ-lactone **139** into olefin **140**, using Petasis' reagent, was followed by coupling with the corresponding aryl triflate via a Suzuki-Miyaura cross-coupling reaction to form **141** (Scheme 32), exclusively with β-conformation.[314] Using another approach, López et al. treated δ-lactone **142** with BnLi to form **143**, which was converted to the monophenyl thioketal that was subsequently reduced to generate **144** in a total yield of 29% from **142** (Scheme 32).[313]

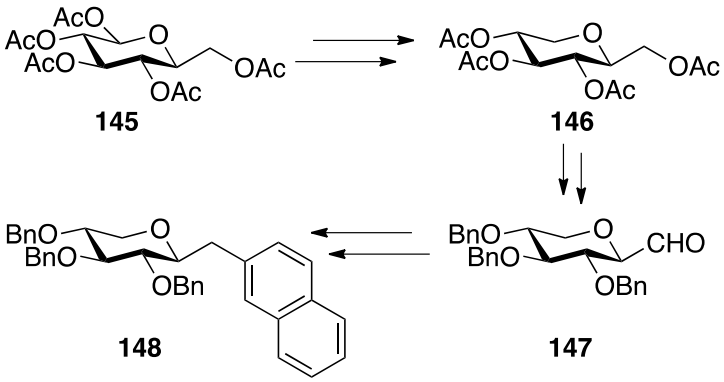


140 **141** **139** R = MOM **142** R = Bn **143** **144**

Scheme 32. Synthetic routes towards *C*-glycosylation starting from δ-lactones.

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.[79] 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**.



Scheme 33. Synthetic route to *C*-xyloside **148**.

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.[369] Based on NMR $^{3}J_{HH}$ coupling constants of the non-exchangeable protons, both forms populate the $^{4}C_{1}$ chair conformation to a very large extent or exclusively. For example, $^{3}J_{H4,H5\text{-pro}R}$ = 10.5 Hz, in agreement with an antiperiplanar arrangement between the protons, and the values of $^{3}J_{H4,H5\text{-pro}S} \approx 5.5$ Hz, $^{3}J_{H3,H4} \approx 9.0$ Hz, and $^{3}J_{H2,H3} \approx 9.4$ Hz are consistent with the $^{4}C_{1}$ 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 $^{1}C_{4}$ chair conformation. In the case of methyl β-D-xylopyranoside **2** (Figure 13), the use of $^{3}J_{H1,H2}$ = 7.8 Hz for the $^{4}C_{1}$ 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]

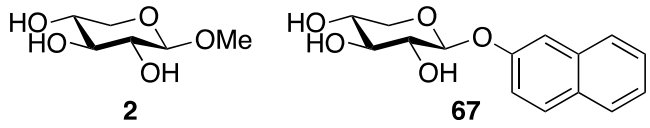


Figure 13. Xylosides with different aglycons.

At this point, it is pertinent to consider not only the $^{1}C_{4}$ chair as an alternative to the $^{4}C_{1}$ 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 $^{4}C_{1}$ chair was still present to >90%, the remaining one being the $^{2}S_{O}$ 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 $^{2}S_{O}$ skew conformation.[371] 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 $^{4}C_{1}$ and $^{1}C_{4}$ 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 ^{1}H NMR spectroscopy. The conformational equilibria of tri-*O*-acetyl-α-D-xylopyranosyl bromide **20 (**Figure 14) and the corresponding chloride were at 31 °C shifted far toward the $^{4}C_{1}$ chair form (>98%).[372] However, the β-anomeric form of the chloride **22**[373] favored instead the $^{1}C_{4}$ chair to ~80% and to an even larger extent for the corresponding per-*O*-benzoylated chloro derivative **149**, populating the $^{1}C_{4}$ chair to ~98%.[372] A similar behavior was deduced for fluoride **150**.[374] For these types of structures, various contributions to the observed equilibria were noted. In particular, the importance of the anomeric effect[375] in orienting the halogen substituent axially. The steric destabilization of arranging substituent groups 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.[376-377]

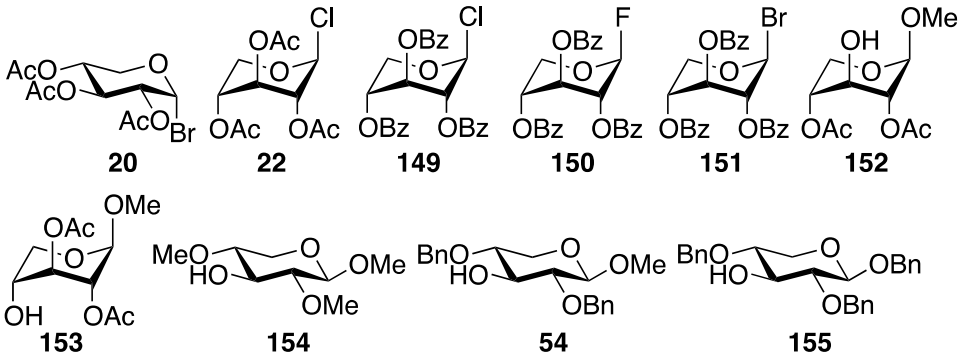


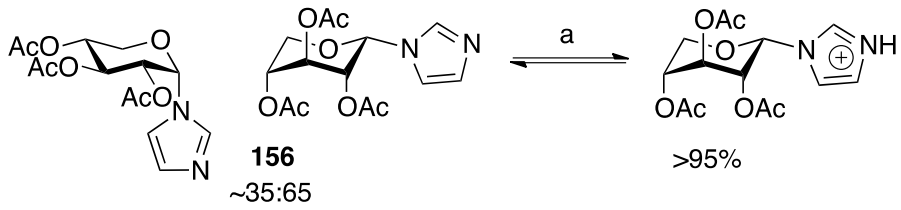
Figure 14. Xylosides with different aglycons and protective groups.

For the per-*O*-benzoylated β-D-xylopyranosyl halides in the crystalline state, the distortions from an ideal $^{1}C_{4}$ conformation toward the $^{5}H_{O}$ conformation were found to differing extent. For example, in tri-*O*-benzoyl-β-D-xylopyranosyl bromide **151** (Figure 14), the van der Waals repulsion between the 1-bromo 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.[378] Subsequently, the α- and β-anomeric forms of mono-, di-, and tri-*O*-acetylated methyl D-xylopyranosides were studied at 18 °C in chloroform-*d*.[379] Irrespective of the substitution patterns of the α-linked methyl glycosides, the $^{4}C_{1}$ chair conformation was exclusively populated. In contrast, for all substitution combinations, the methyl β-D-xylopyranosides contained a component of the $^{1}C_{4}$ 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···HO3 hydrogen bond.

Infrared (IR) spectroscopy was used to characterize xylose derivatives in carbon tetrachloride.[380] In a later study, methyl or benzyl mono- and di-*O*-substituted β-D-xylopyranosides were substituted by methyl, benzyl, or acetyl groups.[381] An IR spectrum of a free hydroxyl group of a secondary alcohol shows an absorption band at 3626 cm^{-1}, which represents a ν_{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 $\Delta\nu_{OH}$ = 7 – 43 cm^{-1} ($^{4}C_{1}$) such as O2···HO3 or O3···HO4, 6-membered rings with $\Delta\nu_{OH}$ = 71 – 106 cm^{-1} ($^{1}C_{4}$) with O1···HO3 or O2···HO4, and 7-membered rings with $\Delta\nu_{OH}$ = 134 – 147 cm^{-1} ($^{4}C_{1}$) such as the band from C3=O···HO4 at 3491 cm^{-1} in methyl 2,3-di-*O*-acetyl-β-D-

xylopyranoside **153** (Figure 14). When the substituent is present in position 3, the $^4C_1$ 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 $^1C_4$ 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 is the $^1C_4$ chair to ~90%, and the alkylated compound methyl 2,4-di-*O*-methyl-β-D-xylopyranoside **154** exclusively populates the $^4C_1$ conformation. Furthermore, the aglycon also affects the conformation, where methyl xyloside **54** populates the $^4C_1$ conformation to ~50%, benzyl xyloside **155** results in exclusive population of the $^4C_1$ chair. Thus, seemingly subtle differences between structures may result in significant changes in the conformational equilibria between the $^4C_1$ and $^1C_4$ 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 $^4C_1$ (35%) and $^1C_4$ (65%) chair forms.[382] Upon protonation, the equilibrium with a cationic aglycon is shifted to >95% of the $^1C_4$ conformation (Scheme 34).



Scheme 34. Reagents and conditions: (a) TFA, $CDCl_3$.

For the corresponding per-*O*-benzoylated and per-*O*-acetylated analogs, substantial conformational shifts to the $^1C_4$ chair were also observed upon protonation. It was concluded that the $^1C_4$ 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** (Figure 15), having an axial substituent at C2 in the $^4C_1$ conformation (present to >95%), was not conformationally affected upon protonation of the imidazole ring. For *N*-(β-D-xylopyranosyl)imidazole **158**, which adopts the $^4C_1$ chair in D_2O solution, protonation to give the cationic form did not reveal any conformational changes from the $^4C_1$ ring form.[383] However, α-anomer **159** exists in a dynamic conformational equilibrium ($^4C_1$: $^1C_4$ ~4:6), which is shifted to ~3:7 upon protonation. In organic solvents, the α-anomeric

form shows increased population of the $^1C_4$ 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 multi-photon dissociation (IRMPD) spectroscopy where the β- and α-anomeric forms of the *N*-imidazole derivatives display the $^4C_1$ and $^1C_4$ conformations, respectively, thereby revealing the relative strengths of the internal non-covalent interactions. Additional spectroscopic and computational studies of D-xylose and xylopyranosides in the gas phase have revealed structural details such as arrangements of intramolecular hydrogen bond networks.[384,385]

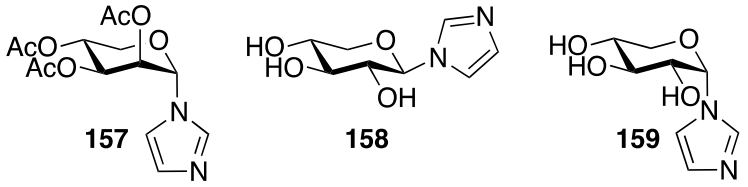
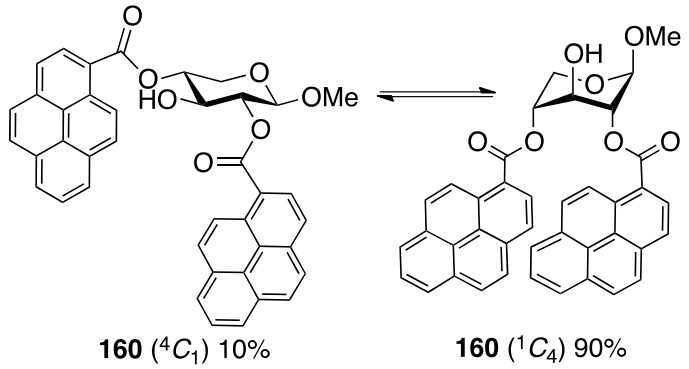


Figure 15. (D-Lyxopyranosyl)imidazole **157** and (D-xylopyranosyl)imidazoles **158** and **159**.

Tong-like derivatives are made by substituting methyl β-D-xylopyranoside by pyrenecarbonyl groups at O2 and O4.[386] Compared to the methyl 2,4-di-*O*-pyrenecarbonyl-β-D-xylopyranoside **160**, which in chloroform-*d* is populated to >90% in the $^1C_4$ 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 $^1C_4$ conformation populated to ~40% in the same solvent, employing also NMR spectroscopy in the analysis.[379] The presence of a hydrogen bond O1···HO3 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 $^1C_4$ 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 $^4C_1$ conformation. These findings were confirmed in more recent computational studies on methyl 2,4-di-*O*-acetyl-β-D-xylopyranoside **152**.[387-388]



160 ($^4C_1$) 10% **160** ($^1C_4$) 90%

Scheme 35. Conformational equilibrium of methyl 2,4-di-*O*-pyrenecarbonyl-β-D-xylopyranoside **160**.

Modifications of the xylose residue with respect to substituents and stereochemistry around the pyranose ring have been made for a number of 2-naphthyl β-D-xylopyranosides.[86, 88, 389-390] These include *O*-methyl derivatives, deoxygenations, fluorine bioisosteres, and *C*-alkylations with methyl or ethyl groups. The alterations performed by change of stereochemistry, compared to the β-D-*xylo*-configuration, result for the inversion of configuration at C2 in the β-D-*lyxo*-configuration, at C3 in the β-D-*ribo*-configuration, and at C4 in the α-L-*arabino*-configuration. For the 2-, 3-, and 4-fluoro bioisosteres of **67**, the $^4C_1$ chair conformation is the major one in polar solvents, but the ^2S_O skew conformation is populated to some extent (5 – 16%). For the nonpolar solvents such as toluene and benzene, the $^1C_4$ chair conformation is also populated significantly, close to 20% in **67**.[389] Interestingly, it is not present in 2-fluoro-2-deoxy analog **161** (Figure 16) in chloroform-*d*, whereas in 3-fluoro-3-deoxy analog **162**, it occurs to a small extent (5%). Most notably, the $^1C_4$ chair is populated to ~25% in 4-fluoro-4-deoxy compound **163**, and the presence of this conformation was further supported by a $^{1H}J_{F4,HO2}$ coupling constant of 2.0 Hz. The latter finding corroborates the interpretation that **67** does indeed populate the $^1C_4$ chair with a hydrogen bond between O4 as the acceptor and HO2 as the donor.

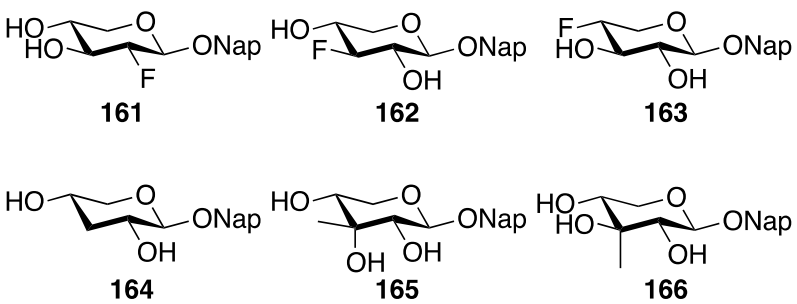


Figure 16. Modified naphthyl xylosides. Nap = 2-naphthyl.

For 3-deoxy compound **164** (Figure 16) in methanol-d_4, a ~1:1 conformational equilibrium is present at room temperature between the $^4C_1$ and $^1C_4$ chair forms, thus revealing a dynamic interchange. This was further investigated by NMR temperature studies between 50 °C and -100 °C.[390] Lowering the temperature decreased the amount of the $^1C_4$ conformation. In the ^{13}C NMR spectra at 200 MHz, the resonances from the C1, C3, and C5 nuclei were observed to coalesce at -60 °C, where after they sharpened again at lower temperatures, a typical behavior for an unequally populated equilibrium. This finding was confirmed by the ^{1}H NMR studies at 800 MHz and at -100 °C, the $^1C_4$ 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 $^4C_1$ conformation is more favored for the *ribo*-configured derivative **165**, compared to the *xylo*-configured derivative **166**. Conversely, in chloroform-*d*, the $^1C_4$ chair form is favored to a larger extent for the latter compound compared to the former. Most interestingly, the $^3J_{C(Me),HO3} = 6.5$ Hz, which is consistent with an *antiperiplanar* arrangement and consequently this conformation is stabilized by an intramolecular O1···HO3 hydrogen bond besides O4···HO2 (Figure 17), the latter being analogous to the one deduced by the 4-fluoro-4-deoxy derivative **163**.

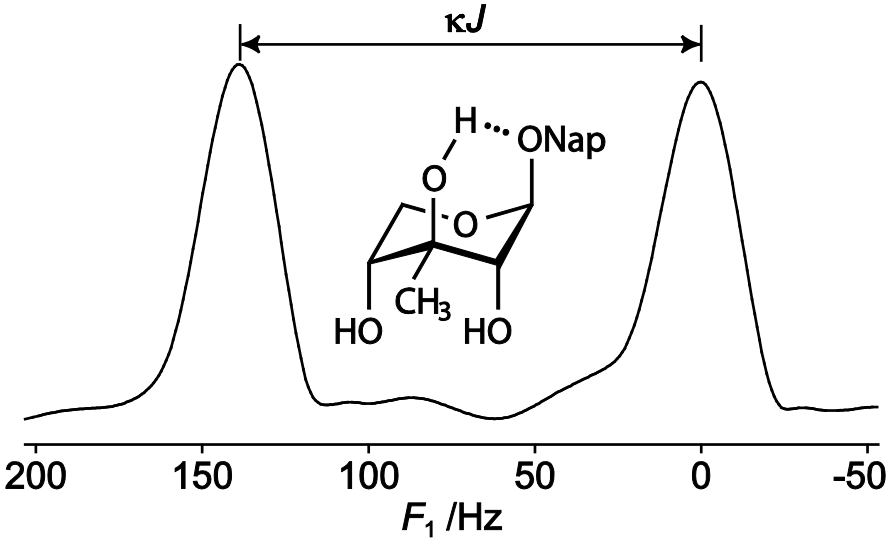


Figure 17. Schematic of **166** in the $^1C_4$ chair conformation and a one-dimensional F_1 projection from a J-HMBC spectrum correlating the heteronuclear scalar coupling between the 3-*C*-methyl group and the HO3 proton. A scaling factor $\kappa = 21.4$ was used in the experiment,

showing an apparent splitting of the doublet by κJ relative to the ^{13}C chemical shift, resulting in $^{3}J_{C(Me),HO3}$ = 6.5 Hz.

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 $^{4}C_1$ to the $^{1}C_4$ chair conformation.[391] In the synthesis of oligosaccharides, suitably protected phenyl 1-seleno- and 1-thio-β-D-xylopyranosides are valuable as donors and introduction of triisopropylsilyl (TIPS) groups give the corresponding trikis-*O*-silyl derivatives in high yield.[392] These superarmed donors, **167** and **168** (Figure 18), in the $^{1}C_4$ conformation, are thus staged for efficient glycosylation reactions. The protective group strategy for radical *C*-glycosylation reactions of xylopyranoses[228] utilized the fact that $^{4}C_1$-restricted substrates, such as BDA-protected **169**, afforded the corresponding α-products whereas the $^{1}C_4$-restricted substrates, such as the above described 1-seleno-TIPS derivative **167**, selectively gave the β-products, as described in Section 4.4.4.

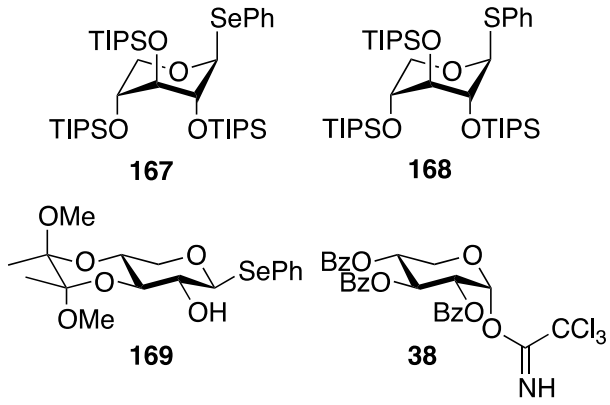


Figure 18. Xylosyl donors with restricted conformations.

Conformational changes were observed for the D-xylopyranose residue in the synthesis of a saponin from *Solanum indicum* L. containing a trisaccharide moiety, viz., β-D-Xyl*p*-(1→3)[α-L-Rha*p*-(1→2)]-β-D-Gal*p*, linked to diosgenin as the aglycon.[393] The trichloroacetimidate donor **38** (Figure 18) was present in the $^{4}C_1$ conformation, but upon glycosylation the resulting 2,3,4-tri-*O*-benzoyl-β-D-xylopyranosyl group changed to the $^{1}C_4$ 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-tri-*O*-benzoyl-1-thio-β-D-xylopyranoside **169** (Figure 19), which exists in the $^4C_1$ chair conformation but also in the presumed $^1C_4$ conformation, by *m*CPBA at -78 °C, leads to the diastereomeric sulfoxides *S*-allyl 2,3,4-tri-*O*-benzoyl-1-thio-β-D-xylopyranoside $(R)_S$-oxide **170** and $(S)_S$-oxide **171**, both of which exist predominantly as the $^4C_1$ chairs.[235] However, oxidation of *S*-allyl 2,3,4-tri-*O*-benzoyl-1-thio-α-D-xylopyranoside **172** leads with high selectivity to the *S*-allyl 2,3,4-tri-*O*-benzoyl-1-thio-α-D-xylopyranoside $(R)_S$-oxide **173**. For a 1-thio-α-D-xylopyranoside in the $^4C_1$ chair conformation, and the *exo*-anomeric effect prevailing with the aglyconic group having a *gauche* relationship to the ring oxygen, the pro-*R* 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 $^4C_1$ to the $^1C_4$ chair (chloroform-*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.

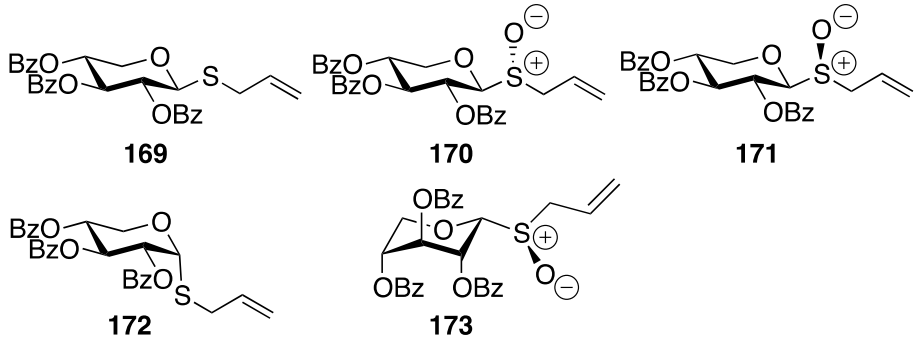
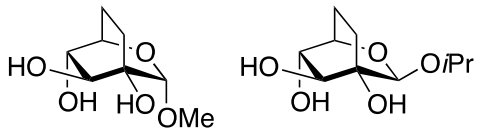


Figure 19. Xylosyl thiols and sulfoxides.

Rates of hydrolysis and of glycosylation reactions were studied for xylose analogs based on a 2-oxabicyclo[2.2.2]octane framework in which the ring conformation becomes locked by a -CH_2CH_2-bridge between the C2 and C5 atoms in alkyl xylopyranoside derivatives.[394] Compound **174** (Figure 20) adopts a $^{2,5}B$ conformation and is hydrolyzed ~10^4 times faster than methyl α-D-xylopyranoside, and compound **175** adopts a ^2S_O conformation and is hydrolyzed ~10^2 times faster than methyl β-D-xylopyranoside. When locked, *S*-phenyl xylosides were used as donors in glycosylation reactions with methanol as acceptor, they reacted ~10^2 times faster than the conformationally flexible *S*-phenyl xylosides. 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.



174 **175**

Figure 20. Conformationally restricted xylosides.

6 Concluding remarks

Despite being an inexpensive and simple carbohydrate, D-xylose poses special problems concerning the synthesis of analogs. The three hydroxyl groups are all equatorial in the $^4C_1$ 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 analogues thereof to address important questions in both mammalian systems and plant biology.

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References

1. Winkelhausen, E.; Kuzmanova, S. *J. Ferment. Bioeng.* **1998**, *86*, 1-14.
2. Ebringerova, A.; Hromadkova, Z.; Heinze, T. *Adv. Polym. Sci.* **2005**, *186*, 1-67.
3. Scheller, H. V.; Ulvskov, P. *Annu. Rev. Plant Biol.* **2010**, *61*, 263-289.
4. Sjöström, E., *Wood Chemistry: Fundamentals and Applications*. 2nd ed.; Academic Press: San Diego, 1993.
5. Teleman, A.; Lundqvist, J.; Tjerneld, F.; Stalbrand, H.; Dahlman, O. *Carbohydr. Res.* **2000**, *329*, 807-815.
6. Puls, J.; Schuseil, J., Chemistry of hemicelluloses: relationship between hemicellulose structure and enzymes required for hydrolysis. In *Hemicellulose and hemicellulases*, Coughlan, M. P.; Hazlewood, G. P., Eds. Portland Press: London, 1993; pp 1-28.
7. Rennie, E. A.; Scheller, H. V. *Curr. Opin. Biotechnol.* **2014**, *26*, 100-107.
8. Urbanowicz, B. R.; Pena, M. J.; Moniz, H. A.; Moremen, K. W.; York, W. S. *Plant J.* **2014**, *80*, 197-206.
9. Ragauskas, A. J.; Williams, C. K.; Davison, B. H.; Britovsek, G.; Cairney, J.; Eckert, C. A.; Frederick, W. J., Jr.; Hallett, J. P.; Leak, D. J.; Liotta, C. L.; Mielenz, J. R.; Murphy, R.; Templer, R.; Tschaplinski, T. *Science (Washington, DC, U. S.)* **2006**, *311*, 484-489.
10. Broekaert, W. F.; Courtin, C. M.; Verbeke, K.; Van de Wiele, T.; Verstraete, W.; Delcour, J. A. *Crit. Rev. Food Sci. Nutr.* **2011**, *51*, 178-194.
11. Immerzeel, P.; Falck, P.; Galbe, M.; Adlercreutz, P.; Nordberg Karlsson, E.; Stalbrand, H. *LWT--Food Sci. Technol.* **2014**, *56*, 321-327.
12. Falck, P.; Precha-Atsawanan, S.; Grey, C.; Immerzeel, P.; Stalbrand, H.; Adlercreutz, P.; Nordberg Karlsson, E. *J. Agric. Food Chem.* **2013**, *61*, 7333-7340.
13. Berger, K.; Falck, P.; Linninge, C.; Nilsson, U.; Axling, U.; Grey, C.; Stalbrand, H.; Nordberg Karlsson, E.; Nyman, M.; Holm, C.; Adlercreutz, P. *J. Agric. Food Chem.* **2014**, *62*, 8169-8178.
14. Granstroem, T. B.; Izumori, K.; Leisola, M. *Appl. Microbiol. Biotechnol.* **2007**, *74*, 273-276.
15. Beerens, K.; Desmet, T.; Soetaert, W. *J. Ind. Microbiol. Biotechnol.* **2012**, *39*, 823-834.
16. Hahn-Haegerdal, B.; Galbe, M.; Gorwa-Grauslund, M. F.; Liden, G.; Zacchi, G. *Trends Biotechnol.* **2006**, *24*, 549-556.
17. Gilbert, H. J.; Stalbrand, H.; Brumer, H. *Curr. Opin. Plant Biol.* **2008**, *11*, 338-348.
18. Gilbert, H. J. *Plant Physiol.* **2010**, *153*, 444-455.
19. Lombard, V.; Golaconda Ramulu, H.; Drula, E.; Coutinho, P. M.; Henrissat, B. *Nucleic Acids Res.* **2014**, *42*, D490-D495.
20. Davies, G.; Henrissat, B. *Structure (London)* **1995**, *3*, 853-859.
21. Sinnott, M. L. *Chem. Rev.* **1990**, *90*, 1171-1202.
22. Jiang, Z.; Zhu, Y.; Li, L.; Yu, X.; Kusakabe, I.; Kitaoka, M.; Hayashi, K. *J. Biotechnol.* **2004**, *114*, 125-134.
23. Hancock, S. M.; Vaughan, M. D.; Withers, S. G. *Curr. Opin. Chem. Biol.* **2006**, *10*, 509-519.
24. Kim, Y.-W.; Fox, D. T.; Hekmat, O.; Kantner, T.; McIntosh, L. P.; Warren, R. A. J.; Withers, S. G. *Org. Biomol. Chem.* **2006**, *4*, 2025-2032.
25. Suurnakki, A.; Tenkanen, M.; Buchert, J.; Viikari, L. *Adv. Biochem. Eng./Biotechnol.* **1997**, *57*, 261-287.
26. Biely, P., Xylanolytic Enzymes. In *Handbook of Food Enzymology*, Whitaker, J. R.; Voragen, A. G. J.; Wong, D. W. S., Eds. Marcel Dekker: New York, 2003; pp 879-915.
27. Jackson, S.; Nicolson, S. W. *Comp. Biochem. Physiol., Part B: Biochem. Mol. Biol.* **2002**, *131*, 613-620.

28. Lachke, A. *Resonance* **2006**, *11*, 90-92.
29. Johnson, S. A.; Nicolson, S. W.; Jackson, S. *Physiol. Biochem. Zool.* **2006**, *79*, 159-168.
30. Lotz, C. N.; Nicolson, S. W. *Funct. Ecol.* **1996**, *10*, 360-365.
31. Taylor, W. H.; Sinha, A.; Khan, I. A.; McDaniel, S. T.; Esko, J. D. *J. Biol. Chem.* **1998**, *273*, 22260-22266.
32. Eixelsberger, T.; Sykora, S.; Egger, S.; Brunsteiner, M.; Kavanagh, K. L.; Oppermann, U.; Brecker, L.; Nidetzky, B. *J. Biol. Chem.* **2012**, *287*, 31349-31358.
33. Ashikov, A.; Routier, F.; Fuhlrott, J.; Helmus, Y.; Wild, M.; Gerardy-Schahn, R.; Bakker, H. *J. Biol. Chem.* **2005**, *280*, 27230-27235.
34. Prydz, K.; Dalen, K. T. *J. Cell Sci.* **2000**, *113*, 193-205.
35. Yip, G. W.; Smollich, M.; Gotte, M. *Mol. Cancer Ther.* **2006**, *5*, 2139-2148.
36. Afratis, N.; Gialeli, C.; Nikitovic, D.; Tsegenidis, T.; Karousou, E.; Theocharis, A. D.; Pavao, M. S.; Tzanakakis, G. N.; Karamanos, N. K. *FEBS J.* **2012**, *279*, 1177-1197.
37. Sasisekharan, R.; Shriver, Z.; Venkataraman, G.; Narayanasami, U. *Nat. Rev. Cancer* **2002**, *2*, 521-528.
38. Fuster, M. M.; Esko, J. D. *Nat. Rev. Cancer* **2005**, *5*, 526-542.
39. Mizumoto, S.; Ikegawa, S.; Sugahara, K. *J. Biol. Chem.* **2013**, *288*, 10953-10961.
40. Rahuel-Clermont, S.; Daligault, F.; Piet, M.-H.; Gulberti, S.; Netter, P.; Branlant, G.; Magdalou, J.; Lattard, V. *Biochem. J.* **2010**, *432*, 303-311.
41. Gotting, C.; Kuhn, J.; Kleesiek, K. *Cell. Mol. Life Sci.* **2007**, *64*, 1498-1517.
42. Schon, S.; Prante, C.; Bahr, C.; Kuhn, J.; Kleesiek, K.; Gotting, C. *J. Biol. Chem.* **2006**, *281*, 14224-14231.
43. Almeida, R.; Levery, S. B.; Mandel, U.; Kresse, H.; Schwientek, T.; Bennett, E. P.; Clausen, H. *J. Biol. Chem.* **1999**, *274*, 26165-26171.
44. Bai, X.; Zhou, D.; Brown, J. R.; Crawford, B. E.; Hennet, T.; Esko, J. D. *J. Biol. Chem.* **2001**, *276*, 48189-48195.
45. Kitagawa, H.; Tone, Y.; Tamura, J.-i.; Neumann, K. W.; Ogawa, T.; Oka, S.; Kawasaki, T.; Sugahara, K. *J. Biol. Chem.* **1998**, *273*, 6615-6618.
46. Sugahara, K.; Mizuno, N.; Okumura, Y.; Kawasaki, T. *Eur. J. Biochem.* **1992**, *204*, 401-406.
47. Sugahara, K.; Kitagawa, H. *Curr. Opin. Struct. Biol.* **2000**, *10*, 518-527.
48. Fransson, L.-A.; Belting, M.; Jonsson, M.; Mani, K.; Moses, J.; Oldberg, A. *Matrix Biol.* **2000**, *19*, 367-376.
49. Ueno, M.; Yamada, S.; Zako, M.; Bernfield, M.; Sugahara, K. *J. Biol. Chem.* **2001**, *276*, 29134-29140.
50. Moses, J.; Oldberg, A.; Fransson, L.-A. *Eur. J. Biochem.* **1999**, *260*, 879-884.
51. Koike, T.; Izumikawa, T.; Tamura, J.-I.; Kitagawa, H. *Biochem. J.* **2009**, *421*, 157-162.
52. Koike, T.; Izumikawa, T.; Sato, B.; Kitagawa, H. *J. Biol. Chem.* **2014**, *289*, 6695-6708.
53. Wen, J.; Xiao, J.; Rahdar, M.; Choudhury, B. P.; Cui, J.; Taylor, G. S.; Esko, J. D.; Dixon, J. E. *Proc. Natl. Acad. Sci. U. S. A.* **2014**, Ahead of Print.
54. Carlsson, P.; Kjellen, L. *Handb. Exp. Pharmacol.* **2012**, *207*, 23-41.
55. Helting, T.; Roden, L. *J. Biol. Chem.* **1969**, *244*, 2790-2798.
56. Okayama, M.; Kimata, K.; Suzuki, S. *J. Biochem.* **1973**, *74*, 1069-1073.
57. Robinson, H. C.; Brett, M. J.; Tralaggan, P. J.; Lowther, D. A.; Okayama, M. *Biochem. J.* **1975**, *148*, 25-34.
58. O'Connell, M. P.; Weeraratna, A. T. *Pigm. Cell Melanoma Res.* **2011**, *24*, 1133-1147.
59. Mani, K.; Belting, M.; Ellervik, U.; Falk, N.; Svensson, G.; Sandgren, S.; Cheng, F.; Fransson, L.-A. *Glycobiology* **2004**, *14*, 387-397.
60. Nilsson, U.; Johnsson, R.; Fransson, L.-A.; Ellervik, U.; Mani, K. *Cancer Res.* **2010**, *70*, 3771-3779.

61. Garud, D. R.; Tran, V. M.; Victor, X. V.; Koketsu, M.; Kuberan, B. *J. Biol. Chem.* **2008**, *283*, 28881-28887.
62. Tsuzuki, Y.; Nguyen, T. K. N.; Garud, D. R.; Kuberan, B.; Koketsu, M. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 7269-7273.
63. Fritz, T. A.; Lugemwa, F. N.; Sarkar, A. K.; Esko, J. D. *J. Biol. Chem.* **1994**, *269*, 300-307.
64. Abrahamsson, C.-O.; Ellervik, U.; Eriksson-Bajtner, J.; Jacobsson, M.; Mani, K. *Carbohydr. Res.* **2008**, *343*, 1473-1477.
65. Robinson, H. C.; Lindahl, U. *Biochem. J.* **1981**, *194*, 575-586.
66. Sobue, M.; Habuchi, H.; Ito, K.; Yonekura, H.; Oguri, K.; Sakurai, K.; Kamohara, S.; Ueno, Y.; Noyori, R.; Suzuki, S. *Biochem. J.* **1987**, *241*, 591-601.
67. Lugemwa, F. N.; Esko, J. D. *J. Biol. Chem.* **1991**, *266*, 6674-6677.
68. Tran, V. M.; Victor, X. V.; Yockman, J. W.; Kuberan, B. *Glycoconjugate J.* **2010**, *27*, 625-633.
69. Tran, V. M.; Kuberan, B. *Bioconjugate Chem.* **2014**, *25*, 262-268.
70. Johnsson, R.; Mani, K.; Cheng, F.; Ellervik, U. *J. Org. Chem.* **2006**, *71*, 3444-3451.
71. Holmqvist, K.; Persson, A.; Johnsson, R.; Lofgren, J.; Mani, K.; Ellervik, U. *Bioorg. Med. Chem.* **2013**, *21*, 3310-3317.
72. Kuberan, B.; Ethirajan, M.; Victor, X. V.; Tran, V.; Nguyen, K.; Do, A. *ChemBioChem* **2008**, *9*, 198-200.
73. Schwartz, N. B.; Galligani, L.; Ho, P.-L.; Dorfman, A. *Proc. Natl. Acad. Sci. U. S. A.* **1974**, *71*, 4047-4051.
74. Schwartz, N. B.; Roden, L. *J. Biol. Chem.* **1975**, *250*, 5200-5207.
75. Fukunaga, Y.; Sobue, M.; Suzuki, N.; Kushida, H.; Suzuki, S. *Biochim. Biophys. Acta* **1975**, *381*, 443-447.
76. Robinson, J. A.; Robinson, H. C. *Biochem. J.* **1981**, *194*, 839-846.
77. Kolset, S. O.; Sakurai, K.; Ivhed, I.; Oevervatn, A.; Suzuki, S. *Biochem. J.* **1990**, *265*, 637-645.
78. Freeze, H. H.; Sampath, D.; Varki, A. *J. Biol. Chem.* **1993**, *268*, 1618-1627.
79. Malmberg, J.; Mani, K.; Saewen, E.; Wiren, A.; Ellervik, U. *Bioorg. Med. Chem.* **2006**, *14*, 6659-6665.
80. Jacobsson, M.; Mani, K.; Ellervik, U. *Bioorg. Med. Chem.* **2007**, *15*, 5283-5299.
81. Gulberti, S.; Lattard, V.; Fondeur, M.; Jacquinet, J.-C.; Mulliert, G.; Netter, P.; Magdalou, J.; Ouzzine, M.; Fournel-Gigleux, S. *J. Biol. Chem.* **2005**, *280*, 1417-1425.
82. Cheng, F.; Johnsson, R.; Nilsson, J.; Fransson, L.-A.; Ellervik, U.; Mani, K. *Cancer Lett. (Shannon, Irel.)* **2009**, *273*, 148-154.
83. Nilsson, U.; Jacobsson, M.; Johnsson, R.; Mani, K.; Ellervik, U. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 1763-1766.
84. Lugemwa, F. N.; Sarkar, A. K.; Esko, J. D. *J. Biol. Chem.* **1996**, *271*, 19159-19165.
85. Raman, K.; Ninomiya, M.; Nguyen, T. K. N.; Tsuzuki, Y.; Koketsu, M.; Kuberan, B. *Biochem. Biophys. Res. Commun.* **2011**, *404*, 86-89.
86. Siegbahn, A.; Aili, U.; Ochocinska, A.; Olofsson, M.; Rönnols, J.; Mani, K.; Widmalm, G.; Ellervik, U. *Bioorg. Med. Chem.* **2011**, *19*, 4114-4126.
87. Nguyen, T. K. N.; Tran, V. M.; Sorna, V.; Eriksson, I.; Kojima, A.; Koketsu, M.; Loganathan, D.; Kjellen, L.; Dorsky, R. I.; Chien, C.-B.; Kuberan, B. *ACS Chem. Biol.* **2013**, *8*, 939-948.
88. Siegbahn, A.; Manner, S.; Persson, A.; Tykesson, E.; Holmqvist, K.; Ochocinska, A.; Roennols, J.; Sundin, A.; Mani, K.; Westergren-Thorsson, G.; Widmalm, G.; Ellervik, U. *Chem. Sci.* **2014**, *5*, 3501-3508.

89. Victor, X. V.; Nguyen, T. K. N.; Ethirajan, M.; Tran, V. M.; Nguyen, K. V.; Kuberan, B. *J. Biol. Chem.* **2009**, *284*, 25842-25853.
90. Raman, K.; Kuberan, B. *Mol. BioSyst.* **2010**, *6*, 1800-1802.
91. Mani, K.; Havsmark, B.; Persson, S.; Kaneda, Y.; Yamamoto, H.; Sakurai, K.; Ashikari, S.; Habuchi, H.; Suzuki, S.; Kimata, K.; Malmstrom, A.; Westergren-Thorsson, G.; Fransson, L.-A. *Cancer Res.* **1998**, *58*, 1099-1104.
92. Bakker, H.; Oka, T.; Ashikov, A.; Yadav, A.; Berger, M.; Rana, N. A.; Bai, X.; Jigami, Y.; Haltiwanger, R. S.; Esko, J. D.; Gerardy-Schahn, R. *J. Biol. Chem.* **2009**, *284*, 2576-2583.
93. Purow, B., Notch Inhibition as a Promising New Approach to Cancer Therapy. In *Notch Signaling in Embryology and Cancer*, Reichrath, J.; Reichrath, S., Eds. Springer US: 2012; Vol. 727, pp 305-319.
94. Whitworth, G. E.; Zandberg, W. F.; Clark, T.; Vocadlo, D. J. *Glycobiology* **2010**, *20*, 287-299.
95. Sethi, M. K.; Buettner, F. F.; Krylov, V. B.; Takeuchi, H.; Nifantiev, N. E.; Haltiwanger, R. S.; Gerardy-Schahn, R.; Bakker, H. *J .Biol. Chem.* **2010**, *285*, 1582-1586.
96. Sethi, M. K.; Buettner, F. F.; Ashikov, A.; Krylov, V. B.; Takeuchi, H.; Nifantiev, N. E.; Haltiwanger, R. S.; Gerardy-Schahn, R.; Bakker, H. *J. Biol. Chem.* **2012**, *287*, 2739-2748.
97. Lee, T. V.; Sethi, M. K.; Leonardi, J.; Rana, N. A.; Buettner, F. F.; Haltiwanger, R. S.; Bakker, H.; Jafar-Nejad, H. *PLoS Genet* **2013**, *9*, e1003547.
98. van Ree, R. *Int. Arch. Allergy Immunol.* **2002**, *129*, 189-197.
99. Faye, L.; Chrispeels, M. *Glycoconjugate J.* **1988**, *5*, 245-256.
100. Starr, R. C.; Marner, F. J.; Jaenicke, L. *Proc. Natl. Acad. Sci. U. S. A.* **1995**, *92*, 641-645.
101. Takanashi, S.-i.; Mori, K. *Eur. J. Org. Chem.* **1998**, *1998*, 43-55.
102. Capon, B. *Chem. Rev.* **1969**, *69*, 407-498.
103. Hanessian, S.; Lou, B. *Chem. Rev. (Washington, D. C.)* **2000**, *100*, 4443-4463.
104. Deng, S.; Yu, B.; Lou, Y.; Hui, Y. *J. Org. Chem.* **1999**, *64*, 202-208.
105. Damez, C.; Bouquillon, S.; Harakat, D.; Henin, F.; Muzart, J.; Pezron, I.; Komunjer, L. *Carbohydr. Res.* **2007**, *342*, 154-162.
106. Roy, D. K.; Bordoloi, M. *J. Carbohydr. Chem.* **2008**, *27*, 300-308.
107. Gorityala, B. K.; Ma, J.; Pasunooti, K. K.; Cai, S.; Liu, X.-W. *Green Chem.* **2011**, *13*, 573-577.
108. Aouad, M. E. A.; Meslouti, A. E.; Uzan, R.; Beaupere, D. *Tetrahedron Lett.* **1994**, *35*, 6279-6282.
109. Sharma, S. K.; Corrales, G.; Penades, S. *Tetrahedron Lett.* **1995**, *36*, 5627-5630.
110. Zerrouki, R.; Billard, L.; Granet, R.; Krausz, P. *Nucleosides, Nucleotides Nucleic Acids* **2004**, *23*, 749-754.
111. Auge, J.; Sizun, G. *Green Chem.* **2009**, *11*, 1179-1183.
112. Delacroix, S.; Bonnet, J.-P.; Courty, M.; Postel, D.; Van Nhien, A. N. *Carbohydr. Res.* **2013**, *381*, 12-18.
113. Pfaffe, M.; Mahrwald, R. *Org. Lett.* **2012**, *14*, 792-795.
114. Schmalisch, S.; Mahrwald, R. *Org. Lett.* **2013**, *15*, 5854-5857.
115. McGeary, R. P.; Rasoul Amini, S.; Tang, V. W. S.; Toth, I. *J. Org. Chem.* **2004**, *69*, 2727-2730.
116. Yu, Y.; Ko, K.-S.; Zea, C. J.; Pohl, N. L. *Org. Lett.* **2004**, *6*, 2031-2033.
117. Moitessier, N.; Chretien, F.; Chapleur, Y.; Humeau, C. *Tetrahedron Lett.* **1995**, *36*, 8023-8026.
118. Rosenberg, H. J.; Riley, A. M.; Marwood, R. D.; Correa, V.; Taylor, C. W.; Potter, B. V. L. *Carbohydr. Res.* **2001**, *332*, 53-66.
119. Drouet, P.; Zhang, M.; Legoy, M. D. *Biotechnol. Bioeng.* **1994**, *43*, 1075-1080.

120. Eneyskaya, E. V.; Brumer, H.; Backinowsky, L. V.; Ivanen, D. R.; Kulminskaya, A. A.; Shabalin, K. A.; Neustroev, K. N. *Carbohydr. Res.* **2003**, *338*, 313-325.
121. Zhang, J.; Kovác, P. *J. Carbohydr. Chem.* **1999**, *18*, 461-469.
122. Excoffier, G.; Gagnaire, D.; Utille, J.-P. *Carbohydr. Res.* **1975**, *39*, 368-373.
123. Li, Y.-w.; Li, Y.-x.; Zhang, W.; Guan, H.-s. *Chin. J. Chem.* **2004**, *22*, 117-118.
124. Johnsson, R.; Ellervik, U. *Synlett* **2005**, *19*, 2939-2940.
125. Vrsanská, M.; Nerinckx, W.; Claeyssens, M.; Biely, P. *Carbohydr. Res.* **2008**, *343*, 541-548.
126. Abad-Romero, B.; Mereiter, K.; Sixta, H.; Hofinger, A.; Kosma, P. *Carbohydr. Res.* **2009**, *344*, 21-28.
127. Watanabe, K.; Itoh, K.; Araki, Y.; Ishido, Y. *Carbohydr. Res.* **1986**, *154*, 165-176.
128. Nudelman, A.; Herzig, J.; Gottlieb, H. E.; Keinan, E.; Sterling, J. *Carbohydr. Res.* **1987**, *162*, 145-152.
129. Herzig, J.; Nudelman, A.; Gottlieb, H. E. *Carbohydr. Res.* **1988**, *177*, 21-28.
130. Itoh, T.; Takamura, H.; Watanabe, K.; Araki, Y.; Ishido, Y. *Carbohydr. Res.* **1986**, *156*, 241-246.
131. Mikamo, M. *Carbohydr. Res.* **1989**, *191*, 150-153.
132. Herzig, J.; Nudelman, A. *Carbohydr. Res.* **1986**, *153*, 162-167.
133. Tran, A. T.; Deydier, S.; Bonnaffé, D.; Le Narvor, C. *Tetrahedron Lett.* **2008**, *49*, 2163-2165.
134. Tiwari, P.; Misra, A. K. *Tetrahedron Lett.* **2006**, *47*, 3573-3576.
135. Bhaumik, K.; Salgaonkar, P. D.; Akamanchi, K. G. *Aust. J. Chem.* **2003**, *56*, 909-911.
136. Violante de Paz Banez, M.; Aznar Moreno, J. A.; Galbis, J. A. *J. Carbohydr. Chem.* **2008**, *27*, 120-140.
137. Nicolaou, K. C.; Mitchell, H. J.; Fylaktakidou, K. C.; Rodríguez, R. M.; Suzuki, H. *Chem. Eur. J.* **2000**, *6*, 3116-3148.
138. Haider, A. F.; Williams, C. K. *J. Carbohydr. Chem.* **2007**, *26*, 411-418.
139. Son, J. B.; Kim, S. N.; Kim, N. Y.; Lee, D. H. *Org. Lett.* **2006**, *8*, 661-664.
140. Nadein, O. N.; Kornienko, A. *Org. Lett.* **2004**, *6*, 831-834.
141. Zandanel, C.; Mioskowski, C.; Baati, R.; Wagner, A. *Tetrahedron* **2009**, *65*, 9395-9402.
142. Koto, S.; Morishima, N.; Takenaka, K.; Kanemitsu, K.; Shimoura, N.; Kase, M.; Kojiro, S.; Nakamura, T.; Kawase, T.; Zen, S. *Bull. Chem. Soc. Jpn.* **1989**, *62*, 3549-3566.
143. Stone, W. E. *Amer. Chem. J.* **1893**, *15*, 653-656.
144. Hudson, C. S.; Johnson, J. M. *J. Am. Chem. Soc.* **1915**, *37*, 2748-2753.
145. Feast, G. C.; Lepitre, T.; Mulet, X.; Conn, C. E.; Hutt, O. E.; Savage, G. P.; Drummond, C. J. *Beilstein J. Org. Chem.* **2014**, *10*, 1578-1588, 1511 pp.
146. Keyari, C. M.; Polt, R. *J. Carbohydr. Chem.* **2010**, *29*, 181-206.
147. Bulman Page, P. C.; Chan, Y.; Liddle, J.; Elsegood, M. R. J. *Tetrahedron* **2014**, *70*, 7283-7305.
148. Gao, M.; Chen, Y.; Tan, S.; Reibenspies, J. H.; Zingaro, R. A. *Heteroat. Chem.* **2008**, *19*, 199-206.
149. Dasgupta, F.; Singh, P. P.; Srivastava, H. C. *Carbohydr. Res.* **1980**, *80*, 346-349.
150. Bhaskar, P. M.; Loganathan, D. *Tetrahedron Lett.* **1998**, *39*, 2215-2218.
151. Bhaskar, P. M.; Loganathan, D. *Synlett* **1999**, 129-131.
152. Mukhopadhyay, B.; Kartha, K. P. R.; Russell, D. A.; Field, R. A. *J. Org. Chem.* **2004**, *69*, 7758-7760.
153. Bartoli, G.; Dalpozzo, R.; de Nino, A.; Maiuolo, L.; Nardi, M.; Procopio, A.; Tagarelli, A. *Green Chem.* **2004**, *6*, 191-192.
154. Dasgupta, S.; Rajput, V. K.; Roy, B.; Mukhopadhyay, B. *J. Carbohydr. Chem.* **2007**, *26*, 91-106.

155. Roy, B.; Dasgupta, S.; Rajput, V. K.; Mukhopadhyay, B. *J. Carbohydr. Chem.* **2008**, *27*, 1-9.
156. Shi, L.; Zhang, G.; Pan, F. *Tetrahedron* **2008**, *64*, 2572-2575.
157. Zhang, J.; Zhang, B.; Zhou, J.; Li, J.; Shi, C.; Huang, T.; Wang, Z.; Tang, J. *J. Carbohydr. Chem.* **2011**, *30*, 165-177.
158. Wu, L.; Yin, Z. *Carbohydr. Res.* **2013**, *365*, 14-19.
159. Das, S. K.; Reddy, K. A.; Krovvidi, V. L. N. R.; Mukkanti, K. *Carbohydr. Res.* **2005**, *340*, 1387-1392.
160. Magnusson, G.; Noori, G.; Dahmen, J.; Frejd, T.; Lave, T. *Acta Chem. Scand., Ser. B* **1981**, *B35*, 213-216.
161. Johnsson, R.; Mani, K.; Ellervik, U. *Bioorg. Med. Chem.* **2007**, *15*, 2868-2877.
162. Garg, H. G.; Hasenkamp, T.; Paulsen, H. *Carbohydr. Res.* **1986**, *151*, 225-232.
163. Jacquinet, J.-C. *Carbohydr. Res.* **2006**, *341*, 1630-1644.
164. Lefever, M. R.; Szabo, L. Z.; Anglin, B.; Ferracane, M.; Hogan, J.; Cooney, L.; Polt, R. *Carbohydr. Res.* **2012**, *351*, 121-125.
165. Schmidt, R. R.; Michel, J.; Roos, M. *Liebigs Ann. Chem.* **1984**, 1343-1357.
166. Oniciu, D.; Bell, R.; McCosar, B.; Bisgaier, C.; Dasseux, J.-L.; Verdijk, D.; Relou, M.; Smith, D.; Regeling, H.; Leemhuis, F.; Ebbers, E.; Mueller, R.; Zhang, L.; Pop, E.; Cramer, C.; Goetz, B.; McKee, A.; Pape, M.; Krause, B. *Synth. Commun.* **2006**, *36*, 365-391.
167. Mori, M.; Ito, Y.; Ogawa, T. *Carbohydr. Res.* **1990**, *195*, 199-224.
168. Ziser, L.; Withers, S. G. *Carbohydr. Res.* **1994**, *265*, 9-17.
169. Chang, C.-W. T.; Hui, Y.; Elchert, B.; Wang, J.; Li, J.; Rai, R. *Org. Lett.* **2002**, *4*, 4603-4606.
170. Brauns, D. H. *J. Am. Chem. Soc.* **1923**, *45*, 833-835.
171. Kunz, H.; Sager, W. *Helv. Chim. Acta* **1985**, *68*, 283-287.
172. Jacobsen, S.; Jensen, S. R.; Pedersen, C. *Acta Chem. Scand.* **1972**, *26*, 1561-1568.
173. Hayashi, M.; Hashimoto, S.-i.; Noyori, R. *Chem. Lett.* **1984**, 1747-1750.
174. Bergamaschi, B. A.; Hedges, J. I. *Carbohydr. Res.* **1996**, *280*, 345-350.
175. Bergamaschi, B. A.; Hedges, J. I. *Carbohydr. Res.* **1995**, *267*, 115-126.
176. Kobayashi, S.; Yoneda, A.; Fukuhara, T.; Hara, S. *Tetrahedron Lett.* **2004**, *45*, 1287-1289.
177. Kobayashi, S.; Yoneda, A.; Fukuhara, T.; Hara, S. *Tetrahedron* **2004**, *60*, 6923-6930.
178. Miethchen, R.; Kolp, G. *J. Fluorine Chem.* **1993**, *60*, 49-55.
179. Fukase, K.; Hase, S.; Ikenaka, T.; Kusumoto, S. *Bull. Chem. Soc. Jpn.* **1992**, *65*, 436-445.
180. Kitamura, M.; Hojo, H.; Nakahara, Y.; Ishimizu, T.; Hase, S. *Glycoconjugate J.* **2004**, *21*, 197-203.
181. Kim, Y.-W.; Chen, H.; Withers, S. G. *Carbohydr. Res.* **2005**, *340*, 2735-2741.
182. Kim, Y.-W.; Zhang, R.; Chen, H.; Withers, S. G. *Chem. Commun. (Cambridge, U. K.)* **2010**, *46*, 8725-8727.
183. Goddard-Borger Ethan, D.; Fiege, B.; Kwan Emily, M.; Withers Stephen, G. *ChemBioChem* **2011**, *12*, 1703-1711.
184. Egan, L. P.; Squires, T. G.; Vercellotti, J. R. *Carbohydr. Res.* **1970**, *14*, 263-266.
185. Ghosh, R.; Chakraborty, A.; Maiti, S. *Tetrahedron Lett.* **2004**, *45*, 9631-9634.
186. Wang, Q.; Fu, J.; Zhang, J. *Carbohydr. Res.* **2008**, *343*, 2989-2991.
187. Hurd, C. D.; Kimbrough, R. D., Jr. *J. Am. Chem. Soc.* **1961**, *83*, 236-240.
188. Tamura, J.-i.; Nishihara, J. *J. Org. Chem.* **2001**, *66*, 3074-3083.
189. Chittenden, G. J. F. *Carbohydr. Res.* **1993**, *242*, 297-301.
190. Ibatullin, F. M.; Selivanov, S. I. *Tetrahedron Lett.* **2002**, *43*, 9577-9580.

191. Giri, S. K.; Kartha, K. P. R. *Synth. Commun.* **2010**, *40*, 3378-3383.
192. Finan, P. A.; Warren, C. D. *J. Chem. Soc.* **1962**, 2823-2824.
193. Capon, B.; Collins, P. M.; Levy, A. A.; Overend, W. G. *J. Chem. Soc.* **1964**, 3242-3254.
194. Sen, A. K.; Banerji, N. *Indian J. Chem., Sect. B* **1989**, *28B*, 818-823.
195. Harreus, A.; Kunz, H. *Liebigs Ann. Chem.* **1986**, 717-730.
196. Bose, N.; Ogawa, A.; von Reuss, S. H.; Yim, J. J.; Ragsdale, E. J.; Sommer, R. J.; Schroeder, F. C. *Angew. Chem., Int. Ed.* **2012**, *51*, 12438-12443.
197. Dale, J. K. *J. Am. Chem. Soc.* **1915**, *37*, 2745-2747.
198. Garazd, Y. L.; Kornienko, E. M.; Maloshtan, L. N.; Garazd, M. M.; Khilya, V. P. *Chem. Nat. Compd.* **2005**, *41*, 508-512.
199. Wen, H.; Lin, C.; Ling, Q.; Ge, H.; Ma, L.; Cao, R.; Wan, Y.; Peng, W.; Wang, Z.; Song, H. *Eur. J. Med. Chem.* **2008**, *43*, 166-173.
200. Chen, H.; Huang, S.-Q.; Xie, J.-Y. *J. Fluorine Chem.* **2006**, *127*, 1130-1136.
201. Xiang, J.-N.; Jiang, L.-H.; Chen, C.-Y.; Fu, Z.-y.; Duan, J.-F. *J. Carbohydr. Chem.* **2006**, *25*, 595-614.
202. Li, J.-F.; Chen, S.-J.; Zhao, Y.; Li, J.-X. *Carbohydr. Res.* **2009**, *344*, 599-605.
203. Xu, W.; Osei-Prempeh, G.; Lema, C.; Davis Oldham, E.; Aguilera, R. J.; Parkin, S.; Rankin, S. E.; Knutson, B. L.; Lehmler, H.-J. *Carbohydr. Res.* **2012**, *349*, 12-23.
204. Satge, C.; Le Bras, J.; Henin, F.; Muzart, J. *Tetrahedron* **2005**, *61*, 8405-8409.
205. Alcaro, S.; Arena, A.; Neri, S.; Ottanà, R.; Ortuso, F.; Pavone, B.; Vigorita, M. G. *Bioorg. Med. Chem.* **2004**, *12*, 1781-1791.
206. Purves, C. B. *J. Am. Chem. Soc.* **1929**, *51*, 3619-3627.
207. Zinner, H.; Koine, A.; Nimz, H. *Chem. Ber.* **1960**, *93*, 2705-2712.
208. Ferrier, R. J.; Furneaux, R. H. *Carbohydr. Res.* **1976**, *52*, 63-68.
209. Contour, M. O.; Defaye, J.; Little, M.; Wong, E. *Carbohydr. Res.* **1989**, *193*, 283-287.
210. Ding, Y. *Synth. Commun.* **1999**, *29*, 3541-3546.
211. Paulsen, H.; Brenken, M. *Liebigs Ann. Chem.* **1988**, 649-654.
212. Gruzman, A.; Shamni, O.; Ben, Y. M.; Sandovski, D.; Elgart, A.; Alpert, E.; Cohen, G.; Hoffman, A.; Katzhendler, Y.; Cerasi, E.; Sasson, S. *J. Med. Chem.* **2008**, *51*, 8096-8108.
213. Weng, S.-S.; Lin, Y.-D.; Chen, C.-T. *Org. Lett.* **2006**, *8*, 5633-5636.
214. Weng, S.-S. *Tetrahedron Lett.* **2009**, *50*, 6414-6417.
215. Kishida, M.; Nishiuchi, M.; Kato, K.; Akita, H. *Chem. Pharm. Bull.* **2004**, *52*, 1105-1108.
216. Suhr, R.; Thiem, J. *J. Carbohydr. Chem.* **2004**, *23*, 261-276.
217. Johnston, J. N.; Paquette, L. A. *Tetrahedron Lett.* **1995**, *36*, 4341-4344.
218. Takeo, K.; Nakagen, M.; Teramoto, Y.; Nitta, Y. *Carbohydr. Res.* **1990**, *201*, 261-275.
219. Hiranuma, S.; Kajimoto, T.; Wong, C.-H. *Tetrahedron Lett.* **1994**, *35*, 5257-5260.
220. Adibekian, A.; Bindschaedler, P.; Timmer, M. S. M.; Noti, C.; Schuetzenmeister, N.; Seeberger, P. H. *Chem. Eur. J.* **2007**, *13*, 4510-4522.
221. Yu, W.; Jin, Z. *J. Am. Chem. Soc.* **2002**, *124*, 6576-6583.
222. Magnusson, G. *J. Org. Chem.* **1977**, *42*, 913-914.
223. Pratt, M. R.; Leigh, C. D.; Bertozzi, C. R. *Org. Lett.* **2003**, *5*, 3185-3188.
224. Dere, R. T.; Kumar, A.; Kumar, V.; Zhu, X.-M.; Schmidt, R. R. *J. Org. Chem.* **2011**, *76*, 7539-7545.
225. Seden, P. T.; Charmant, J. P. H.; Willis, C. L. *Org. Lett.* **2008**, *10*, 1637-1640.
226. Phanumartwiwath, A.; Hornsby, T. W.; Jamalis, J.; Bailey, C. D.; Willis, C. L. *Org. Lett.* **2013**, *15*, 5734-5737.
227. Nicolaou, K. C.; Rodriguez, R. M.; Fylaktakidou, K. C.; Suzuki, H.; Mitchell, H. J. *Angew. Chem., Int. Ed.* **1999**, *38*, 3340-3345.
228. Abe, H.; Shuto, S.; Matsuda, A. *J. Am. Chem. Soc.* **2001**, *123*, 11870-11882.
229. Tzokov, S. B.; Devedjiev, I. T.; Petkov, D. D. *J. Org. Chem.* **1996**, *61*, 12-13.

230. Inoue, H.; Watanabe, M.; Nakayama, H.; Tsuhako, M. *Chem. Pharm. Bull.* **2000**, *48*, 802-807.
231. Larabi, M.-L.; Frechou, C.; Demailly, G. *Tetrahedron Lett.* **1994**, *35*, 2175-2178.
232. El Meslouti, A.; Beaupere, D.; Demailly, G.; Uzan, R. *Tetrahedron Lett.* **1994**, *35*, 3913-3916.
233. Saman, E.; Claeyssens, M.; Kersters-Hilderson, H.; De Bruyne, C. K. *Carbohydr. Res.* **1973**, *30*, 207-210.
234. Agnihotri, G.; Misra, A. K. *Tetrahedron Lett.* **2005**, *46*, 8113-8116.
235. Crich, D.; Mataka, J.; Zakharov, L. N.; Rheingold, A. L.; Wink, D. J. *J. Am. Chem. Soc.* **2002**, *124*, 6028-6036.
236. Garegg, P. J. *Acta Chem. Scand.* **1962**, *16*, 1849-1857.
237. Lee, E.; Bruzzi, A.; O'Brien, E.; O'Colla, P. S. *Carbohydr. Res.* **1979**, *71*, 331-334.
238. Evtushenko, E. V. *Synth. Commun.* **2006**, *36*, 1593-1599.
239. Bashir, N. B.; Phythian, S. J.; Reason, A. J.; Roberts, S. M. *J. Chem. Soc., Perkin Trans. 1* **1995**, 2203-2222.
240. Carpani, G.; Orsini, F.; Sisti, M.; Verotta, L. *Gazz. Chim. Ital.* **1989**, *119*, 463-465.
241. Lopez, R.; Montero, E.; Sanchez, F.; Canada, J.; Fernandez-Mayoralas, A. *J. Org. Chem.* **1994**, *59*, 7027-7032.
242. De, T. C.; Fernandez-Mayoralas, A. *Lett. Org. Chem.* **2004**, *1*, 173-175.
243. Mastihubova, M.; Biely, P. *Carbohydr. Res.* **2004**, *339*, 1353-1360.
244. Marek, M.; Medonos, I.; Kefurt, K.; Jary, J. *Biocatalysis* **1989**, *2*, 235-238.
245. Shimotori, Y.; Hoshi, M.; Soga, K.; Osawa, Y.; Miyakoshi, T. *Carbohydr. Res.* **2014**, *388*, 138-146.
246. López, R.; Pérez, C.; Femández-Mayoralas, A.; Conde, S. *J. Carbohydr. Chem.* **1993**, *12*, 165-171.
247. Mastihubová, M.; Mastihuba, V.; Biely, P. *Carbohydr. Res.* **2004**, *339*, 425-428.
248. Kodera, Y.; Sakurai, K.; Satoh, Y.; Uemura, T.; Kaneda, Y.; Nishimura, H.; Hiroto, M.; Matsushima, A.; Inada, Y. *Biotechnol. Lett.* **1998**, *20*, 177-180.
249. Petrovic, V.; Tomic, S.; Ljevakovic, D.; Tomasic, J. *Carbohydr. Res.* **1997**, *302*, 13-18.
250. Nilsson, M.; Westman, J.; Svahn, C.-M. *J. Carbohydr. Chem.* **1993**, *12*, 23-37.
251. Takeo, K.; Ohguchi, Y.; Hasegawa, R.; Kitamura, S. *Carbohydr. Res.* **1995**, *277*, 231-244.
252. Oscarson, S.; Svahnberg, P. *J. Chem. Soc., Perkin Trans. 1* **2001**, 873-879.
253. Eneyskaya, E. V.; Ivanen, D. R.; Shabalin, K. A.; Kulminskaya, A. A.; Backinowsky, L. V.; Brumer, H., III; Neustroev, K. N. *Org. Biomol. Chem.* **2005**, *3*, 146-151.
254. Yang, B.; Yoshida, K.; Yin, Z.; Dai, H.; Kavunja, H.; El-Dakdouki, M. H.; Sungsuwan, S.; Dulaney, S. B.; Huang, X. *Angew. Chem., Int. Ed.* **2012**, *51*, 10185-10189.
255. Smiatacz, Z. *Carbohydr. Res.* **1974**, *38*, 117-123.
256. Batey, J. F.; Bullock, C.; O'Brien, E.; Williams, J. M. *Carbohydr. Res.* **1975**, *43*, 43-50.
257. Tsuda, Y.; Haque, M. E.; Yoshimoto, K. *Chem. Pharm. Bull.* **1983**, *31*, 1612-1624.
258. Helm, R. F.; Ralph, J.; Anderson, L. *J. Org. Chem.* **1991**, *56*, 7015-7021.
259. Perez-Perez, M.-J.; Rozenski, J.; Herdewijn, P. *Bioorg. Med. Chem. Lett.* **1994**, *4*, 1199-1202.
260. Evtushenko, E. V. *Carbohydr. Res.* **2012**, *359*, 111-119.
261. Kondo, Y. *Carbohydr. Res.* **1982**, *107*, 303-311.
262. Sivakumaran, T.; Jones, J. K. N. *Can. J. Chem.* **1967**, *45*, 2493-2500.
263. Chen, L.; Kong, F. *Carbohydr. Res.* **2002**, *337*, 2335-2341.
264. Khasanova, L. S.; Gimalova, F. A.; Valiullina, Z. R.; Selezneva, N. K.; Ganieva, R. M.; Spirikhin, L. V.; Miftakhov, M. S. *Russ. J. Org. Chem.* **2012**, *48*, 1238-1244.
265. Nishino, S.; Ishido, Y. *Carbohydr. Res.* **1986**, *155*, 161-174.

266. Chalk, R. C.; Ball, D. H. *Carbohydr. Res.* **1973**, *28*, 313-325.
267. Ball, D. H.; Parrish, F. W. *Advan. Carbohyd. Chem.* **1968**, *23*, 233-280.
268. Buchanan, J. G.; Fletcher, R. *J. Chem. Soc., C* **1966**, 1926.
269. Kondo, Y. *Carbohydr. Res.* **1982**, *110*, 339-344.
270. Tsuda, Y.; Nishimura, M.; Kobayashi, T.; Sato, Y.; Kanemitsu, K. *Chem. Pharm. Bull.* **1991**, *39*, 2883-2887.
271. Martinelli, M. J.; Vaidyanathan, R.; Pawlak, J. M.; Nayyar, N. K.; Dhokte, U. P.; Doecke, C. W.; Zollars, L. M. H.; Moher, E. D.; Khau, V. V.; Kosmrlj, B. *J. Am. Chem. Soc.* **2002**, *124*, 3578-3585.
272. Abad-Romero, B.; Haltrich, D.; Potthast, A.; Rosenau, T.; Sixta, H.; Kosma, P. *Macromol. Symp.* **2005**, *232*, 93-97.
273. Ferrier, R. J.; Prasad, D.; Rudowski, A.; Sangster, I. *J. Chem. Soc.* **1964**, 3330-3334.
274. Bochkov, A. F.; Obruchnikov, I. V.; Kochetkov, N. K. *Izv. Akad. Nauk SSSR, Ser. Khim.* **1971**, 1282-1291.
275. Bochkov, A. F.; Obruchnikov, I. V.; Kochetkov, N. K. *Izv. Akad. Nauk SSSR, Ser. Khim.* **1971**, 1291-1295.
276. Goto, F.; Ogawa, T. *Tetrahedron Lett.* **1992**, *33*, 5099-5102.
277. Allen, J. G.; Fraser-Reid, B. *J. Am. Chem. Soc.* **1999**, *121*, 468-469.
278. Yu, W.; Jin, Z. *J. Am. Chem. Soc.* **2001**, *123*, 3369-3370.
279. Hori, M.; Nakatsubo, F. *Carbohydr. Res.* **2001**, *332*, 405-414.
280. Liu, X.; Wada, R.; Boonyarattanakalin, S.; Castagner, B.; Seeberger, P. H. *Chem. Commun.* **2008**, 3510-3512.
281. Haque, M. E.; Kikuchi, T.; Yoshimoto, K.; Tsuda, Y. *Chem. Pharm. Bull.* **1985**, *33*, 2243-2255.
282. Morishima, N.; Koto, S.; Kusuhara, C.; Zen, S. *Bull. Chem. Soc. Jpn.* **1982**, *55*, 631-632.
283. Koto, S.; Morishima, N.; Takenaka, K.; Uchida, C.; Zen, S. *Bull. Chem. Soc. Jpn.* **1985**, *58*, 1464-1468.
284. Wilstermann, M.; Magnusson, G. *J. Org. Chem.* **1997**, *62*, 7961-7971.
285. Chung, M.-K.; Orlova, G.; Goddard, J. D.; Schlaf, M.; Harris, R.; Beveridge, T. J.; White, G.; Hallett, F. R. *J. Am. Chem. Soc.* **2002**, *124*, 10508-10518.
286. Johnsson, R. *Carbohydr. Res.* **2012**, *353*, 92-95.
287. Naleway, J. J.; Raetz, C. R. H.; Anderson, L. *Carbohydr. Res.* **1988**, *179*, 199-209.
288. Rabow, L. E.; Stubbe, J.; Kozarich, J. W. *J. Am. Chem. Soc.* **1990**, *112*, 3196-3203.
289. Rio, S.; Beau, J.-M.; Jacquinet, J.-C. *Carbohydr. Res.* **1991**, *219*, 71-90.
290. Takeo, K.; Murata, Y.; Kitamura, S. *Carbohydr. Res.* **1992**, *224*, 311-318.
291. Tamura, J.-i.; Yamaguchi, A.; Tanaka, J. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 1901-1903.
292. Toyooka, N.; Nakazawa, A.; Himiyama, T.; Nemoto, H. *Heterocycles* **2003**, *59*, 75-79.
293. Jenkins, D. J.; Potter, B. V. L. *J. Chem. Soc., Perkin Trans. 1* **1998**, 41-50.
294. Khasanova, L. S.; Gimalova, F. A.; Torosyan, S. A.; Fatykhov, A. A.; Miftakhov, M. S. *Russ. J. Org. Chem.* **2011**, *47*, 1125-1129.
295. Kongkathip, B.; Kongkathip, N.; Rujirawanich, J. *Synth. Commun.* **2014**, *44*, 2248-2255.
296. Hough, L.; Jones, J. K. N. *J. Chem. Soc.* **1952**, 4349-4351.
297. Garegg, P. J. *Acta Chem. Scand.* **1960**, *14*, 957-958.
298. Petráková, E.; Kovác, P. *Carbohydr. Res.* **1982**, *101*, 141-147.
299. Ernst, C.; Klaffke, W. *J. Org. Chem.* **2003**, *68*, 5780-5783.
300. Levecque, P.; Gammon, D. W.; Kinfe, H. H.; Jacobs, P.; De Vos, D.; Sels, B. *Adv. Synth. Catal.* **2008**, *350*, 1557-1568.
301. Paquette, L. A.; Barriault, L.; Pissarnitski, D.; Johnston, J. N. *J. Am. Chem. Soc.* **2000**, *122*, 619-631.
302. Weimberg, R. *J. Biol. Chem.* **1961**, *236*, 629-635.

303. Buchert, J.; Viikari, L.; Linko, M.; Markkanen, P. *Biotechnol. Lett.* **1986**, *8*, 541-546.
304. Niu, W.; Molefe, M. N.; Frost, J. W. *J. Am. Chem. Soc.* **2003**, *125*, 12998-12999.
305. Pezzotti, F.; Therisod, M. *Carbohydr. Res.* **2006**, *341*, 2290-2292.
306. Janssen, F. W.; Ruelius, H. W. *Biochim. Biophys. Acta, Enzymol.* **1968**, *167*, 501-510.
307. Danneel, H. J.; Roessner, E.; Zeeck, A.; Giffhorn, F. *Eur. J. Biochem.* **1993**, *214*, 795-802.
308. Giffhorn, F.; Kopper, S.; Huwig, A.; Freimund, S. *Enzyme Microb. Technol.* **2001**, *27*, 734-742.
309. Volc, J.; Sedmera, P.; Halada, P.; Prikrylová, V.; Haltrich, D. *Carbohydr. Res.* **2000**, *329*, 219-225.
310. Szarek, W. A.; Schnarr, G. W. *Carbohydr. Res.* **1977**, *55*, C5-C7.
311. Schnarr, G. W.; Szarek, W. A. *Can. J. Chem.* **1978**, *56*, 1752-1757.
312. Augustinsson, B.; Larm, O.; Scholander, E.; Nahar, N. *Carbohydr. Res.* **1986**, *152*, 305-309.
313. Lopez, R.; Fernandez-Mayoralas, A. *J. Org. Chem.* **1994**, *59*, 737-745.
314. Zhong, W.; Moya, C.; Jacobs, R. S.; Little, R. D. *J. Org. Chem.* **2008**, *73*, 7011-7016.
315. Hamilton, J. K.; Smith, F. *J. Am. Chem. Soc.* **1952**, *74*, 5162-5163.
316. Lindberg, B.; Slessor, K. N. *Acta Chem. Scand.* **1967**, *21*, 910-914.
317. Tsuda, Y.; Matsuhira, N.; Kanemitsu, K. *Chem. Pharm. Bull.* **1985**, *33*, 4095-4097.
318. Tsuda, Y.; Hanajima, M.; Matsuhira, N.; Okuno, Y.; Kanemitsu, K. *Chem. Pharm. Bull.* **1989**, *37*, 2344-2350.
319. Watanabe, H.; Nakada, M. *J. Am. Chem. Soc.* **2008**, *130*, 1150-1151.
320. Manner, S.; Ellervik, U. *Synlett* **2014**, *25*, 1271-1274, 1274 pp.
321. Mohanrao, R.; Asokan, A.; Sureshan, K. M. *Chem. Commun. (Cambridge, U. K.)* **2014**, *50*, 6707-6710.
322. Byerley, A. L. J.; Kenwright, A. M.; Steel, P. G. *Tetrahedron Lett.* **1996**, *37*, 9093-9096.
323. Csuk, R.; Furstner, A.; Glanzer, B. I.; Weidmann, H. *J. Chem. Soc., Chem. Commun.* **1986**, 1149-1150.
324. Areces, P.; Carrasco, E.; Mancha, A.; Plumet, J. *Synthesis* **2006**, 946-948.
325. Matsuo, K.; Shindo, M. *Tetrahedron* **2011**, *67*, 971-975.
326. Zhao, J.; Wei, S.; Ma, X.; Shao, H. *Carbohydr. Res.* **2010**, *345*, 168-171.
327. Zhao, J.; Shao, H.; Wu, X.; Shi, S. *Chin. J. Chem.* **2011**, *29*, 1434-1440.
328. Cavallaro, C. L.; Schwartz, J. *J. Org. Chem.* **1995**, *60*, 7055-7057.
329. Kovacs, G.; Toth, K.; Dinya, Z.; Somsak, L.; Micskei, K. *Tetrahedron* **1999**, *55*, 5253-5264.
330. Micskei, K.; Juhasz, Z.; Ratkovic, Z. R.; Somsak, L. *Tetrahedron Lett.* **2006**, *47*, 6117-6120.
331. Alberch, L.; Cheng, G.; Seo, S.-K.; Li, X.; Boulineau, F. P.; Wei, A. *J. Org. Chem.* **2011**, *76*, 2532-2547.
332. Bock, K.; Christiansen, J. K.; Pedersen, C. *Carbohydr. Res.* **1971**, *20*, 73-81.
333. Dunkerton, L. V.; Brady, K. T.; Mohamed, F. *Tetrahedron Lett.* **1982**, *23*, 599-602.
334. Campbell, M. M.; Floyd, A. J.; Lewis, T.; Mahon, M. F.; Ogilvie, R. J. *Tetrahedron Lett.* **1989**, *30*, 1993-1996.
335. Perez-Perez, M.-J.; Doboszewski, B.; Rozenski, J.; Herdewijn, P. *Tetrahedron Asymmetry* **1995**, *6*, 973-984.
336. Yaya, S.; Sorho, S.; Cottier, L.; Descotes, G. *Bull. Chem. Soc. Ethiop.* **2005**, *19*, 233-241.
337. Bozell, J. J.; Tice, N. C.; Sanyal, N.; Thompson, D.; Kim, J.-M.; Vidal, S. *J. Org. Chem.* **2008**, *73*, 8763-8771.
338. Levecque, P.; Gammon, D. W.; Jacobs, P.; De Vos, D.; Sels, B. *Green Chem.* **2010**, *12*, 828-835.

339. Haque, M. E.; Kikuchi, T.; Kanemitsu, K.; Tsuda, Y. *Chem. Pharm. Bull.* **1986**, *34*, 430-433.
340. Haque, M. E.; Kikuchi, T.; Kanemitsu, K.; Tsuda, Y. *Chem. Pharm. Bull.* **1987**, *35*, 1016-1029.
341. Giese, B.; Gilges, S.; Gröninger, K. S.; Lamberth, C.; Witzel, T. *Liebigs Ann. Chem.* **1988**, *1988*, 615-617.
342. Tsuda, Y.; Nishimura, M.; Ito, Y. *Chem. Pharm. Bull.* **1991**, *39*, 1983-1989.
343. Hayes, M. L.; Pennings, N. J.; Serianni, A. S.; Barker, R. *J. Am. Chem. Soc.* **1982**, *104*, 6764-6769.
344. Hricovíniová, Z. *Carbohydr. Res.* **2006**, *341*, 2131-2134.
345. Weinges, K.; Haremsa, S.; Maurer, W. *Carbohydr. Res.* **1987**, *164*, 453-458.
346. Dick, A. J.; Jones, J. K. N. *Can. J. Chem.* **1965**, *43*, 977-982.
347. Renaut, P.; Millet, J.; Sepulchre, C.; Theveniaux, J.; Barberousse, V.; Jeanneret, V.; Vogel, P. *Helv. Chim. Acta* **1998**, *81*, 2043-2052.
348. Kornienko, A.; D'Alarcao, M. *Tetrahedron Lett.* **1997**, *38*, 6497-6500.
349. Kornienko, A.; Turner, D. I.; Jaworek, C. H.; D'Alarcao, M. *Tetrahedron Asymmetry* **1998**, *9*, 2783-2786.
350. Kornienko, A.; d'Alarcao, M. *Tetrahedron Asymmetry* **1999**, *10*, 827-829.
351. Luchetti, G.; Ding, K.; d'Alarcao, M.; Kornienko, A. *Synthesis* **2008**, 3142-3147.
352. Skaanderup, P. R.; Poulsen, C. S.; Hyldtoft, L.; Jorgensen, M. R.; Madsen, R. *Synthesis* **2002**, 1721-1727.
353. Andresen, T. L.; Skytte, D. M.; Madsen, R. *Org. Biomol. Chem.* **2004**, *2*, 2951-2957.
354. Bozo, E.; Boros, S.; Kuszmann, J.; Gacs-Baitz, E.; Parkanyi, L. *Carbohydr. Res.* **1998**, *308*, 297-310.
355. Lalot, J.; Stasik, I.; Demailly, G.; Beaupere, D. *Carbohydr. Res.* **2003**, *338*, 2241-2245.
356. Garcia-Moreno, M. I.; Benito, J. M.; Ortiz Mellet, C.; Garcia Fernandez, J. M. *J. Org. Chem.* **2001**, *66*, 7604-7614.
357. Berges, D. A.; Fan, J.; Devinck, S.; Liu, N.; Dalley, N. K. *Tetrahedron* **1999**, *55*, 6759-6770.
358. Berges, D. A.; Fan, J.; Devinck, S.; Mower, K. *J. Org. Chem.* **2000**, *65*, 889-894.
359. Martinez-Castro, E.; Gonzalez-Benjumea, A.; Lopez, O.; Maya, I.; Alvarez, E.; Fernandez-Bolanos, J. G. *Org. Biomol. Chem.* **2012**, *10*, 4220-4228.
360. Sowden, J. C.; Oftedahl, M. L. *J. Org. Chem.* **1961**, *26*, 1974-1977.
361. Avalos Gonzalez, M.; Jimenez Requejo, J. L.; Palacios Albarran, J. C.; Galbis Perez, J. A. *Carbohydr. Res.* **1986**, *158*, 53-66.
362. Wang, J.; Li, Q.; Ge, Z.; Li, R. *Tetrahedron* **2012**, *68*, 1315-1320.
363. Ranoux, A.; Lemiegre, L.; Benoit, M.; Guegan, J.-P.; Benvegnu, T. *Eur. J. Org. Chem.* **2010**, 1314-1323.
364. Helferich, B.; Ost, W. *Chem. Ber.* **1962**, *95*, 2612-2615.
365. Hoffmann, M. G.; Schmidt, R. R. *Liebigs Ann. Chem.* **1985**, 2403-2419.
366. Shie, J.-J.; Chen, C.-A.; Lin, C.-C.; Ku, A. F.; Cheng, T.-J. R.; Fang, J.-M.; Wong, C.-H. *Org. Biomol. Chem.* **2010**, *8*, 4451-4462.
367. Tamura, S.; Abe, H.; Matsuda, A.; Shuto, S. *Angew. Chem., Int. Ed.* **2003**, *42*, 1021-1023.
368. Junker, H.-D.; Fessner, W.-D. *Tetrahedron Lett.* **1998**, *39*, 269-272.
369. Roslund, M. U.; Sawen, E.; Landstrom, J.; Ronnols, J.; Jonsson, K. H.; Lundborg, M.; Svensson, M. V.; Widmalm, G. *Carbohydr. Res.* **2011**, *346*, 1311-1319.
370. Bérces, A.; Whitfield, D. M.; Nukada, T. *Tetrahedron* **2001**, *57*, 477-491.
371. Mayes, H. B.; Broadbelt, L. J.; Beckham, G. T. *J. Am. Chem. Soc.* **2014**, *136*, 1008-1022.
372. Durette, P. L.; Horton, D. *Carbohydr. Res.* **1971**, *18*, 57-80.
373. Holland, C. V.; Horton, D.; Jewell, J. S. *J. Org. Chem.* **1967**, *32*, 1818-1821.

374. Hall, L. D.; Manville, J. F. *Carbohydr. Res.* **1967**, *4*, 512-513.
375. Thatcher, G. R. J., *The anomeric effect and associated stereoelectronic effects*. American Chemical Society: Washington, 1993.
376. Burkert, U.; Allinger, N. L., *Molecular mechanics*. Washington, D.C., 1982; p 29.
377. Cramer, C. J., *Essentials of computational chemistry : theories and models*. John Wiley: New York, 2002; p 32.
378. Lichtenthaler, F. W.; Lindner, H. J. *Carbohydr. Res.* **1990**, *200*, 91-99.
379. De Bruyn, A.; Anteunis, M.; Van Rijsbergen, R.; Claeyssens, M.; Kovac, P. *J. Carbohydr. Chem.* **1983**, *1*, 301-309.
380. Michell, A. J.; Higgins, H. G. *Tetrahedron* **1965**, *21*, 1109-1120.
381. Kacurakova, M.; Petrakova, E.; Hirsch, J.; Ebringerova, A. *Vib. Spectrosc.* **1994**, *7*, 31-36.
382. Vaino, A. R.; Szarek, W. A. *J. Org. Chem.* **2001**, *66*, 1097-1102.
383. Sagar, R.; Rudic, S.; Gamblin, D. P.; Scanlan, E. M.; Vaden, T. D.; Odell, B.; Claridge, T. D. W.; Simons, J. P.; Davis, B. G. *Chem. Sci.* **2012**, *3*, 2307-2313.
384. Huenig, I.; Painter, A. J.; Jockusch, R. A.; Carcabal, P.; Marzluff, E. M.; Snoek, L. C.; Gamblin, D. P.; Davis, B. G.; Simons, J. P. *Phys. Chem. Chem. Phys.* **2005**, *7*, 2474-2480.
385. Pena, I.; Mata, S.; Martin, A.; Cabezas, C.; Daly, A. M.; Alonso, J. L. *Phys. Chem. Chem. Phys.* **2013**, *15*, 18243-18248.
386. Yuasa, H.; Miyagawa, N.; Nakatani, M.; Izumi, M.; Hashimoto, H. *Org. Biomol. Chem.* **2004**, *2*, 3548-3556.
387. Karamat, S.; Fabian, W. M. F. *J. Phys. Chem. A* **2006**, *110*, 7477-7484.
388. Vitnik, Ž. J.; Fabian, W. M. F. *Computational and Theoretical Chemistry* **2015**, *1051*, 104-109.
389. Roennols, J.; Manner, S.; Siegbahn, A.; Ellervik, U.; Widmalm, G. *Org. Biomol. Chem.* **2013**, *11*, 5465-5472.
390. Roennols, J.; Manner, S.; Ellervik, U.; Widmalm, G. *Org. Biomol. Chem.* **2014**, *12*, 8031-8035.
391. Walford, C.; Jackson, R. F. W.; Rees, N. H.; Clegg, W.; Heath, S. L. *Chem. Commun. (Cambridge)* **1997**, 1855-1856.
392. Abe, H.; Shuto, S.; Tamura, S.; Matsuda, A. *Tetrahedron Lett.* **2001**, *42*, 6159-6161.
393. Gu, G.; Du, Y.; Linhardt, R. J. *J. Org. Chem.* **2004**, *69*, 5497-5500.
394. Amorim, L.; Marcelo, F.; Rousseau, C.; Nieto, L.; Jimenez-Barbero, J.; Marrot, J.; Rauter, A. P.; Sollogoub, M.; Bols, M.; Bleriot, Y. *Chemistry* **2011**, *17*, 7345-7356.