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Modern methods for shortening and extending the carbon chain in carbohydrates at the anomeric center

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1. Introduction

Carbohydrates are the most abundant of the biomolecules in nature, and responsible for two-thirds of the carbon found in the biosphere.[1] In living organisms carbohydrates play important roles in a vast array of biological processes. All cells are coated with a layer of complex carbohydrates, which take part in cell adhesion, cell growth, and intercellular communication.[2] About half of all human proteins are glycosylated and the carbohydrate moieties ensure correct folding, increased stability, and provide epitopes for recognition.[3,4] The carbohydrate-processing enzymes glycosidases and glycosyl transferases control the hydrolysis and the formation of the glycosidic linkage in naturally occurring oligosaccharides. The glycosidases have been the target for several carbohydrate-derived drugs that act as enzyme inhibitors.[5] Contrary to inhibiting biological processes, carbohydrate-based vaccines act in the opposite manner since oligosaccharides conjugated to proteins are able to induce an immune response leading to production of specific antibodies.[6]

The importance of carbohydrates in biological processes as well as the fact that carbohydrates are cheap and easy available have stimulated much interest in synthetic carbohydrate chemistry. The complex structure of carbohydrates makes their synthetic chemistry more diverse than the chemistry of the other two major biomolecules, the amino acids, and the nucleotides. Carbohydrate synthesis mainly involves protecting-group transformations, glycosylation reactions, oxidations/reductions and C–N/C–C bond formation.[7] In the latter category, methods for adjusting the length of the carbon chain in monosaccharides are very useful in order to broaden the synthetic scope of carbohydrates. Smaller carbohydrates are valuable chiral building blocks in the synthetic laboratory while a number of chain-elongated carbohydrates, so-called higher-carbon sugars, are naturally occurring compounds with important biological functions.[8–10] Developing methods for shortening and extending the carbon chain in carbohydrates has been a subject in carbohydrate chemistry for more than a century, and the literature up to 1997 is covered in the book ‘Monosaccharide Sugars: Chemical Synthesis by Chain Elongation, Degradation, and Epimerization’ (Academic Press, 1998).[11] The purpose of the present review is to provide an overview of the synthetic methods for shortening and extending the carbon chain in carbohydrates, which have been presented since 1997.[12] The focus will be on reactions that take place at the anomeric center of aldoses and ketoses.

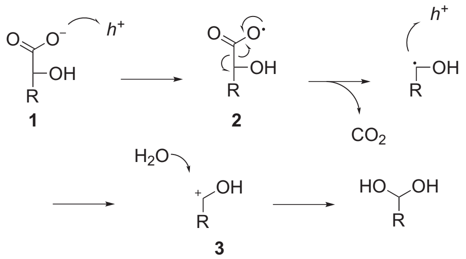
2. Methods for shortening the carbon chain in carbohydrates

2.1. Chain shortening by radical methods

2.1.1. Ruff degradation. The available methods for shortening the chain in unprotected monosaccharides are sparse. The Ruff degradation, which has been known since 1898,[13] converts salts of aldonic acids into aldoses with loss of one carbon atom. The reaction is performed with hydrogen peroxide in alkaline solution in the presence of Fe(III) or Cu(II) salts, where the latter are the most efficient.[14] Due to its importance in the preparation of pentoses, the Ruff degradation continues to receive considerable attention.

The reaction generally occurs in a moderate yield[11] and, since one of the major disadvantages in the Ruff degradation is the separation of the product from large quantities of metal salts, work has been done to cleave carbon dioxide from the aldonate electrochemically or by the use of catalytic amounts of the metal. Jiricny and Stanek utilized a fluidized-bed electrode cell for the production of D-arabinose in approximately 70% yield from sodium D-gluconate without adding any chemical oxidants.[15] The production of D-arabinose from calcium D-gluconate has been achieved in 63% yield by Germain and co-workers using hydrogen peroxide and catalytic amounts of Cu(II)-exchanged zeolites.[16] During the reaction, copper was found to leach from the zeolite and, once the aldonic acid was consumed, copper precipitated on the zeolite again. The catalyst could be recycled twice thereby achieving the advantages of heterogeneous catalysis, although copper was in solution during the reaction.[16]

Several different mechanisms for the Ruff degradation have been proposed over the years, and these have recently been critically reviewed by Stapley and BeMiller.[14] Based on the experimental observations under a variety of conditions they favor a reaction mechanism with two successive one-electron oxidations (Scheme 1). The aldonate **1** is oxidized to an acyloxy radical **2**, which upon loss of carbon dioxide and subsequent oxidation produces a carbocation **3**, that is, captured by the solvent. This mechanism is believed to be valid both in the electrochemical Ruff degradation and in the classical versions, where the anode is replaced by a transition metal, which is regenerated by oxidation with hydrogen peroxide.[14]



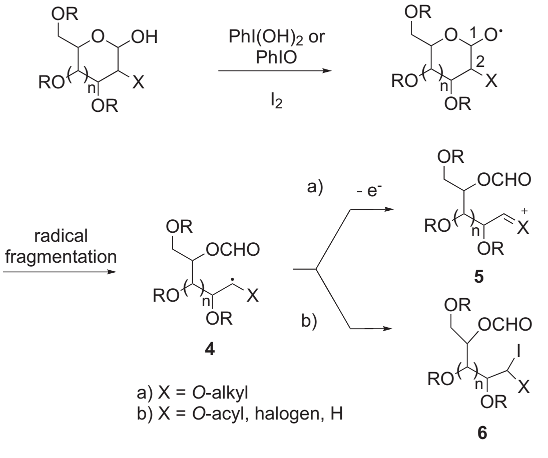
h^+ = anode (or transition metal)

Scheme 1. Proposed mechanism for Ruff degradation.[14]

In transition metal-mediated Ruff degradations the carboxylate and the α-hydroxy group of the aldonate **1** are believed to co-ordinate to the transition metal during the initial oxidation.[14] As a result, uronic acids are not decarboxylated efficiently by iron or copper due to the α-hydroxy group being part of the hemiacetal thereby disabling coordination to the metal, when the uronic acid is in the pyranose form.[17] However, this can be circumvented by switching to the electrochemical method whereby both sodium D-glucuronate and methyl D-glucuronopyranoside have been found to undergo degradation into the corresponding *xylo*-configured pentodialdose.[17]

2.1.2. Alkoxy radical fragmentation. The alkoxy radical fragmentation of anomeric alcohols was first reported in 1992,[18,19] and has, since then, been further developed by Suárez and co-workers to become a useful tool for the synthesis of a variety of chiral building blocks by shortening the carbon chain in aldoses by a single carbon atom.

Under oxidative conditions employing the hypervalent iodine reagents (diacetoxyiodo)benzene or iodosylbenzene, in the presence of iodine, carbohydrate anomeric alcohols undergo alkoxy radical fragmentation cleaving the C1–C2 bond to produce a C2 radical **4**, which can react in two different ways depending on the nature of the substituents at C2 (Scheme 2). The presence of an ether functionality at C2 leads to oxidation of **4** to an oxonium ion **5**, which can be inter- or intramolecularly trapped by nucleophiles (path a). Electron-withdrawing groups decrease the electron density at C2 thereby preventing oxidation of **4**, which is then trapped by iodine leading to 1-iodoalditol **6** with one less carbon (path b). 2-Deoxy- and 2-deoxy-2-haloaldoses also lead to iodine incorporation following path b, and mono-, di-, and trihalo-1-deoxyalditols can be obtained from the corresponding 2-deoxy-,[18] 2-deoxy-2-halo-[20,21], and 2-deoxy-2,2-dihaloaldoses.[22]



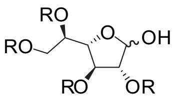
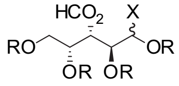
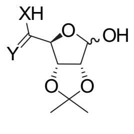
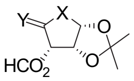
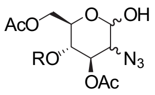
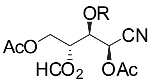
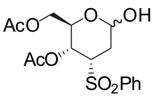
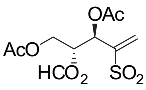
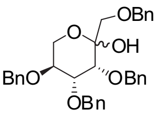
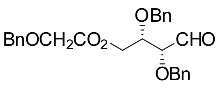
Scheme 2. Alkoxy radical fragmentation.[18]

Fragmentation of 2,3,5,6-tetra-*O*-methyl-D-galactofuranose (Table 1, entry 1) and subsequent nucleophilic attack of acetate from $PhI(OAc)_2$ leads to the corresponding D-lyxose derivative in 85% yield as the mixed acetal. Similar yields are obtained with several benzyl-protected aldoses.[18] The presence of a benzoate at C2 results in the incorporation of iodine to produce the corresponding 1-iodo-D-lyxitol (entry 2). Such iodoalditols can be reduced to the parent alditols by treatment with Bu_3SnH and AIBN, or elongated by radical allylation using allyltributyltin and AIBN (see also Section 3.2.2).[23]

Intramolecular capture of oxonium ions **5** by attack of alcohols, carboxylic acids or carbamates occurs in moderate yield leading to the corresponding cyclized aldoses, alduronic acid lactones or azasugars, respectively (entries 3–5).[24–26] The presence of an azide at C2 leads to aldononitriles with loss of one carbon in excellent yield, and the methodology can even be applied on disaccharides (entries 6 and 7).[27] A sulfone at C3 and no substituent at C2 affords the one carbon shortened alditol possessing a terminal alkene in moderate yield (entry 8).[28] When 2-ketoses are subjected to alkoxy radical fragmentation using the $(CF_3CO_2)_2IPh/I_2$ system, the sugar chain is shortened by two carbon atoms and, in the presence of water, free *aldehydo* sugars can be obtained.[29] Alkoxy radical fragmentation of benzyl-protected L-tagatose, which is readily available from 2,3,4,6-tetra-*O*-benzyl-D-glucopyranose by a samarium(II) iodide-mediated intramolecular hydride shift,[30] gave an L-threose derivative with conveniently differentiated protecting groups at C2, C3, and C4 (entry 9).

Under reductive conditions, alkoxy radicals can be generated from anomeric nitrates or *N*-phthalimido glycosides with Bu_3SnH and AIBN, and the ensuing fragmentation then affords alditols

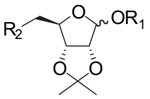
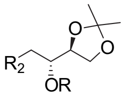
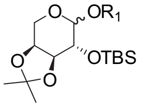
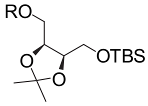
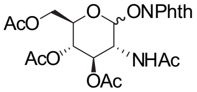
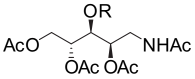
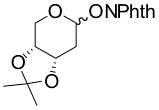
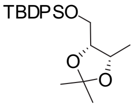
Table 1
Oxidative alkoxy radical fragmentation using $PhI(OAc)_2$ or PhIO and I_2

Entry	Substrate	Substituent(s)	Product	Yield (%)
1		R=Me, X=OAc		85 (1:1)[23]
2		R=Bz, X=I		63 (1:1)[23]
3		X=O, Y=H,H		36[24]
4		X=Y=O		43[25]
5		X=NBoc, Y=H,H		73[26]
6		R=Ac		88[27]
7		R=β-D-Gal		97[27]
8				43[a,28]
9				70[b,29]

[a] Overall yield from triacetylglucal.
[b] $PhI(OAc)_2$ replaced by $(CF_3CO_2)_2IPh$ and H_2O (1 equiv).

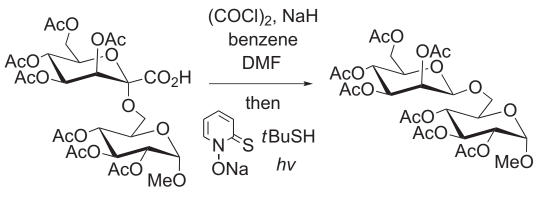
shortened by one carbon atom (Table 2).[31] Partial hydrolysis of the resulting formate is often observed and, under reductive conditions, the degree of hydrolysis depends on the substrate and the reaction time (entries 1, 2, 4, and 5). The methodology requires fully protected carbohydrates, but tolerates functional groups like nitriles and acetamido groups, although the latter afford a moderate yield (entries 3 and 6). 2-Deoxy substrates are easily fragmented to give 1-deoxyalditols (entry 7). In general, *N*-phthalimido derivatives react faster than the corresponding nitrate esters and, due to the instability of the latter compounds in some cases, the two different approaches complement each other very well.

Table 2
Reductive alkoxy radical fragmentation using Bu_3SnH and AIBN[31]

Entry	Substrate	Substituent(s)	Product	Yield (%)	
				R=CHO	R=H
1		R_1=NO_2, R_2=TBSO		79	16
2		R_1=NPhth, R_2=TBSO		42	39
3		R_1=NO_2, R_2=CN		—	83
4		R_1=NO_2		33	18
5		R_1=NPhth		64	31
6				—	47
7				78[a]	—

[a] After hydrolysis of formate and silyl protection.

2.1.3. Barton radical decarboxylation. In an interesting variation of the Hunsdiecker reaction, ulosonic acids are first transformed into *O*-acyl thiohydroxamates (Barton esters) and subsequently subjected to photolysis in the presence of mercaptans to produce one carbon shortened aldoses by a radical decarboxylation process.[32] In contrast to the Hunsdiecker reaction, which generates C_{n-1} 1-bromoalditols,[11] the Barton reductive decarboxylation of 2-ulosonic acids produces C_{n-1} aldoses and, by starting with the ketopyranoside of a given 2-ulosonic acid, the corresponding β-configured aldopyranoside can be formed with excellent stereoselectivity. This is particularly useful for the preparation of β-mannopyranosides as shown with ulosonic acid **7**, which was converted into the Barton ester and then subjected to white-light photolysis to produce mannopyranoside **8** as the pure β-anomer (Scheme 3).[32]

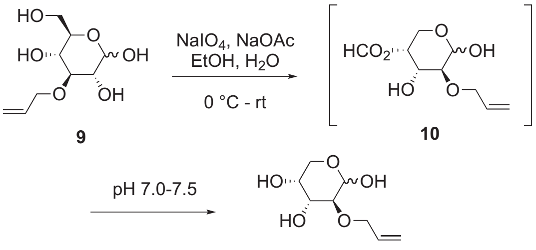


7 67% **8**

Scheme 3. β-Mannoside synthesis from ulosonic acid **7**.[32]

2.2. Oxidative degradation of sugars

2.2.1. Periodate cleavage. Cleavage of 1,2-diols and α-hydroxy carbonyl compounds with periodate or lead tetraacetate to yield the corresponding aldehydes is a well-known and widely applied method for shortening the carbohydrate chain.[11] Oxidative cleavage with sodium periodate is usually performed on partially protected sugars because the oxidation of unprotected sugars cannot be controlled and over-oxidation otherwise occurs. Storz and Vasella applied the periodate oxidation on mono-protected 3-*O*-allyl-D-glucopyranose (**9**), which is easily available in two steps from diacetone D-glucose (Scheme 4).[33] D-Glucose and D-galactose are known to react with sodium periodate primarily in their pyranose form[34] and, by careful control of the pH, only the C1–C2 bond was cleaved by sodium periodate leaving the formyl group as a temporary 'protecting group' on the C4 alcohol in the resulting D-arabinopyranose **10** thereby preventing further periodate cleavage. After quenching the reaction with ethylene glycol and removal of inorganic salts by filtration, adjustment of the pH effected hydrolysis of the intermediate formyl ester. This led to the interesting D-arabinose building block **11** in an excellent overall yield of 95%.[33]



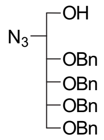
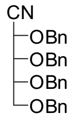
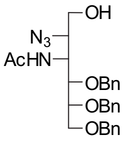
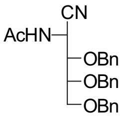
9 **10** **11** 95%

Scheme 4. Periodate cleavage of monoprotected D-glucopyranose.[33]

2.2.2. PCC-Induced shortening of β-azido alcohols. In addition to the alkoxy radical fragmentation (Table 1, entries 6 and 7), aldononitriles can also be produced by an oxidative degradation of 2-azido-2-deoxyalditols with pyridinium chlorochromate (PCC) (Table 3).[35]

The oxidation is performed under very mild conditions using 2 equiv of PCC in dichloromethane at room temperature. On the contrary, β-azido aldose hemiacetals are oxidized to the 2-azidolactones without losing any carbon atoms,[35] and the incompatibility of the PCC-induced degradation with aldoses renders the oxidative alkoxy radical fragmentation in Section 2.1.2 a more widely applicable approach to aldononitriles.

Table 3
Oxidative degradation of β-azido alcohols using PCC[35]

Entry	Substrate	Product	Yield (%)
1			64
2			67

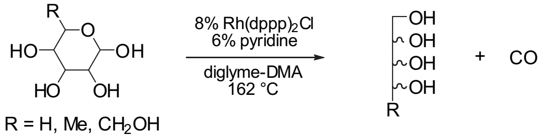
The mechanism for the PCC-mediated degradation of β-azido alcohols is believed to proceed via the 2-azidoaldehyde followed by intramolecular attack of the azide onto the carbonyl group giving a hydroxy-triazole derivative, which is subsequently oxidized by PCC to afford the aldononitrile after loss of carbon monoxide and nitrogen.[35]

2.2.3. Aldose oxidation with oxygen in alkaline solution. A straightforward method for removing one carbon atom from aldoses involves oxidation with molecular oxygen in an aqueous potassium hydroxide solution.[11] This process is amenable to large scale and does not require any protecting groups. The products are the potassium salts of the one-carbon shorter aldonic acids, which can be isolated by crystallization. In this way, D-glucose has been converted into potassium D-arabinonate in 76% yield, D-galactose into potassium D-lyxonate in 68% yield, and L-arabinose into potassium L-erythronate in 64% yield.[36] Subsequent treatment with an acidic ion-exchange resin converts the potassium aldonates into the corresponding aldono-1,4-lactones.[11] The reaction conditions have not seen any further development in recent years, but the exact mechanism is still a matter of debate.[37] Overall, the reaction is believed to proceed by isomerization of the aldose to the corresponding 1,2-enediol, which is then cleaved by molecular oxygen.[37]

2.3. Chain shortening by organometallic methods

2.3.1. Rhodium-catalyzed decarbonylation. A procedure for decarbonylation of unprotected and partially protected aldoses by means of rhodium catalysis has been developed. By employing catalytic amounts of $Rh(dppp)_2Cl$, which is easily prepared in two steps from $RhCl_3$, unprotected aldoses can be decarbonylated to their one-carbon shorter alditols in yields of around 70% by heating to 162 °C in a diglyme—DMA solution (Table 4, entries 1–7).[38] The decarbonylation reaction is limited by the amount of sugar available as the free aldehyde and, as a result, the addition of mutarotation catalysts, such as acetic acid or, more efficiently, pyridine has a beneficial effect on both the reaction time and the yield. N-Acetyl-D-glucosamine (entry 8) suffers from a poor reactivity due to coordination of the N-acetyl group to rhodium thereby leading to a significantly lower yield than the other aldoses. In addition to the desired chain-shortened products, 10–20% of C_{n-1} 1,4-anhydroalditols are formed as byproducts as a result of a rhodium-mediated dehydration of the parent alditol.

Table 4
Catalytic decarbonylation of unprotected aldoses[38]

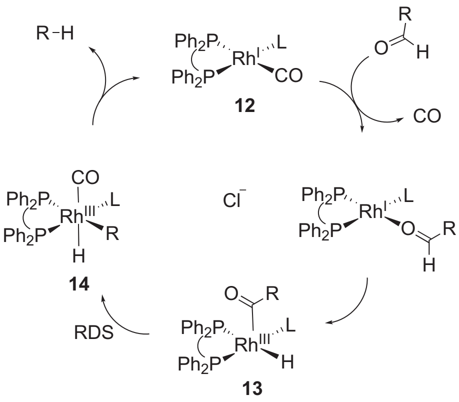


Entry	C_n Aldose	Time (h)	C_{n-1} Alditol	Yield (%)
1	D-Glucose	8	D-Arabinitol	71
2	D-Mannose	8	D-Arabinitol	72
3	D-Galactose	8	D-Arabinitol	56
4	D-Arabinose	6.5	Erythritol	70
5	D-Ribose	6.5	Erythritol	76
6	D-Xylose	7.5	D-Threitol	74
7	L-Rhamnose	10	5-Deoxy-L-arabinitol	71
8	N-Acetyl-D-glucosamine	14.5	1-Acetylamino-1-deoxy-D-arabinitol	40[a]

[a] Pyridine (15%) used.

The catalytic decarbonylation of carbohydrates has been applied in the rhodium-catalyzed Pauson–Khand reaction with enynes in which the aldose acted as a cheap source of carbon monoxide by an in situ decarbonylation.[39]

Experimental and theoretical mechanistic studies have been carried out with simple aldehydes and suggest a catalytic cycle based on the catalytically active species $Rh(dppp)(CO)L^+$ (**12**), where L is a spectator ligand (Scheme 5).[40] The ligand L is most likely a second molecule of carbon monoxide, or, at least initially, a chloride ligand. The mechanism consists of four elementary steps: coordination of the aldehyde to **12** with loss of the carbon monoxide ligand, oxidative addition to produce **13**, migratory extrusion of carbon monoxide to give **14** and, finally, reductive elimination. A comparison of the experimentally determined kinetic isotope effect and the theoretical value from DFT calculations suggests that the migratory extrusion (**13**→**14**) is the rate-determining step.[40]



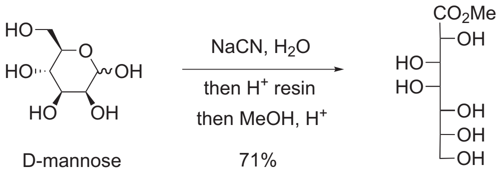
Scheme 5. Proposed catalytic cycle for Rh-catalyzed decarbonylation of aldehydes.[40]

3. Methods for extending the carbon chain in carbohydrates

3.1. Chain elongation by addition of carbanion

3.1.1. Kiliani ascension. The Kiliani ascension is one of the longest-known tools to extend the carbon chain in carbohydrates.[41] The original procedure employed hydrogen cyanide for converting aldoses into the one-carbon longer aldonic acids, but, in the more modern version, sodium cyanide in water is used together with a workup with an acidic ion-exchange resin.[11] Since a new stereocenter is generated in the product, the Kiliani extension gives rise to two C2 epimeric aldonic acids in a ratio ranging from 1:1 to 3:1. Separation can be achieved by crystallization of suitable derivatives, although the yields are often moderate.[11] In a few cases, however, the

Kiliani reaction affords a good yield of a highly crystalline product, such as in the extension of D-xylose into D-gulono-1,4-lactone, D-glucose into D-*glycero*-D-*gulo*-heptono-1,4-lactone, and D-mannose into methyl D-*glycero*-D-*galacto*-heptonate (Scheme 6).[42]



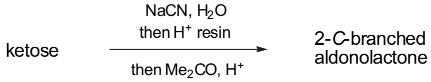
Scheme 6. Kiliani extension of D-mannose into methyl D-*glycero*-D-*galacto*-heptonate.[42]

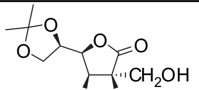
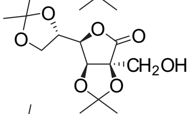
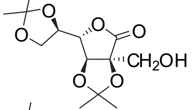
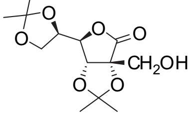
The Kiliani ascension has primarily been used on aldoses due to the low accessibility of several ketoses and difficulties separating the formed products. The Fleet group has developed a new protocol for achieving the Kiliani reaction on ketoses where the two diastereomeric products are separated as the diisopropylidene acetals.[43,44] In this procedure, the ketoses are first treated with aqueous sodium cyanide and the mixture is then subjected to an ion-exchange resin and concentrated. The crude product is reacted with acetone and sulfuric acid to produce the diisopropylidene derivatives of the epimers, which are separated by flash chromatography or crystallization. With D-fructose, D-tagatose, and D-psicose the major diastereomer was isolated in 51, 44, and 38% yield, respectively, by flash chromatography, while L-sorbose gave 17% yield by direct crystallization from the reaction mixture (Table 5).

The problems associated with separation of epimers have also been addressed by Herbert and co-workers by using chromatography on a column of a Sm^{3+}-ion exchange resin. Kiliani ascension of D-erythrose followed by reduction gave an epimeric mixture of D-ribose and D-arabinose, which could be separated on a preparative scale by this method, and the column could be used repeatedly without recharging or cleaning.[45]

3.1.2. Fischer–Sowden homologation. Together with the Kiliani ascension, the Fischer–Sowden homologation[46] is one of the classical ways to obtain one-carbon elongated sugars. In the Fischer–Sowden reaction aldoses are treated with nitromethane and sodium methoxide in methanol followed by workup with an acidic ion-exchange resin to give two epimeric 1-deoxy-1-nitroalditols.[11] These are typically separated by fractional crystallization followed by a Nef reaction[47] with aqueous sodium hydroxide and sulfuric acid to produce the corresponding one-carbon elongated aldoses.

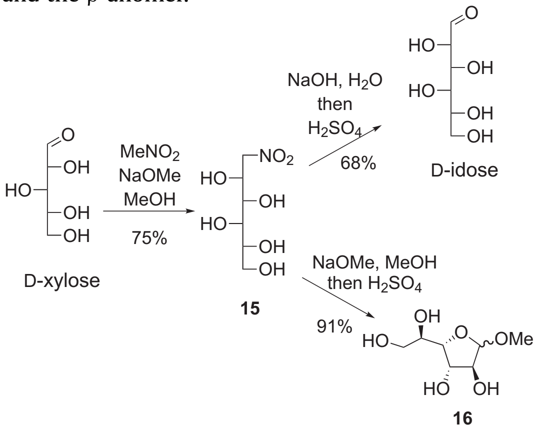
Table 5
One-pot Kiliani ascension and diisopropylidene protection of unprotected ketoses



Entry	Ketose	2-*C*-Branched aldonolactone	Yield (%)
1	D-Fructose		51[43]
2	L-Sorbose		17[43]
3	D-Tagatose		44[44]
4	D-Psicose		38[44]

As in the Kiliani reaction, the Fischer–Sowden homologation gives rise to a 1:1 to 3:1 ratio between the product epimers, and the two addition reactions do not always give the same diastereomer as the major epimer.[11] The Kiliani ascension is often preferred, but the Fischer–Sowden protocol may be useful if the Kiliani reaction fails to give the desired epimer as the major product or is hampered by tedious separation processes.

An example was reported by Dromowicz and Köll where the Fischer–Sowden reaction on D-xylose was optimized (Scheme 7).[48] The separation of the epimeric 1-deoxy-1-nitrohexitols was improved by fractional crystallization and the desired epimer could be isolated in 75% yield. By performing the subsequent Nef reaction under argon, an increased yield of D-idose was obtained giving rise to an overall 51% yield over the two steps.[48] Alternatively, the 1-deoxy-1-nitroalditols may be converted directly into methyl glycofuranosides by treatment with sodium methoxide in methanol followed by addition of sulfuric acid.[49] In this way, methyl D-idofuranoside **16** was obtained in 91% yield from **15** as a 3:2 mixture of the α- and the β-anomer.[49]



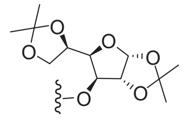
Scheme 7. Improved Fischer–Sowden homologation of D-xylose.[48,49]

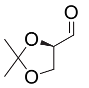
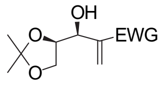
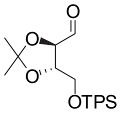
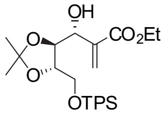
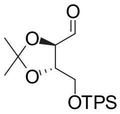
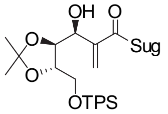
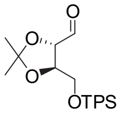
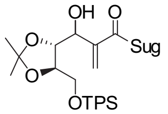
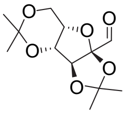
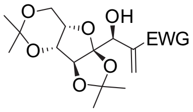
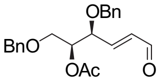
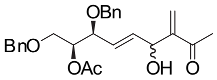
3.1.3. Chain elongation by Baylis–Hillman reaction. Over the last few years, the application of the Baylis–Hillman reaction in carbohydrate chemistry has received considerable interest, in particular from the group of Krishna, who has recently reviewed the field.[50] The reaction requires a free aldehyde and an electron-deficient olefin and is typically carried out with DABCO in either DMSO or a mixture of dioxane and water. The chirality of carbohydrates enables stereoselective Baylis–Hillman reactions and, in Table 6, are shown several approaches for elongation of sugar-derived electrophilic aldehydes. The reaction of ethyl acrylate, methyl vinyl ketone or acrylonitrile with 2,3-*O*-isopropylidene-D-glyceraldehyde occurs in good yield and with a good diastereoselectivity (entries 1–3).[51] The facial selectivity with chiral substrates is typically based on steric effects.[51] Double asymmetric induction using both a sugar-derived acrylate and a sugar aldehyde can lead to an improved diastereoselectivity, as shown in entries 4 and 5. However, the existence of a matched and a mismatched pair of chiral aldehydes and acrylates leads to a change in the diastereoselectivity from excellent to poor, as illustrated in entries 5 and 6.[52] Proper selection of the sugar acrylate can improve the stereoselectivity significantly, but finding suitably matched pairs may be time consuming. As observed for 1-*aldehydo*-2,3;4,6-di-*O*-isopropylidene-L-sorbose (entries 7 and 8), excellent selectivities can also be achieved with non-chiral alkenes as a result of increased steric hindrance at one face of the chiral aldehyde.[51]

α,β-Unsaturated aldehydes derived from sugars cannot easily be used in the Baylis–Hillman reaction, although, in the presence of $Me_2S–TiCl_4$ at 0 °C, moderate yields can be obtained (entry 9). Side

Table 6
Chain elongation of carbohydrates by Baylis–Hillman reaction

Sug =

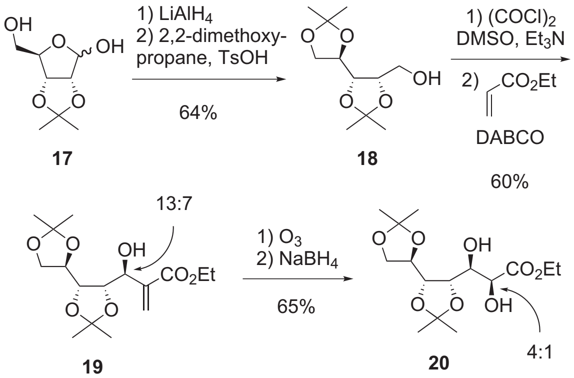


Entry	Aldehyde	EWG	Major product	Yield (%)	dr
1		CO_2Et		82	9:1[51]
2		COMe		69	11:2[51]
3		CN		77	7:1[51]
4		CO_2Et		58	13:7[52]
5		CO-Sug		73	>39:1[52]
6		CO-Sug		78	2:1[52]
7		CO_2Et		80	>39:1[51]
8		CN		85	19:1[51]
9		COMe		55[a,53]	

[a] DABCO replaced by $Me_2S–TiCl_4$ at 0 °C for 15 min.

reactions leading to chloro-substituted byproducts are a major problem, and the reaction has to be stopped before full conversion to afford the Baylis–Hillman product.[53]

If the Baylis–Hillman reaction is combined with ozonolysis, fully hydroxylated higher-carbon sugars can be obtained in relatively few steps. The D-*glycero*-D-*altro*-heptonic acid derivative **20** was isolated in 13% overall yield as the major isomer in six steps from D-ribose, as illustrated in Scheme 8.[54] Reduction and protection of 2,3-*O*-isopropylidene-D-ribofuranose (**17**) afforded the protected alcohol **18**, which was subjected to a Swern oxidation followed by a Baylis–Hillman reaction with ethyl acrylate to give **19**, albeit only as a 13:7 mixture of diastereomers. These could easily be separated, and subsequent ozonolysis and reduction afforded D-*glycero*-D-*altro*-heptonic acid derivative **20** in a 4:1 ratio of diastereomers. Similarly, diacetone D-mannose could be converted into four diastereomeric octonic acid derivatives in nine steps in a 7:3:2:1 ratio.[54]



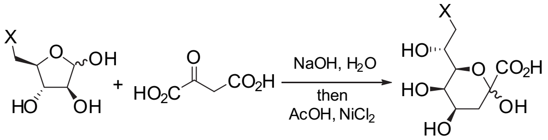
Scheme 8. Synthesis of higher sugars by Baylis–Hillman reaction.[54]

3.1.4. Chain extension based on aldol reaction. In nature, the biosynthesis of monosaccharides is performed by aldol reactions mediated by aldolases. In the chemical laboratory, the aldol reaction has been extensively developed over the past decades and excellent methods have been introduced to control the product stereochemistry.[55] As a result, the aldol reaction has also seen an increasing number of applications for extending the carbon chain in carbohydrates. Under non-chelating conditions, the aldol reaction is relatively insensitive to the protecting groups at the 2- and the 3-hydroxy group of an aldehyde.[56] Instead, the relative stereochemistry at these two positions has a significant impact on the diastereoselectivity with 2,3-*erythro* aldehydes usually giving a good selectivity for the *ribo*-configured product while 2,3-*threo* aldehydes often give less selective addition reactions.[56] A stereochemical model has been proposed to account for these differences.[56] Under chelating conditions, thermodynamic control leads to *anti* products exclusively, whereas under kinetic control the *E* and *Z* enolates predominantly give *anti* and *syn* products, respectively.[11]

Winzar and co-workers recently prepared a range of C8 modified 2-keto-3-deoxy-D-*manno*-octulosonic acid (KDO) derivatives by a sequential aldol condensation–decarboxylation procedure with oxalacetic acid and a C5 modified D-arabinose (Table 7).[57] Improved yields were obtained by employing catalytic amounts of $NiCl_2$ for the decarboxylation step and using a molar excess of oxalacetic acid.[57]

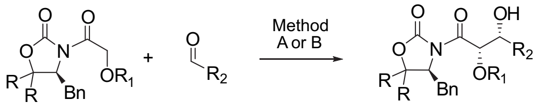
Both the groups of Davies and Seeberger have used aldol reactions with the oxazolidinone auxiliary (Evans aldol) to elongate carbohydrates. This glycolate aldol two-carbon elongation is highly stereoselective and is smoothly carried out using either lithium or boron enolates (Table 8).[58,59] The aldol product in entry 2 was subsequently converted into a protected ethyl thioglycoside of D-galacturonic acid.[59] In entry 3, the *R* enantiomer of the

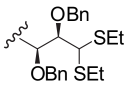
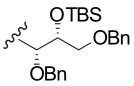
Table 7
KDO derivatives by aldol–decarboxylation procedure[57]



Entry	X	Yield (%)
1	OH	65
2	OMe	84
3	N$_3$	87
4	SH	67

Table 8
Chain elongation by chiral auxiliary aldol reactions[58,59]



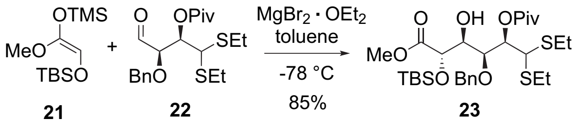
Entry	R$_1$	R$_2$	Method	Yield (%)	dr
1	OBn	CH$_2$OBn	A	77	97:3
2	OPMB		B	90	4.9:1
3	OBn[a]		A	63	>39:1

Method A: Et$_2$BOTf, *i*-Pr$_2$NEt, CH$_2$Cl$_2$, −78 °C, R=Me.[58] Method B: LDA, THF, −78 °C, R=H.[59]

[a] *R* enantiomer of oxazolidinone employed.

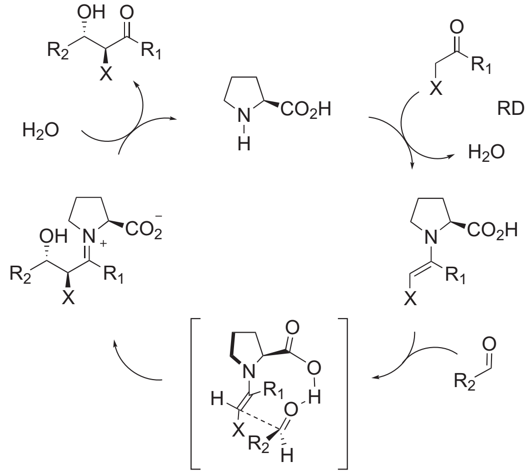
oxazolidinone was employed, since the *S* enantiomer constituted a mismatched pair with the aldehyde and only gave the aldol product as a 77:23 mixture of diastereomers.[58] An iterative elongation procedure can be realized by subsequent protection of the free hydroxy group followed by DIBAL reduction of the oxazolidinone auxiliary to regenerate an aldehyde functionality. This has been used for the preparation of partially protected hexono-1,5-lactones.[58]

The Seeberger group has also used the Mukaiyama aldol reaction for the synthesis of uronic acids (Scheme 9).[60] The chelation-controlled reaction between ketene acetal **21** and aldehyde **22** afforded methyl ester **23** in 85% yield as the only formed diastereomer. Ester **23** was subsequently converted into a protected ethyl thioglycoside of D-glucuronic acid.[60]



Scheme 9. Elongation by Mukaiyama aldol reaction.[60]

Over the last decade, *organocatalytic* aldol reactions have experienced a renaissance in stereoselective synthesis. In these reactions small primary and secondary amines serve as catalysts for the condensation through an enamine mechanism. The catalysts function in much the same way as the type I aldolases in nature where a lysine residue in the active site is responsible for the enamine formation.[55] In organocatalytic aldol reactions, proline has been the most widely employed catalyst and the enamine formation is believed to be the rate-limiting step in the mechanism (Scheme 10). The addition proceeds by activation of the acceptor carbonyl group by the carboxylic acid and, after hydrolysis of the iminium ion, the aldol product is released and the proline catalyst regenerated.[55]

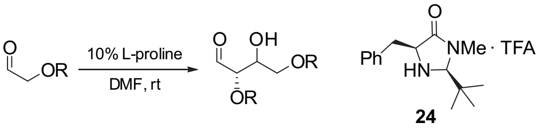


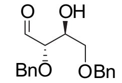
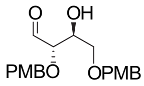
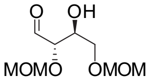
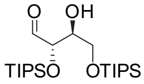
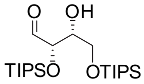
Scheme 10. Mechanism for proline-catalyzed aldol reaction.[55]

Organocatalytic aldol reactions have also been applied for extending the carbon chain in smaller saccharides. In most cases, the donor carbonyl compound has been either glycolaldehyde or dihydroxyacetone and this approach has led to de novo syntheses of a number of aldoses and ketoses.[61,62] The use of glycolaldehyde for saccharide syntheses was initiated by MacMillan in his seminal work on the synthesis of aldotetroses and -hexoses.[63–65] With L-proline as catalyst, various ether-protected glycolaldehydes underwent dimerization into partially protected L-erythroses with good diastereoselectivities and excellent enantioselectivities (Table 9, entries 1–4).[63]

With imidazolidinone catalyst **24**, the diastereoselectivity shifted to afford the D-threose compound as the major product (entry 5).[64] Notably, the product tetroses do not easily undergo additional

Table 9
Organocatalytic dimerization of protected glycolaldehydes



Entry	Product	Yield (%)	*anti*:*syn*	ee (*anti*) (%)
1		73	4:1	98[63]
2		64	4:1	97[63]
3		42	4:1	96[63]
4[a]		92	4:1	95[63]
5[b]		84	1:4	92[c,64]

[a] DMSO used as solvent.

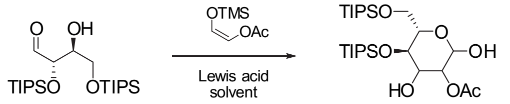
[b] Performed with 10–20% of **24** in ether.

[c] ee for *syn* isomer.

organocatalytic aldol reactions that could have led to product mixtures. Instead, a subsequent Mukaiyama aldol reaction can be carried out with the TIPS-protected L-erythrose (entry 4) to give partially protected L-glucose, L-mannose, and L-allose, depending on the reaction conditions (Table 10).[65] Since the product of the Mukaiyama aldol reaction is a six-membered hemiacetal, a second Mukaiyama reaction does not easily occur and the addition reaction can therefore be stopped after the hexose formation. The diastereoselectivity is highly dependent on the solvent and the Lewis acid in the addition reaction.[65]

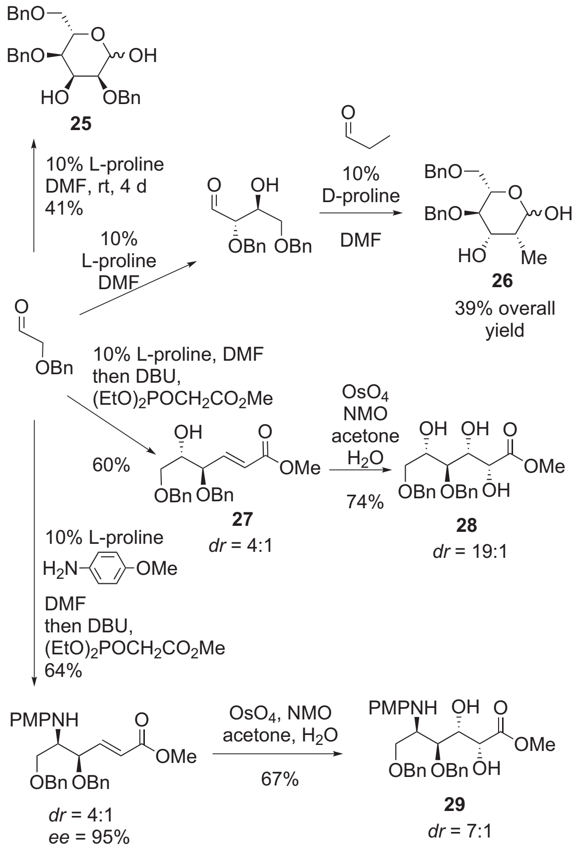
Table 10

Organocatalytic and Lewis acid-catalyzed de novo syntheses of aldohexoses[65]



Product	Lewis acid	Solvent	Yield (%)	*anti*:*syn*	ee (*anti*) (%)
L-Glucose	MgBr$_2$·OEt$_2$	Et$_2$O	79	10:1	95
L-Mannose	MgBr$_2$·OEt$_2$	CH$_2$Cl$_2$	87	>19:1	95
L-Allose	TiCl$_4$	CH$_2$Cl$_2$	97	>19:1	95

Córdova and co-workers have extended the scope of the hexose synthesis by replacing the Mukaiyama aldol reaction with either a second organocatalytic reaction or a Horner–Emmons reaction.[66–68] By using a prolonged reaction time, the L-proline-catalyzed reaction with α-benzyloxyacetaldehyde could be forced to give 41% yield of 2,4,6-tri-*O*-benzyl-L-allopyranose (**25**) with >99% ee (Scheme 11).[66] The slow conversion is probably due to a mismatch in the second aldol reaction between the L-proline-derived enamine and the cross-aldol product from the first dimerization.



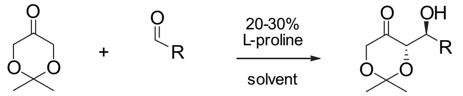
Scheme 11. Hexoses and methyl hexonates from α-benzyloxyacetaldehyde.[66–68]

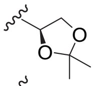
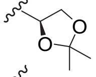
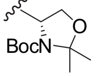
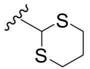
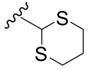
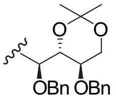
Alternatively, the reaction was stopped after the dimerization of α-benzyloxyacetaldehyde to afford 2,4-di-*O*-benzyl-L-erythrose (see also Table 9, entry 1). This was then subjected to a second organocatalytic reaction with propionaldehyde and D-proline as catalyst, which now proceeded more readily and gave 4,6-di-*O*-benzyl-2-deoxy-2-*C*-methyl-L-mannopyranose (**26**) in 39% overall yield and >99% ee (Scheme 11).[66] If the reaction mixture with the crude 2,4-di-*O*-benzyl-L-erythrose was treated with a phosphorane and DBU, a subsequent Horner–Emmons reaction could be performed in the same pot to afford α,β-unsaturated ester **27** in 60% overall yield as a 4:1 mixture of diastereomers.[67] Dihydroxylation of the C–C double bond in **27** gave methyl 4,6-di-*O*-benzyl-L-altronate **28** in 74% yield as a 19:1 mixture of diastereomers.[67] The aminosugar **29** could be prepared by a similar strategy by performing the L-proline-catalyzed dimerization in the presence of *p*-anisidine (Scheme 11).[68] Unprotected glycolaldehyde will also undergo dimerization with various organocatalysts, but, in these cases, mixtures of erythrose and threose are obtained in moderate yields and with moderate enantioselectivities.[69,70]

Dihydroxyacetone is the other donor carbonyl compound that has been used for de novo synthesis of saccharides by organocatalysis.[62] Unprotected dihydroxyacetone requires an aqueous medium in order to undergo an organocatalyzed reaction with aldehydes and the diastereoselectivity in these cases is usually poor.[71] Protected dihydroxyacetone, however, reacts efficiently with a variety of aldehydes in the presence of an organocatalyst. Isopropylidene-protected dihydroxyacetone has been the most widely used substrate in these reactions and, although it can dimerize in the presence of L-proline, the cross-aldol reaction with aldehydes is a faster transformation.[72] A number of ketoses have been prepared by condensing isopropylidene-protected dihydroxyacetone with smaller aldehydes (Table 11). The reactions are rather slow and require 2–6 days at 2–5 °C for complete

Table 11

Preparation of ketoses by organocatalytic aldol reactions



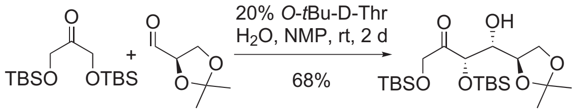
Entry	R	Solvent	Yield (%)	*anti*:*syn*	ee (*anti*) (%)
1	CH$_2$OAc	DMF	60	>15:1	98[73]
2	CH$_2$OBn	DMF	40	>98:2	97[72]
3	CH$_2$OBn	DMSO[a]	85	>19:1	98[75]
4		DMF	76	>98:2	≥98[72]
5		DMSO[a]	74	>19:1	>98[75]
6	 BocN	DMF	80	>98:2	≥96[72]
7	CH(OMe)$_2$	DMF	69	94:6	90[72]
8	CH(OMe)$_2$	DMF	60	18:1	98[73]
9		DMF	88	>98:2	68[72]
10		DMSO[b]	98	99:1	92[74]
11	 OBn OBn	DMSO[b]	51	7:1	–[74]

[a] H$_2$O (5 equiv) also added.

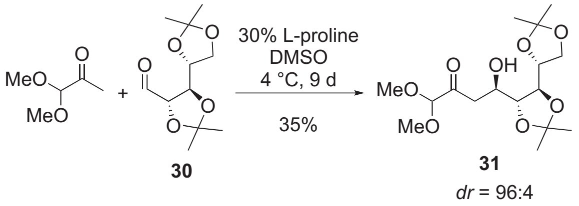
[b] LiCl (1 equiv) also added.

conversion,[72–74] except when 5 equiv of water are added where full conversion is achieved after 24 h at room temperature.[75] The long reaction time may cause some of the acceptor aldehydes to undergo a side reaction by dimerization, which is the main reason for the difference in yield between entries 2 and 3. When chiral acceptor aldehydes are used, match/mismatch situations may arise depending on whether L- or D-proline is employed as the catalyst.[72] Additionally, with dihydroxyacetone is it possible to introduce amino groups in the products if the reactions are carried out in the presence of *p*-anisidine.[75] The product ketoses in Table 11 may also be subjected to an additional aldol reaction mediated by LDA to afford higher-carbon keto sugars.[76]

If dihydroxyacetone is protected with two ether groups and *O*-*tert*-butyl-D-threonine is employed as the catalyst, good levels of *syn* selectivity can be obtained in the aldol reaction.[77] This has been used for the preparation of a protected derivative of D-fructose in 68% yield from the TBS-ether of dihydroxyacetone (Scheme 12).[77] A special donor carbonyl compound for these reactions is the dimethyl acetal of pyruvic aldehyde. This will also react with smaller aldehydes, although the yields are usually lower than those in Table 11 and the reactions are very slow.[78] As an example, the condensation with 2,3;4,5-di-*O*-isopropylidene-D-arabinose (**30**) afforded the protected ulose **31** in 35% yield after 9 days (Scheme 13).[78]

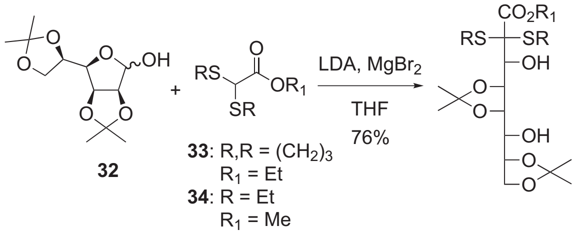


Scheme 12. Synthesis of protected D-fructose.[77]



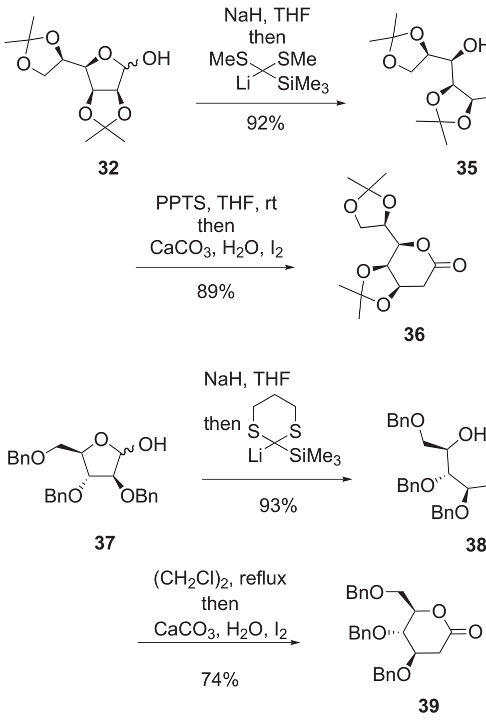
Scheme 13. Chain elongation with pyruvic aldehyde dimethyl acetal.[78]

3.1.5. Chain elongation by treatment with dithioacetals and dithiins. Anions generated from 1,3-dithians with lithium bases, such as *n*-BuLi or LDA have been used for saccharide elongation by addition to aldehydes, lactols, and lactones.[11] Due to the highly basic conditions, only partially protected carbohydrates can be employed for this reaction. Subsequent hydrolysis of the dithioacetal affords the corresponding carbonyl compound. Schmidt and co-workers have utilized the anions of the glyoxylate thioacetals **33** and **34** for elongation of protected sugar lactols.[79,80] High levels of *syn* selectivity are observed if the additions are performed in the presence of magnesium(II) bromide, as illustrated for the reaction with **32** in Scheme 14.[79,80]



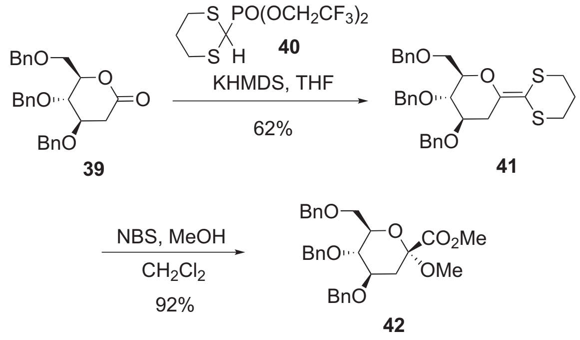
Scheme 14. Chain elongation with dithioacetals.[79]

If a TMS or a dialkylphosphoryl group is bound to the dithioacetal, deprotonation makes it possible to perform a Peterson or a Horner–Emmons reaction with a carbonyl compound.[81,82] This gives rise to a ketene dithioacetal, which can be hydrolyzed to a carboxylic acid. 2-Deoxyaldonolactones can be prepared in this way from furanose hemiacetals, such as **32** and **37** (Scheme 15).[83] Peterson olefination with the anions of 2-trimethylsilyl-1,3-dithiane or the corresponding bis(methylsulfanyl) derivative afforded the dithioacetals **35** and **38**, which upon cyclization and hydrolysis gave the lactones **36** and **39** in good yields.[83]



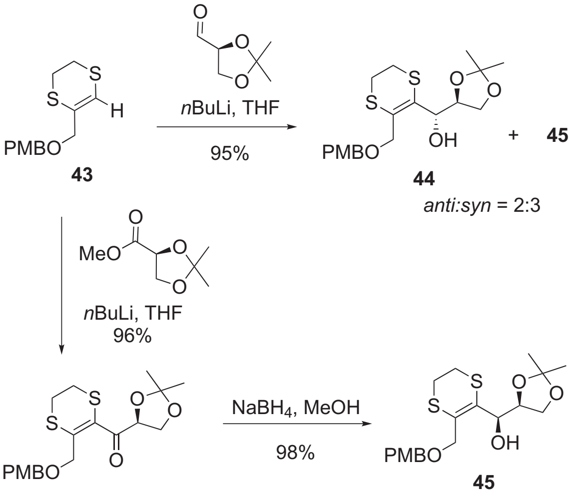
Scheme 15. One-carbon homologation via ketene dithioacetals using Peterson olefination.[83]

The 2-deoxyaldonolactones can be further elongated with the formation of an additional ketene dithioacetal. In this case, the Horner–Emmons reaction with the potassium salt of phosphonate **40** gave the best result (Scheme 16).[84] As an example, lactone **39** was converted into ketene dithioacetal **41**, which upon cleavage with NBS and methanol furnished ulosonic acid derivative **42**.[84]



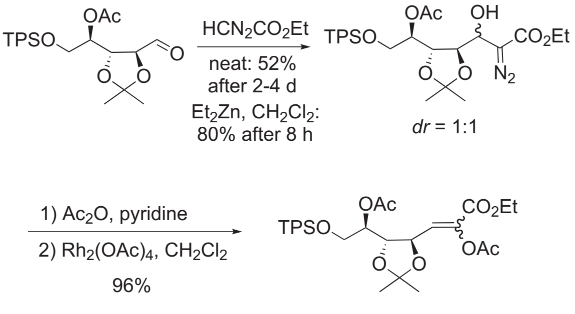
Scheme 16. Horner–Emmons elongation of 2-deoxyaldonolactones via ketene dithioacetals.[84]

A new three-carbon elongation procedure was introduced by the group of Palumbo where 2-substituted 5,6-dihydro-1,4-dithiins were deprotonated with *n*-butyllithium and reacted with sugar electrophiles.[85] Subsequent desulfurization with Raney-Nickel liberated the latent alkene functionality as the *Z* isomer. The homologation has mainly been applied to glyceraldehyde and methyl glycerate (Scheme 17).[86–88] Lithiation of dithiin **43** and reaction with 2,3-*O*-isopropylidene-L-glyceraldehyde afforded a 2:3 mixture of allylic alcohols **44** and **45**. Complete selectivity for the *syn* isomer **45** could be achieved with methyl 2,3-*O*-isopropylidene-L-glycerate as the electrophile followed by reduction with sodium borohydride. The two isomers **44** and **45** could be converted into all eight L-hexoses with desulfurization of the dithiin and dihydroxylation of the resulting alkene as the key steps.[86–88]



Scheme 17. Chain elongation with anion of dithiin **43**.[86–88.]

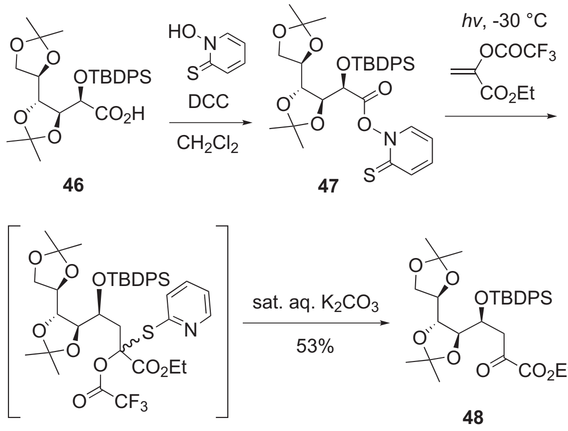
3.1.6. Chain elongation by addition of α-diazo carbonyl compounds. Carbohydrate aldehydes are known to undergo elongation with diazomethane to afford methyl ketones.[11] The group of López-Herrera has extended this reaction to α-diazo carbonyl compounds, such as diazoacetone and ethyl diazoacetate.[89,90] In the absence of additives and a solvent, these diazo compounds undergo addition to carbohydrate aldehydes to afford β-hydroxy-α-diazo carbonyl compounds (Scheme 18).[91] Although the reaction is performed under neat conditions, it is still a rather slow transformation and the yields may vary significantly from one substrate to another.[91] These difficulties have been solved by introducing a new procedure where the addition is performed in the presence of diethylzinc in dichloromethane.[91,92] Under these conditions, carbohydrate hemiacetals are also sufficiently reactive to undergo addition with the diazo compounds.[91] The diazo group in the products can be subsequently removed by catalytic hydrogenation or converted into a vinyl acetate by a two-step procedure (Scheme 18).[91]



Scheme 18. Elongation with ethyl diazoacetate.[91]

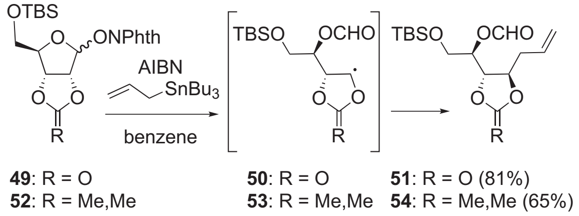
3.2. Chain elongation by radical reactions

3.2.1. Barton radical reaction. Barton and co-workers employed a radical homologation of aldonic acids for the synthesis of 3-deoxy-2-ulosonic acid derivatives.[93,94] By coupling of *N*-hydroxy-2-thiopyridone with aldonic acids, such as protected D-gluconic acid **46**, the corresponding thiohydroxamate esters (Barton esters) like **47** are formed (Scheme 19).[94] Homolytic cleavage of the thiohydroxamate ester by irradiation with a tungsten lamp generates a radical, which after in situ decarboxylation can be trapped by ethyl α-(trifluoroacetoxy)acrylate and a thiopyridyl radical. The thiopyridyl adduct hydrolyzes upon workup with aqueous potassium carbonate to afford the chain-elongated ulosonic acid. In this way, lengthening of gluconic acid **46** was carried out to give ulosonic acid **48** in 53% overall yield as a single diastereomer (Scheme 19).[94] This procedure has also been applied for elongation of 2,3;4,5-di-*O*-isopropylidene-D-ribonic acid.[93]



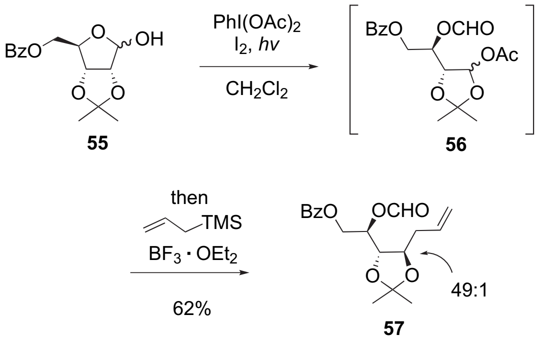
Scheme 19. Chain elongation of aldonic acids using Barton esters.[94]

3.2.2. Tandem alkoxy radical fragmentation–allylation. The alkoxy radical fragmentation, which is usually a chain-shortening process (see Section 2.1.2), can be coupled to a three-carbon extension by a tandem radical fragmentation–allylation reaction. Reductive alkoxy radical fragmentation of *N*-phthalimido glycosides **49** and **52** in the presence of allyltributyltin and AIBN generates an intermediate radical (**50** or **53**), which is trapped by allyltributyltin to produce the corresponding hept-1-enitols **51** and **54** (Scheme 20).[95] The presence of a carbonate at C2 (in **49**) decreases the electron density at this position and enables a faster and higher-yielding reaction with the electron-rich allyltributyltin species (2 h, 81% yield), compared to the isopropylidene acetal **52** (3.5 h, 65%).[95] The formation of **51** and **54** is completely diastereoselective, but some hydrolysis of the formate ester is observed during the reaction (∼10%). By this one-pot transformation, aldoses are first shortened by one carbon atom followed by a three-carbon homologation.



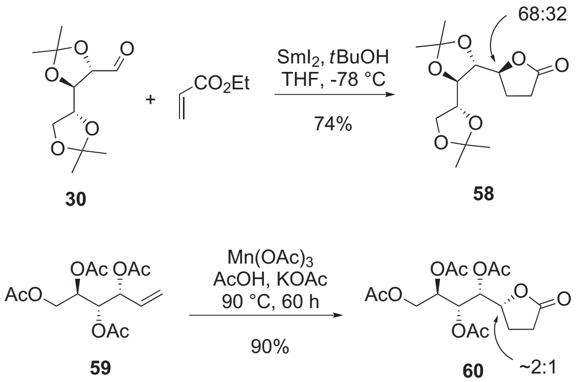
Scheme 20. One-pot alkoxy radical fragmentation–allylation of *N*-phthalimido glycosides.[95]

Alternatively, one carbon shortened aldoses, produced by the previously described *oxidative* alkoxy radical fragmentation (see Section 2.1.2), can be elongated in a one-pot procedure by Lewis acid-mediated allylation (Scheme 21).[96] As mentioned in Section 2.1.2, treatment of anomeric alcohols, such as **55** with (diacetoxyiodo)benzene and iodine produces lower aldoses as their acyclic glycosyl acetates like **56** (Scheme 21).[23] Subsequent addition of allyltrimethylsilane and boron trifluoride etherate affords the allylated product, as illustrated with the formation of **57** in 62% overall yield.[96]



Scheme 21. One-pot alkoxy radical fragmentation–Lewis acid-mediated allylation of aldoses.[96]

3.2.3. *Samarium(II)- and manganese(III)-mediated chain elongation.* Carbohydrates can be extended with two carbon atoms by either a samarium(II) iodide- or a manganese(III) acetate-mediated radical transformation. The reactions have only been applied to protected D-arabinose substrates **30** and **59** (Scheme 22).[97] With samarium(II) iodide, a reductive coupling was performed between aldehyde **30** and ethyl acrylate to give a 68:32 mixture of the D-*gluco* and the D-*manno* configured 2,3-dideoxyoctono-1,4-lactones **58** in 74% yield.[97] Although the diastereoselectivity was moderate, the products could easily be separated by flash chromatography. Alternatively, olefin **59** was reacted with manganese(III) acetate in acetic acid to afford 2,3-dideoxyoctono-1,4-lactones **60** in 90% yield.[97] Interestingly, this transformation occurred with the opposite diastereoselectivity and gave the D-*gluco* and the D-*manno* products in a 1:2 ratio.

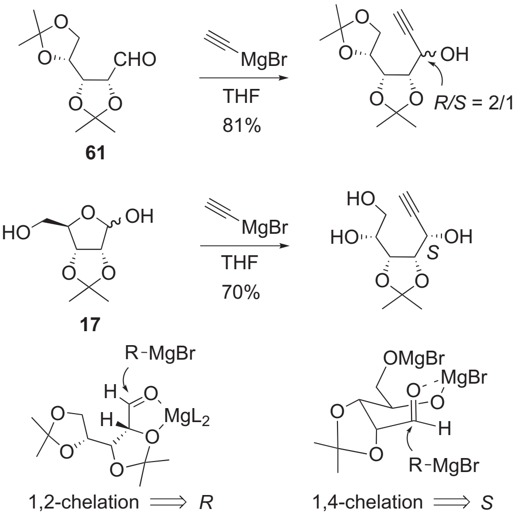


Scheme 22. Samarium(II)- and manganese(III)-mediated elongation of **30** and **59**.[97]

3.3. Organometallic addition reactions to sugar aldehydes, hemiacetals, and lactones

In recent years, the addition of organometallic reagents to various carbohydrates has been one of the most widely employed methods for extending the carbon chain. The substrate can be either a protected carbohydrate aldehyde, a protected/unprotected carbohydrate hemiacetal or a protected aldonolactone. The stereochemical outcome is sometimes difficult to predict and will depend on the presence or absence of chelation and possibly the nature of the chelating species.[11,98] As a result, the reaction conditions, the carbohydrate substrate, and the organometallic reagent will all play a significant role for controlling the stereochemistry in the product.[99]

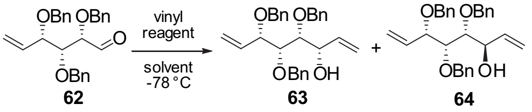
3.3.1. *Addition of organomagnesium, -lithium, and -zinc reagents to aldehydes.* Organomagnesium reagents will usually favor 1,2-chelation and give rise to the 1,2-*syn* (*threo*) diastereomer as the major product.[98] This is observed in the Grignard addition reaction to benzyl-protected aldose hemiacetals and aldehydes where moderate-to-good diastereoselectivities are generally observed in favor of the *threo* isomer.[98,100] With 2,3-*O*-isopropylidene aldehydes and hemiacetals, the outcome depends on the substrate. The oxygen atom in an isopropylidene group participates less effectively in chelation than the oxygen in a benzyl ether and consequently the diastereoselectivity for the Grignard addition to an isopropylidene-protected carbohydrate aldehyde is often moderate.[98] This is illustrated in Scheme 23, where the addition of ethynylmagnesium bromide to 2,3;4,5-di-*O*-isopropylidene-D-ribose (**61**) gave a 2:1 mixture of the *R* and the *S* product, where the former is the expected main product from a 1,2-chelation-controlled addition.[101] With 2,3-*O*-isopropylidene hemiacetals, such as 2,3-*O*-isopropylidene-D-ribofuranose (**17**) and 2,3;5,6-di-*O*-isopropylidene-D-mannofuranose, the selectivity is reversed and the 1,2-*anti* (*erythro*) isomer is the major product in the Grignard addition.[98] This is shown in Scheme 23 with the addition of ethynylmagnesium bromide to **17**, which gave the *S* product as the only observed isomer that was isolated in 70% yield by crystallization.[102] The selectivity reversal has been explained by the formation of a seven-membered chelate to the 4-hydroxy group, which appears to be more favored than a 1,2-chelate with the oxygen at position 2.[101]



Scheme 23. Addition of ethynylmagnesium bromide to 2,3-*O*-isopropylidene-protected D-riboses **61** and **17**.[101,102]

The reaction conditions for the Grignard addition may also have a profound influence on the stereochemical outcome. This was illustrated for the vinyl Grignard addition to aldehyde **62** (and its enantiomer *ent*-**62**) (Table 12).[103,104] The standard reaction conditions with vinylmagnesium bromide in THF gave a 2:1 mixture of the two diastereomers **63** and **64** with the 1,2-*syn* addition product **63** as the major isomer (entry 1).[103] Decreasing the polarity of the

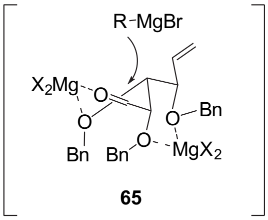
Table 12
Addition of vinyl Grignard and vinyllithium to **62**



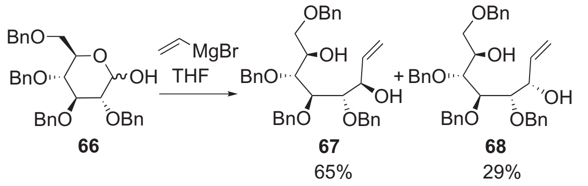
Entry	Vinyl reagent	Solvent	**63**:**64**
1	$CH_2{=}CHMgBr$	THF	2:1[103]
2	$CH_2{=}CHMgBr$	THF/CH_2Cl_2[a]	3:1[103]
3	$CH_2{=}CHMgBr$	CH_2Cl_2	4.3:1[103]
4[b]	$CH_2{=}CHMgBr$	THF/toluene[c]	5:2[104]
5	$CH_2{=}CHMgBr$	CH_2Cl_2[d]	1:1[103]
6	$CH_2{=}CHMgBr$	CH_2Cl_2[e]	1:2[103]
7	$CH_2{=}CHMgBr$	CH_2Cl_2[f]	1:8[103]
8[b]	$CH_2{=}CHMgCl$	THF/toluene[c]	5:1[104]
9	$CH_2{=}CHLi$	THF	1:2.2[103]
10	$CH_2{=}CHLi$	Et_2O	1:3.5[103]

[a] $THF/CH_2Cl_2{=}1:5$.
[b] *ent*-**62** used and *ent*-**63/64** formed.
[c] THF/toluene=1:10.
[d] With 1 equiv $MgBr_2{\cdot}OEt_2$.
[e] With 2 equiv $MgBr_2{\cdot}OEt_2$.
[f] With 3 equiv $MgBr_2{\cdot}OEt_2$.

solvent enhanced the formation of **63** (entries 2–4).[103,104] On the other hand, adding $MgBr_2{\cdot}OEt_2$ as an additive increased the formation of the opposite diastereomer **64** (entries 5–7).[103] The results indicate that the 1,2-chelation leading to the *syn* product **63** is best achieved in a nonethereal solvent and less effectively in the coordinating solvent THF. The reversal in diastereoselectivity upon addition of $MgBr_2{\cdot}OEt_2$ suggests that the coordination mode changes possibly to a 1,3-chelate, such as **65**, which would then favor the *anti* product **64**.[103] A good diastereoselectivity for the *syn* product can also be achieved by using vinylmagnesium chloride (entry 8).[104] This may be due to the lower solubility of magnesium(II) chloride, which would give a lower magnesium concentration in solution and thereby disrupt the formation of the 1,3-chelate. Notably, the addition of vinyllithium to aldehyde **62** affords the 1,2-*anti* product **64** as the major isomer (entries 9 and 10).[103]

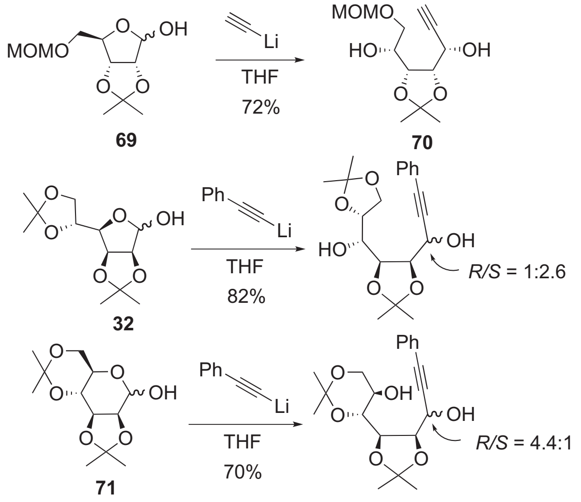


Although the addition of a vinyl Grignard reagent to **62** has been carefully optimized, the results may be difficult to transfer to similar substrates. This was experienced by Cumpstey and co-workers who reacted 2,3,4,6-tetra-*O*-benzyl-D-glucopyranose (**66**) with vinylmagnesium bromide in THF (Scheme 24).[105] These standard conditions gave the two diastereomers **67** and **68** in 65 and 29% yield, respectively, an outcome similar to the result in Table 12, entry 1. However, Cumpstey and co-workers did not observe any improvement or reversal in the diastereoselectivity when trying the other conditions in Table 12, which illustrates that a new substrate is a new addition reaction that has to be carefully analyzed. If these Grignard addition reactions are performed with the corresponding *N*-benzyl glycosylamines as substrates, an *N*-benzylamino group can be introduced in the products.[105,106]



Scheme 24. Addition of vinylmagnesium bromide to 2,3,4,6-tetra-*O*-benzyl-D-glucopyranose **66**.[105]

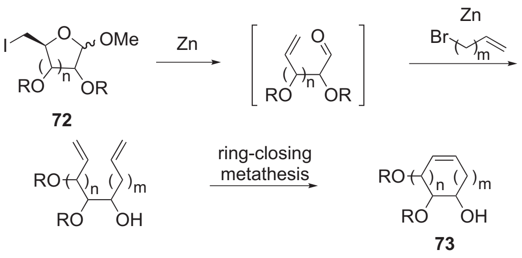
Contrary to magnesium, the lithium cation is not a very effective chelating agent and the addition of organolithium reagents to protected aldose aldehydes and hemiacetals will often occur with a modest diastereoselectivity.[98] Furthermore, the major diastereomer is highly dependent on the structure of the carbohydrate substrate and less dependent on the reaction conditions.[98] Good selectivities, however, can be obtained with some 2,3-*O*-isopropylidene-protected aldoses. Addition of lithium acetylide to 2,3-*O*-isopropylidene-5-*O*-methoxymethyl-D-ribofuranose (**69**) furnished the product with a 20:1 diastereoselectivity where the major isomer **70** from 1,2-*anti* addition was isolated by crystallization in 72% yield (Scheme 25).[107] A similar high selectivity was obtained with the 5-*O*-TBS-protected ribofuranose,[108] while the diastereoselectivity dropped to 2:1 when the reagent was changed to lithium phenylacetylide (not shown).[109] With isopropylidene-protected mannoses, an interesting switch in diastereoselectivity was observed when moving from the furanose to the pyranose substrate. Addition of lithium phenylacetylide to 2,3;5,6-di-*O*-isopropylidene-D-mannofuranose (**32**) gave a 2.6:1 ratio between the 1,2-*syn* and the 1,2-*anti* product in a combined 82% yield (Scheme 25).[99] However, when the same reagent was added to 2,3;4,6-di-*O*-isopropylidene-D-mannopyranose (**71**), the ratio changed to 1:4.4 in favor of the 1,2-*anti* product.[110]



Scheme 25. Addition of lithium acetylides to 2,3-*O*-isopropylidene-protected aldoses.[99,107,110]

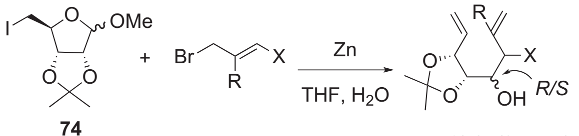
Organozinc reagents are usually not the first choice for the direct alkylation of an aldose aldehyde or hemiacetal.[98] However, in some special cases, zinc reagents may be a valuable alternative for extending the carbon chain. If alkynyllithium reagents are not sufficiently selective in the addition to a protected aldose aldehyde, transmetallation to the corresponding zinc reagent may improve the selectivity in favor of the 1,2-*syn* (*threo*) addition product.[98] Divinylzinc has been shown to give a better diastereoselectivity for the 1,2-*syn* product than vinylmagnesium bromide in the addition to 2,3,5-tri-*O*-benzyl-D-pentofuranoses.[111] Propargylation of protected aldose aldehydes can be achieved with zinc and propargyl bromide under Barbier conditions with very little formation of the related allene.[112,113]

A particularly attractive application of zinc metal for elongation of carbohydrates is achieved when the reaction is combined with a zinc-mediated fragmentation of methyl 5-iodopentofuranosides and 6-iodohexopyranosides (Scheme 26).[114,115] In this tandem reaction, zinc serves a dual role by promoting both the reductive fragmentation and the subsequent alkylation at C1. If the alkylating agent introduces a second C–C double bond, the product will be an α,ω-diene, which can be cyclized by ring-closing olefin metathesis.[114] In this way, the two-step procedure will convert methyl ω-iodoglycosides **72** into functionalized carbocycles **73** that can be further transformed into a variety of natural products.[115–118]



Scheme 26. Zinc-mediated tandem fragmentation–alkylation of ω-iodoglycosides and subsequent ring-closing metathesis.[114,115]

In the zinc-mediated tandem reaction, the alkylation is most commonly carried out with allylic bromides (Scheme 27). A variety of bromides can be employed, as illustrated with the fragmentation–allylation of methyl 5-deoxy-2,3-*O*-isopropylidene-5-iodo-D-ribofuranoside (**74**) in Scheme 27.[114,119–121] The stereochemical outcome depends on the carbohydrate substrate where iodoglycosides with 2,3-*erythro* configuration (from ribose, lyxose, and mannose) give good selectivity for the 1,2-*anti* (*erythro*) product[114,122,123] (except when cinnamylic bromides are employed[114]). For iodoglycosides with 2,3-*threo* configuration, the stereochemical outcome varies, since substrates with *arabino* and *xylo* configuration will favor the 1,2-*anti* addition product,[114,121] while substrates with *gluco* configuration will favor 1,2-*syn* addition.[114,123]



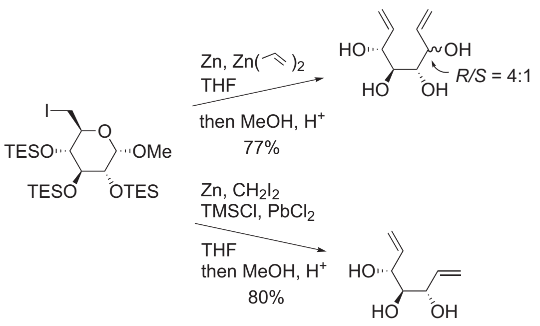
74

a: R = X = H
b: R = CO_2iPr, X = H
c: R = H, X = OBz
d: R = Me, X = OBz

a: 79% (*R*/*S* = 1:4)
b: 98% (*R*/*S* = 1:5)
c: 73% (*R*/*S* = 1:0)
d: 85% (*R*/*S* = 1:0)

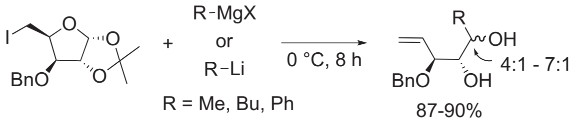
Scheme 27. Fragmentation–allylation with functionalized allylic bromides.[114,119–121.]

Benzylamino groups can be introduced in the products by performing the tandem fragmentation–allylation reaction in the presence of benzylamine.[114] The alkylation can also be performed with propargyl bromide to afford α,ω-enynes, which can be cyclized by ring-closing enyne metathesis.[124] A two-carbon homologation can be carried out if divinylzinc is added during the zinc-mediated fragmentation of the iodoglycoside (Scheme 28).[114] In a similar manner, a one-carbon homologation can be performed if the zinc-mediated fragmentation is carried out in the presence of methylene iodide, a Lewis acid and a catalytic amount of lead(II) chloride (Scheme 28).[114]



Scheme 28. Two- and one-carbon homologation by zinc-mediated tandem reaction.[114]

Besides zinc metal, the tandem fragmentation–alkylation sequence can also be performed with Grignard and organolithium reagents (Scheme 29).[125] Strictly anhydrous conditions and 3.5–5.5 equiv of the organometallic reagents are required, but the method provides a straightforward procedure for the simultaneous introduction of a terminal olefin and a simple alkyl group at C1.[125]

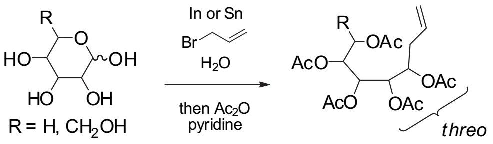


Scheme 29. Fragmentation–alkylation with Grignard and organolithium reagents.[125]

3.3.2. *Indium- and tin-mediated allylation of aldoses.*

In most cases, organometallic addition reactions require a fully protected aldose hemiacetal or aldehyde. With tin and indium, however, allylations can be carried out with unprotected aldoses in aqueous media.[126] The additions are typically performed with 1–2 equiv of the metal and about 3 equiv of allyl bromide either in water, 0.1 M HCl or mixtures with ethanol.[126–128] The rate of the reaction is faster with indium than with tin and, in both cases, increased reactivity is observed when a more finely powdered metal is used.[126,129] With unprotected aldoses, the addition occurs with 1,2-chelation control to give the 1,2-*syn* (*threo*) product as the major diastereomer (Table 13).[126–128] The indium-mediated allylation can also be performed with isopropylidene- and TBS-protected aldoses, where 1,2-chelation is weaker, and, as a result, the 1,2-*anti* (*erythro*) product becomes the major isomer.[121,130,131] Tetraallyltin has also been employed for allylation of unprotected pentoses in aqueous media, but, with this reagent, the diastereoselectivity is lower than that observed in Table 13.[132] The major diastereomer from Table 13, entry 6 has been extended with an additional carbon atom by

Table 13
Indium- and tin-mediated allylation of unprotected sugars



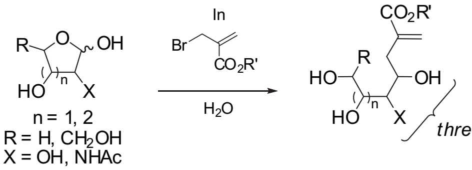
Entry	Aldose	Yield/In[a] (%)	Yield/Sn[a] (%)
1	D-Ribose	95 (5:1)[127]	65 (6:1)[126]
2	D-Arabinose	99 (7:1)[128]	85 (4:1)[126]
3	D-Xylose	96 (18:1)[127]	—
4	D-Lyxose	92 (16:1)[127]	—
5	D-Glucose	63 (5:1)[126]	70 (7:1)[126]
6	D-Mannose	95 (5:1)[128]	90 (6:1)[126]

[a] *threo*/*erythro* ratio in parenthesis.

a rhodium-catalyzed hydroformylation to produce 2,3,4-trideoxy-D-*glycero*-D-*galacto*-decose.[133]

Besides allyl bromide, the additions to unprotected aldoses can also be performed with more functionalized allylic bromides. 2-(Bromomethyl)acrylates and 2-(bromomethyl)acrylic acid have been used for indium-mediated elongation of unprotected aldoses to afford the *threo* isomer as the major product (Table 14).[134–137] Subsequent ozonolysis of the olefin furnishes 3-deoxy-2-ulosonic acids/esters in good overall yields.[134–137]

Table 14
Indium-mediated Reformatsky reaction on unprotected sugars



Entry	Aldose	R′	Yield (%)	*threo*:*erythro*
1	D-Erythrose	*i*-Pr	91	8:1[134]
2	L-Arabinose	Et	>65	1:0[a,135]
3	D-Mannose	Et	>75	1:0[a,135]
4	D-Mannose	H	64	1:0[136]
5	*N*-Acetyl-D-mannosamine	Et	91	4:1[137]
6	*N*-Acetyl-D-mannosamine	H	77	3:1[136]

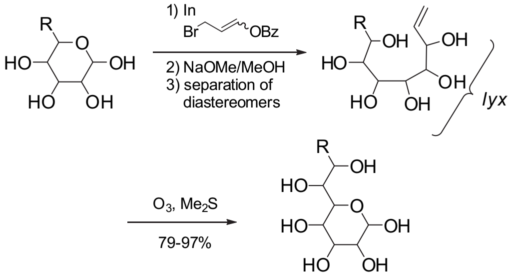
[a] Product isolated as mixture of ethyl ester and lactone.

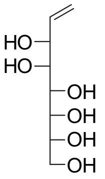
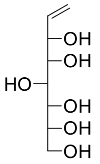
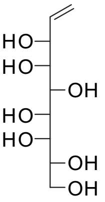
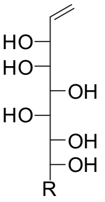
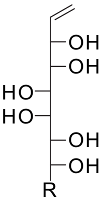
Palmelund and Madsen employed 3-bromopropenyl benzoate in the indium-mediated allylation of unprotected aldoses to afford alditols with a terminal olefin (Table 15).[129] Following the allylation, the crude product was deesterified to give two diastereomers, which were separated. In all cases, the major diastereomer had the *lyxo* configuration at the end of the olefin.[129] Subsequent ozonolysis gave the corresponding heptoses and octoses in good overall yield from the starting pentoses and hexoses.

3.3.3. Metal-mediated additions to aldonolactones. Organometallic reagents can also be added to C1 in aldonolactones and the addition can be stopped at the lactol product. In this case, the carbohydrate substrate has to be fully protected and usually ether or acetal groups are employed. With Grignard and organolithium reagents, the addition occurs in excellent yield, as illustrated with ribonolactone in Table 16.[138–140] Similar yields are obtained for both reagents with benzyl-protected hexonolactones.[141,142] The addition to 6-*O*-acetyl-2,3,4-tri-*O*-benzyl-D-gluconolactone has been studied with several Grignard and organolithium reagents.[143] With the highly reactive methyllithium and allylmagnesium bromide, the addition to C1 was accompanied by partial cleavage of the C6 acetate.[143] With the less reactive phenyl- and benzylmagnesium bromide, the addition to the lactone occurred without concomitant cleavage of the acetate.[143] An alternative reagent for adding a simple methyl group is trimethylaluminum, which, in some cases, may be a good substitute for the more reactive Grignard and lithium reagents.[144]

The addition to an aldonolactone can also be achieved with more functionalized organolithium reagents. Iodomethyllithium, generated in situ from diiodomethane and methyllithium, can be added to the lactone functionality to produce 1-deoxy-1-iodoketoses.[145] This reaction was used in a two-step synthesis of L-fructose **77** from L-arabinonolactone **75** via iodide **76** (Scheme 30).[145] A similar elongation can be performed with 1-ethoxyvinyllithium, as shown in the addition to benzyl-protected

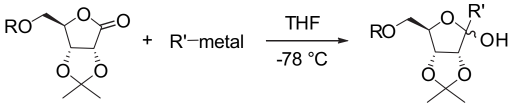
Table 15
Sequential indium-mediated allylation and ozonolysis of unprotected sugars[129]



Entry	Substrate	R	Product	Yield (%)	dr
1	D-Ribose			77[a]	3.5:1
2	D-Arabinose			67[a]	4:1
3	D-Galactose			90[a]	3.5:1
4	D-Xylose	H		75[a]	4.5:1
5	D-Glucose	CH$_2$OH		71[a]	3.5:1
6	D-Lyxose	H		60	8.5:1
7	D-Mannose	CH$_2$OH		71[a]	3:1

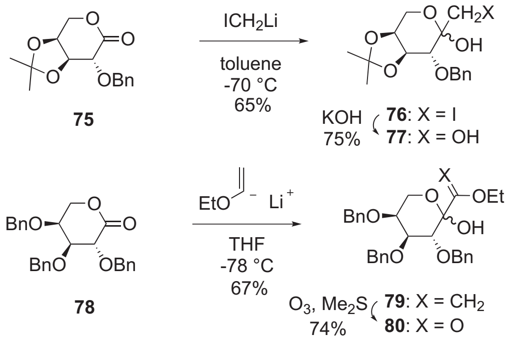
[a] Isolated as peracetate after treatment with Ac$_2$O/pyridine.

Table 16
Addition of Grignard and organolithium reagents to protected ribonolactone



Entry	R	R′-metal	Yield (%)
1	TBDPS	$CH_2{=}CHMgCl$	84[138]
2	TBDPS	$CH_2{=}CHCH_2MgCl$	87[138]
3	TBS	MeLi	98[139]
4	TBDPS	PhLi	95[138]
5	TBS	$TMS{-}C{\equiv}CLi$	93[140]

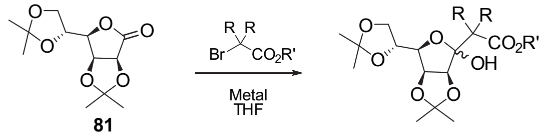
arabinonolactone **78** (Scheme 30).[146] The product **79** was obtained in 67% yield and then subjected to ozonolysis to afford the corresponding ethyl 2-ulosonate **80** with L-*fructo* configuration.[146]



Scheme 30. Elongation of L-arabinonolactones **75** and **78** with functionalized organolithium reagents.[145,146]

2-Deoxy-3-ulosonic acids can be prepared by a metal-mediated Reformatsky-type reaction between an aldonolactone and an α-bromoacetate. The metal can be indium, magnesium or cobalt, as illustrated in Table 17 for 2,3;5,6-di-*O*-isopropylidene-D-mannono-1,4-lactone (**81**).[147–149] The α-bromoacetate may contain other α-substituents, although the yield with indium decreases with electron-withdrawing groups.[148] However, improved yields with ethyl bromodifluoroacetate can be obtained when stronger reducing agents like zinc and samarium(II) iodide are employed, as experienced in the addition to several benzyl-protected aldonolactones.[150] Alternatively, the addition of *tert*-butyl acetate can be performed under basic conditions, where the enolate is first generated with either LDA or LiHMDS.[151–153]

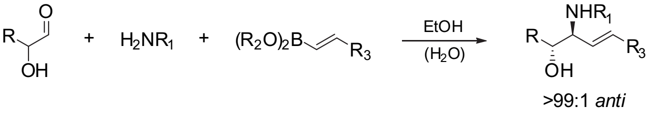
Table 17
Reformatsky-type addition to D-mannonolactone

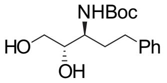
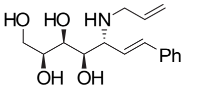
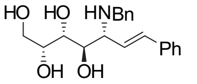
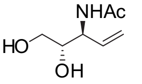
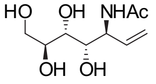
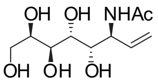


Entry	Metal	R	R′	Yield (%)
1	In	Me	Et	87[147]
2	In	F	Et	49[148]
3	Mg	H	*t*-Bu	80[149]
4	Co(PMe$_3$)$_4$	H	*t*-Bu	91[149]

3.3.4. Chain elongation by Petasis reaction. The multicomponent boronic acid-Mannich reaction between an α-hydroxy aldehyde, a primary or secondary amine and a vinyl- or arylboronic acid (Petasis reaction) is an efficient tool for extending the carbon chain in unprotected sugars.[154] In this way, aldoses are converted into α-amino alcohols elongated with an aryl or a vinyl substituent in a one-pot reaction, and a range of diverse structures can be obtained by selecting different amine and boronic acid substituents.[154–157] The reaction does not require anhydrous conditions and is usually carried out by mixing the reagents in ethanol at room temperature. As depicted in Table 18, α-amino alcohols are formed in good yields and with virtually complete *anti* selectivity by using the standard boronic acid Petasis reaction (entries 1–3). Wong and co-workers have extended the applications of the reaction by introducing an unsubstituted vinyl group (entries

Table 18
Chain elongation by multicomponent Petasis reaction

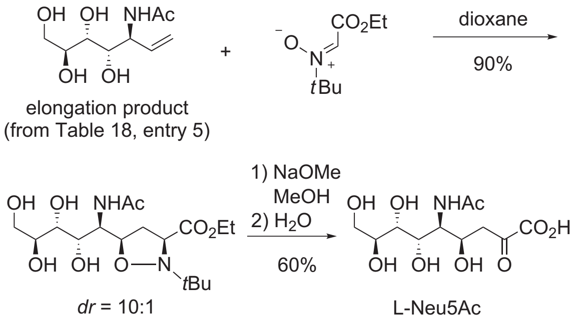


Entry	Aldehyde	R$_1$	R$_2$	R$_3$	Solvent	Product	Yield (%)
1	D-Glyceraldehyde	CH(Ph)$_2$	H	Ph	EtOH		70[a,154]
2	L-Xylose	allyl	H	Ph	EtOH		92[155]
3	D-Lyxose	Bn	H	Ph	EtOH		82[156]
4	D-Glyceraldehyde	CH(PMP)$_2$[c]	Bu	H	EtOH/H$_2$O		60[b,157]
5	L-Arabinose	CH(PMP)$_2$[c]	Bu	H	EtOH/H$_2$O		55[b,157]
6	D-Galactose	CH(PMP)$_2$[c]	Bu	H	EtOH/H$_2$O		50[b,157]

[a] Yield determined after hydrogenolysis of olefin and amine protecting group and subsequent protection with Boc group.
[b] Yield determined after removal of CH(PMP)$_2$ group and protection with Ac group.
[c] PMP=*para*-methoxyphenyl.

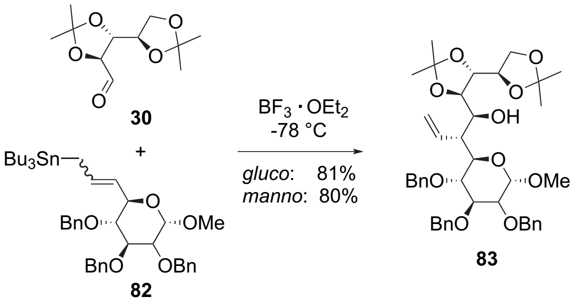
4–6).[157] This was achieved by in situ generation of vinylboronic acid from the corresponding dibutyl ester at 50 °C in ethanol/water (4:1). The yields were slightly lower in the boronic ester variation of the Petasis reaction, but the introduction of an unsubstituted vinyl group is very useful for the synthesis of fully hydroxylated amino sugars.

The reaction was used in a short synthesis of the unnatural enantiomer of sialic acid, where it was combined with a 1,3-dipolar cycloaddition reaction in a second elongation step. The γ-hydroxy-α-keto acid moiety was installed by a diastereoselective nitrone cycloaddition to the vinyl group followed by a base-catalyzed β-elimination to afford the target ulosonic acid in only three steps from L-arabinose (Scheme 31).[157]



Scheme 31. Sialic acid by 1,3-dipolar cycloaddition.[157]

3.3.5. Coupling of two monosaccharides by use of allylstannanes. - With the purpose of synthesizing higher monosaccharides, Jarosz and Gawel have employed sugar-derived allylstannanes to elongate sugar aldehydes at the anomeric position.[158] Treatment of 2,3;4,5-di-*O*-isopropylidene-D-arabinose (**30**) with pyranose-derived allylstannanes **82** (prepared from the corresponding allylic alcohols) and $BF_3 \cdot OEt_2$ at −78 °C afforded the higher-carbon sugars **83** in 81 and 80% yield for the *gluco* and the *manno* isomers, respectively (Scheme 32).[159] With the *gluco* isomer, the allylation was completely *anti* selective, while with the *manno* isomer, 2% of the *syn* product was also isolated.[159]



Scheme 32. Coupling of two monosaccharides by means of allylstannane method.[159]

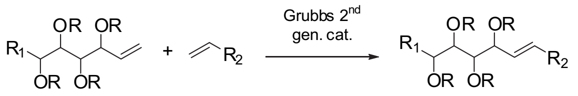
With furanose-derived allylstannanes, on the other hand, decomposition was a major problem.[159] However, under high pressure (13 kbar) and at elevated temperature (57 °C), D-ribofuranose-derived allylstannanes can be coupled to *aldehydo* sugars in excellent yield, albeit the degree of stereoselectivity obtained being highly dependent on the alkene geometry.[160]

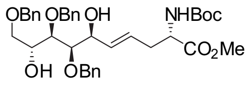
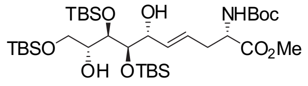
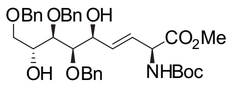
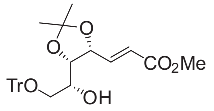
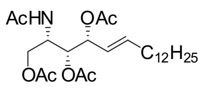
3.4. Transition metal-catalyzed methods for chain elongation

3.4.1. Chain elongation by cross metathesis of ald-1-enitols. Since the development of efficient ruthenium-based metathesis catalysts, ring-closing, ring-opening, and cross-metathesis reactions of olefins have been widely used in carbohydrate chemistry.[161–163] The cross metathesis of straight-chain carbohydrate olefins (aldenitols) is a useful tool for elongating the carbon chain. For a successful cross-metathesis reaction to occur, it is important to suppress the formation of homodimerized products (self metathesis) and to control the geometry of the newly formed double bond. The latter is usually not a problem, since excellent *E*/*Z* selectivities favoring the *E* alkene are generally obtained with carbohydrate-derived terminal olefins.[161] With regard to the selectivity for the cross-metathesis reaction (vs homodimerization), this can be conveniently predicted from the reactivity of the two olefins by using the empirical model suggested by Grubbs and coworkers.[164] Ald-1-enitols are secondary allylic alcohols and thus belong to the type II olefins, which homodimerize slowly and therefore undergo cross metathesis in good yield and selectivity when reacted with more reactive simple type I olefins.[164] When coupling ald-1-enitols with other olefins of similar reactivity, such as acrylates or other secondary allylic alcohols, lower yields and a closer-to-statistical product distribution between cross metathesis and homodimerization are to be expected. However, by using an excess of one of the coupling partners, acceptable yields of the cross-metathesis product can also be obtained in this case.[165,166]

In Table 19 are shown several examples of cross-metathesis reactions between ald-1-enitols and various olefins.[165–167] An excess of the olefin and a rather large amount of Grubbs second generation catalyst are employed, in order to obtain the desired products. In all cases, the *E* alkene is formed with a stereoselectivity greater than 18:1. Although homodimerization is usually an undesired reaction, self metathesis of ald-1-enitols in the absence of other olefins may be used to form symmetrical long-chain sugar structures.[168]

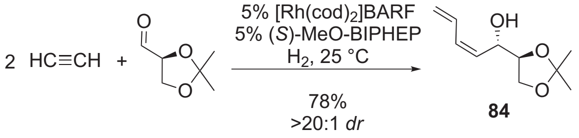
Table 19
Cross metathesis with ald-1-enitols using Grubbs second generation catalyst



Entry	Product	Yield (%)
1		48[165]
2		51[165]
3		68[165]
4		43[a,166]
5		86[167]

[a] $Ti(Oi\text{-}Pr)_4$ (0.3 equiv) added.

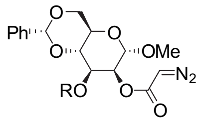
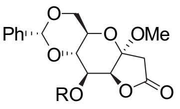
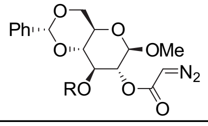
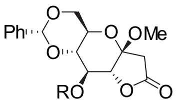
3.4.2. Rhodium-catalyzed hydrogenative coupling of acetylene to aldehydes. Kong and Krische have developed a rhodium-catalyzed hydrogenative coupling of acetylene to aldehydes.[169] By this procedure, the *Z*-butadienylation of L-glyceraldehyde is effected under an atmosphere of acetylene and hydrogen to afford an epimeric mixture of the chain elongated aldehyde **84** in good yield (Scheme 33).[170] The diasteromeric ratio spans from >20:1 to 1:7 and can be elegantly controlled by choosing either enantiomer of the chiral ligand MeO-BIPHEP.[170] The two diastereomers can subsequently be converted into L-hexonic acids by oxidative cleavage of the terminal alkene and dihydroxylation of the internal olefin.[170]



Scheme 33. Rhodium-catalyzed hydrogenative coupling of acetylene to isopropylidene-protected L-glyceraldehyde.[170]

3.4.3. Chain elongation by rhodium-catalyzed carbene C–H insertion. A stereospecific approach to chain-elongated α- and β-ketopyranosides was recently described by Lecourt and coworkers.[171] Rhodium-catalyzed carbene formation and insertion into the anomeric C–H bond in 2-*O*-diazoacetyl pyranosides leads to two-carbon elongated ketopyranosides as their γ-lactones. In this way, 1,2-*trans* manno- and glucopyranosides exclusively afford the corresponding α- and β-ketopyranosides in excellent yield (Table 20). The use of benzyl protecting groups in the 3-position should be avoided, since competitive 1,7-C–H insertion of the rhodium–carbene into the benzylic position is highly favored, thereby reducing the yield of the desired product (entries 3 and 6). The procedure can also be used for elongation at the 1′ position in disaccharides, albeit in slightly lower yields (60–65%).[171] Ring-opening of the γ-lactone may be carried out to produce 2-deoxy-3-ulosonic acid derivatives ready for further functionalization.[171]

Table 20
$Rh_2(OAc)_4$-catalyzed anomeric C–H activation[a,171]

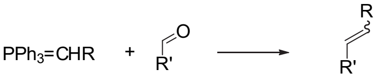
Entry	2-*O*-Diazoacetyl pyranoside	R	Product	Yield (%)
1 2 3		Piv TBS Bn		77 94 20
4 5 6		Piv TBS Bn		90 92 35

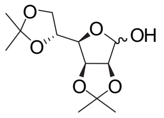
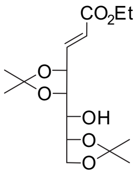
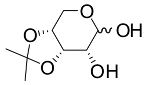
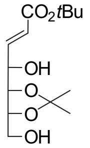
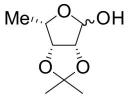
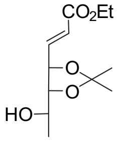
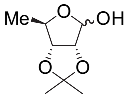
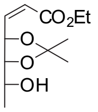
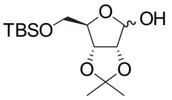
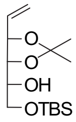
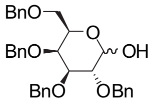
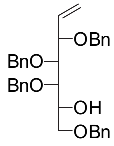
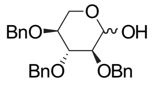
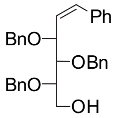
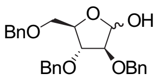
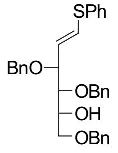
[a] Conditions: 0.5–1.0 mol % $Rh_2(OAc)_4$, 1,2-dichloroethane, 4 Å MS, reflux.

3.5. Chain elongation by olefination

3.5.1. Chain elongation with phosphorane-based ylides. Both phosphorane (Wittig olefination) and phosphonate (Horner–Emmons olefination) ylides have found numerous applications in the chain extension of carbohydrate substrates.[11] The classical Wittig reaction has been the most widely applied olefination method for elongation of aldoses at C1. With protected aldose hemiacetals, both stabilized and nonstabilized Wittig reagents can be employed (Table 21).[172–179] The reactions usually follow the normal rule with regard to olefin geometry, i.e., stabilized phosphoranes predominantly give rise to *E* alkenes (entries 1–3), whereas nonstabilized ylides favor *Z* olefins.[11] Exceptions to this rule, however, are observed, as illustrated in entries 3 and 4, where the L-*lyxo* substrate gave the *E* olefin (entry 3), while the corresponding D-*ribo* compound afforded the *Z* product (entry 4).[174] With semistabilized ylides, both *E* and *Z* alkenes are usually formed and the major product depends on the substrate (entries 7 and 8). With ester-stabilized phosphoranes, the major side reaction is a subsequent Michael addition in the product, where the liberated hydroxy group adds to the α,β-unsaturated ester to form a *C*-glycoside. This side reaction can be suppressed by using bulky ester groups, such as *tert*-butyl or diphenylmethyl.[180]

Table 21
Wittig reactions on protected aldoses



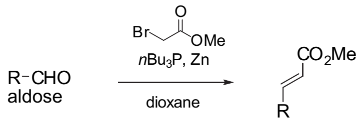
Entry	Aldose	Product	Yield (%)	*E*/*Z*
1			90	18:1[a,172]
2			90	1:0[173]
3			70	5:1[174]
4			90	1:5.2[174]
5			91[175]	
6			72[176]	
7			86	1:2.2[177]
8			77 100	17:3[178] 3:2[b,179]

[a] After dihydroxylation of olefin.
[b] Olefination performed with $Ph_2P(O)CH_2SPh$, *n*-BuLi, THF.

Unprotected aldoses can also be extended by the Wittig reaction if the transformation is performed in a polar solvent, such as dioxane or dioxane/DMF. In this case, only stabilized or semi-stabilized ylides can be employed, since the nonstabilized reagent $\mathrm{Ph_3P{=}CHR}$ (R=alkyl) has been shown to fragment unprotected aldoses by a retro-aldol reaction.[181] Unprotected pentoses, hexoses, and heptoses have been elongated with the stabilized reagent $\mathrm{Ph_3P{=}CHCO_2}t$-Bu to afford α,β-unsaturated esters in yields ranging from 52 to 94% (Table 22).[180,182] For aldoses with 2,3-*threo* configuration, only *E* olefins were obtained, while aldoses with 2,3-*erythro* configuration gave mixtures of the *E* and the *Z* olefin in ratios of about 3:1.[180,182] In the latter case, the mixtures could be avoided by using the more sterically demanding reagent $\mathrm{Ph_3P{=}CHCO_2CHPh_2}$, which only gave *E* olefins.[180,182]

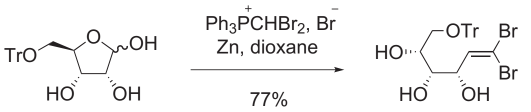
Dihydroxylation of the α,β-unsaturated esters from the Wittig reactions provided an easy route to higher-carbon sugars. A good diastereoselectivity (5:1–8:1) was observed when the dihydroxylation was performed on α,β-unsaturated esters derived from aldoses with 2,3-*threo* configuration (Table 22).[182] For esters derived from aldoses with 2,3-*erythro* configuration, the diastereoselectivity in the dihydroxylation was poor (∼2:1).[182] The stereochemistry of the major diastereomer is in accordance with Kishi's empirical rule for dihydroxylation of allylic alcohols.[183] As a result, the two-step Wittig-dihydroxylation procedure is particularly effective for elongation of aldoses with 2,3-*threo* configuration to afford the corresponding 2,3,4,5-*galacto*-configured aldonic acids. The two steps can be carried out in a one-pot fashion to afford the two-carbon elongated aldonates in good overall yields (Table 22).[182]

Table 23
Wittig-type elongation of unprotected aldoses[184]



Entry	Aldose	Yield (%)
1	D-Ribose	81
2	D-Arabinose	71
3	D-Xylose	74
4	D-Lyxose	82
5	D-Glucose	72
6	D-Mannose	83
7	D-Galactose	89

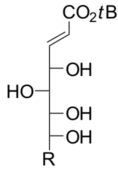
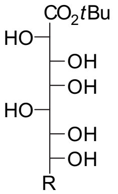
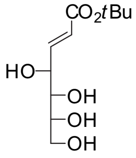
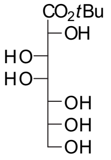
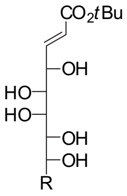
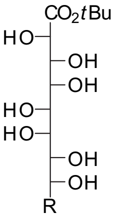
An alternative Wittig olefination of unprotected aldoses was described by Demailly and co-workers, where the reaction was performed in dioxane with methyl bromoacetate, tributylphosphine, and zinc (Table 23).[184] The α,β-unsaturated methyl esters were obtained as pure *E* isomers and in good isolated yields. The purpose of zinc in the reaction is to reduce the initially formed phosphonium salt to the corresponding ylide.[184] The same group has developed a modification of this protocol, where unprotected and partially protected aldoses are converted into 1,1-dibromoald-1-enitols (Scheme 34).[185] The reaction is achieved with dibromomethyl-triphenylphosphonium bromide and zinc, where zinc again reduces the phosphonium salt to the ylide, i.e., $\mathrm{Ph_3P{=}CBr_2}$. Upon treatment with *n*-butyllithium, the product 1,1-dibromoald-1-enitols are converted into the corresponding ald-1-ynitols.[185]



Scheme 34. Dibromomethylenylation of aldoses.[185]

Table 22
Sequential Wittig reaction and dihydroxylation to produce elongated sugars

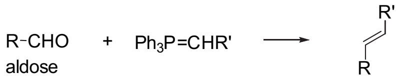
$$\text{aldose} \xrightarrow{\mathrm{PPh_3{=}CHCO_2}t\mathrm{Bu}} \text{unsaturated ester} \xrightarrow{\mathrm{OsO_4,\ NMO}} \text{higher-carbon sugar}$$

Entry	Aldose	Unsaturated ester	Substituent	Yield (%)	*E*/*Z*	Higher-carbon sugar	Yield (%)
1	D-Glucose		R=$\mathrm{CH_2OH}$	66[140]	1:0		76[a,141]
2	D-Glucose		R=$\mathrm{CH_2OH}$				68[a,b,141]
3	D-Xylose		R=H	94[141]	1:0		53[141]
4	D-Xylose		R=H				63[b,141]
5	D-Arabinose			92[140]	1:0		69[141]
6	D-Arabinose						73[b,141]
7	D-Galactose		R=H	76[140]	1:0		85[141]
8	D-Galactose		R=H				77[b,141]
9	D-*Glycero*–D-*galacto*-heptose		R=$\mathrm{CH_2OH}$	52[141]	1:0		54[a,141]

[a] Isolated as 1,4-lactone.
[b] Isolated yield of major isomer after one-pot Wittig-dihydroxylation reaction.

Semistabilized ylides can also be used for the elongation of unprotected aldoses (Table 24).[186,187] Pentoses and hexoses react with $Ph_3P{=}CHPh$ in dioxane to give 1-phenylald-1-enitols in good yields (entries 1–4).[186] The same transformation can be carried out with $Ph_3P{=}CHSPh$ in DMSO to give the chain-elongated products in moderate-to-good yields (entries 5–7).[187] The latter reagent gives excellent selectivity for the *E* olefin, while the selectivity with $Ph_3P{=}CHPh$ is poor in most cases.

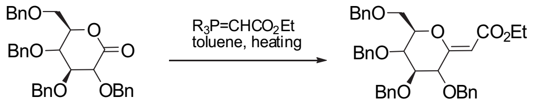
Table 24
Elongation of unprotected aldoses with semistabilized ylides



Entry	Aldose	R′	Yield (%)	*E*/*Z*
1	D-Arabinose	Ph	66	2:1[186]
2	L-Xylose	Ph	68	2:1[186]
3	D-Glucose	Ph	70	3:2[186]
4	D-Galactose	Ph	72	1:0[186]
5	D-Arabinose	SPh	72	1:0[187]
6	D-Glucose	SPh	41	1:0[187]
7	L-Rhamnose	SPh	53	1:0[187]

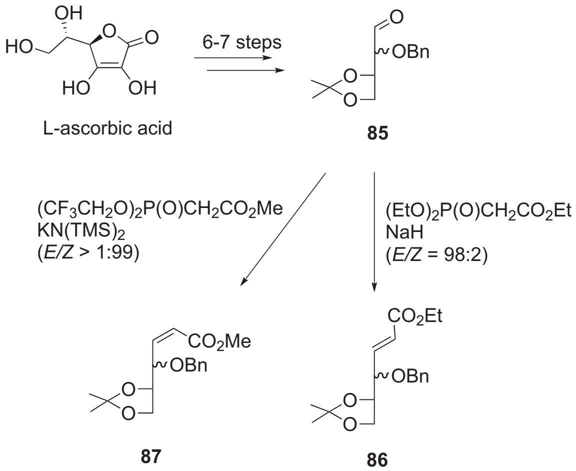
Besides aldoses, the Wittig olefination can also be performed on protected aldonolactones to afford *exo* glycals.[188] However, lactones are less reactive than aldoses and higher temperatures (110–140 °C) are required in this case. Upon reaction with $Ph_3P{=}CHCO_2Et$, benzyl-protected D-glucono- and D-galactono-1,5-lactone gave the corresponding *exo* glycals in good yields and with complete *Z* selectivity (Table 25, entries 1 and 2).[189] The lactone ring size and the stereochemistry at C2 seem to play a major role for the success of these olefinations.[188] As an example, benzyl-protected D-mannono-1,5-lactone reacted very poorly with $Ph_3P{=}CHCO_2Et$ and gave a mixture of the *E* and the *Z* olefins.[189] In addition, five-membered aldonolactones, i.e., aldono-1,4-lactones, furnished the *exo* glycals in moderate-to-good yields with $Ph_3P{=}CHCO_2R$ (R=Me or Et), but the *E*/*Z* selectivities with these lactones were very poor (~1:1).[190,191] Wyatt and co-workers were able to reduce the reaction temperature to 80 °C by using the more reactive reagent $Bu_3P{=}CHCO_2Et$.[192] When applied to benzyl-protected D-mannono-1,5-lactone, this reagent gave the *exo* glycal in good yield favoring the *E* olefin (entry 3).[193]

Table 25
Wittig reaction on perbenzylated hexono-1,5-lactones



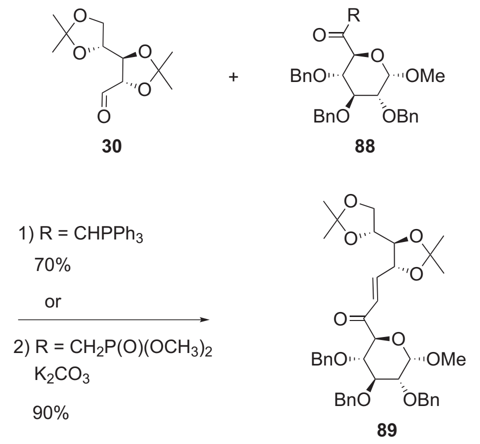
Entry	Lactone configuration	R	Yield (%)	*E*/*Z*
1	D-*Gluco*	Ph	87	0:1[189]
2	D-*Galacto*	Ph	90	0:1[189]
3	D-*Manno*	Bu	84	>9:1[193]

3.5.2. Chain elongation with phosphonate-based ylides. Ermolenko and Sasaki have synthesized all eight L-hexoses by elongation of the two protected L-tetroses **85**, which are available in six and seven steps from L-ascorbic acid (Scheme 35).[194] Wittig reactions on tetroses **85** using the stabilized phosphorane $Ph_3P{=}CHCO_2Et$ gave moderate *E*/*Z* selectivities ranging from 2:1 to 10:1, while the Horner–Emmons approach with the stabilized phosphonate $(EtO)_2P(O)CH_2CO_2Et$ afforded (*E*)-α,β-unsaturated esters **86** in excellent stereoselectivity. With the modified phosphonate $(CF_3CH_2O)_2P(O)CH_2CO_2Me$, the two *Z*-configured unsaturated esters **87** were obtained exclusively. Subsequent asymmetric dihydroxylation of the four unsaturated esters **86** and **87** gave all eight L-aldonic acid derivatives, which were reduced to the corresponding L-aldoses.[194]



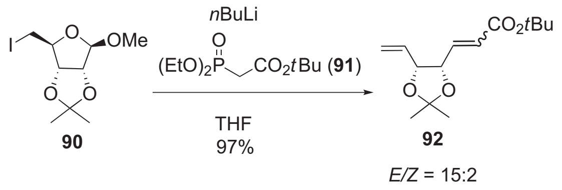
Scheme 35. Elongation of two tetroses **85** with stabilized phosphonates.[194]

Higher sugars with more than 10 carbon atoms can be formed by Wittig or Horner–Emmons olefinations of an *aldehydo* C5 or C6 sugar with a stabilized phosphorus ylide positioned at the non-reducing end of a monosaccharide.[195] The Horner–Emmons approach with stabilized ylides is the most reliable procedure for the preparation of sugars with long carbon chains, since the phosphonate ylides are both easier to prepare and more reactive than the corresponding phosphoranes.[195] Jarosz and Mach prepared the C12 sugar **89** by both procedures through the reaction of glucose-derived ylides **88** with 2,3;4,5-di-*O*-isopropylidene-D-arabinose **30**, as depicted in Scheme 36.[196] As expected when using stabilized ylides, the *E* isomer was obtained in both cases. Compound **89** was subsequently converted into a protected dodecose by reduction of the ketone and dihydroxylation of the alkene.[196]



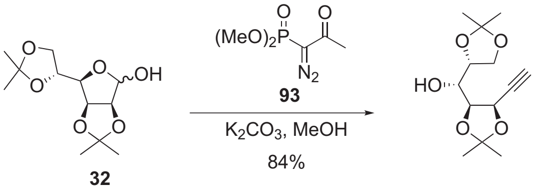
Scheme 36. Preparation of C12 monosaccharide **89** by Wittig and Horner–Emmons reactions.[196]

An interesting tandem fragmentation–Horner–Emmons reaction was recently described, where iodoglycoside **90** was reacted with phosphonate **91** and 2 equiv of butyllithium (Scheme 37).[197] First, a halogen-lithium exchange–fragmentation reaction occurred to produce an intermediate aldehyde, which then underwent a Horner–Emmons reaction in the same pot with the phosphonate **91**. The product diene **92** was isolated in excellent yield as a 15:2 mixture of *E* and the *Z* olefins.[197]



Scheme 37. Tandem fragmentation–Horner–Emmons reaction of iodoglycoside **90**.[197]

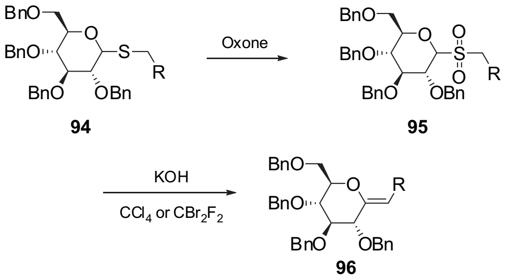
Aldehydes can also be converted into alkynes by using the commercially available phosphonate $(MeO)_2P(O)C(N_2)COMe$ (**93**: Ohira–Bestmann reagent). In basic methanol solution, the acetyl group is cleaved to produce $(MeO)_2P(O)CHN_2$, which can react with an aldose to give the one-carbon longer ald-1-ynitol.[198] The reaction works most effectively with protected aldoses, such as **32**, where good yields of the corresponding ald-1-ynitols can be obtained (Scheme 38).[198]

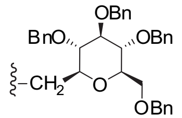


Scheme 38. Elongation with Ohira–Bestmann reagent **93**.[198]

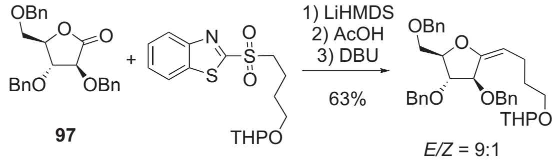
3.5.3. Ramberg–Bäcklund approach to chain-elongated exo glycals. The Ramberg–Bäcklund rearrangement of glycosyl sulfones to produce *exo* glycals was introduced independently by the groups of Taylor and Franck.[199] Base-mediated rearrangement of glycosyl sulfones, such as **95**, which are easily available by oxidation of the corresponding thioglycosides (i.e., **94**), predominantly gave the *Z exo* glycals (i.e., **96**), as illustrated in Table 26.[200,201] For the preparation of *exo* methylene glycals (as in entry 1), slightly improved yields can be obtained by using glycosyl sulfones bearing a chloromethyl substituent instead of a methyl group.[202] Besides being used for the preparation of simple di-, tri-, and tetrasubstituted *exo* glycals, the Ramberg–Bäcklund rearrangement can also be employed for connecting two monosaccharides, which again proceeded with a good selectivity for the *Z* olefin (entry 6).[201]

Table 26
Ramberg–Bäcklund approach to *exo* glycals



Entry	R	Yield (%)	*Z*/*E*
1	H	72	—[200]
2	Ph	83	88:12[200]
3	Me	75	80:20[200]
4	Et	71	92:8[200]
5	$(CH_2)_3OH$	73	80:20[201]
6		57	88:12[201]

3.5.4. Julia olefination. Another method for preparing di-, tri-, and tetrasubstituted *exo* glycals was introduced by Gueyrard and co-workers, where a Julia olefination was performed at C1 on protected aldonolactones.[203] In the synthesis of trisubstituted *exo* glycols, the *E*/*Z* selectivity was highly dependent on the structure of the lactone. The selectivity was poor with benzyl-protected D-glucono-1,5-lactone, while a good selectivity for the *E* isomer was observed with the corresponding D-arabinono-1,4-lactone **97** (Scheme 39).[204]

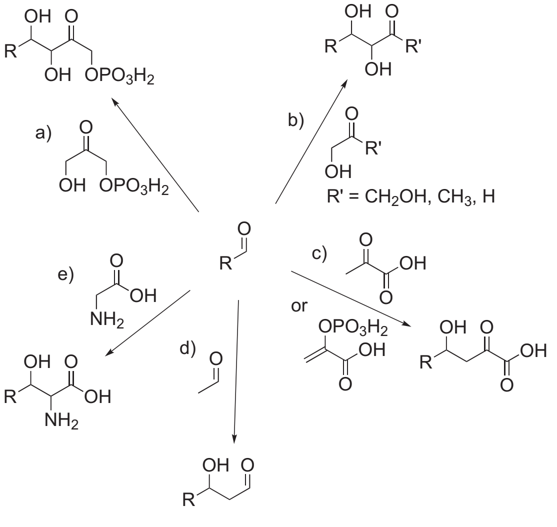


Scheme 39. Formation of *exo* glycals by Julia olefination.[204]

3.6. Chain elongation by enzymatic methods

As an alternative to chemical chain elongation, enzymatic reactions have also been extensively studied in recent years and have emerged as attractive alternatives, even on a preparative scale. Enzymes have several advantages over chemical synthesis, such as high degree of substrate- and stereospecificity, minimum amounts of byproducts, no need for laborious protection/deprotection sequences, and mild reaction conditions (ambient temperature and physiological pH). However, enzyme-catalyzed reactions also have some disadvantages where the major one is derived from their specificity leading to a limited substrate tolerance and a limited number of possible stereochemical outcomes.

3.6.1. Aldolase-catalyzed chain elongation. Aldolases are the most studied class of enzymes for C–C bond formation, and the field of aldolase-catalyzed asymmetric synthesis is expanding rapidly.[205,206] Aldolases catalyze the reaction of an enolizable carbonyl compound (donor) and an acceptor aldehyde. They have a very strict donor specificity, and can be divided into five groups, based on the type of donor required (Scheme 40).[205] In contrast to the strict conservation of the donor within each group, much more variation is allowed in the acceptor.

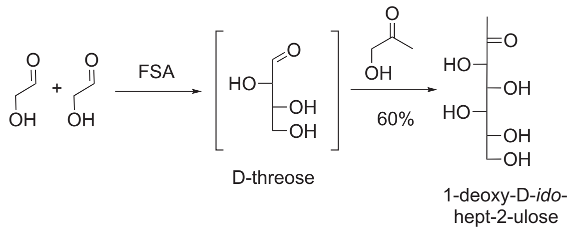


Scheme 40. Aldolases grouped according to donor substrate: (a) dihydroxyacetone phosphate (DHAP); (b) dihydroxyacetone (DHA); (c) pyruvate and phosphoenol pyruvate; (d) acetaldehyde and (e) glycine.[205]

Mechanistically, aldolases can be divided into class I and II. Class I aldolases have a conserved lysine in the active site, which forms an enamine intermediate with the carbonyl group of the donor (similar to the organocatalytic aldol reaction in Section 3.1.4), which then undergoes nucleophilic attack onto the electrophilic acceptor. Class II aldolases make use of a divalent metal ion (usually Zn^{2+}) acting as a Lewis acid polarizing the donor carbonyl group, which then tautomerizes into an enolate that subsequently adds to the acceptor aldehyde.[206]

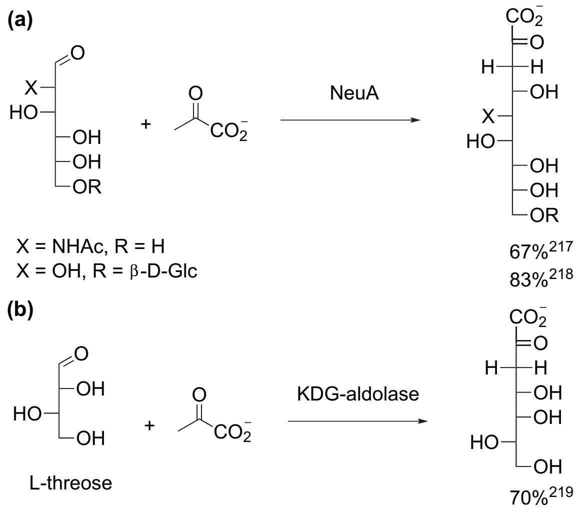
Protein engineering of aldolases to obtain improved stability, activity, and enantioselectivity as well as increased substrate tolerance is receiving significant attention. At the same time, new aldolases are screened, and together these approaches provide the basis for the rapid development of aldolase-catalyzed synthesis.[206,207]

The most studied group of aldolases are the DHAP-dependent aldolases (Scheme 40, a). Unfortunately, a major drawback is the need for expensive and unstable DHAP as the donor. For synthetic uses, non-phosphorylated substrates have the highest potential, and the focus has therefore been shifted toward circumventing the disadvantages of using DHAP as a substrate.[206] Recent efforts in this direction include in situ formation of DHAP by phosphorylation of DHA by a phosphatase,[208] and phytase-catalyzed removal of phosphate from the product in situ.[209] Furthermore, by employing L-rhamnulose-1-phosphate aldolase in borate buffer, DHA can be accepted as a donor, presumably by in situ formation of a DHA–borate ester, which acts as a DHAP mimic.[210] The direct acceptance of DHA as a donor substrate has been realized by the use of D-fructose-6-phosphate aldolase (FSA),[211] transaldolase TalB[212], and a mutant L-rhamnulose-1-phosphate aldolase[213] (Scheme 40, b). In addition, the ability of FSA to use hydroxyacetone and, in particular, glycolaldehyde as donor substrates makes this enzyme extremely promising.[214–216] As an example, dimerization of glycolaldehyde to give D-threose and, in the same pot, elongation with hydroxyacetone to give 1-deoxy-D-*ido*-hept-2-ulose in 60% overall yield was recently reported by Clapés and co-workers (Scheme 41).[214] In the same work, racemic 3-*O*-benzyl-glyceraldehyde was elongated by two carbon atoms by the use of glycolaldehyde to produce a 2:1 mixture of 5-*O*-benzyl-L-xylose and -D-arabinose in 65% yield.[214] The efficient FSA-catalyzed two-carbon elongation based on glycolaldehyde gives ready access to aldoses, as opposed to ketoses and ulosonic acids, which are produced with most other aldolases (Scheme 40, a–c). The only other aldolase, which can be used to make aldoses is 2-deoxy-D-ribose-5-phosphate aldolase (DERA), which adds acetaldehyde to aldehyde acceptors to afford 2-deoxyaldoses (Scheme 40, d).[205]



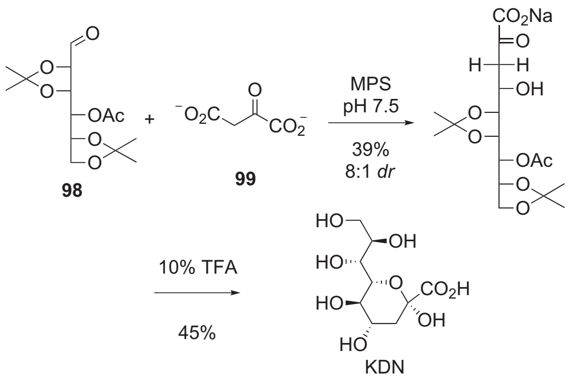
Scheme 41. FSA-catalyzed one-pot preparation of 1-deoxy-D-*ido*-hept-2-ulose by two sequential aldol reactions.[214]

Pyruvate-dependent aldolases are highly efficient for the synthesis of higher 3-deoxy-2-ulosonic acids, such as sialic acids and their analogs (Scheme 40, c).[217] The most studied pyruvate-dependent aldolase is *N*-acetylneuraminic acid lyase (NeuA), which has recently been found to accept disaccharides as acceptors (Scheme 42a).[218] This unprecedented acceptor tolerance is very promising for synthetic applications and enables easy access to disaccharides containing a sialic acid at the reducing end. Another useful example of this group of aldolases is the thermostable 2-keto-3-deoxygluconate aldolase (KDG-aldolase). This has been employed for the preparation of 3-deoxy-L-*lyxo*-hept-2-ulosonate in 70% yield and >99% dr by the addition of pyruvate to L-threose at 50 °C in a continuous-flow reactor using an immobilized enzyme (Scheme 42b).[219] Furthermore, by protein engineering of KDG-aldolase, Bull and co-workers were able to obtain two complementary mutant catalysts each giving opposite C4 stereochemistry during the addition of pyruvate to D-glyceraldehyde.[220]



Scheme 42. Chain elongation by pyruvate-dependent aldolases.

A related aldolase is macrophomate synthase (MPS), which adds pyruvate enolate generated in situ by decarboxylation of oxaloacetate **99** to acceptor aldehydes (Scheme 43).[221] Remarkably, the enzyme readily accepts a wide range of *fully protected* C3–C6 sugar aldehydes (e.g., **98**).[222] Ether, acetal, thioacetal, allyl, benzyl, silyl, and ester protecting groups are tolerated, albeit usually in moderate yields. Some peracetates and aldehydes insoluble in aqueous buffer are, however, not converted by the enzyme. Regardless of the acceptor aldehyde stereochemistry, the 4*S* isomer is formed with good-to-excellent stereoselectivity in all cases, presumably due to selective binding of the aldehyde in the active site. The application of the enzyme for the preparation of 3-deoxy-2-ulosonic acids is illustrated in Scheme 43 with a short synthesis of KDN.[222]

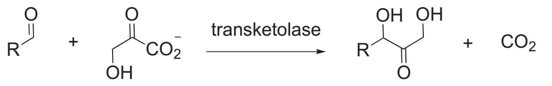


Scheme 43. Macrophomate synthase-catalyzed three-carbon elongation of fully protected sugar aldehydes.[222]

Usually, the ability of enzymes to perform specific transformations in the absence of protecting groups is a major advantage. However, when the product of the enzymatic reaction is not the final product, and some specific sites require further manipulations, the need for introducing protecting groups at a late stage in the synthesis is a significant disadvantage. By employing macrophomate synthase, this limitation is superseded, since protected sugars are readily accepted as substrates for this enzyme. This unprecedented substrate tolerance offers great possibilities to the synthetic chemist, since the advantages of enzymatic reactions can be combined with the power of conventional synthesis. At present, the sole preference for the 4*S*-configured products limits the general applicability of this methodology, and protein engineering would be highly beneficial in order to be able to obtain the 4*R* products.

The acetaldehyde and glycine aldolases (Scheme 40, d and e) have not been studied as extensively with respect to synthetic applications as the dihydroxyacetone phosphate and pyruvate aldolases.[205,206]

3.6.2. Transketolase-catalyzed two-carbon chain elongation. Another enzyme that deserves to be mentioned in relation to chain elongation of carbohydrates is transketolase (TK).[223] TK is able to transfer an α-hydroxy carbonyl (ketol) group from hydroxypyruvate **100** to an aldose, thereby producing the C_{n+2} ketose **101** (Scheme 44). The equilibrium for the reaction is not very favorable, but the process becomes irreversible, since carbon dioxide is lost during the reaction. The enzyme is highly selective with regard to the C2 stereochemistry of chiral α-hydroxy aldehydes and only accepts 2*R* epimers. Furthermore, the newly formed stereocenter always exhibits an *S* configuration (3,4-D-*threo*). The relative rates for the TK-catalyzed reaction of hydroxypyruvate with various aldoses generally decrease with increasing chain length of the aldose acceptors.[224]

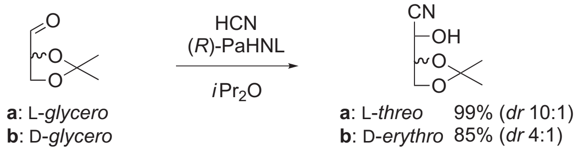


100 **101**

Scheme 44. Transketolase-catalyzed two-carbon elongation of aldoses.[224]

The TK-catalyzed preparation of D-xylulose 5-phosphate from hydroxypyruvate and D-glyceraldehyde 3-phosphate has been optimized by several groups.[225–227] The starting material, D-glyceraldehyde 3-phosphate, can be formed in situ from D-fructose 1,6-phosphate with an aldolase,[226] or from dihydroxyacetone phosphate with an isomerase.[227] The TK-catalyzed elongation can also be performed with D-ribose 5-phosphate to afford the C7 ketose, D-sedoheptulose 7-phosphate, in good yield.[228]

3.6.3. One-carbon chain elongation by enzymatic Kiliani ascension. The Kiliani ascension may be catalyzed by an enzyme to give an improved diastereoselectivity in the addition. This is observed with 2,3-*O*-isopropylidene-glyceraldehyde, where the direct addition of hydrogen cyanide gives the *threo*/*erythro* product in a 3:2 ratio.[229] However, when the addition is performed in the presence of (*R*)-hydroxynitrile lyase from *Prunus amygdalus* ((*R*)-PaHNL), this ratio changes significantly (Scheme 45). The L-isomer of the aldehyde affords a 10:1 ratio between the *threo* and the *erythro* tetrononitrile, while with the D-isomer the ratio is 1:4.[229]



Scheme 45. Enzymatic Kiliani ascension of isopropylidene-protected glyceraldehydes.[229]

4. Concluding remarks

'Half of sugar chemistry resides at the anomeric carbon' as pointed out by Stephen Hanessian.[230] With the current progress in glycobiology, this is more true than ever before and methods for forming and breaking C–C bonds belong to the very heart of carbohydrate synthesis. In recent years, significant new developments have occurred with the use of radical reactions, organometallic transformations and aldol condensations. Although most of the transformations still require protecting groups, new reactions continue to be developed where completely unprotected carbohydrates can be employed as substrates. Controlling the diastereoselectivity in the addition to carbohydrate aldehydes is still not a trivial task. However, much more information is now available on this transformation, which makes it easier to choose the proper aldehyde and nucleophile. All taken together, the available methods for shortening and extending the carbon chain constitute a diverse tool box for the construction of polyhydroxylated compounds from carbohydrates.

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Robert Madsen was born near Varde, Denmark in 1965 and studied Chemistry at the Technical University of Denmark, where he obtained his Ph.D. degree in 1992 under the supervision of Professor Inge Lundt. He then had two periods of postdoctoral studies where the first was performed with Professor Bert Fraser-Reid at Duke University (1992–1994) and the second with Professor Barry M. Trost at Stanford University (1994–1996). In 1996 he returned to the Technical University of Denmark as Associate Professor and was promoted to Full Professor in 2003. His main research interests involve the development of new synthetic methods in the areas of carbohydrate chemistry and organometallic chemistry. He has received the Torkil Holm Foundation Research Prize (2002), the GDCh Liebig Lectureship (2005) and the Bjerrum-Brønsted-Lang Lectureship of the Royal Danish Academy of Sciences and Letters (2007).