Review

A Survey of Recent Synthetic Applications of 2,3-Dideoxy-Hex-2-enopyranosides

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Abstract: Unsaturated carbohydrate derivatives are useful intermediates in synthetic transformations leading to a variety of compounds. The aim of this review is to highlight the rich chemistry of Δ-2,3 unsaturated pyranosides, emphasizing the variety of transformations that have been carried out in these substrates during the last decade.

Keywords: hex-2,3-enopyranosides; cycloaddition; glycosylation; epoxidation; osmylation; Ferrier rearrangement; de novo synthesis

1. Introduction

Hex-2-enopyranoses, e.g., 3, also known as pseudoglycals, have provided fertile ground for synthetic and mechanistic developments in carbohydrate chemistry during the last decades [1,2]. The first report of a molecule belonging to this category was made by Fischer [3], although it was not until a decade later that its correct structure could be established by Bergmann [4]. However, the process 1→3 (Scheme 1), which made hex-2-enopyranosides broadly recognized synthetic intermediates, was only rendered available on a preparative scale in 1969 by Ferrier and Prasad [5]. This reaction has come to be known as the Ferrier I rearrangement, and the cationic intermediate 2 has since played a relevant role in many carbohydrate transformations [6,7]. From the outset, hex-2-enopyranosides have been employed in a plethora of synthetic endeavors [8–10]. Excellent
coverage of the chemistry and synthetic applications of hex-2-enopyranosides has appeared regularly in the yearly issues of *Carbohydrate Chemistry, Specialist Periodical Reports*, until 2003 [11]. The vast contribution to the chemistry of hex-2-eno-pyranosides developed in the Fraser-Reid group, covering more than 20 years of research in the area, has recently been reviewed [12].

The aim of this review is to highlight synthetic transformations on 2,3-dideoxy-hex-2-eno-pyranosides reported during the last decade, 2003–2014.

2. Synthetic Routes to Hex-2-enopyranosides

The most widely used method for the preparation of 2,3-unsaturated hex-2-enopyranosides involves the Ferrier reaction, applied to glycal derivatives. Early studies on the Ferrier rearrangement made use of simple Lewis acids, e.g., BF$_3$·Et$_2$O, as promoters [5]. Since then, considerable attention has been devoted to the investigation of alternative catalysts for this transformation. In this context, a large number of publications involving the use of a variety of metallic, non-metallic, and heterogeneous catalysts have appeared. A report dealing with the promoters and nucleophiles currently used for the Ferrier rearrangement have been recently published, and readers in search of comprehensive information on this reaction are directed to it [13].

Besides the Ferrier rearrangement, outlined in Scheme 1, additional routes to access hex-2-enopyranoses from carbohydrates have also been described. Thus, Fraser-Reid and Boctor made use of the reductive elimination of vicinal disulfonates [14] to gain access to 5 (Scheme 2) [15].

![Scheme 1. Ferrier rearrangement route to hex-2-enopyranoses 3, from glucal 1.](image1)

A more circuitous route to allylic pyranosides from non-carbohydrate sources was developed by Zamojski and Achmatowicz (Scheme 3) [16,17]. In 1971, they reported the oxidative rearrangement of 2-furanylcarbinols into highly functionalized pyranones, e.g., 6→7, to gain access to hex-2-eno-pyranosides 8 (Scheme 3). In the original Achmatowicz approach, the fufuryl carbinol is oxidized with bromine in the presence of methanol under weakly basic conditions. Many other modifications of the original Achmatowicz procedure, such as oxidation of the furan ring with
m-CPBA [18], dimethyldioxirane [19], NBS [20,21], tert-BuOOH\VO(OAc)₂ [22], or H₂O₂-titanium silicalite [23], have also been used for this transformation. This route has the advantage that the original configuration of the alcohol moiety in the furylcarbinol is preserved and, therefore, the method is amenable to the preparation of both D- and L-series [24–26].

Scheme 3. Achmatowicz and Zamojski’s de novo route to hex-2-enopyranosides from furylcarbinols.

The hetero Diels-Alder reaction (HDA) has been amply used in the de novo synthesis of hexoses, and in many those instances 2,3-unsaturated derivatives have been key intermediates in these protocols [27–29]. Pioneering work by Danishefsky’s group had shown that hexoses could be accessed by Lewis acid-catalyzed HDA reaction of alkylated siloxy dienes with aldehydes via the intermediacy of labile 3-O-silyl-2,3-unsaturated glycoside adducts [30,31]. The hetero-Diels Alder reaction between substituted 1,4-dialkoxy-1,3-dienes and activated carbonyl compounds such as glyoxylates also provides access to hex-2-enopyranosides, e.g., 8, from non-carbohydrate sources (Scheme 4a) [32,33]. This process can be promoted simply by heating, [33], by use of high pressure [33], or by Lewis acid catalysis [32]. A HDA reaction has been used to gain access to a pseudo C-disaccharide 10 from a D-glucosamine diene 9 (Scheme 4b) [34]. More recently, a one-pot multicomponent approach to 3-branched-2,3-unsaturated hexopyranoses 11 has been devised by Botta and co-workers (Scheme 4c) [35]. The protocol, in which a monosubstituted alkyne, ethyl vinyl ether and ethyl glyoxalate were combined, involved an enyne cross-metathesis (Grubb’s catalyst, 2nd generation) [36] leading a diene intermediate (A), followed by an in situ HAD reaction.

Scheme 4. Hetero Diels-Alder (HDA) routes to hex-2-eno-pyranosides.
Ring-closure metathesis has become an important tool in organic synthesis and its application to carbohydrate chemistry [37] has included the synthesis of hex-2,3-enopyranose derivatives (Scheme 5). For example, dibenzoate 12 yielded 1-deoxy-hex-2,3-enopyranose 13 via ring-closing metathesis [38].

Scheme 5. Ring-closing metathesis route to hex-2-eno-pyranose derivatives.

An acid-catalyzed domino reaction has been developed by Guaragna and coworkers as a synthetic route to enantiomerically pure L-hex-2-enopyranosides (Scheme 6) [39]. Their strategy started from the three-carbon homologating agent 14, prepared in a few steps from methyl pyruvate, and a chiral building block derived from L-glyceraldehyde 15, which provides the inherent chirality at the C5 stereocenter of the final product, 18 [40]. The ring closure of the intermediate 16 was effected by a domino process triggered by DDQ in CH2Cl2/MeOH involving five steps: MPM protecting-group removal, oxidation of the ensuing primary alcohol, aldehyde dimethoxyacetalation, isopropylidene group cleavage, and ring closure. Finally, desulfuration of 17 with Raney-Ni led to 2,3-unsaturated-L-pyranoside 18.

Scheme 6. Guaragna’s group de novo approach to hex-2-enopyranosides.

3. Reactions of Hex-2-enopyranosides

One of the reasons behind the ample use of hex-2-enopyranosides in carbohydrate chemistry might lie in their rich synthetic potential. They undergo standard alkene-addition reactions including hydrogenation, hydroxylation, oxyamination, or epoxidation, often with very high if not complete stereoselectivity. Incorporation of additional functionality that polarizes the alkene group, such as nitro or sulphonyl substituents, makes Michael-like additions possible, which take place with regiospecific introduction of nucleophiles. Hex-2-enopyranosides are also ideally structured to take part in sigmatropic rearrangements, the most straightforward of which involve compounds with allylic ester groups. Furthermore, the $\Delta^{2,3}$ insaturation in hex-2-enopyranosides confers a higher reactivity to both the anomeric (C-1) acetal and the C-4 hydroxyl group, opening new avenues for nucleophilic functionalization. Oxidative transformations are also of synthetic value since they might lead to unsaturated enones, unsaturated lactones, or to 6-formyl derivatives, depending on the conditions employed.
3.1. Addition Reactions

Hydrogenation reactions of 2,3-enopyranosides have generated interest as a tool for delivering deoxy sugars which are present in biologically intriguing compounds [41,42]. For example, it has been shown that in aminoglycosides, the removal of hydroxyl groups imparts in vitro stability by lessening the abilities of naturally occurring glycosidase enzymes to degrade the structure [43]. In this context, Zhang et al. developed a divergent strategy for constructing uncommon L-sugars with 4-substitution. They employed 2,3-eno-pyranosides 19 and 20 and a combination of typical palladium on carbon hydrogenation and Mitsunobu reactions involving the use of diphenylphosphorylazide (DPPA) (Scheme 7) [44].

![Scheme 7. Zhang’s synthesis of 4-substituted uncommon-sugars.](image)

O’Doherty’s group proposed a diimide reduction as an alternative to the direct hydrogenation reaction of 2,3-enopyranosides where partial hydrogenolysis could compete. The method was applied to allyl alcohol 25 that upon standard hydrogenation conditions produced a significant amount of the hydrogenolysis product 27 (Scheme 8). Thus, by exposing allylic alcohol 25 to an excess of o-nitrobenzenesulfonyl hydrazide (NBSH) and Et$_3$N, an excellent yield of the desired pivalate 26 could be obtained [45].

![Scheme 8. O’Doherty’s diimide reduction of 2,3-enopyranosides.](image)

Cis-hydroxylation of the double bond in hex-2,3-enopyranosides under common conditions (OsO$_4$, H$_2$O$_2$ or RuCl$_3$/NaIO$_4$) normally occurs from the sterically more accessible face of the sugar ring in a process that is very often stereospecific. For example, the dihydroxylation reaction of 2,3-dideoxy-α-D-erythro hex-2-enopyranoside 28, where both the anomeric substituent and the 4-substituent are located below the ring, occurs exclusively from the upper face of the molecule, resulting in formation of α-D-mannopyranoside 29 (Scheme 9a) [26]. However, osmylation of
β-D-erythro-2-enopyranoside 30, where the C-1 and C-4 substituents are disposed in opposite faces of the pyranose, led exclusively to β-D-allopyranoside 31, with the osmium approach taking place anti- to the anomeric substituent (Scheme 9b) [46]. Similarly, dihydroxylation of galactal derivative 32 occurred mostly from the β-face opposite to the anomeric substituent leading to “talo”-derivative 33, although some “gulo” derivative 34 was also obtained (Scheme 9c) [47]. On the other hand, exposure of allylic alcohol 35 to OsO₄/NMO in t-BuOH/H₂O afforded gulose isomer 36 in 80% yield, whereas the protected talose isomer 37 was selectively produced upon treatment of 35 with the TMEDA adduct of OsO₄ (Scheme 9d) [26].

Scheme 9. Cis-dihydroxylation of hex-2,3-enopyranosides by OsO₄.

This methodology has been used by O’Doherty and coworkers in a highly efficient de novo route to various oligosaccharide motifs containing both D- and L-sugars [48]. For example, osmium-catalyzed dihydroxylation of tri-2,3-enopyranoside derivative 38 afforded the 1,4-linked α-rhamno-pyranose 39, while the global reduction of the double bonds with excess diimide provided 2,3-dideoxy oligosaccharide 40 in excellent yield (Scheme 10).

Dihydroxylation products can also be obtained by sequential epoxidation/ring-opening reactions. In these substrates, the stereochemistry of the epoxidation is highly influenced by the nature of the allylic hydroxyl groups. In general, free hydroxyl groups direct the approach of the incoming oxygen atoms to the double bond in a syn manner, whereas an anti-approach is observed when the hydroxyl groups are
protected [49]. Ring-opening of epoxides arising from hex-2,3-enopyranosides tend to form trans-diaxial products, due to the Fürst-Platnner rule [50] and therefore this approach is complementary to the previously mentioned cis-hydroxylation. For instance, hex-2-enopyranoside 41 under common Upjohn conditions gave exclusively methyl L-mannopyranoside 42, whereas L-altropyranoside 44 was obtained after treatment with dimethyldioxirane and the subsequent ring opening of the 2,3-anhydro derivative 43 by acid or by base-catalyzed hydrolysis (Scheme 11) [40].

Scheme 10. O’Doherty’s synthesis of 1,4-linked α-rhamno-trisaccharides.

Joly et al. [51] found that the double bond of L-sugar derivative 45 failed to react with MCPBA. However, when the reaction was performed under the conditions of Payne (H₂O₂/PhCN), a mixture of epoxides 46 and 47 was formed. The long aglycone chain is likely hindering the attack on the α-side of the 2,3-enopyranoside and lowering the overall yield as well. The epoxides were then reductively ring-opened by LiAlH₄ to form ascaroside models 48 and 49 (Scheme 12).

Scheme 11. Alternative routes for cis- and trans-dihydroxylation of hex-2,3-enopyranoside 41.

Scheme 12. Synthesis of ascarosides 48 and 49.
The incorporation of chemical functionality that polarizes the alkene on 2,3-epoxyglycosides makes possible Michael-like additions resulting in the regioselective introduction of nucleophiles. Several examples of Michael reactions on 3-nitro-hex-2-enopyranosides, e.g., 50, were previously reported by Sakakibara’s group. In these reactions, active methylene compounds [52–54] and sterically demanding purine bases [55] reacted regio- and stereoselectively at C-2 from the side opposite to the anomeric substituent (e.g., 51 from α-50 and 52 from β-50) (Scheme 13). Amines, however, produced thermodynamically more stable C-2 equatorial products (53 and 54) irrespective of the anomeric configuration of the starting glycoside [56]. These results have been discussed in terms of electrostatic interactions [57], stereoelectronic control [57], steric hindrance [57], A-strain [58] and also hydrogen bonding [58]. Dideoxy-hex-2-en-4-ulopyranosides, on the other hand, always produced epimeric mixtures at C-2 [59–61].

Scheme 13. Michael addition on isomeric 3-nitro-hex-2-enopyranosides 50.

More recently, Pathak and coworkers have studied the behavior of vinyl sulfone-modified hex-2-enopyranosides. Michael additions, followed by desulfonylation with Na-Hg (6 mol-%) of the resulting adducts [62], allowed the regio- and stereo-selective introduction of nucleophiles in 2,3-enopyranosides. They found a remarkable influence of the protecting groups of the hydroxyl moieties on the reaction patterns [63]. For example, although phenylmethylene-protected vinyl sulfone 55 reacts with both primary and secondary amines in a Michael-fashion, only primary amines react with the dibenzyl-protected, O-trityl protected or unprotected derivatives 56, 57 and 58 respectively (Figure 1).

This strategy has amply been employed by Pathak’s group in the synthesis of a variety of compounds including aminosugars [64], branched-chain sugars [65], isonucleosides [62], and chiral pyrroles [66]. For example, conjugate addition of the anion generated from ethyl isocyanate to vinylsulfone 55 afforded a pyrrole derivative 59, which by subsequent treatment with POCl3/DMF afforded chiral pyrrole 60 (Scheme 14).
On the other hand, 2,3-unsaturated 3-arylsulfinyl pyranosides have been shown to undergo nucleophilic additions at C-2 with facial selectivities that are influenced by the nucleophile and the substituent on the sulfinyl sulphur [67]. For example, the reaction of 61a with primary amines (carbon and sulphur nucleophiles were also used) led to adduct 62a, with the addition of the nucleophile preferring an axial orientation at C-2 and with concomitant elimination of acetic acid to form an allylic bond at $\Delta^{3,4}$. Conversely, the related reaction of 61 with a secondary amine led to a mixture of epimeric 2-deoxy-2-amino compounds 63a where the major product displayed a C-2 equatorial orientation. Furthermore, the influence of the $\alpha$-sulfinyl substituent on the stereochemical outcome of the reaction also became clear. Thus, reaction of stericly congested ($p$-isopropylphenyl)vinyl sulfoxide 61b with pyrrolidine produced a C-2 $\alpha/\beta$ 7:1 epimeric mixture, whereas reaction of pyrrolidine with $p$-tolyl vinyl sulfoxide 61a produced a C-2 $\alpha/\beta$ 3:1 epimeric mixture (Scheme 15). A similar trend was also observed in the reaction of 61a and 61b with primary amines, leading to 62a and 62b, respectively (Scheme 15).
Finally, hex-2-enopyranosides have shown to be popular starting materials in the preparation of biologically relevant 2,3-dideoxy-3-amino sugars in which the amino group is cis to a vicinal (C4-OH) hydroxyl group [68]. Thus, Fraser-Reid’s group introduced the iodine mediated cyclization of (C-4) allylic imidates to the $\Delta^{2,3}$ unsaturation on hex-2-enopyranosides, which directed the cis entry of the nitrogen function [69–71]. Several other functionalities such allylic carbamates or isoureas have been used since in this electrophile induced cyclization. Hydrolysis of the resulting oxazoline paves the way to the desired cis amino alcohol functionality [68]. In this context, Takahashi and co-workers have reported the synthesis of L-vancosamine, L-ristosamine, L-saccharosamine, and L-daunosamine by use of an electrophile-induced [o-iodoxybenzoic acid (IBX)] [72] cyclization of allylic carbamates [73].

3.2. Nucleophilic Substitutions

Reactions that allow the displacement of the C-4 allylic group on 2,3-enopyranosides also open opportunities for functionalization. Early reports were based on the nucleophilic allylic substitution with copper reagents. This possibility was limited to substrates containing acetoxy and pivaloxy, leaving groups to afford anti $S_{N2}$' products in moderate to good yields (Scheme 16) [74–76]. In contrast, reaction of the corresponding benzothiazolyl thio ethers afforded syn $S_{N2}$' adducts [77,78]. More recently, allylic substitution of substrates possessing the picolinoxy group have been studied and it was found that different alkyl and aryl groups could easily be installed on the pyran ring with anti $S_{N2}$' selectivity [79].

![Scheme 16. Allylic substitution reaction on 2,3-enopyranoside 64 and possible regio- and stereoisomers.](image)

Of particular relevance is the Pd-catalyzed substitution of allylic esters or carbonates by carbon and nitrogen nucleophiles [80–85]. A mechanistic picture of this process is displayed in Scheme 17. Even though one or more of these paths may become competitive, the use of more reactive allylic carbonates usually prevents the presence of any palladium(0) complex (66) in solution, and a remarkable selectivity is observed. The net overall retention in the palladium-mediated nucleophilic addition is then attributed to retention of stereochemical integrity during both generation of the $\pi$-allyl-Pd intermediate and the subsequent addition of the nucleophile.
This methodology has been applied to the addition of phenols [86], heterocyclic nucleophiles including uracil derivatives [87], and/or azides [88,89]. Nucleophilic substitution carried out in alkyl α-β-erythro-hex-2-enopyranosides, e.g., 70 and 72, took place with a very high regio- and stereoselectivity to provide C-4 substituted derivatives 71 and 73, respectively (Scheme 18a,b). Likewise, the palladium-catalyzed reaction of 72 with TMSN3 led regio- and stereoselectively to 4-deoxy-4-azido derivative 74 (Scheme 18c). On the other hand, palladium-catalyzed reaction of the epimeric 2,3-dideoxy-α-β-threo-hex-2-enopyranoside 75, with TMSN3 provided a regioisomeric mixture of 76 and 77 arising from attack at positions C-4 and C-2 of the π-allyl complex (Scheme 18d).

Scheme 17. Palladium-mediated allylic substitution.

Scheme 18. Examples of palladium-mediated allylic substitution.
3.3. [3,3]-Sigmatropic Rearrangements

Unsaturated sugar derivatives are ideally structured to take part in [3,3]-sigmatropic rearrangements that allow the construction of carbon-carbon or carbon-heteroatom bonds. For example, in 1973 Ferrier et al. showed that 4-vinyl 2,3-enopyranoside 78 could undergo a Claisen rearrangement upon heating at 185 °C to give the branched-chain aldehyde 79 (Scheme 19a) [90]. The reaction took place readily and in a completely stereoselective manner, as was expected for such suprafacial allyl rearrangement. However, the yield in the mercury-catalyzed preparation of the required vinyl derivative 78 was low (30%). As a synthetic alternative, Krohn et al. described the reaction of the related allylic alcohol 80 with an eightfold excess of orthoacetic ester 81a in the presence of catalytic amounts of propionic acid to afford the corresponding ester 83a in good yield as one single isomer (Scheme 19b) [91]. Similarly, the Eschenmoser variant of the Claisen rearrangement allowed access to 83b (89% yield) from allylic alcohol 80 by using 1.5 equiv. of N,N-dimethylacetamide dimethyl diacetal 81b [91]. The C-4 epimeric allylic alcohol 84, also experienced a Claisen-Johnson rearrangement in a completely stereoselective manner leading to C-2 branched derivative 85, in good yield (Scheme 19c) [92].

![Scheme 19. Examples of Claisen rearrangements.](image_url)

Porco and coworkers evaluated Eu(III)-catalyzed Claisen rearrangement of allyl phenyl ethers derived from hex-2,3-enopyranosides (Scheme 20). The reaction required microwave heating at elevated temperatures (200 °C). Representative allyl and aryl C-glycosides 86a–b underwent [3,3]-sigmatropic rearrangement to provide phenols 87a–b (Scheme 20). However, preliminary studies had demonstrated that this reaction depends on the aglycone substituent as alkynyl C-glycoside 86c did not readily undergo rearrangement, even after prolonged heating with excess Eu(fod)₃ [86].

Related Overman [3,3]-sigmatropic rearrangements have also been used to incorporate amine functions at C-2 position in hex-2,3-enopyranosides. Thus, allylic trichloroacetimidate 89, readily obtained from C-allyl glycoside 88, allowed the efficient installation of a secondary amine at C-2 in compound 90 upon reflux in 1,2-dichlorobenzene in the presence of K₂CO₃ [93]. The analogous reaction with a related epimeric alcohol in allyl glycoside 84 required considerable experimentation, though,
since the expected amide 92 was obtained alongside a chlorinated side-product 93 [94]. It was subsequently found that the formation of allylic chloride 93 was related to the degree of purity of trichloroacetimidate 91 used in the rearrangement. Thus, chromatographically pure imidate 91 underwent the Overman rearrangement to give the expected amide 92 in 82% yield (Scheme 21c). However, when the rearrangement was carried out with non-purified trichloroacetimidate 91, and in the presence of hydroquinone as a radical scavenger, the synthetically useful chloride 93 could obtained as the single product in a moderate yield (Scheme 21d) [95].

3.4. Oxidative Transformations

Oxidative transformations of hex-2,3-enopyranosides are also of synthetic value since they might lead to unsaturated enones, unsaturated lactones, or 6-formyl derivatives, depending on the conditions employed. Oxidation of diols 94 can be attained regioselectively at either O-4, or O-6, to give enones, e.g., 95 [96–101], or aldehydes, e.g., 96 [102], respectively (Scheme 22). For example, ethyl 2,3-dideoxy-α-D-erythro-hex-2-enopyranoside (94, R=Et) undergoes chemoselective allylic oxidation upon treatment with manganese dioxide or pyridinium dichromate to give hex-2-enopyranoside-4-ulose 95,
whereas selective oxidation of the primary hydroxyl group can be effected by a modification of the Corey-Kim procedure [103], as recommended by Fraser-Reid and co-workers, leading to aldehyde 96 [104–106]. The latter compound (R = Et) was used in a stereoselective synthetic approach to (+)-asperlin [107].

**Scheme 22.** Chemoselective oxidation of 2,3-dideoxy-α-D-erythro-hex-2-eno-pyranoside 94.

On the other hand, synthetically useful 2,3-dideoxyhex-2-enono-1,5-lactones 99 can be accessed from hex-2-enopyranosides, e.g., 97, through oxidation (30% H₂O₂, MoO₃). This process, reported by Zamojski’s group, involved dehydration of initially formed allylic hydroperoxides, e.g., 98 (Scheme 5) [108,109]. However, more concise routes to lactones 99 involve the direct oxidation of the corresponding glycols, and in this context the methods described by Lichtentahler’s (mCPBA, BF₃.Et₂O) and Sinaÿ’s (PCC) groups are worthy of mention [110,111].

3.5. Cycloaddition Reactions

In order to participate in cycloaddition processes, the double bond in hex-2-eno-pyranoses has been incorporated into a variety of systems. For instance, oxidized derivatives such as enones 100 (related to 95, Scheme 22) and unsaturated δ-lactones 101 (related to 99, Scheme 23) were used in Diels-Alder [9] and dipolar cycloadditions [112–115] (Figure 2). Homologated derivatives such as isomeric enals 102 and 103 also found use as dienophiles [116] and heterodienophiles [117], and finally isomeric dienes 104 and 105 were reported to undergo stereoselective Diels-Alder reactions with maleic anhydride and dimethyl acetylenedicarboxylate, among other dienophiles [116,118].

**Scheme 23.** Zamojski’s route to unsaturated lactones from hex-2-enopyranosides.

During the last decade, Chmielewski’s group has continued its investigation on 1,3-dipolar cycloaddition of nitrones to carbohydrate derived δ-lactones, e.g., 101. Their research has proven useful from theoretical and practical standpoints, and some of the resulting cycloaddition adducts have been applied to the synthesis of biologically relevant iminosugars [119].
They have reported that the cycloaddition between aldono-1,5-lactones 106–108 and chiral five-membered cyclic nitrone 109 and 110 proceeded exclusively in the \textit{exo} mode, to provide in many instances a single adduct as a result of double asymmetric induction (Figure 3) [120].

In particular, the cycloaddition reaction between lactone 106 and nitrone 110 resulted in the completely stereoselective formation of tricyclic derivative 111 as a consequence of an \textit{exo}-approach of the nitrone and the \textit{anti} addition to both the acetoxymethyl- and the 4-acetoxy group of the lactone (Scheme 24). The latter was then used in the synthesis of 8-homocastanospermine 113, via key-intermediate 112, which after cleavage of the isopropylidene group and hydrogenolysis of the N-O bond underwent intramolecular alkylation of the nitrogen atom, leading ultimately to 113 [121].

Tricyclic adduct 111 was also employed in a related synthesis of a C-1 homologue of australine, 1-homoaustraline 115 (Scheme 25) [122]. Thus, chemistry related to the one mentioned-above when performed on mesylate 114 paved the way to 1-homoaustraline 115.

1,3-Dipolar cycloaddition of six-membered nitrone 116 with lactone 106 gave one single adduct, 117, as the result of the \textit{exo-anti} approach to both substituents of the lactone dipolarophile (Scheme 26) [123]. The latter was next transformed through a series of synthetic steps into mesylate 117 that led to 2,3-dihydroxy-epilupinine 119.
The syntheses described above have benefitted from two key issues: (i) the high stereoselectivity of cycloadditions of simple nitrones to threo-lactones, e.g., 106, when compared to erythro-lactones, e.g., 107, and (ii) the easy rearrangement of the δ-lactone fragment in the adduct to a γ-lactone whose terminal diol could easily be cleaved.

Along this line, the cycloaddition of acyclic nitrones to carbohydrate-lactones was also studied for the preparation of iminosugars (or azasugars) [124]. In this context, cycloaddition of nitrone 120 and lactone 106 produce one single adduct, 121, which was processed by rearrangement to a γ-lactone and removal of the terminal (C-6) hydroxymethyl group into mesyl derivative 122 (Scheme 27). Deprotection of the hydroxy groups in the latter caused immediate intramolecular alkylation of the nitrogen atom leading to ammonium salt 123. Finally, hydrogenolysis of 123 followed by several acetylation/deacetylation processes and hydrogenolysis of the N-benzyl substituent afforded (−)-isofagomine 124 [125].
stereoselective Diels-Alder cycloaddition of cyclopentadiene and enal 125 [128], with the diene approaching the dienophile from the β-face in an exo-mode of addition. Second, the ozonolysis of 126 took place via a completely regioselective cleavage leading to dialdehyde 127. The latter was then transformed in ten steps into pentalenolactone 128.

Scheme 28. Synthetic approach to pentalenolactone 128.

Further studies by this group have addressed the issue of the fragmentation of the primary ozonide in carbohydrate-derived norbornene systems. They showed that, in participating solvents, the remote substitution is responsible for the regioselective fragmentation of the intermediate ozonide [129–131].

A multistep route to previously described enal 135 [128], has also been described (Scheme 29) [132]. The synthesis started with the oxidative cleavage of methyl-α-D-glucopyranoside 129 leading to dialdehyde 130. Treatment of 130 with nitromethane in basic medium led to a mixture of 3-deoxy-3-nitro derivatives 131. Benzylideneation of these derivatives followed by purification of the crude reaction provided epimeric mixture of alcohols 132 that upon elimination, mediated by treatment with MsCl and Et₃N, yielded unsaturated nitro derivative 133. Further processing of 133 via cyano derivative 134 permitted access to 135.

Scheme 29. Spanevello’s synthetic route to enal 135.

Finally, the thermal Diels-Alder reaction between sugar-derived nitroalkene 133 and cyclopentadiene yielded a mixture of exo- and endo- adducts 136 and 137, respectively, where unlike previous examples, an α-facial selectivity in the approach of the diene was observed (Scheme 30) [133].

Scheme 30. Diels-Alder cycloaddition between nitroalkene 133 and cyclopentadiene.
3.6. Glycosylation Reactions

The study of glycosylation reactions of 2,3-unsaturated hexenopyranoses has recently been addressed by mediation of either palladium or Lewis acid catalysis.

3.6.1. Palladium Mediated Glycosylation

Feringa and O’Doherty’s groups addressed the issue of glycosylation with 2,3-unsaturated hexoses functioning as glycosyl donors [134].

Following previous studies on palladium catalyzed allylic substitution on 6-acetoxyl-2H-pyran-3(6H)-ones by alcohols (Scheme 31a) [135], Feringa and co-workers reported the stereoselective palladium catalyzed glycosylation of pyranones (Scheme 31b) [136]. The method proved to be particularly useful in synthesis since retention of stereochemistry at the allylic acetal moiety was observed in the newly formed glycosidic bond.

Scheme 31. Feringa and co-workers’ palladium-catalyzed allylic substitution.

They next explored the feasibility of an iterative protocol based in this chemistry for saccharide synthesis. Thus, diastereoselective catalytic cis-dihydroxylation of 144 followed by acetonide formation on the ensuing diol and reduction of the ketone moiety paved the way to β-L-ribose derivative 145 (Scheme 32). This sugar was next glycosylated with (−)-138 under palladium catalysis [Pd2(dba)3, PPh3] to give disaccharide precursor 146.

Scheme 32. Feringa’s approach to iterative saccharide synthesis.

Shortly after Feringa’s findings, O’Doherty’s group reported on a similar transformation [137]. They studied the behavior of Pd π-allyl intermediates 149 and 150 arising from allylic alcohols 147 or unsaturated ketone 148, respectively, and found that whereas reaction of 147 failed to provide any
unsaturated glycoside 151 (Scheme 33a), π-allyl intermediate 150 reacted with a variety of alcohols to give allylic glycosides 152 in moderate to excellent yields (Scheme 33b). O’Doherty’s group ascribed these contrasting results to the higher electrophilicity of Pd π-allyl intermediate 150 compared to 149. In this context, Lee and co-workers reported that the reaction of intermediates type 149, generated from glycals rather than from hex-2,3-enopyranosides, with alcohol acceptors to give O-glycosylation products, e.g., 151, could be carried out by activating the acceptor via zinc(II) alkoxide formation [138,139].

Further experimentation by O’Doherty’s group led to the use of tert-butyl carbonates 148c as the preferred glycosyl donors. Their explanation for the improved reactivity of 148c versus 148a,b, was that t-BuOH and CO₂, rather than carboxylic acids, were generated as leaving groups.

The Pd-catalyzed glycosylation reaction proceeded with high selectivity for both, α- and β-glycosylation. Thus, using either donor 148a or 148β provided the corresponding glycosides 152a or 152β, with retention of stereochemical integrity at the anomeric center (Scheme 34a,b). The scope of the reaction was investigated with an array of alcohol nucleophiles (Scheme 34). The use of sterically hindered adamantol as a glycosyl acceptor led to moderate yields of adamantyl glycosides (≈52%–54%) along with tert-butyl glycoside 153β (in the glycosylation of 148β, Scheme 34b). Formation of the latter was explained by the presence of “departing” t-BuOH as a competing nucleophile in the reaction media. However, the use of excess glycosyl acceptors or the use of pyvaloyl rather than tert-butoxy carbonyl glycoside donors allows increased yield in the formation of adamantyl glycosides.

The starting pyranones 148 were easily accessible from furan alcohols by Achmatowicz ring-expansion [16,17] followed by stereoselective hemiacetal protection [140].

The diastereoselective palladium-catalyzed glycosylation was also used in the preparation of the pheromone daumone 154, by use of pyranone 155 as the glycosyl donor (Scheme 35) [20]. The latter was prepared in enantiomerically pure form by enantioselective Noyori reduction [141] of acylfuran 157 (Scheme 36). Thus, Noyori reduction of 157 with the enantiomeric catalyst provided furan alcohol 158 in very high enantiomeric excess (93% yield, >96% ee). Ring-expanded pyranone 159 was then obtained by treatment with N-bromosuccinimide (NBS) in THF/H₂O) [16,17]. Diastereoselective acylation of 159 was performed at low temperature with (Boc)₂O provided pyranone donor 155.
Scheme 34. Pd-catalyzed stereoselective glycosylation.

Scheme 35. O’Doherty’s approach to daumone, 154.

Scheme 36. Enantioselective synthesis of α-pyranone 155.

Palladium-catalyzed glycosylation of secondary alcohol 156 with α-pyranone 155 was carried out in CH₂Cl₂ to yield glycoside 160 as a single diastereomer (Scheme 37). Diastereoselective epoxidation of enone 160 to give epoxy-ketone 161 was then followed by a one-pot process involving ketone reduction and epoxide opening to give rhamnose derivative 162. Finally, deprotection and oxidation led to daumone 154.

O’Doherty’s group has also exploited this methodology for the synthesis of oligosaccharides, in particular 1,6-linked and 1,4-linked oligosaccharides, by way of iterative glycosylations combined with diastereoselective ketone reduction and dihydroxylation processes [142].
Scheme 37. Palladium-catalyzed glycosyl coupling and processing to daumone 154.

The iterative glycosylation protocol was also applied to the stereoselective synthesis of digitoxin 163 (Scheme 38) [143,144]. O’Doherty’s retrosynthesis for digitoxin is outlined in Scheme 38 and involved the iterative, diastereoselective, palladium catalyzed glycosylation of digitoxigenin (165) with pyranone 164, which is accessible in enantiomerically pure form from acylfuran 157.

Scheme 38. O’Doherty’s retrosynthesis of digitoxin 163.

The synthetic route started with an enantioselective Noyori reduction of acylfuran 157, followed by the Achmatowicz ring-expansion protocol, and stereoselective anomeric Boc-formation at high temperature to obtain pyranone 164 as the major isomer (Scheme 39). Palladium-catalyzed glycosylation of digitoxigenin (165) with 164 produced glycoside 166, which was processed to dihydroxy acetate 167. Iteration of the glycosylation/pyranose functionalization processes to the di- and trisaccharides 168 and 179, respectively, resulted in the synthesis of digitoxin, 163.

The usefulness of the protocol implemented by O’Doherty’s group from achiral furan 157 via enantioselective reduction, Achmatowicz ring-expansion, and diastereoselective (iterative) palladium-catalyzed glycosylation(s) has been further demonstrated with the successful synthesis of anthrax tetrasaccharide (171) [145–147], the trisaccharide portion of landomyacin A (172) [148], cleistroside-2 (173) and several members other members of the cleistroside (tri- and tetra-rhamnosides)
family [149], as well as the total syntheses of kaempferol glycoside SL101 (174) [150], jadomycin B (175) [151,152], and vineomycinone B2 methyl ester (176) [153] (Figure 4) [154].

Scheme 39. O’Doherty synthesis of digitoxin (163) by iterative palladium-catalyzed glycosylations.

Figure 4. Natural products synthesized by O’Doherty’s group.
The synthetic potential of this protocol is enhanced by the flexibility of the enantioselective reduction of the acyl furans and the stereocontrol in the formation of the anomeric tert-butyl carbonates. Thus acyl furan 157 can be transformed, in a stereocontrolled manner in α-L, β-L, α-D or β-D tert-butyl carbonates 155 and 164, respectively (Scheme 40) [155]. These derivatives were used in the preparation of a collection of 11 methymycin analogues (179) by stereoselective glycosylation of 10-deoxymethylnolide 177 followed by synthetic manipulations of the ensuing pyranones 178 (Scheme 41).

Scheme 40. O’Doherty’s enantio- and stereo-divergent approach to D/L and α/β-pyranones 155 and 164.

Scheme 41. Enantio- and stereo-divergent synthesis of glycosylated methymycin analogues, 179.

Related chemistry was also used in the preparation of the α-L-aculose, α-L-rhodinose, and β-D-olivose trisaccharide-component of PI-080 [156].

Pyranoones with oxygen substituents at the primary position, e.g., 148c, 185, as precursors of 6-hydroxy pyranoses, can analogously be prepared in either enantiomeric form (D/L) from oxygenated acyl furan 180 by way of enantioselective Noyori reduction (181, 182), and Achmatowicz ring-expansion (Scheme 42) [157]. A combination of D- and L-pyranones were used by O’Doherty in the de novo asymmetric synthesis of all-D, all-L, and D-/L- oligosaccharides (see Scheme 10, Section 3.1) [48].
Scheme 42. Enantiodivergent synthesis of pyranones, 148c and 185 from acyl furan 180.

Pyranone 185 has also been used in the preparation of the glycosylated tyrosine portion of mannopetimycin-E, 186 (Scheme 43) [158,159].

Scheme 43. O’Doherty’s retrosynthesis of the disaccharide portion of mannopetimycin-E 186.

Very recently, Liu and co-workers have reported the stereoselective palladium-catalyzed N-glycosylation of α-piclooyl 2,3-unsaturated hexopyranosides, e.g., 187, leading to N-heterocyclic glycosides 188 (Scheme 44) [160]. The method, initially developed and optimized on 3-piclooyl glucals, was compatible with a variety of protecting groups on the glycosyl donor.

Scheme 44. Liu and co-workers’ stereoselective palladium-catalyzed N-glycosylation.

Based on their results, the authors were able to propose a reaction mechanism that is outlined in Scheme 45. The pathway involved simultaneous initial palladium coordination to the double bond
and to the nitrogen of the picoloyl group at the α-face of the sugar to generate intermediate 189. Subsequent cleavage of the picoloyl acid species yielded the π-allyl system depicted as 190. Finally, coordination of the N-nucleophile to the palladium released the picoloyl acid and provided intermediate 191, where an intramolecular nucleophilic addition takes place to yield N-heterocyclic glycosides 188.

Scheme 45. Proposed reaction mechanism for the synthesis of N-glycosides 188.

3.6.2. Lewis-Acid Mediated Glycosylation of 2,3-Unsaturated Glycosyl Acetates

Toshima and co-workers reported on the chemoselective assembly of differently substituted 2,3-unsaturated pyranoses [161,162]. Thus, 2,3-unsaturated-4-keto glycosyl acetates, e.g., 193, were found to display lower reactivity than 2,3-unsaturated-4-hydroxy glycosyl acetates, e.g., 192, in the presence of Lewis acids, and could therefore be used as glycosyl acceptors with the latter acting as glycosyl donors. An implementation of their strategy is outlined in Scheme 46. Accordingly, 4-keto derivative 193 was chemoselectively glycosylated with 192 by use of TMSOTf in CH2Cl2 at −78 °C, to give disaccharide 194 in fairly good yield. Subsequently, the ensuing 4-keto derivative 194 was able to act as a glycosyl donor and was used to glycosylate methyl glucoside 195, in toluene at higher temperature, to yield trisaccharide 196 (TMSOTf, −40 °C). The observed α/β anomeric selectivity was high and in agreement with literature precedents favoring the α-anomer in each case.

Scheme 46. Toshima’s chemoselective glycosylation strategy to trisaccharide 196.

3.6.3. Halonium Ion-Mediated Glycosylation of 2,3-Unsaturated Allyl Glycosides

Taneja and co-workers recently described the remarkable stereoselective α-glycosylation of 2,3-unsaturated allyl glycosides mediated by NBS in the presence of catalytic Zn(OTf)2 [163]. The method was applied to the glycosylation of a variety of alcohols with erythro- and threo- 2,3-unsaturated
allyl glycosides 197 and 198, respectively (Scheme 47). Protecting groups such as acetonide, nitro, or esters proved to be compatible with the reaction conditions.

**Scheme 47.** Taneja’s stereoselective α-glycosylation with allyl glycosides 197 and 198.

### 3.7. Use of 2,3-Unsaturated Hexopyranoses as Chiral Complex Ligands

Carbohydrates have been long used as stereodifferentiating agents [164]. In this context, Boysen and co-workers reported on a phosphinite hybrid ligand 201, based in a 2,3-unsaturated pyranoside [165]. Accordingly, phosphinite 201, readily prepared by reaction of the corresponding unsaturated alcohol with diphenyl chlorophosphine (PPh₂Cl, Et₃N, THF, 70% yield), was employed in the rhodium-catalyzed 1,4-addition of boronic acids to unsaturated ketones and lactones 202. The ensuing products, 203, were obtained with high yields and excellent stereoselectivity when cyclic substrates were involved (Scheme 48). In a recent remarkable development, Boysen and co-workers reported that isomeric erythro-, i.e., 201, and threo-, i.e., 204, phosphinites, behaved as pseudo-enantiomeric olefin ligands in Rh(I)-catalyzed 1,4-additions of aryl and alkenylboronic acids to achiral enones [166]. They also extended the reaction to a variety of alkenyl and aryl boronic acids.

**Scheme 48.** Boysen’s pair of pseudoenantiomeric carbohydrate derived phosphinites 201 and 204, in rhodium catalyzed asymmetric 1,4-addition of phenylboronic acid to unsaturated enones and enoates.
3.8. Miscellaneous

A series of synthetic transformations of de novo hex-2,3-enopyranose derivatives, e.g., 155, into a variety of monosaccharide and deoxy-monosaccharide derivatives have been described by O’Doherty’s group [167]. These transformations make imaginative use of addition, oxidation, and substitution reactions performed on hex-2,3-enopyranoses and 3,4-unsaturated pyranoses, e.g., 207, the latter readily available from the former by Wharton rearrangement (Scheme 49) [168]. Accordingly, Boc-pyranone 155 was converted by way of stereoselective Pd(0) glycosylation into α-benzyl derivative 205, whose epoxidation under basic conditions led stereoselectively to epoxy ketone 206 [169]. Wharton rearrangement of the latter then provided benzyl hex-3,4-enopyranoside 207.

![Scheme 49. Wharton rearrangement of pyranone 205 to hex-3,4-enopyranoside 207.](image)

A synthetic route to α-ascariloside 209, was devised by regio- and stereoselective reaction of 207 with N-iodosuccinimide (NIS) in acetic acid followed by LiAlH₄ reduction of the ensuing β-acetoxy iodide 208 (Scheme 50) [169,170]. An approach to benzyl α-fucoside (211) from 207 was implemented via osmylation of 210 (2-epi-207, prepared by oxidation/reduction of 207) (Scheme 50). It was observed that osmylation of 210 leading to fucose monosaccharides (211) was better carried out on 2-silyl derivative 210b, which produced a 7:1 diastereomeric mixture favoring 211b [211b/212b 7:1]). Conversely, osmylation of 210a led to diastereomeric 212a as the major isomer [211a/212a 1:4)] [169].

![Scheme 50. Synthetic transformations of hex-3,4-enopyranoside 207 leading to α-ascariloside 209 and α-fucosides 211.](image)
4. Conclusions

Hex-2,3-enopyranosides continue to be important intermediates currently used in a variety of synthetic transformations. They are readily available by Ferrier rearrangement of commercially available glycals, although more recently the de novo approach to pyranones, and thence hex-2,3-enopyranosides, has positioned itself as reliable synthetic alternative for their preparation. The latter approach has the advantage of providing access to enantiomeric hex-2,3-enopyranoside pairs. The use of 2,3-unsaturated pyranosides in glycosylation has grown exponentially during the last decade, more than likely because of the success on the stereoselective Pd(0)-mediated glycosyl coupling of α- and β- pyranones.

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Author Contributions

AMG and JCL planned and supervised the review. AMG, FL, SM, and JCL participated in the writing of the manuscript.

Conflicts of Interest

The authors declare no conflict of interest.

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