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Review

Sugars containing α,β-unsaturated carbonyl systems: synthesis and their usefulness as scaffolds in carbohydrate chemistry

Nuno M. Xavier and Amélia P. Rauter*

Departmento de Química e Bioquímica/Centro de Química e Bioquímica, Faculdade de Ciências da Universidade de Lisboa, Edificio C8, 5° Piso, Campo Grande 1749-016 Lisboa, Portugal

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Abstract—The α,β-unsaturated carbonyl function occurs in a wide variety of bioactive natural products. It is usually associated with the bioactivities of these compounds and acts as Michael acceptors for the addition of protein nucleophilic groups. The design and synthesis of sugars containing this functionality has provided a wide range of compounds, which can serve as building blocks of high synthetic versatility. This review deals with the chemistry of sugar-based molecules bearing singly linked or fused unsaturated lactones and ketones along with that of pyranoid enones and enonolactones. Examples are given of their syntheses and transformations into a variety of complex sugar derivatives such as branched-chain sugars, C-nucleosides, *C*-glycosyl derivatives, and various natural products, including selected analogues.

Keywords: α,β-Unsaturated carbonyl systems; Sugar-fused unsaturated lactones; Sugar-linked unsaturated lactones; Sugar-linked unsaturated ketones; α,β-Unsaturated-pyranuloses

Contents

* Corresponding author. Tel.: +351 217500952; fax: +351 217500088; e-mail: aprauter@fc.ul.pt

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1. Introduction

The α,β-unsaturated carbonyl moiety is present in a large number of natural and synthetic products exhibiting a variety of biological properties. Compounds containing such an unsaturated system, notably lactones or cyclic ketones, were described as cytotoxic[1a–e] and as antitumor agents,[1b] antimicrobials,[1f] or as possessing significant antiviral,[1b] gastric antiulcer activities,[1g] among others. Furthermore, it has been shown that the conjugated system plays a fundamental role in determining bioactivity, due to its ability to act as a Michael acceptor for the addition of protein functional groups.[2] In particular, sugars incorporating unsaturated carbonyl motifs have become important synthetic targets not only due to their potential biological profile but also for their use as precursors for the synthesis of many bioactive compounds such as branched-chain sugars or nucleosides.

This review attempts to cover the synthetic strategies used to obtain sugar derivatives containing unsaturated carbonyl moieties in their structure, namely α,β-unsaturated lactones and cyclic ketones. It focuses on the natural occurrence and biological relevance of these compounds, as well as on their use as important intermediates in carbohydrate chemistry.

2. Sugar derivatives containing α,β-unsaturated lactones

The ring system of α,β-unsaturated lactones, especially γ- and δ- lactones, constitutes the central skeleton of many natural products, and is commonly related to a wide range of pharmacological activities. This biological behavior has prompted the investigation of synthetic methodologies for the generation of such motifs over the years.[3] Examples of naturally occurring glycosides containing α,β-unsaturated lactones include the cardiotonic digitoxin,[4] which possesses a butenolide ring at position C17β in the steroid framework, and the butenolide glycoside ranunculin (Fig. 1).[5]

We discuss below the methods that have been employed for the preparation of sugar-linked, sugar-fused, or sugar-based unsaturated lactones, focusing on five- and six-membered ring systems.

2.1. γ-Lactones

2.1.1. γ-Lactones fused to sugars. Five-membered ring unsaturated lactones fused to carbohydrates, namely butenolides [2(5*H*)-furanones], have been used as intermediates for the synthesis of bioactive natural products and branched-chain sugars. This moiety is a structural unit of the mycotoxin patulin (Scheme 1), produced by different species of *Penicillium*, *Aspergillus*, and *Byssochlamys*, which shows significant antibiotic and antibacterial properties, despite being a food contaminant and a general plant toxin.[6] Its synthesis involved oxidation of methyl 3,4-*O*-isopropylidene-β-L-arabinopyranoside **1**, easily prepared from L-arabinose, followed by Wittig olefination of the resulting keto-sugar to afford an approximately 3:1 mixture of the (*E*)-and (*Z*)-unsaturated esters **2a**,**b**. The (*E*)-isomer was subsequently converted into the sugar-fused butenolide **3** after hydrolysis with dilute hydrochloric acid in methanol under reflux. Dehydration of **3** by mesylation–elimination provided

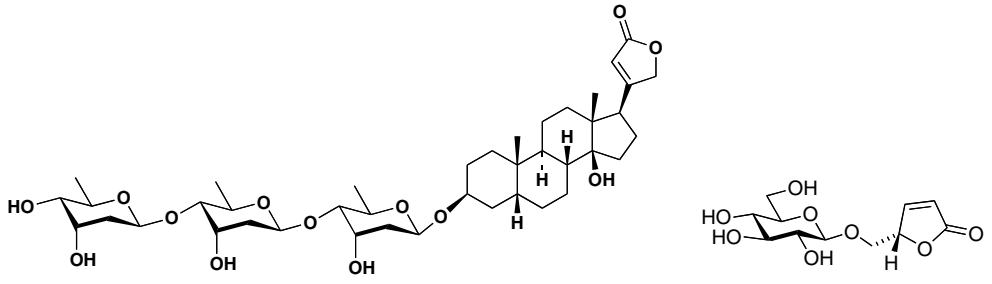
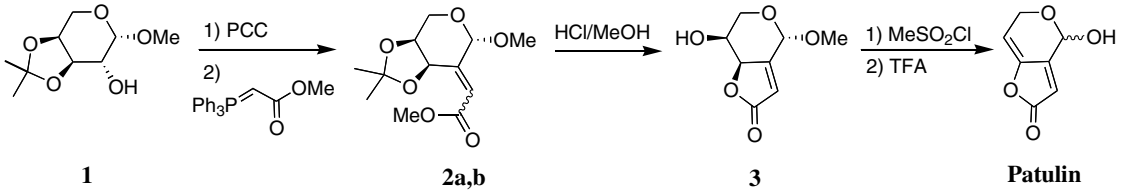


Figure 1. Two examples of naturally occurring glycosides containing α,β-unsaturated lactones.



Scheme 1. Synthesis of patulin.

(*S*)-*O*-methylpatulin, which was then deprotected by treatment with trifluoroacetic acid (TFA) to produce the target molecule.

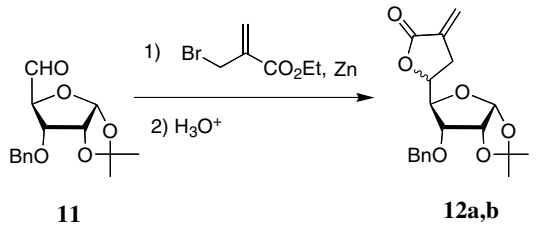
Liu et al.[7] reported the autoxidation of a hexopyranoside-fused butenolide **5**, which was isolated as an intermediate in the one-pot synthesis of the 2-*C*-branched-chain sugar **7**.[7] Insights into the mechanism of this transformation clarified the three main steps involved. Thus, aldol condensation of the glucopyranosid-2-ulose **4** with diethyl malonate proceeded via the butenolide **5**, which was obtained by transesterification and intramolecular cyclization (Scheme 2). This compound was then transformed into **6** by autoxidation. The latter underwent Michael addition in the presence of water, which was followed by decarboxylation, leading to the corresponding branched-chain sugar **7**.

We have also demonstrated an efficient preparative access to butenolides fused to pento- and hexopyranoses (compounds-type **10**) in a few steps starting from commercially-available furanose derivatives (Scheme 3).[8a] The methodology consists of the Wittig olefination of furanos-3-uloses (compounds of the general type **8**), which are easily obtained, followed by acid hydrolysis. This step leads to the cleavage of the acid labile protecting groups (PG), intramolecular lactonization, and isomerization to the pyranose form. Using this synthetic pathway, good overall yields were obtained for the target compounds.

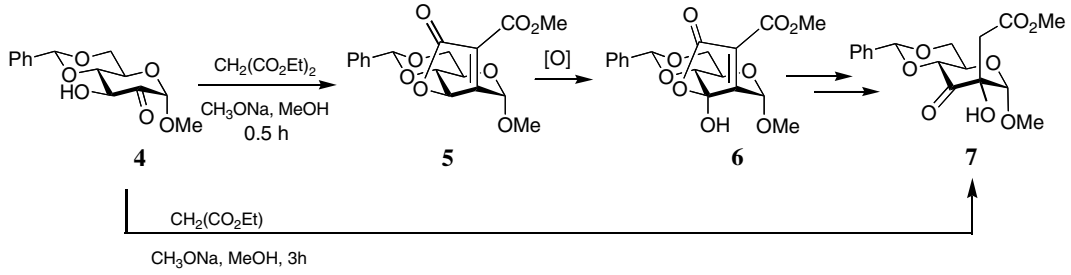
Synthesis of this type of sugar-fused butenolide, using a similar strategy, was published soon afterwards by Goddard-Borger et al.[8b] These molecules were subsequently transformed into 3-methyl-2*H*-furo[2,3-*c*]pyran-2-ones by elimination with DBU.

2.1.2. γ-Lactones linked to sugars. Sugar-linked α,β-unsaturated γ-lactones, notably butenolides and α-methylene-γ-butyrolactones, have attracted much attention owing to their biological and pharmacological properties and their role as synthons for useful sugar derivatives. Our research group has contributed to this field using two different approaches. The introduction of an α-methylene-γ-butyrolactone on a furanose residue (**12a**, **b**) was achieved by a Reformatsky-type reaction of a dialdofuranose **11** with ethyl bromomethylacrylate and zinc to give both C-5 epimers which were easily separated by liquid chromatography (Scheme 4).[9] Some of these compounds proved to have significant fungicidal activity and were particularly effective against *Puccinia recondita*, *Botrytis cinerea*, and *Plasmopara viticola*, being considered to be wheat-, pepper- or wine-protective agents, respectively.[9b]

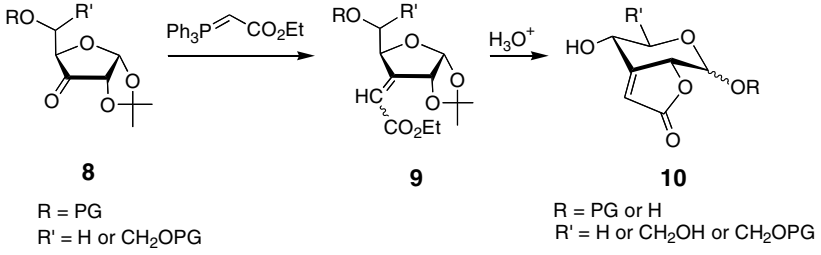
The other approach led to the synthesis of a sugar containing an endocyclic unsaturated lactone functionality, starting from sugar epoxides having the *gluco*- or *allo*-configuration (**13a**,**b**, Scheme 5). Reaction with the



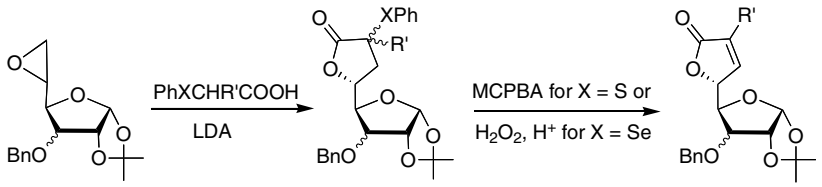
Scheme 4. Synthesis of antifungal sugar-linked α-methylene-γ-lactones.



Scheme 2. Steps involved in the synthesis of the 2-*C*-branched-chain sugar **7**.



Scheme 3. Synthesis of butenolides fused to pento- and hexopyranoses using furanos-3-uloses as precursors.



13a, b **14a, b** X = S or Se **15a, b**

Scheme 5. Synthesis of sugar-linked butenolides from epoxide precursors.

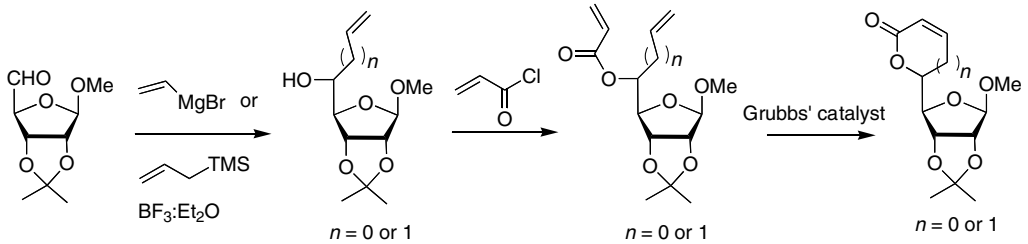
dianion of phenylselenoacetic or -propionic acids, or their thioanalogues, followed by oxidation and elimination afforded the target molecules (**15a**,**b**). The configuration of the single diastereoisomer formed is determined by that of the epoxide starting material.[9b,c] Biological testing of these compounds has demonstrated their efficacy as insecticides for a number of arthropode species such as *Musca domestica* L. (housefly), *Trialeurodes vaporariorum* (Westwood) (glasshouse whitefly), *Drosophila melanogaster* Meig (fruitfly), being particularly potent and selective against fruitflies, and much more active than imidacloprid, the insecticide commercially used. In addition, the compounds were not toxic to *Artemia salina* L. (brine shrimps), a reference organism for the evaluation of the potential toxicity hazard to invertebrates in ecosystems.[10]

The ring-closing metathesis (RCM) of acrylates derived from allylic and homoallylic alcohols has been a convenient reaction to form five- and six-membered unsaturated lactones.[3b] The method has been successfully employed in sugar scaffolds to give C-linked γ- and δ-unsaturated lactones (Scheme 6). The methodology published by Gosh et al.[11] started from the pentodialdose **16**, which was treated with vinylmagnesium bromide or allyltrimethylsilane to give the homoallylic alcohol **17**, which when acylated with acryloyl chloride afforded the acrylate esters **18**. These compounds were subjected to RCM in the presence of Grubbs' catalyst to furnish α,β-unsaturated γ- or δ-lactones **19**. A similar procedure was used for the formation of unsaturated macrocyclic (nine- to fifteen-membered) lactones linked to sugars.[12]

An alternative route to sugar-linked butenolides was based on the conversion of the precursor dialdofuranose (**16**) into Baylis–Hillman adducts (Scheme 7).[13] Reduction of the resulting alkene **20** to the corresponding diol **21**, followed by monoacryloylation at the primary or at the secondary hydroxyl group, gave the corresponding acrylate esters **22**–**23**. The latter compounds, upon RCM, led to the sugar-linked 4-substituted-γ-lactone **24** or the 4,5-disubstituted-γ-lactone **25**.

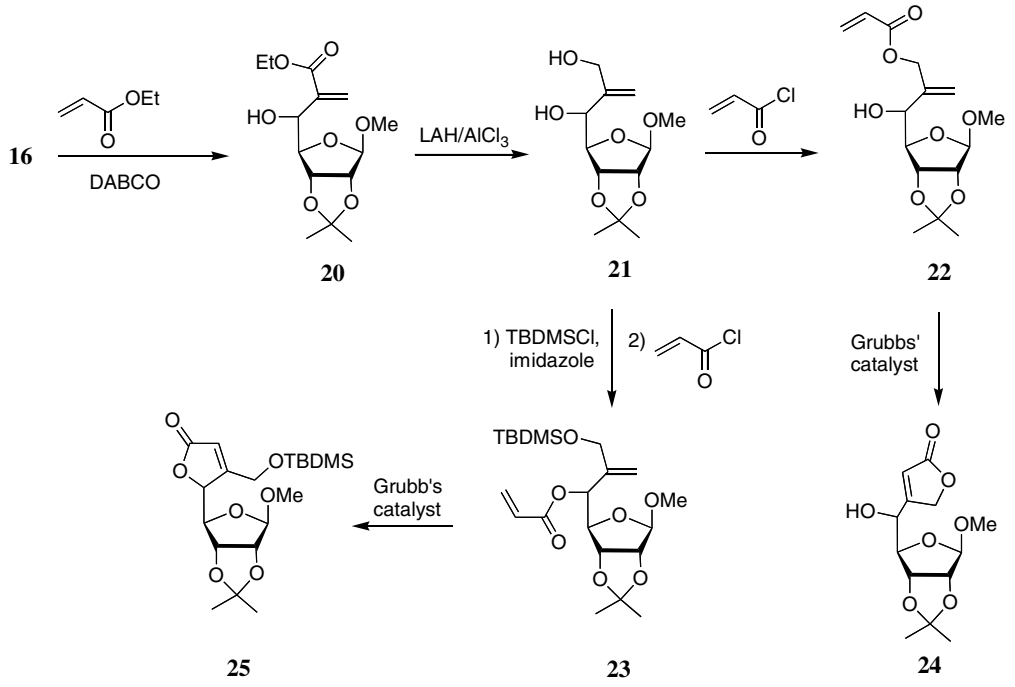
Another useful synthetic tool involved Wittig and iodolactonization reactions using dialdofuranoses as the starting materials (Scheme 8), aiming at sugar-linked butenolides, which were then converted into the corresponding isoxazolidine derivatives.[14] Thus, Wittig olefination of **26** with ethyl 3-oxo(triphenylphosphorylidene)butanoate gave the alkene **27** as an inseparable keto–enol mixture, which on reduction, followed by hydrolysis resulted in the formation of **28**. This compound was converted into the lactone **29** by reaction with I_2 in the presence of aqueous $NaHCO_3$. Subsequent deiodination of **29** with catalytic $NaCNBH_3$–tributyltin chloride, followed by acetylation, provided the butenolide **30**.

Maeba et al.[15] also made use of the versatility of the butenolide moiety to be converted into heterocyclic systems for the synthesis of C-nucleosides. The α,β-unsaturated lactone **32**, C-linked to the anomeric position, was prepared by Jones oxidation of the β-D-ribofuranosyl derivative **31** (Scheme 9). The key intermediate **32** was further transformed into C-nucleosides **33**–**35** possessing pyrrolinone, pyridazinone, and *N*-aminopyrrolinone rings in their structure.

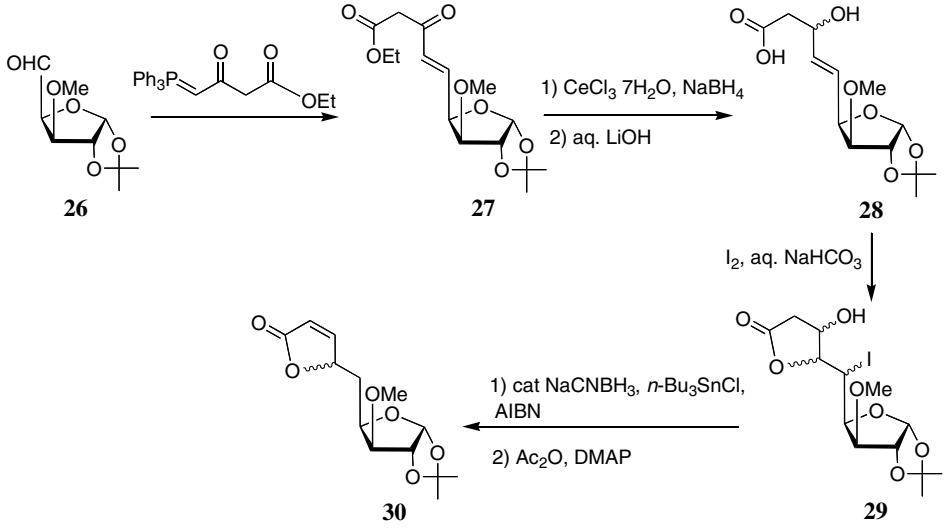


16 **17** **18** **19**

Scheme 6. Synthesis of sugar-linked γ and δ-unsaturated lactones by RCM starting from dialdofuranoses.



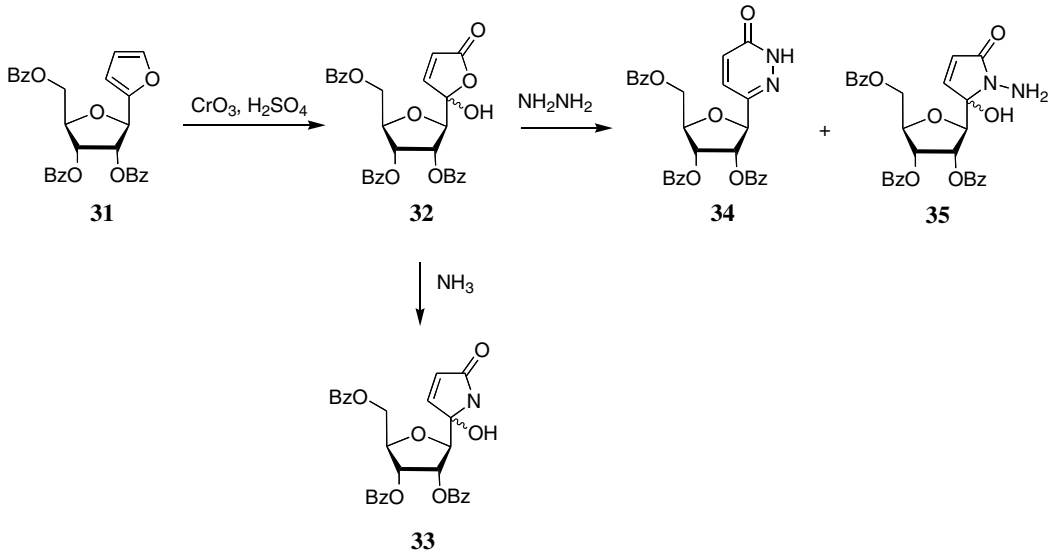
Scheme 7. Synthesis of sugar-linked butenolides by combination of the Baylis–Hillman reaction with RCM.



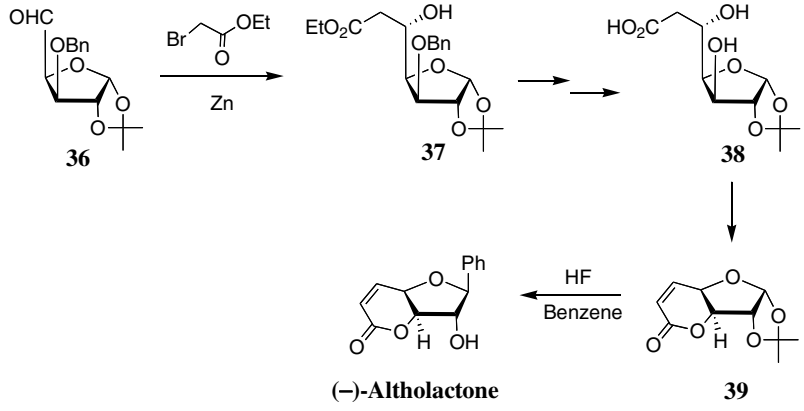
Scheme 8. Synthesis of sugar-linked butenolides by the Wittig olefination–iodolactonization approach.

2.2. δ-Lactones

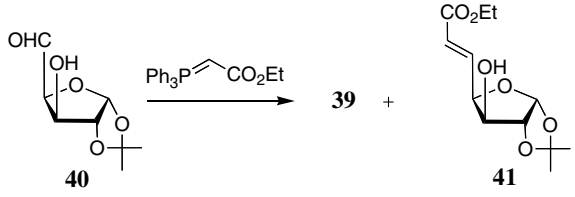
2.2.1. δ-Lactones fused to sugars. Sugar-derived unsaturated δ-lactones have been used as precursors in the synthesis of some naturally occurring compounds, because of their natural product-like profiles, and the possibility of taking advantage of the chirality resident in the sugar moiety. For example, a furanose-fused α,β-unsaturated δ-lactone was a key intermediate for the preparation of the enantiomer of (+)-altholactone, as reported by Gesson et al.[16] (Scheme 10). This sugar-derived bicyclic lactone was isolated from an unknown *Polyalthea* species and from various *Goniothalamus* species and is known to be cytotoxic in vitro showing considerable antitumor activity in vivo.[17] The procedure consisted of a Reformatsky reaction of the aldehyde **36** with ethyl bromoacetate. The resulting β-hydroxy ester **37** was converted into a dihydroxy acid **38** after ester hydrolysis and debenzylation. This latter compound was dehydrated to the furanose-fused unsaturated δ-lactone **39**. Treatment of **39** with hydrogen fluoride in benzene furnished (−)-altholactone.



Scheme 9. Synthesis of a *C*-glycosyl butenolide and its conversion into *C*-nucleosides.



Scheme 10. Synthesis of the non-natural enantiomer of (+)-altholactone via a furanose-fused unsaturated δ-lactone.



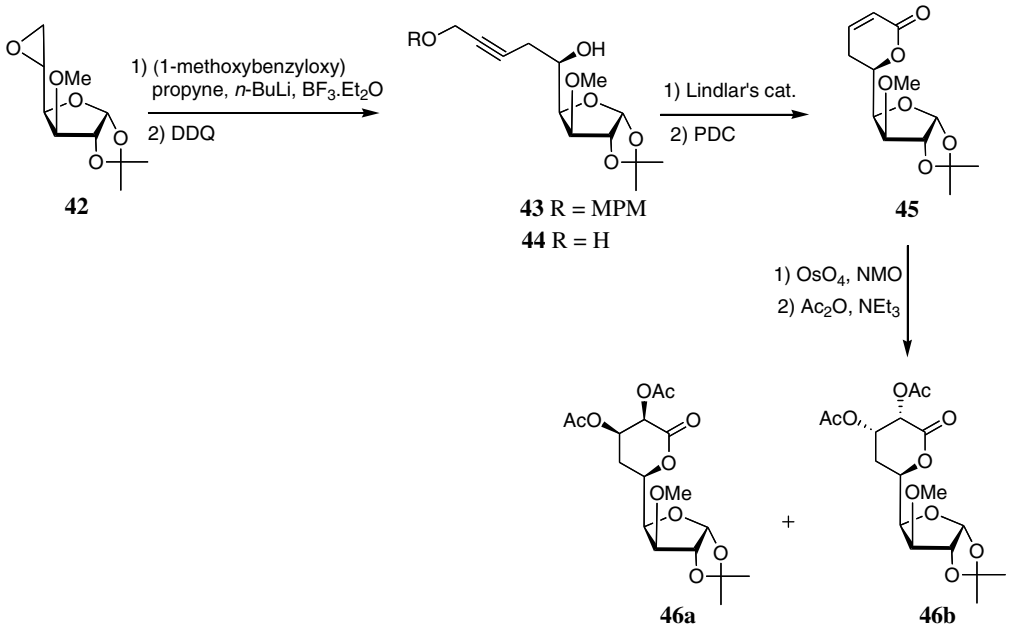
Scheme 11. Synthesis of the furanose-fused unsaturated δ-lactone **39** by the Wittig olefination–intramolecular cyclization approach.

An alternative procedure for the synthesis of the unsaturated-δ-lactone **39** was based on a Wittig reaction of 1,2-*O*-isopropylidene-α-D-*xylo*-pentodialdofuranose **40** with [(ethoxycarbonyl)methylene]triphenylphosphorane, followed by intramolecular lactonization of the (*Z*)-α,β-unsaturated ester (Scheme 11).[18]

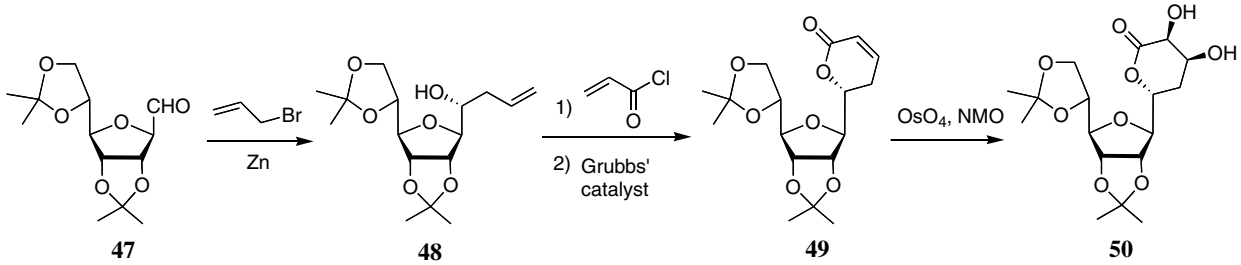
2.2.2. δ-Lactones linked to sugars. We have previously cited the synthesis of α,β-unsaturated δ-lactones linked to sugars by RCM (see Scheme 6). Another approach to these compounds consists of reaction of the epoxide **42** with (1-methoxybenzyloxy)propyne in the presence of *n*-BuLi to afford the alkyne **43**, which, after deprotection of the primary position, gave diol **44** (Scheme 12). Subsequent alkyne reduction with Lindlar's reagent followed by oxidation furnished the α,β-unsaturated δ-lactone **45**, which was successfully used to prepare the C–C linked disaccharides **46a** and **46b** by *cis*-dihydroxylation/acetylation.[19]

The RCM protocol also proved useful in providing a short route to disaccharides (Scheme 13).[20] Accordingly, the reaction of the aldehyde **47** with allyl bromide and activated zinc gave the alcohol **48**, which acroylation, followed by RCM, led to the unsaturated δ-lactone **49**. The target molecule **50** was obtained by *cis*-dihydroxylation of **49** upon treatment with osmium tetroxide.

2.2.3. Pyranoid δ-lactones. Sugar-derived pyranoid α,β-unsaturated δ-lactones (5,6-dihydropyran-2-ones)

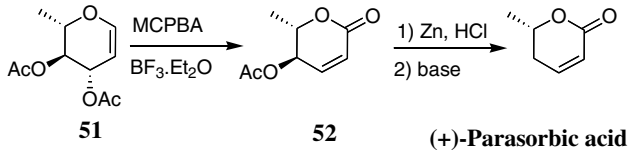


Scheme 12. Synthesis of furanose-linked α,β-unsaturated δ-lactone and its conversion into C(4)–C(5)-linked disaccharides.



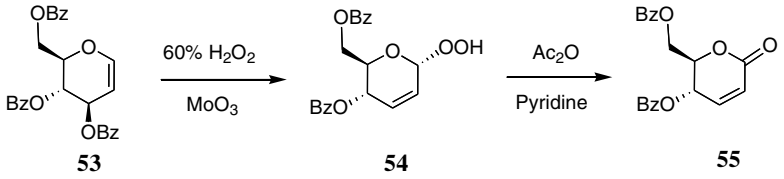
Scheme 13. Synthesis of C(1)–C(5)-linked disaccharides from furanose-linked α,β-unsaturated δ-lactones.

are easily synthesized from glycals, and have been widely used as key chiral intermediates for the preparation of biologically active natural products.[3a,21] In 1982, Jarglis and Lichtenthaler described a one-step procedure for 2,3-unsaturated lactones by oxidation of glycals and 2-acyloxyglycal esters with *m*-chloroperbenzoic acid or pyridinium chlorochromate in the presence of boron trifluoride etherate.[22] This straightforward transformation was a key-step for the synthesis of (+)-parasorbic acid (Scheme 14).[23] The BF_3-mediated peroxidation of a glycal proceeds via a generation of an allylcarboxonium ion, which undergoes subsequent peroxidation to give an intermediate 1-peroxyacyl-hex-2-enopyranose, which upon fragmentation affords the pyranoid enonolactone.[22,24]



Scheme 14. Synthesis of (+)-parasorbic acid via enonolactone **52**, which was obtained by $BF_3 \cdot Et_2O$-induced peroxidation of the L-rhamnose derived glycal **51**.

The oxidation of glycals involving anomeric hydroperoxides as intermediates has been carried out using other catalysts. Fehlhaber et al. reported the oxidation of 1,5-anhydro-3,4,6-tri-*O*-acetyl-2-deoxy-D-*arabino*-hex-1-enitol (non-preferred trivial name: 3,4,6-tri-*O*-acetyl-D-glucal) to the corresponding hydroperoxide with 85% hydrogen peroxide in dioxane, in the presence of sulfuric acid.[25] A different approach, starting from the corresponding benzoyl protected glycal (**53**), also employed hydrogen peroxide as oxidizing agent and made use of molybdenum trioxide as catalyst. The obtained hydroperoxide (**54**) could be converted into unsaturated lactone **55** via dehydration on treatment with acetic anhydride-pyridine (Scheme 15).[26a,b] In addition, 2-*C*-methylene-hydroperoxides could also be



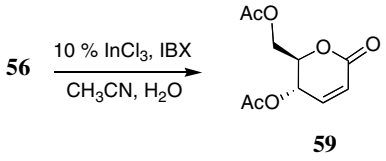
Scheme 15. Synthesis of the pyranoid 2-enono-1,5-lactone **55** by oxidation of tri-*O*-benzoyl-D-glycal **53** to the hydroperoxide **54**, followed by dehydration.

converted into the corresponding exocyclic α,β-unsaturated δ-lactones.[26b,c]

PCC oxidation has also been commonly used for the direct synthesis of sugar-derived pyranoid α,β-unsaturated δ-lactones from glycals.[27] A different methodology for the conversion of glycals to enonolactones has been reported by Rauter et al.[28] Thus, reaction of the glycal **56** with *N*-bromosuccinimide (NBS) and water, followed by oxidation of the intermediate 2-bromolactol **57** with PCC, afforded the 2-bromo-enonolactone **58** (Scheme 16). Further biological assays demonstrated the high insecticidal activity of this compound against fruitflies.[10]

The mild oxidizing agent iodoxybenzoic acid (IBX), in combination with indium trichloride, proved to be an efficient system for the one-pot conversion of glycals to enonolactones (Scheme 17).[29] The reaction involves most likely an indium mediated allylic rearrangement, followed by oxidation of the corresponding lactol.

The versatility of these sugar derivatives as synthons has encouraged their use as precursors for the preparation of bioactive compounds and natural products, typically as Michael acceptors or dipolarophiles in cycloaddition reactions.[30] In particular, the conjugate addition of hydroxylamines and hydrazines to sugar enonolactones has been a suitable method to access various optically active heterocycles such as pyrazolidin-3-ones and isoxazolidin-5-ones, which are useful intermediates for the synthesis of β-lactam antibiotics. Chmielewski and co-workers[30a,b] described the preparation of pyrazolidin-3-ones **61** and isoxazolidin-5-ones **63** by treatment of the enonolactone **59** with hydrazine, hydroxylamine, or their N-substituted derivatives, resulting from the spontaneous intramolecular cyclization of the Michael adducts **60**–**62** (Scheme 18).



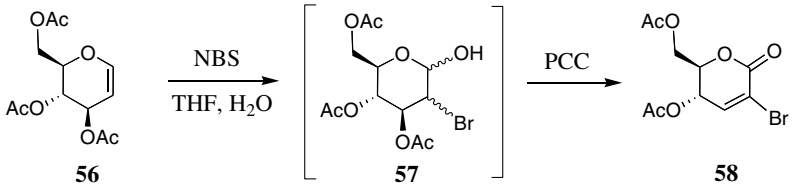
Scheme 17. Synthesis of enonolactone **59** by $InCl_3$ mediated oxidation of glycal **56** with IBX.

3. Sugars containing α,β-unsaturated ketones

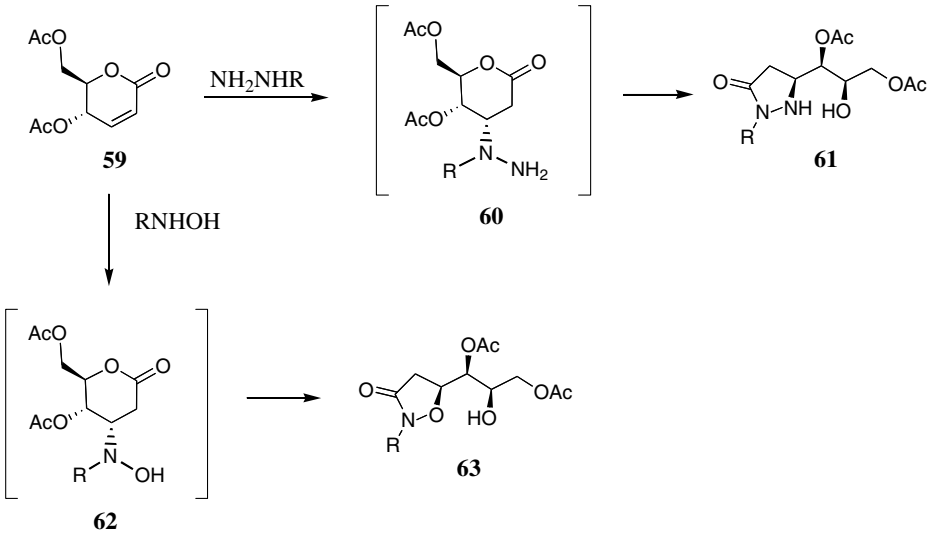
Like their lactone counterparts, carbohydrate-derived α,β-enones, namely cyclic derivatives, are versatile building blocks for the synthesis of natural products and have been employed for the generation of a diversity of chiral molecules. With respect to the naturally occurring enone-containing sugars, we can underline Vineomycin B_2,[31] an anthracycline antibiotic, containing two hex-2-enosyl hexose disaccharide moieties, and the antioxidant Ascopyrone P (APP), a metabolite from fungi which displays antibacterial activity[32] (Fig. 2).

3.1. α,β-Unsaturated ketones linked to sugars

Concerning cyclic α,β-unsaturated ketones linked to sugars, only a few examples have been described in the literature, and those report mainly the use of these compounds as templates for the synthesis of C–C-linked disaccharides.[33] Two different approaches for C–C-linked disaccharides via α,β-enones, starting from dialdofuranoses, were developed by Sharma et al.[33] In one of them (path A, Scheme 19), the sugar-linked enone was prepared by reaction of the aldehyde **26** with furyl lithium and further oxidation and methylation of the furanyl sugar-intermediate **64**.[33a] The second methodology (path B) consisted of the Wittig olefination of **26**



Scheme 16. Synthesis of the insecticidal pyranoid 2-bromo-2-enonolactone **58**.



Scheme 18. Michael addition of hydrazines and hydroxylamines (R = H, Me, Bn) to sugar enonolactone **59**, leading to pyrazolidin-3-ones and isoxazolidin-5-ones.

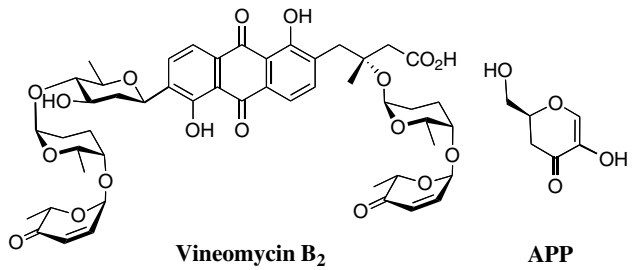


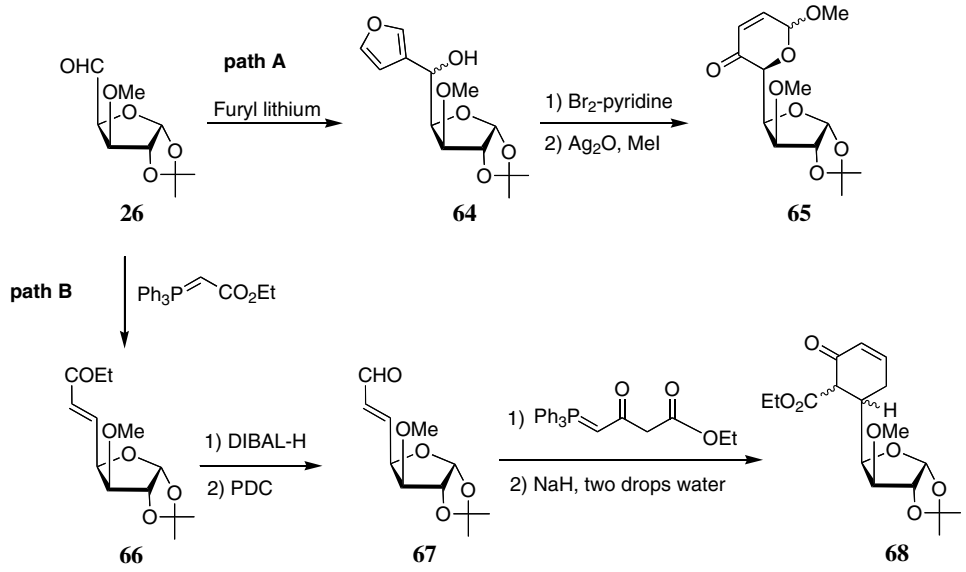
Figure 2. Some naturally occurring α,β-enone-containing sugars.

to give the α,β-unsaturated ester **66**, which was subjected to DIBAL-H reduction and subsequent oxidation with pyridinium dichromate (PDC) to afford the enal **67**.[33b]

The crucial [3+3] annulation reaction of **67** with ethyl 3-oxo-4-(triphenylphosphorylidene)butanoate in the presence of NaH and a drop of water resulted in the formation of sugar-linked α,β-enones **68** as a mixture of diastereoisomers. The desired disaccharides were obtained after enone reduction of **65** and **68**, followed by acetylation and *cis*-dihydroxylation.

3.2. α,β-Unsaturated-pyranuloses

α,β-Unsaturated-pyranuloses continue to serve as reliable scaffolds for the generation of branched-chain sugars and *C*-glycosyl derivatives, highlighted among a diversity of molecular targets. Most of the methodolo-



Scheme 19. Synthesis of furanose-linked α,β-unsaturated δ-ketones as templates for C–C-linked disaccharides.

gies to obtain α,β-unsaturated-pyranuloses use readily available glycals as starting materials. It is not our intention to give an exhaustive coverage of the chemistry of pyranuloses (classical methods were reviewed in 1978 and 1982)[34] but rather to focus on the recent advances in the field, as well as on the synthetic utility of these compounds, namely as universally reactive Michael addition acceptors.

3.2.1. 1-Enopyran-3-uloses. Protected 1-enopyran-3-uloses are of particular interest, mainly for their ability to allow chain extension at the anomeric carbon through 1,4-additions, leading to 2-deoxy-*C*-glycosyl derivatives after reduction of the resulting ketone at position 3. The direct oxidation of allylic alcohols has actually become the most common method for the preparation of hex-1-enopyran-3-uloses. In 1986, Czernecki et al. described a convenient route to these sugar enones by selective oxidation of unprotected glycals with PDC, being the target compounds obtained as major products (Scheme 20).[35]

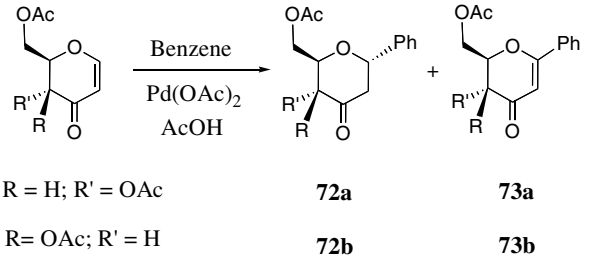
Some years later, this research group reported the oxidation of the D-glycal **66** with a stoichiometric amount of $Pd(OAc)_2$ in aqueous DMF.[36] In an alternative approach, $Pd(OAc)_2$ was used as a catalyst and the transformation carried out in the absence of molecular oxygen. The reaction was performed under an ethylene atmosphere to avoid formation of the glycal reduced product, leading to the desired enones in good to excellent yields.[37]

Palladium catalysts have also been used for further key transformations of hex-1-enopyran-3-uloses, namely in *C*-glycosylation reactions. For example, treatment of peracetylated glycal-derived enones **71** with benzene in the presence of acetic acid and palladium acetate led to mixtures of 2-deoxy-*C*-glycopyranosyl derivatives **72** and arylated enones **73** (Scheme 21).[38]

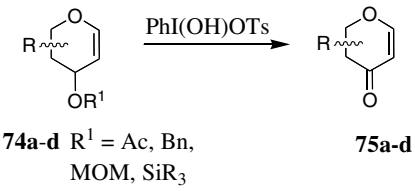
In another research, acetylated and unprotected enones derived from the D-glycal **69** reacted via 1,4-addition with trimethylsilyl cyanide in the presence of a catalytic amount of $Pd(OAc)_2$ to afford the corresponding 3-keto glycosyl cyanides. Heterogeneous catalysis (Pd–C) also worked in the cyanation reaction of **70**.[39]

In extension to the unprotected glycal oxidation, the use of hypervalent iodine reagents for the oxidation of 3-O-protected derivatives has been developed.[40] In the work described by Kirschning et al., glycals **74**, containing different protective groups, were directly converted to the corresponding hex-1-enopyran-3-uloses **75** by [hydroxy(tosyloxy)iodo]benzene in the presence of molecular sieves (Scheme 22).[40a,b] Moreover, the stereochemistry at C-3 in the starting material as well as the nature and the number of protecting groups on the pyran ring do not seem to be determinant factors for the reaction efficiency.[40b] Another hypervalent iodine reagent used for the oxidation of 3-O-protected glycals to enopyran-3-uloses is iodobenzene diacetate [$PhI(OAc)_2$].[40c]

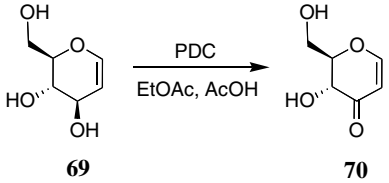
Besides glycal oxidation, other methods, such as cyclocondensation reactions of functionalized dienes with aldehydes, have been reported for the synthesis of enopyran-3-uloses.[41] Danishefsky et al. described the Lewis acid catalyzed cycloadditions of siloxy dienes with aldehydes as a general route to these hexenuloses.[41a] Hence, reaction of diverse aldehydes with *trans*-l-methoxy-3-[(trimethyl)silyloxy]-1,3-butadiene **76** in the presence of zinc chloride afforded the desired enones **78**, which may arise via 1:1 cycloadducts **77** (Scheme 23). These transformations were also carried out with boron trifluoride etherate as catalyst, followed by treatment with trifluoroacetic acid.



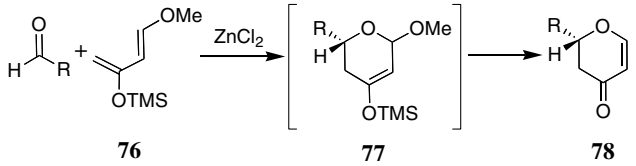
Scheme 21. Palladium mediated arylation of hex-1-enopyran-3-uloses.



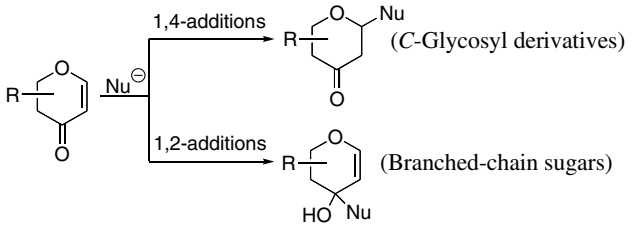
Scheme 22. Synthesis of the enopyran-3-uloses by oxidation of fully protected glycals with [hydroxy(tosyloxy)iodo]benzene.



Scheme 20. Synthesis of the hex-1-enopyran-3-ulose **70** by selective PDC oxidation of unprotected glycal **69**.



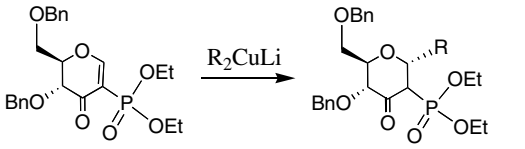
Scheme 23. Synthesis of the enopyran-3-uloses **78** by cycloaddition of a silyloxy diene to aldehydes catalyzed by a Lewis acid.



Scheme 24. Nucleophilic additions to hex-1-enopyran-3-uloses.

1-Enopyran-3-uloses are attractive starting materials for the formation of *C*-glycosyl derivatives and branched-chain sugars due to their tendency to undergo 1,4-additions or 1,2- additions (Scheme 24).[42] Michael-type additions of *O*- and *S*-nucleophiles to hex-l-en-3-uloses have been described using ZnI_2, DBU and KCN–18-crown-6 as catalysts to afford the corresponding ulosides in moderate yields.[42a] Recently, 2-deoxy-1-thio-α-hexopyranosid-3-uloses were synthesized with high diastereoselectivity by 1,4-addition of aryl and alkyl thiols to the enone system, promoted by cesium carbonate.[42b] Silyl- and sulfur-stabilized carbanions and their propensity to afford products of 1,2- or 1,4-additions, varying the combination of substituents attached to the C-l-anion, have also been studied.[42c] Conjugate addition of organometallic reagents to these heterocyclic enones, namely Grignard or organocopper reagents, and insights onto the reaction stereoselectivity have been reported.[42d,e] Leonelli et al. showed that Michael-type organocopper addition to 2-(diethoxyphosphoryl)hex-1-en-3-uloses (**79**) lead preferentially to α-anomers (Scheme 25).[42e] These compounds can be direct precursors of 2-phosphono-α-*C*-glycosyl products **80**.

3.2.2. 2-Enopyranosid-4-uloses. Due to their functionality, 2-enopyranosid-4-uloses have been used as starting materials for nucleophilic additions[43] or cycloaddition reactions[44] to the double bond, and therefore for the generation of branched-chain sugars, isonucleosides or 3-deoxy-(1→2)-disaccharides. These enuloses are generally synthesized using the well-known Ferrier rearrangement of 3-*O*-acyl-glycals,[45] followed by allylic oxidation at C-4.[34,43b,c,44b] In the following example (Scheme 26), iodine catalyzed *O*-glycosylation of the glycal **56**, followed by hydrolysis, afforded unprotected



79 **80a**, **b**, **c** R = Me, Et, Bn

Scheme 25. Michael-type addition of organocopper reagents to 2-(diethoxyphosphoryl)hex-1-en-3-uloses **79** leading to **80**.

2,3-unsaturated glycosides **81**.[43b] The latter were selectively protected at the primary hydroxyl group, being the resulted silyl ethers subjected to PDC oxidation to furnish the hex-2-enopyranosid-4-uloses **82**. Compound **82b** was used for the preparation of new sugar-modified nucleosides by Michael-type addition of silylated bases in the presence of trimethylsilyl triflate as a Lewis acid. The thus obtained adducts **83** were submitted to reduction and desilylation to give the desired products **84**.

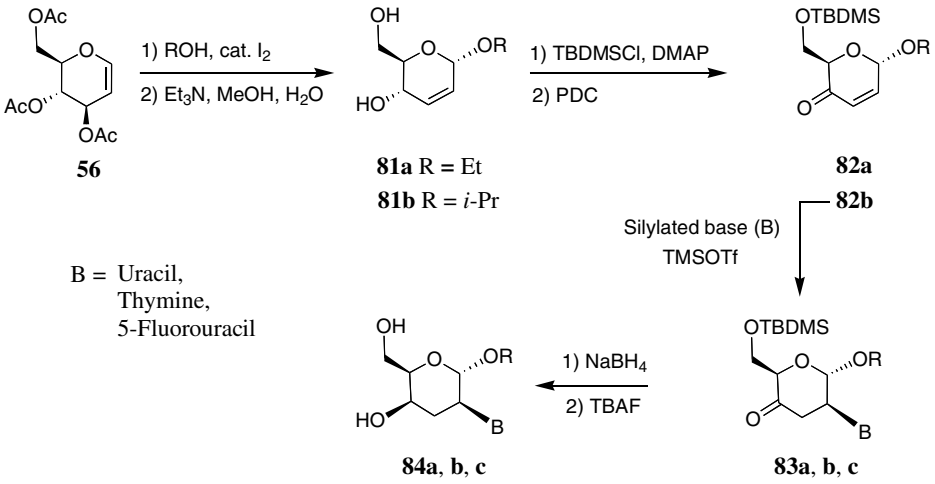
Alternatively, unprotected 2,3-unsaturated pyranosides can be directly converted to the corresponding 2-en-4-uloses by allylic oxidation with activated manganese dioxide, in good yields, as reported by de Freitas Filho et al. (Scheme 27).[44b] The reported 1,3-dipolar cycloaddition of methylideneaniline *N*-oxide to **86** occurred from the opposite side to the aglycone to afford the phenylisoxazolidin-4-uloses **87**. Hydrogenation of these compounds provided branched-chain amino sugars **88**, due to the simultaneous cleavage of the N–O bond of the isoxazolidine system and carbonyl reduction.

A different approach for the synthesis of C-3-branched deoxy sugars from hex-2-enopyranosid-4-uloses was developed by Sagar et al.[46] It consisted of the Morita–Baylis–Hillman (MBH) reaction[47] of various aldehydes with the enuloside **89** in the presence of $TiCl_4$ and TBAI (Scheme 28). By this procedure, C-3-alkylated 2,3-dideoxy sugars **90** were obtained in a diastereoselective manner in very good yields.

The fully unprotected glycal **69** was used by Witczak et al. as a suitable precursor of isolevoglucosenone, the hex-2-enopyranos-4-ulose isomer of levoglucosenone (Scheme 29).[43c] This latter hex-3-enopyranos-2-ulose is prepared by acid catalyzed pyrolysis of cellulose and can be a versatile scaffold for important sugar derivatives.[48] Hence, Ferrier rearrangement of the unprotected D-glycal **69**, promoted by anhydrous copper sulfate and molecular sieves, resulted in the allyl alcohol **91**, which was subsequently oxidized with MnO_2 to give the target isolevoglucosenone.[43c] This compound could be then functionalized into 3-deoxy-(1→2)-2-*S*-thiodisaccharides **93** by base-catalyzed conjugate addition of 1-thiosugars, followed by reduction of the C-4 keto function with L-Selectride®.

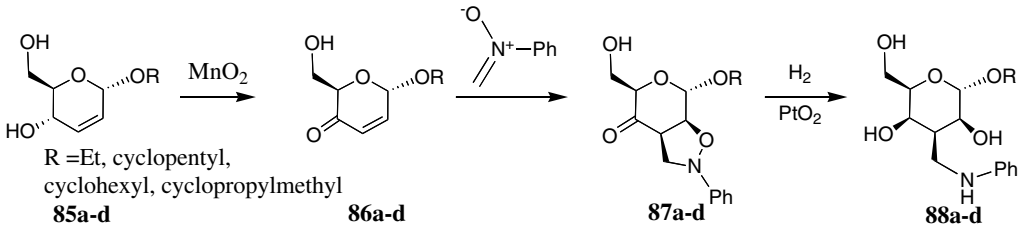
Another methodology for the synthesis of hex-2-enopyranos-4-uloses involves the oxidation of non-carbohydrate furanyl alcohols.[34,48] Ogasawara and co-workers made use of this approach for the preparation of isolevoglucosenone and its enantiomer.[49] For this purpose, 2-vinylfuran **94** was subjected to asymmetric dihydroxylation to give diols **95**, which were oxidized to enones **96** by treatment with *m*-CPBA. Dehydration of **96** in acidic medium provided the desired (+)- and (−)-isolevoglucosenones (Scheme 30).

The oxidation of a furanyl alcohol was also employed by Zhou and O'Doherty[4a] for the preparation of hex-2-



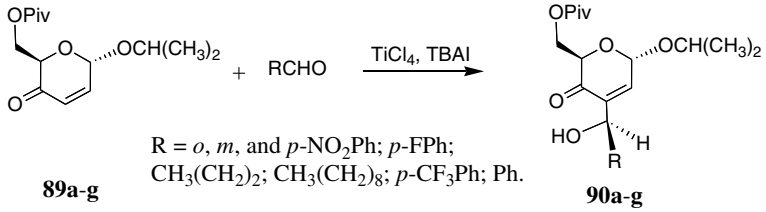
56 **81a** R = Et, **81b** R = *i*-Pr, **82a**, **82b**, **84a, b, c**, **83a, b, c**

Scheme 26. Synthesis of hex-2-enopyranosid-4-uloses via 2,3-unsaturated pyranosides and their conversion into isonucleosides.



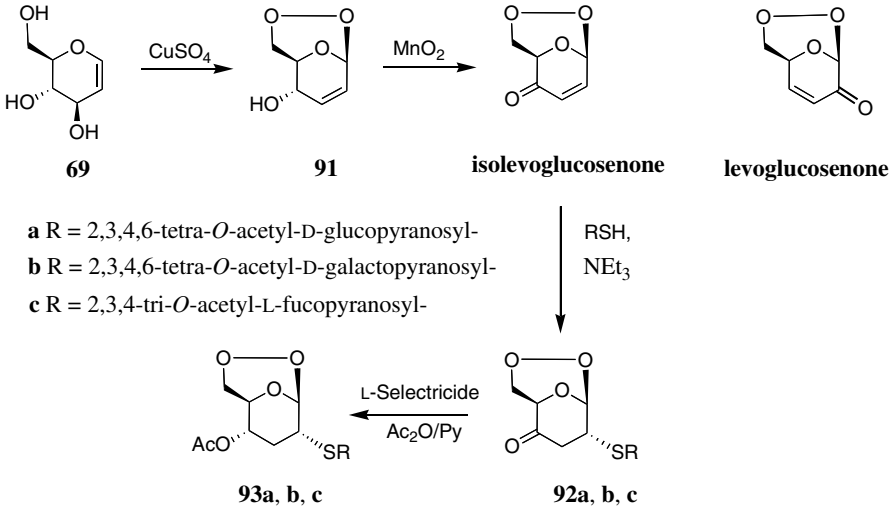
85a-d **86a-d** **87a-d** **88a-d**

Scheme 27. Synthesis of hex-2-enopyranosid-4-uloses **86** by oxidation of unprotected 2,3-unsaturated pyranosides **85**, and their conversion into branched-chain amino sugars **88**.



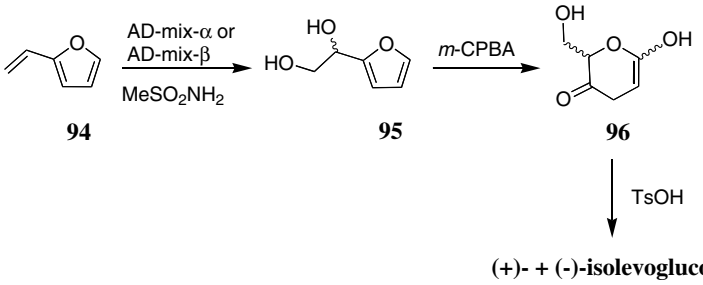
89a-g **90a-g**

Scheme 28. Hex-2-enopyranosid-4-uloses as substrates for MBH reaction with aldehydes, leading to C-3-branched deoxy sugars.



69 **91** **isolevoglucosenone** **levoglucosenone** **93a, b, c** **92a, b, c**

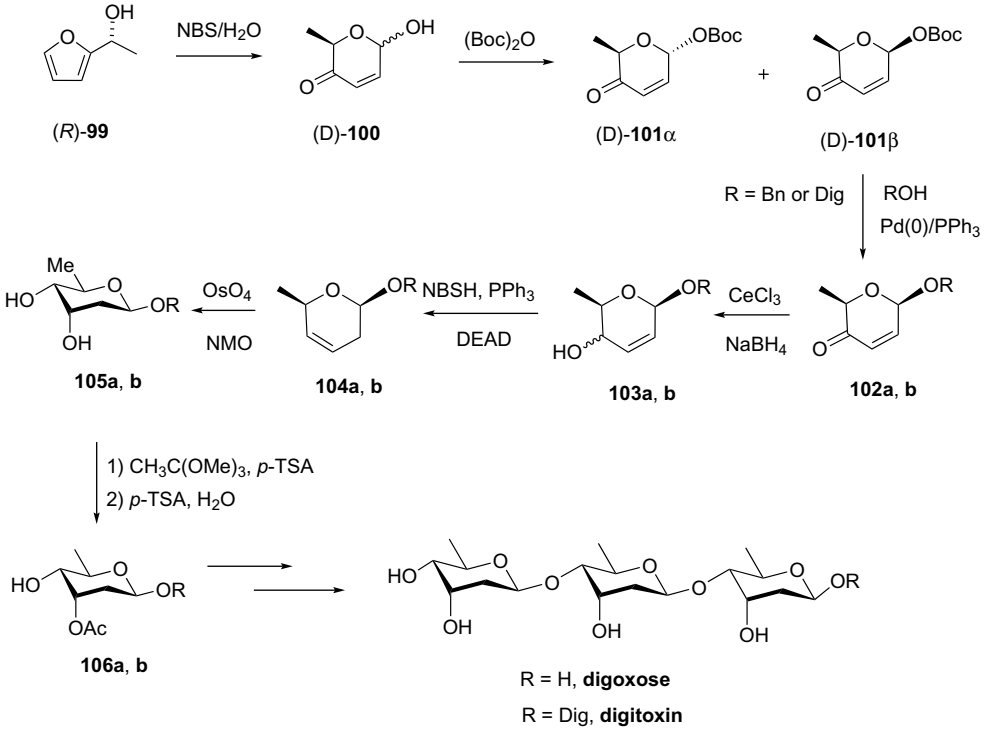
Scheme 29. Synthesis of isolevoglucosenone from unprotected D-glycal **69** and Michael addition of 1-thiosugars to afford *S*-thiodisaccharides **93**.



Scheme 30. Synthesis of (+)- and (−)-isolevoglucosenone via oxidation of furanyl diol **95**.

enopyranos-4-ulose **100**, which was a key compound for the synthesis of the previously mentioned natural product digitoxin (Fig. 1), a cardiac glycoside widely used for the treatment of congestive heart failure and cardiac arrhythmia,[4] and its trisaccharide digoxose. In addition, digitoxin has been reported to possess potential anticancer activities.[4d–g] Hence, oxidation of the alcohol **99** gave the enulose **100**, which was then protected to the *tert*-butyloxycarbonyl esters **101** (Scheme 31). Palladium-catalyzed glycosylation of **101** β with benzyl alcohol or digitoxigenin (Dig), the aglycon of digitoxin, provided the glycosides **102**. The latter compounds were subjected to reduction to the corresponding allylic alcohols **103**, followed by reductive transposition to afford the alkenes **104**. Further dihydroxylation led to the diols **105**, which were regioselectively protected at the axial hydroxyl group by treatment with trimethylorthoacetate in the presence of *p*-toluenesulfonic acid and subsequent acid hydrolysis. The synthetic pathway proceeded iteratively, with the same palladium-catalyzed glycosylation conditions of the resulting alcohols **106** with **101** β, followed by the same steps as described above, and allowing the generation of disaccharides and trisaccharides. The target molecules, digoxose and digitoxin, were obtained after removal of the benzyl and acetyl groups, respectively.

3.2.3. 3-Enopyranos-2-uloses. 3-Enopyranos-2-uloses comprise another class of α,β-unsaturated-pyranuloses in which the α,β-unsaturated keto system can be generated by synthetic transformations on simple glycals with 2-hydroxyglycal generally used for this purpose. Varela and co-workers have made several contributions to this field.[50] An early straightforward procedure for the prep-



Scheme 31. Iterative synthesis of digoxose and digitoxin based on the Pd-catalyzed glycosylation reactions with hex-2-enopyranos-4-ulose **100**.

aration of these compounds consisted of glycosylation of alcohols with 2-acyloxyglycals (e.g., **107**) in the presence of a Lewis acid. The latter is, therefore, responsible for the double allylic rearrangement that occurs in the glycosylation reaction.[50a] Various catalysts have been used in such reactions, namely boron trifluoride diethyl etherate[50a] (Scheme 32) or tin(IV) chloride.[50b,c] Iodine or electrophilic iodine-releasing agents such as *N*-iodosuccinimide also proved to be effective by mediating the glycosylation of alcohols with 2-hydroxyglycal esters to provide enopyranosiduloses.[50d]

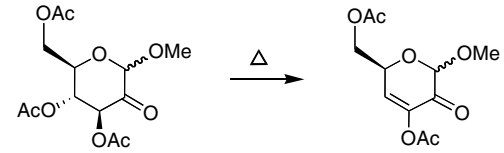
The synthesis of 2-keto α,β-unsaturated *C*-glycosyl derivatives has been described by Herscovici et al.[51] via reaction of peracetylated 2-hydroxyglycals with silyloxy allylic ethers. Condensation of several glycals (**109**) with hexyldimethylsiloxy ether in the presence of zinc bromide led stereoselectively to α-*C*-glycosyl compounds (**110**) (Scheme 33). Insights onto the mechanism of this transformation suggest an attack of the olefin to the glycal at C-1, followed by rearrangement of the resulting carbocation. Further acetolysis of the resulting 2-(acetyloxy)derivatives in the enol ester proceeded with the formation of the target enones.[51a]

In addition to glycals, glycopyranosyl-2-uloses possessing an ester function at the position α to the carbonyl group, for example, **111** (Scheme 34),[52a] can be easily converted into 3-enopyranos-2-uloses (**112**). This arises from the keto–enol tautomerism of the carbonyl compound followed by β-elimination, which frequently occurs spontaneously or under very mild conditions.[52]

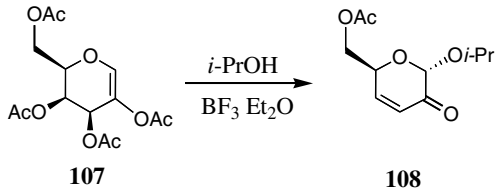
The tendency for β-elimination was also found in the oxidation of partially-protected sugars possessing a free primary or anomeric hydroxyl group, allowing the formation of a variety of α,β-unsaturated carbonyl sugar derivatives. In an early report by Mackie and Perlin,[52c] oxidation of *O*-acyl and *O*-benzoyl protected hexopyranoses containing a free OH-6 with methyl sulfoxide in the presence of sulfur trioxide and triethylamine occurred with elimination either of the 4-acetoxy or the 4-benzoyloxy group to yield 4-deoxy-6-aldehydo-hex-4-enopyranoses. Under the same conditions, oxidation of 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranose afforded the corresponding pyranoid α,β-unsaturated δ-lactone.

3-Enopyranosid-2-uloses can undergo similar conjugate 1,4 addition reactions as previously discussed for the other classes of enuloses. Their usefulness as Michael acceptors has given rise to the formation of 3-deoxy-4-thiopyranosid-2-uloses such as **113** (Scheme 35), by addition of thiols to the enone system,[53] being these compounds precursors of *C*-2 branched-chain 4-thiopyranosides[53a] or heteroanellated pyranosides.[53c]

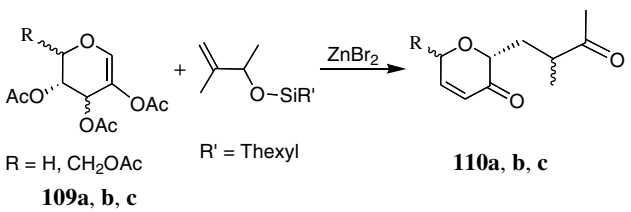
Michael addition to the important sugar precursor levoglucosenone has been reported.[54] One of the most attractive applications of these reactions has been the synthesis of thiodisaccharides.[54b–f] Witczak et al.[54b,c] described the stereoselective synthesis of 3-deoxy-4-*S*-(1→4)-thiodisaccharides by Michael addition of 1-thio-



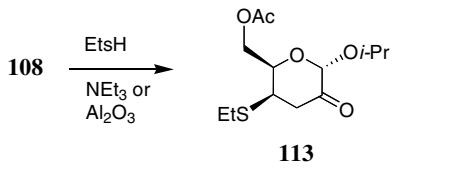
Scheme 34. Facile elimination of AcOH from 3-*O*-acetyl-2-uloside (**111**) to the corresponding enone (**112**).



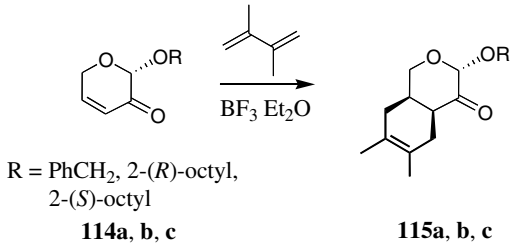
Scheme 32. Synthesis of hex-3-enopyranosid-2-ulose (**108**) by alcohol glycosylation with 2-acyloxyglycal (**107**) using boron trifluoride diethyl etherate as catalyst.



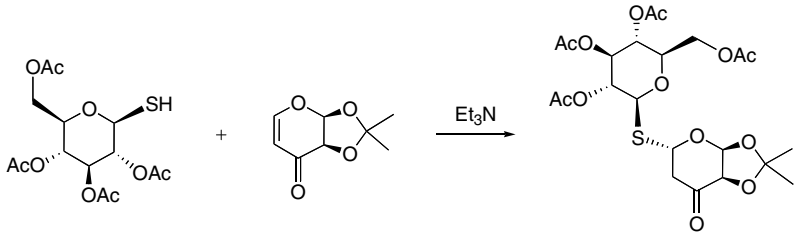
Scheme 33. Synthesis of 3-enopyranos-2-uloses (**110**) by reaction of 2-hydroxyglycals (**109**) with thexyldimethylsiloxy ether in the presence of $ZnBr_2$.



Scheme 35. Michael addition of ethanethiol to hex-3-enopyranosid-2-ulose **108**.



Scheme 36. Diels–Alder cycloadditions of pent-3-enopyranosid-2-uloses (**114**) with 2,3-dimethylbutadiene, catalyzed by boron trifluoride diethyl etherate.



Scheme 37. Stereoselective Michael addition of thiosugar **116** to pent-4-enopyranos-3-ulose **117** with formation of β-(1→5)-4-deoxy-5-*C*-thiodisaccharide **118**.

sugars to levoglucosenone. Analogous additions of per-*O*-acetyl-1-thioglucose to this substrate and other sugar enones have been studied by Thiem and co-workers.[54d] Synthesis of non-glycosidic 4,6′-thioether-linked disaccharides has also been developed, the key step of which was a highly diastereoselective Michael addition of a 6-thiohexopyranoside to a sugar enone.[54f]

Diels–Alder cycloadditions of pent- or hex-3-enopyranosid-2-ulose with dienes, and studies related to their stereoselectivity have been published.[50b,c,55] Thus, the treatment of enones **114** with common dienes under thermal and Lewis acid catalyzed conditions led to bicyclic compounds **115** with diastereofacial selectivities (Scheme 36).[50b] Noteworthy in these syntheses is the fact that these enones are better dienophiles than their cyclohexenones counterparts, which is probably due to the presence of the ring oxygen atom.[50b] Moreover, pent-3-enopyranosid-2-uloses exhibited higher activity than hexenuloses toward dienes.[55a]

3.2.4. 4-Enopyranos-3-uloses. Pent- or hex-4-enopyranosid-3-uloses are practical scaffolds for preparing pyranosides containing a diversity of substituents at C-5, leading to 4-deoxy sugar derivatives. Witczak et al. have recently explored the synthesis of 1,5-*C*-thiodisaccharides by Michael addition of a 1-thiosugar **116** to 4-deoxy-1,2-*O*-isopropylidene-L-*glycero*-pent-4-enopyranos-3-ulose (**117**) (Scheme 37).[56] The reaction proceeded with the stereoselective formation of β-(1→5)-4-deoxy-5-*C*-thiodisaccharide **118** which results from the stereoselective nucleophilic attack at the less hindered face of the enone.

4. Conclusion

A remarkable amount of work has been reported during the last two decades toward the synthesis of α,β-unsaturated carbonyl sugar derivatives. The natural occurrence and the biological activities inherent to the α,β-unsaturated carbonyl moiety has been the driving force for several research groups to incorporate this functionality in carbohydrates. Furthermore, sugars containing α,β-unsaturated lactones or ketones have been attractive building blocks for the synthesis of natural products and new bioactive substances, as well as templates for key transformations due to the variety of reactions that the conjugated system may undergo. This review has illustrated recent advances on the synthesis of this type of compounds, as well as their significance in carbohydrate chemistry, demonstrated by the range of chemical targets they can provide. Nevertheless, as new applications for α,β-unsaturated carbonyl carbohydrate-based compounds are found, exploitation of novel synthetic and efficient methods for their preparation and transformation will continue to encourage the research in the area.

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