

Carbohydrate-Based Lactones: Synthesis and Applications

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Abstract The synthesis and uses of different kinds of carbohydrate-based lactones are described. This group of compounds includes aldolactones, other related monocyclic lactones and bicyclic systems. The latter can arise from uronic acids, carboxymethyl ethers or glycosides, or from C-branched sugars.

Keywords Aldonolactones, Bicyclic lactones, Gluconolactone, Sugar lactones, Synthons, Uronic acids

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Abbreviations

AAPDH	2,2'-Azobis(2-amidinopropan) dihydrochloride
AD	Asymmetric dihydroxylation
AIBN	2,2'-Azobisisobutyronitrile
CMC	Critical micellar concentration
CMG	Carboxymethyl glycoside
CMGL	Carboxymethyl glycoside 2-O-lactones
CSA	Camphorsulfonic acid
DCC	Dicyclohexylcarbodiimide
DEAD	Diethyl azodicarboxylate
DIBAL-H	Diisobutylaluminum hydride
DMAP	4-(Dimethylamino)pyridine
DMJ	1-Deoxymannojirimycin
DNJ	Deoxynojirimycin
GABA	γ -Aminobutyric acid
mCPBA	<i>m</i> -Chloroperoxybenzoic acid
Ms	Mesyl (methanesulfonyl)
MW	Microwave irradiation
NBS	<i>N</i> -Bromosuccinimide
NeuAc	<i>N</i> -Acetyl neuraminic acid
NIS	<i>N</i> -Iodosuccinimide
NMO	<i>N</i> -Methylmorpholine <i>N</i> -oxide
Oct	Octoate (2-ethylhexanoate)
PCC	Pyridinium chlorochromate
PDC	Pyridinium dichromate
Piv	Pivaloyl
PMPOH	<i>p</i> -Methoxyphenol

PPL	Porcine pancreatic lipase
Py	Pyridine
ROP	Ring-opening polymerization
TBAF	Tetrabutylammonium fluoride
TBDMS	<i>tert</i> -Butyldimethylsilyl
Tf	Trifluoromethanesulfonyl (triflyl)
TFA	Trifluoroacetic acid
TFAA	Trifluoroacetic anhydride
TMEDA	<i>N,N,N',N'</i> -Tetramethyl-1,2-ethylenediamine
TMS	Trimethylsilyl
TPAP	Tetrapropylammonium perruthenate
Ts	Tosyl, 4-toluenesulfonyl

1 Introduction

Carbohydrate lactones have found broad applications as building blocks for the synthesis of important bioactive compounds and natural products, and constitute a valuable family of synthons for diverse types of transformations. Previous survey articles were published by De Lederkremer [1], Lundt [2–4], and Fleet [5]. In this revision, emphasis will be given to sustainable approaches involving a limited number of steps, to environmentally friendly synthetic methodologies for conversion of these molecules into functional compounds, and to multi-step sequences for the preparation of more complex targets. Starting with simple and available aldolactones, the chemistry of more elaborated carbohydrate-based lactones, such as α,β -unsaturated δ -lactones as well as other types of bicyclic systems will then be presented and discussed. Allying the chirality inherent to the sugar to the reactivity of the lactone functionality turns these classes of compounds into useful chemical intermediates towards a variety of purposes.

2 Aldonolactone Synthesis

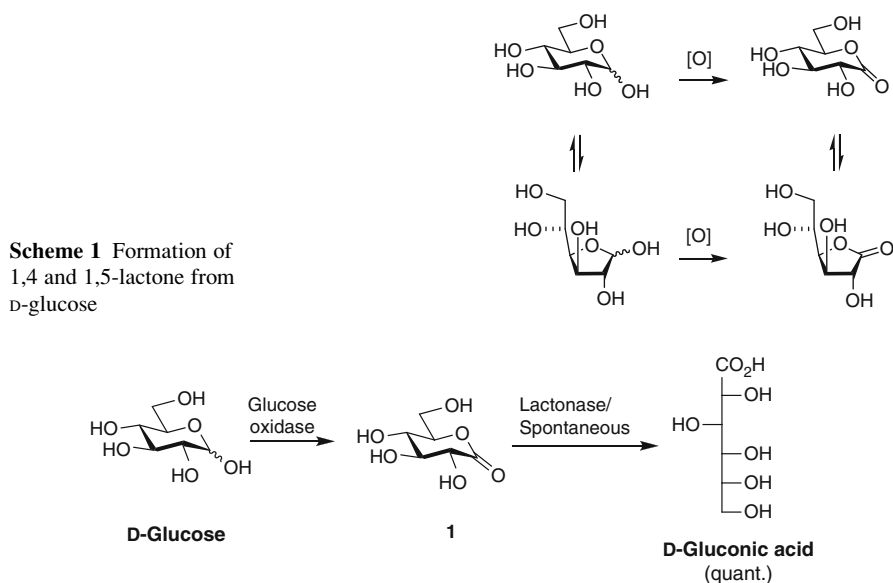
2.1 General Aspects

Aldonolactones are commercially available at low cost, when compared to most of the common monosaccharides. They are typically synthesized by selective anomeric oxidation of unprotected aldoses with bromine [6]. Usually the thermodynamically more stable five-membered lactone (γ -lactone) predominates over the six-membered form, with the exception of D-gluconolactone, which crystallizes as the 1,5-pyranolactone (δ -lactone) [7] (Scheme 1). Another method for the preparation of sugar lactones is the dehydrogenation of unprotected or partially

protected alditols and aldoses catalyzed by a transition metal complex in the presence of a hydrogen acceptor [8–10]. Protected aldoses with a free anomeric hydroxyl group can be converted into the corresponding aldonolactones by common oxidation protocols, such as those employing chromium(VI) reagents [11] or DMSO-based oxidizing systems [12, 13]. Methods for aerobic oxidation of unprotected aldoses over heterogeneous catalysts, including Pd/C, Au/C, or a combination of Bi-Pd/C, have also been developed [14–17]. However enzymatic processes for the synthesis of aldonolactones/aldonic acids are preferred on the industrial scale.

2.2 Glucono-1,5-Lactone

Glucono-1,5-lactone (δ -D-gluconolactone, **1**) is the cyclic ester of D-gluconic acid, which is produced on the industrial scale by enzymatic oxidation of glucose (for a review of the production, properties, and applications of gluconic acid and its derivatives see [18]). This process is mediated by enzymes from selected micro-organisms, including bacteria such as *Pseudomonas* or *Gluconobacter oxydans* and fungi such as *Aspergillus niger*. The method involving *A. niger* is widely used and is based on glucose oxidase. The oxidation pathway consists in the oxidation of glucose to δ -D-gluconolactone, which is mediated by the latter enzyme, followed by hydrolysis to gluconic acid, which may occur spontaneously or be promoted by the lactonase enzyme (Scheme 2). After the fermentation process, the lactone can simply



Scheme 2 Oxidation of D-glucose by *Aspergillus niger*

be recovered from the broth by crystallization. Under appropriate conditions, glucose can be quantitatively converted into gluconic acid. About 100,000 tons of D-gluconic acid, mainly used in the food industry, are produced annually worldwide [19]. Glucono-1,5-lactone (**1**) has widespread application as a food additive, particularly in dairy products, confectionery, and meat.

2.3 Other Aldono-1,5-Lactones

Glycosyl azides have been shown to be useful precursors for the synthesis of aldono-lactones. A viable one-pot procedure for the conversion of per-*O*-alkylated glycopyranosides into the corresponding aldono-1,5-lactones is based on the formation of glycosyl azide intermediates by treatment of the substrates with trimethylsilyl (TMS) azide in the presence of tin(IV) chloride, followed by hydrolysis [20]. In other work, aldono-1,4-lactones and aldono-1,5-lactones could be prepared from glycosyl azides via a two-step methodology consisting in the *N*-bromosuccinimide (NBS) mediated bromination and subsequent hydrolysis of corresponding *N*-bromoiminolactone intermediates [21].

Bierenstiel and Schlaf [22] were able to prepare and isolate for the first time the less stable δ -D-galactonolactone by oxidation of galactose with the Schvo's catalytic system, which is based on the dimeric ruthenium complex $[(C_4Ph_4CO)(CO)_2Ru]_2$. The transformation led to the δ -galactonolactone in 93% yield, against 7% of the isolated γ -lactone isomer. This procedure also allowed the preparation of δ -D-mannonolactone in a much better yield (94%) than that reported in an early procedure [23] based on crystallization from a solution of calcium mannonate in aqueous oxalic acid.

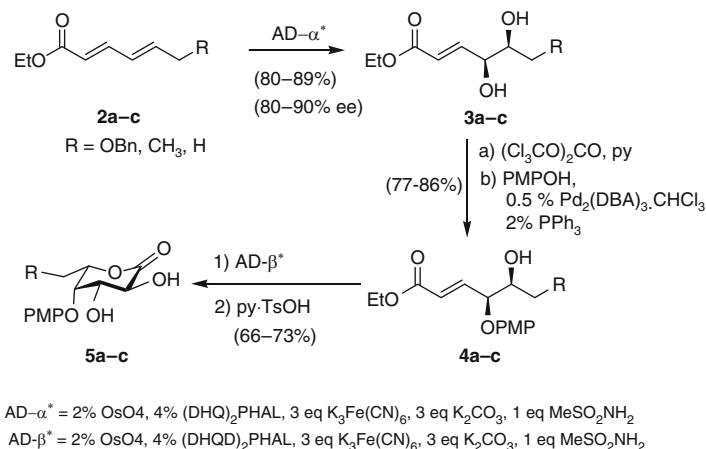
O'Doherty and co-workers have explored the use of 2,4-dienoates as precursors for δ -galactonolactones [24, 25]. The synthetic approach involved sequential dihydroxylation steps of the dienates (**2a–c**) double bonds by Sharpless AD-mix reagent systems (Scheme 3). After the first enantioselective dihydroxylation step, the resulting γ,δ -dihydroxyenoate intermediates (**3a–c**) were protected at the γ -hydroxyl group as cyclic carbonates, which were then treated with *p*-methoxyphenol (PMPOH) in the presence of a Pd(0) catalyst. The resulting 4-*O*-protected derivatives (**4a–c**) were submitted to diastereoselective dihydroxylation affording triols possessing *galacto* configuration, which were then lactonized to give the target L-galactono-1,5-lactones (**5a–c**) or their enantiomers, depending on the order in which the Sharpless reagents were applied [24].

2.4 Aldono-1,4-Lactones

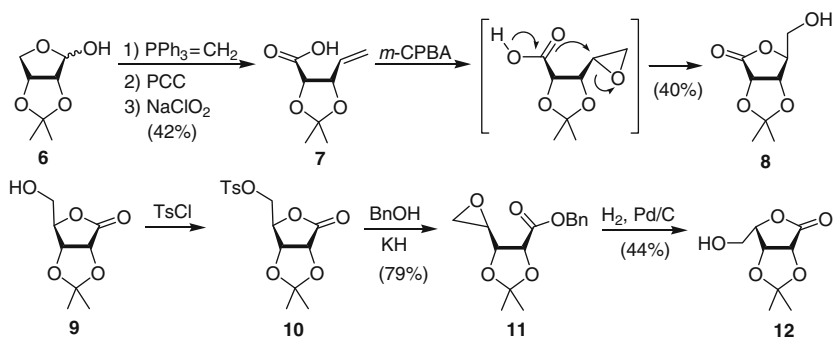
An efficient method for preparing aldono-1,4-lactones (γ -aldono-lactones) as the single products from oxidation of unprotected or partially protected monosaccharides was reported [9]. It consisted in treatment of the latter by catalytic amounts of $[RuH_2(PPh_3)_4]$, in the presence of an excess of benzalacetone (*trans*-4-phenylbut-3-en-2-one) as the hydrogen acceptor, in DMF. The corresponding γ -lactones were

obtained in excellent yields, even in the case of D-glucose, for which no 1,5-lactone was observed. The results suggested that the oxidation step is followed by a ring contraction mechanism, probably promoted by coordination of the catalyst to the endocyclic oxygen and to the carbonyl group, facilitating ring opening and its closure into the more thermodynamically stable five-membered form.

L-Aldonolactones are much less available than their D-enantiomers. Their potential to serve as chiral building blocks for L-sugar derivatives also makes them molecular targets of interest. Stereoselective approaches involving few steps leading to 2,3-*O*-isopropylidene-L-ribo-lactones and L-lyxono-1,4-lactones were reported by Rao and Lahiri [26]. The L-ribo derivative could be synthesized in three steps starting from the easily available isopropylidene-D-erythrose (**6**) (Scheme 4). It was converted into the unsaturated acid **7** by Wittig olefination and further oxidation. Epoxidation of the latter afforded the desired 1,4-lactone



Scheme 3 Synthesis of L-galactono-1,5-lactones from 2,4-hexadienoates



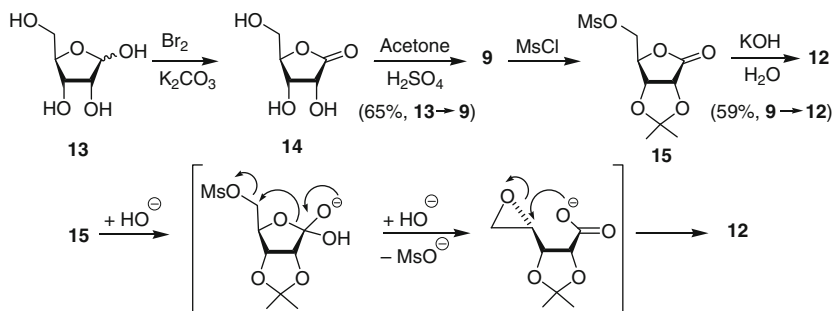
Scheme 4 Synthesis of 2,3-*O*-isopropylidene L-ribo- and L-lyxono-1,4-lactones

(**8**) in 40% yield, due to cyclization of the intermediate epoxide promoted by silica gel when attempting product separation by column chromatography. The synthesis of the L-lyxono-1,4-lactone derivative (**12**) was accomplished starting from D-ribo-1,4-lactone (**9**), of which the 5-*O*-tosyl derivative **10** was treated with the potassium salt of benzyl alcohol to give the epoxy benzyl ester **11**, furnishing directly on catalytic hydrogenation the target compound in 44% yield.

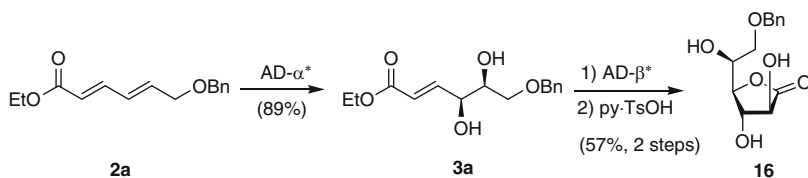
More recently, a simple synthetic route for a large scale production of **12** (2,3-*O*-isopropylidene-L-lyxonolactone) was described [27]. The chosen starting material was D-ribose (**13**), which was oxidized to the corresponding lactone **14** (Scheme 5). The latter was submitted *in situ* to acetonation to provide the 2,3-*O*-isopropylidene derivative **9**, which was then mesylated at OH-5. Treatment of the crude 5-*O*-mesylate **15** with potassium hydroxide led to **12** according to the mechanism proposed in Scheme 5.

L-Galactono-1,4-lactone (**16**) is prepared in three steps (51%, overall yield) from **2a** applying two successive asymmetric dihydroxylations (ADs) [25] (Scheme 6).

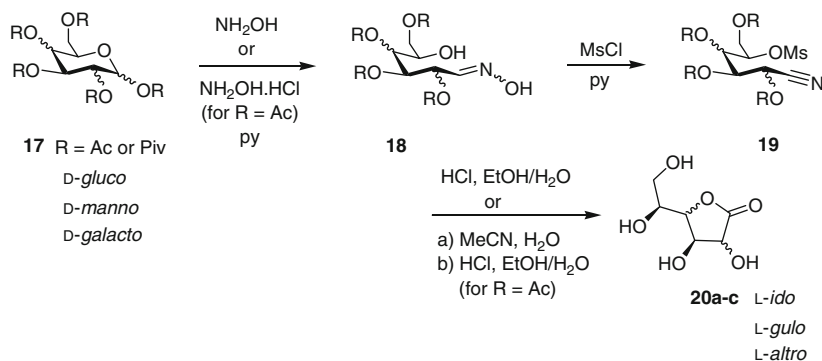
L-Aldono-1,4-lactones can be prepared from D-aldose perpivaloates and peracetates (compounds of type **17**) [28]. The method implies formation of aldoximes (**18**), followed by mesylation (Scheme 7). The resulting 5-*O*-mesyl glyconitrile derivatives (**19**) are then submitted to acid-catalyzed hydrolysis giving the corresponding 1,4-lactones **20a–c**.



Scheme 5 Process for a large scale production of 2,3-*O*-isopropylidene-L-lyxono-1,4-lactone



Scheme 6 L-Galactono-1,5-lactones from 2,4-hexadienoates



Scheme 7 L-Aldono-1,4-lactones from D-aldose per-pivaloates and peracetates

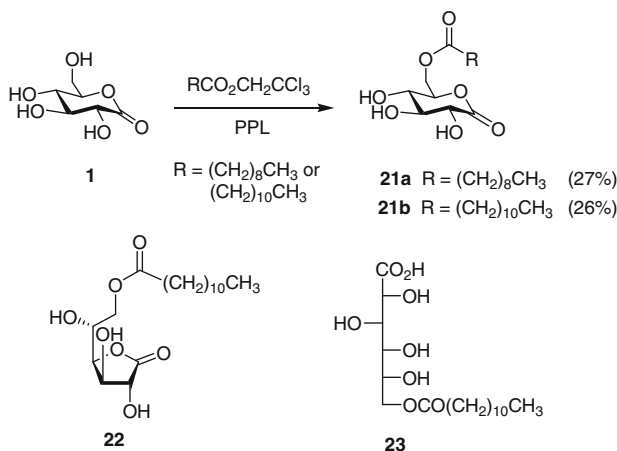
3 Aldonolactones as Useful Chirons

The use of aldonolactones for the preparation of carbasugars and iminosugars has been well explored and documented, particularly by Lundt's group [2–4, 29–31]. Fleet has also given an overview of the utility of sugar lactones as synthons for biologically active compounds [5] and his research group has made major contributions to the synthesis of sugar amino acids from aldonolactones [32–34]. We review here the syntheses of C-glycosyl compounds, L-sugars, aza- and thiosugars, natural products and of surfactants and related polymers that make use of aldonolactones as starting materials.

As shown in chapter, “Synthetic polymers from readily available monosaccharides” by J.A. Galbis and M.G. Garcia-Martin, aldonolactones are useful monomeric materials for the synthesis of biodegradable polymers and bio-compatible polymers for medicinal applications.

3.1 Synthesis of Surfactants and Polymers

Among the aldonolactone-based surfactants are aldonolactone-linked fatty esters which have been prepared by selective acylation of unprotected aldono-1,4-lactones or aldono-1,5-lactones. One of the first reported examples of this type of surfactant was applied to the enzymatic synthesis of 6-O-alkanoylgluconolactones [35]. Thus, 6-O-decanoyl- and 6-O-dodecanoyl- derivatives (**21a** and **21b**, respectively, Scheme 8) were obtained in 26–27% yield by esterification of glucono-1,5-lactone (**1**) at C-6 with the corresponding 2,2,2-trichloroethyl carboxylate in the presence of porcine pancreatic lipase (PPL) as catalyst. Compounds **21a,b** are soluble in water at 90–96°C but precipitate when cooled to 30–37°C. NMR and GC-MS analysis after dissolution and precipitation indicated the presence in the mixture of compound **21b**, the glucono-1,4-lactone-derived ester **22**, and the



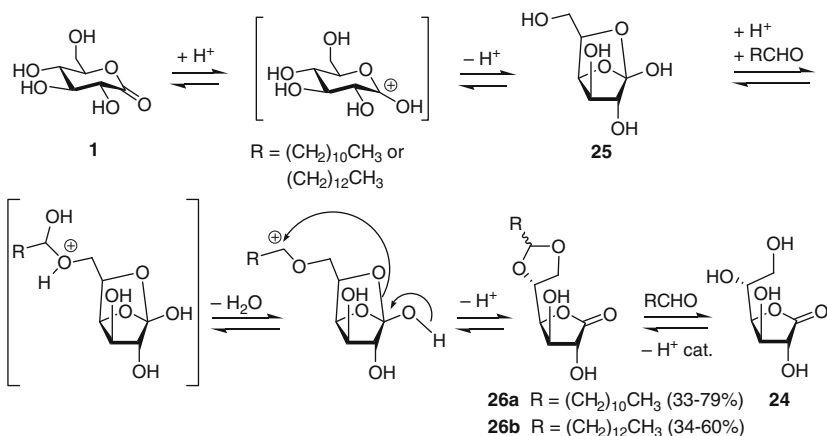
Scheme 8 Enzymatic synthesis of 6-*O*-alkanoylgluconolactones

acyclic dodecanoylgluconic acid **23**, the latter being the major compound. This demonstrates that dissolution of **21b** occurs with hydrolysis of the lactone moiety giving a more soluble mixture of compounds that are more appropriate for detergent applications than the dodecanoylglucono-1,5-lactone itself.

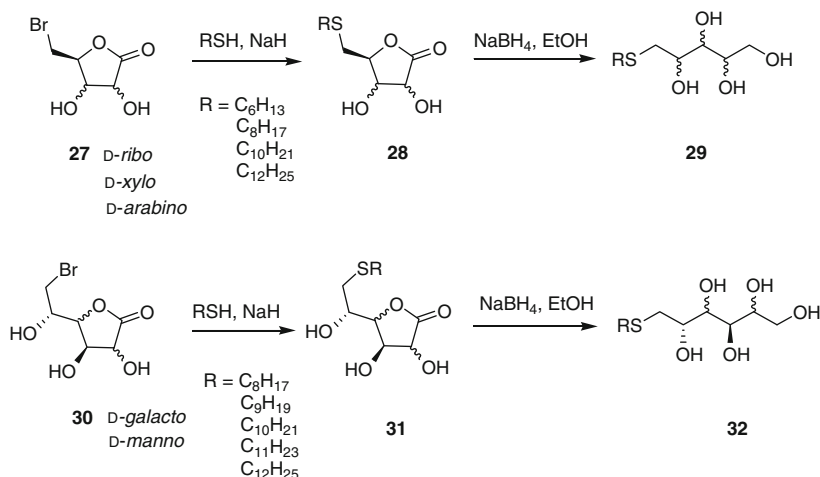
Acylation of D-glucono-1,4-lactone and D-glucono-1,5-lactone with *N*-(11-undecenoyl)-1,3-thiazolidine-2-thione in the presence of triethylamine gave 6-*O*-undecenoyl ester as the single product. In the case of the 1,5-lactone, isomerization to the 1,4-lactone-derived ester was observed, and quantitative conversion was attained when sodium hydride was used as base. In contrast with the expected regioselectivity at OH-6, acylation of L-galactono-1,4-lactone proceeded only at OH-2 although with a rather low yield (ca. 20%). Alternatively, the enzymatic route, employing *Candida antarctica* and an ester, proved to be more efficient, affording only 6-*O*-acylated-1,4-lactone derivatives in yields up to 76 and 85%, by acylation of D-glucono-1,5-lactone and L-galactono-1,4-lactone, respectively. The conversion was shown to increase with the electron-withdrawing character of the ester, while acids proved to be virtually unreactive as acylating agents [36].

Another type of amphiphilic-like structure in which an aldonolactone moiety is present was prepared by acetalization of D-glucono-1,4-lactone (**24**) and D-glucono-1,5-lactone (**1**) with dodecanal or tetradecanal in the presence of methanesulfonic acid (Scheme 9) [37]. Both lactone isomers led to 1,4-lactone acetal derivatives **26a, b** in optimized yields up to 60–79%. A mechanism for the ring contraction was proposed, involving a hemi-orthoester (**25**) as a key intermediate in the addition to the aldehyde. Then, opening of an intermediate bicyclic-fused system and concomitant cyclization led to the acetal **26**.

In the context of the synthesis of carbohydrate-based amphiphilic (alkylsulfanyl) polyols, Beaupère and co-workers explored the access to 5- and 6-alkylsulfanyl derivatives of pentono- and hexonolactones and their corresponding 1-(alkylsulfanyl) pentitol or 1-(alkylsulfanyl)hexitol [38, 39]. Bromolactones **27** and **30** were treated



Scheme 9 Acetalization of D-glucono-1,4-lactone and D-glucono-1,5-lactone with dodecanal or tetradecanal



Scheme 10 Amphiphilic (alkylsulfanyl)aldonolactones and corresponding alditols

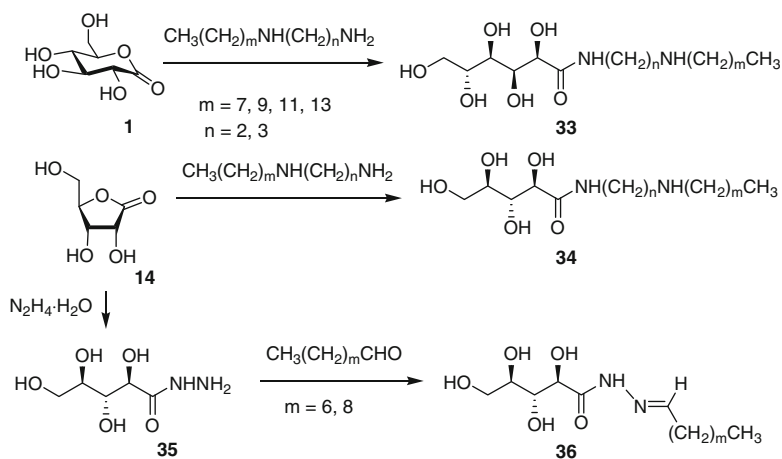
with alkanethiol in the presence of sodium hydride (Scheme 10) giving compounds **28** and **31**, respectively, in good yields (72–95%). Subsequent lactone reduction with $NaBH_4$ provided the 1-S-alkyl-1-thio-alditol derivatives **29** and **32**, respectively. Physico-chemical studies demonstrated surface activity for all compounds **28**, except for the D-ribono derivatives for which no critical micellar concentration (CMC) value was detected [40]. Apart from the lyxitol series, the pentitol derivatives of type **29** were shown to be more efficient in reducing the surface tension than their cyclic counterparts **28**. The mesophasic properties of **28** and **29** were also evaluated [41]. Most of the compounds gave lyotropic and thermotropic liquid crystals, except for the series of D-ribonolactones. This singular behavior for the

*ribo*no derivatives **28** was ascribed to the position of the vicinal hydroxyl groups which are in the same side of the cycle, favoring intramolecular hydrogen bonding.

It has been known for more than 50 years that carbohydrate lactones undergo ring opening by amines. Using long chain primary amines gives access to amphiphilic structures that are emulsifying agents [42, 43] or liquid crystals [44–47]. The preparation of *N*-arylgluconoamides and *N*-alkylgluconoamides by opening of D-glucono-1,5-lactone, and their subsequent conversion into thiogluconamide derivatives, are reported [48]. Some amphiphilic alkyl aldonamides and diacetylenic aldonamides have the propensity to aggregate into supramolecular assemblies, leading to different structural morphologies [49–52]. Amphiphilic glycodendrimers containing aldonoamide moieties at their molecular surfaces have been prepared by coupling polyamine dendrimers with 1,5-D-glucono-1,4-lactone [53–55]. Such macromolecules are shown to behave as unimolecular micelles in water able to solubilize hydrophobic compounds in the dendritic cavities [55]. Highly enantioselective ketone reduction have been carried out in the presence of these systems.

In recent work [56] aldonoamides (**33**, **34**) have been synthesized in moderate to good yields by addition of long-chain *N*-monoalkylated diamines to D-glucono-1,5-lactone **1** or D-ribo-1,4-lactone **14** (Scheme 11). In addition, hydrazones **36** have been obtained by treatment of the intermediate ribonohydrazide **35** with octanal or decanal. All compounds derived from ribonolactone showed moderate activity against *M. tuberculosis*. Some ribonoamides were also active against *Staphylococcus aureus*. The activities increased somewhat with the elongation of their hydrocarbon chains.

The use of carbohydrates as raw materials for the generation of polymers has attracted particular interest in the last two decades not only because of concerns related with sustainability and biocompatibility, but also due to the unique mechanical and physical properties that the sugar units may provide to the material (for

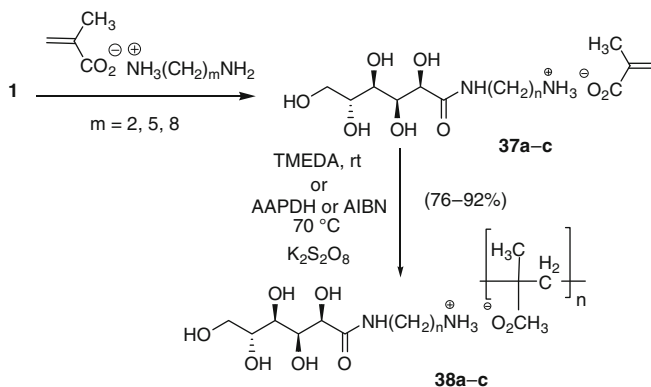


Scheme 11 Amphiphilic compounds by ring-opening of aldonoalactones

reviews on carbohydrate-based polymers see [57–59]). The hydrophilic sugar moiety contributes to the specific three-dimensional structure of the polymer and increases its hydrophilicity and water solubility. Due to their particular characteristics, glycopolymers have found interesting applications as flocculating agents, detergents, surface modifiers, and also in the biomedical field as biomaterials for tissue regeneration, as drugs, and for gene delivery systems (See chapter, “From natural polysaccharides to materials for catalysis, adsorption and remediation”, by Quignard, Di Renzo and Guibal, and chapter, “Synthetic polymers from readily available monosaccharides”, by Galbis and Garcia-Martin).

One of the approaches employed to achieve sugar-based polymers consists in the preparation of monomers comprising the sugar moiety and a polymerizable double bond. Aldonolactones can be useful starting materials for this type of monomers, allowing the introduction of the polymerizable part through selective monofunctionalization of the lactone, without the use of protecting groups. The connection of both parts can be accomplished, for example, through amide linkages. One of the first reported examples applying this approach [60] involved the addition of an aminoalkyl ammonium methacrylate salt, derived from a diamine and methacrylic acid, to D-glucono-1,5-lactone **1** (Scheme 12). The resulting ionic monomers **37** were then subjected to homopolymerization in the presence of a free-radical initiator to give the corresponding polymers **38** in good yields. Studies of the viscosity of their aqueous solution showed a decrease of this parameter when increasing the concentration, proving their polyelectrolyte nature. NMR analysis of polymers **38** revealed their predominant syndiotactic structure. The monomer **37a** ($n = 2$) was also copolymerized with 1-vinylpyrrolidin-2-one and methacrylamide, affording water-soluble copolymers.

Aldonolactones serve as suitable monomers for the generation of homo- and copolymers, especially through ring-opening polymerization (ROP). Among them are the carbohydrate-analogs of ϵ -caprolactone, i.e., aldono-1,6-lactones. The first example of such derivatives and further ROP was reported by Galbis and co-workers [61], see also chapter, “Synthetic polymers from readily available monosaccharides”



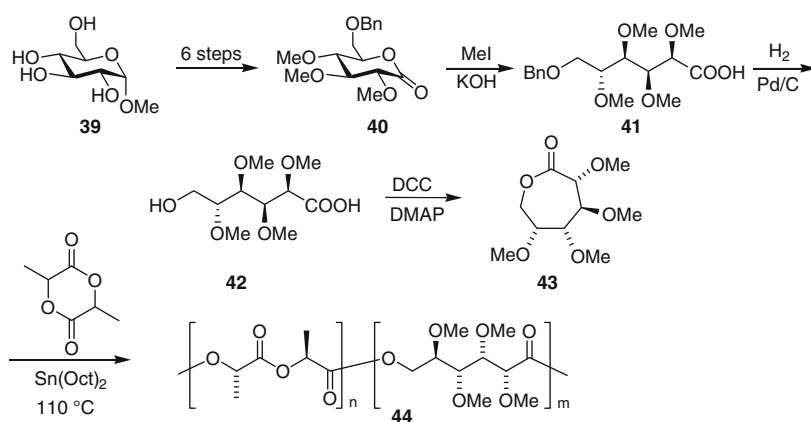
Scheme 12 Gluconolactone-derived vinyl monomers and their polymerization

by J.A. Galbis and M.G. Garcia-Martin. Two alternative routes leading to tetra-*O*-methyl-D-glucono-1,6-lactone **43** were employed, one of them involving the intermediate protected glucono-1,5-lactone **41**, which was prepared from methyl D-glucopyranoside **39**. Opening of the lactone ring of **40**, methylation, and hydrogenation led to the ω -hydroxygluconic acid derivative **42**, which was subsequently converted into **43** by lactonization (Scheme 13). Attempts to homopolymerize **43** failed. However, its copolymerization by bulk ROP with L-lactide Z, using stannous octoate as initiator, provided two copolymers of type **44** containing up to 2.2% of the carbohydrate monomer.

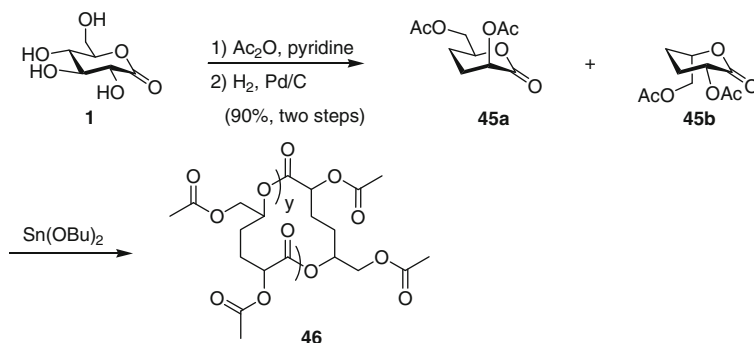
Williams and co-workers [62] have recently explored the ROP of acetylated aldono-1,5-lactones to investigate their propensity to oligomerize/polymerize by a metal alkoxide initiator. Hence, treatment of tetra-*O*-acetyl-D-glucono-1,5-lactone with butane-1,4-diol and stannous octanoate produced only a mixture of mono-, di-, and trialdaric esters. The latter were then subjected to copolymerization with [*R,S*]-lactide using an alkyl zinc initiator, which furnished triblock ABA copolyesters. Soon afterwards, the same group reported the ROP of 3,4-dideoxy-aldonolactones **45**, which were prepared in two steps from D-glucono-1,5-lactone (**1**) [63]. The polymerization was performed in the presence of $\text{Sn}(\text{O}i\text{Bu})_2$, providing mainly cyclic polyesters **46** (Scheme 14).

An interesting type of polymeric network has been obtained by polymerization of D-gluconolactone (**1**) and citric acid (**47**) (Scheme 15) [64]. Instead of proceeding by an ROP mechanism, this polymerization was shown to occur through the esterification reaction between the hydroxyl groups of gluconolactone or citric acid and the carboxylic acid of citric acid, affording biodegradable cross-linked polyesters (**48**).

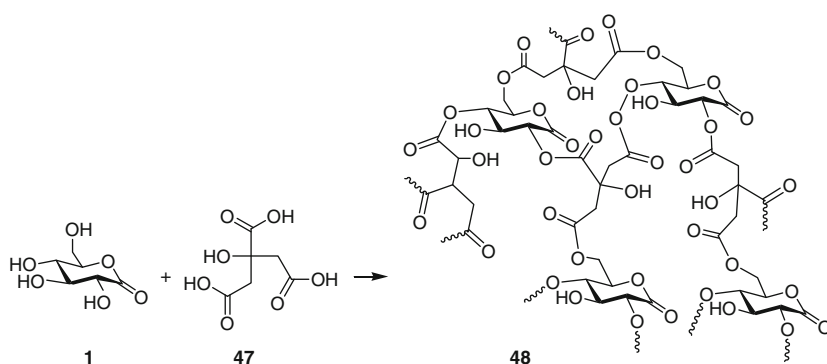
Polyhydroxypolyamides have attracted significant attention since they are more hydrophilic and biodegradable than nylons. Sugar amino acids [65] or aldaric acid



Scheme 13 Synthesis of a ω -hydroxygluconic acid from a protected glucono-1,5-lactone derivative and further copolymerization with L-lactide



Scheme 14 Ring-opening polymerization (ROP) of acetylated aldono-1,5-lactones



Scheme 15 Polymerization of D-gluconolactone and citric acid

derivatives [66, 67] are among the carbohydrate precursors that have been employed for the synthesis of these polyamides.

Simple syntheses of suitable monomers for nylon 5 and nylon 6 analogs, such as 5-amino-5-deoxyaldonic and 6-amino-6-deoxyaldonic acids (**51**, **54**), has been achieved starting from unprotected D-pentono- and hexono-1,4-lactones [68, 69]. Saponification of 5- or 6-azido-D-aldonolactones (*ribo*-, *arabino*-, *xylo*-, *galacto*-, *manno*-, compound types **49** and **52**) provided the corresponding 5- or 6-azido-aldonic acid sodium salts (**50**, **53**). A catalytic hydrogenation after or before treatment with acidic resin afforded compounds **51** and **54** in excellent overall yields (Scheme 16).

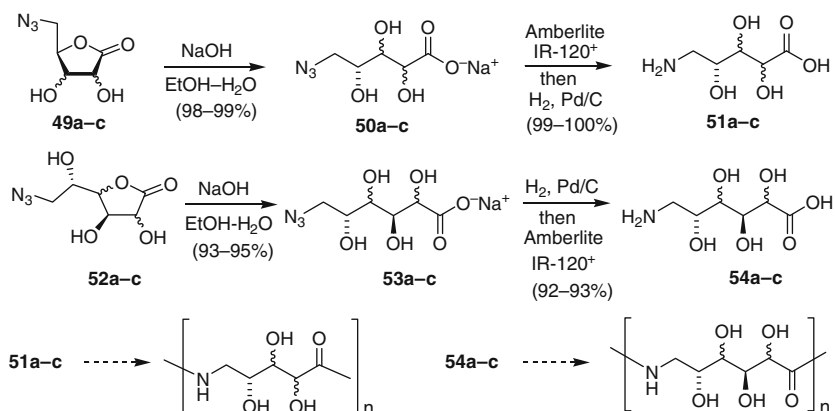
More recently, a similar synthetic strategy involving 2-azido-2-deoxy-D-xylo-1,4-lactone and 2-azido-2-deoxy-D-lyxono-1,4-lactone precursors has been applied for the synthesis of polyhydroxy- α -amino acids, namely (–)-polyoxamic acid and 3,4-diepipolyoxamic acid [70].

Aldonolactone-based fluorinated surfactants have also been reported [71].

3.2 Synthesis of C-Glycosyl Compounds

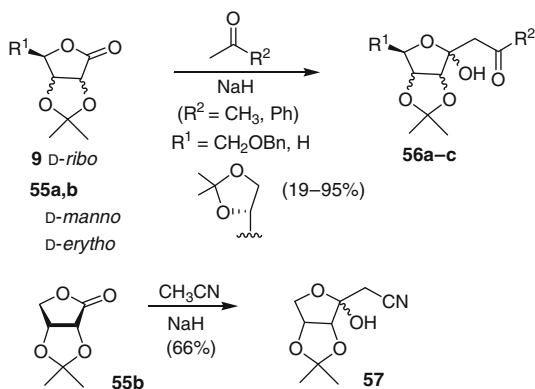
C-Glycosyl compounds are important molecular targets as they occur in Nature and have interesting biological properties (for reviews on C-glycosylation, see [72–75]). Chain extensions of aldono-lactones have been employed to create C–C bond formation at the anomeric center. Claisen-type reactions of aldono-1,4-lactones (e.g., **9**, **55**) with acetone or acetophenone (Scheme 17) generate hemiacetals of type **56a–c** [76]. Similarly, lactone **55b** reacts with CH₃CN/NaH to give hemiacetal **57**.

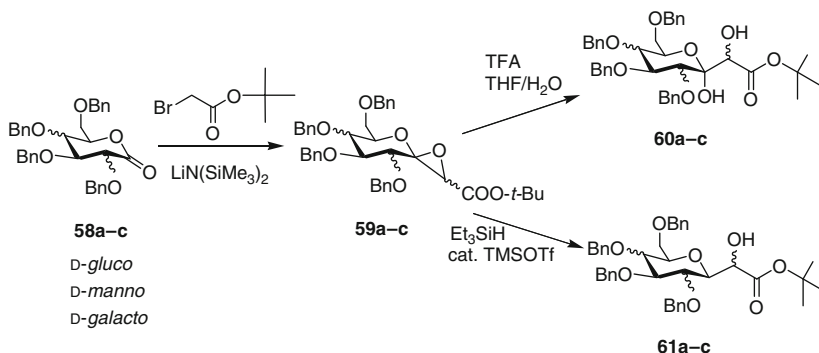
Using the enolate of *tert*-butyl bromoacetate with 1,5-lactones **58** (Scheme 18) led directly to exocyclic epoxides **59**, which were subsequently transformed into compounds **60** [77]. Alternatively, cationic reduction of epoxides **59a–c** provided C-glycosyl compounds **61a–c**. Upon esterification of the latter as



Scheme 16 Synthesis of 5-amino-6-deoxy- or 6-amino-6-deoxyaldonic acid monomers

Scheme 17 C-Glycosylation by Claisen-type reaction of aldono-1,4-lactones with acetone, acetophenone, or acetonitrile





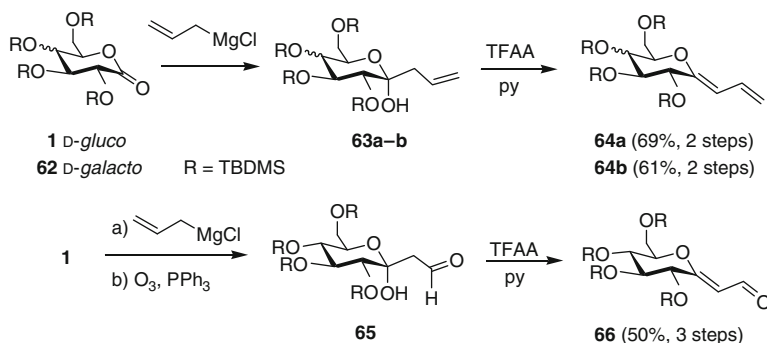
Scheme 18 Claisen condensation of aldonolactones leading to exocyclic epoxides and further conversion into *C*-glycosyl derivatives

trifluoromethanesulfonates, reaction with primary amines furnished the corresponding *C*-glycosylamino esters.

Olefination of protected aldonolactones is a convenient approach to *C*-glycosylation that furnishes *C*-glycosylidene derivatives, often referred to as “*exo*-glycals” [78]. Activated olefins, such as 1-*C*-dichloromethylene [79], 1-*C*-methoxycarbonylmethylene [80], and 1-*C*-cyanomethylene derivatives [81], have been obtained by direct Wittig-type olefination of aldonolactones. Hydrogenation of the *C*-glycosylidene compounds produces the corresponding *C*-glycosyl derivatives with high stereocontrol. However, *exo*-glycals resulting from partially protected aldonolactones, and that possess free hydroxyl groups appropriately located in the sugar ring, were shown to undergo 1,4-addition within the activated double bond to give bicyclic derivatives [82]. This propensity for activated *exo*-glycals to act as Michael acceptors permits the synthesis of *N*-glycosyl β -amino esters through stereoselective 1,4-addition of benzylamine, followed by reduction [83]. The latter compounds can be manipulated as standard amino acids and can enter into peptide synthesis. The synthesis of a variety of tri- and tetrasubstituted *exo*-glycals was accomplished from tetra-*O*-benzyl-*D*-glucono-1,5-lactone applying a modified Julia olefination procedure [84].

Another method for the alkylidenation of aldonolactones uses addition of organometallic reagents [78]. For example, Lin et al. [85] described an efficient route to conjugated anomeric dienes or aldehydes based on the reaction of aldonolactones (**1**, **62**) with allylmagnesium chloride (Scheme 19), giving allyl hemiacetals (e.g., **63a**, **b**). Hemiacetal can be dehydrated [e.g., with $(\text{CF}_3\text{CO})_2\text{O}$] to produce dienes **64a**, **b**, or ozonolyzed (e.g., to give **65**).

C-Glycosyl aromatic compounds are particularly relevant owing to their presence in a variety of biologically important natural products, including antibiotics (for reviews concerning the synthesis and biological profile of *C*-glycosyl aromatic compounds, see [86–89]). Based on the method of Sulikowski and co-workers [90], Li et al. [91] developed an efficient one-pot procedure for the synthesis of a series of



Scheme 19 C-Glycosyl derivatives by addition of allylmagnesium chloride to aldonolactones

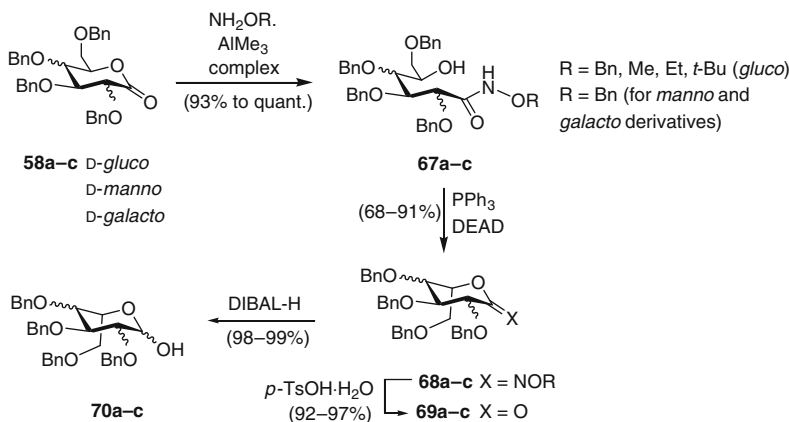
C-aryl glycols in 75–92% yields. It consisted in the addition of aryllithium reagents to variously protected 2-deoxy-aldono-1,5-lactones, followed by treatment with a mixture of pyridine (Py), 4-(Dimethylamino)pyridine (DMAP), and trifluoroacetic anhydride (TFAA).

3.3 Synthesis of L-Aldoses

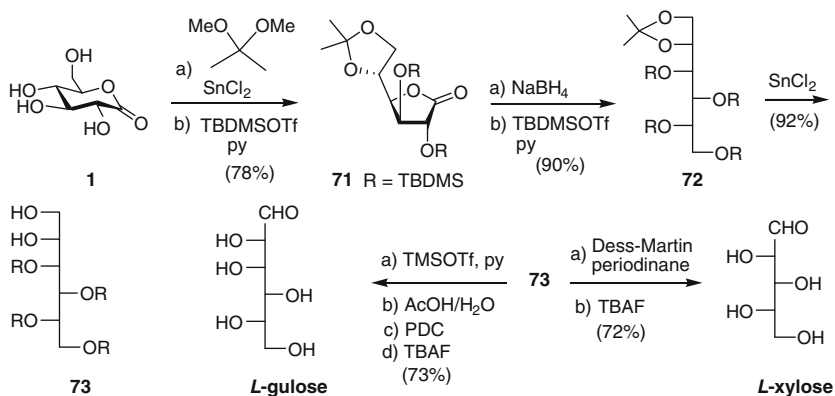
L-Aldoses are scarcely available from natural resources. However, their utility as building blocks for natural products and analogs has prompted the search for efficient methods for their synthesis. Lipták and co-workers [92] have prepared L-glucose through standard manipulations starting from D-gulono-1,4-lactone. The synthetic pathway included conversion of the lactone into 1,2,3,4,5-penta-*O*-benzyl-D-gulitol, 1,2,3,4,5-penta-*O*-acetyl-D-gulitol, or 1,2,3,4,5-penta-*O*-benzoyl-D-gulitol, oxidation at C-6 to the corresponding aldehydes, and further deprotection with concomitant pyranose ring closure. Yields in L-glucose ranged from 34 to 53% overall yield, the best one being obtained from the penta-*O*-acetyl-D-gulitol derivative.

A general and effective four-step procedure for the conversion of D-hexono-1,5-lactones into L-hexoses was developed [93]. It involved alkoxyamination of tetra-*O*-benzyl-aldono-1,5-lactones **58a–c** mediated by Me₃Al to provide the corresponding δ -hydroxyalkoxamates **67a–c**, which were then engaged into an intramolecular cyclization under Mitsunobu displacement conditions (Scheme 20). This cyclization occurred mainly via *O*-alkylation, affording the corresponding oxime derivatives **68a–c** in good yields, all with the expected inversion of configuration at C-5. At this stage, the acid-catalyzed hydrolysis of the oximes to the parent L-glycono-1,5-lactones **69a–c** provided, after reduction with diisobutylaluminum hydride (DIBAL-H), the corresponding tetra-*O*-benzyl-L-hexoses **70a–c**.

A relatively short route has been presented to convert D-glucono-1,5-lactone (**1**) into L-xylose and L-gulose [94] (Scheme 21). Acetalization of **1** gave **71**, the



Scheme 20 Conversion of D-hexono-1,5-lactones into L-hexoses via δ -hydroxyalkoxamate derivatives



Scheme 21 Synthesis of L-aldoses from D-glucono-1,5-lactone

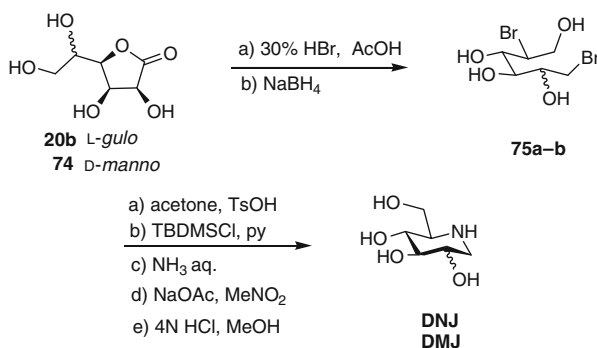
reduction of which with NaBH_4 and subsequent silylation afforded **72**. Deacetylation with SnCl_2 gave **73** which was converted either into L-gulose or L-xylose applying standard reactions.

3.4 Synthesis of Iminoalditols and Analogs

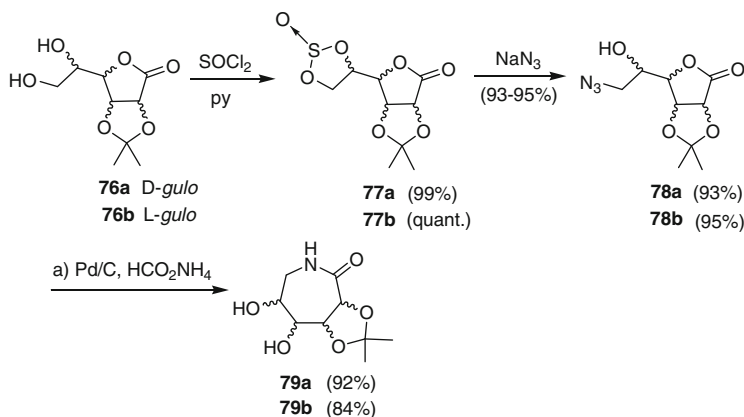
Imino sugars (or imino-dideoxyalditols) are alditols in which the ring etheral moiety has been replaced by an amino group. These sugar mimetics are potential therapeutic agents, particularly due to their ability to act as glycosidase inhibitors [95].

Among them are found the naturally occurring 1-deoxynojirimycin (DNJ) and 1-deoxymannojirimycin (DMJ) [96]. Practical syntheses of DNJ and DMJ start from L-gulono-1,4-lactone (**20b**) and D-mannono-1,4-lactone (**74**), respectively [97]. Key intermediates are 2,6-dibromo-2,6-dideoxy-D-alditol derivatives **75a** and **75b** obtained by 2,6-dibromination of the starting lactones, followed by reduction with NaBH_4 [98, 99]. Then a five-step sequence involving selective partial protection, introduction of an amine functionality, and intramolecular *N*-alkylation, lead to DNJ and DMJ, respectively (Scheme 22).

Related imino alditols such as azepanes or lactam derivatives have been obtained and have shown to be glycosidase inhibitors [96, 100]. Both D- and L-gulonolactone have been converted into polyhydroxylated 1,6-aldonolactams of type **79** in a sequence of straightforward functional transformations, including sulfinylation of the corresponding aldonolactone-derived acetonides **76** that gave 5,6-cyclic sulfites **77** (Scheme 23) [101]. The latter reacted with sodium azide



Scheme 22 Synthesis of 1-deoxynojirimycin (DNJ) and 1-deoxymannojirimycin (DMJ)

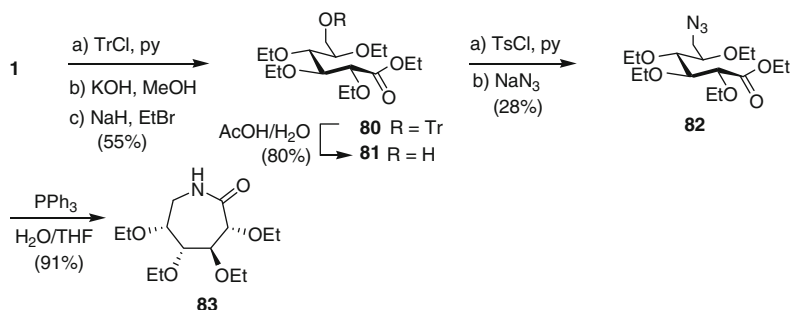


Scheme 23 Synthesis of di-hydroxylated 1,6-aldonolactams via aldonolactone-derived sulfites

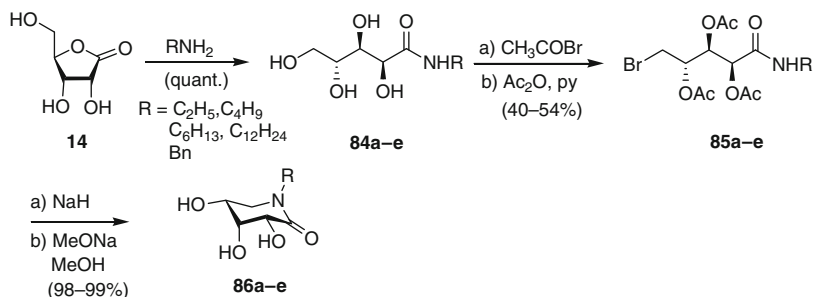
giving 6-azido derivatives **78**. In situ reduction of **78** and *N*-cyclization led to the targeted azepanes **79**.

A concise synthesis of tetra-*O*-ethyl aldono- α -lactam **83** starting from **1** has been reported [102]. After protection of its primary alcoholic moiety as a trityl ether, saponification and treatment with EtBr generated **80**. Acidic hydrolysis liberated **81** that was esterified (tosylate). The latter was displaced with NaN₃ to give azide **82**. Reduction of **82** resulted in lactam **83** (Scheme 24).

Quite often *N*-alkylated imino sugars exhibit stronger glycosidase inhibitory activity than the corresponding non-alkylated derivatives [96, 103]. The synthesis of a series of hydroxylated *N*-alkyl aldono- α -lactam derivatives was recently accomplished in a four-step sequence and good overall yields starting from D-ribo-1,4-lactone (**14**) [104]. Treatment of **14** with primary amines, and subsequent selective bromination of the resulting amides **84** and acetylation, provided the corresponding bromoamide derivatives **85**. The latter were then submitted to intramolecular cyclization to afford the corresponding *N*-alkyl ribonolactams, the transmethanol-lyse of which led to the final compounds **86** (Scheme 25).



Scheme 24 Synthesis of a tetra-*O*-ethylaldono- α -lactam from D-glucono-1,5-lactone



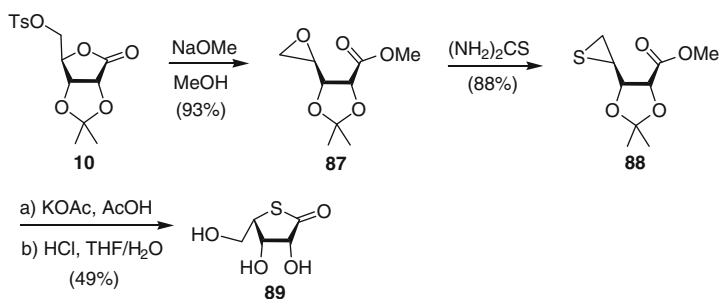
Scheme 25 Synthesis of a *N*-alkylated aldono- α -lactam from ribono-1,4-lactone

3.5 Synthesis of Thiosugars

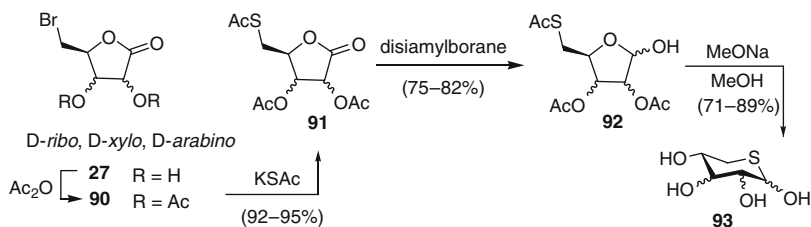
Thiosugars constitute another class of carbohydrate analogs presenting interesting biological and pharmacological properties [105, 106].

4-Thio-L-lyxono-1,4-lactone (**89**) has been prepared starting from 2,3-*O*-isopropylidene-5-*O*-tosyl-D-ribonolactone (**10**, *D*-ribo). **10** was converted first into epoxide **87** (Scheme 26) and then into episulfide **88** on treatment with thiourea. Regioselective opening of the thiirane ring of **88** and simultaneous lactonization, followed by removal of the protecting groups, furnished enantiomerically pure **89**. A similar synthetic pathway was employed for the synthesis of 4-thio-D-ribo-1,4-lactone starting from D-gulono-1,4-lactone [107].

Beaupère and co-workers have proposed a short synthesis of 5-thio-D-pentopyranoses **93** applying a sequence of simple reactions starting from 5-bromopentono-1,4-lactones of type **27** (Scheme 27) [108, 109]. The latter were acetylated and subsequently converted into their corresponding 5-*S*-acetyl-5-thio derivatives **91**. Reduction of **91** into lactols **92** was followed by deprotection, furnishing the desired pentose derivatives **93** in good overall yields.



Scheme 26 Synthesis of 4-thio-L-lyxono-1,4-lactone from 2,3-*O*-isopropylidene-5-*O*-tosyl-D-ribonolactone



Scheme 27 Synthesis of thio-D-pentopyranoses from 5-bromo-D-pentono-1,4-lactones

3.6 Synthesis of Bioactive Natural Products

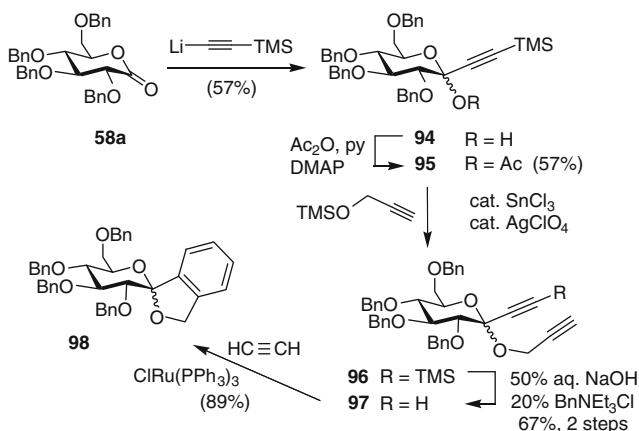
Selected examples of the synthesis of natural product starting from aldonolactones are presented in this section.

Spirocyclic *C*-aryl glycosides are central structural skeletons of papulacandins that constitute a family of novel antifungal antibiotics isolated from a strain of *Papularia sphaerosperna*. They have shown potent in vitro antifungal activity against *Candida albicans*, *Candida tropicalis*, *Pneumocystis carinii*, among other microorganisms [110].

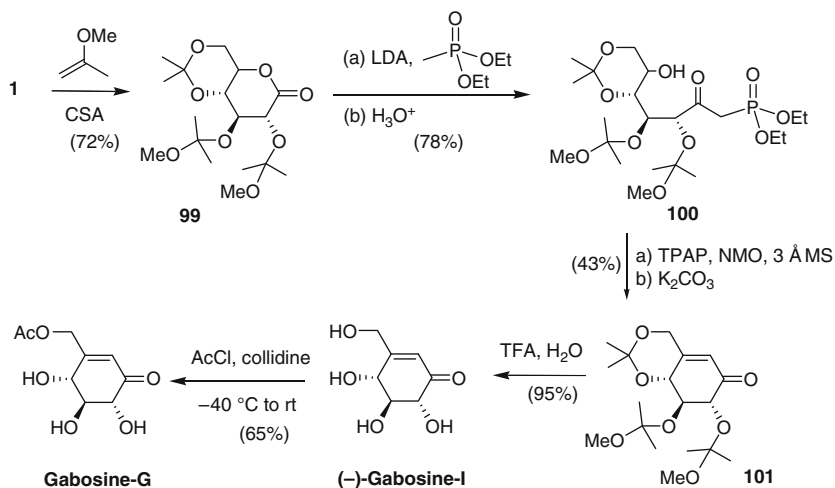
One route to spirocyclic *C*-glycosyl aromatic compounds is based on the addition of functionalized organolithium reagents to *D*-glucono-1,5-lactone (for example [111, 112, 113]). For instance addition of 2-(trimethylsilyl)ethynyllithium to tetra-*O*-benzyl-*D*-glucono-1,5-lactone (**58a**) gave the hemiacetalic 1-*C*-ethynyl derivative **94** as an anomeric mixture (Scheme 28). Acetylation of the tertiary hydroxyl group was followed by Lewis acid-mediated propargylation to give diyne **96**. Desilylation of **96** followed by cyclotrimerization in the presence of Wilkinson's catalyst gave the desired spiroketal core **98** in 89% yield.

Spirocyclic *C*-ribosyl aromatic compounds have also been derived from *D*-ribono-1,4-lactone by a similar strategy. In this case a mild cyclopentadienyl ruthenium complex was used as catalyst for the cycloaddition step [114].

Gabosines which have been isolated from *Streptomyces* strains constitute a family of keto carbasugars, most of them possessing a trihydroxylated cyclohexenone structure. Because of their interesting bioactivities, a large number of synthetic approaches to these compounds have been proposed (for example [115, 116]). The shortest route (four to five steps) to gabosines I and G was accomplished starting



Scheme 28 Synthesis of a spirocyclic *C*-glycosyl aromatic compounds from tetra-*O*-benzyl-*D*-glucono-1,5-lactone



Scheme 29 Synthesis of (-)-gabosine I and gabosine G from D-glucono-1,5-lactone

from D-glucono-1,5-lactone (Scheme 29) [117]. Thus, acetalization of **1** with 2-methoxypropene resulted in the mixed acetal derivative **99** which underwent nucleophilic addition by the anion of diethyl methylphosphonate to afford the β -ketophosphonate **100**. The latter compound was subsequently submitted to a one-pot tetrapropylammonium perruthenate (TPAP) oxidation/ K_2CO_3 -mediated intramolecular Horner-Wadsworth-Emmons olefination, providing enone **101** in 43% yield. Other oxidation/cyclization conditions were less efficient. Deprotection of **101** furnished (-)-gabosine I which, in turn, could be acetylated regioselectively to give gabosine G.

3.7 α,β -Unsaturated Aldonolactones

Sugar-based lactones comprising an α,β -unsaturation are carbohydrate chiral building blocks with biological potential. Rauter and co-workers have reported the first syntheses of α,β -unsaturated lactones linked/fused to sugars and the field was broadly covered in a recent review [118–120]. Concerning monocyclic derivatives, i.e., α,β -unsaturated aldonolactones, a readily available 2,3-unsaturated aldonolactone is L-ascorbic acid (Vitamin C). Its chemistry and usefulness as chiral synthon has been reviewed very recently [121]. It is a versatile starting material for the synthesis of L-hexoses [122, 123]. Both aldono-1,4-lactones and aldono-1,5-lactones have the tendency to undergo β -elimination on acylation to give butenolides or pyranoid α,β -unsaturated aldonolactones, respectively [1]. 2,3-Unsaturated aldono-1,4-lactones are also easily obtained from 2-bromo-2-deoxyaldono-1,4-lactones

through a mild reductive elimination of the C-2 bromine and a *trans*-vicinal acetoxy group that uses of sodium sulfite in methanol [124, 125]. 2-Deoxysugar lactones are intermediates for ulosonic acids [126–128].

Most of the methodologies applied to prepare pyranoid α,β -unsaturated lactones start with glycals [129–132]. The Lichtentaler's group developed a one-pot procedure consisting in the oxidation of glycals and 2-acyloxyglycal esters with *m*-chloroperbenzoic acid in the presence of boron trifluoride etherate [133–136]. Another major contribution to this field was realized by Chmielewski and co-workers. Their method was based on the oxidation of protected glycals with hydrogen peroxide in the presence of molybdenum trioxide catalyst to the corresponding anomeric hydroperoxides, which could then be readily converted into the pyranoid unsaturated lactones on treatment with acetic anhydride/pyridine [137–140]. This group has explored the ability of sugar-based α,β -unsaturated lactones to react as Michael acceptors or as dipolarophiles in cycloaddition reactions, for the synthesis of important molecular targets, including iminosugars and natural compounds of biological interest (for example [141–146]).

4 Bicyclic Carbohydrate-Based Lactones

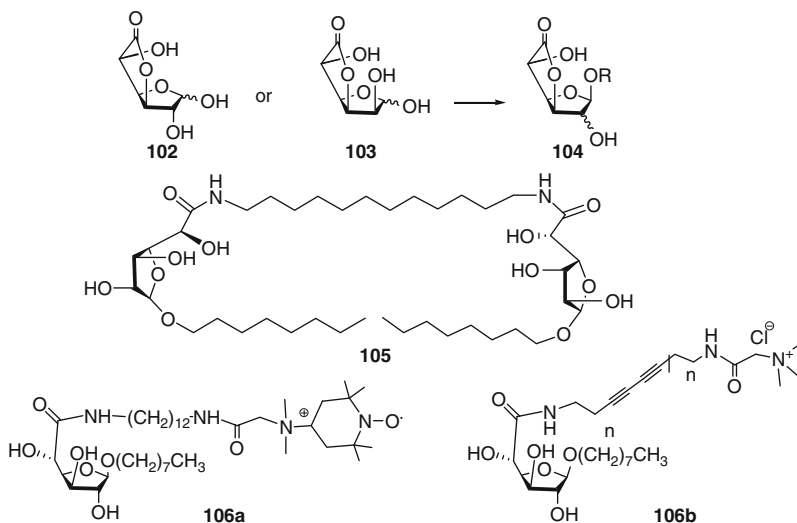
Bicyclic carbohydrate-based lactones can be divided into three classes: (1) lactones involving a carboxy group present on the sugar moiety (uronic and sialic acid lactones), (2) lactones involving a carboxy group formed by derivatization of a sugar hydroxyl group (carboxyalkyl ethers and glycosides), and (3) lactones involving a carboxy group present on a *C*-branched appendage.

When the lactone function of such bicyclic systems is consumed in a ring opening reaction, the main carbohydrate cyclic backbone is maintained in the product, unlike aldonolactones. Selected recent examples will be given in this section.

4.1 Uronic Acid Derived Lactones

The occurrence of uronic acid provides another means of easy access to bicyclic lactones, which can be used for the synthesis of various targets, such as surfactants or pseudo glycopeptides.

Alkyl furanosides can be obtained stereoselectively from the readily available D-glucufuranurono-6,3-lactone **102** arising from D-glucuronic acid, or from D-mannofuranurono-6,3-lactone **103**, which is obtained by acidic hydrolysis of alginic acid (Scheme 30) [147–149]. The lactone function of alkyl glucosides **104** can be opened by amines leading to new amphiphilic derivatives [42]. Pseudo macrocyclic bola-amphiphiles **105** are accessible by treatment of the lactone with a long-chain diamine [150]. Selective monoacylation of diamines can be followed by functionalization



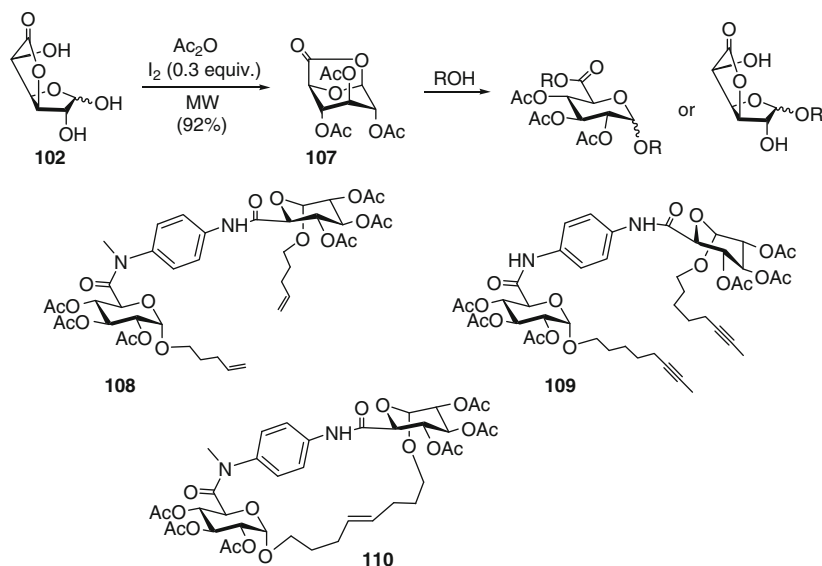
Scheme 30 Bolaphiles derived from uronic acid 6,3-lactones

of the second amino group with different functional moieties, such as a nitroxide for ESR studies (e.g., **106a**) or a cationic glycine betaine for making bolaphiles (e.g., **106b**). Variations of the self-assembly properties of the latter compound was studied as a function of the length and nature of the alkyl chain spacer connecting both polar heads [151–153].

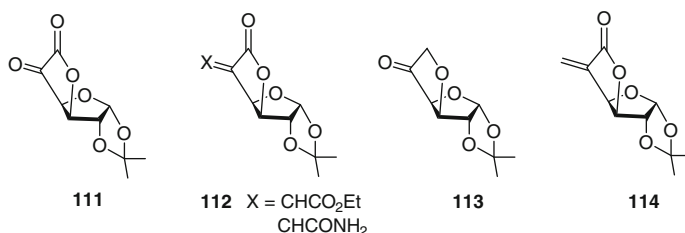
If the anomeric hydroxyl group is involved in the lactone ring (6,1-lactones), such as in compound **107**, the lactone is rapidly opened in the presence of a Lewis acid (Scheme 31). As in Hoffmann's systems arising from [4 + 3] cycloaddition methodology [154, 155], such lactones can be seen as tethered anomeric acetates acting as intramolecular leaving groups. Stereoselective glycosylations can thus be achieved with different selectivities depending on the nature of the substituent at C-2 and on the reaction conditions [catalyst, microwave irradiation (MW)]. In some cases, concomitant esterification of the released carboxylic acid is observed (Scheme 34) [156–158]. When the released carboxylic group reacts with diamines, more elaborated systems such as dienes **108** or diynes **109** can be obtained and used in subsequent intramolecular ring-closing metathesis to form glycopanes such as compound **110** [159].

Rauter and coworkers demonstrated that C-5-alkylidene derivatives **112** of D-hexofuranurono-6,3-lactone can be obtained by Wittig olefination of the α -ketolactone **111** (Scheme 32) [160]. The related α -methylene lactone **114** was prepared in three steps from 3,6-anhydro-1,2-*O*-isopropylidene- α -D-xylo-5-hexulofuranose **113** via Wittig reaction and allylic oxidation.

In a similar manner, sialic acids are liable to lactone formation. In some cases the observed lactones have been suggested to possess enhanced biological



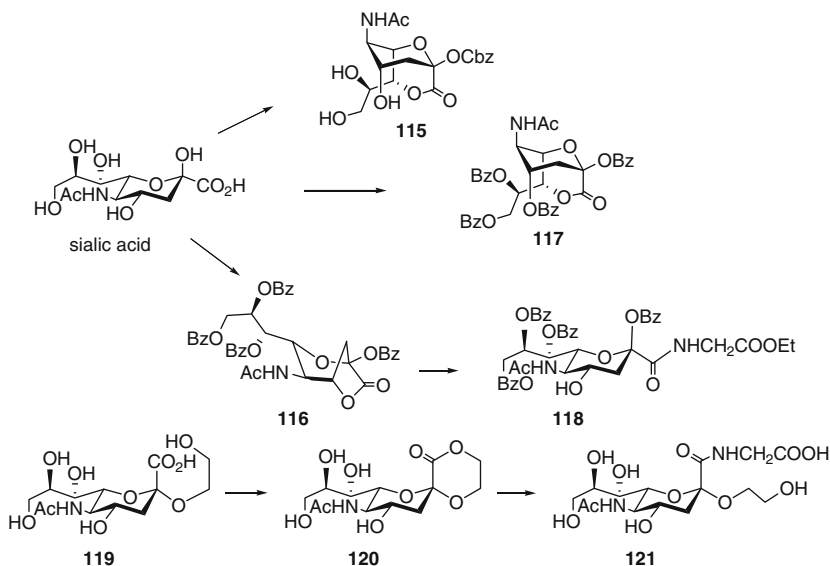
Scheme 31 Opening of glucuronic acid 6,1-lactone



Scheme 32 Alkylidene derivatives of hexuronic acid 6,3-lactone

properties with respect to the corresponding open hydroxyacids [161–163]. Sialic acid 1,7-lactone **115** is readily obtained [164]. It is present in many glycoproteins [165, 166].

Under various acetylation conditions, sialic acid leads to either 1,4-lactone **116** or to the 1,7-lactone **117** depending upon the equatorial or axial orientation of the carboxyl group (Scheme 33). In the presence of a more hindered acylating agent, e.g., CbzCl, an activated acyl intermediate can be formed and quantitative chemoselective 1,7-ring closure into compound **115** has been observed. Lactone **116**, as well as lactone **120** arising from the glycol glycoside **119**, were suggested to be the intermediates in the formation of NeuAc-aminoacid hybrids **117** and **121**. These compounds were designed as potential sialidase inhibitors [161, 167].



Scheme 33 Sialic acid lactones and derivatives

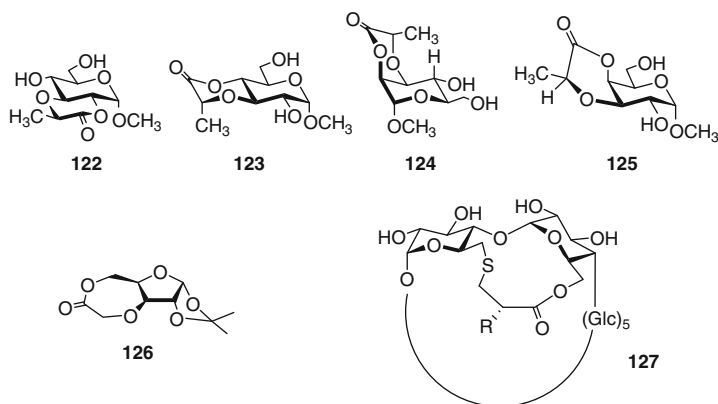
4.2 Lactonized Carboxyalkyl Ethers and Glycosides

4.2.1 Non-Anomeric Carboxyalkyl Ethers

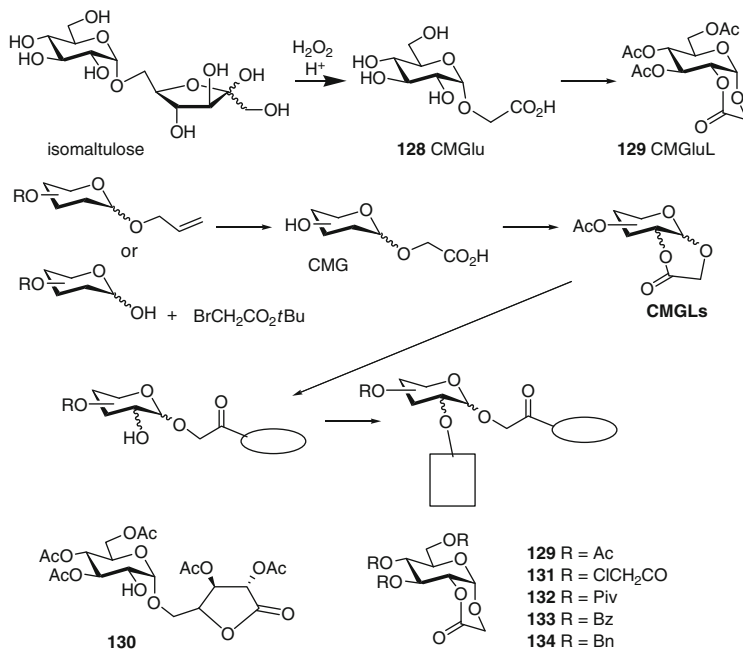
Various carboxyalkyl ethers at non-anomeric positions have been shown to give bicyclic systems which link positions 2,3 or 3,4 of sugars with various configurations through lactone formation. Examples are **122** and **123** (*gluco*), and **124** (*manno*) and **125** (*galacto*), which were derived from 3-*O*-(1-carboxyethyl) substituted methyl glycosides [168, 169] (Scheme 34). Another example is the bicyclic caprolactone **126**, derived from 1,2,5,6-di-*O*-isopropylidene- α -D-glucofuranose in six steps [170]. Modified cyclodextrins of type **127**, that involve lactonization of a carboxymethyl ether residue, have also been reported [171].

4.2.2 Anomeric Carboxymethyl Glycoside Lactones

Queneau and coworkers have developed the chemistry of lactones involving the carboxymethyl residues linked to the anomeric hydroxy group and to OH-2 in several sugars [172–176]. Isomaltulose (Scheme 35) is obtained by bioconversion from sucrose and has been shown to be an interesting starting material for various applications [177–182]. Like isomaltulose, trehalulose, another glucose-fructose disaccharide, and the hydrogenated derivative of isomaltulose, Isomalt[®], were all shown to lead to the same compound **128** (CMGGlu) by oxidation [183–185].



Scheme 34 Non-anomeric bicyclic lactones from carboxyalkyl ethers



Scheme 35 Access to carboxymethyl glycoside lactones

Acetylation of the latter compound led to bicyclic lactone **129**. Another lactone **130** was also observed as side product when the oxidative degradation of the fructose moiety of isomaltulose was incomplete [186].

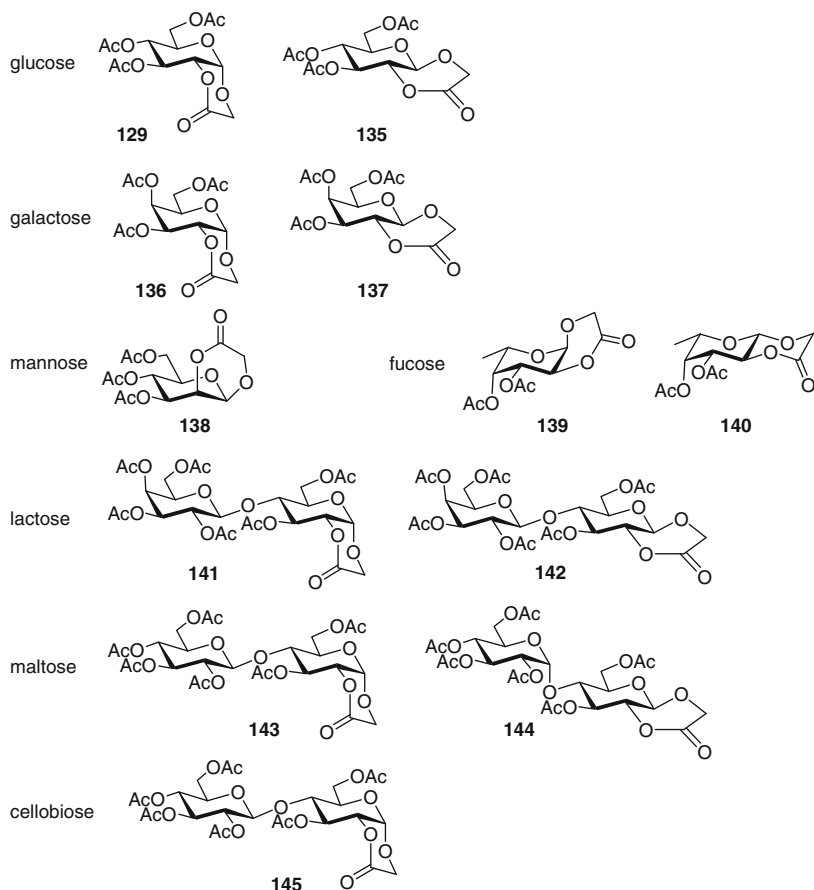
The scope of the method was extended to bicyclic lactones other than the α -D-glucoside arising from isomaltulose. The oxidation of allyl glycosides and the anomeric alkylation of various sugars with *tert*-butyl bromoacetate allowed many structural variations, leading to a full toolbox of carbohydrate-containing synthons in both their anomeric forms, in most cases, including disaccharides [186, 187]. Moreover, the selective opening of the lactone ring of these compounds releases the free 2-OH position which is available for a second functionalization, leading to 1,2-bisfunctionalized carbohydrate derivatives. An explanation for these observations is that a mixed anhydride is formed by reaction of CMG with Ac_2O , followed by nucleophilic attack of OH-2. A similar structure, derived from β -lactoside, had been suggested [188] and a comparable system has been reported in a recent patent [189]. Not only were acetylated products prepared, but also chloroacetyl, pivaloyl (Piv), or benzoyl lactones **131–133**. The allyl glycoside route also permitted the preparation of lactones bearing another protecting group such as benzylated lactone **134** [186].

Non-protected aldoses or those peracetylated on all positions except the anomeric hydroxy group react with *tert*-butyl bromoacetate (DMF , K_2CO_3) giving the corresponding *O*-glycosides [190, 191]. A significant selectivity for α anomers was observed for the reaction on the partially acetylated sugars, whereas some β selectivity (α : β from 1:1 to 1:2) was observed from free sugars. Galactose gives a more complex mixture in which the α -furanosides are the major products [192]. Lactones **129–145** have been prepared according to this route with subsequent treatment with acetic anhydride in Py (Scheme 36).

4.2.3 Use of CMGLs

Alcohols react with carbomethoxy glycoside lactones (CMGLs) under either basic or acidic catalysis. However, the method is limited to acetylated targets, since deprotection of the acetyl groups cannot be achieved without substantial cleavage of the newly formed ester. Amines give stable amides (Scheme 37). Pseudo glycoamino acid hybrids of type **146** [184, 185], pseudo disaccharides **147**, and nucleotide sugars **148** [193] were thus obtained. With the idea that attaching a carbohydrate moiety can provide increased polarity and water solubility, other types of compounds were prepared by this method, such as polymerizable compounds of type **149–151**, and glycoporphyrins **152** designed as photosensitizers for cancer photochemotherapy [194, 195]. Pseudo glycolipids **153** were also prepared by this method [196], and more recently new glycoprobes of type **154** for membranes nonlinear imaging have been derived from lactones **129** and **141** [197].

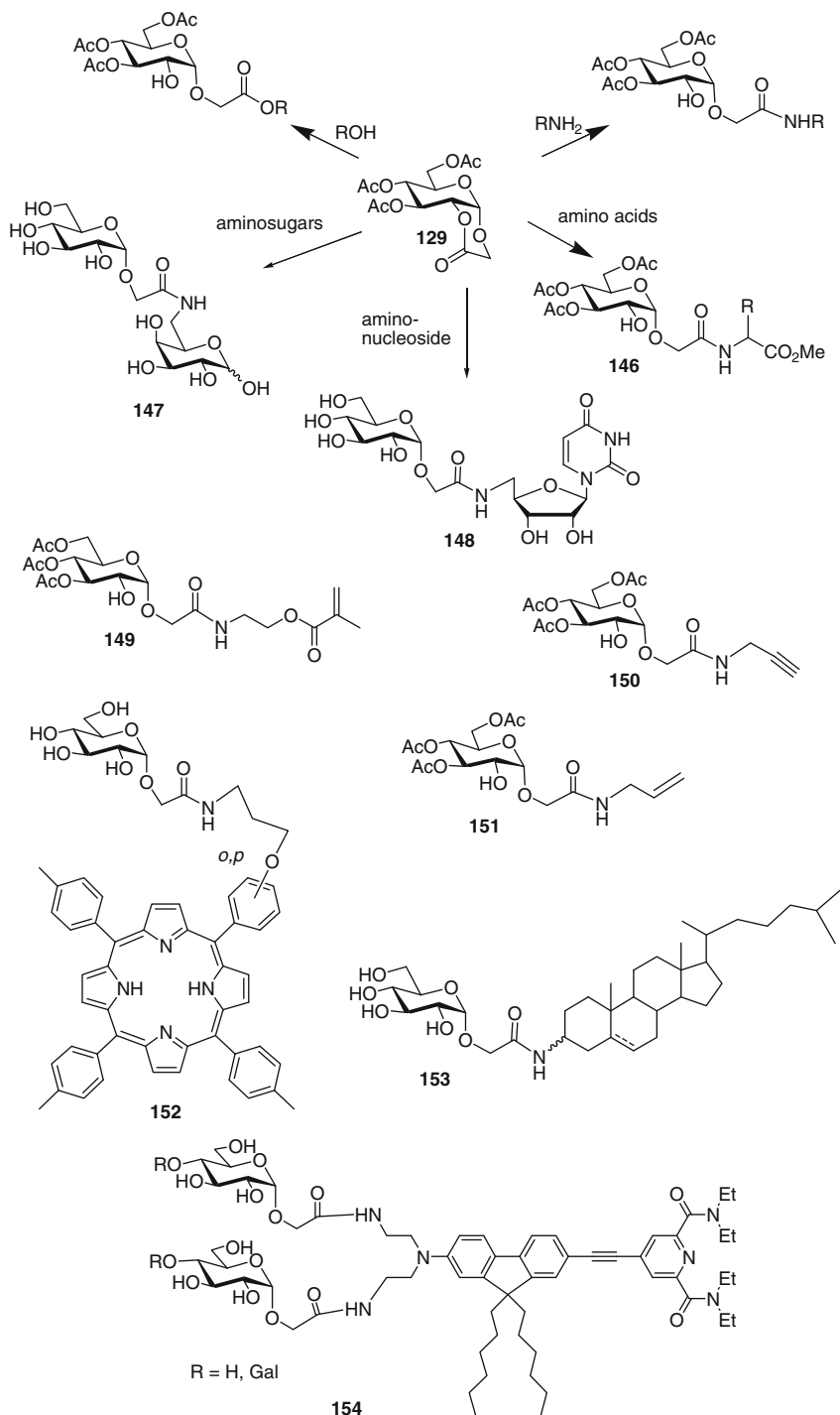
Further functionalization at OH-2 was also explored [187]. From monosaccharidic (α -gluco, **129**) and disaccharidic (α -malto, **143**) CMGLs, several types of bisfunctionalized systems were synthesized by reaction with allylamine or propargylamine. For example, compound **155** was prepared and used in a synthesis of the nucleotide sugar analog **156** (Scheme 38). In the context of studies on the

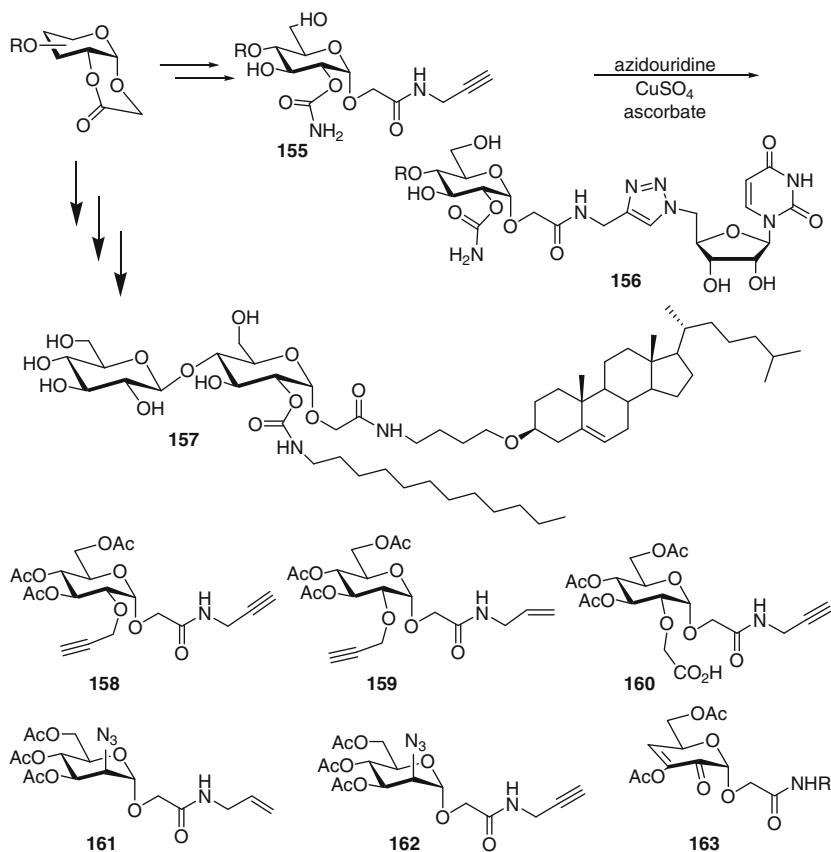


Scheme 36 Mono- and disaccharidic carboxymethyl glycoside lactones

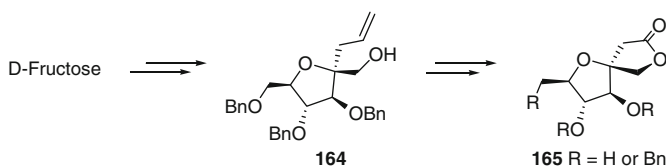
physicochemical behavior of synthetic glycolipids [198–204], new bisfunctionalized compounds such as **157** were recently obtained and found to possess very peculiar hysteretic thermotropic properties [205]. Reactions at OH-2 included carbamata-tions, etherifications leading to diynes, enynes, and carboxy-yenes **158–160** [187]. Substitution by an azide after intermediate triflate formation led to azido alkenes or alkynes **161** and **162**, respectively. The reactivity of the latter compounds as AB monomers is presently being studied. Oxidation of OH-2 generates enones **163** [206].

1-*C*-Allyl sugars have been transformed into spirobicyclic lactones which are the analogous synthons allowing the formation of *C*-glycosyl conjugates. For example, Araújo et al. prepared the intermediate **165** by *C*-allylation of the fully benzylated D-fructose followed by oxidation of the allyl group (Scheme 39) in the context of the evaluation of sugar-fused γ -butyrolactones and lactams as new potential γ -aminobutyric acid (GABA) receptor ligands [207].

**Scheme 37** Examples of conjugates obtained from carboxymethyl glycoside lactones



Scheme 38 Bisfunctional compounds at C-1 and C-2 from CMGLs



Scheme 39 C-Glycosyl anomeric lactone from fructose

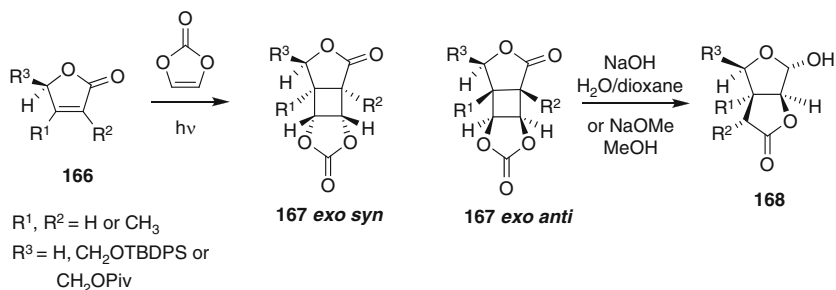
4.3 Fused C-Branched Lactones

Five-membered lactones (γ -butyrolactones) fused to carbohydrates have proven to be convenient synthons towards branched-chain sugars through opening of the lactone unit. Velásques et al. [208] described the synthesis of γ -butyrolactones

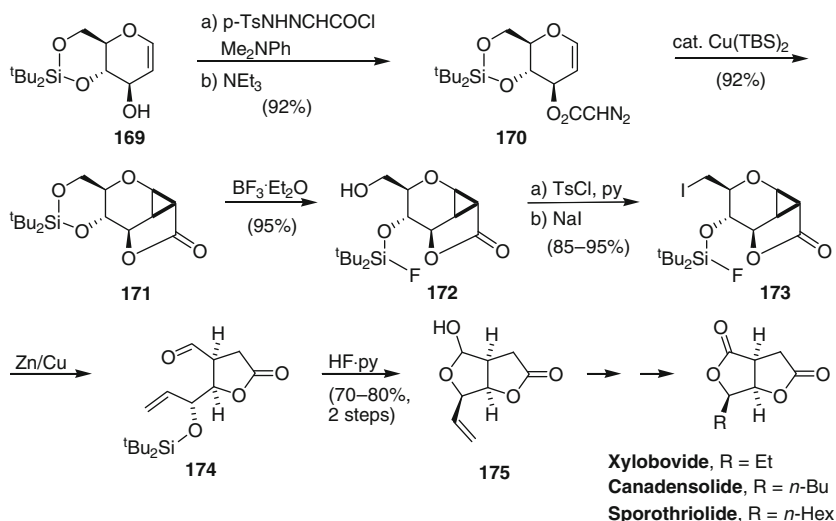
2,3-fused to ribonucleosides by radical intramolecular addition in nucleosides comprising an α,β -unsaturated ester moiety at C-2 or at C-3 of the furanose ring. These bicyclic derivatives were further converted into 2-*C* or 3-*C*-branched chain nucleosides by opening of the lactone moiety with isobutylamine. Font and co-workers [209, 210] made use of homochiral butenolides as precursors for a stereoselective synthesis of γ -butyrolactones 2,3-fused to lyxofuranose units. Thus, photocycloaddition of vinylene carbonate to substituted butenolides (compounds type **166**, Scheme 40), gave selectively the corresponding *anti* cycloadducts **167** in moderate yields. The latter, when treated under basic conditions (0.5 M NaOH in water/dioxane or MeONa in MeOH), underwent rearrangement to afford the target bicyclic compounds **168** in modest to moderate yields.

The intramolecular cyclopropanation of 4,6-di-*O*-protected glycals (such as **169**) has been explored as a key step for the synthesis of advanced intermediates for bislactone natural products [211] (Scheme 41). The glycal-fused cyclopropane **171** was obtained by copper-catalyzed intramolecular cyclopropanation of the glycal-derived diazoacetate **170** in very good yield. It could then be converted into furanose-fused butyrolactone **175** in few steps, including selective monodeprotection to the alcohol **172** and further iodination. The resulting iodine derivative **173** was subjected to a zinc-mediated reductive ring opening cascade to furnish aldehyde **174**. Its desilylation provided bicyclic lactone **175** as a convenient precursor for xylobovide, canadensolide and sporothriolide bisfuranolactones.

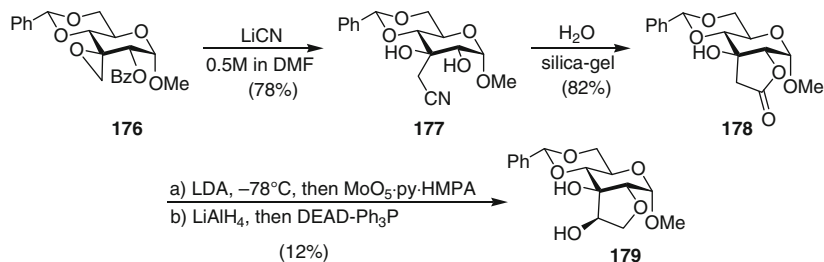
With respect to five-membered lactones fused to hexopyranose units, some approaches have been reported so far and the exploitation of their synthetic potential has led to the access of new carbohydrate derivatives. Bicyclic derivatives of this type are key intermediates in the synthesis of the epimer at C-3 of the sugar moiety contained in miharamycins [212, 213]. The latter are antibiotics known to inhibit strongly *Pyricularia oryzae*, which produces the rice blast disease. These compounds are also considered to be a potential bioterrorism agent (Scheme 42). Hence, the 3,3-spiroepoxide **176** was converted into the 3-*C*-cyanomethyl derivative **177**, the hydrolysis of which led to spontaneous cyclization in the presence of



Scheme 40 Synthesis of furanose-fused γ -butyrolactones by photocycloaddition of vinylene carbonate to substituted butenolides



Scheme 41 Synthesis a furanose-fused butyrolactone from a glycal-derived cyclopropane



Scheme 42 Sugar moiety of miharamycins from hexopyranoside fused butyrolactones

silica gel, giving the sugar-fused lactone **178**. A stereoselective hydroxylation of the latter compound followed by reduction led to the desired miharamycin sugar moiety analog **179**.

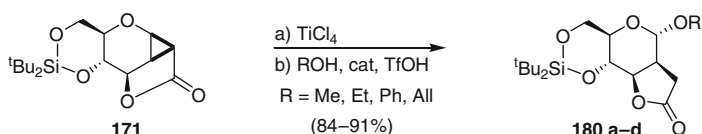
The previously mentioned glycal cyclopropanation method was also applied to the synthesis of γ -butyrolactones 2,3-fused to glycopyranosides (Scheme 43) [214]. Hence, ring opening of the cyclopropane derivative **171** by TiCl_4 , which was followed by in situ addition of alcohol, furnished glycoside-fused butyrolactones **180a–d**, in high yields and good diastereoselectivity (α/β ratio ranging from 6:1 to 15:1).

More recently, another methodology for sugar-fused butyrolactones employing glycal-derived cyclopropane precursors has been described by Chandrasekaran and co-workers (Scheme 44) [215]. In this case, hexofuranose- or hexopyranose-1,2-fused were cyclopropanated into compounds of type **181**. After saponification with

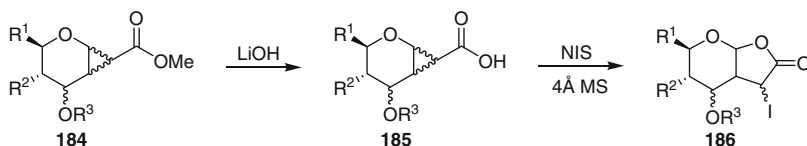
LiOH, giving **182**, iodination with *N*-iodosuccinimide (NIS) provided **183** resulting from homoiodolactonization.

On their side, Yin and Linker [216] made use of a 2-*C*-branched hexopyranoside, the synthesis of which was achieved by addition of dimethyl malonate to tri-*O*-benzyl-*D*-glucal (IUPAC name: 3,4,6-tri-*O*-benzyl-1,5-anhydro-2-deoxy-*D*-arabino-hex-1-enitol, Scheme 45) [217]. Thus, saponification of the 2-*C*-[bis(methoxycarbonyl)]methyl derivative **184** to the corresponding malonic acid **185** was followed by heating in refluxing toluene. This led to decarboxylation and lactonization giving **186**. The method was optimized and applied to the synthesis of pentoses and disaccharides.

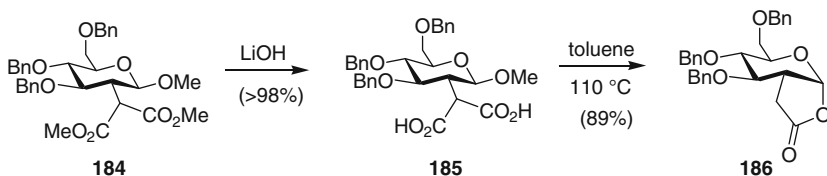
Sugar-derived α,β -unsaturated lactones are relevant motifs considering their ability to act as functionalized substrates for a variety of transformations. Some of them are bioactive [218–222]. An early synthesis of the enantiomer of (+)-altholactone, a natural product with cytotoxic and antitumor activities (for a review on the bioactivity of styryllactones see [223, 224]), involves the preparation of a furanose-fused α,β -unsaturated δ -lactone intermediate **189** [225]. Starting from a α -*D*-xylo-pentodialdofuranose derivative **187**, a Reformatsky reaction with ethyl bromoacetate introduces the carboxylic side chain necessary for intramolecular lactonization (Scheme 46).



Scheme 43 Pyranoside 2,3-fused- γ -butyrolactones from a glycol derived cyclopropane



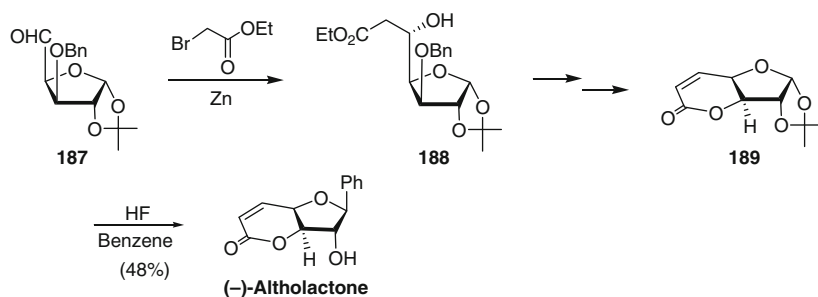
Scheme 44 Synthesis of sugar-1,2-fused iodobutyrolactones from sugar-1,2-fused cyclopropylated esters



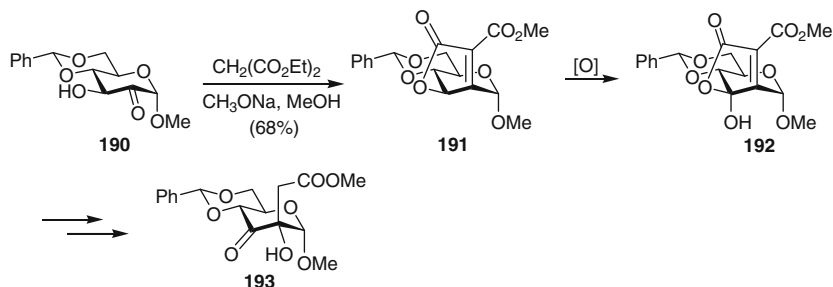
Scheme 45 Synthesis of a hexopyranose-1,2-fused butyrolactone from a 2-*C*-malonyl glucoside

A pentopyranoside-fused butenolide is the key intermediate for the synthesis of the natural micotoxin patulin [226, 227]. Its synthesis involves Wittig olefination of a 3,4-di-*O*-protected arabinopyran-2-uloside, followed by protecting group removal and dehydration (Scheme 47). In other research, the glucopyranosid-2-uloside **190** was converted into the butenolide derivative **191** by aldol condensation with diethyl malonate and transesterification [228]. The latter was shown to be prone to autoxidation, leading to **192**. Subsequent Michael addition with hydroxide ion, followed by decarboxylation, furnishes *C*-branched-chain sugar **193**.

An elegant stereocontrolled route for pyranose-fused butenolides starting from easily synthesized protected furan-3-uloses (compounds of type **194**) has been reported [229, 230] (Scheme 48). It consisted of the synthesis of 3-*C*-branched α,β -unsaturated esters (**195**) by Wittig olefination, followed by acid hydrolysis. Within this latter step, cleavage of the protecting groups (PG), intramolecular transesterification, and furanose-pyranose isomerization occurred, furnishing directly the target bicyclic compounds (**196**, **197**) in good overall yields. This approach was convenient for achieving in a few steps both pento- and hexopyranose-based bicyclic systems comprising the butenolide moiety anchored at C2-C3 or at C3-C4 of the sugar ring, depending on the configuration around the C3-C3' double bond. The feasibility and scope of this methodology were then investigated for the preparation



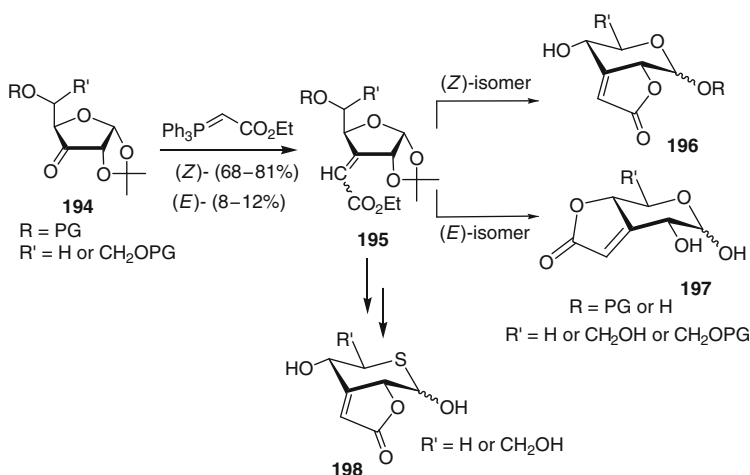
Scheme 46 Synthesis of the non-natural enantiomer of (+)-altholactone via a furanose-fused unsaturated δ -lactone



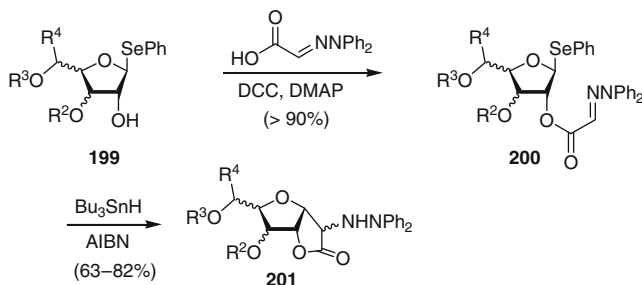
Scheme 47 Synthesis of a 2-*C*-branched-chain sugar via a pyranose-fused butenolide

of 5-thiopento or hexopyranose analogues of type **198** [231]. Thus, after introduction of an additional sulfhydryl functionality at C-5 at the intermediate α,β -unsaturated esters, acid hydrolysis also allowed ring expansion to the thiopyranose form with accompanying butenolide formation, generating new highly functionalized and potential biologically interesting bicyclic thiosugar-based systems.

Fused *C*-glycosyl lactones are also suitable synthons for further elaboration into more complex *C*-glycosyl compounds, including glycoconjugates. In one of the few published methods to afford these bicyclic lactones, protected 1-phenylseleno glycosyl donors possessing a free OH-2 (compounds of type **199**) were converted into the corresponding 2-hydrazoneoesters **200**. The latter were then subjected to radical cyclization (Scheme 49) [232] giving α -hydrazino lactones **201** that could be transformed into the corresponding *C*-glycosyl amino acids through standard functional manipulations.



Scheme 48 Synthesis of butenolides fused to pento- or hexopyranoses and thiosugar analogs from furanos-3-uloses



Scheme 49 Synthesis of furanose-fused *C*-glycosyl α -hydrazino lactones from phenyl-1-seleno glycosyl donors

5 Conclusion

Lactones derived from carbohydrates are building blocks of high synthetic potential. Next to the readily available aldonolactones and uronic acid lactones, some bicyclic systems have recently emerged as useful synthons. Examples of applications encompass functional derivatives such as polymers, as well as more elaborated compounds of physico-chemical or biological relevance.

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