

# Formylation of carbohydrates and the evolution of synthetic routes to artificial oligosaccharides and glycoconjugates\*

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*Abstract:* A highly effective method for the synthesis of formyl *C*-glycosides is described via addition of 2-lithiothiazole or 2-lithiobenzothiazole to sugar lactones, deoxygenation of the resulting ketols, and releasing of the formyl group from the heterocyclic ring. The synthetic utility of these sugar aldehydes is demonstrated by the development of synthetic methods to more elaborate *C*-glycosides. These include various (1 → 6)-*C*-disaccharides and some higher oligomers up to a *C,C,C,C*-pentasaccharide; *C*-glycosyl amino acid isosteres of *N*-glycosyl asparagines; the methylene isostere of β-*D*-galactosyl ceramide; linear and cyclic (2 → 1)-ketoside oligomers. An alternative synthesis of ethylene-bridged glycosyl asparagine isosteres is illustrated by the use of ethynyl *C*-glycosides as starting materials.

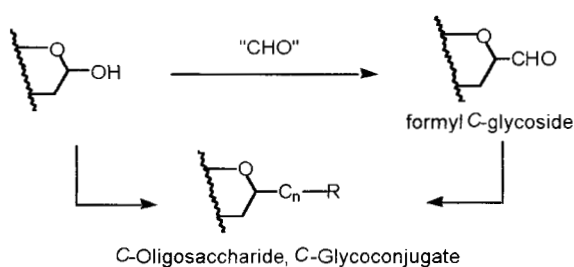
## INTRODUCTION

Classical carbohydrate chemistry has been focused for many years on natural *O*-glycoside synthesis [1]. The intense research has generated several new methods that permit the stereocontrolled assembly of various monosaccharide units through *O*-glycosidic linkages either by solution [2] or solid-phase [3] reactions. Remarkable achievements have been made also in the synthesis of natural glycoconjugates, especially *O*- and *N*-glycopeptides and *O*-glycolipids [4]. Methods for the construction of carbohydrate libraries by combinatorial chemistry have been described [5]. While innovations and further improvements of *O*-glycosidation techniques are still actively pursued, increasing attention is currently addressed to the synthesis of abiological carbohydrate derivatives (artificial sugars) that contain a carbon–carbon bond at the anomeric center (*C*-glycosides) [6]. These isosteres of natural carbohydrates are considered to be tools of great value for the study, at molecular level, of the role that carbohydrate moieties of glycoproteins and glycolipids play in biological processes [7]. A related field of research includes the identification of lead compounds for drug discovery [8] and the developments of carbohydrate-based therapeutics [9] against numerous diseases of high social relevance, such as cancer formation and metastasis, viral and bacterial infections, and inflammation phenomena.

The stereoselective installation of a carbon chain at the anomeric carbon atom of a sugar via a direct *C*-glycosidation reaction can be a difficult task whose level may increase with the complexity of the group *R*. Approaches based on both polar or radical reactions to *C*-oligosaccharides [6,10] and *C*-glycosyl amino acids, [6,11] the precursors of *C*-glycopeptides, have been reported. However, most of the methods are hampered by the low reactivity of the glycosyl acceptor and scarce α/β selectivity; their scope has been often limited to the preparation of a particular structure. A possible way to overcome these problems is to exploit a highly reactive functional group linked through a carbon–carbon bond to the anomeric carbon atom of the sugar. Accordingly, we envisioned reactions of nucleophiles with anomerically linked sugar aldehydes (formyl *C*-glycosides, Gly-CHO), as an entry to more elaborate *C*-glycoside synthesis (Scheme 1).

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Scheme 1

However, the introduction of the formyl group at the anomeric carbon atom of sugar molecules is by far a non trivial problem. Methods based on direct electrophilic formylating agents [12] are hampered by the inherently difficult access to nucleophilic *C*-glycosyl donors [13] (umpolung at the anomeric center) due to the easy  $\beta$ -elimination of the C2 substituent. Hence, the formylation by the use of masked formyl anion equivalents [14] has to be considered. For example, some years ago the synthesis of some  $\beta$ -linked formyl *C*-glycosides was reported by ozonolysis of *C*-glycosyl allenes which in turn were prepared by *C*-glycosidation with a propargyl silane [15]. The modest yields (42–49%) of the isolated sugar aldehydes were ascribed to their partial decomposition under the harsh oxidative conditions. Hence, a precursor of the formyl group combining the characteristics of an easy introduction in the substrate, high stability and facile unmasking are required for the development of an effective synthetic method. These properties appeared to be displayed by the thiazole ring whose equivalence with the formyl group was illustrated in a variety of syntheses carried out in recent years in our [16] and other [17] laboratories. It is noteworthy that while this heterocycle either free or condensed with the phenyl ring as in benzothiazole [18] is stable under various reaction conditions because of its aromatic character [19], the transformation into the formyl group involves a simple procedure constituted of: *N*-methylation ( $\text{CF}_3\text{SO}_2\text{Me}$ ); reduction ( $\text{NaBH}_4$ ); metal-assisted hydrolysis ( $\text{HgCl}_2$  or  $\text{CuCl}_2$  or  $\text{AgNO}_3$ ) (Fig. 1). The mild and neutral conditions under which these reactions take place highlight the thiazole ring as a convenient masked formyl group in multistep syntheses of chiral aldehydes bearing quite sensitive substituents and protective groups. Hence, this report is dealing with the thiazole-based formylation of sugars leading not only to simple formyl *C*-glycosides but also to more elaborate derivatives bearing an additional substituent R linked to the anomeric carbon atom [20].

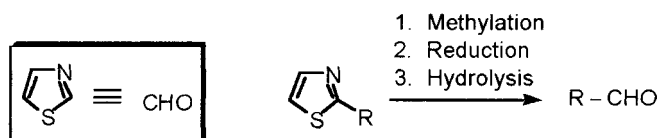
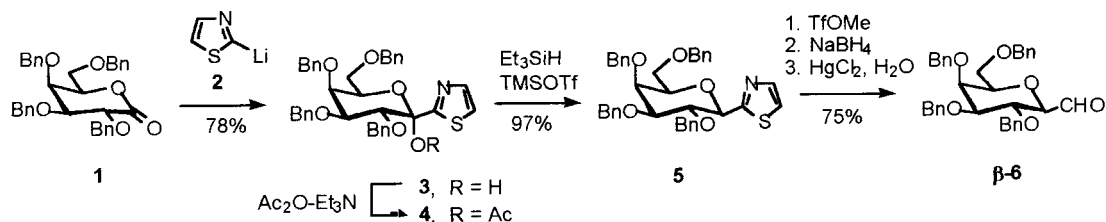


Fig. 1 The thiazole-to-formyl equivalence as a tool for aldehyde synthesis.

## SYNTHESIS OF FORMYL C-GLYCOSIDES

Various efforts to perform a direct glycosylation of thiazole were unsuccessful. Instead, a viable route was developed starting from sugars lactones [21]. Typically, the addition of 2-lithiothiazole **2** to the galactolactone **1** at  $-78^\circ\text{C}$  and aqueous workup afforded the ketol **3** which upon treatment with  $\text{Ac}_2\text{O}$  was transformed into the corresponding *O*-acetate **4** (Scheme 2). Alternatively, the epimer of **4** (*OAc* equatorial and thiazole axial) was obtained by quenching the ketol intermediate (not shown) by  $\text{Ac}_2\text{O}$  at  $-50^\circ\text{C}$ . The deoxygenation of either **4** or its anomer with  $\text{Et}_3\text{SiH-TMSOTf}$  afforded exclusively the  $\beta$ -linked thiazolyl galactoside **5**. This result is in agreement with a stereochemical model wherein the hydride ion attacks the less-hindered face of the sugar oxycarbenium ion existing in a half-chair con-

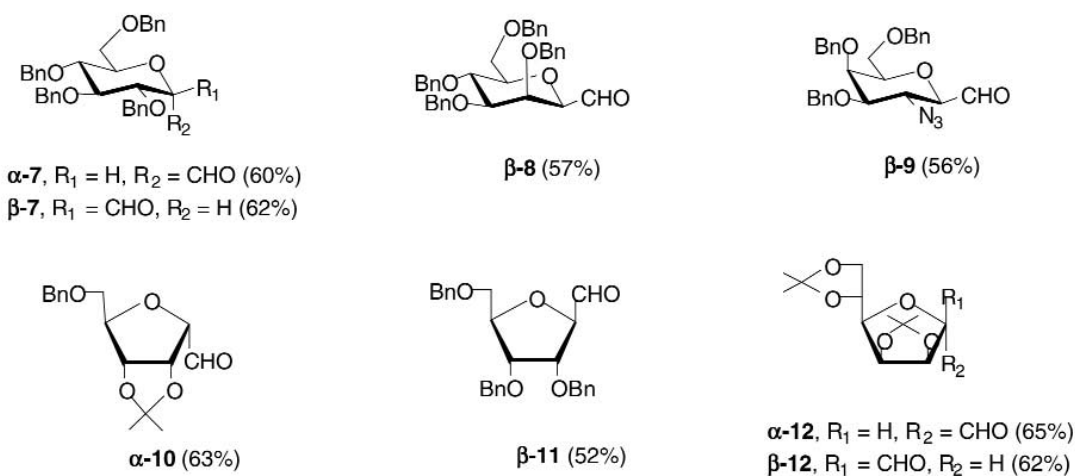
formation. Finally, the transformation of the thiazole ring into the formyl group by the standard protocol afforded the formyl *C*-galactoside (Gal-CHO) **β-6**. The preparation of **β-6** was carried out several times in our laboratory starting from different amounts of **1** ranging from 1 to 15 g.



**Scheme 2**

The same procedure was followed for the preparation of various  $\beta$ -linked and some  $\alpha$ -linked formyl *C*-glycosides (Gly-CHO) in good overall yields (Fig. 2). In more recent work we have observed that benzothiazole serves equally well in this methodology, giving rise to considerable economical advantages [22]. While the scope of this method should be extensible to the preparation of other formyl *C*-glycosides, a limitation becomes apparent when considering that only the  $\alpha$ - or  $\beta$ -linked isomer can be obtained from each starting lactone [23]. A solution of this problem has been found in a few cases. For example, while the deoxygenation of 1-*C*-thiazolyl-D-mannofuranose acetate with  $\text{Et}_3\text{SiH}$  -  $\text{TMSOTf}$  afforded the  $\beta$ -linked thiazolyl *C*-glycoside precursor of the  $\beta$ -formyl *C*-mannofuranoside **β-12**, the use of  $\text{SmI}_2$  and ethylene glycol led to the corresponding  $\alpha$ -isomer precursor of **α-12** [10a].

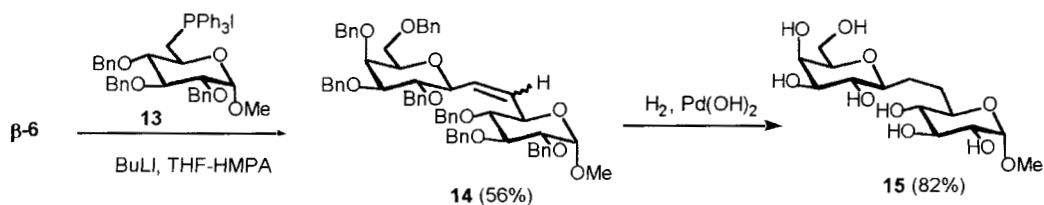
In conclusion, the formylation of sugars via thiazolylation has been demonstrated in a number of cases. It has to be noted that other formyl group equivalents, notably 1,3-dithianyl [24] and ethynyl [25], have been employed for the same purpose, although their use has been limited to a few examples. While the procedure employing 1,3-dithiane does not offer substantial advantages in respect to that with thiazole, the method via alkylation may serve to prepare  $\alpha$ -linked formyl *C*-glycopyranosides that are unaccessible by the other methods. However, the transformation of the alkynyl into the formyl group via reduction to double bond and oxidative cleavage of the latter by  $\text{O}_3$  may not be tolerated by various hydroxy protective groups commonly employed in carbohydrate chemistry.



**Fig. 2** Other formyl *C*-glycosides prepared (yield from lactone).

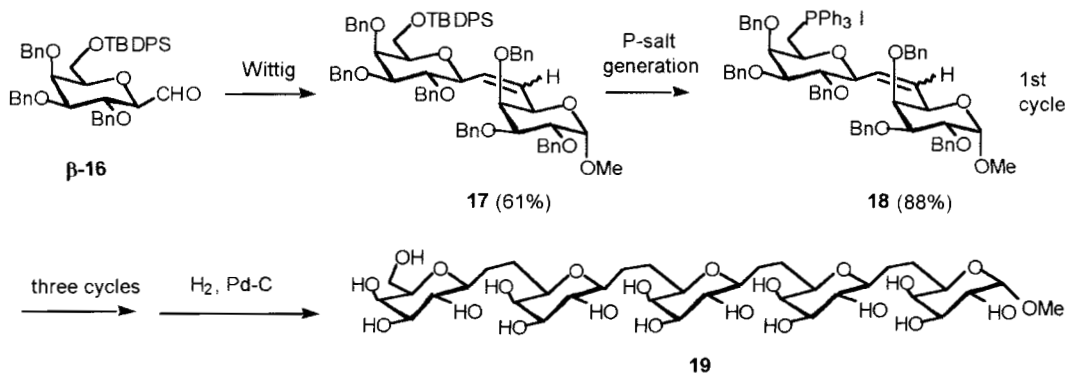
## SYNTHESES WITH THE USE OF FORMYL C-GLYCOSIDES

We first examined the use of formyl *C*-glycosides in an olefination-based approach to (1 → 6)-linked *C*-disaccharides [10a]. The model synthesis of *C*-Galβ1,6Glc **15**, a *C*-analog of allolactose, is illustrated in Scheme 3. The key step was constituted of the Wittig reaction between Gal-CHO **β-6** and the sugar ylide at C6 derived from the phosphonium iodide **13**. The hydrogenolysis of the resulting bis-glycosylated alkene **14** afforded **15** in one step by reduction of the double bond and removal of the benzyl protective groups. A set of ten *C*-disaccharides was prepared by the same procedure. Nine products featured the β-glycosidic linkage as shown in **15**; one α-linked derivative was prepared using the stable formyl *C*-mannofuranoside **α-12** [23]. The intellectual appeal of this method derived from the availability of monosaccharide starting materials and the rewarding observation that the configuration at the carbon atoms bearing the reactive functionalities (formyl and ylide) was conserved throughout the whole procedure.

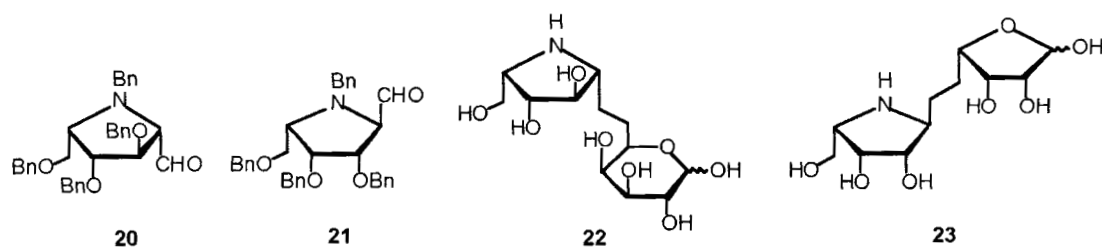


Scheme 3

Suitable sugar aldehydes and phosphonium salts were prepared to broaden this approach for higher homologue synthesis via iterative Wittig reaction. An efficient method was developed employing the Gal-CHO **β-16** as building block. Each cycle was constituted of a Wittig reaction and the introduction of the methylphosphonium group at the nonreducing end of the growing oligosaccharide [26] (Scheme 4). This linear homologation strategy afforded (1 → 6)-linked *C*-oligomers containing galactopyranose residues up to the pentasaccharide **19**. However this appeared not to be the limit of application of the iterative protocol since the overall yields of isolated alkene-sugars were comparable over the four consecutive cycles. Less efficient was an alternative approach employing a sugar methylene phosphorane as building block. Each cycle was constituted of a Wittig reaction and the introduction of the formyl group at the nonreducing end of the constructed oligomer [10c]. The low yields in this method were ascribed to the partial decomposition of the newly formed sugar aldehyde by loss of benzyl alcohol via 1,2-elimination reaction. However, these results are quite remarkable since very few *C*-oligosaccharides containing more than two carbohydrate residues have been so far reported [10h]. These carbon isosteres of natural oligosaccharides are resistant to enzymatic degradation, and therefore they are targeted as potential inhibitors of glycosidases and glycosyltransferases and drug carrier agents endowed with high pharmacodynamic properties.



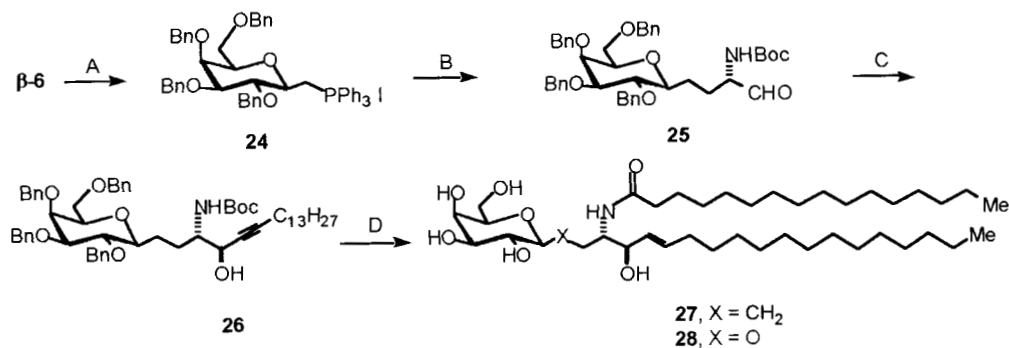
Scheme 4



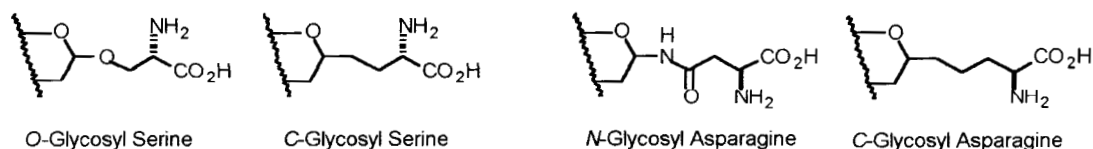
**Fig. 3** Aza-*C*-disaccharides prepared and their formyl aza-*C*-glycoside precursors.

A similar synthetic approach was employed for the synthesis of aza-*C*-disaccharides in which one of the two components was a polyhydroxylated pyrrolidine ring (azasugar). Following the high and specific inhibitor activity of azasugars against glycosidases [27], the synthesis of *C*-oligosaccharides containing these sugar mimics is of current interest [28] since these products may combine the biological activity of the azasugar with the pharmacodynamic properties of a highly resistant carrier to chemical and enzymatic degradations. Accordingly, we have prepared the (1 → 6)- and (1 → 5)-linked aza-*C*-disaccharides **22** and **23** (Fig. 3) via Wittig-type coupling of formyl *C*-azaglycofuranosides (formyl polyhydroxypyrrolidines) with suitable sugar phosphoranes [29a]. The aldehyde building blocks **20** and **21** employed in this synthesis were prepared by amination and chain elongation (aminohomologation) of furanoses (D-arabinose and D-ribose) [29b] since the formylation of azasugars via their lactams proved to be unsuccessful. The aminohomologation of aldehydes is a method developed in our laboratory which essentially involves the conversion into nitrones (iminium cation equivalents) and the addition of thiazole as a masked formylating agent [30].

The synthetic utility of formyl *C*-glycosides was further demonstrated by the synthesis of *C*-glycoconjugates. The introduction of a ceramide residue at C1 of galactose by a carbon–carbon β-linkage was our first endeavour toward the synthesis of an artificial glycosphingolipid [31] (Scheme 5). The target was represented by the methylene isostere **27** of the β-D-galactosyl ceramide **28** with the aim of obtaining an inhibitor of the HIV-1 gp120 binding to **28**. This interaction was considered to be involved in the viral infection of cells lacking the CD4 receptor, a molecule on host lymphoid cells [32]. The synthesis of **27** employed the Gal-CHO **β-6** as starting material [31]. This aldehyde was transformed into the phosphonium iodide **24** (step A) whose ylide was reacted with the Garner aldehyde in an “umpolung” approach [33] to the *C*-galactosyl serinal **25** (step B). The next carbon–carbon bond forming reaction involved the addition of a suitable lithium alkylacetylde to the aldehyde **25** (step C). The construction of the ceramide moiety was completed by the reduction of the triple bond of **26** to double bond and the *N*-acylation of the amino group with palmitoyl chloride (step D).



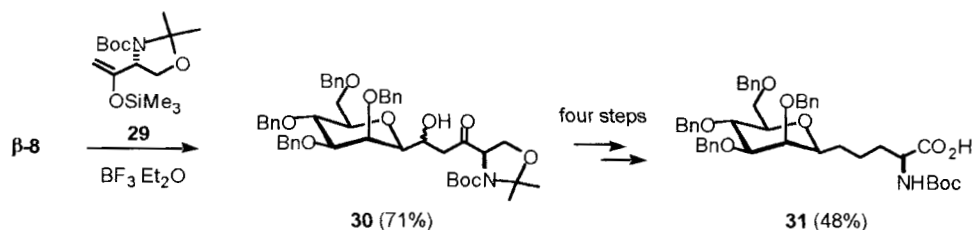
**Scheme 5**



**Fig. 4** *O*-, *N*-, and *C*-glycosyl amino acids.

Studies on the role that sugar moieties play in the biological activity of glycopeptides [7] are posing a pressing need for the synthesis of well-characterized natural glycosides and their unnatural analogs. Fundamental building blocks in the synthesis of artificial glycopeptides having a carbon–carbon bond between the carbohydrate residues and the peptide chain are carbon-linked isosteres of *O*-glycosyl serine (or threonine) and *N*-glycosyl asparagine, the main constituents of natural glycopeptides (Fig. 4).

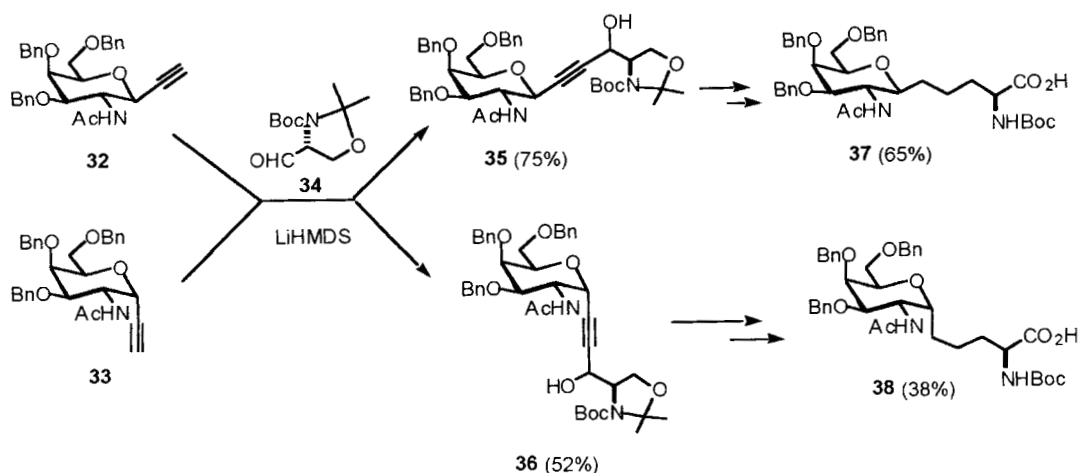
We were spurred to test the synthetic utility of formyl *C*-glycosides in an area of active investigation such as the *C*-glycosyl amino acid synthesis [34]. The sugar aldehydes Gal-CHO **β-6**, Glc-CHO **β-7**, and Man-CHO **β-8** were used as starting materials for the synthesis of ethylene isosteres of *N*-glycosyl asparagines [11a]. The key step in this synthesis was constituted of the Mukaiyama-type coupling of these aldehydes with the oxazolidine silyl enol ether **29** (Scheme 6). This new reagent was designed to serve as a homoalanine carbanion equivalent based on the oxidative cleavage (Jones reagent) of the oxazolidine ring to the  $\alpha$ -amino acid function (glycyl group) [33]. Scheme 6 illustrates the whole reaction sequence starting from Man-CHO **β-8** and leading to the  $\beta$ -*C*-mannosyl asparagine derivative **31**. The transformation of the initially formed *C*-glycoside (hydroxy ketone) **30** into the target product **31** was carried by the removal of the hydroxyl and carbonyl groups (Corey and Barton–McCombie deoxygenations) and cleavage of the oxazolidine ring (Jones oxidation). The same method was employed from the preparation of the  $\beta$ -Gal and  $\beta$ -Glc analogues of **31** starting from **β-6** and **β-7** respectively. The advantages associated with use of Gly-CHO can be appreciated when considering that the direct glycosylation of **29** by trichloroacetimidates of glucose and galactose in the presence of  $\text{BF}_3 \cdot \text{Et}_2\text{O}$  afforded the corresponding *C*-glycosides in relatively low yield (30%) [11a]. Nevertheless, this coupling reaction provided an entry to  $\alpha$ - and  $\beta$ -linked methylene isosteres of galactopyranosyl and glucopyranosyl serines.



**Scheme 6**

However, the Mukaiyama-based method shown in Scheme 6 was limited to the synthesis of  $\beta$ -linked *C*-glycosyl amino acids because most formyl *C*-glycosides were available as  $\beta$ -isomers. Consequently, we were spurred to search an alternative method that would provide either  $\alpha$ - or  $\beta$ -stereoisomers. To this aim, we envisaged the addition reaction of a suitable  $\alpha$ -amino acid equivalent to sugar acetylenes (ethynyl *C*-glycosides) since these compounds can be prepared as configurationally stable  $\alpha$ - and  $\beta$ -isomers. The method is illustrated by the synthesis of the  $\beta$ - and  $\alpha$ -linked sugar amino acids **37** and **38**, the isosteres of 2-acetamido  $\beta$ - and  $\alpha$ -D-galactopyranosyl asparagine (Scheme 7) [11h]. The key carbon–carbon bond forming reaction consisted of the addition of the metalated sugar acetylenes **32** and **33** to the protected D-serinal **34**. The resulting alkynyl *C*-glycosides **35** and **36** were

transformed into the target amino acids via reduction of the triple bond, removal of the hydroxy group, and unmasking of the glycyl group. Fair yields were registered under unoptimized reaction conditions. Preparative methods leading to artificial glycosyl amino acids featuring galactosamine, glucosamine, and mannosamine moieties are of special interest because of the widespread occurrence of these amino sugars in biologically active glycosides [4f,35]. Hence, the same procedure was extended to the preparation of GlcNAc and ManNAc derivatives. Also, the corresponding Gal, Glc, and Man derivatives were prepared through this approach.



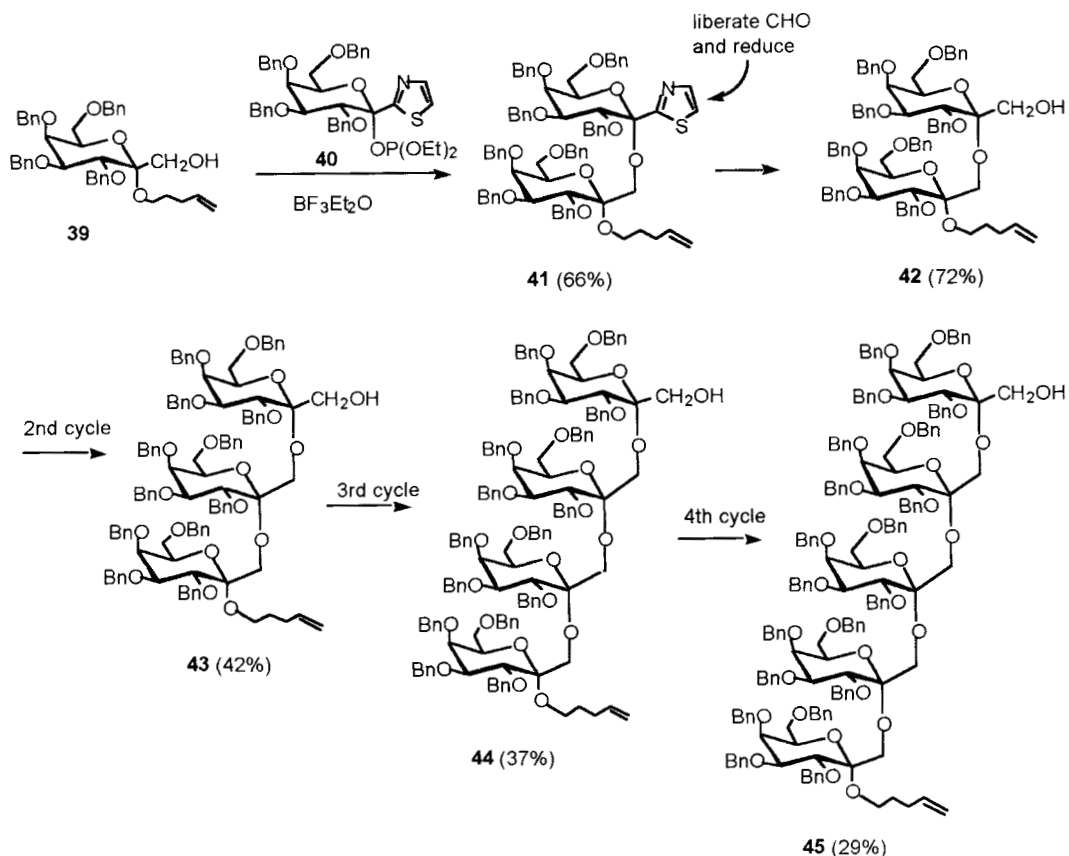
Scheme 7

## SYNTHESIS OF ACYCLIC AND CYCLIC KETOSYL OLIGOMERS

While it may be argued that other manipulatable groups (cyano, 2-furyl, 1,3-dithianyl, alkynyl) can be used in synthetic methods leading to formyl *C*-glycosides, the superior service of 2-thiazolyl becomes apparent in methodologies leading to elaborate glycosides featuring two substituents at the anomeric carbon atom. Thiazolyl ketose acetates (see, for example, compound **4** in Scheme 2), the intermediates in the formyl *C*-glycoside synthesis, turned out to serve as good ketosyl donors under Lewis acid activation in reactions with oxygen, carbon, nitrogen, and phosphorus nucleophiles [20]. This finding was quite unexpected when considering that thiazole is an electron-withdrawing heteroaromatic [19]. Hence, we suggested that the thiazole ring exerts an anchimeric assistance in the removal of the acetoxy group, thus favoring the formation of the sugar oxycarbenium ion, the activated species involved in the polar glycosidation reactions [36]. The resulting thiazolyl *O*-, *C*-, *N*-, and *P*-glycosides were transformed to various ketosyl and ulosonyl derivatives via the formyl group unmasking and the reduction to alcohol or oxidation to carboxylic acid. From these observations a stereoselective synthetic route evolved to linear and cyclic (2 → 1)-ketoside oligomers (Scheme 8) [37].

The method consisted of the installation of ketoside units in hydromethylketosides by iterative glycosylation using the thiazolylketose phosphite **40** as ketosyl donor. This reagent, as well as the initial ketosyl acceptor **39**, a *O*-pentenyl hydroxymethylketoside, was prepared by simple transformations of the thiazolyl ketose **3** shown in Scheme 2. Hence, the first cycle involved the coupling of these reagents and the transformation of the thiazolyl ketodisaccharide **41** to the new ketosyl acceptor **42**. This reaction sequence worked nicely (overall yield 48%) as the glycosidation step afforded the  $\alpha$ -ketoside **41** as a single stereoisomer and the cleavage of the thiazole ring was tolerated by the *O*-pentenyl group. These operations were repeated over three consecutive cycles to give the oligoketosaccharides **43**, **44**, and **45** containing three, four, and five galactopyranose units. Remarkable aspects of this methodology are the glycosidation of **40** with ketosyl donors of increasing size and complexity and the

thiazole-to-formyl unmasking in such systems. However, it has to be noted that the yield of the isolated oligomers decreased substantially from the first to the fourth cycle.

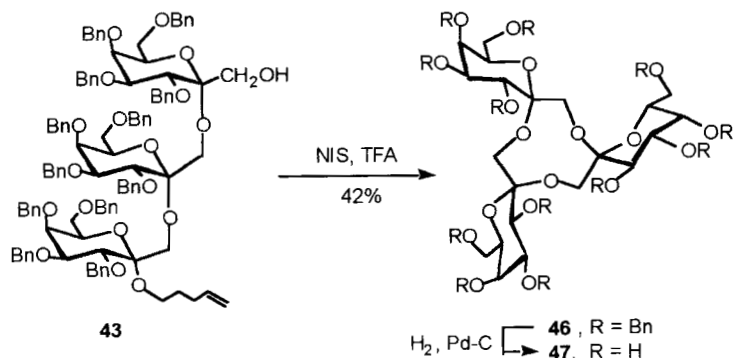


**Scheme 8**

The *O*-pentenyl group was deliberately introduced in the linear oligomers with the aim to obtain cyclic compounds via intramolecular glycosidation. Quite rewardingly, the cyclization of **42** and **43** to the corresponding products occurred readily under the Fraser–Reid glycosylation conditions using *N*-iodosuccinimide (NIS) and trifluoromethanesulfonic acid (TFA) as promoters [38]. On the other hand, the higher homologue **44** under the same conditions gave several products as judged from the MALDI-TOF mass spectrum of the crude reaction mixture. The products included fragments arising from the cleavage of the glycosidic bonds and various cyclic compounds. The structure of the cyclic ketotrisaccharide **46** (Scheme 9) was determined by X-ray crystallography that confirmed the three  $\alpha$ -glycosidic linkages. In addition, it showed that the oxygen atoms of the 1,4,7-trioxanonane ring (9-crown-3 ether) were lying on the same side of the average plane and the pyranose residues were spiroannellated in a propeller-like fashion around the crown ether skeleton. This arrangement created a flexible polyalkoxylated cavity that appeared to be suitable to host cations of various sizes including sodium, potassium, calcium, and magnesium. While compound **46** was only soluble in organic solvents, the hydroxy free ( $\alpha,\alpha,\alpha$ )-D-ketotrisaccharide **47** was water soluble. Natural products related to compound **47** are the so-



called cyclofructins, namely cyclic oligosaccharides constituted by (2 → 1)-linked fructofuranose units which are obtained by enzymatic degradation of inulin [39].



Scheme 9

## CONCLUSIONS

The thiazole-based formylation of sugars provided a scalable preparation of various formyl *C*-glycosides. These compounds have been used as starting materials for the construction of a variety of more elaborate *C*-glycosides via reactions of the formyl group. However, most formyl *C*-glycosides were available as a single stable stereoisomer. On the other hand, ethynyl *C*-glycosides can be prepared as  $\alpha$ - and  $\beta$ -linked pairs. These compounds served as excellent precursors to *C*-glycosyl amino acids, the building blocks in *C*-glycopeptide synthesis. Hence, sugar aldehydes and sugar acetylenes can be used as one- and two-carbon functionalized derivatives of sugars in complementary synthetic approaches to artificial *C*-oligosaccharides and *C*-glycoconjugates. Special attention should be paid to thiazolyketoses, the intermediates in the thiazole-based synthesis of formyl *C*-glycosides. Suitably activated thiazolyketoses proved to be versatile precursors to a broad array of ketosides and useful building blocks in an iterative methodology leading to linear and cyclic oligoketosides.

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23. Compound  **$\beta$ -11** shown in Fig. 2 was erroneously characterized as the  $\alpha$ -isomer in our original publication (ref. 11). The same error was repeated in a subsequent paper (ref. 10a). A revision of this uncorrect assignment will appear in a forthcoming paper.
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