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FEATURE ARTICLE

Thiazolylketoses: a new class of versatile intermediates for glycoside synthesis

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An account is provided on the very recent work carried out in the authors' laboratory dealing with the preparation of thiazolylketose acetates and their use as effective glycosyl donors in reactions with oxygen, carbon, nitrogen and phosphorus nucleophiles. These reagents are formed by addition of 2-lithiothiazole to sugar lactones followed by acetylation of the resulting thiazolylketoses. Coupling reactions, promoted by TMSOTf in CH_2Cl_2, are described with primary and secondary sugar alcohols, trimethylsilyl azide, triethyl phosphite and various *C*-nucleophiles. Suitable transformations of the resulting glycosides are carried out owing to the ready conversion of the thiazole ring into the formyl group followed by reduction to alcohol and/or oxidation to carboxylic acid. Thus, anomeric glycosyl amino acids, ketosyl and ulosonyl disaccharides and phosphonates have been prepared. Special applications include the synthesis of *O*-glycosyl calix[4]arene derivatives (calixsugars) and a cyclic ketotrisaccharide. The triethylsilane reduction of thiazolylketose acetates leads to thiazolyl *C*-glycosides that once subjected to the thiazole-to-formyl conversion afford formyl *C*-glycosides. These anomeric sugar aldehydes are convenient starting reagents for the synthesis of various *C*-glycosides and *C*-glycoconjugates, such as (1→6)-disaccharides and oligosaccharides, glycosyl aminoacids (glycine, serine, asparagine), and a galactocerebroside. Formyl *C*-glycosides participate in the azomethine ylide 1,3-dipolar cycloaddition reaction to C_{60} fullerene to give sugar fullerenes. The cover illustration shows some products of these reactions and a view of Palazzo dei Diamanti (Palace of Diamonds), a beautiful and unique building in the architectural context of Ferrara, constructed in the first half of 1500. The façade of the Palace is decorated with more than eight thousand five-hundred diamond shaped small blocks of marble.

Alessandro Dondoni has been Professor of Organic Chemistry at the University of Ferrara since 1975. His research interests include the design of new reagents and the development of stereoselective synthetic methods. Recent work has been focussed on the preparation of natural product-like compounds, particularly small peptide and glycoconjugate analogues. He started a new program on glycosylated calixarenes and calixarene-containing polymers. In 1999 he obtained the Avogadro–Minakata Lectureship Award of the Chemical Society of Japan and the Ziegler–Natta Lectureship Award of the German Chemical Society. In the same year he was awarded the Lincei National Academy prize in Chemistry sponsored by the Italian Minister of Cultural Heritage and Activities.

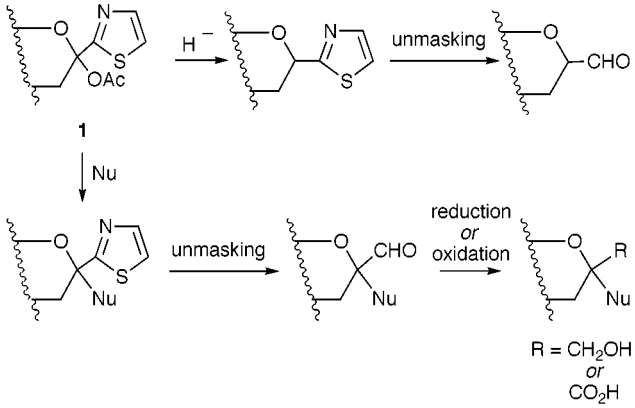
Alberto Marra graduated in Pharmaceutical Sciences from the University of Pisa in 1985 and obtained his PhD in Organic Chemistry from the University Paris VI in 1989 under the supervision of Professor P. Sinaÿ. He spent one more year in Paris at the Ecole Normale Supérieure as Associated Researcher of the French National Research Council. He was postdoctoral Research Associate at the University of Zurich with Professor A. Vasella (1991) and then moved to the University of Ferrara where he joined the group of Professor A. Dondoni. He was appointed to a lectureship in Organic Chemistry at the Faculty of Engineering from 1992 to 1998 and was promoted to the position of Associate Professor in 1998 at the same University. As in his early activities, his present research interest centres on carbohydrate chemistry. Recent work also deals with the synthesis and properties of calixarene derivatives.

Introduction

Carbohydrates, mainly in the form of oligosaccharides and glycoconjugates (glycoproteins and glycolipids), have been recognized in relatively recent years to play a vital role in fundamental biological functions such as cell-to-cell recognition and cell-to-external agents interactions.[1] These processes are manifested in living organisms by various phenomena, some of which are beneficial, such as fertilization and immune defence, some others are detrimental such as inflammation, viral and bacterial infections, cancer metastasis.[2] Problems still exist in determining the exact function at the molecular level of carbohydrate moieties in a given glycoconjugate. To explore these properties, glycobiology, the science dealing with the nature and role of carbohydrates in biological events,[1] is posing a pressing need for access to usable quantities of natural oligosaccharides and glycoconjugates in homogeneous and pure form. However the isolation and purification of these materials from natural sources are quite difficult and when possible provide the products in very low yields. The same need exists for unnatural analogues of oligosaccharides and glycoconjugates that may be used in structure–activity relationship (SAR) and drug development studies. Thus, organic synthesis constantly reinforced and rejuvenated by the design of new reagents and the invention of new methods[3] is providing a great contribution to the solution of these problems. Remarkable progress has been made in recent years in the field of natural oligosaccharide synthesis[4] both in solution and the solid phase as well as glycopeptide[5] and glycolipid synthesis.[6] To this end some monosaccharide building blocks have been conveniently exploited, among which glycals[7] and 1,6-anhydro sugars[8] have proved their importance. Nevertheless, innovations are still required in this area. On the other hand, the synthesis of carbon-linked sugars, *e.g.* disaccharide[9] and a few oligosaccharide[10] isosteres, has been reported in relatively recent years while the methods employed lack generality. The same situation exists for the synthesis of carbon-linked glycosyl amino acids[11] that may serve as building blocks for the preparation of modified glycopeptides. Hence substantial development of existing methods and invention of new approaches are needed in this area as well.

We report in this account on the preparation and use of a new class of sugar building blocks, namely thiazolylketoses, which

activated as *O*-acetyl derivatives **1** serve as efficient glycosyl donors toward various oxygen, carbon, nitrogen and phosphorous nucleophiles (Scheme 1). The thiazole ring of the resulting



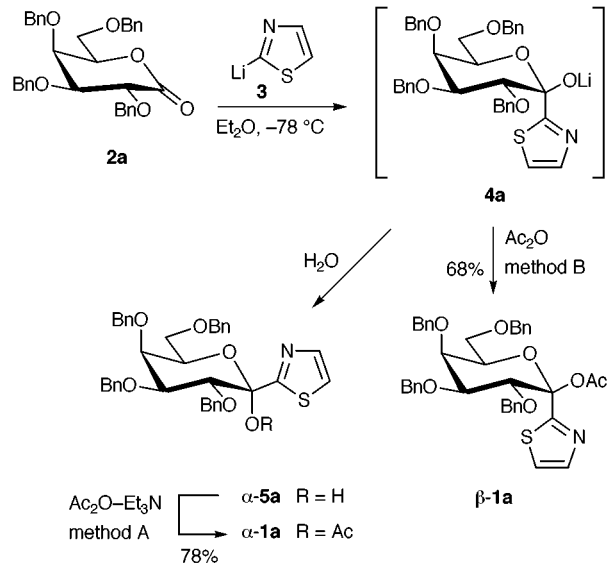
Scheme 1

coupling products is readily transformed into the formyl group that in turn is oxidized to carboxylic acid or reduced to alcohol. A special transformation of acetates **1** consists in their reduction and thiazole-to-formyl conversion, so called *unmasking*, to give formyl *C*-glycosides, a class of valuable intermediates for the synthesis of various and more complex *C*-glycosides.

Preparation of thiazolylketose acetates

Given the well documented service of thiazole as a formyl group equivalent in numerous synthetic methods,[12] the idea that was behind this programme was to install the thiazole ring at the anomeric carbon of sugars and take advantage of the above synthetic equivalence to reach synthetic targets otherwise difficult or impossible to access. While other manipulatable groups, such as cyano,[13] 2-furyl,[14] 1,3-dithianyl,[15] and alkynyl,[16] have been installed at the anomeric carbon of sugars and in some cases transformed into the formyl or carboxylate group, they can hardly compete with thiazole for combining high stability and ready conversion into the corresponding masked functionality under conditions which are tolerated by other protective groups and do not affect the configuration of stereocenters of the molecule. The thiazole-to-formyl protocol consists of a three-reaction sequence (*N*-methylation, reduction, metal-assisted hydrolysis), each step taking place under almost neutral and non-oxidative conditions.[12]

After several unsuccessful approaches of direct glycosylation of thiazole at C-2, the addition of 2-metallated thiazoles to sugar lactones turned out to be the method of choice in our programme.[17] It was not of secondary importance that both reagents can be easily prepared starting from inexpensive, commercially available materials and therefore the reactions can be carried out on a multigram scale. Typically, the reaction of 2,3,4,6-tetra-*O*-benzyl-D-galactonolactone **2a** with 2-lithiothiazole **3**, generated *in situ* from 2-bromothiazole and BuLi at −78 °C in Et_2O, followed by quenching with an aqueous pH 7 buffer produced the thiazolylketose α-**5a** that was isolated in 78% yield by chromatography (Scheme 2). Treatment of this ketose with Ac_2O–Et_3N at room temperature afforded the corresponding *O*-acetate α-**1a** in essentially quantitative yield (method A). On the other hand, quenching the crude reaction mixture at low temperature with Ac_2O, the ketose acetate anomer β-**1a** was obtained in 68% yield (method B). Thus, it appeared that the acetylation at low temperature allows the efficient trapping of the β-ketose **4a**, the product of kinetic selectivity arising from the addition of **3** to the less hindered face of the lactone **2a**. Evidently, the conversion of the β-ketose **4a** into the more stable α-anomer **5a** must occur quite rapidly at room temperature, being very likely controlled by the electronic effect of the ring oxygen (anomeric effect).



Scheme 2

The above reaction scheme was expanded to various pyrano- as well as furano-lactones. In all cases the addition of **3** to the chosen lactone proceeded smoothly to give the thiazolylketose **5** in the hemiketalic form with only occasionally the presence of the open-chain isomer. The corresponding thiazolylketose acetates **1b**–**g** were prepared as either α- or β-anomers depending on the quenching method A or B (Fig. 1). The yields

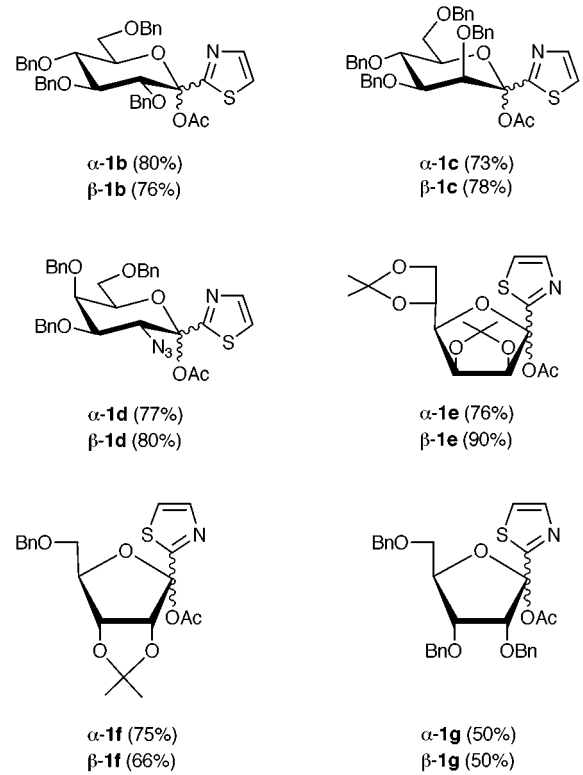
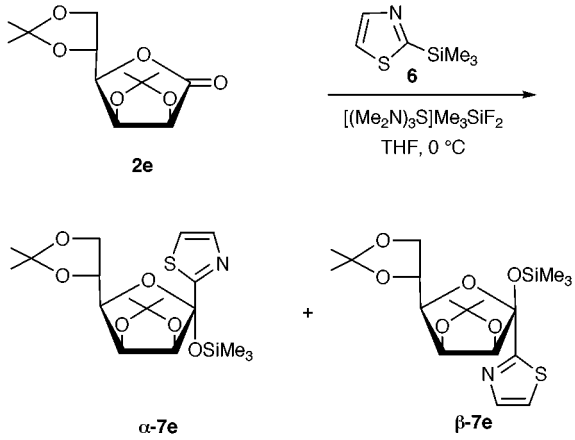


Fig. 1

of isolated products were consistently close to those quoted in Scheme 2. Noteworthy among the compounds prepared is the 2-azidogalactose derivative **1d** since this compound can be the precursor of galactosamine derivatives of biological relevance.[18]

Instead of 2-lithiothiazole **3** generated *in situ* at low temperature, 2-trimethylsilylthiazole (2-TST) **6** can be employed as a stable thiazol-2-yl carbanion equivalent in addition reactions to sugar lactones (Scheme 3). We observed that **6** in the presence of equimolar tris(dimethylamino)sulfonium di-



Scheme 3

fluorotrimethylsilicate (TASF) reacts readily with the D-mannonofuranolactone diacetonide **2e** to give the trimethylsilyl thiazolylketoside **7e** as a mixture of α- and β-anomers in 4.5 : 1 ratio and 92% overall yield.[19] Thus, unlike the spontaneous reactions of 2-TST **6** with other carbon electrophiles (aldehydes, ketones, acyl chlorides),[12] this reaction requires the activation of **6** by a fluoride ion releasing promoter. Although the silylated thiazolylketose **7e** can eventually be converted into the acetate **1e** by desilylation and acetylation, the method does not appear to offer substantial advantages over that employing 2-lithiothiazole **3** since it requires more steps and the use of TASF, an expensive and difficult to handle reagent. In fact, other fluoride ion releasing promoters (Bu_4NF, CsF) proved to be much less efficient in this reaction since the thiazolylketose **5e** was recovered in *ca*. 10% yield together with unreacted **2e**.

Why activation of thiazolylketoses as *O*-acetates?

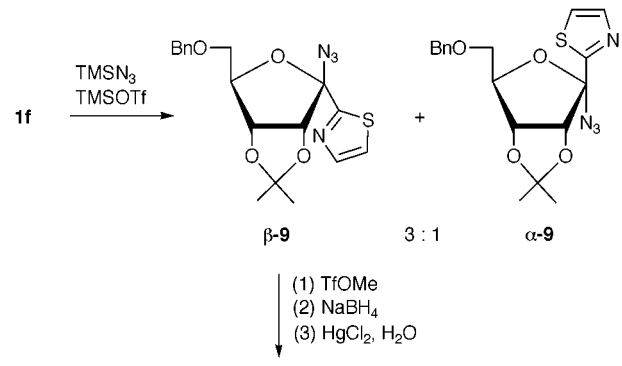
Rather soon at the outset of this research we realized that the thiazolylketose **5a** and the other analogues could hardly be used as glycosyl donors. Efficient ketosyl donors, such as those bearing an electron-rich substituent at the anomeric centre, are known to be very reactive under Lewis acid catalysis at low temperature. For example glycosidation[20] and anomeric deoxygenation[14f,h] of furylketoses occur rapidly under these conditions. On the other hand we failed to reduce various pyrano- and furano-ketoses **5** either under radical or polar conditions.[17] Very likely the electron-poor character of the thiazole ring and interaction with the catalyst through the basic nitrogen atom cause the unsuccessful reactions. Thus, the activation of thiazolylketoses **5** by conversion of the hydroxy group into a better leaving group appeared to be a prerequisite for the use of these compounds as glycosyl donors. The conversion into *O*-acetates **1** turned out to be a winning move since these compounds are easy and inexpensive to prepare, are stable to storage, and nevertheless sufficiently reactive under polar glycosylation conditions. Finally, although their reactions occur at room temperature, the stereoselectivity ranged from good to excellent levels based on high yield of isolated products. Some reactions are illustrated below in support to these anticipated results.

N-Glycosidation and formal synthesis of (+)-hydantocidin

The first test on the ability of thiazolylketose acetates **1** to serve as glycosyl donors (Scheme 1) was carried out with trimethylsilyl azide ($TMSN_3$) as nitrogen nucleophile.[21] Equally important for synthetic purposes, was proving the compatibility of various functional group manipulations, particularly the cleavage of the thiazole ring adjacent to the quite reactive azido group. The synthesis of the peculiar α-azido aldehyde **8** sharing its central carbon atom with the D-ribofuranose ring constituted an interesting target in the above context. The importance of **8** relies on its being an advanced intermediate[22] for the synthesis of the herbicide and plant growth regulator (+)-hydantocidin, a natural product produced by fermentation processes[23] (Scheme 4).

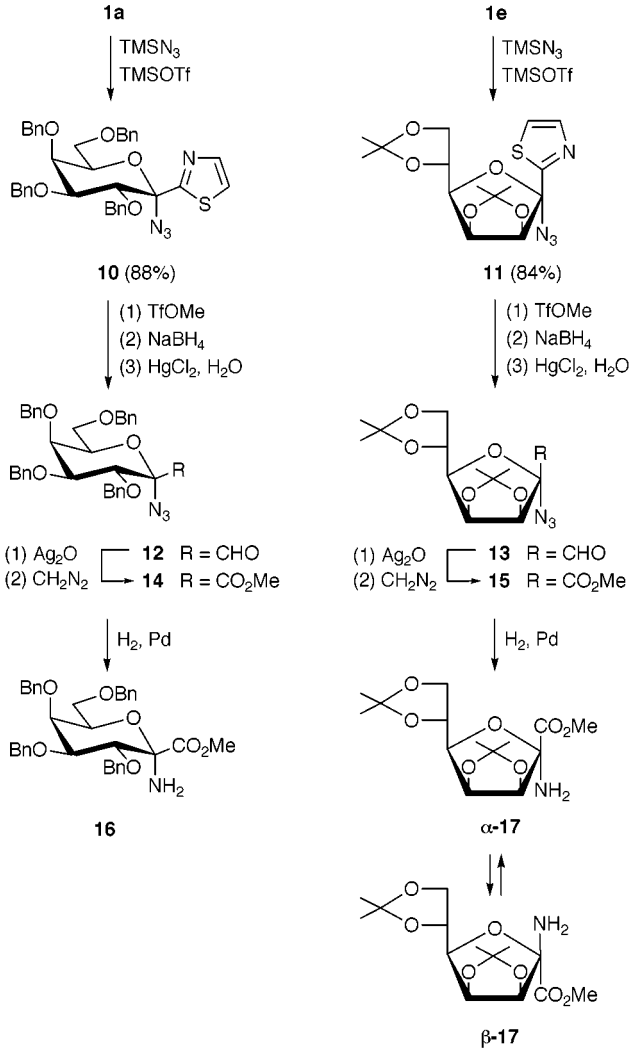
Scheme 4

Either α- or β-anomer of thiazolyl-D-ribofuranose acetate **1f** proved to be an excellent glycosyl donor toward $TMSN_3$ upon activation by trimethylsilyl triflate (TMSOTf) in CH_2Cl_2 at room temperature.[21] In both cases, the reaction afforded the same mixture of α- and β-azido glycosides **9** in 1 : 3 ratio and 84% overall yield (Scheme 5). After separation and identification of the major stereoisomer β-**9**, the conversion to the azido aldehyde **8** was carried out with satisfactory yield (57%) by suitable adjustments of the standard thiazole-to-aldehyde procedure to avoid cycloaddition side-reactions between the *N*-methylthiazolium ring, an intermediate of the unmasking protocol, and the adjacent azido group acting as a 1,3-dipolar partner. The conversion of **8** into the anomeric spirohydantoin of D-ribose featured by (+)-hydantocidin was reported earlier by Mio and co-workers.[22]



Scheme 5

A better evaluation of the scope of the *N*-glycosidation reaction was obtained starting from the D-galactoketopyranose acetate **1a** and the D-mannoketofuranose acetate **1e**. The *N*-glycosidation of these compounds with $TMSN_3$ under the above conditions occurred with high α-selectivity to give exclusively the anomeric azido sugars **10** and **11** in gratifying 88 and 84% isolated yields (Scheme 6). This stereochemical outcome is that expected on the basis of a glycosidation reaction scheme proceeding through a sugar oxycarbenium ion intermediate undergoing a sterically controlled nucleophilic addition (Fig. 2). Evidently, this stereochemical control was much weaker in the case of the D-riboketofuranose **1f** due to the intrinsic configuration of this sugar and consequently the azide **9** was formed as a mixture of α- and β-anomers (Scheme 5). Taking advantage of the modified conditions of the thiazole-to-formyl protocol developed for the conversion of **9** to **8**, compounds **10** and **11** were transformed into the azido aldehydes **12** and **13** without any problem. At this stage, a further elaboration was carried out as a confirmation of the synthetic value of the thiazole sugars **1**. Crude aldehydes **12** and **13** were oxidized to the azido esters **14** and **15** that in turn were transformed into the sugar aminoesters



Scheme 6

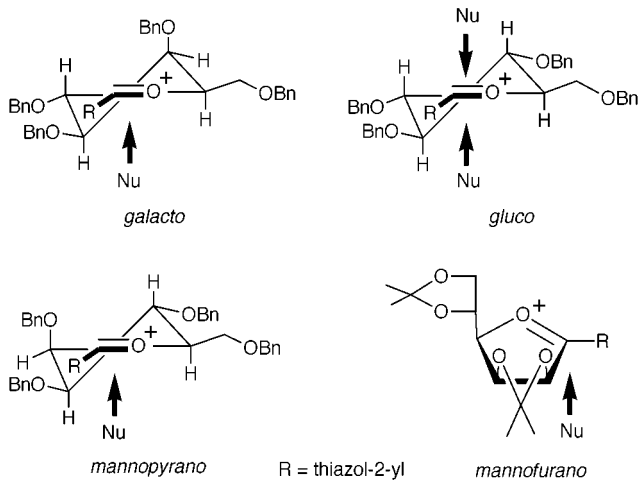


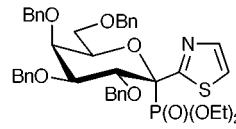
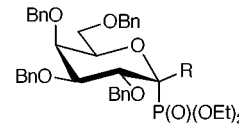
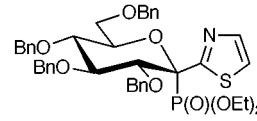
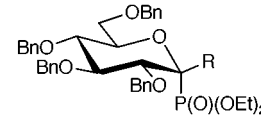
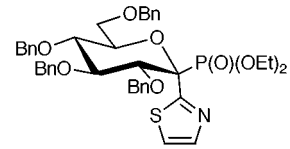
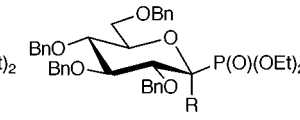
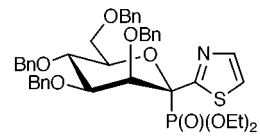
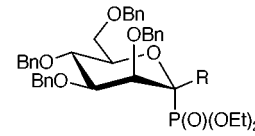
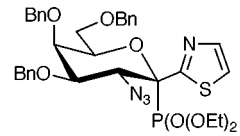
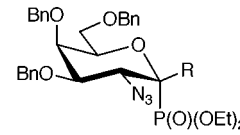
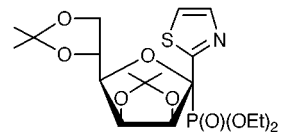
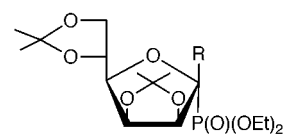
Fig. 2

16 and **17** by selective reduction of the azido group by Pd-catalyzed hydrogenation. Compounds **16** and **17** are representative of a new class of unnatural glycosyl amino acids which can be considered as anomeric sugar glycines wherein the central carbon atom of the amino acid coincides with C-1 of the sugar moiety.

P-Glycosidation by Arbuzov-type reaction

Triethyl phosphite was the model phosphorus nucleophile employed in this study. It underwent α-selective glycosylation reaction by various thiazolylketose acetates **1** in an Arbuzov-type coupling reaction carried out in CH_2Cl_2 at room temperature[24] to give exclusively glycosyl phosphonates **18** as α-D-anomers in high isolated yields (Table 1). As an exception, the

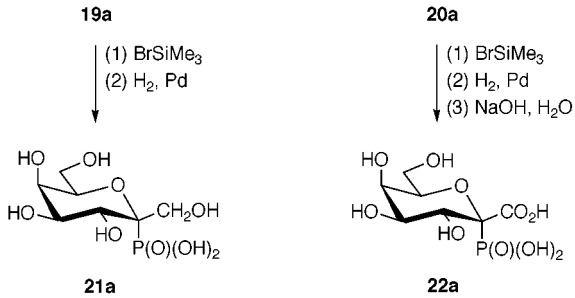
Table 1 *P*-Glycosidation of thiazolyketose acetates **1** with $P(OEt)_3$ (TMSOTf, CH_2Cl_2, room temperature)

Acetate **1**	Phosphonate **18**	Phosphonates **19** and **20**
1a	 **18a** (84%)	 **19a** R = CH_2OH (61%) **20a** R = CO_2Me (62%)
1b	 **α-18b** (52%)	 **α-19b** R = CH_2OH (58%) **α-20b** R = CO_2Me (62%)
1b	 **β-18b** (35%)	 **β-19b** R = CH_2OH (56%) **β-20b** R = CO_2Me (59%)
1c	 **18c** (88%)	 **19c** R = CH_2OH (50%) **20c** R = CO_2Me (51%)
1d	 **18d** (78%)	 **19d** R = CH_2OH (57%) **20d** R = CO_2Me (59%)
1e	 **18e** (93%)	 **19e** R = CH_2OH (56%) **20e** R = CO_2Me (54%)

gluco derivative **18b** although isolated in excellent yield was composed of a mixture of α- and β-anomers in 3:2 ratio. Thus, also in this case the stereochemistry of the glycosidation reaction appears to be controlled by steric factors emerging in the sugar oxycarbenium ion intermediate. The lack of selectivity of the D-glucoketopyranose acetate **1b** is not surprising in view of the small steric difference around the two diastereotopic faces of the corresponding oxycarbenium ion (Fig. 2).

There is current interest in the synthesis of glycosylphosphonate analogues[25] of aldose 1-phosphates, the biological glycosyl donors,[26] because the unnatural *P*-glycosides can act as

inhibitors of carbohydrate processing enzymes and therefore can serve as lead structures in drug discovery against carbohydrate-based metabolic disorders.[2b] Having easy access to thiazolylglycosylphosphonates **18** we were in a position to prepare isopolar glycosylphosphonate analogues of ketose and ulosonic acid 2-phosphates. Accordingly, phosphonates **18a**–**e** were converted into the corresponding aldehydes by the standard thiazole-to-formyl protocol[27] and each product was both reduced to the alcohol **19** (ketosylphosphonate) and oxidized to carboxylic acid **20** (ulosonylphosphonate) (Table 1). Finally, in order to demonstrate a viable route to fully deprotected phosphonic acids, the alcohol and acid protective groups of phosphonates **19a** and **20a** were removed to give the free ketosyl and ulosonyl phosphonic acids **21a** and **22a**, respectively (Scheme 7). It is worth mentioning that the assignment of the anomeric configuration of phosphonates of the *mannopyrano* and *mannofurano* series was carried out by hitherto unreported heteronuclear NOE experiments consisting of the irradiation of the phosphorus nucleus instead of the adjacent protons.[24] In closing this section, it has to be pointed out that phosphonates **19** and **20** represent two new classes of *P*-glycosides. A single example of a ketosylphosphonate was previously reported, *i.e.* the isopolar monophosphonate analogue of β-D-fructose 2,6-bisphosphate prepared in the Vasella laboratory some years ago.[28]

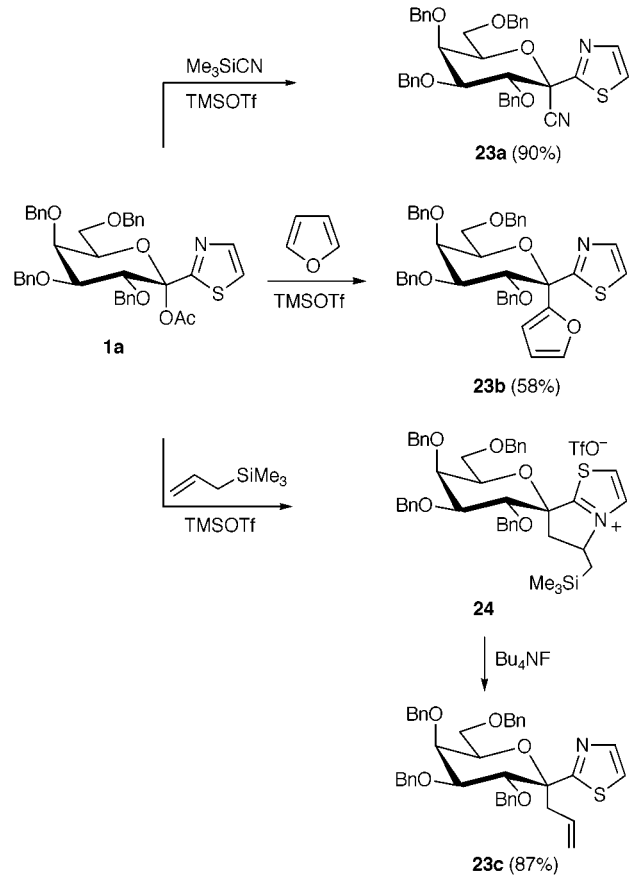


Scheme 7

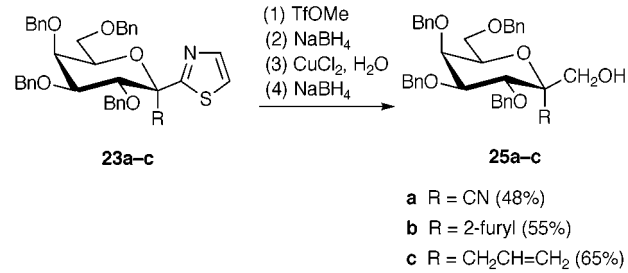
C-Glycosidation and synthesis of a *C*-ketodisaccharide

A positive response on the synthetic utility of thiazolylketose acetates **1** as glycosyl donors came also from their reactions with carbon nucleophiles. The multigram scale coupling of **1a** with trimethylsilyl cyanide (TMSCN), furan and allyltrimethylsilane under the usual mild conditions (TMSOTf, CH_2Cl_2, room temperature) afforded exclusively the corresponding α-D-linked *C*-glycosides **23a**–**c** in good yields (Scheme 8).[29] The allyl derivative **23c** was obtained upon desilylation (Bu_4NF) of the initially formed thiazolium salt **24**. Intuitively, this compound should be formed *via* intramolecular alkylation of the thiazole ring by the anomeric propyl cation intermediate generated in the first step of the *C*-glycosylation reaction. As a further demonstration of the key service of thiazole, the heterocycle of compounds **23a**–**c** was transformed into the formyl group and the resulting crude aldehydes were reduced to give the *C*-ketosides **25a**–**c** (Scheme 9).

Unlike alkyl and aryl *C*-aldosides,[30] *C*-ketosides have been described in only a few instances.[16g,31] The problem of the control of the stereochemistry at the anomeric centre becomes even more difficult in these cases. With the allyl *C*-thiazolylgalactoside **23c** in hand, we sought a rapid entry to the β-D-(1→6)-*C*-ketodisaccharide **30** (Scheme 10), *i.e.* the galactose counterpart of the *C*-Glu-β-D-(1→6)-Glu recently prepared in the Schmidt laboratory starting from the protected D-gluconolactone.[32] Thus, in three successive steps the double bond of the allyl chain of **23c** was hydroxylated, the diol protected as an acetonide, and the thiazole ring transformed into the formyl



Scheme 8

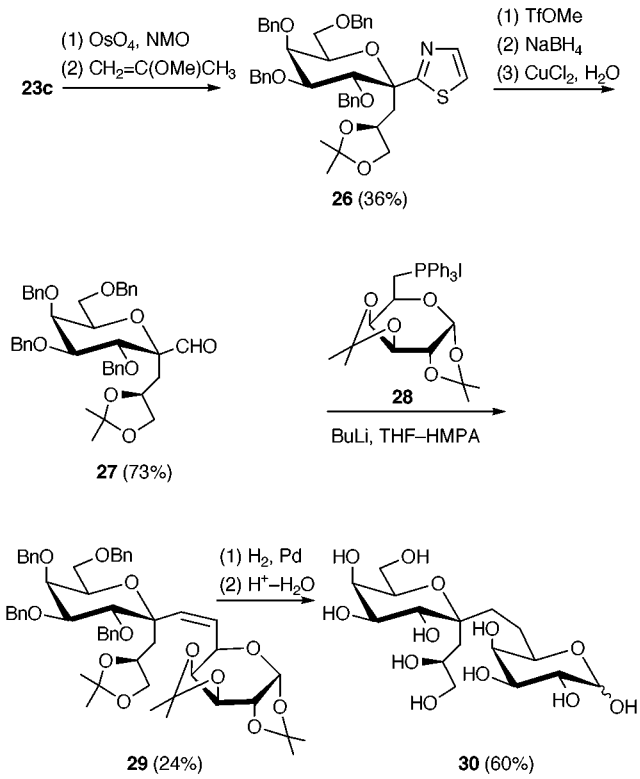


Scheme 9

group. Then the olefination of the aldosulose **27** with the ylide generated from the phosphonium salt **28** gave the olefin **29** as a single *Z*-isomer although in rather low yield (24%). Nevertheless this compound was transformed into the deprotected target product **30** by reduction of the double bond and removal of all hydroxy protective groups.[29] It has been suggested[32] that *C*-ketodisaccharides like **30** can be employed for the synthesis of inhibitors of carbohydrate processing enzymes.

O-Glycosidation with sugar alcohols

At this stage the challenge lay in demonstrating that ketose acetates **1** were suitable glycosyl donors toward more complex nucleophiles such as primary and secondary sugar alcohols. While the *O*-glycosidation of aldoses is routine owing to the numerous efficient methods developed in the last two decades or so,[4] the same reaction with ketoses has been much less exploited. Recent methods have been described involving the use of a phosphite activated fructofuranose[33] and variously activated ketopyranoses.[34] Danishefsky in early syntheses of ulosonic acids[20a] employed furylketoses as glycosyl donors since the furan ring is an electron-rich heterocycle that favours

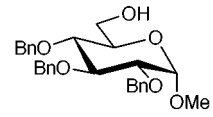
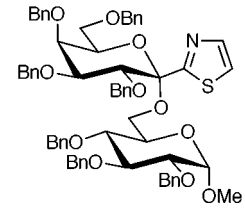
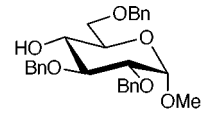
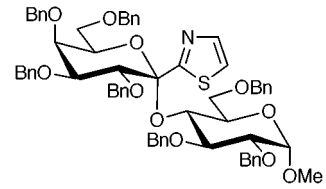
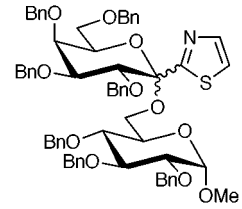
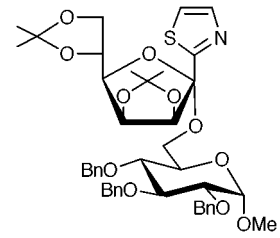
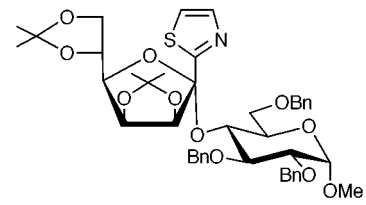


Scheme 10

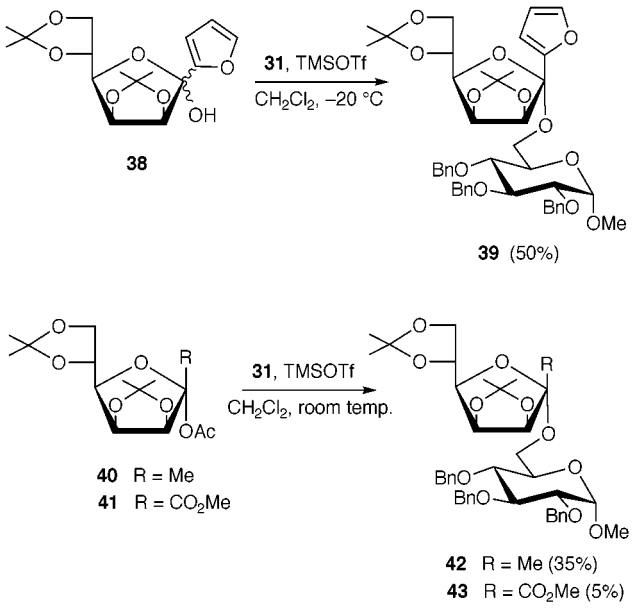
the glycosidation reaction and at the same time serves as a masked carboxylate group. Thus it was quite rewarding to find that despite the electron-poor character of thiazole, either α- or β-anomers of the *galactopyrano*, *glucopyrano* and *mannofuranno* thiazolylketose acetates **1a**, **1b**, and **1e** reacted under the usual conditions (TMSOTf, CH_2Cl_2, room temperature) with methyl 2,3,4-tri-*O*-benzyl- and 2,3,6-tri-*O*-benzyl-α-D-glucopyranoside acceptors **31** and **32** to give the corresponding thiazolylketodisaccharides **33a**-**37e** in fairly good isolated yields[20b] (Table 2). The α-D selectivity was the rule for the reactions of **1a** and **1e**, whereas the gluco derivative **1b** gave α- and β-D-linked disaccharides **35b** in nearly equal amounts. It was proved that the use of the participating solvent acetonitrile does not affect the above stereochemical outcome. These results are in agreement with the transition state models outlined in Fig. 2. The glycosidation of **1e** with the primary sugar alcohol **31** was compared with the reaction of other mannoketofuranosyl donors with the same alcohol (Scheme 11). As expected, the inactivated furylketose **38** reacted more readily than **1e** to give at low temperature the ketodisaccharide **39** in satisfactory yield. On the other hand the glycosidations of the methylketose acetate **40** and methylulosonate acetate **41** were less efficient as judged from the lower yield of isolated ketosyl disaccharide **42** and the almost complete lack of formation of the ulosonyl disaccharide **43.** The role of thiazole on the reactivity of thiazolylketose acetates **1** as glycosyl donors is open to conjecture. It was suggested[20b] that the heterocyclic ring exerts an anchimeric effect as shown in **A** that assists the acetoxy group removal induced by the Lewis acid E and therefore favours the formation of the oxycarbenium ion intermediate **B** (Scheme 12).

It appeared important in the above context to demonstrate the convenient use of thiazolylketoses for the preparation of disaccharides that are otherwise difficult to access. Compound **43** as well as ulosonyl disaccharides in general represent one of those categories of compounds. Thus, the thiazolyl ketodisaccharide **37e** was subjected to the usual thiazole-to-formyl deblocking protocol and the resulting crude aldosulose **44** was both reduced to the ketose **45** and oxidized to the ulosonate **43** in good overall yields (Scheme 13). The same procedure was applied to the other disaccharides of Table 2 to afford similar results.

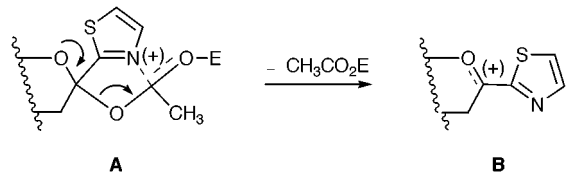
Table 2 *O*-Glycosidation of thiazolyketose acetates **1** with sugar alcohols **31** and **32** (TMSOTf, CH_2Cl_2, room temperature)

Acetate **1**	Alcohol **31** or **32**	Ketodisaccharides **33**–**37**
1a	 **31**	 **33a** (73%)
1a	 **32**	 **34a** (60%)
1b	**31**	 **α-35b** (38%) **β-35b** (25%)
1e	**31**	 **36e** (70%)
1e	**32**	 **37e** (62%)

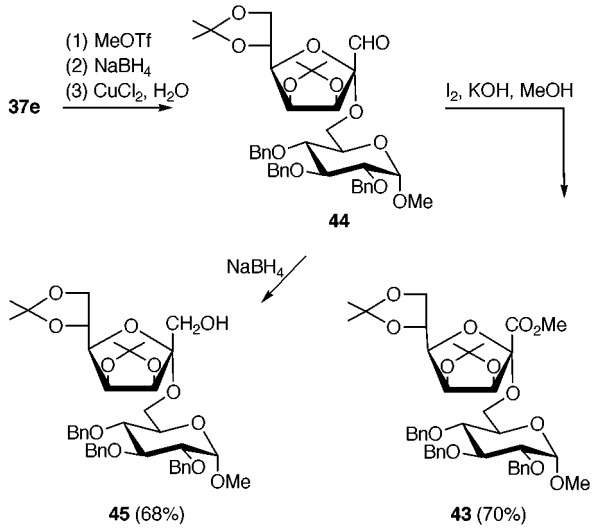
In closing this section a short comment is worth notice with regard to the use of the furyl instead of the thiazolyl group in this synthetic methodology. For example the readily available furylketodisaccharide **39** shown in Scheme 11 is in principle a precursor of the ulosonyl disaccharide **43** *via* the oxidative cleavage of the furan ring to carboxylic acid.[35] In a similar way other ulosonyl disaccharides should be accessible starting from the furyl analogues of compounds **33a**–**37e** of Table 2. However, the strong oxidizing reagents, such as RuO_4 or O_3, that are employed for the unmasking of the carboxylate function from the furan ring impose some caution on the use of this approach since harsh oxidative conditions are likely to be incompatible with various functional and protective groups such as the benzyl group.[36]



Scheme 11



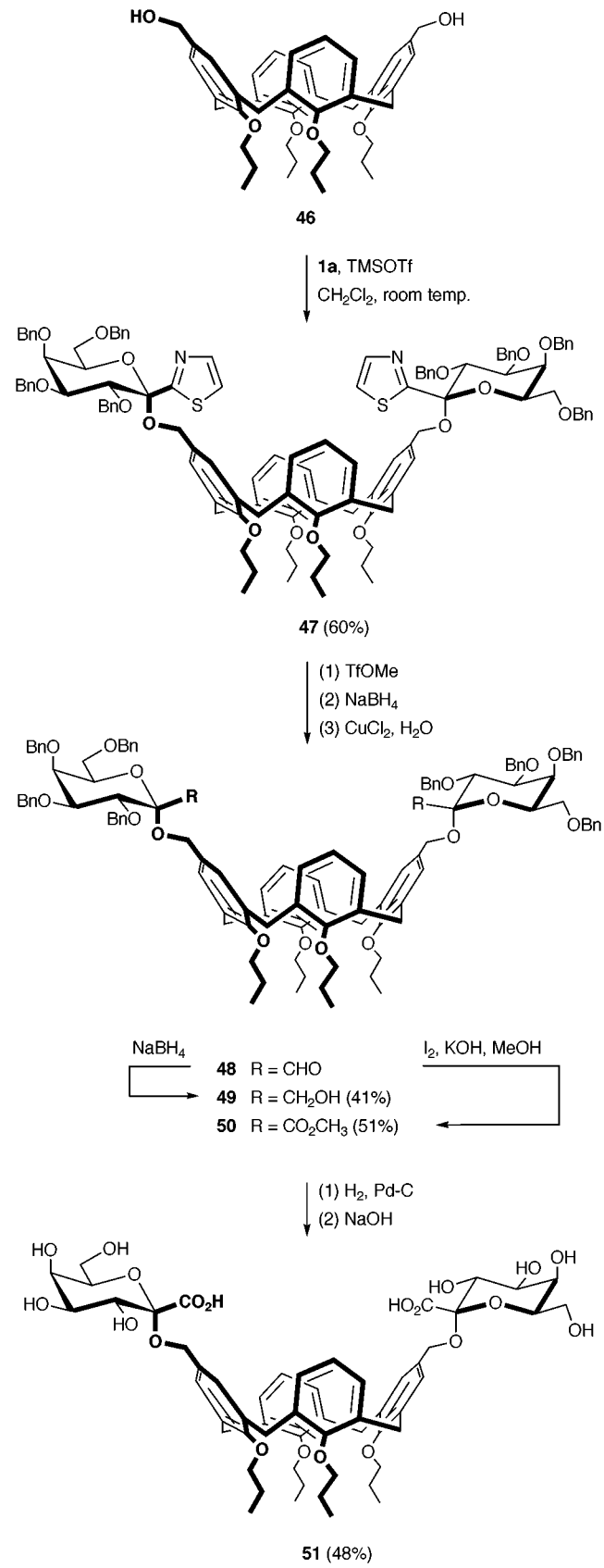
Scheme 12



Scheme 13

O-Glycosidation with calix[4]arene alcohols

The rather special glycosylation of primary alcohols attached to one rim of the quite popular macrocyclic phenol-formaldehyde oligomers called calixarenes,[37] belongs to a research programme in our laboratory aiming at the construction of well organized chiral polar domains anchored to a rigid scaffold.[38] The idea behind this project is to use these potentially water soluble systems, named calixsugars, as selective receptors of chiral highly polar organic molecules. Applications in biological systems can also be foreseen as multivalent ligands and inhibitors.[39] Initial work was centred on the *O*-glycosylation of calix[4]arene derived diols and tetrols with aldoses.[38a,b] Then, the coupling of these polyols with thiazolylketose acetates **1** provided the opportunity of a multiple installation of ketosyl and ulosonyl groups.[40] A complete reaction sequence is illustrated in Scheme 14. The reaction of the D-*galacto*



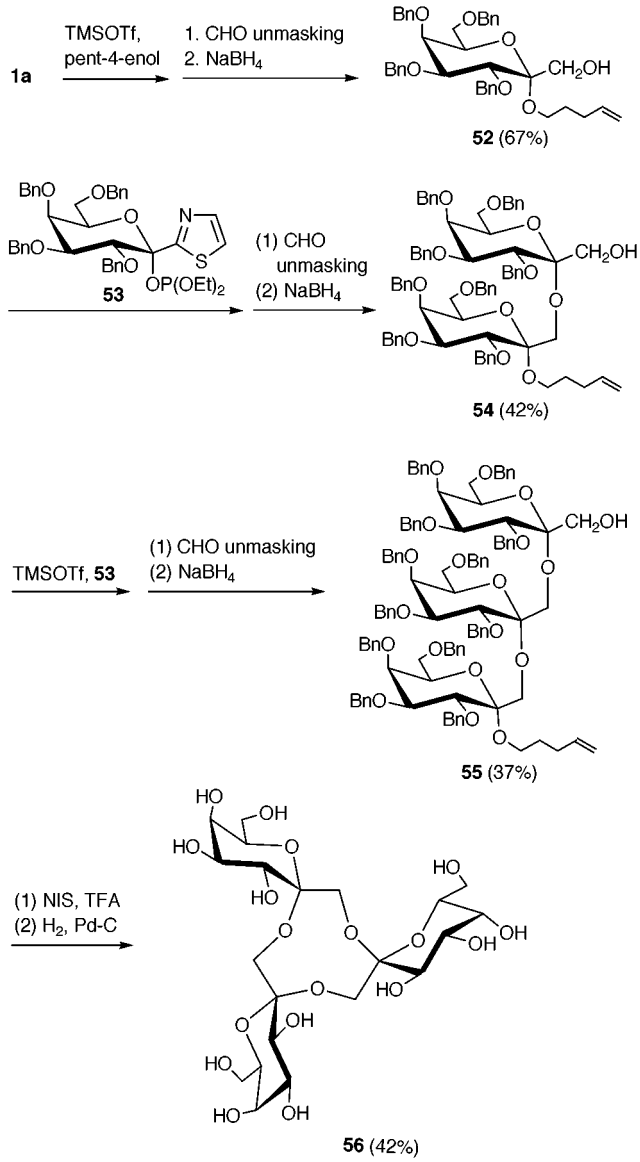
Scheme 14

derivative **1a** with the symmetrical calixarene diol **46** under the usual TMSOTf promoted conditions (CH_2Cl_2, room temperature) afforded the bis-*O*-ketosyl calixarene derivative **47** in good isolated yield. It was firmly established by NMR analysis

that both ketosyl moieties were linked with an α-D (axial) orientation and that the calixarene system retained the cone conformation as in the initial compound **46**. Application of the reaction conditions illustrated in Scheme 13 for the elaboration of **37e** transformed the product **47** into the dialdehyde **48**, which in turn was either reduced to the diol **49** or oxidized to the diester **50**. Finally debenzylation and saponification of **50** afforded the protective group free calixsugar **51** featuring two heptulosonic acid moieties at the upper rim. Compound **51** represents the first member of a class of calixsugars bearing charged functional groups at C-1 of the sugar moieties.

Iterative *O*-glycosidation and synthesis of a cyclic ketotrisaccharide

Having demonstrated the feasibility of the ketodisaccharide synthesis under the thiazolylketose paradigm, we wondered whether the method could be extended to the synthesis of higher oligomers by iterative glycosylation and thiazole cleavage. The orthogonally activated thiazolylketose phosphite **53**, obtained from the thiazolylketose **5a**, and the pentenyl hydroxymethylketoside **52** were used in the stepwise assembly of 2→1-ketoside units to give linear and cyclic D-*galacto*-2-heptulopyranose oligomers[41] (Scheme 15). The first chain-elongation cycle

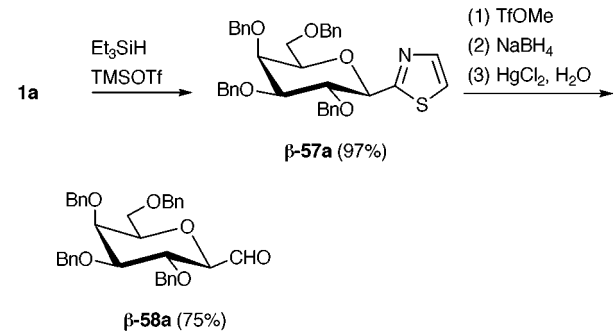


Scheme 15

consisted of the TMSOTf promoted coupling between **53** acting as the glycosyl donor and **52** acting as the acceptor followed by the aldehyde liberation from thiazole and reduction to alcohol. This reaction sequence afforded the ketodisaccharide **54** that in turn was used as the acceptor in a second cycle to give the ketotrisaccharide **55** in satisfactory overall yields. Although there were no apparent indications that we reached the limit of the application of the linear iterative process, the intramolecular cyclization in **55** was demonstrated to occur readily under the Fraser-Reid glycosylation conditions using *N*-iodosuccinimide and trifluoromethanesulfonic acid as promoters.[42] Exhaustive debenzylation of the resulting product afforded the hydroxy group free and water soluble cyclic (α,α,α)-D-ketotrisaccharide **56**. There are no precedents for natural or synthetic cyclic oligosaccharides[4c] similar to compound **56** featuring pyranose units arranged in a spiro fashion around a crown ether skeleton. Related products are the so-called cyclofructins, namely cyclic oligosaccharides constituted by (2→1)-linked fructofuranose units, which are obtained by enzymatic degradation of inulin.[43] Compound **56** can be considered a special type of carbohydrate-based crown ether, *i.e.* a 1,4,7-trioxacyclononane carrying three pyranose rings whose anomeric carbon atoms are part of the methylene bridges. Also from this perspective, no examples can be found in the literature.[44] As a crown-ether, perbenzylated **56** exhibited a remarkable complexing ability in organic solvents toward various ions including calcium and magnesium.

Reduction of thiazolylketose acetates

While the removal of the hydroxy group of the ketose α-**5a** was unsuccessful under various conditions,[17] the corresponding acetates α-**1a** and β-**1a** were readily reduced upon treatment with excess triethylsilane in the presence of TMSOTf as described in the above glycosidation reactions (Scheme 16).



Scheme 16

Under optimized conditions the reaction afforded the β-linked thiazolyl *C*-glycoside β-**57a** in very good isolated yield (97%). This compound was transformed into the corresponding aldehyde β-**58a** that constituted the final target of the whole procedure. The same reaction sequence was employed for the preparation of various α- and β-D-linked formyl *C*-glycosides **58** (Fig. 3) starting from the ketose acetates **1** shown in Fig. 1. Most acetates **1** (*galactopyrano*, *mannopyrano*, *mannofurano*) were reduced with very high levels of diastereoselectivity to give essentially the β-anomer *C*-glycoside **57** according to the transition state models shown in Fig. 2. Thus, in all these cases only the β-linked aldehydes **58c**–**e** were obtained. As expected, the reduction of glucopyranosylketose acetate α-**1b** or β-**1b** was unselective as it afforded a mixture of α- and β-linked *C*-thiazolyl glycosides in a 1:1 ratio. In this case, both α- and β-formyl *C*-glucopyranosides **58b** were prepared. However in a more recent work[45] we observed that the SmI_2 promoted deoxygenation of ketose acetates **1** occurs with opposite diastereoselectivity to that obtained by the use of Et_3SiH–TMSOTf. A remarkable example is the reduction of the *mannofurano* derivative α-**1e** in which the inversion of selectivity is almost complete[9a] (Scheme 17). Therefore both α- and β-linked aldehydes **58e** were prepared with good efficiency

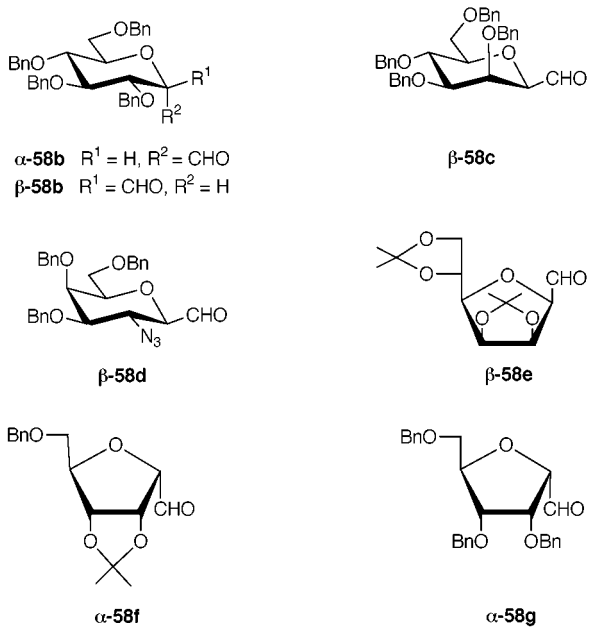
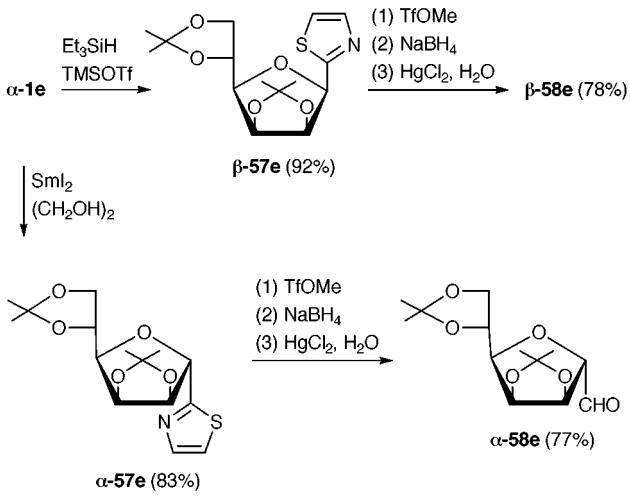


Fig. 3



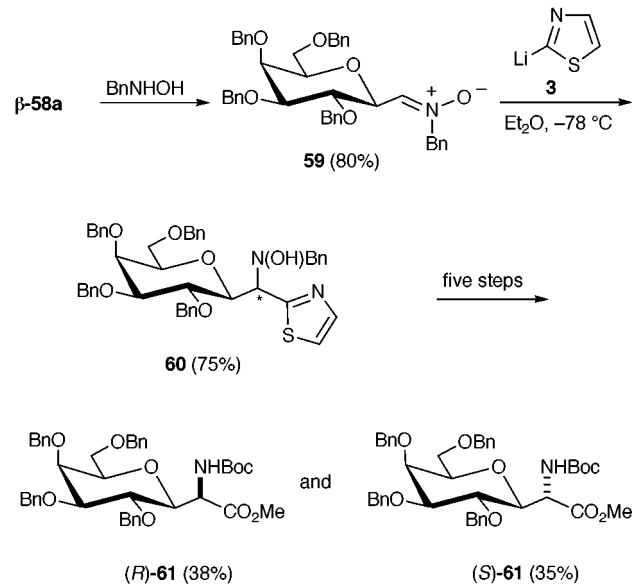
Scheme 17

starting from the same thiazolylketose acetate α-**1e**. Unfortunately the tunable stereoselective reduction was much less efficient with other acetates **1**.

Since the installation of the formyl group at the anomeric carbon of carbohydrates is far from being a trivial problem, other synthetic methods have been reported which use various formyl group equivalents.[10a,15,16e,16j,46] However the application of these methods has often been limited to the synthesis of one or two compounds. On the other hand the efficiency and wide scope of the above thiazole-based method is substantiated by the preparation of a variety of glycopyranosyl and glycofuranosyl aldehydes **58**. The service of the thiazole ring as a formyl group equivalent appeared to have been especially highlighted in this synthetic methodology!

Synthetic applications of formyl *C*-glycosides

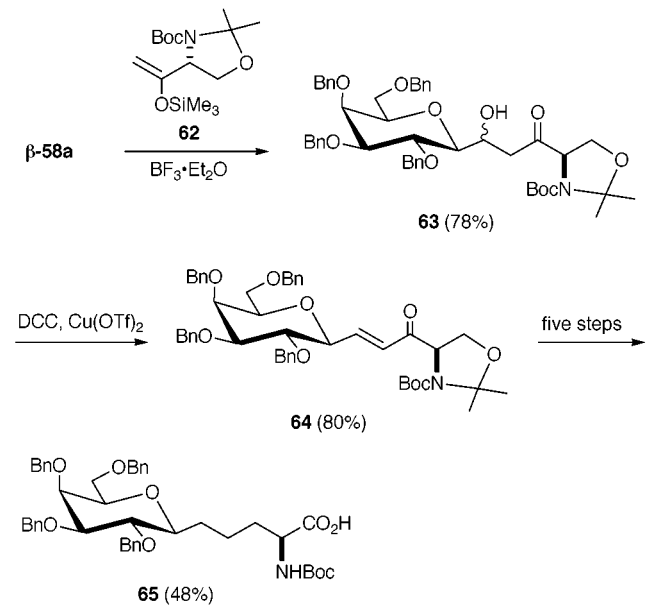
The highly reactive formyl group of sugar aldehydes **58** makes these compounds attractive building blocks in synthetic endeavours to more complex *C*-glycosides. The axial (α-D) or equatorial (β-D) orientation of this substituent already *in situ* on the sugar moiety overcomes the problem associated with the control of the stereochemistry of the *C*-glycosidation reaction. The programme was inaugurated with the synthesis of *C*-glycosyl α-amino acids[20c] by application of a nitrone based aminohomologation technique of aldehydes developed in our group.[12,47] The method is succinctly illustrated in Scheme 18 wherein the key step is the addition of 2-lithiothiazole **3** to the



Scheme 18

nitrone **59** generated from the aldehyde β-**58a**. This reaction afforded the *N*-benzyl hydroxylamine **60** in satisfactory yield (75%) but as a mixture of epimers in *ca*. 3:1 ratio. Suitable elaboration of **60** including reductive *N*-dehydroxylation by $TiCl_3$ and transformation of the thiazole ring into the carboxylate group, afforded the (*R*)- and (*S*)-epimer α-amino ester **61** (*C*-glycosyl glycines) that were individually isolated and characterized (38 and 35%, respectively).[20c]

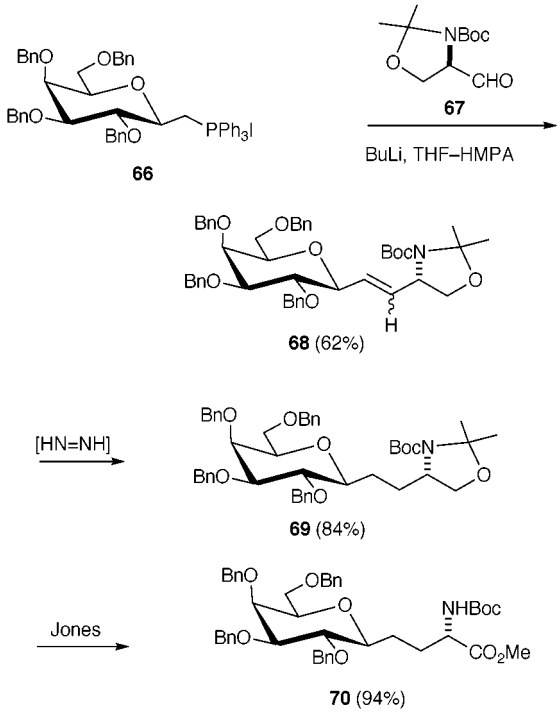
The above synthesis of *C*-glycosyl α-amino acids suffered from poor stereochemical control in the construction of the glycinyl group. The same problem did not exist in a more recent approach to a class of *C*-glycosyl amino acids featuring a three-carbon atom tether.[11] In this method the masked α-amino acid moiety is already present in the form of an oxazolidine ring in the silyl enol ether **62** employed as a reagent in the coupling reaction with the aldehyde β-**58a** (Scheme 19). The resulting



Scheme 19

aldol **63** was isolated as a mixture of diastereomers in good overall yield and transformed into the sugar amino acid **65**

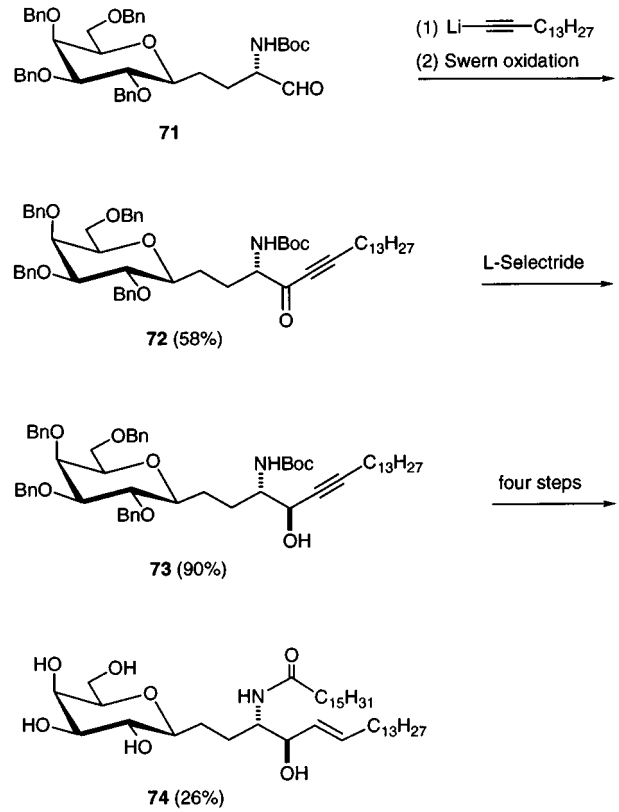
through a series of reactions involving the stepwise removal of the two oxygen atoms from the carbon chain and the oxidative cleavage of the oxazolidine ring. The same reaction sequence was employed for the preparation of the *gluco* and *manno* analogues of **65**. These amino acids represent a class of hitherto unreported carbon-linked isosteres of *N*-glycosyl asparagines wherein the amidic group has been replaced by an ethylene group. In a related programme were also prepared α- and β-linked galactose and glucose serine methylene isosteres by coupling of silyl enol ether **62** with the corresponding glycosyl trichloroacetimidates.[11] Despite considerable efforts, the yield of this glycosidation reaction could not be increased to values higher than 22–32% of isolated product. A complementary approach to this class of *C*-glycosyl amino acid was demonstrated[48] by the synthesis of the galactose derivative **70** (Scheme 20) whose relevance as a precursor to biologically active



Scheme 20

compounds was earlier demonstrated by Bednarski.[49] In our synthesis the aldehyde β-**58a** was transformed into the phosphonium iodide **66** and the ylide generated from the latter was coupled with the quite popular amino aldehyde **67**.[50] From the resulting alkene the conversion to the amino acid **70** was straightforward by reduction of the double bond with *in situ* generated diimide and one-step cleavage of the oxazolidine ring with Jones' reagent.

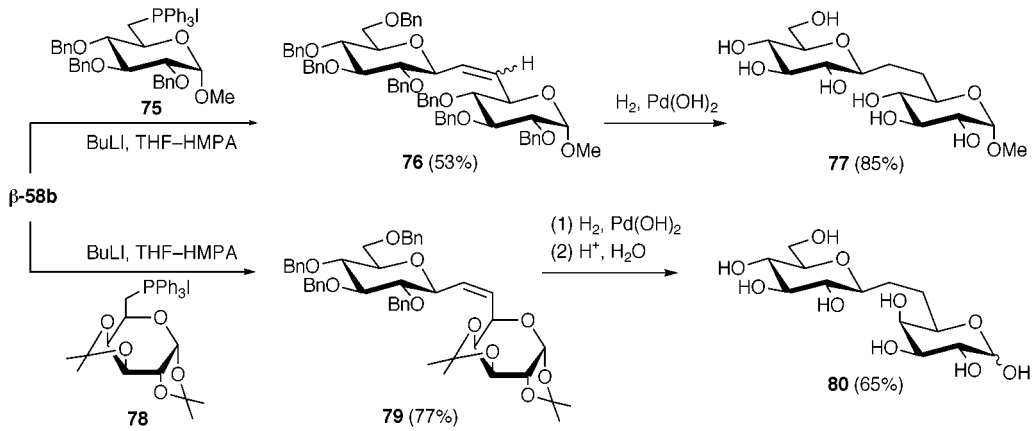
As an extension of the chemistry described above we have considered[51] the synthesis of the carbon-linked galactose cerebroside **74** featuring a carbon–carbon bond between the carbohydrate and the ceramide moieties (Scheme 21). In natural



Scheme 21

compounds these molecular fragments are connected by an oxygen atom. Taking advantage of the satisfactory entry to compound **69** shown in Scheme 20, a rapid assembly of the remaining parts directed to the synthesis of **74** was easily envisaged. By a suitable elaboration of the oxazolidine ring, compound **69** was transformed into the α-amino aldehyde **71** to which pentadec-1-ynyllithium was added and the resulting crude mixture of diastereomeric amino alcohols was oxidized to the ketone **72**. Highly stereoselective reduction of this compound with L-selectride (dr 95%) afforded the amino alcohol **73** showing the correct *anti* relationship between the amino and hydroxy groups as in natural sphingosines. The synthesis of **74** was completed by reduction of the triple bond and replacement of the *N*-Boc with the long chain stearoyl group.

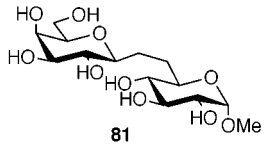
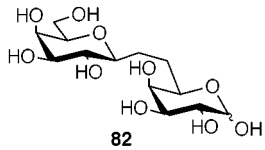
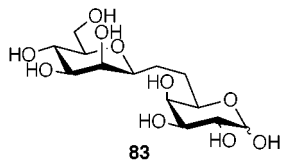
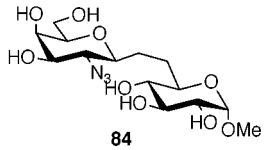
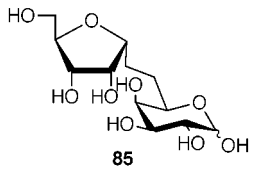
As a further development of this programme, we envisaged the reaction of formyl *C*-glycosides **58** with carbohydrate



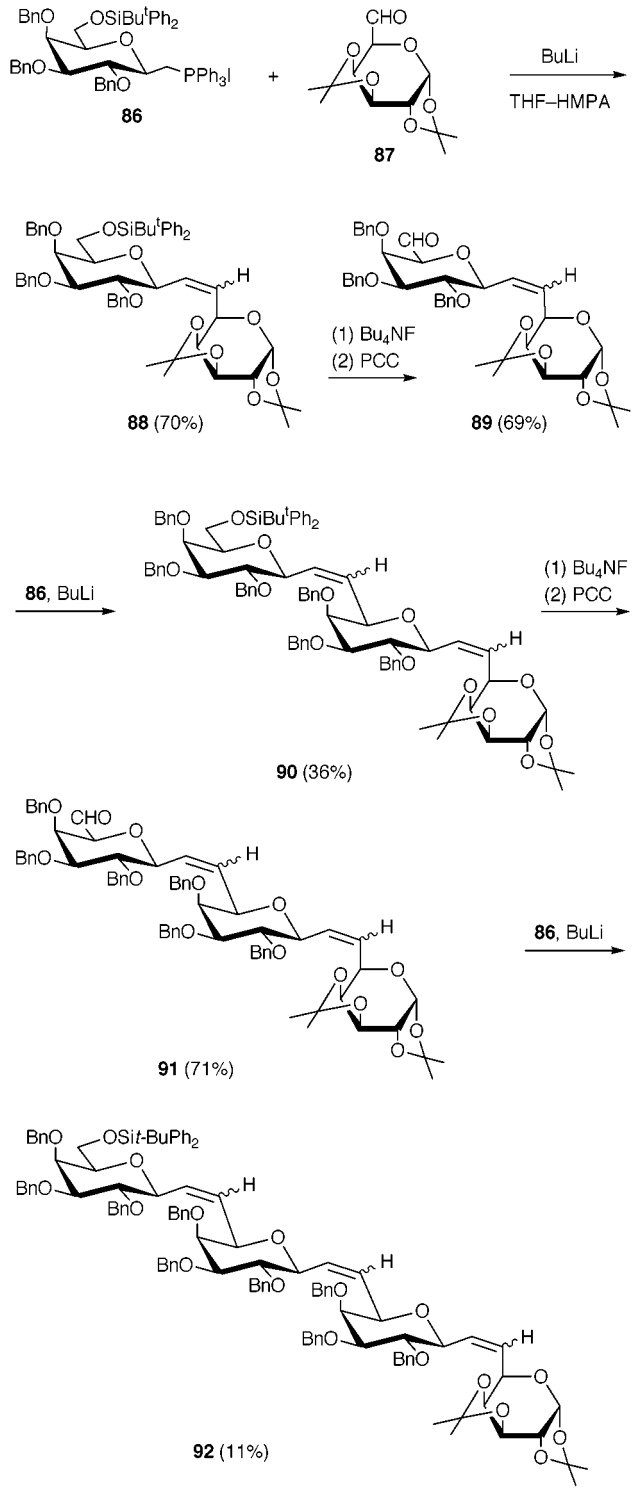
Scheme 22

derivatives bearing a suitable functional group to give carbon-linked disaccharides.[9a] We selected the coupling of **58** with glycopyranose 6-phosphoranes directed to the synthesis of (1→6)-*C*-disaccharides, genuine isosteres of natural products as pointed out by Sinaÿ in the early eighties.[52] The method is illustrated in Scheme 22 showing as an example the synthesis of methyl β-D-*C*-gentiobioside **77** (*C*-Glcβ1,6Glc). A two step reaction sequence constituted by the Wittig olefination of β-**58b** with the ylide generated from the glucopyranose phosphonium salt **75** and the concomitant reduction and debenzylation of the alkene **76** leads to the *C*-disaccharide **77** in a simple and efficient manner.[9a] In a similar way was carried out the synthesis of the *gluco*-to-*galacto*-linked isomer **80** (*C*-Glcβ1,6Gal) with only a minor change that was required for the removal of the isopropylidene protective group. The versatility of this approach was demonstrated in the synthesis of various (1→6)-*C*-disaccharides with both α- and β-linkages (Table 3).

Table 3 Selected (1,6)-*C*-disaccharides prepared form formyl *C*-glycosides **58** by the olefination-reduction sequence

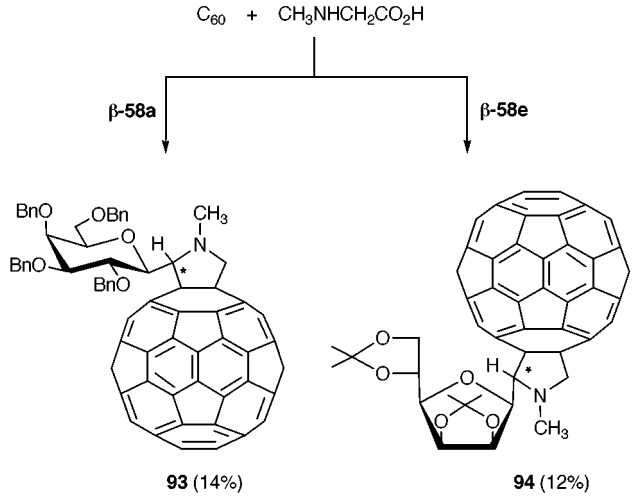
Aldehyde **58**	Phosphonium salt **75** or **78**	*C*-Disaccharides **81**–**85**
β-**58a**	**75**	 **81**
β-**58a**	**78**	 **82**
β-**58c**	**78**	 **83**
β-**58d**	**75**	 **84**
β-**58g**	**78**	 **85**

It was in dealing with this issue that we sought the application of iterative olefination for the assembly of more extensive carbon-linked (1→6)-oligosaccharide chains. In a first approach[10e] the chain growing was initiated by coupling the readily available dialdose **87** with the ylide generated from the phosphonium salt **86** (Scheme 23). The orthogonal protection of the hydroxy groups in the resulting sugar alkene **88** allowed a rapid generation of the aldehyde **89** by desilylation and oxidation of the primary alcohol. This olefination cycle was reiterated twice. Unfortunately the yield of isolated alkene that was rather good in the first cycle (**88**, 70%) dropped substantially in the second (**90**, 36%) and third cycle (**92**, 11%) due to the partial consumption of aldehydes **89** and **91** by 1,2-elimination of BnOH. Nevertheless compounds **88**, **90** and **92** were transformed in the corresponding carbon-linked di-, tri- and tetra-saccharides by desilylation, debenzylation and reduction of the double bonds.



Scheme 23

In closing this section, the use of formyl *C*-glycosides in sugar-fullerene synthesis deserves a short description. Among the multitude of fullerene derivatives that have been prepared in recent years,[53] fullerenes bearing one or more carbohydrate moieties have been reported only in two instances.[54] The interest for glycosylated fullerene derivatives stems from the hope of changing the physicochemical properties of fullerene and improve solubility and biocompatibility. We have installed sugar moieties derived from aldehydes **58** on C_{60} by the Prato azomethine ylide method.[55] In particular, heating a mixture of C_{60} fullerene, *N*-methylglycine (sarcosine), and the aldehyde β-**58a** in refluxing toluene resulted in the formation of a rather



Scheme 24

complex mixture of 1,3-dipolar cycloadducts (Scheme 24). The monoadduct **93** was formed as a 2:1 mixture of diastereomers which were separated and characterized. Similar results were obtained by the use of the aldehyde β-**58e**.

Conclusion

The results that have been presented in this account demonstrate that thiazolylketoses constitute an emerging class of valuable intermediates for carbohydrate synthesis. Once suitably activated by conversion of the anomeric hydroxy group into a good leaving group, they become excellent ketosyl donors. This role appears quite wide in scope as proved by the different types of glycosyl acceptors employed as well as their structural variations. To complete the picture, there is the remarkable contribution of the thiazole ring, which serves as a precursor to various very important functionalities (CHO, CH_2OH, CO_2H), and allows the preparation of various classes of ketosides, some of which are very difficult to access, such as ulosonyl ketosides. The conversion of thiazolylketoses into formyl *C*-glycosides represents a special evolution channel of this chemistry into new synthetic methods for *C*-glycoside synthesis. The synthesis of some important targets (*C*-glycosyl amino acids, *C*-cerebrosides, *C*-oligosaccharides) has been illustrated in this report but further improvements and developments of the methods employed are still required. The extension of these methods to solid-phase techniques should have priority in future research programmes. Other objectives can be also delineated. For example, a formyl *C*-glycoside and compounds derived from it have recently been employed in the Ugi and Passerini multicomponent reactions as an access to glycoconjugate libraries.[56] Thus the combinatorial synthesis in other multicomponent systems, for instance the Biginelli reaction,[57] offers another wide field of application of formyl *C*-glycosides.

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