Synthesis and Uses of *exo*-Glycals

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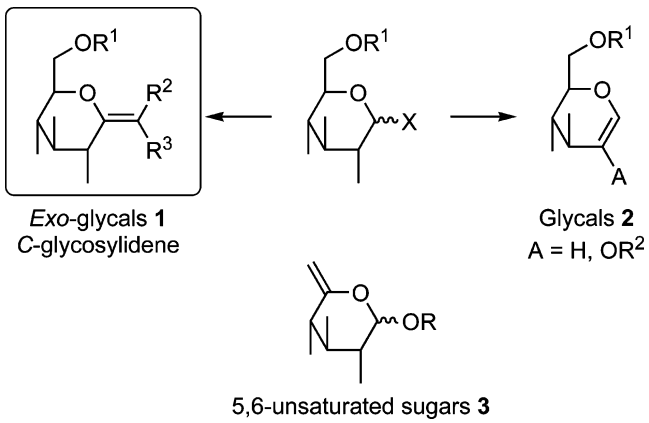
Contents

1. Introduction

C-Glycosyl derivatives are well-known compounds, frequently encountered in Nature. Due to their stability toward hydrolysis, these mimics of *O*-glycosides have been largely studied. Their syntheses have been explored over the years, and a number of creative methods of C−C bond formation at the anomeric center have emerged. *C*-Glycosyl compounds having a carbon−carbon double bond at the anomeric center, e.g., **1**, are less familiar compounds. These *C*-glycosylidene compounds, frequently termed "*exo*-glycals", were almost unknown until recently.[1] In principle, such olefins could be of interest as precursors of *C*-glycosides if the double bond can be reduced with high stereocontrol. The presence of the ring oxygen strongly influences the reactivity of this double bond, so interesting properties should be expected from these olefins. The synthesis of *C*-glycosylidene derivatives needs to be explored as well as their reactivity. The discovery of several direct methods for the formation of a carbon−carbon double bond at the anomeric center of carbohydrates has enlarged the availability of these unsaturated compounds and reinforced their interest. It is worth mentioning that 1,2-unsaturated sugars, the so-called glycals **2**, also displaying an enol ether function at the anomeric center, are well-known and widely used compounds, easily prepared from 1-halogeno sugars or other activated derivatives. Their chemistry is well developed, and a number of reactions can be carried out on glycals.[2] Other useful compounds having an exo carbon−carbon double bond near the ring oxygen are 5,6-unsaturated sugars **3**,[3] which are easily available from 6-halogeno sugars[4] and are interesting intermediates for the formation of a carbon−carbon bond[5,6] and for the well-known Ferrier carbocyclization.[7] These compounds are also referred to as *exo*-glycals. Being involved in the *exo*-glycal research field for several years, it seemed to us of interest now to summarize all the efforts developed by several groups to find innovative methods and reactions in this field. The purpose of this review is to report on the state of the art in *C*-glycosylidene−*exo*-glycal chemistry. In the first part of this review, we will describe the synthetic methods leading to *exo*-glycals, whereas their use in the synthesis of complex sugars will be detailed in the last part of this paper.

Scheme 1



2. Synthesis of exo-Glycals

The first examples of *exo*-glycal were reported in 1975 by Bischofberger et al., who studied the reaction of ethyl isocyanoacetate with lactones.[8] Reduction of the double bond gave anomeric *N*-formyl amino acids. The key reaction developed was a direct olefination reaction, i.e., a one-pot reaction leading in a single

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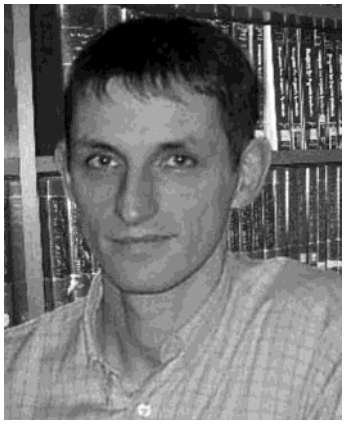


Claude Taillefumier was born in 1967 in Nancy, France, where he studied chemistry and received his Ph.D. degree in organic chemistry in 1995 under the supervision of Dr. Yves Chapleur. During his doctoral studies, he worked on the synthesis of cholesterol biosynthesis inhibitors and more specifically on the preparation of HMG-CoA reductase inhibitors. He was appointed to a lectureship of organic chemistry at the Faculty of Sciences of the Université Henri Poincaré Nancy in 1996. In 2000, he joined the research group of Prof. George W. J. Fleet at the Dyson Perrins Laboratory in Oxford, where he worked on the synthesis and structural determination of peptidomimetic oligomers from oxetane β-amino acids. As from the beginning, his current research at the Department of Chemistry in Nancy is focused on carbohydrate chemistry. His research involves the synthesis and reactivity studies of *exo*-glycals, the chemistry of sugar amino acids, and the use of sugars as peptidomimetic scaffolds.

Yves Chapleur graduated from University of Nancy and obtained his Ph.D. in 1976 under the guidance of Professor Bertrand Castro. He was awarded the Benjamin Delessert prize of the CEDUS in 1977 for his work on saccharose and related sugars. In 1978–1979, he received postdoctoral training with Professor Steve Hanessian at the University of Montreal as a SERC research associate and as a NATO fellowship recipient, working on the total synthesis of the macrolide antibiotic boromycin from carbohydrates. He was appointed as research associate at CNRS and became senior reseacher in 1981. In 1986, he became director of research at CNRS in the Department of Chemistry of the Université Henri Poincaré in Nancy. His research interests are centered around carbohydrates, exploring successively the chemistry of *C*-nucleosides, the total synthesis of Amaryllidaceae alkaloids from sugars, the carbocyclization of sugars, and the chemistry of carbohydrate analogues. In connection with the latter, he chaired two Euroconferences on this topic and edited a book on the subject, *Carbohydrate Mimics: Concepts and Methods*. The current research projects of the group SUCRES ("sugars" in French) are centered around the chemistry of cell signal transduction, the use of sugar as scaffolds, and the construction of macrocyclic sugar-based receptors. A long-standing interest of the group is the use of sugar lactones for the synthesis of *exo*-glycals, *C*-glycosides, and sugar amino acids.

synthetic step to olefin formation. In the course of glycosidase mechanism studies, Brockhaus and Lehmann reported the first example of a *C*-methylene derivative.[9] The synthesis was based on a stepwise procedure in which a *C*-glycosyl derivative, equipped with an iodine atom, is constructed first. Subsequent elimination according to the well-established procedure led to the unsaturated sugar. These two early reports perfectly illustrate the two main ways used to access *exo*-glycals. The first one is the direct formation of an anomeric double bond using an olefination process, starting obviously from a carbonyl group and taking advantage of Wittig-type olefination or other organometallic reagents. In this regard, lactones are ideal, readily available starting compounds. The second way is a stepwise process, based on the creation of a carbon−carbon bond at the anomeric center, followed by subsequent double formation involving an elimination reaction. Here again, sugar lactones are evident but not exclusive substrates.

For the sake of clarity, the synthesis of *exo*-glycals has been arranged according to these two main approaches. The direct methods will be discussed first, whereas the stepwise methods will be presented second.

2.1. Direct Olefination Methods

The use of lactones as starting compounds for direct formation of *exo*-glycals is attractive, provided that a suitable and general reaction could be found. As already mentioned, the reaction of ethyl isocyanoacetate with lactones provided the first solution to *exo*-glycals synthesis.[8] Reduction of *exo*-glycal **5**, obtained from lactone **4**, gave sugar amino acid **6**. However, this pioneering work has not been thoroughly exploited due to facile formation of acyclic sugar oxazole in the presence of excess potassium ethyl isocyanate salt.[9] The reaction of tosylmethyl isocyanide with sugar lactones has been also investigated.[10] In 1984 were described, almost at the same time, two direct olefinations of sugar lactones, opening the way to some *C*-glycosylidene derivatives. One of these methods was a phosphorus-based reaction yielding dichloroolefins, discovered in our group.[11] The second method was a direct methylenation using Tebbe reagent disclosed by Wilcox's group.[12] In both cases, lactones were used as starting materials, giving access to several types of *exo*-glycals. The different methods available will be described below and arranged according to the type of reagents used,

Scheme 2

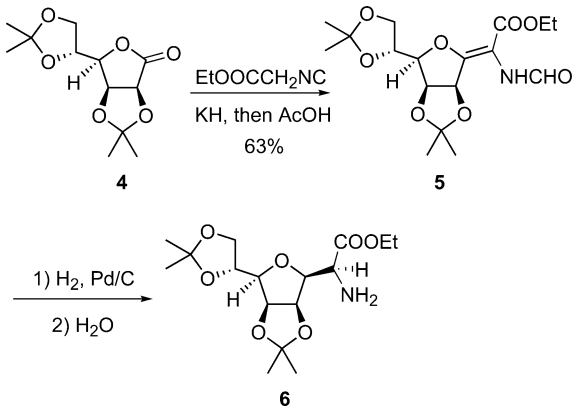


Table 1. Dihaloolefination of Some Lactones

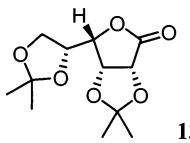
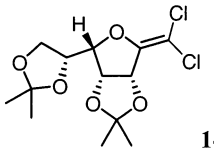
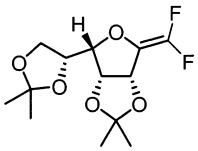
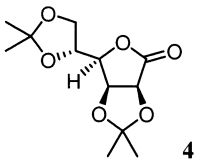
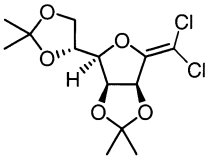
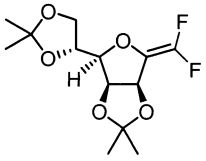
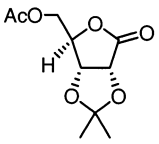
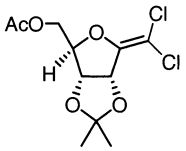
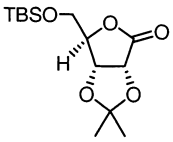
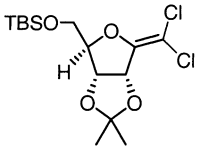
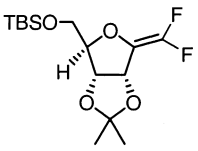
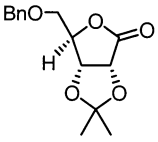
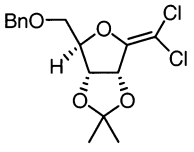
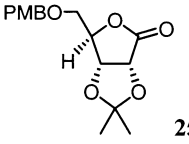
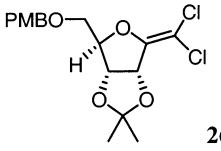
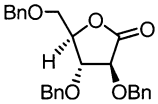
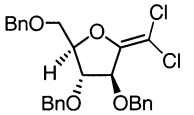
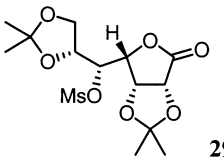
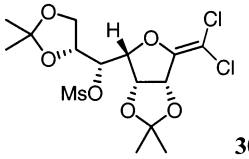
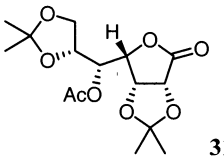
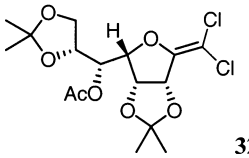
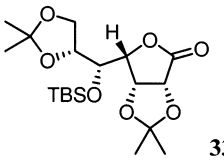
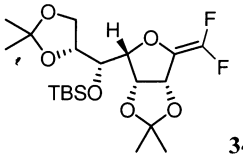
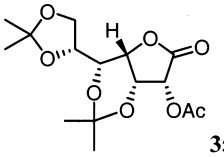
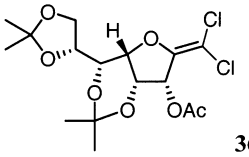
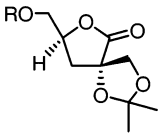
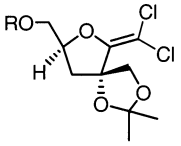
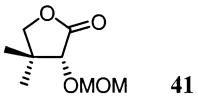
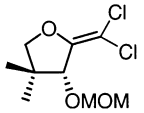
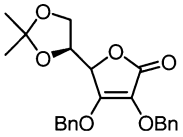
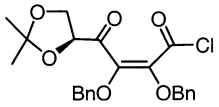
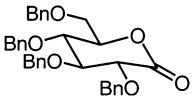
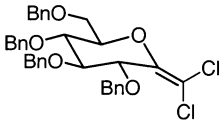
Entry	Substrate	Reaction conditions (yield %)[a]	Product	Ref.
1	 **13**	A (92)	 **14**	11, 17
2		B (85)		22
3		C (67)	 **15**	20, 21
4	 **4**	A (79)	 **16**	11, 17
5		B (95)		22
6		C (56)	 **17**	20, 21
7	 **18**	A (75)	 **19**	17
8	 **20**	A (52)	 **21**	17
9		C (56)	 **22**	20, 21
10	 **23**	D (86)	 **24**	19b
11	 **25**	D (95)	 **26**	19b
12	 **27**	A (0)	 **28**	17
13		B (74)		22

Table 1 (Continued)

Entry	Substrate	Reaction conditions (yield %)[a]	Product	Ref.
14	 **29**	A (62)	 **30**	17
15	 **31**	A (45)	 **32**	17
16	 **33**	C (57)	 **34**	20, 21
17	 **35**	B (45)	 **36**	22
18	 **37**	B (87)	 **38** R = Ac **39** R = Ac **40** R = R = CH_3-C(CCl_2)	22
19	 **41**	B (81)	 **42**	22
20	 **43**	A (73)	 **44**	18
21	 **45**	A (20)	 **46**	17
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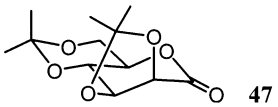
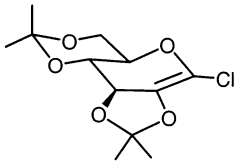
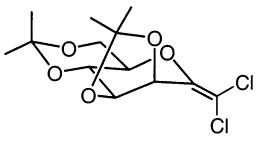
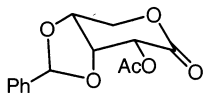
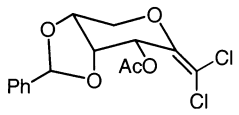
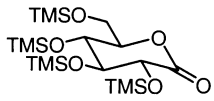
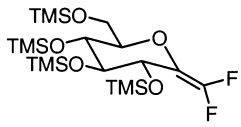
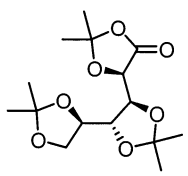
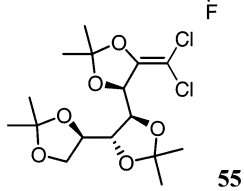
23	 **47**	A (90)	 **48**	18
24	-	B (75)	 **49**	22

Table 1 (Continued)

Entry	Substrate	Reaction conditions (yield %)[a]	Product	Ref.
25	 **50**	B (20)	 **51**	22
26	 **52**	C (66)	 **53**	21
27	 **54**	B (92)	 **55**	22

[a] Reaction conditions: (A) $P(NMe_2)_3$ 3 equiv, CCl_4 4 equiv, CH_2Cl_2, −40 °C; (B) PPh_3 3 equiv, CCl_4 10 equiv, THF, reflux; (C) $P(NMe_2)_3$, CBr_2F_2, Zn, THF, reflux; (D) $P(NMe_2)_3$ 2.2 eqiv., $CBrCl_3$ 3 equiv, CH_2Cl_2, −78 °C to room temperature.

i.e., phosphorus-based reagents used in one-step olefination of carbonyl groups and organometallics recently introduced for the same purpose.

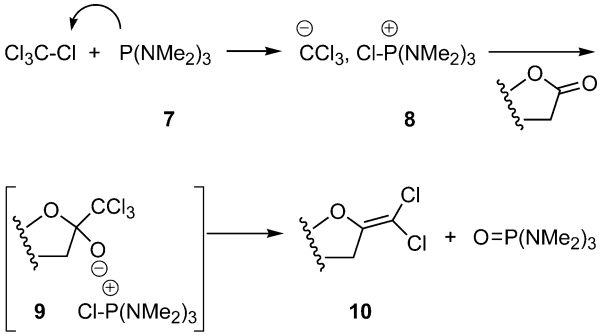
2.1.1. Olefination Using Phosphorus-Based Reagents

Wittig reaction was appealing, but the rather poor reactivity of ester carbonyl groups toward phosphoranes was well established, and only a few reports dealt with olefination of esters, amides, or anhydrides.[13] Only one example of intramolecular Wittig reaction of a sugar derivative was known at that time.[14,15]

All attempts at lactone olefination using standard phosphoranes, carried out in our group at that time, failed due to improper reaction conditions. The presence of an isopropylidene group at position 2,3 of the lactone strongly modifies the reactivity of the lactone. For example, it is possible to prepare lactols from lactones on treatment with sodium borohydride without reduction to the alditol. We reasoned that sugar lactones might behave like ketones if a dioxolane ring is fused to the lactone ring; thus, olefin-forming reactions usable for ketones would be efficient with such sugar lactones.

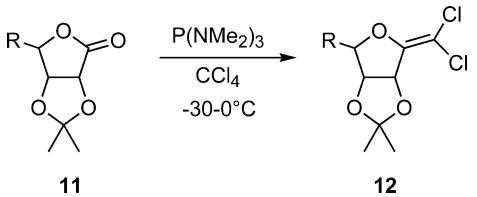
Dichloroolefins attracted our attention, and a particular reagent system, tris(dimethylamino)phosphine (**7**)−tetrachloromethane (TCM), seemed a good candidate to achieve dichloroolefination. This reagent

Scheme 3



is generally used at low temperature and reacts cleanly with aldehydes and ketones.[16] Its mechanism proceeds in two steps: nucleophilic addition of the trichloromethylide anion of **8** on the carbonyl group to form an alcoholate **9**, which immediately reacts with chloro-tris(dimethylamino)phosphonium cation to form an alkoxyphosphonium salt. Subsequent elimination of phosphine oxide gives rise to the formation of olefin **10**. Reasoning that this mechanism was sligthly different from the generally postulated Wittig mechanism, it had a good chance to proceed on sugar lactones, which are prone to nucleophilic addition. Our first attempts were successful and gave excellent yields of dichloroolefins **12** with several bicyclic lactones[11,17] (see Table 1). The reaction was carried out around −30 °C with 3 equiv of phosphine and 4 equiv of TCM. D-Mannono- or

Scheme 4



D-gulono-1,4-lactones **4** and **13** were highly reactive and gave excellent yields of the expected dichloroolefins **14** and **16** (Table 1, entries 1 and 4). Sterically hindered lactones, such as the D-ribose-derived compounds **18** and **20**, reacted slowly and were transformed at 0 °C (Table 1, entries 7 and 8). Nevertheless, 1,4-lactones derived from arabinose, such as **27**, did not react under these conditions (Table 1, entry 12). Ascorbic acid derivative **43** did not give olefin, but ring-opened to form acyl chloride **44** as an *E*/*Z* mixture (Table 1, entry 20). Oxidation at *C*-4 was the result of proton abstraction by the trichloromethylide anion followed by ring-opening to form a ketene, precursor of the acyl chloride.[18] Moreover, 1,5-lactones gave low yields of olefins (20% of **46** from **45**;

Table 1, entry 21), whereas mannono-1,5-lactone **47** gave the vinylic chloride **48** in excellent yield (90%; Table 1, entry 23) instead of the expected dichloroolefin **49**. This was attributed to a facile enolization of lactones **47**, which prevents nucleophilic addition of the trichloromethylide anion on the carbonyl group.

Although the tris(dimethylamino)phosphine−tetrachloromethane system was efficient with several lactones, the reaction suffered some limitations. Attempts to substitute tetrachloromethane for tetrabromomethane did not improve the results, only traces of dibromoolefins being formed.

Very recently, bromotrichloromethane and phosphine **7** were efficiently used by Shiozaki to achieve the dichloromethylenation of protected ribono-lactone derivatives **23** and **25** at low temperature, to yield olefins **24** and **26** in 86% and 95% yield, respectively (Table 1, entries 10 and 11).[19]

An extension of our method to difluoroolefination of sugar lactones came from Motherwell's group. Using the same phosphine reagent **7** associated with dibromodifluoromethane and zinc, a series of difluoroolefins from about the same substrates was obtained.[20,21] This sequence was efficient with 1,4-lactones **4**, **13**, **20**, and **33** (Table 1, entries 3, 6, 9, and 16) and with the 1,5-lactone derived from D-glucose **52**, giving the difluoroolefin **53** in 66% yield in this case (Table 1, entry 26). This better yield in the formation of **53** as compared to the yield of **46** (Table 1, entry 21) is likely due to the use of trimethylsilyl protecting groups instead of the bulky benzyl groups present in **45**.

The lack of reactivity of some lactones with the tris(dimethylamino)phosphine−TCM system prompted us to consider more suitable and widely used reagents to form these compounds. Attempts to use triphenylphosphine (TPP) and TCM had been unsuccessful, although there are a few examples of dichloroolefination of aliphatic and aromatic lactones with this reagent in a paper by Suda.[23]

After considerable experimentation, the TPP−TCM reagent was found efficient for the dichloroolefination of lactones under carefuly controlled conditions.[22,24] Acetonitrile, which was reported as one of the best solvents for such Wittig olefinations,[25] was deleterious in our case, likely due to a reaction of the intermediate phosphorane with acetonitrile. TCM can be also used as solvent but gave minute amounts of dichloroolefins. Finally, the proper conditions were determined to be the use of tetrahydrofuran as the solvent and slow addition, typically using motor-driven syringe, of excess TCM on the refluxing solution of the lactone. A 2-fold excess of TPP (4 equiv because the reaction needs 2 equiv of TPP) and a larger excess of TCM were needed.

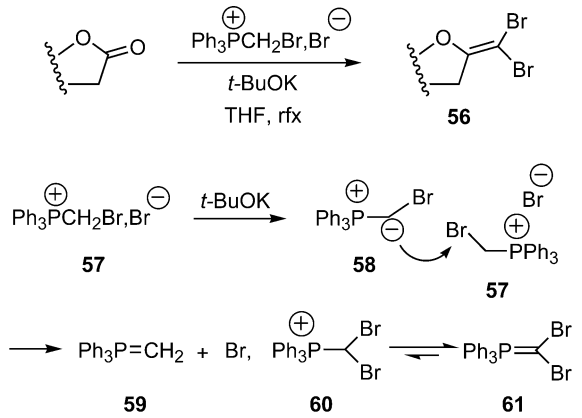
Under these conditions, a large number of lactones were transformed, including 1,4- and 1,5-lactones protected with ether or acetal groups. Table 1 summarizes these results and provides a comparison between the two methods. Lactones **27**, **45**, and **47** were easily transformed into olefins **28**, **46**, and **49** in good yields (Table 1, entries 13, 22, and 24). Surprisingly, ester groups can be used to protect alcohols such as in **35** or **50**, but **36** was obtained in only 45% yield, suggesting some side reactions (Table 1, entries 17 and 25). Thus, it was shown that acetate can react under these conditions. The reactivity of the acetate carbonyl group was found to be close to that of a lactone carbonyl group. A typical case was the reaction of 5-*O*-acetyl isosaccharinolactone **37**.[26] This rather crowed lactone reacted simultaneously at both sites, i.e., lactone and acetate carbonyls. Mixtures of products **38**−**40** were obtained (Table 1, entry 18). Pantolactone derivative **41** gave **42** in 80% yield, although the carbonyl group is neopentylic (Table 1, entry 19). This also showed that MOM ethers are compatible with these reaction conditions, but silyl ethers were not, and chlorination of the corresponding alcohol was observed.[24,27] Pivaloyl groups were less affected and can be used as protecting groups. Dioxolanone **54** derived from gluconolactone also reacted with TPP−TCM, giving **55** in excellent yield (Table 1, entry 27). Non-sugar lactones such as Corey lactone or podophyllotoxin cleanly reacted under these conditions.[22]

These results can be considered as a major breakthrough in the synthesis of *C*-glycosylidene compounds and motivated the search for diversely functionalized olefins. Dichloromethylene triphenylphosphorane is a nonstabilized phosphorane, reacting quite easily with lactone and esters; thus, the Wittig olefination of these "unreactive" carbonyl groups could be just a matter of finding the proper reaction conditions.

Dichloroolefins showed interesting reactivity and prompted the search for more reactive analogues. Sugar-derived dibromoolefins were potentially interesting compounds, not yet prepared in significant yields. Until recently, all attempts to achieve dibromoolefination of lactones using TPP and tetrabromomethane (TBM) were unsuccessful. Monohalogeno olefins being attractive substrates, the reaction of monobromomethylene triphenylphosphorane **58** with lactones was explored. Surprisingly, this reaction gave dibromoolefins **56** instead of the expected monobromo ones.[28] This was tentatively explained by a halogenation reaction of the monobromomethylene phosphorane **58** by a molecule of monobromophosphonium salt **57**, giving the dibromomethylene phosphorane **61**, and then reacting with the lactone. This halogenation reaction gave, as a side product, methyl phosphoranylidene **59**, another phosphorane. Using this strategy, some dibromo *C*-glycosylidene compounds such as **56** are now accessible. Their reactivity is currently being tested in our group. More recently, it was found that, under carefully controlled conditions, TPP and TBM can transform lactones into dibromoolefins.[29] A related and interesting strategy has been proposed by Lamberth to construct monobromo aryl *exo*-glycals.[30] The reaction of triethyl phosphite with aryltrihalomethane in the presence of a sugar lactone gave the expected olefins. The reaction has been applied to D-ribono-1,4-lactone **20** and gluconolactone **45**. Mixture of isomers were obtained in each case. This reaction has been applied to phenyl and pyridinyl rings.

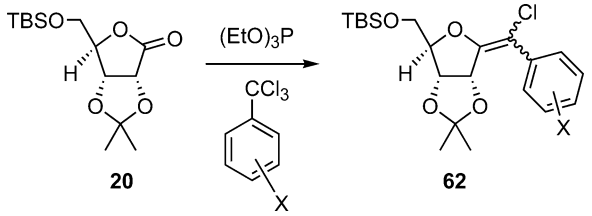
The above results suggested that lactone olefination was dependent to some extent on the stability

Scheme 5



and reactivity of the phosphorane rather than on lactone's intrinsic reactivity. In other words, lactones could react with nonstabilized phosphoranes, provided the latter are stable and reactive under the reaction conditions. It was expected that the reaction with stabilized but less reactive phosphoranes would require harsh conditions. Only intramolecular Wittig olefination of lactones had been reported.[14,31] The reaction of lactones with such phosphoranes was investigated as a means to prepare functionalized *C*-glycosylidene compounds.[32] Obviously, methyltriphenyl phosphoranylidene acetate was first considered. Once again, extensive experimentation was needed to find the proper reaction conditions. Finally, toluene was chosen to allow sufficiently high temperature, a prerequisite to good reaction rate. Nevertheless, the reaction often needed reaction temperatures above 110 °C, so a sealed vessel was used. Excess of phosphorane was also required, likely because this reagent is moderately stable above 120 °C, as shown below.

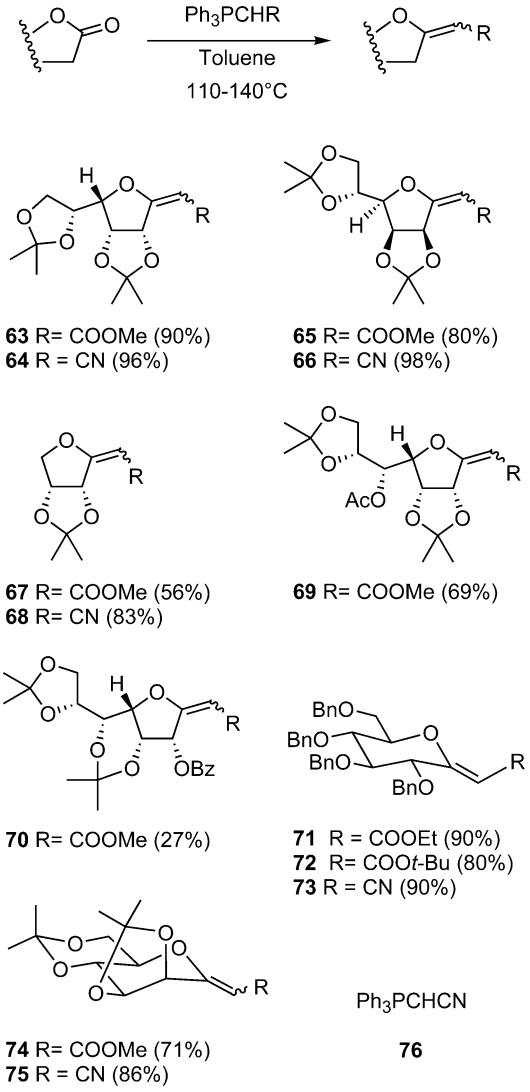
Scheme 6



Our standard repertoire of starting lactones was tested under these conditions and gave good to excellent results in terms of yield. As a trisubstituted double bond is formed, *E* and *Z* isomers can be obtained. Almost no selectivity was observed, except for the D-gluconolactone derivative **71**.

Many protecting groups are tolerated under the above conditions: ethers, silyl ethers, and even esters. In this case, an acetate group remote from the reactive center is compatible, but poor results were obtained with the 2-OBz derivative **70**. This should be the result of steric hindrance. Equally good results were also obtained with *tert*-butyloxy- and (ethyloxycarbonyl)methylene(triphenyl)phosphorane, as shown in the preparation of **71** and **72**. The *Z*/*E* selectivity increased when six-membered-ring lactones were used, only *Z* derivatives being obtained with perbenzylated D-galacto- and D-glucono-lactone.[33] Perbenzylated mannonolactone gave poor results, whereas the tricyclic derivative **74** was formed in acceptable yield under our conditions.[32] 5-*O*-Acetyl-2,3-*O*-isopropylidene-D-ribonolactone cleanly reacts under these conditions.[34]

Scheme 7



This olefination has been extended by Czernecki and Xie to 2-acetamido-2-deoxy sugar lactones derived from galactose and glucose, in rather good yields. In this case also, *O*-benzyl-2-acetamido-2-deoxy-D-mannono-1,5-lactone failed to give olefin and decomposed in refluxing toluene.[33]

It is worthy of note that *exo*-glycals such as **63** or **65** are stable to a variety of conditions, as shown by the facile chain homologation of the aldehyde at C-4 (carbohydrate numbering) using diethylaluminum cyanide.[35]

Recently, we turned our attention to cyanomethylene triphenylphosphorane **76**.[36] This type of Wittig reagent is considered to be more reactive than the corresponding ester.[37] This proved to be the case with sugar lactones, since the reactions were performed in refluxing toluene, giving excellent yields of the expected olefins.[38] As can be seen from Scheme 7, better yields were obtained using phosphorane **76**.

It is interesting to note that this reagent is unstable above 110 °C. Analogous results were obtained with aliphatic esters, lactones, and imides using cyanomethylene triphenylphosphorane while our work was in progress.[39]

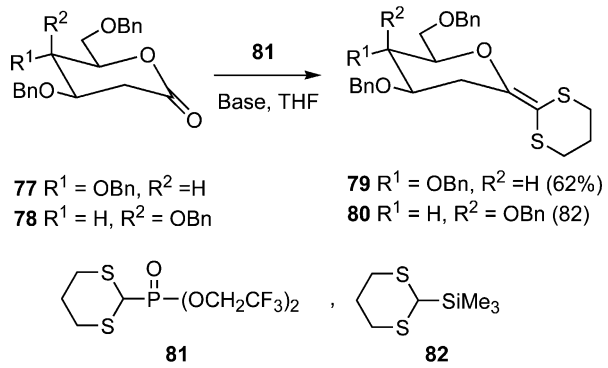
The introduction of microwave (MW) irradiation to perform thermal reactions improved a number of synthetic procedures.[40] A report by Sabitha on the successful use of MW activation of the Wittig olefination of lactones and amides with ethoxycarbonylmethylene(triphenyl)phosphorane prompted us to explore this technology.[41] Again using cyanomethylene triphenylphosphorane **76**, MW activation considerably accelerated the reaction and improved the yield. For example, a reaction performed within 24 h in refluxing toluene can be achieved in 4 min in toluene under MW activation in the same 90% yield.

Olefination using **76** also gave mixtures of *E* and *Z* olefins whatever the activation mode, thermal or microwave. These reaction conditions tolerated many different functional groups: ethers, acetals, and esters. For example, mannose-derived lactone **4** was efficiently transformed into the corresponding olefin **66** (*E*/*Z* 1.7:1) in 76% yield in refluxing toluene and 98% yield using MW activation.[38]

One can conclude from this survey that direct olefination of sugar lactones using Wittig reaction has a wide scope and allows for the formation of differently functionalized olefins. Dihalogenomethylenation, carboxymethylenation, and cyanomethylenation are efficient, easily performed reactions. As will be shown in the second part of this review, the usefulness of these compounds is going to be well established and provides a short entry to a variety of compounds.

The introduction of two sulfur atoms on the *exo*-glycal double bond is of interest as it could allow the double bond to be efficiently transformed into a functional group such as aldehyde or acid, opening the way to many derivatives. Such ketene dithioacetals have been prepared from sugar lactones using Horner−Emmons and Peterson olefination. The first route involved the use of an activated phosphonate introduced by Mikolajczyck.[42] 2-Deoxy 1,5-lactones **77** and **78**, derived from D-glucal and D-galactal, respectively, were treated with the potassium salt of phosphonate **81** to provide the ketene dithioacetals **79** and **80**, respectively, in 72% and 62% yields. The Peterson olefination using dithiane **82** and its anion gave poor results, extensive β-elimination of an alkoxy group on the lactone being observed. This is probably one of the first applications of this olefination on lactone. The ketene acetals were in turn transformed into the corresponding ulosonic esters upon treatment with *N*-bromosuccinimide in methanol. When treated with triphenylphosphine and DBU, 2-bromoacetyl-1,4-lactones underwent intramolecular Wittig olefination to form fused furano-1,4-lactones.[15] These compounds are good intermediates for the synthesis of furanofurans found in many natural compounds, such as goniofufurone[43] or erythroskyrine.[44] Other conditions for the intramolecular olefination of α-hydroxy or α-amino esters have been proposed.[45,46] Olefination of thio-γ-*O*-lactones using

Scheme 8

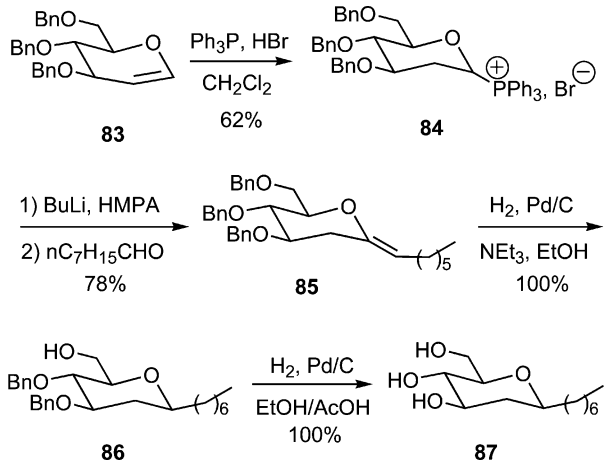


ethyl diazoacetate or ethyl diazomalonate has been reported and is illustrated in the next section.[47] Thionolactones also react with stabilized Wittig reagents. This has been used in the synthesis of a branched-chain *C*-glycoside in relation with the synthesis of FR901464.[48]

A Wittig-based synthesis of *exo*-glycals can be envisioned the other way around, by coupling a sugar-derived phosphorane with an aldehyde or a ketone. In principle, this method would provide access to a large panel of compounds, given that any carbonyl group could be reactive in this Wittig olefination. The main difficulty should arise from the carbohydrate phosphorane. Some derivatives of this kind are known from the pioneering work of Secrist et al.[49] and have been used for the synthesis of complex oligosaccharide analogues.[50] If these phosphoranes derived from primary hydroxyl groups have been used, those located at the anomeric position were less studied until recently. The first example of this approach was reported by Mioskowski and Falck.[51] The phosphonium salt precursor **84** was obtained by addition of triphenylphosphine hydrobromide on glycal **83** at 0 °C (Scheme 9). Treatment of **84** with *n*-butyllithium in THF in the presence of HMPA generated the corresponding phosphorane, which reacted with *n*-octanal to afford the expected *exo*-glycal **85** in 78% yield. Reduction of this compound in the presence of base gave the corresponding β-*C*-glycoside **86**. Subsequent removal of the benzyl groups gave the free *C*-glycoside **87**. In the absence of base, reduction of the labile enol ether bond gave a mixture of α and β derivatives **87** due to *exo*−*endo* isomerization. Although the method is appealing, it is clear that it suffers from a strong limitation. Only 2-deoxy phosphoranes are useful in this approach, the presence of any heteroatom at position 2 of the phosphorane immediately inducing elimination to form the corresponding glycal. Another limitation is the need for a strong base to generate the phosphorane, precluding the use of a number of protective groups. This method has been used in some syntheses of tetrahydropyran-containing natural products.[52] Ring-opening of 1,6-anhydro sugars has been also used as a key step for the synthesis of the phosphonium salts.[52c,53,54]

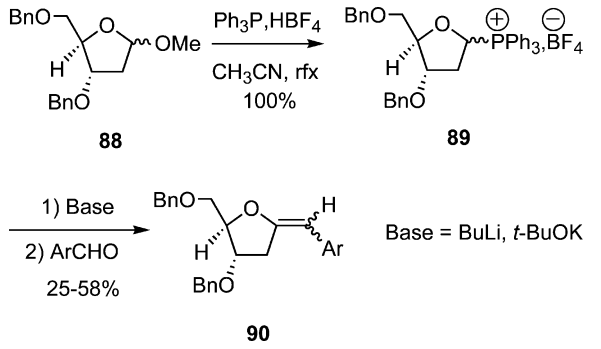
Lieberknecht's group proposed an alternative method to prepare anomeric phosphonium salts by treatment of methyl glycoside **88** with hydrogen triphenylphosphonium tetrafluoroborate in refluxing

Scheme 9



acetonitrile.[55] A series of aromatic aldehydes were reacted with the phosphorane derived from **89** using three different reaction conditions. The best yields (58%) were obtained using potassium *tert*-butoxide in THF. All enol ethers **90** were obtained as *Z*/*E* mixtures with a slight preference for the latter. Conversion of *E* to *Z* isomer was achieved on UV irradiation in the presence of iodine. The same types of compounds have been reported by Veyrières.[53,54] Application to the coupling of a 2-deoxy-galactopyranose-derived phosphorane with Garner aldehyde led to a concise synthesis of *C*-glycosyl amino acid.[56]

Scheme 10

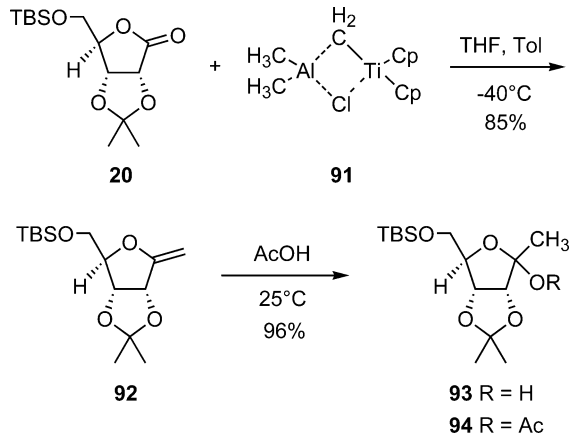


2.1.2. Alkylidenation Using Organometallics

Another interesting use of sugar lactones is methylenation with titanium-based reagent. The so-called Tebbe reagent **91** was well known for the methylenation of ketones and aldehydes.[57] It was also used for the methylenation of esters. A comprehensive review on the titanium-based alkylidenation of carboxylic acid and carbonic acid derivatives has recently appeared.[58] Methylenation of sugar lactones was first disclosed by Wilcox in 1984, and led to interesting developments in carbohydrate chemistry.[12]

In the course of synthetic approaches to the mycotoxins aurovertin and citreoviridin, the methylenation of ribonolactone derivative **20** using Tebbe reagent **91** was reported. The reaction proceeded at −40 °C to give **92** in 85% yield (Table 2, entry 1). The next step was addition of acetic acid to the double bond to provide a single anomeric acetate **93** in excellent yield. The latter was in turn alkylated at the anomeric position on treatment with allyltrimethylsilane in the presence of zinc bromide. This example established the validity of the Tebbe methylenation of sugar lactones. The synthetic utility was demonstrated by a facile electrophilic addition. However, it is interesting to note that Wilcox's total synthesis of citreoviral and citreoviridin relied not on this sequence but on the more convenient methyllithium addition on a ribonolactone derivative.[59] RajanBabu and Reddy further examplified this strategy in 1986.[60] These authors described the methylenation of 1,4-lactones such as D-ribonolactone and D-galactonolactone in useful yields (60−80%) of the corresponding methylene **96** and **98** derivatives, respectively (Table 2, entries 2 and 3).

Scheme 11



Tri-*O*-benzyl-D-arabino-1,4-lactone **27** has also been successfully transformed into methylene derivative **99** in 72% yield (Table 2, entry 4).[61] Dioxolanones derived from sugars were also easily methylenated using the Tebbe reagent.[62]

Protected D-gluconolactone using benzyl (**45**) or silyl ethers (**52**) also gave good yields of **108** and **109**, respectively (Table 2, entries 8 and 10).[60] 2-Deoxy-1,5-lactones also reacted cleanly at low temperature with Tebbe reagent to afford the corresponding methylene derivative **115** in 82% yield (Table 2, entry 14).[63] In the same paper, Sinaÿ et al. described the enol ether **117** derived from methylenation of a methyl ester **116** at −45 °C in 80% yield (Table 2, entry 15). Interestingly, a pivaloyl ester present in this compound was not affected in the reaction. This shows that acetate-protected lactones are not suitable substrates, in contrast to the dichloromethylenation reaction.

Failures in the attempted Tebbe methylenation of ester[64] and aldonolactones have been reported. In another paper, Ali et al. reported the use of an unpurified form of the Tebbe reagent **91**.[65] Although identical results were obtained with tetra-*O*-benzyl-D-gluconolactone with the crude reagent, some lactones such as γ-lactones furnished mixtures of the expected olefins and of the water-addition resulting products. This held for the ribonolactone derivative **20**, which gave the ketose derivative **93** in addition to the methylene derivative **92**. Chromatography was also responsible for the formation of the same compounds. The bicyclic lactone **100** derived from

Table 2. Methylenation of Some Lactones

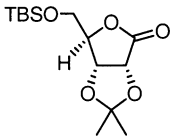
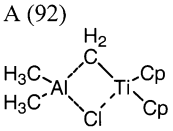
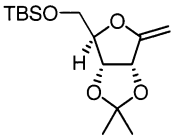
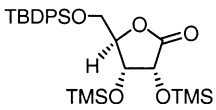
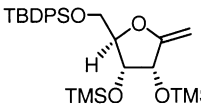
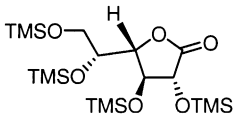
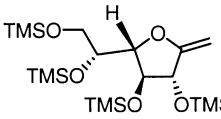
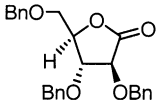
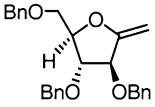
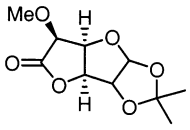
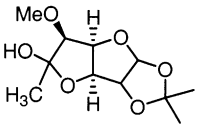
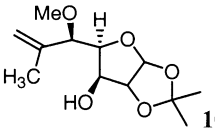
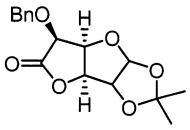
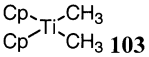
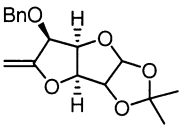
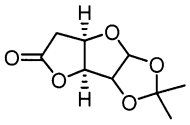
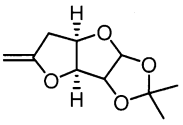
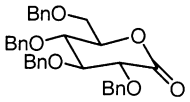
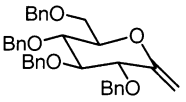
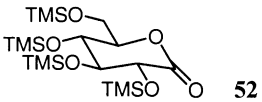
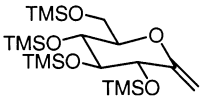
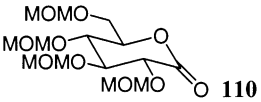
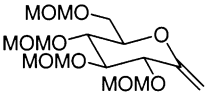
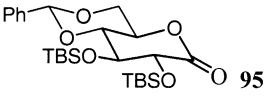
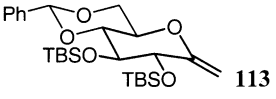
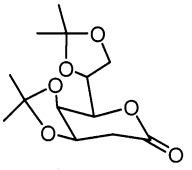
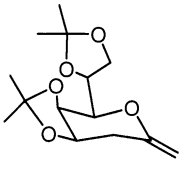
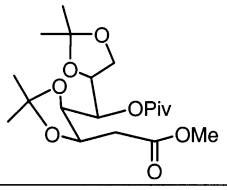
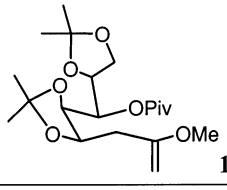
Entry	Substrate	Reaction conditions (yield %)[a]	Product	Ref.
1	 **20**	A (92)  **91**	 **92**	12
2	 **95**	A (92)	 **96**	60
3	 **97**	A (60-80)	 **98**	60
4	 **27**	A (72)	 **99**	61
5	 **100**		 **101**  **102**	65
6	 **104**	B (87%)  **103**	 **105**	66
7	 **106**	B (89%)	 **107**	66
8	 **45**	A (82)	 **108**	60
9		B		73
10	 **52**	A (60)	 **109**	60
11	 **110**	B (79-89)	 **111**	67, 68
12	 **95**	A (100)	 **113**	69
13				
14	 **114**	A (82)	 **115**	63
				63

Table 2 (Continued)

Entry	Substrate	Reaction conditions (yield %)[a]	Product	Ref.
15	 **116**	A (80)	 **117**	63

[a] Reaction conditions: (A) **91**, THF or toluene/THF, −78 °C; (B) **103**, toluene, 65−70 °C.

D-glucurono-6,3 lactone also gave mainly the ketose derivative **101** instead of the expected olefin. Compound **102**, arising from over-methylenation of the intermediate ketose, was also observed (Table 2, entry 5).

The observed side reactions were suppressed when going to dicyclopentadienyl dimethyl titanium reagent **103**,[70] introduced by Petasis for the methylenation of ketones, aldehydes, and esters.[71,72] In contrast to the Tebbe reagent, this aluminum-free reagent operates at high temperature of 60−70 °C in toluene.

Csuk and Glänzer established the usefulness of this reagent in carbohydrate chemistry.[66] D-Mannono-, D-erythrono-, and D-arabino-1,4 lactone were cleanly methylenated in 64−85% yield. It is interesting to note that glucurono-6,3-lactone **104** or the 5-deoxy analogue **106** reacted successfully under these conditions to provide 87% of the methylene derivatives **105** and **107**, respectively (Table 2, entries 6 and 7). The efficiency of the two reagents **103** and **91** is almost the same, as shown by the reaction of lactone **45**, giving **108** in 89% yield (Table 2, compare entries 8 and 9). Tetra-*O*-benzyl-D-mannono-1,5-lactone was also efficiently converted to the 1-*C*-methylene derivative using **103**.[73]

Excellent results were also obtained by Grouiller using the same reagent and 1,4-lactones derived from D-ribose and D-arabinose.[74] No hydration products, observed in the Tebbe reaction, were detected in this case. Finally, methylene *exo*-glycals suitable for ketosides formation have been reported.[75]

It is worthy of note that methylene derivatives, especially those derived from furanoses, are hydrolytically unstable and can be hydrolyzed upon chromatography. Not unexpectedly, disubstituted methylene derivatives are by far more stable.

Interestingly, other reagents have been described for the alkylidenation of esters, such as the Takai[76] and Takeda[77] reagents.[58] The first one is generally prepared in situ from a *gem*-dibromo compound, titanium tetrachloride, and zinc in the presence of TMEDA and/or lead(II) chloride. Poor results have been obtained with aliphatic lactones because of the formation of an open-chain ketone, together with the expected enol ether.[78] To the best of our knowledge, no use of this reagent with sugar lactones has yet been reported. One successful use of this reagent in the methylenation of carbohydrate-derived ester, where Tebbe reagent was ineffective, has been reported.[64] Takai's method would be of interest for the synthesis of substituted *exo*-glycals, which are not accessible by the Wittig olefination with unstabilized ylides.

Titanium alkylidenes, reported first by Takeda,[77] are built from titanocene dichloride and dithioacetals in the presence of magnesium and triethyl phosphite. These reagents successfully transform esters into enol ethers. Here again, no reports of their use in carbohydrate chemistry have appeared, although this method should find many applications.

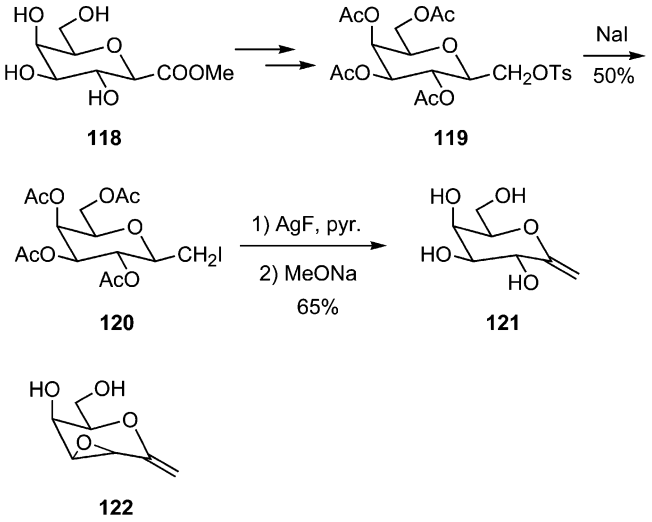
2.2. Stepwise Olefination Methods

2.2.1. Addition–Elimination Reactions

In contrast with the above methods, this approach involves at least two independent steps. In such a sequence, a suitable leaving group, located either on the carbon linked to the anomeric center or at the anomeric center introduced in the first step of the synthetic sequence, undergoes elimination in a subsequent step.

The earliest example for *C*-glycosylidene synthesis is a stepwise synthesis based on the first strategy, frequently used for the synthesis of 5,6-unsaturated sugars.[9] This synthesis started with ester **118**, obtained via cyanation of tetra-*O*-acetyl-α-D-galactosyl bromide. A standard protection−deprotection sequence and ester reduction led to the tosylate **119** in about four steps. Tosylate substitution with sodium iodide gave the iodo derivative **120**. Treatment with silver fluoride in pyridine promoted olefin formation in 94% yield. Subsequent deacetylation gave the target compound **121**. This strategy allowed the synthesis of ^{14}C-labeled **121** by using Na^{14}CN for the cyanation reaction. Along the same lines, an *exo*-glycal **122** bearing an epoxide at position 2,3, a potential affinity labeling compound of hydrolases, has been prepared by a stepwise procedure involving iodohydric acid elimination.[79] In a search for *exo*-glycals as probes for establishment of a glycohydrolase mechanism, unsaturated nitrile **126** and two other olefins, **130** and **131**, have been reported by the same group.[80a] The known aldehyde **123**[80b] was converted to a mixture of alcohols **124**, which were elaborated to the bromides **125**. These compounds were then treated with silver fluoride in pyridine to provide a mixture of unsaturated nitriles. Only the *Z* isomer can be deacetylated to give **126**. The deuterated analogue was obtained in the same way after equilibration of bromides **125** in D_2O. It is interesting to note that the double bond of **126** could

Scheme 12

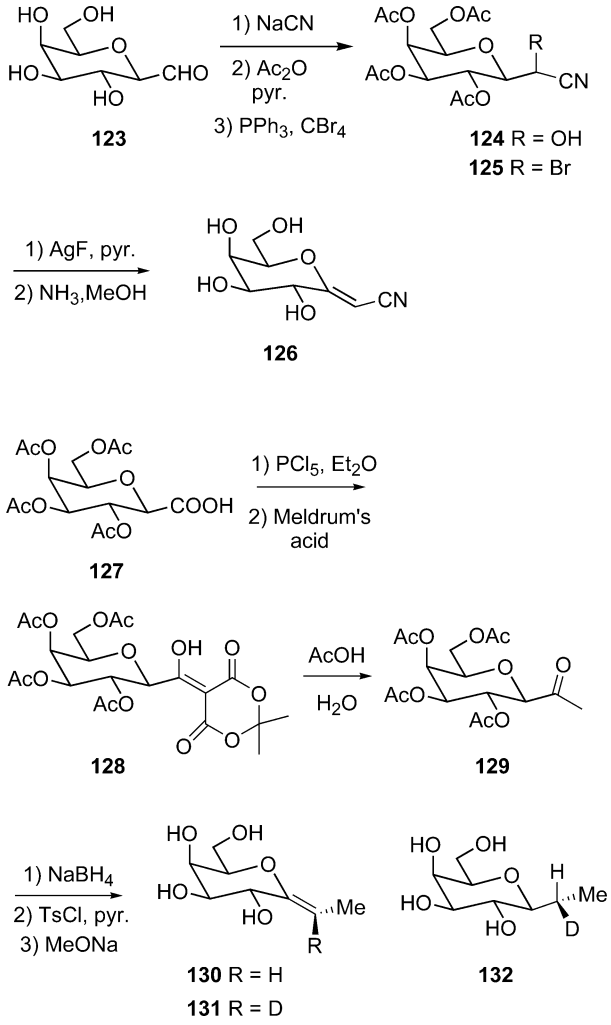


not be hydrated in acidic medium and required high concentrations of galactosidase from *Escherichia coli* to be hydrated. To investigate the mechanism of this enzymic reaction, the stereochemically defined *exo*-glycal **130** and its labeled counterpart were prepared starting from acid **127**, obtained by cyanation of a galactopyranosyl bromide derivative. This sequence involved a one-carbon homologation by condensation of the corresponding acyl chloride with Meldrum's acid. Subsequent decarboxylation gave the methyl ketone **129**, which was then reduced to a separable mixture of alcohols. Tosylation of the alcohol or bromination followed by elimination and deprotection gave the *Z* isomer **130**. Specific deuteration was accomplished by reduction of the benzylated analogue of ketone with $LiAlD_4$. Further treatment as above gave olefin **131**. The gluco analogue of **131** has been prepared in 12 steps by the same route.[81] Although these syntheses proceeded by rather lengthy sequences, the products so obtained were of invaluable help for biochemical studies.[82] These *exo*-glycals were readily hydrated by β-galactosidase, and degradation studies established unambiguously the stereochemical course of the enzymic hydration, which proceeded from the β face of the sugar enol.[83] It is clear that they are substrates of galactosidases, and the geometrical analogy of *exo*-glycals with oxonium ion suggests that some of them could be enzyme inhibitors. Until now, this aspect of *exo*-glycal properties has been poorly investigated.

A similar strategy based on the elimination of a *C*-glycosyl compound was found applicable to seleno-*C*-glycosyl derivatives.[84] The seleno compounds were easily obtained by selenium-mediated 6-*exo*-*trig* ring closure of 6-hydroxy-olefins. Oxidation to the corresponding selenoxide led to smooth elimination of selenophenol and formation of the *exo*-glycal **108** in 90% yield.

The first examples of functionalized *C*-glycosylidene compounds were reported by Trost and Runge.[85] These authors pointed out in their paper that lactone **133** "resisted all attempts to react with Wittig or Emmons−Wadsworth−Horner reagents". Thus, two stepwise procedures were devised. The first one took advantage of a cycloaddition reaction

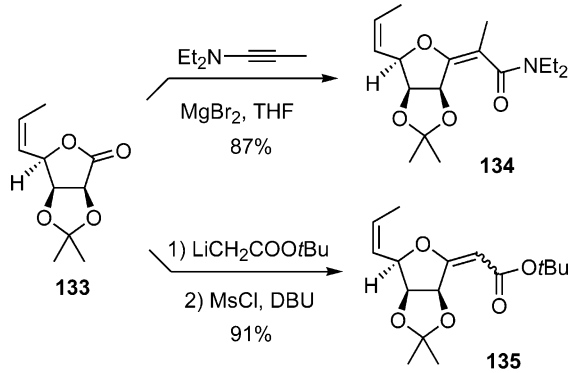
Scheme 13



between the carbonyl group of lactone **133** and ynamines according to the chemistry developed by Ficini et al.[86] An excellent yield of unsaturated amide **134** was obtained. It is clear that this approach did not allow the introduction of an ester group, the corresponding oxygenated reagent being unavailable.

Nucleophilic addition on sugar lactones is well documented. The tertiary alcohol formed in this step can be reduced to produce *C*-glycoside.[87−97] It is conceivable that dehydration of the primary adduct of a carbanion on a sugar lactone will lead to unsaturated compounds if an acidic proton is present on the newly introduced carbon chain.

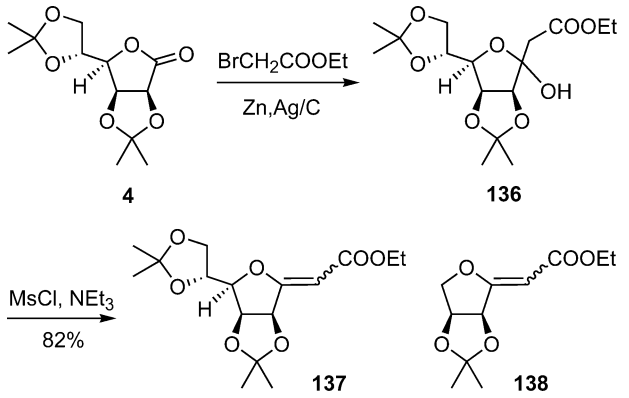
Scheme 14



Accordingly, a two-step sequence was devised by Trost et al., starting with lithio *tert*-butyl acetate condensation on lactone **133**, giving a stable β-hydroxy ester.[85] Analogous reaction on lactones were already known.[14] Subsequent mesylation of the tertiary alcohol in the presence of DBU led to olefin **135**, obtained as a 2:1 *E*/*Z* mixture as shown by NMR.

Many developments of this strategy appeared over the years. For example, simple sugar lactones have been transformed into *exo*-glycals by Csuk and Glänzer, using a Reformatsky-type reaction instead of a low-yielding condensation of lithio acetate derivative.[66] According to this procedure, olefins **137** and **138** were obtained in 81% and 79% yield, respectively.

Scheme 15

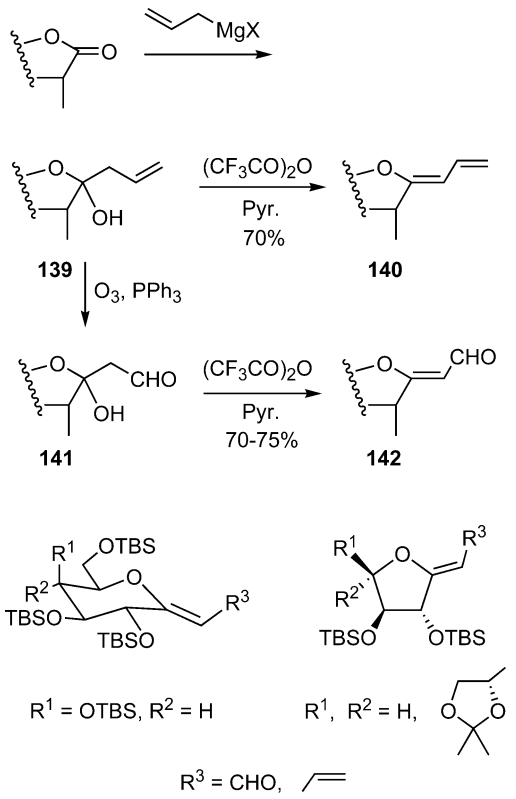


In 2001, two papers by Lin et al. described the reaction of sugar lactones with allyl Grignard reagent. Subsequent treatment with trifluoroacetic anhydride of adduct **139** provided the expected dienes **140** in 60−90% yield.[98] The reactions were performed on *tert*-butyldimethysilyl ether-protected lactones in different series. Accordingly, 1,5-lactones derived from glucose or galactose as well as 1,4-lactones in the same series can be transformed into dienes.

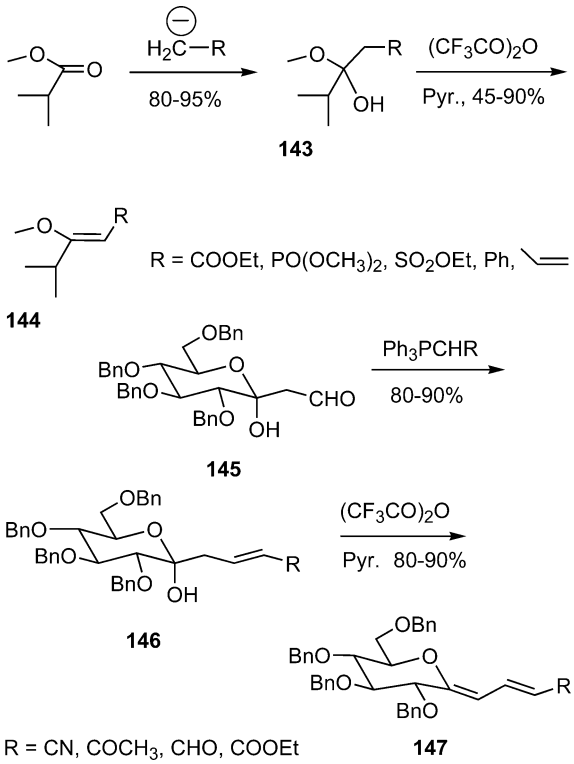
From the primary adduct **139**, it was also shown that ozonolysis of the double bond led to the corresponding aldehyde **141**, which underwent the same dehydration reaction to provide *C*-glycosylidene aldehydes **142** of *Z* configuration. In a second paper, the same group reported the condensation of ester-, phosphonate-, sulfonate-, or benzyl-derived carbanions on lactone to give ketoses **143**. Such nucleophilic addition occurred on tetra-*O*-benzyl-D-glucono-1,5-lactone **45** in 80−90% yield.[99] Subsequent elimination was promoted by trifluoroacetic anhydride to furnish *exo*-glycals **144**. A route to conjugated *exo*-glycals was described starting from allyl adduct, exemplified in the gluco series. Ozonolysis of the double bond gave aldehyde **145**, further homologated by Wittig reaction to α,β-unsaturated nitrile, ketone, aldehyde, and esters **146** (*E*/*Z* mixture). Subsequent dehydration led to a single *Z* isomer **147** with a four-carbon anomeric chain, including two conjugated double bonds.

The high stereocontrol of these dehydration reactions was explained by formation of an oxonium ion upon treatment with trifluoroacetic anhydride. Subsequent double bond formation then occurred by proton abstraction at C1′ (on the chain).[100] A transition state minimizing steric interactions between the

Scheme 16



Scheme 17

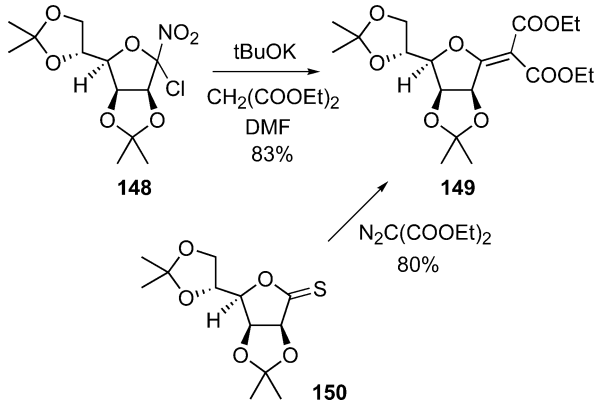


C2 substituent (*O*-benzyl group) and the substituent on the anomeric chain is favored over the other, which places the substituent on the ring oxygen side. Probably stereoelectronic reasons should also be taken into account to explain the high stereoselection in the mannose series where the steric hindrance is lower, the C2 substituent being located upside. This may also be compared with results obtained in the

same series by Taylor using the Ramberg−Bäcklund rearrangement of anomeric sulfones summarized in the following.[101]

Anomeric chloro-nitro sugars such as **148** have been reacted with the carbanion of nitromethane and diethyl malonate.[102] With the latter, subsequent β elimination led to disubstituted *exo*-glycals **149**. The reaction of thio-γ-O-lactones such as **150** with ethyl diazomalonate also gave *exo*-glycals such as **149**.[47] Treatment of the same compound with ethyl diazoacetate in the presence of rhodium catalyst gave a mixture of *E* and *Z* ethyl analogues of **65**. In all the above strategies, a carbanion is condensed on a sugar lactone. The reverse approach involves the condensation of anomeric carbanions on a suitable electrophile. Some examples have been reported by Vasella[103] using 1-nitro sugars. Anomeric enolates have been condensed with complex sugar-derived aldehydes for the construction of *C*-disaccharidic structures via reduction of intermediate *exo*-glycals.[104] This approach found applications en route to herbicidin.[105,106] Further details on these papers can be found in an excellent review by Somsak on anomeric carbanions.[107]

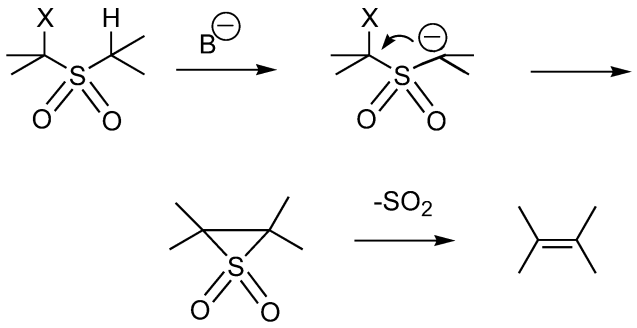
Scheme 18



2.2.2. Ramberg–Bäcklund Olefination

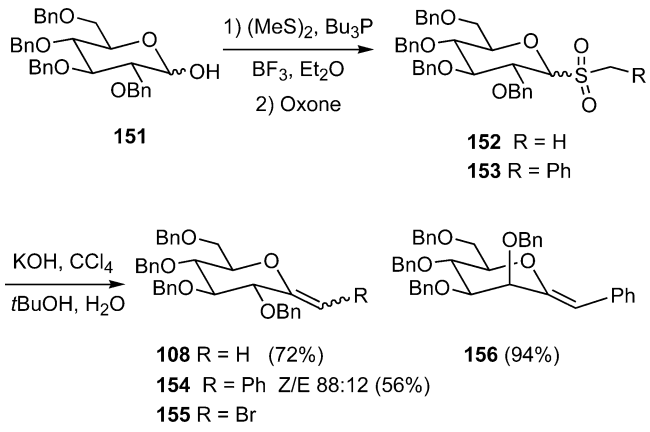
The preparation of olefins from sulfone via the Ramberg−Bäcklund rearrangement is a long-known reaction.[108] The basic principle of this reaction is to use a dissymmetric sulfone which is halogenated at one α position. Treatment with base generates a carbanion at the other α position. Internal carbon−carbon bond formation occurs via episulfone formation, followed by sulfur dioxide elimination to form the carbon−carbon double bond. Sulfones are rather readily available compounds, and efficient protocols to promote the Ramberg−Bäcklund rearrangement by in situ halogenation and subsequent base treatment have been proposed.[109] Two groups have applied this methodology, almost simultaneously, to the synthesis of *exo*-glycals. Anomeric sulfones are easily available by oxidation of thioglycosides, the latter being well-studied compounds as key intermediates in glycosylation reactions.[110−112] Some examples of *C*-glycosylidene available via this method are given below. Using methyl sulfone **152**, easily prepared from **151**, *exo*-methylene sugar **108** was obtained by Taylor et al.[101,113] This method is an alternative to

Scheme 19



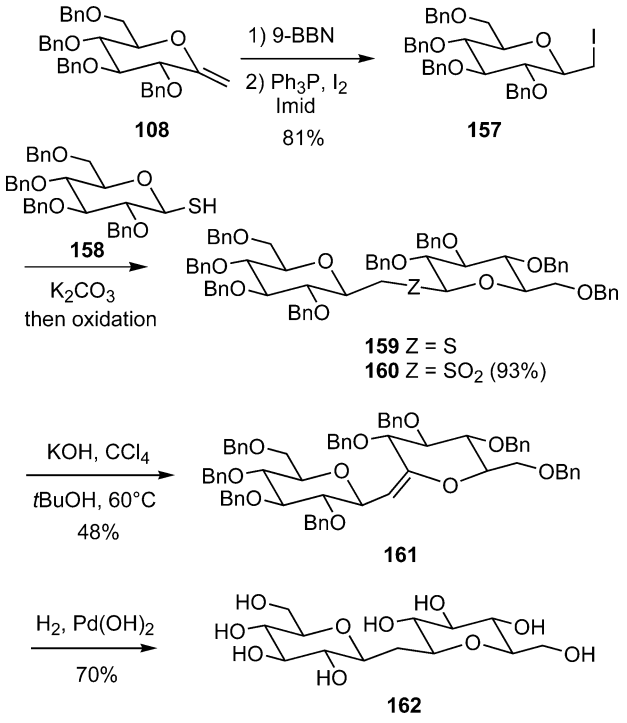
Tebbe methylenation. Yields up to 72% were obtained in the Ramberg−Bäcklund rearrangement. Depending on the reaction conditions, halogenated species such as **155** can be isolated in 15−32% yields. More interesting maybe is the synthesis of disubstituted *exo*-glycals starting from more complex sulfones such as **153**, which rearranged to **154**, obtained as an 88:12 *Z*/*E* mixture in 94% yield. This strategy has been applied to the synthesis of a number of compounds, starting from different sugar sulfones obtained from D-glucose, D-galactose, and D-arabinose. The *Z*/*E* ratio was mainly in favor of the former. More stereoselective was the formation of olefin **156** in the mannose series, which gave only the *Z* isomer. Even disubstituted *exo*-glycals were obtained accordingly but in lower yields. It is also interesting to note that both anomeric sulfones can be used in this process but led to a different *Z*/*E* ratio of the *exo*-glycal. The stereochemical course of the Ramberg−Bäcklund rearrangement has been discussed in detail.[113] This should be compared with the results obtained by Lin et al., who obtained only *Z* isomers in the gluco series.[100]

Scheme 20



Highly complex *exo*-glycals can be prepared by this method. One example came from Taylor's group, who described the synthesis of a *C*-disaccharide based on this approach.[114] The synthesis started from compound **108**, which was transformed into the iodomethyl *C*-glycoside **157**. Coupling of the latter with tetra-*O*-benzylthio glucose **158** gave sulfide **159**. Oxidation to the sulfone **160**, followed by Ramberg−Bäcklund rearrangement, gave the olefin **161** in 48% yield (*Z*/*E* 91:9). Subsequent stereoselective reduction of the double bond and removal of the benzyl

Scheme 21



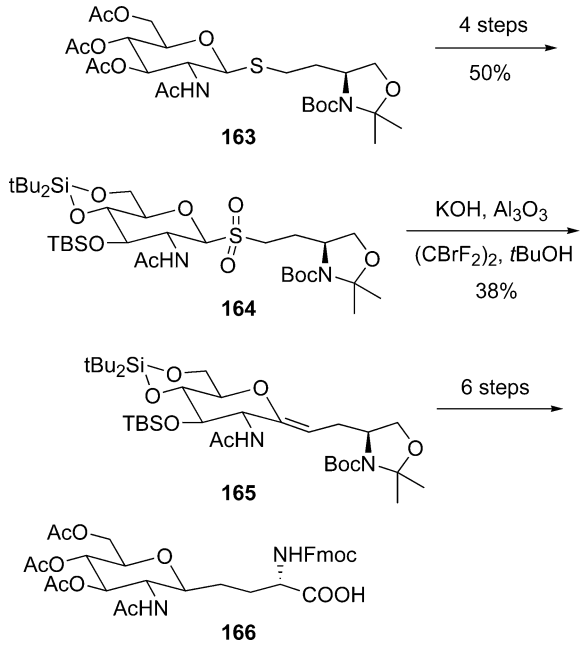
ether groups led to the target *C*-isotrehalose **162**. Franck's group has also developed the same approach. A series of benzylic *C*-glycosides has been prepared via *S*-glycosylation of different substrates, including 2-deoxy ones.[115] Oxidation to the sulfones, followed by Ramberg−Bäcklund rearrangement, gave *E*/*Z* mixtures of the expected *exo*-glycals. Subsequent reduction of the double bond gave *β*-*C*-glycosides in the gluco and manno series.[115] More complex *exo*-glycals en route to complex *C*-glycosides such as *C*-glycerolipids of *N*-acetyl glucosamine,[116] and *C*-glycosyl porphyrines, have been prepared from *C*-glycosylated benzaldehyde derivatives.[117]

Along the same lines, the construction of a complex *exo*-glycal, incorporating a protected chiral amino alcohol, has been described by Ichikawa and Ohnishi.[118] The rearrangement of **164**, performed under Franck conditions,[116] required replacement of the acetyl protecting group of **163** by less base-sensitive silyl ethers. The rearrangement proceeded in 38% yield only, giving the *Z* isomer **165**. Reduction of the double bond gave the *β*-C-glycoside, which was further elaborated to the serine glucosamidine analogue **166**. It is interesting to compare this approach with the construction of the same type of assembly of glucose and serine, also taking advantage of the Ramberg−Bäcklund rearrangement performed between a *β*-C-glycoside of glucose and a thiol.[119] In this case, the rearrangement proceeded one carbon away from the anomeric center, also in modest yield. The construction of unsaturated C-glycosyl compounds and 1,6-*C*-disaccharides using this strategy has been reported recently.[120]

2.2.3. Miscellaneous Methods

Examples of *exo*-glycal formation by reductive elimination of benzoylated fructo- or sorbopyranosyl bromides have been reported.[121] Competitive elimination of benzoate at position 3, forming *endo*-glycals, was also observed.

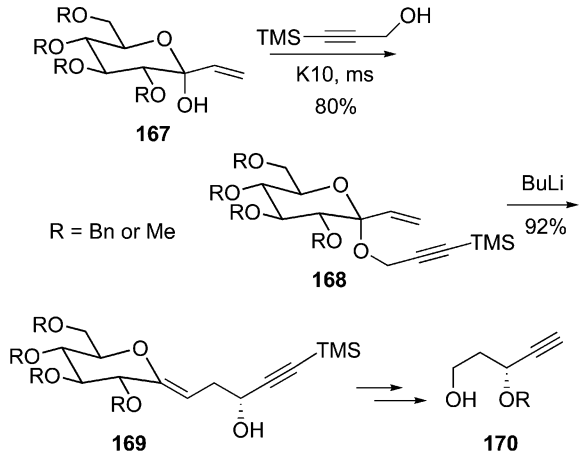
Scheme 22



Although the method was not initially devised to construct this type of substrates, the formation of *exo*-glycals has been reported by Nakai.[122] Treatment of the vinyl ketose **167**, readily obtained from tetra-*O*-benzyl-D-glucose, with trimethyl silylpropargyl alcohol in the presence of montmorillonite K10 and 4-Å molecular sieves gave the α-glycoside **168**. The latter underwent [2,3]-Wittig rearrangement on treatment with butyllithium from −78 to 60 °C to give the olefin **169** in 92% yield as the *Z* isomer. The main interest for the authors lay in the transmission of asymmetry on the newly created chiral center. Ozonolysis of the double bond followed by reduction gave chiral alcohol **170** in up to 95% ee. The same rearrangement could be performed with a substituted olefin (propenyl instead of vinyl) to provide *exo*-glycals with two chiral centers on the newly created appendage. The high functionality of the chain introduced in the *exo*-glycal chain makes this method attractive for the synthesis of complex *C*-glycosides and natural molecules.

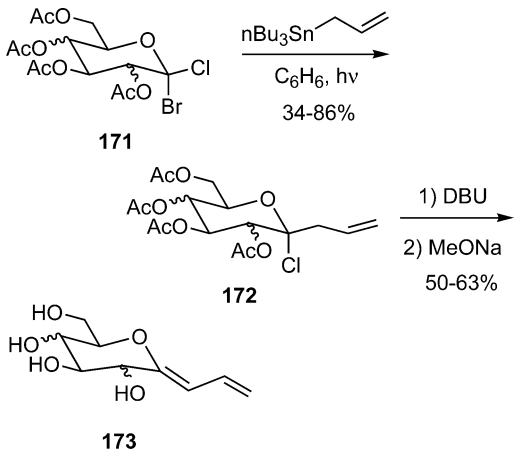
The synthesis of *C*-glycosylidene dienes has been developed by Praly et al. using radical chemis-

Scheme 23



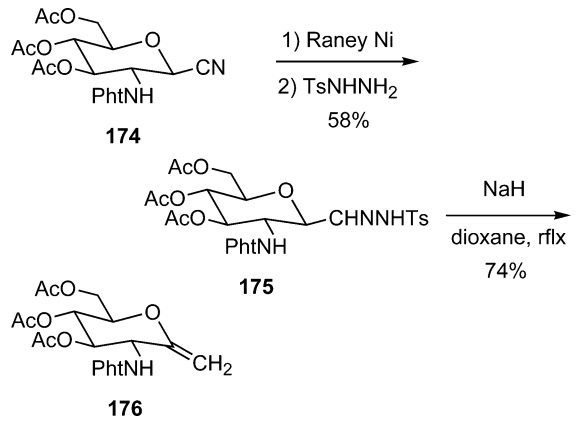
try.[123,124] Exploiting the chemistry of glycopyranosyl dihalides, a modified Keck radical allylation of the bromochloro derivative **171** gave the α-chloro-*β*-*C*-glycosyl derivative **172** in 34−86% yield, depending on the starting hexose. Upon treatment with DBU, elimination occurred, giving the corresponding *exo*-glycal of *Z* configuration (∼40% yield), as shown from NMR data and NOE measurements. Removal of the acetate was cleanly achieved in basic medium to give **173**, establishing the stability of these compounds in basic medium.

Scheme 24



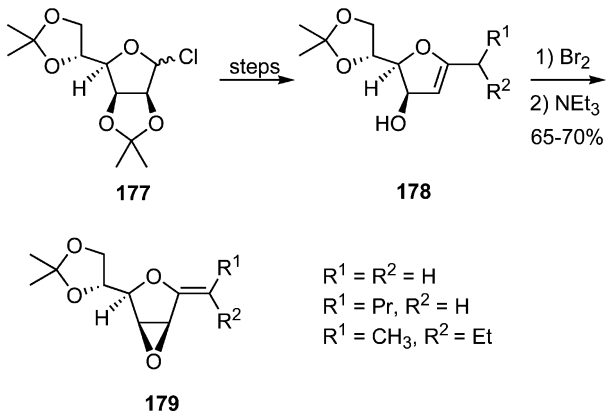
An interesting approach to 1-*C*-methylene sugars has been proposed, based on the treatment of tosyl hydrazones under Bamford−Stevens conditions.[125] These hydrazones were obtained from anomeric cyanide.[126] The reaction conditions are compatible with the presence of acyl protecting groups, as shown for the preparation of *exo*-glycal **176** from **174**. Recently, Lopez proposed a stepwise route to *exo*-

Scheme 25



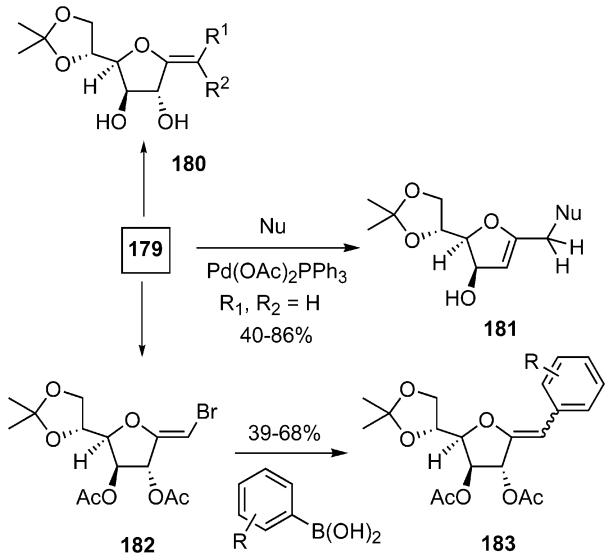
glycal having an epoxide function at position 2,3 of the sugar ring.[127] This route started from *C*-glycal **178**, obtained by reaction of organometallics on the 1-chloro mannosyl derivative **177**. The 3-hydroxy-glucal was subjected to bromine addition, followed by base-induced hydrogen bromide elimination. Fair to good yields of olefins **179** were obtained. The chemistry of these compounds was investigated and led to other classes of *exo*-glycals. Standard epoxide opening of **179** afforded the corresponding diols **180**.

Scheme 26



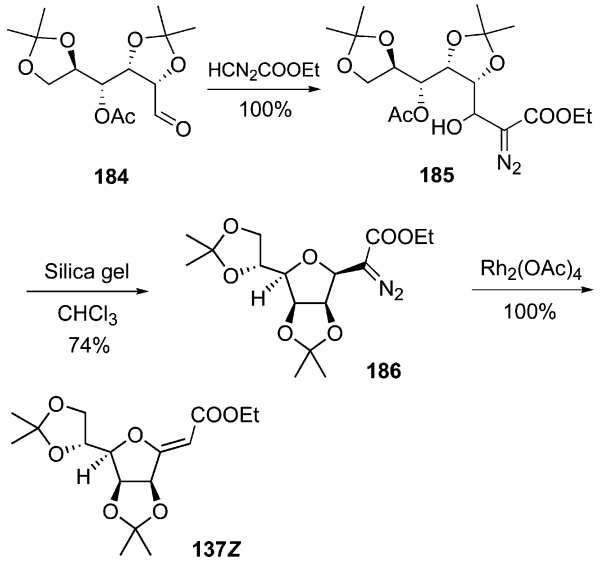
More interestingly, compounds **179** were treated with nucleophiles in the presence of a palladium catalyst to afford substituted *C*-glycals **181**, but this reaction did not proceed with tetrasubstituted olefinic compounds **179**. Epoxy-*exo*-glycals can undergo further bromine addition and subsequent hydrogen bromide elimination to yield a monobromo olefin. Subsequent epoxide opening and acylation gave **182**. This compound can be used in a Suzuki coupling process with substituted aromatics-derived boronic acids.[128] This sequence opens the way to a new class of *exo*-glycals obtained in a single, yet unknown isomeric form of **183**. Open-chain olefins can usually be obtained by

Scheme 27



controlled Wittig elongation of lactols. Further electrophilic cyclization using iodine and sodium carbonate gave the 2-iodoheptonate.[129,130] When this method was applied to 1,2−5,6-di-*O*-isopropylidene-mannofuranose, subsequent dehydroiodination gave *exo*-glycal **137*Z***. The same compound has been obtained by the same group also using acyclic sugar aldehyde **184**, which was reacted with α-diazoester.[131] The resulting alcohol **185** was subsequently cyclized to the 2-diazo-3,6-anhydrooctanoate **186** on silica gel. Upon treatment with rhodium acetate, this compound yielded **137*Z*** as a single isomer. These two methods were not designed primarily to produce *exo*-glycals but could find applications in this field.

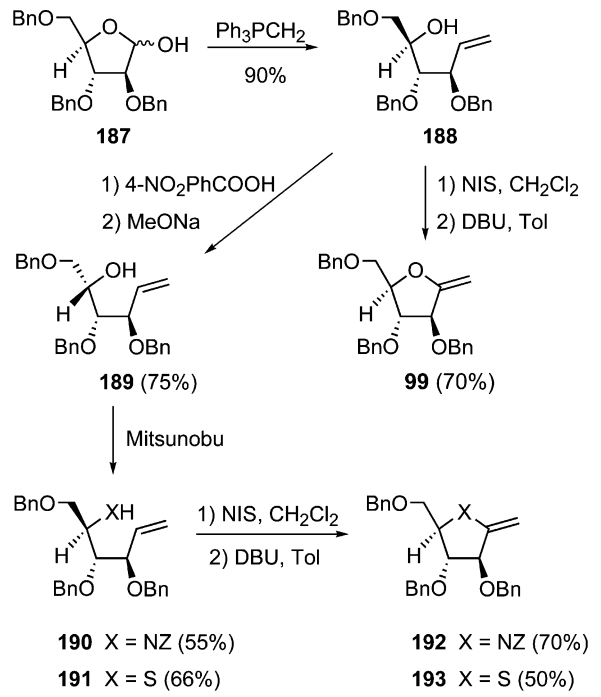
Scheme 28



Wacker oxidation of such an open-chain olefin obtained from arabinose has been reported to give a mixture of the methyl ketoside and the corresponding *exo*-glycal.[132]

Electrophilic cyclization of open-chain sugar olefin has been proposed to form *exo*-glycals and their hetero analogues.[133a] Olefination of reducing sugar **187** according to Sinaÿ's procedure[133b] gave the open-chain olefin **188**. Treatment with *N*-iodosuccinimide, followed by DBU-catalyzed elimination, gave *exo*-glycal **99**. Interestingly, other so-called heteroglycals **192** and **193**, having nitrogen or sulfur atoms in the ring, were prepared by cyclization of the corresponding amino and thio derivatives **190** and **191** by the above-mentioned procedure. Analogously, stepwise iodocyclization of a 4-pentene-1,2-diol, followed by iodohydric acid elimination, has been proposed to prepare a 1-*C*-methylene *exo*-glycal, further elaborated to 1′-C-fluoromethyl-dideoxy-cytidine under the action of Selectfluor.[134]

Scheme 29



3. Synthetic Uses of exo-Glycals

The *exo*-glycal double bond is expected to have a good reactivity, mainly governed by the presence of the ring oxygen substituent. It is clear that electrophilic addition on this electron-rich double bond would be facilitated by formation of a stabilized intermediate oxonium ion. This reactivity should be rather different on *exo*-glycals tri- or tetrasubstituted with electron-withdrawing substituents. This new type of captodative olefinic system should present unexpected reactivity, which needs to be explored. Several examples aiming at the use of *exo*-glycals in the syntheses of more complex structures have appeared, as summarized below.

3.1. Synthesis of *C*-Glycosyl Compounds

C-Glycoside formation from *exo*-glycals is probably one of the first motivations to investigate the chemistry of these compounds. Although there is a large number of available methods to construct *C*-glycosyl derivatives,[135] an approach via *C*-glycosylidene would have some advantages. One advantage would be a high stereocontrol of the double bond reduction due to the sugar template effect. The second would be an access to new type of *C*-glycosides incorporating functional groups which would be impossible to introduce by known *C*-glycosylation methods. Finally, double bond functionalizations would be a unique way to obtain new types of carbohydrate analogues.

3.1.1. Double Bond Reduction

The simple reduction of the double bond of *exo*-glycals has been largely investigated. Introduction of a methyl group at the anomeric position in a stereocontrolled manner is not a straightforward operation. Most methods rely on methyllithium addition on the aldehyde, followed by tetrahydrofuran or tetrahydropyran formation using nucleophilic displacement.[136−138]

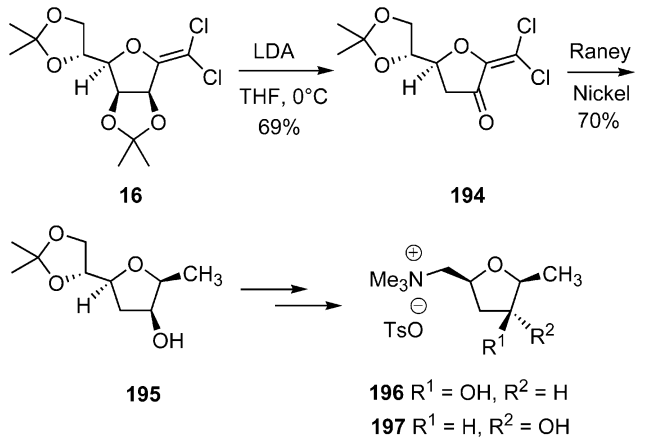
The reduction of *exo*-methylene derivatives obtained via Tebbe olefination of lactones gave obviously the corresponding 1-*C*-methyl glycoside.[12,60] In our group, we also investigated the reduction of the dihalomethylene moiety obtained via the Wittig or Wittig-type dichloromethylenation as a way to prepare the same compounds. Standard catalytic hydrogenation did not give satisfactory results, mainly due to hydrochloric acid formation during this process. After some experimentation, it was found to be more convenient to use Raney nickel in ethyl acetate. Good to excellent yields of 1-*C*-methyl compounds were obtained.

To illustrate this reaction, two examples are given below. The first one shows the use of dichloroolefins for the synthesis of muscarine, a chiral naturally occurring tetrahydrofuran.[139] Other examples will be related to the construction of *C*-glycosides of fucose using the same methodology.

The synthesis of muscarine started with D-mannonolactone-derived dichloroolefin **16**. The first reac-

tion takes advantage of the presence of the dichloromethylene moiety, which makes the allylic proton acidic enough to be abstracted by bases, allowing the splitting of the isopropylidene ring to form the ketone **194**.[11,140] Reduction with Raney nickel gave **195** as the major isomer, together with its C2−C3 epimer (9:1). Several steps led to epimuscarine **196**, and to muscarine **197** after Mitsunobu inversion at C3.

Scheme 30



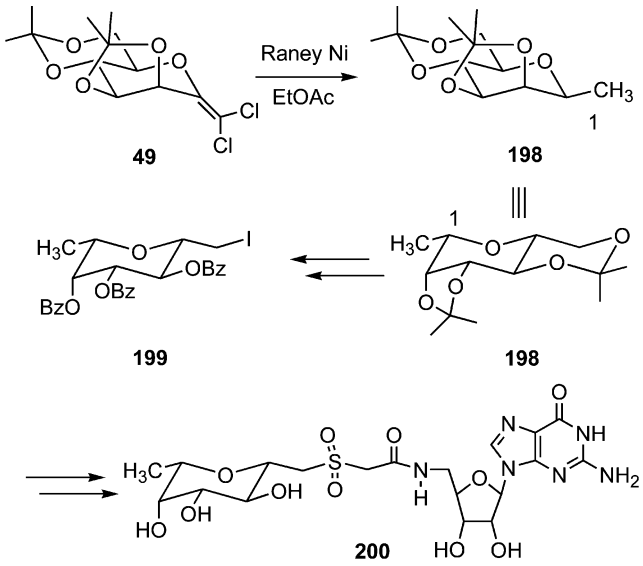
Another synthesis of muscarine derivatives has been recently disclosed, based on the reduction of a methylene *exo*-glycal obtained by a tedious five-step process from (*S*)-(−)-5-hydroxy-2(5*H*)-furanone.[141] The *exo*-glycal was obtained by Tebbe methylenation of the lactone, carried out at −40 °C in a THF/toluene and pyridine mixture. Catalytic reduction of the double bond over Raney nickel under pressure (2 bar) gave an almost 1:1 mixture of epimers in 78% yield for the two steps.

Raney nickel reduction of standard dichloroolefins has been investigated.[17] It should be noted that reduction of **14** or **16** is by far more selective, giving only one *C*-glycoside with the methyl group syn to the dioxolane ring. In the ribo series, the reduction of **21** or **19**, a 9:1 ratio of both diastereoisomers was formed due to some steric hindrance by the C6 protecting group.

In the pyranose series, interesting results were also obtained. Reduction of the gluco derivative **46** with Raney nickel was also selective, giving the 1-*C*-methyl β derivative; i.e., the methyl group is now anti to the C3 neighboring group. This can be explained by the distorted conformation of **46**, which allowed approach of the catalyst by the α less hindered face.

In the manno series, a syn relationship between the C2 methyl group and the dioxolane ring was found upon reduction of olefin **49**. This is illustrated below with the synthesis of an analogue of guanosyl diphosphofucose.[142] Reduction of **49** gave the *C*-glycoside **198** as a single isomer. Looking at this compound in a different way, the methyl group introduced at C1 of a D-mannose derivative now became the C6 methyl group of a L-fucose derivative, having a hydroxymethyl group at the anomeric position. Standard iodination of the primary hydroxyl group led to **199**, which was coupled with the appropriate thioglycolic acid and then with a guanosine derivative to produce, after deprotection, the GDP

Scheme 31

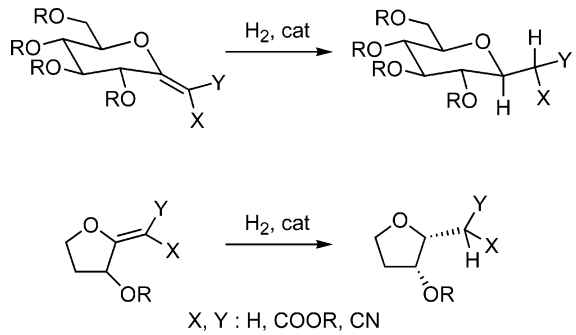


analogue **200**. This stratagem enlarged the repertoire of *C*-glycoside formation reactions.[143] It would have been more tedious to start from L-fucose and to introduce a hydroxymethyl group at the anomeric position.

It is interesting to note that the reduction of difluoro-*exo*-glycals gave difluoromethyl-*C*-glycosides.[20,21]

exo-Glycals **63**−**75**, obtained according to our different Wittig procedures, can be easily catalytically reduced to *C*-glycosides.[38] In most cases this reduction proved highly stereoselective. The stereochemical course of the reduction follows some tendencies. For example, in the glucopyranose series, the β-anomer is formed preferentially,[115] if not exclusively,[33,51,114b,116−119,144] likely due to conformational bias. No direct influence of the substituent at C2 (carbohydrate numbering) was found, 2-deoxy derivatives giving almost exclusively the β-*C*-glycoside.[56,115] In

Scheme 32



the furanose series, the reduction is also stereoselective and governed by the substituent orientation α to the double bond, the major reduction product being in a cis relationship with this substituent.[38] Reduction of 2-deoxy compounds **90** gave an almost 1:1 mixture of anomers.[55]

Some examples of the formation of *C*-glycosides by catalytic reduction of *exo*-glycals have been already described in section II, most of the cited papers dealing with the synthesis of these compounds.

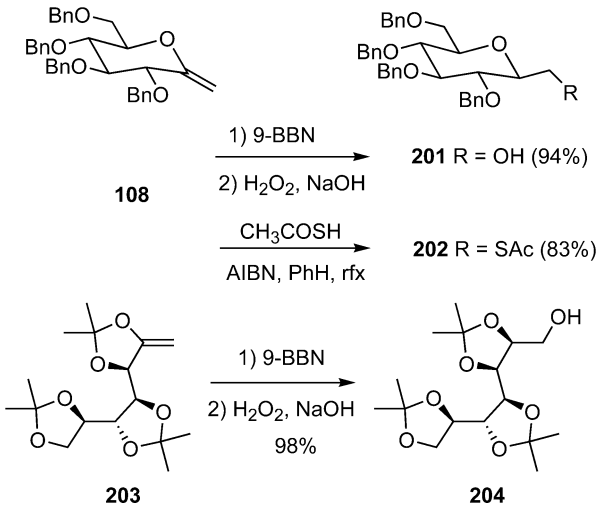
3.1.2. Double Bond Functionalization

Functionalization of *exo*-glycal double bond has been intensively investigated. Introduction of a sulfur atom on the double bond of **108** has been reported by Gervay et al.[145] Radical addition of thioacetic acid allowed the formation of the thioacetyl derivative **202** in 83% yield.

Hydroboration of olefin **108** using 9-BBN, followed by hydrogen peroxide treatment, has been reported to yield the *β*-*C*-glucopyranoside derivative **201** in 94% yield.[60] Hydroboration of the 3,4-di-*O*-(4-methoxybenzyl) analogue of **108** under the same conditions also gave the *β*-*C*-glycoside, but the use of borane−THF complex gave an inseparable mixture of α- and *β*-*C*-glycoside in a 1:2 ratio.[146] The two compounds have been used in the synthesis of inositol phosphates analogues.[147] These procedures allows facile introduction of a one-carbon functional group at the anomeric center with excellent stereocontrol. The corresponding iodo derivative **157** has been prepared by treatment of **201** with Garegg's reagent (Ph_3P, I_2, imidazole).[119]

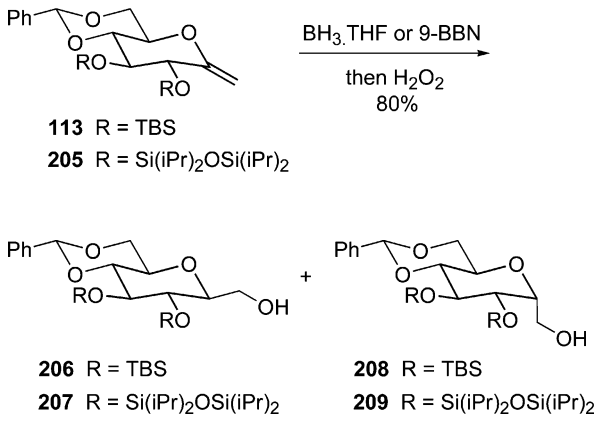
The same type of transformation has been proposed as a means to perform sugar homologation.[62] As an example, dioxolanone **54**, derived from D-gluconolactone, was methylenated with Tebbe reagent to give compound **203** in high yield. Hydroboration−oxidation of this particular *exo*-glycal gave a heptose derivative **204** in 68% yield with up to 98% diastereoselectivity.

Scheme 33



This procedure has been used to convert D-glucose into the AB ring system of ciguatoxin.[69] Tebbe methylenation of the corresponding lactone gave **113**. Subsequent hydroboration with BH_3−THF complex gave a mixture of two anomers in 80% yield. In contrast with the above-cited reports, the α anomer **208** was obtained as the major isomer (1.8:1). In light of the above-mentioned reduction reactions of six-membered-ring *exo*-glycal, it is likely that the pyranose ring adopts a more or less distorded boat conformation, making more accessible the α face and leading to *β* derivatives. The formation of **208** could be explained by the presence of the bulky *tert*-butyl dimethyl silyl ether at O2, which, in such a distorted boat conformation, lies in an axial orientation and impedes the approach of the reagent from the α face. Interestingly, 9-BBN, a bulkier and more stereoselective reagent, did not react. Simply exchanging the

Scheme 34

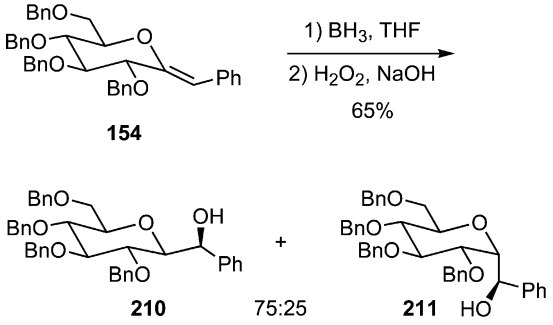


bulky silyl ethers group for a cyclic silyl ether system as in **205** dramatically changed the stereochemical course of the hydroboration reaction. Thus, alcohols **207** and **209** were formed in a 9:1 ratio with BH_3−THF complex, whereas 9-BBN gave rise only to the formation of **207** in 85% yield. This alcohol was further homologated to an allyl group, which was engaged in a ring-closing metathesis reaction with an acrylate group to form a seven-membered unsaturated lactone. The latter was further engaged in the same reaction sequence to form the A ring of ciguatoxin. Other synthetic uses of *exo*-glycal hydroboration in Suzuki coupling reaction will be discussed in the next section.

Very recently, the tetrahydrofuran C ring of the cytotoxic polyether macrolide halicondrin has been constructed by this Tebbe methylenation−hydroboration sequence applied to a fused furano 1,4-lactone.[148]

Functionalization of disubstituted *exo*-glycals would create a new asymmetric center next to the anomeric position. For example, the *Z* olefin **154**, obtained through the Ramberg−Bäcklund rearrangement, has been subjected to a hydroboration−oxidation sequence (BH_3−THF), providing the two diastereomeric alcohols **210** and **211** (3:1 ratio) in 65% yield.[114b,144] It is interesting to note that this reaction is less stereoselective, in contrast with the reported hydroboration of unsubstituted *exo*-glycal. It is likely that the phenyl ring plays a role in the control of the borane approach. This was confirmed by the absence of reaction of **154** with the bulkier 9-BBN. Disubsti-

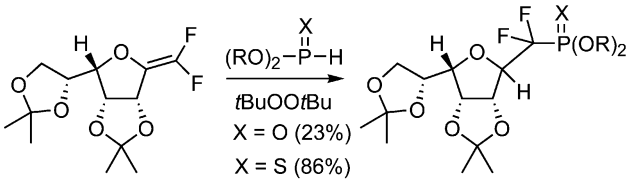
Scheme 35



tuted *exo*-glycals are less reactive than *C*-methylene compounds. In particular, dihaloolefins proved difficult to functionalize efficiently. These compounds are very stable toward aqueous acid or base and cannot be hydrated. For example, acetonide groups of dichloroolefins such as **14** or **16** can be removed without affecting the olefinic bond.

Radical reactions were efficient for the functionalization of the difluoroolefins such as **15**.[149,150] Phosphonyl and thiophosphonyl radicals added to the difluoro double bond to yield the corresponding difluorophosphonates **212** (X = O) and difluorothiophosphonates **212** (X = S) in good yields.[149,150] This reaction has been used in the galactofuranose series to produce a β-*C*-glycosyl phosphonate.[151] Other ap-

Scheme 36



proaches to *C*-glycosides formation, based on the reduction of ketose hemiacetals formed by chemical manipulation of the *exo*-glycal double bond, are given in the following.

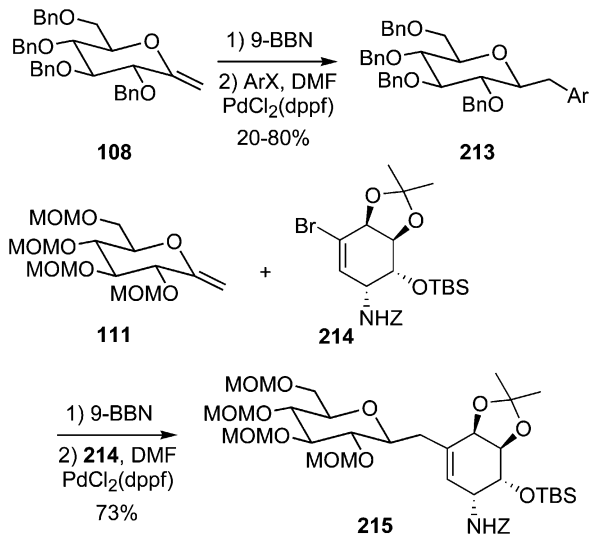
3.1.3. Chain Extension by New Carbon–Carbon Bond Formation

The search for new methods of carbon−carbon bond formation from *exo*-glycals is of interest since it would open the way to new classes of compounds from readily available intermediates.

The Suzuki coupling of alkyl boranes with vinyl halides or activated enol ether has become a well-established method for the construction of complex molecules.[152,153] Hydroboration of enol ether is a straightforward route to alkyl boranes and has prompted the use of *exo*-glycals as starting enol ethers.

RajanBabu and Reddy explored the reaction of **108** with arylmercuric derivatives in the presence of Pd(II) catalyst to introduce an aryl substituent on the *exo*-glycal, opening the way to benzyl-*C*-glycosides.[60] A related approach took advantage of the facile hydroboration of **108** for carbon−carbon bond construction using Suzuki coupling reactions.[73,154] As an example, **108** was transformed into benzyl-β-*C*-glucoside **213** in 67% yield. Only the β anomer was obtained, in line with the results of hydroboration−oxidation reactions. Some substituted aryl halides, including 2-bromopyridine, can be used in this reaction with yields between 21% and 82%. Interestingly, using this coupling reaction, 1,3,5-tribromobenzene can be "*C*-glycosylated" three times, opening the way to aromatic ring-based multivalent scaffolds. Application of this strategy to a more complex vinyl bromide **214**, obtained from bromobenzene, has been reported.[67,154] *exo*-Glycal **111**, obtained in 79% from the corresponding lactone using Petasis reagent, was coupled with vinyl bromide **214** to give the β-anomer **215** in 73% yield. Further manipulation of the double bond of **215** led to the synthesis of a complex aza-*C*-disaccharides (see also ref 73). A vinyl iodide derived

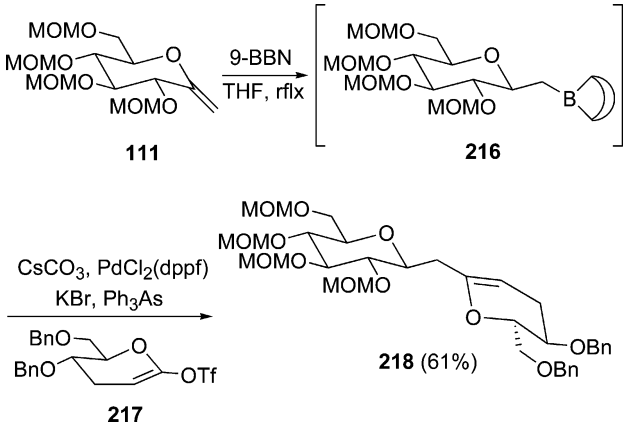
Scheme 37



from Garner aldehyde has been coupled with the β-*C*-organoborane obtained by treatment of **108** with 9-BBN in 78% yield.[119] This opened the way to *C*-glycosyl analogues of glycosyl amino acids.

Coupling of enol triflates derived from 1,5-lactones with alkylborane reagent obtained from **111** has also been reported in relation with ciguatoxin total synthesis.[68] *exo*-Glycal **111** was treated with 9-BBN to give the β-*C*-glycoside **216**. In situ coupling with enol triflate **217**, under palladium catalysis, provided the *C*-disaccharide **218** in 61% yield over the two steps. Triphenylarsine was employed as a co-ligand in this reaction. Alkyl boranes have been also generated starting from 5,6-unsaturated hexoses[155] or other seven-membered-ring *exo*-glycals.[156,157]

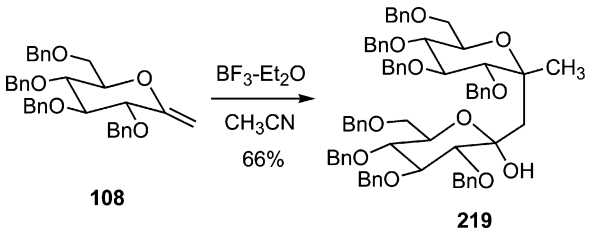
Scheme 38



Several alkylboranes obtained from sugar lactones have been coupled with enol triflates derived from 2,3-dideoxy sugars. The *C*-disaccharides obtained in this way proved interesting substrates for further elaboration into fused polyether frameworks present in marine toxins such as brevetoxins, ciguatoxins, or maitotoxins.[158−160]

The synthesis of *C*-disaccharides using *exo*-glycals as key intermediates has been already mentioned.[114b] This type of carbohydrate mimics has been prepared by Nicotra by simple treatment of the *C*-methylene derivative **108** with a Lewis acid, BF_3-Et_2O.[161] This reaction should proceed via formation of an oxonium cation from **108**, attacked from the α face by another molecule of **108** to give the *C*-disaccharide **219** in 66% yield.

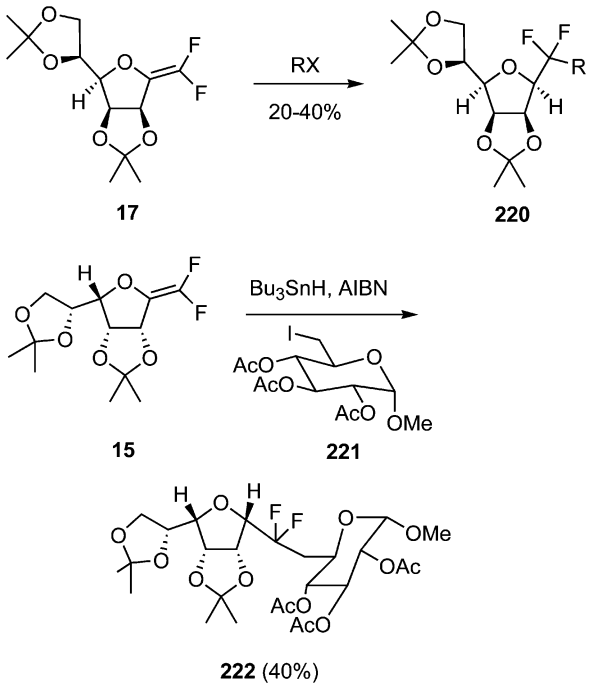
Scheme 39



As mentioned above, difluoro-*exo*-glycals behave as good radical acceptors. This has been exploited by Motherwell et al. to synthesize difluoromethylene-*C*-glycosides using alkyl radicals.[162] The addition of nucleophilic radicals on **17** was rather sluggish, giving the *C*-glycosides **220** in about 20−40% yield, together with some recovered starting material. In this manno series, only the β anomer was formed due to trapping of the intermediate anomeric radical by the less hindered α face. Electrophilic radicals can also be used more efficiently. For example, the radical obtained from ethyl bromoacetate and tri-*n*-butyltin hydride added to difluoroolefin **15** in 51% yield. The yield was lower with olefin **53** (27%), which did not react with nucleophilic radicals.

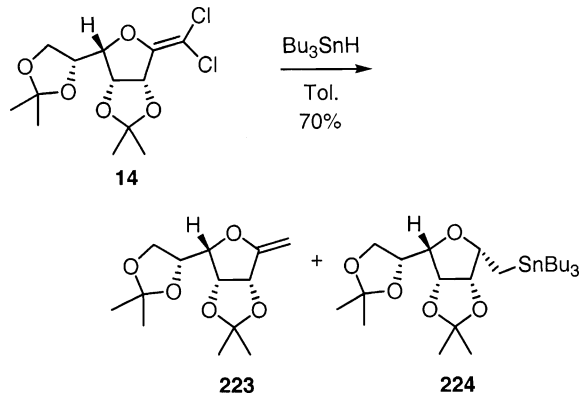
By using carbohydrate-derived nucleophilic radicals, a new class of *C*-disaccharides can be prepared.[163] This is illustrated with the synthesis of the *C*-disaccharide **222** starting from *exo*-glycal **15** and the radical derived from iodide **221**. Only the α anomer was obtained in 40% yield. Again, trapping of the intermediate anomeric radical from the less hindered face can be invoked to explain this result. The addition of malonyl radicals on *exo*-glycals **108** and **99** has been reported.[6] Radical were obtained by reaction of tri-*n*-butyltin hydride with ethyl chloromalonate. The yields were only in the 30% range but can be improved using Bu_3SnH slow addition techniques.

Scheme 40



This example showed that methylene derivatives such as **108** are poor radical acceptors, even when reacted with electrophilic radicals.[164] Unexpectedly, we have been able to show that tributyltin radicals can add to *C*-methylene sugars.[165] Dichloro-*exo*-glycals obtained by our group are very poor radical acceptors. For example, it is possible to carry out radical dechlorination of the double bond of **14** to produce the corresponding *exo*-methylene derivative **223** in 56% yield. This reaction is not possible with benzyl-protected derivatives such as **46** or **28**. This two-step sequence is equivalent to direct methylenation of lactones without use of organometallic species. However, we observed that, in the presence of a large excess of tri-*n*-butyltin radicals, new tin-containing products were formed. They were clearly identified as tri-*n*-butyltin methylene-*C*-glycosides such as **224**. These compounds can be obtained by treatment of **223** with excess tri-*n*-butyl hydride in refluxing toluene. A syn arrangement of the two substituents at C1 and C2 was found as a result of anomeric radical trapping from the less hindered face. The use of a catalytic amount of tri-*n*-butyltin hydride ($NaBH_3$-CN, Bu_3SnCl) allowed complete suppression of this side product formation.

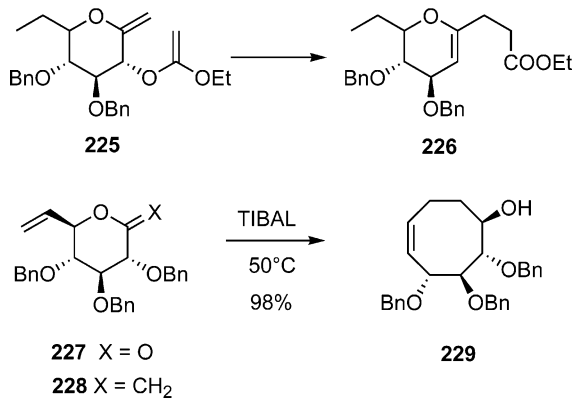
Scheme 41



An example of chain extension using the Claisen−Ireland rearrangement of 2-acyl *exo*-glycal **225** has been described. This method created a 1-*C*-branched *endo*-glycal derivative **226**.[166,167]

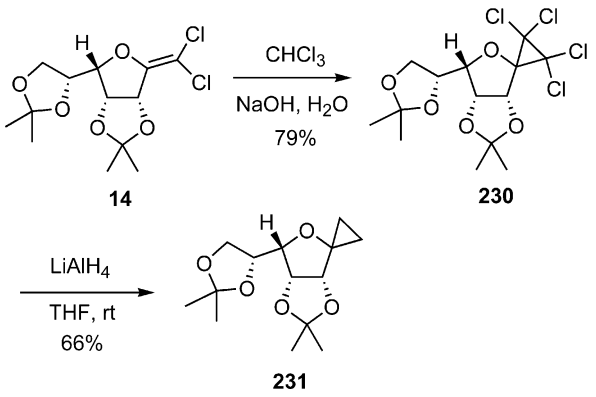
Finally, intramolecular chain extension leading to cyclic derivatives has been investigated. For example 5-vinyl *exo*-glycal **228**, obtained via the Tebbe methylenation of the corresponding lactone **227**, underwent a triisobutylaluminum hydride-promoted sigmatropic rearrangement[168] into cyclooctene **229**, which was further elaborated into saccharidic mimics.[169] The enol ether function of allyl 5,6-hexenopyranosides has been also involved in such a Claisen rearrangement to construct carbocycles from 5-vinyl *exo*-glycals.[170−172]

Scheme 42



Dichloro-*exo*-glycals can be used in a cycloaddition reaction with dichlorocarbenes.[173] This reaction is easily carried out under phase-transfer catalysis and gives excellent yields (70−95%) of the corresponding tetrachlorocyclopropanes such as **230**. Here again, benzyl-protected dichloroolefins were found unreactive. Side reactions of carbene species with benzylic hydrogen may explain this failure. Highly chlorinated species **230** can be dechlorinated using lithium aluminum hydride in THF to produce the corresponding cyclopropane **231** in 74% yield. There are only a few routes available to anomeric cyclopropanes,[174,175] which are interesting tools in glycobiology as potential glycosidase inhibitors.[176] No other examples of cyclopropanation of *exo*-glycals have been reported so far.

Scheme 43



3.2. Synthesis of Ketoses and Ketosides

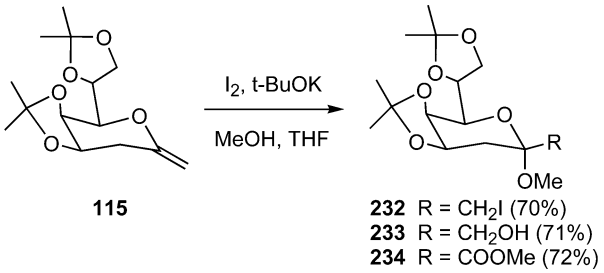
The facile hydration of 1-*C*-methylene sugars on silica gel has been previously pointed out. As already mentioned, the electron-rich character of the *C*-glycosylidene double bond promoted several studies of such addition reactions in the presence of an acid catalyst. The net result of water or alcohol addition on the *exo*-glycal double bond is the formation of a ketose or a ketoside, respectively. Although this type of compound is accessible by direct nucleophilic addition on lactones or by transformation of existing ketoses such as fructose or ketogulonic acid, this aspect of *exo*-glycals chemistry is of interest. Indeed, ketoside formation is not a straightforward process, and controlled addition of complex alcohols on *exo*-glycal should afford a good solution to this problem.

The well-developed chemistry of glycals has been applied for the functionalization of both carbons of the double bond of *exo*-glycal.

Dihydroxylation of the *exo*-methylene group using *N*-methylmorpholine oxide and OsO_4 led efficiently to the corresponding ketose in about 70% yield.[74] This reaction has been generalized to D-manno and D-galacto analogues of **108**, providing the expected diols in up to 90% yields.[177]

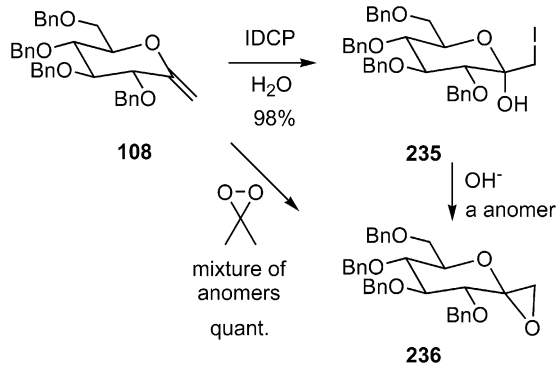
Iodoglycosylation of *exo*-glycal has been investigated as a way to produce KDO derivatives.[63] For example, compound **115** was treated with iodine and potassium *tert*-butoxide in THF/MeOH mixture to give the iodoketoside **232**. Substitution of iodine with cesium carbonate in HMPA at 140 °C gave after saponification the corresponding primary alcohol **233**, which was transformed into the methyl ulosonate **234** using standard procedures. Other examples of ulosonate formation from ketene thioacetals **79** and **80** using *N*-bromosuccinimide and methanol have been described.[178,179]

Scheme 44



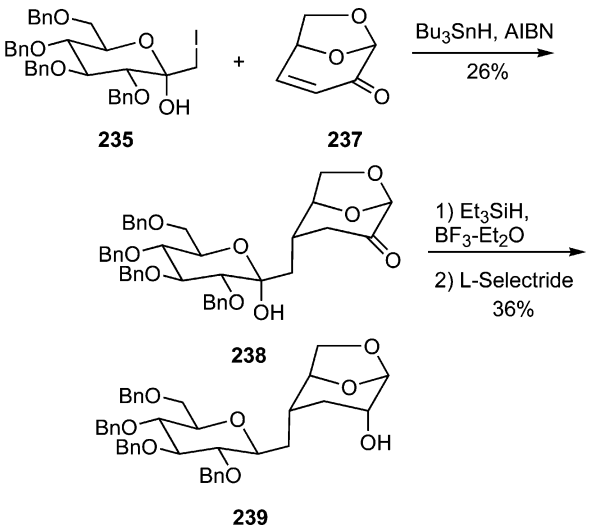
Ketoses can be obtained if water is used instead of methanol. Iodonium *sym*-dicollidine perchlorate (IDCP) has been proposed for the iodohydroxylation of **108**.[180] The iodo derivative **235** can be transformed into epoxide **236** as a single α anomer. The same epoxide was obtained together with the *β* anomer (α/*β* ratio 2:3) on epoxidation of **108** with dimethyldioxirane.[61,145] In the furanose series, *exo*-glycal **99** also gave a mixture of anomeric epoxides.[61]

Scheme 45



The iodo derivative **235** has been used for the construction of a *β*-(1−4)-*C*-disaccharide.[181] Treatment of **235** with tri-*n*-butyltin hydride gave the corresponding radical, which added on the enone system of levoglucosenone **237** to give **238**, albeit in low yield. Further reduction of the tertiary hemiacetal yielded the *C*-glycoside **239**. A possible way to introduce an

Scheme 46



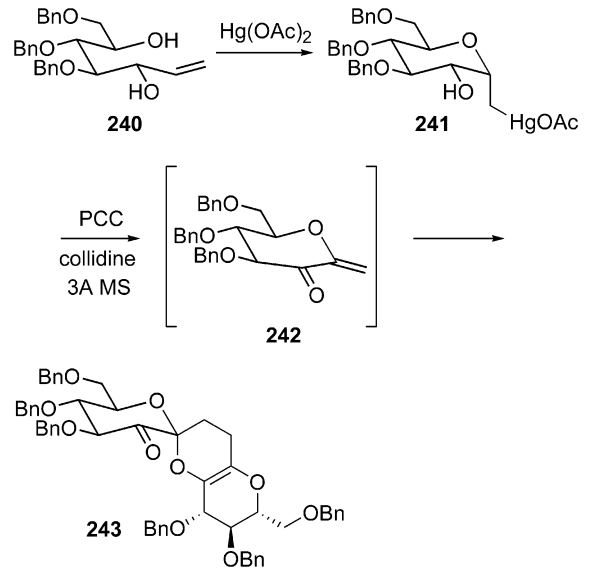
235 237 238 239

oxygen atom at the anomeric center of *exo*-glycal is to involve the double bond in a cycloaddition reaction. The first reported example was a nitrile−oxide cycloaddition on compound **108**, described by Rajan Babu.[60] This approach led efficiently to the ketose derivative, whereas a carbon atom was introduced on the other carbon. The method has not been thoroughly investigated until recently.

Thus, this procedure has been applied by Lieberknecht to 2-deoxy *exo*-glycal obtained using the anomeric phosphoranes approach.[182] The spiro-isoxazolines obtained in this way are present in some naturally occurring compounds.[183] We have recently established that such 1,3-dipolar cycloaddition of nitrones and nitrile oxides with *exo*-glycals **63** and **71** was efficiently carried out upon microwave activation or at room temperature, respectively.[184]

A 2-keto-*exo*-glycal has been constructed from olefin **240** by using mercury salt-catalyzed heterocyclization according to Sinaÿ's procedure, giving **241**.[185] Oxidation of a free hydroxyl group at C2 promoted β elimination to furnish the 2-keto-*exo*-glycal **242**, spontaneously dimerizing by a hetero-Diels−Alder

Scheme 47

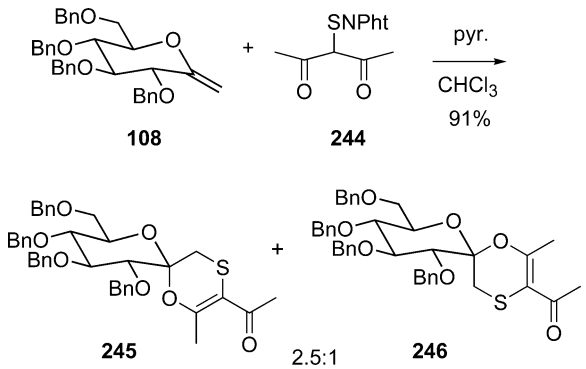


240 241 242 243

reaction between the activated double bond of one molecule and the enone of the other to provide **243**. The electron-rich character of the *exo*-glycal double bond has been exploited in another inverse-electron-demand hetero-Diels−Alder reaction between a methylene−tetrahydropyran and a butylacrolein. This was a key step for the establishment of the spiroketal unit contained in reveromycin B.[186]

The involvement of *exo*-glycals **108** and **99** in such a Diels−Alder reaction with another type of heterodiene obtained from **244** has been reported.[187,188] Anomeric oxathia-spirocycles **245** and **246** were obtained from **108** in 91% yield using this procedure, allowing introduction of two heteroatoms, oxygen and sulfur, at the same time on the double bond. The use of more complex chiral α,α'-dioxothiones obtained from glycals as electron-poor dienophiles led to 2-thio disaccharides.[189] Recently, compound **108** has been

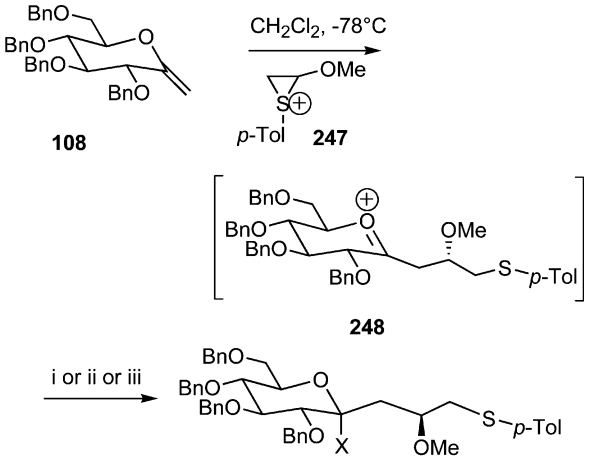
Scheme 48



108 244 245 246

used to prepare ketoses, methyl-ketosides, and *C*-glycosides.[190] This approach made use of the addition of episulfonium **247** on the electron-rich double bond of **108**, giving an intermediate oxonium species **248** in equilibrium with a cyclic sulfonium form (not shown). Treatment with water or methanol or reduction with sodium cyanoborohydride led to the ketose **249**, **250**, and **251**, respectively. In each case, among the four possible diastereoisomers, only the

Scheme 49



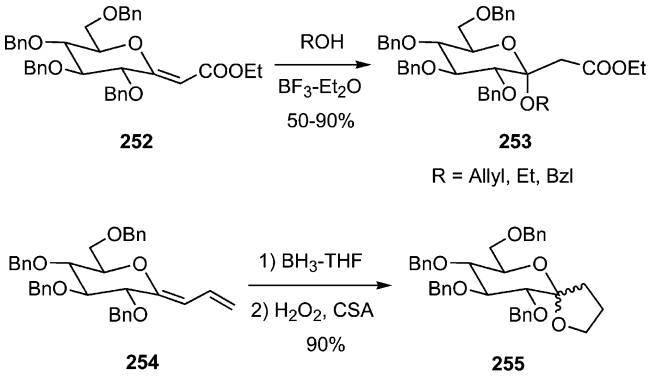
108 247 248

i: H_2O, 0°C **249** X = OH (71%)
ii MeOH, -78-0°C **250** X = OMe (55%)
iii: $NaBH_3CN$, -78-0°C **251** X = H (63%)

β anomers were formed. Simple addition of methanol on *exo*-methylene-glycal in acidic medium is an easy way to produce methyl 1-deoxyketoside. This has been applied to the synthesis of the right-hand pyranose ring of FR901464.[48]

Lin et al. reported a preliminary study on alcohol addition to substituted *exo*-glycals.[191] Dienic systems and activated double bonds were treated with alcohol in the presence of a Lewis acid. Excellent yields of α glycosides **253** were obtained from **252**. Using the

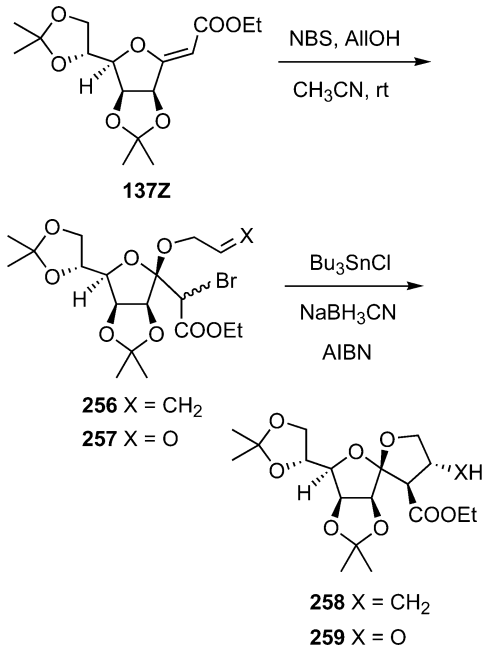
Scheme 50



dienic system **254**, cyclic compounds can be obtained upon treatment with borane−THF complex, followed by oxidation in acidic medium. A mixture of anomers **255** was obtained. Treatment of the mixture with trifluoroacetic acid only gave the α anomer. The same type of compounds has been prepared in the furanose series.[98] The same spirocyclic derivatives **255** have already been prepared by Ramberg−Bäcklund rearrangement of a sulfone equipped with a 3-hydroxypropyl appendage.[114b,144]

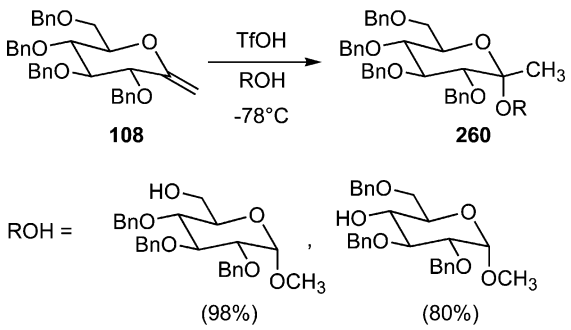
Analogous spirocyclic compounds have been prepared from ketosides.[192] An example of this approach is shown below. Starting from enol ether **137Z**, treatment with *N*-bromosuccinimide in the presence of an alcohol gave the ketoside **256** as a mixture of

Scheme 51



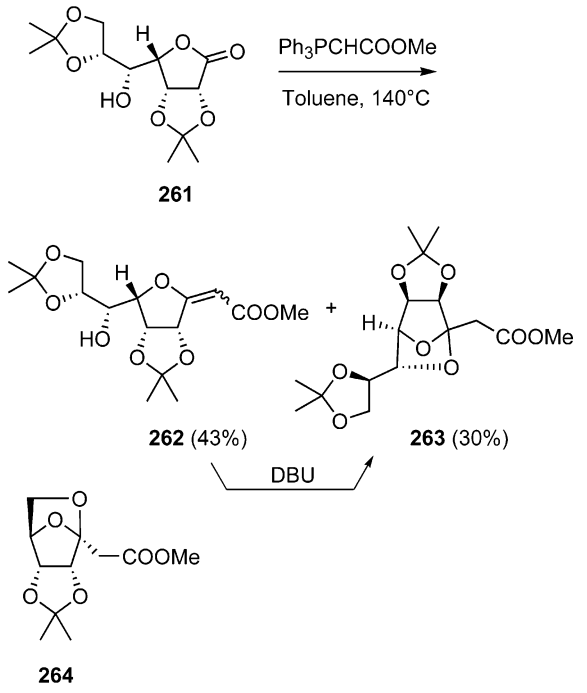
diastereoisomers. Each isomer was separately treated under radical conditions to give the same cyclized product **258** as a single isomer in 85% yield. Some other examples were reported, showing that it is possible to construct tetrahydrofurans or tetrahydropyrans by changing the starting alcohol. The radical cyclization also worked with propargyl derivatives, giving *exo*-olefins. Radical cyclization on aldehyde **257** was also efficient, producing alcohol **259** in 84% yield. As shown above, addition of simple alcohols on the double bond of *exo*-glycals is a straightforward route to ketosides. Disaccharides are seldom constructed with ketoses because activation of these sugars is rather difficult. *exo*-Glycals offer a unique advantage over classical activation in building of complex disaccharides. Ikegami's group has investigated this area, starting from *exo*-methylene derivatives.[193] Almost quantitative yields of disacharides **260** were obtained from **108** upon triflic acid activation with glucose-derived acceptor free at position 6 and 4. α anomers were formed in all cases, even in the presence of a 2-*O*-acetyl group. These reactions have been performed using *exo*-glycals of gluco, manno, and galacto configuration. This disaccharide-forming methodology has been applied to substituted *exo*-glycals derived from 2-deoxy galactose.[194] Catalysts such as BCl_3, $HBr-PPh_3$, or CSA were used mainly at 0 °C or at room temperature. Good to excellent yields of α anomers were obtained, even with 4-chlorophenyl-substituted *exo*-glycals.

Scheme 52



In the frame of our research program on the Wittig olefination of sugar lactones, we discovered that activated *exo*-glycals, i.e., substituted with an ester group like **69**, could be prepared in the presence of free hydroxyl groups, which did not interfere with the process.[195] However, when suitably located on the sugar, this free alcohol can add on the activated double bond. When **261** was treated under our Wittig conditions, the expected olefin **262** (43%, *Z*/*E* 1:1) was formed, together with a compound lacking the hydroxyl group, identified as the bicyclic compound **263** (30%). To confirm that **263** was the result of an intramolecular Michael addition, each isomer of **262** was treated with DBU in refluxing THF to give **263** in 68% and 73% yield, respectively. This was the first time that such a 1,4-addition was carried out on *exo*-glycals. 2,3-*O*-isopropylidene-D-ribono-1,4-lactone was also submitted to the same Wittig conditions to give **264** in 45% yield. In both cases, a five-membered ring was formed. We have shown that it is also possible to carry out such 1,4-addition of a hydroxyl group on

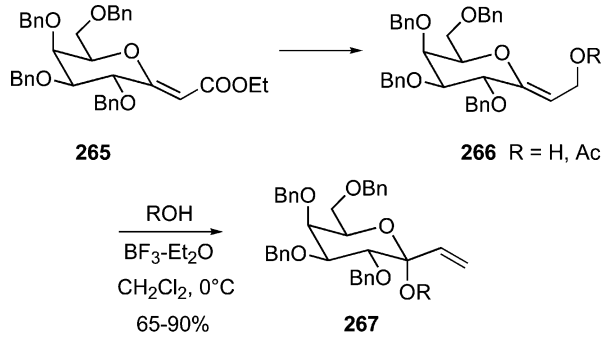
Scheme 53



activated *exo*-glycals to construct six-membered rings.[195] Application of this new acetal-forming reaction in basic medium has been applied to construct the core acetal ring system of zaragozic acids.[196]

While this review was in preparation, an application of the Ferrier rearrangement to *exo*-glycals was disclosed.[197] Reduction of ester **265** gave the corresponding allylic alcohol in 83% yield. This compound or the corresponding acetate **266**, upon treatment with an alcohol under Ferrier conditions (BF_3-Et_2O, 4-Å MS), gave only the α-ketoside **267** in good to excellent yield, even with complex glycosyl acceptors. In the gluco series, the allylic alcohol was used under the same conditions.

Scheme 54



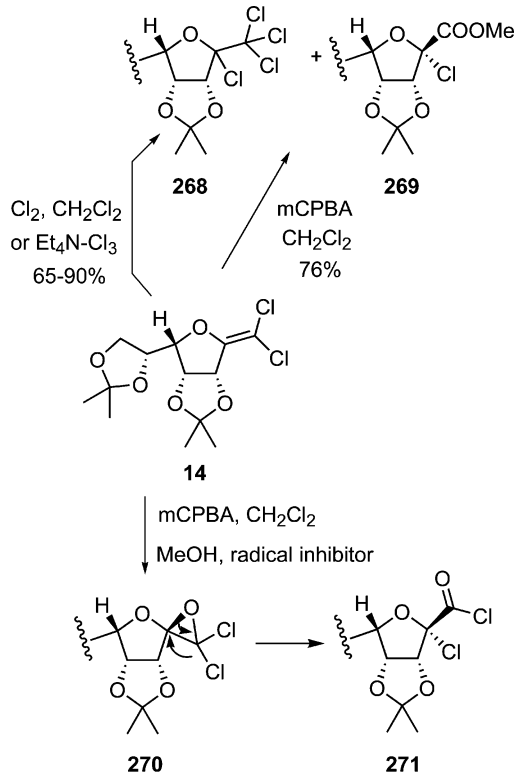
The chemistry of this type of allylic alcohols and acetates has also been investigated in our group. It is interesting to note that furanosyl acetate derived from **282** undergoes allylic rearrangement to a vinyl ketose or ketoside on purification on silica gel.[198a]

3.3. Synthesis of *N*-Glycosides

Glycosylamines are well-known compounds prepared by reaction of a sugar with an amine. This process is involved in many naturally occurring chemical transformations, such as the Maillard reaction and subsequent rearrangements, producing odiferous and nicely tasting compounds during food cooking. Glycosylamines derived from ketoses are quite rare compounds. Some representatives of this interesting class of compounds have been obtained from *exo*-glycals.

While searching new methods for the functionalization of dichloroolefins, we discovered an efficient sequence leading to anomeric α-amino acids. Thus, epoxidation of dichloroolefins was examined as a possible way to transform the dichloro group into an aldehyde. The first attempted epoxidation of **14** using *m*-chloroperbenzoic acid in dichloromethane led to a set of two products. The structure **269** was tentatively assigned to the first compound. The structure of the second compound **268** proved more difficult to establish. The mechanism of this reaction was unclear for a long time, although we suspected that the formation of **268** should be a radical reaction. In short, it was finally found that the chlorination reaction was an electrophilic addition of chlorine on the double bond, this chlorinating species being produced by the reaction of *m*-CPBA with dichloromethane. This reaction was suppressed by addition of a radical inhibitor. Treatment of **14** with Et_4N-Cl_3[199] gave only **268**.[200] The use of a radical inhibitor and added methanol gave only **269**. It was concluded that the epoxidation of dichloroolefins by *m*-CPBA is a very slow reaction, probably due to the steric bulk of the chlorine atoms, giving the dichloroepoxide **270**. It rearranged quickly to the acyl chloride **271**, which reacted with methanol to provide **269**. Because the epoxidation reaction is slow, *m*-CPBA decomposed, probably in a yet unknown radical reaction, and reacted with the solvent to produce a powerful

Scheme 55



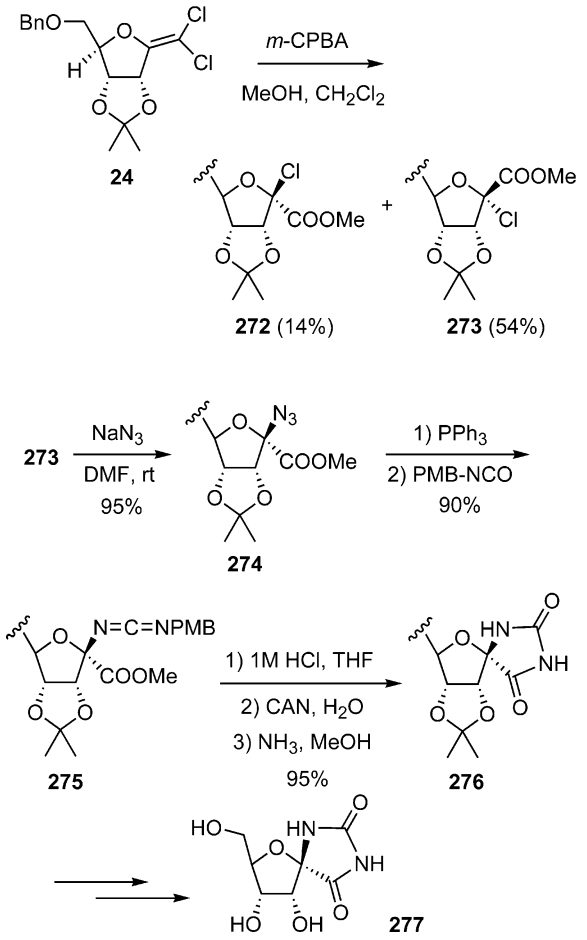
chlorinating species (maybe chlorine itself), which reacted promptly with **14** to give **268**.

An application of this serendipitous discovery was the formation of anomeric α azido-ester by simple substitution of the chlorine atom of **269** with sodium azide in DMF. Net inversion of configuration occurred to produce only one isomer, starting from dichloroolefins **14** and **16**.[201] In the ribo series, mixtures of epimers were obtained because epoxidation took place from both sterically hindered faces of the sugar ring. To illustrate this sequence, a part of the synthesis of hydantocidin, recently disclosed by Shiozaki using our technique, is described below.[19b,107]

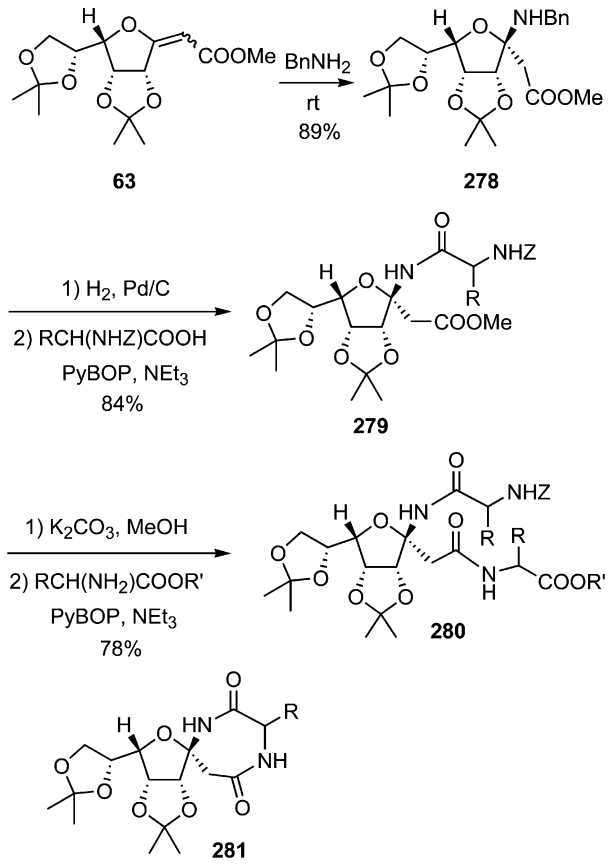
exo-Glycal **24** was treated with *m*-CPBA in a mixture of dichloromethane and methanol at room temperature to give a mixture of epimers **272** and **273** (1:3.8) in 68% overall yield. The synthesis of hydantocidin was performed on pure **273** by treatment with sodium azide in DMF at room temperature to give the α azido ester **274** in 95% yield. Staudinger reaction of **274** gave the intermediate phosphinimide, which upon treatment with *p*-MeO-phenyl isocyanate gave the diimide **275**. Acid hydrolysis and subsequent removal of the *p*-MeO group gave the expected urea that was cyclized into hydantoin in 99% yield on treatment with ammonia in methanol. The final steps involved removal of the benzyl and acetal groups using standard procedures to give hydantocidin **277** in excellent yield. 5-*epi*-Hydantocidin has been prepared from **272** using the same reaction sequence. It is also interesting to note that anomeric isothiocyanate can be prepared from either **272** or **273** by treatment with potassium thiocyanate in DMF at 80 °C. This new class of *N*-glycoside was also cyclized to the thio analogue of hydantocidin.

The activated double bond of *exo*-glycals **63**, **65**, and congeners should be used in Michael addition. Nitrogen seemed an appropriate nucleophile for such reactions. After some experimentation, we found that **63** reacted smoothly in neat benzylamine to produce a single adduct **278** in excellent yield.[202] The benzylamino group was found to be in a trans relationship with the dioxolane ring by NOE measurement and X-ray crystallography. Only one compound was obtained with enoates **63** and **65**, but mixture of anomers were obtained in the ribo series. This reaction has been extended to several *exo*-glycals. This approach gave a short entry to a new class of β-amino acids. The high current interest in this type of compounds and assemblies thereof prompted us to examine the reactivity of these sugar-derived amino acids. Thus, hydrogenolysis of the benzyl group led to the free amine obtained as a mixture of anomers due to equilibration. Nevertheless, amide bond formation with an α-amino acid in the presence of PyBOP as the coupling reagent gave almost exclusively the β anomer of the dipeptide **279**. Ester saponification of this compound allowed a second amide bond formation with another α-amino acid using the same procedure to yield **280**. It is interesting to note that saponification of the ester function of **278** did not proceed for yet unexplained reasons. This reaction proceeded well as soon as the amino group was acylated. Complex tetrapeptidic structures

Scheme 56



Scheme 57



involving alternate β sugar amino acid and standard α amino acids have been prepared by this approach.

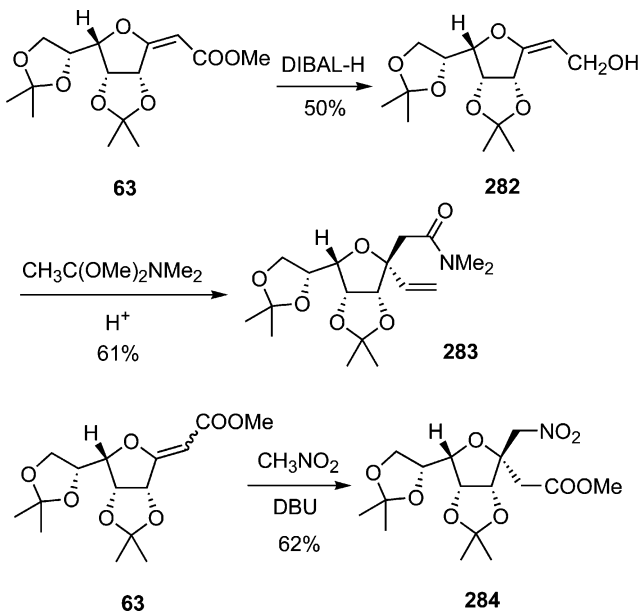
Non-peptidic structures can be constructed from these sugar-derived β-amino acids.[207] For example, cyclization of a dipeptide such as **279** produces seven-membered-ring systems such as **281**. Under the given conditions, dimerization may occur, giving 14-membered-ring systems bearing two sugar units. Compounds **281** can be regarded as nucleoside analogues with potential biological properties.

Another entry to complex nucleosides has been provided by electrophilic activation of furano *exo*-glycal by Selectfluor in connection with the synthesis of 1′-*C*-fluoromethyl-dideoxy-cytidine.[134]

4. Outlook

Until now, *exo*-glycal double bond functionalization mainly focused on the introduction of heteroatoms to construct *O*-glycosides and *N*-glycosides. The formation of a carbon−carbon bond has not been thoroughly explored. Maybe the future of this research should concentrate on this point. Clearly, it should be advantageous to find methods allowing construction of more complex *exo*-glycals from a common, easily accessible platform. This would find applications in the carbohydrate mimics field but also in the more general context of total synthesis. Access to doubly substituted *C*-glycosidic systems, i.e., *C*-ketosides,[203] also constitutes a challenging problem. We are currently exploring this problem starting from *exo*-glycals such as **63**. Reduction of the ester group with diisobutylaluminum hydride gave the expected alcohol **282**. This allylic alcohol was submitted to Eschenmoser−Claisen rearrangement to give the *C*-glycosylidene **283** in moderate yield. The net result of this reaction can be seen as the 1,4-addition of a vinyl substituent at the anomeric position. This rearrangement took place preferentially from the less hindered β-face of the sugar. As for nitrogen derivatives, 1,4-addition on the activated double bond of **63** should be a useful process to introduce a substituent at the anomeric position. For the moment, all attempts to carry out cuprate addition on **63** have failed. Nevertheless, nitromethane reacted cleanly in the presence of DBU with **63** to give the bis-*C*-glycoside **284** in satisfactory yield.[198b] The stereochemistry was tentatively assigned as shown, assuming an attack of the reagent from the less hindered face. This approach paves the way to chiral γ-amino acids whose chemistry is not well developed.

Scheme 58



Suitable *exo*-glycals could be involved in a metathesis reaction with a given olefin to produce a new *exo*-glycal with different substituents. The reactivity of methylene derivatives has been tested by Dötz and co-workers in the reaction with Fischer diphenyl carbene to produce a new anomeric Fischer carbene.[204,205] Aminolysis of these complexes has been described, but other uses of these new species could be expected. The good reactivity of the *exo*-glycal double bond in a ring-closing metathesis has been attested by the construction of bicyclic systems from 2-olefinic substituted systems.[206]

5. Conclusion

In conclusion, the synthesis of *exo*-glycals has found many solutions either by direct olefination or by stepwise reactions. It seems reasonable to say that a wide range of double bond substitutions is now accessible along these two main synthetic routes. The exceptional electronic arrangement of such double bonds confers to *exo*-glycals unusual chemical properties, which need to be explored experimentally and also theoretically. The chemistry of these new unsaturated sugars has already found interesting developments. Many reactions are centered on the functionalization of the double bond with heteroatoms, but extension of the unsaturated system by carbon−carbon bond formation may provide new sugar systems not yet directly attainable. The high synthetic potential of these compounds for the synthesis of complex structures going from simple *C*-glycosides to chiral, highly oxygenated, medium-sized carbocycles has been highlighted in the second part of this review. Moreover, the coupling of complex moieties with *exo*-glycals would provide solutions for the synthesis of carbohydrate mimics, in particular *C*-disaccharides, or other complex assemblies could be prepared by this route. There is no doubt that further studies in the field will unravel unexpected applications such as bis-*C*-glycosides synthesis and new sugar-based scaffolds and will provide us with highly advanced synthetic chiral intermediates en route to complex natural products.

6. Acknowledgment

It is a pleasure to acknowledge Drs. Alphonse Bandzouzi and Mohammed Lakhrissi for their fruitful involvements in the early beginning of our exploration of *exo*-glycal formation and chemistry. Their skillful work allowed important breakthroughs, further explored by two dedicated co-workers, Dr. Younes Lakhrissi and Ms. Carine Chevrier.

7. Abbreviations

Ac	acetyl
AIBN	azo-bis-isobutyronitrile

9-BBN	9-bora-bicyclo[3.3.1]nonane
Bn	benzyl
Boc	*tert*-butoxycarbonyl
Bz	benzoyl
CAN	ceric ammonium nitrate
Cp	cyclopentadienyl
CSA	camphorsulfonic acid
Dba	dibenzylideneacetone
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DIBAL-H	diisobutylaluminum hydride
DMAP	4-(dimethylamino)pyridine
DMF	*N*,*N*-dimethylformamide
DMSO	dimethyl sulfoxide
dppf	1,3-bis-diphenylphosphinoferrocene
dppp	1,3-bis-diphenylphosphinopropane
Fmoc	9-fluorenylmethoxycarbonyl
HMPA	hexamethylphosphoric triamide
IDCP	iodonium dicollidine perchlorate
Imid	imidazol-1-yl
KHMDS	potassium hexamethyldisilazide
LAH	lithium aluminum hydride
LDA	lithium diisopropylamide
LHMDS	lithium hexamethyldisilazide
m-CPBA	*meta*-chloroperbenzoic acid
MOM	methoxymethyl
Ms	mesyl (methanesulfonyl)
MS	molecular sieves
NBS	*N*-bromosuccinimide
NIS	*N*-iodosuccinimide
Ph	phenyl
Pht	phthaloyl
Piv	pivaloyl (2,2-dimethylpropanoyl)
PMB	*p*-methoxybenzyl
PyBOP	benzotriazol-1-yl-oxy-tris(pyrrolidino)phosphonium hexafluorophosphate
Pyr	pyridine
rflx	reflux
TBAF	tetrabutylammoniumfluoride
TBS	*tert*-butyldimethylsilyl
TBDPS	*tert*-butyldiphenylsilyl
Tf	triflyl (trifluoromethanesulfonyl)
THF	tetrahydrofuran
TIBAL	triisobutyl aluminum
TIPS	triisopropylsilyl
TMEDA	*N*,*N*,*N*′,*N*′-tetramethylethylenediamine
TMS	trimethylsilyl
Tol	toluene
Tr	trityl (triphenylmethyl)
Ts	tosyl (4-methylbenzenesulfonyl)
Z	benzyloxycarbonyl

8. References

(1) According to IUPAC recommendation, 2-Carb-17.2, "The term 'glycal' is a non-preferred, trivial name for cyclic enol ether derivatives of sugars having a double bond between carbon atoms 1 and 2 of the ring. It should not be used or modified as a class name for monosaccharide derivatives having a double bond in any other position" (*Pure Appl. Chem.* **1996**, *68*, 1919−2008). The so-called 'exo-glycals' are normally termed using an "anhydro-...-enitol"-based terminology. The term '*C*-glycosylidene' clearly indicates the double substitution at the anomeric centre and should be also used.

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