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Expeditious synthesis of *C*-glycosyl conjugated dienes and aldehydes from sugar lactones

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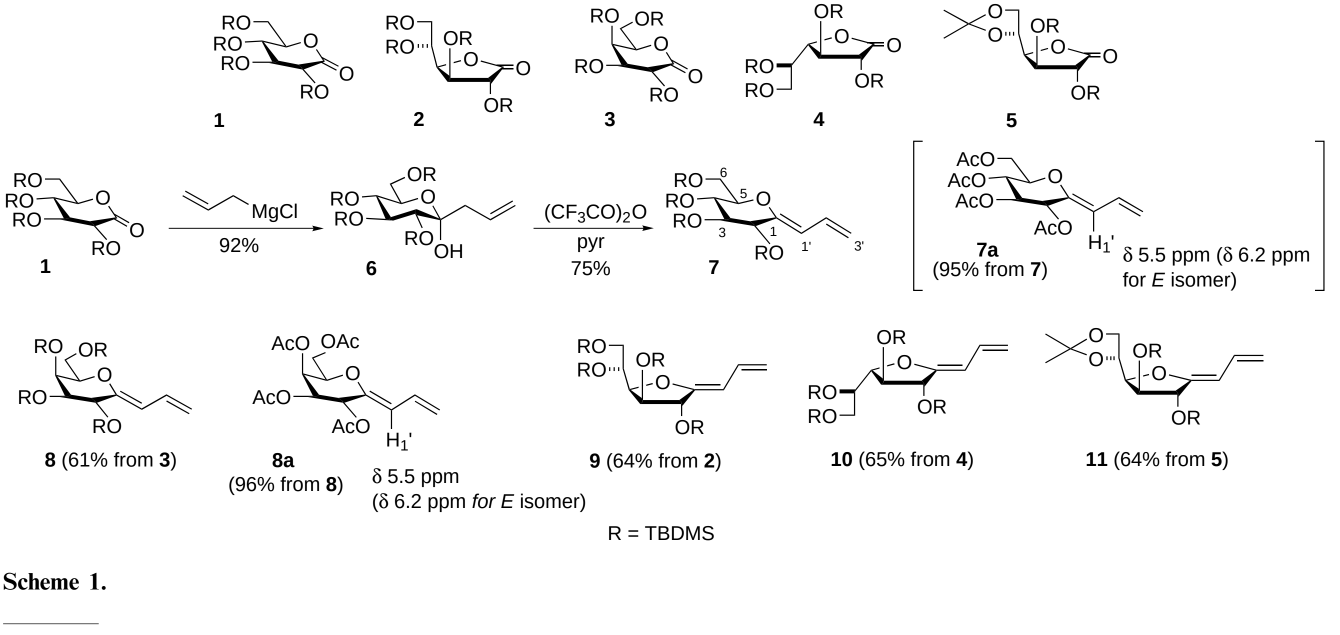
Abstract—Several *C*-glycosyl conjugated dienes were prepared in two steps from protected sugar lactones via addition of allylmagnesium chloride and the subsequent dehydration. A sequence of allylic addition, ozonolysis and dehydration led to the corresponding glycosyl conjugated aldehydes. These conjugated functionalities can be used as diagnostic chromophores for sugar synthesis and purification. The synthetic studies of glycosyl dienes were also pursued. Hydroboration of a sugar diene led to either homoallylic alcohol or spiroacetal depending on the workup conditions. © 2001 Elsevier Science Ltd. All rights reserved.

C-Glycosides, in which the glycosidic oxygen is displaced by a methylene (CH_2), have attracted a great attention in carbohydrate chemistry and glycobiology because they are stable carbohydrate analogs due to their resistance to enzyme hydrolysis. These molecules have been prepared as potential inhibitors of carbohydrate processing enzymes including glycosidases and glycosyltransferases.[1–3] Furthermore, in the preparation of biologically interesting molecules such as the antibiotics nogalamycin[4,5] and gilvocarcin[6,7] the requirement of *C*-glycosides as chiral building blocks has provided impetus to develop various synthetic methods.[8] Herein, we report an efficient procedure to prepare *C*-glycosyl dienes and aldehydes from sugar lactones.

We have reported the preparation of five sugar lactones **1**–**5** as fully protected *t*-butyldimethylsilyl (TBDMS) ethers from the free aldonolactones.[9] Thus, tetra-*O*-*t*-butyldimethylsilyl-D-glucono-1,5-lactone (**1**) reacted with allylmagnesium chloride to give the addition



Scheme 1.

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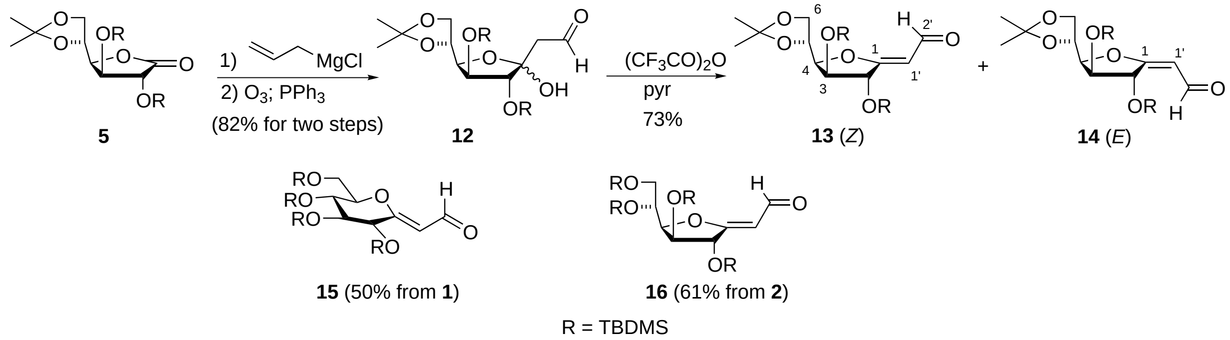
product **6** as an anomeric mixture (7/1) in 92% yield (Scheme 1). Dehydration of **6** was carried out by treatment with trifluoroacetic anhydride (TFA) in the presence of pyridine to give a sugar diene **7** (75% yield) as one single isomer. Replacement of TFA with other reagents (such as MsCl and Ac_2O) or using different bases (such as Et_3N and DMAP) were inefficient. Either no reaction occurred or complicated products resulted under such reaction conditions. Direct coupling of **1** with ally bromide (1 equiv.) using samarium iodide gave the diene **7** in a low yield (less than 10%).[10] Other four conjugated sugar dienes **8**–**11** were similarly prepared from the corresponding lactones **2**–**5** in about 65% overall yields via addition of allylmagnesium chloride and subsequent dehydration (Scheme 1). In order to determine the configuration of $\Delta^{1,1'}$ double bond, the sugar diene **7** was deprotected using tetrabutylammonium fluoride (TBAF) and then acetylated to give the known compound (**7a**) having a (*Z*)-configuration. The H-1′ resonance of **7a** appeared at δ 5.5, whereas that of (*E*)-isomer occurred at a lower field (δ 6.2).[11] Compound **8** was similarly converted to **8a** by substitution of the TBDMS groups with acetates. The H-1′ resonance of **8a** also occurred at δ 5.5, in agreement with the (*Z*)-configuration. Dienes **9**–**11** were inferred to have (*Z*)-configurations as their H-1′ signals also appeared in the region of δ 5.1.

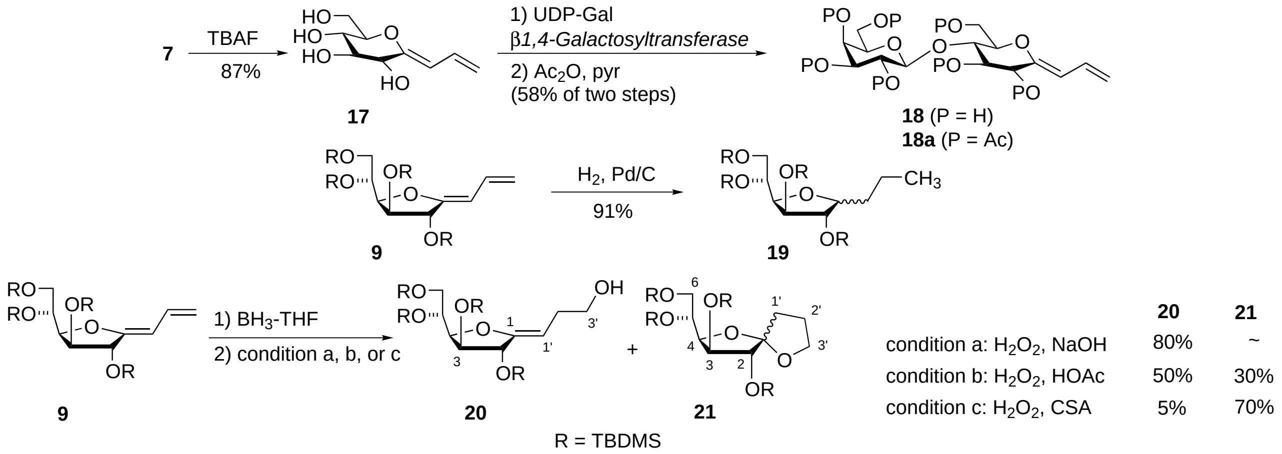
When lactone **5** was subjected to a nucleophilc addition with allylmagnesium chloride, ozonolysis and dehydration (Scheme 2), an isomeric mixture of conjugated aldehydes **13** and **14** (1:1) were obtained in 73% yield. On the basis of NOE experiments, compounds **13** and **14** were determined to have (*Z*)- and (*E*)-configurations, respectively. Accordingly, a 6.6% enhancement of H-1′ in compound **13** was observed by irradiation of H-2 at δ 4.27, whereas a 17.8% enhancement of the aldehyde hydrogen in **14** was found by irradiation of H-2 at δ 4.89. In parallel to dienes **7**–**11**, the H-1′ of (*E*)-isomer **14** appeared at a lower field (δ 5.61 ppm) than that of (*Z*)-isomer **13** (at δ 5.18). The sugar lactones **1** and **2** were also converted to the conjugated aldehydes **15** and **16**. Both **15** and **16** existed as (*Z*)-isomers, as indicated by their H-2 resonances at δ 5.18. Interestingly, tetra-TBDMS-gluconolactone **2** yielded only (*Z*)-enal **16**, whereas glucolactone **5** with a slight change to isopropylidene groups at C5 and C6 yielded a mixture of (*Z*)- and (*E*)-isomers **13** and **14**.

Although there are several previous reports on the synthesis of conjugated *C*-glycosides, major problems arose from the overall low yield of multiple steps and/or no generality applicable to all types of sugars. For instance, a pioneering work by Praly et al. has utilized Keck reaction and DBU-catalyzed dehydrohalogenation to convert peracetylated glycopyranosyl dihalides to sugar dienes in 17–43% yields.[11,12] The availability of the starting materials, obtained in 65–70% from glycosyl halides, further reduced the overall yield and made the procedure less applicable. Czernecki's group has applied Wittig olefination of sugar lactones to form conjugated *C*-glycosyl esters in low yields (<30%).[13,14] Such a method is not applicable to *manno*-type monosaccharides. Taylor et al. have prepared glycosyl sulfones, which undergo Ramberg–Bäcklund rearrangement to give 1-exomethylene sugars (*exo*-glycals).[15–17] It takes four steps to prepare the required glycosyl sulfones in moderate yields (30–40%). This method has not been explored for the synthesis of sugar dienes. On the other hand, our method exhibited the advantages of simplicity and minimized reaction steps.

We also measured the λ_{max} and absorption coefficients of these synthesized glycosyl dienes.[18] Our results indicated that the conjugated dienes and aldehydes were useful chromogenic groups, which could function as indicators in the synthesis and purification of carbohydrates. For instance, the sugar diene **7** had an absorption coefficient of 24,000 cm^{-1} M^{-1} (in hexanes) at 255 nm (λ_{max}). Deprotection of **7** by using TBAF afforded an 87% yield of **17**, which was accepted by β1,4-galactosyltransferase as a substrate even though the sugar ring was in the half chair conformation and the diene group was located in the reducing terminal (Scheme 3). The enzymatic reaction of **17** using β1,4-galactosyltransferase and UDP-galactose produced a disaccharide **18** which was further acetylated to **18a** (58% yield of the two steps) for the purpose of product characterization. The reaction progress and product purification were thus easily monitored by TLC analyses using the diene moiety as a UV sensitive chromophore. In contrast, special derivatizations of common sugar molecules are often required for detection by colorimetry or fluorescence methods.[19]



Scheme 2.



	20	21
condition a: H_2O_2, NaOH	80%	~
condition b: H_2O_2, HOAc	50%	30%
condition c: H_2O_2, CSA	5%	70%

Scheme 3.

Some synthetic investigations of these glycosyl dienes were also demonstrated in the study. For example, catalytic hydrogenation of the sugar diene **9** generated the saturated *C*-glycoside **19** as a mixture of anomers. Hydroboration of sugar diene **9**, followed by oxidation with H_2O_2 and NaOH (condition a in Scheme 3) gave the homoallylic alcohol **20** by selective functionalization of the terminal olefin. If acetic acid, instead of sodium hydroxide, was used to quench the hydroboration intermediate, the isomeric spiroacetals **21** (30% yield) were obtained in addition to **20** (condition b). The yield of **21** was increased to 70% when camphor sulfonic acid (CSA) was added in company with hydrogen peroxide (condition c). Indeed, homoallylic alcohol **20** underwent an acidic cyclization on treatment with CSA to give the acetal **21** in a quantitative yield. Compound **20** exhibited C-1 at δ 158, whereas compound **21** showed C-1 at δ 115 corresponding to the acetal carbon. A DEPT analysis of **21** also indicated that C-1 is a quaternary carbon of acetal. The ^{1}H NMR spectrum of **21** showed non-equivalency for the two germinal hydrogens at C-3′.

In conclusion, we have devised a simple and efficient method for the preparation of conjugated sugar dienes and aldehydes from pertinent sugar lactones. These conjugated sugar molecules are versatile building blocks, as shown by derivatization to homoallylic alcohol, spiroacetal and saturated *C*-glycosides. Using the conjugated moiety is beneficial for monitoring the progress of subsequent reactions and the purification of products, as shown in the enzymatic synthesis of disaccharide **18**.

Acknowledgements

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