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Facile synthesis of conjugated *exo*-glycals

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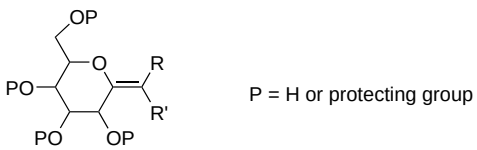
Abstract—Two efficient methods were explored for the synthesis of various conjugated *exo*-glycals: (i) by nucleophilic addition of sugar lactones with a subsequent dehydration, and (ii) by selenylation of *C*-glycosides with a subsequent selenoxide elimination. These reactions occurred in a stereoselective manner to give exclusively or predominantly the (*Z*)-isomers of *exo*-glycals. © 2001 Elsevier Science Ltd. All rights reserved.

1,2-Unsaturated sugars (*endo*-glycals) have been demonstrated as versatile building blocks in the synthesis of various biomolecules. For example, Danishefsky et al. have successfully synthesized a great number of glycosylated natural products and complex oligosaccharides based on the epoxidation of *endo*-glycals.[1–6] 1-Exomethylene sugars (*exo*-glycals; R,R′=H) have drawn increasing attention from synthetic chemists because these molecules have been utilized as valuable glycosidase inhibitors[7] and applied for the preparation of *C*-glycosides.[8] Although 1-exomethylene sugars have been synthesized according to known procedures including the methylenation of sugar lactones by Tebbe reagent[9] and the elimination of pyranoketosyl bromide,[10] there are no general methods to prepare substituted or functionalized *exo*-glycals (R,R′≠H). We herein demonstrate two novel approaches to prepare conjugated *exo*-glycals **3a**–**e**, **6a**–**e** and **10**.



The *exo*-glycal ester **3a** has been prepared by Wittig olefination of sugar lactones.[11] *exo*-Glycals **3b**[12] and **3c**[13] have been obtained as the side products of deoxygenation (of anomeric hydroxyl group) and glycosylation reactions, respectively. Praly et al. have reported the application of Keck reaction for glycosyl dihalide to make a variant of compound **3e**.[14] Taylor and his co-workers have converted *S*-glycosides to a series of *exo*-glycals via Ramburg–Bäcklund rearrangements.[15,16] A [2,3]-Wittig sigmatropic rearrangement has been also reported to prepare an *exo*-glycal analogue of glycosyl serine.[17] However, general utilization of these methods in preparation of other functionalized *exo*-glycals has not been exploited.

The fully protected benzylated lactone **1** was prepared from the commercially available 2,3,4,6-tetra-*O*-benzyl-D-glucopyranose by oxidation with DMSO and acetic anhydride in 95% yield. The sugar lactone **1** was a good substrate for nucleophilic additions,[18] thus it reacted with a variety of nucleophiles to give the pyranoketoses **2a**–**e** in good to excellent yields (Table 1). Dehydration of **2a**–**e** was realized by treatment with trifluoroacetic anhydride (TFAA) and pyridine to generate conjugated *exo*-glycals **3a**–**e**.[19] The *Z* isomers were exclusively produced except for the reaction of **2a** giving a mixture of *Z* and *E* isomers in a ratio of 5:1. The configuration of these products was rigorously determined by NOE experiments and/or comparison with the NMR data in literature.[11–16] The stereochemical outcome was consistent with those reported in literature.[10–17]

In order to extend the conjugation, aldehyde **4** was synthesized in 81% yield by ozonolysis of **2e**. As shown in Table 2, aldehyde **4** reacted with hydrazine and phosphorus ylides to give the condensation products **5a**–**e** in high yields. The subsequent dehydration with TFAA and pyridine thus afforded the conjugated *exo*-glycals **6a**–**e**. The Wittig reaction product **5b** showed two vinyl protons with a large coupling constant of 16 Hz, in agreement with the *E* configuration. Compounds

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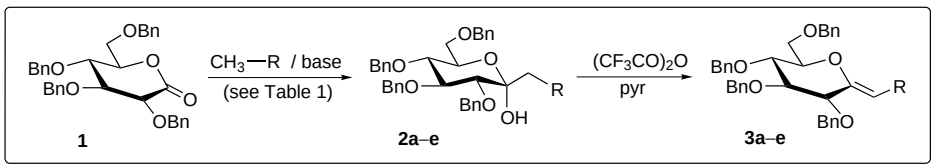
Table 1. Preparation of five conjugated *exo*-glycals **3a–e** via the nucleophilic addition products **2a–e**

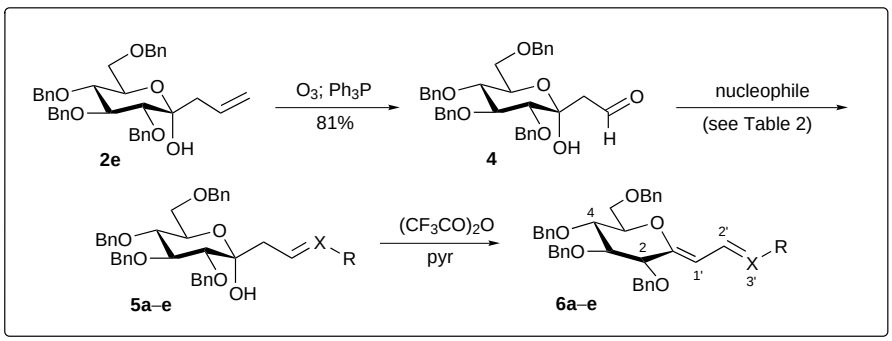


entry	R (see Table 1)
1	CO_2Et
2	$PO(OMe)_2$
3	$SO_2(OEt)$
4	C_6H_5
5	$CH{=}CH_2$

Entry	CH_3–R/base	Addition product	Dehydration product
1	CH_3–CO_2Et/LHMDS	**2a** (95%)	**3a** (90%)[a]
2	CH_3–$PO(OMe)_2$/*n*BuLi	**2b** (92%)	**3b** (81%)
3	CH_3–$SO_2(OEt)$/*n*BuLi	**2c** (81%)	**3c** (83%)
4	$ClMgCH_2$–C_6H_5	**2d** (95%)	**3d** (87%)
5	$ClMgCH_2$–$CH{=}CH_2$	**2e** (82%)	**3e** (85%)

[a] Compound **3a** existed as a mixture of *Z* and *E* isomers (5/1). Compounds **3b–e** all have the *Z* configuration.

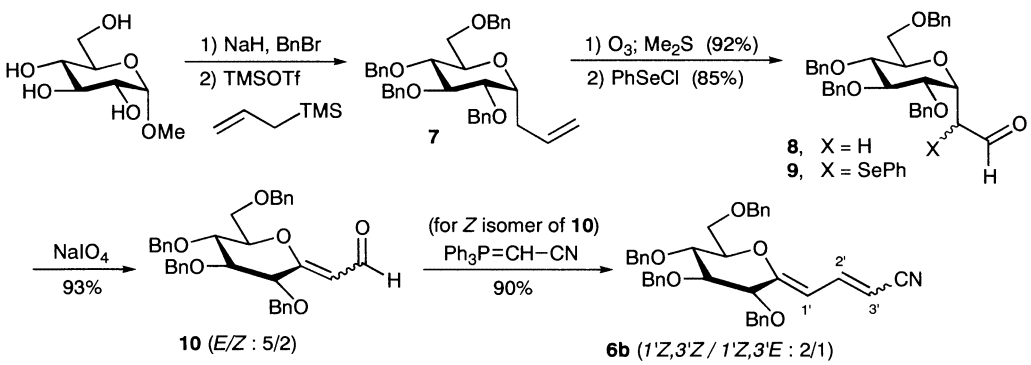
Table 2. Preparation of five conjugated *exo*-glycals **6a–e** via the condensation products **5a–e**



entry	X—R (see Table 2)
1	N—NH_2
2	HC—CN
3	HC—COMe
4	HC—CHO
5	HC—CO_2Et

Entry	Nucleophile	Addition product	Dehydration product
1	H_2N–NH_2	**5a** (–)[a]	**6a** (80%)
2	$Ph_3P{=}CH$–CN	**5b** (83%)	**6b** (95%)
3	$Ph_3P{=}CH$–COMe	**5c** (82%)	**6c** (88%)
4	$Ph_3P{=}CH$–CHO	**5d** (92%)	**6d** (87%)
5	$Ph_3P{=}CH$–CO_2Et	**5e** (84%)	**6e** (91%)

[a] The formation of compound **5a** was not observed. Instead, **6a** was directly obtained in the addition reaction.



Scheme 1.

5c–e with *E* configuration were similarly determined by ^1H NMR analysis. The dehydration products **6a–e** all existed as single isomers, which were assigned to have the (1′*Z*,3′*E*) configuration[20] by analogy to that of **3a–3e**.

We also investigated an alternative method for the preparation of conjugated *exo*-glycals via selenoxide elimination[21] (Scheme 1). *C*-Glycoside **7** was synthesized by allylation of perbenzylated glucoside according to the known procedure.[22] Subjection to ozonolysis

gave aldehyde **8**, which was treated with phenylselenyl chloride to give α-selenylated product **9** as an inseparable diastereomeric mixture in a ratio of 5:2 according to the ^{1}H NMR analysis. Oxidation of **9** with $NaIO_4$, followed by an in situ selenoxide elimination provided the conjugated aldehyde **10** containing a mixture of *E* and *Z* isomers (5:2). The isomers were separated by column chromatography, and the *Z* isomer condensate with a phosphorus ylide afforded the conjugated *exo*-glycal **6b** in 90% yield as a mixture of *E* and *Z* isomers.

As previously mentioned, *exo*-glycals have shown inhibitory activities against glycosidases, and we intended to evaluate the inhibitory effect of the deprotective forms of the products on glycosidases. The catalytic hydrogenolysis of **3a** and **3c** was carried out on 10 wt% Pd/C (20 mol%) to remove the benzyl groups at 25°C for 2 h with EtOH/$CHCl_3$/hexanes (4/1/1). The exocyclic C=C bonds were retained under such reaction conditions; e.g. for the reaction of **3a**, the desired product (**12**) was obtained in 55% yield, in addition to the saturated product (40%, the double bond was reduced). The preliminary assay of glucosidase inhibition looked promising.[23]

In summary, we have established two expeditious procedures to prepare conjugated *exo*-glycals. The deprotection and inhibitory assay of these molecules are currently pursued and will be published in a due course. Furthermore, these unusual glycosides may be elaborated to other biologically interesting molecules such as isosteric phosphonate analogues of glycosyl 1-phosphates,[12] and the mimetics of sugar nucleotides. The latter compounds have been confirmed to be potent inhibitors of glycosyltransferases.[24]

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20. In addition to the analysis based on coupling constants, NOE experiments were executed. For instance, a 6.3% enhancement of H-1′ in compound **5b** was observed by irradiation of H-2, whereas a 4.9 and 2.7% enhancement of H-3′ and H-2 in compound **5b** was found by irradiation of H-1′.
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23. Compounds **2a**, **2c**, **3a** and **3c** have been successfully deprotected and assayed for glucosidase inhibition (α-glucosidase from *Saccharomyces* sp. and β-glucosidase from sweet almond) which shows that the conjugated molecules are more potent than the hydrated ones. For example, deprotecting the benzyl groups of **2a** and **3a** generated products **11** and **12**, respectively. In the presence of β-glucosidase, *p*-nitrophenyl-β-D-glucopyranoside (the chromogenic substrate), and compounds **11** or **12** (200 μM), the former molecule resulted in 98% remaining activity, whereas the latter gave 30% activity in comparison with the control experiment (which contained the substrate only). IC_{50} of **12** was estimated to be about 150 μM. All the detailed inhibitory results will be published in a due course.
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