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One-pot synthesis of 1-*exo*-alkylidene-2,3-anhydro furanoses: convenient precursors for *exo*-glycals and functionalized *C*-glycals

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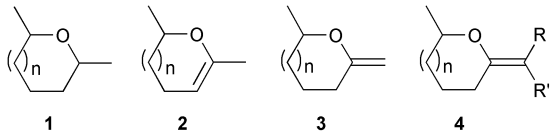
1-*exo*-Methylene-2,3-anhydro furanoses, obtained from *C*-glycals in a one-pot, three step operation can be readily transformed into functionalized *C*-glycals by palladium-catalyzed nucleophilic addition.

Methods for the formation of *C*-glycosides **1** continue to be of considerable interest in carbohydrate chemistry, as well as in organic synthesis.[1] Synthetic efforts in this area have recently focused on the preparation of *C*-glycals, **2**,[2–4] and 1-*exo*-methylene sugars (*exo*-glycals) **3**,[5] which might function as *C*-glycoside precursors by way of the stereoselective functionalization of their enol ether double bond. However, and when compared to *C*-glycals, synthetic methods for the preparation of *exo*-glycals have been less addressed in the literature. The method of choice for the preparation of **3**, would appear to be methylenation of sugar lactones with the Tebbe, or related, reagent.[6,7]

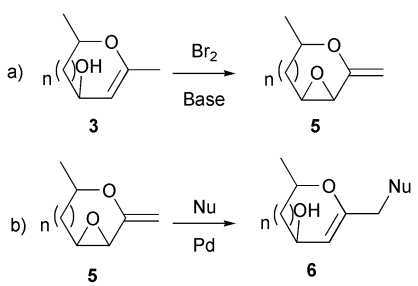


1 **2** **3** **4**

The corresponding substituted *exo*-glycals, **4**, are also of considerable interest and their preparation usually require more laborious efforts. Contributions in this area include Wittig olefination of glycosyl phosponium salts[8] or sugar lactones,[9] Keck reaction of glycosyl dihalides,[10] [2,3]-Wittig sigmatropic rearrangement,[11] Ramberg–Bäcklund rearrangement of *S*-glycosides,[12,13] and, more recently, nucleophilic addition to sugar lactones followed by elimination.[14] Nevertheless, most of these procedures are limited to some special types of *exo*-glycals.[15]

In this communication, we disclose a one-pot method for the transformation of *C*-glycals, **3**, into, previously unknown, 2,3-epoxy-*exo*-glycals **5**[16] (Scheme 1a), and illustrate the synthetic potential of the latter with their transformation into functionalized *C*-glycals **6** (Scheme 1b).

Our synthetic strategy rests on three well-known processes outlined in Scheme 2(a)–(c). We hypothesized that bromination of a glycal, first studied by Lemieux and Fraser-Reid (Scheme 2(a)),[17] epoxide formation from an halohydrin (Scheme 2(b)),[18] and base induced elimination of an anomeric halide (Scheme 2(c)),[10] could take place consecutively, hence transforming a *C*-glycal, **3**, into a 1-*exo*-methylene-2,3-anhydro sugar derivative **5**, in a one-pot operation (Scheme 1(a)).



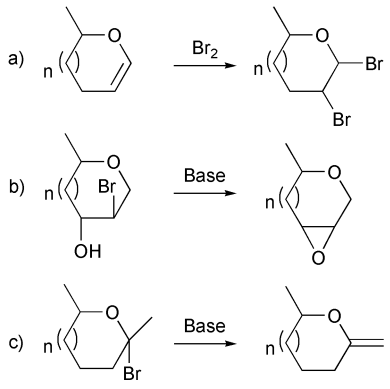
3 **5** **5** **6**

Scheme 1

The feasibility of this transformation (**3**→**5**) is displayed in Table 1. Treatment of *C*-glycals **3a**–**c**, prepared in three steps from D-mannose,† with bromine and triethylamine in dichloromethane led to epoxy *exo*-glycals **5a**–**c**.‡

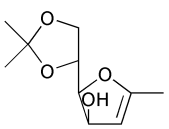
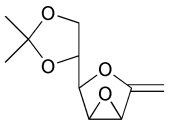
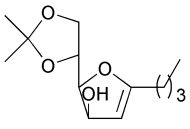
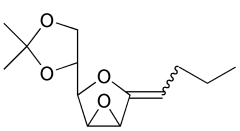
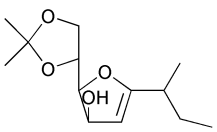
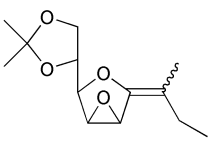
A variety of synthetically useful transformations of the unsaturation of *exo*-glycals has already been described.[5,12*b*,19] Accordingly, we have focused our studies on the reactivity of the oxirane ring, and the allyl epoxide moiety of **5**. Nucleophilic opening of the oxirane ring takes place, with H_2O, at C-2 giving rise to D-glucofuranose derived *exo*-glycals **7a**–**c**.

More interestingly, the allylepoxide moiety undergoes palladium-catalyzed nucleophilic opening with carbon- and nitrogen-nucleophiles and permits the synthesis of functionalized *C*-glycals (Table 2).§



Scheme 2

Table 1 Formation of epoxy *exo*-glycals **5** from *C*-glycals **3**

entry	substrate	product	yield (%)
i	 **3a**	 **5a**	65-70
ii	 **3b**	 **5b**	60-65
iii	 **3c**	 **5c**	60-65

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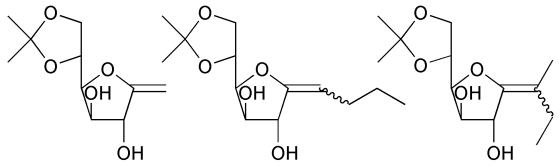
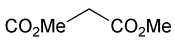
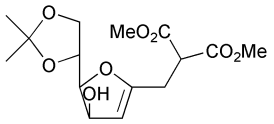
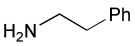
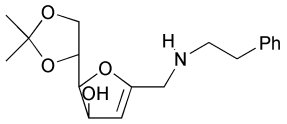
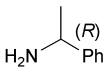
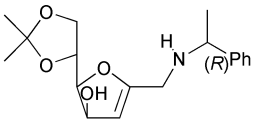
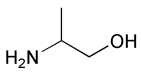
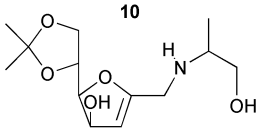
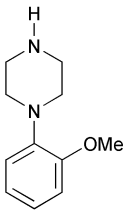
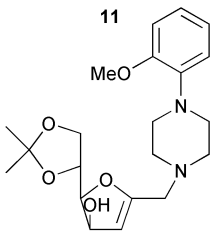
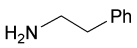
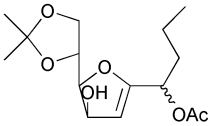


7a **7b** **7c**

Table 2 Palladium-catalyzed nucleophilic opening of allyl epoxides **5**

entry	substrate	nucleophile	product	yield (%)
i	**5a**		 **8**	86
ii	**5a**		 **9**	67
iii	**5a**		 **10**	69
iv	**5a**		 **11**	73
v	**5a**		 **12**	86
vi	**5b**		 **13**	43

Exo-glycal **5a** reacts readily with dimethyl malonate, and primary and secondary amines, to give *C*-glycals **8**–**12** (Table 2, entries *i*–*v*). On the other hand, substituted epoxy glycal **5b**, failed to give the corresponding aminoalkyl *C*-glycal yielding instead acetyl derivative **13** (Table 2, entry *vi*).

In summary, we have reported a one-pot, three step procedure for the transformation of readily accessible 3-OH furanose *C*-glycals, **3**,†[2] into 1-*exo*-methylene-2,3-anhydro furanoses, **5**, which we have shown to be useful precursors for functionalized *C*-glycals **8**–**13**. Extension of this methodology to the pyranose series is currently under study in our laboratory and the results will be reported in due course.

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Notes and references

† The synthetic route involved conversion of D-mannose into 2,3-5,6-di-*O*-isopropylidene D-mannofuranose, followed by anomeric chlorination[20] and reaction of the ensuing glycosyl chloride with the corresponding organolithium, according to ref. 2.

‡ To a solution of the corresponding glycal (≈ 3.0 mmol) in dichloromethane (CH_2Cl_2) (13 mL) containing triethylamine (2 mL mmol^{-1}) at 0 °C was added a solution of bromine (1.1 equiv.) in CH_2Cl_2. The reaction mixture was then allowed to warm to room temperature. When disappearance of the starting material was observed by TLC, an aqueous solution of sodium thiosulfate (10%) was added. The reaction mixture was extracted (CH_2Cl_2), the organic layer dried ($MgSO_4$) and evaporated to afford a residue which was purified by flash chromatography (hexane–ethyl acetate; 95:5).

§ To a solution of *exo*-glycal, **5**, (≈1.2 mmol) in THF (6 mL) under argon were added PPh_3 (1 equiv.), $Pd(OAc)_2$ (0.2 equiv.), and the nucleophile (1.3 equiv.) and the resulting solution kept with stirring at room temperature overnight. The reaction was quenched by addition of an aqueous satd soln of NaCl, extracted with ethyl acetate and the organic layer dried and evaporated to yield a residue which was purified by flash chromatography (hexane–ethyl acetate; 75:25).

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