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A general method for convergent synthesis of functionalized *exo*-glycals based on halogenation and Suzuki cross-coupling of 1-*exo*-methylene sugars

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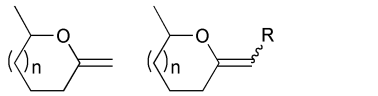
Functionalized *exo*-glycals can be readily obtained by palladium catalyzed Suzuki cross-coupling of halo-*exo*-glycals with boronic acids.

1-*exo*-Methylene sugars (*exo*-glycals), **1**,[1–3] are interesting compounds from a biological and from a synthetic standpoint. They have been used as glycosidase inhibitors,[4] and have proven to be valuable synthetic intermediates.[5-15] A number of procedures have been reported[16] for the preparation of *exo*-glycals, but the method of choice would appear to be methylenation of the corresponding lactones using the Tebbe, or similar, reagent.[1,2,17] The corresponding substituted alkenes **2**



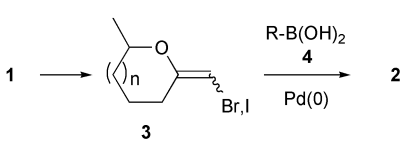
1 **2** **a** n= 0, **b** n= 1

are also of considerable interest. However, only recently a general approach to such compounds has been described. The approach, based on the Ramberg–Bäcklund rearrangement, was reported independently by the groups of Taylor[18] and Franck.[19]

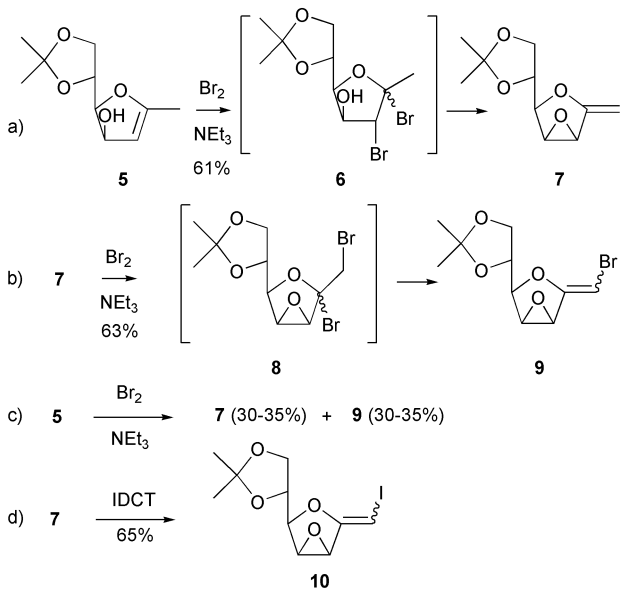
In this context, we were interested in devising a general route to substituted *exo*-glycals and we disclose herein a method that permits the correlation between methylene glycosides **1** and substituted *exo*-glycals **2**. The strategy, displayed in Scheme 1, is based on the Suzuki cross-coupling[20] of halogenated *exo*-glycals **3**,[21] readily accessible from **1**, with boronic acids, **4**.

Our interest in this chemistry emanated from some related work underway in our laboratory. We have described the reaction of *C*-glycals **5**, with bromine in the presence of triethylamine, to afford 1-*exo*-methylene-2,3-anhydrofuranoses **7** (Scheme 2a).[16] The formation, in good yield, of compound **7** seemed to indicate that bromination of the '*endo*'-glycal, **5**, was faster than bromination of the *exo*-glycal moiety in **7** (Scheme 2b). However, compound **9** was detected when *C*-glycal **5** was treated with an excess of bromine. We recognized bromoglycal **9** as a synthetically useful substrate for the synthesis of substituted *exo*-glycals, **2a**, and tried to optimize its preparation. We first investigated the feasibility of the one-pot transformation **5**→**9**, by reacting **5** with excess bromine (3 equiv.) and triethylamine in dichloromethane, unfortunately compound **9** could only be isolated in low yields along with **7** (Scheme 2c). We have since found that compound **9** is better prepared in two steps from **5** (**5**→**7**, **7**→**9**). In this context, *exo*-glycal iodide **10** could be efficiently prepared by treatment of **7** with iodonium dicollidinium triflate (IDCT)[22] (Scheme 2d).

Accordingly, compounds **11**–**14** were prepared, by nucleophilic opening of the 2,3-oxirane moiety in **9** and **10**,† and were

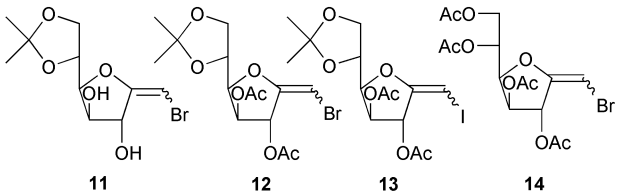


Scheme 1



Scheme 2

reacted with boronic acids **4a**–**e**. The results are shown in Table 1.‡



Fairly to good yields of the corresponding *exo*-glycals **15**–**21**‡ were obtained.

From the results in Table 1 some conclusions could be drawn: a) Acetylation at *O*-2 and *O*-3 resulted in an increased yield of coupled product (entries *i* and *ii*), b) electron deficient and electron rich aryl boronic acids could be used in the cross-coupling reaction, although higher yields were obtained with the former, c) cross-coupling reactions were more rapid when an iodide glycal was used (compare entries *iv* and *vii*), d) tetra-acetyl derivative, **14**, reacted more efficiently than its corresponding diacetate **12** (entries *iv* and *viii*).

The results obtained seem to be in agreement with known mechanistics aspects of the Suzuki cross-coupling:[20] 1) The relative reactivity of alkenyl iodides is higher than that of alkenyl bromides; 2) Oxidative addition is usually the rate-determining step in a catalytic cycle; and 3) 1-alkenyl halides activated by the proximity of electron-withdrawing groups are more reactive to the oxidative addition than those with donating groups. Therefore the alkenyl halides, derived from enol-ethers, employed in this work were not expected to be the best substrates for the cross-coupling reaction. In this context, we were not aware of Suzuki cross-coupling reactions of boronic acids with halides derived from, electron-rich, enol ethers.

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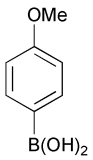
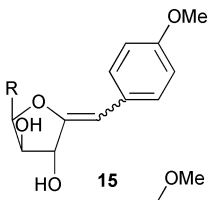
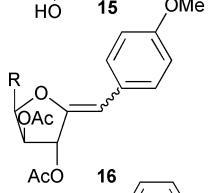
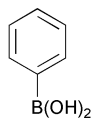
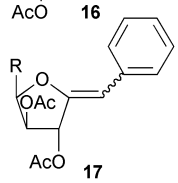
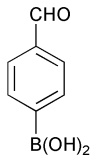
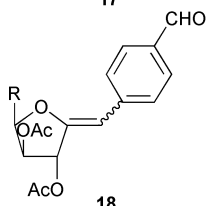
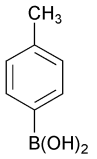
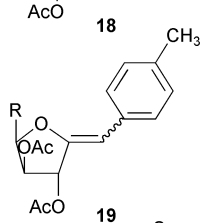
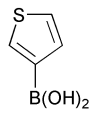
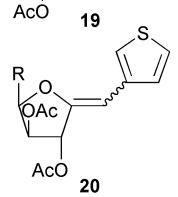
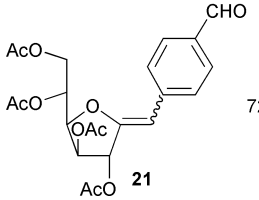
Accordingly, the use of acyl protecting groups, which have been shown to withdraw electron density from the anomeric carbon,[23] has a beneficial effect in the reaction (entries *iv* and *viii*). Only one *exo*-glycal isomer (*Z* or *E*) was obtained, although the stereochemistry has not yet been assigned. Since the Suzuki cross-coupling reaction of alkenyl halides takes place with retention of configuration[20] we believe that halo-*exo*-glycals (**11**–**14**) and their Suzuki products (**15**–**21**) have the same stereochemistry.

In summary, we have described a concise, stereoselective, approach which permits a concise transformation of, readily available, 1-*exo*-methylene sugars into substituted *exo*-glycals. The method, based on the Suzuki cross-coupling of halo *exo*-glycals with boronic acids is one of the first examples of cross-coupling of alkenyl halides attached to electron rich olefins.

Table 1 Suzuki cross-coupling of halo-*exo*-glycals with boronic acids.[ab]

entry	substrate	boronic acid	reaction time (h)	product	yield[a] (%)
i	**11**	 **4a**	10	 **15**	39[b]
ii	**12**	**4a**	10	 **16**	58
iii	**12**	 **4b**	10	 **17**	52
iv	**12**	 **4c**	3	 **18**	68
v	**12**	 **4d**	10	 **19**	48
vi	**12**	 **4e**	20	 **20**	53
vii	**13**	**4c**	1	**18**	75
viii	**14**	**4c**	0.6	 **21**	72

[a] Yield obtained after acetylation and purification. [b] Isolated as its diacetate **16**. R = 5,6-isopropylidene acetal.

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Notes and references

† NBu_4OH, THF : H_2O 10 : 1, reflux, 12–48 h, 75–90% yield.

‡ To a solution of halo-glycal (0.2 mmol) in dimethoxyethane (10 mL) were added 2 M potassium carbonate (2.7 equiv.) and the corresponding boronic acid (1.3 equiv.). The solution is stirred at rt for 10 min under argon, $(PPh_3)_4Pd$ is then added and the solution heated to reflux for the time indicated in Table 1. After cooling to rt the solvent is removed and the residue taken-up in ethyl acetate and washed with brine. The organic layer is dried, concentrated and the *exo*-glycal (**15**–**21**) purified by flash chromatography using hexane : ethyl acetate mixtures as eluent.

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