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# Convergent stereocontrolled synthesis of substituted *exo*-glycals by Stille cross-coupling of halo-*exo*-glycals and stannanes

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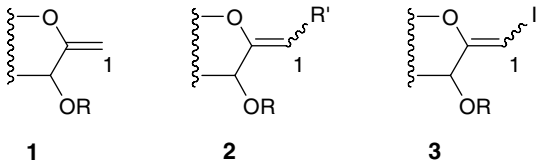
**Abstract**—(*Z*)-*exo*-Glycals can be conveniently prepared in a convergent manner by Stille cross-coupling of (*Z*)-halo(Br,I)-*exo*-glycals and aryl or alkenyl stannanes, the latter are readily obtained by addition of tributylstannyl radicals to terminal alkynes.


1-*exo*-Methylene pyranoses and furanoses (2,6- and 2,5-anhydro-1-deoxy-hept-1-enitols, respectively), currently known as *exo*-glycals, **1**,[1–3] are interesting compounds from a biological and synthetic standpoint. They have been used as glycosidase inhibitors,[4] and have proven to be valuable synthetic intermediates owing to the versatility supplied by the enol ether double bond for further elaboration.[3] The first methods described for the preparation of *exo*-glycals had focused on the methylenation of the corresponding lactones using the Tebbe or Petasis reagents.[1,2,5] More recently, Castillón and co-workers[6] and Gueyrard et al[7] have described novel methods for the preparation of **1**. On the other hand, substituted *exo*-glycals, for example **2**, (Fig. 1) have shown interesting biological properties[8,9] and in recent years, several new methods for their preparation have been reported. These methods include: Wittig olefination of glycosyl phosponium salts[10,11] or sugar lactones,[12–14] Keck reaction of glycosyl dihalides,[15] [2,3]-Wittig sigmatropic rearrangement,[16] Ramberg–Bäcklund rearrangement of *S*-glycosides[17,18] and nucleophilic addition to sugar lactones followed by elimination.[19]



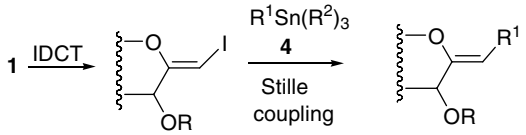
**1** **2** **3**

**Figure 1.** *exo*-Glycal (**1**), substituted *exo*-glycal (**2**), and halo-*exo*-glycal (**3**).

In this context, we have reported several methods for the preparation of substituted furanosidic and pyranosidic *exo*-glycals,[20–23] and in this letter, we disclose a convergent method for the transformation **1** → **2** based on the Stille cross-coupling reaction[24] of halo-*exo*-glycals **3** and stannanes (**4**) (Scheme 1).

The starting materials for our studies, (*Z*)-halo-*exo*-glycals **3a**, **3b**, and **3c**, (Fig. 2) were prepared from the corresponding lactones by methylenation (Petasis reagent)[25] and stereoselective iodination[22] with IDCT (iodonium dicollidinium triflate),[26] or bromination ($Br_2$, $Et_3N$).[21]

In order to evaluate the scope of the synthetic method we chose commercially available tetraphenyltin (**4a**)



**3** **2**

**Scheme 1.** General strategy for the preparation of substituted *exo*-glycals from 1-*exo*-methylene pyranoses.

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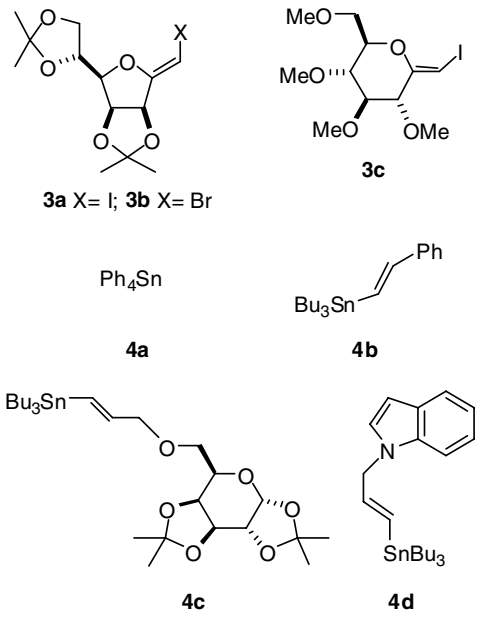



**Figure 2.** Halo-*exo*-glycals and stannananes.

and more elaborated alkenyl stannanes, **4b–d**. The latter were readily obtained by triethyl borane mediated addition of tributyltinhydride to the corresponding alkynes, following a protocol described by Oshima and co-workers.[27–29] Our results are displayed in Table 1.

The Stille cross-coupling reaction[30] worked well with iodo-*exo*-glycals (**3a**, **3c**) but less reactive bromo-*exo*-glycal **3b** failed to yield the expected substituted *exo*-glycal (Table 1, entry 3). For coupling reactions involving stannane **4b** we found advantageous the use of fluoride ion, as recommended by Baldwin and co-workers[31] (Table 1, entries 2 and 5). The (*Z*)-stereochemistry of the starting halo-*exo*-glycal follows our previous studies.[22,23] The stereochemistries of the *exo*-glycals (**5–10**) are in agreement with the fact that Stille cross-coupling reactions of vinyl iodides take place with retention of the configuration.[24d] The stereochemistry of the additional double bond has been assigned by $^1$H NMR based on the observed coupling constants.

In summary, we have disclosed a synthetic route that permits the transformation of, readily available, 1-*exo*-methylene pyranoses and furanoses (**1**) into substituted (*Z*)-*exo*-glycals (**5–10**) by stereoselective halogenation with IDCT, followed by Stille cross-coupling with alkenyl stannanes. The combination of halo-*exo*-glycals with, readily available, structurally complex alkenyl stannanes, paves the way to the preparation of 'interconnected' disaccharide **9** and a hybrid monosaccharide–indole structure, **10**. These transformations are relevant from a synthetic standpoint, and from a biological perspective, since natural products hybrids[32–34] have emerged as a promising approach to diversity oriented synthesis.[35,36] In this context the compounds prepared in this study, and derivatives therefrom, will be tested

**Table 1.** Preparation of substituted *exo*-glycals from halo-*exo*-glycals **3** and stannanes **4**

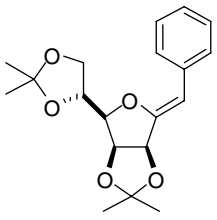
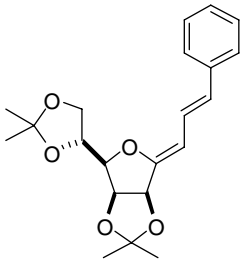
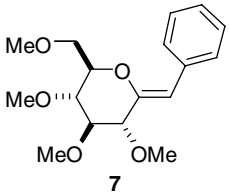
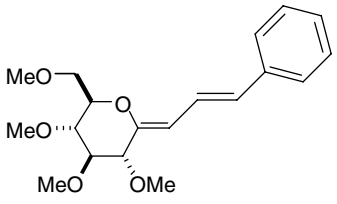
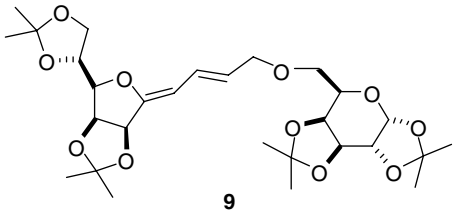
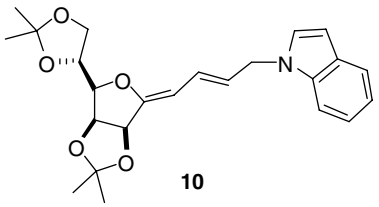
| Entry | Halo-*exo*-glycol | Stannane | Product | Yield (%) |
|---|---|---|---|---|
| 1 | **3a** | **4a** |  **5** | 91[a] |
| 2 | **3a** | **4b** |  **6** | 65[b] |
| 3 | **3b** | **4b** | No reaction | —[a,b] |
| 4 | **3c** | **4a** |  **7** | 86[a] |

**Table 1** (*continued*)

| Entry | Halo-*exo*-glycol | Stannane | Product | Yield (%) |
|---|---|---|---|---|
| 5 | **3c** | **4b** |  **8** | 69[b] |
| 6 | **3b** | **4c** |  **9** | 68[a] |
| 7 | **3b** | **4d** |  **10** | 76[a] |

Reaction conditions: (a) Stannane (1.1 equiv), $Pd(PPh_3)_4$ (5%), CuI (10%), toluene, 100 °C. (b) Stannane (1.1 equiv), CsF (2.0 equiv), $Pd(PPh_3)_4$ (10%), CuI (10%) DMF, 55 °C.

as glycosidase inhibitors and in high-throughput screening studies. Further results in this area will be reported in due course.

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29. *General procedure for the preparation of alkenyl-stannanes*: To a stirred solution of the terminal alkyne (1.0 mol equiv) and tributyltin hydride (1.1 mol equiv) in toluene (10 mL/mmol) was added triethylborane (0.1 mol equiv of an hexane solution) under argon at 0 °C. The reaction mixture was stirred for 24 h and was then concentrated under reduced pressure. The residue was purified by flash chromatography.
30. *General procedure for the Stille cross-coupling reaction: method A*. A toluene solution containing the halo-*exo*-glycal (300 mg) tetraphenyltin (1.1 equiv), $Pd(PPh_3)_4$ (0.05 equiv), and CuI (0.1 equiv.) was heated to 100 °C. The heating was continued until disappearance of the starting material was observed by TLC. The reaction mixture was then allowed to cool to room temperature and treated with KF (saturated aqueous solution) and extracted with ethyl ether. The organic layer was filtered through Celite®, dried (anhydrous $MgSO_4$), filtered, and concentrated. Flash chromatography of the residue (hexane–EtOAc) furnished the corresponding substituted glycal. *Method B*. A mixture of the halo-*exo*-glycal (300 mg) and the organotin reagent (1.1 equiv) was dissolved in DMF (2 mL). Then CsF (2 equiv), CuI (10%), and $Pd(PPh_3)_4$ (10%) were added and the flask was evacuated and refilled with argon several times. The mixture was stirred at 55 °C until disappearance of the starting material was observed by TLC. The reaction mixture was then diluted with $CH_2Cl_2$ (50 mL) and water (25 mL). After vigorous shaking the mixture was filtered through Celite® with $CH_2Cl_2$/EtOAc (200 mL, 1:1). The organic layer was separated, dried (anhydrous $MgSO_4$), filtered, and concentrated. Flash chromatography of the residue (hexane–EtOAc) furnished the corresponding substituted glycal.
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36. *Data for selected compounds*: Compound (**9**). $[\alpha]_D$ +32.0 ($CHCl_3$, *c* 0.53); $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ (ppm): 1.32 (s, 3H), 1.33 (s, 3H), 1.37 (s, 3H), 1.38 (s, 3H), 1.43 (s, 3H), 1.44 (s, 3H), 1.47 (s, 3H), 1.52 (s, 3H), 3.90–4.00 (m, 2H), 4.00–4.20 (m, 5H), 4.20–4.35 (m, 3H), 4.43 (dt, $J = 0.5$, 7.1 Hz, 2H), 4.59 (dd, $J = 2.2$, 7.9 Hz, 2H), 4.70–4.80 (m, 1H), 5.09 (d, $J = 5.4$ Hz, 1H), 5.18 (d, $J = 7.4$ Hz, 1H), 5.53 (d, $J = 4.8$ Hz, 1H); $^{13}C$ NMR (50 MHz, $CDCl_3$) $\delta$ (ppm): 24.4, 24.9, 25.3, 25.8, 25.9, 26.1, 26.8, 26.9, 66.9, 67.2, 68.9, 71.1, 71.2, 71.6, 73.6, 74.4, 78.0, 81.9, 83.8, 96.3, 101.6, 109.2, 109.4, 113.4, 113.7, 131.9, 139.7, 155.1; API-ES positive: 577.3 $(M+Na)^+$. Compound (**10**). $[\alpha]_D$ +93.5 ($CHCl_3$, *c* 0.55); $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ (ppm): 1.33 (s, 3H), 1.34 (s, 3H), 1.45 (s, 3H), 1.54 (s, 3H), 4.01 (dt, $J = 1.5$, 5.7 Hz, 2H), 4.21 (dt, $J = 1.5$, 5.7 Hz, 2H), 4.24–4.35 (m, 2H), 4.61 (dd, $J = 2.4$, 8.1 Hz, 1H), 5.55 (d, $J = 5.1$ Hz, 1H), 6.30 (dd, $J = 6.0$, 15.9 Hz, 1H), 6.61 (d, $J = 15.9$ Hz, 1H), 7.18–7.42 (m, 5H); $^{13}C$ NMR (50 MHz, $CDCl_3$) $\delta$ (ppm): 25.2, 25.7, 26.7, 26.9, 43.6, 66.4, 73.2, 78.1, 80.4, 83.0, 97.9, 101.2, 109.6, 113.7, 119.3, 120.9, 121.4, 124.8, 127.2, 128.7, 129.5, 136.0, 157.3; API-ES positive: 291.0, 412.3 $(M+1)^+$.