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A novel entry to *C*-glycals via diethylzinc-mediated umpolung of π-allyl palladium derived from 1-*exo*-methylene 2,3-anhydrofuranoses

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Abstract—The reaction of aldehydes with allylzinc reagents resulting from the umpolung of π-allyl palladium complexes from 1-*exo*-methylene 2,3-anhydrofuranoses provides a novel entry to *C*-glycals.

Methods for the formation of *C*-glycosides **1** (Fig. 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**[2–6] which might function as *C*-glycoside precursors by way of the stereoselective functionalization of their enol ether double bond.[2,5,6]

Our group has been interested in the preparation of *C*-glycosides,[7,8] *C*-glycals[2,9] and *exo*-glycals **3**.[9–11] We have recently described a synthetic approach to furanoside derived *C*-glycals **2** ($n=1$) based on the palladium-mediated coupling of 1-*exo*-methylene-2,3-anhydrofuranoses **4** with nucleophiles (Scheme 1(a)). In this letter we disclose that epoxy-*exo*-glycal **4** can be successfully coupled with electrophilic (rather than nucleophilic) partners by umpolung of the organopalladium species[12] **5** using diethylzinc, to furnish *C*-glycals **8**.

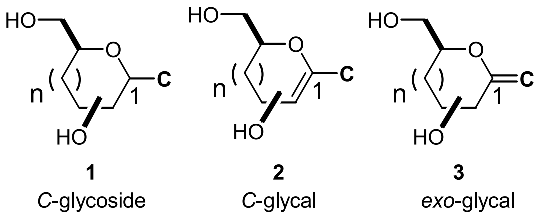
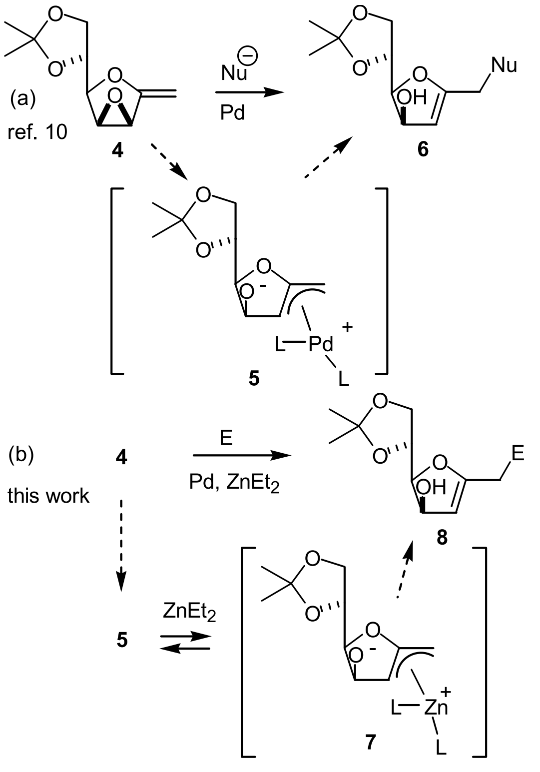


Figure 1. *C*-Glycosides, *C*-glycals and *exo*-glycals ($n=1$ pyranoses; $n=2$ furanoses).



Scheme 1. Synthesis of *C*-glycals by coupling of **4** with electrophiles (E).

The proposed reaction pathway for this transformation[13] would involve oxidative addition of the vinyl epoxide to generate the π-allylpalladium inter-

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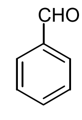
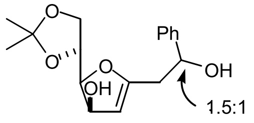
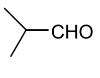
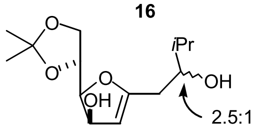
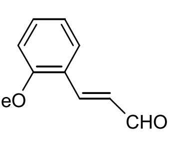
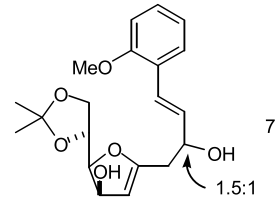
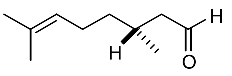
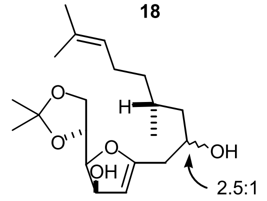
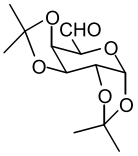
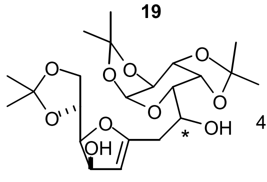
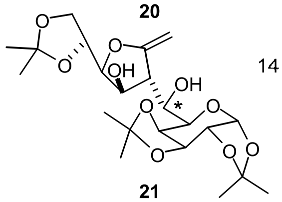
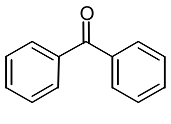
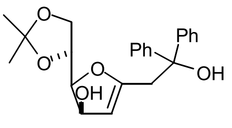
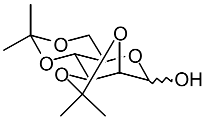
mediate **5** (Scheme 1). Subsequent ligand transfer to Et_2Zn then yields the allylic zinc intermediate **7** which is able to react with its electrophilic partner. Although several examples of this reaction have been reported with allylic substrates, to the best of our knowledge there is no report on the coupling reaction of allylic zinc species arising from vinyl oxiranes with aldehydes. However, one related example involving umpolung of simple vinyloxiranes by indium/palladium-mediated allylation of carbonyl compounds has been described.[14] More recently, on an interesting approach to carbocycles from carbohydrates, Aurrecoechea and co-workers have disclosed the use of $Et_2Zn/Pd(0)$ for the in situ generation of nucleophilic allylzinc species, which reacted with a ring-opened carbohydrate aldehyde.[15]

We have tested aldehydes, ketones and pyranosidic hemiacetals as electrophilic partners. Aldehydes proved to be excellent electrophiles in this coupling reaction. The results in Table 1 show the scope of the Pd-catalyzed reaction. Aromatic, aliphatic and highly functionalized aldehydes furnished good to excellent yields of the corresponding *C*-glycals. Benzaldehyde (Table 1, entry *i*), yielded the *C*-glycal **16** as a diastereomeric mixture in 83% yield. Isobutyraldehyde (entry *ii*), *o*-methoxycinnamaldehyde (entry *iii*), and citronellal (entry *iv*) also yielded the corresponding *C*-glycals as diastereomeric mixtures in good yields. The reaction of **4** with the aldehydo sugar **13**, derived from D-galactose, yielded two single disaccharide analogues **20** and **21**. Reaction with benzophenone **14** was sluggish and yielded **22** in 69% yield (corrected, based on 39% recovered **14**). Hemiacetal **15** failed to react and was recovered unchanged after work-up.

The observed regioselectivity was excellent, affording almost exclusively 1,5-diols **16**–**22**. The reaction of galactose aldehyde **13** gave rise, however, to two regioisomers, thus showing the influence of the carbonyl compound on the regioselectivity.[14,16] On the other hand, the stereoselectivity[17] of these couplings ranged from moderate to excellent depending on the stereochemical bias of the electrophilic partner. When **4** was confronted with benzaldehyde **9**, or *o*-methoxycinnamaldehyde **11** a 1.5:1 mixture of diastereomeric *C*-glycals (**16** and **18**, respectively) was obtained in each case. The stereoselectivity observed in the coupling of **4** with isobutyraldehyde **10**, citronellal **12** and the galactose aldehyde **13** is noteworthy.

In summary, we have reported an efficient strategy for the preparation of synthetically useful *C*-glycals by reaction of unsaturated epoxide **4** with carbonyl compounds.[18] The method is compatible with highly oxygenated substrates and can be applied to the assembly of highly functionalized molecules as has been shown with the preparation of compounds **19**[19] and **20**.[19] The use of this protocol for the preparation of *C*-glycosides and derivatives thereof is underway in our laboratory and will be described in due course.

Table 1. Preparation of *C*-glycals by reaction of **4** with $Pd(PPh_3)_4$ and Et_2Zn in the presence of electrophiles

Entry	Electrophile	Product	Yield (%)
i	 **9**	 **16**	83
ii	 **10**	 **17**	63
iii	 **11**	 **18**	70
iv	 **12**	 **19**	72
v	 **13**	 **20**	43
		 **21**	14
vi	 **14**	 **22**	69[a]
vii	 **15**	No reaction	

[a] Based on 39% recovered **4**. *Only one stereoisomer was observed.

Acknowledgements

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18. **General procedure for allylation reaction**. To a thoroughly degassed (argon) solution of vinyl-epoxide **4** (100 mg, 0.5 mmol), the appropriate carbonyl compound (1.5 equiv., 0.75 mmol) and $Pd(PPh_3)_4$ (24 mg, 0.025 mmol) in dry THF (10 mL), was added Et_2Zn (1.2 mmol, 1.2 mL 1.0 M in hexane). The reaction was then stirred at room temperature until complete disappearance of the starting material (1–3 h). The solution was diluted with ethyl acetate and washed successively with saturated $NaHCO_3$ and brine. The organic layer was then dried (sodium sulfate) and evaporated *without heating* to furnish a residue, which was purified by flash chromatography using hexane:ethyl acetate:triethylamine mixtures as eluant.
19. **Data for selected compounds**: **glycal 19 (minor diastereomer)**: $[\alpha]_{D21}$ −55.0 (*c* 0.51, $CHCl_3$), ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): 5.14–5.06 (m, 1H), 5.02 (d, $J=2.7$ Hz, 1H), 4.92 (dd, $J=6.8$, 2.7 Hz, 1H), 4.49 (ddd, $J=7.7$, 6.3, 4.9 Hz, 1H), 4.23 (dd, $J=7.7$, 6.5 Hz, 1H), 4.16 (dd, $J=8.5$, 6.3 Hz, 1H), 4.02 (dd, $J=8.5$, 4.9 Hz, 1H), 3.94–3.86 (m, 1H), 2.36 (dd, $J=15.0$, 4.0 Hz, 1H), 2.28 (dd, $J=15.0$, 8.2 Hz, 1H), 1.88–2.06 (m, 3H), 1.67 (s, 3H), 1.60 (s, 3H), 1.46 (s, 3H), 1.38 (s, 3H), 1.12–1.36 (m, 4H), 0.91 (d, $J=6.4$ Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 161.1, 131.4, 124.7, 109.3, 101.0, 85.2, 73.7, 73.1, 67.1, 66.9, 44.4, 37.8, 36.9, 28.9, 26.8, 25.7, 25.4, 25.2, 19.1, 17.6.

   Glycal 19 (major diastereomer): mp = 55°C; $[\alpha]_{D21}$ −268.0 (*c* 0.9, $CHCl_3$), ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): 5.12–5.04 (m, 1H), 5.02 (d, $J=2.6$ Hz, 1H), 4.50 (ddd, $J=7.0$, 6.3, 5.1 Hz, 1H), 4.23 (t, $J=7.0$ Hz, 1H), 4.16 (dd, $J=8.6$, 6.3 Hz, 1H), 4.02 (dd, $J=8.6$, 5.1 Hz, 1H), 3.96–3.87 (m, 1H), 2.35 (dd, $J=14.8$, 3.2 Hz, 1H), 2.22 (dd, $J=14.8$, 8.5 Hz, 1H), 1.80–2.02 (m, 3H), 1.68 (s, 3H), 1.59 (s, 3H), 1.45 (s, 3H), 1.37 (s, 3H), 1.42–1.34 (m, 2H), 1.12–1.36 (m, 4H), 0.91 (d, $J=6.4$ Hz, 3H) ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 161.1, 131.4, 124.7, 109.2, 101.1, 85.2, 73.7, 73.1, 67.3, 66.8, 44.6, 36.7, 36.5, 29.3, 26.8, 25.7, 25.3, 25.2, 20.1, 17.7.

   Glycal 20. ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): 5.53 (d, $J=4.9$ Hz, 1H), 5.08 (d, $J=2.6$ Hz, 1H), 4.89 (dd, $J=6.2$, 2.6 Hz, 1H), 4.62 (dd, $J=8.1$, 2.3 Hz, 1H), 4.52–4.44 (m, 2H), 4.31 (dd, $J=5.1$, 2.3 Hz, 1H), 4.23 (t, $J=6.5$ Hz, 1H), 4.14 (dd, $J=8.5$, 6.2 Hz, 1H), 4.04–3.96 (m, 2H), 3.58 (dd, $J=8.2$, 1.6 Hz, 1H), 2.76 (dd, $J=15.2$, 2.6 Hz, 1H), 2.30 (dd, $J=15.2$, 9.2 Hz, 1H), 1.51 (s, 3H), 1.46 (s, 3H), 1.44 (s, 3H), 1.37 (s, 3H), 1.36 (s, 3H), 1.32 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 161.1, 109.3, 108.6, 101.1, 96.5, 85.3, 73.7, 73.1, 70.8, 70.7 (×3), 69.7, 68.4, 66.9, 33.0, 26.9, 26.1, 26.0, 25.3, 25.0, 24.4.

   ***exo*-Glycal 21**. ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): 5.55 (d, $J=5.4$ Hz, 1H), 4.64 (dd, $J=8.0$, 2.2 Hz, 1H), 4.52–4.44 (m, 2H), 4.41 (dd, $J=8.0$, 2.2 Hz, 1H), 4.39–4.27 (m, 3H), 4.26 (bs, 1H), 4.19–4.06 (m, 2H), 4.04–3.96 (m, 2H), 3.82 (dd, $J=9.0$, 2.2 Hz, 1H), 1.53 (s, 3H), 1.45 (s, 3H), 1.42 (s, 3H), 1.36 (s, 6H), 1.32 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 160.2, 110.5, 109.2, 108.5, 96.4, 84.6 (×2), 76.0, 73.4, 70.7 (×3), 70.0, 68.3, 67.6, 52.5, 26.7, 25.9, 25.5, 25.1, 24.7, 24.5.