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AN EFFICIENT METHOD FOR THE SYNTHESIS OF α- AND β-*C*-GLYCOSYL ALDEHYDES

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Abstract. A practical method for the synthesis of α- and β-*C*-glycosyl aldehydes from a single carbohydrate precursor is described.

Carbon-linked glycosyl compounds are important materials in biochemistry as stable analogs of naturally occurring sugars.[1] In our further efforts to synthesize *C*-glycosyl derivatives for cell-surface recognition studies[2], we required a simple method for the construction of β-*C*-glycosyl compounds. *C*-glycosyl compounds with an α-linkage at the anomeric carbon atom are readily accessible using both Lewis-acid catalyzed nucleophilic additions and radical promoted additions to the anomeric center of an appropriately activated carbohydrate derivative.[3,4] In these reactions, the preferred mode of attack at the anomeric center provides the α-linked product with high diastereoselectivity. β-*C*-glycosyl compounds, however, are less readily obtained. Kishi and coworkers and Stork *et. al* have described methods that allow access to β-*C*-glycosyl compounds.[3c,5] Although these methods are general, we were interested in developing a more practical method for the synthesis of multigram quantities of these compounds. We felt that epimerization of α-*C*-glycosyl aldehydes would be a direct and simple route to the β-linked isomer based on results obtained by others in related systems. For example, Masamune, Sharpless and coworkers have described a method to epimerize the acetonide derivative of *erythro* 2,3-dihydroxy aldehydes to their *threo* isomers.[6] Furthermore, Schmidt and Preuss have used a similar reaction to set the stereocenter at C-4 of a modified galactose derivative.[7] Epimerization of the anomeric center of *C*-glycosyl alkenes to give the β-linked product has also been described by Kende and Fujii.[8] However, the strongly acidic conditions used by these researchers are incompatible with sensitive functionalities and most protecting groups. In this letter we describe an efficient method for the synthesis of β-*C*-glycosyl compounds that involves epimerization of α-linked *C*-glycosyl aldehydes under mild basic conditions (Et_3N) to the more stable β-linked isomer (Scheme I). This method is practical and provides either α- or β-linked *C*-glycosyl aldehydes at the anomeric position starting from a single *C*-glycosyl allene precursor.

The synthesis of *C*-glycosyl allenes by the addition of propargyl trimethylsilane to carbohydrate derivatives has been previously described.[9] Methyl (tetra-*O*-benzyl)-α-D-galactopyranoside (**1**) reacts with propargyl trimethylsilane in the presence of trimethylsilyl triflate (TMSOTf) in CH_3CN to give the corresponding α-linked *C*-glycosyl allene **2** with high diastereoselectivity (>20:1). Ozonoylsis[10] of compound **2** gives the α-linked *C*-glycosyl aldehyde **3** which can be epimerized directly to the β-linked *C*-glycosyl aldehyde **4** by treatment of the crude product with a 10% solution of Et_3N in 1:1 isopropanol-CH_2Cl_2 at 25 °C for 24 hours.[11,12] The same procedure can be performed on glucose and mannose derivatives to give the corresponding β-*C*-glycosyl compounds as shown in Table 1.

Scheme I

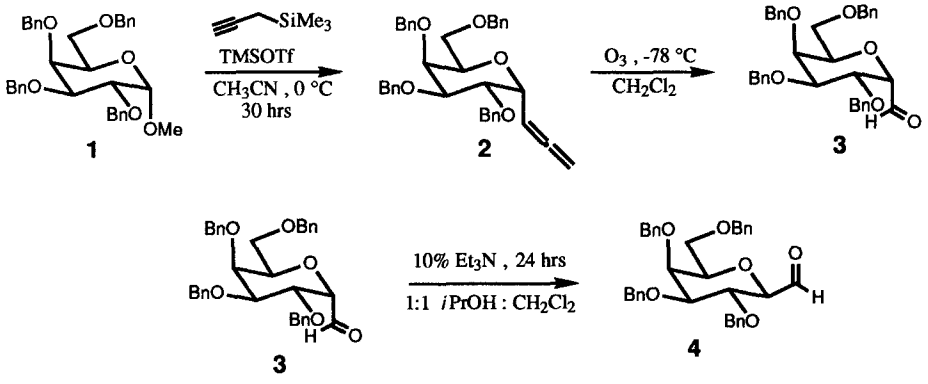
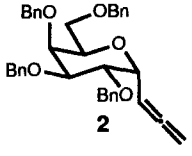
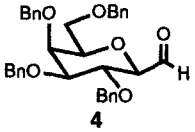
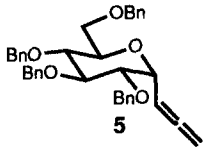
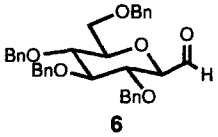
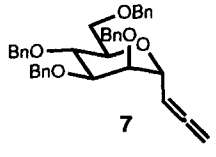
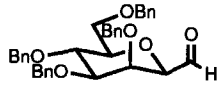


Table 1

Starting allene	β-Linked product	Equilibrium ratio* β /α	Isolated yield‡
 2	 4	10:1	49 %
 5	 6	>20:1	41%
 7	 8	8:1	42 %

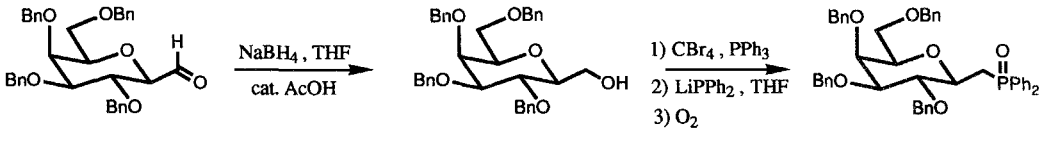
* Equilibrium ratios are measured by NMR integration before purification. The α and β isomers are easily separated by silica gel chromatography.

‡ Isolated yields starting from *C*-glycosyl allene precursors on a 0.5 g scale.

The overall isolated yields of β-*C*-glycosyl aldehydes (starting from the allene precursors) are 40 to 60 % depending on the scale of the reaction (62 % overall yield was obtained when the reaction was performed on a multigram scale) due to decomposition during the ozonoylsis reaction and subsequent purification of the aldehydes.[13] The epimerization reaction, however, results in only a minimal amount of decompostion.[14] The *C*-glycosyl alcohols can be obtained by direct reduction of the crude aldehyde **4** with $NaBH_4$ and a catalytic amount of glacial acetic acid in THF (Scheme II). Alcohol **9** can be further elaborated into useful compounds such as phosphine oxide **10**.[15]

In summary, we have presented a practical method for the synthesis of both α- and β-linked *C*-glycosyl aldehydes. We are currently investigating the utility of these compounds in both Wittig reactions and Henry condensations for the synthesis of carbon-linked disaccharides.

Scheme II



4 **9** **10**

Procedure for the synthesis of (tetra-*O*-benzyl-β-D-galactopyranoside) methanal (4). A solution of 8.20 g (14.6 mmol) of (tetra-*O*-benzyl-α-D-galactopyranoside) allene (**2**) in 150 mL of CH_2Cl_2 was cooled to -78 °C and ozone was bubbled through the solution until it was saturated. The excess ozone was eliminated by bubbling nitrogen through the solution. The solution was warmed to room temperature and 120 mL of isopropanol and 30 mL of Et_3N (final solution 10% v/v) were added. After 24 hours, the solvents were removed *in vacuo* without heating and the crude product was purified by silica gel chromatography eluting with 9:1 cyclohexane-ethyl acetate to afford 5.00 g (62 %) of (tetra-*O*-benzyl-β-D-galactopyranoside) methanal (**4**).[16]

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10. One equivalent of ozone is consumed in the reaction to give the aldehyde product directly without need for an additional reducing step. (a) Kolsaker, P.; Teige, B. *Acta. Chem. Scand.* **1970**, *24*, 2101. (b) Crandall, J. K.; Conover, W. W. *J.C.S. Chem. Comm.* **1973**, 340.
11. We have found that these conditions give the most favorable equilibrium ratios and yields. The structures of the α- and β-linked *C*-glycosyl aldehydes were assigned based on the coupling constant between the proton at the anomeric carbon atom and the adjacent proton at C-2 on the sugar ring.
12. Spectroscopic and analytical data for compounds **2-4** are as follows. Compound **2:** ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.55-3.71 (m, 2H), 3.73 (dd, 1H, J = 2.6, 9.3 Hz), 3.99-4.02 (m, 2H), 4.12-4.16 (m, 1H), 4.42-4.91 (m, 11H), 5.43 (dd, 1H, J = 6.4, 11.9 Hz), 7.28-7.35 (m, 20H); ^{13}C NMR ($CDCl_3$) δ 68.48, 71.70, 71.80, 72.89, 73.09, 73.32, 74.86, 76.54, 79.08, 86.08, 127.42, 127.46, 127.57, 127.61, 127.68, 127.77, 128.16, 128.21, 128.28, 128.32, 138.43, 138.65, 208.90; Anal. calcd for $C_{37}H_{38}O_5$: C, 78.84; H, 6.97. Found C, 79.09; H, 7.13. Compound **3:** ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.63-3.69 (m, 2H), 3.90 (dd, 1H, J = 7.7, 10.8 Hz), 4.06 (dd, 1H, J = 2.8, 4.1 Hz), 4.15 (dd, 1H, J = 4.4, 6.5 Hz, C-2), 4.32 (d, 1H, J = 4.4 Hz, C-1), 4.34-4.37 (m, 1H), 4.50-4.69 (m, 8H), 7.30-7.40 (m, 20H), 9.88 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 66.27, 72.81, 72.87, 73.02, 73.56, 73.73, 75.11, 75.69, 76.33, 127.47, 127.65, 127.61, 127.73, 127.80, 127.87, 127.99, 128.02, 128.06, 128.34, 128.37, 128.45, 137.43, 137.58, 137.88, 137.98, 202.20; high-resolution mass spectrum (FAB^+) calcd for $C_{35}H_{36}O_6Li$ (M + Li) 559.2672, found 559.2677. Compound **4:** ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.58-3.70 (m, 4H), 3.78 (dd, 1H, J = 1.0, 9.9 Hz, C-1), 4.00 (d, 1H, J = 2.6 Hz), 4.08 (app t, 1H, J = 9.6 Hz), 4.44-4.51 (m, 2H), 4.61-4.82 (m, 4H), 4.88-4.97 (m, 2H), 7.28-7.42 (m, 20H), 9.67 (d, 1H, J = 1.0 Hz); ^{13}C NMR ($CDCl_3$) δ 68.60, 72.43, 73.30, 73.56, 74.38, 74.63, 75.21, 77.26, 82.06, 84.24, 127.55, 127.66, 127.77, 127.84, 127.95, 128.07, 128.24, 128.30, 128.35, 128.39, 128.41, 128.47, 137.64, 137.95, 138.34, 197.53; high-resolution mass spectrum (FAB^+) calcd for $C_{35}H_{36}O_6Li$ (M + Li) 559.2672, found 559.2677.
13. Ozonolysis of the mannose *C*-glycosyl allene results in partial epimerization of the intermediate α-linked aldehyde (~ 1:1 β/α). However, treatment with Et_3N results in equilibration to an 8:1 β/α mixture.
14. A minor byproduct of the epimerization reaction derives from β-elimination of the benzyloxy substituent at the 2-position of the sugar. We have found that the epimerization yield in the case of mannose is not significantly different from that of galactose and glucose despite the axial orientation of the benzyloxy substituent.
15. Similar hydroxymethylene compounds have been synthesized previously using other routes. (a) ref 5b. (b) Baumberger, F.; Vasella, A.; *Helvetica Chim. Acta* **1983**, *66*, 2210. (c) Pougny, J.-R.; Nassr, M. A. M.; Sinay, P. *J. C. S. Chem. Comm.* **1981**, 375. (d) Reed, L. A., III; Ito, Y.; Masamune, S.; Sharpless, K. B. *J. Am. Chem Soc.* **1982**, *104*, 6468. (e) Boschetti, A.; Nicotra, F.; Panza, L.; Russo, G. *J. Org. Chem.* **1988**, *53*, 4181.
16. The procedure is the same for both mannose and glucose derivatives.

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