A Rapid Synthesis of Pyranoid Glycals from Glycosyl Bromides

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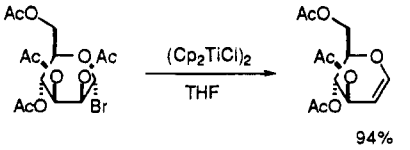
Glycals, or 1,2-unsaturated sugars, are well known[1] synthesis intermediates[2] of particular significance for the preparation of oligosaccharides,[3] carbohydrates,[4] and O-[5] or C-glycosides.[6] Consequently, development of new routes to glycals can have immediate impact on a broad range of synthesis endeavors, especially if these methodologies involve mild conditions which are tolerant of sensitive functionality. The classic synthesis of glycals[1,7] involves treating a peracetylated glycosyl bromide with zinc and acetic acid. To obviate the requirement for acid, myriad methodologies have been explored, including reduction of protected glycosyl halides by alkali metals,[8] Cr(II),[9] Zn,[10] Zn/Ag,[11] Al/Hg,[12] or SmI_2;[13] fragmentation of a 2-*O*-mesylglycosyl chloride;[14] or using thiophenyl glycoside[15] precursors. Although effective, these procedures can suffer shortcomings, including low protecting group compatibility;[8a-d] toxic,[9,12] expensive,[13] or dangerous[8d,11] reagents; low yield;[8b,c,15] or starting materials that involve multistep synthesis from available precursors.[14] We now report a new and efficient procedure for the production of glycals from the corresponding glycosyl bromides, which can be accomplished simply, rapidly and in high yield using an inexpensive and easy to prepare Ti(III) reagent.

Scheme 1



The dimeric Ti(III) species $(Cp_2TiCl)_2$ (**1**)[16] **1** reacts with activated haloalkyls[17] by halogen atom abstraction or with epoxides[18] by "alkoxide" abstraction to give, in both cases, alkyl radicals. Given the stability of glycosyl radicals,[19] it was of interest to learn if **1** could abstract bromine from glycosyl bromides, which are easily, but slowly, obtained by treating the peracetylated sugar with TMS-Br.[20] Indeed, we found **1** completely consumed the glycosyl bromide at room temperature in less than 15 min; elimination of the 2-*O*-acetyl group also occurred, to give the glycal in high yield (Scheme 1). Representative examples of glycal synthesis are listed in Table 1.

By analogy with the oxidative addition of alkyl halides to low-valent early transition metal complexes,[21] we suggest that **1** reacts with a glycosyl bromide by abstraction of Br$^\bullet$ by Ti(III) to give an intermediate glycosyl radical.[19] This radical is then trapped[21] by a second equivalent of Ti(III) to give glycosyltitanium(IV) complex **2**, which then eliminates $Cp_2TiCl(OAc)$[22] to yield the glycal (Scheme 2). We find that using an excess of Ti(III) over the stoichiometric amount gives the highest yields of glycals. If only a stoichiometric amount of Ti(III) is used, the initially formed glycosyl radical reacts with solvent competitively with its capture by Ti(III), giving the anhydroalditol[23] as a byproduct.

In support of an organotitanium(IV) complex intermediate mechanism, we note that reaction of 3,4-di-*O*-acetyl-2-deoxy-β-D-ribopyranosyl bromide with **1** gives **3**, which has been isolated and identified by ^{1}H NMR, and which

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Scheme 2

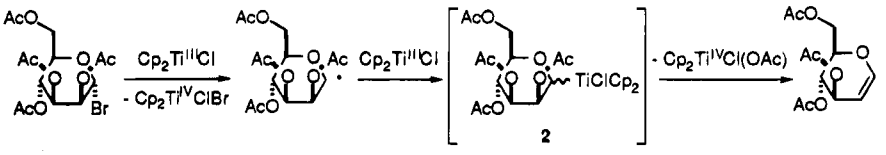
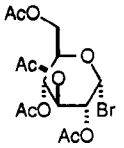
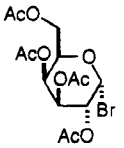
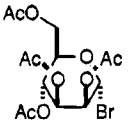
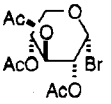
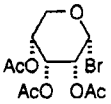
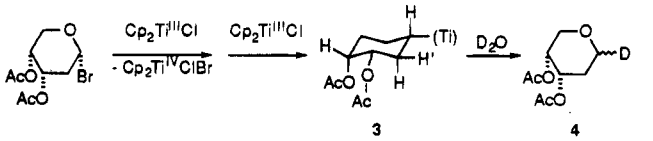


Table 1. Reduction of Glycosyl Bromides to Glycals with $(Cp_2TiCl)_2$

Glycosyl Bromide		Glycal Yield (%, isolated)
	α-D-Glucopyranosyl	82[9]
	α-D-Galactopyranosyl	89[29]
	α-D-Mannopyranosyl[30]	94[9]
	α-D-Xylopyranosyl[31]	89[9]
	D-Ribopyranosyl 90% α, 10%β[20]	70[9]

undergoes cleavage with D_2O[24] to give anhydroalditol **4** (80% d_1). Two diastereomeric components are observed (3:1), which are likely α- and β-anomers, for which assignments were made by analysis of the COSY spectrum. Cp shifts (6.20 and 6.24 ppm) are typical for Cp_2Ti(alkyl)Cl compounds[25] and the difference between chemical shifts of the diastereotopic Cp units (0.04 ppm) is similar to that of simple Zr analogs, such as $Cp_2(Cl)Zr_a$-$OCHRZr_b(Cl)Cp_2$.[26] The chemical shift recorded for H1 is as expected, based on the observed shift of δ 3.36 for the corresponding proton in $Cp_2(Cl)Zr_aOCHRZr_b(Cl)Cp_2$ and the typical downfield shift (*ca.* 1.1 ppm) for Ti *vs* Zr species.[26,27] On the basis of the small couplings noted for H4, this proton is assigned to be equatorial; based on the large couplings for H1, this proton is assigned to be axial (Scheme 3). Thus, the major component is assigned to be the α-Ti anomer and the minor the β-anomer. These results are consistent with those reported for α-facial attack on both glucosyl and mannosyl radicals by Bu_3SnD.[19,28] In the context of glycal synthesis, since both mannosyl and glucosyl bromides give high yields of glucal, both *syn* and *anti* elimination of $Cp_2TiCl(OAc)$ seem possible. We are further examining the mechanism and scope of this process.

Scheme 3



Experimental Section

General. Reaction solvents were dried and distilled prior to use using standard methods. 1,2,3,4,6-Penta-*O*-acetyl-α-D-mannopyranose, 1,2,3,4-tetra-*O*-acetyl-β-D-xylopyranose, and 2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyl bromide were purchased from Sigma Chemical Co. All other starting materials were purchased from Aldrich Chemical Co. and were used without further purifacation.

Synthesis of Peracetylated Glycosyl Bromides.[20] In a typical procedure, under an inert atmosphere 1,2,3,4,6-penta-*O*-acetyl-α-D-mannopyranose (200 mg, 0.51 mmol) was dissolved in 2 mL of clean, dry CH_2Cl_2 and cooled to −40 °C. Bromotrimethylsilane (TMS-Br; 240 mg, 1.53 mmol) was added, and the mixture was stirred as it warmed to room temperature. Bromide synthesis was monitored by NMR. When the reaction was complete, the solvent, excess TMS-Br, and TMS-OAc were removed under vacuum to provide the 2,3,4,6-tetra-*O*-acetyl-α-D-mannopyranosyl bromide (93% by NMR[30]). Other glycosyl bromides were prepared similarly.

Bis(titanocene chloride).[16] A solution of Cp_2TiCl_2 (4.0 g, 1.61 mmol) in 25 mL of THF was prepared under inert atmosphere. Aluminum foil (2.0 g, 74.1 mmol, Aldrich Gold Label) was added to this red solution, and the reaction mixture was stirred overnight. The resulting green solution was filtered, concentrated in vacuo, washed with three 20 mL portions of diethyl ether, filtered, and dried in vacuo to give 3.4 g of $(Cp_2TiCl)_2$ as a light green powder (100% yield).

Synthesis of Peracetylated Glycals. In a typical procedure, a solution of $(Cp_2TiCl)_2$ (300 mg, 0.702 mmol) in 10 mL of THF was prepared in a dry box. 2,3,4,6-Tetra-*O*-acetyl-α-D-mannopyranosyl bromide (180 mg, 0.438 mmol) in 10 mL of THF was added to this stirred, green solution dropwise over the course of 5 min at room temperature. The reaction mixture quickly began to turn brown, and within 10 min was red. The mixture was removed from the dry box and concentrated in vacuo. The residue was dissolved in ether, and the solution was passed through a short column of silica to remove organometallic impurities. Solvent was removed in vacuo to yield 3,4,6-tri-*O*-acetyl-1,5-anhydro-2-deoxy-D-*arabino*-hex-1-enitol (tri-*O*-acetyl-D-glucal) (113 mg; 95%) as an oil.

Tri-*O*-acetyl-2-deoxy-β-D-*erythro*-pentopyranose.[31] 2-Deoxy-β-D-*erythro*-pentose (2-deoxyribose; 0.504 g, 3.76 mmol) was dissolved in a solution composed of 7 mL of acetic anhydride (74.19 mmol, 20 equiv) and 12 mL of pyridine (148.37 mmol, 39.5 mmol). After stirring overnight, the yellow solution was worked up according to the reference, and the product was crystallized from diethyl ether and hexanes. Two crops gave 267 mg of the desired product (27% yield) as clear hexagonal prisms. NMR ($CDCl_3$): δ 6.24 (1H, dd, H1); 5.32−5.24 (1H, m, H3); 5.19 (1H, broad s, H4); 3.99 (1H, dd, H5); 3.83 (1H, dd, H5′);

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2.29–2.17 (1H, m, H2); 2.12 (3H, s, OAc); 2.09 (3H, s, OAc); 2.01 (3H, s, OAc); 1.95–1.85 (1H, m, H2′).

3,4-Di-*O*-acetyl-2-deoxy-β-D-*erythro*-pentopyranosyl Bromide. The title compound was synthesized as described above using 250 mg (0.96 mmol) of 1,3,5-tri-*O*-acetyl-2-deoxy-β-D-*erythro*-pentopyranose and 460 mg (3.03 mmol) of TMS-Br. The reaction took approximately 1 h, and the yield was estimated to be 99% by NMR (CD_2Cl_2): δ 6.74 (1H, d, H1); 5.42 (1H, m, H3); 5.26 (1H, appears as broad s, H4); 4.19 (1H, d, H5); 3.93 (1H, dd, H5′); 2.57 (1H, td, H2); 2.30 (1H, dd, H2′); 2.03 (3H, s, OAc); 2.01 (3H, s, OAc).

Bis(cyclopentadienyl)(3,4-di-*O*-acetyl-2-deoxy-β-D-*erythro*-pentopyranosyl)titanium(IV) Chloride (3). A solution of $(Cp_2TiCl)_2$ (750 mg, 1.75 mmol) in 5 mL of benzene was prepared under inert atmosphere. The green solution was stirred, and 3,4-di-*O*-acetyl-2-deoxy-β-D-*erythro*-pentopyranosyl bromide (250 mg, 0.89 mmol) in 10 mL of benzene was slowly added dropwise, over the course of *ca.* 2 h. During this time the solution slowly changed from green to brown to red. Solvent was removed in vacuo, and the solid residue was extracted with diethyl ether. Orange-red crystals were obtained by low-temperature crystallization from ether/hexane and were a 3:1 mixture of α- and β-anomers of (3,4-di-*O*-acetyl-2-deoxy-D-*erythro*-pentopyranosyl)-$TiCp_2Cl$ contaminated with some $Cp_2TiBrCl$. NMR ($CDCl_3$) for the α-anomer: δ 6.24 (5H, s, Cp); 6.20 (5H, s, Cp′); 4.93 (1H, broad s, H4); 4.60–4.55 (1H, m, H1); 4.01 (1H, d, J_{H2-H3} = 11.5 Hz, H3); 3.78 (1H, d, $J_{H5-H5'}$ =12.2 Hz, H5); 3.12 (1H, d, H5′); 2.30 (1H, m, H2); 2.08 (3H, s, OAc); 1.89 (3H, s, OAc); 1.66 (1H, m, H2′).

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