Rapid Preparation of Variously Protected Glycals Using Titanium(III)

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Glycosyl chlorides and bromides can be rapidly converted to glycals in high yield by reaction with $(Cp_2Ti[III]Cl)_2$. This reagent tolerates a wide range of common carbohydrate protecting groups, including silyl ethers, acetals, and esters; the methodology provides a general route for the preparation of glycals substituted with both acid- and base-labile functionality. A reaction mechanism is proposed that is based on heteroatom abstraction to give an intermediate glycosyl radical. This radical reacts with a second equivalent of Ti(III) to yield a glycosyltitanium(IV) species. β-Heteroatom elimination from the glycosyltitanium(IV) complex gives the glycal.

Glycals are fundamental building blocks for carbohydrate synthesis;[1−3] their use in oligosaccharide construction has been powerfully documented, exploiting an accessible range of these units in which each member can be differentially protected.[4] There remain, however, some practical limitations of even this benchmark methodology. All hydroxyl-protecting groups of each glycal component must be similarly reagent-tolerant, selective protection or deprotection of a particular hydroxyl group can be cumbersome, and synthesis of the protected glycals themselves can be tedious and low yielding because methodologies employed must be tolerant of the reactive glycal functionality. Some limitations of glycal −OH group protection include the fact that although silylation of glycals can be achieved under mild conditions,[5−8] using ethers or, especially, acetal protecting groups can be compromised by the forcing conditions required for −OH group activation. In some cases, ether synthesis necessitates undesirable organotin intermediates. Low selectivity for acetalization can also be problematic. For instance, it is difficult to achieve simultaneous protection of C-4 and C-6 −OH yet leave an unprotected allylic −OH; indeed, acetalization under normal conditions gives a mixture of products from which the 4,6-*O*-acetal-protected glycal can be isolated only in low yield.[9,10] Additionally, benzoate ester or benzyl ether introduction can be compromised by rearrangement or incomplete reaction.[7−10] Novel methods have been introduced to enable formation of protected glycals under mild conditions (e.g., enzymatic introduction of acetyl and benzoyl esters,[11] electrochemical formation of benzyl and methyl ethers,[12] and phase transfer catalysis to prepare benzyl ethers[13]), yet general methods must still be developed that enable the rapid preparation of variously and specifically hydroxyl group-protected glycals.

A strategy complementary to the one based on preformed glycal protection entails a sequence of multivarious, selective synthesis of simple, robust monosaccharide derivatives followed by conversion to the glycal. Classically, glycals have been made by reduction of acetylated glycosyl halides using zinc and acetic acid,[14] but acid use restricts functional group diversity, which might be desirable in the construction of complex glycosides. Methodologies based on lithium reagents[15] or nonacid-based reductive methods can also suffer from functional group incompatibilities; for example, consider nonselec-

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tive reduction of glycosyl derivatives by Na,[16] Li/NH_3,[17,18] sodium or lithium naphthalide,[19−21] Zn/Ag−C,[22] Al/Hg,[23] potassium−graphite laminate,[24] Cr(II),[25,26] or Zn.[27] Alkali metal reduction procedures are compatible only with base-stable groups such as nonbenzylic ethers and acetonides.[16−19,24] Many common routes suffer from low yields[16,19−21,24] or employ toxic[23,25,26] or hazardous[22,24] reagents. Some require reprotection before isolation[26] or entail multistep synthesis to obtain a key precursor.[28] Samarium iodide[29,30] can be a selective reducing reagent, but its high cost argues against its use in practice. A reagent of general utility for glycal synthesis is highly desirable; ideally this reagent would be selective, safe, and easy to use and would create no toxic byproducts. However, heretofore no such reagent use had been demonstrated.

Di(cyclopentadienyl)titanium(III) halide complexes are effective, specific reducing agents for alkyl halides,[31−34] *vic*-dibromides,[34,35] epoxides,[36−41] and aromatic aldehydes;[42] borohydride derivatives also reduce aryl halides,[31,43,44] ketones,[45] aldehydes,[45] and aromatic azo compounds.[46] Titanocene(III) chloride ($[Cp_2TiCl]_2$) is easily prepared by reduction of Cp_2TiCl_2 by zinc dust[47] or aluminum metal;[48] it readily dissociates[47] in coordinating solvents to give the reactive monomer, **1**. Activation of an alkyl halide by **1** likely occurs by "inner sphere" halogen atom abstraction by 1 equiv of Ti(III); this gives Ti(IV) and the carbon-centered radical. Reaction of this radical with a second equivalent of Ti(III) gives an alkyltitanium(IV) complex; β-elimination gives the olefinic product. (Similarly, **1** reacts with epoxides by heteroatom coordination, ultimately to give an alkoxyalkyldititanium(IV) species[40] that can also eliminate to give an olefin.) In this way, the glycal is formed when a glycosyl halide is treated with **1**.[49,50] Operationally, reactions are fast, high-yielding and take place under neutral reaction conditions. This selective reagent accommodates a wide range of functionality and enables easy access to variously protected glycals which previously could be obtained only with great difficulty. In short, the reagent use of **1** provides a means to expand in scope the repertory of accessible glycal building blocks for enhanced control in carbohydrate synthesis.

Experimental Section

Carbohydrate substrates were obtained from Sigma Chemical Co. and Aldrich Chemical Co. and used without further purification. Unless otherwise specified, other materials were obtained from Aldrich Chemical Co. Solvents were obtained from EM Science and were distilled according to standard methods (THF and diethyl ether from sodium benzophenone ketyl, methylene chloride from CaH_2, and benzene from sodium metal).

Bis[(dicyclopentadienyl)titanium(III) chloride] (1).[48] Aluminum foil (Aldrich Gold Label, 2.0 g, 74.1 mmol) was added to a solution of Cp_2TiCl_2 (4.0 g, 1.61 mmol) in 25 mL of THF and was stirred under N_2 for 16 h. The resulting green solution was filtered, concentrated in vacuo, washed with diethyl ether, and dried to give $(Cp_2TiCl)_2$ (**1**) as a light green powder (3.4 g, quant.).

2,3,4,6-Tetra-*O*-acetyl-D-glucopyranose (2b). The title compound was prepared from methyl-2,3,4,6-tetra-*O*-acetyl-glucopyranoside according to the literature.[51] Data for the α-anomer: ^{1}H NMR ($CDCl_3$, 270 MHz) δ 5.51 (1H, m, H3), 5.42 (1H, d, $H_{1\alpha}$), 5.05 (1H, t $J_{H3-H4} = 9.57$ Hz, H_4), 4.86 (1H, dd $J_{H1-H2} = 3.30$ Hz, $J_{H2-H3} = 10.23$ Hz, H_2), 4.27−4.09 (3H, m, H_5, H_6, $H_{6'}$), 2.10−1.95 (12H, m, 4 × OAc).

Synthesis of Acetylated Carbohydrates. Two methods were used for acetylation. **Method A.** A solution of the carbohydrate in pyridine (10 mL/g of the sugar) and acetic anhydride (5 equiv) was stirred for 16 h and then poured into $CHCl_3$ and washed (H_2O, $NaHCO_3$). The organic extracts were dried ($MgSO_4$) and concentrated to give the acetylated sugar.[52] **Method B.** A slurry of the carbohydrate and sodium acetate (1.6 equiv) in acetic anhydride (10 mL/g of NaOAc) was heated at 80−90 °C for 2 h. The mixture was cooled and poured over

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ice. The acetylated sugar was then precipitated and collected by filtration.[53]

Methyl 2,3,4,6-Tetra-*O*-acetyl-α-D-glucopyranoside (2d). The title compound[52] was prepared (88% yield) from methyl α-D-glucopyranoside (Aldrich, 5.07 g, 26.13 mmol).

1,2,3-Tri-*O*-acetyl-4,6-*O*-ethylideneglucopyranose (39). The title compound was prepared in 95% yield as primarily the α-anomer from 4,6-*O*-ethylideneglucose (1.1 g, 5.33 mmol): ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.26 (d, J = 4.03 Hz, H1), 5.48 (dd, J = 9.89, 10.25 Hz, H_3), 5.05 (dd, J = 4.03, 9.89 Hz, H_2), 4.70 (q, J = 5.13, 1H), 4.14 (dd, J = 5.12, 10.25 Hz, H_4), 3.88 (dt, J = 5.13, 9.89 Hz, H_5), 3.53 (d, J = 9.89 Hz, H_6), 3.47 (d, J = 9.89 Hz, $H_{6'}$), 2.18 (s, 3H), 2.08 (s, 3H), 2.02 (s, 3H), 1.36 (d, J = 4.9 Hz, 3H).

1-*O*-Acetyl-2,3,4,6-tetra-*O*-benzylglucopyranose (40). The title compound[54,55] was prepared from 2,3,4,6-tetra-*O*-benzylglucopyranose (93% yield) according to method A.

1-*O*-Acetyl-2,3,4,6-tetra-*O*-methylglucopyranose (41). The title compound was prepared (72% yield) as a mixture of anomers (65% α and 35% β) from 2,3,4,6-tetra-*O*-methylglucopyranose (Sigma, 200 mg, 0.84 mmol): ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.32 (d, J = 3.66 Hz, $H_{1\alpha}$), 5.45 (d, J = 7.69 Hz, $H_{1\beta}$), 3.8−3.2 (m, 18 H), 2.12 (s, 3 H).

1-*O*-Acetyl-2,3:4,6-di-*O*-isopropylidenemannofuranose (42). The title compound[56,57] was prepared in 83% yield from 2,3;4,6-di-*O*-isopropylidene mannofuranose (Aldrich, 1.00 g, 3.84 mmol) according to method A.

1-*O*-Acetyl-2,3:4,6-di-*O*-isopropylidenemannopyranose (43). The title compound[56,57] was prepared from 2,3;4,6-di-*O*-isopropylidenemannopyranose.

1,3,4-Tri-*O*-acetyl-2-deoxy-α-D-*erythro*-pentopyranose (44). The title compound[58] was prepared (27% yield) from 2-deoxyribose according to method A.

1,2,3,4-Tetra-*O*-acetyl-6-*O*-benzylglucose (45). The acetal of 4,6-*O*-benzylideneglucose (Aldrich) was reductively opened according to the literature.[59,60] To an ice-cooled solution of 590 mg (1.5 mmol) of 4,6-*O*-benzylidene glucose in 10 mL of THF under N_2 was added 15 mL of $NaCNBH_3$ (1 M in THF). A solution of HCl (1 M in ether) was added until gas effervescence ceased. The mixture was stirred for 10 min and then poured into CH_2Cl_2 and washed (H_2O, $NaHCO_3$). Concentration gave a yellow syrup that was acetylated by method A to give 485 mg (74%) of the title compound as a white powder (60:40 mixture of α/β anomers): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.2−7.5 (m, 5 H), 6.30 (d, J = 2.93 Hz, $H_{1\alpha}$, 0.6 H), 5.66 (d, J = 8.06 Hz, $H_{1\beta}$, 0.4 H), 5.41 (t, J = 9.89 Hz, 0.6 H), 5.20−5.03 (m, 2.2 H), 4.55−4.38 (m, 2 H), 4.04−4.00 (m, 0.6 H), 3.74−3.72 (m, 0.4 H), 3.54−3.44 (m, 2 H), 2.20−1.81 (m, 12 H).

1,2,3,4-Tetra-*O*-acetyl-6-*O*-*tert*-butyldiphenylsilylglucopyranose (46). A solution of 1,2,3,4-tetra-*O*-acetylglucopyranose (Sigma, 1.0 g, 2.87 mmol), imidazole (215 mg, 3.15 mmol, 1.1 equiv), and *tert*-butyldiphenylchlorosilane (0.8 mL, 3.08 mmol, 1.07 equiv) in 10 mL of CH_2Cl_2 was stirred overnight under N_2. The mixture was poured into water, extracted ($CHCl_3$), washed (H_2O), and dried (Na_2SO_4). Concentration gave 1.65 g (98%) of the title compound as a white solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.82−7.61 (m, 10 H), 5.73 (d, J = 3.6, 1 H), 5.43−5.22 (m, 3 H), 3.84−3.64 (m, 3 H), 2.22 (s, 3 H), 2.02 (s, 6 H), 1.91 (s, 3 H), 1.15 (s, 3 H), 1.05 (s, 6 H).

1,2,3,4-Tetra-*O*-acetyl-6-*O*-benzoylglucopyranose (47). A solution of 1,2,3,4-tetra-*O*-acetylglucopyranose (Sigma, 1.0 g, 2.87 mmol) and benzoyl chloride (0.5 mL, 4.30 mmol, 1.5 equiv) in 5 mL of pyridine was stirred at room temperature for 2 h with exclusion of atmospheric moisture. The mixture was poured into cold saturated $NaHCO_3$, extracted ($CHCl_3$), washed (H_2O), and dried ($MgSO_4$). Concentration gave 1.40 g of crude product as a white solid; this was recrystallized from ethanol to give 1.06 g (82%) of the title compound as white crystals: ^{1}H NMR (270 MHz, $CDCl_3$) δ 8.1 (d, 2 H), 7.5 (t, 1 H), 7.4 (t, 2 H), 5.77 (d, J = 8.24, H_1), 5.31 (t, J = 8.9, H_3), 5.25 (dd, J = 8.9, 9.4 H_4), 5.18 (dd, J = 8.24, 8.9 H_2), 4.50 (dd, J = 12.45, 2.3 H_6) 4.39 (dd, J = 12.45, 4.28 $H_{6'}$), 3.99 (ddd, J = 2.39. 4.28, 9.40 H_5), 2.16 (s, 3H), 2.10 (s, 3H), 2.09 (s, 3H), 2.07 (s, 3H).

3,4,6-Tri-*O*-benzylglucopyranose (48). The title compound[61,62] was prepared in 85% yield from 3,4,6-tri-*O*-benzylglucal.

2,3:4,6-Di-*O*-isopropylidenemannopyranose (49). The title compound was prepared from mannose according to the literature.[56,57]

General Method for the Synthesis of Peracetylated Glycosyl Bromides. Glycosyl bromides were prepared either by reaction with bromotrimethylsilane (method A)[63] or by reaction with bromine and triphenyl phosphite (method B).[64]

Method A. The peracetylated sugar was dissolved in CH_2Cl_2 or $CHCl_3$ and cooled to −40 °C under N_2. Bromotrimethylsilane (TMS-Br) was added, and the mixture was stirred and allowed to warm to room temperature. Reactions were monitored by NMR, and additional TMS-Br was added as needed. When the reaction was complete, the solvent, any excess TMS-Br, and TMS-OAc were removed in vacuo to give the glycosyl bromide as a thick syrup.

Method B. A solution of the peracetylated sugar in THF (4 mL/g) was stirred for 2 h with piperidine (2 mL/g). The mixture was poured into ice−water, extracted ($CHCl_3$), washed (ice-cold 1 M HCl; then $NaHCO_3$), and dried. Concentration gave a syrup that was chromatographed on silica gel (3:2 ethyl acetate/hexanes) to give the lactol. A solution of bromine (1.4 equiv) and triphenyl phosphite (1.4 equiv) in CH_2Cl_2 at 0 °C was allowed to warm to room temperature over 0.5 h. To this was added a solution of the lactol and pyridine (1.3 equiv) in CH_2Cl_2; the mixture was stirred for 15 min and then quenched by the addition of a saturated $NaHCO_3$ solution, extracted, washed, and dried.

2,3,4,6-Tetra-*O*-acetyl-α-D-mannopyranosyl Bromide (4a). The title compound[65] (93% yield) was prepared according to method A from 1,2,3,4,6-penta-*O*-acetyl-α-D-mannopyranose (Aldrich, 200 mg, 0.51 mmol) and TMS-Br (720 mg, 4.71 mmol) by reaction over a period of 3 days.

2,3,4-Tri-*O*-acetyl-α-D-xylopyranosyl Bromide (5). The title compound[66] was prepared (88% yield) according to method A from 1,2,3,4-tetra-*O*-acetyl-β-D-xylopyranose (500 mg, 1.57 mmol) and TMS-Br (910 mg, 5.94 mmol) after stirring for 3 days.

2,3,4-Tri-*O*-acetyl-D-ribopyranosyl Bromide (6). The title compound[63] was prepared (85% yield) according to method A from 1,2,3,4-tetra-*O*-acetyl-α-D-ribopyranose (300 mg, 0.94 mmol) and TMS-Br (7.4 g, 48.37 mmol).

2,3,4,6-Tetra-*O*-benzylglucopyranosyl Bromide (12). The title compound[67] was prepared in quantitative yield from 1-*O*-acetyl-2,3,4,6-tetra-*O*-benzylglucopyranose (**20**) according to method A.

2,3,4,6-Tetra-*O*-methylglucopyranosyl Bromide (13).[68] The title compound was prepared from 1-*O*-acetyl-2,3,4,6-tetra-*O*-methylglucopyranose according to method A: ^{1}H NMR (300

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MHz, $CDCl_3$) δ 6.56 (J = 3.66 Hz, $H_{1\alpha}$), 3.94−3.70 (m, 1 H), 3.70−3.42 (m, 16 H), 3.22−3.16 (m, 1H).

2,3:4,6-Di-*O*-isopropylidenemannopyranosyl Bromide (16). The title compound[57] was prepared from 1-*O*-acetyl-2,3:4,6-di-*O*-isopropylidenemannopyranose by method A.

2,3-Di-*O*-acetyl-4,6-*O*-benzylideneglucosyl Bromide (18). The title compound[65] was prepared in quantitative yield from 1,2,3-tri-*O*-acetyl-4,6-*O*-benzylideneglucose according to method B.

2,3-Di-*O*-acetyl-4,6-*O*-ethylideneglucosyl Bromide (19). The title compound was prepared (31% yield) from 1,2,3-tri-*O*-acetyl-4,6-*O*-ethylideneglucopyranose according to method B: ^{1}H NMR (270 MHz, $CDCl_3$) δ 6.57 (d, J = 3.66 Hz, H_1), 5.57 (dd, J = 9.52, 9.89 Hz, H_3), 4.79 (dd, J = 3.66, 9.52 Hz, H_2), 4.70 (q, J = 4.9, 1H), 4.21−4.05 (m, H_5, H_6), 3.63−3.49 (m, H_4, H_6), 2.11 (s, 3H), 2.10 (s, 3H), 1.36 (d, J = 4.9 Hz, 3H).

2,3,4-Tri-*O*-acetyl-6-*O*-*tert*-butyldiphenylsilylglucosyl Bromide (20). The title compound was prepared (39% yield) from 1,2,3,4-tetra-*O*-acetyl-6-*O*-*tert*-butyldiphenylsilylglucopyranose according to method A. ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.72−7.50 (m, 6H), 7.45−7.27 (m, 4H), 6.69 (d, J = 3.95 Hz, H_1), 5.56 (dd, J = 9.52, 9.88 Hz, H_3), 5.37 (dd, J = 9.52, 10.21 Hz, H_4), 4.85 (dd, J = 3.95, 9.88 Hz, H_2), 4.18−4.09 (m, H_5), 3.8−3.7 (m, 2H), 2.16 (s, 3H), 2.09 (s, 3H), 1.1 (s, 9H).

2,3,4-Tri-*O*-acetyl-6-*O*-benzoylglucosyl Bromide (21). The title compound was prepared (24% yield) from 400 mg (0.88 mmol) of 1,2,3,4-tetra-*O*-acetyl-6-*O*-benzoylglucopyranose according to method B: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.05 (d, J = 7.69, 2 H), 7.60−7.58 (m, 1 H), 7.46 (t, J = 7.69, 2 H), 6.63 (d, J = 4.03, H_1), 5.60 (dd, J = 9.53, 9.88 H_3), 5.28 (dd, J = 9.52), 4.86 (dd, J = 4.03, 9.89 H_2), 4.54−4.424 (m, H_6 × 2, H_5), 2.08 (s, 3H), 2.05 (s, 3H), 2.01 (s, 3H).

2,3,4-Tri-*O*-acetyl-6-*O*-benzylglucosyl Bromide (22). The title compound was prepared (22% yield) from 400 mg (0.91 mmol) of 1,2,3,4-tetra-*O*-acetyl-6-*O*-benzylglucopyranose according to method B: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.27−7.18 (m, 5H), 6.60 (d, J = 3.66 Hz, H_1), 5.49 (dd, J = 9.52, 9.88 Hz, H_3), 5.24 (dd, J = 9.89, 10.25 Hz, H_4), 4.93 (dd, J = 3.66, 9.89 Hz, H_2), 4.68 (d, J = 12.09 Hz, 1H), 4.55 (d, J = 12.09 Hz, 1H), 4.31 (m, H5), 4.23 (d, J = 6.96 Hz, H_6), 4.18 (d, J = 6.95 Hz, $H_{6'}$), 2.05 (s, 3H), 1.89 (s, 3H), 1.80 (s, 3H).

2,3,5-Tri-*O*-acetyl-D-ribofuranosyl Bromide (28). The title compound was prepared in 93% yield according to method A from 1,2,3,5-tetra-*O*-acetyl-β-D-ribofuranose (100 mg, 0.31 mmol) and TMS-Br (174 mg, 1.14 mmol). A mixture of anomers was obtained (33% α, 67% β): ^{1}H NMR ($CDCl_3$, 300 MHz) β-anomer δ 6.23 (1H, s, $H_{1\beta}$), 5.61 (1H, m, H_2), 4.94 (1H, m, H_3), 4.48−4.13 (3H, m, H_4, H_5, $H_{5'}$), 2.06 (3H, s, OAc), 2.05 (3H, s, OAc), 2.02 (3H, s, OAc); α-anomer δ 6.65 (d J_{H1-H2} = 4.03 Hz, $H_{1\alpha}$), 5.69 (1H, m, H_2), 5.20 (1H, m, H_3), 4.48−4.13 (3H, m, H_4, H_5, $H_{5'}$), 2.10 (3H, s, OAc), 2.08 (3H, s, OAc), 2.03 (3H, s, OAc).

2,3;4,6-Di-*O*-isopropylidenemannofuranosyl Bromide (30). The title compound[69] was prepared from 1-*O*-acetyl-2,3;4,6-di-*O*-isopropylidenemannofuranose according to method A.

3,4-Di-*O*-acetyl-2-deoxy-β-D-*erythro*-pentopyranosyl Bromide (34). The title compound [70] was prepared from 1,3,5-tri-*O*-acetyl-2-deoxy-β-D-*erythro*-pentopyranose according to method A.

3,4,6-Tri-*O*-benzylglucopyranosyl Chloride (11a). The title compound[71] was prepared from 3,4,6-tri-*O*-benzylglucopyranose.

2-*O*-Trimethylsilyl-3,4,6-tri-*O*-benzylglucopyranosyl Chloride (11b). The title compound was prepared by silylation of 3,4,6-tri-*O*-benzylglucopyranose according to the literature.[72]

2,3,4,6-Tetra-*O*-acetyl-1-fluoro-D-glucopyranose (2e).[73] 2,3,4,6-Tetra-*O*-acetyl-D-glucopyranose (2.36, 300 mg, 0.86 mmol) was dissolved in $CHCl_3$ and cooled to −10 °C under argon. Diethylaminosulfur trifluoride (DAST, 0.25 mL, 1.89 mmol) was added, and the reaction was monitored by TLC (1:1 hexanes/ethyl acetate) as it was warmed to room temperature. The reaction was complete in 35 min; it was cooled to −30 °C, and 2 mL of methanol was added. The mixture was concentrated and washed (saturated aqueous $NaHCO_3$). The organic fractions were dried ($MgSO_4$), concentrated, and purified by preparatory TLC (1:1 hexanes/ethyl acetate) to give the title compound as a mixture of α- and β-anomers: ^{19}F NMR ($CDCl_3$, $C_6H_5CF_3$ external standard, 254 MHz) δ −138.44 (dd J_{H1-F} = 53.3 Hz, J_{H2-F} = 9.2 Hz, F_β), −150.94 (dd J_{H1-F} = 51.5 Hz, J_{H2-F} = 23.9 Hz, F_α); data for the β-anomer ^{1}H NMR ($CDCl_3$, 270 MHz) δ 5.34 (1H, dd J_{H1-H2} = 5.94 Hz, J_{H1-F} = 51.8 Hz, $H_{1\beta}$), 5.10−5.00 (2H, m, H_3, H_4), 4.88 (1H, m, H2), 4.31−4.15 (3H, m, H_5, H_6, $H_{6'}$), 2.10−2.00 (12H, m, 4 × OAc).

General Method for the Reductive Preparation of Glycals from Glycosyl Halides. All glycals were prepared according to a standard procedure; a representative example is given for tri-*O*-acetyl glucal (**7a**).

A solution of $[Cp_2TiCl]_2$ (**1**, 300 mg, 0.702 mmol of monomer) in 10 mL of THF was prepared under N_2. 2,3,4,6-Tetra-*O*-acetyl-α-D-glucopyranosyl bromide (**2a**, 200 mg, 0.486 mmol) in 10 mL of THF was added by drops to this stirred, green solution. The reaction mixture turned brown and, within 10 min, red. The mixture was concentrated and dissolved in ether. This solution was passed through a short column of silica to remove metallic impurities; the clear solution obtained was concentrated and dried in vacuo to give 108 mg of 3,4,6-tri-*O*-acetyl-1,5-anhydro-2-deoxy-D-*arabino*-hex-1-enitol [26,74] (**3a**) as an oil (82%).

1,5-Anhydro-2-deoxy-3,4,6-tri-*O*-acetyl-D-*arabino*-hex-1-enitol (Tri-*O*-acetyl-D-glucal) (7). The title compound was prepared (95% yield) from 2,3,4,6-tetra-*O*-acetyl-α-D-mannopyranosyl bromide (180 mg, 0.438 mmol) and $[Cp_2TiCl]_2$ (300 mg, 0.702 mmol of monomer).

1,5-Anhydro-2-deoxy-3,4,6-tri-*O*-benzyl-D-*arabino*-hex-1-enitol (Tri-*O*-benzylglucal) (14). Synthesis from 11a. A solution of 55 mg of $(Cp_2TiCl)_2$ (0.13 mmol, 1.5 equiv) in 2.5 mL of THF was prepared under N_2, and a solution of 40 mg of **11a** (0.0.085 mmol) in 2 mL of THF was then added dropwise. The solution changed to reddish-brown and then red over 15 min. Silica gel was added to the reaction mixture and the solvent removed by rotary evaporation. The title compound[24] (40 mg) was obtained as an oil (94% yield) by elution with ether. **Synthesis from 11b.** A solution of 110 mg of $[Cp_2TiCl]_2$ (0.26 mmol, 1.6 equiv) in 2 mL of benzene was prepared under N_2, and a solution of 100 mg of **11b** (0.16 mmol) in 2 mL of THF was added dropwise. The solution changed to reddish-brown and then red over 15 min. The mixture was concentrated in vacuo; ^{1}H NMR analysis of the crude reaction mixture indicated quantitative conversion to the glycal. **Synthesis from 12.** A solution of 250 mg of $[Cp_2TiCl]_2$ (0.58 mmol, 3.0 equiv) in 2 mL of THF was prepared under N_2, and a solution of 110 mg of **12** (0.19 mmol) in 2 mL of THF was added dropwise. The solution changed to reddish-brown and then red over 15 min. The mixture was concentrated in vacuo; ^{1}H NMR analysis of the crude reaction mixture indicated quantitative conversion to the glycal.

1,5-Anhydro-2-deoxy-3,4,6-tri-*O*-methyl-D-*arabino*-hex-1-enitol (3,4,6-Tri-*O*-methylglucal) (15). A solution of 140 mg of $[Cp_2TiCl]_2$ (0.33 mmol, 1.6 equiv) in 2 mL of THF was prepared under N_2, and a solution of 60 mg of 2,3,4,6-tetra-*O*-methylglucosyl bromide (0.2 mmol) in 2 mL of THF was added dropwise. The solution changed to reddish-brown and

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then red over 30 min. Silica gel was added to the reaction mixture, and the solvent was removed by rotary evaporation. The title compound[19] was eluted (Et_2O) as an oil (37 mg, 96%).

1,5-Anhydro-3,4,6-tri-*O*-acetyl-2-deoxy-D-*lyxo*-hex-1-enitol (3,4,6-Tri-*O*-acetyl-D-galactal) (8). The title compound was prepared from 2,3,4,6-tetra-*O*-acetyl-α-D-galactopyranosyl bromide (250 mg, 0.61 mmol) to give 138.8 mg of 3,4,6-tri-*O*-acetyl-D-galactal[66] as an oil (84%).

3,4-Di-*O*-acetyl-1,5-anhydro-2-deoxy-D-*threo*-pent-1-enitol (9). The title compound[26] (144 mg, 89% yield) was prepared from 2,3,4-tri-*O*-acetyl-α-D-xylopyranosyl bromide (280 mg, 0.826 mmol).

3,4-Di-*O*-acetyl-1,5-anhydro-2-deoxy-D-*erythro*-pent-1-enitol (10). The title compound[26] (75 mg, 70% yield) was prepared from 2,3,4-tri-*O*-acetyl-α-D-ribopyranosyl bromide (181 mg, 0.534 mmol) and $(Cp_2TiCl)_2$ (600 mg, 1.65 mmol of monomer).

1,5-Anhydro-4,6-isopropylidene-2-deoxy-D-*arabino*-hex-1-enitol (4,6-*O*-Isopropylideneglucal) (17). A solution of 60 mg of $[Cp_2TiCl]_2$ (0.14 mmol, 1.75 equiv) in 2.5 mL of benzene was prepared under N_2, and a solution of 26 mg of 2,3-di-*O*-acetyl-4,6-*O*-isopropylidenemannopyranosyl bromide (0.08 mmol) in 2 mL of benzene was added dropwise. At the halfway point of bromide addition, a second amount of $[Cp_2TiCl]_2$ (10 mg, 0.02 mmol, 0.25 equiv) was added. The solution changed to reddish-brown and then red over 30 min. Silica gel was added to the reaction mixture, product was extracted, and solvent was removed by rotary evaporation to give **17**[9] (90% yield).

1,5-Anhydro-3-*O*-acetyl-4,6-*O*-benzylidene-2-deoxy-D-*arabino*-hex-1-enitol (3-*O*-Acetyl-4,6-*O*-benzylideneglucal) (23). The title compound[10] was prepared from 2,3-di-*O*-acetyl-4,6-*O*-benzylideneglucosyl bromide (91% yield).

1,5-Anhydro-3-*O*-acetyl-4,6-*O*-ethylidene-2-deoxy-D-*arabino*-hex-1-enitol (3-*O*-Acetyl-4,6-*O*-ethylideneglucal) (24). The title compound was prepared (84% yield) from 2,3-di-*O*-acetyl-4,6-*O*-ethylideneglucosyl bromide (210 mg, 0.60 mmol) and $[Cp_2TiCl]_2$ (400 mg, 0.94 mmol of monomer, 1.6 equiv): ^{1}H NMR (270 MHz, $CDCl_3$) δ 6.32 (dd, J = 6.23, 1.32 Hz, H_1), 5.39 (m, H_3), 4.79 (q, J = 4.95 Hz, 1H), 4.74 (dd, J = 6.23, 1.8 Hz, H_2), 4.22 (dd, J = 4.6, 10.55 Hz, H_6), 3.9−3.77 (m, 2H), 3.67−3.63 (m, 1H), 2.04 (s, 3H), 1.31 (d, J = 4.95 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.81, 145.50, 100.89, 99.76, 69.14, 69.03, 67.95, 21.25, 20.49. Anal. Calcd for $C_{10}H_{14}O_5$: C, 56.07, H, 6.59. Found: C, 55.97; H, 6.69.

6-*O*-*tert*-Butyldiphenylsilyl-1,5-anhydro-3,4-di-*O*-acetyl-2-deoxy-D-*arabino*-hex-1-enitol (3,4-Di-*O*-acetyl-6-*O*-*tert*-butyldiphenylsilylglucal) (25). The title compound[6] was prepared (88%) from 3,4-di-*O*-acetyl-6-*O*-*tert*-butyldiphenylsilylglucosyl bromide (65 mg, 0.11 mmol) and $[Cp_2TiCl]_2$ (0.21 mmol, 2 equiv).

6-*O*-Benzoyl-1,5-anhydro-3,4-di-*O*-acetyl-2-deoxy-D-*arabino*-hex-1-enitol (3,4-Di-*O*-acetyl-6-*O*-benzoylglucal) (26). Ti(III) Reduction. The title compound[75] was prepared (96%) from 3,4-di-*O*-acetyl-6-*O*-benzoylglucosyl bromide (90 mg) and $[Cp_2TiCl]_2$ (0.21 mmol, 2 equiv).

Zr(III) Reduction. A solution of 104 mg of $[Cp_2ZrCl]_2$[76] (0.20 mmol, 2 equiv) in 3 mL of THF was prepared under N_2, and 3,4-di-*O*-acetyl-6-*O*-benzoylglucosyl bromide (60 mg, 0.13 mmol) in 3 mL of THF was added dropwise. The solution turned brown over 5 min. The mixture was stirred for 30 min without additional color change. Upon exposure to air, the solution became pale yellow. The product was extracted with ether, and the solvent was removed by rotary evaporation to give a mixture of title glucal (60% by NMR) and starting material.

6-*O*-Benzyl-1,5-anhydro-3,4-di-*O*-acetyl-2-deoxy-D-*arabino*-hex-1-enitol (3,4-Di-*O*-acetyl-6-*O*-benzylglucal) (27). The title compound[77] was prepared (95%) from 3,4-di-*O*-acetyl-6-*O*-benzyl-glucosyl bromide (90 mg, 0.20 mmol) and $[Cp_2TiCl]_2$ (135 mg, 0.32 mmol, 1.6 equiv).

Reduction of Acetochloromannose (4b). A solution of acetochloromannose (Sigma, 50 mg, 0.14 mmol) in 5 mL of THF was added to a solution of $[Cp_2TiCl]_2$ (112 mg; 0.26 mmol of monomer; 1.88 equiv) under N_2. The mixture was stirred overnight, and silica gel was added to the reaction mixture. Product was extracted, and solvent was removed by rotary evaporation to give tri-*O*-acetylglucal (94%).

Competitive Reduction of Acetobromomannose (4a) in the Presence of Acetochloromannose (4b). A solution of acetochloromannose (48 mg, 0.13 mmol) and acetobromomannose (54 mg, 0.13 mmol) in 5 mL of THF was added to a solution of $[Cp_2TiCl]_2$ (110 mg; 0.26 mmol of monomer) under N_2. After 15 min, analysis by ^{1}H NMR indicated a mixture consisting of 50% tri-*O*-acetyl glucal, 3% mannosyl bromide, and 47% mannosyl chloride.

2-Acetoxymethylfuran (29). 2,3,5-Tri-*O*-acetyl-D-ribofuranosyl bromide (320 mg, 0.94 mmol) was stirred with $[Cp_2TiCl]_2$ (600 mg, 1.41 mmol of monomer) to give 2-acetoxymethylfuran (identified by comparison with authentic sample).[74]

1-(2-Furyl)-1,2-*O*-isopropylideneethane-1,2-diol (31). A solution of 140 mg of $[Cp_2TiCl]_2$ (0.33 mmol of monomer, 1.2 equiv) in 2 mL of THF was prepared under N_2, and a solution of 90 mg of 2,3:4,6-di-*O*-isopropylidenemannopyranosyl bromide (0.28 mmol) in 2 mL of THF was added dropwise. The solution changed to reddish-brown and then red over 15 min. The title compound[19] was identified by ^{1}H NMR.

Attempted Catalytic Reduction of 2,3,4,6-Tetra-*O*-acetyl-α-D-galactopyranosyl Bromide with Cp_2TiCl_2 and Zinc. Titanocene dichloride (80 mg, 0.32 mmol) was dissolved in 10 mL of dry THF containing suspended, powdered zinc metal (140 mg, 2.14 mmol) under inert atmosphere. The solution turned green, and 2,3,4,6-tetra-*O*-acetyl-α-D-galactopyranosyl bromide (210 mg, 0.51 mmol) in 6 mL of THF was added dropwise. The reaction mixture quickly began to turn brown but then returned to green. After 40 min, the mixture was removed from the drybox, filtered, concentrated, and dried in vacuo. The ^{1}H NMR spectrum of the crude reaction mixture showed no evidence of glycal formation.

Attempted Catalytic Reduction of 2,3,4,6-Tetra-*O*-acetyl-α-D-glucopyranosyl Bromide with Cp_2TiCl_2 and Aluminum. Titanocene dichloride (220 mg, 0.88 mmol) was dissolved in 2 mL of dry THF containing metallic aluminum foil (220 mg, 8.15 mmol) under inert atmosphere. The solution turned green, and 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide (490 mg, 1.19 mmol) in 10 mL of THF was added dropwise. The reaction mixture quickly turned reddish-brown but returned to green after 4 h, at which time the mixture was filtered, concentrated, and dried in vacuo. The ^{1}H NMR spectrum of the crude reaction mixture showed no evidence of tri-*O*-acetylglycal formation.

Cp_2Ti(3,4-Di-*O*-acetyl-2-deoxy-D-*erythro*-pentopyranosyl)Cl (36). 3,4-Di-*O*-acetyl-2-deoxy-β-D-*erythro*-pentopyranosyl bromide (250 mg, 0.89 mmol) in 10 mL of benzene was added to a solution of $[Cp_2TiCl]_2$ (750 mg, 1.75 mmol of monomer) in 5 mL of benzene over 1.75 h, under N_2. When addition was complete, the solution was concentrated in vacuo, and the solid residue was extracted with diethyl ether. Hexane was added to the blood-red ether solution until product began to separate; it was then kept overnight at −40 °C. The cold solution was filtered, and the solid was washed with pentane and dried. The orange-red solid obtained was a mixture of two anomers (α/β = 3:1) contaminated with a small amount of Cp_2TiBrCl. For the α-anomer: ^{1}H NMR ($CDCl_3$, 270 MHz) 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′).

3,4-diacetoxydeuteriotetrahydro-2*H*-pyran (50). Cp_2Ti(3,4-di-*O*-acetyl-2-deoxy-D-*erythro*-pentopyranosyl)Cl (200 mg, 0.48 mmol) was dissolved in 4 mL of CH_2Cl_2 under inert atmosphere to a deep red solution, and degassed D_2O (0.15 mL, 8.3 mmol, 90% D) was added. The solution was evaporated in vacuo, the product was extracted with ether and filtered

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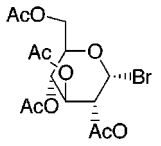
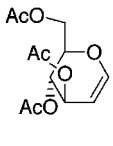
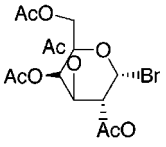
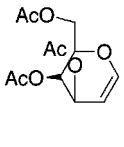
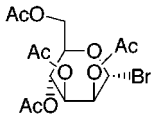
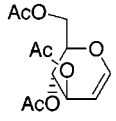
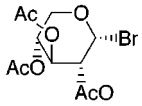
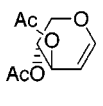
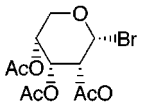
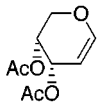
Table 1. Synthesis of Simple Glycals from Pyranosyl Halides and $[Cp_2Ti^{III}Cl]_2$, 1

Pyranosyl Bromide	Glycal	Yield
 **2a**	 **7**	82%
 **3**	 **8**	89%
 **4a**	 **7**	94%
 **5**	 **9**	89%
 **6**	 **10**	70%

through a short plug of silica gel, and the filtrate was concentrated. GC−MS analysis showed the product to be 3,4-diacetoxydeuteriotetrahydro-2*H*-pyran: GC−MS *m*/*z* (relative intensity) 204 (0.17), $M^+ + H^+$, 203 (0.08), M^+, 143 (5.73), $M^+ -$ AcOH, 130 (24.40), 118 (10.54), 102 (12.67), 101 (39.19), 100 (31.64), 99 (5.07), 86 (10.34), 84 (27.71), 83 (100.00), 82 (47.49), 73 (5.53), 72 (5.53), 71 (12.40), 70 (11.12).

Results and Discussion

Effect of the C-1 Substituent. Activation of the anomeric carbon center strongly depends on the substituent at C-1: whereas glycosyl bromides and chlorides are reactive with **1**, anomeric hydroxy, methoxy, acetate, and fluoride derivatives are not. The observed reactivity of glycosyl halides may mirror the C−X bond strength: chlorides are less reactive than the corresponding bromides. Indeed, glycosyl bromides are quickly and effectively reduced by **1** (Table 1). Reactions generally take less than 15 min at room temperature, and completion of the reaction is easily discernible by the color change from green (Ti[III]) to red (Ti[IV]). Complete conversion of glycosyl chlorides usually requires up to several hours, and it is possible to selectively reduce mannosyl bromide (**4a**) in the presence of mannosyl chloride (**4b**) as a result of this marked difference in reactivity (Scheme 1).[50] It is important to note that ring conformational factors and the stereochemistry of leaving group substitution at C-2 have no noticeable effect on the efficacy of glycal synthesis.

Scheme 1. Competitive Reduction of the Mannosyl Bromide vs the Chloride

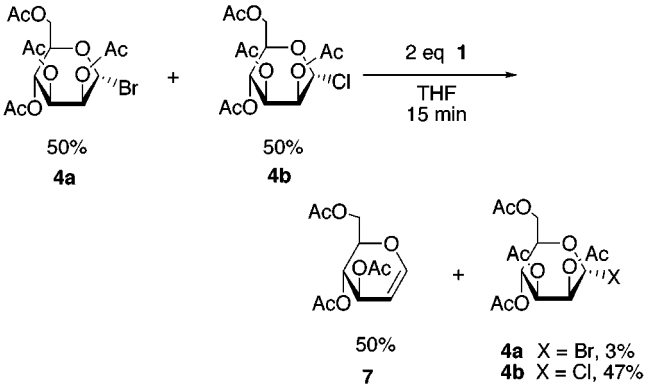
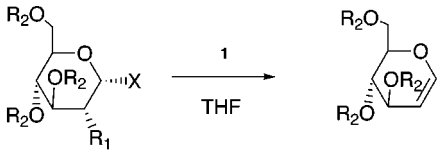


Table 2. Synthesis of Variously Substituted Glycals from Pyranosyl Halides and $[Cp_2Ti^{III}Cl]_2$, 1



pyranosyl halide	X	R_1	R_2	glycal[a] (yield, %)
11a	Cl	OH	Bn	**14** (94)[b]
11b	Cl	OTMS	Bn	**14** (97)[c]
2a	Br	OAc	Ac	**7** (95)[b]
12	Br	OBn	Bn	**14** (98)[c]
13	Br	OMe	Me	**15** (96)[b]

[a] Tri-*O*-acetyl glucal, tri-*O*-benzyl glucal, and tri-*O*-methyl glucal are commercially available compounds. [b] Isolated yield. [c] Yield calculated from ^{1}H NMR spectra of crude reaction mixture.

Effect of the C-2 Substituent. *β*-Elimination for 1-metalated glycosides has been observed in some cases: Facile elimination occurs for C-1 lithiated glycosides with a variety of C-2-O protecting groups,[20,21,78] including 2-*O*-benzyl, 2-*O*-acetyl, and 2-*O*-methoxy. Using **1**, glycal formation was noted for these derivatives and also for 2-OH (Table 2). Elimination does not occur rapidly for 2-O-silylated mannosyl- and glucosyl-Sm(III) compounds,[79] but glycal was prepared readily from the reaction of **1** and the 2-*O*-TMS glycosyl chloride (**11b**). Treating a 2,3-cyclic acetal derivative with **1** gives the free allylic alcohol-substituted glycal by acetal ring fragmentation.[17−19,22,24] Reaction of 2,3:4,6-di-*O*-isopropylidenemannopyranosyl bromide[56] with **1** gave 4,6-*O*-isopropylidene glucal[9] (Scheme 2).

Functional Group Compatibility. The apparent affinity for activated alkyl halides and the broad range

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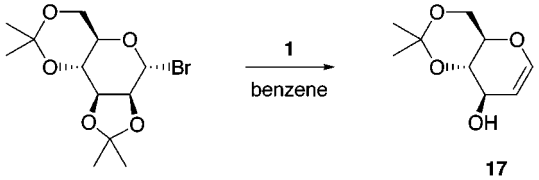
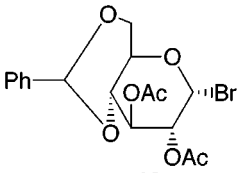
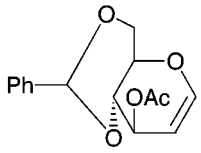
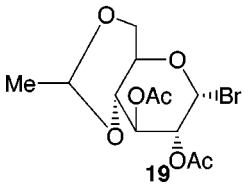
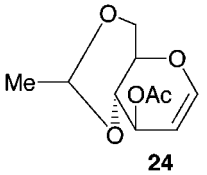
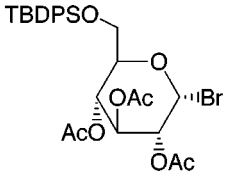
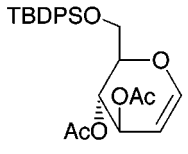
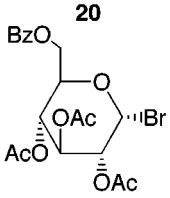
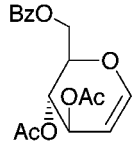
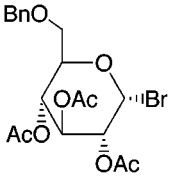
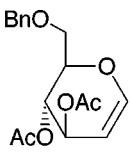
Scheme 2. Reduction of 2,3:4,6-Di-*O*-isopropylidenemannopyranosyl Bromide



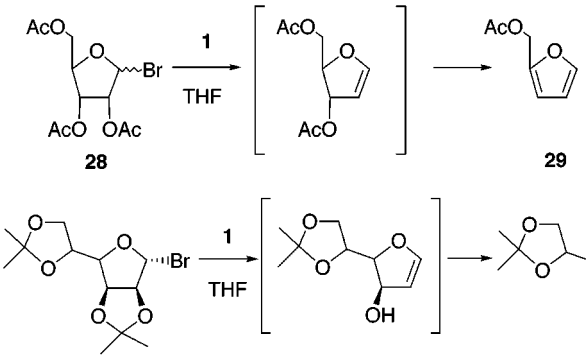
16 **17**

Table 3. Synthesis of Variously Protected Glycals

Pyranosyl Bromide	Glycal	Yield
		91%
18	**23**	
		84%
19	**24**	
		88%
20	**25**	
		96%
21	**26**	
		95%
22	**27**	

of functional groups tolerated by **1** (alcohols,[40] amines,[40] amides,[40] ketones,[33] acids,[42] esters,[40] and aromatic halides[31,44,80,81]), suggest it to be a selective reducing agent. Reaction of variously protected glycosyl halides with **1** gave the corresponding glycals in high yield (Table 3); all common carbohydrate protecting groups, including silyl ethers, acetals, benzyl ethers, and benzoyl esters, were found compatible with glycal synthesis conditions. Ti(III) species **1** seems, therefore, to be a reagent of general use to prepare glycals with hydroxyl groups protected by both acid- and base-labile moieties.

Scheme 3. Reduction of Furanosyl Bromides Gives the Furan



It is difficult to prepare furanoid glycals unless a poor leaving group is present at C3, which prevents furan formation;[82−84] generally, furanoid glycals are synthesized using methoxy or *p*-anisoyl groups at C3. Indeed, none of the desired glycal could be isolated from the reaction of 2,3,5-tri-*O*-acetyl-D-ribofuranosyl bromide with **1**, but 2-acetoxymethylfuran was formed in high yield. It is likely that the glycal is formed, but further elimination takes place under the reaction conditions or during workup (Scheme 3). Similarly, 2,3:5,6-di-*O*-isopropylidenemannosylfuranosyl bromide treated with **1** gave furan **31**[19] during attempted purification.

Mechanistic Aspects of Glycal Formation. Epoxides react[36−41] with **1** by reductive ring opening, followed by trapping of the radical formed by a second equivalent of Ti(III). Elimination of "Ti(IV)−O−Ti(IV)" from the dimetalated species gives the olefin. Reduction of alkyl halides[33,34] by **1** involves a similar process, in which abstraction of $Br^{\bullet}$ from the alkyl halide produces an intermediate organic radical. (Starting from glycosyl halides, trapping of the intermediate glycosyl radical by an activated olefin provides a route to simple *C*-alkyl glycosides.[85]) Capture of the radical by a second equivalent of **1** gives a glycosyltitanium(IV) complex.[86] In a sequence reminiscent of classical studies involving the reaction of Cr(II) with β-substituted alkyl bromides,[87] β-elimination of $Cp_2Ti^{IV}Cl(OR)$ gives the glycal (Scheme 4). Since glycosyl radicals do not decompose by dispro-

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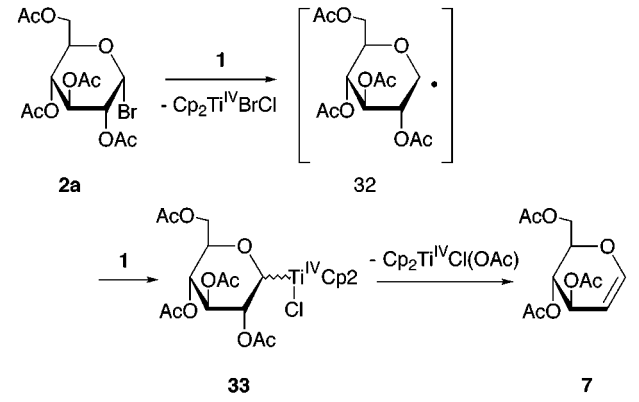
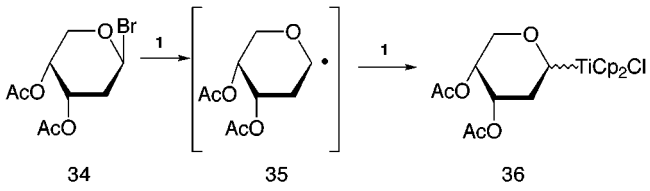
(85) Spencer, R. P.; Schwartz, J. *J. Org. Chem.* **1997**, *62*, 4204−4205.
(86) Other reported glycosylmetallic complexes give acyl products by CO insertion. For glycosylcobalt complexes, see: (a) Ghosez, A.; Göbel, T.; Giese, B. *Chem. Ber.* **1988**, *121*, 1807−1811. (b) Slade, R. M.; Branchaud, B. P. *Organometallics* **1996**, *15*, 2585−2587. (c) Luengo, J. I.; Gleason, J. G. *Tetrahedron Lett.* **1992**, *33*, 6911−6914. (d) Chatani, N.; Ikeda, T. Sano, T.; Sonoda, N.; Kurasawa, H.; Kawasaki, Y.; Muri, S. *J. Org. Chem.* **1988**, *53*, 3387−3389. For glycosylmanganese complexes, see: (e) DeShong, P.; Slough, G. A.; Elango, V.; Trainor, G. L. *J. Am. Chem. Soc.* **1985**, *107*, 7788−7790. (f) DeShong, P.; Slough, G. A.; Elango, V. *Carbohydr. Res.* **1987**, *171*, 342−345. (g) DeShong, P.; Lessen, T. A.; Le, T. X.; Anderson, G.; Sidler, D. R.; Slough, G. A.; von Philipsborn, W.; Vöhler, M.; Zerbe, O. In *The Anomeric Effect and Associated Stereoelectronic Effects*; Thatcher, G. R. J., Ed.; American Chemical Society: Washington, D.C., 1993; pp 227−239. For iron complexes, see: (h) Trainor, G. L.; Smart, B. E. *J. Org. Chem.* **1983**, *48*, 2447−2448. (i) Booysen, J. F.; Bredenkamp, M. W.; Holzapfel, C. W. *Heterocycles* **1993**, *36*, 2195−2202.
(87) Kochi, J. K.; Singleton, D. M. *J. Am. Chem. Soc.* **1968**, *90*, 1582.

Scheme 4. Mechanism of Glycal Synthesis



Scheme 5. Synthesis of a Stable Titanium(IV) Glycoside



portionation or elimination to give glycals, formation of the organometallic is crucial for glycal formation.[88]

The stereochemistry at C-2 of the bromosugar had little impact on reaction with **1** (e.g., mannose; see Table 1), suggesting that the intermediate glycosyltitanium could undergo either syn or anti-elimination to the glycal. Consider glucosyl vs mannosyl cases: anomeric radicals formed from either bromide prefer axial trapping[89] and both radicals exist predominantly in chair conformations.[90] Here, this trapping results in the formation of an α-C−Ti bond; the *β*-acetoxy group would be syn to Ti in the glucosyltitanium complex and anti in the mannosyl one. Regardless of ring "flip" to accommodate the Cp_2-Ti− unit, *β*-acetoxy elimination from the glucosyltitanium compound would occur by a syn pathway (from either an axial-Ti−equatorial-OAc or equatorial-Ti−axial-OAc arrangement). Elimination from the mannosyl intermediate could proceed by an anti pathway; both syn and anti modes of *β*-elimination have been observed for Cr(II) reduction of dihalide.[87]

If the concentration of **1** is low, trapping the glycosyl radical formed by Br• abstraction from the glycosyl halide becomes slow; the radical can then competitively abstract H• from the solvent, giving the anhydroalditol.[32] To maximize glycal yield in even modest H• donor solvents, it is important that the relative concentration of **1** be large compared to that of the bromide; this can be optimized by slowly adding the bromide to the solution of **1**.

The Organotitanium Intermediate. Analysis of the reaction between **1** and 3,4-di-*O*-acetyl-2-deoxy-*β*-D-*erythro*-pentopyranosyl bromide (2-deoxyribosyl bromide) provides support for a mechanism involving an organotitanium(IV) intermediate. Since this sugar lacks heteroatomic substitution at C-2, *β*-heteroatom elimination would not be possible. A solution of the ribosyl bromide was slowly added to a solution of **1** in benzene over a period of 2 h. Following the color change from green to red, Cp_2Ti(3,4-di-*O*-acetyl-2-deoxy-D-*erythro*-pentopyranosyl)Cl (**36**) was isolated as an orange-red crystalline solid. ^1H NMR analysis of the product obtained using a stoichiometric amount of **1** showed it to be a 3:1 mixture of α- and *β*-anomers; if the bromide is added to a small excess of **1**, the α-anomer (**36**α) can be obtained exclusively (Scheme 5).

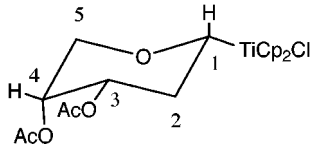


Figure 1. Conformation of **36**α.

A quenching experiment was done to support the contention of a C−Ti bond in **36**α; reaction with D_2O (90% OD) gave the anhydroalditol, which was 80% d_1 by GC−MS analysis. The structural assignment for **36**α was made on the basis of 1-D and 2-D proton NMR analysis. Chemical shifts for the two Cp groups (*δ* 6.24 and 6.20) are similar to those measured for Cp_2Ti(alkyl)Cl compounds, such as $Cp_2Ti(CH_3)Cl$ (*δ* 6.34[91]). The difference in chemical shift between the two diastereomeric Cp units (0.04 ppm) is close to that recorded for $Cp_2(Cl)Zr_a$-$OCHRZr_b(Cl)Cp_2$ (**37**), in which the diastereotopic Cp units on Zr_b have a chemical shift difference of 0.03 ppm.[92] Assignment of H_1 was made by comparison with a Zr analogue. In particular, the chemical shift for the α-protons in $Cp_2Ti(CH_3)Cl$ is *δ* 0.72; for $Cp_2Zr(CH_3)Cl$ it is *δ* −0.39, 1.11 ppm upfield from that for the complex of the more electronegative Ti.[93] For **37** the chemical shift of the alkoxyalkylzirconium proton analogous to H_1 in **36**α is *δ* 3.36 ppm.[94] By comparison with the simple alkyl complexes, it is reasonable to expect a chemical shift for H_1 to be ca. 1.1 ppm downfield, near *δ* 4.46; for H_1 of **36**α, the value *δ* 4.60−4.55 was measured. To elucidate the glycoside stereochemistry, connectivity was determined by COSY NMR; the conformation of the ring was then determined from coupling constant information. The appearance of H_4 as a broad singlet in the 1-D proton NMR indicates small vicinal couplings; H_4 must be equatorial ($^3J_{Heq-Heq}$ and $^3J_{Heq-Hax}$ coupling constants are generally on the order of 0−7 Hz).[95] A large coupling constant was measured for H_1 and $H_2/H_{2'}$, indicating that H_1 must be axial. From these data, it can be deduced that the conformation for **36**α is a $^1C_4$ chair (Figure 1), assuming that steric considerations place the large titanium fragment in an equatorial site.

(88) Glycosyl radicals are sufficiently stable for EPR analysis with no glycal formation. See: Korth, H.-G.; Sustmann, R.; Dupuis, J.; Giese, B. *J. Chem. Soc., Perkin Trans. 2* **1986**, 1453−1459.

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Attempts To Make Glycal Synthesis Catalytic in Titanium. The byproducts of glycal synthesis are a Ti(IV) halide, which may be $Cp_2Ti^{IV}ClBr$, and $Cp_2Ti^{IV}Cl(OR)$, according to the nature of the β-eliminated functionality. Metallic Zn[47] or Al[48] reduces $Cp_2Ti^{IV}Cl_2$ to **1**, so it was of interest to determine if "regeneration" of **1** could be accomplished in situ, enabling a catalytic cycle for glycal synthesis. However, regeneration of Ti(III) from Ti(IV) was slow using either metal, giving a low "steady state" concentration of Ti(III); radical attack on the solvent dominated, resulting in some glycal, but the anhydroalditol was the major reaction product.

Using a Zr(III) Analogue of 1 for Glycal Synthesis. Zr(III) complex $[Cp_2ZrCl]_2$ [76] (**38**) can reduce an alkyl halide,[96] but treatment of 6-*O*-benzoyl-2,3,4-tri-*O*-acetylglucosyl bromide with 2 equiv of **38** gave only 60% conversion to glucal after 30 min (cf. complete reduction by **1** occurs in 15 min). A vacant coordination site on the low-valent metal is likely needed to effect halogen atom abstraction from the glycosyl halide. The dimer $[Cp_2TiCl]_2$ is readily cleaved by coordinating solvents.[47] Evidently, the glycosyl halide can either cleave this dimer, too, or displace coordinated solvent. Complex **38** forms a more robust dimer: crystallographic data are consistent with the presence of a Zr−Zr bond.[97] Strongly coordinating ligands do not readily cleave this dimer,[96] and it may be that (slow) dimer cleavage by the glycosyl halide is responsible for the low rate of glycal synthesis observed.[98]

(96) Barden, M. C.; Schwartz, J. Unpublished results.
(97) Fochi, G.; Guidi, G.; Floriani, C. *J. Chem. Soc., Dalton Trans.* **1984**, 1253−1256.
(98) For another example of slow activation of $[Cp_2ZrCl]_2$, see: Barden, M. C.; Schwartz, J. *J. Org. Chem.* **1997**, *62*, 7520−7521.

Conclusions

It is important to develop simple methods for glycal synthesis, given the high level of interest currently manifested for using these species as chiral building blocks for the synthesis of complex molecules. Titanium(III) reduction of readily available glycosyl halides provides easy access to this class of compounds; because of the specificity of Ti(III) for halogen atom abstraction, methodology based on this reagent can accommodate a broad range of functionality and, thus, can be considered a significant improvement over many, less tolerant reagent-based routes.

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Supporting Information Available: Copies of the ^1H NMR of compounds **19**, **20**, **21**, and **22**. This material is available free of charge via the Internet at http://pubs.acs.org.

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