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Variously Substituted Glycals Are Readily Prepared from Glycosyl Bromides Using $(Cp_2TiCl)_2$

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Abstract: Glycosyl halides, variously substituted with ether, acetal, or ester protecting groups, were converted to the corresponding glycals in high yield by reaction with $(Cp_2TiCl)_2$. A glycosyl chloride was less reactive than the analogous bromide.

Glycals are established as important intermediates in carbohydrate synthesis, yet their implementation is limited by the lack of preparative methodology tolerant of both base and acid labile protecting groups. For example, one common method involves reacting acetylated glycosyl halides with zinc in acetic acid,[1] but acidic conditions can cleave, among others, remote silyl ethers or acetals. Reductive methods, for example using C_8K,[2] Cr(II),[3] Al amalgam,[4] Li/NH_3,[5] Zn/base,[6] and sodium[7] or lithium[8] naphthalide, can show incompatibilities with esters or benzylic ethers; can be substrate limited;[9,10] or can inefficiently utilize expensive reagents, such as SmI_2.[11]

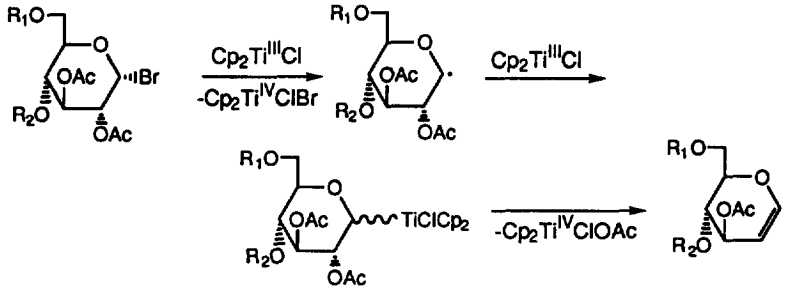
We recently reported a new synthesis of per-*O*-acetylated glycals from glycosyl bromides which is based on inexpensive and easy-to-prepare $(Cp_2TiCl)_2$.[12] Treatment of the bromide with this $Cp_2Ti(III)$ species gives a glycosyltitanium(IV) complex which, following elimination of $Cp_2TiCl(OAc)$, gives the glycal in high yield. Since deoxygenation of epoxides using $(Cp_2TiCl)_2$ (which apparently also proceeds by an alkyltitanium(IV) complex) has been shown to be tolerant of many functional groups, including acetals and silyl ethers,[13] it was of interest to determine if our glycal synthesis would be similarly tolerant, enabling its application to the preparation of glycal derivatives including both acid and base labile functionalities in the same compound.

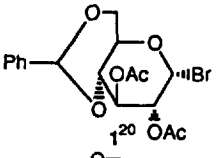
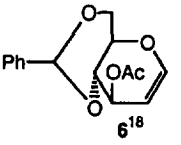
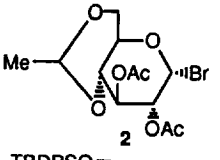
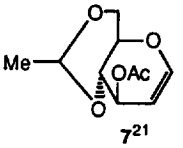
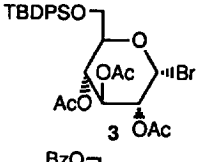
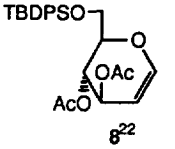
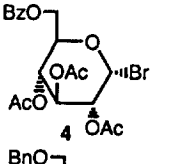
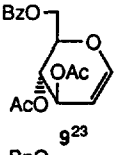
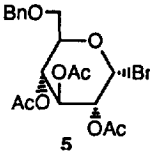
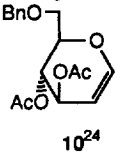
To illustrate the versatility of glycal synthesis using $(Cp_2TiCl)_2$, several variously substituted glycosyl bromides were prepared from 4,6-*O*-ethylidene-glucose, 4,6-*O*-benzylidene-glucose, and 1,2,3,4-tetra-*O*-acetyl-glucose.[14] In a typical reaction, 90 mg (0.20 mmol) of **5** was dissolved in 4 mL of THF under N_2 and slowly added to a solution of 135 mg (0.32 mmol, 1.6 eq) of $(Cp_2TiCl)_2$ in 5 mL of THF at room temperature. The solution turned red over a period of 15 min; this color change is characteristic of oxidation of $Cp_2Ti(III)$ to $Cp_2Ti(IV)$. The reaction mixture was concentrated, and glucal **10** was isolated in 95% yield by ether elution through a short column of silica gel. In a related experiment, 50 mg (0.14 mmol) of acetochloromannose in 3 mL of THF was added under N_2 to a solution of $(Cp_2TiCl)_2$ (110 mg; 0.26 mmol; 1.9 equiv) in 3 mL of THF.

The mixture was stirred overnight, the resulting red solution was concentrated, and 3,4,6-tri-*O*-acetylglucal (35 mg; 94%) was isolated.[15] Further examples of glycal synthesis are given in the Table.

Heretofore, selective preparation of glycals has been problematic; for example, preparation of acetals of glycals can be low-yielding, giving complex mixtures of products.[16-18] In contrast, the method described herein enables rapid preparation of glycal derivatives from readily obtainable, variously protected glycosides.

Table. Preparation of Glycals



(R1, R2) Glycosyl Bromide[19]	(R1, R2) Glycal	Yield
 1[20]	 6[18]	91%
 2	 7[21]	84%
 3	 8[22]	88%
 4	 9[23]	96%
 5	 10[24]	95%

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14. Glycosyl bromides **1** and **3** were prepared by reaction of the acetylated sugar with TMS-Br.[25] Compounds **2** and **4** were obtained by piperidinolysis[26] and subsequent reaction with triphenylphosphine/bromine.[20] Compound **5** was obtained by reductive ring opening[27] of 1,2,3-tri-*O*-acetyl-4,6-*O*-benzylidene-glucose, followed by acetylation, piperidinolysis, and bromination with $(PhO)_3P/Br_2$.
15. It was possible to selectively reduce the acetobromomannose in the presence of the chloro analog. A solution of 48 mg of acetochloromannose (0.13 mmol) and 54 mg of acetobromomannose (0.13 mmol) in 5 mL of THF was added under N_2 to a solution of $(Cp_2TiCl)_2$ (110 mg; 0.26 mmole). After 15 minutes, ^1H NMR indicated a mixture of 50% glucal, 3% mannosyl bromide, and 47% mannosyl chloride remained.
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19. The bromides were characterized by ^1H NMR spectroscopy: **2**: (270 MHz, $CDCl_3$) 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); **3**: (270 MHz, $CDCl_3$) 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); **4**: (300 MHz, $CDCl_3$) 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, H_5), 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); **5**: (300 MHz, $CDCl_3$) 8.05 (d, J = 7.69 Hz, 2H), 7.60-7.58 (m, 1 H), 7.46 (t, J = 7.69, 2 H), 6.63 (d, J = 4.03 Hz, H_1), 5.60 (dd, J = 9.53, 9.88 Hz, H_3), 5.28 (t, J = 9.52 Hz, H_4), 4.86(dd, J = 4.03, 9.89 Hz, H_2), 4.54-4.24 (m, 3H), 2.08 (s, 3H), 2.05 (s, 3H), 2.01 (s, 3H).
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21. ^1H NMR: (270 MHz, $CDCl_3$) 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, $CDCl_3$) 170.81, 145.50, 100.89, 99.76, 69.14, 69.03, 67.95, 21.25, 20.49. Anal. for $C_{10}H_{14}O_5$: C, 55.97; H, 6.69.
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