Notes

Reduction of Glycosyl Bromides to Anhydroalditols by Titanocene Borohydride

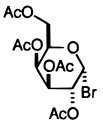
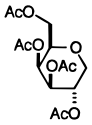
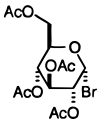
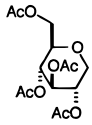
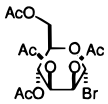
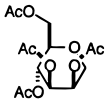
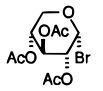
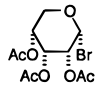
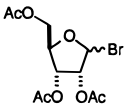
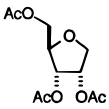
Cullen L. Cavallaro and Jeffrey Schwartz*

Department of Chemistry, Princeton University, Princeton, New Jersey 08544-1009

Received October 20, 1995. (Revised Manuscript Received March 4, 1996)

Anhydroalditols are a class of reduced sugars which are present in many natural systems and which have also been employed as synthesis intermediates. For example, 1,5-anhydro-D-glucitol has been isolated from several plant and animal sources,[1] discovered in human cerebrospinal fluid and blood plasma,[2] and found to be an inhibitor of several enzymes.[3] 1,5-Anhydrohexitols have been used in the synthesis of carbohydrates[4] and nucleosides which have antiviral activity.[5] Anhydroalditols have been synthesized variously, including by dehydration of the glycitol,[6] but the most commonly used pathways involve reduction of glycoside intermediates. Such reductive routes include desulfurization of 1-thio-[7] or isothiocyanate[8] derivatives, reaction of silyl alkyl glycosides with TMSOTf/triethylsilane,[9] or treating a glycosyl halide with LAH.[10] The most commonly used methodology involves reduction of a glycosyl halide with tin hydride and a radical promoter.[11] Yields for this latter process are good, but the toxicity of organotin byproducts and the difficulty of their complete separation from desired materials can be a drawback in pharmaceutical applications. We have recently shown[12] that simple Ti(III) complexes can readily activate glycosyl halides by halogen atom abstraction, and we now report a simple, high-yielding conversion of glycosyl bromides to anhydroalditols using a Ti(III) borohydride complex.

Table 1. Reduction of Glycosyl Bromides to Anhydroalditols by 1

	Glycosyl Bromide	Anhydroalditol	Yield (%)
α-D-Galactopyranosyl			99[9]
α-D-Glucopyranosyl			quant.[9]
α-D-Mannopyranosyl			97[9]
α-D-Xylopyranosyl			92[20]
D-Ribopyranosyl (90% α, 10% β)			90[21]
D-Ribofuranosyl (32% α, 68% β)			80[9]

Reaction between Cp_2TiCl_2 and $NaBH_4$ yields titanocene borohydride[13] (Cp_2TiBH_4; **1**), which we have shown reduces activated alkyl halides *via* a radical intermediate.[14] Since glycosyl radicals[15] are rapidly formed by reaction between glycosyl bromides and $(Cp_2TiCl)_2$[16] it was of interest to learn if **1** could effect reduction of glycosyl halides analogously. Indeed, reduction of the glycosyl halides by **1** can be accomplished rapidly and at room temperature (Table 1).

The mechanism of glycosyl halide reduction likely involves halogen atom abstraction by Ti(III) to give the glycosyl radical (**2**), which then can abstract H• from borohydride (Scheme 1).[17,18] In support of this suggestion, we note the formation of 1-deuterio-2,3,4,6-tetra-*O*-acetyl-1,5-anhydro-D-glucitol (89% d_1) when Cp_2TiBD_4 is used as the reducing agent.

(1) Yamanouchi, T.; Tachibana, Y.; Akanuma, H.; Minoda, S.; Shinohara, T.; Moromizato, H.; Miyashita, H.; Akaoka, I. *Am. J. Physiol.* **1992**, *263*, E268.

(2) (a) Yoshioka, S.; Saitoh, S.; Negishi, C.; Fujisawa, T.; Fujimori, A.; Takatani, O.; Imura, M.; Funabashi, M. *Clin. Chem.* **1983**, *29*, 1396. (b) Yoshioka, S.; Saitoh, S.; Seki, S.; Seki, K. *Clin. Chem.* **1984**, *30*, 188.

(3) (a) Glucosidase: Field, R. A.; Haines, A. H.; Chrystal, E. J. T. *Bioorg. Med. Chem. Lett.* **1991**, *1*, 667. (b) Phosphorylase *a*: Bollen, M.; Malaisse-Lagae, F.; Malaisse, W.; Stalmans, W. *Biochem. Biophys. Acta* **1990**, *1038*, 141.

(4) (a) Barili, P. L.; Berti, G.; Catelani, G.; D'Andrea, F.; Gaudiosi, A. *Gazz. Chim. Ital.* **1994**, *124*, 57. (b) Barili, P. L.; Berti, G.; D'Andrea, F.; Bussolo, V. D.; Granucci, I. *Tetrahedron* **1992**, *48*, 6273. (c) Barili, P. L.; Berti, G.; D'Andrea, F.; Gaudiosi, A. *Carbohydr. Res.* **1991**, *212*, c5.

(5) (a) Verheggen, I.; Van Aerschot, A.; Toppet, S.; Snoeck, R.; Janssen, G.; Balzarini, J.; De Clercq, E.; Herdewijn, P. *J. Med. Chem.* **1993**, *36*, 2033. (b) Van Aerschot, A.; Verheggen, I.; Herdewijn, P. *Bioorg. Med. Chem. Lett.* **1993**, *3*, 1013. (c) Huryn, D. M.; Sluboski, B. C.; Tam, S. Y.; Weigele, M.; Sim, I.; Anderson, B. D.; Mitsuya, H.; Broder, S. *J. Med. Chem.* **1992**, *35*, 2347. (d) Nair, V.; Nuesca, Z. M. *J. Am. Chem. Soc.* **1992**, *114*, 7951.

(6) Duclos, A.; Fayet, C.; Gelas, J. *Synthesis* **1994**, 1087.

(7) Richtmyer, N. K.; Carr, C. J.; Hudson, C. S. *J. Am. Chem. Soc.* **1943**, *65*, 1477.

(8) Witczak, Z. J. *Tetrahedron Lett.* **1986**, *27*, 155.

(9) Bennek, J. A.; Gray, G. R. *J. Org. Chem.* **1987**, *52*, 892.

(10) (a) Ness, R. K.; Fletcher, H. G., Jr.; Hudson, C. S. *J. Am. Chem. Soc.* **1950**, *72*, 4547. (b) Funabashi, M.; Hasegawa, T. *Bull. Chem. Soc. Jpn.* **1991**, *64*, 2528.

(11) (a) Giese, B.; Dupuis, J. *Tetrahedron Lett.* **1984**, *25*, 1349. (b) Kocienski, P.; Pant, C. *Carbohydr. Res.* **1982**, *110*, 330. (c) Auge, J.; David, S. *Carbohydr. Res.* **1977**, *59*, 255.

(12) Cavallaro, C. L.; Schwartz, J. *J. Org. Chem.* **1995**, *60*, 7055.

(13) (a) Nöth H.; Hartwimmer, R. *Chem. Ber.* **1960**, *93*, 2238. (b) Lucas, C. R. *Inorg. Synth.* **1977**, *17*, 91.

(14) Liu, Y.; Schwartz, J. *Tetrahedron* **1995**, *51*, 4471.

(15) (a) Dupuis, J.; Giese, B.; Rüegge, D.; Fischer, H.; Korth, H.-G.; Sustmann, R. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 896. (b) Korth, H.-G.; Sustmann, R.; Dupuis, J.; Giese, B. *J. Chem. Soc., Perkin Trans. 2* **1986**, 1453. (c) Korth, H.-G.; Sustmann, R.; Gröninger, K. S.; Witzel, T.; Giese, B. *J. Chem. Soc., Perkin Trans. 2* **1986**, 1461.

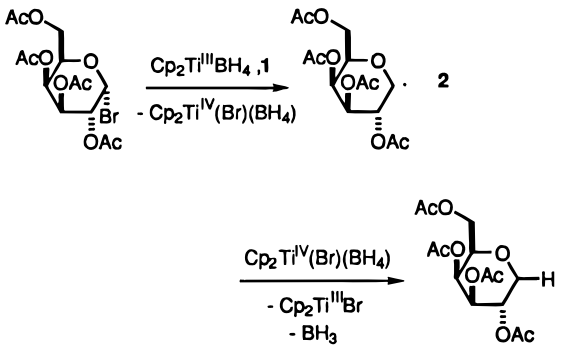
(16) Coutts, R. S. P.; Wailes, P. C.; Martin, R. L. *J. Organomet. Chem.* **1973**, *47*, 375.

(17) A small amount (1−5%) of the glycal is sometimes observed, which might be formed by radical trapping by Ti(III) and Ti(IV)−OAc elimination (see ref 12).

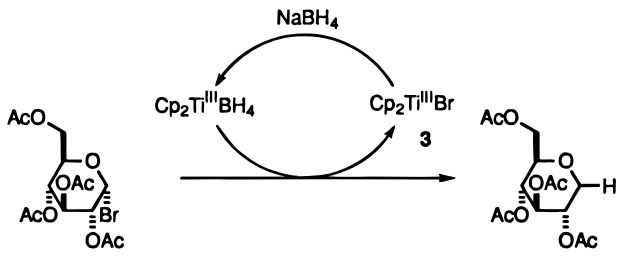
(18) For example, see: Liu, Y.; Schwartz, J. *J. Org. Chem.* **1994**, *59*, 940. Aryl radicals photochemically generated from aryl halides react with BH_4^- by H• abstraction to give $BH_3^{\bullet-}$. See: Barltrop, J. A.; Bradbury, D. *J. Am. Chem. Soc.* **1973**, *95*, 5085. Analogous H• abstraction from Ti(IV)BH_4 would give a Ti(III)BH_3 species.

S0022-3263(95)01880-9 CCC: $12.00

Scheme 1



Scheme 2



We note that **1** prepared *in situ* from Cp_2TiCl_2 and $NaBH_4$ is less effective for glycosyl halide reduction than is isolated **1**. We also note that the Ti^{IV} byproduct of glycosyl halide reduction (**3**) can be recycled to **1** with borohydride, thus enabling a catalytic cycle for anhydroalditol synthesis (Scheme 2).[19] However, in contrast to reaction with *ex situ* prepared **1**, significant glycal byproduct is also obtained (anhydroalditol:glycal ≥ 2:1), likely formed by competitive trapping of **2** by either **1** or **3**.[12]

Experimental Section

General Methods. 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 purification.

Peracetylated Glycosyl Bromides. The title compounds were prepared as described elsewhere.[12]

Dicyclopentadienyltitanium(III) Borohydride.[13b] A solution of Cp_2TiCl_2 (900 mg, 3.61 mmol) and $NaBH_4$ (900 mg, 23.79 mmol) in 15 mL of DME was prepared under inert atmosphere at room temperature. The resulting deep violet solution was filtered to remove inorganic salts and concentrated *in vacuo*. Solids were dissolved in toluene and filtered again. Crystallization from toluene and pentane under N_2 gave 600 mg of Cp_2TiBH_4 as fluffy, purple crystals (86%).

Preparation of 2,3,4,6-Tetra-*O*-acetyl-1,5-anhydro-D-galactitol Using Isolated Cp_2TiBH_4. Under an inert atmosphere, Cp_2TiBH_4 (**1**; 100 mg, 0.518 mmol) was dissolved in 6 mL of THF, giving a purple solution. 2,3,4,6-Tetra-*O*-acetyl-α-D-galactopyranosyl bromide (100 mg, 0.243 mmol) was added. The solution was stirred for 45 min at room temperature, concentrated, and dried *in vacuo*. The crude mixture was dissolved in 2:1 ethyl acetate/hexanes and passed through a short plug of silica gel. Concentration *in vacuo* gave 2,3,4,6-tetra-*O*-acetyl-1,5-anhydro-D-galactitol (80.1 mg; 99%) as a pale yellow oil. Other anhydroalditols were prepared in analogous fashion.

Preparation of 2,3,4,6-Tetra-*O*-acetyl-1,5-anhydro-D-glucitol Using Cp_2TiBH_4 Prepared *in Situ*. Sodium borohydride (170 mg, 4.49 mmol) and Cp_2TiCl_2 (260 mg, 1.04 mmol) were dissolved in 10 mL of dimethoxyethane (DME) under an inert atmosphere to give a purple solution to which 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide (396 mg, 0.96 mmol) was added. The reaction mixture was allowed to stir at room temperature for 2 h and was then concentrated *in vacuo* to give 2,3,4,6-tetra-*O*-acetyl-1,5-anhydroglucitol (83%) and 2,3,4,6-tetra-*O*-acetyl-D-glucal (17%).[12]

Catalyzed Synthesis of 2,3,4,6-Tetra-*O*-acetyl-1,5-anhydro-D-glucitol. Sodium borohydride (40 mg, 1.06 mmol) and Cp_2TiCl_2 (6 mg, 0.02 mmol) were dissolved in 5 mL of dimethoxyethane (DME) under an inert atmosphere to give a pale purple solution to which was added 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide (98 mg, 0.24 mmol). The solution was allowed to stir at room temperature for 20 h and was then concentrated *in vacuo* to give a mixture of 2,3,4,6-tetra-*O*-acetyl-1,5-anhydro-D-glucitol (80%) and 2,3,4,6-tetra-*O*-acetyl-D-glucal (20%).[12]

Acknowledgment. The authors acknowledge support for this work provided by the National Science Foundation.

JO951880G

(19) In a separate experiment, it was found that Cp_2TiCl is easily converted back to **1** using $NaBH_4$.

(20) Paulsen, H.; Schnell, D.; Stenzel, W. *Chem. Ber.* **1977**, *110*, 3707.

(21) ^1H NMR (270 MHz; C_6D_6): δ 5.54 (1H, broad s, H3); 4.95−4.89 (2H, m, H2, H4); 3.56−3.41 (4H, m, H1, H1′, H5, H5′); 1.72 (3H, s, OAc); 1.62 (6H, s, OAc). ^{13}C NMR (75 MHz; C_6D_6): δ 164.1, 163.7 (*C*=O); 63.0 (C3); 62.1 (C2, C4); 59.8 (C1, C5); 15.0, 14.9 (CH_3). IR (NaCl) 1736 cm^{-1} ($\nu_{C=O}$). Anal. C, H. Mp: 129−130 °C (*cf.* 133 °C; Tejima, S.; Maki, T.; Akagi, M. *Chem. Pharm. Bull. (Tokyo)* **1964**, *12*, 528.