Communications

Titanium(III)-Promoted Stereoselective Synthesis of Simple *C*-Glycosides

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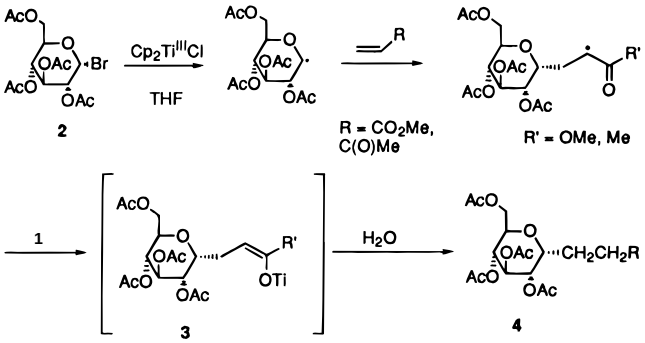
C-Glycosides are an important class of compounds, members of which have been noted for their antitumor, antibacterial, or antiviral activity.[1] Several methods for *C*-glycoside synthesis have been described that are based on coupling of an electrophilically activated sugar component with a nucleophile[2] or of 1-lithio sugars or glycals with electrophiles,[1b] but these routes can suffer from low stereospecificity or functional group incompatibilities. Another method involves trapping a glycosyl radical with an unsaturated substrate.[3] While some of these radical-based routes can give the *C*-glycoside stereoselectively,[3e,h,i] most yield mixtures of anomers, and over-reduction can be problematic.[3a−g] Classically, glycosyl radicals are made by halogen atom abstraction from C-1 using activated tin species derived from alkyltin hydrides and an initiator at elevated temperature. Typically, tin hydride-promoted reactions of mannosyl or galactosyl halides give only the α-glycosides;[3b] mixtures of α- and *β*-coupled products are often obtained from glucosyl derivatives.[3a,b]

The temperature-dependent stereoselectivity of reduction of glucosyl halides using tin deuterides has been noted.[4,5] It has been suggested that an equilibrium mixture of radical conformers exists, and axial radical capture is preferred at low temperature.[5] No intermediate (*C*-glycosyl)alkyl organometallic has been implicated in these olefin addition processes; instead, the adduct radical formed reacts with additional tin hydride to give reduced product. We recently noted that glycals can be prepared from glycosyl halides at or below room temperature using $(Cp_2TiCl)_2$ (**1**), a reagent that is reactive for halogen atom abstraction yet tolerates a broad range of glycoside *O*-protecting groups.[6] Halogen atom abstraction by 1 equiv of Ti(III) gives the pyranos-1-yl radical, which is captured by a second equivalent of Ti(III); *β*-elimination from the resulting Ti(IV) organometallic gives the glycal. We now report that these glycosyl radicals can be competitively trapped by unsaturated organic species to produce simple hexopyranosyl *C*-glycosides with α-stereochemistry (Scheme 1); acrylonitrile likely reacts *via* a similar mechanism involving a ketenimide−titanium intermediate. Because the radical can be generated at relatively low temperature, α-stereoselective coupling is observed, even for glucopyranosyl substrates.

Scheme 1



In a typical procedure, 50 mg of 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide (**2a**) (0.12 mmol) and 200 mg of methyl acrylate (2.40 mmol, 20 equiv) were dissolved in 2 mL of THF under N_2 at room temperature.[7] A green solution of 130 mg of **1** in 25 mL of THF (0.30 mmol, 2.5 equiv of dimer) was added dropwise at room temperature over 30 min. The red reaction mixture was quenched by pouring into 15 mL of water. Extraction, drying, and flash chromatography (Et_2O) gave the *C*-glycoside, which was identified by ^1H NMR comparison with authentic material.[8] Only one species was observed; the characteristic axial−equatorial coupling constant measured for H_4 and H_5 is indicative of an α-glycoside, consistent with expectations for radical generation and capture at room temperature.[3h,i] Other representative examples of *C*-glycoside synthesis are given in Table 1. In each case, radical coupling gave only the α-glycoside;[9] yields were comparable to those reported for trapping of radicals generated by tin species. However, in contrast to methods utilizing tin hydride that yield the final reduced organic adduct directly, the initial product of coupling using **1** is a titanium enolate; NMR analysis showed

(1) (a) Postema, M. H. D. *C-Glycoside Synthesis*; CRC Press: London, 1995. (b) Levy, D. E.; Tang, C. *The Chemistry of C-Glycosides*; Elsevier: Tarrytown, NY, 1995.

(2) See, Czernicki, S. In *Carbohydrates−Synthetic Methods and Applications in Medicinal Chemistry*; Ogura, H., Hasegawa, A., Suami, T., Eds.; VCH: New York, 1991; pp 28−48 and references cited therein.

(3) For Sn-based reduction of glycosyl halides, see: (a) Giese, B.; Dupuis, J.; Nix, M. *Organic Syntheses*; Wiley: New York, 1993; Collect. Vol. VIII, pp 148−153. (b) Giese, B.; Dupuis, J.; Leising, M.; Nix, M.; Lindner, H. J. *Carbohydr. Res.* **1987**, *171*, 329−341. (c) Giese, B.; Dupuis, J. *Angew. Chem., Int. Ed. Engl.* **1983**, *22*, 622−623. (d) Araki, Y.; Endo, T.; Tanji, M.; Nagasawa, J.; Ishido, Y. *Tetrahedron Lett.* **1987**, *28*, 5853−5856. For Sn-based reduction of phenylseleno sugars, see: (e) Adlington, R. M.; Baldwin, J. E.; Basak, A.; Kosyrod, R. P. *J. Chem. Soc., Chem. Commun.* **1983**, 944−945. For Sm-based reduction, see: (f) Mazéas, D.; Strydstrup, T.; Beau, J.-M. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 909−912. (g) DePouilly, P.; Chénedé, A.; Mallet, J.-M.; Sinaÿ, P. *Bull. Soc. Chim. Fr.* **1993**, *130*, 256−265. For reduction using Vitamin B_{12}, see: (h) Abrecht, S.; Scheffold, R. *Chimia* **1985**, *35*, 211−212. For electrochemical generation of the anomeric radical, see: (i) Rondinini, S.; Mussini, P. R.; Ferzetti, V.; Monti, D. *Electrochim. Acta* **1991**, *36*, 1095−1098.

(4) Kahne, D.; Yang, D.; Lim, J. J.; Miller, R.; Pagvaga, E. *J. Am. Chem. Soc.* **1988**, *110*, 8716−8717.

(5) Giese, B.; Dupuis, J. *Tetrahedron Lett.* **1984,** *25*, 1349−1352.

(6) (a) Cavallaro, C. L.; Schwartz, J. *J. Org. Chem.* **1995**, *60*, 7055−7057. (b) Spencer, R. P.; Schwartz, J. *Tetrahedron Lett.* **1996**, *37*, 4357−4360.

(7) Reaction solvents were distilled prior to use using standard methods. 2,3,4,6-Tetra-*O*-acetyl-α-D-glucopyranosyl bromide, 2,3,4,6-tetra-*O*-acetyl-α-D-galactopyranosyl bromide, and 2-deoxyribose were obtained from Sigma Chemical Co. All other materials were obtained from Aldrich Chemical Co. Methyl vinyl ketone, acrylonitrile, and methyl acrylate were evaporatively distilled before use and stored under N_2 at −40 °C.

(8) Signals for H_5 (*δ* 5.10, $J_{4,5} = 5.86$ Hz, $J_{5,6} = 9.52$ Hz), H_6 (*δ* 5.33, $J_{6,7} = 9.52$ Hz), H_7 (*δ* 5.00, $J_{7,8} = 9.52$ Hz) were separate from the glycal byproduct. The numbering is based on suggested guidelines for *C*-glycoside nomenclature.[1b]

(9) No *β*-glycoside was isolated or could be observed in the NMR spectrum of the crude reaction mixture. The only byproduct observed in all cases was the corresponding glycal.

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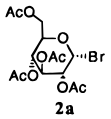
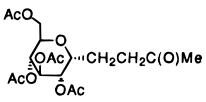
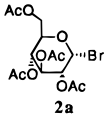
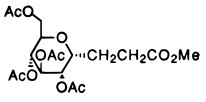
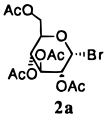
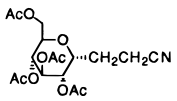
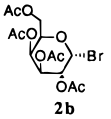
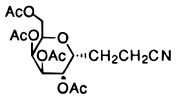
Table 1. Preparation of *C*-Glycosides

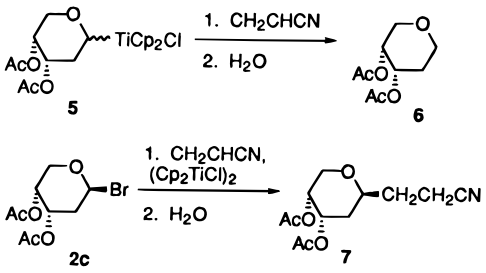
Glycosyl Bromide	Olefin Trap	*C*-Glycoside	Isolated Yield (%)
 **2a**	methyl vinyl ketone		75[3h]
 **2a**	methyl acrylate		55[3e]
 **2a**	acrylonitrile		63[3b]
 **2b**	acrylonitrile		52[3b]

substantial deuterium incorporation at C-2[10] when an aliquot of the reaction mixture was quenched under N_2 with D_2O.

The anomeric radical, and not an intermediate organotitanium species, is the active species for coupling. Reaction of authentic bis(cyclopentadienyl)(3,4-di-*O*-acetyl-2-deoxy-*β*-D-*erythro*-pentopyranosyl)titanium(IV) chloride (**5**)[6a] and acrylonitrile gave only the corresponding anhydroalditol[11] on hydrolysis; no product of conjugate addition was observed using the organometallic (Scheme 2). The anhydroalditol is the expected product from simple hydrolysis of **5**. However, *β*-coupled *C*-glycoside **7** was obtained[12] by reaction of 3,4-di-*O*-acetyl-2-deoxy-*β*-D-*erythro*-pentopyranosyl bromide (**2c**)[13] with **1** in the presence of acrylonitrile (Scheme 2). The stereochemistry of addition at the anomeric carbon, assigned by 2Q-COSY NMR,[12] is opposite to that found for the hexopyranosyl case. This is unremarkable: pentopyranosyl radical *β*-coupling is common.[3b] The observed products are likely the kinetic products of trapping by the initially formed anomeric radical and will thus give coupled products with the same stereochemistry as the starting glycosyl halide.

The complexity of the reaction mixture derived from **2c** stands in contrast to the relatively clean formation of

Scheme 2



C-glycoside[9] from **2a** or **2b**. Reports of coupling in the 2-deoxyglycosyl series[14] are limited to 1-carboxylglycos-1-yl radicals, which are stabilized by both the ring oxygen and the carboxylate group,[14b] and radical allylation gave the coupled product as a mixture of stereoisomers in moderate yield. The 2-deoxyribosyl radical suffers from two drawbacks not noted in the hexopyranosyl case: It lacks stabilization, either by a *β*-OAc substituent or by anomeric substitution, and the pentopyranosyl ring is more flexible and could attain conformations that could allow rapid atom transfer. In this case, fragmentation could be faster than coupling.[15,16]

C-Glycoside synthesis using **1** to activate glycosyl halides has several advantages compared with established methodologies. Unlike Sm(II), **1** is inexpensively and easily prepared[17] from available starting materials. In contrast to tin,[3a-e] titanium is not a toxic element, and the Ti(IV) byproduct of coupling can be recovered readily and recycled. Finally, the likely product of radical capture is a *C*-glycosidic side chain titanium enolate (**3**),[18] and elaboration[19] of this intermediate should be possible. Further studies to this effect are now in progress.

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Supporting Information Available: Copies of ^{1}H NMR, COSY, and ROESY spectra of the mixture of **7** and 1,3,4-tri-*O*-acetyl-2-deoxy-*erythro*-pentopyranose (7 pages).

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(10) Deuterium incorporation was ca. 80%, based on integration for the C-2 proton signal (*δ* 2.41). These protons do not exchange with D_2O as demonstrated using an authentic sample of the methyl acrylate adduct. The adduct radical is not quenched by hydrogen atom abstraction from solvent: When a coupling procedure was carried out in THF-d_8, no deuterium incorporation was detected by NMR.

(11) (a) Cavallaro, C. L. Ph.D. Thesis, Princeton University, 1997. (b) Cavallaro C. L.; Schwartz, J. *J. Org. Chem.* **1996**, *61*, 3863−3864.

(12) A complex mixture, including *β*-coupled **7**, 3,4-di-*O*-acetyl-1,5-anhydro-2-deoxy-D-*erythro*-pent-1-enitol (see: Rico, M.; Santoro, J. *Org. Magn. Reson.* **1976**, *8*, 49−55) and unidentified byproducts, was isolated. The inseparable (1:1) mixture of **7** and residual 1,3,4-tri-*O*-acetyl-2-deoxy-*erythro*-pentopyranose (see: Lemieux, R. U.; Stevens, J. D. *Can. J. Chem.* **1965**, *43*, 2059−2070) was analyzed using gradient-selected 2Q-COSY (30 ms excitation delay) connectivities and ROESY (50 ms excitation delay) interactions at 500 MHz. **7**: ^{1}H (CDCl3) *δ* 5.37 (H_6, $J_{5ax-6} = J_{5eq-6} = J_{7-6} = 3$ Hz), 4.82 (H_7), 3.74 (H_{8eq}), 3.68 (H_4), 3.62 (H_{8ax}), 2.45 (H_{2a}), 2.41 (H_{2b}), 1.82 (H_{5eq}), 1.73 (H_{3a}), 1.66 (H_{3b}), 1.61 (H_{5ax}, $J = 3$, 11.4, 14.1 Hz); ^{13}C ($CDCl_3$) 119.37, 69.61, 67.52, 65.13, 63.69, 35.25, 30.78, 13.55; IR (neat) 2260 (C≡N).

(13) Prepared in situ from 1,3,4-tri-*O*-acetyl-2-deoxy-*β*-*erythro*-pentopyranose. See: Gillard, J. W.; Israel, M. *Tetrahedron Lett.* **1981**, *22*, 513−516.

(14) (a) Wåglund, T.; Claesson, A. *Acta Chem. Scand.* **1992**, *46*, 73−76. (b) Nagy, J. O.; Bednarski, M. D. *Tetrahedron Lett.* **1991**, *32*, 3951−3956. (c) Paulsen, H.; Matschulat, P. *Liebigs Ann. Chem.* **1991**, 487−495.

(15) For examples, see: (a) Crich, D.; Sun, S.; Brunckova, J. *J. Org. Chem.* **1996**, *61*, 605−615. (b) Crich, D.; Hwang, J.-T.; Yuan, H. *J. Org. Chem.* **1996**, *61*, 6189−6198.

(16) Carbohydrate radicals can undergo a 1,5-hydrogen atom shift; this route has been used for epimerization of the C-5 center in glucopyranosides (see: De Mesmacker, A.; Waldner, A.; Hoffmann, P.; Winkler, T. *Synlett* **1994**, 330−332 and references therein). This radical is reduced to the stable, coupled product in the presence of tin hydride.

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

(18) RajanBabu, T. V.; Nugent, W. A. *J. Am. Chem. Soc.* **1994**, *116*, 986−997. An initially formed titanium enolate has also been suggested for Cp_2TiCl reduction of conjugated epoxides; see: Yadav, J. S.; Shekharam, T.; Srinivas, D. *Tetrahedron Lett.* **1992**, *33*, 7973−7976.

(19) For a review of titanium aldol chemistry, see: Peterson, I. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon: London, 1991; Vol. 2, Chapter 1.9. For reports of Cp_2TiCl-enolates, see: Veya, P.; Floriani, C.; Chiesi-Villa, A.; Rizzoli, C. *Organometallics* **1993**, *12*, 4892−4898. Murphy, P. J.; Procter, G.; Russell, A. T. *Tetrahedron Lett.* **1987**, *28*, 2037−2040. Stille, J. R.; Grubbs, R. H. *J. Am. Chem. Soc.* **1983**, *105*, 1664−1665.