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Efficient Syntheses of β-Cyanosugars Using Glycosyl Iodides Derived from Per-*O*-silylated Mono- and Disaccharides

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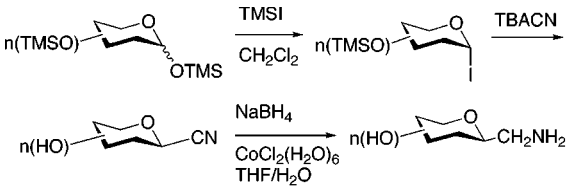
ABSTRACT



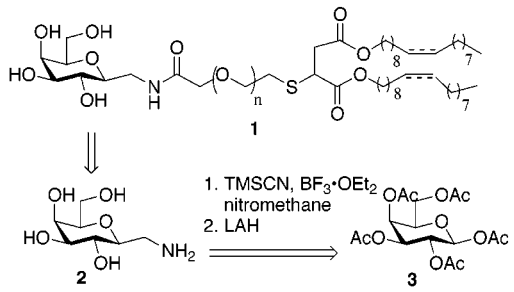
Reported herein is a general method for the efficient syntheses of a variety of β-cyano glycosides through the activation of per-*O*-trimethylsilyl glycosides with TMSI to form α-glycosyl iodides, which undergo S_N2-type displacement when treated with tetrabutylammonium cyanide. The cyanoglycosides were reduced under mild conditions using $NaBH_4$ in the presence of catalytic $CoCl_2(H_2O)_6$ in THF/H_2O to give the corresponding aminomethyl glycosides.

Studies directed toward the synthesis of glycoconjugates, suitable for probing carbohydrate/carbohydrate and carbohydrate/protein recognition processes, often rely upon functionalization of the reducing anomeric center with groups other than naturally occurring *O*- and *N*-glycosides.[1] For example, conjugation through the formation of *C*-glycosides yields analogues that are resistant to enzymatic processes.[2] At the same time, the *C*-glycoside functionality provides a synthetically versatile handle for linking both peptide- and lipid-based conjugates. *C*-Glycoside aldehydes, amines, and carboxylic acids have all been used in this context, and the cyano group can serve as a central precursor to these functionalities.[2]

In our work targeting the synthesis of *C*-linked glycolipids as HIV entry inhibitors, we required β-cyanosugars of both mono- and disaccharides. Recently, improved methods for obtaining α-cyano monosaccharides were reported.[3] However, only limited examples of efficient syntheses of β-cyanosugars have appeared in the literature, and to the best of our knowledge, in none of these cases were the syntheses of β-cyano disaccharides described.[4]

Initially, our work focused on the synthesis of *C*-glycoside analogues of GalCer (**1**), which required 1-*C*-aminomethyl galactose (**2**) (Scheme 1). This compound was readily

Scheme 1



obtained from per-*O*-acetylgalactopyranose (**3**), which was treated with trimethylsilylcyanide and BF_3•OEt_2 in nitromethane followed by reduction with lithium aluminum

(1) Davis, B. G. *J. Chem. Soc., Perkin Trans. 1* **1999**, *22*, 3215.
(2) (a) For a general review, see: Postema, M. H. D. In *C-Glycoside Synthesis*; CRC Press: Boca Raton, FL, 1995. (b) Levy, D. E., Tang, C., Eds. *The Chemistry of C-Glycosides*; Pergamon Press: Oxford, UK, 1995.
(3) (a) Igarashi, Y.; Shiozawa, T.; Ichikawa, Y. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 613. (b) Martin, J.; Jaramillo, L.; Wang, P. G. *Tetrahedron Lett.* **1998**, *39*, 5927.

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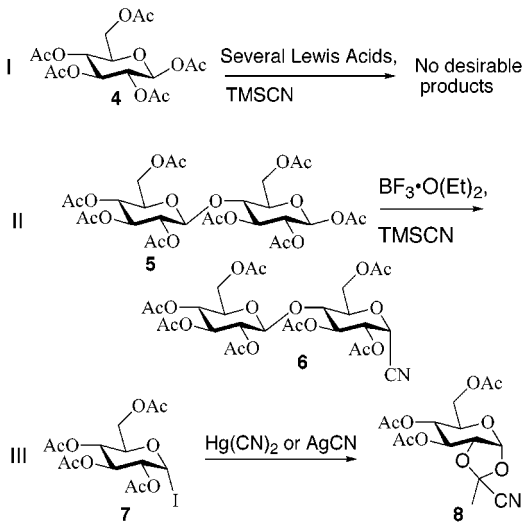
hydride according to the method of Heras et al.[5] Unfortunately, when we attempted to extend this methodology to other simple monosaccharides such as per-*O*-acetylglucopyranoside (**4**) and its C2 epimer, only very low yields of the desired cyanosugars were obtained. Similarly, reaction of per-*O*-acetylated monosaccharides with TMSCN in the presence of other Lewis acids such as $ZnCl_2$, $AlCl_3$, and $SnCl_4$ failed to provide the desired cyanosugars (eq I, Scheme 2). Treatment of per-*O*-acetylcellobiose (**5**) with TMSCN and $BF_3{\cdot}O(Et)_2$ gave only the α-cyanide (eq II, Scheme 2).

Scheme 2

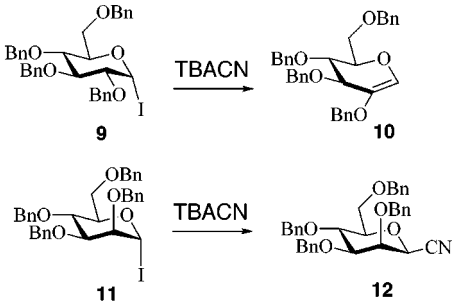


Meyers et al.[4b] reported limited success with mercuric cyanide addition to per-*O*-acetylglucosyl bromide. In our hands, similar transformations with **7** resulted in low yields, and isolation was complicated by the formation of cyanoethylidene derivatives (**8**) (eq III, Scheme 2). Although Lewis acid-catalyzed isomerization of **8** was attempted,[6] yields were not significantly improved and anomeric selectivity remained poor.

In the past few years we have extensively used glycosyl iodides in the synthesis of *O*-, *N*-, and *C*-glycosides.[7] The iodides are readily obtained from the anomeric acetate upon treatment with trimethylsilyl iodide. The trimethylsilyl acetate generated in the reaction can be easily removed by evaporation, yielding the pure glycosyl iodide. Per-*O*-acetyl glycosyl iodides were investigated as donors for cyanide delivery. Several reactions were attempted with both mono- and disaccharide derivatives. Displacement reactions with TBACN, NaCN, or KCN in the presence of crown ethers or via hypervalent silicates (formed by reacting TBAF with TMSCN) all gave 1,2-elimination compounds as the major products.[8]

Earlier, we had shown that reaction of perbenzylated glycosyl iodides with tetrabutylammonium cyanide gave mixed results.[9] For example, with per-*O*-benzylglucosyl iodide (**9**) only a 32% yield of the β-cyanosugar was obtained. The major product was the glycal (**10**) resulting from elimination of HI. When per-*O*-benzylmannosyl iodide (**11**) was reacted under the same conditions, the β-cyano glycoside (**12**) was obtained as the major product (Scheme 3). We were encouraged to learn that the β-cyano functionality could be incorporated without anchiomeric assistance from the C-2 protecting group; nevertheless it was clear that the elimination problem would have to be overcome.

Scheme 3



Hindsgaul and Uchiyama reported that anomeric silyl ethers could serve as precursors to glycosyl iodides.[10] We reasoned that the greater electron donating capability of the silyl protecting group would decrease the acidity of the C-2 hydrogen and suppress possible E-2 reactions. Increased electron donation would also increase the leaving ability of the anomeric iodide, and we anticipated that these two effects, working in concert, would lead to improved yields of β-cyanosugars.

Per-*O*-silylated sugars were prepared by reacting the starting mono- or disaccharide with TMSCl and TEA in DMF.[10] Reactions of the monosaccharides were complete after 4 h whereas the disaccharides required an 8 h reaction time. The silylated sugars were characterized by NMR and high-resolution mass spectrometry. It is interesting to note that the α anomer predominated for all the sugars with the exception of cellobiose (Table 1). The yields for the per-*O*-silylated monosaccharides ranged from 89 to 94%, and the disaccharide yields ranged from 64 to 85%.

The corresponding glycosyl iodides were generated by the addition of TMSI to the silylated carbohydrate in dichloromethane. After an approximately 10 min reaction time at rt, the reaction mixtures were concentrated and the residue was azeotroped with benzene. The iodides were characterized by NMR spectroscopy, which typically showed the anomeric proton between δ 6.7−6.8 ppm, signifying an α anomeric configuration (Table 1).[11] All of the carbohydrate derivatives

(4) (a) Heras, F. G.; Fernandez-Resa, P. *J. Chem. Soc., Perkin Trans. 1* **1982**, 903. (b) Myers, R. W.; Lee, Y. C. *Carbohydr. Res.* **1984**, *132*, 61. (c) Grynkiewicz, G.; BeMiller, J. N. *Carbohydr. Res.* **1983**, *112*, 324.

(5) Heras, F. G.; Fernandez-Resa, P. *J. Chem. Soc., Perkin Trans. 1* **1982**, 903.

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Table 1

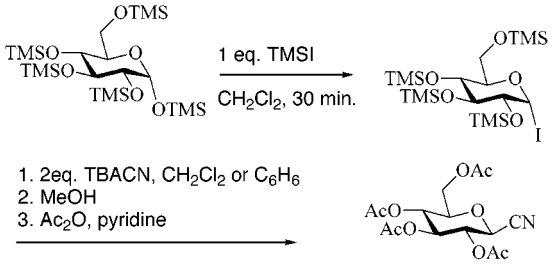
starting material	persilyl derivative % yield	persilyl derivative anomer[a]	persilyl derivative δ, anomeric proton[b]	persilyl α-iodide δ, anomeric proton[b]
glucose	89	α	5.01 (*3.0*)	6.81
galactose	90	α	5.01 (*2.2*)	6.79
L-fucose	94	α	4.98 (*2.8*)	6.84
mannose	92	α	4.88 (*1.6*)	6.74
lactose	64	α	5.02 (*3.2*)	6.75
cellobiose	79	*β*	4.45 (*7.4*)	6.83
melibiose	85	5:1 (α:*β*)	4.40 (*3.0*)	N/A

[a] ^{1}H NMR chemical shift (ppm) in CD_2Cl_2; numbers in parentheses are $J_{1,2}$ (Hz). [b] Trace amounts (~0.1%) of the minor isomer detected by ^{1}H NMR.

shown in Table 1, with the exception of melibiose, provided the desired α iodides in good yields. The *β* interglycosidic linkage present in cellobiose and lactose was stable to brief treatment with TMSI. However, the α interglycosidic linkage of melibiose was readily cleaved with TMSI. Reaction of per-*O*-silylmelibiose with TMSI was extremely sluggish at −20 °C, and when the temperature was raised to 0 °C the cleavage of the glycosidic bond was the predominant reaction, as evidenced by NMR.

The *β*-cyanosugars were generated by reacting the glycosyl iodides with TBACN in either dichloromethane or benzene (Scheme 4). The resulting per-*O*-silylated *C*-cyano glycosides

Scheme 4



were deprotected in refluxing methanol and purified by reverse phase HPLC. To facilitate characterization of the products, the crude deprotected carbohydrates were acetylated and the reaction mixtures purified using silica gel chromatography. As shown in Table 2, the overall reaction yields were better in benzene and generally improved ratios were seen in the less polar solvent. The *β*-cyano *C*-glycosides most likely result from an S_N2-type displacement of the anomeric iodide or perhaps a nonconcerted displacement occurring through a tight ion pair. In either case, one would expect selectivity to be enhanced in benzene relative to dichloromethane.

The results from the above experiments are reported in Table 2. The yields represent a one-pot, four-step process involving glycosyl iodide generation, cyanide incorporation, desilylation, and acetylation. This series of reactions yielded

Table 2

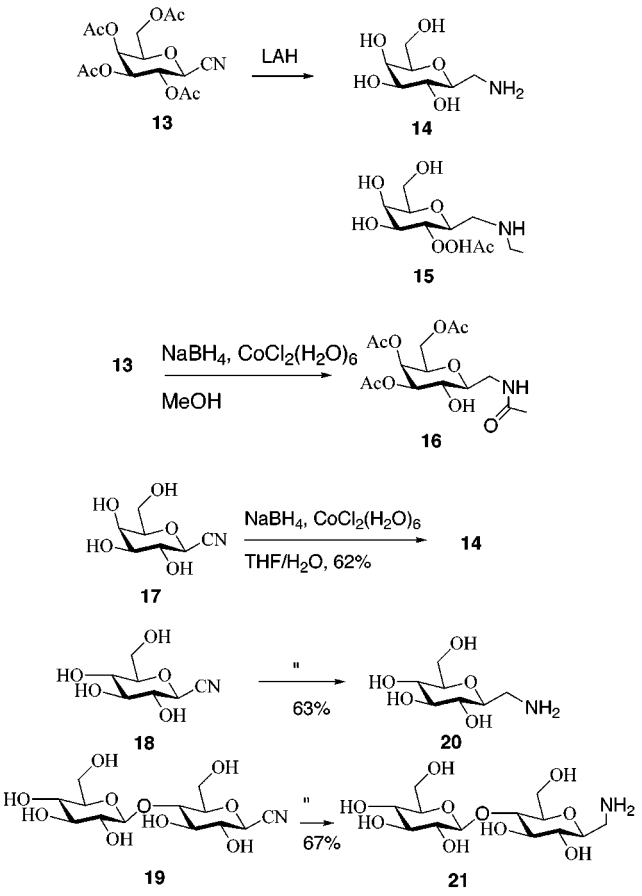
per-*O*-silylated sugar	dichloromethane % yield	dichloromethane *β*:α[a]	benzene % yield	benzene *β*:α[a]
glucose	45	8:1	67	only *β*
galactose	42	5:1	64	6:1
L-fucose			83	14:1
mannose	32	1:1	45	6:1
lactose	17	only *β*	64	only *β*
cellobiose	43	only *β*	68	only *β*

[a] Reaction mixtures were acetylated with Ac_2O/Pyr; % yields and *β*:α ratios based on isolated peracetyl cyano glycosides.

only *β* anomers for glucose, lactose, and cellobiose. A small amount of α anomer was isolated in addition to the predominant *β* anomer, in the cases where galactose, mannose, and fucose served as starting materials. The α anomer may result from in situ anomerization of the α-glycosyl iodide to the *β*-glycosyl iodide by TBAI (which is also generated in situ) and subsequent displacement with TBACN. However, further experimentation is needed to confirm this hypothesis.

It was possible to isolate unprotected glycosyl cyanides from the above reaction sequence without the final acetylation step by purifying the crude reaction mixtures (after

Scheme 5



desilylation step) on reverse phase HPLC using a H_2O/acetonitrile gradient.

We investigated the reduction of the cyano group to provide β-*C*-aminomethyl analogues. Per-*O*-acetylgalactosyl cyanide (**13**) was treated with LAH in refluxing THF to give **14** (Scheme 5). The yield of this reduction was characteristically low, due to acyl transfer and subsequent reduction to the ethylaminomethyl derivative **15**. In an attempt to accomplish the nitrile reduction under mild reducing conditions,[12] **13** was treated with $NaBH_4$ and $CoCl_2(H_2O)_6$ in MeOH. The main product was the *N*-acetyl aminomethyl galactose derivative **16**, indicating that acyl transfer was also a problem under these conditions. Ganem et al. have studied the mechanism of hydride reductions faciliated by $CoCl_2(H_2O)_6$.[13] They found that $NaBH_4$ in the presence of catalytic $CoCl_2(H_2O)_6$ was ideal for reducing nitriles. These conditions were employed with the unprotected cyano carbohydrates isolated after HPLC, as they were readily soluble in THF/H_2O. Galactosyl cyanide **17** was dissolved in 2:1 THF:H_2O and treated with 2 equiv of $NaBH_4$ and catalytic $CoCl_2(H_2O)_6$. Upon purification **14** was obtained in 62% yield. Similarly cyano derivatives of glucose **18** and cellobiose **19** gave the corresponding amines **20** and **21** in 63% and 67%, respectively.

In summary, mono- and β-linked disaccharides can be converted to β-cyano *C*-glycosides in a one pot, four-step procedure. It is notable that anchiomeric assistance is not required to achieve β selectivity. The nitriles can be converted to aminomethyl *C*-glycosides using $NaBH_4$ and catalytic $CoCl_2(H_2O)_6$ in THF/H_2O, providing important precursors for glycoconjugate syntheses.

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Supporting Information Available: Complete experimental details for the syntheses of persilyl carbohydrates, the corresponding cyano carbohydrates, and their reduction products.

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