



A CONCISE SYNTHESIS OF α -GLYCOSYL CYANIDES[†]

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Abstract: A simple procedure has been developed for the synthesis of α -glycosyl cyanides: reactions of *O*-benzylated ethyl 1-thio-glycosides of L-fucose and D-glucose, with TMSCN and MeOTf in ether exclusively gave the corresponding α -glycosyl cyanides in good yields.

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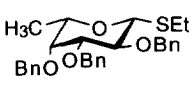
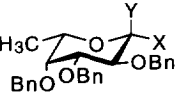
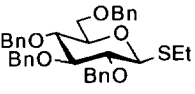
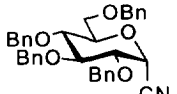
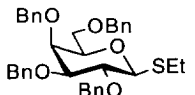
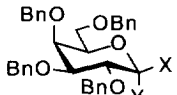
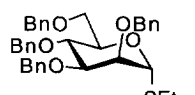
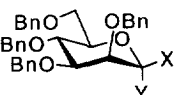
As the critical roles of carbohydrates in a variety of cellular events are being realized,¹ C-glycosides² (carbon-linked glycosides) have been actively investigated as the stable (glycosidase resistant) alternatives to the biologically important glycoconjugates.³ The synthetic procedure for those compounds employing Lewis acid-catalyzed or radical-mediated alkylation of allyl or alkynyl groups⁴ requires additional chemical manipulations such as ozonolysis or oxidative cleavage for their further conjugation.

Glycosyl cyanides have been also employed for the synthesis of C-glycosides,⁵ and have proven to be readily converted to the corresponding C-1 aminomethyl (as glycosidase inhibitors)^{6,7} or COOH,⁸ from which we have recently constructed a new class of carbohydrate analogues in which glycosidic bonds are replaced with amido linkages.⁹ The general synthetic procedure for synthesizing the glycosyl cyanide involves the reaction of per-*O*-acetylated glycosyl halide with Hg(CN)₂ in CH₃NO₂;^{8,10} however, this reaction predominantly yields the β -form of the glycosyl cyanide (1,2-*trans* glycosyl cyanide). Attempts have been made to synthesize α -glycosyl cyanides using the reaction of 1-*O*-acetyl-per-*O*-benzyl pyranoses with TMSCN and BF₃•OEt₂, but the stereoselectivity appeared to be low ($\alpha/\beta \approx 1:1$).^{6,11} For constructing α -C-linked carbohydrate analogues, especially for α -L-fucose and α -D-glucose linkages that are prominent in natural oligosaccharide structures,¹² we report herein a concise synthesis of α -glycosyl cyanides that employs readily obtainable per-*O*-benzylated ethyl 1-thio-glycosides and TMSCN in the presence of MeOTf.

Although glycosylation of thioglycosides has been extensively used to form glycosidic bond,¹³ this approach, to best our knowledge, has not been applied to the synthesis of glycosyl cyanides. We examined the reaction of *O*-benzylated ethyl 1-thio-aldoheopyranoside and TMSCN and MeOTf in a nonpolar solvent, ether.

[†]In this text, we use a nomenclature convention in which compounds with a nitrile group at the anomeric position are named as "glycosyl cyanide" (i.e., 2,3,4-tri-*O*-benzyl- α -L-fucopyranosyl cyanide for compound **5**). This convention is recommended for present purpose because higher-carbon sugar names are not easily applied to describe the relationship between the starting material and the product. Compound **5** would also be named, in another proper convention, as 2,6-anhydro-3,4,5-tri-*O*-benzyl-7-deoxy-L-glycero-D-manno-heptononitrile.

Table 1. Reactions of ethyl 1-thio-glycosides with TMSCN and MeOTf in Et₂O.

Glycosyl donor: ethyl 1-thio-glycoside	Product	Yield	$\alpha:\beta$	Compound	R_F^a	¹ H and ¹³ C NMR data H-1 C≡N
 1^b	 5 X=H, Y=CN (α) 6 X=CN, Y=H (β)	60%	1:0	5^c (6^c)	0.60 0.40 ^d	δ 4.71. (6.1 Hz) δ 116.0 δ 3.99. (9.9 Hz) δ 117.0
 2^e	 7	72%	1:0	7^{c,f,g}	0.55	δ 4.67. (6.0 Hz) δ 115.2
 3^h	 8 X=H, Y=CN (α) 9 X=CN, Y=H (β)	79%	5:1	8^{c,g} 9^{c,g}	0.56 0.50	δ 4.67. (6.1 Hz) δ 115.7 δ 4.01. (9.9 Hz) δ 116.8
 4^e	 10 X=H, Y=CN (α) 11 X=CN, Y=H (β)	68%	3:1	10^{c,i} 11^{c,i}	0.51 0.30	δ 4.82. (2.4 Hz) δ 115.4 δ 4.18. (~0 Hz) δ 116.0

^aIn hexanes:EtOAc=3:1. ^bLönn, H. *Carbohydr. Res.* **1985**, 139, 105. ^cSee ref 19 for physical data. ^dA β -L-fucosyl cyanide derivative (**6**) was obtained from the reaction conducted in CH₃CN as a 1:1 mixture with the α -isomer (**5**) in 63% yield. ^eDasgupta, F.; Garegg, P. J. *Acta Chem. Scand.* **1989**, 43, 471. ^f**7** was also prepared exclusively by the reaction of per-*O*-benzyl trichloroacetimidate derivative, TMSCN, and TMSOTf in CH₂Cl₂ in 72% yield. ^gGarcía López, M.-T.; De las Heras, F. G.; San Félix A. J. *Carbohydr. Chem.* **1987**, 6, 273. ^hSlaghek, T. M.; van Oijen, A. H.; Maas, A. A. M.; Kamerling, J. P.; Vliegthart, J. F. G. *Carbohydr. Res.* **1990**, 207, 237; Basu, S.; Pal, J. N. *Carbohydr. Res.* **1990**, 208, 241. ⁱThe anomeric configurations were tentatively determined by the comparison of NMR data and the optical rotations to those reported for per-*O*-acetylated derivatives.⁸

Thus, treatment of ethyl 2,3,4-tri-*O*-benzyl-1-thio- β -L-fucopyranoside¹⁴ (**1**) with 2 equiv of TMSCN and 2 equiv of MeOTf in the presence of molecular sieves 4A in Et₂O gave an α -fucosyl cyanide (**5**) as a sole product in 62% yield. The structure of **5** was determined by ¹H and ¹³C NMR, and these NMR data were in good agreement with those reported for the antipode, *O*-benzyl α -D-fucosyl cyanide derivative.⁶

General experimental procedure: A suspension of **1**¹⁴ (400 mg, 0.82 mmol), TMSCN (0.22 mL; 2 equiv), flame-dried molecular sieves 4A (1.0 g) in anhydrous Et₂O (15 mL) was stirred for 30 min at room temperature, and the mixture was cooled with ice-water. MeOTf (0.18 mL; 2 equiv) was added to the mixture at 0–5 °C, and the reaction mixture was stirred for 12 h at room temperature. The reaction mixture was diluted with EtOAc and poured onto ice-cold aqueous NaHCO₃. The mixture was filtered through a Celite pad and washed with EtOAc. The filtrate was successively washed with saturated NaHCO₃ and brine, dried over anhydrous MgSO₄, and concentrated in vacuo. The residue was chromatographed on silica gel, with hexane:EtOAc (10:1, v/v), to afford **5** (0.21 g, 60%) as a colorless oil, which crystallized on standing: colorless needles; mp 87.0–87.5 °C (from Et₂O–hexane).

Application of the same treatment to ethyl 1-thio- β -glucoside derivative¹⁵ (**2**) also afforded the α -glucosyl cyanide (**7**)¹¹ exclusively in 72% yield. For the galactose¹⁶ (**3**) and mannose¹⁵ (**4**) derivatives this approach showed somewhat low stereoselectivity (Table 1). When the reaction of **1** was conducted in CH₃CN, a 1:1 mixture of **5** (α -anomer) and **6** (β -anomer) was obtained, indicating the solvent effect from CH₃CN.¹⁷ Together with the results reported by de las Heras and Fernández-Resa that the reaction of per-*O*-acetyl galactose with TMSCN and BF₃•OEt₂ gave a β -galactosyl cyanide,¹⁸ these glycosyl cyanation reactions appear to proceed through a similar mechanism to that of normal *O*-glycosylation reactions.

In summary, we have found that ethyl thio glycoside is an excellent glycosyl donor for the preparation of α -glycosyl cyanide. The procedure described herein will provide a simple and efficient route for constructing the C-glycoside building blocks corresponding to α -L-fucosyl and α -D-glucosyl residues.

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19. Proton assignment in the ^1H NMR data are based on the numbering in "glycosyl cyanide" nomenclature. **2,3,4-Tri-*O*-benzyl- α -L-fucopyranosyl cyanide** or **2,6-anhydro-3,4,5-tri-*O*-benzyl-7-deoxy-L-glycero-D-manno-heptononitrile (5)**. colorless needles; mp 87.0–87.5 °C (from Et₂O–hexane) (Lit.⁶ 88.5–89.5 °C for the antipode D-fucose derivative); $[\alpha]_{\text{D}}^{25}$ –49.7° (c = 1.0, CHCl₃) {Lit.⁶ $[\alpha]_{\text{D}}^{20}$ +49.5° (c = 1.1, CHCl₃) for the antipode D-fucose derivative}. Anal. calcd for C₂₈H₂₉NO₄: C, 75.83; H, 6.59; N, 3.16. found: C, 76.02; H, 6.80; N, 3.21. **2,3,4-Tri-*O*-benzyl- β -L-fucopyranosyl cyanide** or **2,6-anhydro-3,4,5-tri-*O*-benzyl-7-deoxy-L-glycero-D-gluco-heptononitrile (6)**. colorless plates; mp 112.0–112.5 °C (from EtOAc–hexane) (Lit.⁶ 115.5–116.2 °C for the antipode D-fucose derivative); $[\alpha]_{\text{D}}^{25}$ –17.3° (c = 1.0, CHCl₃) {Lit.⁶ $[\alpha]_{\text{D}}^{20}$ +14.2° (c = 1.1, CHCl₃) for the antipode}. Anal. calcd for C₂₈H₂₉NO₄: C, 75.83; H, 6.59; N, 3.16. found: C, 75.83; H, 6.74; N, 3.11. **2,3,4,6-Tetra-*O*-benzyl- α -D-glucopyranosyl cyanide** or **2,6-anhydro-3,4,5,7-tetra-*O*-benzyl-D-glycero-D-gulo-heptononitrile (7)**. colorless oil; $[\alpha]_{\text{D}}^{25}$ +35.2° (c = 1.0, CHCl₃) {Lit.¹¹ $[\alpha]_{\text{D}}$ +37° (c = 1.0, CHCl₃)}. **2,3,4,6-Tetra-*O*-benzyl- α -D-galactopyranosyl cyanide** or **2,6-anhydro-3,4,5,7-tetra-*O*-benzyl-D-glycero-L-manno-heptononitrile (8)**. colorless needles; mp 83.0–83.5 °C (from EtOAc–hexane) (Lit.¹¹ 84–85 °C from EtOAc); $[\alpha]_{\text{D}}^{25}$ +28.1° (c = 1.0, CHCl₃) {Lit.¹¹ $[\alpha]_{\text{D}}$ +29.6° (c = 1, CDCl₃)}. **2,3,4,6-Tetra-*O*-benzyl- β -D-galactopyranosyl cyanide** or **2,6-anhydro-3,4,5,7-tetra-*O*-benzyl-D-glycero-L-gluco-heptononitrile (9)**. colorless needles; mp 86.0–86.5 °C (from EtOAc–hexane) [Lit.¹¹ 85–86 °C]; $[\alpha]_{\text{D}}^{25}$ +13.0° (c = 1.0, CHCl₃) {Lit.¹¹ $[\alpha]_{\text{D}}$ +12.71° (c = 1, CHCl₃)}. **2,3,4,6-Tetra-*O*-benzyl- α -D-mannopyranosyl cyanide** or **2,6-anhydro-3,4,5,7-tetra-*O*-benzyl-D-glycero-D-galacto-heptononitrile (10)**. colorless oil; $[\alpha]_{\text{D}}^{25}$ +27.6° (c = 1.0, CHCl₃); ^1H NMR (300 MHz, CDCl₃) δ 3.74–3.93 (m, 4H, H-2,5,6a,6b), 3.98 (dd, 1H, J = 2.9, 9.0 Hz, H-3), 4.08 (dd, 1H, J = 8.8 Hz, H-4), 4.56 (d, 1H, J = 12.1 Hz, benzylic H-a), 4.59 (d, 1H, J = 10.8 Hz, benzylic H-b), 4.64 (d, 1H, J = 11.7 Hz, benzylic H-c), 4.69 (d, 1H, J = 12.1 Hz, benzylic H-a'), 4.71 (d, 1H, J = 11.7 Hz, benzylic H-c'), 4.72 (s, 2H, benzylic H-d), 4.91 (d, 1H, J = 10.8 Hz, benzylic H-d'); ^{13}C NMR (75 MHz, CDCl₃) δ 65.21, 68.33, 72.55, 72.70, 73.34, 73.70, 74.60, 75.08, 77.00, 79.75, 115.36 (CN), 127.57, 127.67, 127.75, 127.78, 127.82, 127.86, 128.06, 128.29, 128.44, 128.50, 136.94, 137.62, 137.83, 137.94. Anal. calcd for C₃₅H₃₅NO₅: C, 76.48; H, 6.41; N, 2.55. found: C, 76.48; H, 6.62; N, 2.49. **2,3,4,6-Tetra-*O*-benzyl- β -D-mannopyranosyl cyanide** or **2,6-anhydro-3,4,5,7-tetra-*O*-benzyl-D-glycero-D-talo-heptononitrile (11)**. colorless oil; $[\alpha]_{\text{D}}^{25}$ –14.9° (c = 1.0, CHCl₃); ^1H NMR (300 MHz, CDCl₃) δ 3.43 (ddd, 1H, J = 3.0, 4.2, 9.39 Hz, H-5), 3.52 (dd, 1H, J = 2.7, 9.3 Hz, H-3), 3.69 (dd, 1H, J = 4.2, 11.4 Hz, H-6a), 3.73 (dd, 1H, J = 3.0, 11.4 Hz, H-6b), 3.91 (dd, 1H, J = 9.39 Hz, H-4), 3.99 (m, 1H, H-2), 4.18 (s, 1H, H-1), 4.53 (d, 2H, J = 11.4 Hz, benzylic H-a, H-b), 4.60 (d, 1H, J = 12.1 Hz, benzylic H-a'), 4.64 (s, 2H, benzylic H-c), 4.83 (d, 1H, J = 10.8 Hz, benzylic H-b'), 4.91 (d, 1H, J = 11.5 Hz, benzylic H-d), 4.98 (d, 1H, J = 11.5 Hz, benzylic H-d'); ^{13}C NMR (100 MHz, CDCl₃) δ 67.19, 68.65, 72.24, 73.34, 73.78, 73.89, 74.44, 75.11, 80.14, 82.14, 115.95 (CN), 127.35, 127.42, 127.63, 127.68, 127.71, 127.73, 127.85, 128.09, 128.13, 128.15, 128.18, 128.33, 137.29, 137.48, 137.67, 137.76. Anal. calcd for C₃₅H₃₅NO₅: C, 76.48; H, 6.41; N, 2.55. found: C, 76.66; H, 6.52; N, 2.61.