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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.

As the critical roles of carbohydrates in a variety of cellular events are being realized,[1] *C*-glycosides[2] (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 groups[4] 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 CH_3NO_2;[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 BF_3•OEt_2, but the stereoselectivity appeared to be low (α/β = ~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-aldohexopyranoside and TMSCN and MeOTf in a nonpolar solvent, ether.

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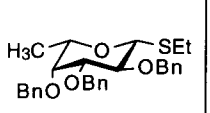
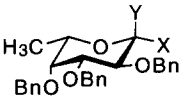
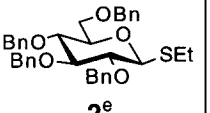
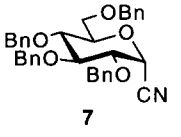
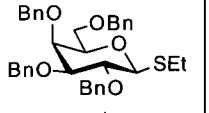
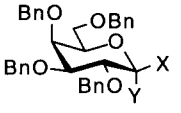
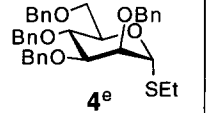
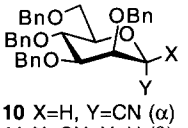
†In this text, we use a nomenclature convention in which compounds with a nitrile group at the anomeric position are named as "glycosyl cyanide" (i.e., 2,3,4-tri-*O*-benzyl-α-L-fucopyranosyl cyanide for compound **5**). This convention is recommended for present purpose because higher-carbon sugar names 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 Et_2O.

Glycosyl donor: ethyl 1-thio-glycoside	Product	Yield	α:β	Compound	R_F[a]	^1H 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]	0.60	δ 4.71. (6.1 Hz)	δ 116.0
				(**6**[c]	0.40)[d]	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]	0.56	δ 4.67. (6.1 Hz)	δ 115.7
				9[c,g]	0.50	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]	0.51	δ 4.82. (2.4 Hz)	δ 115.4
				11[c,i]	0.30	δ 4.18. (~0 Hz)	δ 116.0

[a]In hexanes:EtOAc=3:1. [b]Lönn, H. *Carbohydr. Res.* **1985**, *139*, 105. [c]See ref 19 for physical data. [d]A β-L-fucosyl cyanide derivative (**6**) was obtained from the reaction conducted in CH_3CN as a 1:1 mixture with the α-isomer (**5**) in 63% yield. [e]Dasgupta, 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 CH_2Cl_2 in 72% yield. [g]García López, M.-T.; De las Heras, F. G.; San Félix A. *J. Carbohydr. Chem.* **1987**, *6*, 273. [h]Slaghek, T. M.; van Oijen, A. H.; Maas, A. A. M.; Kamerling, J. P.; Vliegenthart, J. F. G. *Carbohydr. Res.* **1990**, *207*, 237; Basu, S.; Pal, J. N. *Carbohydr. Res.* **1990**, *208*, 241. [i]The 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-fucopyranoside[14] (**1**) with 2 equiv of TMSCN and 2 equiv of MeOTf in the presence of molecular sieves 4A in Et_2O gave an α-fucosyl cyanide (**5**) as a sole product in 62% yield. The structure of **5** was determined by ^1H and ^{13}C 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 Et_2O (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 $NaHCO_3$. The mixture was filtered through a Celite pad and washed with EtOAc. The filtrate was successively washed with saturated $NaHCO_3$ and brine, dried over anhydrous $MgSO_4$, 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 Et_2O–hexane).

Application of the same treatment to ethyl 1-thio-β-glucoside derivative[15] (**2**) also afforded the α-glucosyl cyanide (**7**)[11] exclusively in 72% yield. For the galactose[16] (**3**) and mannose[15] (**4**) derivatives this approach showed somewhat low stereoselectivity (Table 1). When the reaction of **1** was conducted in CH_3CN, a 1:1 mixture of **5** (α-anomer) and **6** (β-anomer) was obtained, indicating the solvent effect from CH_3CN.[17] Together with the results reported by de las Heras and Fernández-Resa that the reaction of per-*O*-acetyl galactose with TMSCN and BF_3•OEt_2 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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15. Dasgupta, F.; Garegg, P. J. *Acta Chem. Scand.* **1989**, *43*, 471.
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17. Vankar, Y. D.; Vankar, P. S.; Behrendt, M.; Schmidt, R. R. *Tetrahedron* **1991**, *48*, 9985.
18. de las Heras, F. G.; Fernández-Resa, P. *J. C. S. Perkin I* **1982**, 903.
19. Proton assignment in the ^{1}H 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 Et_2O–hexane) (Lit.[6] 88.5–89.5 °C for the antipode D-fucose derivative); $[\alpha]_D^{25}$ –49.7° (*c* = 1.0, $CHCl_3$) {Lit.[6] $[\alpha]_D^{20}$ +49.5° (*c* = 1.1, $CHCl_3$) for the antipode D-fucose derivative}. Anal. calcd for $C_{28}H_{29}NO_4$: 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); $[\alpha]_D^{25}$ –17.3° (*c* = 1.0, $CHCl_3$) {Lit.[6] $[\alpha]_D^{20}$ +14.2° (*c* = 1.1, $CHCl_3$) for the antipode}. Anal. calcd for $C_{28}H_{29}NO_4$: 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; $[\alpha]_D^{25}$ +35.2° (*c* = 1.0, $CHCl_3$) {Lit.[11] $[\alpha]_D$ +37° (*c* = 1.0, $CHCl_3$)}.
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); $[\alpha]_D^{25}$ +28.1° (*c* = 1.0, $CHCl_3$) {Lit.[11] $[\alpha]_D$ +29.6° (*c* = 1, $CDCl_3$)}.
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]; $[\alpha]_D^{25}$ +13.0° (*c* = 1.0, $CHCl_3$) {Lit.[11] $[\alpha]_D$ +12.71° (*c* = 1, $CHCl_3$)}.
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; $[\alpha]_D^{25}$ +27.6° (*c* = 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) 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, $CDCl_3$) 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 $C_{35}H_{35}NO_5$: 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; $[\alpha]_D^{25}$ –14.9° (*c* = 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) 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, $CDCl_3$) 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 $C_{35}H_{35}NO_5$: C, 76.48; H, 6.41; N, 2.55. found: C, 76.66; H, 6.52; N, 2.61.

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