Pergamon

Tetrahedron, Vol. 52, No. 27, pp. 9121-9136, 1996

0040-4020/96 $15.00 + 0.00

PII: S0040-4020(96)00440-1

Synthesis and Some Transformations of 1-Azido-glycopyranosyl Cyanides – Precursors of Anomeric α-Amino Acids

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Abstract: Acetylated 1-azido-glycopyranosyl cyanides (of the (*1R*)- **2**, and (*1S*)-D-*galacto* **16**, (*1S*)-D-*arabino* **5**, (*1R*)-D-*gluco* **7**, (*1R*)- **11**, and (*1S*)-D-*xylo* **12** configurations) and *C*-(1-azido-1-deoxy-D-galactopyranosyl)formamide (**19**) were prepared from acetylated 1-halogeno-D-glycopyranosyl cyanides and formamide, resp., by sodium azide in dimethyl sulfoxide. Acetylated (*1S*)- **14** and (*1R*)- **15** 1-chloro-D-galactopyranosyl cyanides were obtained from (*1R*)1-bromo-D-galactopyranosyl cyanide by lithium chloride in dimethyl sulfoxide. 1,3-Dipolar cycloaddition of azide ions to the cyano groups of **2** and **16** afforded acetylated 5-(1-azido-1-deoxy-α- and -β-D-galactopyranosyl)tetrazoles **3** and **17**, resp., while that of dimethyl acetylene dicarboxylate to the azido moiety of **2** gave acetylated dimethyl 1-(1-azido-1-deoxy-β-D-galactopyranosyl)-1,2,3-triazole-4,5-dicarboxylate **20**. Transformation of **3** by ethoxalyl chloride gave acetylated ethyl 2-(1-azido-1-deoxy-α-D-galactopyranosyl)-1,3,4-oxadiazole-5-carboxylate **21**. Copyright © 1996 Elsevier Science Ltd

The crucial role of monosaccharides, their derivatives and oligomers in basic biological phenomena and intercellular communication as understood during the past decade brought about an enormous need for the chemical synthesis of such compounds[1] and their mimetics.[2] Production of a great variety of glycomimetics may provide a useful tool for the glycobiology to get a more precise insight into the interactions of carbohydrate derivatives with various receptors and processing enzymes. Possible means for mimicking natural products by structural analogues can be the replacement of readily hydrolyzable bonds by more stable ones. For instance, glycopeptides in living organisms contain *O*- and *N*-glycosyl amino acids, therefore, *C*-glycosylated amino acid derivatives can be used to mimic their natural counterparts. Several derivatives of this latter type were synthesized having one-three carbon-carbon bonds between the asymmetric centre of the α-amino acid and the anomeric carbon of the sugar.[3] A unique combination of a sugar and an α-amino acid arises when the anomeric carbon is the asymmetric centre of the amino acid. Such compounds have also been described[4] recently, mainly in connection with the chemical synthesis of (+)-hydantocidin,[5] a non-toxic herbicide of natural origin, and its analogues. As expected, anomeric α-amino acids because of their *O,N*-acetal character were inclined to anomerization. This feature made their ensuing reactions more or less inconvenient because of more complex spectroscopic analyses and/or unavoidable separation procedures. On the contrary, their *N*-acylated derivatives

proved configurationally more stable. This may give reason for seeking methods not requiring the amino stage for the formation of amide derivatives. Succesful application of such methods[6] with configurationally stable precursors of anomeric α-amino acids may open a way to their stereochemically more predictable incorporation into peptides.

In the course of our long-lasting interest in synthesizing and investigating the reactivity of anomerically bifunctional monosaccharide derivatives[7,8a,b,d,e,13 and refs. therein] we envisaged that the readily available and stable 1-bromo-glycosyl cyanides[8] offer themselves for introducing a nitrogen functionality in the form of an azido group at the anomeric centre. Such derivatives[7c] are direct precursors of anomeric α-amino acids and can also be transformed into other types of glycomimetics. Compounds containing the α-azidonitrile structural element[9] are subject of current interest, e. g. they afford spiro-heterocycles on catalytic hydrogenation,[10] and undergo unexpected Staudinger-reactions.[11,12] Herein we describe our experiences with the preparation and transformations of 1-cyano-glycopyranosyl azides and a possible mechanism of their formation.

The 1-bromo-glycosyl cyanides are less susceptible towards nucleophilic attack then the acetobromosugars as shown by the longer reaction times and/or more drastic reaction conditions required for their substitution with several nucleophiles.[13] With these preliminaries in mind it was surprising that the reaction of the acetylated (*1R*)1-bromo-D-galactopyranosyl cyanide[8a,b] (**1**) with sodium azide in dimethyl sulfoxide at room temperature

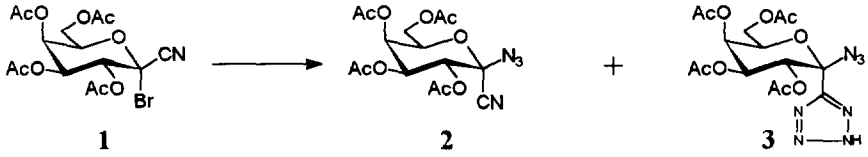


Table 1. Reaction of acetylated (1R)1-bromo-D-galactopyranosyl cyanide (**1**) with azide ions

N_3^- (equivalent)	Solvent	Reaction time at room temp.	Isolated product (%)	
			2	**3**
2 NaN_3	DMSO	5 min	96	
2 NaN_3	DMSO	16 h	56	25
10 NaN_3	DMSO	8 d		84
1 LiN_3	DMF	1.5 h	90	
2 LiN_3	DMF	3 d		72

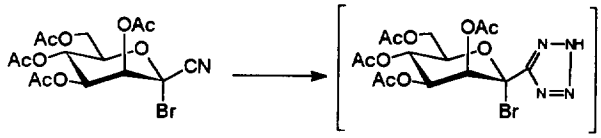
gave the expected acetylated (*1R*)1-azido-D-galactopyranosyl cyanide (**2**) in less than 5 minutes in essentially quantitative yield[7c] (Table 1). Longer reaction time and acidic work-up allowed the isolation of 5-(1-azido-1-deoxy-α-D-galactopyranosyl)tetrazole (**3**) from the reaction mixture, and with sufficiently long time and large excess of reagent **3** was the only product (Table 1). In *N,N*-dimethylformamide with lithium azide these reactions proceeded similarly. The significant difference in rates of the substitution of bromide by azide and the ensuing 1,3-dipolar cycloaddition reactions leading to **2** and **3**, respectively, facilitated the isolation of either of them.

Further reactions with other substrates were performed with 2 equivalents of sodium azide in dimethyl sulfoxide because immiscibility of this solvent with diethyl ether made its removal easier during aqueous work-up of the reaction mixtures. Thus, under these conditions the D-*arabino* configurated 4[8b] gave 5 in 95 % yield. By contrary, the reaction of the D-*gluco* compound 6[8c] was not so clean as the aforementioned ones and 7 was obtained in 25 % yield.

4 5

6 7

In the reaction of the D-*manno* derivative 8[8d] the starting material was detectable by thin layer chromatography even after four hours, but no products appeared under neutral sampling conditions. On acidifying the mixture a new spot of low mobility appeared resembling in this feature tetrazole 3. We did not succeed in isolating this compound, however, the above observations and its lability suggested that 9 might represent its structure.[14] Its formation can be understood in terms of steric hindrance of the anomeric centre by the axial acetoxy group at C-2 which diverts the attacking azide to the cyano group prone to cycloaddition.



8 9

The D-*xylo* configurated 10[8a,b] unexpectedly afforded two products which proved to be anomers 11 and 12. A mixture of the anomeric 1-bromo-D-xylopyranosyl cyanides 10 and 13[8b] also gave these two compounds under the same conditions, however, their ratio was markedly different from that of the starting materials (see Table 2). As these observations were incompatible with the presumable S_N2 substitution experiments were made to get more information on the possible mechanism of the reaction (Table 2). In the presence of bromide ions the ratio of 11 and 12 did not change. Stirring a solution of 10 in dimethyl sulfoxide with 1 equivalent of sodium bromide at room temperature during 30 minutes did not cause observable anomerization, therefore the formation of 12 via a double inversion mechanism (Scheme: 10→13→12) seems unlikely. Neither anomerization nor tetrazole formation was observed with 11 in the presence of 1 equivalent of sodium azide in dimethyl sulfoxide during 40 minutes.

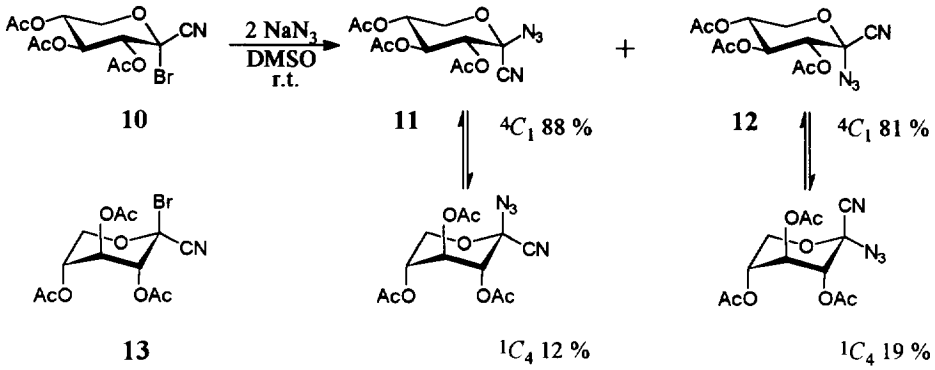


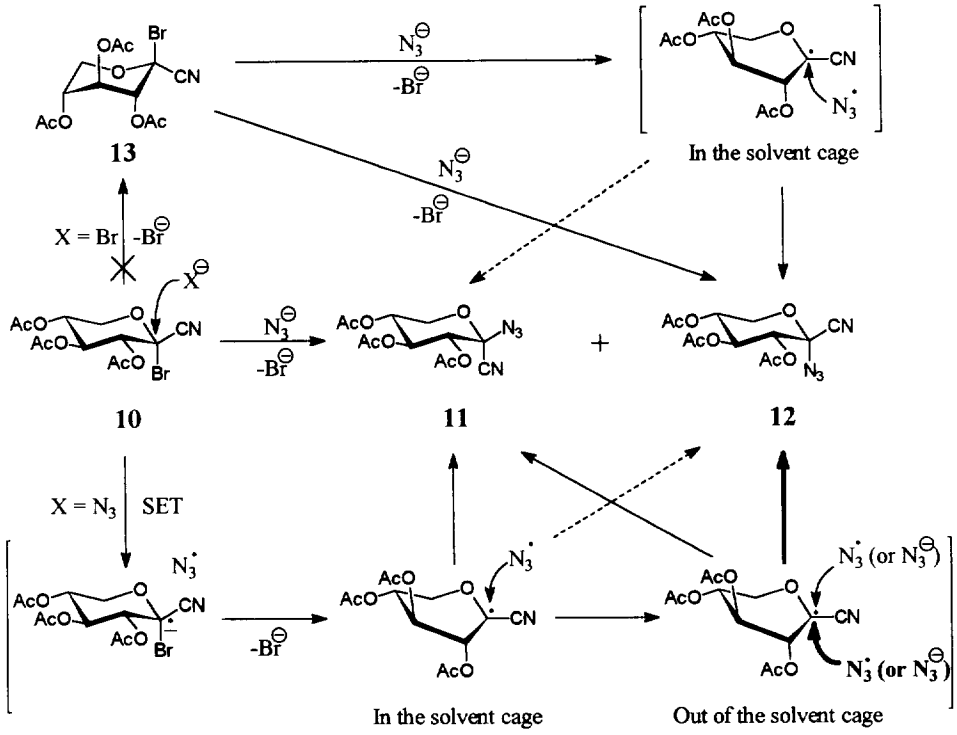
Table 2. Product ratios* of reactions# starting from **10** and **13**

Additive (equivalent)	10	11	12
Starting with **10**			
—		80	20
1 NaBr		80	20
0.1 1,4-dinitrobenzene		85	15
0.2 1,4-benzoquinone	+	<85	<15
0.1 di-*tert*-butyl-nitroxyl		100	
0.1 galvinoxyl		100	
in the dark	<40	<60	+
Starting with a 70 : 30 mixture of **10** and **13**			
—		50	50
0.2 1,4-benzoquinone		70	30
0.3 galvinoxyl		70	30

*On the basis of ^{1}H NMR spectra of the reaction mixtures after 5 min.
Reactions were performed according to the general procedure (see Experimental) with the addition of the indicated compounds to the sodium azide solution.
+The compound's signals can be seen in the spectrum, but its proportion is uncertain.

1,4-Dinitrobenzene used for trapping radical anions[15] had a very slight effect. Radical traps[16] (1,4-benzoquinone, di-*tert*-butyl-nitroxyl, galvinoxyl) caused changes in the product ratio. The reaction was slowed down in the dark.[15] These findings can be explained so (Scheme) that the reaction starts with a light promoted single electron transfer (SET) from the azide ion to the tertiary reaction centre.[17] The radical anion formed in this way looses a bromide ion, and the 1-cyano-D-xylopyranosyl radical[18] may combine in the solvent cage[19] with the azide radical to give **11**. If these two species can leave the solvent cage the anomeric radical may be attacked from the sterically and stereoelectronically preferred α-direction.[20,21] This leads mainly to the formation of **12**, but **11** can also be produced on this pathway. Although the radical traps hamper the formation

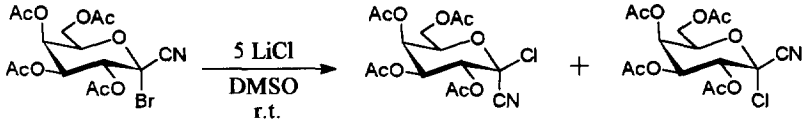
of **12**, it is still present in the reaction starting with a mixture of **10** and **13**. This indicates that **13** gives mainly the inverted **12** either by an ionic or a SET *in the solvent cage* mechanism. In this compound the axial 2-OAc group probably hinders the reaction centre much less as compared to **8** because it exists in a distorted conformation/conformational equilibrium according to the vicinal proton-proton couplings.[8b] Based on these orienting experiments it seems most probable that ionic and SET mechanisms operate parallelly in this reaction. The observed high rates in the reactions of **1**, **4**, and **6** may suggest that the SET in the solvent cage mechanism can be effective also with these substrates.[34]



Scheme

Since the substitution of bromide by azide in the investigated 1-bromo-glycosyl cyanides gave a single anomer in all but one cases other approaches for the preparation of the missing anomers were tried. For the preparation of (*1S*)1-cyano-D-galactopyranosyl azide (**16**) anomerization of **2** in the presence of azide ions was investigated first. With 1 equivalent of sodium azide in dimethyl sulfoxide at room temperature only the slow appearance of tetrazole **3** could be detected by ^{1}H NMR (ratio of **2** and **3** after 6 days ~ 1 : 2). In the presence of 1 equivalent of both boron trifluoride–diethyl ether complex and trimethylsilyl-azide capable to anomerize 1-methoxy-glycosyl azides[22] no change could be observed. Attempts to apply reactions reported for introduction

of an azido group in place of a hydrogen[23] with tetra-*O*-acetyl-β-D-galactopyranosyl cyanide (**1**, H instead of Br) also failed. In a reaction of an equilibrated (~ 9 : 1) mixture of (*1R*)- and (*1S*)1-bromo-D-galactopyranosyl cyanides[13d] under the usual conditions **2** and **16** were detected by ^{1}H NMR spectroscopy. Longer reaction time and acidic work up revealed the formation of both tetrazoles **3** and **17**. However, **16** and **17** were only minor components (10-15 %) in these mixtures. Therefore, we turned our attention to the preparation of 1-chloro-D-galactopyranosyl cyanides **14** and **15** in the hope that these anomers would be stable enough in order to separate them. Reaction of **1** with lithium chloride in dimethyl sulfoxide at room temperature lead to an equilibrated mixture of the *1S* (**14**) and *1R* (**15**) anomers (Table 3). Their ratio was in keeping with the estimated anomeric effect of the cyano group.[13d,24] Fractionated crystallization allowed to isolate **14** in 44 % yield by interrupting the reaction after 18 hours, while **15** was obtained similarly in 49 % yield after 7 days reaction time.



1 **14** **15**

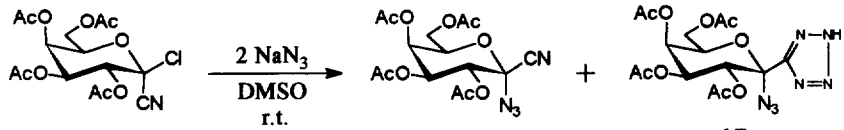
Table 3. Product ratios* in the reaction of **1** with lithium chloride

Reaction time (h)	1	14	15
1	62	38	
4	34	66	
7	<30	<70	+
11	+	<75	<25
18		70	30
26		63	37
46		52	48
117		22	78
168		15	85

* On the basis of ^{1}H NMR spectra of the reaction mixture.
\+ The compound's signals can be seen in the spectrum, but its proportion is uncertain.

Reaction of **14** with azide ions produced the acetylated (*1S*)1-azido-D-galactopyranosyl cyanide (**16**) and the 5-(1-azido-1-deoxy-β-D-galactopyranosyl)tetrazole (**17**). Contrary to the case of **1** the rates of the azide substitution in **14** and the following ring closure were not so different (Table 4), therefore, **16** could only be isolated by column chromatography in 10 % yield when its concentration reached a maximum. A 72 % yield for **17** was obtained by using a large excess of sodium azide during longer reaction time.

Reaction of **15** under the usual conditions proceeded slowlier but analogously to that of **1** to give **2** and **3** (composition of the reaction mixture by ^{1}H NMR: **15** : **2** ~ 2 : 8 after 5 hours; **2** : **3** ~ 7 : 3 after 1 day).



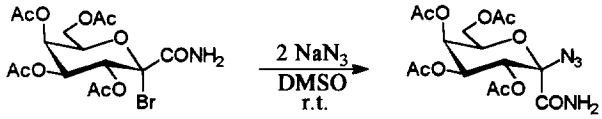
14 16 17

Table 4. Product ratios* in the reaction of **14** with azide ions

Reaction time (h)	14	16	17
0.5	90	10	
4.5	42	47	11
24	10	11	79
48			100

* On the basis of ^{1}H NMR spectra of the reaction mixture.

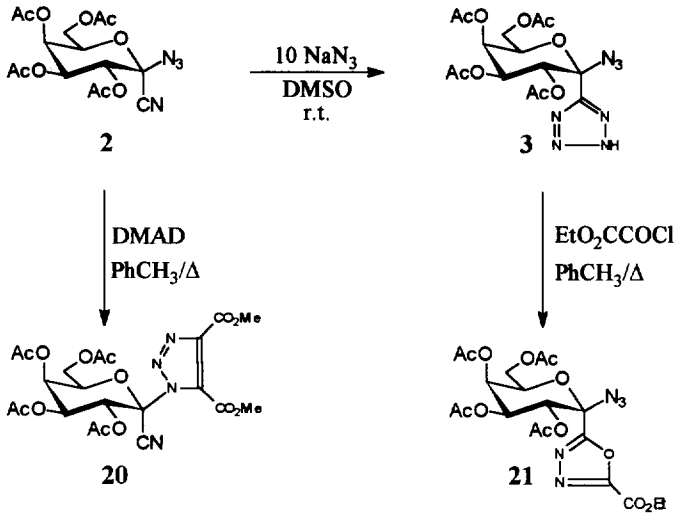
The azide substitution was also extended to the acetylated *C*-(1-bromo-1-deoxy-β-D-galactopyranosyl)formamide[25] (**18**) to give **19** in 91 % yield. Both compounds can be direct precursors for the synthesis of pyranose analogues of (+)-hydantocidin according to published protocols.[26]



18 19

Both anomeric substituents in the 1-azido-glycopyranosyl cyanides can be variously transformed. The formations of the tetrazoles **3** and **17** are examples for such reactions. As the tetrazole ring is isosteric with the carboxyl group[27] these compounds may lead to interesting counterparts of anomeric α-amino acids. The tetrazoles themselves can also be transformed into other heterocycles[28] as exemplified by the reaction of **3** with ethoxalyl chloride to give the oxadiazole-carboxylic ester **21** in 57 % yield. The azide substituent in **2** can also be ring-closed as shown by its transformation with dimethyl acetylene dicarboxylate to the triazol-dicarboxylic acid derivative **20** in 64 % yield.

Structure elucidation of the newly prepared compounds was based mainly on IR and NMR spectroscopy. Presence of the azido group was indicated by strong absorptions around 2130 cm^{-1} in the infrared spectra. The cyano groups were not visible in these spectra in accordance with earlier observations.[29] The vicinal proton-proton coupling constants in the ^{1}H NMR spectra (Table 5) indicated that the molecules existed in the conformations depicted. It is interesting to point out that both **11** and **12** of the conformationally mobile D-*xylo* configuration exist mainly as the $^4C_1$ conformers calculated by using $J_{4a,5a}$ = 11.6 Hz and $J_{4e,5e}$ = 1.5 Hz as limiting values for the $^4C_1$ and $^1C_4$ conformations.[30] This is a new manifestation of the anomeric effects exerted by the azido[31] as well as by the cyano group[13d,24] resembling in their magnitude to that of the methoxy as well as the



acetoxy groups,[32] respectively. From the proton coupled ^{13}C NMR spectra three bond couplings between H-2 and carbon substituents of the anomeric centre could be extracted (Table 6) and allowed to deduce their *gauche* or *trans* relative orientation (Figure). With the knowledge of the conformations and the C-2 configurations this made possible to establish[8a,b,13a,b,d] the absolute configuration for the anomeric carbons. Mass spectrometric investigations of these and other compounds will be published elsewhere.[33]

$^3J_{H\text{-}2,C\text{-}gauche} < {}^3J_{H\text{-}2,C\text{-}trans}$

Figure

In conclusion, with the preparation of a series of 1-cyano-glycopyranosyl azides, and their transformations into C-(1-azido-glycopyranosyl)- and N-(1-cyano-glycopyranosyl)heterocycles a new, simple, and efficient way has been opened to the synthesis of anomeric α-amino acids, their analogues and isosteres, as well as other glycomimetics.

Table 5. ^{1}H NMR data[#] measured for $CDCl_3$ solutions at 200 MHz (δ [ppm], J [Hz])

Compound	H-2 ($J_{2,3}$)	H-3 ($J_{3,4}$)	H-4 ($J_{4,5}$)	H-5 ($J_{5,6}$) ($J_{5,5'}$)*	H-6 ($J_{6,6'}$) H-5'* ($J_{4,5'}$)*	H-6' ($J_{5,6'}$)	Ac	Others
2	5.26 (10.8)	5.19 (2.9)	5.53 (1.2)	4.42 (~6.7)	4.23, 4.21 (two s) ($J_{5,6'}$ ~ 6.8)		2.17, 2.16, 2.08, 1.99	—
3	5.64 (10.7)	5.82 (2.7)	5.58 (<0.5)	4.69 (6.5)	4.17 (11.3)	4.09 (6.5)	2.17, 1.97, 1.93, 1.92	9-9.7 br s NH
5	5.28 (10.6)	5.18 (3.2)	5.41 (2.0)	4.23 (13.8)	4.13 (1.2)	—	2.17, 2.16, 2.01	—
7	5.08 (9.9)	5.36 (9.4)	5.18 (10.0)	4.17 (4.2)	4.38 (12.9)	4.21 (1.9)	2.15, 2.12, 2.06, 2.01	—
11	5.02 (9.7)	5.34 (9.6)	5.06 (5.7)	4.34 (12.0)	3.79 (10.4)	—	2.14, 2.07, 2.04	—
12	5.36 (9.0)	5.31 (~8-9)	5.00 (5.5)	4.16 (11.7)	3.84 (9.7)	—	2.16, 2.06, 2.05	—
14	5.55 (10.6)	5.17 (3.2)	5.54 (~1)	4.42 (5.6)	4.25 (11.5)	4.18 (6.7)	2.21, 2.15, 2.10, 2.01	—
15	5.76 (10.4)	5.30 (3.2)	5.52 (1.2)	4.54 (6.0)	4.22 (11.6)	4.13 (6.9)	2.20, 2.18, 2.07, 1.99	—
16	5.69 (10.4)	5.19 (2.5)	5.48 (~1.3)	4.43 (5.8)	4.19 (11.3)	4.12 (6.4)	2.19, 2.17, 2.07, 1.98	—
17	5.67 (10.5)	5.43 (3.2)	5.59 (1.1)	4.62 (6.4)	4.28 (11.4)	4.21 (6.4)	2.17, 2.07, 2.07, 1.99	9.5-11 br s NH
19	5.49 (10.5)	5.87 (3.2)	5.54 (1.2)	4.94 (6.0)	4.18 (11.4)	4.10 (6.2)	2.17, 2.10, 2.05, 1.98	6.57, 6.50 two s $CONH_2$
20	5.98 (10.7)	5.41 (3.1)	5.61 (1.1)	4.66 (6.6)	4.22 (11.5)	4.16 (6.1)	2.26, 2.08, 2.06, 2.03	4.04, 3.97 two s CO_2CH_3
21	5.66, 5.65, 5.60 3 br s, 3 H			4.62 (6.1)	4.23 (11.5)	4.16 (6.6)	2.22, 2.06, 2.05, 1.99	4.56 (q) CH_2 1.49 (t) CH_3

[#]Listed according to parent sugar numbering. *Applies for the pentose derivatives **5**, **11**, **12**.

Table 6. ^{13}C NMR data[#] measured for $CDCl_3$ solutions at 50.3 MHz (δ [ppm]. *J* [Hz])

Compound	CN	$^3J_{H\text{-}2,(C\text{-}1)C}$	C-1	C-2, C-3, C-4, C-5	C-6	$\underline{C}OCH_3$	$CO\underline{C}H_3$	Others
2	112.07	6.6	87.92	73.41, 69.17, 67.79, 66.22	60.66	170.16, 169.80, 169.48, 168.76	20.57, 20.54, 20.51, 20.38	—
3	155.24 tetrazole	5.1	88.14	71.51, 68.84, 68.58, 67.20	61.09	170.86, 170.25, 170.03, 169.62	20.45, 20.43, 20.36, 20.31	—
5	112.11	7.0	88.39	68.85, 67.99, 66.93, 66.45	—	169.93, 169,53, 168.81	20.79, 20.55, 20.47	—
7	111.69	7.2	87.28	74.09, 70.88, 70.45, 66.60	60.64	170.20, 169.36, 169.05,168.40	20.45, 20.26	—
11	111.87	6.8	87.86	70.53, 70.22, 67.39, 64.16	—	169.63, 169.40, 168.63	20.56, 20.47, 20.42	—
12	112.32	2.3	86.23	69.99, 68.52, 67.36, 61.93	—	169.52, 169.48	20.41, 20.12	—
14	112.34	7.3	89.97	74.87, 70.66, 69.36, 66.07	60.58	169.72, 169.58	20.49, 20.34	—
15	113.21	2.7	89.19	71.95, 67.93, 64.45, 66.34	60.32	170.01, 169.61, 169.36, 168.55	20.38, 20.26	—
16	112.05	2.6	86.65	70.56, 67.32, 67.19, 66.77	60.81	170.10, 169.72, 169.43, 168.59	20.41, 20.27	—
17	157.10 tetrazole	~0	89.09	70.20, 68.54, 68.23, 67.21	61.17	170.38, 169.97, 169.73, 169.09	20.34	—
19	167.59 $CONH_2$	4.7	88.98	72.13, 68.92, 67.76, 67.13	61.29	170.12, 169.77, 169.43	20.34, 20.27	—
20	109.86	—	88.09	74.42, 68.63, 68.11, 65.64	60.22	169.81, 169.47, 169.14, 168.24	20.23, 20.09, 19.84	158.99, 158.26 ($\underline{C}O_2CH_3$) 53.71, 52.58 ($CO_2\underline{C}H_3$)
21	—	—	87.97	72.09, 68.28, 68.09, 66.54	60.58	169.78, 169.54, 169.01, 168.77	20.01	156.89, 153.21 (oxadiazole) 162.12 ($\underline{C}O_2Et$) 63.58 (CH_2), 13.61 (CH_3)

[#]Listed according to parent sugar numbering.

EXPERIMENTAL

Melting points were measured in open capillary tubes or on a Kofler hot-stage and are uncorrected. Optical rotations were determined with a Perkin-Elmer 241 polarimeter at room temperature. IR spectra were taken with a Perkin-Elmer 16 PC FT-IR instrument. NMR spectra were recorded with a Bruker WP 200 SY spectrometer (^{1}H, 200 MHz; ^{13}C, 50.3 MHz). High resolution MS measurements were performed with a VG 7035 instrument by peak matching technique (EI 70 eV, resolution 10000, ion source temp. 150°C). TLC was performed on DC-Alurolle, Kieselgel 60 F_{254} (Merck), and the plates were visualised by gentle heating. For column chromatography Kieselgel 60 (Merck) was used. Organic solutions were dried over anhyd $MgSO_4$ and concentrated in vacuo at 40-50°C (water bath).

General procedure for *per-O-acetyl-1-azido-D-glycopyranosyl cyanides* **2**, **5**, **7**, **11**, **12**, and **16**.—Sodium azide (0.13 g, 2 mmoles) was dissolved in dry dimethyl sulfoxide (5 ml) and a solution of a 1-halogeno-D-glycopyranosyl cyanide (**1**[8a,b], **4**[8b], **6**[8c], **10**[8a,b], **13**[8b], **14**, **15**, 1 mmol) in dry dimethyl sulfoxide (2.5 ml) was added. The mixture was stirred at room temp. for 5 min, unless otherwise stated. It was then diluted with water (~30 ml) and extracted with diethyl ether (5x). The ethereal phase was washed with water, dried, and evaporated to give a raw-product the processing of which is indicated with the individual compounds.

(1R)-2,3,4,6-tetra-O-acetyl-1-azido-D-galactopyranosyl cyanide (*3,4,5,7-tetra-O-acetyl-2-azido-2-deoxy-β-D-galacto-hept-2-ulopyranosononitrile*) **2**.—Prepared from **1**[8a,b] according to the general procedure . Yield of the syrupy raw-product (exhibiting no by-products in the proton spectrum) 96 %, crystallization from abs ethanol (78 % recovery); mp 77-79°C; $[\alpha]_D$ +97 (c 1.61, $CHCl_3$); IR (KBr): ν 2134 cm^{-1} (N_3); Anal. Calcd for $C_{15}H_{18}N_4O_9$ (398.3): C, 45.25; H, 4.55; N, 14.07. Found: C, 45.40; H, 4.47; N, 13.75.

5-(2,3,4,6-tetra-O-acetyl-1-azido-1-deoxy-α-D-galactopyranosyl)tetrazole **3**.—Sodium azide (3.25 g, 50 mmoles) and **1**[8a,b] (2.18 g, 5 mmoles) were stirred in dimethyl sulfoxide (50 ml) at room temp. for 8 days. Water (~200 ml) was added and the solution was stirred with Amberlyst 15 (H^+ form) for 15 min. After filtration of the resin the aqueous phase was extracted with diethyl ether (3x). The extract was dried and concentrated to give syrupy **3** (1.86 g, 84 %), which was sufficiently pure for ensuing transformations. Further purification was achieved by silica gel column chromatography (eluent: toluene- ethyl acetate 7 : 3). $[\alpha]_D$ +31 (c 1.39, $CHCl_3$); IR (film): ν 2130 cm^{-1} (N_3). High resolution MS: Calcd for $C_{15}H_{20}N_7O_9$ $[M + H]^+$ 442.132525. Found 442.13240, Δ (mmu) 1.8 x 10^{-4}.

(1S)-2,3,4-tri-O-acetyl-1-azido-D-arabinopyranosyl cyanide (*3,4,5-tri-O-acetyl-2-azido-2-deoxy-α-D-arabino-hex-2-ulopyranosononitrile*) **5**.—Prepared from **4**[8b] according to the general procedure. Yield of the syrupy raw-product (exhibiting no by-products in the proton spectrum) 95 %, crystallization from abs ethanol (84 % recovery); mp 82-83°C; $[\alpha]_D$ −153 (c 1.62, $CHCl_3$); IR (KBr): ν 2130 cm^{-1} (N_3); Anal. Calcd for $C_{12}H_{14}N_4O_7$ (326.3): C, 44.17; H, 4.32; N, 17.17. Found: C, 44.74; H, 4.27; N, 16.97.

(1R)-2,3,4,6-tetra-O-acetyl-1-azido-D-glucopyranosyl cyanide (*3,4,5,7-tetra-O-acetyl-2-azido-2-deoxy-β-D-gluco-hept-2-ulopyranosononitrile*) **7**.—Prepared from **6**[bc] according to the general procedure. The raw-product was purified by silica gel column chromatography (eluent ethyl acetate-hexanes 15 : 85) to give 25 % yield for the pure material; mp 86-87°C; $[\alpha]_D$ +82 (c 1.0, $CHCl_3$); IR (KBr): ν2126 cm^{-1} (N_3); Anal. Calcd for $C_{15}H_{18}N_4O_9$ (398.3): C, 45.25; H, 4.55; N, 14.07. Found: C, 45.74; H, 4.62; N, 13.87.

(1R)-2,3,4-tri-O-acetyl-1-azido-D-xylopyranosyl cyanide (*3,4,5-tri-O-acetyl-2-azido-2-deoxy-β-D-xylo-hex-2-ulopyranosononitrile*) **11**.—Prepared from a 7 : 3 mixture[8b] of **10** and **13** according to the general procedure. The raw-product was purified by silica gel column chromatography (eluent ethyl acetate-hexanes15 : 85) to give 36 % yield for the pure material; mp 78-80°C; $[\alpha]_D$ +87 (c 0.98, $CHCl_3$); IR (KBr): ν 2128 cm^{-1} (N_3); Anal. Calcd for $C_{12}H_{14}N_4O_7$ (326.3): C, 44.17; H, 4.32; N, 17.17. Found: C, 44.30; H, 4.36; N, 16.97.

(1S)-2,3,4-tri-O-acetyl-1-azido-D-xylopyranosyl cyanide (*3,4,5-tri-O-acetyl-2-azido-2-deoxy-α-D-xylo-hex-2-ulopyranosononitrile*) **12**.—From the above reaction 8 % pure material; mp 176-178°C; $[\alpha]_D$ +53 (c 1.16, $CHCl_3$); IR (KBr): ν 2138 cm^{-1} (N_3); Anal. Calcd for $C_{12}H_{14}N_4O_7$ (326.3): C, 44.17; H, 4.32; N, 17.17. Found: C, 44.10; H, 4.24; N, 17.10.

(1S)-2,3,4,6-tetra-O-acetyl-1-chloro-D-galactopyranosyl cyanide (*3,4,5,7-tetra-O-acetyl-2-chloro-2-deoxy-β-D-galacto-hept-2-ulopyranosononitrile*) **14**.—A solution of **1**[8a,b] (2 g, 4.587 mmoles) and lithium chloride (0.97 g, 22.935 mmoles) in dry dimethyl sulfoxide (36 ml) was stirred at room temp. for 12 hours. Water (~80 ml) was then added and the solution was extracted with diethyl ether (5 x). The ethereal phase was washed with water, dried, and evaporated to give a syrup (1.52 g) which was crystallized *three times* from diethyl ether-hexanes yielding **14** (0.79 g, 44 %); mp 93-94°C; $[\alpha]_D$ +82 (c 1.0, CCl_4); Anal. Calcd for $C_{15}H_{18}ClNO_9$ (391.8): C, 45.98; H, 4.63; N, 3.57; Cl, 9.05. Found: C, 46.21; H, 4.65; N, 3.76; Cl, 9.03.

(1R)-2,3,4,6-tetra-O-acetyl-1-chloro-D-galactopyranosyl cyanide (*3,4,5,7-tetra-O-acetyl-2-chloro-2-deoxy-α-D-galacto-hept-2-ulopyranosononitrile*) **15**.—A solution of **1**[8a,b] (2 g, 4.587 mmoles) and lithium chloride (0.97 g, 22.935 mmoles) in dry dimethyl sulfoxide (36 ml) was stirred at room temp. for 7 days. Water (~80 ml) was then added and the solution was extracted with diethyl ether (5 x). The ethereal phase was washed with water, dried, and evaporated to give a syrup (1.35 g) which was crystallized from abs ethanol yielding **15** (0.89 g, 49 %); mp 96-97°C; $[\alpha]_D$ +144 (c 1.0, CCl_4); Anal. Calcd for $C_{15}H_{18}ClNO_9$ (391.8): C, 45.98; H, 4.63; N, 3.57; Cl, 9.05. Found: C, 45.57; H, 4.32; N, 3.63; Cl, 9.03.

(1S)-2,3,4,6-tetra-O-acetyl-1-azido-D-galactopyranosyl cyanide (*3,4,5,7-tetra-O-acetyl-2-azido-2-deoxy-α-D-galacto-hept-2-ulopyranosononitrile*) **16**.—Prepared from **14** according to the general procedure. Reaction time: 6 hours. The raw-product was purified by silica gel column chromatography (eluent ethyl acetate-hexanes 1 : 4) to give 29 % pure unreacted starting material (**14**), then mixed fractions containing **14** and **16** in 35 : 65 ratio, and finally 10 % yield for pure syrupy **16**; $[\alpha]_D$ +105 (c 1.04, $CHCl_3$); IR (film): ν 2130 cm^{-1} (N_3); Anal. Calcd for $C_{15}H_{18}N_4O_9$ (398.3): C, 45.25; H, 4.55; N, 14.07. Found: C, 45.06; H, 4.48; N, 13.95. Working up the aqueous phase with Amberlyst 15 (H^+) resin gave 25 % of **17**.

5-(2,3,4,6-tetra-O-acetyl-1-azido-1-deoxy-β-D-galactopyranosyl)tetrazole **17**.—Sodium azide (1.99 g, 30.6 mmoles) and **14** (1.2 g, 3.06 mmoles) were stirred in dimethyl sulfoxide (31 ml) at room temp. for 2 days. Water (~100 ml) was added and the solution was stirred with Amberlyst 15 (H^+ form) for 15 min. After filtration of the resin the aqueous phase was extracted with diethyl ether (5x). The extract was dried and concentrated to give syrupy **17** (1.25 g, 95 %), which was sufficiently pure for further transformations. Crystallization from aceton-hexane could be made with 76 % recovery; mp 92-94°C; $[\alpha]_D$ +71 (c 1.02, $CHCl_3$); IR (KBr): ν 2130 cm^{-1} (N_3). High resolution MS: Calcd for $C_{15}H_{20}N_7O_9$ $[M + H]^+$ 442.132325. Found 442.13237, Δ (mmu) 5 x 10^{-4}.

C-*(2,3,4,6-tetra-O-acetyl-1-azido-1-deoxy-β-D-galactopyranosyl)formamide* (*3,4,5,7-tetra-O-acetyl-2-azido-2-deoxy-β-D-galacto-hept-2-ulopyranosonamide*) **19**.—Sodium azide (1.15 g, 17.69 mmoles) was dissolved in dry dimethyl sulfoxide (53 ml) and a solution of 3,4,5,7-tetra-*O*-acetyl-2-bromo-2-deoxy-α-D-*galacto*-hept-2-ulopyranosonamide[23] (**18**, 4 g, 8.81 mmoles) in dry dimethyl sulfoxide (9 ml) was added. After stirring at room temp. for 40 min, it was diluted with water (~100 ml) and extracted with diethyl ether (5 x). The ethereal phase was washed with water, dried, and concentrated to give crystalline **19** (3.35 g, 91 %) sufficiently pure for further transformations. Recrystallization from dichloromethane-hexane with 78 % recovery; mp 81-82°C; $[\alpha]_D$ −10 (c 1.06, $CHCl_3$); IR (KBr): ν 2128 cm^{-1} (N_3); Anal. Calcd for $C_{15}H_{20}N_4O_{10}$ (416.4): C, 43.27; H, 4.84; N, 13.45. Found: C, 42.87; H, 4.81; N, 13.09.

Dimethyl 1-(2,3,4,6-tetra-O-acetyl-1-cyano-1-deoxy-β-D-galactopyranosyl)-1,2,3-triazole-4,5-dicarboxylate **20**.—A solution of **2** (0.8 g, 2 mmoles) and dimethyl acetylene-dicarboxylate (2 ml, 16.2 mmoles) in toluene (8 ml) was boiled under reflux for 20 hours. The mixture was then concentrated to a syrup which was purified by silica gel column chromatography (eluent toluene-ethyl acetate 7 : 3) to give syrupy **20** (0.69 g, 64 %). Crystallization from ethanol; mp 115-116°C; $[\alpha]_D$ +39 (c 1.2, $CHCl_3$); Anal. Calcd for $C_{21}H_{24}N_4O_{13}$ (540.4): C, 46.67; H, 4.48; N, 10.37. Found: C, 46.88; H, 4.30; N, 10.01.

Ethyl 2-(2,3,4,6-tetra-O-acetyl-1-azido-1-deoxy-α-D-galactopyranosyl)-1,3,4-oxadiazole-5-carboxylate **21**.—A solution of **3** (0.53 g, 1.2 mmoles) and ethoxalyl chloride (1 ml, 9 mmoles) in toluene (10 ml) was heated on a boiling water bath for 2 hours. (*Caution! HCl and N_2 evolution! To be made under a fume hood!*) The mixture was then concentrated, the residue dissolved in chloroform. This solution was washed with satd aq sodium-hydrogencarbonate solution and water, dried, and evaporated. Silica gel column chromatography (eluent toluene-ethyl acetate 7 : 3) gave syrupy **21**; $[\alpha]_D$ +84 (c 1.2, $CHCl_3$); IR (film): ν 2130 cm^{-1} (N_3); Anal. Calcd for $C_{19}H_{23}N_5O_{12}$ (513.4): C, 44.44; H, 4.52; N, 13.64. Found: C, 44.70; H, 4.36; N, 13.29.

ACKNOWLEDGEMENT

The authors thank CNRS and the Hungarian Academy of Sciences for supporting their cooperation (N° 4.5.). Financial support from the Hungarian Ministry of Education and in part from the Hungarian National

Science Foundation (Grants: 13/94; 175/95; OTKA T 19339) is gratefully acknowledged. Dr. Z. Dinya is thanked for the high resolution mass spectrometric measurements, and Miss G. Browne for her participation in the preparation of compound 7.

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34. It is hard to differentiate between the S_N2 and SET in the solvent cage pathways since both of them give the same product. However, the picture may be even more complicated as it has been suggested[19] that loss of stereochemical integrity can occur in the solvent cage, too (see dashed arrows on the Scheme). Furthermore, attack of azide ions instead of azide radicals on the sugar radical may result in 1-azido-glycosyl-cyanide radical anions[15] which can transfer electrons to the substrate 1-bromo-glycosyl cyanides thereby building up a chain reaction. At the moment also the question "why do both anomers appear in the reaction of the D-*xylo* configurated substrates only" remains open. In order to understand these processes more deeply further investigations will have to be performed.

(*Received in UK* 12 *April* 1996; *accepted* 9 *May* 1996)