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Behaviour of some 1-C-acceptor-substituted glycals under azidohydroxylation conditions

Ágnes Homolya [a,b], Ivett Jedlóczki [a], Anita Kónya-Ábrahám [a], László Somsák [a], Marietta Tóth [a], László Juhász [a,*]

[a] Department of Organic Chemistry, University of Debrecen, PO Box 400, H-4002, Debrecen, Hungary
[b] University of Debrecen, Doctoral School of Chemistry, PO Box 400, H-4002, Debrecen, Hungary

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Dedicated to Zbigniew J. Witczak on the occasion of his 75th anniversary.

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PIFA
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ABSTRACT

Azidohydroxylation of 1-carbamoyl, 1-methoxycarbonyl and 1-cyano substituted D-*lyxo* and D-*arabino* configured *O*-peracylated glycals was studied and the reaction conditions were optimized. Under these conditions (3 equiv. NaN_3/2 equiv. PIFA/0.3 equiv. TEMPO/50 equiv. H_2O/dry DCM/0 °C/Ar) the expected 3-azido-3-deoxy ulopyranosonic acid derivatives were isolated in good yield with α-D-*galacto* configuration exclusively from the reaction of the 1-carbamoyl and 1-methoxycarbonyl substituted D-*lyxo* configured *O*-peracetylated glycals, while the transformation of the 1-cyano derivative gave a 2,3-vicinal diazide in low yield. The 1-carbamoyl D-*arabino* configured *O*-perbenzoylated glycal gave a mixture of α-D-*gluco* and α-D-*manno* configured azidohydroxylated products with D-*gluco* preference. The analogous 1-methoxycarbonyl derivative gave an inseparable product mixture and no transformation was detected with the respective 1-cyano glycal.

1. Introduction

Glycals are cyclic monosaccharide derivatives having a double bond between the C-1 and C-2 carbon atoms [1,2]. The reactivity of these compounds is characterized by electrophilic ionic and radical additions to the electron rich double bond. The high regioselectivity of the addition reactions is due to the stability of the intermediate glycosylium ion and glycosyl radical, respectively. Glycals are widely used as starting materials for the synthesis of several natural products [2–4], among them aminosugars. Aminosugars, an important class of biologically active compounds, contain one or more amino group instead of hydroxy groups on the sugar ring. They can be found in naturally occurring antibiotics and glycoproteins, and the biological importance of these biomolecules is connected to the aminosugar moiety [5–7]. A general strategy to introduce an amino group into the 2-position of monosaccharides operates *via* the corresponding 2-azido-2-deoxy derivatives which, among others, can be prepared from glycals using azidonitration [8], haloazidation [9,10], azidoselenylation [11] or azidohydroxylation [12].

The presence of an acceptor substituent (such as CN, $CONH_2$ and COOMe) at C-1 of glycals may alter the reactivity of the double bond, and ionic electrophilic addition might not be easy. This specific pattern with the acceptor group results in a so-called capto-dative substitution of C-1 to stabilize radicals very efficiently on that carbon [13,14]. We have elaborated synthetic methods for 1-C-acceptor-substituted glycals [15–18] and a research program has been started to study the chemical properties of these types of glycal derivatives under radical and ionic circumstances [13,19–21].

Azidohydroxylation is a widely used method for the vicinal functionalization of alkenes using various conditions e. g. $CrO_3/NaN_3/AcOH$ [22], $NaN_3/H_2O_2/CH_3CN$ [23], I_2/NaN_3/TBHP or H_2O_2 [24], $TMSN_3/MnBr_2/CH_3CN$ [25], $TMSN_3/O_2$/Acr$^+$MesClO$_4^-$/Blue LED [26], BiI_3/NaN_3/DMF [27], but only one article was published for the direct azidohydroxylation of glycal derivatives by a multicomponent reagent system [12]. This transformation was reported to proceed with excellent regio- and stereoselectivity and high protecting group tolerance. As a continuation of our research to study the reactivity of 1-C-acceptor substituted glycals, we have now investigated the azidohydroxylation of *O*-peracetylated D-*lyxo* and *O*-perbenzoylated D-*arabino* configured 1-CN, 1-$CONH_2$, and 1-COOMe substituted glycals and our observations are presented below.

2. Results and discussion

The starting compounds i.e., D-*lyxo* configured 1-carbamoyl- **1** [16], 1-methoxycarbonyl- **2** [21], 1-cyano-glycals **3** [17] and the D-*arabino*

* Corresponding author.
E-mail address: juhasz.laszlo@science.unideb.hu (L. Juhász).

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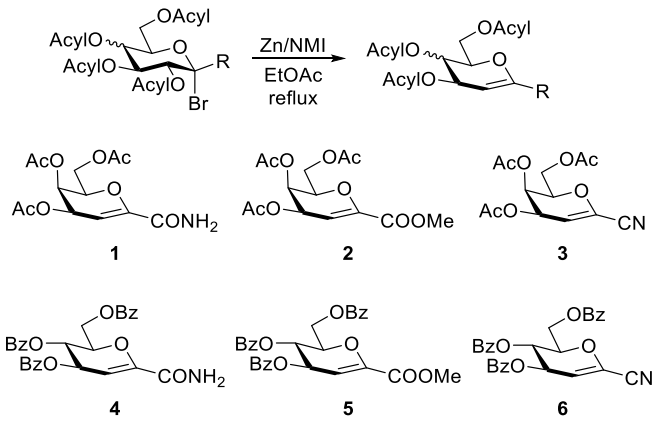


Scheme 1. Synthesis and structure of the studied glycals.

configured 1-carbamoyl- **4** [18], 1-methoxycarbonyl- **5** [18], 1-cyano--glycals **6** [18], were synthesized from the corresponding glyculopyranosyl bromides by our Zn/*N*-methylimidazole mediated reductive elimination method (Scheme 1) [15,17,18].

Azidohydroxylation of carbamoyl substituted glycal **1** was first performed under literature circumstances elaborated by Vankar for unsubstituted glycal derivatives [12] (Scheme 2). The reported azidohydroxylations [12] were complete in 20–60 min and the desired products were isolated in good yields (56–80%).

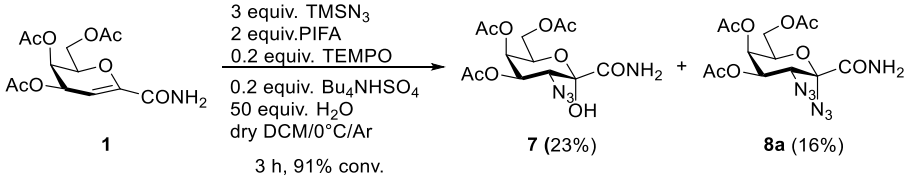
In contrast with these published observations, the transformation of 1-carbamoyl-galactal **1** gave the desired azidohydroxylated compound **7** in a low yield (23%) beside diazide **8a** (16%, Scheme 2). As these isolated yields were far from satisfactory, we have started an optimization procedure.

Optimization of the reaction conditions was started by changing the phase transfer catalyst, because we observed a gas formation [28], which might have indicated the decomposition of $TMSN_3$ (Table 1, entry 1). With $BnEt_3NCl$ (entry 2) the reaction took place in shorter time and the azidohydroxylated compound **7** was isolated with better, but still low yield (28%) beside diazide **8a** (9%) and azidochlorinated compound **9** (13%).

In the case of Bu_4NBr, compound **7** was isolated with worse yield (13%) beside diazide **8a** (14%) and bromoazidated compound **10** (19%), which was the major product of this reaction. Formation of compounds **9** and **10** can be explained by the competition between water and halide anions as nucleophiles. Based on these experiments we used TEBACl as phase transfer catalyst in further experiments and tried to increase the yield of compound **7**.

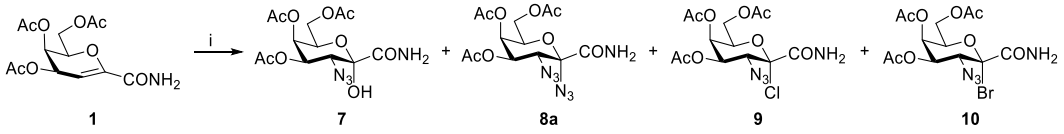
Changing the amount of water had no significant effect on the yield of compound **7** (22%–28%), but longer reaction time and the formation of *cis* and *trans* diazides **8a** and **8b** was observed by reducing the amount of the water from 50 to 10 equivalent (Table 2, entries 1–3).

With 100 equivalent of water (entry 4) the reaction was fast, but the yield of azidochlorinated compound **9** was reduced, and compounds **7** and **8a** were formed in approximately 1 : 1 ratio in low yield. Therefore, we used 50 equivalents of water in further reactions to study the effect of



Scheme 2. Azidohydroxylation of 1-carbamoyl glycal **1** under Vankar's conditions.

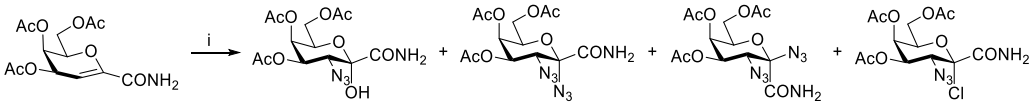
Table 1
Effect of the phase transfer catalyst.



Entry	PTC	Reaction time (h)	Conversion (%)	Products (yield, %)[a]				Product ratio[c]
				7	**8a**	**9**	**10**	
1	Bu_4NHSO_4	3	91	23	16	-	-	-
2	$BnEt_3NCl$	1	100	28	9[b]	13[b]	-	**8a**: **9** = 40 : 60
3	Bu_4NBr	4	90	13	14[b]	–	19[b]	**8a**: **10** = 40 : 60

i: 3 equiv. $TMSN_3$/2 equiv. PIFA/0.2 equiv. TEMPO/0.2 equiv. PTC/50 equiv. H_2O/dry DCM/0 °C/Ar.
[a] Yields were corrected with the conversion.
[b] Inseparable mixture.
[c] Based on the ^1H NMR spectrum of the mixture.

Table 2
Effect of the amount of water.



1 7 8a 8b 9

Entry	Amount of water (equiv.)	Reaction time (h)	Conversion (%)	Products (yield, %)[a]				Product ratio[c]
				7	**8a**	**8b**	**9**	
1	10	3.5	100	23	16[b]	4	15[b]	**8a**: **9** = 53 : 47
2	25	3	91	22	13[b]	–	18[b]	**8a**: **9** = 65 : 35
3	50	1	100	28	9[b]	–	13[b]	**8a**: **9** = 40 : 60
4	100	1.5	100	26	24[b]	–	5[b]	**8a**: **9** = 83 : 17

i: 3 equiv. $TMSN_3$/2 equiv. PIFA/0.2 equiv. TEMPO/0.2 equiv. $BnEt_3NCl$/10–100 equiv. H_2O/dry DCM/0 °C/Ar.
[a] Yields were corrected with the conversion.
[b] Inseparable mixture.
[c] Based on the ^1H NMR spectrum of the mixture.

the amount of the azide source.

Reducing the amount of $TMSN_3$ from 3 to 1.5 equivalent (Table 3, entry 3 *vs.* entry 2) made the reaction slower but, after total conversion of the starting compound, only azidohydroxylated **7** and azidochlorinated **9** could be isolated in very low yields (4% and 7%). Using 1 equivalent of $TMSN_3$ (entry 1) gave only the azidochlorinated derivative **9** in a low yield (14%). Increasing the amount of $TMSN_3$ to 4 or 5 equivalent (entries 4 and 5), total conversion of the starting compound was detected after 2 h, however, this had slightly diminished the yield of azidohydroxylated compound **7** and increased those of diazides **8a** and **8b**. In the next step, we exchanged $TMSN_3$ to NaN_3 (entry 6) and after 1.5 h a total conversion of the starting compound was detected, and the desired compound **7** was isolated in much higher yield than with $TMSN_3$ (41% *vs.* 28%). In addition, the yields of **8a** and **9** were reduced to 8% and 6%, respectively. Using 4 equivalents of NaN_3, **7** was formed with lower yield (31%) beside diazide **8a** (19%) (entry 7).

The outcome of the reaction with 3 equivalents of NaN_3 (Table 3, entry 6) gave a chance to avoid the formation of chlorinated compound **9** by using a crown ether as the phase transfer catalyst (Scheme 3). Using 15C5 as an optimal catalyst for the sodium ion, the reaction was fast (15 min), the formation of compound **9** was not observed, only **7** and **8a** were isolated from the reaction mixture. The yield of **7** was the same as with TEBACl (41%), but a higher amount of **8a** was isolated. With 18C6 (which is optimal for potassium), the reaction was slower (45 min), and only compound **7** could be isolated from the reaction mixture (35%), while compound **8a** was detected by TLC, but could not be isolated by column chromatography.

Next, we proceeded to optimize the reaction by modifying the quantity and quality of the hypervalent iodine reagent while maintaining 18C6 as the phase transfer catalyst (Table 4).

Reducing the amount of PIFA from 2 equiv. to 1.5 equiv., the reaction became slower but the yield of compound **7** was not affected (compare entries 1 and 2). Increasing the amount of this reagent to 2.5 equiv., the rate of the transformation was not changed, but the yield of compound **7** slightly diminished (entry 3, 27%). With PIDA as the hypervalent iodonium reagent, **7** was not formed, only diazide **8a** was isolated in moderate yield (entry 4, 40%).

Modification of the amount of TEMPO between 0.05 equiv. and 0.3 equiv. had no significant effect on the rate of the reactions and the yield of **7**. Compound **7** was isolated in moderate yield (between 26 and 36%) with a short reaction time (25 min) in each case. The best yield (36%) was observed if 0.3 equiv. TEMPO was used.

With respect to the solvent, no transformation was detected in toluene (Table 5, entry 1) but in dry acetonitrile (entry 2) the reaction was completed in 25 min and compound **7** was isolated in moderate yield (30%) beside 1-acetamido-2-azido-2-deoxy-α-D-galactopyranosyl cyanide **11** (22%). The formation of **11** became dominant in the absence of added water in acetonitrile (entry 3).

Finally, the individual reagents were systematically omitted to investigate their effect on the reaction (Table 6).

No transformation was observed without NaN_3, H_2O and PIFA (entries 1–3, respectively). Without TEMPO (entry 4) a mixture of diazides **8a** and **8b** was isolated in moderate yield (37%). Without the crown ether phase transfer catalyst, the reaction time increased (entry 5) and, surprisingly, the desired azidohydroxylated compound **7** was isolated in a better yield (52%) than in the presence of 18C6 (35%).

The transformation was extended to 1-methoxycarbonyl- **2** and 1-cyano-glycals **3**, and the reactions were performed both with and without crown ether phase transfer catalyst.

The azidohydroxylation of glycal **2** was carried out with NaN_3 as the azide source, and the expected **12** was isolated in 54% yield with 18C6 catalyst (Scheme 4). However, without 18C6, **12** could be isolated in an excellent 88% yield. This reaction was repeated with $TMSN_3$ without 18C6, and the reaction was completed in 0.5 h to give **12** in 68% yield.

Azidohydroxylation of 1-cyano-glycal **3** was performed also with and without crown ether catalyst. In the presence of 18C6 only diazide **13** was isolated in low yield after 24 h (Scheme 5). Without the PTC, the rate of the reaction was not changed, but diazide **13** could be isolated in an excellent corrected yield (96%).

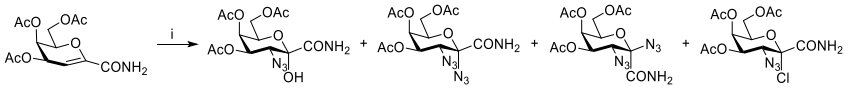
The azidohydroxylation was extended to the D-*arabino* configured 1-C-acceptor substituted D-glycals **4**–**6** using PTC free circumstances. The transformation of 1-carbamoyl substituted glycal **4** resulted in a mixture of D-*gluco* and D-*manno* configured azidohydroxylated derivatives **14** and **15**, respectively (Scheme 6), while the transformation of 1-methoxycarbonyl glycal **5** gave an inseparable mixture of products. No transformation was observed with 1-cyano glycal **6**.

Transformation of an azidohydroxylated compound was tested by the Mitsunobu reaction (Scheme 7) of **12** with 4-nitrophenol to give the corresponding *O*-glycoside in good yield (80%) [29].

2.1. Structural elucidation

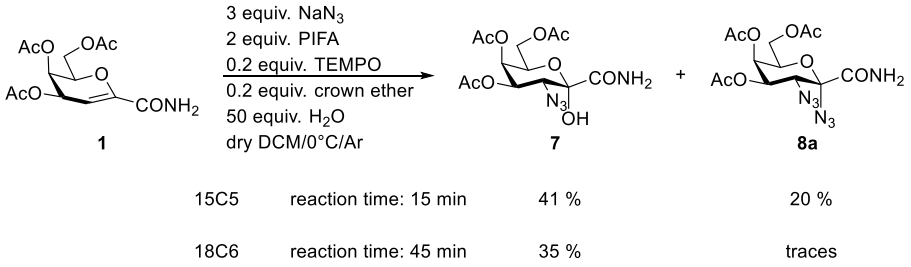
The structural elucidation of the isolated compounds was based on MS, NMR, and IR measurements. The presence of the azido and hydroxy groups in **7**, **12**, **14** and **15** was proved by the characteristic valence vibrations of these functional groups at ~2120 cm^{-1} (ν_{N3}) and ~3450 cm^{-1} (ν_{OH}). In the IR spectra of **8a**, **8b**, **9**, **10**, **13** the ν_{N3} band appeared in the usual range while the ν_{OH} band was expectedly missing. The mass spectra of **9** and **10** clearly showed the expected molecular ion clusters to indicate the presence of a chlorine (M : M+2 = 3 : 1) and a bromine (M : M+2 = 1 : 1) atom in the respective products. The $^5C_2$(D) conformation of the sugar rings and the depicted C-3 configuration followed from the vicinal coupling constants that requires no further comments. The position of the hydroxy group was proved by the

Table 3
Effect of the azide source.



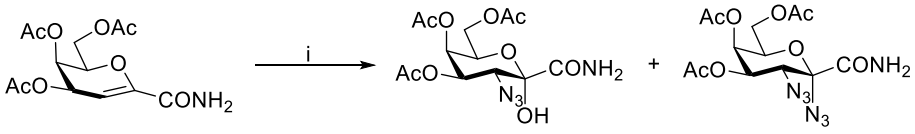
Entry	Azide source	Amount of azide (equiv.)	Reaction time (h)	Conversion (%)	Products (yield, %)[a]				Product ratio[c]
					7	**8a**	**8b**	**9**	
1	$TMSN_3$	1	3	82	–	–	–	14	–
2	$TMSN_3$	1.5	2.5	90	4	-	-	7	–
3	$TMSN_3$	3	2	100	28	9[b]	–	13[b]	**8a**: **9** = 40 : 60
4	$TMSN_3$	4	2	100	23	17[b]	10	14[b]	**8a**: **9** = 55 : 45
5	$TMSN_3$	5	2	100	18	21[b]	13	20[b]	**8a**: **9** = 52 : 48
6	NaN_3	3	1.5	100	41	8[b]	–	6[b]	**8a**: **9** = 58 : 42
7	NaN_3	4	0.41	100	31	19	–	–	-

[a] Yields were corrected with the conversion.
[b] Inseparable mixture.
[c] Based on the ^{1}H NMR spectrum of the mixture. i: azide source/2 equiv. PIFA/0.2 equiv. TEMPO/0.2 equiv. $BnEt_3NCl$/50 equiv. H_2O/dry. DCM/0 °C/Ar.



Scheme 3. Experiments with crown ethers.

Table 4
Effect of the amount and quality of the hypervalent iodine compound.



Entry	Amount of PIFA/PIDA	Reaction time (h)	Conversion (%)	Product (yield, %)
1	1.5 equiv. PIFA	3.5	100	**7** (35)
2	2 equiv. PIFA	0.75	100	**7** (35)
3	2.5 equiv. PIFA	0.75	100	**7** (27)
4[a]	2 equiv. PIDA	3	92	**8a** (40)[b]

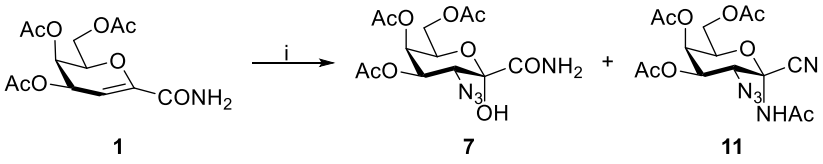
[a] $TMSN_3$ and $BnEt_3NCl$ was used.
[b] Yield was corrected with the conversion and the yield of the isolated pure product. i: 3 equiv. NaN_3/PIFA or PIDA/0.2 equiv. TEMPO/0.2 equiv. 18-crown-6/50 equiv. H_2O/dry DCM/0 °C/Ar.

multiplicity of the signal for H-3 and OH in **7**, **12**, **14** and **15**. A broad singlet for OH protons and a doublet for H-3 around 3.71–4.4 ppm with ^3J = 10–11 Hz in **7**, **12**, **14** and 3.1 Hz in **15** clearly indicate that the azido substituent is attached to C-3 and OH to C-2. This constitution was corroborated by the comparison of the chemical shifts of C-2 and C-3 of the products. In the case of diazides **8a**, **8b** and **13** these signals appear at ~90 ppm (C-2) and 60 ppm (C-3) respectively, which is well correlated with the signal of C-3 of compounds **7**, **9** and **12** (~60 ppm) to indicate the 2-deoxy-2-azido constitution. In the case of benzoylated derivatives **14** and **15** the signals of C-2 correlate well with the C-2 signals of compounds **7**, **9** and **12** (~95 ppm) but the benzoyl protecting groups of **14** and **15** cause a downfield shift of the signal of C-3 with ~4 ppm. The configuration of the anomeric center in diazides **8a**, **8b** could be determined by measuring heteronuclear coupling constants ($^3J_{H\text{-}C}$) between H-3 and C-1 using HSQMBC experiments [30] (Scheme 8, Table 7). These atoms are in a *gauche* relative position in isomer **8a**, and in a *trans*-diaxial position in **8b** as indicated by the smaller/larger coupling constants, respectively.

Although in the cases of **7**, **9**–**13** only single stereoisomers were formed, the measured $^3J_{H\text{-}C}$ coupling constants in the range of 1.9–2.5 Hz strongly suggested the α(D) configuration of the anomeric center (Table 7).

Beside the $^3J_{H\text{-}C}$ coupling constants the chemical shifts of H-4 and H-6 can be considered as another evidence of the anomeric configuration of the products. While the chemical shifts of H-4 and H-6 of **8a** (with an equatorial $CONH_2$ group at C-2) are ~5.1 ppm and ~4.4 ppm, respectively, in the case of **8b** (with an axial $CONH_2$ group at C-2) these signals showed 0.4–0.6 ppm downfield shifts to 5.7 ppm and 4.8 ppm,

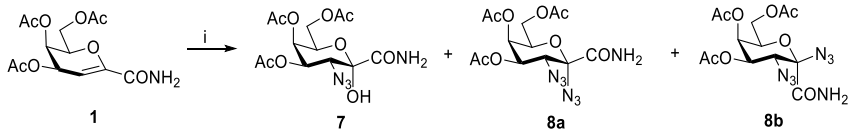
Table 5
Effect of the solvent.



Entry	Solvent	Reaction time (h)	Conversion (%)	Product yield (%)	
				7	**11**
1	dry toluene	no reaction	–	–	–
2	dry ACN	0.42	100	30	22
3[a]	dry ACN	1.33	100	13	38

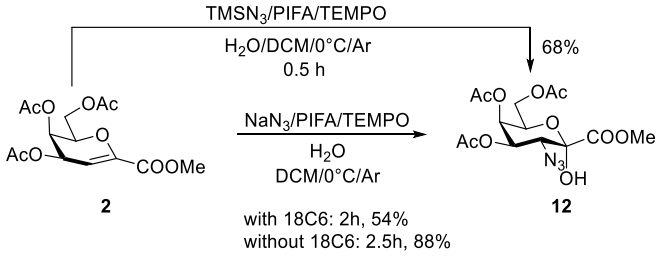
[a] The reaction was carried out without added water. i: 3 equiv. NaN_3/2 equiv. PIFA/0.3 equiv. TEMPO/0.2 equiv. 18-crown-6/50 equiv. H_2O/solvent/0 °C/Ar.

Table 6
Effect of the reagent combinations.

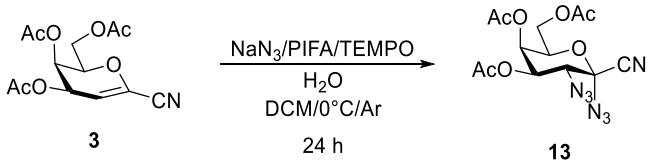


Entry	Omitted reagent	Reaction time (min)	Conversion (%)	Product yield (%)		
				7	**8a**	**8b**
1	NaN_3	no reaction	–	–	–	–
2[a]	H_2O	no reaction	–	–	–	–
3	PIFA	no reaction	–	–	–	–
4	TEMPO	20	100	–		37 (**8a**: **8b** = 70 : 30)[b]
5	18C6	75	100	52	–	–

[a] Based on the TLC of the reaction mixture.
[b] Product ratio based on the ^{1}H NMR spectrum of the inseparable mixture. i: 3 equiv. NaN_3/2 equiv. PIFA/0.3 equiv. TEMPO/0.2 equiv. 18-crown-6/50 equiv. H_2O/dry DCM/0 °C/Ar.



Scheme 4. Azidohydroxylation of 1-methoxycarbonyl glycal **2**.



Scheme 5. Transformation of 1-cyano-glycal **3** under azidohydroxylation conditions.

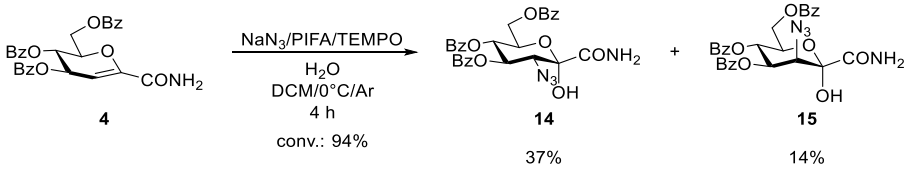
respectively. The chemical shifts of these protons (Table 7) of the acetyl protected compounds **7**, **9**, **10**, **12** and **13** correlated well with the values of **8a** proving the equatorial position of the carbamoyl (**7**, **9**, **10**), methoxycarbonyl (**12**) and nitrile (**13**) substituent at the C-2 carbon.

The low solubility of benzoylated derivatives **14** and **15** did not allow to record the HSQMBC spectra because a sufficiently concentrated solution could not be made. The configuration of these compounds was proved by the comparison of the chemical shifts of skeleton protons with compounds **7**, **8a**, **9**, **10**, **12** and **13**. The chemical shifts of H-6 proton matched well (~4.5 ppm), but the H-4 signal of **14** and **15** showed a 0.6 ppm downfield shift from 5.4 ppm to ~6.00 ppm due to the anisotropic effect of the benzoyl groups. These data agree well with the chemical shifts of compound **17** [31] proving the identical configuration at C-2.

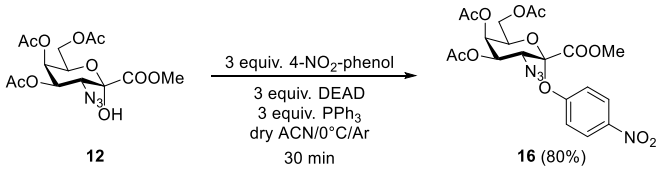
To establish the anomeric configuration of **16** the $^3J_{COOMe\text{-}H3}$ coupling constant of 2.1 Hz was obtained from a HSQMBC experiment to strongly suggest the equatorial position of the COOMe group attached to C-2. In addition, NOE effects were observed between the sugar H-6 and the aromatic H-2'/H-6' protons of the 4-nitrophenyl ring that confirmed the α(D) configuration (Scheme 9).

2.2. Mechanistic considerations

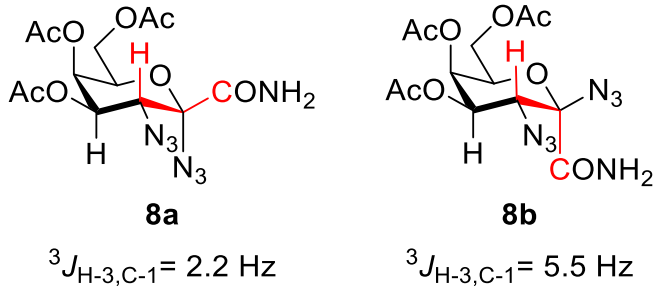
Due to the complexity of the reaction conditions a detailed mechanistic picture is hard to outline, but the main features of these transformations may be explained. The hypervalent iodine(III) compounds show both ionic [32] and radical reactivity [33] however, using a NaN_3/PIFA/TEMPO system the radical pathway is more relevant, and formation of an azide radical is the most probable [33,34]. Formula **A** shows the possible trajectories of the azide radical attack on the most stable $^5H_6$ conformation of glycals (Scheme 10). The α-/β-side attack of the azide radical can result in the capto-dative radicals **C/E**, but the addition from the α-side is more favorable due to the PGO group at the



Scheme 6. Azidohydroxylation of 1-carbamoyl glycal **4**.



Scheme 7. Transformation of compound **12** to *O*-glycoside **16** under Mitsunobu conditions.



Scheme 8. Heteronuclear coupling constant of the red-marked nuclei in **8a** and **8b** determined by HSQMBC experiments.

C-4 position, and this is even more pronounced with an axial PGO at the C-5 carbon. The further transformations of radicals **C** and **E** can be interpreted in two ways: a) the nucleophile present may react with them from the axial direction, which is characteristic of glycosyl radicals [35] to form radical anions **F** and **G** which can be oxidized by PIFA to give the final products **I** and **K**; b) the glycosyl radicals **C** and **E** can be oxidized by PIFA to form glycosyl cations **B** and **D**. The α-/β-side attack of these cations with nucleophiles may lead to compounds **I**, **K** *vs* **H**, **J**, respectively. Formation of α anomers **I**, **K** may be preferable due to the kinetic anomeric effect and can be explained also by the stereoelectronically favored attack of the nucleophiles on the more stable $_4H^5$ conformation of the cyclic oxocarbenium ion [36]. The α-side attack of the nucleophiles may result in a more stable chair-like conformation of the transition state in contrast with a less stable twisted boat conformation of the TS that might be formed by a β-side attack.

The observed regio- and stereoselectivities of these azidohydroxylations correlated well with known literature data for the functionalization of glycals with heteroatom or carbon radicals [37–40].

3. Conclusion

The azidohydroxylation reaction of 1-C-acceptor substituted glycals was studied and optimized using $TMSN_3$ and NaN_3 as azide sources in the presence of PIFA, TEMPO, water and phase transfer catalysts in dry dichloromethane. The optimization process revealed that the highest yield could be reached with NaN_3/PIFA/TEMPO/H_2O in dry dichloromethane without phase transfer catalyst. These conditions significantly differ from the reported ones [12]. Azidohydroxylation of *O*-peracetylated D-*lyxo* configured 1-carbamoyl and 1-methoxycarbonyl glycals gave the corresponding 2-azido-2-deoxy products with D-*galacto* configuration exclusively. With *O*-perbenzoylated D-*arabino* glycals, D-*gluco* and D-*manno* configured products were formed from the 1-carbamoyl substituted derivative with a D-*gluco* preference. In this series, the 1-methoxycarbonyl glycal gave an inseparable product mixture, while the 1-cyano glycal proved unreactive. The application of an azidohydroxylated derivative in a glycosylation reaction with 4-nitrophenol using Mitsunobu condition was also demonstrated. This study has revealed that an acceptor substituent in the 1-position of glycals can very significantly change the reactivity of the parent compounds and demonstrated the closest resemblance of 1-carbamoyl glycals and unsubstituted ones.

4. Experimental

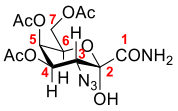
4.1. General methods

The solvents were purified by distillation. Dichloromethane and acetonitrile were refluxed and distilled from P_4O_{10} and stored over 4 Å molecular sieves. Toluene was purified by extraction, dried over $CaCl_2$ and distilled and stored over sodium wires. Optical rotations were determined with a Perkin–Elmer 241 polarimeter at room temperature. IR spectra were recorded on Jasco FT/IR4100 spectrometer. NMR spectra were recorded with Bruker AM Avance DRX 360 MHz (360/91 MHz for $^1H/^{13}C$) or Bruker AM Avance I 400 MHz (400/101 MHz for $^1H/^{13}C$) or Bruker AM Avance II 500 MHz (500/126 MHz for $^1H/^{13}C$) spectrometers. Chemical shifts are referenced to TMS as the internal reference (^1H), or to the residual solvent signals (^{13}C). The assignments of the ^1H and ^{13}C NMR signals of compounds **7**–**16** performed by their COSY and HSQC spectra. The heteronuclear coupling constants ($^3J_{H\text{-}C}$) were determined by HSQMBC experiments. Mass spectra were recorded with maXis II UHR ESI-QTOF MS (Bruker Daltonik, Bremen, Germany) instruments in positive ion mode with electrospray ionization technique. TLC was performed on DC Kieselgel 60 F_{254} (Merck). TLC plates were visualized under 254 nm UV light and/or heating the plates after spraying with one of the following solutions: EtOH/cc. H_2SO_4/*p*-anisaldehyde (95:5:1) or $(NH_4)_6Mo_7O_{24}$/cc. H_2SO_4/H_2O (22 g/20 ml/400 ml). For the flash column chromatography flash silica gel [VWR Chemicals, particle size (40–63 μm)] was applied.

4.2. General procedure for optimization of the azidohydroxylation reactions

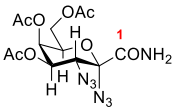
In a flame dried round bottom flask, the corresponding glycal was dissolved in dry solvent, and the solution was cooled down to 0 °C. Under argon atmosphere, the appropriate amount of azide source, the phase transfer catalyst, the hypervalent iodine compound, TEMPO and the water were added. The reaction mixture was stirred at 0 °C and monitored by TLC. After complete conversion (or when no further change was observed), the reaction was quenched with saturated aqueous sodium hydrogen carbonate solution and stirred for further 10 min at room temperature. The aqueous layer was extracted with dichloromethane, then the combined organic layers were washed with water and saturated aqueous sodium chloride solution and dried over anhydrous magnesium sulfate. The drying agent was filtered off, and the solution was concentrated under vacuum. The crude product was purified by flash column chromatography.

Table 7
Characteristic NMR data of compounds **7**–**13** (δ, ^3J).



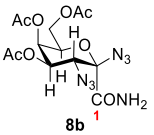
7

	H-3	H-4	H-6	C-2	C-3
δ (ppm)	3.83	5.38	4.47	95.43	60.02
$^3J_{H,H}$ (Hz)	10.8	10.8, 3.3	6.6, 1.2	–	–
$^3J_{H\text{-}3,C\text{-}1}$ (Hz)			2.2		



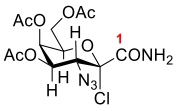
8a

	H-3	H-4	H-6	C-2	C-3
δ (ppm)	3.98	5.14	4.37	90.49	60.19
$^3J_{H,H}$ (Hz)	10.7	10.6, 3.1	6.30	–	–
$^3J_{H\text{-}3,C\text{-}1}$ (Hz)			2.2		



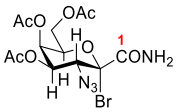
8b

	H-3	H-4	H-6	C-2	C-3
δ (ppm)	3.96	5.70	4.83	89.46	61.36
$^3J_{H,H}$ (Hz)	10.6	10.7, 3.2	6.5, 1.2	–	–
$^3J_{H\text{-}3,C\text{-}1}$ (Hz)			5.5		



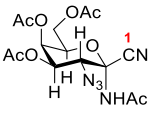
9

	H-3	**H-4**	**H-6**	**C-2**	**C-3**
δ (ppm)	4.37	5.17	4.50	100.00	60.24
$^3J_{H,H}$ (Hz)	10.8	10.7, 3.2	6.4, 1.1	–	–
$^3J_{H\text{-}3,C\text{-}1}$ (Hz)			1.9		



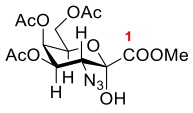
10

	H-3	**H-4**	**H-6**	**C-2**	**C-3**
δ (ppm)	4.03	5.12	4.46	97.01	60.77
$^3J_{H,H}$ (Hz)	10.6	10.8, 3.2	6.2	–	–
$^3J_{H\text{-}3,C\text{-}1}$ (Hz)			–		



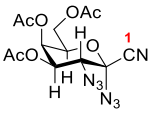
11

	H-3	H-4	H-6	C-2	C-3
δ (ppm)	4.32	5.12	4.22–4.13	78.29	60.73
$^3J_{H,H}$ (Hz)	10.9	10.9, 3.30	–	–	–
$^3J_{H\text{-}3,C\text{-}1}$ (Hz)			2.1		



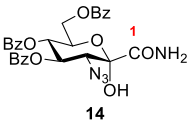
12

	H-3	H-4	H-6	C-2	C-3
δ (ppm)	4.00–4.19	5.37	4.48	95.65	58.40
$^3J_{H,H}$ (Hz)	–	11.0, 3.3	6.7, 1.5	–	–
$^3J_{H\text{-}3,C\text{-}1}$ (Hz)			2.4		



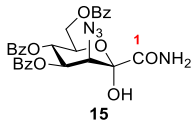
13

	H-3	H-4	H-6	C-2	C-3
δ (ppm)	4.08	5.15	4.37	87.44	59.94
$^3J_{H,H}$ (Hz)	10.7	10.7, 3.1	7.2, 5.9, 1.4	–	–
$^3J_{H\text{-}3,C\text{-}1}$ (Hz)			2.5		



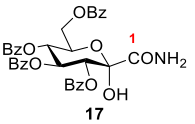
14

	H-3	**H-4**	**H-6**	**C-2**	**C-3**
δ (ppm)	3.71	6.00	4.68–4.61	95.35	64.03
$^3J_{H,H}$ (Hz)	10.2	9.9	–	–	–
$^3J_{H\text{-}3,C\text{-}1}$ (Hz)			–		



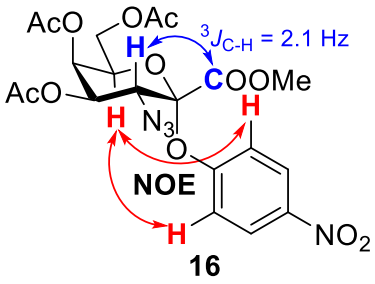
15

	H-3	**H-4**	**H-6**	**C-2**	**C-3**
δ (ppm)	4.39	6.06	4.56	94.78	63.68
$^3J_{H,H}$ (Hz)	3.1	10.0, 3.2	9.3, 4.5, 2.6	–	–
$^3J_{H\text{-}3,C\text{-}1}$ (Hz)			–		



17 ref. [31]

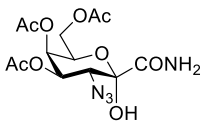
	H-3	**H-4**	**H-6**	**C-2**
δ (ppm)	5.67	6.22	4.70	94.47
$^3J_{H,H}$ (Hz)	9.9	9.6	2.8	–
$^3J_{H\text{-}3,C\text{-}1}$ (Hz)			–	



16

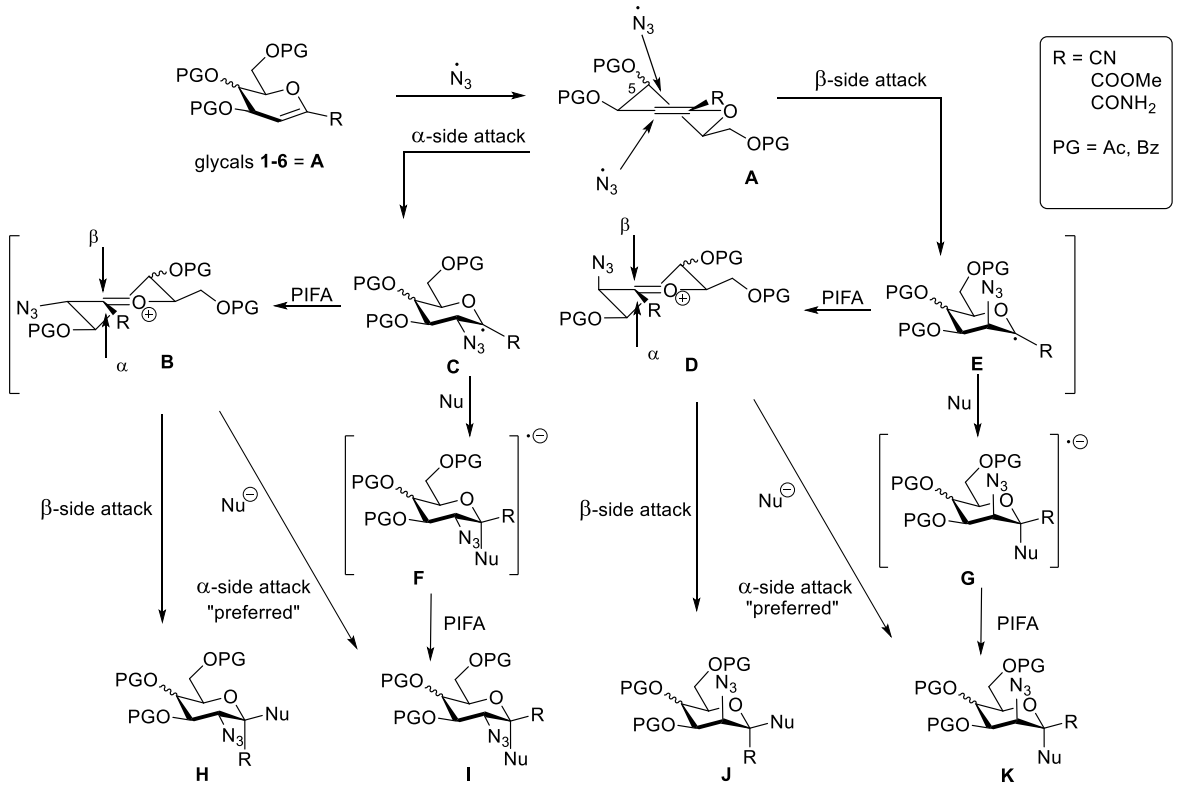
Scheme 9. Detected NOE effect and HSQMBC of **16**.

4.3. 4,5,7-Tri-O-acetyl-3-azido-3-deoxy-α-D-galacto-hept-2-ulopyranosonamide (7)



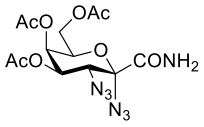
7

31 mg glycal **1** (0.098 mmol, 1 equiv.) and 1.8 ml dry dichloromethane, 19 mg NaN_3 (0.29 mmol, 3 equiv.), 82 mg PIFA (0.19 mmol, 2 equiv.), 5 mg TEMPO (0.032 mmol, 0.3 equiv.) and 86 μl H_2O (4.78 mmol, 50 equiv) were used according to general procedure. Reaction time: 1.25 h. The reaction mixture was quenched with 1.2 ml saturated sodium hydrogen carbonate solution and stirred for further 10 min at room temperature. After the extraction (3 × 3 ml dichloromethane, 1 × 3 ml water, 1 × 3 ml saturated NaCl solution) the crude product was purified by flash column chromatography (eluent: hexane: acetone = 3 : 1) to give 19 mg (52%) of compound **7** as a colorless syrup. R_f = 0.30 (eluent: hexane: acetone = 1 : 1). $[\alpha]_D$ +37 (c 0.32, DCM). ^{1}H NMR (400 MHz, $CDCl_3$) δ(ppm): 6.43 (s, 1H, $CONH_2$), 6.16 (s, 1H, $CONH_2$), 5.50 (dd, J = 3.2, 1.2 Hz, 1H, H-5), 5.38 (dd, J = 10.8, 3.3 Hz, 1H, H-4), 5.10 (s, 1H, OH), 4.48 (td, J = 6.6, 1.4 Hz, 1H, H-6), 4.19–4.07 (m, 2H, H-7, H-7'), 3.84 (d, J = 10.8 Hz, 1H, H-3), 2.18 (s, 3H, CH_3CO), 2.07 (s, 3H, CH_3CO), 2.05 (s, 3H, CH_3CO). ^{13}C NMR (101 MHz, $CDCl_3$) δ(ppm): 170.73, 170.38, 170.09, 169.88 (C═O), 95.43 (C-2), 69.39 (C-4), 69.32 (C-6), 67.52 (C-5), 61.43 (C-7), 60.02 (C-3), 20.83, 20.77 (CH_3CO). IR (KBr, cm^{-1}): 2116 (N_3), 3351 (OH). ESI HRMS positive mode *m/z*: calculated $C_{13}H_{18}N_4NaO_9^+$ $[M+Na]^+$ 397.0966, found 397.0959.



Scheme 10. Interpretation of the regio- and stereochemical outcomes of azidohydroxylation.

*4.4. (4,5,7-Tri-O-acetyl-3-azido-3-deoxy-α-D-galacto-hept-2-ulopyranosylazide)onamide (**8a**)*

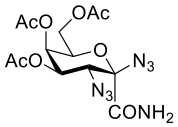


8a

100 mg glycal **1** (0.32 mmol, 1 equiv.) and 6 ml dry dichloromethane, 125 μl $TMSN_3$ (0.94 mmol, 3 equiv.), 15 mg $BnEt_3NCl$ (0.065 mmol, 0.2 equiv.), 204 mg PIDA (0.63 mmol, 2 equiv.), 10 mg TEMPO (0.064 mmol, 0.2 equiv.), and 285 μl H_2O (15.8 mmol, 50 equiv.) were used according to general procedure. Reaction time: 3 h. The reaction mixture was quenched with 4 ml saturated sodium hydrogen carbonate solution and stirred for further 10 min at room temperature. After the extraction (3 × 10 ml dichloromethane, 1 × 10 ml water, 1 × 10 ml saturated NaCl solution) the crude product was purified by flash column chromatography (eluent: hexane: acetone = 3 : 1) to give 47 mg (conversion: 92%, corrected yield: 40%) of compound **8a** as a white amorphous solid. $R_f = 0.52$ (eluent: hexane: acetone = 1 : 1). $[\alpha]_D$ +92 (c 0.23, DCM).

^{1}H NMR (360 MHz, $CDCl_3$) δ(ppm): 6.57 (s, 1H, $CONH_2$), 6.36 (s, 1H, $CONH_2$), 5.47 (dd, *J* = 3.2, 1.3 Hz, 1H, H-5), 5.14 (dd, *J* = 10.7, 3.2 Hz, 1H, H-4), 4.37 (ddd, *J* = 7.0, 5.4, 1.3 Hz, 1H, H-6), 4.26 (dd, *J* = 11.5, 7.2 Hz, 1H, H-7), 4.11 (dd, *J* = 11.5, 5.4 Hz, 1H, H-7'), 3.99 (d, *J* = 10.6 Hz, 1H, H-3), 2.18 (s, 3H, CH_3CO), 2.08 (s, 3H, CH_3CO), 2.07 (s, 3H, CH_3CO). ^{13}C NMR (91 MHz, $CDCl_3$) δ(ppm): 170.71, 169.94, 169.71, 167.30 (C═O), 90.48 (C-2), 70.85 (C-6), 69.53 (C-4), 66.83 (C-5), 61.50 (C-7), 60.19 (C-3), 20.80, 20.71 (CH_3CO). IR (KBr, cm^{-1}): 2118 (N_3). ESI HRMS positive mode *m/z:* calculated $C_{13}H_{17}N_7NaO_8^+$ $[M+Na]^+$ 422.1031, found 422.1027.

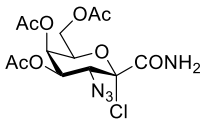
*4.5. (4,5,7-Tri-O-acetyl-3-azido-3-deoxy-β-D-galacto-hept-2-ulopyranosylazide)onamide (**8b**)*



8b

101 mg glycal **1** (0.32 mmol, 1 equiv.) and 6 ml dry dichloromethane, 208 μl $TMSN_3$ (1.6 mmol, 5 equiv.), 15 mg $BnEt_3NCl$ (0.066 mmol, 0.2 equiv.), 273 mg PIFA (0.63 mmol, 2 equiv.), 10 mg TEMPO (0.064 mmol, 0.2 equiv.) and 285 μl H_2O (15.8 mmol, 50 equiv.) were used according to general procedure. Reaction time: 2 h. The reaction mixture was quenched with 4 ml saturated sodium hydrogen carbonate solution and stirred for further 10 min at room temperature. After the extraction (3 × 10 ml dichloromethane, 1 × 10 ml water, 1 × 10 ml saturated NaCl solution) the crude product was purified by flash column chromatography (eluent: hexane: acetone = 3 : 1) to give 17 mg (13%) of compound **8b** as a white amorphous solid beside compounds **7** (18%), **8a** (21%) and **9** (20%) (**8a**: **9** = 52 : 48). $R_f = 0.62$ (eluent: hexane: acetone = 1 : 1). $[\alpha]_D$ −37 (c 0.33, DCM). ^{1}H NMR (500 MHz, $CDCl_3$) δ(ppm): 6.60 (s, 1H, $CONH_2$), 5.76 (s, 1H, $CONH_2$), 5.70 (dd, *J* = 10.7, 3.2 Hz, 1H, H-4), 5.51 (dd, *J* = 3.1, 1.2 Hz, 1H, H-5), 4.83 (td, *J* = 6.5, 1.2 Hz, 1H, H-6), 4.17 (dd, *J* = 11.3, 6.6 Hz, 1H, H-7), 4.10 (dd, *J* = 11.3, 6.4 Hz, 1H, H-7'), 3.96 (d, *J* = 10.6 Hz, 1H, H-3), 2.18 (s, 3H, CH_3CO), 2.06 (s, 3H, CH_3CO), 2.04 (s, 3H, CH_3CO). ^{13}C NMR (91 MHz, $CDCl_3$) δ(ppm): 170.46, 169.93, 169.42, 167.19 (C═O), 89.46 (C-2), 72.70 (C-6), 70.29 (C-4), 66.88 (C-5), 61.44 (C-7), 61.36 (C-3), 20.77, 20.73, 20.65 (CH_3CO). IR (KBr, cm^{-1}): 2117 (N_3). ESI HRMS positive mode *m/z:* calculated $C_{13}H_{17}N_7NaO_8^+$ $[M+Na]^+$ 422.1031, found 422.1028.

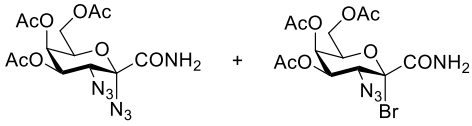
4.6. (4,5,7-Tri-O-acetyl-3-azido-3-deoxy-α-D-galacto-hept-2-ulopyranosylchloride)onamide (9)



9

101 mg glycal **1** (0.32 mmol, 1 equiv.) and 6 ml dry dichloromethane, 42 μl $TMSN_3$ (0.32 mmol, 1 equiv.), 15 mg $BnEt_3NCl$ (0.064 mmol, 0.2 equiv.), 273 mg PIFA (0.63 mmol, 2 equiv.), 10 mg TEMPO (0.064 mmol, 0.2 equiv.), 285 μl H_2O (15.8 mmol, 50 equiv.) were used according to general procedure. Reaction time: 3 h. The reaction mixture was quenched with 4 ml saturated sodium hydrogen carbonate solution and stirred for further 10 min at room temperature. After the extraction (3 × 10 ml DCM, 1 × 10 ml H_2O, 1 × 10 ml saturated NaCl solution) the crude product was purified by flash column chromatography (eluent: hexane: acetone = 3 : 1) to give 15 mg (14%) of compound **9** as a colorless syrup. $R_f = 0.52$ (eluent: hexane: acetone = 1 : 1). $[\alpha]_D$ +77 (c 0.21, DCM). ^1H NMR (500 MHz, $CDCl_3$) δ(ppm): 6.57 (s, 1H, $CONH_2$), 6.34 (s, 1H, $CONH_2$), 5.50 (dd, $J = 3.1$, 1.1 Hz, 1H, H-5), 5.17 (dd, $J = 10.7$, 3.2 Hz, 1H, H-4), 4.50 (td, $J = 6.4$, 1.1 Hz, 1H, H-6), 4.37 (d, $J = 10.8$ Hz, 1H, H-3), 4.24–4.14 (m, 2H, H-7, H-7′), 2.18 (s, 3H, CH_3CO), 2.08 (s, 3H, CH_3CO), 2.07 (s, 3H, CH_3CO). ^{13}C NMR (126 MHz, $CDCl_3$) δ(ppm): 170.46, 169.93, 169.71, 166.80 (C═O), 100.00 (C-2), 72.09 (C-6), 69.79 (C-4), 66.40 (C-5), 61.07 (C-7), 60.24 (C-3), 20.73, 20.66 (**C**H_3CO). IR (KBr, cm^{-1}): 2121 (N_3). ESI HRMS positive mode *m/z:* calculated $C_{13}H_{17}ClN_4NaO_8^+$ $[M+Na]^+$ 415.0627. found 415.0617.

4.7. (4,5,7-Tri-O-acetyl-3-azido-3-deoxy-α-D-galacto-hept-2-ulopyranosylazide)onamide (8a) and (4,5,7-tri-O-acetyl-3-azido-3-deoxy-α-D-galacto-hept-2-ulopyranosylbromide)onamide (10)



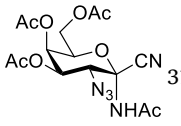
8a **10**

103 mg glycal **1** (0.33 mmol, 1 equiv.) and 6 ml dry dichloromethane, 125 μl $TMSN_3$ (0.94 mmol, 3 equiv.), 21 mg Bu_4NBr (0.065 mmol, 0.2 equiv.), 279 mg PIFA (0.65 mmol, 2 equiv.), 10 mg TEMPO (0.064 mmol, 0.2 equiv.) and 285 μl H_2O (15.8 mmol, 50 equiv.) were used according to general procedure. Reaction time: 4 h. The reaction mixture was quenched with 4 ml saturated sodium hydrogen carbonate solution and stirred for further 10 min at room temperature. After the extraction (3 × 10 ml dichloromethane, 1 × 10 ml water, 1 × 10 ml saturated NaCl solution) the crude product was purified by flash column chromatography (eluent: hexane: acetone = 3 : 1) to give 40 mg of a mixture of compounds **8a** (14%) and **10** (19%) as a white amorphous solid (**5a**: **7** = 40 : 60) beside compound **7** (13%). $R_f = 0.42$ (eluent: hexane: acetone = 1 : 1).

The characteristic NMR data of compound **10** were obtained from the NMR spectra of the mixture, using the fact that compound **10** was synthesized in pure form in a separate yet unpublished azidobromination of **1**.

10: $[\alpha]_D$ +77 (c 0.10, DCM). ^1H NMR (360 MHz, $CDCl_3$) δ(ppm): 6.46 (s, 1H, $CONH_2$), 5.77 (s, 1H, $CONH_2$), 5.50 (dd, $J = 3.3$, 1.3 Hz, 1H, H-5), 5.11 (dd, $J = 10.6$, 3.2 Hz, 1H, H-4), 4.45 (t, $J = 6.2$ Hz, 1H, H-6), 4.24 (dd, $J = 11.6$, 6.6 Hz, 1H, H-7), 4.18 (dd, $J = 11.5$, 6.0 Hz, 1H, H-7′), 4.04 (d, $J = 10.6$ Hz, 1H, H-3), 2.17 (s, 3H, CH_3CO), 2.08 (s, 6H, CH_3CO). ^{13}C NMR (91 MHz, $CDCl_3$) δ(ppm): 170.55, 169.89, 169.74, 167.39 (C═O), 97.08 (C-2), 73.60 (C-6), 70.46 (C-4), 66.09 (C-5), 60.99 (C-7), 60.80 (C-3), 20.80, 20.71 (CH_3CO). IR (KBr, cm^{-1}): 2125 (N_3). ESI HRMS positive mode *m/z:* calculated $C_{13}H_{17}BrN_4NaO_8^+$ $[M+Na]^+$ 459.0122, found 459.0122.

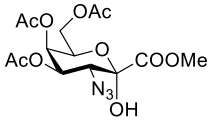
4.8. 2-Acetamido-4,5,7-tri-O-acetyl-3-azido-2,3-dideoxy-α-D-galacto-hept-2-ulopyranosononitrile (11)



11

31 mg glycal **1** (0.098 mmol, 1 equiv.), 1.8 ml dry acetonitrile, 19 mg NaN_3 (0.29 mmol, 3 equiv.), 6 mg 18-crown-6 (0.023 mmol, 0.2 equiv.), 82 mg PIFA (0.19 mmol, 2 equiv.) and 4 mg TEMPO (0.026 mmol, 0.3 equiv.) were used according to general procedure. Reaction time: 1.33 h. The reaction mixture was quenched with 1.2 ml saturated sodium hydrogen carbonate solution and stirred for further 10 min at room temperature. After the extraction (3 × 3 ml dichloromethane, 1 × 3 ml water, 1 × 3 ml saturated NaCl solution) the crude product was purified by flash column chromatography (eluent: hexane: acetone = 4 : 1) to give 15 mg (38%) of compound **11** as a white amorphous solid beside compound **7** (13%). $R_f = 0.35$ (eluent: hexane: acetone = 1 : 1). $[\alpha]_D$ +9 (c 0.22, DCM). ^1H NMR (500 MHz, $CDCl_3$) δ(ppm): 6.83 (s, 1H), 5.34 (d, $J = 2.9$ Hz, 1H, H-5), 5.12 (dd, $J = 10.9$, 3.3 Hz, 1H, H-4), 4.31 (d, $J = 10.9$ Hz, 1H, H-3), 4.21–4.14 (m, 2H, H-6, H-7), 4.09–4.02 (m, 1H, H-7'), 2.21 (s, 3H, CH_3CO), 2.16 (s, 3H, CH_3CO), 2.11 (s, 3H, CH_3CO), 2.03 (s, 3H, CH_3CO). ^{13}C NMR (101 MHz, $CDCl_3$) δ(ppm): 170.59, 170.25, 170.16 (C═O), 115.30 (CN), 78.29 (C-2), 69.23 (C-4), 68.09 (C-6), 66.03 (C-5), 60.84 (C-7), 60.73 (C-3), 23.30, 20.73 (CH_3CO). IR (KBr, cm^{-1}): 2130 (CN, N_3), 3343 (NH). ESI HRMS positive mode *m/z:* calculated $C_{15}H_{19}N_5NaO_8^+$ $[M+Na]^+$ 420.1126, found 420.1124.

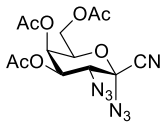
4.9. Methyl (4,5,7-tri-O-acetyl-3-azido-3-deoxy-α-D-galacto-hept-2-ulopyranosonate) (12)



12

31 mg glycal **2** (0.094 mmol, 1 equiv.), 1.8 ml dry dichloromethane, 18 mg NaN_3 (0.28 mmol, 3 equiv.), 78 mg PIFA (0.18 mmol, 2 equiv.), 5 mg TEMPO (0.032 mmol, 0.3 equiv.) and 82 μl H_2O (4.56 mmol, 50 equiv.) were used according to general procedure. Reaction time: 2.5 h. The reaction mixture was quenched with 1.2 ml saturated sodium hydrogen carbonate solution and stirred for further 10 min at room temperature. After the extraction (3 × 3 ml dichloromethane, 1 × 3 ml water, 1 × 3 ml saturated NaCl solution) the crude product was purified by flash column chromatography (eluent: hexane: ethyl acetate = 4 : 1) to give 32 mg (88%) of compound **12** as a white amorphous solid. $R_f = 0.30$ (eluent: hexane: ethyl acetate = 1 : 1). $[\alpha]_D$ +49 (c 0.28, DCM). ^1H NMR (500 MHz, $CDCl_3$) δ(ppm): 5.51–5.47 (m, 1H, H-5), 5.37 (ddd, $J = 11.1$, 3.3, 1.0 Hz, 1H, H-4), 4.47 (t, $J = 6.7$ Hz, 1H, H-6), 4.39 (s, 1H, OH), 4.13 (dd, $J = 11.9$, 7.4 Hz, 1H, H-7), 4.10 (d, $J = 12.2$ Hz, 1H, H-3), 4.05 (dd, $J = 11.3$, 6.6 Hz, 1H, H-7′), 3.95 (s, 3H, OCH_3), 2.18 (s, 3H, CH_3CO), 2.06 (s, 3H, CH_3CO), 2.04 (s, 3H, CH_3CO). ^{13}C NMR (126 MHz, $CDCl_3$) δ(ppm): 170.2, 170.22, 169.79, 168.19 (C═O), 95.65 (C-2), 69.04 (C-4), 68.84 (C-6), 67.48 (C-5), 61.38 (C-7), 58.40 (C-3), 54.32 (OCH_3), 20.79, 20.75 (CH_3CO). IR (KBr, cm^{-1}): 2115 (N_3), 3436 (OH). ESI HRMS positive mode *m/z:* calculated $C_{14}H_{19}N_3NaO_{10}^+$ $[M+Na]^+$ 412.0963, found 412.0963.

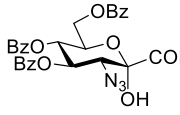
4.10. (4,5,7-Tri-O-acetyl-3-azido-3-deoxy-α-D-galacto-hept-2-ulopyranosylazide)ononitrile (13)



13

30 mg glycal **3** (0.10 mmol, 1 equiv.), 1.8 ml dry dichloromethane, 20 mg NaN_3 (0.31 mmol, 3 equiv.), 87 mg PIFA (0.20 mmol, 2 equiv.), 5 mg TEMPO (0.032 mmol, 0.3 equiv.) and 91 μl H_2O (5.04 mmol, 50 equiv.) were used according to general procedure. Reaction time: 24 h (The reaction was placed for overnight in the fridge.) The reaction mixture was quenched with 1.2 ml saturated sodium hydrogen carbonate solution and stirred for further 10 min at room temperature. After the extraction (3 × 3 ml dichloromethane, 1 × 3 ml water, 1 × 3 ml saturated NaCl solution) the crude product was purified by flash column chromatography (eluent: hexane: ethyl acetate = 4 : 1) to give 15 mg (conversion: 40%, corrected yield: 96%) of compound **13** as a white amorphous solid. $R_f = 0.42$ (eluent: hexane: ethyl acetate = 1 : 1). $[\alpha]_D$ +65 (c = 0.08, DCM). ^{1}H NMR (500 MHz, $CDCl_3$) δ(ppm): 5.45 (dd, $J = 3.1$, 1.1 Hz, 1H, H-5), 5.15 (dd, $J = 10.7$, 3.1 Hz, 1H, H-4), 4.37 (ddd, $J = 7.2$, 5.9, 1.4 Hz, 1H, H-6), 4.17 (dd, $J = 11.6$, 5.9 Hz, 1H, H-7), 4.12 (dd, $J = 11.6$, 7.0 Hz, 1H, H-7'), 4.08 (d, $J = 10.7$ Hz, 1H, H-3), 2.19 (s, 3H, CH_3CO), 2.07 (s, 3H, CH_3CO), 2.07 (s, 3H, CH_3CO). ^{13}C NMR (91 MHz, $CDCl_3$) δ(ppm): 170.28, 169.71, 169.29 (C═O), 112.61 (CN), 87.44 (C-2), 70.69 (C-6), 68.33 (C-4), 66.25 (C-5), 60.91 (C-7), 59.94 (C-3), 20.64, 20.60, 20.53 (CH_3CO). IR (KBr, cm^{-1}): 2120 (CN, N_3). ESI HRMS positive mode *m/z:* calculated $C_{13}H_{15}N_7NaO_7^+$ $[M+Na]^+$ 404.0925, found 404.0920.

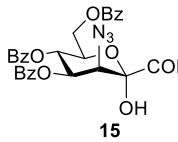
4.11. 4,5,7-Tri-O-benzoyl-3-azido-3-deoxy-α-D-gluco-hept-2-ulopyranosonamide (14)



14

30 mg glycal **4** (0.060 mmol, 1 equiv.), 1.1 ml dry dichloromethane, 12 mg NaN_3 (0.18 mmol, 3 equiv.), 52 mg PIFA (0.12 mmol, 2 equiv.), 3 mg TEMPO (0.019 mmol, 0.3 equiv.) and 54 μl H_2O (3.0 mmol, 50 equiv.) were used according to general procedure. Reaction time: 4 h. The reaction mixture was quenched with 0.8 ml saturated sodium hydrogen carbonate solution and stirred for further 10 min at room temperature. After the extraction (3 × 2 ml dichloromethane, 1 × 2 ml water, 1 × 2 ml saturated NaCl solution) the crude product was purified by flash column chromatography (eluent: hexane: ethyl acetate = 2 : 1 → 1 : 1) to give 12 mg (conversion: 94%, corrected yield: 37%) of compound **14** as a white amorphous solid beside compound **15** (corrected yield: 14%). $R_f = 0.42$ (eluent: hexane: ethyl acetate = 1 : 2). $[\alpha]_D$ + 35 (c 0.21, ACN). ^{1}H NMR (500 MHz, $CDCl_3$) δ(ppm): 8.05–8.00 (m, 2H, aromatics), 7.97–7.92 (m, 2H, aromatics), 7.95–7.90 (m, 2H, aromatics), 7.56 (t, $J = 7.4$ Hz, 1H, aromatics), 7.51 (t, $J = 7.4$ Hz, 2H, aromatics), 7.43 (t, $J = 7.8$ Hz, 2H, aromatics), 7.37 (q, $J = 7.5$ Hz, 4H, aromatics), 6.24 (s, 1H, $CONH_2$), 6.00 (t, $J = 9.9$ Hz, 1H, H-4), 5.71 (t, $J = 9.9$ Hz, 1H, H-5), 5.64 (s, 1H, $CONH_2$), 5.00 (s, 1H, OH), 4.68–4.61 (m, 1H, H-6, overlap with H-7), 4.64–4.59 (m, 1H, H-7, overlap with H-6), 4.47 (dd, $J = 12.6$, 4.9 Hz, 1H, H-7'), 3.71 (d, $J = 10.2$ Hz, 1H, H-3). ^{13}C NMR (126 MHz, $CDCl_3$) δ(ppm): 169.90, 166.32, 165.65, 165.47 (C═O), 133.77, 133.62, 133.43, 130.05, 130.01, 129.90, 129.69, 128.99, 128.63, 128.59 (aromatics), 95.35 (C-2), 71.34 (C-4), 70.76 (C-6), 69.25 (C-5), 64.03 (C-3), 62.80 (C-7). IR (KBr, cm^{-1}): 2108 (N_3). ESI HRMS positive mode *m/z:* calculated $C_{28}H_{24}N_4NaO_9^+$ $[M+Na]^+$ 583.1435, found 583.1435.

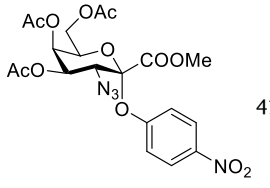
4.12. 4,5,7-Tri-O-benzoyl-3-azido-3-deoxy-α-D-manno-hept-2-ulopyranosonamide (15)



15

30 mg glycal **4** (0.060 mmol, 1 equiv.) and 1.1 ml dry dichloromethane, 12 mg NaN_3 (0.18 mmol, 3 equiv.), 52 mg PIFA (0.12 mmol, 2 equiv.), 3 mg TEMPO (0.019 mmol, 0.3 equiv.) and 54 μl H_2O (3.0 mmol, 50 equiv.) were used according to general procedure. Reaction time: 4 h. The reaction mixture was quenched with 0.8 ml saturated sodium hydrogen carbonate solution and stirred for further 10 min at room temperature. After the extraction (3 × 2 ml dichloromethane, 1 × 2 ml water, 1 × 2 ml saturated NaCl solution) the crude product was purified by flash column chromatography (eluent: hexane: ethyl acetate = 2 : 1 → 1 : 1) to give 5 mg (conversion: 94%, corrected yield: 14%) of compound **15** as a colorless syrup beside compound **14** (corrected yield: 37%). $R_f = 0.22$ (eluent: hexane: ethyl acetate = 1 : 2). $[\alpha]_D$ + 67 (c 0.08, ACN). ^{1}H NMR (400 MHz, $CDCl_3$) δ(ppm): 8.07 (dd, $J = 8.1$, 1.5 Hz, 2H, aromatics), 8.03–7.91 (m, 4H, aromatics), 7.57 (t, $J = 7.5$ Hz, 1H, aromatics), 7.52 (t, $J = 7.5$ Hz, 2H, aromatics), 7.44 (t, $J = 7.7$ Hz, 2H, aromatics), 7.38 (td, $J = 7.9$, 1.9 Hz, 4H, aromatics), 6.69 (s, 1H, $CONH_2$), 6.06 (dd, $J = 9.9$, 3.1 Hz, 1H, H-4), 6.01 (t, $J = 9.7$ Hz, 1H, H-5), 5.82 (s, 1H, $CONH_2$), 4.99 (s, 1H, OH), 4.69 (dd, $J = 12.3$, 2.6 Hz, 1H, H-7), 4.56 (ddd, $J = 9.3$, 4.5, 2.6 Hz, 1H, H-6), 4.45 (dd, $J = 12.3$, 4.5 Hz, 1H, H-7'), 4.39 (d, $J = 3.1$ Hz, 1H, H-3). ^{13}C NMR (101 MHz, $CDCl_3$) δ(ppm): 170.65, 166.66, 165.76, 165.55 (C═O), 133.82, 133.70, 133.41, 130.15, 130.02, 129.94, 129.79, 128.97, 128.65 (aromatics), 94.78 (C-2), 72.06 (C-4), 71.36 (C-6), 66.21 (C-5), 63.68 (C-3), 62.75 (C-7). IR (KBr, cm^{-1}): 3432 (OH), 2114 (N_3). ESI HRMS positive mode *m/z:* calculated $C_{28}H_{24}N_4NaO_9^+$ $[M+Na]^+$ 583.1435, found 583.1427.

4.13. Methyl (p-nitrophenyl 4,5,7-tri-O-acetyl-3-azido-3-deoxy-α-D-galacto-hept-2-ulopyranoside)onate (16)



16

41 mg compound **12** (0.11 mmol, 1 equiv.) was dissolved in 1 ml dry acetonitrile under argon atmosphere, molecular sieves were added, and the solution was cooled down to 0 °C. 82 mg PPh_3 (0.31 mmol, 3 equiv.) and 44 mg 4-NO_2-phenol (0.32 mmol, 3 equiv.) were added. Then 142 μl diethyl azodicarboxylate solution (40% in toluene, ~2,2 mol/l concentration, 0.31 mmol, 3 equiv.) was added dropwise to the reaction mixture, which turned to yellow. After stirring the mixture 30 min at 0 °C, complete conversion was observed based one the TLC monitoring (eluent: hexane: ethyl acetate = 1 : 1). The molecular sieves were filtered off, and the solution was concentrated under vacuum. The crude product was purified by column chromatography (eluent: hexane: acetone = 5 : 1) to give 43 mg (80%) of compound **16** as a colorless syrup. $R_f = 0.48$ (eluent: hexane: ethyl acetate = 1 : 1). $[\alpha]_D$ −6 (c 0.23, DCM). ^{1}H NMR (500 MHz, $CDCl_3$) δ(ppm): 8.22–8.17 (m, 2H, aromatics), 7.27–7.21 (m, 2H, aromatics), 5.53 (dd, $J = 3.2$, 1.5 Hz, 1H, H-5), 5.22 (dd, $J = 11.3$, 3.1 Hz, 1H, H-4), 5.09 (td, $J = 6.6$, 1.5 Hz, 1H, H-6), 4.24 (d, $J = 11.2$ Hz, 1H, H-3), 4.22–4.18 (m, 1H, H-7), 4.17 (dd, $J = 11.3$, 6.4 Hz, 1H, H-7'), 3.76 (s, 3H, OCH_3), 2.18 (s, 3H, CH_3CO), 2.09 (s, 3H, CH_3CO), 2.07 (s, 3H, CH_3CO). ^{13}C NMR (126 MHz, $CDCl_3$) δ(ppm): 170.39, 169.92, 169.59, 166.89 (C═O), 159.33, 143.56, 125.48, 119.01 (aromatics), 101.40 (C-

2), 72.94 (C-6), 69.13 (C-4), 66.27 (C-5), 61.65 (C-7), 61.33 (C-3), 53.55 (OCH_3), 20.78, 20.72, 20.70 (CH_3CO). IR (KBr, cm^{-1}): 2119 (N_3). ESI HRMS positive mode *m/z:* calculated $C_{20}H_{22}N_4NaO_{12}^+$ $[M+Na]^+$ 533.1126, found 533.1126.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.carres.2023.108825.

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