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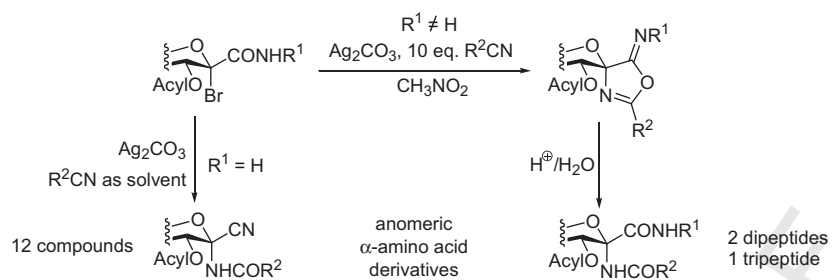
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Graphical abstract

Ritter-type reaction of C-(1-bromo-1-deoxy-D-glycopyranosyl)formamides and its application for the synthesis of oligopeptides incorporating anomeric α -amino acids

pp xxx-xxx

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Katalin Czifrák, Viktor Gyóllai, Katalin E. Kövér, László Somsák*

Department of Organic Chemistry, University of Debrecen, POB 20, H-4010 Debrecen, Hungary

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ABSTRACT

O-Peracetylated or -perbenzoylated C-(1-bromo-1-deoxy-D-glycopyranosyl)formamides of D-glucopyranose, D-galactose, and D-arabino configuration were reacted with Ag(I)-salts or HgO in nitrile solvents to give N-acyl-1-cyano-D-glycopyranosylamines with an axial C–N bond at the anomeric centre. In the presence of HgBr₂, Hg(CN)₂, or InCl₃ the anomer of the above glycosylamine with an equatorial C–N bond was also isolated or detected. In CH₃NO₂ solutions as few as 5–10 equiv of the nitrile were sufficient to get acceptable yields for the products. Under similar conditions N-substituted C-(2,3,4,6-tetra-O-acetyl-1-bromo-1-deoxy- β -D-galactopyranosyl)formamides gave anomeric spiro-oxazoline derivatives which, upon mild acidic hydrolysis, opened up to di- and tripeptides of anomeric α -amino acids.

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1. Introduction

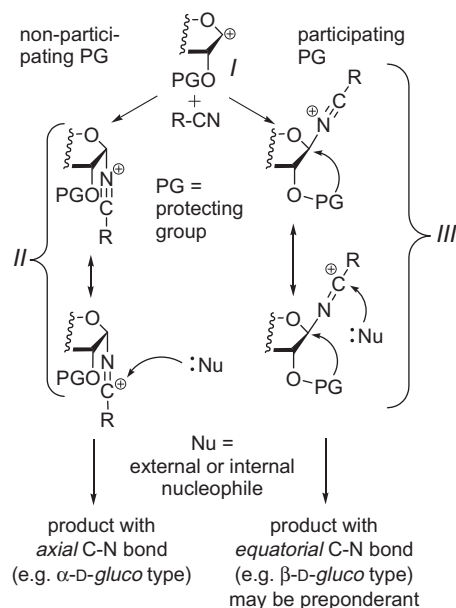
Ritter-type reactions involve combination of a carbocation (carbenium ion) with a nitrile (generally applied in high excess or as the solvent) to give a nitrilium ion which, after ensuing transformations by nucleophiles, may furnish carboxamides as well as heterocycles.^{1,2} Glycosyl-nitrilium ions (II formed from glycosylium ions I and nitriles, Scheme 1) are known to play important roles in directing the stereoselectivity of glycosylation reactions towards the formation of equatorial glycosides.³ On the other hand, attack of various external or internal nucleophiles onto glycosyl-nitrilium ions lead to several types of products rendering these transformations highly valuable in the carbohydrate field as well. Protecting groups in the sugar moieties can have a bearing on the configuration of glycosyl-nitrilium ions which tend to be axial (II) in the presence of non-participating protective groups demonstrated by NMR and computational methods⁴ as well as by the structure of the end-products (vide infra). However, participating protection of the substituent in position 2 may force the formation of equatorial glycosyl-nitrilium ions (III). In these cases high equatorial selectivity can be observed in the products but, interestingly, exclusive axial selectivities were also reported in some transformations.

Thus, in the presence of non-participating 2-substituents, axial N-glycopyranosylamines were obtained from type II intermediates on the action of water,⁵ and N,N-bis-acylamide products were formed with several aromatic carboxylic acids^{6–8} and amino acids^{9–11} as external nucleophiles. Carboxylic acids were also used as internal nucleophiles for the synthesis of several anomeric β -amino acid and peptide derivatives.^{12–15} Further internal O-nucleophiles, such as a 2-O-Zn salt obtained from a 1,2-epoxide¹⁶ and a 2-O-benzyl group¹⁷ gave 1,2-annelated oxazolines, while the CH₂OH appendage of heptulopyranose¹⁸ or fructopyranose¹⁹ derivatives furnished spiro-oxazolines, each with an axial C–N bond at the anomeric carbon. 2-N-Substituents were also observed to attack the axial glycosyl-nitrilium ion and furnished 1,2-annelated imidazolines.^{20,21}

With participating substituents next to the anomeric carbon, the outcome of the reactions is less predictable. With amino acids as well as aromatic carboxylic acids as external nucleophiles 2-deoxy-2-phthalimido²² and 2-deoxy-2-tetrachlorophthalimido¹¹ D-glycopyranosyl derivatives gave equatorial N,N-bis-acylamide type products. Starting from O-perbenzoylated D-glucose, the equatorial amide was formed in low yield accompanied by several by-products in the presence of water as the nucleophile.²³ Under similar conditions O-peracetylated D-glucose, D-galactose, and D-mannose each gave mixtures of axial and equatorial amides with a large excess of the latter. To explain this for the D-mannose case, equilibration of the amides was invoked.²⁴ The internal

* Corresponding author. Tel.: +36 52 512 900/22348; fax: +36 52 512 744.

E-mail address: somsak@tigris.unideb.hu (L. Somsák).



Scheme 1.

nucleophile CH₂OH group of a 3-*O*-benzoyl *D*-fructopyranose derivative gave only one spiro-oxazoline with an axial C–N bond.¹⁹

Unprotected sugars were reported to give 1,2-*cis* configured *N*-glycosylamides in liquid HF with both furanoid and pyranoid rings depending on the sugar configuration.²⁵ *D*-Glucose was converted to *N*-β-*D*-glucopyranosylamides with several nitriles in the presence of TMSOTf–AgClO₄ under mechanochemical conditions.²⁶

Some years ago we reported on the facile transformation of C-(1-bromo-1-deoxy-*D*-glycopyranosyl)formamides into *N*-acyl-1-

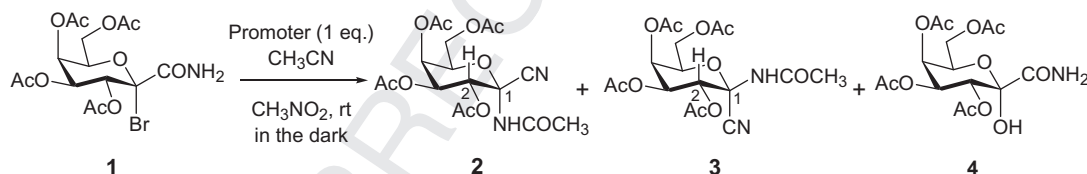
cyano-*D*-glycopyranosylamines in the presence of Ag₂CO₃ in nitriles as solvents.²⁷ In this paper, a detailed investigation of this reaction and its extension to the synthesis of some oligopeptide derivatives with an anomeric α-amino acid moiety are presented.

2. Results and discussion

A Ritter-type reaction of C-(2,3,4,6-tetra-*O*-acetyl-1-bromo-1-deoxy-β-*D*-galactopyranosyl)formamide²⁸ (**1**, Table 1, entry 1) was first observed during an attempted exchange of the bromine to fluorine by AgF in dry CH₃CN. Under such conditions, widely applied for the synthesis of glycosyl fluoride derivatives (see Refs. 29–31 and references cited therein), an unexpected product, actually compound **2** was isolated in 70% yield instead of the expected C-(2,3,4,6-tetra-*O*-acetyl-1-deoxy-1-fluoro-α-*D*-galactopyranosyl)formamide. In the presence of Ag₂CO₃ **1** was transformed to **2** in a very clean reaction (entry 2), while AgOTf gave the same result under significantly shorter reaction time (entry 6). The new product crystallized out during removal of the solvent after the usual work-up, did not exhibit characteristic fluoride couplings, had one exchangeable proton, and five methyl resonances in its ¹H NMR spectrum, and showed a CN signal in the ¹³C NMR spectrum. Vicinal proton–proton couplings indicated that the sugar ring adopted a ⁴C₁ conformation. The CN resonance appeared as a pseudo triplet in the proton coupled carbon spectrum with ~3 Hz splittings due to couplings with H-2 and the NH protons. This allowed us to deduce the equatorial orientation for the CN group based on the ³J_{H-2,CN} coupling in the ⁴C₁ conformation.^{32–34}

Some other promoters³ were also tried to perform this transformation. HgO (entry 7) gave similar results to those obtained with silver salts, but in the presence of HgBr₂, HgO–HgBr₂, Hg(CN)₂, and InCl₃ (entries 8, 12, 13, and 17, respectively) a second product identified as **3**, the anomer of **2**, was also detected and isolated from the mixtures. Appearance of **4**³⁵ in the reaction conducted

Table 1
Reaction of C-(2,3,4,6-tetra-*O*-acetyl-1-bromo-1-deoxy-β-*D*-galactopyranosyl)formamide (**1**) with CH₃CN under various conditions



Entry	Promoter	CH ₃ CN (equiv)	Reaction time	Product ratio (%) by ¹ H NMR		
				2	3	4
1	AgF	As solvent	3 d	70 ^{a,b}	–	–
2	Ag ₂ CO ₃	As solvent	3 d	100	–	–
3		10	5 d	77	–	23
4		5	7 d	68	–	32
5		1.5	12 d	30	–	55 ^c
6	AgOTf	As solvent	1 min	100	–	–
7	HgO	As solvent	8 h	100	–	–
8	HgBr ₂	As solvent	1 d	72	28	–
9		10	1 d	41	33	26
10		5	1 d	30	25	36 ^c
11		1.5	1 d	24	17	46 ^c
12	HgO–HgBr ₂	As solvent	16 h	91	9	–
13	Hg(CN) ₂	As solvent	1 d	84	8	8
14		10	1 d	63	13	13 ^c
15		5	1 d	53	16	21 ^c
16		1.5	1 d	52	10	23 ^c
17	InCl ₃	As solvent	1 d	83	17	–
18		10	1 d	59	29	12
19		5	1 d	71	14	15
20		1.5	1 d	35	24	27 ^c

^a Isolated yield.

^b C-(2,3,4,6-Tetra-*O*-acetyl-1-fluoro-α-*D*-galactopyranosyl)formamide was isolated in ~3% yield from the mother liquor.

^c Together with an unidentified product in ~10–15% ratio.

with Hg(CN)₂ (entry 13) must be due to traces of water in the solvent. The structure of **3** was proven by NMR spectra showing characteristics similar to those of **2**, except for the appearance of the CN resonance as a pseudo triplet type with ~6 Hz coupling constants. Thus, the ³J_{H-2,CN} couplings for **2** and **3** support the gauche and the antiperiplanar arrangements, respectively, of the nuclei involved in the ⁴C₁ conformation, and provide thereby unequivocal evidence for the anomeric configuration of these compounds.^{32–34}

Having in mind the extension of this reaction to nitriles not applicable as solvents, several co-solvents were tried. In the presence of 5 equiv of CH₃CN the transformation of **1** was either incomplete or gave complex product mixtures in CH₂Cl₂, 1,4-dioxane, HMPT, and benzene (in the light of their reactivity alcohols, esters, ketones,³⁶ and sulfoxides³⁶ were not considered as solvents). However, in CH₃NO₂ rather clean reactions were observed: with the mercury(II) salts and InCl₃ (entries 9–11, 14–16, and 18–20, respectively) **2** and **3** were detected and, due to traces of water in the solvent CH₃NO₂, **4** also appeared in increasing ratios as the amount of CH₃CN decreased. A conceivable anomerization of **2** to **3** was excluded by experiments conducted with pure **2** or **3** in CH₃NO₂ in the presence of 2 equiv of HgBr₂ or Hg(CN)₂ showing no change of these compounds even at elevated temperatures such as 100 °C. On the other hand, with Ag₂CO₃ only **4** was observed as a by-product (entries 3–5). Thus, CH₃NO₂ and silver salts facilitate the use of nitriles in smaller excess maintaining the axial selectivity of the reaction.

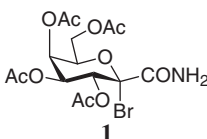
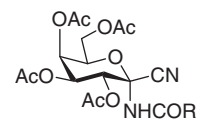
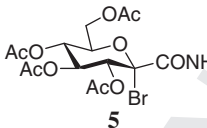
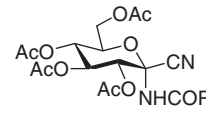
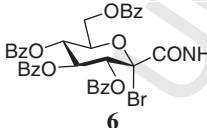
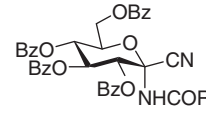
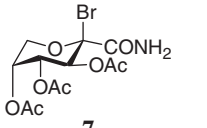
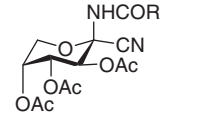
Next the extension of the reaction to other nitriles applied as solvents and to starting C-(1-bromo-1-deoxy-D-glycopyranosyl)formamides **5**,³⁷ **6**,³⁸ and **7**³⁵ besides **1** was investigated (Table 2). In these experiments Ag₂CO₃ was used because of the cost, stability, and easy handling of the reagent. The results show that under these conditions several O-acyl protected 1-acylamino-1-deoxy-D-glycopyranosyl cyanides **8–18** can be obtained in

acceptable to good yields. In each compound the cyano group occupies an equatorial position as shown by the ³J_{H-2,CN} couplings in the range of 2.2–3.2 Hz indicating the incorporation of the nitrile reagent in an axial direction.

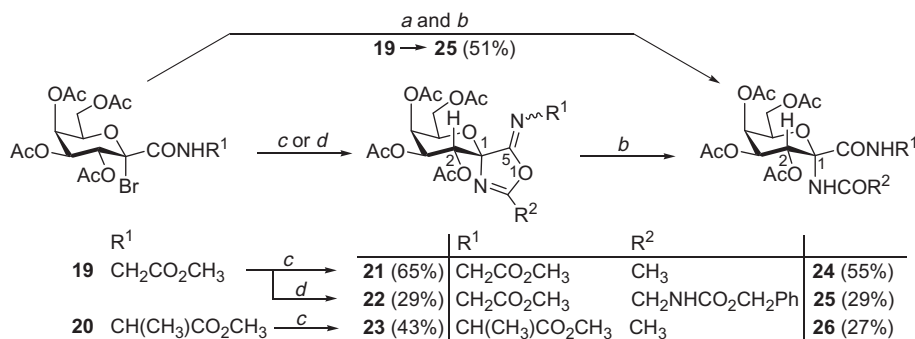
This Ritter-type reaction was also investigated with N-substituted C-(2,3,4,6-tetra-O-acetyl-1-bromo-1-deoxy-β-D-galactopyranosyl)formamides **19**³² and **20** (Scheme 2). Compound **20** was prepared from pentachlorophenyl C-(2,3,4,6-tetra-O-acetyl-1-bromo-1-deoxy-β-D-galactopyranosyl)formate and L-alanine methyl-ester according to the procedure described for **19**.³² Bromides **19** and **20** were each reacted with 1 equiv of Ag₂CO₃ in CH₃CN as the solvent to give the spiro-oxazoline derivatives **21** and **23** in good and modest yield, respectively. The reaction of **19** with 10 equiv of the solid benzyloxycarbonylamino-acetonitrile was performed in CH₃NO₂ in the presence of 1 equiv of Ag₂CO₃ to give the spiro compound **22**.

The structure of compounds **21–23** was established by NMR methods. The absence of exchangeable protons as well as resonances characteristic for imidate type carbons (155.8–158.2 ppm) were in accordance with the spirocyclic structures. Spectra for **22** exhibited two series of resonances indicating the presence of E/Z isomers along the C-5 = N bond, while for **21** and **23** only one isomer was present. This configurational issue was not investigated further. The ⁴C₁ conformation of the sugar rings was unequivocally assigned with the use of vicinal proton–proton coupling constants (see Section 3). The configuration of the anomeric carbon was established on the basis of three-bond heteronuclear couplings between H-2 and the exocyclic imine type carbon C-5 attached to C-1 of the sugar part (parent monosaccharide numbering). These couplings were measured using a sensitivity enhanced gradient long-range ¹³C–¹H correlation experiment (G-HSQMBC),³⁹ and values around 3 Hz indicated gauche arrangement of the relevant atoms in the ⁴C₁ conformation.

Table 2
Preparation of O-peracylated N-acyl-1-cyano-D-glycopyranosylamines

Starting compound	R	Yield (%)	Product
 1	CH ₃ – CH ₃ CH ₂ – CH ₂ =CH– CH ₂ =CH–CH ₂ – CH ₃ OCH ₂ –	2 (76) 8 (74) 9 (57) 10 (62) 11 (24)	
 5	CH ₃ – CH ₃ CH ₂ –	12 (36) ^a 13 (53)	
 6	CH ₃ – CH ₃ CH ₂ – (CH ₃) ₃ C–	14 (78) ³³ 15 (57) 16 (27)	
 7	CH ₃ – CH ₂ =CH–	17 (41) 18 (43)	

^a With 2 equiv AgF.



Scheme 2. Reagents and conditions: (a) 1 equiv AgOTf, 10 equiv PhCH₂OCONHCH₂CN, CH₃NO₂, in the dark, rt; (b) 1 equiv CF₃CO₂H or CH₃CO₂H, 2 equiv H₂O, CH₂Cl₂, rt; (c) 1 equiv Ag₂CO₃, CH₃CN, in the dark, rt; (d) 1 equiv Ag₂CO₃, 10 equiv PhCH₂OCONHCH₂CN, CH₃NO₂, in the dark, rt.

Spiro-oxazolines **21–23** were opened up by mild acidic hydrolysis to peptide derivatives **24–26**, respectively. Carrying out the Ritter-reaction of **19** with benzyloxycarbonylamino-acetonitrile and the hydrolysis of the intermediate spiro-derivative in a **continuous** operation improved the overall yield of **25** to 51% for the two steps.

For **24–26** the NMR structural elucidation showed the presence of amide carbonyls (166.1–167.3 ppm) instead of imidate type carbons. The ³J_{H-2,CONHR¹} couplings were obtained from experiments as above, and the 2.4–2.9 Hz values were indicative of the equatorial position of the CONHR¹ moiety. To corroborate this configurational assignment dipeptide **29**, the anomeric pair of **24**, was also synthesised (Scheme 3). Azide **27**³² was reduced by Raney-Ni to glycosylamine **28**. In this reaction the formation of anomers or anomerisation of the formed glycosylamine cannot be excluded, however, the product **28** isolated from the crude mixture by crystallization existed in the β-D-anomeric configuration as revealed by the ³J_{H-2,CONHR¹} of 5.8 Hz coupling. Conventional acetylation of **28** by AcCl in pyridine gave a mixture of **24** and **29** (possibly due to anomerisation of **28** under the reaction conditions) which could be separated by column chromatography. For **29** the ³J_{H-2,CONHR¹} coupling was 5.3 Hz, and thus these heteronuclear three-bond coupling values for the anomeric pairs **24** and **29** proved the configuration of the anomeric carbon in both compounds.

The formation of the new compounds by nitrile incorporation can be explained following the mechanistic proposal shown in Scheme 4. A promoter facilitates removal of a bromide ion from the substrates (**1**, **5–7**, **19**, **20**) to give glycosylium ion **B**. Axial attack of a nitrile may give glycosyl-nitrilium ion represented by resonance forms **F** and **G**. Intramolecular nucleophilic attack by the amide carbonyl oxygen may lead to spirocyclic intermediate **H** which, on losing a proton, gives spiro-oxazolines **21–23** as well as **D**. Tautomeric ring opening of the oxazoline in **D** and a subse-

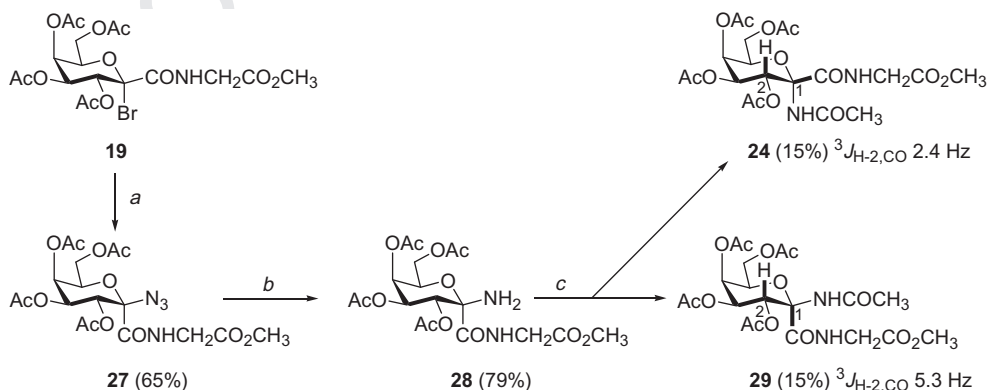
quent tautomerization of **C** result in the end-products **2**, and **8–18**. In the presence of promoters other than silver salts formation of **3** was also observed. Since the anomeric interconversion of **2** and **3** was excluded, this can be accounted for by neighbouring group participation of the acyl protecting groups of O-2 as illustrated by **E** resulting in an equatorial attack of the nitrile. Glycosyl-nitrilium ion **A** may then follow similar transformations as those starting with **G**, and end up with **3** as the isolable product. We have no explanation for the finding that with silver salts no compounds of type **3** were formed.

In conclusion, a Ritter-type reaction of a series of *O*-peracylated C-(1-bromo-1-deoxy-β-D-glycopyranosyl)formamides and nitriles promoted by silver salts gave access to *N*-acyl-1-cyano-β-D-glycopyranosylamines which can be regarded as anomeric α-amino acid derivatives^{40–43} and new derivatives of artificial ketoses.⁴⁴ The reaction was extended to *N*-substituted C-(1-bromo-1-deoxy-β-D-galactopyranosyl)formamides which gave anomeric spiro-oxazoline derivatives. In each of these compounds the newly formed C–N bond at the anomeric carbon was axially oriented in spite of the participating protecting groups at the equatorial O-2. Mild acidic hydrolysis of the spiro-oxazolines led to di- and tripeptides incorporating anomeric α-amino acids, thereby complementing reported synthetic methods for this class of sugar-peptide derivatives.^{45–50}

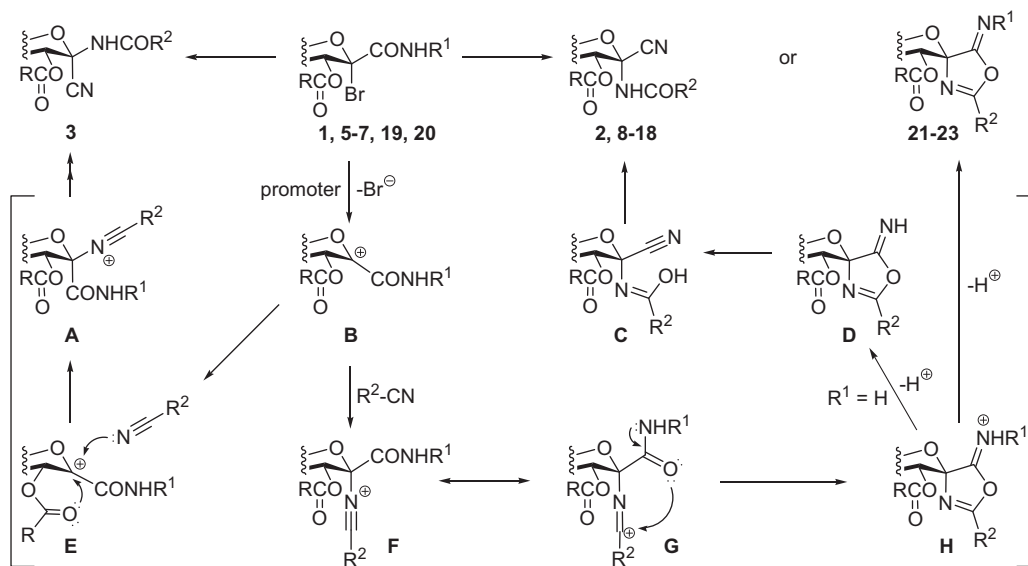
3. Experimental

3.1. General methods

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.



Scheme 3. Reagents and conditions: (a) 2 equiv NaN₃, DMSO, rt; (b) ~2 equiv Raney-Ni, H₂, EtOAc, 70 °C; (c) 2 equiv CH₃COCl, pyridine, rt.



Scheme 4.

NMR spectra were recorded with Bruker 200 (200/50 MHz for $^1\text{H}/^{13}\text{C}$), Bruker 360 (360/90 MHz for $^1\text{H}/^{13}\text{C}$) or Avance DRX 500 (500/125 MHz for $^1\text{H}/^{13}\text{C}$) spectrometers. Chemical shifts are referenced to Me_4Si (^1H), or to the residual solvent signals (^{13}C). TLC was performed on DC-Alurolle Kieselgel 60 F₂₅₄ (Merck), and the plates were visualised under UV light and by gentle heating. For column chromatography Kieselgel 60 (Merck, particle size 0.063–0.200 mm) was used. Organic solutions were dried over anhydrous MgSO_4 and concentrated under diminished pressure at 40–50 °C (water bath). CH_3CN , CH_3NO_2 were distilled from P_2O_5 , other nitriles, AgOTf , and AgF were purchased from Sigma-Aldrich and used without further purification. Ag_2CO_3 was prepared from AgNO_3 and K_2CO_3 , and dried over P_2O_5 .

3.2. General procedure for the preparation of O-peracylated N-acyl-1-cyano-D-glycopyranosylamines (2-acylamino-2-deoxy-hept(hex)-2-ulopyranosonitriles) (2, 8–18)

An O-peracylated C-(1-bromo-1-deoxy-D-glycopyranosyl)formamide (**1**, ²⁸ **5**,³⁷ **6**,³⁸ or **7**,³⁵ 0.25 mmol) was dissolved in a nitrile (1 mL), and silver carbonate (0.07 g, 0.25 mmol) or silver fluoride (0.063 g, 0.50 mmol) was added in one portion. The mixture was stirred at rt in the dark until complete disappearance of the starting material (2–3 days, TLC 3:1 EtOAc–hexane). It was then diluted with acetone (9 mL), filtered through a Celite pad, the filter cake was washed with acetone (3 mL), and the filtrate was concentrated. The residue was purified by column chromatography or crystallisation to give pure products.

3.2.1. N-Acetyl-2,3,4,6-tetra-O-acetyl-1-cyano- α -D-galactopyranosylamine (2-acetamido-3,4,5,7-tetra-O-acetyl-2-deoxy- α -D-galacto-hept-2-ulopyranosonitrile) (**2**)

Prepared from **1** (0.51 g, 1.12 mmol) in CH_3CN according to Section 3.2. Reaction time 2 d, purification by column chromatography (1:3 EtOAc– CHCl_3), yield 0.35 g (76%) white crystals. Mp: 155–156 °C; $[\alpha]_D^{25} +49$ (**c** 1.15, CHCl_3); ^1H NMR (CDCl_3 , 360 MHz): δ (ppm) 7.90 (s, 1H, NH), 5.75 (d, 1H, $J_{2,3}$ 10.7 Hz, H-2), 5.30 (dd, 1H $J_{2,3}$ 10.7 Hz, $J_{3,4}$ 3.4 Hz, H-3), 5.27 (dd, 1H, $J_{3,4}$ 3.4 Hz, $J_{4,5}$ 1.1 Hz, H-4), 4.26 (t, 1H, $J_{5,6}$ 6.0 Hz, $J_{5,6'}$ 6.0 Hz, H-5), 4.10–4.08 (m, 2H, H-6, H-6'), 2.20, 2.19 (2), 2.03, 1.99 (4s, 15H, OCOCH_3 , NHCOCH_3); ^{13}C NMR (CDCl_3 , 90 MHz): δ (ppm) 171.2 (NHCOCH_3), 170.3, 170.0, 169.7 168.2 (CO), 114.7 (CN,

$^3J_{\text{H-2,CN}} = \sim 3.0$), 77.7 (C-1), 67.7, 67.5, 67.3, 66.7 (C-2–C-5), 60.6 (C-6), 22.9 (NHCOCH_3), 20.3 (2), 20.5 (2) (CH_3); Anal. Calcd for $\text{C}_{17}\text{H}_{22}\text{N}_2\text{O}_{10}$ (414.36): C, 49.28; H, 5.35; N, 6.76. Found: C, 48.27; H, 5.43; N, 6.35.

3.2.2. N-Acetyl-2,3,4,6-tetra-O-acetyl-1-cyano- β -D-galactopyranosylamine (2-acetamido-3,4,5,7-tetra-O-acetyl-2-deoxy- β -D-galacto-hept-2-ulopyranosonitrile) (**3**)

Compound **1** (0.50 g, 1.10 mmol) was dissolved in a mixture of dry CH_3NO_2 (5 mL), CH_3CN (10 equiv) was added, and the solution was stirred with freshly activated molecular sieves overnight. HgBr_2 (0.50 g, 1.39 mmol) was added in one portion. The mixture was stirred at rt until complete disappearance of the starting material (TLC, 3:1 EtOAc–hexane) (2–3 days). It was then diluted with CHCl_3 , filtered through a Celite pad, and the filtrate was concentrated under diminished pressure. The residue was dissolved in CHCl_3 and washed several times with 1 M KBr solution in order to remove mercury salts. The crude oil was purified by column chromatography (1:1–3:1 EtOAc–hexane) to give pure products: **2** (0.08 g, 20%) and **3** (0.15 g, 33%), **4** (0.07 g, 15%).

Compound **3** was obtained as white crystals. Mp 161–163 °C; $[\alpha]_D^{25} +262$ (**c** 0.17, CHCl_3); ^1H NMR (CDCl_3 , 360 MHz): δ (ppm) 7.21 (s, 1H, NH), 5.53 (dd, 1H, $J_{3,4}$ 3.1 Hz, $J_{4,5}$ 1.3 Hz, H-4), 5.41 (dd, 1H, $J_{2,3}$ 10.5 Hz, $J_{3,4}$ 3.1 Hz, H-3), 5.22 (d, 1H, $J_{2,3}$ 10.5 Hz, H-2), 4.44 (t, 1H, $J_{5,6}$ 6.8 Hz, $J_{5,6'}$ 6.8 Hz, H-5), 4.21–4.16 (m, 2H, H-6, H-6'), 2.21, 2.16, 2.06 (2), 2.01 (4s, 15H, OCOCH_3 , NHCOCH_3); ^{13}C NMR (CDCl_3 , 90 MHz): δ (ppm) 171.7 (NHCOCH_3), 170.1, 169.6, 169.3 169.1 (CO), 111.9 (CN, $^3J_{\text{H-2,CN}} = \sim 5.8$ Hz), 79.9 (C-1), 71.2, 68.5 (2), 66.1 (C-2–C-5), 60.2 (C-6), 23.1 (NHCOCH_3), 20.5, 20.4, 20.3, 20.2 (CH_3); Anal. Calcd for $\text{C}_{17}\text{H}_{22}\text{N}_2\text{O}_{10}$ (414.36): C, 49.28; H, 5.35; N, 6.76. Found: C, 48.77; H, 5.23; N, 6.00.

3.2.3. N-Propanoyl-2,3,4,6-tetra-O-acetyl-1-cyano- α -D-galactopyranosylamine (3,4,5,7-tetra-O-acetyl-2-deoxy-2-propanamido- α -D-galacto-hept-2-ulopyranosonitrile) (**8**)

Prepared from **1** (0.05 g, 0.11 mmol) in $\text{CH}_3\text{CH}_2\text{CN}$ according to Section 3.2. Reaction time 2 d, purification by column chromatography (1:3 EtOAc– CHCl_3), yield 0.035 g (74%) white crystals. Mp: 186–187 °C; $[\alpha]_D^{25} +55$ (**c** 0.91, CHCl_3); ^1H NMR (CDCl_3 , 360 MHz): δ (ppm) 7.68 (s, 1H, NH), 5.76 (d, 1H, $J_{2,3}$ 10.6 Hz, H-2), 5.30 (dd, 1H, $J_{2,3}$ 10.6 Hz, $J_{3,4}$ 3.4 Hz, H-3), 5.38 (dd, 1H, $J_{3,4}$ 3.4 Hz, $J_{4,5}$ 1.0 Hz, H-4), 4.26 (t, 1H, $J_{5,6}$ 6.6 Hz, $J_{5,6'}$ 6.6 Hz, H-5), 4.10 (m, 2H,

H-6, **H-6'**), 2.42 (q, 2H, J 7.3 Hz, J 7.3 Hz, CH₂), 2.20, 2.17, 2.02, 1.98 (4s, 12H, OCOCH₃), 1.21 (t, 3H, J 7.3 Hz, J 7.3 Hz, CH₃); ¹³C NMR (CDCl₃, 90 MHz): δ (ppm) 174.5 (NHCOCH₂CH₃), 170.3, 170.0, 169.7, 168.1 (CO), 114.8 (CN, ³ $J_{\text{H-2,CN}} = \sim 3.0$), 77.6 (C-1), 67.6 (2), 67.4, 67.3, 66.7 (C-2–C-5), 60.6 (C-6), 28.9 (NHCOCH₂CH₃), 20.3 (2), 20.5 (2) (CH₃), 8.9 (NHCOCH₂CH₃); Anal. Calcd for C₁₈H₂₄N₂O₁₀ (428.39): C, 50.47; H, 5.65; N, 6.54. Found: C, 50.41; H, 5.93; N, 6.67.

3.2.4. *N*-Propenoyl-2,3,4,6-tetra-*O*-acetyl-1-cyano- α -*D*-galactopyranosylamine (3,4,5,7-tetra-*O*-acetyl-2-deoxy-2-propen-amido- α -*D*-galacto-hept-2-ulopyranosonitrile) (9)

Prepared from **1** (0.05 g, 0.11 mmol) in CH₂CHCN according to Section 3.2. Reaction time 2 d, purification by column chromatography (1:3 EtOAc–CHCl₃), yield 0.03 g (57%) white crystals. Mp: 158–160 °C; $[\alpha]_{\text{D}}^{25} +61$ (c 0.80, CHCl₃); ¹H NMR (CDCl₃, 360 MHz): δ (ppm) 7.20 (s, 1H, NH), 6.51 (d, 1H, J 7.3 Hz, CH₂), 6.29 (dd, 1H, J 7.3 Hz, J 6.9 Hz, CH), 5.86 (d, 1H, J 6.9 Hz, CH₂), 5.78 (d, 1H, $J_{2,3}$ 10.6 Hz, H-2), 5.25 (dd, 1H, $J_{2,3}$ 10.6 Hz, $J_{3,4}$ 2.8 Hz, H-3), 5.39 (dd, 1H, $J_{3,4}$ 2.8 Hz, $J_{4,5}$ 1.1 Hz, H-4), 4.23 (t, 1H, $J_{5,6}$ 6.6 Hz, $J_{5,6'}$ 6.6 Hz, H-5), 4.18 (dd, 1H, $J_{6,6'}$ 10.7 Hz, $J_{5,6}$ 6.6 Hz, H-6), 4.09 (dd, 1H, $J_{6,6'}$ 10.7 Hz, $J_{5,6}$ 6.6 Hz, H-6), 2.20, 2.16, 2.02, 1.99 (4s, 12H, OCOCH₃); ¹³C NMR (CDCl₃, 90 MHz): δ (ppm) 170.3 (NHCOCH=CH₂), 170.1, 170.0, 169.7, 168.1 (CO), 130.2 (CH=CH₂), 128.8 (CH=CH₂), 114.5 (CN, ³ $J_{\text{H-2,CN}} = \sim 3.2$), 78.2 (C-1), 68.1, 67.7, 67.6, 66.7 (C-2–C-5), 60.6 (C-6), 20.5 (2), 20.4 (2) (CH₃); Anal. Calcd for C₁₈H₂₂N₂O₁₀ (426.37): C, 50.70; H, 5.20; N, 6.57. Found: C, 49.93; H, 5.12; N, 6.39.

3.2.5. *N*-(But-3-enoyl)-2,3,4,6-tetra-*O*-acetyl-1-cyano- α -*D*-galactopyranosylamine (3,4,5,7-tetra-*O*-acetyl-2-(but-3-enamido)-2-deoxy- α -*D*-galacto-hept-2-ulopyranosonitrile) (10)

Prepared from **1** (0.10 g, 0.22 mmol) in CH₂CHCH₂CN according to Section 3.2. Reaction time 2 d, purification by column chromatography (1:3 EtOAc–CHCl₃), yield 0.06 g (62%) white crystals. Mp: 149–150 °C; $[\alpha]_{\text{D}}^{25} +57$ (c 0.88, CHCl₃); ¹H NMR (CDCl₃, 360 MHz): δ (ppm) 6.85 (s, 1H, NH), 5.99 (m, 1H, CH), 5.38 (d, 1H, $J_{2,3}$ 10.7 Hz, H-2), 5.40–5.35 (m, 2H, H-3, H-4), 5.14 (m, 2H, CH₂), 4.20 (m, 3H, H-5, H-6, **H-6'**), 3.19 (d, 2H, J 7.3 Hz, CH₂), 2.20, 2.16, 2.03, 2.00 (4s, 12H, OCOCH₃); ¹³C NMR (CDCl₃, 90 MHz): δ (ppm) 170.3 (NHCOCH₂CH=CH₂), 170.0, 169.9, 167.8, 167.7 (CO), 129.9 (NHCOCH₂CH=CH₂), 120.5 (NHCOCH₂CH=CH₂), 114.4 (CN, ³ $J_{\text{H-2,CN}} = \sim 3.1$ Hz), 78.0 (C-1), 68.0, 67.7, 67.6, 66.6 (C-2–C-5), 60.7 (C-6), 41.0 (NHCOCH₂CH=CH₂) 20.5 (2), 20.4, 20.3 (CH₃); Anal. Calcd for C₁₉H₂₄N₂O₁₀ (440.40): C, 51.82; H, 5.49; N, 6.36. Found: C, 51.34; H, 5.43; N, 6.55.

3.2.6. *N*-Methoxyacetyl-2,3,4,6-tetra-*O*-acetyl-1-cyano- α -*D*-galactopyranosylamine (3,4,5,7-tetra-*O*-acetyl-2-deoxy-2-methoxyacetamido- α -*D*-galacto-hept-2-ulopyranosonitrile) (11)

Prepared from **1** (0.10 g, 0.22 mmol) in CH₃OCH₂CN according to Section 3.2. Reaction time 2 d, purification by column chromatography (1:3 EtOAc–CHCl₃), yield 0.02 g (24%) white crystals. Mp: 149–151 °C; $[\alpha]_{\text{D}}^{25} +29$ (c 1.22, CHCl₃); ¹H NMR (CDCl₃, 360 MHz): δ (ppm) 7.34 (s, 1H, NH), 5.78 (d, 1H, $J_{2,3}$ 10.9 Hz, H-2), 5.41 (dd, 1H, $J_{3,4}$ 3.2 Hz, $J_{4,5}$ 1.1 Hz, H-4), 5.11 (dd, 1H, $J_{2,3}$ 10.9 Hz, $J_{3,4}$ 3.2 Hz, H-3), 4.22–4.05 (m, 3H, H-5, H-6, **H-6'**), 4.04 (d, 1H, J 6.9 Hz, CH₂), 3.97 (d, 1H, J 6.9 Hz, CH₂), 3.49 (s, 3H, OCH₃), 2.21, 2.17, 2.03, 2.01 (4s, 12H, OCOCH₃); ¹³C NMR (CDCl₃, 90 MHz): δ (ppm) 170.4 (NHCOCH₂OCH₃), 170.1, 169.9, 169.3, 167.7 (CO), 114.1 (CN, ³ $J_{\text{H-2,CN}} = \sim 3.0$), 77.8 (C-1), 71.6 (NHCOCH₂OCH₃), 68.1, 67.8, 67.5, 66.4 (C-2–C-5), 60.5 (C-6), 59.3 (NHCOCH₂OCH₃), 20.6 (2), 20.4, 20.3 (CH₃); Anal. Calcd for C₁₈H₂₄N₂O₁₁ (444.39): C, 48.65; H, 5.44; N, 6.30. Found: C, 50.00; H, 5.70; N, 6.47.

3.2.7. *N*-Acetyl-2,3,4,6-tetra-*O*-acetyl-1-cyano- α -*D*-glucopyranosylamine (2-acetamido-3,4,5,7-tetra-*O*-acetyl-2-deoxy- α -*D*-gluco-hept-2-ulopyranosonitrile) (12)

Prepared from **5** (0.60 g, 1.32 mmol) in CH₃CN with AgF according to Section 3.2. Reaction time 1 d, purification by column chromatography (1:1→3:1 EtOAc–hexane), yield 0.20 g (36%) white crystals. Mp 179–181 °C; $[\alpha]_{\text{D}}^{25} +57$ (c 1.01, acetone).

¹H NMR ((CD₃)₂CO, 200 MHz): δ (ppm) 8.72 (s, 1H, NH), 5.52 (d, 1H, $J_{2,3}$ 10.0 Hz, H-2), 5.42 (dd, 1H, $J_{3,4}$ 4.5 Hz, $J_{4,5}$ 2.4 Hz, H-4), 5.16 (dd, 1H, $J_{2,3}$ 9.8 Hz, $J_{3,4}$ 4.5 Hz, H-3), 4.31 (dd, 1H, $J_{6,6'}$ 12.3 Hz, $J_{5,6}$ 6.0 Hz, H-6), 4.02 (dd, 1H, $J_{6,6'}$ 12.3 Hz, $J_{5,6}$ 6.0 Hz, **H-6'**), 2.11, 2.10, 2.02, 1.99, 1.96 (5s, 15H, NHCOCH₃, OCOCH₃); ¹³C NMR ((CD₃)₂CO, 50 MHz): δ (ppm) 170.7 (NHCOCH₃), 170.4, 170.2, 169.8, 168.9 (CO), 115.9 (CN, ³ $J_{\text{H-2,CN}} = \sim 3.0$ Hz), 78.1 (C-1), 71.5, 71.1, 69.2, 68.5 (C-2–C-5), 61.8 (C-6), 22.9 (NHCOCH₃), 20.5, 20.4 (2), 20.3 (CH₃); Anal. Calcd for C₁₇H₂₂N₂O₁₀ (414.364): C, 49.28; H, 5.35; N, 6.76. Found: C, 48.52; H, 5.60; N, 6.70.

3.2.8. *N*-Propanoyl-2,3,4,6-tetra-*O*-acetyl-1-cyano- α -*D*-glucopyranosylamine (3,4,5,7-tetra-*O*-acetyl-2-deoxy-2-propan-amido- α -*D*-gluco-hept-2-ulopyranosonitrile) (13)

Prepared from **5** (0.31 g, 0.69 mmol) in CH₃CH₂CN according to Section 3.2. Reaction time 3 d, purification by column chromatography (1:3 EtOAc–CHCl₃), yield 0.16 g (53%) white crystals from EtOAc. Mp: 187–189 °C; $[\alpha]_{\text{D}}^{25} +25$ (c 0.61, CHCl₃); ¹H NMR (CDCl₃, 200 MHz): δ (ppm) 6.97 (s, 1H, NH), 5.57 (d, 1H, $J_{2,3}$ 9.8 Hz, H-2), 5.31 (dd, 1H, $J_{3,4}$ 4.4 Hz, $J_{4,5}$ 1.1 Hz, H-4), 5.16 (dd, 1H, $J_{2,3}$ 9.8 Hz, $J_{3,4}$ 4.4 Hz, H-3), 4.29 (dd, 1H, $J_{6,6'}$ 12.5 Hz, $J_{5,6}$ 6.0 Hz, H-6), 4.00 (dd, 1H, $J_{6,6'}$ 12.5 Hz, $J_{5,6}$ 6.0 Hz, H-6), 3.96 (t, 1H, $J_{5,6}$ 6.0 Hz, $J_{5,6'}$ 6.0 Hz, H-5), 2.42 (q, 2H, J 7.3 Hz, J 7.2 Hz, CH₂CH₃), 2.16, 2.11, 2.03 (2) (3s, 12H, OCOCH₃), 1.21 (t, 3H, J 7.3 Hz, J 7.2 Hz, CH₂CH₃); ¹³C NMR (CDCl₃, 50 MHz): δ (ppm) 173.4 (NHCOCH₂CH₃), 170.3, 169.8, 168.7, 167.6 (CO), 114.1 (CN, ³ $J_{\text{H-2,CN}} = \sim 3.0$ Hz), 76.0 (C-1), 70.1, 69.8, 68.2, 66.9 (C-2–C-5), 60.6 (C-6), 28.7 (CH₂CH₃), 20.2, 20.1, 20.0, 19.9 (CH₃), 8.4 (CH₂CH₃); Anal. Calcd for C₁₈H₂₄N₂O₁₀ (428.391): C, 50.47; H, 5.65; N, 6.54. Found: C, 50.03; H, 5.52; N, 6.23.

3.2.9. *N*-Propanoyl-2,3,4,6-tetra-*O*-benzoyl-1-cyano- α -*D*-glucopyranosylamine (3,4,5,7-tetra-*O*-benzoyl-2-deoxy-2-propan-amido- α -*D*-gluco-hept-2-ulopyranosonitrile) (15)

Prepared from **6** (0.30 g, 0.43 mmol) in CH₃CH₂CN according to Section 3.2. Reaction time 2 d, purification by column chromatography (1:3 EtOAc–CH₂Cl₂), yield 0.17 g (57%) white crystals. Mp: 239–241 °C; $[\alpha]_{\text{D}}^{25} +62.0$ (c 1.03, CHCl₃); ¹H NMR (CDCl₃, 360 MHz): δ (ppm): 8.00–7.08 (m, 20H, ArH), 7.71 (s, 1H, NH), 6.88 (pseudo t, 1H, J 9.8 Hz, J 9.2 Hz, H-3 or H-4), 6.36 (d, 1H, $J_{2,3}$ 9.8 Hz, H-2), 5.82 (pseudo t, 1H, J 9.8 Hz, J 9.2 Hz, H-3 or H-4), 4.46–4.40 (m, 3H, H-5, H-6, **H-6'**), 2.40 (pseudo q, 2H, J 7.2 Hz, J 5.2 Hz, CH₂), 1.10 (pseudo t, 3H, J 7.2 Hz, J 5.2 Hz, CH₃); ¹³C NMR (CDCl₃, 90 MHz): δ (ppm): 166.1 (NHCOCH₂CH₃), 166.1, 165.8, 164.8, 164.7 (CO), 134.0–127.4 (benzoyl ArC), 114.8 (CN, ³ $J_{\text{H-2,CN}} = \sim 2.2$ Hz), 77.8 (C-1), 71.4, 70.8, 69.2, 68.5 (C-2–C-5), 62.0 (C-6), 29.0 (NHCOCH₂CH₃), 8.10 (NHCOCH₂CH₃); Anal. Calcd for C₃₈H₃₂N₂O₁₀ (676.69): C, 67.45; H, 4.77; N, 4.14. Found: C, 67.10; H, 4.36; N, 4.01.

3.2.10. *N*-Pivaloyl-2,3,4,6-tetra-*O*-benzoyl-1-cyano- α -*D*-glucopyranosylamine (3,4,5,7-tetra-*O*-benzoyl-2-deoxy-2-pival-amido- α -*D*-gluco-hept-2-ulopyranosonitrile) (16)

Prepared from **6** (0.20 g, 0.28 mmol) in (CH₃)₃CCN according to Section 3.2. Reaction time 2 d, purification by column chromatography (1:2 EtOAc–Hexane), yield 0.06 g (27%) white crystals and compound **4** (0.05 g, 27%). Mp: 226–229 °C; $[\alpha]_{\text{D}}^{25} +37$ (c 0.98, CHCl₃); ¹H NMR (CDCl₃, 360 MHz): δ (ppm): 8.10–7.24 (m, 20H, ArH), 6.85 (s, 1H, NH), 6.13 (d, 1H, $J_{2,3}$ 9.8 Hz, H-2), 5.70 (pseudo

t, 2H, J 9.8 Hz, J 9.2 Hz in each, H-3, H-4), 4.62 (dd, 1H, $J_{6,6'}$ 12.5 Hz, $J_{5,6}$ 2.6 Hz, H-6), 4.46 (dd, 1H, $J_{6,6'}$ 12.6 Hz, $J_{5,6}$ 5.9 Hz, H-6'), 4.34 (ddd, 1H, $J_{4,5}$ 9.8 Hz, $J_{5,6}$ 5.9 Hz, $J_{5,6'}$ 2.6 Hz, H-5), 1.33 (s, 9H, C₄H₉); ¹³C NMR (CDCl₃, 90 MHz): δ (ppm): 177.6 (NHCOC(CH₃)₃), 166.0, 165.9, 164.9, 163.5 (CO), 133.5–127.6 (benzoyl ArC), 114.4 (CN, ³ $J_{H-2,CN} = \sim 2.6$ Hz), 77.8 (C-1), 71.6, 70.6, 69.6, 68.5 (C-2–C-5), 67.0 (NHCOC(CH₃)₃), 62.2 (C-6), 27.2 (NHCOC(CH₃)₃). Anal. Calcd for C₄₀H₃₆N₂O₁₀ (704.74): C, 68.17; H, 5.15; N, 3.97. Found: C, 68.00; H, 4.86; N, 4.11.

3.2.11. *N*-Acetyl-2,3,4-tri-*O*-acetyl-1-cyano- β -D-arabinopyranosylamine (2-acetamido-3,4,5-tri-*O*-acetyl-2-deoxy- β -D-arabino-hex-2-ulopyranosonitrile) (17)

Prepared from **7** (0.14 g, 0.36 mmol) in CH₃CN according to Section 3.2. Reaction time 2 d, purification by column chromatography (1:1 \rightarrow 3:1 EtOAc–Hexane), yield 0.05 g (41%) white crystals from CH₂Cl₂–Et₂O. Mp: 170–172 °C; $[\alpha]_D -29$ (c 1.07, CHCl₃); ¹H NMR (CDCl₃, 360 MHz): δ (ppm) 8.53 (s, 1H, NH), 5.69 (d, 1H, $J_{2,3}$ 9.6 Hz, H-2), 5.34 (dd, 1H, $J_{2,3}$ 9.6 Hz, $J_{3,4}$ 5.0 Hz, H-3), 5.30 (ddd, 1H, $J_{3,4}$ 5.0 Hz, $J_{4,5}$ 2.5 Hz, $J_{4,5'}$ 1.6 Hz, H-4), 4.06 (dd, 1H, $J_{6,6'}$ 13.5 Hz, $J_{5,6}$ 2.5 Hz, H-5), 3.80 (dd, 1H, $J_{6,6'}$ 13.5 Hz, $J_{5,6}$ 1.6 Hz, H-5'), 2.13 (2), 2.08, 1.96 (3s, 12H, OCOCH₃, CH₃); ¹³C NMR (CDCl₃, 90 MHz): δ (ppm) 170.9 (NHCOC(CH₃)₃), 170.1, 169.8, 168.2 (CO), 114.7 (CN, ³ $J_{H-2,CN} = \sim 3.1$ Hz), 78.0 (C-1), 67.9, 66.9, 66.8 (C-2–C-4), 61.6 (C-5), 23.0 (CH₃), 20.7, 20.5, 20.4 (CH₃); Anal. Calcd for C₁₄H₁₈N₂O₈ (342.30): C, 49.12; H, 5.30; N, 8.18. Found: C, 50.10; H, 5.57; N, 8.33.

3.2.12. *N*-Propenoyl-2,3,4-tri-*O*-acetyl-1-cyano- β -D-arabinopyranosylamine (3,4,5-tri-*O*-acetyl-2-deoxy-2-propenamido- β -D-arabino-hex-2-ulopyranosonitrile) (18)

Prepared from **7** (0.31 g, 0.81 mmol) in CH₂CHCN according to Section 3.2. Reaction time 2 d, purification by column chromatography (1:1 \rightarrow 3:1 EtOAc–hexane), yield 0.12 g (43%) as a colourless syrup. $R_f = 0.28$ (1:1 EtOAc–hexane); $[\alpha]_D -28$ (c 1.06, CHCl₃); ¹H NMR (CDCl₃, 200 MHz): δ (ppm) 6.90 (s, 1H, NH), 6.51 (d, 1H, J 7.5 Hz, CH₂), 6.29 (dd, 1H, J 7.5 Hz, J 6.9 Hz, CH), 5.86 (d, 1H, J 7.5 Hz, CH₂), 5.77 (d, 1H, $J_{2,3}$ 8.8 Hz, H-2), 5.28 (dd, 1H, $J_{2,3}$ 8.8 Hz, $J_{3,4}$ 3.5 Hz, H-3), 5.24 (ddd, 1H, $J_{3,4}$ 3.5 Hz, $J_{4,5}$ 2.6 Hz, $J_{4,5'}$ 1.2 Hz, H-4), 4.05–3.94 (m, 2H, H-5, H-5'), 2.18, 2.17, 2.06 (3s, 9H, OCOCH₃); ¹³C NMR (CDCl₃, 50 MHz): δ (ppm) 170.0 (NHCOC(=CH₂)), 169.6, 168.3, 165.6 (CO), 129.7 (CH₂=CH), 128.9 (CH₂=CH), 114.5 (CN, ³ $J_{H-2,CN} = \sim 3.1$ Hz), 78.1 (C-1), 67.7, 66.9, 66.7 (C-2–C-4), 61.6 (C-5), 23.0 (CH₃), 20.7, 20.5, 20.4 (CH₃); Anal. Calcd for C₁₅H₁₈N₂O₈ (354.31): C, 50.85; H, 5.12; N, 7.91. Found: C, 50.30; H, 5.37; N, 8.13.

3.3. *N*-(2,3,4,6-Tetra-*O*-acetyl-1-bromo-1-deoxy- β -D-galactopyranosylcarbonyl)-L-alanine methylester (*N*-(3,4,5,7-tetra-*O*-acetyl-2-bromo-2-deoxy- α -D-galacto-hept-2-ulopyranosonyl)-L-alanine methylester) (20)

Pentachlorophenyl C-(2,3,4,6-tetra-*O*-acetyl-1-bromo-1-deoxy- β -D-galactopyranosyl)formate³² (0.30 g, 0.43 mmol) was dissolved in dry 1,4-dioxane (3 mL) and methyl L-alaninate-HCl (2 equiv), and Et₃N (2 equiv) were added. The reaction mixture was stirred at rt and monitored by TLC (1:1 EtOAc–hexane). After completion of the reaction the solvent was removed. The obtained crude product was purified by column chromatography (1:1 EtOAc–hexane) to give 0.18 g (73%) **20** as colourless oil. $R_f = 0.24$ (1:1 EtOAc–hexane); $[\alpha]_D +83$ (c 0.73, CHCl₃); IR ν_{max} (CHCl₃): 3380, 2958, 1758, 1678, 1374, 1262, 1070 cm⁻¹; ¹H NMR (CDCl₃, 360 MHz) δ (ppm): 7.15 (t, 1H, $J = 6.8$, 6.8 Hz, NH), 5.54 (dd, 1H, $J_{3,4}$ 3.2 Hz, $J_{4,5}$ 1.6 Hz, H-4), 5.42 (d, 1H, $J_{2,3}$ 10.0 Hz, H-2), 5.32 (dd, 1H, $J_{2,3}$ 10.0 Hz, $J_{3,4}$ 3.2 Hz, H-3), 4.60–4.48 (m, 4H, H-5, H-6, H-6', CH), 3.79 (s, 3H, OCH₃), 2.18, 2.12, 2.09, 1.98 (4s, 12H, OCOCH₃), 1.45

(d, 3H, J 6.8 Hz, CH(CH₃)); ¹³C NMR (CDCl₃, 125 MHz) δ (ppm): 172.5 (COOCH₃), 170.2, 169.8, 169.7, 169.1 (CO), 164.2 (CONH, ³ $J_{H-2,CONHCH_2CO_2Me} = 2.2$ Hz), 94.3 (C-1), 73.3, 69.7, 66.4, 66.4 (C-2–C-5), 60.5 (C-6), 52.5 (COOCH₃), 48.0 (CH), 20.8, 20.7, 20.5, 20.4 (CH₃), 17.6 (CH(CH₃)). Anal. Calcd for C₁₉H₂₆N₁Br₁O₁₂ (540.32): C, 42.24; H, 4.85; N, 2.59; Br, 14.79. Found: C, 41.80; H, 4.68; N, 2.44; Br, 15.10.

3.4. *N*-[(1*R*)-2,3,4,6-Tetra-*O*-acetyl-1,5-anhydro-D-galactitol-spiro[1.4]-2-methyl-2-oxazolin-5-ylidene]glycine methylester (21)

Compound **19**³² (0.20 g, 0.38 mmol) was dissolved in dry CH₃CN (2 mL) and Ag₂CO₃ (1.1 equiv) was added. The solution was stirred at rt in the dark until complete transformation of the starting material (4 d, TLC 3:1 EtOAc–hexane). The mixture was filtered on a Celite pad and the solvent was removed from the filtrate. The obtained crude product was purified by column chromatography (3:1 EtOAc–hexane) to give **21** (0.09 g, 65%) as a colourless oil, $R_f = 0.39$ (3:1 EtOAc–hexane), $[\alpha]_D +0.1$ (c 0.44, CHCl₃); ¹H NMR (CDCl₃, 360 MHz): δ (ppm): 5.70 (d, 1H, $J_{2,3}$ 10.6 Hz, H-2), 5.56 (dd, 1H, $J_{3,4}$ 4.0 Hz, $J_{4,5}$ <1 Hz, H-4), 5.46 (dd, 1H, $J_{2,3}$ 10.6 Hz, $J_{3,4}$ 4.0 Hz, H-3), 4.62 (ddd, 1H, $J_{5,6}$ 6.6 Hz, $J_{5,6'}$ 6.6 Hz, $J_{4,5}$ <1 Hz, H-5), 4.25 (s, 2H, CH₂), 4.19 (dd, 1H, $J_{6,6'}$ 11.9 Hz, $J_{5,6}$ 6.6 Hz, H-6), 4.10 (dd, 1H, $J_{6,6'}$ 11.9 Hz, $J_{5,6'}$ 6.6 Hz, H-6'), 3.77 (s, 3H, OCH₃), 2.25 (s, 3H, CH₃), 2.19, 2.03, 2.01, 1.97 (4s, 12H, OCOCH₃); ¹³C NMR (CDCl₃, 125 MHz): δ (ppm): 170.4, 170.2, 170.0, 168.7 (CO), 165.3 (C=N), 158.2 (C=N, ³ $J_{H-2,C=NCH_2COOCH_3} = \sim 3.1$ Hz), 95.7 (C-1), 70.8, 69.5, 68.3, 67.9 (C-2–C-5), 61.4 (C-6), 52.1 (OCH₃), 50.3 (CH₂), 20.7, 20.5, 20.5, 20.4 (OCOCH₃), 14.9 (CH₃); Anal. Calcd for C₂₀H₂₆N₂O₁₂ (486.44): C, 49.38; H, 5.39; N, 5.76. Found: C, 49.55; H, 5.56; N, 5.80.

3.5. *N*-[(1*R*)-2,3,4,6-Tetra-*O*-acetyl-1,5-anhydro-D-galactitol-spiro[1.4]-2-benzyloxycarbonylamino-methyl-2-oxazolin-5-ylidene]glycine methylester (22)

Compound **19** (0.17 g, 0.33 mmol) was dissolved in dry CH₃NO₂ (3 mL), NCC₂NHCOOCH₂Ph (10 equiv) and Ag₂CO₃ (1.1 equiv) were added. The mixture was stirred in the dark at rt for 6 d. After completion of the reaction (TLC, 3:1 EtOAc–hexane) the mixture was filtered on a Celite pad and the solvent was removed. The crude oil was purified by column chromatography (3:1 EtOAc–hexane) to give 0.04 g (29%) of **22** (1:1 mixture of two isomers) as a colourless oil. $R_f = 0.29$ (EtOAc); ¹H NMR (CDCl₃, 360 MHz): δ (ppm): 7.44–7.32 (m, 5H, Ph), 7.01 (s, 1H, NH), 5.71 (d, 1H, $J_{2,3}$ 10.6 Hz, H-2), 5.58–5.52 (m, 2H, H-4, H-4'), 5.48–5.30 (m, 3H, H-2', H-3, H-3'), 5.20–5.14 (m, 2H, CH₂), 4.60–4.62 (m, 2H, H-5, H-5'), 4.32–4.04 (m, 10H, H-6a, H-6a', H-6b, H-6b', CH₂a, CH₂b, CH₂Ph), 3.79 (s, 3H, OCH₃), 2.19, 2.17, 2.13, 2.11, 2.03, 2.01, 1.99, 1.97 (8s, 24H, OCOCH₃); ¹³C NMR (CDCl₃, 125 MHz): δ (ppm): 170.5, 170.3, 170.1 (2), 169.9, 169.4, 168.8 (2) (CO), 168.2 (CO₂CH₃), 165.1 (C=N), 157.1, 157.0 (CO₂CH₂Ph), 135.9–128.2 (aromatics), 95.3 (C-1), 94.1 (C-1'), 73.6, 71.0, 69.8, 69.5, 68.3, 67.9, 67.5, 66.6 (C-2–C-5 and C-2'–C-5'), 71.0 (CH₂), 60.7 (C-6), 60.4 (C-6'), 52.6 (OCH₃), 52.2 (OCH₃'), 41.2 (2) (CH₂, CH₂'), 20.9 (6), 20.5 (CH₃)

3.6. *N*-[(1*R*)-2,3,4,6-Tetra-*O*-acetyl-1,5-anhydro-D-galactitol-spiro[1.4]-2-methyl-2-oxazolin-5-ylidene]-L-alanine methylester (23)

Compound **20** (0.60 g, 1.10 mmol) was dissolved in dry CH₃CN (10 mL) and Ag₂CO₃ (1.1 equiv) was added. After stirring for 4 d in the dark the mixture was filtered on a Celite pad and the solvent was removed. The obtained crude product was purified by column chromatography (3:1 EtOAc–hexane) to give 0.24 g (43%) **23** as a

colourless oil. $R_f = 0.19$ (1:1 EtOAc–hexane), $[\alpha]_D +1$ (c 0.41, CHCl₃); ¹H NMR (CDCl₃, 360 MHz): δ (ppm): 5.65 (d, 1H, $J_{2,3}$ 10.6 Hz, H-2), 5.54 (dd, 1H, $J_{3,4}$ 4.0 Hz, $J_{4,5}$ <1 Hz, H-4), 5.42 (dd, 1H, $J_{2,3}$ 10.6 Hz, $J_{3,4}$ 4.0 Hz, H-3), 4.58 (ddd, 1H, $J_{5,6}$ 6.6 Hz, $J_{5,6'}$ 6.6 Hz, $J_{4,5}$ <1 Hz, H-5), 4.42 (q, 1H, J 6.9 Hz, J 6.4 Hz, CH), 4.18 (dd, 1H, $J_{6,6'}$ 11.9 Hz, $J_{5,6}$ 6.6 Hz, H-6), 4.11 (1H, $J_{6,6'}$ 11.9 Hz, $J_{5,6'}$ 6.6 Hz, H-6'), 3.70 (s, 3H, OCH₃), 2.24 (s, 3H, CH₃), 2.20, 2.03, 2.01, 1.99 (4s, 12H, OCOCH₃), 1.48 (d, 3H, J 6.4 Hz, CH(CH₃)); ¹³C NMR (CDCl₃, 125 MHz): δ (ppm): 171.3, 170.4, 170.2, 169.9 (CO), 165.2 (C=N), 155.8 (C=N, $^3J_{H-2,C=NCH_3} = \sim 3.3$ Hz), 95.5 (C-1), 70.6, 69.5, 68.4, 67.9 (C-2–C-5), 61.3 (C-6), 56.6 (CH), 52.0 (OCH₃), 20.6, 20.5, 20.4, 20.3 (OCOCH₃), 18.2 (CH(CH₃), 14.9 (CH₃); Anal. Calcd for C₂₁H₂₈N₂O₁₂ (500.44): C, 51.12; H, 5.70; N, 6.26. Found: C, 50.85; H, 5.52; N, 5.96.

3.7. General procedure for the hydrolysis of spiro-oxazolines 21–23 to oligopeptides 24–26

Compounds 21–23 each was dissolved in CH₂Cl₂ (1 mL/0.1 mmol), CF₃COOH or AcOH (1 equiv) and water (2 equiv) were added. The mixture was stirred at rt until disappearance of the starting material (TLC, 3:1 EtOAc–hexane). It was then diluted with CH₂Cl₂ and washed with satd aq NaHCO₃ solution (2 × 5 mL), water (5 mL), dried, and the solvent removed. The obtained syrup was purified by column chromatography.

3.7.1. N-(2,3,4,6-Tetra-O-acetyl-1-acetamido-1-deoxy-β-D-galactopyranosylcarbonyl)glycine methylester (N-(2-acetamido-3,4,5,7-tetra-O-acetyl-2-deoxy-α-D-galacto-hept-2-ulopyranosonyl)glycine methylester) (24)

Prepared from 21 (0.05 g, 0.10 mmol) according to General procedure 3.7. Purified by column chromatography (9:1 EtOAc–MeOH), yield (0.02 g, 55%) of 24 as a colourless syrup. $R_f = 0.42$ (9:1 EtOAc–hexane); $[\alpha]_D +69$ (c 0.38, CHCl₃); ¹H NMR (CDCl₃, 360 MHz): δ (ppm): 7.28 (t, 1H, J 5.8 Hz, J 5.8 Hz, NH), 6.37 (s, 1H, NH), 5.45 (d, 1H, $J_{2,3}$ 10.6 Hz, H-2), 5.56 (dd, 1H, $J_{3,4}$ 3.3 Hz, $J_{4,5}$ 1.1 Hz, H-4), 5.22 (dd, 1H, $J_{2,3}$ 10.6 Hz, $J_{3,4}$ 3.3 Hz, H-3), 4.33–3.98 (m, 5H, H-5, H-6, H-6', CH₂), 3.78 (s, 3H, OCH₃), 2.20, 2.09, 2.06, 1.99 (4s, 12H, OCOCH₃), 2.09 (s, 3H, NHCOCH₃); ¹³C NMR (CDCl₃, 125 MHz): δ (ppm): 170.9, 170.5, 170.1, 169.5 (CO), 170.1 (CO₂CH₃), 168.6 (NHCOCH₃), 167.3 (CONHCH₂, $^3J_{H-2,CONHCH_2COOCH_3} = \sim 2.4$ Hz), 83.7 (C-1), 68.7, 68.4, 67.0 (2) (C-2–C-5), 60.8 (C-6), 52.3 (OCH₃), 41.3 (CH₂), 23.5 (NHCOCH₃), 20.6 (3), 20.5 (CH₃); Anal. Calcd for C₂₀H₂₈N₂O₁₃ (504.45): C, 47.62; H, 5.59; N, 5.55. Found: C, 47.44; H, 5.36; N, 5.65.

3.7.2. N-(2,3,4,6-Tetra-O-acetyl-1-Z-glycylamido-1-deoxy-β-D-galactopyranosylcarbonyl)glycine methylester (N-(3,4,5,7-tetra-O-acetyl-2-deoxy-2-Z-glycylamido-α-D-galacto-hept-2-ulopyranosonyl)glycine methylester) (25)

Prepared from 22 (0.04 g, 0.06 mmol) according to Section 3.7. Purified by column chromatography (9:1 EtOAc–MeOH), yield 0.01 g (27%) of 24 as a colourless oil. $R_f = 0.13$ (5:1 EtOAc–hexane); $[\alpha]_D +58$ (c 0.160, CHCl₃); ¹H NMR (CDCl₃, 360 MHz): δ (ppm): 7.38–7.32 (m, 5H, ArH), 7.30 (s, 1H, NH), 7.18 (s, 1H, NH), 5.51 (s, 1H, NH), 5.46 (d, 1H, $J_{2,3}$ 10.6 Hz, H-2), 5.44 (dd, 1H, $J_{3,4}$ 3.4 Hz, $J_{4,5}$ 1.1 Hz, H-4), 5.19 (dd, 1H, $J_{2,3}$ 10.6 Hz, $J_{3,4}$ 3.4 Hz, H-3), 5.12–5.08 (m, 2H, CH₂), 4.29–3.86 (m, 5H, H-5, H-6, H-6', CH₂), 3.77 (s, 3H, OCH₃), 2.20, 2.06, 2.05, 1.95 (4s, 12H, OCOCH₃); ¹³C NMR (CDCl₃, 125 MHz): δ (ppm): 170.6, 170.2, 170, 169.9 (2), 169.5, 168.8, 168.7 (CO₂CH₃, NHCOCH₂, NHCO₂, CO), 166.7 (CONCH₂, $^3J_{H-2,CONHCH_2COOCH_3} = \sim 2.9$ Hz), 156.8 (–CO₂CH₂Ph), 133.0–128.6 (aromatics), 83.8 (C-1), 69.2, 68.5, 67.1 (2) (C-2–C-5), 67.1 (CH₂), 65.6 (CH₂), 60.8 (C-6), 52.4 (OCH₃), 41.4 (2) (CH₂), 20.6 (6), 20.5 (2) (CH₃); Anal. Calcd for C₂₈H₃₅N₃O₁₅ (653.60): C, 51.46; H, 5.40; N, 6.43. Found: C, 51.65; H, 5.56; N, 6.72.

3.7.3. N-(2,3,4,6-Tetra-O-acetyl-1-acetamido-1-deoxy-β-D-galactopyranosylcarbonyl)-L-alanine methylester (N-(2-acetamido-3,4,5,7-tetra-O-acetyl-2-deoxy-α-D-galacto-hept-2-ulopyranosonyl)-L-alanine methylester) (26)

Prepared from 23 (0.05 g, 0.10 mmol) according to Section 3.7. Purified by column chromatography (3:1 EtOAc–hexane), yield 0.015 g (29%) of 26 as colourless oil. $R_f = 0.15$ (EtOAc); $[\alpha]_D +69.0$ (c 0.40, CHCl₃); ¹H NMR (CDCl₃, 360 MHz): δ (ppm): 7.28 (t, 1H, J 5.8 Hz, J 5.8 Hz, NH), 6.27 (s, 1H, NH), 5.46–5.42 (m, 2H, H-2, H-4), 5.19 (dd, 1H, $J_{2,3}$ 10.6 Hz, $J_{3,4}$ 3.3 Hz, H-3), 4.52 (q, 1H, J 6.8 Hz, J 6.4 Hz, CH), 4.35 (dd, 1H, $J_{6,6'}$ 11.9 Hz, $J_{5,6}$ 6.6 Hz, H-6), 4.25 (ddd, 1H, $J_{5,6}$ 6.6 Hz, $J_{5,6'}$ 6.6 Hz, $J_{4,5}$ 0.9 Hz, H-5), 4.14 (1H, dd, $J_{6,6'}$ 11.9 Hz, $J_{5,6'}$ 6.6 Hz, H-6'), 3.79 (s, 3H, OCH₃), 2.23 (s, 3H, NHCOCH₃); 2.10, 2.07, 2.06, 2.00 (4s, 12H, OCOCH₃), 1.46 (d, 3H, J 6.4 Hz, CH(CH₃)); ¹³C NMR (CDCl₃, 125 MHz): δ (ppm): 173.1, 171.3, 171.0, 170.7 (CO), 170.5 (CO₂CH₃), 168.9 (NHCOCH₃), 166.7 (CONHCH₂, $^3J_{H-2,CONHCH_2COOCH_3} = \sim 2.4$ Hz), 83.9 (C-1), 69.2, 68.9, 67.4 (2) (C-2–C-5), 60.8 (C-6), 52.8 (OCH₃), 48.9 (CH), 24.0 (NHCOCH₃), 20.9, 20.6, (2), 20.5 (CH₃), 18.4 (CH(CH₃)); Anal. Calcd for C₂₁H₃₀N₂O₁₃ (518.45): C, 49.90; H, 5.72; N, 5.60. Found: C, 49.63; H, 5.56; N, 5.44.

3.8. N-(2,3,4,6-Tetra-O-acetyl-1-amino-1-deoxy-α-D-galactopyranosylcarbonyl)glycine methylester (N-(3,4,5,7-tetra-O-acetyl-2-amino-2-deoxy-β-D-galacto-hept-2-ulopyranosonyl)glycine methylester) (28)

Azide 27³² (0.10 g, 0.20 mmol) was dissolved in dry EtOAc (5 mL) and Raney-Ni (~0.2 g, 2 equiv) was added to the solution. The mixture was stirred at 70 °C and monitored by TLC (3:1 EtOAc–hexane). After completion of the reaction the mixture was filtered on a Celite pad and the solvent was removed. The obtained syrup was crystallised from EtOH to give 0.07 g (79%) of 28 as a white crystalline product. Mp: 123–126 °C; $[\alpha]_D +77$ (c 1.06, CHCl₃); ¹H NMR (CDCl₃, 360 MHz): δ (ppm): 7.53 (t, 1H, J 5.3 Hz, J 5.3 Hz, NH), 5.62 (dd, 1H, $J_{2,3}$ 11.0 Hz, $J_{3,4}$ 3.2 Hz, H-3), 5.50 (dd, 1H, $J_{3,4}$ 3.2 Hz, $J_{4,5}$ <1 Hz, H-4), 5.24 (d, 1H, $J_{2,3}$ 11.0 Hz, H-2), 5.13 (ddd, 1H, $J_{5,6}$ 6.3 Hz, $J_{5,6'}$ 6.3, $J_{4,5}$ <1 Hz, H-5), 4.18 (dd, 1H, J 18.4 Hz, J 5.3 Hz, CH₂), 4.10 (dd, 1H, $J_{6,6'}$ 11.5 Hz, $J_{5,6}$ 6.3 Hz, H-6), 4.02 (dd, 1H, $J_{6,6'}$ 11.0 Hz, $J_{5,6'}$ 6.3 Hz, H-6'), 3.95 (dd, 1H, J 18.4 Hz, J 5.3 Hz, CH₂), 3.78 (s, 3H, OCH₃); 2.29 (s, 2H, NH₂), 2.16, 2.12, 2.04, 1.95 (4s, 12H, OCOCH₃); ¹³C NMR (CDCl₃, 125 MHz): δ (ppm): 170.4 (CO₂CH₃), 170.3, 170.1, 169.8, 169.6 (CO), 169.5 (CONH, $^3J_{H-2,CONHCH_2COOCH_3} = \sim 5.8$ Hz), 86.5 (C-1), 71.3, 70.4, 68.9, 68.0 (C-2–C-5), 62.0 (C-6), 52.3 (COOCH₃), 40.7 (CH₂), 20.6 (2), 20.5 (2) (CO); Anal. Calcd for C₁₈H₂₆N₂O₁₂ (462.41): C, 46.75; H, 5.67; N, 6.06. Found: C, 46.45; H, 5.76; N, 5.90.

3.9. N-(2,3,4,6-Tetra-O-acetyl-1-acetamido-1-deoxy-α-D-galactopyranosylcarbonyl)glycine methylester (N-(3,4,5,7-tetra-O-acetyl-2-acetamido-2-deoxy-β-D-galacto-hept-2-ulopyranosonyl)glycine methylester) (29)

Compound 28 (0.26 g, 0.56 mmol) was dissolved in dry pyridine (5 mL) and AcCl (0.08 mL, 1.12 mmol) was added. The mixture was stirred at rt overnight and monitored by TLC (99:1 EtOAc–MeOH). The volatiles were then removed, followed by co-evaporations with PhCH₃ (2 × 5 mL). The residue was dissolved in EtOAc (10 mL) and washed with water. The water phase was washed with EtOAc (5 × 10 mL). The combined organic phase was dried, the solvent removed, and the residue purified by column chromatography (99:1 EtOAc–MeOH) to give 0.045 g, (15%) of compound 29 as a colourless oil in the first fraction ($R_f = 0.23$, 99:1 EtOAc–MeOH) and 0.045 g (15%) of compound 24 as the second fraction ($R_f = 0.31$, 99:1 EtOAc–MeOH).

Characterisation data for **29**: $[\alpha]_D +153$ (c 0.078, CHCl₃); ¹H NMR (CDCl₃, 360 MHz): δ (ppm): 7.86 (t, 1H, *J* 5.8 Hz, *J* 5.8 Hz, NH), 7.06 (s, 1H, NH), 5.63 (dd, 1H, *J*_{2,3} 10.5 Hz, *J*_{3,4} 3.3 Hz, H-3), 5.47 (dd, 1H, *J*_{3,4} 3.3 Hz, *J*_{4,5} 1.0 Hz, H-4), 5.23 (d, 1H, *J*_{2,3} 10.5 Hz, H-2), 4.60 (pseudo t, 1H, *J*_{5,6} 6.7 Hz, *J*_{5,6'} 6.4 Hz, H-5), 4.14–3.05 (m, 4H, H-6, H-6', CH₂), 3.74 (s, 3H, OCH₃), 2.15, 2.14, 2.02, 1.96 (4s, 12H, OCOCH₃), 2.01 (s, 3H, NHCOCCH₃); ¹³C NMR (CDCl₃, 125 MHz): δ (ppm): 172.7, 170.2 (3), 169.6 (CO, COOCH₃), 169.3 (NHCOCCH₃), 166.3 (CONHCH₂, ³*J*_{H-2,CONHCH₂COOCH₃} = ~5.3 Hz), 85.8 (C-1), 71.1, 70.1, 68.1, 67.2 (C-2–C-5), 61.2 (C-6), 52.4 (OCH₃), 41.1 (CH₂), 24.1 (NHCOCCH₃), 20.9, 20.6, 20.5 (2) (CH₃); Anal. Calcd for C₂₀H₂₈N₂O₁₃ (504.45): C, 47.62; H, 5.59; N, 5.55. Found: C, 47.14; H, 5.31; N, 5.25.

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