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Synthesis and conformational analysis of methyl 3-amino-2,3-dideoxyhexopyranosiduronic acids, new sugar amino acids, and their diglycotides☆

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Abstract—The synthesis of methyl 3-azido- and 3-amino-2,3-dideoxyhexopyranosiduronic acids and their methyl esters with the -α,β-D-*arabino*-, -α,β-D-*ribo*, and -α,β-L-*lyxo* configurations is presented. The conformations of the synthesized sugar amino acids and their precursors are discussed on the basis of ^{1}H NMR data. The influence of the 5-carboxyl group on the pyranose ring conformation is assessed, and the bonding of the monosugar amino acids into dimeric glycotides, using conventional solution-phase peptide syntheses, is reported.

Keywords: SAAs; Configuration; Conformation; Stability; Homodimeric glycotides

1. Introduction

Sugar amino acids (SAAs) are carbohydrates bearing both an amino group and a carboxyl group. Syntheses and applications of SAAs have recently been widely reviewed.[1–5] Sialic acids, muraminic acid, and glycosaminuronic acids are naturally occurring SAAs. Many molecular recognition events depend on sialic acid residues, located peripherically on glycoproteins. Derivatives of muramic acid and glycosaminuronic acids are found in bacterial cell walls; derivatives of the latter acids are present in certain antibiotics, for example, cancomycins, ezomycin A, and gougerotin. Synthetic SAAs have been used extensively in mimetic studies of oligosaccharides,[6,7] oligonucleotides,[8,9] cyclodextrins,[10,11] and peptides.[12] In order to improve the biological activity of peptides, mixed oligomers of SAAs, and amino acids have been studied.[13,14] Additionally, SAAs have been introduced into the peptide backbone as non-peptide isosteres to achieve desirable secondary structures.[15–19] SAAs are also very useful as polyfunctional scaffolds, where the carboxyl, amino, and hydroxyl groups allow a variety of densely functionalized molecules to be constructed.[20] Thus, the rigid pyranose ring system of a monosaccharide amino acid can be used as a molecular template to display pharmacophoric groups in a well-defined spatial orientation.[21] The synthesis of glycosaminuronic acids usually involves the selective oxidation of the primary hydroxyl group in the amino- or azidosugar.[8,15,21–24]

The previously reported addition of hydrazoic acid to the α,β-unsaturated aldehyde derived from 3,4-di-*O*-acetyl-2,6-anhydro-5-deoxy-D-*lyxo*-hex-5-enopyranonate (commercial name methyl 3,4-di-*O*-acetyl-D-glucuronal) (**1**, Scheme 1) yielded methyl (methyl 4-*O*-acetyl-3-azido-2,3-dideoxy-α,β-D-*arabino*-, and -α,β-D-*ribo*-hexopyranosid)uronates (**2**–**5**)—new SAA precursors.[25] This paper reports on the conversions of **2**–**5** into different 3-azido- and 3-amino-2,3-dideoxyhexopyranosiduronic acid derivatives. Synthesized SAAs, especially those with the D-*arabino* structure, serve as potential

☆ The term 'diglycotide' refers to two aminodeoxy glycosiduronic acid units linked via amide linkages.

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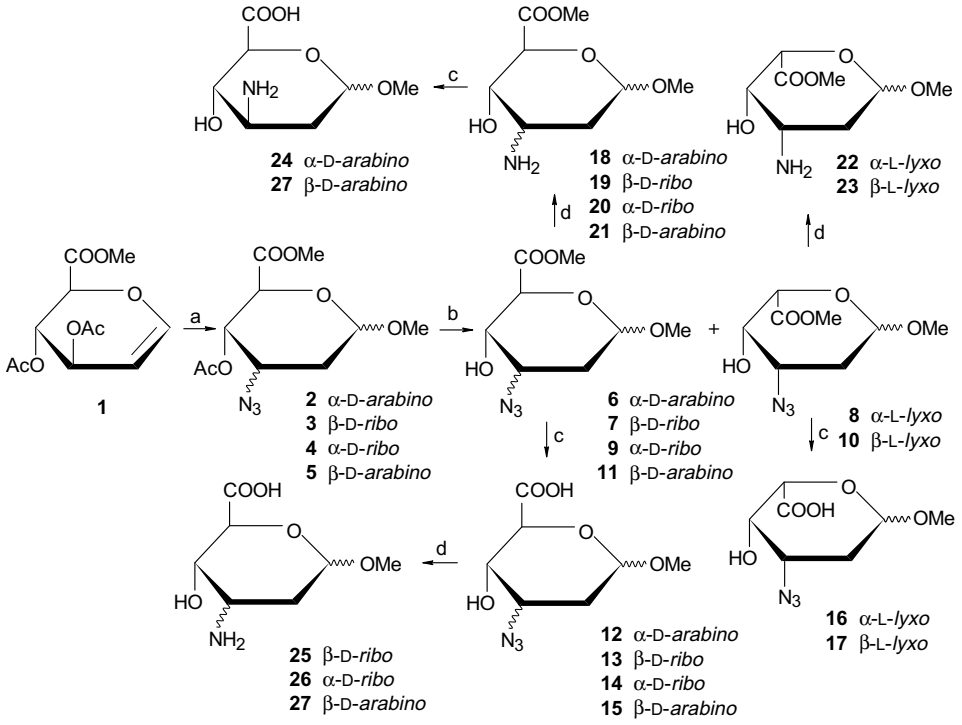
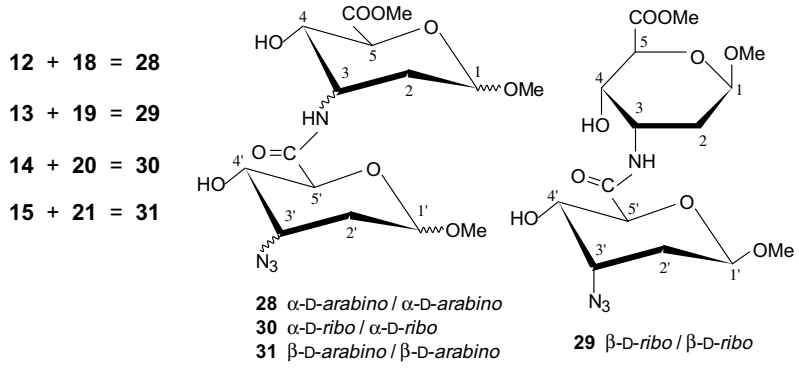


Scheme 1.

peptide β-turn mimetics.[15] Therefore, it is planned to incorporate them into the peptide backbone in order to study its conformation and biological activity. Additionally, the synthesized compounds enable monosugar amino acids to be ligated to dimeric glycotides. Here, particular attention is focused on the conformation of all the synthesized compounds, which are discussed on the basis of the ^{1}H NMR spectra. The application of SAAs as polyfunctional scaffolds or isosters requires the pyranose ring to be rigid with a well-defined spatial orientation. Hence, discussion on the influence of the 5-carboxyl group on the pyranose ring conformation is important.

2. Results and discussion

Attempts were made to separate the above-mentioned methyl (methyl 4-*O*-acetyl-3-azido-2,3-dideoxyhexopyranosid)uronates (**2**–**5**) (Scheme 1) by column chromatography. These resulted in pure **4** (-α-D-*ribo*-) and **5** (-β-D-*arabino*-), and still inseparable mixture of **2** (-α-D-*arabino*-) and **3** (-β-D-*ribo*-) (**2**:**3** ~ 1.5:1, established on the basis of the ^{1}H NMR spectrum). The amounts of products **2**–**5** obtained indicate that the addition of hydrazoic acid to the α,β-unsaturated aldehyde derived from **1** was slightly stereoselective in that more of the D-*arabino* than the D-*ribo* stereoisomers were produced (D-*arabino*:D-*ribo* ~ 2.5:1). Compounds **2**–**5** were each O-deacetylated with sodium methoxide in methanol (0.1 M) to yield the corresponding methyl (methyl 3-azido-2,3-dideoxyhexopyranosid)uronates (**6**–**11**). During the O-deacetylation process, the mixture of **2** and **3** produced three products: **6** (α-D-*arabino*), **7** (β-D-*ribo*), and **8** (α-L-*lyxo*), which were separated by column chromatography. Hence, at this step of the conversions, all four diastereoisomers in question could be separated. Under the basic conditions of the O-deacetylation reaction, small amounts of the β-D-*ribo* substrate **3** changed configuration at the C-5 carbon atom (α relative to the 5-carbomethoxy group). In this way, the third product **8** was isolated. The same happened during the O-deacetylation of **4** which yielded **9** (α-D-*ribo*) and **10** (β-L-*lyxo*), separated by column chromatography. Specifically, it was only the D-*ribo* compounds that epimerized in the basic environment of the reaction; this may mean that the D-*arabino* diastereoisomers are relatively more stable. The carboxylic acids in **6**–**11** were liberated by ester hydrolysis (1 M aq NaOH), which yielded methyl 3-azido-2,3-dideoxy-α-D-*arabino*- (**12**), -β-D-*ribo*- (**13**), -α-D-*ribo*- (**14**), -β-D-*arabino*- (**15**), α-L-*lyxo*- (**16**), and β-L-*lyxo*-hexopyranosiduronic acids (**17**), respectively. The amino terminus in **6**–**11** was deprotected by hydrogenation (10% Pd/C) of the azide to yield methyl (methyl 3-amino-2,3-dideoxy-α-D-*arabino*- (**18**), -β-D-*ribo*- (**19**), -α-D-*ribo*- (**20**) -β-D-*arabino*-

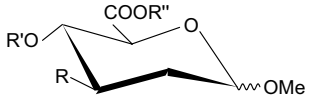
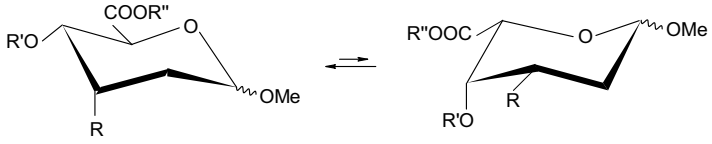
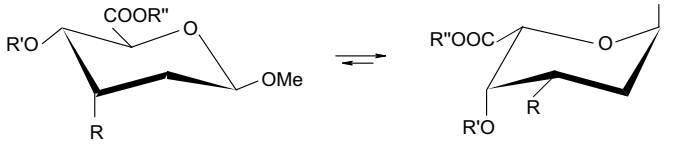
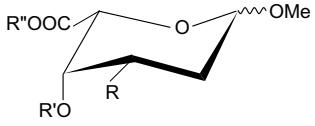


Scheme 2.

(**21**), -α-L-*lyxo*- (**22**), and -β-L-*lyxo*-hexopyranosid)uronates (**23**), respectively. In order to obtain completely unprotected SAAs, 5-carbomethoxy amines **18** and **21** were saponified with 1 M aq NaOH to produce **24** and **27**, and 3-azido acids **13**–**15** were hydrogenated to yield **25**–**27**.

The SAA units were assembled into diglycotides **28**–**31** (Scheme 2) using the methods of two solution-phase peptide synthesis. Thus, equimolar amounts of the SAAs with unprotected carboxylic termini (**12**) and unprotected amino termini (**18**) were coupled in the presence of 1-hydroxybenzotriazole (HOBt, 2 equiv), and dicyclohexylcarbodiimide (DCC, 1 equiv) to produce diglycotide **28** (yield 84%). Analogous coupling of **15** and **21** produced diglycotide **31** (yield 70%). The second procedure involved the coupling of SAAs with unprotected carboxylic termini (**13**–**15**) and SAAs with unprotected amino termini (**19**–**21**) in the presence of 1-hydroxy-7-azabenzotriazole (HOAt, 2 equiv) and *O*-(7-azabenzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate (HATU, 1 equiv). In this way, diglycotides **29**–**31** were synthesized with yields of 70–90%. Both methods appear to be good enough to couple SAAs units into diglycotides.

Table 1. Conformations of the pyranose ring in **2**–**27**

Configuration	Compounds	Conformation
α-D-*arabino* β-D-*arabino* β-D-*ribo*	**2**, **6**, **12**, **18**, **24** **5**, **11**, **15**, **21**, **27** **13**	
α-D-*ribo* β-D-*ribo*	**4**, **9**, **14**, **20**, **26** **7**, **25**	
β-D-*ribo*	**3**, **19**	
α-L-*lyxo* β-L-*lyxo*	**8**, **16**, **22** **10**, **17**, **23**	

2–**5** R″ = Me, R′ = Ac, R = N_3
6–**11** R″ = Me, R′ = H, R = N_3
12–**17** R″ = H, R′ = H, R = N_3
18–**23** R″ = Me, R′ = H, R = NH_2
24–**27** R″ = H, R′ = H, R = NH_2

The NMR spectra of **2**–**27** (Tables 2–4) provide ample confirmation of their configurations and conformations in solution. Thus, the $J_{2a,3}$ 12.2–12.8 Hz, $J_{3,4}$ 9.3–10 Hz, and $J_{4,5}$ 9.2–9.8 Hz coupling constants indicate a D-*arabino* structure and a $^4C_1$ conformation of **2**, **5**, **6**, **11**, **12**, **15**, **18**, **21**, **24**, and **27** (Table 1). The $J_{1,2a}$ 2.9–3.6 Hz coupling constants are diagnostic for the α configuration of **2**, **6**, **12**, **18**, and **24** as is the $J_{1,2a}$ 9.2–9.8 Hz coupling constant for the β configuration of **5**, **11**, **15**, **21**, and **27**. The respective coupling constants of **3**, **4**, **7**, **9**, **13**, **14**, **19**,

Table 2. Chemical shifts (ppm) in the ^{1}H NMR spectra of **2**–**27**

Comp.	Config.	H-1	H-2a	H-2e	H-3	H-4	H-5	OAc	OCH_3	$COOCH_3$
2[a]	α-D-*arabino*	4.93 (d)	1.79 (td)	2.17 (m)	3.99 (ddd)	4.99 (t)	4.23 (d)	2.13 (s)	3.40 (s)	3.77 (s)
3[a]	β-D-*ribo*	4.82 (dd)	1.94 (dt)	2.17 (m)	4.14 (dt)	5.38 (dd)	4.42 (d)	2.16 (s)	3.45 (s)	3.79 (s)
4[a]	α-D-*ribo*	4.85 (t)	2.11 (m)		3.98 (q)	5.22 (dd)	4.66 (d)	2.14 (s)	3.48 (s)	3.80 (s)
5[a]	β-D-*arabino*	4.51 (dd)	1.74 (td)	2.26 (ddd)	3.68 (ddd)	5.01 (t)	3.93 (d)	2.12 (s)	3.52 (s)	3.77 (s)
6[b]	α-D-*arabino*	4.82 (d)	1.62 (td)	2.07 (ddd)	3.72 (ddd)	3.59 (t)	4.05 (d)	—	3.37 (s)	3.79 (s)
7[b]	β-D-*ribo*	4.71 (dd)	1.77 (ddd)	2.07 (ddd)	4.00 (dt)	4.05 (dd)	4.25 (d)	—	3.42 (s)	3.78 (s)
8[b]	α-L-*lyxo*	4.97 (d)	2.18 (td)	1.85 (ddt)	3.68 (ddd)	4.24 (br s)	4.43 (d)	—	3.37 (s)	3.80 (s)
9[b]	α-D-*ribo*	4.77 (t)	2.08 (dt)	2.02 (ddd)	3.88 (q)	3.96 (dd)	4.39 (d)	—	3.40 (s)	3.78 (s)
10[b]	β-L-*lyxo*	4.51 (t)	1.94 (m)		3.48 (td)	4.15 (d)	4.21 (s)	—	3.54 (s)	3.80 (s)
11[b]	β-D-*arabino*	4.57 (dd)	1.43 (td)	2.12 (ddd)	3.56 (m)		3.87 (d)	—	3.46 (s)	3.79 (s)
12[b]	α-D-*arabino*	4.83 (d)	1.62 (td)	2.07 (dd)	3.72 (ddd)	3.58 (t)	4.03 (d)	—	3.39 (s)	—
13[b]	β-D-*ribo*	4.60 (dd)	1.68 (ddd)	1.92 (ddd)	4.06 (q)	3.78 (dd)	3.97 (d)	—	3.47 (s)	—
14[b]	α-D-*ribo*	4.81 (t)	2.07 (ddd)	2.01 (dt)	3.83 (dt)	4.00 (dd)	4.38 (d)	—	3.42 (s)	—
15[b]	β-D-*arabino*	4.58 (dd)	1.45 (td)	2.14 (ddd)	3.56 (m)		3.82 (d)	—	3.48 (s)	—
16[b]	α-L-*lyxo*	4.97 (d)	2.19 (td)	1.85 (dd)	3.69 (ddd)	4.27 (br s)	4.36 (d)	—	3.38 (s)	—
17[b]	β-L-*lyxo*	4.50 (dd)	1.92 (m)		3.47 (m)	4.15 (dd)	4.13 (d)	—	3.53 (s)	—
18[b]	α-D-*arabino*	4.81 (d)	1.60 (td)	2.02 (dd)	3.01 (ddd)	3.36 (t)	4.00 (d)	—	3.36 (s)	3.78 (s)
19[b]	β-D-*ribo*	4.82 (t)	1.96 (ddd)	1.74 (dt)	3.46 (dt)	4.10 (t)	4.31 (d)	—	3.40 (s)	3.76 (s)
20[b]	α-D-*ribo*	4.80 (t)	1.94 (m)		3.07 (q)	3.83 (dd)	4.30 (d)	—	3.40 (s)	3.79 (s)
21[b]	β-D-*arabino*	4.58 (dd)	1.48 (td)	2.11 (ddd)	2.88 (ddd)	3.39 (t)	3.84 (d)	—	3.47 (s)	3.80 (s)
22[b]	α-L-*lyxo*	4.90 (d)	1.92 (td)	1.78 (dd)	3.40 (m)	4.12 (br s)	4.44 (s)	—	3.35 (s)	3.79 (s)
23[b]	β-L-*lyxo*	4.44 (dd)	1.57 (td)	1.78 (ddd)	2.97 (ddd)	3.93 (br s)	4.19 (d)	—	3.50 (s)	3.78 (s)
24[c]	α-D-*arabino*	4.90 (d)	1.89 (td)	2.18 (ddd)	3.47 (ddd)	3.61 (t)	3.88 (d)	—	3.33 (s)	—
25[c]	β-D-*ribo*	4.79 (dd)	1.69 (ddd)	1.88 (ddd)	3.40 (m)	3.83 (dd)	4.00 (d)	—	3.43 (s)	—
26[c]	α-D-*ribo*	4.87 (t)	1.97 (ddd)	2.05 (ddd)	3.59 (m)	3.99 (dd)	4.11 (d)	—	3.38 (s)	—
27[c]	β-D-*arabino*	4.65 (dd)	1.64 (td)	2.29 (ddd)	3.38 (ddd)	3.59 (t)	3.69 (d)	—	3.48 (s)	—

[a] $CDCl_3$.
[b] CD_3OD.
[c] D_2O.

Table 3. The ^{1}H–^{1}H coupling constants (Hz) for **2**–**27**

Comp.	Configur.	$J_{1,2a}$	$J_{1,2e}$	$J_{2a,2e}$	$J_{2a,3}$	$J_{2e,3}$	$J_{3,4}$	$J_{4,5}$
2[a]	α-D-*arabino*	2.93	<1	13.18	12.70	4.88	9.77	9.77
3[a]	β-D-*ribo*	3.42	4.39	13.18	8.79	3.91	3.42	4.88
4[a,b]	α-D-*ribo*	3.91		—	4.89		3.42	7.81
5[a]	β-D-*arabino*	9.77	1.95	13.18	12.70	4.88	9.77	9.28
6[a]	α-D-*arabino*	3.42	1.46	13.19	12.21	4.88	9.76	9.76
7[a]	β-D-*ribo*	6.84	2.44	13.67	3.42	6.84	3.42	7.33
8[c]	α-L-*lyxo*	3.6	1.2	12.8	12.8	4.8	2.8	1.2
9[a]	α-D-*ribo*	3.42	3.90	14.65	5.37	3.91	3.42	7.81
10[a,b]	β-L-*lyxo*	6.84		—	8.79		2.93	<1
11[a]	β-D-*arabino*	9.28	1.95	12.70	12.21	4.40	n.d[d]	9.28
12[a]	α-D-*arabino*	2.93	<1	13.18	12.21	4.89	9.28	9.77
13[c]	β-D-*ribo*	9.2	2.0	14.0	3.2	4.0	3.2	9.2
14[c]	α-D-*ribo*	4.0	4.0	14.0	6.0	4.4	3.2	7.2
15[c]	β-D-*arabino*	9.6	2.0	12.8	12.4	4.4	n.d.	9.2
16[c]	α-L-*lyxo*	4.0	<1	12.8	12.8	4.4	2.8	1.2
17[c]	β-L-*lyxo*	8.0	3.6	n.d.	n.d.	n.d.	2.8	1.6
18[a]	α-D-*arabino*	3.42	<1	13.18	12.21	4.39	9.77	9.77
19[a]	β-D-*ribo*	3.42		13.18	10.25	3.91	3.42	3.91
20[a,b]	α-D-*ribo*	3.42		—	4.39		3.91	8.30
21[a]	β-D-*arabino*	9.28	1.96	12.70	12.21	4.40	9.77	9.27
22[c]	α-L-*lyxo*	3.2	<1	12.8	12.8	4.4	n.d.	<1
23[c]	β-L-*lyxo*	9.6	2.0	12.8	12.4	4.4	3.2	1.2
24[c]	α-D-*arabino*	3.6	1.2	13.2	12.8	4.4	10.0	9.6
25[c]	β-D-*ribo*	6.8	2.8	13.6	4.4	6.4	3.6	7.6
26[c]	α-D-*ribo*	3.6	3.6	14.8	5.6	4.4	4.0	8.0
27[c]	β-D-*arabino*	9.2	2.0	12.4	12.4	4.8	9.6	9.6

[a] 500 MHz.
[b] The H-2 protons are chemically and magnetically equivalent.
[c] 400 MHz.
[d] not determined.

Table 4. Chemical shifts (ppm) in the ^{13}C NMR spectra of **2**–**27**

Comp.	Config.	C-1	C-2	C-3	C-4	C-5	OCH_3	OAc		$COOCH_3$	
								CH_3	C=O	C=O	CH_3
2	α-D-*arabino*	98.1	34.7	57.2	71.6	69.4	55.7	20.9			53.1
3	β-D-*ribo*	99.8	32.2	53.6	69.3	71.9	57.2	21.0	168.8–170.2		52.7
4	α-D-*ribo*	97.8	32.2	55.5	69.5	68.4	56.5	20.9	169.3; 170.1		52.9
5	β-D-*arabino*	101.0	35.6	59.4	71.5	73.9	57.3	20.9	167.9; 169.9		53.1
6	α-D-*arabino*	99.7	35.9	61.2	73.1	73.5	55.5	—	—	171.8	52.9
7	β-D-*ribo*	101.0	34.3	59.7	69.8	75.8	57.2	—	—	172.1	52.7
8	α-L-*lyxo*	99.8	29.5	56.5	69.1	72.4	55.8	—	—	171.4	52.8
9	α-D-*ribo*	97.7	31.4	58.0	68.1	70.8	54.8	—	—	171.7	51.5
10	β-L-*lyxo*	101.3	29.9	58.1	67.4	75.4	55.8	—	—	169.4	51.4
11	β-D-*arabino*	102.7	37.2	63.2	73.3	77.8	57.2	—	—	171.1	53.0
12	α-D-*arabino*	98.3	34.6	60.0	72.0		54.2	—	—	171.8	—
13	β-D-*ribo*	99.4	34.8	60.1	70.6	73.1	55.9	—	—	176.1	—
14	α-D-*ribo*	99.0	32.5	59.2	69.4	72.6	56.2	—	—	173.8	—
15	β-D-*arabino*	102.6	37.2	63.4	73.3	77.7	57.2	—	—	172.4	—
16	α-L-*lyxo*	99.7	29.5	56.8	69.1	72.1	55.7	—	—	172.7	—
17	β-L-*lyxo*	101.3	29.8	58.3	67.4	75.2	55.9	—	—	170.7	—
18	α-D-*arabino*	98.8	36.3	49.1	73.4	72.3	54.2	—	—	171.1	51.6
19	β-D-*ribo*	99.9	32.8	44.4	66.8	74.3	55.9	—	—	171.4	51.2
20	α-D-*ribo*	98.7	33.2	48.3	67.9	69.6	54.8	—	—	170.9	51.6
21	β-D-*arabino*	101.9	37.1	52.2	72.7	76.9	55.9	—	—	170.2	51.6
22	α-L-*lyxo*	96.8	28.7	44.7	65.3	69.4	53.0	—	—	168.6	50.0
23	β-L-*lyxo*	101.9	33.9	49.7	68.1	75.9	55.7	—	—	169.9	51.4
24	α-D-*arabino*	97.4	33.2	50.0	69.0	71.7	54.3	—	—	171.3	—
25	β-D-*ribo*	99.4	34.7	46.3	69.0	74.4	56.7	—	—	177.4	—
26	α-D-*ribo*	97.5	30.3	48.3	65.5	70.9	55.7	—	—	176.3	—
27	β-D-*arabino*	100.4	34.0	52.0	69.3	77.1	57.0	—	—	175.4	—

20, **25**, and **26** confirm their D-*ribo* structure and simultaneously indicate that, with the exception of **13**, none of these compounds adopt the $^4C_1$ conformation in solution. The geometries of SAAs and their derivatives with D-*ribo* configuration may be divided into three categories. The first one is represented solely by **13**, which adopts the $^4C_1$ conformation, as demonstrated by the $J_{4,5}$ 9.2 Hz, and $J_{2a,3}$ 3.2 Hz coupling constants. The $J_{1,2a}$ 9.2 Hz coupling constant indicates the β configuration of the anomeric carbon of **13**. The second category covers compounds with the $J_{4,5}$ 7.2–8.3 Hz, and $J_{2a,3}$ 3.4–6.0 Hz coupling constants, which are characteristic of **4**, **7**, **9**, **14**, **20**, **25**, and **26** (Table 1). But ascribing a concrete boat or skew-boat conformation to these coupling constants is fraught with uncertainty, especially as the NOE experiments performed for compounds **18**–**21** supply no significant data regarding the pyranose ring conformations. We therefore suggest that compounds with the $J_{4,5}$ 7.2–8.3 Hz, and $J_{2a,3}$ 3.4–6.0 Hz coupling constants (**4**, **7**, **9**, **14**, **20**, **25**, and **26**) remain in the $^4C_1 \rightleftarrows {}^1C_4$ conformational equilibrium, though shifted in the $^4C_1$ direction (Table 1). The $J_{1,2a}$ coupling constant of 2.9–4.0 Hz confirms these assignments and indicates an α configuration for glycosides **4**, **9**, **14**, **20**, and **26**. The α configuration of these compounds is also reflected by the high positive optical rotation of **4**, **9**, and **20** ($[\alpha]_D^{20}$ +133, +122, and +125, respectively). Similarly, the $J_{1,2a}$ coupling constant of 6.8 Hz is diagnostic for a β configuration of **7** and **25**, which is confirmed by the negative optical rotation of **7** ($[\alpha]_D^{20}$ −40). The third category of geometries is characteristic with coupling constants $J_{4,5}$ of 4.88 and 3.91 Hz and $J_{2a,3}$ of 8.79 and 10.25 Hz, recorded for **3** and **19**, respectively. This set of coupling constants may indicate that the $^4C_1 \rightleftarrows {}^1C_4$ conformational equilibrium has shifted in the $^1C_4$ direction (Table 1), which is in agreement with the $J_{1,2a}$ coupling constant of 3.42 Hz, indicative rather of the equatorial orientation of the H-1 proton and consequently of the β configuration of **3** and **19**. The negative optical rotation of **19** ($[\alpha]_D^{20}$ −96) supplies additional evidence for the β configuration of the anomeric carbon atom.

The $J_{4,5} \leqslant 1.6$ Hz,[26] and $J_{2a,3}$ 12.4–12.8 Hz coupling constants indicate that SAAs with the L-*lyxo* configurations (**8**, **16**, **17**, **22**, and **23**) adopt the $^1C_4$ conformation in solution (Table 1). The $J_{1,2a}$ 3.2–4.0 Hz coupling constants are diagnostic for the α configuration of **8**, **16**, and **22** as is the $J_{1,2a}$ 9.6 Hz coupling constant for the β configuration of **17** and **23**. In the case of **10**, the H-2 protons are magnetically equivalent. Nevertheless, the $J_{4,5} < 1$ Hz, $J_{2,3}$ 8.79 Hz and $J_{1,2}$ 6.84 Hz coupling constants provide ample confirmation of the $^1C_4$ conformation and -β-L-*lyxo* configuration of **10**.

The findings presented in this paper show that the $^4C_1$ conformation is preferably adopted by methyl 3-azido- and 3-amino-2,3-dideoxyhexopyranosiduronic acids and their derivatives with the D-*arabino* and D-*lyxo* configurations. Although the D-*lyxo* analogs of methyl 3-amino-2,3-dideoxyhexopyranosiduronic acids were not synthesized, we can infer their conformation from the L-*lyxo* enantiomers. The same $^4C_1$ conformation is not stable enough for methyl 3-azido- and 3-amino-2,3-dideoxyhexopyranosiduronic acids and their esters with the D-*ribo* configuration. These facts are important for the application of such SAAs as the rigid isosters or platforms. The $^4C_1$ conformation of 2-deoxy sugars with the D-*arabino* structure, which enables the substituents on the C-3, C-4, and C-5 carbon atoms to be oriented equatorially, has to be more stable than the $^4C_1$ form of their the D-*ribo* analogs. Nevertheless, methyl 3-azido-2,3-dideoxyhexopyranosides with the D-*ribo* configuration, on which we reported earlier, which are analogous to the compounds discussed in this paper, always adopted the $^4C_1$ conformation in solution.[27,28] This means that, unlike the 5-CH_2X group (X = OH, OAc, OTs, I), the 5-COOR group (R = H, Me), does influence the conformational preferences of the pyranose ring. What is the reason for this difference? Most probably, the planarity of the 5-COOR group makes it less bulky than the typical 5-CH_2X group. The different van der Waals radii of these groups may mean that unfavorable 1,3-diaxial interactions in the case of the 5-COOR group are not as strong as in the case of the 5-CH_2X group. It is also possible that specific electronic effects between the polar 5-COOR group and the pyranose ring oxygen atom are responsible for a different conformational behavior of the uronic acid derivatives. The DFT calculations of the conformational space of D-glucuronic acid in the $^4C_1$ conformation demonstrate that repulsion of the carbonyl oxygen and ring oxygen lone pairs strongly determines the rotational preferences of the carboxyl group.[29] It seems that this repulsion should be stronger in the $^4C_1$ than in the $^1C_4$ conformation. This statement results from the fact that dipole of the ring oxygen lone pairs is oriented parallel to the C-5–H bond in the $^1C_4$ conformation, whereas the same dipole in the $^4C_1$ form is oriented parallel to the C-5–CO bond. Hence, the equatorial orientation of the 5-COOR group may be not so important for the stability of the $^4C_1$ conformation (D) as the equatorial orientation of the 5-CH_2X group is. We also noted this particular effect of the 5-$COOCH_3$ group on the conformational stability of methyl 3,4-di-*O*-acetyl-D-glucuronal.[30]

Analysis of the coupling constants of methyl 3-azido- and 3-amino-2,3-dideoxyhexopyranosiduronic acids and their methyl esters with the D-*ribo* configuration shows that the β-D-*ribo* structure is conformationally less stable than the α-D-*ribo* structure. Neither of these structures is stable enough in the $^4C_1$ conformation; even so the conformation of SAAs with the α-D-*ribo* configuration remains the same, irrespective of the changes performed during the chemical conversions (Table 1).

The conformations of β-D-*ribo* compounds are variable and depend on small changes in the structure.

Bonding the monosugar amino acids into dimeric glycotides significantly influences the conformations of the pyranose ring. Analysis of the NMR spectra of **28**–**31** (Tables 5–7) indicates that in the form of diglycotides almost all pyranose rings adopt the $^4C_1$ conformation, even those with the D-*ribo* configuration (Scheme 2). It seems that the amide bond lends a certain rigidity to the geometry of a diglycotide, thereby restricting the conformational changes of the pyranose ring. Therefore, the α-D-*ribo* structure, which in the monosugar form probably remains in the $^4C_1 \rightleftarrows {}^1C_4$ conformational equilibrium shifted in the $^4C_1$ direction, becomes less

Table 5. Chemical shifts (ppm) in the ^{1}H NMR spectra of **28**–**31**

Comp.	Config.	H-1	H-2$_a$	H-2$_e$	H-3	H-4	H-5	NH	OCH_3	$COOCH_3$
28[a]	α-D-*arabino*	4.88 (d)	1.76 (td)	2.21 (ddd)	4.28 (m)	3.70 (t)	4.19 (d)	6.66 (d)	3.41	3.84 (s)
	α-D-*arabino*′	4.85 (d)	1.63 (td)	2.07 (ddd)	3.84 (ddd)	3.62 (t)	4.01 (d)		3.36 (2s)	
29[b]	β-D-*ribo*	4.78 (t)	2.05 (ddd)	1.74 (m)	4.52 (dt)	4.16 (m)	4.28 (d)	n.d.[c]	3.46	3.75 (s)
	β-D-*ribo*′	4.67 (dd)	1.73 (ddd)	1.97 (ddd)	4.07 (q)	3.88 (dd)	4.16 (d)		3.39 (2s)	
30[a]	α-D-*ribo*	4.88 (d)	2.13 (dt)	1.96 (m)	4.56 (sex)	4.03 (m)	4.16 (d)	8.05 (d)	3.44	3.84 (s)
	α-D-*ribo*′	4.80 (d)	1.96 (m)	2.10 (ddd)	4.03 (m)	3.90 (dd)	4.48 (d)		3.43 (2s)	
31[a]	β-D-*arabino*	4.60 (dd)	1.62 (td)	2.30 (ddd)	4.08 (m)	3.84 (m)	3.97 (d)	6.88 (d)	3.53 (s)	3.83 (s)
	β-D-*arabino*′	4.52 (dd)	1.59 (td)	2.15 (ddd)	3.55 (ddd)	3.63 (t)	3.73 (d)			

[a] $CDCl_3$.
[b] CD_3OD.
[c] not determined.

Table 6. The ^{1}H–^{1}H coupling constants (Hz) for **28**–**31**

Comp.	Config.	$J_{1,2a}$	$J_{1,2e}$	$J_{2a,2e}$	$J_{2a,3}$	$J_{2e,3}$	$J_{3,4}$	$J_{3,NH}$	$J_{4,5}$
28	α-D-*arabino*	3.2	1.2	12.8	12.4	4.4	10.0	7.2	9.6
	α-D-*arabino*′	3.6	1.2	13.6	12.4	4.8	9.2		9.6
29	β-D-*ribo*	3.2	2.8	12.8	11.2	4.0	3.6	n.d.[a]	3.2
	β-D-*ribo*′	9.2	2.0	14.0	3.6	3.2	3.6		9.2
30	α-D-*ribo*	4.0	<1	14.4	4.0	4.0	4.0	8.4	9.6
	α-D-*ribo*′	4.4	<1	14.0	n.d.	n.d.	3.6		9.2
31	β-D-*arabino*	8.4	2.0	13.2	12.8	4.8	n.d.	7.2	8.4
	β-D-*arabino*′	9.6	2.0	13.2	12.8	4.8	9.2		9.2

[a] not determined.

Table 7. Chemical shifts (ppm) in the ^{13}C NMR spectra of **28**–**31**

Comp.	Config.	C-1	C-2	C-3	C-4	C-5	OCH_3	C=O	CH_3
28	α-D-*arabino*	98.2	34.9	48.4	71.9;	71.7	55.6	173.2	52.9
	α-D-*arabino*′	98.4	34.2	58.9	73.0	69.6	55.4	171.1	
29	β-D-*ribo*	100.3	30.7	42.3	65.6	74.8	55.9	171.2	51.3
	β-D-*ribo*′	99.4	34.7	60.5	70.1	73.2	55.9	170.8	
30	α-D-*ribo*	98.2	32.3	46.6	69.8	68.9	56.1	174.5	52.9
	α-D-*ribo*′	98.0	32.7	57.2	70.7	65.5	55.8		
31	β-D-*arabino*	101.1	34.6	49.7	70.3	75.7	57.2	171.7	52.9
	β-D-*arabino*′	101.4	35.6	61.4	72.7	73.7		170.3	

flexible in the diglycotide form and adopts the most stable $^4C_1$ conformation. The β-D-*ribo* structure adopts variable conformations in the monosugar form, but on losing flexibility it selects, as it were, the $^4C_1$ conformation for the 3-azidohexopyranosiduronic acid component. Alternatively, the methyl 3-amidohexopyranosiduronate component remains in the $^4C_1 \rightleftarrows {}^1C_4$ conformational equilibrium, but decidedly shifted in the $^1C_4$ direction ($J_{4,5}$ 3.2 Hz, $J_{2a,3}$ 11.2 Hz, and $J_{1,2a}$ 3.2 Hz).

To summarize, this paper presents a simple and efficient synthesis of 3-amino-2,3-dideoxyhexopyranosiduronic acid derivatives. The relatively high diversity of the synthesized diastereoisomers of SAAs permits a discussion of the influence of the configuration on conformational stability. We show that the pyranose ring of 3-amino-2,3-dideoxyhexopyranosiduronic acids and their precursors is less rigid than the analogous pyranose ring of 3-amino-2,3-dideoxyhexopyranosides. This is probably due to the influence of the 5-carboxyl group differing from that of the 5-hydroxymethyl group on the conformational stability of the pyranose ring. The results presented here indicate that the $^4C_1$ conformation is not sufficiently stable for SAAs with the D-*ribo* configuration. Such conformational instability should influence a total stability and increase the free energy of the compounds under discussion. This is probably the reason why methyl 3-azido-2,3-dideoxyhexopyranosiduronates with the D-*ribo* configuration (**7** and **9**) quite readily epimerized to produce new methyl 3-azido-2,3-dideoxyhexopyranosiduronates with the L-*lyxo* configuration (**8** and **10**). The L-*lyxo* configuration is more favorable because compounds with such a structure can adopt a stable $^1C_4$ (L) conformation in solution. Bonding monosugar amino acids into diglycotides via an amide bond makes the structures less flexible. Therefore, most of the pyranose rings in diglycotides adopt the $^4C_1$ conformation, irrespective of the configuration.

3. Experimental

3.1. General methods

Melting points are uncorrected. IR spectra were recorded as Nujol mulls with a Bruker IFS 66 spectrophotometer; ^{1}H and ^{13}C NMR spectra ($CDCl_3$, CD_3OD or D_2O; internal Me_4Si) on a Varian Mercury 400 (400/100 MHz) or on a Unity Plus 500 (500/125 MHz) instruments; positive-ion mode MALDI-TOF mass spectra on a Bruker Biflex III spectrometer; elemental analyses on a Carlo Erba EA1108 instrument. Thin-layer chromatography (TLC) was performed on E. Merck Kieselgel 60 F-254 plates using eluent systems (v/v) A, 4:1 toluene–AcOEt; B, 1:5 toluene–AcOEt; C, 3:1 MeOH–$CHCl_3$ D, 1:3 MeOH–$CHCl_3$; and column chromatography on MN Kieselgel 60 (<0.08 mm) with eluent systems (v/v) A or B.

3.2. Methyl 3,4-di-*O*-acetyl-2,6-anhydro-5-deoxy-D-*lyxo*-hex-5-enopyranonate (1)

This was synthesized as previously reported.[30]

3.3. Methyl (methyl 4-*O*-acetyl-3-azido-2,3-dideoxy-α-D-*arabino*- (2), -β-D-*ribo*- (3), -α-D-*ribo*- (4), and -β-D-*arabino*-hexopyranosid)uronates (5)

These were synthesized as previously reported.[25]

3.4. General procedure for O-deacetylation

Methyl (methyl 4-*O*-acetyl-3-azido-2,3-dideoxyhexopyranosid)uronates (**2**–**5**) (100 mg, 0.37 mmol) were dissolved in 0.1 M solution of NaOMe in abs MeOH (2.2 mL, 0.6 equiv) and stirred at rt for 1 h. The end of deacetylation was detected by TLC (solvent A). The solution was then neutralized with Dowex-50W × 8 (H^+) ion-exchange resin and filtered. The filtrate was evaporated and purified with column chromatography (solvent A).

3.4.1. Methyl (methyl 3-azido-2,3-dideoxy-α-D-*arabino*-(6), -β-D-*ribo*- (7), and -α-L-*lyxo*-hexopyranosid)uronates (8). O-Deacetylation of the mixture of **2** and **3** followed by column chromatography first gave **6** (51%, syrup): $[\alpha]_D^{20}$ +160 (*c* 1.0, CH_3OH); R_f 0.33 (solvent A); IR: *v* 3475 (O–H), 2941, 2840 (C–H), 2106 (N_3), 1748 (C=O) cm^{-1}; MALDI-TOFMS: *m*/*z* 254.1 $(M+Na)^+$, 270.1 $(M+K)^+$.

Eluted second was **7** (32%, syrup): $[\alpha]_D^{20}$ −40 (*c* 1.0, CH_3OH); R_f 0.21 (solvent A); IR: *v* 3464 (O–H), 2938, 2851 (C–H), 2104 (N_3), 1739 (C=O) cm^{-1}; MALDI-TOFMS: *m*/*z* 254.1 $(M+Na)^+$, 270.1 $(M+K)^+$.

Eluted third was **8** (8%, syrup): $[\alpha]_D^{20}$ −54 (*c* 1.0, CH_3OH); R_f 0.11 (solvent A); IR: *v* 3459 (O–H), 2936 (C–H), 2102 (N_3), 1744 (C=O) cm^{-1}; MALDI-TOFMS: *m*/*z* 254.1 $(M+Na)^+$, 270.1 $(M+K)^+$.

3.4.2. Methyl (methyl 3-azido-2,3-dideoxy-α-D-*ribo*- (9) and -β-L-*lyxo*-hexopyranosid)uronates (10). O-Deacetylation of **4** followed by column chromatography gave first **9** (34%, syrup): $[\alpha]_D^{20}$ +122 (*c* 0.6, CH_3OH); R_f 0.19 (solvent A); IR: *v* 3474 (O–H), 2927, 2852 (C–H), 2107 (N_3), 1747 (C=O) cm^{-1}; MALDI-TOFMS: *m*/*z* 254.1 $(M+Na)^+$.

Eluted second was **10** (31%, mp 136–137 °C): $[\alpha]_D^{20}$ +69 (*c* 1.0, CH_3OH); R_f 0.12 (solvent A); IR: *v* 3463 (O–H), 2925, 2852 (C–H), 2101 (N_3), 1755 (C=O) cm^{-1}; MALDI-TOFMS: *m*/*z* 254.1 $(M+Na)^+$, 270.1 $(M+K)^+$; Anal. Calcd for $C_8H_{13}N_3O_5$: C, 41.56; H, 5.67; N, 18.17. Found: C, 41.62; H, 5.62; N, 18.13.

3.4.3. Methyl (methyl 3-azido-2,3-dideoxy-β-D-*arabino*-hexopyranosid)uronate (11). O-Deacetylation of **5** yielded **11** (71%, mp 48–50 °C): $[\alpha]_D^{20}$ +3 (*c* 1.0, CH_3OH); R_f 0.35 (solvent A); IR: *v* 3458 (O–H), 2935, 2852 (C–H), 2101 (N_3), 1747 (C=O) cm^{-1}; MALDI-TOFMS: *m/z* 254.1 $(M+Na)^+$; Anal. Calcd for $C_8H_{13}N_3O_5$: C, 41.56; H, 5.67; N, 18.17. Found: C, 41.34; H, 5.81; N, 17.82.

3.5. General procedure for hydrolysis of 5-methoxycarbonyl group in 6–11

Methyl (methyl 3-azido-2,3-dideoxyhexopyranosid)uronates (**6**–**11**) (100 mg, 0.43 mmol) dissolved in MeOH (2.5 mL) were stirred with 1 M NaOH (aq) (0.43 mL, 1 equiv) at rt for 1 h. The end of hydrolysis was detected by TLC (solvent B). The solution was then neutralized with Dowex-50W × 8 (H^+) ion-exchange resin and filtered, and the filtrate was evaporated.

3.5.1. Methyl 3-azido-2,3-dideoxy-α-D-*arabino*-hexopyranosiduronic acid (12). Hydrolysis of **6** gave **12** (95%, syrup): R_f 0.08 (solvent B); IR: *v* 3418 (COOH and O–H), 2942, 2841 (C–H), 2107 (N_3), 1732 (C=O) cm^{-1}; MALDI-TOFMS: *m/z* 240.0 $(M+Na)^+$, 256.0 $(M+K)^+$.

3.5.2. Methyl 3-azido-2,3-dideoxy-β-D-*ribo*-hexopyranosiduronic acid (13). Hydrolysis of **7** gave **13** (85%): mp 224–227 °C; R_f 0.07 (solvent B); IR: *v* 3429 (COOH and O–H), 2938 (C–H), 2104 (N_3), 1732 (C=O) cm^{-1}; MALDI-TOFMS: *m/z* 240.1 $(M+Na)^+$.

3.5.3. Methyl 3-azido-2,3-dideoxy-α-D-*ribo*-hexopyranosiduronic acid (14). Hydrolysis of **9** gave **14** (90%): mp 99–101 °C; $[\alpha]_D^{20}$ +148 (*c* 1, CH_3OH); R_f 0.06 (solvent B); IR: *v* 3434 (COOH and O–H), 2941, 2842 (C–H), 2108 (N_3), 1737 (C=O) cm^{-1}; MALDI-TOFMS: *m/z* 240.0 $(M+Na)^+$, 256.0 $(M+K)^+$.

3.5.4. Methyl 3-azido-2,3-dideoxy-β-D-*arabino*-hexopyranosiduronic acid (15). Hydrolysis of **11** gave **15** (78%, syrup): $[\alpha]_D^{20}$ +8 (*c* 1, CH_3OH); R_f 0.05 (solvent B); IR: *v* 3414 (COOH and O–H), 2938 (C–H), 2104 (N_3), 1739 (C=O) cm^{-1}; MALDI-TOFMS: *m/z* 240.0 $(M+Na)^+$, 256.0 $(M+K)^+$.

3.5.5. Methyl 3-azido-2,3-dideoxy-α-L-*lyxo*-hexopyranosiduronic acid (16). Hydrolysis of **8** gave **16** (82%, syrup): R_f 0.02 (solvent B); IR: *v* 3416 (COOH and O–H), 2939 (C–H), 2103 (N_3), 1740 (C=O) cm^{-1}; MALDI-TOFMS: *m/z* 240.1 $(M+Na)^+$.

3.5.6. Methyl 3-azido-2,3-dideoxy-β-L-*lyxo*-hexopyranosiduronic acid (17). Hydrolysis of **10** gave **17** (80%, syrup): R_f 0.03 (solvent B); IR: *v* 3352 (COOH and O–H), 2938 (C–H), 2106 (N_3), 1739 (C=O) cm^{-1}; MALDI-TOFMS: *m/z* 240.0 $(M+Na)^+$, 256.0 $(M+K)^+$.

3.6. General procedure for hydrogenation of the azide group

Methyl (methyl 3-azido-2,3-dideoxyhexopyranosid)uronates (**6**–**11**) (100 mg, 0.43 mmol) or methyl 3-azido-2,3-dideoxyhexopyranosiduronic acids (**13**–**15**) were dissolved in abs MeOH (5 mL). The reaction mixture was stirred and argon was bubbled through for 5 min. After this time, the reaction mixture was hydrogenated over a 10% Pd/C catalyst for 1 h. The end of reduction was verified by TLC (solvent C). Then argon was bubbled through the mixture for 5 min. After this time, the reaction mixture was filtered, and the filtrate was evaporated.

3.6.1. Methyl (methyl 3-amino-2,3-dideoxy-α-D-*arabino*-hexopyranosid)uronate (18). Hydrogenation of **6** gave **18** (94%): mp 129–131 °C; $[\alpha]_D^{20}$ +121 (*c* 1.0, CH_3OH); R_f 0.27 (solvent C); IR: *v* 3344 (N–H), 3115 (O–H), 2927, 2912, 2837 (C–H), 1737 (C=O), 1589 (N–H), 1048 (C–N) cm^{-1}; MALDI-TOFMS: *m/z* 206.3 $(M+H)^+$, 228.2 $(M+Na)^+$, 244.3 $(M+K)^+$; Anal. Calcd for $C_8H_{15}NO_5$: C, 46.82; H, 7.37; N, 6.83. Found: C, 46.47; H, 7.38; N, 7.23.

3.6.2. Methyl (methyl 3-amino-2,3-dideoxy-β-D-*ribo*-hexopyranosid)uronate (19). Hydrogenation of **7** gave **19** (96%, syrup): $[\alpha]_D^{20}$ −96 (*c* 1.0, CH_3OH); R_f 0.26 (solvent C); IR: *v* 3348 (N–H), 3183 (O–H), 2932, 2841 (C–H), 1736 (C=O), 1582 (N–H), 1081 (C–N) cm^{-1}; MALDI-TOFMS: *m/z* 206.2 $(M+H)^+$, 228.2 $(M+Na)^+$, 244.1 $(M+K)^+$.

3.6.3. Methyl (methyl 3-amino-2,3-dideoxy-α-D-*ribo*-hexopyranosid)uronate (20). Hydrogenation of **9** gave **20** (90%): mp 116–118 °C; $[\alpha]_D^{20}$ +125 (*c* 1.0, CH_3OH); R_f 0.24 (solvent C); IR: *v* 3368 (N–H), 3102 (O–H), 2956, 2839 (C–H), 1747 (C=O), 1588 (N–H), 1043 (C–N) cm^{-1}; MALDI-TOFMS: *m/z* 206.1 $(M+H)^+$, 228.1 $(M+Na)^+$, 244.0 $(M+K)^+$; Anal. Calcd for $C_8H_{15}NO_5$: C, 46.82; H, 7.37; N, 6.83. Found: C, 46.66; H, 7.40; N, 6.52.

3.6.4. Methyl (methyl 3-amino-2,3-dideoxy-β-D-*arabino*-hexopyranosid)uronate (21). Hydrogenation of **11** gave **21** (98%): mp 138–139 °C; $[\alpha]_D^{20}$ −73 (*c* 1.0, CH_3OH); R_f 0.29 (solvent C); IR: *v* 3351, 3291 (N–H, O–H), 2956, 2928, 2842 (C–H), 1746 (C=O), 1539 (N–H), 1058 (C–N) cm^{-1}; MALDI-TOFMS: *m/z* 206.1 $(M+H)^+$, 228.1 $(M+Na)^+$, 244.1 $(M+K)^+$; Anal. Calcd for $C_8H_{15}NO_5$: C, 46.82; H, 7.37; N, 6.83. Found: C, 47.07; H, 7.43; N, 6.59.

3.6.5. Methyl (methyl 3-amino-2,3-dideoxy-α-L-*lyxo*-hexopyranosid)uronate (22). Hydrogenation of **8** gave **22** (83%, syrup): R_f 0.16 (solvent C); IR: *v* 3347 (N–H, O–H), 2955 (C–H), 1753 (C=O), 1598 (N–H), 1055 (C–N) cm^{-1}; MALDI-TOFMS: *m/z* 206.0 $(M+H)^+$, 228.0 $(M+Na)^+$.

3.6.6. Methyl (methyl 3-amino-2,3-dideoxy-β-L-*lyxo*-hexopyranosid)uronate (23). Hydrogenation of **10** gave **23** (95%): mp 126–128 °C; $[\alpha]_D^{20}$ +58 (*c* 1, CH_3OH); R_f 0.18 (solvent C); IR: *v* 3350, 3291 (N–H, O–H), 2955, 2845 (C–H), 1752 (C=O), 1593 (N–H), 1068 (C–N) cm^{-1}; MALDI-TOFMS: *m/z* 206.1 $(M+H)^+$, 228.1 $(M+Na)^+$ 244.1 $(M+K)^+$; Anal. Calcd for $C_8H_{15}NO_5$: C, 46.82; H, 7.37; N, 6.83. Found: C, 46.49; H, 7.35; N, 6.48.

3.6.7. Methyl 3-amino-2,3-dideoxy-β-D-*ribo*-hexopyranosiduronic acid (25). Hydrogenation of **13** gave **25** (96%, syrup): R_f 0.24 (solvent C); IR: *v* 2700–3600 (NH_3^+, O–H), 2927 (C–H), 1604, 1419 (COO^-) cm^{-1}; MALDI-TOFMS: *m/z* 192.2 $(M+H)^+$, 214.2 $(M+Na)^+$, 230.2 $(M+K)^+$.

3.6.8. Methyl 3-amino-2,3-dideoxy-α-D-*ribo*-hexopyranosiduronic acid (26). Hydrogenation of **14** gave **26** (76%, syrup): R_f 0.24 (solvent C); IR: *v* 2400–3600 (NH_3^+, O–H), 2950, 2901, 2846 (C–H), 1607, 1409 (COO^-) cm^{-1}; MALDI-TOFMS: *m/z* 192.1 $(M+H)^+$, 214.1 $(M+Na)^+$, 230.0 $(M+K)^+$.

3.6.9. Methyl 3-amino-2,3-dideoxy-β-D-*arabino*-hexopyranosiduronic acid (27). Hydrogenation of **15** gave **27** (97%): mp 215–219 °C; R_f 0.27 (solvent C); IR: *v* 2500–3600 (NH_3^+, O–H), 2928 (C–H), 1609, 1417 (COO^-) cm^{-1}; MALDI-TOFMS: *m/z* 192.1 $(M+H)^+$, 214.1 $(M+Na)^+$, 230.0 $(M+K)^+$ Anal. Calcd for $C_7H_{13}NO_5$: C, 43.98; H, 6.85; N, 7.33. Found: C, 43.65; H, 6.75; N, 6.90.

3.7. General procedure for hydrolysis of 5-methoxycarbonyl group in 18 and 21

Methyl (methyl 3-amino-2,3-dideoxyhexopyranosid)uronates (**18** and **21**) (100 mg, 0.49 mmol) dissolved in MeOH (2.5 mL) were stirred with 1 M NaOH (aq) (0.73 mL, 1.5 equiv) at rt for 2 h. The end of hydrolysis was detected by TLC (solvent D). The solution was then neutralized with Dowex-50Wx8 (H^+) ion-exchange resin, filtered, and the filtrate was evaporated.

3.7.1. Methyl 3-amino-2,3-dideoxy-α-D-*arabino*-hexopyranosiduronic acid (24). Hydrolysis of **18** gave **24** (76%): mp 170 °C dec; R_f 0.26 (solvent C); IR: *v* 2500–3600 (NH_3^+, O–H), 2922, 2852 (C–H), 1609, 1409 (COO^-) cm^{-1}; MALDI-TOFMS: *m/z* 192.1 $(M+H)^+$, 214.1 $(M+Na)^+$, 230.0 $(M+K)^+$.

3.7.2. Methyl 3-amino-2,3-dideoxy-β-D-*arabino*-hexopyranosiduronic acid (27). Hydrolysis of **21** gave **27** (84%); all data as in Section 3.6.9.

3.8. Procedure A for synthesis of diglycotides

Methyl 3-azido-2,3-dideoxyhexopyranosiduronic acids (**12** and **15**) (13 mg, 0.06 mmol) and methyl (methyl 3-amino-2,3-dideoxyhexopyranosid)uronates (**17** and **20**) (12.3 mg, 0.06 mmol) were dissolved in dry CH_2Cl_2 (1 mL). Then, HOBt (16.2 mg, 0.12 mmol) and DCC (12.4 mg, 0.06 mmol) were added with stirring, and dry DMF was dropped in to dissolve all compounds. The mixture was stirred at rt and detected by TLC (solvent C). After 1 h, the precipitate was filtered off, the filtrate was evaporated, and the crude product was purified by column chromatography (solvent B).

3.8.1. Methyl {methyl 3-[(methyl 3′-azido-2′,3′-dideoxy-α-D-*arabino*-hexopyranosid)-uronamido]-2,3-dideoxy-α-D-*arabino*-hexopyranosid}uronate (28). Reaction of **12** and **18** gave **28** (84%, syrup): R_f 0.55 (solvent B); IR: *v* 3284–3517 (N–H, O–H), 2928, 2851 (C–H), 2102 (N_3), 1733 (ester C=O), 1655 (amide I), 1544 (amide II) cm^{-1}; MALDI-TOFMS: *m/z* 405.2 $(M+H)^+$, 427.2 $(M+Na)^+$, 443.2 $(M+K)^+$.

3.8.2. Methyl {methyl 3-[(methyl 3′-azido-2′,3′-dideoxy-β-D-*arabino*-hexopyranosid)-uronamido]-2,3-dideoxy-β-D-*arabino*-hexopyranosid}uronate (31). Reaction of **15** and **21** yielded **31** (70%, syrup): R_f 0.49 (solvent B); IR: *v* 3326 (N–H, O–H), 2927, 2850 (C–H), 2103 (N_3), 1743 (ester C=O), 1653 (amide I), 1538 (amide II) cm^{-1}; MALDI-TOFMS: *m/z* 405.2 $(M+H)^+$, 427.2 $(M+Na)^+$, 443.2 $(M+K)^+$.

3.9. Procedure B for synthesis of diglycotides

Methyl 3-azido-2,3-dideoxyhexopyranosiduronic acids (**13**–**15**) (19.5 mg, 0.09 mmol) and methyl (methyl 3-amino-2,3-dideoxyhexopyranosid)uronates (**19**–**21**) (18.5 mg, 0.09 mmol) were dissolved in dry CH_2Cl_2 (1.5 mL). Then, HOAt (24.5 mg, 0.18 mmol) and HATU (34.2 mg, 0.09 mmol) were added with stirring, and dry DMF was dropped in to dissolve all compounds. The mixture was stirred at rt and detected by TLC (solvent C). After 1 h, the precipitate was filtered off, the filtrate was evaporated, and the crude product was purified by column chromatography (solvent B).

3.9.1. Methyl {methyl 3-[(methyl 3′-azido-2′,3′-dideoxy-β-D-*ribo*-hexopyranosid)uronamido]-2,3-dideoxy-β-D-*ribo*-hexopyranosid}uronate (29). Reaction of **13** and **19** gave **29** (91%): mp 78–79 °C; R_f 0.47 (solvent B); IR: *v* 3410 (N–H, O–H), 2936, 2853 (C–H), 2102 (N_3), 1732

(ester C=O), 1651 (amide I), 1538 (amide II) cm^{-1}; MALDI-TOFMS: *m/z* 427.1 $(M+Na)^+$, 443.1 $(M+K)^+$.

3.9.2. Methyl {methyl 3-[(methyl 3′-azido-2′,3′-dideoxy-α-D-*ribo*-hexopyranosid)uronamido]-2,3-dideoxy-α-D-*ribo*-hexopyranosid}uronate (30). Reaction of **14** and **20** gave **30** (53%, syrup): R_f 0.29 (solvent B); IR: *v* 3381 (N–H, O–H), 2926, 2854 (C–H), 2107 (N_3), 1748 (ester C=O), 1660 (amide I), 1538 (amide II) cm^{-1}; MALDI-TOFMS: *m/z* 405.2 $(M+H)^+$, 427.2 $(M+Na)^+$, 443.2 $(M+K)^+$.

3.9.3. Methyl {methyl 3-[(methyl 3′-azido-2′,3′-dideoxy-β-D-*arabino*-hexopyranosid)-uronamido]-2,3-dideoxy-β-D-*arabino*-hexopyranosid}uronate (31). Reaction of **15** and **21** led to **31** (67%, syrup): all data as in Section 3.8.2.

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