Pergamon

Tetrahedron 57 (2001) 6215–6227

TETRAHEDRON

Synthesis of new glycosyl-α-aminoacid derivatives for glycopeptide chemistry

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Received 18 December 2000; revised 14 May 2001; accepted 29 May 2001

Abstract—The synthesis of new *N*- or *C*-protected glycosyl-α-aminoacids and their use to prepare new glycopeptides is described. The overall synthetic strategy to obtain these new α-aminoacid chirons involves four distinct steps from dialdoses: (1) a diastereoselective Darzens reaction between the potassium anion derived from isopropyl dichloroacetate and a suitable protected dialdose, (2) the one-pot transformation of the so-obtained isopropyl glycosyl-α-chloroglycidic ester with magnesium iodide, then sodium hydrogenosulfite, into an isopropyl glycosyl-α-ketoester, (3) the reductive amination of the α-ketoester with (*S*)-α-methylbenzylamine and an hydrogenating reagent, (4) *N*- or *C*-selective deprotection and further peptidic coupling.

1. Introduction

Carbohydrate moieties of glycopeptides play different decisive roles, especially in recognition phenomena.[1] The conformation[2] and solubility[3] of proteins are influenced by the oligosaccharide chain that can also prohibit the proteolytic cleavage.[4] As a result, the synthesis of glycopeptides is an attractive goal for an understanding of the mutual interactions between both moieties and for their biological interest. A lot of works concern the synthesis of models that mimic the natural glycopeptides with a *N*-glycosidic bond between the sugar residue and asparagine or with an *O*-glycosidic bond with hydroxy-containing aminoacids.[5] However, these compounds are sensitive towards acids or bases and represent a challenge to the synthetic chemist which uses acidic or basic conditions in both solution and solid-phase peptide synthesis.[6] Moreover, such as *N*- or *O*-glycopeptides are also subject to both chemical and enzymatic deglycosylation in vivo involving a limitation for their use as potential therapeutic agents.[7] More stable glycosyl analogs with a C–C anomeric bond between the peptide and the carbohydrate moiety[8] or with a C–C bond in another glucidic position have been synthesized to improve the metabolic stability of these potential drugs.[9]

Herein we report the complete study[10] concerning the synthesis of new stable glycosyl α-aminoesters **6a–e/6′a–e**, where the α-C of the glycine moiety is connected to the C-6 of a pyranose or to the C-5 of pentoses, their selective *N*- and *C*-deprotections and their incorporation into a peptide (Fig. 1).

Even though various synthetic approaches to furanosyl α-aminoacid derivatives have been reported over the years especially in the polyoxin series[11] none of them can be applied to the introduction of the α-C-glycine moiety at the C-5 of a furanose (as in **6b–d/6′b–d** that present one C more relatively to the analogue polyoxin moiety), or at the C-6 of a pyranose (as in **6a/6′a**). In this context, a particularly attractive strategy for the asymmetric synthesis of such

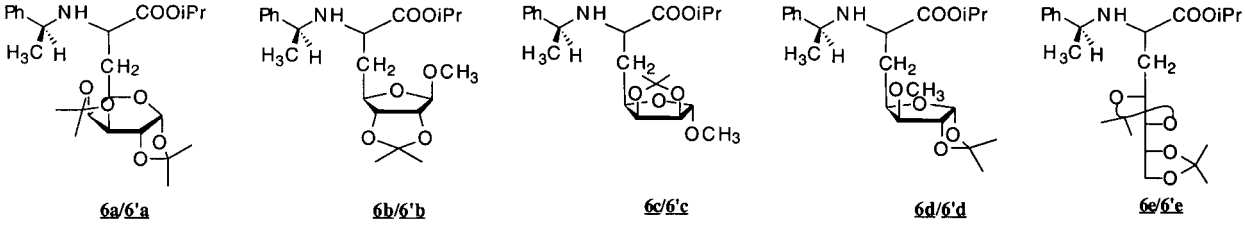

Figure 1.

Keywords: amino acids and derivatives; glycopeptides; amination; reduction.
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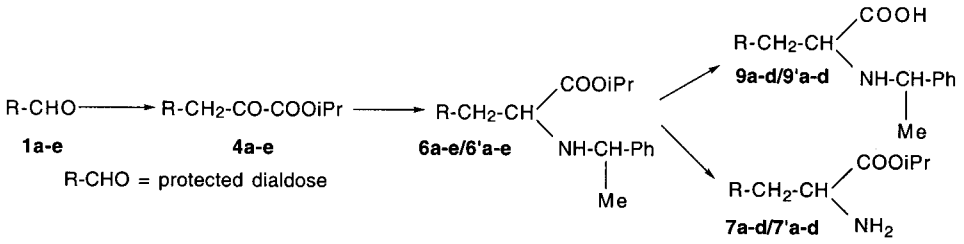
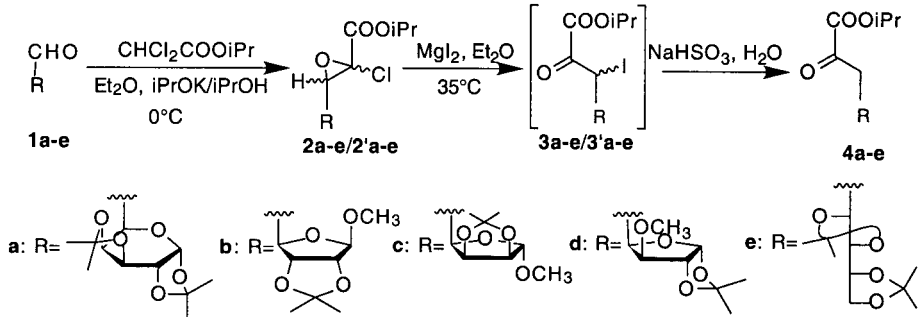


Figure 2.



Scheme 1.

Table 1.

Entry	1	2/2′	Yield %[a,b]	4	Yield %[a]
1	**1a**	**2a/2′a**	87 (84/16)	**4a**	84
2	**1b**	**2b/2′b**	79 (80/20)	**4b**	89
3	**1c**	**2c/2′c**	99 (65/35)	**4c**	67
4	**1d**	**2d/2′d**	86 (73/27)	**4d**	86
5	**1e**	**2e/2′e**	89 (62/38)	**4e**	87

[a] Yield of purified products.
[b] Diastereomer ratio.

systems involves the easy introduction of an α-ketoester moiety on a suitable protected dialdose followed by an aminoreduction and further chemoselective deprotections before coupling (Fig. 2).

2. Results and discussion

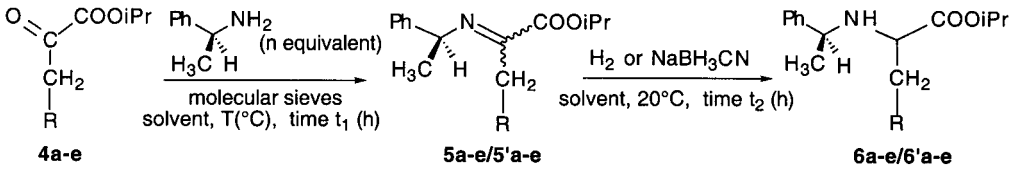
2.1. Synthesis of glycosyl α-ketoesters 4a–e

Glycosyl-α-ketoesters have already been shown by us to be very useful chiral building blocks to obtain bioactive molecules.[12] These starting materials are prepared in two steps from the readily available dialdoses **1a**–**e**: a Darzens reaction between **1a**–**e** and the potassium anion derived from isopropyl dichloroacetate cleanly afforded a diastereomeric mixture of α-chloroglycidic esters **2a**–**e**/**2′a**–**e** in high yield (79–99% yield). The reaction of these glycidic esters **2a**–**e**/**2′a**–**e** with magnesium iodide in diethylether, followed by a treatment with a saturated aqueous sodium hydrogenosulfite solution cleanly afforded the α-ketoesters **4a**–**e** (67–87% yield) via the epimeric no-isolated β-iodo-α-ketoesters **3a**–**e**/**3′a**–**e** (Scheme 1, Table 1).[13]

2.2. Reductive amination of α-ketoesters 4a–e (Scheme 2, Table 2)

With the aim to further obtain *N*-protected α-aminoacids or *N*-deprotected α-aminoesters for peptidic coupling, it was convenient to introduce a benzylamine moiety into **4a**–**e**, that could be selectively removed to lead to the primary amine by hydrogenation. A first attempt was achieved by reaction between benzylamine and α-ketoester **4a** in isopropanol, leading to the corresponding imine, followed by an hydrogenation using Pd/C (10%) as a catalyst. The use of any catalytic mineral or organic acid was prohibited for the formation of the intermediate benzylimine because of the presence of the sugar ketal groups. However, benzylamine was a too powerful nucleophilic reagent and a side-transamidification of the isopropyl ester accompanying the expected aminoproduct was observed in a proportion of 26%. As a result, the use of the more hindered (*S*)-α-methylbenzyl amine was studied to circumvent this difficulty and also because it seemed adaptable to realize a double asymmetric induction with the carbohydrate moiety during the hydrogenation step. Effectively, in these conditions any side-transamidification of the isopropylester was observed, but the imine formation in the case of **4a** was slow, as a consequence of the steric hindrance. The best conditions to reach **5a/5′a** needed 2 equiv. of (*S*)-α-methylbenzylamine in benzene at reflux, for 13 h, in the presence of crushed molecular sieves. For the other α-ketoesters **4b**–**e**, the imines **5b**–**e** were prepared in milder conditions with 2 equiv. of (*S*)-α-methylbenzylamine, in isopropyl alcohol, at room temperature, for 24 h. The imines **5a**–**e**/**5′a**–**e** were not isolated, as a result of their inclination to hydrolyse into starting α-ketoesters **4a**–**e**, but directly submitted to hydrogen in the presence of palladium (10%) on charcoal for 24 h at normal pressure in most cases (procedure A).

The best results for products **6** were obtained in the case of the aminoreduction of the D-galacto α-ketoester **4a/4′a**, whereas relatively poor yields were obtained in furanic and linear series. In the case of the pyranic series we have noted that the reduction step was far more rapid with the hydrogen pressure increase (8 h under a pressure of 10 bar instead of 24 h under the normal pressure). Concurrently the yield increased up



Scheme 2.

Table 2.

Entry	Starting material	Product	n	Solvent	T (°C)	t_1 (h)		t_2 (h)	Overall yield %[a]	Diastereomeric ratio[b]
1	**4a**	**6a/6′a**	1	*i*PrOH	20	24	H_2, 1 bar	24	30	43/57
2	**4a**	**6a/6′a**	1	AcOEt	20	24	H_2, 1 bar	24	36	50/50
3	**4a**	**6a/6′a**	1	C_6H_6	20	24	H_2, 1 bar	24	–	–
4	**4a**	**6a/6′a**	2	*i*PrOH	20	24	H_2, 1 bar	24	70	49/51
5	**4a**	**6a/6′a**	2	*i*PrOH	20	24	H_2, 10 bar	8	86	49/51
6	**4a**	**6a/6′a**	2	C_6H_6	reflux	13	H_2, 10 bar	8	92	45/55
7	**4b**	**6b/6′b**	2	*i*PrOH	20	24	H_2, 1 bar	24	30	54/46
8	**4b**	**6b/6′b**	2	*i*PrOH	20	24	$NaBH_3CN$	3.5	62	70/30
9	**4c**	**6c/6′c**	2	*i*PrOH	20	24	H_2, 10 bar	8	40	60/40
10	**4c**	**6c/6′c**	2	*i*PrOH	20	24	$NaBH_3CN$	3.5	65	60/40
11	**4d**	**6d/6′d**	2	*i*PrOH	20	24	H_2, 1 bar	24	42	50/50
12	**4d**	**6d/6′d**	2	*i*PrOH	20	24	$NaBH_3CN$	3.5	35	53/47
13	**4e**	**6e/6′e**	2	*i*PrOH	20	24	H_2, 1 bar	24	45	39/61

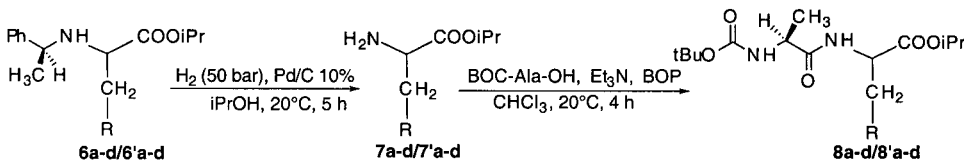
[a] Yield of purified products.
[b] The diastereomeric ratio was evaluated by ^{1}H NMR (250 MHz) on the crude product.

to 86% for **6a/6′a**. This difference was assigned to a partial hydrogenolysis of the α-methylbenzylamine moiety of **6a/6′a** that occured in the reaction medium when the reduction was too slow under normal pressure and that led to **7a/7′a** with a free amino group (Scheme 3). Compound **7a/7′a** was detected only in the crude product and was not eluted on the silicagel chromatographic column during the purification. In the furanic and D-arabino linear series, the products **6b–e** were always accompanied by some quantities of the starting α-ketoesters **4b–e** having not reacted (10–20%), with some corresponding α-hydroxyester reduction products (4–9%). It means that imine formation was not complete in these cases, even after 24 h. These structures obviously needed either a much longer reaction time than in the D-galacto series or a large excess of α-methylbenzylamine. Moreover an important loss of product after purification on a silicagel chromatographic column (about 30%) was associated with the presence in the crude product of the polar α-aminoesters **7b–e/7′b–e** resulted from the side debenzylation during the hydrogenation step. An attempt to increase the hydrogen pressure in the case of **5c/5′c** with the aim to reduce the reduction time and then to decrease this debenzylation, as for **5a**, revealed to be relatively inefficient in the furanic series (compare entries 9, 11, 13).

An improved method was then studied to obtain the secondary amines **6b–d/6′b–d** without side hydrogenolysis, especially in the case of furanic structures. A first attempt with sodium borohydride to reduce the intermediate imine showed no improvement, because the isopropyl ester group was also affected and reduced into alcohol. However, the use of the smooth reductor sodium cyanoborohydride in isopropanol was better, and even though literature recommended the reduction of imine at pH=6–8,[14] the imines **5/5′** were enough reactive to be reduced under basic pH. By this procedure, the imines **5** were reduced with 1 equiv. of sodium cyanoborohydride, with stirring at room temperature for 3.5 h, and quenched by water (procedure B). The crude was concentrated, extracted with chloroform, dried with sodium sulphate, evaporated, and purified on a silicagel chromatography column.

With $NaBH_3CN$ no side hydrogenolysis of the α-methylbenzyl moiety was observed and the sole noticed secondary products were α-hydroxyesters resulted from the reduction of the starting α-ketoesters **4b–d**. The yields increased in all cases, excepted for the D-xylo compound **6d/6′d**, that could be explained by a lower reactivity of the relatively hindered carbonyl in **4d**, due to the proximity of the *cis* methoxy at C-3.

No significant diastereoisomeric excess was noted in the products **6**, that is quite surprising, because it could be supposed, a priori, that the chiral D-sugar moieties combined with the (*S*) configuration of the *N*-α-methylbenzylic carbon would involve a high diastereoselective hydrogenation of the intermediate imines **5**.



Scheme 3.

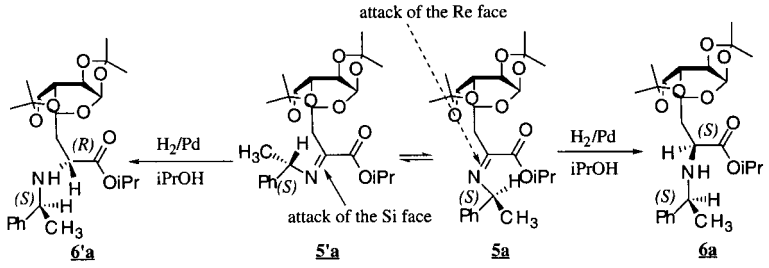


Figure 3.

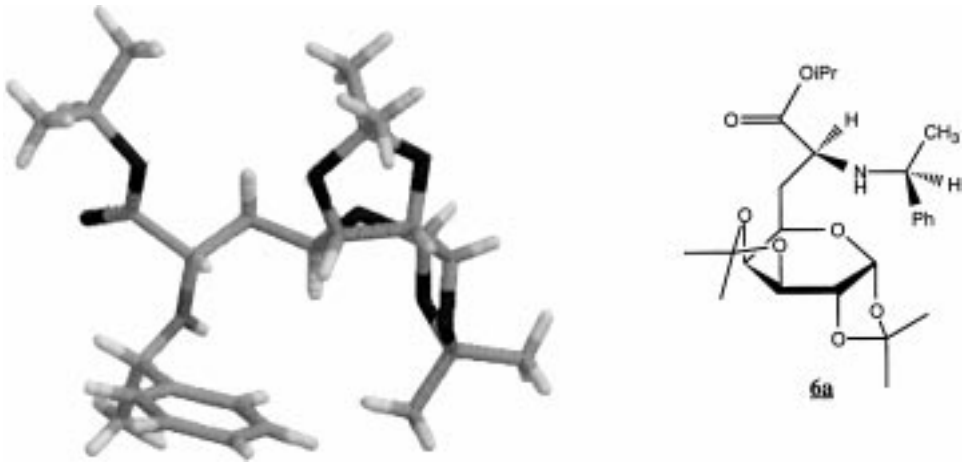


Figure 4.

In fact, the ^{1}H NMR of the crude product **5a**, as an example, indicated the presence of two conformational diastereomers **5a/5′a** (50/50) which differed by the *Z*/*E* conformations of the imine moiety. A non-chelated model described by Harada[15] in the case of aliphatic compounds could be applied to the imine **5a/5′a** and could explain the lack of diastereoselectivity. The stereomer **5a** could lead mainly to the aminoester **6a** (*S*), whereas **5′a** could lead mainly to the aminoester (*R*) (Fig. 3).

Nevertheless, in the particular case of **6a/6′a**, the two diastereoisomers could be easily separated by selective precipitation in diethylether, that compensated for the non-diastereoselectivity of the hydrogenation step: **6a** was insoluble in diethylether whereas **6′a** was completely soluble in this solvent. This interesting property was not found again for the other α-aminoesters **6b–e/6′b–e** that were isolated as a mixture of diastereoisomers.

As a consequence, the structure of pure **6a** was established by X-ray crystallography[16] after recrystallization in chloroform. The α-carbon of the aminoester moiety appeared to be (*S*) (Fig. 4).

2.3. Debenzylation and N-side coupling

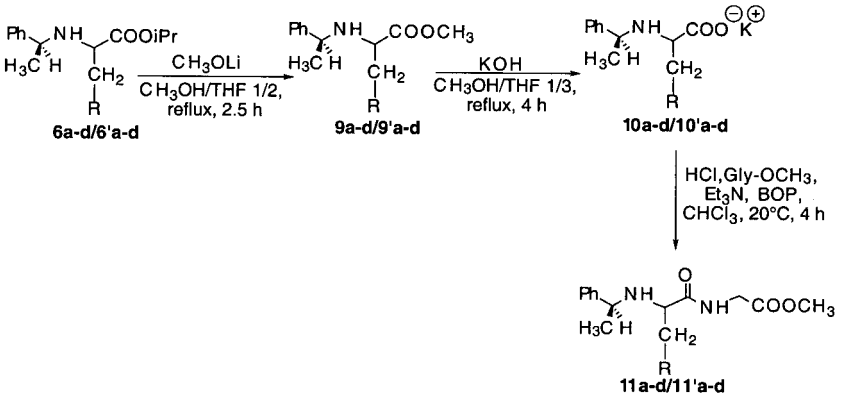
Each mixture of diastereoisomeric compounds **6a–d/6′a–d** was hydrogenolyzed in isopropanol for 5 h in the presence of Palladium on charcoal (10%) and under 50 bar hydrogen pressure.[17] The crude products were then filtered on celite to remove the catalyst, and the resulting primary α-aminoesters **7** were directly coupled during 4 h in chloroform at room temperature with BOC–Ala–OH, triethylamine and benzotriazolyloxy trisdimethylaminophosphonium hexafluorophosphate (BOP) as coupling reagents (Scheme 3, Table 3).[18]

In these conditions the expected dipeptides **8** were obtained with excellent yields and with exactly the same diastereomeric ratios as those of the starting amino synthons **7**. This indicated that coupling reactions were effected without any racemisation and with the same rate with each diastereomer **7a–d** and **7′a–d**. Moreover, coupling conditions were

Table 3.

Entry	Starting material **6**	**7**	Yield %[a]	Dipeptide **8**	Yield %[b]
1	**6a/6′a** 98/2	**7a/7′a** 98/2	95	**8a/8′a** 98/2	93
2	**6a/6′a** 10/90[c]	**7a/7′a** 10/90	97	**8a/8′a** 10/90	80
3	**6c/6′c** 60/40	**7c/7′c** 60/40	97	**8c/8′c** 60/40	64
4	**6d/6′d** 55/45	**7d/7′d** 55/45	99	**8d/8′d** 55/45	87

[a] Yield of crude products.
[b] Yield of purified products.
[c] All diastereomeric ratios were evaluated by ^{1}H NMR (250 MHz) on the crude product.



Scheme 4.

Table 4.

Entry	Starting material **6**	Methyl ester **9**	Yield %[a]	Dipeptide **11**	Yield %[a]
1	**6a**	**9a**	83	**11a**	81
2	**6a/6′a** 10/90	**9a/9′a** 10/90	86	**11a/11′a** 10/90	61
3	**6c/6′c** 60/40	**9c/9′c** 60/40	80	**11c/11′c** 60/40	75
4	**6d/6′d** 55/45	**9d/9′d** 55/45	84	**11d/11′d** 55/45	85

[a] Yield of purified products.

entirely compatible with ketal or ether protections of the carbohydrate moieties.

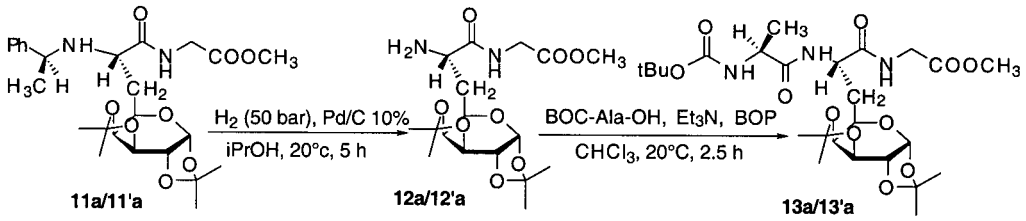
2.4. Hydrolysis of the isopropyl ester group and C-side coupling (Scheme 4, Table 4)

Hydrolysis of the isopropyl ester of **6** proved very difficult and various hydrolysis conditions were studied with **6a/6′a** as model. Neither potassium carbonate in a minimum of water (that was used by us with success for the terminal hydrolysis of the isopropyl ester of a KDO precursor),[12] or KOH in THF/MeOH at different temperatures, or KOH/dicyclohexyl-18-crown-6, gave total hydrolysis. However, the by-product methyl ester **9a/9′a** was partly obtained (63%) with the expected potassium carboxylate **10a/10′a** (13%) after 3 h at reflux of **6a/6′a** with a 1N solution of potassium hydroxide (1 equiv.) in the solvent mixture THF/MeOH 1/2. Prolongation of the reaction time led to product degradation. These results suggested that the isopropyl ester **6a/6′a** was first transesterified into the methyl ester **9a/9′a** that led to the carboxylate **10a/10′a**. As a consequence, it seemed more convenient to obtain **10a/10′a** from methyl ester **9a/9′a** as starting material instead of isopropyl ester **6a/6′a**. Unfortunately the initial Darzens reaction was less efficient with methyl dichloroacetate than with isopropyl dichloroacetate, so that it was more convenient to adjust the complete transesterification of **9a/9′a** from **6a/6′a**. This was successfully effected by stirring a mixture of lithium methylate and isopropyl α-aminoester **6a/6′a** in MeOH/THF (1/2) at reflux during 2.5 h. In these conditions, all the diastereomer methyl esters **9a–d** were obtained and isolated after purification by chromatography on silicagel. It was noted that these transesterifications were carried out without any epimerisation and led to the expected methyl esters in good yields whatever the nature of the carbohydrate moiety. Further hydrolysis of diasteromers **9a–d** with 1 equiv. of 1N potassium hydroxide, in MeOH/THF 1/3 at reflux for 4 h led to the carboxylates **10a–d** which were directly coupled, in situ, with HCl, GlyOMe, in the same coupling conditions as those explained above (Scheme 4, Table 4).

2.5. Introduction of the 2-(1′,2′;3′,4′-di-*O*-isopropylidene-6′-deoxy-α-D-galactopyranosyl)glycine residue inside a peptide (Scheme 5)

As a first example to illustrate the versatility of the method, we have chosen the inclusion of 2-(1′,2′;3′,4′-di-*O*-isopropylidene-6′-deoxy-α-D-galactopyranosyl)glycine between an alanine and a glycine residue. To prevent the classical oxazolone formation and therefore a possible epimerisation, the tripeptide was built from the chiron **6a/6′a** (98/2), by synthesizing first the dipeptide **11a/11′a** (98/2) according to Scheme 4. Secondly, **11a/11′a** (98/2) was debenzylated under the same conditions as those described above to obtain **7** from **6** (Scheme 3). Then, the so-obtained *N*-deprotected crude dipeptide **12a/12′a** (98/2) was coupled with (L)-BOC–Ala–OH in the presence of triethylamine and BOP to give the tripeptide **13a/13′a** (98/2) with an overall yield of 69% from **11a/11′a**, after chromatographic purification. Any epimerisation occurred as can be observed from the invariance of the diastereomeric ratios (Scheme 5).

Because natural glycoproteins include a lot of carbohydrate moities in different positions, the synthesis of peptides with the glycosyl moiety in any determined position represents an exciting challenge. With this aim, we have also studied the vicinal couplings, a priori the most difficult examples, having steric hindrance between two glycosylated aminoacid synthons. At first the carboxylic partner **10a/10′a** (98/2) was coupled with the amino partner **7a/7′a** (98/2) leading to the almost pure **14aa** with an excellent yield, whereas in a



Scheme 5.

second coupling, **10a/10′a** (98/2) reacted with the amino partner **7c/7′c** (60/40) yielded **14ac/14′ac** with a strict stereospecificity. It was noteworthy that these reactions, carried out in the presence of BOP and triethylamine, in chloroform, at room temperature, were rapid and lasted only 2.5 h (Scheme 6).

3. Conclusion

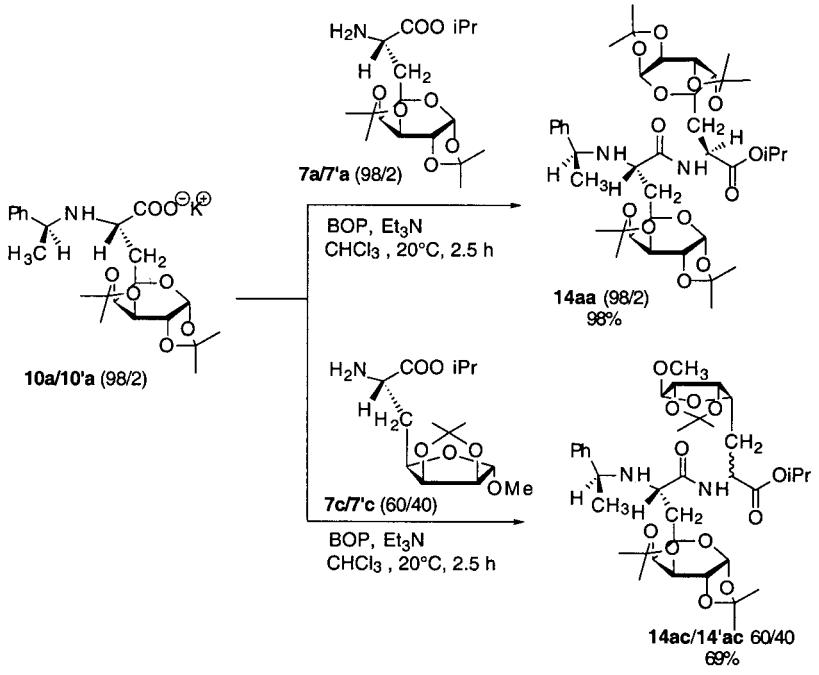
In conclusion, we have described a convenient route to a new class of glycosyl-α-aminoacid derivatives by reductive amination of precursor glycosyl-α-ketoesters and we have shown their use in peptide synthesis. This strategy offers many possibilities for combining together different glycosyl-α-aminoacids or to alternate with natural residues in any position. It allows access to an extremely varied library of glycopeptide analogues with potent biological applications. We are now continuing our investigations to increase the diastereofacial selectivity of the reductive amination for the obtention of pure diastereoisomer chirons, and at the same time we are studying the application of these chirons in solid phase peptide synthesis.

4. Experimental

Mass spectral data were obtained at the Faculté de Chimie, Université Louis Pasteur, Strasbourg. ^{1}H NMR and ^{13}C NMR were run at 250 (or 400 MHz) and 62.5 MHz, respectively. Chemical shifts are given in parts per million (ppm) using the residue solvent peaks as reference relatively to TMS. Tetrahydrofuran (THF) was distilled from sodium-benzophenone ketyl. Dichloromethane was distilled from P_2O_5. Unless otherwise noted, all reactions were performed in oven-dried glassware under an atmosphere of dry nitrogen. Solutions were evaporated under reduced pressure with a rotary evaporator, and the residues were chromatographied on a silica gel column using an ethyl acetate–hexane as eluent unless specified otherwise. All purified products gave satisfactory elemental analysis.

4.1. Procedure A for the reductive amination of glycosyl-α-ketoesters 4

In a typical procedure, 2 equiv. of (*S*)-α-methylbenzylamine (2.47 g, 20.4 mmol) were added to a solution of 1 equiv. of **4a** (3.66 g, 10.2 mmol) in 50 mL of isopropanol. The mixture was stirred at room temperature in the presence of



Scheme 6.

crushed molecular sieves during 24 h and then filtered. To the filtrate was added 1.8 g of palladium on charcoal 10%, and the solution was hydrogenated for 24 h at room temperature under normal pressure, or for 8 h at room temperature under a 10 bar initial pressure. The catalyst was removed by filtration and washed with chloroform. The solution was evaporated to dryness and the residue was purified on a silicagel chromatographic column with CH_2Cl_2/AcOEt (5/1) to give **6a/6′a** (49/51) (4.08 g, 8.8 mmol, 86%).

The diastereomers **6a** and **6′a** could be easily separated by precipitation in diethylether.

4.1.1. Isopropyl 7-[[(1′*S*)-1′-phenylethyl]amino]-6,7-dideoxy-1,2:3,4-di-*O*-isopropylidene-L-glycero-α-D-galacto-octopyranuronate 6a. White powder insoluble in ether. TLC (CH_2Cl_2/AcOEt (5/1)) R_f 0.65; mp 178°C; ^{1}H NMR (250 MHz, $CDCl_3$): δ=7.31–7.21 (m, 5H), 5.45 (d, 1H, J=5.1 Hz), 5.11–5.01 (m, 1H), 4.49 (dd, 1H, J=2.6, 8.1 Hz), 4.26 (dd, 1H, J=2.6, 5.1 Hz), 4.14–4.05 (m, 1H), 3.82–3.74 (m, 2H), 3.05 (dd, 1H, J=5.6, 6.8 Hz), 2.01–1.88 (m, 1H), 1.83–1.71 (m, 1H), 1.63 (s, 3H), 1.56 (s, 1H), 1.39 (s, 3H), 1.34 (s, 3H), 1.33 (d, 3H, J=6.8 Hz), 1.25 (d, 3H, J=5.1 Hz), 1.24 (s, 3H), 1.23 (d, 3H, J=6.0 Hz); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ=174.7, 145.5, 128.3, 127.1, 126.9, 109.0, 108.5, 96.5, 72.0, 70.9, 70.5, 68.0, 64.6, 56.9, 55.9, 33.4, 26.0, 25.9, 25.2, 25.0, 24.3, 21.9, 21.7; IR (KBr): ν=3332, 1722 cm^{-1}; α_D^{20}=−74.8 (c=0.79 g dl^{-1}, $CHCl_3$); MS (ESI): m/z: 464 (MH^+, 100%).

4.1.2. Isopropyl 7-[[(1′*S*)-1′-phenylethyl]amino]-6,7-dideoxy-1,2:3,4-di-*O*-isopropylidene-D-glycero-α-D-galacto-octopyranuronate 6′a. Orange oil soluble in ether. ^{1}H NMR (250 MHz, $CDCl_3$): δ=7.32–7.21 (m, 5H), 5.57 (d, 1H, J=5.0 Hz), 4.93–4.83 (m, 1H), 4.60 (dd, 1H, J=2.6, 7.7 Hz), 4.32 (dd, 1H, J=2.6, 5.0 Hz), 4.23–4.18 (m, 1H), 4.07 (dd, 1H, J=1.7, 7.7 Hz), 3.80–3.73 (m, 1H), 3.47 (dd, 1H, J=3.0, 10.7 Hz), 2.05–1.92 (m, 2H), 1.66 (s, 3H), 1.47 (s, 1H), 1.37 (s, 6H), 1.34 (s, 3H), 1.23 (d, 3H, J=7.3 Hz), 1.18 (d, 3H, J=6.4 Hz), 1.12 (d, 3H, J=6.0 Hz); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ=175.2, 145.8, 128.2, 126.8, 126.7, 108.8, 108.3, 96.5, 73.4, 71.0, 70.4, 67.9, 64.0, 56.6, 55.5, 34.9, 26.2, 25.9, 24.9, 24.2, 22.4, 21.7, 21.6; IR (KBr): ν=3325, 1722 cm^{-1}.

4.1.3. Isopropyl 6-[[(1′*S*)-1′-phenylethyl]amino]-5,6-dideoxy-3-*O*-methyl-1,2-*O*-isopropylidene-D,L-glycero-α-D-xylo-heptofuranuronate 6d/6′d. The starting material **4d** (320 mg, 1.06 mmol) gave **6d/6′d** 50/50 (180 mg, 42%, colourless oil) by procedure A.

6d: TLC (hexane/AcOEt (1/2)) R_f 0.79; ^{1}H NMR (250 MHz, $CDCl_3$): δ=7.31–7.26 (m, 5H), 5.82 (d, 1H, J=3.8 Hz), 5.12–5.04 (m, 1H), 4.45 (d, 1H, J=3.8 Hz), 4.4–4.3 (m, 1H), 3.69–3.61 (m, 1H), 3.17 (d, 1H, J=2.6 Hz), 3.14 (s, 3H), 2.89 (dd, 1H, J=5.1, 9.4 Hz), 1.90–1.80 (m, 2H), 1.54 (s, 4H), 1.32 (s, 3H), 1.29–1.22 (m, 9H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ=174.9, 145.1, 128.4, 127.2, 127.1, 111.2, 104.6, 83.8, 81.7, 77.2, 68.2, 57.5, 56.8, 56.6, 32.1, 26.7, 26.3, 25.1, 21.9, 21.8, 21.7; IR (KBr): ν=3430, 1722 cm^{-1}; MS (ESI): m/z: 408.3 (MH^+, 100%).

6′d: TLC (hexane/AcOEt (1/2)) R_f 0.79; ^{1}H NMR (250 MHz, $CDCl_3$): δ=7.31–7.25 (m, 5H), 5.87 (d, 1H, J=3.8 Hz), 5.04–4.90 (m, 1H), 4.57 (d, 1H, J=3.8 Hz), 4.42–4.36 (m, 1H), 3.81–3.73 (m, 1H), 3.61 (d, 1H, J=3.0 Hz), 3.45–3.35 (m, 1H), 3.32 (s, 3H), 2.04–1.70 (m, 2H), 1.52 (s, 4H), 1.33 (s, 3H), 1.33 (d, 3H, J=6.0 Hz), 1.20 (d, 3H, J=6.4 Hz), 1.17 (d, 3H, J=6.4 Hz); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ=174.7, 145.5, 128.4, 127.2, 126.7, 111.1, 104.4, 84.8, 81.7, 77.1, 68.2, 57.5, 56.8, 56.4, 31.6, 26.7, 26.2, 25.1, 22.7, 21.9, 21.7; IR (KBr): ν=3430, 1722 cm^{-1}; MS (ESI): m/z: 408.3 (MH^+, 100%).

4.1.4. Isopropyl 2-[[(1′*S*)-1′-phenylethyl]amino]-2,3-dideoxy-4,5:6,7-di-*O*-isopropylidene-D,L-glycero-D-arabino-heptouronate 6e/6′e. The starting material **4e** (600 mg, 1.82 mmol) gave **6e/6′e** 39/61 (360 mg, 45%, colourless oil) by procedure A; TLC (hexane/AcOEt (1/1)) R_f 0.50.

6e: ^{1}H NMR (250 MHz, $CDCl_3$): δ=7.27–7.17 (m, 5H), 5.09–4.99 (m, 1H), 4.10–3.95 (m, 1H), 3.95–3.78 (m, 2H), 3.71 (q, 1H, J=6.4 Hz), 3.55–3.42 (m, 2H), 3.17 (dd, 1H, J=6.4 Hz, J=6.8 Hz), 2.12–1.91 (m, 2H), 1.91–1.72 (m, 1H), 1.32 (d, 3H, J=6.4 Hz), 1.31 (s, 6H), 1.28 (s, 6H), 1.22 (d, 3H, J=6.0 Hz), 1.20 (d, 3H, J=6.4 Hz); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ=174.6, 145.2, 128.3, 126.8, 126.7, 109.5, 109.0, 81.2, 77.5, 76.8, 68.0, 67.5, 56.8, 56.7, 37.3, 27.1, 26.8, 26.6, 25.2, 22.6, 21.9, 21.7; IR (KBr): ν=3374, 1722 cm^{-1}; MS (ESI): m/z: 436.4 (MH^+, 100%).

6′e: ^{1}H NMR (250 MHz, $CDCl_3$): δ=7.31–7.22 (m, 5H), 5.01–4.91 (m, 1H), 4.15–3.98 (m, 2H), 3.96–3.85 (m, 2H), 3.78 (q, 1H, J=6.4 Hz), 3.57–3.45 (m, 2H), 3.17 (dd, 1H, J=6.4 Hz, J=6.8 Hz), 1.92–1.78 (m, 2H), 1.58 (br s, 1H), 1.40 (s, 3H),1.39 (s, 3H), 1.36 (d, 3H, J=6.4 Hz), 1.33 (s, 6H), 1.21 (d, 3H, J=6.4 Hz), 1.19 (d, 3H, J=6.4 Hz); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ=174.7, 145.7, 128.3, 126.8, 126.7, 109.5, 108.9, 81.3, 77.5, 76.8, 67.9, 67.5, 56.7, 56.2, 37.1, 27.3, 26.9, 26.6, 25.2, 22.6, 21.8, 21.6; IR (KBr): ν=3325, 1722 cm^{-1}; MS (ESI): m/z: 436.4 (MH^+, 100%).

4.2. Procedure B for the reductive amination of glycosyl-α-ketoesters 4

In a typical procedure, 2 equiv. of (*S*)-α-methylbenzylamine (180 mg, 1.51 mmol) were added to a solution of 1 equiv. of α-ketoester **4a** (270 mg, 0.75 mmol) in 5 mL of isopropanol and the mixture was stirred for 24 h in the presence of crushed molecular sieves. Then, 1 equiv. of sodium cyanoborohydride (47 mg, 0.75 mmol) was added, and the reaction was kept at room temperature during 3.5 h, quenched by water and extracted with chloroform. The organic layer was dried over magnesium sulphate, evaporated under reduced pressure, and the residue was purified by chromatography on a silica gel column.

4.2.1. Isopropyl 6-[[(1′*S*)-1′-phenylethyl]amino]-5,6-dideoxy-1-*O*-methyl-2,3-*O*-isopropylidene-D,L-glycero-β-D-ribo-heptofuranuronate 6b/6′b. The starting material **4b** (200 mg, 0.66 mmol) gave **6b/6′b** (166 mg, 62%, colourless oil) by procedure B; TLC (hexane/AcOEt (1/2)) R_f 0.87.

6b: ^{1}H NMR (250 MHz, $CDCl_3$): δ=7.32–7.20 (m, 5H), 5.03–4.87 (m, 1H), 4.82 (s, 1H), 4.63 (dd, 1H, J=6.0,

3.4 Hz), 4.53 (d, 1H, J=6.0 Hz), 4.05 (ddd, 1H, J=3.4, 5.6, 7.3 Hz), 3.76 (q, 1H, J=6.4 Hz), 3.46 (t, 1H, J=6.4 Hz), 3.29 (s, 3H), 2.09–2.01 (m, 2H), 1.51 (s, 1H), 1.45 (s, 3H), 1.35 (d, 3H, J=6.4 Hz), 1.32 (s, 3H), 1.21 (d, 3H, J=6.4 Hz), 1.18 (d, 3H, J=6.4 Hz); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ=174.2, 145.4, 128.2, 126.9, 126.6, 112.2, 106.6, 85.0, 80.4, 76.5, 67.9, 56.6, 56.1, 54.2, 32.0, 26.0, 24.9, 22.8, 21.7, 21.5; IR (KBr): ν=3380, 1722 cm^{-1}.

6′b: ^{1}H NMR (250 MHz, $CDCl_3$): δ=7.32–7.20 (m, 5H), 5.14–5.04 (m, 1H), 4.79 (s, 1H), 4.65 (dd, 1H, J=5.6, 3.8 Hz, 1H), 4.54 (d, 1H, J=5.6 Hz), 4.15 (m, 1H), 3.73 (q, 1H, J=6.4 Hz), 3.20 (s, 3H), 3.16 (dd, 1H, J=4.8, 9.8 Hz), 1.99–1.75 (m, 2H), 1.52 (s, 1H), 1.43 (s, 3H), 1.34 (d, 3H, J=6.4 Hz), 1.32 (s, 3H), 1.27 (d, 3H, J=6.4 Hz), 1.24 (d, 3H, J=6.4 Hz); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ=175.1, 144.8, 128.2, 126.8, 126.6, 112.0, 106.6, 85.1, 80.8, 76.6, 67.8, 56.3, 56.2, 54.4, 32.9, 26.3, 25.2, 22.3, 21.8, 21.6; IR (KBr): ν=3380, 1722 cm^{-1}.

4.2.2. Isopropyl 6-[[(1′*S*)-1′-phenylethyl]amino]-5,6-dideoxy-1-*O*-methyl-2,3-*O*-isopropylidene-D,L-glycero-α-D-lyxo-heptofuranuronate 6c/6′c. The starting materials **4c** (270 mg, 0.89 mmol) gave **6c/6′c** (235 mg, 65%, colourless oil) by procedure B; TLC (hexane/AcOEt (1/2)) R_f 0.86.

6c: ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.33–7.26 (m, 5H), 5.11–5.04 (m, 1H), 4.79 (s, 1H), 4.46 (d, 1H, J=5.9 Hz), 4.34 (dd, 1H, J=5.9, 3.7 Hz), 4.07 (dt, 1H, J=3.7, 6.8 Hz), 3.71 (q, 1H, J=6.6 Hz), 3.31 (s, 3H), 3.13 (t, 1H, J=6.8 Hz), 1.95 (t, 2H, J=6.8 Hz), 1.86 (br s, 1H), 1.38 (s, 3H), 1.34 (d, 3H, J=6.6 Hz), 1.31 (s, 3H), 1.27 (d, 3H, J=6.4 Hz), 1.23 (d, 3H, J=6.4 Hz); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ=174.7, 145.0, 128.2, 126.8, 126.5, 112.1, 106.7, 84.9, 80.0, 76.8, 67.9, 56.7, 56.5, 54.3, 32.4, 25.9, 24.8, 24.7, 21.7, 21.6.

6′c: ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.33–7.26 (m, 5H), 5.00–4.93 (m, 1H), 4.88 (s, 1H), 4.63 (dd, 1H, J=5.9, 3.4 Hz), 4.56 (d, 1H, J=5.9 Hz), 4.28–4.24 (m, 1H), 3.77 (q, 1H, J=6.6 Hz), 3.50 (dd, 1H, J=4.4, 9.8 Hz), 3.35 (s, 3H), 2.11–2.03 (ddd, 1H, J=8.5, 14.4, 4.4 Hz), 1.86 (br s, 1H), 1.85–1.76 (ddd, 1H, J=4.2, 14.4, 9.8 Hz), 1.45 (s, 3H), 1.33 (d, 3H, J=6.6 Hz), 1.22 (s, 3H), 1.21 (d, 3H, J=6.4 Hz), 1.19 (d, 3H, J=6.4 Hz); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ=174.6, 145.7, 128.2, 126.8, 126.5, 112.1, 106.6, 85.1, 80.7, 76.5, 67.9, 56.7, 56.2, 54.2, 32.5, 26.0, 25.1, 24.7, 21.8, 21.6.

6c/6′c: IR (KBr): ν=3339, 1722 cm^{-1}; MS (ESI): m/z: 408.3 (MH$^+$, 100%), 320.2 ((M−87)$^+$, 85%).

4.3. Hydrogenolysis of glycosyl-α-aminoesters 6

In a typical reaction, 100 mg of palladium 10% on charcoal was added to a solution of **6a/6′a** (98/2) (100 mg, 0.22 mmol) in 10 mL of isopropanol. The mixture was hydrogenated under a 50 bar pressure of hydrogen during 5 h at room temperature, then filtered through celite, and the filtrate was reduced in vacuo to yield **7a/7′a** (98/2) (75 mg, 95%).

4.3.1. Isopropyl 7-amino-6,7-dideoxy-1,2:3,4-di-*O*-isopropylidene-L-glycero-α-D-galacto-octopyranuronate 7a. White powder. ^{1}H NMR (250 MHz, $CDCl_3$): δ=6.01 (br s, 2H), 5.45 (d, 1H, J=5.1 Hz), 5.07 (h, 1H, J=6.0 Hz), 4.58 (dd, 1H, J=2.5, 8.1 Hz), 4.29 (dd, 1H, J=2.5, 5.1 Hz), 4.16 (dd, 1H, J=8.1, 1.7 Hz), 4.07–3.90 (m, 2H), 2.51–2.34 (m, 1H), 2.30–2.15 (m, 1H), 1.60 (s, 3H), 1.43 (s, 3H), 1.33 (s, 3H), 1.30 (s, 3H), 1.26 (d, 6H, J=6.0 Hz); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ=170.7, 109.4, 108.9, 96.3, 72.2, 71.0, 70.2, 69.7, 64.4, 51.2, 30.6, 25.9, 25.8, 24.7, 24.5, 21.6, 21.5; IR (KBr): ν=3409, 3233, 1743 cm^{-1}; MS (ESI): m/z: 360.2 (MH$^+$, 100%).

4.3.2. Isopropyl 7-amino-6,7-dideoxy-1,2:3,4-di-*O*-isopropylidene-D-glycero-α-D-galacto-octopyranuronate 7′a. The starting materials **6a/6′a** 10/90 (300 mg, 0.65 mmol) gave **7a/7′a** 10/90 (226 mg, 97%).

^{1}H NMR (250 MHz, $CDCl_3$): δ=5.51 (d, 1H, J=5.1 Hz), 5.2–5.07 (m, 1H), 4.60 (dd, 1H, J=2.1, 8.1 Hz), 4.32 (dd, 1H, J=2.1, 5.1 Hz), 4.12 (dd, 1H, J=8.1, 1.7 Hz), 4.02–3.95 (m, 1H), 2.68–2.57 (m, 1H), 2.25–2.15 (m, 1H), 1.54 (s, 3H), 1.49 (s, 3H), 1.34 (s, 3H), 1.32 (s, 3H), 1.34–1.29 (m, 6H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ=168.3, 109.8, 109.1, 96.1, 72.4, 71.0, 70.7, 70.2, 64.9, 51.4, 29.2, 26.1, 25.8, 24.7, 24.4, 21.7, 21.6; IR (KBr): ν=3409, 3233, 1743 cm^{-1}; MS (ESI): m/z: 360.2 (MH$^+$, 100%).

4.3.3. Isopropyl 6-amino-5,6-dideoxy-1-*O*-methyl-2,3-*O*-isopropylidene-D,L-glycero-α-D-xylo-heptopyranuronate 7c/7′c. The starting materials **6c/6′c** 60/40 (158 mg, 0.39 mmol) gave **7c/7′c** 60/40 (115 mg, 97%, viscous powder).

7c: ^{1}H NMR (400 MHz, CD_3CN): δ=5.01 (h, 1H, J=6.3 Hz), 4.79 (s, 1H), 4.68–4.64 (m, 1H), 4.51 (d, 1H, J=5.8 Hz), 4.11–4.05 (m, 1H), 3.63–3.56 (m, 1H), 3.27 (s, 3H), 2.59 (br s, 2H), 2.13–1.78 (m, 2H), 1.40 (s, 3H), 1.28 (s, 3H), 1.24 (d, 6H, J=6.3 Hz; ^{13}C NMR (62.5 MHz, $CDCl_3$): δ=168.1, 112.7, 106.7, 85.0, 80.3, 75.4, 70.6, 55.2, 51.6, 32.1, 26.1, 24.9, 21.7; IR (KBr): ν=3416, 1735 cm^{-1}.

7′c: ^{1}H NMR (400 MHz, CD_3CN): δ=5.00 (h, 1H, J=6.3 Hz), 4.81 (s, 1H), 4.68–4.64 (m, 1H), 4.50 (d, 1H, J=5.0 Hz), 4.11–4.05 (m, 1H), 3.63–3.56 (m, 1H), 3.28 (s, 3H), 2.59 (br s, 2H), 2.13–1.78 (m, 2H), 1.40 (s, 3H), 1.28 (s, 3H), 1.27 (d, 6H, J=6.3 Hz); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ=168.5, 113.0, 107.1, 85.1, 80.3, 75.7, 70.5, 54.4, 51.2, 32.9, 26.0, 25.0, 21.5; IR (KBr): ν=3416, 1735 cm^{-1}.

4.3.4. Isopropyl 6-amino-5,6-dideoxy-3-*O*-methyl-1,2-*O*-isopropylidene-D,L-glycero-α-D-xylo-heptopyranuronate 7d/7′d. The starting materials **6d/6′d** 55/45 (70 mg, 0.17 mmol) gave **7d/7′d** 55/45 (51 mg, 99%).

7d: ^{1}H NMR (250 MHz, $CDCl_3$): δ=5.87 (d, 1H, J=3.8 Hz), 5.04 (h, 1H, J=6.2 Hz), 4.56 (d, 1H, J=3.8 Hz), 4.38–4.30 (m, 1H), 3.65–3.57 (m, 2H), 3.40 (s, 3H), 2.7 (br s, 1H), 2.20–1.7 (m, 2H), 1.48 (s, 3H), 1.29 (s, 3H), 1.25 (d, 6H, J=6.2 Hz); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ=174.8, 111.3, 104.6, 84.9, 81.6, 77.2, 68.4, 57.5, 52.0, 32.2, 26.6, 26.1, 21.8, 21.7; IR (KBr): ν=3455, 3403, 1728 cm^{-1}.

7′d: ^{1}H NMR (250 MHz, $CDCl_3$): δ=5.87 (d, 1H,

J=3.8 Hz), 5.03 (h, 1H, J=6.2 Hz), 4.57 (d, 1H, J=3.8 Hz), 4.38–4.30 (m, 1H), 3.65–3.57 (m, 2H), 3.41 (s, 3H), 2.7 (br s, 1H), 2.20–1.7 (m, 2H), 1.48 (s, 3H), 1.29 (s, 3H), 1.25 (d, 6H, J=6.2 Hz); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ=174.2, 111.3, 104.4, 84.6, 81.4, 77.8, 68.6, 57.6, 52.6, 32.4, 26.6, 26.1, 21.8, 21.7; IR (KBr): ν=3455, 3403, 1728 cm^{-1}.

4.4. General procedure for N-side coupling

A mixture of 1 equiv. of α-aminoester **7/7′**, 1.1 equiv. of BOC–Ala–OH, 1.5 equiv. of triethylamine, 1.1 equiv. of BOP, in chloroform, was stirred for 4 h at room temperature. The reaction mixture was then washed with water, and the aqueous layer was extracted with chloroform. The organic layers were joined together and dried over sodium sulphate, then evaporated, and the residue was purified by chromatography on a silica gel column.

4.4.1. Isopropyl 7-[[(2′*S*)-2′-(*tert*-butoxycarbonylamino)-1′-oxopropyl]amino]-6,7-dideoxy-1,2:3,4-di-*O*-isopropylidene-L-glycero-α-D-galacto-octopyranuronate 8a. The starting materials **7a/7′a** (98/2) (75 mg, 0.21 mmol) gave **8a/8′a** (98/2) (103 mg, 93%).

TLC (hexane/AcOEt (1/3)) R_f 0.69; ^{1}H NMR (250 MHz, $CDCl_3$): δ=6.90 (br s, 1H), 5.49 (d, 1H, J=5.1 Hz), 5.33 (d, 1H, J=6.0 Hz), 5.13–4.95 (m, 1H), 4.59 (dd, 1H, J=2.6, 7.7 Hz), 4.55–4.48 (m, 1H), 4.30 (dd, 1H, J=5.1, 2.6 Hz), 4.28–4.23 (m, 1H), 4.13 (dd, 1H, J=1.7, 7.7 Hz), 3.84–3.80 (m, 1H), 2.31–2.17 (m, 1H), 2.14–2.04 (m, 1H), 1.51 (s, 3H), 1.45 (s, 12H), 1.38 (d, 3H, J=6.8 Hz), 1.34 (s, 3H), 1.33 (s, 3H), 1.25 (d, 3H, J=4.2 Hz), 1.21 (d, 3H, J=4.2 Hz); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ=172.4, 170.9, 155.1, 109.4, 108.7, 96.4, 77.5, 72.8, 70.9, 70.1, 69.0, 65.2, 50.9, 49.9, 30.7, 28.3, 26.0, 24.7, 24.5, 21.7, 21.6, 19.2; IR (KBr): ν=3416, 1731, 1714, 1680 cm^{-1}.

4.4.2. Isopropyl 7-[[(2′*S*)-2′-(*tert*-butoxycarbonylamino)-1′-oxopropyl]amino]-6,7-dideoxy-1,2:3,4-di-*O*-isopropylidene]-D-glycero-α-D-galacto-octopyranuronate 8′a. The starting materials **7a/7′**10/90 (0.217 g, 0.60 mmol) gave **8a/8′a** 10/90 (0.255 g, 80%).

TLC (hexane/AcOEt (1/3)) R_f 0.69; ^{1}H NMR (250 MHz, $CDCl_3$): δ=7.46 (br s, 1H), 5.54 (d, 1H, J=5.1 Hz), 5.24 (d, 1H, J=6.0 Hz), 5.08–4.94 (m, 1H), 4.58 (dd, 1H, J=2.6, 8.1 Hz), 4.54–4.47 (m, 1H), 4.31 (dd, 1H, J=5.1, 2.6 Hz), 4.24–4.19 (m, 1H), 4.05 (dd, 1H, J=1.7, 8.1 Hz), 3.95–3.89 (m, 1H), 2.24–2.12 (m, 1H), 2.07–1.98 (m, 1H), 1.55 (s, 3H), 1.44 (s, 9H), 1.42 (s, 3H), 1.37 (d, 3H, J=6.8 Hz), 1.33 (s, 3H), 1.32 (s, 3H), 1.26 (d, 3H, J=6.4 Hz), 1.21 (d, 3H, J=6.4 Hz); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ=172.7, 170.9, 155.0, 109.3, 108.9, 95.8, 78.7, 73.1, 70.6, 70.0, 68.7, 65.2, 50.7, 49.0, 30.7, 28.2, 25.8, 25.7, 24.7, 24.3, 21.6, 18.5; IR (KBr): ν=3437, 3395, 1734, 1714, 1672 cm^{-1}.

4.4.3. Isopropyl 6-[[(2′*S*)-2′-(*tert*-butoxycarbonylamino)-1′-oxopropyl]amino]-5,6-dideoxy-1-*O*-methyl-2,3-*O*-isopropylidene-D,L-glycero-α-D-lyxo-heptofuranuronate 8c/8′c. The starting materials **7c/7′c** 60/40 (30 mg, 0.099 mmol) gave **8c/8′c** 60/40 (30 mg, 64%); TLC (hexane/AcOEt (1/1)) R_f 0.42.

8c: ^{1}H NMR (400 MHz, $CDCl_3$): δ=6.80 (d, 1H, J=5.9 Hz), 5.11–5.01 (m, 2H), 4.82 (s, 1H), 4.66 (dd, 1H, J=5.9, 3.6 Hz), 4.61–4.56 (m, 1H), 4.53 (d, 1H, J=5.9 Hz), 4.21–4.18 (m, 1H), 3.97–3.93 (m, 1H), 3.29 (s, 3H), 2.32–2.26 (m, 1H), 2.21–2.15 (m, 1H), 1.46 (s, 3H), 1.45 (s, 9H), 1.38 (d, 3H, J=7.0 Hz), 1.33 (s, 3H), 1.28 (d, 3H, J=6.5 Hz), 1.26 (d, 3H, J=6.3 Hz); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ=172.2, 171.0, 155.2 112.5, 106.9, 85.0, 80.5, 80.0, 77.2, 69.2, 54.6, 50.8, 50.0, 30.7, 28.3, 26.1, 25.0, 21.8, 21.6, 18.7; IR (KBr): ν=3402, 1735, 1714, 1658 cm^{-1}.

8′c: ^{1}H NMR (250 MHz, $CDCl_3$): δ=7.11–7.05 (br d, 1H), 5.12–4.99 (m, 2H), 4.88 (s, 1H), 4.72–4.66 (m, 1H), 4.60–4.55 (m, 1H), 4.53 (d, 1H, J=6.0 Hz), 4.23–4.16 (m, 1H), 3.98–3.92 (m, 1H), 3.33 (s, 3H), 2.33–2.03 (m, 2H), 1.45 (s, 9H), 1.44 (s, 3H), 1.37 (d, 3H, J=6.8 Hz), 1.31 (s, 3H), 1.26 (d, 3H, J=6.4 Hz), 1.23 (d, 3H, J=6.4 Hz); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ=172.4, 171.0, 155.2 112.6, 106.8, 84.8, 80.5, 80.0, 76.8, 69.1, 54.5, 50.6, 50.0, 30.2, 28.3, 26.0, 24.9, 21.7, 21.5, 18.6; IR (KBr): ν=3402, 1735, 1714, 1658 cm^{-1}.

4.4.4. Isopropyl 6-[[(2′*S*)-2′-(*tert*-butoxycarbonylamino)-1′-oxopropyl]amino]-5,6-dideoxy-3-*O*-methyl-1,2-*O*-isopropylidene-D,L-glycero-α-D-xylo-heptofuranuronate 8d/8′d. The starting materials **7d/7′d** 55/45 (51 mg, 0.17 mmol) gave **8d/8′d** 55/45 (70 mg, 87%); TLC (hexane/AcOEt (1/3)) R_f 0.66.

8d: ^{1}H NMR (250 MHz, $CDCl_3$): δ=7.05–6.95 (m, 1H), 5.89 (d, 1H, J=4.1 Hz), 5.15–5.08 (m, 1H), 5.08–4.99 (m, 1H), 4.67–4.52 (m, 1H), 4.55 (d, 1H, J=4.1 Hz), 4.22–4.16 (m, 2H), 3.59 (d, 1H, J=3.3 Hz), 3.41 (s, 3H), 2.28–2.00 (m, 2H), 1.46 (s, 3H), 1.45 (s, 9H), 1.37 (d, 3H, J=6.9 Hz), 1.31 (s, 3H), 1.26 (d, 3H, J=6.4 Hz), 1.24 (d, 3H, J=6.4 Hz); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ=172.5, 170.9, 155.2, 111.5, 104.6, 84.8, 81.0, 80.0, 77.3, 69.1, 57.6, 50.5, 49.9, 29.9, 28.2, 26.6, 26.1, 21.6, 18.5; IR (KBr): ν=3346, 1715, 1673 cm^{-1}.

8′d: ^{1}H NMR (250 MHz, $CDCl_3$): δ=6.81 (d, 1H, J=7.4 Hz), 5.84 (d, 1H, J=3.6 Hz), 5.15–5.08 (m, 1H), 5.09–4.98 (m, 1H), 4.67–4.52 (m, 1H), 4.57 (d, 1H, J=3.6 Hz), 4.22–4.16 (m, 2H), 3.67 (d, 1H, J=3.1 Hz), 3.43 (s, 3H), 2.28–2.00 (m, 2H), 1.46 (s, 3H), 1.45 (s, 9H), 1.36 (d, 3H, J=7.1 Hz), 1.29 (s, 3H), 1.26 (d, 3H, J=6.2 Hz), 1.25 (d, 3H, J=6.2 Hz); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ=172.5, 171.0, 155.2, 111.4, 104.6, 84.7, 81.3, 80.0, 77.1, 69.1, 57.6, 50.6, 50.0, 30.6, 28.2, 26.6, 26.0, 21.7, 18.5; IR (KBr): ν=3346, 1715, 1673 cm^{-1}.

4.5. General procedure for the transesterification of the isopropyl glycosyl-α-aminoesters 6

1 equiv. (1.3 mmol) of BuLi (2.5 M in hexane) was added dropwise at 0°C to 4.5 mL of methyl alcohol. Then, a solution of 1 equiv. (600 mg, 1.3 mmol) of pure **6a** in 9 mL of THF was added and the mixture was stirred at reflux (60°C) during 2.5 h. The crude was concentrated, washed with water, and the aqueous layer was extracted with dichloromethane. The organic layer was dried over magnesium

sulphate, evaporated, and the residue was purified on a silica gel chromatographic column.

4.5.1. Methyl 7-[[(1′*S*)-1′-phenylethyl]amino]-6,7-dideoxy-1,2:3,4-di-*O*-isopropylidene-L-glycero-α-D-galacto-octo pyranuronate 9a. The pure diastereomer **6a** (370 mg, 0.8 mmol) gave **9a** (289 mg, 83%, white powder); TLC (hexane/AcOEt (1/2)) R_f 0.79; mp 151°C.

^{1}H NMR (250 MHz, $CDCl_3$): δ=7.32–7.20 (m, 5H), 5.46 (d, 1H, *J*=5.1 Hz), 4.48 (dd, 1H, *J*=2.6, 8.1 Hz), 4.27 (dd, 1H, *J*=2.6, 5.1 Hz), 4.11–4.01 (m, 1H), 3.78–3.70 (m, 2H), 3.72 (s, 3H), 3.15 (dd, 1H, *J*=5.6, 7.3 Hz), 2.00–1.90 (m, 1H), 1.89–1.79 (m, 1H), 1.64 (s, 3H), 1.56 (s, 1H), 1.40 (s, 3H), 1.35 (s, 3H), 1.33 (d, 3H, *J*=6.4 Hz), 1.26 (s, 3H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ=175.7, 145.1, 128.2, 127.0, 126.9, 108.9, 108.3, 96.5, 71.8, 70.8, 70.4, 64.5, 56.7, 55.6, 51.6, 33.6, 25.9, 25.8, 25.1, 24.9, 24.3; IR (KBr): ν=3320, 1733 cm^{-1}; MS (ESI): *m/z*: 436.2 (MH^+, 100%); 376.2 ($(M-59)^+$, 55%); α_D^{20}=−69,3 (*c*=2,44 g dl^{-1}, $CHCl_3$).

4.5.2. Methyl 7-[[(1′*S*)-1′-phenylethyl]amino]-6,7-dideoxy-1,2:3,4-di-*O*-isopropylidene-D-glycero-α-D-galacto-octopyranuronate 9′a. The starting materials **6a/6′a** (10/90) (200 mg, 0.43 mmol) gave **9a/9′a** (10/90) (160 mg, 86%); TLC (hexane/AcOEt (1/2)) R_f 0.74.

^{1}H NMR (250 MHz, $CDCl_3$): δ=7.32–7.20 (m, 5H), 5.57 (d, 1H, *J*=5.1 Hz), 4.61 (dd, 1H, *J*=2.6, 8.1 Hz), 4.32 (dd, 1H, *J*=2.6, 5.1 Hz), 4.22–4.16 (m, 1H), 4.08 (dd, 1H, *J*=1.7, 8.1 Hz, 3.76 (q, 1H, *J*=6.4 Hz), 3.56 (s, 3H), 3.54 (dd, 1H, *J*=3.4, 10.0 Hz), 2.06–1.80 (m, 2H), 1.65 (s, 3H), 1.56 (s, 4H), 1.46 (s, 3H), 1.35 (d, 3H, *J*=6.4 Hz), 1.27 (s, 3H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ=176.2, 145.6, 128.2, 127.0, 126.9, 109.0, 108.4, 96.1, 73.4, 71.0, 70.5, 64.0, 56.7, 55.3, 51.5, 35.0, 26.2, 26.0, 25.0, 24.3, 22.5; IR (KBr): ν=3318, 1743 cm^{-1}.

4.5.3. Methyl 6-[[(1′*S*)-1′-phenylethyl]amino]-5,6-dideoxy-1-*O*-methyl-2,3-*O*-isopropylidene-D,L-glycero-α-D-lyxo-heptofuranuronate 9c/9′c. The starting materials **6c/6′c** (60/40) (260 mg, 0.64 mmol) gave **9c/9′c** (60/40) (194 mg, 80%); TLC (hexane/AcOEt (1/2)) R_f 0.76.

9c: ^{1}H NMR (250 MHz, $CDCl_3$): δ=7.32–7.22 (m, 5H), 4.79 (s, 1H), 4.45 (d, 1H, *J*=5.6 Hz), 4.31 (dd, 1H, *J*=5.6, 3.4 Hz), 4.07 (dt, 1H, *J*=3.4, 6.8 Hz), 3.73 (s, 3H), 3.69 (q, 1H, *J*=6.4 Hz), 3.31 (s, 3H), 3.19 (t, 1H, *J*=6.8 Hz), 1.96 (t, 2H, *J*=6.8 Hz), 1.61 (br s, 1H), 1.45 (s, 3H), 1.38 (s, 3H), 1.35 (d, 3H, *J*=6.4 Hz); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ=175.8, 144.9, 128.2, 126.9, 126.6, 112.1, 106.8, 84.9, 80.7, 79.9, 76.5, 56.7, 56.5, 54.3, 32.5, 25.9, 25.0, 24.7.

9′c: ^{1}H NMR (250 MHz, $CDCl_3$): δ=7.32–7.22 (m, 5H), 4.87 (s, 1H), 4.62 (dd, 1H, *J*=5.5, 3.4 Hz), 4.55 (d, 1H, *J*=5.5 Hz), 4.27–4.20 (m, 1H), 3.76 (q, 1H, *J*=6.4 Hz), 3.62 (s, 3H), 3.50 (dd, 1H, *J*=4.7, 9.5 Hz), 3.34 (s, 3H), 2.14–2.03 (m, 1H), 1.88–1.77 (m, 1H), 1.61 (br s, 1H), 1.45 (s, 3H), 1.33 (d, 3H, *J*=6.4 Hz), 1.30 (s, 3H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ=175.6, 145.5, 128.2, 127.0, 126.9, 112.1, 106.7, 85.2, 80.7, 79.9, 76.5, 56.4, 56.3, 54.3, 32.5, 26.0, 25.9, 24.8.

9c/9′c: IR (KBr): ν=3318, 1736 cm^{-1}.

4.5.4. Methyl 6-[[(1′*S*)-1′-phenylethyl]amino]-5,6-dideoxy-3-*O*-methyl-1,2-*O*-isopropylidene-D,L-glycero-α-D-xylo-heptofuranuronate 9d/9′d. The starting materials **6d/6′d** (55/45) (103 mg, 0.25 mmol) gave **9d/9′d** (55/45) (80 mg, 84%); TLC (hexane/AcOEt (1/1)) R_f 0.68.

9d: ^{1}H NMR (250 MHz, $CDCl_3$): δ=7.31–7.21 (m, 5H), 5.82 (d, 1H, *J*=3.8 Hz), 4.45 (d, 1H, *J*=3.8 Hz), 4.37–4.30 (m, 1H), 3.73 (s, 3H), 3.68 (q, 1H, *J*=6.4 Hz), 3.17 (d, 1H, *J*=3.4 Hz), 3.13 (s, 3H), 2.98 (dd, 1H, *J*=5.6, 8.5 Hz), 1.93–1.86 (m, 2H), 1.54 (s, 4H), 1.33 (d, 3H, *J*=6.4 Hz), 1.26 (s, 3H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ=175.9, 145.0, 128.4, 127.1, 126.7, 111.2, 104.6, 85.0, 83.8, 81.6, 77.2, 56.8, 56.4, 51.8, 31.7, 26.7, 25.0, 22.8; IR (KBr): ν=3346, 1731 cm^{-1}.

9′d: ^{1}H NMR (250 MHz, $CDCl_3$): δ=7.31–7.21 (m, 5H), 5.87 (d, 1H, *J*=3.8 Hz), 4.56 (d, 1H, *J*=3.8 Hz), 4.45–4.40 (m, 1H), 3.77 (q, 1H, *J*=6.4 Hz), 3.60–3.58 (m, 4H), 3.46 (dd, 1H, *J*=4.7, 9.4 Hz), 3.33 (s, 3H), 2.08–1.95 (m, 1H), 1.83–1.71 (m, 1H), 1.52 (s, 4H), 1.31 (d, 3H, *J*=6.0 Hz), 1.26 (s, 3H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ=175.8, 145.6, 128.3, 127.0, 126.9, 111.3, 104.5, 85.0, 83.8, 81.7, 77.2, 57.5, 56.3, 51.7, 32.1, 26.3, 25.0, 22.7; IR (KBr): ν=3346, 1731 cm^{-1}.

4.6. General procedure for the hydrolysis of methyl glycosyl-α-aminoesters 9 and C-side coupling

In a typical procedure, a solution of 1 equiv. of isopropyl α-aminoester **9** in a mixture of solvent MeOH/THF 1/3, was added to 1 equiv. of a 1N methanolic solution of potassium hydroxide, and stirred at reflux for 4 h. Then, the crude was reduced, and directly used in C-side coupling. The α-aminocarboxylate **10** was stirred in chloroform with 1.1 equiv. of HCl,Gly-OMe, 1.5 equiv. of triethylamine, and 1.1 equiv. of BOP. The mixture was washed with water, and the aqueous layer was extracted by chloroform. The organic layers were joined together and dried with sodium sulphate, concentrated, and purified by chromatography on a silica gel column to give **11/11′**.

4.6.1. Methyl *N*-[6,7-dideoxy-1,2:3,4-di-*O*-isopropylidene-7-[[(1′*S*)-1′-phenylethyl]amino]-L-glycero-α-D-galacto-octopyranuronoyl]-glycinate 11a. The starting materials **9a/9′** (98/2) (250 mg, 0.57 mmol) gave **11a/11′a** (98/2) (193 mg, 69%); TLC (hexane/AcOEt (1/3)) R_f 0.45.

^{1}H NMR (250 MHz, $CDCl_3$): δ=7.54 (t, 1H, *J*=5.6 Hz), 7.32–7.19 (m, 5H), 5.47 (d, 1H, *J*=5.1 Hz), 4.49 (dd, 1H, *J*=2.6, 7.7 Hz), 4.25 (dd, 1H, *J*=5.1, 2.6 Hz), 4.11–3.99 (m, 2H), 3.90 (dd, 1H, *J*=7.7, 1.8 Hz), 3.87–3.80 (m, 1H), 3.78–3.73 (m, 1H), 3.76 (s, 3H), 3.08 (dd, *J*=4.3, 8.5 Hz), 2.45 (br s, 1H), 2.00–1.90 (m, 1H), 1.86–1.77 (m, 1H), 1.46 (s, 3H), 1.40 (s, 3H), 1.34 (d, 3H, *J*=7.3 Hz), 1.31 (s, 3H), 1.26 (s, 3H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ=175.0, 170.3, 144.7, 128.4, 126.8, 108.9, 108.3, 96.2, 72.7, 70.6, 70.0, 67.1, 59.5, 56.7, 52.1, 40.7, 34.5, 25.9, 25.7, 24.8, 24.3, 24.1; IR (KBr): ν=3346, 1743, 1673 cm^{-1}.

4.6.2. Methyl *N*-[6,7-dideoxy-1,2:3,4-di-*O*-isopropylidene-

7-[[(1′*S*)-1′-phenylethyl]amino]-D-glycero-α-D-galacto-octopyranuronoyl]-glycinate 11′aThe starting materials **9a/9′a** 10/90 (65 mg, 0.15 mmol) gave **11a/11′a** 10/90(45 mg, 61%); TLC (hexane/AcOEt (1/3)) R_f 0.45.

^{1}H NMR (250 MHz, $CDCl_3$): δ=8.07 (t, 1H, J=5.1 Hz), 7.34–7.18 (m, 5H), 5.52 (d, 1H, J=5.1 Hz), 4.57 (dd, 1H, J=2.6, 8.1 Hz), 4.29 (dd, 1H, J=5.1, 2.6 , 4.11 (dd, 1H, J=8.1, 1.7 Hz), 4.00–3.97 (m, 1H), 3.96–3,86 (m, 2H), 3.81–3.73 (m, 1H), 3.76 (s, 3H), 3.20 (dd, J=3.9, 5.6 Hz), 2.22–2.11 (m, 1H), 1.96–1.85 (m, 1H), 1.49 (s, 6H), 1.36 (s, 3H), 1.34 (d, 3H, J=5.6 Hz), 1.26 (s, 3H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ=174.2, 169.4, 144.8, 128.4, 127.0, 109.1, 108.5, 96.3, 73.3, 70.8, 70.3, 65.5, 57.3, 56.4, 51.6, 40.9, 33.5, 26.0, 25.9, 24.9, 24.4; IR (KBr): ν=3437, 3360, 1743, 1666 cm^{-1}.

4.6.3. Methyl *N*-[5,6-dideoxy-1-*O*-methyl-2,3-*O*-isopropylidene-6-[[(1′*S*)-1′-phenylethyl]amino]-D,L-glycero-α-D-lyxo-heptofuranuronoyl]-glycinate 11c/11′c. The starting materials **9c/9′c** 60/40 (117 mg, 0.29 mmol) gave **11c/11′c** 60/40 (95 mg, 75%); TLC (hexane/AcOEt (1/2)) R_f 0.52.

11c: ^{1}H NMR (250 MHz, $CDCl_3$): δ=7.71 (t, 1H, J=5.7 Hz), 7.36–7.19 (m, 5H), 4.84 (s, 1H), 4.48–4.47 (m,2H), 4.22 (dd, 1H, J=6.4, 18.5 Hz), 3.99 (dd, 1H, J=5.7, 18.5 Hz), 3.97–3.91 (m, 1H), 3.78 (s, 3H), 3.74–3.68 (m, 1H), 3.29 (s, 3H), 3.10 (dd, 1H, J=3.8, 9.0 Hz), 2.38 (br s, 1H), 2.05 (ddd, 1H, J=15.0, 4.2, 3.8 Hz), 1.91 (ddd, 1H, J=15.0, 8.0, 9.0 Hz), 1.42 (s, 3H), 1.39 (d, 3H, J=6.4 Hz), 1.26 (s, 3H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ=174.9, 170.3, 144.8, 128.5, 127.1, 126.3, 112.3, 107.5, 84.7, 80.7, 78.8, 59.7, 57.8, 57.2, 40.8, 33.1, 26.0, 24.8, 24.2.

11′c: ^{1}H NMR (250 MHz, $CDCl_3$): δ=8.03 (t, 1H, J=6.4 Hz), 7.36–7.19 (m, 5H), 4.88 (s, 1H), 4.62 (dd, 1H, J=3.4, 6.0 Hz), 4.52 (d, 1H, J=6.0 Hz), 4.13–4.06 (m, 1H), 3.97–3.88 (m, 3H), 3.75 (s, 3H), 3.30 (s, 3H), 3.27–3.23 (m, 1H), 2.38 (br s, 1H), 2.20–2.13 (m, 2H), 1.49 (s, 3H), 1.39 (d, 3H, J=6.4 Hz), 1.32 (s, 3H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ=174.3, 170.2, 144.6, 128.5, 127.2, 126.5, 112.3, 107.1, 84.9, 80.9, 79.0, 59.7, 56.9, 54.9, 40.9, 29.8, 26.2, 24.9, 23.9.

11c/11′c: IR (KBr): ν=3339, 1740, 1670 cm^{-1}.

4.6.4. Methyl *N*-[5,6-dideoxy-3-*O*-methyl-1,2-*O*-isopropylidene-6-[[(1′*S*)-1′-phenylethyl]amino]-D,L-glycero-α-D-xylo-heptofuranuronoyl]-glycinate 11d/11′d. The starting materials **9d/9′d** 55/45 (50 mg, 0.124 mmol) gave **11d/11′d** 55/45 (46 mg, 85%); TLC (hexane/AcOEt (1/3)) R_f 0.51.

11d: ^{1}H NMR (250 MHz, $CDCl_3$): δ=8.16 (t, 1H, J=3.4 Hz), 7.35–7.20 (m, 5H), 5.92 (d, 1H, J=3.8 Hz), 4.55 (d, 1H, J=3.8 Hz), 4.31–4.27 (m, 1H), 3.97 (d, 2H, J=5.9 Hz), 3.92 (q, 1H, J=6.4 Hz), 3.75 (s, 3H), 3.61 (d, 1H, J=3.1 Hz), 3.40 (s, 3H), 3.22 (t, J=4.9 Hz), 2.20–2.12 (m, 2H), 1.51 (br s, 1H), 1.48 (s, 3H), 1.37 (d, 3H, J=6.4 Hz), 1.32 (s, 3H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ=174.3, 170.0, 144.6, 128.4, 126.9, 126.6, 111.4, 85.6, 81.1, 79.6, 77.7, 59.9, 57.7, 56.8, 40.8, 28.7, 26.5, 26.1, 24.4.

11′d: ^{1}H NMR (250 MHz, $CDCl_3$): δ=7.86 (br t), 7.35–7.20 (m, 5H), 5.93 (d, 1H, J=4.1 Hz), 4.52 (d, 1H, J=4.1 Hz), 4.20 (dd, 1H, J=6.7, 18.4 Hz), 4.07–4.03 (m, 1H), 3.98 (dd, 1H, J=4.9, 18.4 Hz), 3.86 (q, 1H, J=6.4 Hz), 3.79 (s, 3H), 3.47 (d, 1H, J=3.3 Hz), 3.33 (s, 3H), 3.03 (dd, 1H, J=3.6, 10.1 Hz), 1.99–1.82 (m, 2H), 1.51 (br s, 1H), 1.48 (s, 3H), 1.39 (d, 3H, J=6.4 Hz), 1.34 (s, 3H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ=175.0, 170.2, 144.8, 127.1, 126.9, 126.6, 111.3, 85.5, 81.0, 79.6, 77.7, 59.9, 57.8, 57.6, 40.6, 32.4, 26.7, 26.2, 24.7.

11d/11′d: IR (KBr): ν=3438, 3353, 1750, 1673 cm^{-1}.

4.7. Introduction of the 2-(1′,2′;3′,4′-di-*O*-isopropylidene 6′-deoxy-α-D-galactopyranosyl)glycine residue inside a peptide

4.7.1. Methyl *N*-[6,7-dideoxy-1,2:3,4-di-*O*-isopropylidene-7-amino-L-glycero-α-D-galacto-octopyranuronoyl]-glycinate 12a. To a solution of **11a/11′a** (98/2) (180 g, 0.37 mmol) in 15 mL of isopropanol was added 0.20 g of palladium 10% on charcoal. The mixture was hydrogenated at room temperature under a 50 bar pressure of hydrogen during 5 h, then filtered through celite, and the filtrate was evaporated in vacuo to yield **12a/12′a** (98/2).

^{1}H NMR (400 MHz, $CDCl_3$): δ=8.63 (br s, 2H); 5.47 (d, 1H, J=4.8 Hz), 4.52 (dd, 1H, J=2.2 Hz, J=7.7 Hz), 4.46–4.38 (m, 1H), 4.25 (dd, 1H, J=2.2 Hz, J=4.8 Hz), 4.12–4.05 (m, 2H), 4.03–3.98 (m, 1H), 3.98–3.86 (m, 1H), 3.67 (s, 3H), 2.32–2.14 (m, 2H), 1.50 (s, 3H), 1.38 (s, 3H), 1.27 (s, 3H), 1.25 (s, 3H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ=170.0, 169.6, 109.0, 108.5, 96.3, 72.0, 70.5, 70.1, 65.9, 52.2, 52.0, 41.2, 31.6, 25.9, 25.7, 24.7, 24.2; IR (KBr): ν=3381, 3219, 1750, 1687 cm^{-1}; MS (ESI): m/z: 389.1 (MH^+, 100%).

4.7.2. Methyl *N*-[6,7-dideoxy-1,2:3,4-di-*O*-isopropylidene-7-[[(2*S*)-2-[[(1,1-dimethylethoxy)carbonyl]amino]-1-oxopropyl]amino]-L-glycero-α-D-galacto-octopyranuronoyl]-glycinate 13a. To a solution of **12a/12′a** (98/2) (140 mg, 0.36 mmol) in 25 mL of chloroform were added 1.1 equiv. (75 mg, 0.39 mmol) of BOC–Ala–OH, 1.5 equiv. (54 mg, 0.54 mmol) triethylamine, 1.1 equiv. (174 mg, 0.39 mmol) of BOP, and the mixture was stirred for 2.5 h at room temperature. The crude was washed with 10 mL of water, and the aqueous layer was extracted with chloroform. The organic layers were joined together and dried over magnesium sulphate, then evaporated. The residue was purified by chromatography on a silica gel column to give the colourless oil **13a/13′a** (98/2) (139 mg, 69% from **11a/11′**); TLC (hexane/AcOEt(1/3)) R_f 0.3.

^{1}H NMR (400 MHz, $CDCl_3$): δ=7.32 (d, 1H, J=4.7 Hz); 7.16–7.11 (m, 1H); 5.57 (d, 1H, J=4.9 Hz), 5.33 (d, 1H, J=5.4 Hz), 4.62 (dd, 1H, J=2.5, 7.9 Hz), 4.51–4.45 (m, 1H), 4.34 (dd, 1H, J=2.5, 4.9 Hz), 4.27–4.23 (m, 1H), 4.19 (dd, 1H, J=1.7, 7.9 Hz), 4.14 (d, 1H, J=6.2 Hz), 4.10 (d, 1H, J=6.2 Hz), 3.90–3.84 (m, 1H), 3.75 (s, 3H), 2.20–2.09 (m, 2H), 1.48 (s, 12H), 1.47 (s, 3H), 1.40 (d, 3H,

J=7.2 Hz), 1.36 (s, 3H), 1.34 (s, 3H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ=173.6, 171.8, 170.4, 155.7, 109.3, 108.8, 96.3, 79.9, 72.9, 70.6, 70.1, 66.4, 52.7, 52.3, 50.6, 41.0, 31.3, 28.2, 25.9, 25.8, 24.8, 24.3, 17.3; IR (KBr): ν=3423, 3367, 1752, 1700, 1686, 1676 cm^{-1}; MS (ESI): *m/z*: 560.3 (MH^+, 18%), 582.2 (MNa^+, 100%).

4.8. Coupling between two glycosyl-α-aminoacids

4.8.1. Isopropyl 6,7-dideoxy-1,2:3,4-di-*O*-isopropylidene-7-[[6,7-dideoxy-1,2:3,4-di-*O*-isopropylidene-7-[[(1′*S*)-1′-phenylethyl]amino]-L-glycero-α-D-galacto-octopyranuronoyl]amino]-L-glycero-α-D-galacto-octopyranuronate 14aa. In a typical procedure, a solution of **10a/10′a** (98/2) (160 mg, 0.34 mmol) in 25 mL of chloroform was stirred during 2 h at room temperature in the presence of 1 equiv. (120 mg, 0,34 mmol) of **7a/7′a** (98/2), 1.1 equiv. (170 mg, 0.37 mmol) of BOP, and some drops of triethylamine to fix the pH at 9. The crude was washed with 10 mL of water, and the aqueous layer was extracted with chloroform. The organic layer was dried over magnesium sulphate, evaporated, and the residue was purified by chromatography on a silica gel column to give **14aa/14′aa** (98/2) (253 mg, 98%) as a white powder; TLC (hexane/AcOEt (1/3)) R_f 0.66; mp 66°C.

^{1}H NMR (250 MHz, $CDCl_3$): δ=8.13 (d, 1H, J=8.1 Hz); 7.37–7.18 (m, 5H); 5.49 (d, 1H, J=4.7 Hz), 5.48 (d, 1H, J=5.1 Hz), 5.15–5.02 (m, 1H), 4.77–4.69 (m, 1H), 4.59 (dd, 1H, J=2.5, 8.1 Hz), 4.51 (dd, 1H, J=2.1, 7.7 Hz), 4.28 (dd, 1H, J=5.1, 7.7 Hz), 4.28 (dd, 1H, J=4.7, 8.1 Hz), 4.17 (dd, 1H, J=2.1, 8.1 Hz), 3.94–3.85 (m, 4H), 3.08 (dd, 1H, J=3.4, 9.8 Hz), 2.42–2.30 (m, 1H), 2.08–1.98 (m, 1H), 1.89–1.79 (m, 2H), 1.58 (s, 3H), 1.52 (s, 3H), 1.49 (s, 3H), 1.47 (s, 3H), 1.41 (s, 3H), 1.36 (s, 3H), 1.35 (s, 3H), 1.34 (d, 3H, J=6.4 Hz), 1.29 (s, 3H), 1.28 (d, 3H, J=6.4 Hz), 1.27 (d, 3H, J=6.4 Hz); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ=174.8, 171.2, 145.0, 128.2, 126.8, 126.6, 109.1, 108.9, 108.8, 108.4, 96.3, 96.2, 72.8, 72.6, 71.0, 70.6, 70.1, 70.0, 68.5, 68.1, 64.3, 60.5, 56.9, 49.1, 34.6, 31.9, 26.4, 26.1, 26.0, 24.9, 24.7, 24.6, 24.3, 23.5, 21.7, 21.6; IR (KBr): ν=3430, 3346, 1736, 1673 cm^{-1}; MS (ESI): *m/z*: 763.4 (MH^+, 100%).

4.8.2. Isopropyl 5,6-dideoxy-1-*O*-methyl-2,3-*O*-isopropylidene-6-[[6,7-dideoxy-1,2:3,4-di-*O*-isopropylidene-7-[[(1′S)-1′-phenylethyl]amino]-L-glycero-α-D-galacto-octopyranuronoyl]amino]-D,L-glycero-α-D-lyxo-heptofuranuronate 14ac/14′ac. The starting materials **10a/10′a** (98/2) (69 mg mg, 0.15 mmol) and **7c/7′c** (60/40) (51 mg, 0.17 mmol) gave **14ac/14′ac** (60/40) (73 mg, 69%); TLC (hexane/AcOEt (1/2)) R_f 0.76.

14ac: ^{1}H NMR (250 MHz, $CDCl_3$): δ=8.06 (d, 1H, J=7.7 Hz); 7.37–7.18 (m, 5H); 5.50 (d, 1H, J=5.1 Hz), 5.15–5.02 (m, 1H), 4.83 (s, 1H), 4.79–4.74 (m, 1H), 4.70–4.64 (m, 1H), 4.57–4.45 (m, 2H), 4.26 (dd, 1H, J=5.1, 1.7 Hz), 4.07–3.71 (m, 4H), 3.29 (s, 3H), 3.10–3.05 (m, 1H), 2.33–2.14 (m, 2H), 1.97–1.81 (m, 3H), 1.61–1.18 (m, 27H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ=174.5, 171.3, 144.8, 128.3, 126.9, 126.1, 112.4, 108.9, 108.8, 96.2, 85.0, 80.5, 76.8, 72.8, 70.6, 70.1, 68.9, 67.7, 60.3, 56.9, 54.4, 50.0, 33.6, 31.2, 26.1, 25.9, 24.9, 24.2, 23.8, 23.7, 21.7, 21.4.

14′ac: ^{1}H NMR (250 MHz, $CDCl_3$): δ=8.13 (d, 1H, J=8.5 Hz); 7.37–7.18 (m, 5H); 5.46 (d, 1H, J=4.7 Hz), 5.15–5.02 (m, 1H), 4.91 (s, 1H), 4.70–4.64 (m, 1H), 4.63–4.60 (m, 1H), 4.57–4.45 (m, 2H), 4.33 (dd, 1H, J=4.7, 2.6 Hz), 4.07–3.71 (m, 4H), 3.32 (s, 3H), 3.16–3.12 (m, 1H), 2.33–2.14 (m, 2H), 1.97–1.81 (m, 3H), 1.61–1.18 (m, 27H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ=174.8, 171.0, 145.0, 128.3, 126.9, 126.1, 112.6, 108.8, 106.7, 96.2, 84.8, 80.7, 76.8, 72.7, 70.8, 70.4, 68.9, 67.5, 60.0, 56.7, 54.4, 50.2, 32.5, 30.2, 26.1, 25.9, 24.9, 24.2, 23.8, 23.7, 21.7, 21.4.

14ac/14′ac: IR (KBr): ν=3423, 3346, 1736, 1673 cm^{-1}.

Acknowledgements

We thank Dr A. van Dorsselaer (Strasbourg University) for the mass spectra.

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