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New glycosyl α-hydroxyesters as key intermediates in a convenient route to glycosyl α-aminoester chirons

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Abstract—This article examines the stereoselective preparation of glycosyl α-hydroxyesters via the asymmetric reduction of glycosyl α-ketoesters, using various chiral or achiral reagents and Bakers' yeast. The diastereomeric excess could exceed 98% for the galacto-series. These glycosyl α-hydroxyesters are used as chiral precursors for the diastereoselective synthesis of glycosyl α-aminoesters synthons.

1. Introduction

The synthesis of α-hydroxyesters and hydroxyacids has received much interest during past years as these compounds are good chiral building blocks for the synthesis of biologically active natural or analogous products,[1] and also since they are used as analogues or precursors of α-aminoesters.[2] As a result, numerous enantioselective preparations of these compounds from α-ketoesters have already been described, especially those concerning the reduction of aliphatic α-ketoesters using different reagents (such as hydrogen with catalyst in heterogen[3] or homogen[4] phase, hindered metallic aluminohydrides or borohydrides,[5] homochiral hydroborating reagents,[6] sodium borohydride/tartric acid,[7] hydrosilane/diop,[8] mimics of nicotinamide adenine dinucleotide (NADH),[9] Bakers' yeast[10] or other biotransformations[11] or recently with SmI_2[12]). However, no stereoselective reduction has been achieved on glycosyl pyruvic esters since, until recently, these compounds were practically unknown. We were recently the first to describe an efficient synthesis of such glycosyl pyruvic esters from dialdoses.[13] Here, we report the asymmetric reduction of these glycosyl α-ketoesters **1a–c**, into the corresponding glycosyl α-hydroxyesters **2a–c** in the α-D-galactose (**a**), β-D-ribose (**b**) and α-D-lyxose (**c**) series. Subsequently, we describe the substitution with a complete inversion of the triflates derived from these glycosyl α-hydroxyesters **2a–c** using sodium azide, followed by the hydrogenation of the resulting azido compounds **3a–c** leading to the glycosyl α-aminoesters **5a–c**. The route to these last compounds completes a recent approach described by us based on a stereoselective aminoreduction of glycosyl α-ketoesters **1**[14] and another direct route to glycosyl α-hydroxyesters based on the reaction between sodium cyanoborohydride and glucidic α-chloroglycidic esters.[15] The aim is to obtain increased stereoselectivity to novel C-linked glycosyl α-aminoacid derivatives, which can be used as convenient building blocks for the synthesis of glycopeptide libraries (Scheme 1).

2. Results and discussion

Based on the assumption that the carbohydrate moiety could induce an asymmetric reduction of the α-carbonyl functionality, the first procedure used to reduce the α-ketoesters **1** into the corresponding α-hydroxyesters **2** was via catalytic hydrogenation in isopropyl alcohol at ambient temperature and under different pressure of hydrogen using palladium over charcoal (10%) as catalyst (procedure A). The results reported in Table 1 showed that the three α-ketoesters **1a–c** studied were cleanly converted to the corresponding expected carbinols **2a–c** in >73% yield, but with a moderate diastereomeric excess (16<de<60%). Even though the hydrogenation was slower under 1bar (entry 1) than under 50bar (entry 2), this resulted in the best diastereomeric excess (de:60%) to give the diastereomer **2a**. The absolute configurations-(*R*) and (*S*) of the new asymmetric carbon C7 in **2a/2′a** (as a viscous oil) were determined by the chemical correlation leading to the glycosyl α-aminoester **4a/4′a** described later in the text. An attempt using sodium borohydride as the reducing reagent with galactosyl α-ketoester **1a** (entry 5) neither improved the diastereomeric excess nor the yield for **2a**. The reason for this poor yield was due to a side reaction that occurred between sodium borohydride and the isopropyl ester of

Keywords: glycosyl α-ketoester; glycosyl α-hydroxyester; glycosyl α-aminoester; Bakers' yeast; sodium cyanoborohydride; catecholborane–oxazaborolidine; sodium azide.
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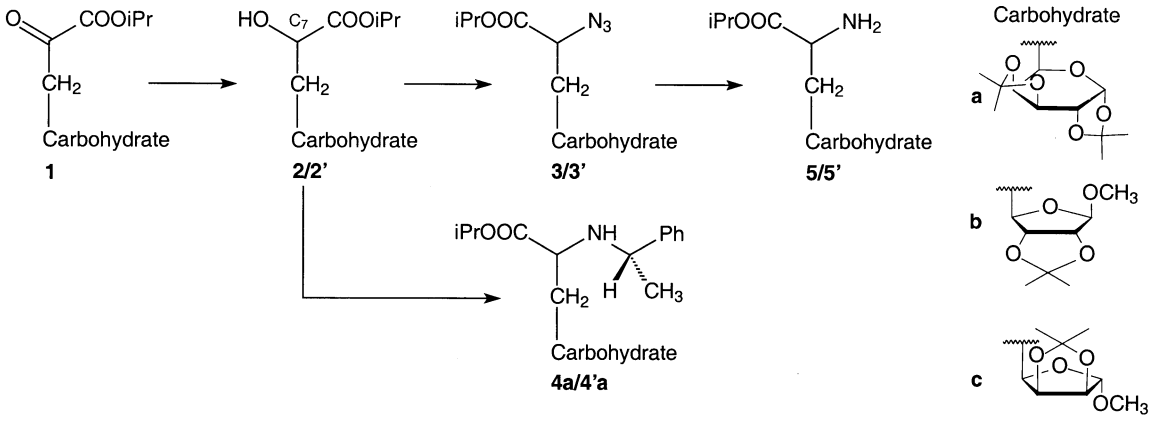


Scheme 1.

1a, leading the corresponding diol.[5b] The C7 configuration of the major diastereomeric product **2a** was again (*S*), resulting from an attack on the *Re* side of the α-keto moiety.

With the use of the mild reducing reagent sodium cyanoborohydride (entry 6), the reaction was found to be much more selective for the α-keto moiety, but with very low diastereomeric excess (procedure B). Although the reduction of ketone with $NaBH_3CN$ was known to require acidic pH as activator,[16] it is noteworthy that in this case the reaction could be carried out in high yield without any activating additive, since the α-keto moiety was highly reactive as a result of the presence of the ester at the α site.

The preliminary results showed that the carbohydrate moiety induced a relatively moderate asymmetric effect on the α-keto moiety of **1a–c**, in contrast to the well known powerful asymmetric induction of a chiral ester moiety on the reduction of aliphatic alkyl pyruvates in the corresponding α-hydroxyesters.[5a]

As a consequence, we studied the asymmetric reduction of these α-ketoesters **1a–c** with a chiral borohydride reagent, catecholborane assisted by (*R*) or (*S*)-5,5-diphenyl-2-methyl-3,4-propano-1,3,2-oxazaborolidine as a chiral catalyst auxiliary (procedure C).[17] By this method, only known to apply to ketones, it was possible to obtain compounds **2a–c** with a high diastereomeric excess. It is noteworthy that the change of the catalyst configuration induced the change of the diastereoselectivity in favour of the other diastereomer **2′a–c** in approximately the same ratio that characterised a stereospecific catalysis (entries 7–12). The best results (yield and diastereomeric excess) were obtained in galactose series as the result of the attack of the less hindered *Re* face of the ketyl group when catecholborane-(*R*) oxazaborolidine was used (C7 (*S*)) (entry 8), whereas *Si* face appeared favoured with catecholborane-(*S*) oxazaborolidine (C7 (*R*)) (entry 7). These results provided additional evidence for the transition state assembly postulated by Itsuno et al.[18] and verified on the basis of NMR[18a] and X-ray crystallography studies.[19] They illustrated a novel interesting case of enzyme-like behaviour of such oxazaborolidine that brought together the reductant and the carbonyl substrate.[20]

The reduction of α-ketoesters **1a–c** using a large amount of

Table 1. Diastereoselective reduction of C-glycosyl α-ketoesters **1** using different reducing agents

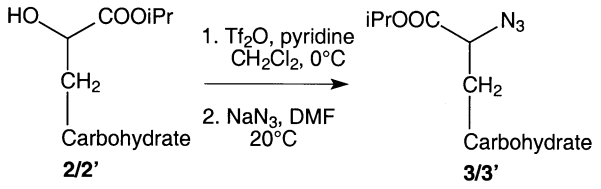
Entry	Starting substrate **1**	Product **2**	Reducing agent and catalyst	Conditions	Yield[a] (%)	Diastereomeric ratio[b]	de[b] (%)	C_7[c]
1	**1a**	**2a/2′a**	Hydrogen, Pd/C 10%	*P*=1 bar, 48 h, *i*PrOH	73	80/20	60	*S*
2	**1a**	**2a/2′a**	Hydrogen, Pd/C 10%	*P*=50 bar, 24 h, *i*PrOH	85	60/40	20	*S*
3	**1b**	**2b/2′b**	Hydrogen, Pd/C 10%	*P*=50 bar, 24 h, *i*PrOH	81	58/42	16	–
4	**1c**	**2c/2′c**	Hydrogen, Pd/C 10%	*P*=50 bar, 24 h, *i*PrOH	86	73/27	46	–
5	**1a**	**2a/2′a**	$NaBH_4$	*i*PrOH, 1 h	47	67/33	34	*S*
6	**1c**	**2c/2′′′c**	$NaBH_3CN$	*i*PrOH, 24 h	82	55/45	10	–
7	**1a**	**2a/2′a**	Catecholborane-(*S*)oxazaborolidine	CH_2Cl_2, 18 h	94	11/89	78	*R*
8	**1a**	**2a/2′a**	Catecholborane-(*R*)oxazaborolidine	CH_2Cl_2, 18 h	81	95/05	90	*S*
9	**1b**	**2b/2′b**	Catecholborane-(*S*)oxazaborolidine	CH_2Cl_2, 18 h	61	85/15	70	–
10	**1b**	**2b/2′b**	Catecholborane-(*R*)oxazaborolidine	CH_2Cl_2, 18 h	39	16/84	68	–
11	**1c**	**2c/2′c**	Catecholborane-(*S*)oxazaborolidine	CH_2Cl_2, 18 h	76	23/77	54	–
12	**1c**	**2c/2′c**	Catecholborane-(*R*)oxazaborolidine	CH_2Cl_2, 18 h	73	92/08	84	–
13	**1a**	**2′a**	Bakers' yeast	H_2O, 17 h	44	–[d]	>98	*R*
14	**1a**	**2′a**	Bakers' yeast	H_2O, 69 h	61	–[d]	>98	*R*
15	**1b**	**2b/2′b**	Bakers' yeast	H_2O, 17 h	48	45/55	10	–
16	**1c**	**2c/2′c**	Bakers' yeast	H_2O, 17 h	70	83/17	66	–

[a] Yield of isolated products after chromatography on a silica gel column.
[b] Determined on the crude product by ^1H NMR analysis.
[c] Configuration of the C7 of the major diastereomer **2**.
[d] Only one diastereomer could be seen by ^1H NMR spectroscopy.

Table 2. Preparation of the α-azidoesters **3/3′** from the α-hydroxyesters **2/2′**

Entry	**2/2′**	C7[a]	**3/3′**	C7[a]	de[b] (%)	Yield[c] (%)
1	**2a/2′a** (95/05)	*S*	**3a/3′a** (05/95)	*R*	90	60
2	**2′a**[d]	*R*	**3a**[d]	*S*	>98	42
3	**2b/2′b** (85/15)	–	**3b/3′b** (15/85)	–	70	61
4	**2b/2′b** (12/88)	–	**3b/3′b** (88/12)	–	76	52
5	**2c/2′c** (92/08)	–	**3c/3′c** (08/92)	–	84	61
6	**2c/2′c** (23/77)	–	**3c/3′c** (77/23)	–	54	62

[a] Configuration of the C7 of the major diastereomer **3**.
[b] Determined on the crude product by ^{1}H NMR analysis.
[c] Yield of isolated products after chromatography on a silica gel column.
[d] Only one diastereomer could be seen by ^{1}H NMR spectroscopy.



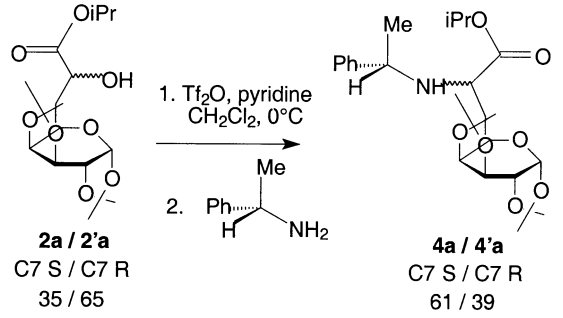
Scheme 2.

Bakers' yeast (*Saccharomyces cerevisiea*) (procedure D) was also studied (entry 13–16). The best diastereomeric excess (>98%) was observed for the reduction of the most hindered starting substrate **1a**, but the reaction was not complete, even after 69 h. With the aim to increase the stereoselectivity in the lyxose series (entry 16), a reduction with Bakers' yeast in the presence of β-cyclodextrin as described by Nakamura et al.[21] was tried but without any amelioration.

In summary, stereoselective reduction of α-ketoesters **1a–c** to the chiral α-hydroxy esters **2a–c** was achieved with two efficient reagents: the catecholborane-(*S*)- or (*R*)-5,5-diphenyl-2-methyl-3,4-propano-1,3,2-oxazaborolidine that gave C-glycosyl α-hydroxyester diastereomers with good diastereomeric excess (54–90%), in rather good yields (81–94% for **2a/2′a**; 73–76% for **2c/2′c**), and the microorganism Bakers' yeast that reduced the C-glycosyl α-ketoesters in a relatively modest yield (44–62%) but with a good diastereomeric excess, especially in the galactose series (>98%). However, it should be noted that the diastereomeric mixtures obtained were not separable.

The azido compounds **3** derived from α-hydroxyesters **2** were then investigated with the aim to further obtain the C-glycosyl α-aminoesters **5** with a better diastereoselectivity than that previously described by us in the preparation of **5** by reductive amination of the α-ketoesters **1**.[14] This method used the (*S*)-α-methylbenzyl amine followed by a hydrogenation step, which was disappointing concerning the selectivity of the asymmetric reduction of imines. Consequently, the C-glycosyl α-hydroxyesters **2** were transformed into the corresponding triflates[22] using trifluoromethanesulfonic anhydride, in the presence of pyridine, in dichloromethane, at 0°C. The non-isolated triflates were directly submitted to a very mild substitution by addition of sodium azide in dimethylformamide, at ambient temperature for 18 h. A stereospecific nucleophilic substitution resulted in a rather good overall yield using a relatively hindered secondary triflate functionality and with a pure inversion of configuration at the C7 (Table 2, Scheme 2).

Moreover, the reaction between the triflate issued from **2a/2′a** (35/65) and (*S*)-α-methylbenzylamine afforded the corresponding product **4a/4′a** (39/61). This stereospecific substitution allowed the unambiguous assignment of the (*S*) C7 configuration to **2a** (and (*R*) C7 to **2′a**) since the absolute configuration of **4a** was known to be (*S*).[14] This assignment was obtained by comparison of the ^{1}H NMR data of **4a** obtained by this route with the ^{1}H NMR data of an authentic crystallised sample of **4a** previously obtained by reductive amination of the α-ketoester **1a** and for which the X-ray crystallographic analysis was realised.[23] Unfortunately, such a correlation did not permit determination of the configuration of the new stereogenic centre of **2b/2′b** and **2c/2′c** because the pure crystallised derivative **4b** or **4c** could never be obtained; as a result, X-ray crystallographic analysis could not be carried out (Scheme 3).[24]



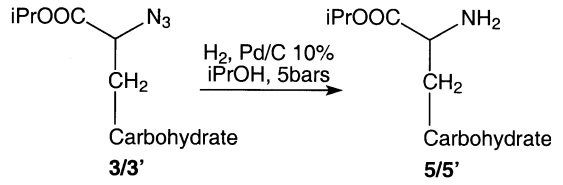
Scheme 3.

The C-glycosyl α-azidoesters **3/3′** were then hydrogenated in isopropyl alcohol under a pressure of 5 bar, for 14 h, leading to the expected C-glycosyl α-aminoesters **5/5′** in excellent yields with complete retention of configuration at the C7 (Table 3, Scheme 4).

Table 3. Reduction of the C-glycosyl α-azidoesters **3/3′** into C-glycosyl α-aminoesters **5/5′**

Entry	**3/3′**	C7[a]	**5/5′**	C7[a]	de[b] (%)	Yield[c] (%)
1	**3a/3′a** (05/95)	*R*	**5a/5′a** (05/95)	*R*	90	93
2	**3a**[d]	*S*	**5a**	*S*	>98[d]	98
3	**3b/3′b** (15/85)	–	**5b/5′b** (15/85)	–	72	94
4	**3b/3′b** (88/12)	–	**5b/5′b** (88/12)	–	76	95
5	**3c/3′c** (08/92)	–	**5c/5′c** (08/92)	–	84	91
6	**3c/3′c** (77/23)	–	**5c/5′c** (77/23)	–	54	87

[a] Configuration of the C7 of the major diastereomer **5**.
[b] Determined on the crude product by ^{1}H NMR analysis.
[c] Yield of crude products.
[d] Only one diastereomer could be seen by ^{1}H NMR spectroscopy.



Scheme 4.

3. Conclusion

In conclusion, the asymmetric reduction of C-glycosyl α-ketoesters allows access to new C-glycosyl α-hydroxyesters with a high stereoselectivity. These compounds can be easily transformed into the corresponding C-glycosyl α-aminoesters containing a stable C–C bond between the carbohydrate and the aminoester moiety. The conventional methods which are applied to transform the C-glycosyl α-hydroxyesters were revealed to be entirely stereospecific and gave access to C-glycosyl α-aminoesters with good to excellent diastereomeric excess, allowing the asymmetric synthesis of each diastereomer. This strategy can be advantageous compared to our precedent route based on the stereoselective aminoreduction of C-glycosyl α-ketoesters to prepare C-glycosyl α-aminoesters.

4. Experimental

4.1. General

Thin layer chromatographies were carried out on silica gel-coated plates (Kieselgel 60-F_{254}, Merck); spots were developed using sulphuric acid. Column chromatographies were performed on silica gel 60 or 70–230 mesh using the indicated eluent, dried and distilled shortly before use. IR spectra of liquids were recorded as thin films on KBr plates with a Nicolet 210 FT-IR spectrophotometer. NMR spectra were recorded on Bruker spectrometers [250 or 400 MHz (^{1}H) and 62.896 MHz (^{13}C)] and reference used was $CDCl_3$. Chemical shifts were given as δ ppm values and J values were given in Hertz (Hz). Mass spectra (FAB) were measured on an Autospec Fited Cesium Gun (Micromass, Manchester). All reactions (except the reactions using Bakers' yeast in water and the reactions under high pressure) were performed under a nitrogen atmosphere. Solvents were purified by standard procedures just before use.

4.2. Synthesis of C-glycosyl α-hydroxyesters 2/2′ by asymmetric reduction of C-glycosyl α-ketoesters 1

Typical procedure A. A solution of 0.34 g (0.95 mmol) of α-ketoester **1a** in 25 ml of isopropyl alcohol with 0.18 g of Pd/C 10% was stirred under a 50 bar pressure of hydrogen for 24 h. The crude product was then filtered on celite to remove the catalyst, the filtrate was evaporated under reduced pressure, and eluted on a silica gel chromatographic column to give 0.29 g (85%) of diastereomers **2a/2′a** (60/40).

Typical procedure B. To a solution of 1 equiv. of α-ketoester **1c** (0.19 g, 0.63 mmol) in 10 ml of isopropyl alcohol was added 1 equiv. (0.040 g, 0.63 mmol) of sodium cyanoborohydride. The mixture was stirred at ambient temperature for 24 h. The crude product was quenched with 2 ml of water, concentrated, extracted with chloroform, dried with magnesium sulfate, evaporated, and eluted on a silica gel chromatographic column to give 0.157 g (82%) of diastereomers **2c/2′c** (55/45).

Typical procedure C. To a solution of 1 equiv. of α-ketoester **1a** (0.35 g, 0.98 mmol) in 6 ml of dichloromethane was added 0.1 equiv. of (*S*)-5,5-diphenyl-2-methyl-3,4-propano-1,3,2-oxazaborolidine (0.027 g, 0.098 mmol) and 1 equiv. of catecholborane (0.118 g, 0.98 mmol). The mixture was stirred during 18 h, then hydrolysed and extracted with dichloromethane. The organic layer was washed three times with water, dried with magnesium sulfate, evaporated, and purified on a silica gel chromatographic column to give 0.33 g of diastereomers **2a/2′a** (11/89).

Typical procedure D. To a solution of α-ketoester **1a** (0.119 g, 0.33 mmol) in 15 ml of water was added Bakers' yeast (3 g). The mixture was stirred at room temperature for 69 h. Acetone (20 ml) was then added; and the mixture was filtered. The filtrate was concentrated and extracted with chloroform (3×20 ml). The organic phase was dried over magnesium sulfate, filtered and evaporated under reduced pressure to yield a colourless oil. The crude product **2′a** was purified on a silica gel chromatographic column to afford 0.072 g of pure **2′a** (61%).

4.2.1. Isopropyl 6-deoxy-1,2:3,4-di-*O*-isopropylidene-L-glycero-α-D-galacto-octopyranuronate 2a. TLC (hexane/AcOEt (2/1)) R_f 0.4; IR ν (cm^{-1}): 3469, 1731; ^{1}H NMR (250 MHz, $CDCl_3$): δ=5.43 (1H, d, J=5.1 Hz, H_1), 5.17–5.02 (1H, m, $COOCH(Me)_2$), 4.61 (1H, dd, J=2.6, 7.7 Hz, H_3), 4.29 (1H, dd, J=5.1, 2.6 Hz, H_2), 4.31–4.26 (1H, m, CHCOO), 4.16–4.09 (2H, m, H_4, H_5), 3.25 (1H, d, J=4.3 Hz, OH), 2.28–2.16 (1H, m, CH_2), 2.05–1.96 (1H, m, CH_2), 1.55 (3H, s, CH_3), 1.45 (3H, s, CH_3), 1.35 (3H, s, CH_3), 1.32 (3H, s, CH_3), 1.27 (3H, d, J=6.0 Hz, $COOCH(CH_3)_2$), 1.26 (3H, d, J=6.4 Hz, $COOCH(CH_3)_2$). ^{13}C NMR δ: 174.1, 109.2, 108.7, 96.2, 72.9, 71.0, 70.3, 69.2, 67.5, 63.7, 33.6, 25.9, 25.8, 24.9, 24.6, 21.7, 21.5; MS FAB$^+$: m/z 361 (MH$^+$, 100%); 345 (30).

4.2.2. Isopropyl 6-deoxy-1,2:3,4-di-*O*-isopropylidene-D-glycero-α-D-galacto-octopyranuronate 2′a. TLC (hexane/AcOEt (1/2)) R_f 0.67; $[\alpha]_D^{20}$=−41 (c 1.3 in $CHCl_3$); IR ν (cm^{-1}): 3441, 1731. ^{1}H NMR (250 MHz, $CDCl_3$): δ=5.54 (1H, d, J=4.7 Hz, H_1), 5.09 (1H, h, J=6.4 Hz, $COOCH(Me)_2$), 4.63 (1H, dd, J=2.6, 8.1 Hz, H_3), 4.32 (1H, dd, J=4.7, 2.6 Hz, H_2), 4.38–4.28 (1H, m, CHCOO), 4.17–4.12 (2H, m, H_4, H_5), 2.89 (1H, d, J=6.0 Hz, OH), 2.26–2.15 (1H, m, CH_2), 1.72–1.57 (1H, m, CH_2), 1.57 (3H, s, CH_3), 1.49 (3H, s, CH_3), 1.36 (3H, s, CH_3), 1.34 (3H, s, CH_3), 1.27 (6H, d, J=6.4 Hz, $COOCH(CH_3)_2$). ^{13}C NMR δ: 174.7, 109.2, 108.8, 96.1, 73.0, 70.6, 70.4, 69.6, 67.3, 63.7, 34.7, 25.7, 25.6, 24.8, 24.0, 21.6, 21.4; MS FAB$^+$: m/z 361 (MH$^+$, 100%), 345 (30).

4.2.3. Isopropyl 5-deoxy-1-*O*-methyl-2,3-*O*-isopropylidene-D,L-glycero-β-D-ribo-heptofuranuronate 2b/2′b. Compound **2b**. TLC (hexane/AcOEt (2/1)) R_f 0.4; IR ν (cm^{-1}): 3473, 1736. ^{1}H NMR (250 MHz, $CDCl_3$): δ=5.17–5.05 (1H, m, $COOCH(Me)_2$), 5.0 (1H, s, H_1), 4.68–4.61 (2H, m, H_2, H_3), 4.56–4.51 (1H, m, H_4), 4.37–4.28 (1H, m, CHCOO), 3.38 (3H, s, OCH_3), 2.84 (1H, d, J=6.0 Hz, OH), 2.23–2.04 (1H, m, CH_2), 1.76–1.57 (1H, m, CH_2), 1.49 (3H, s, CH_3), 1.33 (3H, s, CH_3), 1.29 (3H, d, J=6.4 Hz, $COOCH(CH_3)_2$), 1.28 (3H, d, J=6.2 Hz, $COOCH(CH_3)_2$). ^{13}C NMR δ: 174.4, 112.1, 109.5, 85.3,

84.1, 83.6, 69.2, 68.0, 54.8, 39.7, 26.3, 24.9, 21.5; MS FAB$^+$: *m/z* 305 (MH^+, 15%), 273 (100), 231 (38).

Compound **2′b**. TLC (hexane/AcOEt (2/1)) R_f 0.4; IR ν (cm^{-1}): 3473, 1736. ^1H NMR (250 MHz, $CDCl_3$): δ=5.16–5.06 (1H, m, $COOCH(Me)_2$), 4.97 (1H, s, H_1), 4.69–4.61 (2H, m, H_2, H_3), 4.40 (1H, t, J=7.3 Hz, H_4), 4.27 (1H, dd, J=5.1, 7.3 Hz, CHCOO), 3.36 (3H, s, OCH_3), 3.07 (1H, br s, OH), 2.11–1.90 (2H, m, CH_2), 1.48 (3H, s, CH_3), 1.32 (3H, s, CH_3), 1.29 (6H, d, J=6.0 Hz, $COOCH(CH_3)_2$). ^{13}C NMR δ: 173.8, 112.2, 109.5, 85.2, 84.1, 83.7, 69.4, 68.3, 54.8, 39.1, 26.3, 24.8, 21.4; MS FAB$^+$: *m/z* 305 (MH^+, 15%), 289 (15), 273 (100), 231 (38).

4.2.4. Isopropyl 5-deoxy-1-*O*-methyl-2,3-*O*-isopropylidene-D,L-glycero-α-D-lyxo-heptofuranuronate 2c/2′c. Compound **2c**. TLC (hexane/AcOEt (2/1)) R_f 0.35; IR ν (cm^{-1}): 3451, 1731. ^1H NMR (250 MHz, $CDCl_3$): δ=5.15–5.05 (1H, m, $COOCH(Me)_2$), 4.79 (1H, s, H_1), 4.65 (1H, dd, J=3.9, 6.0 Hz, H_3), 4.54 (1H, d, J=6.0 Hz, H_2), 4.36–4.30 (1H, m, CHCOO), 4.20–4.11 (1H, m, H_4), 3.27 (3H, s, OCH_3), 3.16 (1H, d, J=3.8 Hz, OH), 2.22–2.17 (2H, m, CH_2), 1.45 (3H, s, CH_3), 1.32 (3H, s, CH_3), 1.29 (3H, d, J=6.4 Hz, $COOCH(CH_3)_2$), 1.28 (3H, d, J=6.4 Hz, $COOCH(CH_3)_2$). ^{13}C NMR δ: 174.2, 112.3, 106.6, 85.0, 80.6, 75.3, 69.3, 67.9, 54.2, 32.6, 26.0, 25.0, 21.6, 21.4; MS FAB$^+$: *m/z* 305 (MH^+, 35%), 289 (31), 273 (100), 231 (85).

Compound **2′c**. TLC (hexane/AcOEt (2/1)) R_f 0.35; IR ν (cm^{-1}): 3451, 1731. ^1H NMR (250 MHz, $CDCl_3$): δ=5.16–5.06 (1H, m, $COOCH(Me)_2$), 4.89 (1H, s, H_1), 4.65 (1H, dd, J=3.4, 6.0 Hz, H_3), 4.54 (1H, d, J=6.0 Hz, H_2), 4.39–4.31 (1H, m, CHCOO), 4.21–4.15 (1H, m, H_4), 3.34 (3H, s, OCH_3), 3.04 (1H, d, J=7.2 Hz, OH), 2.32–2.19 (1H, m, CH_2), 2.01–1.90 (1H, m, CH_2), 1.48 (3H, s, CH_3), 1.33 (3H, s, CH_3), 1.29 (3H, d, J=6.4 Hz, $COOCH(CH_3)_2$), 1.28 (3H, d, J=6.4 Hz, $COOCH(CH_3)_2$). ^{13}C NMR δ: 174.2, 112.3, 106.6, 85.0, 80.6, 76.2, 69.2, 68.4, 54.2, 33.2, 25.9, 24.8, 21.6, 21.4; MS FAB$^+$: *m/z* 305 (MH^+, 35%), 289 (31), 273 (100), 231 (85).

4.3. Preparation of the azido compounds 3/3′

Typical procedure. A mixture of 1 equiv. of α-hydroxyester **2a/2′a** (95/5) (0.21 g, 0.58 mmol) and 4 equiv. of pyridine (0.18 g, 2.3 mmol) in 15 ml of dichloromethane was added dropwise at 0°C to a solution of 1.4 equiv. of trifluoromethane sulfonic anhydride (0.23 g, 0.82 mmol) diluted in 2 ml of dichloromethane. The mixture was stirred for 5 min, then 50 equiv. of sodium azide (1.9 g, 29 mmol) and 20 ml of dimethylformamide were added. The mixture was stirred for 16 h, and then concentrated under reduced pressure before 10 ml of water was added. The aqueous layer was extracted with dichloromethane, the organic phase was dried on magnesium sulfate, filtered, and evaporated. Toluene was added, and evaporated again. The crude product was then purified on a silica gel chromatographic column to give 0.135 g (60%) of a colourless oil of **3a/3′a** (5/95).

4.3.1. Isopropyl 7-azido-6,7-dideoxy-1,2:3,4-di-*O*-isopropylidene-L-glycero-α-D-galacto-octopyranuronate 3a. TLC (hexane/AcOEt (2/1)) R_f 0.66; IR ν (cm^{-1}): 2108, 1738. ^1H NMR (250 MHz, $CDCl_3$): δ=5.48 (1H, d, J=5.1 Hz, H_1), 5.16–5.02 (1H, m, $COOCH(Me)_2$), 4.61 (1H, dd, J=2.6, 8.1 Hz, H_3), 4.30 (1H, dd, J=5.1, 2.6 Hz, H_2), 4.14 (1H, dd, J=8.1, 1.7 Hz, H_4), 4.06 (1H, dd, J=6.0, 8.1 Hz, CHCOO), 3.93 (1H, ddd, J=1.7, 9.0, 4.7 Hz, H_5), 2.26–1.97 (2H, m, CH_2), 1.52 (3H, s, CH_3), 1.46 (3H, s, CH_3), 1.35 (3H, s, CH_3), 1.32 (s, 3H, CH_3), 1.30 (3H, d, J=6.4 Hz, $COOCH(CH_3)_2$), 1.29 (3H, d, J=6.4 Hz, $COOCH(CH_3)_2$). ^{13}C NMR δ: 169.4, 109.4, 108.7, 96.3, 72.4, 70.9, 70.4, 69.7, 64.3, 58.9, 31.8, 26.0, 25.8, 24.9, 24.5, 21.7, 21.6.

4.3.2. Isopropyl 7-azido-6,7-dideoxy-1,2:3,4-di-*O*-isopropylidene-D-glycero-α-D-galacto-octopyranuronate 3′a. TLC (hexane/AcOEt (2/1)) R_f 0.71; IR ν (cm^{-1}): 2115, 1738. ^1H NMR (250 MHz, $CDCl_3$): δ=5.52 (1H, d, J=5.1 Hz, H_1), 5.17–5.02 (1H, m, $COOCH(Me)_2$), 4.63 (1H, dd, J=2.6, 8.1 Hz, H_3), 4.33 (1H, dd, J=5.1, 2.6 Hz, H_2), 4.17 (1H, dd, J=3.0, 11.5 Hz, CHCOO), 4.12 (1H, dd, J=8.1, 1.7 Hz, H_4), 4.03–3.97 (1H, m, H_5), 2.27–2.15 (1H, m, CH_2), 1.75–1.63 (1H, m, CH_2), 1.58 (3H, s, CH_3), 1.47 (3H, s, CH_3), 1.35 (6H, s, CH_3), 1.30 (3H, d, J=6.4 Hz, $COOCH(CH_3)_2$), 1.29 (3H, d, J=6.4 Hz, $COOCH(CH_3)_2$). ^{13}C NMR δ: 170.0, 109.3, 108.7, 96.3, 72.9, 70.9, 70.6, 69.6, 63.8, 59.2, 32.0, 25.9, 25.6, 25.0, 24.2, 21.7, 21.6.

4.3.3. Isopropyl 6-azido-5,6-dideoxy-1-*O*-methyl-2,3-*O*-isopropylidene-D,L-glycero-β-D-ribo-heptofuranuronate 3b/3′b. Compound **3b**. TLC (hexane/AcOEt (2/1)) R_f 0.74; IR ν (cm^{-1}): 2109, 1738. ^1H NMR (250 MHz, $CDCl_3$): δ=5.17–5.05 (1H, m, $COOCH(Me)_2$), 4.97 (1H, s, H_1), 4.63 (1H, d, J=6.0 Hz, H_2), 4.59 (1H, d, J=6.0 Hz, H_3), 4.30 (1H, dd, J=6.4, 8.5 Hz, H_4), 3.97 (1H, t, J=7.3 Hz, CHCOO), 3.36 (3H, s, OCH_3), 2.18–1.93 (2H, m, CH_2), 1.49 (3H, s, CH_3), 1.33 (3H, s, CH_3), 1.32 (3H, d, J=6.0 Hz, $COOCH(CH_3)_2$), 1.31 (3H, d, J=6.0 Hz, $COOCH(CH_3)_2$). ^{13}C NMR δ: 169.3, 112.5, 109.8, 85.2, 83.8, 83.6, 70.0, 59.3, 55.1, 36.4, 26.3, 24.9, 21.6.

Compound **3′b**. TLC (hexane/AcOEt (2/1)) R_f 0.70; IR ν (cm^{-1}): 2112, 1739. ^1H NMR (250 MHz, $CDCl_3$): δ=5.16–5.01 (1H, m, $COOCH(Me)_2$), 4.98 (1H, s, H_1), 4.63 (1H, d, J=5.6 Hz, H_2), 4.57 (1H, d, J=5.6 Hz, H_3), 4.36 (1H, dd, J=3.4, 11.5 Hz, H_4), 4.08 (1H, dd, J=3.0, 11.5 Hz, CHCOO), 3.37 (3H, s, OCH_3), 2.14–2.03 (1H, m, CH_2), 1.84–1.72 (1H, m, CH_2), 1.49 (3H, s, CH_3), 1.32 (3H, s, CH_3), 1.29 (3H, d, J=6.4 Hz, $COOCH(CH_3)_2$), 1.28 (3H, d, J=6.4 Hz, $COOCH(CH_3)_2$). ^{13}C NMR δ: 169.9, 112.4, 109.8, 85.3, 83.9, 83.2, 69.7, 59.5, 55.2, 36.6, 26.3, 24.9, 21.6.

4.3.4. Isopropyl 6-azido-5,6-dideoxy-1-*O*-methyl-2,3-*O*-isopropylidene-D,L-glycero-α-D-lyxo-heptofuranuronate 3c/3′c. Compound **3c**. TLC (hexane/AcOEt (2/1)) R_f 0.74; IR ν (cm^{-1}): 2112, 1739. ^1H NMR (250 MHz, $CDCl_3$): δ=5.18–5.03 (1H, m, $COOCH(Me)_2$), 4.88 (1H, s, H_1), 4.65 (1H, dd, J=3.4, 6.0 Hz, H_3), 4.58 (1H, d, J=6.0 Hz, H_2), 4.13–4.05 (2H, m, CHCOO, H_4), 3.33 (3H, s, OCH_3), 2.34–2.22 (1H, m, CH_2), 2.05–1.92 (1H, m, CH_2), 1.47 (3H, s, CH_3), 1.32 (3H, s, CH_3), 1.31 (3H, d, J=6.4 Hz, $COOCH(CH_3)_2$), 1.30 (3H, d, J=6.4 Hz, $COOCH(CH_3)_2$).

^{13}C NMR δ: 169.7, 112.5, 106.7, 85.2, 80.2, 75.7, 69.7, 59.9, 54.4, 30.4, 26.0, 24.8, 21.6, 21.5.

Compound **3′c**. TLC (hexane/AcOEt (2/1)) R_f 0.7; IR ν (cm^{-1}): 2111, 1739. ^{1}H NMR (250 MHz, $CDCl_3$): δ=5.19–5.04 (1H, m, $COOCH(Me)_2$), 4.85 (1H, s, H_1), 4.65 (1H, dd, J=3.4, 6.0 Hz, H_3), 4.56 (1H, d, J=6.0 Hz, H_2), 4.15–4.01 (2H, m, CHCOO, H_4), 3.31 (3H, s, OCH_3), 2.28–2.19 (2H, m, CH_2), 1.47 (3H, s, CH_3), 1.33 (3H, s, CH_3), 1.31 (3H, d, J=6.4 Hz, $COOCH(CH_3)_2$), 1.30 (3H, d, J=6.0 Hz, $COOCH(CH_3)_2$). ^{13}C NMR δ: 169.6, 112.6, 106.7, 85.0, 80.1, 75.9, 69.8, 59.5, 54.4, 30.4, 26.0, 24.9, 21.7, 21.6.

4.4. Reduction of the azido compounds 3/3′ into the aminoesters 5/5′

In a typical procedure, 60 mg of Pd/C 10% was added to a solution of α-azidoester **3a/3′a** (5/95) (120 mg, 0.34 mmol) in 10 ml of isopropanol. The mixture was hydrogenated under a pressure of 5 bar for 14 h. The crude product was filtered on celite to remove the catalyst, and the filtrate was reduced in vacuo to yield **5a/5′a** (5/95) (114 mg, 93%). Spectral data of **5a–c/5′a–c** were recently given in Ref. 14.

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