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Note

Synthesis of bis-(methyl 3,4,6-tri-*O*-acetyl-D-glucopyranosid-2-yl)-oxamides

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Abstract—The synthesis of a new bis-(D-glucopyranosid-2-yl)oxamides via the key intermediate, *N*-acetyl *N*-(methyl 3,4,6-tri-*O*-acetyl-α-D-glucopyranosid-2-yl) oxamic acid chloride (**2α**) is described. Treatment of compound **2α** with methyl 3,4,6-tri-*O*-acetyl-2-amino-2-deoxy-β-D-glucopyranoside afforded *N*-(methyl 3,4,6-tri-*O*-acetyl-α-D-glucopyranosid-2-yl)-*N*′-(methyl 3,4,6-tri-*O*-acetyl-β-D-glucopyranosid-2-yl)-oxamide. Reaction of **2α** with 1,2-diaminoethane afforded 1,2-bis-[*N*,*N*′-(methyl 3′,4′,6′-tri-*O*-acetyl-α-D-glucopyranosid-2′-yl)]ethyloxamide as a main product, while 2-*N*-[*N*′-(methyl 3′,4′,6′-tri-*O*-acetyl-α-D-glucopyranosid-2′-yl)oxamide]-ethyl acetamide was formed as a side product. Reaction of **2α** with 1,3-diamino-2-hydroxypropane gave only 1,3-bis-*N*,*N*-[*N*′-(methyl 3′,4′,6′-tri-*O*-acetyl-2′-deoxy-α-D-glucopyranosid-2′-yl)-oxamido]-2-propanol.

Keywords: Oxamide; Bisoxamide; Amino acids; Peptides; Imidazolidines; NMR

In Studio's aiming to find new glucosyloxamides[1–3] we described the synthesis of an unsymmetrical oxamide. Acylation of methyl 3,4,6-tri-*O*-acetyl-2-acetamido-2-deoxy-α or β-D-glucopyranosides (**1α** or **1β**) with oxalyl chloride afforded *N*-acetyl *N*-(methyl 3,4,6-tri-*O*-acetyl-α or β-D-glucopyranosid-2-yl) oxamic acid chloride (**2α** or **2β**). The reaction of **2** with the corresponding amines gave unsymmetrical oxamides: derivative of D-glucosamine and aliphatic or aromatic amines[1,2] as well as amino acids or dipeptides.[3] On the other hand, the reaction of **2β** with methyl 3,4,6-tri-*O*-acetyl-2-amino-2-deoxy-β-D-glucopyranoside (**4β**) unexpectedly afforded instead of symmetrical *N*,*N*′-bis-(methyl 3,4,6-tri-*O*-acetyl-β-D-glucopyranosid-2-yl)-oxamide, the 2-hydroxy-2-methyl-1,3-bis-(methyl 3′,4′,6′-tri-*O*-acetyl-β-D-glucopyranosid-2′-yl)-imidazolidine-4,5-dione (**6**) a new imidazolidine-4,5-dione.[4]

Continuing our study on the synthesis of symmetrical bisglucosyloxamides, we have found that the obtained product depends on the configuration at C-1 of compound **2**. For compound **2β** the *N*-acetyl group is stable enough to obtain compound **6** in a reaction with **4β**.[4] On the other hand, when compound **2α** was reacted under similar conditions with **4β**, *N*-(methyl 3,4,6-tri-*O*-acetyl-α-D-glucopyranosid-2-yl)-*N*′-(methyl 3,4,6-tri-*O*-acetyl-β-D-glucopyranosid-2-yl)-oxamide (**5**) was obtained. As shown in Scheme 1, the first step of the reaction could be *N*-deacetylation of the acetyl group bonded to C-2–N leading to the formation of *N*-(methyl 3,4,6-tri-*O*-acetyl-α-D-glucopyranosid-2-yl) oxamic acid chloride (**3α**). Compound **3α** in reaction with methyl 3,4,6-tri-*O*-acetyl-2-amino-2-deoxy-β-D-glucopyranoside (**4β**) afforded compound **5** with a good yield. The ^{1}H and ^{13}C NMR spectra of compound **5** are in full agreement with the proposed structure. The ^{1}H NMR spectrum showed two signals for anomeric hydrogen atoms: one at δ 4.43 ppm (d, $J_{1,2}$ = 8.5 Hz) β-D-configuration of one glucosidic bond and the other at δ 4.73 ppm (d, $J_{1,2}$ = 4.0 Hz) α-D-configuration of the other glucosidic bond. Similarly, the ^{13}C NMR spectrum showed two signals for C-1 carbon atoms at 101.3 ppm for β-anomer and 97.96 for α-anomer. The oxamide bridge of compound **5** was confirmed by ^{1}H and ^{13}C NMR data. Hydrogen atoms of amide groups were observed at

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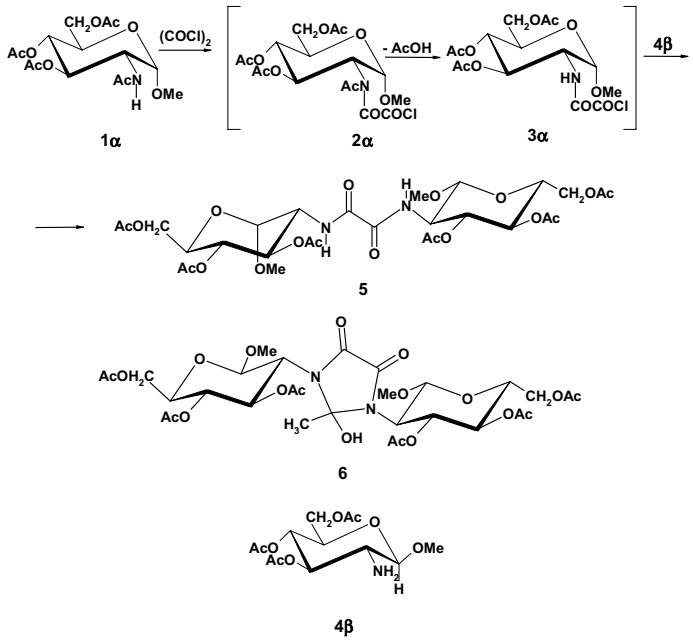


Scheme 1.

7.44 and 7.55 ppm and carbonyl carbons of oxamide bridge at 159.2 and 159.1 ppm.

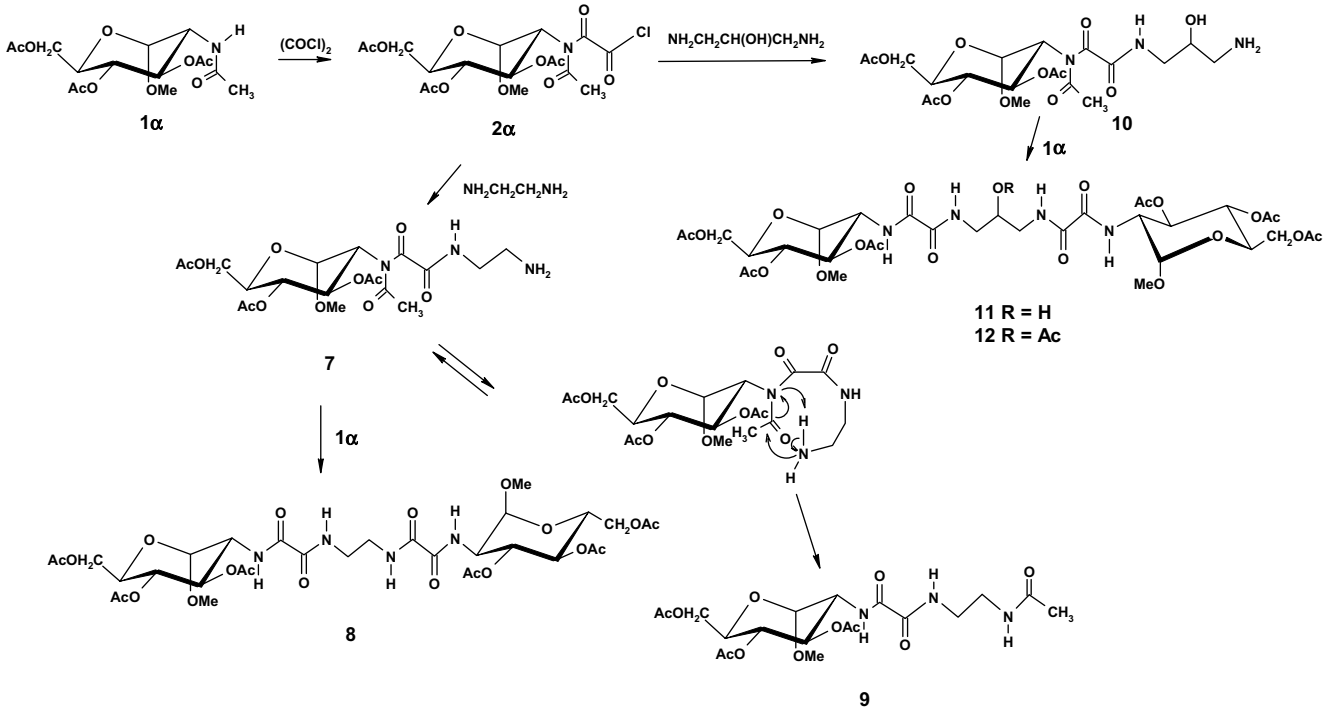
The reaction of 2 equiv of **2α** with 1 equiv of 1,2-diaminoethane afforded 1,2-bis-[*N*,*N*′-(methyl 3′,4′,6′-tri-*O*-acetyl-α-D-glucopyranosid-2′-yl)]ethyloxamide (**8**) as a main product (Scheme 2). Besides compound **8**, 2-*N*-[*N*′-(methyl 3′,4′,6′-tri-*O*-acetyl-α-D-glucopyranosid-2′-yl)oxamide]-ethyl acetamide (**9**) was formed as a side product. As shown in Scheme 2, the formation of **9** can be explained by acetyl migration from the amide group at C-1′ to the terminal amine group of ethylamino residue. The ^{1}H and ^{13}C NMR spectra of the obtained compound **8** are in full agreement with the proposed structure. Since similar protons of both glucopyranoside residues are magnetically equivalent, we observed in NMR spectrum one set of signals. The ^{1}H NMR spectrum showed a signal for anomeric hydrogen atoms at δ 4.92 ppm (d, $J_{1',2'} = 3.5$ Hz). Similarly the ^{13}C NMR spectrum showed signals for C-1′ carbon atoms at 97.64 ppm. The oxamide bridge of compound **8** was confirmed by ^{1}H and ^{13}C NMR data. Two equivalent hydrogen atoms of the amide groups were observed at 7.55 ppm ($N–H_{Glc}$) and two others at 8.09 ppm ($N–H_{CH_2}$). The carbonyl carbons of the oxamide bridge were observed at 159.7 and 159.5 ppm and carbons of ethylene residue appeared at 38.87 ppm.

In the ^{1}H NMR spectrum of **9** the signals of two amide groups appear as triplets at 7.96 and 6.34 ppm, one amine group (NH_{Glcp}) as a doublet at 7.60 ppm, and signals of methyl group of acetamide residue at 2.11 ppm, moreover the carbonyl carbons of acetamide group was observed at 171.2 ppm and the signals of methyl group of acetamide residue appear at 23.13 ppm in ^{13}C NMR spectrum.

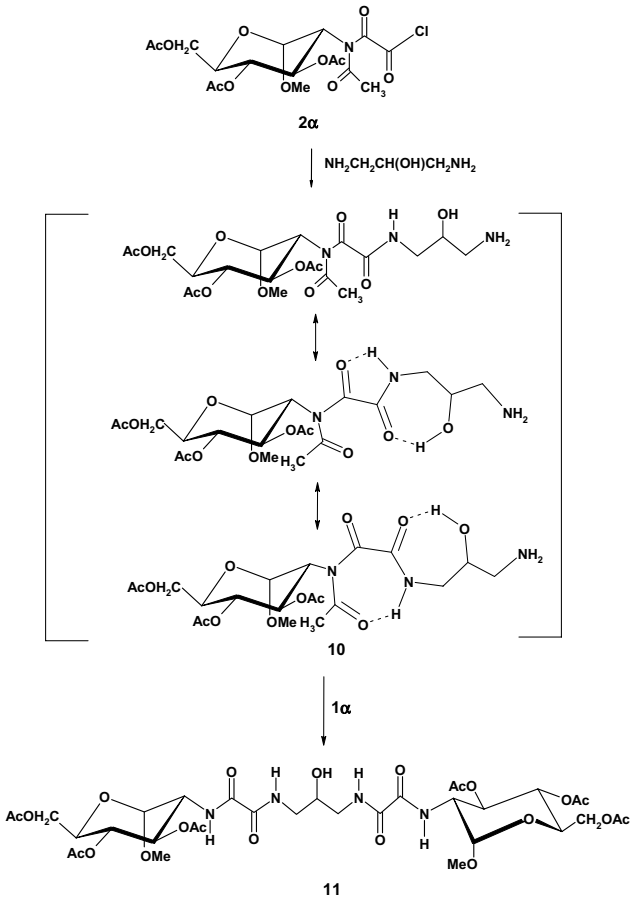
As a result of treatment of 2 equiv of **2α** with 1 equiv of 1,3-diamino-2-hydroxypropane in a similar way as described above, only 1,3-bis-*N*,*N*-[*N*′-(methyl 3′,4′,6′-tri-*O*-acetyl-2′-deoxy-α-D-glucopyranosid-2′-yl)-oxamido]-2-propanol (**11**) was obtained. Acetylation of crude **11** with acetic anhydride and pyridine afforded 1,3-bis-*N*,*N*-[*N*′-(methyl 3′,4′,6′-tri-*O*-acetyl-2′-deoxy-α-D-glucopyranosid-2′-yl)oxamido]-2-propyl acetate (**12**) (Scheme 2).

The ^{1}H NMR spectrum of **12** showed a signal for anomeric hydrogen atoms at δ 4.76 ppm (d, $J_{1',2'} = 3.0$ Hz) and the ^{13}C NMR spectrum showed one signal for both C-1′ carbon atoms at 97.86 ppm. The oxamide bridge of compound **12** was confirmed by ^{1}H and ^{13}C NMR data. Two hydrogen atoms of the amide groups ($N–H_{Glc}$) were observed at 7.62 and 7.60 ppm (2d, $J_{2',NH} = 3$ Hz), moreover two others ($N–H_{CH_2}$) were observed at 7.83 and 7.81 ppm (2t, $J_{CH_2,NH} = 7$ Hz). The signals of two $N–CH_2$ groups and CH group appeared at 3.50 and 5.02 ppm, respectively. Resonances of carbons of $N–CH_2$ groups appeared at 39.68 and 39.54 ppm while the CH group appeared at 70.72 ppm. The resonances of carbonyl carbons of the oxamide bridge appeared at 159.7, 159.6, 159.3 and 159.2 ppm.

As shown in Scheme 2, the first step of the formation of **11** can be acylation of 1,3-diamino-2-hydroxypropane by **2α** giving compound **10**. Then compound **10** can react with **1α** to yield **11**. If we compare the reactions of **2α** with 1,2-diaminoethane and with 1,3-diamino-2-hydroxypropane, we notice that in the case of reaction



Scheme 2.



Scheme 3.

of **2α** with 1,3-diamino-2-hydroxypropane, we did not observe any acetyl group migration giving *N*-acetyl derivative. The absence of acetyl group migration could be explained by intramolecular *N*–H···O=C and O–H···O=C hydrogen bonds formation for compound **10**. The formation of a seven-membered ring and of a five-membered ring makes approach of terminal C-3–NH_2 towards C-1′–NAc group impossible. Such approach is required for acetyl group migration (Scheme 3).

1. Experimental

Optical rotations were measured on a Perkin–Elmer Model 241. The ^1H and ^{13}C NMR spectra were recorded as $CDCl_3$ solutions (internal reference Me_4Si) with a Varian Unity Plus-500 spectrometer. TLC was performed on Silica gel 60 F_{254} (Merck), using dichloromethane–MeOH (4:1) as eluent and detection by UV light or by charring with sulfuric acid. Column chromatography was performed on Silica gel 60 (Merck 230–400 mesh) eluting with dichloromethane–MeOH (4:1).

1.1. *N*-Acetyl *N*-(methyl 3,4,6-tri-*O*-acetyl-α or β-D-glucopyranosid-2-yl) oxamic acid chloride (2α or 2β)

To a solution of **1α** or **1β**[5] (0.75 g; 2.08 mmol) in dichloromethane (5 mL) was added a solution of oxalyl

chloride (1.15 g; 8 mmol) in dichloromethane (8 mL). The reaction mixture was stirred at 0 °C for 10 min and at room temperature for 30 min. TLC then indicated the absence of **1**. Next the reaction mixture was evaporated under reduced pressure and crude product (**2α** or **2β**) was obtained. This product was immediately used for further synthesis.

1.2. *N*-(Methyl 3,4,6-tri-*O*-acetyl-α-D-glucopyranosid-2-yl)-*N*′-(methyl 3,4,6-tri-*O*-acetyl-β-D-glucopyranosid-2-yl)-oxamide (5)

The crude product **2α** (2.07 mmol) was dissolved in CH_2Cl_2 and one and a half fold excess (1.25 g, 3.12 mmol) of HBr salt of **4β** was added. The mixture was stirred at room temperature for 2 h. The resulting mixture was successively washed with HCl (1 M), water and a satd aq $NaHCO_3$, and then dried over $MgSO_4$ and concentrated. The residue was purified by column chromatography with CH_2Cl_2–MeOH (4:1) as eluent. The solvent was evaporated under reduced pressure. Crystallization from ethanol gave **5** (0.78 g, yield 53%). Mp 267–268 °C; $[\alpha]_D^{20}$ +37.6 (*c* 1.0, $CHCl_3$). LSIMS(+)NBA *m*/*z* Calcd for $C_{28}H_{40}O_{18}N_2$ 692.6. Found 715.6 [M+Na]. ^{1}H NMR ($CDCl_3$): δ 7.55, 7.44 (2dd, 2H, $J_{2',NH}$ = 9.5 and 10.0 Hz, 2N–H), 5.26, 5.23 (2dd, 2H, $J_{3',4'}$ = 9.5 and 10.0 Hz, 2H-3′), 5.12 (2dd, 2H, $J_{4',5'}$ = 9.5 Hz, 2H-4′), 4.73 (d, 1H, $J_{1',2'}$ = 4.0 Hz, H-1′α), 4.55 (d, 1H, $J_{1',2'}$ = 8.5, H-1′β), 4.33–4.24 (m, 3H, H-2′ and 2H-6′a), 4.16, 4.11 (2dd, 2H, $J_{5',6b'}$ = 5.0 Hz, 2H-6′b), 3.99–3.93 (m, 3H, H-5′ and 2H-2′), 3.72 (ddd, 1H, $J_{5',6a'}$ = 2.5 Hz, H-5′), 3.49, 3.43 (2s, 6H, 2OMe), 2.11, 2.10, 2.03, 2.02, 1.99, 1.96 (6s, 18H, 6OAc). ^{13}C NMR ($CDCl_3$): δ 170.7, 170.6, 169.5, 170.4, 169.7, 169.4 (6OAc), 156.3, 159.2 (2C=O), 101.3 (C-1′β), 97.86 (C-1′α), 72.27, 71.91 (2C-3′), 71.39, 68.31 (2C-4′), 67.98, 67.60 (2C-5′), 61.94, 61.60 (2C-6′), 57.18, 55.54 (2C-2′), 54.64, 52.22 (2OMe), 20.77, 20.73, 20.60, 20.46 (6OAc).

1.3. 1,2-Bis-[*N*,*N*′-(methyl 3′,4′,6′-tri-*O*-acetyl-α-D-glucopyranosid-2′-yl)]ethyloxamide (8) and 2-*N*-[*N*′-(methyl 3′,4′,6′-tri-*O*-acetyl-α-D-glucopyranosid-2′-yl)oxamide]-ethyl acetamide (9)

To the solution of **2α** in CH_2Cl_2 (2.07 mmol in 10 mL) $NH_2CH_2CH_2NH_2$ (0.09 mL, 1.35 mmol), and a few drops of Et_3N were added. The mixture was stirred at −5 °C for 30 min and than at room temperature for 2 h. The resulting mixture was successively washed with HCl (1 M), water and a satd aq $NaHCO_3$, and then dried over $MgSO_4$ and concentrated. The residue was chromatographed with CH_2Cl_2–MeOH (6:1) to afford pure **8** and **9**. Compound **8** (0.57 g, 34%) was crystallized from ethanol to give white crystals, mp 290–293 °C; $[\alpha]_D^{20}$ +52.8 (*c* 1.0, $CHCl_3$). LSIM(+)NBA *m*/*z* Calcd for $C_{32}H_{46}O_{20}N_4$ 806.7. Found 829.7 [M+Na]. ^{1}H NMR ($CDCl_3$): δ 8.09 (m, 2H, 2N*H*–CH_2), 7.55 (d, 2H, $J_{2',NH}$ = 9.5 Hz, $2NH_{Glcp}$), 5.32 (dd, 2H, $J_{3',4'}$ = 10.4 Hz, 2H-3′), 5.10 (d, 2H, $J_{4',5'}$ = 9.5 Hz, 2H-4′), 4.92 (d, 2H, $J_{1',2'}$ = 3.0 Hz, 2H-1′), 4.35–4.20 (m, 4H, 2H-2′, 2H-6′a), 4.10 (dd, 2H, $J_{5',6'b}$ = 2.5 Hz, $J_{6'a,6'b}$ = 12.0 Hz, 2H-6′b), 3.99–3.90 (m, 2H, 2H-5′), 3.49 (s, 6H, 2OMe), 2.11, 2.03, 1.96 (3s, 18H, 6OAc). ^{13}C NMR ($CDCl_3$): δ 170.7, 169.5 (6OAc), 159.7, 159.5 (4C=O), 97.89 (2C-1′), 70.77 (2C-5′), 68.27 (2C-3′), 67.58 (2C-4′), 61.96, (2C-6′), 55.42 (2OMe), 52.30 (2C-2), 36.87 ($2CH_2$), 20.74, 20.69, 20.61 (6OAc).

Compound **9** (0.083 g, 8%) was crystallized from ethanol giving white crystals, mp 221–224 °C; $[\alpha]_D^{20}$ +67.9 (*c* 1.0, $CHCl_3$). LSIM(+)NBA *m*/*z* Calcd for $C_{19}H_{29}O_{11}N_3$ 475.4. Found 498.4 [M+Na]. ^{1}H NMR ($CDCl_3$): δ 7.86, 6.10 (2t, 2H, 2N*H*–CH_2), 7.60 (d, H, $J_{2',NH}$ = 10.0 Hz, NH_{Glcp}), 5.38 (dd, 1H, $J_{2',3'}$ = 9.5 Hz, H-3′), 5.11 (dd, $J_{3',4'}$ = 10.0 Hz, H-4′), 4.76 (d, 1H, $J_{1',2'}$ = 3.0, H-1′), 3.34–3.22 (m, 2H, H-2′, H-6′a), 4.21 (dd, 1H, $J_{5',6'b}$ = 3 Hz, $J_{6'a,6'b}$ = 12.5 Hz, H-6′b), 3.98 (ddd, 1H, $J_{5',6'a}$ = 4.5 Hz, H-5′), 3.46–3.38 (m, 4H, $2CH_2$), 3.42 (s, 3H, OMe), 2.11 (s, 3H, NAc), 2.03, 1.99, 1,97 (3s, 6H, 3OAc). ^{13}C NMR ($CDCl_3$): δ 171.2 (NAc), 170.7, 169.5 (3OAc), 159.9, 159.6 (2C=O), 97.87 (C-1′), 70.92 (C-5′), 68.24 (C-3′), 67.61 (C-4′), 61.96, (C-6′), 55.55 (OMe), 52.27 (C-2′), 39.85, 39.48 ($2CH_2$), 23.13 (NAc), 20.74, 20.69, 20.61 (3OAc).

1.4. 1,3-Bis-*N*,*N*-[*N*′-(methyl 3′,4′,6′-tri-*O*-acetyl-2′-deoxy-α-D-glucopyranosid-2′-yl)oxamido]-2-propyl acetate (12)

To the solution of **2α** in CH_2Cl_2 (2.07 mmol in 10 mL) excess of 1,3-diamino-2-hydroxypropane dihydrobromide (1.31 g, 5.20 mmol) in 10 mL of CH_2Cl_2 and a few drops Et_3N were added (to pH about 8). The mixture was stirred at 0 °C for 2 h. The resulting mixture was successively washed with HCl (1 M), water satd aq $NaHCO_3$, then dried over $MgSO_4$ and concentrated. The crude product was acetylated with Pyr/Ac_2O. After evaporation, chromatography of the residual syrup CH_2Cl_2–MeOH (4:1) yielded **12** (0.73 g, 40%) as a colourless syrup, $[\alpha]_D^{22}$ +65.2 ($CHCl_3$), ES (+) *m*/*z* LSIM(+)NBA *m*/*z* Calcd for $C_{35}H_{50}O_{22}N_4$ 878.8 $[M]^+$. Found 901.9 $[M+Na]^+$; ^{1}H NMR ($CDCl_3$) δ 7.83, 7.81 (2t, 2H, 2N*H*–CH_2), 7.62, 7.60 (2d, 2H, 2N–H_{GlN}), 5.32 (2dd, 2H, $J_{3',4'}$ = 10.0 Hz, 2H-3′), 5.22 (2dd, 2H, $J_{4',5'}$ = 9.5 Hz, 2H-4′), 5.02–4.98 (m, 2H, 2CH), 4.76 (d, 2H, $J_{1',2'}$ = 3 Hz, 2H-1′), 4.32–4.27 (m, 4H, $J_{2',NH}$ = 9.5, $J_{5',6a'}$ = 5.0 Hz, 2H-2′, 2H-6a′), 4.12 (dd, 2H′, $J_{5',6b'}$ = 2.5, $J_{6a',6b'}$ = 12.0 Hz, 2H-6b′), 3.99 (ddd, 2H, 2H-5′), 3.50 (m, 4H, 2N–CH_2), 3.43 (s, 6H, 2OMe), 2.11, 2.03, 1.98 (3s, 18H, 6OAc), 2.09 (s, 3H, CHOCOC*H*$_3$); 1.72 (t, 2H, CH_2); ^{13}C

NMR ($CDCl_3$) δ 170.7, 170.6, 170.2, 169.5 (7OAc), 159.6, 159.6, 159.3, 159.2 (4C=O), 97.86 (2C-1′), 70.85 (C-3′), 70.72 (CH), 68.22 (2C-4′), 67.59 (2C-5′), 61.92 (2C-6′), 55.51 (2OMe), 52.25 (2C-2′), 39.54, 36.68, (2N–CH_2), 29.66 (CHOCOCH_3), 20.91, 20.71, 20.63, 20.59 (6OAc).

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