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Stereoselective synthesis of α-*C*-glycosides of *N*-acetylgalactosamine

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Abstract

Attempts to synthesise α-*C*-glycosides of *N*-acetylgalactosamine by selective deprotection at C-2′ of allyl α-*C*-galactoside **1** and subsequent amination failed, but opened the way to α-*C*-talopyranosides. The synthesis of α-*C*-glycosides of *N*-acetylgalactosamine was performed from allyl α-*C*-glucopyranoside **9**, which was regioselectively deprotected, stereoselectively aminated at C-2′, and finally epimerised at C-4′. © 2000 Elsevier Science Ltd. All rights reserved.

1. Introduction

The carbohydrate moieties of glycoproteins are known to influence the properties of the parent protein in many diverse ways. First of all, glycosylation not only affects the physical properties of proteins (i.e. folding and conformation) but also influences their biological functions.[1] For example, glycosylation provides protection against proteolysis, influences uptake of serum proteins by the liver, affects intracellular transport of enzymes to lysosomes, determines human blood groups, and regulates leukocyte trafficking to sites of inflammation. In addition, the glycosidic part of glycoproteins is responsible for many intercellular cell surface recognition phenomena.[2,3] In this context, of fundamental biological and pharmaceutical importance are, for example, the aberrant glycosylation patterns of glycoproteins in cancer,[4] the carbohydrate-mediated cell adhesion involved in hematogenous metastasis of cancer[5] and the carbohydrate-based inflammatory response mechanism.[6]

Among the fundamental saccharidic units in biologically relevant glycoproteins, *N*-acetyl α-D-galactosamine plays important roles. Mucin glycoproteins are represented by the common

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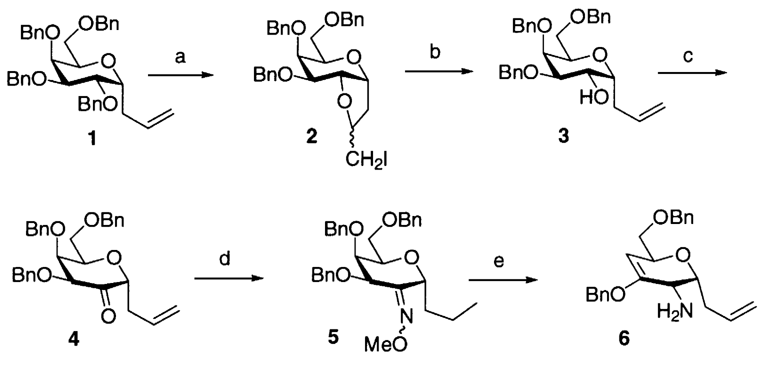
GalNAcα1→*O*-serine or threonine core structure (Tn antigen) found in MUC1–MUC4 and are the most important surface *O*-linked glycoproteins of epithelial cells and of the mucous.[7] The Tn structure in normal cells is cryptic since it is further glycosylated to construct complex *O*-linked glycans on mucin-type glycoproteins, whereas in most human carcinomas this structure is exposed at the cell surface, due to incomplete synthesis of saccharidic chains.[4] The Tn epitope is expressed in over 70% of human epithelial cancers such as lung, colon, stomach and breast carcinomas, the increased expression being correlated with tumour aggressiveness.[8,9] Hence, Tn containing glycoconjugates can be promising as synthetic cancer vaccines.[10]

The main drawback in using *O*-glycoconjugate-based therapeutic approaches is the inherent lack of in vivo stability of such compounds, since native *O*-glycopeptides are easily degraded in both acidic and basic media, and in biological systems by enzymes. Therefore, access to hydrolytically stable saccharidic residues is of great interest. A solution to this problem lies in *C*-glycosides,[11,12] in which the interglycosidic oxygen is replaced with a methylene group. The *C*-glycosidic linkage provides hydrolytic stability to glycopeptides without greatly affecting their structure.

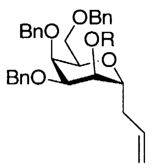
Despite the biological relevance of the Tn antigen, only a couple of examples of the synthesis of α-*C*-glycoside analogues of *N*-acetylgalactosamine have been reported,[13,14] both suffering from the use of the expensive tri-*O*-benzylgalactal as starting material. Here we describe a convenient procedure for the synthesis of α-*C*-glycosidic analogues of *N*-acetylgalactosamine, suitably functionalised for the synthesis of neoglycoconjugates by chemoselective ligation,[15] and eventually having the free hydroxyl group at C-3′ which can be galactosylated in order to obtain T antigen analogues.

2. Results and discussion

The synthetic strategy adopted for our synthesis of an α-*C*-glycosidic analogue of *N*-acetylgalactosamine takes advantage of our observations that polybenzylated allyl *C*-glucosides can be selectively deprotected at C-2′ and then aminated.[16] We first studied the exploitation of this procedure on galactoderivative **1** (Scheme 1). Treatment of 1-(2′,3′,4′,6′-tetra-*O*-benzyl-α-D-galactopyranosyl)-2-propene **1**[17] with iodine afforded the cyclic iodoether **2**, in agreement with what was observed for glucose derivatives.[16] Subsequent ring opening with zinc and acetic acid afforded compound **3** (91% from **1**) in which the 2′-OH was selectively deprotected. In order to convert the free hydroxyl group into an acetamido function, compound **3** was oxidised with PCC in dichloromethane to the corresponding ketone **4** (93%), which was then transformed into two diastereomeric oximes **5** ($MeONH_2 \cdot HCl$, pH 4.5, quantitative yield). Reduction of compound **5** with $LiAlH_4$ afforded mainly the elimination product **6**, obtained in 40% yield, together with a multitude of unidentified by-products. The undesired outcome of this reaction can be explained in the light of the steric hindrance on both the α-face, caused by the allylic appendage, and the β-face, due to the axial benzyloxy group in position 4′. The basicity of the aluminium hydride causes first β-elimination, and secondly reduction of the oxime. The net result of the reaction is the formation of **6**. In order to avoid the elimination reaction, different reducing agents which could operate in acidic conditions were used: zinc in acetic acid,[18] sodium cyanoborohydride in the presence of Lewis acids,[19] sodium borohydride in acetic acid,[20] sodium borohydride in the presence, respectively, of cerium trichloride[21] and nickel dichloride,[22] and catalytic hydrogenation. In either case no reaction occurred. Since every attempt to reduce the oxime **5** failed, we tried reductive amination of ketone **4** with benzylamine and sodium triacetoxyborohydride as reducing agent.[23] However, the desired amine was obtained only in traces, while the main product derived from the reduction of ketone **4** was the allyl *C*-talopyranoside **7** (Fig. 1). Compound **7** is the only product if the reduction is performed with sodium borohydride at −20°C (97% yield); the alcohol was then converted into the corresponding triflate **8** (Fig. 1), but every attempt to displace the triflate with an azido group failed. In summary, selective deprotection at position 2′ by iodination/reductive elimination can be efficiently extended to allyl *C*-glycosides of galactose, and gives access to *C*-talopyranosides.



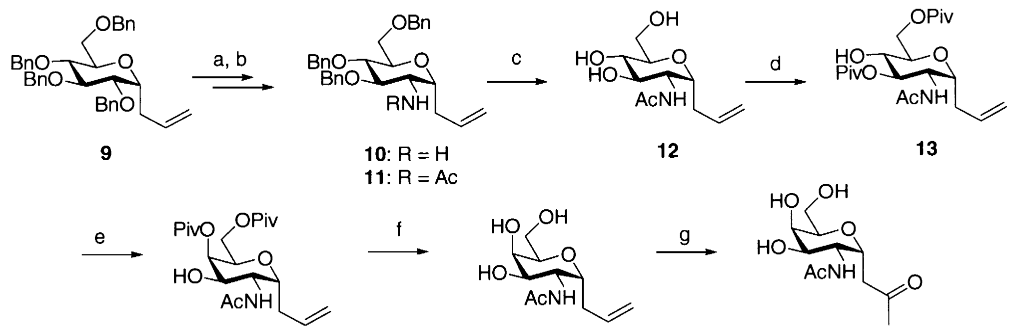
Scheme 1. *Reagents and conditions*: (a) I_2, CH_2Cl_2; (b) Zn, AcOH, THF:MeOH 1:1, 91% over two steps; (c) PCC, CH_2Cl_2, m.s. 4 Å, 93%; (d) NH_2OMe, pH=4.5, quantitative; (e) $LiAlH_4$, THF, 40%



7: R = H
8: R = CF_3SO_2

Fig. 1.

However, following this approach, it was impossible to obtain *C*-glycosides of *N*-acetylgalactosamine. We then decided to take advantage of the possibility to epimerise selectively the C-4′ of *N*-acetylglucosamino derivatives.[24,25] This new strategy uses glucose as a cheap starting material, which can be easily converted into α-*C*-glucoside **9**.[26] Compound **9** was transformed into the α-*C*-glucoside of glucosamine **10**, according to the selective debenzylation–amination procedure,[11] and then acetylated, affording compound **11** (Scheme 2). It is noteworthy that **11** is obtained from **9** in 51% overall yield over six steps. Interestingly, ^1H NMR coupling constants show a $^1C_4$ conformation for compound **11**, probably due to hydrogen bonding between the NH functionality and the oxygen in position 4′. In order to epimerise C-4′, compound **11** must be converted into a suitable protected derivative, having the hydroxyl group in position 4′ deprotected. Compound **11** was then debenzylated with ethanethiol in the presence of boron trifluoride etherate, affording **12**, in quantitative yield (Scheme 2). The triol **12** was selectively protected as the *t*-butylcarbonyl ester at positions 3′ and 6′, affording **13** in 82% yield. The epimerisation was effected taking advantage of acyl migration in basic media, preferring an axial configuration to an equatorial one.[27] The migration/epimerisation reaction was all but trivial; many different conditions were tried for the optimisation of this one pot reaction previously reported on the parent *O*-glycoside.[25] The optimal conditions are as follows: compound **13** was converted into the corresponding triflate by adding triflic anhydride (2.5 equiv.) portionwise to a solution of the alcohol in a 2:1 mixture of pyridine:dichloromethane at 0°C. After the complete consumption of the starting material **13**, water was added to the reaction mixture, affording the α-*C*-glycosidic analogue of *N*-acetylgalactosamine **14** in 84% yield. Deprotection of **14** under Zemplén conditions (NaOMe in MeOH) afforded compound **15** in 87% yield; the allylic appendage was then functionalised by reaction with Na_2PdCl_4 in water (80% yield) giving methyl ketone **16**.



Scheme 2. *Reagents and conditions*: (a) see Ref. 16; (b) Ac_2O, Py, CH_2Cl_2, 83%; (c) EtSH, $BF_3 \cdot OEt_2$, quantitative; (d) PivCl, Py, −20°C, 82%; (e) (i) Tf_2O, Py:CH_2Cl_2 2:1, 0°C; (ii) H_2O, rt, 84%; (f) NaOMe, MeOH, 87%; (g) Na_2PdCl_4, H_2O, 60°C, 80%

In conclusion, the procedure herein described for the synthesis of a Tn antigen analogue exploits selective amination at C-2′ of an allyl *C*-glucoside, easily available from glucose, and epimerisation at C-4′ of the obtained *N*-acetylglucosamine derivative. The allylic appendage of compound **14** can be further functionalised as ketone **16**, suitable for the synthesis of neoglycoconjugates, and the free hydroxyl group at C-3′ can be galactosylated to T antigen analogues.

3. Experimental

3.1. General remarks

^{1}H NMR and ^{13}C NMR spectra were recorded using a Bruker AC 300 or a Varian XL 200 instrument using $CDCl_3$ as solvent unless otherwise stated. Chemical shifts are reported in ppm downfield from TMS as an internal standard. Reported assignments of the ^{1}H NMR spectra were based on 2D proton–proton shift-correlation spectra. Signals of the aromatic carbons in the ^{13}C NMR spectra are not reported. $[\alpha]_D$ values were measured at 20°C and are given in units of 10^{-1} deg cm^2 g^{-1}. Chromatographic purifications were performed by the flash procedure using Merck silica gel 60 (230–400 mesh). TLC was performed on Merck silica gel 60 F_{254} plates and visualised by spraying with a solution prepared with concentrated H_2SO_4 (5 mL), MeOH (45 mL) and water (45 mL), and then heating to 110°C for 5 min. All solvents were dried prior to use.

*3.2. 1-(3′,4′,6′-Tri-*O*-benzyl-α-*D*-galactopyranosyl)-2-propene* ***3***

Under argon atmosphere, iodine (3.86 g, 15.22 mmol) was added to a solution of **1** (4.30 g, 7.61 mmol) in dry CH_2Cl_2 (20 mL) at 0°C. After 30 min the reaction was complete; aqueous $Na_2S_2O_3$ was added and the mixture stirred until the organic phase became colourless. The organic layer was washed with water, then dried over Na_2SO_4, filtered and concentrated to dryness. The crude cyclic iodoether **2** (5.00 g, yellowish oil) was dissolved in a 1:1 mixture of Et_2O:MeOH (40 mL), and Zn (4.90 g, 76.1 mmol) and glacial AcOH (0.87 mL) were added. After 30 min the reaction mixture was filtered over a Celite pad and the solvent evaporated. The residue was dissolved in CH_2Cl_2, and the organic phase washed sequentially with 5% HCl and water. The organic layer was dried over Na_2SO_4, filtered and concentrated to dryness. Purification of the crude product by flash chromatography (8:2, petroleum ether:EtOAc) afforded 3.29 g of **3** (91% yield) as a colourless oil. $[\alpha]_D$=+63.5 (*c* 1, $CHCl_3$); ^{1}H NMR (300 MHz) δ 7.40–7.20 (m, 15H), 5.89–5.75 (m, 1H), 5.12 (d, 1H, *J*=19.2 Hz), 5.06 (d, 1H, *J*=10.2 Hz), 4.74, 4.58 (ABq, 2H, *J*=11.3 Hz), 4.71, 4.56 (ABq, 2H, *J*=11.7 Hz), 4.57, 4.49 (Abq, 2H, *J*=12.0 Hz), 4.10–4.00 (m, 4H), 3.83 (dd, 1H, *J*=10.2, 6.3 Hz), 3.70 (dd, 1H, *J*=10.2, 4.7 Hz), 3.69–3.67 (m, 1H), 2.45–2.37 (m, 2H), 2.08 (bd, 1H, *J*=3.5 Hz); ^{13}C NMR (75.43 MHz) δ 134.77 (d), 116.80 (t), 78.33 (d), 73.30 (d), 73.18 (t), 73.06 (t), 73.04 (t), 72.37 (d), 71.51 (d), 68.62 (d), 67.23 (t), 31.49 (t). Anal. calcd for $C_{30}H_{34}O_5$: C, 75.92%; H, 7.22%. Found: C, 76.01%; H, 7.18%.

*3.3. 1-(3′,4′,6′-Tri-*O*-benzyl-α-*D-lyxo*-hexulopyranosyl)-2-propene* **4**

Alcohol **3** (200 mg, 0.42 mmol) was dissolved in dry CH_2Cl_2 (10 mL), under argon atmosphere. Activated powdered molecular sieves (4 Å, 500 mg) and PCC (136 mg, 0.64 mmol) were added to the solution. After 40 min the reaction mixture was filtered over a Celite pad and the filtrate concentrated. The residue was purified by flash chromatography (8.5:1.5, petroleum ether:EtOAc), affording **4** (184 mg, 93%) as a white solid. Mp 36–38°C; $[\alpha]_D$=+34.2 (*c* 0.5, $CHCl_3$); ^{1}H NMR (300 MHz) δ 7.45–7.20 (m, 15H), 5.92–5.73 (m, 1H), 5.11 (d, 1H, *J*=18.0 Hz), 5.06 (d, 1H, *J*=10.3 Hz), 4.96–4.90 (m, 2H), 4.54–4.49 (m, 5H), 4.33–4.28 (m, 2H), 4.21 (dd, 1H, *J*=7.6, 4.3 Hz), 3.63 (bd, 2H, *J*=5.8 Hz), 2.59–2.52 (m, 1H), 2.41 (dt, 1H, *J*=14.7, 7.6 Hz); ^{13}C NMR (54.29 MHz) δ 208.28 (s), 133.14 (d), 117.79 (t), 82.37 (d), 78.79 (d), 76.31 (d), 75.58 (d), 73.48 (t), 72.84 (t), 72.38 (t), 67.53 (t), 34.70 (t). Anal. calcd for $C_{30}H_{32}O_5$: C, 76.25%; H, 6.83%. Found: C, 76.07%; H, 6.79%.

*3.4. 1-(3′,4′,6′-Tri-*O*-benzyl-α-*D-lyxo*-hexulopyranosyl)-2-propene methyloxime* **5**

Ketone **4** (5.0 g, 10.6 mmol) dissolved in a 1:1 THF:MeOH mixture (30 mL) was stirred overnight with a buffer solution (50 mL) prepared by dissolving $NH_2OMe\cdot HCl$ (5.0 g, 59.9 mmol) and $AcONa\cdot 3H_2O$ (10.0 g, 74.2 mmol) in water (the pH was adjusted to 4.5 with AcOH). The reaction mixture was stirred overnight. The solution was then diluted with EtOAc and the organic layer washed sequentially with satd $NaHCO_3$ and water to neutrality. The crude was purified by flash chromatography (9:1, petroleum ether:EtOAc) affording two products corresponding to the diastereomeric oximes **5** as an amorphous white solid. The two isomers interconvert quite rapidly. The spectral data given below correspond to the major isomer. ^{1}H NMR (300 MHz) δ 7.45–7.20 (m, 15H), 5.81–5.71 (m, 1H), 5.26 (dd, 1H, *J*=8.1, 6.1 Hz), 5.07 (d, 1H, *J*=16.0 Hz), 5.05 (d, 1H, *J*=11.1 Hz), 4.99, 4.68 (ABq, 2H, *J*=11.9 Hz), 4.96, 4.62 (ABq, 2H, *J*=12.1 Hz), 4.42, 4.34 (ABq, 2H, *J*=11.8 Hz), 4.25 (d, 1H, *J*=2.3 Hz), 3.98 (bd, 1H, *J*=2.3 Hz), 3.92 (s, 3H), 3.88 (t, 1H, *J*=6.3 Hz), 3.49 (d, 2H, *J*=6.3 Hz), 2.45 (dt, 1H, *J*=14.4, 8.1 Hz), 2.18 (dt, 1H, *J*=14.4, 6.1 Hz); ^{13}C NMR (54.29 MHz) δ 154.45 (s), 133.42 (d), 117.35 (t), 76.31 (d), 75.66 (d), 74.01 (t), 73.38 (t), 72.37 (t), 71.94 (d), 69.49 (d), 69.11 (t), 61.99 (q), 34.31 (t). Anal. calcd for $C_{31}H_{35}NO_5$: C, 74.23%; H, 7.03%; N, 2.79%. Found: C, 74.45%; H, 6.92%; N, 2.94%.

Compound **6**: Oximes **5** (1.4 g, 2.8 mmol) were dissolved in dry THF (10 mL), the solution cooled to 0°C, and $LiAlH_4$ was added (5.5 mL of a 1 M solution in THF). After 24 h the reaction was quenched by adding EtOAc, the organic layer washed with water, dried over Na_2SO_4 and concentrated to dryness. Purification by flash chromatography afforded **6** (510 mg, 50% yield) as an amorphous solid. ^1H NMR (300 MHz, C_6D_6) δ 7.37–7.03 (m, 10H), 6.02–5.83 (m, 1H), 5.16 (d, 1H, J=17.2 Hz), 5.07 (d, 1H, J=10.3 Hz), 4.63–4.57 (m, 1H), 4.52–4.38 (m, 5H), 3.76 (dt, 1H, J=7.0, 2.1 Hz), 3.52 (dd, 1H, J=9.9, 6.7 Hz), 3.33 (dd, 1H, J=9.9, 5.0 Hz), 2.90 (d, 1H, J=2.5 Hz), 2.59 (dt, 1H, J=14.1, 7.0 Hz), 2.47 (dt, 1H, J=14.1, 7.0 Hz), 1.03 (bs, 2H); ^{13}C NMR (75.43 MHz) δ 157.47 (s), 134.74 (d), 117.00 (t), 93.81 (d), 73.30 (t), 72.24 (2d), 71.19 (t), 69.09 (t), 50.04 (d), 35.38 (t). Anal. calcd for $C_{23}H_{27}NO_3$: C, 75.58%; H, 7.45%; N, 3.83%. Found: C, 74.45%; H, 7.62%; N, 3.94%.

*3.5. 1-(3′,4′,6′-Tri-*O*-benzyl-α-*D*-talopyranosyl)-2-propene* ***7***

To a solution of ketone **4** (100 mg, 0.21 mmol) in 96% EtOH (0.5 mL) cooled to –20°C, $NaBH_4$ (16 mg, 0.42 mmol) was added. After 15 min the reaction was quenched with a 5% aqueous solution of NaOH and diluted with EtOAc. The organic layer was washed with water, dried over Na_2SO_4, filtered and evaporated under reduced pressure. Purification by flash chromatography (9:1, petroleum ether:EtOAc) afforded 97 mg of **7** as a colourless oil (97% yield). $[\alpha]_D$=+17.6 (*c* 1, $CHCl_3$); ^1H NMR (300 MHz, C_6D_6) δ 7.30–7.12 (m, 15H), 5.91–5.82 (m, 1H), 5.06 (d, 1H, J=17.5 Hz), 5.03 (d, 1H, J=9.8 Hz), 4.62, 4.40 (ABq, 2H, J=11.4 Hz), 4.56, 4.51 (ABq, 2H, J=11.6 Hz), 4.42, 4.35 (ABq, 2H, J=11.0 Hz), 4.03 (bdd, 1H, J=9.6, 5.6 Hz), 3.97–3.90 (m, 1H), 3.89–3.82 (m, 3H), 3.63 (bd, 1H, J=2.8 Hz), 3.53–3.51 (m, 2H), 2.22 (t, 2H, J=6.5 Hz); ^{13}C NMR (54.29 MHz) δ 134.24 (d), 117.14 (t), 76.37 (d), 75.74 (d), 74.69 (d), 74.00 (t), 73.36 (t), 72.05 (d), 71.45 (t), 69.09 (d), 67.75 (t), 34.38 (t). Anal. calcd for $C_{30}H_{34}O_5$: C, 75.92%; H, 7.22%. Found: C, 75.84%; H, 7.11%.

*3.6. 1-(2′-Acetamido-3′,4′,6′-tri-*O*-benzyl-2′-deoxy-α-*D*-glucopyranosyl)-2-propene* ***11***

To a solution of amine **10**[16] (1.0 g, 2.11 mmol) in dry CH_2Cl_2 (15 mL), dry pyridine (680 μL, 8.44 mmol) and acetic anhydride (398 μL, 4.22 mmol) were added. After 1 h the solution was washed sequentially with 5% aqueous HCl and water. The organic layer was dried over Na_2SO_4, filtered and concentrated to dryness. The residue was purified by flash chromatography (6:4, petroleum ether:EtOAc), affording 900 mg of **11** as a white solid (83% yield). Mp 115–117°C; $[\alpha]_D$=+4.4 (*c* 1, $CHCl_3$); ^1H NMR (300 MHz) δ 7.45–7.28 (m, 15H, Ph-H), 6.51 (d, 1H, J=9.8 Hz, NH), 5.86–5.75 (m, 1H, H-2), 5.08 (d, 1H, J=17.9 Hz, H-3a), 5.04 (d, 1H, J=10.8 Hz, H-3b), 4.62, 4.49 (ABq, 2H, J=11.8 Hz, PhCH_2O), 4.58, 4.43 (ABq, 2H, J=11.3 Hz, PhCH_2O), 4.52 (bs, 2H, PhCH_2O), 4.25 (t, 1H, J=7.0 Hz, H-5′), 4.20 (bdt, 1H, J=9.8, 1.6 Hz, H-2′), 3.95 (dt, 1H, J=7.3, 1.6 Hz, H-1′), 3.85 (dd, 1H, J=9.9, 7.0 Hz, H-6′a), 3.75 (dd, 1H, J=9.9, 7.0 Hz, H-6′b), 3.70 (t, 1H, J=3.0 Hz, H-3′), 3.58 (bs, 1H, H-4′), 2.32–2.10 (m, 2H, H-1), 1.83 (s, 3H, CH_3CO); ^{13}C NMR (54.29 MHz, C_6D_6) δ 169.53 (s), 135.81 (d), 117.93 (t), 76.26 (d), 75.74 (d), 74.65 (d), 74.18 (t), 72.96 (t), 72.56 (t), 69.45 (t), 69.34 (d), 49.30 (d), 37.30 (t), 23.64 (q). Anal. calcd for $C_{32}H_{37}NO_5$: C, 74.54%; H, 7.23%; N, 2.72%. Found: C, 75.64%; H, 7.15%; N, 2.69%.

*3.7. 1-(2′-Acetamido-2′-deoxy-α-*D*-glucopyranosyl)-2-propene* ***12***

Compound **11** (2.3 g, 4.46 mmol) was dissolved in ethanethiol (22 mL) and $BF_3\cdot OEt_2$ (13 mL) was added dropwise. After 24 h the reaction mixture was neutralised by adding Et_3N (10 mL) and the solvent evaporated. Purification by flash chromatography (8:2, CH_2Cl_2:EtOH) afforded **12** as a white solid in quantitative yield. Mp 176–178°C; $[\alpha]_D$=+108.4 (*c* 1, MeOH); ^1H NMR (300 MHz, MeOD) δ 7.95 (d, 1H, J=5.5 Hz, NH), 5.92–5.73 (m, 1H, H-2), 5.21 (dd, 1H, J=16.3, 2.2 Hz, H-3a), 5.13 (d, 1H, J=9.0

Hz, H-3b), 4.10 (dt, 1H, *J*=10.1, 5.5 Hz, H-1′), 3.94 (bdt, 1H, *J*=10.0, 5.5 Hz, H-2′), 3.75 (dd, 1H, *J*=11.9, 2.8 Hz, H-6′a), 3.67 (dd, 1H, *J*=11.9, 6.8 Hz, H-6′b), 3.62 (t, 1H, *J*=10.0 Hz, H-3′), 3.50–3.44 (m, 1H, H-5′), 3.35 (t, 1H, *J*=10.0 Hz, H-4′), 2.54–2.41 (m, 1H, H-1), 2.28–2.16 (m, 1H, H-1), 1.98 (s, 3H, CH_3CO); ^{13}C NMR (75.43 MHz, D_2O) δ 175.13 (s), 135.15 (d), 118.35 (t), 73.94 (d), 73.52 (d), 71.55 (d), 71.45 (d), 61.74 (t), 54.23 (d), 30.82 (t), 22.75 (q). Anal. calcd for $C_{11}H_{19}NO_5$: C, 53.87%; H, 7.81%; N, 5.71%. Found: C, 53.75%; H, 7.95%; N, 5.89%.

3.8. *1-(2′-Acetamido-2′-deoxy-3′,6′-di-*O*-pivaloyl-α-*D*-glucopyranosyl)-2-propene* ***13***

Triol **12** (1.0 g, 4.07 mmol) was dissolved in a 2:1 mixture of dry pyridine:CH_2Cl_2 (21 mL), and the solution cooled to –20°C; pivaloyl chloride (1 mL, 8.15 mmol) was added portionwise and the reaction mixture allowed to warm to 0°C. After 7 h the organic phase was washed sequentially with 5% aqueous HCl and water. The organic layer was dried over Na_2SO_4, filtered and evaporated. The crude was purified by flash chromatography (98:2, CH_2Cl_2:EtOH). Compound **13** was obtained as an amorphous white solid (1.37 g, 82% yield). $[\alpha]_D$=+16.6 (*c* 0.5, $CHCl_3$); ^1H NMR (300 MHz) δ 6.12 (d, 1H, NH, *J*=8.2 Hz), 5.81–5.70 (m, 1H, H-2), 5.11 (dd, 1H, H-3a, *J*=16.9, 1.3 Hz), 5.07 (d, 1H, H-3b, *J*=9.4 Hz), 5.01 (t, 1H, H-3′, *J*=8.0 Hz), 4.47 (dd, 1H, H-6′a, *J*=11.9, 5.9 Hz), 4.25–4.12 (m, 3H, H-1′, H-2′, H-6′b), 3.76 (ddd, 1H, H-5′, *J*=8.0, 5.9, 2.5 Hz), 3.52 (t, 1H, H-4′, *J*=8.0 Hz), 3.30 (bs, 1H, OH), 2.52–2.20 (m, 2H, H-1), 1.93 (s, 3H, CH_3CO), 1.32–1.15 (m, 18H, $(CH_3)_3C$-); ^{13}C NMR (54.29 MHz) δ 179.41 (s), 178.93 (s), 169.99 (s), 133.70 (d), 117.26 (t), 72.61 (d), 72.08 (d), 71.41 (d), 68.27 (d), 62.79 (t), 50.72 (d), 38.88 (s), 38.78 (s), 31.72 (t), 27.44–26.41 (m), 23.00 (q). Anal. calcd for $C_{21}H_{35}NO_7$: C, 61.00%; H, 8.53%; N, 3.39%. Found: C, 59.94%; H, 8.65%; N, 3.49%.

3.9. *1-(2′-Acetamido-2′-deoxy-4′,6′-di-*O*-pivaloyl-α-*D*-galactopyranosyl)-2-propene* ***14***

Gluco derivative **13** (62 mg, 0.15 mmol) was dissolved in a 2:1 pyridine:CH_2Cl_2 mixture (1 mL) and the solution cooled to 0°C. Triflic anhydride (62 μL, 0.37 mmol) was added portionwise until complete consumption of the starting material; water (148 μL, 8.2 mmol) was then added, and the reaction mixture was allowed to stir overnight at room temperature. The reaction was diluted with CH_2Cl_2, the organic layer washed sequentially with 5% aqueous HCl and water, dried over Na_2SO_4, filtered and evaporated under reduced pressure. Purification by flash chromatography (1:1, petroleum ether:EtOAc+0.2% EtOH) afforded 52 mg of **14** as a yellowish oil (84% yield). $[\alpha]_D$=+50.1 (*c* 1, $CHCl_3$); ^1H NMR (300 MHz) δ 5.99 (d, 1H, NH, *J*=7.7 Hz), 5.81–5.69 (m, 1H, H-2), 5.13 (d, 1H, H-4′, *J*=3.9 Hz), 5.10 (d, 1H, H-3a, *J*=15.5 Hz), 5.05 (d, 1H, H-3b, *J*=9.5 Hz), 4.62 (bt, 1H, H-6′a, *J*=9.7 Hz), 4.36 (ddd, 1H, H-1′, *J*=8.9, 5.0, 3.3 Hz), 4.16 (dt, 1H, H-2′, *J*=7.7, 3.3 Hz), 4.11 (dd, 1H, H-5′, *J*=9.7, 4.4 Hz), 4.03 (dd, 1H, H-6′b, *J*=9.7, 4.4 Hz), 4.01 (dd, 1H, H-3′, *J*=7.7, 3.9 Hz), 2.36–2.15 (m, 3H, H-1, OH), 2.01 (s, 3H, CH_3CO), 1.33–1.13 (m, 18H, $(CH_3)_3C$-); ^{13}C NMR (54.29 MHz) δ 178.04 (s), 170.91 (2s), 133.83 (d), 117.27 (t), 70.70 (d), 68.50 (d), 68.18 (d), 67.58 (d), 60.74 (t), 52.07 (d), 39.01 (s), 38.63 (s), 33.01 (t), 27.04 (6q), 23.04 (q). Anal. calcd for $C_{21}H_{35}NO_7$: C, 61.00%; H, 8.53%; N, 3.39%. Found: C, 60.13%; H, 8.68%; N, 3.64%.

3.10. *1-(2′-Acetamido-2′-deoxy-α-*D*-galactopyranosyl)-2-propene* ***15***

Galacto derivative **14** (80 mg, 0.193 mmol) was dissolved in dry MeOH (2 mL) and a catalytic amount of sodium was added; after 45 min the reaction mixture was neutralised with Amberlite IR-120, filtered and evaporated. Purification of the crude by crystallisation (EtOH/EtOAc) afforded 41 mg of **15** as a white solid (87% yield). Mp 215–217°C; $[\alpha]_D$=+129.0 (*c* 0.85, MeOH); ^{1}H NMR (200 MHz, D_2O) δ 7.99 (d, 1H, NH, *J*=6.4 Hz), 5.92–5.68 (m, 1H, H-2), 5.08 (dd, 1H, H-3a, *J*=17.1, 2.3 Hz), 5.02 (dd, 1H, H-3b, *J*=9.1, 2.3 Hz), 4.30–4.01 (m, 2H, H-1′, H-5′), 3.91 (bs, 1H, H-4′), 3.83–3.65 (m, 4H, H-2′, H-3′, H-6′), 2.32–2.58 (m, 1H, H-1a), 2.09–2.27 (m, 1H, H-1b), 2.00 (s, 3H, CH_3CO). Anal. calcd for $C_{11}H_{19}NO_5$: C, 53.86%; H, 7.80%; N, 5.71%. Found: C, 53.93%; H, 7.69%; N, 5.74%.

*3.11. 1-(2′-Acetamido-2′-deoxy-α-D-galactopyranosyl)-propan-2-one **16***

Compound **15** (24 mg, 0.098 mmol) was dissolved in water (1.5 mL), Na_2PdCl_4 was added and the reaction mixture warmed to 60°C. After 30 min the suspension was filtered on a Celite pad, and the filtrate concentrated to dryness. The crude was purified by flash chromatography (6:4, EtOAc:EtOH), affording 20 mg of ketone **16** as a yellowish oil (80% yield). ^{1}H NMR (300 MHz, MeOD) δ 7.99 (d, 1H, NH, *J*=5.0 Hz,), 4.64 (dt, 1H, H-1′, *J*=9.6, 5.0 Hz), 4.27 (dt, 1H, H-2′, *J*=9.5, 5.0 Hz), 3.96 (t, 1H, H-4′, *J*=2.4 Hz), 3.88–3.63 (m, 4H, H-3′, H-5′, H-6′), 2.91 (dd, 1H, H-1a, *J*=16.0, 9.6 Hz), 2.67 (dd, 1H, H-1b, *J*=16.0, 5.0 Hz), 2.22 (s, 3H, H-3), 2.01 (s, 3H, CH_3CO); ^{13}C NMR (75.43 MHz, MeOD) δ 211.07 (s), 174.80 (s), 76.51 (d), 74.76 (d), 74.02 (d), 71.01 (d), 62.71 (t), 51.71 (d), 42.37 (t), 31.21 (q), 23.36 (q). Anal. calcd for $C_{11}H_{19}NO_6$: C, 50.57%; H, 7.32%; N, 5.38%. Found: C, 50.53%; H, 7.26%; N, 5.42%.

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