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Stereoselective entry into the D-GalNAc series starting from the D-Gal one: a new access to *N*-acetyl-D-galactosamine and derivatives thereof ☆

Lorenzo Guazzelli, Giorgio Catelani *, Felicia D'Andrea, Alessia Giannarelli

Dipartimento di Chimica Bioorganica e Biofarmacia, Università di Pisa, Via Bonanno, 33-I-56126 Pisa, Italy

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ABSTRACT

A new stereoselective preparation of *N*-aceyl-D-galactosamine (**1b**) starting from the known *p*-methoxyphenyl 3,4-*O*-isopropylidene-6-*O*-(1-methoxy-1-methylethyl)-β-D-galactopyranoside (**10**) is described using a simple strategy based on (a) epimerization at C-2 of **10** via oxidation–reduction to give the *talo* derivative **11**, (b) amination with configurational inversion at C-2 of **11** via a S_N2-type reaction on its 2-imidazylate, (c) anomeric deprotection of the *p*-methoxyphenyl β-D-galactosamine glycoside **14**, (d) complete deprotection. Applying the same protocol to 2,3:5,6:3′,4′-tri-*O*-isopropylidene-6′-*O*-(1-methoxy-1-methylethyl)-lactose dimethyl acetal (**4**), directly obtained through acetonation of lactose, the disaccharide β-D-GalNAc*p*-(1→4)-D-Glc*p* (**1a**) was obtained with complete stereoselectivity in good (40%) overall yield from lactose.

1. Introduction

D-Galactosamine (D-GalNH_2) is, after D-glucosamine, the second most abundant natural aminosugar, isolated first in 1914 by Levene and La Forge[2] from chondroitin, a mucopolysaccharide in which D-GalNH_2 is present, as in the structurally related dermatan sulfate,[3] as its acetamido derivative (2-acetamido-2-deoxy-D-galactopyranose, D-GalNAc, **1b**). D-GalNAc is also a constituent of several complex glycoproteins, as for examples: (i) the monosaccharide 'core' of mucines,[4] (ii) oligosaccharide determinants of human blood group antigens,[5] (iii) anti-freeze glycoproteins of anthartic fishes.[5] Furthermore, D-GalNAc has been recently recognised as one of the strongest agonist of the NKR-P1 rat Natural Killer cells receptor.[6] Owing to the biological relevance of D-GalNAc, several approaches to its synthesis in the free form and/or to the synthesis of its derivatives have been proposed, using different carbohydrate starting materials. The two most exploited synthetic channels to D-GalNAc and its derivatives are those based on (a) C-4 epimerization of the largely and cheaply available D-GlcNAc,[7] mimicking thus the biosynthetic pathway; and (b) the amination at C-2 of D-galactose with formal retention of configuration.[8–11] The first D-Gal to D-GalNAc transformation was described in 1976[8] by Paulsen and co-workers using as key reaction the sodium azide opening of the epoxide ring of the intermediate 1,6:2,3-dianhydro-β-D-talopyranoside. A few years later, Lemieux and Ratcliffe[9] used the azidonitration of tri-*O*-acetyl-D-galactal for the synthesis of some 2-azido-2-deoxy-D-galactopyranose derivatives and free D-GalNAc (**1b**). After this key paper, several addition reactions to D-galactal derivatives have been proposed to obtain D-GalNAc and its glycosides, as the Danishefsky's sulfamidoglycosylation,[10] the Gin's acetamidoglycosylation.[11] Furthermore, specific syntheses of D-GalNH_2 starting from L-lyxose[12] and, very recently, D-tagatose[13] have been proposed.

In the frame of a general project on the synthesis of β-D-hexosaminyl-(1→4)-D-Glc*p* disaccharides,[14] we considered the synthesis of β-D-GalNAc*p*-(1→4)-D-Glc*p* (**1a**), a natural disaccharide present in minute amount in the bovine colostrum.[15] The sole reported synthesis of **1a** is based on an enzymatic glycosylation involving a β-(1→4)-*N*-acetylgalactosaminyltransferase.[16] However, the above synthesis does not appear suitable for preparative purposes. Presented herein is a new efficient chemical method for the preparation of the disaccharide **1a** starting from lactose, involving a two-step amination with overall retention of configuration at C-2′ (Chart 1), through the formation of a β-D-talopyranoside intermediate of type **2**. The potentiality of the method has also been demonstrated in the case of a monosaccharide β-D-galactopyranoside, that has been transformed into a known precursor of free D-GalNAc (**1b**) and of some 2-azido-2-deoxy-D-galactopyranoside glycosyl donors.

2. Results and discussion

A straightforward route to β-D-GalNAc*p*-(1→4)-D-Glc*p* (**1a**) was envisaged (Scheme 1) taking advantage of the easy availability of

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* Corresponding author. Tel.: +39 0502219700; fax: +39 0502219660.
E-mail address: giocate@farm.unipi.it (G. Catelani).

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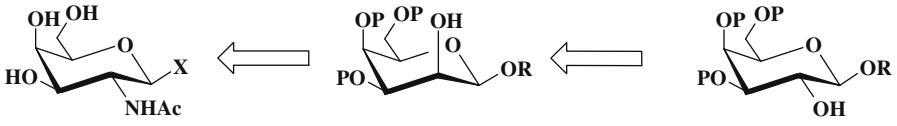
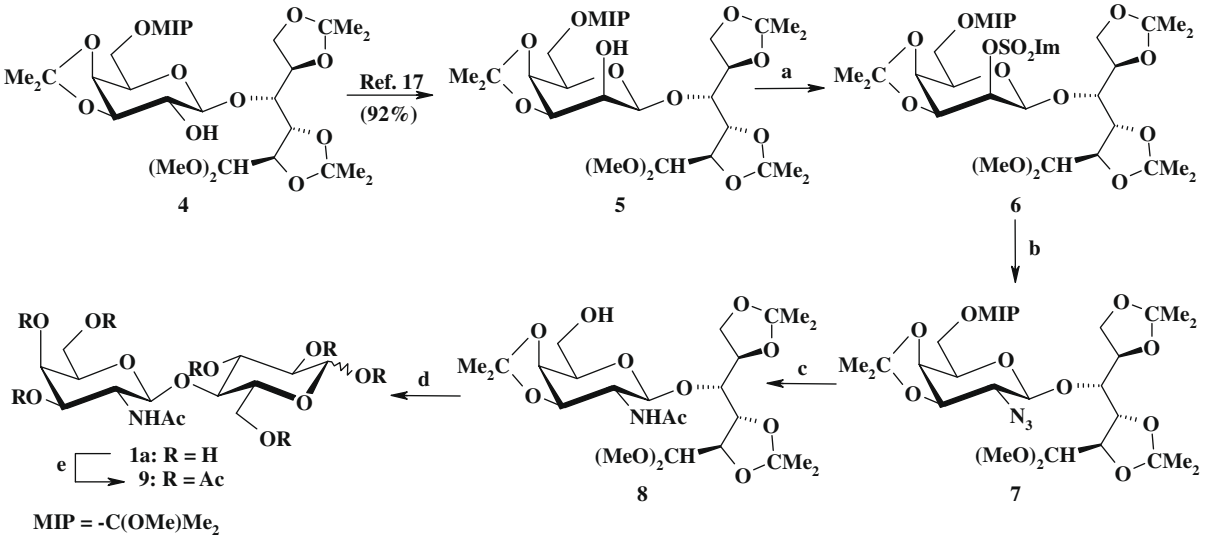


Chart 1. Retrosynthetic approach for transforming a β-D-galactopyranoside unit into a D-GalNAc one.



Scheme 1. Synthesis of β-D-GalNAc*p*-(1→4)-D-Glc*p* disaccharide from lactose. Reagents and conditions: (a) Im_2SO_2, NaH, DMF, −30 °C, 4 h (86%); (b) NaN_3, DMF, 100 °C, 1.2 h (94%); (c) (1) $NiCl_2{\cdot}6H_2O$, $NaBH_4$, MeOH, 0 °C, rt, 2 h; (2) Ac_2O, MeOH, rt, 2 h (86%); (d) 80% aq AcOH, 80 °C, 4 h (90%); (e) Ac_2O, Py, rt, 18 h (95%).

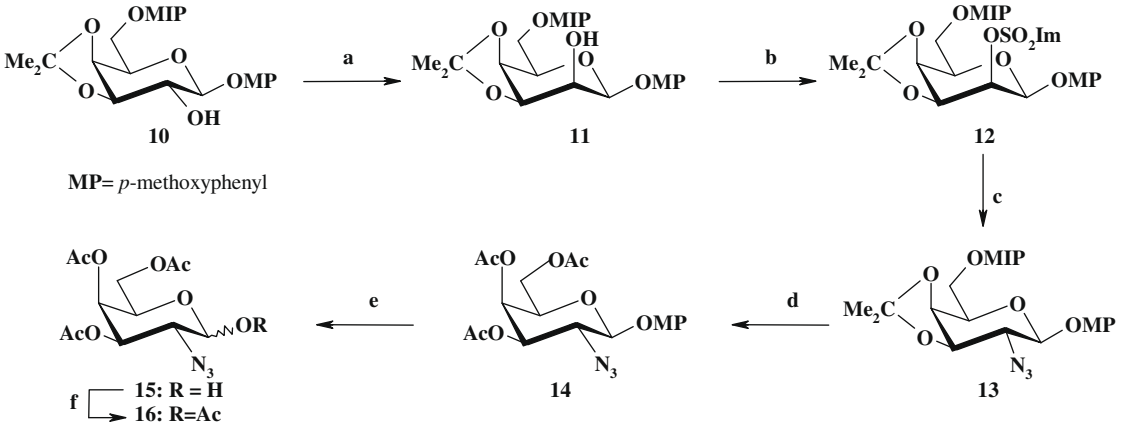
the tetraacetonide **5**,[17] prepared from its C-2′ lactose epimer (**4**) through a completely stereoselective, high yielding (92%) oxidation–reduction sequence.[17] The activation of **5** was made by treatment with imidazyl sulfate (Im_2SO_2) and NaH in DMF at −30 °C, resulting in the corresponding imidazylate **6**, isolated pure by flash chromatography in 86% yield. Compound **6** was then subjected to a S_N2 substitution reaction, with NaN_3 in DMF at 100 °C, which gave, after flash chromatography, the azido derivative **7** in 94% yield. This result confirms the usefulness of the imidazylate leaving group for performing efficient substitution in position 2 of a pyranoside, where other aryl and alkyl sulfonates are known to give unsatisfactory results.[18]

The reduction of the azido group of **7**, employing nickel chloride hexahydrate and sodium borohydride, afforded a single product which was directly submitted to N-acetylation (Ac_2O in MeOH). In the slightly acidic reaction conditions, the labile 6′-mixed acetal group was removed and compound **8** was obtained in 86% yield, after chromatographic purification. The target compound **1a** was instead prepared by complete deprotection of **8** using 80% aq AcOH at 80 °C: the reaction involves the O-deisopropylidenation and the C-1 aldehydo group exposition with concomitant six-membered ring closure. The structure of **1a** as well as its anomeric composition (α/β ratio about 2:3) was established on the basis of its NMR spectra. In particular, the ^1H NMR spectrum was identical to the reported one,[15] while the ^{13}C NMR signals, which have not yet been reported, were assigned by comparison (see Table 1) with those of α- and β-lactose,[19] for the *gluco* portion, and with those of methyl 2-acetamido-2-deoxy-β-D-galactopyranoside[20] (not shown). NMR analysis of the acetylated disaccharide **9**, obtained by treatment of **1a** with Ac_2O in pyridine for 18 h, further confirmed the parent compound structure. It is worthy of note that the transformation of lactose into the 2′-aminated analogue is obtained with a seven-step process involving common reagents and simple manipulations in a very good overall yield (40%), certainly not easily achieved through chemical means starting from the two deprotected monosaccharide components. On the basis of this positive result, the same protocol of C-2 amination with retention of configuration was applied (Scheme 2) to *p*-methoxyphenyl 3,4-*O*-isopropylidene-6-*O*-(1-methoxy-1-methylethyl)-β-D-galactopyranoside (**10**), easily obtainable from commercial penta-*O*-acetyl-β-D-galactopyranose through a simple sequence.[21] Also in this case, the introduction of the azido group

Table 1
^{13}C NMR chemical shifts of α- and β-**1a** and related compounds[a]

Compound	C-1′	C-2′	C-3′	C-4′	C-5′	C-6′	C-1	C-2	C-3	C-4	C-5	C-6
α-Lactose	103.6	72.0	73.5	69.5	76.2	62.0	92.7	72.2	72.4	79.3	71.0	61.0
β-Lactose	103.6	72.0	73.5	69.5	76.2	62.0	96.6	74.8	75.3	79.2	75.6	61.1
Me β-D-GalNAc*p*	103.1	53.0	71.9	68.6	75.8	61.7						
α-**1a**	104.5	55.4	73.5	70.5	78.2	63.8	94.6	74.3	73.8	82.1	72.6	62.9[b]
β-**1a**	104.5	55.4	73.5	70.5	78.2	63.8	98.5	76.5	77.4[b]	81.9	77.3[b]	63.0[b]

[a] Spectra taken in D_2O. Internal reference: 1,4-dioxane for lactose (Ref. 19) and Me β-D-GalNAc (Ref. 20), TMSP for **1a**.
[b] Assignments may be reversed.



Scheme 2. Formal synthesis of D-GalNAc and of 2-deoxy-2-azido-D-galactopyranosyl glycosyl donors. Reagents and conditions: (a) (1) TPAP, NMO, CH_2Cl_2, rt, 2 h; (2) $NaBH_4$, MeOH, 0 °C, 2 h (81% overall); (b) Im_2SO_2, NaH, DMF, −30 °C, 20 min (92%); (c) NaN_3, DMF, 100 °C, 2 h (96%); (d) (1) 80% aq AcOH, 80 °C, 2 h; (2) Ac_2O, Py, rt, 2 h (97% overall); (e) CAN, 3:1 Me_2CO–H_2O, 0 °C, rt, 30 min (81%); (f) Ac_2O, Py, rt, 15 h (95%).

in position 2 was achieved by a high yielding double stereoselective inversion sequence, providing first the preparation of the *talo* derivative **11** through an oxidation at C-2 (TPAP-NMO) followed by reduction of the crude uloside with $NaBH_4$ in MeOH. The stereoselectivity of the reduction was again complete leading to the exclusive formation of **11** (81% isolated yield) due to the β face shielding of the acetonide bridge, which completely inhibits the hydride attack on the same face. The axial hydroxyl function was then activated as sulfonyl imidazole (Im_2SO_2, and NaH in DMF at −30 °C) and **12** was obtained in 92% yield after chromatographic purification. The second inversion–amination was performed, as described for the disaccharide analogue, by treatment with NaN_3 in DMF at 100 °C, resulting in the desired azido derivative **13** in 96% yield. The two consecutive inversions of configuration were easily checked by ^{1}H NMR spectroscopy, on the basis of $J_{1,2}$ and $J_{2,3}$ values (2.1 and 4.5 Hz, respectively, for the *talo* derivative **11**, and 8.6 and 7.5 for the *galacto* one **13**).

Although some reported methods[22] allow the direct transformation of the anomeric *p*-methoxyphenyl into other more reactive leaving groups, our next target was the known azido derivative **15**[23] and its peracetylated derivative **16**.[24]

This goal was achieved by removing first the acetal functions with 80% aq AcOH and acetylation of the crude residue (Ac_2O–Py), resulting in **14** in almost quantitative yield (97%) after chromatographic purification. Removal of the anomeric *p*-methoxyphenyl group was performed with CAN, resulting in **15** (81% yield), which was quantitatively transformed into the peracetate **16** by routine acetylation.

Transformation of α-**16** into D-GalNAc hydrochloride has been described by Lemieux,[9] while **15** constitutes the key precursor of a series of 2-azido-2-deoxy-D-galactopyranosyl donors.[25]

In conclusion, we have performed an easy D-galactose to D-galactosamine transformation with complete stereoselectivity avoiding thus difficult diastereoisomeric separations. Using this new methodology, the first chemical synthesis of the β-D-GalNAc*p*-(1→4)-D-Glc*p* disaccharide has been achieved with excellent yield starting from lactose, while in the monosaccharide series, a new synthesis of D-GalNAc and of some 2-azido-2-deoxy-D-galactopyranosyl donors has been accomplished, complementing thus the existing approaches. This strategy of amination with overall retention of configuration (double inversion) gave good results in both the mono- and disaccharide series and seems to have general applicability and good potentiality in the construction of complex β-D-GalNAc containing oligosaccharides through a first β-galactosylation followed by its C-2 amination with retention of configuration.

3. Experimental

3.1. General methods

General methods are those reported in Ref. 1. ^{1}H and ^{13}C NMR spectra were recorded with an Avance II 250 spectrometer operating at 250.13 MHz (^{1}H) and 62.9 MHz (^{13}C) in the reported solvent (internal standard Me_4Si) and the assignments were made, when possible, with DEPT, HETCOR and COSY experiments. Compounds **5**[17] and **10**[21] were prepared according to the reported procedures.

3.2. 4-*O*-[2-*O*-(1-Imidazolylsulfonyl)-3,4-*O*-isopropylidene-6-*O*-(1-methoxy-1-methylethyl)-β-D-talopyranosyl]-2,3:5,6-di-*O*-isopropylidene-*aldehydo*-D-glucose dimethyl acetal (6)

To a suspension of NaH in mineral oil (60%, 632 mg, 15.8 mmol) pre-washed with hexane under argon atmosphere and cooled to 0 °C, a soln of **5**[17] (1.84 g, 3.17 mmol) in dry DMF (55 mL) was slowly added. The mixture was stirred at 0 °C for 30 min, cooled to −30 °C, treated with Im_2SO_2 (940 mg, 4.74 mmol) and further stirred until TLC analysis (EtOAc) revealed the complete disappearance of the starting material (4 h). The reaction mixture was then cooled to −40 °C, excess of NaH was destroyed by addition of MeOH (0.5 mL) followed by 10 min stirring, and partitioned between Et_2O (50 mL) and crushed iced-water. The organic phase was separated, and the aq layer extracted with Et_2O (4 × 50 mL). The collected organic phases were dried ($MgSO_4$), filtered and concentrated under diminished pressure. The flash chromatographic purification over silica gel of the reaction product (1:3 hexane–EtOAc + 0.1% Et_3N) gave pure **6** (1.93 g, 86%) as a syrup; $[\alpha]_D$ +2.7 (*c*, 1.06, $CHCl_3$); R_f 0.33 (1:3 hexane–EtOAc); ^{1}H NMR (CD_3CN): δ 7.98 (dd, 1H, $J_{2,4}$ 1.3 Hz, $J_{2,5}$ 0.9 Hz, Im-H-2), 7.44 (dd, 1H, $J_{4,5}$ 1.7 Hz, Im-H-4), 7.05 (dd, 1H, Im-H-5), 4.92 (dd, 1H, $J_{1',2'}$ 1.0 Hz, $J_{2',3'}$ 5.7 Hz, H-2′), 4.82 (d, 1H, H-1′), 4.40 (dd, 1H, $J_{3',4'}$ 5.8 Hz, H-3′), 4.36 (d, 1H, $J_{1,2}$ 6.0 Hz, H-1), 4.27 (dd, 1H, $J_{2,3}$ 7.7 Hz, H-2), 4.15 (dt, 1H, $J_{4,5}$ 5.9 Hz, $J_{5,6a} = J_{5,6b}$ 6.1 Hz, H-5), 4.12 (dd, 1H, $J_{4',5'}$ 2.7 Hz, H-4′), 4.04 (dd, 1H, $J_{3,4}$ 1.9 Hz, H-3), 3.94 (dd, 1H, $J_{6a,6b}$ 8.6 Hz, H-6b), 3.85 (dd, 1H, H-6a), 3.84 (ddd, 1H, $J_{5',6'a}$ 6.5 Hz, $J_{5',6'b}$ 6.3 Hz, H-5′), 3.83 (dd, 1H, H-4), 3.63 (dd, 1H, $J_{6'a,6'b}$ 9.6 Hz, H-6′b), 3.55 (dd, 1H, H-6′a), 3.41, 3.40 (2s, each 3H, 2 × OMe-1), 3.14 [s, 3H, C(O*Me*)Me_2], 1.37, 1.36, 1.32, 1.30, 1.29, 1.28 (6s, each 3H, 3 × C*Me*$_2$), 1.22, 1.20 [2s, each 3H, C(OMe)*Me*$_2$]; ^{13}C NMR

(CD_3CN): δ 138.1 (Im-C-2), 130.9 (Im-C-5), 120.1 (Im-C-4), 110.7, 110.3, 109.2 (3 × *C*Me_2), 106.5 (C-1), 100.9 [*C*(OMe)Me_2], 99.1 (C-1′), 79.9 (C-2′), 78.5 (C-4), 77.9 (C-3), 77.1 (C-5), 76.3 (C-2), 73.5 (C-5′), 71.9 (C-3′), 71.1 (C-4′), 66.5 (C-6), 60.3 (C-6′), 56.6, 54.7 (2 × OMe-1), 48.9 [C(O*Me*)Me_2], 27.3, 27.1, 27.0, 25.8, 25.4, 25.3 (3 × *C*Me_2), 24.7, 24.6 [C(OMe)*Me*$_2$]. Anal. Calcd for $C_{30}H_{50}N_2O_{15}S$: C, 50.69; H, 7.09; N, 3.94. Found: C, 50.89; H, 7.43; N, 5.29.

3.3. 4-*O*-[2-Azido-2-deoxy-3,4-*O*-isopropylidene-6-*O*-(1-methoxy-1-methylethyl)-β-D-galactopyranosyl]-2,3:5,6-di-*O*-isopropylidene-*aldehydo*-D-glucose dimethyl acetal (7)

A soln of **6** (3.85 g, 5.41 mmol) and NaN_3 (707 mg, 10.9 mmol) in dry DMF (100 mL) was stirred under argon atmosphere at 100 °C. After 1 h and 20 min, TLC analysis (EtOAc) revealed the complete disappearance of the starting material, the mixture was cooled to rt and partitioned between satd aq $NaHCO_3$ (50 mL) and Et_2O (50 mL). The organic phase was separated and the aq layer extracted with Et_2O (3 × 50 mL). The organic extracts were dried ($MgSO_4$), filtered and concentrated under diminished pressure. Purification of the residue by flash chromatography over silica gel (7:3 hexane–EtOAc + 0.1% of Et_3N) gave pure **7** (3.08 g, 94%) as a clear syrup; $[\alpha]_D$ −30.0 (*c*, 1.0, $CHCl_3$); R_f 0.64 (EtOAc); ^{1}H NMR (CD_3CN): δ 4.63 (d, 1H, $J_{1',2'}$ 8.5 Hz, H-1′), 4.34 (d, 1H, $J_{1,2}$ 6.0 Hz, H-1), 4.32 (t, 1H, $J_{2,3}$ 6.0 Hz, H-2), 4.25 (dt, 1H, $J_{4,5}$ 4.7 Hz, $J_{5,6a} = J_{5,6b}$ 6.4 Hz, H-5), 4.15 (dd, 1H, $J_{3',4'}$ 5.4 Hz, $J_{4',5'}$ 2.1 Hz, H-4′), 4.09 (dd, 1H, $J_{6a,6b}$ 8.5 Hz, H-6b), 4.06 (dd, 1H, $J_{3,4}$ 1.3 Hz, H-3), 4.01 (dd, 1H, H-6a), 3.94 (dd, 1H, H-4), 3.90 (dd, 1H, $J_{2',3'}$ 8.3 Hz, H-3′), 3.84 (ddd, 1H, $J_{5',6'a}$ 6.2 Hz, $J_{5',6'b}$ 6.7 Hz, H-5′), 3.61 (dd, 1H, $J_{6'a,6'b}$ 9.4 Hz, H-6′b), 3.53 (dd, 1H, H-6′a), 3.39, 3.38 (2s, each 3H, 2 × OMe), 3.30 (dd, 1H, H-2′), 3.15 [s, 3H, C(O*Me*)Me$_2$], 1.49, 1.40, 1.33, 1.32, 1.30, 1.29 (6s, each 3H, 3 × *CMe*$_2$), 1.29, 1.30 [2s, each 3H, C(OMe)*Me*$_2$]; ^{13}C NMR (CD_3CN): δ 110.9, 110.7, 108.9 (3 × *C*Me_2), 106.4 (C-1), 102.2 (C-1′), 100.9 [*C*(OMe)Me_2], 78.5 (C-3), 77.9 (C-5), 77.8 (C-3′), 76.7 (C-2), 76.2 (C-4), 73.8 (C-4′), 73.0 (C-5′), 67.3 (C-2′), 66.0 (C-6), 60.4 (C-6′), 56.3, 54.4 (2 × OMe), 48.9 [C(O*Me*)Me$_2$]; 28.4, 27.6, 27.1, 26.7, 26.3, 25.2 (3 × *CMe*$_2$), 24.7, 24.5 C(OMe)*Me*$_2$]. Anal. Calcd for $C_{27}H_{47}N_3O_{12}$: C, 53.54; H, 7.82; N, 6.94. Found: C, 53.47; H, 7.62; N, 7.12.

3.4. 4-*O*-(2-Acetamido-2-deoxy-3,4-*O*-isopropylidene-β-D-galactopyranosyl)-2,3:5,6-di-*O*-isopropylidene-*aldehydo*-D-glucose dimethylacetal (8)

To a soln of **7** (1.40 g, 2.31 mmol) in MeOH (24 mL) cooled to 0 °C, $NiCl_2{\cdot}6H_2O$ (2.75 g, 11.5 mmol) and $NaBH_4$ (699 mg, 18.4 mmol) were added. The soln was warmed to rt and stirred for 2 h. To the mixture were then added brine (50 mL) and, after 10 min, water (50 mL) and $CHCl_3$ (50 mL). The organic phase was separated and the aq layer extracted with $CHCl_3$ (4 × 50 mL). The collected organic extracts were dried ($MgSO_4$), filtered and concentrated at diminished pressure. The residue was dissolved in MeOH (30 mL), Ac_2O (7.5 mL) was added and the mixture was stirred at rt for 2 h when TLC analysis (EtOAc) showed the formation of a new product. The reaction mixture was repeatedly co-evaporated with toluene (4 × 30 mL) under diminished pressure and purified by flash chromatography over silica gel (49:1 $CHCl_3$–MeOH) affording pure **8** (1.09 g, 86%) as a clear syrup; $[\alpha]_D$ +8.15 (*c*, 1.46, MeOH); R_f 0.10 (EtOAc); ^{1}H NMR (CD_3CN): δ 6.47 (d, 1H, $J_{2',NH}$ 8.9 Hz, NH), 4.58 (d, 1H, $J_{1',2'}$ 8.6 Hz, H-1′), 4.50 (dd, 1H, $J_{1,2}$ 6.9 Hz, $J_{2,3}$ 7.0 Hz, H-2), 4.34 (d, 1H, H-1), 4.36–4.05 (m, 4H, H-5, H-3′, H-6′a, H-6′b), 3.97–3.70 (m, 4H, H-5′, H-3, H-6a, H-6b), 3.51 (m, 2H, H-2, H-4), 3.43, 3.42 (2s, each 3H, 2 × OMe), 1.90 (s, 3H, *Me*CON), 1.45, 1.40, 1.32, 1.31, 1.28, 1.26 (6s, each 3H, 3 × *CMe*$_2$); ^{13}C NMR (CD_3CN): δ 170.6 (Me*CO*), 110.2, 110.0, 108.5 (3 × *C*Me_2), 107.6 (C-1), 101.6 (C-1′), 78.6 (C-3), 77.4, 77.3 (C-3′, C-5), 75.7, 75.6 (C-4, C-2), 74.6 (C-4′), 73.5 (C-5′), 65.6 (C-6), 62.5 (C-6′), 57.5, 54.6 (2 × OMe), 55.2 (C-2′), 28.2, 27.4, 26.8, 26.4, 26.3, 24.8 (3 × *CMe*$_2$), 23.3 (*Me*CON). Anal. Calcd for $C_{25}H_{43}NO_{12}$: C, 54.63; H, 7.89; N, 2.55. Found: C, 54.72; H, 7.91; N, 2.58.

3.5. 4-*O*-(2-Acetamido-2-deoxy-β-D-galactopyranosyl)-α,β-D-glucopyranose (1a)

A soln of **8** (450 mg, 0.82 mmol) in 80% aq AcOH (15 mL) was stirred at 80 °C for 4 h and then concentrated under diminished pressure by co-evaporation with toluene (4 × 35 mL). The residue was triturated with EtOAc to give an amorphous white solid (283 mg, 90%) composed (^{13}C NMR, D_2O) by a 2:3 α/β anomeric mixture of **1a**, as established on the basis of the integration of the H-1 signals; $[\alpha]_{D\infty}$ +55.8 (*c*, 0.92, water); selected ^{1}H NMR (D_2O) data of α-**1a**: δ 5.21 (d, 1H, $J_{1,2}$ 3.8 Hz, H-1), 4.52 (d, 1H, $J_{1',2'}$ 8.4 Hz, H-1′); β-**1a**: δ 4.65 (d, 1H, $J_{1,2}$ 8.4 Hz, H-1), 4.51 (d, 1H, $J_{1',2'}$ 8.3 Hz, H-1′), 3.27 (dd, 1H, $J_{2,3}$ 8.8 Hz, H-2); ^{13}C NMR (D_2O) data of α-**1a** and β-**1a** see Table 1 and δ: 177.6 (Me*CO*), 25.0 (*Me*CO). Anal. Calcd for $C_{14}H_{25}NO_{11}$: C, 43.86; H, 6.57; N, 3.65. Found: C, 43.95; H, 6.59; N, 3.66.

3.6. 4-*O*-(2-Acetamido-2-deoxy–3,4,6-tri-*O*-acetyl-β-D-galactopyranosyl]-α,β-1,2,3,6-tetra-*O*-acetyl-D-glucopyranose (9)

Compound **1a** (50 mg, 0.13 mmol) was dissolved in 2:1 pyridine–Ac_2O (3 mL) and the resulting soln was stirred at rt for 18 h and then co-evaporated with toluene (3 × 5 mL) under diminished pressure. Flash chromatographic purification, eluting with EtOAc, afforded pure **9** (84 mg, 95%) as an 1:1 α/β anomeric mixture, as established on the basis of the integration of the H-1 signals; syrup, $[\alpha]_D$ +16.0 (*c*, 1.04, $CHCl_3$); R_f 0.23 (EtOAc); ^{1}H NMR (CD_3CN) of α-**9**: δ 6.38 (d, 1H, $J_{2',NH}$ 9.3 Hz, NH), 6.12 (d, 1H, $J_{1,2}$ 3.8 Hz, H-1), 5.32 (dd, 1H, $J_{2,3}$ 10.4 Hz, $J_{3,4}$ 8.7 Hz, H-3), 5.02 (dd, 1H, $J_{2',3'}$ 11.3 Hz, $J_{3',4'}$ 3.5 Hz, H-3′), 4.90 (dd, 1H, H-2), 4.58 (d, 1H, $J_{1',2'}$ 8.4 Hz, H-1′), 1.82 (s, 3H, *Me*CON); β-**9**: δ 6.36 (d, 1H, $J_{2',NH}$ 9.3 Hz, NH), 5.74 (d, 1H, $J_{1,2}$ 8.3 Hz, H-1), 5.24 (m, 1H, H-3), 5.03 (dd, 1H, $J_{2',3'}$ 11.2 Hz, $J_{3',4'}$ 3.5 Hz, H-3′), 4.92 (dd, 1H, $J_{2,3}$ 9.7 Hz, H-2), 4.59 (d, 1H, $J_{1',2'}$ 8.4 Hz, H-1′), 1.83 (s, 3H, *Me*CON); cluster of signals for both anomers: δ 4.40–3.95 (m, 14H, H-4, H-5, H-6a, H-6b, H-5′, H-6′a, H-6′b), 3.86 (m 2H, H-2′) 2.13, 2.08, 2.07, 2.06, 2.05, 2.04, 2.03, 2.02, 2.01, 2.00, 1.98, 1.97, 1.96, 1.90 (14s, each 3H, 14 × *Me*COO); ^{13}C NMR (CD_3CN) α-**9**: δ 102.1 (C-1′), 89.6 (C-1), 76.1 (C-4), 71.3 (C-5, C-5′), 71.2 (C-3′), 70.6 (C-3), 70.2 (C-2), 67.5 (C-4′), 62.4 (C-6), 62.1 (C-6′), 51.4 (C-2′); β-**9**: δ 102.1 (C-1′), 92.2 (C-1), 75.8, 74.3, 73.3 (C-3, C-4, C-5), 71.3 (C-5′), 71.2 (C-3′), 70.3 (C-2), 68.5 (C-4′), 62.8 (C-6), 62.1 (C-6′), 51.4 (C-2′); cluster of signals for both anomers: δ 171.4–169.9 (Me*CO*), 23.2 (*Me*CON), 21.2–20.8 (*Me*COO). Anal. Calcd for $C_{28}H_{39}NO_{18}$: C, 49.63; H, 5.80; N, 2.07. Found: C, 49.65; H, 5.83; N, 2.08.

3.7. 4-Methoxyphenyl 3,4-*O*-isopropylidene-6-*O*-(1-methoxy-1-methylethyl)-β-D-talopyranoside (11)

A mixture of **10**[21] (320 mg, 0.803 mmol), pre-dried 4-methylmorpholine N-oxide (NMO, 165 mg, 1.41 mmol) and 4 Å powdered molecular sieves (500 mg) in anhyd CH_2Cl_2 (15 mL) was stirred for 30 min at rt under argon atmosphere. Tetrapropylammonium perruthenate (TPAP, 14.1 mg, 0.04 mmol) was then added and the resulting mixture was stirred for 2 h at rt until TLC (9:1 CH_2Cl_2–Me_2CO) revealed complete oxidation of **10**. The mixture was filtered through a Celite-silica gel-Celite triple alternate pad, the filter was washed with CH_2Cl_2 and then with EtOAc, and the organic phase was concentrated under diminished pressure. The residue was dissolved in MeOH (15 mL), $NaBH_4$ (121.4 mg, 3.21 mmol) was added and the mixture was stirred at 0 °C. After 2 h, TLC analysis

(9:1 CH_2Cl_2–Me_2CO) showed the complete disappearance of the 2-uloside. Water (8 mL) was added and the resulting soln was stirred for additional 30 min and then extracted with CH_2Cl_2 (3 × 30 mL). The organic extracts were collected, dried ($MgSO_4$), filtered and concentrated under diminished pressure. Purification of the residue by flash chromatography over silica gel (9:1 CH_2Cl_2–Me_2CO + 0.1% Et_3N) afforded pure **11** (259.2 mg, 81%) as a clear syrup; $[\alpha]_D$ −49.5 (*c*, 0.99, $CHCl_3$); R_f 0.43 (9:1 CH_2Cl_2–Me_2CO); ^{1}H NMR (CD_3CN): δ 7.02, 6.95 (AA'XX' system, 4H, Ar–H), 5.08 (d, 1H, $J_{1,2}$ 2.1 Hz, H-1), 4.37 (dd, 1H, $J_{3,4}$ 7.0 Hz, $J_{2,3}$ 4.5 Hz, H-3), 4.30 (dd, 1H, $J_{4,5}$ 2.1 Hz, H-4), 3.84 (ddd, 1H, $J_{5,6a}$ 6.9 Hz, $J_{5,6b}$ 5.2 Hz, H-5), 3.82 (dd, 1H, H-2), 3.73 (s, 3H, OMe), 3.59 (dd, 1H, $J_{6a,6b}$ 10.0 Hz, H-6a), 3.55 (dd, 1H, H-6b), 3.12 [s, 3H, C(O*Me*)Me_2], 1.52, 1.32 (2s, each 3H, C*Me*$_2$), 1.28 (s, 6H, C(OMe)*Me*$_2$); ^{13}C NMR (CD_3CN): δ 155.9, 152.4 (Ar–C), 118.9, 115.3 (Ar–CH), 110.5 (*C*Me_2), 100.8 [*C*(OMe)Me_2], 99.5 (C-1), 73.9 (C-3), 72.8 (C-4), 72.1 (C-5), 67.0 (C-2), 61.4 (C-6), 56.1 (OMe), 48.8 [C(O*Me*)Me_2], 25.8, 25.4 (C*Me*$_2$), 24.7, 24.6 [C(OMe)*Me*$_2$]. Anal. Calcd for $C_{20}H_{30}O_8$: C, 60.29; H, 7.59. Found: C, 60.47; H, 7.61.

3.8. 4-Methoxyphenyl 2-*O*-(1-imidazolylsulfonyl)-3,4-*O*-isopropylidene-6-*O*-(1-methoxy-1-methylethyl)-β-D-talopyranoside (12)

To a suspension of NaH in mineral oil (60%, 94 mg, 2.34 mmol) pre-washed with hexane under argon atmosphere and cooled to 0 °C, a soln of **11** (186.8 mg, 0.469 mmol) in dry DMF (8 mL) was added. The mixture was stirred at 0 °C for 30 min, cooled to −30 °C, treated with Im_2SO_2 (139 mg, 0.703 mmol) and further stirred at −30 °C. After 20 min, TLC analysis (3:7 hexane–EtOAc) revealed the complete disappearance of the starting material. The reaction mixture was then cooled to −40 °C, excess of NaH was destroyed by addition of MeOH (0.5 mL) followed by 10 min stirring, then partitioned between Et_2O (16 mL) and crushed iced-water. The organic phase was separated, and the aq layer extracted with Et_2O (2 × 16 mL). The collected organic phases were dried ($MgSO_4$), filtered and concentrated under diminished pressure. Flash chromatographic purification over silica gel of the reaction product (2:3 hexane–EtOAc + 0,1% of Et_3N) gave pure **12** (226.6 mg, 92%) as a clear syrup; $[\alpha]_D$ +4.2 (*c*, 1.18, $CHCl_3$); R_f 0.22 (2:3 hexane–EtOAc); ^{1}H NMR (CD_3CN): δ 8.07 (dd, 1H, $J_{2,4}$ 1.3 Hz, $J_{2,5}$ 0.8 Hz, Im-H-2), 7.50 (dd, 1H, $J_{4,5}$ 1.7 Hz, Im-H-4), 7.10 (dd, 1H, Im-H-5), 6.83, 6.72 (AA'XX' system, 4H, Ar–H), 5.03 (dd, 1H, $J_{1,2}$ 1.0 Hz, $J_{2,3}$ 5.5 Hz, H-2), 4.93 (d, 1H, H-1), 4.51 (dd, 1H, $J_{3,4}$ 5.8 Hz, H-3), 4.23 (dd, 1H, $J_{4,5}$ 2.7 Hz, H-4), 4.01 (ddd, 1H, $J_{5,6a}$ 7.4 Hz, $J_{5,6b}$ 4.7 Hz, H-5), 3.71 (s, 3H, OMe), 3.65 (dd, 1H, $J_{6a,6b}$ 10.3 Hz, H-6a), 3.57 (dd, 1H, H-6b), 3.09 [s, 3H, C(O*Me*)Me_2], 1.49, 1.33 (2s, each 3H, C*Me*$_2$), 1.29, 1.28 [2s, each 3H, C(OMe)*Me*$_2$]; ^{13}C NMR (CD_3CN): δ 156.3, 151.3 (Ar–C), 138.3 (Im-C-2), 131.1 (Im-C-5), 120.0 (Im-C-4), 118.6, 115.2 (Ar–CH), 111.4 (*C*Me_2), 100.8 [*C*(OMe)Me_2], 97.3 (C-1), 79.3 (C-2), 73.8 (C-5), 71.9 (C-3), 71.4 (C-4), 60.7 (C-6), 56.1 (OMe), 48.8 [C(O*Me*)Me_2], 25.9, 25.4 (C*Me*$_2$), 24.7, 24.6 [C(OMe)*Me*$_2$]. Anal. Calcd for $C_{23}H_{32}N_2O_{10}S$: C, 52.26; H, 6.10; N, 5.30; S, 6.07. Found: C, 52.46; H, 6.18; N, 5.33; S, 6.11.

3.9. 4-Methoxyphenyl 2-azido-2-deoxy-3,4-*O*-isopropylidene-6-*O*-(1-methoxy-1-methylethyl)-β-D-galactopyranoside (13)

A soln of **12** (91.2 mg, 0.173 mmol) and NaN_3 (22.5 mg, 0.345 mmol) in dry DMF (4 mL) was stirred at 100 °C under argon atmosphere. After 2 h, the mixture was cooled to rt and partitioned between satd aq $NaHCO_3$ (8 mL) and Et_2O (15 mL). The organic phase was separated and the aq layer extracted with Et_2O (3 × 15 mL). The organic extracts were collected, dried ($MgSO_4$), filtered and concentrated under diminished pressure. Purification of the residue by flash chromatography over silica gel (7:3 hexane–EtOAc + 0.1% of Et_3N) gave pure **13** (71 mg, 96%) as a clear syrup; $[\alpha]_D$ +35.5 (*c*, 0.67, $CHCl_3$); R_f 0.32 (7:3 hexane–EtOAc); ^{1}H NMR (CD_3CN): δ 7.03, 6.92 (AA'XX' system, 4H, Ar–H), 4.80 (d, 1H, $J_{1,2}$ 8.6 Hz, H-1), 4.19 (dd, 1H, $J_{3,4}$ 5.3 Hz, $J_{4,5}$ 2.0 Hz, H-4), 4.02 (ddd, 1H, $J_{5,6a}$ 7.0 Hz, $J_{5,6b}$ 5.2 Hz, H-5), 3.98 (dd, 1H, $J_{2,3}$ 7.5 Hz, H-3), 3.75 (s, 3H, OMe), 3.64 (dd, 1H, $J_{6a,6b}$ 10.0 Hz, H-6a), 3.63 (dd, 1H, H-2), 3.59 (dd, 1H, H-6b), 3.12 [s, 3H, C(O*Me*)Me_2], 1.52, 1.32 (2s, each 3H, C*Me*$_2$), 1.31, 1.30 [2s, each 3H, C(OMe)*Me*$_2$]; ^{13}C NMR (CD_3CN): δ 156.5, 151.8 (Ar–C), 119.1, 115.5 (Ar–CH), 111.1 (*C*Me_2), 101.4 (C-1), 100.8 [*C*(OMe)Me_2], 77.9 (C-3), 73.9 (C-4), 73.3 (C-5), 66.0 (C-2), 60.9 (C-6), 56.1 (OMe), 48.8 [C(O*Me*)Me_2], 28.4, 26.4 (C*Me*$_2$), 24.7, 24.6 [C(OMe)*Me*$_2$]. Anal. Calcd for $C_{20}H_{31}N_3O_7$: C, 56.46; H, 7.34; N, 9.88. Found: C, 56.48; H, 7.38; N, 9.91.

3.10. 4-Methoxyphenyl 2-azido-2-deoxy-3,4,6-tri-*O*-acetyl-β-D-galactopyranoside (14)

A soln of **13** (68 mg, 0.16 mmol) in 80% aq AcOH (3 mL) was stirred at 80 °C for 2 h, then concentrated under diminished pressure and co-evaporated with toluene (3 × 8 mL). The residue was dissolved in 2:1 pyridine–Ac_2O (3 mL) and the resulting soln was stirred at rt for 2 h and then co-evaporated with toluene (3 × 8 mL) under diminished pressure. Flash chromatographic purification over silica gel (7:3 hexane–EtOAc) afforded pure **14** (67.8 mg, 97%) as a clear syrup; $[\alpha]_D$ +6.02 (*c*, 0.83, $CHCl_3$); R_f 0.56 (2:3 hexane–EtOAc); ^{1}H NMR (CD_3CN): δ 7.03, 6.90 (AA'XX' system, 4H, Ar–H), 5.33 (dd, 1H, $J_{3,4}$ 3.4 Hz, $J_{4,5}$ 1.0 Hz, H-4), 5.00 (d, 1H, $J_{1,2}$ 8.1 Hz, H-1), 4.92 (dd, 1H, $J_{2,3}$ 10.8 Hz, H-3), 4.24–4.04 (m, 3H, H-6a, H-6b, H-5), 3.98 (dd, 1H, H-2), 3.75 (s, 3H, OMe), 2.21, 2.00, 1.99 (3s, each 3H, 3 × *Me*CO); ^{13}C NMR (CD_3CN): δ 171.2, 171.1, 170.7 (3 × Me*CO*), 156.6, 151.6 (Ar–C), 119.0, 115.6 (Ar–CH), 101.6 (C-1), 71.9 (C-5), 71.8 (C-3), 67.5 (C-4), 62.4 (C-6), 61.6 (C-2), 56.1 (OMe), 20.8 (*Me*CO). Anal. Calcd for $C_{19}H_{23}N_3O_9$: C, 52.17; H, 5.30; N, 9.61. Found: C, 52.20; H, 5.33; N, 9.63.

3.11. 2-Azido-2-deoxy-3,4,6-tri-*O*-acetyl-α,β-D-galactopyranose (15)

To a soln of **14** (67 mg, 0.153 mmol) in 3:1 Me_2CO–water (6 mL), CAN (587 mg, 1.07 mmol) was added at 0 °C, the soln was warmed to rt and stirred for 30 min. It was then concentrated to 3 mL, diluted with CH_2Cl_2 (25 mL), washed with sat aq $NaHCO_3$ (2 × 15 mL), dried ($MgSO_4$), filtered and concentrated under diminished pressure. Purification of the residue by flash chromatography over silica gel (7:3 hexane–EtOAc) afforded known **15**[23] (41 mg, 81%) as a clear syrup composed (NMR, $CDCl_3$) by a mixture of α- and β-anomers in a 3:2 ratio calculated on the basis of the relative intensities of C-1 signals (δ 92.3 and 96.3, respectively); $[\alpha]_{Dinitial}$ +61.7, $[\alpha]_{D\infty}$ +55.5 (*c*, 0.91, MeOH); R_f 0.20 (7:3 hexane–EtOAc); ^{1}H NMR ($CDCl_3$) of α-**15**: δ 5.43 (d, 1H, $J_{1,2}$ 3.3 Hz, H-1), 5.37 (dd, 1H, $J_{2,3}$ 10.0 Hz, $J_{3,4}$ 3.2 Hz, H-3), 4.47 (m, 1H, H-5), 3.74 (dd, 1H, H-2), 3.91 (bs, 1H, OH-1); β-**15**: δ 4.83 (dd, 1H, $J_{2,3}$ 10.9 Hz, $J_{3,4}$ 3.3 Hz, H-3), 4.72 (dd, 1H, $J_{1,2}$ 7.8 Hz, $J_{1,OH}$ 5.3 Hz, H-1), 3.91 (m, 1H, H-5), 3.67 (dd, 1H, H-2), 4.58 (d, 1H, OH-1); cluster of signals for both anomers: δ 5.45 (m, 1H, H-4), 4.08–4.22 (m, 2H, H-6a, H-6b); 2.20–1.97 (m, 9H, 3 × *Me*CO); ^{13}C NMR ($CDCl_3$) α-**15**: δ 92.3 (C-1), 67.6 (C-4), 66.4, 66.3 (C-3, C-5), 57.9 (C-2); β-**15**: δ 96.3 (C-1), 71.1 (C-3), 70.8 (C-5), 68.3 (C-4), 61.9 (C-2); cluster of signals for both anomers: δ 170.7–170.0 (Me*CO*), 61.7, 61.3 (C-6), 20.7–20.5 (*Me*CO). Anal. Calcd for $C_{12}H_{19}N_3O_8$: C, 43.24; H, 5.75; N, 12.61. Found: C, 43.26; H, 5.76; N, 12.62.

3.12. 2-Azido-2-deoxy-1,3,4,6-tetra-*O*-acetyl-α,β-D-galactopyranose (16)

A soln of **15** (32 mg, 0.10 mmol) in 2:1 pyridine-Ac_2O (2 mL) was stirred at rt for 15 h and then co-evaporated with toluene

(3 × 8 mL) under diminished pressure. Flash chromatographic purification over silica gel (1:1 hexane–EtOAc) afforded pure **16** (34 mg, 95%) as a clear syrup, composed (NMR, $CDCl_3$) by a mixture of α- and β-anomers in 1:1 ratio calculated on the basis of the relative integral of H-1 signals (δ 6.28 and 5.50, respectively); R_f 0.65 (1:1 hexane–EtOAc); $[\alpha]_D$ +49.7 (*c*, 0.92, $CHCl_3$); lit.[24] $[\alpha]_D$ +36.7 (*c*, 1.6, $CHCl_3$) for a 2:3 mixture of α- and β-anomers; NMR data were in full accordance with those reported.[24]

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