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

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Abstract – A new stereoselective preparation of *N*-aceyl-D-galactosamine (**1b**) starting from the know *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 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.

Keywords: N-Acetyl-D-galactosamine, Amination with inversion, Epimerization, Lactose, β-D-Galactopyranosides

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 *N*-acetamido derivative (2-deoxy-2-acetamido-D-galactopyranose, D-GalNAc, **1b**). D-GalNAc is also a constituent of several complex glycoproteins, being, for examples, the monosaccharide "core" of mucines,[4] a component of oligosaccharide determinants of human blood group antigens,[5] a constituent of 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 (a) on the C-4 epimerization of the largely and cheaply available D-GlcNAc,[7] mimicking thus the biosynthetic pathway, and (b) on 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. Few years later, Lemieux and Ratcliffe[9] used

[≠]Part 25 of the series "Chemical Valorisation of Milk-derived Carbohydrates". For part 24, see Ref. 1.

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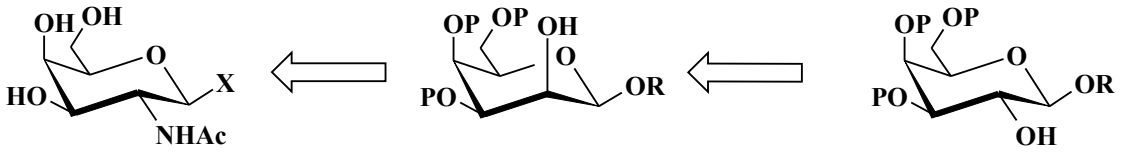
the azidonitration of tri-*O*-acetyl-D-galactal for the synthesis of some 2-azido-2-deoxy-D-galactopyranose derivatives and free D-GalNAc (**1b**). After this key paper, several addition reactions to D-galactal derivatives have been proposed to obtain D-GalNAc and its glycosides, as, the Danishefsky's sulfamidoglycosylation,[10] the Gin's acetamidoglycosylation.[11] Furthermore, specific synthesis 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 do not appears 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-steps amination with overall retention of configuration at C-2' (Chart 1), through the formation of 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 know precursor of free D-GalNAc (**1b**) and of some 2-azido-2-deoxy-D-galactopyranoside glycosyl donors.



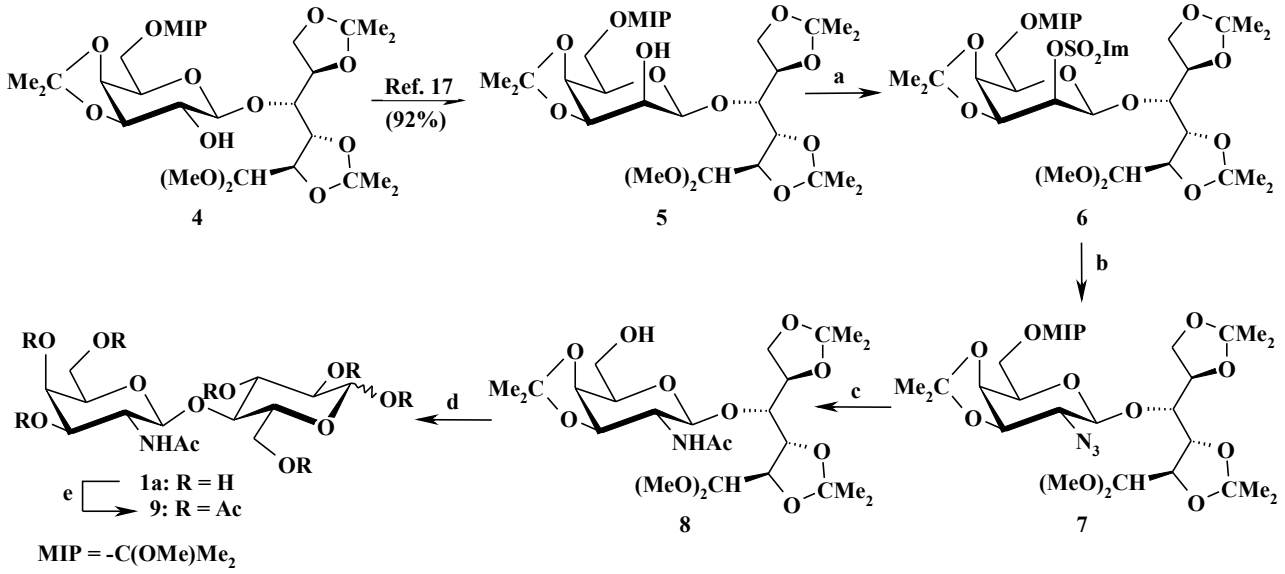
1a: X = 4-*O*-D-glucopyranosyl **2** **3**
1b: X = OH

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

2. Results and Discussion

A straightforward route to β-D-GalNAc*p*-(1→4)-D-Glc*p* (**1a**) was envisaged (Scheme 1) taking advantage from the easily availability of 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, leading to the corresponding imidazylate **6**, isolated pure by flash chromatography in 86% yield. **6** was then subjected to a S_N2 substitution with NaN_3 in DMF at 100 °C, obtaining, 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]

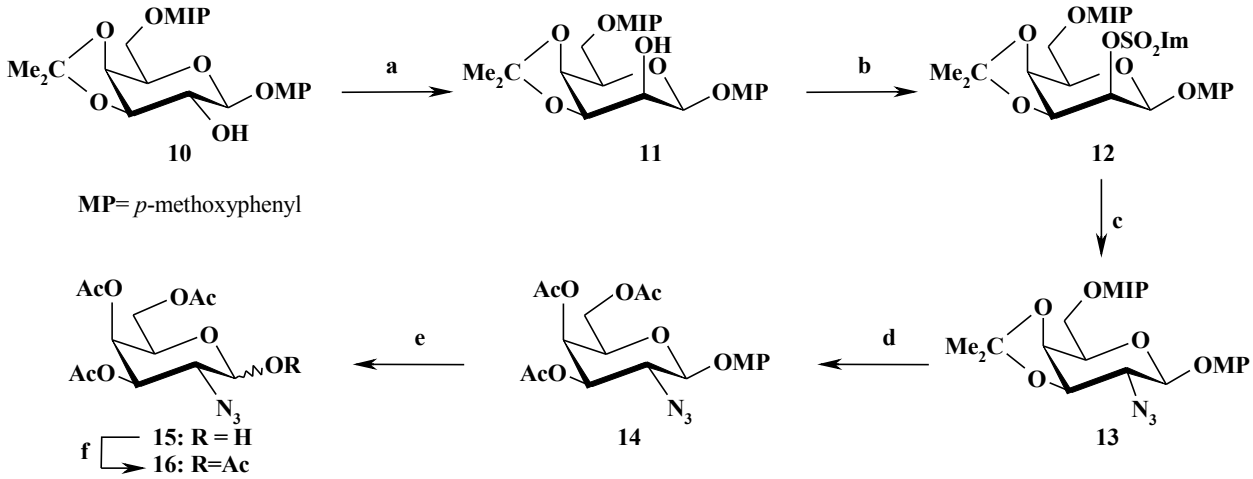


Scheme 1: Synthesis of β -D-GalNAc*p*-(1-->4)-D-Glc*p* disaccharide from lactose. Reagents and conditions: (a) Im_2SO_2, NaH, DMF, -30 °C, 4 h (86%); (b) NaN_3, DMF, 100 °C, 1.2 h (94%); (c) (1) $NiCl_2{\cdot}6H_2O$, $NaBH_4$, MeOH, 0 °C, room temp, 2 h; (2) Ac_2O, MeOH, room temp, 2 h (86%); (d) 80%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

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 acid 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 contemporary concomitant six membered ring closure. The structure of **1a** as well as its anomeric composition (α/β ratio about 2:3) were established on the basis of its NMR spectra. In particular, the ^{1}H NMR spectrum was identical to the reported one,[15] while the ^{13}C NMR signals, not yet reported, were assigned by comparison (see Table 1) with those of α- and β-lactose,[19] for the *gluco* portion, and those of methyl 2-acetamido-2-deoxy-β-D-galactopyranoside[20] (Me β-D-GalNAc, not showed). NMR analysis of the acetylated disaccharide **9**, obtained treating **1a** with Ac_2O in pyridine for 18 h, further confirmed the parent compound structure. It is worth of note that the transformation of lactose into the 2'-aminated analogue is obtained with a 7 steps 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 in position 2 was achieved by an 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, obtaining the desired azido derivative **13** in 96% yield. The two consecutive inversion of configuration were easily checked by ^{1}H NMR, 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] enable the direct transformation of the anomeric *p*-methoxy-phenyl into other more reactive leaving groups, our next target was the known azido derivative **15**[23] and its peracetylated derivative **16**.[24]



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, room temp, 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, room temp, 2 h (97% overall); (e) CAN, 3:1 Me_2CO-H_2O, 0 °C, room temp, 30 min (81%); (f) Ac_2O, Py, room temp, 15 h (95%).

This goal was achieved by a first removal of the acetal functions by acid hydrolysis with 80% aq AcOH and acetylation of the crude residue (Ac_2O-Py), obtaining compound **14** in almost quantitative yield (97%) after chromatographic purification. The removal of the anomeric *p*-methoxy phenyl was performed with CAN, leading to isolate (81% yield) the reducing derivative **15**, that was, finally, quantitatively transformed into the peracetate **16** by routine acetylation.

The 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-galactopyranose glycosyl donors.[25]

In conclusion, we have proposed an easy D-galactose into 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 both in 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 NMR 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 described 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-*aldeydo*-D-glucose dimethyl acetal (6).

To a suspension of 60% NaH in mineral oil (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 at diminished pressure. The flash chromatographic purification over silica gel of the

reaction product, eluting with 1:3 hexane-EtOAc + 0.1% of 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); ^1H 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), 3.84 (dd, 1H, H-6a), 3.80 (dd, 1H, H-4), 3.80 (ddd, 1H, $J_{5',6'a}$ 6.5 Hz, $J_{5',6'b}$ 6.3 Hz, H-5'), 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-*aldeydo*-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 room temp 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 at 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); ^1H 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 × C*Me*$_2$), 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 × C*Me_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-*aldeydo*-D-glucose dimethyl acetal (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 room temp 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 room temp 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-1), 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 × C*Me_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 × C*Me_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 at 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%) constituted (^{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).

1a (50 mg, 0.13 mmol) was dissolved in a 2:1 pyridine-Ac_2O solution (3 mL) and the resulting soln was stirred at room temp for 18 h and then co-evaporated with toluene (3 × 5 mL) under diminished pressure. The 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. **9** was a 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 x *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 4Å powdered molecular sieves (500 mg) in anhyd CH_2Cl_2 (15 mL) was stirred for 30 min at room temp 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 room temp 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 in the order with CH_2Cl_2 and 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 solution 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-1), 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 60% NaH in mineral oil (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 at diminished pressure. The 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-1), 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 room temp 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 at diminished pressure. Purification of the residue by flash chromatography over silica gel, eluting with 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-1), 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 at reduced pressure and co-evaporated with toluene (3 × 8 mL). The residue was dissolved in a 2:1 pyridine-Ac_2O soln (3 mL) and the resulting soln was stirred at room temp for 2 h

and then co-evaporated with toluene (3 × 8 mL). The flash cromatographic 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-1), 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 room temp and stirred for 30 min. The soln was 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 constituted (NMR, $CDCl_3$) by a mixture of α- and β-anomers in 3:2 ratio calculated on the basis of the relative intensities of C-1 signals (δ 92.3 and 96.3, respectively); $[\alpha]_{Dinizial}$ +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 x *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 a 2:1 pyridine-Ac_2O soln (2 mL) was stirred at room temp for 15 h and then co-evaporated with toluene (3 × 8 mL). The flash cromatographic purification over silica gel (1:1 hexane-EtOAc) afforded pure **16** (34 mg, 95%) as a clear syrup, constituted

(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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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]Assigments may be reversed.