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SYNTHESIS OF *p*-NITROPHENYL 6-*O*-(2-ACETAMIDO-2-DEOXY-β-D-GLUCOPYRANOSYL)-β-D-GALACTOPYRANOSIDE AND *p*-NITROPHENYL *O*-β-D-GALACTOPYRANOSYL-(1→3)-*O*-(2-ACETAMIDO-2-DEOXY-β-D-GLUCOPYRANOSYL)-(1→6)-β-D-GALACTOPYRANOSIDE*

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ABSTRACT

Condensation of 2-methyl-(3,4,6-tri-*O*-acetyl-1,2-dideoxy-α-D-glucopyrano)-[2′,1′:4,5]-2-oxazoline with *p*-nitrophenyl 2,3-di-*O*-acetyl-β-D-galactopyranoside (**4**), followed by saponification of the resulting disaccharide derivative, produced *p*-nitrophenyl 6-*O*-(2-acetamido-2-deoxy-β-D-glucopyranosyl)-β-D-galactopyranoside as a crystalline compound. Reaction of 2-methyl-[4,6-di-*O*-acetyl-1,2-dideoxy-3-*O*-(2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyl)-α-D-glucopyrano]-[2′,1′.4,5]-2-oxazoline with **4** in a similar reaction-sequence provided the title trisaccharide compound.

INTRODUCTION

Endoglycosidases, as well as exoglycosidases, seem to be excellent tools for structural studies of glycoproteins and various other complex, sugar-containing molecules. Recently, there has been great interest in the isolation and characterization of various endoglycosidases present in different micro-organisms[2–7], but studies related to these enzymes have been somewhat hampered by the unavailability of suitable substrates for their activity. The enzyme substrates required for such studies have generally been derived from parent glycoproteins, or isolated from various biological resources, but we have initiated a program of developing suitable routes for the chemical synthesis of the oligosaccharides which may be useful in studies relating to the specificity of these enzymes. In these investigations, facile syntheses of *p*-nitrophenyl 6-*O*-(2-acetamido-2-deoxy-β-D-glucopyranosyl)-β-D-galactopyranoside and *p*-nitrophenyl *O*-(β-D-galactopyranosyl)-(1→3)-*O*-(2-acetamido-2-deoxy-β-D-glucopyranosyl)-(1→6)-β-D-galactopyranoside have been accomplished by the oxazoline method[1]. According to Fukuda and Matsumara[7], endo-β-D-galactosidase

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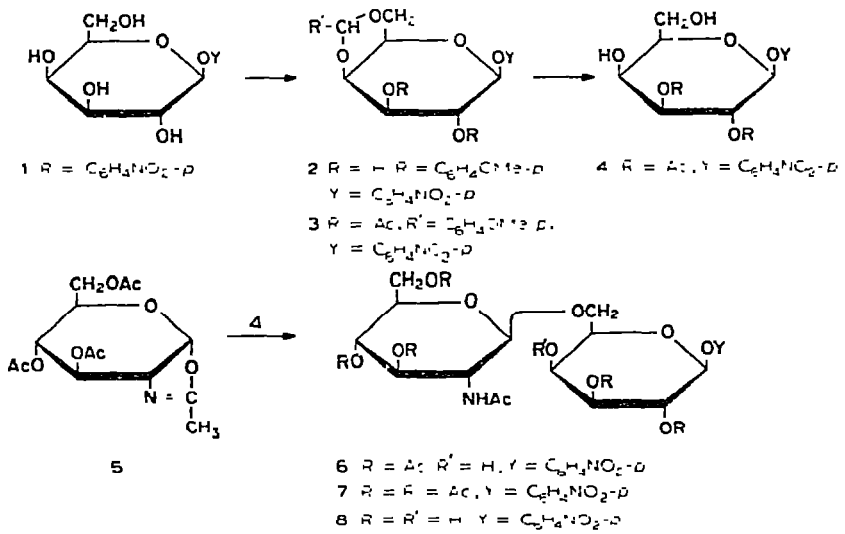
acts on desialyzed, pig-colonic mucin to release 3-*O*-(2-acetamido-2-deoxy-β-D glucopyranosyl)-D-galactose and 3-*O*-(2-acetamido-2-deoxy-6-*O*-sulfato-β-D-gluco pyranosyl)-D-galactose. This enzyme also releases the trisaccharide *O*-(β-D-galacto pyranosyl)-(1→3)-*O*-(2-acetamido-2-deoxy-β-D-glucopyranosyl)-(1→3)-β-D-galactos from lacto-*N*-tetraose [*O*-β-D-Gal-(1→3)-*O*-β-D-GlcNAc-(1→3)-*O*-β-D-Gal-(1→4) D-Glc] and lacto-*N*-tetraitol [*O*-β-D-Gal-(1→3)-*O*-β-D-GlcNAc-(1→3)-*O*-β-D-Gal (1→4)-D-glucitol].

RESULTS AND DISCUSSION

Reaction of 2,3,4,6-tetra-*O*-acetyl-α-D-galactopyranosyl bromide with sodium *p*-nitrophenoxide in anhydrous *N*,*N*-dimethylformamide[8], followed by saponification of the resulting crystalline product, gave *p*-nitrophenyl β-D-galactopyranoside (**1**) in satisfactory yield. Condensation of **1** with *p*-methoxybenzaldehyde in the presence of anhydrous zinc chloride[9] produced the crystalline acetal **2**, which, on treatment with a mixture of pyridine and acetic anhydride, provided the 2,3-diacetate **3** in 83% yield. The cleavage of the *p*-methoxybenzylidene group from **3** was effected under mild conditions with aqueous acetic acid at room temperature, to give compound **4**, which was quite different from *p*-nitrophenyl 2,6-di-*O*-acetyl-β-D-galactopyranoside on the basis of its melting point. However, the two compounds were found to be only slightly distinguishable on the basis of their mobility in t.l.c. and their optical rotations. Nevertheless, these observations clearly suggested that the 3-*O*-acetyl group did not migrate to the 6-hydroxyl group during the removal of the *p*-methoxybenzylidene group from **3**.

It is well known that the signal due to axial, acetoxyl-group protons appears downfield from that due to those of an equatorial group[10]. This observation, as well as proton magnetic resonance studies of *O*-acetyl derivatives of various glycopyranose molecules, reported by S. A. Barker *et al.*[11], suggested that the low-field resonance should be assigned to an axial acetoxyl group at C-4 in *p*-nitrophenyl 2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranoside [τ 7.80, the other acetoxyl signals being at τ 7.92 (6 H, 2 OAc) and 7.97 (1 OAc)] and in *p*-nitrophenyl 2,4,6-tri-*O*-acetyl-β-D-galactopyranoside [τ 7.78, with the other two acetoxyl protons at τ 7.85 and 7.92]. The acetoxyl signals for **4** were found to be at τ 7.86 and 7.92, whereas, for *p*-nitrophenyl 2,6-di-*O*-acetyl-β-D-galactopyranoside, they were at τ 7.85 and 7.89, showing the absence of any axial acetoxyl protons in these two compounds. In order further to establish the structure of **4** as the 2,3-diacetate, a portion of the compound was condensed with *p*-methoxybenzaldehyde in the presence of anhydrous zinc chloride to provide the 4,6-(*p*-methoxybenzylidene) acetal **3** in 26.7% yield.

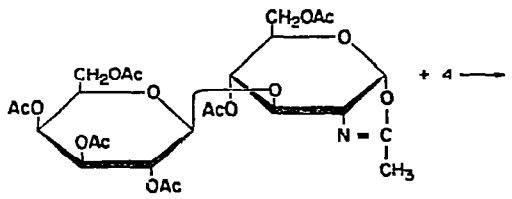
Recently, it has been shown[12] that the 4-hydroxyl group of the D-galacto-pyranosyl group can participate in glycoside formation with a glycosyl halide having a non-participating group at C-2, in the presence of a tetraethylammonium halide (halide ion-catalyzed glycosidation)[13]. Interestingly, under the reaction conditions generally employed for glycosidation, the axial hydroxyl group of the D-galactose



moiety is known to be quite unreactive[13,14]. Flowers *et al.*[15] showed that protected D-galactopyranose derivatives having the 3- and 4-hydroxyl groups free react preferentially at the 3-hydroxyl group in glycosidation reactions. Also, we accomplished the facile synthesis of 6-*O*-α-L-fucopyranosyl-D-galactose[16] from 1,2,3-tri-*O*-benzoyl-α-D-galactopyranose. Furthermore, the latter compound was utilized[17] for the synthesis of 6-*O*-(2-acetamido-2-deoxy-β-D-galactopyranosyl)-D-galactose *via* the oxazoline method, supporting the conclusion that the *O*-benzoyl group did not migrate under the conditions employed for glycosidation.

In the present studies, compound **4** has been employed for the synthesis of the title compounds **8** and **12**. The condensation of **4** with the oxazoline[18] **5** was conducted in 1:1 nitromethane–toluene in the presence of a catalytic amount of *p*-toluenesulfonic acid to provide *p*-nitrophenyl 6-*O*-(2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-β-D-glucopyranosyl)-2,3-di-*O*-acetyl-β-D-galactopyranoside (**6**) as the major product. The infrared spectrum of **6** clearly showed the presence of a free hydroxyl group in the molecule. The n.m.r. spectrum of **6** exhibited the acetyl signals at τ 7.87, 7.90, 7.94, 7.96 (with a shoulder at 7.97), and 8.12 for five *O*-acetyl groups and one acetamido group, whereas the acetyl protons for compound **7** (obtained by acetylation of **6**) appeared at τ 7.82, 7.92, 7.94, 7.96, 7.98 (with a shoulder at 7.99), and 8.15 for six *O*-acetyl groups and one acetamido group. As already mentioned, the low-field resonance signal at τ 7.82 for **7** may be assigned to an axial acetoxyl group, supporting the presence of an axial hydroxyl group in **6**. Treatment of **7** with triethylamine in methanol–water produced the desired disaccharide derivative **8**.

For the synthesis of the trisaccharide derivative **12**, the crude oxazoline **9**, prepared by acetolysis of methyl 2-acetamido-2-deoxy-3-*O*-(2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyl)-α-D-glucopyranoside, was condensed with **4** under similar reaction-conditions, to give the partially protected sugar derivative **10** in ~20%



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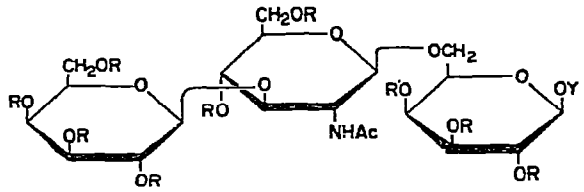

10 R = Ac, R' = H, Y = $C_6H_4NO_2$-*p*
11 R = R' = Ac Y = $C_6H_4NO_2$-*p*
12 R = R' = H Y = $C_6H_4NO_2$-*p*

yield. Treatment of **10** with pyridine–acetic anhydride yielded **11** as a crystalline compound which, on *O*-deacetylation followed by freeze-drying, gave the trisaccharide derivative **12** in 93% yield.

EXPERIMENTAL

General methods. — These are described in ref. 1.

p-*Nitrophenyl β*-D-*galactopyranoside* (**1**). — A solution of 2,3,4,6-tetra-*O*-acetyl-α-D-galactopyranosyl bromide (40.0 g, 97 mmoles) in anhydrous *N*,*N*-dimethylformamide (200 ml) containing sodium *p*-nitrophenoxide (28.7 g, 145 mmoles) was stirred for 16 h at room temperature and then poured into water (3 liters). After 3 h, the impure precipitate was collected by filtration, and washed several times with water. It was air-dried, and recrystallized from ethanol, to give *p*-nitrophenyl 2,3,4,6-tetra-*O*-acetyl-*β*-D-galactopyranoside as long needles, yield 19.8 g (43.5%), m.p. 140–142° (lit.[19] m.p. 144–145°), $[\alpha]_D^{23}$ −11.3° (*c* 1, chloroform) {lit.[19] $[\alpha]_D^{25}$ −8.3° (chloroform)}; n.m.r. data ($CDCl_3$): τ 1.70–2.94 (m, 4 H, $C_6H_4NO_2$), 7.80, 7.92, and 7.97 (12 H, 4 OAc).

A portion (30.0 g) of this compound in absolute methanol (200 ml) was treated with 0.5M sodium methoxide (10 ml). The clear solution thus obtained was kept for 3 h at room temperature, resulting in a thick precipitate of **1**. The mixture was made neutral with acetic acid, and filtered, and the crystalline residue was recrystallized from methanol, to give chromatographically pure **1** (17.5 g, 90.8%), m.p. 180–182° (reported* m.p. 179°), $[\alpha]_D^{23}$ −79.5° (*c* 1, water) {reported* $[\alpha]_D^{20}$ −85° (*c* 2, water)}.

*J. T. Baker, lab. chemical products.

p-*Nitrophenyl 4,6-O-(p-methoxybenzylidene)-β-D-galactopyranoside* (**2**). — A mixture of **1** (5.6 g, 18.6 mmoles), anhydrous zinc chloride (5.5 g), and *p*-methoxybenzaldehyde (50 ml) was stirred at room temperature. A cake formed in the mixture after 15–20 min. An addition of *p*-methoxybenzaldehyde (25 ml) was made, and the contents were shaken for 4 days at room temperature. The resulting, viscous material was diluted with ether (300 ml), and the mixture stirred with ice-cold water (300 ml). The solid material thus obtained was filtered off, washed several times with ice-cold water and ether, and air dried; it was then stirred with hot acetone (300–350 ml), and the suspension filtered. On cooling, the filtrate gave crystals (needles) of **2** (4.5 g, 57.7%), m.p. 220–222°, $[\alpha]_D^{23}$ −134.8° (*c* 1, *N*,*N*-dimethylformamide); ν_{max}^{KBr} 3400 (OH), 1610, 1590 (Ph), 1512, 1345 (NO_2), and 755 cm^{-1} (Ph). The compound was used for the next step without further characterization.

p-*Nitrophenyl 2,3-di-O-acetyl-4,6-O-(p-methoxybenzylidene)-β-D-galactopyranoside* (**3**) — A solution of **2** (4.5 g) in anhydrous pyridine (50 ml) and acetic anhydride (30 ml) was kept for 24 h at room temperature. The mixture was then poured dropwise into ice-water (1.6 liters) with vigorous stirring. The resulting, crystalline material was filtered off, washed several times with water, and air dried. The crystals (5.3 g) were taken up in acetone (30–60 ml), the suspension was filtered through glass wool, and the filtrate was diluted with absolute ethanol, to give chromatographically pure **3** as colorless crystals (4.5 g, 83.3%), m.p. 226–228°, $[\alpha]_D^{23}$ −15.4° (*c* 1, chloroform); ν_{max}^{KBr} 1750 (OAc), 1610, 1590 (Ph), 1515, 1345 (NO_2), and 755 cm^{-1} (Ph).

Anal. Calc. for $C_{24}H_{25}NO_{11}$: C, 57.25; H, 5.01; N, 2.78. Found: C, 57.20; H, 5.08; N, 2.67.

p-*Nitrophenyl 2,3-di-O-acetyl-β-D-galactopyranoside* (**4**). — A suspension of **3** (4.4 g) in acetic acid (80%; 200 ml) was stirred for 10 min at ~40°, to give a clear solution which was kept for 20 h at room temperature. Acetic acid was evaporated off *in vacuo*, and traces of the acid were removed by repeated codistillation with toluene. The residue crystallized from acetone–pentane, to give **4*** (2.8 g, 83.1%), m.p. 177–178°, $[\alpha]_D^{23}$ −5.2° (*c* 0.67, chloroform); ν_{max}^{KBr} 3520 (OH), 1740 (OAc), 1610, 1595 (Ph), 1510, 1345 (NO_2), 1230 (OAc), and 755 cm^{-1} (Ph); n.m.r. data ($CDCl_3$): τ 2.72–2.94 (m, 4 H, $C_6H_4NO_2$), 7.86, and 7.94 (6 H, 2 OAc).

Anal. Calc. for $C_{18}H_{19}NO_{10}$. C, 49.87; H, 4.97; N, 3.93. Found: C, 49.78; H, 5.11; N, 3.47.

A portion (0.2 g) of **4** in *p*-methoxybenzaldehyde (5 ml) containing anhydrous zinc chloride (0.2 g) was stirred for 2 days at room temperature. The mixture was then processed as described for **2**, to give a solid residue which was recrystallized several times from acetone–ethanol, to give **3** (70 mg, 26.7%), m.p. 226–228°.

p-*Nitrophenyl 6-O-(2-acetamido-3,4,6-tri-O-acetyl-2-deoxy-β-D-glucopyranosyl)-2,3-di-O-acetyl-β-D-galactopyranoside* (**6**). — A solution of oxazoline[18] **5** (1.5 g,

*p-Nitrophenyl 2,6-di-*O*-acetyl-β-D-galactopyranoside prepared in our laboratory had m.p. 192–194°, $[\alpha]_D^{23}$ −6.0° (*c* 1, chloroform).

~4.5 mmoles), **4** (1.2 g, 3.1 mmoles), and *p*-toluenesulfonic acid (15 mg) in 1:1 nitromethane–toluene (25 ml) was heated for 2 h at 125–130°, cooled, and the acid neutralized with a few drops of pyridine. The solution was evaporated to a brown residue which was stirred with water (100 ml). The resulting solid was collected by filtration, washed several times with water, and air dried. T.l.c. of the compound (1.7 g) showed the presence of a major spot, and a slightly slower-moving, minor spot. Pure compound **6** was isolated by several recrystallizations from acetone–ether–hexane (yield 1.2 g, 53.9%), m.p. 250–253° (dec.), $[\alpha]_D^{23}$ −16.5° (*c* 0.67, chloroform); ν_{max}^{KBr} 3480 (OH), 3320 (NH), 1740 (OAc), 1660 (Amide I), 1610, 1590 (Ph), 1540 (Amide II), 1520, 1340 (NO_2), 1230 (OAc), and 750 cm^{-1} (Ph); n.m.r. data ($CDCl_3$): τ 1.70–2.90 (m, 4 H, $C_6H_4NO_2$), 7.87, 7.90, 7.94, 7.96 (with a shoulder at 7.97), and 8.12 (18 H, 5 OAc and NAc).

Anal. Calc. for $C_{30}H_{38}N_2O_{18}$: C, 50.42; H, 5.36; N, 3.92. Found: C, 50.69; H, 5.38; N, 3.70.

p-*Nitrophenyl 6*-O-(*2-acetamido-3,4,6-tri*-O-*acetyl-2-deoxy-β*-D-*glucopyranosyl*)-*2,3,4-tri*-O-*acetyl-β*-D-*galactopyranoside* (**7**). — A solution of **6** (0.5 g) in a mixture of pyridine (5 ml) and acetic anhydride (3 ml) was kept for 36 h at room temperature, and then evaporated under diminished pressure; traces of acetic anhydride and pyridine were removed by codistillation with toluene. The solid residue was recrystallized from absolute ethanol, to give chromatographically pure **7** (0.45 g, 85%), m.p. 228–229°, $[\alpha]_D^{23}$ −18° (*c* 1, chloroform); ν_{max}^{KBr} 3285 (NH), 1750 (OAc), 1670 (Amide I), 1610, 1590 (Ph), 1560 (Amide II), 1515, 1340 (NO_2), 1230 (OAc), and 750 cm^{-1} (Ph); n.m.r. data ($CDCl_3$): τ 1.68–2.90 (m, 4 H, $C_6H_4NO_2$), 7.82, 7.92, 7.94, 7.96, 7.98 (with a shoulder at 7.99), and 8.15 (21 H, 6 OAc and NAc).

Anal. Calc. for $C_{32}H_{40}N_2O_{19}$: C, 50.79; H, 5.33; N, 3.70. Found: C, 50.74; H, 5.31; N, 3.63.

p-*Nitrophenyl 6*-O-(*2-acetamido-2-deoxy-β*-D-*glucopyranosyl*)-*β*-D-*galactopyranoside* (**8**). — A solution of **7** (0.3 g) in a mixture of methanol (9 ml), triethylamine (3 ml), and water (2.5 ml) was kept for 24 h at 4°, and then evaporated to dryness. The residue was co-evaporated with toluene. The resulting material crystallized from methanol, to give **8** (0.15 g, 72.4%), m.p. 240–243° (dec.), $[\alpha]_D^{23}$ −99.4° (*c* 0.5, water); ν_{max}^{KBr} 3420–3210 (broad OH and NH), 1655 (Amide I), 1610, 1590 (Ph), 1560 (Amide II), 1510, 1340 (NO_2), and 750 cm^{-1} (Ph).

Anal. Calc. for $C_{20}H_{28}N_2O_{13}\cdot H_2O$: C, 45.97; H, 5.78; N, 5.36. Found: C, 46.37; H, 5.70; N, 5.11.

p-*Nitrophenyl* O-(*2,3,4,6-tetra*-O-*acetyl-β*-D-*galactopyranosyl*)-(*1→3*)-O-(*2-acetamido-4,6-di*-O-*acetyl-2-deoxy-β*-D-*glucopyranosyl*)-(*1→6*)-*2,3-di*-O-*acetyl-β*-D-*galactopyranoside* (**10**). — A solution of crude oxazoline[1] **9** (0.7 g), **4** (0.58 g, 1.5 mmoles), and *p*-toluenesulfonic acid (15 mg) in 1:1 nitromethane–benzene (20 ml) was heated for 90 min at 130–135°, solvent (~5 ml) being distilled off during the reaction*. The resulting, brown solution was cooled, made neutral with a few drops

*The reaction was conducted in a Dean and Stark apparatus; distillate was removed from the limb.

of pyridine, and evaporated *in vacuo*. The residue was stirred overnight with water, the suspension filtered, and the solid air-dried. It was recrystallized from acetone–ether–hexane, to give **10** (0.15 g). The mother liquor afforded an additional amount of **10** (0.15 g); total yield, 19.5%; m.p. 140–142°, $[\alpha]_D^{23}$ −6.5° (*c* 1, chloroform); ν_{max}^{KBr} 3510–3325 (broad OH and NH), 1740 (OAc), 1670 (Amide I), 1610, 1590 (Ph), 1540 (Amide II), 1515, 1340 (NO_2), 1230 (OAc), and 750 cm^{-1} (Ph); n.m.r. data ($CDCl_3$): τ 1.8–1.90 (m, 4 H, $C_6H_4NO_2$), 4.0 (1 H, d, *J* 8 Hz, NH), and 7.84–8.04 (27 H, 8 OAc and NAc).

Anal. Calc. for $C_{42}H_{54}N_2O_{26}\cdot H_2O$: C, 49.41; H, 5.52; N, 2.74. Found: C, 49.45; H, 5.39; N, 2.56.

p-*Nitrophenyl* O-(*2,3,4,6-tetra*-O-*acetyl*-β-D-*galactopyranosyl*)-(*1→3*)-O-(*2-acetamido-4,6-di*-O-*acetyl-2-deoxy*-β-D-*glucopyranosyl*)-(*1→6*)-*2,3,4-tri*-O-*acetyl*-β-D-*galactopyranoside* (**11**). — A solution of **10** (0.15 g) in anhydrous pyridine (3 ml) and acetic anhydride (2 ml) was kept for 36 h at room temperature. Evaporation, and co-distillation with toluene, produced a residue which crystallized from acetone–ether–hexane, to give **11** (0.1 g, 64%), m.p. 133–135°, $[\alpha]_D^{23}$ −5° (*c* 0.65, chloroform): ν_{max}^{KBr} 3380 (NH, not a sharp band), 1750 (OAc), 1670 (Amide I), 1610, 1595 (Ph), 1545 (Amide II), 1515, 1340 (NO_2), 1230 (OAc), and 755 cm^{-1} (Ph); n.m.r. data ($CDCl_3$): τ 1.68–2.90 (m, 4 H, $C_6H_4NO_2$), 4.12 (1 H, d, *J* 8 Hz), and 7.82–8.04 (30 H, 9 OAc and NAc).

Anal. Calc. for $C_{44}H_{56}N_2O_{27}\cdot H_2O$: C, 49.71; H, 5.47; N, 2.63. Found: C, 49.87; H, 5.53; N, 2.46.

p-*Nitrophenyl* O-β-D-*galactopyranosyl*-(*1→3*)-O-(*2-acetamido-2-deoxy*-β-D-*glucopyranosyl*)-(*1→6*)-β-D-*galactopyranoside* (**12**). — A suspension of **11** (70 mg) in methanol (3 ml) was stirred with triethylamine (1 ml) and water (0.8 ml). The clear solution obtained after 15–20 min was kept for 36 h in the cold, and evaporated; co-distillation with toluene produced a solid residue which was stirred with de-ionized water (10 ml), and the suspension filtered through a Celite pad. The clear filtrate was freeze-dried, to give **12** as amorphous material (45 mg, 93.4%), $[\alpha]_D^{23}$ −53° (*c* 0.5, water); ν_{max}^{KBr} 3410–3380 (broad OH, NH), 1660 (Amide I), 1610, 1575 (Ph), 1550 (Amide II), 1520 (NO_2), and 750 cm^{-1} (Ph).

Anal. Calc. for $C_{26}H_{38}N_2O_{18}\cdot 2H_2O$: C, 44.44; H, 6.02; N, 3.98. Found: 44.24; H, 5.65; N, 3.79.

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