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Note

Side products of glycosidation with selected 2-acetamido-2-deoxy-D-glucopyranosides

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Abstract

Allyl 2-acetamido-4,6-*O*-benzylidene-2-deoxy-3-*O*-formyl-α-D-glucopyranoside, *N*-acetyl-2,3,4-tri-*O*-acetyl-L-fucopyranosylamine and products of *O*-acetyl group migration were found as side products during glycosidation of selected 2-acetamido-2-deoxy-D-glucopyranosides. © 2002 Elsevier Science Ltd. All rights reserved.

Keywords: Acetyl migration; 2-Acetamido-2-deoxy-D-glucopyranosides; *N*-Acetyl-2,3,4-tri-*O*-acetyl-L-fucopyranosylamine; ^{1}H and ^{13}C NMR

In our work on disaccharides containing 2-acetamido-2-deoxy-D-glucopyranose (*N*-acetylglucosamine) units, we do not develop new synthetic methodology but rather apply known chemistry in as efficient manner as possible to the solution of synthetic problems. In many laboratories, side reactions have been found to occur during glycosidation reactions, such as aglycon transfer,[1,2] acyl transfer[3,4] or formylation.[5,6] So we decided to share problems which have occurred in our lab.

Allyl 2-acetamido-4,6-*O*-benzylidene-2-deoxy-α-D-glucopyranoside (**2**), prepared from allyl 2-acetamido-2-deoxy-α-D-glucopyranoside[7] (**1**), was used as a glycosyl acceptor in the reaction with methyl 2,3,4-tri-*O*-acetyl-α-D-glucopyranosyluronate bromide[8] (**3**). Silver triflate was used as the promoter in the reactions studied. Unchanged substrates were found in the post-reaction mixtures, which indicated low reactivity of both compounds under these conditions. In the next reaction (Reaction 1, see Section 1) the more reactive methyl 2,3,4-tri-*O*-acetyl-α-D-glucopyranosyluronate trichloroacetimidate[9] (**5**) was used as the glycosyl donor, and trimethylsilyl triflate was the promoter. Under these reaction conditions, allyl 2-acetamido-3-*O*-acetyl-4,6-*O*-benzylidene-2-deoxy-α-D-glucopyranoside (**7**) was formed in almost 50% yield as a product of intermolecular *O*-acetyl group migration. Additional *O*-acetyl group signals at δ 2.06 (^{1}H NMR) and δ 171.430, 23.587 (^{13}C NMR) confirmed its structure (Scheme 1).

In the reaction between **2** and **5**, we expected disaccharide formation. In the literature, it is described that in some reactions of glycopyranosyl bromides[3] and trichloroacetimidates[4] with unreactive glycosyl acceptors, *O*-acetyl migration as the side reaction is known.

In some cases an *O*-allyl group on the anomeric carbon atom can cause lower activity of the glycosyl acceptor.[10] To find what is the influence of the double bond in the *O*-allyl group on this reaction, propyl 2-acetamido-4,6-*O*-benzylidene-2-deoxy-α-D-glucopyranoside (**4**) was prepared and used in a similar reaction. In the reaction of **3** with **5** in the presence of silver triflate (Reaction 2), a small amount of the desired disaccharide (about 5%) and almost 20% propyl 2-acetamido-3-*O*-acetyl-4,6-*O*-benzylidene-2-deoxy-α-D-glucopyranoside (**6**) were formed. The results indicate that the influence of a double bond on the reactivity of compound **2** could be of no great importance. On the other hand, the lower reactivity of uronic acid derivatives is well known.[11,12] To answer the question whether too low activities of compounds **3** and **5** as glycosyl donors can cause unsatisfactory results in the synthesis of disaccharides, 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide (**6**) was used as the model compound (Reaction 3). After the reaction of **2** with **6** in the

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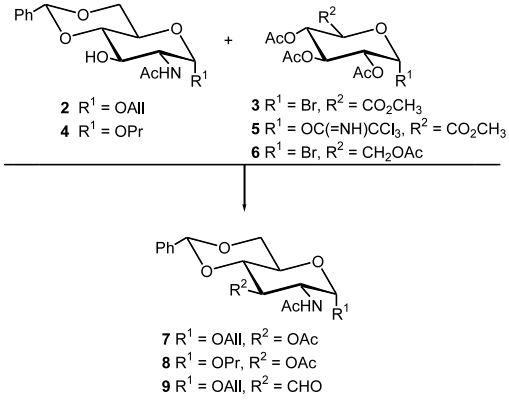
presence of silver triflate, a more complex mixture was formed. Apart from substrates and a small amount of the desired disaccharide (about 5%), two major products were formed. The first, allyl 2-acetamido-3-*O*-acetyl-4,6-*O*-benzylidene-2-deoxy-α-D-glucopyranoside (**7**) was isolated in 17% yield. Its presence, as before, could be explained as a result of intermolecular migration of the *O*-acetyl group. The second product **9**, formed in a yield similar to that of compound **7**, was a derivative of compound **2** in which the 3-OH group was protected by an unknown residue. The presence of signals of *N*-acetyl, *O*-benzylidene and *O*-allyl groups in the NMR spectra and the absence of the free hydroxyl group signal in the infrared spectrum confirmed that it is a derivative of **2**. There were two additional signals in the NMR spectra. In the ^{1}H spectrum, we found the signal of one proton at 8.11 ppm and in the ^{13}C spectrum, the signal of a carbon atom at 160.96 ppm. A DEPT spectrum of **9** indicated that this additional carbon atom is bonded to one proton. Signals of coupling between the proton at 8.11 ppm and C-3 and H-3 and the carbon at 160.96 on the HMBC spectrum proved the allyl 2-acetamido-4,6-*O*-benzylidene-2-deoxy-3-*O*-formyl-α-D-glucopyranoside structure for **9**. Pozsgay and Nanasi[6] reported the formation of a 6-*O*-formyl derivative as a side product of glycosidation, what they explained as a Vilsmeier-type formylation with *N*,*N*-dimethylformamide. In our case, we did not use DMF, so the mechanism for the formation of **9** must be some other reaction. Additionally we carried out the reaction of **2** with 2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranosyl trichloroacetimidate in DMF, and the expected disaccharide was formed with almost 70% yield, which will be described in another article.

Next we prepared a very reactive glycosyl donor, 2,3,4-tri-*O*-acetyl-L-fucopyranosyl bromide (**10**). In the reaction of **10** with **2** or **4**, we state formation of desired disaccharides with almost 50% yield and as side products **7** and **8**, respectively. Much more interesting were products of reaction of **10** with allyl or propyl 2-acetamido-3,6-di-*O*-bezyl-2-deoxy-D-glucopyranoside (**13** and **14**) in acetonitrile. In both cases the expected disaccharide was formed in small amounts (about 5%). Beside products of *O*-acetyl migration, which were formed in almost 30% yield, both anomers of *N*-acetyl-2,3,4-tri-*O*-acetyl-L-fucopyranosylamine (**15**) were formed in about 30% yield. Their structures were confirmed by NMR spectroscopy. Three singlets of CH_3/OAc and a doublet of three protons bonded to C-6 in the ^{1}H NMR spectrum indicated a tri-*O*-acetylfucopyranosyl structure. An addition, a singlet of CH_3/NAc at δ 1.99 (2.03 for β anomer), coupled with the H-1 doublet of NH/NAc at δ 6.34 (β 6.74) and doublet of doublets of the anomeric proton at δ 5.13 (β 5.87; $J_{1\alpha.2}$ 3.2, $J_{1\beta,2}$ 7.2, $J_{1\alpha,NH}$ 9.2, $J_{1\beta,NH}$ 8.0 Hz) confirm the presence of an *N*-acetyl group bonded to C-1. The presence of an *N*-acetyl group in this compound was confirmed by signals of CH_3/NAc at δ 20.79 (β 20.88) and a carboxyl carbon atom at δ 170.03 (β 169.60) in the ^{13}C NMR spectrum.

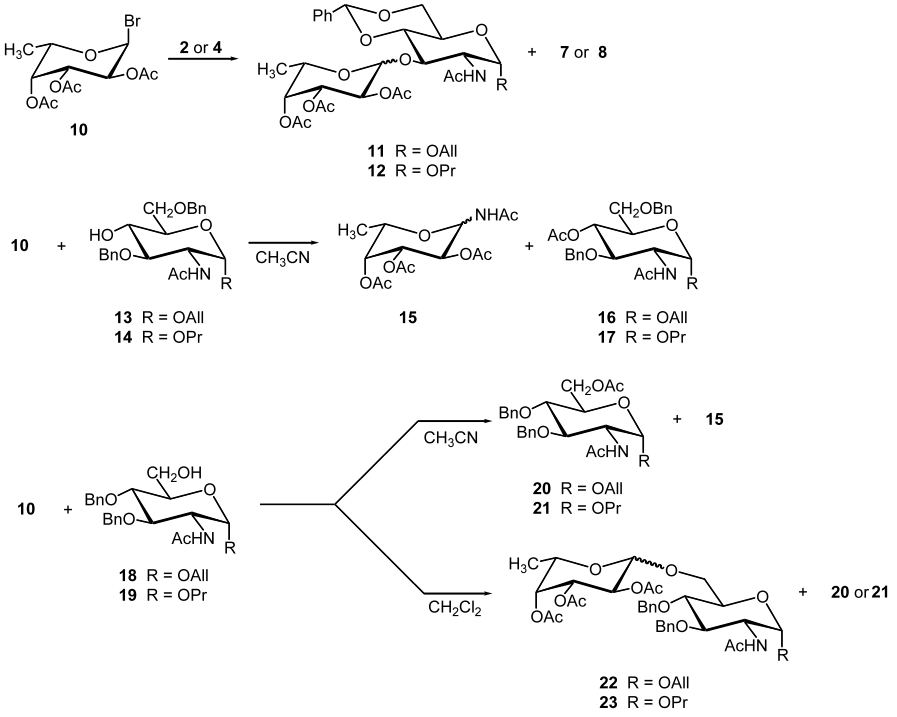
Similar results were obtained when **10** reacted with allyl or propyl 2-acetamido-3,4-di-*O*-benzyl-2-deoxy-D-glucopyranoside (**18** and **19**) in acetonitrile. Products of migration of the *O*-acetyl group at C-6 and **15** were formed in about 40 and 50% yield, respectively. When reactions of **10** with **18** or **19** were carried out in dichloromethane, the expected disaccharides allyl and propyl 2,3,4-tri-*O*-acetyl-L-fucopyranosyl-(1→6)-2-acetamido-4,6-di-*O*-benzyl-2-deoxy-D-glucopypanoside (**22** and **23**) were formed in good yield, and **15** was not found. These results indicate that **15** is a side product of the reaction of a very reactive **10** in acetonitrile as a solvent. In order to prevent this problem, another solvent (e.g., dichloromethane) should be used (Scheme 2).



Scheme 1.

1. Experimental

General methods.—All reactions were carried out in commercially available dry solvents (Fluka, water $< 0.005\%$). Thin-layer chromatography (TLC) was performed with E. Merck pre-coated Silica Gel 60 F_{254} plates, and detection of compounds was achieved by charring after spraying with 5% H_2SO_4 in EtOH. Silica gel (70–230 mesh) and redistilled solvents were used for column chromatography. ^{1}H and ^{13}C NMR spectra were recorded at 25 °C with a Varian Mercury spectrometer at 400 and 100 MHz, respectively, with Me_4Si as internal standard. Assignments were based on homonuclear decoupling experiments, and homo- and heteronuclear correlation. Infrared spectra were recorded on a Bruker IFS-66 instrument. Optical rotations were measured with a JASCO J-20 polarimeter. Elemental analyses were carried out on a Carlo–Erba apparatus.



Scheme 2.

Reaction 1.—A mixture of allyl 2-acetamido-4,6-*O*-benzylidene-2-deoxy-α-D-glucopyranoside (**2**) (80 mg, 0.23 mmol, prepared adopting the Warren and Jeanloz procedure[7]), methyl 2,3,4-tri-*O*-acetyl-α-D-glucopyranosyluronate trichloroacetimidate (**5**) (128 mg, 0.27 mmol), and powdered 4 Å molecular sieves (0.1 g) in anhyd CH_2Cl_2 (5 mL) was stirred at rt under a dry nitrogen atmosphere. The mixture was cooled to −60 °C, and trimethylsilyl triflate (TMSOTf, 40 L) was added. The mixture was stirred for 1 h at −60 °C, and then for 16 h at rt. Diisopropylethylamine (0.1 mL) was then added, and the mixture was diluted with CH_2Cl_2 (10 mL), filtered and concentrated. The residue was eluted from a column of silica gel with 2:1 EtOAc–toluene to give allyl 2-acetamido-3-*O*-acetyl-4,6-*O*-benzylidene-2-deoxy-α-D-glucopyranoside (**7**) (46 mg, 51%) as an oil: $[\alpha]_D$ +67° (*c* 0.9, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 7.45–7.35 (m, 5 H, Ph), 5.91 (m, 1 H, =CH–), 5.83 (d, 1 H, NH), 5.53 (s, 1 H CH<), 5.30 (m, 2 H, =CH_2), 4.88 (d, 1 H, $J_{1,2}$ 3.6 Hz, H-1), 4.35 (m, 1 H, $J_{2,3}$ 10.0 Hz, H-2), 4.29 (q, 1 H, H-6′), 4.21 (m, 1 H, OCH_2), 4.01 (m, 1 H, OCH_2), 3.94 (m, 1 H, $J_{4,5}$ 10.0 Hz, H-4), 3.77 (m, 2 H, H-5,6), 3.73 (t, 1 H, H-3), 2.07 (s, 3 H, $OCOCH_3$), 1.98 (s, 3 H, $NCOCH_3$). ^{13}C NMR: δ 171.43 ($OCOCH_3$), 170.07 ($NCOCH_3$), 137.02 (CH=), 133.23–126.26 (Ph), 118.48 (CH_2=), 101.72 (*C*HPh<), 97.26 (C-1), 79.19 (C-4), 70.50 (C-3), 69.07 (OCH_2), 68.91 (C-6), 63.22 (C-5), 52.82 (C-2), 23.59 ($OCOCH_3$), 21.28 ($NCOCH_3$). Anal. Calcd for $C_{20}H_{25}NO_7$: C, 61.38; H, 6.39; N, 3.58. Found: C, 61.73; H, 6.44; N, 3.46.

Reaction 2.—Propyl 2-acetamido-4,6-*O*-benzylidene-2-deoxy-α-D-glucopyranoside (**4**) (250 mg, 0.71 mmol) in a mixture of dry 15:1 CH_2Cl_2–acetonitrile (16 mL) was stirred at rt under dry nitrogen, and silver triflate (400 mg, 1.55 mmol) was added. After 15 min, methyl 2,3,4-tri-*O*-acetyl-α-D-glucopyranosyluronate bromide (**3**) (380 mg, 0.96 mmol) in dry CH_2Cl_2 (10 mL) was added dropwise, and the mixture was stirred for 24 h at rt. Diisopropylethylamine (0.4 mL) was then added, and the mixture was diluted with CH_2Cl_2 (15 mL), filtered, washed with 10% brine, satd aq $NaHCO_3$, and water, dried with magnesium sulfate, and concentrated. The residue was eluted from a column of silica gel with 20:4:1 toluene–acetone–MeOH to give propyl 2-acetamido-3-*O*-acetyl-4,6-*O*-benzylidene-2-deoxy-α-D-glucopyranoside (**8**) (54 mg, 19%) as an oil: $[\alpha]_D$ +51° (*c* 1.6, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 7.47–7.32 (m, 5 H, Ph), *5.*79 (d, 1 H, N*H*), 5.53 (s, 1 H, C*H*<), 5.31 (t, 1 H, $J_{3,4}$ 10.0 Hz, H-3), 4.82 (d, 1 H, $J_{1,2}$ 3.6 Hz, H-1), 4.32 (m, 1 H, $J_{2,3}$ 10.4 Hz, H-2), 4.28 (q, 1 H, H-6′), 3.90 (m, 1 H, $J_{5,6}$ 10.4 Hz, H-5), 3.77 (t, 1 H, H-6), 3.73 (q, 1 H, $J_{4,5}$ 9.6 Hz, H-4), 3.67 (m, 1 H, OCH_2), 3.38 (m, 1 H, OCH_2), 2.06 (s, 3 H, $OCOCH_3$), 1.96 (s, 3 H, $NCOCH_3$), 1.64 (m, 2 H, CH_2), 0.96 (t, 3 H, CH_3). ^{13}C NMR: δ 171.45 ($OCOCH_3$), 170.01 ($NCOCH_3$), 137.14–126.28 (Ph), 101.73 (*C*H<), 98.04 (C-1), 79.30 (C-4), 70.68 (C-3), 70.28 (OCH_2), 69.18 (C-6), 63.12 (C-5), 52.99 (C-2), 23.55 ($OCOCH_3$), 22.99 (CH_2), 21.27 ($NCOCH_3$), 10.98 (CH_3). Anal. Calcd for $C_{20}H_{27}NO_7$: C, 61.07; H, 6.87; N, 3.56. Found: C, 60.92; H, 6.67; N, 3.34.

The desired disaccharide propyl (methyl 2,3,4-tri-*O*-acetyl-β-D-glucopyranosyl)uronate-(1→3)-2-acetamido-4,6-*O*-benzylidene-2-deoxy-α-D-glucopyranoside was obtained as an oil only in 4.7% yield.

Reaction 3.—Allyl 2-acetamido-4,6-*O*-benzylidene-2-deoxy-α-D-glucopyranoside (**2**) (2.0 g, 5.7 mmol) in a mixture of dry 2:1 CH_2Cl_2–CH_3CN (60 mL) was stirred at rt under dry nitrogen, and silver triflate (3.7 g, 14.2 mmol) was added. After 15 min, 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide (**6**) (5.1 g, 12.4 mmol) in dry CH_2Cl_2 (15 mL) was added dropwise, and the mixture was stirred for 24 h at rt. Diisopropylethylamine (1 mL) was added, and the mixture was diluted with CH_2Cl_2 (30 mL), filtered, washed with 10% brine, satd aq $NaHCO_3$, and water, dried with magnesium sulfate, and concentrated. The residue was eluted from a column of silica gel with 20:4:1 toluene–acetone–MeOH, then the second fraction was eluted again with 2:1 EtOAc–toluene to give two compounds. The first was allyl 2-acetamido-3-*O*-acetyl-4,6-*O*-benzylidene-2-deoxy-α-D-glucopyranoside (**7**) (0.32 g, 17%) as an oil. The second compound was allyl 2-acetamido-4,6-*O*-benzylidene-2-deoxy-3-*O*-formyl-α-D-glucopyranoside (**9**) (0.38 g, 19%) as an oil: $[\alpha]_D$ +66° (*c* 1.1, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 8.11 (s, 1 H, CHO), 7.46–7.34 (m, 5 H, Ph), 5.90 (m, 1 H, =CH), 5.79 (d, 1 H, NH), 5.53 (s, 1 H, CH<), 5.43 (t, 1 H, $J_{3,4}$ 10.4 Hz, H-3), 5.29 (m, 2 H, $=CH_2$), 4.88 (d, 1 H, $J_{1,2}$ 4.0 Hz, H-1), 4.43 (m, 1 H, $J_{2,3}$ 9.6 Hz, H-2), 4.29 (q, 1 H, H-6′), 4.21 (m, 1 H, OCH_2), 4.01 (m, 1 H, OCH_2), 3.95 (m, 1 H, $J_{5,6}$ 10.4 Hz, H-5), 3.79 (t, 1 H, $J_{6,6'}$ 12.0 Hz, H-6), 3.76 (t, 1 H, $J_{4,5}$ 10.0 Hz, H-4), 1.97 (s, 3 H, $NCOCH_3$). ^{13}C NMR: δ 170.00 ($NCOCH_3$), 160.96 (CHO), 136.91 (CH=), 133.17–126.25 (Ph), 118.61 (CH_2=), 101.79 (*C*HPh<), 97.37 (C-1), 79.12 (C-4), 0.22 (C-3), 69.05 (OCH_2), 69.00 (C-6), 63.24 (C-5), 52.39 (C-2), 23.58 ($NCOCH_3$). Anal. Calcd for $C_{19}H_{23}NO_7$: C, 60.47; H, 6.14; N, 3.71. Found: C, 60.04; H, 6.11; N, 3.45.

The third compound, allyl 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl-(1→3)-2-acetamido-4,6-*O*-benzylidene-2-deoxy-α-D-glucopyranoside, was obtained in 4.8% yield after column chromatography.

Reaction 4.—A mixture of allyl 2-acetamido-3,4-di-*O*-benzyl-2-deoxy-α-D-glucopyranoside (**18**) (110 mg, 0.25 mmol, prepared from allyl 2-acetamido-3-*O*-benzyl-4,6-*O*-benzylidene-2-deoxy-α-D-glucopyranoside by cleavage the *O*-benzylidene ring with $NaBH_3CN$) in dry acetonitrile (12 mL), was stirred at rt under dry nitrogen, and silver triflate (280 mg, 1.08 mmol) was added. After 15 min, 2,3,4-tri-*O*-acetyl-L-fucopyranosyl bromide (**10**) (320 mg, 0.91 mmol) in dry CH_3CN (8 mL) was added dropwise, and the mixture was stirred for 24 h at rt. Next diisopropylethylamine (1 mL) was added, and the mixture was diluted with CH_2Cl_2 (30 mL), filtered, washed with 10% brine, satd aq $NaHCO_3$, and water, dried with magnesium sulfate, and concentrated. The residue was eluted from a column of silica gel with 20:4:1 toluene–acetone–MeOH, and then the second fraction was eluted again with 2:1 EtOAc–toluene to give three compounds. The first was allyl 2-acetamido-6-*O*-acetyl-3,4-di-*O*-benzyl-2-deoxy-α-D-glucopyranoside (**20**) (49 mg, 40.7%) as an oil; the second and the third compounds were both anomers of *N*-acetyl-2,3,4-tri-*O*-acetyl-L-fucopyranosylamine (**15**) (129 mg, 43%; α:β 1:2.7). α anomer: ^{1}H NMR ($CDCl_3$): δ 6.34 (d, 1 H, NH), 5.13 (dd, 1 H, $J_{1,2}$ 3.2, $J_{1,NH}$ 9.2 Hz, H-1), 5.19 (t, 1 H, H-2), 5.09 (dd, 1 H, $J_{3,4}$ 9.2 Hz, H-3), 5.29 (dd, 1 H, $J_{4,5}$ 8.4 Hz, H-4), 3.94 (m, 1 H, $J_{5,6}$ 6.8 Hz, H-5), 1.20 (d, 3 H, H-6, H-6′ and H-6″), 2.18–2.00 (9 H, 3 × $OCOCH_3$); ^{13}C NMR: δ 171.69–170.58 (3 C, $OCOCH_3$), 170.03 ($NHCOCH_3$), 78.53 (C-1), 68.60 (C-2), 71.39 (C-3), 70.49 (C-4), 70.95 (C-5), 16.26 (C-6), 23.59–20.82 (3 C, $OCOCH_3$), 20.79 ($NHCOCH_3$); β anomer: ^{1}H NMR ($CDCl_3$): δ 6.74 (d, 1 H, NH), 5.87 (dd, 1 H, $J_{1,2}$ 7.2, $J_{1,NH}$ 8.0 Hz, H-1), 5.39 (dd, 1 H, H-2), 5.27 (m, 2 H, H-3, H-4), 3.99 (dd, 1 H, $J_{5,6}$ 6.4 Hz, H-5), 1.15 (d, 3 H, H-6, H-6′ and H-6″), 2.19–2.04 (9 H, 3 × $OCOCH_3$); ^{13}C NMR: δ 174.18–170.92 (3 C, $OCOCH_3$), 169.60 ($NHCOCH_3$), 74.76 (C-1), 69.10 (C-2), 70.75 (C-3), 68.27 (C-4), 65.68 (C-5), 16.29 (C-6), 23.59–20.94 (3 C, $OCOCH_3$), 20.88 ($NHCOCH_3$). Anal. Calcd for $C_{14}H_{21}NO_8$: C, 50.76; H, 6.34; N, 4.23. Found: α anomer C, 50.46; H, 6.24; N, 4.08; β anomer C 50.61; H 6.23; N 4.17.

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References

1. Leigh, D. A.; Smart, J. P.; Truscello, A. M. *Carbohydr. Res.* **1995**, *276*, 417–424.
2. Belot, F.; Jacquinet, J. C. *Carbohydr. Res.* **1996**, *276*, 79–86.
3. Urban, F. J.; Moore, B. S.; Breitenbach, R. *Tetrahedron Lett.* **1990**, *16*, 4421–4424.
4. Ziegler, T.; Kovač, P.; Glaudemans, C. P. J. *Justus Liebigs Ann. Chem.* **1990**, 613–615.
5. Hough, L.; Lewis, A. W. *Carbohydr. Res.* **1975**, *42*, 173–174.
6. Pozsgay, V.; Nanasi, P. *Carbohydr. Res.* **1979**, *68*, 157–160.
7. Warren, Ch. D.; Jeanloz, R. W. *Carbohydr. Res.* **1977**, *53*, 67–84.
8. Bowering, W. D.; Timell, T. E. *J. Am. Chem. Soc.* **1960**, *82*, 2827–2830.
9. Jacquinet, J. C. *Carbohydr. Res.* **1990**, *199*, 153–181.
10. Dasgupta, F.; Anderson, L. *Carbohydr. Res.* **1990**, *202*, 239–255.
11. Nakahara, Y.; Ogawa, T. *Tetrahedron Lett.* **1987**, *28*, 2731–2734.
12. Lönn, H.; Lönngren, J. *Carbohydr. Res.* **1984**, *132*, 39–44.