Monatsh Chem (2009) 140:1245–1250
DOI 10.1007/s00706-009-0172-0

ORIGINAL PAPER

Selection of protecting groups and synthesis of a β-1,4-Glc*N*Ac-β-1,4-Glc*N* unit

Toshinari Kawada · Yuko Yoneda

Received: 28 March 2009 / Accepted: 29 July 2009 / Published online: 1 September 2009

Abstract The synthesis of the disaccharide *tert*-butyldimethylsilyl (4-*O*-acetyl-2-azido-3,6-di-*O*-benzyl-2-deoxy-β-D-glucopyranosyl)-3,6-di-*O*-benzyl-2-deoxy-2-phthalimido-β-D-glucopyranoside, designed as a repeating unit appearing in oligo- and polysaccharides, which exhibits a distinguished "obverse–reverse" property in β-1,4-glucan chain, was accomplished. This disaccharide was synthesized by glycosylation of a phthalimido sugar with an azido sugar. A selective removal of the two different protecting groups at C-2 for obtaining 2-acetamido-4-*O*-(2-amino-2-deoxy-β-D-glucopyranosyl)-2-deoxy-β-D-glucopyranose indicates that the selection and combination, using phthalimido and azido as protecting groups, are an excellent strategy for synthesizing such target disaccharides.

Keywords Carbohydrates · Drug research · Glycosides · Oligosaccharides

Introduction

The β-1,4-glucan chain consists of monosaccharide residues turning in a "obverse–reverse" manner, thus potentially exhibits two faces. The potential two faces cannot be recognized in the original chain, but would be distinguished by introducing the same functional group at the same carbon position in each monosaccharide moiety of the two neighboring residues. This β-1,4-glucan presenting two faces is one of the most promising novel nano-materials, since two different properties can be attached on alternate sides [1].

For synthesizing β-1,4-glucans having two faces originating from the monosaccharide residue, it is a prerequisite that one of the constituents of the disaccharide unit has two kinds of protecting groups that can be cleaved selectively. Both protecting groups should be stable under the reaction conditions for the introduction and/or cleavage of the alternate protecting group and during the glycosylation reaction applied for extension of the glucan chain.

Chitin/chitosan, one of typical β-1,4-glucans, show higher nucleophilicity for attachment of a variety of functional groups by means of acetamido/free amino groups at the C-2 position. Hence, oligo- and polysaccharides repeating 2-amino-2-deoxy-D-glucose (D-glucosamine) and 2-acetamido-2-deoxy-D-glucose (*N*-acetyl-D-glucosamine) alternatively are interesting target molecules, which present model compounds of de-acetylated chitin having randomly distributed acetyl groups (degree of substitution = 0.5) [2].

In this manuscript, the selection of two protecting groups, the synthesis of a repeating disaccharide unit and suitable de-protection conditions are described.

Results and discussion

The repeating disaccharide unit contains two kinds of D-glucosamine residues with different protecting groups at C-2, finally converted into free amino and acetamido groups, respectively. The acetamido group itself is a potential protecting group, but it easily forms an oxazoline under glycosylation conditions and leads to complex product mixtures [3–5]. After promising preliminary reactions and searching the literature [6], the azido and phthalimido groups were selected as protecting groups. The azido group

T. Kawada (✉) · Y. Yoneda
Graduate School of Life and Environmental Sciences,
Kyoto Prefectural University, Shimogamo, Sakyo-ku,
Kyoto 606-8522, Japan
e-mail: kawada@kpu.ac.jp

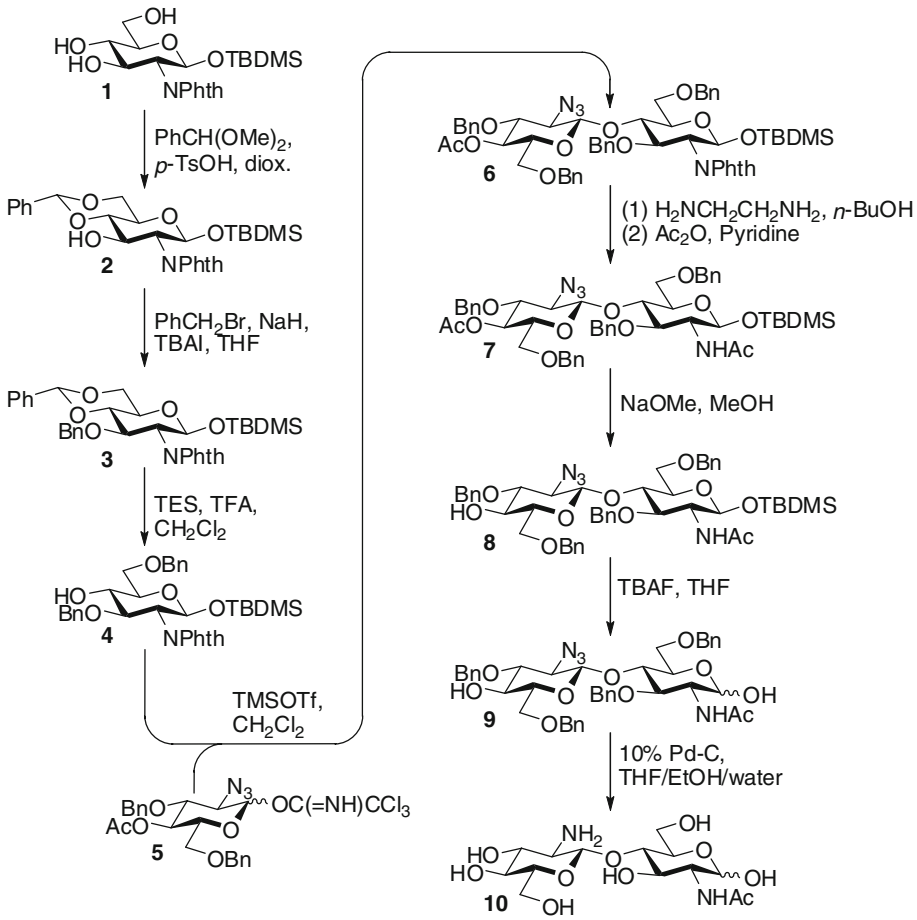
is known to be stable under several conditions, though its introduction process is crucial. The phthaloyl group is also stable under various conditions and usually can be easily introduced and cleaved [7]. Both azido and phthalimido groups can be converted into free amino groups and/or acetamido groups [8].

The phthalimido group at C-2 performs neighboring group participation [4, 9] to ensure β-selective glycoside formation for a gluco-type donor. In the case of glycosylation reactions using azido donors, the stereochemical outcome and yield highly depend on reaction conditions and reaction partners [10, 11]. Based on the knowledge above, a phthalimido moiety, not an azido moiety, is advantageous for use as a glycosyl donor. However, if the phthalimido donor is used in our case, the synthesized disaccharide equips an azido group at its reducing end, which indicates disadvantages for the following glysosylation reaction used as a glycosyl donor. Hence, a disaccharide **6** was designed to have the phthalimido group at the neighboring position, albeit the azido donor is used as a glycosyl donor.

The synthetic route for the repeating disaccharide unit is presented in Scheme 1.

tert-Butyldimethylsilyl 2-deoxy-3,6-di-*O*-benzyl-2-phthalimido-β-D-glucopyranoside (**4**) was prepared from established compound **1** [12–14] via benzylidenation, benzylation, and selective reductive ring-opening reaction of the benzylidene moiety. The glycosylation reaction between phthalimido acceptor **4** and azido donor **5** was conducted under trimethylsilyl trifluoromethanesulfonate (TMSOTf) promotion in dichloromethane at −20 °C using the same molar amount of **4** and **5**. The imidate **5** was consumed within 2 h, and a mixture of α- and β-glycosides was produced. The anomers were separated with flash column chromatography (ethyl acetate:toluene = 1:15, v/v) to obtain β-glycoside **6** (26%). Normally the glycosylation reaction in acetonitrile preferentially gives β-glycosides; however, in this case many by-products were observed. Other catalysts, such as boron trifluoride–diethyl etherate, trifluoromethanesulfonic acid, silver trifluoromethanesulfonate and tin (II) trifluoromethanesulfonate, afforded lower yields than that obtained with TMSOTf. The ^{1}H NMR spectrum of **6** shows two doublets for anomeric protons at $\delta = 4.48$ and 5.34 ppm, having coupling constants 8.3 and 8.1 Hz, respectively, thus indicating that both glycosidic bonds are β-configured.

Scheme 1



Disaccharide **6** was treated with ethylenediamine in *n*-butanol [15] for 8 h until all starting material **6** was consumed. The crude reaction product was directly used in the acetylation reaction to obtain acetamido disaccharide **7** in 53% yield over two steps. The acetyl and *tert*-butyldimethylsilyl (TBDMS) groups were sequentially cleaved to afford compound **9** in 82% yield. Subsequently, the azido and benzyl groups were converted to the free amino and hydroxyl groups, respectively, by hydrogenation using 10% palladium–carbon at normal pressure to give disaccharide **10** in 72% yield. We were able to establish a straightforward method for the preparation of disaccharide repeating units, using suitable protecting groups.

Experimental

General methods

Nuclear magnetic resonance (NMR) spectra were measured with tetramethylsilane as an internal standard. The assignments of the signals were determined using ^{1}H–^{1}H correlated spectroscopy and/or ^{13}C–^{1}H heteronuclear multiple-quantum correlation technique. Coupling constants (J) are given in Hz. Anhydrous dichloromethane and tetrahydrofuran were prepared by distilling from phosphorus pentoxide and sodium/benzophenone. Flash column chromatography was performed on silica gel (Wakogel FC-40). Preparative thin-layer chromatography (TLC) was done on silica gel plates (Kieselgel 60 F_{254}, Merck). Results of elemental analyses agreed favorably with calculated values. Unless otherwise indicated, the usual workup for each reaction mixture consists of extraction with ethyl acetate, washing with brine, drying over sodium sulfate, and evaporation in vacuo.

tert-Butyldimethylsilyl 4,6-O-benzylidene-2-deoxy-2-phthalimido-β-D-glucopyranoside (**2**, $C_{27}H_{33}NO_7Si$)

A solution of 23.8 g TBDMS 2-deoxy-2-phthalimido-β-D-glucopyranoside (**1**, 56.2 mmol) [12–14], 16.9 cm^3 benzaldehyde dimethyl acetal (113.0 mmol) and 214 mg *p*-toluenesulfonic acid monohydrate (1.10 mmol) in 357 cm^3 1,4-dioxane was agitated under reduced pressure (30 mmHg) at 30 °C for 13 h. The reaction mixture was neutralized with sodium bicarbonate and filtered. The filtrate was concentrated in vacuo to give crude crystals. Recrystallization from ethanol gave 25.0 g derivative **2** (87%) as colorless crystals. $R_f = 0.53$ (EtOAc/*n*-hexane, 1:2, v/v); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = -0.10$, 0.14 (s, 6H, 2 × Si*Me*), 0.69 (s, 9H, *t*-Bu), 3.19 (br s, 1H, 3-O*H*), 3.55 (t, 1H, $J_{3,4} = 8.7$ Hz, $J_{4,5} = 8.7$ Hz, H-4), 3.57 (ddd, 1H, $J_{4,5} = 8.7$ Hz, $J_{5,6a} = 4.6$ Hz, $J_{5,6b} = 10.1$ Hz, H-5), 3.78 (t, 1H, $J_{5,6b} = 10.1$ Hz, $J_{6a,6b} = 10.1$ Hz, H-6b), 4.15 (dd, 1H, $J_{1,2} = 8.0$ Hz, $J_{2,3} = 10.6$ Hz, H-2), 4.28 (dd, 1H, $J_{5,6a} = 4.6$ Hz, $J_{6a,6b} = 10.1$ Hz, H-6a), 4.67 (dd, 1H, $J_{2,3} = 10.6$ Hz, $J_{3,4} = 8.7$ Hz, H-3), 5.42 (d, 1H, $J_{1,2} = 8.0$ Hz, H-1), 5.54 (s, 1H, C*H*Ph), 7.32–7.51 (m, 5H, Ph), 7.60–7.82 (m, 4H, Phthaloyl) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = -5.7$, −4.0 (2 × Si*Me*), 17.3 (Cq), 25.1 (*t*-Bu), 58.8 (C-2), 66.1 (C-5), 68.0 (C-3), 68.5 (C-6), 82.2 (C-4), 93.7 (C-1), 101.7 (*C*HPh), 123.2 (Phthaloyl), 126.3, 128.2, 129.1, 131.4, 137.0 (Ph) ppm; $[\alpha]_D = -33.0°cm^3g^{-1}dm^{-1}$ ($c = 1.0$, $CHCl_3$).

tert-Butyldimethylsilyl 3-O-benzyl-4,6-O-benzylidene-2-deoxy-2-phthalimido-β-D-glucopyranoside

(**3**, $C_{34}H_{39}NO_7Si$)

To a stirred solution of 25.0 g **2** (48.9 mmol) in 145 cm^3 anhydrous THF 2.35 g sodium hydride dispersed in mineral oil (60%, 58.7 mmol) and 812 mg tetra-*n*-butylammonium iodide (TBAI, 2.20 mmol) were added at 0 °C. After 30 min 6.89 cm^3 benzyl bromide (58.7 mmol) was added to the reaction mixture, and stirring was continued at room temperature for 2 h. Finally, the reaction mixture was filtered through a pad of Celite and worked up to give a yellow solid. Recrystallization from EtOH gave 22.8 g (78%) **3** as colorless crystals. $R_f = 0.54$ (EtOAc/*n*-hexane, 1:4, v/v); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = -0.12$, 0.13 (s, 6H, 2 × Si*Me*), 0.67 (s, 9H, *t*-Bu), 3.65 (ddd, 1H, $J_{4,5} = 9.0$ Hz, $J_{5,6a} = 5.1$ Hz, $J_{5,6b} = 10.1$ Hz, H-5), 3.83 (t, 1H, $J_{3,4} = 9.0$ Hz, $J_{4,5} = 9.0$ Hz, H-4), 3.86 (t, 1H, $J_{5,6b} = 10.1$ Hz, $J_{6a,6b} = 10.1$ Hz, H-6b), 4.18 (dd, 1H, $J_{1,2} = 8.3$ Hz, $J_{2,3} = 10.6$ Hz, H-2), 4.35 (dd, 1H, $J_{5,6a} = 5.1$ Hz, $J_{6a,6b} = 10.1$ Hz, H-6a), 4.45 (dd, 1H, $J_{2,3} = 10.6$ Hz, $J_{3,4} = 9.0$ Hz, H-3), 4.50–4.80 (m, 2H, CH_2Ph), 5.42 (d, 1H, $J_{1,2} = 8.3$ Hz, H-1), 5.62 (s, 1H, C*H*Ph), 6.88–7.54 (m, 10H, Ph), 7.70–7.73 (m, 4H, Phthaloyl) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = -5.6$, −4.3 (2 × Si*Me*), 17.5 (Cq), 25.2 (*t*-Bu), 58.0 (C-2), 66.2 (C-5), 68.8 (C-6), 73.9–74.3 (2 × *C*H_2Ph), 74.3 (C-3), 83.2 (C-4), 93.9 (C-1), 101.3 (*C*HPh), 123.2 (Phthaloyl), 126.1, 127.3, 128.0–129.0, 133.8, 138.0 (2 × Ph) ppm; $[\alpha]_D = +28.0°cm^3\ g^{-1}\ dm^{-1}$ ($c = 1.0$, $CHCl_3$).

tert-Butyldimethylsilyl 3,6-di-O-benzyl-2-deoxy-2-phthalimido-β-D-glucopyranoside (**4**, $C_{34}H_{41}NO_7Si$)

To a stirred solution of 6.10 g **3** (10.1 mmol) in 48.8 cm^3 anhydrous CH_2Cl_2 8.00 cm^3 triethylsilane (TES, 50.1 mmol) and 3.86 cm^3 trifluoroacetic acid (50.1 mmol) were added at 0 °C. After stirring at room temperature for 5 h, the reaction mixture was worked up to give an oily residue. The residue was purified by flash column chromatography using a solvent mixture of EtOAc/toluene (1:7, v/v) to give 4.50 g (74%) **4** as a colorless oil. $R_f = 0.47$ (EtOAc/*n*-hexane, 1:2, v/v); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = -0.11$, 0.03 (s, 6H, 2 × Si*Me*), 0.65 (s, 9H, *t*-Bu), 3.04 (br s, 1H, 4-O*H*), 3.65 (ddd, 1H, $J_{4,5} = 9.6$ Hz, $J_{5,6a}$

= 5.0 Hz, $J_{5,\ 6b}$ = 4.6 Hz, H-5), 3.78 (dd, 1H, $J_{5,\ 6b}$ = 4.6 Hz, $J_{6a,\ 6b}$ = 10.1 Hz, H-6b), 3.82 (dd, 1H, $J_{5,\ 6a}$ = 5.0 Hz, $J_{6a,\ 6b}$ = 10.1 Hz, H-6a), 3.83 (dd, 1H, $J_{3,\ 4}$ = 8.3 Hz, $J_{4,\ 5}$ = 9.6 Hz, H-4), 4.12 (dd, 1H, $J_{1,\ 2}$ = 8.3 Hz, $J_{2,\ 3}$ = 11.0 Hz, H-2), 4.28 (dd, 1H, $J_{2,\ 3}$ = 11.0 Hz, $J_{3,\ 4}$ = 8.3 Hz, H-3), 4.54–4.76 (m, 2H, CH_2Ph), 5.36 (d, 1H, $J_{1,\ 2}$ = 8.3 Hz, H-1), 7.67–7.80 (m, 4H, Phthaloyl) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = −5.6, −4.3 (2 × Si*Me*), 17.4 (Cq), 25.2 (*t*-Bu), 57.5 (C-2), 70.8 (C-6), 73.7 (2 × *C*H_2Ph), 74.1 (C-5), 74.2 (C-4), 78.4 (C-3), 93.3 (C-1), 123.0–123.2 (Phthaloyl), 127.3, 127.6–128.2, 128.4, 129.0, 131.6, 133.7, 137.7, 138.2 (2 × Ph) ppm; $[\alpha]_D$ = +21.0°cm^3 g^{-1} dm^{-1} (*c* = 1.0, $CHCl_3$).

tert-Butyldimethylsilyl 4-O-(4-O-acetyl-2-azido-3,6-di-O-benzyl-2-deoxy-β-D-glucopyranosyl)-3,6-di-O-benzyl-2-deoxy-2-phthalimido-β-D-glucopyranoside
(**6**, $C_{56}H_{64}N_4O_{12}Si$)
To a stirred solution of 3.4 g trichloroacetoimidoyl 4-*O*-acetyl-2-azido-3,6-di-*O*-benzyl-2-deoxy-α/β-D-glucopyranoside (**5**, 6.0 mmol) [16–18] and 3.6 g **4** (6.0 mmol) in 40 cm^3 anhydrous CH_2Cl_2 22 mm^3 TMSOTf (120 µmol) were added dropwise at −20 °C. After stirring for 1 h, the reaction mixture was neutralized with triethylamine and worked up to afford a yellow oily residue. The residue was purified by flash column chromatography using a solvent mixture of EtOAc/toluene (1:15, v/v) to give a colorless oil that was crystallized from EtOH to obtain 1.56 g (26%) colorless crystals of **6**. R_f = 0.52 (EtOAc/*n*-hexane, 1:2, v/v); ^{1}H NMR (500 MHz, $CDCl_3$): δ = −0.10, 0.04 (s, 6H, 2 × Si*Me*), 0.67 (s, 9H, *t*-Bu), 1.83 (s, 3H, CH_3CO), 3.31 (t, 1H, $J_{2',\ 3'}$ = 9.6 Hz, $J_{3',\ 4'}$ = 9.6 Hz, H-3′), 3.35–3.39 (m, 2H, H-5′, H-6′b), 3.43 (dd, 1H, $J_{1',\ 2'}$ = 8.3 Hz, $J_{2',\ 3'}$ = 9.6 Hz, H-2′), 3.47–3.50 (m, 1H, H-6′a), 3.66 (ddd, 1H, $J_{4,\ 5}$ = 9.7 Hz, $J_{5,\ 6a}$ = 3.3 Hz, $J_{5,\ 6b}$ = 1.2 Hz, H-5), 3.79 (dd, 1H, $J_{5,\ 6b}$ = 1.2 Hz, $J_{6a,\ 6b}$ = 11.0 Hz, H-6b), 3.98 (dd, 1H, $J_{5,\ 6a}$ = 3.3 Hz, $J_{6a,\ 6b}$ = 11.0 Hz, H-6a), 4.15 (dd, 1H, $J_{1,\ 2}$ = 8.1 Hz, $J_{2,\ 3}$ = 10.9 Hz, H-2), 4.16 (dd, 1H, $J_{3,\ 4}$ = 8.7 Hz, $J_{4,\ 5}$ = 9.7 Hz, H-4), 4.32 (dd, 1H, $J_{2,\ 3}$ = 10.9 Hz, $J_{3,\ 4}$ = 8.7 Hz, H-3), 4.35–4.59 (m, 6H, CH_2Ph), 4.48 (d, 1H, $J_{1',\ 2'}$ = 8.3 Hz, H-1′), 4.56–4.81 (m, 2H, CH_2Ph), 4.99 (t, 1H, $J_{3',\ 4'}$ = 9.6 Hz, $J_{4',\ 5'}$ = 9.6 Hz, H-4′), 5.34 (d, 1H, $J_{1,\ 2}$ = 8.1 Hz, H-1), 6.83–7.40 (m, 20H, 4 × Ph), 7.59–7.78 (m, 4H, Phthaloyl) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = −5.6, −4.3 (2 × Si*Me*), 17.5 (Cq), 20.7 (*C*H_3CO), 25.3 (*t*-Bu), 57.8 (C-2), 66.9 (C-2′), 68.1 (C-6), 69.4 (C-6′), 71.1 (C-4′), 73.3 (C-5′), 73.7–74.7, 76.6 (4 × *C*H_2Ph), 74.9 (C-5), 76.7 (C-3), 78.2 (C-4), 80.6 (C-3′), 93.4 (C-1), 101.0 (C-1′), 123.0 (Phthaloyl), 127.4–128.4, 131.5–131.6, 133.6, 137.6–138.6 (4 × Ph), 169.6 (CH$_3$*C*O) ppm; $[\alpha]_D$ = −1.0°cm^3 g^{-1} dm^{-1} (*c* = 1.0, $CHCl_3$).

tert-Butyldimethylsilyl 2-acetamido-4-O-(4-O-acetyl-2-azido-3,6-di-O-benzyl-2-deoxy-β-D-glucopyranosyl)-3,6-di-O-benzyl-2-deoxy-β-D-glucopyranoside
(**7**, $C_{50}H_{64}N_4O_{11}Si$)
To a solution of 100 mg compound **6** (0.10 mmol) in 5 cm^3 *n*-butanol 270 mm^3 ethylenediamine (3.96 mmol) was added dropwise at 0 °C. The reaction mixture was stirred at 90 °C for 8 h, and finally the solvent was removed by co-evaporation with EtOH to afford a yellowish residue. The residue was re-dissolved in 3 cm^3 pyridine and 5 cm^3 acetic anhydride was added at 0 °C. The reaction mixture was stirred overnight at room temperature. After workup a yellowish residue was obtained, which was purified by flash column chromatography using a solvent mixture of EtOAc/*n*-hexane (1:2, v/v) to yield 47.0 mg (53%) **7** as a colorless oil. R_f = 0.61 (EtOAc/*n*-hexane, 1:2, v/v); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.07, 0.11 (s, 6H, 2 × Si*Me*), 0.87 (s, 9H, *t*-Bu), 1.80, 1.82 (s, 6H, 2 × CH_3CO), 3.28 (t, 1H, $J_{2',\ 3'}$ = 9.6 Hz, $J_{3',\ 4'}$ = 9.6 Hz, H-3′), 3.31–3.36 (m, 2H, H-5′, H-6′b), 3.35 (ddd, 1H, $J_{1,\ 2}$ = 7.6 Hz, $J_{2,\ 3}$ = 8.8 Hz, H-2), 3.40 (dd, 1H, $J_{1',\ 2'}$ = 8.3 Hz, $J_{2',\ 3'}$ = 9.6 Hz, H-2′), 3.44 (dd, 1H, $J_{5',\ 6'a}$ = 3.5 Hz, $J_{6'a,\ 6'b}$ = 10.3 Hz, H-6′a), 3.57 (ddd, 1H, $J_{4,\ 5}$ = 8.8 Hz, $J_{5,\ 6a}$ = 3.2 Hz, $J_{5,\ 6b}$ = 2.1 Hz, H-5), 3.79 (dd, 1H, $J_{5,\ 6b}$ = 2.1 Hz, $J_{6a,\ 6b}$ = 11.0 Hz, H-6b), 3.90 (dd, 1H, $J_{5,\ 6a}$ = 3.2 Hz, $J_{6a,\ 6b}$ = 11.0 Hz, H-6a), 4.01 (t, 1H, $J_{2,\ 3}$ = 8.8 Hz, $J_{3,\ 4}$ = 8.8 Hz, H-3), 4.07 (t, 1H, $J_{3,\ 4}$ = 8.8 Hz, $J_{4,\ 5}$ = 8.8 Hz, H-4), 4.29–4.39 (m, 4H, CH_2Ph), 4.45 (d, 1H, $J_{1',\ 2'}$ = 8.3 Hz, H-1′), 4.53–4.87 (m, 4H, CH_2Ph), 4.98 (t, 1H, $J_{3',\ 4'}$ = 9.6 Hz, $J_{4',\ 5'}$ = 9.6 Hz, H-4′), 5.01 (d, 1H, $J_{1,\ 2}$ = 7.6 Hz, H-1), 5.47 (br s, 1H, N*H*), 7.22–7.30 (m, 20H, 4 × Ph) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = −5.3, −4.3 (2 × Si*Me*), 17.9(Cq), 20.7, 23.5 (2 × *C*H$_3$CO), 25.6 (*t*-Bu), 58.5 (C-2), 66.5 (C-2′), 68.4 (C-6), 69.5 (C-6′), 71.1 (C-4′), 73.3 (C-5′), 73.4, 73.5, 73.8, 74.9 (4 × *C*H_2Ph), 74.6 (C-5), 76.8 (C-3), 78.1 (C-4), 80.5 (C-3′), 95.0 (C-1), 100.8 (C-1′), 127.4–128.4, 137.6–139.0 (4 × Ph), 169.6, 169.9 (2 × CH$_3$*C*O) ppm; $[\alpha]_D$ = −14.0°cm^3 g^{-1} dm^{-1} (*c* = 1.0, $CHCl_3$).

tert-Butyldimethylsilyl 2-acetamido-4-O-(2-azido-3,6-di-O-benzyl-2-deoxy-β-D-glucopyranosyl)-3,6-di-O-benzyl-2-deoxy-β-D-glucopyranoside (**8**, $C_{48}H_{62}N_4O_{10}Si$)
To a solution of 240 mg **7** (0.26 mmol) in 3 cm^3 methanol 15.0 mm^3 sodium methoxide solution in methanol (28%, 0.27 mmol) was added dropwise at 0 °C. The reaction mixture was stirred at room temperature for 9 h and afterwards was neutralized with DOWEX 50W-X8 (H^+) resin. The resin was filtered off; the filtrate was concentrated in vacuo and purified by flash column chromatography using a solvent mixture of EtOAc/*n*-hexane (1:2, v/v) to yield 182 mg (78%) **8** as a colorless oil. R_f = 0.57 (EtOAc/*n*-hexane, 1:2, v/v); ^{1}H NMR

(500 MHz, $CDCl_3$): $\delta = 0.07$, 0.11 (s, 6H, 2 × Si*Me*), 0.87 (s, 9H, *t*-Bu), 1.80 (s, 3H, C*H*$_3$CO), 2.97 (d, 1H, $J_{4',\ OH} = 1.9$ Hz, 4-O*H*), 3.18 (t, 1H, $J_{2',\ 3'} = 9.7$ Hz, $J_{3',\ 4'} = 9.7$ Hz, H-3′), 3.21 (ddd, 1H, $J_{4',\ 5'} = 9.7$ Hz, $J_{5',\ 6'a} = 5.1$ Hz, $J_{5',\ 6'b} = 5.5$ Hz, H-5′), 3.31 (dd, 1H, $J_{1',\ 2'} = 8.3$ Hz, $J_{2',\ 3'} = 9.7$ Hz, H-2′), 3.36 (ddd, 1H, $J_{1,\ 2} = 7.4$ Hz, $J_{2,\ 3} = 9.0$ Hz, $J_{2,\ NH} = 7.8$ Hz, H-2), 3.50 (dd, 1H, $J_{5',\ 6'b} = 5.5$ Hz, $J_{6'a,\ 6'b} = 10.1$ Hz, H-6′b), 3.56 (ddd, 1H, $J_{4,\ 5} = 9.0$ Hz, $J_{5,\ 6a} = 3.7$ Hz, $J_{5,\ 6b} = 2.3$ Hz, H-5), 3.59 (dd, 1H, $J_{5',\ 6'a} = 5.1$ Hz, $J_{6'a,\ 6'b} = 10.1$ Hz, H-6′a), 3.64 (t, 1H, $J_{3',\ 4'} = 9.7$ Hz, $J_{4',\ 5'} = 9.7$ Hz, H-4′), 3.76 (dd, 1H, $J_{5,\ 6b} = 2.3$ Hz, $J_{6a,\ 6b} = 11.0$ Hz, H-6b), 3.89 (dd, 1H, $J_{5,\ 6a} = 3.7$ Hz, $J_{6a,\ 6b} = 11.0$ Hz, H-6a), 3.97 (t, 1H, $J_{2,\ 3} = 9.0$ Hz, $J_{3,\ 4} = 9.0$ Hz, H-3), 4.03 (t, 1H, $J_{3,\ 4} = 9.0$ Hz, $J_{4,\ 5} = 9.0$ Hz, H-4), 4.40 (d, 1H, $J_{1',\ 2'} = 8.3$ Hz, H-1′), 4.42–4.99 (m, 8H, C*H*$_2$Ph), 4.99 (d, 1H, $J_{1,\ 2} = 7.4$ Hz, H-1), 5.45 (d, 1H, $J_{2,\ NH} = 7.8$ Hz, N*H*), 7.21–7.40 (m, 20H, 4 × Ph) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = -5.3$, −4.3 (2 × Si*Me*), 17.9 (*C*H$_3$CO), 25.6 (*t*-Bu), 58.3 (C-2), 66.2 (C-2′), 68.5 (C-6), 70.7 (C-6′), 73.1 (C-4′), 73.2 (C-5′), 73.2–73.6 (4 × *C*H$_2$Ph), 74.6 (C-5), 77.3 (C-4), 78.1 (C-3), 82.6 (C-3′), 95.0 (C-1), 100.8 (C-1′), 127.3–128.5 (4 × Ph), 169.2 (CH$_3$*C*O) ppm; $[\alpha]_D = -13.0°\text{cm}^3\ \text{g}^{-1}\ \text{dm}^{-1}$ ($c = 1.0$, $CHCl_3$).

2-Acetamido-4-O-(2-azido-3,6-di-O-benzyl-2-deoxy-β-D-glucopyranosyl)-3,6-di-O-benzyl-2-deoxy-β-D-glucopyranose (**9**, $C_{42}H_{48}N_4O_{10}$)

To a stirred solution of 110 mg **8** (0.12 mmol) in 1 cm^3 anhydrous THF 3.70 mm^3 acetic acid (61.6 μmol) and 180 mm^3 tetra-*n*-butylammonium fluoride solution (TBAF, 1.0 M in THF, 0.18 mmol) were added at 0 °C. After stirring at room temperature for 24 h, another portion of 180 mm^3 TBAF solution (0.18 mmol) was added, then the reaction mixture was heated to 50 °C, and stirring was continued for 10 h. The reaction mixture was worked up to give a colorless residue, which was purified by flash column chromatography using a solvent mixture of EtOAc/*n*-hexane (1:1, v/v) to give a colorless oil that was crystallized from EtOH to yield 76.0 mg (82%) colorless crystals of **9**. $R_f = 0.21$ (EtOAc/toluene, 2:1, v/v); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 1.78$ (s, 3H, C*H*$_3$CO), 3.01 (d, 1H, $J_{4',\ OH} = 2.3$ Hz, 4-O*H*), 3.12 (dd, 1H, $J_{2',\ 3'} = 10.1$ Hz, $J_{3',\ 4'} = 9.2$ Hz, H-3′), 3.30 (dd, 1H, $J_{1',\ 2'} = 8.2$ Hz, $J_{2',\ 3'} = 10.1$ Hz, H-2′), 3.47 (dd, 1H, $J_{5',\ 6'b} = 6.0$ Hz, $J_{6'a,\ 6'b} = 10.1$ Hz, H-6′b), 3.54 (dd, 1H, $J_{5',\ 6'a} = 4.6$ Hz, $J_{6'a,\ 6'b} = 10.1$ Hz, H-6′a), 3.62 (t, 1H, $J_{3',\ 4'} = 9.2$ Hz, $J_{4',\ 5'} = 9.2$ Hz, H-4′), 3.62 (ddd, 1H, $J_{4',\ 5'} = 9.2$ Hz, $J_{5',\ 6'a} = 4.6$ Hz, $J_{5',\ 6'b} = 6.0$ Hz, H-5′), 3.69 (dd, 1H, $J_{5,\ 6b} = 2.3$ Hz, $J_{6a,\ 6b} = 11.0$ Hz, H-6b), 3.70 (dd, 1H, $J_{2,\ 3} = 8.3$ Hz, $J_{3,\ 4} = 9.4$ Hz, H-3), 3.90 (dd, 1H, $J_{5,\ 6a} = 3.7$ Hz, $J_{6a,\ 6b} = 11.0$ Hz, H-6a), 3.99 (t, 1H, $J_{3,\ 4} = 9.4$ Hz, H-4), 4.10 (d, 1H, $J_{1,\ OH} = 3.2$ Hz, 1-O*H*), 4.03–4.07 (m, 2H, H-2, H-5), 4.24 (d, 1H, $J_{1',\ 2'} = 8.2$ Hz, H-1′), 4.40–4.86 (m, 8H, C*H*$_2$Ph), 5.08 (m, 1H, H-1α) 5.22 (t, 1H, $J_{1,\ 2} = 7.4$ Hz, H-1*β*), 5.45 (d, 1H, $J_{2,\ NH} = 8.7$ Hz, N*H*), 7.22–7.42 (m, 20H, 4 × Ph) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 23.2$ (*C*H$_3$CO), 52.9 (C-2), 66.1 (C-2′), 68.2 (C-6), 70.3 (C-5), 70.8 (C-6′), 73.8 (C-4′), 72.9 (C-5′), 73.2–73.6 (4 × *C*H$_2$Ph), 76.9 (C-4), 77.2 (C-3), 82.6 (C-3′), 91.6 (C-1), 101.0 (C-1′), 127.3–128.5 (4 × Ph), 170.4 (CH$_3$*C*O) ppm; $[\alpha]_D = +16.0°\text{cm}^3\ \text{g}^{-1}\ \text{dm}^{-1}$ ($c = 1.0$, $CHCl_3$).

2-Acetamido-4-O-(2-amino-2-deoxy-β-D-glucopyranosyl)-2-deoxy-β-D-glucopyranose (**10**, $C_{14}H_{26}N_2O_{10}$)

Compound **9** (289 mg, 0.38 mmol) was dissolved in 15 cm^3 of a solvent mixture (THF/EtOH/H_2O = 1:1:0.5) containing 145 mg 10% palladium on carbon, and the resulting mixture was stirred under hydrogen for 24 h at 25 °C. The catalyst was removed by filtration, and the filtrate was evaporated to dryness. The residue was purified by flash column chromatography using a solvent mixture of MeOH/CH_2Cl_2/H_2O (6:4:1, v/v/v) to give 104 mg (72%) **10** as a colorless oil. $R_f = 0.40$ (MeOH/CH_2Cl_2/H_2O, 6:4:1, v/v/v); ^{13}C NMR (125 MHz, CD_3OD): $\delta = 22.6$ (*C*H$_3$CO), 55.6 (C-2), 58.5 (C-2′), 62.1 (C-6′), 62.5 (C-6), 70.8 (C-5), 71.5 (C-3), 71.5 (C-4′), 77.6 (C-3′), 78.4 (C-5′), 81.2 (C-4), 92.2 (C-1), 104.4 (C-1′), 173.5 (CH$_3$*C*O) ppm; $[\alpha]_D = -13.0°\text{cm}^3\ \text{g}^{-1}\ \text{dm}^{-1}$ ($c = 1.0$, MeOH).

Acknowledgments This research was conducted with the support of a Grant-in-Aid for Scientific Research (18658133) from the Japan Society for the Promotion of Science (JSPS).

References

1. Waldmann TA (1991) Science 252:1657
2. Vaorumb KJ, Anthonsen MA, Grasdalen H, Smidsrod O (1991) Carbohydr Res 217(1):19
3. Heidelas JE, Lees WJ, Pale P, Whitesides GM (1992) J Org Chem 57(1):146
4. Banoub J, Boullanger P, Lafont D (1992) Chem Rev 92:1167
5. Macmillan D, Daines AM, Bayrhuber M, Flitsch SL (2002) Org Lett 4(9):1467
6. Greene TW, Wuts PGM (1991) Protective groups in organic synthesis, 2nd edn. Wiley, New York, pp 309–405, 437–440
7. Bamford MJ, Pichel JC, Husman W, Potel B, Storer R, Wier NG (1995) J Chem Soc Perkin Trans I 9:1181
8. Figueroa-Perez S, Verez-Bencomo V (1998) Tetrahedron Lett 39(50):9143
9. Schmidt RR (1998) Pure Appl Chem 70(2):397
10. Schmidt RR, Kinzy W (1994) Adv Carbohydr Chem Biochem 50:21
11. Belen Cid M, Fransisco A, Marint-Lomas M (2005) Chem Eur J 11(3):928
12. Ito H, Ishida H, Waki H, Ando S, Kiso M (2000) Glycoconj J 16(10):585
13. Chung R, Moquist P, Finney N (2004) Carbohydr Res 339(8):1531

14. Yang G, Henning L, Findeisen M, Oehme R, Giesa S, Welzel P (2004) Helv Chim Acta 87(7):1794
15. Demchenko AV, Boons GJ (2001) J Org Chem 66:2547
16. Jacquine JC (1990) Carbohydr Res 199(2):153
17. Martin-Lomas M, Khiar N, Gracia S, Koessler JL, Nieto PM, Rademacher TW (2000) Chem Eur J 6(19):3608
18. Fraser-Reid B, Anikumar G, Nair LG, Olsson LM, Mercedes G, Daniel J (2000) Isr J Chem 40(3–4):252