

An Expeditious Route to *N*-Acetyl-D-galactosamine from *N*-Acetyl-D-glucosamine Based on the Selective Protection of Hydroxy Groups

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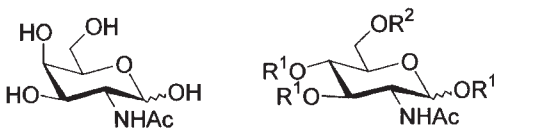
GalNAc (**1**) was straightforwardly prepared from GlcNAc (**2a**) in six steps. Selective protection of the hydroxy groups on the C-1, C-3, and C-6 positions at the same time was performed by the treatment of TBDPS chloride (5.5 eq.) in DMF in 70% yield. The nucleophilic attack with CsOAc or KOBz on the chloromethylsulfonyloxy group at C-4 worked well (69–77% yield), accompanied by an unexpected rearrangement, to give the furanose products (**6**). The deprotection of all silyl and acyl groups under acidic conditions and the re-acetylation provided GalNAc (**1**) in 51% yield.

N-Acetyl-D-galactosamine (GalNAc, **1**, Fig. 1) is a component of mucin-type glycoprotein and of a blood type-determining oligosaccharide that plays important roles in physiological events. There have been many longstanding demands from synthetic carbohydrate chemistry and biochemistry researchers, for its supply in large quantity. Natural resources, however, are rather limited, the only main source being chondroitin sulfates[1] from the cartilage of shark fins. In turn, chemical synthesis from a protected form of galactal has been developed via azidonitration, sulfamidoglycosylation and related methods.[2] Although in its biosynthesis, the epimerization at the 4-position occurs at the step of UDP-*N*-acetyl-D-glucosamine, the chemical synthesis of GalNAc from GlcNAc incurs considerable difficulties. Classical approaches[3] have suffered from the multistep protection to provide the precursors whose hydroxy groups are liberated at the proper positions. Crout and co-workers reported an enzyme-catalyzed regioselective hydrolysis of pentaacetates toward a short-step synthesis;[4] however, the availability of that specific hydrolase is limited. Here we describe a short and direct approach by means of a one-step selective introduction of the three protective groups, liberating only one hydroxy group at the C-4 position, as the key-step.

Our first attempt at the selective triphenylmethylation (tritylation) of the less hindered hydroxy groups of GlcNAc (**2a**, Fig. 1) by way of **2b** only resulted in a complex mixture of partially protected derivatives. Treatment with *t*-butyldimethylsilyl (TBDMS) chloride gave products on which three TBDMS groups were introduced; however, those products were an anomeric mixture with one free hydroxy group at the C-3 and C-4 positions and were not separable on chromatography. In contrast, the increased steric hindrance of *t*-butyldiphenylsilyl (TBDPS)[5] over that of TBDMS was surprisingly effective. The treatment with TBDPS chloride in DMF (room temperature, 47 h) provided two products. These were tri-TBDPS ethers with the desired C-4 free hydroxy group (**4a**, Fig. 2, 70%) as the major product together with the regioisomeric C-3 free hydroxy form (**3a**, 24%), obtained in an easily separable fashion ($\Delta R_f/SiO_2 = 0.33$, hexane/EtOAc = 2/1) over conventional silica-gel column chromatography. The position of free hydroxy groups were confirmed after acetylation judged from the downfield-shifted proton signals [**3b**: $\delta = 4.73$ ($J_{2,3} = 10.3$ Hz, $J_{3,4} = 7.6$ Hz, H3); **4b**: 5.03 ($J_{3,4} = 9.3$ Hz, $J_{4,5} = 9.3$ Hz, H4)].

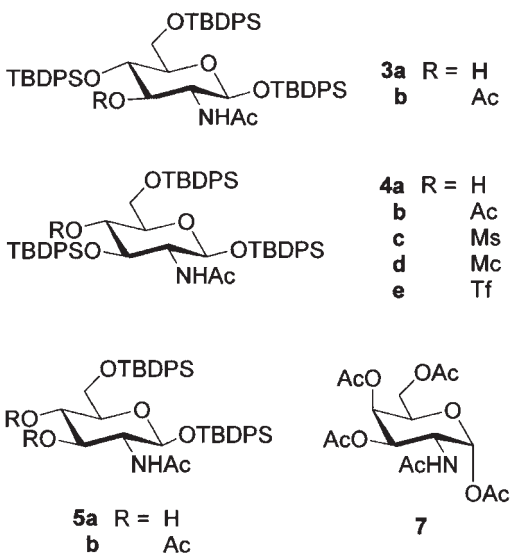
We became interested in the reason of selective formation of **3a** and **4a** when the reaction was quenched at the initial stage, only 1 h after the commencement. The monoprotected form **2c** (Fig. 1) was isolated only in a low (11%) yield. In turn, the ac-



1 (GalNAc)

2a	R^1 = H	R^2 = H	(GlcNAc)
b	H	trityl	
c	H	TBDPS	
d	Ac	TBDPS	

Fig. 1.



3a R = H
b Ac

4a R = H
b Ac
c Ms
d Mc
e Tf

5a R = H
b Ac

7

Fig. 2.

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cumulation of the bis-silylated intermediate (**5a**, Fig. 2, 53%) was observed. In this case, the isolated yields of **4a** and **3a** were 11 and 2%, respectively. The structure of **5a** was confirmed after the derivation to **5b** by ^{1}H NMR [$\delta = 4.89$ ($J_{2,3} = 9.7$ Hz, $J_{3,4} = 9.8$ Hz, H3) and 5.22 ($J_{4,5} = 9.6$ Hz, H4)]. The preferential reaction at the sterically less hindered β-anomer at the C-1 position of **2c** occurred, contrary to the oxygen anomeric effect. As the major product in the initial stage was **5a**, there was no large difference between the rates of the silylation on the primary hydroxy group at C-6 and on the secondary hydroxy group at C-1.

The reason for the predominant silylation of the C-3 position (**4a**) was further examined. When the isolated **3a** and **4a** were independently treated under strongly basic conditions[6] in aq. NaOH/EtOH, starting either from **3a** or **4a**, the product became the same equilibrated mixture of **3a** and **4a** in a 3:2 ratio. In contrast, under the reaction conditions of the silylation itself (TBDPSCl/imidazole/DMF), there was negligible migration of the protective group, although such a phenomenon had previously been reported.[5b] We concluded that the predominant formation of **4a** occurred due to the steric hindrance of the C-6 TBDPSoxy group at the stage of 1,6-di-TBDPS ether, although the isomer **3a** is more thermodynamically stable. The reaction proceeded in a kinetic manner, as judged from the comparison of the ratio between **3a** and **4a**, 1:5.5 (1 h) and 1:2.9 (47 h), respectively. Alkaline treatment (aq. NaOH/EtOH) of **3a** enabled the recycling of the undesired isomer to the further production of **4a** (39%) with the recovery of **3a** (59%), in a preparative scale.

The next and the most important task was the inversion of the configuration at C-4. Around it, there is a severe steric hindrance of silyl groups but no apparent neighboring group participation. Preliminary studies on the well-known three candidates revealed that the reactivity of the mesylate (**4c**) was very low. At elevated temperature, there was further decomposition of the product. The triflate (**4e**), expected to show the highest reactivity and on whose structurally similar substrates so far the substitution reaction had been successful,[4,7] however, was too unstable for this attempted conversion, even at the stage of formation and purification. In contrast, the reaction of chloromethanesulfonate, which was developed by Shimizu and coworkers,[8] worked well to give the desired product. We then elaborated the reaction conditions for the efficient introduction of the chloromethylsulfonyl group. As the initial attempts on the use of pyridine as the base only resulted in the recovery of unreacted starting material, we realized the importance of the efficient generation of sulfene,[9] a highly active species. Indeed, under the conditions of the use of chloromethanesulfonyl chloride (McCl, 2 eq.) and triethylamine (Et_3N, 6 eq.) at room temperature, the reaction proceeded smoothly to give the desired product in 72% yield, together with recovery of the starting material (28%). Any change in the reaction temperature, the solvent or the ratio of McCl/Et_3N resulted only in an increase of the unreacted starting material. The chloromethanesulfonate (**4d**) was then treated with CsOAc (3 eq.) with 18-crown-6 in toluene.[7b] The addition of the crown ether ensured the homogeneity of the reaction mixture to facilitate the inversion reaction. The highest yield (69%) of the resulting acetate (**6a**) was recorded at reflux temperature.

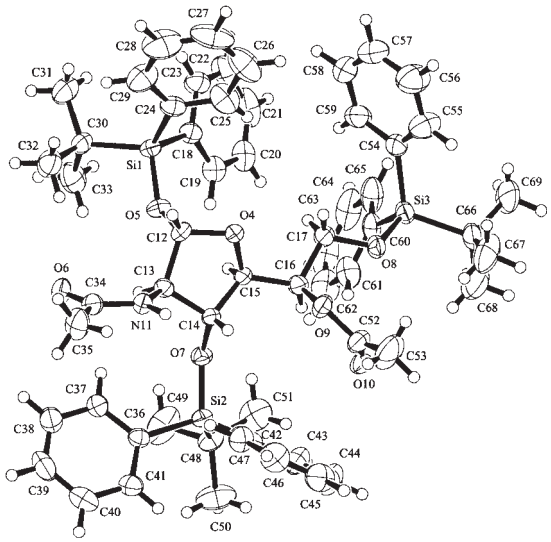
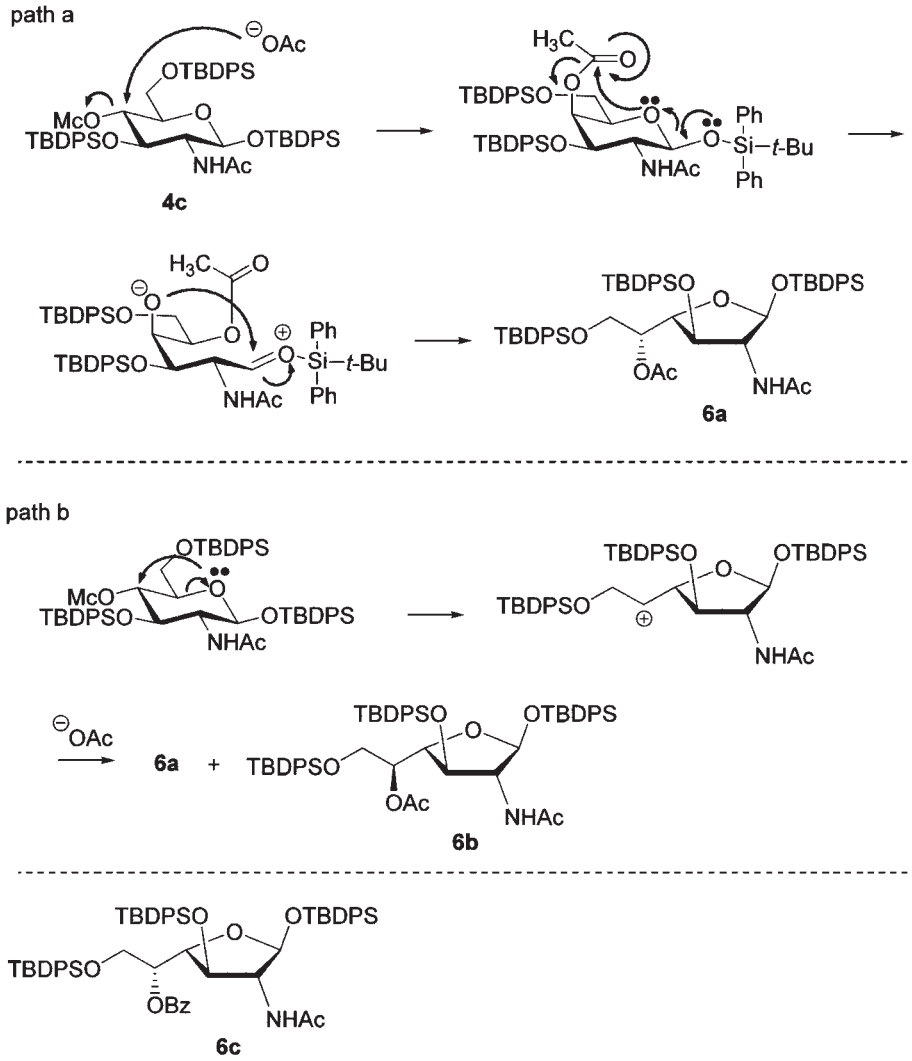


Fig. 3.

Based on its ^{1}H NMR spectrum, the abnormal vicinal coupling constants ($J_{1,2} = J_{2,3} = 0$ Hz) did not indicate the typical $^4C_1$ pyranose chair conformation. First, we suspected that the product occupied the boat or some unknown conformation of the pyranose, but the downfield-shifted signal of H-5 ($\delta = 4.69$) was inconsistent with the proposed structures. Finally, the X-ray crystallographic analysis of the recrystallized sample clarified the unexpected furanose structure of **6a**, as shown in Fig. 3. The identity between the crystalline sample (recovery: 69%) and the mother liquor was confirmed.

A plausible mechanism of the rearrangement is shown in Scheme 1. The inverting displacement of the chloromethylsulfonyloxy group of **4c** with acetate is instantly followed by the neighboring group participation of a ring oxygen atom (path a), assisted by the electron-donating property of the 1-siloxy substituent, to provide a stabilized oxonium intermediate. The all *trans*-relationship of the substituents, which avoids the steric repulsion, can explain the formation of the furanose structure of **6a**, as had so far been experienced in the preferential furanose formation of a galactosaminide.[10] Neither of the reactions proceeded at low temperature, and we could not detect any trace of the proposed intermediate. The possibility of direct attack of the pyranose ring oxygen atom (path b) into a carbenium ion species is negligible, due to the well-defined configuration at C-5 with perfect retention of the stereochemistry without any trace of the isomer **6b**. The change of the nucleophile to the benzoate anion,[3a,11] could not prevent the rearrangement to give **6c**, although the low migratory nature of benzoate ester had so far been reported.[12] The higher yield (77%) and the easier handling of the reagent were beneficial effects of the non-hygroscopic property of KOBz, instead of CsOAc.

Due to the rather strange furanose structure in **6a**, the deprotection of the silyl protective group as well as the acyl group was somewhat troublesome. Initial attempts at the deprotection of **6a** by either TBAF (tetrabutylammonium fluoride) or HF/pyridine treatment, expecting the simultaneous deacylation under basic conditions, resulted only in a complex mixture. This situation was effectively solved by a stepwise transformation and purification procedure, including hydrolysis under a strong-



Scheme 1.

ly acidic condition (6 M HCl) to give the fully deprotected galactosamine hydrochloride, and the subsequent acetylation, to give **7**[13] (Fig. 2) in 61% yield; mp 170–173 °C (lit.[4] 169–171 °C); $[\alpha]_D$ +96.3° ($CHCl_3$) [lit.[4] $[\alpha]_D$ +97° ($CHCl_3$)]. Finally, alkaline hydrolysis of the *O*-acetyl protective groups in **7** was successful and the pure GalNAc (**1**)[1c,4] was obtained in 84% yield; mp 154.5–155.5 °C (lit.[4] 156–158 °C); $[\alpha]_D$ +86.1° (H_2O, equilibrated for 3 h) [lit.[1c] $[\alpha]_D$ +86.1° (H_2O, equilibrated)]. When the same procedure was attempted to deprotect the benzoate **6c**, however, the reaction resulted in a complex mixture.

In conclusion, GalNAc (**1**) was straightforwardly prepared from GlcNAc (**2**) in six steps, based on the selective protection with the TBDPS groups and the nucleophilic inversion at C-4 on the chloromethylsulfonyloxy group to provide a furanose key intermediate (**6**), by a rearrangement of the pyranose precursor (**4c**). The five steps to the pentaacetate (**7**) in the present work were more than three steps, demonstrated in the well-known azidonitration approach[2a] from tri-*O*-acetyl-D-galactal, which is available from D-galactose in three steps.[14] However, the inexpensiveness of the starting material (GlcNAc), an increased total yield (18% from GlcNAc/11% from galactose), and the variety of the regioselectively protected pure intermediates (**3**–**5**) are attractive.

Experimental

Analytical and preparative thin-layer chromatography (TLC) procedures were developed on E. Merck Silica-Gel 60 F_{256} plates (No. 5715; 0.25 mm and 5744; 0.50 mm), respectively. Column chromatography was performed on Kanto Chemical Co., Inc. Silica-Gel 60 (spherical; 100–210 μm, 37558-79). NMR spectra were measured on a JEOL EX-270, GX-400 spectrometer (^1H at 270 and 400 MHz, and ^{13}C at 100 MHz). ^1H chemical shifts are referenced with $CHCl_3$ at 7.26 ppm or HDO at 4.80 ppm and ^{13}C chemical shifts with $CDCl_3$ at 77.0 ppm. IR spectra were determined on a Jasco FT/IR-410 spectrometer. Optical rotations were measured on a Jasco DIP 360 polarimeter. Melting points were measured by Yanaco MP-S3.

2-Acetamido-1,4,6-tris-*O*-*t*-butyldiphenylsilyl-2-deoxy-β-D-glucopyranose (3a) and 2-Acetamido-1,3,6-tris-*O*-*t*-butyldiphenylsilyl-2-deoxy-β-D-glucopyranose (4a). GlcNAc **2** (200.7 mg, 0.91 mmol) was dissolved in DMF (2.2 mL) under an argon atmosphere. Imidazole (307.0 mg, 4.96 mmol) and *t*-butyldiphenylsilyl chloride (1.16 mL, 4.97 mmol, 5.5 eq.) were added to the

solution with stirring. The reaction was monitored by silica-gel TLC (hexane–ethyl acetate, 2:1). After stirring for 47 h at room temperature, the mixture was quenched by the addition of water, and the aqueous layer was extracted with a mixture of hexane–ethyl acetate (1:1). The organic layers were combined, washed with a saturated aqueous $NaHCO_3$ solution, water and brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by silica-gel column chromatography (35 g). Elution with hexane–ethyl acetate (5:1) afforded **3a** (207.9 mg, 24%) and **4a** (596.5 mg, 70%). **3a**: $R_f = 0.18$ (hexane–ethyl acetate, 2:1); mp 217–219 °C; $[\alpha]_D^{20}$ +9.2° (*c* 1.00, $CHCl_3$); IR 3579 (OH), 3288 (NH), 1651 cm^{-1} (C=O); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.83 (9H, s, *t*-Bu), 0.97 (9H, s, *t*-Bu), 1.07 (9H, s, *t*-Bu), 1.63 (3H, s, Ac), 3.34–3.62 (6H, m, H2-6), 3.85 (1H, d, $J_{4,OH} = 10.7$ Hz, OH), 4.71 (1H, d, $J_{1,2} = 7.3$ Hz, H1), 5.09 (1H, d, $J_{2,NH} = 6.9$ Hz, NH), 7.16–7.70 (30H, m, Ph); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 19.2, 19.6, 23.3, 26.8, 26.9, 27.1, 58.5, 64.2, 73.5, 75.7, 77.8, 95.3, 127.5, 127.7, 127.8, 129.3, 129.4, 129.5, 129.9, 132.5, 132.8, 133.1, 133.3, 133.4, 133.5, 135.6, 135.7, 135.8, 170.9. Found: C, 71.66; H, 7.39; N, 1.45%. Calcd for $C_{56}H_{69}NO_6Si_3$: C, 71.83; H, 7.43; N, 1.50%. The structure was further confirmed by the derivatization to the corresponding acetate **3b**. ^{1}H NMR ($CDCl_3$, 270 MHz) δ 0.69 (9H, s, *t*-Bu), 0.98 (9H, s, *t*-Bu), 1.05 (9H, s, *t*-Bu), 1.13 (3H, s, Ac), 1.56 (3H, s, Ac), 3.43 (1H, ddd, $J_{4,5} = 7.8$ Hz, $J_{5,6a} = 7.8$ Hz, $J_{5,6b} = 2.1$ Hz, H5), 3.71 (2H, m, H4, H6a), 3.98 (2H, m, H2, H6b), 4.54 (1H, d, $J_{1,2} = 8.1$ Hz, H1), 4.73 (1H, dd, $J_{2,3} = 10.3$ Hz, $J_{3,4} = 7.6$ Hz, H3), 4.99 (1H, d, $J_{2,NH} = 9.9$ Hz, NH), 7.20–7.43 (20H, m, Ph), 7.52–7.68 (10H, m, Ph). **4a**: $R_f = 0.51$ (hexane–ethyl acetate, 2:1); mp 73.5–75.5 °C; $[\alpha]_D^{22}$ −9.1° (*c* 1.00, $CHCl_3$); IR 3571 (OH), 1664 cm^{-1} (C=O); ^{1}H NMR ($CDCl_3$, 270 MHz) δ 1.02 (9H, s, *t*-Bu), 1.03 (9H, s, *t*-Bu), 1.05 (9H, s, *t*-Bu), 1.49 (3H, s, Ac), 2.83 (1H, ddd, $J_{4,5} = 9.2$ Hz, $J_{5,6a} = 3.6$ Hz, $J_{5,6b} = 3.1$ Hz, H5), 3.51 (1H, dd, $J_{2,3} = 10.1$ Hz, $J_{3,4} = 8.7$ Hz, H3), 3.61 (1H, dd, $J_{6a,6b} = 10.7$ Hz, H6a), 3.68 (1H, dd, H6b), 3.89 (1H, dd, H4), 4.03 (1H, ddd, $J_{1,2} = 8.1$ Hz, $J_{2,NH} = 9.4$ Hz, H2), 4.36 (1H, d, H1), 4.65 (1H, d, NH), 7.16–7.43 (15H, m, Ph), 7.55–7.71 (15H, m, Ph); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 19.1, 19.3, 19.7, 23.5, 26.8, 26.9, 58.2, 63.2, 71.8, 74.7, 76.8, 96.1, 127.2, 127.3, 127.6, 127.6, 127.7, 127.9, 129.4, 129.5, 129.7, 129.9, 132.7, 132.9, 133.1, 133.2, 133.3, 133.9, 134.7, 135.4, 135.5, 135.7, 135.8, 135.9, 169.4. Found: C, 71.79; H, 7.43; N, 1.46%. Calcd for $C_{56}H_{69}NO_6Si_3$: C, 71.83; H, 7.43; N, 1.50%. The structure was further confirmed by the derivatization to the corresponding acetate **4b**. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.91 (9H, s, *t*-Bu), 0.99 (9H, s, *t*-Bu), 1.02 (9H, s, *t*-Bu), 1.15 (3H, s, Ac), 1.47 (3H, s, Ac), 3.15 (1H, ddd, $J_{4,5} = 9.3$ Hz, $J_{5,6a} = 2.4$ Hz, $J_{5,6b} = 5.6$ Hz, H5), 3.45 (1H, dd, $J_{6a,6b} = 11.6$ Hz, H6a), 3.55 (1H, dd, H6b) 3.71 (1H, ddd, $J_{1,2} = 8.8$ Hz, $J_{2,NH} = 8.8$ Hz, $J_{2,3} = 9.3$ Hz, H2), 4.05 (1H, dd, $J_{3,4} = 9.3$ Hz, H3), 4.54 (1H, d, H1), 4.66 (1H, d, NH), 5.03 (1H, dd, H4), 7.19–7.72 (30H, m, Ph).

2-Acetamido-1,3,4-tris-*O*-acetyl-6-*O*-*t*-butyldiphenylsilyl-2-deoxy-α-D-glucopyranose (2d). ^{1}H NMR ($CDCl_3$, 270 MHz) δ 1.04 (9H, s, *t*-Bu), 1.92 (3H, s, Ac), 1.95 (3H, s, Ac), 2.06 (3H, s, Ac), 2.16 (3H, s, Ac), 3.69 (2H, m, H6a, H6b), 3.83 (1H, ddd, $J_{4,5} = 9.6$ Hz, $J_{5,6a} = 3.2$ Hz, $J_{5,6b} = 3.2$ Hz, H5), 4.47 (1H, ddd, $J_{1,2} = 3.5$ Hz, $J_{2,NH} = 8.9$ Hz, $J_{2,3} = 9.7$ Hz, H2), 5.21 (1H, dd, $J_{3,4} = 9.9$ Hz, H3), 5.30 (1H, dd, H4), 5.51 (1H, d, NH), 6.23 (1H, d, H1), 7.36–7.66 (10H, m, Ph). The anomeric proton of the minor (3.8:1) of β-isomer appeared at $\delta = 5.65$ ($J_{1,2} = 8.7$ Hz).

2-Acetamido-3,4-di-*O*-acetyl-1,6-di-*O*-*t*-butyldiphenylsilyl-2-deoxy-β-D-glucopyranose (5b). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.03 (9H, s, *t*-Bu), 1.09 (9H, s, *t*-Bu), 1.80 (3H, s, Ac), 1.82 (3H, s, Ac), 2.00 (3H, s, Ac), 3.17 (1H, ddd, $J_{4,5} = 9.6$ Hz, $J_{5,6a} = 2.8$ Hz, $J_{5,6b} = 2.8$ Hz, H5), 3.55 (2H, m, H6a, H6b), 4.24 (1H, ddd, $J_{1,2} = 8.3$ Hz, $J_{2,NH} = 9.8$ Hz, $J_{2,3} = 9.7$ Hz, H2), 4.50 (1H, d, H1), 4.89 (1H, dd, $J_{3,4} = 9.8$ Hz, H3), 5.07 (1H, d, NH), 5.22 (1H, dd, H4), 7.29–7.70 (20H, m, Ph).

2-Acetamido-1,3,6-tris-*O*-*t*-butyldiphenylsilyl-2-deoxy-4-methylsulfonyl-β-D-glucopyranose (4c). The starting material **4a** (50.0 mg, 0.05 mmol) was dissolved in diethyl ether (0.3 mL) under an argon atmosphere. Methanesulfonyl chloride (16.4 μL, 0.21 mmol, 4.2 eq.) and triethylamine (29.8 μL, 0.21 mmol, 4.2 eq.) were added to the solution with stirring at room temperature. The reaction was monitored by silica-gel TLC, developed with hexane–ethyl acetate (2:1). After stirring for 4 h at room temperature, the mixture was quenched by the addition of water, and the aqueous layer was extracted with ethyl acetate. The organic layers were combined, washed with water and brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by silica-gel column chromatography. Elution with hexane–ethyl acetate (8:1) afforded **4c** (46.4 mg, 86% yield). ^{1}H NMR ($CDCl_3$, 270 MHz) δ 0.98 (9H, s, *t*-Bu), 1.02 (9H, s, *t*-Bu), 1.08 (9H, s, *t*-Bu), 1.11 (3H, s, Ac), 2.56 (3H, s, Me), 3.40 (1H, ddd, $J_{4,5} = 6.8$ Hz, $J_{5,6a} = 4.5$ Hz, $J_{5,6b} = 4.4$ Hz, H5), 3.60 (1H, ddd, $J_{1,2} = 8.6$ Hz, $J_{2,NH} = 6.6$ Hz, $J_{2,3} = 6.7$ Hz, H2), 3.81 (1H, dd, $J_{6a,6b} = 11.1$ Hz, H6a), 3.93 (1H, dd, H6b), 4.55 (1H, dd, $J_{3,4} = 6.6$ Hz, H3), 4.69 (1H, d, H1), 4.88 (1H, d, NH), 4.91 (1H, dd, H4), 7.16–7.83 (30H, m, Ph).

2-Acetamido-1,3,6-tris-*O*-*t*-butyldiphenylsilyl-4-chloromethylsulfonyl-2-deoxy-β-D-glucopyranose (4d). In the same manner as described for the methylsulfonylation, **4a** (200.0 mg, 0.21 mmol) was treated with chloromethanesulfonyl chloride (38.1 μL, 0.43 mmol, 2.0 eq.) for 3 h. The work-up and the purification as above afforded **4d** (161.4 mg, 72% yield). $[\alpha]_D^{20}$ −1.1° (*c* 1.00, $CHCl_3$); IR 3442 (NH), 1685 cm^{-1} (C=O); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.98 (9H, s, *t*-Bu), 1.03 (9H, s, *t*-Bu), 1.10 (9H, s, *t*-Bu), 1.11 (3H, s, Ac), 3.42 (1H, ddd, $J_{4,5} = 6.3$ Hz, $J_{5,6a} = 3.9$ Hz, $J_{5,6b} = 4.6$ Hz, H5), 3.65 (1H, ddd, $J_{1,2} = 8.3$ Hz, $J_{2,NH} = 6.3$ Hz, $J_{2,3} = 6.6$ Hz, H2), 3.79 (1H, dd, $J_{6a,6b} = 11.1$ Hz, H6a), 3.96 (1H, d, $J_{ClCH_2} = 12.7$ Hz, ClCHa), 4.00 (1H, dd, H6b), 4.14 (1H, d, ClCHb), 4.55 (1H, dd, $J_{3,4} = 6.5$ Hz, H3), 4.71 (1H, d, H1), 4.90 (1H, d, NH), 5.02 (1H, dd, H4), 7.16–7.85 (30H, m, Ph); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 19.1, 19.2, 19.5, 23.0, 26.6, 26.8, 26.9, 53.8, 58.1, 63.0, 72.9, 74.5, 80.7, 94.5, 127.4, 127.6, 127.7, 127.9, 129.6, 129.7, 129.8, 129.9, 130.0, 132.6, 132.6, 132.7, 132.8, 133.0, 134.2, 135.2, 135.5, 135.6, 135.7, 169.1. Found: C, 65.17; H, 6.76; N, 1.28%. Calcd for $C_{57}H_{70}ClNO_8SSi_3$: C, 65.27; H, 6.73; N, 1.34%.

2-Acetamido-5-*O*-acetyl-1,3,6-tris-*O*-*t*-butyldiphenylsilyl-2-deoxy-β-D-glucofuranose (6a). The chloromethanesulfonate **4d** (457.5 mg, 0.44 mmol) was dissolved in toluene (6.5 mL) under an argon atmosphere. 18-Crown-6 (345.8 mg, 1.31 mmol) and cesium acetate (251.1 mg, 1.31 mmol) were added to the solution with stirring, and the mixture became homogeneous. The reaction was monitored by TLC, developed with hexane–ethyl acetate (2:1). The mixture was stirred for 4 h at 120 °C. After cooling, water was added, and the aqueous layer was extracted with ethyl acetate. The combined organic layer was washed with water and brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by silica-gel column chromatography. Elution with hexane–ethyl acetate (4:1) afforded **6a** (293.0 mg, 69% yield). A small amount was recrystallized from hexane to give an analytical sam-

ple of **6a**. Mp 119.4–120.0 °C; $[\alpha]_D^{22}$ −28.2 (*c* 1.00, $CHCl_3$); IR 3284 (NH), 1747 (C=O), 1651 cm^{-1} (C=O); ^1H NMR ($CDCl_3$, 270 MHz) δ 0.99 (9H, s, *t*-Bu), 1.11 (9H, s, *t*-Bu), 1.12 (9H, s, *t*-Bu), 1.25 (3H, s, Ac), 1.79 (3H, s, Ac), 3.46 (1H, dd, $J_{5,6a} = 6.4$ Hz, $J_{6a,6b} = 10.1$ Hz, H6a), 3.54 (1H, dd, $J_{5,6b} = 6.6$ Hz, H6b), 3.71 (1H, d, $J_{3,4} = 3.5$ Hz, H3), 4.51 (1H, dd, $J_{4,5} = 3.3$ Hz, H4), 4.57 (1H, d, $J_{2,NH} = 9.1$ Hz, H2), 4.69 (1H, ddd, H5), 5.12 (1H, s, H1), 5.23 (1H, d, NH), 7.21–7.46 (15H, m, Ph), 7.57–7.73 (15H, m, Ph); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 19.2, 19.4, 20.8, 23.2, 26.7, 26.9, 27.0, 61.8, 63.5, 72.8, 79.6, 83.4, 102.5, 127.4, 127.5, 127.6, 127.7, 127.8, 129.5, 129.6, 129.7, 129.8, 129.9, 132.7, 132.8, 133.0, 133.1, 134.7, 135.4, 135.5, 135.7, 135.8, 136.2, 168.0, 169.2. Found: C, 71.10; H, 7.24; N, 1.38%. Calcd for $C_{58}H_{71}NO_7Si_3$: C, 71.20; H, 7.31; N, 1.43%.

2-Acetamido-5-*O*-benzoyl-1,3,6-tris-*O*-*t*-butyldiphenylsilyl-2-deoxy-β-D-glucofuranose (6c). In the same manner as described for **6a**, the chloromethanesulfonate **4d** (110.9 mg, 0.11 mmol) was treated with 18-crown-6 (150.7 mg, 0.57 mmol) and potassium benzoate (84.7 mg, 0.53 mmol) in toluene (1.8 mL) for 18 h at room temperature to 120 °C. The work-up and the purification as above afforded **6c** (84.5 mg, 77% yield). $[\alpha]_D^{22}$ −32.1 (*c* 1.00, $CHCl_3$); IR 3429 (NH), 1728 (C=O), 1685 cm^{-1} (C=O); ^1H NMR ($CDCl_3$, 400 MHz) δ 0.95 (9H, s, *t*-Bu), 1.12 (18H, s, *t*-Bu), 1.23 (3H, s, Ac), 3.59 (1H, dd, $J_{5,6a} = 5.9$ Hz, $J_{6a,6b} = 10.4$ Hz, H6a), 3.68 (1H, dd, $J_{5,6b} = 7.1$ Hz, H6b), 3.74 (1H, d, $J = 3.9$ Hz, H3), 4.53 (2H, m, H2, H4), 4.92 (1H, d, NH), 5.09 (1H, ddd, $J_{4,5} = 2.1$ Hz, H5), 5.16 (1H, d, H1), 7.19–7.45 (15H, m, Ph), 7.50–7.82 (15H, m, Ph); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 19.2, 19.4, 22.5, 26.7, 26.9, 27.0, 62.5, 63.5, 73.2, 80.1, 84.0, 102.6, 127.4, 127.5, 127.6, 127.8, 128.4, 129.4, 129.5, 129.6, 129.7, 129.8, 132.7, 132.8, 133.0, 133.1, 133.2, 133.3, 135.4, 135.5, 135.7, 135.8, 135.9, 165.1, 168.1. Found: C, 72.72; H, 7.07; N, 1.35%. Calcd for $C_{63}H_{73}NO_7Si_3$: C, 72.47; H, 7.34; N, 1.30%.

2-Acetamido-1,3,4,6-tetra-*O*-acetyl-2-deoxy-α-D-galactopyranose (7). A mixture of **6a** (122.6 mg, 0.13 mmol) and 6 M HCl (6 mL) was heated under reflux for 24 h. After cooling to room temperature, the mixture was azeotropically concentrated in vacuo with EtOH. The residue was dissolved in pyridine (0.5 mL) and acetic anhydride (0.5 mL) was added. After stirring for 23 h at room temperature, the mixture was quenched by the addition of MeOH. After the mixture was concentrated in vacuo water was added, and the aqueous layer was extracted with ethyl acetate. The combined organic solution was dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by silica-gel column chromatography. Elution with hexane–ethyl acetate (8:1) afforded **7** (29.8 mg, 61% yield). A small amount was solidified upon standing, and the analytical sample was recrystallized from EtOH to give pure **7**. Mp 170–173 °C (lit.[4] 169–171 °C); $[\alpha]_D^{25}$ +96.3° (*c* 1.00, $CHCl_3$) [lit.[4] $[\alpha]_D$ +97° (*c* 1.0, $CHCl_3$)]; IR 3296 (NH), 1749 cm^{-1} (C=O); ^1H NMR ($CDCl_3$, 400 MHz) δ 1.96 (3H, s, Ac), 2.04 (6H, s, Ac), 2.18 (6H, s, Ac), 4.06 (1H, dd, $J_{5,6a} = 6.2$ Hz, $J_{6a,6b} = 11.2$ Hz, H6a), 4.12 (1H, dd, $J_{5,6b} = 6.5$ Hz, H6b), 4.24 (1H, dd, H5), 4.74 (1H, ddd, $J_{1,2} = 3.5$ Hz, $J_{2,NH} = 10.4$ Hz, $J_{2,3} = 11.7$ Hz, H2), 5.23 (1H, dd, $J_{3,4} = 3.4$ Hz, H3), 5.39 (1H, d, NH), 5.43 (1H, d, H4), 6.22 (1H, d, H1); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 20.6, 20.7, 20.9, 23.1, 46.9, 61.2, 66.6, 67.7, 68.4, 91.2, 168.7, 170.0, 170.1, 170.9. Found: C, 49.21; H, 6.09; N, 3.49%. Calcd for $C_{16}H_{23}NO_{10}$: C, 49.36; H, 5.95; N, 3.60%.

2-Acetamido-2-deoxy-D-galactopyranose (1). A mixture of **7** (43.3 mg, 0.11 mmol), 2 M NaOH (1.2 mL), and EtOH (0.3 mL) was stirred at room temperature. After stirring for 1 h, the mixture was quenched by the addition of 1 M HCl and azeotropically concentrated in vacuo with EtOH. The residue was diluted with water (10 mL), and desalted by AC-220-10 on Asahi Chemical Micro Acylyzer S1. At the initial stage, the conductivity was 23 mS and after the desaltation at 4.3 V (0.69 A), it reached 0.1 mS. The mixture was concentrated in vacuo and the residue was purified by preparative TLC. Elution with ethyl acetate–EtOH–water (63:25:12) afforded **1** (20.7 mg, 84% yield) as an oil. This was solidified upon standing, and an analytical sample was recrystallized from EtOH to give pure **1**. Mp 154.5–155.5 °C (lit.[4] 156–158 °C); $[\alpha]_D^{22}$ +86.1° (*c* 1.00, H_2O, equilibrated for 3 h) [lit.[1c] $[\alpha]_D$ +86.1° (*c* 1.0, H_2O, final)]; IR 3332 (OH), 1641 cm^{-1} (C=O); ^1H NMR ($CDCl_3$, 400 MHz) δ 2.05 (3H, s, Ac), 3.66–3.94 (m), 4.00 (1H, d, $J = 2.9$ Hz, H4α), 4.09–4.15 (2H, m, H2α, H5α), 4.64 (1H, d, $J_{1,2} = 8.3$ Hz, H1β), 5.23 (1H, d, $J_{1,2} = 3.4$ Hz, H1α); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 22.7, 23.0, 51.0, 54.4, 61.7, 61.9, 68.1, 68.6, 69.3, 71.2, 71.8, 75.9, 91.7, 96.1, 175.3, 175.5. The NMR spectra were identical with the spectrum of an authentic mixture of the anomers of 2-acetamido-2-deoxy-D-galactopyranose (Wako Pure Chemical Industries, Ltd., 013-12821). Found: C, 43.14; H, 6.85; N, 6.05%. Calcd for $C_8H_{15}NO_6$: C, 43.44; H, 6.83; N, 6.33%.

X-ray Crystal Structure Analysis of 6a. Crystal data: orthorhombic, $P2_12_12_1$, $a = 22.847(4)$, $b = 24.910(3)$, $c = 9.9146(13)$ Å, $V = 5642.5(13)$ Å^3, $Z = 4$, $D_x = 1.152$ g cm^{-3}. A colorless needle crystal grown from hexane was used. The X-ray intensities were measured on a Rigaku AFC-7R four-circle diffractometer with Mo Kα radiation. The positional and anisotropic thermal parameters of non-H atoms were refined, and all the H atoms were positioned geometrically ($R = 0.047$). There is an intermolecular N–H···O hydrogen bond between the acetamido groups, forming one-dimensional molecular chains along the *c* axis. Calculations were performed using the TEXSAN crystallographic software package (Version 1.11) of Molecular Structure Corporation.

Crystallographic data have been deposited at the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK and copies can be obtained on request, free of charge, by quoting the publication citation and the deposition number CCDC-221140.

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References

1 a) P. A. Levene and F. B. La Forge, *J. Biol. Chem.*, **20**, 433 (1915). b) C. S. Hudson and J. K. Dale, *J. Am. Chem. Soc.*, **38**, 1431 (1916). c) S. Roseman and J. Ludowieg, *J. Am. Chem. Soc.*, **76**, 301 (1954). d) S. Suzuki, *J. Biol. Chem.*, **253**, 3580 (1960).

2 a) R. U. Lemieux and R. M. Ratcliffe, *Can. J. Chem.*, **57**, 1244 (1979). b) D. A. Griffith and S. J. Danishefsky, *J. Am. Chem. Soc.*, **112**, 5811 (1990). c) J. Liu and D. Y. Gin, *J. Am. Chem. Soc.*, **124**, 9789 (2002).

3 a) P. H. Gross, F. Du Bois, and R. W. Jeanloz, *Carbohydr. Res.*, **4**, 244 (1967). b) J. Hill and L. Hough, *Carbohydr. Res.*, **8**, 398 (1968). c) Y. Fukuda, H. Sasai, and T. Suami, *Bull. Chem.*

Soc. Jpn., **55**, 1574 (1982). d) R. P. McGeary, K. Wright, and I. Toth, *J. Org. Chem.*, **66**, 5102 (2001).

4 D. Chaplin, D. H. G. Crout, S. Bornemann, D. W. Hutchinson, and R. Khan, *J. Chem. Soc., Perkin Trans. 1*, **1992**, 235.

5 a) Y. Ikeda, K. Furukawa, and H. Yamada, *Carbohydr. Res.*, **337**, 1499 (2002). b) M. S. Arias-Pérez, M. S. López, and M. J. Santos, *J. Chem. Soc., Perkin Trans. 2*, **2002**, 1549.

6 Y. Torisawa, M. Shibasaki, and S. Ikegami, *Chem. Pharm. Bull.*, **31**, 2607 (1983).

7 a) J. Alais and S. David, *Carbohydr. Res.*, **201**, 69 (1990). b) K. Sato, A. Yoshimoto, and Y. Takai, *Bull. Chem. Soc. Jpn.*, **70**, 885 (1997). c) K. Sato, H. Seki, A. Yoshitomo, H. Nanaumi, Y. Takai, and Y. Ishido, *J. Carbohydr. Chem.*, **17**, 703 (1998). d) I. Matsuo, M. Isomura, R. Walton, and K. Ajisaka, *Tetrahedron Lett.*, **37**, 8795 (1996). e) I. Matsuo, M. Isomura, and K. Ajisaka, *J. Carbohydr. Chem.*, **18**, 841 (1999). f) A. Fürstner and I. Konetzki, *Tetrahedron Lett.*, **39**, 5721 (1998). g) L. Cipolla, B. L. Ferla, L. Lay, F. Peri, and F. Nicotra, *Tetrahedron: Asymmetry*, **11**, 295 (2000). h) T. Sawada, S. Fujii, H. Nakano, S. Ohtake, and O. Habuchi, 23rd Japanese Carbohydrate Symposium, PI-27, August 22, Yokohama (2002).

8 T. Shimizu, S. Hiranuma, and T. Nakata, *Tetrahedron Lett.*, **37**, 6145 (1996).

9 S. N. Lyashchuk, Y. G. Skrypnik, and V. P. Besrodnyi, *J. Chem. Soc., Perkin Trans. 2*, **1993**, 1153.

10 R. T. Lee, T. C. Wong, and Y. C. Lee, *J. Carbohydr. Chem.*, **5**, 343 (1986).

11 A. J. H. Houssa, J. Kenyon, and H. Phillips, *J. Chem. Soc.*, **1929**, 1700.

12 S. Akai, T. Naka, Y. Takebe, and Y. Kita, *Chem. Pharm. Bull.*, **48**, 1519 (2000).

13 a) M. Stacey, *J. Chem. Soc.*, **1944**, 272. b) B. Weismann, *J. Org. Chem.*, **31**, 2505 (1966). c) T. C. Wong, R. R. Townsend, and Y. C. Lee, *Carbohydr. Res.*, **170**, 27 (1987). d) M. A. Findeis, *Int. J. Pept. Protein Res.*, **43**, 477 (1994).

14 a) P. A. Levene and R. S. Tipson, *J. Biol. Chem.*, **93**, 631 (1931). b) A. P. Kozikowski and J. Lee, *J. Org. Chem.*, **55**, 863 (1990). c) R. Bukowski, L. M. Morris, R. J. Woods, and T. Weimar, *Eur. J. Org. Chem.*, **2001**, 2697.