Preparation of Novel 1,6-Anhydro-β-lactose Derivatives for the Synthesis of *N*-Acetyllactosamine-Containing Oligosaccharides[1)]

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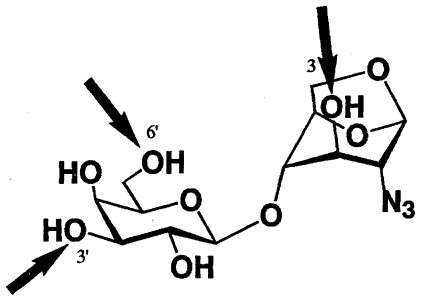
Versatile intermediates for the syntheses of cell-surface oligosaccharides bearing *N*-acetyllactosamine units have been prepared from a readily available 1,6-anhydro-β-lactose as a key starting material. Regioselective chemical manipulations of 1,6-anhydro-β-lactose were carried out in a stepwise procedure and gave fully-protected lactosamine derivatives. It was clearly suggested that modification at C-3′ position of the galactose residue and the following introduction of a sterically hindered leaving group at C-2 position of the reducing glucose remarkably accelerated and facilitated further derivatization of this potential disaccharide material. Selective generation of hydroxyl groups at C-3, C-3′, and/or C-6′ positions proceeded smoothly in mild conditions and afforded a series of fully-functionalized disaccharide-acceptors in high yields.

Recent progress in glycobiology emphasizes the biological importance of oligosaccharides on the cell surfaces.[2)] Cell surface oligosaccharides of asparagine-linked type glycoproteins have been found to contain invariable "core" structures produced from an *N*,*N*′-diacetylchitobiose unit at the reducing terminal and three mannose residues. The core structure is additionally modified with a variety of oligosaccharide chains so as to carry individual molecular information. On the other hand, *N*-acetyllactosamine [Gal*p*β(1→4)Glc*p*NAc, LacNAc] has also been known as one of the most important and common disaccharide components found in the complex and hybrid types of *N*-linked oligosaccharides.[3)] Further modifications of this LacNAc moiety with sialic acid and L-fucose residues lead to a famous sialyl Lewis x (sLe^x) structure and other important antigenic carbohydrates.[4)] It has also been suggested that a variety of *N*-acetyllactosamine-polymers named lactosaminoglycans represent biosignals or markers of aging and malignant alterations of cells.[5)]

Thus, our attention has recently been directed toward the significance of *N*-acetyllactosamine-containing oligosaccharides as cell surface receptors in biological systems. Chemical syntheses and biochemical utilization of LacNAc-related oligosaccharides, therefore, have been regarded as effective and powerful strategies to investigate the relationship between chemical structures and biological functions of glycoconjugates. Actually, the syntheses of this class of oligosaccharides have previously been reported by a number of investigators.[6—22)] It was therefore of interest to design some "standardized intermediates" [23)] modified in a manner that allows their use as versatile building blocks to produce a variety of LacNAc-containing complex carbohydrate-architectures with shorter and easier synthetic routes than those of the conventional methods.

In the course of our works on the synthesis of partial structures of complex carbohydrates, we have demonstrated that naturally occurring or readily obtainable disaccharides sometimes facilitate synthetic routes of complex glycoconjugates.[24)] For example, chitobiose octaacetate prepared from chitin by chemoenzymatic degradations was efficiently utilized for constructing some useful "core" synthons of *N*-linked type oligosaccharides[25,26)] and a unique trisaccharide sequence of glycoprotein hormone, lutropin.[27)] In addition, we have preliminarily reported that a conformationally restricted 1,6-anhydro-β-lactose can be also applied for the synthetic studies on the lactosamine-containing longer and complicated carbohydrates through an easy manipulation of this disaccharide material.[1,28)]

A number of biologically important oligosaccharide structures have been identified as involving *N*-acetyllactosamine units; several examples are listed in Fig. 1. In addition to the Le^x (**A**) and sialyl Le^x (**B**, **C**) structures known as specific ligands of selectins, their sulfated analogues (**D**, **E**) and basic structure of the lactosaminoglycan (**F**) related to Ii antigenic carbohydrates might also be systematically and efficiently synthesized by means of novel 1,6-anhydro-β-lactose derivatives. We considered that synthetic strategy using 1,6-anhydro-β-lactose will permit the facile preparation of the novel standardized intermediates for the convergent block-synthesis of these carbohydrates, because all hydroxyl groups of this conformationally restricted disaccharide can be distinguished by chemoselective modifications. Thus, we describe herein the synthesis of novel 1,6-anhydro-β-lactose derivatives for creating a variety of important oligosaccharides.



A Galβ(1→4)GlcNAc
3
↑
Fucα 1

B Neu5Acα(2→6)Galβ(1→4)GlcNAc
3
↑
±[Fucα 1]

D 6S-Galβ(1→4)GlcNAc
3
↑
±[Fucα 1]

C Neu5Acα(2→3)Galβ(1→4)GlcNAc
3
↑
±[Fucα 1]

E 3S-Galβ(1→4)GlcNAc
3
↑
±[Fucα 1]

F ±[Galβ(1→4)GlcNAcβ1]
↓
6
[3Galβ(1→4)GlcNAcβ1→] $_n$ 3Galβ(1→4)GlcNAc

Fig. 1. Typical examples of LacNAc-related oligosaccharides in nature.

Results and Discussion

Selective Modifications of 1,6-Anhydro-β-lactose. In order to synthesize the standardized intermediates for *N*-acetyllactosamine-containing complex oligosaccharides, our attention was first directed toward the regioselective manipulations of 1,6-anhydro-β-lactose. Although the chemistry of 1,6-anhydro-β-lactose was partly discussed in the previous papers,[29—31] there is no systematic study on the preparation and use of the key intermediates from this disaccharide material. Tejima et al. had reported that the *p*-tosylation or benzoylation reaction of the known 4′,6′-*O*-benzylidene-1,6-anhydro-β-lactose afforded a complicated mixture of the substituted products and the reactivity of the C-3′ hydroxyl group was found to be much higher than those of other secondary hydroxyl groups.[29] Therefore, we considered that the following two important steps must be required for the preparation of versatile building blocks: (a) protections of highly reactive 3′-OH group of the galactose residue prior to the introduction of an appropriate leaving group at C-2 position of 1,6-anhydroglucose residue, and (b) selective introduction at C-2 position of a sterically hindered leaving group, 2,4,6-triisopropylbenzenesulfonyl group.[32]

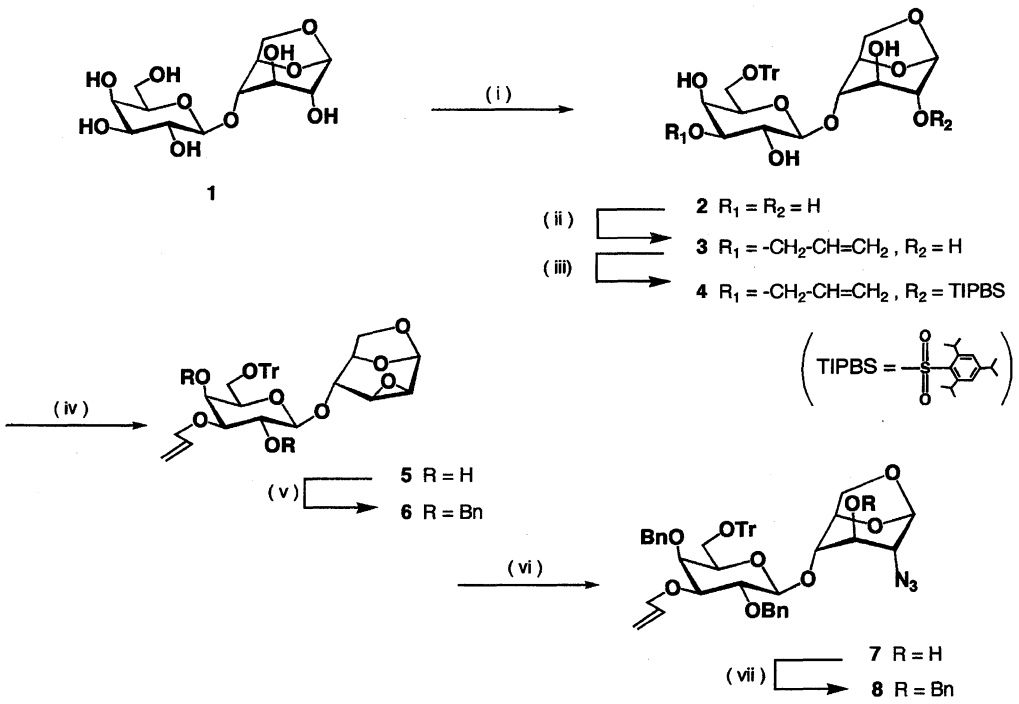
Scheme 1 indicates a synthetic route of the standardized intermediates **7**—**11**designed in this study. Firstly, 4-*O*-(6-*O*-triphenylmethyl-β-D-galactopyranosyl)-(1→4)-1,6-anhydro-β-D-glucopyranose (**2**)[28] was converted to its 3′-*O*-allylated derivative **3** in 73% yield through the specific activation of cis 1,2-diol groups with dibutyltin oxide according to the method reported by Ogawa et al.[33] Since the usual *p*-tosylation reaction of **3** was found to give an undesired mixture of mono- and di-substituted compounds, we employed 2,4,6-triisopropylbenzenesulfonyl chloride instead of *p*-toluenesulfonyl chloride as a sterically hindered reagent to provide this step with regiospecificity at C-2 position of the glucose residue. As anticipated, sulfonylation of tetraol **3** with this reagent proceeded smoothly and regioselectively in the presence of 4-dimethylaminopyridine to afford the intermediate **4** in 73% yield. Intramolecular nucleophilic substitution of the compound **4** by treatment with an aqueous solution of 1 M sodium hydroxide (1 M = 1 mol dm^{-3}) gave an epoxide **5** in 92% yield. After the benzylation of **5**, nucleophilic attack by azido anion to the epoxide **6** occurred stereospecifically to afford a key compound **7** having an unprotected hydroxyl group at C-3 position in 77% yield. Finally, a fully protected intermediate **8** was obtained by benzylation in 94% yield and utilized for further derivatization study. Chemical shifts and coupling constants of ^{1}H NMR spectra of all new compounds described here are summarized in Tables 1 and 2.

Selective Deprotections of a Key Intermediate 8. For the selective generations of hydroxyl group at C-3′ or/and C-6′ positions, appropriate conditions for the deprotection of compound **8** were carefully examined, as indicated in Scheme 2. Treatment of this material with 90% acetic acid aqueous solution at 70 °C for 1 h quantitatively yielded C-6′ hydroxyl derivative **9** without any influence on other protective groups. On the other hand, deprotection of 3′-*O*-allyl group by ultrasonication in 90% acetic acid aqueous solution with palladium(II) chloride and sodium acetate[34] was found to give derivative **10** bearing an unprotected hydroxyl group at C-3′ position in 65% yield, together with 18% yield of 3′,6′-diol **11**. It was also found that this 3′,6′-diol type derivative **11** could be obtained in 75% yield by the sequential treatment under the conditions for preparation of compounds **9** and **10** as described above. Chemical structures of these materials were elucidated by fully assigned ^{1}H NMR data listed in Tables 1 and 2; the satisfactory results of the elemental analyses are shown in the Experimental section.

The investigation concerning the versatility of these functional glycosyl acceptors in glycoconjugate synthesis is currently under way, and we have preliminarily examined and demonstrated the availability of compounds **10** and **11** for the facile preparation of the linear and branch type lactosaminoglycan analogs. The results including enzyme-assisted modification study of these intermediates will be reported shortly.[35]

Experimental

Materials and Methods. Unless otherwise stated, all commercially available solvents and reagents were used without further purification. Chloroform ($CHCl_3$), methanol (MeOH), and toluene were stored over molecular sieves 4 Å (MS 4 Å) before use. Pyridine was dried over potassium hydroxide, and tetrahydrofuran (THF) and *N*,*N*-dimethylformamide (DMF) were distilled before



Scheme 1. Reagents and conditions. (i) triphenylmethyl chloride, 4-dimethylaminopyridine, pyridine, 90 °C, 24 h; Ac_2O, pyridine; then, NaOMe/MeOH–THF, 25 °C, 3 h, (ii) dibutyltin oxide, toluene, 140 °C, 4 h; then, 3-bromo-1-propene, 80 °C, 5 h; (iii) 2,4, 6-triisopropylbenzenesulfonyl chloride, 4-dimethylaminopyridine, pyridine, r. t., 16 h; (iv) 1 M NaOHaq/MeOH–THF, r. t., 12 h; (v) benzyl bromide, sodium hydride, DMF, r. t., 42 h; (vi) sodium azide, cesium fluoride, 120 °C, 15 h; (vii) benzyl bromide, sodium hydride, DMF, r. t., 18 h.

Table 1. ^{1}H NMR Data of the Ring Protons for the Synthesized Compounds[a)]

	Chemical shifts (δ) and multiplicity								
Hydr. Atm	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**
H-1	5.38, brs	5.43, brs	5.70, d	5.70, d	5.27, brs	5.49, brs	5.51, brs	5.49, brs	5.51, brs
H-2	3.38, brs	4.35[b)]	3.44[b)]	3.43[b)]	3.22, d	3.20, brs	3.25, brs	3.21, brs	3.27, brs
H-3	3.95, brs	3.93[b)]	4.00, brs	3.89, brs	3.79[b)]	3.82, brs	3.90, brs	3.97, brs	3.91, brs
H-4	3.68, brs	3.65, d	3.46[b)]	3.42[b)]	3.41, d	3.78[b)]	3.76, brs	3.76[b)]	3.75, brs
H-5	4.65, d	4.63, d	4.55, t	4.46[b)]	4.39[b)]	4.64, d	4.62, d	4.52[b)]	4.61, d
H-6a	3.58[b)]	3.61, dd	3.73, d	3.67, d	3.56[b)]	3.72, t	3.72, t	3.60[b)]	3.72, d
H-6b	3.69[b)]	3.85, d	3.73, d	3.67, d	3.68[b)]	4.02, d	4.03, d	4.05, d	4.07, d
H-1′	4.36, d	4.37[b)]	4.44, d,	4.46, d	4.32, d	4.41, d	4.43, d	4.44, d	4.44, d
H-2′	3.80, dd	3.82[b)]	3.81[b)]	3.77, dd	3.76[b)]	3.78[b)]	3.85, dd	3.76[b)]	3.78[b)]
H-3′	3.30, dd	3.30, dd	3.36, dd	3.38[b)]	3.32, dd	3.37, dd	3.42, dd	3.48[b)]	3.68, dd
H-4′	3.99, d	3.96, d	4.05, br	3.86, d	3.69[b)]	3.87, d	3.79, d	3.84, d	3.78[b)]
H-5′	3.48[b)]	3.47[b)]	3.54, t	3.41[b)]	3.26, brt	3.32[b)]	3.34, t	3.31, brt	3.41, t
H-6a′	3.35[b)]	3.41[b)]	3.42[b)]	3.22, dd	3.14, dd	3.32[b)]	3.68[b)]	3.48[b)]	3.56, dd
H-6b′	3.45[b)]	3.42[b)]	3.44[b)]	3.50, dd	3.52, dd	3.47, ddd	3.54, brm	3.57[b)]	3.68[b)]

a) ^{1}H NMR data were measured in $CDCl_3$ at 27 °C with tetramethylsilane as an internal standard. b) Overlapped and could not be determined. c) Compounds **1** and **2**′s ^{1}H NMR data are described in previous papers, Refs. 30 and 27, respectively.

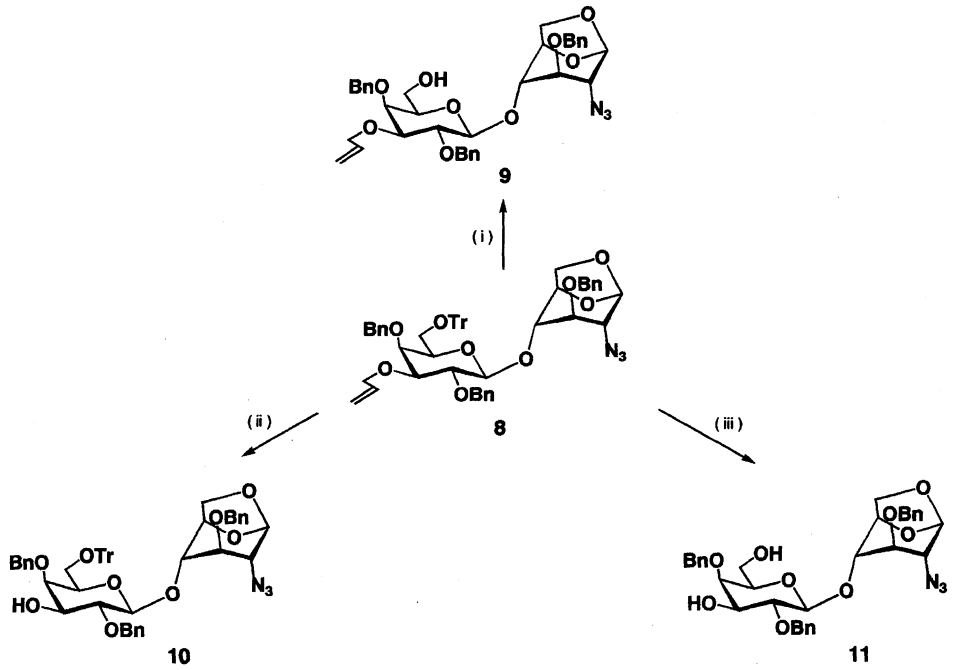
use. ^{1}H NMR spectra were recorded at 400 MHz with a JEOL EX-400 or JEOL ALPHA-400 spectrometer in chloroform-*d* at 27 °C, using tetramethylsilane (TMS) as internal standard. Ring-proton assignments in NMR spectra were made by first-order analysis of the spectra and supported by HH-COSY experiments. Reactions were monitored by thin-layer chromatography (TLC) on a precoated plate of silica gel 60 F_{254} (layer thickness, 0.25 mm; E. Merck, Darmmstadt, Germany). For detection of the sugar components, TLC sheets were sprayed with (a) a solution of 85 : 10 : 5 (v/v/v) methanol–concd sulfuric acid–*p*-anisaldehyde, and heated for a few minutes (for carbohydrate detection), or with (b) an aqueous solution of 5 wt% potassium permanganate and heated similarly (for detection of double bonds). Column chromatography was performed on silica-gel (Wakogel C-200; 100—200 mesh, Wako Pure Chemical Industries Co., Ltd., Japan).

4-*O*-(3-*O*-Allyl-6-*O*-triphenylmethyl-*β*-D-galactopyranosyl)-(1→4)-1,6-anhydro-*β*-D-glucopyranose (3). To a solution of **2**[28)] (6.57 g, 11.6 mmol) in toluene (100 mL) was added dibutyltin

Table 2. ^{1}H–^{1}H Coupling Constants for the Synthesized Compounds[a)]

Coupled protons	*J*-values (Hz)								
	3	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**
$J_{1,2}$	< 1	< 1	2.84	2.90	< 1	< 1	< 1	< 1	< 1
$J_{2,3}$	< 1	b	< 1	< 1	6.60	< 1	< 1	< 1	< 1
$J_{3,4}$	< 1	5.74	< 1	< 1	7.61	< 1	< 1	< 1	< 1
$J_{4,5}$	< 1	< 1	< 1	b)	< 1	< 1	< 1	b)	< 1
$J_{5,6a}$	5.92	5.03	4.34	4.36	5.28	5.96	5.86	b)	6.15
$J_{5,6b}$	< 1	< 1	4.34	4.36	b)	< 1	< 1	< 1	< 1
$J_{6a,6b}$	b)	7.20	< 1	< 1	b)	7.33	7.33	7.12	7.35
$J_{1',2'}$	7.81	7.39	7.74	7.75	7.58	8.06	8.06	6.98	6.96
$J_{2',3'}$	9.92	9.40	9.40	9.72	9.90	9.53	9.53	b)	9.90
$J_{3',4'}$	3.00	3.16	3.23	2.96	2.97	2.93	2.92	2.90	3.15
$J_{4',5'}$	< 1	< 1	< 1	< 1	< 1	< 1	< 1	< 1	< 1
$J_{5',6a'}$	b)	b)	b)	5.99	5.60	b)	5.86	5.80	5.59
$J_{5',6b'}$	b)	b)	7.83	6.40	6.27	8.80	6.60	6.26	6.51
$J_{6a',6b'}$	b)	11.09	b)	9.13	9.90	11.73	b)	b)	10.12

a) ^{1}H NMR data were measured in the same condition as described in Table 1. b) Overlapped and could not be determined. c) Compounds **1** and **2**′s ^{1}H NMR data were described in previous papers, Refs. 30 and 27, respectively.



Scheme 2. Reagents and conditions. (i) 90% AcOHaq, 70 °C, 1 h; (ii) palladium(II) chloride, sodium acetate, 90% AcOHaq, sonication at r. t., 6 h; (iii) 90% AcOHaq, 70 °C, 1 h; then palladium(II) chloride, sodium acetate, sonication at r. t., 2 h.

oxide (3.17 g, 12.7 mmol); the mixture was stirred for 4 h at 140 °C with continuous azeotropic removal of water. After evaporation to the half volume, 3-bromo-1-propene (50 mL) was added and the mixture was stirred for 5 h at 80 °C. The mixture was evaporated and the residual syrup was chromatographed on silica-gel with 160 : 2 : 1 (v/v/v) chloroform–methanol–triethylamine as the eluant to afford compound **3** (5.12 g, 73%): $R_f = 0.62$ [65 : 15 : 1 (v/v/v); chloroform–methanol–water]; $[\alpha]_D^{23}$ −48.1° (*c* 0.26, $CHCl_3$); mp 132 °C; ^{1}H NMR ($CDCl_3$) δ = 7.44—7.19 (m, 15 H, aromatic), 5.94 (ddd, 1 H, *J* = 17.09, 10.51, and 5.67 Hz, CH_2=C*H*), 5.34 [dd, 1 H, *J* = 17.09 and 1.50 Hz, CH_2=CH (trans)], 5.20 [dd, 1 H, *J* = 10.51 and 1.50 Hz, CH_2=CH (cis)], 4.19 (m, 2 H, CH_2=CH–CH_2), 3.90, 3.19, 2.96, and 2.18 (each br, 4 H, 2, 3, 2′, and 4′–OH); the data of the ring protons are listed in Tables 1 and 2. Anal. Calcd for $C_{34}H_{38}O_{10}$: C, 67.31; H, 6.31%. Found: C, 67.21; H, 6.30%.

4-*O*-(3-*O*-Allyl-6-*O*-triphenylmethyl-β-D-galactopyranosyl)-(1→4)-1,6-anhydro-2-*O*-(2,4,6-triisopropylbenzenesulfonyl)-β-D-glucopyranose (4). To a solution of **3** (4.0 g, 6.58 mmol) in pyridine (60 mL) were added 4-dimethylaminopyridine (DMAP) (2.01 g, 16.5 mmol) and 2,4,6-triisopropylbenzenesulfonyl chloride (TIPBS-Cl) (4.99 g, 16.5 mmol). The mixture was stirred under nitrogen atmosphere for 16 h at room temperature. The solution was evaporated and the residue was extracted with chloroform. The organic layer was washed successively with 0.5 M sulfuric acid, saturated aqueous sodium hydrogencarbonate, and brine, dried over anhydrous magnesium sulfate, filtered off through

a celite bed, and evaporated. The residue was chromatographed on silica-gel with 180 : 15 : 1 (v/v/v) toluene–ethyl acetate–triethylamine to give a crystalline mass of **4** (4.2 g, 73%): $R_f = 0.55$ [1 : 1 (v/v); toluene–ethyl acetate]; $[\alpha]_D^{23}$ −2.0° (*c* 0.25, $CHCl_3$); mp 96—97 °C; ^{1}H NMR ($CDCl_3$) $\delta = 7.32$—7.20 (m, 17 H, aromatic), 5.94 (ddd, 1 H, $J = 17.22$, 10.34, and 5.77 Hz, CH_2=C*H*), 5.31 [dd, 1 H, $J = 17.09$ and 1.50 Hz, CH_2=CH (trans)], 5.22 [dd, 1 H, $J = 10.34$ and 1.50 Hz, CH_2=CH (cis)], 4.19 (m, 2 H, CH_2=CH–CH_2), 4.13 (m, 3 H, $(CH_3)_2$–C*H*), 2.87 (br, 2 H, 2′ and 4′-OH), 2.44 (br, 1 H, 3-OH), 1.26 and 1.24 [each s, each 9 H, $(CH_3)_2$–CH]; the data of the ring protons are given in Tables 1 and 2. Anal. Calcd for $C_{49}H_{60}O_{12}S$: C, 67.41; H, 6.93%. Found: C, 66.98; H, 6.81%.

4-*O*-(3-*O*-Allyl-6-*O*-triphenylmethyl-β-D-galactopyranosyl)-(1→4)-1,6:2,3-dianhydro-β-D-mannopyranose (5). To a solution of **4** (1.30 g, 1.49 mmol) in 1 : 1 (v/v) methanol–tetrahydrofuran (20 mL) was added an aqueous solution of 1 M sodium hydroxide (4.47 mL) and the mixture was stirred at room temperature overnight. The mixture was concentrated and the residual oil was dissolved in chloroform, washed with brine, dried, and evaporated in vacuo. The residual syrup was purified by chromatography on a silica-gel with 180 : 30 : 1 toluene–ethyl acetate–triethylamine as an eluant to give a crystalline powder of **5** (810 mg, 92%): $R_f = 0.52$ [5 : 4 : 1 (v/v/v); chloroform–ethyl acetate–methanol]; $[\alpha]_D^{23}$ −17.1° (*c* 0.24, $CHCl_3$); mp 98—100 °C; ^{1}H NMR ($CDCl_3$) $\delta = 7.46$—7.21 (m, 15 H, aromatic), 5.96 (ddd, 1 H, $J = 17.18$, 10.38, and 4.36 Hz, CH_2=C*H*), 5.33 [dd, 1 H, $J = 17.18$ and 1.42 Hz, CH_2=CH (trans)], 5.23 [dd, 1 H, $J = 10.34$ and 1.42 Hz, CH_2=CH (cis)], 4.21 (m, 2 H, CH_2=CH–CH_2), 2.78 (br, 2 H, 2′ and 4′-OH), 2.44 (br, 1 H, 3-OH), 1.26 and 1.24 [each s, each 9 H, $(CH_3)_2$–CH], 2.78 (br, 1 H, 2′-OH), and 2.43 (br, 1 H, 4′-OH); the data of the ring protons are given in Tables 1 and 2. Anal. Calcd for $C_{34}H_{36}O_9$: C, 69.37; H, 6.16%. Found: C, 69.40; H, 6.15%.

4-*O*-(3-*O*-Allyl-2,4-di-*O*-benzyl-6-*O*-triphenylmethyl-β-D-galactopyranosyl)-(1→4)-1,6 : 2,3-dianhydro-β-D-mannopyranose (6). To a solution of compound **5** (800 mg, 1.36 mmol) in DMF (30 mL) were added sodium hydride (60% oil suspension; 163 mg, 4.08 mmol) and benzyl bromide (0.83 mL, 6.80 mmol); the mixture was then stirred at room temperature. After 18 h, to the solution were added the same amounts of sodium hydride and benzyl bromide; this mixture was stirred for 24 h. Excess of sodium hydride was quenched carefully by addition of methanol. Then, the solution was evaporated and the residue was dissolved in ethyl acetate. The organic layer was successively washed with water and brine, and dried over anhydrous magnesium sulfate. The mixture was filtered and purified by silica-gel column chromatography with 140 : 20 : 1 (v/v/v) hexane–ethyl acetate–triethylamine as an eluant to give amorphous powdery **6** (980 mg, 94%): $R_f = 0.59$ [2 : 1 (v/v); hexane–ethyl acetate]; $[\alpha]_D^{23}$ −22.3° (*c* 0.31, $CHCl_3$); mp 88 °C; ^{1}H NMR ($CDCl_3$) $\delta = 7.41$—7.16 (m, 25 H, aromatic), 5.93 (ddd, 1 H, $J = 17.25$, 10.41 and 5.21 Hz, CH_2=C*H*), 5.33 [dd, 1 H, $J = 17.26$ and 1.50 Hz, CH_2=CH (trans)], 5.20 [dd, 1 H, $J = 10.41$ and 1.49 Hz, CH_2=CH (cis)], 4.91—4.48 (m, 4 H, Ph-CH_2), and 4.20 (m, 2 H, CH_2=CH–CH_2); the data of the ring protons are given in Tables 1 and 2. Anal. Calcd for $C_{48}H_{48}O_9$: C, 74.98; H, 6.29%. Found: C, 74.58; H, 6.38%.

4-*O*-(3-*O*-Allyl-2,4-di-*O*-benzyl-6-*O*-triphenylmethyl-β-D-galactopyranosyl)-(1→4)-1,6-anhydro-2-azido-2-deoxy-β-D-glucopyranose (7). A mixture of **6** (350 mg, 0.455 mmol), cesium fluoride (690 mg, 4.55 mmol), and sodium azide (300 mg, 4.55 mmol) dissolved in DMF (20 mL) was stirred under nitrogen atmosphere for 15 h at 120 °C. After cooling to room temperature, the mixture was diluted with water and the residue was extracted with ethyl acetate. The organic layer was washed with brine and dried over anhydrous magnesium sulfate. The solution was filtered, concentrated, and the residual syrup was subjected to chromatography on a silica-gel column with 140 : 20 : 1 (v/v/v) toluene–etheyl acetate–triethylamine as an eluant to give **7** (285 mg, 77%) as an crystalline powder: $R_f = 0.48$ [2 : 1 (v/v); hexane–ethyl acetate]; $[\alpha]_D^{23}$ −20.0° (*c* 0.22, $CHCl_3$); mp 83 °C; ^{1}H NMR ($CDCl_3$) $\delta = 7.64$—7.11 (m, 25 H, aromatic), 5.93 (ddd, 1 H, $J = 17.16$, 10.56, and 5.28 Hz, CH_2=C*H*), 5.33 [dd, 1 H, $J = 17.16$ and 1.65 Hz, CH_2=CH (trans)], 5.21 [dd, 1 H, $J = 10.56$ and 1.65 Hz, CH_2=CH (cis)], 4.83—4.45 (m, 4 H, Ph-CH_2), 4.18 (m, 2 H, CH_2=CH–CH_2), and 1.56 (brs, 1 H, 3-OH); the data of the ring protons are given in Tables 1 and 2. Anal. Calcd for $C_{48}H_{49}N_3O_9$: C, 71.07; H, 6.08; N, 5.18%. Found: C, 71.00; H, 6.00; N, 5.12%.

4-*O*-(3-*O*-Allyl-2,4-di-*O*-benzyl-6-*O*-(triphenylmethyl)-β-D-galactopyranosyl)-(1→4)-1,6-anhydro-2-azido-3-*O*-benzyl-2-deoxy-β-D-glucopyranose (8). To a solution of **7** (270 mg, 0.33 mmol) in DMF (20 mL) were added sodium hydride (60%; 40 mg, 1.0 mmol) and benzyl bromide (0.21 mL, 1.7 mmol); this mixture was stirred at room temperature for one night. Compound **8** was successfully obtained according to the same procedure as for the purification of **6**, in high yield (281 mg, 94%): $R_f = 0.61$ [2 : 1 (v/v); hexane–ethyl acetate]; $[\alpha]_D^{23}$ −9.9° (*c* 0.24, $CHCl_3$); mp 104 °C; ^{1}H NMR ($CDCl_3$) $\delta = 7.43$—7.12 (m, 30 H, aromatic), 5.95 [ddd, 1 H, $J = 16.86$, 10.26, and 5.13 Hz, CH_2=C*H*], 5.34 [dd, 1 H, $J = 16.86$ and 1.45 Hz, CH_2=CH (trans)], 5.20 [dd, 1 H, $J = 10.25$ and 1.46 Hz, CH_2=CH (cis)], 4.97—4.49 (m, 6 H, Ph-CH_2), and 4.20 (m, 2 H, CH_2=CH–CH_2); the data of the ring protons are given in Tables 1 and 2. Anal. Calcd for $C_{55}H_{55}N_3O_9$: C, 73.23; H, 6.15; N, 4.66%. Found: C, 73.19; H, 6.16; N, 4.61%.

4-*O*-(3-*O*-Allyl-2,4-di-*O*-benzyl-β-D-galactopyranosyl)-(1→4)-1,6-anhydro-2-azido-3-*O*-benzyl-2-deoxy-β-D-glucopyranose (9). The solution of **8** (500 mg, 0.554 mmol) in acetic acid (18.0 mL) and deionized water (2.0 mL) was stirred at 70 °C for 1 h. The solution was extracted with chloroform and the organic layer was successively washed with ice water, saturated aqueous sodium hydrogencarbonate, and brine. After drying over anhydrous magnesium sulfate powder, the solution was concentrated and the residual syrup was applied on silica-gel chromatography with 200 : 10 : 1 (v/v/v) toluene–ethyl acetate–triethylamine as an eluant, to give pure **2** (360 mg, 98%) as an amorphous mass: $R_f = 0.45$ [3 : 2 (v/v); hexane–ethyl acetate]; $[\alpha]_D^{23}$ −15.4° (*c* 0.20, $CHCl_3$); ^{1}H NMR ($CDCl_3$); $\delta = 7.45$—7.30 (m, 15 H, aromatic), 5.98 (ddd, 1 H, $J = 16.85$, 10.99, and 5.86 Hz, CH_2=C*H*), 5.36 [dd, 1 H, $J = 16.85$ and 1.47 Hz, CH_2=CH (trans)], 5.23 [dd, 1 H, $J = 10.99$ and 1.46 Hz, CH_2=CH (cis)], 5.01—4.65 (m, 6 H, Ph-CH_2), 4.25 (m, 2 H, CH_2=CH–CH_2), and 3.09 (br m, 1 H, 6′-OH); the data of the ring protons are given in Tables 1 and 2. Anal. Calcd for $C_{36}H_{41}N_3O_9$: C, 65.54; H, 6.26; N, 6.37%. Found: C, 65.41; H, 6.32; N, 6.12%.

4-*O*-(2,4-Di-*O*-benzyl-6-*O*-triphenylmethyl-β-D-galactopyranosyl)-(1→4)-1,6-anhydro-2-azido-3-*O*-benzyl-2-deoxy-β-D-glucopyranose (10). To a solution of **8** (480 mg, 0.532 mmol) in acetic acid (9.0 mL) and H_2O (1.0 mL) were added sodium acetate (218 mg, 2.60 mmol) and palladium(II) chloride (189 mg, 1.06 mmol). The de-*O*-allylation reaction was carried out in a ultrasonicator (Bransonic, Model 3210J) for 6 h under 35 °C. The mixture was filtered off through a celite bed, and extracted with chloroform. The organic layer was washed with saturated aqueous sodium hydrogencarbonate and brine. The solution was dried over anhydrous magnesium sulfate, filtered, and evaporated. The residual syrup was subsequently chromatographed on a silica gel column with 200 : 100 : 1 (v/v/v) hexane–ethyl acetate–triethylamine as an

eluant, giving rise to the C-3′ hydroxyl derivative **10** as a syrup form (290 mg, 61%): $R_f = 0.50$ [2 : 1 (v/v); hexane–ethyl acetate]; $[\alpha]_D^{23}$ +13.4° (*c* 0.21, $CHCl_3$); ^{1}H NMR ($CDCl_3$) $\delta = 7.37$—7.12 (m, 30 H, aromatic), 5.04—4.49 (m, 6 H, Ph-CH_2), and 2.23 (br, 1 H, 3′-OH); the data of the ring protons are given in Tables 1 and 2. Anal. Calcd for $C_{52}H_{51}N_3O_9$: C, 72.46; H, 5.96; N, 4.87%. Found: C, 72.17; H, 6.01; N, 4.72%.

4-*O*-(2,4-Di-*O*-benzyl-β-D-galactopyranosyl)-(1→4)-1,6-anhydro-2-azido-3-*O*-benzyl-2-deoxy-β-D-glucopyranose (11). A solution of **8** (300 mg, 0.333 mmol) in acetic acid (9.0 mL) and deionized water (1.0 mL) was stirred at 70 °C for 1 h. After cooling to room temperature, to the solution was added sodium acetate (136 mg, 1.66 mmol) and palladium(II) chloride (118 mg, 0.665 mmol). The mixture was sonicated and worked out according to the method described for the preparation of compound **9**. Finally, the crude product was purified by silica-gel chromatography with 100 : 200 : 1 (v/v/v) toluene–ethyl acetate–triethylamine as eluant to give 3′,6′-diol derivative **11** (154 mg, 75%): R_f = [2 : 1 (v/v); hexane–ethyl acetate]; $[\alpha]_D^{23}$ +2.0° (*c* 0.19, $CHCl_3$); ^{1}H NMR ($CDCl_3$) $\delta = 7.40$—7.30 (m, 15 H, aromatic), 5.10—4.64 (m, 6 H, Ph-CH_2), and 3.09 (br, 2 H, 3′ and 6′-OH), and the data of the ring protons are given in Tables 1 and 2. Anal. Calcd for $C_{33}H_{37}N_3O_9$: C, 63.96; H, 6.02; N, 6.78%. Found: C, 63.78; H, 6.20: N, 6.80%.

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