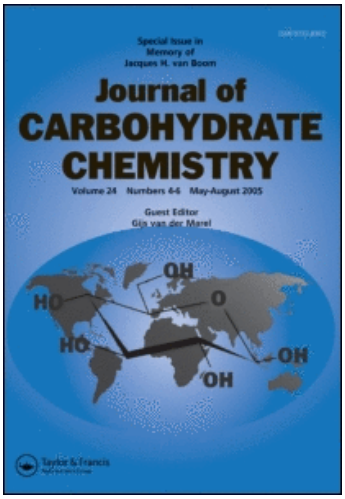

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Chemical Transformation of a 1-Deoxynojirimycin Derivative into 1-Deoxymannojirimycin and 1-Deoxygalactostatin

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CHEMICAL TRANSFORMATION OF A 1-DEOXYNOJIRIMYCIN DERIVATIVE INTO 1-DEOXYMANNOJIRIMYCIN AND 1-DEOXYGALACTOSTATIN

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ABSTRACT

Treatment of 2,3-di-*O*-benzyl-*N*-benzyloxycarbonyl-6-*O*-*t*-butyldiphenylsilyl-1,5-dideoxy-1,5-imino-D-glucitol (**4**) with sodium hydride resulted in an intramolecular cyclization concomitant with silyl migration, giving the carbamate derivative **5** in good yield. This was efficiently converted into 1-deoxymannojirimycin (**2**) *via* regioselective *p*-toluenesulfonylation followed by an inversion reaction at the C-2 position. On the other hand, the monochloromethylsulfonate **10** obtained from **4** underwent configurational change at the C-4 position by the action of sodium benzoate. The resulting benzoate **11** was deprotected to afford 1-deoxygalactostatin (**3**).

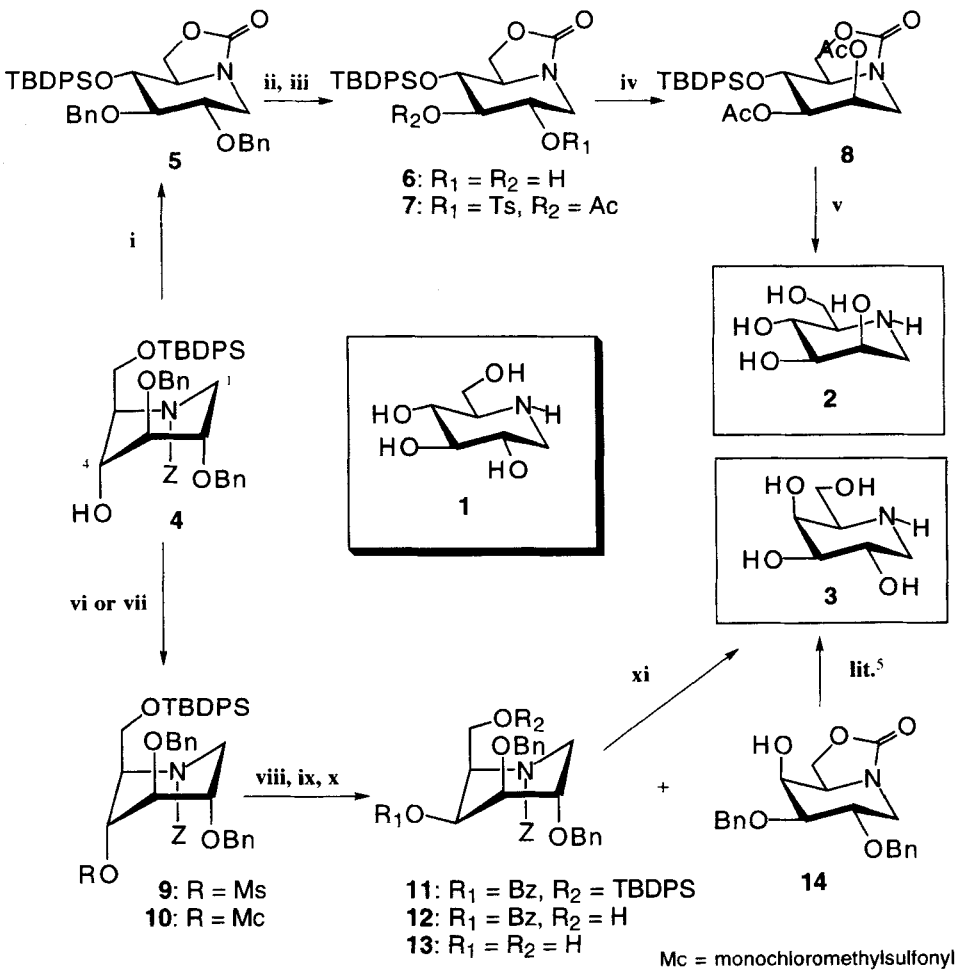
INTRODUCTION

Polyhydroxylated piperidines, as represented by 1-deoxynojirimycin (**1**), constitute a major class of inhibitors of glycosidases and glycoprotein-processing enzymes.[1] These alkaloids have recently attracted much attention from synthetic organic chemists[2-5] because of their potential chemotherapeutic utility for treatment of diabetes, cancer and viral infections. In the preceding paper, we established a simple method for preparation of

2,3-di-*O*-benzyl-*N*-benzyloxycarbonyl-6-*O*-*t*-butyldiphenylsilyl-1,5-dideoxy-1,5-imino-D-glucitol (**4**) and synthesized a mimic of the basic repeating disaccharide unit of heparan sulfate therefrom.[6] In order to extend the utility of **4**, our attention has next been directed towards 1-deoxymannojirimycin (**2**)[3,7] and 1-deoxygalactostatin (**3**).[4,5,8] The former has been shown to possess a potent inhibitory activity against several mannosidases[9] and bovine α-L-fucosidase,[10] whereas the latter is known to be a strong galactosidase inhibitor.[8,11] Until now, many approaches to the preparation of these inhibitors have been developed.[3-5] We have therefore designed a versatile synthetic route including multifunctional nojirimycin derivatives that are suitably protected in order to allow attachment of glycosidic residues, thus leading to new pseudooligosaccharides. Described herein is the transformation of **4** into two glycosidase inhibitors (**2** and **3**).

RESULTS AND DISCUSSION

The target compounds **2** and **3** have the D-*manno* and D-*galacto* configuration, respectively. Our common synthetic strategy directed towards these inhibitors involved S_N2 displacement of a good leaving group by a carboxylate anion. Synthesis of **2** began with protection of the 4-OH in **4** with a *t*-butyldiphenylsilyl (TBDPS) group (Scheme). The bulky protecting group was expected to enable a regioselective functionalization between the C-2 and C-3 hydroxyl groups liberated in a later step. After making trial of several reaction conditions, we have found that brief treatment of **4** with sodium hydride (1.05 eq.) in *N,N*-dimethylformamide (DMF) at 0 °C gave rise to intramolecular cyclic carbamate formation accompanied with a silyl migration reaction, affording the 4-*O*-silyl derivative **5** in good yield. Prolonged exposure of **4** to base resulted in a mixture of more polar substances. Structure elucidation of **5** was mainly achieved on the basis of NMR analyses; all ring protons of **5** were unambiguously assigned using the decoupling technique and the presence of TBDPS group at C-4 position was confirmed by ^1H-^{29}Si-PFG-HMBC spectra.[12] This novel intramolecular reaction enabled us to prepare **2** from **4**. The two benzyl groups of **5** were removed by hydrogenolysis using palladium on carbon as a catalyst to give diol **6** in 85% yield. As it was established by ^1H NMR analyses that **6** exists as the $^4C_1$ conformer carrying two equatorial hydroxyl groups, regioselective tosylation by activation with di-*n*-butyltin oxide[13] was initially attempted. Unexpectedly,



Scheme. *Reagents and conditions*: i, NaH (1.05 eq.), DMF, 0 °C (68%); ii, H_2, 10% Pd-C, EtOAc, AcOH, H_2O, rt (85%); iii, TsCl (2.4 eq.), DMAP (1.0 eq.), Et_3N (3.0 eq.), CH_2Cl_2, rt, and then Ac_2O (85%); iv, CsOAc (20 eq.), 18-Crown-6 (1.5 eq.), toluene, 100 °C (77%); v, NaOH, aq. EtOH, 65 °C (89%); vi, MsCl (1.5 eq.), CH_2Cl_2, pyridine, 0 °C (93%); vii, McCl (1.2 eq.), 2,6-lutidine (2.5 eq.), CH_2Cl_2, 0 °C (quant.); viii, BzONa (5.0 eq.), HMPA, 70 or 120 °C (54% from **9**, 60% from **4** *via* **10**); ix, TBAF (1.3 eq.), AcOH (1.3 eq.), THF, rt (87%); x, NaOMe, MeOH, rt (72% for **13**, 21% for **14**); xi, H_2, 10% Pd-C, EtOAc, AcOH, H_2O, rt (55%).

two regioisomers were obtained in rather low yields. On the other hand, reaction of **6** with a small excess of *p*-toluenesulfonyl chloride (*p*-TsCl) and triethylamine in the presence of *N,N*-dimethylaminopyridine (DMAP) proceeded nicely to afford the desired monotosylate derivative **7** in 85% yield after acetylation in a one pot manner. The high regioselectivity

seemed to be responsible for the steric hindrance of TBDPS group at C-4 position. The tosylate **7** was treated with a large excess of cesium acetate in the presence of 18-crown-6[14] in toluene at 100 °C to give the diacetyl derivative **8** (77% yield). Its 400 MHz ^{1}H NMR spectrum in $CDCl_3$ showed a signal assignable to the C-2 methyne proton at δ 5.26 (ddd, 1H, $J_{1a,2}$ 1.8, $J_{1b,2}$ 2.5, $J_{2,3}$ 2.8 Hz), indicating the *manno* configuration of **8**. Attempts to apply conventional inversion methods using sodium acetate or sodium benzoate in DMF to **7** gave unsatisfactory results. Finally, all protecting groups in **8** were removed by treatment with sodium hydroxide in aqueous ethanol, after purification by ion-exchange column chromatography, affording 1-deoxymannojirimycin (**2**) in good yield.

Alternatively, compound **4** was subjected to methanesulfonylation or chloromethylsulfonylation[15] under standard conditions. The resulting mesylate **9** reacted slowly with sodium benzoate in hexamethylphosphoric triamide (HMPA) at 120 °C to furnish benzoate **11** in 50% yield from **4**. By using the corresponding chloromethylsulfonyl derivative **10**, the yield of **11** was increased by 10% under milder conditions (80 °C for 7h). The TBDPS group in **11** was cleaved by tetrabutylammonium fluoride in the presence of acetic acid, affording the hydroxy benzoate **12** in 87% yield. Upon treatment with sodium methoxide, **12** gave **13** in 72% yield along with the cyclic carbamate derivative **14**[5] (21% yield). Finally, all the benzyl groups in **13** were removed by hydrogenolysis to give 1-deoxygalactostatin (**3**). In addition, **14** was also converted into **3** according to the known procedure.[5]

In conclusion, a facile synthesis of **2** and **3** from **4** has been developed which is suitable for large-scale preparations. Several intermediates prepared in the present work could be of interest as useful building blocks for developing new glycosidase inhibitors with a pseudooligosaccharidic structure.

EXPERIMENTAL

General Procedures. Melting points were determined in a capillary with an Ishii melting-point apparatus and are reported uncorrected. Optical rotations were determined with a JASCO DIP-370 polarimeter. NMR spectra were recorded on JEOL JNM-α 400 or GX 500 spectrometers in a $CDCl_3$ solution (unless otherwise specified), using tetramethylsilane as internal standard. Column chromatography was performed on silica

gel 60 (230-400 mesh, E. Merck, Darmstadt, Germany). Merck precoated silica gel 60 F_{254} plates, 0.25 or 1.0 mm thickness, were used for analytical or preparative thin-layer chromatography, respectively.

2,3-Di-*O*-benzyl-4-*O*-*tert*-butyldiphenylsilyl-5-*N*,6-*O*-carbamoyl-1,5-dideoxy-1,5-imino-D-glucitol (5). To a stirred solution of **4** (1.01 g, 1.41 mmol) in *N,N*-dimethylformamide (5 mL) was added sodium hydride (60% suspension in oil, 59 mg, 1.48 mmol) at 0 °C under an argon atmosphere. After stirring for 5 min at 0 °C, the reaction mixture was poured into ice-sat. NH_4Cl solution, and then extracted with chloroform. The extracts were washed with water and brine, dried over $MgSO_4$ and concentrated. The residue was chromatographed on a column of silica gel with hexane-ethyl acetate (4:1) to give **5** (580 mg, 68%) as a semisolid, mp 142.5-143.5 °C (EtOH-$CHCl_3$), $[\alpha]_D^{27}$ +82.9° (*c* 0.88, $CHCl_3$); ^1H NMR δ 0.96 (9H, s, *t*-Bu), 2.77 (1H, dd, $J_{1a,1b}$ = 13 Hz, $J_{1a,2}$ = 10 Hz, H-1a), 3.46 (1H, ddd, $J_{1a,2}$ = 10 Hz, $J_{1b,2}$ = 5.9 Hz, $J_{2,3}$ = 8.8 Hz, H-2), 3.56 (1H, dd, $J_{5,6a}$ = 5.4 Hz, $J_{6a,6b}$ = 9.3 Hz, H-6a), 3.59-3.61 (2H, m, H-3, H-4), 3.71 (1H, ddd, $J_{4,5}$ = $J_{5,6b}$ = 8.3 Hz, $J_{5,6a}$ = 5.4 Hz, H-5), 3.88 (1H, dd, $J_{5,6b}$ = 8.3 Hz, $J_{6a,6b}$ = 9.3 Hz, H-6b), 4.05 (1H, dd, $J_{1a,1b}$ = 13 Hz, $J_{1b,2}$ = 5.9 Hz, H-1b), 4.46, 4.56 (2H, each d, J = 11 Hz, 2-C*H*Ph), 4.55, 4.97 (2H, each d, J = 11 Hz, 3-C*H*Ph), 7.05-7.70 (20H, m, Ph); ^{13}C NMR δ 42.3 (C-1), 58.1 (C-5), 66.5 (C-6), 75.5 (C-4), 78.0 (C-2), 84.3 (C-3); ^{29}Si NMR δ -3.70 (4-*O*-Si).

Anal. Calcd for $C_{37}H_{41}O_5NSi$: C, 73.11; H, 6.80; N, 2.30. Found: C, 73.14; H, 6.81; N, 2.31.

4-*O*-*tert*-Butyldiphenylsilyl-5-*N*,6-*O*-carbamoyl-1,5-dideoxy-1,5-imino-D-glucitol (6). A mixture of **5** (570 mg, 0.94 mmol) and 10% Pd-C (60 mg) in ethyl acetate-water-acetic acid (40 : 5 : 2; v/v/v, 4.7 mL) was stirred at room temperature under a hydrogen atmosphere for 3 days. The catalyst was then filtered off and washed with aq. methanol. The filtrate and washings were combined and concentrated. The residue was chromatographed on a column of silica gel with toluene-ethyl acetate (1:1) to give **6** (341 mg, 85%) as a semisolid, mp 138-139 °C (MeOH), $[\alpha]_D^{27}$ +27.4° (*c* 0.76, $CHCl_3$); ^1H NMR δ 1.05 (9H, s, *t*-Bu), 2.23 (1H, d, $J_{3,OH}$ = 3.4 Hz, 3-OH), 2.44 (1H, d, $J_{2,OH}$ = 2.4 Hz, 2-OH), 2.76 (1H, dd, $J_{1a,1b}$ = 13 Hz, $J_{1a,2}$ = 10 Hz, H-1a), 3.34 (1H, dd, $J_{3,4}$ = 9.3 Hz, $J_{4,5}$ = 8.8 Hz, H-4), 3.38 (1H, m, H-2), 3.52 (1H, ddd, $J_{2,3}$ =

9.2Hz, $J_{3,4}$ = 9.3 Hz, $J_{3,OH}$ = 3.4 Hz, H-3), 3.69 (1H, ddd, $J_{4,5}$ = 8.8 Hz, $J_{5,6a}$ = 4.9 Hz, $J_{5,6b}$ = 8.3 Hz, H-5), 3.79 (1H, dd, $J_{5,6a}$ = 4.9 Hz, $J_{6a,6b}$ = 8.8 Hz, H-6a), 3.99 (1H, dd, $J_{1a,1b}$ = 13 Hz, $J_{1b,2}$ = 5.9 Hz, H-1b), 4.21 (1H, dd, $J_{5,6b}$ = 8.3 Hz, $J_{6a,6b}$ = 8.8 Hz, H-6b), 7.44-7.71 (10H, m, Ph).

Anal. Calcd for $C_{23}H_{29}O_5NSi$: C, 64.61; H, 6.84; N, 3.28. Found: C, 64.28; H, 6.93; N, 3.18.

3-*O*-Acetyl-4-*O*-*tert*-butyldiphenylsilyl-5-*N*,6-*O*-carbamoyl-2-*O*-*p*-toluenesulfonyl-1,5-dideoxy-1,5-imino-D-glucitol (7). To a stirred mixture of **6** (22 mg, 0.05 mmol), *N,N*-dimethylaminopyridine (6.1 mg, 0.05 mmol) and triethylamine (21 μL, 0.15 mmol) in dichloromethane (0.6 mL) was added *p*-toluenesulfonyl chloride (11 mg, 0.06 mmol) at room temperature under an argon atmosphere, and the mixture was stirred for 2.5 h. Additional *p*-toluenesulfonyl chloride (11 mg, 0.06 mmol) was added and stirring was further continued for 1.5 h. Acetic anhydride (0.1 mL) was added to the resulting mixture and stirring was further continued for 0.5 h. The reaction mixture was poured into ice-water, and then extracted with chloroform. The extracts were successively washed with dil. HCl solution, sat. $NaHCO_3$ solution, water and brine, dried over $MgSO_4$ and concentrated. The residue was chromatographed on a column of silica gel with hexane-ethyl acetate (2:1→1:1) to give **7** (27 mg, 85%), $[\alpha]_D^{27}$ +8.0° (*c* 0.44, $CHCl_3$); ^1H NMR δ 0.97 (9H, s, *t*-Bu), 1.57 (3H, s, Ac), 2.44 (3H, s, Ts), 2.89 (1H, dd, $J_{1a,1b}$ = 13 Hz, $J_{1a,2}$ = 11 Hz, H-1a), 3.57 (1H, t, $J_{3,4}$ = $J_{4,5}$ = 9.2 Hz, H-4), 3.61 (1H, dd, $J_{5,6a}$ = 5.2 Hz, $J_{6a,6b}$ = 9.2 Hz, H-6a), 3.70 (1H, ddd, $J_{4,5}$ = 9.2 Hz, $J_{5,6a}$ = 5.2 Hz, $J_{5,6b}$ = 8.7 Hz, H-5), 3.93 (1H, dd, $J_{1a,1b}$ = 13 Hz, $J_{1b,2}$ = 6.1 Hz, H-1b), 4.03 (1H, ddd, $J_{4,5}$ = 9.2 Hz, $J_{5,6a}$ = 5.2 Hz, $J_{5,6b}$ = 8.7 Hz, H-5), 4.33 (1H, ddd, $J_{1a,2}$ = 11 Hz, $J_{1b,2}$ = 6.1 Hz, $J_{2,3}$ = 9.5 Hz, H-2), 5.21 (1H, dd, $J_{2,3}$ = 9.5 Hz, $J_{3,4}$ = 9.2 Hz, H-3), 7.32-7.73 (14H, m, Ph).

Anal. Calcd for $C_{32}H_{37}O_8NSiS{\cdot}0.5H_2O$: C, 60.74; H, 6.05; N, 2.21; S, 5.07. Found: C, 60.61; H, 5.78; N, 2.15; S, 5.19.

2,3-Di-*O*-acetyl-4-*O*-*tert*-butyldiphenylsilyl-5-*N*,6-*O*-carbamoyl-1,5-dideoxy-1,5-imino-D-mannitol (8). A mixture of **7** (79 mg, 0.13 mmol), cesium acetate (484 mg, 2.53 mmol) and 18-crown-6 (42 mg, 0.16 mmol) in toluene (3.0 mL) was heated at 100 °C for 22 h with stirring under an argon atmosphere, and then cooled.

The reaction mixture was diluted with $CHCl_3$, washed with water and brine, and dried over $MgSO_4$, concentrated. The residue was chromatographed on a column of silica gel with toluene-ethyl acetate (4:1) to give **8** (50 mg, 77%), mp 158-159 °C (EtOH), $[\alpha]_D^{27}$ -18.2° (*c* 0.71, $CHCl_3$); ^1H NMR δ 1.01 (9H, s, *t*-Bu), 1.31 (3H, s, Ac), 1.79 (3H, s, Ac), 3.15 (1H, dd, $J_{1a,1b}$ = 15 Hz, $J_{1a,2}$ = 1.8 Hz, H-1a), 3.80 (1H, ddd, $J_{4,5}$ = 9.2 Hz, $J_{5,6a}$ = 3.7 Hz, $J_{5,6b}$ = 7.9 Hz, H-5), 3.83 (1H, t, $J_{3,4}$ = $J_{4,5}$ = 9.2 Hz, H-4), 3.88 (1H, dd, $J_{1a,1b}$ = 15 Hz, $J_{1b,2}$ = 2.5 Hz, H-1b), 4.03 (1H, dd, $J_{5,6a}$ = 3.7 Hz, $J_{6a,6b}$ = 9.2 Hz, H-6a), 4.36 (1H, dd, $J_{5,6b}$ = 7.9 Hz, $J_{6a,6b}$ = 9.2 Hz, H-6b), 4.86 (1H, dd, $J_{2,3}$ = 2.8 Hz, $J_{3,4}$ = 9.2 Hz, H-3), 5.26 (1H, ddd, $J_{1a,2}$ = 1.8 Hz, $J_{1b,2}$ = 2.5 Hz, $J_{2,3}$ = 2.8 Hz, H-2), 7.36-7.74 (10H, m, Ph).

Anal. Calcd for $C_{27}H_{33}O_7NSi$: C, 63.38; H, 6.50; N, 2.74. Found: C, 63.43; H, 6.53; N, 2.79.

1,5-Dideoxy-1,5-imino-D-mannitol (2). A solution of **8** (32.2 mg, 0.063 mmol) in 1M NaOH-ethanol (1 : 2; v/v, 1.8 mL) was heated at 60-65 °C with stirring under an argon atmosphere for 1.5 h, and then cooled to room temperature. The resulting solution was directly poured into a column of Dowex 50W-X8 (H^+) resin. The alkaloid fractions, eluted with 1M NH_4OH, were combined and concentrated to give **2** (9.2 mg, 89%) as a solid, mp 183-185 °C (MeOH-ether) [lit.[3a] mp 183-185 °C]; $[\alpha]_D^{26}$ -45.9° (*c* 0.16, H_2O), [lit.[3c] $[\alpha]_D$ -40.0° (*c* 0.90, H_2O)]; ^1H NMR (D_2O) δ 2.51 (1H, td, $J_{4,5}$ = 9.3 Hz, $J_{5,6}$ = 3.9 Hz, H-5), 2.79 (1H, dd, $J_{1a,1b}$ = 14 Hz, $J_{1a,2}$ = 1.5 Hz, H-1a), 3.03 (1H, dd, $J_{1a,1b}$ = 14 Hz, $J_{1b,2}$ = 2.6 Hz, H-1b), 3.59 (1H, dd, $J_{2,3}$ = 2.9 Hz, $J_{3,4}$ = 9.3 Hz, H-3), 3.64 (1H, t, $J_{3,4}$ = $J_{4,5}$ = 9.3 Hz, H-4), 3.78 (2H, brd, J = 3.9 Hz, H-6a, H-6b), 4.02 (1H, m, H-2); ^{13}C NMR (D_2O) δ 50.9, 63.1, 63.2, 70.9, 71.7, 77.1.

2,3-Di-*O*-benzyl-*N*-benzyloxycarbonyl-6-*O*-*tert*-butyldiphenylsilyl-4-*O*-methanesulfonyl-1,5-dideoxy-1,5-imino-D-glucitol (9). To a stirred solution of **4** (1.72 g, 2.40 mmol) in dichloromethane-pyridine (2 : 1; 9 mL) was added dropwise methanesulfonyl chloride (0.28 mL, 3.61 mmol) at 0 °C. After stirring for 3.5 h at 0 °C, ice was added and stirring was further continued for 12 h. The reaction mixture was poured into ice-water, and then extracted with chloroform. The extracts were successively washed with dil. HCl solution, sat. $NaHCO_3$ solution, water and brine, dried over $MgSO_4$ and concentrated. The residue was chromatographed on a column of silica gel with

hexane-ethyl acetate (8:1 → 4:1) gave **9** (1.78 g, 93%), $[\alpha]_D^{23}$ +15.3° (*c* 0.35, $CHCl_3$); ^1H NMR (DMSO-d_6, 80 °C) δ 0.98 (9H, s, *t*-Bu), 3.00-3.06 (4H, brs, Ms-, H-1a), 3.66 (1H, brs, H-2), 3.87 (1H, dd, $J_{5,6a}$ = 7.6 Hz, $J_{6a,6b}$ = 10 Hz, H-6a), 3.89 (1H, dd, $J_{2,3}$ = 3.0 Hz, $J_{3,4}$ = 3.6 Hz, H-3), 3.96 (1H, dd, $J_{5,6b}$ = 6.7 Hz, $J_{6a,6b}$ = 10 Hz, H-6b), 4.10 (1H, brd, $J_{1a,1b}$ = 12 Hz, H-1b), 4.47-4.65 (4H, m, PhC*H*), 4.65 (1H, m, H-5), 4.99 (1H, dd, $J_{3,4}$ = 3.6 Hz, $J_{4,5}$ = 3.0 Hz, H-4), 4.99, 5.10 (2H, each brd, J = 12 Hz, PhC*H*), 7.21-7.59 (25H, m, Ph).

Anal. Calcd for $C_{45}H_{51}O_8NSiS$: C, 68.07; H, 6.47; N, 1.76; S, 4.04. Found: C, 68.02; H, 6.53; N, 1.67; S, 3.92.

2,3-Di-*O*-benzyl-*N*-benzyloxycarbonyl-6-*O*-*tert*-butyldiphenylsilyl-4-*O*-monochloromethylsulfonyl-1,5-dideoxy-1,5-imino-D-glucitol (10). To a stirred solution of **4** (103 mg, 0.14 mmol) and 2,6-lutidine (42 μL, 0.36 mmol) in dichloromethane (0.8 mL) was added dropwise chloromethylsulfonyl chloride (15 μL, 0.17 mmol) at 0 °C under an argon atmosphere. After stirring for 3 h at 0 °C, ice-water was added and stirring was further continued for 3 h. The reaction mixture was poured into ice-water, and then extracted with chloroform. The extracts were successively washed with dil. HCl solution, sat. $NaHCO_3$ solution, water and brine, dried over $MgSO_4$ and concentrated to give **10** (120 mg) as an unstable oil. This was employed in the next step without further purification.

^1H NMR δ 1.00 (9H, s, *t*-butyl), 3.05-3.11 (1H, m, H-1a), 3.50-4.75 (12H, m, H-1b, H-2, H-3, H-5, H-6a, H-6b, CH_2S, PhC*H*), 4.88-5.32 (3H, m, H-4, PhC*H*), 7.21-7.59 (25H, m, Ph).

4-*O*-Benzoyl-2,3-di-*O*-benzyl-*N*-benzyloxycarbonyl-6-*O*-*tert*-butyldiphenylsilyl-1,5-dideoxy-1,5-imino-D-galactitol (11). a) A mixture of **9** (1.38 g, 1.74 mmol) and sodium benzoate (1.25 g, 8.68 mmol) in hexamethylphosphoric triamide (20 mL) was stirred at 120 °C under an argon atmosphere for 16 h. After cooling, the reaction mixture was poured into water, before the resulting solution was extracted with ether. The extracts were successively washed with water and brine, dried over $MgSO_4$ and concentrated. The residue was chromatographed on a column of silica gel with toluene-ethyl acetate (250:1 → 100:1) to give **11** (761 mg, 54%).

b) A mixture of **10** (120 mg, 0.14 mmol) and sodium benzoate (104 mg, 0.72 mmol) in hexamethylphosphoric triamide (2 mL) was stirred at 65-70 °C under an argon atmosphere for 7 h. The reaction mixture was treated by the method described above to give **11** (71 mg, 60% from **4**), $[\alpha]_D^{24}$ +10.2° (*c* 0.84, $CHCl_3$); ^1H NMR (DMSO-d_6, 80 °C) δ 0.92 (9H, s, *t*-Bu), 3.16 (1H, dd, $J_{1a,1b}$ = 15 Hz, $J_{1a,2}$ = 1.5 Hz, H-1a), 3.77 (1H, brs, H-2), 3.94~3.97 (2H, m, H-3, H-6a), 4.20 (1H, brd, H-1b), 4.27 (1H, dd, $J_{5,6b}$ = 9.0 Hz, $J_{6a,6b}$ = 11 Hz, H-6b), 4.50~4.63 (4H, m, PhC*H*), 4.85 (1H, m, H-5), 5.04, 5.17 (2H, each d, J = 13 Hz, PhC*H*), 5.47 (1H, dd, $J_{3,4}$ = 2.9 Hz, $J_{4,5}$ = 6.4 Hz, H-4), 7.13-7.83 (30H, m, Ph).

Anal. Calcd for $C_{51}H_{53}O_7NSi$: C, 74.70; H, 6.51; N, 1.71. Found: C, 74.73; H, 6.55; N, 1.65.

4-*O*-Benzoyl-2,3-di-*O*-benzyl-*N*-benzyloxycarbonyl-1,5-dideoxy-1,5-imino-D-galactitol (12). To a stirred mixture of **11** (700 mg, 0.85 mmol) and acetic acid (67 mg, 1.12 mmol) in tetrahydrofuran (6 mL) was added tetrabutylammonium fluoride (a 1.0 M solution in tetrahydrofuran; 1.12 mL) at room temperature under an argon atmosphere, the mixture then being stirred for 43 h. The reaction mixture was diluted with ethyl acetate, successively washed with water and brine, dried over $MgSO_4$ and concentrated. The residue was chromatographed on a column of silica gel with toluene-ethyl acetate (8:1) to give **12** (421 mg, 87% yield), $[\alpha]_D^{23}$ +1.4° (*c* 0.35, $CHCl_3$); ^1H NMR (DMSO-d_6, 80 °C) δ 3.39 (1H, dd, $J_{1a,1b}$ = 15 Hz, $J_{1a,2}$ = 1.5 Hz, H-1a), 3.70 (1H, m, H-6a), 3.80 (1H, brs, H-2), 3.95 (1H, dd, $J_{2,3}$ = 3.7 Hz, $J_{3,4}$ = 3.4 Hz, H-3), 3.97 (1H, m, H-6b), 4.20 (1H, brd, $J_{1a,1b}$ = 15 Hz, H-1b), 4.38 (1H, brt, OH), 4.50, 4.60 (2H, each d, J = 12 Hz, PhC*H*-), 4.58 (1H, m, H-5), 4.64 (2H, brs, PhC*H*), 5.10, 5.11 (2H, each d, J = 13 Hz, PhC*H*), 5.47 (1H, dd, $J_{3,4}$ = 3.4 Hz, $J_{4,5}$ = 6.1 Hz, H-4), 7.24-7.97 (20H, m, Ph).

Anal. Calcd for $C_{35}H_{35}O_7N$: C, 72.27; H, 6.07; N, 2.41. Found: C, 72.02; H, 6.08; N, 2.44.

2,3-Di-*O*-benzyl-*N*-benzyloxycarbonyl-1,5-dideoxy-1,5-imino-D-galactitol (13) and 2,3-Di-*O*-benzyl-5-*N*,6-*O*-carbamoyl-1,5-dideoxy-1,5-imino-D-galactitol (14). To a stirred solution of **12** (350 mg, 0.62 mmol) in methanol (5 mL) was added sodium methoxide (20 mg, 0.45 mmol). The mixture was stirred at

room temperature for 6 h, neutralized with Dowex 50 W-X8 (H^+ form) resin, and filtered. The filtrate was concentrated, and the residue was chromatographed on a column of silica gel with toluene-ethyl acetate (4:1) to give **13** (207 mg, 72%). Further elution with toluene-ethyl acetate (2:1) gave **14** (50 mg, 21%) as needles.

13. $[\alpha]_D^{24}$ +12.6° (*c* 0.90, $CHCl_3$); ^1H NMR (DMSO-d_6, 60 °C) δ 3.18 (1H, brd, $J_{1a,1b}$ = 14 Hz, H-1a), 3.65~3.68 (2H, m, H-2, H-3), 3.72 (1H, ddd, $J_{5,6a}$ = 4.6 Hz, $J_{6a,6b}$ = 12 Hz, $J_{6a,OH}$ = 5.9 Hz, H-6a), 3.83 (1H, ddd, $J_{5,6b}$ = 8.8 Hz, $J_{6a,6b}$ = 12 Hz, $J_{6b,OH}$ = 5.6 Hz, H-6b), 3.98 (1H, ddd, $J_{3,4}$ = 2.7 Hz, $J_{4,5}$ = 5.9 Hz, $J_{4,OH}$ = 5.4 Hz, H-4), 4.11 (1H, brd, $J_{1a,1b}$ = 14 Hz, H-1b), 4.23 (1H, dd, $J_{6a,OH}$ = 5.9 Hz, $J_{6b,OH}$ = 5.6 Hz, 6-OH), 4.29 (1H, ddd, $J_{4,5}$ = 5.9 Hz, $J_{5,6a}$ = 4.6 Hz, $J_{5,6b}$ = 8.8 Hz, H-5), 4.42, 4.54 (2H, each d, J = 12 Hz, PhC*H*-), 4.58, 4.68 (2H, each d, J = 12 Hz, PhC*H*-), 4.99 (1H, d, $J_{4,OH}$ = 5.4 Hz, 4-OH), 5.03, 5.06 (2H, each d, J = 13 Hz, PhC*H*), 7.21-7.35 (15H, m, Ph).

Anal. Calcd for $C_{28}H_{31}O_6N$: C, 70.42; H, 6.54; N, 2.93. Found: C, 70.33; H, 6.68; N, 2.91.

14. mp 179-179.5 °C (EtOH) {lit.[5] mp 176 °C}, $[\alpha]_D^{24}$ +3.3° (*c* 0.36, $CHCl_3$) {lit.[5] $[\alpha]_D^{20}$ +5.0 ° (*c* 0.70, $CHCl_3$)}; ^1H NMR (DMSO-d_6, 40 °C) δ 2.71 (1H, dd, $J_{1a,1b}$ = 13 Hz, $J_{1a,2}$ = 10 Hz, H-1a), 3.47 (1H, dd, $J_{2,3}$ = 9.3 Hz, $J_{3,4}$ = 2.3 Hz, H-3), 3.72 (1H, ddd, $J_{1a,2}$ = 10 Hz, $J_{1b,2}$ = 6.2 Hz, $J_{2,3}$ = 9.3 Hz, H-2), 3.83 (1H, ddd, $J_{4,5}$ = 1.7 Hz, $J_{5,6a}$ = 4.2 Hz, $J_{5,6b}$ = 8.5 Hz, H-5), 3.89 (1H, dd, $J_{1a,1b}$ = 13 Hz, $J_{1b,2}$ = 6.2 Hz, H-1b), 3.95 (1H, brt, $J_{3,4}$ = 2.3 Hz, $J_{4,5}$ = 1.7 Hz, H-4), 4.17 (1H, dd, $J_{5,6a}$ = 4.2 Hz, $J_{6a,6b}$ = 8.3 Hz, H-6a), 4.24 (1H, t, $J_{5,6b}$ = 8.5 Hz, $J_{6a,6b}$ = 8.3 Hz, H-6b), 4.60, 4.70 (2H, each d, J = 12 Hz, PhC*H*), 4.66 (2H, brs, PhC*H*), 5.29 (1H, d, $J_{4,OH}$ = 4.4 Hz, 4-OH), 7.24-7.40 (10H, m, Ph).

Anal. Calcd for $C_{21}H_{23}O_5N$: C, 68.28; H, 6.28; N, 3.79. Found: C, 68.05; H, 6.24; N, 3.81.

1,5-Dideoxy-1,5-imino-D-galactitol (3). Compound **13** (117 mg, 0.26 mmol) was hydrogenated as described for **6**, and then purified by using ion-exchange chromatography (Dowex 50W-X8, H^+ form) eluting with 1M ammonium hydroxide solution. After solvent evaporation, the residual syrup was dissolved in a small amount of methanol and then precipitated by addition of acetone. Reprecipitation with ethanol and

acetone gave **3** (22 mg, 55%) as a hygroscopic powder, $[\alpha]_D^{23}$ +49.6° (*c* 0.16, H_2O), {lit.[8] $[\alpha]_D^{23}$ +52.8° (*c* 1.0, H_2O)}; ^1H NMR (D_2O) δ 2.41 (1H, dd, $J_{1a,1b}$ = 13 Hz, $J_{1a,2}$ = 11 Hz, H-1a), 2.79 (1H, brt, H-5), 3.15 (1H, dd, $J_{1a,1b}$ = 13 Hz, $J_{1b,2}$ = 5.3 Hz, H-1b), 3.49 (1H, dd, $J_{2,3}$ = 9.8 Hz, $J_{3,4}$ = 3.1 Hz, H-3), 3.62 (1H, dd, $J_{5,6a}$ = 7.0 Hz, $J_{6a,6b}$ = 11 Hz, H-6a), 3.67 (1H, dd, $J_{5,6b}$ = 6.5 Hz, $J_{6a,6b}$ = 11 Hz, H-6b), 3.78 (1H, ddd, $J_{1a,2}$ = 11 Hz, $J_{1b,2}$ = 5.3 Hz, $J_{2,3}$ = 9.8 Hz, H-2), 4.02 (1H, dd, $J_{3,4}$ = 3.1 Hz, $J_{4,5}$ = 1.4 Hz, H-4); ^{13}C NMR (D_2O) δ 49.4, 59.4, 61.8, 68.5, 69.7, 75.5.

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