# Highly Selective Synthesis of 1-*N*-Iminosugars of the D-Glucose and -Glucuronic Acid Types

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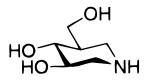
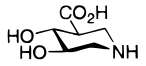
Members of a new class of iminosugars, the 1-*N*-iminosugars, have been known to act as specific and potent inhibitors of $\beta$-glycosidases.[1−3] [In this text, we use a nomenclature convention in which compounds with a nitrogen atom at the anomeric position (piperidine derivatives) are named as "1-*N*-iminosugars". They are also called isofagomine derivatives or 1-azasugars.] Although these 1-*N*-iminosugars have great potential as useful molecular probes to study the biological implication of $\beta$-glycosidases, their syntheses are rather tedious because of the lack of a well-established method for introducing the aminomethyl (or its equivalent) group required to produce the 1-*N*-iminosugar. In our ongoing program of developing inhibitors of glycozymes (enzymes involved in carbohydrate biosynthetic and catabolic pathways), we needed to establish a general synthetic route to provide these iminosugars in large quantity for further study of their biological activity. Herein we describe an efficient synthetic approach that provides the easy access to 1-*N*-iminosugar derivatives of glucose **1** and glucuronic acid **2**, starting from a readily obtainable (*R*)-2,3-*O*-cyclohexylidene-glyceraldehyde **3**.[4]




**1**




**2**

**Synthesis of D-Glucose Type 1-*N*-Iminosugar 1.** Horner-Emmons condensation[5] of the (*R*)-2,3-*O*-cyclohexylidene-glyceraldehyde **3**[4] using trimethylphosphonoacetate and sodium hydride afforded the $\alpha,\beta$-unsaturated methyl ester **4** in an *E*/*Z* ratio of 10:1 in 83% yield[6] (Scheme 1). Treatment of **4** with DIBAL in $CH_2Cl_2$ gave the allylic alcohol **5**, which was subjected to Sharpless asymmetric epoxidation[7] with diethyl L-(+)-tartrate to afford the epoxy alcohol **6** in 90% yield.

**Table 1. Nucleophilic Epoxy Ring Opening Reaction of 6 with $CN^-$**

| entry | conditions | yield | product ratio (**7a**:**7b**) |
|---|---|---|---|
| 1 | $Et_2AlCN$/toluene/rt/48 h | 91% | 1:1 |
| 2 | LiCN/THF/reflux/5 h | 50% | 10:1 |
| 3 | KCN/$Bu_4NI$/Ti(O*i*Pr)$_4$/DMSO/rt/60 h | >90% | 12:1 |

Because our strategy was to introduce a cyanide group in a diastereo- and regioselective manner to construct the 1-*N*-iminopyranose framework, we examined the regioselective ring opening reaction of the epoxide **6** with a cyanide anion (Table 1). When Nagata's reagent,[8] diethylaluminum cyanide ($Et_2AlCN$), was applied, an excellent yield of a cyano diol derivative was obtained. However, almost no regioselectivity was observed, and the reaction afforded the desired 2-cyanide derivative **7a** and 3-cyanide derivative **7b** in a ratio of 1:1[9] (entry 1). The regioselectivity was determined on the basis of the $^1$H NMR spectrum of the product, in which the H-2 of the 2-CN isomer **7a** appeared at $\delta$ 2.93 ppm as a doublet of triplets, and the H-3 of the 3-CN isomer **7b** appeared at $\delta$ 3.13 ppm as a doublet of doublets (Figure 1). This result was consistent with our previous observation in the reaction of (2*R*,3*S*)-3-[(trityl)oxy]oxiranemethanol with $Et_2AlCN$, in which the C-3 attack was favorable.[10]

When the epoxide was treated with a highly reactive LiCN[11] prepared in situ from lithium hydride and acetone cyanohydrin, the desired product **7a** was obtained in good regioselectivity (10:1) but in low chemical yield as a result of a competing side reaction[12] (50% based on recovered staring material) (entry 2).

Good regioselectivity was obtained by treating the epoxide **6** under the Sharpless conditions,[13] with KCN and $Bu_4NI$ in the presence of Ti(O-*i*Pr)$_4$ (entry 3). Although the reaction proceeded rather slowly (60 h at room temperature), an enhanced chemical yield and regioselectivity were observed, with **7a** and **7b** being formed in a ratio of 12:1 (>90% yield).

We speculated that the addition of Ti(O-*i*Pr)$_4$ to **6** could form a relatively rigid complex such as complex A (Figure 1),[14] in which the backside of the C-3 position of the

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(1) (a) Ichikawa, M.; Ichikawa, Y. *Bioorg. Med. Chem.* **1995**, *3*, 161−165. (b) Ichikawa, Y.; Igarashi, Y.; Ichikawa, M.; Suhara, Y. *J. Am. Chem. Soc.* **1998**, *120*, 3007−3018.

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(4) (a) Sugiyama, T.; Sugawara, H.; Watanabe, M.; Yamashita, K. *Agric. Biol. Chem.* **1984**, *48*, 1841−1844. (b) Chattopadhyay, A.; Mamdapur, V. R. *J. Org. Chem.* **1995**, *60*, 585−587.

(5) Iida, H.; Yamazaki, N.; Kibayashi, C. *J. Org. Chem.* **1987**, *52*, 3337−3342.

(6) They were easily separable on silica gel chromatography. $R_f$ values for the *E*- and *Z*-isomers were 0.5 and 0.6 in EtOAc−hexanes (1:4), respectively.

(7) (a) Katsuki, T.; Sharpless, K. B. *J. Am. Chem. Soc.* **1980**, *102*, 5974−5976. (b) Katsuki, T.; Lee, W. M.; Ma, P.; Martin, V. S.; Masamune, S.; Sharpless, K. B.; Tuddenham, D.; Walker, F. J. *J. Org. Chem.* **1982**, *47*, 1373−1378.

(8) Nagata, W.; Yoshioka, M.; Okamura, T. *Tetrahedron Lett.* **1966**, 847−852.

(9) Although **7a** and **7b** were separable on silica gel TLC (**7a**, $R_f$ = 0.31 and **7b**, $R_f$ = 0.21 in $CHCl_3$−EtOAc−MeOH 10:1:1), we purified the desired regioisomer (the 2-CN derivative) after the silylation as **8**. For the comparison, the two regioisomers **7a** and **7b** were differentiated by their $^1$H NMR spectra in which the methyne proton at the carbon attached to the CN appears at $\delta$ 2.93 ppm as a doublet of triplets (H-2) for **7a**, whereas for **7b** it appears at $\delta$ 3.13 ppm as a doublet of doublets (H-3).

(10) Makino, K.; Ichikawa, Y. *Tetrahedron Lett.* **1998**, *39*, 8245−8248.

(11) Ciaccio, J. A.; Stanescu, C.; Bontemps, J. *Tetrahedron Lett.* **1992**, *33*, 1431−1434.

(12) Unexpectedly the cyclohexylidene group seemed to come off during the reaction, as evidenced by the cyclohexanone formation on TLC.

(13) Caron, M.; Sharpless, K. B. *J. Org. Chem.* **1985**, *50*, 1557−1560.

(14) We generated this structure using the semiempirical PM3 transition metal method of Spartan (version 4.1.1).

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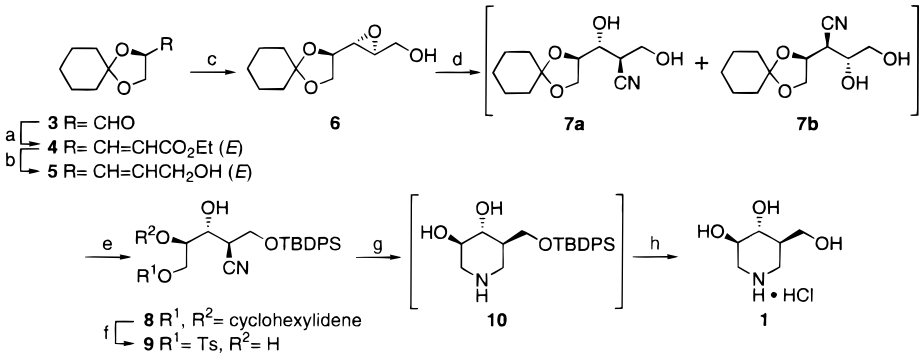
**Scheme 1**[a]




[a] Reagents and conditions: (a) $(MeO)_2P(O)CH_2CO_2Me$/NaH/benzene/THF ($E$:$Z$ = 10:1, 83%); (b) DIBAL/$CH_2Cl_2$ (92%); (c) Ti(O-*i*Pr)$_4$/(+)-diethyl tartrate/*t*BuOOH/$CH_2Cl_2$ (90%); (d) KCN/$Bu_4NI$/Ti(O-*i*Pr)$_4$/DMSO; (e) TBDPSCl/imidazole/DMF (88% in twp steps); (f) (1) 80% AcOH (2) *p*-TsCl/pyridine (70% in two steps); (g) $H_2$/Raney Ni/EtOH; (h) 2 N HCl (58% in two steps).

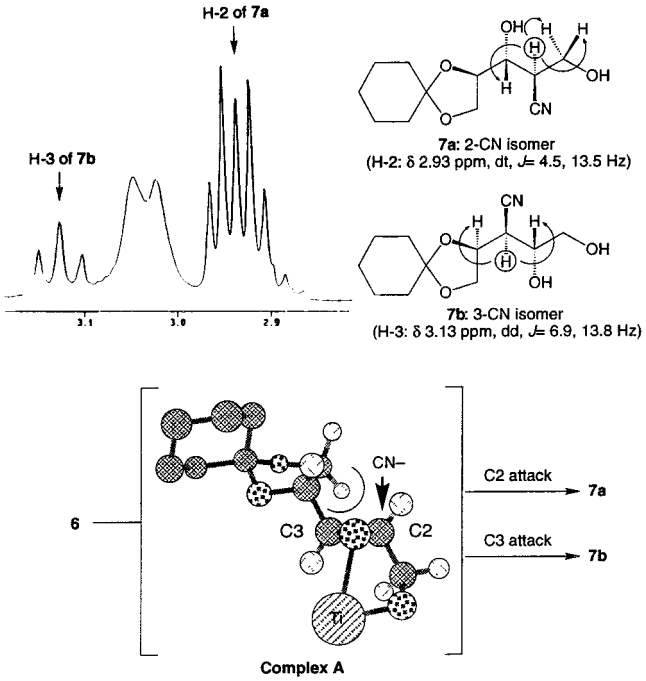
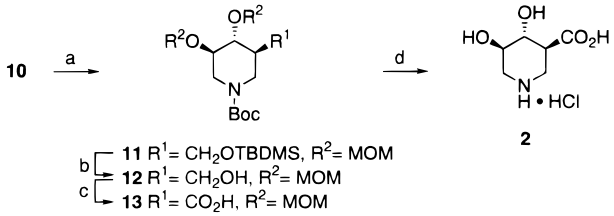



**Figure 1.** $^1$H NMR spectrum of a mixture of **7a** and **7b** used to determine the regioselectivity of the reaction of **6** and $CN^-$ and a proposed conformation of the complex formed between **6** and Ti(OiPr)$_4$.

epoxide **6** was blocked by a hydrogen of the C-5 methylene group; in contrast, the C-2 position would be well opened to the $CN^-$ backside-attack by the complex formation of the hydroxymethyl and the epoxide oxygen groups with the titanium.

A mixture of **7a** and **7b** was treated with *tert*-butylchlorodiphenyl silane (TBDPSCl)[15] to give **8** in high yield. The cyclohexylidene group in **8** was selectively removed with 80% acetic acid to afford the corresponding triol. The triol derivative was selectively tosylated at the C-5 primary alcohol with *p*-toluenesulfonyl chloride in pyridine to give **9** in good yield. Hydrogenation with Raney Ni first reduced the nitrile group to the corresponding aminomethyl group, which then displaced the 5-OTs group and allowed the intramolecular cyclization to proceed to give a silyl-protected 1-*N*-iminosugar derivative **10**. Finally, treatment of **10** with 2 N HCl gave the D-glucose type 1-*N*-iminosugar **1**.[1b,2a]

**Scheme 2**[a]




[a] Reagents and conditions: (a) $Boc_2O/Et_3N$/MeOH (62% in two steps from **9**); (b) (1) MOMCl/*i*Pr$_2$NEt/$CH_2Cl_2$, (2) $Bu_4NF$/THF (74% in two steps); (c) (1) $(COCl)_2$/DMSO/$Et_3N/CH_2Cl_2$ (2) $H_2O_2/NaClO_2/NaHPO_4/CH_3CN-H_2O$ (82% in two steps); (d) 3 N HCl (89%).

**Synthesis of D-Glucuronic Acid Type 1-*N*-Iminosugar 2.** The D-glucuronic acid type 1-*N*-iminosugar **2** was also prepared from the synthetic intermediate **10**, which was treated this time with $Boc_2O$ to give **11** as a single product (Scheme 2). The diol moiety was protected with methoxymethyl (MOM) groups, and the silyl protecting group was removed with $Bu_4NF$ to give **12**. Oxidation to the corresponding uronic acid derivative **13** was carried out stepwise:[1b] first with DMSO and $(COCl)_2$,[16] giving an aldehyde group, and further with $H_2O_2$ and $NaClO_2$[17] in a $CH_3CN-$phosphate buffer to produce a D-glucuronic acid derivative **13**. All of the protecting groups of **13** were removed by 3 N HCl to provide the glucuronic acid type 1-*N*-iminosugar **2**.[1b]

In summary, we have described an efficient synthetic procedure for 1-*N*-iminosugars of D-glucose **1** (25% overall yield) and D-glucuronic acid **2** (14% overall yield) from readily obtainable (*R*)-2,3-*O*-cyclohexylidene-glyceraldehyde employing Sharpless asymmetric epoxidation and the regioselective epoxide ring opening reaction with cyanide.

This synthetic route has allowed preparation of substantial amounts of 1-*N*-iminosugars for further study of their effects in biological systems in which glycozymes play a key role.

## Experimental Section

**General Methods.** The reagents used were purchased from Aldrich, Sigma, or Acros, and the solvents were reagent grade and used as supplied. $^1$H NMR spectra were recorded at 300

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MHz, and $^{13}C$ NMR spectra were recorded at 75 MHz. Internal standards used in $^1H$ NMR spectra were TMS ($\delta$ 0.00) for $CDCl_3$ and HOD ($\delta$ 4.78) for $D_2O$ and in $^{13}C$ NMR were $CDCl_3$ ($\delta$ 75.0) for $CDCl_3$ and $CH_3CN$ ($\delta$ 1.30) for $D_2O$. Mass spectral data were analyzed by the Mass Spectrometry Laboratory at University of Illinois and Mass Spectrometry Facility at Johns Hopkins University.

**Methyl (4*S*)-4,5-(Cyclohexylidenedioxy)-(2*E*)-pentenoate (4).** To a mixture of NaH (6.5 g, 163.8 mmol) in benzene (80 mL) was added a solution of trimethylphosphonoacetate (26 mL, 180 mmol) in THF (100 mL) at 0 °C, and the mixture was stirred at the same temperature for 1 h. Then, a solution of (*R*)-2,3-*O*-cyclohexylidene glyceraldehyde **3**[4] (14.0 g, 81.9 mmol) in THF (80 mL) was added, and the resulting mixture was allowed to warm to room temperature and stirred for 2 h. The reaction mixture was poured into ice water (250 mL) and extracted with EtOAc. The combined extracts were washed with brine, dried ($MgSO_4$), and concentrated. The residue was chromatographed on silica gel with EtOAc−hexane (1:6) to give the *E*-isomer **4** (14.1 g, 76%) and *Z*-isomer (1.4 g, 7%) as a colorless oil: $^1H$ NMR ($CDCl_3$) $\delta$ 1.35 (m, 3H, cyclohexylidene group), 1.56 (m, 7H, cyclohexylidene group), 3.61 (dd, 1H, $J$ = 7.5 Hz), 3.69 (s, 3H), 4.12 (dd, 1H, $J$ = 6.9, 7.8 Hz), 4.61 (dd, 1H, $J$ = 5.7, 3 Hz), 6.06 (d, 1H, $J$ = 15.3 Hz), 6.83 (dd, 1H, $J$ = 5.4, 15.3 Hz); $^{13}C$ NMR ($CDCl_3$) $\delta$ 23.5, 23.6, 24.8, 35.0, 35.8, 51.3, 68.1, 74.3, 110.4, 121.4, 145.2, 166.0; HRMS FAB calcd for $C_{12}H_{18}O_4$ ($M^+$) 226.1205, found. 226.1208.

**(4*S*)-4,5-(Cyclohexylidenedioxy)-(2*E*)-penten-1-ol (5).** To a solution of **4** (5.0 g, 22 mmol) in $CH_2Cl_2$ (150 mL) under argon was added a 1.0 M solution of DIBAL in toluene (44.0 mL, 44 mmol) at 0 °C, and the mixture was stirred for 2 h at room temperature. Acetone (20 mL) was slowly added to the reaction mixture. An aqueous sodium potassium tartrate solution (100 mL) and EtOAc (200 mL) were subsequently added, and the resulting mixture was stirred until the layers were clearly separated. The aqueous layer was extracted with EtOAc, and the combined extracts were washed with brine, dried ($MgSO_4$), and concentrated. The residue was chromatographed on silica gel with EtOAc−hexane (1:3) to give **5** (4.0 g, 92%) as a colorless oil: $^1H$ NMR ($CDCl_3$) $\delta$ 1.24 (m, 3H, cyclohexylidene group), 1.46 (m, 7H, cyclohexylidene group), 3.42 (m, 2H, 1H of hydroxyl group), 3.93 (m, 3H), 4.37 (dd, 1H, $J$ = 7.2, 13.8 Hz), 5.53 (dd, 1H, $J$ = 7.5, 15.6 Hz), 5.76 (dt, 1H, $J$ = 5.1, 9.9, 15.6 Hz); $^{13}C$ NMR ($CDCl_3$) $\delta$ 23.5, 23.5, 24.7, 35.0, 35.9, 61.7, 68.6, 75.8, 109.6, 127.9, 133.1; HRMS FAB calcd for $C_{11}H_{18}O_3$ ($M^+$) 198.1256, found 198.1259.

**(2*S*,3*R*,4*R*)-2,3-Epoxy-4,5-(cyclohexylidenedioxy)pentan-1-ol (6).** To a slurry of flame-dried powdered MS4A (15 g) in dry $CH_2Cl_2$ (400 mL) under argon were sequentially added titanium tetraisopropoxide (23.4 mL, 78.6 mmol) and diethyl L-(+)-tartrate (13.5 mL, 78.6 mmol) at −20 °C, and the mixture was stirred for 30 min. A solution of **5** (10.4 g, 52.4 mmol) in dry $CH_2Cl_2$ (120 mL) was added, and the resulting mixture was stirred at −20 °C for 30 min. A solution of *tert*-butylhydroperoxide in decane (5.0−6.0M, 21 mL, 104.8 mmol) was subsequently added dropwise to the mixture, and the resulting mixture was kept for 16 h at −15 °C. Aqueous tartaric acid (10%, 200 mL) was added at −20 °C, and the whole was allowed to warm to room temperature. After being stirred for 1 h, the reaction mixture was filtered, and the filtrate was extracted with $CH_2Cl_2$. The combined extracts were washed with brine, dried ($MgSO_4$), and concentrated. The residue was chromatographed on silica gel with EtOAc−hexane (1:6) to give **6** (10.1 g, 90%) as a colorless oil: $^1H$ NMR ($CDCl_3$) $\delta$ 1.30 (br s, 3H, cyclohexylidene group), 1.51 (m, 7H, cyclohexylidene group), 2.01 (br s, 1H, hydroxyl group), 2.97 (dd, 1H, $J$ = 2.4, 4.8 Hz), 3.03 (dd, 2H, $J$ = 2.4, 4.8 Hz, 1H of hydroxyl group), 3.54 (dd, 1H, $J$ = 3.9, 12.6 Hz), 3.74 (m, 1H), 3.81 (dd, 1H, $J$ = 1.8, 12.9 Hz), 4.00 (m, 2H); $^{13}C$ NMR ($CDCl_3$) $\delta$ 23.5, 23.7, 24.8, 34.8, 35.7, 55.1, 55.4, 60.8, 65.4, 74.6, 110.3; HRMS FAB calcd for $C_{11}H_{18}O_4$ ($M^+$) 214.1205, found 214.1207.

**(2*R*,3*R*,4*R*)-1-[(*tert*-Butyldiphenylsilyl)oxy)]-2-cyano-4,5-(cyclohexylidenedioxy)-3-hydroxypentane (8).** To a stirred solution of **6** (3.3 g, 15.4 mmol) in DMSO (60 mL) under argon were added potassium cyanide (2.5 g, 38.5 mmol) and tetrabutylammonium iodide (10.2 g, 27.7 mmol) at room temperature, and then titanium tetraisopropoxide (11.4 mL, 38.5 mmol) was slowly added. The reaction mixture was stirred at room temperature for 60 h, diluted with EtOAc (200 mL), and poured into aqueous $NaHCO_3$ solution (100 mL). The resulting mixture was extracted with EtOAc, and the combined extracts were washed with brine, dried ($MgSO_4$), and concentrated. This was employed for the next step without further purification.

To a solution of the above mixture (4.0 g) in DMF (60 mL) were added imidazole (3.4 g, 43.1 mmol) and *tert*-butylchlorodiphenyl silane (5.1 mL, 18.5 mmol) at 0−5 °C, and the mixture was stirred for 2 h at room temperature. The reaction mixture was poured into ice-cooled aqueous $NaHCO_3$ solution (150 mL) and extracted with $Et_2O$. The combined extracts were successively washed with aqueous $NaHCO_3$ solution and brine, dried ($MgSO_4$), and concentrated. The residue was chromatographed on silica gel with EtOAc−hexane (1:30) to give the **8** (6.5 g, 88% in 2 steps) as a colorless oil: $^1H$ NMR ($CDCl_3$) $\delta$ 1.14 (s, 9H), 1.44 (m, 3H, cyclohexylidene group), 1.51 (m, 7H, cyclohexylidene group), 2.35 (d, 1H, $J$ = 8.7 Hz), 2.88 (dt, 1H, $J$ = 4.5, 13.8 Hz), 3.95 (m, 3H), 4.11 (m, 2H), 4.45 (dt, $J$ = 2.1, 6.3, 8.7 Hz), 7.43 (m, 6H), 7.77 (m, 4H); $^{13}C$ NMR ($CDCl_3$) $\delta$ 19.3, 23.6, 23.9, 25.0, 26.7, 34.2, 35.9, 39.1, 60.6, 65.7, 68.1, 75.3, 110.5, 118.6, 27.8, 129.9, 123.0, 135.6, 135.6; HRMS FAB calcd for $C_{28}H_{38}NO_4Si$ ($M + H)^+$ 480.2570, found 480.2571.

**(2*R*,3*R*,4*S*)-1-[(*tert*-Butyldiphenylsilyl)oxy)]-2-cyano-3,4-dihydroxy-5-[(*p*-toluenesulfonyl)oxy]pentane (9).** A solution of **8** (2.0 g, 4.2 mmol) in 80% acetic acid (30 mL) was stirred at room temperature for 40 h. The resulting reaction mixture was then concentrated and coevaporated with toluene (30 mL × 2), and the residue was employed for the next step without further purification.

To a stirred solution of the above residue (1.7 g) in pyridine (40 mL) was added *p*-toluenesulfonyl chloride (1.0 g, 5.5 mmol) in one portion at room temperature, and the resulting mixture was stirred for 4 h at room temperature. The reaction mixture was poured into ice water (100 mL) and extracted with EtOAc. The combined extracts were successively washed with aqueous $NaHCO_3$ solution and brine, dried ($MgSO_4$), and concentrated. The residue was chromatographed on silica gel with EtOAc−hexane (1:4) to give **9** (1.6 g, 70% in 2 steps) as a colorless oil: $^1H$ NMR ($CDCl_3$) $\delta$ 1.01 (s, 9H), 2.44 (s, 3H), 3.00 (dt, 2H, $J$ = 4.5, 13.5 Hz), 3.39 (br, 1H, hydroxyl group), 3.98 (m, 3H), 4.17 (bs, 3H), 7.34 (d, 2H, $J$ = 8.4 Hz), 7.42 (m, 6H), 7.70 (m, 4H), 7.82 (d, 2H, $J$ = 8.4 Hz); $^{13}C$ NMR ($CDCl_3$) $\delta$ 19.1, 21.5, 26.6, 37.5, 60.5, 67.9, 68.8, 70.3, 118.4, 127.6, 129.9, 132.2, 132.3, 135.4, 135.5, 145.2; HRMS FAB calcd for $C_{29}H_{36}NO_6SSi$ ($M + H)^+$ 554.2032, found 554.2031.

**D-Glucose Type 1-*N*-Iminosugar: (3*R*,4*R*,5*R*)-5-(Hydroxymethyl)-piperidine-3,4-diol Hydrochloride Salt (1).** A solution of **9** (2.0 g, 3.6 mmol) and Raney Ni (5 mL) in EtOH (20 mL) was stirred vigorously under $H_2$ atmosphere at room temperature for 50 h. After removal of the catalyst by filtration, the filtrate was concentrated to give a crude product **10**, which was employed for the next step without further purification.

A solution of the residue **10** in 2 N HCl (15 mL) was stirred overnight at room temperature, and the reaction mixture was concentrated. The residue was diluted with water (10 mL) and applied onto a column of Dowex 50W-X8 [$H^+$] resin. The column was washed with water, and the product was eluted out with 3% $NH_4OH$. The fractions containing **1** were pooled and concentrated. The residue was chromatographed on silica gel with 2-propanol−$H_2O$−$NH_4OH$ (7:2:1) to give chromatographically pure **1**. Water (10 mL) and 1 N HCl (20 mL) were added to the residue, and the solution was concentrated to form a hydrochloride salt of the iminosugar. The residue was applied onto a column of Sephadex G-25 (2 cm × 65 cm) and eluted with water. The fractions containing **1** were pooled and lyophilized from water to afford **1** (300 mg, 58% in 2 steps) as a colorless amorphous powder (HCl salt): $^1H$ and $^{13}C$ NMR spectra were in good agreement with those reported;[1b,2a] $^1H$ NMR ($D_2O$) $\delta$ 1.91−2.02 (m, 1H, H-5), 2.88 (t, 1H, $J$ = 11.9 Hz), 2.97 (t, 1H, $J$ = 12.7 Hz), 3.48−3.56 (m, 3H), 3.71−3.85 (m, 3H); $^{13}C$ NMR ($D_2O$) $\delta$ 43.6, 45.6, 49.4, 61.8, 71.1, 73.9; HRMS FAB calcd for $C_6H_{13}NO_3$ ($M + H)^+$ 148.0974, found 148.0976.

***tert*-Butyl (3*R*,4*R*,5*S*)-5-[(*tert*-Butyldiphenylsilyl)oxy)]-3,4-dihydroxypiperidine-1-carboxylate (11).** A mixture of **9** (1.6 g, 2.9 mmol) and Raney Ni (3 mL) in EtOH (20 mL) was stirred vigorously under $H_2$ atmosphere at room temperature

for 50 h. After removal of the catalyst by filtration, the filtrate was concentrated to give a crude product **10**, which was employed for the next step without further purification.

A mixture of the residue **10**, $Boc_2O$ (1.2 g, 5.8 mmol), and $Et_3N$ (0.8 mL, 5.8 mmol) in MeOH (30 mL) was stirred for 12 h at room temperature and concentrated. The residue was chromatographed on silica gel with EtOAc−hexane (1:4) to give **11** (850 mg, 62% in 2 steps) as a colorless oil: $^1$H NMR ($CDCl_3$) $\delta$ 1.07 (9H, s), 1.45 (9H, s), 1.79 (br s, 1H), 2.53 (m, 2H), 3.49 (br s, 2H), 3.78 (br s, 2H), 4.03−4.16 (m, 1H), 4.25 (br s, 1H), 7.40−7.44 (m, 6H), 7.65−7.68 (m, 4H); $^{13}$C NMR ($CDCl_3$) 19.1, 26.8, 28.3, 46.5, 71.6, 80.1, 127.8, 129.9, 135.5 (d), 154.4; HRMS FAB calcd for $C_{27}H_{39}NO_5Si$ $(M + H)^+$ 486.2676, found 486.2684.

***tert*-Butyl (3*R*,4*R*,5*S*)-5-(Hydroxymethyl)-3,4-di-*O*-methoxymethyl-3,4-dihydroxypiperidine-1-carboxylate (12).** To a stirred solution of **11** (0.5 g, 1.0 mmol) and $i$Pr$_2$NEt (0.5 mL, 2.8 mmol) in $CH_2Cl_2$ (15 mL) was added MOMCl (0.23 mL, 3.0 mmol) at 0−5 °C, and the mixture was allowed to warm to room temperature and stirred for 30 h at room temperature. The reaction mixture was poured into ice-cooled aqueous $NaHCO_3$ solution (150 mL) and extracted with $Et_2O$. The combined extracts were successively washed with aqueous $NaHCO_3$ solution and brine, dried ($MgSO_4$), and concentrated. The residue was employed for the next step without further purification.

A mixture the above residue and $Bu_4NF$ (1 M solution in THF, 1.3 mL, 1.5 mmol) in THF (20 mL) was stirred for 4 h at room temperature. The reaction mixture was poured into $H_2O$ (30 mL)−EtOAc (50 mL), and the aqueous layer was re-extracted with EtOAc. The combined extracts were successively washed with aqueous $NaHCO_3$ solution and brine, dried ($MgSO_4$), and concentrated. The residue was chromatographed on silica gel with EtOAc−hexane (1:2) to give **12** (340 mg, 74% in two steps) as a colorless oil: $^1$H NMR ($CDCl_3$) $\delta$ 1.38 (s, 9H), 1.63 (br s, 1H), 2.91−2.94 (br s, 2H), 3.31 (s, 3H), 3.36 (s, 3H), 3.45−3.48 (m, 3H), 3.78−3.86 (m, 2H), 4.62 (m, 3H), 4.82 (d, 1H, $J$ = 6.6 Hz); $^{13}$C NMR ($CDCl_3$) $\delta$ 28.2, 42.9, 55.4, 56.0, 60.4, 79.9, 95.9, 98.3, 154.7; HRMS FAB calcd for $C_{15}H_{30}NO_7$ $(M + H)^+$ 336.2022, found 336.2024.

***tert*-Butyl (3*R*,4*R*,5*S*)-5-Carboxyl-3,4-di-*O*-methoxymethyl-3,4-dihydroxypiperidine-1-carboxylate (13).** A solution of DMSO (0.17 mL, 2.4 mmol) in $CH_2Cl_2$ (5 mL) was added dropwise to a cooled solution of $(COCl)_2$ (0.14 mL, 1.6 mmol) in $CH_2Cl_2$ (20 mL) at −78 °C, and the mixture was stirred for 30 min. To this mixture was added dropwise a solution of **12** (270 mg, 0.8 mmol) in $CH_2Cl_2$ (10 mL) at −78 °C, and the resulting mixture was stirred another 1.5 h at the same temperature. A solution of $Et_3N$ (0.6 mL, 4.0 mmol) in $CH_2Cl_2$ (10 mL) was then added to the reaction mixture, which was gradually warmed to 0−5 °C over 30 min. The reaction mixture was poured into ice water and extracted with EtOAc. The combined extracts were successively washed with water, aqueous $NaHCO_3$ solution, and brine, dried ($MgSO_4$), and concentrated to give an aldehyde derivative, which was employed for the next step without further purification.

To a mixture of the above aldehyde and $NaH_2PO_4 \cdot H_2O$ (1.1 g, 8.0 mmol) in $CH_3CN$ (15 mL)−$H_2O$ (3 mL) were successively added a 35% $H_2O_2$ solution (0.09 mL, 1.0 mmol) and a solution of $NaClO_2$ (80%, 110 mg, 1.0 mmol) in water (10 mL) at 0−5 °C, and the resulting mixture was stirred for 1h at room temperature. The reaction was terminated by the addition of $Na_2SO_3$ (100 mg), and the resulting mixture was extracted with EtOAc. The combined extracts were successively washed with water and brine, dried ($MgSO_4$), and concentrated. The residue was chromatographed on silica gel with $CHCl_3$−MeOH (50:1) to give **13** (230 mg, 82% in two steps) as a colorless oil: $^1$H NMR ($CDCl_3$) $\delta$ 1.40 (s, 9H), 2.58 (ddd, 1H, $J$ = 4.2, 9.3, 12.9 Hz), 2.85 (dd, 1H, $J$ = 9.3, 13.2 Hz), 3.10 (br s, 1H), 3.30 (s, 3H), 3.33 (s, 3H), 3.48 (br s, 1H), 3.86 (dd, 1H, $J$ = 8.4 Hz), 3.98−4.08 (m, 2H), 4.62−4.67 (m, 3H), 4.80 (d, 1H, $J$ = 6.0 Hz); $^{13}$C NMR ($CDCl_3$) $\delta$ 28.1, 47.3, 55.5, 55.9, 77.2, 78.1, 80.5, 96.1, 97.4, 154.4, 175.2; HRMS FAB calcd for $C_{15}H_{28}NO_8$ $(M + H)^+$ 350.1815, found 350.1815.

**D-Glucuronic Acid Type 1-*N*-Iminosugar: (3*R*,4*R*,5*S*)-5-Carboxylpiperidine-3,4-diol Hydrochloride Salt (2).** A solution of **13** (100 mg, 0.29 mmol) in 3 N HCl (15 mL) was stirred overnight at room temperature and concentrated. The residue was chromatographed on silica gel with 2-propanol−$H_2O$−$NH_4OH$ (7:2:1) to give chromatographically pure **2**. Water (10 mL) and 1 N HCl (20 mL) were added to the residue, and the solution was concentrated to form a hydrochloride salt of the iminosugar **2**. The iminosugar **2** was further purified by a column of Sephadex G-25 (2 cm × 65 cm) eluted with water. The fractions containing **2** were pooled and lyophilized from water to afford **2** (50 mg, 89%) as a colorless amorphous powder (HCl salt): NMR data of **2** were in good accordance to those reported;[1b] $^1$H NMR ($D_2O$) $\delta$ 2.77 (ddd, 1H, $J$ = 4.2, 7.4, 7.8 Hz, H-5), 2.94 (dd, 1H, $J$ = 7.5, 12.9 Hz, H-2ax), 3.24 (dd, 1H, $J$ = 7.8, 13.2 Hz, H-6ax), 3.34 (dd, 1H, $J$ = 3.9, 12.9 Hz, H-2eq), 3.38 (dd, 1H, $J$ = 5.1, 13.2 Hz, H-6eq), 3.76 (ddd, 1H, $J$ = 3.3, 7.2, 7.7 Hz, H-3), 3.93 (t, 1H, $J$ = 6.9 Hz, H-4); $^{13}$C NMR ($D_2O$) $\delta$ 44.2, 46.2, 47.9, 69.0, 71.9, 175.7; HRMS FAB calcd for $C_6H_{12}NO_4$ $(M + H)^+$ 162.0766, found 162.0766.

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**Supporting Information Available:** $^1$H and $^{13}$C NMR spectra for compounds **1**−**6**, **8**, **9**, and **11**−**13**. This material is available free of charge via the Internet at http://pubs.acs.org.

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