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SYNTHESIS OF BENZYL TETRA-*O*-ACETYL-α-L-GLUCOPYRANOSIDE FROM BENZYL 2,3-DIDEOXY-β-D-*ERYTHRO*-HEX-2-ENOPYRANOSIDE

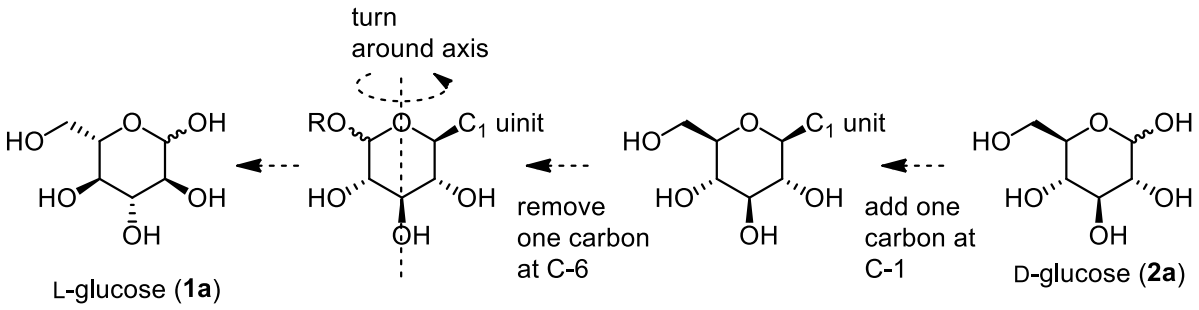
Hayato Okazaki, Yuji Ueda, Kengo Hanaya, Mitsuru Shoji, and Takeshi Sugai*

Department of Pharmaceutical Sciences, Keio University, 1-5-30 Shibakoen, Minato-ku, Tokyo 105-8512, Japan; E-mail: sugai-tk@pha.keio.ac.jp

Abstract – Benzyl tetra-*O*-acetyl-α-L-glucopyranoside was synthesized from benzyl 2,3-dideoxy-β-D-*erythro*-hex-2-enopyranoside in six steps and 19% overall yield. Epoxidation from the β-side of the double bond between C-2 and C-3 of the starting material along with the subsequent regioselective ring opening by the backside attack of a hydroxide ion at C-3 furnished an intermediate with D-*ido*-stereochemistry. The inversion at C-5 was performed by an epimerization, by way of an *N*-cyclohexylenamine, after the chemoselective oxidation at primary hydroxy group of the C-6 to an aldehyde. The present synthesis of L-glucose derivatives implies the sequential stereochemical inversion of C-2 to C-5 of D-glucose. As the present synthesis keeps the whole skeleton and the order of carbon atoms based on the original numbering of D-glucose, it would work well for the synthesis of specifically labeled derivatives, beginning from isotopically labeled D-glucoses.

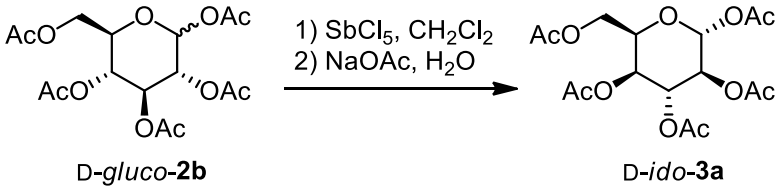
INTRODUCTION

Many efforts have been devoted to the preparation of L-sugars from naturally abundant D-sugars, and have ingeniously utilized the stereochemistry and the oxidation state of carbon atoms involved in the starting material.[1] Most of the previously reported examples to prepare L-glucose (**1a**) from D-glucose (**2a**) added one carbon at C-1, and removed one carbon by cleaving the C−C bond between C-5 and C-6 (Scheme 1).[2-9] In those examples, the original skeleton was inverted and C-1 to C-5 were regarded as C-5 to C-1, respectively.



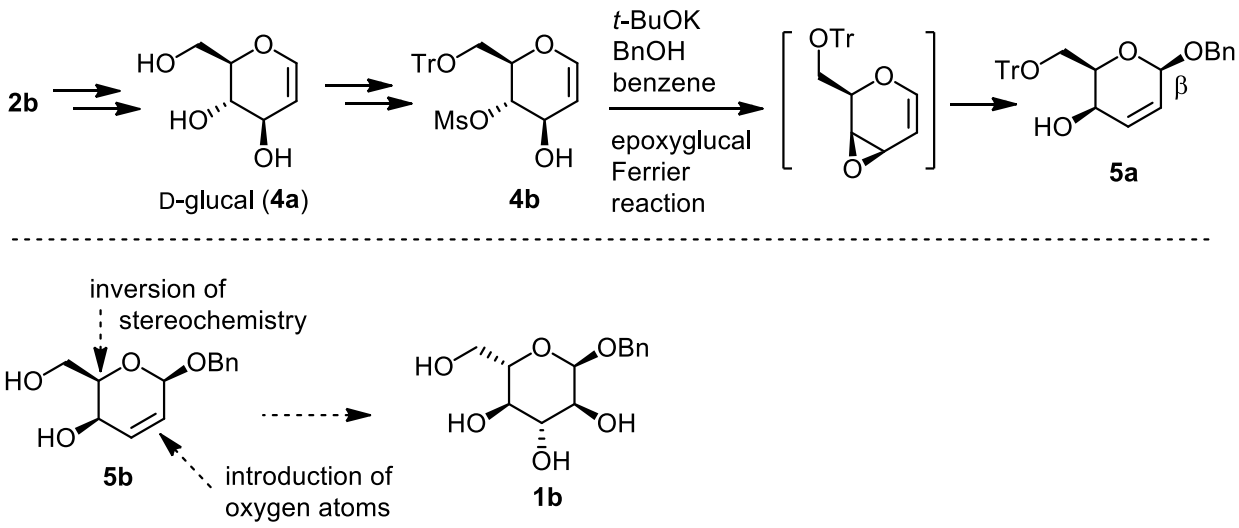
Scheme 1. Previously reported important transformations to L-glucose (**1a**) from D-glucose (**2a**)

In contrast, Paulsen and co-workers attempted an entirely different approach, which was the simple stereochemical inversion of C-2 to C-5 (Scheme 2). They treated penta-*O*-acetyl-D-glucose (**2b**) with $SbCl_5$, and they obtained the D-*ido*-configuration as the pentaacetyl form (**3a**) in one pot, with three configurations at C-2 to C-4, which were inverted compared with that of the starting material.[10]



Scheme 2. Paulsen's one-pot contiguous stereochemical inversion at C-2 to C-4 of D-glucose derivative **2b** to D-idose derivative **3a**

Crotti and co-workers reported an interesting variation[11,12] of the Ferrier reaction[13] of D-glucal derivatives such as **4b**, which can be prepared from **2b** through several steps. The reaction accompanies the inversion at C-4 with the concomitant introduction of a double bond between C-2 and C-3.

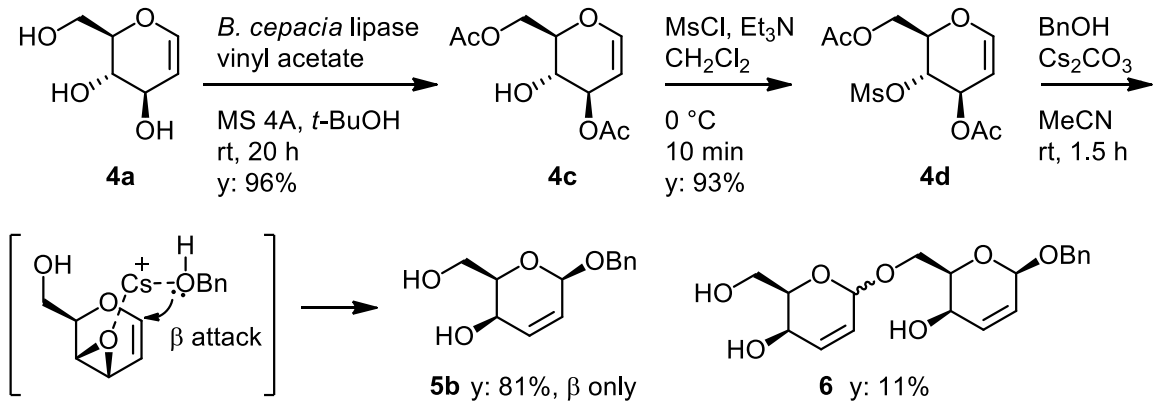


Scheme 3. Crotti's Ferrier reaction of an epoxyglucal intermediate and our planned synthesis of L-glucose derivative **1b** from **5b**

The resulting product **5a** can be submitted to vicinal dihydroxylation, to recover all functional groups in the sugar. We envisioned that the introduction of oxygen atoms with the appropriate stereochemistry on an analogous substance **5b** and the inversion of the stereochemistry in C-5 at the later step, would enable the transformation of **5b** into L-glucose derivative **1b** (Scheme 3).

RESULTS AND DISCUSSION

We independently developed a transformation similar to Crotti's work (Scheme 4). D-Glucal (**4a**) was regioselectively acetylated[14] to **4c** and the subsequent methylsulfonylation of the liberated hydroxy group at C-4 furnished **4d** in 89% yield. Our first attempt was the treatment of **4d** with benzyl alcohol, *n*-butyllithium and *N*,*N*,*N*,*N*-tetramethylethylenediamine, and **5b** was obtained in 44% yield. All acetyl groups were removed by the action of benzyl alkoxide under the reaction conditions. X-Ray crystallographic analysis revealed exclusive β-orientation at the anomeric position,[15] which indicated the formation of an epoxide intermediate. As the product **5b** gradually decomposed under the reaction conditions, a higher yield could not be obtained by varying the reaction time and/or reaction temperature. We were disappointed that with Crotti's potassium *tert*-butoxide,[11] the product was a 1:1 mixture of the α- and β-anomers in yields as low as 10%.

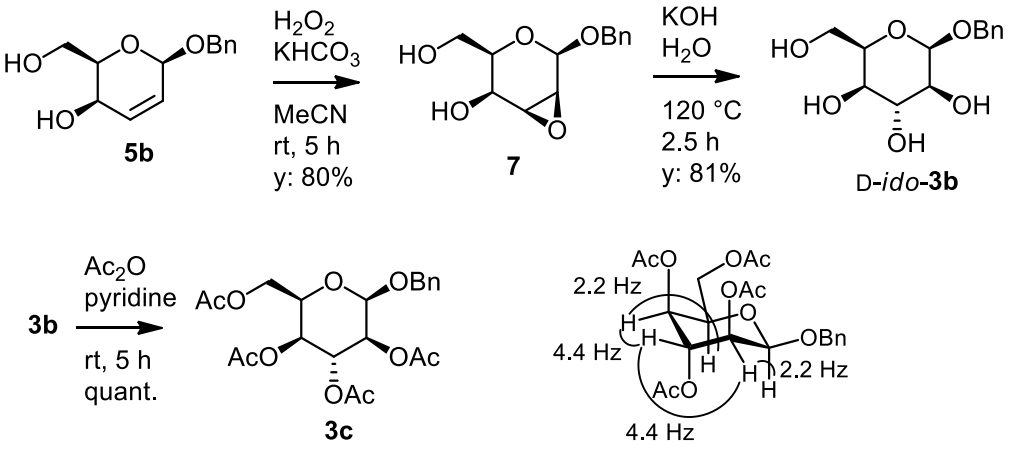


Scheme 4. Short and stereoselective synthesis of **5b** from **4a**, *via* a Ferrier reaction of an epoxyglucal intermediate

We thought both of the weakening the basicity of the reagents and Lewis acidity of metallic cation to be important for the stability of the product. For the improvement of β-selectivity, a larger atomic radius of metallic cation would be advantageous by allowing the coordination between oxygen atoms in the epoxide and benzyl alcohol. For these reasons, we chose cesium carbonate as the next candidate. The solvent was MeCN, in which the solubility of cesium carbonate is high. Under these conditions, the reaction proceeded with good β-stereoselectivity and in higher yield (64%). In this case, a side product (24%) was observed, whose dimeric structure (**6**) was suggested by its ^{1}H-NMR and mass spectra.

Finally, an increase in the number of equivalents of benzyl alcohol from 10 to 20 improved the yield (81%) of **5b**, which was isolated in a crystalline form, and side product formation was suppressed (11%) (Scheme 4). Our presently developed route has two advantages, 1) ready accessibility of the reaction substrate **4d** from **4a**, and 2) ease of isolation and high purity of product **5b** owing to its crystalline property.

Toward the synthesis of L-glucose, the addition of an oxygen atom at C-2 and C-3 was achieved by Payne oxidation[16] to give **7** in 80% yield. The next step was a regioselective ring opening reaction of the β-oriented epoxide. Simple aqueous alkaline conditions at high temperature[17] were effective, to furnish **3b** in 81% yield. The stereochemistry of the product was confirmed by the coupling constants in the ^{1}H-NMR data of the corresponding acetate **3c** (Scheme 5), which indicated that the three acetoxy groups each occupied an axial orientation. The nucleophilic attack of the hydroxide ion exclusively occurred at C-3. The β-orientation of the substituent on the anomeric position was important for achieving such a high regioselectivity. That is, when the stereochemistry at the anomeric position was reversed to be α, which is predominant under conventional Ferrier conditions,[13] we observed a lower preference for the nucleophilic attack at C-3 in a structurally similar substrate.[18]

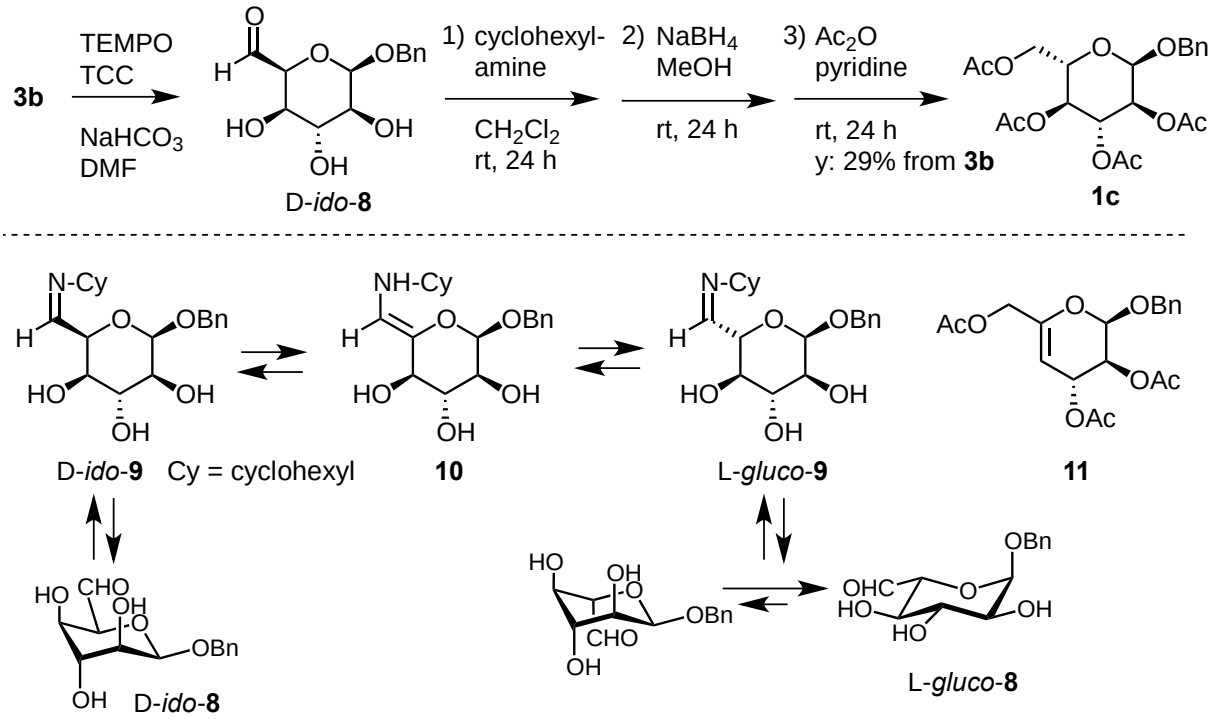


Scheme 5. Synthesis of D-idoside **3b** from **5b**, and the confirmation of the stereochemistry as **3c**

The remaining task was the stereochemical inversion from the D-*ido* configuration to the L-*gluco* configuration at C-5. Previously reported examples[19,20] regarding π-facial selective hydroboration of 6-deoxy-hex-5-enopyranosides described the preferential formation of the D-*ido*-configuration over the L-*gluco*-configuration. As an alternative, the epimerization at C-5 was realized by way of an aldehyde **8** (Scheme 6). The β-benzyloxy group at C-1 in the starting material would be effective in influencing the equilibrium of epimerization. Such an anomeric alkoxy substituent occupies the thermodynamically stable axial position and with the three hydroxy groups at C-2 to C-4, promotes the epimerization at the

position adjacent to the aldehyde group, so that all substituents except for that at C-1 adopt the equatorial position.

The transformation of **3b** to L-*gluco*-**1c** was achieved in this way, although the yield was moderate (29%, four steps from **3b**). First, the primary hydroxy group at C-6 in **3b** was selectively oxidized to aldehyde **8**, by the action of 2,2,6,6-tetramethylpiperidine 1-oxyl (TEMPO), trichloroisocyanuric acid (TCC), and sodium hydrogen carbonate in *N*,*N*-dimethylformamide (DMF).[21] The crude aldehyde was submitted to the sequential three-step treatment as follows: 1) cyclohexylamine in CH_2Cl_2, 2) reduction of the crude mixture including polar impurities with sodium borohydride in MeOH, and 3) acetylation of all resulting hydroxy groups for the ease of purification of the product. The epimerization is presumed to occur by way of the *N*-cyclohexylenamine **10** of the imines D-*ido*- and L-*gluco*-**9**. Note that the undesired isomer D-*ido*-**3b** was not obtained at all. The stereochemistry of **1c** was confirmed by the comparison of the sign of the optical rotation [$[\alpha]_D^{21}$ –135.6 (*c* 1.00, $CHCl_3$)] and ^{1}H-NMR spectrum with the antipodal D-*gluco* isomer [lit.[22] $[\alpha]_D^{25}$ +144.1 (*c* 2.01, $CHCl_3$)].



Scheme 6. Inversion of the stereochemistry at C-5 by way of an aldehyde **8** to L-glucose derivative **1c**

Before the above-mentioned result, several amines other than cyclohexylamine were examined. First, the use of two secondary amines was attempted. With the use of piperidine, the formation of **11** could not be avoided and the epimerization was slow, resulting in a mixture of L-*gluco*-**1c** (5%), D-*ido*-**3c** (5%), and **11** (8%), after acetylation. Di-*n*-butylamine also furnished a complex mixture in lower yield. We concluded that the increased basicity of secondary amines was deleterious, promoting the elimination of

acetate on C-4, at the stage of iminium ion formation. Moreover, the enhanced stability of the enamine intermediate resulted in the lower combined yield of the products. In the case of another primary amine, *n*-butylamine, although the yield of **1c** was slightly higher (36%) compared with the use of cyclohexylamine, **3c** (24%) was also obtained after acetylation. A bulkier substituent such as a cyclohexyl group was advantageous in the equilibrium between the D-*ido*- and L-*gluco*-imines, but the reason for the lower combined yield in the case of cyclohexylamine is not clear.

In addition, an attempt at the epimerization of aldehyde **8** itself, which was exposed to basic conditions with KOH in aqueous EtOH,[23] resulted in the formation of **11** in 21% yield after acetylation, but the desired **1c** was obtained only in a trace amount. β-Elimination of the hydroxy group at C-4 also predominated, in this case, under strongly basic conditions.

In conclusion, benzyl 2,3-dideoxy-β-D-*erythro*-hex-2-enopyranoside (**5b**) was transformed to a protected form of L-glucose (**1c**) with 19% overall yield in six steps. The π-facial selective epoxidation from the β-side of the double bond between C-2 and C-3 of **5b** proceeded smoothly. The subsequent ring opening occurred exclusively at C-3 of **7**, taking advantage of the β-substituent at the anomeric position. Chemoselective oxidation at C-6 of **3b** furnished an aldehyde **8**. The inversion at C-5 with D-*ido* stereochemistry was performed, presumably by way of *N*-cyclohexylenamine **10**. The β-benzyloxy group involved in this route was effective also at the stage of epimerization. As the present synthesis keeps the whole skeleton and the order of carbon atoms based on the original numbering of D-glucose, it would work well for the synthesis of specifically labeled derivatives, starting from isotopically labeled D-glucoses.

EXPERIMENTAL

All mps are uncorrected. ^{1}H-NMR spectra were measured at 500 MHz and ^{13}C-NMR spectra were measured at 125 MHz on an Agilent INOVA-500 spectrometer. IR spectra were measured as ATR on a Jeol FT-IR SPX60 spectrometer. High resolution mass spectra were recorded on Jeol JMS-T100LP AccuTOF. Optical rotation values were recorded on a Jasco P-1010 polarimeter. Silica Gel 60 (spherical and neutral; 100-210 μm, 37560-79) from Kanto Chemical Co. was used for column chromatography. Preparative TLC was performed with Merck Silica Gel 60 F_{254} plates (0.5 mm thickness, No. 5744).

3,6-Di-*O*-acetyl-4-*O*-methylsulfonyl-D-glucal (4d)

To a solution of **4c** (500 mg, 2.17 mmol)[14] in anhydrous CH_2Cl_2 (11 mL), triethylamine (454 μL, 3.26 mmol) was added under an argon atmosphere. After cooling to 0 °C, methylsulfonyl chloride (203 μL, 2.61 mmol) was added, and the mixture was stirred for 10 min at the same temperature. The progress of

the reaction was checked by silica gel TLC, developed with $CHCl_3$/MeOH (50:1), R_f for **4d**: 0.61. After consumption of starting material, the mixture was diluted with H_2O and organic materials were extracted with $CHCl_3$ three times. The combined extract was washed sequentially with $NaHCO_3$ aq solution and brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The residue was charged on a silica gel column (20 mL). Elution with hexane/AcOEt (2:1) furnished **4d** (672 mg, quantitative) as a yellow oil; ^{1}H-NMR ($CDCl_3$) δ: 2.10 (3H, s), 2.12 (3H, s), 3.08 (3H, s), 4.29 (1H, dd, J = 2.9, 5.1, 8.3), 4.30 (1H, dd, J = 2.9, 12.5), 4.44 (1H, dd, J = 5.1, 12.5), 4.83 (1H, dd, J = 3.0, 6.2), 5.00 (1H, dd, J = 6.1, 8.3), 5.51 (1H, ddd, J = 1.2, 3.0, 6.1), 6.47 (1H, dd, J = 1.2, 6.2); ^{13}C-NMR ($CDCl_3$) δ: 20.39, 20.67, 38.37, 60.86, 67.38, 72.79, 73.63, 98.41, 145.51, 170.07, 170.26.

Benzyl 2,3-dideoxy-β-D-*erythro*-hex-2-enopyranoside (5b)

To a solution of **4d** (669 mg, 2.17 mmol) in MeCN (22 mL) were added Cs_2CO_3 (1.41 g, 4.33 mmol) and benzyl alcohol (4.53 mL, 43.5 mmol), and the mixture was stirred for 1.5 h at room temperature under an argon atmosphere. The progress of the reaction was checked by silica gel TLC, developed with AcOEt, R_f for **5b**: 0.67; **6**: 0.21. After consumption of starting material, the mixture was diluted with H_2O and organic materials were extracted with $CHCl_3$ three times. The combined extract was washed with brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The residue was charged on a silica gel column (40 mL). Elution with hexane/AcOEt (2:1) furnished **5b** (414 mg, 81%) as a colorless solid; mp 80-81 °C; $[\alpha]_D^{22}$ –107 (*c* 1.33, EtOH); IR cm^{-1}: 3292, 2937, 2872, 1377, 1325, 1176, 1144, 1122, 1051, 970, 951, 876, 787, 744, 696; ^{1}H-NMR ($CDCl_3$) δ: 1.97 (1H, d, J = 10.6), 2.21 (1H, dd, J = 5.9, 7.3), 3.79 (1H, ddd, J = 3.1, 4.3, 6.7), 3.88 (1H, ddd, J = 4.3, 7.3, 12.0), 3.97 (1H, ddd, J = 5.9, 6.7, 12.0), 4.02-4.09 (1H, m), 4.70 (1H, d, J = 11.8), 4.92 (1H, d, J = 11.8), 5.18 (1H, ddd, J = 1.1, 1.3, 1.5), 5.89 (1H, ddd, J = 1.0, 1.1, 10.0), 6.14 (1H, ddd, J = 1.3, 4.6, 10.0), 7.26-7.40 (5H, m); ^{13}C-NMR ($CDCl_3$) δ: 62.5, 62.9, 70.3, 75.1, 96.5, 127.9, 128.0, 128.4, 130.2, 130.9, 137.2.

Further purification of more polar fractions of the above-mentioned chromatography with preparative TLC developed with AcOEt twice furnished **6** as a colorless oil; ^{1}H-NMR ($CDCl_3$, 3:7 mixture of α- and β-anomers) δ: 3.70-4.08 (7H, m), 4.16 (0.7H, dd, J = 6.1, 10.3), 4.32 (0.3H, br,), 4.66 (1H, dd, J = 7.6, 12.4), 4.89 (1H, dd, J = 4.4, 12.4), 5.10-5.30 (2H, m), 5.82-5.96 (2H, m), 6.06-6.20 (2H, m), 7.26-7.40 (5H, m); HR-MS (ESI+) Calcd for $C_{19}H_{24}NaO_7$ $[M+Na]^+$ 387.1420, Found 387.1418.

Benzyl 2,3-dideoxy-2,3-epoxy-β-D-talopyranoside (7)

To a solution **5b** (700 mg, 2.96 mmol) in MeCN (14 mL) were added $KHCO_3$ (91 mg, 0.909 mmol) and H_2O_2 (30% solution, 2.1 mL, 25.9 mmol), and the mixture was stirred for 5 h at room temperature. The progress of the reaction was checked by silica gel TLC, developed with hexane/AcOEt (1:2), R_f for **7**:

0.12. After consumption of starting material, the reaction was quenched with $Na_2S_2O_3$ aq. solution, and organic materials were extracted with AcOEt five times. The combined extract was washed with brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The residue was charged on a silica gel column (30 mL). Elution with hexane/AcOEt (2:1) furnished **7** (598 mg, 80%) as a colorless solid; mp 115-116 °C; $[\alpha]_D^{21}$ –80.7 (*c* 1.00, MeOH); IR cm^{-1}: 3394, 2931, 2877, 1454, 1396, 1367, 1329, 1250, 1107, 1078, 1041, 906, 754, 698; ^{1}H NMR ($CDCl_3$) δ: 3.42 (1H, ddd, *J* = 2.7, 4.9, 7.0), 3.34 (1H, d, *J* = 3.9), 3.58 (1H, dd, *J* = 3.9, 5.1), 3.77 (1H, dd, *J* = 4.9, 11.7), 3.83 (1H, dd, *J* = 7.0, 11.7), 3.93 (1H, br), 4.72 (1H, d, *J* = 12.1), 4.88 (1H, s), 4.95 (1H, d, *J* = 12.1), 7.28-7.42 (5H, m); ^{13}C-NMR ($CDCl_3$) δ: 53.0, 53.8, 61.3, 61.8, 70.8, 77.5, 96.7, 128.1 (×3), 128.5 (×2), 136.8; HR-MS (ESI+) Calcd for $C_{13}H_{16}NaO_5$ $[M+Na]^+$ 275.0911, Found 275.0895.

Benzyl β-D-idopyranoside (3b)

To a solution of **7** (85 mg, 0.337 mmol) in H_2O (6.7 mL) was added KOH (378 mg, 6.74 mmol), and the mixture was stirred for 2.5 h at 120 °C (bath temperature). The progress of the reaction was checked by silica gel TLC, developed with AcOEt, R_f for **3b**: 0.24. After consumption of starting material, the reaction was cooled to 0 °C and quenched with NH_4Cl aq. solution, and organic materials were extracted with AcOEt five times. The combined extract was washed with brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The residue was charged on a silica gel column (3 mL). Elution with hexane/AcOEt (1:2) furnished **3b** (74 mg, 81%) as a colorless amorphous solid; $[\alpha]_D^{21}$ –75.2 (*c* 1.95, MeOH); IR cm^{-1}: 3358, 2891, 2362, 1456, 1018, 847, 733, 698; ^{1}H-NMR (CD_3OD) δ: 3.52 (1H, dd, *J* = 1.5, 3.4), 3.61 (1H, dd, *J* = 0.9, 3.6), 3.77 (1H, dd, *J* = 6.8, 11.2), 3.82 (1H, dd, *J* = 6.8, 11.2), 3.88 (1H, ddd, *J* = 1.5, 5.1, 6.8), 3.95 (1H, dd, *J* = 3.4, 3.6), 4.70 (1H, d, *J* = 11.9), 4.79 (1H, s), 4.93 (1H, d, *J* = 11.9), 7.24-7.42 (5H, m); ^{13}C-NMR ($CDCl_3$) δ: 62.8, 70.3, 71.2, 71.4, 71.9, 76.5, 99.2, 128.8, 129.3 (×2), 129.4 (×2), 139.0; HR-MS (ESI+) Calcd for $C_{13}H_{18}NaO_6$ $[M+Na]^+$ 293.1002, Found 293.1001.

The stereochemistry of **3b** was confirmed after conversion to the corresponding acetate **3c** in a conventional manner; ^{1}H-NMR (CD_3CN) δ: 1.78 (3H, s), 1.80 (3H, s), 1.82 (3H, s), 1.83 (3H, s), 3.92-4.10 (3H, m), 4.39 (1H, d, *J* = 12.0), 4.58 (1H, dd, *J* = 2.2, 4.4), 4.63 (1H, d, *J* = 12.0), 4.67 (1H, dd, *J* = 2.2, 4.4), 4.72 (1H, d, *J* = 2.2), 4.91 (1H, dd, *J* = 4.4, 4.4), 7.06-7.18 (5H, m).

Benzyl 2,3,4,6-tetra-*O*-acetyl-α-L-glucopyranoside (1c)

To a solution of **3b** (41 mg, 0.152 mmol) in DMF (3.0 mL) were added $NaHCO_3$ (382 mg, 4.55 mmol), TEMPO (catalytic amount) and TCC (18 mg, 77.4 μmol) at 0 °C under an argon atmosphere. After being stirred for 2.5 h at the same temperature, the reaction was quenched with $Na_2S_2O_3$ aq. solution, and

organic materials were extracted with AcOEt five times. The combined extract was washed with brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. This was employed for the next step without further purification.

To the solution of the above-mentioned **8** in CH_2Cl_2 (3.0 mL) was added cyclohexylamine (17 μL, 0.148 mmol) at room temperature under an argon atmosphere. After being stirred for 24 h at the same temperature, the reaction was quenched with H_2O (10 mL), and concentrated *in vacuo*. This was employed for the next step without further purification.

To the solution of the above-mentioned crude product in MeOH (3.0 mL) was added $NaBH_4$ (29 mg, 0.767 mmol) at room temperature. After being stirred for 21 h at the same temperature, the reaction was quenched with H_2O (10 mL), and concentrated *in vacuo* to give crude **1b**. This was employed for the next step without further purification.

To the solution of the above-mentioned crude product in pyridine (758 μL) was added acetic anhydride (143 μL, 1.51 mmol), and the mixture was stirred for 19 h at room temperature. The progress of the reaction was checked by silica gel TLC, developed with hexane/AcOEt (2:1), R_f for **1c**: 0.38. After consumption of starting material, the reaction was cooled to 0 °C and quenched with $NaHCO_3$ aq. solution (2.0 mL), and organic materials were extracted with AcOEt three times. The combined extract was washed with brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The residue was charged on a silica gel column (5 mL). Elution with hexane/AcOEt (5:1) furnished **1c** (19 mg, 29% in four steps) as a colorless solid; mp 107-108 °C; $[\alpha]_D^{21}$ –135.6 (*c* 1.00, $CHCl_3$), [lit.[22] $[\alpha]_D^{25}$ +144.1 (*c* 2.01, $CHCl_3$) for D-**1c**]; IR cm^{-1}: 2360, 2341, 1367, 1215, 1034, 895, 739, 698; ^{1}H-NMR ($CDCl_3$) δ: 2.01 (3H, s), 2.02 (3H, s), 2.03 (3H, s), 2.10 (3H, s), 4.01 (1H, dd, *J* = 2.5, 12.2), 4.04 (1H, ddd, *J* = 2.5, 4.2, 9.8), 4.24 (1H, dd, *J* = 4.2, 12.2), 4.57 (1H, d, *J* = 12.2), 4.73 (1H, d, *J* = 12.2), 4.88 (1H, dd, *J* = 3.9, 10.2), 5.09 (1H, dd, *J* = 9.5, 9.8), 5.13 (1H, d, *J* = 3.9), 5.53 (1H, dd, *J* = 9.5, 10.2), 7.28-7.40 (5H, m), ^{13}C NMR ($CDCl_3$) δ: 20.60, 20.62, 20.69, 20.73, 61.7, 67.4, 68.5, 70.0, 70.1, 70.7, 95.0, 127.9 (×2), 128.2, 128.5 (×2), 136.6, 169.6, 170.0, 170.1, 170.7; HR-MS (ESI+) Calcd for $C_{21}H_{26}NaO_{10}$ $[M+Na]^+$ 461.1415, Found 461.1424. Its spectral data were in good accordance with that of the enantiomer previously reported.[22]

Side product **11**: ^{1}H-NMR ($CDCl_3$) δ: 2.01 (3H, s), 2.03 (3H, s), 2.08 (3H, s), 4.43 (1H, d, *J* =12.4), 4.45 (1H, d, *J* =12.4), 4.65 (1H, d, *J* =12.3), 4.84 (1H, d, *J* =12.3), 5.04 (1H, d, *J* = 2.8), 5.13 (1H, dd, *J* = 2.7, 7.6), 5.19 (1H, d, *J* = 2.7), 5.54 (1H, dd, *J* = 2.8, 7.6), 7.28-7.40 (5H, m).

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