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Industrial-Scale Preparation of a Key Intermediate for the Manufacture of Therapeutic SGLT2 Inhibitors

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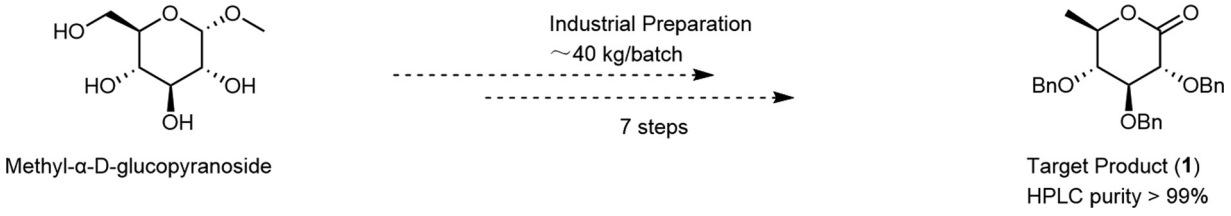

Abstract

(3*R*,4*S*,5*R*,6*R*)-3,4,5-tris(benzyloxy)-6-methyltetrahydro-2*H*-pyran-2-one (**1**) is a key intermediate for the preparation of promising SGLT2 inhibitors currently undergoing clinical tests for diabetes therapy. However, fewer reports have demonstrated the preparation of compound **1** at an industrial scale. In this article, an efficient preparation of the intermediate for the industrial production was explored from commercially available methyl-α-*D*-glucopyranoside in seven steps, including TBS protection, benzyl protection, TBS removal, iodination, reduction, demethylation, and oxidation. The batch of the validation process was 42.82 kg with a HPLC purity of 99.31%. The main advantages of this approach are that the total cost is lower than the reported laboratory-scale synthetic method, the quality is reproducible, and the process is safe and environmentally friendly.

Keywords
- SGLT2 inhibitors
- (3*R*,4*S*,5*R*,6*R*)-3,4,5-tris(benzyloxy)-6-methyltetrahydro-2*H*-pyran-2-one
- industrial production
- safe and environmentally friendly

Introduction

Diabetes is a progressive and chronic metabolic disease caused by insulin deficiency or insulin resistance, eventually leading to severe complications. Although many antihyperglycemics are clinically available, hyperglycemia is still difficult to control. There is a great demand for developing new therapeutic agents with novel mechanisms. SGLT2 (sodium-glucose cotransporter 2) inhibitors are a new type of antidiabetic drugs developed rapidly in recent years, and its action mechanism is different from that of the traditional drugs for this disease. Specifically, the SGLT2 inhibitors promote the

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excretion of excessive glucose in blood into the urine, while inhibiting the reabsorption of glucose by the renal tubules and reducing blood glucose by increasing urine glucose. Compared with other antihyperglycemics, SGLT2 inhibitors also have the advantages of a wide application range, for example, not easy to be hypoglycemia, lowering blood pressure, and reducing body fat. This is a new type of antihyperglycemics with broad application prospects.[1] In recent years, the structure–activity relationship analyses of SGLT2 inhibitors have been reported. The deletion of a 6-OH group on the sugar moiety (6-Me pyranose) led to the discovery of novel SGLT2 inhibitors with clinical priority (►**Fig. 1**).[2–6] Therein, (3*R*,4*S*,5*R*,6*R*)-3,4,5-tris(benzyloxy)-6-methyltetrahydro-2*H*-pyran-2-one (1) as a precursor is often used to synthesize a series of novel 6-Me pyranose SGLT2 inhibitors.

The laboratory-scale synthetic route of **1** has been explored and reported.[4–10] The synthetic route is described in **Scheme 1**. Methyl-α-*D*-glucopyranoside (**2**) was chosen as the starting material, protected and deprotected to give intermediate **3** in three steps. The 6-OH intermediate **3** could be halogenated to give halide **4** in several different ways. The halide **4** was reduced by reductants or catalytic hydrogenation to give methyl 6-deoxyglucoside **5**, which was hydrolyzed with a strong acid to afford lactol **6** as an epimeric mixture. Lactol **6** was oxidized to give the target lactone **1**. Although the above-reported synthetic routes were reasonably designed, and the starting material is relatively economic, there are still some disadvantages that are not suitable for industrialization. First, a NaH/DMF system was used in almost all benzylation protection steps of hydroxyl groups on the sugar ring. Brimacombe et al and Buckley et al[11,12] have reported the thermal instability of NaH/DMF; there will be greater risks on scaling because as reaction volume increases, heat-removal rate will be decreased drastically. Second, Bu_3SnH/AIBN is usually used as a reductant to reduce halide **4** in some research papers, but the organotin reagent is highly toxic for organisms and difficult to dispose. Catalytic hydrogenation could reduce halide **4** but with the side reaction of debenzylation. LAH is highly reactive but not suitable for industrial production. Finally, the by-product of Albright–Goldman oxidation (Ac_2O/DMSO) is Me_2S, which is very unpleasant and unfriendly to the environment. For oxidation of lactol **6**, the cost of using ICl/Cs_2CO_3 is relatively expensive. Therefore, there is an urgent need to develop a low-cost and scalable industrial process for the preparation of compound **1** for the subsequent manufacture of new SGLT2 inhibitors and corresponding clinical drug products.

Based on the analysis of the reported synthetic routes of compound **1**, we adopted a production-friendly procedure from the existing technical solutions.[13,14] The improved synthetic technology showed industrialization potentiality, and gets rid of the operations that did not meet the requirements of safe production and environmental protection. As shown in **Scheme 2**, methyl-α-*D*-glucopyranoside (**2**) was used as the starting material, the 6-OH group of which was protected with TBS, and the remaining hydroxyl groups were benzylated to obtain compound **7**, followed by the removal of the TBS group of **7** with TBAF·$3H_2O$ to yield compound **3**.[13] The 6-OH group of compound **3** was subjected to iodination and $NaBH_4$ reduction to give compound **5**, which underwent hydrolysis demethylation, and metal-free oxidative lactonization[14] to produce the target lactone (**1**). It should be noted that the above-mentioned route requires solving two

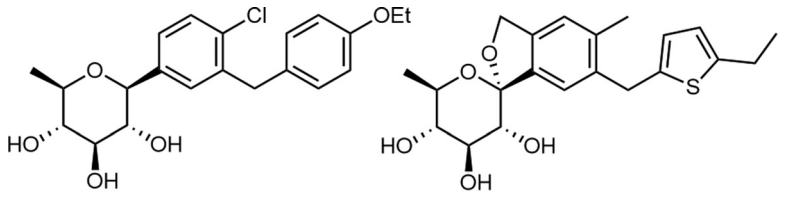
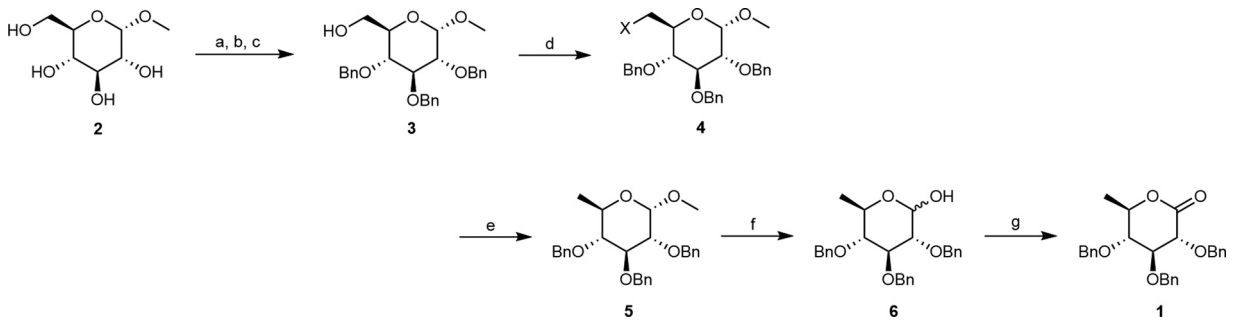
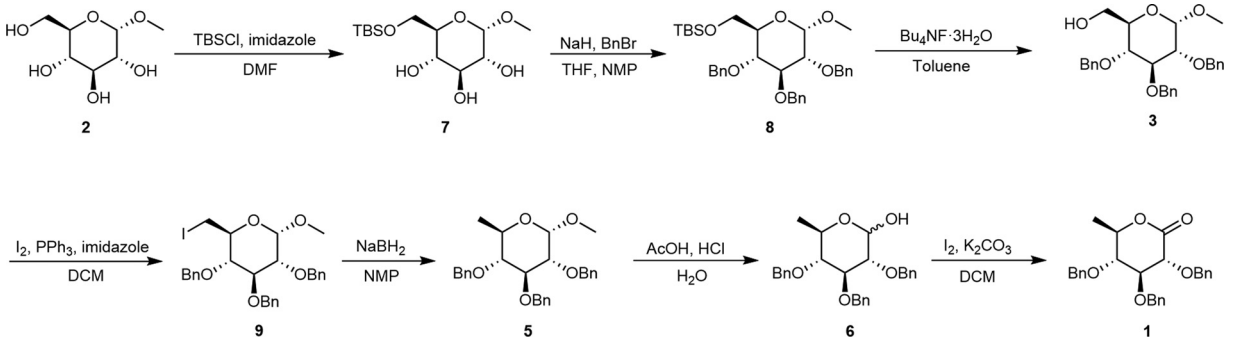


Fig. 1 Clinical research phase of 6-Me pyranose SGLT2 inhibitors.



Scheme 1 The reported synthetic route of compound **1**. Reagents and conditions: (a) TBSCl or TIPSCl, imidazole, DMF; (b) NaH, BnBr, DMF; (c) TBAF, THF; (d) Ph_3P, CBr_4, DMF, THF, X = Br; or I_2, PPh_3, imidazole, toluene, X = I; or (i) MsCl, Py, DCM. (ii) KI, DMF, X = I. (e) Bu_3SnH, AIBN, toluene; or 10% Pd/C, H_2, Et_3N, MeOH/THF; or LAH/THF; (f) 3 mol/L H_2SO_4, aq. AcOH; or 6 mol/L HCl, aq. AcOH; (g) Ac_2O/DMSO, or ICl/Cs_2CO_3, DCM.



Scheme 2 The improved industrial synthetic route of compound **1**.

technical problems: (1) the benzylation of compound **7** to prepare compound **8** and (2) the choice of oxidant for the oxidation of compound **6** to compound **1**. By optimizing the above synthetic route, the two key technical problems were solved and a 40 kg/batch of compound **1** was prepared. The new scheme has the advantages of low cost, high quality, safety, environmental friendliness, and large-scale production.

Results and Discussion

The synthesis of compound **7** was obtained from the TBS protection of 6-OH group of **2** followed by a simple work-up. Compound **7** is usually an oil because it contains a small amount of silanol impurity, which had little effect on the following benzylation reaction, thus, compound **7** was directly used without further purification. According to the existing literature reports, the traditional synthesis of compound **8** is to benzylate 3,4,5-OH groups of compound **7** with NaH/BnBr in a polar aprotic solvent (DMF). The polar aprotic solvents commonly used in industrialization include DMF, DMAc, DMSO, NMP, HMPA, and DMI. These polar aprotic solvents have good solubility for organic chemicals and some inorganic matters, and favor to improve the reaction activity by solvation of the reactants. However, the disadvantages are the instability especially the coexistence of DMF, DMAc, and DMSO with NaH (►**Fig. 2**) that is very dangerous when used in industrial production.[15] HMPA has certain toxicity, and it is necessary to avoid large-scale use in production. DMI is expensive, resulting in higher costs of production. Therefore, NMP was selected as one of the reaction solvents for benzylation of 3,4,5-OH in this article. To control the reaction rate, we used THF as the initial reaction solvent, and the order of adding starting materials and reagents was also investigated. Our results showed that after adding NaH, **7**, and BrBn, NMP was added dropwise under

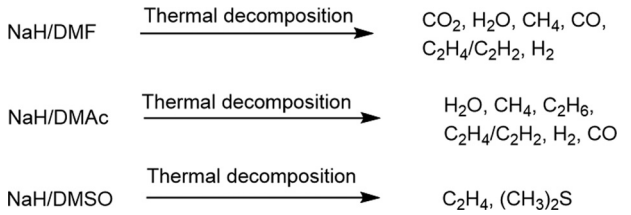


Fig. 2 Thermal instability of NaH/DMF, NaH/DMAc, and NaH/DMSO mixtures.

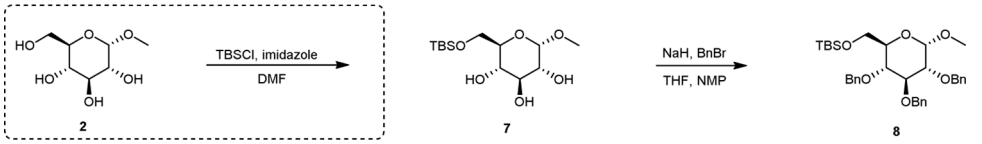
temperature control to gradually increase the solubility of reactants and the polarity of the reaction system. The reaction can be completed while ensuring the safety of production.

We also investigated the effect of the equiv. of NaH/BrBn (based on compound **2**) as well as the solvent and temperature of the crystallization on the yield of compound **8** (►**Table 1**). The test results showed that compound **8** could be obtained by benzylation with 4 equiv. of NaH and 3 equiv. of BrBn, and then crystallized at −10 to −15°C in methanol after posttreatment, with a yield of 65%.

Through employing TBAF trihydrate, the silyl-protecting group of compound **8** was removed to obtain compound **3**, which underwent a three-step reaction, according to the physical and chemical properties of each intermediate, to give compound **6**. We have comprehensively considered the simplicity of the reaction, the work-up operations, and the equipment turnover rate in industrial production. The reactions were all easy to work up without purification, and the resulting products were directly used in the next steps without further purification.

The preparation of target product **1** from compound **6** in pilot rum is another research focus of this article. There are several methods for lactol oxidizing to lactone, and the methods with industrial potentiality (cheap and easy to get) currently include: DMSO oxidation method (Swern reagent or Albright–Goldman reagent),[16,17] chromium-based reagents (PCC or PDC),[18–21] halogen (Br_2,[20] or I_2,[14] or ICl[10])/carbonate, etc. The oxidation of lactol generally uses DMSO as an oxidant, but DMSO is correspondingly reduced to dimethyl sulfide (►**Fig. 3**). Dimethyl sulfide is an odorous gas, which pollutes the environment and brings great pressure on environmental protection. The disadvantage of chromium-based reagents is the introduction of chromium, a highly toxic metal, which requires strict limit control with poor atom economy. Using halogen/carbonate as oxidizing agents, there are no disadvantages associated with using the oxidizing agents described above, and the work-up process is relatively simple to handle. Br_2 can react with the benzyl group in the molecular structure, while the price of ICl is higher and commercially limited. Therefore, we use I_2/K_2CO_3 to carry out the oxidation reaction of the lactol. Fusaro et al reported the preparation of the corresponding lactones by oxidation of lactols in CH_2Cl_2 using 3 equiv. of I_2 and 3 equiv. of K_2CO_3.[14] Since the feeding scale of the literature is too small (0.1 g), we investigate the effect of the

Table 1 Screening of benzylation reaction[a]



Entry	NaH (equiv.)[b]	BrBn (equiv.)[b]	Crystallization solvent/temp (°C)[c]	Yield (%)[d]
1	3.0	3.0	MeOH/5–10	37
2	3.0	3.0	EtOH/5–10	31
3	3.0	3.5	MeOH/5–10	28
4	3.5	3.0	MeOH/5–10	44
5	4.0	3.0	MeOH/5–10	55
6	4.5	3.0	MeOH/5–10	56
7	4.0	3.0	MeOH/−5–0	60
8	4.0	3.0	MeOH/−10 to −15	65

[a]Reaction conditions: NaH (60%) was dispersed in THF, and cooled to 0°C, **7** (0.21 mol based on compound **2**, obtained without further purification from **2**) solution in THF was added slowly while maintaining the reaction temperature below 40°C, followed by the addition of BnBr. Then, the reaction mixture was cooled to 20 to 25°C and held for 12 hours. NMP (40 mL) was slowly added thereto while maintaining the reaction temperature not more than 40°C. The reaction course was monitored by TLC at 1-hour interval.
[b]Equiv. based on compound **2**.
[c]The product crystallized from alcohol.
[d]Isolated yield.

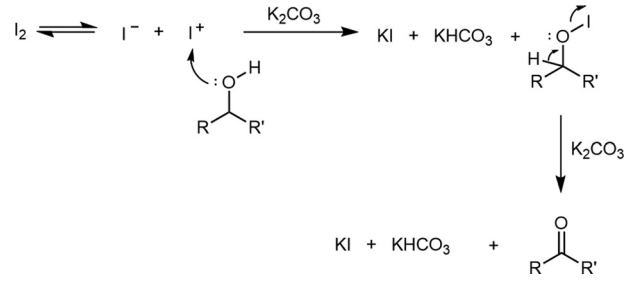
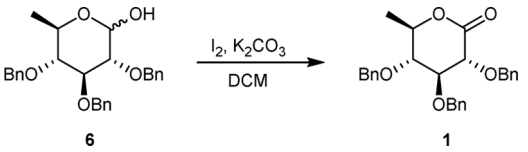


Fig. 3 Mechanism of I_2/K_2CO_3 oxidant of alcohols to carbonyl compounds.

equiv. of I_2 and K_2CO_3 for the reaction conversion on a larger scale (►**Table 2**).

The experimental results showed that the equiv. of I_2 and K_2CO_3 was very important to the reaction time; when the equiv. of I_2 and K_2CO_3 was 1:2, 1:2.5, and 1.05:2.5, the reaction time was longer than 30 hours (►**Table 2**, entries 1–3), while 1.1 equiv. of I_2 and 2.5 equiv. of K_2CO_3 were used, the reaction was complete within 20 hours, and the yield was 97.3% (►**Table 2**, entry 4). When equiv. of I_2 and K_2CO_3 was further increased to 1.15:2.5 and 1.15:3.0, respectively, there

Table 2 Results for the study of 6 to 1 with I_2 and K_2CO_3[a]



Entry	I_2 (equiv.)	K_2CO_3 (equiv.)	Reaction time (hour)[b]	1 (%)[c]
1	1	2	>30	91.2
2	1	2.5	>30	92.7
3	1.05	2.5	>30	95.6
4	1.1	2.5	20	97.3
5	1.15	2.5	20	98.2
6	1.15	3.0	20	98.3

[a]Reaction conditions: 52.1 g (0.12 mol) of **6** (obtained by crystallization from cyclohexane), I_2, and K_2CO_3 were dissolved in 300 mL DCM and then the mixture was heated at reflux.
[b]The reaction course was monitored by TLC at 1-hour interval.
[c]Monitored by HPLC (not isolated yield).

was no obvious difference in the reaction time and yield (►**Table 2**, entries 5 and 6). After the reaction, the residual I_2 was quenched with vitamin C. After simple posttreatment, the product **1** was precipitated in cyclohexane and recrystallized from methanol in a yield of 55% (from **3** to **1**) with a purity of more than 99%.

Conclusion

In this article, we designed and optimized a synthetic technology of (3*R*,4*S*,5*R*,6*R*)-3,4,5-tris(benzyloxy)-6-methyltetrahydro-*2H*-pyran-2-one (compound **1**) with great industrialization value. Our approach started from commercially available methyl-α-*D*-glucopyranoside in seven steps, including TBS protection, benzyl protection, TBS removal, iodination, reduction, demethylation, and oxidation. The highlight of this synthetic technology lies in eliminating the dangerous processes from reported routes, simplifying the reaction, work-up operations, and improving equipment turnover rate (intermediates of four steps are directly used in the next step without further purification). The resulting process is confirmed to be a low-cost, low-polluting method that can be used for large-scale oxidation of lactol to obtain lactone, achieving the goal of a simple and efficient process in industrial production and high purity of the final product. Using this preparation route, the whole process was validated with 40 kg/batch of **1** in four continuous batches. The process is stable and the product quality is controllable.

Experimental Section

General

All materials were commercial industrial products and used without further purification. Nuclear magnetic resonance (NMR) spectra were recorded on a Bruker AVANCE II 400 (400 MHz) with tetramethylsilane as an internal standard in $CDCl_3$ solution. Chemical shifts are given in δ values (ppm), and coupling constants (*J* values) are given in Hz. Electrospray ionization mass spectra were acquired on a Waters ZQ2000 spectrometer. Reactions' time was monitored by thin-layer chromatography (TLC) on JIANGYOU silica gel aluminum cards (0.2 mm thickness) with a fluorescent indicator (254 nm). Reaction progress and compound purity were determined by high-performance liquid chromatography (HPLC) on Agilent 1200 (Agilent Technologies, California, United States). HPLC method A: Thermo scientific-C18 column, C18 (5 μm, 150 mm × 4.6 mm); mobile phase A (0.5% H_3PO_4 in water) and B (CH_3CN), from 50:50 A/B to 30:70 A/B over 20 minutes, 30:70 A/B to 25:75 A/B over 10 minutes, 25:75 A/B to 5:95 A/B over 9 minutes, 5:95 A/B to 50:50 A/B over 1 minute, and keep 50:50 A/B over 5 minutes; detection at 210 nm; flow rate = 1.0 mL/min.

Preparation of Methyl 6-*O*-(*tert*-butyldimethylsilyl)-α-*D*-glucopyranoside (Compound 7)

A dry and clean 500 L glass-lined reactor was charged with DMF (160 kg). Then, starting material **2** (40.00 kg, 206.0 mol) and imidazole (28.05 kg, 411.4 mol) were added. The mixture was cooled to 10 to 20°C, and TBSCl (34.15 kg, 226.9 mol) was added under 40°C. The resulting reaction mixture was stirred for 3 hours upon completion of the reaction, confirmed by TLC (5:1, DCM/MeOH). The reaction mixture was cooled to 20°C, added toluene (140 kg) and water (120 kg), and stirred for 0.5 hours at 20 to 30°C. The resulting mixture was phase-separated. The organic phase was washed with saturated brine solution (40 kg) and concentrated under vacuum (−0.08 MPa, 80°C) to afford **7** as a pale-yellow oil, which was directly used in the next step without further purification. After cooling, anhydrous THF (75 kg) was added into the crude product and stirred until the oil dissolves completely.

Preparation of Methyl 2,3,4-tri-*O*-benzyl-6-*O*-(*tert*-butyldimethylsilyl)-α-*D*-glucopyranoside (Compound 8)

A dry and nitrogen-purged 1,000 L glass-lined reactor was charged with anhydrous THF (210 kg), and cooled to 0°C, and then NaH (60%, 28.02 kg, 700.4 mol) was added carefully. The mixture was warmed to 20 to 25°C, and a solution of **7** in THF was slowly added to the reaction while maintaining the reaction temperature below 40°C, followed by the addition of BnBr (89.84 kg, 525.3 mol). After the addition, the reaction was cooled to 20 to 25°C and held for 12 hours. Then, NMP (40 kg) was slowly added thereto while maintaining the reaction temperature not more than 40°C. After the addition, the reaction was cooled to 20 to 25°C and held for 12 hours. When TLC (10:1, PE/EA) indicated the reaction was complete, the reaction mixture was quenched by drop-wise addition of MeOH (16 kg) and water (360 kg). The resulting mixture was stirred for 0.5 hours and phase-separated. The organic phase was washed with saturated brine solution (40 kg) and phase-separated. The organic phase was concentrated under vacuum (−0.08 MPa, 70°C). The residue was solvent-exchanged with MeOH (40 kg) and then concentrated (−0.08 MPa, 70°C). MeOH (240 kg) was added. The resulting mixture was stirred at −10 to −15°C for 3 hours, and the resulting slurry was filtered with a centrifuge. The filter cake was dried in a rotary conical dryer at 30 to 60°C under reduced pressure ($P \leq -0.08$ MPa) until MeOH ≤ 0.5% to give **8** (77.5 kg, cream color solid, 65% from **2** to **8**). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.42–7.33 (m, 15H), 5.03 (d, J = 10.8 Hz, 1H), 4.96–4.84 (m, 3H), 4.75–4.68 (m, 3H), 4.07 (t, J = 9.2 Hz, 1H), 3.85 (d, J = 2.8 Hz, 2H), 3.65 (dt, 1H), 3.60–3.55 (m, 2H), 3.43 (s, 3H), 0.96 (s, 9H), 0.11 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 138.89, 138.61, 138.34, 128.45, 128.42, 128.12, 128.08, 127.85, 127.68, 127.62, 97.96, 82.22, 80.35, 77.86, 77.42, 77.10, 76.78, 75.86, 75.02, 73.37, 71.59, 62.36, 54.92, 25.97, 18.35, −5.11, −5.32. MS-ESI (*m*/*z*) calcd. for $C_{34}H_{46}O_6Si$ $[M + NH_4]^+$ 596.34, found: 596.35.

Preparation of Methyl 2,3,4-tri-*O*-benzyl-*D*-glucopyranoside (Compound 3)

$Bu_4NF{\cdot}3H_2O$ was preheated to 80°C until it melts completely. A dry and clean 1,000 L glass-lined reactor was charged with toluene (230 kg), then compound **8** (76.40 kg, 132.0 mol) and $Bu_4NF{\cdot}3H_2O$ (54.14 kg, 171.6 mol) were added thereto. After the addition, the reaction was heated to 40 to 45°C and held for 3 hours. When TLC (3:1, PE/EA) indicated the reaction was complete, the reaction mixture was quenched by water

(330 kg). The resulting mixture was stirred for 0.5 hours and phase-separated. The organic phase was washed with water (330 kg) and phase-separated. The organic phase was concentrated under vacuum (−0.08 MPa, 70°C). The residue was solvent-exchanged with cyclohexane (26 kg) and then concentrated (−0.08 MPa, 70°C). Cyclohexane (157 kg) was added. The resulting mixture was stirred at 10 to 15°C for 8 hours, and the resulting slurry was filtered with a centrifuge. The filter cake was dried in a rotary conical dryer at 50 to 60°C under reduced pressure ($P \leq -0.08$ MPa) until cyclohexane ≤ 0.5% to give **3** (49.05 kg, off-white solid, 80%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.45–7.32 (m, 15H), 5.07 (d, $J = 10.8$ Hz, 1H), 4.98–4.84 (m, 3H), 4.75–4.66 (m, 3H), 4.10 (t, $J = 9.2$ Hz, 1H), 3.83–3.72 (m, 3H), 3.64–3.57 (m, 2H), 3.43 (s, 3H), 2.01 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 138.88, 138.29, 138.23, 128.52, 128.45, 128.15, 128.05, 128.00, 127.98, 127.89, 127.65, 98.24, 82.02, 80.14, 77.57, 77.55, 77.23, 76.91, 75.76, 75.06, 73.44, 70.86, 61.85, 55.23. MS-ESI (m/z) calcd. for $C_{28}H_{32}O_6$ $[M + NH_4]^+$ 482.25, found: 482.25.

Preparation of Methyl 6-deoxy-6-iodo-2,3,4-tri-*O*-benzyl-α-*D*-glucopyranoside (Compound 9)

A dry and clean 1,000 L glass-lined reactor was charged with DCM (610 kg), then **3** (83.62 kg, 180 mol), PPh_3 (49.57 kg, 189 mol), and imidazole (12.87 kg, 189 mol) were added thereto. Then, the mixture was cooled to 10 to 20°C, and I_2 (50.25 kg, 198 mol) was added in portions thereto below 40°C. After the addition, the reaction was heated to 30 to 40°C and held for 3 hours. When TLC (3:1, PE/EA) indicated the reaction was complete, the reaction mixture was quenched by vitamin C (3.60 kg), K_2CO_3 (8.64 kg), and water (270 kg). The resulting mixture was stirred for 0.5 hours and phase-separated. The organic phase was washed with water (270 kg) and phase-separated. The organic phase was concentrated under vacuum (−0.08 MPa, 70°C). The residue was solvent-exchanged with cyclohexane (70.2 kg) and then concentrated (−0.08 MPa, 70°C). Cyclohexane (210.6 kg) was added. The resulting mixture was stirred at 10 to 15°C for 3 hours, and the resulting slurry was filtered with a centrifuge and the filter cake (Ph_3PO) was washed with cyclohexane (70.2 kg). The mother liquid was collected by another 500 L glass-lined reactor and concentrated (−0.08 MPa, 70°C) to give **9** as an amber oil, which was directly used in the next step without further purification. After cooling, NMP (426 kg) was added into the crude product and stirred until the oil dissolves completely.

Preparation of Methyl 6-deoxy-2,3,4-tri-*O*-benzyl-α-*D*-glucopyranoside (Compound 5)

A clean and nitrogen-purged 1,000 L glass-lined reactor was charged with a solution of **9** in NMP, and $NaBH_4$ (13.62 kg, 360 mol) was added thereto. After the addition, the reaction was heated to 30 to 35°C and held for 12 hours. When HPLC indicated the reaction was complete, the reaction mixture was added slowly into water (450 kg) in another 1,500 L glass-lined reactor. Then, cyclohexane (160 kg) was added thereto and stirred for 2 hours and phase-separated. The organic phase was washed with water (200 kg × 2) and concentrated (−0.08 MPa, 70°C) to give **5** as a colorless oil, which was directly used in the next step without further purification. After cooling, AcOH (400 kg) was added into the crude product and stirred until the oil dissolves completely.

Preparation of 2,3,4-tri-*O*-benzyl-6-deoxy-*D*-glucopyranose (Compound 6)

A clean 1,500 L glass-lined reactor was charged with a solution of **5** in AcOH, then 31% HCl (40 kg) and water (216 kg) were added thereto. After the addition, the reaction was heated to 85 to 90°C and held for 12 hours. When TLC (10:1, PE/EA) indicated the reaction was complete, the mixture was cooled to 40 to 45°C. Then, toluene (350 kg) was added to the reaction and stirred for 0.5 hours and phase-separated. The organic phase was washed with water (400 kg × 2) and concentrated (−0.08 MPa, 70°C) to give **6** as a light brown oil, which was directly used in the next step without further purification. After cooling, DCM (600 kg) was added into the crude product and stirred until the oil dissolves completely.

Preparation of (3*R*,4*S*,5*R*,6*R*)-3,4,5-tris(benzyloxy)-6-methyltetrahydro-2*H*-pyran-2-one (Compound 1)

A clean 1,500 L glass-lined reactor was charged with a solution of **6** in DCM, then K_2CO_3 (49.76 kg, 360 mol) and I_2 (40.20 kg, 158.4 mol) were added thereto. The resulting reaction mixture was heated at reflux for 8 hours upon the completion of the reaction confirmed by TLC (10:1, PE/EA) sampling. The reaction mixture was quenched by vitamin C (5.08 kg) and water (580 kg). After phase-separated, the organic phase was washed with water (580 kg) and concentrated (0 to −0.08 MPa, 60°C). The residue was solvent-exchanged with cyclohexane (46 kg) and then concentrated (−0.08 MPa, 70°C). Cyclohexane (93 kg) was added. The resulting mixture was stirred at 5 to 10°C for 6 hours, and the resulting slurry was filtered with a centrifuge. The filter cake was recrystallized from MeOH and dried in a rotary conical dryer at 30 to 60°C under reduced pressure ($P \leq -0.08$ MPa) until MeOH ≤ 0.5%, to give **1** (42.82 kg, white solid, 55% from **3** to **1**, HPLC purity: 99.31%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.47–7.36 (m, 15H), 5.05 (d, $J = 11.6$ Hz, 1H), 4.81–4.74 (m, 3H), 4.69–4.63 (m, 3H), 4.24 (d, $J = 5.2$ Hz, 1H), 4.02 (t, $J = 5.2$ Hz, 1H), 3.48 (dd, $J = 8.8$, 5.6 Hz, 1H), 1.51 (d, $J = 6.4$ Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.11, 137.57, 137.50, 136.98, 128.63, 128.60, 128.57, 128.49, 128.28, 128.13, 128.11, 128.08, 81.44, 81.25, 77.63, 77.48, 77.31, 76.99, 74.73, 73.55, 73.34, 73.07, 18.43. MS-ESI (m/z) calcd. for $C_{27}H_{28}O_5$ $[M + NH_4]^+$ 450.23, found: 450.22.

Conflict of Interest
None declared.

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