Development of a Scalable Synthesis of Tofogliflozin

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S *Supporting Information*

ABSTRACT: An efficient and scalable synthesis of an antidiabetic drug, tofogliflozin (**1**), which was identified as a highly selective sodium glucose cotransporter 2 (SGLT2) inhibitor, is described. A key factor in the synthesis of **1** was the selection of the purpose-designed protecting group, which plays a strategic role in protection, chemoselective activation, and crystalline purification. The developed and optimized method made it possible to prepare **1** on a multidecagram scale without any column chromatography.
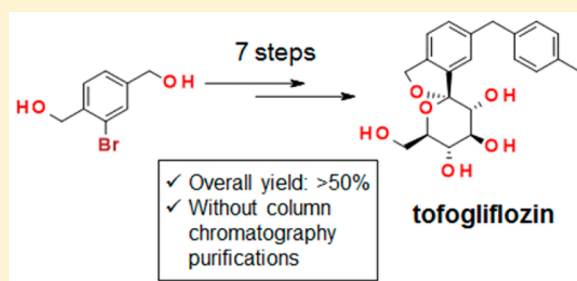
ofogliflozin (**1**), (1S,3′R,4′S,5′S,6′R)-6-[(4-ethylphenyl)-methyl]-6′-(hydroxymethyl)-3′,4′,5′,6′-tetrahydro-3H-spiro[2-benzofuran-1,2′-pyran]-3′,4′,5′-triol, is a highly selective SGLT2 inhibitor which was launched in Japan as a new antidiabetic drug.[1] In the process of our research and development plan, a large amount of **1** was required for *in vivo* pharmacological and toxicological studies. Therefore, we undertook research to investigate a scalable synthetic route, and herein we wish to report a newly established synthetic route of **1**.

In the analysis of the medicinal chemistry route (Scheme 1),[2] which had been established in reference to the methods of the synthetic intermediates of antibiotic papulacandins,[3] difficulty was encountered for large scale synthesis. All the intermediates with benzyl protections (**7**, **8**, **9**, and **10**) tended to be gummy and were difficult to isolate as solids by filtration, which forced us to use cost- and time-inefficient column chromatography purification in most steps.

Initially, a retrosynthesis was outlined as shown in Figure 1. Our key concept was to set compound **15** as a key intermediate for the following reasons: (1) to allow the use of easily accessible aglycone **3** and D-gluconolactone **11** with the same chiral centers as D-glucose in order to synthesize **15**; (2) to permit the distinction between the two hydroxy groups of **3** by intramolecular spirocyclization reaction; (3) to facilitate easy quality control of the product **15** after C−C bond formation, because **15** is crystalline; and (4) to allow only the benzyl part to be involved in a Suzuki-type reaction to introduce the 4-ethylphenyl group after full esterification of **15**. Also, **17** needs to be crystalline as a precursor of **1** for easy quality control of the product after the Suzuki-type reaction. Therefore, we screened the protecting groups of **1** in order to find crystalline

intermediates. Both tetra-acetylated compound **17a** and tetra-methoxylcarbonylated compound **17b** were prepared from **1** (Scheme 2). As a result, fortunately, **17b** was obtained as a crystalline solid.

After obtaining crystalline intermediate **17b**, synthesis of the spirocyclized intermediate **15** was investigated. One key factor in the synthesis of **15** was selecting the protecting groups for **3** and **11**. The addition reaction of protected **3** with protected **11** was to proceed under strongly basic conditions, whereas the spiroketal cyclization could be conducted after deprotection under acidic conditions. From many base-tolerant and acid-removable protecting groups of the sugar part, we selected the trimethylsilyl (TMS) groups. TMS-protected gluconolactone **12**[4] was synthesized as described in the literature.[5] Compound **12** had an oily and moisture-sensitive nature, but it could be used in the next addition reaction without further purification after the extraction procedure. Diol **3** was protected with the 1-methoxy-1-methylethyl group, which is also base-tolerant and acid-removable. Actually, **3** was reacted with 2-methoxypropene by using a catalytic amount of pyridinium *p*-toluenesulfonate (PPTS) to obtain the oily compound **13**, which was also used in the next addition reaction without further purification after the extraction procedure.

Diprotected **13** in anhydrous toluene was halogen−metal exchanged with *n*-BuLi and reacted with **12** to give the coupled intermediate **14**. Removal of all the protecting groups of the crude **14** under acidic conditions, followed by stereospecific spirocyclization, resulted in producing the key intermediate **15** as a single isomer.[6] Interestingly, the β-isomer of **15** was not

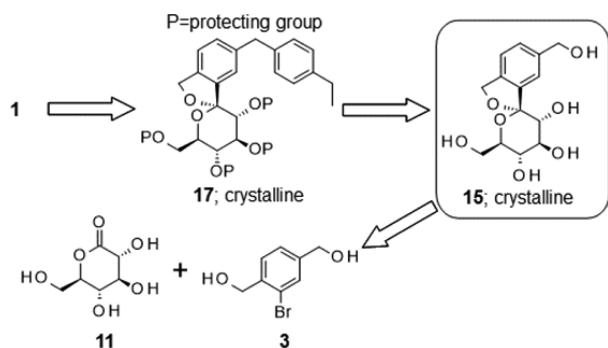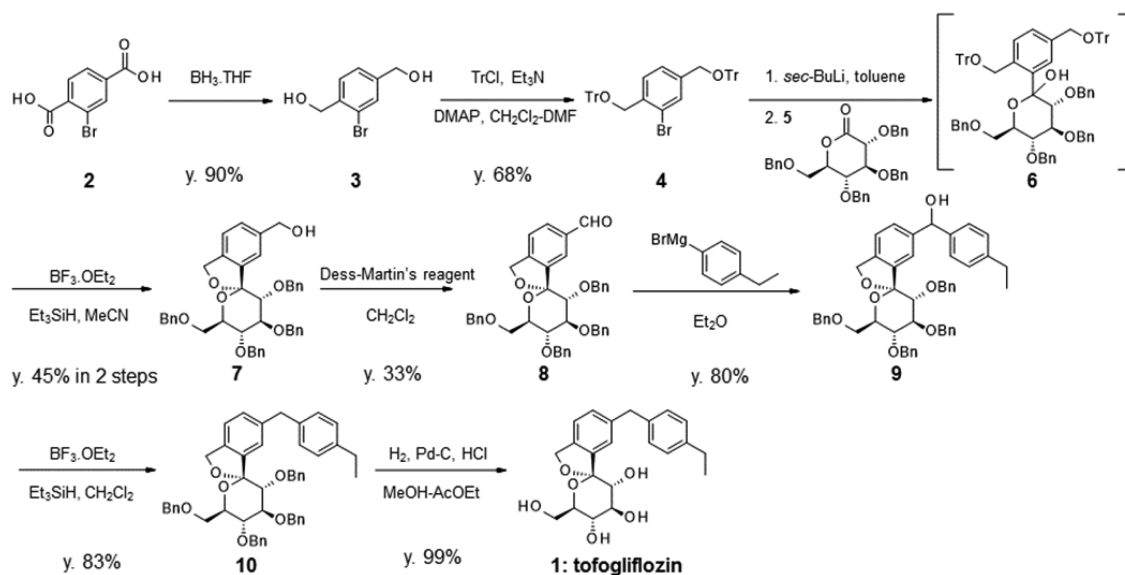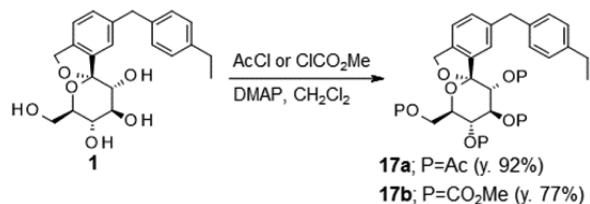**Scheme 1. A Medicinal Chemistry Route of 1**

Figure 1. A newly designed retrosynthesis.

Scheme 2. Synthesis of Two Tetra-Protected Compounds for Crystalline Investigation

observed at all. It was thought that this spirocyclization proceeded stereoselectively by the anomeric effect. Finally, pure **15** was obtained by trituration with MTBE as a stable crystal.
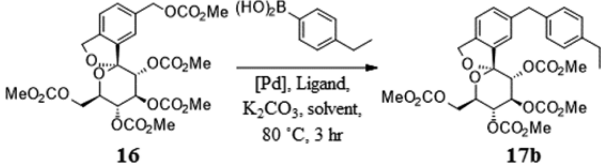
Next, we investigated the methoxycarbonylation reaction. Permethoxycarbonylation of five hydroxy groups of **15** was achieved by use of stoichiometric DMAP and methyl chloroformate in CH_2Cl_2. The use of Et_3N with or without a catalytic amount of DMAP resulted in insufficient reaction conversion because of competitive decomposition of $ClCO_2Me$. Compound **16** obtained by the extraction workup procedure was used in the coupling reaction without further purification.

Then, we investigated Suzuki-type coupling reaction conditions of **16** with 4-ethylphenylboronic acid in order to prepare **17b**, following Kuwano's report.[7] It described the importance of the ligand bite angle, which influenced the

reaction rate in the reaction. Therefore, we first evaluated some phosphine ligands (10 mol %) in the presence of **16** (1.0 equiv), 4-ethylphenylboronic acid (1.5 equiv), $[Pd(\eta^3\text{-}C_3H_5)\text{-}Cl]_2$ (APC, 10 mol %), and K_2CO_3 (3.0 equiv) in DMF (0.2 M) (Table 1). As a result, bidentate phosphine ligands and APC afforded some satisfactory results, being in close agreement with Kuwano's results (entries 1−6). A bidentate ligand, 1,1′-bis(diphenylphosphino)ferrocene (DPPF), which has high availability and economy, was also similarly acceptable as compared to 1,4-bis(diphenylphosphino)butane (DPPB) (entry 7). Moreover, we optimized the reaction conditions by using DPPF, focusing on the Pd source, amount of the base, reaction concentration, and solvent. The reaction conversion rate was slightly decreased with $Pd(OAc)_2$, which is an absolutely low cost catalyst precursor (entry 8), but it was improved by a higher reaction concentration (entry 9). The amount of carbonate-hydrolyzed products was reduced by using 1.0 equiv of base (entry 10). Under a high concentration with 1 equiv of base, **16** completely disappeared to give **17b** in 77% isolated yield (entry 11). In addition, solvent screening was conducted in order to diminish the hydrolysis products. Toluene, 1,4-dioxane, and DME resulted in reduction of the hydrolysis products (entries 12−14), suggesting that the hydrolysis can be avoided by using nonpolar solvents. We selected DME, since an easy workup procedure was achieved, as described below.

A Pd-coupling reaction to introduce the distal phenyl group was successfully performed under the conditions in entry 14 of Table 1 on a 100 g scale. The residual Pd was precipitated by adding 20 mol % of N-acetyl-L-cysteine (NAC) to the reaction mixture, and it was efficiently removed by filtration. In addition, treatment of the crude mixture with EtOH and water containing 20 mol % of NAC afforded the crystalline **17b** with >99 area% of purity and <1 ppm of residual Pd in 88% yield.

Permethoxylcarbonylated compound **17b** was hydrolyzed with aqueous sodium hydroxide solution in DME. Under the conditions, the reaction mixture was heterogeneous and temperature elevation was observed, which suggests difficulty in controlling the reaction initiation. Thus, MeOH was used as a cosolvent, which made the reaction mixture homogeneous

## Table 1. Optimization of Coupling Reaction Conditions[a]

entry	concn (M)	ligand	[Pd]	K$_2$CO$_3$ (eq)	solvent	LCMS area% 16:17b: hydrolysis[b]	yield (%)[c]
1	0.2	PPh$_3$	APC	3.0	DMF	51:11:38	—
2	0.2	DPPE	APC	3.0	DMF	77:<1:23	—
3	0.2	DPPP	APC	3.0	DMF	76:<1:24	—
4	0.2	DPPB	APC	3.0	DMF	5:86:9	—
5	0.2	DPPPent	APC	3.0	DMF	25:59:16	—
6	0.2	DPPHex	APC	3.0	DMF	34:47:19	—
7	0.2	DPPF	APC	3.0	DMF	10:83:7	—
8	0.2	DPPF	Pd(OAc)$_2$	3.0	DMF	17:73:10	—
9	1.0	DPPF	Pd(OAc)$_2$	3.0	DMF	3:79:18	—
10	0.2	DPPF	Pd(OAc)$_2$	1.0	DMF	6:90:4	—
11	1.0	DPPF	Pd(OAc)$_2$	1.0	DMF	0:95:5	74
12	1.0	DPPF	Pd(OAc)$_2$	1.0	toluene	0:99:1	—
13	1.0	DPPF	Pd(OAc)$_2$	1.0	1,4-dioxane	0:99:1	—
14	1.0	DPPF	Pd(OAc)$_2$	1.0	DME	0:>99:<1	85

[a]All the reactions were conducted in solvent (0.2 M or 1.0 M) at 80 °C for 3 h. Pentacarbonate 16 (100 mg, 0.17 mmol), [Pd] cat. (10 mol %). Ligand (10 mol %), 4-ethylphenylboronic acid (1.5 equiv), and K$_2$CO$_3$ (1.0 or 3.0 equiv) were used. [b]Hydrolysis compounds mean the total amount of some demethoxycarbonyl compounds. [c]Isolated yield by reversed-phase column chromatography.

Scheme 3. A Newly Established Route without Any Column Chromatography
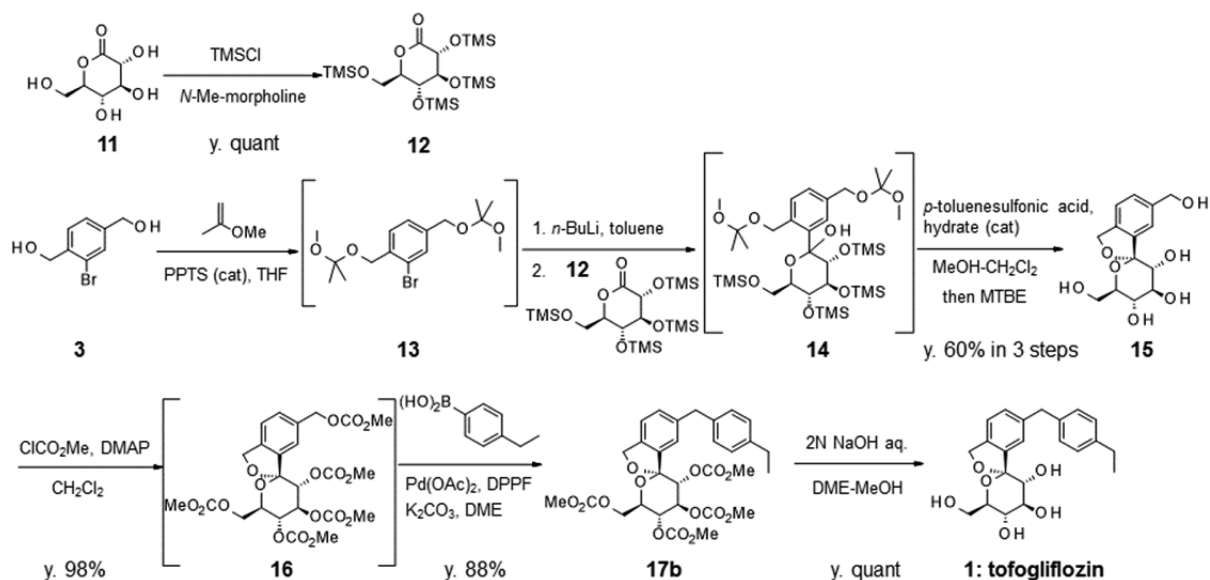
Scheme 4. Synthesis of Metabolite 19
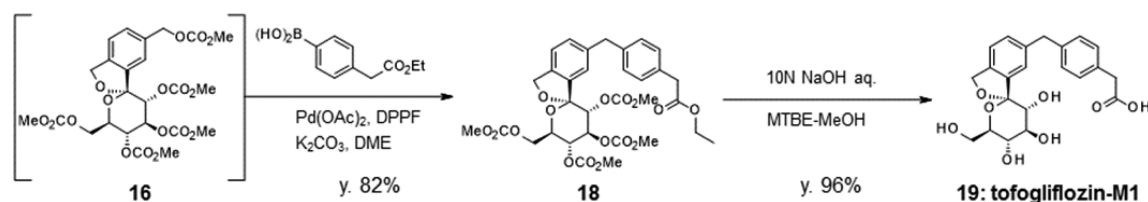
and the reaction controllable by modifying the addition rate of sodium hydroxide. Finally, 1 with >99% purity was obtained by extraction and concentration in quantitative yield as a colorless amorphous solid. This early process route is summarized in Scheme 3.[8] This newly developed method achieved a higher overall yield compared to the previous one (Scheme 1).

According to the established method, we also synthesized a major human metabolite of 1, a carboxylic acid 19, into which

the ethyl moiety of **1** was oxidized by CYPs (Scheme 4).[9] Pentamethoxycarbonylated **16** was reacted with the corresponding boronic acid reagent (purchased from Combi-Blocks Inc.) under our best reaction conditions (Table 1, entry 14) to afford the coupled product **18** in 82% yield, and then the highly hydrophilic metabolite **19** was obtained in 96% yield after hydrolysis.

In conclusion, we have successfully constructed an effective and scalable synthetic route for the antidiabetic drug, tofogliflozin **1**, that does not use column chromatography purification, and by which several decagrams of **1** can be supplied for *in vivo* pharmacological and toxicological studies. Our key success factor was selecting the optimal protecting groups for the purpose of chemoselective activation and crystalline purification, which indicates that they play critical roles in the establishment of the early process. Moreover, we demonstrated that this method was utilized to synthesize a human metabolite **19**.

■ EXPERIMENTAL SECTION

All reactions were carried out under an argon or a nitrogen atmosphere. All solvents and reagents were purchased from commercial sources without further drying. Melting points (mp's) were determined by using differential scanning calorimetry (DSC). Optical rotations were measured with a polarimeter at the sodium D line (589 nm). ^{1}H NMR spectra were recorded on 400 MHz spectrometers. Chemical shifts were reported in parts per million (δ) downfield from tetramethylsilane (δH 0.00) as an internal standard. Data are presented as follows: chemical shift (δ, ppm), integration, multiplicity (br = broad, s = singlet, d = doublet, t = triplet, q = quartet, and m = multiplet), and coupling constant. ^{13}C NMR spectra were recorded on 100 MHz spectrometers. The following internal reference was used (DMSO-d_6; 39.5, CD$_3$OD; δ 49.0, CDCl$_3$; δ 77.0). Mass spectra (MS) were measured using ESI mode. High resonance mass (HRMS) analysis data were recorded using EI mode or ESI mode by Q-TOF.

2,3,4,6-Tetrakis-O-trimethylsilyl-D-glucono-1,5-lactone (12). This titled compound was synthesized from D-gluconolactone (**11**) according to the literature.[5]

(2-Bromo-4-hydroxymethylphenyl)methanol (3).[2] To a solution of commercially available 2-bromoterephthalic acid (**2**) (575 g, 2.34 mol) in THF (5.75 L), a THF solution of BH$_3$ (1.0 M, 5.86 L) was added at 0 °C dropwise for 2.5 h, and the mixture was stirred for 1 h at 0 °C. The mixture was gradually warmed up to 35 °C over 3.5 h. The reaction mixture was cooled to 0 °C and quenched by dropwise addition of MeOH (1.15 L) over 30 min. Then, the mixture was concentrated in vacuo. The residue was dissolved in MeOH (1.72 L), and then water (10.3 L) was added; the mixture was then stirred at 0 °C for 30 min. The off-white solid was filtered and washed with water (1.15 L × 3) and heptanes (2.30 L) to obtain **3** (426 g, 84%) as a white crystal; mp 108−109 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 4.47 (2H, d, *J* = 5.6 Hz), 4.49 (2H, d, *J* = 5.4 Hz), 5.29 (1H, t, *J* = 5.6 Hz), 5.39 (1H, t, *J* = 5.4 Hz), 7.31 (1H, d, *J* = 7.8 Hz), 7.47 (1H, d, *J* = 7.8 Hz), 7.48−7.49 (1H, m); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 61.9, 62.5, 120.8, 125.5, 127.9, 129.7, 139.1, 143.4; HRMS (EI) calcd for C$_8$H$_9$BrO$_2$ [M]$^+$ 215.9786, found 215.9787.

(1S,3′S,4′S,5′S,6′R)-3′,4′,5′,6′-tetrahydro-6,6′-bis(hydroxymethyl)-spiro[2-benzofuran-1(3H),2-[2H]pyran]-3′,4′,5′-triol (15). To a solution of **3** (800 g, 3.69 mol) in THF (4.00 L), PPTS (46.3 g, 0.18 mol) was added at rt, and the mixture was cooled to 0 °C. 2-Methoxypropene (797 g, 11.1 mol) was dropwise added to this solution at the same temperature. After stirring at 10 °C for 2 h, the reaction was quenched by dropwise addition of saturated K$_2$CO$_3$ aq. solution (4.00 L) and water (4.00 L) at 10 °C. The resulting mixture was extracted with heptane (4.00 L). The organic layer was washed with brine (4.00 L) and dried over anhydrous Na$_2$SO$_4$ (200 g). The mixture was concentrated in vacuo to obtain crude **13** (1.27 kg) as a yellow oil.

To a solution of crude **13** (630 g, 1.74 mol) in anhydrous toluene (3.78 L), 2.67 M *n*-BuLi in hexane solution (650 mL, 1.74 mol) was added dropwise over 45 min at 5 °C under a nitrogen atmosphere, and the resultant mixture was stirred under the same conditions for 20 min. After this solution was cooled at −70 °C, a solution of prepared **12** (810 g, 1.74 mol) in anhydrous toluene (1.89 L) was added to the resultant mixture dropwise over 2 h below −60 °C. After the mixture stirred at this temperature for 30 min, satd. NH$_4$Cl (3.78 L) and water (1.89 L) were added thereto. After the resultant mixture was warmed up to rt, the mixture was separated. The resultant organic layer was washed with satd. NH$_4$Cl (3.78 L) and then dried over anhydrous Na$_2$SO$_4$ (158 g). The mixture was then concentrated in vacuo to obtain crude **14** (1.30 kg) as an orange oil. This reaction was carried out one more time on the same scale to afford another 1.30 kg batch of crude intermediate **14**.

All the obtained **14** (2.61 kg, 3.49 mol) was dissolved in THF (5.23 L) and MeOH (2.61 L), and *p*-toluenesulfonic acid hydrate (133 g, 700 mmol) was added at rt. The mixture was stirred at rt for 2 h and then cooled at 0 °C. MTBE (2.61 L) was added to the mixture, and the mixture was stirred at 0 °C for 1 h. The precipitate was collected by filtration. The obtained solid was dried in vacuo to obtain **15** (663 g, 60% from **3**) as a white crystal; mp 193−194 °C; [α]$_D^{25}$ +43.8° (*c* 1.07, H$_2$O); ^{1}H NMR (400 MHz, CD$_3$OD) δ: 3.46−3.49 (1H, m), 3.63−3.69 (1H, m), 3.75−3.85 (4H, m), 4.64 (2H, s), 5.10 (1H, d, *J* = 12.5 Hz), 5.15 (1H, d, *J* = 12.5 Hz), 7.23−7.27 (1H, m), 7.30−7.37 (2H, m); ^{13}C NMR (100 MHz, CD$_3$OD) δ: 62.8, 65.0, 71.9, 73.5, 74.9, 76.2, 76.3, 111.6, 121.8, 121.9, 129.2, 140.2, 141.2, 142.5; MS (ESI) *m/z*: 299 [M + H]$^+$; HRMS (ESI) calcd for C$_{14}$H$_{19}$O$_7$ [M + H]$^+$ 299.1125, found 299.1119.

(1S,3′R,4′S,5′S,6′R)-6-[(Methoxycarbonyloxy)methyl]-3′,4′,5′,6′-tetrahydro-3′,4′,5′-tris(methoxycarbonyloxy)-6′-[(methoxycarbonyloxy)methyl]-spiro[2-benzofuran-1(3H),2-[2H]pyran] (16). To a solution of **15** (600.0 g, 2.01 mol) and DMAP (1.55 kg, 12.7 mol) in anhydrous CH$_2$Cl$_2$ (6.00 L), methyl chloroformate (933 mL, 12.1 mol) was added dropwise over 70 min at −10 °C. The reaction mixture was stirred for 30 min at 0 °C and then for 3 h at rt. 10% KHSO$_4$ aq. solution (6.00 L) was added to the mixture, and the resultant mixture was separated. The resultant organic layer was washed with 10% KHSO$_4$ aq. solution (6.00 L × 2) and satd. NaHCO$_3$ (6.00 L) and then dried over anhydrous Na$_2$SO$_4$ (600 g). The mixture was concentrated in vacuo to obtain crude **16** (1.16 kg, 98%) as a light-yellow amorphous solid; [α]$_D^{13}$ +9.29° (*c* 1.01, CHCl$_3$); ^{1}H NMR (400 MHz, CDCl$_3$) δ: 3.55 (3H, s), 3.78 (6H, s), 3.81 (6H, s), 4.23 (1H, dd, *J* = 2.7, 11.7 Hz), 4.33 (1H, dd, *J* = 4.2, 11.7 Hz), 4.36−4.41 (1H, m), 5.11−5.24 (5H, m), 5.41 (1H, d, *J* = 10.3 Hz), 5.51 (1H, t, *J* = 9.6 Hz), 7.24−7.26 (1H, m), 7.41−7.45 (2H, m); ^{13}C NMR (100 MHz, CDCl$_3$) δ: 54.9, 55.0, 55.1, 55.3, 55.4, 65.5, 68.9, 69.5, 72.5, 73.1, 74.5, 75.5, 108.3, 121.2, 122.7, 130.2, 135.4, 135.5, 140.6, 154.4, 154.7, 154.9, 155.3, 155.5; MS (ESI) *m/z*: 589 [M + H]$^+$; HRMS (ESI) calcd for C$_{24}$H$_{29}$O$_{17}$ [M + H]$^+$ 589.1399, found 589.1399.

(1S,3′R,4′S,5′S,6′R)-6-[(4-Ethylphenyl)methyl]-3′,4′,5′,6′-tetrahydro-3′,4′,5′-tris(methoxycarbonyloxy)-6′-[(methoxycarbonyloxy)methyl]-spiro[2-benzofuran-1(3H),2-[2H]pyran] (17b). In a round flask, **16** (104 g, 177 mmol), potassium carbonate (24.4 g, 177 mmol), 4-ethylphenylboronic acid (37.1 g, 247 mmol), Pd(OAc)$_2$ (3.97 g, 17.7 mmol), and DPPF (11.8 g, 21.2 mmol) were added. DME (200 mL) was added, and the reaction mixture was heated at 85 °C for 3.5 h. After cooling, AcOEt (50.0 mL) and *N*-acetyl-L-cysteine (5.50 g) were added to the mixture. The resultant mixture was stirred for 1 h at a water-bath temperature. The resultant mixture was filtered by Celite and washed with AcOEt. The filtrate was concentrated in vacuo, and the obtained residue was recrystallized from EtOH (400 mL) and H$_2$O (40.0 mL) with *N*-acetyl-L-cysteine (5.50 g) to obtain **17b** (96.1 g, 88%) as a white crystal; mp 128−129 °C; [α]$_D^{23}$ +29.3° (*c* 1.18, CHCl$_3$); ^{1}H NMR (400 MHz, CDCl$_3$) δ: 1.20 (3H, t, *J* = 7.7 Hz), 2.60 (2H, q, *J* = 7.7 Hz), 3.50 (3H, s), 3.76 (3H, s), 3.77 (3H, s), 3.81 (3H, s), 3.96 (2H, s), 4.23 (1H, dd, *J* = 2.8, 12.0 Hz), 4.33 (1H, dd, *J* = 4.5, 12.0 Hz), 4.36−4.40 (1H, m), 5.11−5.20 (3H, m), 5.41 (1H, d, *J* = 10.0 Hz), 5.51 (1H, t, *J* = 10.0 Hz), 7.07−

7.14 (4H, m), 7.14 (1H, d, J = 7.8 Hz), 7.19 (1H, dd, J = 1.5, 7.8 Hz), 7.31 (1H, d, J = 1.5 Hz); ^{13}C NMR (100 MHz, CDCl$_3$) δ: 15.6, 28.4, 41.3, 55.0, 55.0, 55.2, 55.4, 65.6, 69.5, 72.6, 73.2, 74.6, 75.6, 108.4, 121.0, 123.3, 127.9, 128.7, 131.1, 135.2, 137.9, 138.0, 141.4, 142.0, 154.5, 154.7, 155.0, 155.4; MS (ESI) m/z: 619 [M + H]$^+$; HRMS (ESI) calcd for C$_{30}$H$_{35}$O$_{14}$ [M + H]$^+$ 619.2021, found 619.2025.

(1S,3$'R$,4$'S$,5$'S$,6$'R$)-6-[(4-Ethylphenyl)methyl]-6$'$-(hydroxy-methyl)-3$'$,4$'$,5$'$,6$'$-tetrahydro-3H-spiro[2-benzofuran-1,2$'$-pyran]-3$'$,4$'$,5$'$-triol (1, tofogliflozin).[2] To a solution of **17b** (89.9 g, 145 mmol) in DME (653 mL) and MeOH (73.0 mL), 2 N NaOH aq. solution (726 mL, 1.45 mol) was added dropwise for 1 h at water-bath temperature. After stirring at rt for 1 h, 2 N H$_2$SO$_4$ aq. solution (436 mL) was added slowly to the mixture. Water (700 mL) was added to the mixture, and the resultant mixture was extracted with AcOEt (500 mL × 2). The resultant organic layer was washed with brine (1.00 L) and then dried over anhydrous Na$_2$SO$_4$ (250 g). The mixture was concentrated *in vacuo* to obtain **1** (57.3 g, quant) as a colorless amorphous solid; [α]$_D^{26}$ +24.2° (*c* 1.02, MeOH); ^{1}H NMR (400 MHz, CD$_3$OD) δ: 1.19 (3H, t, J = 7.6 Hz), 2.58 (2H, q, J = 7.6 Hz), 3.42−3.47 (1H, m), 3.63−3.67 (1H, m), 3.75−3.88 (4H, m), 3.95 (2H, s), 5.06 (1H, d, J = 12.5 Hz), 5.12 (1H, d, J = 12.5 Hz), 7.07−7.14 (4H, m), 7.17−7.23 (3H, m); ^{13}C NMR (100 MHz, CD$_3$OD) δ: 16.3, 29.4, 42.3, 62.8, 71.9, 73.4, 74.9, 76.2, 76.4, 111.6, 121.8, 123.6, 128.9, 129.9, 131.1, 139.7, 139.9, 140.2, 142.6, 143.2; MS (ESI) m/z: 387 [M + H]$^+$; HRMS (ESI) calcd for C$_{22}$H$_{27}$O$_6$ [M + H]$^+$ 387.1802, found 387.1801.

[(2$'R$,3S,4$'S$,5$'R$)-3$'$,4$'$,5$'$-Triacetoxy-5-[(4-ethylphenyl)-methyl]spiro[1H-isobenzofuran-3,6$'$-tetrahydropyran]-2$'$-yl]-methyl Acetate (17a) for Crystalline Investigation (Scheme 2). To a solution of **1** (200 mg, 518 μmol) and DMAP (348 mg, 2.85 mmol) in anhydrous CH$_2$Cl$_2$ (2.00 mL), acetyl chloride (185 μL, 2.59 mmol) was added at 0 °C. The reaction mixture was stirred for 10 min at 0 °C and then for 20 h at rt. 2 N HCl aq. solution was added to the mixture, and the resultant mixture was extracted with CH$_2$Cl$_2$. The resultant organic layer was washed with brine and then dried over anhydrous Na$_2$SO$_4$. The mixture was concentrated *in vacuo*, and the residue was purified by reversed-phase column chromatography (ODS, 0.1% formic acid in H$_2$O/0.1% formic acid in MeCN) to obtain **17a** (264 mg, 92%) as a colorless amorphous solid; [α]$_D^{18}$ +22.6° (*c* 1.04, CHCl$_3$); ^{1}H NMR (400 MHz, CDCl$_3$) δ: 1.22 (3H, t, J = 7.6 Hz), 1.71 (3H, s), 2.00 (3H, s), 2.05 (3H, s), 2.07 (3H, s), 2.61 (2H, q, J = 7.6 Hz), 3.97 (2H, s), 4.05 (1H, dd, J = 2.2, 12.2 Hz), 4.27 (1H, dd, J = 3.9, 12.2 Hz), 4.33 (1H, ddd, J = 2.2, 3.9, 10.3 Hz), 5.11 (1H, d, J = 12.5 Hz), 5.20 (1H, d, J = 12.5 Hz), 5.27−5.32 (1H, m), 5.57−5.65 (2H, m), 7.06−7.08 (2H, m), 7.10−7.15 (3H, m), 7.18 (1H, dd, J = 1.2, 7.8 Hz), 7.26 (1H, d, J = 1.5 Hz); ^{13}C NMR (100 MHz, CDCl$_3$) δ: 15.6, 20.3, 20.7, 20.7, 20.8, 28.4, 41.3, 62.1, 68.6, 70.0, 71.0, 71.9, 73.0, 108.8, 120.9, 123.1, 128.0, 128.8, 130.9, 135.9, 137.9, 137.9, 141.6, 142.1, 169.3, 169.6, 170.2, 170.8; MS (ESI) m/z: 555 [M + H]$^+$; HRMS (ESI) calcd for C$_{30}$H$_{34}$O$_{10}$Na [M + Na]$^+$ 577.2050, found 577.2050.

Ethyl 2-[4-[[(3S,3$'R$,4$'S$,5$'R$,6$'R$)-3$'$,4$'$,5$'$-Tris(methoxy-carbonyloxy)-6$'$-(methoxycarbonyloxymethyl)spiro[1H-2-benzofuran-3,2$'$-oxane]-5-yl]methyl]phenyl]acetate (18). In a sealed tube, **16** (200 mg, 340 μmol), potassium carbonate (47.0 mg, 340 μmol), [4-(2-ethoxy-2-oxoethyl)phenyl]boronic acid (99.0 mg, 476 μmol), Pd(OAc)$_2$ (3.80 mg, 17.0 μmol), and DPPF (11.3 mg, 20.0 μmol) were added. DME (340 μL) was added, and the reaction mixture was heated at 85 °C for 6 h. After cooling, formic acid (100 μL) was added to the mixture. The resultant mixture was purified by reversed-phase chromatgraphy (ODS, 0.1% formic acid in H$_2$O/0.1% formic acid in MeCN) to afford roughly purified compound **18**. The obtained residue was recrystallized from MeOH (1.40 mL) with N-acetyl-L-cysteine (2.77 mg) to obtain **18** (189 mg, 82%) as a white crystal; mp 90−91 °C; [α]$_D^{19}$ +23.7° (*c* 1.02, CHCl$_3$); ^{1}H NMR (400 MHz, CDCl$_3$) δ: 1.24 (3H, t, J = 7.3 Hz), 3.50 (3H, s), 3.56 (2H, s), 3.76 (3H, s), 3.77 (3H, s), 3.81 (3H, s), 3.97 (2H, s), 4.13 (2H, q, J = 7.3 Hz), 4.23 (1H, dd, J = 2.6, 11.9 Hz), 4.31−4.40 (2H, m), 5.10−5.21 (3H, m), 5.40 (1H, d, J = 10.0 Hz), 5.51 (1H, t, J = 9.7 Hz), 7.10−7.15 (3H, m), 7.17−7.20 (3H, m), 7.31 (1H, s); ^{13}C NMR (100

MHz, CDCl$_3$) δ: 14.1, 41.0, 41.3, 55.0, 55.1, 55.2, 55.4, 60.8, 65.6, 69.5, 72.6, 73.2, 74.6, 75.6, 108.4, 121.0, 123.4, 129.0, 129.3, 131.1, 131.9, 135.3, 138.1, 139.5, 141.0, 154.5, 154.7, 155.0, 155.4, 171.6; MS (ESI) m/z: 694 [M + H$_2$O]$^+$; HRMS (ESI) calcd for C$_{32}$H$_{36}$O$_{16}$Na [M + Na]$^+$ 699.1901, found 699.1910.

2-[4-[[(3S,3$'R$,4$'S$,5$'S$,6$'R$)-3$'$,4$'$,5$'$-Trihydroxy-6$'$-(hydroxy-methyl)spiro[1H-2-benzofuran-3,2$'$-oxane]-5-yl]methyl]-phenyl]acetic Acid (19). To a solution of **18** (486 mg, 718 μmol) in MTBE (2.43 mL) and MeOH (3.65 mL), 10 N NaOH aq. solution (718 μL, 7.18 mmol) was added dropwise over 5 min at 60 °C. After stirring at 60 °C for 2 h, the reaction mixture was cooled to rt, and formic acid (500 μL) was added. The resultant mixture was purified by reversed-phase chromatography (ODS, 0.1% formic acid in H$_2$O/0.1% formic acid in MeCN) to afford the desired compound **19** (286 mg, 96%) as a colorless amorphous solid by lyophilization; [α]$_D^{19}$ +17.7° (*c* 1.03, MeOH); ^{1}H NMR (400 MHz, CD$_3$OD) δ: 3.41−3.48 (1H, m), 3.54 (2H, s), 3.65 (1H, dd, J = 5.6, 12.0 Hz), 3.74−3.83 (4H, m), 3.98 (2H, s), 5.07 (1H, d, J = 12.5 Hz), 5.13 (1H, d, J = 12.5 Hz), 7.07−7.14 (4H, m), 7.17−7.23 (3H, m); ^{13}C NMR (100 MHz, CD$_3$OD) δ: 41.7, 42.2, 62.8, 71.8, 73.4, 74.9, 76.2, 76.4, 111.6, 121.9, 123.7, 130.0, 130.5, 131.2, 133.9, 140.0, 140.2, 141.1, 142.3, 175.9; MS (ESI) m/z: 415 [M − H]$^-$; HRMS (ESI) calcd for C$_{22}$H$_{23}$O$_8$ [M − H]$^-$ 415.1393, found 415.1397.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b02734.

^{1}H and ^{13}C NMR spectra of all compounds (PDF)

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Notes

The authors declare no competing financial interest.

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(6) We have reported the configuration of the anomeric carbon of **1** is an α-anomer from X-ray analysis of monoacetylated tofogliflozin (ref 2). Compound **1** prepared at that time was synthesized by the alternative scheme proposed here, but compound **15** obtained by spirocyclization was also converted into **1** as shown in this manuscript, and it was identified as the same compound by ^{1}H NMR data. In conclusion, we determined that the stereo-configuration of the anomeric carbon of **15** was an α-anomer.

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