JOC The Journal of Organic Chemistry

Note

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J. Org. Chem., **Just Accepted Manuscript** • DOI: 10.1021/acs.joc.5b02734 • Publication Date (Web): 12 Feb 2016

ACS Publications

The Journal of Organic Chemistry is published by the American Chemical Society. 1155 Sixteenth Street N.W., Washington, DC 20036

Development of a Scalable Synthesis of Tofogliflozin

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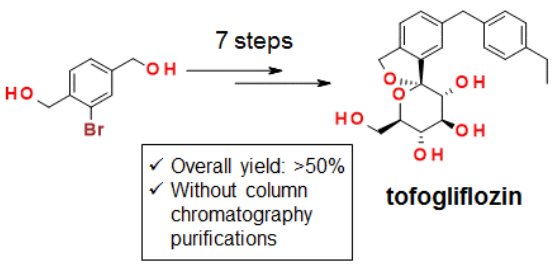
TOC graphic



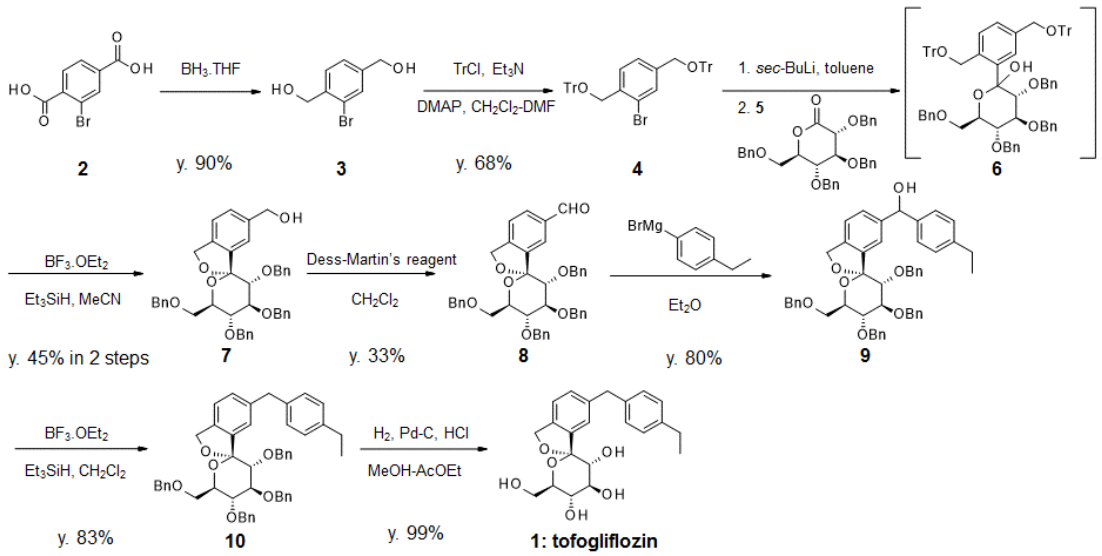
Abstract

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. One of the keys for 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 multi-decagram scale without any column chromatography.

Tofogliflozin (**1**), (1*S*,3'*R*,4'*S*,5'*S*,6'*R*)-6-[(4-ethylphenyl)methyl]-6'-(hydroxymethyl)-3',4',5',6'-tetrahydro-3*H*-spiro[2-benzofuran-1,2'-pyran]-3',4',5'-triol, is a highly selective SGLT2 inhibitor and it 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] it had a difficulty 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.

Scheme 1. A medicinal chemistry route of **1**



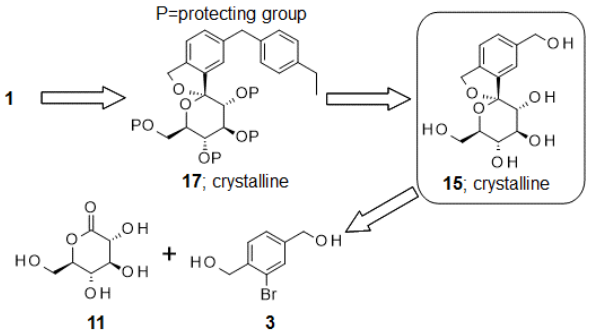
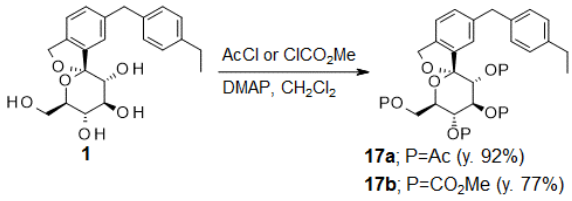


Figure 1. A newly designed retrosynthesis

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.

Scheme 2. Synthesis of two tetra-protected compounds for crystalline investigation



After obtaining crystalline intermediate **17b**, synthesis of the spirocyclized intermediate **15** was investigated. One of the keys for the synthesis of **15** was selecting the protecting groups for **3** and **11**. The addition reaction of protected **3** with protected **11** was supposed to proceed under a strongly basic condition, whereas the spiroketal cyclization could be conducted after deprotection under an acidic condition. 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 literatures.[5] Compound **12** had an oily and moisture-sensitive nature, but it could be used in the next addition reaction without further purifications after the extraction procedure. A 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.

Di-protected **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 condition, followed by stereospecific spirocyclization, resulted in producing the key

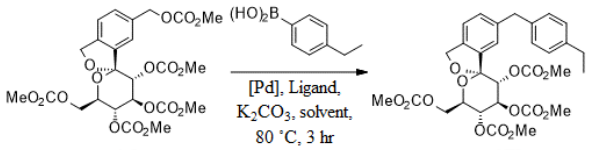
intermediate **15** as a single isomer.[6] Interestingly, β-isomer of **15** was not observed at all. It was supposed that this spirocyclization proceeded stereoselectively by the anomeric effect. Finally, pure **15** was obtained by trituration with MTBE as a stable crystal.

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 work-up 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 equivalent), 4-ethylphenylboronic acid (1.5 equivalents), $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ (APC, 10 mol%), and K_2CO_3 (3.0 equivalents) in DMF (0.2M) (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 acceptable as the same as 1,4-bis(diphenylphosphino)butane (DPPB) (Entry 7). Moreover, we optimized the reaction condition 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 higher reaction concentration (Entry 9). The amount of carbonate-hydrolyzed products was reduced by using 1.0 equivalent base (Entry 10). Under high concentration with 1 equivalent 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 work-up procedure was achieved, as described below.

Table 1. Optimization of coupling reaction conditions[a]



16 **17b**

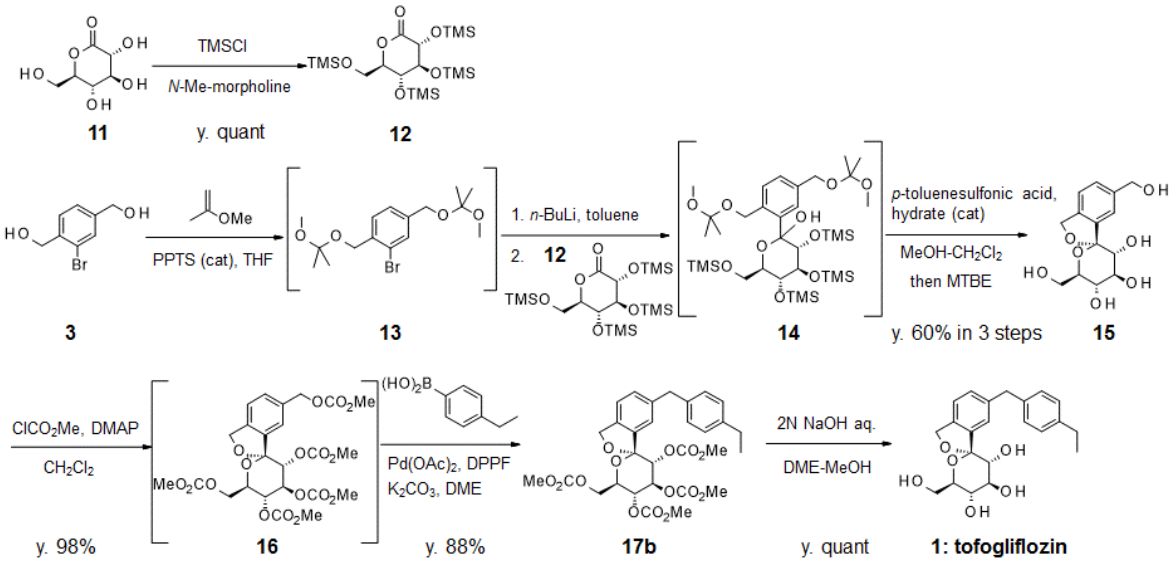
Entry	Conc. (M)	Ligand	[Pd]	K_2CO_3 (eq)	solvent	LCMS area% **16** : **17b** : hydrolysis[b]	Yield (%)[c]
1	0.2	PPh_3	APC	3.0	DMF	51 : 11 : 38	—
2	0.2	DPPE	APC	3.0	DMF	77 : <1 : 23	—
3	0.2	DPPP	APC	3.0	DMF	76 : <1 : 24	—
4	0.2	DPPB	APC	3.0	DMF	5 : 86 : 9	—
5	0.2	DPPPent	APC	3.0	DMF	25 : 59 : 16	—
6	0.2	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 (0.2M or 1.0M) 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 eq), and K_2CO_3 (1.0 eq. or 3.0 eq.) were used. [b] Hydrolysis compounds mean the total amount of some de-methoxycarbonyl compounds. [c] Isolated yield by reverse-phase column chromatography.

Pd coupling reaction to introduce the distal phenyl group was successfully performed under the condition in Entry 14 of Table 1 on a hundred gram 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.

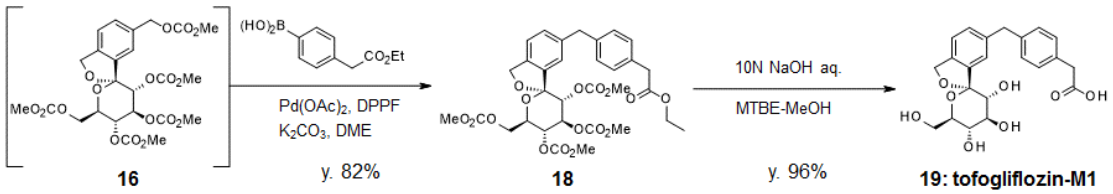
Permethoxylcarbonylated compound **17b** was hydrolyzed with aqueous sodium hydroxide solution in DME. Under the condition, the reaction mixture was heterogeneous and temperature elevation was observed, which suggests a difficulty in controlling the reaction initiation. Thus, MeOH was used as a co-solvent,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

Scheme 3. A newly established route without any column chromatography



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 condition (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.

Scheme 4. Synthesis of metabolite **19**



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) 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_3OD; δ 49.0, $CDCl_3$; δ 77.0). Mass

spectra (MS) were measured using ESI mode. High resonance mass (HRMS) analysis 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 ºC. The mixture was gradually warmed up to 35 ºC over 3.5 h. The reaction mixture was cooled to 0 ºC 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 and the mixture was stirred at 0 ºC for 30 min. The off-white solid was filtered and washed with water (1.15 L x 3) and heptanes (2.30 L) to obtain **3** (426 g, 84%) as a white crystal; mp 108–109 ºC; ^{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 $C_8H_9BrO_2$ $[M]^+$ 215.9786, found 215.9787.

(1*S*,3'*S*,4'*S*,5'*S*,6'*R*)-3',4',5',6'-tetrahydro-6,6'-bis(hydroxymethyl)-spiro[2-benzofuran-1(3*H*),2-[2*H*]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 ºC. 2-Methoxypropene (797 g, 11.1 mol) was dropwise added to this solution at the same temperature. After stirring at 10 ºC for 2 h, the reaction was quenched by dropwise addition of saturated K_2CO_3 aq. solution (4.00 L) and water (4.00 L) at 10 ºC. 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_2SO_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 condition for 20 min. After this solution was cooled at −70 ºC, 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 ºC. After stirring at this temperature for 30 min, satd. NH_4Cl (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_4Cl (3.78 L), and then dried over anhydrous Na_2SO_4 (158 g). The mixture was then concentrated *in vacuo* to obtain the 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 ºC. MTBE (2.61 L) was added to the mixture, and the mixture was stirred at 0 ºC 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 ºC; $[\alpha]_D^{25}$ +43.8º (*c* 1.07, H_2O); ^{1}H NMR (400 MHz, CD_3OD) 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_3OD) 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.

(1*S*,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(3*H*),2-[2*H*]pyran] (16). To a solution of **15** (600.0 g, 2.01 mol) and DMAP (1.55 kg, 12.7 mol) in anhydrous CH_2Cl_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 ºC and 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 x 2) and satd. $NaHCO_3$ (6.00 L), and then dried over anhydrous Na_2SO_4 (600 g). The mixture was concentrated *in vacuo* to obtain crude **16** (1.16 kg, 98%) as a light-yellow amorphous solid; $[\alpha]_D^{13}$ +9.29 º (*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.

(1*S*,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(3*H*),2-[2*H*]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 ºC 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_2O (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 ºC; $[\alpha]_D^{23}$ +29.3 º (*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.

(1*S*,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 (1, tofogliflozin).[2] To a solution of **17b** (89.9 g, 145 mmol) in DME (653 mL) and MeOH (73.0 mL), 2N NaOH aq. solution (726 mL, 1.45 mol) was added dropwise for 1 hr at water-bath temperature. After stirring at rt for 1 h, 2N H_2SO_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 x 2). The resultant organic layer was washed with brine (1.00 L), and then dried over anhydrous Na_2SO_4 (250 g). The mixture was concentrated *in vacuo* to obtain **1** (57.3 g, quant) as a colorless amorphous solid; $[\alpha]_D^{26}$ +24.2º (*c* 1.02, MeOH); ^{1}H NMR (400 MHz, CD_3OD) 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_3OD) 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*,3*S*,4'*S*,5'*R*)-3',4',5'-Triacetoxy-5-[(4-ethylphenyl)methyl]spiro[1*H*-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_2Cl_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 ºC and for 20 h at rt. 2N HCl aq. solution was added to the mixture, and the resultant mixture was extracted with CH_2Cl_2. The resultant organic layer was washed with brine, and then dried over anhydrous Na_2SO_4. The mixture was concentrated *in vacuo* and the residue was purified by reverse-phase column chromatography (ODS, 0.1% formic acid in H_2O / 0.1% formic acid in MeCN) to obtain **17a** (264 mg, 92%) as a colorless amorphous solid; $[\alpha]_D^{18}$ +22.6 º (*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-[[(3*S*,3'*R*,4'*S*,5'*R*,6'*R*)-3',4',5'-tris(methoxycarbonyloxy)-6'-(methoxycarbonyloxymethyl)spiro[1*H*-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 ºC for 6 h. After cooling, formic acid (100 μL) was added to the mixture. The resultant mixture was purified by reverse-phase chromatgraphy (ODS, 0.1% formic acid in H_2O / 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 ºC; $[\alpha]_D^{19}$ +23.7 º (*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 $[M+H_2O]^+$; HRMS (ESI) calcd for $C_{32}H_{36}O_{16}Na$ $[M+Na]^+$ 699.1901, found 699.1910.

2-[4-[[(3*S*,3'*R*,4'*S*,5'*S*,6'*R*)-3',4',5'-trihydroxy-6'-(hydroxymethyl)spiro[1*H*-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), 10N NaOH aq. solution (718 μL, 7.18 mmol) was added dropwise over 5 min at 60 ºC. After stirring at 60 ºC for 2 hr, the reaction mixture was cooled to rt, and formic acid (500 μL) was added. The resultant mixture was purified by reverse-phase chromatography (ODS, 0.1% formic acid in H_2O / 0.1% formic acid in MeCN) to afford the desired compound **19** (286 mg, 96%) as a colorless amorphous solid by lyophilization.; $[\alpha]_D^{19}$ +17.7º (*c* 1.03, MeOH); ^{1}H NMR (400 MHz, CD_3OD) 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_3OD) 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. ^{1}H-NMR and ^{13}C-NMR spectra of all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENT

We are very grateful to Professor emeritus of Tohoku University Kunio Ogasawara (formerly a scientific advisor in our company) for many scientific and constructive suggestions. We thank Ms. Hitomi Suda, Mr. Yuichiro Ishiguro, and Ms. Masako Arai for mass spectrometry measurements, Dr. Noriyuki Takata for X-ray structure analysis, and Mr. Satoshi Tanida for DSC measurements. We also thank Editing Services at Chugai Pharmaceutical Co., Ltd for assistance with English usage.

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6. We have reported the configuration of the anomeric carbon of **1** is alpha-anomer from X-ray analysis of mono-acetylated 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 alpha-anomer.

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