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Org. Process Res. Dev., **Just Accepted Manuscript** • DOI: 10.1021/acs.oprd.6b00175 • Publication Date (Web): 27 Sep 2016

Just Accepted

ACS Publications

Organic Process Research & Development is published by the American Chemical Society. 1155 Sixteenth Street N.W., Washington, DC 20036

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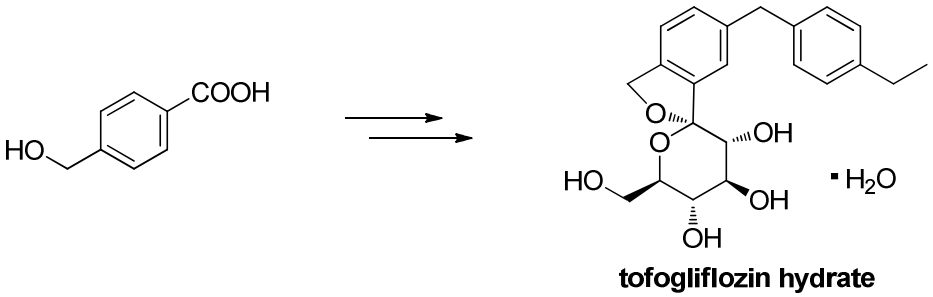
TOC graphic



tofogliflozin hydrate

Abstract

A newly process for the synthesis of tofogliflozin hydrate, a sodium-glucose co-transporter type 2 (SGLT2) inhibitor, was described. Three improvements were achieved, including the development of a regioselective Friedel-Crafts reaction, a high-yield reduction and a mild metal-halogen exchange. These improvements ultimately resulted in the isolation of tofogliflozin hydrate as a white solid in > 99% purity (HPLC area) and 23% overall yield after 12 steps without column chromatography.

Keywords :

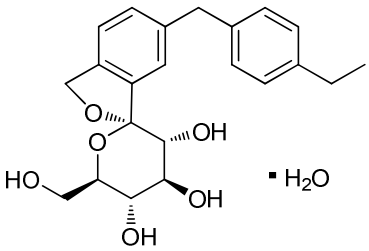
tofogliflozin hydrate

SGLT2

Friedel-Crafts reaction

metal-halogen exchange

Tofogliflozin hydrate (Figure 1), as a novel SGLT2 inhibitor,[1] has been shown that its treatment for Type 2 diabetes is safe and well tolerated to patients, without any specific or clinically relevant concerns.[1c] Hence, it has already been approved and launched in Japan.



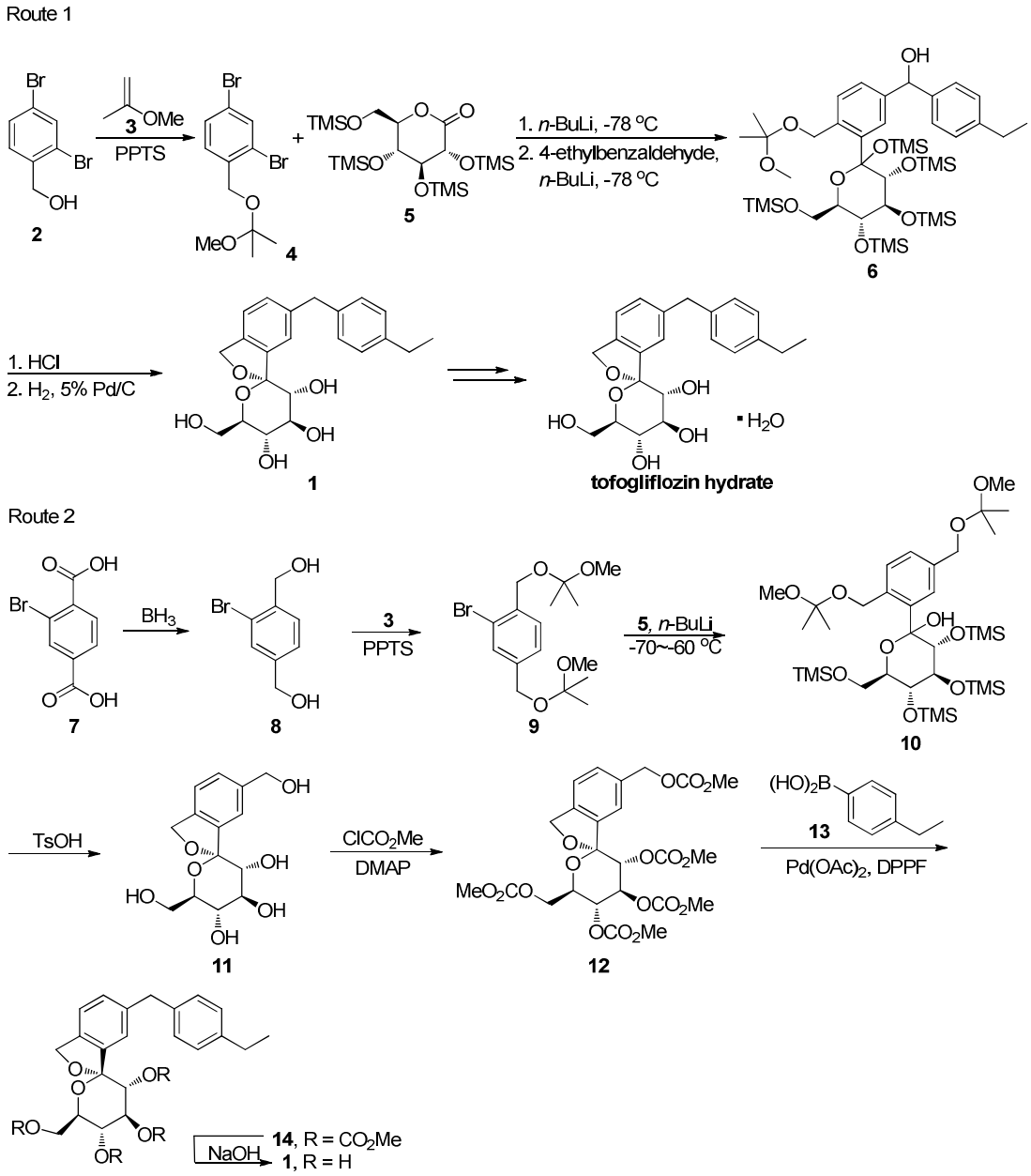
tofogliflozin hydrate

Figure 1. Tofogliflozin Hydrate

There are two scalable synthetic routes reported to prepare tofogliflozin.[2] An efficient production synthesis of tofogliflozin hydrate from alcohol **2** was first described by Murakata et al. (Scheme 1, route 1).[2a] In 2016, Ohtake et al. reported an improved synthetic route, which achieved in just 7 linear steps (Scheme 1, route 2).[2b] They selected the optimal protecting groups for the purpose of chemoselective activation and crystalline purification, and obtained the pure tofogliflozin in a good overall yield. However, these methods suffer from several drawbacks. Firstly, some reagents, such as BH_3 (Scheme 1, route 2) and 2-Methoxyproene (**3**, Scheme 1), are toxic or highly volatile. Meanwhile, the use of Palladium reagents may lead to an excess of

residual heavy metal in the final product. Secondly, manufacturing costs in these methods are high due to the application of expensive raw materials and reagents. Last but not least, the key tactical stages that involve Br/Li exchange of aryl bromide followed by addition to gluconolactone **5** need the cryogenic conditions (< -60 ^{o}C), and this method is not suitable for industrial production. Herein, we report a newly developed synthetic method for tofogliflozin hydrate starting from readily available raw materials and affording good overall yield.

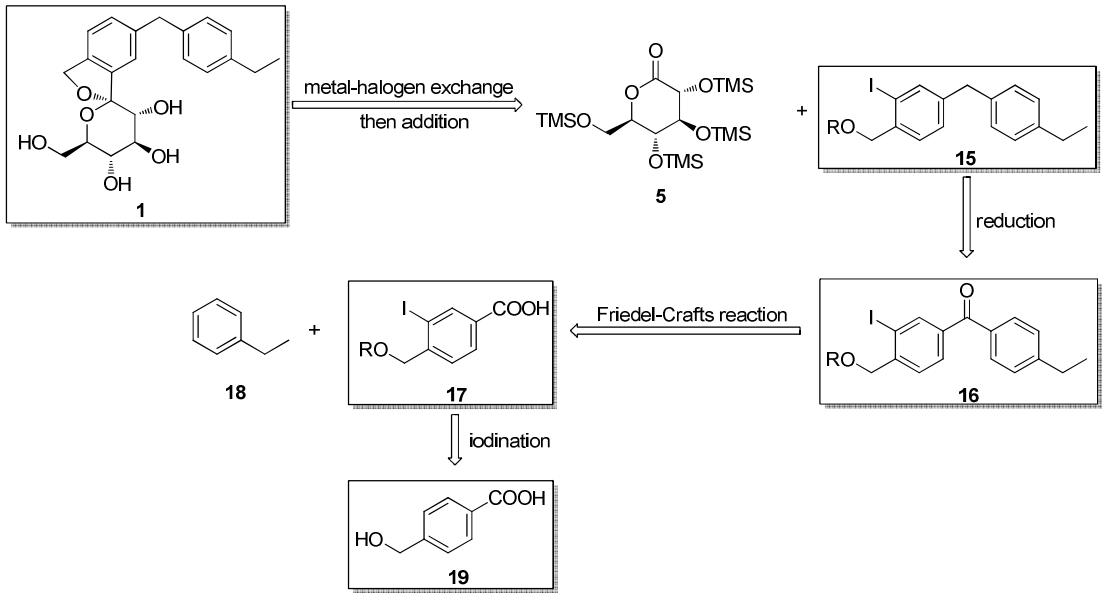
Scheme 1. Reported Scalable Synthetic Routes of Tofogliflozin



Our new retrosynthesis is depicted in Scheme 2, which is partially inspired from the synthetic route of empagliflozin by Wang's group.[3] As shown in Scheme 2, the tofogliflozin (**1**) could be directly prepared from

advanced fragments **5** and **15** with a metal-halogen exchange and an addition reaction. Then, the compound **15** could be synthesized from the intermediate **16** by reduction. For the intermediate **16**, it could be synthesised from the precursor **17** and ethylbenzene **18** with a Friedel-Crafts reaction. At last, the aryl iodide **17** could be generated through an iodination from cheap commercially available 4-(hydroxymethyl)benzoic acid **19**.

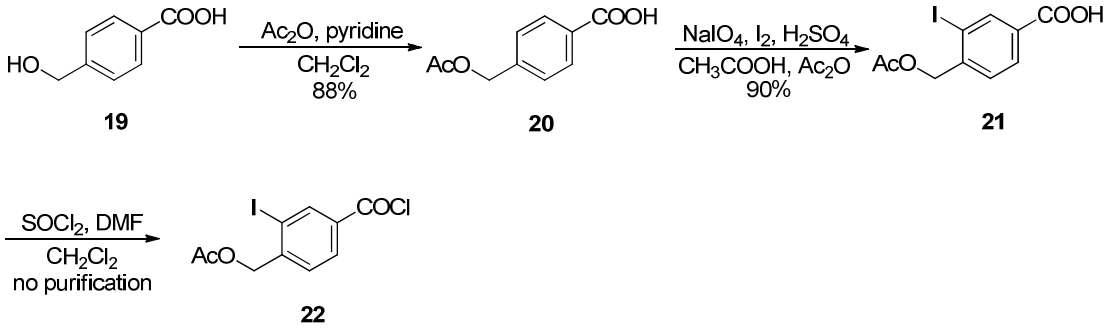
Scheme 2. Retrosynthetic Analysis of Tofogliflozin



The synthesis of tofogliflozin (**1**) began with the construction of iodo-substituted **21** and **22** (Scheme 3). The acid **19** was used as the starting material and the hydroxyl group was protected through acetylation to afford ester **20**,[4] which proceeded smoothly under the Lulinski's optimized

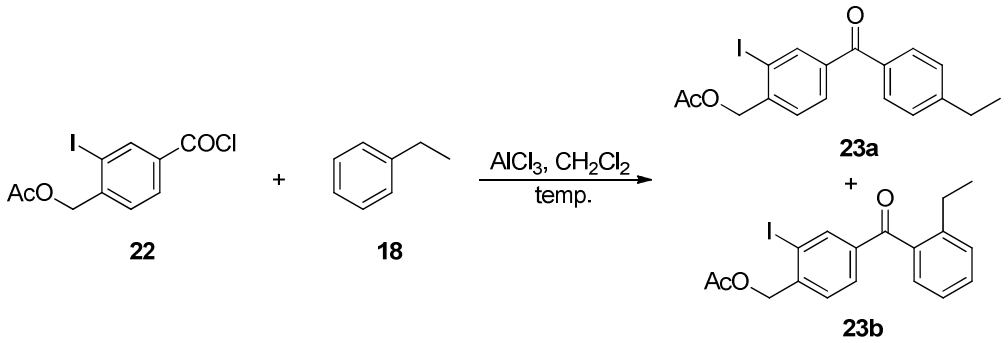
condition to provide the desired intermediate **21** in good yield and excellent regioselectivity.[5] Then, the Compound **21** was reacted with thionyl chloride by using a catalytic amount of *N*,*N*-dimethylformamide to obtain iodo-substituted **22**, which was used in the next step without further purification.

Scheme 3. Preparation of Iodo-Substituted 21 and 22



With the fragment **22** in hand, the next step was the Friedel-Crafts reaction. In order to convert compound **22** into the ketone **23a**, a series of conditions was explored (Table 1).

Table 1. Optimization of Friedel-Crafts Reaction[a]



entry	$AlCl_3$ (equiv)	**18** (equiv)	temperature (^oC)	Yield (%)[b]	*para*/*ortho* (**23a**/**23b**)[e]
1	1.1	1.5	0	22[c]	37
2	2.2	1.5	0	40[d]	34
3	3.3	1.5	0	37[d]	31
4	2.2	2.5	0	43[d]	35
5	2.2	3.5	0	50[d]	36
6	2.2	4.5	0	48[d]	35
7	2.2	3.5	10	53[d]	31
8	2.2	3.5	20	59[d]	34
9	2.2	3.5	reflux	64[d]	33

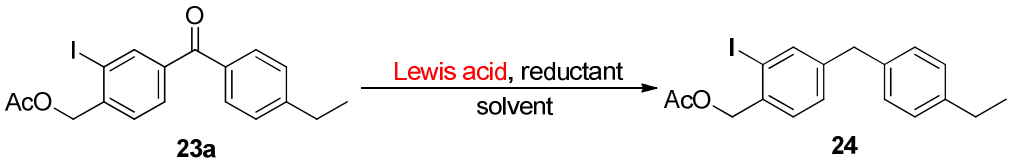
[a] All reactions were conducted at a concentration of 0.47 M. [b] Isolated yield from **21**. [c] Isolated yield after purification by column chromatography. [d] Isolated yield after crystallization from isopropanol and water. [e] Ratio of *para* to *ortho* was determined by HPLC.

The amount of $AlCl_3$ was first investigated, and 2.2 equivalents provided the best yield (Table 1, entries 1–3). As the amount of ethylbenzene (**18**) increased, the yield was improved from 43% to 50% (Table 1, entries 4 and 5). However, a lower yield of 48% was found with the presence of 4.5 equiv of ethylbenzene (Table 1, entry 6). Then, the results of the following experiments depicted that the reaction went better with the higher temperature (Table 1, entries 7–9). Notably, a good yield (64% from **21**,

Table 1, entry 9) was achieved in reflux with the presence of 2.2 equiv of $AlCl_3$ and 3.5 equiv of ethylbenzene. In addition, the *para*-selectivities of the reactions were excellent and no significantly change was found under the different conditions (Table 1, entries 1–9).

The next step was the reduction of ketone **23a** to aryl iodide **24**, and different reducing conditions were tested (Table 2).

Table 2. Optimization of Reducing Reaction



23a **24**

entry	Lewis acid (equiv)	reductant (equiv)	solvent	Yield (%)[b]
1	$AlCl_3$ (2)	$NaBH_4$ (1.5)	THF	NP
2	–	Et_3SiH (2)	CF_3COOH	26
3[a]	$BF_3{\cdot}Et_2O$ (2)	Et_3SiH (2)	CH_2Cl_2/CH_3CN (1:2)	83
4[a]	$AlCl_3$ (2)	Et_3SiH (2)	CH_2Cl_2/CH_3CN (1:2)	43
5[a]	$AlCl_3$ (2)	1,1,3,3-tetramethyldisiloxane	CH_2Cl_2/CH_3CN	85

		(2)	(1:2)	
6[a]	$AlCl_3$ (3)	1,1,3,3-tetramethyldisiloxane (2)	CH_2Cl_2/CH_3CN (1:2)	96
7[a]	$AlCl_3$ (3)	1,1,3,3-tetramethyldisiloxane (2)	toluene	34

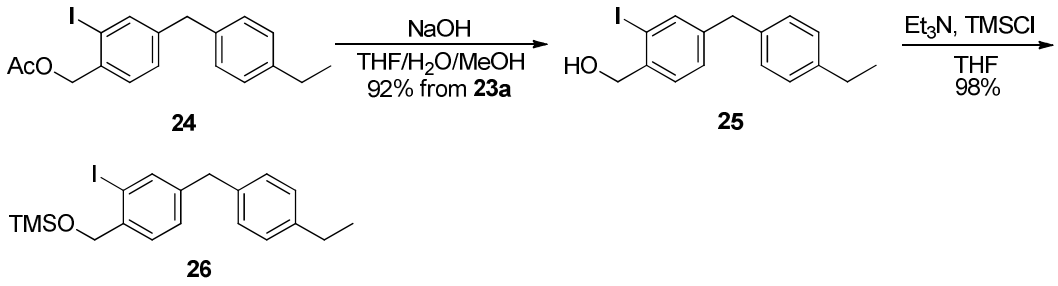
[a] the reaction was conducted at a concentration of 0.25 M. [b] Isolated yield after purification by column chromatography. NP = no product.

We first used $AlCl_3$ as Lewis acid and $NaBH_4$ as reductant,[6] but no desired product was obtained (Table 2, entry 1). On the basis of the condition described in Kiuchi's report,[7] the desired product **24** was obtained, albeit with a low 26% yield (Table 2, entry 2). Our succeeding investigations found that a very good yield of product **24** could be obtained using BF_3 as Lewis acid in solvent mixtures of CH_2Cl_2 and CH_3CN (Table 2, entry 3). However, when low toxic reagent $AlCl_3$ was used, the yield was decreased to 43% (Table 2, entry 4). Fortunately, the aryl iodide **24** was obtained in good yield when 1,1,3,3-tetramethyldisiloxane was used as reductant, and the best yield (96%) was encountered at the presence of 3 equiv of $AlCl_3$ (Table 2, entries 5 and 6). However, if the solvent (CH_2Cl_2/CH_3CN) was replaced by toluene, the reaction, carried out under the same condition as in entry 6, provided a poor yield (Table 2, entry 7). The LC-MS analysis showed that

the acetoxy group on compound **24** could be reacted with toluene when the reaction was conducted in presence of $AlCl_3$.[8]

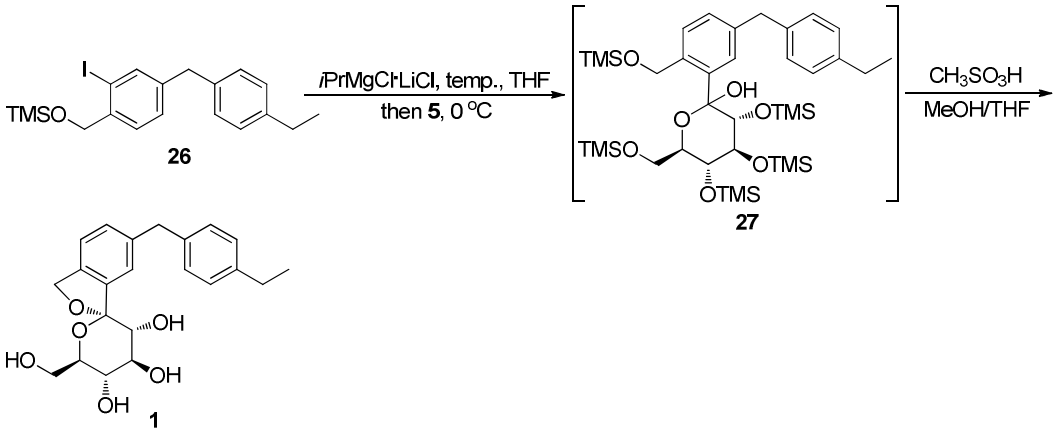
The acetate **24** was deprotected by saponification to give alcohol **25** in high purity and 92% yield over two steps. After protection with TMSCl, The compound **26** was obtained in nearly quantitative yield and used in the next step immediately (Scheme 4).

Scheme 4. Preparation of Aryl Iodide 26



Next, our attention focused on the metal-halogen exchange with *i*PrMgCl·LiCl. Taking into account the instability of TMS group, the protecting groups in oily intermediate **27** were removed using methanesulfonic acid,[9] followed by spirocyclization to afford the stable compound **1** which could be purified easily. Different reaction temperatures and the amount of Grignard reagent were tested to determine the effects on the reaction (Table 3).

Table 3. Optimization of I/Mg Exchange with *i*PrMgCl·LiCl[a]



entry	*i*PrMgCl·LiCl (equiv)	temperature (°C)	isolated yield of **1** (%)
1	1.1	0	41[b]
2	1.1	-10	63[b]
3	1.1	-20	71[b]
4	1.1	-30	70[b]
5	1.5	-20	37[b]
6	2.0	-20	trace

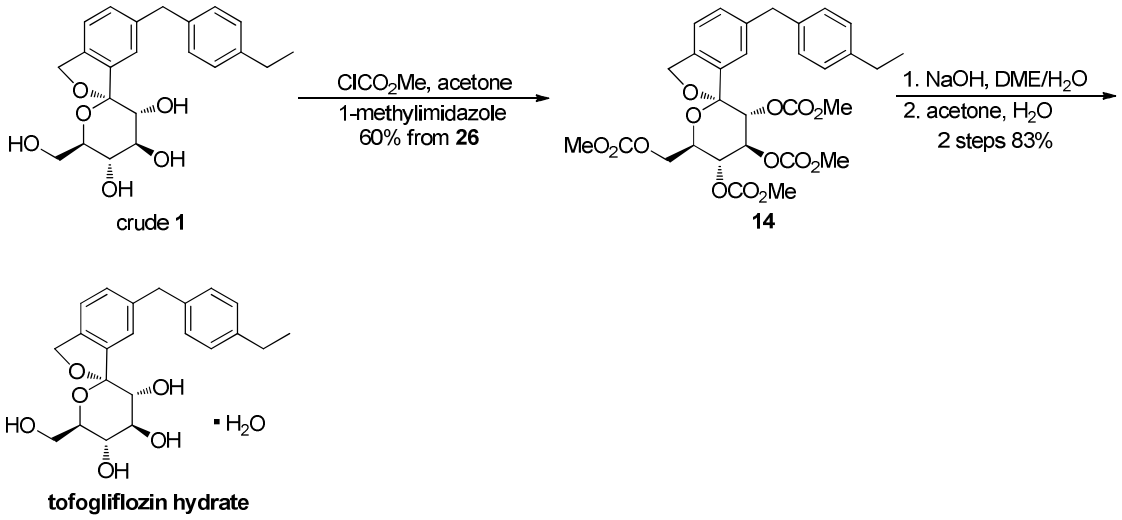
[a] All reactions were conducted at a concentration of 1.07 M. [b] Isolated yield after purification by column chromatography.

As shown in Table 3, the data revealed that -20 °C was the best temperature for the I/Mg exchange (Table 3, entry 3). Further decreasing reaction temperatures to -30 °C did not significantly change the yield (Table 3, entry 4). However, the same reactions performed under a higher

temperature resulted in decreased yields (Table 3, entries 1 and 2). Moreover, the amount of *i*PrMgCl·LiCl remarkably affected reaction efficiency. The more equivalents of Grignard reagent were used, the less compound **1** was obtained (Table 3, entries 5 and 6). These results were similar to those published by Wang et al., who observed that excess Grignard reagent was closely correlated with decreasing amounts of desired product on the synthesis of empagliflozin.[3]

Conversion of crude product **1** obtained in the previous step to high-purity tofogliflozin hydrate involved three additional manipulations (Scheme 5).

Scheme 5. Preparation of Tofogliflozin Hydrate



According to the reported method,[2a] when the compound **1** was treated with methyl chloroformate in the presence of 1-methylimidazole in acetone and then crystallized from a mixture of ethanol, methyl tert-butyl ether and

isopropanol, the crystalline intermediate **14** was obtained with an overall yield of 60% from **26**. Finally, treatment of the compound **14** with NaOH in solvent mixtures of 1,2-dimethoxyethane and water, followed by crystallization from aqueous acetone to furnish tofogliflozin hydrate with > 99% purity in 83% yield over two steps.

In summary, we have developed a practical and scalable synthetic route for the SGLT2 inhibitor tofogliflozin hydrate which proceeds in 12 linear steps and in 23% overall yield. One of the key steps involved in the transformation of aryl iodide **26** to the corresponding crude tofogliflozin **1** was accomplished by a mild process of I/Mg exchange and addition. Meanwhile, the conditions of Friedel-Crafts reaction and reduction have been optimized. This newly developed synthesis of tofogliflozin, starting from cheap 4-(hydroxymethyl)benzoic acid **19** and no using expensive reagents, is cost-effective albeit requiring synthetic steps longer than the reported routes and has potential for scale manufacturing.

Experimental Section

All starting materials, reagents and solvents were purchased from commercial suppliers and used without further purification. ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were measured and chemical shifts

were reported in ppm using TMS or the residual solvent peak as a reference. High resonance mass (HRMS) analyses were recorded using ESI mode by Q-TOF. Infrared spectra were recorded on FT-IR. Optical rotations were determined on a polarimeter at 589 nm. The water content (KF) was determined by Karl Fisher titration.

4-(acetoxymethyl)benzoic acid (20).[4] A 5 L three-necked flask was charged with 4-Hydroxymethylbenzoic acid **19** (213 g, 1.40 mol), CH_2Cl_2 (1.40 L), acetic anhydride (700 mL), and pyridine (23.3 mL). The mixture was heated to reflux and stirred for 2 h. The solvent was evaporated under reduced pressure. To the resulting residue was added water (4.00 L) and the mixture was heated to reflux and stirred for 2 h. The reaction mixture was cooled to 0~5 ^{o}C, stirred for 2 h and filtered. The wet cake was washed with water (1.00 L) and dried at 60 ^{o}C for 8 h to give **20** (239 g, 88%) as a white solid. Mp: 127−129 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 (d, J = 7.8 Hz, 2H), 7.46 (d, J = 7.8 Hz, 2H), 5.19 (s, 2H), 2.15 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.8, 170.8, 141.9, 130.4, 129.0, 127.7, 65.4, 20.8. HRMS (ESI) m/z: $[M+NH_4]^+$ Calcd for $C_{10}H_{14}NO_4$ 212.0917; Found 212.0905. IR (KBr, cm^{-1}) ν: 3600, 3079, 2944, 1733, 1683, 1616, 1578, 1517, 1430, 752.

4-(acetoxymethyl)-3-iodobenzoic acid (21). A 5 L three-necked flask was charged with sodium periodate (143g, 0.670 mol), diiodine (114 g, 0.448 mol), acetic acid (932 mL), and acetic anhydride (466 mL). The

resulting mixture was vigorously stirred and concentrated sulfuric acid (914 g, 9.33 mol) was added while keeping the internal temperature below 5 °C. 4-(acetoxymethyl)benzoic acid **20** (233 g, 1.20 mol) was added portionwise and the resulting slurry was stirred at 30 °C for 20 h. To the reaction mixture was added ice water (1.10 L) followed by addition of 15% aqueous Na_2SO_3 (1.10 L). The slurry was stirred at 20 °C for 0.5 h and filtered. The wet cake was washed with water (1.00 L) and dried at 70 °C for 8 h to give **21** (346 g , 90%) as a off-white solid. Mp: 170−172 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.58 (s, 1H), 8.09 (d, *J* = 8.0 Hz, 1H), 7.48 (d, *J* = 8.0 Hz, 1H), 5.17 (s, 1H), 2.19 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.4, 169.5, 144.2, 141.0, 130.3, 130.0, 128.5, 96.9, 69.6, 20.8. HRMS (ESI) m/z: $[M+NH_4]^+$ Calcd for $C_{10}H_{13}INO_4$ 337.9884; Found 337.9875. IR (KBr, cm^{-1}) ν: 3427, 3077, 2943, 1728, 1685, 1598, 1557, 1487, 1423, 1236, 759.

4-(4-ethylbenzoyl)-2-iodobenzyl acetate (23a). A 5 L three-necked flask was charged with 4-(acetoxymethyl)-3-iodobenzoic acid **21** (320 g, 1.00 mol), CH_2Cl_2 (2.67 L), and DMF (1.8 mL). The mixture was cooled to 0~5 °C and then thionyl chloride (297 g, 2.50 mol) was added dropwise. The mixture was heated to reflux, stirred for 3 h and then concentrated under reduced pressure to give **22** as a off-white solid without further purification.

A 5 L three-necked flask was charged with the above residue, CH_2Cl_2 (2.13 L), and ethylbenzene **18** (427 mL, 3.50 mol). The mixture was cooled

to 0~5 °C and aluminum chloride (293 g, 2.20 mol) was added portionwise while keeping the internal temperature below 10 °C. The mixture was heated to reflux and stirred for 0.5 h. Ice water (2.00 L) was added and the resulting mixture was extracted with ethyl acetate (2.00 L × 3). The combined organic layer was concentrated under reduced pressure. To the resulting residue was added isopropanol (1.60 L) and water (533 mL). The mixture was heated to reflux and then cooled to 20 °C over the course of 2 h. The slurry was stirred for additional 2 h at 20 °C and filtered. The wet cake was washed with isopropanol/water (320 mL, v/v = 2:1) and dried at 50 °C for 8 h to give **23a** (261 g, 64% from **21**) as a white solid. Mp: 69−71 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.26 (s, 1H), 7.76-7.72 (m, 3H), 7.47 (d, *J* = 7.9 Hz, 1H), 7.32 (d, *J* = 7.8 Hz, 2H), 5.18 (s, 2H), 2.75 (q, *J* = 7.6 Hz, 2H), 2.19 (s, 3H), 1.29 (t, *J* = 7.6 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.1, 170.3, 149.9, 142.1, 140.4, 139.1, 134.3, 130.3, 129.6, 128.4, 127.9, 97.2, 69.5, 28.9, 20.8, 15.1. HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{18}H_{18}IO_3$ 409.0295; Found 409.0287. IR (KBr, cm^{-1}) ν: 3455, 3056, 2984, 2932, 1744, 1661, 1607, 1595, 1551, 1413, 1226, 1050, 751.

(4-(4-ethylbenzyl)-2-iodophenyl)methanol (25). A 5 L three-necked flask was charged with 4-(4-ethylbenzoyl)-2-iodobenzyl acetate **23a** (250 g, 0.61 mol), dichloromethane (815 mL), acetonitrile (1.63 L), and 1,1,3,3-tetramethyldisiloxane (164 g, 1.22 mol). The mixture was cooled to

0~5 °C and aluminum chloride (245 g, 1.84 mol) was added portionwise. The mixture was warmed to 25 °C and stirred for 20 h. To the reaction mixture was added ice water (2.00 L) and then stirred for 0.5 h. The resulting mixture was extracted with ethyl acetate (1.00 L × 3). The combined organic layer was concentrated under reduced pressure to give crude **24** as a colorless oil without further purification. A small sample was obtained as a colorless solid by chromatographic purification on silica gel. Mp: 53−54 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 (s, 1H), 7.26 (d, *J* = 8.0 Hz, 1H), 7.14 (d, *J* = 8.0 Hz, 1H), 7.11 (d, *J* = 7.8 Hz, 2H), 7.06 (d, *J* = 7.8 Hz, 2H), 5.08 (s, 2H), 3.86 (s, 2H), 2.60 (q, *J* = 7.6 Hz, 2H), 2.09 (s, 3H), 1.21 (t, *J* = 7.6 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.4, 143.5, 142.2, 139.7, 137.1, 135.9, 129.5, 128.8, 128.7, 128.0, 98.7, 69.8, 40.5, 28.3, 20.8, 15.5. HRMS (ESI) m/z: $[M+NH_4]^+$ Calcd for $C_{18}H_{23}INO_2$ 412.0768; Found 412.0762. IR (KBr, cm^{-1}) ν: 3437, 3047, 2959, 2922, 1742, 1598, 1557, 1486, 1451, 1239, 1032, 808, 479.

A 5 L three-necked flask was charged with the above residue, THF (480 mL), methanol (480 mL), and 15% aqueous sodium hydroxide (480 mL). The slurry was stirred at 25 °C for 4 h and filtered. The wet cake was washed with water (1.00 L) and dried at 70 °C for 8 h to give **25** (199 g , 92% from **23a**) as a white solid. Mp: 105−107 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 (s, 1H), 7.34 (d, *J* = 7.8 Hz, 1H), 7.18 (d, *J* = 7.8 Hz, 1H), 7.13 (d, *J* = 7.7

Hz, 2H), 7.08 (d, *J* = 7.7 Hz, 2H), 4.64 (s, 2H), 3.89 (s, 2H), 2.62 (q, *J* = 7.6 Hz, 2H), 1.86 (br s, 1H), 1.22 (t, *J* = 7.6 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.9, 142.2, 140.3, 139.4, 137.3, 129.1, 128.7, 128.5, 128.0, 97.8, 69.0, 40.5, 28.4, 15.5. HRMS (ESI) m/z: $[M+NH_4]^+$ Calcd for $C_{16}H_{21}INO$ 370.0662; Found 370.0662. IR (KBr, cm^{-1}) ν: 3269, 2921, 2864, 1659, 1512, 1437, 1061, 1027, 556.

(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] (14). A 5 L three-necked flask was charged with (4-(4-ethylbenzyl)-2-iodophenyl)methanol **25** (190 g, 0.54 mol), THF (1.80 L), and triethylamine (109 g, 1.08 mol). The mixture was cooled to 0~5 °C and TMSCl (88.0 g, 0.810 mol) was added dropwise. The mixture was warmed to 25 °C and stirred for 1 h. To the mixture was added ice water (2.00 L) and then stirred for 10 min. The resulting mixture was extracted with CH_2Cl_2 (2.00 L × 3). The combined organic layers were washed with brine and dried over anhydrous Na_2SO_4. The solid was filtered off, and the mother liquid (water content < 0.1%) was concentrated under reduced pressure to give **26** (225 g , 98%) as a colorless oil without further purification.

A 3 L three-necked flask was charged with the above aryl iodide **26** and THF (495 mL). The mixture was cooled to -20~-25 °C and *i*PrMgCl·LiCl

(1.30 M in THF, 448 mL, 0.582 mol) was added dropwise. After stirring at -20~-25 °C for 0.5 h, to the mixture was added (3*R*,4*S*,5*R*,6*R*)-3,4,5-tris((trimethylsilyl)oxy)-6-(((trimethylsilyl)oxy)methyl) tetrahydro-2*H*-pyran-2-one **5** (309 g, 0.662 mol) while keeping the internal temperature below -15 °C. The mixture was warmed to 0~5 °C and stirred for 1 h. To the mixture was added 10% aqueous ammonium chloride (1.00 L) and then warmed to 25 °C. The resulting mixture was extracted with ethyl acetate (600 mL × 3). The combined organic layers were dried over anhydrous Na_2SO_4. The solid was filtered off, and the mother liquid was concentrated under reduced pressure. the residue was used in the next step without further purification.

A 5 L three-necked flask was charged with the above residue and THF (1.35 L). The mixture was cooled to 0~5 °C and methanesulfonic acid (0.05 M in methanol, 540 mL, 0.027 mol) was added dropwise. After stirring at 0~5 °C for 15 h, to the resulting mixture was added saturated aqueous sodium bicarbonate (900 mL). The mixture was concentrated under reduced pressure to a low volume (~900 mL). To the mixture was added 1,2-dimethoxyethane (1.80 L), water (1.80 L) and n-hexane (2.70 L). The organic layer was separated and the aqueous layer was extracted with ethyl acetate (1.20 L × 3). The combined organic layers were dried over anhydrous Na_2SO_4. The solid was filtered off, and the mother liquid was

concentrated under reduced pressure to give crude tofogliflozin **1** as a colorless foam without further purification.

A 3 L three-necked flask was charged with the above product, acetone (800 mL), and 1-methylimidazole (433 g, 5.27 mol). The mixture was cooled to 0~5 ^{o}C and methyl chloroformate (332 g, 3.51 mol) was added dropwise. The mixture was warmed to 25 ^{o}C and stirred for 1 h. To the resulting mixture was added water (1.00 L) and then extracted with ethyl acetate (540 mL × 3). The combined organic layer was concentrated under reduced pressure. To the residue was added ethanol (1.08 L), methyl tert-butyl ether (180 mL) and isopropanol (270 mL). The mixture was heated to reflux and slowly cooled to 25 ^{o}C over the course of 4~5 h. The slurry was stirred for additional 1 h at 25 ^{o}C and filtered. The wet cake was washed with ethanol/isopropanol (100 mL, v/v=3:1) and dried at 60 ^{o}C for 6 h to give **14** (196 g, 60% from **26**) as a white solid. Mp: 128−130 ^{o}C. $[\alpha]^{20}_{D}$ = +30.9 (c = 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 (s, 1H), 7.20 (d, *J* = 8.0 Hz, 1H), 7.14 (d, *J* = 8.0 Hz, 1H), 7.12-7.07 (m, 4H), 5.51 (t, *J* = 9.6 Hz, 1H), 5.41 (d, *J* = 9.9 Hz, 1H), 5.21-5.10 (m, 3H), 4.39-4.36 (m, 1H), 4.35-4.31 (m, 1H), 4.25-4.22 (m, 1H), 3.96 (s, 2H), 3.81 (s, 3H), 3.77 (s, 3H), 3.76 (s, 3H), 3.50 (s, 3H), 2.60 (q, *J* = 7.5 Hz, 2H), 1.20 (t, *J* = 7.6 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.3, 154.9, 154.7, 154.4, 141.9, 141.4, 138.0, 137.9, 135.2, 131.0, 128.7, 127.9, 123.2, 120.9, 108.4, 75.5, 74.6, 73.1, 72.6, 69.4,

65.6, 55.3, 55.1, 54.9, 54.9, 41.3, 28.3, 15.5. HRMS (ESI) m/z: $[M+NH_4]^+$ Calcd for $C_{30}H_{38}NO_{14}$ 636.2287; Found 636.2280. IR (KBr, cm^{-1}) ν: 3485, 2963, 2929, 2880, 1760, 1452, 1272, 808, 785. Spectroscopic data were identical with those reported.[2]

Tofogliflozin hydrate.[2a] A 3 L three-necked flask was charged with **14** (193 g, 0.312 mol), 1,2-dimethoxyethane (1.17 L), and 16% aqueous sodium hydroxide (936 mL). The mixture was stirred for 3 h at 25 °C and then neutralized to pH 6~7 by the addition of conc. HCl while keeping the internal temperature below 5 °C. The resulting mixture was extracted with ethyl acetate (780 mL × 3). The combined organic layers were dried over anhydrous Na_2SO_4. The solid was filtered off, and the mother liquid was concentrated under reduced pressure to give tofogliflozin **1** as a colorless amorphous solid.

A 3 L three-necked flask was charged with the above solid, acetone (390 mL), and water (390 mL). The mixture was heated to 50 °C and then cooled to 5 °C over the course of 1.5 h. Water (1.56 L) was slowly added to the solution over the course of 3 h while keeping the internal temperature below 10 °C. The slurry was stirred for additional 2 h at 5 °C and filtered. The wet cake was washed with water (260 mL) and dried at 25 °C in vacuo for 30 h to give **tofogliflozin hydrate** (105 g, 83% from **14**) as a white solid with 99.56% purity by HPLC. Water content: 4.47%. Mp: 71−80 °C. $[\alpha]^{20}_D$ =

+23.9 (c = 1.0, CH_3OH). ^1H NMR (400 MHz, CD_3OD) δ 7.23-7.18 (m, 3H), 7.12-7.08(m, 4H), 5.13 (d, *J* = 12.4 Hz, 1H), 5.07 (d, *J* = 12.4 Hz, 1H), 3.96 (s, 2H), 3.83-3.73 (m, 4H), 3.65 (dd, *J* = 11.9, 5.5 Hz, 1H), 3.41-3.47 (m, 1H), 2.59 (q, *J* = 7.6 Hz, 2H), 1.19 (t, *J* = 7.6 Hz, 3H). ^{13}C NMR (100 MHz, CD_3OD) δ 143.2, 142.6, 140.2, 139.9, 139.7, 131.2, 129.9, 128.9, 123.6, 121.8, 111.6, 76.4, 76.2, 74.9, 73.4, 71.9, 62.8, 42.3, 29.5, 16.3. HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{22}H_{27}O_6$ 387.1802; Found 387.1805. IR (KBr, cm^{-1}) ν: 3362, 2962, 2927, 1637, 1513, 1429, 1095, 1034, 808, 770. Spectroscopic data were identical with those reported.[1b, 2]

ASSOCIATED CONTENT

Supporting Information. ^1H NMR and ^{13}C NMR spectra of all compounds.

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Notes

The authors declare no competing financial interest.

REFERENCES

1. (a) Suzuki, M.; Honda, K.; Fukazawa, M.; Ozawa, K.; Hagita, H.; Kawai, T.; Takeda, M.; Yata, T.; Kawai, M.; Fukuzawa, T.; Kobayashi, T.; Sato, T.; Kawabe, Y.; Ikeda, S. *J. Pharmacol. Exp. Ther.* **2012**, *341*, 692. (b) Ohtake, Y.; Sato, T.; Kobayashi, T.; Nishimoto, M.; Taka, N.; Takano, K.; Yamamoto, K.; Ohmori, M.; Yamaguchi, M.; Takami, K.; Yeu, S.-H.; Ahn. K.-H.; Matsuoka, H.; Morikawa, K.; Suzuki, M.; Hagita, H.; Ozawa, K.; Yamaguchi, K.; Kato, M.; Ikeda, S. *J. Med. Chem.* **2012**, *55*, 7828. (c) Ikeda, S.; Takano, Y.; Cynshi, O.; Tanaka, R.; Christ, A. D.; Boerlin, V.; Beyer, U.; Beck, A.; Ciorciaro, C.; Meyer, M.; Kadowaki, T. *Diabetes, Obesity and Metabolism* **2015**, *17*, 984.
2. (a) Murakata, M.; Ikeda, T.; Kimura, N.; Kawase, A.; Nagase, M.; Yamamoto, K.; Takata, N.; Yoshizaki, S.; Takano, K. Crystal of spiroketal derivative, and process for production thereof. *European Appl.* EP 2308886 A1, April 13, **2011**. (b) Ohtake, Y.; Emura, T.; Nishimoto, M.; Takano, K.; Yamamoto, K.; Tsuchiya, S.; Yeu, S.; Kito, Y.; Kimura, N.; Takeda, S.; Tsukazaki, M.; Murakata, M.; Sato, T. *J. Org. Chem.* **2016**, *81*, 2148.
3. Wang, X.; Zhang, L.; Byrne, D.; Nummy, L.; Weber, D.; Krishnamurthy, D.; Yee, N.; Senanayake, C. H. *Org. Lett.* **2014**, *16*, 4090.

4. Suzuki, T.; Ando, M.; Miyazoe, H.; Kameda, M.; Sekino, E.; Moriya, M. Diaryl ketimine derivative. *European Appl.* EP 2072519 A1, June 24, **2009**.

5. Lulinski, P.; Skulski, L. *Bull. Chem. Soc. Jpn.* **2000**, *73*, 951.

6. Liou, J.; Wu, Y.; Li, S.; Xu, G. Processes for the preparation of SGLT2 inhibitor. *PCT Int. Appl.* WO 2010022313 A2, February 25, **2010**.

7. Kiuchi, M.; Adachi, K.; Kohara, T.; Minoguchi, M.; Hanano, T.; Aoki, Y.; Mishina, T.; Arita, M.; Nakao, N.; Ohtsuki, M.; Hoshino, Y.; Teshima, K.; Chiba, K.; Sasaki, S.; Fujita, T. *J. Med. Chem.* **2000**, *43*, 2946.

8. (a) Mertins, K.; Iovel, I.; Kischel, J.; Zapf, A.; Beller, M. *Angew. Chem. Int. Ed.* **2005**, *44*, 238. (b) Zolfigol, M. A.; Vahedi, H.; Azimi, S.; Moosavi-Zare, A. R. *Synlett* **2013**, *24*, 1113. (c) Zhang, S.; Zhang, X.; Ling, X.; He, C.; Huang, R.; Pan, J.; Li, J.; Xiong, Y. *RSC Adv.* **2014**, *4*, 30768.

9. (a) Xu, B.; Lv, B.; Feng, Y.; Xu, G.; Du, J.; Welihinda, A.; Sheng, Z.; Seed, B.; Chen, Y. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 5632. (b) Liu, Y.-H.; Fu, T.-M.; Ou, C.-Y.; Fan, W.-L.; Peng, G.-P. *Chin. Chem. Lett.* **2013**, *24*, 131.