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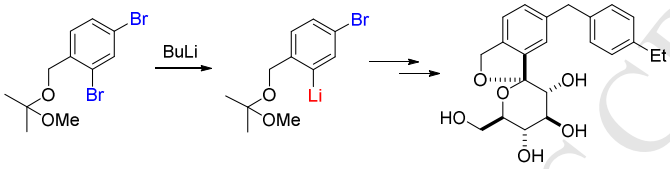

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The regioselective bromine-lithium exchange reaction of alkoxymethyldibromobenzene: a new strategy for the synthesis of tofogliflozin as a SGLT2 inhibitor for the treatment of diabetes

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ABSTRACT

The regioselective bromine-lithium exchange reaction of 2,4-dibromo-1-(1-methoxy-1-methylethoxymethyl)benzene (**2**), which resulted in optimized selectivity of 220:1, is described. Applying this method to the synthesis of tofogliflozin (**1**) as a SGLT2 inhibitor is also described. Selective and sequential metalation-functionalization of **2** led to the synthesis of **1** in 47% overall yield.

1. Introduction

Metalation of aromatic compounds has become a well-known and powerful tool in synthetic organic chemistry. In particular, extensive research on halogen-metal exchange reactions of aryl halides has been reported.[1] We became interested in the halogen-metal exchange reaction of a dihalobenzene derivative, because selective and sequential metalation-functionalization would enable us to form two carbon-carbon bonds regioselectively at the desired positions. Taking into account substrate availability, we focused our attention on the reaction of homo-dihalogenated benzene derivatives (Figure 1). We also envisioned that use of alkoxymethyl-2,4-dihalobenzene as a substrate would lead to the efficient synthesis of a carbon backbone of tofogliflozin (**1**), which is a sodium glucose cotransporter 2 (SGLT2) inhibitor for the treatment of diabetes (Figure 2).[2,3]

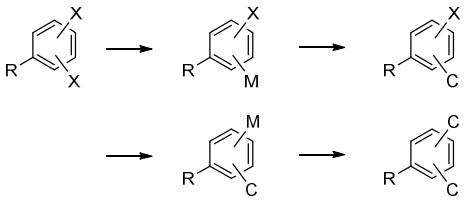


Figure 1. C-C bonds formation by selective and sequential metalation-functionalization.

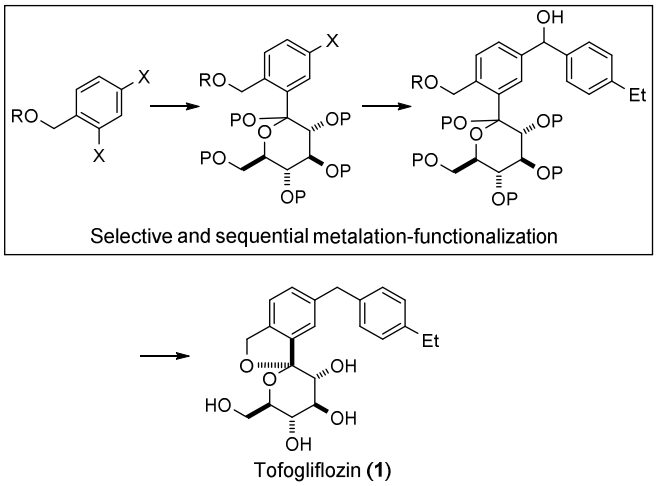


Figure 2. Synthesis of tofogliflozin.

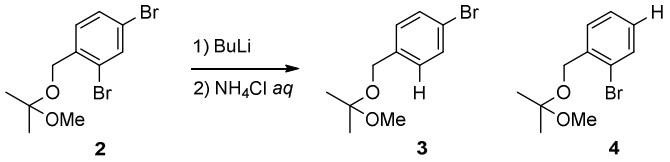
To simplify the metalation process, we decided to use BuLi alone as a reagent for halogen-metal exchange.[4] There are several reports of selective metalation of homo-dihalobenzene derivatives with BuLi alone,[5] however, little is known about the sequence of regioselective halogen-metal exchange followed by anion trap beginning with alkoxymethyl-2,4-dihalobenzene. Herein, we describe the efficient sequential bromine-lithium exchange reactions of alkoxymethyl-2,4-dibromobenzene **2** and

application of the reaction to the synthesis of tofogliflozin (**1**) as three-component coupling process.

2. Results and discussion

2.1. Regioselective protonation via bromine-lithium exchange

As shown in Scheme 1, 2,4-dibromo-1-(1-methoxy-1-methylethoxymethyl)benzene **2**, which was readily prepared from a commercially available dibromobenzyl alcohol, was chosen as a substrate for the bromine-lithium exchange reaction. It was anticipated that the oxygen atoms of the methoxymethoxy group would coordinate with a lithium atom, and the bromine-lithium exchange at the *ortho*-position driven by proximity effect would be favorable.[6]



Scheme 1. Regioselective protonation *via* bromine-lithium exchange.

To explore the regioselectivity of the bromine-lithium exchange reaction of **2**, the reactions with BuLi were quenched with aqueous NH_4Cl to afford *para*-bromobenzene **3** and *ortho*-bromobenzene **4** (Scheme 1). The results are listed in Tables 1 and 2.

Table 1. Bromine-lithium exchange of **2** in THF.[a]

Entry	Temp. (°C)	Addition of BuLi (min)	Mixing (min)	Yield (%)[b]		Selectivity (**3**/**4**)[c]
				3	**4**	
1	−78	3	1	66	23	3:1
2	−80	2	60	65	20	3:1

[a]All reactions were carried out with 1.48 mmol of **2** and 1.1 equivalent of BuLi. Volume of THF was 8 v/w. [b]Determined by crude ^{1}H NMR spectra, with durene as an internal standard. [c]Determined by crude ^{1}H NMR spectra.

When the reaction was carried out by using a 1.1 equivalent of BuLi in THF at −78 °C, the ratio of **3** to **4** was only 3:1, and the starting material **2** was not fully consumed (entry 1 in Table 1). Even with prolonged mixing after adding BuLi, the reaction did not reach completion (the amount of starting material **2** remaining; with entry 1 was 2% and with entry 2 was 4%) and the selectivity did not change either (entry 2 in Table 1). This pattern of selectivity implied that when BuLi coordinated with THF it could easily react with the *para*-position without interacting with the methoxymethoxy group.

Table 2. Bromine-lithium exchange of **2** in toluene-MTBE.[a]

Entry	Temp. (°C)	Addition of BuLi (min)	Mixing (min)	Selectivity (**3**/**4**)[b]
1	−80	3	30	9:1
2	−80	2	60	9:1
3	−30	3	30	9:1
4	0	3	1	16:1
5	0	3	30	16:1
6	0	30	0	40:1

[a]All reactions were carried out with 1.48 mmol of **2** and 1.1 equivalent of BuLi. Volume of toluene-MTBE was 8 v/w (7.3:0.7). [b]Determined by crude NMR spectra.

To develop a system that would achieve better coordination control for the *ortho*-selectivity, next we examined the reaction in a non-coordinating solvent, in which BuLi would exist in a highly aggregated state and the reactivity would be reduced,[7] while the coordination of the oxygen of **2** would enhance the reactivity. Thus, toluene was used as a non-coordinating solvent; however, the reaction mixture became a suspension due to the insolubility of lithated compounds. After screening several solvents, it was found that the addition of a small amount of *tert*-butyl methyl ether (MTBE) was effective in keeping the mixture homogeneous. When the reaction was carried out in a mixture of toluene and MTBE (7.3:0.7) at −80°C, the selectivity was improved, and the ratio of **3** to **4** was 9:1 (entry 1 in Table 2). Although the selectivity did not change between −80°C and −30 °C, the reaction at 0 °C afforded the desired product **3** in a ratio of 16:1 (entry 4 in Table 2). Although the selectivity was independent of the mixing time at 0 °C, the effects of the length of time taken to add BuLi were remarkable. When BuLi was introduced slowly over 30 min at 0 °C, the ratio of **3** to **4** reached 40:1 (entry 6 in Table 2).

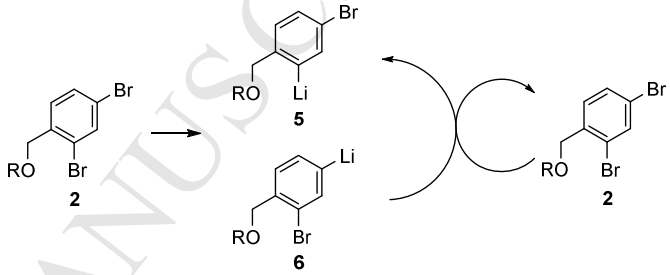


Figure 3. Mechanistic rationale for bromine-lithium exchange of **2**.

A mechanistic rationale for this interesting phenomenon is depicted in Figure 3. The slow addition of BuLi would give time for further bromine-lithium exchange reaction between *para*-lithiated product **6** and the remaining starting material **2**.[8] This process could allow for the conversion of the undesired *para*-lithiated product **6** to the desired *ortho*-lithiated product **5**, because *para*-lithiated product **6** would be converted back to **2**, which then could produce *ortho*-lithiated product **5** as a major product. Thus, the dibromide is presumably acting as a mediator to increase the overall regioselectivity.

Table 3. Bromine-lithium exchange of **2** in toluene-MTBE, with additional 0.3 equivalent of **2**.[a]

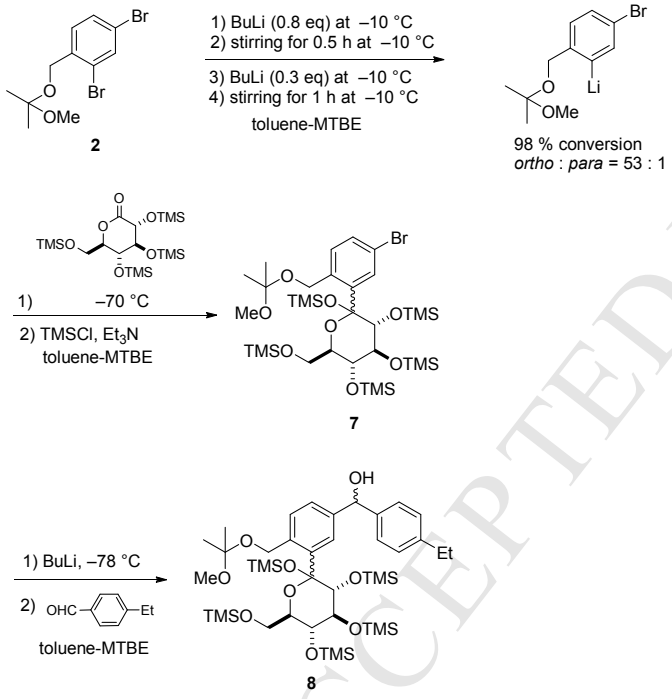
Entry	Temp. (°C)	Addition of BuLi (min)	Mixing (min)	Additional mixing (min)[b]	Selectivity (**3**/**4**)[c]
1	−78	3	30	30	8:1
2	−30	3	30	30	10:1
3	0	3	1	30	220:1

[a]All reactions were carried out with 1.1 equivalent of BuLi for the initial amount of **2**. Total volume of toluene-MTBE was 10.4 v/w (9.5:0.9). [b]Mixing time after adding 0.3 equivalent of **2** to a reaction mixture of **2** and BuLi. [c]Determined by crude NMR spectra.

To test this working hypothesis, we added an additional 0.3 equivalent of **2** to the reaction mixture that had been treated with BuLi. Although the selectivity at both −78 °C and −30 °C was similar to that in previous conditions (entries 1 and 2 in Table 3 *vs* entries 1 and 3 in Table 2), raising the reaction temperature to 0 °C was found to enhance the *ortho*-selectivity dramatically. The product ratio of **3** to **4** from the reaction with an additional 0.3 equivalent of **2** at 0 °C reached 220:1, which shows that use of an additional amount of **2** resulted in high selectivity (entry 3 in Table 3).

2.2. Practical double additions via selective bromine-lithium exchange

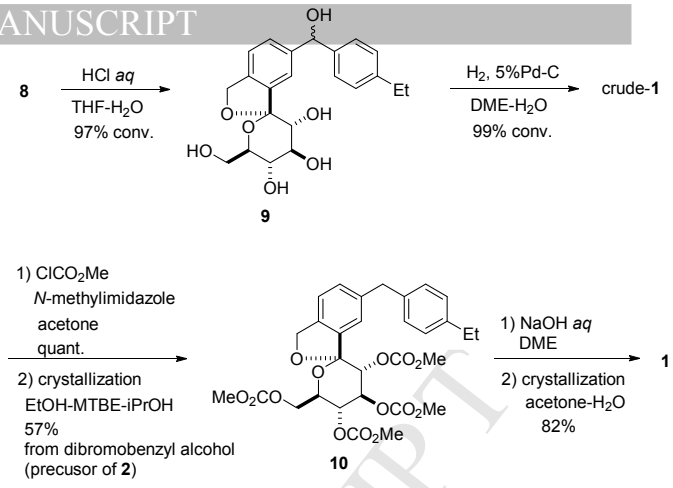
Next, we turned our attention to applying this selective lithiation method to the synthesis of tofogliflozin (**1**). Considering a cost-effective synthetic procedure for practical production, the reaction conditions were modified to incorporate the split addition of BuLi to avoid excessive use of **2**. As shown in Scheme 2, to create and maintain an environment in which **2** exists during lithium-bromine exchange, 0.8 equivalent of BuLi was added first. After stirring for 30 min at −10 to 0 °C, another 0.3 equivalent of BuLi was introduced to drive the reaction to completion. This resulting mixture was added to trimethylsilylgluconolactone, and then alkoxide generated was trapped by trimethylsilyl chloride to afford **7** as an epimeric mixture. The second lithiation using BuLi was followed by the addition of 4-ethylbenzaldehyde to afford double 1,2-additions product **8**. The sequence of these 1,2-additions were achieved in a one-pot process.[9] The *ortho*-regioselectivity of the first lithiation was attained at a ratio of 53:1 (98% conversion). It is of note that when the addition of BuLi was split, the regioselectivity of the bromine-lithium exchange was high enough in practical production to form double carbon-carbon bonds at the desired positions.



Scheme 2. Practical double additions *via* selective bromine-lithium exchange.

2.3. Synthesis and purification of tofogliflozin

After we had established an efficient method of achieving highly selective and sequentially controlled lithiation-functionalization, 1,2-additions adduct **8** was converted to tofogliflozin (**1**), as shown in Scheme 3. To attain telescoping process for practical production, the crude **8** was treated with aqueous hydrochloric acid to construct a spiro-ring and also to remove both the methoxymethylethyl group and the trimethylsilyl group to afford benzhydrol **9** (97% conversion). Hydrogenolysis of **9** using 5% Pd-C afforded tofogliflozin (**1**) as a crude product in 99% conversion.



Scheme 3. Synthesis and purification of **1**.

Purification was achieved by way of recrystallizing its carbonate derivative; namely, the crude product **1** was treated with methyl chloroformate and *N*-methylimidazole as a base followed by recrystallization (EtOH-MTBE-^{i}PrOH) to afford tetracarbonate **10**, isolated yield of which reached 57% from the primus dibromobenzyl alcohol (precursor of **2**). Hydrolysis of **10** by aqueous sodium hydroxide followed by crystallization (acetone-H_2O) afforded tofogliflozin (**1**) in 82% isolated yield. Thus, a high overall yield of 47% (isolated yield) was achieved.

3. Conclusion

In summary, bromine-lithium exchange reaction of 2,4-dibromo-1-(1-methoxy-1-methylethoxymethyl)benzene **2** in a highly regioselective manner was realized by use of BuLi alone. Dibromide as a starting material was found to be a mediator that increased the selectivity of the reaction. Furthermore, the efficient three-component coupling process was accomplished, which ultimately led to the synthesis of tofogliflozin (**1**). The method of selective lithiation mentioned here should be useful for the preparation of unsymmetrical trisubstituted benzene derivatives.

4. Experimental section

4.1. General

All reactions were carried out under a nitrogen atmosphere unless otherwise noted. All reagents were purchased from commercial sources and used without further purification unless otherwise noted. Melting points were measured on a capillary melting point apparatus (Büchi) or a differential scanning calorimetry (DSC) apparatus (Mettler Toledo). FT-IR spectra were performed with a FT/IR-480 plus (JASCO) spectrometer. ^{1}H NMR (500 MHz) and ^{13}C NMR (125 MHz) were recorded on a JNM-ECP 500 (JEOL) spectrophotometer with tetramethylsilane or the solvent resonance as an internal standard. Mass spectra were measured on a LCT Premier XE (Waters) spectrophotometer. Specific rotation was measured on a P-2200 (JASCO) digital polarimeter. Column chromatography was performed on silica gel. HPLC analysis was performed on Agilent 1100 (Agilent). Preparative reversed-phase HPLC was performed on PLC761 system (GL Science).

4.2. 2,4-Dibromo-1-(1-methoxy-1-methylethoxymethyl)benzene (2)

Under a nitrogen atmosphere, to a solution of 2,4-dibromobenzyl alcohol (40 g, 0.15 mol) and 2-methoxypropene

(144 mL, 1.5 mol) in THF (300 mL) was added pyridinium *p*-toluenesulfonic acid (75 mg, 0.30 mmol) at 0 °C, and the whole was stirred for 1 h. The reaction mixture was poured into saturated $NaHCO_3$ at 0 °C. The resulting mixture was extracted with toluene. The organic layer was washed with saturated NaCl, and dried over Na_2SO_4. The solvent was removed under reduced pressure to give **2** as an oil quantitatively. The product was used in the next step without further purification. ^{1}H NMR ($CDCl_3$) δ 1.44 (6H, s), 3.22 (3H, s), 4.48 (2H, s), 7.42 (1H, d, *J* = 8.0 Hz), 7.44 (1H, dd, *J* = 1.5, 8.0 Hz), 7.68 (1H, d, *J* = 1.5 Hz); ^{13}C NMR ($CDCl_3$) δ 24.82, 49.16, 62.26, 101.01, 121.32, 122.99, 129.94, 130.85, 134.90, 137.98; IR (KBr) 2989, 2941, 1581, 1464, 1375, 1080, 1059, 814 cm^{-1}; HRMS (APPI+) (*m/z*): Calcd for $C_{11}H_{14}Br_2NaO^+$ $[M+Na]^+$ 358.9253, Found 358.9244.

4.3. Synthesis of 4-bromo-1-(1-methoxy-1-methylethoxymethyl) benzene (3)

To a solution of 4-bromobenzyl alcohol (7.48 g, 40.0 mmol) and pyridinium *p*-toluenesulfonic acid (20.1 mg, 0.08 mmol) in THF (60 mL) was added 2-methoxypropene (38.3 mL, 400 mmol) at −20 °C, and the whole was stirred at the same temperature for 15 h. The reaction mixture was poured into saturated $NaHCO_3$ at 0 °C. The resulting mixture was extracted with toluene. The organic layer was washed with water, and dried over Na_2SO_4. The solvent was removed under reduced pressure to give **3** as an oil quantitatively. ^{1}H NMR ($CDCl_3$) δ 1.41 (6H, s), 3.24 (3H, s), 4.43 (2H, s), 7.21−7.24 (2H, m), 7.44−7.47 (2H, m).

4.4. Synthesis of 2-bromo-1-(1-methoxy-1-methylethoxymethyl) benzene (4)

To a solution of 2-bromobenzyl alcohol (1.90 g, 10.2 mmol) and pyridinium *p*-toluenesulfonic acid (2.0 mg, 0.008 mmol) in THF (20 mL) was added 2-methoxypropene (10 mL, 104 mmol) at 0 °C, and the whole was stirred at the same temperature for 1 h. The reaction mixture was poured into saturated $NaHCO_3$. The resulting mixture was extracted with AcOEt. The organic layer was washed with NaCl, and dried over Na_2SO_4. The solvent was removed under reduced pressure to give **4** as an oil quantitatively. ^{1}H NMR ($CDCl_3$) δ 1.46 (6H, s), 3.24 (3H, s), 4.55 (2H, s), 7.10−7.14 (1H, m), 7.29−7.33 (1H, m), 7.51−7.55 (2H, m).

4.5. Typical procedure for bromine-lithium exchange followed by protonation (Entry 4 in Table 2)

Under a nitrogen atmosphere, to a solution of 2,4-dibromo-1-(1-methoxy-1-methylethoxymethyl)benzene (**2**) (500 mg, 1.48 mol) in toluene (3.65 mL) and *tert*-butyl methyl ether (0.35 mL) was added a solution of *n*-BuLi in hexane (1.6 M, 1.01 mL, 1.62 mmol) at 0 °C over 3 min, and then the mixture was stirred for 1 min. The reaction was quenched with saturated NH_4Cl. The resulting mixture was extracted with AcOEt. The organic layer was washed with saturated NaCl, and dried over Na_2SO_4. The solvent was removed under reduced pressure to give a mixture of 4-bromo-1-(1-methoxy-1-methylethoxymethyl)benzene (**3**) and 2-bromo-1-(1-methoxy-1-methylethoxymethyl)benzene (**4**). The ratio of **3** to **4** was estimated to be 16/1 through the integration of a benzylic proton in **3** [δ 4.43 (2H)] and a benzylic proton in **4** [δ 4.55 (2H)] in ^{1}H NMR. The yield was calculated with durene as an internal standard.

4.6. Typical procedure for bromine-lithium exchange, with additional 0.3 equivalent of 2, followed by protonation (Entry 3 in Table 3)

Under a nitrogen atmosphere, to a solution of 2,4-dibromo-1-(1-methoxy-1-methylethoxymethyl)benzene (**2**) (500 mg, 1.48 mol) in toluene (3.65 mL) and *tert*-butyl methyl ether (0.35 mL) was added a solution of *n*-BuLi in hexane (1.6 M, 1.01 mL, 1.62 mmol) at 0 °C over 3 min, and then the mixture was stirred for 1 min. To the resulting mixture was added a solution of 2,4-dibromo-1-(1-methoxy-1-methylethoxymethyl)benzene (**2**) (150 mg, 0.44 mol) in toluene (1.1 mL) and *tert*-butyl methyl ether (0.11 mL), and then the whole was stirred at 0 °C for 30 min. The reaction was quenched with saturated NH_4Cl. The resulting mixture was extracted with AcOEt. The organic layer was washed with saturated NaCl, and dried over Na_2SO_4. The solvent was removed under reduced pressure to give a mixture of 4-bromo-1-(1-methoxy-1-methylethoxymethyl)benzene (**3**) and 2-bromo-1-(1-methoxy-1-methylethoxymethyl)benzene (**4**). The ratio of **3** to **4** was estimated to be 220/1 through the integration of a benzylic proton in **3** [δ 4.43 (2H)] and a benzylic proton in **4** [δ 4.55 (2H)] in ^{1}H NMR.

4.7. (2,3R,4S,5R)-Tetrakis(trimethylsilyloxy)-6R-trimethylsilyloxymethyl-2-[5-bromo-2-(1-methoxy-1-methylethoxymethyl)phenyl]tetrahydropyran (7)

To a solution of 2,4-dibromo-1-(1-methoxy-1-methylethoxymethyl)benzene **2** (277 g, 820 mmol) in toluene (2616 mL) and *t*-butyl methyl ether (262 mL) was added dropwise a solution of *n*-BuLi in hexane (1.54 M, 426 mL, 656 mmol) at −10 °C. The whole was stirred at −10 °C for 0.5 h. To the resulting mixture was added a solution of *n*-BuLi in hexane (1.54 M, 160 mL, 246 mmol) at −10 °C. The whole was stirred for 1 h at the same temperature. The mixture was cooled to −48 °C and added dropwise to a solution of 3,4,5-tris(trimethylsilyloxy)-6-(trimethylsilyloxymethyl)tetrahydropyran-2-one (402 g, 862 mol) in THF (2012 mL) at −77 °C. After the reaction mixture was stirred at −70 °C for 1.5 h, triethylamine (24 mL, 172 mmol) and trimethylsilyl chloride (98 g, 903 mmol) were added successively, and the resulting mixture was warmed to 0 °C to give a solution containing the compound **7**. This solution was used in the next step. To determine the regioselectivity of bromine-lithium exchange reaction, a small portion of the reaction mixture was taken before addition of lactone, and quenched with saturated NH_4Cl. The selectivity (**3**/**4** = 53/1) was calculated based on the area ratio measured by HPLC (column: Ascentis Express C18, 3.0 mm I.D. x 100 mm, 2.7 μm ; 2mM $AcONa/H_2O$ with acetonitrile, gradient operation 30% to 98%; flow rate, 1.0 mL/min). For analytical data of **7**, the solvent was removed and the resulting residue was purified by preparative HPLC (column; Inertsil ODS-3, 20 mm I.D. x 250 mm; acetonitrile, 30 mL/min) to give **7** as two isolated epimers (**7a** and **7b**). **7a**: colorless oil. $[\alpha]_D^{20}$ +19.2 (*c* 1.5, MeCN); ^{1}H NMR ($CDCl_3$) δ −0.30 (9H, s), 0.10 (9H, s), 0.10 (9H, s), 0.16 (9H, s), 0.17 (9H, s), 1.41 (3H, s), 1.43 (3H, s), 3.20 (3H, s), 3.39 (1H, t, *J* = 9.0 Hz), 3.43 (1H, d, *J* = 9.0 Hz), 3.62 (1H, dd, *J* = 10.5, 7.5Hz), 3.81−3.89 (3H, m), 4.62 (1H, d, *J* = 13.2 Hz), 4.81 (1H, d, *J* = 13.2 Hz), 7.38 (1H, dd, *J* = 8.8, 2.5Hz), 7.46 (1H, d, *J* = 8.8 Hz), 7.70 (1H, d, *J* = 2.5 Hz); ^{13}C NMR($CDCl_3$) δ −0.3, 0.4, 1.3, 1.4, 2.1, 25.0, 25.2, 48.9, 61.3, 63.2, 73.0, 74.6, 76.4, 77.3, 100.6, 102.9, 120.1, 130.2, 131.1, 133.8, 136.4, 142.7; IR (KBr) 2956, 1593, 1562, 1377, 1252, 1151, 1082, 841 cm^{-1}; HRMS (ESI+) (*m/z*): Calcd for $C_{32}H_{65}BrNaO_8Si_5^+$ $[M+Na]^+$ 819.2601, Found 819.2595. **7b**: colorless oil. $[\alpha]_D^{20}$ +5.6 (*c* 1.5, MeCN); ^{1}H NMR (toluene-d_8, 80 °C) δ −0.16 (9H, s), 0.18 (9H, s), 0.22 (9H, s), 0.23 (9H, s), 0.29 (9H, s), 1.405(3H, s), 1.412 (3H, s), 3.16 (3H, s), 3.87 (1H, dd, *J* = 10.5, 4.3 Hz), 3.98 (1H, dd, *J* = 4.3, 1.5 Hz), 4.02 (1H, dd, *J* = 10.5, 2.5 Hz), 4.14 (1H, brs), 4.26−4.28 (1H, m), 4.39−4.41 (1H, m), 4.90−4.96 (2H, m), 7.34 (1H, dd, *J* = 8.5, 1.5 Hz), 7.70 (1H, d, *J* = 8.5 Hz), 7.97 (1H, brs); ^{13}C NMR(toluene-d_8, 80 °C) δ 0.7, 1.1, 1.9, 2.3, 3.0, 26.95, 26.04, 49.7, 62.0, 64.0, 65.0, 75.7, 75.9, 83.0, 101.7, 103.6, 121.5, 132.0, 132.1, 133.3, 145.4, due to

overlap between an aromatic carbon and solvent peaks, not all carbons resonances were visible; IR (KBr): 2956, 1591, 1562, 1377, 1252, 1182, 1107, 841 cm^{-1}; HRMS (ESI+) (*m/z*): Calcd for $C_{32}H_{65}BrNaO_8Si_5^+$ $[M+Na]^+$ 819.2601, Found 819.2599.

4.8. (2,3R,4S,5R)-Tetrakis(trimethylsilyloxy)-6R-trimethylsilyloxymethyl-2-[5-(4-ethylphenyl)hydroxymethyl-2-(1-methoxy-1-methylethoxymethyl)phenyl]tetrahydropyran (8)

To the solution of **7**, which was obtained in the previous step, was added dropwise a solution of *n*-BuLi in hexane (1.54 M, 1119 mL, 1724 mmol) at −78 °C. The whole was stirred at –78 °C for 1 h. To the resulting mixture was added dropwise 4-ethylbenzaldehyde (242 g, 1806 mmol) at –78 °C, and the mixture was stirred at the same temperature for 2.5 h. After addition of the mixture to 20%NH_4Cl (aq), the organic layer was washed with water. The solvent was evaporated under reduced pressure to give a product containing **8** as an oil (879 g). This product was used in the next step without further purification. For analytical data of **8**, a portion of the oil was purified by preparative HPLC (column: Inertsil ODS-3, 20 mm I.D. x 250 mm; acetonitrile, 30 mL/min) to give two mixtures (**8a** and **8b**: each containing diastereomers). **8a**: colorless oil. ^{1}H NMR ($CDCl_3$) δ −0.47 (4.8H, s), −0.40 (4.2H, s), −0.003−0.004 (5H, m), 0.07−0.08 (13H, m), 0.15−0.17 (18H, m), 1.200 and 1.202 (3H, each t, *J* = 8.0 Hz), 1.393 and 1.399 (3H, each s), 1.44 (3H, s), 2.61 (2H, q, *J* = 8.0 Hz), 3.221 and 3.223 (3H, each s), 3.43 (1H, t, *J* = 8.5 Hz), 3.54 (1H, dd, *J* = 8.5, 3.0 Hz), 3.61−3.66 (1H, m), 3.80−3.85 (3H, m), 4.56 and 4.58 (1H, each d, *J* = 12.4 Hz), 4.92 and 4.93 (1H, each d, *J* = 12.4 Hz), 5.80 and 5.82 (1H, each d, *J* = 3.0Hz), 7.14 (2H, d, *J* = 8.0 Hz), 7.28−7.35 (3H, m), 7.50−7.57 (2H, m); HRMS (ESI+) (*m/z*): Calcd for $C_{41}H_{76}NaO_9Si_5^+$ $[M+Na]^+$ 875.4228, Found 875.4238. **8b**: colorless oil. ^{1}H NMR (toluene-d_8, 80 °C) δ −0.25 (4H, s), −0.22 (5H, s), 0.13 (5H, s), 0.16 (4H, s), 0.211 and 0.214 (9H, each s), 0.25 (9H, s), 0.29 (9H, s), 1.21 (3H, t, *J* = 7.5 Hz), 1.43 (3H, s), 1.45 (3H, s), 2.49 (2H, q, *J* = 7.5 Hz), 3.192 and 3.194 (3H, each s), 3.91−4.04 (4H, m), 4.33−4.39 (2H, m), 4.93 (1H, d, *J* = 14.5 Hz), 5.10−5.17 (1H, m), 5.64 and 5.66 (1H, each s), 7.03 (2H, d, *J* = 8.0 Hz), 7.28−7.35 (3H, m), 7.59−7.64 (1H, m), 7.87−7.89 (1H, m); HRMS (ESI+) (*m/z*): Calcd for $C_{41}H_{76}NaO_9Si_5^+$ $[M+Na]^+$ 875.4228, Found 875.4272.

4.9. 1,1-Anhydro-1-C-[5-(4-ethylphenyl)hydroxymethyl-2-(hydroxymethyl)phenyl]-β-D-glucopyranose (9)

A part of the oil containing **8** (628 g out of 879 g), which was obtained in the previous step, was dissolved in THF (991 mL). To the solution were added water (63 mL) and aqueous 1N HCl (23 mL), and the whole was stirred at 28 °C for 7 h. After addition of triethylamine (3.8 mL, 25.8 mmol), the solvent was removed under reduced pressure. The resulting residue was dissolved in water (198 mL) and 1,2-dimethoxyethane (396 mL), and the solution was washed with heptane (595 mL). To the aqueous layer were added water (99 mL) and 1,2-dimethoxyethane (198 mL), and the resulting solution was washed with heptane (595 mL). The solvent was removed under reduced pressure to give a product containing **9** as an oil (247 g). This product was used in the next step without further purification. For analytical data of **9**, a portion of the oil was purified by column chromatography on silica gel (Purif-Pack, 60 μm, dichloromethane/methanol; methanol: 5% to 15%) to give a mixture of two epimers. After addition of aqueous acetonitrile, one of the epimers was obtained as a solid (**9a**). The mother liquor was evaporated, and the residue was purified by preparative HPLC (column: Inertsil ODS-3, 20 mm I.D. 250 mm; 20% acetonitrile in water, 20 mL/min) to give another epimer as an amorphous solid (**9b**). **9a**: white solid, mp 78 °C (DSC apparatus). $[\alpha]_D^{20}$ +29.4 (*c* 1.52, MeOH); ^{1}H NMR (CD_3OD) δ 1.19 (3H, t, *J* = 7.5 Hz), 2.60 (2H, q, *J* = 7.5 Hz), 3.42−3.48 (1H, m), 3.64 (1H, dd, *J* = 6.0, 12.0 Hz), 3.75−3.83 (4H, m), 5.08 (1H, d, *J* = 12.5 Hz), 5.14 (1H, d, *J* = 12.5 Hz), 5.78 (1H, s), 7.14 (2H, d, *J* = 8.0 Hz), 7.24 (1H, d, *J* = 8.5 Hz), 7.27 (2H, d, *J* = 8.0 Hz), 7.39 (1H, s), 7.40 (1H, d, *J* = 8.5 Hz); ^{13}C NMR (CD_3OD) δ 17.2, 30.5, 63.9, 72.9, 74.4, 76.0, 77.3, 77.5, 77.8, 112.6, 122.5, 122.8, 128.9, 129.8, 123.0, 141.0, 142.1, 144.1, 145.6, 147.0; IR (ATR): 3313, 2924, 1701, 1649, 1541, 1099, 1065, 1011 cm^{-1}; HRMS (ESI+) (*m/z*): Calcd for $C_{22}H_{27}O_7^+$ $[M+H]^+$ 403.1751, Found 403.1750, Calcd for $C_{22}H_{26}NaO_7^+$ $[M+Na]^+$ 425.1571, Found 425.1591. **9b**: colorless amorphous solid. $[\alpha]_D^{20}$ +11.1 (*c* 1.44, MeOH); ^{1}H NMR (CD_3OD) δ 1.20 (3H, t, *J* = 7.4 Hz), 2.61 (2H, q, *J* = 7.4 Hz), 3.42−3.48 (1H, m) , 3.65 (1H, dd, *J* = 5.9, 11.9 Hz), 3.75−3.83 (4H, m), 5.08 (1H, d, *J* = 12.9 Hz), 5.15 (1H, d, *J* = 12.9 Hz), 5.79 (1H, s), 7.14 (2H, d, *J* = 7.9 Hz), 7.23 (1H, d, *J* = 7.4 Hz), 7.28 (2H, d, *J* = 7.9 Hz), 7.36 (1H, d, *J* = 8.4 Hz), 7.42 (1H, s); ^{13}C NMR (CD_3OD) δ: 17.1, 30.4, 63.7, 72.8, 74.2, 75.8, 77.1, 77.3, 77.5, 112.5, 122.1, 122.5, 128.7, 129.6, 130.0, 140.9, 141.89, 144.0, 145.4, 146.8; IR (KBr): 3367, 2929, 1699, 1649, 1510, 1063, 1007 cm^{-1}; HRMS (ESI+) (*m/z*): Calcd for $C_{22}H_{27}O_7^+$ $[M+H]^+$ 403.1751, Found 403.1747, Calcd for $C_{22}H_{26}NaO_7^+$ $[M+Na]^+$ 425.1571, Found 425.1579.

4.10. Tofogliflozin (1)

A part of the oil containing **9** (125 g out of 247 g), which was obtained in the previous step, was dissolved in 1,2-dimethoxyethane (400 mL). To the solution were added water (150 mL) and 5% Pd/C (19 g, water content ratio: 50%). The mixture was stirred under hydrogen at room temperature for 6 h. After filtration, the residue was washed with a mixture of 1,2-dimethoxyethane (250 mL) and water (250 mL). The filtrate and washings were combined. To this mixture was added 1,2-dimethoxyethane (500 mL), and the resulting mixture was washed with *n*-heptane (1000 mL x 2). To the aqueous layer were added AcOEt (500 mL) and aqueous 25% NaCl (600 g). The organic layer was washed with aqueous 15% NaCl (600 g), and the solvent was removed under reduced pressure. To the resulting residue was added acetone (500 mL), and the solvent was removed under reduced pressure to give **1** (106 g; 93.9% purity: calculated based on the area ratio measured by HPLC; column: Atlantis dC18, 4.6 mm I.D. x 75 mm, 3 μm; H_2O with acetonitrile, gradient operation 2% to 100%; flow rate, 1.2 mL/min). The purification was carried out in the next step by way of the synthesis of carbonate derivative.

4.11. Purification of tofogliflozin (1)

4.11.1. Synthesis of 1,1-anhydro-1-C-[5-(4-ethylphenyl)methyl-2-(hydroxymethyl)phenyl]-2,3,4,6-tetra-O-methoxycarbonyl-β-D-glucopyranose (10)

The product **1** (106 g), which was obtained in the previous step, and *N*-methylimidazole (318 mL, 3994 mmol) were dissolved in acetone (400 mL). To the solution was added methyl chloroformate (182 mL, 2367 mmol) at 15 °C. The mixture was allowed to warm to 18 °C, and then stirred for 3 h. After addition of water (800 mL), the mixture was extracted with AcOEt (800 mL). The organic layer was washed with aqueous solution of 10% $NaHSO_3$ and 5% NaCl (800 mL), and then washed with 20% NaCl (800 mL x 2). The solvent was removed under reduced pressure. After addition of ethanol, *t*-butyl methyl ether and 2-propanol, the mixture was heated to 74 °C to dissolve the residue. The solution was stirred at 55 °C for 1 h. After precipitation of solid, the mixture was cooled to 25 °C over 1.5 h. To the resulting mixture was added 2-propanol (270 mL), and then the mixture was stirred at 25 °C for 1 h. Filtration and

dryness under reduced pressure to give **10** [104 g; total yield from 2,4-dibromo-1-(1-methoxy-1-methylethoxymethyl)benzene **2**, 57%] as a white solid; mp 129−130 °C (capillary melting point apparatus). Spectra data spectra data were identical to those reported previously.[3c]

4.11.2. Conversion of 10 to tofogliflozin (1)

To a solution of **10** (82 g) in 1,2-dimethoxyethane (328 mL) was added dropwise aqueous 4N NaOH (265 mL, 1060 mmol) at 40 °C. The mixture was stirred at the same temperature for 4.5 h. After addition of water (82 mL), the organic layer was washed with a solution of 18% $NaH_2PO_4 \cdot 2H_2O$ and 12%$Na_2HPO_4 \cdot 12H_2O$ (410 mL). After addition of AcOEt (410 mL), the organic layer was washed with 25% NaCl. (410 mL x 2). The solvent was removed under reduced pressure. To the resulting residue were added acetone and water, and then the solvent was evaporated under reduced pressure. After recrystallization from acetone and water, to the resulting crystal was added water (246 mL), and then the mixture was stirred at 4 °C for 1 h. Filtration and dryness under reduced pressure to give **1** as monohydrate crystal (44g, water content 4.47%; 82%); white powder, mp 71−92 °C (capillary melting point apparatus). Spectra data were identical to those reported previously.[3a]

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at

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Highlights

- Highly regioselective bromine-lithium exchange reaction of dibromobenzene derivative was realized.
- Dibromide as a starting material was found to be a mediator that increased the selectivity.
- Tofogliflozin was synthesized *via* three-component coupling.