

Synthesis and Biological Evaluation of Thiophene-*C*-glucosides as Sodium-Dependent Glucose Cotransporter 2 Inhibitors

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Received May 27, 2013; accepted August 1, 2013

The synthesis and structure–activity relationship (SAR) of thiophene-*C*-glucosides have been explored, and the human sodium-dependent glucose cotransporter 2 (hSGLT2) inhibitory activities and rat urinary glucose excretion (UGE) effects of 3a–f were evaluated. As a result, they showed good hSGLT2 inhibitory activities and rat UGE effects. In particular, the chlorothiophene derivative 3f showed remarkable inhibitory activity against hSGLT2.

Key words sodium-dependent glucose cotransporter; glucal-boronate; thiophene-*C*-glucoside

The kidney contributes to glucose homeostasis by reabsorbing approximately 180 g of glucose from the glomerular filtrate each day. Renal glucose reabsorption is mediated predominantly by sodium-dependent glucose cotransporter 2 (SGLT2), which is located in the early convoluted segment (S1) of the proximal tubule, and to a lesser extent by SGLT1, which is found in the more distal, straight section of the proximal tubule (S3).^{1–6} In normoglycemia, all filtered glucose is transported from the tubular lumen to the blood. However, under hyperglycemic conditions, the reabsorption process is saturated and urinary glucose excretion (UGE) increases linearly.⁷ Inhibitors of SGLTs have attracted attention as a means to reduce blood glucose concentration independent of insulin action.⁸ By enhancing glucose excretion into the urine, SGLT2 inhibitors would intuitively lead to a significant loss of calories. Their potential advantage would be reducing blood glucose and leading to weight loss. Thus, they could be used at any stage of type 2 diabetes.⁹

In recent decades, several potent SGLT2 inhibitors have been developed,^{10,11} of which, phenyl-*C*-glucoside **1** and thienylmethyl-substituted *C*-glucoside **2** (canagliflozin) (Fig. 1) were disclosed as SGLT2 inhibitors by Bristol-Myers Squibb Co.¹² and Mitsubishi Tanabe Pharma,¹³ respectively. Accordingly, to explore novel *C*-glucoside compounds, we evaluated a series of 4-ethylbenzyl-substituted thiophene-*C*-glucosides **3**¹⁴ (Fig. 1) for SGLT2 inhibitory activity and rat UGE effect.

Results and Discussion

Chemistry The synthetic route to thiophene-*C*-glucoside **3a–f** was shown in Fig. 2, based on our reported reaction of aryl halide with glucal-boronate ester **4**.¹⁵ Coupling reaction using dichlorobis(triphenylphosphine)palladium (PdCl₂(PPh₃)₂) between aglycons **7a–f** and glucal-boronate **4** gave **5a–f**, followed by stereoselective hydroboration and oxidation using H₂O₂ in alkaline conditions yielded **6a–f** with the desired β-configuration (*J*_{1,2} ≈ 9.5 Hz). Finally, *O*-silyl groups of **6a–f** were deprotected with tetra-*n*-butylammonium fluoride (TBAF) to afford thiophene-*C*-glucosides **3a–f**.¹⁶

Synthesis of thiophene aglycons **7a–f** are shown in Fig. 3. Aglycons **7a–c** were synthesized by coupling reaction between

the corresponding thiophenecarbaldehyde **8–10** and 4-ethylphenylmagnesium bromide to give **11–13**, respectively, followed by reduction of the hydroxyl group with triethylsilane and BF₃·OEt₂. Dibromothiophene **14** was lithiated selectively on 2-position by *n*-BuLi in Et₂O,¹⁷ and treated with 4-ethylbenzaldehyde to generate alcohol **15**. The resulting hydroxyl group was reduced by combination of LiAlH₄ and AlCl₃¹⁷ to afford aglycon **7d** in moderate yield. 3-Chlorothiophene-2-carboxylic acid (**16**) was lithiated using lithium diisopropylamide (LDA) and brominated with 1,2-dibromotetrafluoroethane to generate bromothiophene **17**. The carboxylic acid function of **17** was reacted with *N,O*-dimethylhydroxylamine to give the Weinreb amide, followed by reaction with diisobutylaluminum hydride (DIBAL-H) to yield aldehyde **18**. A coupling reaction between **18** and 4-ethylphenylmagnesium bromide generated **19**, after which reduction of the hydroxyl group with triethylsilane and BF₃·OEt₂ gave aglycon **7e**. Aglycon **7f** was synthesized in a manner similar to the synthesis of **7e** from commercially available **20**.

Biological Activity We evaluated the effects of thiophene-*C*-glucosides **3** (Fig. 1) on human SGLT2 (hSGLT2) activity and on urinary glucose excretion (UGE) in male

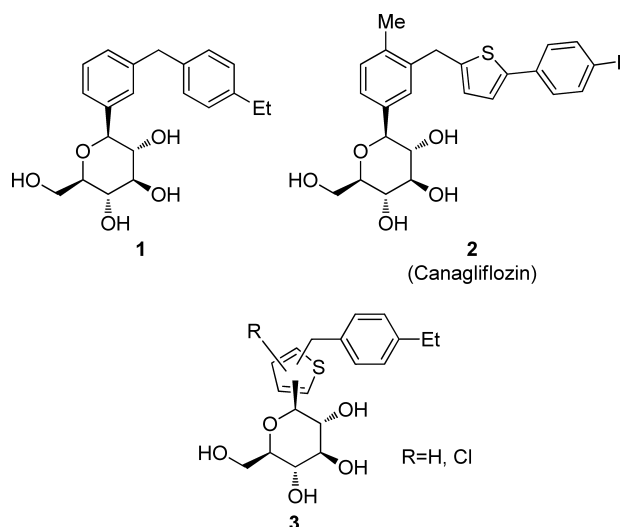


Fig. 1. Aryl-*C*-glucosides

The authors declare no conflict of interest.

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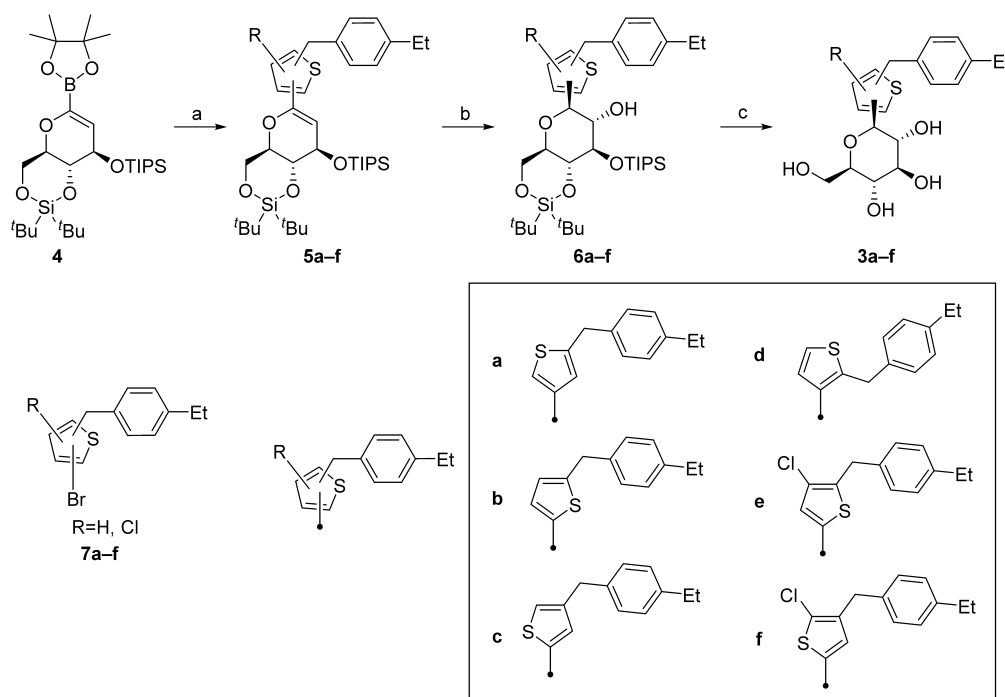


Fig 2. Synthesis of Thiophene-*C*-glucosides

Reagents and conditions: (a) **7a–f**, PdCl₂(PPh₃)₂, 2 M aq. Na₂CO₃, DME, 80°C (16–68%). (b) BH₃-THF, THF, 0°C, then 30% aq. H₂O₂, 3 M aq. NaOH (22–66%). (c) TBAF, THF (33–92%).

Sprague-Dawley (SD) rats per 200 g of body weight over 24 h. Table 1 summarizes the structure–activity relationship (SAR) of compounds **3a–f**. 1,3-Oriented disubstituted thiophene derivatives **3a**, **3b**, and **3c** showed moderate hSGLT2 inhibitory activity (IC₅₀: 23.6 nM, 19.1 nM, and 76.0 nM, respectively). These compounds also induced rat UGE (580, 782, 826 mg/d for **3a–c**, respectively). On the other hand, 1,2-oriented disubstituted thiophene derivative **3d** resulted in significant decrease of hSGLT2 inhibitory activity (IC₅₀: 2559 nM). Similar to the case of the *C*-glucoside hSGLT2 inhibitors,¹⁸⁾ 1,3-orientation of the glucose moiety relative to the distal phenyl ring is considered to be preferable rather than 1,2-substitution.

Furthermore, we explored chlorine-substituted thiophene rings (**3e**, **f**⁶⁾). hSGLT2 inhibitory activity of **3e** (IC₅₀: 64.0 nM) was decreased by approximately 3-fold with respect to non-substituted thiophene (**3b**, IC₅₀: 19.1 nM), while that of **3f** (IC₅₀: 4.0 nM) was approximately 20-fold more potent than non-substituted thiophene (**3c**, IC₅₀: 76.0 nM). As a result of molecular minimization calculation for **3e** and **3f**,¹⁹⁾ it was found that they had different angles between chlorine atom and glucose moiety on thiophene ring. There is approximately 20° angle difference between chlorine atom and glucose moiety of **3e** and **3f** (135.33° vs. 154.38°), as shown in Fig. 4. Thus, we speculated that chlorine atom of **3e** was not affected the inhibitory activity, while chlorine atom of **3f** might be located in a favorable orientation, thereby improving inhibitory activity. In addition, hSGLT2 inhibitory activity and UGE effect of compound **3f** were comparable to those of phenyl-*C*-glucoside **1** (hSGLT2; IC₅₀=4.0 nM vs. 5.1 nM, rUGE; 1381 mg/d vs. 1485 mg/d, respectively).

From these findings, we concluded that benzene ring (**1**) could be replaced by 2-chlorothiophene ring (**3f**) in the expression of hSGLT2 inhibitory activity and rat UGE effect.

Conclusion

In summary, we described the synthesis, hSGLT2 inhibitory activities and rat UGE effects of thiophene-*C*-glucosides **3a–f**. They showed good hSGLT2 inhibitory activities and rat UGE effects. Especially, chlorothiophene derivative **3f** showed remarkable inhibitory activity against hSGLT2 (IC₅₀=4.0 nM) and good rat UGE effect (1381 mg/d). Further replacement of the chlorine atom of **3f** with other substituents would be worth examining.

Experimental

Chemistry All reactions were carried out under inert gas or with CaCl₂ tube and reaction mixtures were stirred magnetically. All reagents and solvents were purchased from commercial suppliers and used without further purification unless otherwise noted. Reaction products were monitored by TLC using 0.25 mm E. Merck silica gel plates (60 F254) and were visualized using UV light or 5% phosphomolybdic acid in 95% EtOH. NMR spectra were collected on JEOL JNM-ECX400P and Varian UNITY INOVA500 spectrometers. Chemical shifts were given in parts per million (ppm) downfield from internal reference tetramethylsilane standard; coupling constants (*J* value) were given in hertz (Hz). Infrared spectra were measured on Perkin-Elmer PARAGON1000. atmospheric pressure chemical ionization (APCI)- and electrospray ionization-mass spectrometry (ESI-MS) spectra were obtained on Finnigan MAT SSQ7000C or ThermoQuest LCQ Advantage eluting with 10 mM AcONH₄-MeOH. GC-MS spectra were measured on Shimadzu GCMS-QP2010. All compounds were found to be >95% pure by HPLC analysis unless otherwise noted.

Typical Experimental Procedure for the Synthesis of 1-Arylglucal Derivatives (4*aR*, 8*R*, 8*aR*)-2,2-Di-*tert*-butyl-6-[5-(4-ethylbenzyl)-3-thienyl]-8-[(triisopropylsilyl)-

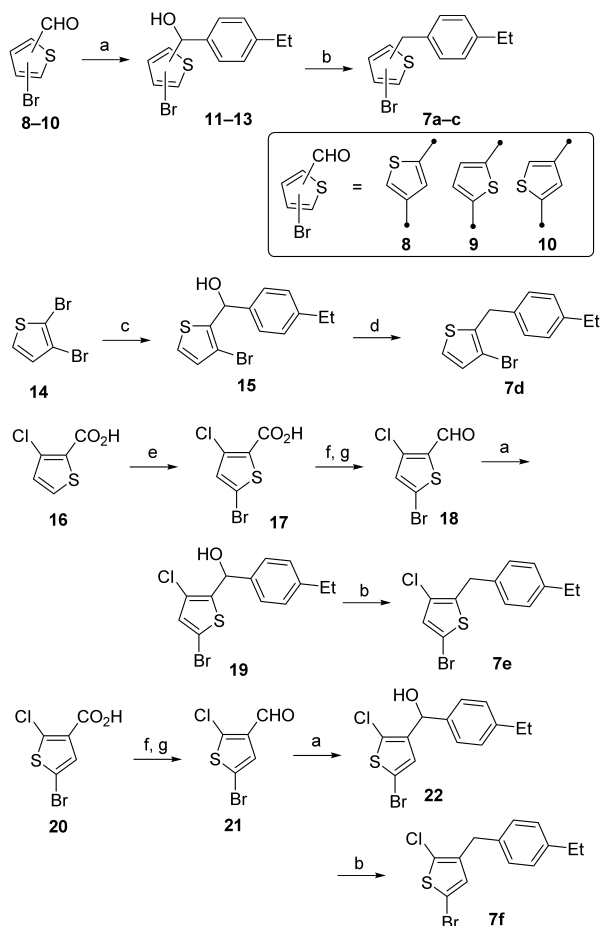


Fig. 3. Synthesis of Thiophene Aglycons

Reagents and conditions: (a) 4-Ethylphenylmagnesium bromide, THF, 0°C (42–100%). (b) Et_3SiH , $\text{BF}_3 \cdot \text{OEt}_2$, CH_2Cl_2 (52–89%). (c) *n*-BuLi, Et_2O , -70°C , then 4-ethylbenzaldehyde, Et_2O , -70°C (93%). (d) LiAlH_4 , AlCl_3 , Et_2O , rt (75%). (e) LDA, THF, -70°C , then $\text{BrCF}_2\text{CF}_2\text{Br}$, -70°C (65%). (f) *N,N*-Dimethylhydroxylamine hydrochloride, EDCI-HCl, HOBT, Et_3N , CH_2Cl_2 , rt (55–93%). (g) DIBAL-H, THF, -70°C (34–94%).

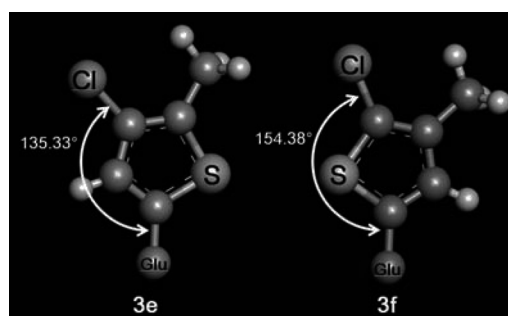
oxy]-4,4a,8,8a-tetrahydropyrano[3,2-*d*][1,3,2]dioxasiline (**5a**): To a mixture of boronic acid ester **4**¹⁵ (4.4 g, 6.57 mmol) and aryl bromide **7a** (1.23 g, 4.38 mmol) in 1,2-dimethoxyethane (DME) (25 mL) was added dichlorobis(triphenylphosphine)-palladium (154 mg, 0.219 mmol) and 2M aqueous Na_2CO_3 (11 mL, 21.9 mmol), then the mixture was refluxed for 4 h. The mixture was cooled to ambient temperature and diluted with AcOEt, then washed with water, brine, dried over sodium sulfate, and filtered. After the filtrate was concentrated, the crude material was purified by silica gel column chromatography (hexane–AcOEt=100:0–97:3) to give compound **5a** (454 mg, 16%) as colorless syrup. $^1\text{H-NMR}$ (300 MHz, CDCl_3) δ : 7.16 (d, $J=1.4$ Hz, 1H), 7.12–7.14 (m, 4H), 6.82 (d, $J=1.4$ Hz, 1H), 5.03 (d, $J=2.2$ Hz, 1H), 4.52 (dd, $J=2.2$ Hz, 6.8 Hz, 1H), 4.26 (dd, $J=5.1$ Hz, 9.1 Hz, 1H), 3.90–4.10 (m, 5H), 2.63 (q, $J=7.6$ Hz, 2H), 1.22 (t, $J=7.5$ Hz, 3H), 1.08–1.14 (m, 21H), 1.08 (s, 9H), 1.00 (s, 9H). MS (APCI, m/z) 643 (M+H).

(4a*R*,8*R*,8a*R*)-2,2-Di-*tert*-butyl-6-[5-(4-ethylbenzyl)-2-thienyl]-8-[[triisopropylsilyl]oxy]-4,4a,8,8a-tetrahydropyrano[3,2-*d*][1,3,2]dioxasiline (**5b**): The titled compound was prepared in the same manner as described for **5a** using **7b** instead of **7a** in 40% yield as pale yellow semisolid. $^1\text{H-NMR}$ (500 MHz, $\text{DMSO-}d_6$) δ : 7.14–7.19 (m, 5H), 6.94 (s, 1H), 5.05

Table 1. SAR Exploration of Thiophene-C-glucosides

Compound	Het	hSGLT2 IC ₅₀ (nM)	Rat UGE ^{a)} (mg/d)
3a		23.6	580
3b		19.1	782
3c		76.0	826
3d		2559	NT ^{b)}
3e		64.0	615
3f		4.0	1381
1		5.1	1485

a) Each compound was orally administered at a dose of 30 mg/kg to male Sprague–Dawley (SD) rats. Urinary glucose excretion (UGE) data over 24 h were normalized per 200 g body weight. b) NT: Not tested.

Fig. 4. Calculated Angle between Chlorine Atom and Glucose Moiety (Glu) of **3e** and **f**

(d, $J=2.2$ Hz, 1H), 4.52–4.55 (m, 1H), 4.20–4.24 (m, 1H), 3.80–4.14 (m, 6H), 2.57 (q, $J=7.6$ Hz, 2H), 1.16 (t, $J=7.5$ Hz, 3H), 1.05–1.11 (m, 21H), 1.04 (s, 9H), 0.97 (s, 9H). MS (APCI, m/z) 643 (M+H).

(4a*R*,8*R*,8a*R*)-2,2-Di-*tert*-butyl-6-[4-(4-ethylbenzyl)-2-thienyl]-8-[[triisopropylsilyl]oxy]-4,4a,8,8a-tetrahydropyrano[3,2-*d*][1,3,2]dioxasiline (**5c**): The titled compound was prepared in the same manner as described for **5a** using **7c** instead of **7a** in 40% yield as pale yellow oil. $^1\text{H-NMR}$ (500 MHz, $\text{DMSO-}d_6$) δ : 6.98–7.17 (m, 6H), 5.06 (d, $J=2.2$ Hz, 1H),

4.49–4.52 (m, 1H), 4.20–4.22 (m, 1H), 3.80–4.00 (m, 6H), 2.55 (q, $J=7.6$ Hz, 2H), 1.15 (t, $J=7.6$ Hz, 3H), 1.05–1.10 (m, 21H), 1.03 (s, 9H), 0.96 (s, 9H). MS (APCI, m/z) 643 (M+H).

(4a*R*,8*R*,8a*R*)-2,2-Di-*tert*-butyl-6-[2-(4-ethylbenzyl)-3-thienyl]-8-[(triisopropylsilyloxy)-4,4a,8,8a-tetrahydropyrano[3,2-*d*][1,3,2]dioxasilin-7-ol (5d): The titled compound was prepared in the same manner as described for 5a using 7d instead of 7a in 53% yield as colorless amorphous solid. ¹H-NMR (300 MHz, CDCl₃) δ : 7.05–7.13 (m, 4H), 7.05 (d, $J=5.3$ Hz, 1H), 7.00 (d, $J=5.3$ Hz, 1H), 4.88 (d, $J=2.2$ Hz, 1H), 4.47 (dd, $J=2.2$, 6.9 Hz, 1H), 4.25 (ABq, $J=16.3$ Hz, 1H), 4.20 (ABq, $J=16.3$ Hz, 1H), 3.94–4.06 (m, 3H), 3.79–3.89 (m, 1H), 2.61 (q, $J=7.7$ Hz, 2H), 1.22 (t, $J=7.5$ Hz, 3H), 1.04–1.12 (m, 21H), 0.99 (s, 9H), 0.85 (s, 9H). MS (APCI, m/z) 643 (M+H).

(4a*R*,8*R*,8a*R*)-2,2-Di-*tert*-butyl-6-[4-chloro-5-(4-ethylbenzyl)-2-thienyl]-8-[(triisopropylsilyloxy)-4,4a,8,8a-tetrahydropyrano[3,2-*d*][1,3,2]dioxasilin-7-ol (5e): The titled compound was prepared in the same manner as described for 5a using 7e instead of 7a in 68% yield as colorless viscous oil. ¹H-NMR (300 MHz, CDCl₃) δ : 7.13 (m, 4H), 6.93 (s, 1H), 5.05 (d, $J=2.5$ Hz, 1H), 4.50 (dd, $J=2.4$, 6.6 Hz, 1H), 4.23 (dd, $J=4.9$, 10.2 Hz, 1H), 4.04 (s, 2H), 3.90–4.08 (m, 3H), 2.62 (q, $J=7.7$ Hz, 2H), 1.22 (t, $J=7.7$ Hz, 3H), 1.08–1.14 (m, 21H), 1.06 (s, 9H), 0.98 (s, 9H). MS (ESI, m/z) 677/679 (M+H).

(4a*R*,8*R*,8a*R*)-2,2-Di-*tert*-butyl-6-[5-chloro-4-(4-ethylbenzyl)-2-thienyl]-8-[(triisopropylsilyloxy)-4,4a,8,8a-tetrahydropyrano[3,2-*d*][1,3,2]dioxasilin-7-ol (5f): The titled compound was prepared in the same manner as described for 5a using 7f instead of 7a in 59% yield as colorless oil. ¹H-NMR (300 MHz, CDCl₃) δ : 7.12 (d, $J=8.4$ Hz, 2H), 7.07 (d, $J=8.3$ Hz, 2H), 6.76 (s, 1H), 5.00 (d, $J=2.5$ Hz, 1H), 4.49 (dd, $J=2.4$, 6.6 Hz, 1H), 4.22 (dd, $J=4.8$, 10.4 Hz, 1H), 3.98–4.06 (m, 2H), 3.92 (dd, $J=4.6$, 9.9 Hz, 1H), 3.83 (s, 2H), 2.60 (q, $J=7.7$ Hz, 2H), 1.22 (t, $J=7.7$ Hz, 3H), 1.08–1.13 (m, 21H), 1.05 (s, 9H), 0.98 (s, 9H). MS (ESI, m/z) 677/679 (M+H).

Typical Experimental Procedure for the Synthesis of β -D-Glucopyranosyl Derivatives (4a*R*,6*S*,7*S*,8*R*,8a*R*)-2,2-Di-*tert*-butyl-6-[5-(4-ethylbenzyl)-3-thienyl]-8-[(triisopropylsilyloxy)hexahydropyrano[3,2-*d*][1,3,2]dioxasilin-7-ol (6a): To a solution of compound 5a (385 mg, 0.60 mmol) in tetrahydrofuran (THF) (5 mL) was added borane-tetrahydrofuran complex (1.0 M in THF, 2.12 mL, 2.40 mmol) dropwise at 0°C. After being stirred at 0°C for overnight, the mixture was added 30% aqueous hydrogen peroxide (5 mL) and 3 N aqueous sodium hydroxide (5 mL), and stirred at 0°C for 4 h. The reaction mixture was extracted with Et₂O, washed with brine, dried over sodium sulfate, and filtered. The filtrate was concentrated and dried, then the crude material was purified by silica gel column chromatography (hexane–AcOEt=100:0–97:3) to give compound 6a (192 mg, 42%) as colorless syrup. ¹H-NMR (300 MHz, CDCl₃) δ : 7.13–7.16 (m, 4H), 7.10 (d, $J=0.9$ Hz, 1H), 6.82 (d, $J=1.3$ Hz, 1H), 4.26 (d, $J=9.5$ Hz, 1H), 4.17 (dd, $J=4.9$, 10.1 Hz, 1H), 4.07 (s, 2H), 3.74–3.91 (m, 3H), 3.44–3.53 (m, 2H), 2.63 (q, $J=7.5$ Hz, 2H), 2.03 (d, $J=2.8$ Hz, 1H), 1.22 (t, $J=7.5$ Hz, 3H), 1.09–1.14 (m, 21H), 1.06 (s, 9H), 1.00 (s, 9H). MS (APCI, m/z) 678 (M+NH₄).

(4a*R*,6*S*,7*S*,8*R*,8a*R*)-2,2-Di-*tert*-butyl-6-[5-(4-ethylbenzyl)-2-thienyl]-8-[(triisopropylsilyloxy)hexahydropyrano[3,2-*d*][1,3,2]dioxasilin-7-ol (6b): The titled compound was prepared in the same manner as described for 6a using 5b instead of 5a in 66% yield as colorless oil. ¹H-NMR (500 MHz, DMSO-

*d*₆) δ : 7.12–7.18 (m, 5H), 6.84 (s, 1H), 4.89 (d, $J=7.7$ Hz, 1H), 4.21 (d, $J=9.7$ Hz, 1H), 4.02–4.08 (m, 3H), 3.70–3.76 (m, 1H), 3.64–3.68 (m, 2H), 3.40–3.48 (m, 1H), 3.20–3.26 (m, 1H), 2.56 (q, $J=7.6$ Hz, 2H), 1.15 (t, $J=7.7$ Hz, 3H), 1.04–1.09 (m, 21H), 1.02 (s, 9H), 0.96 (s, 9H). MS (APCI, m/z) 678 (M+NH₄).

(4a*R*,6*S*,7*S*,8*R*,8a*R*)-2,2-Di-*tert*-butyl-6-[4-(4-ethylbenzyl)-2-thienyl]-8-[(triisopropylsilyloxy)hexahydropyrano[3,2-*d*][1,3,2]dioxasilin-7-ol (6c): The titled compound was prepared in the same manner as described for 6a using 5c instead of 5a in 61% yield as colorless oil. ¹H-NMR (500 MHz, DMSO-*d*₆) δ : 7.03–7.17 (m, 5H), 6.86 (s, 1H), 5.04 (d, $J=6.9$ Hz, 1H), 4.44 (d, $J=9.5$ Hz, 1H), 4.00–4.05 (m, 1H), 3.80–3.85 (m, 3H), 3.62–3.75 (m, 2H), 3.47–3.54 (m, 1H), 3.16–3.22 (m, 1H), 2.55 (q, $J=7.6$ Hz, 2H), 1.15 (t, $J=7.7$ Hz, 3H), 1.05–1.08 (m, 21H), 1.01 (s, 9H), 0.96 (s, 9H). MS (APCI, m/z) 678 (M+NH₄).

(4a*R*,6*S*,7*S*,8*R*,8a*R*)-2,2-Di-*tert*-butyl-6-[2-(4-ethylbenzyl)-3-thienyl]-8-[(triisopropylsilyloxy)hexahydropyrano[3,2-*d*][1,3,2]dioxasilin-7-ol (6d): The titled compound was prepared in the same manner as described for 6a using 5d instead of 5a in 60% yield as colorless gum. ¹H-NMR (300 MHz, CDCl₃) δ : 7.10–7.18 (m, 5H), 7.00 (d, $J=5.3$ Hz, 1H), 4.40 (d, $J=9.7$ Hz, 1H), 4.16 (ABq, $J=16.1$ Hz, 2H), 4.12 (dd, $J=5.0$, 10.3 Hz, 1H), 3.74 (m, 3H), 3.58 (ddd, $J=2.9$, 8.2, 10.6 Hz, 1H), 3.44 (ddd, $J=4.9$, 8.7, 10.0 Hz, 1H), 2.62 (q, $J=7.5$ Hz, 2H), 1.90 (d, $J=2.9$ Hz, 1H), 1.22 (t, $J=7.5$ Hz, 3H), 1.10–1.14 (m, 21H), 1.06 (s, 9H), 1.01 (s, 9H). MS (APCI, m/z) 678 (M+NH₄).

(4a*R*,6*S*,7*S*,8*R*,8a*R*)-2,2-Di-*tert*-butyl-6-[4-chloro-5-(4-ethylbenzyl)-2-thienyl]-8-[(triisopropylsilyloxy)hexahydropyrano[3,2-*d*][1,3,2]dioxasilin-7-ol (6e): The titled compound was prepared in the same manner as described for 6a using 5e instead of 5a in 46% yield as colorless viscous oil. ¹H-NMR (500 MHz, DMSO-*d*₆) δ : 7.14–7.16 (m, 4H), 6.94 (s, 1H), 5.22 (d, $J=7.6$ Hz, 1H), 4.43 (d, $J=9.6$ Hz, 1H), 4.04 (dd, $J=4.8$, 10.1 Hz, 1H), 3.80 (ABq, $J=16.0$ Hz, 2H), 3.60–3.73 (m, 3H), 3.49–3.55 (m, 1H), 3.10–3.15 (m, 1H), 2.57 (q, $J=7.6$ Hz, 2H), 1.16 (t, $J=7.7$ Hz, 3H), 1.05–1.08 (m, 21H), 1.00 (s, 9H), 0.96 (s, 9H). MS (APCI, m/z) 712/714 (M+NH₄).

(4a*R*,6*S*,7*S*,8*R*,8a*R*)-2,2-Di-*tert*-butyl-6-[5-chloro-4-(4-ethylbenzyl)-2-thienyl]-8-[(triisopropylsilyloxy)hexahydropyrano[3,2-*d*][1,3,2]dioxasilin-7-ol (6f): The titled compound was prepared in the same manner as described for 6a using 5f instead of 5a in 37% yield as colorless viscous oil. ¹H-NMR (500 MHz, DMSO-*d*₆) δ : 7.09–7.15 (m, 4H), 6.81 (s, 1H), 5.20 (d, $J=7.7$ Hz, 1H), 4.41 (d, $J=9.5$ Hz, 1H), 4.04 (dd, $J=4.9$, 10.0 Hz, 1H), 3.80 (ABq, $J=15.1$ Hz, 2H), 3.68–3.74 (m, 1H), 3.60–3.68 (m, 1H), 3.49–3.54 (m, 1H), 3.36–3.42 (m, 1H), 3.09–3.16 (m, 1H), 2.55 (q, $J=7.5$ Hz, 2H), 1.15 (t, $J=7.5$ Hz, 3H), 1.04–1.10 (m, 21H), 1.00 (s, 9H), 0.95 (s, 9H). MS (APCI, m/z) 712/714 (M+NH₄).

Typical Experimental Procedure for the Synthesis of 1-Aryl- β -D-glucopyranoses (1*S*)-1,5-Anhydro-1-[5-(4-ethylbenzyl)-3-thienyl]-D-glucitol (3a): To a solution of compound 6a (192 mg, 0.29 mmol) in THF (5 mL) was added TBAF (1.0 M in THF, 1.45 mL, 1.45 mmol) dropwise, then the mixture was stirred at 60°C for 3 h. The mixture was concentrated and dried, then the crude material was purified by silica gel column chromatography (CHCl₃–MeOH=100:0–90:10) to give compound 3a (60 mg, 57%) as a colorless powder. ¹H-NMR (500 MHz, DMSO-*d*₆+D₂O) δ : 7.18 (d, $J=8.1$ Hz, 2H), 7.17 (s, 1H), 7.14 (d, $J=8.0$ Hz, 2H), 6.86 (s, 1H), 4.05 (s, 2H), 4.02 (d, $J=9.3$ Hz, 1H), 3.66 (d, $J=11.7$ Hz, 1H), 3.41 (dd, $J=5.9$,

11.5 Hz, 1H), 3.08–3.24 (m, 4H), 2.57 (q, $J=7.7$ Hz, 2H), 1.16 (t, $J=7.5$ Hz, 3H). MS (APCI, m/z) 382 (M+NH₄).

(1S)-1,5-Anhydro-1-[5-(4-ethylbenzyl)-2-thienyl]-D-glucitol (**3b**): The titled compound was prepared in the same manner as described for **3a** using **6b** instead of **6a** in 46% yield as colorless solid. ¹H-NMR (500 MHz, DMSO-*d*₆) δ : 7.17 (d, $J=8.2$ Hz, 2H), 7.16 (s, 1H), 7.14 (d, $J=8.2$ Hz, 1H), 6.85 (s, 1H), 4.86 (d, $J=4.7$ Hz, 1H), 4.85 (d, $J=5.3$ Hz, 1H), 4.81 (d, $J=5.6$ Hz, 1H), 4.44 (t, $J=6.0$ Hz, 1H), 4.04 (s, 2H), 4.00 (d, $J=9.2$ Hz, 1H), 3.64–3.70 (m, 1H), 3.41 (dd, $J=6.1$, 10.7 Hz, 1H), 3.10–3.24 (m, 4H), 2.56 (q, $J=7.8$ Hz, 2H), 1.16 (t, $J=7.6$ Hz, 3H). MS (APCI, m/z) 382 (M+NH₄). mp 100–102°C. HPLC 99.3% ($t_R=2.17$ min, Sumipax ODS (3 μ m particle size, 4.6 \times 50 mm), 0.05% trifluoroacetic acid (TFA) in MeCN–0.05% TFA in H₂O (40/60)).

(1S)-1,5-Anhydro-1-[4-(4-ethylbenzyl)-2-thienyl]-D-glucitol (**3c**): The titled compound was prepared in the same manner as described for **3a** using **6c** instead of **6a** in 33% yield as colorless solid. ¹H-NMR (500 MHz, DMSO-*d*₆) δ : 7.14 (d, $J=8.2$ Hz, 2H), 7.11 (d, $J=8.2$ Hz, 2H), 7.04 (s, 1H), 6.87 (s, 1H), 4.98 (d, $J=5.8$ Hz, 1H), 4.94 (d, $J=5.0$ Hz, 1H), 4.91 (d, $J=5.3$ Hz, 1H), 4.44 (t, $J=5.7$ Hz, 1H), 4.20 (d, $J=9.5$ Hz, 1H), 3.82 (s, 2H), 3.67 (dd, $J=5.6$, 9.9 Hz, 1H), 3.36–3.42 (m, 1H), 3.17–3.24 (m, 2H), 3.06–3.16 (m, 2H), 2.55 (q, $J=7.5$ Hz, 2H), 1.15 (t, $J=7.5$ Hz, 3H). MS (APCI, m/z) 382 (M+NH₄). mp 132–134°C. HPLC 99.8% ($t_R=2.22$ min, Sumipax ODS (3 μ m particle size, 4.6 \times 50 mm), 0.05% TFA in MeCN/0.05% TFA in H₂O (40/60)).

(1S)-1,5-Anhydro-1-[2-(4-ethylbenzyl)-3-thienyl]-D-glucitol (**3d**): The titled compound was prepared in the same manner as described for **3a** using **6d** instead of **6a** in 81% yield as colorless amorphous powder. ¹H-NMR (500 MHz, DMSO-*d*₆) δ : 7.20 (d, $J=8.5$ Hz, 2H), 7.19 (d, $J=5.1$ Hz, 1H), 7.11 (d, $J=8.0$ Hz, 2H), 6.98 (d, $J=5.3$ Hz, 1H), 4.96 (d, $J=4.5$ Hz, 1H), 4.90 (d, $J=5.1$ Hz, 1H), 4.85 (d, $J=5.6$ Hz, 1H), 4.42 (t, $J=5.8$ Hz, 1H), 4.25 (d, $J=9.3$ Hz, 1H), 4.10 (ABq, $J=15.9$ Hz, 2H), 3.67 (dd, $J=5.6$, 9.9 Hz, 1H), 3.40–3.48 (m, 1H), 3.24–3.37 (m, 2H), 3.20–3.24 (m, 1H), 3.14–3.20 (m, 1H), 2.56 (q, $J=7.5$ Hz, 2H), 1.16 (t, $J=7.5$ Hz, 3H). MS (APCI, m/z) 382 (M+NH₄). HPLC 97.2% ($t_R=2.89$ min, Sumipax ODS (3 μ m particle size, 4.6 \times 50 mm), 0.05% TFA in MeCN/0.05% TFA in H₂O (35/65)).

(1S)-1,5-Anhydro-1-[4-chloro-5-(4-ethylbenzyl)-2-thienyl]-D-glucitol (**3e**): The titled compound was prepared in the same manner as described for **3a** using **6e** instead of **6a** in 87% yield as colorless amorphous powder. ¹H-NMR (500 MHz, DMSO-*d*₆+D₂O) δ : 7.16 (s, 4H), 6.96 (s, 1H), 4.22 (d, $J=9.7$ Hz, 1H), 4.02 (s, 2H), 3.66 (d, $J=11.7$ Hz, 1H), 3.40 (dd, $J=5.6$, 11.2 Hz, 1H), 3.20–3.26 (m, 2H), 3.02–3.12 (m, 2H), 2.57 (q, $J=7.4$ Hz, 2H), 1.16 (t, $J=7.6$ Hz, 3H). MS (APCI, m/z) 416/418 (M+NH₄). HPLC 98.8% ($t_R=2.46$ min, Sumipax ODS (3 μ m particle size, 4.6 \times 50 mm), 0.05% TFA in MeCN–0.05% TFA in H₂O (45/55)).

(1S)-1,5-Anhydro-1-[5-chloro-4-(4-ethylbenzyl)-2-thienyl]-D-glucitol (**3f**): The titled compound was prepared in the same manner as described for **3a** using **6f** instead of **6a** in 92% yield as colorless amorphous powder. ¹H-NMR (500 MHz, DMSO-*d*₆) δ : 7.13 (s, 4H), 6.84 (s, 1H), 5.18 (d, $J=5.9$ Hz, 1H), 4.99 (d, $J=5.0$ Hz, 1H), 4.94 (d, $J=5.5$ Hz, 1H), 4.46 (t, $J=5.8$ Hz, 1H), 4.17 (d, $J=9.5$ Hz, 1H), 3.80 (s, 2H), 3.66 (dd, $J=5.7$, 10.2 Hz, 1H), 3.36–3.43 (m, 1H), 3.17–3.26 (m, 2H), 3.02–3.11 (m, 2H),

2.55 (q, $J=7.5$ Hz, 2H), 1.14 (t, $J=7.7$ Hz, 3H). MS (APCI, m/z) 416/418 (M+NH₄). HPLC 98.8% ($t_R=2.53$ min, Sumipax ODS (3 μ m particle size, 4.6 \times 50 mm), 0.05% TFA in MeCN–0.05% TFA in H₂O (45/55)).

(4-Bromo-2-thienyl)(4-ethylphenyl)methanol (**11**) To a suspension of **8** (4.78 g, 25 mmol) in THF (40 mL) was added 4-ethylphenylmagnesium bromide solution (0.5 N THF solution, 50 mL, 100 mmol) at 0°C over 10 min. After being stirred at 0°C for 30 min, the reaction mixture was quenched with saturated aqueous NH₄Cl and extracted with AcOEt. The extract was washed with brine and dried over magnesium sulfate, and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (hexane–AcOEt=97:3–84:16) to give titled compound **11** (5.37 g, 72%) as colorless oil. ¹H-NMR (300 MHz, CDCl₃) δ : 7.33 (d, $J=7.9$ Hz, 2H), 7.21 (d, $J=7.9$ Hz, 2H), 7.15 (d, $J=1.5$ Hz, 1H), 6.76 (dd, $J=1.1$, 1.5 Hz, 1H), 5.95 (d, $J=4.1$ Hz, 1H), 2.66 (q, $J=7.7$ Hz, 2H), 2.37 (d, $J=4.0$ Hz, 1H), 1.24 (t, $J=7.7$ Hz, 3H). MS (APCI, m/z) 279/281 (M+H – H₂O).

4-Bromo-2-(4-ethylbenzyl)thiophene (**7a**) To a cold (–78°C) solution of **11** (297 mg, 1 mmol) in CH₂Cl₂ (3 mL) was added Et₃SiH (319 μ L, 2 mmol) and BF₃·OEt₂ (190 μ L, 1.5 mmol), and the mixture was gradually warmed to room temperature over a period of 1 h. The reaction mixture was basified with saturated aqueous NaHCO₃ and extracted with CH₂Cl₂. The extract was washed with brine and dried over magnesium sulfate, and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (hexane–AcOEt=100:0–95:5) to give titled compound **7a** (280 mg, 50%) as colorless oil. ¹H-NMR (300 MHz, CDCl₃) δ : 7.13–7.14 (m, 4H), 7.02 (d, $J=1.5$ Hz, 1H), 6.68–6.71 (m, 1H), 4.06 (s, 2H), 2.63 (q, $J=7.5$ Hz, 2H), 1.23 (t, $J=7.5$ Hz, 3H). MS (APCI, m/z) not ionized.

(5-Bromo-2-thienyl)(4-ethylphenyl)methanol (**12**) The titled compound was prepared in the same manner as described for **11** using **9** instead of **8** in quantitative yield as slightly yellow oil. ¹H-NMR (300 MHz, CDCl₃) δ : 7.33 (d, $J=8.0$ Hz, 2H), 7.21 (d, $J=8.4$ Hz, 2H), 7.15 (d, $J=1.4$ Hz, 1H), 6.77 (dd, $J=1.1$, 1.5 Hz, 1H), 5.95 (d, $J=3.8$ Hz, 1H), 2.66 (q, $J=7.7$ Hz, 2H), 2.39 (d, $J=4.1$ Hz, 1H), 1.24 (t, $J=7.5$ Hz, 3H). MS (APCI, m/z) 279/281 (M+H–H₂O).

2-Bromo-5-(4-ethylbenzyl)thiophene (**7b**) The titled compound was prepared in the same manner as described for **7a** using **12** instead of **11** in 70% yield as colorless oil. ¹H-NMR (300 MHz, CDCl₃) δ : 7.14 (m, 4H), 7.02 (d, $J=1.5$ Hz, 1H), 6.70 (d, $J=1.5$ Hz, 1H), 4.06 (s, 2H), 2.63 (q, $J=7.5$ Hz, 2H), 1.23 (t, $J=7.5$ Hz, 3H). MS (GC-EI, m/z) 280/282 (M⁺).

(5-Bromo-3-thienyl)(4-ethylphenyl)methanol (**13**) The titled compound was prepared in the same manner as described for **11** using **10** instead of **8** in 75% yield as slightly yellow oil. ¹H-NMR (500 MHz, DMSO-*d*₆) δ : 7.29 (s, 1H), 7.26 (d, $J=8.0$ Hz, 2H), 7.15 (d, $J=8.0$ Hz, 2H), 7.01 (s, 1H), 5.86 (d, $J=4.5$ Hz, 1H), 5.63 (d, $J=4.3$ Hz, 1H), 2.57 (q, $J=7.7$ Hz, 2H), 1.16 (t, $J=7.5$ Hz, 3H). MS (APCI, m/z) 279/281 (M+H–H₂O).

2-Bromo-4-(4-ethylbenzyl)thiophene (**7c**) The titled compound was prepared in the same manner as described for **7a** using **13** instead of **11** in 63% yield as colorless oil. ¹H-NMR (500 MHz, DMSO-*d*₆) δ : 7.18 (brs, 1H), 7.13 (s, 4H), 7.02 (brs, 1H), 3.83 (s, 2H), 2.56 (q, $J=7.6$ Hz, 2H), 1.15 (t, $J=7.6$ Hz, 3H). MS (GC-EI, m/z) 280/282 (M⁺).

(3-Bromo-2-thienyl)(4-ethylphenyl)methanol (**15**) To a

cold (-78°C) solution of *n*-BuLi (2.44 M in *n*-hexane, 18.5 mL, 45 mmol) in Et_2O (30 mL) was added **14** (10.9 g, 45 mmol) in Et_2O (10 mL). After being stirred at -78°C for 1 h, a solution of 4-ethylbenzaldehyde (6.03 g, 45 mmol) in Et_2O (5 mL) was added dropwise over 1 h. After 10 min, the reaction mixture was quenched with saturated aqueous NH_4Cl and extracted with Et_2O . The extract was washed with brine and dried over magnesium sulfate, and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (hexane–AcOEt=96:4–75:25) to give titled compound **15** (12.46 g, 93%) as colorless oil. $^1\text{H-NMR}$ (300 MHz, CDCl_3) δ : 7.38 (d, $J=8.1$ Hz, 2H), 7.23 (dd, $J=0.5, 5.2$ Hz, 1H), 7.19 (d, $J=8.2$ Hz, 2H), 6.92 (d, $J=5.3$ Hz, 1H), 6.13 (d, $J=3.3$ Hz, 1H), 2.64 (q, $J=7.5$ Hz, 2H), 2.45 (d, $J=3.5$ Hz, 1H), 1.23 (t, $J=7.5$ Hz, 3H). MS (APCI, m/z) 279/281 (M+H– H_2O).

3-Bromo-2-(4-ethylbenzyl)thiophene (7d) To an ice-cold (0°C) suspension of LiAlH_4 (2.6 g, 68.5 mmol) and AlCl_3 (9.0 g, 67.4 mmol) in Et_2O (35 mL) was added **15** (12.4 g, 42 mmol) in Et_2O (10 mL). After being stirred at room temperature for 18 h, the reaction mixture was poured into ice water and extracted with Et_2O . The extract was washed with saturated aqueous NaHCO_3 , brine and dried over magnesium sulfate, and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (hexane) to give titled compound **7d** (8.77 g, 75%) as colorless oil. $^1\text{H-NMR}$ (300 MHz, CDCl_3) δ : 7.11–7.19 (m, 5H), 6.92 (d, $J=5.3$ Hz, 1H), 4.08 (s, 2H), 2.62 (q, $J=7.5$ Hz, 2H), 1.22 (t, $J=7.5$ Hz, 3H). MS (GC-ESI, m/z) 280/282 (M^+).

5-Bromo-3-chlorothiophene-2-carboxylic Acid (17) To a cold (-78°C) solution of *i*- Pr_2NH (6.80 mL, 48.5 mmol) in THF (75 mL) was added *n*-BuLi (1.59 M in *n*-hexane, 30.5 mL, 48.5 mmol) dropwise over 10 min. After being stirred at -78°C for 30 min, a solution of **16** (3.92 g, 24 mmol) in THF (40 mL) was added dropwise over 5 min. After being stirred for 30 min, 1,2-dibromo-1,1,2,2-tetrafluoroethane (6.00 mL, 50.1 mmol) was added to a reaction mixture, and stirred for 30 min. The reaction mixture was poured into H_2O (100 mL) and 10% aqueous HCl was added to adjust pH 2. After being extracted with AcOEt, the extract was washed with brine and dried over magnesium sulfate, and the solvent was evaporated under reduced pressure. The residue was triturated with *i*- Pr_2O –*n*-hexane to give titled compound **17** (3.79 g, 65%) as colorless solid. $^1\text{H-NMR}$ (500 MHz, $\text{DMSO-}d_6$) δ : 7.62 (s, 1H), 7.48 (s, 1H). MS (ESI, m/z) 239/241/243 (M–H). mp 106–107 $^{\circ}\text{C}$.

5-Bromo-3-chlorothiophene-2-carbaldehyde (18) To a mixture of **17** (3.79 g, 15.7 mmol) and *N,O*-dimethylhydroxylamine hydrochloride (1.84 g, 18.9 mmol) in CH_2Cl_2 (110 mL) were added HOBt (3.18 g, 23.5 mmol) and EDCI·HCl (4.51 g, 23.5 mmol) at 0°C , then Et_3N (11.0 mL, 78.9 mmol) was added and the mixture was stirred at room temperature for 18 h. After the mixture was poured into H_2O , extracted with CHCl_3 , and organic layer was combined and washed with brine, dried over Na_2SO_4 , filtered and evaporated. The residue was purified by silica gel column chromatography (hexane–AcOEt=95:5–85:15) to give Weinreb amide (2.46 g, 55%) as a yellow oil.

To a solution of above Weinreb amide (2.73 g, 9.59 mmol) in THF (50 mL) was added DIBAL-H (1.0 M solution in toluene, 11.0 mL, 11.0 mmol) dropwise over 15 min at -78°C . After

being stirred for 30 min, AcOEt (7.2 mL) was added and the mixture was gradually warmed to 0°C , then 10% aqueous HCl (10 mL) was added and poured into H_2O (50 mL). The resulting mixture was extracted with AcOEt, and combined organic layer was washed with saturated aqueous NaHCO_3 and brine, dried over Na_2SO_4 , filtered and evaporated. The residue was purified by silica gel column chromatography (hexane–AcOEt=100:0–97:3) to give titled compound **18** (2.03 g, 94%) as a pale yellow oil. $^1\text{H-NMR}$ (500 MHz, $\text{DMSO-}d_6$) δ : 9.86 (s, 1H), 7.66 (s, 1H). MS (ESI, m/z) 239/241/243 (M+H+MeOH– H_2O).

(5-Bromo-3-chloro-2-thienyl)(4-ethylphenyl)methanol (19) The titled compound was prepared in the same manner as described for **11** using **18** instead of **8** in quantitative yield as slightly yellow oil. $^1\text{H-NMR}$ (500 MHz, $\text{DMSO-}d_6$) δ : 7.28 (d, $J=8.0$ Hz, 2H), 7.18 (d, $J=7.2$ Hz, 2H), 7.17 (s, 1H), 6.50 (d, $J=3.7$ Hz, 1H), 5.87 (d, $J=3.6$ Hz, 1H), 2.57 (q, $J=7.5$ Hz, 2H), 1.15 (t, $J=7.6$ Hz, 3H). MS (APCI, m/z) 313/315/317 (M+H– H_2O).

5-Bromo-3-chloro-2-(4-ethylbenzyl)thiophene (7e) The titled compound was prepared in the same manner as described for **7a** using **19** instead of **11** in 83% yield as colorless oil. $^1\text{H-NMR}$ (500 MHz, $\text{DMSO-}d_6$) δ : 7.24 (s, 1H), 7.16 (m, 4H), 4.09 (s, 2H), 2.57 (q, $J=7.5$ Hz, 2H), 1.16 (t, $J=7.5$ Hz, 3H). MS (APCI, m/z) not ionized.

5-Bromo-2-chlorothiophene-3-carbaldehyde (21) The titled compound was prepared in the same manner as described for **18** using **20** instead of **17** in 31% yield as colorless oil. $^1\text{H-NMR}$ (500 MHz, $\text{DMSO-}d_6$) δ : 9.84 (s, 1H), 7.53 (s, 1H). MS (ESI, m/z) 239/241/243 (M–H).

(5-Bromo-2-chloro-3-thienyl)(4-ethylphenyl)methanol (22) The titled compound was prepared in the same manner as described for **11** using **21** instead of **8** in 70% yield as slightly yellow oil. $^1\text{H-NMR}$ (500 MHz, $\text{DMSO-}d_6$) δ : 7.27 (d, $J=8.1$ Hz, 2H), 7.17 (d, $J=8.0$ Hz, 2H), 7.14 (s, 1H), 6.08 (d, $J=4.5$ Hz, 1H), 5.70 (d, $J=4.7$ Hz, 1H), 2.56 (q, $J=7.7$ Hz, 2H), 1.15 (t, $J=7.5$ Hz, 3H). MS (APCI, m/z) 313/315/317 (M+H).

5-Bromo-2-chloro-3-(4-ethylbenzyl)thiophene (7f) The titled compound was prepared in the same manner as described for **7a** using **22** instead of **11** in 89% yield as colorless oil. $^1\text{H-NMR}$ (500 MHz, $\text{DMSO-}d_6$) δ : 7.14 (m, 4H), 7.10 (s, 1H), 3.83 (s, 2H), 2.55 (q, $J=7.5$ Hz, 2H), 1.15 (t, $J=7.7$ Hz, 3H). MS (APCI, m/z) not ionized.

Pharmacology. Sodium-Dependent Glucose Uptake in Chinese Hamster Ovary (CHO) Cells Expressing hSGLT2 Parental CHOK cells expressing hSGLT2²⁰ were used in these experiments. For the uptake assay, cells were seeded into 24-well plates, and were post-confluent on the day of assay.

Cells were rinsed one time with 400 μL Assay Buffer (137 mM NaCl, 5 mM KCl, 1 mM CaCl_2 , 1 mM MgCl_2 , 50 mM *N*-(2-hydroxyethyl)piperazine-*N'*-2-ethanesulfonic acid (HEPES), 20 mM Tris Base, pH 7.4), and were pre-incubated with the solutions of compounds (250 μL) for 10 min at 37°C . The transport reaction was initiated by addition of 50 μL α -methyl-D-glucopyranoside (AMG)¹⁴C-AMG solution (16.7 μCi ; final concentration, 0.5 mM) and incubated for 120 min at 37°C . After the incubation, the AMG uptake was halted by aspiration of the incubation mixture followed by immediate washing three times with phosphate buffered saline (PBS). The cells were solubilized in 0.3 N NaOH of 300 μL and the radioactivity associated with the cells was monitored by a liquid scintilla-

tion counter (Quantasart™ (Packard, Boston, MA, U.S.A.)). Inhibitory concentration of 50% (IC_{50}) was calculated by non-linear least squares analysis using a four-parameter logistic model (Prism version 4; GraphPad Software, San Diego, CA, U.S.A.).

UGE Study Male SD rats aged 4–5 weeks were obtained from Japan SLC (Shizuoka, Japan) and were used for experiments at 6 weeks of age after acclimation period. The animals were divided into experimental groups matched for body weight ($n=3$). The compounds were prepared in vehicles as suspension or solution. UGE studies were performed after two-day acclimation period in metabolic cages. The compounds or vehicle were orally administered at a dose of 30 mg/kg in 0.2% CMC–0.2% Tween 80. Urine samples were collected for 24 h using metabolic cages to measure urinary glucose excretion. Urine glucose contents were determined by an enzymatic assay kit (UGLU-L, Serotec, Hokkaido, Japan). All animals were allowed free access to a standard pellet diet (CRF1; Oriental Yeast Co., Ltd., Tokyo, Japan) and tap water. All animal experimental procedures were approved by Institutional Animal Care and Use Committee of Mitsubishi Tanabe Pharma Corporation.

Acknowledgment We thank Prof. Tsutomu Ishikawa, Faculty of Pharmaceutical Science, Graduate School of Chiba University, for helpful discussion.

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