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Novel thiophenyl *C*-aryl glucoside SGLT2 inhibitors as potential antidiabetic agents

Suk Ho Lee [a,b], Kwang-Seop Song [a], Jong Yup Kim [a], Misuk Kang [a], Jun Sung Lee [a], Seung-Hwan Cho [a], Hyun-Ju Park [b], Jeongmin Kim [a], Jinhwa Lee [a,*]

[a] *Research Center, Green Cross Corporation, 303 Bojeong-Dong, Giheung-Gu, Yongin, Gyeonggi-Do 446-770, Republic of Korea*
[b] *College of Pharmacy, Sungkyunkwan University, Cheoncheon-Dong, Jangan-Gu, Suwon, Gyeonggi-Do 440-746, Republic of Korea*

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ABSTRACT

Novel thiophene *C*-aryl glucoside SGLT2 inhibitors were designed and synthesized. Two different types of thiophene derivatives were readily prepared. Among the compounds tested, ethylphenyl at the distal ring **71p** showed the best in vitro inhibitory activity in this series to date (IC_{50} = 4.47 nM) against SGLT2.

1. Introduction

Diabetes has become an augmenting concern to the world's population. In 2007, approximately 246 million people were influenced by the disease, with an additional 7 million people developing the disease every year.[1] The ADA states, 'Diabetes mellitus is a group of metabolic diseases characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both. The chronic hyperglycemia of diabetes is associated with long-term damage, dysfunction, and failure of various organs, especially the eyes, kidneys, nerves, heart, and blood vessels'.[2] There are two identified form of diabetes: Type 1 diabetes is distinguished as an autoimmune disease involving pancreatic β-cells, while type 2 diabetes is associated with β-cell dysfunction[3] and is defined by a defect in glucose regulation and metabolism. Type 2 diabetes is the most dominant disorder of glucose homeostasis, accounting for nearly 90–95% of all cases of diabetes. While diabetes is often a result of impaired insulin secretion or action, the actual measure of diabetes relates to glucose levels.

Sodium-dependent glucose cotransporters (SGLTs) couple the transport of glucose against a concentration gradient with the simultaneous transport of Na^+ down a concentration gradient.[4] Two important SGLT isoforms have been cloned and identified, SGLT1 and SGLT2.[5] SGLT1 is typically in the GI tract of humans and the GI tract represents a major locus of action of SGLT1 in glucose trafficking. Also, SGLT1 is located in the kidney and the heart where its expression regulates cardiac glucose transport.[6] SGLT1 is a high-affinity, low-capacity transporter and therefore accounts for only a small fraction of renal glucose reabsorption.[7] In contrast, SGLT2 is a low-affinity, high-capacity transporter located exclusively at the apical domain of the epithelial cells in the early proximal convoluted tubule. It is estimated that 90% of renal glucose reabsorption is facilitated by SGLT2; the remaining 10% is likely mediated by SGLT1 in the late proximal straight tubule.[8] Since SGLT2 appears to be responsible for the majority of renal glucose reabsorption based on human mutation studies,[9] it has become a target of therapeutic interest.

Scientists at Bristol-Myers Squibb has identified dapagliflozin (Fig. 1), a potent, selective SGLT2 inhibitor for the treatment of type 2 diabetes.[10–12] At present, dapagliflozin is the most advanced SGLT2 inhibitor in clinical trials. On the other hand, Mitsubishi Tanabe, in collaboration with Johnson & Johnson, is developing canagliflozin **2**, another novel *C*-glucoside-derived SGLT2 inhibitor.[13] In addition, Boehringer Ingelheim (BI 10773), Lexicon (LX4211), Astellas (ASP1941), and Pfizer (PF-04971729) are reported to be in various phase of clinical trials.[14] Our efforts on identifying inhibitors that target SGLT2 have been previously described.[15]

In the present study, *C*-glucosides bearing thiophene ring at the proximal ring were exploited in order to develop novel SGLT2 targeting antidiabetic agents. We envisioned that replacement of

* Corresponding author. Tel.: +82 31 260 9892; fax: +82 31 260 9020.
E-mail address: jinhwalee@greencross.com (J. Lee).

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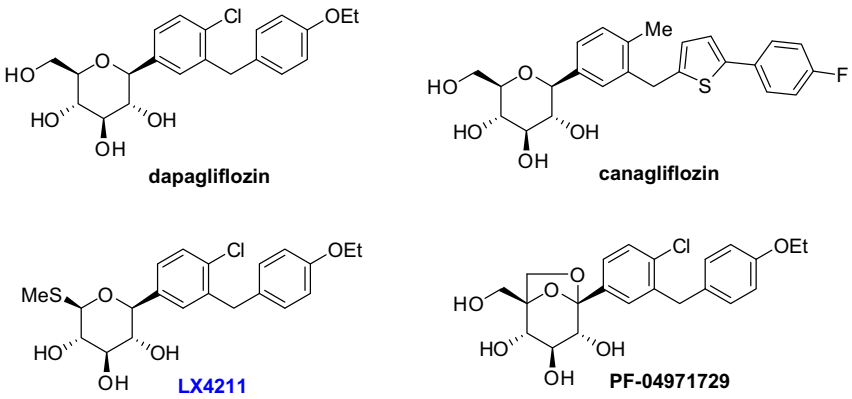


Figure 1. Structures of *C*-aryl glucoside SGLT2 inhibitors.

the proximal ring of dapagliflozin with a well-known analogy for phenyl ring would be a worthy approach for modulating physicochemical property, possibly to improve biological activity. For this purpose, structure of dapagliflozin was modified into **A** bearing thiophene at the proximal ring as shown in Figure 2. Herein, we report design, synthesis, and biological evaluation of benzylthiophenyl glucoside congeners.

2. Results and discussion

2.1. Chemistry

The synthesis of various thienyl bromides was shown in Scheme 1. Friedel–Crafts acylation of anisole with 5-bromo-2-chlorothiophene-3-carbonyl chloride, formed form 5-bromo-2-chlorothiophene-3-carboxylic acid **1** with oxalyl chloride, generated the desired diarylketone **2** in 98% yield. The reduction of diarylketone **2** by triethylsilane in the presence of boron trifluoride etherate provided aglycon **3** in 82% yield. 4-((5-Bromo-2-chlorothiophen-3-yl)methyl)phenol, the key intermediate **4**, was generated via demethylation with BBr_3 in quantitative yield. Alkylated aglycons such as **5** or **6** were generated via alkylation with alkyl halide in the presence of suitable base such as cesium carbonate or with corresponding alcohol with DIAD and PPh_3 under Mitsunobu reaction conditions.

The synthesis of various thienyl iodides was shown in Scheme 2. 5-Bromo-2-methylthiophene-3-carboxylic acid **8** was obtained in good yield (84%) by bromination at the thiophene ring of 2-methylthiophene-3-carboxylic acid **7** using bromine generated from pyridinium tribromide in glacial acetic acid.[16] Friedel–Crafts

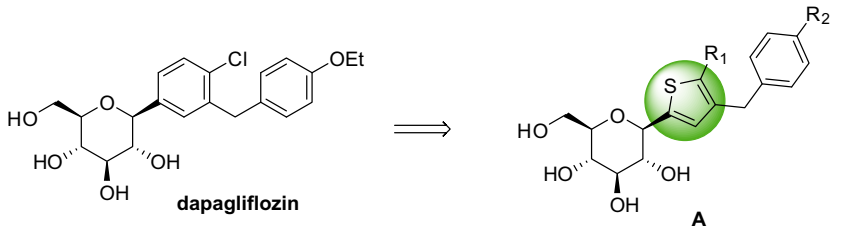
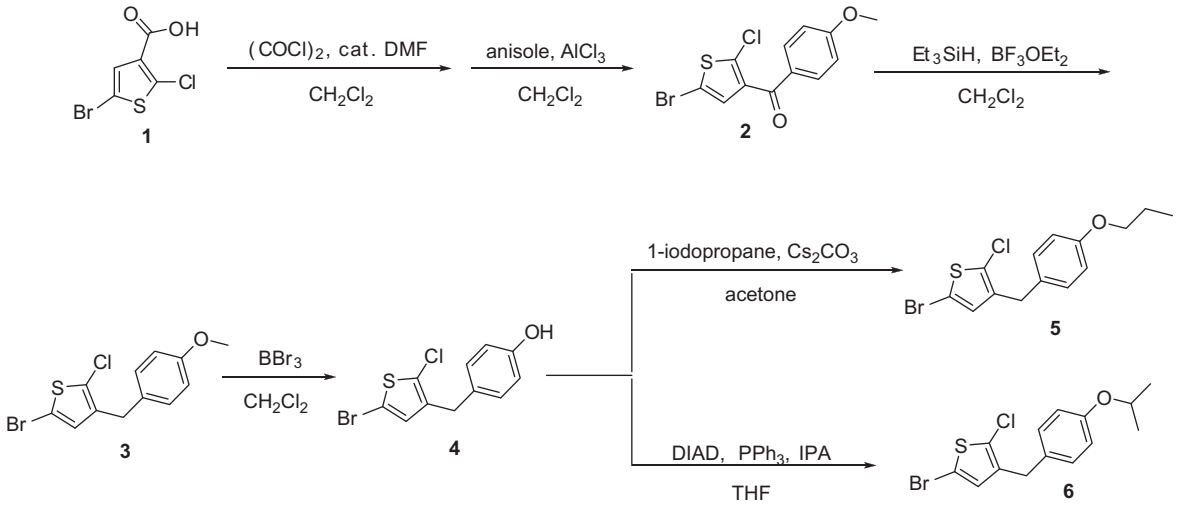


Figure 2. Exploration of *C*-glucoside bearing thiophene at the proximal ring.

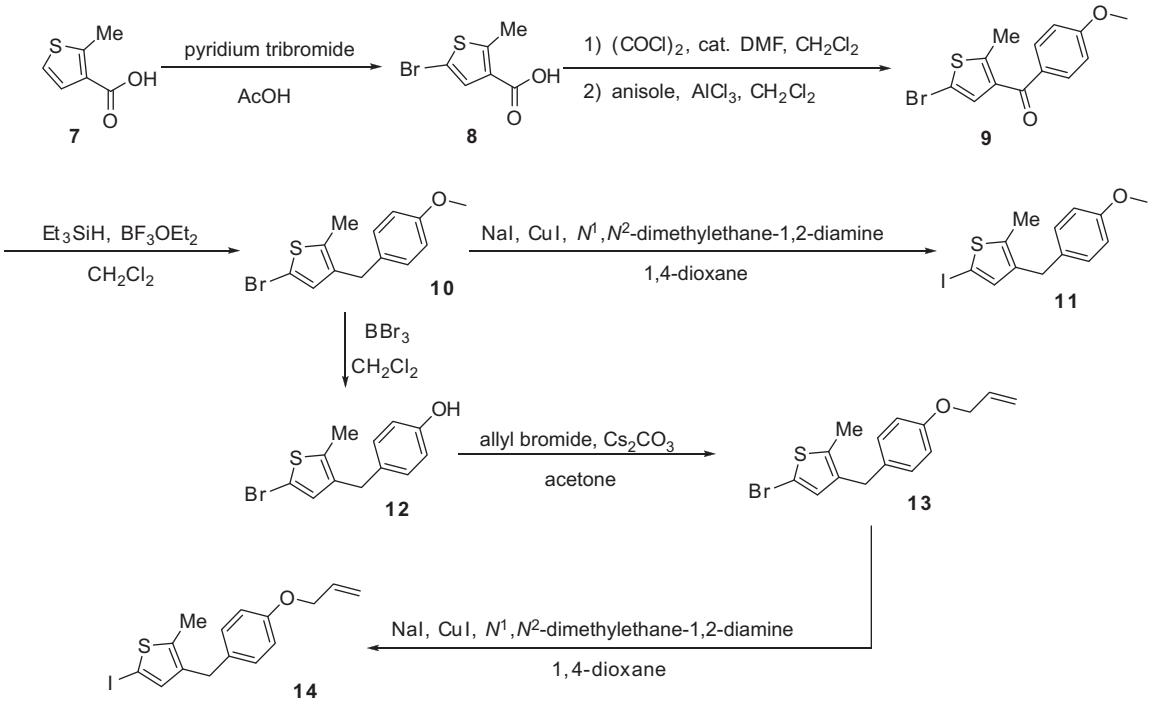


Scheme 1. Preparation of various thienyl bromides.

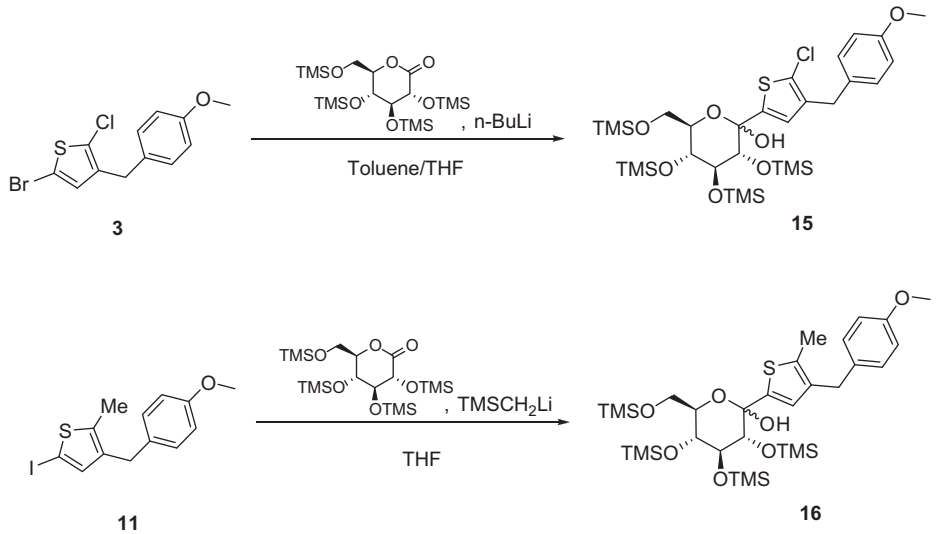
acylation of anisole with 5-bromo-2-methylthiophene-3-carbonyl chloride, formed form 5-bromo-2-chlorothiophene-3-carboxylic acid **8** with oxalyl chloride, generated the desired diarylketone **9** in 83% yield. The reduction of diarylketone **2** by triethylsilane in the presence of boron trifluoride etherate provided aglycon **10** in quantitative yield. A copper-catalyzed halogen exchange reaction was performed to prepare thienyl iodides **11** from the corresponding bromides **10** using *N*,*N*′-dimethylethylenediamine ligand at high temperature (120 °C).[17] Phenol **12** was generated via demethylation of aglycon **10** with BBr_3. Allylation of aglycon **12** with allyl bromide under basic conditions, followed by copper-catalyzed halogen exchange reaction in the presence of NaI, CuI, and *N*,*N*′-dimethylethylenediamine ligand at high temperature (approx 120 °C), produced the corresponding iodide **14** in high yield.[17]

The general procedures for addition of organometallic compound to gluconolactone which were utilized in this study are illustrated in Scheme 3. Thus, lithium-bromine exchange of bromide **3** using *n*-butyllithium, followed by addition of the nascent lithiated aromatic compound to gluconolactone, produced a mixture of the corresponding lactols **15**. Alternatively, a mixture of lactols **16** was smoothly prepared via lithium-iodine exchange of **11** using (trimethylsilyl)methyllithium.[18]

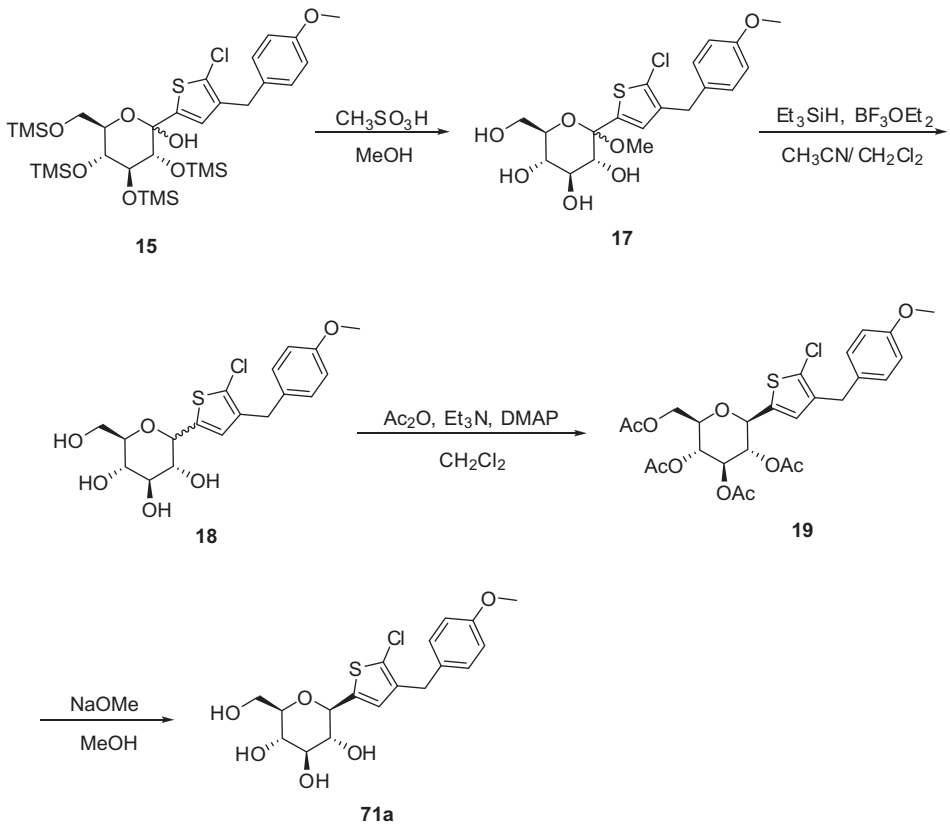
The synthesis of a target compound, β-anomer of tetraol **20** was illustrated in Scheme 4. First, the lactol **15** was converted in situ to the desilylated *O*-methyl lactols by treatment with methansulfonic acid in methanol at cold conditions (−78 to −50 °C). The reduction of the anomeric methoxy group of lactol **17** using triethylsilane and boron trifluoride diethyl etherate was performed to generate



Scheme 2. Preparation of various thienyl iodides.



Scheme 3. Addition of lithiated compound to gluconolactone.



Scheme 4. Preparation of *C*-aryl glucoside containing 2-chlorothiophene.

the corresponding tetraol **18** (β-anomer/α-anomer = 3:1). Finally, peracetylation using Et_3N and acetic anhydride in the presence of DMAP, subsequently selective crystallization from ethanol, followed by hydrolysis using sodium methoxide yielded the target compound **20** in 48% yield for the five steps.

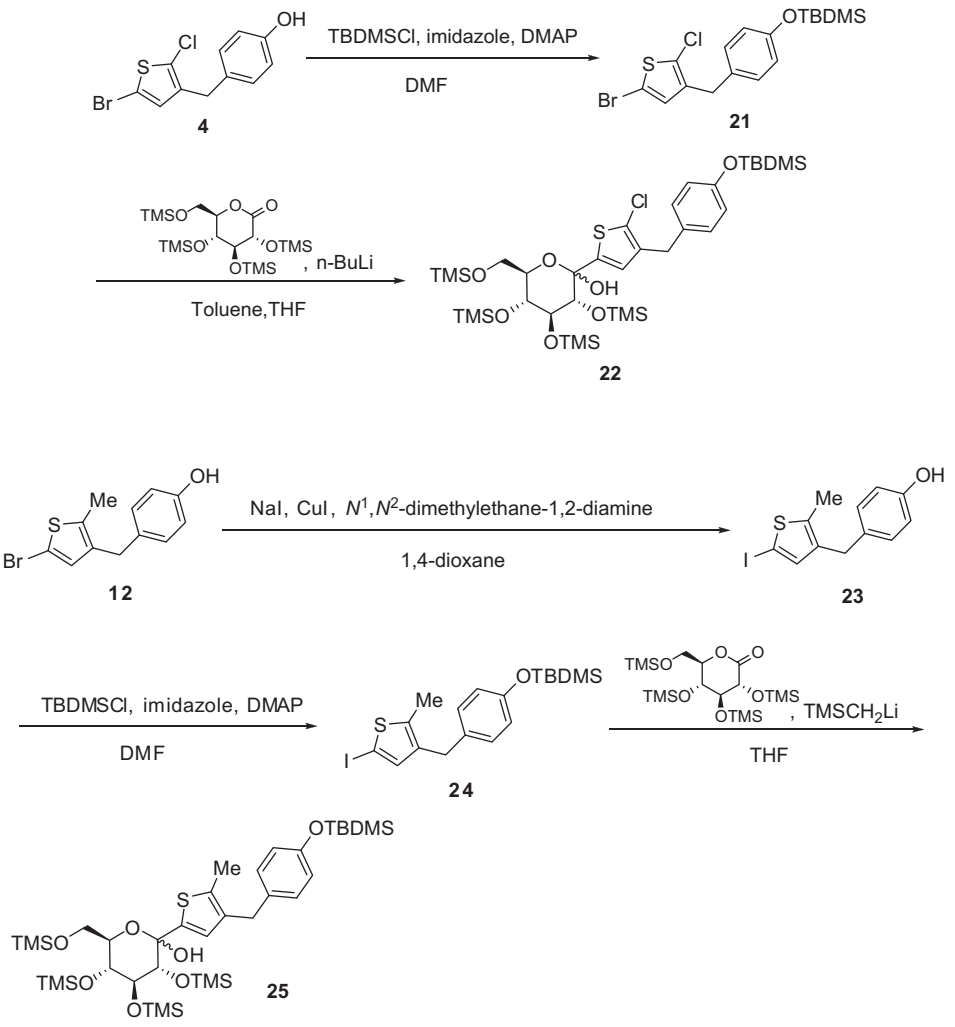
The phenol **4** was used as a starting material in preparing the chlorothiophene-containing *C*-aryl glucoside as shown in Scheme 5. Protection of phenol **4** with TBDMS group, followed by addition of the nascent organometallic compound **21** to TMS-protected gluconolactone **1**, produced a mixture of the corresponding lactols **22**. Alternatively, the phenol **12** was used as a starting material in preparing the methylthiophene-containing *C*-aryl glucoside as shown in Scheme 5. Copper-catalyzed halogen exchange reaction using NaI, CuI, and *N*,*N*′-dimethylethylenediamine ligand at high temperature (120 °C) and protection of phenol **23** with TBDMS group generated iodide **24**. Finally, a mixture of lactols **25** was smoothly prepared via lithium-iodine exchange of **24** using (trimethylsilyl)methyllithium.

The synthesis of β-anomer of pentaol **71c** was shown in Scheme 6. First, the lactol **22** was converted in situ to the desilylated *O*-methyl lactols by treatment with methansulfonic acid in methanol at low temperature (−78 to −50 °C). The reduction of the anomeric methoxy group of lactol **26** using triethylsilane and boron trifluoride diethyl etherate was performed to generate the corresponding mixture of pentaol **27**. Finally, peracetylation using Et_3N and acetic anhydride in the presence of DMAP, selective crystallization from ethanol, followed by hydrolysis using sodium methoxide yielded the pentaol **71c** in 20% yield for the five steps.

The derivatization of pentaol **71a** was shown in Scheme 7. The phenol **29** was alkylated with alkyl halide under basic conditions to provide ether **71f**, albeit in low yield.

Another route of synthesis of chlorothiophene-containing *C*-aryl glucoside was shown in Scheme 8. Reduction of acid **1** with borane dimethylsulfide, followed by protection of the resulting alcohol **31** with TIPSCl produced bromide **32**. Metal–halogen exchange of halogenated compound **32** with n-butyllithium, followed by addition of the nascent organometallic compound to perbenzylated gluconolactone, produced a mixture of the corresponding lactols **33** (β-anomer/α-anomer = 2:1), which were reduced using triethylsilane and boron trifluoride diethyl etherate, followed by desilylation, afforded alcohol **35** in 89% yield for three steps. The alcohol **35** was converted to benzoate with benzoyl chloride in the presence of Et_3N. A mixture of α,β-isomers of **36** was resolved after selective crystallization from ethanol to produce the required β-isomer **36** in high separation yield. Hydrolysis of benzoate **36** with lithium hydroxide monohydrate in aqueous ethanol and THF solution generated β-anomer of alcohol **37** in high yield. The alcohol **37** was converted to bromide **38** using phosphorus tribromide and pyridine. The bromide **38** was coupled with corresponding boronic acid in the presence of Pd catalyst and Cs_2CO_3. Finally, peracetylation using Et_3N and acetic anhydride in the presence of DMAP, followed by hydrolysis using sodium methoxide yielded the target compound **41** in 17% yield for the two steps.[19]

An efficient conversion of 3-methylthiophene-2-carbonyl chloride (**42**) into a Weinreb amide **43** was achieved by treatment of *N*,*O*-dimethylhydroxylamine hydrochloride and TEA under mild conditions in quantitative yield. Reaction of Weinreb amide **43** with proper organometallic nucleophiles, such as Grignard reagents (Scheme 9, route a) and organolithium reagents (Scheme 9, route b), produced the desired ketones **44**. Bromothiophenyl intermediate **45** was obtained in good yield (60–70%) by bromina-



Scheme 5. Preparation of chlorothiophene-containing *C*-aryl glucoside intermediate.

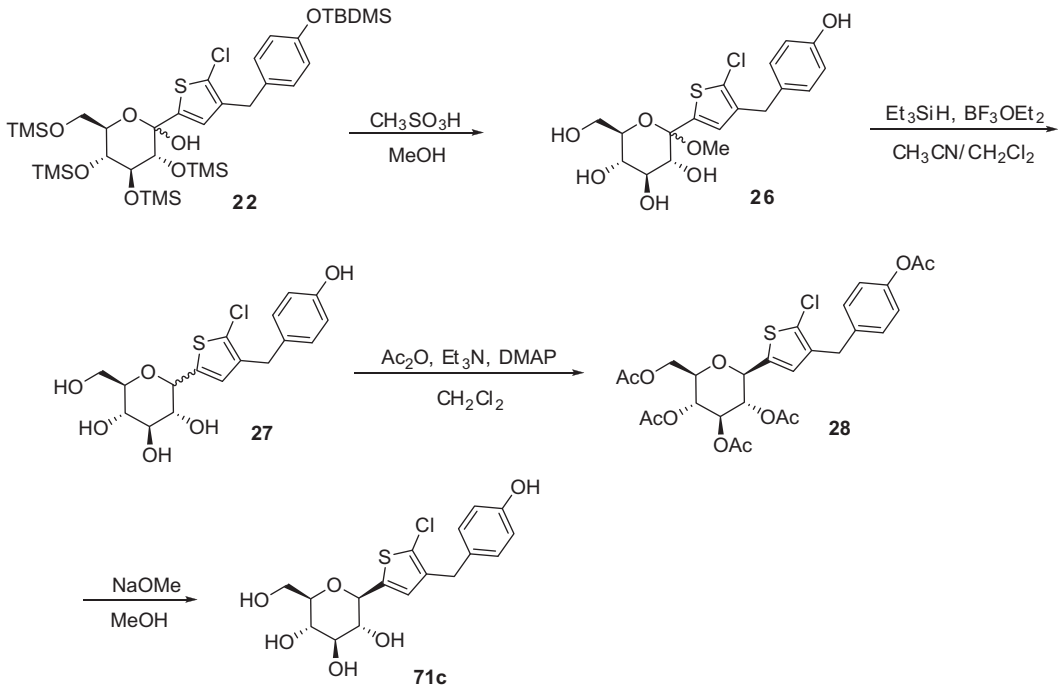
tion at the thiophene ring of **44** using bromine generated from pyridinium tribromide in glacial acetic acid. The reduction of diaryl ketone **45** to compound **46** was accomplished by treatment of excess triethylsilane in the presence of boron trifluoride etherate. The copper-catalyzed halogen exchange reaction was performed to produce thienyl iodides **47** from the corresponding bromides **46** using *N*,*N*′-dimethylethylenediamine ligand at high temperature (approx 110 °C) (Scheme 9).

Lithiated thienyl moieties were prepared from the corresponding thienyl iodides **47** by treatment of (trimethylsilyl)methyllithium and coupled with persilylated lactone **49** at low temperature (−50 to −40 °C). The resulting lactols **49** were converted in situ to the desilylated *O*-methyl lactols **50** by treatment with methanesulfonic acid in methanol at low temperature (−78 to −50 °C). The anomeric methoxy group of **50** was reduced using triethylsilane and BF_3 etherate to generate the corresponding tetraol **51**. The small amount of α-anomer and other impurities in the crude tetraols **51** were removed by reverse phase preparative HPLC to afford the target compounds **51** (Scheme 10).

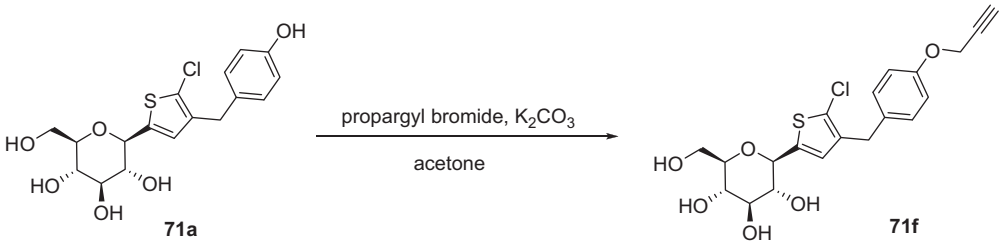
Another approach toward *C*-aryl glucoside 3-methylthiophene is described in Scheme 11. Thus, bromide **56** underwent Suzuki-type coupling reaction (trimethylboroxine, tricyclohexylphosphine tetrafluoroborate, $Pd(OAc)_2$, K_3PO_4, aq toluene, reflux for 18 h) to transform to dimethylthiophene **57** in 70% yield.[20] Hydrolysis of **56** and **57** with sodium methoxide in methanol produced the desired 3-bromo-4-methylthiophenyl compound **72h** and 3,4-dimethylthiophenyl compound **72j**, respectively. Also, bromide **56** underwent Ullmann-type coupling and concomitant total deacetylation to provide 3-methoxy-4-methylthiophenyl compound **72i**.[21]

2.2. Structure–activity relationship studies

The cell-based SGLT2 AMG (methyl-α-D-glucopyranoside) inhibition assay was performed to evaluate the inhibitory effects of all prepared compounds on *h*SGLT2 activities.[22,23] Exploration of the SAR began by replacing the phenyl moiety at the proximal ring position of dapagliflozin with 5-chloro-4-benzylthiophenyl moiety. These initial results are shown in Table 1. Substitution of 4-methoxy on the phenyl ring showed moderate activity (**71a**, IC_{50} = 86.5 nM). One more carbon homologation provided an improved activity (**71b**, IC_{50} = 34.6 nM), while further elongation at the position slightly decreased in vitro inhibitory activity against *h*SGLT2. Olefin, alkyne or oxygen-containing chains are tolerable at this position, but none of them appeared more potent than the simple ethoxy group. Replacement for the substituent with 4-hydroxy (**71c**, IC_{50} = 34.6 nM) reduced inhibitory activity against *h*SGLT2 in approximately fourfold, suggesting that acidic substituents may not be tolerated at this position. Replacement for the substituent with thiomethyl **71j** improved inhibitory activity against



Scheme 6. Preparation of pentaol-containing 2-chlorothiophene.



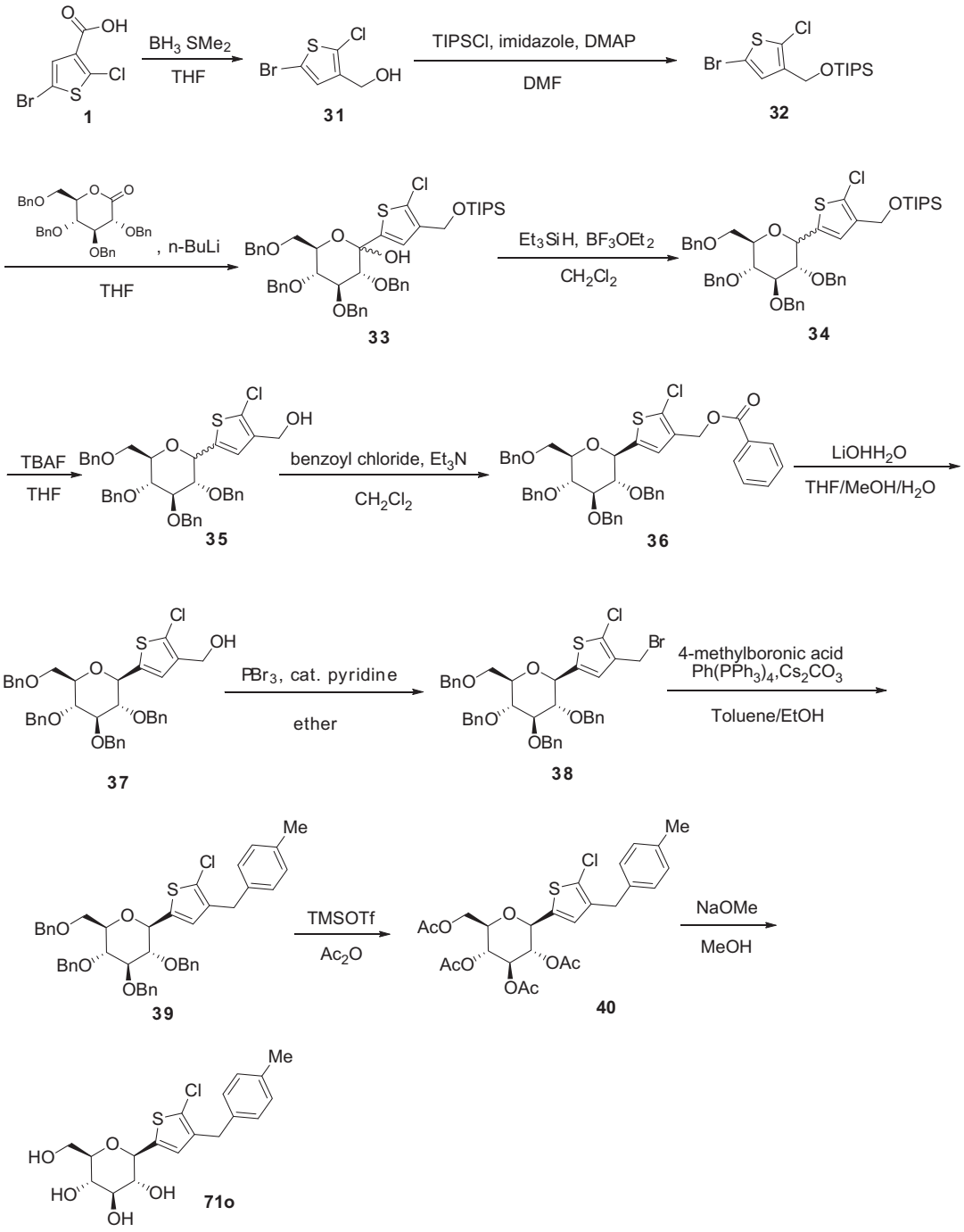
Scheme 7. Example of derivatization at phenol.

*h*SGLT2 in approximately threefold. However, homologated ethylsulfide **71k** lost inhibitory activity against *h*SGLT2 in fourfold. Branched alkoxides at this position were also tested. Interestingly, isopropoxy **71l** improved inhibitory activity against *h*SGLT2 in threefold (IC_{50} = 11.9 nM) than ethoxy **71b** (IC_{50} = 34.6 nM). However, cyclic moiety such as cyclopentyloxy (**71m**, IC_{50} = 57.2 nM) or tetrahydrofuran-3-yloxy (**71n**, IC_{50} = 162 nM) dropped activity in fivefold or even 15-fold, respectively, suggesting that simple branched chain is more appropriate than bulkier ring structure for this region. Introduction of an alkyl chain at the C-4 position of benzyl group demonstrated promising in vitro inhibitory activity against *h*SGLT2. Among benzylthiophenyl compounds thus tested, 4-ethylbenzylthiophene (**71p**, IC_{50} = 4.47 nM) turned out to be more active than the corresponding 4-methyl group (**71o**, IC_{50} = 60.2 nM) or 4-propyl group (**71q**, IC_{50} = 10.3 nM), implying the importance of appropriate lipophilicity for the region. On the other hand, diaryl-type **71r** in this series exhibited less favorable activity (**71r**, IC_{50} = 91.3 nM). Of note is that replacement of chlorine with methyl at the C-5 position of thiophene consistently improved inhibitory activity against *h*SGLT2 across the board (**71s**–**71w**) in approximately twofold to eightfold, respectively.

Table 2 shows the structure–activity consequences upon alternation of the substituents pattern at the proximal thiphenyl ring. Compounds bearing alkoxides at C-4 position of the distal benzyl ring were prepared and tested. These compounds showed only moderate *h*SGLT2 inhibitory activities (**72a**, IC_{50} = 71.4 nM; **72b**, IC_{50} = 68.9 nM). Subsequently, compounds with halogen or small aliphatic chains were prepared and tested. Either chloro **72c** (IC_{50} = 451 nM) or *t*-butyl **49** (IC_{50} = 88.3 nM) did not improve in vitro activity against *h*SGLT2. Among benzylthiophenyl compounds tested, 4-ethylbenzylthiophene (**72f**, IC_{50} = 24.8 nM) turned out to be more active than the corresponding 4-methyl group (**72e**, IC_{50} = 69.6 nM) or 4-propyl group (**72g**, IC_{50} = 59.8 nM). Since 4-ethylbenzylthiophenyl **72f** showed the favorable inhibitory activity against *h*SGLT2, exploration was driven around C-3 position of thiophene with maintaining 4-ethylbenzyl at the C-5 position of thiophenyl ring. Bromine at C-3 position of thiophene **72h** demonstrated twofold improvement in inhibitory activity against *h*SGLT2. Incorporation of methyl at C-3 position of thiophene **72i** resulted in similar level of inhibitory activity (IC_{50} = 29.3 nM), while methoxide at the particular position demonstrated twofold loss of inhibitory activity against *h*SGLT2 (**72i**, IC_{50} = 49.5 nM). Thus, the series of thiophenyl compounds in Table 2 appear to show slightly less inhibitory activity than the series in Table 1, indicating the importance of attachment position of substituents on the proximal thiophenyl ring.

3. Conclusion

In the present study, *C*-glucosides incorporating thiophenyl motif at the proximal ring position were exploited in order to



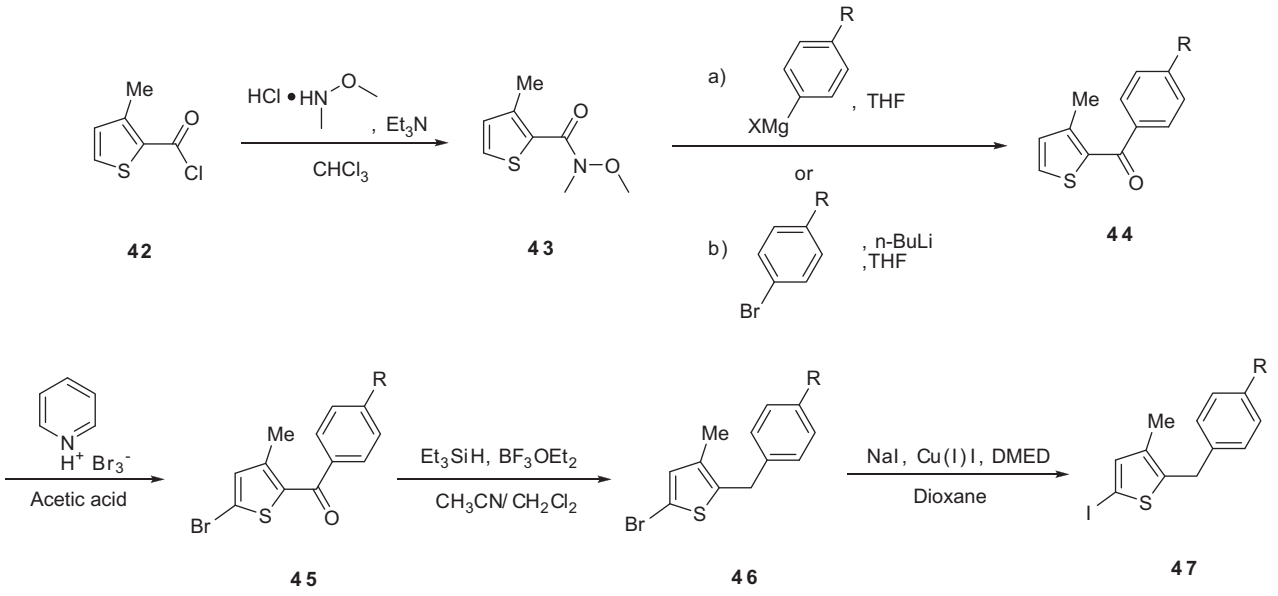
Scheme 8. Another route toward chlorothiophene-containing *C*-aryl glucoside.

discover and develop novel SGLT2 targeting antidiabetic agents. We envisioned that replacement of the proximal ring of dapagliflozin with a phenyl surrogate would be a worthy approach to modulate physicochemical property. Along the line, two series of novel *C*-aryl glucoside SGLT2 inhibitors containing thiophenyl ring at the proximal ring postion were designed and synthesized. Among the compounds tested, 5-chloro-4-(ethylbenzyl)thiophene **71p** showed the best in vitro inhibitory activities to date in this series (IC_{50} = 4.47 nM) against *h*SGLT2. Although this series of compounds failed to advance as a development candidate, the current chemistry shown in here allowed us to synthesize difficult, yet desirable targets in a relatively straightforward fashion.

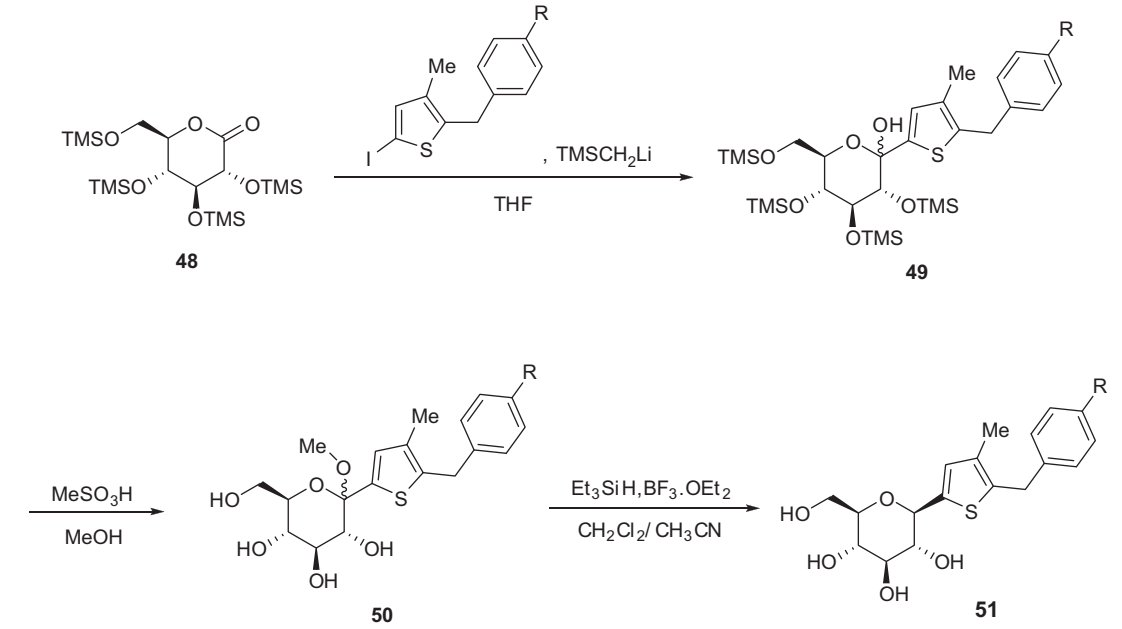
4. Experimental

4.1. General methods

All reactions are conducted under an inert atmosphere at room temperature, unless otherwise noted. All reagents were purchased at the highest commercial quality and used without further purification, unless otherwise indicated. Microwave reaction was conducted with a Biotage Initiator microwave reactor. NMR spectra were obtained on a Varian 400-MR (400 MHz ^{1}H) spectrometer. NMR spectra were recorded in ppm (δ) relative to tetramethylsilane (δ = 0.00) as an internal standard unless stated otherwise and



Scheme 9. Preparation of various 3-methylthiophene-2-carbonyl chloride.



Scheme 10. Preparation of *C*-aryl glucoside containing 3-methylthiophene.

are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, quint = quintet, sext = sextet, m = multiplet, and br = broad), coupling constant, and integration. Mass spectra were obtained with an Agilent 6110 quadruple LC-MSD (ESI+). Preparative HPLC purifications were performed on a Gilson® purification system. For preparative HPLC, ca. 100 mg of a product was injected in 1 mL of methanol onto a SunFire Prep C_{18} OBD 5 μm 30 × 100 mm Column with a 30 min gradient from 5 to 90% acetonitrile in water and a 45 mL/min flow rate. Biotage® SP1 and Isolera purification systems were used for normal phase column chromatography with ethyl acetate and hexane. Flash chromatography was performed using E. Merck 230–400 mesh silica gel according to the procedure of Still et al. Reactions were monitored by either thin-layer chromatography (TLC) on 0.25 mm E. Merck silica gel plates (60F-254) using UV light and *p*-anisaldehyde solution as visualizing agents or HPLC analysis on an Agilent 1200 series system.

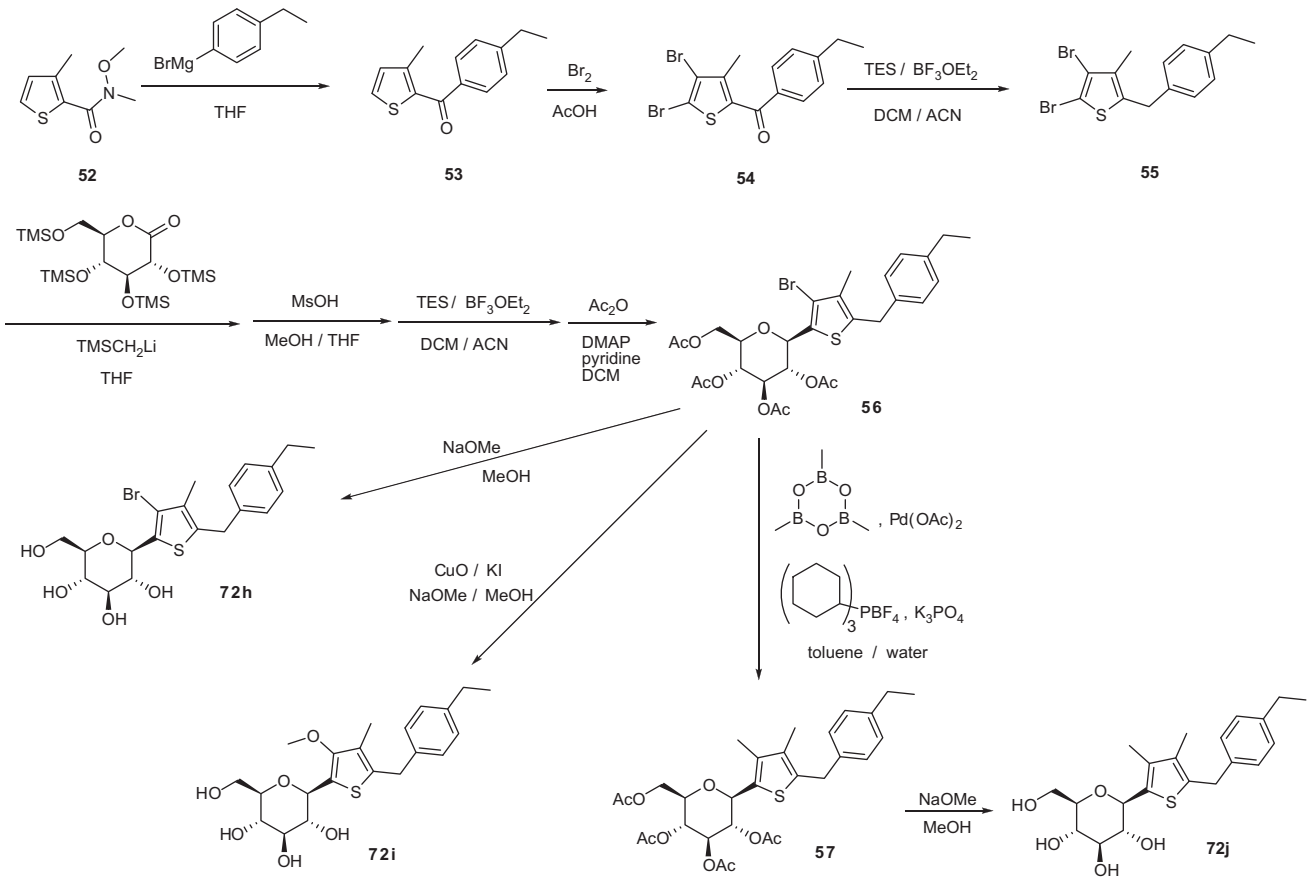
4.2. Chemistry

4.2.1. Synthesis of 5-bromo-2-chlorothiophene-3-carboxylic acid (1)

The title compound **1** was prepared from commercially available 2-chloro-3-methylthiophene according to the known procedure (US 5840917 A1).

4.2.2. Synthesis of (5-bromo-2-chlorothiophen-3-yl)(4-methoxyphenyl)methanone (2)

To a solution of acid **1** (2.0 g, 8.28 mmol) in CH_2Cl_2 (50 mL) were added oxalyl chloride (0.87 mL, 9.94 mmol) and catalytic amounts



Scheme 11. Alternative route toward *C*-aryl glucoside-containing 3-methylthiophene.

of DMF at room temperature. The mixture was stirred at room temperature for 3 h. The mixture was evaporated in vacuo and dried under high vacuum. The crude acid chloride was dissolved with CH_2Cl_2 (30 mL) and cooled to 0 °C. To the mixture was added anisole (0.9 mL, 8.28 mmol) at 0 °C and stirred at 0 °C for 5 min. To the reaction mixture was added $AlCl_3$ (1.2 g, 8.28 mmol) portionwise at 0 °C. The mixture was stirred at 0 °C for 30 min, warmed up to room temperature and stirred at room temperature for 15 h. The mixture was poured into ice-water and extracted with CH_2Cl_2 (50 mL × 2). The combined organic layer was dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by silica column chromatography (Biotage®) to provide the intermediate **2** (2.68 g, 98%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (d, J = 8.4 Hz, 2H), 7.01 (s, 1H), 6.96 (d, J = 8.4 Hz, 2H), 3.90 (s, 3H).

4.2.3. Synthesis of 5-bromo-2-chloro-3-(4-methoxybenzyl)-thiophene (3)

To a solution of methanone **2** (2.68 g, 8.08 mmol) in CH_2Cl_2/CH_3CN (20:20 mL) were added triethylsilane (3.9 mL, 24.2 mmol) and boron trifluoride diethyl etherate (3.1 mL, 24.2 mmol) at 0 °C. The mixture was warmed up to room temperature slowly and stirred at room temperature for 15 h. To the mixture was added aq saturated K_2CO_3 solution (50 mL) slowly and extracted with EtOAc (50 mL × 2). The combined organic layer was dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by silica column chromatography (Biotage®) to provide the desired product **3** (2.09 g, 82%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.09 (d, J = 8.0 Hz, 2H), 6.83 (d, J = 8.0 Hz, 2H), 6.66 (s, 1H), 3.80 (s, 2H), 3.78 (s, 3H).

4.2.4. Synthesis of 4-((5-bromo-2-chlorothiophen-3-yl)methyl)-phenol (4)

To a solution of thiophene **3** (5.44 g, 17.1 mmol) in CH_2Cl_2 (50 mL) was added boron tribromide (20 mL, 1 M in CH_2Cl_2) at 0 °C. The mixture was warmed up to room temperature slowly and stirred at room temperature for 3 h. To the mixture was added aq 1 N HCl solution (35 mL) dropwise at 0 °C and H_2O was added to the mixture. The mixture was extracted with EtOAc (50 mL × 2). The combined organic layer was dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude product **4** was dried under high vacuum and used without further purification (5.1 g, 99%).

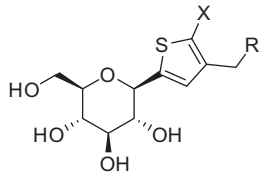
4.2.5. Synthesis of 5-bromo-2-chloro-3-(4-propoxybenzyl)-thiophene (5)

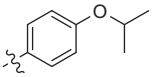
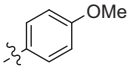
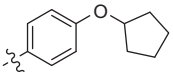
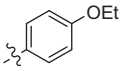
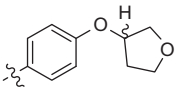
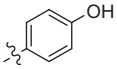
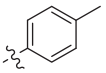
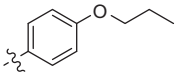
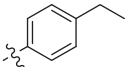
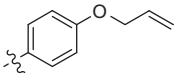
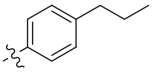
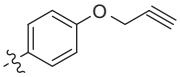
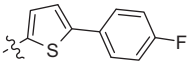
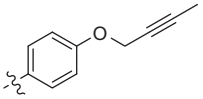
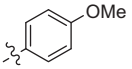
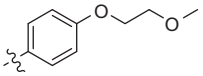
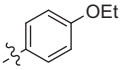
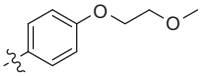
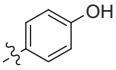
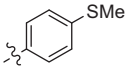
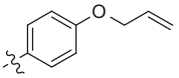
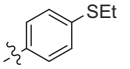
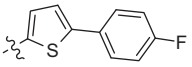
To a solution of phenol **4** (500 mg, 1.65 mmol) in acetone (25 mL) were added 1-iodopropane (0.5 mL, 4.95 mmol) and Cs_2CO_3 (460 mg, 4.95 mmol) at room temperature. The mixture was stirred at 60 °C for 12 h. The reaction mixture was cooled to room temperature and filtered off through celite®. The filtrate was concentrated in vacuo. The residue was purified by silica column chromatography (Biotage®) to provide the intermediate **5** (600 mg, 99%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.06 (d, J = 8.0 Hz, 2H), 6.84 (d, J = 8.0 Hz, 2H), 6.66 (s, 1H), 3.89 (t, J = 6.8 Hz, 2H), 3.79 (s, 2H), 1.79 (sextet, J = 7.2 Hz, 2H), 1.03 (t, J = 7.2 Hz, 3H).

4.2.6. Synthesis of 5-bromo-2-chloro-3-(4-isopropoxybenzyl)-thiophene (6)

To a solution of phenol **4** (1 g, 3.29 mmol) and PPh_3 (1.8 g, 6.58 mmol) in THF (25 mL) was added DIAD (1.3 mL, 6.58 mmol) at room temperature. The mixture was stirred at room

Table 1
In vitro inhibitory activity against *h*SGLT2



Compound	X	R	*h*SGLT2[a] IC_{50} (nM)	Compound	X	R	*h*SGLT2[a] IC_{50} (nM)
Dapagliflozine			0.49 ± 0.04[b]	**71l**	Cl		11.9
71a	Cl		86.5	**71m**	Cl		57.2
71b	Cl		34.6	**71n**	Cl		162
71c	Cl		140	**71o**	Cl		60.2
71d	Cl		65.0	**71p**	Cl		4.47
71e	Cl		54.6	**71q**	Cl		10.3
71f	Cl		111	**71r**	Cl		91.3
71g	Cl		94	**71s**	Me		11.5
71h	Cl		115	**71t**	Me		8.73
71i	Cl		70.7	**71u**	Me		50.2
71j	Cl		12.8	**71v**	Me		27.5
71k	Cl		48.4	**71w**	Me		21.1

[a] These data were determined by single determination.
[b] The IC_{50} value was obtained by in-house multiple determinations.

temperature for 30 min. 2-Propanol (0.4 mL, 4.94 mmol) was added to the reaction mixture. The reaction mixture was stirred at room temperature for 20 h. The mixture was extracted with EtOAc/H_2O (50:50 mL) and was dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by silica column chromatography (Biotage®) to provide the desired product **6** (913 mg, 80%). ^1H NMR (400 MHz, $CDCl_3$) δ 7.06 (d, J = 8.4 Hz, 2H), 6.81 (d, J = 8.4 Hz, 2H), 6.67 (s, 1H), 4.54–4.47 (m, 1H), 3.79 (s, 2H), 1.38 (d, J = 6.0 Hz, 6H).

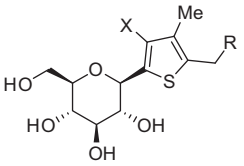
4.2.7. Synthesis of 5-bromo-2-methylthiophene-3-carboxylic acid (8)

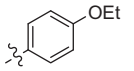
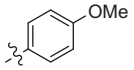
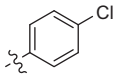
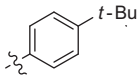
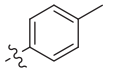
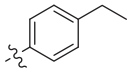
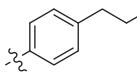
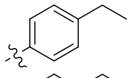
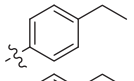
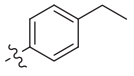
To a solution of 2-methylthiophene-3-carboxylic acid (2.44 g, 17.2 mmol, prepared from commercially available thiophene-3-carboxylic acid according to the known procedure (US 5840917 A1)) was added pyridium tribromide (6.3 g) in AcOH (30 mL) at room temperature. The mixture was stirred at 40 °C for 4 h. The mixture was cooled to room temperature and poured into H_2O (350 mL) with stirring. The product was precipitated and the suspension was stirred at room temperature for 1 h. The precipitated solid was filtered, washed with H_2O (500 mL) and dried under high vacuum at 45 °C. The crude product was used without further purification (3.18 g, 84%). ^1H NMR (400 MHz, $CDCl_3$) δ 7.38 (s, 1H), 2.70 (s, 3H); MS calcd for $C_6H_5BrO_2S$ (MW 221.07), found $[M+H]^+$ 221.

4.2.8. Synthesis of (5-bromo-2-methylthiophen-3-yl)(4-methoxyphenyl)methanone (9)

To a solution of acid **8** (10 g, 45.2 mmol) in CH_2Cl_2 (200 mL) were added oxalyl chloride (4.8 mL, 54.3 mmol) and catalytic amounts of DMF at room temperature. The mixture was stirred at room temperature for 2 h. The mixture was concentrated in vacuo and dried under high vacuum. The crude acid chloride was dissolved with CH_2Cl_2 (200 mL) and cooled to 0 °C. To the mixture was added anisole (5.0 mL, 45.2 mmol) at 0 °C and stirred at 0 °C for

Table 2
In vitro inhibitory activity against *h*SGLT2



Compound	X	R	*h*SGLT2[a] IC_{50} (nM)
Dapagliflozine			0.49 ± 0.04[b]
72a	H		71.4
72b	H		68.9
72c	H		451
72d	H		88.3
72e	H		69.6
72f	H		24.8
72g	H		59.8
72h	Br		12.4
72i	OMe		49.5
72j	Me		29.3

[a] These data were determined by single determination.
[b] The IC_{50} value was obtained by in-house multiple determinations.

5 min. To the reaction mixture was added $AlCl_3$ (6.0 g, 45.2 mmol) portionwise at 0 °C. The mixture was stirred at 0 °C for 2 h, warmed up to room temperature and stirred at room temperature for 15 h. The mixture was poured into ice-water and extracted with CH_2Cl_2 (100 mL × 2). The combined organic layer was dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude product was tritulated with MeOH (100 mL) and stirred at 0 °C for 1 h. The precipitated solid was filtered and washed with MeOH (50 mL). The solid was dried under high vacuum and used without further purification (11.7 g, 83%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (d, J = 6.8 Hz, 2H), 7.26 (s, 1H), 6.95 (d, J = 6.8 Hz, 2H), 3.88 (s, 3H), 2.53 (s, 3H); MS calcd for $C_{13}H_{11}BrO_2S$ (MW 311.19), found $[M+H]^+$ 311.

4.2.9. Synthesis of 5-bromo-3-(4-methoxybenzyl)-2-methylthiophene (10)

To a solution of methanone **9** (11.7 g, 37.6 mmol) in CH_2Cl_2/CH_3CN (90:90 mL) were added triethylsilane (15.0 mL, 94.0 mmol) and boron trifluoride diethyl etherate (12.0 mL, 94.0 mmol) at 0 °C. The mixture was warmed up to room temperature slowly and stirred at room temperature for 15 h. To the mixture was added aq saturated K_2CO_3 solution (100 mL) slowly and extracted with EtOAc (100 mL × 2). The combined organic layer was dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by silica column chromatography (Biotage®) to provide the desired product **10** (11.2 g, 100%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.03 (d, J = 8.8 Hz, 2H), 6.83 (d, J = 8.8 Hz, 2H), 3.78 (s, 3H), 3.74 (s, 2H), 2.31 (s, 2H).

4.2.10. Synthesis of 5-iodo-3-(4-methoxybenzyl)-2-methylthiophene (11)

To a solution of bromide **10** (1.5 g, 5.05 mmol) in 1.4-dioxane (10 mL) were added NaI (1.5 g, 10.1 mmol), CuI (0.1 g, 0.51 mmol) and N^1,N^2-dimethylethane-1,2-diamine (0.11 mL, 1.01 mmol) at room temperature. The reaction mixture was evacuated and backfilled with nitrogen. The mixture was stirred 120 °C for 18 h. The mixture was cooled to room temperature and filtered off through Celite. The filtrate was extracted with EtOAc/H_2O (50:50 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude product **11** was dried under high vacuum and used without further purification (2.32 g, 79%).

4.2.11. Synthesis of 4-((5-bromo-2-methylthiophen-3-yl)-methyl)phenol (12)

To a solution of bromide **10** (9.7 g, 32.6 mmol) in CH_2Cl_2 (100 mL) was added boron tribromide (40 mL, 39.2 mmol, 1 M in CH_2Cl_2) dropwise at 0 °C. The mixture was warmed up to room temperature slowly and stirred at room temperature for 3 h. To the mixture was added aq. 1 N HCl solution (200 mL) dropwise at 0 °C. The mixture was extracted with CH_2Cl_2 (150 mL × 2). The combined organic layer was dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by silica column chromatography (Biotage®) to provide the desired product **12** (5.64 g, 61%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.99 (d, J = 6.0 Hz, 2H), 6.75 (d, J = 6.0 Hz, 1H), 6.65 (s, 1H), 4.73 (s, 1H), 3.73 (s, 2H), 2.31 (s, 3H).

4.2.12. Synthesis of 3-(4-(allyloxy)benzyl)-5-bromo-2-methylthiophene (13)

To a solution of phenol **12** (860 mg, 3.04 mmol) in acetone (20 mL) were added allyl bromide (0.5 mL, 4.56 mmol) and Cs_2CO_3 (2.0 g, 6.08 mmol) at room temperature. The mixture was stirred at 60 °C for 2 h. The reaction mixture was cooled to room temperature and filtered off through celite. The filtrate was concentrated in vacuo. The residue was purified by silica column chromatography (Biotage®) to provide the intermediate **13** (906 mg, 92%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.07 (d, J = 8.4 Hz, 2H), 6.85 (d, J = 8.4 Hz, 2H), 6.19–5.99 (m, 1H), 5.40 (doublet and doublet, J = 17.2, 1.6 Hz, 1H), 5.27 (doublet and doublet, J = 10.8, 1.2 Hz, 1H), 4.51 (d, J = 5.2 Hz, 2H), 3.80 (s, 2H), 2.31 (s, 3H).

4.2.13. Synthesis of 5-iodo-3-(4-methoxybenzyl)-2-methylthiophene (14)

To a solution of bromide **13** (906 mg, 2.80 mmol) in 1.4-dioxane (10 mL) were added NaI (841 mg, 5.61 mmol), CuI (54 mg, 0.28 mmol) and N^1,N^2-dimethylethane-1,2-diamine (0.06 mL, 0.56 mmol) at room temperature. The reaction mixture was evacuated and backfilled with nitrogen. The mixture was stirred 120 °C for 18 h. The mixture was cooled to room temperature and filtered off through Celite®. The filtrate was extracted with EtOAc/H_2O (50:50 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude product **14** was dried under high vacuum and used without further purification (846 mg, 81%).

4.2.14. Synthesis of (3*R*,4*S*,5*R*,6*R*)-2-(5-chloro-4-(4-methoxybenzyl)thiophen-2-yl)-3,4,5-tris(trimethylsilyloxy)-6-((trimethylsilyloxy)methyl)-tetrahydro-2*H*-pyran-2-ol (15)

To a solution of bromide **3** (2.09 g, 5.06 mmol) in toluene/THF (30:15 mL) at −78 °C under an atmosphere of nitrogen was added dropwise *n*-butyllithium (2.5 M in hexanes, 2.6 mL, 6.58 mmol), and the mixture was stirred for 40 min at the same temperature. Then a solution of TMS-protected gluconolactone (2.4 g,

6.58 mmol) in toluene (20 mL) was added dropwise, and the mixture was stirred for 1 h at the same temperature. The reaction mixture was quenched by addition of saturated ammonium chloride. After complete addition, the solution was gradually raised to room temperature. The organic layer was separated and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated in vacuo to yield the title compound **15**, which was carried on to the next step without further purification.

4.2.15. Synthesis of (3*R*,4*S*,5*R*,6*R*)-2-(4-(4-methoxybenzyl)-5-methylthiophen-2-yl)-3,4,5-tris(trimethylsilyloxy)-6-((trimethylsilyloxy)methyl)-tetrahydro-2*H*-pyran-2-ol (16)

A mixture of TMS-protected gluconolactone (2.6 g, 5.47 mmol) and iodide **11** (1.57 g, 4.56 mmol) in THF (30 mL) was added trimethylsilylmethyl lithium (1.0 M in pentane, 9.6 mL, 9.58 mmol) at −65 °C. The mixture was allowed to slowly warm to −45 °C over 2 h. To a mixture was added aq saturated $NaHCO_3$ solution to quench the reaction. After dilution with water, the mixture was stirred at room temperature for 30 min and extracted with EtOAc. The organic layer was dried over anhydrous $MgSO_4$, filtered and concentrated in vacuo. The crude title compound **16** was carried on to the next step without further purification.

4.2.16. Synthesis of (2*R*,3*R*,4*S*,5*R*,6*R*)-2-(acetoxymethyl)-6-(5-chloro-4-(4-methoxybenzyl)thiophen-2-yl)-tetrahydro-2*H*-pyran-3,4,5-triyl triacetate (19)

Step 1: To a solution of crude alcohol **15** (3.57 g, 5.06 mmol) in THF (50 mL) were added CH_3SO_3H (0.6 N in MeOH, 17 mL, 10.1 mmol) at −78 °C. The mixture was allowed to slowly warm to −40 °C. To a mixture was added aq saturated $NaHCO_3$ solution (50 mL) to quench the reaction. After dilution with water, the mixture was stirred at room temperature for 30 min and extracted with EtOAc (100 mL). The organic layer was dried over anhydrous $MgSO_4$, filtered and concentrated in vacuo. The crude (3*R*,4*S*,5*S*,6*R*)-2-(5-chloro-4-(4-methoxybenzyl)thiophen-2-yl)-6-(hydroxymethyl)-2-methoxy-tetrahydro-2*H*-pyran-3,4,5-triol (**17**) (2.43 g) was carried on to the next step without further purification.

Step 2: To a solution of compound **17** (2.43 g) in CH_2Cl_2/CH_3CN (25:25 mL) were added triethylsilane (1.8 mL, 11.3 mmol) and boron trifluoride diethyl etherate (1.5 mL, 11.3 mmol) at −60 °C. The mixture was allowed to slowly warm to −5 °C. To a mixture was added aq saturated $NaHCO_3$ solution (20 mL) to quench the reaction and extracted with EtOAc (100 mL). The combined organic layer was dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude (3*R*,4*S*,5*S*,6*R*)-2-(5-chloro-4-(4-methoxybenzyl)thiophen-2-yl)-6-(hydroxymethyl)-2-methoxy-tetrahydro-2H-pyran-3,4,5-triol (**18**) (2.17 g) was carried on to the next step without further purification.

Step 3: To a solution of compound **18** (2.17 g) in CH_2Cl_2 (50 mL) were added Ac_2O (5.1 mL, 54.1 mmol), Et_3N (7.5 mL, 54.1 mmol) and catalytic amount of DMAP at 0 °C. The mixture was stirred at 0 °C for 15 min and at room temperature for 15 h. The mixture was concentrated under reduced pressure to remove volatiles. The residue was diluted with EtOAc (50 mL), washed with H_2O (100 mL), aq 1 N HCl solution (100 mL) and brine (100 mL) successively. The organic layer was dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by silica column chromatography (Biotage®) to provide the mixture of beta and alpha anomers of the titled compound **19** (1.9 g). The anomeric mixture of **19** was recrystallized with EtOH (50 mL). The precipitate was collected by filtration and washed with cold EtOH (30 mL) and dried under high vacuum to obtain the title compound **19** (1.37 g, 48% (5-steps)). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.05 (d, J = 8.8 Hz, 2H), 7.82 (d, J = 8.8 Hz, 2H), 6.57 (s, 1H), 5.27–5.12 (m, 2H), 5.04 (t, J = 9.6 Hz, 1H), 4.50 (d, J = 9.6 Hz, 1H), 4.27–4.13 (m, 2H), 3.83–3.71 (m, 6H), 2.08 (s, 3H), 2.03 (s, 3H), 1.99 (s, 3H), 1.78 (s, 3H); MS calcd for $C_{26}H_{29}ClO_{10}S$ (MW 569.02), found $[M+Na]^+$ 591.

4.2.17. Synthesis of (2*R*,3*R*,4*S*,5*S*,6*R*)-2-(5-chloro-4-(4-methoxybenzyl)thiophen-2-yl)-6-(hydroxymethyl)-tetrahydro-2*H*-pyran-3,4,5-triol (71a)

To a suspension of acetate **19** (1.37 g, 2.41 mmol) in MeOH (20 mL) was added NaOMe (25 wt % in MeOH, 0.3 mL) at room temperature. The mixture was stirred at room temperature for 1 h. Glacial AcOH was added to the mixture to acidify the mixture. The mixture was concentrated under reduced pressure. The residue was purified by prep HPLC (C_{18}) to provide the title compound **71a** (604 mg, 63%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.13 (d, J = 8.4 Hz, 2H), 6.86 (d, J = 8.4 Hz, 2H), 6.82 (s, 1H), 5.18 (d, J = 6.0 Hz, 1H), 4.99 (d, J = 5.2 Hz, 1H), 4.94 (d, J = 5.6 Hz, 1H), 4.46 (t, J = 6.0 Hz, 1H), 4.17 (d, J = 9.2 Hz, 1H), 3.77 (s, 2H), 3.73–3.63 (m, 4H), 3.40 (quintet, J = 6.0 Hz, 1H), 3.27–3.16 (m, 2H), 3.11–3.01 (m, 2H); MS calcd for $C_{18}H_{21}ClO_6S$ (MW 400.87), found $[M+Na]^+$ 423.

4.2.18. (2*R*,3*R*,4*S*,5*S*,6*R*)-2-(5-Chloro-4-(4-ethoxybenzyl)thiophen-2-yl)-6-(hydroxymethyl)-tetrahydro-2H-pyran-3,4,5-triol (71b)

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.11 (d, J = 8.8 Hz, 2H), 6.86–6.81 (m, 3H), 5.18 (d, J = 5.6 Hz, 1H), 4.99 (d, J = 5.2 Hz, 1H), 4.94 (d, J = 5.2 Hz, 1H), 4.46 (t, J = 5.6 Hz, 1H), 4.17 (d, J = 9.6 Hz, 1H), 3.98 (quartet, J = 7.2 Hz, 2H), 3.77 (s, 2H), 3.71–3.63 (m, 1H), 3.40 (quintet, J = 6.0 Hz, 1H), 3.26–3.17 (m, 2H), 3.11–3.02 (m, 2H), 1.30 (t, J = 7.2 Hz, 3H); MS calcd for $C_{19}H_{23}ClO_6S$ (MW 414.09), found $[M+Na]^+$ 437.

4.2.19. (2*R*,3*R*,4*S*,5*S*,6*R*)-2-(5-Chloro-4-(4-(methylthio)benzyl)-thiophen-2-yl)-6-(hydroxymethyl)-tetrahydro-2*H*-pyran-3,4,5-triol (71j)

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.23–7.14 (m, 4H), 6.84 (s, 1H), 5.19 (d, J = 5.6 Hz, 1H), 4.99 (d, J = 5.2 Hz, 1H), 4.94 (d, J = 5.2 Hz, 1H), 4.45 (t, J = 6.0 Hz, 1H), 4.17 (d, J = 9.2 Hz, 1H), 3.81 (s, 2H), 3.72–3.63 (m, 1H), 3.40 (quintet, J = 6.0 Hz, 1H), 3.25–3.16 (m, 2H), 3.11–3.01 (m, 2H), 2.43 (s, 3H); MS calcd for $C_{18}H_{21}ClO_5S_2$ (MW 416.94), found $[M+Na]^+$ 439.

4.2.20. (2*R*,3*R*,4*S*,5*S*,6*R*)-2-(5-Chloro-4-(4-(ethylthio)benzyl)thiophen-2-yl)-6-(hydroxymethyl)-tetrahydro-2*H*-pyran-3,4,5-triol (71k)

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.25 (d, J = 8.0 Hz, 2H), 7.16 (d, J = 8.0 Hz, 2H), 6.85 (s, 1H), 5.20 (d, J = 6.0 Hz, 1H), 5.06–4.91 (m, 2H), 4.46 (t, J = 5.6 Hz, 1H), 4.18 (d, J = 9.6 Hz, 1H), 3.81 (s, 2H), 3.71–3.63 (m, 1H), 3.40 (quintet, J = 6.0 Hz, 1H), 3.26–3.17 (m, 2H), 3.12–3.02 (m, 2H), 2.93 (quartet, J = 7.2 Hz, 2H), 2.93 (t, J = 7.2 Hz, 3H); MS calcd for $C_{19}H_{23}ClO_5S_2$ (MW 430.97), found $[M+Na]^+$ 453.

4.2.21. (2*R*,3*R*,4*S*,5*S*,6*R*)-2-(5-Chloro-4-(4-isopropoxybenzyl)-thiophen-2-yl)-6-(hydroxymethyl)-tetrahydro-2*H*-pyran-3,4,5-triol (71l)

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.10 (d, J = 8.4 Hz, 2H), 6.86–6.79 (m, 3H), 5.18 (d, J = 6.0 Hz, 1H), 4.99 (d, J = 6.0 Hz, 1H), 4.94 (d, J = 5.6 Hz, 1H), 4.54 (septet, J = 6.0 Hz, 1H), 4.46 (t, J = 6.0 Hz, 1H), 4.17 (d, J = 9.2 Hz, 1H), 3.76 (s, 2H), 3.71–3.63 (m, 1H), 3.40 (quintet, J = 6.0 Hz, 1H), 3.26–3.17 (m, 2H), 3.13–3.03 (m, 2H), 1.23 (d, J = 6.0 Hz, 6H); MS calcd for $C_{20}H_{25}ClO_6S$ (MW 428.93), found $[M+Na]^+$ 451.

4.2.22. (2*R*,3*R*,4*S*,5*S*,6*R*)-2-(5-Chloro-4-(4-(cyclopentyloxy)-benzyl)thiophen-2-yl)-6-(hydroxymethyl)-tetrahydro-2*H*-pyran-3,4,5-triol (71m)

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.10 (d, J = 8.8 Hz, 2H), 6.82 (d, J = 8.8 Hz, 2H), 6.79 (s, 1H), 5.18 (d, J = 5.6 Hz, 1H), 4.99 (d, J = 4.8 Hz, 1H), 4.94 (d, J = 5.2 Hz, 1H), 4.75 (quintet, J = 6.0 Hz, 1H), 4.45 (t, J = 6.0 Hz, 1H), 4.17 (d, J = 9.2 Hz, 1H), 3.76 (s, 2H), 3.70–3.54 (m, 1H), 3.39 (quintet, J = 6.0 Hz, 1H), 3.26–3.17 (m, 2H), 3.13–3.03 (m, 2H), 1.94–1.82 (m, 2H), 1.73–1.63 (m, 4H), 1.61–1.52 (m, 2H); MS calcd for $C_{22}H_{27}ClO_6S$ (MW 454.96), found [M+Na]$^+$ 477.

4.2.23. (2*R*,3*R*,4*S*,5*S*,6*R*)-2-(5-Chloro-4-(4-(tetrahydrofuran-3-yloxy)benzyl)thiophen-2-yl)-6-(hydroxymethyl)-tetrahydro-2*H*-pyran-3,4,5-triol (71n)

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.12 (d, J = 8.4 Hz, 2H), 6.87–6.79 (m, 3H), 5.18 (d, J = 5.2 Hz, 1H), 5.02–4.91 (m, 2H), 4.45 (t, J = 5.2 Hz, 1H), 4.17 (t, J = 9.6 Hz, 1H), 3.88–3.63 (m, 8H), 3.40 (quintet, J = 6.0 Hz, 1H), 3.26–3.17 (m, 2H), 3.12–3.01 (m, 2H), 2.23–2.12 (m, 1H), 1.98–1.88 (m, 1H); MS calcd for $C_{21}H_{25}ClO_7S$ (MW 456.94), found [M+Na]$^+$ 479.

4.2.24. (2*R*,3*R*,4*S*,5*S*,6*R*)-2-(5-Chloro-4-((5-(4-fluorophenyl)thiophen-2-yl)methyl)thiophen-2-yl)-6-(hydroxymethyl)-tetrahydro-2*H*-pyran-3,4,5-triol (71r)

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.65–7.57 (m, 2H), 7.29 (d, J = 3.6 Hz, 1H), 7.25–7.18 (m, 2H), 6.95 (s, 1H), 6.90 (d, J = 3.2 Hz, 1H), 5.23 (d, J = 5.2 Hz, 1H), 5.01 (d, J = 4.8 Hz, 1H), 4.96 (d, J = 4.8 Hz, 1H), 4.47 (t, J = 6.0 Hz, 1H), 4.21 (d, J = 9.2 Hz, 1H), 4.05 (s, 2H), 3.74–3.65 (m, 1H), 3.47–3.35 (m, 1H), 3.28–3.18 (m, 2H), 3.15–3.03 (m, 2H); MS calcd for $C_{21}H_{20}ClFO_5S_2$ (MW 470.96), found [M+Na]$^+$ 493.

4.2.25. (2*R*,3*S*,4*S*,5*R*,6*R*)-2-(Hydroxymethyl)-6-(4-(4-methoxybenzyl)-5-methylthiophen-2-yl)-tetrahydro-2*H*-pyran-3,4,5-triol (71s)

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.09 (d, J = 8.4 Hz, 2H), 6.83 (d, J = 8.4 Hz, 2H), 6.69 (s, 1H), 4.95–4.87 (m, 3H), 4.42 (t, J = 5.6 Hz, 1H), 4.12 (d, J = 9.2 Hz, 1H), 3.73–3.62 (m, 6H), 3.39 (quintet, J = 6.0 Hz, 1H), 3.23–3.13 (m, 2H), 3.12–3.03 (m, 2H), 2.33 (s, 3H); MS calcd for $C_{19}H_{24}O_6S$ (MW 380.46), found [M+Na]$^+$ 403.

4.2.26. (2*R*,3*R*,4*S*,5*S*,6*R*)-2-(4-(4-Ethoxybenzyl)-5-methylthiophen-2-yl)-6-(hydroxymethyl)-tetrahydro-2*H*-pyran-3,4,5-triol (71t)

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.07 (d, J = 8.4 Hz, 2H), 6.83 (d, J = 8.4 Hz, 2H), 6.69 (s, 1H), 4.94–4.87 (m, 3H), 4.43 (t, J = 6.0 Hz, 1H), 4.12 (d, J = 9.2 Hz, 1H), 3.96 (quartet, J = 7.2 Hz, 2H), 3.68 (s, 2H), 3.65 (quartet and doublet, J = 5.6, 1.6 Hz, 1H), 3.40 (quintet, J = 6.0 Hz, 1H), 3.23–3.14 (m, 2H), 3.13–3.05 (m, 2H), 2.32 (s, 3H), 1.29 (t, J = 7.2 Hz, 3H); MS calcd for $C_{20}H_{26}O_6S$ (MW 394.48), found [M+Na]$^+$ 417.

4.2.27. (2*R*,3*R*,4*S*,5*S*,6*R*)-2-(4-((5-(4-fluorophenyl)thiophen-2-yl)methyl)-5-methylthiophen-2-yl)-6-(hydroxymethyl)-tetrahydro-2*H*-pyran-3,4,5-triol (71w)

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.63–7.56 (m, 2H), 7.27 (d, J = 3.2 Hz, 1H), 7.24–7.17 (m, 2H), 6.86 (d, J = 3.6 Hz, 1H), 6.82 (s, 1H), 4.96 (d, J = 6.0 Hz, 1H), 4.94 (d, J = 4.8 Hz, 1H), 4.90 (d, J = 5.2 Hz, 1H), 4.43 (t, J = 5.6 Hz, 1H), 4.16 (d, J = 9.2 Hz, 1H), 4.00 (s, 2H), 3.66 (quartet and doublet, J = 5.6, 1.6 Hz, 1H), 3.39 (quintet, J = 6.0 Hz, 1H), 3.25–3.17 (m, 2H), 3.15–3.05 (m, 2H), 2.36 (s, 3H); MS calcd for $C_{22}H_{23}FO_5S_2$ (MW 450.54), found m/z [M+Na]$^+$ 473.

4.2.28. Synthesis of (4-((5-bromo-2-chlorothiophen-3-yl)-methyl)phenoxy)(*tert*-butyl)dimethylsilane (21)

To a solution of phenol **4** (3.0 g, 9.88 mmol) in DMF (20 mL) were added TBDMSCl (1 M in CH_2Cl_2, 20 mL, 19.8 mmol), imidazole (2.1 g, 29.6 mmol) and DMAP (0.25 g, 1.98 mmol) at room temperature. The mixture was stirred at ambient temperature for 14 h. The mixture was extracted with EtOAc/H_2O (75:250 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by silica column chromatography (Biotage®) to provide the title compound **21** (4.12 g, 99%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.99–6.91 (m, 2H), 6.83 (s, 1H), 6.81–6.72 (m, 2H), 3.64 (s, 2H), 0.96 (s, 9H), 0.15 (s, 6H).

4.2.29. Synthesis of (3*R*,4*S*,5*R*,6*R*)-2-(4-(4-(*tert*-butyldimethylsilyloxy)benzyl)-5-chlorothiophen-2-yl)-3,4,5-tris(trimethylsilyloxy)-6-((trimethylsilyloxy)methyl)-tetrahydro-2*H*-pyran-2-ol (22)

To a solution of bromide **22** (4.12 g, 9.86 mmol) in toluene/THF (40:20 mL) at −78 °C under an atmosphere of nitrogen was added dropwise *n*-butyllithium (2.5 M in hexanes, 4.0 mL, 9.86 mmol), and the mixture was stirred for 45 min at the same temperature. Then a solution of TMS-protected gluconolactone (3.8 g, 8.22 mmol) in toluene (20 mL) was added dropwise, and the mixture was stirred for 1 h at the same temperature. The reaction mixture was quenched by addition of saturated ammonium chloride. After complete addition, the solution was gradually raised to room temperature. The organic layer was separated and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated in vacuo to yield the title compound **15**, which was carried on to the next step without further purification.

4.2.30. Synthesis of 4-((5-iodo-2-methylthiophen-3-yl)methyl)-phenol (23)

To a solution of bromide **12** (960 mg, 3.39 mmol) in 1.4-dioxane (10 mL) were added NaI (1.1 g, 6.78 mmol), CuI (100 mg, 0.34 mmol) and N^1,N^2-dimethylethane-1,2-diamine (0.1 mL, 0.68 mmol) at room temperature. The reaction mixture was evacuated and backfilled with nitrogen. The mixture was stirred 120 °C for 18 h. The mixture was cooled to room temperature and filtered off through celite®. The filtrate was extracted with EtOAc/H_2O (50:50 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude product **23** was dried under high vacuum and used without further purification (540 mg, 48%).

4.2.31. Synthesis of *tert*-butyl(4-((5-iodo-2-methylthiophen-3-yl)methyl)phenoxy)dimethylsilane (24)

To a solution of phenol **23** (0.54 g, 1.64 mmol) in DMF (15 mL) were added TBDMSCl (1 M in CH_2Cl_2, 3.5 mL, 3.28 mmol), imidazole (0.35 g, 4.92 mmol) and DMAP (50 mg, 0.33 mmol) at room temperature. The mixture was stirred at ambient temperature for 15 h. The mixture was extracted with EtOAc/H_2O (50:150 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by silica column chromatography (Biotage®) to provide the title compound **24** (0.65 g, 89%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.00–6.91 (m, 2H), 6.83 (s, 1H), 6.77–6.71 (m, 2H), 3.75 (s, 2H), 2.34 (s, 3H), 0.97 (s, 9H), 0.17 (s, 6H).

4.2.32. Synthesis of (3*R*,4*S*,5*R*,6*R*)-2-(4-(4-(*tert*-butyldimethylsilyloxy)benzyl)-5-methylthiophen-2-yl)-3,4,5-tris(trimethylsilyloxy)-6-((trimethylsilyloxy)methyl)-tetrahydro-2*H*-pyran-2-ol (25)

A mixture of TMS-protected gluconolactone (0.65 g, 1.46 mmol) and iodide **24** (0.82 g, 1.75 mmol) in THF (20 mL) was added trimethylsilylmethyl lithium (1.0 M in pentane, 3.1 mL, 3.07 mmol)

at −65 °C. The mixture was allowed to slowly warm to −45 °C over 1 h. To a mixture was added aq saturated $NaHCO_3$ solution to quench the reaction. After dilution with water, the mixture was stirred at room temperature for 30 min and extracted with EtOAc. The organic layer was dried over anhydrous $MgSO_4$, filtered and concentrated in vacuo. The crude title compound **25** was carried on to the next step without further purification.

4.2.33. Synthesis of (2*R*,3*R*,4*S*,5*R*,6*R*)-2-(4-(4-acetoxybenzyl)-5-chlorothiophen-2-yl)-6-(acetoxymethyl)-tetrahydro-2*H*-pyran-3,4,5-triyl triacetate (28)

Step 1: To a solution of crude alcohol **22** (1.51 g, 1.88 mmol) in THF (50 mL) were added CH_3SO_3H (0.6 N in MeOH, 6.3 mL, 3.76 mmol) at −78 °C. The mixture was allowed to slowly warm to −40 °C. To a mixture was added aq saturated $NaHCO_3$ solution (50 mL) to quench the reaction. After dilution with water, the mixture was stirred at room temperature for 30 min and extracted with EtOAc (100 mL). The organic layer was dried over anhydrous $MgSO_4$, filtered and concentrated in vacuo. The crude (3*R*,4*S*,5*S*,6*R*)-2-(5-chloro-4-(4-hydroxybenzyl)thiophen-2-yl)-6-(hydroxymethyl)-2-methoxy-tetrahydro-2*H*-pyran-3,4,5-triol (**26**) (1.1 g) was carried on to the next step without further purification.

Step 2: To a solution of compound **26** (1.1 g) in CH_2Cl_2/CH_3CN (20:20 mL) were added triethylsilane (0.70 mL, 4.14 mmol) and boron trifluoride diethyl etherate (0.55 mL, 4.14 mmol) at −60 °C. The mixture was allowed to slowly warm to −5 °C. To a mixture was added aq saturated $NaHCO_3$ solution (25 mL) to quench the reaction and extracted with EtOAc (100 mL). The combined organic layer was dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude (3*R*,4*S*,5*S*,6*R*)-2-(5-chloro-4-(4-hydroxybenzyl)thiophen-2-yl)-6-(hydroxymethyl)-tetrahydro-2*H*-pyran-3,4,5-triol (**27**) (0.85 g) was carried on to the next step without further purification.

Step 3: To a solution of compound **27** (0.85 g) in CH_2Cl_2 (20 mL) were added Ac_2O (2.1 mL, 22.0 mmol), Et_3N (3.1 mL, 22.0 mmol) and catalytic amount of DMAP at 0 °C. The mixture was stirred at 0 °C for 15 min and at room temperature for 12 h. The mixture was concentrated under reduced pressure to remove volatiles. The residue was diluted with EtOAc (50 mL), washed with H_2O (100 mL), aq. 1 N HCl solution (100 mL) and brine (100 mL) successively. The organic layer was dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by silica column chromatography (Biotage®) to provide the mixture of beta and alpha anomers of the title compound **28** (0.67 g). The anomeric mixture of **28** was recrystallized with EtOH (20 mL). The precipitate was collected by filtration and washed with cold EtOH (20 mL) and dried under high vacuum to obtain β-anomer of the title compound **28** (0.41 g, 33% (four-steps)). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.15 (d, J = 8.4 Hz, 2H), 6.99 (d, J = 8.4 Hz, 2H), 6.59 (s, 1H), 5.27–5.13 (m, 2H), 5.04 (d, J = 9.6 Hz, 1H), 4.51 (d, J = 10.0 Hz, 1H), 4.27–4.13 (m, 2H), 3.89–3.77 (m, 3H), 2.28 (s, 3H), 2.08 (s, 3H), 2.04 (s, 3H), 1.99 (s, 3H), 1.77 (s, 3H); MS calcd for $C_{27}H_{29}ClO_{11}S$ (MW 597.03), found $[M+Na]^+$ 619.

4.2.34. Synthesis of (2*R*,3*R*,4*S*,5*S*,6*R*)-2-(5-chloro-4-(4-hydroxybenzyl)thiophen-2-yl)-6-(hydroxymethyl)-tetrahydro-2*H*-pyran-3,4,5-triol (71c)

To a suspension of acetate **28** (413 mg, 0.617 mmol) in MeOH (15 mL) was added NaOMe (25 wt % in MeOH, 0.2 mL) at room temperature. The mixture was stirred at room temperature for 1 h. Glacial AcOH was added to the mixture to acidify the mixture. The mixture was concentrated under reduced pressure. The residue was purified by prep HPLC (C_{18}) to provide the title compound **71c** (130 mg, 55%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.00 (d, J = 8.4 Hz, 2H), 6.81 (s, 1H), 6.67 (d, J = 8.0 Hz, 2H), 5.19 (br s, 1H), 4.98 (br s, 2H), 4.47 (br s, 1H), 4.17 (d, J = 9.2 Hz, 1H), 3.73–3.62 (m, 3H), 3.43–3.37 (m, 1H), 3.24–3.14 (m, 3H), 3.12–3.02 (m, 2H); MS calcd for $C_{17}H_{19}ClO_6S$ (MW 386.85), found $[M+Na]^+$ 409.

4.2.35. Synthesis of (2*R*,3*R*,4*S*,5*S*,6*R*)-2-(4-(4-hydroxybenzyl)-5-methylthiophen-2-yl)-6-(hydroxymethyl)-tetrahydro-2*H*-pyran-3,4,5-triol (71u)

^{1}H NMR (400 MHz, DMSO-d_6) δ 9.15 (s, 1H), 6.96 (d, J = 8.4 Hz, 2H), 6.66 (d, J = 8.4 Hz, 2H), 6.64 (s, 1H), 4.97–4.88 (m, 3H), 4.41 (t, J = 6.0 Hz, 1H), 4.12 (d, J = 9.2 Hz, 1H), 3.71–3.61 (m, 3H), 3.41 (quintet, J = 6.0 Hz, 1H), 3.24–3.14 (m, 2H), 3.13–3.03 (m, 2H), 2.31 (s, 3H); MS calcd for $C_{18}H_{22}O_6S$ (MW 366.43), found $[M+Na]^+$ 389.

4.2.36. Synthesis of (2*R*,3*R*,4*S*,5*S*,6*R*)-2-(5-chloro-4-(4-(prop-2-ynyloxy)benzyl)thiophen-2-yl)-6-(hydroxymethyl)-tetrahydro-2*H*-pyran-3,4,5-triol (71f)

To a solution of phenol **71a** (124 mg, 0.320 mmol) in acetone (10 mL) were added propargyl bromide (80 wt % in toluene, 1.7 g, 11.2 mmol) and Cs_2CO_3 (1.5 g, 11.2 mmol) at room temperature. The mixture was stirred at 50 °C for 20 h. The reaction mixture was cooled to room temperature and filtered off through celite**28**. The filtrate was concentrated in vacuo. The residue was purified by prep HPLC (C_{18}) to provide the title compound **71f** (51 mg, 38%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.14 (d, J = 8.8 Hz, 2H), 6.92 (d, J = 8.8 Hz, 2H), 6.84 (s, 1H), 5.20 (d, J = 5.6 Hz, 1H), 5.02 (d, J = 4.8 Hz, 1H), 4.97 (d, J = 5.2 Hz, 1H), 4.74 (d, J = 2.4 Hz, 2H), 4.46 (d, J = 5.6 Hz, 1H), 4.17 (d, J = 9.2 Hz, 1H), 3.78 (s, 2H), 3.71–3.64 (m, 1H), 3.56–3.51 (m, 1H), 3.40 (quintet, J = 6.0 Hz, 1H), 3.25–3.16 (m, 2H), 3.13–3.02 (m, 2H); MS calcd for $C_{20}H_{21}ClO_6S$ (MW 424.90), found $[M+Na]^+$ 447.

4.2.37. (2*R*,3*R*,4*S*,5*S*,6*R*)-2-(5-Chloro-4-(4-propoxybenzyl)thiophen-2-yl)-6-(hydroxymethyl)-tetrahydro-2*H*-pyran-3,4,5-triol (71d)

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.11 (d, J = 8.4 Hz, 2H), 6.88–6.81 (m, 3H), 5.21 (d, J = 6.0 Hz, 1H), 5.03 (d, J = 4.0 Hz, 1H), 4.97 (d, J = 5.2 Hz, 1H), 4.47 (t, J = 6.0 Hz, 1H), 4.17 (d, J = 9.2 Hz, 1H), 3.87 (t, J = 7.6 Hz, 2H), 3.77 (s, 2H), 3.69–3.62 (m, 1H), 3.41 (quintet, J = 6.0 Hz, 1H), 3.24–3.17 (m, 2H), 3.13–3.02 (m, 2H), 1.70 (sextet, J = 7.2 Hz, 2H), 0.96 (t, J = 7.2 Hz, 3H); MS calcd for $C_{20}H_{25}ClO_6S$ (MW 428.93), found $[M+Na]^+$ 451.

4.2.38. (2*R*,3*R*,4*S*,5*S*,6*R*)-2-(4-(4-(Allyloxy)benzyl)-5-chlorothiophen-2-yl)-6-(hydroxymethyl)-tetrahydro-2*H*-pyran-3,4,5-triol (71e)

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.12 (d, J = 8.4 Hz, 2H), 6.88 (d, J = 8.4 Hz, 2H), 6.83 (s, 1H), 6.08–5.96 (m, 1H), 5.37 (doublet and quartet, J = 17.2, 1.6 Hz, 1H), 5.27–5.17 (m, 2H), 5.01 (d, J = 4.8 Hz, 1H), 4.96 (d, J = 5.2 Hz, 1H), 4.56–4.51 (m, 2H), 4.47 (t, J = 5.6 Hz, 1H), 4.17 (d, J = 9.6 Hz, 1H), 3.77 (s, 2H), 3.71–3.63 (m, 1H), 3.40 (quintet, J = 6.0 Hz, 1H), 3.26–3.16 (m, 2H), 3.11–3.02 (m, 2H); MS calcd for $C_{20}H_{23}ClO_6S$ (MW 426.91), found $[M+Na]^+$ 449.

4.2.39. (2*R*,3*R*,4*S*,5*S*,6*R*)-2-(4-(4-(But-2-ynyloxy)benzyl)-5-chlorothiophen-2-yl)-6-(hydroxymethyl)-tetrahydro-2*H*-pyran-3,4,5-triol (71g)

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.13 (d, J = 8.4 Hz, 2H), 6.88 (d, J = 8.4 Hz, 2H), 6.84 (s, 1H), 5.18 (d, J = 4.8 Hz, 1H), 4.98 (d, J = 4.8 Hz, 1H), 4.93 (d, J = 5.2 Hz, 1H), 4.68 (quartet, J = 2.4 Hz, 2H), 4.45 (t, J = 5.2 Hz, 1H), 4.17 (t, J = 9.2 Hz, 1H), 3.78 (s, 2H), 3.71–3.62 (m, 1H), 3.40 (quintet, J = 6.0 Hz, 1H), 3.25–3.17 (m, 2H), 3.13–3.02 (m, 2H), 3.40 (t, J = 1.8 Hz, 3H); MS calcd for $C_{21}H_{23}ClO_6S$ (MW 438.92), found m/z 461.

4.2.40. (2*R*,3*R*,4*S*,5*S*,6*R*)-2-(5-Chloro-4-(4-(2-methoxyethoxy)-benzyl)thiophen-2-yl)-6-(hydroxymethyl)-tetrahydro-2*H*-pyran-3,4,5-triol (71h)

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.10 (d, J = 8.4 Hz, 2H), 6.86 (d, J = 8.8 Hz, 2H), 6.83 (s, 1H), 5.18 (d, J = 6.0 Hz, 1H), 5.00 (d, J = 4.8 Hz, 1H), 4.95 (d, J = 5.6 Hz, 1H), 4.46 (t, J = 6.0 Hz, 1H), 4.17 (d, J = 9.2 Hz, 1H), 4.07–4.02 (m, 2H), 3.77 (s, 2H), 3.71–3.49 (m, 3H), 3.39 (quintet, J = 6.0 Hz, 1H), 3.29 (s, 3H), 3.25–3.17 (m, 2H), 3.12–3.02 (m, 2H); MS calcd for $C_{20}H_{25}ClO_7S$ (MW 444.93), found $[M+Na]^+$ 467.

4.2.41. (2*R*,3*R*,4*S*,5*S*,6*R*)-2-(5-Chloro-4-(4-(2-ethoxyethoxy)-benzyl)thiophen-2-yl)-6-(hydroxymethyl)-tetrahydro-2*H*-pyran-3,4,5-triol (71i)

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.12 (d, J = 8.4 Hz, 2H), 6.86 (d, J = 8.8 Hz, 2H), 6.82 (s, 1H), 5.19 (d, J = 5.6 Hz, 1H), 5.00 (d, J = 4.4 Hz, 1H), 4.95 (d, J = 5.2 Hz, 1H), 4.46 (t, J = 5.6 Hz, 1H), 4.17 (d, J = 9.2 Hz, 1H), 4.08–4.02 (m, 2H), 3.77 (s, 2H), 3.71–3.62 (m, 3H), 3.48 (quartet, J = 7.2 Hz, 2H), 3.39 (quintet, J = 6.0 Hz, 1H), 3.27–3.15 (m, 2H), 3.12–3.03 (m, 2H), 1.12 (t, J = 7.2 Hz, 3H); MS calcd for $C_{21}H_{27}ClO_7S$ (MW 458.95), found $[M+Na]^+$ 481.

4.2.42. (2*R*,3*R*,4*S*,5*S*,6*R*)-2-(4-(4-(Allyloxy)benzyl)-5-methyl-thiophen-2-yl)-6-(hydroxymethyl)-tetrahydro-2*H*-pyran-3,4,5-triol (71v)

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.08 (d, J = 8.8 Hz, 2H), 6.84 (d, J = 8.4 Hz, 2H), 6.70 (s, 1H), 6.09–5.97 (m, 1H), 5.37 (quartet and doublet, J = 17.6, 1.6 Hz, 1H), 5.23 (quartet and doublet, J = 17.6, 1.6 Hz, 1H), 4.98–4.87 (m, 3H), 4.51 (doublet and triplet, J = 5.2, 1.6 Hz, 2H), 4.40 (t, J = 5.2 Hz, 1H), 4.12 (d, J = 9.2 Hz, 1H), 3.71 (s, 2H), 3.69–3.62 (m, 1H), 3.40 (quintet, J = 6.0 Hz, 1H), 3.26–3.15 (m, 2H), 3.14–3.03 (m, 2H), 2.31 (s, 3H); MS calcd for $C_{21}H_{26}O_6S$ (MW 406.49), found $[M+Na]^+$ 429.

4.2.43. Synthesis of (5-bromo-2-chlorothiophen-3-yl)methanol (31)

To a solution of acid **1** (3.0 g, 12.4 mmol) in THF (50 mL) were added borane dimethylsulfide complex (10 M in THF, 3.2 mL, 31.1 mmol) at 0 °C. The mixture was stirred at 0 °C for 15 min, at room temperature for 45 min, and at 65 °C for 2 h. The reaction mixture was cooled to 0 °C. To the mixture were added MeOH (30 mL), H_2O (250 mL) dropwise at 0 °C. The mixture was extracted with EtOAc (100 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated in vacuo to obtain the title compound 3**1** (2.8 g, 99%). The crude alcohol **31** was carried on to the next step without further purification.

4.2.44. Synthesis of (5-bromo-2-chlorothiophen-3-yl)methoxy)-triisopropylsilane (32)

To a solution of alcohol **31** (2.8 g, 12.3 mmol) in DMF (25 mL) were added TIPSCl (5.3 mL, 24.6 mmol), imidazole (2.5 g, 36.9 mmol) and DMAP (0.3 g, 2.46 mmol) at room temperature. The mixture was stirred at ambient temperature for 14 h. The mixture was extracted with EtOAc/H_2O (75:250 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by silica column chromatography (Biotage**28**) to provide the title compound **32** (4.0 g, 85%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.01 (s, 1H), 4.66 (s, 2H), 1.19–1.11 (m, 3H), 1.07 (d, J = 9.2 Hz, 18H).

4.2.45. Synthesis of (3*R*,4*S*,5*R*,6*R*)-3,4,5-tris(benzyloxy)-6-(benzyloxymethyl)-2-(5-chloro-4-((triisopropylsilyloxy)-methyl)thiophen-2-yl)-tetrahydro-2*H*-pyran-2-ol (33)

To a solution of bromide **32** (4.0 g, 5.06 mmol) in THF (40 mL) at −78 °C under an atmosphere of nitrogen was added dropwise *n*-butyllithium (2.5 M in hexanes, 4.2 mL, 10.5 mmol), and the mixture was stirred for 40 min at the same temperature. Then a solution of benzyl-protected gluconolactone (4.7 g, 8.75 mmol) in THF (20 mL) was added dropwise, and the mixture was stirred for 2.5 h at the same temperature. The reaction mixture was quenched by addition of saturated ammonium chloride. After complete addition, the solution was gradually raised to room temperature. The organic layer was separated and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated in vacuo to yield the title compound **33**, which was carried on to the next step without further purification.

4.2.46. Synthesis of ((2-chloro-5-((3*R*,4*S*,5*R*,6*R*)-3,4,5-tris(benzyloxy)-6-(benzyloxymethyl)-tetrahydro-2*H*-pyran-2-yl)thiophen-3-yl)methoxy)triisopropylsilane (34)

To a solution of alcohol **33** (8.53 g, 10.1 mmol) in CH_2Cl_2 (50 mL) were added triethylsilane (3.3 mL, 20.2 mmol) and boron trifluoride diethyl etherate (2.6 mL, 20.2 mmol) at −60 °C. The mixture was allowed to slowly warm to −20 °C. To a mixture was added aq saturated K_2CO_3 solution (50 mL) to quench the reaction. The mixture was evaporated under reduced pressure to remove CH_2Cl_2 and extracted with EtOAc (100 mL). The combined organic layer was dried over $MgSO_4$, filtered, and concentrated in vacuo to yield the title compound **34** (8.22 g), which was carried on to the next step without further purification.

4.2.47. Synthesis of (2-chloro-5-((3*R*,4*S*,5*R*,6*R*)-3,4,5-tris(benzyloxy)-6-(benzyloxymethyl)-tetrahydro-2*H*-pyran-2-yl)thiophen-3-yl)methanol (35)

To a solution of compound **34** (8.22 g) in THF (50 mL) was added TBAF (1 M in THF, 20 mL, 19.9 mmol) dropwise at 0 °C. The mixture was stirred at room temperature for 2 h. The mixture was extracted with EtOAc/H_2O (100:250 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by silica column chromatography (Biotage®) to provide the title compound **35** (5.2 g, 89% (3-steps)). MS calcd for $C_{39}H_{39}ClO_6S$ (MW 671.24), found $[M+Na]^+$ 693.

4.2.48. Synthesis of (2-chloro-5-((2*R*,3*R*,4*S*,5*R*,6*R*)-3,4,5-tris(benzyloxy)-6-(benzyloxymethyl)-tetrahydro-2*H*-pyran-2-yl)thiophen-3-yl)methyl benzoate (36)

To a solution of alcohol **35** (5.2 g, 7.75 mmol) in CH_2Cl_2 (50 mL) were added Et_3N (3.5 mL, 23.3 mmol) and benzoyl chloride (1.2 mL, 10.1 mmol) at 0 °C. The mixture was allowed to slowly warm to room temperature and stirred at room temperature for 15 h. The mixture was washed with aq saturated $NaHCO_3$ solution. The organic layer was dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by silica column chromatography (Biotage®) to provide the mixture of beta and alpha anomers of the title compound (6.1 g). The anomeric mixture of **36** was recrystallized with EtOH (50 mL). The precipitate was collected by filtration and washed with cold EtOH (30 mL) and dried under high vacuum to obtain β-anomer of the title compound **36** (4.64 g, 77%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (d, J = 8.4 Hz, 2H), 7.58–7.52 (m, 1H), 7.44–7.36 (m, 2H), 7.35–7.24 (m, 13H), 7.21–7.11 (m, 5H), 7.08–7.01 (m, 3H), 5.27 (s, 2H), 4.94 (s, 2H), 4.67–4.53 (m, 3H), 4.42 (d, J = 9.2 Hz, 1H), 4.24 (d, J = 10.4 Hz, 1H), 3.81–3.69 (m, 4H), 3.62–3.52 (m, 1H), 3.50–3.42 (m, 1H); MS calcd for $C_{46}H_{43}ClO_7S$ (MW 775.35), found $[M+Na]^+$ 797.

4.2.49. Synthesis of (2-chloro-5-((2*R*,3*R*,4*S*,5*R*,6*R*)-3,4,5-tris(benzyloxy)-6-(benzyloxymethyl)-tetrahydro-2*H*-pyran-2-yl)thiophen-3-yl)methanol (37)

To a solution of benzoate **36** (4.5 g, 5.80 mmol) in THF/MeOH/H_2O (30:10:10 mL) was added LiOH monohydrate (0.73 g, 17.4 mmol) at room temperature. The mixture was stirred at room

temperature for 5 h. The mixture was extracted with EtOAc/aq saturated NH_4Cl solution (100:100 mL). The organic layer was dried over anhydrous $MgSO_4$, filtered and concentrated in vacuo to yield the title compound **37** (3.86 g, 99%), which was carried on to the next step without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38–7.22 (m, 17H), 7.21–7.15 (m, 2H), 7.13–7.05 (m, 2H), 6.98 (s, 1H), 4.94–4.82 (m, 3H), 4.69–4.62 (m, 3H), 4.59–4.52 (m, 3H), 4.40 (d, J = 9.2 Hz, 1H), 4.22 (d, J = 7.2 Hz, 1H), 3.80–3.68 (m, 4H), 3.62–3.55 (m, 1H), 3.46 (t, J = 8.8 Hz, 1H); MS calcd for $C_{39}H_{39}ClO_6S$ (MW 671.24), found $[M+Na]^+$ 693.

4.2.50. Synthesis of (2*R*,3*R*,4*S*,5*R*,6*R*)-3,4,5-tris(benzyloxy)-2-(benzyloxymethyl)-6-(4-(bromomethyl)-5-chlorothiophen-2-yl)-tetrahydro-2*H*-pyran (38)

To a solution of alcohol **37** (3.86 g, 5.75 mmol) in ether (50 mL) were added phosphorus tribromide (0.3 mL, 2.88 mmol) and catalytic amount of pyridine at 0 °C. The mixture was allowed to warm to room temperature and stirred at room temperature for 2 h. The mixture was extracted with EtOAc/H_2O (100:150 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated in vacuo. The organic layer was dried over anhydrous $MgSO_4$, filtered and concentrated in vacuo to yield the title compound **38** (4.1 g, 97%), which was carried on to the next step without further purification.

4.2.51. Synthesis of (2*R*,3*R*,4*S*,5*R*,6*R*)-3,4,5-tris(benzyloxy)-2-(benzyloxymethyl)-6-(5-chloro-4-(4-methylbenzyl)thiophen-2-yl)-tetrahydro-2*H*-pyran (39)

To a solution of bromide **38** (850 mg, 1.16 mmol) in toluene/EtOH (18:2 mL) were added 4-methylphenylboronic acid (200 mg, 1.39 mmol), tetrakis(triphenylphosphin)palladium (70 mg, 0.058 mmol) and Cs_2CO_3 (770 mg, 2.32 mmol) at room temperature. The mixture was stirred at 120 °C. The mixture was cooled to room temperature and filtered off thorough silica gel to remove insoluble materials. The filtrate was extracted with EtOAc/H_2O (100:150 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by silica column chromatography (Biotage®) to provide the title compound **39** (611 mg, 71%). MS calcd for $C_{46}H_{45}ClO_5S$ (MW 745.36), found $[M+Na]^+$ 767.

4.2.52. Synthesis of (2*R*,3*R*,4*S*,5*R*,6*R*)-2-(acetoxymethyl)-6-(5-chloro-4-(4-methylbenzyl)thiophen-2-yl)-tetrahydro-2*H*-pyran-3,4,5-triyl triacetate (40)

To a solution of compound **39** (611 mg, 0.819 mmol) in acetic anhydride (15 mL) was added TMSOTf (1.2 mL, 6.55 mmol) at −30 °C. The mixture was allowed to slowly warm to room temperature and stirred at room temperature for 2 h. The mixture was cooled to 0 °C and aq saturated $NaHCO_3$ solution (50 mL) was added to the mixture at 0 °C to quench the reaction. The mixture was diluted with EtOAc (50 mL) and washed with aq saturated $NaHCO_3$ solution (50 mL × 3). The organic layer was dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by silica column chromatography (Biotage®) to provide the title compound **40** (339 mg, 75%). MS calcd for $C_{26}H_{29}ClO_9S$ (MW 553.02), found $[M+Na]^+$ 575.

4.2.53. Synthesis of (2*R*,3*R*,4*S*,5*S*,6*R*)-2-(5-chloro-4-(4-methylbenzyl)thiophen-2-yl)-6-(hydroxymethyl)-tetrahydro-2*H*-pyran-3,4,5-triol (71o)

To a suspension of acetate **40** (339 mg, 0.612 mmol) in MeOH (15 mL) was added NaOMe (25 wt % in MeOH, 0.2 mL) at room temperature. The mixture was stirred at room temperature for 1 h. Glacial AcOH was added to the mixture to acidify the mixture. The mixture was concentrated under reduced pressure. The residue was purified by prep HPLC (C_{18}) to provide the title compound **71o** (55 mg, 23%) ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.10 (s, 4H), 6.82 (s, 1H), 5.19 (d, J = 5.6 Hz, 1H), 5.00 (d, J = 4.8 Hz, 1H), 4.95 (d, J = 5.2 Hz, 1H), 4.46 (t, J = 5.6 Hz, 1H), 4.17 (d, J = 9.2 Hz, 1H), 3.79 (s, 2H), 3.60–3.51 (m, 1H), 3.40 (quintet, J = 6.0 Hz, 1H), 3.25–3.16 (m, 2H), 3.11–3.02 (m, 2H), 2.25 (s, 3H); MS calcd for $C_{18}H_{21}ClO_5S$ (MW 384.87), found $[M+Na]^+$ 407.

4.2.54. (2*R*,3*R*,4*S*,5*S*,6*R*)-2-(5-Chloro-4-(4-ethylbenzyl)thiophen-2-yl)-6-(hydroxymethyl)-tetrahydro-2*H*-pyran-3,4,5-triol (71p)

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.13 (s, 4H), 6.84 (s, 1H), 5.17 (d, J = 6.0 Hz, 1H), 4.99 (d, J = 5.2 Hz, 1H), 4.93 (d, J = 5.2 Hz, 1H), 4.45 (t, J = 6.0 Hz, 1H), 4.17 (d, J = 9.6 Hz, 1H), 3.80 (s, 2H), 3.71–3.63 (m, 1H), 3.45–3.36 (m, 1H), 3.26–3.17 (m, 2H), 3.13–3.02 (m, 2H), 2.55 (quartet, J = 7.2 Hz, 2H), 1.15 (t, J = 7.6 Hz, 3H); MS calcd for $C_{19}H_{23}ClO_5S$ (MW 398.90), found $[M+Na]^+$ 421.

4.2.55. (2*R*,3*R*,4*S*,5*S*,6*R*)-2-(5-Chloro-4-(4-propylbenzyl)thiophen-2-yl)-6-(hydroxymethyl)-tetrahydro-2*H*-pyran-3,4,5-triol (71q)

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.11 (s, 4H), 6.84 (s, 1H), 5.17 (d, J = 6.0 Hz, 1H), 4.97 (d, J = 5.2 Hz, 1H), 4.93 (d, J = 5.2 Hz, 1H), 4.44 (t, J = 6.0 Hz, 1H), 4.17 (d, J = 9.2 Hz, 1H), 3.80 (s, 2H), 3.66 (quartet and doublet, J = 5.6, 1.6 Hz, 1H), 3.41 (quintet, J = 6.0 Hz, 1H), 3.24–3.17 (m, 2H), 3.12–3.02 (m, 2H), 2.54–2.45 (m, 2H), 1.55 (sextet, J = 7.2 Hz, 2H), 0.88 (t, J = 7.2 Hz, 3H); MS calcd for $C_{20}H_{25}ClO_5S$ (MW 412.93), found $[M+Na]^+$ 435.

4.2.56. Synthesis of *N*-methoxy-*N*,3-dimethylthiophene-2-carboxamide (43)

To a mixture of *N*,*O*-dimethylhydroylamine hydrochloride (5.85 g, 60 mmol) and TEA (16.7 mL, 120 mmol) in chloroform was added 3-methylthiophene-2-carbonyl chloride (**42**, 4.89 mL, 40 mmol) at 0 °C. Then, the reaction temperature was raised to room temperature, and maintained for overnight. The reaction mixture was subsequently washed with aq HCl solution (1 M, 50 mL) and brine. The organic phase was dried $MgSO_4$ and evaporated under vacuum to provide the intermediate **43** (7.47 g, ~100%) as a yellow oil, which was used without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 (d, J = 5.2 Hz, 1H), 6.90 (d, J = 5.2 Hz, 1H), 3.71 (s, 3H), 3.34 (s, 3H), 2.55 (s, 3H); MS calcd for $C_8H_{11}NO_2S$ (MW 185.24), found $[M+H]^+$ 186.

4.2.57. Synthesis of (3-Methylthiophen-2-yl)(4-propylphenyl)-methanone (44, via route a)

To a solution of the Weinreb amide **43** (3.78 g, 20.4 mmol) in anhydrous THF (61.3 mL) was added dropwise (over a 10-min period) a solution of 4-n-propylphenylmagnesium bromide (81.6 mL, 0.5 M in THF) under nitrogen atmosphere at 0 °C. The reaction mixture was allowed to warm to room temperature and stirred for 16 h. The mixture was poured into a 1 M HCl solution (50 mL) and extracted with EtOAc (100 mL). The organic phase was subsequently washed with brine, dried over $MgSO_4$ and evaporated under vacuum. The residue was further purified by silica column chromatography (Biotage®) to provide (3-methylthiophen-2-yl)(4-propylphenyl)methanone (**44**, 3.15 g, 12.9 mmol, 63%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (d, J = 8.4 Hz, 2H), 7.47 (d, J = 5.2 Hz, 1H), 7.27 (d, J = 8.0 Hz, 2H), 7.00 (d, J = 4.8 Hz, 1H), 2.66 (t, J = 7.2 Hz, 2H), 2.48 (s, 3H), 1.73–1.64 (m, 2H), 0.96 (t, J = 7.2 Hz, 3H); MS calcd for $C_{15}H_{16}OS$ (MW 244.35), found $[M+H]^+$ 245.

4.2.58. Synthesis of (5-bromo-3-methylthiophen-2-yl)(4-propylphenyl)methanone (45)

To a solution of (3-methylthiophen-2-yl)(4-propylphenyl)methanone (**44**, 1.12 g, 4.58 mmol) in acetic acid (4.67 mL) was added pyridinium tribromide (3.67 g, 11.5 mmol). The

reaction mixture was heated to 50 °C for 3 h. After cooling to room temperature, the mixture was poured into water (50 mL) and extracted with EtOAc (100 mL). The organic phase was dried over $MgSO_4$ and evaporated under vacuum. The residue was further purified by silica column chromatography (Biotage®) to provide (5-bromo-3-methylthiophen-2-yl)(4-propylphenyl)methanone (**45**, 0.95 g, 2.95 mmol, 64%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (d, J = 8.4 Hz, 2H), 7.27 (d, J = 8.0 Hz, 2H), 6.98 (s, 1H), 2.66 (t, J = 7.6 Hz, 2H), 2.43 (s, 3H), 1.73–1.64 (m, 2H), 0.96 (t, J = 7.6 Hz, 3H); MS calcd for $C_{15}H_{15}BrOS$ (MW 323.25), found $[M+H]^+$ 323.

4.2.59. Synthesis of 5-Bromo-3-methyl-2-(4-propylbenzyl)-thiophene (46)

To a solution of (5-bromo-3-methylthiophen-2-yl)(4-propylphenyl)methanone (**45**, 0.95 g, 2.95 mmol) in DCM (9.4 mL) and ACN (9.4 mL) was added triethylsilane (1.42 mL, 8.85 mmol) followed by BF_3 etherate (1.11 mL, 8.85 mmol) under nitrogen atmosphere at 0 °C. The reaction mixture was allowed warmed to room temperature and stirred for 16 h. The mixture was poured into a saturated K_2CO_3 solution (50 mL) and extracted with EtOAc (100 mL). The organic phase was dried over $MgSO_4$ and evaporated under vacuum. The residue was further purified by silica column chromatography (Biotage®) to provide 5-bromo-3-methyl-2-(4-propylbenzyl)thiophene (**46**, 0.86 g, 2.77 mmol, 94%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.10 (s, 4H), 6.75 (s, 1H), 3.95 (s, 2H), 2.55 (t, J = 7.6 Hz, 2H), 2.12 (s, 3H), 1.67–1.57 (m, 2H), 0.93 (t, J = 7.6 Hz, 3H); MS calcd for $C_{15}H_{17}BrS$ (MW 309.26), found $[M+H]^+$ 309.

4.2.60. Synthesis of 5-Iodo-3-methyl-2-(4-propylbenzyl)-thiophene (47)

To a mixture of 5-bromo-3-methyl-2-(4-propylbenzyl)thiophene (**46**, 0.86 g, 2.77 mmol), sodium iodide (0.83 g, 5.53 mmol) and copper(I) iodide (0.053 g, 0.277 mmol) in dioxane (5.2 mL) was added *N*,*N*′-dimethylethylenediamine (0.060 mL, 0.553 mmol). The resulting mixture was heated to 110 °C and stirred for 16 h. After cooling to room temperature, the reaction mixture was filtered through a plug of Celite® and then washed with EtOAc (50 mL). The filtrate was washed with brine and dried over $MgSO_4$. The organic phase was evaporated under vacuum to provide 5-iodo-3-methyl-2-(4-propylbenzyl)thiophene (0.95 g, 2.66 mmol, 96%) as a yellow oil, which was used without further purification. MS calcd for $C_{15}H_{17}IS$ (MW 356.26), found $[M]^+$ 356.

4.2.61. Synthesis of (4-ethoxyphenyl)(3-methylthiophen-2-yl)-methanone (44, via route b)

To a solution of 4-bromophenetole (1.86 mL, 13.0 mmol) in anhydrous THF (15 mL) was added dropwise (over a 5-min period) a solution of *n*-BuLi (6.0 mL, 2.5 M in hexane) under nitrogen atmosphere at −78 °C. The resulting mixture was stirred at −78 °C for 1 h, and then a solution of the Weinreb amide **43** (1.85 g, 10.0 mmol) in anhydrous THF (5.0 mL) was added dropwise (over a 10-min period). The reaction mixture was allowed to warm to room temperature and stirred for 16 h. The mixture was poured into a 1 M HCl solution (25 mL) and extracted with EtOAc (50 mL). The organic phase was subsequently washed with brine, dried over $MgSO_4$ and evaporated under vacuum. The residue was further purified by silica column chromatography (Biotage®) to provide (4-ethoxyphenyl)(3-methylthiophen-2-yl)methanone (**44**, 1.52 g, 6.16 mmol, 62%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (d, J = 8.8 Hz, 2H), 7.45 (d, J = 5.2 Hz, 1H), 7.98 (d, J = 4.8 Hz, 1H), 6.94 (d, J = 9.2 Hz, 2H), 4.11 (q, J = 6.8 Hz, 2H), 2.40 (s, 3H), 1.45 (t, J = 6.8 Hz, 3H); MS calcd for $C_{14}H_{14}O_2S$ (MW 246.32), found $[M+H]^+$ 247.

4.2.62. Synthesis of (2*R*,3*S*,4*S*,5*R*,6*R*)-2-(hydroxymethyl)-6-(4-methyl-5-(4-propylbenzyl)thiophen-2-yl)tetrahydro-2*H*-pyran-3,4,5-triol (51)

Step 1: To a solution of 5-iodo-3-methyl-2-(4-propylbenzyl)thiophene (**47**, 0.95 g, 2.66 mmol) and (3R,4S,5R,6R)-3,4,5-tris(trimethylsilyloxy)-6-((trimethylsilyloxy)methyl)tetrahydro-2*H*-pyran-2-one (200, 1.37 g, 2.93 mmol) in THF (8.53 mL) was added dropwise (over a 5-min period) a (trimethylsilyl)lithium solution (5.32 mL, 1.0 M in pentane) under nitrogen atmosphere at −50 °C. The reaction temperature was maintained −40 and −50 °C for 2 h. The reaction was quenched with a saturated $NaHCO_3$ solution (20 mL), and then extracted with EtOAc (50 mL). The organic phase was dried over $MgSO_4$ and evaporated under vacuum to provide the crude intermediate ((3*R*,4*S*,5*R*,6*R*)-2-(4-methyl-5-(4-propylbenzyl)thiophen-2-yl)-3,4,5-tris(trimethylsilyloxy)-6-((trimethylsilyloxy)methyl)tetrahydro-2*H*-pyran-2-ol) (**49**).

Step 2: The crude ((3*R*,4*S*,5*R*,6*R*)-2-(4-methyl-5-(4-propylbenzyl)thiophen-2-yl)-3,4,5-tris(trimethylsilyloxy)-6-((trimethylsilyloxy)methyl)tetrahydro-2*H*-pyran-2-ol) (**49**) was dissolved in anhydrous THF (13.6 mL). To the resulting solution was added dropwise a solution of methanesulfonic acid (0.31 mL in 8 mL MeOH) under nitrogen atmosphere at −78 °C. The reaction temperature was maintained −50 and −78 °C for 2 h. The reaction was quenched with a saturated $NaHCO_3$ solution (20 mL), and then extracted with EtOAc (50 mL). The organic phase was dried over $MgSO_4$ and evaporated under vacuum to provide the crude intermediate ((3*R*,4*S*,5*S*,6*R*)-6-(hydroxymethyl)-2-methoxy-2-(4-methyl-5-(4-propylbenzyl)thiophen-2-yl)tetrahydro-2*H*-pyran-3,4,5-triol) (**50**), which was used without further purification. MS calcd for $C_{22}H_{30}O_6S$ (MW 422.54), found $[M-OMe]^+$ 391.

Step 3: To a solution of crude (3*R*,4*S*,5*S*,6*R*)-6-(hydroxymethyl)-2-methoxy-2-(4-methyl-5-(4-propylbenzyl)thiophen-2-yl)tetrahydro-2*H*-pyran-3,4,5-triol (**50**) in DCM (11.8 mL) and ACN (11.8 mL) was added triethylsilane (0.786 mL, 4.90 mmol) followed by BF_3 etherate (0.611 mL, 4.90 mmol) under nitrogen atmosphere at −60 °C. The reaction temperature was maintained −60 and −30 °C for 2 h. The reaction was quenched with a saturated $NaHCO_3$ solution (20 mL), and then extracted with EtOAc (50 mL). The organic phase was dried over $MgSO_4$ and evaporated under vacuum. The residue was further purified by prep HPLC (C_{18}) to provide the title compound **51** (391 mg, 0.996 mmol, 37%). ^{1}H NMR (400 MHz, CD_3OD) δ 6.97 (s, 4H), 6.73 (s, 1H), 4.19 (d, J = 9.6 Hz, 1H), 3.89 (s, 2H), 3.75 (d, J = 10.0 Hz, 1H), 3.57–3.51 (m, 1H), 3.33–3.24 (m, 4H), 2.44 (t, J = 7.6 Hz, 2H), 2.03 (s, 3H), 1.54–1.46 (m, 2H), 0.82 (t, J = 7.2 Hz, 3H); MS calcd for $C_{20}H_{26}O_5S$ (MW 391.51), found $[M-OH]^+$ 375.

4.2.63. (2*R*,3*R*,4*S*,5*S*,6*R*)-2-(5-(4-Ethoxybenzyl)-4-methylthiophen-2-yl)-6-(hydroxymethyl)tetrahydro-2*H*-pyran-3,4,5-triol (72a)

^{1}H NMR (400 MHz, CD_3OD) δ 7.18 (d, J = 8.8 Hz, 2H), 6.92 (s, 1H), 6.90 (d, J = 8.8 Hz, 2H), 4.38 (d, J = 9.6 Hz, 1H), 4.09 (q, J = 7.2 Hz, 2H), 4.05 (s, 2H), 3.95 (d, J = 11.6 Hz, 1H), 3.76–3.71 (m, 1H), 3.53–3.42 (m, 4H), 2.22 (s, 3H), 1.45 (t, J = 7.2 Hz, 3H); MS calcd for $C_{20}H_{26}O_6S$ (MW 394.48), found $[M-OH]^+$ 377.

4.2.64. (2*R*,3*S*,4*S*,5*R*,6*R*)-2-(Hydroxymethyl)-6-(5-(4-methoxybenzyl)-4-methylthiophen-2-yl)tetrahydro-2*H*-pyran-3,4,5-triol (72b)

^{1}H NMR (400 MHz, CD_3OD) δ 7.08 (d, J = 8.8 Hz, 2H), 6.81 (s, 1H), 6.79 (d, J = 8.8 Hz, 2H), 4.26 (d, J = 9.6 Hz, 1H), 3.93 (s, 2H), 3.83 (d, J = 11.6 Hz, 1H), 3.73 (s, 3H), 3.63–3.59 (m, 1H), 3.41–3.30 (m, 4H), 2.10 (s, 3H); MS calcd for $C_{19}H_{24}O_6S$ (MW 380.46), found $[M-OH]^+$ 363.

4.2.65. (2*R*,3*R*,4*S*,5*S*,6*R*)-2-(5-(4-Chlorobenzyl)-4-methylthiophen-2-yl)-6-(hydroxymethyl)tetrahydro-2*H*-pyran-3,4,5-triol (72c)

^{1}H NMR (400 MHz, CD_3OD) δ 7.23 (d, J = 8.8 Hz, 2H), 7.15 (d, J = 8.8 Hz, 2H), 6.82 (s, 1H), 4.27 (d, J = 9.6 Hz, 1H), 4.00 (s, 2H), 3.83 (d, J = 12.0 Hz, 1H), 3.62–3.59 (m, 1H), 3.39–3.30 (m, 4H), 2.10 (s, 3H); MS calcd for $C_{18}H_{21}ClO_5S$ (MW 384.87), found $[M-OH]^+$ 367.

4.2.66. (2*R*,3*R*,4*S*,5*S*,6*R*)-2-(5-(4-*tert*-Butylbenzyl)-4-methylthiophen-2-yl)-6-(hydroxymethyl)tetrahydro-2*H*-pyran-3,4,5-triol (72d)

^{1}H NMR (400 MHz, CD_3OD) δ 7.27 (d, J = 8.4 Hz, 2H), 7.09 (d, J = 8.4 Hz, 2H), 6.80 (s, 1H), 4.26 (d, J = 9.2 Hz, 1H), 3.96 (s, 2H), 3.83 (d, J = 12.0 Hz, 1H), 3.63–3.59 (m, 1H), 3.39–3.32 (m, 4H), 2.12 (s, 3H), 1.27 (s, 9H); MS calcd for $C_{22}H_{30}O_5S$ (MW 406.54), found $[M-OH]^+$ 389.

4.2.67. (2*R*,3*S*,4*S*,5*R*,6*R*)-2-(Hydroxymethyl)-6-(4-methyl-5-(4-methylbenzyl)thiophen-2-yl)tetrahydro-2*H*-pyran-3,4,5-triol (72e)

^{1}H NMR (400 MHz, CD_3OD) δ 7.04 (s, 4H), 6.80 (s, 1H), 4.26 (d, J = 9.6 Hz, 1H), 3.95 (s, 2H), 3.83 (d, J = 11.6 Hz, 1H), 3.63–3.59 (m, 1H), 3.41–3.30 (m, 4H), 2.26 (s, 3H), 2.10 (s, 3H); MS calcd for $C_{19}H_{24}O_5S$ (MW 364.46), found $[M-OH]^+$ 347.

4.2.68. (2*R*,3*R*,4*S*,5*S*,6*R*)-2-(5-(4-Ethylbenzyl)-4-methylthiophen-2-yl)-6-(hydroxymethyl)tetrahydro-2*H*-pyran-3,4,5-triol (72f)

^{1}H NMR (400 MHz, CD_3OD) δ 7.07 (s, 4H), 6.80 (s, 1H), 4.26 (d, J = 9.2 Hz, 1H), 3.96 (s, 2H), 3.83 (d, J = 12.0 Hz, 1H), 3.63–3.59 (m, 1H), 3.41–3.32 (m, 4H), 2.57 (q, J = 7.6 Hz, 2H), 2.11 (s, 3H), 1.18 (t, J = 7.6 Hz, 3H); MS calcd for $C_{20}H_{26}O_5S$ (MW 378.48), found $[M-OH]^+$ 361.

4.2.69. (2*R*,3*S*,4*S*,5*R*,6*R*)-2-(Hydroxymethyl)-6-(4-methyl-5-(4-propylbenzyl)thiophen-2-yl)tetrahydro-2*H*-pyran-3,4,5-triol (72g)

^{1}H NMR (400 MHz, CD_3OD) δ 6.97 (s, 4H), 6.73 (s, 1H), 4.19 (d, J = 9.6 Hz, 1H), 3.89 (s, 2H), 3.75 (d, J = 10.0 Hz, 1H), 3.57–3.51 (m, 1H), 3.33–3.24 (m, 4H), 2.44 (t, J = 7.6 Hz, 2H), 2.03 (s, 3H), 1.54–1.46 (m, 2H), 0.82 (t, J = 7.2 Hz, 3H); MS calcd for $C_{21}H_{28}O_5S$ (MW 392.51), found $[M-OH]^+$ 375.

4.2.70. Synthesis of (2*R*,3*R*,4*S*,5*R*,6*R*)-2-(acetoxymethyl)-6-(3-bromo-5-(4-ethylbenzyl)-4-methylthiophen-2-yl)-tetrahydro-2*H*-pyran-3,4,5-triyl triacetate (56)

4.2.70.1. Step 1: (4-Ethylphenyl)(3-methylthiophen-2-yl)methanone (53).

To a solution of *N*-methoxy-*N*,3-dimethylthiophene-2-carboxamide (**52**) (*J. Med. Chem.*, **2001**, *44*, 863) (5.00 g, 27.0 mmol) in THF (30 mL) was added 4-ethylphenylmagnesium bromide (0.5 M in THF, 108 mL, 54.0 mmol) at 0 °C. The resulting solution was stirred at ambient temperature overnight. The reaction mixture was quenched by adding MeOH (20 mL) and concentrated in vacuo. The crude residue was purified on Biotage® purification apparatus to yield the title compound (4.42 g, 19.2 mmol, 71%) as brown oil.

^{1}H NMR (400 MHz, $CDCl_3$) 7.77 (dd, J = 6.4, 2.0 Hz, 2H), 7.47 (d, J = 4.8 Hz, 1H), 7.29 (dd, J = 8.0, 0.4 Hz, 2H), 7.00 (dd, J = 4.8, 0.4 Hz, 1H), 2.73 (q, J = 7.6 Hz, 2H), 2.48 (s, 3H), 1.28 (t, J = 7.6 Hz, 3H).

4.2.70.2. Step 2: (4,5-Dibromo-3-methylthiophen-2-yl)(4-ethylphenyl)methanone (54).

To a solution of (4-ethylphenyl)(3-methylthiophen-2-yl)methanone (**53**) (4.42 g, 19.2 mmol) in AcOH (30 mL) was added bromine (3.9 mL, 76.8 mmol) slowly. The resulting solution was stirred at ambient temperature overnight. The reaction mixture was quenched by adding saturated $Na_2S_2O_3$ solution (20 mL) and extracted with EtOAc (2 × 50 mL). The organic layer was washed with brine and dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude residue was purified on Biotage® purification apparatus to yield the title compound (4.28 g, 10.6 mmol, 55%) as a yellow solid.

^{1}H NMR (400 MHz, $CDCl_3$) 7.72 (dd, J = 6.4, 2.0 Hz, 2H), 7.31 (dd, J = 6.4, 2.0 Hz, 2H), 2.74 (q, J = 7.6 Hz, 2H), 2.45 (s, 3H), 1.28 (t, J = 7.6 Hz, 3H); MS calcd for $C_{14}H_{12}Br_2OS$ (MW 388.12), found $[M+H]^+$ 387.

4.2.70.3. Step 3: 2,3-Dibromo-5-(4-ethylbenzyl)-4-methylthiophene (55).

To a solution of (4,5-dibromo-3-methylthiophen-2-yl)(4-ethylphenyl)methanone (**54**) (4.28 g, 10.6 mmol) in DCM/CH_3CN (30:30 mL) were added triethylsilane (5.1 mL, 31.9 mmol) and borontrifluoride diethyletherate (3.1 mL, 25.4 mmol) at 0 °C. The resulting solution was stirred at ambient temperature overnight. The reaction mixture was quenched by adding MeOH (10 mL) and concentrated in vacuo. The crude residue was purified on Biotage® purification apparatus to yield the title compound (3.65 g, 9.76 mmol, 92%) as yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) 7.12 (ABq, $\Delta\nu_{AB}$ = 18.2 Hz, J_{AB} = 8.4 Hz, 4H), 4.00 (s, 2H), 2.63 (q, J = 7.6 Hz, 2H), 2.19 (s, 3H), 1.22 (t, J = 7.6 Hz, 3H).

4.2.70.4. Step 4: (2*R*,3*R*,4*S*,5*R*,6*R*)-2-(Acetoxymethyl)-6-(3-bromo-5-(4-ethylbenzyl)-4-methylthiophen-2-yl)-tetrahydro-2*H*-pyran-3,4,5-triyl triacetate (56).

To a solution of 2,3-dibromo-5-(4-ethylbenzyl)-4-methylthiophene (**55**) (3.65 g, 9.76 mmol) and (3*R*,4*S*,5*R*,6*R*)-3,4,5-tris(trimethylsilyloxy)-6-((tirmethylsilyloxy)methyl)-tetrahydropyran-2-one (5.01 g, 10.7 mmol) in THF (50 mL) was added (trimethylsilyl)methyllithium (1 M solution in pentane, 20 mL, 19.5 mmol) at −50 °C. The resulting solution was stirred at −50 to −40 °C for 2 h. After addition of saturated $NaHCO_3$ solution (20 mL), the mixture was extracted with EtOAc (3 × 30 mL). The organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude residue was dissolved in THF (30 mL) and cooled to −78 °C. To this solution was added a solution of methanesulfonic acid (1.5 mL, 23.4 mmol) in MeOH at −78 °C. The resulting mixture was warmed to −50 °C over a period of 2 h. and then saturated $NaHCO_3$ solution (30 mL) was added to the solution. After extraction of the reaction mixture with EtOAc (50 mL × 3), the organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude residue was dissolved in DCM/CH_3CN (20:20 mL) and cooled to −60 °C. To this solution were added triethylsilane (3.5 mL, 22.2 mmol) and borontrifluoride diethyletherate (2.2 mL, 17.7 mmol). The resulting mixture was warmed to −30 °C over a period of 2 h. and then saturated $NaHCO_3$ solution (20 mL) was added to the solution. After extraction of the reaction mixture with EtOAc (50 mL × 3), the organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude residue was dissolved in DCM (20 mL). To this solution were added dimethylaminopyridine (106 mg, 0.870 mmol), pyridine (4.2 mL, 52.2 mmol), and acetic anhydride (4.1 mL, 43.5 mmol). The resulting mixture was stirred at ambient temperature overnight and then water (30 mL) was added to the solution. After extraction of the reaction mixture with EtOAc (50 mL × 2), the organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude residue was purified on Biotage® purification apparatus to yield the title compound (1.22 g, 1.95 mmol, 20%) as a yellow solid.

^{1}H NMR (400 MHz, $CDCl_3$) 7.10 (ABq, $\Delta\nu_{AB}$ = 20.8 Hz, J_{AB} = 8.4 Hz, 4H), 5.33 (t, J = 7.2 Hz, 1H), 5.20–5.13 (m, 2H), 4.88 (d, J = 10.0 Hz, 1H), 4.23–4.13 (m, 2H), 4.02 (d, J = 3.2 Hz, 2H), 3.86–3.81 (m, 1H), 2.62 (q, J = 7.6 Hz, 2H), 2.11 (s, 3H), 2.07 (s,

3H), 2.04 (s, 3H), 2.00 (s, 3H), 1.90 (s, 3H), 1.22 (t, J = 7.6 Hz, 3H); MS calcd for $C_{28}H_{33}BrO_9S$ (MW 625.53), found $[M+Na]^+$ 647.

4.2.71. Synthesis of (2*R*,3*R*,4*S*,5*S*,6*R*)-2-(3-bromo-5-(4-ethylbenzyl)-4-methylthiophen-2-yl)-6-(hydroxymethyl)tetrahydro-2*H*-pyran-3,4,5-triol (72h)

To a suspension of acetate (**56**) (200 mg, 0.320 mmol) in MeOH (5 mL) was added NaOMe (25 wt % in MeOH, 0.1 mL) at room temperature. The mixture was stirred at room temperature for 1 h. Glacial AcOH was added to the mixture to acidify the mixture. The mixture was concentrated under reduced pressure. The residue was purified by prep HPLC (C_{18}) to provide the title compound **71h** (80 mg, 55%). ^{1}H NMR (400 MHz, CD_3OD_3) δ 7.10 (s, 4H), 4.60 (d, J = 9.2 Hz, 1H), 4.04 (d, J = 3.2 Hz, 2H), 3.86–3.80 (m, 1H), 3.63–3.58 (m, 1H), 3.44–3.40 (m, 2H), 3.39–3.32 (m, 2H), 2.58 (q, J = 7.6 Hz, 2H), 2.14 (s, 3H), 1.18 (t, J = 7.6 Hz, 3H); MS calcd for $C_{20}H_{25}BrO_5S$ (MW 457.38), found $[M-OH]^+$ 441.

4.2.72. Synthesis of (2*R*,3*R*,4*S*,5*S*,6*R*)-2-(5-(4-ethylbenzyl)-3-methoxy-4-methylthiophen-2-yl)-6-(hydroxymethyl)-tetrahydro-2*H*-pyran-3,4,5-triol (72i)

To a solution of (2*R*,3*R*,4*S*,5*R*,6*R*)-2-(acetoxymethyl)-6-(3-bromo-5-(4-ethylbenzyl)-4-methylthiophen-2-yl)-tetrahydro-2*H*-pyran-3,4,5-triyl triacetate (**56**) (200 mg, 0.320 mmol) in NaOMe (25wt% in MeOH, 10 mL, 43.2 mmol) were added cupric oxide (25.5 mg, 0.320 mmol) and KI (53.1 mg, 0.320 mmol). The resulting solution was stirred at 120 °C overnight. The reaction mixture was filtered through celite® bed and concentrated in vacuo. The crude residue was purified on reverse phase preparative HPLC to yield the title compound (24.3 mg, 0.0595 mmol, 19%) as a yellow solid. ^{1}H NMR (400 MHz, MeOD) 7.11–7.09 (m, 4H), 4.52 (dd, J = 6.4, 2.4 Hz, 1H), 3.96 (ABq, $\Delta\nu_{AB}$ = 14.0 Hz, J_{AB} = 16.0 Hz, 2H), 3.84 (dd, J = 12.0, 2.0 Hz, 1H), 3.79 (s, 3H), 3.60 (dd, J = 12.0, 6.0 Hz, 1H), 3.43 (dd, J = 6.4, 2.4 Hz, 2H), 3.39–3.35 (m, 2H), 2.60 (q, J = 7.6 Hz, 2H), 2.04 (s, 3H), 1.20 (t, J = 7.6 Hz, 3H); MS calcd for $C_{21}H_{28}O_6S$ (MW 408.51), found $[M+Na]^+$ 431.

4.2.73. Synthesis of (2*R*,3*R*,4*S*,5*R*,6*R*)-2-(acetoxymethyl)-6-(5-(4-ethylbenzyl)-3,4-dimethylthiophen-2-yl)-tetrahydro-2*H*-pyran-3,4,5-triyl triacetate (57)

To a solution of (2*R*,3*R*,4*S*,5*R*,6*R*)-2-(acetoxymethyl)-6-(3-bromo-5-(4-ethylbenzyl)-4-methylthiophen-2-yl)-tetrahydro-2*H*-pyran-3,4,5-triyl triacetate (**56**) (200 mg, 0.320 mmol) in toluene/water (4:2 mL) were added trimethylboroxine (134 μL, 0.960 mmol), $Pd(OAc)_2$ (7.2 mg, 0.0320 mmol), tricylcohexylphosphine tetrafluoroborate (23.6 mg, 0.0640 mmol), and K_3PO_4 (272 mg, 1.28 mmol). The mixture was stirred at 100 °C overnight. The reaction mixture was filtered through celite bed and concentrated in vacuo. The crude residue was purified on Biotage® purification apparatus to yield the title compound (125 mg, 0.223 mmol, 70%) as a yellow solid. MS calcd for $C_{29}H_{36}O_9S$ (MW 560.66), found $[M+Na]^+$ 583.

4.2.74. Synthesis of (2*R*,3*R*,4*S*,5*S*,6*R*)-2-(5-(4-ethylbenzyl)-3,4-dimethylthiophen-2-yl)-6-(hydroxymethyl)-tetrahydro-2*H*-pyran-3,4,5-triol (72j)

To a solution of (2*R*,3*R*,4*S*,5*R*,6*R*)-2-(acetoxymethyl)-6-(5-(4-ethylbenzyl)-3,4-dimethylthiophen-2-yl)-tetrahydro-2*H*-pyran-3,4,5-triyl triacetate (**57**) (125 mg, 0.223 mmol) in MeOH (5 mL) was added NaOMe (25 wt % in MeOH, 310 μL, 1.34 mmol). The reaction mixture was stirred at ambient temperature for 2 h before AcOH (2 mL) was added. Purification by reverse phase preparative HPLC provided the title compound (24.8 mg, 0.0632 mmol, 28%) as a brown solid.

^{1}H NMR (400 MHz, MeOD) 7.08 (s, 4H), 4.50 (d, J = 9.2 Hz, 1H), 3.99 (ABq, $\Delta\nu_{AB}$ = 10.4 Hz, J_{AB} = 16.0 Hz, 2H), 3.84 (dd, J = 12.0, 2.0 Hz, 1H), 3.62 (dd, J = 12.0, 6.0 Hz, 1H), 3.45–3.35 (m, 4H), 2.59 (q, J = 7.6 Hz, 2H), 2.12 (s, 3H), 2.05 (s, 3H), 1.19 (t, J = 7.6 Hz, 3H); MS calcd for $C_{21}H_{28}O_5S$ (MW 392.51), found $[M+Na]^+$ 415.

4.3. In vitro assay

4.3.1. Cloning and cell line construction for human SGLT2

Human SGLT2 (*h*SGLT2) gene was amplified by PCR from cDNA-Human Adult Normal Tissue Kidney (Invitrogen, Carlsbad, CA). The *h*SGLT2 sequence was cloned into pcDNA3.1(+) for mammalian expression and were stably transfected into Chinese hamster ovary (CHO) cells. SGLT2-expressing clones were selected based on resistance to G418 antibiotic (Geneticin®, Invitrogen, Carlsbad, CA) and activity in the ^{14}C-α-methyl-D-glucopyranoside (^{14}C-AMG) uptake assay.

4.3.2. Inhibitory effects on human SGLT2 activities

For sodium-dependent glucose transport assay, cells expressing *h*SGLT2 were seeded into a 96-well culture plate at a density of 5×10^4 cells/well in RPMI medium 1640 containing 10% fetal bovine serum. The cells were used 1 day after plating. They were incubated in pretreatment buffer (10 mM HEPES, 5 mM Tris, 140 mM choline chloride, 2 mM KCl, 1 mM $CaCl_2$, and 1 mM $MgCl_2$, pH 7.4) at 37 °C for 10 min. They were then incubated in uptake buffer (10 mM HEPES, 5 mM Tris, 140 mM NaCl, 2 mM KCl, 1 mM $CaCl_2$, 1 mM $MgCl_2$, and 1 mM ^{14}C-nonlabeled AMG pH 7.4) containing ^{14}C-labeled (8 μM) and inhibitor or dimethyl sulfoxide (DMSO) vehicle at 37 °C for 2 h. Cells were washed twice with washing buffer (pretreatment buffer containing 10 mM AMG at room temperature) and then the radioactivity was measured using a liquid scintillation counter. IC_{50} was determined by nonlinear regression analysis using GraphPad PRISM.[21,22]

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References and notes

1. International Diabetes Federation *Diabetes Atlas*, 3rd ed.; International Diabetes Federation: Brussels, Belgium, 2006.
2. American Diabetes Association *Diabetes Care* **2004**, *27*, S5–S10.
3. Dwarakanathan, A. *J. Insur. Med.* **2006**, *38*, 20–30.
4. Mackenzie, B.; Loo, D. D. *J. Biol. Chem.* **1996**, *20*, 32678–32683.
5. Wright, E. M. *Am. J. Physiol.* **2001**, *280*, F10–F18.
6. Zhou, L.; Cryan, E. V.; D'Andrea, M. R.; Belkowski, S.; Conway, B. R.; Demarest, K. T. *J. Cell Biochem.* **2003**, *90*, 339–346.
7. Evans, S.; Grasset, E.; Heyman, M.; Dumonitier, A. M.; Beau, J. P.; Desjeux, J.-F. *J. Pediatr. Gastroenterol. Nutr.* **1985**, *4*, 878–886.
8. Moe, O. W.; Berry, C. A.; Rector, F. C. In *The Kidney*; Brenner, B. M., Rector, F. C., Eds., 5th ed.; WB Saunders Co.: Philadelphia, 2000; pp 375–415.
9. van den Heuvel, L. P.; Assink, K.; Willesen, M.; Monnens, L. *Hum. Genet.* **2002**, *111*, 544–547.
10. Ellsworth, B. A.; Meng, W.; Patel, M.; Girotra, R. N.; Wu, G.; Sher, P.; Hagan, D.; Obermeier, M.; Humphreys, W. G.; Robertson, J. G.; Wang, A.; Han, S.; Waldron, T.; Morgan, N. N.; Whaley, J. M.; Washburn, W. N. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 4770–4773.
11. Meng, W.; Ellsworth, B. A.; Nirschl, A. A.; McCann, P. J.; Patel, M.; Girotra, R. N.; Wu, G.; Sher, P. M.; Morrison, E. P.; Biller, A. A.; Zahler, R.; Deshpande, P. P.; Pullockaran, A.; Hagan, D. L.; Morgan, N.; Taylor, J. R.; Obermeier, M. T.; Humphreys, W. G.; Khanna, A.; Discenza, L.; Robertson, J. G.; Wang, A.; Han, S.; Wetterau, J. R.; Janovitz, E. B.; Flint, O. P.; Whaley, J. M.; Washburn, W. N. *J. Med. Chem.* **2008**, *51*, 1145–1149.
12. Washburn, W. N. *J. Med. Chem.* **2009**, *52*, 1785–1794.
13. (a) Nomura, S.; Sakamaki, S.; Hongu, M.; Kawanski, E.; Koga, Y.; Sakamoto, T.; Yamamoto, Y.; Ueta, K.; Kimata, H.; Nakayama, K.; Tsuda-Tsukimoto, M. Presented at the 238th American Chemical Society National Meeting and Exposition, Washington, DC, August 16–20, 2009; Medi-151.; (b) Nomura, S.; Sakamaki, S.; Hongu, M.; Kawanshi, E.; Koga, Y.; Sakamoto, T.; Yamamoto, Y.;

Ueta, K.; Kimata, H.; Nakayama, K.; Tsuda-Tsukimoto, M. *J. Med. Chem.* **2010**, *53*, 6355–6360.
14. (a) Boehringer Ingelheim Pharmaceuticals, www.clinicaltrials.gov, 2010, NCT01164501.; (b) Lexicon Pharmaceuticals, www.clinicaltrials.gov, 2009, NCT00962065.; (c) Astellas Pharma Inc., www.clinicaltrials.gov, 2010, NCT01135433.; (d) Mascitti, V. Presented at the 240th American Chemical Society National Meeting and Exposition, Boston, MA, August 22–26, 2010; Medi-151.; (e) Mascitti, V.; Maurer, T. S.; Robinson, R. P.; Bian, J.; Boustany-Kari, C. M.; Brandt, T.; Collman, B. M.; Kalgutkar, A. S.; Klenotic, M. K.; Leininger, M. T.; Lowe, A.; Maguire, R. J.; Masteson, V. M.; Miao, Z.; Mukaiyama, E.; Patel, J. D.; Pettersen, J. C.; Preville, C.; Samas, B.; She, L.; Sobol, Z.; Steppan, C. M.; Stevens, B. D.; Thuma, B. A.; Tugnait, M.; Zeng, D.; Zhu, T. *J. Med. Chem.* **2011**, *54*, 2952.
15. (a) Lee, J.; Lee, S.-H.; Seo, H. J.; Son, E.-J.; Lee, S. H.; Jung, M. E.; Lee, M.; Han, H.-K.; Kim, J.; Kang, J.; Lee, J. *Bioorg. Med. Chem.* **2010**, *18*, 2178; (b) Kim, M. J.; Lee, J.; Kang, S. Y.; Lee, S.-H.; Son, E.-J.; Jung, M. E.; Lee, S. H.; Song, K.-S.; Lee, M.; Han, H.-K.; Kim, J.; Lee, J. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 3420; Song, K.-S.; Lee, S. H.; Kim, M. J.; Seo, H. J.; Lee, J.; Lee, S.-H.; Jung, M. E.; Son, E.-J.; Lee, M.; Kim, J.; Lee, J. *ACS Med. Chem. Lett.* **2011**, *2*, 182–187.
16. Takeda Chemical Industries, Ltd, US 5840917 A1, 1998
17. Sedelmeier, J.; Bolm, C. J. *Org. Chem.* **2005**, *70*, 6904.
18. (a) Bristol-Myers Squibb Company, US 7375213 B2, 2008.; (b) Janssen Pharmaceutical N.V. and Mitsubishi Tanabe Pharmaceutical Corporation, WO 2009/035969 A1.
19. Angibeaud, P.; Utile, J.-P. *Synthesis* **1991**, 737.
20. Boehringer Ingelheim International GMBH, WO 2008/101939.
21. Fournier Dit Chabert, J.; Joucla, L.; David, E.; Lemaire, M. *Tetrahedron* **2004**, *60*, 3221.
22. Han, S.; Hagan, D. L.; Taylor, J. R.; Xin, L.; Meng, W.; Biller, S. A.; Wetterau, J. R.; Washburn, W. N.; Whaley, J. M. *Diabetes* **2008**, *57*, 1723.
23. Katsuno, K.; Fujimori, Y.; Takemura, Y.; Hiratochi, M.; Itoh, F.; Komatsu, Y.; Fujikura, H.; Isaji, M. *J. Pharmacol. Exp. Ther.* **2007**, *320*, 323.