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Syntheses of SGLT2 Inhibitors by Ni- and Pd-Catalyzed Fukuyama Coupling Reactions

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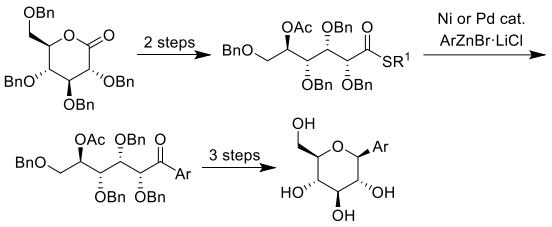
ABSTRACT: Nickel- and palladium-catalyzed Fukuyama coupling reactions of a *D*-gluconolactone-derived thioester with arylzinc reagents at ambient temperature provided the corresponding multifunctional aryl ketones in high yield. Ligand screening for the nickel-catalyzed Fukuyama coupling reactions indicated that 1,2-bis(dicyclohexylphosphino)ethane (dCype) served as a superior supporting ligand to improve the product yield. In addition, Pd/C was a practical alternative that enabled ligand-free Fukuyama coupling reactions and was efficiently applied to the key C-C bond-forming step to prepare Canagliflozin and Dapagliflozin, which are diabetic SGLT2 inhibitors of current interest.



INTRODUCTION

Sodium-glucose cotransporter-2 (SGLT2) inhibitors, a class of anti-hyperglycemic agents, have attracted much attention in recent years due to their effective control and regulation of type-2 diabetes in a safe and well-tolerated manner.[1] SGLT2 inhibitors function through a unique non-insulin dependent mechanism to reduce renal tubular glucose reabsorption, which consequently reduces blood glucose levels and contributes to control blood pressure and weight.[2] Accordingly, the FDA has approved SGLT2 inhibitors, such as Canagliflozin (Invokana®), Dapagliflozin (Farxiga®), and Empagliflozin (Jardiance®), as drugs for type-2 diabetes, all of which contain aryl-*C*-glycoside is the key structural motif, as shown in (Figure 1).[3]

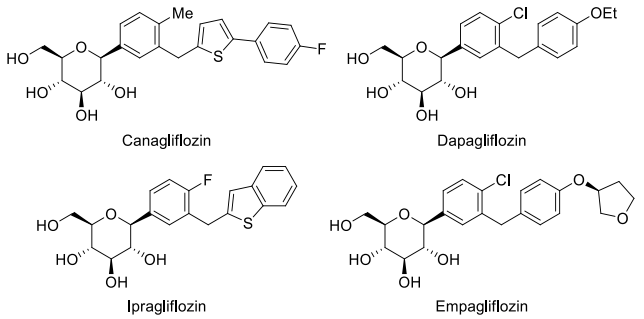


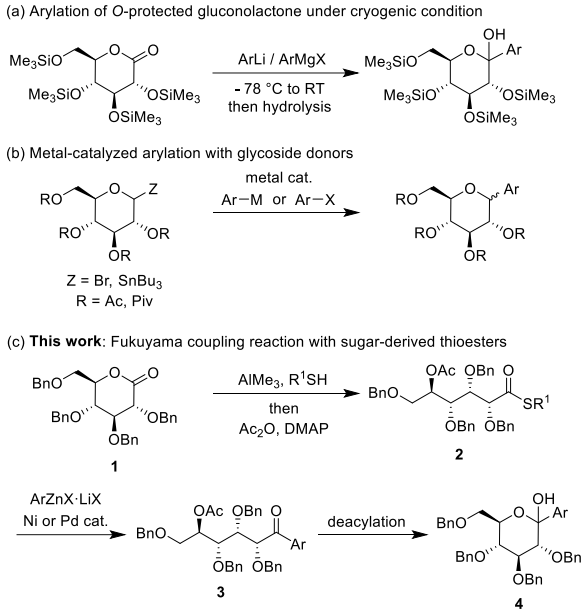
Figure 1. SGLT2 Inhibitors (aryl-*C*-glycosides)

Carbon-carbon bond formation for synthesizing an aryl-*C*-glycoside skeleton is well investigated, and two strategies are usually applied to install aryl groups.[4-10] The first approach is *C*-arylation of readily available *O*-protected gluconolactone with aryllithium or arylmagnesium reagents (Scheme 1(a)).[6-7] The target β-aryl-*C*-glycosides, such as Canagliflozin, are obtained as the major isomer by combining with stereoselective reductive dehydroxylation using R_3SiH and $BF_3{\cdot}OEt_2$. The drawbacks of the synthetic strategy are poor functional group compatibility and inevitable cryogenic conditions for the initial arylation step because of the high reactivity of aryllithium and aryl Grignard reagents.[6-7] The second approach is arylation of glycosyl donors with arylmetal reagents or aryl halides, which has been conducted under mild reaction conditions in combination with or without transition metal catalysts (Scheme 1(b)).[8-11] Cross-coupling reactions of glycosyl bromides with arylzinc (Negishi coupling) or aryl Grignard (Kumada-Tamao coupling) as well as aryl halides (reductive coupling) have been extensively explored in the last 15 years, though the stereoselectivity of the anomeric position, α and β, is highly dependent on the sugar motif, protecting groups, aryl substituents, and stereochemistry of the original glycosyl donors.[8-11] In this context, stereoselective β-*C*-glycosylation reaction is recently reported using α-isomers of glycosyl bromides and arylzinc reagents.[10b] Pd-catalyzed β-selective *C*-arylation with aryl halides is accomplished utilizing glycosyl stannane (Stille coupling), though prior synthesis of β-isomers of glycosyl stannanes is required.[12]

In this context, we envisioned the use of the catalytic *C*-arylation of protected gluconolactone-derived thioesters with arylmetal reagents, and we used the Fukuyama coupling reaction[13] as the most suitable approach for synthesizing SGLT2 inhibitors in industrial scale in terms of not only avoiding halogenation-dehalogenation sequences but also removing cryogenic conditions. Starting from benzyl-protected gluconolactone **1**, synthetically useful thioester **2** should be easily accessible by $AlMe_3$-mediated thioesterification *via* opening of the lactone ring, and a subsequent Fukuyama coupling reaction is a key step for preparing ketone **3** followed by deacylation to

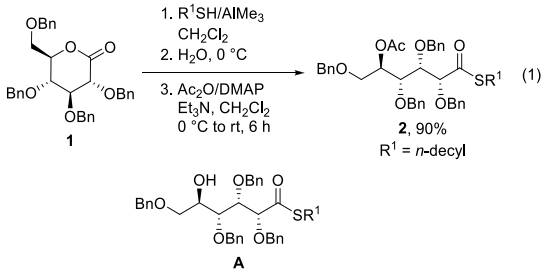
give aryl-*C*-glycoside **4** (Scheme 1(c)). Herein, we report our search for a practical synthesis of the SGLT2 inhibitors Canagliflozin and Dapagliflozin *via* nickel- and palladium-catalyzed Fukuyama coupling reactions for the formation of β-*C*-arylglycosides.

Scheme 1. Formation of Aryl-*C*-Glycosides from Glycoside Donors and Gluconolactone



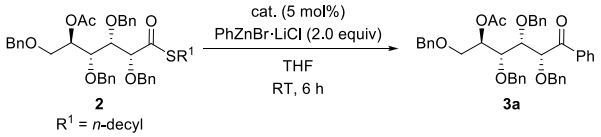
RESULTS AND DISCUSSION

We started by preparing the thioester **2** from benzyl-protected *D*-gluconolactone **1**. Reaction of **1** with a mixture of decanethiol and $AlMe_3$ (both in 1.0 equiv) at 0 °C in CH_2Cl_2 for 2 h[14] followed by hydrolysis and *in situ* acylation by acetic anhydride/4-dimethylaminopyridine (DMAP) afforded **2** in 90% yield (eq 1). In this reaction, thioester **A** having a hydroxyl group at the δ position was initially formed by hydrolysis of the reaction mixture, and it was necessary to treat **A** under the acylation condition at 0 °C; otherwise, lactonization of **2** easily occurred to regenerate the original compound **1**. The isolated thioester **2** was stable toward hydrolysis and lactonization, and used for further Fukuyama coupling reactions.



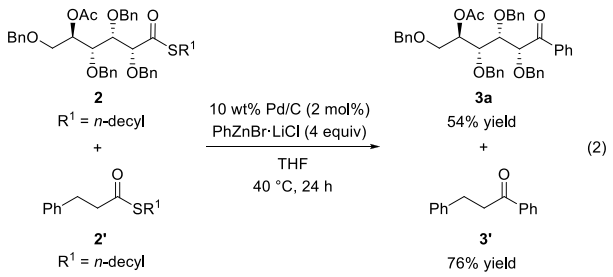
Reaction of the thioester **2** with 2 equiv of PhZnBr was selected as a model reaction for the Fukuyama coupling reaction, and results of the catalyst screening of nickel, cobalt, iron, and palladium complexes *under ligand-free conditions* are shown in Table 1. In the presence of 5 mol% of $NiCl_2(thf)_2$, cross-coupling product **3a** was obtained in 46% yield, and unreacted **2** was recovered from the reaction mixture (entry 1). Other nickel(II) sources, such as $Ni(OAc)_2$ and $Ni(acac)_2$, resulted in a lower yield (entries 2 and 3). In sharp contrast, cobalt(II) and iron(II) chlorides were inactive for the Fukuyama coupling reaction (entries 4 and 5). We also tested palladium sources for this coupling reaction: $Pd(OAc)_2$ is typically used for various coupling reactions, but the yield of **3a** was almost the same as $NiCl_2(thf)_2$, and the typically used Pd(0) source, $Pd_2(dba)_3$, was less active under the ligand-free condition. In sharp contrast, 10 wt% Pd/C (2 mol% catalyst loading) showed excellent catalytic activity to give **3a** in 70% yield after 48 h at 40 °C. Moderate yield of corresponding coupling product **3a** was also observed in the presence of a typical Fukuyama coupling catalyst $PdCl_2(PPh_3)_2$ at room temperature and at 40 °C (entries 9 and 10). We further conducted reaction of thioester **2** with 3 equiv of PhZnBr and 10 wt% Pd/C as a catalyst under Fukuyama coupling conditions at 40 °C for 48 h, showing slightly better yield of product **3a** (entry 11), though the amount of the byproduct, biphenyl, was increased. Without any catalyst, unreacted starting thioester **2** was recovered, indicating the requirement of Ni and Pd catalysts for the Fukuyama coupling reaction (entry 12). Although sugar-derived thioesters possess many ether moieties within the molecules and are less reactive (*vide infra*), these Ni- and Pd-catalyzed systems overcame the limitations and represent the first example of a Fukuyama coupling reaction employing a thioester with a sugar linkage.[15] In fact, under the optimized reaction conditions with the 10 wt% Pd/C catalyst, we conducted a competitive experiment using **2** and simple thioester **2'** as substrates, and ketone **3'** was obtained in better yield (eq 2).

Table 1. Catalyst Screening for Fukuyama Coupling Reaction Using Sugar-derived Thioester 2



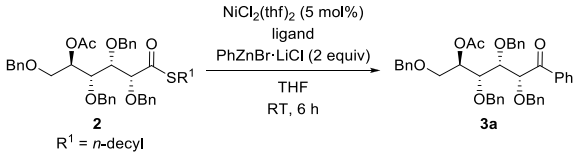
entry	cat.	**3a** (%)[b]	entry	cat.	**3a** (%)[b]
1	$NiCl_2(thf)_2$	46	7	$Pd_2(dba)_3$	<5
2	$Ni(acac)_2$	30	8[c]	Pd/C	70
3	$Ni(OAc)_2$	38	9	$PdCl_2(PPh_3)_2$	52
4	$CoCl_2(thf)_2$	trace	10[d]	$PdCl_2(PPh_3)_2$	64
5	$FeCl_2(thf)_2$	trace	11[e]	Pd/C	81
6	$Pd(OAc)_2$	43	12[f]	-	n.d.

[a] Reaction conditions: **2** (0.25 mmol, 1.0 equiv), PhZnBr·LiCl (0.5 mmol, 2.0 equiv, prepared from $ZnBr_2$·LiCl and PhMgBr), catalyst (5 mol%), RT, THF, 6 h. [b] Isolated yield. [c] 10 wt% Pd/C (2 mol%), 40 °C, THF, 48 h. [d] 40 °C, THF, 48 h. [e] PhZnBr·LiCl (0.75 mmol, 3.0 equiv), 10 wt% Pd/C (2 mol%), 40 °C, THF, 48 h. [f] Without catalyst. n.d. = not detected.



We next screened for the best supporting ligand for $NiCl_2(thf)_2$, and the results are summarized in Table 2. Monodentate phosphine ligands resulted in moderate yields of **3a**. Reaction with bidentate ligands having a C2-C4 carbon linkage afforded **3a** in 47%-56% yield, while the use of dppf gave **3a** in the same yield (56%) as observed for dppe. Other bidentate phosphine ligands, such as DPEphos and Xantphos, afforded **3a** in 34% and 20% yields (entries 8 and 9), although a Xantphos-ligated nickel complex showed high catalytic activity for thioesters with a simple aliphatic chain.[13d] On the other hand, the ligand dCype showed better catalytic activity, giving **3a** in 65% yield (entry 10). In addition, we checked the effect of chelating ligands dppe and dCype, for palladium-catalyzed reactions, but those catalysts were less effective compared with the ligand-free Pd/C catalyst (entries 11 and 12). Accordingly, we selected Pd/C as the best catalyst to promote the practical applicability of our strategy using a Fukuyama coupling reaction for preparing various sugar-derived ketones and biologically active β-aryl-*C*-glycosides, such as Canagliflozin and Dapagliflozin.

Table 2. Ligand Screening for Fukuyama Coupling Reaction Using Sugar-derived Thioester 2[a]

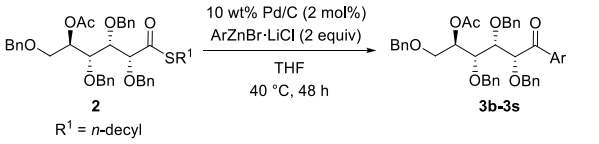


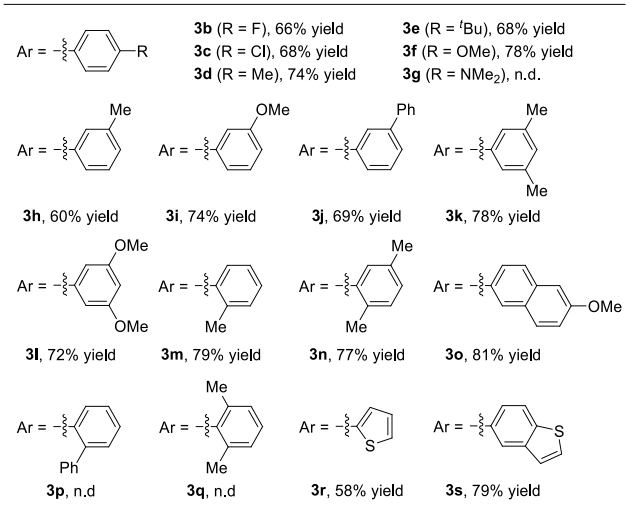
entry	ligand	**3a** (%)[b]	entry	ligand	**3a** (%)[b]
1	PPh_3	52	7	dppf	56
2	PCy_3	60	8	DPEphos	34
3	P(2-furyl)$_3$	24	9	Xantphos	20
4	dppe	56	10	dCype	65
5	dppp	53	11[c]	dppe	36
6	dppb	47	12[c]	dCype	12

[a]Reaction conditions: **2** (0.25 mmol, 1.0 equiv), PhZnBr·LiCl (0.5 mmol, 2.0 equiv, prepared from $ZnBr_2$·LiCl and PhMgBr), $NiCl_2(thf)_2$ (5 mol%), ligand (10 mol% for monodentate phosphine and 5 mol% for bidentate phosphine), RT, THF, 6 h. [b] Isolated yield. [c] $PdCl_2$ (5 mol%) was used instead of $NiCl_2(thf)_2$.

Having developed an efficient synthetic protocol for a Fukuyama coupling reaction of sugar derivatives, we examined substrate scope and limitations of arylzinc reagents including *ortho*, *meta*, and *para*-substitutents, and the results were shown in Table 3. Coupling reactions with a series of *para*-substituted arylzinc reagents gave the corresponding ketones (**3b-f**) in good yields, while a dimethylamino group was not applicable probably due to the coordination of the *tert*-amine moiety. Interestingly, *para*-halo substituted aryl zinc reagents were tolerant under the reaction conditions without participation of the reactive halo terminus for Fukuyama coupling reaction. *Meta*-methyl, methoxy, phenyl, dimethyl, and dimethoxy substituents on the aryl ring were applicable to afford the corresponding ketones (**3h-l**) in 60-78% yields, respectively. Further study of *ortho*-substituted arylzinc reagents with thioester **2** gave the corresponding coupling products (**3m-n**) in good yields, whereas *ortho*-phenyl and bulky *ortho*-dimethyl-substituted ones were inactive for this coupling reaction. 6-Methoxy-2-naphthyl zinc reagent also afforded the corresponding cross-coupling product **3o** in excellent yield. In addition to the phenyl and naphtyl rings, heteroarylation with 2-thienyl and benzo[*b*]thiophen-5-yl zinc reagents afforded **3r** and **3s** in good yields, respectively.

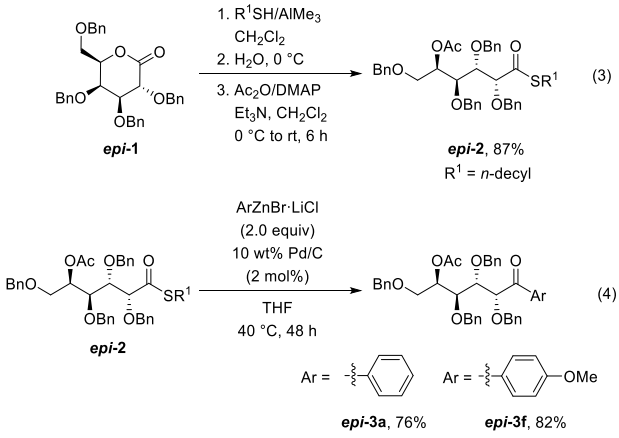
Table 3. Substrate Scope and Limitations of Arylzinc Reagents in Pd/C-catalyzed Fukuyama Coupling Reaction[a]



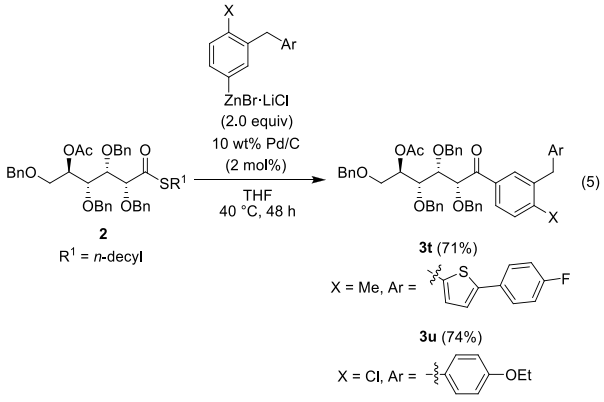


[a]Reaction conditions: **2** (0.25 mmol, 1.0 equiv), ArZnBr·LiCl (0.5 mmol, 2.0 equiv, prepared from $ZnBr_2$·LiCl and ArMgBr), 10 wt% Pd/C (2 mol%), 40 °C, THF, 48 h. Isolated yield. n.d. = not detected.

This Fukuyama coupling reaction is also viable with other sugar precursors. For example, benzyl-protected *D*- galactonolactone ***epi*-1**, was subjected to thioesterification under the same reaction conditions as **1**, giving thioester ***epi*-2** in 87% yield (eq. 3). Further Fukuyama coupling with arylzinc reagents produced the cross-coupling products ***epi*-3a** and ***epi*-3f** in 76% and 82% yields respectively (eq. 4).

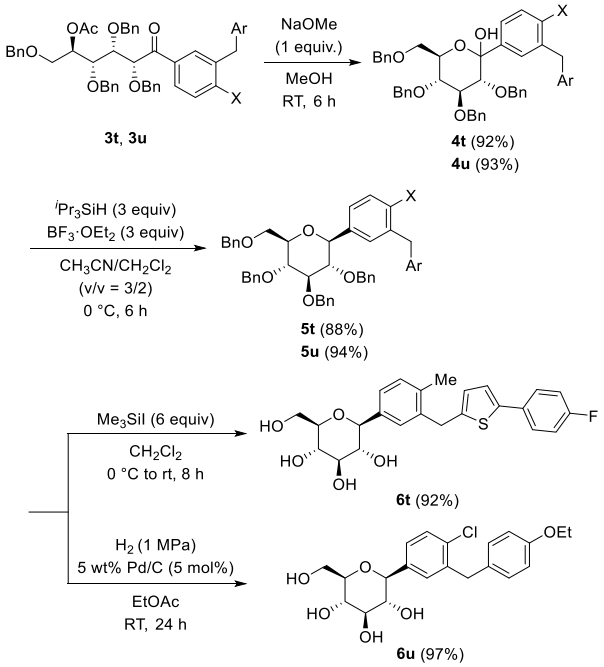


Compatibility of various aromatic substituents on the arylzinc reagents enabled us to apply this Fukuyama coupling reaction to the synthesis of anti-diabetic SGLT2 inhibitors. The required arylzinc reagents were prepared by treating $ZnBr_2$ with the corresponding aryl Grignard reagents.[16] Thioester **2** and 10 wt% Pd/C (2 mol% on Pd cat.) were mixed with *in situ*-prepared ArZnBr·LiCl in THF at 40 °C for 48 h, giving **3t** in 71% yield. No catalyst deactivation was observed even in the presence of a thiophene moiety in the arylzinc motif (eq 5). In a similar manner, ketone **3u** was isolated in 74% yield without any dechlorination of the aryl chloride moiety.



We examined further transformations of **3t** and **3u** to β-aryl-*C*-glycosides *via* cyclic acetal formation and reductive dehydroxylation (Scheme 2). Initially, treatment of **3t** and **3u** with NaOMe in MeOH at room temperature afforded hemiacetals **4t** and **4u** in high yields,[17a] where intramolecular cyclization of the deacetylated intermediates effectively proceeded. Further treatment of **4t** and **4u** with $^{i}Pr_3SiH$ and $BF_3{\cdot}OEt_2$ (both in 3 equiv) in CH_2Cl_2/CH_3CN at 0 °C resulted in exclusive formation of β-isomers, **5t** (88%) and **5u** (94%).[17a-d,18] The high β-selectivity is ascribed to the steric bulkiness around the silicon center: in fact, using Et_3SiH instead of $^{i}Pr_3SiH$ under the similar reaction conditions resulted in lower stereoselectivity (α/β = 1/3~1/4), and lower reaction temperature was necessary to improve the β-selectivity.[18] Finally, benzyl deprotection of the **5t** and **5u** was achieved by following a typical de-benzylation method. The presence of a thiophene moiety in **5t** impaired hydrogenolysis using Pd/C, and we accordingly applied Me_3SiI as a Lewis acid for **5t** at 0 °C, affording the de-benzylated product **6t** in 92% yield. In contrast, hydrogenolysis of the benzylether was compatible with **5u** upon using 5 mol% of Pd/C in EtOAc under a H_2 atmosphere (1 MPa): de-benzylated product **6u** was obtained in 97% yield without contamination of the α-isomer. Notably, even in the presence of an aryl chloride moiety within **5u**, no hydrodehalogenation was observed under the reaction conditions.

Scheme 2. Preparation of Canagliflozin and Dapagliflozin



SUMMARY

We report a new practical strategy for synthesizing pharmaceutically important aryl-*C*-glycosides *without cryogenic conditions*. Nickel- and palladium-catalyzed Fukuyama coupling reactions of *D*-gluconolactone derived thioester **2** with arylzinc reagents provided ketones **3t** and **3u** as important synthetic intermediates, and subsequent cyclization, reductive dehydroxylation, and removal of the benzyl groups gave Canagliflozin and Dapagliflozin, respectively. Further synthetic applications of the present approach to other SGLT2 inhibitors are under current investigation in our laboratories and will be disclosed in due course.

EXPERIMENTAL SECTION

GENERAL EXPERIMENTAL DETAILS. All reactions were performed under argon atmosphere using the standard Schlenk technique and argon-filled glove box. Aryl zinc reagents were prepared by following the literature procedures.[16] Anhydrous solvents were purchased from Kanto Chemical and further purified by passing through activated alumina under positive argon pressure using Grubbs column (Glass Counter

Solvent Dispending System, Nikko Hansen & Co., Ltd.). ^{i}PrMgCl (2.0 M in THF) and $AlMe_3$ (2.0 M in toluene) were purchased and used as received. Other chemicals and solvents were used as received. ^{1}H NMR spectra were measured on a Bruker AV400M (400 MHz) spectrometer at 303 K in 5 mm NMR tubes. Data were reported as follows: chemical shifts in ppm (δ) from tetramethylsilane or the residual solvent as an internal standard in $CHCl_3$ at δ 7.27, DMSO at δ 2.51, and MeOH at δ 3.31, integration multiplicity (s = singlet, d = doublet, t = triplet, dd = doublet of doublets, m = multiplet, dt = doublet of triplets, and ddd = doublet of doublet of doublets), coupling constants (Hz), and integration. $^{13}C\{^1H\}$ NMR spectra were measured on a Bruker AV400M (100 MHz) spectrometer at 303 K with complete proton decoupling. All ^{13}C NMR chemical shifts were reported in ppm (δ) relative to carbon resonances in $CDCl_3$ at δ 77.1 / DMSO-d_6 at δ 39.5. High resolution mass spectra were obtained on JEOL JMS 700. Flash column chromatography was performed by using silica gel 60 (0.040–0.0663 nm, 230–400 mesh ASTM).

Preparation of PhZnBr·LiCl [16]

An oven-dried 30 mL Schlenk-tube containing a magnetic stir bar was charged in a glove box with anhydrous $ZnBr_2$ (450 mg, 2.0 mmol, 1 equiv.) and anhydrous LiCl (85 mg, 2.0 mmol, 1 equiv.), which was then dried in oil bath (100 °C) under vacuum. After flushing the Schlenk-tube with argon, THF (6 mL) was added and stirred for 5-10 min. Phenylmagnesium bromide (1 M in THF) (2 mL, 2.0 mmol, 1.0 equiv.) was added. The reaction mixture was stirred at RT for 1 h and diluted with THF to make approx. 0.25 M concentration as determined by titration with I_2/LiCl, which was used immediately for coupling reactions.

Synthesis of compound 1

A solution of 2,3,4,6-tetra-*O*-benzyl-*D*-glucopyranose (5.0 g, 9.24 mmol) in DMSO (25 mL) was stirred at RT for 30 min under an argon atmosphere. Acetic anhydride (15 mL) was added slowly within 5 min at RT. After the complete addition, the reaction mixture was stirred at RT for 20 h. The reaction progress was monitored by TLC analysis, and then the reaction mixture was diluted with toluene (100 mL). 1 N HClaq (120 mL) was slowly added to quench the excess acetic anhydride. The reaction mixture was stirred at RT for 20 min. After the phase separation, the organic layer was washed with a 1 M aqueous $NaHCO_3$ (3 x 50 mL). Finally, Organic phase was washed with water (15 mL) and brine (15 mL), and then dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The crude material was purified by column chromatography on silica gel (ethyl acetate/hexane = 2/20 ~ 3/20) to afford 2,3,4,6-tetra-*O*-benzyl-*D*-gluconolactone (**1**, 4.8 g, 96%) as a colorless oil.[19a] ^{1}H NMR (400 MHz, $CDCl_3$, 30 ºC) δ 7.39-7.16 (m, 20H), 4.97 (d, *J* = 11.4 Hz, 1H), 4.73-4.44 (m, 8H), 4.12 (d, *J* = 6.4 Hz, 1H), 3.96-3.89 (m, 2H), 3.73-3.64 (m, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, 30 ºC) δ 169.4, 137.7, 137.6, 137.6, 137.1, 128.6, 128.5$_3$, 128.4$_8$, 128.2, 128.0$_9$, 128.0$_7$, 128.0, 127.9, 81.1, 78.3, 77.5, 76.2, 74.0, 73.8, 73.7$_8$, 73.7, 68.4; IR (KBr): 3031, 2921, 2867, 1758, 1457, 1172, 1098, 734, 697 cm^{-1}; HRMS: $[M + H]^+$ calcd for $C_{34}H_{35}O_6$ 539.2428; found 539.2420.

Synthesis of compound *epi*-1

A solution of 2,3,4,6-tetra-*O*-benzyl-*D*-galactopyranose (5.0 g, 9.24 mmol) in DMSO (25 mL) was stirred at RT for 30 min under an argon atmosphere. Acetic anhydride (15 mL) was added slowly within 5 min at RT. After the complete addition, the reaction mixture was stirred at RT for 20 h. The reaction progress was monitored by TLC analysis, and then the reaction mixture was diluted with toluene (100 mL). 1 N HCl aq (120 mL) was slowly added to quench the excess acetic anhydride. The reaction mixture was stirred at RT for 20 min. After the phase separation, the organic layer was washed with a 1 M aqueous $NaHCO_3$ (3 x 50 mL). Finally, Organic phase was washed with water (15 mL) and brine (15 mL), and then dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The crude material was purified by column chromatography on silica gel (ethyl acetate/hexane = 2/20 ~ 3/20) to afford 2,3,4,6-tetra-*O*-benzyl-*D*-galactonolactone (***epi*-1**, 4.34 g, 87%) as a colorless oil.[19b] ^{1}H NMR (400 MHz, $CDCl_3$, 30 ºC) δ 7.42 – 7.39 (m, 2H), 7.36 – 7.21 (m, 18H), 5.17 (d, *J* = 11.0 Hz, 1H), 4.92 (d, *J* = 11.3 Hz, 1H), 4.81 – 4.71 (m, 2H), 4.68 (d, *J* = 11.9 Hz, 1H), 4.60 (d, *J* = 11.3 Hz, 1H), 4.50 (d, *J* = 11.7 Hz, 1H), 4.48 – 4.40 (m, 2H), 4.33 (ddd, *J* = 7.6, 5.5, 1.6 Hz, 1H), 4.15 (t, *J* = 1.9 Hz, 1H), 3.87 (dd, *J* = 9.5, 2.2 Hz, 1H), 3.74 – 3.62 (m, 2H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, 30 ºC) δ 170.1, 137.9, 137.7, 137.6, 128.6, 128.6$_2$, 128.6, 128.5, 128.1$_4$, 128.1$_2$, 128.1, 128.0$_3$, 128.0, 127.9$_6$, 127.7, 80.3, 77.4 (2 C), 75.4, 74.9, 73.8, 72.9, 72.7, 67.7; IR (KBr): 3063, 2920, 2872, 1751, 1455, 1206, 1172, 1105, 737, 698 cm^{-1}; HRMS: $[M + H]^+$ calcd for $C_{34}H_{35}O_6$ 539.2428; found 539.2432.

Synthesis of thioester 2

Step I: To a solution of decanethiol (1.61 g, 9.3 mmol) in anhydrous CH_2Cl_2 (30 mL) cooled at 0 °C was added Me_3Al (9.3 mL, 9.3 mmol, 1 M in toluene) dropwise over 15 min and the mixture was stirred for another 30 min. A solution of compound **1** (5.0 g, 9.3 mmol) in anhydrous CH_2Cl_2 (20 mL) was added slowly over a period of 20 min. After 2 h the reaction mixture was diluted with CH_2Cl_2 (20 mL) and poured slowly into a 250 mL beaker containing ice cooled water (100 mL) with stirring. 1 N HCl aq (30 mL) was added, and organic layer was quickly separated. The aqueous layer was further extracted with cold CH_2Cl_2 (3 x 100 mL). The combined organic layers were washed with water, brine, dried over Na_2SO_4, and filtration with pad of silica (4 cm) using CH_2Cl_2 as eluent, giving crude **A**. The crude **A** was subsequently used for the next step without purification.

Step II: Under an argon atmosphere, to a solution of crude **A** in anhydrous CH_2Cl_2 (100 mL) cooled at 0 °C was added Ac_2O (2.6 mL, 27 mmol) followed by DMAP (23 mg, 2 mol%). After 5 minutes Et_3N (3.8 mL, 27 mmol) was added slowly and the mixture was then stirred under argon at RT for 12 h. The reaction mixture was quenched with water (50 mL), and the organic product was extracted with dichloromethane (3 x 50 mL). The combined organic phase was washed with water (50 mL) and brine (50 mL), and dried over anhydrous Na_2SO_4. After decantation, the mixture was concentrated. The crude material was purified by silica gel column chromatography (ethyl acetate/hexane = 1/20 ~ 2/20) to afford thioester **2** (6.32 g, 90% from **1**) as a colorless liquid. ^{1}H NMR (400 MHz, $CDCl_3$, 30 ºC) δ 7.40 (d, *J* = 6.5 Hz, 2H), 7.36-7.15

(m, 18H), 5.15 (q, *J* = 4.3 Hz, 1H), 4.79 (d, *J* = 10.8 Hz, 1H), 4.71 (d, *J* = 11.4 Hz, 1H), 4.65-4.39 (m, 6H), 4.25 (d, *J* = 4.3 Hz, 1H), 4.01-3.95 (m, 2H), 3.82 (dd, *J* = 10.6, 4.1 Hz, 1H), 3.65 (dd, *J* = 10.6, 5.7 Hz, 1H), 2.84 (t, *J* = 7.4 Hz, 2H), 1.96 (s, 3H), 1.55 (m, 2H), 1.41-1.18 (m, 14H), 0.88 (t, *J* = 6.7 Hz, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, 30 ºC) δ 201.9, 170.0, 138.5, 138.1, 138.0, 137.1, 128.7, 128.4, 128.4, 128.3_6, 128.3, 128.2, 128.0_4, 128.0, 127.8, 127.7, 127.6, 127.5, 85.3, 80.3, 78.5, 75.7, 74.7, 74.5, 73.2, 72.9, 68.1, 31.9, 29.6, 29.6, 29.4, 29.2, 29.1, 28.4, 22.7, 21.1, 14.2; IR (KBr): 3065, 3031, 2924, 2855, 1743, 1678, 1455, 1371, 1238, 1172, 1026, 738, 699 cm^{-1}; HRMS: $[M + H]^+$ calcd for $C_{46}H_{59}O_7S$ 755.3981; found 755.3976.

Synthesis of thioester *epi*-2

Step I: To a solution of decanethiol (0.872 g, 5 mmol) in anhydrous CH_2Cl_2 (30 mL) cooled at 0 °C was added Me_3Al (5 mL, 5 mmol, 1 M in toluene) dropwise over 15 min and the mixture was stirred for another 30 min. A solution of compound ***epi*-1** (2.7 g, 5 mmol) in anhydrous CH_2Cl_2 (20 mL) was added slowly over a period of 20 min. After 2 h the reaction mixture was diluted with CH_2Cl_2 (20 mL) and poured slowly into a 250 mL beaker containing ice cooled water (100 mL) with stirring. 1 N HCl aq (30 mL) was added, and organic layer was quickly separated. The aqueous layer was further extracted with cold CH_2Cl_2 (3 x 100 mL). The combined organic layers were washed with water, brine, dried over Na_2SO_4, and filtration with pad of silica (4 cm) using CH_2Cl_2 as eluent, giving crude compound **B**. The crude compound **B** was subsequently used for the next step without purification.

Step II: Under an argon atmosphere, to a solution of crude compound **B** in anhydrous CH_2Cl_2 (70 mL) cooled at 0 °C was added Ac_2O (1.5 mL, 15 mmol) followed by DMAP (13 mg, 2 mol%). After 5 minutes Et_3N (2.1 mL, 15 mmol) was added slowly and the mixture was then stirred under argon at RT for 12 h. The reaction mixture was quenched with water (50 mL), and the organic product was extracted with dichloromethane (3 x 50 mL). The combined organic phase was washed with water (50 mL) and brine (50 mL), and dried over anhydrous Na_2SO_4. After decantation, the mixture was concentrated. The crude material was purified by silica gel column chromatography (ethyl acetate/hexane = 1/20 ~ 2/20) to afford thioester ***epi*-2** (3.3 g, 87% from ***epi*-1**) as a colorless liquid. ^1H NMR (400 MHz, $CDCl_3$, 30 ºC) δ 7.40 – 7.35 (m, 2H), 7.35 – 7.17 (m, 18H), 5.43 – 5.39 (m, 1H), 4.83 (d, *J* = 11.2 Hz, 1H), 4.56 (dd, *J* = 11.2, 5.5 Hz, 2H), 4.47 – 4.29 (m, 6H), 4.07 (dd, *J* = 7.7, 2.8 Hz, 1H), 3.95 (dd, *J* = 7.8, 2.9 Hz, 1H), 3.66 (dd, *J* = 10.1, 6.3 Hz, 1H), 3.59 (dd, *J* = 10.1, 6.0 Hz, 1H), 2.87 (t, *J* = 7.4 Hz, 2H), 2.00 (s, 3H), 1.60 – 1.52 (m, 2H), 1.38 – 1.16 (m, 14H), 0.87 (t, *J* = 6.7 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, 30 ºC) δ 203.4, 170.6, 138.3, 138.0, 137.8, 137.3, 128.5, 128.4_4, 128.4_3, 128.4, 128.3, 128.2, 128.0, 127.8, 127.7_8, 127.7_3, 127.6, 127.3, 84.8, 80.2, 77.4, 76.1, 74.7, 74.1, 73.7, 73.1, 71.4, 68.4, 32.0, 29.6_4, 29.6, 29.4, 29.2, 29.1, 28.5, 22.8, 21.2, 14.2; IR (KBr): 3064, 3031, 2925, 2855, 1744, 1675, 1498, 1457, 1373, 1236, 1172, 1089, 1026, 734, 697 cm^{-1}; HRMS: $[M + H]^+$ calcd for $C_{46}H_{59}O_7S$ 755.3981; found 755.4001.

General procedure for ligand-free Fukuyama coupling reaction (Tables 1)

An oven dried Schlenk tube was charged with catalyst (0.0125 mmol, 0.05 equiv.) and THF (1 mL) under argon atmosphere. Thioester **2** (0.25 mmol, 190 mg) in THF (2 mL) was added to the reaction mixture followed by addition of PhZnBr·LiCl (0.50 mmol, 2 mL) in THF (0.25 M) by syringe. The reaction mixture was stirred at RT for 6 h. The reaction mixture was quenched with water, and extracted with ethyl acetate (3 x 30 mL). The organic extract was washed with brine, dried over anhydrous Na_2SO_4, and concentrated after filtration. The crude mixture was purified by silica gel column chromatography (ethyl acetate/hexane = 1/20 ~ 2/20) to afford the desired compound **3a**.

Pd/C-catalyzed Fukuyama coupling reaction (Table 1, entry 8)

An oven dried Schlenk tube was cooled under argon atmosphere and charged with thioester **2** (0.25 mmol, 190 mg) followed by addition of 10 wt% Pd/C (0.0005 mmol, 5.4 mg) and THF (2 mL). PhZnBr·LiCl solution (0.25 M in THF) (0.50 mmol, 2 mL) was added in dropwise manner to the reaction mixture by syringe. The reaction mixture was further stirred at 40 °C for 48 h. Allowed the reaction to cool to RT, and then the reaction mixture was quenched with water (1 mL). The reaction mixture was filtered through pad of celite with ethyl acetate (3 x 30 mL). The filtrate was washed with water and brine, and dried over anhydrous Na_2SO_4. After decantation and evaporation, the residue was purified by silica gel column chromatography (ethyl acetate/hexane = 1/20 ~ 2/20) to afford compound **3a** (115 mg, 0.175 mmol, 70%) as a colorless oil. Unreacted starting thioester **2** (53 mg, 27%) was recovered, and biphenyl (14 mg, 36%) obtained as a side product.

Characterization data of compound **3a**. ^1H NMR (400 MHz, $CDCl_3$, 30 ºC) δ 7.92 (d, *J* = 7.8 Hz, 2H), 7.47 (t, *J* = 7.4 Hz, 1H), 7.37-7.22 (m, 15H), 7.21-7.11 (m, 5H), 7.06-7.00 (m, 2H), 5.27 (q, *J* = 5.2 Hz, 1H), 4.89 (d, *J* = 4.2 Hz, 1H), 4.73-4.55 (m, 4H), 4.53-4.46 (m, 3H), 4.31 (d, *J* = 10.8 Hz, 1H), 4.21 (dd, *J* = 6.8, 4.3 Hz, 1H), 4.07 (dd, *J* = 6.8, 3.4 Hz, 1H), 3.87 (dd, *J* = 10.2, 5.4 Hz, 1H), 3.63 (dd, *J* = 10.2, 5.5 Hz, 1H), 1.98 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, 30 ºC) δ 199.0, 169.9, 138.4, 137.9, 137.8, 137.1, 136.0_5, 133.1, 129.0, 128.8, 128.5, 128.4, 128.3, 128.2_6, 128.1_9, 128.0, 127.9, 127.8, 127.7_3, 127.7, 127.5, 127.4_5, 82.7, 80.4, 79.6, 75.3, 74.6, 73.2, 73.1, 72.6, 67.9, 21.1; IR (KBr): 3065, 3028, 2925, 2868, 1748, 1684, 1557, 1538, 1449, 1369, 1236, 1090, 1027, 738, 696 cm^{-1}; HRMS: $[M + H]^+$ calcd for $C_{42}H_{43}O_7$ 659.3009; found 659.3004.

Large Scale Fukuyama coupling reaction of 2 and PhZnBr·LiCl catalyzed by Pd/C

An oven dried Schlenk tube was cooled under argon atmosphere and charged with thioester **2** (1.0 mmol, 755 mg) followed by addition of 10 wt% Pd/C (0.020 mmol, 21.6 mg) and THF (6 mL). PhZnBr·LiCl solution (0.25 M in THF) (2.0 mmol, 8 mL) was added in dropwise manner to the reaction mixture by syringe. The reaction mixture was further stirred at 40 °C for 48 h. Allowed the reaction to cool to RT, and then the reaction mixture was quenched with water (1 mL). The reaction mixture was filtered through pad of celite with

ethyl acetate (3 x 50 mL). The filtrate was washed with water and brine, and dried over anhydrous Na_2SO_4. After decantation and evaporation, the residue was purified by silica gel column chromatography (ethyl acetate/hexane = 1/20 ~ 2/20) to afford compound **3a** as a colorless oil (468 mg, 0.71 mmol, 71%). Unreacted starting thioester **2** (181 mg, 24%) was recovered.

General procedure for Ni-catalyzed Fukuyama coupling reaction (Tables 2)

An oven dried Schlenk tube was charged with $NiCl_2(thf)_2$ (0.0125 mmol, 0.05 equiv.), ligand (10 mol% for monodentate phosphine and 5 mol% for bidentate phosphine), and THF (1 mL) under argon atmosphere. Thioester **2** (0.25 mmol, 190 mg) in THF (2 mL) was added to the reaction mixture, followed by addition of PhZnBr·LiCl (0.50 mmol, 2 mL) in THF (0.25 M) by syringe. The reaction mixture was stirred at RT for 6 h. The reaction mixture was quenched with water and extracted with ethyl acetate (3 x 30 mL). The organic extract was washed with brine, dried over anhydrous Na_2SO_4, and then the mixture was concentrated after filtration. The crude mixture was purified by silica gel column chromatography (ethyl acetate/hexane = 1/20 ~ 2/20) to afford the desired compound **3a**.

Competitive experiment using Pd/C catalyst

An oven dried Schlenk tube was cooled under argon atmosphere and charged with thioester **2** (0.25 mmol, 190 mg), thioester **2'** (0.25 mmol, 77 mg), 10 wt% Pd/C (0.005 mmol, 5.4 mg), and THF (2 mL). PhZnBr·LiCl (0.25 M in THF) (1.0 mmol, 4 mL) was added to the reaction mixture by syringe. The reaction mixture was stirred at 40 °C for 24 h. Allowed the reaction to cool to RT, and then reaction was quenched with water (1 mL). Reaction mixture filtered through pad of celite and washed with ethyl acetate (3 x 30 mL). The filtrate was washed with water and brine, and dried over anhydrous Na_2SO_4. After decantation and evaporation, the residue was purified by silica gel column chromatography (ethyl acetate/hexane = 1/20 ~ 2/20) to afford **3a** (89 mg, 0.135 mmol, 54%) and **3'** (40 mg, 0.19 mmol, 76%).

Characterization data of compound **3'**[20]. ^{1}H NMR (400 MHz, $CDCl_3$, 30 ºC) δ 7.95 (d, *J* = 7.3 Hz, 2H), 7.55 (t, *J* = 7.4 Hz, 1H), 7.45 (t, *J* = 7.6 Hz, 2H), 7.32 – 7.23 (m, 4H), 7.20 (t, *J* = 7.0 Hz, 1H), 3.30 (t, *J* = 7.7 Hz, 2H), 3.07 (t, *J* = 7.7 Hz, 2H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, 30 ºC) δ 199.3, 141.5, 137.1, 133.2, 128.7$_4$, 128.7, 128.6, 128.2, 126.3, 40.6, 30.3.

General procedure for Pd/C-catalyzed Fukuyama coupling reaction (Table 3, for compounds 3b-3s; *epi*-3a and *epi*-3f)

An oven dried Schlenk tube was cooled under argon atmosphere and charged with thioester **2** (0.25 mmol, 190 mg) followed by addition of 10 wt% Pd/C (0.005 mmol, 5.4 mg) and THF (2 mL). ArZnBr·LiCl solution (0.25 M in THF) (0.50 mmol, 2 mL) was added in dropwise manner to the reaction mixture by syringe. The reaction mixture was further stirred at 40 °C for 48 h. Allowed the reaction to cool to RT, and then the reaction mixture was quenched with water (1 mL). The reaction mixture was filtered through pad of celite with ethyl acetate (3 x 30 mL). The filtrate was washed with water and brine, and dried over anhydrous Na_2SO_4. After decantation and evaporation, the residue was purified by silica gel column chromatography (ethyl acetate/hexane = 1/20 ~ 3/20) to afford compound **3**

Characterization data of compound **3b**. Purified by silica gel column chromatography (ethyl acetate/hexane = 1/20 ~ 3/20) as a colorless oil (112 mg, 66% yield); ^{1}H NMR (400 MHz, $CDCl_3$, 30 ºC) δ 7.96 (dd, *J* = 8.8, 5.6 Hz, 2H), 7.36 – 7.12 (m, 18H), 7.00 (dd, *J* = 7.5, 2.1 Hz, 2H), 6.88 (t, *J* = 8.7 Hz, 2H), 5.28 – 5.25 (m, 1H), 4.77 (d, *J* = 4.0 Hz, 1H), 4.68 – 4.47 (m, 7H), 4.31 (d, *J* = 10.8 Hz, 1H), 4.17 (dd, *J* = 7.0, 4.1 Hz, 1H), 4.08 (dd, *J* = 7.0, 3.4 Hz, 1H), 3.89 (dd, *J* = 10.2, 5.4 Hz, 1H), 3.65 (dd, *J* = 10.2, 5.5 Hz, 1H), 1.99 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, 30 ºC) δ 197.9, 170.1, 165.8 (d, *J* = 256.0 Hz), 138.5, 138.0, 137.8, 137.0, 132.4 (d, *J* = 3.0 Hz), 132.1, 132.0, 128.9, 128.6, 128.5, 128.4, 128.3, 128.2, 128.1, 127.9, 127.8$_5$, 127.6 (d, *J* = 7.1 Hz), 115.4 (d, *J* = 21.2 Hz), 83.4, 80.6, 79.7, 75.5, 74.8, 73.4, 73.3, 72.7, 68.1, 21.2; IR (KBr): 3066, 3031, 2925, 2862, 1742, 1700, 1600, 1509, 1454, 1369, 1242, 1155, 1025, 744, 700 cm^{-1}; HRMS: [M + H]$^+$ calcd. for $C_{42}H_{42}FO_7$ 677.2915; found 677.2914.

Characterization data of compound **3c**. Purified by silica gel column chromatography (ethyl acetate/hexane = 1/20 ~ 3/20) as a colorless oil (118 mg, 68% yield); ^{1}H NMR (400 MHz, $CDCl_3$, 30 ºC) δ 7.84 (d, *J* = 8.6 Hz, 2H), 7.33 – 7.21 (m, 15H), 7.20 – 7.12 (m, 5H), 7.00 (dd, *J* = 7.8, 1.5 Hz, 2H), 5.24 – 5.27 (m, 1H), 4.77 (d, *J* = 4.0 Hz, 1H), 4.69 – 4.53 (m, 4H), 4.53 – 4.46 (m, 3H), 4.30 (d, *J* = 10.9 Hz, 1H), 4.16 (dd, *J* = 7.0, 4.1 Hz, 1H), 4.08 (dd, *J* = 7.0, 3.4 Hz, 1H), 3.89 (dd, *J* = 10.2, 5.5 Hz, 1H), 3.64 (dd, *J* = 10.2, 5.4 Hz, 1H), 1.99 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, 30 ºC) δ 198.3, 170.1, 139.6, 138.5, 138.0, 137.7, 137.0, 134.4, 130.8, 128.9, 128.6$_3$, 128.6$_1$, 128.5, 128.4$_3$, 128.4, 128.2$_2$, 128.2, 127.9$_3$, 127.9, 127.7, 127.6, 83.3, 80.6, 79.7, 75.5, 74.8, 73.5, 73.4, 72.7, 68.1, 21.2; IR (KBr): 3062, 3032, 2951, 2869, 1737, 1686, 1589, 1495, 1453, 1373, 1235, 1096, 1025, 745, 697 cm^{-1}; HRMS: [M + H]$^+$ calcd. for $C_{42}H_{42}ClO_7$ 693.2619; found 693.2610.

Characterization data of compound **3d**. Purified by silica gel column chromatography (ethyl acetate/hexane = 1/20 ~ 3/20) as a colorless oil (125 mg, 74% yield); ^{1}H NMR (400 MHz, $CDCl_3$, 30 ºC) δ 7.85 (d, *J* = 8.2 Hz, 2H), 7.33 – 7.22 (m, 13H), 7.20 – 7.14 (m, 5H), 7.07 – 7.04 (m, 4H), 5.29 – 5.25 (m, 1H), 4.89 (d, *J* = 4.3 Hz, 1H), 4.69 – 4.56 (m, 4H), 4.54 – 4.45 (m, 3H), 4.33 (d, *J* = 10.8 Hz, 1H), 4.21 (dd, *J* = 6.8, 4.3 Hz, 1H), 4.05 (dd, *J* = 6.8, 3.5 Hz, 1H), 3.87 (dd, *J* = 10.3, 5.4 Hz, 1H), 3.63 (dd, *J* = 10.2, 5.5 Hz, 1H), 2.36 (s, 3H), 1.98 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, 30 ºC) δ 198.3, 170.1, 144.1, 138.6, 138.1, 138.0, 137.4, 133.7, 129.21, 129.2, 128.9, 128.6, 128.4$_3$, 128.4$_1$, 128.3, 128.2, 128.0, 127.9, 127.8, 127.6, 127.5, 82.7, 80.6, 79.8, 75.4, 74.7, 73.3, 73.1, 72.7, 68.0, 21.8, 21.2; IR (KBr): 3064, 3030, 2921, 2866, 1738, 1685, 1606, 1497, 1453, 1370, 1238, 1096, 1024, 742, 698 cm^{-1}; HRMS: [M + H]$^+$ calcd. for $C_{43}H_{45}O_7$ 673.3165; found 673.3174.

Characterization data of compound **3e**. Purified by silica gel column chromatography (ethyl acetate/hexane = 1/20 ~ 3/20) as a colorless oil (122 mg, 68% yield); ^{1}H NMR (400 MHz, $CDCl_3$, 30 ºC) δ 7.86 (d, *J* = 8.6 Hz, 2H), 7.39 – 7.23 (m, 16H), 7.18 – 7.13 (m, 4H), 7.05 – 7.02 (m, 2H), 5.30 – 5.26 (m, 1H), 4.90 (d, *J* = 4.3 Hz, 1H), 4.69 – 4.46 (m, 7H), 4.32 (d, *J* = 10.8 Hz, 1H), 4.20 (dd, *J* = 6.8, 4.3 Hz, 1H), 4.07 (dd, *J* = 6.9, 3.5 Hz, 1H), 3.89 (dd, *J* = 10.2, 5.4 Hz, 1H), 3.64 (dd, *J* = 10.3,

5.5 Hz, 1H), 1.98 (s, 3H), 1.30 (s, 9H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, 30 ºC) δ 198.2, 170.1, 157.0, 138.6, 138.1, 138.0, 137.4, 133.5, 129.0, 128.9, 128.6, 128.5, 128.4, 128.3, 128.2, 128.0, 127.9, 127.8, 127.6, 127.5$_5$, 125.5, 82.5, 80.6, 79.9, 75.4, 74.8, 73.4, 73.0, 72.8, 68.1, 35.2, 31.2, 21.2; IR (KBr): 3062, 3031, 2962, 2867, 1737, 1672, 1604, 1497, 1455, 1365, 1236, 1100, 1026, 734, 697 cm^{-1}; HRMS: $[M + H]^+$ calcd. for $C_{46}H_{51}O_7$ 715.3629; found 715.3632.

Characterization data of compound **3f**. Purified by silica gel column chromatography (ethyl acetate/hexane = 1/20 ~ 3/20) as a colorless oil (135 mg, 78% yield); ^1H NMR (400 MHz, $CDCl_3$, 30 ºC) δ 7.96 (d, *J* = 8.9 Hz, 2H), 7.35 – 7.22 (m, 13H), 7.20 – 7.15 (m, 5H), 7.06 – 7.03 (m, 2H), 6.72 (d, *J* = 8.9 Hz, 2H), 5.30 – 5.28 (m, 1H), 4.85 (d, *J* = 4.3 Hz, 1H), 4.68 – 4.54 (m, 4H), 4.50 – 4.45 (m, 3H), 4.35 (d, *J* = 10.8 Hz, 1H), 4.19 (dd, *J* = 6.7, 4.4 Hz, 1H), 4.05 (dd, *J* = 6.8, 3.5 Hz, 1H), 3.89 (dd, *J* = 10.3, 5.3 Hz, 1H), 3.80 (s, 3H), 3.64 (dd, *J* = 10.3, 5.5 Hz, 1H), 1.98 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, 30 ºC) δ 197.2, 170.1, 163.7, 138.6, 138.1, 138.0, 137.3, 131.6, 129.1, 128.9, 128.5, 128.4$_3$, 128.4$_1$, 128.3, 128.1, 128.0, 127.9, 127.8, 127.6, 127.5, 113.7, 82.9, 80.7, 79.8, 75.5, 74.7, 73.3, 73.0, 72.7, 68.1, 55.5, 21.2; IR (KBr): 3063, 3031, 2911, 2867, 1739, 1671, 1600, 1510, 1453, 1368, 1238, 1098, 1026, 736, 698 cm^{-1}; HRMS: $[M + H]^+$ calcd. for $C_{43}H_{45}O_8$ 689.3114; found 689.3115.

Characterization data of compound **3h**. Purified by silica gel column chromatography (ethyl acetate/hexane = 1/20 ~ 3/20) as a colorless oil (101 mg, 60% yield); ^1H NMR (400 MHz, $CDCl_3$, 30 ºC) δ 7.73 – 7.70 (m, 2H), 7.37 – 7.27 (m, 8H), 7.25 – 7.13 (m, 12H), 7.07 – 7.05 (m, 2H), 5.30 – 5.26 (m, 1H), 4.88 (d, *J* = 4.3 Hz, 1H), 4.65 – 4.45 (m, 7H), 4.35 (d, *J* = 10.8 Hz, 1H), 4.20 (dd, *J* = 6.7, 4.4 Hz, 1H), 4.05 (dd, *J* = 6.7, 3.6 Hz, 1H), 3.86 (dd, *J* = 10.4, 5.2 Hz, 1H), 3.64 (dd, *J* = 10.4, 5.6 Hz, 1H), 2.26 (s, 3H), 1.98 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, 30 ºC) δ 199.4, 170.1, 138.6, 138.3, 138.1, 138.0, 137.3, 136.3, 134.0, 129.7, 128.9, 128.6, 128.4, 128.3$_9$, 128.3, 128.2, 128.0, 127.9, 127.8$_2$,127.8, 127.5$_9$, 127.5$_7$, 126.3, 82.7, 80.6, 79.7, 75.4, 74.7, 73.3, 73.1, 72.8, 68.1, 21.4, 21.2; IR (KBr): 3063, 3030, 2917, 2866, 1737, 1676, 1602, 1496, 1455, 1370, 1237, 1094, 1027, 737, 697 cm^{-1}; HRMS: $[M]^+$ calcd. for $C_{43}H_{45}O_7$ 673.3165; found 673.3163.

Characterization data of compound **3i**. Purified by silica gel column chromatography (ethyl acetate/hexane = 1/20 ~ 3/20) as a colorless oil (128 mg, 74% yield); ^1H NMR (400 MHz, $CDCl_3$, 30 ºC) δ 7.51 – 7.47 (m, 2H), 7.33 – 7.21 (m, 13H), 7.19 – 7.12 (m, 6H), 7.08 – 7.02 (m, 3H), 5.29 – 5.26 (m, 1H), 4.89 (d, *J* = 4.2 Hz, 1H), 4.67 – 4.46 (m, 7H), 4.31 (d, *J* = 10.9 Hz, 1H), 4.22 (dd, *J* = 6.8, 4.2 Hz, 1H), 4.07 (dd, *J* = 6.8, 3.5 Hz, 1H), 3.86 (dd, *J* = 10.3, 5.4 Hz, 1H), 3.67 (s, 3H), 3.63 (dd, *J* = 10.2, 5.5 Hz, 1H), 1.98 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, 30 ºC) δ 198.7, 170.1, 159.7, 138.5, 138.0$_3$, 138.0, 137.5, 137.3, 129.4, 128.9, 128.6, 128.4, 128.3, 128.3, 128.2, 128.0, 127.9$_1$, 127.9, 127.8, 127.6, 127.5$_7$, 121.6, 120.1, 113.1, 82.8, 80.7, 79.7, 75.4, 74.7, 73.3, 73.2, 72.7, 68.0, 55.4, 21.2; IR (KBr): 3064, 3032, 2929, 2867, 1737, 1672, 1623, 1484, 1456, 1270, 1240, 1029, 741, 699 cm^{-1}; HRMS: $[M + H]^+$ calcd. for $C_{43}H_{45}O_8$ 689.3114; found 689.3118.

Characterization data of compound **3j**. Purified by silica gel column chromatography (ethyl acetate/hexane = 1/20 ~ 3/20) as a colorless oil (127 mg, 69% yield); ^1H NMR (400 MHz, $CDCl_3$, 30 ºC) δ 8.19 (t, *J* = 1.7 Hz, 1H), 7.87 (dt, *J* = 7.8, 1.3 Hz, 1H), 7.72 – 7.70 (m, 1H), 7.45 – 7.26 (m, 16H), 7.25 – 7.21 (m, 4H), 7.18 – 7.16 (m, 2H), 7.12 – 7.09 (m, 2H), 7.05 – 7.02 (m, 2H), 5.31 – 5.27 (m, 1H), 4.89 (d, *J* = 4.3 Hz, 1H), 4.65 – 4.35 (m, 8H), 4.23 (dd, *J* = 6.8, 4.3 Hz, 1H), 4.09 (dd, *J* = 6.8, 3.6 Hz, 1H), 3.86 (dd, *J* = 10.3, 5.1 Hz, 1H), 3.64 (dd, *J* = 10.3, 5.6 Hz, 1H), 1.97 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, 30 ºC) δ 199.5, 170.1, 141.6, 140.3, 138.5, 138.0, 137.9, 137.2, 136.8, 131.8, 128.9, 128.8$_6$, 128.7, 128.6, 128.5, 128.4$_5$, 128.3, 128.2, 128.1, 128.0, 127.9$_5$, 127.9, 127.8, 127.7$_7$, 127.6, 127.3, 127.1, 83.2, 80.6, 79.6, 75.4, 74.7, 73.3, 72.8, 68.0, 65.6, 21.2; IR (KBr): 3064, 3030, 2918, 2860, 1736, 1670, 1584, 1454, 1397, 1235, 1108, 1028, 736, 696 cm^{-1}; HRMS: $[M]^+$ calcd. for $C_{48}H_{47}O_7$ 735.3322; found 735.3318.

Characterization data of compound **3k**. Purified by silica gel column chromatography (ethyl acetate/hexane = 1/20 ~ 3/20) as a colorless oil (134 mg, 78% yield); ^1H NMR (400 MHz, $CDCl_3$, 30 ºC) δ 7.54 (s, 2H), 7.34 – 7.27 (m, 4H), 7.27 – 7.21 (m, 10H), 7.19 – 7.07 (m, 7H), 5.31 – 5.27 (m, 1H), 4.88 (d, *J* = 4.4 Hz, 1H), 4.63 – 4.60 (m, 3H), 4.53 – 4.40 (m, 5H), 4.19 (dd, *J* = 6.5, 4.5 Hz, 1H), 4.02 (dd, *J* = 6.5, 3.8 Hz, 1H), 3.85 (dd, *J* = 10.6, 4.8 Hz, 1H), 3.64 (dd, *J* = 10.6, 5.8 Hz, 1H), 2.22 (s, 6H), 1.98 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, 30 ºC) δ 199.8, 170.1, 138.6, 138.1, 137.4, 136.5, 135.0, 128.8, 128.5, 128.4$_8$, 128.4, 128.3$_7$, 128.3, 128.2, 128.0, 127.9, 127.8, 127.7, 127.6, 127.5, 126.9, 82.6, 80.7, 79.5, 75.4, 74.5, 73.2, 73.1, 72.8, 68.1, 21.3, 21.2; IR (KBr): 3063, 3028, 2917, 2849, 1738, 1665, 1598, 1496, 1454, 1395, 1237, 1107, 1028, 735, 696 cm^{-1}; HRMS: $[M]^+$ calcd. for $C_{44}H_{47}O_7$ 687.3322; found 687.3326.

Characterization data of compound **3l**. Purified by silica gel column chromatography (ethyl acetate/hexane = 1/20 ~ 3/20) as a colorless oil (130 mg, 72% yield); ^1H NMR (400 MHz, $CDCl_3$, 30 ºC) δ 7.33 – 7.21 (m, 13H), 7.18 – 7.16 (m, 5H), 7.12 (d, *J* = 2.3 Hz, 2H), 7.07 (dd, *J* = 6.5, 2.9 Hz, 2H), 6.60 (t, *J* = 2.3 Hz, 1H), 5.29 – 5.25 (m, 1H), 4.89 (d, *J* = 4.2 Hz, 1H), 4.68 – 4.47 (m, 7H), 4.35 (d, *J* = 10.9 Hz, 1H), 4.23 (dd, *J* = 6.8, 4.2 Hz, 1H), 4.05 (dd, *J* = 6.8, 3.6 Hz, 1H), 3.84 (dd, *J* = 10.3, 5.3 Hz, 1H), 3.66 (s, 6H), 3.61 (dd, *J* = 10.3, 5.6 Hz, 1H), 1.98 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, 30 ºC) δ 198.7, 170.1, 160.8, 138.5, 138.1, 138.0, 137.3, 128.8, 128.5, 128.4, 128.3$_7$, 128.3$_1$, 128.2, 128.0, 127.9$_3$, 127.9, 127.8, 127.6, 127.6, 106.8, 105.9, 82.8, 80.8, 79.6, 75.4, 74.6, 73.2, 72.8, 67.8, 55.6, 21.2; IR (KBr): 3064, 3032, 2923, 2865, 1738, 1701, 1592, 1456, 1239, 1206, 1157, 1098, 1071, 735, 699 cm^{-1}; HRMS: $[M + H]^+$ calcd. for $C_{44}H_{47}O_9$ 719.3220; found 719.3229.

Characterization data of compound **3m**. Purified by silica gel column chromatography (ethyl acetate/hexane = 1/20 ~ 2/20) as a colorless oil (133 mg, 79% yield); ^1H NMR (400 MHz, $CDCl_3$, 30 ºC) δ 7.68 (dd, *J* = 7.8, 1.4 Hz, 1H), 7.37 – 7.22 (m, 13H), 7.21 – 7.16 (m, 7H), 7.13 – 7.09 (m, 2H), 7.02 (td, *J* = 7.6, 1.3 Hz, 1H), 5.27 – 5.24 (m, 1H), 4.75 (d, *J* = 4.2 Hz, 1H), 4.69 – 4.45 (m, 7H), 4.33 (d, *J* = 10.8 Hz, 1H), 4.18 (dd, *J* = 7.1, 4.2 Hz, 1H), 4.08 (dd, *J* = 7.0, 3.5 Hz, 1H), 3.86 (dd, *J* = 10.3, 5.1 Hz, 1H), 3.66 (dd, *J* = 10.3, 5.7 Hz, 1H), 2.38 (s, 3H), 1.98 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, 30 ºC) δ 202.8, 170.1, 138.6, 138.5$_8$, 138.2, 138.1, 137.3, 136.4, 131.9, 131.4,

129.9, 129.4, 129.2, 128.9, 128.6, 128.4, 128.3, 128.1$_9$, 128.1$_8$, 128.0, 127.9$_6$, 127.9, 127.6, 127.5$_5$, 125.3, 83.7, 80.4, 79.7, 75.4, 74.8, 73.5, 73.4, 73.0, 68.0, 21.2, 20.9; IR (KBr): 3062, 3030, 2918, 2867, 1736, 1699, 1599, 1496, 1454, 1370, 1237, 1097, 1027, 735, 697 cm^{-1}; HRMS: [M]$^+$ calcd. for $C_{43}H_{45}O_7$ 673.3165; found 673.3165.

Characterization data of compound **3n**. Purified by silica gel column chromatography (ethyl acetate/hexane = 1/20 ~ 3/20) as a colorless oil (133 mg, 77% yield); ^{1}H NMR (400 MHz, $CDCl_3$, 30 ºC) δ 7.50 (s, 1H), 7.32 – 7.27 (m, 6H), 7.24 – 7.11 (m, 16H), 5.29 – 5.25 (m, 1H), 4.72 (d, *J* = 4.4 Hz, 1H), 4.67 (d, *J* = 10.8 Hz, 1H), 4.62 (d, *J* = 11.4 Hz, 1H), 4.53 – 4.40 (m, 6H), 4.17 (dd, *J* = 6.8, 4.4 Hz, 1H), 4.05 (dd, *J* = 6.8, 3.6 Hz, 1H), 3.86 (dd, *J* = 10.5, 4.7 Hz, 1H), 3.68 (dd, *J* = 10.5, 5.9 Hz, 1H), 2.35 (s, 3H), 2.12 (s, 3H), 1.98 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, 30 ºC) δ 203.6, 170.1, 138.6, 138.3, 138.1, 137.4, 136.6, 135.2, 134.9, 132.1, 131.6, 130.0, 128.8, 128.5, 128.4, 128.3, 128.2, 128.1$_7$, 128.0, 127.9, 127.8, 127.7$_9$, 127.6, 127.5, 83.8, 80.6, 79.7, 75.5, 74.6, 73.4, 73.3, 73.0, 68.1, 21.2, 20.8, 20.3; IR (KBr): 3063, 3030, 2919, 2865, 1736, 1685, 1496, 1454, 1370, 1237, 1096, 1027, 735, 697 cm^{-1}; HRMS: [M]$^+$ calcd. for $C_{44}H_{47}O_7$ 687.3322; found 687.3318.

Characterization data of compound **3o**. Purified by silica gel column chromatography (ethyl acetate/hexane = 1/20 ~ 3/20) as a colorless oil (150 mg, 81% yield); ^{1}H NMR (400 MHz, $CDCl_3$, 30 ºC) δ 8.46 (d, *J* = 1.7 Hz, 1H), 7.97 (dd, *J* = 8.6, 1.7 Hz, 1H), 7.63 (d, *J* = 8.6 Hz, 1H), 7.63 (d, *J* = 8.6 Hz, 1H), 7.57 (d, *J* = 9.5 Hz, 1H), 7.32 – 7.19 (m, 14H), 7.16 – 7.08 (m, 6H), 7.03 (dd, *J* = 7.4, 2.1 Hz, 2H), 5.34 – 5.31 (m, 1H), 4.99 (d, *J* = 4.4 Hz, 1H), 4.69 – 4.40 (m, 8H), 4.26 (dd, *J* = 6.6, 4.4 Hz, 1H), 4.07 (dd, *J* = 6.6, 3.7 Hz, 1H), 3.94 (s, 3H), 3.87 (dd, *J* = 10.5, 4.9 Hz, 1H), 3.66 (dd, *J* = 10.5, 5.7 Hz, 1H), 1.98 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, 30 ºC) δ 198.7, 170.1, 160.0, 138.5, 138.0, 137.9, 137.4, 137.3, 131.5$_5$, 131.5$_2$, 131.2, 128.8, 128.5, 128.4, 128.3$_8$, 128.2, 128.1, 128.0, 127.8, 127.7$_6$, 127.5, 127.5, 127.0, 125.4, 119.5, 105.8, 82.8, 80.7, 79.5, 75.4, 74.5, 73.2, 73.1, 72.7, 68.1, 55.5, 21.2; IR (KBr): 3061, 3032, 2934, 2865, 1737, 1671, 1624, 1480, 1456, 1369, 1271, 1237, 1100, 1026, 738, 697 cm^{-1}; HRMS: [M + H]$^+$ calcd. for $C_{47}H_{47}O_8$ 739.3271; found 739.3270.

Characterization data of compound **3r**. Purified by silica gel column chromatography (ethyl acetate/hexane = 1/20 ~ 3/20) as a colorless oil (97 mg, 58% yield); ^{1}H NMR (400 MHz, $CDCl_3$, 30 ºC) δ 7.89 (d, *J* = 3.7 Hz, 1H), 7.60 (d, *J* = 4.8 Hz, 1H), 7.33 – 7.14 (m, 18H), 7.02 – 7.00 (m, 2H), 6.94 (t, *J* = 4.0 Hz, 1H), 5.27 – 5.23 (m, 1H), 4.70 – 4.43 (m, 9H), 4.15 (dd, *J* = 6.6, 4.5 Hz, 1H), 4.04 (dd, *J* = 6.5, 3.9 Hz, 1H), 3.86 (dd, *J* = 10.4, 4.9 Hz, 1H), 3.66 (dd, *J* = 10.4, 5.6 Hz, 1H), 1.97 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, 30 ºC) δ 192.2, 170.1, 142.0, 138.6, 138.0, 137.9, 137.1, 134.5, 134.3, 128.7, 128.5, 128.4$_7$, 128.3, 128.2, 128.1$_3$, 128.1, 128.0, 127.9, 127.8, 127.6$_4$, 127.6, 84.4, 80.7, 79.3, 75.7, 74.8, 73.5, 73.4, 72.8, 68.1, 21.2; IR (KBr): 3065, 3032, 2918, 2868, 1736, 1656, 1497, 1454, 1412, 1235, 1094, 1027, 735, 696 cm^{-1}; HRMS: [M + H]$^+$ calcd. for $C_{40}H_{41}O_7S$ 665.2573; found 665.2572.

Characterization data of compound **3s**. Purified by silica gel column chromatography (ethyl acetate/hexane = 1/20 ~ 3/20) as a colorless oil (141 mg, 79% yield); ^{1}H NMR (400 MHz, $CDCl_3$, 30 ºC) δ 8.45 (d, *J* = 1.6 Hz, 1H), 7.91 (dd, *J* = 8.5, 1.7 Hz, 1H), 7.75 (d, *J* = 8.5 Hz, 1H), 7.45 (d, *J* = 5.4 Hz, 1H), 7.31 – 7.20 (m, 14H), 7.15 (dd, *J* = 6.7, 2.8 Hz, 2H), 7.13 – 7.08 (m, 3H), 7.01 (dd, *J* = 7.5, 1.9 Hz, 2H), 5.31 (q, *J* = 5.3 Hz, 1H), 4.95 (d, *J* = 4.3 Hz, 1H), 4.67 – 4.45 (m, 7H), 4.37 (d, *J* = 10.8 Hz, 1H), 4.25 (dd, *J* = 6.7, 4.3 Hz, 1H), 4.08 (dd, *J* = 6.7, 3.6 Hz, 1H), 3.88 (dd, *J* = 10.4, 5.2 Hz, 1H), 3.65 (dd, *J* = 10.3, 5.6 Hz, 1H), 1.98 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, 30 ºC) δ 199.0, 170.1, 144.5, 139.3, 138.5, 138.0, 137.9, 137.2, 132.7, 128.9, 128.6, 128.4, 128.3, 128.1$_3$, 128.1, 127.9, 127.8$_3$, 127.8, 127.6, 127.5$_6$, 125.5$_3$, 124.9, 124.3, 122.4, 83.0, 80.7, 79.7, 75.5, 74.7, 73.3, 73.2, 72.7, 68.1, 21.2; IR (KBr): 3066, 3030, 2923, 2864, 1739, 1674, 1595, 1497, 1454, 1369, 1238, 1095, 1027, 738, 697 cm^{-1}; HRMS: [M + H]$^+$ calcd. for $C_{44}H_{43}O_7S$ 715.2729; found 715.2732.

Characterization data of compound ***epi*-3a**. Purified by silica gel column chromatography (ethyl acetate/hexane = 1/20 ~ 3/20) as a colorless oil (125 mg, 76% yield); ^{1}H NMR (400 MHz, $CDCl_3$, 30 ºC) δ 8.08 (d, *J* = 8.3 Hz, 2H), 7.53 (t, *J* = 7.4 Hz, 1H), 7.37 (t, *J* = 7.6 Hz, 2H), 7.39 – 7.21 (m, 16H), 7.16 – 7.11 (m, 4H), 5.44 – 5.41 (m, 1H), 4.92 – 4.91 (m, 1H), 4.61 (d, *J* = 11.3 Hz, 1H), 4.54 (d, *J* = 11.7 Hz, 1H), 4.47 – 4.29 (m, 6H), 4.17 (dd, *J* = 8.2, 3.1 Hz, 1H), 4.05 (dd, *J* = 8.9, 1.9 Hz, 1H), 3.70 – 3.63 (m, 1H), 3.59 (dd, *J* = 10.2, 6.8 Hz, 1H), 1.96 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, 30 ºC) δ 200.5, 170.6, 138.2, 138.1, 137.4$_5$, 137.4, 136.0, 133.5, 129.4, 128.6, 128.5, 128.4, 128.3$_8$, 128.3, 128.0, 127.9, 127.8, 127.7$_8$, 127.7, 127.5, 83.4, 80.4, 76.4, 74.6, 74.1, 73.2, 72.7, 71.5, 68.4, 21.2; IR (KBr): 3064, 3032, 2927, 2870, 1742, 1688, 1561, 1541, 1456, 1371, 1236, 1099, 1071, 741, 693 cm^{-1}; HRMS: [M + H]$^+$ calcd for $C_{42}H_{43}O_7$ 659.3009; found 659.3006.

Characterization data of compound ***epi*-3f**. Purified by silica gel column chromatography (ethyl acetate/hexane = 1/20 ~ 3/20) as a colorless oil (141 mg, 82% yield); ^{1}H NMR (400 MHz, $CDCl_3$, 30 ºC) δ 8.13 (d, *J* = 8.9 Hz, 2H), 7.37 – 7.06 (m, 21H), 6.84 (d, *J* = 8.6 Hz, 2H), 5.48 – 5.43 (m, 1H), 4.87 (d, *J* = 3.0 Hz, 1H), 4.62 (d, *J* = 11.3 Hz, 1H), 4.54 (d, *J* = 11.6 Hz, 1H), 4.47 – 4.25 (m, 6H), 4.14 (dd, *J* = 7.6, 2.5 Hz, 1H), 4.04 (dd, *J* = 8.2, 2.5 Hz, 1H), 3.84 (s, 3H), 3.67 (dd, *J* = 9.7, 6.4 Hz, 1H), 3.59 (dd, *J* = 9.9, 6.4 Hz, 1H), 1.98 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, 30 ºC) 198.9, 170.7, 163.9, 138.3, 138.1, 137.5, 131.9, 129.1, 128.7, 128.5, 128.4, 128.3, 128.2, 128.0, 127.8$_1$, 127.8, 127.7, 127.5, 113.8, 83.6, 80.5, 76.4, 74.7, 74.1, 73.1, 72.6, 71.5, 68.4, 55.6, 21.3; IR (KBr): 3061, 3030, 2929, 2871, 1736, 1685, 1598, 1509, 1457, 1374, 1257, 1086, 1027, 737, 698 cm^{-1}; HRMS: [M + H]$^+$ calcd. for $C_{43}H_{45}O_8$ 689.3114; found 689.3122.

Synthesis of compound 3t

Step I: Under an argon atmosphere, to a solution of anhydrous lithium chloride (56 mg, 1.324 mmol, 1.02 equiv.) in THF (2 mL) was added ^{i}PrMgCl in THF (2 M, 0.70 mL, 1.4 mmol, 1.06 equiv.) at 0 °C. Solution of 2-(5-iodo-2-methylbenzyl)-5-(4-fluorophenyl)thiophene (540 mg, 1.324 mmol, 1 equiv.) in THF (5 mL) was added dropwise to the reaction mixture at 0 °C, and the reaction mixture was stirred at RT for 1 h. The reaction mixture was transferred to a solution of $ZnBr_2$ (300 mg, 1.324 mmol, 1 equiv.) in THF (5 mL) at RT. The mixture was stirred at RT for further 1 h, and used for the next step.

Step II: Freshly prepared arylzinc bromide solution was added dropwise to a Schlenk tube containing thioester **2** (500 mg,

0.66 mmol, 0.5 equiv.) and 10 wt% Pd/C (15 mg, 0.013 mmol) in THF (5 mL). The reaction mixture was stirred at 40 °C for 48 h, and then reaction was quenched with water (1 mL). The reaction mixture was filtered through celite with ethyl acetate (3 x 100 mL). The filtrate was washed with water and brine, and dried over anhydrous Na_2SO_4. After decantation and evaporation, the residue was purified by silica gel column chromatography (ethyl acetate/hexane = 1/20 ~ 3/20) to afford compound **3t** as a colorless oil (406 mg, 0.47 mmol, 71%). ^{1}H NMR (400 MHz, $CDCl_3$, 30 ºC) δ 7.50 (d, *J* = 1.3 Hz, 1H), 7.43 (dd, *J* = 7.8, 1.6 Hz, 1H), 7.41 – 7.14 (m, 21H), 7.07 – 7.04 (m, 2H), 7.00 – 6.93 (m, 3H), 6.60 (d, *J* = 3.5 Hz, 1H), 4.95 – 4.84 (m, 3H), 4.70 – 4.59 (m, 3H), 4.42 (d, *J* = 10.4 Hz, 1H), 4.19 – 4.14 (m, 2H), 4.04 (d, *J* = 16.0 Hz, 1H), 3.91 (d, *J* = 10.4 Hz, 1H), 3.89 – 3.74 (m, 4H), 3.40 (d, *J* = 9.6 Hz, 1H), 3.16 (s, 3H), 2.34 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, 30 ºC) δ 198.5, 170.1, 162.2 (d, *J* = 245.3 Hz), 142.7, 142.6, 141.8, 138.6, 138.5$_5$, 138.1, 138.0, 137.4, 134.5, 130.8 (d, *J* = 3.4 Hz), 130.7, 130.3, 128.8, 128.5, 128.4$_2$, 128.4, 128.3, 128.2, 128.0, 127.9$_1$, 127.9, 127.8, 127.5$_8$, 127.5$_5$, 127.2 (d, *J* = 8.0 Hz), 126.2, 122.8, 115.8 (d, *J* = 21.8 Hz), 82.9, 80.7, 79.5, 75.5, 74.6, 73.3, 73.1, 72.7, 68.1, 34.1, 21.2, 19.9; IR (KBr): 3062, 3031, 2918, 2864, 1737, 1675, 1605, 1509, 1455, 1371, 1236, 1094, 1027, 808, 736, 699 cm^{-1}; HRMS: [M + Na]$^+$ calcd. for $C_{54}H_{51}FO_7SNa$ 885.3237; found 885.3229.

Synthesis of compound 4t

An oven dried Schlenk tube was cooled to room temperature and charged with compound **3t** (370 mg, 0.423 mmol) in MeOH (10 mL) at room temperature. To that solution, NaOMe (23 mg, 0.423 mmol) was added under argon atmosphere, and the reaction mixture was stirred at RT for 6 h. The reaction mixture was neutralized with 1N HCl aq (2 mL). All the solvent was evaporated, and the crude product was purified by silica gel column chromatography (ethyl acetate/hexane = 1/10 ~ 4/10) to afford compound **4t**[21] (320 mg, 0.39 mmol, 92%) as a yellowish solid. ^{1}H NMR (400 MHz, $CDCl_3$, 30 ºC) δ 7.52 (s, 1H), 7.47 – 7.43 (m, 1H), 7.39 – 7.09 (m, 21H), 7.03 – 6.89 (m, 5H), 6.61 (d, *J* = 3.5 Hz, 1H), 4.89 – 4.86 (m, 3H), 4.68 – 4.62 (m, 2H), 4.53 (d, *J* = 12.3 Hz, 1H), 4.38 (d, *J* = 10.6 Hz, 1H), 4.19 – 4.03 (m, 4H), 3.94 (d, *J* = 10.5 Hz, 1H), 3.87 – 3.82 (m, 2H), 3.71 (d, *J* = 11.1 Hz, 1H), 3.60 (d, *J* = 9.3 Hz, 1H), 3.08 (s, 1H), 2.33 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, 30 ºC) δ 162.2 (d, *J* = 246.6 Hz), 143.6, 141.6, 140.6, 138.9, 138.8, 138.5, 138.1, 137.8, 136.9, 130.9 (d, *J* = 3.3 Hz), 130.6, 128.5$_2$, 128.5$_0$, 128.4$_4$, 128.3$_8$, 128.3, 128.1, 127.9, 127.8, 127.7$_3$, 127.7, 127.6, 127.2 (d, *J* = 8.0 Hz), 125.9, 125.0, 122.8, 115.8 (d, *J* = 21.6 Hz), 98.0, 85.5, 83.6, 78.5, 75.8, 75.7, 75.2 73.5, 72.4, 69.1, 34.5, 19.4; IR (KBr): 3500, 3064, 3028, 2917, 2864, 1602, 1545, 1508, 1470, 1453, 1354, 1229, 1100, 1027, 835, 798, 729, 697 cm^{-1}; HRMS: [M + Na]$^+$ calcd. for $C_{52}H_{49}FO_6SNa$ 843.3132; found 843.3123.

Synthesis of compound 5t

To a solution of compound **4t** (250 mg, 0.304 mmol) in acetonitrile/dichloromethane (3:2) (10 mL) under argon atmosphere was added ^{i}Pr$_3$SiH (0.19 mL, 0.913 mmol), and the reaction mixture cooled to 0 °C. $BF_3{\cdot}Et_2O$ (0.13 mL, 0.913 mmol) was added dropwise to the reaction mixture at 0 °C over a period of 20 minute. After complete addition, the reaction mixture was stirred at 0 °C for 6 h. After consumption of the starting material, aqueous solution of $NaHCO_3$ (20 mL) was slowly added to the reaction mixture at 0 °C, and allowed the reaction mixture to room temperature. Then reaction mixture was extracted with dichloromethane (3 × 40 mL). After the phase separation, the organic layer was washed with brine and then dried over anhydrous Na_2SO_4. Filtration and concentration under reduced pressure gave crude oil which was purified by flash silica gel column chromatography (ethyl acetate/hexane = 1/10 ~ 3/10) to afford compound **5t**[21] as a colorless gum (216 mg, 0.268 mmol, 88%). The ^{1}H NMR measurement indicated formation of the β-isomer. ^{1}H NMR (400 MHz, $CDCl_3$, 30 ºC) δ 7.37 – 7.24 (m, 17H), 7.22 – 7.14 (m, 6H), 6.98 – 6.93 (m, 5H), 6.63 (d, *J* = 3.6 Hz, 1H), 4.93 – 4.85 (m, 3H), 4.66 – 4.62 (m, 2H), 4.54 (d, *J* = 12.3 Hz, 1H), 4.36 (d, *J* = 10.4 Hz, 1H), 4.22 (d, *J* = 9.5 Hz, 1H), 4.17 – 4.08 (m, 2H), 3.89 (d, *J* = 10.4 Hz, 1H), 3.81 – 3.74 (m, 4H), 3.60 – 3.53 (m, 2H), 2.33 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, 30 ºC) δ 162.2 (d, *J* = 247.4 Hz), 143.7, 141.6, 138.9, 138.6, 138.4, 138.3, 138.1, 137.4, 136.6, 131.0 (d, *J* = 3 Hz), 130.7, 129.1, 128.6, 128.5$_3$, 128.5, 128.3$_3$, 128.3, 128.1, 127.9, 127.8, 127.7, 127.6, 127.2 (d, *J* = 8.1 Hz), 126.6, 126.0, 122.8, 115.8 (d, *J* = 21.2 Hz), 86.8, 84.7, 81.8, 79.6, 78.6, 75.8, 75.2, 75.1, 73.6, 69.3, 34.4, 19.4; IR (KBr): 3064, 3030, 2917, 2857, 1598, 1508, 1498, 1453, 1362, 1232, 1096, 1068, 833, 735, 698 cm^{-1}; HRMS: [M + Na]$^+$ calcd. for $C_{52}H_{49}FO_5SNa$ 827.3182; found 827.3176.

Compound **5t** was also synthesized using Et_3SiH, but cooling to -40 °C was necessary for the high β-selectivity: To a solution of compound **4t** (450 mg, 0.548 mmol) in acetonitrile/dichloromethane (3:2) (10 mL) under argon atmosphere was added Et_3SiH (0.27 mL, 1.65 mmol), and the reaction mixture cooled to - 40 °C. $BF_3{\cdot}Et_2O$ (0.21 mL, 1.65 mmol) was added dropwise to the reaction mixture at - 40 °C over a period of 30 minute. After complete addition, the reaction mixture was stirred at - 40 °C for 6 h. After consumption of the starting material, aqueous solution of $NaHCO_3$ (20 mL) was slowly added to the reaction mixture at -10 °C, and allowed the reaction mixture to room temperature. Then reaction mixture was extracted with dichloromethane (3 × 40 mL). After the phase separation, the organic layer was washed with brine and then dried over anhydrous Na_2SO_4. Filtration and concentration under reduced pressure gave crude oil which was purified by flash silica gel column chromatography (ethyl acetate/hexane = 1/10 ~ 3/10) to afford compound **5t** (β-isomer) as a colorless gum (401 mg, 0.498 mmol, 91%).

Synthesis of compound 6t

To a solution of compound **5t** (200 mg, 0.248 mmol) in dichloromethane (15 mL) under argon atmosphere, trimethylsilyl iodide (0.35 mL, 1.49 mmol) was added dropwise at 0 °C. After complete addition, the reaction mixture was allowed to warm to RT and stirred for 8 h. The reaction mixture was evaporated to dryness. The crude material was purified by column chromatography on silica gel (MeOH/DCM = 1/30 ~ 1/20) to afford (2S,3R,4R,5S,6R)-2-(3-((5-(4-fluorophenyl)thiophen-2-yl)methyl)-4-methylphenyl)-6-(hydroxymethyl)tetrahydro-2*H*-pyran-3,4,5-triol (Canagliflozin) (**6t**, 102 mg, 92%).[9] ^{1}H NMR (400 MHz, DMSO-d_6, 30 ºC) δ 7.61 – 7.57 (m, 2H), 7.27 (d, *J* = 4.4 Hz, 1H), 7.22 – 7.10 (m, 5H), 6.79 (d, *J* = 3.6 Hz, 1H), 4.99 (br, 2H, OH), 4.79

(br, 1H, OH), 4.45 (br, 1H, OH), 4.15 (d, *J* = 16 Hz, 1H), 4.09 (d, *J* = 16 Hz, 1H), 3.96 (d, *J* = 9.6 Hz, 1H), 3.69 (d, *J* = 11.2 Hz, 1H), 3.46 – 3.41 (m, 1H), 3.29 – 3.14 (m, 4H), 2.26 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6, 30 ºC) δ 161.4 (d, *J* = 243 Hz), 143.6, 140.2, 138.2, 137.3, 134.9, 130.5 (d, *J* = 3.1 Hz), 129.6, 129.0, 126.9 (d, *J* = 8 Hz), 126.3, 126.2, 123.4, 115.9 (d, *J* = 21.6 Hz), 81.3, 81.2, 78.5, 74.7, 70.4, 61.4, 33.4, 18.8; IR (KBr): 3588, 3398, 2978, 2925, 1645, 1611, 1509, 1477, 1438, 1395, 1300, 1243, 1133, 1087, 1047, 920, 826, 798, 703, 628 cm^{-1}; HRMS: $[M + Na]^+$ calcd for $C_{24}H_{25}FO_5SNa$ 467.1304; found 467.1299.

Synthesis of compound 3u

Step I: An oven dried Schlenk tube was cooled under argon atmosphere and charged with 4-bromo-1-chloro-2-(4-ethoxybenzyl)benzene (0.163 g, 0.50 mmol) and magnesium turnings (0.10 g, 4.1 mmol), followed by addition of THF (5 mL) and 1,2-dibromoethane (0.05 mL). The reaction mixture was heated to reflux to initiate the reaction. After the reaction initiated, additional 4-bromo-1-chloro-2-(4-ethoxybenzyl)benzene (0.49 g, 1.5 mmol) in THF (10 mL) was added dropwise to the reaction mixture, and allowed the reaction mixture to reflux for 3 h. Then, the reaction mixture was cooled to room temperature. The freshly prepared Grignard reagent was added to a solution of $ZnBr_2$ (450 mg, 2 mmol, 1 equiv.) and LiCl (85 mg, 2 mmol, 1 equiv.) in dry THF at RT and stirred for 1 h.

Step II: Freshly prepared arylzinc bromide was added dropwise to a Schlenk tube containing thioester **2** (756 mg, 1 mmol) and 10 wt% Pd/C (22 mg, 0.020 mmol) in THF (5 mL). The reaction mixture was stirred at 40 °C for 48 h, and then reaction was quenched with water (1 mL). The reaction mixture was filtered through celite with ethyl acetate (3 x 100 mL). The filtrate was washed with water and brine, and dried over anhydrous Na_2SO_4. The mixture was decanted and evaporated. The residue was purified by silica gel column chromatography (ethyl acetate/hexane = 1/20 ~ 3/20) to afford compound **3u** (613 mg, 0.74 mmol, 74%) as a colorless gum. ^1H NMR (400 MHz, $CDCl_3$, 30 ºC) δ 7.82 (d, *J* = 1.3 Hz, 1H), 7.68 (dd, *J* = 8.3, 1.6 Hz, 1H), 7.33 – 7.12 (m, 19H), 6.99 (d, *J* = 6.8 Hz, 2H), 6.95 (d, *J* = 8.5 Hz, 2H), 6.71 (d, *J* = 8.5 Hz, 2H), 5.24 (q, *J* = 4.9 Hz, 1H), 4.73 (d, *J* = 4.5 Hz, 1H), 4.62 – 4.42 (m, 7H), 4.31 (d, *J* = 10.8 Hz, 1H), 4.13 – 4.09 (m, 1H), 4.02 – 3.99 (m, 1H), 3.94 – 3.88 (m, 4H), 3.84 (dd, *J* = 10.4, 5.0 Hz, 1H), 3.63 (dd, *J* = 10.4, 5.5 Hz, 1H), 1.97 (s, 3H), 1.34 (t, *J* = 7.0 Hz, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, 30 ºC) δ 198.6, 170.1, 157.7, 139.5, 138.4, 138.0, 137.8, 137.1, 134.8, 131.8, 130.7, 130.0, 129.6, 128.7, 128.6, 128.4_5, 128.4, 128.3_8, 128.3, 128.2, 128.1, 127.9_3, 127.9, 127.8, 127.7, 127.6, 114.6, 83.6, 80.6, 79.2, 77.4, 75.5 74.6, 73.3, 72.7, 68.1, 63.5, 38.4, 21.2, 15.0; IR (KBr): 3064, 3032, 2929, 2866, 1734, 1686, 1605, 1511, 1454, 1370, 1244, 1046, 1027, 824, 738, 697 cm^{-1}; HRMS: $[M + Na]^+$ calcd. for $C_{51}H_{51}ClO_8Na$ 849.3170; found 849.3165.

Synthesis of compound 4u

An oven dried Schlenk tube was cooled to room temperature and charged with compound **3u** (500 mg, 0.604 mmol) in MeOH (30 mL) at room temperature. To that solution, NaOMe (33 mg, 0.604 mmol) was added under argon atmosphere, and the reaction mixture was stirred at RT for 6 h. Then, the reaction mixture was neutralized with 1N HClaq (4 mL). All the solvent was evaporated to afford the crude product, and further purification by silica gel column chromatography (ethyl acetate/hexane = 1/10 ~ 4/10) to afforded compound **4u**[22] (442 mg, 0.563 mmol, 93%) as a colorless solid. ^1H NMR (400 MHz, $CDCl_3$, 30 ºC) δ 7.44 (d, *J* = 1.9 Hz, 1H), 7.37 (dd, *J* = 8.3, 2.0 Hz, 1H), 7.32 – 7.12 (m, 19H), 7.01 (d, *J* = 8.5 Hz, 2H), 6.91 (d, *J* = 6.7 Hz, 2H), 6.71 (d, *J* = 8.6 Hz, 2H), 4.86 (s, 2H), 4.85 (d, *J* = 10.1 Hz, 1H), 4.63 (d, *J* = 10.9 Hz, 1H), 4.58 (d, *J* = 12.3 Hz, 1H), 4.49 (d, *J* = 12.3 Hz, 1H), 4.42 (d, *J* = 10.7 Hz, 1H), 4.14 – 3.85 (m, 7H), 3.83 – 3.74 (m, 2H), 3.68-3.65 (m, 1H), 3.48 (d, *J* = 9.3 Hz, 1H), 3.12 (s, 1H), 1.35 (t, *J* = 7.0 Hz, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, 30 ºC) δ 157.5, 141.4, 138.9, 138.7, 138.6, 138.4, 137.4, 134.5, 131.4, 129.8, 129.4, 129.0, 128.5, 128.5, 128.3, 128.1, 127.9, 127.8_4, 127.8, 127.7_2, 127.7, 127.6, 125.7, 114.6, 97.8, 84.9, 83.7, 78.5, 75.8, 75.6, 75.2, 73.5, 72.4, 69.0, 63.4, 38.6, 15.0; IR (KBr): 3396, 3063, 3030, 2925, 2866, 1609, 1582, 1509, 1453, 1361, 1242, 1099, 1027, 827, 732, 698 cm^{-1}; HRMS: $[M + Na]^+$ calcd. for $C_{49}H_{49}ClO_7Na$ 807.3065; found 807.3060.

Synthesis of compound 5u

To a solution of compound **4u** (239 mg, 0.304 mmol) in acetonitrile/dichloromethane (3:2) (10 mL) under argon atmosphere was added $^iPr_3SiH$ (0.19 mL, 0.913 mmol), and the reaction mixture cooled to 0 °C. $BF_3{\cdot}Et_2O$ (0.13 mL, 0.913 mmol) was added dropwise to the reaction mixture at 0 °C over a period of 20 minute. After complete addition, the reaction mixture was stirred at 0 °C for 6 h. After consumption of the starting material, aqueous solution of $NaHCO_3$ (20 mL) was slowly added to the reaction mixture at 0 °C, and allowed the reaction mixture to room temperature. After extraction with dichloromethane (3 x 40 mL), the organic layer was washed with brine and dried over anhydrous Na_2SO_4. Filtration and concentration under reduced pressure gave the crude oil. Further purification by flash silica gel column chromatography (ethyl acetate/hexane = 1/20 ~ 3/10) afforded (2R,3R,4R,5S,6S)-3,4,5-tris(benzyloxy)-2-(benzyloxymethyl)-6-(4-chloro-3-(4-ethoxybenzyl)phenyl)tetrahydro-2*H*-pyran (**5u**)[22] as a colorless gum (220 mg, 0.286 mmol, 94%). The ^1H NMR indicated formation of the β-isomer. ^1H NMR (400 MHz, $CDCl_3$, 30 ºC) δ 7.35 (d, *J* = 8.1 Hz, 1H), 7.32 – 7.16 (m, 20H), 7.03 (d, *J* = 8.6 Hz, 2H), 6.91 – 6.88 (m, 2H), 6.73 (d, *J* = 8.6 Hz, 2H), 4.93 – 4.84 (m, 3H), 4.65 – 4.59 (m, 2H), 4.53 (d, *J* = 12.3 Hz, 1H), 4.39 (d, *J* = 10.5 Hz, 1H), 4.15 (d, *J* = 9.5 Hz, 1H), 4.06 (d, *J* = 15.4 Hz, 1H), 3.97 – 3.92 (m, 3H), 3.83 (d, *J* = 10.5 Hz, 1H), 3.79 – 3.71 (m, 4H), 3.57 – 3.54 (m, 1H), 3.45 – 3.40 (m, 1H), 1.37 (t, *J* = 7.0 Hz, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, 30 ºC) δ 157.6, 139.1, 138.8, 138.5, 138.3_4, 138.3, 137.8, 134.0, 131.4, 130.6, 129.9, 129.6, 128.6, 128.5, 128.4, 128.1, 127.9, 127.8_6, 127.8_3, 127.8, 127.7_6, 127.7, 126.8, 114.6, 86.9, 84.3, 81.1, 79.6, 78.5, 75.8, 75.3, 75.1, 73.6, 69.2, 63.5, 38.5, 15.0; IR (KBr): 3062, 3031, 2932, 2868, 1610, 1584, 1511, 1454, 1392, 1244, 1209, 1099, 1044, 1027, 832, 733, 696 cm^{-1}; HRMS: $[M + Na]^+$ calcd. for $C_{49}H_{49}ClO_6Na$ 791.3115; found 791.3109.

Compound **5u** was also synthesized using Et_3SiH, but cooling to -40 °C was necessary for the high β-selectivity: To a solution of compound **4u** (426 mg, 0.54 mmol) in acetonitrile/dichloromethane (3:2) (10 mL) under argon atmosphere was added Et_3SiH (0.27 mL, 1.65 mmol), and then the reaction

mixture was cooled to - 40 °C. $BF_3{\cdot}Et_2O$ (0.21 mL, 1.65 mmol) was added dropwise to the reaction mixture at - 40 °C over a period of 30 minute. After complete addition, the reaction mixture was stirred at - 40 °C for 6 h. After consumption of the starting material, aqueous solution of $NaHCO_3$ (20 mL) was slowly added to the reaction mixture at - 10 °C, and allowed the reaction mixture to room temperature. After extraction with dichloromethane (3 x 40 mL), the organic layer was washed with brine and dried over anhydrous Na_2SO_4. Filtration and concentration under reduced pressure gave the crude oil. Further purification by flash silica gel column chromatography (ethyl acetate/hexane = 1/20 ~ 3/10) afforded (2R,3R,4R,5S,6S)-3,4,5-tris(benzyloxy)-2-(benzyloxymethyl)-6-(4-chloro-3-(4-ethoxybenzyl)phenyl)tetrahydro-2*H*-pyran (**5u**) as a colorless gum (402 mg, 0.522 mmol, 96%). The ^{1}H NMR indicated formation of the β-isomer.

Synthesis of compound 6u

To a solution of **5u** (100 mg, 0.13 mmol) in EtOAc (5 mL) was added 5 wt% Pd/C (14 mg, 6.5 µmol, 5 mol% on metal basis) in autoclave under argon. The atmosphere was replaced to dihydrogen, and the mixture was stirred at RT for 24 h. The reaction mixture was filtered through celite with EtOAc (3 x 40 mL), and all the volatiles of the filtrate was evaporated to give crude compound. The mixture was purified by column chromatography ($MeOH/CH_2Cl_2$ (1/30-1/20) to afford (2S,3R,4R,5S,6R)-2-(4-chloro-3-(4-ethoxybenzyl)phenyl)-6-(hydroxymethyl)tetrahydro-2*H*-pyran-3,4,5-triol (Dapagliflozin) (**6u**, 52 mg, 97%).[22] ^{1}H NMR (400 MHz, CD_3OD, 30 ºC) δ 7.35 – 7.31 (m, 2H), 7.28 – 7.26 (m, 1H), 7.09 (d, *J* = 8.4 Hz, 2H), 6.79 (d, *J* = 8.5 Hz, 2H), 4.08 (d, *J* = 9.5 Hz, 1H), 4.03 – 3.96 (m, 3H), 3.89 – 3.85 (m, 1H), 3.71 – 3.66 (m, 1H), 3.47 – 3.26 (m, 5H), 1.35 (t, *J* = 7.0 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, CD_3OD, 30 ºC) δ 158.9, 140.0, 139.9, 134.5, 132.9, 131.9, 130.8, 130.1, 128.2, 115.5, 82.9, 82.2, 79.8, 76.5, 71.9, 64.5, 63.1, 39.2, 15.2; IR (KBr): 3568, 3386, 3032, 2958, 2924, 2855, 1611, 1508, 1451, 1439, 1269, 1243, 1177, 1047, 825, 797, 735, 699 cm^{-1}; HRMS: $[M + Na]^+$ calcd. for $C_{21}H_{25}ClO_6Na$ 431.1237; found 431.1231.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI:
^{1}H and ^{13}C{^{1}H} NMR of starting materials and products (PDF).

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