Supporting Information

Synthesis and SAR of Thiazolylmethylphenyl Glucoside as Novel *C*-Aryl Glucoside SGLT2 Inhibitors

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EXPERIMENTAL SECTION

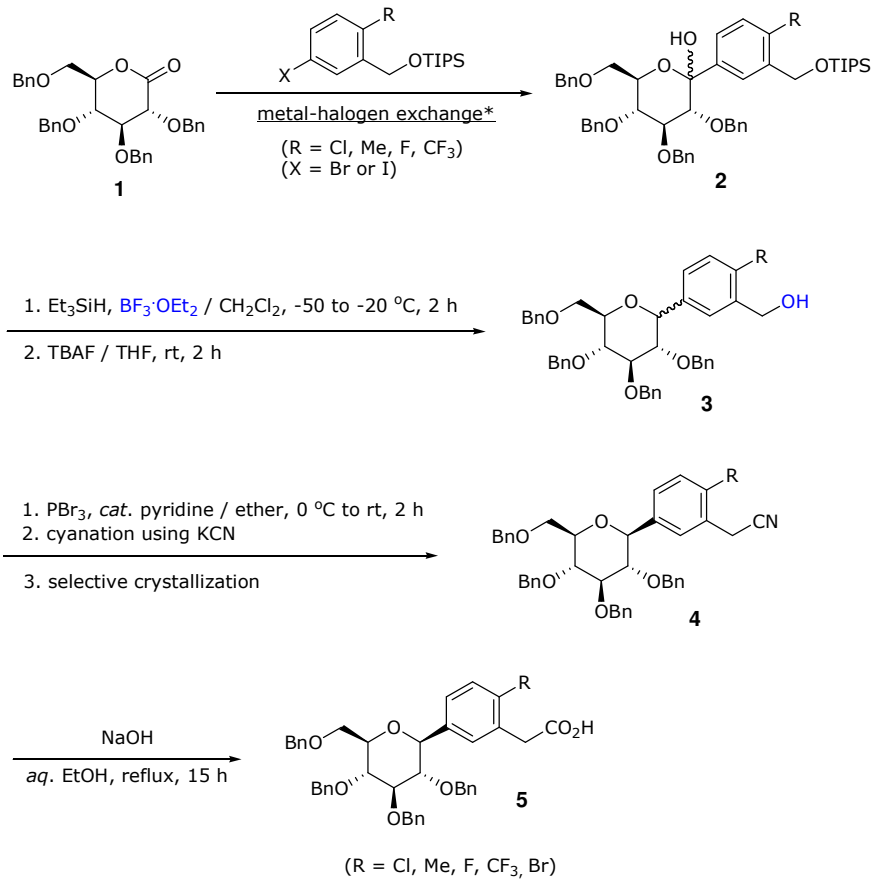
As used herein the symbols and conventions used describing the processes, schemes and examples of the present invention are consistent with those used in the contemporary scientific literature, for example, the *Journal of the American Chemical Society* or the *Journal of Biological Chemistry*.

Hz (Hertz)
T_r (retention time)
MeOH (methanol)
TFA (trifluoroacetic acid)
EtOH (ethanol)
DMSO (dimethylsulfoxide)
DCM (dichlromethane)
DMF (*N,N*-dimethylformamide)
CDI (1,1-carbnyldiimidazole)
TES (Triethylsilyl)
HOBt (1-hydroxybenzotriazole)
Boc (*tert*-butyloxycarbonyl)
NMM (*N*-methyl morpholine)
TBAF (tetra-*n*-butylammonium fluoride)
DMAP (4-dimethylaminopyridine)
HPLC (high pressure liquid chromatography)
EDCI (1-ethyl-3-[3-dimethylaminopropyl]carbodiimide hydrochloride)
DME (1,2-dimethoxyethane)
DIEA (*N,N*'-diisopropylethylamine)
TMSI (iodotrimethylsilane)
TMSOTf (trimethylsilyl trifluoromethanesulfonate)
MW (micrwave irradiation)
TLC (thin layer chromatography)
RP (reverse phase)
i-PrOH (isopropanol)
TEA (triethylamine)
THF (tetrahydrofuran)
EtOAc (ethyl acetate)
HOAc (acetic acid)
Ac (acetyl)
Bn (benzyl)

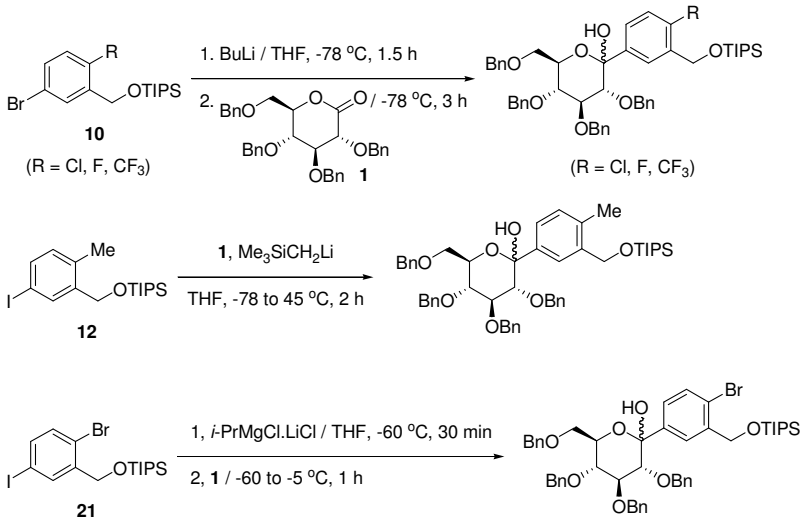
All reactions are conducted under an inert atmosphere at room temperature, unless otherwise noted. *n*-Butyllithium (Aldrich) was titrated with *N*-benzylbenzamide as indicator. All reagents were purchased at the highest commercial quality and used without further purification, unless otherwise indicated. All experiment involving moisture- and/or air-sensitive compounds were performed in oven- and/or flame-dried glassware with rubber septa under a positive pressure of nitrogen using standard Schlenck technique. Microwave reaction was conducted with a Biotage

Initiator microwave reactor. NMR spectra were obtained on a Varian 400-MR (400 MHz ^{1}H, 100 MHz ^{13}C) spectrometer. NMR spectra were recorded in ppm (δ) relative to tetramethylsilane (δ = 0.00) as an internal standard unless stated otherwise and 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. ^{13}C NMR spectra were referenced to the residual chloroform-d_1 (δ = 77.0) or DMSO-d_6 (δ = 39.7). Mass spectra were obtained with an Agilent 6110 quadruple LC-MSD (ESI+). High resolution mass spectra were obtained on a Jeol JMS-700 Mstation (10 kV, HFAB). Optical rotations were obtained on a Rudolph Autopol III digital polarimeter. 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 C18 OBD 5 μm 30x100 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.

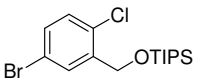
Scheme 1. Preparation of Key Intermediates **5**



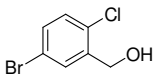
Metal-halogen exchange reaction*



(5-Bromo-2-chlorobenzyloxyl)triisopropylsilane (**10a**)

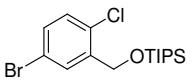


Step 1: 5-Bromo-2-chlorobenzyl alcohol



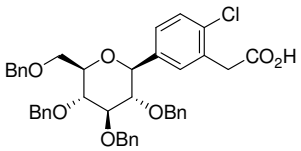
To a solution 5-bromo-2-chlorobenzoic acid (100 g , 425 mmol) in tetrahydrofuran (500 mL) at 0 ℃ was added borane dimethyl sulfide complex (170 mL, 170 mmol). The resulting mixture was stirred with gradual warming to ambient temperature over 15 h, re-cooled to 0 ℃, and quenched with MeOH. The mixture was diluted with water and extracted with EtOAc. The organic layer was washed with brine, dried over anhydrous $MgSO_4$, filtered and evaporated *in vacuo* to yield the titiled compound as a white solid, which was used without further purification. . ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 (d, *J* = 2.4 Hz, 1H), 7.36 (dd, *J* = 8.4, 2.4 Hz, 1H), 7.22 (d, *J* = 8.4 Hz, 1H), 7.76 (d, *J* = 6.4 Hz, 2H), 1.93 (t, *J* = 6.4 Hz, 1H); [M-OH^-]+ 203..

Step 2: (5-Bromo-2-chlorobenzyloxyl)triisopropylsilane (**10a**)

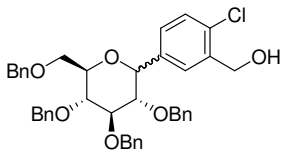


To a solution of 5-bromo-2-chlorobenzyl alcohol (425 mmol) in DMF (400 mL) was added imidazle (58 g, 850 mmol), 4-(dimethylamino)pyridine (2.6 g, 21 mmol), and triisopropylsilyl chloride (136 mL, 638 mmol). The resulting solution was stirred at ambient temperature for 15 h, diluted with a saturated ammonium chloride and extracted with EtOAc. The organic layer was washed with water then brine, dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The crude residue was purified by column chromatography to yield the titled compound 32 (152 g, 403 mmol, 95%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (d, *J* = 2.4 Hz, 1H), 7.31 (dd, *J* = 8.4, 2.4 Hz, 1H), 7.16 (d, *J* = 8.4 Hz, 1H), 4.83 (s, 2H), 1.25-1.17 (m, 3H), 1.11 (d, *J* = 6.8 Hz, 18H).

2-(2-Chloro-5-((2*S*,3*S*,4*R*,5*R*,6*R*)-3,4,5-tris(benzyloxy)-6-(benzyloxymethyl)-tetrahydro-2*H*-pyran-2-yl)phenyl)acetic acid (**5**)



Step 1: (2-Chloro-5-((3*S*,4*R*,5*R*,6*R*)-3,4,5-tris(benzyloxy)-6-(benzyloxy-methyl)-tetrahydro-2*H*-pyran-2-yl)phenyl)methanol



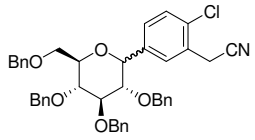
To a solution of bromide **10** (R = Cl) (97 g, 257 mmol) in THF (1 L) at -78 °C under an atmosphere of nitrogen was added dropwise *n*-butyllithium (2.5 M in hexanes, 103 mL, 257 mmol), and the mixture was stirred for 1.5 h at the same temperature. Then a solution of lactone **1** (106 g, 198 mmol) in THF (500 mL) was added dropwise, and the mixture was stirred for 3 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 a yellow oil, which was carried on to the next step without further purification.

To a stirred -50 °C solution of the lactols **2** in dichloromethane (500 mL) was added triethylsilane (63 mL, 396 mmol) followed by boron trifluoride diethyl etherate (50 mL, 396 mmol) at a rate such that the reaction temperature was maintained between -40 and -50 °C. The solution was allowed to warm to -10 °C over 2 h prior to quenching with saturated potassium carbonate. After removal of organic volatiles under reduced pressure, the residue was partitioned between EtOAc and water. Following extraction of the aqueous layer with EtOAc, the combined organic layers were washed with water prior to drying over anhydrous $MgSO_4$. Filtration and concentration under reduced pressure yielded a yellow oil, which was carried on to the next step without further purification.

To a solution of (2-chloro-5-((3*S*,4*R*,5*R*,6*R*)-3,4,5-tris(benzyloxy)-6-(benzyloxymethyl)-tetrahydro-2*H*-pyran-2-yl)benzyloxy)triisopropylsilane in THF (500 mL) was added tetrabutylammonium fluoride (1.0 M in THF, 594 mL, 594 mmol) and the reaction mixture stirred at ambient temperature for 2 h. After removal of organic volatiles under reduced pressure, the residue was partitioned between EtOAc and saturated ammonium chloride. 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*. The crude residue was purified on column chromatography to provede the titled compound (168 g, 98%, *ca*. 2:1 mixture of anomers (β:α)) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) β-anomer: δ 7.50 (s, 1H), 7.38-7.17 (m, 20H), 6.94-6.92 (m, 2H), 4.96-4.46 (m, 9H), 4.23 (d, *J* = 9.2 Hz, 1H), 3.86 (d, *J* = 10.4 Hz, 1H), 3.81-3.67(m, 4H), 3.61-3.59 (m, 1H), 3.44 (t, *J* = 9.2 Hz, 1H); α-anomer: δ 7.78 (s, 1H), 7.63 (dd, *J* = 8.4, 1.6 Hz, 1H), 7.38-7.17 (m, 19H), 7.13-7.10 (m, 2H), 5.15 (d, *J* = 3.6 Hz, 1H), 4.96-4.46 (m, 8H), 4.01-3.95 (m, 2H), 3.83-3.64 (m, 5H), 3.55-

3.51 (m, 1H); MNa+ 687.

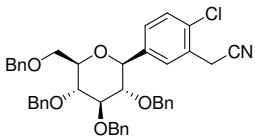
Step 2: 2-(2-Chloro-5-((3*S*,4*R*,5*R*,6*R*)-3,4,5-tris(benzyloxy)-6-(benzyloxymethyl)-tetrahydro-2*H*-pyran-2-yl)phenyl)acetonitrile (**4a**)



To a solution of (2-chloro-5-((3*S*,4*R*,5*R*,6*R*)-3,4,5-tris(benzyloxy)-6-(benzyloxy-methyl)-tetrahydro-2*H*-pyran-2-yl)phenyl)methanol (130 g, 195 mmol) in ether (600 mL) at 0 ^{o}C was added pyridine (0.79 mL, 9.8 mmol) and phosphorus tribromide (6.4 mL, 68 mmol). The reaction was allowed to slowly warm to room temperature over 15 h and refluxed 1 h. After cooling to room temperature, the reaction mixture was diluted with EtOAc and washed with water then brine. The organic extract was dried over anhydrous $MgSO_4$, filtered, and evaporated *in vacuo* to yield a yellow solid, which was carried on to the next step without further purification.

To a solution of the (2*R*,3*R*,4*R*,5*S*)-3,4,5-tris(benzyloxy)-2-(benzyloxymethyl)-6-(3-(bromomethyl)-4-chlorophenyl)-tetrahydro-2*H*-pyran in ethanol (260 mL) and water (130 mL) was added potassium cyanide (31.8 g, 488 mmol). The reaction mixture was refluxed overnight. After cooling to room temperature, the mixture was diluted with water and extracted with EtOAc. The organic layer was washed with brine, dried over anhydrous $MgSO_4$, filtered and evaporated *in vacuo*. Purification was accomplished by chromatography to provide the titled compound **4a** (105g, 80%, *ca*. 2:1 mixture of anomers (β:α)). ^{1}H NMR (400 MHz, $CDCl_3$) β-anomer: δ 7.48 (s, 1H), 7.37-7.17 (m, 20H), 6.93-6.91 (m, 2H), 4.93 (s, 2H), 4.86 (d, *J* = 10.8 Hz, 1H), 4.63 (d, *J* = 10.8 Hz, 1H), 4.62 (d, *J* = 12.4 Hz, 1H), 4.56 (d, *J* = 12.4 Hz, 1H), 4.52 (d, *J* = 10.8 Hz, 1H), 4.22 (d, *J* = 9.6 Hz, 1H), 3.93 (d, *J* = 10.8 Hz, 1H), 3.84-3.68 (m, 6H), 3.62-3.58 (m, 1H), 3.43 (t, *J* = 8.8 Hz, 1H); α-anomer: δ 7.83 (d, *J* = 1.6 Hz, 1H), 7.64 (dd, *J* = 8.4, 1.6 Hz, 1H), 7.37-7.19 (m, 19H), 7.13-7.10 (m, 2H), 5.11 (d, *J* = 2.8 Hz, 1H), 4.93-4.46 (m, 8H), 3.96-3.92 (m, 2H), 3.79-3.71 (m, 3H), 3.70-3.62 (m, 2H), 3.55-3.51 (m, 1H); MNa+ 696.

Step 3: 2-(2-Chloro-5-((2*S*,3*S*,4*R*,5*R*,6*R*)-3,4,5-tris(benzyloxy)-6-(benzyloxymethyl)-tetrahydro-2H-pyran-2-yl)phenyl)acetonitrile (**β-4a**)

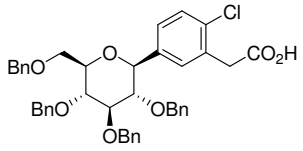


The mixture of cyanides **4a** (105 g, 156 mmol, *ca*. 2:1 β:α) was slurried in ethanol (1 L) and heated to reflux with stirring. The reaction mixture was held at reflux for 1 h to ensure that all of

solution had homogenized. It was then cooled evenly at 15 °C/h to ambient temperature and stirred overnight at this temperature. The resulting solid was isolated by filtration and dried *in vacuo* to yield the titled compound **β-4a** (53 g, 51%) as a white solid.

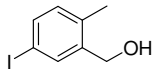
$[\alpha]_D^{21}$ -10.6 (c 1.01, chloroform); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 (s, 1H), 7.37-7.17 (m, 20H), 6.93-6.91 (m, 2H), 4.93 (s, 2H), 4.86 (d, *J* = 10.8 Hz, 1H), 4.63 (d, *J* = 10.8 Hz, 1H), 4.62 (d, *J* = 12.4 Hz, 1H), 4.56 (d, *J* = 12.4 Hz, 1H), 4.52 (d, *J* = 10.8 Hz, 1H), 4.22 (d, *J* = 9.6 Hz, 1H), 3.93 (d, *J* = 10.8 Hz, 1H), 3.84-3.68 (m, 6H), 3.62-3.58 (m, 1H), 3.43 (t, *J* = 8.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 129.49, 128.86, 128.45, 128.38, 128.26, 128.08, 128.01, 127.87, 127.82, 127.70, 127.68, 127.67, 127.64, 127.61, 139.09, 138.52, 138.23, 138.07, 137.41, 132.97, 129.49, 128.86, 128.45, 128.38, 128.26, 128.08, 128.01, 127.87, 127.82, 127.70, 127.68, 127.67, 127.64, 127.61, 116.57, 86.87, 83.59, 80.47, 79.41, 78.28, 75.67, 75.16, 74.96, 73.47, 69.07, 22.12; HRMS (FAB, 6 keV) calcd for $C_{42}H_{41}ClNO_5$ ($[M+H]^+$) 674.2673, found 674.2672; MNa+ 696.

Step 4: 2-(2-Chloro-5-((2*S*,3*S*,4*R*,5*R*,6*R*)-3,4,5-tris(benzyloxy)-6-(benzyloxymethyl)-tetrahydro-2*H*-pyran-2-yl)phenyl)acetic acid (**5**)

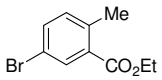


To a solution of cyanide **β-4a** (53 g, 79 mmol) in EtOH (300 mL) was added *aq*. NaOH solution (8.0 *N*, 300 mL, 2.4 mol). The reaction mixture was refluxed overnight. After cooling to room temperature, hydrochloric acid (3.0 *N*) was added to neutralize the reaction mixture. The mixture was diluted with water and extracted with EtOAc. The organic layer was washed with water and brine prior to drying over anhydrous $MgSO_4$. Filtration and concentration under reduced pressure yielded the titled compound **5** (54 g, 98%) as a white solid. $[\alpha]_D^{21}$ -4.7 (c 1.10, chloroform); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37-7.14 (m, 21H), 6.93-6.90 (m, 2H), 4.94 (d, *J* = 10.8 Hz, 1H), 4.90 (d, *J* = 10.8 Hz, 1H), 4.86 (d, *J* = 11.2 Hz, 1H), 4.63 (d, *J* = 10.8 Hz, 1H), 4.62 (d, *J* = 14.0 Hz, 1H), 4.55 (d, *J* = 12.4 Hz, 1H), 4.43 (d, *J* = 10.4 Hz, 1H), 4.20 (d, *J* = 9.6 Hz, 1H), 3.88 (d, *J* = 10.8 Hz, 1H). 3.81-3.70 (m, 6H), 3.59-3.56 (m, 1H), 3.43 (t, *J* = 8.8 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 171.84, 139.10, 138.69, 138.66, 138.17, 133.72, 133.49, 131.99, 129.18, 128.68, 128.66, 128.45, 128.26, 128.19, 128.10, 128.00, 127.92, 127.87, 127.84, 86.25, 83.53, 80.14, 78.77, 78.55, 74.97, 74.51, 74.30, 72.75, 69.39, 39.19; MNH_4+ 710 and MNa+ 715.

(5-Iodo-2-methylphenyl)methanol (**12a**)

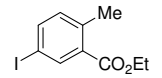


Step 1: Ethyl 5-bromo-2-methylbenzoate (**12aa**)



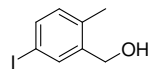
To a mixture of 5-bromo-2-methylbenzoic acid (50.0 g, 233 mmol) in EtOH (700 mL) was added *c*-H_2SO_4 (50 mL) at 0 °C. The mixture was warmed-up to room temperature and stirred at 100°C for 15 h. The mixture was cooled to room temperature and evaporated in *vacuo* to remove EtOH. The residue was diluted with EtOAc and washed with H_2O, *aq.* saturated $NaHCO_3$ solution. The organic layer was dried over anhydrous $MgSO_4$, filtered, and concentrated in *vacuo*. The residue was purified by silica column chromatography to provide the intermediate **12aa** (39.0 g, 69%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (d, *J* = 1.6 Hz, 1H), 7.71 (dd, *J* = 8.0, 2.0 Hz, 1H), 6.99 (d, *J* = 8.0 Hz, 1H), 4.32 (q, *J* = 7.2 Hz, 2H), 2.55 (s, 3H), 1.40 (t, *J* = 7.2 Hz, 2H); MH+ 243.

Step 2: Ethyl 5-iodo-2-methylbenzoate (**12ab**)



To a solution of bromide **12aa** (39.0 g, 161 mmol) in 1,4-dioxane (150 mL) were added NaI (48.2 g, 321 mmol), CuI (1.6 g, 8.03 mmol) and *N*,*N*'-dimethylethyldiamine (1.8 mL, 16.1 mmol). The mixture was evacuated and backfilled with N_2. The mixture was stirred at 110 °C for 15 h. The mixture was cooled to room temperature and filtered off through celite. The filtrated was evaporated under vacuum to remove solvent. The residue was diluted with EtOAc and washed with *aq.* 50% NH_4Cl solution. The organic layer was dried over anhydrous $MgSO_4$, filtered, and concentrated in *vacuo*. The residue was purified by silica column chromatography to provide the titled compound **12ab** (41.3 g, 89%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.20 (d, *J* = 1.6 Hz, 1H), 7.68 (dd, *J* = 8.0, 2.0 Hz, 1H), 6.98 (d, *J* = 8.0 Hz, 1H), 4.35 (q, *J* = 7.2 Hz, 2H), 2.53 (s, 3H), 1.39 (t, *J* = 7.2 Hz, 2H); MH+ 291.

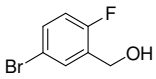
Step 3: (5-Iodo-2-methylphenyl)methanol (**12a**)



To a solution of ester 4 (41.0 g, 141 mmol) in THF (300 mL) was added lithium borohydride (2.0 M in THF, 212 mL). The reaction mixture was refluxed overnight. After cooling to 0 °C, the reaction was quenched by addition of *aq.* saturated NH_4Cl solution. The mixture was diluted

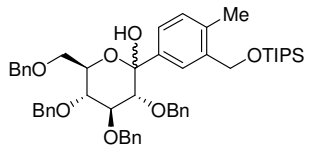
with water and extracted with EtOAc. The organic layer was washed with brine, dried over anhydrous $MgSO_4$, filtered and evaporated *in vacuo* to yield the titled compound (34.0 g, 97%) as a white solid, which was carried on to the next step without further purification. [M-OH^-]+ 231.

(5-Bromo-2-fluorophenyl)methanol



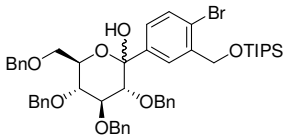
To a solution of 5-bromo-2-fluorobenzaldehyde (30.0 g, 148 mmol) in EtOH was added sodium borohydride (8.39 g, 222 mmol) at 0 °C. The resulting mixture was stirred with gradual warming to ambient temperature over 15 h, re-cooled to 0 °C, and quenched with *aq.* saturated NH_4Cl solution. The mixture was extracted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, filtered and evaporated in vacuo to yield the titled compound (30.3 g, quantitative) as a white sold, which was carried on to the next step without further purification. [M-OH^-]+ 187.

(3*R*,4*S*,5*R*,6*R*)-3,4,5-Tris(benzyloxy)-6-(benzyloxymethyl)-2-(4-methyl-3-((triisopropylsilyloxy)methyl)phenyl)-tetrahydro-2*H*-pyran-2-ol (13)



A mixture of gluconolactone **1** (11.6 g, 21.5 mmol) and iodide **12** (6.7 g, 16.5 mmol) in THF (55 mL) was added trimethylsilylmethyl lithium (1.0 M in pentane, 35 mL) 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 titled compound **13** was carried on to the next step without further purification.

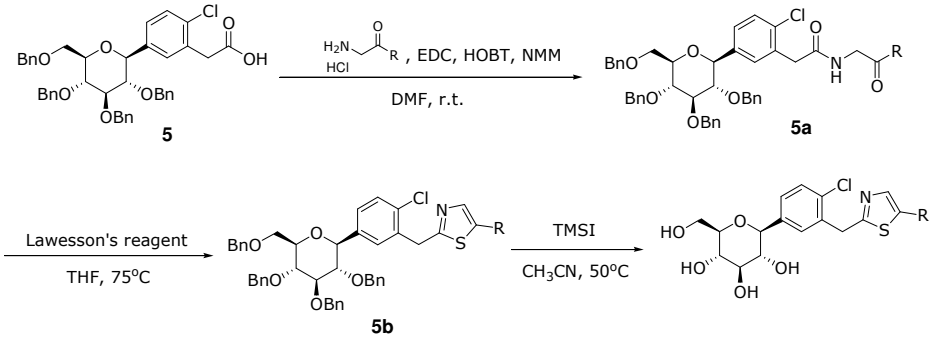
(3*R*,4*S*,5*R*,6*R*)-3,4,5-Tris(benzyloxy)-6-(benzyloxymethyl)-2-(4-bromo-3-((triisopropylsilyloxy)methyl)phenyl)-tetrahydro-2*H*-pyran-2-ol (22)



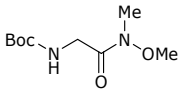
To a solution of 4-bromo-1-iodobenzene **21** (18.1 g, 38.5 mmol) at -60 °C was added dropwise

isopropylmagnesium chloride lithium chloride complex (1.0 M in THF, 50 mL), and the mixture was stirred for 30 min at the same temperature. Then a solution of lactone **1** (26.9 g, 50.0 mmol) in THF (30 mL) was added dropwise. The mixture was allowed to slowly warn to -5 ^{o}C over 1 h. To a mixture was added *aq*. saturated NH_4Cl solution to quench the reaction. After dilution with water, the mixture was extracted with EtOAc. The organic layer was washed with brine, dried over anhydrous $MgSO_4$, filtered and evaporated *in vacuo* to yield the crude titled compound **22**, which was carried on to the next step without further purification.

Scheme 2. Representative Scheme for Preparation of **14a ~ 14aa** and **15a ~ 15h**

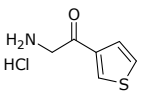


<u>*tert*-Butyl 2-(methoxy(methyl)amino)-2-oxoethylcarbamate (**31a**)</u>



To a mixture of *N*-Boc-glycine (10.0 g, 57.1 mmol), *N*,*O*-dimethylhydroxylamine hydrochloride (6.68 g, 68.5 mmol), EDCI (13.1 g, 68.5 mmol), and HOBt (9.26 g, 68.5 mmol) in CH_2Cl_2 (200 mL) was added NMM (31.4 mL, 285 mmol). The resulting mixture was stirred at room temperature for 15 h. The reaction mixture was poured into 1.0 M HCl solution, and extracted with EtOAc. The organic phase was washed with a saturated $NaHCO_3$ solution and brine, and then dried over anhydrous $MgSO_4$. After evaporation of solvent, the residue was triturated with hexanes (100 mL) to provide the Weinreb amide **31a** (10.2 g, 82%) as white solid.

<u>2-Amino-1-(thiophen-3-yl)ethanone hydrochloride</u>



Step 1: *tert*-Butyl 2-oxo-2-(thiophen-3-yl)ethylcarbamate

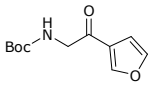
To a solution of the Weinreb amide **31a** (1.53 g, 7 mmol) in anhydrous THF (10 mL) was added

dropwise (over a 10-min period) a solution of thiophen-3-ylmagnesium iodide (0.3 M in THF, 50 mL) under nitrogen atmosphere at 0 °C. The reaction mixture was allowed to warm to room temperature and stirred for 18 h. The mixture was poured into a saturated NH_4Cl solution and extracted with EtOAc. The organic phase was dried over anhydrous $MgSO_4$, filtered and evaporated under vacuum. The residue was further purified by silica column chromatography to provide the titled compound (776 mg, 46 %). MNa+ 264.

Step 2: 2-Amino-1-(thiophen-3-yl)ethanone hydrochloride

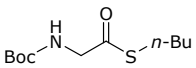
To a mixture of *tert*-butyl 2-oxo-2-(thiophen-3-yl)ethylcarbamate (776 mg, 3.21 mmol) in Et_2O (3 mL) was added a HCl solution (4.0 M in dioxane , 6 mL) at 0 °C. After stirring at 0 °C for 10 min, the resulting mixture was allowed warmed up to room temperature and stirred for 2 h. The reaction mixture was evaporated under vacuum to provide the titled compound (570 mg, quantitative) as a white solid. MH+ 142.

tert-Butyl 2-(furan-3-yl)-2-oxoethylcarbamate



To a solution of *n*-BuLi (2.5 M in hexane, 7.68 mL) in anhydrous ether (10 mL) was added dropwise (over a 20-min period) a solution of 3-bromofuran (2.35 g, 16 mmol) in anhydrous THF (15 mL) under nitrogen atmosphere at -78 °C. After stirring at -78 °C for 20 min, a solution of the Weinreb amide **31a** (1.75 g, 8 mmol) in THF (15 mL) was added slowly to the mixture. The reaction mixture was allowed to warm to room temperature and stirred for 18 h. The mixture was poured into a saturated $NaHCO_3$ solution and extracted with EtOAc. The organic phase was dried over anhydrous $MgSO_4$, filtered and evaporated under vacuum. The residue was further purified by silica column chromatography to provide the titled compound (671 mg, 37 %). MNa+ 248.

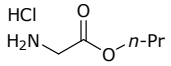
S-Butyl 2-(tert-butoxycarbonylamino)ethanethioate



To a mixture of *N*-Boc-glycine (3.50 g, 20 mmol), EDCI (4.22 g, 22 mmol), and HOBt (2.97 g, 22 mmol) in CH_2Cl_2 (100 mL) was added DIEA (8.71 mL, 50 mmol). After stirring at room temperature for 1 h, 1-buthanethiol (5.37 mL, 50 mmol) was added and the resulting mixture was stirred for 15 h. The reaction mixture was poured into 1.0 M HCl solution, and extracted with CH_2Cl_2. The organic phase was washed with a saturated $NaHCO_3$ solution, brine and dried over anhydrous $MgSO_4$. The solution was evaporated under vacuum to

provide the titled compound (1.72 g, 35 %), which was carried on to the next step without further purification. MNa+ 270.

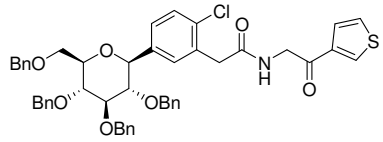
Propyl 2-aminoacetate hydrochloride



To a solution of glycine hydrochloride (4.5 g, 40. 3 mmol) in *n*-propanol (60 mL) was slowly added $SOCl_2$ (13.5 mL) at room temperature. The reaction mixture was stirred at 70 ^oC for 15 h. After cooling to room temperature, the mixture was evaporated under vacuum to provide the titled compound (6.1 g, 98 %) as a white solid. MH+ 118.

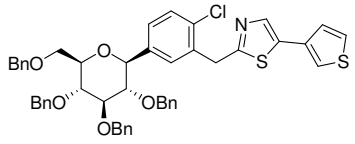
(2*S*,3*R*,4*R*,5*S*,6*R*)-2-(4-Chloro-3-((5-(thiophen-3-yl)thiazol-2-yl)methyl)phenyl)-6-(hydroxymethyl)-tetrahydro-2*H*-pyran-3,4,5-triol (**14y**)

Step 1: 2-(2-Chloro-5-((2*S*,3*S*,4*R*,5*R*,6*R*)-3,4,5-tris(benzyloxy)-6-(benzyloxymethyl)-tetrahydro-2*H*-pyran-2-yl)phenyl)-*N*-(2-oxo-2-(thiophen-3-yl)ethyl)acetamide (**5a**)



To a mixture of the carboxylic acid **5** (1.04 g, 1.5 mmol), 2-amino-1-(thiophen-3yl)ethanone hydrochloride (533 mg, 3.0 mmol), EDCI (575 mg, 3.0 mmol), and HOBt (507 mg, 3.75 mmol) in DMF (10 mL) was added NMM (0.83 mL, 7.5 mmol). The resulting mixture was stirred at room temperature for 15 h. The reaction mixture was poured into HCl solution (1.0 M, 50 mL), and extracted with EtOAc. The organic phase was dried over anhydrous $MgSO_4$, filtered and evaporated under vacuum. The residue was further purified by silica column chromatography to provide the titled amide compound (529 mg, 0.65 mmol, 43 %). MH+ 816.

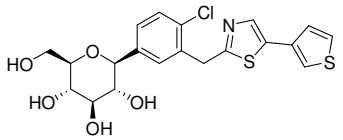
Step 2: 2-(2-Chloro-5-((2*S*,3*S*,4*R*,5*R*,6*R*)-3,4,5-tris(benzyloxy)-6-(benzyloxymethyl)-tetrahydro-2*H*-pyran-2-yl)benzyl)-5-(thiophen-3-yl)thiazole (**5b**)



To a solution of the amide (529 mg, 0.65 mmol) from Step 1 in anhydrous THF (10 mL) was added Lawesson reagent (524 mg, 1.30 mmol). The reaction mixture was refluxed overnight. After cooling to room temperature, the reaction mixture was poured into a saturated

$NaHCO_3$ solution, and extracted with EtOAc. The organic phase was dried over anhydrous $MgSO_4$, filtered and evaporated under vacuum. The residue was further purified by silica column chromatography to provide the titled thiaole compound **5b** (482 mg, 91 %). MH+ 815.

Step 3: (2*S*,3*R*,4*R*,5*S*,6*R*)-2-(4-Chloro-3-((5-(thiophen-3-yl)thiazol-2-yl)methyl)phenyl)-6-(hydroxymethyl)-tetrahydro-2*H*-pyran-3,4,5-triol (**14y**)



To a solution of the perbenzylated thiaozole compound **5b** (308 mg, 0.378 mmol) in acetonitrile (5.0 mL) was added in TMSI (5.0 mL). The resulting mixture was heated at 50 °C for 24 h. After cooling to 0 °C, the reaction was quenched with MeOH, and then evaporated under vacuum. The residue was redissolved in MeOH and further purified by prep HPLC (C18) to provide the titled compound **14y** (103 mg, 60 %) as a white solid. ^{1}H NMR (400 MHz, CD_3OD_3) δ 7.80 (s, 1H), 7.53-7.51 (m, 2H), 7.47-7.45 (m, 1H), 7.41-7.36 (m, 2H), 7.31-7.29 (m, 1H), 4.44 (d, *J* = 2.0 Hz, 2H), 4.13 (d, *J* = 9.2 Hz, 1H), 3.84 (d, *J* = 12.0 Hz, 1H), 3.74-3.66 (m, 1H), 3.43-3.30 (m, 4H); ^{13}C NMR (100 MHz, CD_3OD_3) δ 169.6, 140.9, 138.4, 136.3, 136.1, 134.7, 133.1, 132.2, 130.5, 129.8, 128.3, 127.1, 122.9, 82.8, 82.3, 79.8, 76.7, 72.0, 63.2, 38.1. Positive HR-FAB-MS *m/z* : 454.0545 $[M+H]^+$ (calcd for C20H21ClNO6S: 454.0550).

(2*S*,3*R*,4*R*,5*S*,6*R*)-2-(4-chloro-3-((5-ethylthiazol-2-yl)methyl)phenyl)-6-(hydroxymethyl)-tetrahydro-2*H*-pyran-3,4,5-triol (**14a**)

^{1}H NMR (400 MHz, CD_3OD) δ 7.47 (s, 1H), 7.39-7.35 (m, 2H), 7.33 (s, 1H), 4.38 (d, *J* = 3.2 Hz, 2H), 4.11 (d, *J* = 9.2 Hz, 1H), 3.88-3.85 (m, 1H), 3.71-3.66 (m, 1H), 3.48-3.33 (m, 4H), 2.79 (q, *J* = 7.6 Hz, 2H), 1.25 (d, *J* = 7.6 Hz, 3H); MH+ 400.

(2*S*,3*R*,4*R*,5*S*,6*R*)-2-(3-((5-Butylthiazol-2-yl)methyl)-4-chlorophenyl)-6-(hydroxymethyl)-tetrahydro-2*H*-pyran-3,4,5-triol (**14b**)

^{1}H NMR (400 MHz, CD_3OD) δ 7.48 (s, 1H), 7.39-7.34 (m, 2H), 7.33 (s, 1H), 4.39 (d, *J* = 2.2 Hz, 2H), 4.12 (d, *J* = 9.2 Hz, 1H), 3.89-3.84 (m, 1H), 3.72-3.66 (m, 1H), 3.48-3.33 (m, 4H), 2.77 (t, *J* = 7.2 Hz, 2H), 1.62-1.54 (m, 2H), 1.39-1.30 (m, 2H), 0.91 (t, *J* = 7.2 Hz, 3H); MH+ 428.

(2*S*,3*R*,4*R*,5*S*,6*R*)-2-(4-Chloro-3-((5-pentylthiazol-2-yl)methyl)phenyl)-6-(hydroxymethyl)-tetrahydro-2*H*-pyran-3,4,5-triol (**14c**)

^{1}H NMR (400 MHz, CD_3OD) δ 7.47 (s, 1H), 7.39-7.33 (m, 2H), 7.31 (s, 1H), 4.38 (d, *J* = 4.2 Hz, 2H), 4.11 (d, *J* = 9.6 Hz, 1H), 3.88-3.84 (m, 1H), 3.72-3.65 (m, 1H), 3.47-3.33 (m, 4H), 2.76 (t, *J* = 7.2 Hz, 2H), 1.64-1.56 (m, 2H), 1.36-1.26 (m, 4H), 0.88 (t, *J* = 7.2 Hz, 3H); MH+ 442.

(2*S*,3*R*,4*R*,5*S*,6*R*)-2-(4-Chloro-3-((5-hexylthiazol-2-yl)methyl)phenyl)-6-(hydroxymethyl)-tetrahydro-2*H*-pyran-3,4,5-triol (**14d**)

^{1}H NMR (400 MHz, CD_3OD) δ 7.48 (s, 1H), 7.39-7.34 (m, 2H), 7.33 (s, 1H), 4.39 (d, *J* = 2.8 Hz, 2H), 4.12 (d, *J* = 9.6 Hz, 1H), 3.88-3.84 (m, 1H), 3.74-3.64 (m, 1H), 3.47-3.32 (m, 4H), 2.77 (t, *J* = 7.6 Hz, 2H), 1.63-1.55 (m, 2H), 1.36-1.25 (m, 6H), 0.87 (t, *J* = 6.8 Hz, 3H); MH+ 456.

(2*S*,3*R*,4*R*,5*S*,6*R*)-2-(4-Chloro-3-((5-isopropylthiazol-2-yl)methyl)phenyl)-6-(hydroxymethyl)-tetrahydro-2*H*-pyran-3,4,5-triol (**14f**)

^{1}H NMR (400 MHz, CD_3OD) δ 7.48 (s, 1H), 7.39-7.35 (m, 2H), 7.33 (s, 1H), 4.38 (d, *J* = 2.8 Hz, 2H), 4.12 (d, *J* = 9.6 Hz, 1H), 3.89-3.85 (m, 1H), 3.71-3.66 (m, 1H), 3.48-3.33 (m, 4H), 3.18-3.12 (m, 1H), 1.27 (d, *J* = 7.2 Hz, 6H); MH+ 414.

(2*S*,3*R*,4*R*,5*S*,6*R*,*E*)-2-(3-((5-(but-2-en-2-yl)thiazol-2-yl)methyl)-4-chlorophenyl)-6-(hydroxymethyl)-tetrahydro-2*H*-pyran-3,4,5-triol (**14g**)

^{1}H NMR (400 MHz, CD_3OD) δ 7.48 (s, 1H), 7.46 (s, 1H), 7.39-7.34 (m, 2H), 5.86 (q, *J* = 6.8 Hz, 1H) , 4.37 (d, *J* = 2.8 Hz, 2H), 4.12 (d, *J* = 9.2 Hz, 1H), 3.88-3.84 (m, 1H), 3.71-3.66 (m, 1H), 3.48-3.34 (m, 4H), 1.98 (s, 3H), 1.74 (d, *J* = 7.2 Hz, 3H); MH+ 426.

(2*S*,3*R*,4*R*,5*S*,6*R*)-2-(3-((5-Allylthiazol-2-yl)methyl)-4-chlorophenyl)-6-(hydroxymethyl)-tetrahydro-2*H*-pyran-3,4,5-triol (**14h**)

^{1}H NMR (400 MHz, CD_3OD) δ 7.48 (s, 1H), 7.39-7.34 (m, 3H), 6.52 (s, 1H), 6.48 (s, 1H), 6.02-5.94 (m, 1H), 4.38 (d, *J* = 2.8 Hz, 2H), 4.12 (d, *J* = 9.2 Hz, 1H), 3.88-3.84 (m, 1H), 3.71-3.66 (m, 1H), 3.48-3.33 (m, 4H), 1.81 (d, *J* = 6.4 Hz, 2H); MH+ 412.

(2*S*,3*R*,4*R*,5*S*,6*R*)-2-(4-Chloro-3-((5-cyclopentylthiazol-2-yl)methyl)phenyl)-6-(hydroxymethyl)-tetrahydro-2*H*-pyran-3,4,5-triol (**14i**)

^{1}H NMR (400 MHz, CD_3OD) δ 7.49 (s, 1H), 7.43 (s, 1H), 7.40-7.35 (m, 2H), 4.43 (d, *J* = 1.6 Hz, 2H), 4.12 (d, *J* = 9.2 Hz, 1H), 3.89-3.84 (m, 1H), 3.71-3.66 (m, 1H), 3.48-3.33 (m, 4H),

3.24-3.22 (m, 1H), 2.15-2.06 (m, 2H), 1.82-1.74 (m, 2H), 1.73-1.64 (m, 2H), 1.59-1.52 (m, 2H); MH+ 440.

(2*S*,3*R*,4*R*,5*S*,6*R*)-2-(4-Chloro-3-((5-cyclohexylthiazol-2-yl)methyl)phenyl)-6-(hydroxymethyl)-tetrahydro-2*H*-pyran-3,4,5-triol (**14j**)

^{1}H NMR (400 MHz, CD_3OD) δ 7.47 (s, 1H), 7.38-7.34 (m, 2H), 7.33 (s, 1H), 4.38 (d, *J* = 3.2 Hz, 2H), 4.11 (d, *J* = 9.6 Hz, 1H), 3.88-3.84 (m, 1H), 3.71-3.66 (m, 1H), 3.48-3.33 (m, 4H), 2.84-2.77 (m, 1H), 1.98-1.93 (m, 2H), 1.82-1.64 (m, 3H), 1.45-1.31 (m, 4H), 1.28-1.22 (m, 1H); MH+ 454.

(2*S*,3*R*,4*R*,5*S*,6*R*)-2-(4-Chloro-3-((5-ethoxythiazol-2-yl)methyl)phenyl)-6-(hydroxymethyl)-tetrahydro-2*H*-pyran-3,4,5-triol (**14k**)

^{1}H NMR (400 MHz, CD_3OD) δ 7.45 (s, 1H), 7.38-7.33 (m, 2H), 6.92 (s, 1H), 4.28 (d, *J* = 2.4 Hz, 2H), 4.11 (d, *J* = 9.6 Hz, 1H), 4.06 (q, *J* = 6.8 Hz, 2H), 3.86 (d, *J* = 12.0 Hz, 1H), 3.72-3.66 (m, 1H), 3.48-3.30 (m, 4H), 1.34 (t, *J* = 6.8 Hz, 3H); MH+ 416.

(2*S*,3*R*,4*R*,5*S*,6*R*)-2-(4-Chloro-3-((5-propoxythiazol-2-yl)methyl)phenyl)-6-(hydroxymethyl)-tetrahydro-2*H*-pyran-3,4,5-triol (**14l**)

^{1}H NMR (400 MHz, CD_3OD) δ 7.45 (s, 1H), 7.38-7.32 (m, 2H), 6.92 (s, 1H), 4.28 (d, *J* = 2.8 Hz, 2H), 4.11 (d, *J* = 9.6 Hz, 1H), 3.97 (t, *J* = 6.4 Hz, 2H), 3.88-3.84 (m, 1H), 3.72-3.66 (m, 1H), 3.48-3.30 (m, 4H), 1.79-1.70 (m, 2H), 0.98 (t, *J* = 7.6 Hz, 3H); MH+ 430.

(2*S*,3*R*,4*R*,5*S*,6*R*)-2-(4-Chloro-3-((5-(pentyloxy)thiazol-2-yl)methyl)phenyl)-6-(hydroxymethyl)-tetrahydro-2*H*-pyran-3,4,5-triol (**14n**)

^{1}H NMR (400 MHz, CD_3OD) δ 7.45 (s, 1H), 7.39-7.33 (m, 2H), 6.92 (s, 1H), 4.28 (d, *J* = 2.8 Hz, 2H), 4.11 (d, *J* = 9.6 Hz, 1H), 4.00 (t, *J* = 6.4 Hz, 2H), 3.88-3.84 (m, 1H), 3.71-3.66 (m, 1H), 3.47-3.30 (m, 4H), 1.76-1.69 (m, 2H), 1.41-1.32 (m, 4H), 0.91 (t, *J* = 7.2 Hz, 3H); MH+ 458.

(2*S*,3*R*,4*R*,5*S*,6*R*)-2-(4-Chloro-3-((5-(ethylthio)thiazol-2-yl)methyl)phenyl)-6-(hydroxymethyl)-tetrahydro-2*H*-pyran-3,4,5-triol (**14o**)

^{1}H NMR (400 MHz, CD_3OD) δ 7.57 (s, 1H), 7.50 (s, 1H), 7.40-7.35 (m, 2H), 4.42 (d, *J* = 2.4 Hz, 2H), 4.12 (d, *J* = 9.6 Hz, 1H), 3.88-3.84 (m, 1H), 3.71-3.66 (m, 1H), 3.47-3.30 (m, 4H), 2.75 (q, *J* = 7.6 Hz, 2H), 1.21 (t, *J* = 7.6 Hz, 3H); MH+ 432.

(2*S*,3*R*,4*R*,5*S*,6*R*)-2-(4-Chloro-3-((5-(propylthio)thiazol-2-yl)methyl)phenyl)-6-

(hydroxymethyl)-tetrahydro-2*H*-pyran-3,4,5-triol (**14p**)

^{1}H NMR (400 MHz, CD_3OD) δ 7.55 (s, 1H), 7.50 (s, 1H), 7.40-7.35 (m, 2H), 4.41 (d, *J* = 2.4 Hz, 2H), 4.12 (d, *J* = 9.2 Hz, 1H), 3.88-3.84 (m, 1H), 3.71-3.65 (m, 1H), 3.47-3.30 (m, 4H), 2.72 (t, *J* = 7.2 Hz, 2H), 1.61-1.52 (m, 2H), 0.96 (t, *J* = 7.2 Hz, 3H); MH+ 446.

(2*S*,3*R*,4*R*,5*S*,6*R*)-2-(3-((5-(Butylthio)thiazol-2-yl)methyl)-4-chlorophenyl)-6-(hydroxymethyl)-tetrahydro-2*H*-pyran-3,4,5-triol (**14q**)

^{1}H NMR (400 MHz, CD_3OD) δ 7.59 (s, 1H), 7.51 (s, 1H), 7.41-7.35 (m, 2H), 4.30 (d, *J* = 2.0 Hz, 2H), 4.13 (d, *J* = 9.2 Hz, 1H), 3.88-3.84 (m, 1H), 3.72-3.66 (m, 1H), 3.48-3.35 (m, 4H), 2.76 (t, *J* = 7.2 Hz, 2H), 1.56-1.50 (m, 2H), 1.43-1.36 (m, 2H), 0.88 (t, *J* = 7.6 Hz, 3H); MH+ 460.

(2*S*,3*R*,4*R*,5*S*,6*R*)-2-(4-Chloro-3-((5-(pentylthio)thiazol-2-yl)methyl)phenyl)-6-(hydroxymethyl)-tetrahydro-2H-pyran-3,4,5-triol (**14r**)

^{1}H NMR (400 MHz, CD_3OD) δ 7.55 (s, 1H), 7.50 (s, 1H), 7.40-7.35 (m, 2H), 4.41 (d, *J* = 2.0 Hz, 2H), 4.12 (d, *J* = 9.2 Hz, 1H), 3.88-3.85 (m, 1H), 3.71-3.67 (m, 1H), 3.48-3.30 (m, 4H), 2.74 (t, *J* = 7.2 Hz, 2H), 1.58-1.51 (m, 2H), 1.38-1.26 (m, 4H), 0.87 (t, *J* = 7.2 Hz, 3H); MH+ 474.

(2*S*,3*R*,4*R*,5*S*,6*R*)-2-(4-Chloro-3-((5-(4-fluorophenyl)thiazol-2-yl)methyl)phenyl)-6-(hydroxymethyl)-tetrahydro-2*H*-pyran-3,4,5-triol (**14t**)

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.01 (s, 1H), 7.64-7.59 (m, 2H), 7.47 (s, 1H), 7.41 (d, *J* = 8.0 Hz, 1H), 7.30-7.27 (m, 1H), 7.23-7.18 (m, 2H), 4.40 (d, *J* = 6.0 Hz, 2H), 4.01 (d, *J* = 9.2 Hz, 1H), 3.67 (d, *J* = 10.4 Hz, 1H), 3.44-3.33 (m, 1H), 3.25-3.06 (m, 4H); MH+ 466.

(2S,3R,4R,5S,6R)-2-(3-((5-(biphenyl-4-yl)thiazol-2-yl)methyl)-4-chlorophenyl)-6-(hydroxymethyl)tetrahydro-2H-pyran-3,4,5-triol (**14u**)

^{1}H NMR (400 MHz, $CDCl_3/CD_3OD$ =1/1) δ 7.87 (s, 1H), 7.65-7.59 (m, 6H), 7.54 (d, *J* = 2.0 Hz, 1H), 7.47-7.42 (m, 4H), 7.40-7.34 (m, 2H), 4.49 (s, 2H), 4.19 (d, *J* = 9.2 Hz, 1H), 3.93-3.90 (m, 1H), 3.79-3.75 (m, 1H), 3.54-3.44 (m, 3H), 3.39-3.37 (m, 1H); MH+ 524.

(2*S*,3*R*,4*R*,5*S*,6*R*)-2-(4-Chloro-3-((5-(furan-2-yl)thiazol-2-yl)methyl)phenyl)-6-(hydroxymethyl)-tetrahydro-2*H*-pyran-3,4,5-triol (**14v**)

^{1}H NMR (400 MHz, CD_3OD) δ 7.79 (s, 1H), 7.52-7.51 (m, 2H), 7.41-7.35 (m, 2H), 6.61 (d, *J* = 3.2, 1H), 6.48-6.46 (m, 1H), 4.45 (d, *J* = 2.4 Hz, 2H), 4.13 (d, *J* = 9.2 Hz, 1H), 3.88-3.85 (m, 1H), 3.71-3.66 (m, 1H), 3.46-3.33 (m, 4H); ^{13}C NMR (100 MHz, CD_3OD_3) δ 170.0, 147.5,

144.3, 140.9, 137.9, 136.2, 134.7, 132.2, 130.8, 130.6, 129.9, 113.6, 108.5, 82.8, 82.4, 79.8, 76.7, 72.0, 63.2, 38.0. Positive HR-FAB-MS *m/z* : 438.0781 $[M+H]^+$ (calcd for C20H21ClNO6S: 438.0778).

(2*S*,3*R*,4*R*,5*S*,6*R*)-2-(4-Chloro-3-((5-(furan-3-yl)thiazol-2-yl)methyl)phenyl)-6-(hydroxymethyl)-tetrahydro-2*H*-pyran-3,4,5-triol (**14w**)

^{1}H NMR (400 MHz, CD_3OD) δ 7.77 (s, 1H), 7.71 (s, 1H), 7.55-7.51 (m, 2H), 7.41-7.35 (m, 2H), 6.67 (s, 1H), 4.43 (d, *J* = 2.0 Hz, 2H), 4.13 (d, *J* = 9.6 Hz, 1H), 3.86 (d, *J* = 12.0 Hz, 1H), 3.73-3.66 (m, 1H), 3.43-3.32 (m, 4H): ^{13}C NMR (100 MHz, CD_3OD_3) δ 169.6, 145.6, 141.0, 140.9, 138.8, 136.3, 134.6, 132.2, 131.9, 130.5, 129.8, 118.4, 110.2, 82.8, 82.3, 79.8, 76.7, 72.0, 63.2, 38.1. Positive HR-FAB-MS *m/z* : 438.0780 $[M+H]^+$ (calcd for C20H21ClNO6S: 438.0778).

(2*S*,3*R*,4*R*,5*S*,6*R*)-2-(4-Chloro-3-((5-(thiophen-2-yl)thiazol-2-yl)methyl)phenyl)-6-(hydroxymethyl)tetrahydro-2*H*-pyran-3,4,5-triol (**14x**)

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.72 (s, 1H), 7.52 (d, *J* = 1.6 Hz, 1H), 7.43-7.35 (m, 3H), 7.18 (dd, *J* = 4.0, 1.0 Hz, 1H), 7.05-6.98 (m, 1H), 4.81 (s, 4H), 4.45-4.31 (m, 2H), 4.13 (d, *J* = 9.6 Hz, 1H), 3.88 (dd, *J* = 12.0, 1.6 Hz, 1H), 3.69 (dd, *J* = 12.0, 5.2 Hz, 1H), 3.48-3.25 (m, 4H); ^{13}C NMR (100 MHz, CD_3OD_3) δ 170.1, 140.9, 138.5, 136.2, 134.7, 134.5, 134.0, 132.2, 130.6, 129.9, 129.2, 127.7, 127.1, 82.8, 82.3, 79.8, 76.7, 72.0, 63.2, 38.1. Positive HR-FAB-MS *m/z* : 454.0553 $[M+H]^+$ (calcd for C20H21ClNO6S: 454.0550).

(2*S*,3*R*,4*R*,5*S*,6*R*)-2-(4-Chloro-3-((5-(5-chlorothiophen-2-yl)thiazol-2-yl)methyl)phenyl)-6-(hydroxymethyl)tetrahydro-2*H*-pyran-3,4,5-triol (**14z**)

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.88 (s, 1H), 7.45 (d, *J* = 2.4 Hz, 1H), 7.43-7.38 (m, 1H), 7.29 (dd, *J* = 8.0, 2.0 Hz, 1H), 7.15 (d, *J* = 3.6 Hz, 1H), 7.09 (d, *J* = 4.0 Hz, 1H), 4.92 (br, 4H), 4.45-4.35 (m, 2H), 4.07-3.95 (m, 1H), 3.66 (dd, *J* = 11.6, 1.6 Hz, 1H), 3.47-3.38 (m, 1H), 3.37-3.04 (m, 4H); MH+ 488.

(2*S*,3*R*,4*R*,5*S*,6*R*)-2-(3-(2,5'-Bithiazol-2'-ylmethyl)-4-chlorophenyl)-6-(hydroxymethyl)-tetrahydro-2*H*-pyran-3,4,5-triol (**14aa**)

^{1}H NMR (400 MHz, CD_3OD) δ 8.12 (s, 1H), 7.76 (d, *J* = 3.2 Hz, 1H), 7.57-7.55 (m, 2H), 7.42-7.37 (m, 2H), 4.49 (d, *J* = 2.4 Hz, 2H), 4.14 (d, *J* = 9.2 Hz, 1H), 3.87 (d, *J* = 12.4 Hz, 1H), 3.73-3.67 (m, 1H), 3.48-3.36 (m, 4H); MH+ 455.

(2*S*,3*R*,4*R*,5*S*,6*R*)-2-(3-((5-(Furan-2-yl)thiazol-2-yl)methyl)-4-methylphenyl)-6-(hydroxymethyl)tetrahydro-2*H*-pyran-3,4,5-triol (**15a**)

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.89 (s, 1H), 7.68 (d, *J* = 1.6 Hz, 1H), 7.25 (s, 1H), 7.17-7.08 (m, 2H), 6.73 (d, *J* = 3.2 Hz, 1H), 6.57-6.51 (m, 1H), 4.90 (d, *J* = 4.0 Hz, 2H), 4.72 (d, *J* = 5.6 Hz, 1H), 4.41 (t, *J* = 5.6 Hz, 1H), 4.33-4.25 (m, 2H), 3.84 (d, *J* = 9.2 Hz, 1H), 3.71-3.63 (m, 1H), 3.45-3.36 (m, 1H), 3.27-3.08 (m, 4H), 2.21 (s, 3H), MH+ 418.

(2*R*,3*S*,4*R*,5*R*,6*S*)-2-(Hydroxymethyl)-6-(4-methyl-3-((5-(thiophen-3-yl)thiazol-2-yl)methyl)phenyl)tetrahydro-2*H*-pyran-3,4,5-triol (**15b**)

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.88 (s, 1H), 7.54-7.49 (m, 2H), 7.39-7.33 (m, 1H), 7.31-7.25 (m, 2H), 7.18 (d, *J* = 7.6 Hz, 1H), 4.84 (s, 4H), 4.34 (s, 2H), 4.10 (d, *J* = 9.2 Hz, 1H), 3.86 (dd, *J* = 12.0, 2.0 Hz, 1H), 3.68 (dd, *J* = 12.0, 5.6 Hz, 1H), 3.48-3.31 (m, 4H), 2.20 (s, 3H); MH+ 434.

(2*S*,3*R*,4*R*,5*S*,6*R*)-2-(4-Bromo-3-((5-(furan-2-yl)thiazol-2-yl)methyl)phenyl)-6-(hydroxymethyl)-tetrahydro-2*H*-pyran-3,4,5-triol (**15c**)

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.96 (s, 1H), 7.75 (d, *J* = 2.0 Hz, 1H), 7.63 (d, *J* = 8.4 Hz, 1H), 7.53 (d, *J* = 2.0 Hz, 1H), 7.27 (dd, *J* = 8.4, 2.0 Hz, 1H), 6.82 (d, *J* = 3.2 Hz, 1H), 6.61 (dd, *J* = 3.2, 2.0 Hz, 1H), 4.90 (br, 4H), 4.49 (d, *J* = 16.0 Hz, 1H), 4.45 (d, *J* = 16.0 Hz, 1H), 4.06 (d, *J* = 9.6 Hz, 1H), 7.73 (d, *J* = 10.0 Hz, 1H), 3.48 (dd, *J* = 11.6, 5.6 Hz, 1H), 3.32-3.11 (m, 4H); MH+ 482.

(2*S*,3*R*,4*R*,5*S*,6*R*)-2-(4-Bromo-3-((5-(thiophen-3-yl)thiazol-2-yl)methyl)phenyl)-6-(hydroxymethyl)-tetrahydro-2*H*-pyran-3,4,5-triol (**15d**)

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.99 (s, 1H), 7.74-7.73 (m, 1H), 7.65-7.63 (m, 1H), 7.60 (d, J = 8.4 Hz, 1H), 7.51 (d, J = 1.6 Hz, 1H), 7.43 (dd, J = 5.2, 4.6 Hz, 1H), 7.25 (dd, J = 8.4, 2.0 Hz, 1H), 5.85 (br, 4H), 4.46 (d, J = 16.0 Hz, 1H), 4.41 (d, J = 16.0 Hz, 1H), 4.03 (d, J = 9.2 Hz, 1H), 3.71 (d, J = 10.0 Hz, 1H), 3.46 (dd, J = 11.6, 5.6 Hz, 1H), 3.30-3.09 (m, 4H); MH+ 498.

(2*S*,3*R*,4*R*,5*S*,6*R*)-2-(4-Fluoro-3-((5-(furan-2-yl)thiazol-2-yl)methyl)phenyl)-6-(hydroxymethyl)tetrahydro-2*H*-pyran-3,4,5-triol (**15e**)

^{1}H NMR (400 MHz, DMSO-d_6) δ7.93 (s, 1H), 7.74 (d, *J* = 2.0 Hz, 1H), 7.44 (dd, *J* = 7.2, 2.0 Hz, 1H), 7.34-7.32 (m, 1H), 7.18 (t, *J* = 9.2 Hz, 1H), 6.81 (d, *J* = 3.6 Hz, 1H), 6.60 (dd, *J* = 3.6, 2.0 Hz, 1H), 4.40 (d, *J* = 16.0 Hz, 1H), 4.35 (d, *J* = 16.0 Hz, 1H), 4.04 (d, *J* = 9.6 Hz, 1H), 3.71 (dd, *J* = 11.6, 1.2 Hz, 1H), 3.46 (dd, *J* = 12.0, 5.6 Hz, 1H), 3.31-3.11 (m, 4H); MH+ 422.

(2*S*,3*R*,4*R*,5*S*,6*R*)-2-(4-Fluoro-3-((5-(thiazol-3-yl)thiazol-2-yl)methyl)phenyl)-6-(hydroxymethyl)tetrahydro-2*H*-pyran-3,4,5-triol (**15f**)

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.96 (s, 1H), 7.73 (dd, *J* = 2.8, 1.2 Hz, 1H), 7.64 (dd, *J* = 5.2, 2.8 Hz, 1H), 7.43 (dd, *J* = 5.2, 1.2 Hz, 2H), 7.34-7.30 (m, 1H), 7.17 (t, *J* = 9.2 Hz, 1H), 4.37 (d, *J* = 16.0 Hz, 1H), 4.32 (d, *J* = 16.0 Hz, 1H), 4.03 (d, *J* = 9.6 Hz, 1H), 3.70 (dd, *J* = 11.6, 2.0 Hz, 1H), 3.45 (dd, *J* = 12.0, 5.6 Hz, 1H), 3.29-3.11 (m, 4H); MH+ 438.

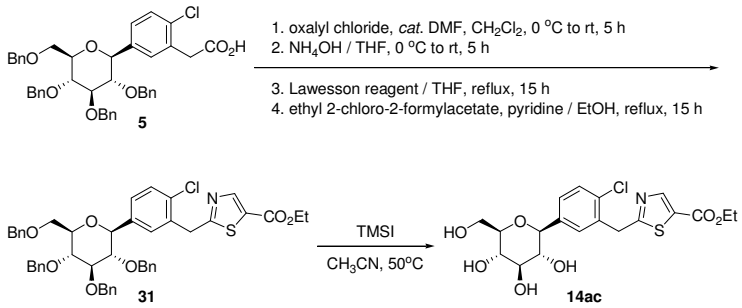
(2S,3R,4R,5S,6R)-2-(3-((5-(Furan-2-yl)thiazol-2-yl)methyl)-4-(trifluoromethyl)phenyl)-6-(hydroxymethyl)-tetrahydro-2H-pyran-3,4,5-triol (**15g**)

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.95 (s, 1H), 7.77-7.71 (m, 2H), 7.61 (s, 1H), 7.52 (d, *J* = 8.0 Hz, 1H), 6.80 (d, *J* = 2.0 Hz, 1H), 6.61-6.55 (m, 1H), 4.96 (br s, 3H), 4.51 (t, *J* =16.8 Hz, 3H), 4.14 (d, *J* = 9.2 Hz, 1H), 3.72 (d, *J* = 10.8 Hz, 1H), 3.48 (dd, *J* = 11.6, 5.6 Hz, 1H), 3.32-3.15 (m, 4H); MH+ 472.

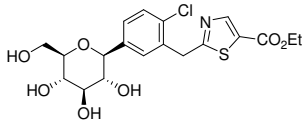
(2*R*,*3S*,4*R*,5*R*,6*S*)-2-(Hydroxymethyl)-6-(3-((5-(thiophen-3-yl)thiazol-2-yl)methyl)-4-(trifluoromethyl)phenyl)tetrahydro-2*H*-pyran-3,4,5-triol (**15h**)

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.99 (s, 1H), 7.76-7.72 (m, 2H), 7.67-7.62 (m, 1H), 7.61 (s, 1H), 7.52 (d, *J* = 8.4 Hz, 1H), 7.43 (dd, *J* = 5.2, 1.2 Hz, 1H), 5.05-4.94 (m, 3H), 4.54-4.42 (m, 2H), 4.13 (d, *J* = 9.6 Hz, 1H), 3.77-3.64 (m, 1H), 3.53-3.42 (m, 1H), 3.31-3.07 (m, 5H); MH+ 488.

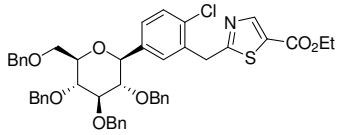
Scheme 2. Preparation of **14ac**



Ethyl 2-(2-chloro-5-((2S,3R,4R,5S,6R)-3,4,5-trihydroxy-6-(hydroxymethyl)-tetrahydro-2H-pyran-2-yl)benzyl)thiazole-5-carboxylate (**14ac**)



Step 1: Ethyl 2-(2-chloro-5-((2*S*,3*S*,4*R*,5*R*,6*R*)-3,4,5-tris(benzyloxy)-6-(benzyloxymethyl)-tetrahydro-2*H*-pyran-2-yl)benzyl)thiazole-5-carboxylate (**31**)

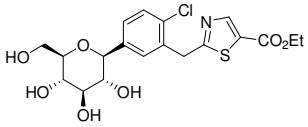


To a solution of carboxylic acid **5** (2.5 g, 3.6 mmol) and DMF (0.1 mL) in CH_2Cl_2 (12 mL) under nitrogen atmosphere, was slowly added oxalyl chloride (1.28 mL, 7.2 mmol) at 0 ^oC. After an additional stirring at 0 ^oC for 15 min, the reaction mixture was stirred at room temperature for 5 h. The mixture was evaporated under vacuum to provide acyl chloride (2.6 g). The residue was dissolved in THF (25 mL) and to the solution of acyl chloride was added NH_4OH (10 mL) at 0 ^oC. The reaction mixture was warmed to room temperature and stirred for 5 h. The mixture was evaporated under vacuum to provide amide (2.6 g).

To a solution of the crude amide in anhydrous THF (40 mL) was added Lawesson's reagent (874 mg, 2.16 mmol). The reaction mixture was refluxed for 15 h. After cooling to room temperature, the reaction mixture was poured into a saturated $NaHCO_3$ solution, and extracted with EtOAc. The organic phase was dried over anhydrous $MgSO_4$, filtered and evaporated under vacuum to provide the crude thioamide.

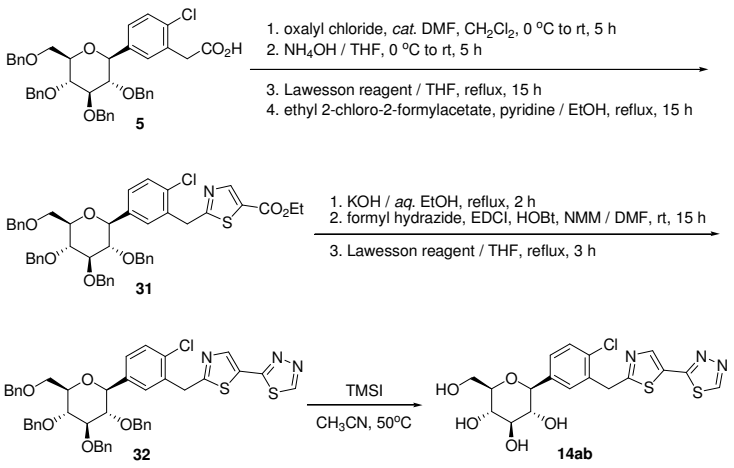
To a solution of the thioamide residue and ethyl-2-chloro-2-formylacetate (1.35 g, 9.0 mmol) in EtOH (30 mL) was added pyridine (0.5 mL). The reaction mixture was stirred at 80 ^oC for 15 h. The reaction mixture was poured into a 1.0 M HCl solution, and extracted with CH_2Cl_2. The organic phase was dried over anhydrous $MgSO_4$, filtered and evaporated under vacuum. The residue was further purified by silica column chromatography to provide the ester intermediate **31** (1013 mg, 35 %, 4 steps). MH+ 804.

Step 2: Ethyl 2-(2-chloro-5-((2S,3R,4R,5S,6R)-3,4,5-trihydroxy-6-(hydroxymethyl)-tetrahydro-2H-pyran-2-yl)benzyl)thiazole-5-carboxylate (**14ac**)

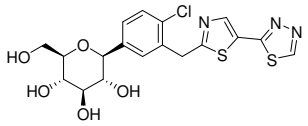


The titled compound was obtained in the same manner as in Scheme 2. ^1H NMR (400 MHz, CD_3OD) δ 8.23 (s, 1H), 7.53 (s, 1H), 7.42-7.38 (m, 2H), 4.48 (d, *J* = 2.4 Hz, 2H), 4.30 (q, *J* = 7.2 Hz, 2H), 4.14 (d, *J* = 9.6 Hz, 1H), 3.87 (d, *J* = 12.4 Hz, 1H), 3.71-3.67 (m, 1H), 3.48-3.30 (m, 4H), 1.31 (t, *J* = 7.2 Hz, 3H); MH+ 444.

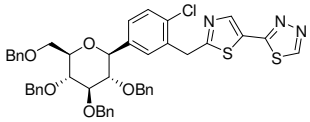
Scheme 3. Preparation of **14ab**



(2*S*,3*R*,4*R*,5*S*,6*R*)-2-(3-((5-(1,3,4-Thiadiazol-2-yl)thiazol-2-yl)methyl)-4-chlorophenyl)-6-(hydroxymethyl)-tetrahydro-2*H*-pyran-3,4,5-triol (**14ab**)



Step 1: 2-(2-(2-Chloro-5-((2*S*,3*S*,4*R*,5*R*,6*R*)-3,4,5-tris(benzyloxy)-6-(benzyloxymethyl)-tetrahydro-2*H*-pyran-2-yl)benzyl)thiazol-5-yl)-1,3,4-thiadiazole (**32**)



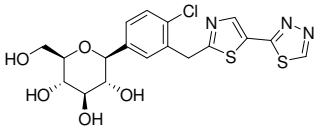
The mixture of the ester **31** (910 mg, 1.13 mmol) and KOH (254 mg, 4.52 mmol) in EtOH/THF (1:2, 30 mL) was refluxed for 2 h. After cooling to room temperature, the reaction mixture was poured into a 1.0 M HCl solution, and extracted with CH_2Cl_2. The organic phase was dried over anhydrous $MgSO_4$ and evaporated under vacuum to provide a carboxylic acid (769 mg, 0.99 mmol).

To a mixture of the carboxylic acid (769 mg, 0.99 mmol), EDCI (380 mg, 1.98 mmol), HOBt (268 mg, 1.98 mmol) and formylhydrazine (90 mg, 1.49 mmol) in DMF (10 mL) was added NMM (0.44 mL, 3.96 mmol). After stirring at room temperature for 15 h, the reaction mixture was poured into brine, and extracted with EtOAc. The organic phase was washed with a saturated $NaHCO_3$ solution and dried over anhydrous $MgSO_4$. The solution was evaporated under vacuum to provide a hydrazide intermediate (810 mg, 0.99 mmol).

To a solution of the hydrazide intermediate (810 mg, 0.99 mmol) in anhydrous THF (10 mL) was added Lawesson's reagent (1002 mg, 2.48 mmol). The reaction mixture was refluxed for 3 h. After cooling to room temperature, the reaction mixture was poured into a saturated $NaHCO_3$ solution, and extracted with EtOAc. The organic phase was dried over $MgSO_4$, filtered

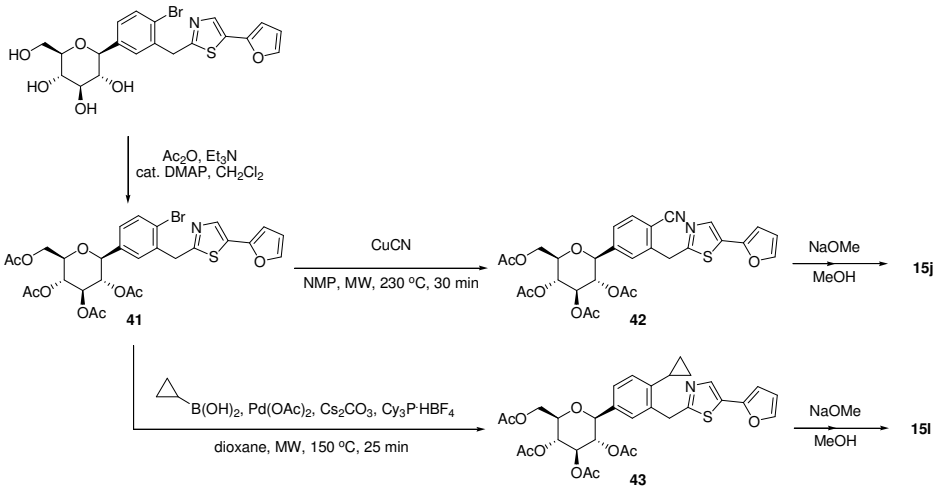
and evaporated under vacuum to provide the titled compound **32** (403 mg, 44 %). MH+ 816.

Step 2: (2*S*,3*R*,4*R*,5*S*,6*R*)-2-(3-((5-(1,3,4-Thiadiazol-2-yl)thiazol-2-yl)methyl)-4-chlorophenyl)-6-(hydroxymethyl)-tetrahydro-2*H*-pyran-3,4,5-triol (**14ab**)

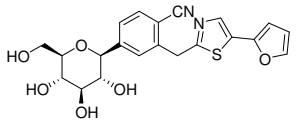


The titled compound was obtained in the same manner as in Scheme 2. ^{1}H NMR (400 MHz, CD_3OD) δ 9.41 (s, 1H), 8.28 (s, 1H), 7.57 (m, 1H), 7.44-7.38 (m, 2H), 4.53 (d, *J* = 2.0 Hz, 2H), 4.15 (d, *J* = 9.6 Hz, 1H), 3.87 (d, *J* = 12.4 Hz, 1H), 3.72-3.67 (m, 1H), 3.48-3.30 (m, 4H); MH+ 456.

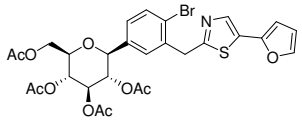
Scheme 4. Preparation of **15i**, **15j** and **15l**



2-((5-(Furan-2-yl)thiazol-2-yl)methyl)-4-((2*S*,3*R*,4*R*,5*S*,6*R*)-3,4,5-trihydroxy-6-(hydroxymethyl)-tetrahydro-2*H*-pyran-2-yl)benzonitrile (**15j**)

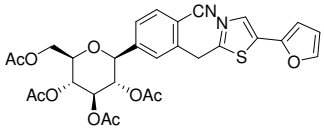


Step 1: (2*R*,3*R*,4*R*,5*S*,6*S*)-2-(Acetoxymethyl)-6-(4-bromo-3-((5-(furan-2-yl)thiazol-2-yl)methyl)phenyl)-tetrahydro-2*H*-pyran-3,4,5-triyl triacetate (**41**)



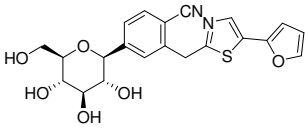
To a solution of (2*S*,3*R*,4*R*,5*S*,6*R*)-2-(4-bromo-3-((5-(furan-2-yl)thiazol-2-yl)methyl)phenyl)-6-(hydroxymethyl)-tetrahydro-2*H*-pyran-3,4,5-triol (750 mg, 1.55 mmol) and DMAP (19 mg, 0.16 mmol) in CH_2Cl_2 (16 mL) was slowly added acetic anhydride (1.18 mL, 12.4 mmol) and triethylamine (2.17 mL, 15.5 mmol) at 0 ^oC. After an additional stirring at 0 ^oC for 15 min, the reaction mixture was stirred at room temperature for 3 h. The mixture was evaporated *in vacuo* to remove CH_2Cl_2. The residue was diluted with EtOAc and washed with water, 1.0 M HCl solution and brine. The organic layer was dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by silica column chromatography to provide the intermediate **41** (974 mg, 97%) as a white solid. MH+ 650.

Step 2: (2*R*,3*R*,4*R*,5*S*,6*S*)-2-(Acetoxymethyl)-6-(4-cyano-3-((5-(furan-2-yl)thiazol-2-yl)methyl)phenyl)-tetrahydro-2*H*-pyran-3,4,5-triyl triacetate (**42**)



The bromide **41** (300 mg, 0.46 mmol) was added to a microwave reaction tube containing copper(I) cyanide (124 mg, 1.38 mmol) in NMP. The capped reaction tube was placed in a microwave reactor and the mixture irradiated at 230 ^oC for 30 min. After dilution with EtOAc, the organic layer was washed with 15% NH_4OH solution prior to drying over anhydrous $MgSO_4$. After filtration and concentration under reduced pressure, the residue was purified by silica column chromatography to provide the cyanide **42** (208 mg, 76%) as a white solid. MH+ 597.

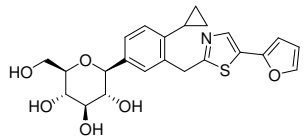
Step 3: 2-((5-(Furan-2-yl)thiazol-2-yl)methyl)-4-((2*S*,3*R*,4*R*,5*S*,6*R*)-3,4,5-trihydroxy-6-(hydroxymethyl)-tetrahydro-2*H*-pyran-2-yl)benzonitrile (**15j**)



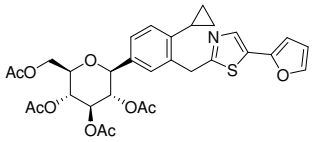
To a solution of the peracetylate **42** (208 mg, 0.35 mmol) in MeOH (10 mL) was added NaOMe (25 wt. % in MeOH, 0.2 mL). The reaction mixture was stirred at ambient temperature for 3 h. Acetic acid was added to neutralize the reaction mixture and concentrated in vacuo. The residue was redissolved in MeOH and further purified by prep HPLC (C18) to provide the titled compound (106 mg, 71 mmol) as a white solid. ^1H NMR (400 MHz, DMSO-d_6) δ 7.96 (s, 1H), 7.83 (d, J = 8.0 Hz, 1H), 7.75 (d, J = 1.6 Hz, 1H), 7.63 (s, 1H), 7.49 (dd, J = 8.0, 1.2 Hz, 1H),

6.83 (d, *J* = 3.2 Hz, 1H), 6.61-6.59 (m, 1H), 5.01 (br, 3H), 4.49 (br, 1H), 4.14 (d, *J* = 9.2 Hz, 1H), 4.10 (br, 1H), 3.72 (d, *J* = 11.6 Hz, 1H), 3.52-3.45 (m, 1H), 3.33-3.18 (m, 4H), 3.10 (t, *J* = 9.2 Hz, 1H)

(2*S*,3*R*,4*R*,5*S*,6*R*)-2-(4-Cyclopropyl-3-((5-(furan-2-yl)thiazol-2-yl)methyl)phenyl)-6-(hydroxymethyl)-tetrahydro-2*H*-pyran-3,4,5-triol (**15l**)

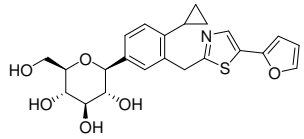


Step 1: (2*R*,3*R*,4*R*,5*S*,6*S*)-2-(Acetoxymethyl)-6-(4-cyclopropyl-3-((5-(furan-2-yl)thiazol-2-yl)methyl)phenyl)-tetrahydro-2*H*-pyran-3,4,5-triyl triacetate (**43**)



The bromide **41** (300 mg, 0.46 mmol) was added to a microwave reaction tube containing cyclopropylboronic acid (86.9 mg, 1.01 mmol), palladium(II) acetate (31 mg, 46 μmol), tricyclohexylphosphonium tetrafluoroborate (68 mg, 0.18 mmol) and cesium carbonate (601 mg, 1.84 mmol) in dioxaone (5 mL). The capped reaction tube was placed in a microwave reactor and the mixture irradiated at 150 ^{o}C for 25 min. After dilution with EtOAc, the organic layer was washed with water and brine prior to drying over anhydrous $MgSO_4$. After filtration and concentration under reduced pressure, the residue was purified by silica column chromatography to provide the cyclopropane **43** (56 mg, 20%) as a yellow oil. MH+ 612.

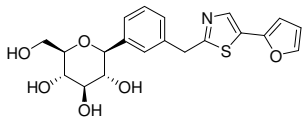
Step 2: (2*S*,3*R*,4*R*,5*S*,6*R*)-2-(4-Cyclopropyl-3-((5-(furan-2-yl)thiazol-2-yl)methyl)phenyl)-6-(hydroxymethyl)-tetrahydro-2*H*-pyran-3,4,5-triol (**15l**)



The titled compound was obtained in the same manner as in Scheme 4. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.95 (s, 1H), 7.44 (d, *J* = 1.2 Hz, 1H), 7.32 (d, *J* = 1.6 Hz, 1H), 7.22 (dd, *J* = 8.4, 1.6 Hz, 1H), 6.99 (d, *J* = 8.0 Hz, 1H), 6.80-6.79 (m, 1H), 6.61-6.59 (m, 1H), 4.52 (d, *J* = 13.2 Hz, 2H), 4.00 (d, *J* = 9.2 Hz, 1H), 3.72 (d, *J* = 11.6 Hz, 1H), 3.49-3.44 (m, 1H), 3.32-3.27 (m, 1H), 3.21-3.16 (m, 3H), 1.99-1.95 (m, 1H), 0.89-0.85 (m, 2H), 0.63-0.59 (m, 2H); MH+ 444.

(2*S*,3*R*,4*R*,5*S*,6*R*)-2-(3-((5-(Furan-2-yl)thiazol-2-yl)methyl)phenyl)-6-(hydroxymethyl)-

tetrahydro-2*H*-pyran-3,4,5-triol (**15i**)

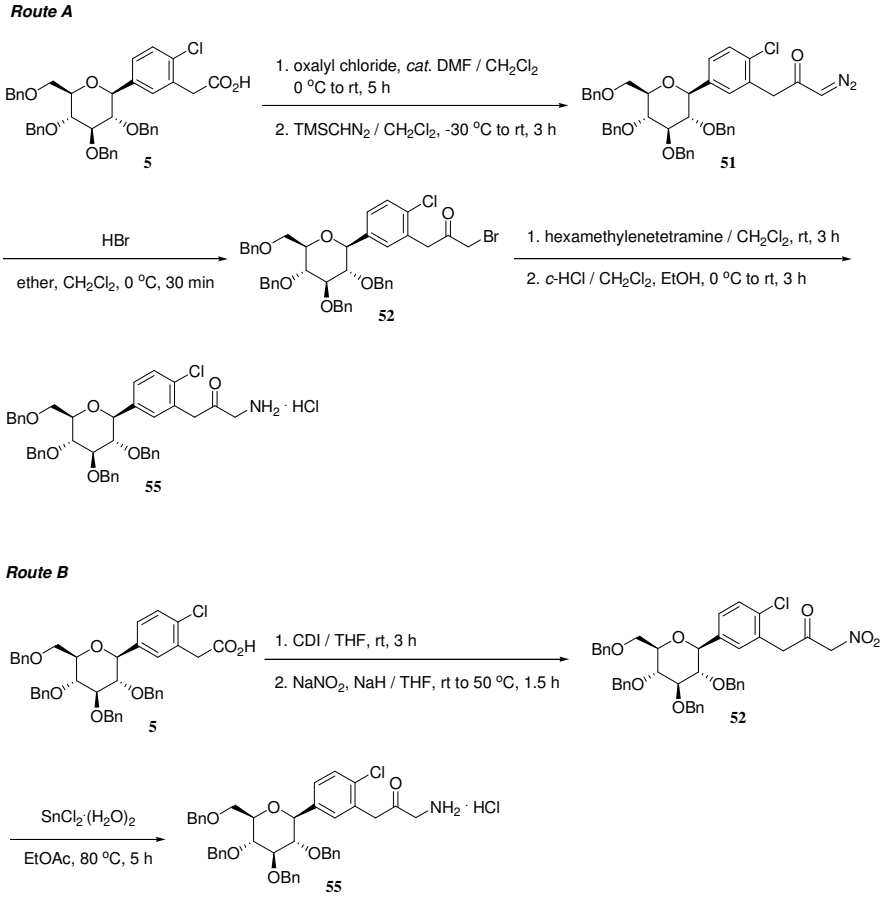


The titled compound was obtained as a side product in Scheme 4. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.95 (s, 1H), 7.74 (d, *J* = 1.6 Hz, 1H), 7.35-7.22 (m, 4H), 6.79 (d, *J* = 3.2 Hz, 1H), 6.60 (dd, *J* = 3.2, 1.6 Hz, 1H), 4.94 (d, *J* = 4.8 Hz, 2H), 4.78 (d, *J* = 6.0 Hz, 1H), 4.45 (t, *J* = 6.0 Hz, 1H), 4.34 (s, 3H), 4.02 (d, *J* = 9.2 Hz, 1H), 3.74-3.69 (m, 1H), 3.49-3.43 (m, 1H), 3.33-3.15 (m, 4H); MH+ 404.

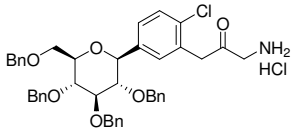
2-((5-(Thiophen-3-yl)thiazol-2-yl)methyl)-4-((2*S*,3*R*,*4R*,5*S*,6*R*)-3,4,5-trihydroxy-6-(hydroxymethyl)-tetrahydro-2*H*-pyran-2-yl)benzonitrile (**15k**)

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.99 (s, 1H), 7.82 (d, *J* = 8.0 Hz, 1H), 7.76 (dd, *J* = 2.8, 1.2 Hz, 1H), 7.65 (dd, *J* = 4.8, 2.8 Hz, 1H), 7.62 (s, 1H), 7.49 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.44 (dd, *J* = 4.8, 1.2 Hz, 1H), 5.03 (d, *J* = 5.2 Hz, 1H), 5.00 (d, *J* = 5.2 Hz, 1H), 4.98 (d, *J* = 6.0 Hz, 1H), 4.54 (s, 2H), 4.48 (t, *J* = 5.6 Hz, 1H), 4.11 (d, *J* = 5.6 Hz, 1H), 3.71 (dd, *J* = 10.0, 5.6 Hz, 1H), 3.47 (quint, *J* = 6.0 Hz, 1H), 3.32-3.06 (m, 4H); MH+ 445.

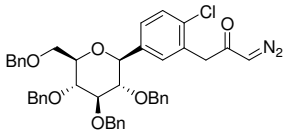
Scheme 5. Preparation of key Intermediate **55**



1-Amino-3-(2-chloro-5-((2*S*,3*S*,4*R*,5*R*,6*R*)-3,4,5-tris(benzyloxy)-6-(benzyloxymethyl)-tetrahydro-2*H*-pyran-2-yl)phenyl)propan-2-one hydrochloride (**55**, Route A)



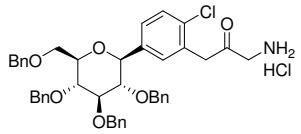
Step 1: 1-(2-Chloro-5-((2*S*,3*S*,4*R*,5R,6*R*)-3,4,5-tris(benzyloxy)-6-(benzyloxymethyl)-tetrahydro-2*H*-pyran-2-yl)phenyl)-3-diazopropan-2-one (**51**)



To a solution of the carboxylic acid **5** (4.5 g, 6.49 mmol) in CH_2Cl_2 (25 mL) under nitrogen atmosphere was added oxalyl chloride (0.85 mL, 9.74 mmol) and DMF (0.2 mL) at 0 °C. After an additional stirring at 0 °C for 15 min, the reaction mixture was stirred at room temperature for 5 h. The mixture was evaporated under vacuum to provide acyl chloride (4.70 g).

The residue was dissolved in CH_2Cl_2 (25 mL) and slowly added to a solution of (trimethylsilyl)diazomethane (2.0 M in ether, 6.49 mL) in anhydrous CH_2Cl_2 (27 mL) under nitrogen atmosphere at -30 °C. The reaction mixture was gradually warmed to room temperature over a period of 3 h, and then quenched with MeOH. The mixture was evaporated under vacuum and the residue was further purified by silica column chromatography to provide the titled compound (2.09 g, 45%). MNa+ 739.

Step 2: 1-Amino-3-(2-chloro-5-((2*S*,3*S*,4*R*,5*R*,6*R*)-3,4,5-tris(benzyloxy)-6-(benzyloxymethyl)-tetrahydro-2*H*-pyran-2-yl)phenyl)propan-2-one hydrochloride (**51**)

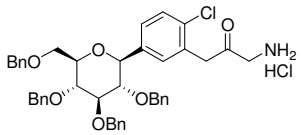


To a solution of α-diazoketone compound (2.09 g, 2.91 mmol) from Step 1 in Et_2O/CH_2Cl_2 (4:1, 32 mL) was added *c*-HBr (1.15 mL) at 0 °C. After stirring at 0 °C for 30 min, the mixture was quenched using a saturated $NaHCO_3$ solution and extracted with EtOAc. The organic phase was washed with brine, dried over anhydrous $MgSO_4$, filtered and evaporated under vacuum to afford α-bromoketone compound (2.19 g, 98%) as a yellow solid. MNa+ 793.

The crude α-bromoketone compound (2.19 g, 2.84 mmol) was dissolved in CH_2Cl_2 (12 mL), and hexamethylenetetramine (490 mg, 3.50 mmol) was added at room temperature. After stirring for 3 h, the white suspension was evaporated under vacuum to remove the voliatile solvent.

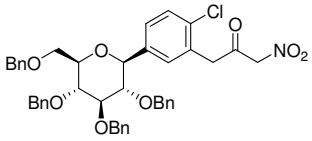
The crude quaternary ammonium salt was redissolved in CH_2Cl_2/EtOH (1:1, 35 mL) and stirred at 0 °C. To a resulting solution was added *c*-HCl (4.4 mL) and stirred at 0 °C for 30 min. After an additional stirring at room temperature for 3 h, the mixture was poured into brine and extracted with CH_2Cl_2. The organic phase was dried over over anhydrous $MgSO_4$, filtered and evaporated under vacuum to provide the titled compound (2.11 g, quantitative) as a pale brown solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32-7.13 (m, 21H), 6.89-6.87 (m, 2H), 4.91-4.80 (m, 4H), 4.59-4.45 (m, 5H), 4.17 (d, *J* = 9.6 Hz, 1H), 3.88-3.58 (m, 9H). MH+ 706.

1-Amino-3-(2-chloro-5-((2*S*,3*S*,4*R*,5*R*,6*R*)-3,4,5-tris(benzyloxy)-6-(benzyloxymethyl)-tetrahydro-2*H*-pyran-2-yl)phenyl)propan-2-one hydrochloride (**55,** Route B)



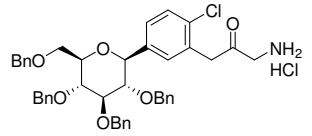
Step 1: 1-(2-Chloro-5-((2*S*,3*S*,4*R*,5*R*,6*R*)-3,4,5-tris(benzyloxy)-6-(benzyloxymethyl)-tetrahydro-

2*H*-pyran-2-yl)phenyl)-3-nitropropan-2-one (**52**)



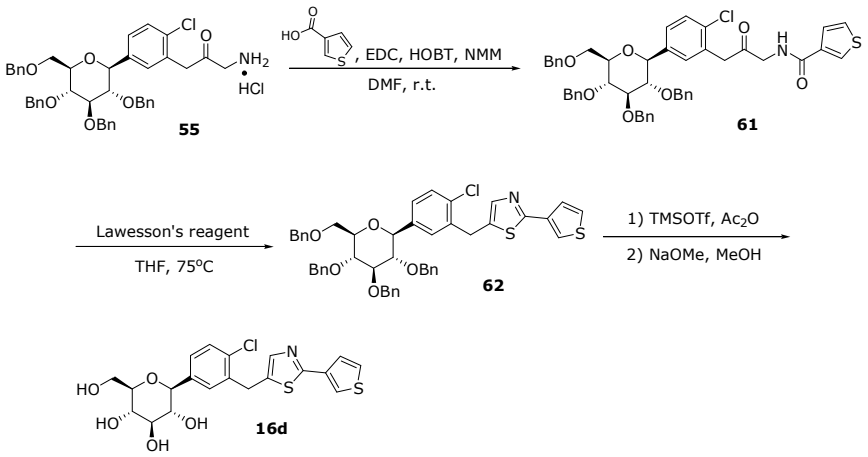
To a anhydrous THF (22 mL) solution of the carboxylic acid **5** (2.97 g, 4.28 mmol) was added 1,1'-carbonyl diimidazole (800 mg, 4.93 mmol) at room temperature. In separate flask, nitromethane (0.92 mL, 17.12 mmol) was added to a THF (9 mL) solution of NaH (200 mg, 4.93 mmol). The resulting white suspension was stirred at room temperature for 3 h. Then the prepared acyl imidazole solution was added to the suspension through a cannula at room temperature. After the transfer, the mixture was heated to 50 ^{o}C for 1.5 h. It was cooled to room temperature and quenched with 1.0 M HCl. The organic layer was extracted with ethyl acetate, dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by silica column chromatography to provide the titled compound (3.13 g, 99%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43-7.37 (m, 3H), 7.34-7.29 (m, 13H), 7.22-7.14 (m, 5H), 6.95-6.92 (m, 2H), 5.22 (s, 2H), 4.93 (s, 2H), 4.86 (d, *J* = 10.8 Hz, 1H), 4.64-4.51 (m, 4H), 4.21 (d, *J* = 9.6 Hz, 1H), 3.94-3.87 (m, 2H), 3.83-3.67 (m, 5H), 3.61-3.58 (m, 1H), 3.42 (t, d, *J* = 8.8 Hz, 1H); MNa+ 758.

Step 2: 1-Amino-3-(2-chloro-5-((2*S*,3*S*,4*R*,5*R*,6*R*)-3,4,5-tris(benzyloxy)-6-(benzyloxymethyl)-tetrahydro-2*H*-pyran-2-yl)phenyl)propan-2-one hydrochloride (**55**, Route B)



To the ethyl acetate (23 mL) solution of the nitro ketone (1.7g, 2.31 mmol) from step 1 was added Tin(II) chloride dehydrate (1.6 g, 6.93 mmo) under nitrogen atmosphere. The mixture was then heated to reflux for 5 h. It was cooled to room temperature and concentrated. The residue was purified by reverse-phase filtration on a C18 column using 0.1 % TFA/MeOH and 0.1 % TFA/water as solvents to give the pure amino ketone TFA salt. The amino ketone TFA salt was converted to the corresponding amino ketone HCl salt using 2.0 M HCl in ether solution at 0 ^{o}C and evaporated under vacuum to provide the titled compound HCl salt (1.55 g, 90 %) as a white solid. ^{1}H NMR (400 MHz, CD_3OD) δ 7.40-7.36 (m, 3H), 7.34-7.29 (m, 3H), 7.29-7.22 (m, 10H), 7.18-7.14 (m, 5H), 6.93-6.90 (m, 2H), 4.89-4.85 (m, 2H), 4.83-4.79 (m, 1H), 4.61-4.55 (m, 2H), 4.48 (d, *J* = 12.0 Hz, 1H), 4.40 (d, *J* = 10.8 Hz, 1H), 4.23 (d, *J* = 9.2 Hz, 1H), 4.07 (s, 2H), 4.01 (d, *J* = 12.4 Hz, 1H), 3.90 (d, *J* = 10.8 Hz, 1H), 3.78-3.66 (m, 5H), 3.58 (dt, *J* = 9.6, 3.2 Hz, 1H), 3.46 (t, *J* = 9.2 Hz, 1H); MH+ 706.

Scheme 6. Representative Scheme for Preparation of **16a ~ 16d**



((2S,3R,4R,5S,6R)-2-(4-Chloro-3-((2-(thiophen-3-yl)thiazol-5-yl)methyl)phenyl)-6-(hydroxymethyl)tetrahydro-2H-pyran-3,4,5-triol(**16d**)

To a mixture of amine **55** (1.66 g, 2.23 mmol), 3-thiophenecarboxylic acid (384 mg, 3.00 mmol), EDCI (767 mg, 4.00 mmol), and HOBt (541 mg, 4.00 mmol) in DMF (15 mL) was added NMM (0.88 mL, 8.00 mmol). The resulting mixture was stirred at room temperature for 16 hours. The reaction mixture was poured into a HCl solution (1M, 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 the intermediate **61** (950 mg, 1.16 mmol, 52 %). MH+ 816.

To a solution of the intermediate **61** (950 mg, 1.16 mmol) in anhydrous THF (10 mL) was added Lawesson reagent (942 mg, 2.33 mmol). The reaction mixture was refluxed overnight. After cooling to room temperature, the reaction mixture was poured into a saturated $NaHCO_3$ 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 the intermediate **62** (624 mg, 0.766 mmol, 66 %). MH+ 814.

The perbenzylated thiazole **62** (624 mg, 0.766 mmol) was dissolved in Ac_2O (10 mL) and stirred at -30 ^oC. Trimethylsilyl trifluoromethanesulfonate (1.0 mL) in Ac_2O (1.5 mL) was slowly added to the above mixture. The resulting mixture was gradually warmed to room temperature and stirred for 16 hours. The reaction mixture was quenched with a saturated $NaHCO_3$ solution (100 mL), and then extracted with EtOAc (100 mL). The organic phase was dried over $MgSO_4$ and evaporated under vacuum to provide a crude peracetylated compound (458 mg, 0.736 mmol). To a solution of the peracetylated compound (458 mg, 0.736 mmol) in

MeOH (15 mL) was added NaOMe (1 mL, 25 % in MeOH). After stirring for 3 hours, the reaction mixture was neutralized with acetic acid (about 2-3 mL). The resulting mixture was evaporated under vacuum to remove the volatile solvent. The residue was redissolved in MeOH and purified by prep HPLC (reverse phase column) to provide the title compound **16d** (58 mg, 0.13 mmol, 17 %). ^{1}H NMR (400 MHz, CD_3OD) δ 7.60 (s, 1H), 7.51-7.46 (m, 4H), 7.39-7.32 (m, 2H), 4.31 (d, *J* = 2.0 Hz, 2H), 4.12 (d, *J* = 9.6 Hz, 1H), 3.86 (d, *J* = 11.2 Hz, 1H), 3.72-3.66 (m, 1H), 3.47-3.32 (m, 4H); ^{13}C NMR (100 MHz, CD_3OD_3) δ 164.7, 141.7, 140.9, 138.6, 138.1, 136.7, 134.2, 131.6, 130.5, 129.3, 128.4, 126.9, 125.2, 82.8, 82.4, 79.9, 76.7, 72.0, 63.2, 31.8. Positive HR-FAB-MS *m/z* : 454.0550 $[M+H]^+$ (calcd for C20H21ClNO6S: 454.0550).

.

(2*S*,3*R*,4*R*,5*S*,6*R*)-2-(4-Chloro-3-((2-(furan-2-yl)thiazol-5-yl)methyl)phenyl)-6-(hydroxymethyl)tetrahydro-2*H*-pyran-3,4,5-triol (**16a**)

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.79 (s, 1H), 7.62 (s, 1H), 7.42 (d, *J* = 2.0 Hz, 1H), 7.38 (d, *J* = 8.4 H, 1H), 7.25 (dd, *J* = 8.0, 2.0 Hz, 1H), 6.98 (d, *J* = 3.2 Hz, 1H), 6.63-6.61 (m, 1H), 4.99 (br s, 2H), 4.86 (br s, 1H), 4.44 (br s, 1H), 4.27 (d, *J* = 3.6 Hz, 2H), 3.98 (d, *J* = 9.2 Hz, 1H), 3.66 (d, *J* = 11.2 Hz, 1H), 3.43-3.31 (m, 1H), 3.23-3.11 (m, 3H), 3.06 (t, *J* = 8.8 Hz, 1H); ^{13}C NMR (400 MHz, DMSO-d_6) δ 156.7, 148.7, 145.0, 142.1, 140.6, 137.0, 136.7, 132.0, 130.8, 129.3, 128.7, 113.0, 109.2, 81.7, 81.0, 78.8, 75.2, 70.8, 61.8, 30.5; MH+ 438.

(2*S*,3*R*,4*R*,5*S*,6*R*)-2-(4-Chloro-3-((2-(furan-3-yl)thiazol-5-yl)methyl)phenyl)-6-(hydroxymethyl)tetrahydro-2*H*-pyran-3,4,5-triol (**16b**)

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.30 (s, 1H), 7.78 (s, 1H), 7.60 (s, 1H), 7.44 (d, *J* = 0.8 Hz, 1H), 7.41 (d, *J* = 6.4 Hz, 1H), 7.28 (dd, *J* = 6.4, 1.2 Hz, 1H), 6.87 (s, 1H), 4.99 (br s, 2H), 4.86 (br s, 1H), 4.44 (br s, 1H), 4.28 (d, *J* = 6.0 Hz, 2H), 4.00 (d, *J* = 7.6 Hz, 1H), 3.69 (d, *J* = 9.2 Hz, 1H), 3.44-3.42 (m, 1H), 3.25-3.20 (m, 2H), 3.17-3.14 (m, 1H), 3.09 (t, *J* = 7.2 Hz, 1H); ^{13}C NMR (400 MHz, DMSO-d_6) δ 158.9, 145.2, 142.0, 141.4, 140.6, 136.8, 136.6, 132.0, 130.8, 129.3, 128.6, 121.7, 109.2, 81.7, 81.0, 78.8, 75.2, 70.8, 61.8, 30.6; MH+ 438.

(2*S*,3*R*,4*R*,5*S*,6*R*)-2-(4-Chloro-3-((2-(thiophen-2-yl)thiazol-5-yl)methyl)phenyl)-6-(hydroxymethyl)tetrahydro-2*H*-pyran-3,4,5-triol (**16c**)

^{1}H NMR (400 MHz, CD_3OD) δ 7.51-7.46 (m, 4H), 7.39-7.32 (m, 2H), 7.08-7.06 (m, 1H), 4.30 (d, *J* = 2.8 Hz, 2H), 4.12 (d, *J* = 9.2 Hz, 1H), 3.86 (d, *J* = 12.0 Hz, 1H), 3.71-3.66 (m, 1H), 3.47-

3.30 (m, 4H); ^{13}C NMR (100 MHz, CD_3OD_3) δ 163.1, 141.8, 140.9, 138.7, 138.1, 138.0, 134.2, 131.6, 130.5, 129.4, 129.2, 129.1, 128.0, 82.8, 82.4, 79.9, 76.7, 72.0, 63.2, 31.8. Positive HR-FAB-MS *m/z* : 454.0547 $[M+H]^+$ (calcd for C20H21ClNO6S: 454.0550).

<In vitro assay>

Cloning and cell line construction for human SGLT2

Human SGLT2 (hSGLT2) gene was amplified by PCR from cDNA-Human Adult Normal Tissue Kidney (Invitrogen). The hSGLT2 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) and activity in the ^{14}C-α-methyl-d-glucopyranoside (^{14}C-AMG) uptake assay.

Inhibitory Effects on human SGLT2 Activities

For sodium-dependent glucose transport assay, cells expressing hSGLT2 were seeded into a 96-well culture plate at a density of 5 X 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 [Katsuno, K. *et al*. *J*. *Pharmacol*. *Exp*. *Ther*. 2007, *320*, 323-330; Han, S. *et al*. *Deabetes*, 2008, *57*, 1723-1729].

<Urinary glucose excretion in normal animals>

Animals

Male Sprague-Dawley (SD) rats were purchased by Charles River Laboratory. All animals were housed at 23±2 °C under a 12-h light/dark cycle (light on 7:00) and were fed a standard chow and water *ad libitum*.

Urinary glucose excretion in normal animal

For glucosuria assessment, overnight-fasted SD rats (5 weeks of ages) were placed into metabolism cages for baseline urine collection over 24 h. Rats were weighted, randomized into experimental groups (n = 4) and orally administered with 50% aqueous glucose solution (2 g/kg) and drugs. Rats were returned to metabolism cages for 24h urine collection. After the urine volume had been measured, the glucose concentration in the urine was determined using a LabAssay™ (Wako Pure Chemicals). These data were normalized per 200g body weight [Katsuno, K. *et al*. *J*. *Pharmacol*. *Exp*. *Ther*. 2007, *320*, 323-330; Han, S. *et al*. *Deabetes*, 2008, *57*, 1723-1729].