gem-Dimethyl-bearing *C*-Glucosides as Sodium-glucose Co-transporter 2 (SGLT2) Inhibitors

Shi, Yongheng[a,b](史永恒) Zhao, Guilong*[,b](赵桂龙) Lou, Yuanyuan[c](楼袁媛)
Wang, Yuli[b](王玉丽) Shao, Hua[b](邵华) Liu, Wei[b](刘巍)
Xu, Weiren[a,b](徐为人) Tang, Lida*[,b](汤立达)

[a] *School of Pharmacy, Tianjin Medical University, Tianjin 300070, China*
[b] *Tianjin Key Laboratory of Molecular Design and Drug Discovery, Tianjin Institute of Pharmaceutical Research, Tianjin 300193, China*
[c] *College of Chemistry and Molecular Engineering, Qingdao University of Science and Technology, Qingdao, Shandong 266042, China*

Three novel *gem*-dimethyl *C*-glucosides were designed as sodium-glucose co-transporter 2 (SGLT2) inhibitors, and their syntheses started from *D*-glucose and three 2-substituted-5-bromobenzoic acids were achieved via a facile 8-step protocol, with the key step being anhydrous aluminum chloride-catalyzed Friedel-Crafts alkylation of tertiary alcohols and phenetol. These three SGLT2 inhibitors were evaluated *in vivo* with a mice oral glucose tolerance test (OGTT), and the anti-hyperglycemic activities of all these three compounds were comparable with that of the positive control Dapagliflozin.

Keywords sodium-glucose co-transporter 2 (SGLT2), *gem*-dimethyl, synthesis, Friedel-Crafts alkylation, oral glucose tolerance test (OGTT)

Introduction

Patients with type 2 diabetes suffer from hyperglycemia that is a consequence of impaired insulin secretion in pancreatic *β*-cells combined with insulin resistance in peripheral tissues, which resulted in a variety of diabetic complications due to the so-called "glucose toxicity".[1] Therefore, the goal of the therapy for type 2 diabetic patients is the strict control of blood glucose levels within the normal range.

Over 99% of plasma glucose that is filtered in the renal glomerulus is reabsorbed in the renal proximal tubules by a class of transporter known as sodium-glucose co-transporter (SGLT), and at least two subtypes of this co-transporter have been identified so far, SGLT1 and SGLT2. It has been established that SGLT2 is mainly responsible for this reabsorption process,[2] and therefore, inhibition of renal SGLT2 can lead to the excretion of plasma glucose into urine by decreasing the reabsorption of glucose into blood, thus lowering the blood glucose levels in type 2 diabetic patients. In view of the fact that inhibition of SGLT1 was associated with gastrointestinal side effect,[2] the selective inhibition of SGLT2 became a promising novel therapy for the treatment of type 2 diabetes.

The natural product phlorizin has long been a well-documented glucosuric agent (Figure 1); however, phlorizin has proved to be nonselective against SGLT2 versus SGLT1 and metabolically liable to *β*-glucosedase-mediated cleavage in the small intestine.[3] Encouraged by the observations found in the investigation of phlorizin described above, several selective SGLT2 inhibitors, such as T-1095,[4] sergliflozin[5] and dagapliflozin,[2] have been developed by the drug discovery industry based on the structure of phlorizin after exploration of the molecular structure[6] and biological screening[7-9] of phlorizin derivatives (Figure 1), and we also found a number of *S*-glycosides[10,11] and *N*-glycosides[12] as SGLT2 inhibitors during the discovery of our own SGLT2 inhibitors.

However, all the SGLT2 inhibitors possessing a non-*C*-glucoside structure found in the earlier stage of drug discovery, such as *O*-glucosides, *S*-glucosides and *N*-glucosides, have proved to be considerably less potent than the *C*-glucosides represented by Dapagliflozin in the latter stage, and therefore all the non-*C*-glucosides were discontinued during the clinical trials. The structure of the SGLT2 inhibitors that are now still in clinical trials are almost all *C*-glucosides (Figure 2). The benzylic methylene group between the two aryl rings was labile to the degradation *in vivo* to be hydroxylated, and the degradation product was not an SGLT2 inhibitor.[13] Based on all these observations discussed above, we designed and synthesized a series of *C*-glucosides **11a**—**11c** with a *gem*-dimethyl functionality using Dapagliflozin as structure template (Scheme 1).

* E-mail: zhao_guilong@126.com; Tel.: 0086-022-23003529; Fax: 0086-022-23006862; tangld@163.net; Tel. and Fax: 0086-022-23006950
Received October 11, 2010; revised January 27, 2011; accepted February 16, 2011.
Project supported by Key Projects of Tianjin Science and Technology Support Plan (No. 10ZCKFSH01300) and National Key Projects for the Innovative Drug (No. 2009ZX09301-008-N-11).

CHINESE JOURNAL OF CHEMISTRY

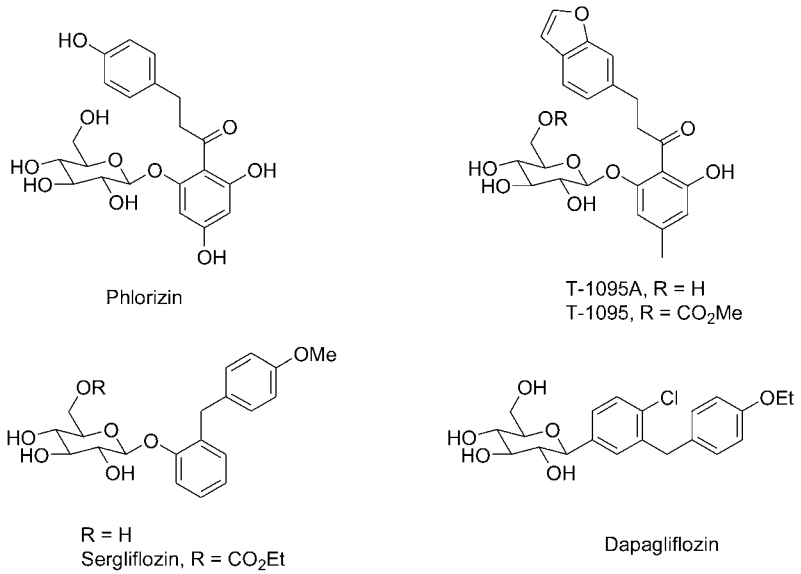


Figure 1 Molecular structures of some well-established SGLT inhibitors.

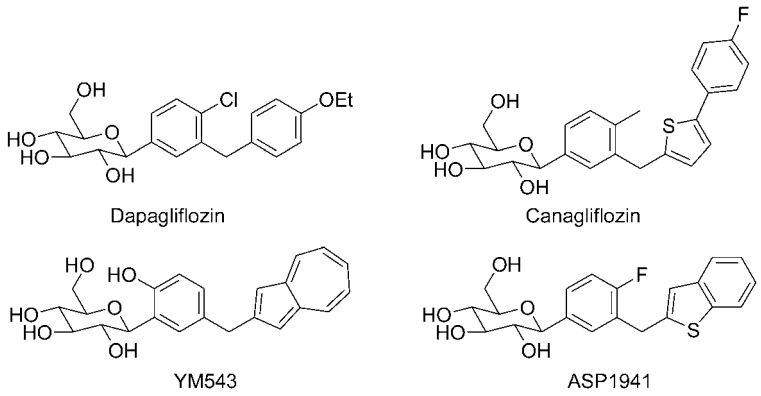


Figure 2 Molecular structures of some SGLT2 inhibitors that are now in clinical trials.

Experimental

Melting points were determined with an XT-4 microscopic melting point apparatus and uncorrected. ^{1}H NMR spectra were recorded on a Bruker AV400 spectrometer at 400 MHz, with DMSO-d_6 as solvent and TMS as internal standard. The HR-MS data were obtained on an Agilent Q-TOF 6510 mass spectrometer using electrospray ionization (ESI) technique.

The intermediate 2,3,4,6-tetra-*O*-trimethylsilyl-*D*-glucolactone (**2**) was prepared from commercially available *D*-glucolactone according to known procedures.[2,14] All the reagents employed were of analytical grade unless otherwise noted. The dried THF and toluene were distilled from sodium/benzophenone ketyl and the dried dichloromethane was distilled from calcium hydride.

General procedure for the preparation of ethyl 2-substituted-5-bromobenzoate (4a—4c)

A 250 mL round-bottomed flask equipped with a Dean-Stark trap and a reflux condenser was charged with 100 mmol of commercially available 2-substituted-5-bromobenzoic acids **3a**—**3c**, 70 mL of absolute ethanol and 70 mL of benzene, and the mixture thus obtained was stirred in an ice-water bath followed by dropwise addition of 10 mL of concentrated sulfuric acid. The resulting mixture was stirred at reflux with azeotropic removal of water until all the staring benzoic acids **3a**—**3c** were consumed completely as indicated by TLC analysis.

On cooling, the reaction mixture was slowly poured into 500 mL of cooled water, and the mixture thus obtained was stirred and extracted with three 100 mL portions of dichloromethane. The combined extracts were washed with 200 mL×2 of saturated brine until aqueous pH=7, dried over sodium sulfate and evaporated on a rotary evaporator to afford the crude products **4a**—**4c** as colorless oils, which were purified by column chromatography to yield the pure products **4a**—**4c** as colorless oils.

Ethyl 5-bromo-2-chlorobenzoate (4a) Colorless oil, 92%. ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 7.95 (d,

J=2.4 Hz, 1H), 7.77 (dd, J=2.4, 8.4 Hz, 1H), 7.53 (d, J=8.8 Hz, 1H), 4.32 (q, J=7.1 Hz, 2H), 1.31 (t, J=7.0 Hz, 3H). HRMS (ESI-Q-TOF) calcd for $C_9H_9BrClO_2$ ([M(^{79}Br)+H]$^+$) 262.9474, found 262.9481; for $C_9H_9BrClO_2$ ([M(^{81}Br)+H]$^+$) 264.9454, found 264.9459.

Ethyl 5-bromo-2-fluorobenzoate (4b) Colorless oil, 91%. ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 7.94 (dd, J=2.8, 6.4 Hz, 1H), 7.82—7.86 (m, 1H), 7.33 (dd, J=8.8, 10.8 Hz, 1H), 4.31 (q, J=7.2 Hz, 2H), 1.30 (t, J=7.0 Hz, 3H). HRMS (ESI-Q-TOF) calcd for $C_9H_9BrFO_2$ ([M(^{79}Br) + H]$^+$) 246.9770, found 246.9774; for $C_9H_9BrFO_2$ ([M(^{81}Br)+H]$^+$) 248.9749, found 248.9748.

Ethyl 5-bromo-2-methylbenzoate (4c) Colorless oil, 96%. ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 7.89 (d, J=2.0 Hz, 1H), 7.65 (dd, J=2.2, 8.2 Hz, 1H), 7.28 (d, J=8.4 Hz, 1H), 4.28 (q, J=7.2 Hz, 2H), 2.45 (s, 3H), 1.31 (t, J=7.0 Hz, 3H). HRMS (ESI-Q-TOF) calcd for $C_{10}H_{12}BrO_2$ ([M(^{79}Br)+H]$^+$) 243.0021, found 243.0018; for $C_{10}H_{12}BrO_2$ ([M(^{81}Br) + H]$^+$) 245.0000, found 245.0003.

General procedure for the preparation of 1-methyl-1-(2-substituted-5-bromophenyl)ethanol (5a—5c)

A dried 250 mL round-bottomed flask was charged with 90 mmol of starting esters **4a**—**4c**, a magnetic bar and 150 mL of dried THF, flushed with nitrogen and sealed with a rubber septum. The flask was cooled with an ice-water bath and the stirring was initiated. Into the stirred mixture was added dropwise 180 mmol of commercially available methyl magnesium chloride (60 mL; 3 mol/L in THF) through syringe, and after addition the resulting mixture was stirred at this temperature for another 0.5 h.

The reaction mixture was slowly poured into 500 mL of saturated brine followed by addition of 300 mL of dichloromethane, and the resulting mixture was stirred, brought to pH=4—5 with glacial acetic acid and filtered off through celite. From the filtrate was separated the organic phase, and the aqueous phase was back-extracted with 100 mL of dichloromethane. The combined organic phases were washed with saturated brine, dried over sodium sulfate and evaporated on a rotary evaporator to afford the crude products **5a**—**5c** as colorless oils, which were purified by column chromatography to yield the pure products **5a**—**5c** as colorless crystals after drying *in vacuo* at room temperature.

1-(5-Bromo-2-chlorophenyl)-1-methylethanol (5a) Colorless crystals, 88%, m.p. 47—48 ℃; ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 7.95 (d, J=2.8 Hz, 1H), 7.44 (dd, J=2.6, 8.6 Hz, 1H), 7.33 (d, J=8.0 Hz, 1H), 5.46 (s, 1H), 1.56 (s, 6H). HRMS (ESI-Q-TOF) calcd for $C_9H_{11}BrClO$ ([M(^{79}Br) + H]$^+$) 248.9682, found 248.9688; for $C_9H_{11}BrClO$ ([M(^{81}Br)+H]$^+$) 250.9661, found 250.9669.

1-(5-bromo-2-fluorophenyl)-1-methylethanol (5b) Colorless crystals, 85%, m.p. 63—64 ℃; ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 7.72 (dd, J=2.6, 7.4 Hz, 1H), 7.42—7.46 (m, 1H), 7.10 (dd, J=8.6, 11.4 Hz, 1H), 5.41 (s, 1H), 1.45 (d, J=0.8 Hz, 6H). HRMS (ESI-Q-TOF) calcd for $C_9H_{11}BrFO$ ([M(^{79}Br)+H]$^+$) 232.9977, found 232.9979; for $C_9H_{11}BrFO$ ([M(^{81}Br) + H]$^+$) 234.9957, found 234.9958.

1-(5-Bromo-2-methylphenyl)-1-methylethanol (5c) Colorless crystals, 91%, m.p. 73—74 ℃; ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 7.60 (d, J=2.4 Hz, 1H), 7.27 (dd, J=2.4, 8.0 Hz, 1H), 7.05 (d, J=8.4 Hz, 1H), 5.05 (s, 1H), 2.44 (s, 3H), 1.47 (s, 6H). HRMS (ESI-Q-TOF) calcd for $C_{10}H_{14}BrO$ ([M(^{79}Br)+H]$^+$) 229.0228, found 229.0231; for $C_{10}H_{14}BrO$ ([M(^{81}Br)+H]$^+$) 231.0208, found 231.0212.

General procedure for the preparation of 4-[1-(2-substituted-5-bromobenzyl)-1-methylethyl]phenetol (6a—6c)

A dried 250 mL round-bottomed flask was charged with 70 mmol of starting alcohols **5a**—**5c**, 80 mmol (9.77 g) of phenetol and 150 mL of dried dichloromethane, and the resulting mixture was stirred and cooled with an ice-water bath. Subsequently, 90 mmol (12.00 g) of anhydrous aluminum chloride was added portionwise in 15 min. After addition, the reaction mixture was stirred at room temperature for another 3 h until all the starting alcohols **5a**—**5c** were consumed completely as indicated by TLC analysis.

The reaction mixture was slowly poured into 400 mL of cooled saturated brine while stirring, and the resulting mixture was extracted with three 100 mL portions of dichloromethane. The combined extracts were washed with 100 mL×2 of saturated brine, dried over sodium sulfate and evaporated on a rotary evaporator to give the crude products **6a**—**6c** as colorless oils, which solidified to white solids on standing at room temperature. The crude products **6a**—**6c** were triturated overnight with 100 mL of petroleum ether with five drops of ethyl acetate to furnish the pure products **6a**—**6c** as colorless crystals after drying *in vacuo* at room temperature.

4-[1-(5-Bromo-2-chlorophenyl)-1-methylethyl]-phenetol (6a) Colorless crystals, 83%, m.p. 85—86 ℃; ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 7.76 (d, J=2.4 Hz, 1H), 7.47 (dd, J=2.4, 8.4 Hz, 1H), 7.25 (d, J=8.4 Hz, 1H), 6.96 (d, J=8.8 Hz, 2H), 6.78 (d, J=9.2 Hz, 2H), 3.96 (q, J=7.1 Hz, 2H), 1.64 (s, 6H), 1.29 (t, J=7.0 Hz, 3H). HRMS (ESI-Q-TOF) calcd for $C_{17}H_{19}BrClO$ ([M(^{79}Br)+H]$^+$) 353.0308, found 353.0311; for $C_{17}H_{19}BrClO$ ([M(^{81}Br)+H]$^+$) 355.0287, found 355.0288.

4-[1-(5-Bromo-2-fluorophenyl)-1-methylethyl]-phenetol (6b) Colorless crystals, 80%, m.p. 76—77 ℃; ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 7.54—7.57 (m, 1H), 7.44—7.48 (m, 1H), 6.99—7.07 (m, 3H), 6.77—6.81 (m, 2H), 3.96 (q, J=6.9 Hz, 2H), 1.60 (s, 6H), 1.29 (t, J=7.0 Hz, 3H). HRMS (ESI-Q-TOF) calcd for $C_{17}H_{19}BrFO$ ([M(^{79}Br)+H]$^+$) 337.0603, found 337.0601; for $C_{17}H_{19}BrFO$ ([M(^{81}Br)+H]$^+$) 339.0583, found 339.0583.

4-[1-(5-Bromo-2-methylphenyl)-1-methylethyl]-phenetol (6c) Colorless crystals, 83%, m.p. 72—73 ℃; ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 7.61 (d, J=2.4

Hz, 1H), 7.32 (dd, J=2.2, 8.2 Hz, 1H), 6.96—7.00 (m, 3H), 6.80 (d, J=8.8 Hz, 2H), 3.96 (q, J=6.9 Hz, 2H), 1.68 (s, 3H), 1.56 (s, 6H), 1.29 (t, J=6.8 Hz, 3H). HRMS (ESI-Q-TOF) calcd for $C_{18}H_{22}BrO$ ([M(^{79}Br)+H]$^+$) 333.0854, found 333.0859; for $C_{17}H_{19}BrClO$ ([M(^{81}Br)+H]$^+$) 335.0834, found 335.0837.

General procedure for the preparation of methyl 1-{4-substituted-3-[1-(4-ethoxyphenyl)-1-methylethyl]-phenyl}-*α*/*β*-*D*-glucopyranose (7a—7c)

A dried 250 mL round-bottomed flask was charged with 50 mmol of dried **6a**—**6c**, 100 mL of dried THF and a magnetic bar, flushed with nitrogen and sealed with a rubber septum. The flask was cooled with liquid nitrogen-absolute ethanol to −78 ℃ and the stirring wixture was initiated. To the reaction mixture was added dropwise 60 mmol (37.5 mL; 1.6 mol/L in *n*-hexane) of *n*-butyl lithium through syringe, after addition the resulting mixture was stirred at this temperature for another 0.5 h. To the reaction mixture was added dropwise 80 mmol (37.35 g) of 2,3,4,6-tetra-*O*-trimethylsilyl-*D*-glucolactone (**2**) in 20 mL of dried toluene through syringe. After addition, the reaction mixture was stirred at this temperature for another 0.5 h. To the reaction mixture was added 100 mmol (9.61 g) of methanesulfonic acid in 30 mL of absolute methanol. The resulting mixture was warmed slowly to room temperature and stirred at room temperature overnight.

The reaction mixture was slowly poured into 200 mL of saturated aqueous sodium bicarbonate, and the resulting mixture was stirred at room temperature for another 0.5 h, brought to pH=4—5 with concentrated hydrochloric acid and extracted with three 50 mL portions of dichloromethane. The combined extracts were washed with 200 mL×2 of saturated brine until aqueous pH=7, dried over sodium sulfate and evaporated on a rotary evaporator to afford the crude products **7a**—**7c** as deep yellow oils after drying *in vacuo* at room temperature. These crude products **7a**—**7c** were used directly in the next step without further purification.

General procedure for the preparation of 2,3,4,6-tetra-*O*-acetyl-1-deoxy-1-{4-substituted-3-[1-(4-ethoxyphenyl)-1-methylethyl]phenyl}-*β*-*D*-glucopyranose (10a—10c)

A dried 250 mL round-bottomed flask was charged with crude **7a**—**7c** prepared in the above step and 150 mL of dried dichloromethane, and the resulting mixture was stirred on an ice-water bath. Subsequently, 100 mmol (11.63 g) of triethylsilane was added in one portion, followed by dropwise addition of 50 mmol (7.10 g) of boron trifluoride etherate. After addition, the reaction mixture was stirred at room temperature overnight.

To the reaction mixture was slowly added 200 mL of saturated sodium bicarbonate, and the stirring was continued for another 0.5 h. The mixture was brought to pH=4—5 with concentrated hydrochloric acid, and the organic phase was separated. The aqueous phase was back-extracted with 100 mL of dichloromethane. The combined extracts were washed with 200 mL×2 of saturated brine until aqueous pH=7, dried over sodium sulfate and evaporated on a rotary evaporator to afford the crude products **8a**—**8c** as brown oils, which were used in the next step without further purification.

The crude **8a**—**8c** were dissolved in 50 mL of glacial acetic acid and 100 mL of acetic anhydride and 50 mmol (4.10 g) of anhydrous sodium acetate were added. The resulting mixture was stirred at reflux for 0.5 h.

On cooling, the reaction mixture was poured into 400 mL of ice-water, and the resulting mixture was stirred at room temperature for 5 h and extracted with three 100 mL portions of dichloromethane. The combined extracts were washed successively with 200 mL of saturated aqueous sodium bicarbonate and 100 mL×2 of saturated brine, dried over sodium sulfate and evaporated on a rotary evaporator to afford the crude products **9a**—**9c**.

The crude products **9a**—**9c** were purified by column chromatography to furnish the pure products **10a**—**10c** as white foams.

2,3,4,6-Tetra-*O*-acetyl-1-deoxy-1-{4-chloro-3-[1-(4-ethoxyphenyl)-1-methylethyl]phenyl}-*β*-*D*-glucopyranose (10a) White foam, 44% (overall yield from **6a**). ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 7.58 (s, 1H), 7.27 (s, 2H), 6.90 (d, J=8.8 Hz, 2H), 6.76 (d, J=8.8 Hz, 2H), 5.39 (t, J=9.6 Hz, 1H), 5.13 (t, J=9.6 Hz, 1H), 5.05 (t, J=9.6 Hz, 1H), 4.78 (d, J=9.6 Hz, 1H), 4.14—4.15 (m, 2H), 4.06—4.11 (m, 1H), 3.95 (q, J=6.9 Hz, 2H), 2.02 (s, 3H), 2.01 (s, 3H), 1.94 (s, 3H), 1.82 (s, 3H), 1.64 (s, 6H), 1.28 (t, J=7.0 Hz, 3H). HRMS (ESI-Q-TOF) calcd for $C_{31}H_{38}ClO_{10}$ ([M+H]$^+$) 605.2154, found 605.2159.

2,3,4,6-Tetra-*O*-acetyl-1-deoxy-1-{3-[1-(4-ethoxyphenyl)-1-methylethyl]-4-fluorophenyl}-*β*-*D*-glucopyranose (10b) White foam, 41% (overall yield from **6b**). ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 7.39—7.42 (m, 1H), 7.26—7.30 (m, 1H), 7.01 (d, J=8.4 Hz, 1H), 6.99 (d, J=8.4 Hz, 2H), 6.77 (d, J=8.4 Hz, 2H), 5.38 (t, J=9.4 Hz, 1H), 5.11 (t, J=9.8 Hz, 1H), 5.05 (t, J=9.6 Hz, 1H), 4.72 (d, J=10.0 Hz, 1H), 4.12—4.13 (m, 2H), 4.06—4.09 (m, 1H), 3.96 (q, J=6.9 Hz, 2H), 2.02 (s, 3H), 2.01 (s, 3H), 1.94 (s, 3H), 1.78 (s, 3H), 1.60 (s, 6H), 1.26—1.30 (t, J=6.8 Hz, 3H); HR-MS (ESI-Q-TOF) calcd for $C_{31}H_{38}FO_{10}$ ([M+H]$^+$) 589.2449, found 589.2448.

2,3,4,6-Tetra-*O*-acetyl-1-deoxy-1-{3-[1-(4-ethoxyphenyl)-1-methylethyl]-4-methylphenyl}-*β*-*D*-glucopyranose (10c) White foam, 46% (overall yield from **6c**). ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 7.43 (s, 1H), 7.12—7.14 (m, 1H), 7.00 (d, J=8.0 Hz, 1H), 6.93 (d, J=8.4 Hz, 2H), 6.78 (d, J=8.8 Hz, 2H), 5.38 (t, J=9.6 Hz, 1H), 5.02—5.12 (m, 2H), 4.70 (d, J=9.6 Hz, 1H), 4.13—4.14 (m, 2H), 4.07—4.10 (m, 1H), 3.96 (q, J=6.9 Hz, 2H), 2.02 (s, 3H), 2.01 (s, 3H), 1.94 (s, 3H), 1.79 (s, 3H), 1.71 (s, 3H), 1.57 (s, 6H), 1.29 (t, J=7.0 Hz, 3H). HRMS (ESI-Q-TOF) calcd for $C_{32}H_{41}O_{10}$ ([M+H]$^+$) 585.2700, found 585.2707.

General procedure for the preparation of 1-deoxy-1-{4-substituted-3-[1-(4-ethoxyphenyl)-1-methylethyl]-phenyl}-*β*-*D*-glucopyranose (11a—11c)

A dried 250 mL round-bottomed flask was charged with 5 mmol (0.11 g) of sodium and 100 mL of absolute methanol, and the mixture was stirred until all the sodium disappeared to form a clear solution, into which was added 20 mmol of starting **10a**—**10c**. The stirring was continued at room temperature until both the starting **10a**—**10c** and the intermediates formed were consumed completely as indicated by TLC analysis. Dried strongly acidic resin (5 g) was added, and the resulting mixture was stirred at room temperature overnight until the pH＝7.

The mixture was filtered off, and the filtrate was evaporated on a rotary evaporator to afford the products **11a**—**11c** as white foams, which were further dried on an oil pump at room temperature to furnish the pure products **11a**—**11c** as white foams.

1-Deoxy-1-{4-chloro-3-[1-(4-ethoxyphenyl)-1-methylethyl]phenyl}-*β*-*D*-glucopyranose (11a) White foam, 100%. ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 7.62 (s, 1H), 7.23 (s, 2H), 6.97 (d, J＝8.8 Hz, 2H), 6.76 (d, J＝8.8 Hz, 2H), 4.93—4.95 (m, 2H), 4.87 (d, J＝5.6 Hz, 1H), 4.46 (t, J＝5.8 Hz, 1H), 4.09 (d, J＝9.6 Hz, 1H), 3.95 (q, J＝6.9 Hz, 2H), 3.71—3.75 (m, 1H), 3.44—3.50 (m, 1H), 3.24—3.30 (m, 2H), 3.15—3.22 (m, 2H), 1.65 (s, 3H), 1.65 (s, 3H), 1.29 (t, J＝7.0 Hz, 3H). HRMS (ESI-Q-TOF) calcd for $C_{23}H_{30}ClO_6$ ($[M+H]^+$) 437.1731, found 437.1728.

1-Deoxy-1-{3-[1-(4-ethoxyphenyl)-1-methylethyl]-4-fluorophenyl}-*β*-*D*-glucopyranose (11b) White foam, 97%. ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 7.43—7.45 (m, 1H), 7.23—7.27 (m, 1H), 7.04 (d, J＝8.8 Hz, 2H), 6.95 (dd, J＝8.4, 12.0 Hz, 1H), 6.77 (d, J＝8.8 Hz, 2H), 4.93 (d, J＝4.8 Hz, 2H), 4.81 (d, J＝6.0 Hz, 1H), 4.45 (t, J＝5.8 Hz, 1H), 4.06 (d, J＝9.2 Hz, 1H), 3.96 (q, J＝6.9 Hz, 2H), 3.69—3.74 (m, 1H), 3.43—3.49 (m, 1H), 3.15—3.32 (m, 4H), 1.61 (s, 3H), 1.60 (s, 3H), 1.29 (t, J ＝ 7.0 Hz, 3H). HRMS (ESI-Q-TOF) calcd for $C_{23}H_{30}FO_6$ ($[M+H]^+$) 421.2026, found 421.2027.

1-Deoxy-1-{3-[1-(4-ethoxyphenyl)-1-methylethyl]-4-methylphenyl}-*β*-*D*-glucopyranose (11c) White foam, 99%. ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 7.47 (s, 1H), 7.09—7.12 (m, 1H), 6.95—7.01 (m, 3H), 6.78 (d, J＝8.8 Hz, 1H), 4.90—4.91 (m, 2H), 4.73 (d, J＝5.2 Hz, 1H), 4.43 (t, J＝5.8 Hz, 1H), 4.03 (d, J＝9.2 Hz, 1H), 3.96 (q, J＝7.1 Hz, 2H), 3.70—3,74 (m, 1H), 3.42—3.48 (m, 1H), 3.22—3.25 (m, 3H), 3.17—3.20 (m, 1H), 1.71 (s, 3H), 1.58 (s, 6H), 1.29 (t, J＝7.0 Hz, 3H). HRMS (ESI-Q-TOF) calcd for $C_{24}H_{33}O_6$ ($[M+H]^+$) 417.2277, found 417.2283.

Oral glucose tolerance test (OGTT)

Mice (20—22 g, 6/group) were fasted overnight and the test compounds **11a**—**11c** (1% CMC-Na; 25 mg/kg and 20 mL/kg) or only vehicle (1% CMC-Na; 20 mL/kg) was orally administered. After 2 h, the mice were challenged with glucose at 2 g/kg intraperitoneally and at a volume of 10 mL/kg. The control mice received water only. Blood samples were collected from the orbital vein 0.5, 1, 2, 3 and 4 h after the glucose challenge for the determination of blood glucose levels. The blood glucose levels were determined using commercially available kits based on a well-established glucose oxidase method.

The blood glucose concentration-time plot for each compound was thus plotted, and the inhibition rate was calculated as follows: inhibition rate＝[AUC(vehicle)－AUC(compounds **11a**—**11c**)]/[AUC(vehicle) － AUC (control)]×100%, wherein the AUC represents the area under curve for the plot of each compound, vehicle or control.

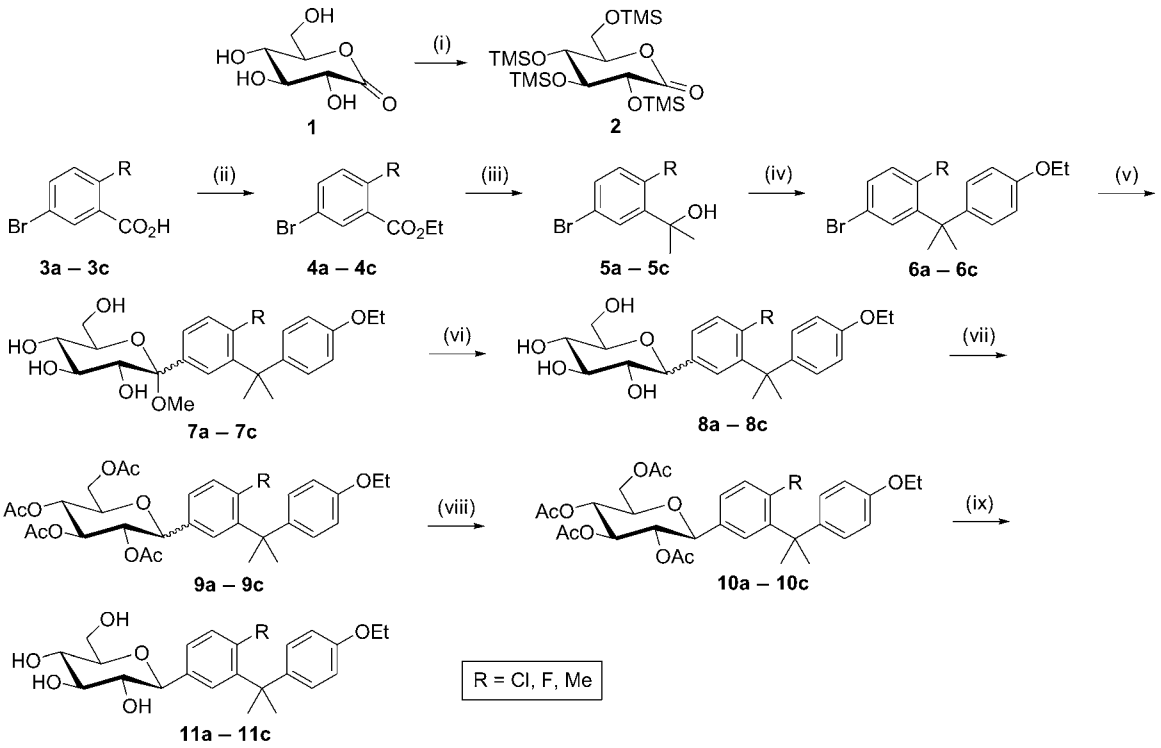
Results and discussion

The synthetic route to the target molecules **11a**—**11c** was depicted in Scheme 1. Commercially available *D*-glucolactone **1** was treated with trimethylsilyl chloride (TMSCl) in the presence of *N*-methylmorpholine (NMM) to give pertrimethylsilylated *D*-glucolactose (**2**) according to known procedures.[2,13] Commercially available 2-substituted-5-bromobenzoic acids **3a**—**3c** were esterified with ethanol in the presence of concentrated sulfuric acid and benzene at reflux with azeotropic removal of water to afford the corresponding esters **4a**—**4c**, which were subsequently treated with 2 equiv. of methyl magnesium chloride to furnish the tertiary alcohols **5a**—**5c**. Treatment of the mixture of tertiary alcohols **5a**—**5c** and phenetol with anhydrous aluminum chloride as catalyst of Friedel-Crafts alkylation in dichloromethane smoothly produced the desired *gem*-dimethyl compounds **6a**—**6c**. Initial attempts to bring about this conversion with other acidic catalysts (MsOH, TfOH, TFA, BF_3•Et_2O and concentrated H_2SO_4) all failed due to the complete formation of corresponding olefins resulting from the E1 elimination of a water molecule from the starting tertiary alcohols mediated by these acids (Scheme 2). Thus, tertiary alcohol **5a** was treated with a variety of acids in the presence of phenetol in dichloromethane at 0 ℃ to room temperature; however, only the elimination product olefin **5Ea** was detected and isolated and no desired coupling product **6a** was observed in all cases. ^{1}H NMR (DMSO-d_6, 400 MHz) for **5Ea** is as follows: 7.46—7.50 (m, 1H), 7.45 (d, J＝2.4 Hz, 1H), 7.39 (d, J＝8.4 Hz, 1H), 5.28—5.29 (m, 1H), 4.96—4.97 (m, 1H), 2.02—2.03 (m, 3H).

An alternative attempt that included the conversion of **5a** to its corresponding tertiary alkyl chloride **5Ca** and the anticipated subsequent Friedel-Crafts alkylation was also unsuccessful because part of the tertiary alcohol **5a** decomposed to its corresponding olefin **5Ea** while others was converted to desired tertiary alkyl chloride **5Ca** (Scheme 3). Unfortunately, after aqueous work-up no desired **5Ca** was detected and only **5Ea** was observed, indicating that all the desired **5Ca** formed during this conversion decomposed during the aqueous work-up.

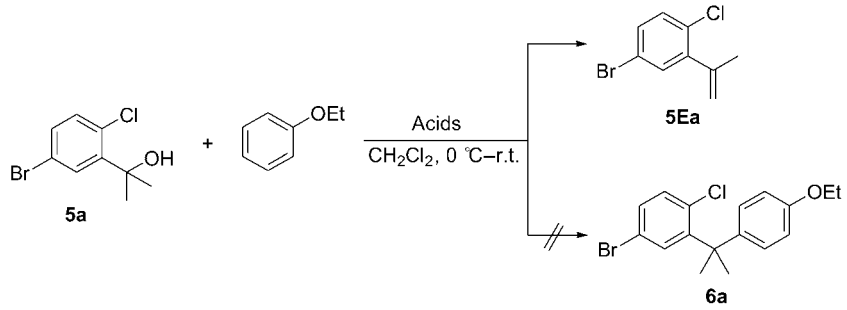
CHINESE JOURNAL OF CHEMISTRY

Scheme 1 Synthetic route to target molecules **11a**—**11c**



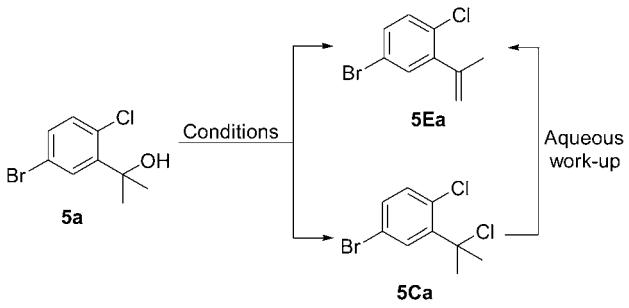
Reagents and conditions: (i) TMSCl (6.0 equiv.)/NMM (8.0 equiv.)/THF, 0—35 ℃; (ii) CH_2SO_4/EtOH/PhH, reflux; (iii) 2MeMgCl/THF, 0—5 ℃; (iv) $AlCl_3$/PhOEt/CH_2Cl_2, 0 ℃—r.t.; (v) *n*-BuLi/THF, −78 ℃; then, **2**/toluene, −78 ℃; finally, MsOH/MeOH, r.t.; (vi) Et_3SiH/BF_3•Et_2O, CH_2Cl_2, 0 —5 ℃ and then r.t.; (vii) NaOAc/Ac_2O/AcOH, reflux; (viii) column chromatography; (xi) NaOMe/MeOH, r.t.; then, strongly acidic resin (H^+ form).

Scheme 2 Formation of olefin **5Ea** resulting from the elimination of **6a**—**6c**



Acids: (1) MsOH; (2) TfOH; (3) TFA; (4) BF_3•Et_2O; (5) CH_2SO_4.

Scheme 3 Unsuccessful synthesis of tertiary chloride **5Ca**



Condtions: (1) $SOCl_2/CH_2Cl_2$, r.t.; (2) PCl_3/CH_2Cl_2, r.t.

The aryl bromides **6a**—**6c** were treated with *n*-butyl lithium at −78 ℃ to produce corresponding aryl lithiums, which were trapped *in situ* with pertrimethylsilyl-glucolactone **2** to afford methyl 1-*C*-glucosides **7a**—**7c** after treatment of the adducts of **6a**—**6c** and **2** with MsOH/MeOH at room temperature. The methyl 1-*C*-glucosides **7a**—**7c** were reduced with Et_3SiH/BF_3•Et_2O to give rise to the 1-deoxylated products **8a**—**8c**, which individually consisted of two corresponding anomers. Subsequently, **8a**—**8c** were peracetylated by treatment of **8a**—**8c** with acetic anhydride at reflux in the presence of anhydrous sodium acetate as catalyst to furnish the corresponding **9a**—**9c**, from which the pure *β*-anomers **10a**—**10c** were separated and purified by column chro-

matography. Finally, the desired products **11a**—**11c** were generated by treatment of **10a**—**10c** with sodium methoxide in absolute methanol at room temperature and subsequent neutralization with dried strongly acidic resin (H^+ form).

Table 1 The Inhibition rates of blood glucose levels of compounds **11a**—**11c** in OGTT

Compound	Dapagliflozin	**11a**	**11b**	**11c**
Inhibition rate/%	78	80	60	65

The antihyperglycemic activity of compounds **11a**—**11c** was evaluated *in vivo* with a mice oral glucose tolerance test (OGTT), and the inhibition rates of blood glucose levels were summarized in Table 1. The positive control Dapagliflozin was prepared according to known procedures.[2,14] As shown in Table 1, **11a**—**11c** were all comparable with the positive control Dapagliflozin in terms of antihyperglycemic activity, with **11a** being slightly more potent than positive control Dapagliflozin and **11b**—**11c** were slightly less potent than Dapagliflozin. The potent antihyperglycemic activity exhibited by these three compounds **11a**—**11c** suggested that the modification of the diphenylmethane functionality by the *gem*-dimethyl group was favorable, and all these three compounds were promising as the anti-diabetic agent for the treatment of type 2 diabetes.

In summary, the designed *gem*-dimethyl-bearing SGLT2 inhibitors based on Dapagliflozin were synthesized by an exquisite synthetic route, and three obtained compounds were evaluated by *in vivo* animal model OGTT to reveal that addition of the *gem*-dimethyl functionality was tolerated in terms of pharmacodynamics since almost no hypoglycemic activity was lost on addition of the *gem*-dimethyl functionality.

References

1 Arakawa, K.; Ishihara, T.; Oku, A.; Nawano, M.; Ueta, K.; Kitamura, K.; Matsumoto, M.; Saito, A. *Brit. J. Pharmacol.* **2001**, *132*, 578.

2 Meng, M.; Ellsworth, B. A.; Nirschl, A. A.; McCann, P. J.; Patel, M.; Girotra, R. N.; Wu, G.; Sher, P. M.; Morrison, E. P.; Biller, S. A.; Zahler, R.; Deshpande, P. P.; Pullockaran, A.; Hagan, D. L.; Morgan, N. N.; Taylor, J. R.; Obermeier, M. T.; Humphreys, W. G.; Khanna, A.; Discenza, L.; Robertson, J. M.; Wang, A.; Han, S.; Wetterau, J. R.; Janovitz, E. B.; Flint, O. P.; Whaley, J. M.; Washburn, W. N. *J. Med. Chem.* **2008**, *51*, 1145.

3 Link, J. T.; Sorensen, B. K. *Tetrahedron Lett.* **2000**, *41*, 9213.

4 Tsujihara, K.; Hongu, M.; Saito, K.; Inamasu, M.; Arakawa, K.; Oku, A.; Matsumoto, M. *Chem. Pharm. Bull.* **1996**, *44*, 1174.

5 Katsuno, K.; Fujimori, Y.; Takemura, Y.; Hiratochi, M.; Itoh, F.; Komatsy, Y.; Fujikura, H.; Isaji, M. *J. Pharmacol. Exp. Ther.* **2007**, *320*, 323.

6 Ellsworth, B. A.; Meng, M.; Patel, M.; Girotra, R. N.; Wu, G.; Sher, P. M.; Hagan, D. L.; Obermeier, M. T.; Humphreys, W. G.; Robertson, J. M.; Wang, A.; Han, S.; Waldron, T. L.; Morgan, N. N.; Whaley, J. M.; Washburn, W. N. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 4770.

7 Ueta, K.; Ishihara, T.; Matsumoto, Y.; Oku, A.; Nawano, M.; Fujita, T.; Saito, A.; Arakawa, K. *Life Sci.* **2005**, *76*, 2655.

8 Ueta, K.; Yoneda, H.; Oku, A.; Nishiyama, S.; Saito, A.; Arakawa, K. *Biol. Pharm. Bull.* **2006**, *29*, 114.

9 Oku, A.; Ueta, K.; Nawano, M.; Arakawa, K.; Kano-Ishihara, T.; Matsumoto, M.; Saito, A.; Tsujihara, K.; Anai, M.; Asano, T. *Eur. J. Pharmacol.* **2000**, *391*, 183.

10 Gao, Y. L.; Zhao, G. L.; Liu, W.; Wang, Y. L.; Xu, W. R.; Wang, J. W. *Chin. J. Chem.* **2010**, *28*, 605.

11 Wang, Z. F.; Zhao, G. L.; Liu, W.; Wang, Y. L.; Shao, H.; Xu, W. R.; Tian, L. J. *Chin. J. Org. Chem.* **2010**, *30*, 849 (in Chinese).

12 Gao, Y. L.; Zhao, G. L.; Liu, W.; Shao, H.; Wang, Y. L.; Xu, W. R.; Tang, L. D.; Wang, J. W. *Indian J. Chem.* **2010**, *49B*, 1499.

13 Obermeier, M.; Yao, M.; Khanna, A.; Koplowitz, B.; Zhu, M.; Li, W.; Komoroski, B.; Kasichayanula, S.; Discenza, L.; Washburn, W.; Meng, W.; Ellsworth, B. A.; Whaley, J. M.; Humphreys, W. G. *Drug Metab. Disp.* **2010**, *38*, 405.

14 Shao, H.; Zhao, G. L.; Liu, W.; Wang, Y. L.; Xu, W. R.; Tang, L. D. *Chin. J. Synth. Chem.* **2010**, *18*, 389 (in Chinese).

(E1010113 Sun, H.; Zheng, G.)

