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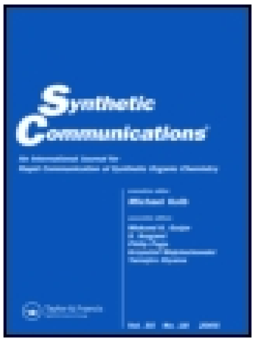

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Facile and green synthesis of dapagliflozin

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ABSTRACT

A facile and green synthetic route was developed for the preparation of dapagliflozin (**1**), a selective sodium-dependent glucose cotransporter 2 inhibitor for the treatment of type 2 diabetes. Key reaction steps include a direct Friedel–Crafts acylation and a synthesis of diaryl ketal moiety in one-pot manner without waste water generation. Furthermore, the reduction of the diaryl ketone and C-phenylglucoside were achieved in one-pot manner to generate dapagliflozin (**1**) more efficiently. The synthetic route featured the usage of commercial available and easily handling reagents with shorter reaction steps and less waste disposal.

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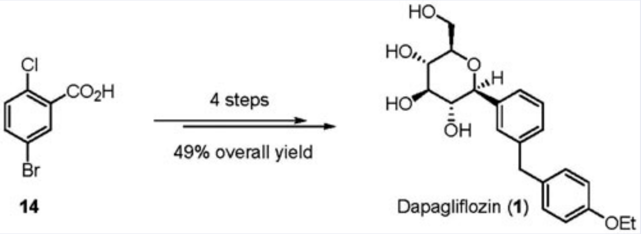
Dapagliflozin; di-aryl ketal; glycoside; green chemistry; one-pot synthesis

GRAPHICAL ABSTRACT



Introduction

C-glycosides are ubiquitous natural products with great importance in medicinal chemistry.[1] One class of medicinally important aryl glycosides active against diabetes are the selective sodium-dependent glucose cotransporter 2 (SGLT-2) inhibitors,[2–3] several exemplified by dapagliflozin (**1**), canagliflozin (**2**), empagliflozin (**3**) and ipragliflozin (**4**), as shown in Figure 1.

The typical synthesis method of these aryl glycosides was based on the reaction of protected aldonolactones with aryllithium or aryl Grignard reagents to generate lactols,

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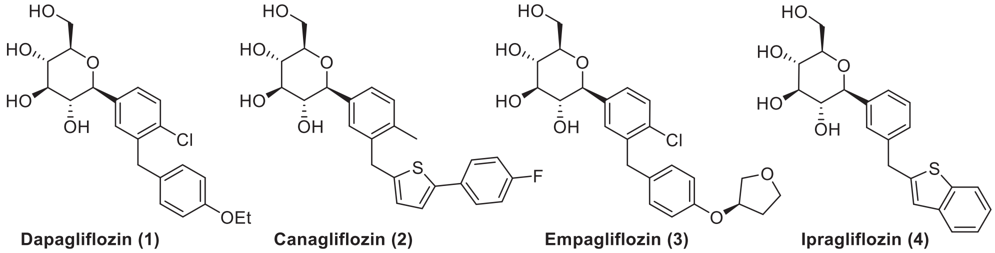


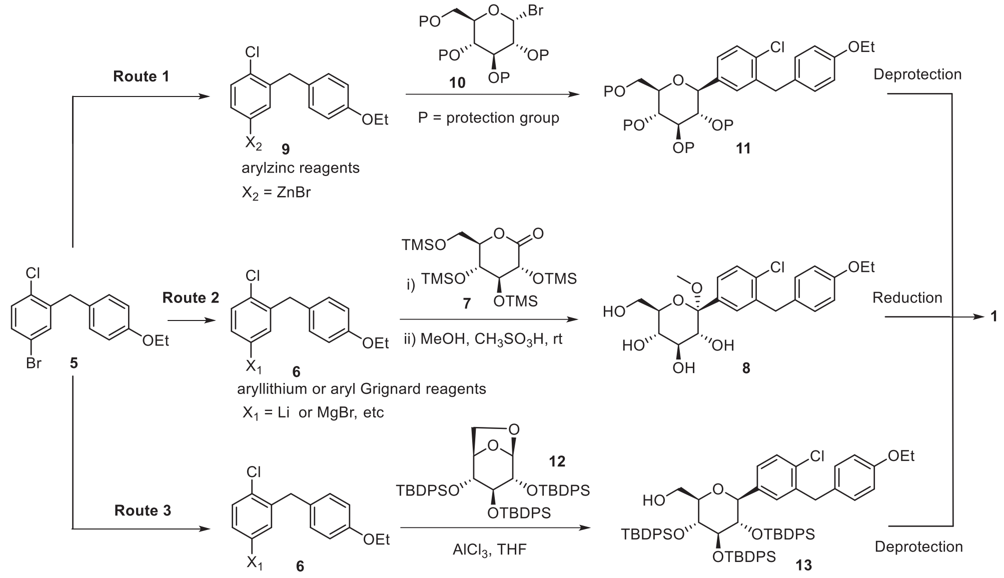
Figure 1. Representative SGLT-2 inhibitors.

which needs to be reduced in the next reaction step.[3–5] Alternative method included the cross-coupling reaction between glycosyl bromides and arylzinc reagents, leading to *β*-arylated glycosides.[3] Specifically, for the preparation of dapagliflozin (**1**), there are two main reported strategies as shown in Scheme 1 (routes 1 and 2).[3,6,7] A similar method was disclosed in patent WO2013068850, in which direct C-glycosylation between the Grignard reagent **6** and the protected levoglucosan **12** was achieved to give *β*-arylated glycosides **13** (Scheme 1, route 3).[8] As a common starting material in different methods according to the literature, the aryl halide **5** was synthesized from 5-bromo-2-chlorobenzoic acid **14** in three steps.[9] Initially, acylation was achieved by thionyl chloride or oxalyl chloride. Then, a Friedel–Crafts acylation mediated by $AlCl_3$ in anhydrous CH_2Cl_2 was carried out. Finally, reduction of the diaryl ketone intermediate was achieved by using Et_3SiH in the presence of $BF_3{\cdot}Et_2O$ in dichloromethane to give **5** in excellent overall yield.

Classical Friedel–Crafts acylation of aromatic compounds required more than one equivalent of Lewis acid such as $AlCl_3$. This was due to the complexation of $AlCl_3$ with ketone intermediate. A large amount of toxic waste was generated in this step. Considering the ecological and economical problems associated with the waste disposal, the usage of oxalyl chloride and $AlCl_3$ was not recommended for the large-scale preparation of dapagliflozin. Furthermore, the preparation of the common intermediate **5** and late-stage transformations involving two reduction steps, diaryl ketone reduction and 1 C-phenylglucoside, needed to be performed. Therefore, it was highly desirable to develop environmentally friendly protocols to prepare dapagliflozin. Scientists were trying to pursue direct and eco-friendly Friedel–Crafts acylations. Indeed, anisole and phenetole were electron-rich arene and active reagents in Friedel–Crafts acylation reaction. Progress has been made to achieve greener Friedel–Crafts acylations by using inorganic solid supported reagents[10] or solid acids[11–12] as catalysts. Direct Friedel–Crafts acylation of aromatic carboxylic acid with anisole has also been reported. For instance, the combination of graphite with methylsulfonic acid[13] or *p*-toluenesulfonic acid,[14] the combination of TFAA with $BF_3{\cdot}Et_2O$[15] and methanesulfonic anhydride[16–17] were investigated to promote this reaction.

Results and discussion

Based on the information above and the fact that both diaryl ketone and 1 C-phenylglucoside could be reduced by silane in the presence of catalytic amount of

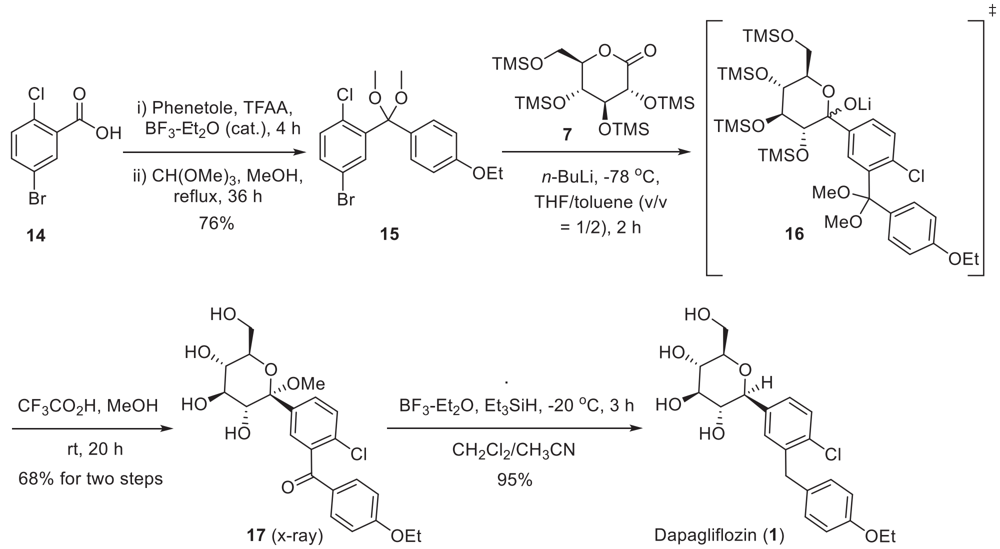


Scheme 1. The reported synthetic routes to dapagliflozin (**1**).

$BF_3{\cdot}Et_2O$,[6,7,9,18] we herein have developed a green synthetic strategy for dapaglifozin (**1**) as shown in Scheme 2.

Our synthesis started from commercially available 5-bromo-2-chlorobenzoic acid **14** and gluconolactone. An interesting result lied in the fact that both Friedel–Crafts acylation and ketallization could be realized by catalytic amount of $BF_3{\cdot}Et_2O$ to afford **15** in 76% overall yield in a one-pot manner. Gratifyingly, the diaryl ketal **15** could be easily crystallized from the reaction mixture without any other work-up operations. Similar to the reported processes,[8] a condensation between **15** and **7** was carried out under −78 °C in THF, followed by full deprotection of silyl groups in the presence of CF_3CO_2H in CH_3OH in a one-pot manner to yield compound **17** in 68% overall yield. It was satisfying that the intermediate **17** was also easy to crystallize from the reaction mixture in good quality. The single crystal of compound **17** was obtained in THF, and its structure was confirmed by X-ray diffraction analysis (Figure 2). In contrast, compound **8** was a syrupy foaming solid, which was very difficult to crystallize, as reported in the previous literatures.[8] Finally, Reduction of **17** was conducted by Et_3SiH in the presence of $BF_3{\cdot}Et_2O$ in CH_2Cl_2/CH_3CN to provide dapagliflozin (**1**) in high yield. The product could be purified in >98% purity upon crystallization from ethyl acetate and heptanes.

Compared with the previous synthetic strategies, obvious improvement includes the conduction of the reduction of diaryl ketone and 1 C-phenylglucoside in one step (**17**→**1**). This method could minimize the waste generation and improve the productivity. Additionally, it is well known that the control of genotoxic impurities is difficult and very important for APIs (active pharmaceutical ingredients). For example, the sulfonate is a typical genotoxic impurity with very low limitation requirements in drugs. At the beginning of this research, compound **14** was selected as the starting material,



Scheme 2. Green synthesis of dapaglifozin (**1**).

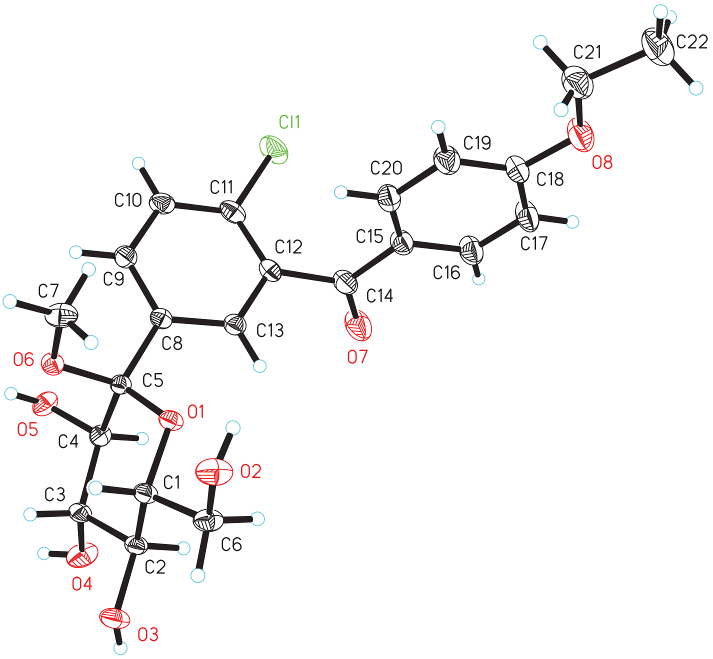


Figure 2. X-ray structure of intermediate **17**.

which was converted to ketal **15** by using catalytic amounts of CH_3SO_3H and CH_3OH. Similarly, methylsulfonic acid and methanol were also used in the quenching stage of condensation reaction to yield C-phenylglucoside **17** following a reported literature.[7] These procedures inevitably introduced methanesulfonate as the genotoxic impurity into APIs. In order to avoid the generation of sulfonate, ketalization was attempted with weak acids. Fortunately, BF_3Et_2O and CF_3CO_2H were used to replace methylsulfonic acid successfully in this report, which avoided the possibility of generating genotoxic impurities.

Experimental

General

^{1}H NMR and 13C NMR spectra were recorded with a Bruker WM-400 MHz spectrometer. The chemical shifts (δ scale) of the ^{1}H NMR data are indicated in ppm relative to tetramethyl silane (TMS) ($\delta = 0.00$ ppm). The ^{1}H NMR data are reported as follows: chemical shift (δ, ppm), multiplicity [s (singlet), d (doublet), t (triplet), q (quarterlet), m (multiplet or unresolved)], coupling constant (*J*) in Hz, integration. The LC–MS data were recorded with Shimadzu LCMS-2010EV Mass spectrometers. The melting point was recorded with a digital melting point meter (Hanon MP490). All reagents were commercially obtained and used as received.

Synthesis of dapaglifozin (1)

Under N_2 atmosphere, to a four-necked round-bottom flask equipped with a mechanical stirrer, a thermometer and an addition funnel, was added **16** (9.1 g, 20 mmol), CH_3CN (27 mL), CH_2Cl_2 (27 mL) and Et_3SiH (13.4 g, 120 mmol). The resulting suspension was cooled to –25 °C, and a solution of $BF_3 \cdot Et_2O$ (14.2 g, 100 mmol) in CH_2Cl_2 (14.2 mL) was added dropwise to the reaction mixture over 15 min, keeping the temperature below –20 °C. The reaction mixture was stirred at –20 °C for 3 h and then warmed to 35 °C and kept stirring for additional 4 h. Aqueous $NaHCO_3$ (90 mL) was added slowly to quench the reaction and the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 (20 mL × 2). The combined organic layers were concentrated under reduced pressure to obtain dapaglifozin as a light yellow solid: yield (7.8 g, 95%); melting point (m.p.) 88–90 °C; ^{1}H NMR (400 MHz, DMSO-d_6): $\delta = 7.37$ (d, $J = 8.0$ Hz, 1H), 7.32 (d, $J = 1.6$ Hz, 1H), 7.23 (dd, $J = 8.0$, 1.6 Hz, 1H), 7.09 (d, $J = 8.4$ Hz, 2H), 6.82 (d, $J = 8.4$ Hz, 2H), 4.94–4.95 (m, 2H), 4.82 (d, $J = 5.6$ Hz, 1H), 4.44 (t, $J = 6.0$ Hz, 1H), 3.93–4.02 (m, 5H), 3.68–3.72 (m, 1H), 3.42–3.48 (m, 1H), 3.08–3.29 (m, 4H), 1.29 (t, $J = 7.2$ Hz, 3H) ppm; 13C NMR (100 MHz, DMSO-d_6) δ 15.15, 38.13, 61.83, 63.36, 70.78, 75.18, 78.78, 81.17, 81.68, 114.77, 127.82, 129.13, 130.03, 131.27, 131.69, 132.39, 138.27, 140.14, 157.37; LC–MS (ESI$^+$): *m/z* (%) = 431 (M^+ + Na, 100), 433 (32). Anal. calcd. for $C_{21}H_{25}ClO_6$: C, 61.69; H, 6.16; Cl, 8.67; found C, 61.72; H, 6.18; Cl, 8.64.

Full experimental detail, copies of ^{1}H and 13C NMR spectra of compound **1**, **15**, **17**, and X-ray data of **17** are provided. This material can be found via the "Supplementary content" section of this article's webpage.

Conclusions

In summary, we have developed a facile and green protocol for the preparation of SGLT-2 inhibitor dapaglifozin (**1**) in four overall steps from readily available 5-bromo-2-chlorobenzoic acid **14** and gluconolactone. The direct Friedel–Crafts reaction and the synthesis of diaryl ketal **15** were successfully performed in a one-pot manner without waste water generation. Furthermore, the reduction of diaryl ketone and C-phenylglucoside moieties was also achieved in one step, leading to shorter synthetic route and less waste. The intermediate **15** and **17** could be easily purified *via* crystallization. Considering the control of genotoxic impurity, CH_3SO_3H was replaced by CF_3CO_2H/$BF_3{\cdot}Et_2O$. Thus, this method provided an efficient strategy to prepare dapaglifozin (**1**), which was suitable for large-scale production and expected to be extended to the preparation of other similar SGLT-2 inhibitors.

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