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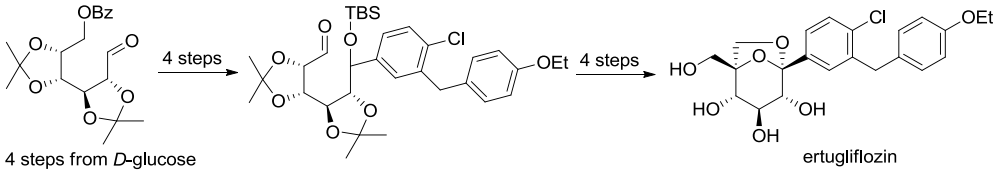
Graphical Abstract



Synthesis of Ertugliflozin from D-Glucose[†]

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Keywords: ertugliflozin; D-glucose; Grignard reaction; benzylic oxidation; SGLT2 inhibitors

Abstract: A new synthesis of ertugliflozin from D-glucose in 7% overall yield is reported. The reaction sequence involves conversion of D-glucose to a fully protected open chain D-glucose aldehyde in 4 steps, further installation of the aglycon group by a Grignard reaction, introduction of the hydroxymethyl group by a sequential oxidation/aldol reaction/Canizzarro reduction, and finally benzylic oxidation and global deprotection.

Diabetes is a group of metabolic diseases caused by high blood glucose concentrations either because insulin production in the body is inadequate (type 1 diabetes) or because body cells are not responding well to insulin (type 2 diabetes), or both. Type 2 diabetes is the most common glucose homeostatic disorder that accounts for 90-95% of all cases of diabetes, and is a major risk factor for the development of both micro- and macro-vascular complications.[1] Glycemic control and prevention of over-complications is a major health objective for a significant portion of humanity. The previously applied therapies focus on targeting insulin resistance and insulin secretion, carbohydrate digestion, glucagon production, and providing exogenous insulin.[2] Treatment with traditional glucose lowering therapies, including metformin, sulphonylureas and insulin, are being phased out due to gastrointestinal side effects, weight gain and hypoglycaemia. This has led to research into newer alternatives such as selective sodium-glucose transporter-2 (SGLT2) inhibitors.[3]

[†] Respectfully dedicated to Prof. K. C. Nicolaou for his outstanding contribution to Organic Synthesis

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SGLT2 are proteins in the human body with high glucose capacity, and are responsible for 90% of glucose reabsorption in the kidney. SGLT2 inhibitors block glucose resorption in the kidney thereby increasing its excretion and lowering glucose blood levels. The mechanism of action of this new class of drugs also offers further glucose control allowing for increased insulin sensitivity and glucose uptake in muscle cells, reduced gluconeogenesis and improved first phase insulin release from beta cells. Thus, hyperglycemia is controlled in a glucose-dependent but insulin independent manner.

Inspired by the natural product phlorizin, a number of *O*- and *C*-glucosides were developed, and among them dapagliflozin and canagliflozin are now on the market as SGLT2 inhibitors (Fig. 1). In addition, researchers at Pfizer disclosed a new class of such *C*-glucosides with a unique dioxa-bicyclo[3.2.1]octane structure and among them ertugliflozin (**1**) represents one of the most potent and selective SGLT2 inhibitors.[4] Recently, the US Food and Drug Administration (FDA) approved ertugliflozin (Steglatro) for the treatment of glycemic control in patients with type 2 diabetes as a drug taken on its own as a fixed-dose, or in combination with metformin and sitagliptin, which are both oral antihyperglycemic agents.

Ertugliflozin (**1**) was first prepared from D-glucose in 13 steps[4a] but in very low overall yield (0.3%). In the crucial step, an advanced intermediate Weinreb amide was treated with the lithiated aryl aglycon to give the final precursor, which was then converted to ertugliflozin by deprotection, unfortunately together with its epimer which needed to be separated by HPLC. In a substantially improved synthesis of ertugliflozin (**1**) by the same research group, also suitable for the synthesis of any compound of this class,[4b] commercially available di-*O*-isopropylidene mannofuranose was converted into the target molecule in 5 steps and 25% overall yield. This approach, however, was found to be unsuitable for large scale preparations, mainly due to the lack of crystalline intermediates and the requirement for low temperature reactions.

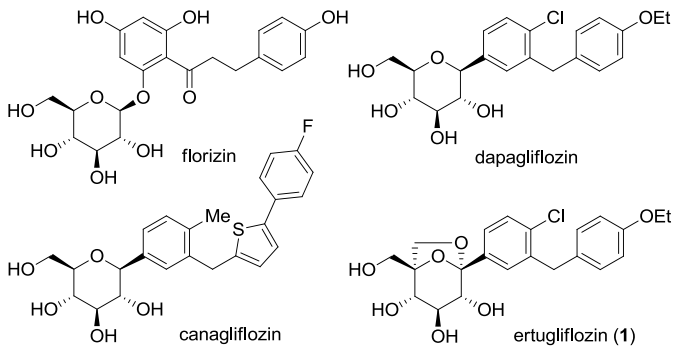
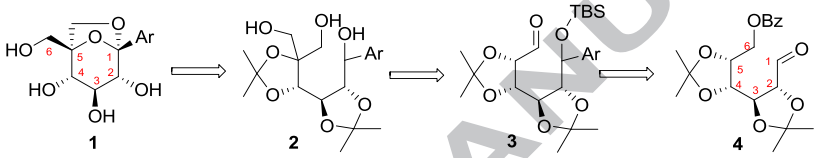


Figure 1. Structures of selected gliflozins

In two more recent approaches, D-glucose derivatives were used by Pfizer researchers as starting materials. Firstly, persilylated D-gluconolactone was converted into ertugliflozin in several steps involving *inter alia* Grignard addition, selective desilylation, oxidation and aldol-crossed-Cannizzaro reactions.[5] Although this process could be scaled up in very good overall yields, it was not commercially viable. However, it enabled toxicological and clinical tests for the development of ertugliflozin as a medicine. Finally, Pfizer laboratories developed a practical and commercially acceptable process for the preparation of ertugliflozin in a 12-step sequence, starting from 2,3,4,6-tetra-O-benzyl-D-glucose,[6] which involved nucleophilic hydroxymethylation of a ketogluconamide intermediate, and a highly efficient arylation of the protected diol thus obtained.

Recently, we reported a novel synthesis of ertuglifozin, starting from a known protected hydroxymethyl L-erythrose derivative, which was easily accessible from L-arabinoze.[7] Standard manipulations afforded an aldehyde intermediate, which after aldol condensation with 1-(4-chloro-3-(4-ethoxybenzyl)phenyl)ethanone led to formation of the carbon skeleton of the target molecule. Dihydroxylation of the formed double bond and global deprotection gave ertugliflozin in eight steps with 4% overall yield from known protected hydroxymethyl-L-erythrose. However, the undesired diastereoselectivity in the dihydroxylation step represents a drawback of this approach, compared to the existing synthesis methods. With the aim to improve the synthesis of ertugliflozin, we examined a different approach to ertugliflozin (**1**) using much cheaper D-glucose as the starting material.

The designed new synthesis of ertugliflozin is depicted in Scheme 1. Ertugliflozin (**1**) and other compounds of this class varying in the aglycon part (Ar), could be prepared by benzylic oxidation of **2**, followed by complete TFA deprotection. Compound **2** is the product of sequential aldol – Cannizzaro reactions of aldehyde **3** with formaldehyde, which in turn could be derived from the known fully protected D-glucose **4**[8] by a Grignard addition and further standard selective protection/deprotection manipulations. Compared to the first reported synthesis,[4a] where epimerization was observed in this step, the Grignard addition introducing the aglycon part of the glycoside takes place on a more reactive aldehydic carbonyl, expecting thus to avoid epimerization of the neighboring chiral carbon.



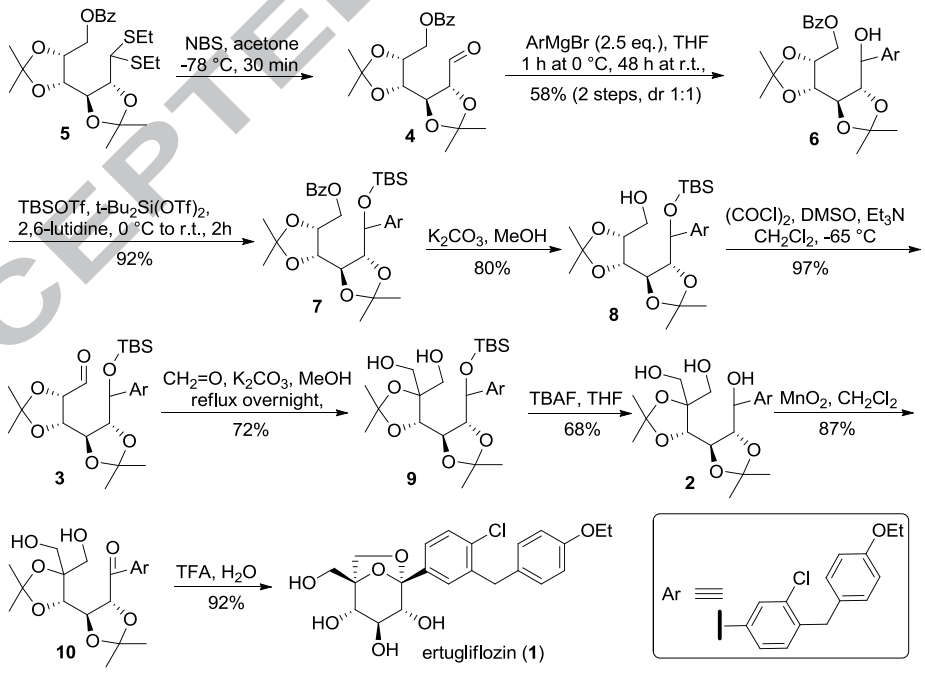
Scheme 1. Retrosynthetic analysis of ertugliflozin (**1**)

In our hands, known fully protected D-glucose **4** was prepared in 4 steps from D-glucose, using modified literature procedures[9] (Scheme 2). This conversion involved diethyl dithiacetal formation, benzoylation of the primary hydroxyl group, protection of the secondary hydroxyl groups as acetonides and finally deprotection of the aldehyde group (for details, see ESI). From a number of successful deprotection procedures applied, the use of NBS in acetone gave the best yields. Grignard addition of the aglycon part led to the formation of a *ca*. 1:1 inseparable diastereomeric mixture of benzylic alcohols **6** and to our delight no epimerization was observed, as shown by HPLC/MS analysis, where the two peaks appeared gave the correct molecular ion.

In the next step, we needed to protect the free benzylic hydroxyl group before hydrolysis of the benzoic ester. This step proved laborious, presumably due to steric hindrance, and the introduction of the TBS group using literature procedures[10] was very slow affording low yields of **7**. After experimentation, we found that high yields of the silylated product **7** were obtained (92%) when compound **6** was treated with TBS triflate (1.5 equiv.), di(*tert*-butylsilyl) ditriflate (0.25 equiv.), 2,6-

lutidine (2 equiv.) and a catalytic amount of DMAP for 1 h at 0 °C and then 0.5 h at rt. Although the role of di(*tert*-butylsilyl) ditriflate is not obvious, it is possible that di(*tert*-butylsilyl) ditriflate acting as a Lewis acid coordinates with an oxygen of the triflate group of TBS triflate, thus activating the later in its reaction with the alcohol. Nevertheless, this is an interesting point, which needs further detailed examination.

The benzoate was then cleaved with K_2CO_3 in MeOH and the resulting primary hydroxyl group was oxidized to give aldehyde **3** in high yield, which upon treatment with formaldehyde and K_2CO_3 in MeOH at reflux afforded the desired branched diol **9** in 72% yield, evidently *via* a sequential aldol reaction/Cannizzaro reduction. This substrate has the required carbon skeleton with the correct stereochemistry and what remained was achieved in three simple steps: the TBS group was removed using TBAF and the product was subjected to benzylic oxidation with MnO_2 to give ketone **10**, which was easily converted to ertugliflozin upon global deprotection with TFA, with physical and spectral data identical to those reported in the literature.



Scheme 2. Synthesis of ertugliflozin (**1**)

In conclusion, we have achieved a new synthesis of ertugliflozin (**1**) from D-glucose in 7% overall yield in 12 steps (16.2% from known compound **5** in 9 steps). Regarding the number of steps and yields, this synthesis is comparable with above mentioned syntheses. However, our synthesis starts from inexpensive D-glucose and, in addition, utilizes simple methods and cheap materials and reagents.

SUPPORTING INFORMATION

Experimental procedure and copies of ^{1}H and ^{13}C NMR spectra of compounds reported are available in the Supporting Information.

ACKNOWLEDGMENT

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Highlights:

- A new synthesis of ertugliflozin from D-glucose in 7% overall yield
- A new method for silylation of a hindered alcohol was developed
- Successful sequential aldol reaction/Cannizzaro reduction