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Studies towards the synthesis of ertugliflozin from L-Arabinose

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ABSTRACT

A new method for the diastereoselective synthesis of enantiomerically pure ertugliflozin was developed. The crucial step involves an aldol condensation between 1-(4-chloro-3-(4-ethoxybenzyl)phenyl)ethanone and (4R,5R)-5-(((*tert*-butyldimethylsilyl)oxy)methyl)-2,2-dimethyl-5-((trityloxy)methyl)-1,3-dioxolane-4-carbaldehyde, which was prepared from known 2-C-trityloxymethyl-2,3-*O*-isopropylidene-L-erythrose (easily accessible in three steps from L-arabinose) by standard reduction/oxidation and protection/deprotection manipulations. Dihydroxylation of the aldol condensation product and further global deprotection led to the formation of the target molecule.

1. Introduction

Diabetes is a metabolic disorder characterized by an increase in blood sugar (hyperglycaemia) and a glucose metabolism disorder, either as a result of decreased insulin secretion or because of decreased sensitivity of body cells to insulin [1]. Diabetes has a chronic course and can cause a number of serious complications, such as cardiovascular disease, chronic renal failure, retinal lesions, nerve damage, erectile dysfunction, etc. Current treatments include insulin, metformin, sulfonylureas, PPARgamma agonists, DPP-IV inhibitors and GLP-1 agonists. Although these medicines are effective in treatments, there exists safety concern for long term treatment. Therefore, there is a substantial need to identify new classes of treatments for diabetes [2].

There is currently a fierce interest for the development of new selective sodium-glucose transporter-2 (SGLT2) inhibitors. SGLT2 inhibition lowers the renal glucose concentration and the maximum glucose reabsorption capacity of the kidney, which results in increased urinary glucose excretion. Using the natural product phlorizin as a lead compound, a number of *C*-glucosides developed and among them dapagliflozin, canagliflozin and empagliflozin are now in the market as SGLT2 inhibitors [3] (Fig. 1).

In addition, researchers at Pfizer recently disclosed a new class of such *C*-glucosides with a unique dioxa-bicyclo[3.2.1]octane structure, and among them ertugliflozin is one of the most potent and selective SGLT2 inhibitors [4]. A few months ago, 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, both oral antihyperglycemic agents.

Ertugliflozin was firstly prepared from D-glucose in 13 steps [4a] but in very low overall yield (0.3%) and required HPLC separation from its C4 epimer. A more attractive synthesis of ertugliflozin was reported from the same labs, starting from diacetone-α-D-mannofuranose [4b]. This research team prepared the target compound in 5 steps and 25% overall yield, but this approach found to be unsuitable for large scale preparations, mainly due to the lack of crystalline intermediates and the requirement for low temperature reactions.

To overcome this problem, Pfizer's researchers turned their attention to the use of D-glucose derivatives as starting materials. Firstly, they started from persilylated D-gluconolactone, which was converted to ertugliflozin in several steps involving *inter alia* Grignard addition, selective desilylation, oxidation and aldol-crossed-Cannizzaro reaction [5]. Although this process could be scaled up in very good overall yields, it was found not commercially

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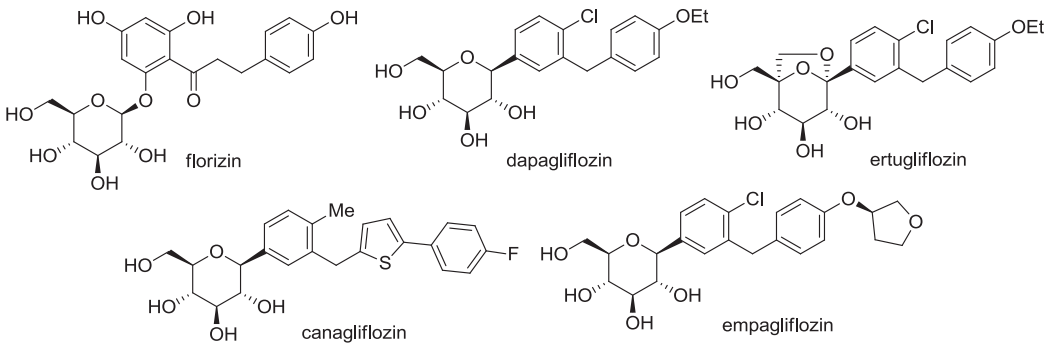


Fig. 1. Structures of selected gliflozins.

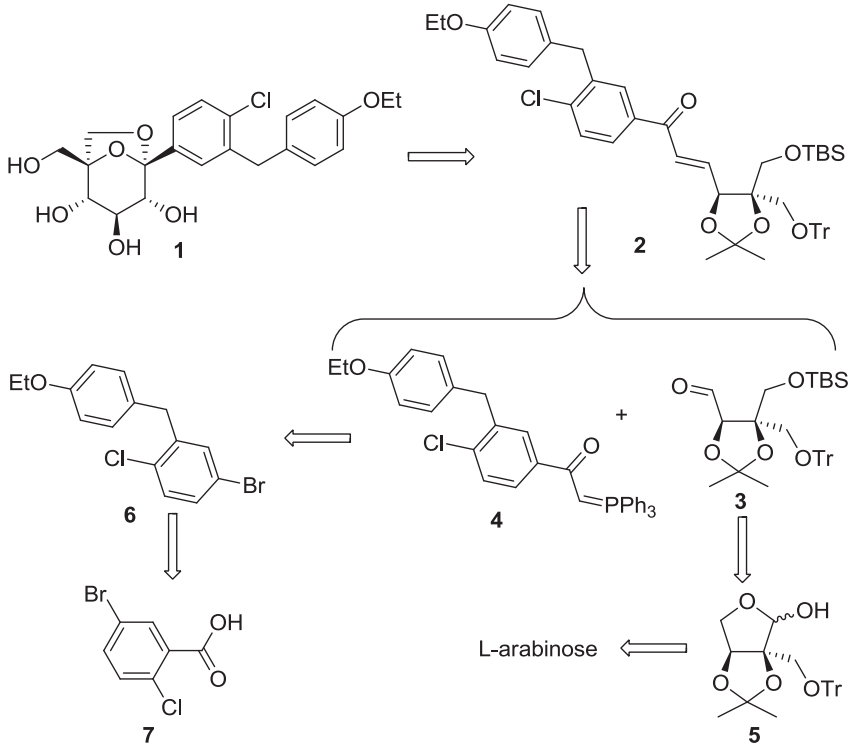
viable. Finally, the Pfizer laboratories developed a practical and commercially acceptable process for the preparation of ertugliflozin in a 12-step sequence, starting from 2,3,4,6-tetra-O-benzyl-D-glucose [6], which involved nucleophilic hydroxymethylation of a ketogluconamide intermediate, and a highly efficient arylation of the protected diol thus obtained.

2. Results and discussion

Taking into account its current interest, we designed a new synthesis of ertugliflozin, depicted in Scheme 1. According to this retrosynthetic analysis, ertugliflozin (**1**) could be prepared from enone **2** by a correct diastereoselective dihydroxylation and further global deprotection, which allows the resulting polyhydroxylated ketone to be self-organized towards the desired product. Compound **2** could be prepared by a Wittig reaction between the stable ylide **4**, accessible from 5-bromo-2-chlorobenzoic acid (**7**) *via* compound **6** [7] by standard manipulations, and aldehyde **3**, which in turn could be obtained from the known erythrose template **5** [8] by reduction and careful protection-deprotection manipulations.

To this end, we firstly focused on the synthesis of aldehyde **3** (Scheme 2). Protected hydroxymethyl L-erythrose **5**, a known useful building block prepared in three steps from L-arabinose [8], was reduced by $NaBH_4$ to diol **8**. In order to discern the two primary hydroxyl groups in **8**, protection of the less hindered one was attempted. Among several reagents and protecting protocols used, the pivaloylation was more selective resulting in the formation of desired monopivaloylated product **9** along with the byproducts **10** and **11**, which as easily separable can be recycled by methanolysis with KOH to **8**. The free hydroxyl group in **9** was then protected with TBS-Cl, the pivaloyl group was removed by methanolysis and the new alcohol was oxidized by pyridinium dichromate (PDC) to afford aldehyde **3**, in 26% overall yield from **5**.

We then proceeded into the next step, which was the synthesis of ylide **4**. As depicted in Scheme 3, 5-bromo-2-chlorobenzoic acid (**7**) was converted to its chloride and a subsequent Friedel-Crafts reaction afforded ketone **14**, which was further reduced to give compound **15** [7], in quantitative yields. Lithiation of the latter with



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