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Graphical Abstract

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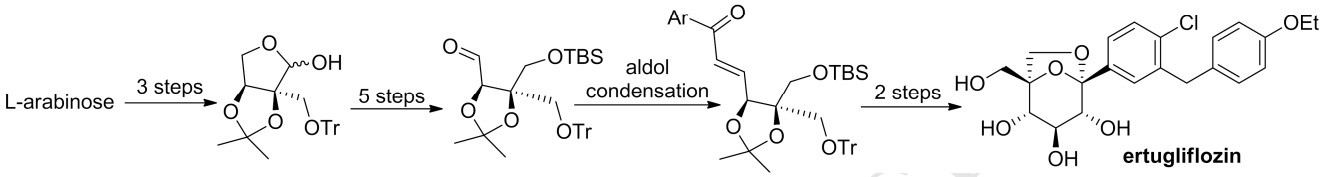

Studies towards the Synthesis of Ertugliflozin from L-Arabinose

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Keywords:
ertugliflozin
L-arabinose
dihydroxylation
aldol condensation
SGLT2 inhibitors

Abstract:

A new method for the diastereoselective synthesis of enantiomerically pure ertugliflozin was developed. The crucial step involes an aldol condensation between 1-(4-chloro-3-(4-ethoxybenzyl)phenyl)ethanone and (4*R*,5*R*)-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.

Indroduction

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] (Figure 1).

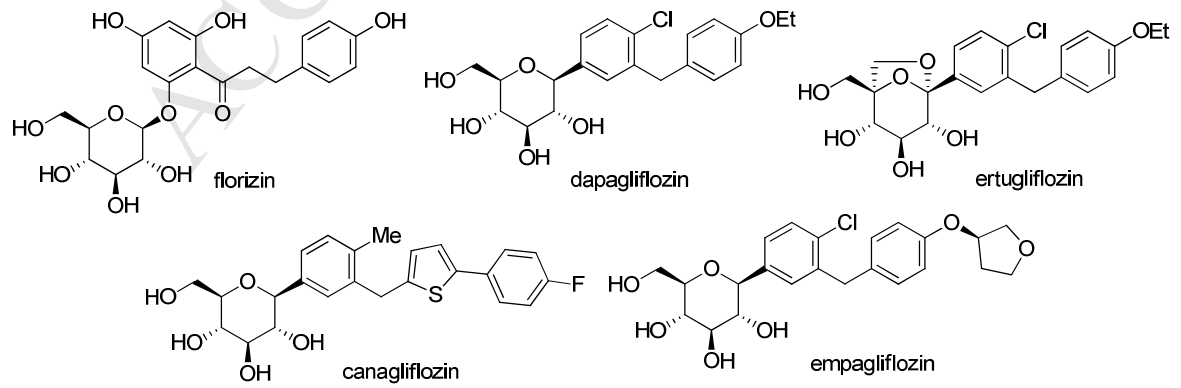


Figure 1. Structures of selected gliflozins

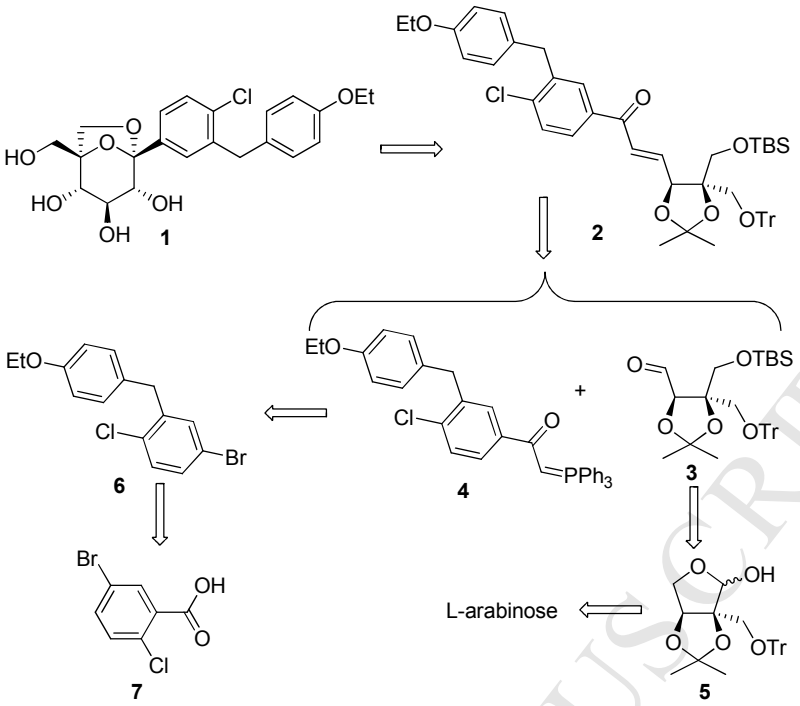
In addition, researchers at Pfizer recently disclosed a new class of such *C*-glucosides with a unique dioxa-bicyclo[3.2.1]octane structure, and among them ertugliflozin is one of the most potent and selective SGLT2 inhibitors.[4] A few months ago, the US Food and Drug Administration (FDA) approved ertugliflozin (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 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.

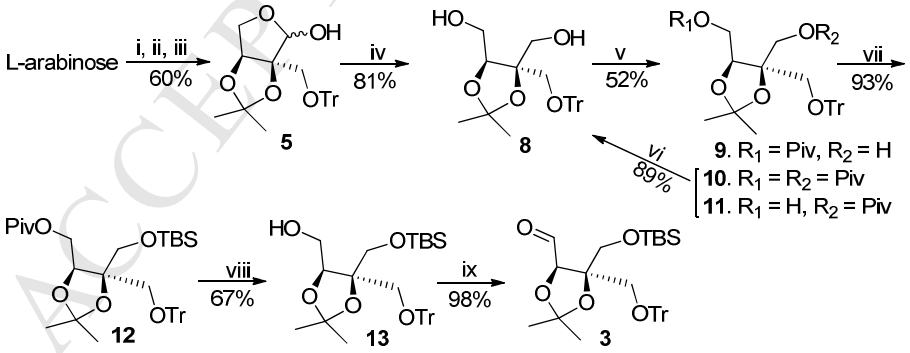
Results and Discussion

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.



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

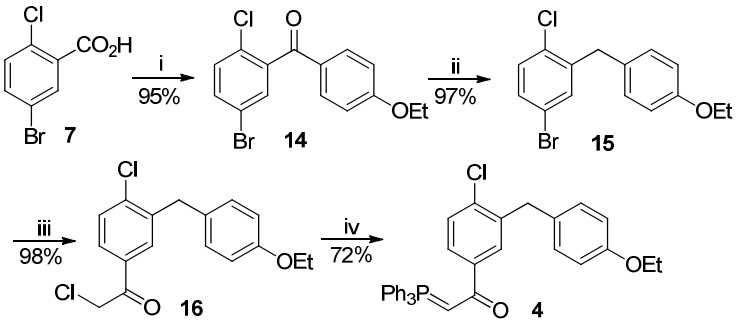
To this end, we firstly focused on the synthesis of aldehyde **3** (Scheme 2). Protected hydroxymethyl L-erythrose **5**, a known useful building block prepared in three steps from L-arabinose,[8] was reduced by $NaBH_4$ to diol **8**. In order to discern the two primary hydroxyl groups in **8**, protection 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**.



Scheme 2. Reagents and conditions: (i) 2,2-Dimethoxypropane, TsOH, DMF, 3 h, then $NaIO_4$ H_2O, 12 h, then Na_2CO_3; (ii) HCHO, K_2CO_3, MeOH, 65 °C; (iii) TrCl, pyridine, 60 °C; (iv) $NaBH_4$, MeOH, 0 °C to reflux, 2 h; (v) PivCl, pyridine, DMAP, DCM, 0 to 20 °C, 12 h; (vi) KOH, MeOH, 20 °C, 12 h; (vii) TBSCl, imidazole, DMAP, DCM, 0 to 20 °C, 12 h; (viii) KOH, MeOH, 20 °C, 2 h; (ix) PDC, DCM, reflux, 4 h.

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 n-BuLi and reaction of the lithiated product with the Weinreb amide

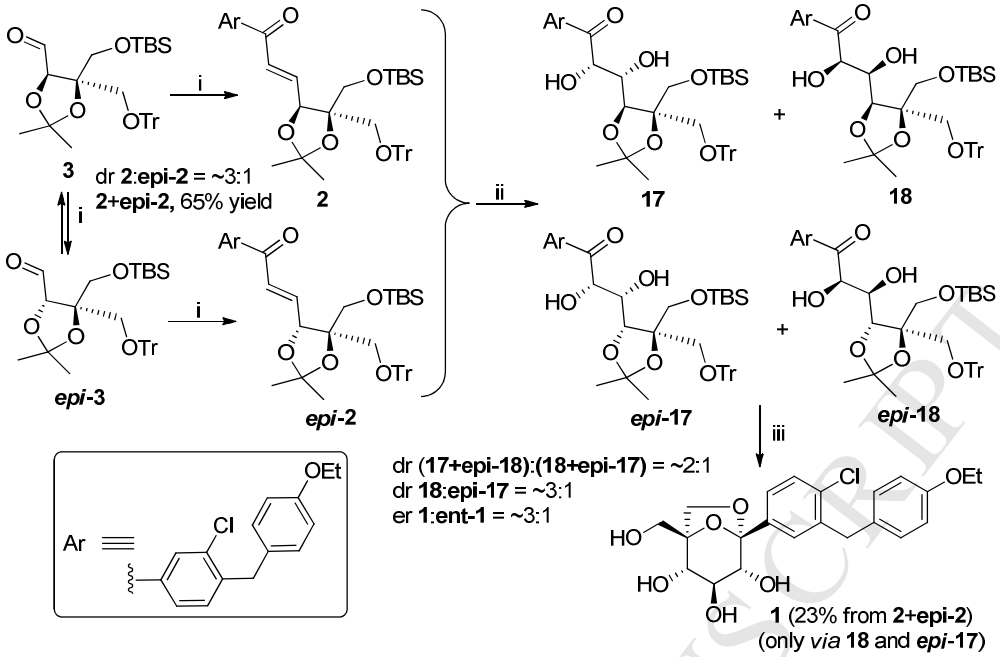
$ClCH_2CON(Me)OMe$ led to the formation of the desired ylide precursor **16**, which was then easily converted to **4** by standard procedures.



Scheme 3. Reagents and conditions: (i) oxalyl chloride, DCM, DMF (cat.), 20 °C, 12 h, then phenetole, DCM, $AlCl_3$, -20 to 20 °C, 1 h; (ii) $BF_3{\cdot}OEt_3$, Et_3SiH, $ClCH_2CH_2Cl$/MeCN, 0 to 50 °C, 3 h; (iii) n-Buli, THF, -78 °C, 45 min, then $ClCH_2CON(Me)OMe$, THF, -78 °C, 3 h; (iv) PPh_3, MeCN, reflux, 12 h, then Na_2CO_3, 20 °C, 3 h.

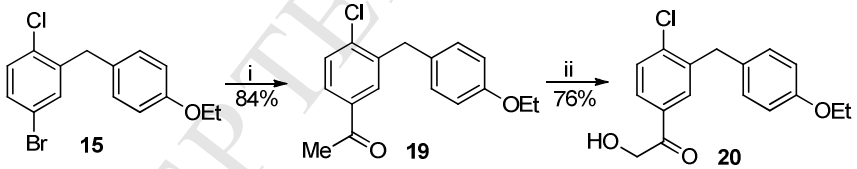
The Wittig reaction of aldehyde **3** with ylide **4** required reflux in toluene in order to reach its completion (Scheme 4). This caused an extended epimerization of aldehyde **3**, leading to an inseparable (by column chromatography) mixture of diastereoisomers **2** and **epi-2**, in varying ratios, depending on the exact reaction conditions, such as temperature and reaction time. When the Wittig reaction was interrupted before its completion, the unreactive aldehyde **3** was isolated and its NMR data clearly indicated that it was a mixture of epimers **3** and ***epi*-3**. HPLC/MS analysis of the Wittig product revealed that this intermediate had an average **2**/**epi-2** diastereomeric ratio of *ca.* 3:1, with the non-epimerized product **2** to be the major one, as shown by comparing the ^1H NMR spectrum of this mixture with that of pure **2**, prepared independently (Scheme 6).

Dihydroxylation of **2** can lead to the formation of **17** and **18**, whereas ***epi*-17** and ***epi*-18** are the possible dihydroxylation products of **epi-2**. From all of these possible products, only compound **18** deprotection could afford ertugliflozin (**1**) by deprotection, while ***epi*-17** leads to the formation of ***ent*-1**, since deprotected **18** and ***epi*-17** are enantiomers. Unfortunately, the inseparable mixture of **2**/**epi-2** upon dihydroxylation with OsO_4 lead to the formation of two diastereoisomeric mixtures **17**/***epi*-18** and **18**/***epi*-17** in ratio 2:1, respectively, which were separated chromatographically and without complete characterization were treated with TFA. Under these conditions, the minor slower moving dihydroxylated product **18**/***epi*-17** gave ertugliflozin with NMR data identical to those reported in the literature for the authentic compound and with *ca.* 50% ee, as found from its $[\alpha]_D$ [+4.0 (c 0.5, MeOH)] compared to the $[\alpha]_D$ value of authentic ertugliflozin[4b] {$[a]_D^{25}$ +8.0 (c 0.5, MeOH)}. It also indicated that the **18**/***epi*-17** ratio is also *ca.* 3:1.



Scheme 4. Reagents and conditions: (i) compound **4**, toluene, reflux, 12 h; (ii) OsO_4, NMO, acetone/H_2O (4:1), 20 °C, 12 h, (iii) TFA/H_2O (9:1), 20 °C, 1 h.

Summarizing the above results, we had to solve two major problems in the way to prepare enantimerically pure ertugliflozin: to avoid epimerization and to improve the diastereoselection in the dihydroxylation step. To overcome the epimerization problem, we considered several alternative pathways in order to connect the aglycon and sugar parts of ertugliflozin. In a first plan, it was likely that a base promoted aldol reaction between hydroxyketone **20** (Scheme 5) and aldehyde **3** could directly lead to the formation of desired product **18**, along with its all possible *syn-/anti*-diastereomeric adducts. The diastereoselectivity of aldol addition could then controlled by selecting the proper catalyst. Similar diastereoselective reactions with related educts have been reported in the literature.[9]

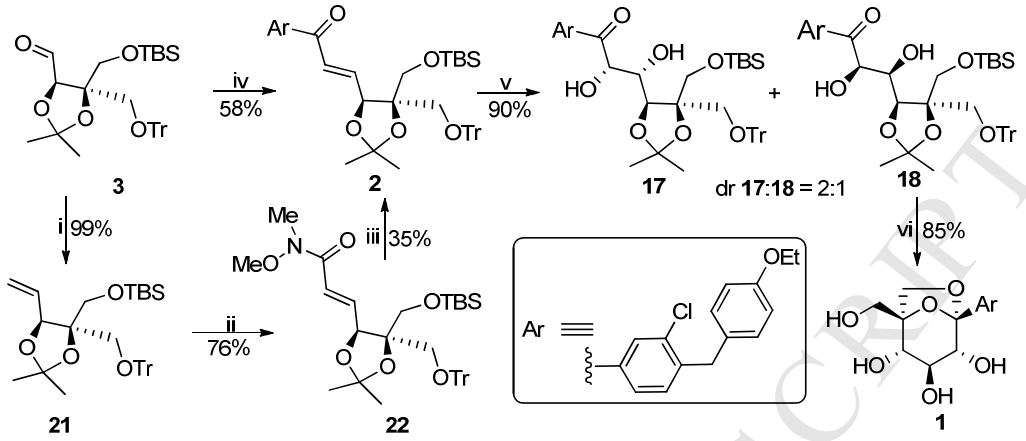


Scheme 5. Reagents and conditions: (i) Mg, THF, reflux, 1 h, then $(CH_3CO)_2O$, THF, -20 to 20 °C, 3 h; (ii) PIDA, KOH, MeOH, 0 to 20°C, 12 h.

Hydroxyketone **20** was easily prepared from **15** in two steps. Firstly, lithiation of **15** and further reaction with acetic anhydride afforded methylketone **19**, which was then oxidized with phenyliodine diacetate (PIDA) in the presence of KOH in methanol to give **20** in 64% overall yield from **15**. A mixture of hydroxyketone **20** and aldehyde **3** was treated with a number of organic bases (Et_3N, pyridine, quinine, quinchonine, L-proline, etc.) in different reaction conditions regarding solvents and temperature in prolonged reaction times. Always, the reaction was very slow and after several days, more than 70% of reactants remained unchanged, and a number of products had been formed, as shown in TLC. Since the isolation and characterization of these products was proved extremely difficult, the mixture was treated with TFA, but no amount of **1** was identified.

At this point, we turned our attention in the preparation of enone **2** by an indirect method with the scope of avoiding epimerization. Thus, we firstly tried a Wittig reaction of aldehyde **3** with the simple reactive ylide $Ph_3P{=}CH_2$ in low temperature, in order to avoid epimerization. To our satisfaction, product **21** was obtained in 99% yield in enantiomerically pure form, as shown by NMR. Further cross metathesis with Weinreb acrylamide led to the desired amide **22**, and its reaction with the lithiated

compound **15** (Scheme 3) afforded enone **2**. However, long reaction times and moderate overall yields led us to search for a more convenient method. Better results were obtained by an aldol condensation of aldehyde **3** and ketone **19** using LDA as a base at low temperature to afford desired enone **2** in 58% yield.



Scheme 6. Reagents and conditions: (i) Ph_3PCH_3Br, THF, addition of n-BuLi at -78 °C, stirring at -60 °C, 1 h, then addition of **3** at -78 °C and stirring, 2 h, then stirring at 20 °C, 12 h; (ii) CH_2=CHCON(Me)OMe, Grubbs 2nd generation catalyst, THF, reflux, 4 days; (iii) compound **15**, n-BuLi, -78 °C, 45 min, 1 h, then 20 °C, 2 days; (iv) compound **19**, LDA, THF, -78 °C to 20 °C, 12 h; (v) OsO_4, NMO, citric acid, acetone/H_2O (4:1), 20 °C, 12 h; (vi) TFA/H_2O (9:1), 20 °C, 1 h.

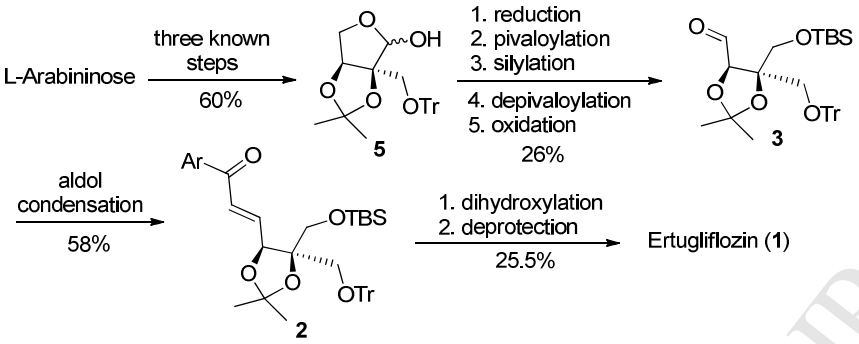
We then turned our attention in an attempt to improve the diastereoselectivity in the dihydroxylation step. A plethora of conditions in the dihydroxylation reaction were tried, regarding reagent (OsO_4, K_2OsO_4, $NaIO_4$, $KMnO_4$, AgOAc + I_2), co-oxidant [NMO, $K_3Fe(CN)_6$], additives (citric acid, methane sulfonamide, L(+)-tartaric acid, K_2CO_3), temperature, solvent and catalyst ratio, including the classic mixtures [$K_3Fe(CN)_6$, K_2CO_3, $(DHQ)_2PHAL$, OsO_4, methane sulfonamide] and [$K_3Fe(CN)_6$, K_2CO_3, $(DHQ)_2AQN$, OsO_4, methane sulfonamide] and also the commercial AD-mix α and AD-mix β, but always the undesired faster moving product **17** was the major one. The best **17**:**18** ratio obtained was 2:1 when the dihydroxylation proceeded with OsO_4, NMO, citric acid, in acetone/H_2O (4:1), 20 °C, 12 h, with 90% total yield, favoring unfortunately the undesired diastereoisimer **17**. Finally, compound **18** was converted to **1** in 85% yield, by treatment with TFA with spectral and physical data identical to those reported for **1**.

It is worthy to mention that there was no appreciable difference in the diastereoselection when each of AD-mix α and AD-mix β was used as catalysts in the dihydroxylation of **2**, both of them favoring exclusively the formation of the undesired diastereoisimer **18**. This observation led us in the conclusion that the intrinsic substrate-driven induction selectivity is superior to the selectivity induced by the catalyst. It is likely that each one of the bulky AD-mix α and AD-mix β catalysts are strongly hindered to approach the desired side of the double bond because of the substrate bias, much stronger than OsO4 itself. Attempted removing of the TBS protecting group in order to reduce the substrate bias led, unfortunately, to an intramolecular 1,4-addition reaction.

3. Conclusion

The following Scheme 7 summarizes the achieved steroselective synthesis of ertugliflozin (**1**). It was synthesized in eight steps with 4% overall yield from known trityloxymethyl L-erythrose **5**, which in our hands was prepared from cheap commercial L-arabinose, in three steps and 60% overall yield. Reduction of **5** with $NaBH_4$ and a further protection-deprotection sequence lead to the formation of key-aldehyde **3**, in 26% overall yield from **5**. This yield is practically higher, since undesired products **10** and **11** (Scheme 2) can be recycled. The carbon skeleton of the target molecule was constructed by

an aldol condensation of **3** with the aromatic methylketone **19**, whereas dihydroxylation of the resulting double bond and further global deprotection afforded ertugliflozin (**1**) in 15% from **3**.



Scheme 7. Overall synthetic scheme for ertugliflozin (**1**)

All above steps involve simple experimental manipulation and utilize cheap materials and reagents. Unfortunately, the undesired reverse stereoselectivity in the dihydroxylation step is a drawback of our approach which lacks the existing synthesis methods. Possibly, replacing the acetonide by a more flexible protecting group in the erythrose backbone could allow the correct diastereoselection in the dihydroxylation step by selecting the proper catalyst. Studies towards this direction are in progress.

4. Experimental section

4.1. General

All reagents are commercially available and were used without further purification. Solvents were dried by standard methods. The progress of reactions was checked by thin layer chromatography (TLC) on Merck silica gel 60F254 glass plates (0.25 mm). The spots were visualised by heat staining with anisaldehyde in ethanol/sulfuric acid. Column chromatography was performed with Merck silica gel 60 (0.063-0.200 mm). Melting points were determined with a Kofler hot-stage microscope. ^{1}H and ^{13}C NMR spectra were recorded at 300 or 500 MHz and 75 or 126 MHz, respectively. ^{1}H NMR chemical shifts (δ) are reported in ppm relative to tetramethylsilane (δ = 0.0 ppm), using the residual solvent signal as an internal standard (δ = 7.26, singlet, for $CDCl_3$), or using tetramethylsilane itself. The proton resonances are annotated as: chemical shift, multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br., broad), coupling constant (*J* [Hz]), and integration. ^{13}C NMR chemical shifts are reported in ppm, and spectra were calibrated using the central line of the triplet at δ = 77.0 ppm for $CDCl_3$. IR spectra were recorded with an FTIR instrument as indicated. High-resolution mass spectra (HRMS) were obtained using the electrospray technique, positive mode.

4.2 2,3-O-Isopropylidene-L-erythrose

L-Arabinose (5.0 g, 33.3 mmol), p-toluenesulphonic acid (127 mg, 0,67 mmol) and 2,2-dimethoxypropane (12.3 mL, 100 mmol) were stirred in DMF (34 mL) for 3 h. After neutralization, with solid Na_2CO_3 (70mg, 0,67mmol), solids were filtered off and washed with DCM and volatiles were removed under reduced pressure. The residue was dissolved in water (80 mL) and solid $NaIO_4$ (17.8 g, 83,3 mmol) was added in portions under vigorous stirring to the aqueous layer and the mixture stirred for 12 h, when solid Na_2CO_3 was added carefully until pH=7. Solids were filtered off and washed with DCM. Aqueous layer was extracted with ethyl acetate (4x120 mL), the combined organic layers were dried over Na_2SO_4 and the solvent was evaporated off. The residue was purified by column chromatography, with hexane/ethyl acetate (3:1) as eluent, to give 2,3-O-isopropylidcne-L-erythrose (5.40 g, 77%) as an α/β (1:10) mixture of anomers with spectral and physical data in agreement to those reported in the literature.[8a]

4.3 2,3-O-Isopropylidene-2-hydroxymethyl-L-erythrose

A mixture of 2,3-O-Isopropylidene-L-erythrose (4.07 g, 25.6 mmol), MeOH (115 mL) and aqueous methanolic solution formaldehyde (17.6 mL, 256 mmol) was heated with stirring to boiling point, whereupon potassium carbonate was added in small portions (about 500mg) every 20 minutes as the previous dose was almost dissolved. The end of the reaction was indicative at the point where the dissolution of the potassium carbonate was much slower, whereas the color of the reaction started to darken. After cooling the mixture to ambient temperature, the solid suspended particles were removed by filtration and the filtrate was transferred to an extraction funnel along with DCM (120 mL) and aqueous NaCl (sat.) (90 mL). The organic layer was separated and the aqueous was washed several times with EA (9x200 mL) until all of the product was transferred to the organic solvent. The organic layers were combined, dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by column chromatography with hexane/ethyl acetate (2:1) as eluent, to give a mixture of anomers of 2,3-O-isopropylidene-2-hydroxymethyl-L-erythrose (4.14 g, 86%, ratio of α/β *ca.* 1:2) as a colorless oil with spectral and physical data in agreement to those reported in the literature.[8b]

*4.4 2,3-O-Isopropylidene-2-trityloxymethyl-L-erythrose (**5**)*

2,3-O-Isopropylidene-2-hydroxymethyl-L-erythrose (4.07 g, 21.4 mmol) was dissolved in 45 ml of dry pyridine, and 6.6 g (23.6 mmol) of TrCl were added in one portion. The reaction mixture was heated at 60 °C for 36 hours under argon atmosphere, then was allowed to return to room temperature, diluted with 100 ml of toluene and washed with aq. NaCl (sat.) (3x100 mL). The organic layer was dried (Na_2SO_4), the solvent was evaporated off under reduced pressure and the residue was chromatographed (EtOAc/hexanes 1:5) to give a mixture of anomers **5** (8.14 g, 90%, ratio of α/β *ca.* 2:1) as a thick oil with spectral and physical data in agreement to those reported in the literature.[8b]

*4.5 ((4S,5S)-2,2-Dimethyl-4-((trityloxy)methyl)-1,3-dioxolane-4,5-diyl)dimethanol (**8**)*

To a solution of compound **5**[8b] (1.2 g, 2.76 mmol) in MeOH (40 mL), $NaBH_4$ (261 mg, 6.9 mmol) was added with stirring in portions to avoid foaming at 0 °C and then, the reaction mixture was refluxed for about 2 h where TLC showed consumption of the starting material. The mixture was brought to ambient temperature, H_2O (100 mL) and AcOH were added to adjust the pH to 5. The resulting mixture was extracted with EtOAc (3x200 mL) and the organic layer was dried over Na_2SO_4, the solvent was evaporated off under reduced pressure and the residue was chromatographed on a silica gel column (hexane/ethyl acetate 3:1) to give product **8** (970 mg, 81%) as a viscous white oil. $[a]_D^{25}$ +11.8 (c 7.0, $CHCl_3$). FTIR (neat film) 3444, 3058, 2986, 2934, 1637, 1448 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 7.47 (m, 6H), 7.33-7.23 (m, 9H), 3.95 (t, *J* = 5.3 Hz, 1H), 3.85 (dd, *J* = 11.9, 5.3 Hz, 1H), 3.80 (dd, *J* = 11.9, 5.3 Hz, 1H), 3.77 (d, *J* = 11.9 Hz, 1H), 3.70 (d, *J* = 11.9 Hz, 1H), 3.46 (d, *J* = 9.7 Hz, 1H), 3.15 (d, *J* = 9.7 Hz, 1H), 2.30 (br s, 2H), 1.47 (s, 3H), 1.32 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 143.4, 128.6, 127.9, 127.2, 108.5, 87.2, 83.2, 79.9, 65.7, 62.6, 60.4, 28.2, 26.2. LC-MS (ESI positive) m/z: 435 $[M+H]^+$ HRMS m/e: $C_{27}H_{31}O_5$ $[(M+H)^+]$ calcd: 435.2166, found: 435.2169.

*4.6 ((4S,5S)-5-(Hydroxymethyl)-2,2-dimethyl-5-((trityloxy)methyl)-1,3-dioxolan-4-yl)methyl pivalate (**9**)*

Dry pyridine (0.16 mL), pivaloyl chloride (198 mg, 0.2 mL) and DMAP (5 mg) were successively added to a stirred solution of diol **8** (600 mg, 1.38 mmol) in dry DCM (12 mL) under argon atmosphere at 0 °C. The mixture was stirred for 1 h at 0 °C and then allowed to stir at ambient temperature for 12 h where TLC showed consumption of the starting material. The reaction was quenched by addition of saturated aqueous $NaHCO_3$ (50 mL) and the mixture was extracted with DCM (3x100 mL). The combined organic layers were dried over Na_2SO_4, the solvent was evaporated off under reduced pressure and the residue was chromatographed on a silica gel column (hexane/ethyl acetate 8:1) to give firstly compound **10** as a white foam (280 mg, 35%), followed by product **9** (365 mg, 52%) as a colorless viscous oil and finally compound **11** (38 mg, 8%). For compound **9**, $[a]_D^{25}$ -9.1 (c 0.44, $CHCl_3$). FTIR (neat film) 3451, 2978, 1732, 1635, 1480 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 7.48 (m, 6H), 7.31–7.21 (m, 9H), 4.35 (dd, *J* = 11.7, 4.9 Hz, 1H), 4.24 (dd, *J* = 11.5, 6.6 Hz, 1H),

4.13 (dd, *J* = 6.6, 4.9 Hz, 1H), 3.73 (d, *J* = 11.5 Hz, 1H), 3.70 (d, *J* = 11.5 Hz, 1H), 3.41 (d, *J* = 9.7 Hz, 1H), 3.22 (d, *J* = 9.7 Hz, 1H), 1.49 (s, 3H), 1.35 (s, 3H), 1.12 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) *δ* 177.9, 143.4, 128.7, 127.9, 127.2, 108.9, 87.1, 83.4, 77.7, 65.3, 62.6, 62.1, 38.6, 28.3, 27.1, 26.3. LC-MS (ESI positive) m/z: 541 $[M+Na]^+$ HRMS m/e: $C_{32}H_{38}NaO_6$ $[(M+Na)^+]$ calcd: 541.2561, found: 541.2572.

*4.7 Recycling of (2R,3S)-2,3-O-Isopropylidene-2,3-dihydroxy-2-((trityloxy)methyl)butane-1,4-diyl bis(2,2-dimethylpropanoate) (**10**) and ((4R,5S)-5-(Hydroxymethyl)-2,2-dimethyl-4-((trityloxy)methyl)-1,3-dioxolan-4-yl)methyl pivalate (**11**)*

The above prepared compound **10** (750 mg, 1.9 mmol) was dissolved in MeOH (20 mL) and then solid KOH (160 mg, 2.84 mmol) was added. The mixture was stirred for 12 h where consumption of the starting material was observed. Then, H_2O (15 mL) was added and the mixture was extracted with DCM (3x30 mL). The combined organic layers were dried with (Na_2SO_4) and the solvent was removed under reduced pressure. The residue was chromatographed (hexane/ethyl acetate 5:1), whereby 640 mg of viscous white product **8** (89%) was obtained. Similarly, compound **11** was converted to **8**, approximately with the same yield.

*4.8 ((4S,5R)-5-(((tert-Butyldimethylsilyl)oxy)methyl)-2,2-dimethyl-5-((trityloxy)methyl)-1,3-dioxolan-4-yl)methyl pivalate (**12**)*

Imidazole (85.3 mg, 1.25 mmol), TBSCl (215 mg, 1.42 mmol) and DMAP (7 mg) were successively added to a stirred solution of compound **9** (300 mg, 0.57 mmol) in dry DCM (8 mL) under argon atmosphere at 0 °C. The mixture was stirred for 1 h at 0 °C and then allowed to stir for 12 h at ambient temperature. Saturated aqueous $NaHCO_3$ (20 mL) was then added and then the mixture was extracted with DCM (2x10 mL). The combined organic layers were dried over Na_2SO_4, the solvent was removed under reduced pressure and the residue was chromatographed on a silica gel column (hexane/ethyl acetate 10:1) to give product **12** (335 mg, 93%) as a white viscous oil. $[a]_D^{25}$ -5.0 (c 1.44, $CHCl_3$). FTIR (neat film) 2956, 2930, 2857, 1732, 1635, 1463 cm^{-1}. (500 MHz, $CDCl_3$) δ 7.49 (m, 6H), 7.31–7.19 (m, 9H), 4.27 (dd, *J* =11.1, 2.6 Hz, 1H), 4.18 (m, 2H), 3.66 (d, *J* = 10.1 Hz, 1H), 3.59 (d, *J* = 10.1 Hz, 1H), 3.32 (d, *J* = 9.8 Hz, 1H), 3.21 (d, *J* = 9.8 Hz, 1H), 1.47 (s, 3H), 1.39 (s, 3H), 1.15 (s, 9H), 0.78 (s, 9H), 0.01 (s, 3H), -0.07 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 178.1, 143.8, 128.8, 127.7, 126.9, 108.3, 86.7, 83.3, 77.3, 64.4, 63.0, 62.5, 38.6, 28.5, 27.2, 26.4, 25.8, 18.0, -5.6, -5.7. LC-MS (ESI positive) m/z: 655 $[M+Na]^+$ HRMS m/e: $C_{38}H_{52}NaO_6Si$ $[(M+Na)^+]$ calcd: 655.3425, found: 655.3431.

*4.9 ((4S,5R)-5-(((tert-Butyldimethylsilyl)oxy)methyl)-2,2-dimethyl-5-((trityloxy)methyl)-1,3-dioxolan-4-yl)methanol (**13**)*

Solid KOH (80 mg, 1.42 mmol) was added to a solution of compound **12** (300 mg, 0.47 mmol) in methanol (10 mL) and mixture was stirred at ambient temperature for about 2 h where consumption of the starting material was observed by TLC. Water (10 mL) was then added and the mixture was extracted with DCM (3x100 mL). The combined organic layers were dried over Na_2SO_4, the solvent was removed under reduced pressure and the residue was chromatographed on a silica gel column (hexane/ethyl acetate 10:1) to give product **13** (175 mg, 67%) as a white viscous foam, $[a]_D^{25}$ -11.7 (c 9.2, $CHCl_3$). FTIR (neat film) 3459, 2928, 1635, 1448 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.50 (m, 6H), 7.28-7.22 (m, 9H), 4.13 (t, *J* = 6.3 Hz, 1H), 3.75 (m as br s, 2H), 3.68 (d, *J* = 10.0 Hz, 1H), 3.66 (d, *J* = 10.0 Hz, 1H), 3.30 (d, *J* = 10.0 Hz, 1H), 3.18 (d, *J* = 10.0 Hz, 1H), 2.70 (br s, 1H), 1.47 (s, 3H), 1.43 (s, 3H), 0.77 (s, 9H), 0.03 (s, 3H), -0.08 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 143.8, 128.8, 127.7, 127.0, 108.1, 86.8, 83.7, 78.6, 65.2, 62.4, 60.7, 28.5, 26.3, 25.7, 18.0, -5.7, -5. 9. LC-MS (ESI positive) m/z: 571 $[M+Na]^+$ HRMS m/e: $C_{33}H_{44}NaO_5Si$ $[(M+Na)^+]$ calcd: 571.2850, found: 571.2845.

*4.10 (4R,5R)-5-(((tert-Butyldimethylsilyl)oxy)methyl)-2,2-dimethyl-5-((trityloxy)methyl)-1,3-dioxolane-4-carbaldehyde (**3**)*

PDC (220 mg, 0.58 mmol) was added to a solution of alcohol **13** (160 mg, 0.29 mmol) in 10 ml dry DCM (10 mL) and the mixture was refluxed for 4 h where consumption of the starting material was observed by TLC. The solvent was then evaporated off and the residue was chromatographed on a silica gel column (dichloromethane) to give aldehyde **3** (155 mg, 98%), which was used in the next steps without further purification. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.50 (s, 1H), 7.47 (m, 6H), 7.22-7.30 (m, 9H), 4.45 (s, 1H), 3.64 (d, *J* = 10.4, 2H), 3.53 (d, *J* = 10.4, 2H), 3.35 (d, *J* = 10.0, 2H), 3.30 (d, *J* = 10.0, 2H), 1.56 (s, 3H), 1.43 (s, 3H), 0.77 (s, 9H), -0.08 (s, 3H), -0,13 (s, 3H).

*4.11 (5-Bromo-2-chlorophenyl)(4-ethoxyphenyl)methanone (**14**)*

Oxalyl chloride (1.9 mL, 21.3 mmol) and DMF (30 µL) were added to a solution of 5-bromo-2-chlorobenzoic acid (5.0 g, 21.3 mmol) in dry DCM (10 mL) and the mixture was stirred at room temperature for 12 h. Volatiles were then evaporated off under reduced pressure and the crude 5-bromo-2-chlorobenzoyl chloride was dissolved in dry DCM (10 mL). The resulting solution was cooled at -5 °C and phenetole (2.6 g, 21.3 mmol) was added. Then, the mixture was further cooled at -20 °C, whereupon $AlCl_3$ (2.8 g, 21.3 mmol) was gradually added. After 1 h of stirring at room temperature, the reaction mixture was placed in an ice bath and water (40 mL) was added in portions. The resulting mixture was extracted with DCM (3x 80 mL) and the combined organic layers were washed with 1N HCl (2x50 mL), H_2O, 1N NaOH (2x50 mL) and brine before dried over Na_2SO_4. Concentration and column column chromatography on silica gel (hexane/ethyl acetate 10:1) afforded compound **14** as a white solid (6.86 g, 95%) with spectral and physical data identical to those reported in the literature, m.p. 68-70 °C (lit. m.p. 60 °C[7a] and 68-72 °C[7c]). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.76 (d, *J* = 8.8, 2H), 7.53 (dd, *J* = 2.2, 8.4, 1H), 7.48 (d, *J* = 2.2, 1H), 7.32 (d, *J* = 8.4, 1H), 6.93 (d, *J* = 8.8, 2H), 4.11 (q, *J* = 7.0, 2H), 1.45 (t, *J* = 7.0, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) 192.0, 163.9, 140.7, 133.7, 132.6, 131.5, 131.4, 130.1, 128.6, 120.5, 114.5, 63.9, 14.6. LC-MS (ESI positive) m/z: 340 $[M+H]^+$.

*4.12 4-Bromo-1-chloro-2-(4-ethoxybenzyl)benzene (**15**)*

Et_3SiH (6.76 mL, 42.34 mmol) was added to a solution of compound **14** (6.0 g, 17.8 mmol) in 1:2 mixture of dry 1,2-dichloroethane/acetonitrile (2:1, 60 mL) and the mixture was cooled in an ice bath. $BF_3 \cdot OEt_2$ (2.53 mL, 20.51 mmol) was added and the mixture was heated at 50 °C for 3 h and then cooled at room temperature. Aqueous 7N KOH (30 mL) was added and the aqueous layer was extracted with dichloromethane (2x100 mL). The combined organic layers were washed with 2N KOH (2x) and brine and dried over Na_2SO_4. The solvent was removed under reduced pressure and the residue was chromatographed on a silica gel column (hexane/ethyl acetate 15:1) to give product **15** (5.6 g, 97%) as colorless crystals, with spectral and physical data identical to those reported in the literature,[7] m.p. 40-42 °C (lit. m.p. 37 °C[7a] and 40-41 °C[7b]). ^{1}H NMR (400 MHz, $CDCl_3$) 7.20-7.28 (m, 3H), 7.08 (d, *J* = 8.8, 2H), 6.83 (d, *J* =8.8, 2H), 4.00 (q, *J* = 7.0, 2H), 3.96 (s, 2H), 1.40 (t, *J* = 7.0, 3H); ^{13}C NMR (125 MHz, CDCl3) 157.6, 141.3, 133.5, 133.1, 130.9, 130.5, 130.4, 130.0, 120.4, 114.6, 63.4, 38.2, 14.9. LC-MS (ESI positive) m/z: 325 $[M+H]^+$.

*4.13 2-Chloro-1-(4-chloro-3-(4-ethoxybenzyl)phenyl)ethanone (**16**)*

To a cold solution (-78 °C) of compound **15** (470 mg, 1.45 mmol) in dry THF (3 mL) 1.6 N solution of n-BuLi in hexanes (0.13 mL) was added dropwise. The mixture was stirred at this temperature for 45 min and to this mixtute a solution of 2-chloro-*N*-methoxy-*N*-methylacetamide (200 mg, 1.45 mmol) in dry THF (2 mL) was added dropwise at -78 °C. Stirring was continued for 3 h at this temperature where the consumption of the starting material was checked by TLC. Saturated aqueous solution of NH_4Cl (5 mL) was then added, followed by extraction with of DCM (3x8 mL). The combined organic layers ware dried over Na_2SO_4, the solvent was removed under reduced pressure and the residue was chromatographed on a silica gel column (hexane/ethyl acetate 12:1) to give product **16** (455 mg, 98%) as a colorless oil. FTIR (neat film) 3033, 1702, 1629 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.74 (d, *J* = 2.0 Hz, 1H), 7.72 (dd, *J* = 8.3, 2.0 Hz, 1H), 7.47 (d, *J* = 8.3 Hz, 1H), 7.09 (d, *J* = 8.6 Hz, 2H), 6.83 (d,

J = 8.6 Hz, 2H), 4.58 (s, 2H), 4.07 (s, 2H), 4.00 (q, *J* = 7.0 Hz, 2H), 1.40 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 190.2, 157.7, 140.4, 140.2, 132.8, 130.8, 130.2, 130.1, 129.9, 127.5, 114.7, 63.4, 45.8, 38.3, 14.7. LC-MS (ESI positive) m/z: 361 $[M+K]^+$ HRMS m/e: $C_{17}H_{16}KO_2$ $[(M+K)^+]$ calcd: 361.0159, found: 361.0156.

*4.14 1-(4-chloro-3-(4-ethoxybenzyl)phenyl)-2-(triphenylphosphoranylidene)ethanone (**4**)*

Triphenylphosphine (330 mg, 1.25 mmol,) was added to a solution of compound **16** (400 mg, 1.25 mmol,) in dry acetonitrile (12 mL) and the mixture was refluxed for 12 h. Aqueous solution of Na_2CO_3 (130 mg) in water (5 mL) was then added and the mixture was stirred for 3 h, followed by extraction with DCM (3x20 ml). The combined organic layers were dried over Na_2SO_4, the solvent was removed under reduced pressure and the residue was chromatographed on a silica gel column (hexane/ethyl acetate 7:1) to give product **4** (480 mg, 72%) as colorless crystals, m.p. 193-197 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.86 (s, 1H), 7.75 (d, *J* = 7.9, 1H), 7.70 (m, 6H), 7.55 (m, 3H), 7.47 (m, 6H), 7.32 (d, *J* = 7.9, 1H), 4.35 (d, *J* = 16.6, 1H), 4.05 (s, 2H), 3.98 (q, *J* = 7.9, 2H), 1.37 (t, *J* = 7.9, 3H). LC-MS (ESI positive) m/z: 549 $[M+H]^+$ HRMS m/e: $C_{35}H_{31}{}^{35}ClO_2P$ $[(M+H)^+]$ calcd: 549.1745, found: 549.1755.

*4.15 Ertugliflozin (**1**) via the Wittig reaction*

A solution of aldehyde **3** (510 mg, 0.95 mmol) and ylide **4** (580 mg, 1.05 mmol) in toluene (10 mL) was reflux for 12 h. Then, the solvent was evaporated off and the residue was chromatographed on a silica gel column (hexane/ethyl acetate 10:1) to give a c.a. 3:1 inseparable mixture of **2/epi-2** (507 mg, 65%) as a colorless oil. This mixture (50 mg, 0.061 mmol) was dissolved in acetone/water (4:1) (4 mL), then NMO (7 μL, 0.07 mmol, 1.2 eq.) and a catalytic amount of OsO_4 solution 4% in water (22 μL) were added and the resulting mixture was stirred for about 12 h at ambient temperature, where TLC showed the consumption of the starting material and the formation of two products. A solution of $NaHSO_3$ (180 mg) in H_2O (5 mL) was then added and the resulting mixture was stirred for 0.5 h. Solids were filtered off and the solution was extracted with EA (3x30 mL). The organic layers were dried over Na_2SO_4, the solvent was removed under reduce pressure and the residue was chromatographed on a silica gel column (hexane/ethyl acetate 7:1) to give firstly a mixture of **17**/**epi-18** (39.5 mg, 76%), followed by **18**/**epi-17** (13 mg, 23%). The slower moving **18**/**epi-17** was dissolved in a mixture of TFA/H_2O (9:1) (2.1 mL). The mixture was stirred at ambient temperature for 1 h and then the solvent was removed under reduced pressure. The residue was dissolved in EA and washed with water, 1M aqueous NaOH and brine. The organic layer was dried with Na_2SO_4, the solvent was removed under reduced pressure and the residue was chromatographed on a silica gel column (20% MeOH in CH_2Cl_2) to give ertugliflozin (**1**) (12 mg, 92%), with NMR spectra identical to those reported in the literature.[4b] $[\alpha]_D{}^{25}$ +4.0 (c 0.5, MeOH).

*4.16 1-(4-Chloro-3-(4-ethoxybenzyl)phenyl)ethanone (**19**)*

Activated magnesium (744 mg, 31 mmol) was added to dry THF (30 mL) and a few drops of a solution of compound **15** (0.5 g, 1.55 mmol) in dry THF (5 mL) were initially added to this mixture. To initiate the reaction a drop of CH_3I is added, if necessary. Then, the rest of solution of compound **15** was added and the mixture was refluxed for 1 h. The mixture was subsequently cooled at -20 °C, a solution of acetic anhydride (633 mg, 6.2 mmol) in dry THF (4 mL) was added dropwise and the resulting solution was left to stir at room temperature for 3 h. Water (5 mL) was then added to the mixture followed by careful addition of about 0.8 ml of a 50% aqueous NaOH solution to adjust the pH to 8. The mixture was extracted wit DCM (3x20 mL), the combined organic layers were dried over Na_2SO_4, the solvent was removed under reduced pressure and the residue was chromatographed on a silica gel column (hexane/ethyl acetate 7:1) to give compound **19** (380 mg, 84%) as white crystals, m.p. 50-52 °C. FTIR (neat film) 3048, 2979, 1682, 1630, 1583 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.76 (d, *J* = 2.1 Hz, 1H), 7.74 (dd, *J* = 8.2, 2.1 Hz, 1H), 7.46 (d, *J* = 8.2 Hz, 1H), 7.10 (d, *J* = 8.6 Hz, 2H), 6.83 (d, *J* = 8.6 Hz, 1H), 4.09 (s, 2H), 4.01 (q, *J* = 7.0 Hz, 2H), 2.52 (s, *3H)*, 1.40 (t, *J* = 7.0 Hz

2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 197.1, 157.6, 139.7, 139.4, 135.7, 130.7, 130.6, 129.8, 129.8, 127.4, 114.6, 63.4, 38.4, 26.6, 14.8. LC-MS (ESI positive) m/z: 259 $[M\text{-}CH_2CH_3]^+$ HRMS m/e: $C_{15}H_{12}{}^{35}ClO_2$ $[(M\text{-}CH_2CH_3)^+]$ calcd: 259.0520, found: 259.0528.

*4.17 1-(4-Chloro-3-(4-ethoxybenzyl)phenyl)-2-hydroxyethanone (**20**)*

KOH (1.07 mg, 19 mmol) and PIDA (1.2 g, 3.73 mmol) were added to a stirred solution of ketone **19** (1.0 g, 3.5 mmol) in methanol (8.5 mL) at 0 °C and the mixture was allowed to stir overnight at ambient temperature. The mixture was then extracted with DCM (20 mL) and with ethyl acetate (2x20 mL). The combined organic layers were dried Na_2SO_4, then filtered and concentrated. Methanol (0.1 mL) and aqueous 2M HCl (0.1 mL) were added to the residue and the resulting mixture was stirred for 1 h. The solvent was removed under reduced pressure and the residue was chromatographed on a silica gel column (hexane/ethyl acetate 6:1) to give firstly the PhI byproduct, followed by compound **20** (810 mg, 76%) as white crystals, m.p. 55-57 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.76 (d, *J* = 2.1 Hz, 1H), 7.74 (dd, *J* = 8.2, 2.1 Hz, 1H), 7.46 (d, *J* = 8.2 Hz, 1H), 7.10 (d, *J* = 8.6 Hz, 2H), 6.83 (d, *J* = 8.6 Hz, 1H), 4.09 (s, 2H), 4.01 (q, *J* = 7.0 Hz, 2H), 3.55 (s, *2H),* 1.40 (t, *J* = 7 Hz 2H), 0.67 (s, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 197.1, 157.6, 139.7, 139.4, 135.7, 130.7, 130.6, 129.8, 129.8, 127.4, 114.6, 63.4, 38.4, 26.6, 14.8. LC-MS (ESI positive) m/z: 327 $[M+Na]^+$ HRMS m/e: $C_{17}H_{17}{}^{35}ClNaO_3$ $[(M+Na)^+]$ calcd: 327.0758, found: 327.0755.

*4.18 tert-Butyl(((4R,5S)-2,2-dimethyl-4-((trityloxy)methyl)-5-vinyl-1,3-dioxolan-4-yl)methoxy)dimethylsilane (**21**)*

A solution of 1.6 M n-BuLi in hexanes (0.42 mL, 0.682 mmol) was added dropwise at -78 °C to a stirred solution of Ph_3PCH_3Br (210 mg, 0.6 mmol) in dry THF (1 mL) containing catalytic amount of 12-crown-4 (10 mg). The mixture was then stirred at -40 °C for 1 h, before cooled again to -78 °C, where a solution of aldehyde **3** (110 mg, 0.2 mmol) in dry THF (1 mL) was added dropwise. The resulting mixture was agitated for 2 h at temperatures below -60 °C and then left to stir for 12 hours at ambient temperature. Then, the mixture was cooled in an ice bath, a saturated aqueous solution of NH_4Cl (3 mL) was added and the mixture was extracted with DCM (3x5 mL). The combined organic layers were dried over Na_2SO_4, the solvent was removed under reduced pressure and the residue was chromatographed on a silica gel column (hexane/ethyl acetate 6:1) to give product **21** (110 mg, 99%) as a colorless oil, $[a]_D^{25}$ -2.45 (c 0.75, $CHCl_3$). FTIR (neat film) 3061, 2929, 1638, 1618, 1491 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.49 (m, 6H), 7.30-7.22 (m, 9H), 5.87 (m, 1H), 5.30 (d, *J* = 17.2 Hz, 1H), 5.15 (d, *J* = 10.5 Hz, 1H), 4.55 (d, *J* = 6.3 Hz, 1H), 3.69 (d, *J* = 10.5 Hz, 1H), 3.49 (d, *J* = 10.5 Hz, 1H), 3.37 (d, *J* = 9.5 Hz, 1H), 3.17 (d, *J* = 9.5 Hz, 1H), 1.49 (s, 3H), 1.40 (s, 3H), 0.79 (s, 9H), -0.01 (s, 3H), -0.04 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 144.0, 132.8, 128.8, 127.7, 126.9, 117.2, 108.2, 86.7, 84.1, 80.4, 64.1, 63.3, 28.6, 26.6, 25.8, 18.1, -5.6; LC-MS (ESI positive) m/z: 567 $[M+Na]^+$ HRMS m/e: $C_{34}H_{44}NaO_4Si$ $[(M+Na)^+]$ calcd: 567.2901, found: 567.2912.

*4.19 (E)-3-((4S,5R)-5-(((tert-Butyldimethylsilyl)oxy)methyl)-2,2-dimethyl-5-((trityloxy)methyl)-1,3-dioxolan-4-yl)-N-methoxy-N-methylacrylamide (**22**)*

Compound **21** (118 mg, 0.22 mmol) was dissolved in dry THF (2 mL) and then a solution of *N*-methoxy-*N*-methylacrylamide (126.5 mg, 1.1 mmol) in dry THF (2 mL) and Grubbs 2nd generation catalyst (9.64 mg, 0.015 mmol, 7 mol%) were added. The mixture was refluxed for 4 days and then filtered through a Celite pad, the solvent was evaporated off and the residue was chromatographed on a silica gel column (hexane/ethyl acetate 12:1) to give product **22** (105 mg, 76%) as a yellowish oil, $[a]_D^{25}$ -2.85 (c 0.75, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.50 (m, 6H), 7.28-7.22 (m, 9H), 6.90 (dd, *J* = 15.4, 4.9 Hz, 1H), 6.62 (d, *J* = 15.4 Hz, 1H), 4.75 (dd, *J* = 4.9, 1.5 Hz, 1H), 3.63 (s, 3H), 3.61 (d, *J* = 10.1 Hz, 1H), 3.47 (d, *J* = 10.1 Hz, 1H), 3.41 (d, *J* = 9.7 Hz, 1H), 3.23 (d, *J* = 9.7 Hz, 1H), 3.22 (s, 3H), 1.51 (s, 3H), 1.43 (s, 3H), 0.75 (s, 9H), -0.05 (s, 3H), -0.07(s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.0, 143.8, 140.6, 128.8, 127.8, 127.0, 119.0, 108.8, 86.8, 84.8, 78.8, 64.1, 63.2, 61.6, 28.6, 26.9,

26.6, 25.8, 18.1, -5.6, -5.7. LC-MS (ESI positive) m/z: 632 $[M+H]^+$ HRMS m/e: $C_{37}H_{50}NO_6Si$ $[(M+H)^+]$ calcd: 632.3402, found: 632.3397.

*4.20 (E)-3-((4S,5R)-5-(((tert-Butyldimethylsilyl)oxy)methyl)-2,2-dimethyl-5-((trityloxy)methyl)-1,3-dioxolan-4-yl)-1-(4-chloro-3-(4-(ethoxymethyl)benzyl)phenyl)prop-2-en-1-one (**2**)*

Method A: A solution of 1.6 M n-BuLi in hexanes (0.1 mL, 0.158 mmol) was added dropwise at -78 °C to a stirred solution of compound **15** (50 mg, 0.158 mmol) in dry THF (2.5 mL) and the mixture was stirred at this temperature for 45 min. Then, a solution of amide **22** (100 mg, 0.158 mmol, 1 eqiv.) in THF (1 mL) was added dropwise to this mixture at the same temperature, the resulting mixture was stirred at this temperature for another 1 h, and then left at ambient temperature for 2 days. Then, the mixture was cooled in an ice bath, a saturated aqueous solution of NH_4Cl (3 mL) was added and the mixture was extracted with DCM (3x5 mL). The combined organic layers were dried over Na_2SO_4, the solvent was removed under reduced pressure and the residue was chromatographed on a silica gel column (hexane/ethyl acetate 10:1) to give product **2** (45 mg, 35%) as a colorless oil.

Method B: An LDA solution in THF was prepared by adding dropwise at -78 °C a solution of 1.6 M n-BuLi in hexanes (0.28 mL, 0.45 mmol) to a solution of dry DIPA (0.07 mL, 0.5 mmol), in dry THF (5 mL). The solution was stirred for 15 minutes at 0 °C and then the temperature was again brought to -78 °C, whereupon a solution of compound **19** (120 mg, 0.41 mmol) in dry THF (1 mL) was added dropwise, followed by stirring for another 15 min. Then, aldehyde **3** (261 mg, 0.49 mmol) was added dropwise at -78 °C and the resulting mixture was stired for 15 min at this temperature and furthermore for 1 h at 0 °C and for 12 h at ambient temperature. A saturated aqueous solution of NH_4Cl (10 mL) was then added and the mixture was extracted with DCM (3x15 mL). The combined organic layers were dried over Na_2SO_4, the solvent was removed under reduced pressure and the residue was chromatographed on a silica gel column (hexane/ethyl acetate 25:1) to give product **2** (195 mg, 58%) as a colorless oil, $[a]_D^{25}$ -18.1 (c 12, $CHCl_3$). FTIR (neat film) 3060, 3033, 1674, 1627, 1591, 1591, 1491 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 7.74 (s, 1H), 7.69 (d, *J* = 8.4 Hz, 1H), 7.51 (m, 6H), 7.44 (d, *J* = 8.4 Hz, 1H), 7.28-7.22 (m, 9H), 7.08 (d, *J* = 8.3 Hz, 2H), 7.05 (d, *J* = 15.4 Hz, 1H), 6.97 (dd, *J* = 15.4 Hz, 4.1 Hz, 1H), 6.83 (d, *J* = 8.3 Hz, 2H), 4.84 (d, *J* = 4.1 Hz, 1H), 4.08 (s, 2H), 4.00 (q, *J* = 6.9 Hz, 2H), 3.56 (d, *J* = 9.8 Hz, 1H), 3.45 (d, *J* = 9.9 Hz, 2H), 3.28 (d, *J* = 9.9 Hz, 1H), 1.52 (s, 3H), 1.45 (s, 3H), 1.39 (t, *J* = 6.9 Hz, 3H), 0.68 (s, 9H), -0.14 (s, 3H).-0.15 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 188.7, 157.6, 143.8, 142.7, 139.6, 139.1, 136.4, 131.0, 130.6, 129.8, 129.7, 128.7, 127.8, 127.7, 127.1, 124.1, 114.5, 108.9, 86.9, 84.9, 78.5, 64.0, 63.3, 63.1, 38.4, 28.6, 26.6, 25.7, 18.0, 14.8, -5.7, -5.8; LC-MS (ESI positive) m/z: 839 $[M+Na]^+$ HRMS m/e: $C_{50}H_{57}{}^{35}ClNaO_6Si$ $[(M+Na)^+]$ calcd: 839.3505, found: 839.3510.

*4.21 Ertugliflozin (**1**) via the aldol condensation reaction*

Compound **2** (50 mg, 0.061 mmol) was dissolved in acetone/water (4:1, 4 mL), and NMO (7 μL, 0.070 mmol) and OsO_4 solution 4% in H_2O (22 μL) were subsequently added. The mixture was stirred for 12 h at ambient temperature, where TLC showed consumption of the starting material and the formation of two products. A solution of $NaHSO_3$ (180 mg) in H_2O (5 mL) was then added and the resulting mixture was stirred for 0.5 h. Solids were filtered off and the solution was extracted with EA (3x30 mL). The organic layers were dried over Na_2SO_4, the solvent was removed under reduce pressure and the residue was chromatographed on a silica gel column (hexane/ethyl acetate 7:1) to give firstly compound **17** (32 mg, 60%), followed by compound **18** (16 mg, 30%). The slower moving product (**18**) was dissolved in a mixture of TFA/H_2O (9:1) (2.1 mL). The mixture was stirred at ambient temperature for 1 h and then the solvent was removed under reduced pressure. The residue was dissolved in EA and washed with water, 1M aqueous NaOH and brine. The organic layer was dried with Na_2SO_4, the solvent was removed under reduced pressure and the residue was chromatographed on a silica gel column (20% MeOH in CH_2Cl_2) to give ertugliflozin (**1**) as an amorphous solid (7 mg, 85%), with spectral and analytical data identical to those reported in the

literature.[4b] $[a]_D^{25}$ +8.0 (c 0.5, MeOH) {lit.[4b] $[a]_D^{25}$ +8.0 (c 0.5, MeOH)}. ^{1}H NMR (500 MHz, MeOD) δ 7.44 (d, *J* = 1.6 Hz, 1H), 7.37 (d, *J* = 8.3, 1.6 Hz, 1H), 7.34 (d, *J* = 8.3 Hz, 1H), 7.08 (d, *J* = 8.4 Hz, 2H), 6.79 (d, *J* = 8.4 Hz, 2H), 4.14 (d, *J* = 7.5 Hz, 1H), 4.02 (s, 2H), 3.98 (q, *J* = 7.0 Hz, 2H), 3.82 (d, *J* = 12.5 Hz, 1H), 3.77 (d, *J* = 8.3 Hz, 1H), 3.67 (d, *J* = 12.5 Hz, 1H), 3.64 (d, *J* = 8.3 Hz, 1H), 3.58 (d, *J* = 7.5 Hz, 1H), 3.54 (d, *J* = 7.5 Hz, 1H), 1.35 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (126 MHz, MeOD) δ 157.4, 138.3, 137.1, 133.6, 131.4, 129.4, 129.1, 128.4, 125.7, 114.0, 108.2, 84.8, 77.9, 76.3, 71.7, 66.5, 63.0, 60.5, 37.8, 13.8. LC-MS (ESI positive) m/z: 437 $[M+H]^+$ HRMS m/e: $C_{22}H_{26}{}^{35}ClO_7$ $[(M+H)^+]$ calcd: 437.1361, found: 437.1368.

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