Organic Process Research & Development

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Commercial Route Research and Development for SGLT2 Inhibitor Candidate Ertugliflozin

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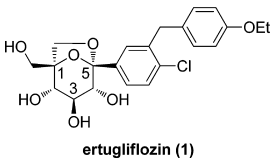
Supporting Information

ABSTRACT: A practical synthesis of SGLT2 inhibitor candidate ertugliflozin (**1**) has been developed for potential commercial application. The highly telescoped process involves only three intermediate isolations over a 12-step sequence. The dioxabicyclo[3.2.1]octane motif is prepared from commercially available 2,3,4,6-tetra-*O*-benzyl-D-glucose, with nucleophilic hydroxymethylation of a 5-ketogluconamide intermediate as a key step. The aglycone moiety is introduced via aryl anion addition to a methylpiperazine amide. High chemical purity of the API is assured through isolation of the crystalline penultimate intermediate, tetraacetate **39**. A cocrystalline complex of the amorphous solid **1** with L-pyroglutamic acid has been prepared in order to improve the physical properties for manufacture and to ensure robust API quality.

INTRODUCTION

The synthetic C-aryl glycoside ertugliflozin **1** is a sodium glucose cotransporter 2 (SGLT2) inhibitor currently in clinical development for the potential treatment of type 2 diabetes mellitus (Figure 1).[1−4] A medicinal chemistry synthesis of **1** was designed to enable the preparation of analogues on gram scale during candidate selection, but was undesirable for large, multikilogram scale manufacture.[5,6] This first-generation synthesis involved 13 linear steps from D-glucose, performed in an overall yield of 0.3% and required HPLC purification to isolate **1** from a mixture of C4 epimers. The key step in the route involved arylation of Weinreb amide **2** with aryllithium **3** (Scheme 1, Approach A).



ertugliflozin (1)

Figure 1. Structure of SGLT2 inhibitor candidate ertugliflozin (**1**).

This general strategy involving arylation of an open-chain gluconamide was potentially applicable for large scale synthesis of **1**, but a more expeditious approach to the point of convergency would be required. Furthermore, it was clear that the C5 tertiary alcohol of **2** needed to be protected prior to introduction of the aryl anion. Not only does the free hydroxyl consume one equivalent of the anion, it contributes to epimerization at C2, presumably via intramolecular deprotonation of ketone **4** through a six-membered transition state. As the ertugliflozin program transitioned into clinical development, an attractive alternative synthesis was reported by the medicinal chemistry team.[7] This stereoselective route provided **1** in a much-improved 26% overall yield from diacetone-α-D-mannofuranose. This approach was also deemed unsuitable for large scale application, however, primarily due to a lack of crystalline isolable intermediates and the requirement for cryogenic reaction temperatures in setting key stereochemistry.

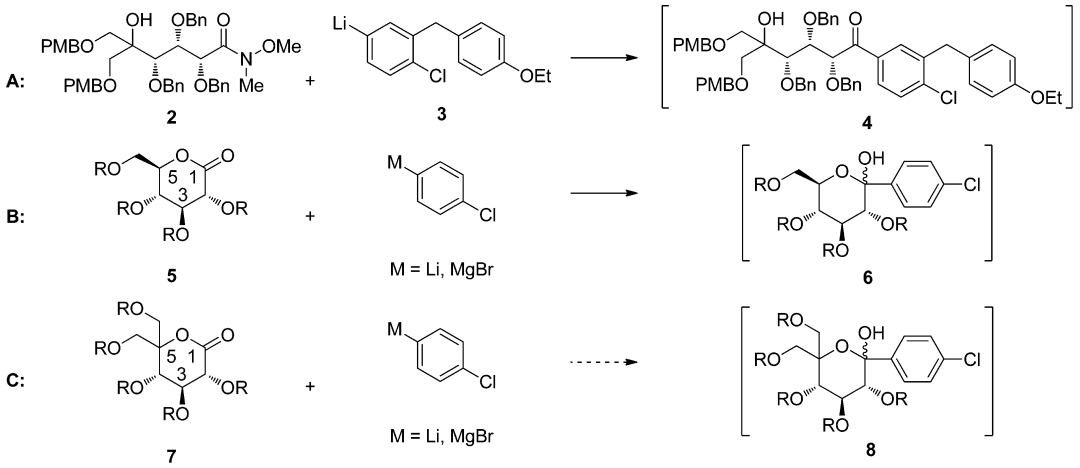
A more recent report[8] describes the second-generation synthesis developed and implemented for manufacture of API in support of early clinical studies. Although this process was successfully scaled to produce tens of kilograms of ertugliflozin in a pilot plant setting, the significantly larger quantities of API required for phase 3 and beyond, prompted development of a more efficient, scale-friendly process.

Evaluating Synthetic Approaches to the Carbohydrate Core. Among the published syntheses of SGLT2 inhibitor candidates under pharmaceutical evaluation, the direct arylation of protected gluconolactones of type **5** is most prevalent (Scheme 1, Approach B).[8−13] This strategy provides rapid access to the target compounds and is highly convergent. Recent advances, such as protection of the gluconolactone hydroxyls as labile TMS ethers,[14,15] have made this general approach particularly attractive for large scale, since a dedicated protecting group removal step is unnecessary. On the basis of this precedent, the initial strategy to **1** targeted utilization of the analogous approach C (Scheme 1). Thus, fully protected D-gluconolactone analogues, with an additional hydroxymethyl substituent at C5 (i.e., **7**), were required for further conversion to compounds **8** via aryl anion addition to the lactone carbonyl.

Received: October 7, 2013
Published: December 20, 2013

   dx.doi.org/10.1021/op4002802 | *Org. Process Res. Dev.* 2014, 18, 66−81

Scheme 1. General synthetic approaches considered



Although our initial strategies employed D-glucose as the primary building block for the preparation of the advanced carbohydrate backbone of **1**, we considered a wide range of chiral pool candidates during design and development of the second-generation synthesis (Figure 2). After a period of rapid route scouting on small scale, the most promising synthetic approaches were further assessed for viability on larger scale. Several routes reached a proof of concept phase in the laboratory, but were either relatively lengthy or exceedingly costly, making them unsuitable for commercialization (e.g., D-apiose, L-arabinose, and L-tartaric acid approaches).

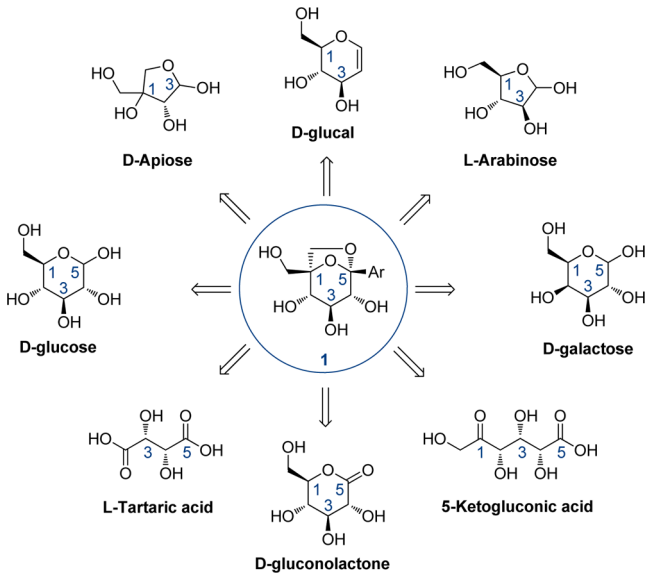
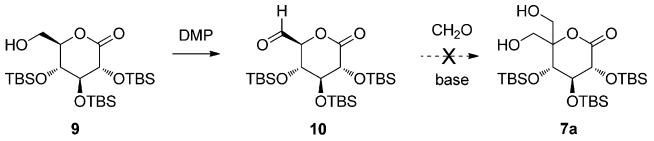


Figure 2. Potential precursors to **1** from the chiral pool.

Other carbohydrates highlighted in Figure 2 failed to provide access to useful advanced intermediates due to a gap in technology. For example, D-glucal has been showed to engage in Heck-type C-arylation reactions.[16,17] However, β-hydride elimination of the intermediate alkyl palladium complex leads to the C3−C4 olefin, destroying the C3 stereocenter. Likewise, D-galactose has been utilized in a high-yielding C1 hydroxymethylation with paraformaldehyde.[18] However, known pathways for inversion of the C2 stereocenter of galactose were unsuccessful on the C1 homologated substrates. Unfortunately, 5-ketogluconic acid proved very challenging to manipulate. This material lies predominately in the furanose form under acidic conditions and readily decomposes at alkaline pH. Protection of the hydroxyl groups in advance of reaction with aryl nucleophiles was not forthcoming.

A sensible approach to **7** involved persilyl protection of D-gluconolactone, followed by selective deprotection of the primary TBS ether to form alcohol **9** (Scheme 2). Oxidation of the primary hydroxyl of **9** to the corresponding aldehyde **10**[19] was accomplished with Dess−Martin periodinane. However, this compound proved to be very unstable, and was incompatible with the reductive alkylation conditions required for hydroxymethylation to diol **7a**.[7] Lactone hydrolysis and elimination byproducts predominated.

Scheme 2. Attempted preparation of 7a from D-gluconolactone

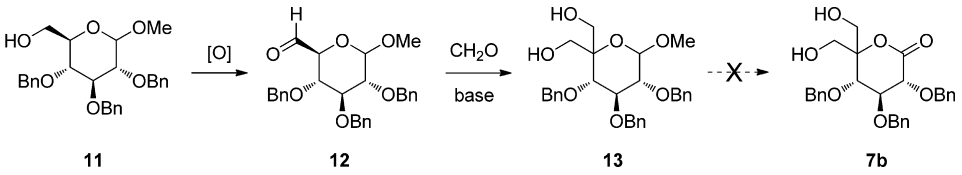


We also attempted to access diols of type **7** by utilizing tribenzyl-methyl-D-glucopyranoside (**11**), to minimize byproducts arising from degradation of lactone **10** (Scheme 3). While the key reductive hydroxymethylation step was comparatively more successful, an efficient sequence for conversion of methylpyranoside **13** to lactone **7b** was not forthcoming. This lengthy, unproductive approach was ultimately abandoned.

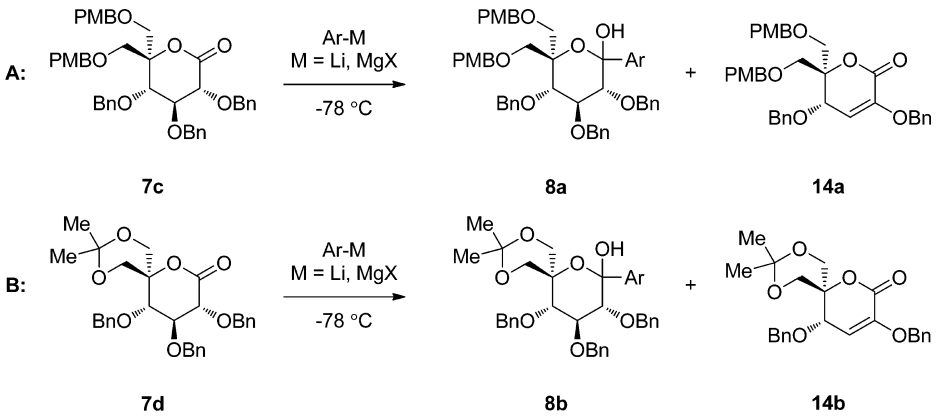
Attempted Arylation of Lactones 7. Next, the open-chain protected amide utilized in the original medicinal chemistry synthesis (i.e., Weinreb amide **2**) was converted to lactone **7c** via selective deprotection of the PMB ethers followed by acid-catalyzed lactonization. While clearly not a feasible long-term strategy, owing to the large number of steps associated with preparation of amide **2**, this allowed for quick evaluation of lactones of type **7** in the key arylation reaction (Scheme 4, reaction A). Surprisingly, reaction of **7c** with aryl anions failed to provide the desired C-aryl glycoside **8a**; unsaturated lactone **14a** was the only product identified. In silico models suggested the additional substitution at C5 may be blocking approach of the bulky aryl nucleophile, although

dx.doi.org/10.1021/op4002802 | Org. Process Res. Dev. 2014, 18, 66−81

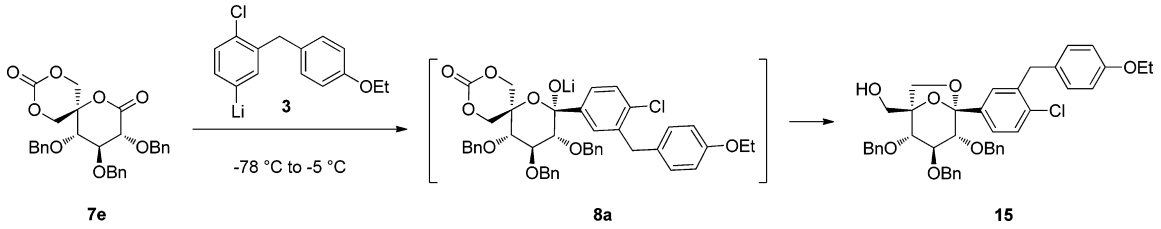
Scheme 3. Attempted preparation of 7b from methyl-D-glucopyranose



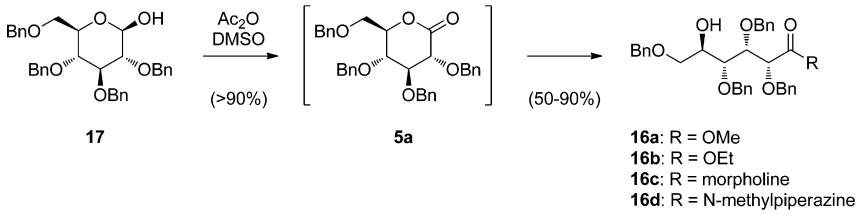
Scheme 4. Arylation attempts with C6-substituted gluconolactone derivatives



Scheme 5. Arylation attempts with cyclic carbonate 7e



Scheme 6. Preparation of open-chain substrates



challenges in accomplishing nucleophilic aryl anion addition to gluconolactones lacking a C5 substituent have also been documented.[20]

To test the hypothesis regarding steric hindrance, the PMB groups on **7c** were removed to provide diol **7b**, which was subsequently converted to the corresponding dimethylacetonide **7d** (Scheme 4, reaction B). Models now suggested at least one face of the lactone carbonyl was accessible for attack by aryl nucleophiles, but multiple attempts yielded only elimination product **14b**.

Cyclic carbonate **7e** was then prepared from diol **7b** and CDI, albeit in very low yield. This lactone was also evaluated in a handful of arylation reactions (Scheme 5). Interestingly, addition of aryllithium **3** to **7e** provided desired C1 addition product **8a**; no elimination product was observed. Furthermore, the intermediate alkoxide **8a** partially converted to the bridging ether **15** prior to quench. While this was clearly a breakthrough for the "lactone approach" to API **1**, carbonate **7e** proved to be very difficult to prepare from diol **7b** or other reasonable precursors.[21] Furthermore, the long, linear sequences required to access carbonate **7e** from a suitable chiral pool source made this strategy impractical for large scale.

The addition of a hydroxymethyl substituent at C5 of the gluconolactone (e.g., **7**) has a profound impact on the outcome of this arylation reaction (Scheme 1, approach C). We turned focus to acyclic analogues of the carbohydrate (i.e., gluconamides such as **2**), according to precedented reactivity from the first-generation synthesis (Scheme 1, approach A).

Evaluation of D-Gluconic Acid Derivatives. Various D-gluconic acid analogues **16a–d** were prepared via the two-step sequence illustrated in Scheme 6. Benzyl protecting groups were chosen for their ability to tolerate a broad range of reaction conditions, the extensive precedent in carbohydrate chemistry, and the relative ease of their removal via hydrogenolysis.[22] Thus, compound **17** was converted to lactone **5a** under modified Swern conditions in nearly quantitative

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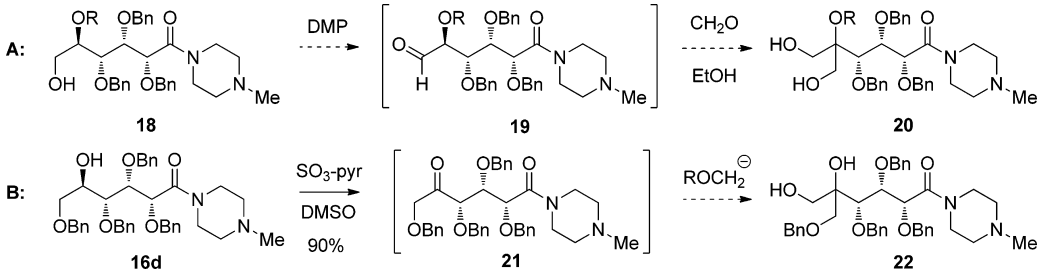
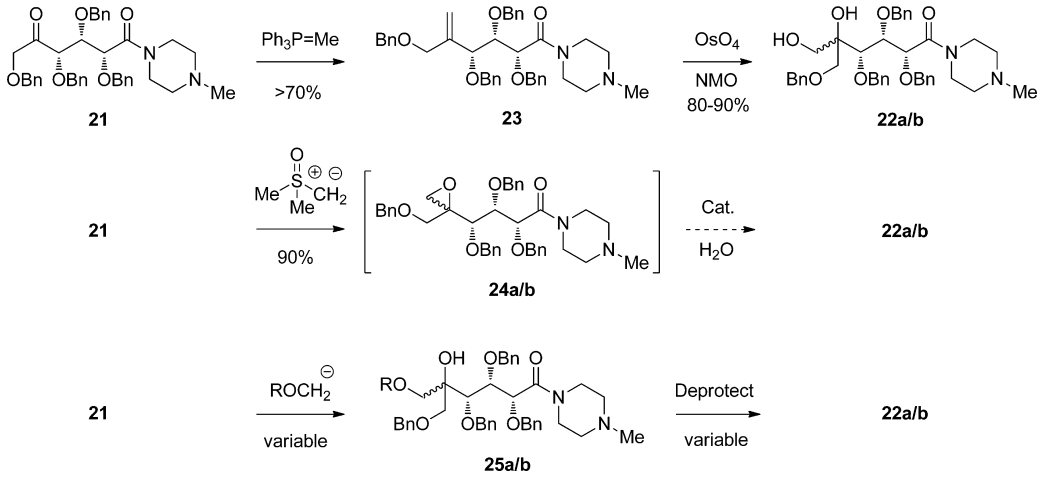
Scheme 7. Complementary hydroxymethylation strategies



Scheme 8. Nucleophilic hydroxymethylation of ketoamide 21



yield.[23] A range of oxidants was evaluated for this transformation; TPAP-NMO[24] and TEMPO-NaOCl[9] are among the conditions that have been reported, and these were also effective on laboratory scale. Lactone **5a** was then converted to esters **16a** and **16b**, or amides **16c** and **16d**, by treatment with the appropriate alcohol or amine, respectively. Compounds were selected for their presumed reactivity in the downstream aryl anion addition step.[25−27] As anticipated, hydroxyesters **16a** and **16b** converted back to lactone **5a** at an appreciable rate—even during storage as isolated oils held under refrigeration. The morpholine amide **16c** was significantly more stable in its open-chain form but was a thick oil that resisted crystallization despite considerable effort. The methylpiperazine derivative **16d**, containing a basic tertiary nitrogen, was prepared to enable salt formation that could render the compound crystalline and easier to handle. Fortuitously, **16d** was found to be a crystalline solid as its free base at ambient temperature, requiring no salt formation for its isolation.

Introducing the Key Hydroxymethyl Substituent. With a reliable supply of hydroxyamide **16d** in hand, the key imperative became introduction of the hydroxymethyl substituent. Two complementary approaches for this transformation were considered (Scheme 7). The first (approach A) required selective oxidation of the C6 primary alcohol of **18** to the corresponding aldehyde **19**.[28] The resulting compound could then participate in an aldol condensation with formaldehyde. Utilization of a stoichiometric excess of formaldehyde would promote Cannizzaro-type in situ reduction of the aldehyde and lead to the desired diol **20**.[7] Challenges associated with this strategy were quickly realized. Perhaps most disconcerting was the relative incompatibility of the gluconic acid derivatives to the alkaline conditions required for the hydroxymethylation. Elimination, retro-aldol, and hydrolysis byproducts were observed. Furthermore, the oxidation step was not straightforward, as formation of the carboxylic acid (i.e., overoxidation product) was difficult to control. In parallel with efforts on "electrophilic hydroxymethylation" (i.e., formaldehyde as a source of CH_2−OH) was a study of alternative "nucleophilic" strategies (i.e., $ROCH_2$-M) for hydroxymethylation to convert ketoamide **21**, obtained from secondary alcohol **16d** via Parikh−Doering[29] oxidation, to diol **22** (Scheme 7, approach B).

Ketoamide **21** proved to be a versatile intermediate, as several options were successfully demonstrated in the laboratory for preparation of diol diastereomers **22a/b** (Scheme 8). Although not ideal for large scale, the two-step sequence involving Wittig methylenation, followed by dihydroxylation with OsO_4 provided **22a/b** in excellent overall yield. Treatment of ketoamide **21** with the Corey−Chaykovsky reagent[30] provided the corresponding epoxide **24a/b** in reasonable unoptimized yield; however, a brief study aimed at further conversion to diol **22a/b** was unsuccessful.[31]

Critical Evaluation of Hydroxymethyl Anion Equivalents. The third, and ultimately most successful "nucleophilic hydroxymethylation" approach studied, involved reaction of **21** with a one-carbon nucleophile to install the protected hydroxymethyl group, providing tertiary alcohol **22a/b** after removal of the primary hydroxyl protecting group from **25a/b**.

Numerous hydroxymethyl anion synthons are precedented,[32−36] but most have significant drawbacks, including:

(1) Cryogenic reaction temperatures are often required due to poor solution stability of the hydroxymethyl anions.
(2) Precursors to the anions are often toxic and/or mutagenic alkyl halides.

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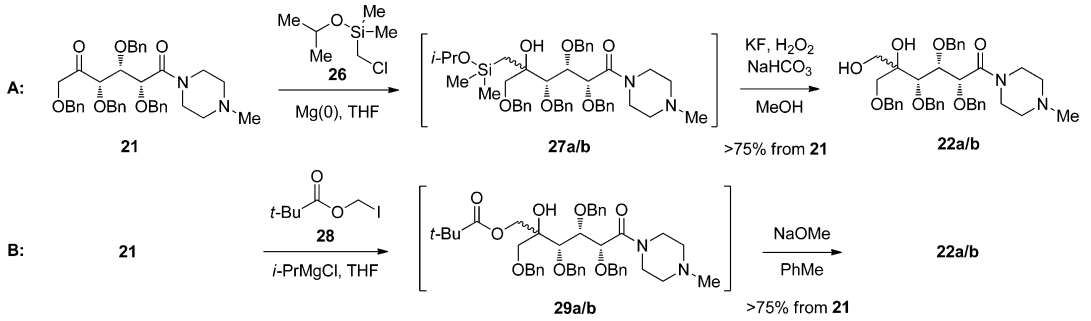
Scheme 9. "Nucleophilic" hydroxymethylation via Grignard reagents



Scheme 10. Preparation of crystalline intermediates 30a/b·oxalate and 30a free base

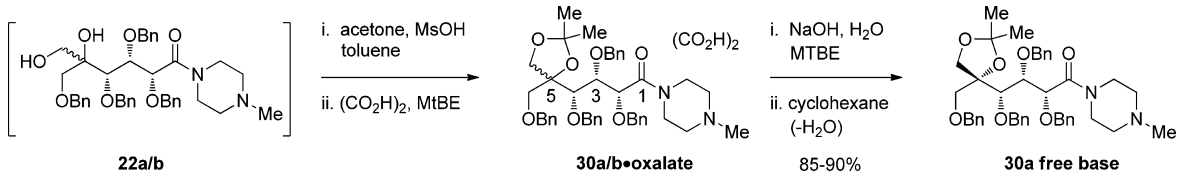
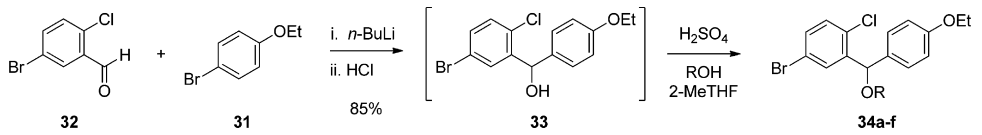


Table 1. Preparation of aryl bromide pre-nucleophiles



entry	ether **34**	R	isolated yield[a]	MP (°C)[b]
1	**34a**	Et	98.8	40.0
2	**34b**	*i*-Pr	74.3	54.2
3	**34c**	*n*-Bu	79.0	35.7
4	**34d**	Ph	0[c]	N/A
5	**34e**	Bn	88.6	62.3
6	**34f**	$Ph(CH_2)_2$	80.5	56.3

[a]Yields for conversion of **33** to **34a–f**. [b]Melting point onset determined by DSC. [c]The major product was Friedel–Crafts C4-alkylation of PhOH.

(3) Analytical characterization and in-process controls (IPCs) are challenging to develop and implement in a manufacturing environment.
(4) The additional step required to liberate the alcohol is often incompatible with sensitive functionality in the reaction product.

Nevertheless, precedented reagents for nucleophilic hydroxymethylation were evaluated, concentrating on those with the greatest potential for success in large-scale applications. An effective reagent would need to be highly chemoselective (for ketone vs amide) and liberate the desired diol under mild conditions in order to avoid epimerization or decomposition of the labile product. While no single reagent satisfied all criteria, it was determined that two deserved additional consideration (Scheme 9).

The first Grignard reagent evaluated is derived from chloromethylsiloxane **26** (Scheme 9, Option A).[37] This Grignard exhibits excellent solution-stability and exquisite selectivity for addition to the ketone function of ketoamide **21**. At a typical reaction temperature near −20 °C, intermediate **27a/b** was prepared as a 3:2 mixture of diastereoisomers (favoring the 5*R* isomer), but both compounds converge to a single product later in the synthesis. Tamao–Fleming oxidation liberates the masked diol isomers **22a/b**.[36,38−41] The second method involves the Grignard reagent derived from iodomethyl pivalate **28** (Scheme 9, option B). Developed largely by Knochel and co-workers,[35] this chemistry is applicable to a broad range of electrophiles. The reagent is prepared via Grignard exchange with *i*PrMgCl at low temperature. This reagent also showed excellent selectivity for addition to the ketone of **21**, providing the intermediate pivalate ester **29a/b** as the exclusive addition product. Interestingly, this reagent exhibits high facial selectivity at −78 °C, providing a 95:5 mixture of diastereoisomers at C5, favoring the 5*R* isomer, **29a**. The diols **22a/b** could be liberated by reaction with solid NaOMe in toluene or cyclopentyl methyl ether (CPME). The two nucleophilic hydroxymethylation processes performed in comparable yield during laboratory trials, providing **22a/b** from **21** in ∼75% overall yield.

Preparation of Piperazine Amide 30a/b·Oxalate. Many attempts to protect diols **22a/b** in advance of the arylation step failed, presumably due to steric hindrance surrounding the tertiary alcohol. Success was eventually realized, however, by forming the dimethylacetonide **30a/b** with acetone or DMP in the presence of MsOH or *p*-TsOH (Scheme 10). The diastereomeric mixture of products **30a/b** was found to be a sticky oil, and thus a salt was formed between the basic tertiary nitrogen of **30a/b** and oxalic acid. The identification of a stable crystalline intermediate at this point in the synthesis was a critical breakthrough, as this allowed for effective purge of

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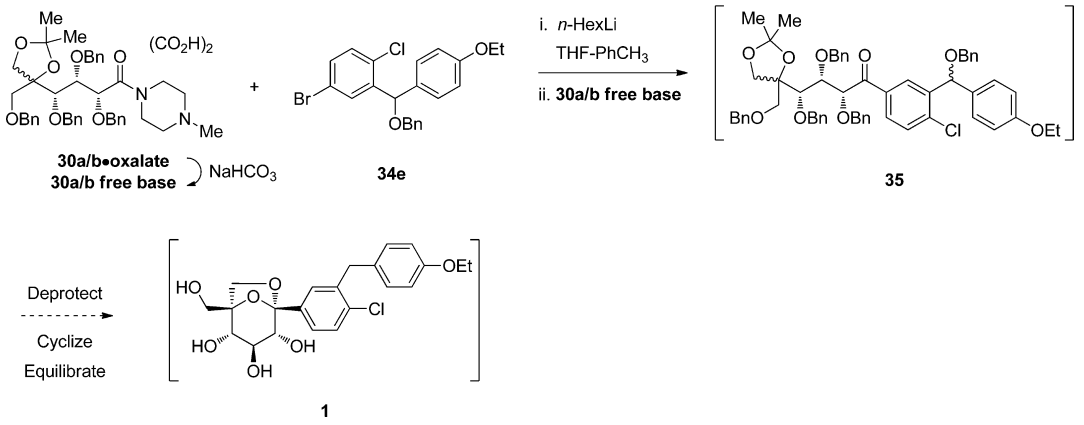
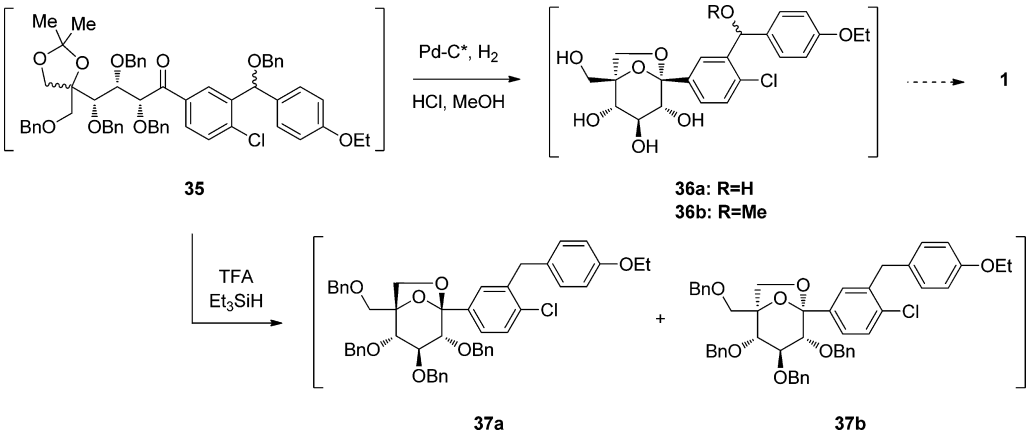
Scheme 11. Preparation of amorphous ertugliflozin (1)



Scheme 12. Options for deprotection/cyclization of 35



process-related impurities such as minor C2 and C4 diastereoisomers (resulting from epimerization during processing), unreacted starting materials, reactants, and reagents, and inorganic materials. The upgrade in purity immediately before the key convergent (i.e., arylation) step also translated to increased process performance in the end-game operations. Interestingly, neutralization of the **30a**/**b** oxalate salt with aqueous NaOH in MTBE, followed by removal of water via azeotropic distillation with cyclohexane, provided the crystalline free base **30a** (5*R* diastereomer) as the exclusive product. Both Grignard options A and B (Scheme 9) were effective in producing **30a** via this protocol.

Identification of an Optimal Aryl Bromide. With a crystalline amide intermediate in hand, we turned our attention to identification of a suitable aryl pre-nucleophile. We desired a compound that could be prepared via a short, scale-friendly synthetic sequence and offered excellent crystallinity and stability that allowed for bulk preparation and long-term storage, since we envisioned this building block would serve as one of two regulatory starting materials if the synthesis was commercialized. After an evaluation of several related building blocks, we decided to target benzhydryl ethers, as described in Table 1.[42] The two-step, one-pot sequence begins by halogen metal exchange between 1-bromo-4-ethoxybenzene **31** and an alkyllithium (e.g., *n*-BuLi or *n*-HexLi), or via Grignard formation, to provide the corresponding aryl anion. This intermediate is combined with 5-bromo-2-chlorobenzaldehyde **32** to afford benzhydryl alcohol **25** in excellent yield, as determined by UHPLC/MS analysis. Intermediate **33** may be isolated or treated directly with an alcohol in the presence of H_2SO_4 to provide the corresponding benzhydryl ethers **34a**–**f**. Evaluation of the properties of each, and performance in the subsequent reaction with amide **30**, led us to selection of the benzyl-protected ether **34e** for further development. Both batch and flow reactor options have been demonstrated for the preparation of ether **34e** on multigram scale.

Preparation of Aryl Ketone 35. In order to complete the synthesis of ertugliflozin, the crystalline salt **30a**/**b**·oxalate was first converted to the corresponding free base.[43] Although the 5*R* isomer **30a** could be isolated as a crystalline solid from cyclohexane (Scheme 10), both diastereomers were equally effective in downstream chemistry, so isolation was typically avoided. Instead, a solution of **30a**/**b** was dried via azeotropic distillation with toluene and then was reacted with the aryl anion obtained by treatment of aryl bromide **34e** with *n*-BuLi or *n*-HexLi in THF (Scheme 11).[44,45] Only monoaddition to amide **30a**/**b** was observed, even when multiple equivalents of aryl anions were employed. Computational modeling suggests strong stabilization of the tetrahedral intermediate, formed upon addition of the aryl anion, via intramolecular chelation to both C2- and C3-benzyloxy substituents.[46] It should also be noted that no detectable epimerization of the C2 stereocenter was observed in this step. Following an acidic quench and aqueous partition, a complex mixture of diastereomers **35** was obtained due to the presence of a racemic stereocenter at the benzhydryl ether and a variable mixture of isomers created in the hydroxymethylation.[47] The complex mixture of isomers presumably contributes to the undesirable physical properties

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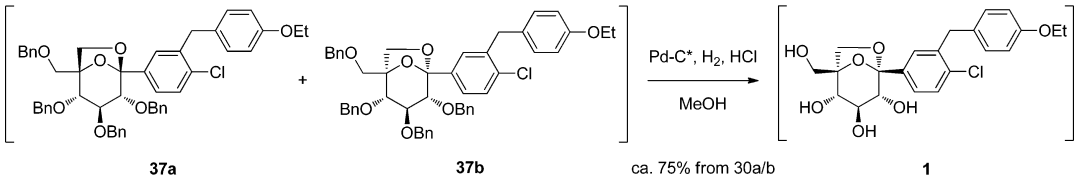
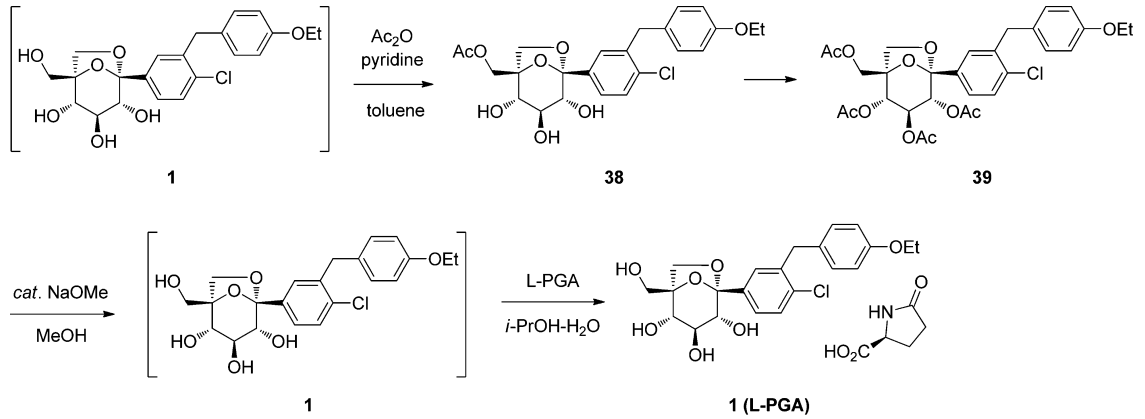
Scheme 13. Conversion of 37a/b to 1



Scheme 14. Preparation of cocrystalline 1·L-PGA



of this compound, rendering it a gummy oil after silica gel chromatography. As a result, this material was not isolated, but was carried directly into subsequent steps as a solution.

Evaluation of Deprotection and Glycosylation Sequences. The aryl ketone **35** is an open-chain, fully protected form of the final synthetic target **1**. Several strategies were evaluated for sequential removal of the acetonide, benzyl ethers, and benzhydryl substituent, with a focus on balancing chemical yields and product purity profile with overall process efficiency (Scheme 12).[48] The most attractive option involved global deprotection and ether formation/thermodynamic equilibration in a single step. Thus, **35** was subjected to catalytic hydrogenolysis under acidic conditions. It was found that the benzyl ethers and acetonide were cleaved readily, and near-complete etherification resulted, but a mixture of benzhydryl alcohols **36a** and methyl ethers **36b** were obtained. Attempts to cleave these benzhydryl substituents under more forcing hydrogenolysis conditions led to competitive reduction of the aryl chloride, as well as C2 epimerization and traces of C1 reduction. Treatment of the mixture with various reducing agents, with and without acid catalysis, produced desired product **1** with modest purity. Therefore, we chose a more conservative, stepwise approach for our end-game. Treatment of crude solutions of **35** with a mild hydride source (e.g., Et_3SiH) in the presence of an acid (e.g., TFA) led to deprotection of both the acetonide and benzhydryl ethers, affording a mixture of two diastereomers **37a/b**. This mixture could not be readily isolated and purified via crystallization, as it was found to exist as a semisolid. As a result, this intermediate was also used directly in subsequent steps as a crude solution.

Fortunately, both isomers **37a/b** converged to the desired target compound **1** during removal of the benzyl groups via metal-catalyzed hydrogenolysis under acidic conditions (Scheme 13). In the absence of acid, the debenzylation proceeded smoothly, but a mixture of bridging ether diastereoisomers of **1** was obtained. Treatment of this mixture with HCl promoted equilibration of the bridging ethers, providing the desired isomer of **1** as the only detectable product. Analysis of the crude reaction mixture against a purified standard of **1** confirmed >75% overall yield for the three-step sequence.

Preparation of a Crystalline Analogue for Purity Upgrade. Unfortunately, utilization of the crude stream of **1** produced via this sequence yielded cocrystal with unacceptable chemical purity for pharmaceutical applications. Therefore, opportunities for derivatization of **1** that would enable purification via crystallization without adding excessive cost or complexity were targeted.[49] Both the primary monoacetate **38** and tetraacetate derivative **39** were prepared by reaction with the appropriate stoichiometric quantity of Ac_2O or AcCl and a suitable base (e.g., NMI, pyridine, or iPr_2NEt) (Scheme 14).[50] The acetate products could be recrystallized to high purity from a range of solvents (e.g., *i*PrOH, MeOH). Several related compounds (e.g., pivalate, benzoate) were also prepared via analogous protocols, but the low cost, high crystallinity, and reasonably low molecular weight of the acetates made them the most sensible choice for large-scale use. Furthermore, the crystallization processes for isolation of **38** and **39** were found to be particularly effective at purging process-related impurities to very low levels. Since formation of monoacetate **38** required strict control of parameters that could prove challenging on large scale, tetraacetate **39** was pursued for further optimization.

Preparation of Ertugliflozin (1)·L-PGA. Following the purity upgrade offered by isolation of **39**, acetate groups were removed with catalytic NaOH or NaOMe, providing a fairly pure solution of **1**. Despite extensive screening, a crystalline free form of ertugliflozin (**1**) has not been identified. This compound exists as a hygroscopic amorphous solid with a low glass transition temperature. Since the compound is also nonionizable near physiological pH, salt forms were not pursued as a viable option. Instead, ertugliflozin (**1**) was subjected to solvate and cocrystal form screening. Only two crystalline forms have been identified: L-proline and L-pyroglutamic acid (L-PGA) cocrystals. As the L-PGA cocrystal

dx.doi.org/10.1021/op4002802 | Org. Process Res. Dev. 2014, 18, 66−81

proved to possess superior physical properties, it became the focus of further development.

Thus, the crude solution of ertugliflozin (**1**) was converted to its L-PGA cocrystal by combination with L-PGA acid in a mixture of *i*PrOH and water. Despite the miscibility of these two solvents under normal circumstances, the presence of **1** and L-PGA leads to an interesting biphase. The more hydrophobic **1** resides primarily in *i*-PrOH droplets, while the polar L-PGA resides in the aqueous phase. Cocrystallization occurs with high efficiency at the interface (Figure 3). The

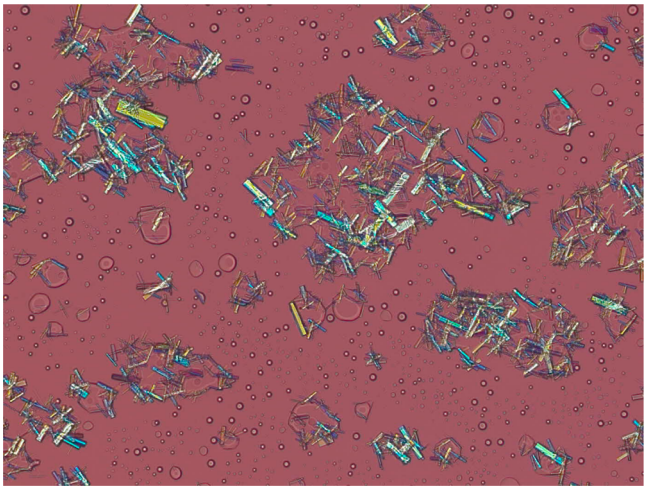


Figure 3. Biphasic cocrystallization of ertugliflozin (**1**)·L-PGA.

cocrystalline product is driven from this biphase in high yield by use of a stoichiometric excess of L-PGA. A reslurry in either toluene or acetonitrile provides cocrystalline **1**·L-PGA complex of high analytical purity and with an approximate stoichiometric ratio of 1:1 (**1**:L-PGA).

■ CONCLUSION

In conclusion, an efficient, stereoselective synthesis of SGLT2 inhibitor candidate ertugliflozin (**1**) was identified and developed (Scheme 15). The 12-step process starts from tetra-*O*-benzyl-D-glucose **17** and includes only three isolated intermediates (**16d**, **30a**/**b**·oxalate, and **39**) over the longest linear sequence, due to a lack of crystallinity of most intermediates. Highlights of this process include two regioselective, scale-friendly options for nucleophilic hydroxymethylation of ketogluconamide **21**, a highly efficient arylation of piperazine amide **30a**/**b** as the key convergent step, a global acid-promoted deprotection sequence that allows multiple isomers to converge at a single desired product, and the use of the highly crystalline late-stage tetraacetate **39** to purge process-related impurities prior to isolation of the final cocrystalline ertugliflozin (**1**)·L-PGA complex.

■ EXPERIMENTAL SECTION

General. All starting materials were prepared by Pfizer Chemical Research and Development (Groton, CT). All reactions were monitored by reverse phase UHPLC using a Waters Acquity LC/PDA/SQD equipped with a CSH phenylhexyl (100 mm × 2.1 mm, 1.7 μm) column with a column temperature of 45 °C and a flow rate of 0.4 mL/min. A 30-min linear gradient was employed, with initial conditions of 95% aqueous trifluoroacetic acid and 5% acetonitrile and final conditions of 100% acetonitrile. Approximate retention times (min): **30a**/**b** (13.3−13.5), **34e** (20.1), **35** (25.2−25.6), **37a**/**b** (23.4−23.6), **1** (10.6), **38** (12.6), **39** (17.3).

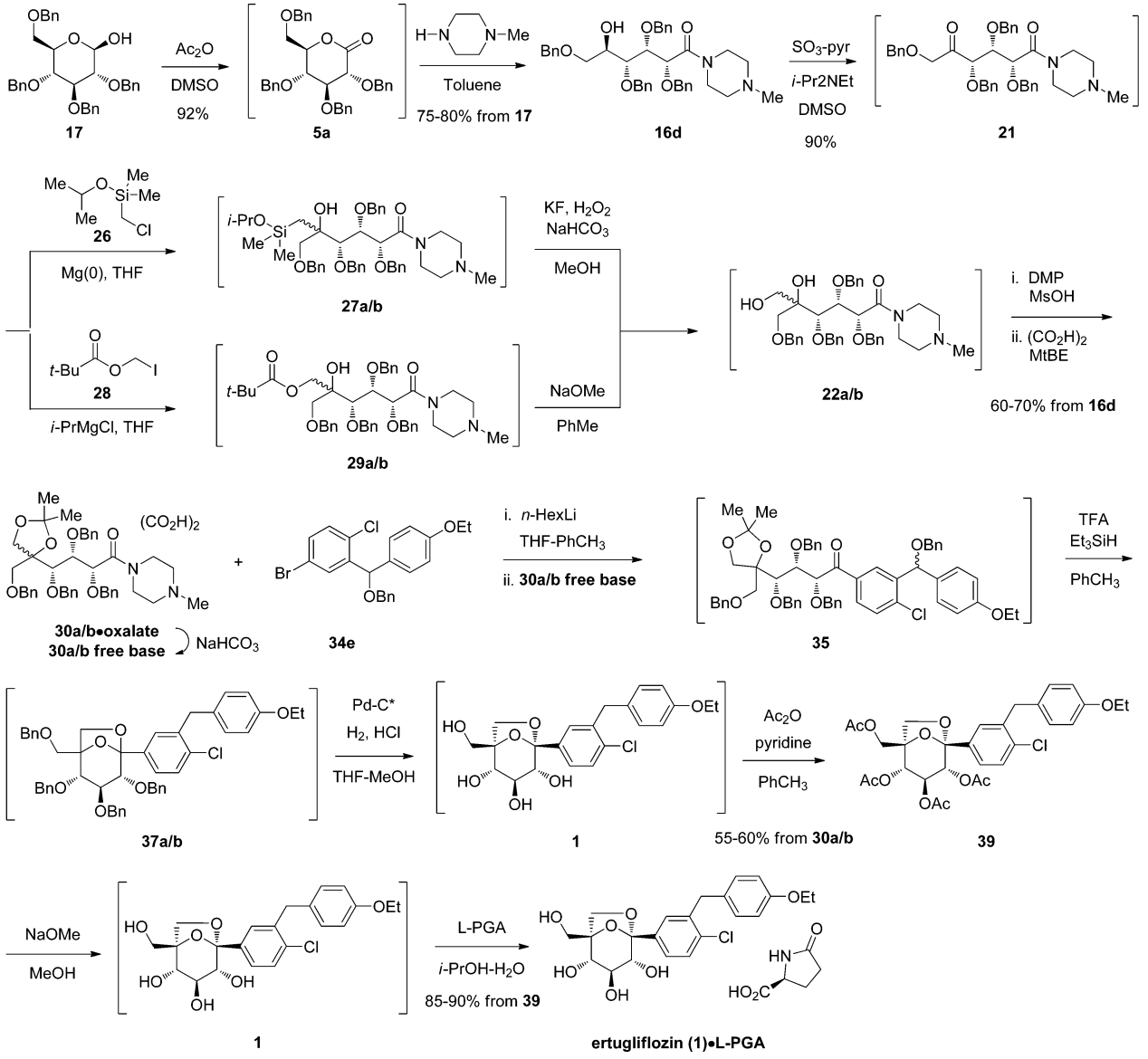
The powder X-ray diffraction patterns of monoacetate **38** (Figure 2) and tetraacetate **39** (Figure 3) were carried out on a Bruker AXS - D8 Advance diffractometer using Cu radiation source. The tube voltage and amperage were set to 40 kV and 40 mA, respectively. The divergence slit was fixed at 1 mm, whereas the scattering and the receiving slits were set at 0.6 mm. Diffracted radiation was detected by a scintillation counter detector. Data were collected in the $\theta-\theta$ goniometer at the Cu wavelength Kα_1 = 1.54056 Å from 3.0° to 40.0° 2θ using a step size of 0.040° and a step time of 2.0 s. Samples were prepared by placement in a Nickel Disk (Gasser & Sons, Inc. Commack, NY) and rotated during data collection. Data were collected and analyzed using Bruker Diffrac Plus software (Version 2.6). Bruker AXS DIFFRACplus Basic EVA 12 software was used to visualize and evaluate the PXRD diffractograms. PXRD data files (.raw) were not processed prior to peak searching. Generally, a threshold value of 2.0 and a width value of 0.3 were used to make preliminary peak assignments. The results are summarized in the Supporting Information.

(3*R*,4*S*,5*R*,6*R*)-3,4,5-Tris(benzyloxy)-6-((benzyloxy)-methyl)tetrahydro-2*H*-pyran-2-one (5a). A solution of 2,3,4,6-tetra-*O*-benzyl-D-glucopyranose **17** (25.0 g) in dimethyl sulfoxide (100 mL, 4 L/kg) was stirred at 20−25 °C for 30 min under a nitrogen atmosphere. Acetic anhydride (75 mL, 3 L/kg) was added at a rate of 5 mL/min (∼15 min) at 15−25 °C. After complete addition, the reaction mixture was stirred for 18−24 h at 20−25 °C. After complete reaction was confirmed by UHPLC/MS analysis, the reaction mixture was diluted with toluene (225 mL, 9 L/kg) and a 3.3N aqueous solution of HCl (225 mL, 9 L/kg) was slowly added to quench the excess acetic anhydride. The reaction mixture was stirred for 20 min at 20−25 °C to complete this quench. The phases were separated, the aqueous layer was discarded, and the organic layer was washed with a 2 M aqueous phosphate buffer (pH 7, 225 mL, 9 L/kg). After stirring for 20 min at 20−25 °C, the phases were separated, and the organic layer was dried over sodium sulfate (as needed) and filtered. Analysis of the filtrate indicated 26.9 g of lactone **5a** was present (924 mg/g potency, 94.6% purity, 92% yield).

(2*R*,3*S*,4*R*,5*R*)-2,3,4,6-Tetrakis(benzyloxy)-5-hydroxy-1-(4-methylpiperazin-1-yl)hexan-1-one (16d). A solution of tetra-*O*-benzyl gluconolactone **5a** (14.7 wt/wt%, 50 g) in toluene (340 g total solution mass) was stirred at 20−25 °C under nitrogen. *N*-Methylpiperazine (23.24 g, 2.5 equiv) was then added at a rate of ∼0.5 mL/min (∼52 min) at ≤30 °C. After complete addition, the reaction mixture was stirred at 20−25 °C for 18 h. Complete reaction was confirmed by UHPLC/MS analysis, and then water (250 mL, 5 L/kg) was added, the biphasic mixture was stirred for 20 min at 20−25 °C, and then the aqueous layer was discarded. After a second identical treatment with water (250 mL, 5 L/kg), heptane (500 mL, 10 L/kg) was added at a rate of 10 mL/min to produce a slurry. After complete addition, the slurry was cooled to 10−15 °C and stirred for at least 30 min. Solids were collected on a Büchner funnel, rinsed with heptane (100 mL, 2 L/kg), and dried under vacuum at 40 °C for 12−18 h to provide **16d** (59.3 g) as a white solid (MP = 94−95 °C). UHPLC-MS: Potency 914 mg/g, purity 96.7%, 76.2% from **17**. ^{1}H NMR (DMSO-d_6, 400 MHz, 25 °C): δ 7.44−7.13 (m, 20H), 5.10 (d, J = 5.6 Hz, 1H), 4.68 (s, 2H), 4.64−4.42 (m, 7H), 4.17 (dd, J = 6.6, 4.2

dx.doi.org/10.1021/op4002802 | *Org. Process Res. Dev.* 2014, 18, 66−81

Scheme 15. Preparation of ertugliflozin (1)·L-PGA



Hz, 1H), 3.96−3.84 (m, 1H), 3.72−3.60 (m, 2H), 3.60−3.39 (m, 5H), 2.28 −2.00 (m, 4H), 2.08 (s, 3H). ^{13}C NMR (DMSO-d_6, 101 MHz, 25 °C): δ 167.2, 138.7, 138.7, 138.4, 137.8, 128.2, 128.2, 128.1, 128.1, 127.8, 127.7, 127.6, 127.5, 127.4, 127.3, 127.2, 79.8, 79.8, 79.5, 74.6, 73.1, 72.4, 71.6, 71.5, 69.5, 54.6, 54.3, 45.5, 44.6, 41.6. HRMS: (ESI$^+$) Calcd for $C_{39}H_{47}N_2O_6$ (M + H)$^+$: 639.34286, Found: 639.34228.

(2*R*,3*S*,4*S*)-2,3,4,6-Tetrakis(benzyloxy)-1-(4-methylpiperazin-1-yl)hexane-1,5-dione (21). To a pale-yellow solution of **16d** (154 g, 241.1 mmol) in toluene (462 mL, 3 L/kg,) and DMSO (308 mL, 2 L/kg) under nitrogen was charged *N*,*N*-diisopropylethylamine (186.9 g, 252 mL, 1446 mmol,) at 20−25 °C. After this addition, the hazy solution was cooled to 5 °C. A solution of sulfur trioxide pyridine complex (76.74 g, 482.2 mmol) in DMSO (308 mL, 2 L/kg) was then added at ≤15 °C (ca. 30 min addition time). The reaction mixture was stirred at 5−10 °C until complete conversion was confirmed by UHPLC-MS analysis. Toluene (462 mL, 3 L/kg) was then added, followed by the slow addition of ammonium hydroxide (5% w/w in water, 924 mL, 6 L/kg). Following complete addition, the mixture was stirred for 10 min at 20−25 °C (pH 10−11), and then the phases were separated. The organic phase was washed with saturated aqueous sodium chloride (462 mL, 3 L/kg) and then was concentrated under vacuum to ∼450 mL. Toluene (924 mL, 6 L/kg) was added, and the solution was concentrated under vacuum to ∼770 mL (water content ≤0.06% per KF analysis). A solution potency measurement (UHPLC/MS) indicated 90% yield for ketone **21**. The bulk crude product was utilized directly in the subsequent step; however, a small portion of the mixture was removed and concentrated for characterization of ketone **21** (semisolid). ^{1}H NMR (DMSO-d_6, 400 MHz, 25 °C): δ 7.07−7.45 (m, 20H), 4.28−4.70 (m, 8H) 4.43 (d, J = 11.3 Hz, 1H), 4.50 (d, J = 11.3 Hz, 1H), 4.54 (d, J = 11.3 Hz, 1H), 4.66 (d, J = 11.3 Hz, 1H), 4.23 (dd, J = 5.9, 4.0 Hz, 1H), 3.24−3.60 (m, 4H), 1.94−2.27 (m, 4H), 2.08 (s, 3H). ^{13}C NMR (DMSO-d_6, 101 MHz, 25 °C): δ 206.0, 166.8, 137.8, 137.7, 137.6, 137.4, 128.3, 128.2, 128.2, 128.2, 127.9, 127.9, 127.7, 127.7, 127.5, 127.5, 81.6, 79.9, 77.4, 73.8, 73.6, 72.8, 72.1, 71.4, 54.6, 54.2, 45.4, 44.6, 41.5. HRMS: (ESI$^+$) Calcd for $C_{39}H_{44}N_2O_6Na$ (M + Na)$^+$: 659.30916, Found: 659.30872.

dx.doi.org/10.1021/op4002802 | *Org. Process Res. Dev.* 2014, 18, 66−81

(2*R*,3*S*,4*S*)-2,3,4-Tris(benzyloxy)-4-(4-((benzyloxy)-methyl)-2,2-dimethyl-1,3-dioxolan-4-yl)-1-(4-methylpiperazin-1-yl)butan-1-one oxalate (30a/b). ***30a:30b*** *(1.4:1) via Grignard Option A. Grignard.* A suspension of magnesium filings (16.72 g, 687.8 mmol) in dry THF (366 mL) was heated to 65 °C with high agitation under an atmosphere of nitrogen. 1,2-Dibromoethane (3.88 g, 20.63 mmol) was then added over 5 min, followed by the slow addition of chloromethyl dimethylisopropoxysilane **26** (86.01 g, 515.9 mmol) in THF (86 mL).

CAUTION: An exotherm of 2 °C occurred during the first 20% of the addition. This exothermic event could be considerably greater if the induction period is extended and accumulation occurs; thus, an addition period of at least 30 min is advisable, along with suitable headspace in the reaction vessel to account for foaming and rapid boiling.

Following complete addition of silane **26**, the reaction was stirred for 1.5 h at 65 °C. GC analysis of an aliquot that had been quenched into isopropyl alcohol and filtered indicated <2% **26** remaining. The solution of Grignard reagent thus prepared was then cooled to −25 °C for immediate use in the next step. Alternately, this solution (1.0−1.1M) was stored between 5 and 25 °C for up to 4 days with no significant loss of potency.

To the solution of Grignard (515.9 mmol) was added a solution of **21** (146 g, 229.3 mmol) in cyclopentyl methyl ether (CPME) (292 mL) at ≤15 °C. Following complete addition, the reaction was stirred for an additional 30 min at −20 °C, and then analysis by UHPLC/MS confirmed complete conversion to methylsilane adduct **27a/b** (target specification ≤2% **21**). The reaction was quenched by the slow addition of saturated aqueous ammonium chloride (365 mL) and then was diluted with water (365 mL) and CPME (438 mL). The temperature was allowed to warm to a maximum of 5 °C during the addition and was further warmed to 20 °C after complete addition. The mixture was filtered to remove any remaining Mg residues, and then the phases were separated. The organic phase was washed with water (365 mL) and then analyzed for potency of **27a/b**. The bulk crude product was utilized directly in the subsequent step; however, a small portion of the mixture was removed and concentrated for characterization of **27a/b** (semisolid). ^{1}H): δ (DMSO-d_6, 600 MHz, 25 °C): δ 7.39−7.14 (m, 20H), 4.80 (d, J = 11.5 Hz, 0.5H), 4.73 (d, J = 11.5 Hz, 1H), 4.63−4.36 (m, 7.5H), 4.24 (dd, J = 5.1, 4.4 Hz, 0.5H), 4.04 (b, 1H), 3.92 (sep, J = 6.1 Hz, 0.5H), 3.86 (sep, J = 6.1 Hz, 0.5H), 3.70 (b, 1H), 3.66 (d, J = 4.4 Hz, 0.5H), 3.53−3.45 (b, 2H), 3.53 (d, J = 9.1 Hz, 0.5H), 3.49 (d, J = 9.3 Hz, 0.5H), 3.45 (d, J = 9.3 Hz, 0.5H), 3.42 (d, J = 9.1 Hz, 0.5H), 3.35 (b, 1H), 2.26−2.08 (b, 4H), 1.11 (d, J = 14.9 Hz, 0.5H), 1.04−0.99 (m, 1H), 1.04 (d, J = 6.1 Hz, 1.5H), 1.03 (d, J = 6.1 Hz, 1.5H), 1.00 (d, J = 6.1 Hz, 1.5H), 0.99 (d, J = 6.1 Hz, 1.5H), 0.09 (s, 1.5H), 0.06 (s, 3H), 0.05 (s, 1.5H). ^{13}C NMR (DMSO-d_6, 150.8 MHz, 25 °C): δ 167.60, 167.50, 139.33, 139.02, 138.67, 138.56, 138.29, 138.23, 138.08, 137.66, 128.16, 128.12, 128.08, 128.07, 128.00, 127.97, 127.93, 127.80, 127.78, 127.75, 127.72, 127.64, 127.55, 127.41, 127.39, 127.28, 127.19, 127.09, 126.97, 82.02, 81.67, 81.49, 78.60, 77.94, 76.95, 76.02, 75.40, 74.78, 74.56, 73.67, 73.53, 73.38, 73.15, 72.52, 72.27, 71.99, 71.69, 64.07, 63.96, 54.77, 54.68, 54.33, 45.50, 44.53, 44.31, 41.65, 41.58, 25.71, 1.14. HRMS: (ESI$^+$) Calcd for $C_{45}H_{61}N_2O_7Si$ (M + H)$^+$: 769.42428, Found: 769.42377.

Oxidation. The crude solution of **27** prepared above (115 g, 149.5 mmol) in THF/CPME (575 mL) was adjusted to a concentration of 5 L/kg by either addition of CPME or concentration at 35 °C (30−35 mbar). Methanol (517.5 mL) was then added, followed by KF (14.25 g, 245.3 mmol) and sodium bicarbonate (12.6 g, 149.5 mmol) at 20 °C. Hydrogen peroxide (35 mass % in water, 52 mL, 598 mmol) was then added dropwise over approximately 10 min.

CAUTION: The 35% hydrogen peroxide was diluted to 29% with water prior to addition for safety; an exotherm of 3 °C was observed during the addition of the diluted peroxide at this scale.

Following complete addition, the reaction was stirred for 18 h at 25 °C, and then analysis of a sample quenched into aqueous sodium bisulfite indicated complete conversion to diol **22a/b**[51] (target specification ≤2.5% **27a/b** or analogues[52]). The reaction was then slowly added to a solution of sodium bisulfite (77.81 g, 747.7 mmol) in water (575 mL) and stirred for 15 min.

CAUTION: This is a highly exothermic quench that must be carried out with caution. Precooling the quench mixture to 5 °C is recommended. The complete consumption of peroxide was confirmed with test strips before proceeding.

Following the quench operation, the reaction mixture was warmed to 20 °C, CPME (345 mL) was added, and the mixture was stirred for 15 min. The layers were then separated, the organic phase was washed with saturated aqueous NaCl (345 mL), and the solution was carefully concentrated under vacuum with a jacket temperature of 35 °C to 345 mL (3 L/kg). CPME (805 mL) was then added, and the solution was concentrated under vacuum with a jacket temperature of 35 °C to approximately 690 mL (6 L/kg, target specification KF ≤ 0.06%). In situ yield of **22a/b** (determined by UHPLC via comparison to a chromatographed standard) was typically >75%. The bulk crude product was utilized directly in the subsequent step; however, a small portion of the mixture was removed and concentrated for characterization of diol **22a/b** (semisolid). ^{1}H NMR (DMSO-d_6, 600 MHz, 25 °C): δ 7.38−7.16 (m, 20H), 4.74 (d, J = 11.5 Hz, 0.62H), 4.73 (d, J = 11.5 Hz, 0.38H), 4.70 (d, J = 11.3 Hz, 0.38H), 4.65 (d, J = 11.3 Hz, 0.62H), 4.59 (d, J = 11.3 Hz, 0.62H), 4.56 (d, J = 11.3 Hz, 0.76H), 4.55−4.45 (m, 4.62H), 4.44 (d, J = 11.5 Hz, 0.62H), 4.38 (d, J = 11.3 Hz, 0.38H), 4.30−4.27 (m, 1H), 3.97 (d, J = 5.3 Hz, 0.38H), 3.85 (d, J = 5.0 Hz, 0.62H), 3.72−3.38 (m, 8H), 2.32−2.11 (b, 4H), 2.13 (s, 1.14H), 2.11 (s, 1.86H). ^{13}C NMR (DMSO-d_6, 150.8 MHz, 25 °C): δ 167.73, 167.72, 139.8, 139.0, 138.70, 138.67, 138.6, 138.53, 137.84, 137.83, 128.17, 128.13, 128.12, 128.0, 128.00, 127.97, 127.81, 127.80, 127.8, 127.7, 127.6, 127.5, 127.4, 127.3, 127.23, 127.20, 127.1, 127.0, 82.1, 81.8, 78.3, 77.9, 76.3, 76.1, 73.8, 73.74, 73.69, 73.6, 72.7, 72.5, 72.01, 71.95, 71.7, 62.9, 62.8, 54.4, 54.1, 45.1, 44.2, 41.4. HRMS: (ESI$^+$) Calcd for $C_{40}H_{49}N_2O_7$ (M + H)$^+$: 669.35343, Found: 669.35321.

Acetonide and Oxalate Formation. To a solution of **22a/b** (100 g) in CPME (6 L/kg; 600 mL), prepared as described above, was added 2,2-dimethoxypropane (4 equiv; 62.29 g) at 20−25 °C. Methanesulfonic acid (2.5 equiv; 35.92 g) was added, and then the reaction was stirred at 20−25 °C for 30 min. Analysis by UHPLC indicated complete reaction (target specification ≤2% **22a/b**). The reaction was transferred into a vessel containing 20% aqueous dipotassium phosphate solution (600 mL, 6 L/kg), and the biphasic mixture was stirred for 15 min. The phases were split, and the upper organic phase was washed with saturated aqueous NaCl (5 L/kg; 500 mL). The organic layer was then dried and concentrated via distillation to

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250 mL total reaction volume (internal temperature ≤ 106 °C). The reaction mixture was then cooled to 50 °C where a solution of oxalic acid (14.81 g, 1.1 equiv) in MtBE (600 mL) was added over 100 min (1 mL/min). The resulting mixture was stirred for an additional 30 min at 50 °C following complete addition and was then seeded with **30a**/**b**·oxalate (100 mg). The reaction mixture was stirred for 3 h at 50 °C, was cooled to 20 °C over 3 h, and then was stirred for an additional 3 h. Solids were collected by filtration, washed with MTBE (100 mL), and then dried under full vacuum at 25−30 °C to provide **30a**/**b**·oxalate (72 g) as a white solid (MP = 109−112 °C). ^{1}H NMR (DMSO-d_6, 600 MHz, 25 °C): δ 7.37−7.19 (m, 20H), 4.77 (d, J = 11.4 Hz, 0.58H), 4.76 (d, J = 11.4 Hz, 0.84H), 4.73 (d, J = 11.2 Hz, 0.58H), 4.65 (d, J = 11.4 Hz, 0.58H), 4.64 (d, J = 11.0 Hz, 0.42H), 4.63 (d, J = 11.0 Hz, 0.58H), 4.62 (d, J = 6.8 Hz, 0.58H), 4.58 (d, J = 12.3 Hz, 0.58H), 4.54−4.46 (m, 3H), 4.44 (d, J = 12.1 Hz, 0.42H), 4.40 (d, J = 3.8 Hz, 0.42H), 4.39 (d, J = 11.1 Hz, 0.42H), 4.19 (dd, J = 6.8, 3.1 Hz, 0.58H), 4.14 (dd, J = 5.9, 3.8 Hz, 0.42H), 4.13 (d, J = 8.8 Hz, 0.42H), 4.03 (b, 0.42H), 3.91 (d, J = 9.3 Hz, 0.58H), 3.87 (b, 0.58H), 3.86 (d, J = 3.1 Hz, 0.58H), 3.82 (d, J = 9.0 Hz, 0.42H), 3.68 (d, J = 9.3 Hz, 0.58H), 3.67 (b, 2H), 3.56 (d, J = 10.6 Hz, 0.58H), 3.55 (b, 1H), 3.54 (d, J = 10.2 Hz, 0.42H), 3.51 (d, J = 10.2 Hz, 0.42H), 3.48 (d, J = 10.6 Hz, 0.58H), 2.91−2.57 (b, 4H), 2.47 (s, 3H), 1.42 (s, 1.26H), 1.34 (s, 1.26H), 1.29 (s, 1.74H), 1.18 (s, 1.74H). ^{13}C NMR (DMSO-d_6, 150.8 MHz, 25 °C): δ 168.10, 167.42, 163.45, 138.61, 138.41, 138.05, 137.98, 137.93, 137.38, 137.18, 128.21, 128.17, 128.15, 128.13, 128.12, 128.04, 127.98, 127.80, 127.77, 127.71, 127.66, 127.62, 127.50, 127.45, 127.43, 127.36, 127.33, 127.32, 127.21, 127.10, 127.06, 109.52, 108.39, 85.22, 83.99, 82.99, 81.08, 78.49, 78.08, 77.90, 76.38, 74.27, 73.96, 73.63, 72.63, 72.41, 71.81, 71.52, 67.33, 67.21, 52.92, 52.80, 52.69, 52.58, 43.12, 42.84, 42.67, 42.35, 42.29, 27.28, 26.62, 26.03, 26.00. HRMS: (ESI$^+$) Calcd for $C_{43}H_{53}N_2O_7$ (M + H)$^+$: 709.38473, Found: 709.38489.

***30a:30b** (94:6) via Grignard Option B. Grignard.* A solution of iodomethyl pivalate **28** (95 g, 389 mmol) in anhydrous THF (500 mL) was cooled to −75 °C under a nitrogen atmosphere. A solution of isopropylmagnesium chloride (236 mL, 471 mmol) in THF (commercial 2 M solution) was then added slowly, while maintaining an internal temperature of ≤−60 °C. After stirring for 1 h at ≤−60 °C, GC/MS analysis of an aliquot that had been quenched into MeOH indicated >95% conversion to the corresponding Grignard reagent (as measured by formation of methyl pivalate). A solution of **21** (100 g, 157 mmol) in toluene (500 mL total solution) was then added slowly to the Grignard solution, while maintaining an internal reaction temperature of ≤60 °C (∼30 min addition time). Following complete addition, the solution was stirred for 15 min at ≤60 °C, and then UHPLC analysis indicated <3% **21** remaining. The reaction was warmed to 0 °C over 1−2 h and then quenched by the slow addition of acetic acid (36 mL, 37.7 g, 628 mmol) in toluene (100 mL), while maintaining an internal temperature of ≤15 °C. The mixture was further diluted with toluene (400 mL) and then warmed to 25 °C where saturated aqueous sodium bicarbonate (500 mL) was added. The mixture was stirred for 15 min after this addition to afford an aqueous layer with pH 8 and a clear organic phase. The organic layer was washed with water (500 mL), and then concentrated via atmospheric distillation to a volume of 500 mL (final internal temperature observed during the distillation = 113 °C, final KF target ≤0.06%). The crude product was utilized directly in the subsequent step; however, a small portion of the mixture was removed and concentrated for characterization of pivalate **29a**/**b** (thick oil). ^{1}H NMR (DMSO-d_6, 600 MHz, 25 °C): δ 7.37−7.13 (m, 20H), 5.24 (s, 1H), 4.76 (d, J = 11.5 Hz, 1H), 4.63 (d, J = 11.3 Hz, 1H), 4.61 (d, J = 11.3 Hz, 1H), 4.59 (d, J = 11.3 Hz, 1H), 4.54 (d, J = 5.5 Hz, 1H), 4.49 (d, J = 11.5 Hz, 1H), 4.48 (s, 2H), 4.46 (d, J = 11.3 Hz, 1H), 4.25 (m, 2H), 4.10 (d, J = 11.5 Hz, 1H), 3.85 (d, J = 4.7 Hz, 1H), 3.70 (b, 1H), 3.61 (d, J = 10.2 Hz, 1H), 3.59 (d, J = 10.2 Hz, 1H), 3.50 (b, 2H), 3.38 (b, 1H), 2.28 (b, 1H), 2.17 (b, 2H), 2.10 (s, 3H), 2.08 (b, 1H), 1.11 (s, 9H). ^{13}C NMR (DMSO-d_6, 150.8 MHz, 25 °C): δ 177.0, 167.4, 138.7, 138.4, 137.6, 128.1, 128.0, 127.96, 127.7, 127.6, 127.5, 127.4, 127.3, 127.23, 127.20, 127.1, 82.0, 78.3, 77.4, 75.0, 73.7, 73.6, 72.7, 71.8, 71.6, 65.7, 54.6, 54.2, 45.4, 44.4, 41.6, 38.2, 26.8. HRMS: (ESI$^+$) Calcd for $C_{45}H_{57}N_2O_8$ (M + H)$^+$: 753.41094, Found: 753.41144.

Pivalate Cleavage. A solution of crude pivalate **29a**/**b** (118 g, 157 mmol) in toluene (500 mL total solution) was diluted with toluene (210 mL), and the water content was measured by KF titration (target ≤0.03%). The solution was then cooled to 5 °C, and solid sodium methoxide (12 g, 218 mmol) was added. The resulting mixture was stirred for 4 h at 0−5 °C, and then UHPLC/MS analysis confirmed complete conversion to intermediate diol **22a**/**b** (target specification ≤5% **29a**/**b**).

Acetonide and Oxalate Formation. Methanesulfonic acid (29 mL, 436 mmol) was slowly added at 0−5 °C to the solution of **22a**/**b**, followed by 2,2-dimethoxypropane (73 mL, 593 mmol). Following complete addition, the temperature was increased to 20−25 °C, and the reaction was stirred for 30 min before UHPLC/MS analysis confirmed complete conversion to acetonide **30a**/**b** (target specification ≤1% **22a**/**b**). The mixture was then quenched with saturated aqueous sodium bicarbonate (502 mL), the organic phase was washed with water (502 mL), and the solution was dried via azeotropic distillation with toluene at atmospheric pressure to a final volume of 300 mL (final internal temperature 113 °C, target specification KF ≤0.1% water). The reaction mixture was cooled to 50 °C and then diluted with MTBE (502 mL). A solution of oxalic acid (13.3 g, 148 mmol) in MTBE (118 mL) was then slowly added, while maintaining the internal temperature at 50 °C (15 min addition). After stirring for 0.5 h at 50 °C, the solution was seeded with crystalline **30a**/**b** oxalate (100 mg) and stirred slowly for 3 h at 50 °C. The resulting slurry was cooled to 20 °C at a rate of 10 °C/h, and then slowly stirred for an additional 5 h at 20 °C. The solids were collected by filtration, the cake was washed with MTBE (100 mL) and then dried to constant weight under vacuum at 25−30 °C to provide **30a**/**b** oxalate (75 g, 60% from **21**) as a white crystalline solid (MP = 111−113 °C). ^{1}H NMR (DMSO-d_6, 500 MHz, 25 °C): δ 7.37−7.19 (m, 20H), 4.77 (d, J = 11.4 Hz, 1H), 4.73 (d, J = 11.2 Hz, 1H), 4.65 (d, J = 11.4 Hz, 1H), 4.63 (d, J = 11.0 Hz, 1H), 4.62 (d, J = 6.7 Hz, 1H), 4.58 (d, J = 12.3 Hz, 1H), 4.53 (d, J = 12.3 Hz, 1H), 4.52 (d, J = 11.4 Hz, 1H), 4.51 (d, J = 11.4 Hz, 1H), 4.19 (dd, J = 6.7, 3.1 Hz, 1H), 3.91 (d, J = 9.2 Hz, 1H), 3.88 (b, 1H), 3.68 (d, J = 9.2 Hz, 1H), 3.67 (b, 2H), 3.56 (d, J = 10.6 Hz, 1H), 3.55 (b, 1H), 3.48 (d, J = 10.6 Hz, 1H), 2.84−2.64 (b, 4H), 2.48 (s, 3H), 1.29 (s, 3H), 1.18 (s, 3H). ^{13}C NMR (DMSO-d_6, 125.8 MHz, 25 °C): δ 167.4, 163.5, 138.6, 138.1, 137.9, 137.4, 128.21, 128.17, 128.12, 128.05, 127.8, 127.7, 127.6, 127.5, 127.1, 127.06, 108.4, 85.2, 81.1, 78.5, 78.1, 74.3, 73.6, 72.6, 71.5, 67.3, 52.9, 52.7, 43.1, 42.6, 27.3, 26.0.

dx.doi.org/10.1021/op4002802 | Org. Process Res. Dev. 2014, 18, 66−81

(2*R*,3*S*,4*S*)-2,3,4-Tris(benzyloxy)-4-((*R*)-4-((benzyloxy)-methyl)-2,2-dimethyl-1,3-dioxolan-4-yl)-1-(4-methylpiperazin-1-yl)butan-1-one (30a free base). A suspension of **30a**/**b** oxalate prepared via Grignard option B (150.0 g, 188.0 mmol) in MTBE (1.5 L) was charged with 1 N NaOH (405 mL, 405 mmol) and water (405 mL). The resulting mixture was stirred under a nitrogen atmosphere at 40 °C for 30 min to provide a brown solution. The phases were separated, the organic layer was washed with water (500 mL) and then concentrated at 45 °C/150 Torr to a volume of ∼450 mL. Cyclohexane (500 mL) was then added, and the mixture was concentrated at atmospheric pressure to a volume of ∼400 mL (internal temperature 78 °C). Additional cyclohexane (500 mL) was added, and the distillation was repeated to an end volume of ∼550 mL (internal temperature ∼83 °C). The solution was then cooled to ∼40 °C, and seed crystals of **30a** free base (500 mg) were added. The resulting light suspension was stirred at 40 °C for ∼2 h, and then was cooled to 12 °C over 4 h and stirred with low agitation (100 rpm) for 18 h. The resulting thick slurry was filtered, the solids were washed with cyclohexane (3 × 80 mL) and dried under vacuum (30 °C/40 Torr) to provide **30a** free base (115.7g, 87%) as off-white crystals (MP = 87 °C). The minor diastereomer **30b** was not detected by UHPLC. Purity >99.5% (UHPLC/MS). ^{1}H NMR (DMSO-d_6, 500 MHz, 25 °C): δ 7.38−7.19 (m, 20H), 4.78 (d, J = 11.4 Hz, 1H), 4.76 (d, J = 10.6 Hz, 1H), 4.63 (d, J = 11.4 Hz, 1H), 4.62 (d, J = 7.17 Hz, 1H), 4.61 (d, J = 11.5 Hz, 1H), 4.56 (d, J = 12.3 Hz, 1H), 4.53 (d, J = 12.3 Hz, 1H), 4.51 (d, J = 11.5 Hz, 1H), 4.49 (d, J = 11.4 Hz, 1H), 4.18 (d, J = 7.17 Hz, 2.87 Hz, 1H), 3.92 (d, J = 9.1 Hz, 1H), 3.86 (d, J = 2.87 Hz, 1H), 3.66 (d, J = 9.1 Hz, 1H), 3.64 (b, 1H), 3.55 (d, J = 10.6 Hz, 1H), 3.53−3.44 (b, 2H), 3.47 (d, J = 10.6 Hz, 1H), 3.39 (b, 1H), 2.29−2.04 (b, 4H), 2.08 (s, 3H), 1.29 (s, 3H), 1.17 (s, 3H). ^{13}C NMR (DMSO-d_6, 125.8 MHz, 25 °C): δ 167.1, 138.7, 138.2, 137.9, 137.5, 128.17, 128.15, 128.1, 128.0, 127.8, 127.60, 127.57, 127.43, 127.36, 127.04, 127.01, 108.2, 85.4, 81.3, 78.6, 78.1, 74.3, 73.6, 72.7, 71.7, 71.3, 67.2, 54.5, 54.2, 45.4, 44.6, 41.5, 27.4, 26.0. HRMS: (ESI$^+$) Calcd for $C_{43}H_{53}N_2O_7$ (M + H)$^+$: 709.38473, Found: 709.38407.

2-((Benzyloxy)(4-ethoxyphenyl)methyl)-4-bromo-1-chlorobenzene (34e). To a solution of 4-ethoxyphenylmagnesium bromide (0.5 M in 2-MeTHF, 11.0 L, 5.47 mol) at 0 °C was added a solution of 5-bromo-2-chlorobenzaldehyde **32** (1.0 kg, 4.56 mol) in 2-MeTHF (4.6 L) over approximately 1 h. Following complete addition, the reaction was stirred for 1−2 h at 0 °C, and then UHPLC-MS analysis indicated complete conversion to intermediate alcohol **33**. Sulfuric acid (98%, 170 mL, 3.19 mol) was then added slowly, followed by benzyl alcohol (990 g, 9.11 mol). The resulting solution was heated to reflux (76−85 °C) and stirred for 20 h. UHPLC/MS analysis then indicated complete conversion of alcohol **33** to ether **34e** (target specification ≤3% **33**). The reaction was quenched with water (5 L), the layers were separated, and the organic layer was washed with water (5 L). The organic layer was distilled to a minimum volume (<1.5 L) under reduced pressure, and then methanol (4 L) was added and the solution cooled to −10 °C over 60 min. The batch was seeded with 1 mol % **34e**, and the resulting slurry was stirred slowly for 10 h, filtered, and washed with cold methanol (4 L). The cake was dried under vacuum (55 °C, 21 in Hg) to provide **34e** (1.48 kg, 75%) as a white solid (MP (DSC onset) = 62.3 °C). Potency >96% (UHPLC/MS). ^{1}H NMR ($CDCl_3$, 400.13 MHz): δ 7.87 (d, J = 2.5 Hz, 1H), 7.38 (m, 5H), 7.37 (m, 2H), 7.31 (d, J = 8.5 Hz, 1H), 7.21 (d, J = 8.5 Hz, 1H), 6.89 (m, 2H), 5.77 (s, 1H), 4.54 (m, 2H), 4.04 (q, J = 7.0 Hz, 2H), 1.43 (t, J = 7.0 Hz, 3H). ^{13}C NMR ($CDCl_3$, 100.61 MHz): δ 158.7, 142.1, 137.9, 131.8, 131.6, 131.5, 131.0, 130.9, 128.9, 128.5, 127.9, 127.8, 121.0, 114.4, 78.3, 70.8, 63.4, 14.9. HRMS Calcd for $C_{22}H_{24}O_2NBrCl$ (M + NH_4^+): 448.06735, Found 448.06796.

4Bromo-1-chloro-2-(ethoxy(4-ethoxyphenyl)methyl)-benzene (34a). This compound was prepared from isolated **33** according to the general procedure described for the benzyl ether analogue **34e** to afford **34a** in 98.8% yield as a white solid (MP (DSC onset) = 40 °C). ^{1}H NMR ($CDCl_3$, 400.13 MHz): δ 7.79 (d, J = 2.5 Hz, 1H), 7.31 (m, 2H), 7.29 (d, J = 8.5 Hz, 1H), 7.20 (d, J = 8.5 Hz, 1H), 6.87 (m, 2H), 5.67 (s, 1H), 4.03 (q, J = 6.9 Hz, 2H), 3.54 (m, 2H), 1.42 (t, J = 7 Hz, 3H), 1.28 (t, J = 6.9 Hz, 3H). ^{13}C NMR ($CDCl_3$, 100.61 MHz): δ 158.6, 142.4, 132.0, 131.4, 130.9, 128.7, 121.0, 114.4, 78.9, 64.7, 63.4, 15.3, 14.9. HRMS Calcd for $C_{17}H_{18}O_2BrCl$: 368.01732, Found 368.01747.

4-Bromo-1-chloro-2-((4-ethoxyphenyl)(isopropoxy)-methyl)benzene (34b). This compound was prepared from isolated **25** according to the general procedure described for the benzyl ether analogue **34e** to afford **34b** in 74.3% yield as a white solid (MP (DSC onset) = 54.2 °C). ^{1}H NMR ($CDCl_3$, 400.13 MHz): δ 7.81 (d, J = 2.3 Hz, 1H), 7.29 (m, 2H), 7.27 (d, J = 8.3 Hz, 1H), 7.18 (d, J = 8.3 Hz, 1H), 6.85 (m, 2H), 5.81 (s, 1H), 4.02 (q, J = 6.8 Hz, 2H), 3.63 (m, 1H), 1.41 (t, J = 6.8 Hz, 3H), 1.24 (d, J = 6.0 Hz, 3H), 1.22 (d, J = 6.0 Hz, 3H). ^{13}C NMR ($CDCl_3$, 100.61 MHz): δ 158.5, 142.9, 132.6, 131.6, 131.3, 131.2, 130.8, 128.6, 128.4, 121.0, 114.5, 114.3, 75.9, 69.5, 63.4, 22.3, 14.8. HRMS Calcd for $C_{18}H_{20}O_2BrCl$: 382.03297, Found 382.03302.

4-Bromo-2-(butoxy(4-ethoxyphenyl)methyl)-1-chlorobenzene (34c). This compound was prepared from isolated **25** according to the general procedure described for the benzyl ether analogue **34e** to afford **34c** in 79.0% yield as a white solid (MP (DSC onset) = 35.7 °C). ^{1}H NMR ($CDCl_3$, 400.13 MHz): δ 7.77 (d, J = 2.3 Hz, 1H), 7.30 (m, 2H), 7.28 (d, J = 8.5 Hz, 1H), 7.20 (d, J = 8.5 Hz, 1H), 6.87 (m, 2H), 5.64 (s, 1H), 4.03 (q, J = 6.9 Hz, 2H), 3.46 (t, J = 6.5 Hz, 2H), 1.64 (m, 2H), 1.45 (m, 2H), 1.42 (t, J = 6.5 Hz, 3H), 0.93 (t, J = 7.4 Hz, 3H). ^{13}C NMR ($CDCl_3$, 100.61 MHz): δ 158.6, 142.5, 132.1, 131.8, 131.4, 130.9, 128.7, 121.0, 114.3, 79.0, 69.0, 63.4, 31.9, 19.4, 14.9, 13.9. HRMS Calcd for $C_{19}H_{22}O_2BrCl$: 396.04862, Found 396.04880.

4-Bromo-1-chloro-2-((4-ethoxyphenyl)(phenethoxy)-methyl)benzene (34f). This compound was prepared from isolated **25** according to the general procedure described for the benzyl ether analogue **34e** to afford **34f** in 80.5% yield as a white solid (MP (DSC onset) = 56.3 °C). ^{1}H NMR ($CDCl_3$, 400.13 MHz): δ 7.69 (d, J = 2.5 Hz, 1H), 7.33 (m, 2H), 7.28 (m, 1H), 7.23 (m, 5H), 7.20 (m, 1H), 6.85 (m, 2H), 5.68 (s, 1H), 4.03 (q, J = 6.9 Hz, 2H), 3.69 (t, J = 7.0 Hz, 2H), 2.98 (t, J = 7.2 Hz, 2H), 1.43 (t, J = 7.2 Hz, 3H). ^{13}C NMR ($CDCl_3$, 100.61 MHz): δ 158.6, 142.3, 138.8, 131.9, 131.7, 131.4, 130.9, 130.8, 129.0, 128.7, 128.4, 126.3, 121.0, 114.3, 79.1, 70.1, 63.4, 36.5, 14.9. HRMS Calcd for $C_{23}H_{22}O_2BrClNa$ (M + Na^+): 467.03839, Found 467.03902.

(2*R*,3*S*,4*S*)-2,3,4-Tris(benzyloxy)-1-(3-((benzyloxy)(4-ethoxyphenyl)methyl)-4-chlorophenyl)-4-(4-((benzyloxy)methyl)-2,2-dimethyl-1,3-dioxolan-4-yl)-butan-1-one (35). *Salt Break.* Amide **30a**/**b**·oxalate[53] (10.09 g) and toluene (100 mL) were combined in a suitable reaction vessel to afford a white suspension at ambient temperature. A

dx.doi.org/10.1021/op4002802 | Org. Process Res. Dev. 2014, 18, 66−81

solution of saturated aqueous sodium bicarbonate (55 mL) was then added to the oxalate salt slurry, and the resulting mixture was allowed to stir for 10 min. The reaction mixture was transferred into a separatory funnel, and the aqueous phase (pH 7) was removed. The organic phase was washed with additional saturated aqueous sodium bicarbonate (20 mL, pH 9) and then was dried over sodium sulfate, filtered, and concentrated to an orange-brown solution (~15 mL).

Lithiation. Aryl bromide **34e** (6.49 g), toluene (60 mL) and 2methyl tetrahydrofuran (6.5 mL) were charged to a second reaction vessel to afford a clear, colorless solution. This was cooled to 20 °C with stirring under a positive pressure of nitrogen. A solution of *n*-butyllithium in hexane (2.5 M, 6.5 mL) was then added over 10 min at −15 °C. Following complete addition, the reaction was allowed to stir for 10−20 min before use in the arylation step.

Arylation. The solution of free base **30a/b** in toluene (~15 mL) was then added to the aryllithium prepared above over 10 min at −15 °C. After complete addition, UHPLC analysis confirmed reaction completion. The reaction was therefore quenched via addition of 1 N hydrochloric acid (50 mL), and was then warmed to 20 °C. The phases were separated, and the organic phase was washed with saturated aqueous sodium chloride (30 mL), dried with sodium sulfate, filtered, and concentrated to an orange-brown oil. The crude product was purified by silica gel column chromatography using an ethyl acetate/hexanes gradient as eluent to afford a mixture of stereoisomers of **35**[53] (10.83 g). Alternately, the crude, partially concentrated solution of **35** may be used directly without chromatography in the next step. ^{1}H NMR (DMSO-d_6, 600 MHz, 25 °C): δ 8.47 (d, J = 2.0 Hz, 1H), 8.41 (d, J = 2.0 Hz, 1H), 7.89 (dd, J = 8.3, 2.0 Hz, 1H), 7.88 (dd, J = 8.3, 2.0 Hz, 1H), 7.47 (d, J = 8.3 Hz, 1H), 7.46 (d, J = 8.3 Hz, 1H), 7.31−7.15 (m, 25H), 7.03 (d, J = 7.6 Hz, 2H), 7.01 (d, J = 7.6 Hz, 2H), 6.80 (d, J = 8.6 Hz, 2H), 6.79 (d, J = 8.6 Hz, 2H), 5.77 (s, 1H), 5.76 (s, 1H), 5.00 (m, 2H), 4.69 (d, J = 11.7 Hz, 1H), 4.68 (d, J = 11.7 Hz, 1H), 4.64−4.53 (m, 4H), 4.49−4.30 (m, 14H), 3.94−3.89 (m, 4H), 3.88−3.85 (m, 4H), 3.71 (d, J = 11.2 Hz, 1H), 3.69 (d, J = 11.2 Hz, 1H), 3.51−3.43 (m, 4H), 1.29 (s, 3H), 1.28 (s, 3H), 1.26 (t, J = 7.0 Hz, 3H), 1.25 (t, J = 7.0 Hz, 3H), 1.11 (s, 3H), 1.10 (s, 3H). ^{13}C NMR (DMSO-d_6, 150 MHz, 25 °C): δ 198.18, 197.96, 158.05, 139.91, 139.88, 138.33, 138.30, 137.83, 137.80, 137.76, 137.65, 137.58, 137.46, 137.41, 136.89, 136.76, 134.86, 134.74, 131.23, 131.18, 129.74, 129.69, 128.95, 128.89, 128.83, 128.62, 128.18, 128.16, 128.14, 128.01, 127.95, 127.79, 127.65, 127.60, 127.56, 127.50, 127.47, 127.46, 127.41, 127.28, 127.26, 127.20, 127.17, 127.11, 127.09, 127.06, 114.11, 108.84, 108.74, 84.73, 84.66, 84.37, 84.18, 78.94, 78.76, 78.36, 78.33, 78.10, 77.81, 74.17, 74.02, 73.78, 73.74, 72.58, 72.50, 72.11, 72.03, 71.58, 71.49, 70.01, 69.96, 68.09, 67.94, 62.85, 48.64, 27.10, 27.05, 26.74, 26.03, 14.49, 14.48. HRMS: (ESI$^+$) Calcd for $C_{60}H_{61}Cl_1O_9Na$ $(M + Na)^+$: 983.38963, Found: 983.39026.

(2*S*,3*S*,4*R*)-2,3,4-Tris(benzyloxy)-1-((benzyloxy)-methyl)-5-(4-chloro-3-(4-ethoxybenzyl)phenyl)-6,8-dioxabicyclo[3.2.1]octane (37a/b). A solution of aryl ketones **35**[53] (8.06 g) and toluene (40 mL) was treated with trifluoroacetic acid (3.2 mL) and triethylsilane (10.4 mL) at ambient temperature. After complete reaction, according to UHPLC/MS analysis (target <2% **35** isomers remaining), saturated aqueous sodium bicarbonate was added. The layers were separated, the organic phase was washed with water and saturated aqueous sodium chloride and then dried over sodium sulfate, filtered, and concentrated to an oil. The crude oil was purified by silica gel column chromatography using an ethyl acetate−hexanes gradient as eluent to afford the major stereoisomer **37a** for characterization purposes (5.56 g).[53] Preferably, the crude, partially concentrated solution of **37a/b** is used directly without chromatography in the next step. ^{1}H NMR (DMSO-d_6, 500 MHz, 25 °C): δ 7.43 (d, J = 2.5 Hz, 1H), 7.71−7.14 (m, 21H), 7.03 (d, J = 8.6 Hz, 2H), 6.86 (d, J = 7.3 Hz, 2H), 6.73 (d, J = 8.6 Hz, 2H), 4.57 (s, 2H), 4.56 (d, J = 12.2 Hz, 1H), 4.52 (d, J = 11.4 Hz, 1H), 4.48 (d, J = 12.2 Hz, 1H), 4.41 (d, J = 11.4 Hz, 1H), 4.21 (d, J = 11.8 Hz, 1H), 4.14 (d, J = 7.0 Hz, 1H), 4.02 (d, J = 11.8 Hz, 1H), 3.98 (s, 2H), 3.96 (d, J = 9.4 Hz, 1H), 3.91 (q, J = 7.0 Hz, 2H), 3.86 (s, 1H), 3.71 (d, J = 7.0 Hz, 1H), 3.64 (d, J = 9.4 Hz, 1H), 3.61 (s, 1H), 3.57 (s, 1H), 1.27 (t, J = 7.0 Hz, 3H). ^{13}C NMR (DMSO-d_6, 125 MHz, 25 °C): δ 156.8, 138.1, 138.0, 137.92, 137.88, 137.61, 132.8, 131.1, 129.4, 128.8, 128.6, 128.33, 128.28, 128.15, 128.1, 127.9, 127.8, 127.68, 127.66, 127.63, 127.58, 127.51, 127.4, 125.6, 114.2, 106.5, 82.7, 76.8, 75.1, 74.5, 72.9, 71.3, 71.1, 70.9, 68.9, 68.3, 62.8, 37.5, 14.6. HRMS (**28a**): (ESI$^+$) Calcd for $C_{50}H_{49}Cl_1O_7Na$ $(M + Na)^+$: 819.30590, Found: 819.30676.

(1*S*,2*S*,3*S*,4*R*,5*S*)-5-(4-Chloro-3-(4-ethoxybenzyl)-phenyl)-1-(hydroxymethyl)-6,8-dioxabicyclo[3.2.1]-octane-2,3,4-triol (1). A pressure reactor was charged with 5% Pd/C (Johnson Matthey-type A5R87L, 20 wt %, 2.8 g). A solution of tetra-*O*-benzyl ether isomers **37a/b** (14 g) in methanol (28 mL) and toluene (560 mL) was then added, followed by 36.5% aqueous hydrochloric acid (2.39 mL). The vessel was purged successively with nitrogen (4×) and hydrogen (4×), and then the slurry was warmed to 25 °C. The vessel was then pressurized to 50 psi with hydrogen and stirred for 18 h. The vessel was then purged with nitrogen (4×). The catalyst was removed via filtration, and the cake was washed with methanol. UHPLC analysis indicated complete conversion to **1**. The in situ yield, obtained by UHPLC via comparison to a chromatographed standard was typically 55−60% from **30a/b**. The crude product was typically utilized directly in the subsequent step; however, a portion of the mixture was purified by silica gel column chromatography to afford an analytically pure sample of **1** as a white solid after concentration. ^{1}H NMR (DMSO-d_6, 600 MHz, 25 °C): δ 7.40 (d, J = 2.1 Hz, 1H), 7.39 (d, J = 8.3 Hz, 1H), 7.30 (dd, J = 8.3, 2.1 Hz, 1H), 7.09 (d, J = 8.6 Hz, 2H), 6.83 (d, J = 8.6 Hz, 2H), 5.19 (d, J = 5.5, 1H), 4.97 (d, J = 5.6, 1H), 4.89 (d, J = 6.7, 1H), 4.75 (t, J = 6.0, 1H), 3.99 (s, 2H), 3.98 (d, J = 7.0 Hz, 1H), 3.97 (q, J = 6.9 Hz, 2H), 3.63 (dd, J = 12.4, 6.0 Hz, 1H), 3.54 (dd, J = 7.9, 5.5 Hz, 1H), 3.49 (dd, J = 12.4, 6.0 Hz, 1H), 3.46 (d, J = 7.0 Hz, 1H), 3.43 (td, J = 7.9, 5.6 Hz, 1H), 3.40 (dd, J = 7.8, 6.8 Hz, 1H), 1.30 (t, J = 6.9, 3H). ^{13}C NMR (DMSO-d_6, 150 MHz, 25 °C): δ 156.8, 138.0, 137.6, 132.5, 131.0, 129.5, 129.2, 128.3, 126.1, 114.2, 107.6, 84.9, 77.3, 76.0, 71.4, 66.1, 62.8, 59.8, 37.5, 14.6. HRMS: (ESI$^-$) Calcd for $C_{22}H_{24}Cl_1O_7$ $(M - H)^-$: 435.12160, Found: 435.11993.

((1*R*,2*S*,3*S*,4*R*,5*S*)-5-(4-Chloro-3-(4-ethoxybenzyl)-phenyl)-2,3,4-trihydroxy-6,8-dioxabicyclo[3.2.1]octan-1-yl)methyl Acetate (38). A solution of **1** (26.4 g) in toluene (270 mL) and pyridine (6.6 mL) was charged to a suitable reaction vessel. The solution was cooled to −10 °C, and then acetic anhydride (5.8 mL) was added over 5 min. The reaction was stirred for 60 min at −10 °C, and then was warmed slowly to 20 °C and stirred for 18 h to provide a slurry. Toluene (100 mL) was then added, followed by water (200 mL). After

dx.doi.org/10.1021/op4002802 | *Org. Process Res. Dev.* 2014, 18, 66−81

stirring for 15 min, the water layer was removed and the solids were collected by filtration. The cake was washed with additional water and toluene, then solids were dried under vacuum at room temperature to provide monoacetate **38** (19.2 g, 79.7%) as a white solid (MP = 160 °C). UHPLC/MS: 97.6% product, 2.0% C-4 acetate isomer, 0.4% 1. ^{1}H NMR (DMSO-d_6, 500 MHz, 25 °C): δ 7.400 (d, J = 8.3 Hz, 1H), 7.398 (d, J = 2.1 Hz, 1H), 7.30 (dd, J = 8.3, 2.1 Hz, 1H), 7.09 (d, J = 8.7 Hz, 2H), 6.83 (d, J = 8.7 Hz, 2H), 5.50 (d, J = 5.7 Hz, 1H), 5.10 (d, J = 5.6 Hz, 1H), 5.01 (d, J = 6.6 Hz, 1H), 4.27 (d, J = 12.4 Hz, 1H), 4.07 (d, J = 12.4 Hz, 1H), 4.06 (d, J = 7.4 Hz, 1H), 3.99 (s, 2H), 3.97 (q, J = 7.0 Hz, 2H), 3.58 (t, J = 6.5 Hz, 1H), 3.50 (dd, J = 7.4, 0.9 Hz, 1H), 3.44 (m, 1H), 3.42 (m, 1H), 2.02 (s, 3H), 1.29 (t, J = 7 Hz, 3H). ^{13}C NMR (DMSO-d_6, 125 MHz, 25 °C): δ 170.1, 156.9, 137.8, 137.6, 132.7, 131.1, 129.6, 129.2, 128.5, 126.1, 114.3, 108.2, 82.8, 77.2, 75.7, 71.2, 66.4, 62.8, 62.0, 37.6, 20.6, 14.7. HRMS: (ESI$^+$) Calcd for $C_{24}H_{28}Cl_1O_8$ $(M + H)^+$: 479.14672, Found: 479.14630.

(1*R*,2*S*,3*S*,4*R*,5*S*)-1-(Acetoxymethyl)-5-(4-chloro-3-(4-ethoxybenzyl)phenyl)-6,8-dioxabicyclo[3.2.1]octane-2,3,4-triyl Triacetate (39). A solution of 1 (83 g), toluene (830 mL) and pyridine (122 mL) was cooled to 5 °C with stirring. Acetic anhydride (108 mL) was then added over 15 min. Following complete addition, the reaction was stirred at 5 °C for 1 h then at 20 °C for 23 h. The reaction mixture was then cooled to 5 °C where water (800 mL) was added over 10 min. The resulting mixture was stirred at 5 °C for 15 min then was warmed to 20 °C before the phases were separated. The organic phase was then washed with water (500 mL), dried over magnesium sulfate, filtered, and concentrated at 40 °C/50 Torr to an oil. Isopropanol (1.2 L) was added, and the resulting solid−liquid mixture was heated to 60 °C to provide a solution. This solution was cooled to 45 °C over 1 h and then seeded with tetraacetate 39 (50 mg). This resulted in formation of a thick slurry that was thinned by the addition of isopropanol (100 mL). The solids were collected after 1 h at 20 °C, the cake was washed with isopropanol (2 × 100 mL) and dried under vacuum to afford tetraacetate 39 (102.0 g. 88.7%) as a white crystalline solid (MP (DSC onset) = 135 °C). UHPLC/MS purity: 99.6%, 0.4% triacetate. The crystallization liquors were concentrated to 300 mL at 40 °C/40 Torr. The resulting slurry was stirred at 20 °C for 1 h, and then solids were collected, washed with isopropanol, and dried under vacuum at 20 °C. This provided a second crop of tetraacetate 39 (6.2 g, 5.4%) of slightly lower purity (UHPLC/MS purity: 93.7%, 6.3% triacetate). ^{1}H NMR (DMSO-d_6, 500 MHz, 25 °C): δ 7.46 (d, J = 8.3 Hz, 1H), 7.39 (d, J = 2.1 Hz, 1H), 7.33 (dd, J = 8.3, 2.1 Hz, 1H), 7.06 (d, J = 8.6 Hz, 2H), 6.83 (d, J = 8.7 Hz, 2H), 5.35 (dd, J = 8.4, 0.8 Hz, 1H), 5.25 (t, J = 8.4 Hz, 1H), 5.19 (d, J = 8.4 Hz, 1H), 4.47 (d, J = 12.8 Hz, 1H), 4.34 (d, J = 8.4 Hz, 1H), 4.04 (d, J = 12.8 Hz, 1H), 4.03 (d, J = 15.2 Hz, 1H), 3.97 (d, J = 15.2 Hz, 1H), 3.97 (q, J = 7.0 Hz, 2H), 3.79 (dd, J = 8.4, 0.8 Hz, 1H), 2.02 (s, 3H), 2.00 (s, 3H), 1.92 (s, 3H), 1.66 (s, 3H), 1.29 (t, J = 7 Hz, 3H). ^{13}C NMR (DMSO-d_6, 125 MHz, 25 °C): δ 169.71, 169.70, 169.1, 168.6, 157.0, 138.6, 134.4, 133.9, 130.9, 129.5, 129.2, 128.7, 125.4, 114.3, 106.9, 82.6, 74.8, 72.2, 68.7, 67.9, 62.9, 60.4, 37.4, 20.39, 20.36, 20.32, 19.9, 14.6. HRMS: (ESI$^+$) Calcd for $C_{30}H_{33}Cl_1O_{11}Na$ $(M + Na)^+$: 627.16036, Found: 627.16211.

(1*S*,2*S*,3*S*,4*R*,5*S*)-5-(4-Chloro-3-(4-ethoxybenzyl)-phenyl)-1-(hydroxymethyl)-6,8-dioxabicyclo[3.2.1]-octane-2,3,4-triol, (1:1) Compound with (*S*)-5-Oxopyrrolidine-2-carboxylic Acid (1·L-PGA). *Deacetylation.* To a stirring solution of NaOMe (0.5 M in MeOH, 0.65 mL) in MeOH (40 mL) at 20 °C was added tetra-*O*-acetate **39** (20.0 g) in two solid portions separated by 15 min. The additions provided a slurry that gave way to a solution after a few min. After stirring for ∼3 h, UHPLC/MS analysis of an aliquot indicated <2% combined monoacetate intermediates, and so the crude solution was carried directly into the subsequent cocrystallization step. For the purpose of characterization, a small portion of the mixture was concentrated to dryness on a rotovap and then further dried under high vacuum, to provide amorphous ertugliflozin (**1**) as a white solid mass. ^{1}H NMR (DMSO-d_6, 600 MHz, 25 °C): δ 7.40 (d, J = 2.1 Hz, 1H), 7.39 (d, J = 8.3 Hz, 1H), 7.30 (dd, J = 8.3, 2.1 Hz, 1H), 7.09 (d, J = 8.6 Hz, 2H), 6.83 (d, J = 8.6 Hz, 2H), 5.19 (d, J = 5.5, 1H), 4.97 (d, J = 5.6, 1H), 4.89 (d, J = 6.7, 1H), 4.75 (t, J = 6.0, 1H), 3.99 (s, 2H), 3.98 (d, J = 7.0 Hz, 1H), 3.97 (q, J = 6.9 Hz, 2H), 3.63 (dd, J = 12.4, 6.0 Hz, 1H), 3.54 (dd, J = 7.9, 5.5 Hz, 1H), 3.49 (dd, J = 12.4, 6.0 Hz, 1H), 3.46 (d, J = 7.0 Hz, 1H), 3.43 (td, J = 7.9, 5.6 Hz, 1H), 3.40 (dd, J = 7.8, 6.8 Hz, 1H), 1.30 (t, J = 6.9, 3H). ^{13}C NMR (DMSO-d_6, 150 MHz, 25 °C): δ 156.8, 138.0, 137.6, 132.5, 131.0, 129.5, 129.2, 128.3, 126.1, 114.2, 107.6, 84.9, 77.3, 76.0, 71.4, 66.1, 62.8, 59.8, 37.5, 14.6. HRMS: (ESI$^-$) Calcd for $C_{22}H_{24}Cl_1O_7$ $(M - H)^-$: 435.12160, Found: 435.11993.

Cocrystal Formation. A solution of **1** (4.80 g) in MeOH (17.3 mL) was concentrated under vacuum (30 Torr) at 40 °C to minimal volume. The residue was taken up in *i*-PrOH (18.7 mL) and the resulting solution was passed through a speck-free filter into a suitable reaction vessel. The solution was heated to 60 °C where water (18.7 mL) was added. In a second reaction vessel, L-pyroglutamic acid (3.91 g) was dissolved in water (56.2 mL). This solution was passed through a polishing filter into the reactor containing **1**. The resulting mixture was heated to 80 °C, and then was cooled to 40 °C at 3 °C/minute and seeded. The mixture was granulated for 10 h at 40 °C, and then cooled to 20 °C at 0.1 °C/min. The resulting white slurry was isolated on a Coors filter, washed with toluene (2 × 9.8 mL), and was dried under vacuum at 55 °C for 4 h to provide **1**·L-PGA (5.26 g, 85.3%) as a white crystalline solid (MP (DSC onset) = 142.5 °C). ^{1}H NMR (DMSO-d_6, 600 MHz, 25 °C): δ 7.90 (bs, 1H), 7.40 (d, J = 2.1 Hz, 1H), 7.39 (d, J = 8.3 Hz, 1H), 7.30 (dd, J = 8.3, 2.1 Hz, 1H), 7.09 (d, J = 8.6 Hz, 2H), 6.83 (d, J = 8.6 Hz, 2H), 5.19 (bs, 1H), 4.97 (bs, 1H), 4.90 (bs, 1H), 4.75 (bs, 1H), 4.06 (ddd, J = 9.0, 4.3, 0.7 Hz, 1H), 3.99 (s, 2H), 3.98 (d, J = 7.2 Hz, 1H), 3.97 (q, J = 7.0 Hz, 2H), 3.63 (dd, J = 12.5, 4.5 Hz, 1H), 3.54 (d, J = 7.8 Hz, 1H), 3.49 (dd, J = 12.5, 4.5 Hz, 1H), 3.46 (d, J = 7.2 Hz, 1H), 3.43 (t, J = 7.9 Hz, 1H), 3.40 (dd, J = 7.9, 5.5 Hz, 1H), 2.32 (m, 1H), 2.12 (m, 2H), 1.96 (m, 1H), 1.30 (t, J = 7.0, 3H). ^{13}C NMR (DMSO-d_6, 150 MHz, 25 °C): δ 176.9, 174.3, 156.8, 138.0, 137.6, 132.5, 131.0, 129.5, 129.2, 128.3, 126.1, 114.2, 107.6, 84.9, 77.3, 76.0, 71.4, 66.1, 62.8, 59.8, 54.6, 37.5, 28.9, 24.5, 14.6. HRMS: (ESI$^-$) Calcd for $C_{27}H_{31}Cl_1N_1O_{10}$ $(M - H)^-$: 564.16420, Found: 564.16315.

■ ASSOCIATED CONTENT

Supporting Information

Copies of ^{1}H and ^{13}C NMR spectra, powder X-ray diffraction (PXRD) patterns for compounds **38** and **39**, and single-crystal X-ray structure determination of compound **1**·L-PGA. This material is available free of charge via the Internet at http://pubs.acs.org.

dx.doi.org/10.1021/op4002802 | Org. Process Res. Dev. 2014, 18, 66−81

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Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

The authors gratefully acknowledge Bao Nguyen and David Foley for NMR analysis, Andy Palm for process analytical technology (PAT) support, Kapildev Arora for single-crystal X-ray structure determination of anhydrous **1**·L-PGA, and Yuriy Abramov for computational modeling. We also thank current and past members of the ertugliflozin API Technical Team, the Pfizer Structural Elucidation Group, the Pfizer Chemical Research & Development and Analytical Research & Development Management Teams, and the global Pfizer brainstorming session participants for valuable contributions to the program.

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(41) Oxidative conversion of **27** to diols **22a/b** can also be achieved by reaction with sodium perborate. TBAF has been found to accelerate the rate of the reaction but is not required. The practical utility of this alternative for large-scale application is being investigated, and details will be reported separately.

(42) Benzhydryl amines and thioethers were also prepared, but ethers were selected for additional study due to their relative simplicity, low cost, and excellent compatibility with downstream processing.

(43) Several procedures were identified for conversion to **30a/b** (free base) in the laboratory, including treatment of **30a/b·oxalate** with solid Na_3PO_4 in toluene, or neutralization with aqueous solutions of NaOH or $NaHCO_3$.

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(46) Resubmission of isolated aryl ketone **35** to the reaction conditions resulted in rapid formation of the expected tertiary alcohol, providing further evidence of a stabilized tetrahedral intermediate in the reaction or aryl anions derived from **34e** with amide **30a/b**.

(47) A diastereomeric mixture of ~3:2 was obtained from the Grignard option A, while Grignard option B typically resulted in a 95:5 mixture of diastereomers at C5.

(48) Process efficiency, in this context, refers to number of unit operations, total reactor volume, total processing time, and isolated yield.

(49) Purification of this intermediate by column chromatography is an option for laboratory scale, but this is far less desirable for large-scale manufacture.

(50) Mascitti, V. Dioxa-bicyclo[3.2.1]octane-2,3,4-triol derivatives. Application: WO/2010/IB54775, 2011/051864, 2011.

(51) A significant quantity of the methylpiperazine-*N*-oxide derivative of **22a/b** is observed via UHPLC/MS analysis at this stage of the reaction in the absence of a sodium bisulfite treatment. This byproduct coverts quantitatively to **22a/b** during the workup.

(52) The isopropoxy group of **27** readily exchanges with water and MeOH to form silanol and methyl ether analogues, respectively.

(53) Grignard approach B (Scheme 4) was utilized for the preparation of **22**, so the diastereomeric ratio at C5 was approximately 95:5 favoring the (5*R*) isomer. The (5*S*) isomer performs in an equivalent manner throughout the process. Both isomers converge to a single product **1** during treatment with acid during/after the hydrogenolysis step.

dx.doi.org/10.1021/op4002802 | *Org. Process Res. Dev.* 2014, 18, 66−81