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Commercial Route Research and Development for SGLT2 Inhibitor Candidate Ertugliflozin

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S 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**

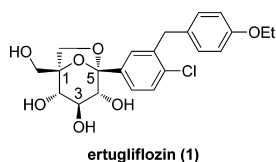


Figure 1. Structure of SGLT2 inhibitor candidate ertugliflozin (**1**).

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).

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 convergence 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 develop-

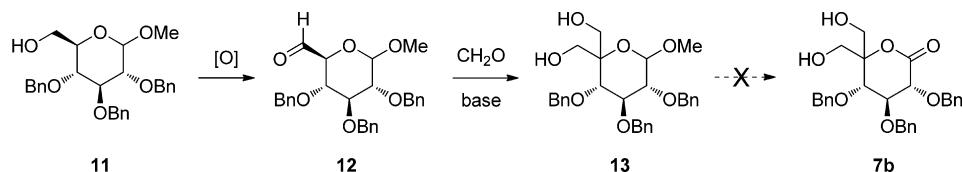
ment, an attractive alternative synthesis was reported by the medicinal chemistry team.⁷ This stereoselective route provided **1** in a much-improved 26% overall yield from diacetone- α -D-mannofuranose. This approach was also deemed unsuitable for large scale application, however, primarily due to a lack of crystalline isolable intermediates and the requirement for cryogenic reaction temperatures in setting key stereochemistry.

A more recent report⁸ 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.

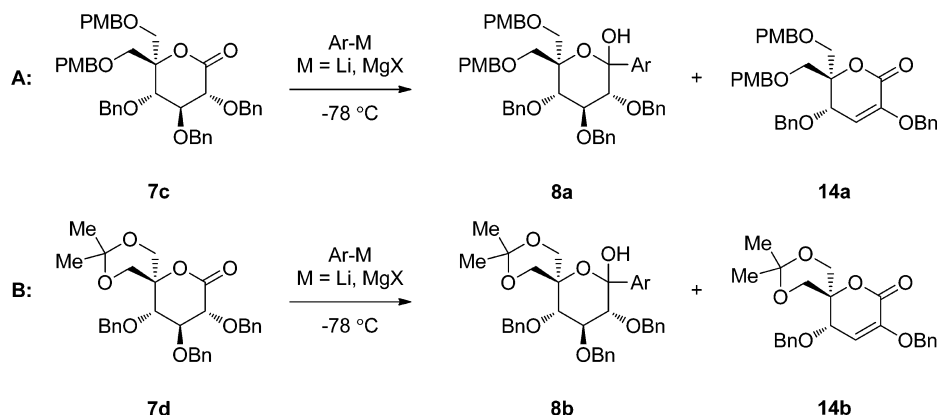
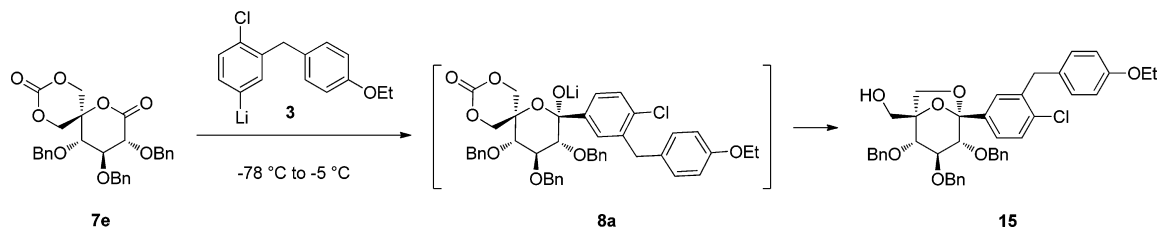
Evaluating Synthetic Approaches to the Carbohydrate Core. Among the published syntheses of SGLT2 inhibitor candidates under pharmaceutical evaluation, the direct arylation of protected gluconolactones of type **5** is most prevalent (Scheme 1, Approach B).^{8–13} This strategy provides rapid access to 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.

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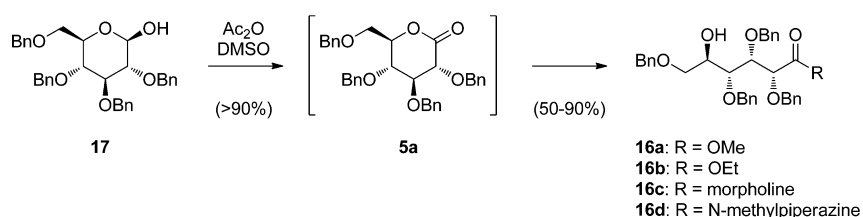
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Scheme 3. Attempted preparation of **7b** from methyl-D-glucopyranose

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 dimethylacetone **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**.

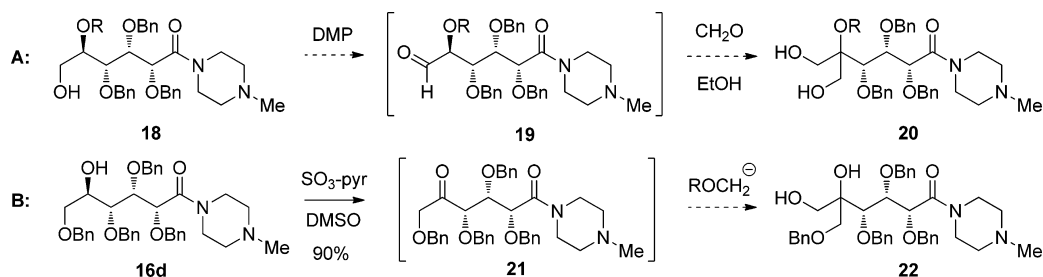
Cyclic carbonate **7e** was then prepared from diol **7b** and CDI, albeit in very low yield. This lactone was also evaluated in a handful of arylation reactions (Scheme 5). Interestingly, addition of aryllithium **3** to **7e** provided desired C1 addition product **8a**; no elimination product was 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.

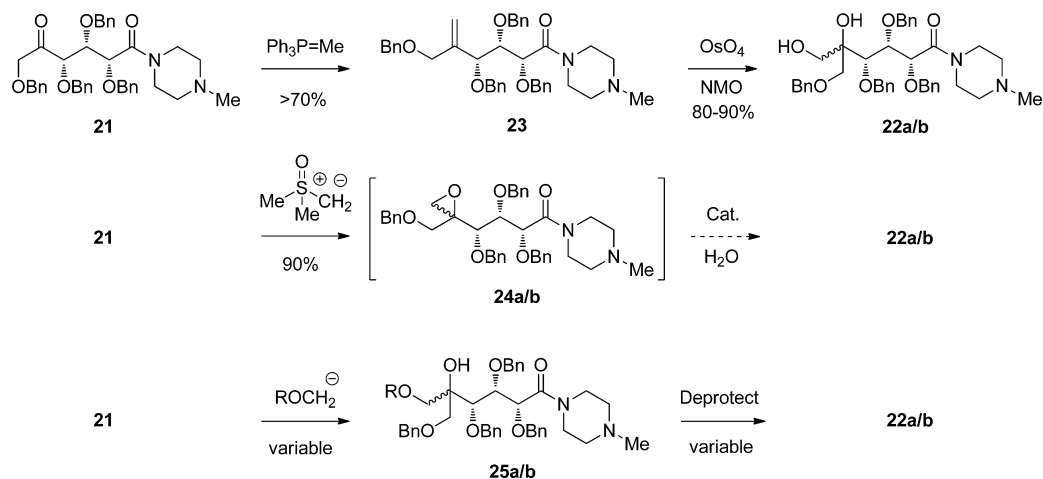
The addition of a hydroxymethyl substituent at C5 of the gluconolactone (e.g., **7**) has a profound impact on the outcome of this arylation reaction (Scheme 1, approach C). We turned focus to acyclic analogues of the carbohydrate (i.e., gluconamides such as **2**), according to precedented reactivity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

Scheme 7. Complementary hydroxymethylation strategies



Scheme 8. Nucleophilic hydroxymethylation of ketoamide 21



yield.²³ A range of oxidants was evaluated for this transformation; TPAP-NMO²⁴ and TEMPO-NaOCl⁹ 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 CH₂–OH) was a study of alternative “nucleophilic” strategies (i.e., ROCH₂–M) for hydroxymethylation to convert ketoamide **21**, obtained from secondary alcohol **16d** via Parikh–Doering²⁹ oxidation, to diol **22** (Scheme 7, approach B).

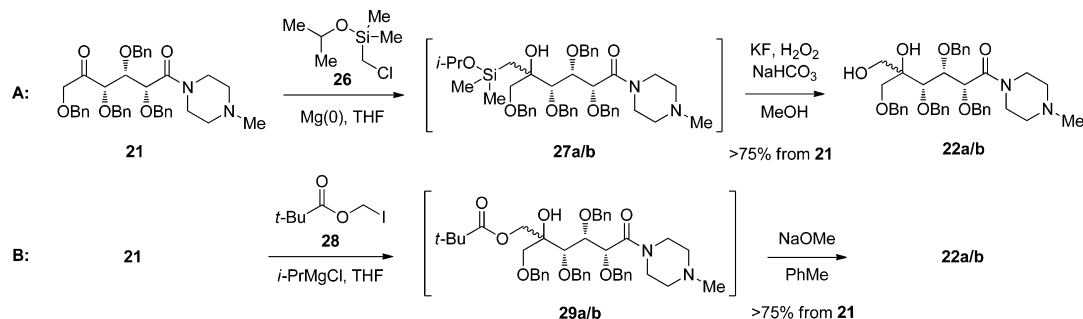
Ketoamide **21** proved to be a versatile intermediate, as several options were successfully demonstrated in the laboratory for preparation of diol diastereomers **22a/b** (Scheme 8). Although not ideal for large scale, the two-step sequence involving Wittig methylenation, followed by dihydroxylation with OsO₄ provided **22a/b** in excellent overall yield. Treatment of ketoamide **21** with the Corey–Chaykovsky reagent³⁰ 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 predated,^{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.

Scheme 9. “Nucleophilic” hydroxymethylation via Grignard reagents



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

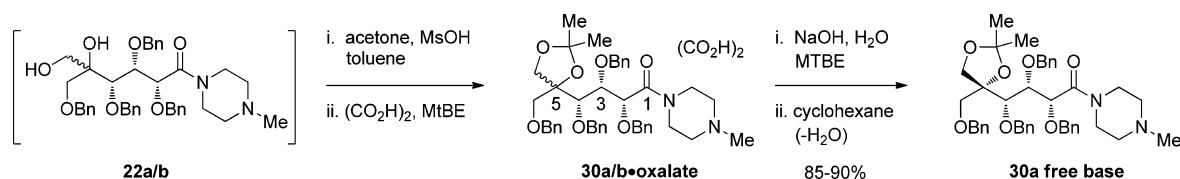
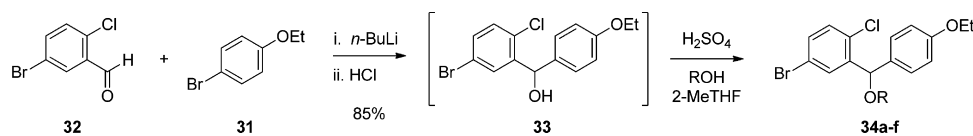


Table 1. Preparation of aryl bromide pre-nucleophiles



entry	ether 34	R	isolated yield ^a	MP (°C) ^b
1	34a	Et	98.8	40.0
2	34b	<i>i</i> -Pr	74.3	54.2
3	34c	<i>n</i> -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

^aYields for conversion of 33 to 34a–f. ^bMelting point onset determined by DSC. ^cThe major product was Friedel–Crafts C4-alkylation of PhOH.

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

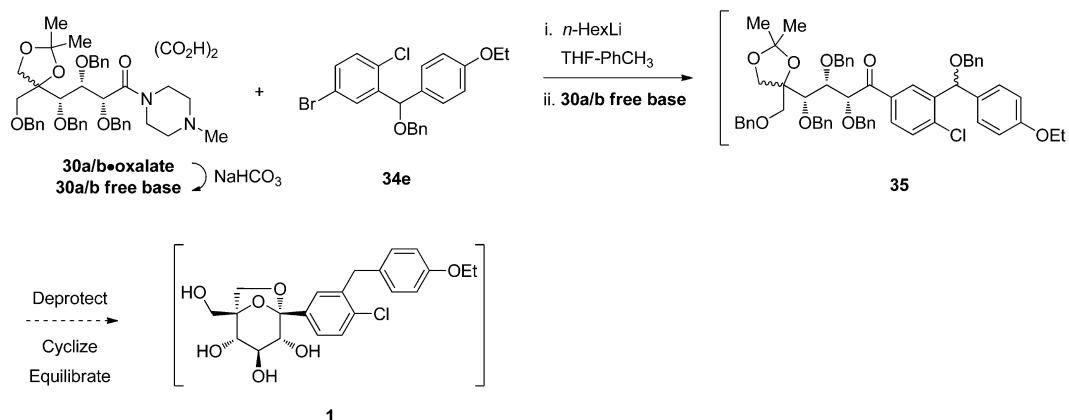
Nevertheless, precedented reagents for nucleophilic hydroxymethylation were evaluated, concentrating on those with the greatest potential for success in large-scale applications. An effective reagent would need to be highly chemoselective (for ketone vs amide) and liberate the desired diol under mild 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

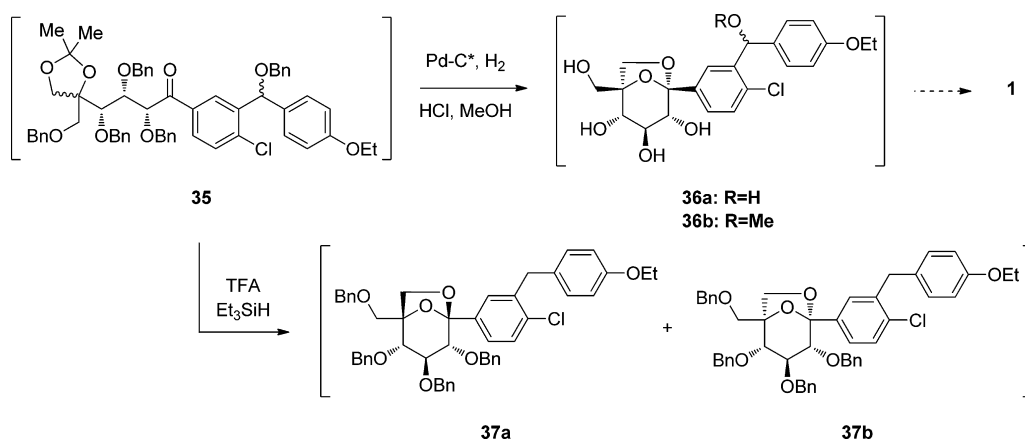
pivalate 28 (Scheme 9, option B). Developed largely by Knochel and co-workers,³⁵ this chemistry is applicable to a broad range of electrophiles. The reagent is prepared via Grignard exchange with *i*PrMgCl at low temperature. This reagent also showed excellent selectivity for addition to the ketone of 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 dimethylacetone 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

Scheme 11. Preparation of amorphous ertugliflozin (1)



Scheme 12. Options for deprotection/cyclization of 35



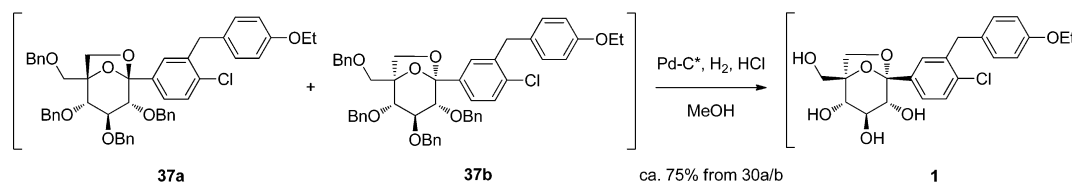
process-related impurities such as minor C2 and C4 diastereoisomers (resulting from epimerization during processing), unreacted starting materials, reactants, and reagents, and inorganic materials. The upgrade in purity immediately before the key convergent (i.e., arylation) step also translated to increased 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 alkyl lithium (e.g., $n\text{-BuLi}$ or $n\text{-HexLi}$), 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

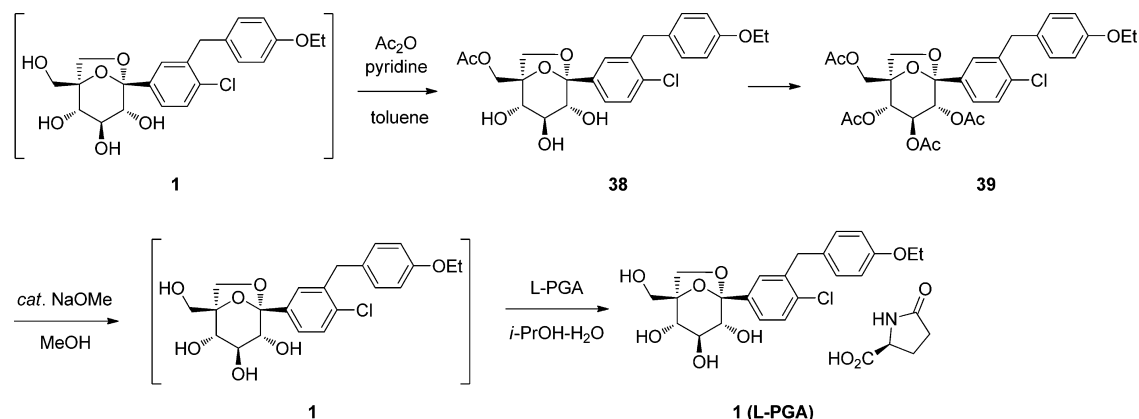
isolated or treated directly with an alcohol in the presence of H_2SO_4 to provide the corresponding benzhydryl ethers 34a–f. Evaluation of the properties of each, and performance in the subsequent reaction with amide 30, led us to selection of the benzyl-protected ether 34e for further development. 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 $n\text{-BuLi}$ or $n\text{-HexLi}$ 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

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 $i\text{Pr}_2\text{NEt}$) (Scheme 14).⁵⁰ The acetate products could be recrystallized to high purity from a range of solvents (e.g., $i\text{PrOH}$, 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-pyrogutamic acid (L-PGA) cocrystals. As the L-PGA cocrystal

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 biphasic system. 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

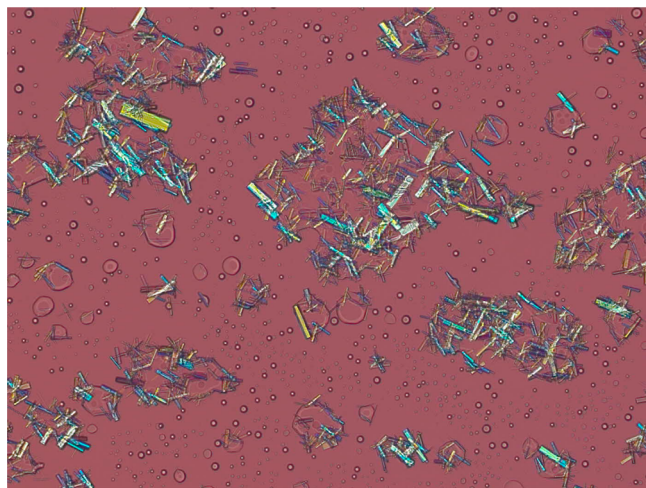


Figure 3. Biphasic cocrystallization of ertugliflozin (**1**)-L-PGA.

cocrystalline product is driven from this biphasic system 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 phenyl-hexyl (100 mm × 2.1 mm, 1.7 μ m) 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

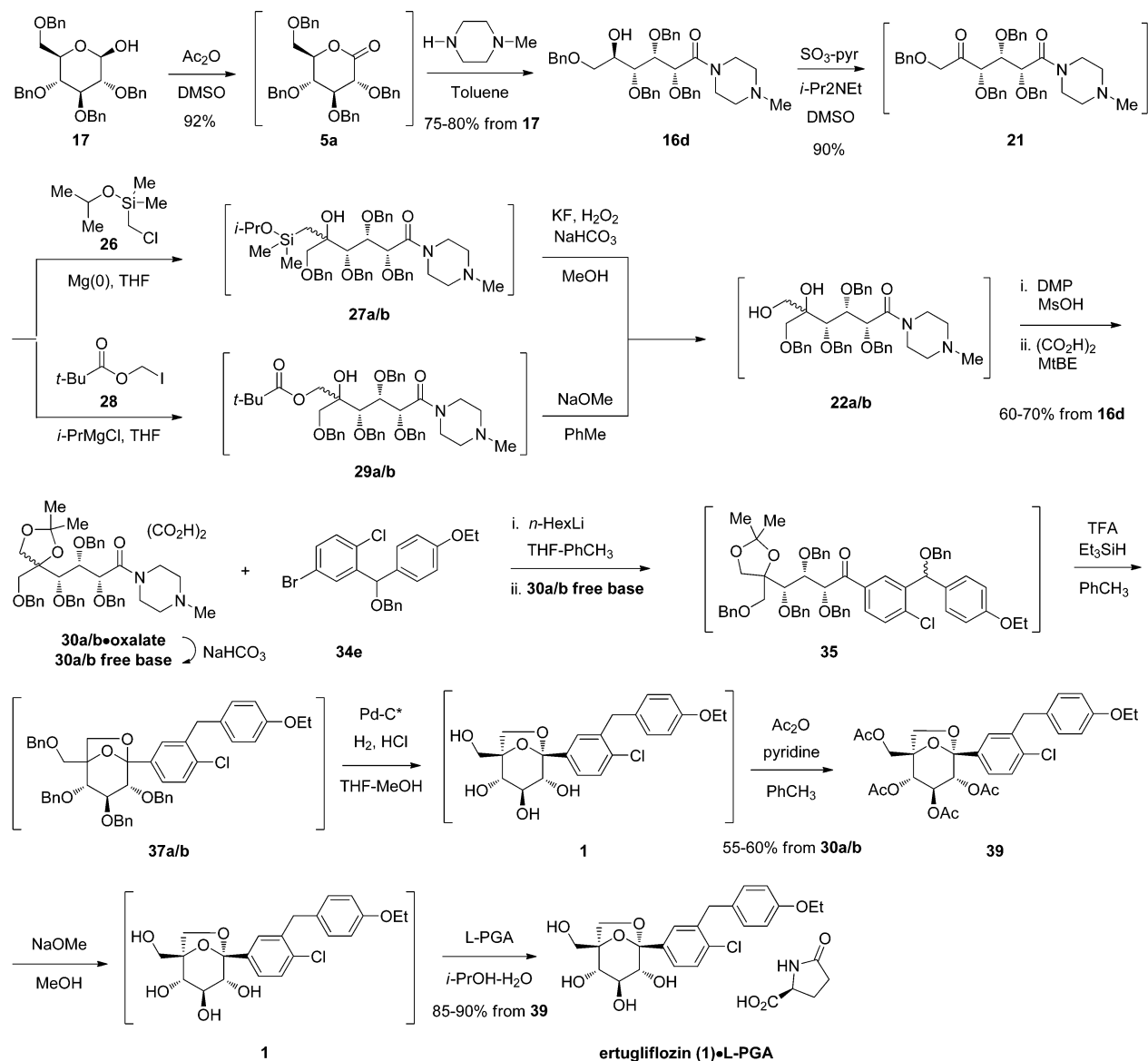
conditions of 100% acetonitrile. Approximate retention times (min): **30a/b** (13.3–13.5), **34e** (20.1), **35** (25.2–25.6), **37a/b** (23.4–23.6), **1** (10.6), **38** (12.6), **39** (17.3).

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 θ - θ goniometer at the Cu wavelength $K\alpha_1 = 1.54056$ 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.

(3R,4S,5R,6R)-3,4,5-Tris(benzyloxy)-6-((benzyloxy)-methyl)tetrahydro-2H-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).

(2R,3S,4R,5R)-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**. ¹H 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, $J = 6.6, 4.2$

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



H_z, 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). ¹³C 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 C₃₉H₄₇N₂O₆ (M + H)⁺: 639.34286, Found: 639.34228.

(2R,3S,4S)-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). ¹H 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). ¹³C 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, 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 C₃₉H₄₄N₂O₆Na (M + Na)⁺: 659.30916, Found: 659.30872.

(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). ¹H): 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). ¹³C 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 C₄₅H₆₁N₂O₇Si (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 analogues⁵²). 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). ¹H 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). ¹³C 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 C₄₀H₄₉N₂O₇ (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

250 mL total reaction volume (internal temperature $\leq 106\text{ }^{\circ}\text{C}$). The reaction mixture was then cooled to $50\text{ }^{\circ}\text{C}$ 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 $50\text{ }^{\circ}\text{C}$ following complete addition and was then seeded with **30a/b**-oxalate (100 mg). The reaction mixture was stirred for 3 h at $50\text{ }^{\circ}\text{C}$, was cooled to $20\text{ }^{\circ}\text{C}$ 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 $25\text{--}30\text{ }^{\circ}\text{C}$ to provide **30a/b**-oxalate (72 g) as a white solid (MP = $109\text{--}112\text{ }^{\circ}\text{C}$). ^1H NMR (DMSO- d_6 , 600 MHz, $25\text{ }^{\circ}\text{C}$): δ 7.37–7.19 (m, 20H), 4.77 (d, $J = 11.4\text{ Hz}$, 0.58H), 4.76 (d, $J = 11.4\text{ Hz}$, 0.84H), 4.73 (d, $J = 11.2\text{ Hz}$, 0.58H), 4.65 (d, $J = 11.4\text{ Hz}$, 0.58H), 4.64 (d, $J = 11.0\text{ Hz}$, 0.42H), 4.63 (d, $J = 11.0\text{ Hz}$, 0.58H), 4.62 (d, $J = 6.8\text{ Hz}$, 0.58H), 4.58 (d, $J = 12.3\text{ Hz}$, 0.58H), 4.54–4.46 (m, 3H), 4.44 (d, $J = 12.1\text{ Hz}$, 0.42H), 4.40 (d, $J = 3.8\text{ Hz}$, 0.42H), 4.39 (d, $J = 11.1\text{ Hz}$, 0.42H), 4.19 (dd, $J = 6.8, 3.1\text{ Hz}$, 0.58H), 4.14 (dd, $J = 5.9, 3.8\text{ Hz}$, 0.42H), 4.13 (d, $J = 8.8\text{ Hz}$, 0.42H), 4.03 (b, 0.42H), 3.91 (d, $J = 9.3\text{ Hz}$, 0.58H), 3.87 (b, 0.58H), 3.86 (d, $J = 3.1\text{ Hz}$, 0.58H), 3.82 (d, $J = 9.0\text{ Hz}$, 0.42H), 3.68 (d, $J = 9.3\text{ Hz}$, 0.58H), 3.67 (b, 2H), 3.56 (d, $J = 10.6\text{ Hz}$, 0.58H), 3.55 (b, 1H), 3.54 (d, $J = 10.2\text{ Hz}$, 0.42H), 3.51 (d, $J = 10.2\text{ Hz}$, 0.42H), 3.48 (d, $J = 10.6\text{ Hz}$, 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, $25\text{ }^{\circ}\text{C}$): 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 $\text{C}_{43}\text{H}_{53}\text{N}_2\text{O}_7$ (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 $-75\text{ }^{\circ}\text{C}$ 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 $\leq -60\text{ }^{\circ}\text{C}$. After stirring for 1 h at $\leq -60\text{ }^{\circ}\text{C}$, 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 $\leq 60\text{ }^{\circ}\text{C}$ (~ 30 min addition time). Following complete addition, the solution was stirred for 15 min at $\leq 60\text{ }^{\circ}\text{C}$, and then UHPLC analysis indicated $<3\%$ **21** remaining. The reaction was warmed to $0\text{ }^{\circ}\text{C}$ 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 $\leq 15\text{ }^{\circ}\text{C}$. The mixture was further diluted with toluene (400 mL) and then warmed to $25\text{ }^{\circ}\text{C}$ 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 = $113\text{ }^{\circ}\text{C}$, final KF target

$\leq 0.06\%$). 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). ^1H NMR (DMSO- d_6 , 600 MHz, $25\text{ }^{\circ}\text{C}$): δ 7.37–7.13 (m, 20H), 5.24 (s, 1H), 4.76 (d, $J = 11.5\text{ Hz}$, 1H), 4.63 (d, $J = 11.3\text{ Hz}$, 1H), 4.61 (d, $J = 11.3\text{ Hz}$, 1H), 4.59 (d, $J = 11.3\text{ Hz}$, 1H), 4.54 (d, $J = 5.5\text{ Hz}$, 1H), 4.49 (d, $J = 11.5\text{ Hz}$, 1H), 4.48 (s, 2H), 4.46 (d, $J = 11.3\text{ Hz}$, 1H), 4.25 (m, 2H), 4.10 (d, $J = 11.5\text{ Hz}$, 1H), 3.85 (d, $J = 4.7\text{ Hz}$, 1H), 3.70 (b, 1H), 3.61 (d, $J = 10.2\text{ Hz}$, 1H), 3.59 (d, $J = 10.2\text{ Hz}$, 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, $25\text{ }^{\circ}\text{C}$): 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 $\text{C}_{45}\text{H}_{57}\text{N}_2\text{O}_8$ (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 $\leq 0.03\%$). The solution was then cooled to $5\text{ }^{\circ}\text{C}$, and solid sodium methoxide (12 g, 218 mmol) was added. The resulting mixture was stirred for 4 h at $0\text{--}5\text{ }^{\circ}\text{C}$, and then UHPLC/MS analysis confirmed complete conversion to intermediate diol **22a/b** (target specification $\leq 5\%$ **29a/b**).

Acetonide and Oxalate Formation. Methanesulfonic acid (29 mL, 436 mmol) was slowly added at $0\text{--}5\text{ }^{\circ}\text{C}$ to the solution of **22a/b**, followed by 2,2-dimethoxypropane (73 mL, 593 mmol). Following complete addition, the temperature was increased to $20\text{--}25\text{ }^{\circ}\text{C}$, and the reaction was stirred for 30 min before UHPLC/MS analysis confirmed complete conversion to acetonide **30a/b** (target specification $\leq 1\%$ **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 $113\text{ }^{\circ}\text{C}$, target specification KF $\leq 0.1\%$ water). The reaction mixture was cooled to $50\text{ }^{\circ}\text{C}$ 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 $50\text{ }^{\circ}\text{C}$ (15 min addition). After stirring for 0.5 h at $50\text{ }^{\circ}\text{C}$, the solution was seeded with crystalline **30a/b** oxalate (100 mg) and stirred slowly for 3 h at $50\text{ }^{\circ}\text{C}$. The resulting slurry was cooled to $20\text{ }^{\circ}\text{C}$ at a rate of $10\text{ }^{\circ}\text{C}/\text{h}$, and then slowly stirred for an additional 5 h at $20\text{ }^{\circ}\text{C}$. The solids were collected by filtration, the cake was washed with MTBE (100 mL) and then dried to constant weight under vacuum at $25\text{--}30\text{ }^{\circ}\text{C}$ to provide **30a/b** oxalate (75 g, 60% from **21**) as a white crystalline solid (MP = $111\text{--}113\text{ }^{\circ}\text{C}$). ^1H NMR (DMSO- d_6 , 500 MHz, $25\text{ }^{\circ}\text{C}$): δ 7.37–7.19 (m, 20H), 4.77 (d, $J = 11.4\text{ Hz}$, 1H), 4.73 (d, $J = 11.2\text{ Hz}$, 1H), 4.65 (d, $J = 11.4\text{ Hz}$, 1H), 4.63 (d, $J = 11.0\text{ Hz}$, 1H), 4.62 (d, $J = 6.7\text{ Hz}$, 1H), 4.58 (d, $J = 12.3\text{ Hz}$, 1H), 4.53 (d, $J = 12.3\text{ Hz}$, 1H), 4.52 (d, $J = 11.4\text{ Hz}$, 1H), 4.51 (d, $J = 11.4\text{ Hz}$, 1H), 4.19 (dd, $J = 6.7, 3.1\text{ Hz}$, 1H), 3.91 (d, $J = 9.2\text{ Hz}$, 1H), 3.88 (b, 1H), 3.68 (d, $J = 9.2\text{ Hz}$, 1H), 3.67 (b, 2H), 3.56 (d, $J = 10.6\text{ Hz}$, 1H), 3.55 (b, 1H), 3.48 (d, $J = 10.6\text{ Hz}$, 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, $25\text{ }^{\circ}\text{C}$): 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.

(2R,3S,4S)-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). ¹H 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). ¹³C 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 C₄₃H₅₃N₂O₇ (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). ¹H NMR (CDCl₃, 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). ¹³C NMR (CDCl₃, 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 C₂₂H₂₄O₂NBrCl (M + NH₄⁺): 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). ¹H NMR (CDCl₃, 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). ¹³C NMR (CDCl₃, 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 C₁₇H₁₈O₂BrCl: 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). ¹H NMR (CDCl₃, 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). ¹³C NMR (CDCl₃, 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 C₁₈H₂₀O₂BrCl: 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). ¹H NMR (CDCl₃, 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). ¹³C NMR (CDCl₃, 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 C₁₉H₂₂O₂BrCl: 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). ¹H NMR (CDCl₃, 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). ¹³C NMR (CDCl₃, 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 C₂₃H₂₂O₂BrClNa (M + Na⁺): 467.03839, Found 467.03902.

(2R,3S,4S)-2,3,4-Tris(benzyloxy)-1-(3-((benzyloxy)(4-ethoxyphenyl)methyl)-4-chlorophenyl)-4-((benzyloxy)methyl)-2,2-dimethyl-1,3-dioxolan-4-yl)-butan-1-one (35). Salt Break. Amide **30a/b**-oxalate⁵³ (10.09 g) and toluene (100 mL) were combined in a suitable reaction vessel to afford a white suspension at ambient temperature. A

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 2-methyl 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. ¹H 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). ¹³C 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 C₆₀H₆₁Cl₁O₉Na (M + Na)⁺: 983.38963, Found: 983.39026.

(2S,3S,4R)-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. ¹H 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). ¹³C 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 C₅₀H₄₉Cl₁O₇Na (M + Na)⁺: 819.30590, Found: 819.30676.

(1S,2S,3S,4R,5S)-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 ASR87L, 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. ¹H 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 Hz, 1H), 4.97 (d, *J* = 5.6 Hz, 1H), 4.89 (d, *J* = 6.7 Hz, 1H), 4.75 (t, *J* = 6.0 Hz, 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 Hz, 3H). ¹³C 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 C₂₂H₂₄Cl₁O₇ (M – H)[–]: 435.12160, Found: 435.11993.

((1R,2S,3S,4R,5S)-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

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**. ¹H 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). ¹³C 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 C₂₄H₂₈Cl₁O₈ (M + H)⁺: 479.14672, Found: 479.14630.

(1R,2S,3S,4R,5S)-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). ¹H 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). ¹³C 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 C₃₀H₃₃Cl₁O₁₁Na (M + Na)⁺: 627.16036, Found: 627.16211.

(1S,2S,3S,4R,5S)-5-(4-Chloro-3-(4-ethoxybenzyl)phenyl)-1-(hydroxymethyl)-6,8-dioxabicyclo[3.2.1]octane-2,3,4-triyl, (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. ¹H 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). ¹³C 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 C₂₂H₂₄Cl₁O₇ (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-pyrroglutamic 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). ¹H 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). ¹³C 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 C₂₇H₃₁Cl₁N₁O₁₀ (M − H)[−]: 564.16420, Found: 564.16315.

■ ASSOCIATED CONTENT

● Supporting Information

Copies of ¹H and ¹³C 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>.

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Notes

The authors declare no competing financial interest.

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REFERENCES

- (1) Kalgutkar, A. S.; Tugnait, M.; Zhu, T.; Kimoto, E.; Miao, Z.; Mascitti, V.; Yang, X.; Tan, B.; Walsky, R. L.; Chupka, J.; Feng, B.; Robinson, R. P. *Drug Metab. Dispos.* **2011**, *39*, 1609.
- (2) Maurer, T. S.; Ghosh, A.; Haddish-Berhane, N.; Sawant-Basak, A.; Boustany-Kari, C. M.; She, L.; Leininger, M. T.; Zhu, T.; Tugnait, M.; Yang, X.; Kimoto, E.; Mascitti, V.; Robinson, R. P. *AAPS J.* **2011**, *13*, 576.
- (3) Miao, Z.; Nucci, G.; Amin, N.; Sharma, R.; Mascitti, V.; Tugnait, M.; Vaz, A. D.; Callegari, E.; Kalgutkar, A. S. *Drug Metab. Dispos.* **2013**, *41*, 445.
- (4) Mascitti, V.; Collman, B. M., Preparation of dioxo-bicyclo[3.2.1]-octane-2,3,4-triol derivatives as antidiabetic agents. Application: WO/2009/IB53626, 2010/023594, 2010.
- (5) Mascitti, V.; Maurer, T. S.; Robinson, R. P.; Bian, J.; Boustany-Kari, C. M.; Brandt, T.; Collman, B. M.; Kalgutkar, A. S.; Klenotic, M. K.; Leininger, M. T.; Lowe, A.; Maguire, R. J.; Masterson, V. M.; Miao, Z.; Mukaiyama, E.; Patel, J. D.; Pettersen, J. C.; Preville, C.; Samas, B.; She, L.; Sobol, Z.; Steppan, C. M.; Stevens, B. D.; Thuma, B. A.; Tugnait, M.; Zeng, D.; Zhu, T. *J. Med. Chem.* **2011**, *54*, 2952.
- (6) Mascitti, V.; Thuma, B. A.; Smith, A. C.; Robinson, R. P.; Brandt, T.; Kalgutkar, A. S.; Maurer, T. S.; Samas, B.; Sharma, R. *MedChemComm* **2013**, *4*, 101.
- (7) Mascitti, V.; Preville, C. *Org. Lett.* **2010**, *12*, 2940.
- (8) See the preceding article in this journal (Brandt, et al.) for a detailed report on the second-generation synthesis to ertugliflozin.
- (9) Deshpande, P. P.; Singh, J.; Pullockaran, A.; Kissick, T.; Ellsworth, B. A.; Gougoutas, J. Z.; Dimarco, J.; Fakes, M.; Reyes, M.; Lai, C.; Lobinger, H.; Denzel, T.; Ermann, P.; Crispino, G.; Randazzo, M.; Gao, Z.; Randazzo, R.; Lindrud, M.; Rosso, V.; Buono, F.; Doubleday, W. W.; Leung, S.; Richberg, P.; Hughes, D.; Washburn, W. N.; Meng, W.; Volk, K. J.; Mueller, R. H. *Org. Process Res. Dev.* **2012**, *16*, 577.
- (10) Kim, M. J.; Lee, J.; Kang, S. Y.; Lee, S.-H.; Son, E.-J.; Jung, M. E.; Lee, S. H.; Song, K.-S.; Lee, M.-W.; Han, H.-K.; Kim, J.; Lee, J. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 3420.
- (11) Lee, J.; Lee, S.-H.; Seo, H. J.; Son, E.-J.; Lee, S. H.; Jung, M. E.; Lee, M.; Han, H.-K.; Kim, J.; Kang, J.; Lee, J. *Bioorg. Med. Chem.* **2010**, *18*, 2178.
- (12) Nomura, S.; Sakamaki, S.; Hongu, M.; Kawanishi, E.; Koga, Y.; Sakamoto, T.; Yamamoto, Y.; Ueta, K.; Kimata, H.; Nakayama, K.; Tsuda-Tsukimoto, M. *J. Med. Chem.* **2010**, *53*, 6355.
- (13) Ohtake, Y.; Sato, T.; Kobayashi, T.; Nishimoto, M.; Taka, N.; Takano, K.; Yamamoto, K.; Ohmori, M.; Yamaguchi, M.; Takami, K.; Yeu, S.-Y.; Ahn, K.-H.; Matsuoka, H.; Morikawa, K.; Suzuki, M.; Hagita, H.; Ozawa, K.; Yamaguchi, K.; Kato, M.; Ikeda, S. *J. Med. Chem.* **2012**, *55*, 7828.
- (14) Murphy, P. V.; McDonnell, C.; Hamig, L.; Paterson, D. E.; Taylor, R. J. K. *Tetrahedron Asymmetry* **2003**, *14*, 79.
- (15) Singh, J.; DiMarco, J.; Kissick, T. P.; Deshpande, P.; Gougoutas, J. Z. *Carbohydr. Res.* **2002**, *337*, S65.
- (16) Farr, R. N.; Outten, R. A.; Cheng, J. C. Y.; Daves, G. D., Jr. *Organometallics* **1990**, *9*, 3151.
- (17) Friesen, R. W.; Loo, R. W. J. *Org. Chem.* **1991**, *56*, 4821.
- (18) Mazur, A. W.; Hiler, G. D., II. *J. Org. Chem.* **1997**, *62*, 4471.
- (19) Yang, Y.-Y.; Yang, W.-B.; Teo, C.-F.; Lin, C.-H. *Synlett* **2000**, 1634.
- (20) Schmidt, R. R.; Frick, W. *Tetrahedron* **1988**, *44*, 7163.
- (21) Modeling studies carried out on diol **7b** illustrated that the two primary alcohols were not in close proximity in the minimized structure.
- (22) Allyl protecting groups, as well as a range of substituted benzyl derivatives, were also demonstrated to be feasible.
- (23) Rajanikanth, B.; Seshadri, R. *Tetrahedron Lett.* **1989**, *30*, 755.
- (24) Kang, S. Y.; Song, K.-S.; Lee, J.; Lee, S.-H.; Lee, J. *Bioorg. Med. Chem.* **2010**, *18*, 6069.
- (25) Martin, R.; Romea, P.; Tey, C.; Urpi, F.; Vilarrasa, J. *Synlett* **1997**, 1414.
- (26) The utility of morpholine amides as electrophiles has been documented; however, the use of methylpiperazine amides as precursors to aryl ketones appears to be unprecedented.
- (27) Kaku, T.; Tsujimoto, S.; Matsunaga, N.; Tanaka, T.; Hara, T.; Yamaoka, M.; Kusaka, M.; Tasaka, A. *Bioorg. Med. Chem.* **2011**, *19*, 2428.
- (28) Oxidation of primary alcohol **18** to aldehyde **19** was only briefly studied. Dess–Martin periodinane was found to be moderately effective, but was not optimized.
- (29) Parikh, J. R.; Doering, W. v. E. *J. Am. Chem. Soc.* **1967**, *89*, 5505.
- (30) Corey, E. J.; Chaykovsky, M. J. *Am. Chem. Soc.* **1965**, *87*, 1353.
- (31) A range of Lewis and Brønsted acids were screened as catalysts in attempts to open epoxide **24** with water or benzyl alcohol. Debenzylation, elimination, and other destructive reactivity was observed, but desired products were not detected.
- (32) Corey, E. J.; Eckrich, T. M. *Tetrahedron Lett.* **1983**, *24*, 3163.
- (33) Corey, E. J.; Eckrich, T. M. *Tetrahedron Lett.* **1983**, *24*, 3165.
- (34) Hara, R.; Furukawa, T.; Horiguchi, Y.; Kuwajima, I. *J. Am. Chem. Soc.* **1996**, *118*, 9186.
- (35) Avolio, S.; Malan, C.; Marek, I.; Knochel, P. *Synlett* **1999**, 1820.
- (36) Tamao, K.; Kakui, T.; Kumada, M. *J. Am. Chem. Soc.* **1978**, *100*, 2268.
- (37) Tamao, K.; Ishida, N.; Ito, Y.; Kumada, M. *Org. Synth.* **1990**, *69*, 96.
- (38) Donohoe, T. J.; Winship, P. C. M.; Pilgrim, B. S.; Walter, D. S.; Callens, C. K. A. *Chem. Commun. (Cambridge, U. K.)* **2010**, *46*, 7310.
- (39) Tamao, K.; Ishida, N.; Ito, Y.; Kumada, M. *Org. Synth.* **1990**, *69*, 96.
- (40) Fleming, I.; Barbero, A.; Walter, D. *Chem. Rev.* **1997**, *97*, 2063.
- (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 Na₃PO₄ in toluene, or neutralization with aqueous solutions of NaOH or NaHCO₃.
- (44) The corresponding Grignard and turbo-Grignard reagents were also prepared and evaluated.
- (45) Krasovskiy, A.; Knochel, P. *Angew. Chem., Int. Ed.* **2004**, *43*, 3333.

(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. Dioxo-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 converts 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 (*SR*) isomer. The (*SS*) 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.