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Development of an Early-Phase Bulk Enabling Route to Sodium-Dependent Glucose Cotransporter 2 Inhibitor Ertugliflozin

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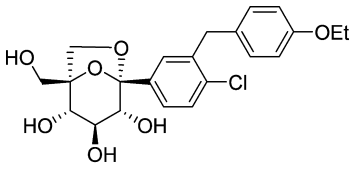
Supporting Information

ABSTRACT: The development and optimization of a scalable synthesis of sodium-dependent glucose cotransporter 2 inhibitor, ertugliflozin, for the treatment of type-2 diabetes is described. Highlights of the chemistry are a concise, four-step synthesis of a structurally complex API from known intermediate **4** via persilylation−selective monodesilylation, primary alcohol oxidation, aldol-crossed-Cannizzaro reaction, and solid-phase acid-catalyzed bicyclic ketal formation. The final API was isolated as the L-pyroglutamic acid cocrystal.

INTRODUCTION

Ertugliflozin **1**, a glucose-derived *C*-glycoside that contains a novel bridged bicyclic ketal motif, is a selective sodium-dependent glucose cotransporter (SGLT) 2 inhibitor for the treatment of diabetes (Figure 1).[1] SGLT2 inhibition provides



ertugliflozin (1)

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

an insulin-independent mechanism for regulation of glucose homeostasis in type-2 diabetes mellitus (T2DM) patients. SGLT2 is expressed exclusively in the renal proximal tubule cells of the kidney, and inhibition of this transporter promotes urinary glucose excretion that helps to avert hyperglycemia in diabetics.[2] Manufacture of multikilogram quantities of **1** was required for toxicological and clinical evaluation, and this paper describes the enabling work that resulted in the delivery of early active pharmaceutical ingredient (API) campaigns.

Medicinal Chemistry Synthesis. The synthetic route employed by our medicinal chemistry colleagues for analoging efforts (Scheme 1) relied on late-stage introduction of the aryl substituent via addition of a metalated aryl species to the Weinreb amide of an acyclic version of the glucose backbone.[3] This route provided an acetophenone intermediate that underwent cyclization followed by global deprotection to provide final analogue targets. From a throughput perspective, this route was long and linear with a low overall yield (13 steps with 0.3% yield) and as such was not appropriate for consideration as a route amenable to manufacture kilogram quantities of API in a short time frame. More recently, our medicinal chemistry colleagues have reported a much more efficient route to ertugliflozin starting from D-mannose.[4] Also, the strategy of arylating an acyclic Weinreb amide intermediate was revisited for development of the commercial route.[5]

Synthesis of Known Compound 4. As a starting point for a scalable synthesis of ertugliflozin (**1**), intermediate **4** can be made from TMS-gluconolactone **2** and the requisite aryl bromide **3** (Scheme 2) as reported in the literature.[6,7] To obtain **4**, we modified the published procedure, which gave an isolated product C1 anomer ratio of 85:15, by stirring the final reaction mixture at room temperature until the ratio was ≥98:2. This facilitated tracking downstream intermediates via HPLC (i.e., only had to monitor a single diastereomer vs two diastereomers). We also made modifications to the reaction workup procedure to reduce solvent volumes and isolated tetrol **4** as the crystalline methanol solvate.[8] The solvated methanol was removed via vacuum oven drying to obtain amorphous product in 65−71% isolated yield and >98% purity.

Evaluation of C6 Oxidation without Protecting Groups. Our strategy to introduce the requisite hydroxymethylene functionality at the C5 position of the sugar required the oxidation of the C6 hydroxy group to an aldehyde. A number of attempts were made to selectively oxidize tetrol **4** to C6 aldehyde **6** with no secondary hydroxyl group protection. Although enzymatic C6 oxidation is known for galactose using galactose oxidase (opposite C4 stereochemistry compared to glucose), there was no enzyme known to catalyze the analogous oxidation for glucose.[9] Of the various conditions tried, the cryogenic Swern protocol (DMSO, oxalyl chloride, NEt_3) showed promise with ∼50% conversion, but this initial result could not be improved upon as overoxidation became apparent with increased amounts of oxidant. TEMPO-based oxidations were tried with numerous stoichiometric oxidants with no positive results despite literature reports of the successful oxidation of sugars without C1 aryl substitution.[10,11] Either no reaction or overoxidation to the carboxylic acid was observed.

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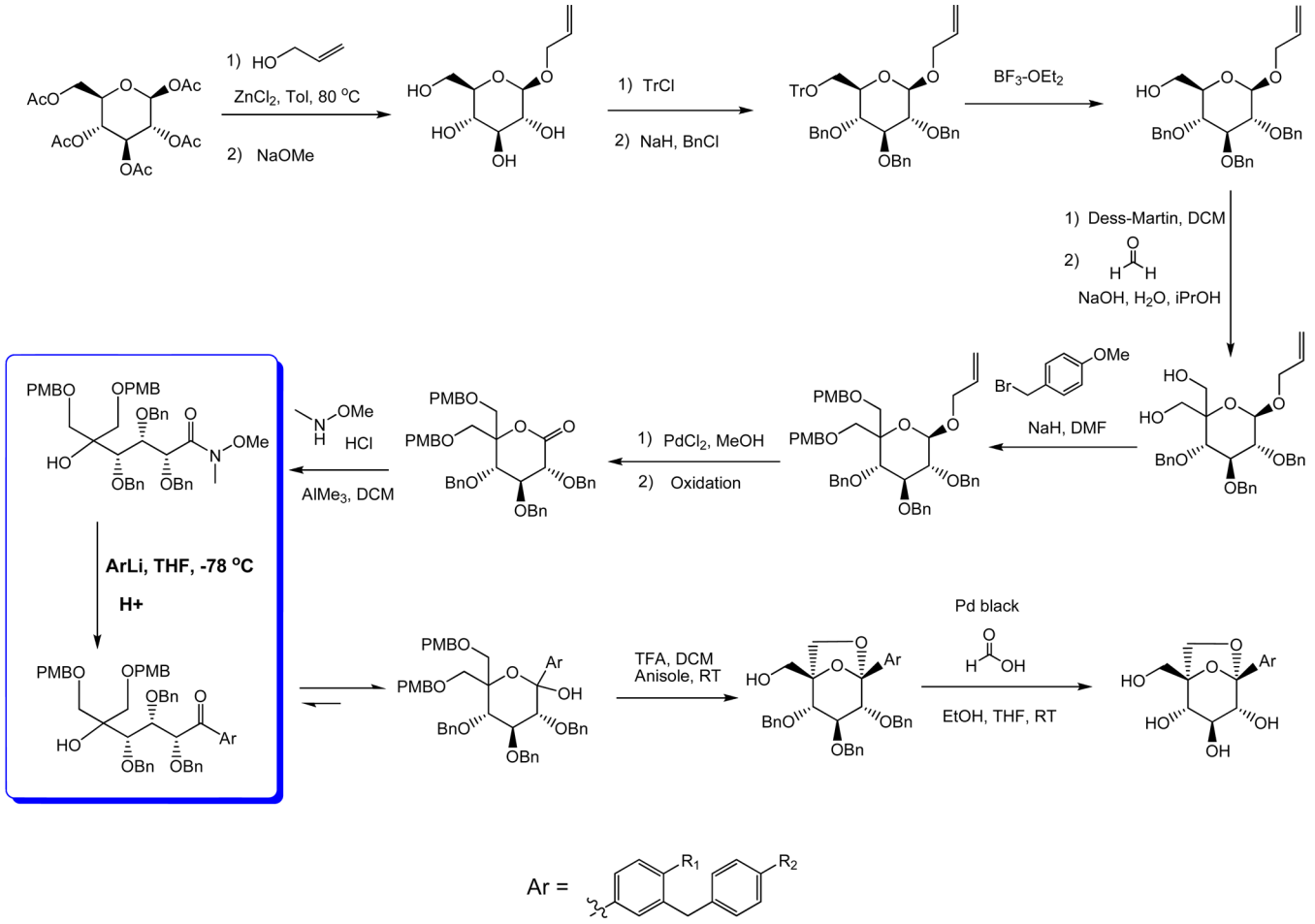
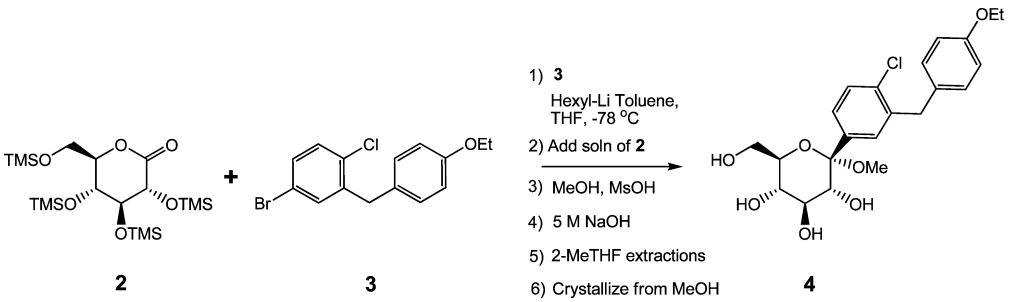
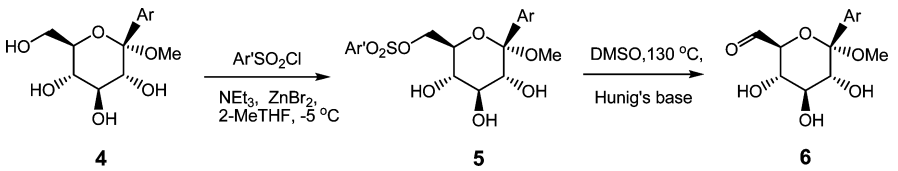
Scheme 1. Medicinal chemistry route for late-stage introduction of structural diversity



Scheme 2. *C*-glycoside formation



Scheme 3. Kornblum oxidation of arylsulfonate esters



Another approach that showed some promise was a Kornblum-type oxidation, which was carried out by selectively activating the C6 primary hydroxyl group as a sulfonate ester and heating in DMSO with base (Scheme 3).[12] The *p*-toluenesulfonate ester formed the desired oxidation product, but required high reaction temperature and gave incomplete conversion along with various byproducts, most notably sulfonate ester hydrolysis to give back **4**.

With the aim of lowering the reaction temperature required for DMSO to displace the sulfonate ester and undergo clean oxidation to give aldehyde **6**, we then looked at sulfonate esters[13] with electron-withdrawing groups as shown in Table 1. The *p*-nitro analogue (entry 1) worked reasonably well but had

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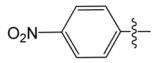
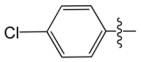
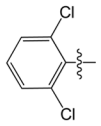
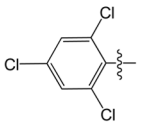
Table 1. Screen of arylsulfonate esters in the Kornblum oxidation[b]

Entry	Ar'	DSC Onset Temp	DSC Energy	Ratio of 6: 5: 4		
1		89°C	872 J/g	87	2	11
2		94°C	244 J/g	47	47	6
3		77°C	366 J/g	89	1	10
				93[a]	1	6
4		81°C	167 J/g	91[a]	0	9

[a]5 equiv iPr_2NEt used as base. [b]Note: All substrates were screened across time (5−30 min) and temperature (90−145 °C). For comparison purposes, the 15 min residence time at 130 °C results are shown. These reactions were run using 5 equiv collidine as base in 10 volumes DMSO as solvent unless otherwise noted.

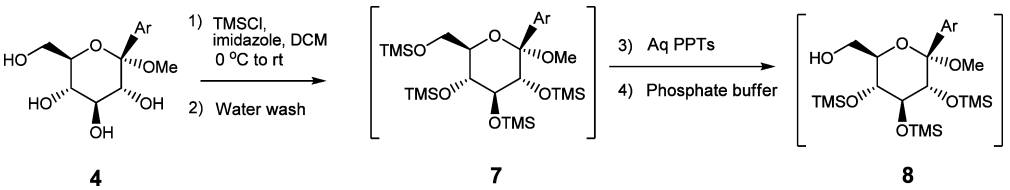
higher thermal potential compared to the chloro-substituted sulfonate esters. The *p*-chloro analogue (entry 2) was less reactive under the desired flow conditions, but did give complete conversion in lab-scale batch pilots where the reaction went to completion in 2 h at 135 °C. The 2,6-dichloro and 2,4,6-trichloro analogues (entries 3 and 4) gave the best results and comparable reaction profiles, with the 2,6-dichloro substrate giving slightly less hydrolysis byproduct **4**.

When the synthesis of the 2,6-dichloroarylsulfonate ester starting material (**5**) was scaled up to ∼100 g for a proof-of-concept run on the flow system, it decomposed during silica gel chromatography and during solvent removal *in vacuo* at 40−50 °C. The instability of our starting material, therefore, made the Kornblum oxidation route nonviable for scale-up. Additionally, the aldehyde product (**6**) was not isolable as a single compound from the successful experiments. However, it was demonstrated on small scale that the crude aldehyde solution could be carried directly into the next step chemistry with success, although this concept was not pursued further. Project timelines for API delivery did not allow for further follow-up on the Kornblum oxidation approach.

Revised Approach Using Protecting Groups. With attempts at a scalable, selective, direct oxidation of the C6 hydroxy group exhausted, we turned to a global protection, selective monodeprotection, and oxidation strategy. We looked at peracetylation of tetrol **4** followed by selective C6 enzymatic monodeacetylation, but after reaction optimization, the conversion for the monodeacetylation reaction was only 20%. We then looked at persilylation of **4** with TMSCl to give **7**, followed by monodesilylation using catalytic K_2CO_3 in MeOH at 0 °C to provide alcohol **8** (Scheme 4).[14] These conditions worked fairly well but had the disadvantage of multiple solvent exchanges: from the dichloromethane solvent for the persilylation reaction, to methanol for the monodesilylation reaction, and then to a nonalcoholic solvent for the subsequent oxidation reaction. Also, upon prolonged exposure of the monodesilylated product (**8**) to methanol during distillation, overdesilylation products started to appear. Once overdesilylation starts to occur, a statistical mixture of all silylated products results. Since dichloromethane was identified as the optimal solvent for the subsequent oxidation step, we sought to identify conditions that would selectively desilylate the C6 TMS-ether without changing the solvent. A hint of how to proceed came from a pilot of the persilylation reaction where pyridine was used as solvent and base. After workup and chromatography, there was 75% monodesilylated product **8** present. Attempts to use aqueous pyridine-HCl gave ∼65% desired monodesilylated product but also produced a significant amount of overdesilylated products. However, aqueous pyridinium *p*-toluenesulfonate (PPTs) was found to cleanly provide the desired monodesilylation product **8**.

The optimized conditions employed 5 equiv of aqueous PPTs in 2 volumes of water and gave >90% conversion to alcohol **8** within 8 h. Interestingly, the monodesilylated product appears to be in equilibrium with persilylated starting material **7** as well as very minor amounts of overdesilylated products. Another subtle observation was that when commercially available PPTs was dissolved in water and then aged, the profile for the monodesilylation reaction deteriorated over time in that large amounts of overdesilylated products began to appear. A likely culprit was that pyridine in the concentrated aqueous PPTs solution was evaporating off, thus leaving free *p*-TsOH available to indiscriminately promote silyl ether hydrolysis. This was easily remedied by freshly making the aqueous PPTs by mixing 5 equiv of *p*-TsOH with 5.5 equiv of pyridine (0.5 equiv extra pyridine as a buffer). So the final protocol was to make persilylated sugar **7**, wash with water to remove the imidazole−HCl byproduct, and then stir the crude dichloromethane solution with concentrated aqueous PPTs for 8 h to provide monodesilylated product, **8**. The phases were simply separated, and the dichloromethane layer was washed with pH 7 buffer, followed by azeotropic drying of the solution, which was then ready for the subsequent oxidation step.

Scheme 4. Persilylation/selective monodesilylation



4 **7** **8**

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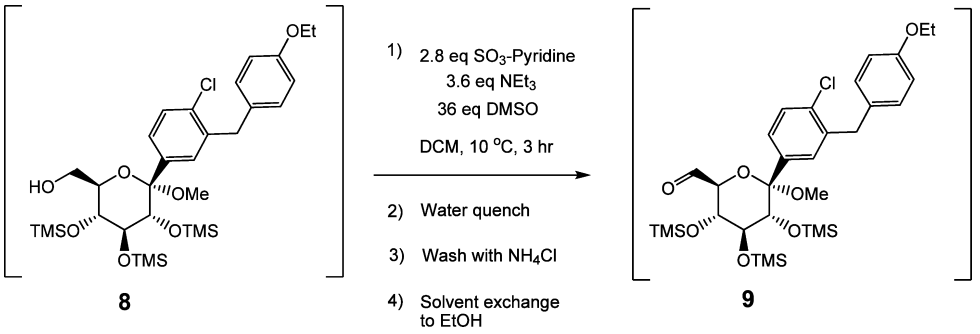
Scheme 5. Oxidation of C6 hydroxy group to aldehyde



Parikh–Doering Oxidation. The oxidation reaction to give aldehyde **9** used sulfur trioxide pyridine complex (Scheme 5). Initially, the reaction was run by dissolving SO_3-pyridine in DMSO, then adding this solution to the alcohol–triethylamine solution at room temperature per standard protocol.[15] This performed well on lab scale but gave poor results in the first Kilolab run due to longer processing times.

Follow-up experiments confirmed that as SO_3-pyridine was aged in DMSO at room temperature over 2 h, followed by addition of alcohol **8**, the conversion to aldehyde **9** dropped off significantly (<50% conversion). Furthermore, react-IR data showed that the DMSO–SO_3 adduct degraded over time in DMSO. Therefore, the procedure was modified so that alcohol **8**, NEt_3, and DMSO were dissolved in dichloromethane and cooled to 10 °C, then SO_3-pyridine was added portionwise as a solid or as a slurry in dichloromethane. After stirring 3 h at 10 °C, the reaction was typically complete.

During a brief solvent screen (CH_2Cl_2, EtOAc, THF, 2-MeTHF) of this reaction using 5 equiv of DMSO, impurity **10** (Figure 2) was observed at levels of 15% (CH_2Cl_2) to 100%

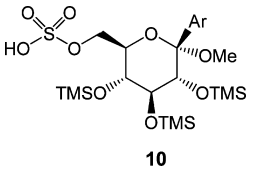


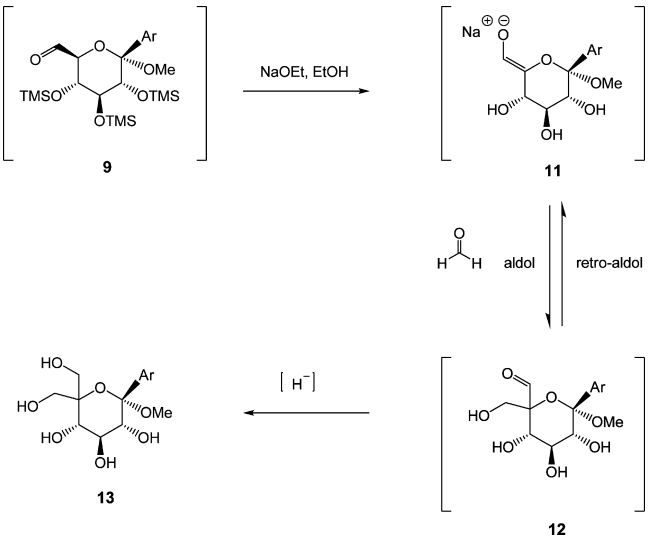
Figure 2. SO_3-adduct impurity.

(THF, 2-MeTHF). By increasing the amount of DMSO to 40 equiv, this impurity was significantly diminished with EtOAc or CH_2Cl_2 as solvent.

Aldol Crossed-Cannizzaro Reaction. In the next step, aldehyde **9** was treated with base in the presence of formaldehyde, promoting three sequential reactions: global desilylation and enolization to form sodium enolate **11**, an aldol reaction with formaldehyde to give aldol product **12**, and crossed-Cannizzaro reduction[16] of aldehyde **12** to give pentol product **13** (Scheme 6).

The main issue with this reaction is formation of undesired byproducts. Figure 3 shows the main impurities that have been identified by LCMS. Compound **4** is the most significant impurity and results from Cannizzaro reduction of **9** as well as from desilylation of **7** (present in starting material **9**). Initial reaction conditions used aqueous K_3PO_4 or Cs_2CO_3 as base and gave a ~50:50 ratio of **13**:**4**. This ratio was improved to ~80:20 by switching to anhydrous reaction conditions and using NaOEt as base. The elimination product **14** results from a dehydration reaction occurring in place of aldehyde enolate

Scheme 6. Aldol crossed-Cannizzaro reaction



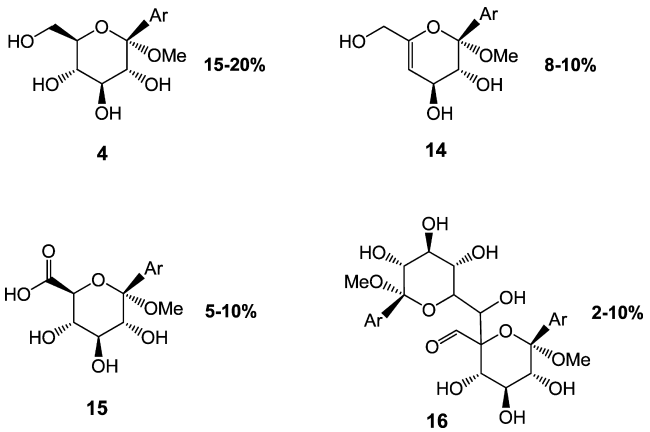


Figure 3. Aldol crossed-Cannizzaro reaction major byproducts.

addition to the formaldehyde electrophile. The carboxylic acid byproduct **15** forms when the starting material aldehyde acts as the hydride donor in the Cannizzaro reaction instead of formaldehyde, thus becoming oxidized in the process. The formation of self-aldol dimer **16** is surprising, especially at levels of 10% or higher. This finding makes more sense after realizing that the self-aldol dimer formation is likely not reversible (can form stable intramolecular hemiacetal under basic conditions) whereas the aldolization with formaldehyde has been shown to be readily reversible by HPLC. Carboxylic acid **15** and self-aldol

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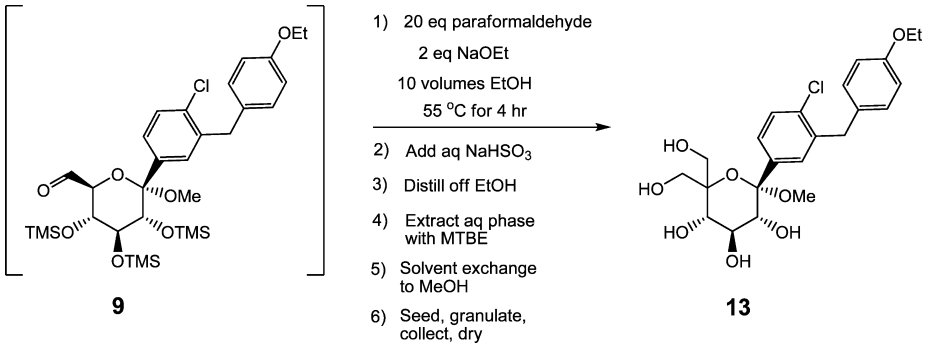
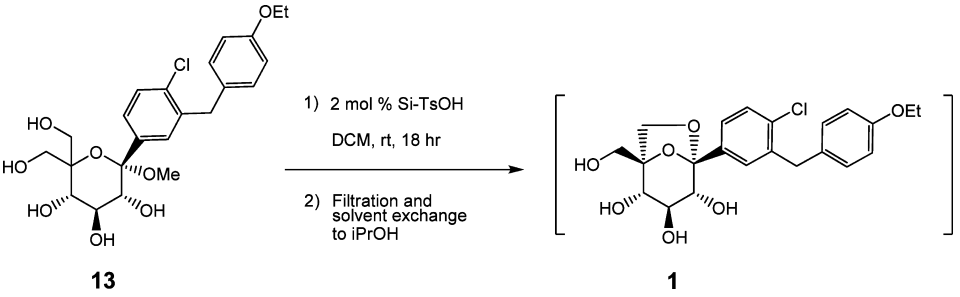
Scheme 7. Aldol crossed-Cannizzaro reaction conditions



Scheme 8. Bicyclic ketal formation



dimer **16** formation were suppressed by increasing to 20 equiv of paraformaldehyde.

The final process (Scheme 7) was to take the crude DCM solution of aldehyde **9** and exchange the solvent to ethanol, add paraformaldehyde (20 equiv), and warm the resultant slurry to 55 °C (paraformaldehyde not in solution). Then NaOEt (2 equiv) was added as a 21 wt % solution in ethanol to give a clear solution (NaOEt depolymerizes the paraformaldehyde). When the reaction was complete, 18 equiv of aqueous sodium bisulfite ($NaHSO_3$) was added to the 55 °C solution and stirred for 30 min. The $NaHSO_3$ reacts with excess formaldehyde to give the formaldehyde–sodium bisulfite addition compound.[17] This renders the excess formaldehyde nonvolatile during further batch processing. The remainder of the workup consisted of ethanol removal via distillation and extraction of product **13** into MTBE. Process safety testing of the aqueous bisulfite side stream solution, by warming to 60 °C and holding for 24 h, indicated the potential for the liberation of a noncondensable gas (formaldehyde and/or sulfur dioxide). After adjusting the pH of the side stream from its initial value of 5–6 up to 7, the pressure buildup in the test cell was <0.2 bar upon re-evaluation. Thus, the pH of waste streams generated during scale-up were adjusted to 7 before drumming up for disposal.

During early pilots, pentol **13** was purified by flash chromatography to remove the numerous reaction byproducts. The purified product spontaneously crystallized from a MeOH–toluene solution as the MeOH solvate. This material was subsequently used to seed a crude methanol solution of **13** post workup and afforded isolated pentol product in 97–98% purity. Interestingly, major impurity **4**, which was present at a ~20% level in the crude methanol solution, purged very well. This finding was even more surprising, given the fact that tetrol **4** was also isolated as the crystalline MeOH solvate in the first step of the synthesis as mentioned above (Scheme 2). Vacuum oven drying of the **13**-MeOH solvate drives off the methanol to leave behind amorphous material.

Intermediates **7**, **8**, and **9** were all oils or foams, and thus, the steps to make these compounds were telescoped together with no isolations. The main challenge of the telescoped sequence in converting tetrol **4** to pentol **13** was to avoid premature desilylation of reaction intermediates. Therefore, processing in the Kilolab was carried out continuously until product **13** was isolated as a solid in 41% overall yield.

The initially isolated pentol product **13** typically contained 2–3% of tetrol **4**. If this impurity is carried forward, it forms a dimer with final API that cannot be purged during crystallization of API, so a recrystallization of **13** was performed. Dried amorphous **13** containing impurity **4** quickly dissolved in MeOH and then gave a very thick suspension. When this mixture was warmed to 50 °C and held for 1 h, it became free-flowing, likely due to a form conversion. The isolated recrystallized product was obtained in 94% yield and ≥99.8% purity. Once again, the solvated methanol was removed via vacuum oven drying to give amorphous **13**. Thorough drying was required as residual MeOH levels of >5 wt % lead to incomplete reaction in the subsequent step.

Formation of Final API. The conversion of pentol **13** to bridged bicyclic ketal **1** was originally carried out in the presence of stoichiometric trifluoroacetic acid (Scheme 8). Although the cyclization readily occurred with 10 mol % TFA, using a solid-phase acid catalyst was more convenient for post reaction removal. Using a 1–2 mol % loading of SiliaBond tosic acid in dichloromethane gave clean conversion to **1**.[18]

When the bicyclic ketal formation was carried out in acetate solvents (EtOAc, iPrOAc), small amounts of acetylated impurities were observed. The reaction in dichloromethane typically goes to >98% completion after 1 h but needs to stir for ~18 h to completely consume starting material. After reaction completion, the solid-phase acid catalyst was simply filtered off, and the solution of **1** was taken directly into the

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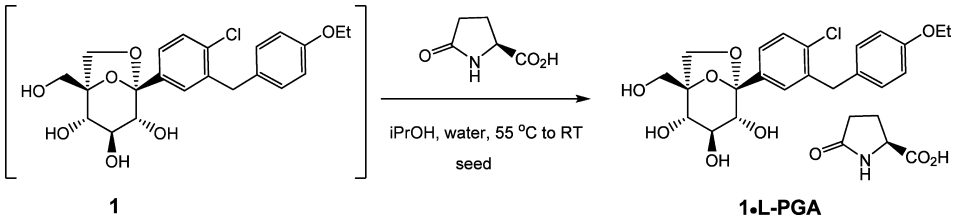
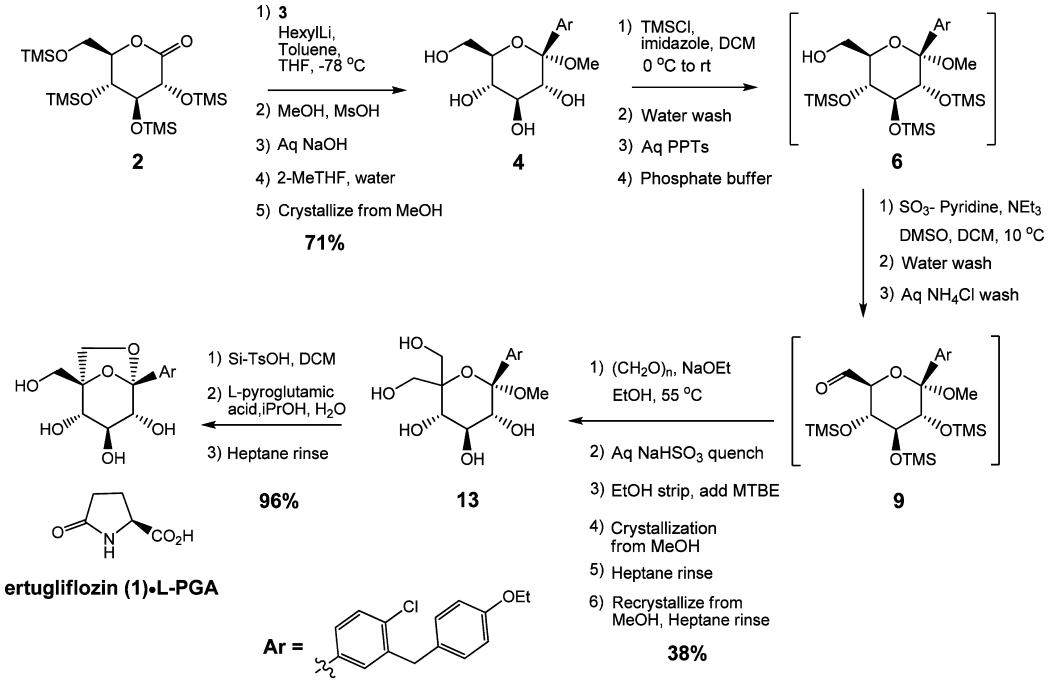
Scheme 9. L-Pyroglutamic acid co-crystal formation



Scheme 10. Overall synthetic scheme for ertugliflozin (1) ·L-PGA



cocrystallization step. The ability to start with very pure pentol **13** was a major advantage since the bicyclic ketal formation was quantitative and gave off one equivalent of methanol as the only byproduct. This was important since the cocrystallization process did not purge organic impurities very well due to the mostly aqueous nature (80% v/v) of the solvent mixture.

The final API exists as an amorphous foam that was inappropriate for clinical development; however, treatment of **1** with L-pyroglutamic acid (L-PGA) provides a clinically viable cocrystalline complex.[19] A concentrated solution of **1** in 1:1 2-propanol:water was warmed to 55 °C and treated with an aqueous solution of L-pyroglutamic acid followed by cooling, seeding, and drying to provide excellent yield of **1**·L-PGA in a typical ratio of 1.0:1.1 of **1**:L-PGA (Scheme 9). Final API purity was typically ≥99.9% by HPLC. The properties of the cocrystal are interesting in that bicyclic ketal **1** will selectively dissolve in most organic solvents except hydrocarbons and water, while L-pyroglutamic acid is highly soluble in water. These divergent properties made it challenging to identify a good solvent to rinse solids from the tank to the filter and to rinse the filter cake. In the end, since the solution contained only high-purity API, the chilled mother liquor was used for rinsing operations. The anhydrous **1**·L-PGA cocrystal has poor solubility in MTBE, so a high-yielding reslurry operation was possible. This was employed for some lots to deagglomerate the initially isolated solids as an alternative to milling, while other lots were milled with a Fitz mill. The MTBE reslurry was also demonstrated to remove non-API-related organic impurities. The one-pot conversion of pentol **13** to **1**·L-PGA was also explored using L-PGA as acid to promote the bicyclic ketal formation; however, the two step sequence described above gave better yield and purity of API.

■ CONCLUSIONS

The overall synthesis for the manufacture of ertugliflozin (**1**) is shown below in Scheme 10. The yield for the five-step process was 26%. This synthesis was employed for three campaigns that delivered seven discrete batches of API (from 1.1 kgA to 10.8 kgA) for a total of 43 kgA of API, enough to cover all project needs from regulatory toxicology studies through the start of phase 3 clinical trials. A few key highlights are the discovery of novel selective monodesilylation conditions for the primary silyl ether hydrolysis of the persilylated sugar, the efficient aldol crossed-Cannizzaro reaction to provide the requisite quaternary center at C5, and the identification of the MeOH solvate of pentol **13** as a key purification point in the synthesis to set the final API purity. This process is not commercially viable,[5] so this synthesis represents a "fit-for-purpose" route that facilitated toxicology and clinical testing to demonstrate the viability of ertugliflozin as a new treatment for diabetes.

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EXPERIMENTAL SECTION

General. TMS-gluconolactone **2** was purchased from SAFC and Asymchem. 4-Bromo-1-chloro-2-(4-ethoxybenzyl)benzene (**3**) was purchased from Asymchem.

Reactions were monitored by HPLC analysis using an Agilent 1100 series HPLC equipped with a Waters XBridge C18 column (4.6 mm × 75 mm), 3 min hold with 0.05%/60%/40% (v/v/v) DEA/methanol/water then gradient elution from 0.05%/60%/40% (v/v/v) DEA/methanol/water to 0.05% (v/v) DEA/methanol over 7 min, hold for 3 min, then from 0.05% (v/v) DEA/methanol to 0.05%/60%/40% (v/v/v) DEA/methanol/water with 2 min equilibration time; flow rate = 2.0 mL/min, 25 °C, 225 nm detection. Key retention times: **3** (3.42 min), **4** (1.28 min), **6** (4.10 min), **7** (4.53 min), **9** (4.14 min, 4.17 min − split peak), **13** (1.10 min), **1** (1.00 min). HRMS data obtained on an Agilent 1290 with Agilent 6230 TOF LC/MS.

*Preparation of (2S,3R,4S,5S,6R)-2-(4-Chloro-3-(4-ethoxybenzyl)phenyl)-6-(hydroxymethyl)-2-methoxytetrahydro-2H-pyran-3,4,5-triol (**4**).* A solution of TMS-gluconolactone (**2**) (14.09 kg, 30.2 mol) in toluene (17 L, 1.2 L/kg) was cooled to −15 °C and held for later use.

A solution of 4-bromo-1-chloro-2-(4-ethoxybenzyl)benzene (**3**) (8.00 kg, 24.6 mol) in toluene (48 L, 6 L/kg) and THF (16 L, 2 L/kg) was cooled to −84 °C followed by addition of hexyllithium (2.3 M in hexane, 8.04 kg, 26.5 mol) over 20 min at ≤−74 °C followed by stirring for 40 min. Once the halogen−metal exchange reaction was deemed complete by HPLC or React IR, the −15 °C toluene solution of **2** prepared above was added over 1 h at ≤−74 °C and then stirred 1 h. Next, a solution of MsOH (3.24 kg, 33.7 mol) in MeOH (40 L) was added as a 10 °C solution in 40 L over 50 min at ≤−71 °C. The reaction mixture was warmed to room temperature over 5 h and then stirred for 20 h to ensure >98% single anomer product present by HPLC (actual anomer ratio 99.3:0.7). The reaction was then basified by adding 5 M aqueous NaOH (3.1 L) and stirred for 1 h. The pH was checked by pulling a sample, stripping the organic solvent, and then reconstituting in 2-MeTHF/water and checking the pH of the aqueous phase which was found to be pH 9−10. Precipitated inorganic salts were filtered off and rinsed with toluene (24 L). The filtrate was concentrated to 80 L *in vacuo*, then diluted with toluene (48 L), and concentrated to 80 L total volume. This was done to remove THF and MeOH (<1% each) before aqueous workup. The crude toluene solution of **4** was diluted with 2-MeTHF (80 L) and washed with water (40 L) followed by concentrating the organic phase *in vacuo* to 32 L. To this solution was added toluene (48 L) followed by concentrating to 32 L *in vacuo* to remove 2-MeTHF solvent (<1%). Note: 2-MeTHF cosolvent was needed to give good phase separation during water wash. The solvent was exchanged from toluene to MeOH by doing a constant volume distillation *in vacuo* while adding MeOH (120 L) over 8 h at 30 °C. GC headspace results showed 0.05% remaining toluene. After cooling to room temperature, the MeOH solution of crude **4** was seeded with a MeOH slurry of crystalline MeOH-**4** solvate, stirred for 5 h at room temperature, and then cooled to −15 °C and stirred 2 h before isolating solids via filtration. The filter cake was washed with heptane (8 L), and the solids were dried in a vacuum oven at 40 °C for 47 h to provide 7.69 kg (71%) of **4** as an off-white solid. Note: Oven drying drives off MeOH such that the isolated product is amorphous **4** and not the crystalline **4**-MeOH solvate. ^{1}H NMR (MeOH-d_4, 600 MHz): δ 7.56 (d, J = 1.8 Hz, 1H), 7.47 (dd, J = 8.5, 2.1 Hz, 1H), 7.38 (d, J = 8.2 Hz, 1H), 7.11 (d, J = 8.2 Hz, 2H), 6.81 (d, J = 8.8 Hz, 2H), 4.10 (d, J = 15.3 Hz, 1H), 4.01 (d, J = 15.3 Hz, 1H), 4.00 (q, J = 7.0 Hz, 2H), 3.95 (dd, J = 12.0, 2.1 Hz, 1H), 3.83 (dd, J = 12.0, 5.6 Hz, 1H), 3.77 (t, J = 9.1 Hz, 1H), 3.61 (ddd, J = 10.0, 5.6, 2.0 Hz, 1H), 3.44 (t, J = 9.4 Hz, 1H), 3.11 (d, J = 9.4 Hz, 1H), 3.09 (s, 3H), 1.37 (t, J = 7.0 Hz, 3H). ^{13}C NMR (MeOH-d_4, 150 MHz): δ 159.0, 139.8, 139.3, 135.1, 133.2, 132.1, 130.9, 130.1, 128.5, 115.7, 102.6, 78.8, 76.2, 75.2, 71.9, 64.7, 63.0, 49.8, 39.5, 15.4. HRMS: (ESI$^-$) Calcd for $C_{22}H_{27}Cl_1O_7$ $(M - H)^-$: 437.1364, Found: 437.1373.

*Preparation of ((2R,3R,4S,5R,6S)-6-(4-Chloro-3-(4-ethoxybenzyl)phenyl)-6-methoxy-3,4,5-tris-(trimethylsilyloxy)tetrahydro-2H-pyran-2-yl)methanol (**6**).* A solution of imidazole (18.3 kg, 267.9 mol) and **4** (24 kg, 54.7 mol) in DCM (240 L, 10 L/kg) was cooled to 5 °C (Note: Some imidazole precipitates upon cooling.) and chlorotrimethylsilane (28.0 kg, 257.0 mol) was added over 40 min at ≤12 °C. The reaction was warmed to room temperature and stirred for 1 h at which point HPLC confirmed reaction completion. Note: The IPC sample was pulled and washed with water before analyzing to show 98% conversion. Water (120 L, 5 L/kg) was added followed by stirring for 20 min and then phase separation. A solution of pyridinium *p*-toluene sulfonate was made by dissolving *p*-toluenesulfonic acid monohydrate (51.5 kg, 270.7 mol) and pyridine (24.0 kg, 303.4 mol) in water (64 L, 2.7 L/kg). This PPTs solution was added to the crude DCM solution of **7** and the biphasic mixture stirred for 8 h at room temperature to give predominantly monodesilylation product **6**. Note: The ratio of monodesilylated product **6** to persilylated starting material **7** was 92:8 (equilibrium ratio). The layers were separated, and the DCM phase was washed with pH 7 phosphate buffer (120 L, 5 L/kg) . Note: buffer made by dissolving NaH_2PO_4 (3.06 kg) and Na_2HPO_4 (5.38 kg) in water (120 L). The DCM phase was azeotropically dried by concentrating under partial vacuum to 38 L. The crude DCM solution of **6** was taken directly into the next step with an assumed yield of 90% (32.25 kg) based on HPLC assay.

*Preparation of (2S,3R,4S,5R,6S)-6-(4-Chloro-3-(4-ethoxybenzyl)phenyl)-6-methoxy-3,4,5-tris-(trimethylsilyloxy)tetrahydro-2H-pyran-2-carbaldehyde (**9**).* Note: At the beginning of processing, an in-line aqueous oxone scrubber was set up to oxidize the dimethylsulfide liberated during processing. To the 38 L DCM solution containing **6** (~32.25 kg, 49.2 mol) was added DCM (124 L, 5 L/kg total DCM) followed by cooling to 10 °C. Dimethyl sulfoxide (138.4 kg, 1771.3 mol) was added (exothermic) followed by NEt_3 (18.0 kg, 177.9 mol). Sulfur trioxide−pyridine complex (22.0 kg, 138.2 mol) was slurried in DCM (324 L, 10 L/kg) and added to the reactor over 45 min at <12 °C and stirred for 3 h at 10 °C. Note: For smaller kilolab runs the SO_3−pyridine was added in three portions as a solid and gave slightly better conversion. Once reaction completion (≤5% of **6**) was confirmed by HPLC, water (149 L) was added followed by warming to room temperature and separating the phases. The DCM phase was washed with saturated aqueous NH_4Cl (149 L) and concentrated under partial vacuum to a final volume of 57 L. To this solution was added EtOH (127 L) followed by concentrating *in vacuo* to a final volume of 38 L. GC headspace confirmed removal of DCM (<1%). The crude EtOH solution of **9** was taken directly into the next step with an assumed yield of 85% (27.33 kg) based on HPLC assay.

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*Preparation of (2S,3R,4S,5S)-2-(4-chloro-3-(4-ethoxybenzyl)phenyl)-6,6-bis(hydroxymethyl)-2-methoxytetrahydro-2H-pyran-3,4,5-triol (**13**).* Note: Reactor vented through an aqueous MeOH scrubber to sequester formaldehyde and an oxone scrubber to oxidize dimethylsulfide. To the 38 L EtOH solution containing **9** (~27.33 kg, 41.8 mol) was added EtOH (194 L, 8.5 L/kg total EtOH). Paraformaldehyde (25.0 kg, 832.5 mol) was slurried in EtOH (76 L) and added to the reactor followed by heating to 55 °C. To the warm reaction mixture was added 20 wt % NaOEt in EtOH (27.11 kg, 83.6 mol) over 5 min and the reaction stirred for 4 h. Reaction completion (<5% of intermediate **12**) was confirmed by HPLC analysis. While still at 55 °C, a solution of sodium bisulfite (78.3 kg, 752.4 mol) in water (272 L) was added over 20 min followed by stirring another 30 min before cooling to 35 °C and stripping off most of the EtOH solvent under partial vacuum. The remaining aqueous phase was extracted with MTBE (273 L) followed by phase separation. The MTBE phase was washed with of water (164 L), then the water wash was back extracted with MTBE (150 L). The two MTBE extracts were combined and concentrated under partial vacuum to a final volume of 40 L followed by addition of MeOH (109 L). The solution was concentrated under partial vacuum to a volume of 40 L followed by addition of MeOH (109 L) and concentrating to a volume of 91 L. GC analysis indicated no residual MTBE was present. The crude MeOH product solution was seeded with crystalline **13**-MeOH solvate and then granulated for 8 h at room temperature before cooling to 5 °C, stirring for another 2 h, collecting solids *via* filtration, and rinsing with cold (−15 °C) MeOH (21 L) and room temperature heptane (55 L). After vacuum oven drying for three days at 40 °C, pentol **13** (10.63 kg, 41% from compound **4**) was isolated as a off-white solid with 98% purity. Note: Oven drying drives off MeOH such that the isolated product is amorphous **13** and not the crystalline **13**-MeOH solvate.

The main impurity **4** was purged to low levels from **13** by doing a recrystallization from MeOH. To MeOH (55 L, 6.3 L/kg) was added **13** (8.77 kg, 18.7 mol). The resulting slurry was warmed to 50 °C and stirred for 1 h (initially thick slurry becomes free-flowing) before cooling to room temperature and granulating for 2 h. The slurry was cooled to −15 °C and stirred for 2 h before collecting the solids *via* filtration followed by rinsing with cold (−15 °C) MeOH (9 L) and room temperature heptane (38 L). After vacuum oven drying for 23 h at 50 °C, pentol **13** (8.23 kg, 94%) was isolated as a pure white solid with 99.8% purity, and compound **4**, at <0.2% level. Note: Oven drying drives off MeOH such that the isolated product is amorphous **13** and not the crystalline **13**-MeOH solvate.

^{1}H NMR (MeOH-d_4, 600 MHz): δ 7.55 (d, J = 2.3 Hz, 1H), 7.50 (dd, J = 8.2, 2.3 Hz, 1H), 7.36 (d, J = 8.2 Hz, 1H), 7.11 (d, J = 8.8 Hz, 2H), 6.81 (d, J = 8.8 Hz, 2H), 4.18 (d, J = 11.2 Hz, 1H), 4.10 (d, J = 15.2 Hz, 1H), 4.03−3.93 (m, 4H), 4.01 (q, J = 7.0 Hz, 2H), 3.85 (d, J = 11.7 Hz, 1H), 3.79 (d, J = 9.4 Hz, 1H), 3.13 (s, 3H), 3.08 (d, J = 9.4 Hz, 1H), 1.37 (t, J = 7.0 Hz, 3H). ^{13}C NMR (MeOH-d_4, 150 MHz): δ 159.0, 140.2, 139.7, 135.0, 133.2, 132.2, 131.0, 130.0, 128.6, 115.7, 103.7, 81.7, 78.9, 74.0, 71.9, 65.8, 64.6, 63.7, 51.4, 39.5, 15.4. HRMS: (ESI$^-$) Calcd for $C_{23}H_{29}Cl_1O_8$ $(M - H)^-$: 467.1470, Found: 467.1478.

*Preparation of (1R,2S,3S,4R,5R)-5-(4-Chloro-3-(4-ethoxybenzyl)phenyl)-1-(hydroxymethyl)-6,8-dioxabicyclo-[3.2.1]octane-2,3,4-triol (**1**).* To a solution of **13** (8.23 kg, 17.5 mol) in DCM (41 L, 5 L/kg) was added Silia*Bond* tosic acid (516 g, 0.35 mol) followed by stirring for 18 h at room temperature. HPLC confirmed reaction completion (<0.2% **13** remaining). The silica-bound acid catalyst was removed via filtration through a 0.5 μm cartridge. The crude DCM solution of **1** was taken directly into the next step with an assumed yield of 100% (7.67 kg) based on HPLC assay.

*Preparation of **1**·L-PGA.* The DCM solution of **1** (~7.67 kg, 17.56 mol) was concentrated atmospherically to 19 L followed by addition of iPrOH (40 L) and then concentrated *in vacuo* down to 18.5 L (2.4 L/kg) at 35 °C. GC analysis confirmed DCM removal (<0.5%). The iPrOH solution of **1** was partially cooled to 30 °C, and water (10.7 L, 1.4 L/kg) was added, followed by weighing the solution (26.0 kg). More iPrOH (0.9 kg) was added to bring total solution weight to 26.9 kg and was heated to 55 °C. In a separate container was added water (31.7 L) and L-pyroglutamic acid (6.80 kg, 52.7 mol) to give a solution that was then added to the iPrOH solution of **1** over 1 h followed by cooling to room temperature over 2 h. Seeds of **1**·L-PGA were added to induce crystallization followed by stirring for 18 h at room temperature, cooling to 3 °C, and stirring another 2 h before collecting solids via filtration. The first 5 L of mother liquor was collected and used to rinse the remaining solids in the tank onto the filter followed by rinsing the filter cake with room temperature heptane (2 × 23 L). The isolated solids were dried in the vacuum oven at 35 °C for 6 h and then at 55 °C for 9 h to give **1**·L-PGA (9.59 kg, 96%) as a pure white solid with HPLC purity of 99.9%. The ratio of **1**:L-PGA was 1.0:1.10.

^{1}H NMR (MeOH-d_4, 600 MHz): δ 7.46 (d, J = 1.8 Hz, 1H), 7.39 (dd, J = 8.2, 2.3 Hz, 1H), 7.36 (d, J = 8.2 Hz, 1H), 7.09 (d, J = 8.8 Hz, 2H), 6.80 (d, J = 8.8 Hz, 2H), 4.26 (dd, J = 9.4, 4.7 Hz, 1H), 4.15 (d, J = 7.0 Hz, 1H), 4.04 (s, 2H), 3.99 (q, J = 7.0 Hz, 2H), 3.85 (d, J = 12.3 Hz, 1H), 3.79 (dd, J = 8.2, 1.2 Hz, 1H), 3.69 (d, J = 12.3 Hz, 1H), 3.66 (t, J = 7.9 Hz, 1H), 3.62−3.58 (m, 1H), 3.56 (d, J = 8.2 Hz, 1H), 2.53−2.46 (m, 1H), 2.41−2.29 (m, 2H), 2.20−2.14 (m, 1H), 1.36 (t, J = 7.0 Hz, 3H). ^{13}C NMR (MeOH-d_4, 150 MHz): δ 181.3, 175.9, 159.0, 139.9, 138.7, 135.2, 133.0, 131.0, 130.7, 130.0, 127.3, 115.7, 109.8, 86.4, 79.5, 77.9, 73.3, 68.2, 64.7, 62.2, 57.1, 39.5, 30.6, 26.2, 15.4. HRMS: (ESI$^-$) Calcd for $C_{22}H_{25}Cl_1N_1O_7$ $(M - H)^-$: 435.1210, Found: 435.1216.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Copies of ^{1}H and ^{13}C NMR spectra for compounds **4**, **13**, and **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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