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# Process Development of Sotagliflozin, a Dual Inhibitor of Sodium–Glucose Cotransporter-1/2 for the Treatment of Diabetes

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**ABSTRACT:** The development of an efficient manufacturing process for sotagliflozin (LX4211), a dual inhibitor of sodium–glucose cotransporter-1/2 (SGLT-1/2) for the treatment of diabetes, is described. Sotagliflozin features five contiguous chiral centers on the carbohydrate core flanked by a thioether group and a biaryl moiety. Three chiral centers are obtained from the starting material L-xylose, while the other two were established (or modified) *via* three highly stereoselective transformations: Luche reduction (dr: 97/3), dynamic kinetic resolution of anomeric hemiacetal (dr: 95/5), and Lewis acid-promoted thiolation (dr: 1000/1). Global deprotection of the resulting penultimate intermediate with catalytic sodium methoxide followed by recrystallization furnishes sotagliflozin. The longest linear sequence consists of 10 steps from L-xylose with an overall yield of 40%. This process has been performed on multi-hundred kilogram batches to satisfy the drug substance development demands.

**KEYWORDS:** *SGLT, diabetes, stereoselective, Luche reduction, DKR, thiolation*



## INTRODUCTION

Inhibitors of sodium-dependent glucose cotransporters (SGLT) for the treatment of diabetes mellitus[1] have attracted considerable attention. Several SGLT2-selective inhibitors, which lower blood glucose levels by inhibiting reabsorption of glucose in the kidneys, have received regulatory approval.[2] Clinical studies of Lexicon's drug candidate sotagliflozin (LX4211, Figure 1), a dual inhibitor of SGLT1 (expressed primarily in the intestine) and SGLT2 (expressed primarily in the kidneys), have shown benefits of reducing glucose absorption in the GI tract for patients with renal function impairment.[3]

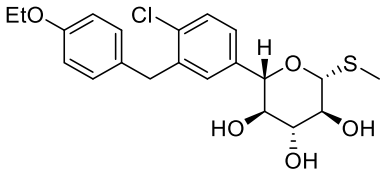


**Figure 1.** Sotagliflozin (LX4211).

Sotagliflozin features five contiguous chiral centers on the carbohydrate core flanked by a thioether group and a biaryl moiety. The initial medicinal chemistry synthetic route[4] started with protection of L-xylose as a bis-acetonide, followed by selective deprotection of the six-membered ring acetonide[5] to give monoacetonide **1** (Scheme 1). After the manipulation of protecting groups, the primary alcohol was oxidized to aldehyde **3** which was coupled with *in situ*-prepared aryl lithium **4-Li** to give benzylic alcohol **5**. Because of poor diastereoselectivity, **5** was oxidized to ketone **6** and then predominantly reduced to the desired diastereomer **7S** (dr: 9/1) *via* Luche reduction.[6] Deprotection of the acetonide and ring expansion under acidic conditions gave tetraol **8** (1/1 anomers). The latter was peracetylated to tetraacetate **9** and then treated sequentially with HBr/HOAc and NaSMe to afford triacetate **10R**.[7] Finally, deprotection by treatment with ammonia in MeOH furnished sotagliflozin. This synthesis is lengthy (15 steps) mainly due to the protection/deprotection steps and adjustment of the oxidation state. Additional drawbacks include the stability concerns of aldehyde **3**, cryogenic conditions required for preparing and handling aryl lithium **4-Li**, and the use of corrosive HBr.

A more concise medicinal chemistry route (11 steps)[4] was later devised starting with the conversion of L-glucose to a bis-acetonide, followed by selective deprotection of the six-membered ring acetonide to give **11** (Scheme 2). Cleavage of the vicinal diol with $NaIO_4$, followed by oxidation of the resulting aldehyde with bromine in methanol afforded methyl ester **12**.[8] Treatment of the latter with morpholine and catalytic *n*-BuLi gave morpholine amide **13**, an economical substitute[9] for the Weinreb amide. Coupling of **13** with aryl lithium **4-Li** gave ketone **6** which was converted to tetraacetate **9** following the same chemistry in the first medicinal chemistry route. TMSOTf promoted thiolation with thiourea, followed by treatment with MeI and Hunig's base afforded triacetate **10R**. Finally, deprotection with sodium methoxide in MeOH furnished sotagliflozin.

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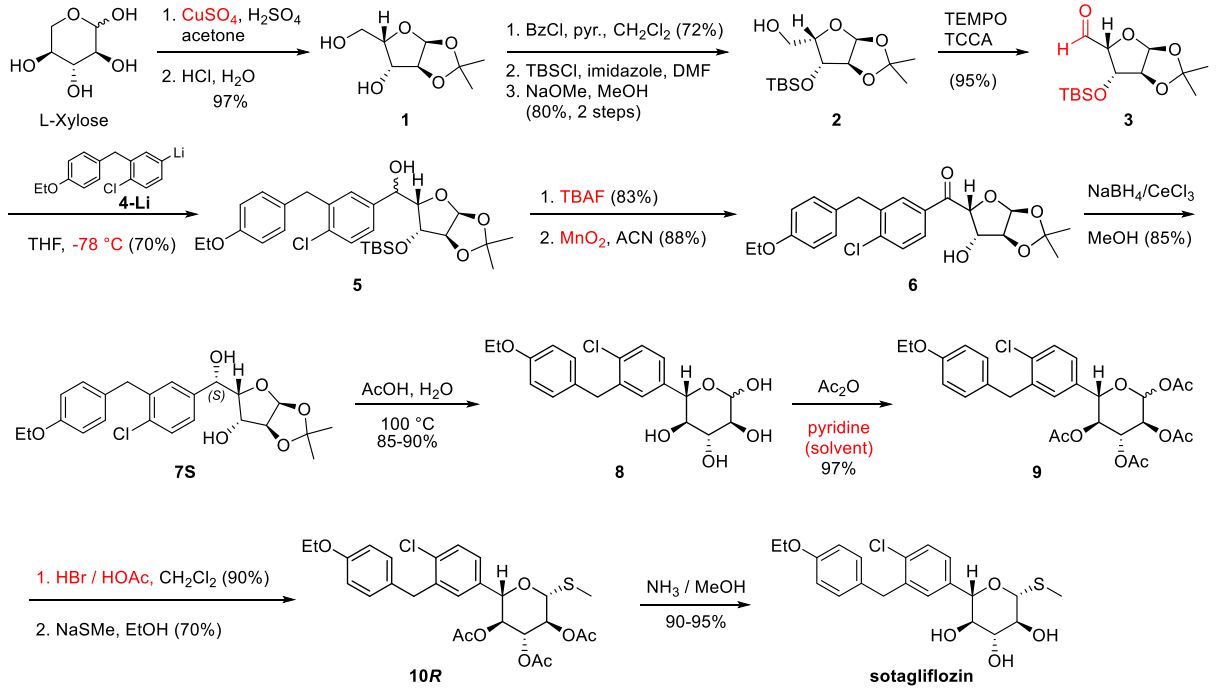
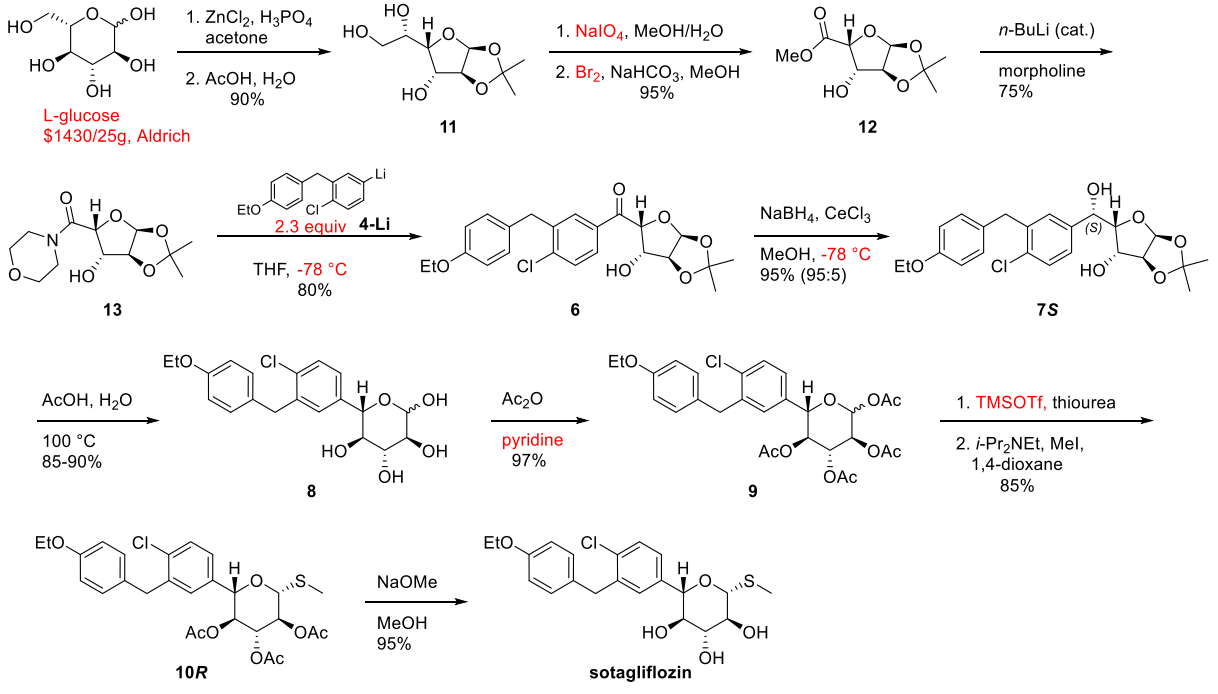
**Scheme 1. First Medicinal Chemistry Route to Sotagliflozin**




**Scheme 2. Second Medicinal Chemistry Route to Sotagliflozin**




While the second medicinal route is more concise and gives a higher yield (~30 *vs* ~12% overall), it also has several significant drawbacks. First, L-glucose is expensive ($1430/25 g, Sigma-Aldrich) and not available in bulk quantities. Sodium periodate is also expensive and poor in atom economy. Usage of hazardous elemental bromine is undesirable. Furthermore, the free hydroxy group on amide **13** consumes an equivalent of valuable aryl lithium **4-Li**. Therefore, a hybrid process chemistry route was designed to circumvent most of these issues (Scheme 3).

Using L-xylose as the starting material obviated the need for costly L-glucose and $NaIO_4$. Substituting **4-Li** with the corresponding aryl Grignard reagent (**4-MgX**) should circumvent the need for cryogenic conditions. Stereoselective Luche reduction of ketone **6** and Lewis acid-promoted thiolation of tetraacetate **9** using thiourea were retained. Isolation of several crystalline intermediates should facilitate impurity purging without resorting to column chromatography.

## RESULTS AND DISCUSSION

**Preparation of Morpholine Amide 13.** The synthesis of morpholine amide **13** started with the global protection of L-xylose to bis-acetonide **15**, followed by selective deprotection of



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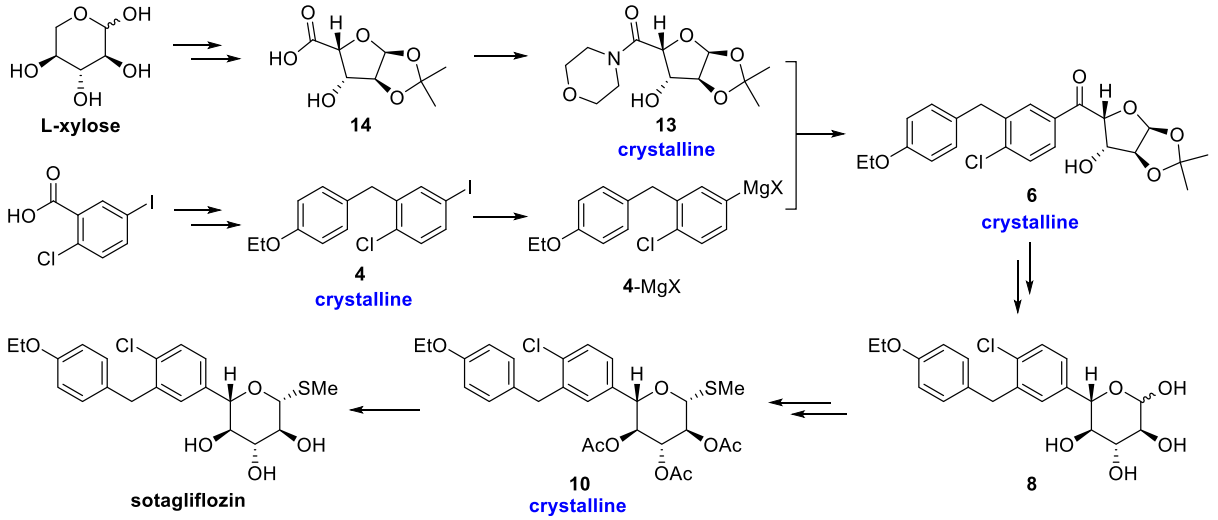
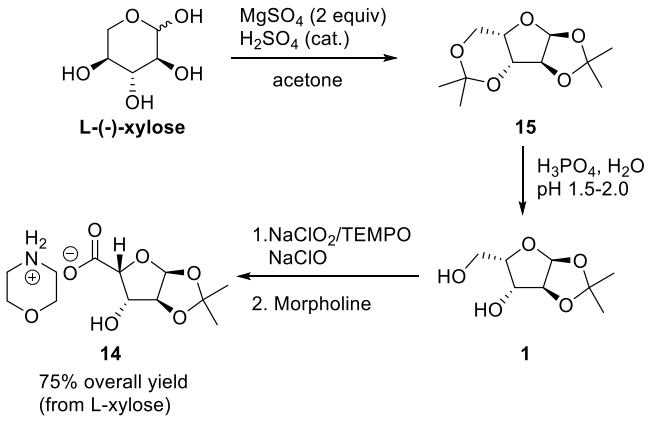
**Scheme 3. Process Chemistry Synthetic Plan for Sotagliflozin**




the six-membered ring acetonide to give monoacetonide **1** (Scheme 4). Oxidation of the exposed primary alcohol to carboxylic acid **14**, followed by amidation gave morpholine amide **13**.

**Scheme 4. Preparation of Carboxylic Acid 14**




For the bis-acetonide formation step, $CuSO_4$ (5 equiv) was substituted with environmentally benign $MgSO_4$ (2 equiv). A strong acid ($H_2SO_4$ cat.) was more effective than milder phosphoric acid, achieving complete conversion in ~20 h at 20−25 °C. After quenching the reaction with concentrated aqueous ammonia, the inorganic precipitate was removed by filtration, and the filtrate was concentrated and codistilled with water (until residual acetone <0.5% w/w) to give an aqueous solution of bis-acetonide **15**. For the selective deprotection of the six-membered ring acetonide, it is crucial to control the pH, temperature, and reaction time to minimize overhydrolysis. The optimal pH (~2) was readily achieved and maintained with 0.1 equiv of $H_3PO_4$. The reaction mixture was stirred at 20−25 °C until bis-acetonide **15** decreased to ~2% [gas chromatography (GC)]. Pushing the reaction further proved counterproductive due to overhydrolysis. To obviate the multiple tetrahydrofuran (THF) extractions of highly water-soluble product (**1**), the reaction mixture was neutralized with $K_2HPO_4$ and carried forward to the next step.

Oxidation of the primary alcohol (**1**) to carboxylic acid **14** was challenging due to the presence of a secondary alcohol and its sensitivity to acidic conditions. The lack of a chromophore also hampered the reaction optimization. The commonly used bleach/TEMPO (cat)/KBr (cat) protocol[10] gave unreproducible results (20−70% yield). TEMPO-catalyzed oxidation with $PhI(OAc)_2$ in acetonitrile/water was ineffective.[11] Trichloroisocyanuric acid[12] with catalytic TEMPO gave a cleaner reaction, but removal of the cyanuric acid byproduct was problematic. $RuCl_3$-catalyzed oxidation with bleach gave only 57% yield due to competitive oxidation of the secondary alcohol. Finally, oxidation with sodium chlorite ($NaClO_2$) and catalytic TEMPO and NaClO afforded promising results.[13] Solutions of $NaClO_2$ and $NaClO/K_2HPO_4$ were prepared separately to minimize the generation of chlorine dioxide (explosive at high concentrations).[14] A small portion of each solution was added to a phosphate-buffered (pH ~5) aqueous acetonitrile of **1** to initiate the reaction, and the remainders were then charged slowly to minimize the accumulation of oxidants in the reactor. The reactor headspace was swept with a gentle nitrogen flow to prevent chlorine/chlorine oxides from reaching high concentrations. The product (**14**) was extracted into 2-MeTHF after acidification to pH ~2. The crude product solution was not very stable due to cleavage of the acetonide catalyzed by the innate carboxylic acid. To mitigate the risk, morpholine (used for the next step) was added as a stabilizer. To our delight, the morpholine salt of **14** crystallized almost instantly. This discovery was utilized for isolating high purity **14** in 75% overall yield (3-steps from L-xylose, 400 kg).

The conversion of carboxylic acid **14** to morpholine amide **13** using conventional coupling reagents was surprisingly challenging. With EDC/HOBT or TBTU, the yields ranged from 30 to 60%. The purity was also unsatisfactory even after purification by silica gel chromatography. Another major challenge was the removal of reagent-related byproducts from highly water-soluble **13** (250 mg/mL). Therefore, alternative amidation methods that do not require stoichiometric coupling agents were investigated.

Yamamoto[15] reported that 3,5-bis(trifluoromethyl)-phenylboronic acid was an effective catalyst for the amidation of carboxylic acids (Scheme 5). However, its high cost and availability on scale prompted us to investigate cheaper boric acid as an alternative.[16] Gratifyingly, refluxing a mixture of carboxylic acid **14**, morpholine, and 20 mol % boric acid in toluene with azeotropic removal of water afforded complete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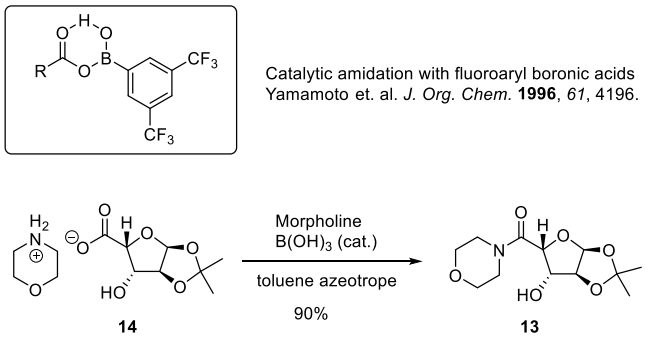
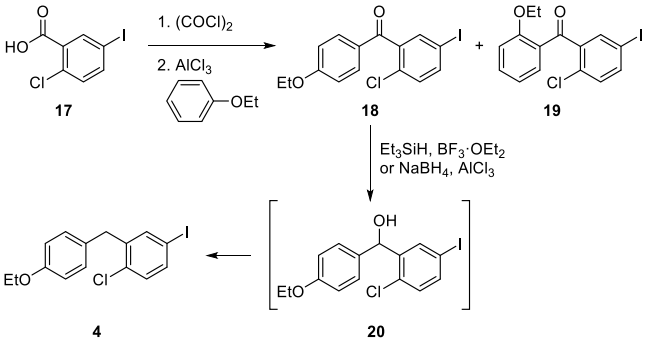
**Scheme 5. Amidation of 14 to Morpholine Amide 13**




conversion to morpholine amide **13**. As a bonus, boric acid could be easily removed by filtration. Excess morpholine could be removed by codistillation with toluene to minimize yield loss in the mother liquor to give **13** in excellent yield (90%) (toluene/*n*-heptane). On production scale, the codistillation was deemed too time consuming and morpholine was removed by aqueous acetic acid washes instead. The product was crystallized from DCM/*n*-heptane in 90% yield (600 kg scale).

**Preparation of Biaryl Iodide 4.** The synthesis of biaryl iodide **4** was based on the chemistry of the bromide analogue.[17] Treatment of 2-chloro-5-iodobenzoic acid (**17**) with oxalyl chloride and catalytic dimethylformamide (DMF) followed by $AlCl_3$-promoted Friedel–Crafts acylation of ethoxybenzene gave biaryl ketone **18** (Scheme 6). The unusually large variations

**Scheme 6. Preparation of Aryl Iodide 4**




in regioselectivity (8/1 to 100/1) were traced to the moisture levels in DCM (Table 1). By minimizing moisture in the reaction system, consistently high regioselectivity (~100/1) was achieved to afford **18** in 85% isolated yield and with 99% purity (425 kg scale).

Exhaustive reduction of biaryl ketone **18** was accomplished by treatment with $Et_3SiH$ and $BF_3{\cdot}Et_2O$ in acetonitrile affording biaryl iodide **4** in 89% yield with >99.5% purity (450 kg scale).[18] Curiously, the putative alcohol intermediate **20** was not observed during the reaction, presumably due to its higher reactivity. To further reduce the cost, an alternative process

**Table 1. Influence of Water on Regioselectivity**

| | regioisomer | |
|---|---|---|
| moisture in DCM (w/w %) | **18** (%) | **19** (%) |
| 0.15 | 88.2 | 11.8 |
| 0.07 | 92.3 | 7.7 |
| 0.01 | 99.5 | 0.5 |

using $NaBH_4$ and $AlCl_3$ in THF[a] was developed[19] affording biaryl iodide **4** in 90–95% yield with >99.5% purity (250 kg scale).

**Preparation of Ketone 6.** For the synthesis of ketone **6**, coupling of morpholine amide **13** with the aryl Grignard (**4-MgX**) was used instead of aryl lithium (**4-Li**) to avoid the required cryogenic conditions. The preparation of aryl Grignard by treatment of aryl iodide **4** with *i*-PrMgCl in THF was facile even at −30 °C (<0.5 h) but was conducted more economically at −10 °C in the plant. To avoid consuming an equivalent of valuable aryl Grignard, the hydroxy group in **13** was deprotonated with *t*-BuMgCl (1.1 equiv) without any epimerization of the $\alpha$-chiral center.

The coupling reaction of the aryl Grignard and morpholine amide **13** was facile at −10 to −20 °C affording ketone **6** without noticeable bis-addition or epimerization. However, significant yield variability (70–90%) was encountered without apparent changes in the reaction profile [high-performance liquid chromatography (HPLC)]. The root cause was traced to the formation of non-UV active *i*-propyl ketone **21a** due to inadvertent overcharge of *i*-PrMgCl. Therefore, *i*-PrMgCl was slightly undercharged initially, and a second charge (if necessary) was performed based on the amount of unreacted biaryl iodide **4**. This protocol avoided sampling/titration of highly air-/moisture-sensitive *i*-PrMgCl while still compensated for residual moisture in the reaction system (Scheme 7).

The reaction was initially quenched with aq $NH_4Cl$ and acidified with aq HCl to achieve a clean phase separation as well as to remove the morpholine byproduct. The latter was shown to catalyze the epimerization of the $\alpha$-chiral center of the ketone to **21b** (*via* an enamine intermediate) during processing. To mitigate the risk of premature cleavage of the acetonide due to the large pH swing during pH adjustment with HCl, the reaction mixture was quenched with 18% aqueous citric acid (~4 vol) instead. However, magnesium citrate sometimes precipitated which would not dissolve even at 40 °C. Fortunately, the induction period for the precipitation could be prolonged to >24 h by lowering the workup temperature to 0 °C. The product was crystallized from EtOAc/*n*-heptane in 85–90% yield and with >99% purity, and its absolute configurations were confirmed by single-crystal X-ray crystallography data (Figure 2).

**Conversion of Ketone 6 to Tetraacetate 9.** Conversion of ketone **6** to tetraacetate **9** entailed stereoselective Luche reduction (dr: 97/3), deprotection of the acetonide/concomitant ring expansion to tetraol **8** (1/1 anomers), followed by DKR (dynamic kinetic resolution) *via* stereoselective acetylation (dr: 96/4) (Scheme 8).

The screened multiple reagents ($NaBH(OAc)_3$, $Zn(BH_4)_2$, $BH_3{\cdot}$DEA, pinacolborane, 9-BBN *etc.*) gave poor results. Interestingly, catecholborane afforded the undesired diastereomer **7*R*** exclusively (Table 2, entry 1). $LiAlH(t\text{-}BuO)_3$ gave high stereoselectivity (dr: 92/8) at −65 °C, but its high cost and cryogenic conditions rendered this option unattractive (entry 2). Transfer hydrogenation with ((*R*,*R*)-TsDPEN, $(Cp^*IrCl_2)_2$, $HCO_2K$) was sluggish but gave high stereoselectivity (dr: 92/8) (entry 3). The best result was obtained using $NaBH_4/CeCl_3{\cdot}7H_2O$ in methanol (Luche reduction) (dr: 90/10) (entry 4). Surprisingly, decreasing the temperature was ineffective in enhancing the stereoselectivity (entries 4–7). Initial solvent screen (THF, ACN, THF/MeOH, and ACN/MeOH) suggested that the polar solvent (MeOH) should give better stereoselectivity. Unfortunately, highly polar solvent systems [DMF, dimethyl sulfoxide (DMSO), formamide, ethylene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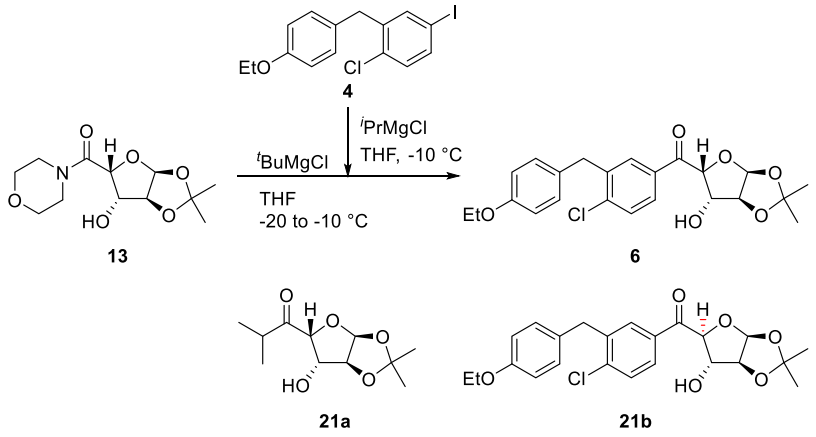
**Scheme 7. Preparation of Ketone 6**



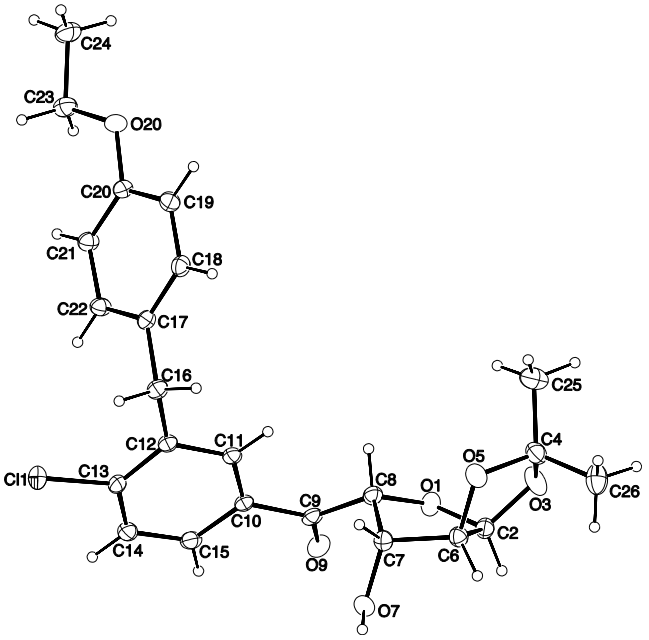




**Figure 2.** Single-crystal X-ray crystallography of ketone **6**. Note: ORTEP drawing of molecule of the asymmetric unit with 30% probability thermal ellipsoids.

glycol, MeOH/water, THF/water, and ACN/water] afforded disappointing results. Surprisingly, EtOH offered significantly higher stereoselectivity (dr: 95/5) than MeOH (entry 8). However, this trend did not hold for IPA (dr: 90/10) probably because most of the $CeCl_3{\cdot}7H_2O$ remained undissolved (entry 9).

**Table 2. Stereoselective Reduction of Ketone 6**

| entry | reagent | solvent | temp (°C) | (7*S*/7*R*) |
|---|---|---|---|---|
| 1 | catecholborane | THF | −15 | 0/100 |
| 2 | LiAlH(*t*-BuO)$_3$ | THF | −65 | 92/8 |
| 3 | (*R*,*R*)-TsDPEN, [Cp*IrCl$_2$]$_2$, $HCO_2K$ | ACN/$H_2O$ | 40 | 92/8 |
| 4 | $NaBH_4/CeCl_3{\cdot}7H_2O$ | MeOH | 20 | 90/10 |
| 5 | $NaBH_4/CeCl_3{\cdot}7H_2O$ | MeOH | 0 | 91/9 |
| 6 | $NaBH_4/CeCl_3{\cdot}7H_2O$ | MeOH | −25 | 92/8 |
| 7 | $NaBH_4/CeCl_3{\cdot}7H_2O$ | MeOH | −65 | 94/6 |
| 8 | $NaBH_4/CeCl_3{\cdot}7H_2O$ | EtOH | 20 | 95/5 |
| 9 | $NaBH_4/CeCl_3{\cdot}7H_2O$ | IPA | 20 | 90/10 |

With this promising lead, the reaction conditions were further optimized systematically. In contrast to methanol, decreasing the temperature markedly increased the stereoselectivity (58/1 at −25 °C; 100/1 at −65 °C) (Table 3, entries 3−4). Reducing the usage of $CeCl_3$ from 1.0 to 0.5 equiv did not incur significant penalty in stereoselectivity (Table 3, entry 5). However, further cuts did impart noticeable drops in selectivity (Table 3, entries 6−8).

With the low solubility of the starting material, a high solvent volume (>50 vol) was required for its complete dissolution.

**Scheme 8. Preparation of Tetraacetate 9*R***

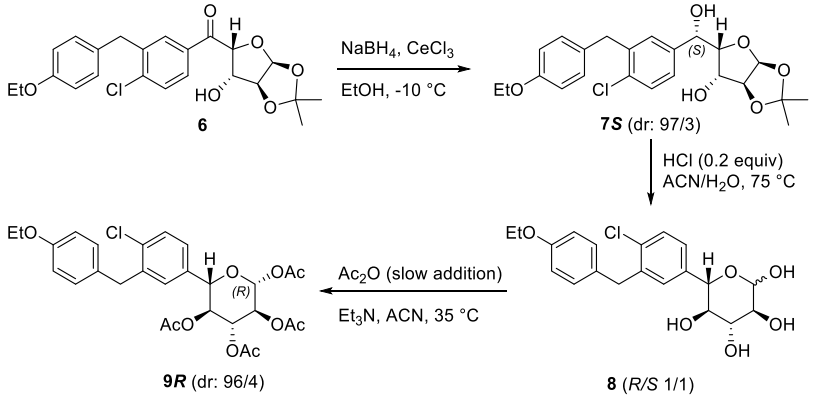





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**Table 3. Optimization of Luche Reduction in EtOH**

| entry | $CeCl_3 \cdot 7H_2O$ (equiv) | temp (°C) | EtOH (vol) | 7*S*/7*R* | 7*R* (%) |
|---|---|---|---|---|---|
| 1 | 1.0 | 22 | 20 | 17/1 | 5.6 |
| 2 | 1.0 | 0 | 20 | 30/1 | 3.3 |
| 3 | 1.0 | −25 | 20 | 58/1 | 1.7 |
| 4 | 1.0 | −65 | 20 | 100/1 | 1.0 |
| 5 | 0.50 | −25 | 20 | 66/1 | 1.5 |
| 6 | 0.25 | −25 | 20 | 38/1 | 2.6 |
| 7 | 0.10 | −25 | 20 | 9.6/1 | 9.4 |
| 8 | 0.05 | −25 | 20 | 6.3/1 | 13.7 |
| 9 | 0.50 | −25 | 10 | 50/1 | 2.0 |
| 10 | 0.50 | −5 | 5.6 | 30/1 | 3.2 |

Fortunately, the product was very soluble in the reaction medium which permitted reduced solvent usage by allowing the starting material to gradually dissolve as the reaction progressed. It was important to keep the addition rate of $NaBH_4$ below the dissolution rate of ketone **6** as $NaBH_4$ decomposed rapidly (<5 min) in the presence of $CeCl_3$ in protic solvents. Thus, a solution of $NaBH_4$ (0.4−0.5 equiv) in 1 N aq NaOH (to stabilize $NaBH_4$)[20] was slowly (5 h) added to a suspension of **6** in 5−6 volumes of ethanol at −5 to −10 °C to afford the product with high stereoselectivity (3% 7*R*) (Table 3, entry 10). The amount (0.1 vol) of 1 N NaOH was kept to a minimum to avoid significant deterioration in stereoselectivity. Residual boric acid must be completely removed by washing with dilute NaOH in the workup to prevent stalling of the acetylation of tetraol **8** due to the formation of boric acid−tetraol complex **32** (Scheme 9).[21] The crude product solution in acetonitrile was carried forward to the next step.

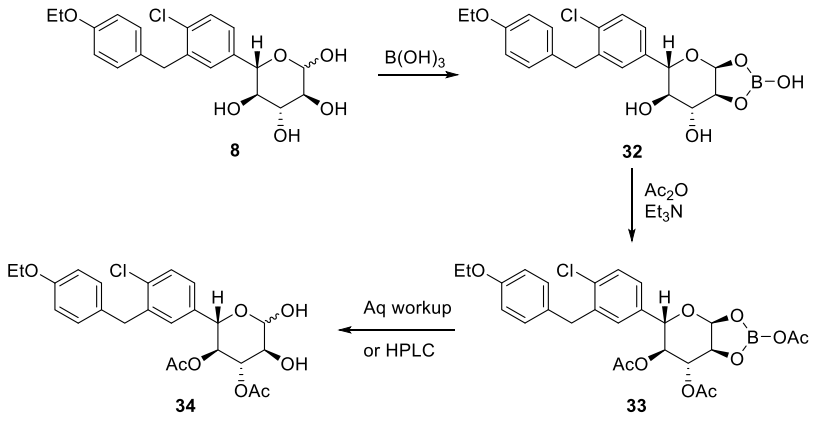
For the deprotection and concomitant ring expansion of diol 7*S* to tetraol **8**, the aqueous acetonitrile solution of 7*S* was treated with 0.2 equiv of HCl at 75 °C for 2−3 h to give a 1/1 anomeric mixture of tetraol **8**. Quenching the reaction with aqueous $K_2CO_3$ and extraction with MTBE led to significant emulsification during the brine wash as well as noticeable product degradation *via* the Cannizzaro reaction. Therefore, the reaction mixture was simply saturated with NaCl, and the resulting organic layer was carried forward to the next step after azeotropic distillation with acetonitrile (until KF <1.0%).

Peracetylation of tetraol **8** ($Ac_2O$, cat. DMAP) typically gave a 1/1 to 3/1 anomeric mixture of tetraacetate **9**. The stereoselectivity was considered inconsequential as both anomers were converted to the desired product in the TMSOTf-catalyzed thiolation. The discovery of a crystalline form of the major anomer (9*R*) encouraged us to introduce an isolation point for better impurity control. To minimize the yield penalty of losing the minor anomer (9*S*), conversion of the latter to the desired anomer (9*R*) *via* a crystallization-driven DKR was attempted. With mild Lewis acids ($Ag_2CO_3$ and AgOTs), no conversion was observed in acetic anhydride at 15 °C. Stronger Lewis acid ($BF_3 \cdot Et_2O$, 2 equiv) promoted the interconversion but in the opposite direction. For example, the undesired isomer (9*S*) increased from 40 to 80% in 4 h at 15 °C, indicating that the desired anomer is thermodynamically unfavorable. Indeed, under equilibration conditions ($Ac_2O$/AcOH/$H_2SO_4$ = 10/4/0.1, 90 °C 24 h), 9*S* increased to 91%.

Another strategy pursued was to leverage the facile anomeric equilibration of tetraol **8** to achieve DKR *via* stereoselective acetylation. Initial screening of bases in acetonitrile with catalytic DMAP gave disappointing results (dr: 1/1). Serendipitously, when DMAP was omitted, much higher selectivity was observed (dr: 8/1 with $Et_3N$), albeit at a slower reaction rate. Solvent screening results showed that highly polar solvents (DMSO, DMF, DMAc, and NMP) gave the lowest selectivity while chlorinated solvents (DCM, DCE, and chloroform) the highest (dr: 15/1 in chloroform). The stereoselectivity also improved with increasing $Et_3N$ charge, plateauing at 6 equiv. Surprisingly, decreasing the temperature from 20 to 0 °C led to decreased stereoselectivity (from 9/1 to 5/1). This unusual behavior was attributed to the significantly higher activation energy for the anomeric equilibration[22] than that of acetylation.[23] Consequently, decreasing the temperature imparts greater rate reduction of anomeric equilibration than that of the acetylation, leading to a deficiency of anomer 8*S* and thereby decreased selectivity. Conversely, lowering the concentration of acetic anhydride should decrease the acetylation rate without impacting the rate of anomeric equilibration. Indeed, excellent stereoselectivity (dr: 25/1) was achieved by slowly adding acetic anhydride (5 h) to a mixture of tetraol **8** and $Et_3N$ (6 equiv) in acetonitrile at 30−40 °C. The product (9*R*) was crystallized from IPA in 80% overall yield (from ketone **6**, 3-steps) with 99% purity.

**Stereoselective Thiolation of Tetraacetate 9 to Triacetate 10*R*.** Thiolation was achieved by treatment of the tetraacetate with TMSOTf and thiourea followed by MeI and Hunig's base to give predominantly the desired triacetate **10*R*** (dr: 94/6, Scheme 10). The high stereoselectivity was attributed to nucleophilic attack of thiourea from underneath the oxonium ion **22** stabilized by the neighboring acetate group. The resulting

**Scheme 9. Effect of Boric Acid in the Acetylation Step**



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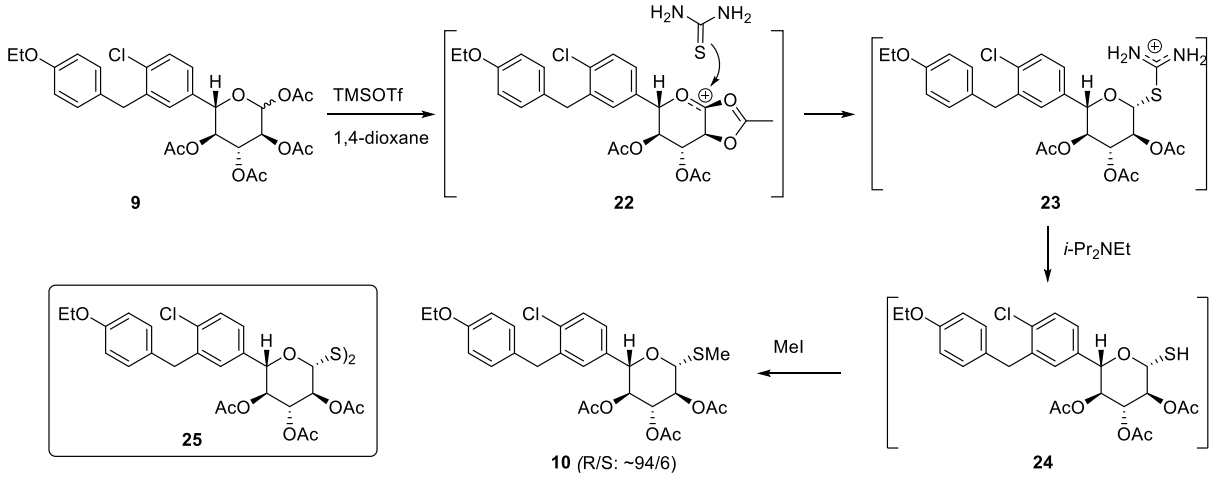
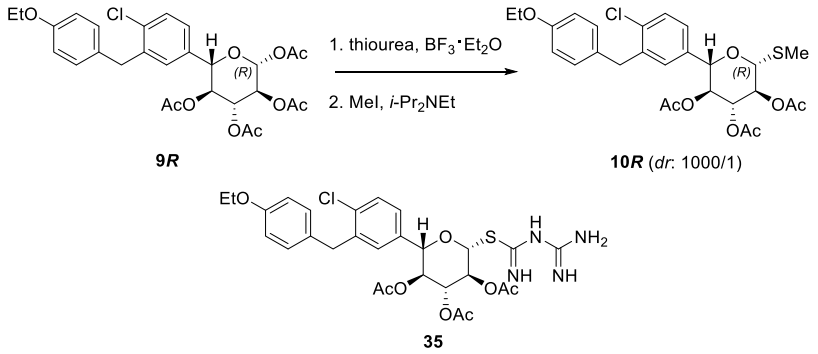
**Scheme 10. Stereoselective Thiolation of Tetraacetate 9**




**Scheme 11. Stereoselective Thiolation with $BF_3$·$Et_2O$**




isothiourea intermediate (**23**) proved quite stable under acidic conditions and could be isolated as its tetrafluoroborate salt. For the methylation stage, it is important to add MeI prior to Hunig's base to minimize the formation of disulfide dimer **25**.

As TMSOTf was a main cost driver for the thiolation step, more economical $BF_3$·$Et_2O$ was evaluated (Scheme 11).[24] With 1.5 equiv $BF_3$·$Et_2O$, only 3% isothiourea **23** was observed after 24 h at rt in 1,4-dioxane. The reaction was much faster in DCM, reaching 90% conversion under similar conditions. The thiolation reached 99% conversion in 3 h at 40 °C by increasing $BF_3$·$Et_2O$ to 2.5 equiv. As a bonus, the stereoselectivity was much higher due to milder reaction conditions (1000/1). Interestingly, the minor anomer of the tetraacetate (**9*S***) was essentially inert under milder reaction conditions. For the methylation step, a notable impurity (~4%) was identified as guanidine **35** (HRMS). It could be converted to triacetate **10*R*** but only slowly. The conversion was greatly accelerated by adding the cosolvent MeOH (2 vol).

Although the reaction was generally very clean, the formation of small amounts of side products derived from thiol **24** and DCM prompted a search for an alternative solvent. Toluene gave an intractable gel, while acetonitrile offered a less clean reaction. On the other hand, EtOAc and IPAc performed well, affording isothiourea **23** cleanly (99% conversion in 3−4 h, 55 °C). EtOAc was selected for a more efficient solvent exchange during workup and isolation. The product was isolated in 95% yield and >99% purity from IPA/water (300 kg scale).

**Global Deprotection to Sotagliflozin.** With penultimate triacetate **10*R*** in hand, a simple deprotection by treatment with NaOMe in MeOH afforded sotagliflozin. Only catalytic NaOMe (0.1 equiv) was required as the base was regenerated in MeOH. Interestingly, no partial deprotection intermediates were observed during the reaction. This was likely due to their higher reactivity because of shuttling of NaOMe by neighboring hydroxy groups. Adding water to the reaction mixture as an antisolvent often gave various sotagliflozin hydrates that were difficult to filter and dry. Subsequently discovered anhydrous form I sotagliflozin not only filtered and dried rapidly but also provided better impurity purging. It was consistently produced from MeOH/water (>70/30). The wet cake of "form I" sotagliflozin turned out to be a methanol solvate which readily desolvated upon drying. Single-crystal X-ray crystallography data confirmed the absolute configurations of sotagliflozin as well as the presence of methanol (Figure 3). Form I sotagliflozin was converted to the thermodynamically most stable polymorph (form II) by recrystallization in MEK/*n*-heptane in 95% yield.

## ■ CONCLUSIONS

An efficient manufacturing process for Lexicon's SGLT-1/2 dual inhibitor sotagliflozin was developed. The synthesis starts with protection of L-xylose as a bis-acetonide (Scheme 12). Selective deprotection of the 6-membered ring acetonide, followed by oxidation of the unveiled primary alcohol using sodium chlorite with catalytic TEMPO and bleach gave carboxylic acid **14**, which was isolated as a crystalline morpholine salt. Boric acid-catalyzed amidation of **14** with morpholine afforded morpholine amide **13** (an economical substitute for the Weinreb amide) in 90% yield. Coupling reaction of **13** with *in situ*-prepared aryl Grignard (**4-MgX**) afforded ketone **6** in a high yield (85−90%). The latter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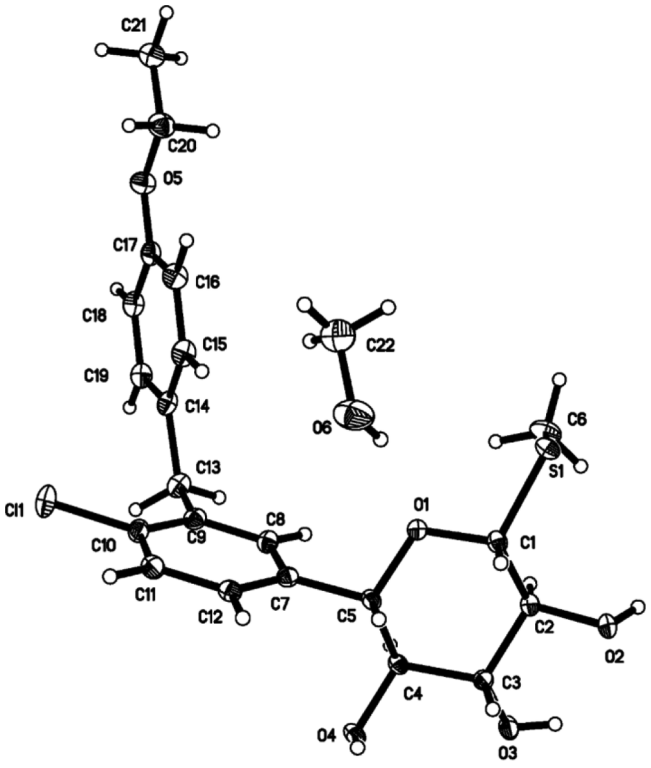



**Figure 3.** Single-crystal X-ray crystallography of the sotagliflozin methanol solvate.

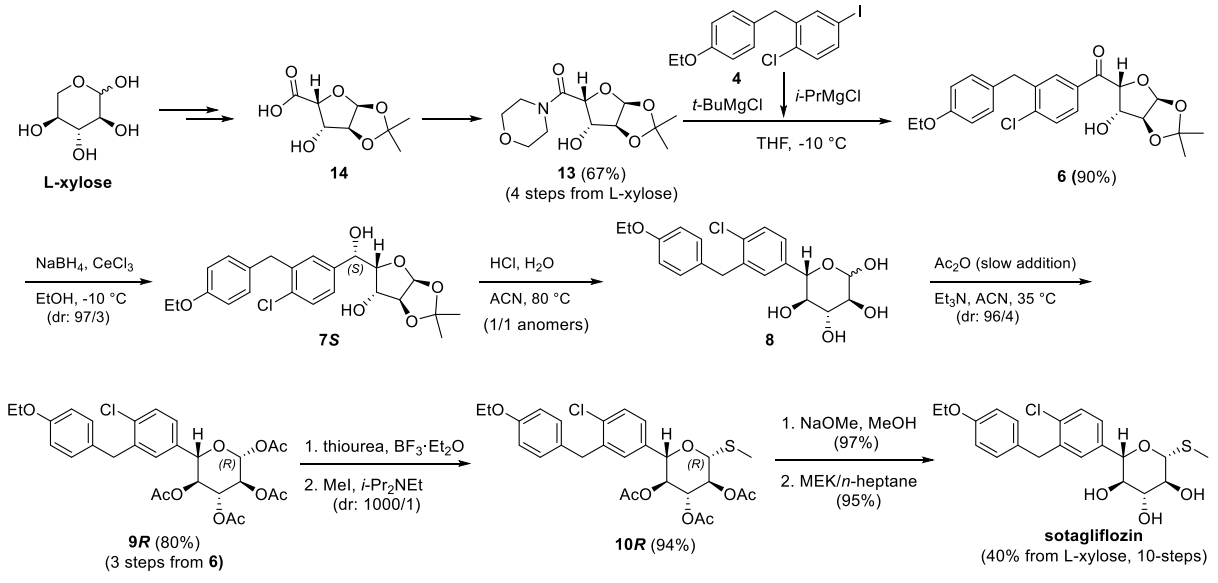
was reduced to 7***S*** *via* a highly stereoselective Luche reduction (dr: 97/3) in ethanol. Cleavage of the acetonide and the concomitant ring expansion by treatment with aqueous acid afforded tetraol **8** as a 1/1 anomeric mixture. DKR of tetraol **8** *via* stereoselective acetylation (dr: 96/4) afforded high purity (>99%) tetraacetate **9*R*** in 80% overall yield from ketone **6** (3-steps). By taking advantage of neighboring group assistance, a highly stereoselective (dr: 1000/1) Lewis acid ($BF_3$·$Et_2O$)-promoted thiolation of tetraacetate **9*R***, followed by methylation with methyl iodide afforded triacetate **10*R*** in excellent yield (95%) and purity (>99.5%). Global deprotection by treatment with catalytic sodium methoxide in MeOH, followed by recrystallization from MEK/*n*-heptane furnished sotagliflozin drug substance (form II). The longest linear sequence consisted of 10 chemical steps from L-xylose with ∼40% overall yield (average 91% per step). This process has been utilized for the manufacturing of thousands of kilograms of sotagliflozin to support the clinical studies for commercialization.

## EXPERIMENTAL SECTION

**General.** All reagents and materials were used as received, unless otherwise specified. Reactions were monitored by reverse-phase HPLC, using a C18 or phenyl-hexyl column with water/ACN or water/MeOH as a mobile phase and TFA as a modifier. Melting point information was acquired using a melting-point apparatus or based on the peak temperature on a differential scanning calorimeter (DSC). NMR spectra were acquired in deuterated solvents on 400 MHz ($^1$H) spectrometers. Mass spectrometry data were obtained during LC−MS analysis. Compound purity data were determined by reverse phase HPLC and/or $^1$H NMR with an internal standard.

*(3aS,5S,6R,6aS)-5-(Hydroxymethyl)-2,2-dimethyltetrahydrofuro[2,3-d][1,3]dioxol-6-ol* (***1***). A mixture of L-xylose (280.0 kg), acetone (2300 kg), and anhydrous $MgSO_4$ (505 kg, 2.25 equiv) was stirred for 30 min. Concentrated $H_2SO_4$ (53 kg, 0.3 equiv) was added at 20−25 °C and the reaction mixture stirred until reaction completion (∼24 h, residual L-xylose by HPLC with ELSD). The reaction was quenched with conc. aq ammonia (84 kg, ∼0.7 equiv) until the pH reached 7.5−8.5. The reaction mixture was filtered and the filter cake washed with acetone (970 kg). The combined filtrate was concentrated to a low volume under reduced pressure (0.08 MPa) at < 45 °C. Water (1680 kg) was added and the mixture was concentrated again until residual acetone was ≤0.5 wt %. The aqueous solution of bis-acetonide **15** was used for the next step. An analytical sample was obtained by concentrating the acetone solution to an oil. $^1$H NMR (DMSO-$d_6$): $\delta$ ppm 1.23 (s, 3H), 1.25 (s, 3H), 1.386 (s, 3H), 1.390 (s, 3H), 2.82 (d, $J$ = 13.5 Hz, 1H), 3.91 (d, $J$ = 1.0 Hz, 1H), 4.06 (dd, $J$ = 13.5, 2.4 Hz, 1H), 4.27 (d, $J$ = 2.2 Hz, 1H), 4.46 (d,

**Scheme 12. Sotagliflozin Manufacturing Process Summary**



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$J$ = 3.8 Hz, 1H), 5.87 (d, $J$ = 3.8 Hz, 1H); $^{13}$C NMR (100 MHz, DMSO-$d_6$): $\delta$ ppm 18.74, 26.03, 26.47, 28.80, 59.42, 71.10, 72.65, 84.06, 96.80, 104.50, 110.62.

The aq solution of bis-acetonide **15** was acidified to pH 1.8−2.2 with $H_3PO_4$ (16.6 kg, 0.1 equiv) and stirred at 20−25 °C until residual bis-acetonide **15** was ≤2.5% (∼24 h; product **1** and residual **15** were monitored by GC; over-hydrolysis product L-xylose by HPLC with ELSD). The reaction mixture was neutralized with $K_2HPO_4{\cdot}3H_2O$ (50.8 kg) to pH 6.0−7.0 and used for the next step. An analytical sample of diol **1** (hygroscopic and low-melting solid) was obtained by extraction with EtOAc, passing through a silica gel plug, concentrating to an oil, and crystallization from 2/1 *n*-heptane/EtOAc. GC−MS $[M + H]^+$ calcd, 191.1; found, 191.2; $^1$H NMR (DMSO-$d_6$): $\delta$ ppm 1.22 (s, 3H), 1.37 (s, 3H), 3.51 (dd, $J$ = 11.1, 5.8 Hz, 1H), 3.61 (dd, $J$ = 11.1, 5.1 Hz, 1H), 3.93−4.00 (m, 1H), 3.96 (s, 1H), 4.36 (d, $J$ = 3.8 Hz, 1H), 4.86 (br s, 2H), 5.79 (d, $J$ = 3.5 Hz, 1H); $^{13}$C NMR (DMSO-$d_6$): $\delta$ ppm 26.19, 26.73, 59.01, 73.59, 81.42, 85.19, 104.40, 110.44.

*Morpholin-4-ium (3aS,5R,6S,6aS)-6-Hydroxy-2,2-dimethyltetrahydrofuro[2,3-d][1,3]dioxole-5-carboxylate (**14**).* $NaClO_2$ (353 kg) was dissolved in water (810 kg) at 20−25 °C. Separately, 10% NaClO (540 kg) was added to a mixture of $K_2HPO_4$ (437 kg) in water (345 kg) at 20−25 °C with stirring to give a solution. $K_2HPO_4$ (111 kg), $KH_2PO_4$ (300 kg), acetonitrile (840 kg), and TEMPO (3.5 kg) were added to the aqueous solution of diol **1** obtained above. A portion of the $NaClO_2$ solution (227 kg) and the NaClO solution (60 kg) above were charged over 1 h at 15−25 °C. A gentle nitrogen sweep of the reactor headspace (>3 m$^3$/h) was maintained throughout the reaction to prevent accumulation of chlorine oxide in the headspace. A second portion of the $NaClO_2$ solution (305 kg) and NaClO solution (42 kg) were charged over ∼2 h at 15−25 °C. The remainder of the $NaClO_2$ solution (620 kg) was added over ∼3 h at 15−25 °C. After 1−2 h of aging, a portion of the NaClO solution (480 kg) was slowly (6−8 h) charged. Additional TEMPO (1.8 kg) was added followed by slow addition (6−8 h) of the remaining NaClO solution (560 kg). The reaction mixture was agitated at 20−25 °C until reaction completion (5−8 h) and then quenched with $Na_2SO_3$ (115 kg) in portions at 5−25 °C. The inorganic precipitate was filtered off and the filter cake washed with water (100 kg). The pH of the combined filtrate was adjusted to 7−8 with 30% NaOH (∼280 kg) and then washed with 2-MeTHF twice (100 kg × 2) to remove TEMPO-related neutral impurities. The aqueous layer was acidified with $H_3PO_4$ (600 kg) to pH = 2.0−2.2 and extracted with 2-MeTHF (1400 kg × 5). The combined organic layer was concentrated to 4000−5000 L under reduced pressure below 25 °C. Morpholine (198 kg) was charged in portions at 15−30 °C and the suspension aged at 20−25 °C for 3−4 h, slowly (5 h) cooled from −5 to 0 °C, and aged for 6−8 h. The solids were collected by filtration and dried under reduced pressure (0.08 MPa) at 15−30 °C for 12−16 h to afford the morpholine salt of the carboxylic acid **14** as a white solid (398 kg, 95% wt, 73.3% overall yield from L-xylose). mp 166 °C (DSC peak); $^1$H NMR ($D_2O$): $\delta$ ppm 1.25 (s, 1H), 1.40 (s, 1H), 3.18 (m, 2H), 3.84 (m, 2H), 4.30 (d, $J$ = 3.2 Hz, 1H), 4.53 (d, $J$ = 3.2 Hz, 1H), 4.58 (d, $J$ = 3.6 Hz, 1H), 5.96 (d, $J$ = 3.6 Hz, 1H); $^{13}$C NMR ($D_2O$): $\delta$ 25.1, 25.6, 43.1, 63.6, 75.0, 81.7, 84.2, 104.6, 112.5, 174.5.

*((3aS,5R,6S,6aS)-6-Hydroxy-2,2-dimethyltetrahydrofuro-[2,3-d][1,3]dioxol-5-yl)(morpholino)methanone (**13**).* A mixture of morpholine salt of **14** (650 kg), morpholine (260 kg, 1.3 equiv), boric acid (26 kg, 0.2 equiv), and toluene (2210 kg) was refluxed for 14−18 h with a Dean−Stark trap to remove water. After confirming completion of the reaction, the reaction mixture was diluted with toluene (580 kg), stirred at 30−50 °C, and filtered to remove solids. The filter cake was washed with toluene (230 kg), and water (1390 kg) was added to the combined filtrate. The mixture was acidified with AcOH (180 kg) to pH = 6−7 and the organic layer was washed with dilute AcOH (23 kg + 580 kg water) (aq pH = 6−7). The aqueous layer was extracted four times with DCM (4870, 4870, 3450, and 2300 kg) and the combined organic layer was concentrated under reduced pressure below 45 °C until residual DCM was ≤0.5%. The distillation residue was heated to 70−90 °C, diluted with heptane (3944 kg), cooled to 0−5 °C (6 h), and agitated for 10 h. The solid was filtered and dried under reduced pressure at 20−30 °C (24 h) to afford morpholine amide **13** as a yellow solid (520 kg, 99% wt, 90% yield). mp 137.2 °C (DSC peak); LC−MS $[M + H]^+$ calcd, 274.1; found, 274.1; $^1$H NMR ($CDCl_3$): $\delta$ ppm 1.29 (s, 3H), 1.45 (s, 3H), 3.49−3.38 (m, 2H), 3.80−3.55 (m, 6H), 4.42 (d, $J$ = 2.2 Hz, 1H), 4.55 (d, $J$ = 3.7 Hz, 1H), 4.57 (d, $J$ = 2.5 Hz, 1H), 5.06 (br s, 1H), 5.96 (d, $J$ = 3.7 Hz, 1H); $^{13}$C NMR ($CDCl_3$): $\delta$ ppm 25.94, 26.86, 42.17, 46.30, 66.49, 66.83, 75.59, 76.12, 83.64, 105.41, 111.77, 167.63; Anal. Calcd for $C_{12}H_{19}NO_6$: C, 52.74; H, 7.01; N, 5.13. Found: C, 52.71; H, 7.04; N, 5.14.

*(2-Chloro-5-iodophenyl)(4-ethoxyphenyl)methanone (**18**).* To a mixture of 2-chloro-5-iodobenzoic acid (**17**) (426 kg, 1.0 equiv), DMF (1.5 kg, 1.4 mol %), and methylene chloride (2820 kg) was slowly charged oxalyl chloride (230 kg, 1.20 equiv) at 15−25 °C. The mixture was aged at 20−30 °C for 2 h, concentrated to 500−600 L, and then diluted with methylene chloride (620 kg) to give a solution of acyl chloride. The latter was transferred into a mixture of ethoxybenzene (212 kg, 1.16 equiv) and $AlCl_3$ (247 kg, 1.24 equiv) in methylene chloride (1610 kg) at 5−15 °C. The reaction mixture was aged at 5−15 °C until reaction completion (2 h) and then quenched with 2 N aq HCl (1394 kg) at <30 °C. The organic layer was separated and washed sequentially with 2 N HCl (1170 kg), 10% sodium bicarbonate (2127 kg), and brine (1080 kg). The washed organic layer was concentrated to a low volume, diluted with ethanol (2655 kg) and water (425 kg), heated to 70−75 °C to dissolve the solids, then slowly cooled to 15−20 °C, and aged for 16 h to crystallize the product. The suspension was filtered and the filter cake was dried under reduced pressure at 40−50 °C to afford 511 kg of biaryl ketone **18** (88% yield, 99.9% purity by HPLC). mp 101−103 °C; $^1$H NMR ($CDCl_3$): $\delta$ ppm 1.44 (t, $J$ = 7.1 Hz, 3H), 4.10 (q, $J$ = 7.1 Hz, 2H), 6.92 (d, $J$ = 9.1 Hz, 2H), 7.17 (d, $J$ = 8.6 Hz, 1H), 7.66 (d, $J$ = 2.1 Hz, 1H), 7.70 (dd, $J$ = 8.4, 2.1 Hz, 2H), 7.76 (d, $J$ = 8.8 Hz, 2H); $^{13}$C NMR ($CDCl_3$): $\delta$ ppm 14.7, 64.0, 91.4, 114.5, 128.6, 131.0, 131.6, 132.6, 137.3, 139.6, 141.0, 163.8, 191.9; Anal. Calcd for $C_{15}H_{12}ClIO_2$: C, 46.60; H, 3.13. Found: C, 46.80; H, 3.28.

*1-Chloro-2-(4-ethoxybenzyl)-4-iodobenzene (**4**). Option (a) reduction with $Et_3SiH/BF_3{\cdot}OEt_2$.* To a mixture of biaryl ketone **18** (450 kg) and triethylsilane (455 kg) in acetonitrile (1450 kg) was charged $BF_3{\cdot}OEt_2$ (66 kg) at <30 °C and the mixture was aged for 0.5 h. Additional $BF_3{\cdot}OEt_2$ (331 kg) was slowly added below 30 °C and the mixture stirred at 20−30 °C until reaction completion (2 h). The reaction mixture was concentrated to 300−400 L (−0.09 MPa, <55 °C), diluted with water (2000 kg), cooled to 0−5 °C, aged for 2 h, and filtered. The wet cake was dissolved in acetonitrile (650 kg) at 45−50 °C, cooled to 0−5 °C, aged for 3−4 h, and filtered. The filter cake


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was dried under reduced pressure (−0.08 MPa) at 45−55 °C to afford 384 kg of biaryl iodide **4** (89% yield, 99.9% HPLC purity). *Option (b) reduction with $AlCl_3$/$NaBH_4$.* To precooled THF (444 kg, 0−5 °C) was added $AlCl_3$ (129 kg, 1.5 equiv) in portions below 35 °C (highly exothermic!).[b] The mixture was stirred at 20−25 °C until all the solid dissolved (2 h) and then cooled to 0−5 °C. $NaBH_4$ (29.4 kg, 1.2 equiv) was added and the mixture aged for 1 h at 0−5 °C before warming to 50 °C. A solution of ketone **18** (250 kg, 1.0 equiv) in THF (250 kg) was slowly added (5 h) and the reaction mixture aged at 65−70 °C until reaction completion (12 h). The reaction mixture was cooled to 15−20 °C and then slowly quenched into precooled (5−10 °C) 2 N HCl (1000 kg) below 25 °C (**caution**: gas evolution!). After aging for 0.5 h, MTBE (401 kg) was added and the mixture stirred for 0.5 h. The organic layer was separated and washed sequentially with 2 N HCl (520 kg), 7% aq $NaHCO_3$ (500 kg) (**caution**: gas evolution!), and 5% aq. $Na_2SO_4$ (516 kg). The washed organic layer was concentrated to 375−500 L below 40 °C and flushed with EtOH (480 kg × 2) until residual THF was <1.0%. The distillation residue was diluted with EtOH (750 kg) and heated to 50−55 °C to dissolve the solid. Water (376 kg) was slowly (3−4 h) added and the resulting suspension slowly (3−4 h) cooled to 15−20 °C, aged for 2−3 h, and filtered. The filter cake was washed with water (180 kg) and recrystallized from acetone/water by dissolving it in acetone (524 kg) at 20−25 °C and adding antisolvent water (1000 kg) over 2−3 h. After aging for 2−3 h, the suspension was filtered and the filter cake was washed with water (230 kg). Drying at 40−50 °C in a vacuum oven afforded 224 kg of biaryl iodide **4** (92% yield, 99.7% purity). mp 65.8 °C (DSC peak); HRMS, calcd for $C_{15}H_{15}ClIO$ $[M + H]^+$, 372.9856; found, 372.9851; $^1$H NMR ($CDCl_3$): $\delta$ ppm 1.45 (t, $J$ = 7.0 Hz, 3H), 4.00 (s, 2H), 4.05 (q, $J$ = 7.0 Hz, 2H), 6.88 (d, $J$ = 8.8 Hz, 2H), 7.08−7.13 (m, 3H), 7.46−7.51 (m, 2H); $^{13}$C NMR ($CDCl_3$): $\delta$ ppm 14.97, 38.12, 63.43, 91.79, 114.62, 129.96, 130.47, 131.23, 134.23, 136.58, 139.55, 141.60, 157.65; Anal. Calcd for $C_{15}H_{14}ClIO$: C, 48.35; H, 3.79; Cl, 9.51; I, 34.06. Found: C, 48.61; H, 3.75; Cl, 9.71; I, 33.77.

*(4-Chloro-3-(4-ethoxybenzyl)phenyl)((3aS,5R,6S,6aS)-6-hydroxy-2,2-dimethyltetrahydrofuro[2,3-d][1,3]dioxol-5-yl)-methanone (**6**).* To a solution of aryl iodide **4** (637 kg, 1.06 equiv) in THF (1730 L, 3.9 vol) was added *i*-PrMgCl (18%, 871 kg, 157 kg active, 0.95 equiv) over 5 h at 0 °C. The mixture was aged for 1 h at 0 °C to give the aryl Grignard **4-MgX** (additional *i*-PrMgCl may be added based on the IPC result). Meanwhile, to a solution of morpholine amide **13** (440 kg active, 1.00 equiv) in THF (1487 L) was added *t*-BuMgCl (20.3%, 1001 kg, 203 kg active, 1.08 equiv) over 5 h at −5 °C. The mixture was cooled to −10 °C and then the aryl Grignard prepared above was added over 5 h. After stirring for 1.5 h, IPC showed complete conversion. The reaction mixture was quenched into 18% aq citric acid (357 kg citric acid monohydrate + 1493 kg water) at 0−5 °C and stirred for 1 h. The organic layer was separated, washed with 25% aq NaCl (880 kg × 2), and concentrated to ∼1500 L under reduced pressure. The distillation residue was codistilled with EtOAc (1450 L × 3) and diluted with EtOAc (1450 L). It was passed through activated carbon cartridges, concentrated to ∼1350 L, and heated to 60 °C. *n*-Heptane (1221 kg) was added over 2 h, followed by seeds of ketone **6** (1.3 kg). After aging for 0.5 h, more *n*-heptane (2716 kg) was added over 2 h and the mixture aged for 1 h. The suspension was slowly cooled to 10 °C, aged, and filtered. The filter cake was washed with *n*-heptane (448 L) and dried to give ketone **6** (607.5 kg, 87% yield). mp 121.6 °C (DSC peak); LC−MS $[M + H]^+$ calcd, 433.1; found, 433.1; $^1$H NMR ($CDCl_3$): $\delta$ ppm 1.36 (s, 3H), 1.41 (t, $J$ = 7.0 Hz, 3H), 1.53 (s, 3H), 2.98 (d, $J$ = 4.6 Hz, 1H), 4.01 (q, $J$ = 6.8 Hz, 3H), 4.07 (d, $J$ = 12 Hz, 1H), 4.11 (d, $J$ = 12 Hz, 1H), 4.54 (dd, $J$ = 3.9, 3.2 Hz, 1H), 4.57 (d, $J$ = 3.8 Hz, 1H), 5.2 (d, $J$ = 2.8 Hz, 1H), 6.05 (d, $J$ = 3.5 Hz, 1H), 6.84 (d, $J$ = 8.6 Hz, 2H), 7.10 (d, $J$ = 8.6 Hz, 2H), 7.48 (d, $J$ = 8.3 Hz, 1H), 7.80 (d, $J$ = 2.0 Hz, 1H), 7.86 (dd, $J$ = 8.2, 2.2 Hz, 1H); $^{13}$C NMR ($CDCl_3$): $\delta$ ppm 14.84, 26.16, 26.89, 38.3, 63.34, 76.42, 82.09, 84.22, 105.31, 112.15, 114.67, 114.67, 128.3, 129.89, 129.95, 129.95, 130.22, 131.31, 133.92, 140.01, 140.52, 157.67, 195.84. Anal. Calcd for $C_{23}H_{25}ClO_6$: C, 63.81; H, 5.82; Cl, 8.19. Found: C, 64.17; H, 5.77; Cl, 8.43.

*(3aS,5S,6R,6aS)-5-((S)-(4-Chloro-3-(4-ethoxybenzyl)-phenyl)(hydroxy)methyl)-2,2-dimethyltetrahydrofuro[2,3-d]-[1,3]dioxol-6-ol (**7S**).* A solution of $NaBH_4$ (30.0 kg, 0.50 equiv) in 4.5% aq NaOH (89.3 kg) was slowly (5 h) added to a mixture of ketone **6** (680 kg, 1.00 equiv) and $CeCl_3$·$7H_2O$ (293 kg, 0.50 equiv) in EtOH (3600 L) at −10 °C. The mixture was aged for 0.5 h and HPLC showed complete conversion (>99%) (stereoselectivity: **7*S***/**7*R*** ∼97:3). The reaction mixture was quenched with water (1360 L) at <20 °C, aged for 1 h, concentrated to ∼1700 L, and then diluted with MTBE (4080 L) and water (2040 L). The mixture was acidified with 19% aq HCl (∼200 kg) to pH 2−3. The layers were separated and the organic layer was sequentially washed with 2% NaOH (1635 kg) and 10% NaCl (1600 kg × 3), concentrated to ∼2400 L, and codistilled with ACN (3800 L) to give a solution of crude **7*S*** in ACN (∼2400 L). A sample of a hydrate of **7*S*** was isolated from wet MTBE/heptane (1/5). X-ray diffraction confirmed its crystallinity, DSC showed a broad peak at ∼50 °C, and thermogravimetric analysis showed 3.8% weight loss between 30 and 60 °C. A sample of anhydrous **7*S*** was obtained as a white solid by crystallization from MTBE/heptane (1/5, 35−0 °C). mp 86 °C (DSC peak); $^1$H NMR ($CDCl_3$): $\delta$ ppm 1.30 (s, 3H), 1.40 (t, $J$ = 7.0 Hz, 3H), 1.45 (s, 3H), 3.17 (d, $J$ = 3.79 Hz, 1H), 3.97−4.01 (m, 3H), 4.03−4.05 (m, 2H), 4.09−4.12 (m, 2H), 4.48 (d, $J$ = 3.5 Hz, 1H), 5.15 (t, $J$ = 3.8 Hz, 1H), 6.00 (d, $J$ = 3.8 Hz, 1H), 6.79−6.86 (m, 2H), 7.09 (d, $J$ = 8.6 Hz, 2H), 7.19 (d, $J$ = 2.0 Hz, 1H), 7.26 (dd, $J$ = 8.0, 2.0 Hz, 1H), 7.39 (d, $J$ = 8.3 Hz, 1H); $^{13}$C NMR ($CDCl_3$): $\delta$ ppm 15.04, 26.29, 26.91, 38.57, 63.62, 73.04, 75.57, 82.24, 85.34, 105.20, 111.97, 114.80, 125.30, 128.73, 130.07, 131.31, 134.12, 138.25, 139.79, 157.71.

*(3S,4R,5R,6S)-6-(4-Chloro-3-(4-ethoxybenzyl)phenyl)-tetrahydro-2H-pyran-2,3,4,5-tetraol (**8**).* Water (1360 L, 2.0 vol) and 32% aq HCl (31 L, 0.20 equiv) were added to the solution of crude **7*S*** in ACN obtained above and the mixture was aged at 75 °C until reaction completion (2 h). The reaction mixture was cooled to <40 °C and salted with solid NaCl (272 kg). The resulting organic layer was separated, washed with 25% aq NaCl (1620 kg × 2), concentrated to 2.5 vol, and dried by azeotropic distillation with ACN (2280 L × 3) until KF <0.3%. The distillation residue (∼1700 L) was diluted with ACN (700 L), heated to 40 °C, and filtered to remove the small amount of NaCl precipitate to give a solution of tetraol **8** as a 1/1 anomer in ACN. LC−MS $[M + NH_4]^+$ calcd, 412.2; found, 412.0; $^1$H NMR (DMSO-$d_6$): $\delta$ ppm 1.29 (t, $J$ = 7.0 Hz, 3H), 3.03−3.10 (m, 1H), 3.14 (t, $J$ = 9.1 Hz, ∼0.5H), 3.25 (t, $J$ = 8.9 Hz, ∼0.5H), 3.31 (dd, $J$ = 9.5, 3.7 Hz, ∼0.5H), 3.54 (t, $J$ = 9.2 Hz, ∼0.5H), 3.93−4.00 (m, 4H), 4.05 (d, $J$ = 9.4 Hz, ∼0.5H), 4.46 (d, $J$ = 7.7 Hz, ∼0.5H), 4.51 (d, $J$ = 9.7 Hz, ∼0.5H), 5.01 (d, $J$ = 3.5 Hz, ∼0.5H) 6.83 (d, $J$ = 8.7 Hz, 2H), 7.08 (d, $J$ = 8.6 Hz, 2H), 7.21 (dd, $J$ = 8.3, 2.0 Hz, 1H), 7.30 (t, $J$ = 2.4 Hz, 1H) 7.36 (t, $J$ = 7.9


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Hz, 1H); $^{13}$C NMR (DMSO-$d_6$): $\delta$ ppm 14.71, 37.63, 62.89, 72.36, 74.86, 75.45, 76.73, 76.89, 92.81, 97.36, 114.30, 127.37, 127.50, 128.65, 129.59, 131.24, 131.78, 131.94, 137.94, 138.01, 139.31, 139.86, 156.92.

*(2R,3S,4R,5S,6S)-6-(4-Chloro-3-(4-ethoxybenzyl)phenyl)-tetrahydro-2H-pyran-2,3,4,5-tetrayl Tetraacetate (**9R**).* To the above-obtained solution of tetraol **8** in ACN was added $Et_3N$ (1325 L, 6.0 equiv) followed by slow addition (5 h) of $Ac_2O$ (887 L, 6.0 equiv) at 30−35 °C. After aging for 3 h, the reaction mixture was cooled to 5−10 °C, quenched with IPA (580 L, 0.85 vol), aged at 15−20 °C for 1 h, concentrated to ∼2040 L, diluted with IPA (2040 L), aged at 55 °C for 2 h, cooled to −5 °C over 3 h, and aged for 2 h. The suspension was filtered and the filter cake washed with precooled IPA (1600 L, −5 °C) and dried at <50 °C under reduced pressure to give 690 kg of **9R** as an off-white solid, with 79% overall yield from ketone **6**, 99.5% purity. mp 143.5 °C (DSC peak); LC−MS $[M + NH_4]^+$ calcd, 580.2; found, 580.3; $^1$H NMR (DMSO-$d_6$): $\delta$ ppm 1.29 (t, $J$ = 7.0 Hz, 3H), 1.69 (s, 3H), 1.94 (s, 3H), 2.02 (s, 3H), 2.06 (s, 3H), 3.92−4.03 (m, 4H), 4.89 (d, $J$ = 9.60 Hz, 1H), 5.08 (t, $J$ = 9.6 Hz, 1H), 5.17 (dd, $J$ = 9.9, 8.3 Hz, 1H), 5.48 (t, $J$ = 9.6 Hz, 1H), 6.02 (d, $J$ = 8.3 Hz, 1H), 6.83 (d, $J$ = 8.6 Hz, 2H), 7.06 (d, $J$ = 8.6 Hz, 2H), 7.27 (s, 1H), 7.28 (d, $J$ = 9.5 Hz, 1H), 7.42 (d, $J$ = 7.8 Hz, 1H); $^{13}$C NMR (DMSO-$d_6$): $\delta$ ppm 14.49, 19.84, 20.09, 20.14, 20.31, 37.21, 62.70, 69.89, 71.56, 71.84, 74.41, 90.93, 114.13, 126.59, 129.27, 129.42, 130.14, 130.71, 133.06, 135.09, 138.45, 156.79, 168.26, 168.67, 168.95, 169.29.

*(2S,3S,4R,5S,6R)-2-(4-Chloro-3-(4-ethoxybenzyl)phenyl)-6-(methylthio)tetrahydro-2H-pyran-3,4,5-triyl Triacetate (**10R**).* $BF_3{\cdot}Et_2O$ (203 kg, 2.48 equiv) was added to a mixture of tetraacetate **9R** (325 kg, 1.0 equiv), thiourea (49.3 kg, 1.12 equiv), and EtOAc (1174 L, 3.6 vol) at 55 °C and the mixture was aged at 55 °C for 3 h to give a thick suspension of isothiourea **23**. An analytical sample of **23**·$HBF_4$ salt was obtained by filtering a small sample of the suspension and washing the filter cake with water, followed by drying. mp 202.8 °C (DSC peak); LC−MS $[M + H]^+$ calcd, 579.2; found, 579.2; $^1$H NMR (DMSO-$d_6$): $\delta$ ppm 1.30 (t, $J$ = 7.0 Hz, 3H), 1.71 (s, 3H), 1.97 (s, 3H), 2.08 (s, 3H), 3.92−4.03 (m, 4H), 4.79 (d, $J$ = 9.4 Hz, 1H), 5.28−5.42 (m, 3H), 5.70 (d, $J$ = 9.3 Hz, 1H), 6.83 (d, $J$ = 8.6 Hz, 2H), 7.07 (d, $J$ = 8.6 Hz, 2H), 7.29−7.38 (m, 2H), 7.44 (d $J$ = 8.1 Hz, 1H), 9.10 (br s, 4H); $^{13}$C NMR (DMSO-$d_6$): $\delta$ ppm 14.61, 19.94, 20.16, 20.27, 37.44, 62.92, 68.87, 71.32, 72.60, 78.56, 80.26, 114.35, 126.93, 129.43, 129.56, 130.46, 130.84, 133.42, 135.03, 138.58, 156.99, 166.17, 168.38, 169.32, 169.42. After cooling the reaction mixture to −2 °C, MeI (107 kg, 1.30 equiv) was added, followed by MeOH (652 L, 2.0 vol) and slow addition of $i$-$Pr_2NEt$ (449 kg, 6.0 equiv). The reaction mixture was aged at 20 °C for 1 h and then at 35 °C until reaction completion (∼3 h). It was concentrated to 976 L (3.0 vol), codistilled with IPA (1305 L × 2), diluted with IPA (1305 L, 4.0 vol) and water (976 L, 3.0 vol), and aged at 20 °C for 1 h. The suspension was filtered, the filter cake washed sequentially with 2/1 IPA/water (1958 L, 6.0 vol) and IPA (1057 L, 3.3 vol), and dried to give 298 kg of triacetate **10R** as a white solid, 94% yield, >99.7% purity. mp 157.6 °C (DSC peak); LC−MS $[M + NH_4]^+$ calcd, 568.2; found, 568.3; $^1$H NMR (DMSO-$d_6$): $\delta$ ppm 1.29 (t, $J$ = 6.95 Hz, 3H), 1.70 (s, 3H), 1.94 (s, 3H), 2.04 (s, 3H), 2.09 (s, 3H), 3.92−4.03 (m, 4H), 4.70 (d, $J$ = 9.9 Hz, 1H), 4.88 (d, $J$ = 9.9 Hz, 1H), 5.05 (t, $J$ = 9.8 Hz, 1H), 5.14 (t, $J$ = 9.8 Hz, 1H), 5.36 (t, $J$ = 9.5 Hz, 1H), 6.80−6.86 (m, 2H), 7.04−7.11 (m, 2H), 7.25 (d, $J$ = 2.0 Hz, 1H), 7.30 (dd, $J$ = 8.2, 2.2 Hz, 1H), 7.42 (d, $J$ = 8.1 Hz, 1H); $^{13}$C NMR (DMSO-$d_6$): $\delta$ ppm 10.25, 14.63, 19.99, 20.24, 20.41, 37.37, 62.85, 68.72, 72.25, 72.92, 77.51, 80.99, 114.27, 126.57, 129.32, 129.63, 130.11, 130.87, 132.99, 136.05, 138.56, 156.95, 168.42, 169.13, 169.43.

*(2S,3R,4R,5S,6R)-2-(4-Chloro-3-(4-ethoxybenzyl)phenyl)-6-(methylthio)tetrahydro-2H-pyran-3,4,5-triol (Sotagliflozin Form I).* NaOMe (30 wt % in MeOH, 16 kg, 0.08 equiv) was added to a suspension of triacetate **10R** (597 kg, 1.0 equiv) in MeOH (2474 L, 4.2 vol) and the mixture aged at 45 °C until reaction completion (∼4 h). Water (961 L, 1.61 vol) was added and the mixture was seeded with LX4211 (2.4 kg form I) at 40 °C, aged (6 h), cooled to −7 °C (5 h), aged (6 h), and filtered. The filter cake was washed with cold (−10 °C) MeOH/water (416/179 L) and dried under reduced pressure to give 448 kg of sotagliflozin (form I) as a white solid, 97% yield, 99.9% purity. LC−MS $[M + NH_4]^+$ calcd, 442.2; found, 442.0; mp 123 °C (DSC peak); $^1$H NMR (DMSO-$d_6$): $\delta$ ppm 1.30 (t, $J$ = 6.9 Hz, 3H), 2.04 (s, 3H), 3.17 (ddd, $J$ = 9.5, 8.6, 5.7 Hz, 1H), 3.19 (ddd, $J$ = 9.5, 8.6, 5.7 Hz, 1H), 3.27 (dt, $J$ = 8.6, 5.0 Hz, 1H), 3.97 (q, $J$ = 7.0 Hz, 2H), 3.95−4.02 (m, 2H), 4.10 (d, $J$ = 9.5 Hz, 1H), 4.35 (d, $J$ = 9.5 Hz, 1H), 4.95 (d, $J$ = 5.7 Hz, 1H), 5.13 (d, $J$ = 5.0 Hz, 1H), 5.22 (d, $J$ = 5.7 Hz, 1H), 6.84 (d, $J$ = 8.8 Hz, 2H), 7.10 (d, $J$ = 8.8 Hz, 2H), 7.21 (dd, $J$ = 8.1, 2.1 Hz, 1H), 7.27 (d, $J$ = 2.1 Hz, 1H), 7.39 (d, $J$ = 8.1 Hz, 1H); $^{13}$C NMR (DMSO-$d_6$): $\delta$ ppm 10.95, 14.65, 37.56, 62.83, 72.07, 74.32, 77.89, 80.58, 85.35, 114.25, 127.06, 128.73, 129.63, 130.42, 131.05, 132.01, 138.03, 139.02, 156.89. Anal. Calcd for $C_{27}H_{31}ClO_8S$: C, 59.35; H, 5.93; Cl, 8.34; O, 18.83; S, 7.55. Found: C, 59.29; H, 5.95; Cl, 8.45; O, 18.88; S, 7.48.

*Sotagliflozin Form II.* Sotagliflozin (form I, 193 kg) was dissolved in methyl ethyl ketone (MEK) (763 L, 4.0 vol) at 55−60 °C and filtered through a polishing filter with a small rinse of MEK (153 L, 0.8 vol). *n*-Heptane (preheated to 65−70 °C) (1435 L, 7.4 vol) was added over ∼2 h followed by sotagliflozin form II seeds (2.1 kg). The mixture was aged at 65−70 °C for 6 h and more *n*-heptane (preheated to 65−70 °C) (1111 L, 4.9 vol) was added over 7 h. The mixture was aged at 75−80 °C for 7 h, cooled to 20 °C over 4 h, and aged. The suspension was filtered and the filter cake was washed with *n*-heptane (4.8 vol). The wet cake was dried under reduced pressure furnishing sotagliflozin form II (DSC peak 134 °C) as the final drug substance (183 kg, 95% yield).

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.oprd.0c00359.

Copies of $^1$H and $^{13}$C NMR spectra for new compounds (PDF)

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## Notes

The authors declare no competing financial interest.

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## ■ ADDITIONAL NOTES

[a]Satisfactory safety evaluation results were obtained before being implemented in the plant.

[b]Satisfactory safety evaluation data were obtained before scale-up.

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