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Efficient Synthesis of Empagliflozin, an Inhibitor of SGLT-2, Utilizing an $AlCl_3$-Promoted Silane Reduction of a β-Glycopyranoside

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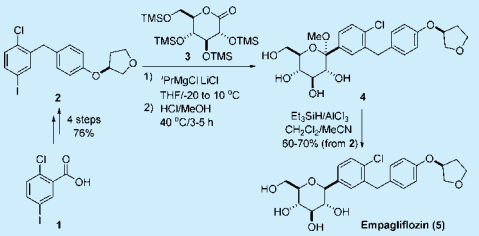
Supporting Information

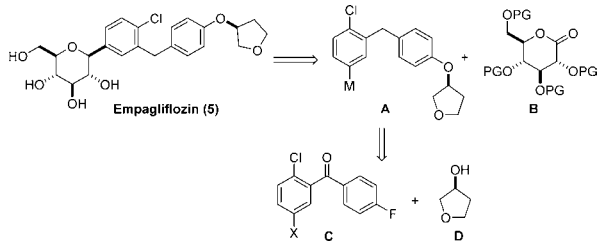
ABSTRACT: An efficient production synthesis of the SGLT-2 inhibitor Empagliflozin (**5**) from acid **1** is described. The key tactical stage involves I/Mg exchange of aryl iodide **2** followed by addition to glucono lactone **3** in THF. Subsequent in situ treatment of the resulting lactol with HCl in MeOH produces β-anomeric methyl glycopyranoside **4** which is, without isolation, directly reduced with Et_3SiH mediated by $AlCl_3$ as a Lewis acid in CH_2Cl_2/MeCN to afford **5** in 50% overall yield. The process was implemented for production on a metric ton scale for commercial launch.



Empagliflozin (**5**), currently in late phase development along with other similar compounds including Dapagliflozin and Canagliflozin, is a medicinally important aryl glycoside intended for treatment of type 2 diabetes.[1] Due to potentially high commercial importance, we required development of an efficient process to satisfy the need for metric ton production of **5**.[2]

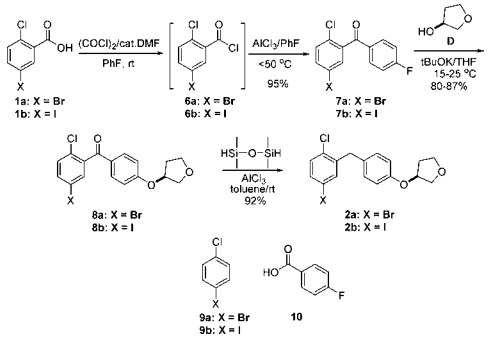
Based on the popular methodology developed by Kishi and others[3] that addresses the diastereoselective synthesis of β-anomers of *C*-glycosides utilizing an α-face hydride reduction of an anomerically stabilized carbenium intermediate,[4] a retrosynthetic pathway was proposed (Scheme 1). Empagliflozin **5**, bearing a β-aryl substituent at the *C*-1 position, can be disconnected to the key aryl-metal **A** and δ-gluconolactone derivative **B**. Aryl-metal species **A** can be readily obtained via fluorobenzophenone **C** and chiral 3-hydroxy tetrahydrofuran **D**.

Scheme 1. Retrosynthetic Analysis of Empagliflozin 5



Our studies began by focusing on obtaining access to aryl-metal species **A**. We first utilized a highly regioselective Friedel–Crafts reaction of 5-halo-2-chlorobenzoyl chlorides **6a/b**,[5] which were prepared from commercially available 5-halo-2-chlorobenzoic acids **1a/b** (Scheme 2). Fluorobenzophenones **7a/b** were subsequently isolated in ~95% yield following recrystallizations from aqueous isopropanol.

Scheme 2. Synthesis of Iodo- and Bromo-Substituted 2a/b



Aromatic substitution of **7a/b** was performed with commercially available (*S*)-3-hydroxytetrahydrofuran **D** and ^{t}BuOK in THF at 15–25 °C to afford benzophenones **8a/b** in 80–87% isolated yields after a solvent switch and direct crystallization from aqueous isopropanol. It is worthy to note that a high water content in the THF solution of **7a/b** and (*S*)-3-hydroxytetrahydrofuran led to an undesirable level of degradation products **9a/b** and **10**, leading to lower recovery of benzophenones **8a/b**. Reduction of **8a/b** was achieved using 1,1,3,3-tetramethyldisiloxane in the presence of aluminum chloride in toluene. The reduced products **2a/b** were isolated in 92% yield by crystallization from aqueous acetonitrile after basic treatment of the crude reaction mixture with 10% NaOH to destroy polymeric siloxane byproducts.

We initiated formation of the aryl-metal species **A** using bromide **2a** first. It was found that Br/Mg exchange of **2a** with the ^{i}PrMgCl·LiCl complex proceeded slowly, even at an elevated temperature of up to 40 °C which also led to simultaneous decomposition.[6] Br/Li exchange with ^{n}BuLi or

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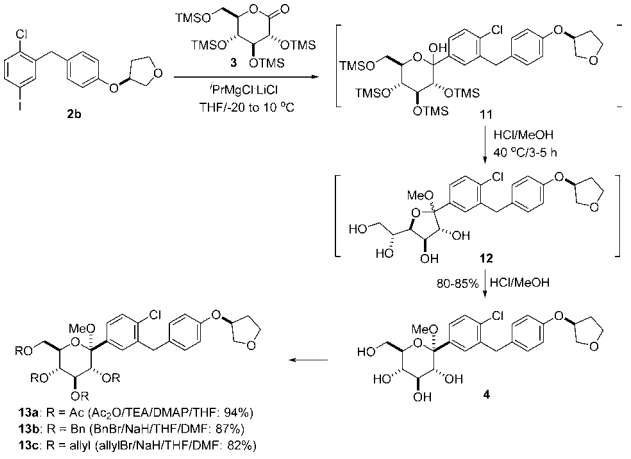
the ^{n}BuLi/^{n}BuMgCl complex was successful, and subsequent addition to commercially available persilylated gluconolactone **3**[7] gave rise to the desired methyl β-lactol **4**. Considering the demanding requirements associated with the use of ^{n}BuLi, such as cryogenic conditions (←40 °C) and reagent handling, the analogous iodide **2b** was chosen for the process even though bromide **2a** is more desirable from an economical standpoint.

Although complete I/Mg exchange of **2b** with ^{i}PrMgCl was reached in 30 min at −20 °C, the subsequent addition to **3** was sluggish even at room temperature, resulting in decomposition of the arylmagnesium chloride throughout the course of the prolonged reaction. However, by employing Knochel's ^{i}PrMgCl·LiCl complex for exchange, the addition to **3** was proven to be effective to yield intermediate lactol **11** (Scheme 3).

Scheme 3. Preparation of Methyllactol 4 and Methyl Tetra-*O*-protected Lactols 13a−c

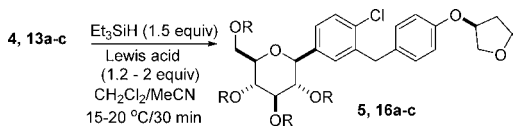


Without workup, the resulting mixture was subjected to treatment with 5 N HCl in methanol to a pH of 2−3 at about 40 °C. Following pH adjustment, latol **11** was completely converted to a 1:1 mixture of α/β methyl furanoketal **12** as the dominant components. This mixture was transformed to methyl β-pyranoketal **4** over about 3−5 h monitored by HPLC. After workup and solvent switch to methylene chloride, the resultant solution of **4** (crude product is an oil; 85% HPLC assay yield from **2b**) was directly used for the reduction to **5.**

Next, our attention focused on the desired reduction of glucopyranoside **4**. In general, the diastereoselectivity of Lewis acid mediated silane reductions of tetra-*O*-protected glycopyranosides to β-*C*-glycosides varies from moderate to high.[3,4,8] Better results are typically achieved with conformationally restricted substrates.[9] While few accounts were reported for *O*-unprotected substrates, no details on β-selectivity were discussed.[1b,c] We felt that methyl β-glycopyranoside **4**, though conformationally flexible, would be practically advantageous with no *O*-protection if good diastereoselectivity could be achieved during reduction.

For our studies, several tetra-*O*-protected derivatives **13a−c** were prepared (via **4**, Scheme 3) for investigation in parallel with **4**. When a mixture of crude **4** and Et_3SiH in CH_3CN/CH_2Cl_2[10] was treated with $BF_3{\cdot}OEt_2$, the reaction proceeded smoothly at 15−20 °C. To our surprise, β-*C*-glycoside **5** was obtained almost exclusively in about 65% isolated yield with <0.1 A% of α-anomer detected after crystallization from isopropyl acetate (IPAc, Table 1).

Table 1. Lewis Acid Promoted Reduction of 4 and 13a−c with Et_3SiH



entry	substrate	Lewis acid	β:α (area %)[a]	isolated yield of **5**, **16a−c**
1	**4**	$BF_3{\cdot}Et_2O$	>99:1	63[b]
2	**4**	$AlCl_3$	>99:1	67[b]
3	**13a**	$AlCl_3$	15:1	58 (R: Ac)[b]
4	**13b**	$BF_3{\cdot}Et_2O$	5:1	83 (R: Bn)[c]
5	**13b**	$AlCl_3$	5:1	87 (R: Bn)[c]
6	**13c**	$BF_3{\cdot}Et_2O$	7:1	90 (R = allyl)[c]
7	**13c**	$AlCl_3$	7:1	87 (R = allyl)[c]

[a]Area % by HPLC of the reaction mixture. [b]Crystallization from IPAc. [c]As an inseparable β/α mixture by chromatography.

It was anticipated that the reduction would produce <5% of furanosides **15a/b** since the crude **4** contained 2%−3% of furanoketal **11**. However, up to 20% of this byproduct was generated in some pilot plant batches as a 1:1 mixture of α/β anomers (Figure 1). A careful study revealed that the water

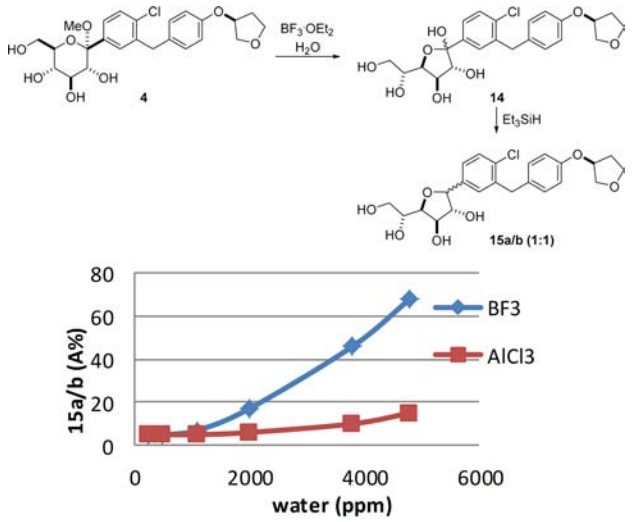


Figure 1. Effect of water content on the formation of impurity **15** (α/β 1:1).

content of the reaction mixture was attributable to this side reaction through a fast interconversion of **4** to lactol **14**. Furanosides **15a/b** were found to be the major products when the water content was >4000 ppm. Therefore, a low KF of the reaction mixture was specified in order to prevent the formation of **15a/b**.

Next, we focused on the Lewis acid used to mediate reduction. To the best of our knowledge, pyranoside reduction using $AlCl_3$ as a Lewis acid had not appeared in the literature prior to our studies; this reagent is much more preferable over $BF_3{\cdot}OEt_2$ for practical reasons. We were pleased to find that addition of **4** in CH_2Cl_2 to Et_3SiH and a suspension of $AlCl_3$ in CH_3CN produced results comparable to $BF_3{\cdot}OEt_2$.[11] Furthermore, the reaction with $AlCl_3$ was much less sensitive to

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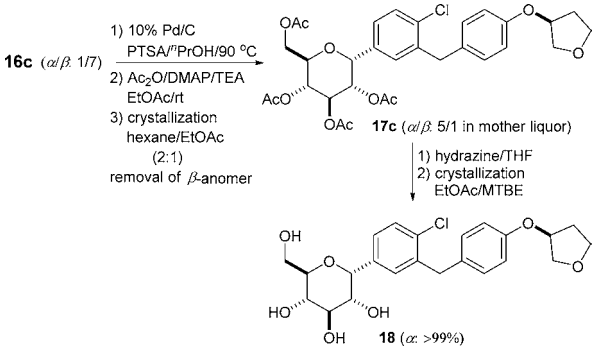
water content, which allowed for development of a more robust process. After 30 min at room temperature, the reaction mixture was quenched by careful addition of water. Azeotropic distillation and a solvent switch to IPAc was followed by crystallization and isolation of **5** crystallized in 60−70% yield.

In contrast to the excellent selectivity observed for *O*-unprotected **4**, the reduction of **13b−c** using $BF_3{\cdot}OEt_2$ generated significant amounts of α-anomers with a β/α ratio of 5−7:1. Using $AlCl_3$ as a Lewis acid provided no improvements, as we anticipated that a possible chelation effect may restrict the confirmation which would enhance the anomeric effect (Table 1). The reduction of substrate **13a** with $BF_3{\cdot}OEt_2$ was very sluggish, even after the addition of water as described in the literature.[14] $AlCl_3$ was proven to be much more effective, giving the desired product **16a** in 15:1 selectivity.

In order to confirm the relative stereochemistry and obtain material for use as an analytical standard, β/α-anomeric mixtures of **16b−c** were used to prepare quantities of the pure α-anomer **18** (Scheme 4). Deprotection of *O*-tetra-allyl

Scheme 4. Preparation of α-Anomer 18

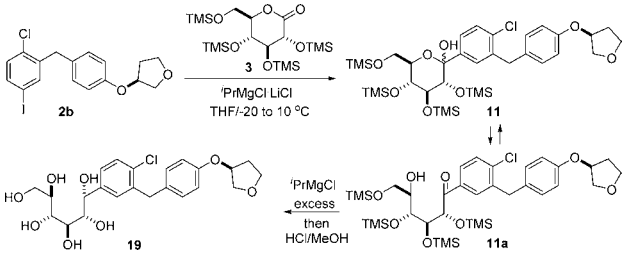


protected **16c** with a 7:1 of β/α ratio was performed using 10% palladium on carbon in the presence of *p*-TsOH in *n*-propanol at 90 °C for 5 days. The resulting product was transformed to *O*-tetra-acetate **17c**, which was further subjected to crystallization in a 2:1 mixture of hexane/EtOAc in order to remove the β-anomer. This sequence upgraded the filtrate α/β anomer ratio to 5:1 from the original 1:7. The crude **17c** filtrate was then treated with hydrazine in THF, and α-anomer **18** of >99% purity crystallized from a mixture of EtOAc and MTBE with an overall yield of 3% from **16c**.

It is also noteworthy that a single diastereomeric impurity was detected at various levels during the preparation of **4**, which was proven to be derived from the reduction of the corresponding ring opening ketone **11a**, in equilibrium with **11**,[12] by ^{i}PrMgCl·LiCl (Table 2). The relative stereochemistry of **19** was rationalized by the Felkin−Ann model[13] and supported by the stereochemistry of $NaBH_4$ reduction of a α-siloxyacetophenone.[14] As indicated in Table 2, excess Grignard reagent was closely correlated with increasing amounts of **19**, which became the major product when more than a 2-fold excess of ^{i}PrMgCl·LiCl was added (entry 4).[15] Following this investigation, the addition of ^{i}PrMgCl·LiCl was strictly controlled to minimize formation of **19** in the crude mixture and allow for a better recovery of **5** at the end.

In summary, we have developed a concise, robust process for the production of SGLT-2 inhibitor Empagliflozin (**5**) on a metric ton scale. The synthesis features a highly β-selective $AlCl_3$-promoted silane reduction of a methyl β-glycopyranoside. The selectivity of reduction of *O*-unprotected glycopyranosides to β-*C*-glycosides was also better understood. The one-stage process involves four chemical transformations from **2** to **5** without isolation of intermediates and precise control over the purity profile of the final drug substance.

Table 2. Formation of Impurity 19



entry	Grignard (equiv)	**4** (area %)[a]	**19** (area %)[a]	isolated yield of **19**[b]
1	1.1	84	<3	/
2	1.2	75	10	/
3	1.5	41	38	20
4	2.2	<1	77	57

[a]Area % by HPLC of the reaction mixture. [b]Crystallization from MeOH.

■ ASSOCIATED CONTENT

Supporting Information

Spectroscopic data and copies of ^{1}H/^{13}C NMR spectra for **2a−b**, **4**, **5**, **6a/b−8a/b**, **12**, **13a−c**, **15a/b**, **16a/c**, **18**, **19**. 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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