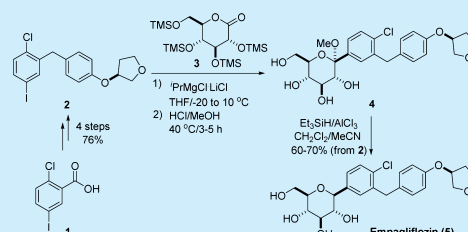


Efficient Synthesis of Empagliflozin, an Inhibitor of SGLT-2, Utilizing an AlCl_3 -Promoted Silane Reduction of a β -GlycopyranosideXiao-jun Wang,* Li Zhang, Denis Byrne, Larry Nummy, Dirk Weber,[†] Dhileep Krishnamurthy, Nathan Yee, and Chris H. Senanayake

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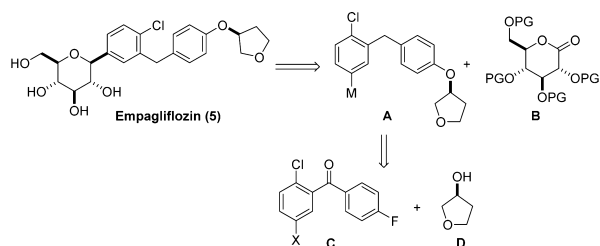
Supporting Information

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 $\text{CH}_2\text{Cl}_2/\text{MeCN}$ to afford **5** in 50% overall yield. The process was implemented for production on a metric ton scale for commercial launch.

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

Empagliflozin (**5**), currently in late phase development along with other similar compounds including Dapagliflozin and Canagliflozin, is a medically 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 others³ 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**,

Scheme 1. Retrosynthetic Analysis of 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**.

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.

Aromatic substitution of **7a/b** was performed with commercially available (*S*)-3-hydroxytetrahydrofuran **D** and $t\text{BuOK}$ 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 $i\text{PrMgCl}\cdot\text{LiCl}$ complex proceeded slowly, even at an elevated temperature of up to 40 °C which also led to simultaneous decomposition.⁶ Br/Li exchange with $n\text{BuLi}$ or

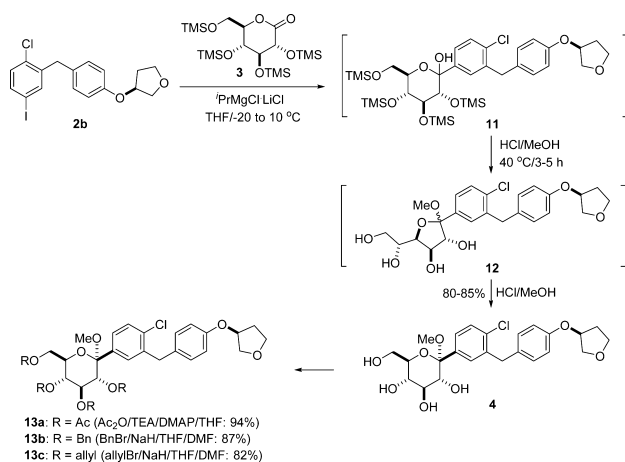
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the $n\text{-BuLi}/n\text{-BuMgCl}$ complex was successful, and subsequent addition to commercially available persilylated gluconolactone **3**⁷ gave rise to the desired methyl β -lactol **4**. Considering the demanding requirements associated with the use of $n\text{-BuLi}$, such as cryogenic conditions ($<-40\text{ }^{\circ}\text{C}$) 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 $i\text{-PrMgCl}$ was reached in 30 min at $-20\text{ }^{\circ}\text{C}$, 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 $i\text{-PrMgCl}\cdot\text{LiCl}$ complex for exchange, the addition to **3** was proven to be effective to yield intermediate lactol **11** (Scheme 3).

Scheme 3. Preparation of Methylactol **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 $40\text{ }^{\circ}\text{C}$. Following pH adjustment, lactol **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 $\text{CH}_3\text{CN}/\text{CH}_2\text{Cl}_2$ ¹⁰ was treated with $\text{BF}_3\cdot\text{OEt}_2$, the reaction proceeded smoothly at $15\text{--}20\text{ }^{\circ}\text{C}$. To our surprise, β -C-glycoside **5** was obtained almost exclusively in about 65% isolated yield with

$<0.1\text{ A\%}$ 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	$\beta:\alpha$ (area %) ^a	isolated yield of 5 , 16a–c
1	4	$\text{BF}_3\cdot\text{Et}_2\text{O}$	$>99:1$	63 ^b
2	4	AlCl_3	$>99:1$	67 ^b
3	13a	AlCl_3	15:1	58 (R: Ac) ^b
4	13b	$\text{BF}_3\cdot\text{Et}_2\text{O}$	5:1	83 (R: Bn) ^c
5	13b	AlCl_3	5:1	87 (R: Bn) ^c
6	13c	$\text{BF}_3\cdot\text{Et}_2\text{O}$	7:1	90 (R = allyl) ^c
7	13c	AlCl_3	7:1	87 (R = allyl) ^c

^aArea % by HPLC of the reaction mixture. ^bCrystallization from IPAc. ^cAs 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

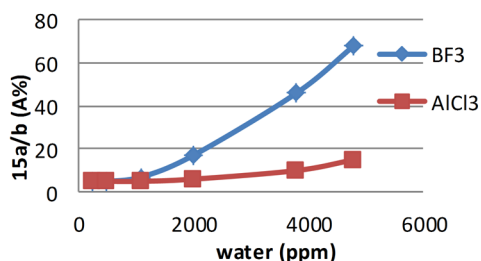
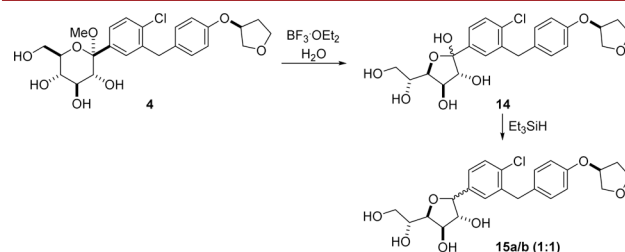


Figure 1. Effect of water content on the formation of impurity **15** (α/β 1:1).

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 $>4000\text{ ppm}$. Therefore, a low KF of the reaction mixture was specified in order to prevent the formation of **15a/b**.

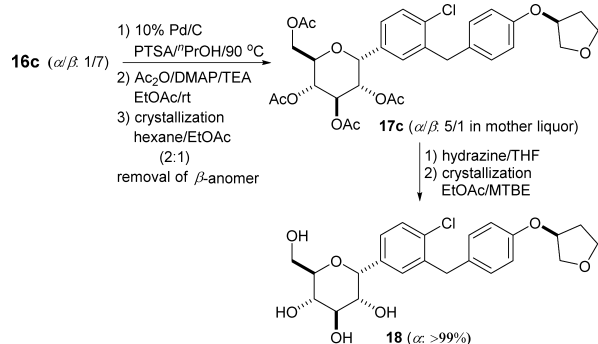
Next, we focused on the Lewis acid used to mediate reduction. To the best of our knowledge, pyranoside reduction using AlCl_3 as a Lewis acid had not appeared in the literature prior to our studies; this reagent is much more preferable over $\text{BF}_3\cdot\text{OEt}_2$ for practical reasons. We were 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 $\text{BF}_3\cdot\text{OEt}_2$.¹¹ Furthermore, the reaction with AlCl_3 was much less sensitive to

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 $\text{BF}_3 \cdot \text{OEt}_2$ 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 $\text{BF}_3 \cdot \text{OEt}_2$ 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**

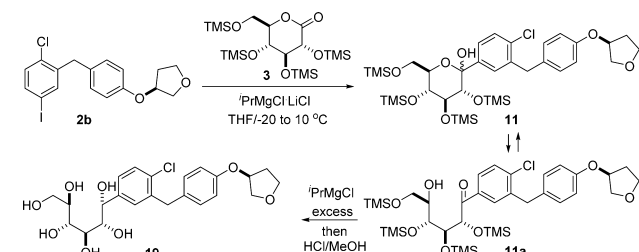


protected **16c** with a 7:1 of β/α ratio was performed using 10% palladium on carbon in the presence of *p*-TsOH in *n*-propanol at 90 °C for 5 days. The resulting product was transformed to *O*-tetra-acetate **17c**, which was further subjected to crystallization in a 2:1 mixture of hexane/EtOAc in 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 $^i\text{PrMgCl} \cdot \text{LiCl}$ (Table 2). The relative stereochemistry of **19** was rationalized by the Felkin–Ann model¹³ 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 $^i\text{PrMgCl} \cdot \text{LiCl}$ was added (entry 4).¹⁵ Following this investigation, the addition of $^i\text{PrMgCl} \cdot \text{LiCl}$ 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 -glycopyranose

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

^aArea % by HPLC of the reaction mixture. ^bCrystallization from MeOH.

side. 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.

■ ASSOCIATED CONTENT

Supporting Information

Spectroscopic data and copies of $^1\text{H}/^{13}\text{C}$ 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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