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β-Selective C-Arylation of Diisobutylaluminum Hydride Modified 1,6-Anhydroglucose: Synthesis of Canagliflozin without Recourse to Conventional Protecting Groups

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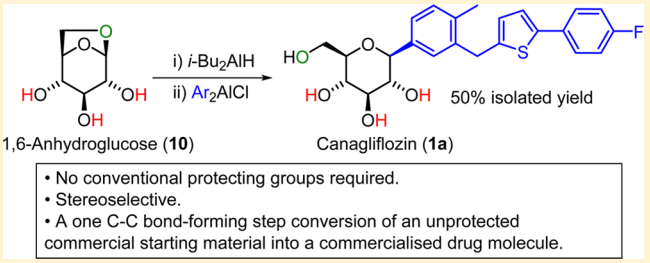
Supporting Information

ABSTRACT: The β-selective phenylation of benzyl and boronate protected 1,6-anhydroglucose and the direct phenylation of unprotected 1,6-anhydroglucose (**10**), pretreated with *i*-Bu_2AlH, *i*-Bu_3Al, Et_3Al, Me_3Al, or *n*-octyl$_3Al$, with triphenylalane or aryl(chloro)alanes is reported. The utility of the unprotected version of the method is demonstrated by the synthesis of the SGLT2 inhibitor, canagliflozin (**1a**), from commercially available **10** in one C−C bond-forming step. This approach circumvents the need for conventional protecting groups, and therefore no formal protection and deprotection steps are required.



INTRODUCTION

The β-*C*-arylglucosides canagliflozin (**1a**), dapagliflozin (**1b**), ipragliflozin (**1c**), and empagliflozin (**1d**) (Figure 1) are

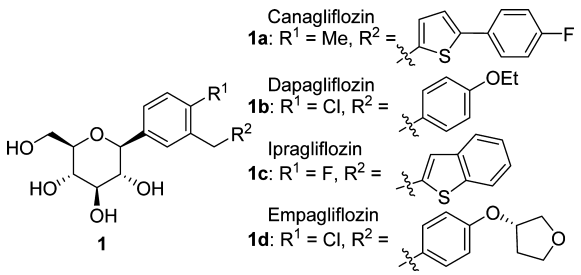


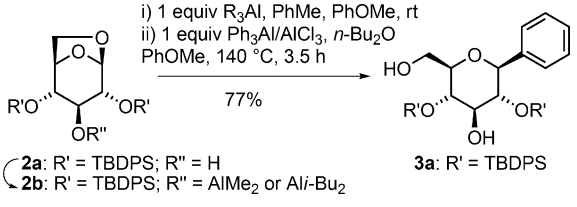
Figure 1. β-*C*-Arylglucosides useful for the treatment of diabetes.

members of a new class of antidiabetes active pharmaceutical ingredient known as Sodium-coupled GLucose co-Transporter 2 (SGLT2) inhibitors (**1**).[1] Owing to their therapeutic effectiveness, this class of compound has received much attention.[2] In 1988 and 1989 Kraus et al. and Czernecki et al. independently[3] reported that per-benzyl-protected β-*C*-arylglucosides can be prepared by the 1,2-addition of aryllithium or aryl Grignard compounds to 2,3,4,6-tetra-*O*-benzyl-D-gluconolactone followed by silane reduction. Owing to the only moderate anomeric selectivity (4:1 β:α) and use of benzyl ether protection in the original method, improvements have since been made,[4] including the use of silyl and acetyl protection and modification of the reducing agent, that have allowed β:α-selectivity as high as 65:1 and rendered the method viable for the preparation of drug candidates on a multikilogram scale.[5]

More recently several new approaches to β-*C*-arylglucoside synthesis have been reported including Lemaire et al.[6] transition-metal-free stereoselective (>99:1 β:α) arylation of a per-*O*-pivaloyl protected glucosyl bromide substrate with diaryl zinc reagents and Sakamaki et al.[7] palladium-catalyzed Suzuki cross-coupling of a glucal pinacol boronate with aryl bromides followed by a hydroboration-oxidation sequence.

Additionally, we recently reported[8] that 2,4-di-*O*-TBDPS protected 1,6-anhydro-β-D-glucopyranose **2a** can be arylated with high stereoselectivity to produce β-*C*-aryl-glucosides, such as **3a** (Scheme 1), using triarylalanes, aryl(halo)alanes,

Scheme 1. Arylation of 2b with Ph_3Al



aryl(alkyl)haloalanes, or aryl(alkyl)alanes. Demonstrated by the synthesis of the SGLT2 inhibitors canagliflozin (**1a**) and dapagliflozin (**1b**), the arylalanes were prepared from aryl lithium compounds or Grignard reagents and $AlCl_3$. Activation of the triarylalanes with $AlCl_3$ and filtration produced metal halide-free aryl(chloro)alanes, Ar_mAlCl_n, that possessed in-

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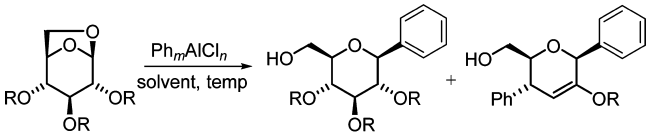
creased reactivity. Despite the presence of the unprotected C3 hydroxyl group in **2a**, pretreatment with 1 equiv of Me_3Al or *i*-Bu_2AlH to form alkoxy(dialkyl)alanes **2b** allowed efficient phenylation giving **3a** in high yield with 1 equiv of Ph_3Al. In the absence of Me_3Al or *i*-Bu_2AlH 2 equiv of Ph_3Al were required to achieve the same yield confirming that the dialkylalanyl moiety behaved as a hydroxyl protecting group. Arylalanes, vinylalanes, propargylalanes, and/or their derivatives have been used in the arylation, vinylation and propargylation of hydroxy-protected 1,2-anhydrofuranose and 1,2- and 1,6-anhydropyranose derivatives.[9] Herein we report further work on the arylation of 1,6-anhydroglucose derivatives and ultimately demonstrate that 1,6-anhydro-*β*-D-glucopyranose (**10**) can be arylated *without the need of conventional protecting groups in essentially one synthetic step*.

RESULTS AND DISCUSSION

Arylation of Tri-*O*-protected Substrates. As reported previously,[8] whereas the arylation of 2,4-di-*O*-TBDPS protected substrate **2b** was efficient, treatment of 2,3,4-tri-*O*-TBS substrate **2c** in PhOMe with commercial Ph_3Al in *n*-Bu_2O (Table 1, entry 1) only produced a 12% isolated yield of *β*-*C*-arylglucoside **3b**. In addition to **3b**, 16% of a compound found by mass spectrometry to have a molecular mass of 396 was isolated by column chromatography. This product, characterized by an unusual double arylation of the 1,6-anhydroglucose backbone, was tentatively assigned the structure **8a** following 1D and 2D NMR spectroscopy and further characterization as its ketone and 2,4-dinitrophenylhydrazone derivatives.[10a] By contrast, treatment of the known[11] tri-*O*-benzyl-protected analogue **2d** with Ph_3Al (entry 2) provided the desired product **3c** in good isolated yield (64%) along with a doubly arylated enol ether coproduct (11%) tentatively assigned the structure **8b**, partly by analogy to **8a**, and benzyl alcohol.[10b] Benzylation of **3c** provided the known[4a] tetra-*O*-benzyl derivative *β*-**4** (Figure 2) that was shown by HPLC comparison to an authentic mixture of *α*-**4** and *β*-**4** to comprise a 0.4:99.6 mixture of the *α*- and *β*-anomers demonstrating that the arylation was highly *β*-stereoselective. This is consistent with the high stereoselectivity witnessed in the arylation of **2b** and supports our previous supposition that an unprotected, *β*-disposed hydroxyl group at C3 is not required to direct the *β*-selective arylation of 1,6-anhydro-*β*-D-glucopyranose derivatives.[8a] The same degree of efficiency was obtained using PhOMe as solvent (entry 3). The metal halide-free phenyl(chloro)alanes Ph_2AlCl (entry 4) or $Ph_{2.5}AlCl_{0.5}$ (entry 5),[12] that were found particularly effective in the arylation of **2b**,[8a] prepared by combining commercial Ph_3Al in *n*-Bu_2O with $AlCl_3$ in THF, were also tested. Surprisingly, HPLC yields of only 7−12% of **3c** were produced after 4 h along with significant levels of benzyl alcohol. Further heating led to degradation of the product indicating that the tri-*O*-benzyl substrate and product were not compatible with aryl(chloro)alanes.

Table 1. Arylation of Tri-*O*-protected Analogues[a]



entry	2	Ph_mAlCl_n	solvent	temp (°C)/ time (h)	product	yield (%)[b]
1	**2c**	Ph_3Al	PhOMe	140/23	**3b**	12[c]
2	**2d**	Ph_3Al	*n*-Bu_2O	140/6	**3c**	64[d]
3	**2d**	Ph_3Al	PhOMe	120/6	**3c**	62
4	**2d**	Ph_2AlCl	PhOMe	120/4	**3c**	7[e,f]
5	**2d**	$Ph_{2.5}AlCl_{0.5}$	PhOMe	120/4	**3c**	12[e,g]

[a]Reaction conditions: 2 equiv of Ph_mAlCl_n unless otherwise stated. [b]Isolated yield unless otherwise stated. [c]HPLC showed that no more **3b** was formed after about 12 h. 16% of **8a** was isolated. See Henschke et al.[8a] for experimental details. [d]11% of **8b** was isolated. [e]HPLC yield. [f]63% unreacted **2d** and 0.39 equiv of BnOH with respect to **2d**. [g]55% unreacted **2d** and 0.44 equiv of BnOH with respect to **2d**.

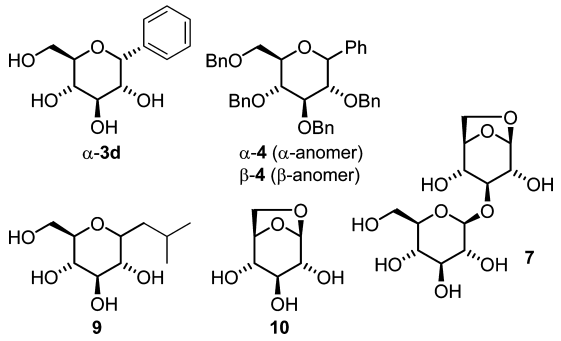


Figure 2. Miscellaneous compounds.

Arylation of 2,4-*O*-Boronic Ester-Protected Substrates. When the known[13] 2,4-*O*-phenylboronic ester **2e**, synthesized by the condensation of 1,6-anhydroglucose **10** and $PhB(OH)_2$ in a Dean−Stark assembly, was analyzed by TLC or reverse phase HPLC or by ^1H NMR spectroscopy in moist d_6-DMSO, only 1,6-anhydroglucose and $PhB(OH)_2$ were detected. Wanting to exploit the apparent lability of this protecting group it was envisioned that direct conversion of **2e** to unprotected *β*-*C*-arylglucosides, such as *β*-**3d**, should be possible with only a simple reaction quench and no need for isolation of the boronate-protected *C*-glucoside product.

Indeed, when **2e** was heated with Ph_2AlCl in PhMe overnight followed by a MeOH quench and column chromatography, a 34% yield of arylglucoside *β*-**3d** was obtained, along with 4% of disaccharide **7**[14] and 23% unreacted 1,6-anhydroglucose (Table 2, entry 1).[15] The chromatographically isolated yield of *β*-**3d** was improved to 55% (entry 2) when **2e** was prepared and arylated in one pot: 1,6-anhydroglucose was condensed with $PhB(OH)_2$ in PhMe (Dean−Stark apparatus), mixed with PhCN and 1 equiv of Ph_3Al in *n*-Bu_2O, concentrated under vacuum to remove PhMe and *n*-Bu_2O, and heated for 3 h. HPLC analysis of the product mixture prior to purification showed *β*-**3d**, $PhB(OH)_2$, PhOH, and benzene but did not reveal detectable amounts of the *α*-anomer, *α*-**3d**, indicating that the reaction was highly stereoselective.[16] Arylation was very rapid (≤3.5 h) and provided good HPLC yields of *β*-**3d** when phenyl(chloro)-alanes were used (entries 4 and 5, Table 2). Although slower (16 h), the use of 2.4 equiv of $Ph_{2.5}AlCl_{0.5}$ in PhCN allowed arylation at as low as 80 °C while providing a pleasing 67% HPLC yield (entry 6).[17]

In an attempt to find more atom economic boronic ester protecting groups, several dimers were targeted. While condensation of 1,6-anhydroglucose with 1,4-benzene diboronic acid failed to give the desired product, condensation of tetrahydroxydiboron (entry 7) in dioxane under Dean−Stark

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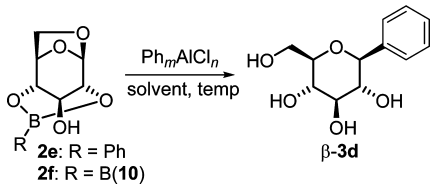
Table 2. Arylation of 2,4-*O*-Boronic Esters 5[a]



entry	2	Ph$_m$AlCl$_n$	solvent	time (h)	yield (%)[b]
1	**2e**	1.5 equiv of Ph$_2$AlCl	PhMe[c]	20	34[d]
2	**2e**[e]	1 equiv of Ph$_3$Al	PhCN	2.5	55[d,f]
3	**2e**	3 equiv of Ph$_3$Al	$C_6H_4Cl_2$	6	63[d]
4	**2e**	2.4 equiv of Ph$_{2.5}$AlCl$_{0.5}$	PhCl	3.5	67[d]
5	**2e**	2 equiv of Ph$_{2.2}$AlCl$_{0.8}$	PhOMe[g]	2.5	71
6	**2e**	2.4 equiv of Ph$_{2.5}$AlCl$_{0.5}$	PhCN[h]	16	67
7	**2f**[e]	3 equiv of Ph$_3$Al	dioxane	24	53[I]
8	NA[j]	3 equiv of Ph$_3$Al	PhOMe	6	26[h]
9	**2e**	3 equiv of Ph$_3$Al	PhOMe	6	65[f]

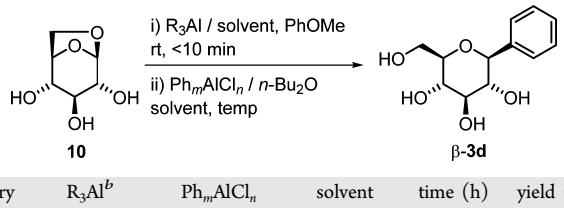
[a]Reaction conditions: internal temperature about 140 °C, unless otherwise stated. [b]HPLC yield calibrated to an internal standard unless otherwise stated. [c]Heated under reflux. [d]Isolated yield following column chromatography. [e]**10** was esterified with the boronic acid in a Dean−Stark apparatus and was used directly without isolation. [f]No α-anomer was detected by HPLC. [g]Internal temperature 110 °C. [h]Internal temperature 80 °C. [I]HPLC showed 1.2% of α-**3d**. [j]**10** was mixed with 1 equiv of PhB(OH)$_2$ prior to arylation but the boronic ester **2e** was not preformed. [h]HPLC showed 1.7% of α-**3d**.

conditions provided a mixture of products (^{1}H NMR spectroscopy) tentatively containing **2f** and/or its isomer(s) that upon arylation with Ph$_3$Al furnished a 53% HPLC yield of β-**3d** and 1.2% of α-**3d**.

To demonstrate the importance of preforming the boronic ester, direct arylation of a mixture of 1,6-anhydroglucose and 1 equiv of PhB(OH)$_2$ (entry 8) with 3 equiv of Ph$_3$Al was tested. As compared to the same arylation with boronic ester **2e** (entry 9) that provided a 65% HPLC yield of β-**3d** with no detectable amounts of the α-anomer, a 26% yield of β-**3d** was obtained along with 1.7% of α-anomer α-**3d**. That any **3d** was formed in this control experiment was, however, unexpected and suggested that direct arylation of 1,6-anhydroglucose, without recourse to conventional hydroxyl group protection, might be possible.

Direct Arylation of 1,6-Anhydroglucose Pretreated with *i*-Bu$_2$AlH. Having identified above that the arylation of 1,6-anhydroglucose (**10**) could be accomplished without preformation of the boronic ester the direct arylation of **10** without recourse to a protecting group installing step was examined[18] using Ph$_3$Al. Pleasingly, heating **10** and 6 equiv of Ph$_3$Al (1.0 M in *n*-Bu$_2$O) in dioxane (Table 3, entry 1) produced over a 66 h period a 73% HPLC yield of 1-C-phenyl-β-D-glucoside (β-**3d**), along with 1.8% of the α-anomer α-**3d**, providing proof of concept. Following aqueous workup and column chromatography a somewhat lower isolated yield (48%) was obtained, owing to difficulties separating the water-soluble β-**3d** from the excess of aluminum residues. The reaction was more rapid in PhOMe, but the yields increased only slightly as the amounts of the additional Ph$_3$Al were increased from 1 to 3 equiv (entries 2−4). To reduce the amount of the arylalane, which would be desirable for the synthesis of β-*C*-arylglucoside drugs such as **1** that possess more complex aryl side chains, and in an analogous strategy to

Table 3. Arylation of 10 Pretreated with Alanes[a]



entry	R$_3$Al[b]	Ph$_m$AlCl$_n$	solvent	time (h)	yield (%)[c]
1	Ph$_3$Al	Ph$_3$Al[b]	dioxane[d]	66	73[e]
2	Ph$_3$Al	Ph$_3$Al[f]	PhOMe	14	43
3	Ph$_3$Al	Ph$_3$Al	PhOMe	22	47
4	Ph$_3$Al	Ph$_3$Al[b]	PhOMe	23	50
5	Me$_3$Al	Ph$_3$Al	PhOMe	38	32
6	*i*-Bu$_2$AlH	Ph$_3$Al	PhOMe[g]	43	38
7	*i*-Bu$_2$AlH	Ph$_3$Al	PhOMe[h]	38	55
8	*i*-Bu$_2$AlH	Ph$_3$Al	PhOMe	48	65[I]
9	*i*-Bu$_2$AlH	Ph$_3$Al	*n*-Bu$_2$O	61	62
10	*i*-Bu$_2$AlH	Ph$_3$Al	PhCl	19	52
11	*i*-Bu$_2$AlH	Ph$_3$Al	Ph$_2$O	6	39
12	*i*-Bu$_2$AlH	Ph$_3$Al	PhCN	4	24
13	*i*-Bu$_2$AlH	Ph$_3$Al	PhMe[d]	37	47
14	*i*-Bu$_2$AlH	Ph$_3$Al	dioxane[d]	72	46
15	*i*-Bu$_2$AlH	Ph$_{1.5}$AlCl$_{1.5}$	PhOMe	18	36
16	*i*-Bu$_2$AlH	Ph$_2$AlCl	PhOMe	16	58
17	*i*-Bu$_2$AlH	Ph$_{2.5}$AlCl$_{0.5}$	PhOMe	24	74[j]
18	*i*-Bu$_2$AlH	Ph$_{2.5}$AlCl$_{0.5}$	*n*-Bu$_2$O	21	74[k]
19	*i*-Bu$_2$AlH	Ph$_{2.5}$AlCl$_{0.5}$	PhCl	21	74[l]
20	*i*-Bu$_2$AlH	Ph$_{2.5}$AlCl$_{0.5}$	Ph$_2$O	26	72[m]
21	Et$_3$Al	Ph$_{2.5}$AlCl$_{0.5}$	PhOMe	18	65
22	*i*-Bu$_3$Al	Ph$_{2.5}$AlCl$_{0.5}$	PhOMe	24	72
23	*n*-octyl$_3$Al	Ph$_{2.5}$AlCl$_{0.5}$	PhOMe	48	53[n]

[a]Reaction conditions: 2 equiv of Ph$_m$AlCl$_n$ unless otherwise stated. Internal temperature 140 °C unless otherwise stated. [b]3 equiv. [c]HPLC yield calibrated to internal standard unless otherwise stated. [d]Under reflux. [e]48% isolated yield following workup and column chromatography. [f]1 equiv. [g]100 °C internal temperature. [h]120 °C internal temperature. [I]51% isolated yield following workup and column chromatography. [j]4.0% of α-**3d** and 0.50% of **9** was detected by HPLC analysis. Isolated yield by column chromatography was 65%. [k]4.4% of α-**3d** and 0.47% of **9** was detected by HPLC analysis. [l]3.2% of α-**3d** and 0.49% of **9** was detected by HPLC analysis. [m]4.0% of α-**3d** and 0.53% of **9** was detected by HPLC analysis. [n]The reaction was still ongoing at 48 h with 40% unreacted **10** detected by HPLC.

that which we reported previously for **2a**,[8a] **10** was pretreated with 3 equiv of Me$_3$Al (entry 5) instead of Ph$_3$Al, followed by arylation with 2 equiv of Ph$_3$Al. This resulted in a disappointing 32% yield, however. Although **10** was not soluble in PhOMe, when 3 equiv of *i*-Bu$_2$AlH were used in the pretreatment step homogeneous solutions were produced that provided improved yields of β-**3d**, that increased with increasing temperature, in the subsequent arylation step (entries 6−8). In fact a 65% HPLC yield was achieved along with only trace amounts of the isobutylated derivative **9** when the arylation was performed at 140 °C for 48 h (entry 8).[19] Following column chromatography a 51% isolated yield was obtained. When a suspension of **10** in d_8-THF was treated with 3 equiv of *i*-Bu$_2$AlH in PhMe, vigorous bubbling occurred followed by the generation of a colorless, homogeneous solution. Analysis by ^{1}H NMR spectroscopy[20a] suggested that at least three components had formed, confirming that in d_8-THF, at least, modification of **10** with *i*-Bu$_2$AlH does not produce a single component that is directly analogous to 2,3,4-tri-*O*-protected 1,6-anhydroglucose

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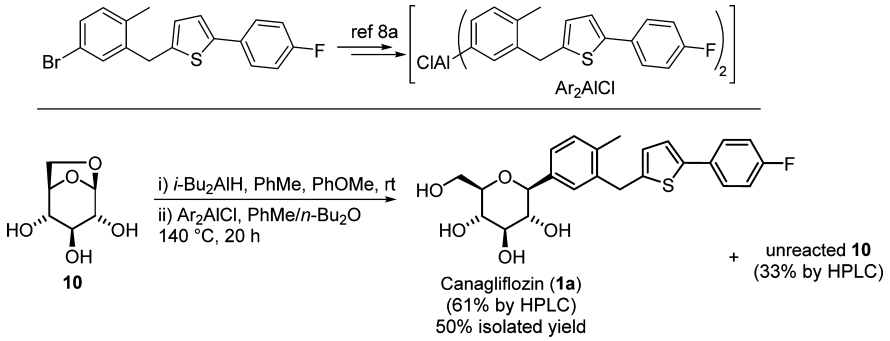
Scheme 2. Synthesis of Canagliflozin by the Arylation of 1,6-Anhydroglucose (10) Pretreated with *i*-Bu_2AlH



compounds such as **2c** or **2d**. Solvent screening (entries 9−14) showed that while *n*-Bu_2O was comparable to PhOMe in terms of yield of *β*-**3d**, PhCl, Ph_2O, PhCN, PhMe, and dioxane provided less satisfactory results.[20b] Consistent with the phenylation of **2a** pretreated with Me_3Al,[8a] the rate of arylation of **10** pretreated with *i*-Bu_2AlH in PhOMe was significantly increased (16−24 h) by the use of phenyl(chloro)alanes, Ph_mAlCl_n (entries 15−17), prepared by mixing Ph_3Al and $AlCl_3$. $Ph_{2.5}AlCl_{0.5}$ provided the best HPLC yield (entry 17; 74%) and gave a pleasing 65% isolated yield following careful aqueous workup to reduce losses of the water-soluble product and column chromatography. Entry 17 was repeated using *n*-Bu_2O (entry 18), PhCl (entry 19), or Ph_2O (entry 20) as solvent.[20b] HPLC yields were significantly improved (72−74%) upon those using the same solvents with Ph_3Al as the arylating agent (cf. entries 9−11), although around 3−4% *α*-**3d** was formed. The mass balance in these tests was partially accounted for by unreacted **10** with HPLC typically showing between 10 and 25% remaining.

Using the entry 17 conditions, Et_3Al (entry 21), *i*-Bu_3Al (entry 22), and *n*-octyl$_3$Al (entry 23) were tested in the pretreatment step of **10** in place of *i*-Bu_2AlH.[20b] Whereas arylation rates and yields using Et_3Al and *i*-Bu_3Al were similar to those using *i*-Bu_2AlH, pretreatment with *n*-octyl$_3$Al resulted in much slower arylation.

Synthesis of Canagliflozin from 1,6-Anhydroglucose Pretreated with *i*-Bu_2AlH. Following on from the results of the above-described model studies, the synthesis of canagliflozin (**1a**) from 1,6-anhydroglucose (**10**) was conducted (Scheme 2). The arylating agent Ar_2AlCl (Ar = (3-[[5-(4-fluorophenyl)-2-thienyl]methyl]-4-methylphenyl) was prepared as described previously.[8a] A PhMe−*i*-Pr_2O solution of 3-[[5-(4-fluorophenyl)-2-thienyl]methyl]-4-methylphenyl bromide was treated with *n*-BuLi in *n*-hexane at 0 °C followed by reaction with $AlCl_3$ in *n*-Bu_2O at 90 °C. Following dilution with PhMe and concentration to remove the *i*-Pr_2O, the resulting solution was filtered to remove the LiCl. An attempt to use this reagent without filtration resulted in effectively no arylation occurring. 1,6-Anhydroglucose in PhOMe was treated with 3 equiv of *i*-Bu_2AlH prior to being heated at 140 °C together with 2 equiv of the above prepared arylating agent in PhMe/*n*-Bu_2O. After 18 h reaction 61% **1a** and 33% unreacted **10** were witnessed by calibrated HPLC (using internal standards); however, no further **1a** was formed after another 2 h, and following aqueous workup and column chromatography a 50% isolated yield of 97.7%-pure canagliflozin was obtained.

CONCLUSION

In conclusion, the *β*-selective phenylation of protected 1,6-anhydroglucose **2** using triphenyl- (Ph_3Al) or phenyl(chloro)-alanes (Ph_mAlCl_n) has been demonstrated. The preparation and use of boronate **2e** as a substrate was more convenient than TBS- and benzyl-protected analogues **2c** and **2d**, respectively, because the entire process starting from 1,6-anhydro-*β*-D-glucopyranose (**10**) and finishing at *β*-**3d** could be conducted in one pot. Ultimately, however, it was discovered that **10** itself could be directly arylated in the absence of conventional protecting groups by heating **10** with an excess of Ph_3Al or by pretreatment with *i*-Bu_2AlH, *i*-Bu_3Al, Et_3Al, Me_3Al, or *n*-octyl$_3$Al, followed by heating with Ph_3Al or Ph_mAlCl_n. In comparison to the conventional method[3] that starts with commercial gluconolactone, which requires global hydroxy group protection and several synthetic steps following arylation, the method described herein is concise and should provide a strong basis for further innovation in *β*-C-arylglucoside synthesis. Before this can be fully realized, however, there remains a need to reduce the amount of arylating agent (typically 2 equiv with respect to **10**) and to lower the reaction temperature. In exploratory studies[8b] using **2a** both Ti- and Ga-based arylating agents showed promise, and perhaps these can replace the Al-reagents reported herein. Finally, the potential of this method for the preparation of drug molecules was demonstrated by the synthesis of canagliflozin (**1a**) from 1,6-anhydroglucose (**10**) without the isolation of any hydroxy group-protected intermediates or product.

EXPERIMENTAL SECTION

Materials and Methods. Experiments were conducted under anhydrous conditions in a nitrogen atmosphere using Schlenk techniques. Solvents were dried over 3 or 4 Å molecular sieves, and oven-dried glassware and gastight syringes were used. High resolution electrospray ionization (ESI) mass spectrometry was performed using a QToF tandem mass analyzer. ^1H and ^{13}C NMR spectra were recorded in the specified deuterated solvents at 400 and 100 MHz, respectively. Commercially obtained or in-house prepared solutions of organometallic reagents were titrated using standard titration methods, including Knochel's method.[21] Commercial 1,6-anhydro-*β*-D-glucopyranose (**10**), *i*-Bu_2AlH (DIBAL; 1.0 M in PhMe), Ph_3Al (1.0 M in *n*-Bu_2O), Et_3Al (1.0 M in *n*-hexane), *i*-Bu_3Al (1.0 M in *n*-hexane), and *n*-octyl$_3$Al (25% in hexanes), and $AlCl_3$ (0.5 M in THF; titrated by Eriochrome cyanine R spectrophotometric method[22]) were used as supplied. A reference sample of canagliflozin (**1a**; see spectra below) was acquired from a commercial source. Authentic samples of *α*-**3d** and *β*-**3d** were acquired as described in the Supporting Information section of ref 8a. Spectra of the known[4a] compounds 2,3,4,6-tetra-*O*-benzyl-1-*C*-phenyl-*α*-D-glucopyranoside (*α*-**4**) and 2,3,4,6-tetra-*O*-benzyl-1-*C*-phenyl-*β*-D-glucopyranoside (*β*-**4**) were presented in the

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Supporting Information section of ref 8a. 1,6-Anhydro-2,3,4-tri-*O*-benzyl-β-D-glucopyranose (**2d**) was prepared as reported by Fürstner et al.[23] Determination of the stereoselectivity in the arylation of **2d** (see Table 1) with Ph_3Al providing 2,3,4-tri-*O*-benzyl-1-*C*-phenyl-glucopyranoside (**3c**) was achieved by benzylation of the crude **3c** (see below) to give crude 2,3,4,6-tetra-*O*-benzyl derivative **4**. Comparison of the crude **4** by HPLC analysis (see Figure S5 in the Supporting Information) to reference samples of known[4a] 2,3,4,6-tetra-*O*-benzyl derivatives α-**4** and β-**4** (prepared as described in the Supporting Information of ref 8a) was used to identify the peaks. HPLC analysis was conducted on an Agilent ZORBAX SB-Phenyl column (5 μm, 4.6 × 250 mm) at 40 °C, monitoring at 220 nm, eluting at a flow rate of 1.0 mL/min with a linear gradient of 50% water/50% MeOH to 20% water/80% MeOH from 0 to 5 min followed by a linear gradient of 20% water/80% MeOH to 100% MeOH from 5 to 30 min; α-**4** eluted at 21.6 min, while β-**4** eluted at 22.6 min (see chromatograms in Supporting Information). Determination of the stereoselectivity and quantitation (yield) of **3d** and level of **9** formed in the arylation of **2e**, **2f**, or **10** for Table 2 and Table 3 and reaction monitoring for the synthesis of canagliflozin was achieved by HPLC analysis using an Agilent ZORBAX SB-Aq column (3.5 μm, 4.6 × 150 mm) at 35 °C that was isocratically eluted for 5 min using 100% water followed by a linear elution gradient from 0% MeCN (containing 0.01% TFA)/100% water to 95% MeCN (containing 0.01% TFA)/5% water for 27 min using a flow rate of 1 mL/min. Both a UV detector (monitoring at 210 nm; see Figure S6 in the Supporting Information) and ELSD (Evaporative Light-Scattering Detector; monitoring at 50 °C, 1.8 L/min gas flow; see Figure S7 in the Supporting Information) were used in series to cooperatively monitor the HPLC runs. Analysis samples were prepared by mixing reaction aliquots with 5% TFA in 1:2 water/MeCN (1 wt % cinchonine was added when the levels of **10** and β-**3d** were to be determined by ELSD). The UV detector was used to monitor and quantify UV-active reaction components including α-**3d** (t_R 9.4 min), β-**3d** (t_R 8.1 min), and canagliflozin (**1a**; t_R 21.5 min). The levels of the reaction components were determined with respect to an internal standard (4-pentylbiphenyl; t_R 28.85 min) that was added (10−20 mol % with respect to 1,6-anhydro-β-D-glucopyranose (**10**)) to the reaction prior to initiation. The following calibrated relative response factors (on a mole: mole basis with respect to 4-pentylbiphenyl) were used: β-**3d** 0.23; α-**3d** 0.23. To monitor and determine the levels of UV-inactive compounds **10** (t_R 2.2 min) and **9** (t_R 11.0 min) the ELSD was used. α-**3d** (t_R 9.5 min) and β-**3d** (t_R 8.0 min) could also be detected using the ELSD. The levels of the reaction components were determined with respect to an external standard (cinchonine; t_R 15.71 min) that was preadded to the sample solvent (5% TFA in 1:2 water/MeCN) and the following calibrated relative response factors (on a mole: mole basis with respect to cinchonine): β-**3d** 0.43; **10** 0.41 were used. Compound **9** was determined by area% with respect to β-**3d**. When the ELSD detector was conducted in series following the UV detector, the t_R of the peaks ELSD chromatogram showed a delay of ca. 0.1 min as compared to when detected using the UV detector. The peaks corresponding to β-**3d** and α-**3d** were determined by analysis of authentic samples of β-**3d** and α-**3d** that were prepared as reported in the Supporting Information of ref 8a.

*Arylation of **2c** with Ph_3Al for Table 1, Entry 1 and Isolation of Side Product **8a**.* In addition to the column chromatographic isolation of 2,3,4-tri-*O*-*tert*-butyldimethylsilyl-1-*C*-phenyl-β-D-glucopyranoside (**3b**; 69 mg, 12%) from the arylation of 1,6-anhydro-2,3,4-tri-*O*-*tert*-butyldimethylsilyl-β-D-glucopyranose (**2c**; 0.51 g, 1.0 mmol) reported in the Experimental Section of ref 8a, 63 mg (16%) of a reaction side product that herein is proposed (see Supporting Information for support of this structure) to be (4*R**)-2-*O*-*tert*-butyldimethylsilyl-3-deoxy-2,3-dehydro-4-phenyl-1-*C*-phenyl-β-D-glucopyranoside (**8a**) was also isolated by column chromatography. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45−742 (m, 2H), 7.40−7.33 (m, 5H), 7.33−7.28 (m, 3H), 5.13 (dd, *J* = 3.2, 1.6 Hz, 1H), 5.01 (dd, *J* = 1.6, 1.6 Hz, 1H), 3.79 (ddd, *J* = 9.8, 3.0, 1.8 Hz, 1H), 3.69 (ddd, *J* = 9.5, 5.5, 3.5 Hz, 1H), 3.57 (br, 2H), 0.70 (s, 9H), 0.16 (s, 3H), −0.04 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.7, 141.8, 139.6, 128.7, 128.6, 128.4, 128.2, 128.1, 127.0, 105.4, 81.0, 79.4, 62.8, 42.8, 25.3, 17.7, −4.6, −5.0; LCMS (ESI) *m*/*z* 397 (100, $[M + H]^+$), 398 (22, $[M + H + 1]^+$), 419 (91, $[M + Na]^+$).

*General Procedure for the Synthesis of 2,3,4-Tri-O-benzyl-1-C-phenyl-β-D-glucopyranoside (β-**3c**) by the Arylation of **2d** with Arylalanes Ph_mAlCl_n for Table 1, Entries 2−5.* These compounds were prepared by heating an *n*-Bu_2O (4.0 mL; Table 1, entry 2) or PhOMe (4.0 mL; Table 1, entries 3, 4, or 5) solution of 1,6-anhydro-2,3,4-tri-*O*-benzyl-β-D-glucopyranose (**2d**; 0.43 g, 1.0 mmol) and Ph_3Al (2.0 mL, 2.0 mmol, 1.0 M in *n*-Bu_2O), or Ph_2AlCl (2.0 mmol; a mixture of Ph_3Al (1.3 mL, 1.3 mmol, 1.0 M in *n*-Bu_2O) and $AlCl_3$ (1.3 mL, 0.67 mmol, 0.5 M in THF)), or $Ph_{2.5}AlCl_{0.5}$ (2.0 mmol; Ph_3Al (1.67 mL, 1.67 mmol, 1.0 M in *n*-Bu_2O) and $AlCl_3$ (0.67 mL, 0.33 mmol, 0.5 M in THF)) at 140 or 120 °C for 4−6 h. After cooling to ambient temperature, THF (10 mL), then diatomaceous earth (1 g), then 15% aqueous NaOH (1 mL), and then Na_2SO_4 (2 g) were added sequentially to the product mixture, and the resulting suspension was stirred and then filtered. The filtrate was concentrated to give a yellow oil (HPLC, LCMS, and ^{1}H NMR spectroscopic analysis showed the crude product to be mostly composed of β-**3c**, **8b**, BnOH, and biphenyl) which was purified by silica gel column chromatography (eluting with 1:20 EtOAc/*n*-heptane) affording the product 2,3,4-tri-*O*-benzyl-1-*C*-phenyl-β-D-glucopyranoside (β-**3c**; entry 2:0.32 g, 64% or entry 3:0.31 g, 62%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48−7.31 (m, 15H), 7.24−7.19 (m, 3H), 6.95−6.92 (m, 2H), 5.00 (d, *J* = 11.2 Hz, 1H), 4.95 (d, *J* = 10.8 Hz, 1H), 4.94 (d, *J* = 11.2 Hz, 1H), 4.74 (d, *J* = 10.8 Hz, 1H), 4.41 (d, *J* = 10.0 Hz, 1H), 4.31 (d, *J* = 9.6 Hz, 1H), 3.93 (ddd, *J* = 11.8, 6.1, 2.6 Hz, 1H), 3.87 (dd, *J* = 9.0, 9.0 Hz, 1H), 3.81−3.70 (m, 3H), 3.59−3.53 (m, 2H), 1.97 (dd, *J* = 6.8, 6.8, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.0, 138.6, 138.0, 137.6, 128.54, 128.52, 128.47, 128.26, 128.23, 128.1, 128.0, 127.744, 127.735, 127.69, 127.67, 86.6, 84.3, 81.7, 79.4, 78.3, 75.7, 75.2, 74.9, 62.4; FTIR (neat) 3447, 3088, 3063, 3031, 2871, 1497, 1454, 1398, 1359, 1211, 1151, 1067, 1028, 751, 736, 697 cm^{-1}; $[\alpha]_D^{20}$ = −6.6 (*c* 1.0, MeOH); LCMS (ESI) *m*/*z* 528 (100, $[M + NH_4]^+$), 529 (35, $[M + NH_4 + 1]^+$), 533 (5, $[M + Na]^+$); ESI QTof calculated for $[C_{33}H_{34}O_5 + NH_4]^+$ = 528.2745, found 528.2771; mp 111.1 °C. Additionally, a side product tentatively assigned the structure **8b** was also isolated by column chromatography (46 mg (contaminated with 65 mol % (by ^{1}H NMR with respect to **8b**) BnOH which is equivalent to 7.2 mg), equivalent to 38.8 mg of **8b**, 11%). The proposed structure for **8b** was supported by LCMS and ^{1}H and ^{13}C NMR analysis (see the Supporting Information) and by analogy to **8a** (see above). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.1−7.5 (m, 15H), 5.26 (d, *J* = 1.2 Hz, 1H), 4.88 (s, 1H), 4.80 (d, *J* = 12.8 Hz, 1H), 4.76 (d, *J* = 12.8 Hz, 1H), 4.61 (t, *J* = 5.8 Hz, 1H), 3.66 (m, 1H), 3.52 (m, 1H), 3.34 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.8, 143.1, 140.3, 137.6, 129.0, 128.9, 128.8, 128.7, 128.5, 128.4, 127.9, 127.1, 126.9, 100.1, 82.3, 77.8, 68.6, 63.4, 61.7, 42.2; LCMS (ESI) *m*/*z* 355 (13, $[M + H - H_2O]^+$), 373 (57, $[M + H]^+$), 390 (100, $[M + NH_4]^+$), 395 (44, $[M + Na]^+$). Further confirmation of the structure of β-**3c** was obtained by 1) conversion of β-**3c** to its known per-benzyl derivative, 2,3,4,6-tetra-*O*-benzyl-1-*C*-phenyl-β-D-glucopyranoside (β-**4**) (benzylation procedure: crude **3c** (18 mg, 0.03 mmol) in THF (2 mL) was treated with NaH (60% dispersion in mineral oil; 1.8 mg, 0.045 mmol) for 1 h at room temperature, then benzyl bromide (10 μL, 0.08 mmol) was added, and the mixture was stirred at 50 °C overnight (TLC shows complete conversion) before being diluted with EtOAc, extracted with water, and washed with brine giving crude β-**4**), which conformed with that reported by Ellsworth et al.[4a] (see spectra of an authentic sample of β-**4** in the Supporting Information section of ref 8a), and 2) hydrogenolysis of β-**3c** affording 1-*C*-phenyl-β-D-glucopyranoside (β-**3d**) as confirmed by ^{1}H NMR spectroscopy (spectroscopic comparison of this material to an authentic sample of β-**3d** is shown in the Supporting Information).

Synthesis of 1,6-anhydro-β-D-glucopyranose 2,4-*O*-phenylboronate (**2e**; see spectra below) was prepared as reported by Spring et al.[13b] and following filtration was washed with PhMe and was then used without purification, whereas in some cases crude boronic ester **2e** was used directly in arylation reactions without isolation from its PhMe solution. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83−7.87 (m, 2H), 7.46−

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7.51 (m, 1H), 7.37−7.42 (m, 2H), 5.65 (t, J = 2.4 Hz, 1H), 4.63−4.67 (m, 1H), 4.58 (d, J = 8.0 Hz, 1H), 4.19−4.22 (m, 1H), 4.12−4.16 (m, 1H), 4.08−4.10 (m, 1H), 3.94 (dd, J = 7.6 Hz, 4.8 Hz, 1H), 3.44 (d, J = 8.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 134.6, 131.5, 128.0, 101.9, 76.8, 70.6, 70.5, 69.3, 66.5 (the *ipso* carbon (attached to B) signal was not observed due to low intensity). Also see the spectra in the Supporting Information. Boronic ester **2e** is water sensitive. Addition of 1 drop of water to **2e** in d_6-DMSO in an NMR tube showed complete hydrolysis back to 1,6-anhydro-β-D-glucopyranose (**10**) and $PhB(OH)_2$ (see the Supporting Information).

Attempted synthesis of the 2,4,2′,4′-*O*-diboron dimer **2f** of 1,6-anhydro-β-D-glucopyranose was conducted by heating a mixture of 1,6-anhydro-β-D-glucopyranose (**10**; 324 mg, 2 mmol) and tetrahydroxydiboron (90 mg, 1 mmol) in dioxane (40 mL) under reflux in a Dean−Stark apparatus (with molecular sieves installed in the side arm) for 15 h. ^{1}H NMR analysis (see ^{1}H NMR spectrum in the Supporting Information) of an aliquot of the product mixture that was evaporated to dryness indicated that it was composed of a mixture of products tentatively containing **2f**.

*Synthesis of 1-C-phenyl-β-D-glucopyranoside (β-**3d**) by the arylation of **2e** and **2f** with arylalanes Ph_mAlCl_n for Table* 2 and characterization of side product **7**. To a solution of 1,6-anhydro-β-D-glucopyranose 2,4-*O*-phenylboronate (**2e**; 248 mg, 1.0 mmol; alternatively, the crude **2e** product mixture was directly used in arylations (e.g., entry 2) without isolation of **2e**) in PhOMe (5 mL), or another solvent reported in Table 2, at ambient temperature was added Ph_3Al (3.0 mL, 3.0 mmol, 1.0 M in Bu_2O), or Ph_2AlCl (for entry 1: a mixture of Ph_3Al (1.0 mL, 1.0 mmol, 1.0 M in n-Bu_2O) and $AlCl_3$ (1.0 mL, 0.50 mmol, 0.5 M in THF) was used), or $Ph_{2.5}AlCl_{0.5}$ (for entries 4 and 6: a mixture of Ph_3Al (2.0 mL, 2.0 mmol, 1.0 M in n-Bu_2O) and $AlCl_3$ (0.8 mL, 0.4 mmol, 0.5 M in THF or neat $AlCl_3$)), or $Ph_{2.2}AlCl_{0.8}$ (for entry 5: a mixture of Ph_3Al (1.5 mL, 1.50 mmol, 1.0 M in n-Bu_2O) and $AlCl_3$ (1.1 mL, 0.55 mmol, 0.5 M in THF)). The mixture was heated at 140 °C (internal temperature), or as otherwise stated in Table 2, for 2.5−24 h. The product mixture was quenched by treatment with MeOH (3 mL) or 5% TFA in MeCN (3 mL) followed by concentration under reduced pressure to remove the volatiles followed by chromatographic purification of the residue over silica gel (eluting with 1:10 MeOH/DCM) providing β-**3d**. The spectroscopic data for β-**3d** conformed with that reported in ref 8a and is also presented in the Supporting Information. In addition to β-**3d** and unreacted starting material that was recovered as 1,6-anhydro-β-D-glucopyranose (**10**), a polar side product was also isolated by column chromatography that was tentatively characterized as 1,6-anhydro-3-*O*-β-D-glucopyranosyl-β-D-glucopyranose (**7**) using a combination of LCMS analysis and ^{1}H, ^{13}C, DEPT-135, HMQC, COSY, HMBC (a correlation between H1′ and C3 supports the proposed (1 → 3)-disaccharide linkage), and NOESY NMR experiments (see spectra in the Supporting Information). ^{1}H NMR (400 MHz, d_4-MeOH) δ 5.41 (1H, s), 4.59 (1H, m), 4.40 (1H, d, J = 7.6 Hz), 4.23 (1H, d, J = 7.2 Hz), 3.94 (1H, m), 3.94 (1H, m), 3.73 (1H, m), 3.73 (1H, m), 3.66 (1H, m), 3.66 (1H, m), 3.40 (1H, m), 3.33 (1H, m), 3.29 (1H, m), 3.21 (1H, t, J = 8.4 Hz); ^{13}C NMR (100 MHz, d_4-MeOH) δ 103.9, 101.6, 80.4, 76.4, 76.8, 76.2, 73.6, 70.2, 69.1, 68.1, 64.8, 61.4; LCMS (ESI) m/z 342 (100, $[M + NH_4]^+$), 347 (15, $[M + Na]^+$), 363 (10, $[M + K]^+$).

*Synthesis of 1-C-Phenyl-β-D-Glucopyranoside (β-**3d**) by the Arylation of i-Bu_2AlH-Pretreated **10** with Arylalanes Ph_mAlCl_n for Table 3.* The following example from Table 3, entry 17 is representative of the general method used for the other entries in Table 3 with appropriate changes to the solvent used and the arylating agent (for Ph_2AlCl, Ph_3Al (1.6 mL, 1.6 mmol, 1.0 M in n-Bu_2O) and $AlCl_3$ (1.7 mL, 0.85 mmol, 0.5 M in THF) were used, and for $Ph_{1.5}AlCl_{1.5}$, Ph_3Al (1.2 mL, 1.2 mmol, 1.0 M in n-Bu_2O) and $AlCl_3$ (2.5 mL, 1.3 mmol, 0.5 M in THF) were used). Reactions were terminated when HPLC analysis showed no further formation of β-**3d**. For entries 21−23, commercially acquired 1.0 M Et_3Al in n-hexane, 1.0 M i-Bu_3Al in n-hexane, and 25% n-octyl$_3$Al in hexanes were used, respectively, in place of 1.0 M i-Bu_2AlH in PhMe. To a suspension of 1,6-anhydro-β-D-glucopyranose (**10**; 204 mg, 1.26 mmol) and 4-pentylbiphenyl (47 mg, 0.21 mmol; used as an internal standard when an HPLC yield was required; see Figures S1, S2, and S3 in the Supporting Information that show reaction plots for Table 3, entries 8−14, entries 18−20, entries 21−23, respectively) in PhOMe (5 mL) was added i-Bu_2AlH (3.7 mL, 3.7 mmol, 1.0 M in PhMe) over a 2 min period at ambient temperature. Vigorous evolution of gas was observed, and a homogeneous solution was formed. After having been stirred for 5 min (gas formation had ceased) Ph_3Al (2.1 mL, 2.1 mmol, 1.0 M in n-Bu_2O) and $AlCl_3$ (0.81 mL, 0.41 mmol, 0.5 M in THF) were added to the colorless solution resulting in the formation of a dark green to black solution. The solution was heated at 140 °C for 24 h at which time HPLC assay analysis indicated a 74% yield based on the internal standard (4-pentylbiphenyl). After cooling to ambient temperature, THF (100 mL), diatomaceous earth (10 g), and 10% aq. NaOH (3 mL) were sequentially added to the product mixture, and the resulting suspension was filtered. The filtrate was concentrated to give a yellow oil that was purified by silica gel column chromatography (eluting with 1:20 to 1:10 MeOH/DCM) to give β-**3d** (198 mg, 65%).

*Reference Sample of 1-C-Isobutyl-D-glucopyranoside (**9**), a Minor Side Product in the Arylation of **10** Treated with i-Bu_2AlH.* To a suspension of 1,6-anhydro-β-D-glucopyranose (**10**; 324 mg, 2.00 mmol) in PhOMe (5 mL) in an oven-dried, two-neck flask was added over a 2 min period i-Bu_3Al (10 mL, 10 mmol, 1.0 M in hexanes). After having been stirred at ambient temperature for 5 min the colorless and clear solution was heated at 140 °C for 19 h. After the solution cooled to ambient temperature, THF (20 mL), diatomaceous earth (2 g), and 15% aq. NaOH (2 mL) were added sequentially, and the resulting suspension was stirred at ambient temperature for 2 h. Anhydrous Na_2SO_4 (2 g) was added, and the mixture was stirred for 30 min and was then filtered. The filtrate was concentrated and purified by silica gel column chromatography (eluting with 1:40 to 1:5 MeOH−DCM) to give **9** (30 mg, 7%). LCMS (ESI) m/z 238 (100, $[M + NH_4]^+$), 458 (28, $[2\ M + NH_4]^+$). Although the configuration of C1 was not determined, it was presumed that compound **9** was 1-C-isobutyl-β-D-glucopyranoside (β-**9**) (see ^{1}H NMR spectrum in the Supporting Information).

*Synthesis of Canagliflozin (**1a**) by the Arylation of i-Bu_2AlH-Pretreated **10**.* To 1,6-anhydro-β-D-glucopyranose (**10**; 124 mg, 0.76 mmol) and 4-pentylbiphenyl (51 mg; used as an internal standard so that the reaction could be monitored by HPLC assay) in PhOMe (4 mL) was added i-Bu_2AlH (2.29 mL, 2.29 mmol, 1.0 M in PhMe) over a 2 min period at ambient temperature. After having been stirred for 5 min (gas formation had ceased) the colorless, homogeneous solution was added by syringe into a solution of bis-(3-[[5-(4-fluorophenyl)-2-thienyl]methyl]-4-methylphenyl)chloroalane in n-Bu_2O/PhMe (1.52 mmol; prepared exactly as described in ref 8a). The flask was washed with PhOMe (1 mL), and this was also added into the reaction mixture. The mixture was then heated at 140 °C for 20 h (see the reaction monitoring plot (Figure S4) in the Supporting Information; showed 61% **1a** at 18 h by UV analysis, calibrated to the internal standard, 4-pentylbiphenyl, and 33% **10** (upon ELSD analysis, calibrated to the internal standard, cinchonine)), then the mixture was cooled to ambient temperature, diluted with THF (15 mL), and cooled to 0 °C. Celite 545 (2.0 g) and 10% aq. NaOH (3.0 mL) were added slowly, and the suspension was stirred at ambient temperature for 1 h. Anhydrous Na_2SO_4 (2.0 g) was added, and the mixture was filtered through a pad of Celite 545. The flask and the Celite pad were washed with THF (10 mL) giving a yellow clear filtrate. The Celite was slurried with MeOH (10 mL) for 0.5 h and was filtered again. The filtrates were combined and concentrated to afford an oil which was chromatographed over a column of silica gel eluting with MeOH/DCM (1:10) to give 97.7% HPLC-pure (see the UV and ELSD chromatograms in the Supporting Information) canagliflozin (**1a**) as a white power (170 mg, 50%). ^{1}H and ^{13}C NMR spectra (see the Supporting Information) conformed to that reported in the Supporting Information of ref 6 in ref 8a and were identical to those of a commercially acquired sample of canagliflozin. $[\alpha]_D^{25}$ = +15.3 (c 1.0, MeOH) (the commercial canagliflozin had an $[\alpha]_D^{25}$ = +16.1 (c 1.0, MeOH); HRMS ESI QTof calculated for $[C_{24}H_{25}FO_5S$ +

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$NH_4]^+$ = 462.1750, found 462.1745; mp 99.2 °C (the commercial canagliflozin had a mp of 100.6 °C).

■ ASSOCIATED CONTENT

Supporting Information

1D and 2D NMR spectra of **10**, **10** in d_8-THF pretreated with *i*-Bu_2AlH, **8a**, **8aa**, **8ab**, **2d**, crude and isolated *β*-**3c**, **8b**, *β*-**3d**, crude **2e**, **2e** treated with water, tentative **2f**, **9**, tentative **7**, **1a**; Figures S1, S2, S3, and S4 provide reaction plots for Table 3, entries 8−14, entries 18−20, entries 21−23, and the synthesis of canagliflozin, respectively. Figures S5, S6, and S7 show HPLC chromatograms for the arylation of **2d** and the arylation of **10** pretreated *i*-Bu_2AlH. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b00601.

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Notes

The authors declare no competing financial interest.

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(10) Formal elimination of the C3−O group was also seen in the arylation of **2a** (see ref 8a), but this was not accompanied by arylation of the sugar ring. (a) See the Supporting Information for experimental details and spectra of **8a** as well as spectra of its ketone derivative, (4*R**)-2-keto-3-deoxy-4-phenyl-1-*C*-phenyl-*β*-D-glucopyranoside (**8aa**), and its hydrazone derivative, (4*R**)-2,3-dideoxy-4-phenyl-1-*C*-phenyl-*β*-D-glucopyranoside 2-(2,4-dinitrophenyl)hydrazone (**8ab**). (b) See the Supporting Information for experimental details and spectra of **8b**.

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(12) Organoalanes can exist in solution as equilibrium mixtures (see: Zhou, S.; Wu, K.-H.; Chen, C.-A.; Gau, H.-M. *J. Org. Chem.* **2009**, *74*, 3500−3505 and Zhou, S.; Chuang, D.-W.; Chang, S.-J.; Gau, H.-M. *Tetrahedron: Asymmetry* **2009**, *20*, 1407−1412). Fractional stoichiometry represents a mixture of species; for example, $Ph_{2.5}AlCl_{0.5}$ represents a mixture of Ph_3Al and Ph_2AlCl but may include other permutations that might exist in equilibrium.

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(14) Structure supported by LCMS and 1D and 2D NMR spectroscopy (see the Supporting Information).

(15) In a control experiment, heating **2e** in PhCN under reflux did not produce *β*-**3d**; however, after 3 days an ca. 1:1 mixture of **10** and disaccharide **7** were detected by TLC analysis.

(16) This was further confirmed by analysis of an extracted-ion chromatogram (XIC) constructed from the LCMS data; no ions corresponding to an isomer of *β*-**3d** were seen at the retention time that the *α*-anomer was known to elute.

(17) PhOMe, *n*-Bu_2O, PhMe, 1,4-dioxane, PhCN, and even MeCN could be used as reaction solvent; however, PhOMe and PhCN appeared better media to conduct the reaction in.

(18) A quantitative HPLC method using ELSD and UV detection in series was developed so that the consumption of UV-inactive **10** and the formation of UV-active *β*-**3d** could be monitored throughout the reaction.

(19) After aqueous workup to separate *β*-**3d** from the aluminum residues the ^1H NMR spectrum (see the Supporting Information) showed essentially only *β*-**3d**, PhOMe, *n*-Bu_2O, and sodium phenoxide.

(20) See (a) spectra or, (b) reaction plots, in the Supporting Information.

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