

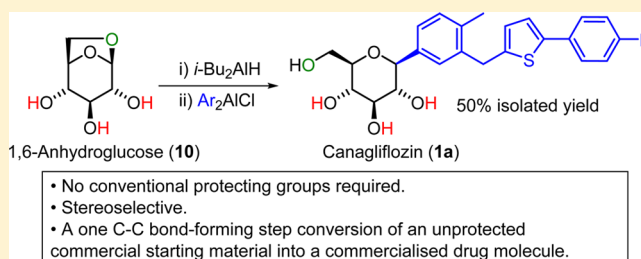
β -Selective C-Arylation of Diisobutylaluminum Hydride Modified 1,6-Anhydroglucose: Synthesis of Canagliflozin without Recourse to Conventional Protecting Groups

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S Supporting Information

ABSTRACT: The β -selective phenylation of benzyl and boronate protected 1,6-anhydroglucose and the direct arylation of unprotected 1,6-anhydroglucose (**10**), pretreated with *i*-Bu₂AlH, *i*-Bu₃Al, Et₃Al, Me₃Al, or *n*-octyl₃Al, 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

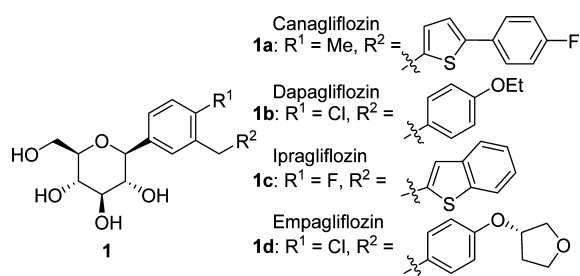


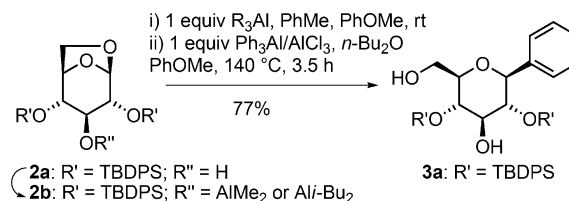
Figure 1. β -C-Arylglucosides useful for the treatment of diabetes.

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. independently³ 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 glacial pinacol boronate with aryl bromides followed by a hydroboration-oxidation sequence.

Additionally, we recently reported⁸ 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 Ph₃Al



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 AlCl₃. Activation of the triarylalanes with AlCl₃ 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-

Table 1. Arylation of Tri-O-protected Analogues^a

Reaction scheme: Ph_nAlCl_n , solvent, temp

2c: R = TBS
2d: R = Bn

3b: R = TBS
3c: R = Bn

8a: R = TBS
8b: R = Bn

entry	2	Ph_nAlCl_n	solvent	temp (°C)/ time (h)	product	yield (%) ^b
1	2c	Ph_3Al	PhOMe	140/23	3b	12 ^c
2	2d	Ph_3Al	<i>n</i> - 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	$\text{Ph}_{2.5}\text{AlCl}_{0.5}$	PhOMe	120/4	3c	12 ^{e,g}

^aReaction conditions: 2 equiv of Ph_nAlCl_n unless otherwise stated. ^bIsolated yield unless otherwise stated. ^cHPLC showed that no more **3b** was formed after about 12 h. 16% of **8a** was isolated. See Henschke et al.^{8a} for experimental details. ^d11% of **8b** was isolated. ^eHPLC yield. ^f63% unreacted **2d** and 0.39 equiv of BnOH with respect to **2d**. ^g55% unreacted **2d** and 0.44 equiv of BnOH with respect to **2d**.

arylglycoside **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 known¹¹ 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} Benzoylation 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**

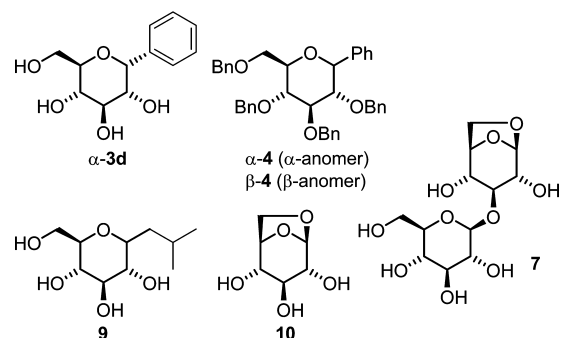


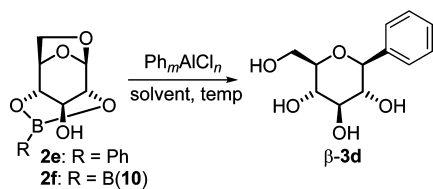
Figure 2. Miscellaneous compounds.

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 $\text{Ph}_{2.5}\text{AlCl}_{0.5}$ (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.

Arylation of 2,4-O-Boronic Ester-Protected Substrates. When the known¹³ 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-arylglycosides, such as β -3d, should be possible with only a simple reaction quench and no need for isolation of the boronate-protected C-glycoside product.

Indeed, when **2e** was heated with Ph_2AlCl in PhMe overnight followed by a MeOH quench and column chromatography, a 34% yield of arylglycoside 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 $\text{Ph}_{2.5}\text{AlCl}_{0.5}$ 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

Table 2. Arylation of 2,4-O-Boronic Esters 5^a

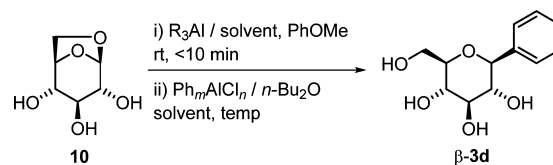
entry	2	Ph_mAlCl_n	solvent	time (h)	yield (%) ^b
1	2e	1.5 equiv of Ph_2AlCl	PhMe ^c	20	34 ^d
2	2e ^e	1 equiv of Ph_3Al	PhCN	2.5	55 ^{d,f}
3	2e	3 equiv of Ph_3Al	$\text{C}_6\text{H}_4\text{Cl}_2$	6	63 ^d
4	2e	2.4 equiv of $\text{Ph}_{2.5}\text{AlCl}_{0.5}$	PhCl	3.5	67 ^d
5	2e	2 equiv of $\text{Ph}_{2.5}\text{AlCl}_{0.8}$	PhOMe ^g	2.5	71
6	2e	2.4 equiv of $\text{Ph}_{2.5}\text{AlCl}_{0.5}$	PhCN ^h	16	67
7	2f ^e	3 equiv of Ph_3Al	dioxane	24	53 ⁱ
8	NA ^j	3 equiv of Ph_3Al	PhOMe	6	26 ^h
9	2e	3 equiv of Ph_3Al	PhOMe	6	65 ^f

^aReaction conditions: internal temperature about 140 °C, unless otherwise stated. ^bHPLC yield calibrated to an internal standard unless otherwise stated. ^cHeated under reflux. ^dIsolated yield following column chromatography. ^e10 was esterified with the boronic acid in a Dean–Stark apparatus and was used directly without isolation. ^fNo α -anomer was detected by HPLC. ^gInternal temperature 110 °C. ^hInternal temperature 80 °C. ⁱHPLC showed 1.2% of α -3d. ^j10 was mixed with 1 equiv of PhB(OH)_2 prior to arylation but the boronic ester 2e was not performed. ^kHPLC showed 1.7% of α -3d.

conditions provided a mixture of products (¹H NMR spectroscopy) tentatively containing 2f and/or its isomer(s) that upon arylation with Ph_3Al 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_3Al 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.

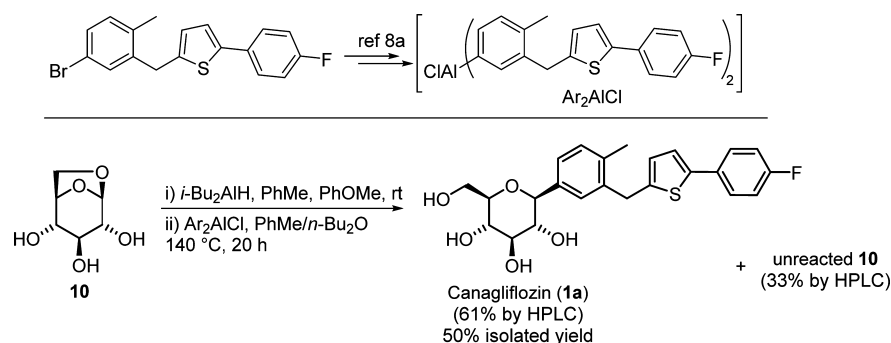
Direct Arylation of 1,6-Anhydroglucose Pretreated with *i*-Bu₂AlH. Having identified above that the arylation of 1,6-anhydroglucose (10) could be accomplished without preformation of the boronic ester the direct arylation of 10 without recourse to a protecting group installing step was examined¹⁸ using Ph_3Al . Pleasingly, heating 10 and 6 equiv of Ph_3Al (1.0 M in *n*-Bu₂O) 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_3Al 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_3Al^b	Ph_mAlCl_n	solvent	time (h)	yield (%) ^c
1	Ph_3Al	Ph_3Al^b	dioxane ^d	66	73 ^e
2	Ph_3Al	Ph_3Al^f	PhOMe	14	43
3	Ph_3Al	Ph_3Al	PhOMe	22	47
4	Ph_3Al	Ph_3Al^b	PhOMe	23	50
5	Me_3Al	Ph_3Al	PhOMe	38	32
6	<i>i</i> -Bu ₂ AlH	Ph_3Al	PhOMe ^g	43	38
7	<i>i</i> -Bu ₂ AlH	Ph_3Al	PhOMe ^h	38	55
8	<i>i</i> -Bu ₂ AlH	Ph_3Al	PhOMe	48	65 ⁱ
9	<i>i</i> -Bu ₂ AlH	Ph_3Al	<i>n</i> -Bu ₂ O	61	62
10	<i>i</i> -Bu ₂ AlH	Ph_3Al	PhCl	19	52
11	<i>i</i> -Bu ₂ AlH	Ph_3Al	Ph ₂ O	6	39
12	<i>i</i> -Bu ₂ AlH	Ph_3Al	PhCN	4	24
13	<i>i</i> -Bu ₂ AlH	Ph_3Al	PhMe ^d	37	47
14	<i>i</i> -Bu ₂ AlH	Ph_3Al	dioxane ^d	72	46
15	<i>i</i> -Bu ₂ AlH	$\text{Ph}_{1.5}\text{AlCl}_{1.5}$	PhOMe	18	36
16	<i>i</i> -Bu ₂ AlH	Ph_2AlCl	PhOMe	16	58
17	<i>i</i> -Bu ₂ AlH	$\text{Ph}_{2.5}\text{AlCl}_{0.5}$	PhOMe	24	74 ^j
18	<i>i</i> -Bu ₂ AlH	$\text{Ph}_{2.5}\text{AlCl}_{0.5}$	<i>n</i> -Bu ₂ O	21	74 ^k
19	<i>i</i> -Bu ₂ AlH	$\text{Ph}_{2.5}\text{AlCl}_{0.5}$	PhCl	21	74 ^l
20	<i>i</i> -Bu ₂ AlH	$\text{Ph}_{2.5}\text{AlCl}_{0.5}$	Ph ₂ O	26	72 ^m
21	Et_3Al	$\text{Ph}_{2.5}\text{AlCl}_{0.5}$	PhOMe	18	65
22	<i>i</i> -Bu ₃ Al	$\text{Ph}_{2.5}\text{AlCl}_{0.5}$	PhOMe	24	72
23	<i>n</i> -octyl ₃ Al	$\text{Ph}_{2.5}\text{AlCl}_{0.5}$	PhOMe	48	53 ⁿ

^aReaction conditions: 2 equiv of Ph_mAlCl_n unless otherwise stated. Internal temperature 140 °C unless otherwise stated. ^b3 equiv. ^cHPLC yield calibrated to internal standard unless otherwise stated. ^dUnder reflux. ^e48% isolated yield following workup and column chromatography. ^f1 equiv. ^g100 °C internal temperature. ^h120 °C internal temperature. ⁱ51% isolated yield following workup and column chromatography. ^j4.0% of α -3d and 0.50% of 9 was detected by HPLC analysis. Isolated yield by column chromatography was 65%. ^k4.4% of α -3d and 0.47% of 9 was detected by HPLC analysis. ^l3.2% of α -3d and 0.49% of 9 was detected by HPLC analysis. ^m4.0% of α -3d and 0.53% of 9 was detected by HPLC analysis. ⁿThe 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_3Al (entry 5) instead of Ph_3Al , followed by arylation with 2 equiv of Ph_3Al . This resulted in a disappointing 32% yield, however. Although 10 was not soluble in PhOMe, when 3 equiv of *i*-Bu₂AlH 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*-Bu₂AlH in PhMe, vigorous bubbling occurred followed by the generation of a colorless, homogeneous solution. Analysis by ¹H NMR spectroscopy^{20a} suggested that at least three components had formed, confirming that in *d*₈-THF, at least, modification of 10 with *i*-Bu₂AlH does not produce a single component that is directly analogous to 2,3,4-tri-O-protected 1,6-anhydroglucose

Scheme 2. Synthesis of Canagliflozin by the Arylation of 1,6-Anhydroglucose (10) Pretreated with *i*-Bu₂AlH

compounds such as **2c** or **2d**. Solvent screening (entries 9–14) showed that while *n*-Bu₂O was comparable to PhOMe in terms of yield of **β-3d**, PhCl, Ph₂O, PhCN, PhMe, and dioxane provided less satisfactory results.^{20b} Consistent with the phenylation of **2a** pretreated with Me₃Al,^{8a} the rate of arylation of **10** pretreated with *i*-Bu₂AlH in PhOMe was significantly increased (16–24 h) by the use of phenyl(chloro)alanes, Ph_{*m*}AlCl_{*n*} (entries 15–17), prepared by mixing Ph₃Al and AlCl₃. 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*-Bu₂O (entry 18), PhCl (entry 19), or Ph₂O (entry 20) as solvent.^{20b} HPLC yields were significantly improved (72–74%) upon those using the same solvents with Ph₃Al 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, Et₃Al (entry 21), *i*-Bu₃Al (entry 22), and *n*-octyl₃Al (entry 23) were tested in the pretreatment step of **10** in place of *i*-Bu₂AlH.^{20b} Whereas arylation rates and yields using Et₃Al and *i*-Bu₃Al were similar to those using *i*-Bu₂AlH, pretreatment with *n*-octyl₃Al resulted in much slower arylation.

Synthesis of Canagliflozin from 1,6-Anhydroglucose Pretreated with *i*-Bu₂AlH. 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 Ar₂AlCl (Ar = (3-[[5-(4-fluorophenyl)-2-thienyl]methyl]-4-methylphenyl)) was prepared as described previously.^{8a} A PhMe–*i*-Pr₂O 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 AlCl₃ in *n*-Bu₂O at 90 °C. Following dilution with PhMe and concentration to remove the *i*-Pr₂O, 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*-Bu₂AlH prior to being heated at 140 °C together with 2 equiv of the above prepared arylating agent in PhMe/*n*-Bu₂O. 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- (Ph₃Al) or phenyl(chloro)alanes (Ph_{*m*}AlCl_{*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 Ph₃Al or by pretreatment with *i*-Bu₂AlH, *i*-Bu₃Al, Et₃Al, Me₃Al, or *n*-octyl₃Al, followed by heating with Ph₃Al or Ph_{*m*}AlCl_{*n*}. In comparison to the conventional method³ 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 ¹³C 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 Knoche's method.²¹ Commercial 1,6-anhydro- β -D-glucopyranose (**10**), *i*-Bu₂AlH (DIBAL; 1.0 M in PhMe), Ph₃Al (1.0 M in *n*-Bu₂O), Et₃Al (1.0 M in *n*-hexane), *i*-Bu₃Al (1.0 M in *n*-hexane), and *n*-octyl₃Al (25% in hexanes), and AlCl₃ (0.5 M in THF; titrated by Eriochrome cyanine R spectrophotometric method²²) 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

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 Ph₃Al 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 μ m, 4.6 \times 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 μ m, 4.6 \times 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 Ph₃Al 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. ¹H NMR (400 MHz, CDCl₃) δ 7.45–7.42 (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); ¹³C NMR (100 MHz, CDCl₃) 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_{*n*}AlCl_{*n*} for Table 1, Entries 2–5.** These compounds were prepared by heating an *n*-Bu₂O (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 Ph₃Al (2.0 mL, 2.0 mmol, 1.0 M in *n*-Bu₂O), or Ph₂AlCl (2.0 mmol; a mixture of Ph₃Al (1.3 mL, 1.3 mmol, 1.0 M in *n*-Bu₂O) and AlCl₃ (1.3 mL, 0.67 mmol, 0.5 M in THF)), or Ph_{2.5}AlCl_{0.5} (2.0 mmol; Ph₃Al (1.67 mL, 1.67 mmol, 1.0 M in *n*-Bu₂O) and AlCl₃ (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 Na₂SO₄ (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 ¹H 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. ¹H NMR (400 MHz, CDCl₃) 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); ¹³C NMR (100 MHz, CDCl₃) 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}; [α]_D²⁰ = –6.6 (c 1.0, MeOH); LCMS (ESI) m/z 528 (100, [M + NH₄]⁺), 529 (35, [M + NH₄ + 1]⁺), 533 (5, [M + Na]⁺); ESI QTOF of calculated for [C₃₃H₃₄O₅ + NH₄]⁺ = 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 ¹H 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 ¹H and ¹³C NMR analysis (see the Supporting Information) and by analogy to **8a** (see above). ¹H NMR (400 MHz, CDCl₃) 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); ¹³C NMR (100 MHz, CDCl₃) 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 – H₂O]⁺), 373 (57, [M + H]⁺), 390 (100, [M + NH₄]⁺), 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 μ L, 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 ¹H 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. ¹H NMR (400 MHz, CDCl₃) δ 7.83–7.87 (m, 2H), 7.46–

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 tetrahydrodiboron (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. ^1H NMR analysis (see ^1H 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 $n\text{-Bu}_2\text{O}$) and AlCl_3 (1.0 mL, 0.50 mmol, 0.5 M in THF) was used), or $\text{Ph}_{2.5}\text{AlCl}_{0.5}$ (for entries 4 and 6: a mixture of Ph_3Al (2.0 mL, 2.0 mmol, 1.0 M in $n\text{-Bu}_2\text{O}$) and AlCl_3 (0.8 mL, 0.4 mmol, 0.5 M in THF or neat AlCl_3)), or $\text{Ph}_{2.2}\text{AlCl}_{0.8}$ (for entry 5: a mixture of Ph_3Al (1.5 mL, 1.50 mmol, 1.0 M in $n\text{-Bu}_2\text{O}$) 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 ^1H , ^{13}C , DEPT-135, HMQC, COSY, HMBC (a correlation between H1' and C3 supports the proposed (1 \rightarrow 3)-disaccharide linkage), and NOESY NMR experiments (see spectra in the Supporting Information). ^1H 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, $[\text{M} + \text{NH}_4]^+$), 347 (15, $[\text{M} + \text{Na}]^+$), 363 (10, $[\text{M} + \text{K}]^+$).*

*Synthesis of 1-C-Phenyl- β -D-Glucopyranoside (β -3d) by the Arylation of $i\text{-Bu}_2\text{AlH}$ -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 $n\text{-Bu}_2\text{O}$) and AlCl_3 (1.7 mL, 0.85 mmol, 0.5 M in THF) were used, and for $\text{Ph}_{1.5}\text{AlCl}_{1.5}$, Ph_3Al (1.2 mL, 1.2 mmol, 1.0 M in $n\text{-Bu}_2\text{O}$) 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 $n\text{-hexane}$, 1.0 M $i\text{-Bu}_3\text{Al}$ in $n\text{-hexane}$, and 25% $n\text{-octyl}_3\text{Al}$ in hexanes were used, respectively, in place of 1.0 M $i\text{-Bu}_2\text{AlH}$ 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 $i\text{-Bu}_2\text{AlH}$ (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 $n\text{-Bu}_2\text{O}$) 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 $i\text{-Bu}_2\text{AlH}$. 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 $i\text{-Bu}_3\text{Al}$ (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, $[\text{M} + \text{NH}_4]^+$), 458 (28, $[2\text{M} + \text{NH}_4]^+$). Although the configuration of C1 was not determined, it was presumed that compound **9** was 1-C-isobutyl- β -D-glucopyranoside (β -9) (see ^1H NMR spectrum in the Supporting Information).*

*Synthesis of Canagliflozin (**1a**) by the Arylation of $i\text{-Bu}_2\text{AlH}$ -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 $i\text{-Bu}_2\text{AlH}$ (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 $n\text{-Bu}_2\text{O}$ /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 S45 (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 S45. 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 powder (170 mg, 50%). ^1H 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 QT of calculated for $[\text{C}_{24}\text{H}_{25}\text{FO}_5\text{S}]^+$*

NH₄⁺ = 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*-Bu₂AlH, **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*-Bu₂AlH. 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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- (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 Ph₃Al and Ph₂AlCl 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*-Bu₂O, 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*-Bu₂O, and sodium phenoxide.
- (20) See (a) spectra or, (b) reaction plots, in the Supporting Information.
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