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β-Selective C-Arylation of Silyl Protected 1,6-Anhydroglucose with Arylalanes: The Synthesis of SGLT2 Inhibitors

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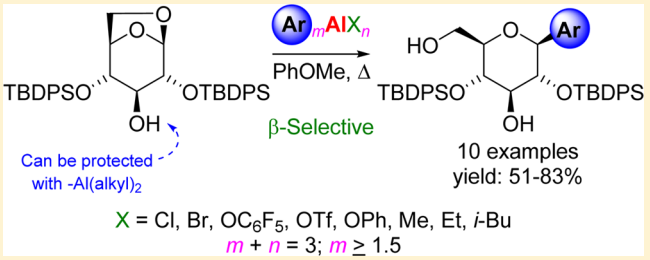
Supporting Information

ABSTRACT: The stereoselective arylation of hydroxy protected 1,6-anhydro-β-D-glucose with arylalanes to provide β-C-arylglucosides is reported. Modification of triarylalanes, Ar_3Al, with strong Brønsted acids (HX) or $AlCl_3$ produced more reactive arylating agents, Ar_2AlX, while the incorporation of alkyl dummy ligands into the arylating agents was also viable. Me_3Al and i-Bu_2AlH were found useful in the *in situ* blocking of the C3-hydroxyl group of 2,4-di-*O*-TBDPS protected 1,6-anhydroglucose. The utility of the method was demonstrated by the synthesis of the SGLT2 inhibitor, canagliflozin.



INTRODUCTION

While many approaches exist for the formation of *C*-glycosidic bonds,[1] the coupling of electrophilic glycosyl donors with carbon nucleophiles is probably most used in *C*-glucoside synthesis.[2] Since 2012, four members (Figure 1) of a new class

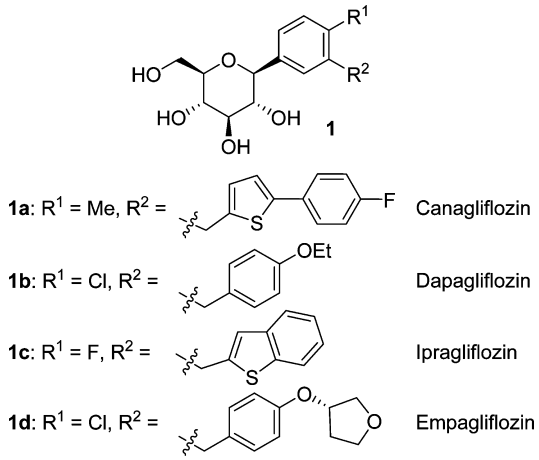


Figure 1. β-C-arylglucoside SGLT2 inhibitors approved for the treatment of diabetes.

of antidiabetes active pharmaceutical ingredient (API), known as Sodium-coupled GLucose co-Transporter 2 (SGLT2) inhibitors (**1**),[3] have received marketing approval. These compounds, canagliflozin (**1a**), dapagliflozin (**1b**), ipragliflozin (**1c**), and empagliflozin (**1d**),[4] are structurally archetypical of a plethora of synthetic, biologically active β-C-arylglucosides that have been reported. Varying by only the diaryl methylene side chain, the close structural similarity of these compounds renders them good targets for a new synthetic platform technology.

Conventionally, β-C-arylglucosides are prepared by variants of the Kraus et al. and Czernecki et al. approach that comprises the low-temperature addition of aryllithium or arylmagnesium compounds to per-hydroxyl protected gluconolactones, followed by reduction with silane reagents in the presence of $BF_3{\cdot}OEt_2$, separation of the resulting anomers, and deprotection (see the top route in Scheme 1).[5] The only moderate β-anomeric selectivity (4:1 β:α when using $Et_3SiH/BF_3{\cdot}OEt_2$) witnessed in the silane reduction step of the traditionally used per-benzyl protected gluconolactone was later addressed at Bristol-Myers Squibb by the use of bulky silane reagents (up to 45:1 β:α)[6a] or by conversion of the lactol 1,2-addition product to a per-acetyl protected methyl *C*-arylglucoside derivative, followed by reduction with $Et_3SiH/BF_3{\cdot}OEt_2$ in the presence of water (19:1 up to >65:1 β:α).[6b] This and other improvements to the gluconolactone approach have allowed for the multi-kilogram scale synthesis of SGLT2 inhibitors, as exemplified for a dapagliflozin analogue from commercially available gluconolactone.[7] Perhaps the best advance in β-C-arylglucosides synthesis since publication of the original gluconolactone method was reported by Lemaire et al.[8a] In their transition-metal-free approach, a per-*O*-pivaloyl protected glucosyl bromide substrate was rapidly arylated with diaryl zinc reagents that were prepared by the lithiation of aryl halides, followed by transmetalation with a zinc bromide−lithium bromide complex. Good yields and high stereoselectivity were achieved over a

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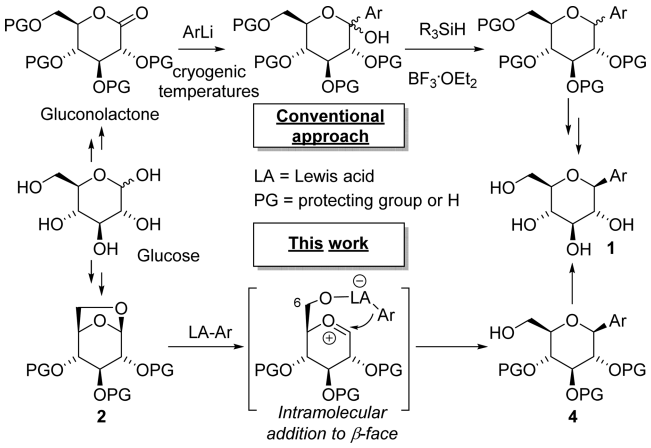
Scheme 1. Conventional (Top) and Conceptual *C*-Arylation Strategy (Bottom) for the Synthesis of *β*-*C*-Arylglucosides 4 and 1



range of aryl nucleophiles, and the usefulness of the method was exemplified by the synthesis of canagliflozin (**1a**) and dapagliflozin (**1b**). Sakamaki et al.[8b] demonstrated the preparation of a selection of *β*-*C*-arylglucosides by the boronation of a tri-*O*-silyl protected D-glucal substrate, palladium-catalyzed Suzuki cross-coupling of the thus generated glucal pinacol boronate with aryl bromides, followed by a hydroboration−oxidation sequence with a borane−THF complex and basic hydrogen peroxide, and finally TBAF-promoted desilylation. Cossy et al. produced *α*-*C*-arylglucosides from per-*O*-acetyl protected glucosyl bromide with moderate selectivity using Grignard reagents in the presence of a Co(III) catalyst; however, these possessed the opposite C1-configuration of SGLT2 inhibitors.[8c]

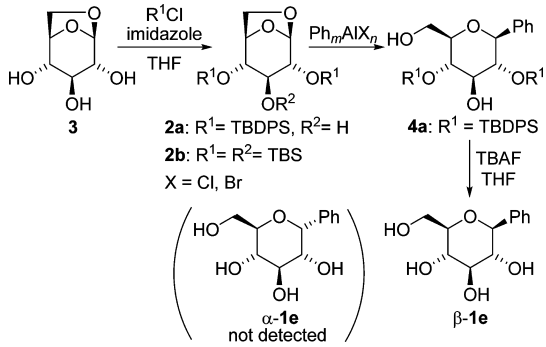
Inspired by experience in oligosaccharide synthesis, we were intrigued by the possibility of utilizing a protected derivative **2** of 1,6-anhydro-*β*-D-glucose (**3**) as the electrophile in a nucleophilic coupling with aryl nucleophiles (see the bottom route in Scheme 1). With 1,6-anhydroglucose possessing the same oxidation state as glucose, no reduction step would be required, in contrast to the gluconolactone approach. While the relative inertness of the 1,3-dioxolane ring of **2** rendered non-Lewis acid assisted nucleophilic attack unviable, literature precedent[9] for the allylation of 2,3,4-tri-*O*-benzyl-1,6-anhydroglucose (**2**: PG = Bn) in the presence of $BF_3{\cdot}OEt_2$ or TMSOTf suggested that Lewis acid assisted nucleophilic attack would be possible but would favor the undesired *α*-anomer. To mitigate this, the requisite aryl nucleophile and a Lewis acid could be combined into a single agent able to (i) coordinate to and open the 1,3-dioxolane ring of compound **2** to furnish an oxocarbenium ion and, (ii) while covalently bound to the C6 oxygen as an ate complex of the opened 1,3-dioxolane ring, deliver the aryl anion directly to the requisite *β*-face of the oxocarbenium ion, thereby furnishing the desired *β*-*C*-arylglucosides **4**. This approach would be synthetically succinct and potentially highly stereoselective owing to substrate control and finds precedent in the alkynylation and arylation of anhydrofuranose and anhydropyranose derivatives (see below).

Having investigated this, we report herein a method that arylates with high stereoselectivity the protected 1,6-anhydroglucose derivative **2a** with arylalanes, delivering hydroxy protected *β*-*C*-arylglucosides **4** in one step; transition metals and cryogenic temperatures are not required.[10]

RESULTS AND DISCUSSION

Preliminary Results. While *tert*-butyldimethylsilylation of commercially available 1,6-anhydroglucose[11] (**3**) furnished tri-*O*-*tert*-butyldimethylsilyl (TBS) protected sugar **2b**, exhaustive silylation with *tert*-butyldiphenylsilyl (TBDPS) chloride gave the 2,4-di-*O*-TBDPS protected derivative **2a** (Scheme 2). In an initial screening study, **2a** was treated with mixtures of PhLi or PhMgBr in the presence of B-, Al-, Ga-, Ti-, Zn-, In-, La-, or Hf-based Lewis acids. Although various Ti(IV) salts or $GaCl_3$ provided promise, the combination of PhLi or PhMgBr with $AlCl_3$, which was presumed to generate arylaluminum compounds and metal halide salts, led to efficient, albeit slow, conversion of **2a** to the desired protected product *β*-*C*-phenylglucoside **4a**.[12] By contrast, when tri-*O*-TBS protected derivative **2b** was subjected to the same conditions, considerable decomposition occurred, and subsequent studies were, therefore, focused on the use of **2a**.

Scheme 2. *β*-*C*-Arylation of Protected 1,6-Anhydroglucose



Organoaluminums can donate alkyl or aryl carbanions to other metals, including Rh(I), Ti(IV), or Pd(II), making them useful in asymmetric addition reactions and cross-couplings.[13] The relatively high Lewis acidity of the aluminum centers combined with nucleophilic organic ligands renders organoaluminum reagents also useful as synthetic reagents on their own.[14] For example, in related work, Yamamoto et al.[15] demonstrated the stereoretentive cleavage and *alkylation* of 1,3-dioxolane and 1,3-dioxane rings using *alkyl*aluminum derivatives and Vasella et al.[16] used silyl protected propargylaluminum dichloride in the *β*-selective *alkyn*ylation of protected 1,6-anhydrohexoses. Rainier et al.[17] have shown that Ph_3Al and $(2\text{-furyl})_3Al$ are able to *arylate* an oxirane derivative of tri-*O*-benzyl-D-glucal to provide *α*-*C*-*aryl*glucosides, while *β*-*C*-*aryl*arabinonucleosides were prepared by Sietz et al. using an excess of tri*aryl*aluminum reagents and 3,5-di-*O*-TBS or TBDPS protected 1,2-anhydroarabinose.[18] Both of these arylation reactions, however, utilize cryogenic temperatures (≤−65 °C) due to the high reactivity of both the oxiranes and arylaluminum compounds. The relatively low toxicity and affordability of aluminum derivatives was attractive from a scale-up perspective, and detailed investigations ensued in our laboratories.

Examination of Arylalanes as Arylating Agents of 1,6-Anhydroglucose 2a. The conversion of **2a** to **4a** was investigated in PhMe using commercially available Ph_3Al (1 M solution in $n\text{-}Bu_2O$) (see Figure S1 in the Supporting Information).[19] Whereas 2 equiv of Ph_3Al provided a 77% HPLC yield in 118 h, yields of <50% were observed when using

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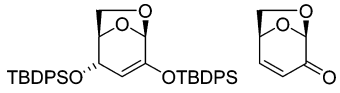
0.25 up to 1.5 equiv, despite only 0.33 equiv theoretically being required to effect full conversion.

Next, as per the preliminary screening study, phenylalane reagents were prepared *in situ* from PhMgBr in Et_2O and $AlCl_3$ in THF.[20] Varying the relative molar ratio of these reagents allowed precise control over the composition of the arylating agent and provided access to the more reactive aryl(halo)-alanes, Ph_mAlX_n[21] (where X is Cl and Br). Arylation rates in PhMe increased when (i) THF and Et_2O were removed by evaporation before arylation, and (ii) as the ratio of the aryl anion (Ar) to halide (X) decreased, consistent with the increasing Lewis acidity of the aluminum center. Arylating reagents Ph_mAlX_n (2 equiv) having m/n ratios 2.5:0.5 and 3.0:0 gave HPLC yields of **4a** of about 65−70% in about 25−55 h, while a 2:1 ratio led to around a 50% HPLC yield (see Figure S2 in the Supporting Information). Predictably, the non-Lewis acidic tetraarylalane ate complex, $[Ph_4Al]MgX$, provided no significant reaction within 24 h.[22] Paralleling the 2 equiv threshold seen when using commercially available Ph_3Al, while 1 equiv of $Ph_{2.5}AlX_{0.5}$ in PhMe only gave a 40% HPLC yield, 2, 3, and 4 equiv all provided about a 70% yield of **4a** (see Figure S3 in the Supporting Information). The necessity for at least 2 equiv of arylating reagent to effect good conversion of **2a** to **4a** was explained by the presence of the unprotected C3 hydroxyl of **2a** and is addressed below.

Solvent screening (see Figure S4 in the Supporting Information) showed that, while arylation was ineffective in THF[23] using 2 equiv of $Ph_{2.5}AlX_{0.5}$, yields of around 70−80% were witnessed in PhMe, PhCl, PhOMe, or *n*-Bu_2O as solvent. Moderate yields were seen in Ph_2O (65%), dioxane (51%), and benzonitrile (30%), while arylation in the highly polar solvents diglyme, pyridine, and NMP failed to provide good yields of glucoside **4a**. Although PhCl proved a particularly good solvent in terms of reaction rate and yield (80%), it was undesirable from a toxicity perspective.[24] Instead, PhOMe,[25] which provided superior solubilization, reaction rate, or stirrability as compared to PhMe, PhCl, or *n*-Bu_2O, was selected for the subsequent studies. Re-examination (see Figure S5 in the Supporting Information) of the aryl anion/halide ratios m/n using PhOMe as solvent revealed a similar trend to that in PhMe; however, the best yields were witnessed using the more Lewis acidic m/n ratios of 2.5:0.5 (83%; 28 h) and 2:1 (83%; 21 h), while severe decomposition occurred when m/n was 1:2.

In addition to the desired product **4a** (t_R 24.0 min) and small amounts of biphenyl (t_R 13.7 min), benzene (t_R 10.1 min), and phenol (t_R 6.6 min), HPLC analysis of the reaction mixture revealed the formation of a closely eluting coproduct (t_R 23.5 min). Desilylation of the unpurified, crude product mixture using TBAF in THF, followed by HPLC comparison to a mixture of authentic α-**1e** and β-**1e**,[26] showed, to our surprise, no detectable amounts of α-anomer α-**1e**, revealing that the arylation reaction was highly β-selective. LCMS analysis of the coproduct indicated that it was instead a dehydrated derivative of TBDPS protected 1,6-anhydroglucose **2a**. When reaction aliquots were treated with 5% TFA in MeCN before HPLC analysis, however, the major coproduct (t_R 23.5 min) was no longer detectable and instead significant amounts of *tert*-butyldiphenylsilanol (TBDPSOH; t_R 14.2 min) were produced along with a new, relatively weakly UV-active, fast eluting impurity (t_R 3.9 min). Under the same HPLC sample preparation conditions, however, neither TBDPS protected **2a** nor the β-*C*-arylglucoside product **4a** produced TBDPSOH, indicating that it was produced by acidic catalyzed/promoted decomposition of the coproduct. Following isolation by column chromatography, 1D and 2D NMR spectroscopy revealed that the coproduct was 1,6-anhydrosilylenol ether **5**. Consistent with this, treatment of **5** with 5% TFA in MeCN produced (−)-levoglucosenone (**6**), the fast eluting impurity, as confirmed by reference to a commercial sample (Figure 2).



5 6

Figure 2. Silylenol ether **5** and (−)-levoglucosenone (**6**).

The level of TBDPSOH, produced when reaction aliquots were treated with 5% TFA in MeCN before HPLC analysis,[27] was then used as a proxy for 1,6-anhydrosilylenol ether **5** formed in the arylations, and in fact, its level was a good measure of reaction performance.

Scope of the Arylation Reaction and Stereoselectivity. Having determined the stoichiometry, solvent, and Ph_mAlX_n m/n ratio (Table 1, entry 1), the scope was extended to other *C*-arylglucosides by varying the aryl Grignard or lithium reagent. Simple aromatics (entries 2 and 3) provided good HPLC yields, while the two 4-halo substituted aromatics tested (entries 4 and 5) provided lower yields and required a higher reaction temperature. While the heteroaromatic furyl group (entry 6) was readily transferred to the substrate, thienyl (entry 7) and 4-methoxyphenyl (entry 8) groups were more challenging due to competitive, albeit manageable, degradation of the *C*-arylglucoside products. Satisfyingly, this methodology was also applicable to the synthesis of the 2,4-di-*O*-TBDPS protected derivatives **4i** and **4j** of canagliflozin (**1a**; entry 9) and dapagliflozin (**1b**; entry 10), respectively. These were subsequently desilylated with TBAF in THF to provide the respective SGLT2 inhibitors **1a** and **1b** for proof of concept.

In the absence of reference samples of the α-anomers of the *C*-arylglucosides, high-resolution LCMS analyses of the crude product mixtures were conducted for **4c**, **4d**, **4f**, and **4h** and extracted-ion chromatograms (XICs) using the mass-to-charge ratios of the corresponding ammonium adducts were created from the resultant data sets. No isomer peaks were detectable in the XICs, indicating that the arylation reactions proceeded with high stereoselectivity, consistent with that already shown for the phenyl analogue **4a**. This was further confirmed for canagliflozin (**1a**) following deprotection of the crude mixture of **4i** with TBAF in THF and re-analysis without purification; again, no isomer peak was detected. In addition to ^{1}H NMR spectroscopic identification of the desilylated products of **4a**, **4i**, and **4j** by comparison to spectra of authentic samples of β-**1e**,[26] canagliflozin (**1a**), and dapagliflozin (**1b**), respectively, the coupling constants $J_{1,2}$ of **4a**−**4j** (9.2−10.0 Hz) were consistent with C1-β-configured *C*-arylglucosides.[8b]

Examining the Effect of Metal Halides. Although sometimes having a positive influence,[28] magnesium salts have also been reported to interfere in some reactions involving organoaluminum reagents.[13b,29] Given this, a better understanding of the influence of the magnesium and lithium halide byproducts, formed during arylalane synthesis, was sought. Two equivalents of the arylating agent was used to account for the unprotected C3-hydroxyl of **2a** that results in the formation of alkoxy(diphenyl)alane **7a** (see below). Whereas **2a** converted to **4a** in a 81% HPLC yield using commercially available Ph_3Al

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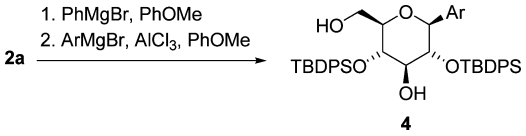
Table 1. Arylation of 2a To Produce β-*C*-Arylglucosides 4

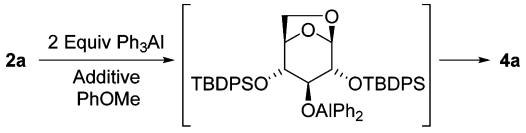


4

entry[a]	Ar	temp (°C)[b]	time (h)	product	yield **4** (%)[c]	β/α selectivity[d]
1	Ph	120	28	**4a**	83	>99:1
2	4-tolyl	120	26	**4b**	59	ND
3	mesityl	140	16	**4c**	67	>99:1
4	4-Cl-Ph	140	22	**4d**	47	>99:1
5	4-F-Ph	140	4	**4e**	56	ND
6	2-furyl[e]	120	16	**4f**	78	>99:1
7	2-thienyl	120	4	**4g**	60[f]	ND
8	4-MeO-Ph	120	8	**4h**	54[f,g,h]	>99:1
9	Ar[1][i]	140	5	**4i**	68	>99:1
10	Ar[2][j]	120	8	**4j**	51	ND

[a]The arylating agent $Ar_{2.5}AlX_{0.5}$ (2 equiv) was prepared in PhOMe using $AlCl_3$ in THF and the corresponding Grignard reagent at rt. **2a** in PhOMe was deprotonated with PhMgBr in Et_2O. The mixture was concentrated under reduced pressure to remove THF and Et_2O. [b]Internal solution temperature. [c]HPLC yields with reference to 1,2,4,5-tetramethylbenzene (internal standard). [d]See explanation in the main text. [e]2-Furyllithium was used as the aryl source. [f]Competing decomposition of the arylation product was observed. [g]Some demethylated product formed from **4h** as the reaction proceeded. [h]The arylating reagent was $(4\text{-}MeOC_6H_4)_2AlCl$. [i]Ar[1] is 3-[[5-(4-fluorophenyl)-2-thienyl]methyl]-4-methylphenyl. **2a** was deprotonated with *n*-BuLi. [j]Ar[2] is 4-chloro-3-[(4-ethoxyphenyl)methyl]phenyl.

Table 2. Influence of Additives on the Arylation of 2a with Ph_3Al



7a

entry	additive	time (h)	yield **4a** (%)[a]	unreacted **2a**	TBDPSOH[b]
1	none	31	81	9	33
2	1 equiv $MgCl_2$	23	61	17	51
3	1 equiv $MgBr_2$	6	64	4	66
4	6 equiv LiCl	12	26	30	51
5	1 equiv $Mg(OTf)_2$	33	67	13	37
6	3 equiv $Mg(OTf)_2$	23	70	16	31
7	1 equiv Ph_4PCl	19	35	34	37
8	2 equiv Ph_4PCl	48	0	82	28
9	4 equiv Ph_4PCl	48	0	86	18
10	1 equiv Ph_4PBr	8	39	28	33
11	2 equiv Ph_4PBr	12	7	66	32
12	3 equiv Ph_4PBr	12	9	45	53
13	4 equiv Ph_4PBr	12	8	40	57

[a]HPLC yields determined by reference to 1,2,4,5-tetramethylbenzene (internal standard). [b]Reaction aliquots were treated with 5% TFA in MeCN before HPLC analysis, resulting in the conversion of **5** into TBDPSOH (the values presented may be approximate).

(Table 2, entry 1), the addition of 1 equiv of $MgCl_2$ (entry 2) resulted in a decreased 61% HPLC yield, 17% unreacted **2a**, and a relatively high level of TBDPSOH (51%), indicating increased elimination to produce **5**. Although the reaction rate increased when spiked with 1 equiv of $MgBr_2$ (entry 3), an even higher level of TBDPSOH (66%) was observed. Notably, a low 26% yield of **4a** was witnessed along with 30% of unreacted **2a** and 51% of TBDPSOH when the reaction was conducted in the presence of 6 equiv of LiCl (entry 4). By contrast, addition of 1 equiv or 3 equiv of $Mg(OTf)_2$ (entries 5 and 6) to the reaction resulted in about a 70% HPLC yield of **4a** with similar conversion rates to that of the unadulterated reaction, indicating that the halide ion(s) rather than the metal itself were predominantly responsible for the observed deleterious effect. To confirm this, reactions (entries 7–13) were spiked with $[Ph_4P]Cl$ or $[Ph_4P]Br$ to avoid interference from metal ions (see Figure S6 in the Supporting Information). Whereas 1 equiv of $[Ph_4P]Cl$ (equivalent to 0.5 equiv of chloride per aluminum; entry 7) reduced the yield of **4a** to 35% (19 h), leaving 34% unreacted **2a** and 37% TBDPSOH, 2 and 4 equiv (entries 8 and 9) of the chloride salt inhibited arylation altogether. Although a similar phenomenon occurred when reactions were spiked with $[Ph_4P]Br$ (entries 10–13), even an excess failed to completely inhibit the reaction. It was, therefore, evident that free halides were detrimental to this reaction while the presence of metal counterions (Li and Mg) appeared to moderate the phenomenon.

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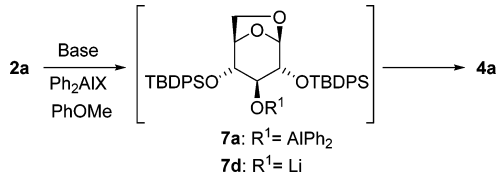
Table 3. Arylation of 2a Using Activated Phenylalanes



entry	base[a]	Ph_2AlX	time (h)	yield **4a** (%)[b]	unreacted **2a**	TBDPSOH[c]
1	Ph_3Al	1 equiv Ph_2AlOTf	2.5	81	3	31
2	Ph_3Al	1 equiv Ph_2AlCl	8	85	1	36
3	Ph_3Al	1 equiv $Ph_2AlOC_6F_5$	12	82	3	24
4	Ph_3Al	1 equiv Ph_2AlOPh	24	69	10	45
5	Ph_3Al	1 equiv Ph_2AlO*i*-Pr	21	44	14	53
6	Ph_3Al	0.5 equiv Ph_2AlCl	5	67	8	62
7	Ph_3Al	2 equiv Ph_2AlCl	3	90	0	21
8	Ph_3Al	3 equiv Ph_2AlCl	4	94	0	15
9	*n*-BuLi	1 equiv Ph_3Al	31	0	68	9
10	*n*-BuLi	2 equiv Ph_3Al	30	0	89	24
11	*n*-BuLi	2 equiv Ph_2AlCl	3	86	2	35
12	Ph_3Al[d]	1 equiv Ph_2AlCl–LiCl	2	72	0.8	54

[a]1 equiv of base used. [b]HPLC yields as determined by reference to 1,2,4,5-tetramethylbenzene (internal standard). [c]Reaction aliquots were treated with 5% TFA in MeCN before HPLC analysis (the TBDPSOH values presented may be approximate). [d]**2a** was reacted with 2 equiv of $Ph_{2.5}AlCl_{0.5}$, which comprises a mixture of Ph_3Al and Ph_2AlCl. 1 equiv of LiCl was added.

Metal-Halide-Free, Brønsted Acid Activated Arylating Agents. Attention was turned to arylating agents free of magnesium or lithium halide salts (Table 3). Additionally, the relationship between Lewis acidity of the alane and reactivity was further explored. To this end, commercial Ph_3Al was modified by premixing with TfOH, C_6F_5OH, PhOH, or *i*-PrOH, while salt-free Ph_2AlCl was prepared by mixing Ph_3Al and $AlCl_3$.[30] As expected, the rate of arylation using these reagents increased with decreasing p*K*a of the Brønsted acids used (Figure 3).[31] For the OTf (entry 1), Cl (entry 2), or

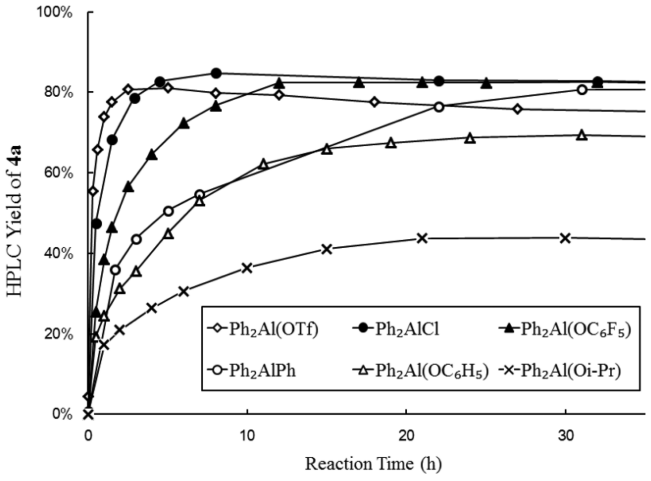


Figure 3. Arylation of **2a** using activated arylalanes.

OC_6F_5[15] (entry 3) modified alanes, the arylation reactions reached HPLC yields of ≥80% much more rapidly than Ph_3Al (entry 1, Table 2). Both the OPh (Table 3, entry 4) and O*i*-Pr (entry 5) ligands, on the other hand, deactivated the arylating reagent and reduced yields significantly, with respect to Ph_3Al, and more TBDPSOH was produced when HPLC samples were prepared under acidic conditions. That the alkoxy(diphenyl)-alane was not a good arylating agent is consistent with the low yields generated when arylating **2a** with 1 equiv of Ph_3Al or $Ph_{2.5}AlX_{0.5}$ that form **7a**. That is, the alkoxy(diphenyl)alane moiety of **7a** is not thought to be a good *intra-* or *inter*molecular arylating agent. From a scale-up perspective, the high reaction rate and yield, the ease of preparation (i.e., mixing of Ar_3Al and $AlCl_3$), and with cost considerations in mind, aryl(chloro)alanes were favored as arylating reagents and were used in subsequent studies.

Arylations of alkoxy(diphenyl)alane **7a**, formed from **2a** in the presence of Ph_3Al (see later), using 0.5 equiv through to 3 equiv of Ph_2AlCl (Table 3, entries 6–8) were typically complete within several hours; however, at least 1 equiv of Ph_2AlCl (entry 2) was required to achieve HPLC yields of over 80%. Yields increased as the amounts of Ph_2AlCl were increased. Notably, arylation of lithium alkoxide **7d** (**2a** was deprotonated using *n*-BuLi) instead of **7a** with 1 equiv or 2 equiv of Ph_3Al (entries 9 and 10) failed to produce **4a**. This was explained by the formation of the non-Lewis acidic, and therefore unreactive, arylaluminate complexes [Ph(**7a**)]Li or [Ph_4Al]Li (along with **7a**), respectively.[22] Under the same conditions, however, arylation of lithium alkoxide **7d** with 2 equiv of Ph_2AlCl provided efficient (3 h; entry 11) conversion to **4a** (86% HPLC yield), despite halide salts (LiCl: entry 4 and [Ph_4P]Cl/Br: entries 7–13, Table 2) retarding arylations using Ph_3Al. This contrast indicated that triarylalanes and aryl(halo)-alanes possessed different tolerances to halides. Additionally, competitive scavenging of the halide by the halide metal counterion and the aluminum arylating agent might explain why the arylation reactions using aryl(halo)alanes prepared *in situ* from Grignard or organolithium reagents described earlier were able to proceed effectively in the presence of these salts. To test this, **2a** was converted to **7a** and was reacted with 1 equiv of Ph_2AlCl in the presence of 1 equiv of LiCl (entry 12). The arylation was very rapid and produced a superior yield (72%) of **4a** as compared to all halide spiking experiments in Table 2 that used the triarylalane, Ph_3Al, as arylating agent.

With the intent of increasing aryl anion efficiency,[32] methyl, ethyl, or isobutyl dummy ligands[18,33] were incorporated into

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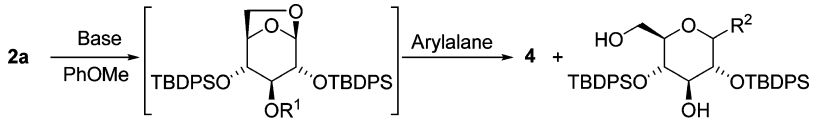
Table 4. Arylation of 7 Using Arylalanes and Modified Arylalanes



7a: $R^1 = AlPh_2$ **8a**: R^2= Me
7b: $R^1 = AlMe_2$ **8b**: R^2= Et
7c: $R^1 = Al\textit{i}\text{-}Bu_2$ **8c**: R^2= *i*-Bu
7d: R^1= Li **8d**: R^2= H

entry	base[a]	7	arylalane[b]	time (h)	yield 4 (%)[c]	8 (%)	TBDPSOH (%)
1	*n*-BuLi	**7d**	3 equiv Ph(Me)AlCl	6	75	10 (**8a**)	24
2	*n*-BuLi	**7d**	3 equiv Ph(Et)AlCl	6	72	4 (**8b**)	32
3	*n*-BuLi	**7d**	3 equiv Ph(*i*-Bu)AlCl	6	70	0.5 (**8c**) 7 (**8d**)	34
4	Me_3Al	**7b**[d]	1 equiv Ph_3Al	17	78 (1)	3 (**8a**)	33
5	*i*-Bu_2AlH	**7c**[e]	1 equiv Ph_3Al	19	72 (0.7)	1 (**8c**) 2 (**8d**)	29
6	Me_3Al	**7b**[d]	1 equiv Ph_2AlCl	1	33 (14)	10 (**8a**)	68[f]
7	Me_3Al	**7b**[d]	2 equiv Ph_2AlCl	1	66 (2)	2 (**8a**)	50
8	*i*-Bu_2AlH	**7c**[e]	1 equiv Ph_2AlCl	9	53 (3)	2 (**8c**) 8 (**8d**)	52
9	Me_3Al	**7b**[d]	1 equiv Ph_3Al/10 mol % $AlCl_3$	8	78	7 (**8a**)	23
10	Me_3Al	**7b**[d]	1 equiv Ph_3Al/20 mol % $AlCl_3$	3.5	77	8 (**8a**)	21
11	Me_3Al	**7b**[d]	1 equiv $Ph_{1.5}AlMe_{1.5}$[g]	19	53 (8)	7 (**8a**)	52
12	Me_3Al	**7b**[d]	2 equiv $Ph_{1.5}AlMe_{1.5}$[g]	2	67 (3)	7 (**8a**)	30
13	Me_3Al	**7b**[d]	1 equiv $Ph_3Al{-}(LiCl)_3$[h]	18	33 (40)	2 (**8a**)	29
14	Me_3Al	**7b**[d]	1 equiv Ph_3Al[i]	61	83 (1)[j]	1 (**8a**)	26
15	Me_3Al	**7b**[d]	1.5 equiv $Ar^1{}_3Al$[k]	26	16 (80)	ND[l]	6.9
16	Me_3Al	**7b**[d]	2 equiv $Ar^1{}_{2.5}AlCl_{0.5}$[k]	13	62 (8)	ND[l]	34
17	Me_3Al	**7b**[d]	2 equiv $Ar^1{}_2AlCl$[k]	5	62[m] (2)	ND[l]	29
18	*n*-BuLi	**7d**	2 equiv $Ar1_2AlCl$[k]	4	55 (5)	ND[l]	53

[a]1 equiv of base was used. [b]The internal reaction temperature was 140 °C. [c]HPLC yields as determined by reference to 1,2,4,5-tetramethylbenzene (internal standard); amounts in the parentheses are unreacted **2a**. Reaction aliquots were treated with 5% TFA in MeCN prior to HPLC analysis producing TBDPSOH (the values presented may be approximate). [d]**7b** was prepared by mixing **2a** with Me_3Al at rt for 5 min. [e]**7c** was prepared by mixing **2a** with *i*-Bu_2AlH at rt for 5 min. [f]Increased to 85% within another 1 h. [g]Equimolar amounts of Ph_3Al and Me_3Al were mixed. [h]Prepared by mixing $AlCl_3$ and PhLi in 1:3 ratio at 140 °C for 2 h. [i]As per footnote *h*, then filtered to remove solids. [j]For comparison to entry 4, at 34 h, 78% HPLC yield of **4** and 8% unreacted **2a**, 1.3% **8a** and 20% TBDPSOH were detected. [k]Ar^1 is 3-[[5-(4-fluorophenyl)-2-thienyl]methyl]-4-methylphenyl. [l]Due to impurity overlap, the level of **8a** was not determined. In the preparative scale run, ^{1}H NMR spectroscopy indicated a >10:1 ratio of **4i**/**8a** before purification. [m]A preparative scale furnished 75% isolated yield of protected canagliflozin **4i** after column chromatography.

the arylalanes by premixing the appropriate alkylalanes, Ph_3Al, and $AlCl_3$.[34] Reasonably rapid conversion of lithium alkoxide **7d** and good yields of arylated product **4a** (Table 4, entries 1−3) were witnessed, but no advantage was seen.

Aluminum-Based Hydroxy Blocking Groups. In view of the unproductive consumption of the first molar equivalent of the arylalane upon reaction with **2a** to form alkoxy(diphenyl)-alane **7a**, blocking of the C3 hydroxyl group of **2a** with alkyl aluminum groups prior to the arylation was examined next. When sugar **2a** was treated with Me_3Al in PhMe or *i*-Bu_2AlH (DIBAL) in PhMe at rt, rapid evolution of gas was observed, confirming that deprotonation had occurred. The corresponding phenyl analogue **7a**, formed during the arylation of **2a** with Ph_3Al, was prepared for reference by reaction of **2a** with Ph_3Al in *n*-Bu_2O. All three sugar aluminum adducts **7a**, **7b**, and **7c** (Figure 4) were stable at rt in benzene-d_6 for at least 4 days. In the case of **7b**, along with the disappearance of the C3-OH signal from **2a**, a six-proton singlet corresponding to an *Al,Al*-dimethyl group was seen at −0.92 ppm in the ^{1}H NMR spectrum, consistent with that reported for alkoxy(dimethyl)-alanes.[35,36] While successive treatment of **7b** with another 2 equiv of Me_3Al produced significant changes in the chemical shift of the ring protons, a fourth equivalent resulted in essentially no change, suggesting that **7b** possesses two Lewis basic sites able to coordinate organoalanes (see spectra in the Supporting Information). A 1D-selective NOESY (DPFGSE) experiment indicated strong through-space interactions between the six proton singlet of the dimethylaluminum moiety and H2, H3, H4, and H6a of the sugar ring and a weaker interaction with the aryl groups of the TBDPS protecting groups. Subsequent treatment of the alkoxyalanes **7a**, **7b**, or **7c** with aq. NaOH returned sugar **2a** unaltered, as confirmed by ^{1}H NMR spectroscopy and LCMS analysis, showing that the alumination was reversible.

Arylation of Dialkyl(alkoxy)alanes. The preformed di*methyl*(alkoxy)alane **7b** described above was subjected to arylation in PhOMe with 1 equiv of Ph_3Al under the standard conditions. Pleasingly, an HPLC yield of 78% (entry 4, Table 4) was obtained along with only 3% of *C*-methylglucoside **8a**, while a slightly lower yield (72%) was observed when the preformed di*isobutyl*(alkoxy)alane **7c** was arylated under the same conditions (entry 5). This confirmed that dialkylalanyl groups could serve as hydroxyl protecting groups. By contrast, and with reference to the high yielding arylation of

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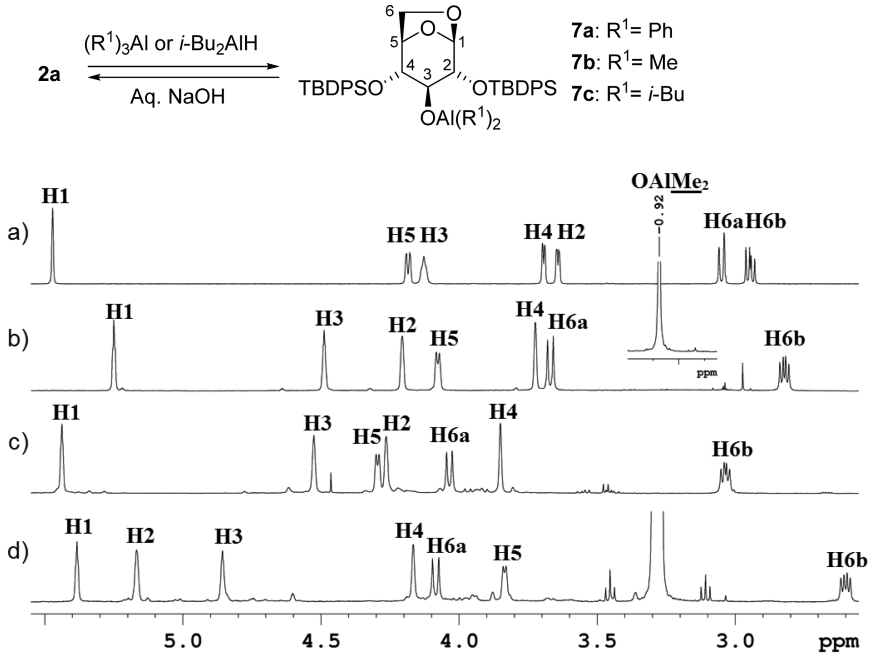

Figure 4. Disubstituted(alkoxy)alanes **7a**, **7b**, and **7c**. (a) ^{1}H NMR spectrum of **2a** in benzene-d_6. (b) Partial ^{1}H NMR spectrum of **2a** in benzene-d_6 after treatment with 1 equiv of Me_3Al (in PhMe). (c) Partial ^{1}H NMR spectrum of **2a** in benzene-d_6 after treatment with 1 equiv of *i*-Bu_2AlH (in PhMe). (d) Partial ^{1}H NMR spectrum of **2a** after treatment with 1 equiv of Ph_3Al (in *n*-Bu_2O; seen at 3.1−3.5 ppm) in benzene-d_6.

di*phenyl*(alkoxy)alane **7a** (Table 3, entry 2), however, it was surprising that arylation of di*methyl*aluminum derivative **7b** with 1 equiv of Ph_2AlCl, chosen for its greater reactivity and superior aryl anion economy to Ph_3Al, only gave a 33% yield (Table 4, entry 6) accompanied by relatively high amounts of TBDPSOH (68%) and *C*-methylglucoside **8a** (10%). Increasing the amount of Ph_2AlCl to 2 equiv (entry 7) or using 1 equiv of Ph_2AlCl with di*isobutyl*(alkoxy)alane **7c** (entry 8) proved better, but still fell short of expectation (>70%). Pleasingly, when 1 equiv of Ph_3Al pretreated with small amounts of $AlCl_3$ was used instead (entries 9 and 10), arylation of **7b** gave good yields (77−78%) and more rapid reaction than when Ph_3Al was used.

Taking all results together, our original conclusion that effective arylation was dependent upon there being at least 2 equiv of arylating reagent with respect to the sugar substrate was revised; instead, only 1 equiv was needed. However, at least 3 equiv of aryl anion with respect to the sugar substrate was required for good conversion (i.e., for >70%). Significant ligand mobility is believed to occur between the sugar C3-alkoxyalane and arylating agent, consistent with that reported for aryl(alkyl)alanes[13h,i] and explaining the formation of side product **8**.

Aryl(alkyl)alanes[18] prepared by premixing[13h] of Ph_3Al and Me_3Al were able to arylate **7b** (entries 11 and 12) but did not prove better than Ph_3Al or the phenyl(chloro)alane systems. As indicated during the preliminary screening studies, arylation of tri-*O*-TBS protected substrate **2b** did not prove effective. This was re-examined using 1 or 2 equiv of Ph_3Al in PhOMe under the optimized conditions. Consistent with the original result, however, no better than a 12% yield of 2,3,4-tri-O-*tert*-butyldimethylsilyl-1-*C*-phenyl-*β*-D-glucopyranoside could be isolated following column chromatography. By contrast, the di*methyl*aluminum moiety serves as an effective *in situ*-generated C3-hydroxyl blocking group.

Real-Case Arylation: The Synthesis of Canagliflozin. Although some triarylaluminum compounds are crystalline solids,[13,20] they are nevertheless moisture-sensitive and require handling under strictly anhydrous conditions. With attempts to synthesize *tris*-(3-[[5-(4-fluorophenyl)-2-thienyl]methyl]-4-methylphenyl)alane, required for canagliflozin synthesis, from the Grignard reagent or aryl lithium and $AlCl_3$ providing gum-like, waxy semisolids, it was reasoned that it would be better to generate the triarylalane in solution, filter off the metal halide salts, and use the filtrate directly in the arylation reaction. This was modeled by arylating di*methyl*(alkoxy)alane **7b** in PhOMe with 1 equiv of a 2 M *n*-Bu_2O solution of Ph_3Al that was prepared in-house from PhLi and $AlCl_3$.[37] When filtration to remove the LiCl was omitted, the arylation failed to reach completion; a 33% HPLC yield was observed after 18 h (Table 4, entry 13), mirroring the arylation of **2a** with commercial Ph_3Al spiked with LiCl (Table 2, entry 4). By contrast, when the Ph_3Al solution was filtered (Table 4, entry 14) to remove the precipitated LiCl, the subsequent arylation of di*methyl*(alkoxy)alane **7b** provided a comparable yield to the commercial reagent (entry 4), reconfirming earlier observations that LiCl *poisoned* triarylalanes.

To further demonstrate the applicability of our methodology to the synthesis of SGLT2 inhibitors, aryl bromide **9a** in PhMe−*i*-Pr_2O was lithiated with *n*-BuLi in *n*-hexane at 0 °C, transmetalated with $AlCl_3$ in *n*-Bu_2O at 90 °C, and diluted with PhMe. The *i*-Pr_2O was removed by evaporation, and the solution was filtered to remove the LiCl and was concentrated further. Disappointingly though, arylation of di*methyl*(alkoxy)-alane **7b** in PhOMe using 1.5 equiv of the PhMe solution of *tris*-(3-[[5-(4-fluorophenyl)-2-thienyl]methyl]-4-methylphenyl)alane (**10**; Ar^1_3Al) provided only a 16% HPLC yield of 2,4-di-*O*-protected canagliflozin **4i** (entry 15) along with 80% unreacted starting material. Evidently, as compared to the corresponding Ph_3Al model system (e.g., see entry 4), the more bulky aryl moiety reduced the reactivity of the arylalane. To

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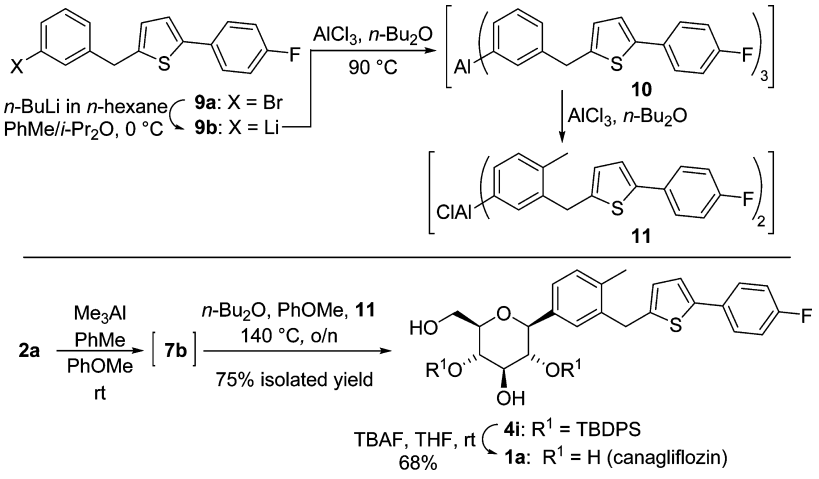
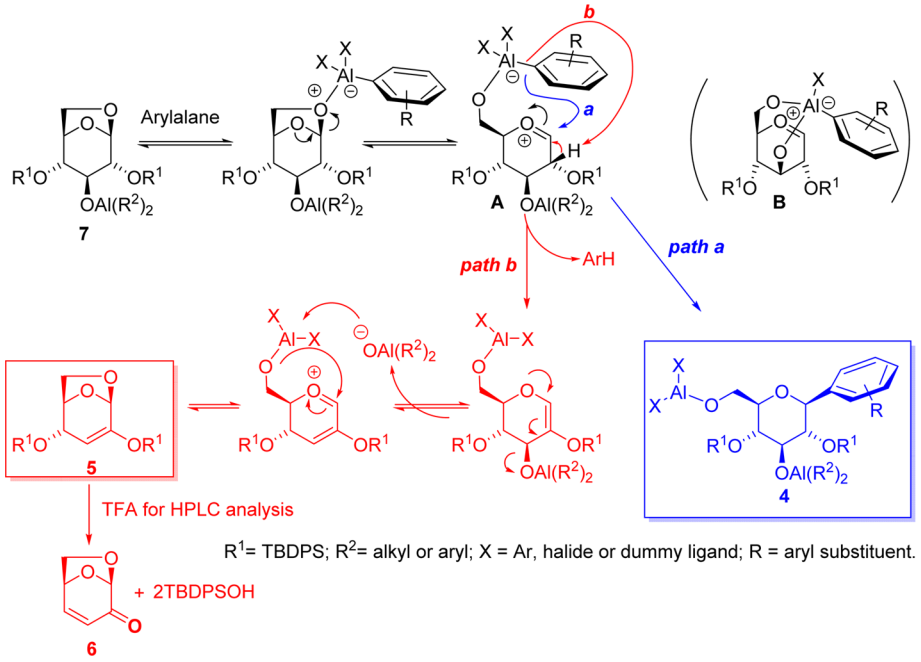
Scheme 3. Synthesis of Canagliflozin via the Arylation of 2a with an Aryl(halo)alane



Scheme 4. Proposed Mechanism To Account for the Coformation of *β*-*C*-Arylglucoside 4 and Silylenol Ether 5



solve this, the triarylalane **10** was preactivated by treatment with $AlCl_3$ in *n*-Bu_2O. Following the above conclusion that 3 equiv or more of aryl anion was necessary for good reaction performance, 2 equiv of the aryl(halo)alanes was used. This resulted in improved reaction times and a yield of greater than 60% (entries 16 and 17). For comparative purposes, the sugar was deprotonated with *n*-BuLi instead of Me_3Al, giving **7d**, and was then arylated under the same conditions (entry 18). A slightly lower HPLC yield (55%) of **4i** was obtained, and more TBDPSOH (53%) was seen than in the test (29%; entry 17) using Me_3Al. Comparison of this result to the corresponding model reaction using Ph_2AlCl and *n*-BuLi (Table 3, entry 11) again showed that the bulkier aryl moiety reduced reaction efficiency. Finally, entry 17 was repeated on a preparative scale, providing an improved 75% yield of chromatographically purified 2,4-di-*O*-protected canagliflozin (**4i**; Scheme 3) that was converted into canagliflozin (**1a**) by desilylation using TBAF in THF.

Over the course of these investigations, it was noted that the formation of *β*-*C*-arylglucosides **4** and the enol ether side-product **5** were inextricably linked. Although the proportion of the two differed under different reaction conditions, the relative rates of their formation implied a common intermediate. We propose that arylation first involves the formation of a complex between the arylalanes and the C6-O ether linkage of the sugar, and ring opening of the 1,6-anhydro ring then produces the requisite oxocarbenium ion **A** that undergoes either (i) the desired arylation (*path a*) to furnish *C*-arylglucoside **4**, possibly by *ipso* substitution,[38] or (ii) the undesired elimination pathway (*path b*) via C2 deprotonation to ultimately produce enol ether **5** (Scheme 4). While *path b* is seemingly less favored, examination of a Dreiding model of the oxocarbenium ion suggests that selection of either *path a* or *path b* might require only a small reorientation of the C6-O arylaluminate moiety, making exclusion of unwanted *path b* difficult.[39] Finally, in related work by Vasella et al.[16] on the stereoretentive alkynylation of 1,6-anhydrohexoses using trimethylsilyl pro-

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tected propargylaluminum dichloride to yield β-*C*-alkynylglycosides, it was proposed that a bidentate alkynylaluminum chloride ate complex bridging the C3-O and C6-O positions delivered the alkyne to the oxocarbenium ion. Basic modeling of the analogous complex **B** in our system showed it to be very rigid, and the resulting conformational restriction might hinder aryl group delivery to the oxocarbenium ion while forcing the bulky C2-OTBDPS and C4-OTBDPS groups into an unfavorable 1,3-diaxial relationship. By contrast, a model of complex **A** shows that the C6-O-aluminum ate complex possesses greater freedom, allowing for the requisite alignment of the aryl group with the oxocarbenium ion while relieving the 1,3-diaxial interaction. Delivery of the aryl group from complex **A** to the α-face of the oxocarbenium ion on the other hand appears highly unfavorable, requiring an implausible contortion of the sugar ring, and would be further encumbered by the C2-O-TBDPS group. Moreover, we have shown[10] that 1,6-anhydro-2,3,4-tri-*O*-benzyl-β-D-glucopyranose can be arylated in good yield with high stereoselectivity (>99:1 β:α ratio) using Ph_3Al, confirming that a covalent bond between C3-O and the arylating agent is not necessarily required for arylation to occur nor for providing the observed high stereoselectivity. Given these reasons, it is believed that complex **A** sufficiently explains the high stereoselectivity witnessed in this reaction.

CONCLUSION

A new approach useful for the preparation of β-*C*-*aryl*glucosides that utilizes arylalanes that are readily prepared from $AlCl_3$ and Grignard reagents or aryl lithium compounds has been established. Modification of triarylalanes by replacing one or more aryl groups with the conjugate bases of strong Brønsted acids produced more reactive arylating agents, while incorporation of alkyl dummy ligands into the arylating agents produces viable arylating agents too. Of the modified arylalanes, aryl(chloro)alanes were most practical, and fine-tuning of the stoichiometric ratio of the aryl anion and halide ligands, which was required on a case-by-case basis, resulted in significantly different reactivity and product yields. In fact, triarylalanes, aryl(halo)alanes, aryl(alkyl)haloalanes, and aryl(alkyl)alanes were all shown to be effective arylating agents. The reaction was tolerant of a range of aryl groups but was sensitive to the presence of halide salts, particularly when using triarylalanes. This problem was mitigated by removal of the salts by filtration before arylation. Despite the presence of a free hydroxyl group on the sugar substrate, blocking was accomplished by *in situ* treatment of the sugar with common alkyl aluminum reagents, including Me_3Al or *i*-Bu_2AlH. This approach avoids a dedicated protection and deprotection step, and it has not escaped our attention that the blocking of hydroxyl groups with alkyl aluminum reagents might find other synthetic applications where a conventional protecting group would otherwise be required.

Over the course of our investigations using the model arylalane, Ph_3Al, reaction times were reduced from 118 h in the early studies in PhMe to just 3.5 h in PhOMe by activation of the arylalanes with $AlCl_3$ while maintaining good yields. The loading of Ph_3Al was decreased from 2 equiv down to 1 equiv by blocking of the C3 hydroxyl group of **2a** by pretreatment with Me_3Al. Finally, this methodology has been shown[10] to be workable using other hydroxyl protecting groups and will be reported in due course.

EXPERIMENTAL SECTION

Materials and Methods. Experiments were conducted under anhydrous conditions in a nitrogen atmosphere using Schlenk techniques. Solvents were dried over 3 Å molecular sieves and oven-dried glassware and gastight syringes were used. Commercially obtained or in-house prepared solutions of organometallic reagents were regularly titrated prior to use using standard titration methods, including Knochel's method.[40] $AlCl_3$ was titrated by the Eriochrome cyanine R spectrophotometric method.[41] 1,6-Anhydro-β-D-glucopyranose (**3**), Grignard reagents, PhLi, and Ph_3Al (1.0 M in *n*-Bu_2O) were purchased and used as supplied. Reference samples of canagliflozin (**1a**), dapagliflozin (**1b**), and levoglucosenone (**6**) were aquired from commercial sources. Authentic samples of α-**1e** and β-**1e** were prepared as per ref 26. Analyses of crude reaction mixtures or isolated products were performed by reversed-phase HPLC on an XDB-C18 column (3.5 μm, 4.6 × 150 mm) at 30 °C monitoring at 210 nm, eluting with a linear gradient from 10% to 100% 0.1% aq. TFA−MeCN for 15 min, followed by isocratic elution with MeCN for 12 min at a 1 mL/min flow rate. Samples for HPLC analysis were pretreated with 5% TFA in MeCN (1000 μL per 10 μL of reaction sample). When HPLC yields were required, the following HPLC assay method was used: 1,2,4,5-tetramethylbenzene (ca. 0.4 equiv with respect to **2a**) was added into the reaction prior to heating, and the peak area % of the peak of interest (e.g., **2a**, **4a**, or TBDPSOH) was then corrected using its predetermined relative response factor with respect to 1,2,4,5-tetramethylbenzene at 210 nm (**2a**: 4.36, **4a**: 4.78, TBDPSOH: 1.90; compounds **4b**−**h** were assumed to have similar response factors as **4a**, whereas compounds **8a**−**d** were assumed to have the same response factor as **2a**) and compared to the peak area % of 1,2,4,5-tetramethylbenzene. β-*C*-Arylglucoside **4a**, biphenyl, benzene, phenol, and silyl enol ether **5** were seen at t_R 24.0, 13.7, 10.1, 6.6, and 23.5 min, respectively. β-*C*-Arylglucosides **4b**, **4c**, **4d**, **4e**, **4f**, **4g**, and **4h** were seen at t_R 25.3, 28.3, 24.6, 23.0, 21.9, 22.9, and 23.0 min, respectively. β-*C*-Arylglucosides **4i** and **4j** were analyzed using the following HPLC conditions: XBridge C8 column (3.5 μm, 4.6 × 150 mm) at 40 °C monitoring at 210 nm, eluting with a linear gradient from 50:50 to 0:100 (v/v) of 0.02% TFA−H_2O and 0.02% TFA−MeCN for 18 min, followed by isocratic elution with 100% 0.02% TFA−MeCN for 7 min at a 1.2 mL/min flow rate). **4i** and **4j** were seen at t_R 20.5 and 20.4 min, respectively, while the relative response factors in this system of **2a**, **4i**, and **4j** were 3.45, 4.20, and 5.35, respectively. High-resolution electrospray ionization (ESI) mass spectrometry was performed using a QToF tandem mass analyzer.

1,6-Anhydro-2,4-di-*O*-*tert*-butyldiphenylsilyl-β-D-glucopyranose (2a). To a suspension solution of 1,6-anhydro-β-D-glucopyranose (**3**, levoglucosan, 1.83 g, 11.3 mmol) and imidazole (3.07 g, 45.2 mmol) in THF (10 mL) at 0 °C was added dropwise a solution of TBDPSCl (11.6 mL, 45.2 mmol) in THF (10 mL). After the mixture was stirred at rt until **3** was consumed (TLC), water (10 mL) was added and the mixture was extracted with EtOAc (20 mL × 2), washed with brine (10 mL), dried over Na_2SO_4, and concentrated. Column chromatography (eluting with 1:20 EtOAc−*n*-heptane) afforded the title compound as a white powder (5.89 g, 81%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82−7.76 (m, 4H), 7.73−7.70 (m, 4H), 7.49−7.37 (m, 12H), 5.17 (s, 1H), 4.22 (d, *J* = 4.8 Hz, 1H), 3.88−3.86 (m, 1H), 3.589−3.586 (m, 1H), 3.49−3.46 (m, 2H), 3.30 (dd, *J* = 7.4, 5.4 Hz, 1H), 1.146 (s, 9H), 1.142 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.87 (CH × 2), 135.84 (CH × 2), 135.82 (CH × 2), 135.80 (CH × 2), 133.7 (C), 133.5 (C), 133.27 (C), 133.21 (C), 129.92 (CH), 129.90 (CH), 129.87 (CH), 129.86 (CH), 127.81 (CH_2 × 2), 127.80 (CH_2 × 2), 127.75 (CH_2 × 4), 102.3 (CH), 76.9 (CH), 75.3 (CH), 73.9 (CH), 73.4 (CH), 65.4 (CH_2), 27.0 (CH_3 × 6), 19.3 (C × 2); FT-IR (neat) 3482, 3071, 3049, 2958, 2931, 2894, 2857, 1472, 1427, 1391, 1362, 1024, 999, 900, 825, 841, 702 cm^{-1}; $[\alpha]_D^{20}$ = −26.3 (*c* 1.0, MeOH); ESI QTof calculated for $[C_{38}H_{46}O_5Si_2 + NH_4]^+$ = 656.3222, found 656.3213; mp 126.7 °C.

2,4-Di-*O*-*tert*-butyldiphenylsilyl-1-*C*-phenyl-β-D-glucopyranoside (4a). *Method A: Using PhMgBr−$AlCl_3$ in PhMe and 2.0 equiv of $Ph_{2.5}AlCl_{0.5}$.* $AlCl_3$ (4.0 mL, 2.0 mmol, 0.5 M solution in THF) and phenylmagnesium bromide (1.9 mL, 5.0 mmol, 2.6 M

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solution in Et_2O) were combined to give a black solution. After being stirred at rt for 1 h, the solvent was evaporated under reduced pressure (50 Torr) to remove the THF and Et_2O, followed by addition of PhMe (6.0 mL). To a solution of **2a** (0.64 g, 1.0 mmol) in PhMe (3.0 mL) at rt was added phenylmagnesium bromide (0.4 mL, 1.0 mmol, 2.6 M solution in Et_2O), and after stirring for about 5 min, the mixture was partially concentrated under reduced pressure (50 Torr) to remove the THF and Et_2O. The remaining PhMe solution was added to the previously prepared aluminum mixture, followed by dilution with PhMe (1.0 mL). The mixture was heated under gentle reflux for 27 h, at which time HPLC assay analysis indicated a 76% yield. After cooling to rt, THF (20 mL), 10% aqueous NaOH (2 mL), diatomaceous earth (2 g), and Na_2SO_4 (5 g) were added to the product mixture sequentially, and the resulting suspension was filtered. The filtrate was concentrated to give an orange oil that was purified by silica gel column chromatography (eluting with 1:6 EtOAc−*n*-heptane) to give the title compound as a white solid (0.46 g, 64%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 (dd, J = 8.2, 1.4 Hz, 2H), 7.57 (dd, J = 8.0, 1.6 Hz, 2H), 7.46−7.33 (m, 12H), 7.31−7.24 (m, 7H), 7.17−7.14 (m, 2H), 4.28 (d, J = 9.6 Hz, 1H), 3.89 (ddd, J = 11.4, 8.2, 2.8 Hz, 1H), 3.85−3.79 (m, 1H), 3.61 (ddd, J = 9.3, 6.3, 2.7 Hz, 1H), 3.53−3.48 (m, 2H), 3.41 (dd, J = 9.4, 8.6 Hz, 1H), 1.77 (dd, J = 8.0, 5.2 Hz, 1H, OH), 1.23 (d, J = 4.8 Hz, 1H, OH), 1.01 (s, 9H), 0.62 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.6 (C), 136.6 (CH × 2), 136.2 (CH × 2), 135.5 (C), 135.3 (CH × 2), 135.0 (CH × 2), 134.9 (C), 132.9 (C), 132.0 (C), 129.8 (CH), 129.7 (CH), 129.4 (CH), 129.3 (CH), 128.7 (CH × 2), 128.5 (CH), 128.4 (CH × 2), 127.6 (CH × 6), 127.3 (CH × 2), 82.9 (CH), 80.6 (CH), 79.4 (CH), 76.5 (CH), 72.9 (CH), 62.8 (CH_2), 27.3 (CH_3 × 3), 26.7 (CH_3 × 3), 19.7 (C), 19.2 (C); FT-IR (neat) 3574, 3069, 3045, 2955, 2929, 2891, 2856, 1472, 1461, 1427, 1390, 1360, 1137, 1111, 1090, 1061, 1029, 998, 937, 918, 889, 863, 834, 821, 799, 760, 739, 699, 640, 607 cm^{-1}; $[\alpha]_D^{20}$ = +22.5 (c 1.0, MeOH); ESI QTof calculated for $[C_{44}H_{52}O_5Si_2 + Na]^+$ = 739.3245, found 739.3245; mp 78.2 °C.

Method B: Using PhMgBr−$AlCl_3$ in PhOMe and 2.0 equiv of $Ph_{2.5}AlCl_{0.5}$. $AlCl_3$ (4.0 mL, 2.0 mmol, 0.5 M solution in THF) and phenylmagnesium bromide (1.9 mL, 5.0 mmol, 2.6 M solution in Et_2O) were combined to give a black solution. After being stirred at rt for 1 h, the mixture was diluted with PhOMe (5.0 mL) and was concentrated under reduced pressure (50 Torr) to remove the THF and Et_2O. To a solution of **2a** (0.64 g, 1.0 mmol) in PhOMe (3.0 mL) at rt was added phenylmagnesium bromide (0.4 mL, 1.0 mmol, 2.6 M solution in Et_2O), and after stirring for about 5 min, the mixture was partially concentrated under reduced pressure (50 Torr) to remove the THF and Et_2O. The remaining PhOMe solution was added to the previously prepared aluminum mixture, followed by dilution with PhOMe (2.0 mL). The mixture was heated at 120 °C for 28 h, at which time HPLC assay analysis indicated an 83% yield of the title compound.

Method C: Using Ph_3Al−$AlCl_3$ and the Recovery of Phenyl Anion. $AlCl_3$ (0.60 mL, 0.30 mmol, 0.5 M in THF) and Ph_3Al (1.7 mL, 1.7 mmol, 1.0 M in *n*-Bu_2O) were mixed at rt to give a black-colored solution. To this mixture was added a solution of **2a** (0.64 g, 1.0 mmol) in PhOMe (4.0 mL) at rt. The mixture was concentrated under reduced pressure (50 Torr) at 60 °C (external bath temperature) to remove the THF. The remaining mixture (comprising PhOMe−*n*-Bu_2O as solvent) was heated at 120 °C for 6 h, at which time HPLC assay analysis indicated an 84% yield of the title compound. After cooling to rt, an aliquot (0.5 mL) of the reaction product mixture was added into a solution of iodine (0.25 g, 0.98 mmol) and LiCl (5.0 mL, 0.5 M in THF). The black-colored mixture was stirred at rt for 2 h, at which time HPLC assay analysis indicated a 59% yield of iodobenzene and a 33% recovery of benzene based on the theoretical amount of phenyl anion remaining after the arylation of **2a**.

Method D: Using Ph_3Al−$AlCl_3$ and n-BuLi as the Deprotonating Base. $AlCl_3$ (1.4 mL, 0.70 mmol, 0.5 M in THF) and Ph_3Al (1.3 mL, 1.3 mmol, 1.0 M in *n*-Bu_2O) were mixed at rt to give a light brown-colored solution. To a solution of **2a** (0.64 g, 1.0 mmol) in PhOMe (4.0 mL) was added *n*-BuLi (0.42 mL, 1.0 mmol, 2.4 M in *n*-hexane) at rt, and after stirring for about 5 min, the resulting mixture was then added to the above prepared aluminum mixture. The mixture was concentrated under reduced pressure (50 Torr) at 60 °C (external bath temperature) to remove the THF. The remaining mixture (comprising PhOMe−*n*-Bu_2O as solvent) was heated at 120 °C for 3 h, at which time HPLC assay indicated an 86% yield of the title compound.

Method E: Using $Ph_2Al(X)$ as the Arylating Reagent (for Table 3). To stirred solutions of Ph_3Al (2.0 mL, 2.0 mmol, 1.0 M in *n*-Bu_2O) were added (i) TfOH (88 μL, 1.0 mmol) dropwise at −78 °C, and then the mixture warmed to rt and was stirred for 0.5 h, or (ii) C_6F_5OH (184 mg, 1.0 mmol) at rt and stirred for 20 min, or (iii) C_6H_5OH (94 mg, 1.0 mmol) at rt and then stirred at 120 °C for 0.5 h, or (iv) *i*-PrOH (77 μL, 1.0 mmol) at rt then stirred at 70 °C for 0.5 h, to afford light yellow clear solutions. Solutions of **2a** (0.64 g, 1.0 mmol) in PhOMe (4.0 mL) were added to the above prepared 1:1 solutions of Ph_3Al and $Ph_2Al(X)$ at rt and stirred for 5 min. The mixtures were then heated at 120 °C and were monitored by HPLC assay.

*Method F: **7b** with Ph_3Al (1.0 equiv) and 20% $AlCl_3$.* To a solution of **2a** (0.64 g, 1.0 mmol) in PhOMe (4.0 mL) at rt was added Me_3Al (0.5 mL, 1.0 mmol, 2.0 M in PhMe), and this was stirred until bubbling ceased to provide **7b**. After stirring for 5 min at rt, to the solution was added Ph_3Al (1.0 mL, 1.0 mmol, 1.0 M in *n*-Bu_2O) and then $AlCl_3$ (0.4 mL, 0.2 mmol, 0.5 M in THF). The reaction mixture was heated at 140 °C for 3.5 h, at which time HPLC assay indicated a 77% yield of the title compound.

1,6-Anhydro-2,4-di-*O*-*tert*-butyldiphenylsilyl-3-*O*-(Al,Al-disubstituted-*alanyl*)-β-D-glucopyranose 7a, 7b, or 7c. To solutions of **2a** (1.0 equiv) in benzene-d_6 (3 mL) was added (i) Ph_3Al (1.0 equiv, 0.8 M in *n*-Bu_2O), or (ii) Me_3Al (1.0 equiv, 1.8 M in PhMe), or (iii) *i*-Bu_2AlH (1.0 equiv, 0.6 M in PhMe) at rt. The resultant solutions were directly analyzed by ^{1}H NMR spectroscopy (see the Supporting Information). To the mixtures was then added 10% aq. NaOH (1.0 mL), and the mixtures were filtered and concentrated. The ^{1}H NMR and LCMS analyses of the residues showed that compound **2a** was recovered in all cases.

2,4-Di-*O*-*tert*-butyldiphenylsilyl-6,8-dioxabicyclo[3.2.1]oct-3-ene (5). An analytically pure sample of **5** was prepared by heating a mixture of **2a** (3.00 g, 4.70 mmol) and Ph_3Al (2.3 mL, 2.3 mmol, 1.0 M in *n*-Bu_2O) in PhMe (60 mL) at 140 °C for 21 h. The mixture was cooled and diluted with MeTHF and 10% w/w NaOH (5 mL). The organic layer was washed with brine (60 mL) and concentrated. The residue was purified by silica gel column chromatography (eluting with 1:10 v/v EtOAc−*n*-heptane) to give the title compound as a colorless oil (230 mg, 7.9%). Unreacted staring material **2a** (1.34 g. 45%) was also recovered. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70−7.68 (m, 2H), 7.60−7.57 (m, 2H), 7.53−7.45 (m, 5H), 7.42−7.36 (m, 5H), 7.32−7.21 (m, 6H), 5.46 (d, J = 1.2 Hz, 1H), 4.50 (ddd, J = 6.3, 3.3, 1.5 Hz, 1H), 4.06 (ddd, J = 4.9, 1.5, 1.5 Hz, 1H), 3.70 (dd, J = 7.6, 6.8 Hz, 1H), 3.47 (dd, J = 5.0, 1.4 Hz, 1H), 2.94 (dd, J = 7.6, 2.0 Hz, 1H), 1.04 (s, 9H), 1.00 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.6 (C), 135.63 (CH × 2), 135.53 (CH × 2), 135.39 (CH × 2), 135.31 (CH × 2), 133.6 (C), 133.4 (C), 132.2 (C), 131.3 (C), 129.86 (CH), 129.76 (CH), 129.60 (CH), 129.51 (CH), 127.74 (CH × 2), 127.57 (CH × 2), 127.53 (CH × 2), 127.43 (CH × 2), 100.4 (CH), 98.8 (CH), 77.0 (CH), 68.6 (CH), 63.1 (CH_2), 26.8 (CH_3 × 3), 26.3 (CH_3 × 3), 19.1 (C), 19.0 (C); FT-IR (neat) 3071, 3049, 2958, 2931, 2858, 1659, 1589, 1472, 1428, 1224, 1113, 1075, 937 cm^{-1}; ESI QTof calculated for $[C_{38}H_{44}O_4Si_2 + Na]^+$ = 643.2670, found 643.2678; $[\alpha]_D^{25}$ = +58.4 (c 1.0, $CHCl_3$).

Levoglucosenone (6). Compound **5** (130 mg) was dissolved in 5% v/v TFA−MeCN (10 mL) and was stirred at rt for 30 min. The solution was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (eluting with 5−10% v/v MeOH−DCM) to give the title compound as a light yellow oil (20 mg, 76%). The characterization data were consistent with those reported in the literature and to a commercial reference sample.[42] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 (dd, J = 10.0, 4.4 Hz, 1H), 6.15 (dd, J = 9.8, 1.8 Hz, 1H), 5.39 (d, J = 1.6 Hz, 1H), 5.04 (dd, J = 4.8, 4.8 Hz, 1H), 3.93 (dd, J = 6.8, 4.8 Hz, 1H), 3.80 (d, J = 6.8 Hz, 1H); ^{13}C

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NMR (100 MHz, $CDCl_3$) δ 188.8 (C), 147.9 (CH), 127.0 (CH), 101.7 (CH), 71.8 (CH), 66.6 (CH_2); FT-IR (neat) 2958, 2920, 2850, 1717, 1697, 1378, 1256, 1105, 971, 890, 830 cm^{-1}; $[\alpha]_D^{25}$ = −528.6 (*c* 1.0, $CHCl_3$).

1-*C*-Phenyl-β-D-glucopyranoside (β-1e). To a solution of 2,4-di-*O*-*tert*-butyldiphenylsilyl-1-*C*-phenyl-β-D-glucopyranoside (**4a**, 1 g, 1.4 mmol) in THF (5 mL) at rt was added TBAF (14 mL, 14 mmol, 1.0 M in THF). After the starting material was consumed (TLC), the product mixture was added to a mixture of Dowex 50WX8-400 ion-exchange resin (8 g), $CaCO_3$ (3 g) and MeOH (10 mL).[43] After stirring at rt for 1 h, the mixture was filtered and the filter cake was washed with MeOH (20 mL). The filtrate was concentrated, and the resulting residue was purified by column chromatography (eluting with 1:10 v/v MeOH−DCM), affording the title compound (0.24 g, 72%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.36−7.26 (m, 5H), 4.97−4.95 (m, 2H, OHs), 4.79 (d, *J* = 6.0 Hz, 1H, OH), 4.46 (t, *J* = 5.8 Hz, 1H, OH), 4.01 (d, *J* = 9.2 Hz, 1H), 3.71 (ddd, *J* = 11.8, 5.6, 1.8 Hz, 1H), 3.48−3.42 (m, 1H), 3.31−3.14 (m, 4H + OH); ^{13}C NMR (100 MHz, CD_3OD) δ 139.5 (C), 127.7 (CH × 2), 127.62 (CH × 2), 127.55 (CH), 82.3 (CH), 80.8 (CH), 78.4 (CH), 75.0 (CH), 70.6 (CH), 61.8 (CH_2); LCMS (ESI) *m*/*z* 258 (100, $[M + NH_4]^+$), 263 (69, $[M + Na]^+$), 503 (25, $[2M + Na]^+$). The data conform to those in the reported literature.[5]

2,4-Di-O-*tert*-butyldiphenylsilyl-1-*C*-(4-methylphenyl)-β-D-glucopyranoside (4b). PhOMe (6 mL), $AlCl_3$ (0.5 M in THF, 4.0 mL, 2.0 mmol), and 4-methylphenylmagnesium bromide (5.0 mL, 5.0 mmol, 1.0 M in THF) were mixed at rt to give a black solution, which was then stirred at rt for 1 h. To a solution of **2a** (0.64 g, 1.0 mmol) in PhOMe (3.0 mL) at rt was added phenylmagnesium bromide (0.38 mL, 1.0 mmol, 2.6 M solution in Et_2O), and after stirring for about 5 min, the mixture was added to the above prepared aluminum mixture via syringe, followed by additional PhOMe (1.0 mL) to rinse the flask. The mixture was concentrated under reduced pressure (50 Torr) at 60 °C (external bath temperature) to remove THF and Et_2O. The remaining mixture was heated at 120 °C for 26 h, at which time HPLC assay analysis showed a 59% yield of adduct **4b**. After cooling to rt, the reaction was treated with 10% aqueous NaOH (1 mL), THF (10 mL), and diatomaceous earth at rt. The mixture was filtered, and the filter cake was washed with THF. The combined filtrates were concentrated, and the crude product was purified by column chromatography (eluting with 1:10 v/v EtOAc−*n*-heptane), affording the title compound (405 mg, 55%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69−7.67 (m, 2H), 7.60−7.57 (m, 2H), 7.45−7.33 (m, 12H), 7.31−7.25 (m, 4H), 7.09 (d, *J* = 8.2 Hz, 2H), 7.04 (d, *J* = 8.2 Hz, 2H), 4.26 (d, *J* = 9.6, 1H), 3.89 (dd, *J* = 11.8, 2.6 Hz, 1H), 3.82 (dd, *J* = 8.4, 8.4 Hz, 1H), 3.64−3.59 (m, 1H), 3.54−3.48 (m, 2H), 3.41 (dd, *J* = 9.2, 8.4 Hz, 1H), 2.35 (s, 3H), 1.02 (s, 9H), 0.65 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$;) δ 138.1 (C), 136.4 (CH × 2), 136.1 (CH × 2), 135.5 (C), 135.4 (C), 135.2 (CH × 2), 134.9 (CH × 2), 134.8 (C), 132.8 (C), 132.0 (C), 129.6 (CH), 129.5 (CH), 129.3 (CH), 129.1 (CH), 128.9 (CH × 2), 128.5 (CH × 2), 127.48 (CH × 4), 127.46 (CH × 2), 127.1 (CH × 2), 82.6 (CH), 80.4 (CH), 79.4 (CH), 76.3 (CH), 72.8 (CH), 62.7 (CH_2), 27.2 (CH_3 × 3), 26.5 (CH_3 × 3), 21.1 (CH_3), 19.5 (C), 19.1 (C); FT-IR (neat) 3579, 3070, 3047, 2956, 2929, 2892, 2856, 1472, 1462, 1427, 1390, 1360, 1111, 1062, 999, 865, 841, 821, 740, 702, 646, 621, 612 cm^{-1}; $[\alpha]_D^{20}$ = +32.0 (*c* 1.0, MeOH); LCMS (ESI) *m*/*z* 748 (100, $[M + NH_4]^+$), 753 (2, $[M + Na]^+$); ESI QTof calculated for $[C_{45}H_{54}O_5Si_2 + Na]^+$ = 753.3402, found 753.3423; mp 91.9 °C.

2,4-Di-O-*tert*-butyldiphenylsilyl-1-*C*-(2,4,6-trimethylphenyl)-β-D-glucopyranoside (4c). The same reaction procedure and workup was used as for **4b** above, except mesitylmagnesium bromide (0.8 M in THF) was used instead. HPLC assay analysis indicated a 67% yield of the title compound had been achieved after 16 h at 140 °C. Column chromatography (eluting with 1:10 v/v EtOAc−*n*-heptane) afforded 494 mg (65%) of the title compound. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 (dd, *J* = 7.8, 1.4 Hz, 2H), 7.58 (dd, *J* = 8.0, 1.6 Hz, 2H), 7.46−7.25 (m, 16H), 6.86 (s, 1H), 6.77 (s, 1H), 4.84 (dd, *J* = 14.4, 5.2 Hz, 1H), 3.94−3.90 (m, 1H), 3.79−3.76 (m, 2H), 3.60 (ddd, *J* = 9.1, 6.5, 2.5 Hz, 1H), 3.53−3.48 (m, 1H), 3.43−3.37 (m, 1H), 2.49 (s, 3H), 2.29 (s, 3H), 1.89 (s, 3H), 1.84 (dd, *J* = 7.6, 5.2 Hz, 1H, OH), 1.21−1.20 (m, 1H, OH), 1.03 (s, 9H), 0.65 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.7 (C), 137.3 (C), 137.2 (C), 136.5 (CH × 2), 136.1 (CH × 2), 135.6 (C), 135.2 (CH × 2), 134.9 (C), 134.8 (CH × 2), 133.0 (C), 131.7 (C), 131.3 (C), 130.9 (CH), 129.60 (CH), 129.58 (CH), 129.3 (CH), 129.11 (CH), 129.07 (CH), 127.51 (CH × 2), 127.46 (CH × 2), 127.45 (CH × 2), 127.3 (CH × 2), 80.7 (CH), 80.0 (CH), 78.2 (CH), 74.3 (CH), 72.9 (CH), 63.0 (CH_2), 27.2 (CH_3 × 3), 26.4 (CH_3 × 3), 21.7 (CH_3), 20.8 (CH_3), 20.1 (CH_3), 19.6 (C), 18.9 (C); FT-IR (neat) 3577, 3070, 3047, 2955, 2929, 2889, 2856, 1472, 1462, 1427, 1390, 1373, 1360, 1110, 1090, 1059, 998, 936, 883, 851, 821, 809, 739, 700, 680, 622, 612 cm^{-1}; $[\alpha]_D^{20}$ = +24.0 (*c* 1.0, MeOH); LCMS (ESI) *m*/*z* 776 (100, $[M + NH_4]^+$), 781 (3, $[M + Na]^+$); ESI QTof calculated for $[C_{47}H_{58}O_5Si_2 + Na]^+$ = 781.3715, found 781.3712; mp 76.2 °C.

2,4-Di-O-*tert*-butyldiphenylsilyl-1-*C*-(4-chlorophenyl)-β-D-glucopyranoside (4d). The same reaction procedure and workup was used as for **4b** above, except 4-chlorophenylmagnesium bromide (0.8 M in THF) was used instead. HPLC assay analysis showed a 47% yield of the title compound had been achieved after 22 h at 140 °C. Column chromatography (eluting with 1:15 v/v EtOAc−*n*-heptane) afforded 328 mg (44%) of the title compound. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 (d, *J* = 8.0, 1.2 Hz, 2H), 7.48 (d, *J* = 8.0, 1.6 Hz, 2H), 7.37−7.16 (m, 16H), 7.13−7.11 (m, 2H), 6.96−6.94 (m, 2H), 4.15 (d, *J* = 9.6 Hz, 1H), 3.78 (ddd, *J* = 11.4, 8.0, 2.4 Hz, 1H), 3.72 (ddd, *J* = 8.4, 8.4, 4.8 Hz, 1H), 3.50 (ddd, *J* = 9.2, 6.4, 2.6 Hz, 1H), 3.44−3.29 (m, 3H), 1.59 (dd, *J* = 7.8, 5.4 Hz, 1H, OH), 1.19−1.18 (m, 1H, OH), 0.92 (s, 9H), 0.57 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.0 (C), 136.4 (CH_2 × 2), 136.1 (CH_2 × 2), 135.2 (CH_2 × 2), 135.1 (C), 134.9 (CH_2, × 2), 134.7 (C), 134.2 (C), 132.7 (C), 131.8 (C), 129.9 (CH × 2), 129.73 (CH), 129.66 (CH), 129.4 (CH), 129.2 (CH), 128.4 (CH × 2), 127.57 (CH × 2), 127.56 (CH × 2), 127.55 (CH × 2), 127.3 (CH × 2), 82.1 (CH), 80.5 (CH), 79.2 (CH), 76.4 (CH), 72.7 (CH), 62.7 (CH_2), 27.2 (CH_3 × 3), 26.6 (CH_3 × 3), 19.5 (C), 19.1 (C); FT-IR (neat) 3575, 3070, 3047, 2955, 2930, 2892, 2856, 1493, 1472, 1462, 1427, 1390, 1360, 1265, 1138, 1112, 1090, 1063, 1015, 998, 938, 863, 821, 798, 740, 701, 639, 621, 611 cm^{-1}; $[\alpha]_D^{20}$ = +39.5 (*c* 1.0, MeOH); LCMS (ESI) *m*/*z* 768 (100, $[M + NH_4]^+$), 773 (5, $[M + Na]^+$); ESI QTof calculated for $[C_{44}H_{51}ClO_5Si_2 + Na]^+$ = 773.2856, found 773.2852; mp 84.6 °C.

2,4-Di-O-*tert*-butyldiphenylsilyl-1-*C*-(4-fluorophenyl)-β-D-glucopyranoside (4e). The same reaction procedure and workup was used as for **4b** above, except 4-fluorophenylmagnesium bromide (1.9 M in THF) was used instead. HPLC assay analysis indicated a 56% yield of adduct **4e** for 4 h at 140 °C. Column chromatography (eluting with 1:20 v/v EtOAc−*n*-heptane) afforded 395 mg (54%) of the title compound. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68−7.66 (m, 2H), 7.58−7.56 (m, 2H), 7.46−7.25 (m, 16), 7.10−7.07 (m, 2H), 6.96−6.91 (m, 2H), 4.26 (d, *J* = 9.6 Hz, 1H), 3.88 (dd, *J* = 12, 2.4 Hz, 1H), 3.82 (t, *J* = 8.4 Hz, 1H), 3.60 (ddd, *J* = 9.3, 6.3, 2.7 Hz, 1H), 3.53−3.38 (m, 3H), 1.01 (s, 9H), 0.65 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.7 (d, *J* = 245 Hz, C), 136.4 (CH × 2), 136.1 (CH × 2), 135.1 (CH × 2, C × 1), 134.9 (CH × 2), 134.7 (C), 134.4 (d, *J* = 3.1 Hz, C), 132.7 (C), 131.8 (C), 130.2 (d, *J* = 8.1 Hz, CH × 2), 129.68 (CH), 129.64 (CH), 129.4 (CH), 129.2 (CH), 127.53 (CH × 2), 127.52 (CH × 4), 127.2 (CH × 2), 115.0 (d, *J* = 21.3 Hz, CH × 2), 82.0 (CH), 80.5 (CH), 79.2 (CH), 76.4 (CH), 72.7 (CH), 62.7 (CH_2), 27.1 (CH_3 × 3), 26.6 (CH_3 × 3), 19.5 (C), 19.1 (C); FT-IR (neat) 3577, 3070, 3048, 2956, 2931, 2892, 2857, 1513, 1472, 1427, 1390, 1361, 1227, 1189, 1112, 1093, 1063, 999, 832, 822, 800, 740, 702, 642, 626, 610 cm^{-1}; $[\alpha]_D^{20}$ = +20.0 (*c* 1.0, MeOH); ESI QTof calculated for $[C_{44}H_{51}FO_5Si_2 + Na]^+$ = 757.3151, found 757.3131; mp 155.9 °C.

2,4-Di-O-*tert*-butyldiphenylsilyl-1-*C*-(2-furyl)-β-D-glucopyranoside (4f). To a chilled (−76 °C) solution of furan (2.5 mL, 34.3 mmol) in THF (21.5 mL) was added *n*-BuLi (21.5 mL, 34.3 mmol, 1.6 M in *n*-hexane). The mixture was stirred for 1 h and was then warmed to rt. The concentration of the 2-furyllithium solution was determined to be 0.5 M by titration. PhOMe (6 mL), $AlCl_3$ (0.5 M in THF, 4.0 mL, 2.0 mmol), and the above prepared 2-furyllithium

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(10 mL, 5 mmol, 0.5 M in THF) were mixed at rt to give a black solution, which was stirred at rt for 1 h. To a solution of **2a** (0.64 g, 1.0 mmol) in PhOMe (3.0 mL) at rt was added phenylmagnesium bromide (0.38 mL, 1.0 mmol, 2.6 M solution in Et_2O). After stirring for about 5 min, the solution was then added into the above prepared aluminum mixture via syringe, followed by additional PhOMe (1.0 mL) to rinse the flask. The mixture was concentrated under reduced pressure (50 Torr) at 60 °C (external bath temperature) to remove the THF and Et_2O. The remaining mixture was heated at 120 °C for 16 h, at which time HPLC assay analysis indicated a 78% yield of adduct **4f**. After cooling to rt, the reaction was treated with 10% aqueous NaOH (1 mL), THF (10 mL), and diatomaceous earth at rt; then, the mixture was filtered and the filter cake was washed with THF. The combined filtrates were concentrated, and the crude product was purified by column chromatography (eluting with 1:15 v/v EtOAc−*n*-heptane), affording the title compound (482 mg, 68%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68−7.65 (m, 2H), 7.58−7.56 (m, 2H), 7.50−7.48 (m, 2H), 7.45−7.26 (m, 15H), 6.28 (dd, J = 3.2, 1.6 Hz, 1H), 6.13 (d, J = 3.2 Hz, 1H), 4.39 (d, J = 9.2 Hz, 1H), 3.92−3.87 (m, 1H), 3.81−3.70 (m, 2H), 3.58 (ddd, J = 9.2, 6.6, 2.4 Hz, 1H), 3.53−3.47 (m, 1H), 3.39 (dd, J = 9.0, 9.0 Hz, 1H), 1.79 (dd, J = 6.4, 6.4 Hz, 1H, OH), 1.31 (d, J = 4.4 Hz, 1H, OH), 1.01 (s, 9H), 0.76 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.3 (C), 142.2 (CH), 136.3 (CH × 2), 136.1 (CH × 2), 135.21 (C), 135.18 (CH × 2), 135.0 (CH × 2), 134.7 (C), 132.6 (C), 132.1 (C), 129.7 (CH), 129.6 (CH), 129.4 (CH), 129.2 (CH), 127.58 (CH × 2), 127.56 (CH × 2), 127.5 (CH × 2), 127.3 (CH × 2), 110.4 (CH), 110.1 (CH), 80.3 (CH), 79.4 (CH), 75.3 (CH), 74.1 (CH), 72.5 (CH), 62.7 (CH_2), 27.2 (CH_3 × 3), 26.6 (CH_3 × 3), 19.5 (C), 19.1 (C); FT-IR (neat) 3572, 3070, 3047, 2955, 2929, 289, 2856, 1472, 1427, 1390, 1360, 1137, 1111, 1091, 1009, 999, 855, 821, 802, 779, 739, 701, 628, 621, 612 cm^{-1}; $[\alpha]_D^{20}$ = +16.0 (c 1.0, MeOH); ESI QTof calculated for $[C_{42}H_{50}NaO_6Si_2^+]$ = 729.3038, found 729.3027; mp 174.2 °C.

2,4-Di-O-*tert*-butyldiphenylsilyl-1-*C*-(2-thienyl)-*β*-D-glucopyranoside (4g). The same reaction procedure and workup was used as for **4b** above, except 2-thienylmagnesium bromide (1.0 M in THF) was used instead. HPLC assay analysis indicated a 60% yield of the title compound had been achieved after 4 h at 120 °C. An analytically pure sample of **4g** was obtained by the workup used as for **4b** above, followed by purification by column chromatography (eluting with 1:10 v/v EtOAc−*n*-heptane). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 (dd, J = 8.0, 1.2 Hz, 2H), 7.59 (dd, J = 8.0, 1.2 Hz, 2H), 7.51−7.30 (m, 16H), 7.26−7.24 (m, 1H), 6.96−6.94 (m, 2H), 4.62 (d, J = 9.6 Hz, 1H), 3.93 (dd, J = 11.6, 2.0 Hz, 1H), 3.82 (ddd, J = 10.2, 6.6, 1.8 Hz, 1H), 3.64 (ddd, J = 9.3, 6.3, 2.7 Hz, 1H), 3.57−3.51 (m, 2H), 3.45 (dd, J = 9.0, 9.0 Hz, 1H), 1.27 (d, J = 4.4 Hz, OH), 1.05 (s, 9H), 0.75 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.4 (C), 136.4 (CH × 2), 136.1 (CH × 2), 135.4 (C), 135.1 (CH × 2), 134.9 (CH × 2), 134.7 (C), 132.7 (C), 131.9 (C), 129.7 (CH), 129.6 (CH), 129.3 (CH), 129.2 (CH), 127.54 (CH_2 × 2), 127.52 (CH_2 × 4), 127.25 (C), 127.24 (CH × 2), 126.4 (CH), 125.6 (CH), 80.5 (CH), 79.3 (CH), 77.8 (CH), 77.2 (CH), 72.5 (CH), 62.6 (CH_2), 27.2 (CH_3 × 3), 26.5 (CH_3 × 3), 19.5 (C), 19.1 (C); FT-IR (neat) 3577, 3070, 3047, 2956, 2930, 2892, 2856, 1472, 1462, 1427, 1390, 1360, 1188, 1111, 1090, 999, 851, 822, 800, 740, 701, 624, 610 cm^{-1}; $[\alpha]_D^{20}$ = +12.5 (c 1.0, MeOH); LCMS (ESI) m/z 740 (100, $[M + NH_4]^+$), 745 (5, $[M + Na]^+$); ESI QTof calculated for $[C_{42}H_{50}NaO_5SSi_2^+]$ = 745.2810, found 745.2808; mp 87.2 °C.

2,4-Di-O-*tert*-butyldiphenylsilyl-1-*C*-(4-methoxyphenyl)-*β*-D-glucopyranoside (4h). The same reaction procedure and workup was used as for **4b** above, except 4-methoxyphenylmagnesium bromide (0.5 M in THF) was used instead. HPLC assay analysis indicated a 54% yield of the title compound had been achieved after 8 h at 120 °C. An analytically pure sample of **4h** was obtained by purification using column chromatography (eluting with 1:15 v/v EtOAc−*n*-heptane). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 (dd, J = 8.0, 1.2 Hz, 2H), 7.57 (dd, J = 8.0, 1.2 Hz, 2H), 7.46−7.33 (m, 13H), 7.30−7.25 (m, 3H), 7.04 (d, J = 8.4 Hz, 2H), 6.79 (d, J = 8.8 Hz, 2H), 4.23 (d, J = 9.6 Hz, 1H), 3.88 (ddd, J = 11.3, 8.3, 2.7 Hz, 1H), 3.83−3.78 (m, 1H), 3.81 (s, 3H), 3.59 (ddd, J = 9.2, 6.4, 2.6 Hz, 1H), 3.53−3.46 (m, 2H), 3.40 (dd, J = 8.8, 8.8 Hz, 1H), 1.77 (dd, J = 8.0, 5.2 Hz, 1H, OH), 1.25 (d, J = 4.8 Hz, 1H, OH), 1.01 (s, 9H), 0.65 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.7 (C), 136.5 (CH × 2), 136.1 (CH × 2), 135.4 (C), 135.2 (CH × 2), 135.0 (CH × 2), 134.9 (CH), 132.8 (C), 132.0 (C), 130.8 (C), 129.8 (CH × 2), 129.7 (CH), 129.6 (CH), 129.3 (CH), 129.2 (CH), 127.52 (CH × 4), 127.50 (CH × 2), 127.2 (CH × 2), 113.7 (CH × 2), 82.3 (CH), 80.3 (CH), 79.4 (CH), 76.3 (CH), 72.8 (CH), 62.8 (CH_2), 55.4 (CH_3), 27.2 (CH_3 × 3), 26.6 (CH_3 × 3), 19.6 (C), 19.1 (C); FT-IR (neat) 3578, 3070, 3047, 2957, 2931, 2892, 2856, 1515, 1472, 1463, 1427, 1390, 1249, 1177, 1112, 1105, 1063, 1034, 999, 823, 801, 741, 703, 644, 622, 611 cm^{-1}; $[\alpha]_D^{20}$ = +35.0 (c 1.0, MeOH); ESI QTof calculated for $[C_{45}H_{54}NaO_6Si_2^+]$ = 769.3351, found 769.3330; mp 151.9 °C.

2,4-Di-O-*tert*-butyldiphenylsilyl-1-*C*-(3-((5-(4-fluorophenyl)-thiophen-2-yl)methyl)-4-methylphenyl)-*β*-D-glucopyranoside (4i). To a mixture of 2-(5-bromo-2-methylbenzyl)-5-(4-fluorophenyl)-thiophene (**9a**, 1.5 g, 4.15 mmol), magnesium powder (0.33 g, 13.7 mmol), and THF (9 mL) was added 1,2-dibromoethane (95 μL, 1.4 μmol). The mixture was heated under reflux until the reaction initiated. A solution of **9a** (2.5 g, 6.92 mmol) in THF (15 mL) was then added to the mixture dropwise, and the mixture was then stirred for 2 h under reflux. The mixture was cooled to rt and titrated to determine its concentration. The thus prepared 3-[[5-(4-fluorophenyl)-2-thienyl]methyl]-4-methylphenylmagnesium bromide (0.29 M in THF, 17 mL, 5.0 mmol) was mixed with $AlCl_3$ (4.0 mL, 2.0 mmol, 0.5 M in THF) at rt, giving a black solution that was stirred at rt for 1 h. To a solution of **2a** (0.64 g, 1.0 mmol) in PhOMe (3.0 mL) at rt was added *n*-BuLi (0.4 mL, 1.0 mmol, 2.5 M solution in n-Bu_2O). After stirring for about 5 min, the solution was then added into the above prepared aluminum mixture via syringe, followed by additional PhOMe (1.0 mL) to rinse the flask. The mixture was concentrated under reduced pressure (50 Torr) at 60 °C to remove the THF and Et_2O, and PhOMe (6 mL) was then added. The remaining mixture was heated at 140 °C for 5 h, at which time HPLC assay analysis indicated a 68% yield of adduct **4i**. After cooling to rt, the reaction was treated with 10% aqueous NaOH (1 mL), THF (10 mL) and diatomaceous earth (1 g) at rt; then, the mixture was filtered and the filter cake was washed with THF. The combined filtrates were concentrated, and the crude product was purified by silica gel column chromatography (eluting with 1:20 v/v MTBE−*n*-heptane) to give the title compound (0.51 g, 56%) as a white powder. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 (d, J = 8.0 Hz, 2H), 7.57 (d, J = 7.6 Hz, 2H), 7.52−7.48 (m, 2 H), 7.46−7.21 (m, 16H), 7.13−7.03 (m, 5H), 6.98 (d, J = 7.6 Hz, 1H), 6.59 (d, J = 3.2 Hz, 1H), 4.27 (d, J = 9.2 Hz, 1H), 4.08 (s, 2H), 3.92−3.88 (m, 1H), 3.83−3.78 (m, 1H), 3.63−3.59 (m, 1H), 3.56−3.50 (m, 2H), 3.42 (dd, J = 9.0, 9.0 Hz, 1H), 2.33 (s, 3H), 1.82 (br, 1H, OH), 1.21 (d, J = 4.8 Hz, 1H, OH), 1.02 (s, 9H), 0.66 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.0 (d, J = 245 Hz, C), 143.1 (C), 141.4 (C), 137.9 (C), 136.8 (C), 136.5 (C), 136.4 (CH × 2), 136.1 (CH × 2), 135.23 (C), 135.17 (CH × 2), 135.0 (CH × 2), 134.8 (C), 132.8 (C), 132.2 (C), 130.8 (d, J = 3.4 Hz, C), 130.4 (CH), 130.0 (CH), 129.7 (CH), 129.5 (CH), 129.3 (CH), 129.1 (CH), 127.53 (CH × 2), 127.52 (CH_2 × 2), 127.48 (CH × 2), 127.17 (CH × 2), 127.10 (CH × 2), 127.03 (CH), 125.9 (CH), 122.6 (d, J = 1.1 Hz, CH), 115.7 (d, J = 21.6 Hz, CH × 2), 82.6 (CH), 80.4 (CH), 79.4 (CH), 76.2 (CH), 72.8 (CH), 62.7 (CH_2), 34.1(CH_2), 27.2 (CH_3 × 3), 26.6 (CH_3 × 3), 19.5, (C), 19.3 (CH_3),19.2 (C); FT-IR (neat) 3579, 3070, 3048, 2956, 2929, 2856, 1589, 1509, 1427, 1232, 1111, 822 cm^{-1}; $[\alpha]_D^{23}$ = +34.9 (c 1.0, MeOH); LCMS (ESI) m/z 938 (100, $[M + NH_4]^+$), 943 (10, $[M + Na]^+$); ESI QTof calculated for $[C_{56}H_{61}FO_5SSi_2 + NH_4]^+$ = 938.4101, found 938.4093; mp 77.9 °C.

2,4-Di-O-*tert*-butyldiphenylsilyl-1-*C*-(4-chloro-3-(4-ethoxybenzyl)phenyl)-*β*-D-glucopyranoside (4j) Using Method A. To a mixture of 1-(5-bromo-2-chlorobenzyl)-4-ethoxybenzene (1.5 g, 4.6 mmol), magnesium powder (0.54 g, 22.2 mmol), and THF (12 mL) was added 1,2-dibromoethane (0.16 mL, 2.3 μmol). The mixture was heated under reflux until the reaction initiated. A solution of 1-(5-bromo-2-chlorobenzyl)-4-ethoxybenzene (4.5 g, 13.8 mmol) in THF (28 mL) was added dropwise, and the mixture was stirred for 1 h under reflux. The mixture was cooled to rt and titrated to determine its

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concentration. The above prepared 4-chloro-3-[(4-ethoxyphenyl)-methyl]phenyl magnesium bromide (31 mL, 10 mmol, 0.32 M in THF) solution and $AlCl_3$ (0.5 M in THF, 8.0 mL, 4.0 mmol) were mixed at rt to give a black solution, which was stirred at rt for 1 h. To a solution of **2a** (0.64 g, 1.0 mmol) in PhOMe (3.0 mL) at rt was added phenylmagnesium bromide (0.38 mL, 1.0 mmol, 2.6 M solution in Et_2O). After stirring for about 5 min, the solution was then added into the above prepared aluminum mixture via syringe, followed by additional PhOMe (1.0 mL) to rinse the flask. The mixture was concentrated under reduced pressure (50 Torr) at 60 °C (external bath temperature) to remove THF and Et_2O, and then PhOMe (6 mL) was added. The reaction mixture was heated at 120 °C for 8 h, at which time HPLC assay analysis indicated a 51% yield of adduct **4j**. After cooling to rt, the reaction was treated with 10% aqueous NaOH (1 mL), THF (10 mL), and diatomaceous earth at rt; then, the mixture was filtered and the filter cake was washed with THF. The combined filtrates were concentrated, and the crude product was purified by silica gel column chromatography (eluting with 1:30 EtOAc/*n*-heptane), affording the title compound (0.30 g, 34%) as a white powder. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66−7.64 (m, 2H), 7.56−7.54 (m, 2H), 7.45−7.32 (m, 13H), 7.29−7.22 (m, 4H), 7.06 (d, J = 8.4 Hz, 2H), 7.00 (d, J = 1.6 Hz, 1H), 6.87 (dd, J = 8.4, 1.6 Hz, 1H), 6.82 (d, J = 8.4 Hz, 2H), 4.18 (d, J = 9.2 Hz, 1H), 4.02 (q, J = 7.1 Hz, 2H), 3.96 (d, J = 10.4 Hz, 2H), 3.86 (dd, J = 11.4, 1.8 Hz, 1H), 3.77 (t, J = 8.4, Hz, 1H), 3.58−3.36 (m, 4H), 1.42 (t, J = 6.8 Hz, 3H), 1.00 (s, 9H), 0.64 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.4 (C), 138.8 (C), 137.4 (C), 136.3 (CH × 2), 136.1 (CH × 2), 135.2 (CH × 2), 135.0 (C), 134.9 (CH × 2), 134.8 (C), 134.2 (C), 132.7 (C), 132.0 (C), 131.6 (CH), 131.1 (C), 129.8 (CH × 2), 129.7 (CH), 129.6 (CH), 129.44 (CH), 129.39 (CH), 129.2 (CH), 127.56 (CH × 2), 127.55 (CH × 2), 127.52 (CH × 2), 127.3 (CH × 3), 114.4 (CH × 2), 82.2 (CH), 80.5 (CH), 79.3 (CH), 76.3 (CH), 72.7 (CH), 63.4 (CH_2), 62.7 (CH_2), 38.2 (CH_2), 27.1 (CH_3 × 3), 26.6 (CH_3 × 3), 19.5 (C), 19.1 (C), 14.9 (CH_3); FT-IR (neat) 3578, 3070, 3048, 2930, 2894, 2857, 1612, 1589, 1510, 1427, 1265, 1243, 1109, 820 cm^{-1}; $[\alpha]_D^{23}$ = +39.7 (*c* 1.0, MeOH); ESI QTof calculated for $[C_{53}H_{61}ClO_6Si_2 + NH_4]^+$ = 902.4033, found 902.4018; mp 83.2 °C.

Synthesis of Canagliflozin (1a) by the Arylation of 7b. To a cooled (0 °C) solution of **9a** (2.25 g, 6.2 mmol) in PhMe (18 mL) and *i*-Pr_2O (8.9 mL) was added dropwise *n*-BuLi (4.7 mL, 7.5 mmol, 1.6 M solution in *n*-hexane), affording a clear orange solution.[44] After stirring at 0 °C for another hour (HPLC showed >99% conversion), $AlCl_3$ solution (3.1 mL, 2.5 mmol, 0.81 M in *n*-Bu_2O) was added dropwise to give a light yellow milky solution.[45] The mixture was stirred at 0 °C for 30 min and was heated at 90 °C for another 2 h. The resulting milk-like solution was concentrated under reduce pressure (50−100 Torr) in 90 °C to about 10 mL. The residual milky yellow-colored liquid was diluted with PhMe (6 mL) and was concentrated again to 10 mL. The residue was cooled, stirred at rt for 1 h, and filtered. The filtrate was concentrated under reduced pressure (50−100 Torr) at 90 °C, and the concentration was determined to be 1.1 M (1.32 mmol of tris(3-[[5-(4-fluorophenyl)-2-thienyl]methyl]-4-methylphenyl)alane in PhMe) by HPLC analysis.[46] A solution of $AlCl_3$ (0.82 mL, 0.66 mmol, 0.81 M in *n*-Bu_2O) was added to the above prepared triarylalane solution to give bis(3-[[5-(4-fluorophenyl)-2-thienyl]methyl]-4-methylphenyl)chloroalane (1.98 mmol). To a solution of **2a** (0.64 g, 1.0 mmol) in PhOMe (4 mL) was added dropwise Me_3Al (0.50 mL, 1.0 mmol, 2.0 M solution in PhMe). The resulting colorless solution of **7b** was transferred via syringe to the bis-arylchloroalane solution at rt. PhOMe (1.0 mL) was used to wash the flask. The reaction mixture was then heated at 140 °C, and the reaction progress was monitored by HPLC. After the reaction was complete (ca. 15 h), the mixture was cooled to 0 °C and diluted with THF (10 mL). Diatomaceous earth (1.0 g) and 15% aq. NaOH (2.0 mL) were added slowly and the suspension was stirred at rt for 1 h. Anhydrous Na_2SO_4 (2.0 g) was added, and the mixture was further stirred for 30 min. The resulting mixture was filtered through a pad of diatomaceous earth, and after washing with THF (20 mL), the filtrate was dried over anhydrous Na_2SO_4 (0.5 g), concentrated, and purified by column chromatography over silica gel (eluting with 1:40 to 1:6 v/v EtOAc−*n*-heptane) to yield protected canagliflozin **4i** as a light yellow power (687 mg, 75% yield). To a solution of **4i** (687 mg from the previous step, 0.75 mmol) in THF (3 mL) was added TBAF (3.0 mL, 3.0 mmol, 1 M in THF), affording a clear orange solution. After stirring for 4 h at rt, the solution was diluted with MeOH (10 mL), and $CaCO_3$ (0.60 g) and Dowex resin 50WX8 (1.8 g; 200−400 mesh) were added.[43] The suspension was stirred vigorously at rt for 1 h and was filtered through diatomaceous earth. The filter cake was washed with THF (20 mL), and the clear yellow filtrate was concentrated to afford a brown viscous oil that was purified by column chromatography over silica gel (eluting with 1:30 v/v MeOH−DCM) to yield canagliflozin (**1a**) as an off-white power (226 mg, 68% yield). The characterization data were identical with those reported[8a] and with those obtained from analysis of a commercial reference sample. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.62−7.57 (m, 2H), 7.28 (d, J = 3.6 Hz, 1H), 7.23−7.12 (m, 5H), 6.80 (d, J = 3.6 Hz, 1H), 4.94 (d, J = 4.4 Hz, 2H, OH), 4.74 (d, J = 6.0 Hz, 1H, OH), 4.53 (dd, J = 5.8, 5.8 Hz, 1H, OH), 4.16 (d, J = 16 Hz, 1H), 4.10 (d, J = 16 Hz, 1H), 3.97 (d, J = 9.6 Hz, 1H), 3.73−3.69 (m, 1H), 3.47−3.42 (m, 1H), 3.28−3.17 (m, 4H), 2.27 (s, 3H); LCMS (ESI) m/z 462 (100, $[M + NH_4]^+$), 467 (3, $[M + Na]^+$); ESI QTof calculated for $[C_{24}H_{25}FO_5S + H]^+$ = 445.1479, found 445.1466.

1,6-Anhydro-2,3,4-tri-O-*tert*-butyldimethylsilyl-β-D-glucopyranose (2b). To a suspension of 1,6-anhydro-β-D-glucopyranose (**3**, 5.0 g, 30.8 mmol) and imidazole (14.7 g, 216 mmol) in THF (40 mL) at 0 °C was added dropwise a solution of TBSCl (23.2 g, 154 mmol) in THF (10 mL). The mixture was stirred at rt overnight. Water (50 mL) was added, and the mixture was extracted twice with EtOAc (100 mL each) and concentrated. Column chromatography (eluting with 1:10 v/v DCM−*n*-heptane) separately afforded the title compound (6.4 g, 41%) as a white solid, and 1,6-anhydro-2,4-di-*O*-*tert*-butyldimethylsilyl-β-D-glucopyranose (4.3 g, 36%) as a white powder. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.28−5.27 (m, 1H), 4.37−4.35 (m, 1H), 4.10 (dd, J = 6.8, 0.8 Hz, 1H), 3.67 (dd, J = 6.4, 6.4 Hz, 1H), 3.62−3.60 (m, 1H), 3.50 (d, J = 1.2 Hz, 1H), 3.45 (d, J = 1.2 Hz, 1H), 0.94 (s, 9H), 0.93 (s, 9H), 0.92 (s, 9H), 0.12 (s, 3H), 0.113 (s, 6H), 0.105 (s, 3H), 0.100 (s, 3H), 0.096 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$;) δ 102.0 (CH), 76.4 (CH), 75.3 (CH), 72.8 (CH), 71.8 (CH), 64.4 (CH_2), 25.81 (CH_3 × 3), 25.77 (CH_3 × 3), 25.64 (CH_3 × 3), 18.1 (C), 18.0 (C), 17.8 (C), −4.51 (CH_3), −4.563 (CH_3), −4.568 (CH_3), −4.59 (CH_3), −4.7 (CH_3), −4.8 (CH_3); FT-IR (neat) 2952, 2929, 2893, 2857, 1472, 1463, 1361, 1327, 1255, 1101, 1083, 892, 833, 773, 670 cm^{-1}; $[\alpha]_D^{20}$ = −25.1 (*c* 1.0, MeOH); ESI QTof calculated for $[C_{24}H_{52}O_5Si_3 + H]^+$ = 505.3195, found 505.3224; mp 67.0 °C. **1,6-Anhydro-2,4-di-*O*-*tert*-butyldimethylsilyl-β-D-glucopyranose**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.29 (s, 1H), 4.39 (d, J = 4.8 Hz, 1H), 3.86 (d, J = 7.2 Hz, 1H), 3.68 (dd, J = 7.2, 5.2 Hz, 1H), 3.55−3.52 (m, 2H), 3.64−3.45 (m, 1H), 2.09 (d, J = 5.2 Hz, 1H, OH), 0.943 (s, 9H), 0.938 (s, 9H), 0.140 (s, 3H), 0.130 (s, 6H), 0.126 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$;) δ 103.8 (CH), 78.3 (CH), 75.8 (CH), 74.7 (CH), 74.5 (CH), 66.6 (CH_2), 25.8 (CH_3 × 6), 18.14 (C), 18.10 (C), −4.58 (CH_3), −4.67 (CH_3), −4.71 (CH_3), −4.81 (CH_3); FT-IR (neat) 3493, 2954, 2929, 2895, 2857, 1473, 1463, 1407, 1389, 1362, 1254, 1108, 1074, 1005, 896, 837, 776, 669 cm^{-1}; $[\alpha]_D^{20}$ = −31.5 (*c* 1.0, MeOH); ESI QTof calculated for $[C_{18}H_{38}O_5Si_2 + H]^+$ = 391.2331, found 391.2331; mp 65.9 °C.

2,3,4-Tri-O-*tert*-butyldimethylsilyl-1-C-phenyl-β-D-glucopyranoside. To a solution of 1,6-anhydro-2,3,4-tri-*O*-*tert*-butyldimethylsilyl-β-D-glucopyranose (**2b**, 0.51 g, 1.0 mmol) in PhOMe (4.0 mL) at rt was added Ph_3Al (2.0 mL, 2.0 mmol, 1.0 M in *n*-Bu_2O). The mixture was heated at 140 °C for 23 h. After cooling to rt, THF (10 mL), diatomaceous earth (1 g), 15% aqueous NaOH (1 mL), and anhydrous Na_2SO_4 (2 g) were added sequentially 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 v/v EtOAc−*n*-heptane) to give the title compound (69 mg, 12%) as a light yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44−7.42 (m, 2H), 7.38−7.34 (m, 2H), 7.32−7.30 (m, 1H), 4.66 (d, J = 5.6 Hz, 1H), 4.00 (dd, J = 9.2, 4.4 Hz, 1H), 3.94−3.90 (m, 2H), 3.85−3.79 (m, 3H), 2.34 (dd, J = 6.0, 6.0 Hz, 1H, OH), 0.98 (s, 9H), 0.94 (s, 9H), 0.88 (s, 9H), 0.16 (s, 6H), 0.15 (s,

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3H), −0.03 (s, 6H), −0.27 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.5 (C), 128.1 (CH × 2), 127.7 (CH), 127.6 (CH × 2), 81.8 (CH), 81.3 (CH), 78.0 (CH), 77.9 (CH), 71.9 (CH), 64.4 (CH_2), 25.9 (CH_3 × 9), 17.96 (C), 17.95 (C), 17.87 (C), −4.1 (CH), −4.2 (CH), −4.3 (CH), −4.6 (CH), −4.9 (CH), −5.1 (CH); FT-IR (neat) 3447, 2954, 2929, 2895, 2857, 1472, 1463, 1389, 1361, 1257, 1096, 1006, 883, 814, 775, 698 cm^{-1}; $[\alpha]_D^{20}$ = +9.5 (*c* 1.0, MeOH); LCMS (ESI) *m*/*z* 583 (100, $[M + H]^+$), 584 (44, $[M + H + 1]^+$), 605 (46, $[M + Na]^+$); ESI QTof calculated for $[C_{30}H_{58}O_5Si_3 + NH_4]^+$ = 600.3930, found 600.3924.

■ ASSOCIATED CONTENT

Supporting Information

^{1}H, ^{13}C, and 2D NMR spectra of all compounds; Figures S1−S7; HPLC chromatograms of α-**1e** and β-**1e**; XICs and high-resolution mass spectra of **4c**, **4d**, **4f**, **4h**, and **1a**; ^{1}H NMR experiments of (i) addition of Me_3Al (4 equiv) to **2a**, and (ii) addition of Me_3Al (2 equiv) to **2b**, followed by addition of THF (2 equiv); and ESI mass spectra of **1b** prepared by desilylation of **4j** from Table 1, and of **8a**. 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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■ REFERENCES

(1) (a) Wu, Q.-P.; Simons, C. *Synthesis* **2004**, 1533−1553. (b) Štambaský, J.; Hocek, M.; Kočovský, P. *Chem. Rev.* **2009**, *109*, 6729−6764.

(2) Du, Y. G.; Linhardt, R. J. *Tetrahedron* **1998**, *54*, 9913−9959.

(3) (a) Sheridan, C. *Nat. Biotechnol.* **2012**, *30*, 899−900. (b) Hardman, T. C.; Dubrey, S. W. *Diabetes Ther.* **2011**, *2*, 133−145. (c) Bays, H. *Curr. Med. Res. Opin.* **2009**, *25*, 671−681. (d) Washburn, W. N. *Expert Opin. Ther. Pat.* **2009**, *19*, 1485−1499. (e) Washburn, W. N. *J. Med. Chem.* **2009**, *52*, 1785−1794.

(4) (a) Nomura, S.; Kawanishi, E.; Ueta, K. U.S. Patent 7,943,788, May 17, 2011. (b) Meng, W.; Ellsworth, B. A.; Nirschl, A. A.; McCann, P. J.; Patel, M.; Girotra, R. N.; Wu, G.; Sher, P. M.; Morrison, E. P.; Biller, S. A.; Zahler, R.; Deshpande, P. P.; Pullockaran, A.; Hagan, D. L.; Morgan, N.; Taylor, J. R.; Obermeier, M. T.; Humphreys, W. G.; Khanna, A.; Discenza, L.; Robertson, J. G.; Wang, A.; Han, S.; Wetterau, J. R.; Janovitz, E. B.; Flint, O. P.; Whaley, J. M.; Washburn, W. N. *J. Med. Chem.* **2008**, *51*, 1145−1149. (c) Kadokura, T.; Zhang, W.; Krauwinkel, W.; Leeflang, S.; Keirns, J.; Taniuchi, Y.; Nakajo, I.; Smulders, R. *Clin. Pharmacokinet.* **2014**, *53*, 975−988. (d) Grempler, R.; Thomas, L.; Eckhardt, M.; Himmelsbach, F.; Sauer, A.; Sharp, D. E.; Bakker, R. A.; Mark, M.; Klein, T.; Eickelmann, P. *Diabetes, Obes. Metab.* **2012**, *14*, 83−90.

(5) (a) Kraus, G. A.; Molina, M. T. *J. Org. Chem.* **1988**, *53*, 752−753. (b) Czernecki, S.; Ville, G. *J. Org. Chem.* **1989**, *54*, 610−612.

(6) (a) Ellsworth, B. A.; Doyle, A. G.; Patel, M.; Caceres-Cortes, J.; Meng, W.; Deshpande, P. P.; Pullockaran, A.; Washburn, W. N. *Tetrahedron: Asymmetry* **2003**, *14*, 3243−3247. (b) Deshpande, P. P.; Singh, J.; Pullockaran, A.; Kissick, T.; Ellsworth, B. A. *J. Org. Chem.* **2007**, *72*, 9746−9749.

(7) Deshpande, P. P.; Singh, J.; Pullockaran, A.; Kissick, T.; Ellsworth, B. A.; Gougoutas, J. Z.; Dimarco, J.; Fakes, M.; Reyes, M.; Lai, C.; Lobinger, H.; Denzel, T.; Ermann, P.; Crispino, G.; Randazzo, M.; Gao, Z.; Randazzo, R.; Lindrud, M.; Rosso, V.; Buono, F.; Doubleday, W. W.; Leung, S.; Richberg, P.; Hughes, D.; Washburn, W. N.; Meng, W.; Volk, K. J.; Mueller, R. H. *Org. Process Res. Dev.* **2012**, *16*, 577−585.

(8) (a) Lemaire, S.; Houpis, I. N.; Xiao, T.; Li, J.; Digard, E.; Gozlan, C.; Liu, R.; Gavryushin, A.; Diène, C.; Wang, Y.; Farina, V.; Knochel, P. *Org. Lett.* **2012**, *14*, 1480−1483. (b) Sakamaki, S.; Kawanishi, E.; Nomura, S.; Ishikawa, T. *Tetrahedron* **2012**, *68*, 5744−5753. (c) Nicolas, L.; Angibaud, P.; Stansfield, I.; Bonnet, P.; Meerpoel, L.; Reymond, S.; Cossy, J. *Angew. Chem., Int. Ed.* **2012**, *51*, 11101−11104.

(9) (a) Lewis, M. D.; Cha, J. K.; Kishi, Y. *J. Am. Chem. Soc.* **1982**, *104*, 4976−4978. (b) Panek, J. S.; Sparks, M. A. *J. Org. Chem.* **1989**, *54*, 2034−2038. (c) Hager, D.; Paulitz, C.; Tiebes, J.; Mayer, P.; Trauner, D. *J. Org. Chem.* **2013**, *78*, 10784−10801.

(10) Henschke, J. P.; Lin, C.-W.; Wu, P.-Y.; Hsiao, C.-N.; Liao, J.-H.; Hsiao, T.-Y. PCT Int. Appl. Pub. WO 2013/068850, 2013.

(11) (a) Zottola, M. A.; Alonso, R.; Vite, G. D.; Fraser-Reid, B. *J. Org. Chem.* **1989**, *54*, 6123−6125. (b) Boons, G.-J.; Isles, S.; Setälä, P. *Synlett* **1995**, 755−756. (c) Alvarez, E.; Pérez, R.; Rico, M.; Rodríguez, R. M.; Suárez, M. C.; Martín, J. D. *Synlett* **1996**, 1082−1084. (d) Tanaka, T.; Huang, W. C.; Noguchi, M.; Kobayashi, A.; Shoda, S. *Tetrahedron Lett.* **2009**, *50*, 2154−2157. (e) Rao, M. V.; Nagarajan, M. *Carbohydr. Res.* **1987**, *162*, 141−144.

(12) The structure of **4a** was supported by 1D (^{1}H and ^{13}C) and 2D NMR spectroscopy and high-resolution mass spectroscopy, and proven by desilylation and spectroscopic comparison to an authentic sample of β-**1e** that was prepared as per ref 26.

(13) (a) Siewert, J.; Sandmann, R.; von Zezschwitz, P. *Angew. Chem., Int. Ed.* **2007**, *46*, 7122−7124. (b) Hawner, C.; Müller, D.; Gremaud, L.; Felouat, A.; Woodward, S.; Alexakis, A. *Angew. Chem., Int. Ed.* **2010**, *49*, 7769−7772. (c) Hirner, S.; Kolb, A.; Westmeier, J.; Gebhardt, S.; Middel, S.; Harms, K.; von Zezschwitz, P. *Org. Lett.* **2014**, *16*, 3162−3165. (d) Chen, C.-A.; Wu, K.-H.; Gau, H.-M. *Angew. Chem., Int. Ed.* **2007**, *46*, 5373−5376. (e) Biradar, D. B.; Zhou, S. L.; Gau, H.-M. *Org. Lett.* **2009**, *11*, 3386−3389. (f) Zhou, S.; Chen, C.-R.; Gau, H.-M. *Org. Lett.* **2010**, *12*, 48−51. (g) Wu, K.-H.; Gau, H.-M. *J. Am. Chem. Soc.* **2006**, *128*, 14808−14809. (h) Zhou, S.; Wu, K.-H.; Chen, C.-A.; Gau, H.-M. *J. Org. Chem.* **2009**, *74*, 3500−3505. (i) Zhou, S.; Chuang, D.-W.; Chang, S.-J.; Gau, H.-M. *Tetrahedron: Asymmetry* **2009**, *20*, 1407−1412. (j) Blum, J.; Gelman, D.; Baidossi, W.; Shakh, E.; Rosenfeld, A.; Aizenshtat, Z. *J. Org. Chem.* **1997**, *62*, 8681−8686. (k) Tanaka, S.; Mori, A. *Eur. J. Org. Chem.* **2014**, 1167−1171.

(14) Yakura, T.; Tanaka, K.; Kitano, T.; Uenishi, J.; Ikeda, M. *Tetrahedron* **2000**, *56*, 7715−7721.

(15) (a) Ishihara, K.; Hanaki, N.; Yamamoto, H. *J. Am. Chem. Soc.* **1991**, *113*, 7074−7075. (b) Ishihara, K.; Hanaki, N.; Yamamoto, H. *J. Am. Chem. Soc.* **1993**, *115*, 10695−10704.

(16) (a) Alzeer, J.; Cai, C.; Vasella, A. *Helv. Chim. Acta* **1995**, *78*, 242−264. (b) Vasella, A. *Pure Appl. Chem.* **1998**, *70*, 425−430. (c) Bohner, T. V.; Beaudegnies, R.; Vasella, A. *Helv. Chim. Acta* **1999**, *82*, 143−160. (d) Stichler-Bonaparte, J.; Bernet, B.; Vasella, A. *Helv. Chim. Acta* **2002**, *85*, 2235−2257.

(17) Allwein, S. P.; Cox, J. M.; Howard, B. E.; Johnson, H. W. B.; Rainier, J. D. *Tetrahedron* **2002**, *58*, 1997−2009.

(18) Singh, I.; Seitz, O. *Org. Lett.* **2006**, *8*, 4319−4322.

(19) The consumption of **2a** and formation of **4a** were monitored by HPLC. Adjustments of peak area % based on the response factor of reaction components with respect to an internal standard (1,2,4,5-tetramethylbenzene) meant that reaction yields could be determined throughout the reaction without the need for workup and isolation.

(20) De Mal, V. S. J.; Oliver, J. P. *Organometallics* **1989**, *8*, 827−830.

(21) Given that mixed organoalanes can exist in solution as equilibrium mixtures,[13h,i] this formula is used for simplicity and represents the stoichiometric ratio of the aryl anion, aluminium, and the additional ligand X, when present. Fraction stoichiometry represents mixture of species; for example, $Ph_{2.5}AlX_{0.5}$ represents a

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mixture of Ph_3Al and Ph_2AlX, but may include other permutations that might exist in equilibrium.
(22) Krieck, S.; Görls, H.; Westerhausen, M. *Organometallics* **2008**, *27*, 5052−5057.
(23) When a 2:1 complex of Me_3Al and **2b** (prepared in an NMR tube by the addition of 2 equiv of Me_3Al to **2b**) in benzene-d_6 at rt was treated with 2 equiv of THF, the original spectrum for **2b** was obtained. Both signals for THF were found significantly upfield of free THF, indicating that transfer of Me_3Al from **2b** to THF had occurred (see the Supporting Information for corresponding spectra). Thus, apart from lowering the temperature of reflux, THF is believed to be a better coordinator of organoalanes than 1,6-anhydroglucose derivatives, making it a poor solvent for the arylation reaction.
(24) See: *Guideline Q3C (R5): Impurities: Guidelines for Residual Solvents*; International Conference on Harmonisation (ICH); 2011.
(25) (a) PhOMe has been reported to be a useful and industrially friendly solvent; see: Desmurs, J.-R.; Ratton, S. *Ind. Chem. Libr.* **1996**, 481−488. (b) PhOMe has also been shown to be helpful for Grignard reactions; see: Lewis, R. N.; Wright, J. R. *J. Am. Chem. Soc.* **1952**, *74*, 1253−1257.
(26) α-**1e** and β-**1e** were prepared separately by synthesis of their 3,4,6-tri-*O*-benzyl derivatives as per ref 17, benzylation (on ca. 0.5−1 mmol scales) using 1.5 equiv of BnBr and 3 equiv of NaH (60% suspension) in THF at 50 °C overnight to give their 2,3,4,6-tetra-*O*-benzyl derivatives in ca. 80% isolated yields (spectroscopically identical to those described in ref 6a), followed by hydrogenolysis as per ref 5b. See the Supporting Information for analytical data.
(27) Treatment of reaction aliquots with 5% TFA in MeCN before HPLC analysis resulted in improved reproducibility of the analytical data.
(28) Miyoshi, T.; Matsuya, S.; Tsugawa, M.; Sato, S.; Ueda, M.; Miyata, O. *Org. Lett.* **2013**, *15*, 3374−3377.
(29) Rainier, J. D.; Cox, J. M. *Org. Lett.* **2000**, *2*, 2707−2709.
(30) The reagents stoichiometry (2 equiv of Ph_3Al and 1 equiv of the Brønsted acids XH) was selected such that a mixture of Ph_3Al and Ph_2AlX (where X is OTf, OC_6F_5, OPh, or O*i*-Pr) was generated; Ph_3Al being more basic than Ph_2AlX would react with **2a** to form **7a**, leaving 1 equiv of Ph_2AlX in solution to effect the arylation of **7a**. For comparative purposes, Ph_2AlCl/Ph_3Al was prepared by mixing 1.7 equiv of Ph_3Al and 0.3 equiv of $AlCl_3$.
(31) As discussed later, reaction of **2a** with Ph_3Al provides **7a**, and this was used as a substrate in the following tests by mixing **2a** with a suitable mixture of Ph_3Al and the modified alane derivatives.
(32) Quenching the product mixture with excess I_2 and LiCl in THF allowed recovery of the aryl side chain, as its iodide, from the unreacted arylaluminium reagent. From a typical arylation using **7a** and 1 equiv of Ph_2AlCl in PhOMe, HPLC analysis indicated 1.8 equiv of PhI formed, based on the sugar after the I_2−LiCl quench (see ref 40). This equates to a 59% recovery of the phenyl anion based on that theoretically remaining following arylation.
(33) Gao, H.; Knochel, P. *Synlett* **2009**, 1321−1325.
(34) Phenyl(halo)*alkyl*alanes were prepared by mixing of R_3Al (when R = Me or *i*-Bu) or Et_2AlCl, Ph_3Al and $AlCl_3$ and heating at ca. 120 °C for 30 min, before reaction with lithium alkoxide **7d**. Treatment of **2a** with Me_3Al or *i*-Bu_3Al was conducted separately to produce reference samples of the *C*-alkylglucosides **8a** (see the Supporting Information) and **8c**, respectively, and the reduced product **8d**. These were supported by LCMS analysis.
(35) (a) Mole, T. *Aust. J. Chem.* **1966**, *19*, 373−379. (b) Berg, D. J.; Andersen, R. A. *Organometallics* **2003**, *22*, 627−632.
(36) Further changes in the chemical shift of the sugar protons were witnessed upon the addition of consecutive equivalents of Me_3Al to **7b**; however, the fourth equivalent (based on **2a**) resulted in a negligible impact on the main peaks. When **2a** was treated with 4 equiv of Me_3Al in PhMe at rt for 13 days, LCMS analysis showed a 33:44 peak area % mixture of *C*-methylglucoside **8a** and **2a**. After workup, a 24% yield of a *C*-methylglucoside **8a** (see the Supporting Information) was obtained.
(37) PhLi and $AlCl_3$ were mixed at 0 °C and then stirred at rt for 5 min, followed by heating at 140 °C for 2 h. The mixture was then cooled to rt for 30 min, and filtered where required; the solvent mixture was composed of a 2:1 ratio of PhOMe and *n*-Bu_2O.
(38) (a) Perrin, C. L.; Skinner, G. A. *J. Am. Chem. Soc.* **1971**, *93*, 3389−3394. (b) Moodie, R. B.; Schofield, K. *Acc. Chem. Res.* **1976**, *9*, 287−292.
(39) As suggested by a reviewer, the C3-alkoxyalane may be competitively activated, generating a carbocation at C3, which then undergoes a [1,2]-hydride shift and deprotonation at C2 to give enol ether **5**. The same reviewer suggested that arylation may proceed in an intermolecular fashion.
(40) Krasovskiy, A.; Knochel, P. *Synthesis* **2006**, 890−891.
(41) See: *Standard Methods for the Examination of Water and Wastewater* at http://www.standardmethods.org/store/ProductView.cfm?ProductID=492.
(42) Sarotti, A. M.; Fernández, I.; Spanevello, R. A.; Sierra, M. Á; Suárez. *Org. Lett.* **2008**, *10*, 3389−3392.
(43) Kaburagi, Y.; Kishi, Y. *Org. Lett.* **2007**, *9*, 723−726.
(44) (a) Bailey, W. F.; Luderer, M. R.; Jordan, K. P. *J. Org. Chem.* **2006**, *71*, 2825−2828. (b) Jedlicka, B.; Crabtree, R. H. *Organometallics* **1997**, *16*, 6021−6023.
(45) (a) Bagh, B.; Schatte, G.; Green, J. C.; Müller, J. *J. Am. Chem. Soc.* **2012**, *134*, 7924−7936. (b) Koller, J.; Bergman, R. G. *Organometallics* **2010**, *29*, 3350−3356. (c) Petrie, M. A.; Power, P. P.; Rasika Dias, H. V.; Ruhlandt-Senge, K.; Waggoner, K. M.; Wehmschulte, R. J. *Organometallics* **1993**, *12*, 1086−1093.
(46) An aliquot of the triarylalane solution was treated with an I_2−LiCl solution in THF (see ref 40). The amount of aryliodide formed was quantitated by HPLC with respect to the internal standard 1,2,4,5-tetramethylbenzene.

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