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Remarkable β-Selectivity in the Synthesis of β-1-*C*-Arylglucosides: Stereoselective Reduction of Acetyl-Protected Methyl 1-*C*-Arylglucosides without Acetoxy-Group Participation

Prashant P. Deshpande,*,‡ Bruce A. Ellsworth,*,† Frederic G. Buono,‡ Annie Pullockaran,⊥ Janak Singh,⊥ Thomas P. Kissick,⊥ Ming-H. Huang,⊥ Hildegard Lobinger,§ Theodor Denzel,§ and Richard H. Mueller‡

Process Research and Development, Bristol-Myers Squibb, 1 Squibb Drive, New Brunswick, New Jersey 08903, Bristol-Myers Squibb, Princeton, New Jersey 08543, Bristol-Myers Squibb, Regensburg, Germany, and Department of Metabolic Disease Discovery Chemistry, Bristol-Myers Squibb, Hopewell, New Jersey 08534

prashant.deshpande@bms.com

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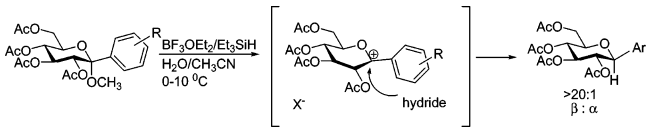

An efficient and practical process to generate β-*C*-arylglucoside derivatives was achieved. The process described involves Lewis acid mediated ionic reduction of a peracetylated 1-*C*-aryl methyl glucoside derived from the addition of an aryl-Li to selectively protected δ-D-gluconolactone. The reduction of the 2-acetoxy-1-*C*-oxacarbenium ion intermediates proceeds with a high degree of selectivity to give β-*C*-arylglucosides without 2-acetoxy group participation. Furthermore, during the reduction process we also identified an unprecedented critical role of water. By changing from the usual benzyl ether protecting groups because of cost and chemical compatibility concerns, the new process is made additionally efficient and highly selective.

β-1-*C*-Arylglucosides belong to a class of natural products that are known for their biological activity and medicinal properties, and stereochemical control is the major challenge of their chemical synthesis.[1,2] We report a new synthesis of β-*C*-arylglucosides where we observed that ester-protected glucosides bearing a 1-*C*-aryl group can be reduced under ionic conditions with a high degree of selectivity despite concerns that participation by a C-2 acetoxy group might interfere with hydride delivery from the α-face as well as ring deactivation may not allow an efficient reduction process. We have discovered, also unexpectedly, the critical role of water during the Lewis acid mediated reductions with silanes. This simple change from the traditional use of benzyl ethers to ester protecting groups enables a new and more efficient synthetic method of β-1-*C*-arylglucosides.

One popular method to prepare this class of compounds, developed by Kishi[3] and extended to the synthesis of *C*-arylglucosides by Kraus,[4,5] involves addition of an aryllithium reagent to a 2,3,4,6-tetra-*O*-benzyl-D-gluconolactone followed by the reduction of the resulting lactol with Et_3SiH.[2] We wished to avoid the use of 2,3,4,6-tetra-*O*-benzyl-D-glucose as the carbohydrate synthon for several reasons: the starting material is expensive, thereby limiting its usefulness for a commercial process; the starting material must be oxidized at C-1 to a lactone that is syrupy, thus posing stability concerns, and this same C-1 position is reduced later in the sequence; the intermediate lactol does not always give high selectivity in the reduction process;[6] and more critically, hydrogenolytic deprotection conditions are incompatible with our desired range of functional groups.[7,8] Several of these concerns are resolved by the use of *per*-trimethylsilyl-D-gluconolactone **1** and the subsequent use of acetate protecting groups. This lactone was previously used by Horton and co-workers[9] in the synthesis of 1-*C*-methyl glucose derivative **4** due to the ease of trimethylsilyl ether protection/deprotection, and relative stability of this group under strongly basic alkyllithium addition conditions.[9] In that synthesis the intermediate peracetylated lactol (**2**) was reduced under Raney Ni conditions via a proposed episulfonium intermediate **3**,

‡ Bristol-Myers Squibb, New Brunswick.
⊥ Bristol-Myers Squibb, Princeton.
§ Bristol-Myers Squibb, Regensburg.
† Bristol-Myers Squibb, Hopewell.

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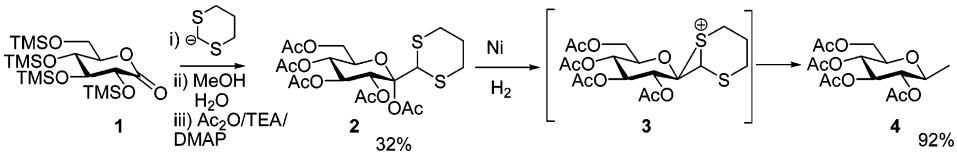
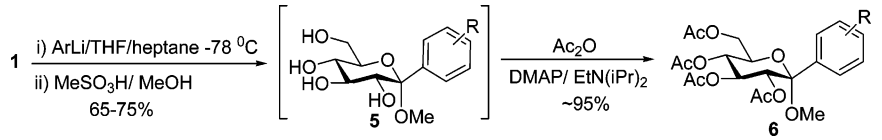
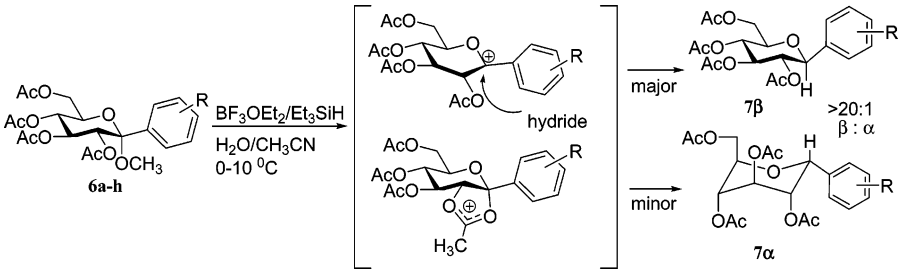
SCHEME 1. Synthesis of an Alkyl Glucoside 4



SCHEME 2. Synthesis of an 1-*C*-Aryl Methyl Glucoside 6



SCHEME 3. Synthesis of *β*-*C*-Arylglucoside 7



Scheme 1;[10] this methodology is not applicable for the synthesis of the targeted pharmaceutically important aryl-substituted sugar derivatives.

Starting with lactone **1**, we prepared several 1-*C*-aryl methyl glucosides **5** according to a modification of Barrett's protocol[11] to study the Lewis acid-mediated silane reduction. First, we significantly improved the yields of the addition of a variety of aryl lithiums to persilylated gluconolactone (**1**) by replacing THF with THF/toluene or THF/heptanes solvent combinations. We observed that lower solvent polarity[12a,b] and low temperature provided significant improvements in the yield as enolization and de-silylation were suppressed.[12c] Subsequent *in situ* transketalization with methanesulfonic acid/methanol prevented the formation of open chain carbohydrate derivatives while concomitantly removing the TMS protecting groups.[9] The resulting methyl 1-*C*-arylglucosides **5** were protected to give the corresponding tetraacetates **6a**−**h** in a one pot process (Scheme 2).

Acetate groups are well-known to stabilize proximal carbenium ion intermediates by anchimeric assistance, and this strategy is often used to control selectivity in the formation of 1,2-*trans*-glucosides.[13,14] They also participate in substitution reactions and silane-mediated reductions under cationic conditions.[15−17] Since we wanted to perform a cationic reduction with 1,2-*syn*-hydride delivery, the choice of an acetyl group may seem unusual. However, the steric and electronic effects of the 1-*C*-aryl group may outweigh the neighboring effect of the acetate group on the oxocarbenium ion intermediate.

TABLE 1. Selectivities of the Reduction of Peracetylated 1-*C*-Arylglucosides 6a−i (Scheme 3)

compd **6**	R	**7**: *β*:α ratio[a]
a	4-Me	30:1
b	3-Me	20:1
c	2-Me	20:1
d	4-OMe	>65:1
e	4-Cl	22:1
f	3,4,5-(OMe)$_3$	22:1
g	3-*i*-Pr	24:1
h	aryl = 2-naphthyl	19:1
i (6-deoxy)	4-Me	48:1

[a] The content of the α isomer was estimated by HPLC and LCMS.

We report that, in the case of methyl tetra-*O*-acetyl-1-*C*-arylglucosides **6a**−**h** (Scheme 3 and Table 1), a C-2-acetoxy group does not participate to any extent to direct delivery of the hydride from the *β*-face of the oxocarbenium ion intermediate (Scheme 3). When peracetylated glucosides (**6a**−**h**) were subjected to $BF_3{\cdot}Et_2O$-mediated reduction with triethylsilane in acetonitrile, we observed a highly selective reduction from the α-face to give *β*-1-*C*-aryl-1-deoxyglucosides **7** (Table 1) in good yields.

Initially, the reactions carried out on small scale advanced to completion, furnishing *β*-isomers **7a**−**e**[18] and **7f**−**i** with high selectivity. However, on a multikilogram scale, we noticed that the reaction stalled and the reduction was incomplete, although its selectivity was not affected. Further investigations revealed

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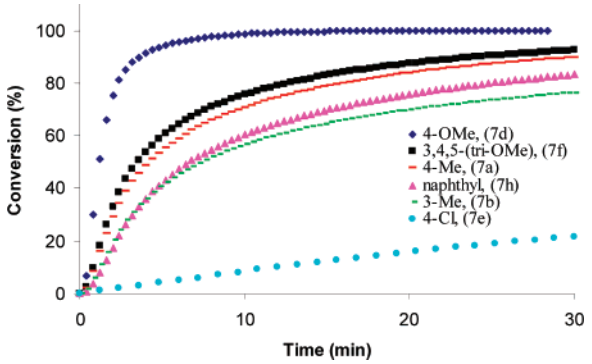

FIGURE 1. Substituent effects on reduction rate (eq 1).

that the presence of water in the reaction mixture was critical for this reduction process.[19] On laboratory scale, the reactions did not stall, presumably as a result of the presence of adventitious water. We established that 1 mole of water and >2 equiv of $BF_3{\cdot}Et_2O$ were required to drive the reduction to completion.

We propose that the addition of water to $BF_3{\cdot}Et_2O$ generates a strong Bronsted acid, such as $F_3B^-O^+H_2$, that may accelerate the formation of an oxocarbenium ion intermediate.[20] This reagent combination appears to be essential to compensate for the inductive deactivating effect of the acetoxy substituents. This proposal is consistent with our previous observations[6] that reduction of tetrabenzyl-1-*C*-arylglucopyranose lactols does not require added water since stronger coordination of the Lewis acid is expected with the lactol (as compared to methyl ketal **6**). The reduction of the electron-rich *p*-methoxy-substituted analogue (**6d**) performed well under anhydrous conditions since oxocarbenium ion formation may be facilitated by the *p*-MeO-aryl group in this case.

We also established that the reduction *selectivity* of *C*-arylglucosides does not strongly depend on the nature of the aryl substituent. For example, benzylic cation destabilizing and stabilizing substituents in compounds **6e** (R = Cl) and **6d** (R = OMe) provided products **7e**[12e] and **7d**,[12c,d] respectively, with high β-stereoselectivity and in good yield. The reductions were also followed by reaction calorimetry[21] to determine the influence of aryl substituents on the reaction rate. As is evident from the plots in Figure 1, electron-withdrawing groups, as in **6e**, cause a slower reaction than analogues carrying electron-rich groups (e.g., **6d**). The overall reactivity trend was p-OMe > 3,4,5-tri-OMe > *p*-Me > 2-naphthyl > *m*-Me > *p*-Cl (Figure 1).

The C-6 protecting group is also known to influence reactivity at the anomeric center of carbohydrates,[22] so compound **6i** (Table 1), lacking a C-6 acetoxy substituent, was prepared following a literature method[23] and subjected to our reduction conditions. We still observed high selectivity (48:1) to form the β-*C*-aryl-glycosylated product **7i**. Evidently, the C-6 acetoxy group played no role in the β selectivity of compound **7**. Therefore, in the case of peracetylated 1-*C*-arylglucosides, neighboring groups do not participate to stabilize the oxocarbenium ion during the reduction reaction. A similar observation was also reported by Giannis and Sandhoff[24] during the allylation of peracetylated glucopyranoses with allylsilane and $BF_3{\cdot}Et_2O$.

Our results provide sufficient evidence for a predominantly axial hydride attack that is most likely due to the known stereoelectronic preference of glucosides.[25] Thus, we are able to produce β-*C*-arylglucosides as the major products.

This communication describes an efficient, general, and practical process to generate peracetylated *C*-arylglucoside derivatives. Our initial concern that the Lewis acid-mediated silyl hydride reduction of peracetylated substrates, such as compound **6**, might not reduce efficiently and not provide good β-selectivity due to C-2 ester neighboring group participation[26] proved unfounded. We also show that the less expensive and more readily available triethylsilane can be used for the reduction to obtain peracetylated *C*-arylglucosides with >96% selectivity for the β-anomer, unlike the reduction of benzyl protected phenyl-glucosides,[6] where sterically hindered silanes are required to achieve high selectivity. We show also the unprecedented role of water in the reduction reaction with a plausible explanation.

Since the trimethylsilyl-protected lactone (**1**) can be prepared in one step by using very inexpensive starting materials, this process is more practical for the synthesis of commercial *C*-arylglucoside products. This method allows the use of a greater diversity of aryl substituents, avoiding chemical incompatibilities with hydrogenolytic deprotections used in the 2,3,4,6-tetra-*O*-benzyl-D-gluconolactone[2] route, and providing improved stereoselectivity in the reduction process as compared to tetra-*O*-benzyl-protected 1-*C*-arylglucosides. These advantages have made it the route of choice for us on any scale.[7]

Experimental Section

(I) General Procedure for the Syntheses of Methyl 1-*C*-Arylglucoside Tetraacetates 6a−i. A dry, three-necked, round-bottomed flask equipped with a magnetic stirrer and internal temperature probe was charged with aryl bromide (39.6 mmol) under nitrogen gas atmosphere. Dry THF (15 mL) and toluene (60 mL) were added and the resulting solution was cooled with stirring to −78 °C. *n*-BuLi (10 M in hexanes, 4.75 mL) was added, keeping

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(19) The reduction of compound **7e** was studied with varying concentrations of water (0.4, 0.7, 1.0, 1.3, and 1.6 equiv). The conversions for these concentrations were 89%, 97.6%, 97.8%, 92.9%, and 71.5%, respectively, with no change in the β-selectivity.

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the internal temperature <−65 °C. After 1 h at −78 °C, the lithiation reaction was complete by HPLC (an aliquot was quenched into methanol and diluted with acetonitrile for HPLC).

In a second round-bottomed flask, persilylated gluconolactone[9] (47.5 to 55.4 mmol) was stirred in toluene (50 mL) and cooled to −78 °C. The solution of aryl lithium from above was then cannulated into this solution, keeping the internal temperature <−65 °C. After 2 h at −78 °C, the reaction mixture was warmed to −50 °C. A solution of methanesulfonic acid (6 mL, 92.5 mmol) in methanol (100 mL) was added and the mixture was then slowly warmed to room temperature. After18 h, saturated aqueous $NaHCO_3$ was added slowly and the aqueous layer was extracted with EtOAc (2 × 200 mL). The EtOAc extracts were combined with the organic layer, washed with saturated $NaHCO_3$ solution and brine, and dried ($MgSO_4$). The mixture was filtered, and the solvent was removed on a rotary evaporator. The product was dried under pump vacuum to give the methyl glucoside. The crude material was used in the next reaction. DMAP (26 mg, 0.2 mmol), Hunig's base (22 mL, 123 mmol), and acetic anhydride (11 mL, 117 mmol) were added sequentially to a solution of the crude methyl 1-*C*-arylglucoside (∼22 mmol) in toluene (120 mL) under nitrogen atmosphere at ambient temperature. After stirring for 6 h the reaction was complete by HPLC. A 1 N H_3PO_4 solution was added to the reaction mixture to neutralize to pH 6.5−7 and the aqueous layer was extracted further with EtOAc (100 mL). The organic extracts were combined and washed with brine (50 mL), dried ($MgSO_4$), and filtered. The filtrate was evaporated and the product was purified by silica gel column chromatography, using EtOAc/heptane as the eluents. The fractions containing the desired product were combined and concentrated, and the material was dried under vacuum to yield the peracetylated methyl 1-*C*-arylglucosides (**6a**−**i**, ∼70−80% yields based on aryl bromide).

(II) General Procedure for the Reduction of Methyl 1-*C*-Arylglucosides (6a−i) to 7a−i. A solution of methyl glucoside **6** (1.0 mmol) in CH_3CN (5 mL) was prepared at room temperature under nitrogen atmosphere and the water content was adjusted to 1 mol equiv (Karl Fischer analysis) by addition of needed water. The solution was cooled in an ice bath and Et_3SiH (0.5 mL, 3.2 mmol) was added. To this solution was added $BF_3{\cdot}Et_2O$ (0.3 mL, 2.4 mmol) over 5 min, and the mixture was allowed to warm to 15 °C over 20 min. Upon completion, the reaction was quenched with aqueous saturated $NaHCO_3$ (3 mL); the pH of the aqueous layer was 7. The organic layer was washed with brine (5 mL) and the solution was dried ($MgSO_4$). The mixture was filtered and the solvent was evaporated to give the corresponding product **(7a−i)**.

4-(2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranosyl)toluene (7a):[18a] ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.79 (s, 3H), 1.99 (s, 3H), 2.01 (s,3H), 2.07 (s, 3H), 2.31(s, 3H), 3.83 (m,1H), 4.12 (m,1H), 4.26 (dd, *J* = 12.3, 4.9 Hz, 1H), 4.34 (d, *J* = 9.8 Hz, 1H), 5.13 (t, *J* = 9.5 Hz, 1H), 5.21 (t, *J* = 9.6 Hz, 1H), 5.31 (t, *J* = 9.3 Hz, 1H), 7.12 (d, *J* = 8.0 Hz, 2H), 7.21 ppm (d, *J* = 8.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.37, 20.59, 20.62, 20.72, 21.17, 62.33, 68.56, 72.49, 74.26, 75.99, 80.09, 127.03, 129.08, 133.12, 138.63, 168.86, 169.46, 170.33, 170.69 ppm. Compound **7a**: HRMS calcd for $C_{21}H_{26}O_9$ (M + NH_4) 440.1921, found 440.1905.

3-(2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranosyl)toluene (7b):[18a] ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.8 (s, 3 H), 2.00 (s, 3 H), 2.06 (s, 3 H), 2.09 (s, 3 H), 2.34 (s, 3H), 3.81−3.83 (ddd, *J* = 10.0, 4.72, 2.42 Hz, 1 H), 4.16 (dd, *J* = 12.3 and 2.2 Hz, 1 H), 4.3 (dd, *J* = 4.8, 8.5 Hz, 1 H), 4.37 (d, *J* = 9.7 Hz, 1 H), 5.14 (t, *J* = 9.7 Hz, 1 H), 5.23 (t, *J* = 9.7 Hz, 1 H), 5.33 (t, *J* = 9.7 Hz, 1 H), 7.12 (d, *J* = 7.9 Hz, 2 H), 7.16 (s, 1 H), 7.22 (t, *J* = 7.9 Hz, 1 H). ^{13}C NMR (100 MHz, $CDC1_3$) δ ppm 20.4, 20.6, 20.8, 21.4, 62.4, 68.7, 72.6, 74.3, 76.1, 80.3, 124.3, 127.7, 128.3, 129.7, 136.1, 138.1, 166.9, 169.5, 170.4, 170.7. HRMS calcd for $C_{21}H_{26}O_9$ (M+H) = 423.1655, found 423.1673.

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Supporting Information Available: General methods and ^{1}H and ^{13}C NMR are for compounds **6a**−**i**, **7c**−**i**, and **8**. This material is available free of charge via the Internet at http://pubs.acs.org.

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