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C-Arylglucoside synthesis: triisopropylsilane as a selective reagent for the reduction of an anomeric *C*-phenyl ketal

Bruce A. Ellsworth,[a,*] Abigail G. Doyle,[a,†] Manorama Patel,[a] Janet Caceres-Cortes,[b] Wei Meng,[a] Prashant P. Deshpande,[c] Annie Pullockaran[c] and William N. Washburn[a]

[a]*Department of Metabolic Disease Discovery Chemistry, Bristol-Myers Squibb, PO Box 5400, Princeton, NJ 08543, USA*
[b]*Department of Preclinical Candidate Optimization, Bristol-Myers Squibb, PO Box 5400, Princeton, NJ 08543, USA*
[c]*Department of Process Research and Development, Bristol-Myers Squibb, PO Box 5400, Princeton, NJ 08543, USA*

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Abstract—Reduction of tetra-*O*-benzyl-protected 1*C*-phenylglucoside using triethylsilane and $BF_3{\cdot}OEt_2$ has been reported (Czernecki, S.; Ville, G. *J. Org. Chem.* **1989**, *54*, 610–612) to give exclusively 2,3,4,6-tetra-*O*-benzyl-β-1*C*-phenyl-1-deoxyglucoside. We have determined that this reduction actually gives a 4:1 mixture of anomers (β:α). We observed that the selectivity of the reduction is influenced by the steric bulk of the silane. The use of triisopropylsilane as a reducing agent gives >35:1 ratio (β:α) of 2,3,4,6-tetra-*O*-benzyl-β-1*C*-phenyl-1-deoxyglucoside.

1. Introduction

We were interested in a versatile, selective synthesis of β-*C*-aryl glucosides, an important class of natural products.[1,2] Among the many synthetic methods for preparation of β-*C*-arylglucosides,[3,4] we utilized the addition of an aryllithium reagent to an appropriately protected gluconolactone followed by reduction of the intermediary lactol. However, during these gram-scale syntheses of *C*-arylglucosides,[5] a lower level of selectivity was observed than anticipated based on published reports of the silane-mediated reduction of 2,3,4,6-tetra-*O*-benzyl-1*C*-phenylglucoside (Fig. 1, compound **2** R = Ph).[6]

This finding was unexpected since protected gluconolactone is often used as a glycosyl-donor in conjunction with carbon nucleophiles to selectively generate β-*C*-glucosides via the general route outlined in Figure 1.[6–13] Although reductions of the intermediate ketal (structure **2**) generally provide glycosides with the alkyl- or aryl substituents in the β-configuration, Kishi et al. reported that the reduction of alkyl-glycoside **4** proceeded with modest selectivity (Scheme 1). The reduction of hemiketal **4** gave 3:1 ratio of equatorial (β) and axial products (α) with Et_3SiH; whereas, substitution of tri-*n*-propylsilane increased the β:α selectivity to 7:1, demonstrating that these reductions are sensitive to the steric bulk of the reducing agent.[14,15] During the synthesis of *C*-thiazoylglycosides, Dondoni et al. observed that the triethylsilane reduction of ketal **7** generated a 1:1 ratio of equatorial (β) to axial (α) products (Scheme 2). They, too, demonstrated that more sterically demanding

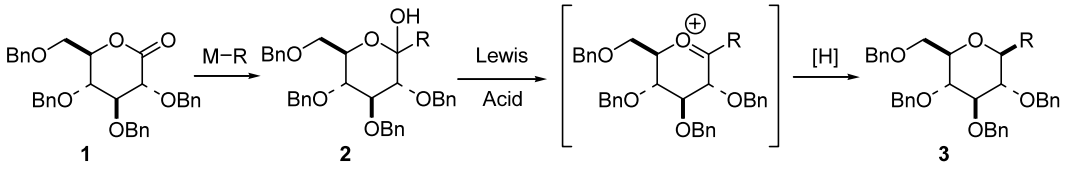

Figure 1. Synthesis of β-*C*-arylglucosides via organometallic addition to gluconolactone.

* Corresponding author. Tel.: 1-609-818-4965; fax: 1-609-818-3460.; e-mail: bruce.ellsworth@bms.com
† Current address: Dept. of Chemistry, Mudd Building Box 151, Stanford University, Stanford, CA 94305-5080, USA

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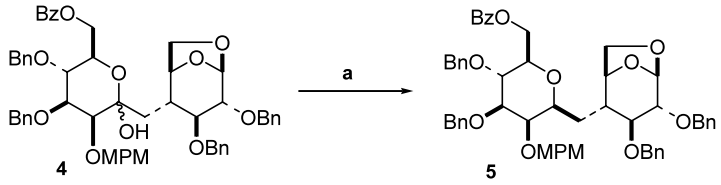
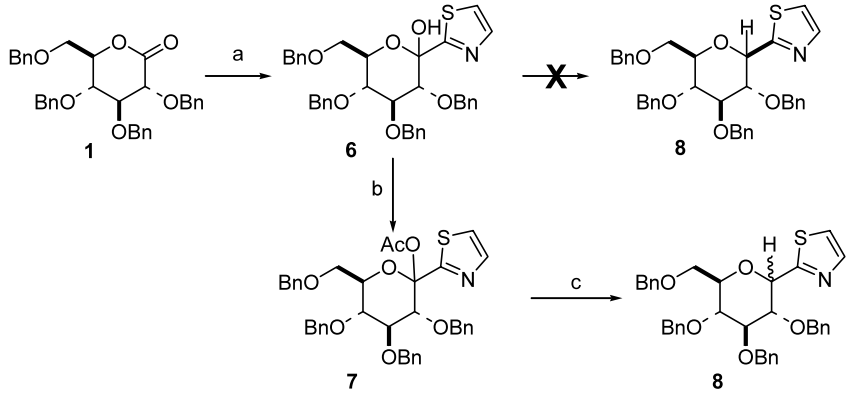


Scheme 1. Synthesis of alkylglycosides. *Reagents*: (a) n-Pr_3SiH, $BF_3{\cdot}OEt_2$, CH_3CN, −20°C gives a 7:1 ratio of **5** (β) to its α-isomer.[14,15]



Scheme 2. Synthesis of 1-*C*-thiazoylglucosides.[16] *Reaction conditions*: (a) 2-lithiothiazole, Et_2O/THF; (b) TEA, CH_2Cl_2, Ac_2O; (c) TMS-OTf (10 equiv.), Et_3SiH, CH_2Cl_2.

reducing agents can influence the outcome, since the substitution of phenyldimethylsilane increased selectivity to 2:1 β:α linked products.[16]

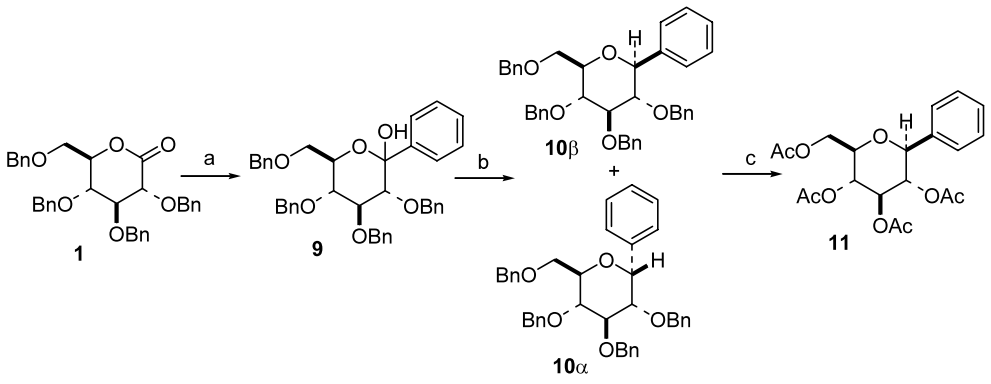
2. Results and discussion

To delineate better the factors controlling the stereochemical course of formation of β-arylglucosides, we investigated the reduction of phenyl ketal **9** (Scheme 3) which was prepared as an undetermined diastereotopic mixture by addition of phenyllithium to 2,3,4,6-tetra-*O*-benzylgluconolactone **1**, as previously reported.[6] Treatment with $BF_3{\cdot}OEt_2$ and Et_3SiH converted ketal **9** in 99% yield to glucoside **10**; however, HPLC analysis in conjunction with LC-MS revealed **10** to be a 4:1 isomeric mixture. When this product mixture was hydrogenated over Pd/C and exhaustively acetylated, following the procedure of Czernecki and Ville,[6] only pure 2,3,4,6-tetra-*O*-acetyl-β-1*C*-phenyl-1-deoxyglucose was obtained. More careful analysis revealed that the minor component was preferentially lost during the hydrogenolysis step, thereby producing the appearance of a completely stereoselective ketal reduction.

Although separation of the mixture **10β,α** was very difficult by silica chromatography, the minor product, upon isolation via semi-preparative reverse-phase HPLC, was determined to be 2,3,4,6-tetra-*O*-benzyl-α-1*C*-phenyl-1-deoxyglucoside **10α**. NOESY experiments confirmed the configuration of the minor product, as **10α**. Selective 1D TOCSY experiments of the product mixture **10** provided further confirmation of the reaction outcome (Fig. 2) via spectra corresponding to the individual α- and β-deoxyglucoside spin systems. In conclusion, reduction of phenylketal **9** with $BF_3{\cdot}OEt_2$ and Et_3SiH unambiguously generates a 4:1 (β:α) mixture of products.

Having established product identity and analytical conditions, the dependence of product composition on the reducing agent was determined. The results, obtained with a set of ten silanes as well as DIBAL, are summarized in Table 1. Yields were essentially invariant (ca. 95%); however, composition ranged from 2:1 to 45:1. The critical factor promoting beta selectivity appears to be the steric bulk surrounding the silyl hydride center. Of all the common, commercially available silane reagents evaluated, the highest beta selectivity (45:1 β:α) was obtained with triisopropylsilane. This ability to dramatically enhance formation of the beta anomer by reduction of 2,3,4,6-tetra-*O*-benzyl-1*C*-arylglucosides provides a practical means to prepare pure β-1*C*-aryl-1-deoxyglucoside on multigram-scale without necessitating difficult chromatographic separations or crystallizations of modestly enriched anomeric mixtures.

We propose that, in the case of *C*-alkyl- and *C*-arylglucosides, the usual anomeric influence on the facial reactivity of oxocarbenium ions is mitigated by substitution. Although we have not probed the electronic- or steric contributions of the aryl-glycoside in depth, comparable selectivity patterns have been obtained using triethylsilane and triisopropylsilane on a large number of C-arylglucoside substrates.[5]

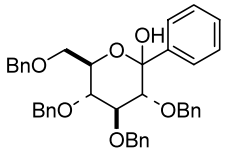


Scheme 3. Synthesis of α- and β-*C*-phenylglucosides. *Reaction conditions*: (a) PhLi 1.8 M in hexanes, THF, −78°C; (b) $BF_3{\cdot}OEt_2$, Et_3SiH, CH_3CN/CH_2Cl_2 (3:1), −40°C; (c) (i) H_2 (atm.), $Pd(OH)_2$, EtOAc, (ii) Ac_2O, pyridine, DMAP, CH_2Cl_2, 0°C.

3. Conclusion

We have discovered that the reduction of 2,3,4,6-tetra-*O*-benzyl-1*C*-phenylglucoside is moderately selective using triethylsilane. The use of triisopropylsilane in the reduction of *C*-arylglucosides gives higher selectivity for β-arylglucoside product, thereby facilitating the isolation and characterization of intermediates toward the synthesis of β-*C*-arylglucosides on multigram scale.

4. Experimental



4.1. 2,3,4,6-Tetra-*O*-benzyl-1*C*-phenylglucose 9

Synthesis according to previous reports.[6] $[\alpha]_D^{25} = +19.5$ (*c* 1.0, $CHCl_3$) ^1H NMR ($CDCl_3$, 400 MHz) δ 7.64 (dd, 2H, $J = 1.6$, 8.3 Hz), 7.41–7.16 (m, 21H), 6.98 (dd, 2H, $J = 1.5$, 5.3 Hz), 4.94–4.86 (m, 3H), 4.65 (d, 2H, 9.0 Hz), 4.55 (d, 1H, $J = 12.3$ Hz), 4.39 (d, 1H, 10.1 Hz), 4.18 (ddd, 1H, $J = 1.7$, 6.1, 10.1 Hz), 4.08 (t, 1H, $J = 9.2$ Hz), 3.88–3.83 (m, 2H), 3.80 (d, 1H, 10.5 Hz), 3.73 (dd, 1H, $J = 1.7$, 11.0 Hz), 3.07 (s, 1H) ^{13}C ($CDCl_3$, 100 MHz) δ 142.2, 138.8, 138.7, 138.3, 137.2, 128.6, 128.4, 128.2, 127.9, 127.7, 127.6, 126.1, 97.9, 85.1, 83.4, 78.3, 75.7, 75.5, 73.3, 72.1, 69.0.

Anal. calcd for $C_{40}H_{40}O_6$ theoretical: C, 77.89; H, 6.53 observed: C, 77.67; H, 6.50

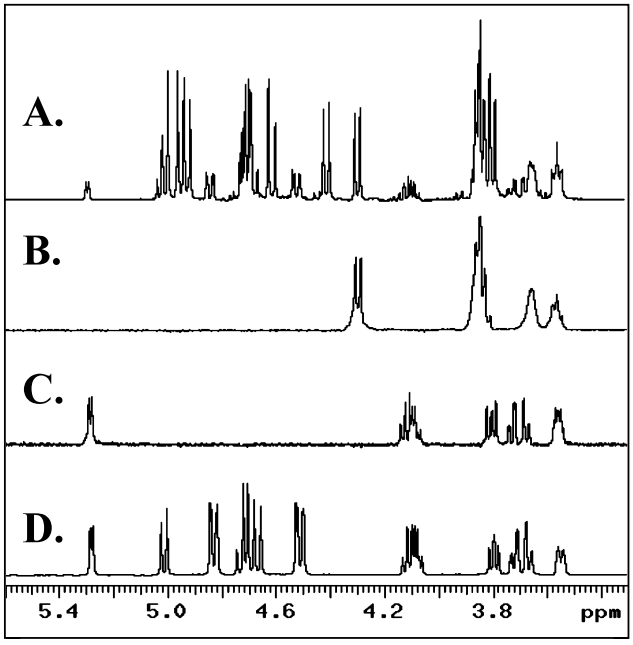


Figure 2. NMR spectra of the reduction product mixture and purified phenyldeoxyglucoside **10**; **A.** Proton spectra of the product mixture containing both α and β deoxyglucosides **10**; **B.** and **C.** 1D-TOCSY spectra of **10β** and **10α** deoxyglucoside, respectively, upon selective excitation of the anomeric proton; **D.** Proton spectra of the purified α-deoxyglucoside. Note: Benzylic protons are visible in spectra A and D, whereas selective excitation does not reveal these proton signals in spectra B and C.

4.2. General procedure for ketal reductions

To a cooled (−40°C) solution of 2,3,4,6-tetra-*O*-benzyl-1*C*-phenylglucose (0.1 mmol) and silane (2 equiv.) in

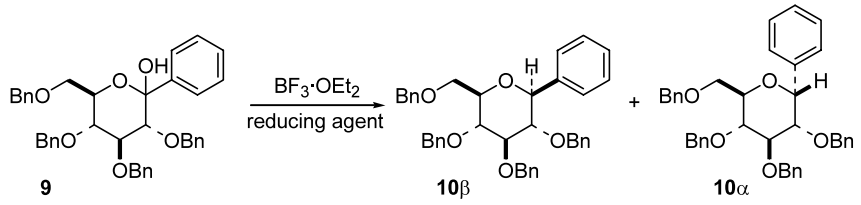
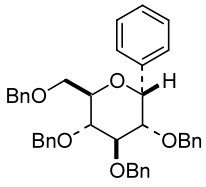


Table 1. Results of the reduction of ketal **9** to deoxyglucoside **10** (Scheme 3)

Silane	Ratio (β-α)
$PhSiH_3$	2:1
n-Pr_3SiH	3:1
Me_2PhSiH	4:1
Et_3SiH	4:1
$(Me_3Si)_3SiH$	4:1
i-Bu_3SiH	7:1
Ph_3SiH	16:1
t-$BuMe_2SiH$	24:1
DIBAL	25:1
i-Pr_3SiH	45:1

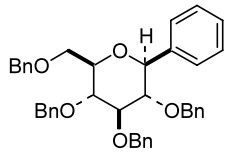
acetonitrile/CH_2Cl_2 (3:1) was added $BF_3{\cdot}OEt_2$. Upon stirring for 1 h at –40°C, an aliquot was removed for HPLC analysis of reaction progress. When the reduction was complete, the solution was stirred at room temp. for 30 min with 1 mL of saturated aqueous potassium carbonate. The solution was extracted twice with 50 mL of ethyl acetate. The combined organic layers were washed with 50 mL of brine, dried over $MgSO_4$ and evaporated to give the product as an oil. HPLC analysis was performed at 1 mg/mL in methanol. Column: YMC S-3 ODS (C-18) 6.0×150 mm. Solvent program: 100% solvent B (isocratic). Solvent B: 90% methanol/water+0.2% H_3PO_4. Flow rate: 1.5 mL/min. Monochrome detection at 220 nm. Retention time: α isomer **10α** 7.0 min, β isomer **10β** 7.5 min. Product ratios (Table 1) are reported as the average of duplicate reductions.

4.3. (1*R*)-2,3,4,6-Tetra-*O*-benzyl-1*C*-phenyl-1-deoxyglucose 10α



$[\alpha]_D^{25} = +95.5$ (c 0.02, $CHCl_3$) ^1H NMR ($CDCl_3$, 400 MHz) δ 7.74 (d, 2H, $J=7.8$ Hz), 7.35–7.22 (m, 21H), 7.11–7.09 (m, 2H), 5.24 (d, 1H, $J=5.2$ Hz, H_1), 4.97 (app. d, 1H, $J=11.1$ Hz), 4.80 (d, 1H, $J=2.0$ Hz), 4.77 (d, 1H, $J=1.7$ Hz), 4.70–4.61 (m, 3H), 4.48 (m, 2H), 4.10–4.01 (m, 2H, H-2+H-3), 3.77–3.73 (m, 1H, H-4), 3.70–3.61 (m, 2H, H-6+H-6′), 3.53–3.49 (m, 1H, H-5). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 138.6, 138.2, 138.1, 138.0, 137.8, 128.3, 128.0, 127.9, 127.8, 127.7, 127.6, 127.4, 82.0, 81.3, 78.3 (C-4), 75.0, 74.7, 73.6, 73.4 (C-1), 73.1, 72.3 (C-5), 69.0 (C-6) Anal. calcd for $C_{40}H_{40}O_5$ HRMS [M+NH4] 618.3219, found m/z 618.3240.

4.4. (1*S*)-2,3,4,6-Tetra-*O*-benzyl-1*C*-phenyl-1-deoxyglucose 10β



$[\alpha]_D^{25} = +11.1$ (c 0.38, $CHCl_3$) ^1H NMR ($CDCl_3$, 400 MHz), δ 7.52–7.14 (m, 23H), 6.93–6.91 (m, 2H), 4.98–4.86 (m, 3H), 4.68–4.55 (m, 3H), 4.36 (d, 1H, $J=10.1$ Hz), 4.25 (d, 1H, $J=9.3$ Hz, H-1), 3.82–3.73 (m, 5H), 3.61–3.60 (m, 1H), 3.55–3.50 (m, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 139.0, 138.7, 138.4, 138.2, 137.6, 128.4, 128.3, 128.2, 128.0, 127.7, 86.7, 84.4, 81.7, 79.3, 78.3, 75.6, 75.1, 74.9, 73.4, 69.1. Anal. calcd for $C_{40}H_{40}O_5$ theoretical: C, 79.97; H, 6.71, found: C, 79.80; H, 6.82.

4.5. NMR characterization 10α, 10β

Proton and TOCSY-1D experiments were collected on a Varian INOVA 500 MHz spectrometer in $CDCl_3$ at 25°C. Proton spectra were acquired with 6.6 μs pulse at 55dB, 1s relation delay, 16 transients, 16384 complex points and 5204.94 Hz spectral width. TOCSY-1D experiments were acquired with 6.6 μs pulse at 55dB, 1.5 s relaxation delay, 512 transients, 16384 complex points, 5204.94 Hz spectral width, MLEV spin lock mixing array between 0 and 195 ms in 15 ms increments, selective 180° shaped pulse for anomeric protons as follows: α at 5.28ppm, 127.2 ms at –7 dB and β at 4.29ppm, 134.4 ms at –7 dB.

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