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Stereodirected Synthesis of Aryl α-*C*-Glycosides from 2-*O*-Arylsilyl-glucopyranosides

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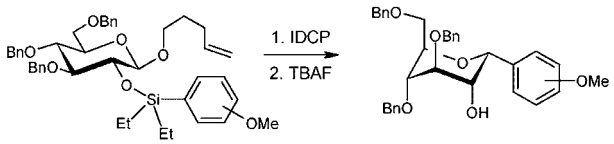
ABSTRACT



An efficient procedure for the stereoselective synthesis of aryl α-*C*-glycosides is presented. The key step of the method is the intramolecular delivery of the aryl group from a 2-*O*-aryldialkylsilyl substituent to the anomeric carbon by an electrophilic *ipso*-desilylation; this process leads exclusively to the product having the 1,2-cis configuration.

The *C*-aryl glycosidic linkage is found in a variety of natural products, many of which exhibit useful biological activities (e.g., *C*-glycosyl flavonoids, antibiotics of the gilvocarcin family, the pluramycins, etc).[1−3] In most of these structures, in particular those carrying a common hexopyranoid unit, the pseudoglycosidic linkage is in the thermodynamically more favorable β-configuration: for example, with two exceptions,[4,5] all of the numerous *C*-glycosyl flavonoids that have been isolated have a β-C-glycosidic linkage.[5] Also, the synthetic procedures developed for the C-arylation of activated hexopyranose derivatives,[6−8] by Friedel−Crafts-type processes or by reactions with arylmetals, have generally led predominantly or exclusively to β-C-glycosylated aromatic compounds. In fact, procedures yielding only the α-epimers are very rare:[9] in these methods, the stereoselectivity depends strongly on the nature of the aglycone and on the conditions of the reaction, and the selectivity is not easily rationalized, which makes them unpredictable. One notable exception is the intramolecular 1,2-cis-C-glycosylation of 2-O-benzylated glycosides, a method originally developed in our laboratory in the furanose series[10] and extended to a glucopyranose derivative.[11]

To generalize the intramolecular C-arylation procedure and make it a reliable synthesis of α-*C*-aryl glucopyranosides, we have investigated a wide variety of tethers between O-2 and an aromatic group in order to achieve an intramolecular delivery of the aromatic aglycone ("IAD"-type process)[12]

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(Figure 1). We wish to report here the most significant results of this investigation.

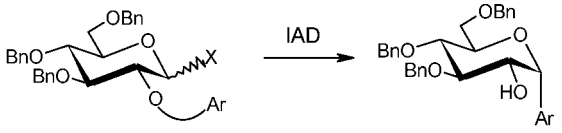
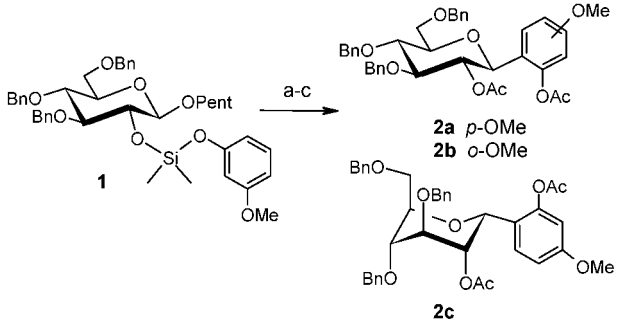


Figure 1. Intramolecular aromatic aglycone delivery.

Prompted by successful internal reactions of 4-pentenyl β-glucopyranosides carrying various benzyl groups at O-2,[13] we have performed our investigations using a 4-pentenyl group as a convenient latent activator of the anomeric position.[14]

In our first plan, we envisaged the utilization of a silaketal linker between the glycoside O-2 position and a phenolic function of the aromatic aglycone. The aryloxysilyl group might in fact react either by transferring the *O*-aryl group to C-1 (intramolecular *O*-glycoside formation[12]) or by undergoing the alkylation of the electron-rich aglycone. Remarkably, the silaketal **1** led, upon reaction with iodonium dicollidine perchlorate (IDCP) followed by complete desilyation of the resulting products, to *C*-aryl glycosides only. These products were, however, obtained as a mixture of α- and β-epimers and of regioisomers, with predominance of the β-anomers (Scheme 1).

Scheme 1[a]



[a] Conditions: (a) IDCP (2 equiv), CH_2Cl_2; (b) Bu_4NF, THF; (c) Ac_2O, pyridine. Yield = 39% (three steps). Ratio of **2a**:**2b**:**2c** = 2:2:1.

In view of these results, we sought to shorten the tether and decided to use an arylsilyl group as the source of the aromatic aglycone by way of an *ipso* electrophilic substitution process. We have already reported a series of C-glycosylations in the furanose series that are believed to occur by way of this process,[15] and an example of phenyl group migration from silicon to carbon by this type of reaction has recently been described.[16] This method is expected to provide stereocontrol of the aglycone transfer since the intramolecular substitution must occur by way of a five-membered cyclic intermediate (Figure 2) and should thus lead to a 1,2-*cis*-*C*-aryl glycoside (an α-*C*-glycoside in the *gluco* series).

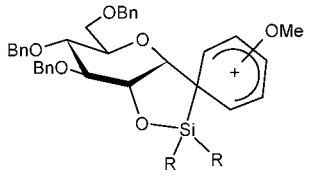
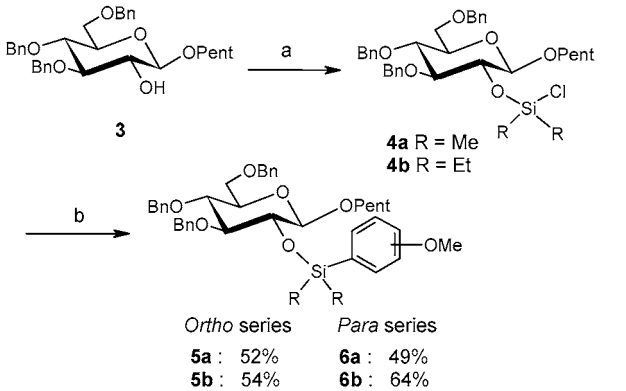


Figure 2. σ-Complex of the *ipso* substitution.

Preliminary studies with the 2-*O*-(*p*-tolyldimethylsilyl) derivative of **3**, prepared by silylation of **3** with commercial *p*TolSiMe$_2$Cl, were unsuccessful. As silylating reagents carrying an activated aromatic group were not commercially available, we elected to create the aryldialkylsilyl substituent directly onto the glucopyranoside scaffold.

For this purpose, the required precursor, namely, the partially protected 4-pentenyl β-D-glucopyranoside **3**, was prepared in three steps and in an overall yield of 59% from tetra-*O*-acetyl-α-D-glucopyranosyl bromide as described previously.[13] Compound **3** was treated with butyllithium at -78 °C and then with an excess of the corresponding dichlorodialkylsilane (alkyl = methyl or ethyl) in THF (Scheme 2); the product thus formed was freed from excess

Scheme 2[a]



[a] Conditions: (a) (i) BuLi (1.1 equiv), THF, -78 °C; (ii) R_2SiCl_2 (b) ArLi, THF, $-78 \rightarrow 0$ °C.

silylating agent and solvent by evaporation in vacuo. The resulting crude 2-*O*-chlorodialkylsilyl derivatives **4** were then

(12) *O*-Glycoside formation by IAD: Jung, K.-H.; Müller, M.; Schmidt, R. R. *Chem. Rev.* **2000**, *100*, 4423−4442. *C*-Glycoside formation by IAD via silicon tether: Bols, M.; Skrydstrup, T. *Chem. Rev.* **1995**, *95*, 1253−1277.

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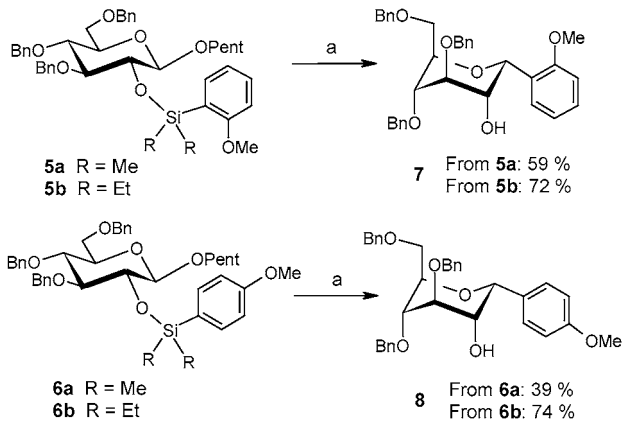
reacted with the aryllithium derived from *ortho*- or *para*-bromoanisole. The 2-*O*-arylsilyl derivatives of **3**, compounds **5** (ortho series) and **6** (para series) were sufficiently stable to be purified by flash chromatography on silica gel and could be isolated in yields ranging from 50 to 65%.

Treatment of compounds **5** and **6** with IDCP in dichloromethane followed by complete desilylation[17] using TBAF in THF gave the internal C-arylation products **7** and **8** in good to excellent yields[18] (Scheme 3). As shown by NMR

Scheme 3[a]



[a] Conditions. (a) (i) IDCP (2 equiv), CH_2Cl_2; (ii) Bu_4NF, THF.

data (see below), the products are obtained exclusively as the α-anomer. Overall, the yields of the reactions were higher and the operations somewhat more convenient using the diethylsilyl linker compared to the dimethylsilyl linker.

The complete 1,2-cis stereoselectivity of the reaction and its complete regioselectivity with respect to the aglycone substitution is strong evidence that the reaction occurs by way of an internal substitution of the Ar−Si bond by the electrophilic anomeric carbon generated upon activation of the pentenyl group with IDCP (intermediate shown in Figure 2). Alternate mechanisms involving preliminary cleavage of the aromatic group or arylsilyl group and intermolecular arylation are highly unlikely.

To facilitate the structural analysis of the final products, compounds **7** and **8** were acetylated to afford **9** and **10**, respectively; **7** and **8** were also debenzylated by hydrogenolysis (H_2/Pd) and acetylated to give **11** and **12** (Figure 3).

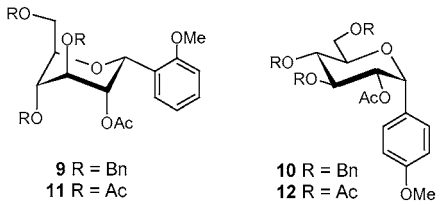


Figure 3. Acetylated derivatives.

According to ^{1}H NMR data,[19] it is evident that the pyranose ring in the ortho-disubstituted *C*-aryl glycoside derivatives **9** and **11** adopts a conformation remote from the $^4C_1$ conformation characteristic of the *β*-anomer. The magnitude of the $^3J_{H,H}$ coupling constants indicates that these compounds exist in a flexible conformation or as an equilibrium between the $^1C_4$ and $^4C_1$ chair forms. In the para-disubstituted derivatives, the ring adopts a conformation closer to the $^4C_1$ conformation with a nearly axial aryl group, in particular in the peracetate **12**. Studies concerning the conformation of α-*C*-aryl glycosides have been very lim-

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(17) The nature of the silylated species formed in the reaction and isolated before treatment with TBAF could not be identified.

(18) **Typical Experimental Procedure: Formation of the Arylsilyl Group.** Compound **3** (220 mg, 0.38 mmol) was stirred in dry THF (3 mL) at −78 °C under argon. Butyllithium (312 μL, 1.36 M in hexane, 0.42 mmol) was added, and the mixture was stirred for 30 min at −78 °C before the addition of *freshly distilled* dichlorodiethylsilane (288 μL, 1.93 mmol). Stirring was continued at room temperature over a period of 2 h. The solvent and excess silane were then evaporated in vacuo. Butyllithium (709 μL, 1.36 M in hexane, 0.96 mmol) was added to a solution of *para*-bromoanisole (216 mg, 3 equiv) in dry THF (3 mL) at −78 °C under argon, and the mixture was stirred for 45 min at −78 °C. The crude chlorosilylated sugar derivative was dissolved in dry THF (1 mL), and this solution was added to the solution of aryllithium. The mixture was stirred for 10 min at −78 °C and then warmed to room temperature. When the reaction was complete (TLC), the solvent was evaporated; ethyl acetate (20 mL) was added, and the organic phase was washed with saturated aqueous $NaHCO_3$. The organic phase was dried over $MgSO_4$, and the solvent was removed in vacuo. Flash chromatography (silica gel, eluent petroleum ether/AcOEt 9:1) provided the desired product **6b** (175 mg, 64%). ***C*-Arylation.** A solution of 2-*O*-arylsilyl sugar derivative **6b** (118 mg, 0.17 mmol) in dry CH_2Cl_2 (15 mL) was stirred in the presence of 4 Å molecular sieves. After 1 h, IDCP (iodonium dicollidine perchlorate) (154 mg, 2 equiv) was added and the mixture was stirred in the dark at room temperature for 4 h. The solids were removed by filtration, and the organic phase was successively washed with 10% aqueous $Na_2S_2O_4$, 1 N HCl, and saturated aqueous $NaHCO_3$. The organic layer was dried over $MgSO_4$ and the solvent removed in vacuo. Bu_4NF (90 mg, 2 equiv) was added to a solution of the residue in THF (15 mL) at 0 °C. After 2 h, the solvent was removed in vacuo. Flash chromatography (silica gel, eluent petroleum ether/AcOEt 7:1) provided the desired product **8** (69 mg, 74%).

(19) **Compound 9:** selected ^{1}H NMR data (250 MHz, $CDCl_3$) δ 3.76−3.88 (m, 6H, H-4,6a,6b, OCH_3), 3.92 (d, 1H, J = 3.1, 4.7 Hz, H-3), 4.20 (m, 1H, J = 4.7, 4.7, 6.6 Hz, H-5), 5.42 (t, 1H, J = 2.8 Hz, H-2), 5.52 (d, 1H, $J_{1,2}$ = 2.0 Hz, H-1). **Compound 10:** selected ^{1}H NMR data (250 MHz, $CDCl_3$) δ 3.65−3.85 (m, 7H, H-4,5,6a,6b, OCH_3), 4.05 (t, 1H, J = 6.7 Hz, H-3), 5.20 (d, 1H, $J_{1,2}$ = 4.7 Hz, H-1), 5.26 (dd, 1H, J = 4.7, 6.9 Hz, H-2). **Compound 11:** syrup; $[\alpha]_D^{23}$+24.7 (c = 1.0, $CHCl_3$); ^{1}H NMR (250 MHz, C_6D_6; ref δ = 7.16) δ 1.44, 1.62, 1.63, 1.68 (4s, 4 × 3H, 4 $COCH_3$), 3.30 (s, 3H, OCH_3), 4.34 (dd, 1H, $J_{5,6a}$ = 4.0, $J_{6a,6b}$ = 11.6 Hz, H-6a), 4.47 (q, 1H, $J \approx$ 4 Hz, H-5), 4.61 (dd, 1H, $J_{5,6b}$ = 6.1 Hz, H-6b), 5.47 (t, 1H, $J \approx$ 5.6 Hz, H-4), 5.76 (t, 1H, $J \approx$ 4.7 Hz, H-3), 5.89 (t, 1H, $J \approx$ 3.5 Hz, H-2), 5.94 (d, 1H, $J_{1\ 2}$ = 2.9 Hz, H-1), 6.56 (d, 1H, J = 8.3 Hz, H-3′), 7.0 and 7.17 (2t, 2H, J = 7−8 Hz, H-4′,5′), 7.95 (d, 1H, J = 7.6 Hz, H-6′); ^{13}C NMR (62.9 MHz, C_6D_6) δ 20.04, 20.24, 20.30 ($COCH_3$), 55.1 (OCH_3), 62.06 (C-6), 67.78, 67.95, 69.66, 71.10, 73.10 (C-1−5), 110.48, 120.36, 125.7, 129.10 (CH_{Ar}), ∼128 (C_{Ar}), 156.62 (C_{Ar}−OMe), 168.8−170 (C═O). Compound **12**: mp 104−105 °C; $[\alpha]_D^{23}$ +86.5 (c = 1.1, $CHCl_3$); ^{1}H NMR (250 MHz, C_6D_6; ref δ = 7.16) δ 1.53, 1.63, 1.69 and 1.74 (4s, 4 × 3H, 4 $COCH_3$), 3.27 (s, 3H, OCH_3), 3.85 (ddd, 1H, $J_{4,5}$ = 8.6, $J_{5,6a}$ = 2.9, $J_{5,6b}$ = 5.1 Hz, H-5), 4.08 (dd, 1H, $J_{6a,6b}$ = 12.2 Hz, H-6a), 4.31 (dd, 1H, H-6b), 5.37 (d, 1H, $J_{1,2}$ = 6 Hz, H-1), 5.39 (t, 1H, J = 8.8 Hz, H-4), 5.55 (dd, 1H, $J_{1,2}$ = 5.3, $J_{2,3}$ = 8.4 Hz, H-2), 5.97 (t, 1H, J = 8.2 Hz, H-3), 6.71 (d, 2H, J = 8.8 Hz, H-2′,6′), 7.51 (d, 2H, H-3′,5′); ^{13}C NMR (62.9 MHz, C_6D_6) δ 20.14, 20.23, 20.29, 20.36 (4 × $COCH_3$), 54.79 (OCH_3), 62.09 (C-6), 69.22 (C-4), 70.68 (C-5), 71.17 (C-3), 71.57 (C-2), 73.29 (C-1), 114.27 (CH_{Ar}), 128.19 (Cq_{Ar}), 129.93 (CH_{Ar}), 159.95 (C_{Ar}−OMe), 169.09, 169.29, 169.82, 170.03 (C═O).

ited: simple α-*C*-glucopyranosyl benzene derivatives were shown to be characterized by a solvent-dependent conformational equilibrium in which the $^4C_1$ form was predominant.[20]

In conclusion, the intramolecular reactions of 4-pentenyl 2-*O*-arylsilyl glucopyranosides promoted by a mild Lewis acid provided a convenient and completely stereoselective approach to α-*C*-aryl glucosides. This process provides the first reliable and generalizable method of synthesis of the challenging α-epimers of the *C*-aryl glycoside family. It is also the first example of a "traceless" intramolecular delivery of an aromatic aglycone to form a *C*-aryl glycoside. The application of this methodology to more complex aromatic aglycones and its extension to mannopyranoside substrates, with the goal of achieving exclusive *β*-selectivity, are under investigation in our laboratory and will be reported in due course.

Supporting Information Available: Spectral data for compounds **2c**, **5b**, **6b**, and **9**−**12**. This material is available free of charge via the Internet at http://pubs.acs.org.

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