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HYDROBORATION OF C-ARYLGLUCALS. SYNTHESIS OF THE β-C-ARYLGLUCOSIDE NUCLEUS OF CHAETIACANDIN

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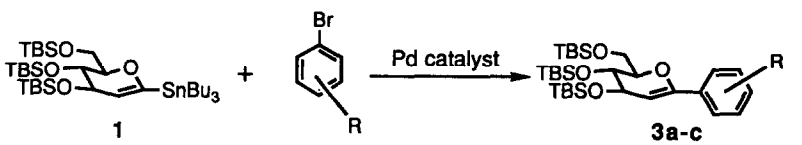
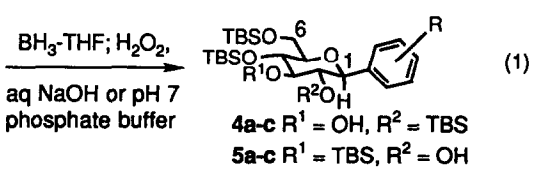
Abstract: The hydroborations of the C-arylglucals **3a-c** obtained from palladium catalyzed coupling reactions, provide the corresponding β-C-arylglucosides. Depending upon the conditions chosen for the oxidative workup, either the alcohols **5a-c** or the products resulting from silyl migration (**4a-c**) are readily obtained. The palladium catalyzed coupling-hydroboration sequence has been applied to the synthesis of the β-C-arylglucoside nucleus of chaetiacandin, an anti-yeast antibiotic of the papulacandin family.

The synthesis of C-arylglycosides[1] has recently become an active area of research due to the antibiotic and antitumor activity that is exhibited by many of these carbohydrate derivatives. The stereoselective formation of the unique C-C bond that directly links the carbohydrate residue and the aromatic moiety has been the primary focus in the preparation of the C-arylglycosides.[2]

We have recently reported that C-arylglucals **3** are readily accessible by the palladium catalyzed coupling of 3,4,6-tri-*O*-(tert-butyldimethylsilyl)-1-tributylstannyl-D-glucal **1** and aryl bromides **2** (eq 1).[3] In order to be useful as a general method for the synthesis of naturally occurring C-arylglycosides, it was imperative that we demonstrate that the double bond present in **3** could be utilized for the stereoselective introduction of appropriate C1 and C2 substituents. Herein, we report that the hydrations (via hydroboration-oxidation) of three representative C-arylglucals **3a-c** provide the corresponding β-C-arylglucosides (eq 1), a structural framework found in a variety of C-aryglycoside natural products.[1] Depending upon the conditions chosen for the oxidative workup, either the alcohols **5a-c** or the products resulting from silyl migration (**4a-c**) are readily available.





(1)

Thus, THF solutions of the C-arylglucals **3a-c** were treated with BH_3-THF[5] as described in Table I. When tlc analysis indicated the complete consumption of starting material, the reaction mixtures were oxidized with

H_2O_2 in the presence of aqueous NaOH or pH 7 phosphate buffer, and the alcohols **4a-c** or **5a-c** were isolated in the yields indicated. From the results summarized in Table I, several points are noteworthy.

Qualitatively, the rate of hydroboration was dependant upon the nature of the aromatic substituent, with electron rich aromatics (**3a** and **3b**) reacting faster than electron poor materials (**3c**). The subsequent oxidation step was uniformly slow in all of the cases studied, irrespective of the choice of oxidation method A or B (Table I). Optimum results for the oxidation were obtained only after prolonged reaction times at room temperature (up to 48h) or somewhat shorter times at reflux. The differences in the isolated yields of the β-C-phenylglucosides **4a** and **5a** due to this reaction parameter are reflected in Entries 1-4.

Table I. Hydroboration of C-Arylglucals 3a-c

Entry	Substrate	Time[a]	Oxidation Conditions[b]	Product (Yield, %)[c]
1	**3a**	8h	A (8h)	**4a** (44)
2	**3a**	7h	A (21h)	**4a** (69)[d]
3	**3a**	8.5h	B (21h)	**5a** (29)
4	**3a**	8h	B (24h)[e]	**5a** (44)
5	**3b**	6h	A (22h)	**4b** (65)
6	**3b**	6h	B (48h)	**5b** (82)
7	**3c**	24h	A (48h)	**4c** (71)
8	**3c**	24h	B (48h)	**5c** (64)[d]

[a]Hydroborations carried out using 2.5 eq of BH_3-THF at 0°C for the indicated time, followed by 30 min at room temperature. [b]Oxidations (A = H_2O_2, aq NaOH; B = H_2O_2, pH 7 phosphate buffer) carried out at room temperature for the indicated time. [c]Yield of isolated, chromatographically purified material. These materials were characterized by ^1H and ^{13}C NMR, IR, high resolution mass spec and/or elemental analysis. [d]A small amount of the α-C-arylmannoside was isolated and identified. [e]Oxidation conducted at reflux temperature.

The reaction mixtures are reasonably clean, providing in all cases one major component that was assigned as the corresponding β-C-arylglucoside (vide infra). These materials arise from the expected[6] regio- and stereoselective attack of BH_3-THF on the α-face of **3a-c**. Minor components resulting from β-face approach (α-C-arylmannosides) were isolated in only two cases (Entries 2 and 8) although they may have been present in small amounts in the other reaction mixtures.

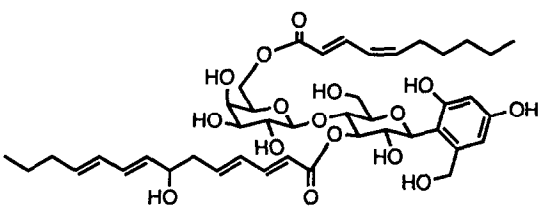
Perhaps the most interesting feature of the reaction is the surprising propensity of the silyl protecting group (TBS) on the C3 hydroxyl to migrate to the newly introduced C2 oxygen atom under basic oxidizing conditions (Entries 1, 2, 5, 7). This facile rearrangement to provide **4a-c** appears to be quantitative. Presumably, the silyl migration takes place via the intermediate C2 alkoxide and generates the more thermodynamically stable C3 alkoxide via a 1,4-O to O silyl rearrangement.[7,8] In contrast, none of the rearranged products **4a-c** are produced

under buffered oxidizing conditions. In these cases, the products are the expected β-C-arylglucosides **5a-c** (Entries 3, 4, 6, 8).

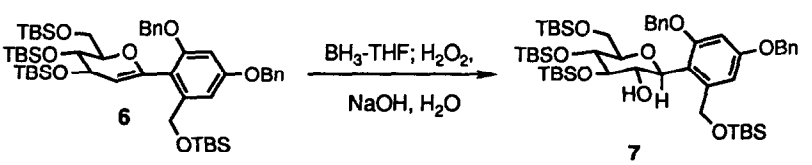
The configurations of the two newly introduced stereocenters at C1 and C2, and the location of the labile TBS group (C2 or C3 hydroxyl), were established by ^{1}H NMR spectroscopy. For example, decoupling of the H1 doublet (δ 4.05, J = 8.9 Hz) in the spectrum of **4a** ($CDCl_3$) simplified the H2 resonance at δ 3.40 (t, J = 8.9 Hz) to a doublet. The magnitude of the coupling constants[9] revealed the mutual trans-diaxial relationships of H1-H2 and H2-H3 and secured the assignment of the gluco configuration. Irradiation of the hydroxyl proton resonance (δ 2.04, d, J = 3.1 Hz) resulted in a collapse of the H3 resonance (δ 3.51, dt, J = 3.1, 8.9 Hz) to a triplet, confirming C3 as the site of the free hydroxyl moiety. In a similar manner, the free hydroxyl in **5a** was placed at C2 since the pyran proton (δ 3.41, dt, J = 8.9, 5.8 Hz) that is coupled to the hydroxylic proton simplified upon irradiation of the H1 doublet (δ 4.20, J = 8.9 Hz). The analyses described above for **4a** and **5a** were uniformly successful in establishing the identities of **4b,c** and **5b,c**.[10]

With the structural assignments in hand, a useful *a priori* method for specifying the location of the TBS protecting group (C2 or C3 hydroxyl) could be deduced by inspection of the chemical shifts of the TBS methyl resonances in the ^{1}H NMR spectra of **4a-c** and **5a-c** ($CDCl_3$). One methyl singlet was observed between δ -0.65 ppm and δ -0.74 ppm in each of the spectra of **4a-c**, whereas the furthest upfield resonance for any methyl group in **5a-c** was observed at δ -0.02 ppm. The proximity of the TBS group, located at C2 in **4a-c**, to the shielding cone of the aromatic moiety at C1 is apparently responsible for this dramatic upfield shift.

We have utilized the palladium catalyzed coupling-hydroboration sequence in the synthesis of the β-C-arylglucoside nucleus of chaetiacandin, an anti-yeast antibiotic of the papulacandin family.[4] Hydroboration of **6**, an intermediate similar to that employed by us in the synthesis of the papulacandin tricyclic spiroketal nucleus,[11] provided **7** in 70% yield. It is interesting to note that in this case, basic oxidative workup conditions did not result in migration of the silyl protecting group from the C3 to the C2 hydroxyl. Presumably, this result is due to the severely sterically encumbered environment imparted to the C2 hydroxyl by the highly substituted aromatic at C1. The derived C-arylglycoside was shown to possess the β-gluco configuration of the chaetiacandin nucleus by the



Chaetiacandin



observation of the H1 (δ 4.71, d, J = 10.0 Hz) and H2 (δ 3.73, dd, J = 9.1, 10.0 Hz) resonances in the ^{1}H NMR spectrum (CD_3OD) of the fully deprotected material.

Thus, we have demonstrated that the hydroborations of the C-arylglucals **3** and **6** readily provide the β-C-arylglucosides **4** or **5** and **7**, establishing the viability of this protocol for the preparation of this important class of natural products. The ablility to choose the placement of the labile TBS group (C2 or C3) should prove to be useful for the preparation of differentially substituted C-arylglycosides. Further work is underway to extend this methodology in order to access other C-arylglycoside structural types.

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    5b: δ 2.11 (d, 1H, OH, J = 6.2 Hz), 3.45 (m, 1H, H2), 4.85 (d, 1H, H1, J = 9.2 Hz).
    4c: δ 2.09 (d, 1H, OH, J = 3.2 Hz), 3.56 (dt, 1H, H3, J = 3.2, 8.9 Hz), 4.22 (d, 1H, H1, J = 8.9 Hz).
    5c: δ 2.08 (d, 1H, OH, J = 7.2 Hz), 3.38 (ddd, 1H, H2, J = 5.5, 7.2, 8.5 Hz), 4.39 (d, 1H, H1, J = 8.5 Hz)
11. Presented by R.W. Friesen and C.F. Sturino at the 73rd Canadian Chemical Conference, Halifax, Nova Scotia, Canada, July 15-20, 1990. Abstract No. 892 OR-G15.

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