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Efficient Route to 2-Deoxy β-*O*-Aryl-D-Glycosides via Direct Displacement of Glycosyl Iodides

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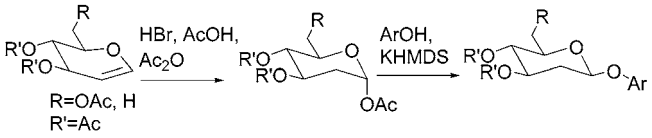
ABSTRACT

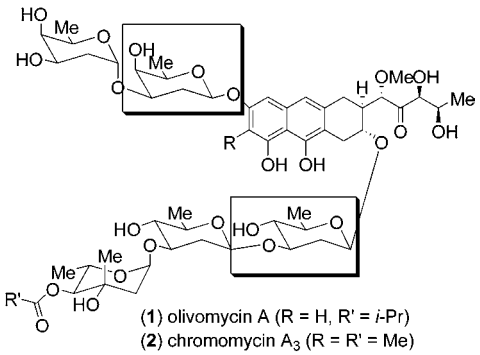


The conversion of glycals to 2-deoxy glycosyl acetates followed by reaction with trimethylsilyl iodide affords the corresponding glycosyl iodides, which readily undergo substitution with aryl alkoxy anions to provide 2-deoxy-β-*O*-aryl glycosides. Direct displacement of the anomeric iodide alleviates the need to introduce temporary C-2 stereodirecting groups that require subsequent removal. The only observable byproducts from the glycosylations result from elimination of HI giving the starting glycals, which can be recycled through the reaction sequence.

Deoxygenated carbohydrates are major structural components of numerous natural products possessing important biological properties.[1] For example, 2,6-dideoxy hexopyranoses are common structural units of olivomycin (**1**) and chromomycin (**2**) antitumor antibiotics (Figure 1). These compounds are of interest not only due to their biological profiles but also because of the synthetic challenges they present. With a methylene at C-2, there is no apparent functionalizable handle with which to direct glycosylation.

Two general strategies for entry into 2-deoxy glycosides have been pursued.[2] Most commonly, a directing group is temporarily introduced at C-2, the acceptor is then incorporated, and in a third step the C-2 substituent is exchanged with hydrogen (Figure 2).[3] Removal of the C-2 directing group often requires toxic reagents, which introduce impurities that are difficult to remove. Moreover, this approach involves additional steps that can be avoided with direct addition strategies (vide infra).[4]

Falck and co-workers have employed triphenylphosphine-hydrogen bromide (TPHB) as a soft catalyst to promote direct addition of various acceptors to glycals.[5] These methodologies successfully circumvent Ferrier rearrangement and



(**1**) olivomycin A (R = H, R' = *i*-Pr)
(**2**) chromomycin A_3 (R = R' = Me)

Figure 1.

(1) (a) Kirsching, A.; Bechthold, A. F.-W.; Rohr, J. *Top. Curr. Chem.* **1997**, *188*, 1. (b)Weymouth-Wilson, A. C. *Nat. Prod. Rep.* **1997**, *14*, 99.
(2) (a) Veyrieres, A. *Carbohydr. Chem. Biol.* **2000**, *1*, 367. (b) Franck, R.; Marzabadi, C. *Tetrahedron* **2000**, *56*, 8385.
(3) (a) Takiura, K.; Honda, S. *Carbohydr. Res.* **1972**, *23*, 369. (b) Monneret, C.; Choay, P. *Carbohydr. Res.* **1981**, *96*, 299. (c) Giese, B.; Gilges, S.; Groninger, K. S.; Lamberth, G.; Witzel, T. *Liebigs Ann. Chem.* **1988**, 615. (d) Geise, B.; Kopping, B. *Tetrahedron Lett.* **1989**, *30*, 681. (e) Thiem, J.; Klafke, W. *Top. Curr. Chem.* **1990**, *154*, 285. (f) Gervay, J.; Danishefsky, S. *J. Org. Chem.* **1991**, *56*, 5448. (g) Roush, W. R.; Briner, K.; Sebesta, D. P. *Synlett.* **1993**, 264. (h) Roush, W. R.; Bennett, C. E. *J. Am. Chem. Soc.* **1999**, *121*, 3541. (i) Roush, W. R.; Narayan, S. *Org. Lett.* **1999**, *1*, 899. (j) Roush, W. R.; Durham, T. B. *Org. Lett.* **2003**, *5*, 1871.

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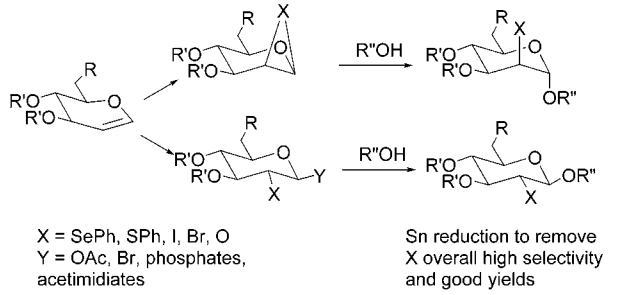


Figure 2.

directly introduce hydrogen at C-2, but α-glycosides often predominate due to the kinetic anomeric effect.[6] More recently, studies by McDonald and co-workers suggest that substituent effects may moderate the stereochemical outcome in these reactions.[7]

As a part of our ongoing investigations probing the utility of glycosyl iodides,[8] it occurred to us that 2-deoxy-*β*-glycosides may be readily accessible via direct displacement of α-glycosyl iodides, which in turn would be derived from glycals (Figure 3). Our previous studies have shown that

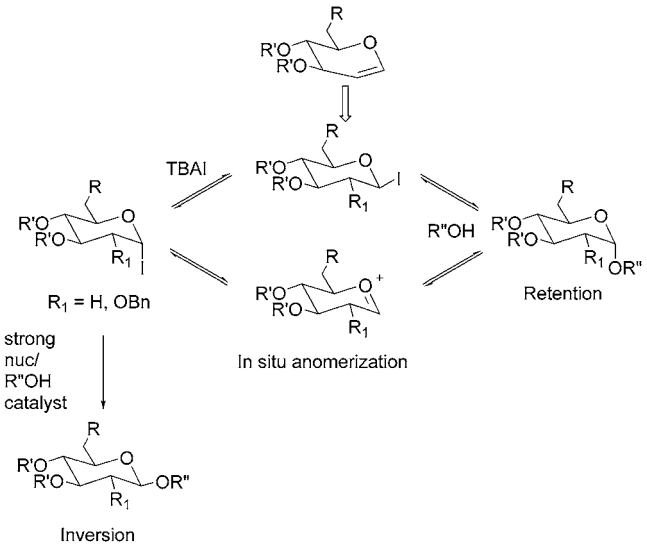
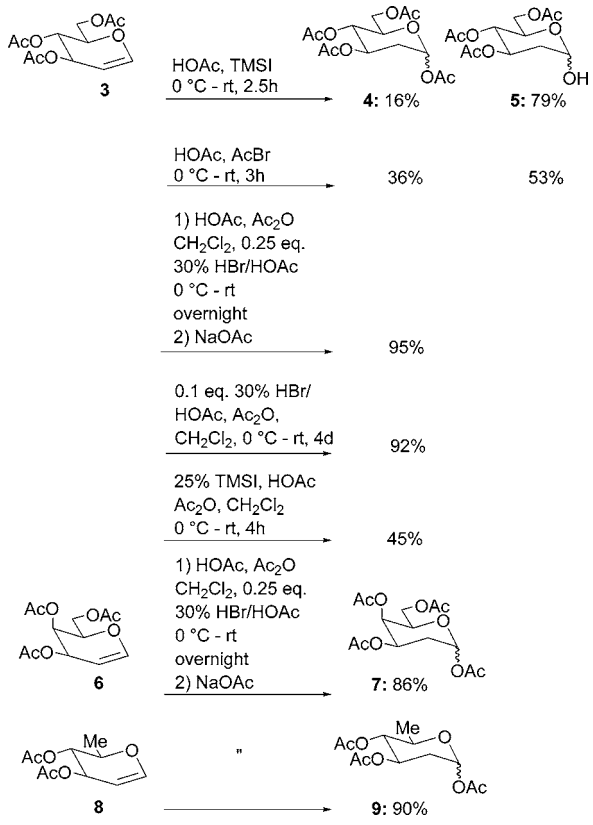


Figure 3.

reaction conditions promoting in situ anomerization provide α-glycosides either by nucleophilic displacement of the *β*-iodide or by axial addition to an oxacarbenium intermediate. Conversely, strong nucleophiles typically yield *β*-glycosides by S_N2-like attack on the thermodynamically more stable α-glycosyl iodide. We were encouraged by the report that glycosyl bromides yield *β*-glycosides when activated with insoluble silver catalysts,[9] and we anticipated that glycosyl iodides would offer clear advantages in direct displacement reactions, including the ability to do reactions under anionic conditions, with increased stereoselectivities, and decreased reaction times.[10]

Glycosyl iodides are efficiently prepared in situ from the corresponding anomeric acetate upon reaction with trimethylsilyl iodide (TMSI). We therefore set out to prepare 2-deoxy and 2,6-dideoxy glycosyl acetates by the direct addition of acetic acid to glycals (Scheme 1). In our initial

Scheme 1



investigations, treatment of **3** with stoichiometric amounts of anhydrous hydrogen iodide, generated in situ from TMSI and anhydrous acetic acid, quickly provided **4** as well as hemiacetal **5**. When equimolar hydrogen bromide, produced from acetyl bromide and anhydrous acetic acid, was used, a mixture of **4** and **5** was also obtained in comparable time to the hydrogen iodide assisted approach. Both conversions

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(8) (a) Gervay, J.; Nguyen, T. N.; Hadd, M. J. *Carbohydr. Res.* **1997**, *300*, 119. (b) Hadd, M. J.; Gervay, J. *Carbohydr. Res.* **1999**, *320*, 61. (c) Gervay, J. *Org. Synth.: Theory Appl.* **1998**, *4*, 121. (d) Bhat, A. S.; Gervay-Hague, J. *Org. Lett.* **2001**, *3*, 2081.

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(10) Gervay, J.; Hadd, M. J. *J. Org. Chem.* **1997**, *62*, 6961.

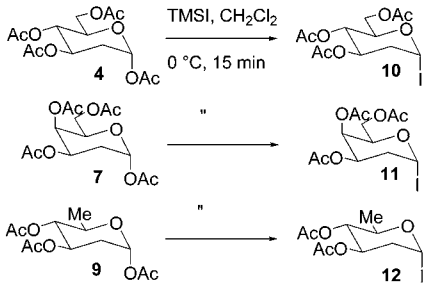
typically gave high overall mass recovery, and although **5** predominated in these reactions, acetylation quickly furnished **4**. These results are in accord with the belief that softer acids suppress the Ferrier I, as allylic rearrangement products were not detected.[5]

To simplify our strategy, we chose to employ commercially available 30 wt % HBr/HOAc and added acetic anhydride to the reaction mixture to suppress the formation of **5**. Using substoichiometric amounts of HBr in acetic acid (25% molar to the glycal) in combination with anhydrous acetic anhydride, we were able to generate primarily **4** in high yields, again without rearranged products. Treatment of **3** with catalytic TMSI in HOAc and Ac_2O also afforded the 2-deoxy-tetra-*O*-acetate (**4**) in comparable time. However, after aqueous workup and chromatography, **4** was recovered in only 45% yield, as C-1 hydrolysis had also occurred. Using 0.1 molar equiv of HBr/HOAc with respect to the glycal also provided **4**, but longer times, 4 days, were required for completion. Since HBr/HOAc is cheaper than TMSI and there were no obvious advantages to using HI generated in situ, we opted for the more cost-efficient route.

The reactions were performed on multigram scale, and the workup was facilitated by the addition of sodium acetate (NaOAc) to neutralize HBr, resulting in NaBr precipitation. Filtration of the salts, rotoevaporation to dryness, and recrystallization from ethyl acetate−hexanes supplied the tetra-*O*-acetate **4** (>90%) in short order. The general applicability of this method was further illustrated by the reactions of **6** and **8**, providing 2-deoxygalactosyl acetate **7** and 2,6-dideoxyglucosyl acetate **9**, respectively.

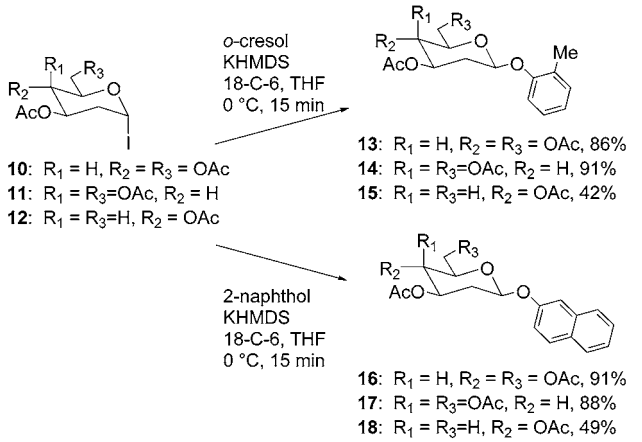
With a simple route affording large quantities of building blocks in hand, formation of 2-deoxy glycosyl iodides by the method of Thiem and Meyer was explored.[11] As we anticipated, treatment of **4** with TMSI at 0 °C for 15 min in dichloromethane afforded 1-iodo-2-deoxy-3,4,6-tri-*O*-acetyl-α-D-arabino-pyranoside (**10**). Quantitative conversion to the α-iodide was evidenced by ^{1}H NMR data showing a dramatic downfield shift of the anomeric proton (δ 6.95 ppm) when compared with the anomeric acetate (δ 6.25 ppm).[12] Glycosyl iodides **11** and **12** were synthesized in a similar fashion (Scheme 2).

Scheme 2



The glycosyl iodides were subsequently reacted with arylalkoxy anions under direct displacement conditions (KHMDS, 18-crown-6). As shown in Scheme 3, addition of

Scheme 3



10: R_1 = H, R_2 = R_3 = OAc
11: R_1 = R_3=OAc, R_2 = H
12: R_1 = R_3=H, R_2 = OAc

13: R_1 = H, R_2 = R_3 = OAc, 86%
14: R_1 = R_3=OAc, R_2 = H, 91%
15: R_1 = R_3=H, R_2 = OAc, 42%

16: R_1 = H, R_2 = R_3 = OAc, 91%
17: R_1 = R_3=OAc, R_2 = H, 88%
18: R_1 = R_3=H, R_2 = OAc, 49%

o-cresolate or naphthoate anions to the 2-deoxyglucosyl **10** and 2-deoxygalactosyl **11** iodides was complete within 15 min, producing the *β*-*O*-aryl-glycosides **13**, **14**, **16**, and **17** as the only detectable glycosylation products.

The anomeric configuration was assigned on the basis of C1−H1 coupling constants obtained[13] from a modified HSQC experiment.[14] By lowering the ^{1}H-decoupling power, the ^1J and ^2J resonances were detected.[15] A one-dimensional slice from the F2 axis revealed ^1J and ^2J couplings of the anomeric carbon and proton. For example, at 500 MHz, the ^1J C1−H1 coupling of **16** was calculated to be 160.3 Hz and the ^2J large H1−$H2_{ax}$ was 9.8 Hz. The ^1J C1−H1 coupling was identical to those calculated from data of ^{1}H-coupled full NOE ^{13}C-spectra. However, since the HSQC is a proton-based experiment, the spectroscopic data were acquired more quickly and with less material than is required for ^{13}C experiments.

It is notable that comparable *β*-selectivity was obtained for both the glucosyl and galactosyl iodides, as stereochemical control is often diminished when employing 2-deoxygalactosyl donors.[3j] Nucleophilic displacement of 2,6-dideoxyglucosyl iodide **12** also provided the *β*-*O*-aryl-glycosides **15** and **18** as the only detected glycosylation products; however, the reactions were not as efficient when compared to donors **10** and **11**. Under the basic conditions of addition, 1,2-elimination became the alternate pathway, resulting in regeneration of the starting glycal **8**. The propensity of **12** to undergo elimination is presumably due to increased electron density relative to **10** and **11**, which have electron-withdrawing groups at C-6. We have previously reported that stereoelectronic effects attenuate elimination.[16]

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(12) Experiments were performed in deuteriochloroform at 298 K.
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In conclusion, our studies demonstrate that direct addition of acetic acid to glycals results in high yields of 2-deoxy glycosyl acetates, which can be readily converted to the corresponding α-glycosyl iodides in quantitative yield. Substitution of the iodides with arylalkoxy anions, in what is presumably an S_N2-like displacement, results in highly stereoselective reactions to afford 1-*O*-aryl-2-deoxy-*β*-D-glycopyranosides. Glycals are the only observable byproducts, and they can be easily recycled to the corresponding glycosyl iodide via the 2-deoxy-glycosyl acetate precursors. The ability to readily recycle the glycal byproducts is an important advantage given that many natural products contain rare 2-deoxy-L-sugars.[17]

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Supporting Information Available: Experimental procedures and complete characterizations for compounds **4** and **7**−**18**. This material is available free of charge via the Internet at http://pubs.acs.org.

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