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Stereoselective Synthesis of 2-Deoxy-β-Galactosides via 2-Deoxy-2-bromo- and 2-Deoxy-2-iodo-galactopyranosyl Donors

Timothy B. Durham and William R. Roush*

Department of Chemistry, University of Michigan, Ann Arbor, Michigan 48109

roush@umich.edu

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ABSTRACT



A series of 2-bromo- and 2-iodo-galactopyranosyl acetates and trichloroacetimidates were evaluated as glycosyl donors for the synthesis of 2-deoxygalactopyranosides. The best selectivity for the β -glycosidic linkage was achieved by using 6-deoxy-3,4-carbonate-protected galactosyl donors.

2-Deoxy carbohydrates are structurally important components of numerous biologically active natural products.¹ The ability to control the stereochemistry of 2-deoxy glycosidic linkages represents an important and challenging synthetic problem.^{2,3} Recent reports from these laboratories and others have demonstrated the use of 2-deoxy-2-iodo- and 2-deoxy-2bromo-glucopyranosyl acetates,^{4–8} trichloroacetimidates,^{9,10} and fluorides¹¹ as highly diastereoselective glycosidating agents for the synthesis of 2-deoxy- β -glucosides (and also of 2-deoxy- α -glucosides).^{4,6} The utility of these procedures

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has been demonstrated in syntheses of the landomycin A hexasaccharide 12 and olivomycin $A.^{13}$

Given our continued interest in 2-deoxy glycosides, we wanted to extend our efforts to the synthesis of 2-deoxy- β -galactosides. Prior to this study, we were aware of one published example of a β -selective glycosidation reaction of a 2-deoxy-2-bromo-galactopyranosyl acetate, which proceeded with excellent selectivity.⁸ Other work, however, indicated that the β -selectivity of glycosidation reactions of 2-thioaryl-2-deoxygalacto-pyranosyl donors is lower than that of corresponding donors in the glucopyranosyl series.¹⁴ Therefore, we decided to evaluate the utility of 2-deoxy-2-halogalactopyranosyl acetates and trichloroacetimidates for the synthesis of 2-deoxy- β -galactosides.

2,6-Dideoxy- β -galactoside units are found in many of the aureolic acid antibiotics, including mithramycin¹⁵ and UCH9,^{16,17} as well as the recently isolated durhamycins.

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Durhamycin A (1, Scheme 1) is a potent inhibitor of HIV-1 Tat transactivation.¹⁸ The unusual biological activity of 1 and the presence of a challenging 2,6-dideoxy- β -galactosidic linkage make it an excellent synthetic target. In this context, the 2-deoxy-2-iodogalactopyranosyl acetate 2 (Scheme 1) initially appeared to be an appropriate precursor of the 2-deoxy- β -galactoside unit ("D") in 1.

Donor 2 was prepared starting from protected galactal 4 (Scheme 2).¹⁹ Displacement of the tosylate with Bu_4NBr



followed by treatment with NIS and AcOH provided the desired iodo acetate **6** as a 1:1 mixture of anomers along with *talo* isomer **5**. After selective deprotection of the anomeric acetate unit of **6** with hydrazine,²⁰ conversion of

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the resultant hemiacetal to imidate 2 was achieved by treatment with Cl₃CCN and DBU.^{21,22}

Imidate **2** was then subjected to TBSOTf-promoted glycosidation with model acceptor **7** (Scheme 2). Surprisingly, this reaction was only modestly β -selective (60:40 β : α).²³ Further, we observed that imidate **2** is highly unstable. This led us to change the C(2) directing group to a more electronegative bromide substituent, which we hoped would increase the stability of the donor. We also decided to change the C(4)-protecting group to a benzyl ether, since it seemed possible that the axial C(4) acetate unit in **2** might participate in the glycosidation reaction by interacting with any C(1)cationic intermediates, thereby decreasing the reaction stereoselectivity compared to previously studied examples in the 2-deoxy-2-halo-glucopyranosyl series.

Accordingly, donors 9 and 10 were examined in glycosidation reactions with 7, as well as with the less hindered acceptor 13 (Scheme 3). Unfortunately, neither 9 or 10



^{*a*} Conditions: donor (2 equiv), acceptor (1 equiv), TBSOTf (0.1–0.3 equiv), CH₂Cl₂, -78 °C.

displayed synthetically useful β -selectivity in these reactions. Differences in the directing ability of the C(2)-Br and C(2)-I substituents were observed in the reactions with **7**, but not with **13**.

Changes to the C(6)-substituent also had a relatively minor effect on the selectivity of the glycosidation reactions, as the results summarized in Scheme 3 (9 and 10 with C(6)tosyloxy substituents) and Scheme 4 (C(6)-benzyloxy substituted donors 16 and 17) indicate. Interestingly, however, our results for the glycosidation reaction of donor 17 and galactoside acceptor 22 (Scheme 4) are not in agreement with the literature report for this reaction,⁸ which indicated that β -galactoside 23 was formed selectively. In our our hands, this reaction was only moderately β -selective, in agreement

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⁽²³⁾ All reported ratios were determined by ¹H NMR analysis of the crude reaction mixtures. Stereochemical assignments of all isolated products were made using ¹H, ¹³C, and COSY NMR analysis.



^{*a*} Conditions: TMSOTf (0.5 equiv) was added to a mixture of donor (2 equiv) and acceptor (1 equiv), CH_2Cl_2 , -30 to -23 °C.

with the other reactions of donors **16** and **17** (Scheme 4). Deoxygenation of C(6) altogether, as in the case of donor **24**, resulted in glycosidation reactions that were modestly α -selective (Scheme 5). While these results indicated that





the C(6)-substituent on the galactopyranosyl donor can influence the diastereoselectivity of the glycosidation reactions, access to a highly β -selective 2-deoxy-2-halogalactopyranosyl donor still eluded us.

In previous studies of the glycosidation reactions of 2-deoxy-2-iodoglucopyranosyl acetates and trichloroacetimidates, we speculated that stereoselectivity might be governed by the conformational preferences of intermediate pyranosyl oxocarbenium ions.^{24–26} Evidence was also presented indicating that glycosyl triflates are not intermediates in glycosidation reactions of 2-iodoglucosyl donors.^{10,27} Several groups have calculated the conformational preferences of substituted pyranosyl oxocarbenium ions and have reported that C(3) and C(4) oxygen substituents have a strong preference for pseudoaxial orientation due to electronic stabilization of the cationic center (e.g., conformation **27**, Figure 1).^{28–30} However, in studies with donors containing



Figure 1. Stereochemical considerations.

4,6-benzylidiene protecting groups,¹⁰ high β -selectivity was obtained even though ions such as **27** are inaccessible.³¹ An implication of the latter study is that the β -selectivity might be governed by substitution reactions of iodonium ion intermediates rather than oxocarbenium ions. In contrast, the results summarized in Schemes 2–5 suggest that halonium ion intermediates are not significantly involved in the glycosidation reactions of 2-deoxy-2-halo-galactopyranose donors, since the large amounts of α -glycosides produced in these reactions require that oxocarbenium ions play a substantial role.^{28,32}

Assuming that cationic intermediates play a greater role in the reactions of the 2-deoxy-2-halogalactopyranosyl donors than in the glucopyranosyl series, selectivity is then determined either by the conformational preferences of ions **30** and **31** or by the relative reactivity of these two similar species. In contemplating strategies to increase the preference for reaction by way of **30**, we were reminded of studies by Danishefsky, who demonstrated that the β -selectivity of glycosidation reactions of 2,3-epoxy sugars in the galactose series were considerably enhanced when the 3,4-hydroxyl

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groups were protected as a 3,4-carbonate group.³³ Accordingly, we targeted **32** as a key reactive intermediate. The cis-fusion of the cyclic 3,4-protecting group encourages **32** to adopt the indicated boatlike conformation with the C(2)-X substituent in a pseudoaxial position, which should direct the glycosidation in a β -selective manner.³¹

To test this hypothesis, we studied the glycosidation reactions of the 3,4-acetonide-protected donor **34** and also the 3,4-carbonate-protected donors **37**, **39**, and **40** (Schemes 6 and 7). Donors **34** and **40** gave, in most cases, only modest



selectivity in reactions with 7 and 13. Gratifyingly, 6-deoxy donors 37 and 39 displayed good to excellent β -selectivities with a variety of carbohydrate acceptors (7, 13, and 49). It is noteworthy that these two donors complement each other in their reactivity profiles such that, under identical conditions, donor 39 undergoes glycosidation at -78 °C, while donor 37 requires a significantly higher temperature (0 °C) for reaction to occur. However, it remains unclear at present why donors 37 and 39 display such very different selectivity patterns in reactions with similar acceptors.

In conclusion, we have developed two 3,4-carbonateprotected 2,6-dideoxy-2-halo-galactosyl donors (**37** and **39**) that provide access to 2,6-dideoxy- β -galactosides with high diastereoselectivity. Selectivity decreases, however, with rigid donors **34** and **40** containing C(6)-oxygenated substituents or when the donor lacks a cyclic 3,4-protecting group (**2**, **9**, **10**, **16**, **17**, and **24**). Further studies into the origin of selectivity with donors **37** and **39** are in progress. Application of this methodology to the synthesis of the CDEF tetrasaccharide unit of Durhamycin A (**1**) is reported in the following paper in this issue.



^{*a*} Conditions: (a) TMSOTF (0.2 equiv) was added to donor (2 equiv) and acceptor (1 equiv) at 0 °C, CH_2Cl_2 ; (b) TBSOTF (0.3 equiv) was added to donor (2 equiv) and acceptor (1 equiv) at -78 °C, CH_2Cl_2 .

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Supporting Information Available: Experimental protocols and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org. OL034393T

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