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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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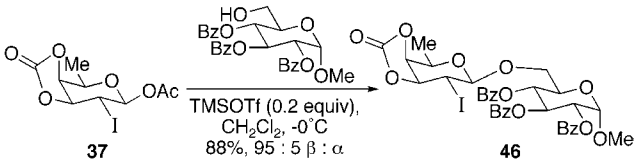
ABSTRACT



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-2-bromo-glucopyranosyl acetates,[4−8] trichloroacetimidates,[9,10] and fluorides[11] 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 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 mithramycin[15] and UCH9,[16,17] as well as the recently isolated durhamycins.

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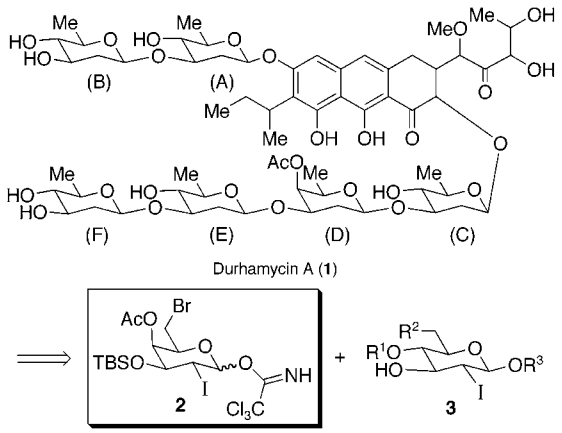
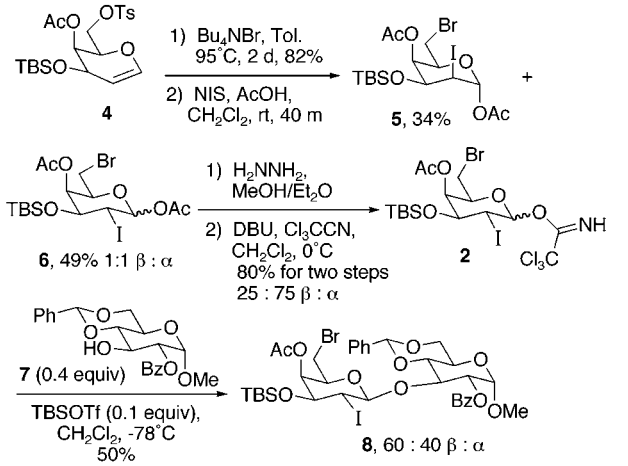
Scheme 1



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 the resultant hemiacetal to imidate **2** was achieved by treatment with Cl_3CCN and DBU.[21,22]

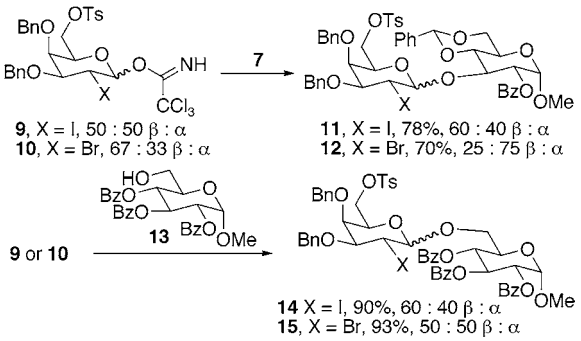
Scheme 2



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** 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**.

Scheme 3[a]



[a] Conditions: donor (2 equiv), acceptor (1 equiv), TBSOTf (0.1−0.3 equiv), CH_2Cl_2, −78 °C.

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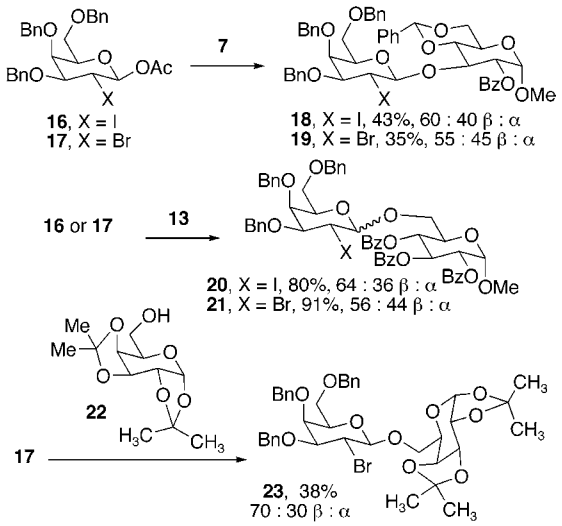
(23) All reported ratios were determined by ^{1}H NMR analysis of the crude reaction mixtures. Stereochemical assignments of all isolated products were made using ^{1}H, ^{13}C, and COSY NMR analysis.

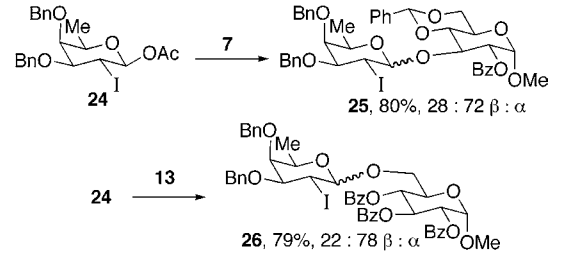
Scheme 4[a]



[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

Scheme 5[a]



[a] Conditions: TMSOTf (0.2 equiv) was added to a mixture of donor (2 equiv) and acceptor (1 equiv) in CH_2Cl_2 at 0 °C.

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

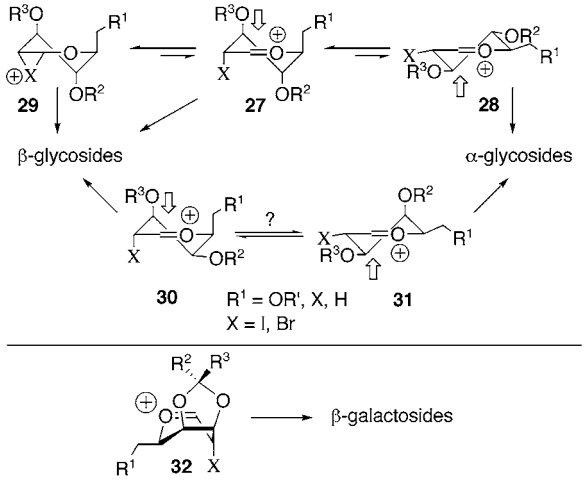


Figure 1. Stereochemical considerations.

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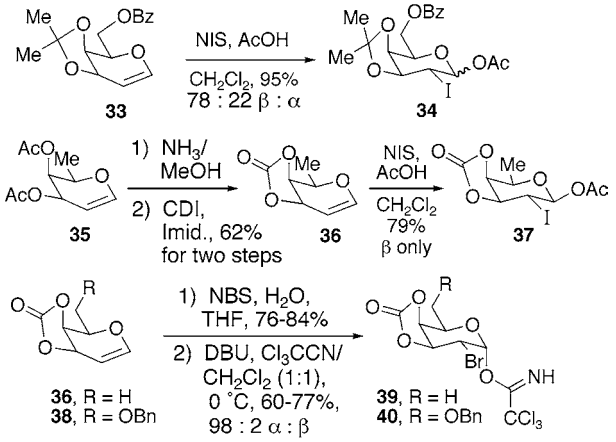
groups were protected as a 3,4-carbonate group.[33] Accordingly, we targeted **32** as a key reactive intermediate. The cis-fusion of the cyclic 3,4-protecting group encourages **32** to adopt the indicated boatlike conformation with the C(2)-X substituent in a pseudoaxial position, which should direct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

Scheme 6



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-carbonate-protected 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.

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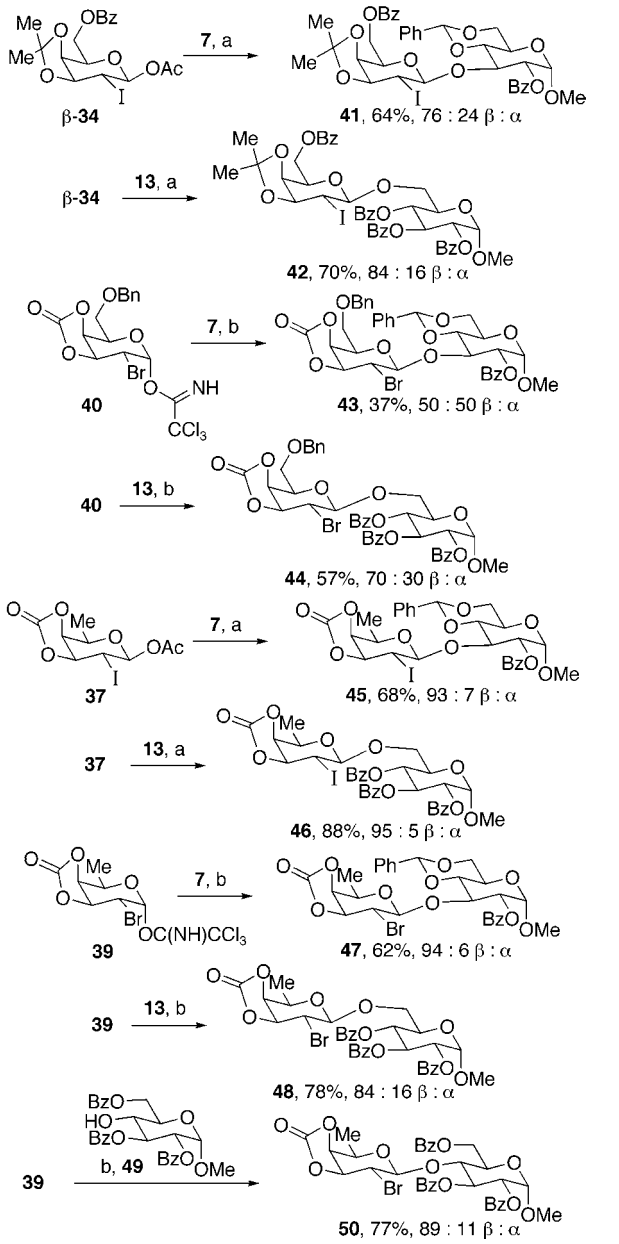
Scheme 7[a]



[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.

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