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2-Deoxy-2-iodo-α-mannopyranosyl and -talopyranosyl Acetates: Highly Stereoselective Glycosyl Donors for the Synthesis of 2-Deoxy-α-glycosides

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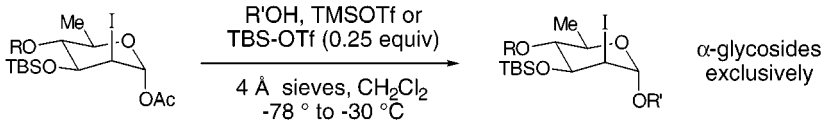
ABSTRACT



TMS-OTf- or TBS-OTf-promoted glycosidation reactions of 2-deoxy-2-iodo-α-mannopyranosyl acetates 8–10 and the 2-deoxy-2-iodo-α-talopyranosyl acetate 11 provide the corresponding 2-deoxy-2-iodo-α-pyranosides, precursors to 2-deoxy-α-glycosides, as the only observed reaction products.

2-Deoxy-α-glycosides are important structural components of many biologically active natural products.[1] In many cases, 2-deoxy-α-glycosides may be synthesized with excellent selectivity from suitably activated 2-deoxyglycosyl precursors.[2] These α-glycosides are also readily accessible from the oxidative coupling[3] of glycal precursors with an alcohol acceptor, most frequently using *N*-iodosuccinimide (NIS) or iodonium bis-*sym*-collidine perchlorate [(*sym*-collidine)$_2$I$^+$ ClO$_4^-$] as the electrophilic oxidant.[3−7] Several years ago, in connection with our initial studies on the synthesis of olivomycin A,[8] we developed a new method for synthesis of α-L-olivomycosides via the reaction of the α-L-2-deoxy-2-iodo acetate donor **1** with alcohols using TMS-OTf as the activating agent (Figure 1).[9,10] Motivation to develop this new procedure, which entails the decoupling of the glycal activation step from the subsequent glycosidation event, was provided by several literature reports,[11−13] reinforcing our own experience,[9,14] that the stereoselectivity of the NIS and (*sym*-collidine)$_2$I$^+$ ClO$_4^-$ iodoalkoxylation reaction of glycals sometimes give less than perfect stereocontrol. We subse-

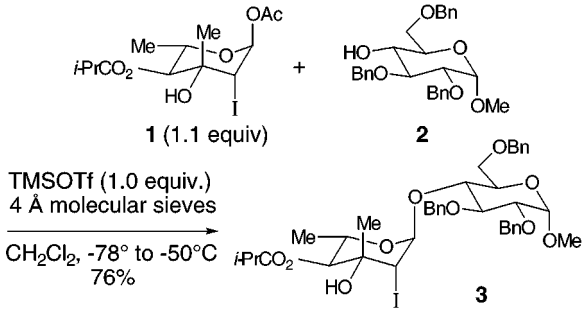


Figure 1. α-Selective glycosidation reactions of **1**.[9,10]

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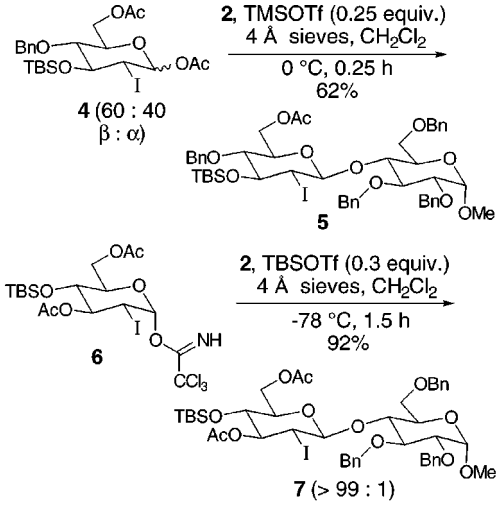

Figure 2. β-Selective glycosidation reactions of 2-deoxy-2-iodoglycopyranosyl acetates (**4**) and trichloroacetimidates (**5**).[16,17]

quently demonstrated that iodoacetate **1** exhibits outstanding stereoselectivity in its reactions with glycoside acceptors. In all the cases examined thus far, we have not observed any stereoisomers other than the α-manno glycosides represented by structure **3** in Figure 1.[10,15] This method has also proven applicable to the solid-phase synthesis of di- and trisaccharides, again with outstanding stereoselectivity.[15]

We recently demonstrated that the glycosidation reactions of 2-deoxy-2-iodoglycopyranosyl acetates (**4**) and trichloroacetimidates (**5**) constitute a general and highly stereoselective route to 2-deoxy-β-glycosides (Figure 2).[16,17] Because the only α-glycosidations we had examined involved use of α-L-2-deoxy-2-iodo-olivomycosyl acetate **1** as the glycosyl donor,[10] we were interested in exploring a wider range of substrates in order to determine the scope of this process.[18] We report herein our studies of α-glycosidation reactions of 2-deoxy-2-iodomannopyranosyl and 2-deoxy-2-iodotalopyranosyl acetates. We demonstrate that this new α-glycosidation protocol has considerable generality and that 2-deoxy-2-iodo-α-mannopyranosides—precursors to 2-deoxy-

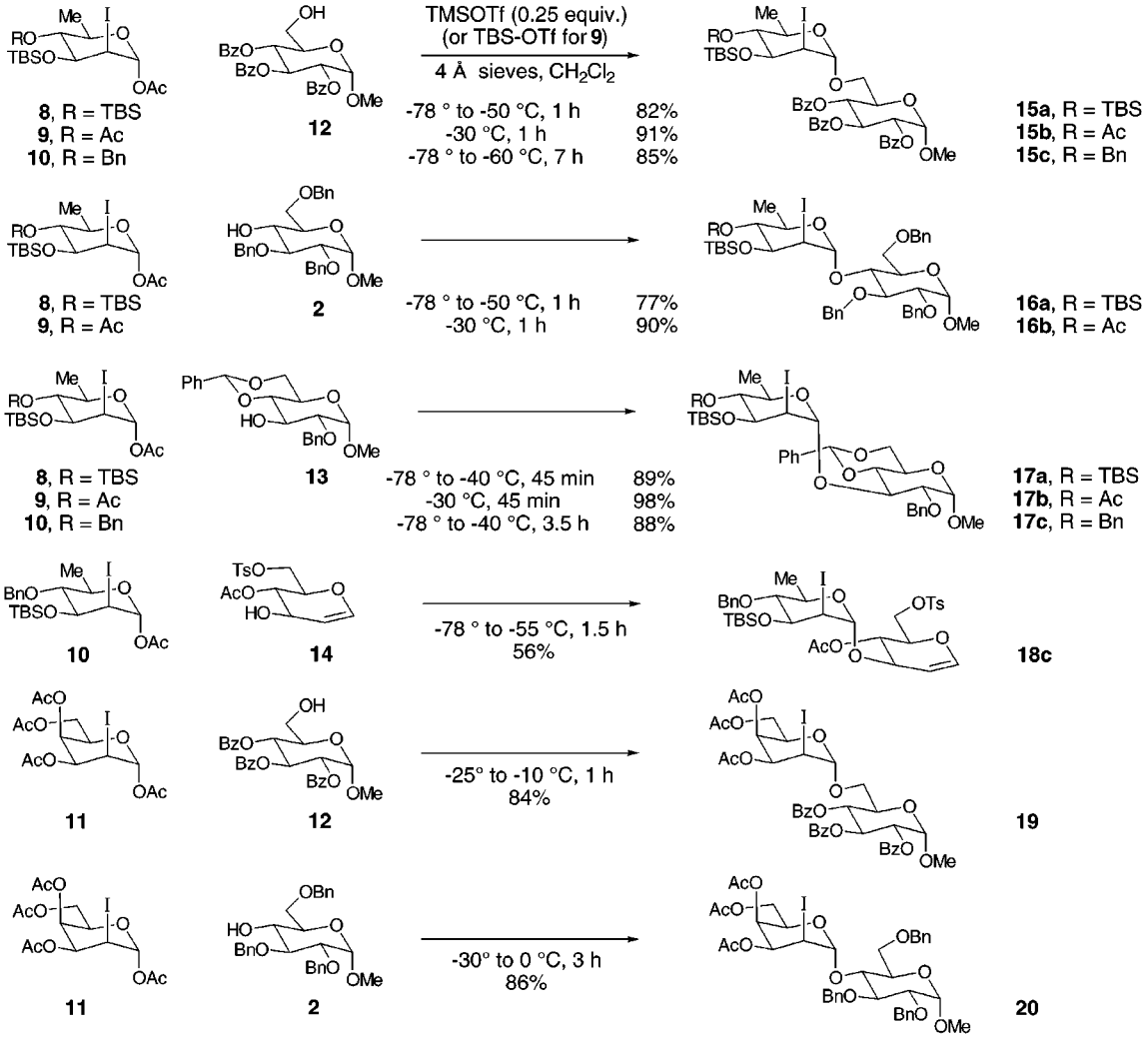

Figure 3. Glycosidation reactions of 2-deoxy-2-iodo-α-mannopyranosyl acetates **8**−**10** and 2-deoxy-2-iodo-α-talopyranosyl acetate **11**.

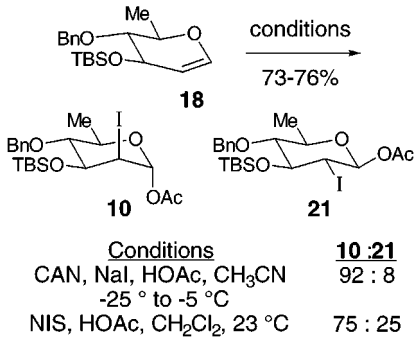

Figure 4. Iodoacetoxylation of glycals.[20]

α-glycosides—are obtained with outstanding stereoselectivity, as foreshadowed by our earlier studies with **1**.

Results of the glycosidation reactions of 2-deoxy-2-iodomannopyranosyl acetates **8**−**10** and the 2-deoxy-2-iodotalopyranosyl acetate **11** are summarized in Figure 3.[19] The glycosyl donors were synthesized by using our recently disclosed glycal iodoacetoxylation procedure that involves treatment of a glycal with cerium(IV) ammonium nitrate (CAN), NaI, and HOAc in CH_3CN at −25 °C.[20] This procedure typically provides the desired 2-deoxy-2β-iodo-α-pyranosyl acetates with ≥ 10−12:1 selectivity. By way of comparison, in most cases these glycosyl donors are obtained with considerably lower stereoselectivity by iodoacetoxylation of the glycals with *N*-iodosuccinimide (NIS) and HOAc in CH_3CN at ambient or subambient temperatures. A representative pair of glycal iodoacetoxylation reactions are presented in Figure 4. The CAN−NaI−HOAc procedure is also more stereoselective than the recently introduced method involving diacetoxyiodine(I) salts.[18]

Glycosidation reactions of **8**−**11** were performed by treating a mixture of the 2-deoxy-2-iodoglycosyl acetate donor (1.0 equiv) and 1.25 equiv of glycosyl acceptor (**2**, **12**−**14**) with 0.25 equiv of trimethylsilyl triflate (TMS−OTf) in CH_2Cl_2 in the presence of 4 Å molecular sieves. The reactions utilizing glycosyl donors **8** and **10**, with C(4)-OTBS or -OBn protecting groups, were typically complete within 1 h at reaction temperatures between −78 and −50 °C. This level of reactivity is essential for successful glycosidation of the sensitive glycal acceptor **14**, which decomposes in the presence of TMS-OTf at temperatures above −50 °C (see the synthesis of **18c**). However, glycosyl donor **9**, which possesses a deactivating C(4)-OAc unit, and donor **11**, with acetate substituents at C(3), C(4), and C(6), are considerably less reactive than either **8** or **10** and require temperatures of −30 °C or above for reactions to occur at an appreciable rate. Owing to the relatively high reaction temperatures required for glycosidation reactions of **9**, various amounts (typically 10−20% of the product mixture) of trisaccharides were obtained when TMS-OTf was used as the promoter, resulting from exchange of the silyl group (from TBS to TMS) at C(3) of the glycoside products, followed by glycosidation with an additional equivalent of **9**. One such example is presented in Figure 5. We anticipated that it would

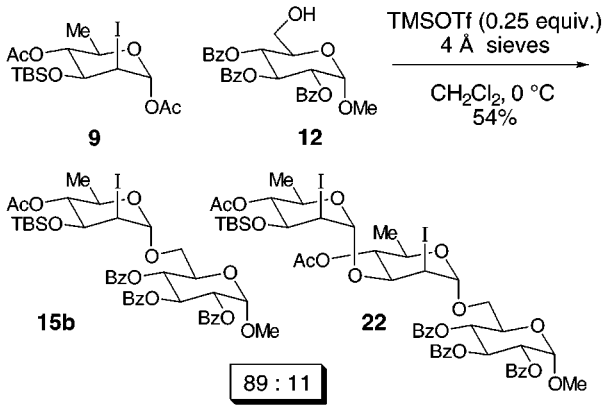

Figure 5. Competitive trisaccharide formation in glycosidation reactions of **9** using TMS-OTf as the promoter.

be possible to suppress trisaccharide formation by using *tert*-butyldimethylsilyl triflate (TBS-OTf) as the activating reagent, since the silyl exchange reaction would then be degenerate; we also suspected that the C(3)-TBS-protected disaccharide (e.g., **15b**) would not be a suitable glycosyl acceptor. Fortunately, as summarized in Figure 3, glycosidation reactions of **9** using 0.25 equiv of TBS-OTf as the promoter are highly efficient (90−98% isolated yields of **15b**−**17b**), with no evidence whatsoever of competitive trisaccharide formation. We have previously used TBS-OTf as the promoter of glycosidation reactions of sensitive

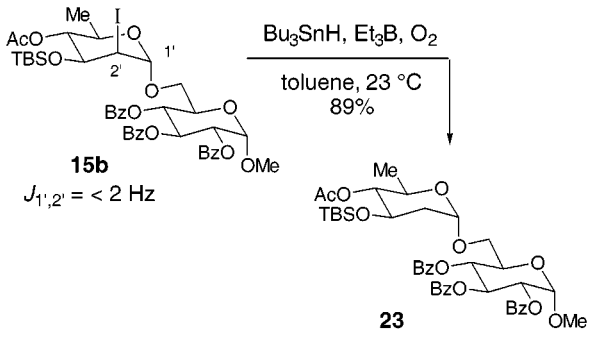

Figure 6. Representative stereochemical assignment.

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substrates,[8,17] in all cases taking advantage of the diminished Lewis acidity of this reagent compared to TMS-OTf to minimize production of unwanted side products.

A remarkable feature of the glycosidation reactions summarized in Figure 3 is that a single stereoisomeric glycoside was obtained in each case. No evidence for production of any of the other possible diastereomeric glycosides was obtained. The assignment of stereochemistry in all cases rests on the small $J_{1',2'}$ coupling constants observed ($\leq$2 Hz) and the fact that 2-deoxy-α-glycosides are obtained following reductive removal of the C(2′)-iodo substituent (Figure 6).[21]

In summary, we have demonstrated that the glycosidation reactions of 2-deoxy-2-iodo-α-mannopyranosyl acetates **8**−**10** and the 2-deoxy-2-iodo-α-talopyranosyl acetate **11** are highly stereoselective, in every case providing the targeted 2-deoxy-2-iodo-α-glycosides as the only observed reaction products. Applications of this methodology to the synthesis of biologically active 2-deoxy-α-glycosides will be reported in due course.

Acknowledgment. We thank the NIH (GM 38907) for support of this research.

Supporting Information Available: Representative experimental procedures for the glycosidation reactions and Bu_3SnH reductions of the 2-deoxy-2-iodoglycosides and tabulated spectroscopic data for **15a**−**c**, **16a,b**, **17a**−**c**, **18c**, **19**, **20**, and **23**−**25**. This material is available free of charge via the Internet at http://pubs.acs.org.

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