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2-Deoxy-2-iodo- and 2-Deoxy-2-bromo-α-glucopyranosyl Trichloroacetimidates: Highly Reactive and Stereoselective Donors for the Synthesis of 2-Deoxy-β-glycosides

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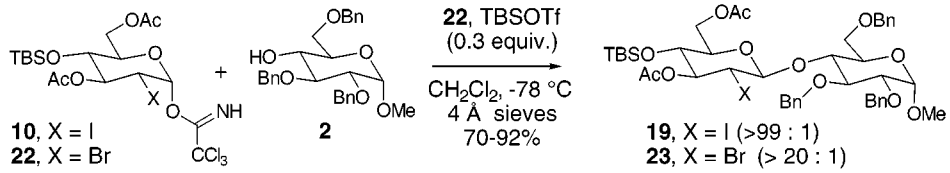
ABSTRACT



2-Deoxy-2-iodo- and 2-deoxy-2-bromoglucopyranosyl trichloroacetimidates 8–10 and 22 are extremely useful precursors of 2-deoxy-β-glycosides. These reactive glycosyl donors undergo highly stereoselective glycosidation reactions at −78 °C with a range of glycosyl acceptors using TBS-OTf as the activating agent. β-Glycosides are obtained with ≥ 19:1 selectivity in six of the seven examples reported herein.

We recently reported a highly stereoselective synthesis of 2-deoxy-2-iodo-β-glucopyranosides, precursors of 2-deoxy-β-glycosides, using 2-deoxy-2-iodo-glucopyranosyl acetates as the glycosyl donors.[2] We observed that certain donors, such as the 6-deoxy-glucosyl acetate **1**, are highly reactive and undergo rapid, high-yielding glycosidation reactions at −78 °C, as illustrated by the coupling of **1** and **2** (Figure 1). The high reactivity of **1** is due in part to the fact that this compound exists in a twist boat conformation (see **1′**), which increases the reactivity of this donor compared to those in the normal chair conformation.[2] The lack of oxygenation at C(6) also increases the reactivity of the anomeric center.[3,4] In contrast, all other glycosyl donors that adopt the normal $^4C_1$ conformation and/or have deactivating heteroatom substituents at C(6) required much higher glycosidation reaction temperatures, as illustrated by the glycosidation reaction of **2** and **4**. One additional complication with the use of glycosyl acetates such as **4** is that under the reaction conditions the β-glycosyl acetates equilibrate with the α-acetate anomers, which are considerably less reactive as glycosylating agents. Although the α-acetates can be used as substrates for these reactions, the α-anomers generally require temperatures 20−30 °C warmer for productive couplings than for the β-glycosyl acetates. Consequently, 2-deoxy-2-iodoglycosyl acetate donors such as **4** are not suitable substrates for glycosidation with glycals or other acceptors containing Lewis acid sensitive functionality.

These considerations prompted us to identify a more reactive glycosyl activating group that would permit the synthesis of 2-deoxy-2-iodo-β-glycosides to be performed at −78 °C. Glycosyl trichloroacetimidates have proven to be an extremely useful class of glycosyl donors.[5,6] On the basis of our experience with 2-deoxy-2-thiophenylglycosyl trichloroacetimidates,[7,8] we anticipated that 2-deoxy-2-iodoglycosyl trichloroacetimidates would have the reactivity characteristics that we desired. Accordingly, we have developed and report herein the glycosidation reactions of these new donors.

The preparation of the glycosyl trichloroacetimidate **8** is representative.[9] Selective benzoylation (C_6H_5COCl, pyridine,

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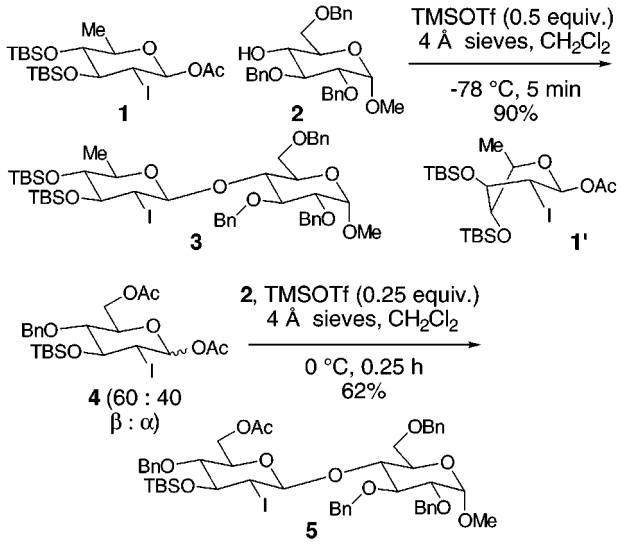

Figure 1. β-Selective glycosidation reactions of iodo acetate donors **1** and **4**.[2]

CH_2Cl_2, 74%) of C(4)-OH of the readily available anhydro sugar **6**[10,11] followed by silylation of C(3)-OH (TBS-OTf, 2,6-lutidine, CH_2Cl_2, 0 °C, 99%) and acetolysis of the anhydro bridge (TFA, Ac_2O, 23 °C, 97%) provided **7** as an anomeric mixture in 71% overall yield. Selective cleavage of the anomeric acetate using aqueous hydrazine in MeOH (99%)[12] and then treatment of the pyranose with excess NaH in Cl_3CCN (as solvent)[7] at −40 °C to −20 °C gave the α-imidate **8** in 79% yield (78% from **7**). Glycosyl donors **9** and **10** were similarly prepared starting from **6** (Figure 2). However, in both of these cases the efficiency of the trichloroacetonitrile activation step was somewhat diminished (64% and 46%, respectively), owing to the high reactivity and poor chemical stability of these particular compounds.

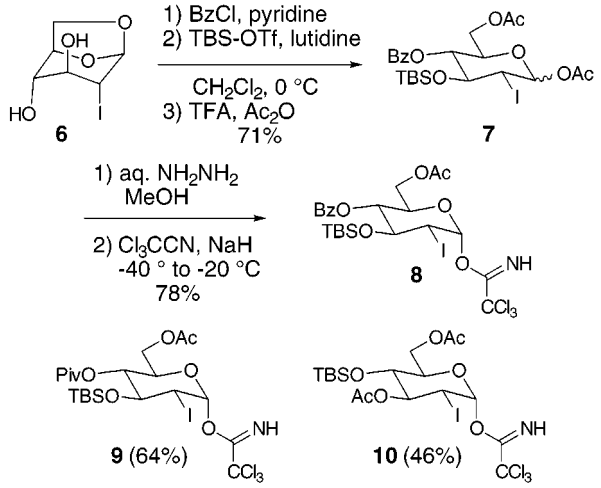

Figure 2. Synthesis of 2-deoxy-2-iodo-α-glucosyl trichloroacetimidates **8**−**10**.

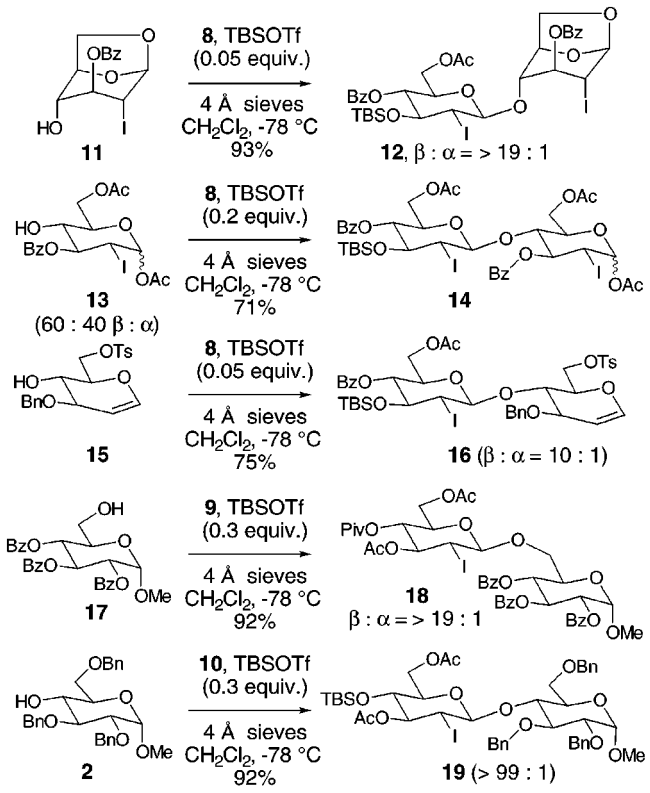

Figure 3. Highly β-selective glycosidation reactions of 2-iodoglycosyl trichloroacetimidates **8**−**10**.

Results of representative glycosidation reactions of the 2-iodoglycosyl imidate donors **8**−**10** with monosaccharide acceptors **2**, **11**, **13**, **15**, and **17** are summarized in Figure 3. These reactions were performed at −78 °C in CH_2Cl_2 using 1.5−3 equiv of the donors in the presence of 0.05−0.3 equiv of TBS-OTf as the activator. In most cases the reactions were complete within a 0.5−1.5 h period. (In other work we have observed that TBS-OTf is superior to TMS-OTf for glycosidations of sensitive substrates.[8,13]) As is clearly evident from these examples, the efficiency and especially the stereoselectivity of these reactions are excellent. It is noteworthy that the β-glycosides were produced with ≥ 10:1 selectivity in all cases, with the reaction of **8** and **15** being the only case that proceeded with less than 19:1 β-selectivity. The

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conditions are sufficiently mild that the very acid sensitive glycal **15** can be glycosylated efficiently. Owing to the poor solubility of **13** under the reaction conditions (−78 °C, CH_2Cl_2), the coupling of **13** and **8** did not go to completion and 26% of **13** was recovered. Nevertheless, the successful use of **13** as a glycosyl acceptor attests to the significantly greater reactivity of the 2-deoxy-2-iodoglycosyl imidates compared to the 2-deoxy-2-iodoglycosyl acetates, thereby enabling the synthesis of disaccharides (e.g., **14**) already suitably activated for a subsequent glycosidation reaction at higher reaction temperature.[2]

Glycosyl donors **8** and **9** containing strong electron withdrawing C(4)-acyl substituents are considerably more stable and less reactive than **10**, which is quite sensitive to handling and decomposes readily even upon attempted storage. Because we anticipated the need to use glycosyl donors containing C(4)-silyloxy or C(4)-ether protecting groups, it was desirable to develop a more stable glycosyl donor as an equivalent of **10**. We anticipated that the analogous 2-bromo-2-deoxyglycosyl imidate **22** would be less reactive and more stable than **10**, due to the greater electronegativity of the 2-bromo substituent which should inductively destabilize the transition state leading to oxonium ion intermediates. Thiem has previously demonstrated that 2-bromo-2-deoxyglycosyl bromides are useful precursors to 2-deoxy-β-glycosides via silver silicate promoted glycosidations (although the stereoselectivity of these reactions is generally $\leq$ 6:1).[14,15]

2-Bromo-2-deoxyglycosyl imidate **22** was synthesized starting from tri-O-acetyl-D-glucal, **20**. Anhydro sugar **21** was prepared by methanolysis of **20** followed by intramolecular bromoetherification (NBS, $(Bu_3Sn)_2O$, CH_3CN; 64% from **21**) and then selective protection of the C(4)-OH as a TBS ether. The bromoetherification sequence employed here is an improvement over the literature procedure that involves the reaction of the stannylated glucal with Br_2 in $CHCl_3$ and provides a 9:1 mixture of the 1,6-anhydro-2-bromo-*gluco*- and -*manno* isomers.[10] Acetolysis of the anhydro linkage of **21** followed by deprotection of the anomeric acetate and then activation of the pyranose gave the imidate **22** in ca. 40% overall yield using the conditions described for the synthesis of **8** from **7**. Imidate **22** indeed proved to be more robust than **10** and underwent highly β-selective glycosidation reactions with acceptors **2** and **24**, as summarized in Figure 4.

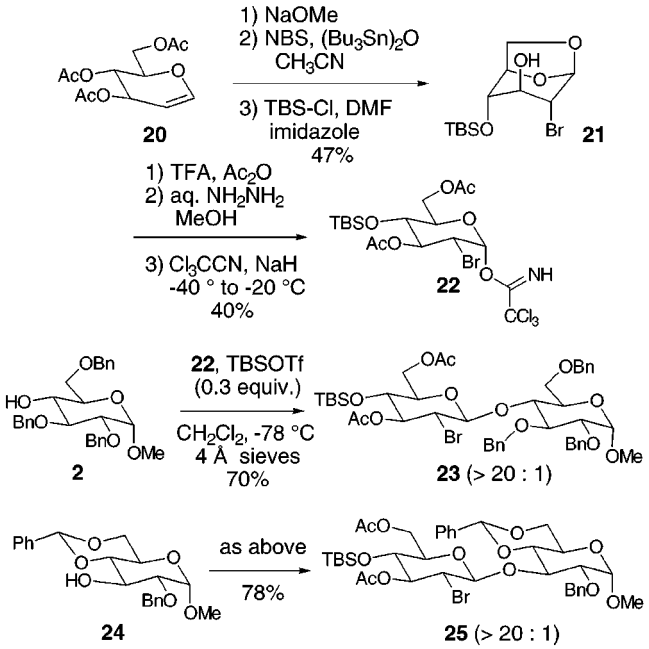

Figure 4. Synthesis and β-selective glycosidation reactions of 2-deoxy-2-bromo-α-glucosyl trichloroacetimidate **22**.

In summary, we have demonstrated that 2-deoxy-2-iodoglycosyl imidates **8**−**10** and 2-deoxy-2-bromoglycosyl imidate **22** are highly reactive glycosyl donors. These donors undergo highly stereoselective glycosidation reactions with a range of monosaccharide acceptors to give 2-deoxy-2-iodo- and 2-deoxy-2-bromo-β-glycosides, precursors of 2-deoxy-β-glycosides, with $\geq$ 19:1 selectivity. It is noteworthy that the 2-deoxy-2-iodoglycosyl imidates are substantially more reactive than the 2-deoxy-2-iodoglycosyl acetates previously reported from our laboratory.[2] Application of this methodology to the synthesis of biologically relevant 2-deoxy-β-glycosides is in progress and will be reported in due course.

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Supporting Information Available: Representative experimental procedures for synthesis of the 2-deoxy-2-iodo- and 2-deoxy-2-bromo-α-glucosyl trichloroacetimidates and their glycosidation reactions; spectroscopic data for **8**−**10**, **12**, **14**, **16**, **18**, **19**, **21**−**23**, and **25**. This material is available free of charge via the Internet at http://pubs.acs.org.

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