

# 2-Deoxy-2-iodo- and 2-Deoxy-2-bromo- $\alpha$ -glucopyranosyl Trichloroacetimidates: Highly Reactive and Stereoselective Donors for the Synthesis of 2-Deoxy- $\beta$ -glycosides

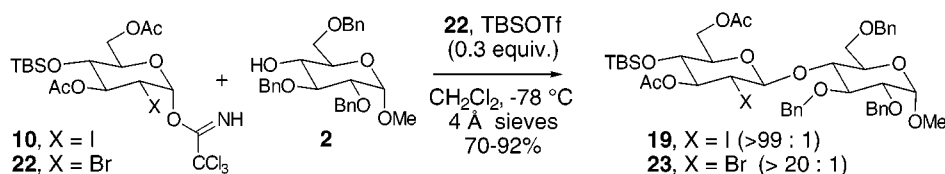
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## ABSTRACT



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

We recently reported a highly stereoselective synthesis of 2-deoxy-2-iodo- $\beta$ -glucopyranosides, precursors of 2-deoxy- $\beta$ -glycosides, using 2-deoxy-2-iodo-glucopyranosyl acetates as the glycosyl donors.<sup>2</sup> We observed that certain donors, such as the 6-deoxy-glucosyl acetate **1**, are highly reactive and undergo rapid, high-yielding glycosidation reactions at  $-78^\circ\text{C}$ , 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.<sup>2</sup> The lack of oxygenation at C(6) also increases the reactivity of the anomeric center.<sup>3,4</sup> In contrast, all other glycosyl donors that adopt the normal  $^4\text{C}_1$  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

$\beta$ -glycosyl acetates equilibrate with the  $\alpha$ -acetate anomers, which are considerably less reactive as glycosylating agents. Although the  $\alpha$ -acetates can be used as substrates for these reactions, the  $\alpha$ -anomers generally require temperatures 20–30  $^\circ\text{C}$  warmer for productive couplings than for the  $\beta$ -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- $\beta$ -glycosides to be performed at  $-78^\circ\text{C}$ . Glycosyl trichloroacetimidates have proven to be an extremely useful class of glycosyl donors.<sup>5,6</sup> On the basis of our experience with 2-deoxy-2-thiophenylglycosyl trichloroacetimidates,<sup>7,8</sup> 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.

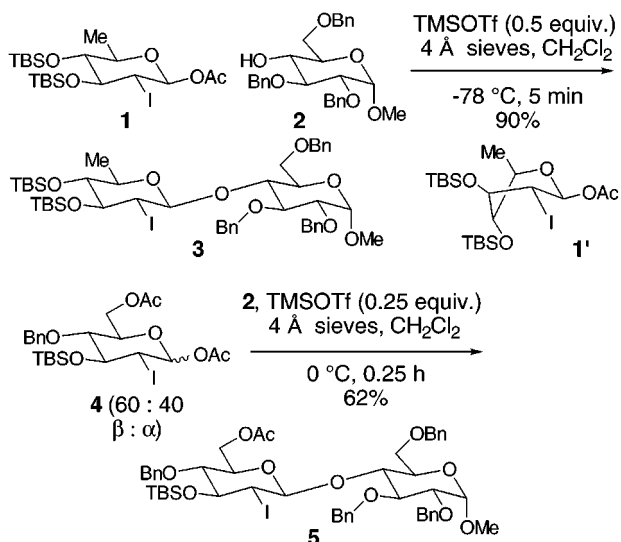
The preparation of the glycosyl trichloroacetimidate **8** is representative.<sup>9</sup> Selective benzylation ( $\text{C}_6\text{H}_5\text{COCl}$ , pyridine,

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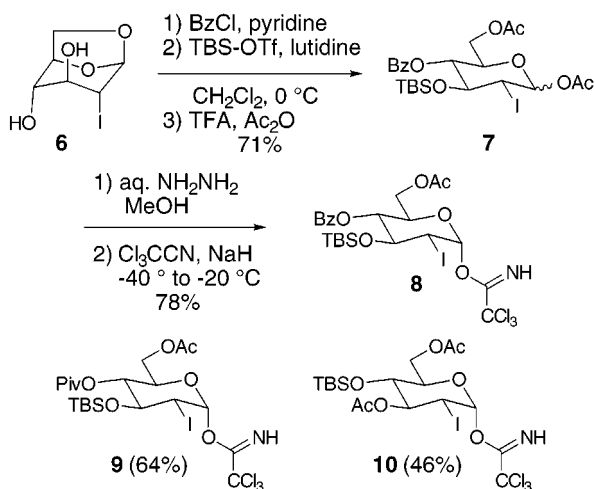
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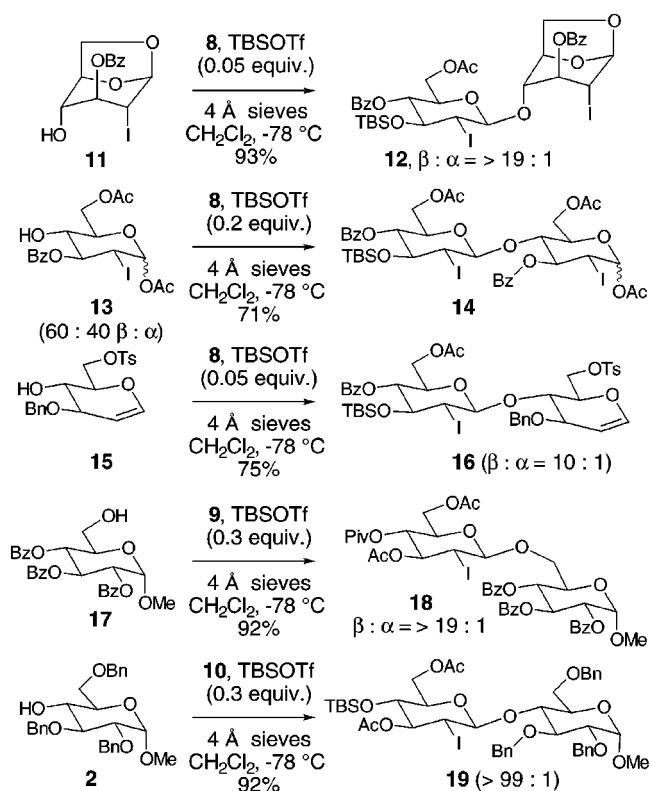


**Figure 1.**  $\beta$ -Selective glycosidation reactions of iodo acetate donors **1** and **4**.<sup>2</sup>

$\text{CH}_2\text{Cl}_2$ , 74%) of C(4)-OH of the readily available anhydro sugar **6**<sup>10,11</sup> followed by silylation of C(3)-OH (TBS-OTf, 2,6-lutidine,  $\text{CH}_2\text{Cl}_2$ , 0 °C, 99%) and acetylation of the anhydro bridge (TFA,  $\text{Ac}_2\text{O}$ , 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%)<sup>12</sup> and then treatment of the pyranose with excess NaH in  $\text{Cl}_3\text{CCN}$  (as solvent)<sup>7</sup> at  $-40^\circ\text{C}$  to  $-20^\circ\text{C}$  gave the  $\alpha$ -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- $\alpha$ -glucosyl trichloroacetimidates **8–10**.



**Figure 3.** Highly  $\beta$ -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  $-78^\circ\text{C}$  in  $\text{CH}_2\text{Cl}_2$  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.<sup>8,13</sup>) As is clearly evident from these examples, the efficiency and especially the stereoselectivity of these reactions are excellent. It is noteworthy that the  $\beta$ -glycosides were produced with  $\geq 10:1$  selectivity in all cases, with the reaction of **8** and **15** being the only case that proceeded with less than 19:1  $\beta$ -selectivity. The

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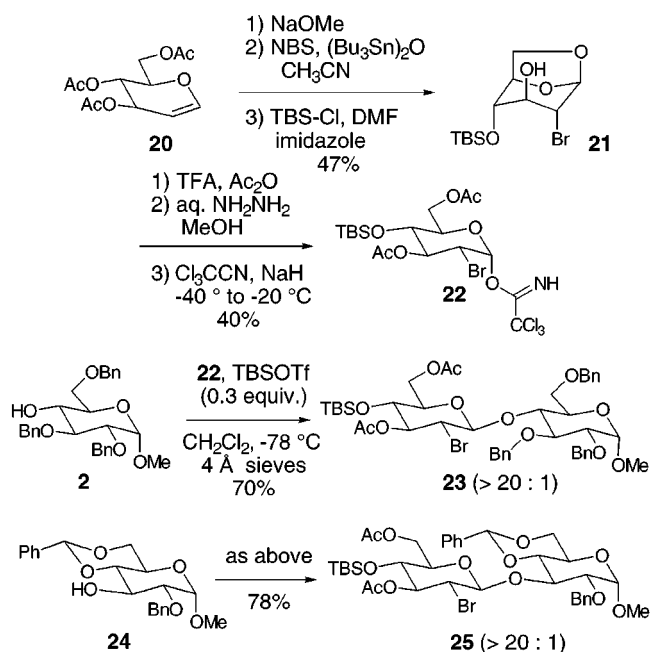
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conditions are sufficiently mild that the very acid sensitive glycal **15** can be glycosylated efficiently. Owing to the poor solubility of **13** under the reaction conditions ( $-78\text{ }^{\circ}\text{C}$ ,  $\text{CH}_2\text{-Cl}_2$ ), the coupling 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.<sup>2</sup>

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- $\beta$ -glycosides via silver silicate promoted glycosidations (although the stereoselectivity of these reactions is generally  $\leq 6:1$ ).<sup>14,15</sup>

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,  $(\text{Bu}_3\text{Sn})_2\text{O}$ ,  $\text{CH}_3\text{CN}$ ; 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  $\text{Br}_2$  in  $\text{CHCl}_3$  and provides a 9:1 mixture of the 1,6-anhydro-2-bromo-*gluco*- and -*manno* isomers.<sup>10</sup> 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  $\beta$ -selective glycosidation reactions with acceptors **2** and **24**, as summarized in Figure 4.

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**Figure 4.** Synthesis and  $\beta$ -selective glycosidation reactions of 2-deoxy-2-bromo- $\alpha$ -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- $\beta$ -glycosides, precursors of 2-deoxy- $\beta$ -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.<sup>2</sup> Application of this methodology to the synthesis of biologically relevant 2-deoxy- $\beta$ -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- $\alpha$ -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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