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Mechanistic studies on the stereoselective formation of glycosyl iodides: first characterization of β-D-glycosyl iodides

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Abstract

Treatment of glycosyl acetates with one equivalent of iodotrimethylsilane at low temperature results in the quantitative formation of glycosyl iodides. Carbohydrates that possess a participating group at the C-2 position initially form β-D-glycosyl iodides, which quickly equilibrate to the α-iodo anomers. The β anomer of peracetylated glucose reacts faster than the α anomer, presumably because the C-2 acetate can assist in displacing the silylated anomeric acetate. In contrast, the α anomer reacts faster than the β anomer in substrates lacking a participating group at C-2. For example, activation of 1-*O*-acetyl-2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranose leads to formation of the β iodide, while the corresponding β acetate produces the α iodide. Although the β iodides quickly equilibrate to the α anomers, they can be prepared in sizable quantities at low temperatures where equilibration is slow. This report describes the first stereoselective formation and characterization of β-D-glycosyl iodides. © 1997 Elsevier Science Ltd.

Keywords: Glycosyl iodides; β-D-Glycosyl iodides; NMR characterization

1. Introduction

Glycosyl iodides were first prepared by reaction of glycosyl bromides with sodium iodide in acetone [1]. More than 50 years later, Thiem and Meyer reported that glycosyl acetates, methyl glycosides, 1,6-anhydrosugars, and glycosyl acetals react with iodotrimethylsilane (Me_3SiI) to produce α-D-glycosyl iodides [2]. Other protocols for producing α-D-glycosyl iodides include reaction of anomeric hydroxyls with iodoenamines [3], and reaction of anomeric acetates with iodic acid in glacial acetic acid [4]. Purified α-D-glycosyl iodides have served as glycosyl donors in only a few cases [5,6], and the general consensus has been that these compounds are too reactive to be generally useful [7]. In situ generation of glycosyl iodides, from activated donors, and their subsequent glycosylation is an alternative approach [8]. In these reactions, both α- and β-D-glycosyl iodides have been proposed as intermediates, depending upon the stereochemical outcome. However, until this report β-D-glycosyl iodide formation had never been directly observed. Clearly, the inherent instability of anomeric iodides poses challenges in develop-

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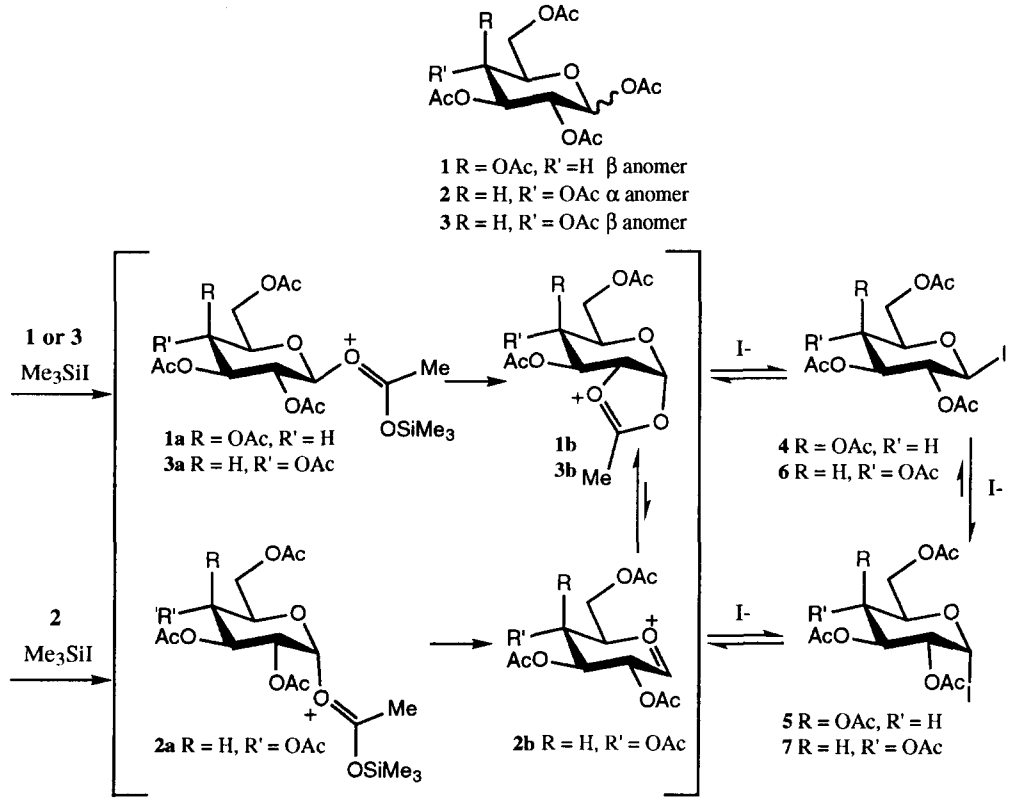
ing useful glycosylation protocols. These compounds are susceptible to both thermal and photochemical homolytic bond cleavage, creating the possibility for competing radical reactions [9]. However, we reasoned that if the iodides could be generated under mild conditions, then perhaps nucleophilic displacement with various glycosyl acceptors could be effected. Furthermore, stereoselective formation of either the α- or β-D-glycosyl iodides could lead to stereoselective glycosylation protocols. Reported herein are mechanistic studies on the stereoselective generation of various glycosyl iodides and the first NMR characterization of the β-iodo anomers.

2. Results and discussion

We began our studies by reinvestigating the reactions of peracetylated sugars with Me_3SiI. Thiem and Meyer performed these reactions at 80 °C in toluene with yields ranging from 68–80% [2]. We were concerned that even small amounts of decomposition products could adversely affect subsequent glycosylations; therefore, our experiments were performed at low temperatures in deuterated solvents in order to monitor the reaction course using NMR spectroscopy.

The β anomer of peracetylated D-galactose (**1**) was reacted with 1.2 equiv of Me_3SiI in dichloromethane-d_2 at −20 °C. After 60 min, evidence of the starting material and two new products was seen in the NMR spectrum (product ratio 17:1). The anomeric proton of the major product appeared as a doublet at δ 5.79 (J 9.5 Hz), while that of the minor product appeared at δ 7.09 (J 4.2 Hz). As the reaction progressed the starting material completely reacted leaving two products which equilibrated over several hours (Scheme 1). The NMR spectrum of 2,3,4,6-tetra-*O*-acetyl-α-D-galactopyranosyl iodide (**5**) had been reported by Thiem [2], and it matched the spectrum of the minor product. The major product was determined to be 2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyl iodide (**4**). After careful experimentation it was found that compound **4** could be prepared in large quantities at −40 °C (1 equiv Me_3SiI) where equilibration was slow enough to afford an approximately 30:1 mixture of β:α anomers.

We next looked at the reactions of the α and β anomers of peracetylated glucose (**2** and **3**, respectively). Compound **2** ($t_{1/2}$ ~ 8 h) reacted much slower than did **1** ($t_{1/2}$ ~ 8 min). The β iodide **6** was the first product to form, and over time it equilibrated to



Scheme 1.

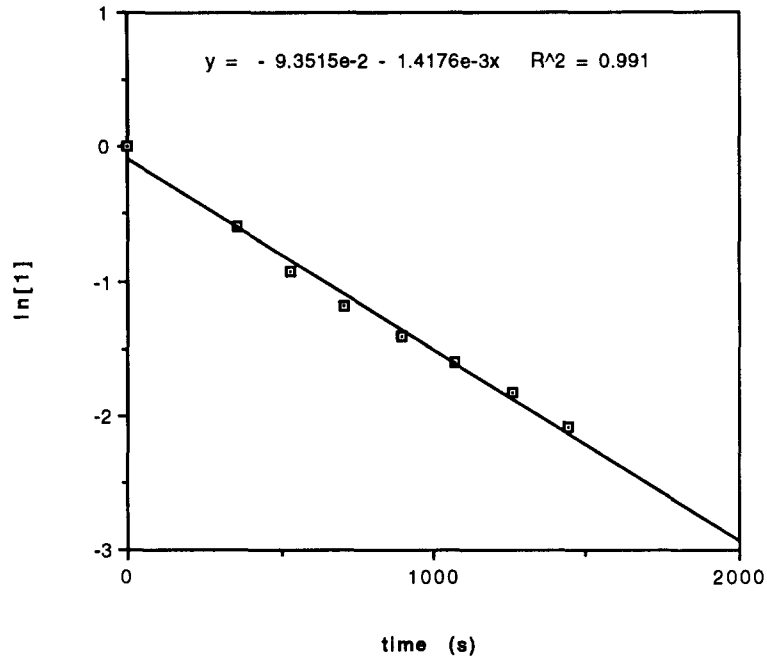


Fig. 1. First-order rate plot for **1**.

the α iodide **7**. These rates are approximated assuming a unimolecular rate-determining step, although the data suggest competing processes are at play (vide infra). In order to assure that the rate differences were not due to the stereochemistry at the C-4 position, **3** was subjected to the reaction conditions. The β anomer of peracetylated glucose **3** ($t_{1/2} \sim 17$ min) reacted similarly to **1** (**3** → **6** → **7**) suggesting that they follow similar reaction pathways.

A proposed mechanism of glycosyl iodide formation from peracetylated sugars is illustrated in Scheme 1. The rate data for reaction of the β acetates **1** and **3**

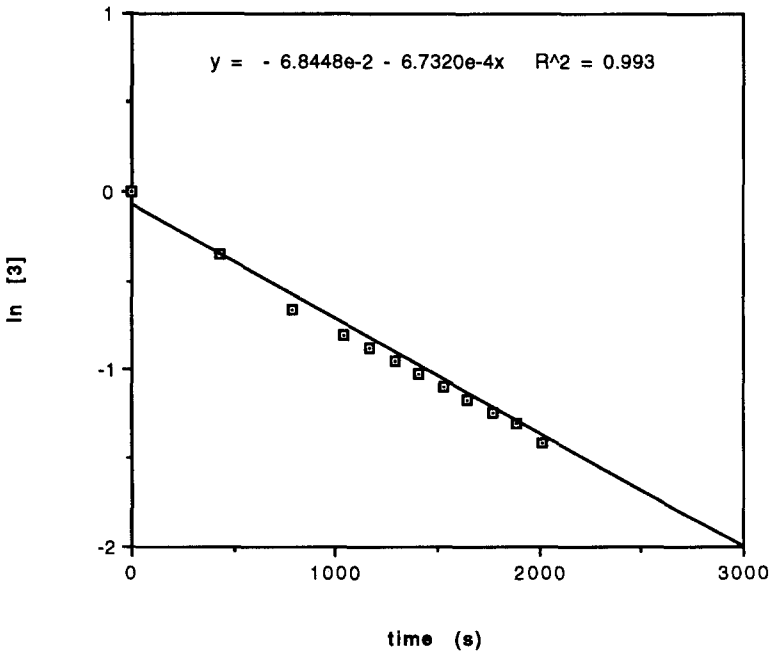


Fig. 2. First-order rate plot for **3**.

Table 1
Rate data for compounds **1**, **2**, and **3**

Compound	Rate (k)	$t_{1/2}$ (s)	R^2
1	1.42×10^{-3}	4.94×10^{2}	0.99
3	6.73×10^{-4}	1.04×10^{3}	0.99
2 (1st order)	2.38×10^{-5}	2.88×10^{4}	0.96
2 (2nd order)	3.25×10^{-5}	not determined	0.98

support a unimolecular rate-determining step (see Figs. 1 and 2 and Table 1). The reaction is thought to proceed through displacement of the silylated anomeric acetate (**1a** and **3a**) by the C-2 acetate to form a stabilized oxonium intermediate (**1b** and **3b**). Iodide can then attack the oxonium intermediates to produce the β glycosyl iodides (**4** and **6**) [10]. The

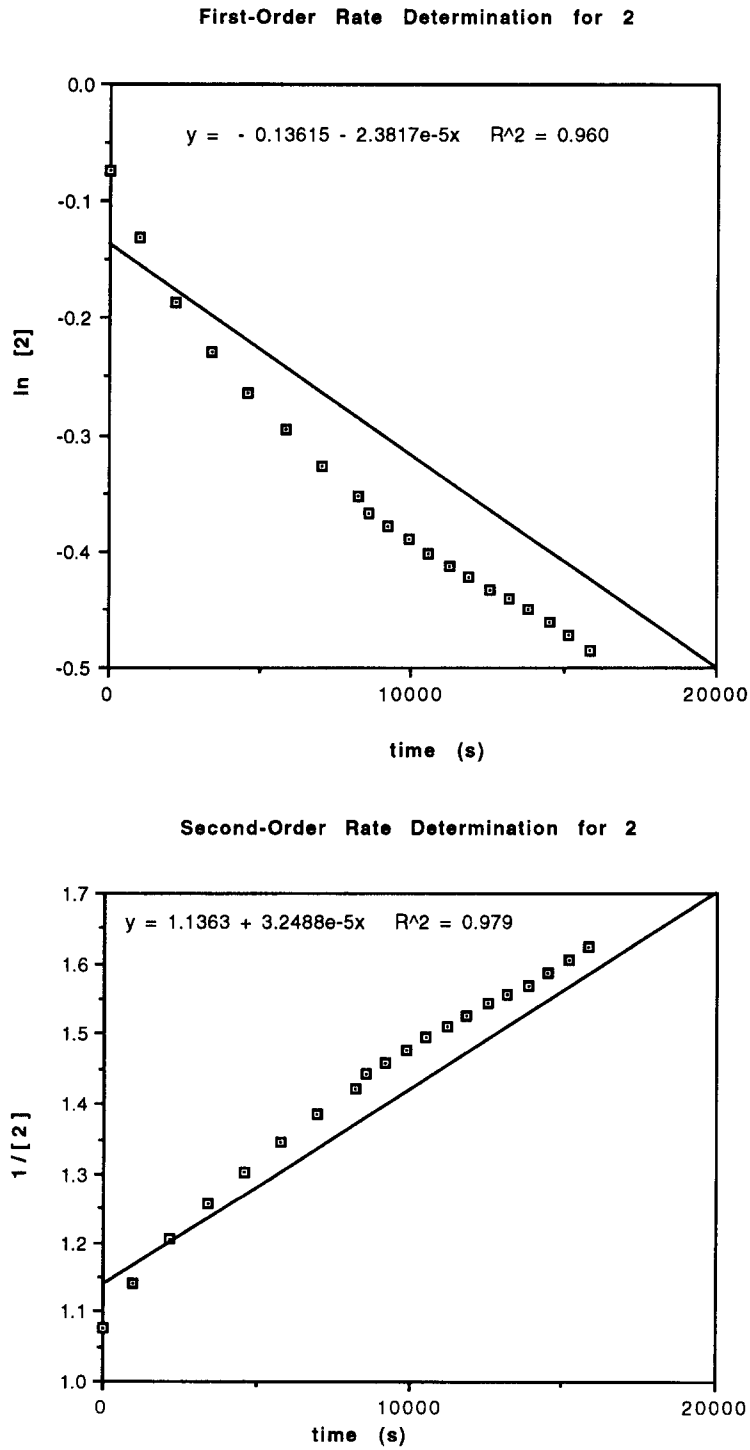
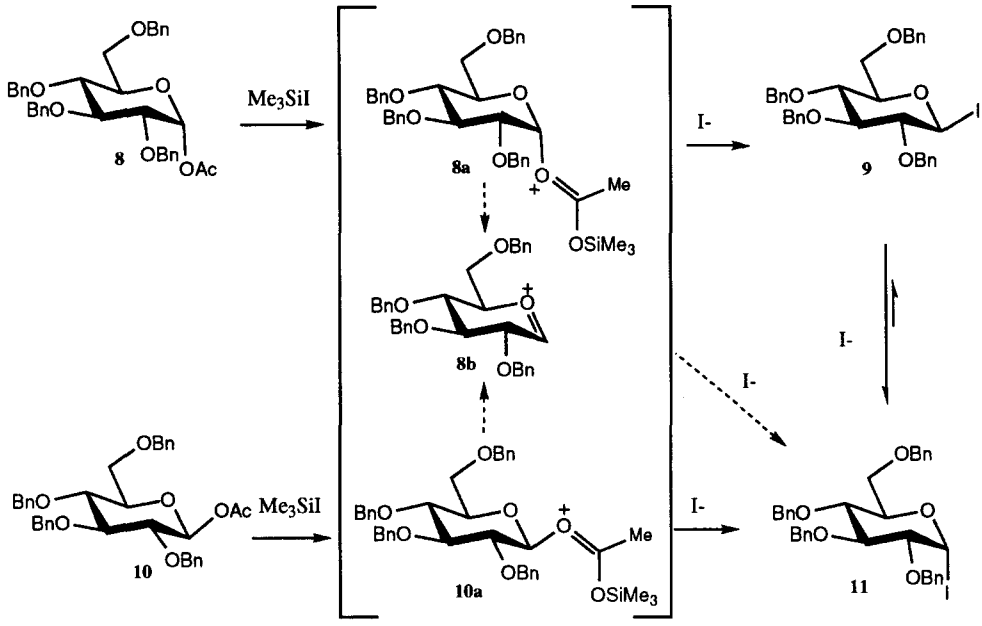


Fig. 3. First- and second-order rate plots for **2**.



Scheme 2.

rate data for reaction of **2** is less definitive, suggesting that competing reactions are occurring (see Fig. 3 and Table 1). Once the α-trimethylsilylacetoxonium intermediate **2a** is formed, it can react by either a unimolecular or bimolecular pathway. The unimolecular process involves displacement of the anomeric acetate to form the oxonium intermediate **2b**, which can be stabilized by the C-2 acetate to form **3b**, and subsequently **5**. Alternatively, iodide can directly attack **2a** giving **6** in a bimolecular process. Both of the reaction pathways are orders of magnitude slower than the reaction pathway of the β acetates. The α-iodide **7** results from either iodide trapping of the oxonium species (**2b**) or by direct displacement of the β iodide **6**.

In order to probe the importance of the C-2 acetate in enhancing the rate of the β-peracetylated sugars relative to the α anomers, we decided to study the reactions of 1-*O*-acetyl-2,3,4,6-tetra-*O*-benzyl-α,β-D-glucopyranoses **8** and **10** [1]. We reasoned that oxonium formation should occur more readily from the α-trimethylsilylacetoxonium intermediate (**9a**) due to better orbital overlap [12]. Furthermore, the positively charged α-anomeric acetate should be more reactive toward iodide displacement, due to the reverse anomeric effect [12,13]. When compound **8** was treated with Me_3SiI at -40 °C in dichloromethane-d_2, the reaction was complete before the NMR spectrum could be acquired, and only the α iodide **11** was observed. This compound had been previously prepared using a Finkelstein reaction on the anomeric bromide, but no NMR spectral data was reported [5]. When the reaction was cooled to -100 °C, formation of the β iodide (**9**) was observed, as well as its equilibration to **11**. In contrast, the β acetate (**10**) did not react at -100 °C. However, upon warming to 10 °C **11** began to appear in the spectrum, and the reaction was complete within 30 min.

Scheme 2 outlines the proposed mechanism of glycosyl iodide formation from sugars without C-2 participating groups. The rate-determining step for reaction of **8** is believed to be formation of **8a**, which subsequently undergoes nucleophilic attack by iodide to give **9**. Attack of **9** by iodide produces the more stable α anomer **11** under the reaction conditions. Due to rapid reaction rates, we cannot rule out the possibility that oxonium formation (**8b**) is a competing process that directly leads to the formation of **11**. Formation of the α iodide from **10** is believed to occur via direct displacement of the silylated acetate (**10a** → **11**).

In summary, we have demonstrated that glycosyl iodides can be stereoselectively and quantitatively generated at low temperatures from anomeric acetates. The only byproduct of the reaction is trimethylsilyl acetate, which can be easily removed in

[1] These compounds were prepared using an analogous procedure for preparing anomeric benzoates [11].

vacuo. Although equilibration of the β iodides readily occurs at room temperature, these compounds can be prepared in sizable quantities at low temperatures. Glycosylations with β-D-glycosyl iodide donors is currently under investigation in our laboratories.

3. Experimental

General methods.—Proton and carbon nuclear magnetic resonance spectra were recorded on either a Bruker AM 250 or Varian Unity 300 spectrometer. Chemical shifts are reported in parts per million relative to the residual solvent peak. ^{1}H NMR data are reported in the order of chemical shift, number of protons, multiplicity (s = singlet, d = doublet, q = quartet, m = multiplet, br = broad) and the coupling constant in hertz (Hz).

General procedure for the formation peracetylated glycosyl iodides.—The α and β anomers of 1,2,3,4,6-penta-*O*-acetyl-D-glucose (Aldrich) and the β anomer of 1,2,3,4,6-penta-*O*-acetyl-D-galactose (**1**) were dissolved in dichloromethane-d_2 in 0.26 M concentrations and placed in an NMR tube. Iodotrimethylsilane (1 equiv, from Geleste) was added directly into the NMR tube, and the reaction was followed by NMR spectroscopy using either a Bruker 250 or a Varian 300 spectrometer. These reactions were performed at different temperatures as indicated. Variable-temperature experiments were performed on the Varian 300 instrument.

*2,3,4,6-Tetra-*O*-acetyl-β-D-galactopyranosyl iodide* (**4**).—^{1}H NMR (CD_2Cl_2): δ 5.81 (d, 1 H, *J* 9.5 Hz, H-1), 5.50 (t, 1 H, *J* 9.8 Hz, H-2), 5.45 (dd, 1 H, H-4), 4.95 (dd, 1 H, *J* 9.9, 3.3 Hz, H-3), 4.10 (m, 2 H), 4.00 (dd, 1 H, *J* 12.53, 6.43 Hz), 2.16 (s, 3 H), 2.05 (s, 3 H), 2.02 (s, 3 H), 1.94 (s, 3 H). ^{13}C NMR (CD_2Cl_2): δ 170.53, 170.40, 170.06, 169.19, 77.24, 72.29, 70.66, 67.53, 61.72, 57.68, 21.01, 20.66–20.77 (3 C).

*2,3,4,6-Tetra-*O*-acetyl-α-D-galactopyranosyl iodide* (**5**).—^{1}H NMR (CD_2Cl_2): δ 7.10 (d, 1 H, *J* 4.15 Hz, H-1), 5.47 (dd, 1 H), 5.24 (dd, 1 H, *J* 10.53, 3.34 Hz), 4.35 (dd, 1 H, *J* 10.52, 4.19 Hz), 4.06–4.27 (m, 3 H), 2.13 (s, 3 H), 2.08 (s, 3 H), 2.03 (s, 3 H), 1.97 (s, 3 H). ^{13}C NMR (CD_2Cl_2): δ 170.48, 170.05–170.21 (3 C), 76.30, 74.22, 70.01, 67.83, 66.97, 61.17, 21.06, 20.71–20.76 (3 C).

*2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranosyl iodide* (**6**).—^{1}H NMR (CD_2Cl_2): δ 5.82 (d, 1 H, *J* 9.3 Hz, H-1), 5.28 (t, 1 H, *J* 9.11 Hz), 5.13 (m, 2 H), 4.20 (dd, 1 H, *J* 12.62, 4.79 Hz), 4.09 (dd, 1 H, *J* 10.24, 2.29 Hz), 3.74–3.81 (m, 1 H, H-5), 2.01 (s, 3 H), 2.00 (s, 3 H), 1.94 (s, 3 H), 1.92 (s, 3 H). ^{13}C NMR (CD_2Cl_2): δ 170.22, 169.68, 169.12, 168.72, 77.75 (C-1), 74.99, 71.50, 67.52, 61.56, 56.58, 20.50, 20.41, 20.28 (2 C).

*2,3,4,6-Tetra-*O*-acetyl-α-D-glucopyranosyl iodide* (**7**).—^{1}H NMR (CD_2Cl_2): δ 6.98 (d, 1 H, *J* 4.07 Hz, H-1), 5.39 (dd, 1 H, *J* 16.31, 9.8 Hz), 5.15 (t, 1 H, *J* 9.98 Hz), 4.29 (dd, 1 H *J* 12.79, 4.25 Hz), 4.18 (dd, 1 H, *J* 9.86, 4.23 Hz), 4.04 (m, 2 H), 2.03 (s, 3 H), 2.01 (s, 3 H), 1.99 (s, 3 H), 1.96 (s, 3 H). ^{13}C NMR (CD_2Cl_2): δ 170.15, 169.56, 169.35, 169.22, 74.98 (C-1), 73.74, 71.50, 70.09, 66.71, 60.80, 20.52, 20.33, 20.28 (2 C).

*1-*O*-Acetyl-2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranose* (**8**) *and 1-*O*-acetyl-2,3,4,6-tetra-*O*-benzyl-β-D-glucopyranose* (**10**).—2,3,4,6-Tetra-*O*-benzyl-D-glucopyranose (1 g, 1.8 mmol) was dissolved in 5 mL of pyridine, and then 0.2 mL (2.8 mmol, 1.6 equiv) of acetyl chloride was *cautiously* added dropwise to the mixture. The mixture was refluxed for approximately one h and quenched by addition of ethyl acetate and washed once with H_2O. The crude material was purified by flash chromatography using 5:1 hexane–ethyl acetate to obtain a 55% overall yield of a 4:1 mixture of the β and α anomers, respectively [11]. The anomers were separated by HPLC (Waters 510, Millipore HPLC) using a 6:1 hexane–ethyl acetate +9% acetone solvent system.

*1-*O*-Acetyl-2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranose* (**8**).—^{1}H NMR ($CDCl_3$): δ 7.17–7.32 (m, 20 H), 6.29 (d, 1 H, *J* 3.55 Hz, H-1), 4.92 (d, 1 H, *J* 11.0 Hz), 4.84 (d, 1 H, *J* 10.8 Hz), 4.80 (d, 1 H, *J* 11 Hz), 4.69 (d, 1 H, *J* 11.4 Hz), 4.64 (d, 1 H, *J* 11.4 Hz), 4.56 (d, 1 H, *J* 10.9 Hz), 4.54 (d, 1 H, *J* 11.9 Hz), 4.46 (d, 1 H, *J* 11.8 Hz), 3.95–3.83 (m, 2 H), 3.60–3.76 (m, 4 H), 2.12 (s, 3 H).

*1-*O*-Acetyl-2,3,4,6-tetra-*O*-benzyl-β-D-glucopyranose* (**10**).—^{1}H NMR ($CDCl_3$): δ 7.16–7.35 (m, 20 H), 5.59 (d, 1 H, *J* 8.03 Hz), 4.77–4.92 (m, 5 H), 4.56 (d, 2 H, *J* 12.5 Hz), 4.48 (d, 1 H, *J* 11.79 Hz), 3.52–3.72 (m, 6 H), 2.06 (s, 3 H).

*General procedure for the formation 2,3,4,6-tetra-*O*-benzyl-D-glycosyl iodides.*—The reactions to form the 2,3,4,6-tetra-*O*-benzyl-D-glucopyranosyl iodides were performed similarly to the procedures described for the peracetylated analogs except 0.013 M concentrations in CD_2Cl_2 were used. The reactions were followed by NMR spectroscopy at temperatures ranging from −100 to 10 °C on the Varian Unity 300 instrument.

2,3,4,6-Tetra-O-benzyl-β-D-glucopyranosyl iodide (**9**).—^{1}H NMR (−100 °C, CD_2Cl_2): δ 6.99–7.70 (m, 20 H), 5.61 (d, 1 H, *J* 9.04 Hz), 4.32–5.00 (m, 8 H), 3.39–3.85 (m, 6 H).

2,3,4,6-Tetra-O-benzyl-α-D-glucopyranosyl iodide (**11**) [5].—^{1}H NMR (CD_2Cl_2): δ 7.19–7.40 (m, 20 H), 6.96 (d, 1 H, *J* 3.7 Hz, H-1), 4.94 (d, 1 H, *J* 10.9 Hz), 4.85 (d, 1 H, *J* 10.9 Hz), 4.79 (d, 1 H, *J* 10.9 Hz), 4.71 (d, 1 H, *J* 11.46 Hz), 4.60 (d, 1 H, *J* 11.5 Hz), 4.56 (d, 1 H, *J* 10.83 Hz), 4.53 (d, 1 H, *J* 11.8 Hz), 4.49 (d, 1 H, *J* 11.8 Hz), 3.63–3.89 (m, 5 H), 2.81 (dd, 1 H, *J* 8.78 and 3.94 Hz).

Reaction kinetics.—Rate constants for the disappearance of the starting material for compounds **1**, **2**, and **3** were obtained by following the reaction to at least 75% completion except for the per-*O*-acetyl-α-D-glucose (went to 50% completion) with 1 equiv of Me_3SiI in CD_2Cl_2 at −40 °C over a period of time. First- and second-order kinetic plots were graphed for each reaction: ln[A] versus time (s) and 1/[A] versus time (s), respectively (A = per-*O*-acetyl-D-glucose and per-*O*-acetyl-D-galactose). The concentration of the starting material, [A], was obtained by dividing the integral value corresponding to the peak of the anomeric proton of the starting material over the sum of the integrals of the H-1 peaks of the α- and β-iodo sugars formed and the H-1 from the starting sugar. The first-order plots gave better correlation than did the second-order plots for the β sugars. The plots for the per-*O*-acetyl-D-glucose were not as conclusive as to whether first-order or second-order kinetics prevailed, as neither one showed true linearity. The R^2 obtained was 0.96 and 0.98 for the ln[A] and 1/[A] plots, respectively. The rate constants were obtained from the slope of the plots as shown in Table 1. The data in Table 1 indicate that the reactions proceed fastest for per-*O*-acetyl-β-D-galactose (**1**), followed by per-*O*-acetyl-β-D-glucose (**3**) with the per-*O*-acetyl-α-D-glucose (**2**) reacting slowest.

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References

[1] B. Helferich and R. Gootz, *Chem. Ber.*, 62 (1929) 2788–2792.
[2] J. Thiem and B. Meyer, *Chem. Ber.*, 113 (1980) 3075–3085.
[3] B. Ernst and T. Winkler, *Tetrahedron Lett.*, 30 (1989) 3081–3084.
[4] R.K. Ness, H.G. Fletcher, Jr., and C.S. Hudson, *J. Am. Chem. Soc.*, 72 (1950) 2200–2205.
[5] F.J. Kronzer and C. Schuerch, *Carbohydr. Res.*, 34 (1974) 71–78.
[6] Z. Tocik, R.A. Earl, and J. Beranék, *Nucleic Acids Res.*, 8 (1980) 4755–4761; Y. Araki, T. Endo, M. Tanji, J. Nagasawa, and Y. Ishido, *Tetrahedron Lett.*, 28 (1987) 5853–5856; H. Paulsen, V. Rutz, and I. Brockhausen, *Liebigs Ann. Chem.*, (1992) 747–758.
[7] R.R. Schmidt, *Angew. Chem. Int. Ed. Engl.*, 25 (1986) 212–235.
[8] S.-I. Hashimoto, T. Honda, and S. Ikegami, *Tetrahedron Lett.*, 31 (1990) 4769–4772; U. Schmid and H. Waldmann, *Tetrahedron Lett.*, 37 (1996) 3837–3840.
[9] B. Geise, S. Gilges, K.S. Groninger, C. Lamberth, and T. Witzel, *Liebigs Ann. Chem.*, (1988) 615–617; K.S. Groninger, K.F. Jager, and B. Giese, *Liebigs Ann. Chem.*, (1987) 731–732.
[10] H. Paulsen, *Adv. Carbohydr. Chem. Biochem.*, 26 (1971) 127–195.
[11] A.B. Charette, J.-F. Marcoux, and B. Coté, *Tetrahedron Lett.*, 32 (1991) 7215–7218.
[12] E. Juaristi, and G. Cuevas, *Tetrahedron*, 48 (1992) 5019–5087, and references therein.
[13] A.R. Vaino, S.S.C. Chan, W.A. Szarek, and G.R.J. Thatcher, *J. Org. Chem.*, 61 (1996) 4514.