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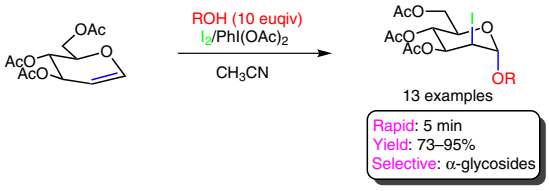
A Rapid and Diastereoselective Synthesis of 2-Deoxy-2-iodo-α-glycosides and its Mechanism for Diastereoselectivity

Wenjiao Yuan[a,c]
Yali Liu[b]
Chunbao Li*[a]

[a] Department of Chemistry, School of Science, Tianjin University, Tianjin 300350, P. R. of China
lichunbao@tju.edu.cn
[b] Department of Pharmaceutical Engineering, School of Chemical Engineering, Hebei University of Technology, Tianjin 300130, P. R. of China
[c] Department of Biochemical Engineering, Tianjin Modern Vocational Technology College, Tianjin 300350, P. R. of China



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Abstract Reductive deiodination of 2-deoxy-2-iodo-glycoside is an efficient and practical approach for the synthesis of 2-deoxyglycosides, which are moieties of bioactive compounds. However, inseparable diastereoisomers are usually formed in the preparation of 2-deoxy-2-iodo-glycosides via glycosylation of glycals with alcohols using current methods. To overcome this problem, a rapid and diastereoselective transformation of glycals and alcohols into 2-deoxy-2-iodo-α-glycosides enabled by I_2/PhI(OAc)$_2$ has been developed. 14 glycals, derived from 13 monosaccharides and one disaccharide, diastereoselectively yielded α-glycosides. Only in two cases the diastereoselectivity of the glycosylation was poor. The yields of glycosylation range from 73% to 95%, and the reactions are finished in only five minutes. Investigations for better diastereoselectivity by comparing I_2/Ph(OAc)$_2$- with I_2/Cu(OAc)$_2$-mediated glycosylations using UV analysis have been conducted.

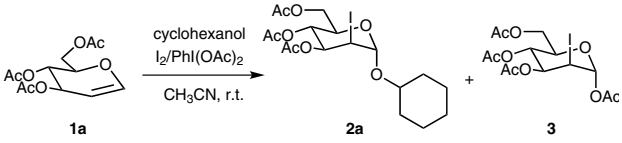
Key words 2-deoxy-2-iodo-glycoside, selective glycosylation, glycal, alcohol, iodine, iodobenzene diacetate

As moieties occurring in many biologically active natural products,[1] drugs,[2] and important intermediates[3] in organic synthesis, 2-deoxy sugars[4] are well-known. However, efficient and selective syntheses of 2-deoxy sugar derivatives remains a challenge in carbohydrate chemistry and natural product synthesis.[5] Due to the absence of neighboring substituents such as OR, diastereoselective preparations of specific 2-deoxy-glycosides are hardly achieved using a direct glycosylation reaction.[6] Consequently, several indirect methods[7] are established to solve this problem. For example, reductive deiodination of 2-deoxy-2-iodo-glycosides is a reliable and practical approach to yield 2-deoxy sugars with an indirect glycosylation strategy.[8] 2-Deoxy-2-iodo-glycosides have been synthesized via glycosylation of glycals with glycosyl acceptor in the presence of iodate reagent and oxidant, such as NIS,[9a] NH_4I/H_2O_2,[9b] NaI/CAN,[9c] I_2/CAN,[9d] I_2/Cu(OAc)$_2$,[9e] NIS/PPh_3,[9f] Me_3SI(OAc)$_2$,[9g] etc. Nevertheless, diastereoisomers are inevitably formed with these methods, which are difficult to separate by column chromatography.

Herein we wish to report a rapid and diastereoselective transformation of glycals and glycosyl acceptors into 2-deoxy-2-iodo-α-glycosides mediated by I_2/PhI(OAc)$_2$.[10] A mechanism is proposed that rationalizes the better α-manno selectivity of our method compared to the literature ones.

Initially, glucal **1a** (1 equiv) was treated with cyclohexanol (1 equiv) in the presence of I_2 (0.6 equiv) and PhI(OAc)$_2$ (1.2 equiv) in acetonitrile at room temperature. 2-Deoxy-2-iodo-α-D-mannopyranosyl acetate **3** was produced in 79%

Table 1 Optimization of Glycosylation Reaction Conditions[a]



1a 2a 3

Entry	Cyclohexanol (equiv)	Solvent	Yield of **2a** (%)[b]	Yield of **3** (%)[b]
1	1	CH_3CN	–	79
2	2	CH_3CN	–	77
3	5	CH_3CN	33	58
4	8	CH_3CN	74	13
5	10	CH_3CN	88	–
6	10	CH_2Cl_2	80	–
7	10	toluene	75	–
8	10	THF	56	–

[a] Glucal (1 mmol), I_2 (0.6 mmol), PhI(OAc)$_2$ (1.2 mmol) in CH_3CN (4 mL) at r.t.
[b] All yields were isolated yields.

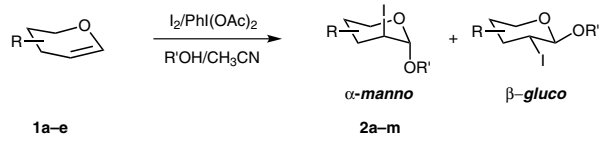
yield (Table 1, entry 1). Increasing the amount of glycosyl acceptor cyclohexanol from one equivalent to two, five, and eight equivalents, the mixture of compounds **2a** and **3** were formed in 0% and 77%, 33% and 58%, 74% and 13% yields, respectively (Table 1, entries 2–4). Further increasing the amount of cyclohexanol to ten equivalents, the reaction was quickly finished in five minutes and only cyclohexyl 2-deoxy-2-iodo-α-D-mannopyranoside (**2a**) was formed in 88% yield. A screen of various solvents, including CH_2Cl_2, toluene, and THF, indicated that acetonitrile was the optimal solvent. Hence, the optimized conditions were glucal (1 equiv), excess glycosyl acceptor (10 equiv), $PhI(OAc)_2$ (1.2 equiv), and I_2 (0.6 equiv) in acetonitrile at room temperature for five minutes (Table 1, entry 5).

To further demonstrate the synthetic potential of this method, we conducted this reaction on glycals derived from D-glucose (Table 2, entries 1–9), D-xylose (Table 2, entry 10), D-arabinose (Table 2, entry 11), D-galactose (Table 2, entry 12), and D-maltose (Table 2, entry 13) and glycosyl acceptor including primary (Table 2, entries 2–4, 6, and 7), secondary (Table 2, entries 1, 5, 9–13), and tertiary alcohols (Table 2, entry 8). All the rates of these reactions were rapid, only taking five minutes. The yields of these reactions ranged from good to excellent (73–95%). Only in the two cases of glycosylation of methanol with glucal and of isopropanol with xylal poor diastereoselectivity was observed (Table 2, entries 2 and 10). For the rest of glycosylations, α-manno products were synthesized diastereoselectively. The diastereoselectivity of this method is better than most of the current methods. In previous reports, the glycosylation products were almost always mixtures of α-manno and β-gluco, which are often inseparable [11] In addition, this method provides α-linked 2-deoxy-2-iodo-glycosides in shorter reaction times and higher yields.

An experiment was carried out to further investigate the influence of excess alcohol on glycosylation. A solution of 0.6 equivalents of I_2 and 1.2 equivalents of $PhI(OAc)_2$ in CH_3CN was stirred for five minutes, followed by slow addition of one equivalent of glucal and ten equivalents of EtOH to the above resulting solution. It was found that only compound **3** was obtained in 80% yield. Hence, excess alcohols are required for generation of **2a–m** from glycals to enhance the competitive edge of alcohol over AcO^-.

To understand the much better diastereoselectivity of our method over those in the literature,[7] we conducted a comparison experiment to indirectly analyze the concentrations of unreacted iodine in the reaction solutions via UV measurements (Figure 1). In the $I_2/PhI(OAc)_2$-mediated reaction, its absorption reduced from 0.972 to nearly 0 in one minute, while in the $I_2/Cu(OAc)_2$-mediated reaction the absorption reduced from 0.498 to 0.325 in one minute, to 0.232 in ten minutes, and to 0.098 in 60 minutes. This strongly suggests that $PhI(OAc)_2$is much more efficient than $Cu(OAc)_2$ in oxidizing I_2 to I^+. In the $I_2/PhI(OAc)_2$-mediated reaction, the concentration of I_2 is very low.

Table 2 Selective Synthesis of 2-Deoxy-2-iodo-glycosides Enabled by $I_2/PhI(OAc)_2$[a] and its Comparisons with the Literature Results



1a–e 2a–m

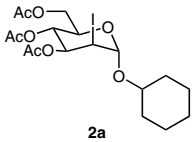
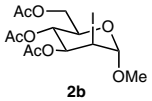
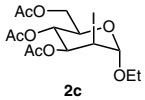
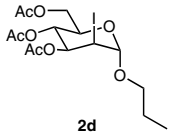
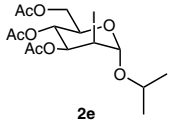
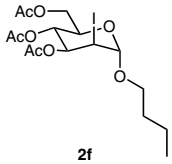
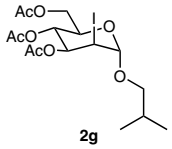
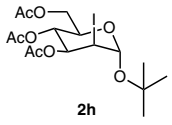
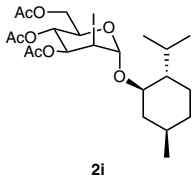
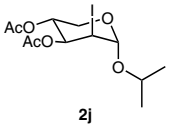
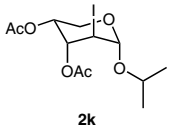
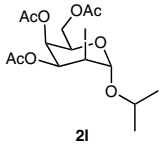
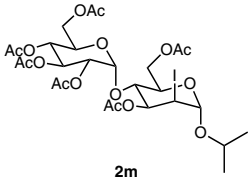
Entry	Product	Yield (%) dr (α-manno/β-gluco) This work[b]	Lit.[c]
1	 2a	88 only α	77[9d] 8:1[9d]
2	 2b	85 4:1	98[9e] 5:1[9e]
3	 2c	92 only α	95[9e] 7:1[9e]
4	 2d	88 >24:1	92[9e] 7:1[9e]
5	 2e	94 only α	80[9e] 9:1[9e]
6	 2f	85 only α	90[9e] 7:1[9e]
7	 2g	80 only α	–
8	 2h	91 only α	51[9e] 14:1[9e]

Table 2 (continued)

Entry	Product	Yield (%) dr (α-manno/β-gluco) This work[b]	Lit.[c]
9	 **2i**	82 only α	77[9d] 8:1[9d]
10	 **2j**	82 4:3	–
11	 **2k**	87 only α	–
12	 **2l**	95 >20:1	–
13	 **2m**	73 >14:1	–

[a]Glycal (1 mmol), $PhI(OAc)_2$ (1.2 mmol), I_2 (0.6 mmol), and alcohol (10 mmol) in CH_3CN (4 mL) at r.t. for 5 min.
[b]Isolated yields: dr determined by ^1H NMR analysis.
[c]Yield and anomer ratios reported by references.

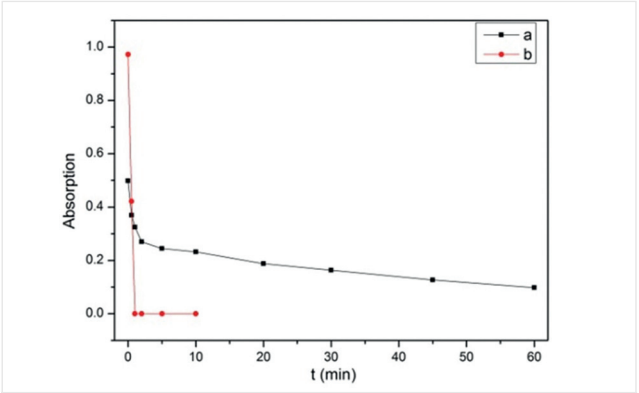
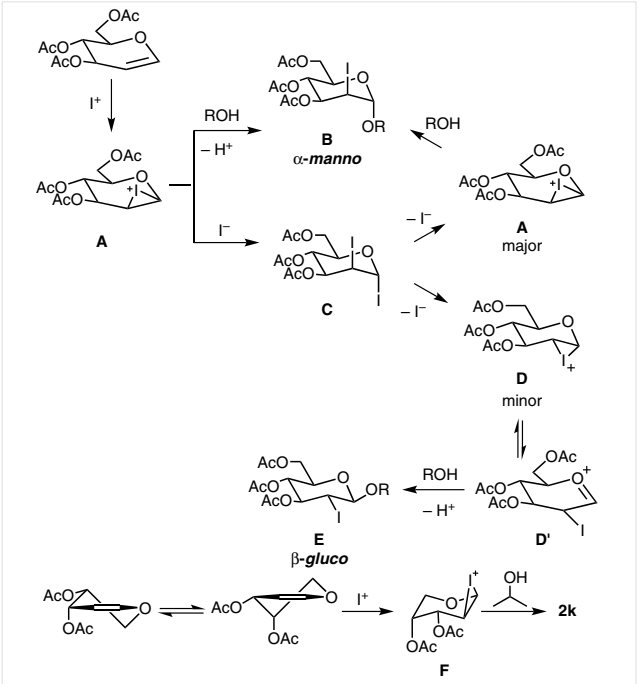


Figure 1 UV-absorption comparison between $I_2/PhI(OAc)_2$-mediated glycosylation (red) and $I_2/Cu(OAc)_2$-mediated glycosylation (black) (for conditions, see ref.[12]).



Scheme 1 Possible ways to α-manno and β-gluco isomers in glycosylation

According to these facts, the following mechanism is proposed (Scheme 1). Oxidation of I_2 by $PhI(OAc)_2$ leads to I^+, parts of them may be in the form of AcOI. This iodonium ion is in association with the β-OAc of C-3[13] and forms β-oriented three-membered iodonium. Nucleophilic attack by sugar acceptor at C-1 yields α-manno product **B**. However, if I^- is in high concentration, as in the case of glycosylation mediated by $Cu(OAc)_2$, it will compete with sugar acceptor to open the three-membered ring, forming diiodide **C**, which via neighboring-group participation forms minor intermediate **D**. **D′** is attacked by sugar acceptor to afford β-gluco product **E**, diastereoisomer of **B**.

In the case of **2k** (Table 2, entry 11), the two neighboring AcO groups at C-3 and C-4 are both on the same side, which makes the α-side hindered and probably weakens the association between I^+ and AcO^- at C-3. In contrary to glucal, the α-side of diacetyl arabinal has no hindered groups. All these factors favor the α-oriented iodonium **F**, which leads to **2k**. The same argument is applicable to the poor selectivity in the formation of **2j**, because the β-side hindrance of diacetyl xylal is larger than diacetyl arabinal and smaller than triacetyl glucal.

In summary, we have developed a rapid and diastereoselective method for synthesis of 2-deoxy-2-iodo-α-glycosides from glycals and glycosyl acceptors. A highly selective access to α-manno isomer in glycosylation under our reaction conditions has been realized. On the basis of control experiment, we propose a reaction mechanism and discuss

the influence of $PhI(OAc)_2$ and $Cu(OAc)_2$ on the diastereoselectivity glycosylations. And the better performance of this procedure is attributed to the $PhI(OAc)_2$ efficiency in oxidizing I_2 into I^+.

Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0036-1588440.

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(10) **General Procedures for Preparation of 2-Deoxy-2-iodo-α-glycosides**

To a solution of glycal (1 mmol), alcohol (10 mmol), and $PhI(OAc)_2$ (1.2 mmol) in CH_3CN (4 mL) was added I_2 (0.6 mmol), the mixture was stirred at r.t. for 5 min. After addition of EtOAc (50 mL) to the reaction mixture, the organic phase was washed with sat. $Na_2S_2O_3$, water and brine, dried over anhydrous Na_2SO_4, and concentrated. The residue was further purified by column chromatography to afford final product.

Cyclohexyl 3,4,6-Tri-*O*-acetyl-2-deoxy-2-iodo-α-D-mannopyranoside (2a)

438.5 mg, yield 88%, colorless syrup. ^1H NMR (400 MHz, $CDCl_3$): δ = 5.37 (t, *J* = 9.7 Hz, 1 H), 5.32 (s, 1 H), 4.69 (dd, *J* = 9.4, 4.3 Hz, 1 H), 4.51 (dd, *J* = 4.2, 0.9 Hz, 1 H), 4.26–4.16 (m, 2 H), 4.16–4.09 (m, 1 H), 3.60 (ddd, *J* = 13.1, 9.1, 3.8 Hz, 1 H), 2.12 (s, 3 H), 2.10 (s, 3 H), 2.07 (s, 3 H), 1.92–1.84 (m, 2 H), 1.78–1.72 (m, 2 H), 1.59–1.50 (m, 1 H), 1.48–1.37 (m, 1 H), 1.36–1.20 (m, 4 H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 170.69, 169.87, 169.56, 99.59, 76.92, 69.20, 69.15, 67.86, 62.38, 33.19, 31.59, 30.70, 25.45, 24.10, 23.84, 20.98, 20.73, 20.68.

***i*-Propyl 3,4-Di-*O*-acetyl-2-deoxy-2-iodo-α-D-arabinopyranoside (2k)**

337.2 mg, yield 87%, white solid. ^1H NMR (400 MHz, $CDCl_3$): δ = 5.53 (s, 1 H), 5.19–5.04 (m, 1 H), 4.87 (d, *J* = 7.5 Hz, 1 H), 4.16 (dd, *J* = 7.5, 3.2 Hz, 1 H), 4.02–3.90 (m, 2 H), 3.81 (dd, *J* = 11.3, 9.4 Hz, 1 H), 2.20 (s, 3 H), 2.03 (s, 3 H), 1.24 (dd, *J* = 8.1, 6.3 Hz, 6 H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 169.68, 169.54, 99.64, 72.41, 70.23, 66.67, 61.76, 27.59, 23.29, 21.65, 20.80, 20.71. HRMS: *m/z* calcd for $C_{12}H_{20}O_6IH$ [M + H^+]: 387.0299; found: 387.0302.

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(12) **I_2/PhI(OAc)$_2$-Mediated Glycosylation**

Glycal (1 mmol), alcohol (10 mmol), I_2 (0.6 mmol), and $PhI(OAc)_2$ (1.2 mmol) in CH_3CN (4 mL).

I_2/Cu(OAc)$_2$-Mediated Glycosylation

Glycal (0.4 mmol), alcohol (0.6 mmol), I_2 (0.6 mmol), molecular sieves 4 Å (0.108 g) and $Cu(OAc)_2$ (0.6 mmol) in CH_2Cl_2 (4 mL). These reaction solutions (diluted at 30 times by $CHCl_3$) are measured by UV at 530 nm.

(13) Shimizu, M.; Morita, O.; Itoh, S.; Fujisawa, T. *Tetrahedron Lett.* **1992**, *33*, 7003.