An Efficient and Cost-Effective Preparation of Di-*O*-Acetyl-D-Rhamnal

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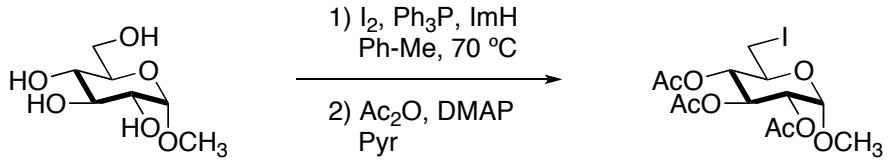
SUPPLEMENTARY INFORMATION

Experimental procedures and spectroscopic data for compounds **1**, **3**, and **4**.

General Procedures. All non-aqueous reactions were carried out in flame-dried round-bottomed flasks under an atmosphere of argon. Air- and moisture-sensitive liquids were transferred by oven-dried stainless steel syringes. Reactions were conducted at room temperature (approximately 22 ºC) unless otherwise noted. Flash chromatography was performed with the indicated solvents using standard grade silica gel SiliaFlash® P60 (particle size 230-400 mesh) from Silicycle Incorporated. Reactions were monitored by thin-layer chromatography (TLC) using 0.25 mm thickness precoated glass-backed silica gel plates containing F254 indicator manufactured by EMD. Visualization was accomplished with UV light and aqueous *p*-anisaldehyde, phosphomolybdic acid, or potassium permanganate stain solution followed by charring on a hot plate. Yields refer to chromatographically and spectroscopically pure compounds unless otherwise stated.

Materials. Anhydrous reaction solvents such as methylene chloride, pyridine, and toluene were purchased from Acros. All other commercial reagents were purchased from either Sigma-Aldrich or Acros and used as received without additional purification.

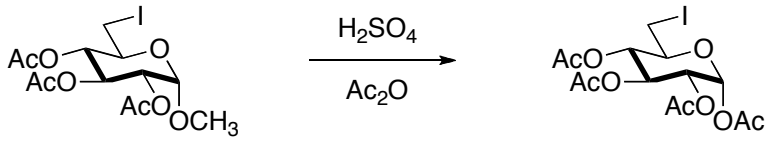
Instrumentation. Infrared spectra were recorded using a Perkin-Elmer Spectrum One FT-IR spectrometer equipped with a Universal ATR Sampling Accessory and are reported in terms of frequency of absorption (cm^{-1}). ^{1}H NMR spectra were measured at 400 MHz on a JEOL ECS-400 spectrometer and are reported relative to deuterated solvent signals. Data for ^{1}H NMR spectra are reported as follows: chemical shift (δ ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, dd = doublet of doublets, qt = quartet of triplets, m = multiplet, app = apparent), coupling constants (Hz), and integration. ^{13}C NMR spectra were measured at 100 MHz on a JEOL ECS-400 spectrometer and are reported relative to deuterated solvent signals. Accurate mass measurements were performed by Dr. William Boggess of the Mass Spectrometry and Proteomics Facility at the University of Notre Dame. Optical rotations were measured using a Jasco P-2000 digital polarimeter and are reported as follows $[\alpha]_{\lambda}^{T}$, (c g/100 mL, solvent).



2 **3**

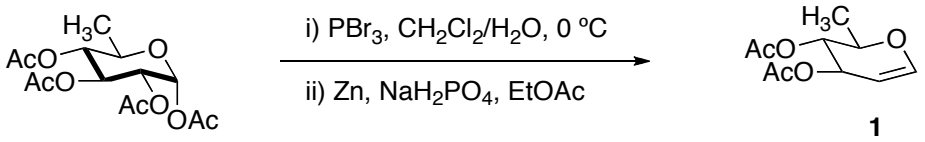
Methyl α-D-2,3,4-triacetoxy-6-deoxy-6-iodoglucopyranoside (3): To a solution of methyl α-D-glucopyranoside (5.00 g, 25.8 mmol) in toluene (500 mL) at room temperature was added triphenylphosphine (10.1 g, 38.6 mmol) followed by imidazole (5.30 g, 3.00 mmol) and iodine (9.15 g, 1.40 mmol) and the reaction was heated to 70 ºC for 2 hrs. The reaction was cooled to room temperature and water (50 mL) was added and the mixture was stirred vigorously for 10 min. The organic layer was extracted with water (1 X 50 mL) and the combined aqueous layers were concentrated *in vacuo*. The residue was placed on a high vacuum manifold to afford 11.0 g of methyl α-D-6-deoxy-6-iodoglucopyranoside as an off-white solid.

To a solution of methyl α-D-6-deoxy-6-iodoglucopyranoside (11.0 g, 25.8 mmol) obtained above in pyridine (52.0 mL) at room temperature was added acetic anhydride (14.6 mL, 155 mmol) followed by 4-dimethylaminopyridine (0.32 g, 2.58 mmol) and the reaction continued stirring at room temperature for 6 hrs at which time additional acetic anhydride (7.30 mL, 77.3 mmol) was added and the reaction continued stirring at room temperature for 21 hrs. The solvent was removed *in vacuo* and the residue was dissolved in toluene (100 mL) and washed with water (100 mL). The combined organic layers were concentrated *in vacuo* to afford 9.97 g (90% from methyl α-D-glucopyranoside) of methyl α-D-2,3,4-triacetoxy-6-deoxy-6-iodoglucopyranoside (**3**) as an off-white solid: $[\alpha]_D^{22}$ = +78.0 (*c* = 0.06, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.42 (dd, *J* = 10.0, 9.2 Hz, 1H), 4.92 (d, *J* = 3.6 Hz, 1H), 4.85-4.80 (m, 2H), 3.77-3.72 (m, 1H), 3.43 (s, 3H), 3.26 (dd, *J* = 11.0, 2.3 Hz, 1H), 3.09 (dd, *J* = 11.0, 8.2 Hz, 1H), 2.03 (s, 3H), 2.01 (s, 3H), 1.96 (s, 3H); ^{13}C NMR (100 MHz) δ 170.0, 169.9, 169.6, 96.5, 72.3, 70.7, 69.5, 68.5, 55.6, 20.6, 20.6, 20.4, 3.63; IR (neat): 1737, 1371, 1262, 1226, 1199, 1179, 1032; HRMS (ESI) calcd for $C_{13}H_{19}INaO_8$ $(M+Na)^+$ 453.0017, found 453.0018.



3 **4**

Acetoxy α-D-2,3,4-triacetoxy-6-deoxy-6-iodoglucopyranoside (4): To a solution of methyl α-D-2,3,4-triacetoxy-6-deoxy-6-iodoglucopyranoside (**3**) (9.97 g, 23.2 mmol) in acetic anhydride (124 mL) at room temperature was added concentrated sulfuric acid (2.50 mL, 46.9 mmol) and the reaction continued stirring at room temperature for 18 hrs. The solvent was removed *in vacuo* and the resulting orange residue was dissolved in EtOAc (250 mL) and H_2O (250 mL) and stirred vigorously for 15 min. The reaction was extracted with EtOAc (3 X 60 mL) and the combined organic layers were washed with saturated $NaHCO_3$ (5 X 250 mL) then H_2O (2 X 250 mL). The organic layers were dried over Na_2SO_4, filtered, and concentrated *in vacuo* to afford 9.34 g of **4** as an off-white solid (88%): $[\alpha]_D^{22}$ = +69.9 (*c* = 0.05, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.28 (d, *J* = 3.6 Hz, 1H), 5.42 (t, *J* = 9.6 Hz, 1H), 5.03 (dd, *J* = 10.0, 3.6 Hz, 1H), 4.94 (t, *J* = 9.6 Hz, 1H), 3.79-3.75 (m, 1H), 3.27 (dd, *J* = 11.0, 2.7 Hz, 1H), 3.10 (dd, *J* = 11.0, 6.0 Hz, 1H), 2.13 (s, 3H), 2.02 (s, 3H), 1.97 (s, 3H), 1.96 (s, 3H); ^{13}C NMR (100 MHz) δ 170.1, 169.5, 169.2, 168.6, 88.7, 72.0, 70.4, 69.3, 69.1, 20.8, 20.6, 20.5, 20.3, 3.39; IR (neat): 1757, 1738, 1378, 1260, 1215, 1033, 1018 cm^{-1}; HRMS (ESI) calcd for $C_{14}H_{19}INaO_9$ $(M+Na)^+$ 480.9966, found 480.9970.



1

Di-*O*-acetyl-D-rhamnal (1): To a solution of acetoxy α-D-2,3,4-triacetoxy-6-deoxyglucopyranoside (1.34 g, 4.03 mmol) in CH_2Cl_2 (13.0 mL) at 0 ºC was added a solution of PBr_3 (0.64 mL, 6.85 mmol) in H_2O (0.45 mL) and the reaction continued stirring for 10 mins at which time the reaction was warmed to room temperature and stirred for 2 hrs. The reaction was diluted with CH_2Cl_2 (26 mL) and washed with H_2O (1 X 25 mL), saturated $NaHCO_3$ (1 X 25 mL), and brine (2 X 25 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated *in vacuo* to afford a pale yellow oil that was used immediately in the next step without further purification.

The yellow oil obtained above was dissolved in EtOAc (8.00 mL) followed by the addition of saturated NaH_2PO_4 (16.0 mL), and Zn metal (3.30 g). The reaction continued stirring at room temperature for 90 mins at which time the reaction was extracted with EtOAc (3 X 15 mL). The combined organic layers were washed with H_2O (1 X 50 mL), saturated $NaHCO_3$ (1 X 50 mL), and brine (1 X 50 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated *in vacuo* to provide di-*O*-acetyl-D-rhamnal (**1**) as a clear oil (55%): $[\alpha]_D^{22}$ = -37.1 (*c* = 0.08, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.41 (d, *J* = 6.4 Hz, 1H), 5.31-5.30 (m, 1H), 5.00 (dd, *J* = 7.8, 6.4 Hz, 1H), 4.75 (dd, *J* = 6.4, 3.2 Hz, 1H), 4.08 (app qt, *J* = 6.8 Hz, 1H), 2.06 (s, 3H), 2.02 (s, 3H), 1.29 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz) δ 175.2, 174.4, 150.5, 103.2, 77.0, 76.2, 25.6, 25.4, 21.1; IR (neat): 1734, 1648, 1371, 1215, 1045, 1023 cm^{-1}; HRMS (ESI) calcd for $C_{10}H_{14}NaO$ $(M+Na)^+$ 237.0733, found 237.0772.