The One Pot Conversion of Glycals to *cis*-1,2-isopropylidenes

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EXPERIMENTAL

All commercial materials were used without purification, unless otherwise noted. CH₂Cl₂, THF, and diethyl ether were passed through neutral alumina columns prior to use. Toluene was passed through neutral alumina and copper (II) oxide columns before use. Methanol and DMF were purchased anhydrous and used without further purification. Analytical thin-layer chromatography was performed on E. Merck silica gel 60 F254 plate (0.25 mm). Compounds were visualized by cerium sulfate-ammonium molybdate stain and heating. Liquid chromatography was performed using forced flow of the indicated solvent on silica (230-400 Mesh).

Methyl 3-*O*-benzyl-1,2-*O*-isopropylidene- α -D-glucopyranosiduronate (1). Glycal **10a** (193 mg, 0.51 mmol) was coevaporated three times with toluene and dissolved in CH₂Cl₂ (1 mL). The reaction mixture was cooled to 0°C and DMDO (8 mL, ~0.08 M in acetone) was added. The reaction mixture was stirred for 10 min and ethyl vinyl ether (50 μ L, 0.5 mol) was added and the reaction mixture stirred an additional 10 min. Zinc (II) chloride (102 μ L, 0.5 M in Et₂O) was added, the reaction mixture

brought to room temperature and stirred for 18 h. The reaction mixture was poured into water (100 mL) and the aqueous phase extracted with CH_2Cl_2 (2 x 100 mL) and ethyl acetate (2 x 50 mL). The combined organic layers were dried over MgSO_4 , filtered, and the solvent removed under reduced pressure.

The crude material was dissolved in THF (5 mL) and tetrabutylammonium fluoride (560 μL , 1.0 M in THF) was added. The reaction mixture was stirred for 30 min and poured into saturated NH_4Cl . The aqueous phase was extracted with CH_2Cl_2 (2 x 100 mL) and ethyl acetate (2 x 50 mL). The combined organic layers were dried over MgSO_4 , filtered, and the solvent removed under reduced pressure.

The residue was dissolved in CH_2Cl_2 (1 mL) and water (0.5 mL), saturated NaHCO_3 (2 mL), KBr (6 mg, 0.05 mmol), and tetrabutylammonium bromide (8 mg, 0.025 mmol) were added. The reaction mixture was cooled to 0°C and 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO) (~2 mg) was added. Bleach (2.5 mL) was added in five portions ten minutes apart; the reaction turned deep yellow. After complete addition of the bleach the reaction mixture was stirred for 1.5 h at 0°C . Methanol was added until the reaction was decolorized and stirred for 15 min. The reaction mixture was diluted with water (50 mL) and extracted with CH_2Cl_2 (75 mL). The aqueous layer was acidified by dropwise addition of conc. HCl until the pH was less than 2 and extracted with CH_2Cl_2 (3 x 75 mL) and ethyl acetate (50 mL). The combined organic layers were dried over MgSO_4 , filtered, and the solvent removed under reduced pressure.

The crude acid was coevaporated twice with toluene and dissolved in DMF (1 mL) under argon. To the reaction mixture was added KHCO_3 (100 mg, 1 mmol) and methyl iodide (63 μL , 1 mmol). The reaction was stirred for 16 h at room temperature. The reaction mixture was diluted with ethyl acetate (100 mL) and washed with water, saturated $\text{Na}_2\text{S}_2\text{O}_3$, and brine. The organic layer was dried over MgSO_4 , filtered, and the solvent removed under reduced pressure. Flash silica gel column chromatography (hexanes-ethyl acetate 85:15) yielded **1** (83 mg, 0.245 mmol, 48%) as a clear oil. Spectra were consistent with reported data.¹

1,2-*O*-isopropylidene-3,4,6-tri-*O*-benzyl- α -D-glucopyranoside (2b). Followed general procedure to yield: 33 mg, 67%. Spectra were consistent with reported data.²

1,2-*O*-isopropylidene-3,4,6-tri-*O*-acetyl- α -D-glucopyranoside (3b). Followed general procedure to yield: 7 mg, 20%. Spectra were consistent with reported data.³

6-*O*-*t*-Butyldiphenylsilyl-3,4-di-*O*-pivaloyl-D-glucal (4a) Glycal **14** (278 mg, 0.72 mmol) was dissolved in CH₂Cl₂ (6 mL) and pyridine (0.93 mL). DMAP (17.5 mg, 0.14 mmol) and trimethylacetyl chloride (360 μ L, 2.9 mmol) were added and the reaction mixture was stirred for 18 h at room temperature. Water (2 mL) was added and the reaction mixture stirred for 3 h to quench the acid chloride. The reaction mixture was poured into ethyl acetate (100 mL) and the organic layer was extracted with saturated NaHCO₃ (50 mL) and brine (50 mL). The organic layer was dried over MgSO₄, filtered, and the solvent removed under reduced pressure. Flash silica gel column chromatography (hexanes-ethyl acetate 30:1) yielded **4a** (210 mg, 0.38 mmol, 52.5%) as a clear oil. Rf. 0.44 (hexanes:ethyl acetate 9:1). $[\alpha]^{24}_{\text{D}}$: -10.0, (c = 0.87). IR (thin film, NaCl plate) 2962, 1732, 1651 cm⁻¹. ¹HNMR (500 MHz, CDCl₃) δ 7.60-7.70 (m, 4H), 7.36-7.45 (m, 6H), 6.44 (d², J = 6.1, 1.2 Hz, 1H), 5.29-5.31 (m, 1H), 5.23-5.25 (m, 1H), 4.75 (d², J = 6.1, 3.2 Hz, 1H), 4.15-4.18 (m, 1H), 3.85 (d², J = 11.5, 6.1 Hz, 1H), 3.77 (d², J = 11.5, 2.8 Hz, 1H), 1.13 (s, 9H), 1.10 (s, 9H), 1.07 (s, 9H). ¹³CNMR (125 MHz, CDCl₃) δ 178.0, 176.7, 146.0, 135.9, 133.4, 133.3, 129.9, 129.85, 127.9, 98.6, 77.2, 67.7, 67.0, 62.2, 38.9, 38.8, 27.2, 27.19, 26.9, 19.4. ESI MS (C₃₂H₄₄O₆Si) m/z (M + Na⁺) calcd 575.2799, obsd 575.2812.

6-*O*-*t*-Butyldiphenylsilyl-1,2-*O*-isopropylidene-3,4-di-*O*-pivaloyl- α -D-glucopyranoside (4b). Followed general procedure to yield: 37 mg, 60%. Rf. 0.54 (hexanes:ethyl acetate 4 :1). $[\alpha]^{24}_{\text{D}}$: +9.72, (c = 1.23). IR (thin film, NaCl plate) 2963, 1739 cm⁻¹. ¹HNMR (500 MHz, CDCl₃) δ 7.72 (ψ t, 2H), 7.70 (ψ t, 2H), 7.35-7.67 (m, 6H), 5.64 (d, J = 4.8 Hz, 1H), 5.12-5.15 (m, 2H), 4.16-4.18 (m, 1H), 3.96-3.99 (m, 1H), 3.80 (d², J = 11.5, 2.3 Hz, 1H), 3.70 (d², J = 11.5, 4.5 Hz, 1H), 1.59 (s, 3H), 1.37 (s, 3H), 1.23 (s, 9H), 1.13 (s, 9H), 1.06 (s, 9H). ¹³CNMR (125 MHz, CDCl₃) δ 177.1, 177.0, 135.9, 135.8,

133.45, 133.4, 129.85, 129.8, 127.9, 109.8, 97.1, 73.4, 70.5, 69.8, 67.5, 63.3, 38.9, 38.8, 27.2, 27.1, 27.0, 26.5, 25.9, 19.5. ESI MS ($C_{35}H_{50}O_8Si$) m/z ($M + Na^+$) calcd 649.3167, obsd 649.3144.

3,4-Di-*O*-acetyl-6-*O*-triisopropylsilyl-D-glucal (5a) Glycal **13** (91 mg, 0.3 mmol) was dissolved in CH_2Cl_2 (2.5 mL) and pyridine (0.5 mL). DMAP (4 mg, 0.03 mmol) and acetyl chloride (113 μ L, 1.2 mmol) were added and the reaction mixture was stirred for 3 h at room temperature. Water (1 mL) was added and the reaction mixture stirred for 1 h to quench the acid chloride. The reaction mixture was poured into ethyl acetate (100 mL) and the organic layer was extracted with saturated $NaHCO_3$ (50 mL) and brine (50 mL). The organic layer was dried over $MgSO_4$, filtered, and the solvent removed under reduced pressure. Flash silica gel column chromatography (hexanes-ethyl acetate 10:1) yielded **5a** (92 mg, 0.24 mmol, 80%) as a clear oil. Rf. 0.46 (hexanes:ethyl acetate 4:1). $[\alpha]_D^{24}$: -2.33, ($c = 1.27$). IR (thin film, NaCl plate) 2944, 2867, 1743, 1651 cm^{-1} . 1H NMR (500 MHz, $CDCl_3$) δ 6.47 (d, $J = 5.8$ Hz, 1H), 5.31 (m, 2H), 4.75 (m, 1H), 4.13 (m, 1H), 3.90 (d, $J = 4.8$ Hz, 2H), 2.07 (s, 3H), 2.04 (s, 3H), 1.02-1.13 (m, 21H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.3, 169.6, 146.2, 98.3, 67.7, 67.5, 61.6, 21.3, 21.1, 18.1, 18.05, 12.1. ESI MS ($C_{19}H_{34}O_6Si$) m/z ($M + Na^+$) calcd 409.2017, obsd 409.2014.

3,4-Di-*O*-acetyl-1,2-*O*-isopropylidene-6-*O*-triisopropylsilyl- α -D-glucopyranoside (5b). Followed general procedure to yield: 31 mg, 75%. Rf. 0.29 (hexanes:ethyl acetate 4:1). $[\alpha]_D^{24}$: +14.6, ($c = 1.25$). IR (thin film, NaCl plate) 2943, 2867, 1751 cm^{-1} . 1H NMR (500 MHz, $CDCl_3$) δ 5.61 (d, $J = 4.8$ Hz, 1H), 5.20 (ψt, 1H), 5.04 (m, 1H), 4.18 (m, 1H), 3.94 (m, 1H), 3.86 (d², $J = 11.2, 2.7$ Hz, 1H), 2.10 (s, 3H), 2.07 (s, 3H), 1.60 (s, 3H), 1.35 (s, H), 0.97-1.14 (m, 21H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.9, 169.7, 109.8, 97.0, 73.5, 71.1, 70.0, 68.5, 63.5, 26.5, 25.8, 21.15, 21.1, 18.1, 18.10, 12.1. ESI MS ($C_{22}H_{40}O_8Si$) m/z ($M + Na^+$) calcd 483.2385, obsd 483.2376.

3-*O*-Benzyl-4-*O*-*t*-butyldimethylsilyl-6-*O*-triisopropylsilyl-D-glucal (6a) Glycal **10a** (516 mg, 1.31 mmol) was coevaporated three times with toluene and dissolved in DMF (3mL). Imidazole (178 mg, 2.6 mmol) and TBDMS-Cl (217 mg, 1.44 mmol) were added and the reaction mixture stirred 16 h at room temperature. The reaction mixture was poured into ethyl acetate (200 mL) and washed with water,

brine, and saturated NaHCO₃ (50 mL each). The organic layer was dried over MgSO₄, filtered, and the solvent removed under reduced pressure. Flash silica gel column chromatography (hexanes-ethyl acetate 50:1) yielded **6a** (564 mg, 1.11 mmol, 85%) as a clear oil. Rf. 0.63 (hexanes:ethyl acetate 10:1). $[\alpha]_D^{24}$: -21.1, (c = 0.88). IR (thin film, NaCl plate) 2944, 2866, 1652 cm⁻¹. ¹HNMR (500 MHz, CDCl₃) δ 7.26-7.37 (m, 5H), 6.40 (d², *J* = 6.1, 1.1 Hz, 1H), 4.82 (d², *J* = 6.1, 2.8 Hz, 1H), 4.61 (d, *J* = 11.6 Hz, 1H), 4.51 (d, *J* = 11.6 Hz, 1H), 4.00-4.05 (m, 2H), 3.87-3.95 (m, 3H), 1.05-1.15 (m, 21H), 0.88 (s, 9H), 0.10 (s, 3H), 0.08 (s, 3H). ¹³CNMR (125 MHz, CDCl₃) δ 144.9, 138.7, 128.5, 127.9, 127.6, 98.9, 80.0, 76.6, 70.2, 68.1, 62.5, 26.1, 18.4, 18.2, 18.15, 12.2, -4.0, -4.7. ESI MS (C₂₈H₅₀O₄Si₂) *m/z* (M + Na⁺) calcd 529.3140, obsd 529.3150.

3-*O*-Benzyl-4-*O*-*t*-butyldimethylsilyl-1,2-*O*-isopropylidene-6-*O*-triisopropylsilyl- α -D-glucopyranoside (6b**).** Followed general procedure to yield: 43 mg, 75%. Rf. 0.48 (hexanes:ethyl acetate 9:1). $[\alpha]_D^{24}$: +7.42, (c = 1.20). IR (thin film, NaCl plate) 2940, 2866 cm⁻¹. ¹HNMR (500 MHz, CDCl₃) δ 7.28-7.38 (m, 5H), 5.61 (d, *J* = 4.9 Hz, 1H), 4.75 (d, *J* = 11.7 Hz, 1H), 4.61 (d, *J* = 11.7 Hz, 1H), 4.22 (ψt, 1H), 3.96 (d², *J* = 11.2, 2.0 Hz, 1H), 3.90 (d², *J* = 9.0, 4.8 Hz, 1H), 3.86 (d², *J* = 11.2, 4.3 Hz, 1H), 3.70-3.73 (m, 2H), 1.55 (s, 3H), 1.35 (s, 3H), 1.04-1.14 (s, 21H), 0.87 (s, 9H), 0.08 (s, 3H), 0.04 (s, 3H). ¹³CNMR (125 MHz, CDCl₃) δ 138.3, 128.5, 127.8, 127.75, 109.0, 97.5, 82.0, 76.2, 73.9, 72.0, 68.4, 63.4, 27.1, 26.2, 26.0, 18.2, 18.18, 12.3, -3.9, -4.8. ESI MS (C₃₁H₅₆O₆Si₂) *m/z* (M + Na⁺) calcd 603.3508, obsd 603.3491.

3-*O*-Benzyl-4,6-*p*-methoxybenzylidene-D-glucal (7a**)** This material was prepared as previously reported.⁴

3-*O*-Benzyl-1,2-*O*-isopropylidene-4,6-*p*-methoxybenzylidene- α -D-glucopyranoside (7b**).** Followed general procedure to yield: 9.5 mg, 6:1 of an inseparable mixture of diastereomers, 22%. ESI MS (C₂₄H₂₈O₇) *m/z* (M + Na⁺) calcd 451.1727, obsd 451.1723.

4,6-Di-*t*-butylsilylidene-D-glucal (8a**)** This material was prepared as previously reported.⁵

4,6-Di-*t*-butylsilylidene-1,2-*O*-isopropylidene- α -D-glucopyranoside (8b). Followed general procedure to yield: 6.5 mg, 18%. Rf. 0.28 (hexanes:ethyl acetate 4:1). $[\alpha]^{24}_{\text{D}}$: +22.5, ($c = 0.39$). IR (thin film, NaCl plate) 3431, 2935 cm^{-1} . ^1H NMR (500 MHz, CDCl_3) δ 5.54 (d, $J = 4.9$ Hz, 1H), 4.19 (m, 1H), 4.09 (d^2 , $J = 6.1, 5.1$ Hz, 1H), 3.85-3.89 (m, 2H), 3.77-3.84 (m, 1H), 3.65-3.69 (m, 1H), 2.67 (d, $J = 1.9$ Hz, 1H), 1.58 (s, 3H), 1.41 (s, 3H), 1.06 (s, 9H), 1.00 (s, 9H). ^{13}C NMR (125 MHz, CDCl_3) δ 108.4, 98.0, 77.2, 77.1, 76.2, 67.4, 66.3, 28.2, 27.6, 27.5, 27.1, 22.9, 20.1. ESI MS ($\text{C}_{17}\text{H}_{32}\text{O}_6\text{Si}$) m/z ($\text{M} + \text{Na}^+$) calcd 383.1860, obsd 383.1875.

3,6-Di-*O*-triisopropylsilyl-D-glucal (9a) This material is isolated as a byproduct from the synthesis of compound **13**.⁶ Rf. 0.41 (hexanes:ethyl acetate 9:1). $[\alpha]^{24}_{\text{D}}$: -10.3, ($c = 0.79$). IR (thin film, NaCl plate) 3496, 2944, 2867, 1645 cm^{-1} . ^1H NMR (500 MHz, CDCl_3) δ 6.3 (d^2 , $J = 6.1, 1.4$ Hz, 1H), 4.72 (d^2 , $J = 6.2, 2.8$ Hz, 1H), 4.31 (m, 1H), 4.09 (d^2 , $J = 10.9, 5.3$ Hz, 1H), 3.90-3.97 (m, 2H), 3.83 (m, 1H), 2.55 (d, $J = 4.2$ Hz, 1H), 1.03-1.58 (m, 42H). ^{13}C NMR (125 MHz, CDCl_3) δ 143.4, 103.5, 78.4, 71.7, 69.5, 63.7, 18.28, 18.27, 18.13, 12.6, 12.1. ESI MS ($\text{C}_{24}\text{H}_{50}\text{O}_4\text{Si}_2$) m/z ($\text{M} + \text{Na}^+$) calcd 481.3140, obsd 481.3128.

1,2-*O*-isopropylidene-3,6-di-*O*-triisopropylsilyl- α -D-glucopyranoside (9b). Followed general procedure to yield: 37 mg, 70%. Rf. 0.36 (hexanes:ethyl acetate 9:1). $[\alpha]^{24}_{\text{D}}$: -30.4, ($c = 1.13$). IR (thin film, NaCl plate) 3508, 2949, 2867 cm^{-1} . ^1H NMR (500 MHz, CDCl_3) δ 5.56 (d, $J = 4.3$ Hz, 1H), 4.16-4.20 (m, 1H), 3.74-4.00 (m, 3H), 2.71 (d, $J = 4.5$ Hz, 1H), 1.59 (s, 3H), 1.36 (s, 3H), 1.03-1.18 (m, 42H). ^{13}C NMR (125 MHz, CDCl_3) δ 109.6, 96.8, 76.8, 73.7, 72.1, 66.1, 26.8, 25.5, 18.2, 18.16, 18.13, 12.4, 12.0. ESI MS ($\text{C}_{27}\text{H}_{56}\text{O}_6\text{Si}_2$) m/z ($\text{M} + \text{Na}^+$) calcd 555.3508, obsd 555.3498.

3-*O*-Benzyl-6-*O*-triisopropylsilyl-D-glucal (10a) This material was prepared as previously reported.¹

3-*O*-Benzyl-1,2-*O*-isopropylidene-6-*O*-triisopropylsilyl- α -D-glucopyranoside (10b). Followed general procedure to yield: 34 mg, 73%. Rf. 0.41 (hexanes:ethyl acetate 4:1). $[\alpha]^{24}_{\text{D}}$: -4.22, ($c = 1.02$). IR (thin film, NaCl plate) 3495, 2942, 2897 cm^{-1} . ^1H NMR (500 MHz, CDCl_3) δ 7.24-7.40 (m, 5H),

5.60 (d, $J = 4.6$ Hz, 1H), 4.75 (ψd, 2H), 4.29 (ψt, 1H), 4.05 (d², $J = 9.9, 4.1$ Hz, 1H), 3.91-3.95 (m, 1H), 3.97-3.8 (m, 3H), 3.03 (d, $J = 2.9$ Hz, 1H), 1.57 (s, 3H), 1.37 (s, 3H), 1.04-1.18 (m, 21H). ¹³CNMR (125 MHz, CDCl₃) δ 138.0, 128.6, 128.1, 109.5, 97.3, 80.0, 76.5, 72.3, 71.6, 70.7, 65.7, 27.2, 26.1, 18.1, 12.0. ESI MS (C₂₅H₄₂O₆Si) m/z (M + Na⁺) calcd 489.2643, obsd 489.2640.

1,2-*O*-isopropylidene-3-tri-*O*-benzyl-α-D-galactopyranoside (11b). Followed general procedure to yield: 38 mg, 78%. Rf. 0.39 (hexanes:ethyl acetate 4:1). $[\alpha]^{24}_D$: +37.7, ($c = 1.23$). IR (thin film, NaCl plate) 3031, 2933 cm⁻¹. ¹HNMR (500 MHz, CDCl₃) δ 7.27-7.42 (m, 15H), 5.59 (d, $J = 4.2$ Hz, 1H), 4.93 (d, $J = 11.6$ Hz, 1H), 4.81 (d, $J = 12.2$ Hz, 1H), 4.70 (d, $J = 12.2$ Hz, 1H), 4.62 (d, $J = 11.6$ Hz, 1H), 4.52 (d, $J = 11.9$ Hz, 1H), 4.46 (d, $J = 11.9$ Hz, 1H), 4.33 (d², $J = 6.2, 4.2$ Hz, 1H), 4.09-4.12 (m, 1H), 4.03 (ψt, 1H), 3.61-3.71 (m, 3H), 1.48 (s, 3H), 1.40 (s, 3H). ¹³CNMR (125 MHz, CDCl₃) δ 138.7, 138.4, 138.1, 128.6, 128.5, 128.45, 128.1, 128.05, 127.9, 127.8, 127.75, 127.7, 109.4, 97.7, 80.8, 78.5, 77.48, 77.2, 77.0, 74.6, 73.7, 73.2, 73.15, 71.6, 68.3, 28.5, 27.3. ESI MS (C₃₀H₃₄O₆) m/z (M + Na⁺) calcd 513.2248, obsd 513.2258.

3,4-Carbonate-6-*O*-triisopropylsilyl-D-galactal (12a) This material was prepared as previously reported.⁷

6-*O*-Triisopropylsilyl-D-glucal (13) This material was prepared as previously reported.⁶

6-*O*-*t*-Butyldiphenylsilyl-D-glucal (14) This material was prepared as previously reported.⁸

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4b

5a

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5b

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6b

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7b

8b

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9b

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11b