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Note

Synthesis and chemistry of 4,6-*O*-di-(*tert*-butyl)silanediyl-D-glucal

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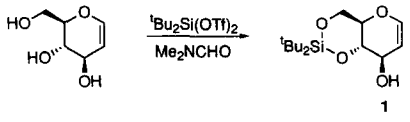
The selective protection of D-glucal simultaneously at the 4- and 6-hydroxy positions has received considerable attention due to the usefulness and versatility of the allylic hydroxy moiety [1]. However, previous syntheses have produced low yields or have involved multiple protection–deprotection steps. For example, synthesis of 4,6-*O*-isopropylidene-D-glucal from D-glucal proceeds in 50% yield [2], and the 4,6-*O*-di-(*tert*-butyldimethylsilyl) glucal derivative involves four steps in 58% overall yield [3]. The most recent, developed by Jackson and Dorgan, reported a modest 74% yield using tetra(isopropyl)disiloxane; however, due to the high cost of the dichlorotetraisopropyldisiloxane reagent, this synthesis is not economical on a larger scale [4] [1]. Recently we initiated a program involving the synthesis and chemistry of cyclopropanated glucals [5] and required a more convenient and economical preparation of a 4,6-*O*-protected glucal. This Note describes a high-yielding, facile synthesis, which should be of use in synthetic carbohydrate chemistry.

The synthesis of 4,6-*O*-di-(*tert*-butyl)silanediyl-D-glucal (Scheme 1) used the strategy reported by Furusawa et al. for the protection of ribonucleosides [6]. Slow addition of di-*tert*-butylsilyl ditriflate to a solution of D-glucal [7] in dry *N,N*-dimethylformamide at −40 °C provides **1** in 96% yield. The reaction is complete in 45 min, and **1** is conveniently isolated as a white solid. This procedure shows excellent reproducibility from the milligram to multigram scale.



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Scheme 1.

In order to ascertain the stability and chemistry of **1**, we have performed several reactions well established in carbohydrate chemistry [2] (Scheme 2). Treatment of **1** with acetic anhydride and pyridine gave the crude acetate as a colorless oil that was suitable for further use without purification. *C*-Glycosylation to produce **2** was achieved by treatment of the crude acetate with allyltrimethylsilane and 25 mol% trimethylsilyl triflate. The conversion of **1** to **2** was achieved in 91% isolated yield with an 88:1 ratio of α:β isomers [3] [9]. Finally, deprotection of the

[1] 1,3-Dichloro-1,1,3,3-tetraisopropyldisiloxane may currently be purchased from Aldrich Chemical Co. at $24 per gram.

[2] For references see ref. [8].

[3] The stereochemistry at C-4 (the "anomeric" carbon) was determined by ^{1}H NMR spectroscopy [δ 4.18 (1 H, $J_{4,5}$ 2.0 Hz)] and assigned by comparison to known glycosides (see ref. [9]). The ratio of the isomers was determined by GLC–MS on the crude mixture.

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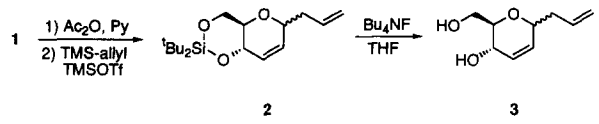

Scheme 2.

C-glycosylic compound could be achieved with Bu_4NF in THF to produce **3** in 98% yield. Selective deprotection of **2** at the 6-position was attempted; however, we were unable to achieve reproducible results.

In conclusion, a facile, high-yielding, inexpensive synthesis of a 4,6-*O*-protected glucal has been developed. This method provides a notable improvement in yield and convenience over previous protection strategies.

1. Experimental

General.—Di-*tert*-butylsilyl bis(trifluoromethanesulfonate), allyltrimethylsilane, and trimethylsilyl triflate (Me_3SiOTf) were purchased from Aldrich Chemical Co. and used as received. *N,N*-Dimethylformamide (Me_2NCHO), CH_2Cl_2, and pyridine were distilled from CaH_2 and stored over molecular sieves. Tetrahydrofuran (THF) was distilled from sodium/benzophenone before use. Standard syringe techniques were employed for handling air-sensitive reagents, and all reactions were carried out under argon. Elemental analyses were obtained from Huffman Laboratories, Inc., Golden, CO, and HRMS was obtained from the University of Colorado, Boulder, CO.

*4,6-O-Di-(*tert*-butyl)silanediyl-*D*-glucal* (**1**).—To a soln of D-glucal (2.192 g, 15.00 mmol) in 60 mL of Me_2NCHO at −40 °C was added $^tBu_2Si(OTf)_2$ (6.02 mL, 16.5 mmol) dropwise over 15 min. The soln was stirred an additional 30 min, and pyridine (1.46 mL, 18.0 mmol) was added and stirred 5 min. The soln was diluted with 300 mL of ether and washed once with 75 mL of satd $NaHCO_3$, twice with 75 mL of H_2O, and dried ($MgSO_4$). Flash chromatography on silica gel with 4:1 hexanes–EtOAc gave 4.143 g (96% yield) of a white solid **1**: IR ($CDCl_3$): ν 3588, 2940, 2865, 1655, 1474 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 6.23 (dd, 1 H, *J* 2.3, 6.0 Hz, H-1), 4.72 (dd, 1 H, *J* 1.9, 6.0 Hz, H-2), 4.26 (d, 1 H, *J* 6.1 Hz, H-3), 4.14 (dd, 1 H, *J* 4.6, 9.9 Hz, H-4), 4.00–3.78 (m, 3 H, H-5, H-6), 2.33 (br s, 1 H, OH), 1.04 (s, 9 H, *t*-Bu), 0.96 (s, 9 H, *t*-Bu); ^{13}C NMR (75 MHz, $CDCl_3$): δ 143.6 (C-1), 103.0 (C-2), 77.4 (C-3), 72.3 (C-4), 70.2 (C-5), 65.7 (C-6), 27.5 (CMe_3), 26.9 (CMe_3), 22.8 (CMe_3), 19.9 (CMe_3). Anal. Calcd for $C_{14}H_{26}O_4Si$: C, 58.70; H, 9.15. Found: C, 58.68; H, 9.19.

*4,8-Anhydro-1,2,3,5,6-pentadeoxy-7,9-O-di-(*tert*-butyl)silanediyl-*D*-ribo-nona-1,5-dienitol* (**2**).—To a soln of **1** (308.3 mg; 1.076 mmol) in 2 mL of CH_2Cl_2 at 23 °C was added pyridine (874 μL, 10.8 mmol) followed by Ac_2O (509 μL, 5.38 mmol). The soln was stirred for 10 h then poured into 20 mL of H_2O and extracted three times with 20 mL of CH_2Cl_2. The combined organic layers were washed once with H_2O (20 mL) and dried ($MgSO_4$). The soln was concd under reduced pressure and then concd from toluene (2 × 40 mL) to remove excess pyridine. The resulting colorless oil (356.8 mg) of the monoacetate was suitable for use without further purification: IR (neat): ν 2945, 2861, 1745, 1237, 1130 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 6.28 (dd, 1 H, *J* 1.5, 5.9 Hz, H-1), 5.35 (dt, 1 H, *J* 2.0, 7.3 Hz, H-3), 4.69 (dd, 1 H, *J* 2.0, 5.9 Hz, H-2), 4.14 (m, 2 H, H-4, H-5), 3.93 (m, 2 H, H-6), 2.08 (s, 3 H, Ac), 1.03 (s, 9 H, *t*-Bu), 0.95 (s, 9 H, *t*-Bu); ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.7 (CO), 145.0 (C-1), 100.6 (C-2), 73.6 (C-3), 72.9 (C-5), 72.3 (C-4), 65.8 (C-6), 27.4 (CMe_3), 26.9 (CMe_3), 21.2 (CMe_3), 19.8 (CMe_3).

To the crude acetate (356.8 mg) in 3 mL of CH_2Cl_2 at −20 °C was added allyltrimethylsilane (257 μL, 1.61 mmol) followed by Me_3SiOTf (52 μL, 0.269 mmol). The soln was stirred 8 h, allowing it to gradually warm to 0 °C, then it was poured into 10 mL of satd aq $NaHCO_3$, extracted three times with ether (20 mL), and dried ($MgSO_4$). Flash chromatography on silica gel with 12:1 hexanes–EtOAc gave 304 mg (91% yield for both steps) of **2** as a colorless oil: IR (neat): ν 2940, 2866, 1470, 1090, 866, 836 cm^{-1}; ^1H NMR of major isomer (300 MHz, $CDCl_3$): δ 5.89–5.61 (m, 3 H), 5.20 (m, 2 H), 4.32 (d, 1 H, *J* 8.6 Hz), 4.18 (m, 1 H), 4.07 (dd, 1 H, *J* 4.9, 9.9 Hz), 3.80 (t, 1 H, *J* 9.9 Hz), 3.50 (m, 1 H), 2.40 (m, 1 H), 2.27 (m, 1 H), 1.02 (s, 9 H), 0.96 (s, 9 H); ^{13}C NMR of major isomer (75 MHz, $CDCl_3$): δ 134.5, 130.3, 128.4, 117.4, 73.4, 70.3, 68.8, 67.5, 38.3, 27.5, 27.1, 22.7, 20.0. HRMS: *m/z* Calcd for $C_{17}H_{30}O_3Si$: 310.1964. Found: 310.1961.

*Preparation of 4,8-anhydro-1,2,3,5,6-pentadeoxy-*D*-ribo-nona-1,5-dienitol* (**3**).—To a soln of **2** (218.0 mg, 0.702 mmol) in 3 mL of THF at 0 °C was added Bu_4NF (386 mg, 1.47 mmol). The soln was stirred 3 h at 0 °C then poured into 10 mL of H_2O, extracted

three times with ether (20 mL), and dried ($MgSO_4$). Flash chromatography on silica gel with 1:4 hexanes–EtOAc gave 117 mg (98% yield) of a colorless oil. Comparison of FTIR, HRMS, and NMR to literature values verified the structure [10].

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