24 Simplifying Access to 3,4-Di-*O*-acetyl-1,5 anhydro-2,6-dideoxy-D-*lyxo*-hex-1-enitol (3,4-Di-*O*-acetyl-D-fucal)*

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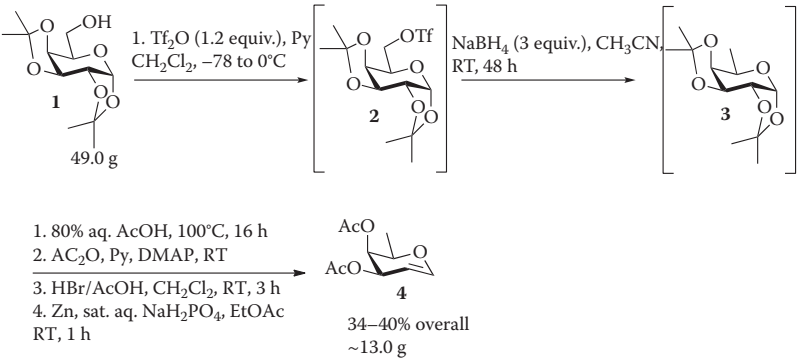

* Trivial name based on D-fucal is not recommended because this glycal does not exhibit the configuration of D-fucose.

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N-Acetyl-D-fucosamine (D-FucNAc) is a rare sugar found in a variety of bacterial glycoconjugates.[1] Chemical synthesis of their repeating units heavily relies on the use of orthogonally protected D-FucNAc-derived building blocks, which are available from diverse precursors.[2] Azidonitration of the title 3,4-di-*O*-acetyl-D-fucal[2b,3] (3,4-di-*O*-acetyl-1,5-anhydro-2,6-dideoxy-D-*lyxo*-hex-1-enitol) has been routinely used in this laboratory to produce large quantities (>20.0 g) of D-fucosamine and derivatives thereof. Accessing the title compound[3] on a large scale from commercially available D-fucose is prohibitively expensive. We have developed a convenient, six-step procedure to produce this valuable compound in 34%–40% overall yield, starting from commercially available 1,2:3,4-di-*O*-isopropylidene-D-galactose.

EXPERIMENTAL

General Methods

All reagents, unless otherwise stated, were purchased from Sigma-Aldrich. 1,2:3,4-Di-*O*-isopropylidene-D-galactose was purchased from Carbosynth and used without purification. ^{1}H and ^{13}C NMR spectra were recorded on Varian Mercury 300 MHz spectrometer. Chemical shifts are reported in parts per million (ppm) relative to internal $CDCl_3$. NMR data are presented as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, dd = doublet of doublet, m = multiplet and/or multiple resonances); coupling constants are reported in hertz. All NMR signals were assigned on the basis of ^{1}H NMR, homonuclear correlation spectroscopy, and HSQC experiments. Mass spectra were recorded on a high-resolution Shimadzu LCMS-IT-TOF mass spectrometer. Column chromatography was performed on silica gel G60 (Silicycle, 60–200 μm, 60 Å). TLC analysis was conducted on silica gel 60 F_{254} (EMD Chemicals, Inc., Savannah, GA), with detection by UV light (254 nm) where applicable, and by charring with 10% sulfuric acid in ethanol or a solution of $(NH_4)_6Mo_7O_2{\cdot}4\ H_2O$ (25 g/L) in 10% sulfuric acid in ethanol. All reactions were carried out under argon atmosphere, unless specified otherwise. Solutions in organic solvents were dried with $MgSO_4$ and concentrated at 40°C/2 kPa.

3,4-Di-*O*-acetyl-1,5-anhydro-2,6-dideoxy-D-*lyxo*-hex-1-enitol (4)

A 1 L round-bottom flask equipped with an equal-pressure-dropping funnel capped with a rubber septum and a magnetic stirring bar was charged with a syrupy 1,2:3,4-di-*O*-isopropylidene-D-galactose (**1**; 49.0 g, 188.26 mmol). Pyridine (70 mL) and CH_2Cl_2 (300 mL) were added, and Tf_2O (42 mL, 244.7 mmol) was added within 20 min with stirring at –78°C. The mixture was allowed to attain room temperature within 15 min, after which it turned dark red and TLC (3:7 Et_2O–hexane) showed the presence of a single product (R_f = 0.7, c.f. R_f = 0.3 for the starting material). CH_2Cl_2 (300 mL) was added; the mixture was transferred to a 2 L separatory funnel and washed with 1 M HCl (500 mL). The organic solution was dried and concentrated to give the triflate **2** as a dark-purple syrup.* It was dis-

* The syrupy triflate tends to spontaneously crystallize at this stage. Color has no effect on the quality of this intermediate.

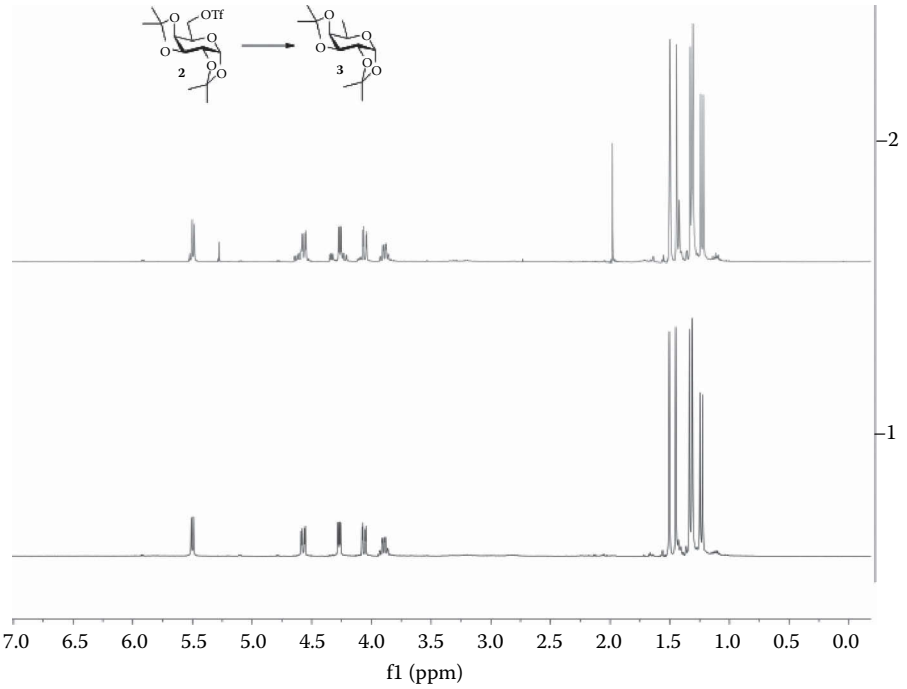

FIGURE 24.1 Monitoring the conversion **2**→**3** by ^{1}H NMR spectroscopy (300 MHz). Top spectrum: after 24 h; bottom spectrum: after 48 h.

solved in CH_3CN (200 mL), and solid $NaBH_4$ (22.0 g, 581 mmol) was then added in five portions over 10 min, after which the mixture became light yellow.

The resulting suspension was stirred at room temperature for 48 h, after which the ^{1}H NMR analysis of the crude mixture showed the reaction to be complete (Figure 24.1; among other things, disappearance of the dd at 4.3 ppm).* The mixture was diluted with CH_2Cl_2 (500 mL), transferred to a 2 L separatory funnel, and successively washed with water and 1 M HCl.† The organic solution was dried and concentrated, affording the crude 1,2:3,4-di-*O*-isopropylidene-D-fucose (**3**) as a yellow syrup. Chromatography (0:1→3:7 EtOAc–hexane) afforded product suitable for further synthetic manipulations.

The crude **3** was dissolved in 80% aq. AcOH (200 mL), and the solution was heated at 100°C for 16 h, after which it turned dark brown and TLC (1:9 CH_3OH–CH_2Cl_2) showed the presence of D-fucose (R_f = 0.3) along with minor less-polar contaminants. The solution was then concentrated to dryness and co-evaporated

* No difference in R_f of the starting material and that of the product is observed. For analysis by NMR, a small portion of the mixture was diluted with CH_2Cl_2 and washed with 1 M HCl. The organic layer was dried, concentrated, and analyzed. It was found that after 24 h some starting material was still present. After additional 24 h, the reaction was complete. The ^{1}H NMR spectrum of the crude material indicated that the product **3** was sufficiently pure for the next step.

† Caution: effervescence!

with toluene (3 × 100 mL) to remove traces of water and acetic acid. The resulting syrup was dissolved in pyridine (200 mL), and Ac_2O (150 mL) and DMAP (150 mg) were added. The mixture was stirred at room temperature overnight, concentrated to dryness, and the solution of the residue in CH_2Cl_2 (300 mL) was washed with 1 M HCl (200 mL). The organic layer was dried and concentrated to afford the crude peracetate as dark-brown syrup. It was dissolved in CH_2Cl_2 (100 mL), and hydrogen bromide (50 mL, ~33% solution in acetic acid) was added. The flask was closed with a glass stopper, and the mixture was stirred at room temperature for 3 h, upon which TLC (1:1, EtOAc–hexane) showed the presence of the bromide ($R_f = 0.7$).* The mixture was diluted with CH_2Cl_2 (100 mL) and washed successively with cold water (200 mL) and sat. $NaHCO_3$ (200 mL). The organic layer was dried and concentrated to give the intermediate bromide as orange syrup.

The crude bromide was dissolved in EtOAc (200 mL), followed by addition of sat. NaH_2PO_4 (150 mL). Zn dust (100 g) was then slowly added over a period of 30 min while maintaining vigorous stirring to prevent caking. After the addition of Zn was complete, the stirring at room temperature was continued for 30 min, whereupon the organic layer turned light yellow. TLC (1:1, EtOAc–hexane) indicated the reaction to be complete.† The mixture was diluted with EtOAc (100 mL) and successively washed with water and sat. $NaHCO_3$. The organic layer was dried and concentrated to give the crude product over six steps as yellow oil. Chromatography (0:1→1:4→3:7 EtOAc–hexane) gave the pure glycal **4** as clear oil. This material is sufficiently pure for most synthetic manipulations. Crystallization (Et_2O–hexane) afforded analytically pure product as white crystals, 13.7 g (34%–40%,‡ over six steps). M.p. 47.5–48.5°C, (lit.[3] 49°C) (Et_2O–hexane); $[\alpha]_D$ −14.3 (*c* 1, $CHCl_3$); $[\alpha]_D$ −12.0 (*c* 1.8, acetone); $[\alpha]_D$ −8.8[3] (*c* 1.8, acetone) $R_f = 0.7$ (1:1 EtOAc–hexane). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.27 (3H, d, H-6, $J = 6.3$ Hz), 2.01 (3H, s, OAc), 2.15 (3H, s, OAc), 4.21 (1H, q, H-5, $J = 6.78$ Hz), 4.63 (1H, ddd, H-3, $J = 1.8$, 6.3, 9.8 Hz), 5.28 (1H, d, H-2, $J = 5.1$ Hz), 5.57 (1H, broad s, H-4), 6.46 (1H, dd, H-1, $J = 1.6$, 6.2 Hz). ^{13}C NMR ($CDCl_3$): δ 16.6 (C-6), 20.9 × 2 (2 × OAc), 64.8 (C-4), 66.4 (C-2), 71.6 (C-5), 98.3 (C-3), 146.0 (C-1). ESI HRMS (*m/z*): $[M + Na]^+$ calcd for $C_{10}H_{14}O_5$, 237.0739; found: 237.0704. Anal. calcd for $C_{10}H_{14}O_5$: C, 56.07; H, 6.59. Found: C, 56.08; H, 6.58.

ACKNOWLEDGMENTS

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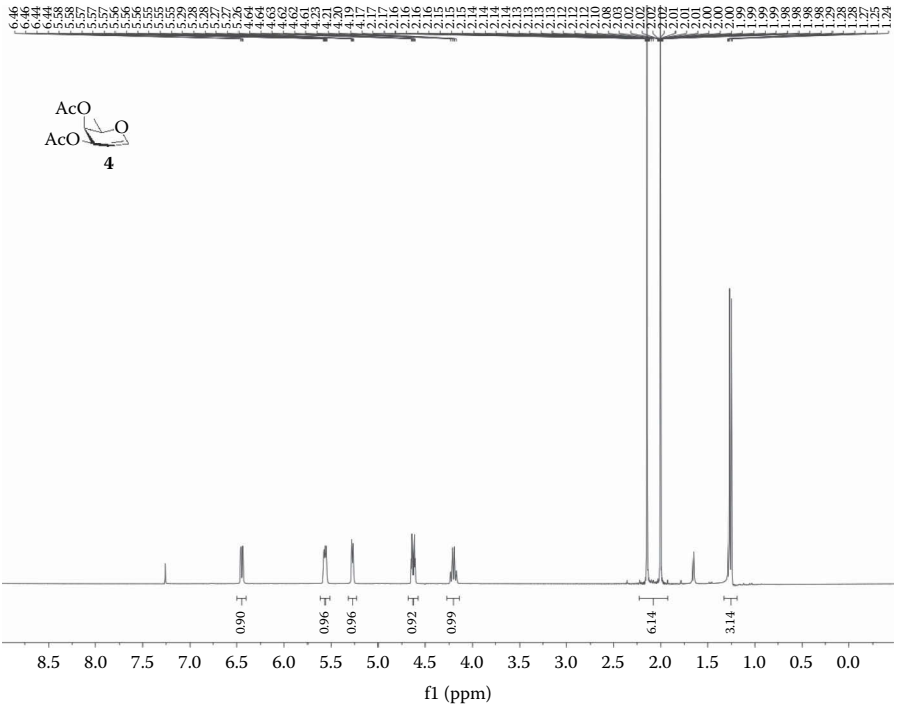
* A small trace of the hemiacetal ($R_f = 0.3$) is usually detected at this stage. Subsequent workup should be performed as quickly as possible due to instability of the bromide.

† No difference in R_f between the bromide and the fucal is observed; however, the fucal produces a distinct gray color upon dipping the TLC plate in the sulfuric acid reagent and charring.

‡ The overall yield varies depending on the reaction scale. Reported is the highest and the lowest yield we could obtain.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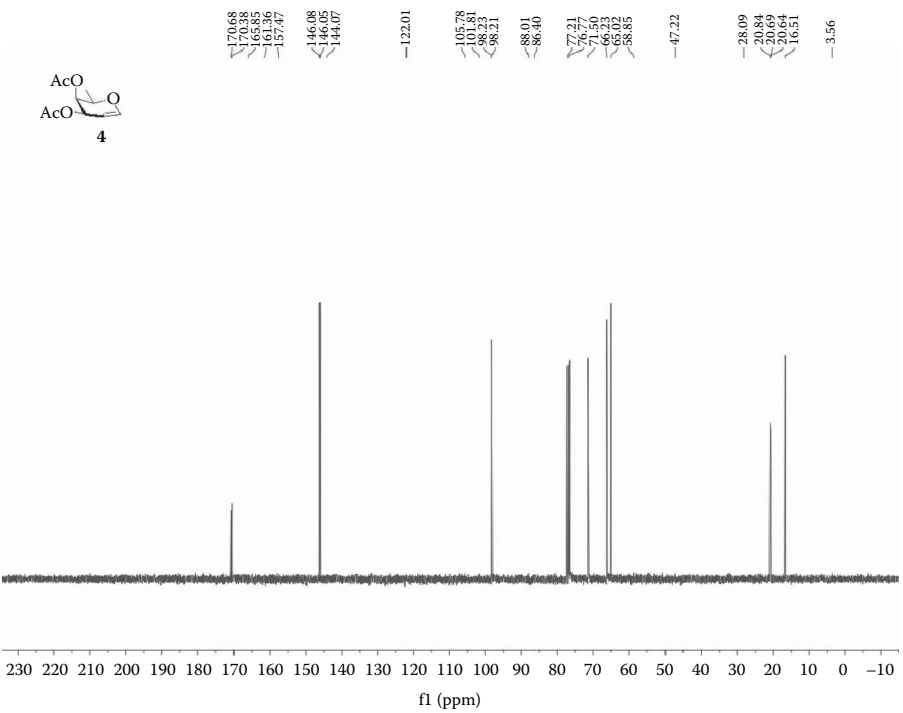
AcO
O
4
0.90
0.96
0.96
0.92
0.99
6.14
3.14
f1 (ppm)


AcO
AcO
O
4
f1 (ppm)

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