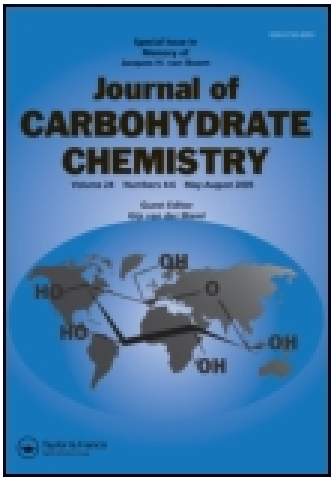

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Azidonitration of Di-O-acetyl-L-fucal: X-Ray Crystal Structures of Intermediate Azidodeoxysugars and of the Bacterial Aminosugar N-Acetyl-L-fucosamine

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Azidonitration of Di-*O*-acetyl-L-fucal: X-Ray Crystal Structures of Intermediate Azidodeoxysugars and of the Bacterial Aminosugar *N*-Acetyl-L-fucosamine

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The azidonitration of di-*O*-acetyl-L-fucal has previously been shown to be an efficient route to the bacterial aminosugar *N*-acetyl-L-fucosamine. Upon repeating this sequence, with updated versions of the glycal formation and amide installation steps, we have obtained X-ray crystal structures of several of the addition products, which are now reported along with the solid-state structure of *N*-acetyl-L-fucosamine itself.

Keywords Azidonitration; L-Fucal; *N*-Acetyl-L-fucosamine; Aminosugar; X-ray structure

INTRODUCTION

Azidonitration of glycals, as first reported by Lemieux,[1] has long been a useful and reliable method for the construction of 2-azido-2-deoxysugars. An excellent example of the preparative-scale application of this chemistry is the synthesis of *N*-acetyl-L-fucosamine (*N*-acetyl-2-amino-2,6-dideoxy-L-galactose) **1** by Horton and Anisuzzaman, which still serves as the most reliable synthetic approach to this compound.[2] More recently, aminosugar **1** has been reported

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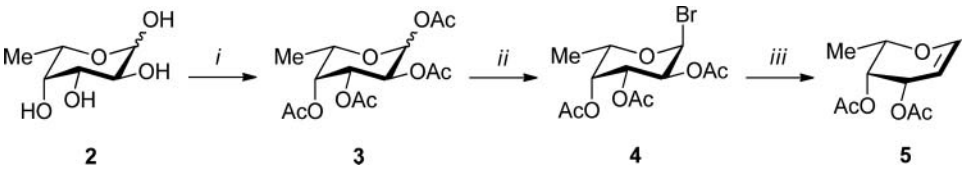
to be an important component of several bacterial polysaccharides, notably in strains of *Staphylococcus aureus* and *Pseudomonas aeruginosa*, and studies have described its detailed biosynthesis and incorporation into capsules.[3] Accordingly, the enzymatic construction of aminosugar **1** now presents several viable protein targets for potential interaction with synthetic glycomimetics, especially considering that this aminosugar is not utilized in human biochemistry. With this long-term goal in mind, we have repeated the azidonitration chemistry on di-*O*-acetyl-L-fucal, with updated methods applied at two of the steps, and obtained crystal structures of two of the intermediate azide products, as well as the solid-state structure of *N*-acetyl-L-fucosamine itself.

RESULTS AND DISCUSSION

The traditional route to 3,4-di-*O*-acetyl-L-fucal (**5**) requires, firstly, the acetylation of L-fucose (**2**) to produce the tetra-*O*-acetate **3** (Scheme 1). Bromination with HBr in acetic acid then affords the α-bromide **4**, which is subsequently treated with, for example, Zn dust to generate the glycal in good yield.[4] Alternative methods for elimination from glycosyl bromides have been developed recently, notably the use of catalytic Cp_2TiCl_2 by Skrydstrup and co-workers.[5] In our hands, application of this latter method to glycosyl bromide **4** on an 11.7-mmol scale provided 3,4-di-*O*-acetyl-L-fucal (**5**) in 88% isolated yield.



Scheme 1: Synthesis of **5**. *Reagents and conditions:* (*i*) Ac_2O, pyridine, 0°C, 12 h; (*ii*) HBr, AcOH, 25°C, 3 h; (*iii*) Cp_2TiCl_2, Mn, TMSCl, THF, 25°C, 12 h.

Azidonitration on fucal **5**, as described previously by Horton[2] and also by Thiem,[6] on a 10-mmol scale resulted in the isolation of a mixture of mostly the anomeric nitrates **6** in 71% crude yield, which was then used without further purification for the subsequent acetolysis. After reacting this crude mixture with acetic acid, Ac_2O, and NaOAc at reflux for 5 h, the 1,3,4-tri-*O*-acetyl-2-azidodeoxy-α/β-L-fucoses (**7**) were isolated in 52.6% yield after column chromatography, along with a mixture of 1-*N*-acetyl-3,4-di-*O*-acetyl-2-azidodexy-α/β-L-fucopyranosylamines (**8**), isolated in 40% yield. In both cases, the *alpha* anomers of **7** and **8** could be isolated in crystalline form from boiling ethanol solution to provide material suitable for single-crystal X-ray diffraction. Glycosyl amide **8α** was previously reported by Lehman and co-workers as a product of the reaction of nitrates **6α/β** with concentrated NH_4OH followed by standard acetylation,[7] and a related glycosyl amide was also formed in

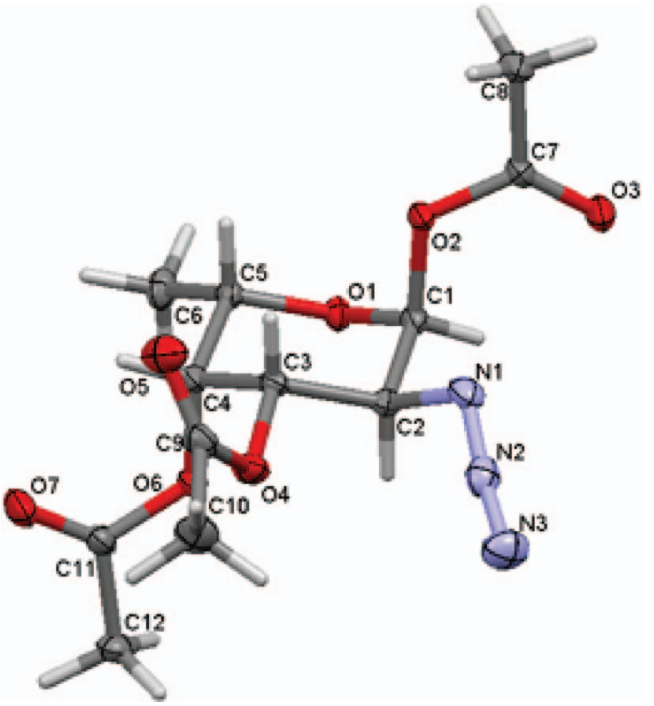


Figure 1: ORTEP plot of **7*α*** (50% probability of the thermal ellipsoids) (color figure available online).

the original Lemieux work during the addition reaction of 3,4-di-*O*-acetyl-D-galactal using CAN and NaN_3.[1] The amide might be formed by oxidation of an intermediate glycosyl radical to the carbonium ion, followed by trapping of the carbonium ion by solvent (acetonitrile) and then hydrolysis.[1] The X-ray structures of both **7*α*** (Fig. 1, Tables 1 and 2)[8] and the monohydrate of **8*α*** (Fig. 2, Table 1)[9] clearly establish the *alpha* anomeric configuration of both compounds. Interestingly, the orientation of the glycosyl amide group in **8*α*** is revealed to have the C-1 and amide NH protons aligned in an *anti* relationship, which is mirrored in $CDCl_3$ solution where the ^1H NMR spectrum shows the H-1–N-H coupling constant to be 9.89 Hz. An overlay of the two structures (**7*α*** and **8*α***) indicates an almost perfect match-fitting for C-1 to C-6 with a root mean square (rms) deviation of only 0.0224Å.

In the earlier synthesis of *N*-acetyl-L-fucosamine by Horton and Anisuzzaman, azides **7** were reduced with H_2 and the resultant amines acylated in the typical manner.[2] In the current work we employed Staudinger-type chemistry, in which the azide is treated with a phosphine and the resulting phosphinimine ylide acylated, and found our own modification using

Table 1: Details of X-ray crystallographic studies on **7α**, **8α·H₂O**, and **1**

	(7α)	**(8α·H₂O)**	**(1)**
Chemical formula	$C_{12}H_{17}N_3O_7$	$C_{12}H_{18}N_4O_6{\cdot}H_2O$	$C_8H_{15}NO_5$
M_r	315.29	332.32	205.21
Crystal syst., space group	Monoclinic, $P2_1$	Monoclinic, $C2$	Monoclinic, $P2_1$
a, b, c (Å)	8.6446 (4), 7.0539 (4), 12.2080 (6)	26.4805 (13), 6.9125 (3), 8.8419 (4)	9.2232 (5), 5.6143 (3), 9.4582 (5)
β (°)	97.989 (1)	95.421 (1)	106.299 (1)
V (Å^3)	737.20 (6)	1611.24 (13)	470.08 (4)
Z	2	4	2
F(000)	332	704	220
D_x (Mg m^{-3})	1.420	1.370	1.450
No. of reflections for cell measurement	6878	7976	5428
θ range (°) for cell meas.	2.4–30.5	2.3–30.5	2.7–30.5
μ (mm^{-1})	0.12	0.11	0.12
Crystal shape	Block	Block	Plate
Color	Colorless	Colorless	Colorless
Crystal size (mm)	0.60 × 0.21 × 0.14	0.39 × 0.21 × 0.18	0.60 × 0.47 × 0.26
Scan method	ω scans	ω scans	ω scans
T_{min}, T_{max}	0.862, 0.984	0.919, 0.980	0.899, 0.969
No. of meas., indep. and obs. ($I > 2\sigma(I)$) reflections	8808, 2404, 2310	9712, 2647, 2572	5562, 1548, 1536
R_{int}	0.025	0.021	0.024
θ values (°)	$\theta_{max} = 30.5$, $\theta_{min} = 1.7$	$\theta_{max} = 30.5$, $\theta_{min} = 1.5$	$\theta_{max} = 30.5$, $\theta_{min} = 2.2$
Range of h, k, l	$h = -12\rightarrow12$, $k = -10\rightarrow9$, $l = -17\rightarrow17$	$h = -36\rightarrow37$, $k = -9\rightarrow9$, $l = -12\rightarrow12$	$h = -13\rightarrow12$, $k = -8\rightarrow8$, $l = -13\rightarrow13$
$R(F^2 > 2\sigma(F^2))$, $wR(F^2)$, S	0.041, 0.108, 1.07	0.038, 0.098, 1.10	0.030, 0.083, 1.10
No. of reflections	2404	2647	1548
No. of parameters	218	257	157
No. of restraints	1	6	1
$\Delta\rho_{max}$, $\Delta\rho_{min}$ (e Å^{-3})	1.05, −0.21	0.41, −0.18	0.36, −0.17

Table 2: Hydrogen-bond parameters of **8**α·H_2O

D—H···*A*	*D*—H (Å)	H···*A* (Å)	*D*···*A* (Å)	*D*—H···*A* (°)
N4—H4A···O8^{i}	0.82 (3)	2.06 (3)	2.8845 (19)	177 (2)
O8—H8D···O3^{ii}	0.839 (18)	1.904 (18)	2.7347 (18)	170 (3)
O8—H8E···O5	0.84 (2)	2.00 (2)	2.838 (3)	173 (5)
O8—H8F···O8^{i}	0.82 (2)	2.08 (3)	2.846 (2)	155 (6)

Symmetry code(s): (i) -*x* + 1, *y*, -*z* + 2; (ii) -*x* + 1, *y* – 1, -*z* + 2.

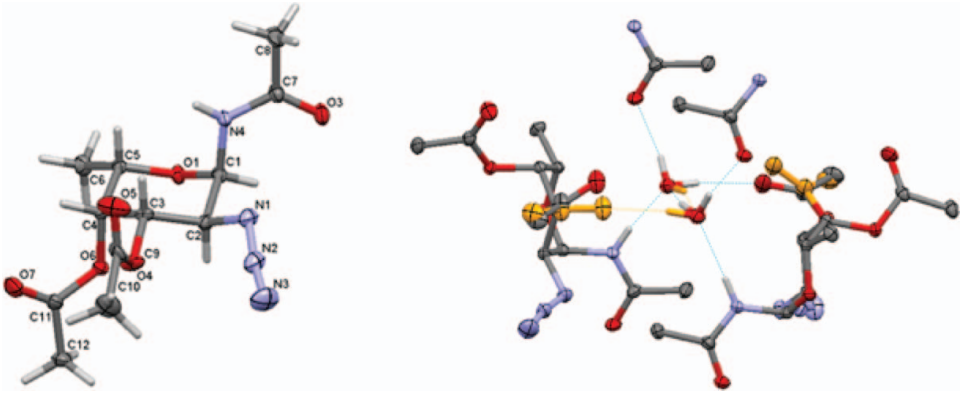
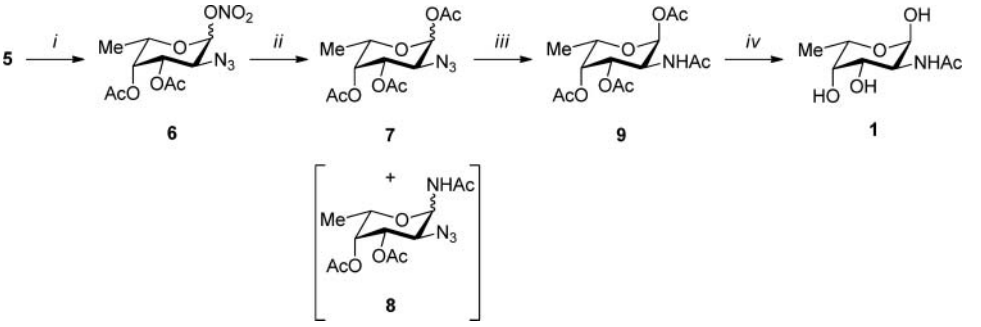


Figure 2: ORTEP plots of **8**α·H_2O (50% probability of the thermal ellipsoids). Left: one molecule with the atom naming scheme and the solvate water molecule and disorder omitted for clarity. Right: Partial packing view highlighting the disorder induced by the symmetry-incompatible hydrogen bonding interactions of the solvate water molecules. A twofold symmetry axis passes between the two symmetry-equivalent water molecules. Highlighted in orange is the second orientation of the disordered sections realized for 50% of the structure (see Experimental section for details of the disorder). Dashed lines represent hydrogen bonds. Parts of molecules and H atoms not involved in displayed hydrogen bonds are omitted for clarity (color figure available online).



Scheme 2: Synthesis of **1**. *Reagents and conditions:* (*i*) CAN, NaN_3, CH_3CN, –15°C, 12 h; (*ii*) NaOAc, AcOH, Ac_2O, reflux, 5 h; (*iii*) DPPE, AcCl, THF, 25°C, 3 h; (*iv*) $NaOCH_3$, CH_3OH, rt, 3 h.

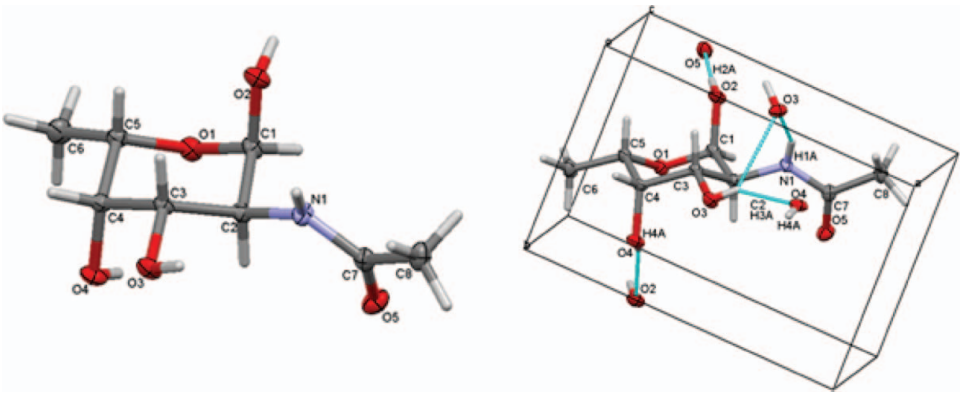


Figure 3: ORTEP plot of **1** (50% probability of the thermal ellipsoids). Left: One individual molecule. Right: Next neighbor, hydrogen bonding atoms shown (color figure available online).

bis(diphenylphosphino)ethane (DPPE) to be applicable here.[10] The byproduct formed here is a very polar bis(phosphine)bisoxide, which aids in separation from other materials (Scheme 2). Thus, treating azidodeoxysugar **7α** with 0.65 equivalents of DPPE, in the presence of 2.0 equivalents of acetyl chloride, afforded 1,3,4-tri-*O*-acetyl-2-*N*-acetyl-2-deoxy-α-L-fucosamine (**9**) in 82% yield. The structure of **9** was confirmed from NMR spectroscopy and mass spectral data, with its physical characteristics being consistent with those observed previously.[2]

With **9** in hand, traditional deacetylation with NaOMe in MeOH was uneventful and provided the parent *N*-acetylated aminosugar, *N*-acetyl-α-L-fucosamine (**1**), upon crystallization from hot ethanol. The structure of **1** has now been confirmed independently through X-ray crystallography (Fig. 3, Table 1).[11] After removal of the acetyl protecting groups, molecules of **1** are able to interact with each other through an extensive network of strong intermolecular N—H···O and O—H···O hydrogen bonding interactions (Table 3, Fig. 4). All hydroxyl O—H groups and the amide N—H functionality act as hydrogen

Table 3: Hydrogen-bond parameters of **1**

D—H···*A*	*D*—H (Å)	H···*A* (Å)	*D*···*A* (Å)	*D*—H···*A* (°)
N1—H1A···O3^{i}	0.85 (2)	2.16 (2)	2.9356 (15)	151 (2)
O2—H2A···O5^{ii}	0.92 (2)	1.74 (2)	2.6531 (14)	178 (2)
O3—H3A···O4^{i}	0.75 (3)	2.28 (3)	2.8892 (14)	139 (3)
O3—H3A···O3^{i}	0.75 (3)	2.31 (3)	2.9187 (6)	139 (2)
O4—H4A···O2^{iii}	0.84 (2)	2.05 (3)	2.8150 (15)	151 (2)

Symmetry code(s): (i) $-x+1, y-1/2, -z$; (ii) $-x+1, y-1/2, -z+1$; (iii) $x, y+1, z$.

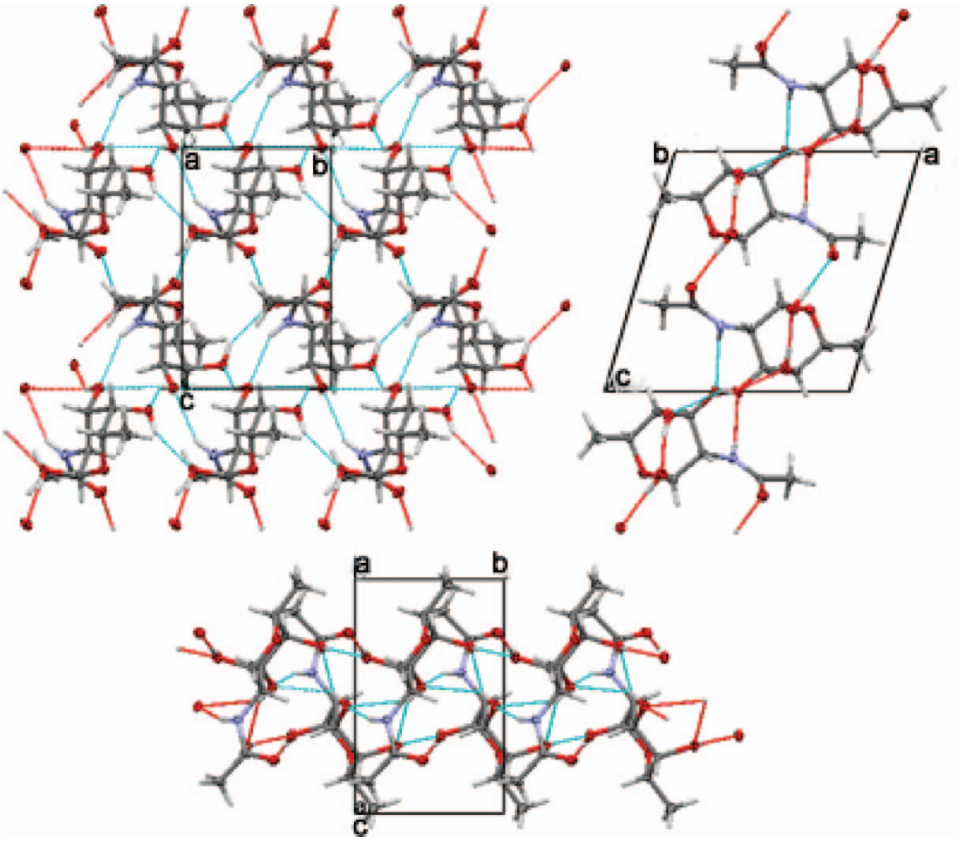


Figure 4: Intermolecular H-bonding network and packing interactions exhibited by aminosugar **1** viewed along the direction of (a) the a-axis perpendicular to the hydrogen bonded layers of molecules, and (b) and (c) along the b- and c-axis cutting through those layers. Tightly hydrogen bonded double strands of molecules can be seen in (a) that stretch parallel to the b-axis with only a few hydrogen bonds connecting parallel strands (color figure available online).

bonding donors, and all oxygen atoms, with the notable exception of the pyranose ring O atom O1, function as acceptors for hydrogen bonds. One of the hydroxyl functionalities, that of O3, forms a bifurcated hydrogen bond, interacting strongly with both O3 and O4 of neighboring molecules (graph set motif R21(5)). O3 also acts as the acceptor of a hydrogen bond originating from a neighboring amido group (graph set motif R12(7)). Originating from this cluster of H-bonds around O3 and O4 are chains of O—H···O bonds involving the hydroxyl group of O2, acting both as acceptor and donor, and the acetyl oxygen atom O5, which functions as a termination point of the chains of O—H···O hydrogen bonds. In combination of all interactions, an intricate hydrogen bonding network is formed that organizes the molecules of **1** into tightly hydrogen bonded layers perpendicular to the direction of the unit cell a-axis.

Within these one-molecule-thick sheets, molecules are arranged parallel and antiparallel to each other, with the two methyl groups of each molecule (the acetyl amide and the fucosamine methyl groups) forming the top and bottom boundary of the hydrogen bonded layers. No hydrogen bonds are established in the direction of these long axes of the molecules between parallel layers. Within the 2-D sheets, additional double strands of molecules can be made out that stretch along the b-axis direction. Within these strands, molecules are connected through multiple hydrogen bonds each as described above, while molecules of parallel strands are connected only through one hydrogen bond, between the hydroxyl group of O2 and the acetyl oxygen atom O5.

The orientation of the NHAc moiety relative to the fucopyranosyl ring in the solid-state structure of **1** (Fig. 3) shows H2 and the NH group to be aligned at an angle of 148°. In the ^{1}H NMR spectrum of this material, collected in *d6*-DMSO, the observed H2–NH coupling of 8.79 Hz indicates that a similar alignment is also occurring in solution.

In conclusion, the structure of the bacterial aminosugar *N*-acetyl-L-fucosamine (**1**) has been obtained through single-crystal X-ray diffraction, along with two of the intermediate azidodeoxysugars (**7α** and **8α**·H_2O) formed along the azidonitration route to **1** developed previously by Horton and Anisuzzaman.[2] The detailed structure of **1** may now aid in the design and synthesis of related glycomimetics that are capable of interacting with the proteins responsible for its construction in bacteria.

EXPERIMENTAL

General Methods

Reagents and solvents were used as received and reactions were carried out in oven-dried glassware under nitrogen atmosphere unless noted. Analytical TLC was performed on Whatman aluminum-backed plates coated with 60 Å silica gel, and spots were detected by treating the plate with 5% H_2SO_4 in 95% ethanol, *p*-anisaldehyde in ethanol, or phosphomolybdic acid in aqueous ethanol and then heating the plate. Products were purified by flash column chromatography using 60 Å silica gel (230–400 mesh) and/or recrystallization from the indicated solvent(s). ^{1}H and ^{13}C NMR spectra were collected at 400 MHz and 100 MHz, respectively, using Varian Gemini 2000 or Bruker Avance 400 MHz spectrometers in $CDCl_3$ or d_6-DMSO as solvents. Chemical shifts are reported relative to the added tetramethylsilane standard. Low-resolution mass spectra were collected on a Bruker Esquire HP 1100 mass spectrometer, and X-ray diffraction data were obtained using a Bruker AXS SMART APEX CCD diffractometer at 100(2) K using monochromatic Mo Kα radiation with omega scan technique using the SMART software.[12] The unit cells were refined and the data integrated using SAINT+.[13] The structures

were solved by direct methods and refined by full-matrix least squares against $F2$ with all reflections using SHELXTL.[14] All nonhydrogen atoms were refined anisotropically. Methyl H atoms were placed in geometrically idealized positions allowing the initial torsion angle to be determined by a difference Fourier analysis [C-H = 0.96 Å and $U_{iso}(H) = 1.5_{eq}(C)$]. All other hydrogen atoms were located in difference density Fourier maps and their positions were freely refined. O-H distances in the water molecule in the structure of **8α**·H_2O were restrained to be 0.84(2)Å. $U_{iso}(H)$ were set to $1.5_{eq}(O)$ for hydroxyl and water H atoms, and to 1.2_{eq}(C/N) for all others. Friedel equivalents were merged prior to refinement and the absolute structure of the compounds was assigned based on the unchanged configuration of carbon atoms also present in the starting material.

Disorder is observed in the structure of **8α**·H_2O. Hydrogen bonding of the solvate water molecule with its symmetry equivalent across a twofold axis leads to disorder of one of the water hydrogen atoms (in a 1:1 ratio), with the hydrogen atom forming a hydrogen bond between the two water molecules in one of the alternative positions and forming a hydrogen bond with O5 of one of the acetyl groups of the organic entity in its other position. This in turn induces disorder of the acetyl group in a 1:1 ratio. The disordered acetyl groups were restrained to be flat, and the overlapping carbon atoms C9 and C9b, and C10 and C10b were each constrained to have identical ADPs.

Synthesis of 3,4-Di-O-acetyl-L-fucal from L-Fucose

*1,2,3,4-Tetra-O-acetyl-α/β-L-fucoses (**3**)*

Formed from L-fucose (2.5 g, 15.2 mmol), Ac_2O (7.5 mL), and pyridine (25 mL) to yield the known α- and β-tetra-*O*-acetyl-L-fucoses (**3**) as a colorless syrup (α:β ratio = 14:1, 4.89 g, 96%). ^{1}H NMR for **3α** ($CDCl_3$): $\delta = 1.14$ (d, 3H, H-6, $J = 6.22$ Hz), 1.99 (s, 3H, $COCH_3$), 2.00 (s, 3H, $COCH_3$), 2.13 (s, 3H, $COCH_3$), 2.17 (s 3H, $COCH_3$), 4.26 (q, 1H, H-5, $J = 6.22$ Hz), 5.04 (dd, 1H, H-4, $J = 3.66$, 10.62 Hz), 5.24–5.30 (m, overlapping, 2H, H-2, H-3), 6.32 (d, 1H, H-1, $J = 2.93$ Hz). MS (ESI): m/z calculated: 332.11; m/z found: 355.1 (M+Na). The data is consistent with that reported previously for **3**.[15]

*2,3,4-Tri-O-acetyl-α-L-fucosyl bromide (**4**)*

Prepared from a mixture of α/β-tetraacetates **3** (4.6 g, 13.86 mmol) and 30% HBr in acetic acid (20.0 mL) to give the glycosyl bromide **4** as a light brown syrup (4.18 g, 85.5%). ^{1}H NMR ($CDCl_3$): $\delta = 1.20$ (d, 3H, H-6, $J = 6.59$ Hz), 2.00 (s, 3H, $COCH_3$), 2.10 (s, 3H, $COCH_3$), 2.16 (s, 3H, $COCH_3$), 4.39 (q, 1H, H-5, $J = 6.59$ Hz), 5.01 (dd, 1H, H-2, $J = 4.03$, 10.62 Hz), 5.35 (d, 1H, H-4, $J = 3.30$ Hz), 5.39 (dd, 1H, H-3, $J = 3.30$, 10.62 Hz), 6.68 (d, 1H, H-1, $J = 4.03$). ^{13}C NMR ($CDCl_3$): $\delta = 16.6$, 21.6, 21.7, 21.8, 68.8, 69.4, 70.9, 71.0, 90.5, 170.6,

170.9, 171.1. The spectral properties match those reported earlier for bromide **4**.[16]

*3,4-Di-*O*-acetyl-*L*-fucal (**5**)*

According to the method of Skrydstrup and co-workers,[5] 2,3,4-tri-*O*-acetyl-α-L-fucosyl bromide (**4**, 4.13 g, 11.7 mmol), Cp_2TiCl_2 (1.90 g, 7.6 mmol), Mn powder (1.24 g, 22.5 mmol), and TMSCl (0.4 mL) in dry THF (50 mL) gave the known 3,4-di-*O*-acetyl-L-fucal (**5**) as a pale yellow syrup (2.2 g, 88%). ^{1}H NMR ($CDCl_3$): $\delta = 1.27$ (d, 3H, H-6, $J = 6.59$ Hz), 2.02 (s, 3H, $COCH_3$), 2.16 (s, 3H, $COCH_3$), 4.21 (q, 1H, H-5, $J = 6.59$ Hz), 4.64 (ddd, 1H, H-3, $J = 1.83$, 6.22, 9.89 Hz), 5.28 (m, 1H, H-2), 5.57 (m, 1H, H-4), 6.46 (dd, 1H, H-1, $J = 1.83$, 6.22 Hz). ^{13}C NMR ($CDCl_3$): $\delta = 17.8$, 22.0, 22.2, 66.2, 67.4, 72.7, 99.4, 147.1, 171.4, 171.7. The collected data are consistent with that of a previously reported sample of **5**.[17]

Azidonitration of 3,4-Di-O-acetyl-L-fucal

*2-Azido-1-*O*-nitro-3,4-di-O-acetyl-α/β-L-fucose (**6**)*

Using Thiem's approach,[6] sodium azide (1.6 g, 24.6 mmol), ceric ammonium nitrate (CAN, 18.25 g, 33.3 mmol), and 3,4-di-*O*-acetyl-L-fucal (**5**, 2.21 g, 10.3 mmol) in anhydrous acetonitrile (100 mL) gave a yellow solid (α:β ratio = 3:1, 2.45 g, 71%) identified mostly as nitrates **6** from NMR spectra. For **6**α: ^{1}H NMR ($CDCl_3$): $\delta = 1.18$ (d, 3H, H-6, $J = 6.48$ Hz), 2.07 (s, 3H, $COCH_3$), 2.19 (s, 3H, $COCH_3$), 4.10 (dd, 1H, H-2, $J = 4.18$, 11.30 Hz), 4.31 (q, 1H, H-5, $J = 6.44$ Hz), 5.26 (dd, 1H, H-3, $J = 3.30$, 11.46 Hz), 5.35 (dd, 1H, H-4, $J = 1.13$, 3.23 Hz), 6.32 (d, 1H, H-1 $J = 4.12$ Hz). ^{13}C NMR ($CDCl_3$): $\delta = 15.7$, 20.4(2), 20.44, 55.7, 67.9, 68.8, 69.6, 97.3, 169.4, 170.0. For **6**β: ^{1}H NMR ($CDCl_3$): $\delta = 1.24$ (d, 3H, H-6, $J = 6.44$ Hz), 2.06 (s, 3H, $COCH_3$), 2.19 (s, 3H, $COCH_3$), 3.56 (dd, 1H, H-2, $J = 8.94$, 10.62), 3.87 (dq, 1H, H-5, $J = 6.41$, 0.95 Hz), 4.60 (d, 1H, H-1, $J = 8.88$ Hz), 4.85 (dd, 1H, H-3, $J = 3.32$, 10.64 Hz), 5.22 (dd, 1H, H-4 $J = 0.80$, 3.28 Hz). ^{13}C NMR ($CDCl_3$): $\delta = 15.9$, 20.5(2), 60.3, 69.1, 71.2, 71.8, 89.1, 169.6, 170.2.

*1,3,4-tri-*O*-acetyl-2-azidodeoxy-α/β-L-fucose (**7**) and 1,3,4-tri-*O*-acetyl-2-azidodeoxy-α-L- fucopyranosylamine (**8α**)*

The crude mixture from the previous experiment (2.4 g, 7.18 mmol) was dissolved in acetic acid (70 mL), NaOAc (4.3 g, 51.9 mmol) and Ac_2O (3 mL) were added, and the solution was refluxed for 5 h and then poured into ice water. The mixture was extracted with CH_2Cl_2 (4 × 30 mL) and the combined organic layers were washed with saturated $NaHCO_3$ (3 × 25 mL) and once with saturated NaCl solution (25 mL). The organic layer was dried ($MgSO_4$),

filtered, and reduced in vacuum, and the residue was purified by flash chromatography (3:1 pet. ether/EtOAc) to afford 1.19 g (52.6%) of an α/β mixture of azidoacetates **7** and 0.9 g (40%) of azidoamide **8**. The α-anomers of **7** and **8** were crystallized out by vapor diffusion and from hot ethanol, respectively.

For **7α/β**: ^{1}H NMR ($CDCl_3$): $\delta = 1.13$ (d, 3H, H-6α, $J = 6.59$ Hz), 1.20 (d, 3H, H-6β, $J = 6.59$ Hz), 2.05 (s, 3H, $COCH_3\beta$), 2.06 (s, 3H, $COCH_3\beta$), 2.15 (s, 3H, $COCH_3\alpha$), 2.17 (s, 3H, $COCH_3\alpha$), 2.18 (s, 3H, $COCH_3\beta$), 2.19 (s, 3H, $COCH_3\beta$), 3.81 (dd, 1H, H-2β, $J = 8.79$, 10.98 Hz), 3.89 (dd, 1H, H-2α, $J = 3.66$, 11.72 Hz), 3.90 (q, 1H, H-5β, $J = 6.59$ Hz), 4.19 (q, 1H, H-5α, $J = 6.22$ Hz), 4.87 (dd, 1H, H-3β, $J = 3.30$, 10.98 Hz), 5.22 (d, 1H, H-4β, $J = 4.03$ Hz), 5.28–5.32 (m, overlapping, 2H, H-3α, H-4α), 5.51 (d, 1H, H-1β, $J = 8.79$ Hz), 6.27 (d, 1H, H-1α, $J = 3.66$ Hz). ^{13}C NMR (α anomer) ($CDCl_3$): $\delta = 17.2$, 21.9(2), 22.3, 57.9, 68.4, 70.3, 71.2, 91.8, 170.0, 170.9, 171.4. ^{13}C NMR (β anomer) ($CDCl_3$): $\delta = 17.2$, 21.9(2), 22.2, 60.8, 70.4, 71.4, 72.8, 94.0, 169.8, 170.7, 171.3. These spectral characteristics match those reported previously for a mixture of **7α/β**;[6] the structure of **7α** has now been confirmed independently by X-ray diffraction.

For **8α**: ^{1}H NMR ($CDCl_3$): $\delta = 1.13$ (d, 3H, H-6, $J = 6.44$ Hz), 2.10 (s, 3H, $COCH_3$), 2.11 (s, 3H, $COCH_3$), 2.20 (s, 3H, $COCH_3$), 4.01 (q, 1H, H-5, $J = 6.39$ Hz), 4.16 (dd, 1H, H-2, $J = 5.53$, 11.08 Hz), 5.22 (d, 1H, H-4, $J = 2.68$ Hz), 5.27 (dd, 1H, H-3, $J = 3.34$, 11.10 Hz), 5.86 (dd, 1H, H-1, $J = 5.58$, 8.06 Hz), 7.38 (d, 1H, H-N, $J = 8.08$ Hz). ^{13}C NMR ($CDCl_3$): $\delta = 16.2$, 20.7, 20.8, 23.2, 56.7, 65.4, 70.1, 70.2, 75.4, 170.7, 170.8, 171.6. These spectra are consistent with the structure of **8**α proposed previously by Lehman[7] and confirmed here independently by X-ray diffraction.

Synthesis of *N*-Acetyl-L-fucosamine

*1,2,3,4-tetra-O-acetyl-α-L-fucosamine (**9**)*

This compound was prepared by our previously reported method using Staudinger chemistry with DPPE as the phosphine.[10] 1,3,4-Tri-*O*-acetyl-2-azidodeoxy-α-L-fucose (**7α**) (0.32 g, 1.00 mmol) and acetyl chloride (0.14 mL, 2.0 mmol) were dissolved in dry THF (7.3 mL) at rt, and then bis(diphenylphosphino)ethane (DPPE, 0.26 g, 0.65 mmol) dissolved in dry THF (3 mL) was added dropwise. After 3 h at rt, saturated $NaHCO_3$ solution (5 mL) was added and the mixture was stirred for an additional 2 h at rt. After evaporation of the organic solvent, the aqueous solution was extracted with CH_2Cl_2 (3 × 10 mL) and the combined organics were washed with H_2O (2 × 10 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The residue was purified by flash column chromatography (7:1, EtOAc/hexanes) to obtain the previously reported 1,2,3,4-tetra-*O*-acetyl-α-L-fucosamine (**9**) as a colorless syrup (0.27 g, 82 %), which could be crystallized from hot ethanol.[2,7] ^{1}H NMR ($CDCl_3$) for **9**: $\delta = 1.15$ (d, 3H, H-6, $J = 6.49$ Hz), 1.95 (s, 3H, $COCH_3$), 2.01 (s,

3H, $COCH_3$), 2.17 (s, 3H, $COCH_3$), 2.19 (s, 3H, $COCH_3$), 4.22 (q, 1H, H-5, J = 6.44 Hz), 4.64 (ddd, 1H, H-2, J = 3.56, 8.91, 11.76 Hz), 5.21 (dd, 1H, H-3, J = 3.14, 11.62 Hz), 5.26 (d, 1H, H-4, J = 2.52 Hz), 6.19 (d, 1H, H-1, J = 3.64 Hz), 6.61 (d, 1H, N-H, J = 8.88 Hz). ^{13}C NMR ($CDCl_3$): δ = 16.1, 20.7, 20.72, 20.90, 20.93, 46.7, 67.0, 68.1, 69.9, 91.4, 169.5, 170.6, 170.73, 170.75. MS (ESI): m/z calculated: 331.13; m/z found: 354.1 (M+Na). The H-1–H-2 coupling constant of 3.64 Hz is consistent with the *alpha* anomer of **9** reported previously by Horton.[2]

*N-Acetyl-α-L-fucosamine (**1**)*

Deacetylation of 1,2,3,4-tetra-*O*-acetyl-α-L-fucosamine (**9**, 0.13 g, 0.39 mmol) was accomplished according to the method previously described by Horton and Anisuzzaman;[2] the residue obtained upon workup was extracted into hot EtOAc, the solution evaporated, and the solid obtained recrystallized from EtOH to afford *N*-acetyl-α-L-fucosamine (**1**) as colorless crystals that were suitable for X-ray diffraction analysis (0.075 g, 93.7%). ^{1}H NMR (d_6-DMSO): δ = 1.03 (d, 3H, H-6, J = 6.59 Hz), 1.80 (s, 3H, $COCH_3$), 3.46 (d, 1H, H-4, J = 2.56 Hz), 3.60 (dd, 1H, H-2, J = 3.30, 11.35 Hz), 3.88 (dd, 1H, H-3, J = 3.30, 10.98 Hz), 3.93 (q, 1H, H-5, J = 6.59 Hz), 4.27 (d, 1H, OH, J = 7.32 Hz), 4.49 (d, 1H, OH, J = 4.39 Hz), 4.83 (t, 1H, H-1, J = 4.03 Hz), 6.25 (d, 1H, OH, J = 4.03 Hz), 7.52 (d, 1H, NH, J = 8.79 Hz). ^{13}C NMR (d_6-DMSO): δ = 18.5, 24.5, 51.5, 66.7, 69.0, 72.8, 92.5, 171.1. Spectra reported here are consistent with those published by Horton,[2] and the structure of **1**α is now confirmed here independently by X-ray diffraction.

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