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C–H-Deprotonation mediated by a remote *syn*-axial acetoxy group—an unprecedented double bond formation upon cyanation of the dimer from L-fucal

Andreas H. Franz,[a] Vyacheslav V. Samoshin,[a] Chris Myers,[b] Allen D. Hunter,[b] Paul H. Gross[a,*]

[a]*Department of Chemistry, University of the Pacific, 3601 Pacific Avenue, Stockton, CA 95211, USA*
[b]*Department of Chemistry, Youngstown State University, YSU Structure Center, 1 University Plaza, Youngstown, OH 44555, USA*

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Abstract

Replacement of the anomeric acetate by a cyanide group in the dimer of di-*O*-acetyl-L-fucal by the action of mild Lewis acid [$Hg(CN)_2$–$HgBr_2$–Me_3SiCN], resulted not only in the desired transformation but also in the introduction of an additional double bond between C-2A and C-3A. Due to its configuration, the remote C-4A acetoxy group may facilitate the deprotonation by functioning as an internal base. ^{1}H NMR spectroscopy and X-ray crystallography indicate that the conformations of both rings A and B and their relative orientation in the resulting C-linked disaccharidic glycosyl cyanide, 4-*O*-acetyl-2-C-(4-*O*-acetyl-2,3-dideoxy-α-L-*threo*-hex-2-enopyranosyl)-2,3-dideoxy-2-eno-α-L-fucopyranosyl cyanide, in solution are virtually identical to the crystal structure.

Keywords: L-Fucal dimer; Cyanation; Double bond formation

1. Results and discussion

Due to the increasing importance of C-disaccharides as mimics of natural O-disaccharides, we became interested[1,2] in the chemistry of glycal dimers, e.g., the dimers **2** from tri-*O*-acetyl-D-glucal (3,4,6-tri-*O*-acetyl-D-*arabino*-2-deoxy-hex-1-enopyranose, **1**),[3] and **4** from di-*O*-acetyl-L-fucal (3,4-di-*O*-acetyl-L-*lyxo*-2,6-dideoxy-hex-1-enopyranose, **3**) (Scheme 1). We found in the dimer **4** a startling deviation from the 'normal' reaction of glycosyl acetates with cyanation reagent. Although the dimer from L-fucal (**4**) had only a stereochemical difference in the relative disposition of the 4-acetoxy group, the substitution of the anomeric acetoxy group was attended by elimination of AcOH, with deprotonation at C-2.

Glycosyl acetates are potential precursors for C-glycosyl compounds. DeLas Heras and co-workers have shown that glycosyl acetates, or glycals, can be transformed with BF_3–Me_3SiCN in nitromethane into glycosyl cyanides, or 2,3-unsaturated glycosyl cyanides, respectively.[4] Alternatively, glycosyl bromides and glycals have been treated with $Hg(CN)_2$ as the cyanide source to yield the corresponding glycosyl cyanides.[5–7] Acetal protected glycosyl fluorides gave mixtures of cyanides and isocyanides with Et_2AlCN.[8] More recently, alternative methods for the preparation of 2,3-unsaturated glycosyl cyanides from protected or unprotected glycals have been developed.[9,10] A milder reagent [10] for the introduction of a cyanide functionality, [$Hg(CN)_2$–$HgBr_2$–Me_3SiCN in THF–MeCN (2:3)], has been used to transform tri-*O*-acetyl-D-glucal into 2,3-unsaturated di-*O*-acetyl-D-glucosyl cyanide.[11]

This reagent, applied to compound **2**, replaced the anomeric acetate group in ring A, to give the expected glycosyl cyanide **5** (Scheme 1).[12] However, compound **4** (from tri-*O*-acetyl-L-fucal) gave unexpectedly the doubly unsaturated cyanide **6** (Scheme 1).

* Corresponding author. Fax: +1-209-9462607
E-mail addresses: adhunter@cc.ysu.edu (A.D. Hunter), afranz_bus@yahoo.com (P.H. Gross).

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The structure for **6** (Scheme 1) was based on ^{1}H NMR data. ^{1}H–^{1}H-COSY correlations were used to assign the signals in ^{1}H NMR spectrum. When compared to the standard set of coupling constants for 2,3-enopyranosyl systems published previously,[2,3] relatively large $^3J_{1B,2B}$ 3.5 Hz and $^3J_{3B,4B}$ 5.1 Hz (in $CDCl_3$) indicate that the equilibrium between the two half-chair forms of ring B in **6** lies significantly towards the shown ^5H_O-conformation with pseudo-equatorial positions for both H-1B and H-4B protons, implying a pseudo-axial position for ring A at C-1B. The value $^3J_{3A,4A}$ 5.4 Hz indicates a pseudo-axial acetoxy group on ring A. Analogously, relatively large values of $^3J_{1B,2B}$ 3.3 Hz and $^3J_{3B,4B}$ 5.1 Hz (in $CDCl_3$) indicated pseudo-equatorial positions for both H-1B and H-4B in compound **4** (Scheme 1),[1,12] with similar values observed in acetone-d_6, pyridine-d_5 and Me_2SO-d_6. Close chemical shifts of H-2B and H-3B in $CDCl_3$ obscured the coupling information. The geometry of **4** was also supported by NOEDIF experiments (in $CDCl_3$), with NOE between H-2A and H-5B.[12] In contrast with compound **2**,[2] ring B in product **4** shows preference for the half-chair conformation, in which ring A adopts a pseudo-axial position at C-1B.

Molecular mechanics calculations (MM +)[13] supported the pseudo-axial position of ring A on ring B in **6**. The most stable calculated conformation for **6** has the half-chair form of ring B shown in Scheme 1, whereas the alternative half-chair form for B possesses a 2–3 kcal/mol higher energy.

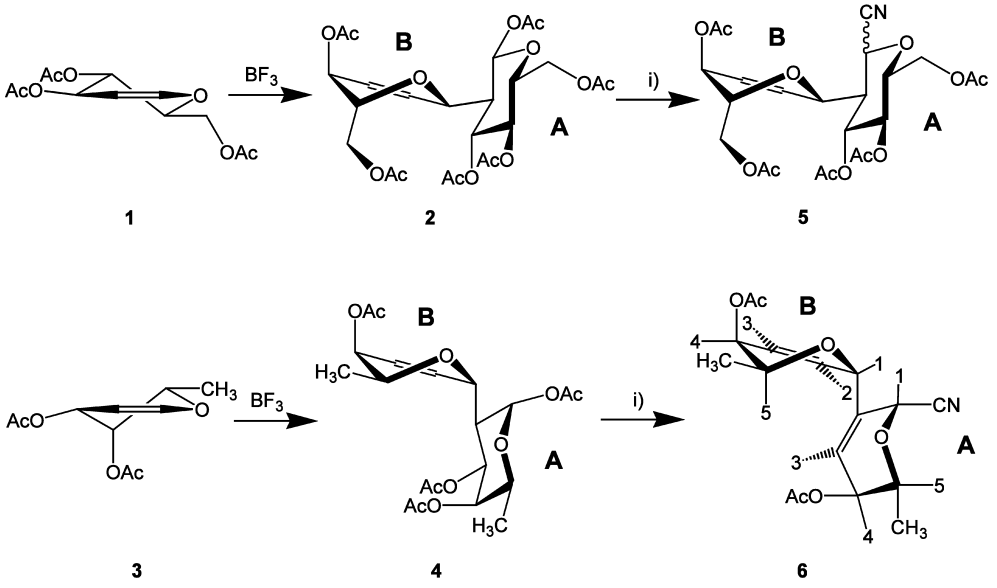
The configuration of **6** is consistent with NOEs between H-1B and H-1A, and between H-5B and H-1A (NOEDIF experiments). Protons H-1B and H-5B are *trans* to each other consistent with the previously established[1,12] stereochemistry for the precursor **4**. Saturation of H-3A caused a weak NOE at H-2B. No other diagnostic *trans*-annular NOEs were observed. Thus, both H-1A and H-1B are pseudo-equatorial, and the configuration at C-1A is α (Scheme 1). It is consistent with an observed 'W-coupling': $^4J_{1A,3A}$ 1.5 Hz.

The X-ray diffraction structure of compound **6**[14] was found to be unambiguously consistent with the NMR data. Thus, the observed crystal structure is virtually identical to the solution structure described above.

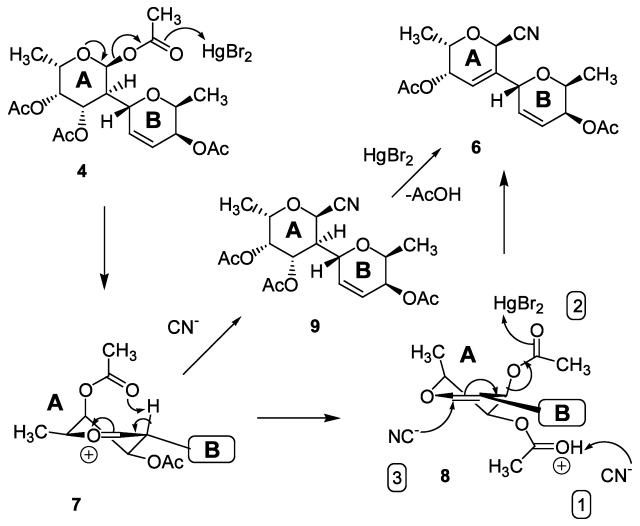
Possible mechanisms for the formation of **6** are shown in Scheme 2. A relief of steric strain may be a driving force for this acetic acid elimination found for cyanation of **4** in the present study, but not observed earlier[12] for cyanation of **2**. Indeed, the molecular mechanics calculations (MM +)[13] revealed a substantially higher steric strain (by 3–4 kcal/mol) in the most stable conformation of **4** as compared with 6A,6B-dideoxy analog of **2**, which is a stereoisomer of **4**.

Removal of the anomeric acetoxy group from **4** results in a partially flattened oxonium ion **7** (Scheme 2), possibly stabilized by the electrostatic attraction with a carbonyl oxygen from the axial acetoxy group at C-4A.

A likely mechanism involves the removal of H-2A from **7** by basic cyanide ion and formation of glycal **8**, which reacts further with cyanide as a nucleophile in an S'_N-reaction ('Ferrier rearrangement') to give **6** (Scheme 2). The remote C-4A acetoxy group, which functions as an internal base, may facilitate the elimination of H-2A in **7** by intramolecularly removing and transporting the proton ultimately to external CN^- (step 1 in **8**), like a miniature crane. Such a 'crane effect' does not work in **2**, which has a different orientation of C-4A acetoxy



Scheme 1. (i) $Hg(CN)_2$–$HgBr_2$–Me_3SiCN, THF–MeCN (2:3), RT, 36 h (**5**) or 24 h (**6**); yield 93% (**5**), 34% (**6**).



Scheme 2. Possible mechanistic scheme for the formation of **6**.

group.[2] [12] Finally, the S'_N-reaction with cyanide ion occurs at the unhindered α-face of C-1A (steps 2 and 3 in **8**; Scheme 2).

Less likely appears to be an intermediate formation of **9**, presumably a metastable compound (analogous to **2**→**5**), which could have been found among the reaction products, but was not. A rigorous exclusion of the pathway via **9** would require its synthesis and subjection to the reaction conditions. Presently, we know of no way to do that.

2. Experimental

2.1. 3,4,6-Tri-*O*-acetyl-2-*C*-(4,6-di-*O*-acetyl-2,3-dideoxy-α-D-*erythro*-hex-2-enopyranosyl)-2-deoxy-α/β-D-glucopyranosyl cyanide (5)

1,3,4,6-Tetra-*O*-acetyl-2-*C*-(4,6-di-*O*-acetyl-2,3-dideoxy-α-D-*erythro*-hex-2-enopyranosyl)-2-deoxy-β-D-glucopyranose (**2**, 80 mg, 0.147 mmol) was suspended in dry THF (7 mL) and dry MeCN (5 mL). After addition at rt of $Hg(CN)_2$ (0.18 g, 0.74 mmol, 5 equiv), $HgBr_2$ (7.2 mg, 0.02 mmol), and Me_3SiCN (0.04 mL, 0.3 mmol), the suspension was stirred for 36 h, after that it had turned into a clear solution. The reaction was monitored by TLC (4:3 EtOAc–hexane), and was complete in 36 h. The solvent was removed in vacuo and the remainder was re-suspended in CH_2Cl_2 and filtered through Celite. The main product was crystallized from EtOH (2 days at −20 °C). Yield 70 mg (93%), mp 114–116 °C, $[\alpha]_D^{25}$ +225° (*c* 0.5, $CHCl_3$); MS (APcI−): *m*/*z* [$M^{\bullet -}$] 511.38, *m*/*z* [$M^{\bullet -} - Ac - H_2$] 466.35; MS (APcI+): *m*/*z* $[M + Na]^+$ 534.12, *m*/*z* $[M + K]^+$ 550.10. NMR analysis disclosed this product as an anomeric mixture (α/β 1:2) of the cyanide. There was no evidence for the formation of the isomeric isocyanide. ^{1}H NMR ($CDCl_3$) α anomer, saturated ring 'A', unsaturated ring 'B': δ 1.97 (s, 3 H, CH_3^{ac}), δ 2.00 (s, 3 H, CH_3^{ac}), δ 2.01 (s, 6 H, 2 CH_3^{ac}), δ 2.02 (s, 3 H, CH_3^{ac}), δ 2.05 (s, 3 H, CH_3^{ac}), δ 2.37 (dt, 1 H, $^3J_{2,1}$ 5.1, $^3J_{2,3}$ 11.4, $^3J_{2,1B}$ 5.1, $^4J_{2,4} < 1$, H-2A), δ 3.88 (dd, 1 H, $^3J_{6b,5}$ 3.3, $^3J_{6b,6a}$ 12.0, H-6bB), δ 4.02–4.12 (m, 3 H, H-5A, H-5B, H-6aA), δ 4.27 (dd, 1 H, $^3J_{6b,5}$ 4.5, $^3J_{6b,6a}$ 12.6, H-6bA), δ 4.32 (dd, 1 H, $^3J_{6b,5}$ 9.3, $^3J_{6b,6a}$ 12.0, H-6bB), δ 4.39 (dd, 1 H, $^3J_{1,2} < 1$, $^4J_{1,3}$ 2.1, $^3J_{1,2A}$ 4.8, H-1B), δ 4.88 (d, 1 H, $^3J_{1,2}$ 4.8, H-1A), δ 4.87 (1 H, subm., H-4B), δ 4.93 (dd, 1 H, $^3J_{4,3}$ 9.0, $^3J_{4,5}$ 10.2, H-4A), δ 5.45 (dd, 1 H, $^3J_{3,2}$ 11.1, $^3J_{3,4}$ 9.0, H-3A), δ 5.82 (dd, 1 H, $^3J_{2,1} < 1$, $^3J_{2,3}$ 10.5, $^4J_{2,4}$ 1.5, H-2B), δ 5.97 (ddd, 1 H, $^3J_{3,2}$ 10.2, $^4J_{3,1}$ 1.8, $^3J_{3,4}$ 4.8, H-3B); ^{13}C NMR ($CDCl_3$): 21.03, 21.13, 21.51, 47.33 (C-2A), 60.37, 62.03, 63.80, 64.47, 64.52, 69.47, 70.16, 74.40, 76.32, 116.45 (CN), 124.23, 132.67, 169.90, 170.28, 170.60, 170.73, 171.10; ^{1}H NMR ($CDCl_3$) β anomer, saturated ring 'A', unsaturated ring 'B': 1.94 (s, 3 H, CH_3^{ac}), 2.00 (s, 3 H, CH_3^{ac}), 2.02 (s, 6 H, 2 CH_3^{ac}), 2.02 (s, 3 H, CH_3^{ac}), 2.05 (s, 3 H, CH_3^{ac}), 2.28 (dt, 1 H, $^3J_{2,1}$ 10.8, $^3J_{2,3}$ 10.8, $^3J_{2,1B}$ 1.2, H-2A), 3.61 (ddd, 1 H, $^3J_{5,4}$ 9.9, $^3J_{5,6a}$ 1.8, $^3J_{5,6b}$ 4.5, H-5A), 3.74 (dd, 1 H, $^3J_{6a,5}$ 3.6, $^3J_{6a,6b}$ 12.3, H-6aB), 4.04 (dd, 1 H, $^3J_{6a,5}$ 2.1, $^3J_{6a,6b}$ 12.6, H-6aA), 4.19 (dd, 1 H, $^3J_{6b,5}$ 4.8, $^3J_{6b,6a}$ 12.3, H-6bA), 4.35 (dd ~ s, 1 H, $^3J_{1,2} < 1$, $^4J_{1,3} < 1$, $^3J_{1,2A} < 1$, H-1B), 4.45 (dd, 1 H, $^3J_{6b,5}$ 9.9, $^3J_{6b,6a}$ 12.0, H-6bB), 4.52 (d, 1 H, $^3J_{1,2}$ 11.1, H-1A), 4.82 (ddd ~ d, 1 H, $^4J_{4,2} < 1$, $^3J_{4,3}$ 5.1, $^3J_{4,5} < 1$, H-4B), 4.90 (t, 1 H, $^3J_{4,3}$ 9.9, $^3J_{4,5}$ 9.9, H-4A), 5.31 (dd, 1 H, $^3J_{3,2}$ 10.5, $^3J_{3,4}$ 9.6, H-3A), 6.00 (dd, 1 H, $^3J_{2,1}$ 1.2, $^3J_{2,3}$ 10.5, $^4J_{2,4} < 1$, H-2B), 6.07 (ddd, 1 H, $^4J_{3,1}$ 2.4, $^3J_{3,2}$ 10.2, $^3J_{3,4}$ 5.4, H-3B); ^{13}C NMR ($CDCl_3$): 20.87, 20.97, 21.34, 47.09, 60.18, 62.10, 63.65, 64.29, 64.35, 69.28, 69.97, 74.19, 76.12, 116.30 (CN), 124.01, 132.53, 169.72, 170.10, 170.42, 170.49, 170.72; Anal. Calcd. for $C_{23}H_{29}NO_{12}$: C, 54.2; H, 5.7; N, 2.7. Found: C, 54.6; H, 6.1; N, 2.7.

2.2. 4-*O*-Acetyl-2-*C*-(4-*O*-acetyl-2,3-dideoxy-α-L-*threo*-hex-2-enopyranosyl)-2,3-dideoxy-2-eno-α-L-fucopyranosyl cyanide (6)

1,3,4-Tri-*O*-acetyl-2-*C*-(4-*O*-acetyl-2,3,6-trideoxy-α-L-*threo*-hex-2-enopyranosyl)-2-deoxy-α-L-fucopyranose (**4**, 2.3 g, 5.37 mmol) was suspended in dry THF (20 mL) and dry MeCN (40 mL). After addition at rt of $Hg(CN)_2$ (6.8 g, 26.85 mmol, 5 equiv), $HgBr_2$ (0.22 g, 0.6 mmol), and Me_3SiCN (1.6 mL, 12 mmol), the suspension was stirred for 24 h, after that it had turned into a clear solution. The reaction was monitored by TLC (4:3 EtOAc–hexane), and was complete in 24 h. The solvent was removed in vacuo and the remainder was re-suspended in CH_2Cl_2 and filtered through Celite. The main product was crystallized upon removal of solvent to give white crystals. Yield 0.72 g (34%), mp 137–139 °C, $[\alpha]_D^{25}$ +413° (*c* 1, $CHCl_3$); NMR analysis

yielded no evidence for the formation of the isomeric isocyanide. ^{1}H NMR ($CDCl_3$), saturated ring 'A', unsaturated ring 'B': δ 1.19 (d, 3 H, $^3J_{6,5}$ 6.6, CH_3), δ 1.31 (d, 3 H, $^3J_{6,5}$ 6.6, CH_3), δ 3.77 (dd, 1 H, $^3J_{5,6}$ 6.3, $^3J_{5,4}$ 2.4, H-5B), δ 4.10 (dd, 1 H, $^3J_{5,6}$ 6.3, $^3J_{5,4}$ 2.4, H-5A), δ 4.83 (ddd $\sim$ dd, 1 H, $^3J_{1,2}$ 3.5, $^4J_{1,3}$ 1.5, $^4J_{1,3A} < 1$, H-1B), δ 4.98 (ddd $\sim$ dd, 1H, $^4J_{4,2} < 1$, $^3J_{4,3}$ 4.8, $^3J_{4,5}$ 2.4, H-4B), δ 5.10 (ddd, 1 H, $^3J_{4,3}$ 5.7, $^3J_{4,5}$ 2.1, $^5J_{4,1}$ 1.8, H-4A), δ 5.31 (dd $\sim$ d, 1 H, $^4J_{1,3}$ 1.5, $^5J_{1,4} < 1$, H-1A), δ 6.00 (dt, 1 H, $^3J_{3,4}$ 5.4, $^4J_{3,1}$ 1.5, $^4J_{3,1B}$ 1.5, H-3A), δ 6.08 (ddd $\sim$ dd, 1 H, $^3J_{2,1}$ 3.3, $^3J_{2,3}$ 9.9, $^4J_{2,4} < 1$, H-2B), δ 6.18 (ddd, 1 H, $^4J_{3,1}$ 1.5, $^3J_{3,2}$ 10.2, $^3J_{3,4}$ 5.1, H-3B); ^{13}C NMR ($CDCl_3$): 16.14, 16.68, 21.20, 21.27, 63.96, 64.57, 65.34, 66.91, 76.94, 116.02 (CN), 125.90, 126.49, 129.82, 136.90, 170.50, 170.80; Anal. Calcd. for $C_{17}H_{21}NO_6$: C, 60.9; H, 6.3; N, 4.3. Found: C, 60.8; H, 6.4; N, 4.2.

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