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Selective formation of C-2 azidodeoxy-D-glucose derivatives from D-glucal precursors using the azidonitration reaction

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Abstract

A series of glucals, protected by cyclic acetal protecting groups to conformationally constrain the C-4 and C-6 hydroxyl groups, were subjected to the azidonitration reaction to furnish the corresponding C-2 azidodeoxy-D-glucoses. 4,6-*O*-Isopropylidene-3-*O*-triisopropylsilyl-D-*arabino*-hex-1-enitol afforded 2-azido-2-deoxy-4,6-*O*-isopropylidene-3-*O*-triisopropylsilyl-D-glucopyranosyl nitrate and its D-manno isomer in a 20:1 ratio. These findings allow the azidonitration reaction to be now used for the preparation of a variety of glucosamine building blocks from differentially protected glucal precursors.

Keywords: Azidonitration; Glucals; Conformational restriction; 2-Amino-2-deoxy-D-glycosides

1. Introduction

The realization that complex carbohydrates are involved in many biologically important signal transduction processes has led to increased interest in the development of novel strategies for the synthesis of these biopolymers [1]. 2-Amino-2-deoxy glycosides are frequently encountered constituents of many naturally occurring glycoconjugates. Some methods for the introduction of a C-2 azido functionality rely upon the conversion of the free amino group to the corresponding azide by diazotransfer [2], while others are based on the displacement of other C-2 alkylsulfonyl groups [3,4]. Additional protocols rely on the installation of a C-2 azide from glycal precursors. The conversion of glycals into 2-azido-2-deoxyglycosyl nitrates that function as 2-amino-2-deoxy glycoside precursors is commonly effected by the azidonitration reaction that was developed by Lemieux and Ratcliffe in 1979 [5]. The anomeric nitrate group can be readily converted into a hydroxyl [6], halide [5,7], or acetyl functionality [8] and allows for access to a variety of glycosyl donors containing a nonparticipating 2-azido group. Reaction of protected D-galactal **1** with ceric ammonium nitrate (CAN) and sodium azide results in the formation of a mixture of anomers of the desired 2-azido-2-deoxy-D-galactose derivative **2** as well as varying amounts of D-talose side product **3** containing the axial 2-azido moiety (Scheme 1) [5]. The azidonitration reaction is presumably initiated by the addition of an azide radical and pro-

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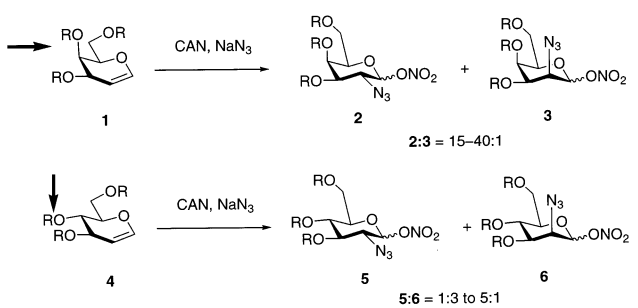
ceeds regioselectively to yield anti-Markovnikov products [5]. Stereoselectivity of this preparatively very useful transformation was found to be greatly dependent upon the configuration of the C-4 center. The axial C-4 substituent in the case of galactal **1** guarantees good selectivity for the installation of an equatorial C-2 azido moiety, but selectivities vary considerably depending upon the protecting group ensemble [15–40:1 of **2** (D-galacto) to **3** (D-talo)] [5].

In the case of D-glucal **4** that carries an equatorial C-4 substituent, unpredictable ratios of products containing an equatorial or an axial C-2 azido group have been obtained. Selectivities ranging from 3:1 in favor of the 2-azido-2-deoxy-D-mannose derivative **6** to a 5:1 ratio in favor of the 2-azido-2-deoxy-D-glucose derivative **5** have been reported [9]. Selectivity of the reaction was found to depend upon the reaction temperature, the ratio of the reactants and the protecting groups employed. Consequently, the utility of the azidonitration reaction for the synthesis of glucosamine building blocks from protected glucals has severely suffered from the capricious stereoselectivity. In addition, separation of the mixtures of stereoisomers is extremely tedious if at all possible. Clearly, the development of reaction conditions that would overcome this problem could allow for rapid access to a variety of D-glucosamine building blocks from D-glucal precursors.

We present here results of a systematic study aimed at the development of reaction conditions and protecting group ensembles that allow for the efficient conversion of D-glucal precursors into 2-azido-2-deoxy-D-glucose derivatives. Use of conformationally constrained D-glucals yielded 70% of the desired D-glucose derivative **5** in a ratio of up to 20:1 over the undesired D-mannose derivative **6**.



Scheme 1.

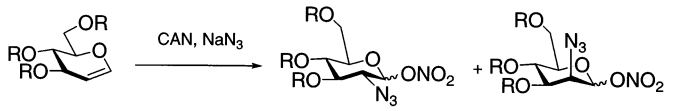
2. Results and discussion

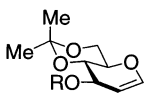
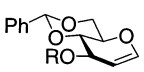
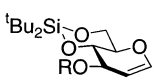
During studies aimed at the synthesis of complex oligosaccharides and glycoconjugates containing D-glucosamine building blocks, we encountered the necessity to access differentially protected glucose building blocks containing a C-2 azido functionality. Glycals had served well as starting materials in the synthesis of a range of complex oligosaccharides, but while the azidonitration reaction had resulted in excellent selectivity in the case of D-galactal, protected D-glucals resulted in greatly varying selectivities that compromised synthetic utility (vide supra). Simple models as well as low-level semiempirical calculations (AM 1)[1] suggested that in the case of a protected D-galactal the top face of the molecule is sterically more congested than the bottom face. Therefore, attack from the less-hindered face of the glycal would preferentially fashion the desired equatorial azide. Modeling of tri-*O*-acetyl- and tri-*O*-benzyl-protected D-glucals showed that neither face of the molecule appeared particularly hindered, thus supporting the lack of selectivity observed experimentally. Models of D-glucals containing a 4,6-*O*-isopropylidene acetal as well as a C-3 protecting group suggested that the top face was significantly more crowded than the bottom face of the molecule. Previous studies had suggested that steric effects influence the selectivity of the azidonitration reaction involving glucals [10]. Azidonitration reactions based on these simple models confirmed the trends and resulted in preparatively useful reactions (Table 1).

Reaction of acetylated D-glucal **7** furnished the desired C-2 azide-substituted D-glucose **8** in 8:1 excess over the D-mannose derivative **9**. While **10**, which contained the sterically more demanding pivaloyl group, surprisingly exhib-

[1] Low-level AM1 calculations were performed with MacSpartan 1.1 desktop modeling software.

Table 1
Azidonitration of conformationally constrained D-glucals



Substrate	R		α,β-D-gluco	:	α-D-manno		Yield (%)
	Ac	**7**	**8a,b**	8	1	**9**	71
	Piv	**10**	**11a,b**	5.5	1	**12**	66
	Bn	**13**	**14a,b**	14	1	**15**	59
	TBDMS	**16**	**17a,b**	12	1	**18**	68
	TIPS	**19**	**20a,b**	20	1	**21**	71
	Ac	**22**	**23a,b**	6	1	**24**	66
	Bn	**25**	**26a,b**	10	1	**27**	61
	TIPS	**28**	**29a,b**	11	1	**30**	63
	Ac	**31**	**32a,b**	3	1	**33**	75

ited lower selectivity, the introduction of a C-3 benzyl protecting group in **13** did result in a 14:1 ratio of desired **14** over the undesired D-mannose derivative **15**. C-3 silyl protecting groups provided additional bulk and resulted in increased yields as well as excellent selectivities. In the case of TIPS-protected D-glucal **19**, the desired D-glucose derivative was obtained in a 20:1 ratio over the D-mannose side product. Selectivity was entirely lost when no protecting group was present on C-3 (data not shown). Modeling suggested that added bulk in the C-3 position may lead to increased twisting of the *O*-isopropylidene ring, thereby forcing the C-4 hydrogen in close proximity over C-2.

When benzylidene acetals were used to constrain C-4 and C-6 (Table 1, entries 6–8) selectivities were slightly lower than in the isopropylidene cases, but significantly increased over glucal substrates that did not contain a cyclic protecting group. Use of a cyclic di-*tert*-butylsilane protecting group (Entry 9) resulted in increased yield (75%), but low selectivity (3:1). In cases where a cyclic carbonate was employed to protect C-4 and C-6, no selectivity was encountered (data not shown).

The increase in selectivity as a consequence of the use of a cyclic protecting group resulted in a less complex reaction mixture, which in turn greatly facilitated product purification. Still, in many cases contaminating D-mannose side products copurify at the stage of the anomeric nitrate, but may be easily separated after hydrolysis and functionalization of the anomeric position. The desired C-2 azidodeoxy-D-glucoses can now be prepared in multigram quantities, and conversion into glycosyl donors may be achieved after hydrolysis of the anomeric nitrate using published procedures [4].

In conclusion, C-2 azidodeoxy-D-glucoses can be prepared from D-glucal precursors in good yield and selectivity when cyclic acetal protecting groups are used to conformationally constrain the C-4 and C-6 hydroxyl groups. These findings allow for the azidonitration reaction to be used for the preparation of a variety of D-glucosamine building blocks from differentially protected D-glucal precursors.

3. Experimental

General methods.—All chemicals were reagent grade and were used as supplied except

where noted. CAN and sodium azide were dried in vacuo over silica gel prior to use. Protected D-glucals **7** [11], **13** [12], **16** [12], **22** [13], **25** [14] and **31**[15] were prepared following published procedures. Dichloromethane and MeCN were distilled from CaH_2 under N_2. Anhydrous DMF was used as purchased. Analytical thin-layer chromatography (TLC) was performed on E. Merck Silica Gel 60 F_{254} plates (0.25 mm). Compounds were visualized by dipping the plates in a cerium sulfate–ammonium molybdate solution, followed by heating. Liquid column chromatography was performed using forced flow of the indicated solvent on Sigma H-type silica (10–40 μm). ^{1}H NMR spectra were obtained on a Varian Mercury 300 (300 MHz) and are reported in parts per million (δ) relative to $CHCl_3$ (7.27 ppm). Coupling constants (J) are reported in Hz. ^{13}C NMR spectra were obtained on Varian Mercury 300 (75 MHz) and are reported in δ relative to $CDCl_3$ (77.23 ppm) as the internal reference.

*4,6-*O*-Isopropylidene-3-*O*-pivaloyl-*D*-arabino-hex-1-enitol* (**10**).—4-Dimethylaminopyridine (DMAP, 680.5 mg, 5.570 mmol) was added to a solution of 4,6-*O*-isopropylidene-D-*arabino*-hex-1-enitol [16] (249.4 mg, 1.339 mmol) in CH_2Cl_2 (1.3 mL) under argon at ambient temperature. The resulting suspension was stirred until the precipitate had dissolved, then trimethylacetyl chloride (330 μL, 2.68 mmol) was added. The reaction mixture was stirred for 3.5 h at ambient temperature and quenched with water. After dilution with CH_2Cl_2 and phase separation, the aq phase was extracted three times with CH_2Cl_2. The combined organic phases were dried ($MgSO_4$), filtered and evaporated. Flash chromatography (12:1 hexanes–EtOAc) furnished **10** (338.7 mg, 94%) as a colorless solid. $[\alpha]_D^{24}$ −75.3° (*c* 0.97, CH_2Cl_2); IR (thin film) 1721 (CO), 1647, 1160, 1116, 863 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 6.35 (dd, *J* 1.5, 6.3 Hz, 1 H, H-1), 5.40–5.34 (m, 1 H, H-3), 4.70 (dd, *J* 2.1, 6.0 Hz, 1 H, H-2), 4.10–3.78 (m, 4 H, H-4, H-5, H-6a, H-6b), 1.51 (s, 3 H, $C(CH_3)_2$), 1.41 (s, 3 H, $C(CH_3)_2$), 1.21 (s, 9 H, $C(CH_3)_3$); ^{13}C NMR ($CDCl_3$): δ 178.2, 145.4, 101.1, 99.8, 70.1, 69.9, 68.9, 61.8, 38.9, 29.0, 27.1, 19.1; FABMS: *m/z* [M$^+$] Anal. Calcd: 270.1467. Found 270.1464.

*4,6-*O*-Isopropylidene-3-*O*-triisopropylsilyl-*D*-arabino-hex-1-enitol* (**19**).—Imidazole (158.7 mg, 2.331 mmol) and triisopropylsilyl chloride (360 μL, 1.68 mmol) were added to a solution of 4,6-*O*-isopropylidene-D-*arabino*-hex-1-enitol [16] (210.0 mg, 1.128 mmol) in DMF (2.5 mL) under argon at ambient temperature. The reaction mixture was stirred for 12 h and quenched with water. After addition of CH_2Cl_2 and phase separation, the aq phase was extracted three times with CH_2Cl_2. The combined organic phases were dried ($MgSO_4$), filtered and evaporated. Flash chromatography (10:1 hexanes–EtOAc) furnished **19** (313.7 mg, 82%) as a colorless oil. $[\alpha]_D^{24}$ −52.0° (*c* 1.00, CH_2Cl_2); IR (thin film) 1638, 1382, 1232, 1102, 875 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 6.26 (dd, *J* 1.6, 6.2 Hz, 1 H, H-1), 4.69 (dd, *J* 1.9, 6.2 Hz, 1 H, H-2), 4.43 (ddd, *J* 1.9, 7.2, 7.2 Hz, 1 H, H-3), 3.95 (dd, *J* 5.6, 10.9 Hz, 1 H, H-6a), 3.88–3.78 (m, 2 H, H-4, H-6b), 3.76–3.66 (m, 1 H, H-5), 1.52 (s, 3 H, $C(CH_3)_2$), 1.42 (s, 3 H, $C(CH_3)_2$), 1.18–1.04 (m, 21 H, $Si(CH(CH_3)_2)_3$); ^{13}C NMR ($CDCl_3$): δ 143.3, 105.9, 99.7, 73.6, 69.9, 68.0, 62.0, 29.3, 19.2, 18.2, 12.6; FABMS: *m/z* [M$^+$] Anal. Calcd: 342.2226. Found 342.2223.

*4,6-*O*-Benzylidene-3-*O*-triisopropylsilyl-*D*-arabino-hex-1-enitol* (**28**).—Imidazole (145.4 mg, 2.136 mmol) and triisopropylsilyl chloride (340 μL, 1.589 mmol) were added to a solution of 4,6-*O*-benzylidene-D-*arabino*-hex-1-enitol [16] (250.1 mg, 1.068 mmol) in DMF (2.0 mL) under argon at ambient temperature. The reaction mixture was stirred for 11 h and quenched with water. After addition of CH_2Cl_2 and phase separation, the aq phase was extracted three times with CH_2Cl_2. The combined organic phases were dried ($MgSO_4$), filtered and evaporated. Flash chromatography (10:1 hexanes–EtOAc) furnished **28** (388.1 mg, 93%) as a colorless solid. $[\alpha]_D^{24}$ −63.9° (*c* 1.24, CH_2Cl_2); IR (thin film) 1638, 1464, 1234, 1108, 882, 696 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.55–7.35 (m, 5H, Ph), 6.33 (dd, *J* 1.6, 6.2 Hz, 1 H, H-1), 5.63 (s, 1 H, CHPh), 4.77 (dd, *J* 1.9, 6.2 Hz, 1 H, H-2), 4.68–4.63 (m, 1 H, H-3), 4.42–4.35 (m, 1 H, H-6a), 3.96–3.80 (m, 3 H, H-4, H-5, H-6a), 1.22–1.04 (m, 21 H, $Si(CH(CH_3)_2)_3$); ^{13}C NMR ($CDCl_3$): δ 143.3, 137.5, 129.0, 128.2, 126.3, 105.8, 101.7, 81.1, 68.9, 68.5, 67.5, 18.1, 12.5;

FABMS: m/z [M^+] Anal. Calcd: 390.2226. Found: 390.2231.

General procedure for azidonitration of glucals.—A mixture of cerium(IV) ammonium nitrate (3 equiv) and sodium azide (1.6 equiv) was added to a solution of glucal in MeCN (0.2 M except for **25** (0.1 M)) at −20 °C under argon. The resulting suspension was vigorously stirred at −15 °C until TLC analysis (3:2 hexanes–EtOAc) indicated complete consumption of starting material. Ethyl acetate and water were added, and the organic phase was washed two times with water, dried ($MgSO_4$), filtered and evaporated. Flash chromatography (6:1 hexanes–EtOAc) furnished the product as a mixture of α,β-D-gluco and α-D-manno isomers of the anomeric nitrates. The ratio of D-gluco to D-manno configuration was determined by ^{1}H NMR spectroscopy of the crude mixture material and the purified isomer mixture. Separation of the isomers could be achieved by flash chromatography (30:1 → 15:1 hexanes–EtOAc).

*Azidonitration of 3-*O*-acetyl-4,6-*O*-isopropylidene-*D*-arabino-hex-1-enitol* (**7**).—The reaction was conducted on a 0.6 mmol scale, 3 h reaction time; 71%, ratio of 8:1 α,β-D-gluco–α-D-manno.

*3-*O*-Acetyl-2-azido-2-deoxy-4,6-*O*-isopropylidene-α-D-glucopyranosyl nitrate* (**8a**).—The product was a colorless solid: $[\alpha]_D^{24}$ + 117.6° (*c* 0.86, CH_2Cl_2); IR (thin film) 2114 (N_3), 1753 (CO), 1659 (NO_2), 1281, 1133, 824 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 6.28 (d, *J* 4.4 Hz, 1 H, H-1), 5.37 (dd, *J* 9.3, 10.3 Hz, 1 H, H-3), 3.94–3.89 (m, 2 H, H6a, H-6b), 3.78–3.66 (m, 3 H, H-2, H-4, H-5), 2.17 (s, 3 H, Ac–CH_3), 1.49 (s, 3 H, $C(CH_3)_2$), 1.41 (s, 3 H, $C(CH_3)_2$); ^{13}C NMR ($CDCl_3$): δ 169.6, 100.3, 97.5, 71.7, 69.6, 66.6, 61.9, 60.5, 29.1, 21.1, 19.3; FABMS: m/z [M^+] Anal. Calcd 332.0968. Found: 332.0961.

*3-*O*-Acetyl-2-azido-2-deoxy-4,6-*O*-isopropylidene-β-D-glucopyranosyl nitrate* (**8b**).—The product was a colorless solid: $[\alpha]_D^{24}$ − 49.9° (*c* 1.03, CH_2Cl_2); IR (thin film) 2114 (N_3), 1748 (CO), 1670 (NO_2), 1233, 1027, 827 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 5.63 (d, *J* 8.4 Hz, 1 H, H-1), 5.15 (dd, *J* 9.5, 9.5 Hz, 1 H, H-3), 3.97 (dd, *J* 5.3, 11.0 Hz, 1 H, H-6a), 3.77 (dd, *J* 11.0, 11.0 Hz, 1 H, H-6b), 3.69 (dd, *J* 9.7, 9.7 Hz, 1 H, H-4), 3.57 (dd, *J* 8.7, 9.7 Hz, 1 H, H-2), 3.48 (ddd, *J* 5.3, 9.7, 9.7 Hz, 1 H, H-5), 2.17 (s, 3 H, Ac–CH_3), 1.49 (s, 3 H, $C(CH_3)_2$), 1.40 (s, 3 H, $C(CH_3)_2$); ^{13}C NMR ($CDCl_3$): δ 169.5, 100.3, 98.4, 72.2, 71.1, 68.4, 61.69, 61.66, 29.0, 21.1, 19.2; FABMS: m/z [M^+] Anal. Calcd: 332.0968. Found: 332.0960.

*3-*O*-Acetyl-2-azido-2-deoxy-4,6-*O*-isopropylidene-α-D-mannopyranosyl nitrate* (**9**).—The product was a colorless solid: $[\alpha]_D^{24}$ + 94.0° (*c* 1.00, CH_2Cl_2); IR (thin film) 2108 (N_3), 1748 (CO), 1662 (NO_2), 1228, 822 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 6.12 (d, *J* 1.2 Hz, 1 H, H-1), 5.15 (dd, *J* 4.1, 10.3 Hz, 1 H, H-3), 4.28 (dd, *J* 1.2, 4.1 Hz, 1 H, H-2), 4.19–4.10 (m, 1 H, H-4), 3.92–3.78 (m, 3 H, H-5, H-6a, H-6b), 2.19 (s, 3 H, Ac–CH_3), 1.55 (s, 3 H, $C(CH_3)_2$), 1.42 (s, 3 H, $C(CH_3)_2$); ^{13}C NMR ($CDCl_3$): δ 170.1, 100.6, 98.1, 70.3, 68.0, 67.6, 61.8, 59.6, 29.2, 20.9, 19.5; FABMS: m/z [M^+] Anal. Calcd: 332.0968. Found: 332.0963.

*Azidonitration of 4,6-*O*-isopropylidene-3-*O*-pivaloyl-*D*-arabino-hex-1-enitol* (**10**).—The reaction was conducted on a 0.8 mmol scale, 5 h reaction time; yield 66%, ratio of 5.5:1 α,β-D-gluco–α-D-manno.

*2-Azido-2-deoxy-4,6-*O*-isopropylidene-3-*O*-pivaloyl-α-D-glucopyranosyl nitrate* (**11a**).—The product was a colorless solid: $[\alpha]_D^{24}$ + 74.8° (*c* 0.86, CH_2Cl_2); IR (thin film) 2114 (N_3), 1752 (CO), 1657 (NO_2), 1279, 1135, 823 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 6.28 (d, *J* 4.1 Hz, 1 H, H-1), 5.37 (dd, *J* 9.3, 10.3 Hz, 1 H, H-3), 3.98–3.85 (m, 2 H, H-6a, H-6b), 3.77 (m, 3 H, H-2, H-4, H-5), 1.47 (s, 3 H, $C(CH_3)_2$), 1.39 (s, 3 H, $C(CH_3)_2$), 1.25 (s, 9 H, $C(CH_3)_3$); ^{13}C NMR ($CDCl_3$): δ 177.0, 100.2, 97.5, 71.9, 69.5, 66.5, 62.0, 60.5, 39.3, 29.1, 27.2, 19.3; FABMS: m/z [M^+] Anal Calcd: 374.1437. Found: 374.1434.

*2-Azido-2-deoxy-4,6-*O*-isopropylidene-3-*O*-pivaloyl-β-D-glucopyranosyl nitrate* (**11b**).—The product was a colorless solid: $[\alpha]_D^{24}$ − 18.1° (*c* 0.53, CH_2Cl_2); IR (thin film) 2116 (N_3), 1743 (CO), 1672 (NO_2), 1286, 1103, 827 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 5.62 (d, *J* 8.7 Hz, 1 H, H-1), 5.17 (dd, *J* 9.7, 9.7 Hz, 1 H, H-3), 3.99 (dd, *J* 5.3, 10.9 Hz, 1 H, H-6a), 3.77 (dd, *J* 10.6, 10.6 Hz, 1 H, H-6b), 3.70 (dd, *J* 9.7, 9.7 Hz, 1 H, H-4), 3.62 (dd, *J* 8.7, 9.7 Hz, 1 H, H-2), 3.50 (ddd, *J* 5.3, 9.7, 9.7 Hz, 1 H, H-5), 1.47 (s, 3 H, $C(CH_3)_2$), 1.38 (s, 3 H, $C(CH_3)_2$),

1.26 (s, 9 H, $C(CH_3)_3$); ^{13}C NMR ($CDCl_3$): δ 177.0, 100.1, 98.4, 77.4, 72.2, 71.3, 68.3, 61.8, 39.2, 29.1, 27.2, 19.2; FABMS: m/z [M^+] Anal. Calcd: 374.1437. Found 374.1442.

*Azidonitration of 3-*O*-benzyl-4,6-*O*-isopropylidene-*D*-arabino-hex-1-enitol* (**13**).—The reaction was conducted on a 0.7 mmol scale, 7 h reaction time; yield 59%, ratio of 14:1 α,β-D-gluco–α-D-manno.

*2-Azido-3-*O*-benzyl-2-deoxy-4,6-*O*-isopropylidene-α-D-glucopyranosyl nitrate* (**14a**).—The product was a colorless oil: $[\alpha]_D^{24}$ +61.0° (*c* 1.00, CH_2Cl_2); IR (thin film) 2114 (N_3), 1656 (NO_2), 1280, 1135, 824 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.40–7.33 (m, 5 H, Ph), 6.21 (d, *J* 4.4 Hz, 1 H, H-1), 4.92 (d, *J* 10.9 Hz, 1 H, CH_2Ph), 4.79 (d, *J* 10.9 Hz, 1 H, CH_2Ph), 3.94–3.70 (m, 6 H, H-2, H-3, H-4, H-5, H-6a, H-6b), 1.52 (s, 3 H, $C(CH_3)_2$), 1.47 (s, 3 H, $C(CH_3)_2$); ^{13}C NMR ($CDCl_3$): δ 137.7, 128.6, 128.3, 128.2, 100.0, 97.5, 77.0, 75.2, 74.9, 66.4, 62.0, 61.2, 29.3, 19.4; FABMS: m/z [M^+] Anal. Calcd: 380.1332. Found: 380.1337.

*2-Azido-3-*O*-benzyl-2-deoxy-4,6-*O*-isopropylidene-β-D-glucopyranosyl nitrate* (**14b**).—The product was a colorless oil: $[\alpha]_D^{24}$ −14.3° (*c* 0.51, CH_2Cl_2); IR (thin film) 2116 (N_3), 1666 (NO_2), 1286, 1100, 826 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.40–7.33 (m, 5 H, Ph), 5.50 (d, *J* 8.4 Hz, 1 H, H-1), 4.91 (d, *J* 10.9 Hz, 1 H, CH_2Ph), 4.79 (d, *J* 10.9 Hz, 1 H, CH_2Ph), 3.96 (dd, *J* 5.6, 10.9 Hz, 1 H, H-6a), 3.82–3.72 (m, 2 H, H-4, H-6b), 3.61 (dd, *J* 8.7, 9.0 Hz, 1 H, H-3), 3.51 (dd, *J* 8.7, 9.0 Hz, 1 H, H-2), 3.40 (ddd, *J* 5.3, 10.0, 10.0 Hz, 1 H, H-5), 1.52 (s, 3 H, $C(CH_3)_2$), 1.46 (s, 3 H, $C(CH_3)_2$); ^{13}C NMR ($CDCl_3$): δ 137.7, 128.6, 128.4, 128.2, 100.0, 98.4, 80.1, 75.2, 74.0, 68.0, 62.4, 61.8, 29.3, 19.3; FABMS: m/z [M^+] Anal. Calcd: 380.1332. Found: 380.1330.

*Azidonitration of 4,6-*O*-isopropylidene-3-*O*-(tert-butyldimethylsilyl)-D-arabino-hex-1-enitol* (**16**).—The reaction was conducted on a 0.5 mmol scale, 6 h reaction time; yield 68%, ratio of 12:1 α,β-D-gluco–α-D-manno.

*2-Azido-2-deoxy-4,6-*O*-isopropylidene-3-*O*-(tert-butyldimethylsilyl)-α-D-glucopyranosyl nitrate* (**17a**).—The product was a colorless solid: $[\alpha]_D^{24}$ +84.5° (*c* 1.00, CH_2Cl_2); IR (thin film) 2113 (N_3), 1661 (NO_2), 1281, 1132, 839 cm^{-1}; ^1H NMR ($CDCl_3$): δ 6.27 (d, *J* 4.1 Hz, 1 H, H-1), 3.92–3.68 (m, 4 H, H-3, H-5, H-6a, H-6b), 3.63–3.53 (m, 2 H, H-2, H-4), 1.50 (s, 3 H, $C(CH_3)_2$), 1.43 (s, 3 H, $C(CH_3)_2$), 0.93 (s, 9H, $C(CH_3)_3$), 0.20 (s, 3 H, CH_3), 0.15 (s, 3 H, CH_3); ^{13}C NMR ($CDCl_3$): δ 100.0, 98.1, 74.1, 71.1, 66.6, 63.9, 61.9, 29.1, 25.9, 19.0, 18.4, −4.0, −4.8; FABMS: m/z [M^+] Anal. Calcd: 404.1727. Found: 404.1734.

*Mixture of 2-Azido-2-deoxy-4,6-*O*-isopropylidene-3-*O*-(tert-butyldimethylsilyl)-β-D-glucopyranosyl nitrate* (**17b**) *and 2-azido-2-deoxy-4,6-*O*-isopropylidene-3-*O*-(tert-butyldimethylsilyl)-α-D-mannopyranosyl nitrate* (**18**).—Product **17b** was a colorless solid that contained about 20% of **18**: IR (thin film) 2118 (N_3), 1669 (NO_2), 1267, 1102, 844 cm^{-1}; **17b** ^1H NMR ($CDCl_3$): δ 5.53 (d, *J* 8.9 Hz, 1 H, H-1), 3.99–3.91 (m, 1 H, H-6a)#, 3.75 (dd, *J* 10.5, 10.5 Hz, 1 H, H-6b)#, 3.60 (dd, *J* 8.8, 8.8 Hz, 1 H, H-3), 3.52 (dd, *J* 8.8, 8.8 Hz, 1 H, H-4), 3.40–3.30 (m, 2 H, H-2, H-5), 1.49 (s, 3 H, $C(CH_3)_2$), 1.41 (s, 3 H, $C(CH_3)_2$)#, 0.94–0.91 (m, 9 H, $C(CH_3)_3$)#, 0.16 (s, 3 H, CH_3), 0.12 (s, 3 H, CH_3); **18**: 6.08 (d, *J* 1.6 Hz, 1 H), 4.04 (dd, *J* 3.8, 9.3 Hz, 1 H), 1.52 (s, 3 H), 0.15 (s, 3 H), 0.14 (s, 3 H); **17b** ^{13}C NMR ($CDCl_3$): δ 99.9, 98.6, 74.4, 73.3, 68.1, 65.2, 61.8, 29.1, 25.91, 19.1, 18.4, −4.0, −4.7; **18**: 100.2, 98.9, 70.92, 70.87, 67.6, 62.4, 29.2, 25.94, 19.4, 18.5, −4.1, −4.6; FABMS: m/z [M^+] Anal. Calcd: 404.1727. Found: 404.1730. (# indicates that signals of **17b** and **18** overlap).

*Azidonitration of 4,6-*O*-isopropylidene-3-*O*-triisopropylsilyl-D-arabino-hex-1-enitol* (**19**).—The reaction was conducted on 0.9 mmol scale, 3 h reaction time; yield 71%, ratio of 20:1 α,β-D-gluco–α-D-manno.

*2-Azido-2-deoxy-4,6-*O*-isopropylidene-3-*O*-(triisopropylsilyl)-α-D-glucopyranosyl nitrate* (**20a**).—The product was a colorless oil: $[\alpha]_D^{24}$ +84.5° (*c* 1.00, CH_2Cl_2); IR (thin film) 2112 (N_3), 1661 (NO_2), 1280, 1133, 824 cm^{-1}; ^1H NMR ($CDCl_3$): δ 6.28 (d, *J* 4.4 Hz, 1 H, H-1), 4.00 (dd, *J* 9.0, 9.7 Hz, 1 H, H-3), 3.90–3.85 (m, 1 H, H-6a), 3.82–3.55 (m, 4 H, H-2, H-4, H-5, H-6b), 1.49 (s, 3 H, $C(CH_3)_2$), 1.41 (s, 3 H, $C(CH_3)_2$), 1.22–1.14 (m, 3 H, $Si(CH(CH_3)_2)_3$), 1.13–1.04 (m, 18 H, $Si(CH(CH_3)_2)_3$); ^{13}C NMR ($CDCl_3$): δ 100.1, 98.0, 74.3, 71.5, 66.6, 64.3, 61.9, 29.2, 19.0, 18.4,

13.2; FABMS: *m/z* [M^+] Anal. Calcd: 446.2197. Found: 446.2204.

*2-Azido-2-deoxy-4,6-*O*-isopropylidene-3-*O*-(triisopropylsilyl)-β-*D*-glucopyranosyl nitrate* (**20b**).—The product was a colorless oil: $[\alpha]_D^{24}$ −13.7° (*c* 1.00, CH_2Cl_2); IR (thin film) 2891 (N_3), 1634 (NO_2), 1286, 1134, 835 cm^{-1}; ^1H NMR ($CDCl_3$): δ 5.57 (d, *J* 8.8 Hz, 1 H, H-1), 3.94 (dd, *J* 5.4, 10.8 Hz, 1 H, H-6a), 3.76 (dd, *J* 10.3, 10.3 Hz, 1 H, H-6b), 3.75 (dd, *J* 8.8, 8.8 Hz, 1 H, H-3), 3.55 (dd, *J* 8.8, 9.6 Hz, 1 H, H-4), 3.39 (dd, *J* 8.8, 8.8 Hz, 1 H, H-2), 3.34 (ddd, *J* 5.3, 9.6, 9.6 Hz, 1 H, H-5), 1.48 (s, 3 H, $C(CH_3)_2$), 1.40 (s, 3 H, $C(CH_3)_2$), 1.14–1.04 (m, 21 H, $Si(CH(CH_3)_2)_3$); ^{13}C NMR ($CDCl_3$): δ 100.0, 99.0, 74.6, 73.6, 68.2, 65.5, 61.7, 29.1, 19.0, 18.4, 13.1; FABMS: *m/z* [M^+] Anal. Calcd: 446.2197. Found: 446.2199.

*Azidonitration of 3-*O*-acetyl-4,6-*O*-benzylidene-*D*-arabino-hex-1-enitol* (**22**).—The reaction was conducted on 0.6 mmol scale, 7 h reaction time; yield 66%, ratio of 7:1 α,β-*D*-gluco–α-*D*-manno.

*3-*O*-Acetyl-2-azido-4,6-*O*-benzylidene-2-deoxy-α-*D*-glucopyranosyl nitrate* (**23a**).—The product was a colorless solid: $[\alpha]_D^{24}$ +97.9° (*c* 0.68, CH_2Cl_2); IR (thin film) 2113 (N_3), 1753 (CO), 1658 (NO_2), 1280, 1132, 823 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.50–7.35 (m, 5 H, Ph), 6.33 (d, *J* 4.3 Hz, 1 H, H-1), 5.56 (dd, *J* 9.7, 10.4 Hz, 1 H, H-3), 5.52 (s, 1 H, CHPh), 4.34 (dd, *J* 4.9, 10.4 Hz, 1 H, H-6a), 4.10 (ddd, *J* 4.9, 9.8, 10.0 Hz, 1 H, H-5), 3.81–3.68 (m, 3 H, H-2, H-4, H-6b), 2.17 (s, 3 H, Ac–CH_3); ^{13}C NMR ($CDCl_3$): δ 169.6, 136.5, 129.5, 128.5, 126.3, 102.1, 97.3, 78.7, 69.2, 68.4, 65.5, 60.3, 21.0; FABMS: *m/z* [M^+] Anal. Calcd: 380.0968. Found: 380.0964.

*Mixture of 3-*O*-acetyl-2-azido-4,6-*O*-benzylidene-2-deoxy-β-*D*-glucopyranosyl nitrate* (**23b**) *and 3-*O*-acetyl-2-azido-4,6-*O*-benzylidene-2-deoxy-α-*D*-mannopyranosyl nitrate* (**24**).—The product was a colorless solid: IR (thin film) 2116 (N_3), 1759 (CO), 1672 (NO_2), 1221, 1106, 826 cm^{-1}; **23b**: ^1H NMR ($CDCl_3$) δ 7.50–7.35 (m, 5 H, Ph)#, 5.70 (d, *J* 8.7 Hz, 1 H, H-1), 5.51 (s, 1 H, CHPh), 5.38–5.30 (m, 1 H, H-3)#, 4.42–4.38 (m, 1 H, H-6a), 3.84–3.76 (m, 1 H, H-6b)#, 3.71–3.62 (m, 3 H, H-2, H-4, H-5), 2.18 (s, 3 H, Ac-CH_3)#; containing about 20% **24**: δ 7.50–7.35 (m, 5 H, Ph), 6.16 (d, *J* 1.5 Hz, 1 H, H-1), 5.59 (s, 1 H, CHPh), 5.38–5.30 (m, 1 H, H-3), 4.34–4.28 (m, 2 H, H-2, H-6a), 4.21–4.02 (m, 2 H, H-4, H-5), 3.84–3.76 (m, 1 H, H-6b); **23b**: ^{13}C NMR ($CDCl_3$): δ 169.6, 136.5, 129.5, 128.5, 126.3, 101.9, 98.4, 78.0, 71.7, 68.2, 67.3, 61.6, 21.0; containing about 20% **24**: 170.1, 126.4, 102.3, 97.9, 75.1, 69.9, 66.5, 59.5, 20.8; FABMS: *m/z* [M^+] Anal. Calcd: 380.0968. Found: 380.0971; (# indicates signals of **23b** and **24** overlap).

*Azidonitration of 3-*O*-benzyl-4,6-*O*-benzylidene-*D*-glucal* (**25**).—The reaction was conducted on a 0.5 mmol scale, 7 h reaction time; yield 61%, ratio of 10:1 α,β-*D*-gluco–α-*D*-manno.

*Data for 2-azido-3-*O*-benzyl-4,6-*O*-benzylidene-2-deoxy-α-*D*-glucopyranosyl nitrate* (**26a**) *and β-*D*-glucopyranosyl nitrate* (**26b**).—These were found as described in the literature [10a].

*Azidonitration of 4,6-*O*-benzylidene-3-*O*-triisopropylsilyl-*D*-arabino-hex-1-enitol* (**28**).—The reaction was conducted on 0.6 mmol scale, 6 h reaction time; yield 63%, ratio of 11:1 α,β-*D*-gluco–α-*D*-manno.

*2-Azido-4,6-*O*-benzylidene-2-deoxy-3-*O*-triisopropylsilyl-α-*D*-glucopyranosyl nitrate* (**29a**).—The product was a colorless solid: $[\alpha]_D^{24}$ +60.5° (*c* 1.00, CH_2Cl_2); IR (thin film) 2114 (N_3), 1661 (NO_2), 1279, 1135, 825, 684 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.48–7.35 (m, 5 H, Ph), 6.31 (d, *J* 4.4 Hz, 1 H, H-1), 5.47 (s, 1 H, CHPh), 4.30 (dd, *J* 4.7, 10.3 Hz, 1 H, H-6a), 4.17 (dd, *J* 9.3, 9.3 Hz, 1 H, H-3), 4.00 (ddd, *J* 4.7, 9.7, 9.7 Hz, 1 H, H-5), 3.74 (dd, *J* 10.3, 10.3 Hz, 1 H, H-6b), 3.68 (dd, *J* 4.4, 9.7 Hz, 1 H, H-2), 3.56 (dd, *J* 9.3, 9.3 Hz, 1 H, H-4), 1.14–0.98 (m, 21 H, $Si(CH(CH_3)_2)_3$); ^{13}C NMR ($CDCl_3$): δ 136.6, 129.6, 128.3, 126.4, 102.8, 97.8, 81.8, 71.0, 68.5, 65.5, 64.1, 18.2, 13.1; FABMS: *m/z* [M^+] Anal. Calcd: 494.2197. Found: 494.2190.

*2-Azido-4,6-*O*-benzylidene-2-deoxy-3-*O*-triisopropylsilyl-β-*D*-glucopyranosyl nitrate* (**29b**).—The product was a colorless solid: $[\alpha]_D^{24}$ −39.8° (*c* 1.00, CH_2Cl_2); IR (thin film) 2115 (N_3), 1673 (NO_2), 1285, 1105, 826, 697 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.48–7.35 (m, 5 H, Ph), 5.64 (d, *J* 8.7 Hz, 1 H, H-1), 5.49 (s, 1 H, CHPh), 4.36 (dd, *J* 4.7, 10.6 Hz, 1 H, H-6a), 3.94 (dd, *J* 9.0, 9.0 Hz, 1 H, H-3), 3.78

(dd, *J* 10.3, 10.3 Hz, 1 H, H-6b), 3.62–3.49 (m, 2 H, H-4, H-5), 3.47 (dd, *J* 9.0, 9.0 Hz, 1 H, H-2), 1.13–1.00 (m, 21 H, $Si(CH(CH_3)_2)_3$); ^{13}C NMR ($CDCl_3$): δ 136.7, 129.5, 128.3, 126.3, 102.5, 98.8, 81.0, 74.1, 68.4, 67.1, 65.3, 18.3, 13.0; FABMS: *m*/*z* [M^+] Anal. Calcd: 494.2197. Found: 494.2194.

Azidonitration of 3-O-*acetyl-4,6*-O-*di-(*tert-*butyl)silanediyl*-D-arabino-*hex-1-enitol* (**31**).—The reaction was conducted on 0.6 mmol scale, 5 h reaction time; yield 75%, ratio of 3:1 α,β-D-gluco–α-D-manno.

Mixture of 3-O-*acetyl-2-azido-2-deoxy-4,6*-O-*di-(*tert-*butyl)silanediyl*-α-D-*glucopyranosyl nitrate* (**32a**) *(37%) and 3*-O-*acetyl-2-azido-2-deoxy-4,6*-O-*di-(*tert-*butyl)silanediyl*-α-D-*mannopyranosyl nitrate* (**33**) *(63%).*—The product was a colorless solid: IR (thin film) 2112 (N_3), 1758 (CO), 1665 (NO_2), 1225, 825 cm^{-1}; **32a**: ^1H NMR ($CDCl_3$): δ 6.25 (d, *J* 5.0 Hz, 1 H, H-1), 5.34 (dd, *J* 9.0, 10.9 Hz, 1 H, H-3), 4.27–3.82 (m, 4 H, H-4, H-5, H-6a, H-6b)$^{\#}$, 3.70 (dd, *J* 4.4, 10.6 Hz, 1 H, H-2), 2.17 (s, 3 H, Ac–CH_3), 1.07 (s, 9 H, $C(CH_3)_3$)$^{\#}$, 0.98 (s, 9 H, $C(CH_3)_3$)$^{\#}$; containing about 63% **33**: 6.10 (d, *J* 1.6 Hz, 1 H, H-1), 5.19 (dd, *J* 4.1, 9.7 Hz, 1 H, H-3), 4.27–3.82 (m, 5 H, H-2, H-4, H-5, H-6a, H-6b), 2.19 (s, 3 H, Ac–CH_3), 1.04 (s, 9 H, $C(CH_3)_3$), 0.99 (s, 9 H, $C(CH_3)_3$): **32a**: ^{13}C NMR ($CDCl_3$): δ 169.4, 96.9, 74.8, 71.5, 69.2, 65.8, 59.5, 27.2, 26.7, 22.6, 20.5, 19.9; containing about 63% **33**: 169.8, 97.5, 71.8, 71.0, 70.1, 59.3, 27.3, 26.8, 20.4, 19.5; FABMS: *m*/*z* [M^+] Anal. Calcd: 432.1676. Found: 432.1686; ($^{\#}$ indicates signals of **32a** and **33** overlap).

3-O-*Acetyl-2-azido-2-deoxy-4,6*-O-*di-(*tert-*butyl)silanediyl*-β-D-*glucopyranosyl nitrate* (**32b**).—Product is a colorless solid: $[\alpha]_D^{24}$ −55.3° (*c* 2.00, CH_2Cl_2); IR (thin film) 2118 (N_3), 1759 (CO), 1674 (NO_2), 1220, 828 cm^{-1}; ^1H NMR ($CDCl_3$): δ 5.63 (d, *J* 8.7 Hz, 1 H, H-1), 5.12 (dd, *J* 10.0, 10.0 Hz, 1 H, H-3), 4.21 (dd, *J* 5.3, 10.3 Hz, 1 H, H-6a), 3.89 (dd, *J* 10.3, 10.3 Hz, 1 H, H-6b), 3.84 (dd, *J* 9.3, 9.3 Hz, 1 H, H-4), 3.65–3.52 (m, 2 H, H-2, H-5), 2.17 (s, 3 H, Ac–CH_3), 1.04 (s, 9 H, $C(CH_3)_3$), 0.98 (s, 9 H, $C(CH_3)_3$); ^{13}C NMR ($CDCl_3$): δ 169.7, 98.4, 74.5, 74.4, 71.5, 65.8, 60.9, 27.4, 26.9, 22.8, 20.8, 20.1; FABMS: *m*/*z* [M^+] Anal. Calcd: 432.1676. Found: 432.1682.

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