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Unexpected Incorporation of Bromine at a Non-anomeric Position during the Synthesis of an O^2-Glycosylated Diazeniumdiolate

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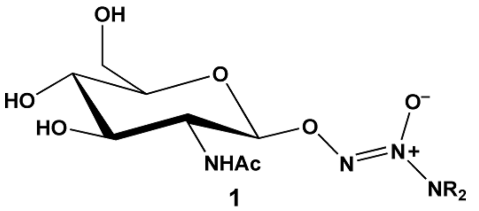
We recently reported that the novel NO-releasing O^2-glycosylated diazeniumdiolates of structure **1** showed promising anti-parasitic activity against *Leishmania major*.[1] While preparing some 2-deoxyglucose analogs for lead optimization, we have observed the facile displacement of acetate by bromide from the 4-position of peracetylated 2-deoxyglucose **2**, as shown in *Scheme 1*, providing a convenient synthesis of 4-brominated 2,4-dideoxyglucose derivatives that would otherwise be difficult to access by currently preferred, directed synthetic routes.



1

a) R = Et **b)** $R_2 = -(CH_2)_4-$

In an effort to prepare compound **4a**, peracetylated 2-deoxyglucose **2** was treated with HBr in glacial acetic acid. A tar assumed to be bromide **3** was formed and immediately

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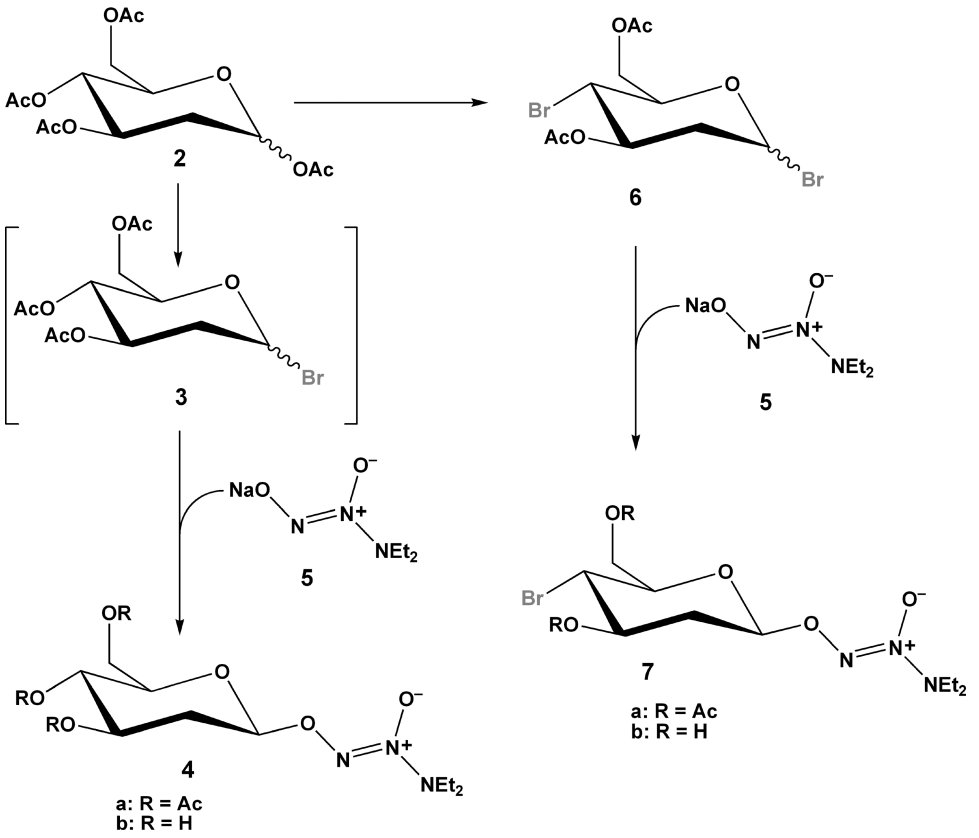

Scheme 1

reacted with diazeniumdiolate salt **5** to generate a product expected to be **4a**. However, this easily crystallized, sharp-melting product was characterized by elemental analysis values that were vastly different from our expectation. Further examination revealed the presence of only two methyl singlets in the proton NMR, and mass spectrometry pointed to the presence of a bromine atom in the molecular ion isotopic cluster. Detailed analysis of the ^{1}H NMR spectral properties showed that the halide had replaced the C4 acetoxy group with retention of configuration. Further work-up afforded **7a** in 38% yield. The product **7a** was deacetylated with methoxide in methanol to produce **7b**. An alternate bromination procedure using $BiBr_3$ and trimethylsilyl bromide gave 4-α-bromo-2,4-dideoxyglucosyl bromide diacetate **6,** presumably the same glycosylating agent produced in the HBr/HOAc reaction. The reaction with $BiBr_3$ was rapid, efficient, and gave a higher yield of **6** than the HBr procedure.

Diazeniumdiolates generate up to two moles of NO upon hydrolysis under various conditions. Replacement of the C4 acetoxy group of compound **4b** by bromine had little effect (only about three-fold) on hydrolysis rates at pH values of 14, 7.4, and 3.8–4.6 (*Table 1*), a key predictor of anti-leishmanial activity.[1]

In conclusion, we have discovered a novel and simple $BiBr_3$/TMS bromide-mediated preparation of compound **6**, an extremely useful intermediate in the preparation of the

Table 1
Half-lives of Hydrolysis at 37°C for Diazeniumdiolated Glycosides of Structure $Et_2NN(O)=NOR$

	pH		
R	14[a]	7.4[b]	3.8–4.6
β-(4-α-Bromo)-2,4-dideoxy-D-glucosyl **(7b)**	72 min	1.5 days	1.8 days[c]
β-(2-Deoxy)-D-glucosyl **(4b)**[1]	23 min	0.5 days	1.2 days[d]

[a]) 1.0 M NaOH.
[b]) 0.1 M phosphate.
[c]) 0.95 M citrate at pH 4.6.
[d]) 0.05 M citrate at pH 3.8.

2-deoxy sugars primed for further functionality at C4. In particular, compounds **7a** and **7b** offer an electrophilic center at C4, making it potentially useful for further reaction with nucleophiles, including peptide chains or additional saccharides.

Experimental Section

Starting materials were purchased from Aldrich Chemical Co. (Milwaukee, WI). NMR spectra were obtained in chloroform-*d* or deuterium oxide on a Varian UNITY INOVA spectrometer; chemical shifts (δ) are reported in parts per million (ppm) downfield from tetramethylsilane or 3-(trimethylsilyl)propionic-*2,2,3,3-d*$_4$ acid, sodium salt. Ultraviolet (UV) spectra were recorded on an Agilent model 8453 or a Hewlett-Packard model 8451A diode array spectrophotometer. ESI-MS analysis was performed on a Finnigan LCQ DECA ion trap mass spectrometer. Elemental analyses were performed by Atlantic Microlab, Inc. (Norcross, GA) and Midwest Microlab (Indianapolis, IN).

Isolation of O^2*-(3,6-Di-O-acetyl-4-[α-bromo]-2,4-dideoxy-β-D-glucopyranosyl) 1-(N,N-Diethylamino)diazen-1-ium-1,2-diolate (7a) (JS-33–45) from Deoxyglucose Tetraacetate 2 with HBr in glacial Acetic Acid*

2-Deoxy-D-glucose (Sigma-Aldrich) was acylated with acetic anhydride and pyridine using the general method of Wolfrom and Thompson.[2] The spectral properties of the product, **2**, matched those in the published report. A solution of 6.0 g (0.018 mol) of **2** in 12 mL of 30% HBr/acetic acid at 0°C was allowed to warm to room temperature and stirred for 20 hours. The reaction mixture was diluted with 200 mL of dichloromethane and washed with water. The organic layer was washed three times with aqueous 5% sodium bicarbonate solution, dried over sodium sulfate, and filtered through a layer of anhydrous magnesium sulfate. Evaporation of the solvent gave 3.60 g of **6** as a black tar. A 2.35 g portion of the crude product **6** was dissolved in 25 mL of tetrahydrofuran. The resulting solution was added dropwise to a cold slurry of 1.1 g (0.007 mol) of **5**[3] in 20 mL of dimethyl sulfoxide containing 200 mg of anhydrous sodium carbonate. After stirring at room temperature under nitrogen for 72 hours, the solution was diluted with 200 mL of ether and filtered

into a separatory funnel, washed with water, dried over sodium sulfate, and filtered through a layer of magnesium sulfate. Evaporation of the solvent gave 2.09 g of a brown oil. Purification was carried out on a 25-mm × 300-mm glass column packed with 70 g of silica gel suspended in 10:1 dichloromethane:ethyl acetate. Elution was performed using the same solvent system to give 1.12 g (38% based on 2.35 g of starting material) of **7a** as a colorless crystalline solid, mp 87.8°C. ESI mass spectroscopy confirmed the presence of bromide in the molecule (M^+ 425 and 427); further NMR analysis using COSY and HSQC acquisitions demonstrated that the bromide was at the C-4 equatorial position: UV (EtOH) λ_{max} (ε) 228 nm (10 mM^{-1} cm^{-1}). ^{1}H NMR ($CDCl_3$): δ 1.11 (t, 6 H, $J = 7.0$ Hz, C$\underline{H}_3$CH$_2$-), 2.09 (s, 3 H, C$\underline{H}_3$C=O), 2.12 (s, 3 H, C$\underline{H}_3$C=O), 2.43–2.52 (m, 1 H, H2), 2.71–2.76 (m, 1 H, H2′), 3.18 (q, 4 H, $J = 7.1$ Hz, CH$_3$C$\underline{H}_2$-), 3.63–3.67 (m, 1 H, H5), 4.09–4.25 (m, 3 H, H3, H6′ and H6), 5.12 (t, 1 H, $J = 9.9$ Hz, H4), 5.25 (dd, 1 H, $J = 2.2$ and 10.1 Hz, H1). ^{13}C NMR δ 11.50, 20.65, 20.68, 38.97, 45.26, 48.45, 62.40, 70.78, 74.40, 99.89, 169.30, 170.63.

Anal. Calcd for $C_{14}H_{25}BrN_3O_7$: C, 39.52; H, 5.69; N, 9.88. Found: C, 39.60; H, 5.67; N, 9.81.

Bromination of 2 via $BiBr_3$

The general procedure of Montero *et al.*[4] was used to brominate compound **2**. To a solution of 641 mg (1.93 mmol) of **2** in 10 mL of dichloromethane were added 90 mg (0.2 mmol) of bismuth tribromide (Sigma-Aldrich) and four equivalents (1.03 mL, 8 mmol) of trimethylsilyl bromide under a nitrogen atmosphere. The solution was stirred at room temperature for 2 hours, diluted with dichloromethane, washed with 5% sodium bicarbonate solution, dried over sodium sulfate, and filtered. Evaporation of the solvent gave 551 mg of **6** as a gray-brown oil. The TLC and NMR of this crude product matched the TLC and NMR of the over-brominated compound **6** described in the previous paragraph.

O^2-[4-(α-Bromo)-2,4-dideoxy-β-D-glucopyranosyl] 1-(N,N-diethylamino)diazen-1-ium-1,2-diolate (7b) (JS-33–48)

The general procedure of Wolfram and Thompson[5] was used in the deacetylation step. A solution of 936 mg (2.2 mmol) of **7a** in 40 mL of methanol was treated with 150 μL of 25% methanolic sodium methoxide and stirred at room temperature. The progress of the hydrolysis was followed on silica-gel TLC using 50:1 dichloromethane:methanol. After 2 hours, 1 g of pre-washed Dowex-50W resin was added to the reaction mixture and stirred for 30 min. Filtration and evaporation of the filtrate gave a colorless solid that was purified on silica gel, eluted with 5:1 dichloromethane:ethyl acetate. Pure **7b** was isolated in 98% yield (738 mg) mp 121–123 °C; UV (EtOH) λ_{max} (ε) 226 nm (7.9 $mM^{-1}cm^{-1}$). ^{1}H NMR (D_2O) δ 1.07 (t, 6 H, $J = 7.1$ Hz, C$\underline{H}_3$CH$_2$-), 2.27–2.38 (m, 1 H, H2), 2.74–2.80 (m, 1 H, H2′), 3.18 (q, 4 H, $J = 7.1$ Hz, CH$_3$C$\underline{H}_2$-), 3.56–3.62 (m, 1 H, H5), 3.70 (t, 1 H, $J = 9.7$ Hz, H4), 3.82–3.95 (m, 3 H, H3, H6′, and H6), 4.17–4.26 (m, 1 H, H3′), 5.53 (dd, 1 H, $J =$ 2.2 and 13.0 Hz, H1). ^{13}C NMR ($CDCl_3$) δ 11.50, 38.96, 48.37, 51.57, 62.50, 71.74, 77.48, 100.08.

Anal. Calcd for $C_{10}H_{20}BrN_3O_5 \cdot \frac{1}{4}CH_2Cl_2$: C, 33.88; H, 5.69; N, 11.56. Found: C, 33.54; H, 5.57; N, 11.55.

Acknowledgments

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Syntheses of C-1 Axial Derivatives of L-Menthol

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Derivatives of menthol have interesting ^{1}H NMR spectra and often, complete assignments of the protons and determination of the configuration of substituents on the cyclohexane ring are difficult. As part of a project to investigate the NMR properties of menthol derivatives, several axially substituted menthanes **(3–6)** were prepared and their structures established.[1]

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