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The First Synthesis of a Nitromethylene-Linked *C*-(1→2)-Disaccharide

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Abstract: The Michael addition of the 2,3 4,6-di-*O*-isopropylidene-β-D-mannopyranosyl-nitromethane nucleophile to 1,2-dideoxy-3,4:5,6-di-*O*-isopropylidene-1-nitro-D-*arabino*-hex-1-enitol affords a dinitro adduct that can be regioselectively reduced on the primary nitromethyl group to the oxime of the corresponding nitromethylene-linked *C*-(1→2)-disaccharide.

In the last decade, disaccharide mimics known as *C*-disaccharides, in which the anomeric linking oxygen atom is replaced by a methylene group, have attracted tremendous interest due to their resistance to chemical and enzymatic hydrolysis of the *C*-glycosyl linkage. This structural modification of natural compounds makes them useful as competetive inhibitors and nonmetabolizable inducers. In 1990, as the technology surrounding the preparation of *C*-disaccharides progressed,[1] glycopyranosylnitromethanes began to be used as convenient starting materials for the synthesis of *C*-disaccharides by Martin and Lai[2] and others.[3] As a part of our research on synthesis of *C*-(1→2)-disaccharides,[4] we introduce here a novel and efficient route for the preparation of (1→2)-nitromethylene-linked *C*-disaccharides and illustrate the utility of fully acetalated β-D-mannopyranosylnitromethane as a convenient glycosyl donor in its Michael addition to 1,2-dideoxy-3,4:5,6-diisopropylidene-1-nitro-D-*arabino*-hex-1-enitol.

The starting 2,3:4,6-diisopropylidene-β-D-mannopyranosylnitromethane (2,6-anhydro-1-deoxy-3,4:5,7-di-*O*-isopropylidene-1-nitro-D-*glycero*-D-*galacto*-heptitol) (**1**) and 1,2-dideoxy-3,4:5,6-diisopropylidene-1-nitro-D-*arabino*-hex-1-enitol (**2**) were readily prepared from D-mannose and D-arabinose, respectively, according to our original methods of preparation and isolation.[5] The base-catalysed addition of the nucleophile generated from **1** with DBU to glycosyl acceptor **2** was carried out in THF as solvent at -78 °C (Scheme 1). The expected adducts **3** were obtained in a practically quantitative yield. The formation of adducts **3** was recognized by ^{13}C NMR and mass spectral analyses. The former tool of analysis clearly indicated the presence of three of the four theoretically possible diastereoisomers of **3**. 2,6-Anhydro-7,8-dideoxy-1,3:4,5:9,10:11,12-tetra-*O*-isopropylidene-7-nitro-8-*C*-nitromethyl-D-*erythro*-L-*gluco*-D-*manno*-

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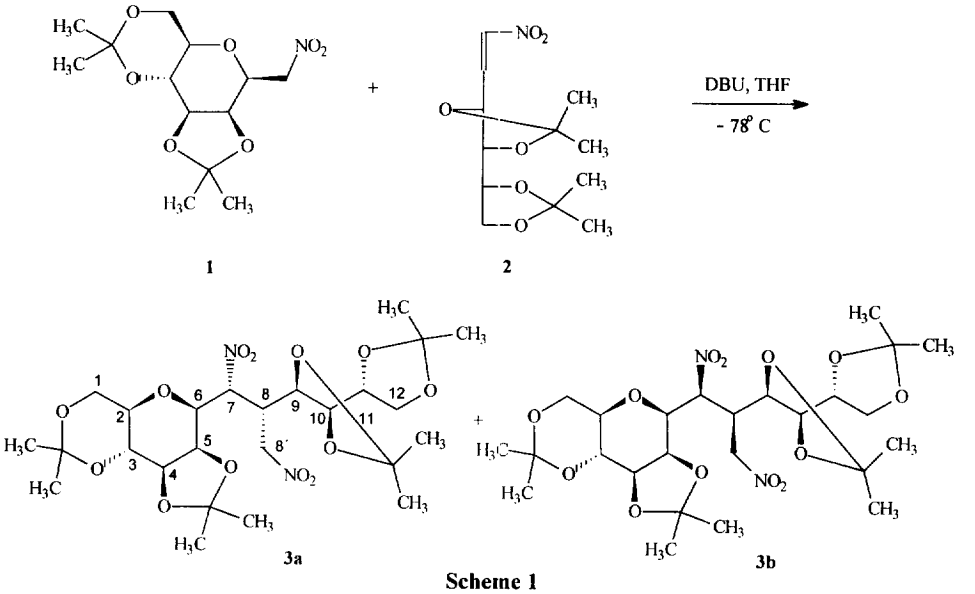
dodecitol (**3a**) was separated by column chromatography using a mixture of hexane - ethyl acetate (2:1) as the major diastereoisomer.[6] Also a mixture of two other diastereoisomers of **3** (a ratio *ca* 3:1 by ^{13}C NMR) was obtained, which was crystallized to give 2,6-anhydro-7,8-dideoxy-1,3:4,5:9,10:11,12-tetra-*O*-isopropylidene-7-nitro-8-*C*-nitromethyl-D-*erythro*-L-*gulo*-D-*manno*-dodecitol (**3b**). Structures of **3a** and **3b** were determined by X-ray crystallography.[7]



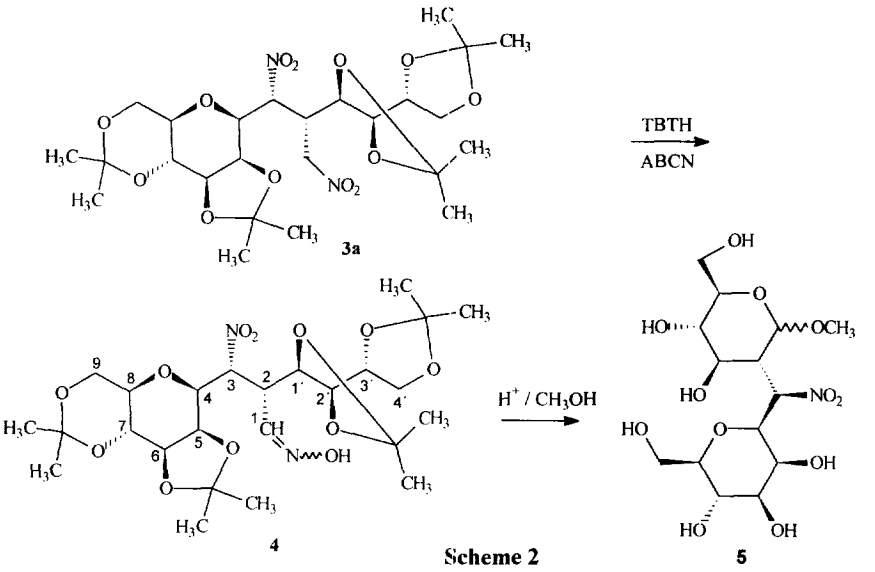
1 **2**

3a **3b**

Scheme 1

The dinitro derivative **3a** was regioselectively reduced by treatment with tributyltin hydride (TBTH) in the presence of 1,1′-azobis(cyclohexanecarbonitrile) (ABCN) in refluxing benzene to give the corresponding, fully acetalated oxime of nitromethylene-linked (1→2)-disaccharide **4** in a good yield.[8,9] Compound **4** can be deprotected affording an interesting mimetic of 2-*O*-β-D-mannopyranosyl-D-glucose (Scheme 2).[10]

The structural elucidation of **4** was accomplished by ^{1}H, ^{13}C NMR (including DEPT and HETCOR) and mass spectral analyses. The ^{13}C NMR spectra of **4** exhibited signals at δ = 39.3 ppm, which are characteristic for 2-deoxy-2-*C*-branched carbon atom.[11] The ^{13}C NMR chemical shifts also clearly indicated the presence of both 1,3-dioxane (δ = 100 ppm) and three 1,3-dioxolane (δ ≈ 112—110 ppm) rings. Especially diagnostic for the formation of **4** was the appearance of two signals for CH=N–OH at δ ≈ 146—148 ppm in its ^{13}C NMR spectrum.[10] Structures of *E* and *Z* isomers (1:3.8) of **4** were assigned on the basis of ^{1}H NMR spectrum.[8,11] The value of the proton chemical shift of the CH=N signal of *E* isomer of **4** was observed at δ = 7.35 ppm; that of the corresponding *Z* isomer appeared at a higher field (δ = 6.89 ppm). Morever, structures of *E* and *Z* isomers of **4** were also determined by evidence from $^{1}H/^{1}H$ NOE difference spectra.[11]



Scheme 2

In conlusion, this new methodology constitutes an expeditious entry into interesting mimetic of *O*-β-D-mannopyranosyl-(1→2)-D-glucose based on 1,4-Michael addition of glycosylnitromethane to nitrohexenitol. Preparation of other analogues of natural (1→2)-disaccharides is underway.

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References and Notes

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6. To a solution of **1** (303 mg, 1 mmol) in dry THF (10 ml) cooled to -78 °C was added DBU (150 µl, 1 mmol) under argon atmosphere. The mixture was stirred for 10 min and then nitroalkene **2** (273 mg, 1 mmol) disolved in dry THF (3 ml) was added dropwise. After stirring for 4 h at -78 °C, the temperature was allowed to rise to -40 °C and the reaction was quenched by addition of acetic acid (115 µl, 2 mmol). Then a mixture of water and ethyl acetate was added and stirring was maintained for 10 min at

rt. The organic phase was separated and the aqueous phase was extracted with ethyl acetate (2 × 10 ml). The combined organic phases were washed (aq. $NaHCO_3$), dried (Na_2SO_4) and concetrated to give adducts **3**. Flash chromatography (hexane-ethyl acetate 2:1) afforded **3a** in 60% yield and a mixture of two other diastereoisomers in 35 % yield. After crystallization from heptane-ethyl acetate (5:1), the mixture afforded **3b** in a 24% yield.

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9. A mixture of **3a** (288 mg, 0.5 mmol), TBTH (0.8 ml, 1.5 mmol), and ABCN (20 mg) in benzene (5 ml) was stirred at 80 °C for 5 h. Then the reaction mixture was cooled to room temperature and the solvent was removed under reduced pressure. Flash chromatography of the residue (silica gel) afforded **4** in a 77% yield.
10. Compound **5**: ^{13}C NMR (methanol-d_4) major isomer: 98.3 (C-1); 84.3 (CH-NO_2); 82.7, 79.2, 74.4, 74.2, 73.4, 72.2, 71.6, 68.4 (8 CH-O); 63.0, 62.6 (2 CH_2-O); 52.9 (OMe); 44.8 (branch CH). Structural assigment of **5** was determined on a basis of their per-*O*-acetylated derivatives (**6**). Mass spectrum of **6** exhibited the characteristic peaks for the per-*O*-acetylated glycopyranosylnitromethyl moiety, which have occurred also in the mass spectra of per-*O*-acetylated analogues of **3**.[7]
11. Analytical and spectroscopic data for compound **3a**: Mp 155-158°; $[\alpha]_D$ -30.0° (*c* 1.0, acetone); ^1H NMR (300 MHz, acetone-d_6): δ 5.33 (dd, 1H, $J_{7,8}$ 2.9 Hz, $J_{6,7}$ 10.1 Hz, H-7); 5.28 (dd, 1H, $J_{8,8'a}$ 2.1 Hz, $J_{8'a,8'b}$ 16.4 Hz, H-8′a of CH_2-NO_2); 4.81 (dd, 1H, $J_{5,6}$ 2.6 Hz, H-6); 4.74 (dd, 1H, $J_{8,8'b}$ 7.3 Hz, H-8′b of CH_2-NO_2); 4.47 (dd, 1H, $J_{4,5}$ 5.3 Hz, H-5); 4.16—4.08 (m, 3H, H-4, H-11, H-12a); 3.97 (dd, 1H, $J_{8,9}$ 8.0 Hz, $J_{9,10}$ 5.8 Hz, H-9); 3.88 (dd, 1H, $J_{10,11}$ 7.5 Hz, H-10); 3.85—3.75 (m, 2H, H-3, H-12b); 3.73 (dd, 1H, $J_{1a,1b}$ 10.7 Hz, $J_{1a,2}$ 5.8 Hz, H-1a); 3.68 (dd, 1H, $J_{1b,2}$ 10.0 Hz, H-1b); 3.47 (m, 1H, H-8); 3.20 (td, 1H, $J_{2,3}$ 10.0, H-2); 1.53, 1.50, 1.42, 1.38, 1.37, 1.32, 1.31, 130 (8s, 24H, 8 Me of acetals). ^{13}C NMR (acetone-d_6): δ 111.1, 110.6, 110.5, 100.1 (4 C of acetals); 87.7 (C-7); 80.7 (C-10); 79.7 (C-9); 77.0 (C-4); 76.9 (C-11); 75.6 (C-6); 73.5 (C-3); 73.2 (C-5); 73.0 (CH_2-NO_2); 70.4 (C-2); 67.9 (C-12), 62.1 (C-1), 39.3 (C-8), 29.1, 28.5, 27.5, 27.0, 26.6, 26.2, 25.3, 19.1 (8 Me). Anal. Calcd for $C_{25}H_{40}N_2O_{13}$: C, 52.08; H, 6.99; N, 4.86. Found: C, 52.32; H, 6.83; N, 4.83. Compound **4**: Mp 226-228°; ^{13}C NMR (75 MHz, acetone-d_6) *Z* isomer: δ 145.0 (C-1), 112.1, 110.3, 110.2, 100.0 (4 C of acetals); 88.7 (C-3); 81.6 (C-2′); 78.1 (C-1′); 77.1 (C-3′); 76.8 (C-6); 76.1 (C-4); 73.5 (C-7); 73.4 (C-5); 70.0 (C-8); 67.4 (C-4′); 62.2 (C-13); 38.2 (C-2); 29.4, 28.7, 28.5, 28.3, 26.7, 26.6, 25.3, 19.1 (8 Me). Anal. Calcd for $C_{25}H_{40}N_2O_{12}$: C, 53.56; H, 7.19; N, 5.00. Found: C, 53.52; H, 7.35; N, 4.79.
12. Detailed NMR study of *E* and *Z* isomers of **4** will be the subject of another report.