Synthesis of 1,6-anhydro-3-bromo-3,4-dideoxy-β-D-*threo*-hex-3-enopyranose

M. S. Miftakhov, I. N. Gaisina, F. A. Valeev, and O. V. Shitikova*

Institute of Organic Chemistry, Ufa Research Center of the Russian Academy of Sciences, 71 prosp. Oktyabrya, 450054 Ufa, Russian Federation. Fax: +7 (347 2) 342 914

A preparative method for chemo- and stereoselective reduction of 3-bromolevoglucosenone into 1,6-anhydro-3-bromo-3,4-dideoxy-β-D-*threo*-hex-3-enopyranose using $Zn(BH_4)_2$ was developed.

Key words: 3-bromolevoglucosenone, zinc borohydride, reduction.

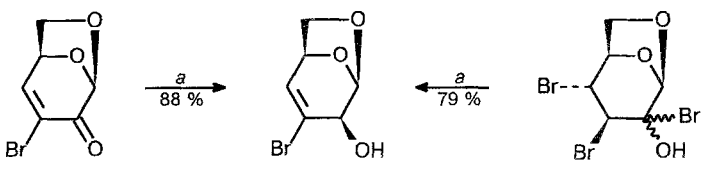
In this work, we report a synthesis of unsaturated *vic*-bromohydrine (**1**), a novel versatile chiral block functionalized by groups of different types. This allows one to perform, in addition to reactions involving O-containing centers, cross-coupling with participation of a Br atom, generation of the corresponding anionic and radical vinyl-type intermediates, *etc.* This opens new prospects in implementing "chiron approaches" to complex natural compounds.

To prepare the target compound, we intended to perform a one-step **2** → **1** transformation by regio- and stereoselective reduction of ketone **2**, a readily accessible product of levoglucosenone bromination[1] (Scheme 1). However, taking into account that structure **2** contains a strongly activated double bond with a highly reactive Br atom, we anticipated that the reduction would occur somewhat ambiguously. Therefore, we assumed that we would also have to use, as an alternative to **2**, its latent equivalent **3** (see Ref. 1). Considering the predicted stereoselectivity of the reduction of compound **2**, it should be noted that we expected preferential reduction into *threo*-alcohols to occur, in analogy with the known data for levoglucosenone,[2,3] with which the stereochemical result of the reaction is exclusively determined by steric control of the direction of attack of the reagent by the 1,6-anhydro bridge.

To perform the intended transformations of compounds **2** and **3** into alcohol **1**, we examined a series of reducing agents and found that $Zn(BH_4)_2$ (see Ref. 4) is the most appropriate, soft reagent, which allows exceedingly smooth and chemoselective transformation of the starting substrates into synthon **1** (see Scheme 1).

It should be noted that the above optimal transformations were preceded by experiments using readily available $LiAlH_4$ and $NaBH_4$; these preliminary experiments did not give results acceptable from the preparative viewpoint. For example, reduction of compound **2** with $LiAlH_4$ in ether at 0 °C afforded two *threo*-alcohols **1** and **4** easily separable on SiO_2. The reaction of the less nucleophilic $NaBH_4$ with **2** gave the target alcohol **1** (39 %) along with isomeric bromohydrins **5** (yield 50 %). Under similar conditions, the reaction involving tribromo-derivative **3** also gave an isomeric pair **4** and **6** as well as epimeric saturated alcohols **7** and **8**, also characterized as acetates **9**. The ease of blocking the hydroxyl group in compound **1** was demonstrated by its transformation into acetate **10**.

Scheme 1



2 **1** **3**

Reagents and conditons: *a*. $Zn(BH_4)_2$, Et_2O, 0 °C.

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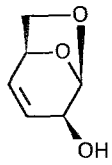
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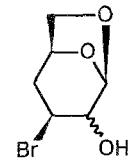
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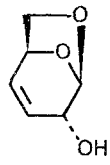
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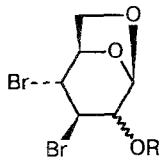
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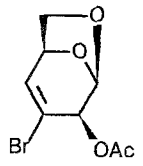
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R = H (**8**), Ac (**9**)

Experimental

IR spectra were obtained on a UR-20 spectrophotometer in thin layers or in Nujol. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AM-300 spectrometer with working frequencies of 300 and 75.47 MHz, respectively, using $SiMe_4$ as the internal standard and $CDCl_3$ as the solvent. TLC analyses were carried out on Silufol chromatographic plates. Chromatographic analyses were performed on a Chrom-5 chromatograph [column length 1.2 m, SE-30 stationary phase, helium as the carrier gas, working temperature 50—300 °C (12 °C min^{-1})]. Optical rotations were recorded on a Perkin-Elmer 141 polarimeter. Mass spectra were measured on an MKh-1306 instrument, ionizing voltage 70 eV, temperature in the ionization chamber 50—100 °C.

1,6-Anhydro-3-bromo-3,4-dideoxy-β-D-*threo*-hex-3-enopyranose (1). ***A.*** A solution of $Zn(BH_4)_2$ in ether [8 mL; obtained from $ZnCl_2$ (4.0 g) and $NaBH_4$ (2.7 g) in Et_2O (200 mL)] was added dropwise at 0 °C to a solution of bromide **2** (0.45 g, 2.2 mmol) in dry Et_2O (4 mL). After the reaction was complete (TLC), the reaction mixture was cautiously diluted with 3 % aqueous HCl (5 mL), extracted with ether, dried with Na_2SO_4, and concentrated. The residue was recrystallized from an ether—hexane mixture (3 : 1) to give bromohydrin **1** (0.40 g, 88 %). R_f 0.37 (ethyl acetate—pentane, 3 : 7), m.p. 72—74 °C (in a sealed capillary), $[\alpha]_D^{20}$ −69.3° (*c* 1.0, $CHCl_3$). IR, ν/cm^{-1}: 3430 (COH); 1645 (C=C). ^{1}H NMR ($CDCl_3$), δ: 2.46 (d, OH, J = 11.5 Hz); 3.77 (dd, 1 H, 6-H$_{exo}$, J = −6.8 and 4.5 Hz); 3.89 (d, 1 H, 6-H$_{endo}$, J = −6.8 Hz); 4.30 (dd, 1 H, 2-H, J = 2.8 and 11.5 Hz); 4.69 (dd, 1 H, 5-H, J = 4.5 and 4.9 Hz); 5.59 (d, 1 H, 1-H, J = 2.8 Hz); 6.50 (d, 1 H, 4-H, J = 4.9 Hz). ^{13}C NMR ($CDCl_3$), δ: 70.69 (C-6); 72.74 (C-2); 72.92 (C-5); 100.78 (C-1); 126.43 (C-3); 132.35 (C-4). MS (EI), *m/z* (I_{rel}(%)): 206 $[M]^+$ (2), 188 $[M-H_2O]^+$ (77), 175 $[M-CH_2OH]^+$ (79), 160 $[M-CHO-OH]^+$ (65), 132 $[M-CHO-OH-CO]^+$ (18), 81 $[M-CHO-OH-Br]^+$ (13), 53 $[M-CHO-OH-Br-CO]^+$ (100).

B. Treatment of tribromide **3** with a $Zn(BH_4)_2$ solution (2 mL) by the above procedure gave 0.06 g (79 %) of compound **1**.

1,6-Anhydro-3-bromo-3,4-dideoxy-β-D-*glycero*-hex-3-enopyranose (2) was obtained by the known procedure[1]: m.p. 49 °C (from a Et_2O—hexane mixture, 3 : 7), $[\alpha]_D^{18}$ −496.1° (*c* 1.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$), δ: 3.82 (d, 1 H, 6-H$_{endo}$, J = −7.1 Hz); 3.90 (dd, 1 H, 6-H$_{exo}$, J = −7.1 and 4.6 Hz); 5.09 (dd, 1 H, 5-H, J = 4.6 and 5.0 Hz); 5.55 (s, 1 H, 1-H); 7.69 (d, 1 H, 4-H, J = 5.0 Hz). ^{13}C NMR ($CDCl_3$), δ: 66.52 (C-6); 73.49 (C-5); 100.81 (C-1); 122.25 (C-3); 147.94 (C-4); 182.36 (C-2).

1,6-Anhydro-2,3,4-tribromo-3,4-dideoxy-β-D-*manno(gluco)*-pyranose (3): m.p. 103—105 °C (from Me_2CO). ^{13}C NMR (DMSO-d_6), δ of the main *manno*-isomer **3**: 53.14 (C-4); 61.36 (C-3); 64.29 (C-6); 76.11 (C-5); 93.15 (C-2); 102.87 (C-1).

Reduction of 3-bromolevoglucosenone. ***A.*** $LiAlH_4$ (0.09 g, 2.4 mmol) was added in portions to a cooled solution (0 °C) of ketone **2** (0.50 g, 2.4 mmol) in Et_2O (5 mL). The mixture was stirred for 15 min with TLC monitoring. When compound **2** was consumed, the reaction was terminated by adding 3 % aqueous HCl (5 mL), the Et_2O was distilled off, and the mixture was extracted with CH_2Cl_2 (3 × 50 mL). The combined extracts were dried with Na_2SO_4 and concentrated. The residue was chromatographed on SiO_2 using ethyl acetate—pentane (3 : 7) as the eluent to give 0.3 g of a mixture of alcohols **1** and **4** in a 5 : 1 ratio. Alcohols **1** and **4** were isolated in pure state by repeated chromatography of the mixture on a column with SiO_2.

B. A mixture of $NaBH_4$ (0.08 g, 2.2 mmol) and compound **2** (0.30 g, 1.4 mmol) in MeOH (4 mL) was added to MeOH (6 mL) precooled to 0 °C. The mixture was stirred for 20 min and diluted with H_2O (10 mL). The MeOH was distilled off, and the residue was extracted with CH_2Cl_2 (3 × 25 mL). The combined extracts were dried with Na_2SO_4 and concentrated. Chromatography gave 0.21 g of alcohols **1** and **5** in a 4 : 5 ratio.

1,6-Anhydro-3,4-dideoxy-β-D-*threo*-hex-3-enopyranose (4): R_f 0.19 (ethyl acetate—hexane, 3 : 7), m.p. 68—69 °C, $[\alpha]_D^{13}$ −30.8° (*c* 1.0, $CHCl_3$) [*cf.* Ref. 2: m.p. 67—69 °C, $[\alpha]_D^{20}$ −34° (*c* 1.0, $CHCl_3$); *cf.* Ref. 3: m.p. 70—70.5 °C, $[\alpha]_D^{20}$ −30° (*c* 1.0, $CHCl_3$)]. ^{1}H NMR ($CDCl_3$), δ: 2.60 (br.s, OH); 3.72 (dd, 1 H, 6-H$_{exo}$, J = −6.6 and 4.2 Hz); 3.80 (d, 1 H, 6-H$_{endo}$, J = −6.6 Hz); 4.30 (br.s, 1 H, 2-H); 4.62 (t, 1 H, 5-H, J = 4.2 Hz); 5.48 (dd, 1 H, 1-H, J = 2.0 and 2.5 Hz); 5.67 (ddd, 1 H, 3-H, J = 2.0, 2.3 and 9.8 Hz); 6.08 (dd, 1 H, 4-H, J = 9.8 and 4.2 Hz). The ^{1}H NMR spectrum obtained agrees with that reported in the literature.[5] ^{13}C NMR ($CDCl_3$), δ: 68.69 (C-2); 70.65 (C-6); 71.12 (C-5); 101.21 (C-1); 129.04 (C-3); 130.64 (C-4).

1,6-Anhydro-3-bromo-3,4-dideoxy-β-D-*lyxo(xylo)*-hexopyranose (5): R_f 0.35 (ethyl acetate—hexane, 3 : 7). *xylo*-Isomer of **5**: ^{1}H NMR ($CDCl_3$), δ: 2.10 (m, 1 H, 4-H); 2.45 (m, 1 H, 4-H); 2.40 (br.s, OH); 3.70—3.90 (m, 3 H, 6-H$_{endo}$, 6-H$_{exo}$, 2-H); 4.05 (ddd, 1 H, 3-H, J = 11.5, 8.9 and 7.1 Hz); 4.3 (dd, 1 H, 5-H, J = 11.5 and 3.0 Hz); 5.52 (d, 1 H, 1-H, J = 2.7 Hz). ^{13}C NMR ($CDCl_3$), δ: 36.20 (C-4); 46.97 (C-3); 66.61 (C-6); 69.56 (C-2); 73.42 (C-5); 101.32 (C-1). *lyxo*-Isomer of **5**: ^{1}H NMR ($CDCl_3$), δ: 2.30—2.40 (m, 2 H, 4-H); 2.40 (br.s, OH); 3.70—3.90 (m, 3 H, 6-H$_{endo}$, 6-H$_{exo}$, 2-H); 4.46 (ddd, 1 H, 3-H, J = 12.5, 6.1, and 3.7 Hz); 4.55 (m, 1 H, 5-H); 5.40 (br.s, 1 H, 1-H, J = 3.7 Hz). ^{13}C NMR ($CDCl_3$), δ: 39.80 (C-4); 48.82 (C-3); 67.82 (C-6); 73.62 (C-5); 76.09 (C-2); 102.12 (C-1).

C. Reduction of compound **3** (0.53 g) with $LiAlH_4$ (0.09 g) in 5 mL of Et_2O by a procedure similar to that for **2** gave 0.31 g of a mixture containing epimers of compounds **4** and **6** in a 1 : 1 ratio, saturated alcohols **7** (*threo* : *erythro* = 2 : 1),

and a mixture of *manno*- and *gluco*-isomers of dibromides **8** in a 10 : 3 ratio.

1,6-Anhydro-3,4-dideoxy-β-D-*erythro*-hex-3-enopyranose (6): R_f 0.11 (ethyl acetate—pentane, 3 : 7), m.p. 52.5—53 °C, $[\alpha]_D^{23}$ −229° [*cf.* Ref. 3: m.p. 53—54 °C, $[\alpha]_D^{20}$ −236° (*c* 1.0, $CHCl_3$)]. ^1H NMR ($CDCl_3$), δ: 2.59 (br.s, OH); 3.58—3.67 (m, 2 H, 6-H_{exo}, 6-H_{endo}); 4.66 (dd, 1 H, 5-H, J = 1.0 and 3.8 Hz); 5.48 (br.s, 1 H, 1-H); 5.78 (ddd, 1 H, 3-H, J = 2.1, 4.1, and 9.8 Hz); 6.14 (dd, 1 H, 4-H, J = 4.3 and 9.8 Hz). The ^1H NMR spectrum agrees with that reported previously.[5] ^{13}C NMR ($CDCl_3$), δ: 55.77 (C-2); 68.89 (C-6); 70.51 (C-5); 102.60 (C-1); 126.43 (C-3); 130.64 (C-4).

1,6-Anhydro-3,4-dideoxy-β-D-*threo*(*erythro*)-hexopyranose (7): R_f 0.19 (ethyl acetate—hexane, 3 : 7). ^1H NMR ($CDCl_3$), δ: 1.40—1.60 (m, 2 H, 3-H_2C); 1.78—2.04 (m, 2 H, 4-H_2C); 2.40 (br.s, OH); 3.55—3.60 (m, 1 H, 5-H); 3.75—3.90 (m, 2 H, 6-H_2C); 4.43 (br.s, 1 H, 2-H); 5.27 (br.s, 1 H, 1-H). *threo*-Isomer of **7**: ^{13}C NMR ($CDCl_3$), δ: 25.92 (C-3); 27.79 (C-4); 68.13 (C-6); 68.95 (C-2); 72.77 (C-5); 102.92 (C-1). *erythro*-Isomer of **7**: ^{13}C NMR ($CDCl_3$), δ: 23.23 (C-3); 24.76 (C-4); 66.72 (C-2); 66.79 (C-6); 73.26 (C-5); 102.06 (C-1).

1,6-Anhydro-3,4-dibromo-3,4-dideoxy-β-D-*manno*(*gluco*)-hexopyranose (8): R_f 0.25 (ethyl acetate—hexane, 3 : 7). *gluco*-Isomer of **8**: ^1H NMR ($CDCl_3$), δ: 3.20 (br.s, OH); 3.65 (dd, 1 H, 6-H, J = −8.2 and 3.5 Hz); 3.80 (dd, 1 H, 2-H, J = 3.9 and 2.1 Hz); 4.17 (d, 1 H, 6-H, J = −8.2 Hz); 4.31 (dd, 1 H, 4-H, J = 11.1 and 3.3 Hz); 4.36 (dd, 1 H, 3-H, J = 11.1 and 3.9 Hz); 4.65 (dd, 1 H, 5-H, J = 3.5 and 3.3 Hz); 5.45 (d, 1 H, 1-H, J = 2.1 Hz). ^{13}C NMR ($CDCl_3$), δ: 51.13 (C-3); 55.19 (C-4); 64.39 (C-6); 71.98 (C-2); 76.63 (C-5); 101.18 (C-1). *manno*-Isomer of **8**: ^{13}C NMR ($CDCl_3$), δ: 51.36 (C-3); 56.27 (C-4); 65.64 (C-6); 76.63 (C-5); 77.00 (C-2); 101.79 (C-1).

1,6-Anhydro-2-*O*-acetyl-3,4-dibromo-3,4-dideoxy-β-D-*manno*(*gluco*)-hexopyranose (9) was obtained in 81 % yield by acylation of compound **8** in an Ac_2O—Py mixture (1 : 2) at 0 °C. R_f 0.60 (ethyl acetate—hexane, 3 : 7). *manno*-Isomer of **9**: ^1H NMR ($CDCl_3$), δ: 2.14 (s, 3 H, CH_3); 3.80 (dd, 1 H, 6-H_{exo}, J = −8.3 and 4.9 Hz); 4.11 (dd, 1 H, 3-H, J = 9.2 and 10.2 Hz); 4.30 (d, 1 H, 6-H_{endo}, J = −8.3 Hz); 4.38 (dd, 1 H, 4-H, J = 2.5 and 10.2 Hz); 4.75 (dd, 1 H, 5-H, J = 2.5 and 4.9 Hz); 5.00 (dd, 1 H, 2-H, J = 1.3 and 9.2 Hz); 5.49 (d, 1 H, 1-H, J = 1.3 Hz). ^{13}C NMR ($CDCl_3$), δ: 20.71 (CH_3); 49.31 (C-3); 51.22 (C-4); 65.69 (C-6); 76.09 (C-2); 76.78 (C-5); 99.74 (C-1); 169.66 (CO). *gluco*-Isomer of **9**: ^1H NMR ($CDCl_3$), δ: 2.19 (s, 3 H, CH_3); 3.85 (dd, 1 H, 6-H_{exo}, J = −8.3 and 4.4 Hz); 4.25 (m, 1 H, 3-H); 4.30 (d, 1 H, 6-H_{endo}, J = −8.3 Hz); 4.38 (m, 1 H, 4-H); 4.68 (dd, 1 H, 5-H, J = 2.5 and 4.4 Hz); 5.08 (d, 1 H, 2-H, J = 2.2 Hz); 5.51 (d, 1 H, 1-H, J = 2.2 Hz). ^{13}C NMR ($CDCl_3$), δ: 20.71 (CH_3); 50.21 (C-3); 51.22 (C-4); 64.52 (C-6); 71.56 (C-2); 76.94 (C-5); 99.45 (C-1); 169.66 (CO).

1,6-Anhydro-2-*O*-acetyl-3-bromo-3,4-dideoxy-β-D-*threo*-hex-3-enopyranose (10) was obtained in 75 % yield by acylation of compound **1** in an Ac_2O—Py mixture (1 : 2) at 0 °C. $[\alpha]_D^{20}$ −67.2 (*c* 1.0, $CHCl_3$). ^1H NMR ($CDCl_3$), δ: 2.15 (s, 3 H, CH_3); 3.52 (ddd, 1 H, 6-H, J = −6.8, 4.2, and 0.9 Hz); 3.95 (d, 1 H, 6-H, J = −6.8 Hz); 4.63 (dd, 1 H, 5-H, J = 4.8 and 4.2 Hz); 5.55 (dd, 1 H, 2-H, J = 2.6 and 1.1 Hz); 5.60 (d, 1 H, 1-H, J = 2.6 Hz); 6.53 (ddd, 1 H, 4-H, J = 4.8, 1.1, and 0.9 Hz). ^{13}C NMR ($CDCl_3$), δ: 20.62 (CH_3); 70.93 (C-6); 72.51 (C-2); 73.40 (C-5); 98.56 (C-1); 120.35 (C-3); 134.17 (C-4), 170.09 (CO).

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