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Levoglucosenone-derived precursors for the stereoselective synthesis of methylene-expanded analogues of C-nucleosides

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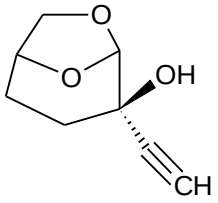
Experimental

NMR spectra were collected on a Bruker DR-500 instrument [working frequencies of 500.13 MHz (^{1}H) and 125.76 MHz (^{13}C)]. Mass spectra were obtained on a Finnigan MAT/INCOS 50 instrument (70 eV) using direct probe injection. Elemental analysis was accomplished with the automated Perkin-Elmer 2400 CHN microanalyzer. Levoglucosenone (200g, purity 95%) 1,6-anhydro-3,4-dideoxy-b-D-*glycero*-hex-3-enopyranos-2-ulose was purchased from Chemical Block Ltd **(**www.chemblock.com**).**

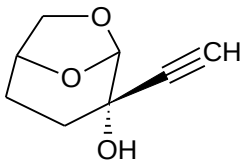
1,6-Anhydro-3,4-dideoxy-2-*C*-ethynyl-β-D-*threo*-hexopyranose (1a).



(1.95 g, 63 %) as a white solid. Mp 78–80 °C; R_f = 0.59 ($CHCl_3$/CH_3OH, 10:1.5); $[\alpha]_D^{18}$ -32.3 (c 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.25 (s, 1H, HC(O-)$_2$), 4.57 (br.s, 1H, HCO), 3.91, 3.84 (AB, *J* 7.3, *J* 4.8, 2H, CH_2O), 2.57 (s, 1H, HC≡), 2.33 (s, 1H, OH), 2.20-2.04 (m, 2H, CH_2), 1.96-1.81 (m, 1H, C*H*H), 1.68-1.57 (m, 1H, CH*H*); ^{13}C NMR (125.76 MHz, $CDCl_3$) δ 103.3 (CH),

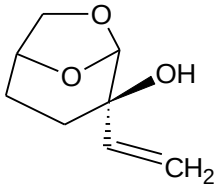
83.18 (C≡), 73.89 (CH), 72.93 (C), 68.53 (C≡), 68.14 (CH_2), 31.84 (CH_2), 27.10 (CH_2). EIMS *m/z* 108 (7), 107 (10), 79 (37), 68 (50), 57 (12), 55 (24), 53 (76), 51 (23), 43 (36), 41 (60), 39 (100). Anal. Calcd for $C_8H_{10}O_3$ (154.163) (%): C, 62.33; H, 6.54. Found (%): C, 62.25; H, 6.67.

1,6-Anhydro-3,4-dideoxy-2-*C*-ethynyl-β-D-*erythro*-hexopyranose (1b).



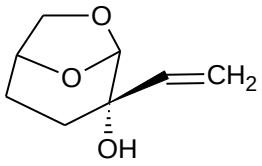
(0.15 g, 4.8 %) as a white solid. Mp 68–70 °C; R_f 0.64 ($CHCl_3$/CH_3OH, 10:1.5); $[\alpha]_D^{18}$ -126.2 (c 1.0,$CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.27 (s, 1H, $HC(O\text{-})_2$, 4.57 (br.d, *J* 2.0, 1H, HCO), 3.98, 3.85 (AB, *J* 7.4, *J* 5.0, 2H, CH_2O), 2.61 (s, 1H, OH), 2.52 (s, 1H, HC≡), 2.19-2.13 (m, 1H, C*H*H), 2.10-2.03 (m, 1H, CH*H*), 1.96-1.91 (m, 1H, C*H*H), 1.53-1.49 (m, 1H, CH*H*); ^{13}C NMR (125.76 MHz, $CDCl_3$) δ 103.11 (CH), 83.98 (C≡), 73.09 (C), 72.88 (CH), 67.45 (C≡), 67.32 (CH_2), 29.76 (CH_2), 24.77 (CH_2). EIMS *m/z* 154 $[M]^+$ (0.2), 125 (2), 108 (27), 107 (39), 79 (83), 68 (97), 57 (26), 55 (51), 53 (95), 51 (35), 43 (55), 41 (97), 39(100). Anal. Calcd for $C_8H_{10}O_3$ (154.163) (%): C, 62.33; H, 6.54. Found (%): C, 62.25; H, 6.67.

1,**6-Anhydro-3,4-dideoxy-2-*C*-ethenyl-β-D-*threo*-hexopyranose (2a).**



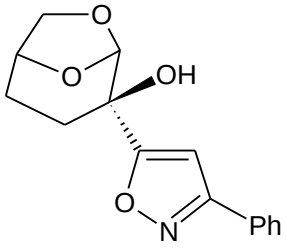
(1.3 g, 42 %) as a white solid. Mp 61–64 °C; R_f = 0.47 ($CHCl_3$/CH_3OH, 10:1.5); $[\alpha]_D^{25}$ -52.3 (c 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.11 (dd, *J* 17.4, *J* 11.0, 1H, -CH=), 5.45 (dd, *J* 17.4, *J* 1.6, 1H, =C*H*H), 5.22 (dd, *J* 11.0, *J* 1.6, 1H, =CH*H*), 5.0 (s, 1H, $HC(O\text{-})_2$, 4.56 (br.s, 1H, HCO), 3.91, 3.83 (AB, *J* 7.1, *J* 5.0, 2H, CH_2O), 2.23 (s, 1H, OH), 2.0-1.93 (m, 1H, C*H*H), 1.90-1.85 (m, 1H,CH*H*), 1.80-1.74 (m, 1H, C*H*H), 1.61-1.57 (m, 1H, CH*H*); ^{13}C NMR (125.76 MHz, $CDCl_3$) δ 137.79 (C=), 114.79 (C=), 105.10 (CH), 73.08 (CH), 72.43 (C), 67.85 (CH_2), 31.10 (CH_2), 26.99 (CH_2). EIMS *m/z* 110 (7), 107 (1), 95 (8), 79 (6), 70 (49), 68 (7), 57 (11), 55 (100), 53 (17), 51 (8), 43 (38), 41 (46), 39 (50). Anal. Calcd for $C_8H_{12}O_3$ (156.179) (%): C, 61.52; H, 7.74. Found (%): C, 61.60; H, 7.68.

1,6-Anhydro-3,4-dideoxy-2-*C*-ethenyl-β-D-*erythro*-hexopyranose (2b).



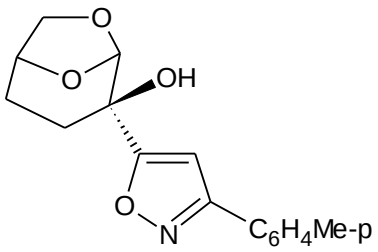
(0.12 g, 3.8 %) as a white solid. Mp 58−62 ^{0}C; R_f = 0.54 ($CHCl_3$/CH_3OH, 10:1.5); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.85 (dd, *J* 17.4, *J* 10.6, 1H, -CH=), 5.38 (dd, *J* 17.4, *J* 1.6, 1H, =C*H*H), 5.15 (dd, *J* 10.6, *J* 1.6, 1H, =CH*H*), 4.95 (s, 1H, HC(O-)$_2$, 4.50 (br.s, 1H, HCO), 3.89, 3.78 (AB, *J* 7.2, *J* 5.3, 2H, CH_2O), 2.75 (s, 1H, OH), 2.13-1.81 (m, 2H, CH_2), 1.55-1.43 (m, 2H, CH_2). ^{13}C NMR (125.76 MHz, $CDCl_3$) δ 152.41 (C=), 121.10 (C=), 118.20 (CH), 82.97 (CH), 81.45 (C), 74.80 (CH_2), 33.02 (CH_2), 32.94 (CH_2). EIMS *m/z* 156 $[M]^+$ (0.3), 110 (28), 107 (10), 95 (11), 79 (17), 70 (73), 68 (12), 57 (21), 55 (100), 53 (27), 51 (14), 43 (49), 41 (86), 39 (61). Anal. Calcd for $C_8H_{12}O_3$ (156.179) (%): C, 61.52; H, 7.74. Found (%): C, 61.68; H, 7.60.

1,6-Anhydro-3,4-dideoxy-2-*C*-(3-phenylisoxazol-5-yl)-β-D-*threo*-hexopyranose (3)



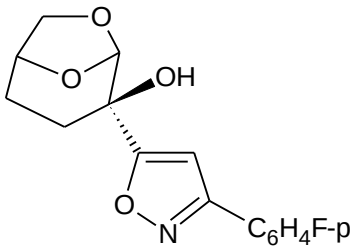
Yield 0.37 g, (67%) as a white solid. Mp 166–169 °C; R_f 0.4 ($CHCl_3$/CH_3OH, 10:1.5); $[\alpha]_D^{19}$ +4.2 (c 1, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.84-7.91 (m, 2H, Ph), 7.47-7.44 (m, 3H, Ph), 6.66 (s, 1H, =CH), 5.44 (s, 1H, HC(O-)$_2$), 4.64 (br.s, 1H, HCO), 4.00, 3.92 (AB, *J* 7.2, *J* 5.6, 2H, CH_2O), 2.55 (s, 1H, OH), 2.47-2.41 (m, 1H,C*H*H), 2.25-2. 31 (m, 1H,CH*H*), 2.01-1.96 (m, 1H, C*H*H), 1.75-1.65 (m, 1H, CH*H*); ^{13}C NMR (125.76 MHz, $CDCl_3$) δ 172.42, 162.21, 129.98, 128.88, 128.86, 126.82, 103.19, 100.32, 73.12, 70.86, 68.27, 29.75, 27.04. EIMS *m/z* 273 $[M]^+$ (6), 227 (11), 187 (32), 159 (10), 145 (15), 144 (100), 117 (24), 116 (18), 104 (12), 103 (7), 96 (9), 89 (14), 77 (75), 68 (9), 63 (14), 57 (24), 55 (31), 53 (14), 51 (49), 43 (41), 41 37), 39 (49). Anal. Calcd for $C_{15}H_{15}NO_4$ (273.283) (%): C, 65.92; H, 5.53; N, 5.13. Found (%): C, 65.80; H, 5.42; N, 5.21.

1,6-Anhydro-3,4-dideoxy-2-*C*-[3-(4-methylphenyl)isoxazol-5-yl]-β-D-*threo*-hexopyranose (4).



Following the typical procedure for **3**, with **1a** (0.31 g, 0.002 mol), Et_3N (0.6 g, 0.006 mol) and 4-$CH_3C_6H_4CCl$=NOH (0.51 g, 0.003 mol) followed by column chromatography gave **4** (0.4 g, 70%) as white solid, mp 158–162 °C; R_f = 0.35 ($CHCl_3$/CH_3OH, 10:1.5); $[\alpha]_D^{19}$ +3.0 (c 1, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.72-7.68 (m, 2H, Ar), 7.28-7.24 (m, 2H, Ar), 6.63 (s, 1H, =CH), 5.44 (s, 1H, HC(O-)$_2$), 4.63 (br.s, 1H, HCO), 4.00, 3.92 (AB, *J* 7.2, *J* 5.6, 2H, CH_2O), 2.6 (s, 1H, OH), 2.47-2.41 (m, 1H, C*H*H), 2.4 (s, 3H, CH_3), 2.25-2. 31 (m, 1H, CH*H*), 2.01-1.96 (m, 1H, C*H*H), 1.75-1.65 (m, 1H, CH*H*); ^{13}C NMR (125.76 MHz, $CDCl_3$) δ 172.18, 162.15, 140.10, 129.55, 126.70, 126.03, 103.20, 100.23, 73.11, 70.85, 68.25, 29.75, 27.05, 21.38. EIMS *m/z* 287 $[M]^+$ (22), 241 (20), 202 (17), 201 (90), 186 (22), 173 (16), 158 (100), 131 (78), 130 (76), 124 (26), 118 (70), 117 (23), 116 (21), 103 (20), 96 (17), 91 (99), 89 (32), 83 (16), 77 (39), 68 (21), 65 (83), 63 (37), 57 (46), 55 (78), 53 (33), 51 (39), 43 (77), 41 (76), 39 (83). Anal. Calcd for $C_{16}H_{17}NO_4$ (287.310) (%): C, 66.89; H, 5.96; N, 4.88. Found (%): C, 66.79; H, 5.88; N, 4.85.

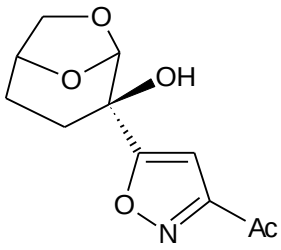
1,6-Anhydro-3,4-dideoxy-2-*C*-[3-(4-fluorophenyl)isoxazol-5-yl]-β-D-*threo*-hexopyranose (5).



Following the typical procedure for **3**, with **1a** (0.31 g, 0.002 mol), Et_3N (0.6 g, 0.006 mol) and 4-FC_6H_4CCl=NOH (0.52 g, 0.003 mol) followed by column chromatography gave **5** (0.44 g, 75 %) as white solid, mp 117–119 °C; R_f = 0.45 ($CHCl_3$/CH_3OH 10:1.5); $[\alpha]_D^{19}$ +3.4 (c 1, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.83-7.76 (m, 2H, Ar), 7.19-7.10 (m, 2H, Ar), 6.63 (s, 1H, =CH), 5.43 (s, 1H, HC(O-)$_2$), 4.64 (br.s, 1H, HCO), 4.00, 3.91 (AB, *J* 7.2, *J* 5.0, 2H, CH_2O), 2.65 (s, 1H, OH), 2.48-2.37 (m, 1H, C*H*H), 2.29-2.12 (m, 1H, CH*H*), 2.05-1.90 (m, 1H, C*H*H), 1.74-1.66 (m, 1H, CH*H*);

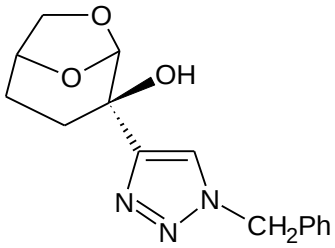
^{13}C NMR (125.76 MHz, $CDCl_3$) δ 172.62, 163.78 (d, *J* 242.7), 161.29, 128.75 (d, *J* 8.8), 125.11 (d, *J* 3.5), 116.0 (*J* 21.4), 103.16, 100.19, 73.11, 70.87, 68.27, 29.76, 27.03. EIMS *m/z* 291 $[M]^+$ (7), 245 (9), 205 (35), 163 (15), 162 (100), 135 (32), 134 (42), 122 (16), 121 (12), 108 (8), 107 (22), 95 (49), 75 (35), 68 (16), 63 (6), 57 (43), 55 (48), 53 (17), 51 (11), 43 (61), 41 51), 39 (53). Anal. Calcd for $C_{15}H_{14}FNO_4$ (291.2734) (%): C, 61.85; H, 4.84; N, 4.81. Found (%): C, 61.86; H, 5.84; N, 4.88.

1,6-Anhydro-3,4-dideoxy-2-*C*-(3-acetylisoxazol-5-yl)-β-D-*threo*-hexopyranose (6).



A mixture of 1,6-Anhydro-3,4-dideoxy-2-*C*-ethynyl-β-D-*threo*-hexopyranose (0.3 g, 0.002 mol) and ammonium cerium(IV) nitrate[13] (0.558 g, 0.002 mol) in acetone (8 ml) was stirred under reflux for 5 h. The reaction mixture was extracted with ether (3×10 ml) and washed with aq. $NaHCO_3$ solution (2×5 ml), saturated aq. NaCl (2×5 ml). The ethereal solution was dried over Na_2SO_4 and concentrated in a vacuum. The resulting oil (0.39 g) was purified by flash chromatography ($CHCl_3$/CH_3OH). Yield **(6)** (0.24 g, 54 %) as a white solid. Mp 82−85 °C; R_f = 0.34 ($CHCl_3$/CH_3OH, 10:1.5); $[\alpha]_D^{19}$ -9.2 (c 1.6, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.73 (s, 1H, =CH), 5.39 (s, 1H, HC(O-)$_2$), 4.62 (br.s, 1H, HCO), 3.98, 3.91 (AB, *J* 7.2, *J* 5.2, 2H, CH_2O), 2.70 (s, 1H, OH), 2.66 (s, 3H, CH_3), 2.40-2.36 (m, 1H, C*H*H), 2.16-2. 2.09 (m, 1H, CH*H*), 2.02-1.95 (m, 1H, C*H*H), 1.76-1.67 (m, 1H, CH*H*); ^{13}C NMR (125.76 MHz, $CDCl_3$) δ 191.99, 173.69, 161.73, 102.66, 100.83, 73.07, 70.73, 68.32, 29.80, 27.30, 26.95. HRMS (ESI) calcd for $C_{11}H_{13}NO_5$ + H = 240.0866, found 240.0861. Anal. Calcd for $C_{11}H_{13}NO_5$ (239.2241) (%): C, 55.23; H, 5.48; N, 5.85. Found (%): C, 55.30; H, 5.58; N, 5.93.

1,6-Anhydro-3,4-dideoxy-2-*C*-(1-benzyl-1,2,3-triazol-4-yl)-β-D-*threo*-hexopyranose (7).



A mixture of **1a** (0.162 g, 0.00105 mol), benzyl azide (0.133 g, 0.001 mol), and $Cu(OAc)_2 \cdot H_2O$ (36 mg, 0.2 mmol) in water (5 ml) was vigorously stirred for 1 h and extracted with EtOAc (2×5 ml).

The solvent was removed in vacuo and the residue was crysrallized from benzene to yield **7** (241 mg, 84%) as a white solid. Mp 112–113 °C.

^{1}H NMR (500 MHz, DMSO-d_6) δ 8.10 (s, 1H, H-2'); 7.36 (m, 5H, Ph); 5.56 (s, 2H, CH2); 5.28 (s, 1H, H-1); 5.18 (s, 1H, H-6); 4.44 (br.s, 1H, OH); 3.89 (d, J = 7.06 Hz, 1H, H-6); 3.66 (t, J = 6.01 Hz, 1H, H-5); 2,25 (m, 1H, H-3); 1.87 (m, 2H, H-4); 1.54 (m, 1H, H-3); HRMS (ESI) calcd for $C_{15}H_{17}N_3O_3$ + H = 288.1343, found 288.1339. Anal. Calcd for $C_{15}H_{17}N_3O_3$ (287.32) (%): C, 62.71; H, 5.96; N, 14.62. Found (%): C, 62.81; H, 5.90; N, 14.51.