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SYNTHESIS OF LABELLED 2-DEOXYALDOSES. HYDROXYL GROUP PARTICIPATION IN THE REDUCTION OF INTERMEDIATE KETENE DITHIOACETALS BY LITHIUM ALUMINUM HYDRIDE[1]

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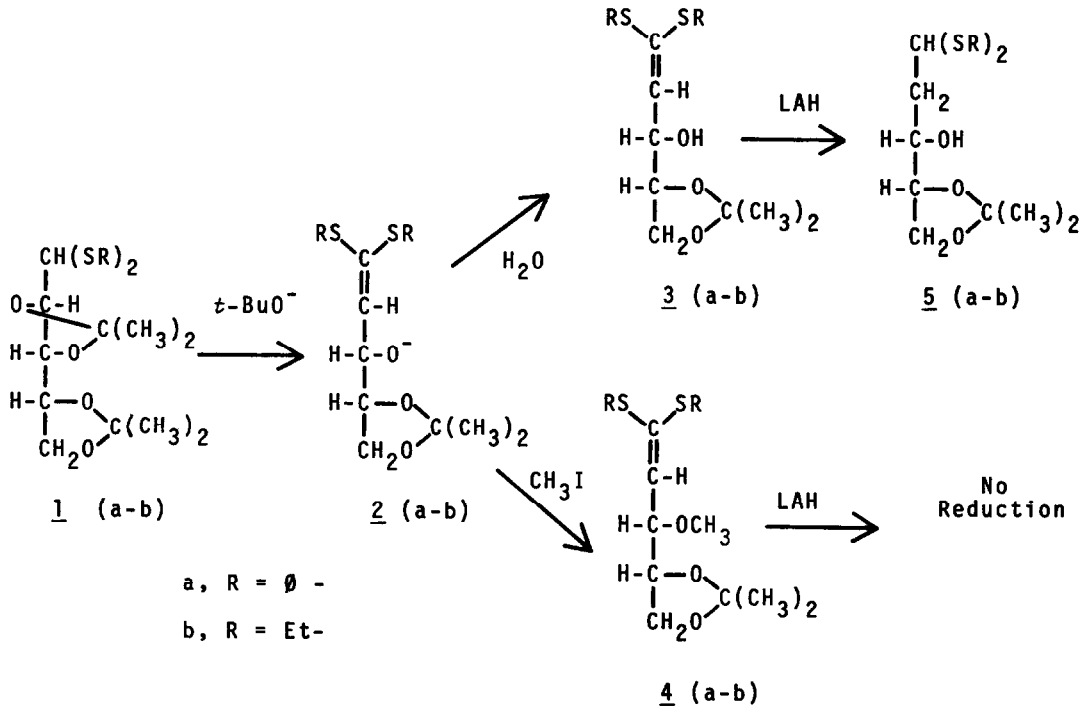
Treatment of 2,3:4,5-di-O-isopropylidene-D-arabinose diphenyl dithioacetal (1a) with sodium methylsulfinyl carbanion in DMSO has previously been shown[2] to produce 2a *via* extraction of the acidic C-1 hydrogen and concomitant elimination of acetone. Workup of the reaction with water gave 2-deoxy-4,5-O-isopropylidene-



D-*erythro*-pent-1-enose diphenyl dithioacetal (3a) in 44% yield, but the addition of methyl iodide produced the corresponding O-methyl ether (4a). Attempts to reduce the ketene dithioacetal derivative 4a with Raney nickel failed.[3] The ketene dithioacetals 3a and 4a were also found to be unstable in acid,[4] and therefore the known reduction method involving a protonation-hydride transfer sequence with trifluoroacetic acid-triethylsilane[5] is also not applicable.

We now report that 2-deoxy-4,5-O-isopropylidene-D-*erythro*-pent-1-enose diethyl dithioacetal (3b) is reduced in good yield to 2-deoxy-4,5-O-isopropylidene-D-*erythro*-pentose diethyl dithioacetal (5b) on treatment with lithium aluminum hydride in tetrahydrofuran. Under the same conditions, the corresponding O-methyl derivative (4b) is not reduced, demonstrating that the reduction of 3b is facilitated by the free hydroxyl group at C-3. Because of the ease with which free sugars can be converted to their fully protected acyclic dithioacetal derivatives, this elimination-reduction sequence provides an excellent general synthetic route to the 2-deoxyaldoses and their isotopically labeled derivatives.

Treatment of 1b[6,7,8] with 1.5 eq of *t*-BuOK in DMSO:THF (1:3 v/v) for 1.5 h at room temperature, followed by aqueous workup and chromatography on silica gel, gave 3b (80%, oil); pmr (C_6D_6, TMS internal); δ1.10, t, J = 6Hz, 6H [$C\underline{H}_3CH_2S$-]; 1.29, 1.44, two s, 6H [$-C(C\underline{H}_3)_2$]; 2.40-2.92, complex, 5H [-CO$\underline{H}$, $CH_3C\underline{H}_2S$-]; 3.76-4.22, complex, 3H [H-4, H-5]; 4.97, d of d, J = 4Hz and 8Hz, 1H [H-3]; 6.08, d, J = 8Hz [H-2]; cmr ($CDCl_3$, TMS external); δ13.56, 14.67 [$\underline{C}H_3CH_2S$-]; 24.88, 26.00, 26.65, 27.13 [$CH_3\underline{C}H_2S$-, $-C(\underline{C}H_3)_2$]; 64.94 [C-5]; 69.24 [C-4]; 77.71 [C-3]; 108.98; [$-\underline{C}(CH_3)_2$]; 133.18 [C-2]; 134.90 [C-1]. M^+, m/e 278.1016 ($C_{12}H_{22}O_3S_2$ requires 278.1010).[9]

Treatment of 1b with 1.5 eq of *t*-BuOK in DMSO:THF (1:3, v/v) for 1.5 h at room temperature gave the alkoxide (2b) which was alkylated by the addition of 5 eq methyl iodide (2 h at room temperature). Aqueous workup of the reaction mixture and chromatography on silica gel gave 4b (80%, oil); pmr ($CDCl_3$, TMS internal); δ1.23, 1.26, two t, J = 8Hz, 6H [$C\underline{H}_3CH_2S$-]; 1.31, 1.38, two s, 6H [$-C(C\underline{H}_3)_2$]; 2.60-2.88, complex, 4H [$CH_3C\underline{H}_2S$-]; 3.26, s, 3H [$-OC\underline{H}_3$]; 3.62-4.18, complex, 3H [H-4,5]; 4.26-4.48, multiplet, 1H [H-3]; 5.58, d, J = 8Hz [H-2]; cmr ($CDCl_3$, TMS internal); δ14.13, 15.24 [$\underline{C}H_3CH_2S$-]; 25.36, 26.47, 26.98, 27.50 [$CH_3\underline{C}H_2S$-, $(\underline{C}H_3)_2C$-]; 56.66 [$\underline{C}H_3O$-]; 66.76 [C-5]; 77.66, 79.28 [C-3,4]; 109.69 [$(CH_3)_2\underline{C}$-]; 133.50 [C-2]; 137.39 [C-1].[9]

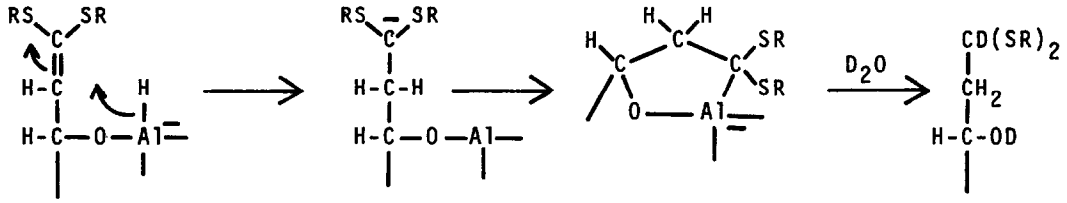
Reduction of 3b was accomplished by the dropwise addition of a solution in THF to a stirred slurry of lithium aluminum hydride (4 eq) in THF. After 3.5 h at room temperature, excess LAH was destroyed and the reaction mixture was worked up in the usual way[10] to give 5b, pure by thin layer chromatography and nmr analysis (80%, oil); pmr ($CDCl_3$, TMS internal); δ1.27, t, J = 8Hz, 6H [$C\underline{H}_3CH_2S$-]; 1.35, 1.41, two s, 6H [$-C(C\underline{H}_3)_2$]; 1.81-2.05, complex, 2H [H-2];

2.45-2.81, complex, 5H [-CO$\underline{H}$], $CH_3\underline{C}H_2S$-]; 3.81-4.15; complex, 5H [H-1,3,4,5]; cmr ($CDCl_3$, TMS internal); δ14.51 [$\underline{C}H_3CH_2S$-]; 23.75, 24.46, 25.37, 26.71 [$CH_3\underline{C}H_2S$-, -C($\underline{C}H_3)_2$]; 39.32 [C-2]; 48.39 [C-1]; 65.97 [C-5]; 70.05, 78.82 [C-3,4]; 109.55 [-$\underline{C}(CH_3)_2$]. M^+, m/e 280.1175 ($C_{12}H_{24}O_3S_2$ requires 280.1166).[9]

Reduction of 3b with lithium aluminum hydride as described above, followed by the addition of excess D_2O prior to workup gave 1-deutero-2-deoxy-4,5-O-isopropylidene-D-*erythro*-pentose in 80% yield. pmr ($CDCl_3$, TMS internal); δ1.24, t, J = 7Hz, 6H [$C\underline{H}_3CH_2S$-]; 1.33,1.41, two s, 6H [-C($C\underline{H}_3)_2$]; 1.93, complex, 2H [H-2]; 2.50-2.84, complex, 4H [$CH_3\underline{C}H_2S$-]; 3.30, broad s, 1H [-CO$\underline{H}$]; 3.83-4.10, complex, 4H [H-3,4,5]; cmr ($CDCl_3$, TMS internal); δ14.52 [$\underline{C}H_3CH_2S$-]; 23.36, 24.32, 25.30, 26.65 [$CH_3\underline{C}H_2S$-, -C($\underline{C}H_3)_2$]; 39.23 [C-2]; 48.10, weak t, J = 22Hz [C-1]; 65.95 [C-5]; 69.61, 78.73 [C-3,4]; 109.32 [-$\underline{C}(CH_3)_2$]. M^+, m/e 281.1256 ($C_{12}H_{23}O_3DS_2$ requires 281.1229).

The reduction of 3b was also accomplished with lithium aluminum deuteride, followed by H_2O workup, to give 2-deutero-2-deoxy-4,5-O-isopropylidene-D-*erythro*-pentose diethyl dithioacetal (82%, oil); pmr ($CDCl_3$, TMS internal); δ1.19, t, J = 7Hz 6H [$C\underline{H}_3CH_2S$-]; 1.29, 1.35, two s, 6H [-C($C\underline{H}_3)_2$]; 1.90, d, J = 10Hz [H-2]; 2.41-2.73, complex, 4H [$CH_3\underline{C}H_2S$-]; 3.20, broad s, 1H [-CO$\underline{H}$]; 3.75-4.07, complex, 5H [H-1,3,4,5]; cmr ($CDCl_3$, TMS internal); δ14.51 [$\underline{C}H_3CH_2S$-]; 23.51, 24.38, 25.34, 26.68 [-C($\underline{C}H_3)_2$, $CH_3\underline{C}H_2S$-]; 38.99, t, J = 19Hz [C-2]; 48.15 [C-1]; 66.01 [C-5]; 69.74, 78.83 [C-3,4]; 109.47 [-$\underline{C}(CH_3)_2$]. M^+, m/e 281.1232 ($C_{12}H_{23}O_3DS_2$ requires 281.1229). When the lithium aluminum deuteride reduction of 3b was followed by a D_2O workup, however, 1,2-dideutero-2-deoxy-4,5-O-isopropylidene-D-*erythro*-pentose diethyl dithioacetal was produced (70%, oil); pmr ($CDCl_3$, TMS internal); 1.26, t, J = 7Hz, 6H [$C\underline{H}_3CH_2S$-]; 1.34, 1.41, two s, 6H [-C($C\underline{H}_3)_2$]; 1.96, broad s, 1H [H-2]; 2.48-2.82, complex, 4H [$CH_3\underline{C}H_2S$-]; 3.17, broad s, 1H [-CO$\underline{H}$]; 3.80-4.08, complex, 4H [H-3,4,5]; cmr (TMS internal); δ14.49 [$\underline{C}H_3CH_2S$-]; 23.37, 24.32, 25.31, 26.64 [-C($\underline{C}H_3)_2$, $CH_3\underline{C}H_2S$-]; 39.05, t, J = 19Hz [C-2]; 48.25, weak t, J = 22Hz [C-1]; 66.00 [C-5]; 69.63, 78.77 [C-3,4]; 109.41 [-$\underline{C}(CH_3)_2$]. M^+, m/e 282.1272 ($C_{12}H_{22}O_3D_2S_2$ requires 282.1291).

These results demonstrate that reduction proceeds *via* hydride transfer at C-2, with water serving as the proton donor at C-1. Because of the obligatory requirement for the free C-3 hydroxyl group, the reaction is envisioned to proceed *via* directed hydride transfer through the alkoxyaluminum hydride salt (6) to yield the stabilized carbanion (7) or the cyclic alkoxy aluminum salt (8). Hydrolysis of the latter salt during workup would then result in the observed incorporation of solvent hydrogen. A similar mechanism has been proposed for the LAH reductive rearrangement of allylic acetals to vinyl ethers.[11]



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Conversion of 2-deoxy-4,5-O-isopropylidene-D-*erythro*-pentose diethyl dithioacetal (5b) to 2-deoxy-4,5-O-isopropylidene-D-*erythro*-pentose dimethyl acetal was accomplished in 80% yield as previously described.[7,12] Hydrolysis of the intermediate dimethylacetal in 0.1N trifluoroacetic acid for 1 h at room temperature gave 2-deoxy-D-*erythro*-pentose in 90% yield, virtually pure by pmr spectroscopy. Chromatography of the crude product on Bio-Gel P-2 in water (2.5 x 98 cm) gave pure 2-deoxy-D-*erythro*-pentose, which gave the expected colorimetric test for 2-deoxyaldoses,[13] and had pmr and cmr[14] spectra identical to those of authentic 2-deoxy-D-*erythro*-pentose.

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