

# An Efficient Synthesis of L-Ascorbic Acid and [5-<sup>2</sup>H]-L-Ascorbic Acid

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**Summary** L-Ascorbic acid has been synthesized *via* the regio- and stereo-selective reduction of D-threo-2,5-hexodiulosonic acid; this procedure also can be used for preparation of the 5-deuterio-compound.

THERE has been much recent interest in the synthesis of L-ascorbic acid<sup>1</sup> and in specifically labelled derivatives<sup>2</sup> of this biologically important molecule. We report herein a novel synthesis based on the regio- and stereo-selective reduction of D-threo-2,5-hexodiulosonic acid (1).<sup>3</sup>

D-threo-2,5-Hexodiulosonic acid is readily available in high yield (85%) by the oxidation of glucose with various species of *Acetobacter* and *Pseudomonas* bacteria.<sup>4</sup> The gross structure of (1) was first determined by Katznellson and his co-workers,<sup>5</sup> and confirmed by the work of Kondo,<sup>6</sup> Wakisaka,<sup>7</sup> and Bernearts and DeLey.<sup>8</sup> Exhaustive reduction of (1) with NaBH<sub>4</sub> has been reported to afford a mixture of D-gluconic, D-mannonic, L-idonic, and L-gulononic acids.<sup>5,7,8</sup> Ruff oxidation of the mixture afforded a mixture of D-arabinose and L-xylose in which D-arabinose (containing the undesired configuration at C-5) was claimed to be the major component.<sup>7</sup> Catalytic hydrogenation of (1) was reported to afford, regioselectively, a mixture of L-xylo- (2a) and D-arabino-2-hexulosonic acid (3a) in which the latter (also containing the undesired configuration at C-5) predominated.<sup>7,9,10</sup>

Our recent determination of the solution structure of (1) by <sup>13</sup>C n.m.r. spectroscopy as the hydrated pyranose form depicted<sup>11</sup> casts some light on the above observations. If it is assumed that (1) is reduced in its stable pyranose form, catalytic reduction of the cyclohexylidene-like 5-keto-unit would be expected to occur predominately from the equatorial face of the molecule, affording the keto-acid isomer (2b) which is in agreement with the observed results.† However, ample precedent exists which suggests the *opposite* stereochemical result would be obtained in the reduction of (1) with a hydride reductant.<sup>12</sup>

Indeed we have found that the reduction of the sodium salt of (1) in water at 0 °C with 0.25 equiv. of NaBH<sub>4</sub> affords in 89% yield a mixture of the keto-acids (2a) and (3a) in the ratio of 86:14.‡ Also formed is a mixture of the four hexonic acids L-gulonic, L-idonic, D-mannonic, and D-gluconic (in a ratio of *ca.* 40:27:19:15)‡ in 3–4% yield. That the observed stereochemical result is due to the axial delivery of hydride in the sterically biased cyclohexylidene-like system (1) is supported by the exclusively axial delivery of hydride in the recently reported reduction of the protected 2,5-hexodiulosonate (5).<sup>2a</sup>

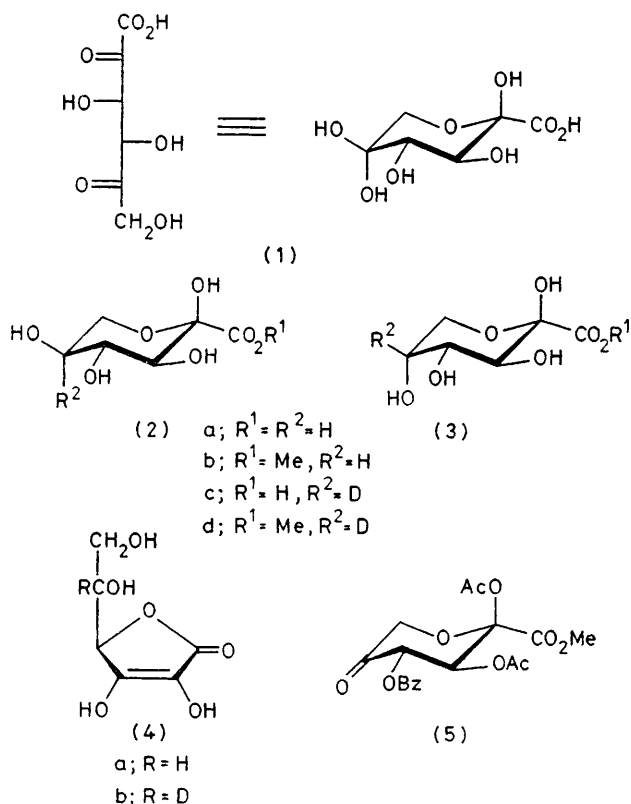
† The catalytic reduction of (1) in water at pH 8 with Raney Ni catalyst and hydrogen (40 lb in<sup>-2</sup>) at ambient temperature was re-examined. On uptake of 1 equiv. of hydrogen, h.p.l.c. analysis of the reaction mixture indicated a regioselective formation of (2a) and (3a) (20:80, 82% yield) (ref. 12) thus confirming and quantifying Wakisaka's earlier observation.

‡ Ratios were determined by h.p.l.c. analysis using Dowex 50 × 8 column in calcium form. Yields were determined using an Aminex-25 anion exchange column in the formate form.

§ Dowex-50 × 8 Resin in calcium form using water as eluant.

¶ Based on g.l.c. analysis of the per-trimethylsilylated methyl esters on a 2 m OV-210 column.

\*\* All compounds reported give satisfactory combustion analysis and exhibit physical and spectral data consistent with the assigned structures.



The mixture of 2-keto-acids derived from the NaBH<sub>4</sub> reduction of (1) is separable by either ion-exclusion chromatography§ or conversion of the mixture into the corresponding methyl esters followed by silica gel chromatography or fractional crystallization. Thus, lyophilization of the aqueous reduction mixture of (1), followed by esterification of the freeze-dried solids in methanol (using Dowex-50 ion exchange resin, hydrogen form) with azeotropic removal of trimethyl borate, affords an 85:15 mixture of the esters (2b) and (3b) in 88% yield¶ from which (2b) is obtained in 62% isolated yield on crystallization from methanol (m.p. 154–155 °C).\*\* Lactonization of (2b) with NaHCO<sub>3</sub> in refluxing methanol generates sodium L-ascorbate in 93% yield [57% overall from (1)]. Conversion into the free acid followed by crystallization from methanol affords L-ascorbic acid (4a) {m.p. 188–189 °C, [α]<sub>D</sub><sup>20</sup> +21° (c 10, H<sub>2</sub>O)} identical with authentic L-ascorbic acid.

The utility of this synthesis for the formation of C-5 labelled L-ascorbic acid is demonstrated by the reduction of (1) with NaBD<sub>4</sub> at 0 °C in water to give (2c) and (3c) (85:15) in 81% yield. Isolation of the reduced acids by ion-exclusion chromatography§ afforded the calcium salt of (2c) in 70% yield. Esterification as above generated methyl [5-<sup>3</sup>H<sub>1</sub>]-L-xylo-2-hexulosonate (2d) in 59% isolated yield. Lactonization, followed by isolation of the free acid, produced [5-<sup>3</sup>H<sub>1</sub>]-L-ascorbic acid (4b) (m.p. 186–188 °C) in 41% overall yield.

The unexpectedly high regio- and stereo-selective nature of the sodium borohydride reduction of (1) offers a convenient and highly efficient synthesis of L-ascorbic acid and its C-5 labelled derivatives.

We thank J. D. Winchester for assay development.

(Received, 20th March 1979; Com. 290.)

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