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A Novel Synthesis of L-Ascorbic Acid

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A three steps synthesis of L-ascorbic acid (I) from D-glucuronolactone (III) is described.

L-Ascorbic acid (I), occurring in many kinds of animals and plants, has an activity of anti-scurvy and contains two asymmetric carbons, C_4 and C_5, configurations of which are similar to those of L-(+)-threose (II), possessing the L-threo configurations at the corresponding positions. Since Reichstein and Grüssner[1] succeeded in the first synthesis of I from D-glucose by seven steps, many workers have reported the other synthetic methods.[2~4]

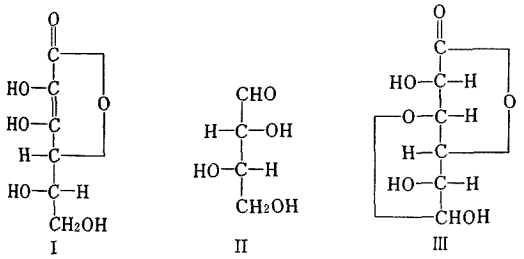


FIG. 1.

Now we wish to describe a novel simple synthesis of I from D-glucuronolactone (III) by only three steps. D-Glucuronolactone, easily available by oxidation of amylose, was employed as a starting material, because this compound has been known as a key intermediate in the biosynthesis of ascorbic acid, and if C_5-hydroxyl group of III can be oxidized and successively C_1-carbonyl function can be reduced, the inversion of D-threo enantiomer (III), to the desired L-threo one (I), would be accomplished without difficulty. This scheme could be considered the most facile synthesis of L-ascorbic acid. Figure 2 shows this synthetic scheme by present authors.

At first, to oxidize C_5-hydroxyl group selectively, the protection of C_1 and C_2-hydroxyl functions was necessary and this was easily achieved by acetonide formation, that is, treating III with anhydrous acetone in the presence of sulfuric acid to give 1,2-O-isopropylidene-α-D-glucofuranosidurono-6,3-lactone(IV) in 71% yield. The acetonide (IV) was oxidized with manganese dioxide at low temperature to afford 1,2-O-isopropylidene-α-D-glucofuranosidurono-5-urose-6,3-lactone[5~7] (V) in an excellent yield.

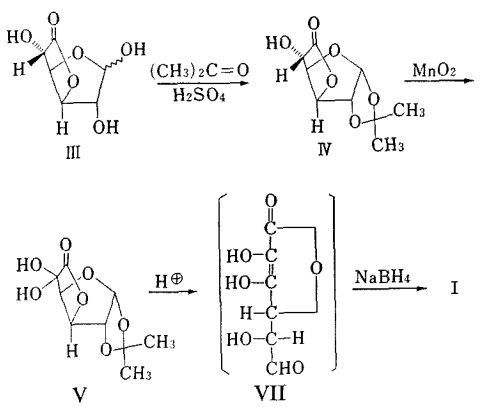
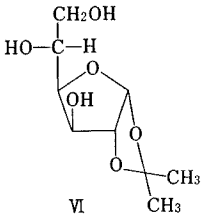


FIG. 2.

Recently Bakke and Theander[4] reported the synthesis of V by the oxidation of 1,2-O-isopropylidene-α-D-glucofuranose (VI) with oxygen in the presence of platium under slightly acidic conditions (pH 3~4.5). The compound V obtained by present precedure was proved to be of higher purity than that by Bakke's method by the comparison of the physical data.

Fianlly in order to transform V to I the formyl group should be selectively reduced after removal of the isopropylidene group. Treatment of V with 1 N sulfuric acid for



VI

FIG. 3.

1 hr at 90°C afforded a crude aldehde (VII) whose structure was supported by IR spectrum, showing the absorption at 1620 cm^{-1} and 1680 cm^{-1} due to carbon-carbon double bond and C_1 formyl group respectively.

Without purification the aldehyde (VII) was reduced with $NaBH_4$ in water at 0°C for 2 hr to give crystalline L-ascorbic acid in 56% yield isolated after the treatment with cation-exchange resin. Synthetic L-ascorbic acid was completely identical with an authentic sample on the basis of mixed melting point, IR, NMR and $[\alpha]_D$ data.

As described above a novel simple synthesis of L-ascorbic acid from D-glucuronolactone was developed and the merit of the present synthesis is that the reaction precedure was carried out under a mild condition in a good total yield (overall 32%) and required only three steps.

EXPERIMENTAL

1, 2-O-Isopropylidene-α-D-glucofuranosidurono-6,3-lactone (IV). A solution of III (20 g) in acetone (500 ml) was stirred with conc. H_2SO_4 (16 ml) and the stirring was continued at room temperature for 4 hr. Then the mixture was neutralized by an addition of Na_2CO_3 (40 g), stirred at 60°C and filtered through celite to remove the formed Na_2SO_4. The filtrate was concentrated and the residue was dissolved in ethyl acetate. The solution was washed with sat. NaCl aq and concentrated to afford crystalline product which was washed with ether and recrystallized from benzene. Pure crystalline was obtained in 74% yield mp 140~142°C. IR ν_{max}: 3430, 1770, 1380 cm^{-1}.

1, 2-O-Isopropylidene-α-D-glucofuranosidurono-5urose-6,3-lactone (V). A mixture of IV (3 g) and MnO_2 (12 g) in acetone (50 ml) was stirred at 5~10°C for 12 hr. The reaction mixture was filtered and the filtrate was concentrated *in vacuo* to give the colorless solid which was recrystallized from water. Pure product was obtained in 81% yield as a hydrate form. mp 147~148°C. IR ν_{max}^{KBr} cm^{-1}: 3360, 3310, 1780, 1380. NMR $\delta_{TMS}^{CD_3COCD_3}$: 1.35 (3H, s), 1.50 (3H, s), 4.58 (1H, d, J=3.6 Hz), 4.87 (1H, d, J=4 Hz), 4.90 (1H, d, J=4 Hz), 6.14 (1H, s), 6.00 (1H, d, J=3.6 Hz), 6.47 (1H, s). *Anal.* Found: C, 46.32; H, 5.07. Calcd. for $C_9H_{12}O_7$: C, 46.56; H, 5.12%.

L-Ascorbic acid (I). A solution of V (4 g) in 1 N H_2SO_4 (35 ml) was stirred at 90°C for 1 hr. After cooling to room temperature, 1 N NaOH was added until the reaction mixture was neutralized and the solvent was removed *in vacuo* and the residue was extracted with ethanol. The extract was concentrated and the residue was dissolved in water. To this 1 N NaOH was again added to neutralize completely and after $NaBH_4$ (220 mg) was added at once the solution was allowed to stand at 0°C for 2 hr. The reaction mixture was diluted with distilled water (150 ml) and the aqueous solution was passed through the column of cation exchange resin (Amberlite IR 120,100 ml) three times. Solvent was removed *in vacuo*, and to remove boric acid from the residue, methanol (50 ml) and a small portion of AcOH was added and the mixture was concentrated under reduced pressure.

This opperation was repeated three times to remove inorganic material completely.

Trituration of the residue with EtOH and $CHCl_3$ afforded crystalline L-ascorbic acid (1.62 g, 56%) which was recrystallized from MeOH. mp 190~191°C (lit. 190~192°C). $[\alpha]_D^{12}$ = +44.3 (c=1.3 MeOH) (lit. $[\alpha]_D^{23}$ = +48 (c=1, MeOH)). IR ν_{max}^{KBr}: 3500, 3400, 3200, 1750, 1650. NMR $\delta_{DSS}^{D_2O}$: 3.82 (2H, d, J= 3.2 Hz), 4.10 (1H, t, d, J=3.2, 1.0 Hz), 5.13 (1H, d, J=1.0 Hz). *Anal.* Found: C, 40.86; H, 4.55. Calcd. for $C_6H_8O_6$: C, 40.92; H, 4.58.

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