New Syntheses of L-Ascorbic Acid (Vitamin C)

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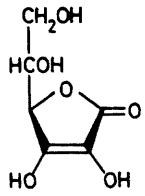
Summary Two new syntheses of L-ascorbic acid (**1**) are described, the first involving the selective oxidation of 3,5-*O*-benzylidene-L-gulono-1,4-lactone (**4a**) to 3,5-*O*-benzylidene-L-*xylo*-hexulosono-1,4-lactone hydrate (**4b**) and hydrolysis of (**4b**) to (**1**), and the second involving the regiospecific conversion of L-gulono-1,4-lactone (**3**) into ethyl 3,5 : 4,6-*O*-dibenzylidene-L-gulonate (**5**) followed by oxidative and hydrolytic conversion of (**5**) into ethyl L-*xylo*-hexulosonate (**6a**), a known precursor of L-ascorbic acid (**1**).

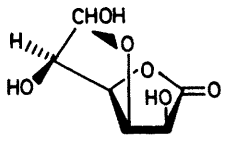
L-ASCORBIC ACID (**1**) syntheses in general have as their last step the acid or base catalysed cyclization of L-*xylo*-hexulosonic acid (**6b**) or a derivative thereof.[1] In contrast, the last step in the biosynthesis of L-ascorbic acid is the direct enzymatic oxidation of L-gulono-1,4-lactone (**3**).[2] An efficient chemical synthesis of (**1**) from L-gulono-1,4-lactone has not yet been reported. Since L-gulono-1,4-lactone is readily available by the hydrogenation of D-glucuronolactone (**2**),[3,4a] we were interested in syntheses of (**1**) from L-gulono-1,4-lactone (**3**) which would take advantage of the fact that the lactone ring was already formed. The direct chemical oxidation of (**3**) has failed to afford acceptable yields of (**1**) since (**1**) is more easily oxidized than (**3**) and thus under most oxidation conditions (**1**) will not survive.[4] Thus, the oxidation of (**3**) must be carried out on a derivative which would be stable to the oxidation conditions, but would afford (**1**) under mild hydrolysis conditions. The successful accomplishment of this approach to L-ascorbic acid (**1**) as well as a second method which affords (**1**) *via* a new, regiospecifically protected derivative of L-gulonic acid is reported herein.

The best procedure for the preparation of L-ascorbic acid (**1**) from L-gulonolactone (**3**) in which the lactone ring was not cleaved involved the selective oxidation of 3,5-*O*-benzylidene-L-gulono-1,4-lactone (**4a**) with manganese dioxide to 3,5-*O*-benzylidene-L-*xylo*-hexulosono-1,4-lactone hydrate† (**4b**) in 70—90% yield. Compound (**4a**) was

† The structures of all new compounds were consistent with the analytical and spectral data obtained.



(1)



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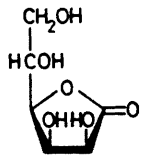

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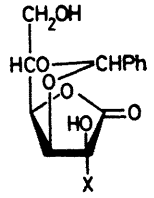
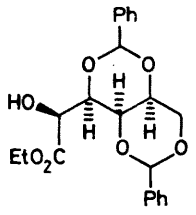


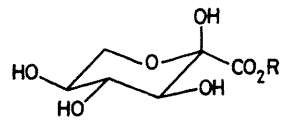
(4) a; X = H
b; X = OH

prepared[5]‡ in 65% recrystallized yield by stirring (**3**) with 4 equiv. of benzaldehyde using HCl gas as the acid catalyst. Hydrolysis of (**4b**) with aqueous acetic acid afforded L-ascorbic acid (**1**) (70% yield by iodine titration, 59% isolated yield) which was identical with an authentic sample by t.l.c., g.l.c., i.r., n.m.r., and m.p. comparison. Control experiments showed that L-*xylo*-hexulosonic acid (**6b**) was not converted into (**1**) under the hydrolysis conditions, thereby demonstrating that (**4b**) was directly hydrolysed to (**1**). If (**4b**) was stirred in anhydrous methanol containing HCl gas, (**1**) was not formed but rather methyl L-*xylo*-hexulosonate (**6**, R=Me) was obtained. This ester has been converted into (**1**) by either acid or base catalysis.[1]

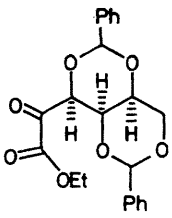
During a study of alternative methods for the preparation of (**4a**), it was discovered that when L-gulono-1,4-lactone (**3**) was treated with 4 equiv. of benzaldehyde diethyl acetal and conc. HCl, ethyl 3,5:4,6-*O*-dibenzylidene-L-gulonate† (**5**) was formed (m.p. 203—204 °C) in 84% yield. The oxidation of this novel, regiospecifically protected derivative of L-gulonic acid (**3**) with trifluoroacetic anhydride and dimethyl sulphoxide[6] afforded ethyl 3,5:4,6-*O*-dibenzylidene-L-*xylo*-hexulosonate† (**7**) in 90% yield, which on hydrolysis in acetic acid–water afforded ethyl L-*xylo*-hexulosonate (**6a**) in 86% yield. This material was identical with an authentic sample of (**6a**) prepared by esterification of L-*xylo*-hexulosonic acid (**6b**) in ethanol.[7]



(5)



(6) a; R = Et
b; R = H



(7)

Ethyl L-*xylo*-hexulosonate (**6a**) has been converted in 92% yield into L-ascorbic acid.[8] Thus the novel, regiospecific method for preparing (**5**) from (**3**) provides the key§ for converting (**3**) into (**1**).

These methods for the synthesis of L-ascorbic acid provide efficient syntheses of [6-^{2}H]- and [6-^{3}H]-derivatives of (**1**) since the reduction of D-glucuronolactone (**2**) has been carried out with sodium [^{3}H]borohydride[9] and clearly could be carried out catalytically with deuteriated or tritiated hydrogen to provide L-[6-^{2}H]- or [6-^{3}H]-gulono-1,4-lactone. In addition (**4a**), (**4b**), (**5**), and (**7**) may prove to be useful intermediates in the preparation of derivatives of gulono-1,4-lactone, idono-1,4-lactone, ascorbic acid, gulonic acid (and ester), idonic acid (and ester), gulose, idose, gulitol (5-glucitol), and iditol.

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‡ The selective protection of L-gulono-1,4-lactone (**3**) with other aliphatic and aromatic aldehydes will be reported in due course.

§ The use of other alcohols, aldehydes, and oxidation procedures will be reported in due course. Attempts to extend this method to galactono-1,4-lactone were unsuccessful since a complex mixture of products resulted. L-Idonic acid afforded ethyl 2,4:3,5-*O*-dibenzylidene-L-idonate. Details will be reported in due course.

[1] T. Reichstein and A. Grussner, *Helv. Chim. Acta*, 1934, **17**, 311; T. Reichstein, A. Grussner, and R. Oppenauer, *ibid.*, 1933, **16**, 561; D. F. Hinkley and A. M. Hoinowsky, U.S. P. 3,721,663 (1973); W. N. Haworth and E. L. Hirst, *Chem. and Ind.*, 1933, **482**, 645; B. Helferich and O. Peters, *Ber.*, 1937, **70**, 465; T. Ogawa, K. Taguchi, N. Takasaka, M. Mikata, and M. Matsui, *Carbohydrate Res.*, 1976, **51**, C1; C.-Y. Chen, H. Yamamoto, and T. Kwan, *Chem. and Pharm. Bull* (*Japan*), 1970, **18**, 1305; B. E. Gray, U.S. P. 2,421,611 (1947); H. S. Isbell, *J. Res. Nat. Bur. Stand.*, 1944, **33**, 45.

[2] L. W. Mapson, 'Biogenesis of L-Ascorbic Acid in Plants and Animals,' in 'The Vitamins,' eds: W. H. Sebrell, Jr. and R. S. Harris, Academic Press, New York, 1967, p. 369.

[3] M. Ishidate, Y. Imai, Y. Hirasaka, and K. Umemoto, *Chem. and Pharm. Bull.* (*Japan*), 1965, **13**, 173; G. P. 618,907 (1935), Hoffman-LaRoche and Co.

[4] The direct chemical oxidation of (**3**) has been reported to provide ascorbic acid in low (10%) yield: (a) W. Berends and T. Konings, *Rec. Trav. chim.*, 1955, **74**, 1365; (b) B. Coleby, *Chem. and Ind.*, 1957, 111.

[5] M. Matsui, M. Okada, and M. Ishidate (*Yakugaku Zasshi*, 1966, **86**, 110) first prepared (**4a**) in 43% yield using conc. HCl as catalyst.

[6] S. L. Huang, K. Omura, and D. Swern, *J. Org. Chem.*, 1976, **41**, 957, 3329.

[7] G. Drefahl and B. Gross, *J. prakt. Chem.*, 1955, **1**, 153.

[8] R. Bogoczeck, Pol. Pat. 57,573 (1969) (*Chem. Abs.*, 1970, **72**, 13024x).

[9] R. L. Taylor and H. E. Conrad, *Biochemistry*, 1972, **11**, 1383.