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An Efficient Three Step Synthesis of Vitamin C from L-Galactono-1,4-lactone, a By-product of the Sugar Industry

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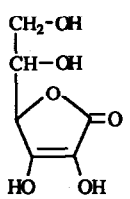
Abstract : An efficient and short synthesis of vitamin C has been accomplished from L-galactono-1,4-lactone via methyl 3,5:4,6-di-O-ethylidene-L-galactonate.

Following the isolation of vitamin C **1** by Szent-Györgyi in 1928[1] and its structure determination by Hirst et al. five years later[2] considerable effort has been directed towards the synthesis of this novel vitamin.[3] In their pioneering synthesis of **1** from D-glucose, Reichstein and Grüssner[4] combined fermentative and chemical approaches as early as 1934. Apart from the intrinsic challenge that the synthesis of this natural product presents, it also displays a number of interesting biological activities.[5]

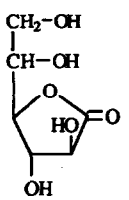
We wish to describe a novel, practical synthesis of **1** (in three steps) from L-galactono-1,4-lactone **2**. This sugar is a by-product of the sugar industry and is available in large quantities. The conversion of **2** to **1** has in fact been attempted by others, though without success.[6]

It occurred to us that the lactone **2** bears a striking resemblance to our target. Our initial plan was to selectively oxidize its position 2 which would then give vitamin C directly after enolization. Although similar oxidation of L-gulono-1,4-lactone has been reported, this reaction is not very efficient.[6] In fact, in the particular case of lactone **2**, conditions were not found which could effect this oxidation.



vitamin C

1



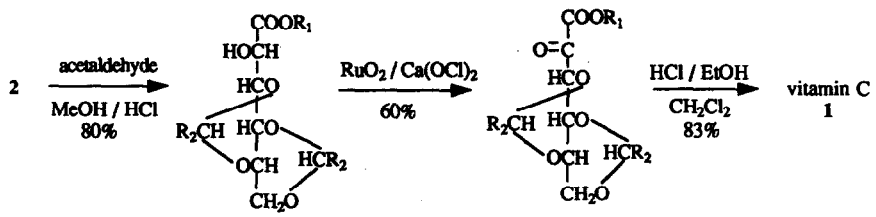
L-galactono-1,4-lactone

2

We then turned to an alternative strategy involving opening of the lactone ring (through ester formation) with simultaneous selective protection of positions 3,4,5,6 (through acetal formation). This would leave a free hydroxyl at position 2 for subsequent oxidation.

Initial attempts to effect this lactone opening-protection step using a methanolic HCl solution of either 2,2-dimethoxypropane, 2,2-dimethoxycyclohexane or benzaldehyde did not give the desired product. However, when **2** was treated with methanolic HCl solution of acetaldehyde (room temperature, 6 hrs) the desired methyl 3,5:4,6-di-O-ethylidene galactonate **3a** was the only product isolated in 80% yield (optimized). No other isomeric acetal could be detected.

The derivative **3b** was synthesized in a similar manner from acetaldehyde and EtOH (50% yield) and **3c** from propionaldehyde and MeOH (53% yield).



3a $R_1 = R_2 = CH_3$

3b $R_1 = CH_2CH_3$; $R_2 = CH_3$

3c $R_1 = CH_3$; $R_2 = CH_2CH_3$

4 $R_1 = R_2 = CH_3$

The structures of di-O-acetals **3a** and **3c** were established by analysis of their ^1H NMR spectra before and after acetylation. In particular the H-2 proton underwent an expected 0.5 ppm downfield chemical shift following acetylation. In the case of **3b** it was not possible to distinguish between H-2 and H-3 as the coupling constant $J_{3,4}$ was almost 0. However, its structure was established by X-ray analysis. The ^{13}C NMR spectra of **3a, 3b** and **3c** were also consistent with the proposed structure.

Having in hand the protected derivative **3a**, various methods were tried in order to carry out the oxidation to the α-keto ester **4**. However, only one of the several methods tried met with success. Thus, $RuCl_3$ / NaOCl[7] (in 15% aqueous solution) in CH_2Cl_2 gave the desired methyl 2-keto-3,5:4,6-di-O-ethylidene galactonate **4** but only in 15% isolated yield. Oxidation proceeded much more efficiently using $RuCl_3$ / $Ca(OCl)_2$ (solid) in a mixture of CH_2Cl_2-CH_3CN-H_2O (1:1:0.1) and in the presence of celite. The required α-keto-ester **4** could then be isolated in 60% yield.

Transformation of the key intermediate **4** into vitamin C was effected as described by Rumpf[8] (HCl, EtOH, CH_2Cl_2 at 60°C). The overall yield of this three step[9] synthesis from lactone **2** is 40%.

Acknowledgement

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