An Expedient and Practical Three-Step Synthesis of Vitamin C from a Byproduct of the Sugar Industry: The L-Galactono-1,4-lactone Pathway

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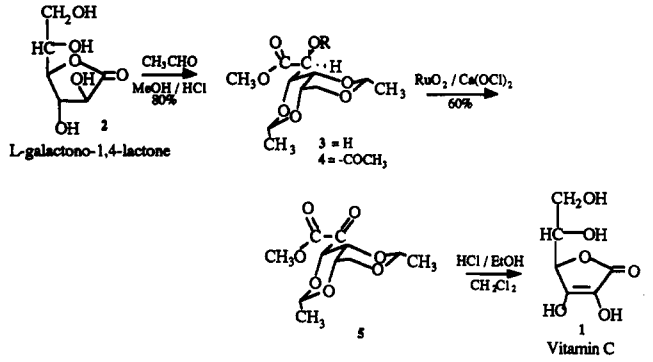
Received October 26, 1992 (Revised Manuscript Received September 1, 1993)

Since its isolation by Szent-Györgyi[1] in 1928 and the determination of its structure by Hirst *et al.*[2] 5 years later, considerable effort has been directed towards the synthesis of vitamin C.[3] Apart from the intrinsic challenge that its synthesis presents, this natural product displays a number of biological activities and thus represents a worthwhile target for chemists.

The most frequently used starting material for the synthesis of **1** is D-glucose.[4] However, we report in this paper the use of L-galactono-1,4-lactone (**2**),[5] a byproduct of the beet sugar industry, for a three-step synthesis of vitamin C. Our initial plan was to selectively oxidize the 2-position of lactone **2** which would then give vitamin C directly after enolization. Although a similar oxidation of L-gulono-1,4-lactone has been reported, it was not efficient.[6] We, likewise, could not find conditions by which to effect the direct oxidation of L-galactono-1,4-lactone or its 5,6-*O*-isopropylidene derivative.



The unsuccessful outcome of the direct oxidation of lactone **2** into vitamin C was disappointing, but not altogether surprising. These negative results can be attributed to the more hindered nature of the "cyclic" lactone **2** in comparison with its acyclic ester **3** and, more importantly to the facile and rapid oxidation of **1** into dehydro-L-ascorbic acid, followed by further degradation.[7]

We turned, therefore, to an alternative strategy involving opening of lactone **2** to an acyclic ester with simultaneous regioselective acetalization at positions 3–6, leaving a free hydroxyl at position 2 for subsequent oxidation. Initial attempts to effect a lactone opening, acetalization step by using a methanolic HCl solution of either 2,2-dimethoxypropane or 1,1-dimethoxycyclohexane failed, and treatment of **2** with benzaldehyde under acidic conditions gave an intractable mixture as reported earlier.[6] However, when **2** was reacted with a methanolic HCl solution of acetaldehyde for 6 h at ambient temperature, the desired methyl 3,5:4,6-di-*O*-ethylidenegalactonate (**3**) was isolated in 80% optimized yield. No other regioisomeric product could be detected by ^{1}H NMR of the crude reaction mixture.

The structure of di-*O*-acetal **3** was evident from a comparison of its ^{1}H NMR spectra before and after acetylation. In particular, proton H-2 underwent an expected 0.5 ppm downfield shift following acetylation. The ^{13}C NMR spectra of **3** and **4** were also consistent with the structures proposed.

With the required protected di-*O*-acetal derivative **3** in hand, we explored the oxidation of **3** into the elusive, key intermediate 2-keto-L-galactonic ester **5**. Several of the methods reported in the literature for the oxidation of aldonic esters into the corresponding 2-keto esters were investigated. Most of the procedures were found to be unsatisfactory. Attempts to convert **3** into **5** included reagents such as Dess–Martin,[8] PDC, and 4-methoxy-2,2,6,6-tetramethylpiperidine *N*-oxide/NaOCl.[9]

After these initial failures, we chose to focus our attention on ruthenium-based oxidizing agents such as tetra-*N*-propylammonium perruthenate (TPAP)[10] and ruthenium tetraoxide (RuO_4) in the presence of a co-oxidant such as *N*-methylmorpholine *N*-oxide (NMO), $NaIO_4$, NaOCl, or $Ca(OCl)_2$. Normally, the oxidant dissolves in organic solvents and can be used for either stoichiometric or catalytic oxidations of secondary alcohols to carbonyl functions. These oxidizing agents tolerate the presence of multiple functional groups. Using a stoichiometric amount of TPAP for oxidation of **3** in CH_2Cl_2 as solvent, only 5% of **5** was isolated. It is interesting to note that **3** was not oxidized using catalytic quantities of TPAP in the presence of NMO; only the unchanged starting material was recovered.

Next, we studied the conversion of **3** into **5** by ruthenium tetraoxide. The latter can be generated from RuO_2 or $RuCl_3$ with NaOCl or $NaIO_4$. The oxidation of **3** into the corresponding α-keto ester **5** using the RuO_2–$NaIO_4$ system was also unsuccessful. However, RuO_2–NaOCl, which had previously been employed for the oxidation of ethyl 3,5:4,6-di-*O*-methylene-L-galactonate into ethyl α-keto-3,5:4,6 di-*O*-methylene-L-galactonate (prepared from L-arabinose)[11] converted **3** into keto ester **5** in 15% yield. Encouraged by this first, but still unsatisfactory result, we next performed the oxidation of **3** with RuO_2–NaOCl

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0022-3263/93/1958-7281$04.00/0

in CH_2Cl_2–CH_3CN (1:1), as described by Sharpless,[12] and the 2-keto ester **5** was obtained in 30% yield.

The low yield for the transformation of **3** into **5** prompted us to try an identical series of reaction conditions, except with solid $Ca(OCl)_2$ as the cooxidant. When **3** was treated with RuO_2–$Ca(OCl)_2$ in a mixture of CH_2Cl_2–CH_3CN–H_2O (1:1:0.05) the yield of the pure α-keto ester **5** was increased to 40%. We further anticipated that the inclusion of celite might lead to an improvement of this yield. Accordingly, the oxidation yield was 60%. The structure of the 2-keto-L-galactonate ester **5** was established by its spectral and analytical data.

It is evident that the transformation of **3** into **5** in 60% optimized yield can be attributed to the oxidizing power of the RuO_4 catalyst. Without the addition of the ruthenium catalyst no oxidation took place. The catalytic oxidation has been improved steadily with the help of the judicious choice of the solid cooxidant $Ca(OCl)_2$, the composition of the mixture of solvent (CH_2Cl_2:CH_3CN:H_2O = 1:1:0.05), and addition to the medium of celite as a surface-increasing agent of the catalyst.

Finally, it remained to convert ketone **5** under acidic conditions into vitamin C. This task was achieved according to a known procedure.[13] Thus, treatment of **5** with acid (HCl, EtOH, CH_2Cl_2 at 60 °C over 6 h) provided vitamin C, whose spectral and chromatographic properties matched those of an authentic sample, in 83% yield. The overall yield of this three-step synthesis from L-galactono-1,4-lactone was 40% .

This starting material has not, to the best of our knowledge, been used before for synthetic purposes and serves to confirm the importance of the L-galactono-1,4-lactone pathway[14–16] for the potential, industrial production of vitamin C.

Experimental Section

General. The melting points were taken on a Leitz apparatus and are uncorrected. Optical rotations were measured at 20 ± 2 °C with a Perkin-Elmer 241 polarimeter. ^1H (at 200 MHz) and ^{13}C NMR spectra were recorded in $CDCl_3$ on a Bruker AC-200 spectrometer. All chemical shifts are reported in ppm units downfield from Me_4Si. Infrared (IR) spectra were recorded on a Perkin-Elmer 297 spectrometer. Reactions were monitored by TLC on silica gel 60 PF_{254} (Merck) and detected by charring with sulfuric acid. Preparative TLC was carried out on silica gel 60 PF_{254} (Merck). Column chromatography was performed on silica gel SDS (40-60 mesh) and Florisil (100–200 mesh) under a pressure of 0.2 atm (flash chromatography). HPLC analyses were performed using a refractometer as detector and CN-modified silica gel (Econosil 10 μm) column. Elemental analyses were performed at the ICSN-CNRS. Unless otherwise stated, all solvents were dried by conventional methods, and the reactions were carried out in oven-dried glassware under an atmosphere of argon.

Methyl 3,5:4,6-Di-*O*-ethylidene-L-galactonate (3). To a stirred solution of dry methanol (120 mL) containing dry HCl gas (3 g; 0.08 mol) at 0–5 °C was added acetaldehyde (80 mL) and **2** (20 g; 0.12 mol). The mixture was kept for 5 h at 0–5 °C and then at room temperature for an additional 10 h. The solution was neutralized by addition of $NaHCO_3$ and filtered through a Celite pad, and the filtrate was evaporated under reduced pressure to a syrupy residue. The residue was extracted with CH_2Cl_2:H_2O = 1:1, and the extract was washed with water, dried ($MgSO_4$), and evaporated to give the oily **3** in 80% yield: $[\alpha]_D$ = −10° (*c* = 0.55, CH_2Cl_2); IR (film) 1750 cm^{-1}; ^1H NMR δ 1.33 (d, 3H, $CH_{3\text{-ethylidene}}$), 1.46 (d, 3H, $CH_{3\text{-ethylidene}}$), 4 (s, 3H, $CH_{3\text{-ester}}$), 4.13 (m, 3H, H-4, H-5, H-6'), 4.26 (m, 2H, H-6, H-3), 4.75 (d, 1H, H-2, $J_{2,3}$ = 3 Hz), 4.93 (q, 1H, $CH_{ethylidene}$), 5.56 (q, 1H, $CH_{ethylidene}$); ^{13}C NMR δ 21.1, 21 ($2CH_{3\text{-ethylidene}}$), 52.6 ($CH_{3\text{-ester}}$), 69.1 (C-6), 68.0, 70.5, 74.1, 75.6 (C-2; C-3; C-4; C-5), 95.9, 98.9 ($2CH_{ethylidene}$), 172.9 (C-1). Anal. Calcd for $C_{11}H_{18}O_7$: C, 50.37; H, 6.92. Found: C, 50.38; H, 6.95.

Methyl 2-*O*-Acetyl-3,5:4,6-di-*O*-ethylidene-L-galactonate (4). Acetic anhydride was added to stirred solution of **3** dissolved in dry pyridine at 0 °C. Vigorous stirring was continued for 6 h at room temperature. The mixture was evaporated to dryness under reduced pressure, and the residue was subjected to flash chromatography yielding ester **4** (93%): mp 153–154 °C; $[\alpha]_D$ = −31° (*c* = 1.22, $CHCl_3$); IR (film) 1740 cm^{-1}; ^1H NMR δ 1.33 (q, 6H, $2CH_{3\text{-ethylidene}}$), 2.16 (s, 3H, $CH_{3\text{-acetate}}$), 3.66 (d, 1H, H-4, $J_{4,5}$ = 1.5 Hz), 3.73 (d, 1H, H-6, $J_{6,6'}$ = 12 Hz), 3.75 (s, 3H, $CH_{3\text{-ester}}$), 3.85 (dd, 1H, H-6', $J_{5,6'}$ = 8 Hz), 4.13 (dd, 1H, H-5), 4.36 (d, 1H, H-3), 4.73 (q, 1H, $CH_{ethylidene}$), 5.23 (q, 1H, $CH_{ethylidene}$), 5.33 (d, 1H, H-2, $J_{2,3}$ = 4.5 Hz); ^{13}C NMR δ 20.7, 20.9 ($2CH_{3\text{-ethylidene}}$), 21.2($CH_{3\text{-acetate}}$), 52.6 ($CH_{3\text{-ester}}$), 69.1 (C-6), 68, 69.8, 74.2, 74.3 (C-2; C-3; C-4; C-5), 96.4, 98.6 ($2CH_{ethylidene}$), 167.5, 169.5 (C-1; $CO_{acetate}$); Anal. Calcd for $C_{13}H_{20}O_8$: C, 51.31; H, 6.63. Found: C, 51.54; H, 6.83.

Methyl 2-Keto-3,5:4,6-di-*O*-ethylidene-L-galactonate (5). To a vigorously stirred solution of **3** (310 mg; 1.2 mmol) in dry degassed CH_2Cl_2 (8 mL) and CH_3CN (8 mL) were added $RuCl_3$ (20 mg; 0.1 mmol), $Ca(OCl)_2$ (500 mg, 3.6 mmol), and celite (500 mg) under argon atmosphere. The stream of argon gas was then stopped. After being stirred for 10 min further, H_2O (0.8 mL) was added, and the reaction was monitored by TLC (EtOAc: heptane = 6:4). After an additional 3 h, 2-propanol (1 mL) was added, the reaction was filtered through a Celite pad, and the filtrate was concentrated under reduced pressure. The residue was dissolved in ethyl acetate (5 mL) and pentane (20 mL). After 5 min, the solvent was decanted and concentrated. This operation was repeated once again to afford an oily product, which was purified by HPLC using a CN-modified silica gel column (Econosil 10 μm) (EtOAc:heptane = 50:50). Analytically pure **5** (160 mg) was isolated in 60% yield: $[\alpha]_D$ = −10° (*c* = 0.9, CH_2Cl_2); IR (film) 1740, 1750 cm^{-1}; ^1H NMR δ 1.55 (d, 6H, $2CH_{3\text{-ethylidene}}$), 3.96 (dd, H-6', *J* = 8, 12 Hz), 4.05 (s, 3H, $CH_{3\text{-ester}}$), 4.23 (m, H-4, H-5, H-6), 4.95 (q, 1H, $CH_{ethylidene}$), 5.06 (q, 1H, $CH_{ethylidene}$), 5.23 (d, 1H, H-3, $J_{3,4}$ = 2 Hz); ^{13}C NMR δ 20.9, 20.95 ($2CH_{3\text{-ethylidene}}$), 53.2 ($CH_{3\text{-ester}}$), 68.9 (C-6), 67.6, 67.7, 78.6 (C-3, C-4, C-5), 96.5, 99.1 ($2CH_{ethylidene}$), 162.4 (C-1), 193.1 (C-2). Anal. Calcd for $C_{11}H_{16}O_7$: C, 50.77; H, 6.20. Found: C, 50.89; H, 6.12.

Transformation of α-Keto Ester 5 into Vitamin C (1). A mixture of **5** (100 mg, 0.3 mmol), CH_2Cl_2 (1 mL), and EtOH–HCl (0.15 mL, from a standard solution, prepared from 130 mL of EtOH (96%) and 13 mL of HCl (12 N)) was stirred at 60 °C over 10 h while argon was bubbled through the solution. The precipitated vitamin C was decanted, and the solid was treated with hot CH_2Cl_2 and filtered under argon. The solid was recrystallized from methanol yielding 50 mg (83%) of white powder. Its ^1H and ^{13}C NMR, UV, and IR spectra and its melting point were indistinguishable from those of authentic vitamin C.

Acknowledgment. We thank Dr. R. H. Dodd and the reviewers for the enlightening suggestions in the preparation of this manuscript.

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