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(54) **Process for preparing 3,5:4,6- protected derivatives of L- or D- gulonic acid, their use in preparing 2-keto-L- or D- gulonic acid or their esters of L- or D- ascorbic acid, and certain novel 2-nitrato-gulonate intermediates**

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REC. TRAV. CHIM. DES PAYS-BAS, vol. 74, Aug.—Sept. 1955, Amsterdam W. Berends and J. Konings, pages 1365/1370.

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Process for preparing 3,5:4,6- protected derivatives of L- or D- gulonic acid, their use in preparing 2-keto-L- or D- gulonic acid or their esters or L- or D- ascorbic acid, and certain novel 2-nitrato-gulonate intermediates

A synthetic route to ascorbic acid is provided in which a 3,5:4,6-protected derivative of gulonic acid is prepared from gulono-1,4-lactone. Oxidation of the derivative and hydrolysis of the resulting products affords 2-ketogulonic acid or ester thereof which can be readily converted to ascorbic acid by known methods. The invention also relates to certain intermediates prepared by said route.

L-ascorbic acid, or vitamin C, is required in the human diet and is widely sold in tablet form and as an additive in various foodstuffs to meet this need. In all animals except primates and guinea pigs L-ascorbic acid is biosynthetised from D-glucose. The final step in this biosynthesis is the enzymatic conversion of L-gulono-1,4-lactone to L-ascorbic acid. British Patent 763,055 discloses the conversion of L-gulono-1,4-lactone to L-ascorbic acid in about 40% yield by the use of an enzymatic oxidation system.

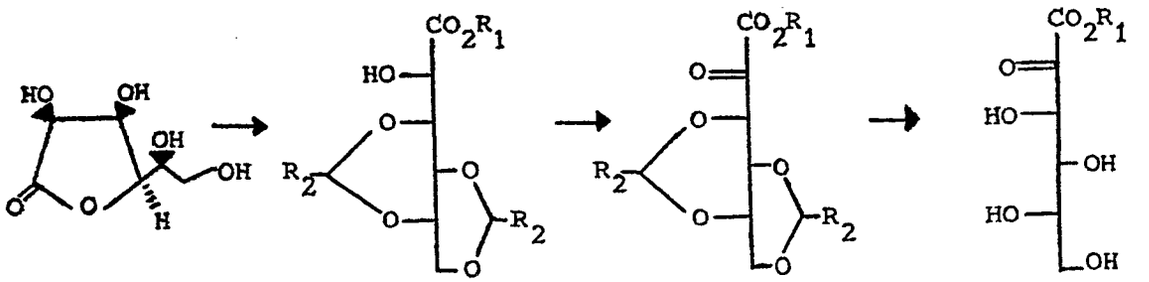
L-ascorbic acid and some of its derivatives are employed as antioxidants in foodstuffs to prevent rancidity, to prevent browning of cut fruit and in meat curing. D-ascorbic acid may also be used.

Attempts to effect the direct conversion of gulono-1,4-lactone to ascorbic acid by chemical means have only partly been successful since over-oxidation and degradation reactions produce undesirable by-products. However, low yields of L-ascorbic acid have been produced by oxidation. For example, Berends and Konings, Rec. Trav. Chim. des Pays-Bas, *74*, 1365 (1955), discloses the use of Fenton's reagent to give a 10% yield of L-ascorbic acid. The most successful and common method of producing L-ascorbic acid is based on a multi-step synthesis from D-glucose going through sorbose and 2-ketogulonic acid as described by Reichstein and Grussner, Helv. Chim. Acta., *17*, 311 (1934).

U.S. Patent 2,847,421 discloses a process for the production of intermediates 3,5:4,6-diethylidene-L-gulonic acid and its simple esters and salts in the synthesis of ascorbic acid from D-sorbitol. It also discloses methyl-2-keto-3,5:4,6-diethylidene-L gulonate and its corresponding ethyl, propyl and *n*-butyl esters as having utility in the preparation of ascorbic acid

This invention is concerned with a process in which the starting material, gulono-1,4-lactone is reacted with a dialkyl aldehyde acetal or an aldehyde and an alkanol to provide a 3,5:4,6-protected derivative of gulonic acid. Oxidation affords the ester of xylo-hexulosonic acid. Hydrolysis yields 2-ketogulonic acid or ester or ascorbic acid.

In the process of the present invention, a 3,5:4,6-protected derivative of L-gulonic acid (II) is prepared from L-gulono-1,4-lactone (I). Oxidation yields the L-xylo-hexulosonate (III) which on hydrolysis affords 2-keto-L-gulonic acid or its ester (IV) or directly affords L-ascorbic acid. The complete synthetic scheme is represented as follows:—



(I) (II) (III) (IV)

wherein R_1 is alkyl of 1 to 6 carbon atoms and R_2 is alkyl having 1 to 6 carbon atoms, phenyl, monosubstituted or disubstituted phenyl wherein the substituents are alkyl having 1 to 6 carbon atoms, alkoxy having 1 to 6 carbon atoms, chloro, bromo, fluoro or nitro.

It is to be understood that the process of the present invention is also applicable for the preparation of intermediates for the synthesis of D-ascorbic acid starting with D-gulono-1,4-lactone in place of L-gulono-1,4-lactone. D-gulono-1,4-lactone can be prepared from D-xylose by the process described in Organic Synthesis IV, 506 (1963).

The first step in the present process is the formation of a 3,5:4,6-protected derivative of L- or D-gulonic acid. This may be effected by contacting the appropriate gulano-1,4-lactone with at least two equivalents of an alkyl or aryl aldehyde of the formula R_2CHO. The preferred alkyl aldehyde is acetaldehyde and the preferred aryl aldehyde is benzaldehyde. The reaction is conducted in the presence of at least one equivalent of an alcohol of the formula R_1OH. A modest excess of alcohol may be used with the excess considered a solvent or diluent. The preferred alcohols are methanol, ethanol, propanol or isopropanol. A catalytic amount of an acid having a pK_a less than 3 is added in an amount preferably between about 0.05 and 1.5 moles per mole of gulono-1,4-lactone. Suitable acid catalysts

include, but are not limited to, hydrochloric acid, hydrobromic acid, hydrofluoric acid, sulfuric acid, p-toluenesulfonic acid and sulfonic ion exchange resins. The reaction is conducted at 0—70°C, preferably 20—30°C until the reaction is substantially complete (1—20 hours). Alternatively, the gulono-1,4-lactone is contacted with at least two equivalents of an aldehyde dialkyl acetal of formula $R_2CH(OR_1)_2$ in the absence of an accompanying alcohol, but also in the presence of an acid having a pK_a less than 3 at a temperature of 0° to 70°C.

The second step in the present process is the oxidation of the unprotected hydroxy group at the 2-position of the protected lactone to keto. This may be effected by any method known in the art for the oxidation of secondary alcohols to ketones. A preferred oxidising agent is a sulfoxonium salt formed from a mixture of dimethyl sulfoxide and, for example, acetic anhydride or trifluoracetic anhydride in the presence of a base such as triethylamine. A useful cemical combination is potassium periodate and ruthenium dioxide in the presence of a base such as potassium carbonate. The oxidation is typically conducted in an organic solvent inert to oxidation conditions. Examples of suitable solvents include, but are not limited to, dimethyl formamide, pyridine, dimethyl sulfoxide, dichloromethane and acetone. It is not necessary that the intermediate be fully soluble in the organic medium. Temperatures suitable for the oxidation reaction will vary according to the type of oxidation employed. For example, in oxidation via sulfoxonium salts, the oxidation may be conducted at −60° to about 100°C depending on the method used to generate the sulfoxonium salts. The very low temperature is required only when trifluoracetic anhydride is used to generate the initial sulfoxonium salt. The reaction is preferably carried out at 0° to 50°C. Oxidation by potassium periodate and ruthenium dioxide is conducted at about −10°C to about 50°C preferably about 0°C to room temperature. Before proceeding to the next step of the process the oxidized intermediate is preferably separated from any excess oxidizing agent, for example, by filtration of solid catalyst residues or by extraction or recrystallisation of the product.

The oxidation process may also be accomplished by first contacting the di-*O*-alkylidene or arylidene-gulonate at about −20°C with acetic anhydride and nitric acid to form the 2- nitrato-gulonate. The isolated product in a solvent such as diethyl ether at 0—5°C is stirred for about 15 minutes following the addition of triethylamine. The resulting homogeneous solution following the addition of dichloromethane is further stirred at 0—5° and then worked up to yield the xylo-hexulosonate.

The final step in the process is the hydrolysis of the xylo-hexulsonate to the 2-ketogulonic acid or ester, under acid conditions at a temperature in the range of about 35° to 150°C. Temperatures of about 50° to 75°C are preferred. The choice of solvent-acid mixture is not critical with examples of useful mixtures as follows:

water-methanol, Amberlite (Registered Trade Mark) IR—120 sulfonic acid exchange resin,
isopropanol-water, catalytic amount of concentrated sulfuric acid.
acetonitrile-methanol, Dowex (Registered Trade Mark) 50—X8 sulfonic acid exchange resin,
water-acetic acid,
ethylene glycol-tetrahydrofuran, methanesulfonic acid.

The 2-ketogulonic acid ester can be hydrolysed to the free acid or it can be converted by further reaction to ascorbic acid. Alternatively, the alkyl 3,5:4,6-di-*O*-protected xylo-hexulsonate can be converted to ascorbic acid under acid catalysed hydrolysis conditions which are known to convert 2-ketogulonic acid, methyl 2-ketogulonate or diacetone-2-ketogulonic acid or ester to ascorbic acid.

The invention also includes the 2-nitrato derivatives of the compounds of the formula (II); also the D- isomers of these compounds.

Example I

Methyl 3,5:4,6-Di-*O*-benzylidene-L-gulonate

To 11.2 ml (113 mmol) of benzaldehyde and 2.3 ml (57 mmol) of methanol was added 5.04 g (28.3 mmol) of L-gulono-1,4-lactone followed by 1.12 ml (13.4 mmol) of concentrated hydrochloric acid. On stirring for 20 hours at room temperature the initially mobile slurry turned solid. The reaction mixture was triturated with ether and filtered. The solids were washed with ether, two times with water, and then ether After drying *in vacuo*, white solid weighed 6.2 g (16.1 mmol), 57% based on unrecovered gulonolactone, 82%), m.p. 177—180°. Recrystallisation from benzene-acetone afforded analytically pure material, m.p. 180—183°: $[\alpha]_D^{23}$ + 64.5° (DMF); i.r. (KBr) 3340, 1733 cm^{-1}: n.m.r. (DMSO-d_6) δ_H 3.65 (s, 3, —OCH_3), 3.86—4.53 (m, 6), 5.66 (s, 2, —OCHO—), 6.10 (d, 1, J = 5, —OH), 7.2—7.63 (m, 10, aromatic); ms 386 (1.9), 385 (5.2), 297 (13.1), 149 (25.9), 107 (40.6), 106 (21.7), 105 (100), 91 (57.8), 79 (26.5), 78 (10.7), 77 (38.9).

Analysis:

Calculated for	$C_{21}H_{22}O_7$:	C, 65.27; H, 5.74.
Found:		C, 65.22; H, 5.74.

Example II

The method of Example I may be repeated replacing benzaldehyde with each of the following aldehydes:

acetaldehyde	o-methylbenzaldehyde
propionaldehyde	m-methylbenzaldehyde
n-valeraldehyde	3,4-dichlorobenzaldehyde
n-hexaldehyde	o-methoxybenzaldehyde
o-nitrobenzaldehyde	o-chlorobenzaldehyde
o-fluorobenzaldehyde	o-butoxybenzaldehyde
m-bromobenzaldehyde	o-hexoxybenzaldehyde

Example III

Ethyl 3,5:4,6-Di-*O*-benzylidene-L-gulonate

To a 250 ml flask under nitrogen was added 10.1 g (56.7 mmol) of L-gulono-1,4-lactone, 44g (244 mmol) of benzaldehyde diethyl acetal, and 2.5 ml (30 mmol) of concentrated hydrochloric acid. The reaction was initially exothermic. After 2 hours the reaction was solid and this solid mixture stood at room temperature for 17 hours. The reaction was worked up by triturating with 100 ml of ether three times, water two times, and ether two times. After drying under vacuum, the resulting crystalline solid weighed 21.0 g (52.5 mmol, 92.6%) which was pure by t.l.c. This material was recrystallised from 500 ml of chloroform and 200 ml of diisopropyl ether. The first crop of crystals weiged 16.7 g (41.7 mmol, 74%) and the second crop of crystals weighed 2.3 g (5.7 mmol, 10%) m.p. 203—204°: $[\alpha]_D^{23}$ + 61.2° (DMF); i.r. (KBr) 3330, 1724 cm^{-1}: n.m.r. (DMSO-d_6) δ_H 1.13 (t, 3, J = 6.5, —CH_3), 4.07 (m, 8), 5.68 (s, 2, —OCHO—), 6.03 (d, 1, J = 5, —OH), 7.40 (s, 10, aromatic); n.m.r. (DMSO-d_6) δ_C 172.2 (l, s, —CO_2—), 138.4, 138.0 (2, s, aromatic), 128.6, 127.9, 126.0, 125.9, (6, —CH—, aromatic), 99.4, 99.1 (2, d, —OCHO—), 78.4, 69.83, 67.8 (4, each a d, —OCH—), 69.79 (1, t, —CH_2O—), 60.1 (1, t, —O*C*H_2CH_3), 14.2 (1, q, —CH_2); ms 400 (0.8), 297 (10.1), 149 (20.7), 107 (33.3), 106 (28.4), 105 (100), 91 (45.0), 81 (10.6), 79 (18.2), 77 (38.6), 51 (13.1), 44 (10.6), 43 (10.2).

Analysis:

Calculated for $C_{22}H_{24}O_7$: C, 66.06; H, 6.05

Found: C, 65.97; H, 6.03.

Example IV

The method of Example III may be repeated replacing benzaldehyde diethyl acetal with each of the following aldehyde dialkyl acetals:

acetaldehyde diethyl acetal

acetaldehyde dimethyl acetal

propionaldehyde dipropyl acetal

n-valeraldehyde dimethyl acetal

n-hexaldehyde dibutyl acetal

o-nitrobenzaldehyde dihexyl acetal

o-fluorobenzaldehyde diethyl acetal

o-bromobenzaldehyde diethyl acetal

o-methylbenzaldehyde dimethyl acetal

m-methylbenzaldehyde dipropyl acetal

3,4-dichlorobenzaldehyde diethyl acetal

o-chlorobenzaldehyde diethyl acetal

o-methoxybenzaldehyde diethyl acetal

o-chlorobenzaldehyde diethyl acetal

o-butoxybenzaldehyde dimethyl acetal

o-hexoxybenzaldehyde diethyl acetal

Example V

Ethyl 3,5:4,6-Di-*O*-benzylidene-L-gulonate from Benzaldehyde and Ethanol

To 11.2 ml (113 mmol) of benzaldehyde and 1.63 ml (28.3 mmol) of ethanol was added 5.04 g (28.3 mmol) of L-gulono-1,4-lactone followed by 1.12 ml (13.4 mmol) of concentrated hydrochloric acid. The reaction mixture was initially a mobile slurry which turned solid on stirring at room temperature for 20 hours. The reaction mixture was triturated with ether and then filtered. The solid was washed with ether and then two times with water. After drying, this white crystalline solid weighed 2.92 g (7.3 mmol, 26%). Based on unrecovered gulonolactone the yield was 47%. This material was identical with that prepared in Example III.

Example VI

Isopropyl 3,5:4,6-Di-*O*-benzylidene-L-gulonate

To a solution of 40.4 ml (0.40 ml) of benzaldehyde and 38.2 ml of ispropanol was added 8.9 g (0.050 mol) of L-gulono-4,4-lactone followed by 2.0 ml (0.024 mol) of concentrated hydrochloric acid. The reaction mixture was stirred at room temperature for 30 minutes at which time 0.10 g of seed crystals was added. This solution was stirred at room temperature for 72 hours. It was then triturated with ether, filtered, and the solids were washed three times with ether, three times with water, and two times with ether. After drying under vacuum, 7.67 g (18.5 mmol, 37%) of a white solid was recovered. The yield based on unrecovered L-gulano1,4-lactone was 49%. Analytically pure material was obtained by recrystallisation from ethyl acetate, m.p. 183—186°: i,r, (KBr) 3356, 1715 cm^{-1}: n.m.r. (DMSO-d_6) δ_H 1.07 and 1.15 (two d, 6, J = 7, —CH_3), 3.97—4.40 (m, 6), 4.97 (heptet, 1, J = 7, —OC*H*$(CH_3)_2$), 5.73 (s, 2, —OCHO—), 6.06 (m, 1, —OH), 7.47 (s, 10, aromatic); ms 414 (0.6), 413 (3.4), 297 (16.6), 149 (28.5), 107 (38.0), 106 (20.9), 105 (100), 91 (42.0), 77 (25.3), 44 (16.4), 43 (11.0).

Analysis:

Calculated for $C_{23}H_{26}O_7$: C, 66.65; H, 6.32

Found: C, 66.51; H, 6.25.

Example VII

Methyl 3,5:4,6-Di-*O*-ethylidene-L-gulonate

To 5.0 g (28.1 mmol) of L-gulono-1,4-lactone was added 12.2 ml (112.3 mmol) of acetaldehyde dimethyl acetal. Hydrogen chloride gas was bubbled through the heterogeneous solution. The reaction mixture gradually became homogeneous and was stirred at room temperature for 20 hours. The reaction mixture was concentrated and the resulting solid was triturated with ether affording 3.67 g (14.0 mmol, 50%) of material. In addition, the ether filtrate afforded 2.93 g (11.2 mmol, 40%) of solid which by t.l.c. was pure material. The triturated solid was recrystallised from chloroform and then ethyl acetate to afford analytically pure material, m.p. 137—140° (lit.* 144—145.5°): $[\alpha]_D^{27}$ + 20.5° (DMF); i.r. (KBr) 3436, 1748 cm^{-1}: n.m.r. (DMSO-d_6) δ_H 1.20 (d, 3, J = 5, —CH_3), 1.25 (d, 3, J = 5, —CH_3), 3.67 (s, 3, —OCH_3), 3.72—4.33 (m, 6), 4.77 (g, 2, J = 5, —C*H*CH_3), 5.22 (d, 1, J = 6, —OH); n.m.r. (DMSO-d_6) δ_C 172.7 (s, —CO_2—), 97.60 (d, —OCHO—), 97.55 (d, —OCHO—), 78.0, 69.1, 67.5, 67.0 (d, —CO—), 68.7 (t, —CH_2O—), 51.4 (q, —OCH_3), 20.9 (q, —CH_3), 20.7 (q, —CH_3); exact mass ($C_{11}H_{18}O_7$—H), 261.0988 (calculated 261.1002).

Analysis:

Calculated for $C_{11}H_{18}O_7$: C, 50.37; H, 6.91

Found: C, 50.63; H, 6.86

*A. A. D'Addieco, U.S. 2,847,421 (1958).

Example VIII

The methods of Examples I to VII may be repeated replacing L-gulono-1,4-lactone with D-gulono-1,4-lactone to obtain the corresponding D-gulonates.

Example IX

Ethyl 3,5:4,6-Di-*O*-benzylidene-L-xylo-hexulosonate

To a dry 250 ml 3-neck flask under nitrogen was added 30 ml of dry dichloromethane. To this was added at −60° 1.4 ml (10 mmol) of trifluoroacetic anhydride followed by 10 mmol (0.71 ml) of dry dimethylsulfoxide. This solution was stirred at −60° or lower for 30 minutes and then 2.00 g (5.0 mmol) of ethyl 3,5:4,6-di-*O*-benzylidene-L-gulonate in 30 ml of dry chloromethane was added over a 10 minute period while maintaining the temperature below −45°. The resulting solution was stirred at less than −60° for 30 minutes, then 2 ml (14.4 mmol) of triethylamine was added. After 20 minutes at less than −60°, the solution was allowed to warm to room temperature and stirred for 2.25 hours. An additional 40 ml of dichloromethane was added to the reaction mixture which was then extracted two times with 50 ml of 1N hydrochloric acid, two times with 50 ml of water, one time with 50 ml of brine and dried with sodium sulfate. Removal of the solvent *in vacuo* afforded 1.94 g (4.9 mmol, 98%) of an off-white solid which was one spot by t.l.c. Recrystallisation from benzene-acetone afforded analytically pure material, m.p. 192—194°. This material can also be recrystallised from chloroform-diisopropyl ether: $[\alpha]_D^{23}$ + 10.4° (DMF); i.r. (KBr) 1754, 1733 cm^{-1}: n.m.r. (DMSO-d_6) δ_H 1.27 (t, 3, J = 7, —CH_3), 4.27 (m, 5), 4.78 (m, 1), 5.53 (d, 1, J = 2, —COCHO), 5.72 (s, 1, —OCHO—), 5.88 (s, 1, —OCHO—), 7.40 (m, 10, aromatic); n.m.r. (DMSO-d_6) δ_C 188.0 (1, CO), 159.8 (1, —CO_2—), 137.8, 137.6 (2, C, aromatic), 128.9, 128.6, 128.0, 126.2, 125.7 (10, —CH, aromatic), 99.1, 98.6 (2, —OCHO—), 80.3, 69.8, 69.0, 68.8 (4), 62.2 (1, —OCH_2CH_3), 13.9 (1, —CH_3); ms 397 (0.1), 396 (0.6), 298 (13.8), 297 (69.8), 191 (14.9), 149 (10.6), 107 (36.7), 106 (23.1), 105 (94.8), 91 (100), 85 (41.5), 79 (28.4), 78 (10.0), 77 (39.7), 57 (10.4), 51 (11.5).

Analysis:

Calculated for $C_{22}H_{22}O_7$: C, 66.32; H, 5.56

Found: C, 66.29; H, 5.69.

Example X

Ethyl 3,5:4,6-Di-*O*-benzylidene-L-xylo-hexulosonate

To a dry 1-1 3-neck flask under nitrogen was added 100 ml of dry dichloromethane followed by 4.3 ml (4.73 g, 60.6 mmol) of dry dimethyl sulfoxide. This solution was cooled to −60° and 8.5 ml (60.0 mmol) of trifluoroacetic anhydride was added while maintaining the reaction temperature below −55°. After 30 minutes at −60° or less, 290 ml of dichloromethane containing 12.0 g (30.0 mmol) of ethyl 3,5:4,6-di-*O*-benzylidene-L-gulonate was added over a 45 minute period. The reaction temperature was kept below −50°. The reaction was stirred for an additional 30 minutes at −55° and then 12.6 ml (90 mmol) of triethylamine was added. After 30 minutes at −55°, the solution was stirred at room temperature for 2 hours. An additional 200 ml of dichloromethane was added and the reaction mixture was extracted two times with 300 ml of 1N hydrochloric acid, two times with 300 ml of water, and two times with 300 ml of brine. After drying the organic layer with sodium sulfate, the solvent was removed *in vacuo* affording 11.78 g (29.6 mmol, 98.7%) of a white solid which was identical with material prepared in Example IX.

This oxidation can also be carried out using dimethyl-sulfoxide and acetic anhydride.

Example XI

Ethyl 3,5:4,6-Di-*O*-benzylidene-L-xylo-hexulosonate

To a 35 ml flask was added 7 ml of dichloromethane and 0.40 g (1.0 mmol) of ethyl 3,5:4,6-di-*O*-benzylidene-L-gulonate followed by 33 mg (0.24 mmol) of potassium carbonate, 0.299 g (1.30 mmol) of potassium periodate, and 7 mg of ruthenium dioxide. After 6 hours, an additional 33 mg (0.24 mmol) of potassium carbonate, 0.299 g (1.30 mmol) of potassium periodate, and 7 mg of ruthenium dioxide was added. The reaction mixture was stirred for 18 hours and then diluted with dichloromethane, extracted two times with water, two times with brine, and dried with sodium sulfate. Concentration *in vacuo* afforded a white solid (0.328 g, 0.82 mmol, 82%) which was recrystallised from ethyl acetate. This afforded 0.188 g (0.47 mmol, 47%) of white needles, m.p. 195—198°. This material was identical with material prepared in Example IX.

Example XII

Isopropyl 3,5:4,6-Di-*O*-benzylidene-L-xylo-hexulosonate

To a dry 50 ml 3-neck flask under nitrogen was added 12 ml of dry dichloromethane and 0.85 ml (6 mmol) of trifluoroacetic anhydride. This solution was cooled to −60° and 0.43 ml (6 mmol) of dimethylsulfoxide was added. After stirring for 30 minutes, 17 ml of dichloromethane containing 1.24 g

(3.0 mmol) of isopropyl 3,5:4,6-di-*O*-benzylidene-L-gulonate was added to the reaction mixture while maintaining the temperature below −50°. After 30 minutes at −55° or lower, 1.26 ml (9 mmol) of triethylamine was added. The resulting solution was stirred at −55° for 45 minutes and then at room temperature for 2.5 hours. The reaction was worked up by adding dichloromethane and extracting two times with 1N hydrochloric acid, three times with water, and once with brine. After drying with sodium sulfate, the solvent was removed *in vacuo* affording 1.29 g (3.15 mmol, 104%) of a white solid. Recrystallisation from chloroform isopropyl ether afforded 0.649 g (1.58 mmol, 52.5%) of analytically pure white needles, m.p. 188—191°: (KBr) 1754, 1739 cm^{-1}: n.m.r. (DMSO-d_6) δ_H 1.23 and 1.30 (two d, 6, J = 6, —CH_3), 4.23 (m, 3), 4.73 (m, 1), 5.12 (heptet, 1, J = 6, —C*H*$(CH_3)_2$), 5.50 (d, 1, J = 3, —OCCHO—), 5.70 (s, 1, —OCHO—), 5.87 (s, 1 —OCHO—), 7.43 (m, 10, aromatic); ms 413 (0.1), 412 (0.3), 411 (1.7), 298 (16.4), 297 (76.9), 191 (20.1), 149 (19.7), 107 (61.0), 106 (20.9), 105 (86.4), 91 (100), 85 (35.9), 79 (17.2), 77 (18.5), 44 (10.1).

Analysis:

Calculated for	$C_{23}H_{24}O_7$:	C, 66.97; H, 5.86
Found:		C, 66.10; H, 5.79.

Example XIII

Ethyl 3,5:4,6-Di-*O*-benzylidene-2-nitrato-L-gulonate

To a 25 ml 3-neck flask containing 5 ml of acetic anhydride at −20° was added dropwise 2 ml of nitric acid. This solution was then warmed to −10° at which point an exothermic reaction took place causing the temperature to rise to 5°. After cooling to −10°, 4.4 ml of this solution was added with stirring to a solution of 1.16 g (2.90 mmol) of ethyl 3,5:4,6-di-*O*-benzylidene-L-gulonate in 30 ml of dry dichloromethane and 2 ml of acetic anhydride at −15°. After 25 minutes the reaction mixture was poured onto 200 ml of ice-water. After stirring for 30 minutes, the reaction mixture was extracted with dichloromethane which was washed with saturated sodium bicarbonate, brine, and then dried with sodium sulfate. The solvent was removed *in vacuo* affording 1.254 g (2.82 mmol, 97%) of a white solid. Recrystallisation from isopropyl alcohol afforded 0.81 g (1.82 mmol, 63%) of white crystals, m.p. 189—190°: $[\alpha]_D^{23}$ + 25.6° (DMF); i.r. (KBr) 3333, 1745, 1642, 1252 cm^{-1}: n.m.r. (DMSO-d_6) δ_H 1.1 (t, 3 J = 7, —CH_3), 2.97—4.77 (m, 8), 5.53 (d, 1, J = 8, —$HCONO_2$), 5.72 (s, 1, —OCHO—), 5.80 (s, 1, —OCHO—), 7.40 (s, 10, aromatic); ms 445 (4.2), 444 (54.4), 443 (98.1), 398 (26.8), 107 (12.4), 106 (34.4) 105 (100.0), 91 (43.2), 77 (56.5), 51 (13.3), 44 (59.2), 43 (11.3), 40 (32.4).

Analysis:

Calculated for	$C_{22}H_{23}O_9N$:	C, 59.32; H, 5.20; N 3.14
Found:		C, 59.59; H, 5.28; N, 2.99.

Example XIV

Ethyl 3,5:4,6-Di-*O*-benzylidene-2-nitrato-L-gulonate

To a 500 ml 3-neck flask was added 10.0 g (25 mmol) of ethyl 3,5:4,6-di-*O*-benzylidene-L-gulonate followed by 258 ml of dichloromethane. After cooling the resulting slurry to−15°, 17.2 ml of acetic anhydride was added. To a 100 ml 3-neck flask was added 27 ml of acetic anhydride. After cooling to 0°, 10.9 ml of 70% nitric acid was added dropwise maintaining the reaction temperature between −3° and 2°. The addition was complete in 45 minutes and the reaction mixture was allowed to warm to 7°. Under these conditions no exothermic reaction occurred. After cooling to less than 0°, this solution was added via a jacketed addition funnel cooled with methanol-ice to the acetic anhydride solution containing 3,5:4,6-di-*O*-benzylidene-L-gulonate. The reaction mixture was maintained at −10° to −15° during the addition. The white slurry gradually became homogeneous. After 30 minutes, the reaction mixture was poured onto 2 l of ice-water and mechanically stirred for 0.5 hours. This solution was extracted eight times with 100 ml of dichloromethane, then the combined organic layers were extracted two times with 300 ml of saturated sodium bicarbonate and 300 ml of brine. After drying with sodium sulfate, the solvent was removed *in vacuo* affording a white solid which was recrystallised from 800 ml of isopropanol. The first crop of crystals weighed 7.59 g (17.1 mmol, 68%), m.p. 186—188°. An additional 1.24 g of material was obtained by concentration of the mother liquor and crystallisation (2.80 mmol, 11%) for a total yield of 79%.

Example XV

Ethyl 3,5:4,6-Di-*O*-benzylidene-L-xylo-hexulosonate from Ethyl 3,5:4,6-Di-*O*-benzylidene-2-nitrato-L-gulonate

To 24 ml of diethyl ether containing 0.433 (0.97 mmol) of ethyl 3,5:4,6-di-*O*-benzylidene-2-

nitrato-L-gulonate at 0—5° was added 0.14 ml (1.0 mmol) of triethylamine. This heterogeneous solution was stirred for 15 minutes, then 20 ml of dichloromethane was added. The resulting homogeneous solution was stirred for 5 minutes at 0—5° and then worked up by adding 30 ml of dichloromethane and extracting with 25 ml of 1N hydrochloric acid two times, 25 ml of saturated sodium bicarbonate two times, 50 ml of brine, and finally drying with sodium sulfate. Removal of the solvent *in vacuo* afforded 0.374 g (0.94 mmol, 97%) of the desired ketone contaminated with residual starting material. Recrystallisation afforded material which was identical with that prepared in Example IX to XI.

Example XVI

The methods of Example IX to XV may be repeated replacing the L-gulonates with the D-gulonates to obtain the corresponding D-xylo-hexulosonates.

Example XVII

Ethyl 2-Keto-L-gulonate

To 15 ml of 70% acetic acid-water was added 1.19 g (3.0 mmol) of ethyl 3,5:4,6-di-*O*-benzylidene-L-*xylo*-hexulosonate. The resulting heterogeneous solution was heated at 70—75°. After 3 hours the solution was homogeneous and was heated for an additional hour. The solvent was removed *in vacuo* affording a white foam, 0.574 g (2.59 mmol, 86%). This material was identical by t.l.c., h.p.l.c., i.r., ^{1}H-n.m.r. and ^{13}C-n.m.r. with an authentic sample of ethyl 2-keto-L-gulonate prepared according to the method of Drefahl and Gross.*

This hydrolysis has also been carried out using: water-methanol, Amberlite IR—120 sulfonic acid cation exchange resin

isopropanol-water, catalytic amount of concentrated sulfuric acid

acetonitrile-methanol, Dowex 50—XB sulfonic acid cation exchange resin

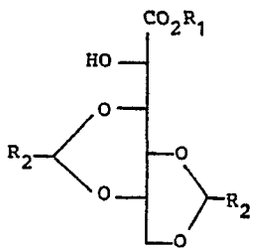
ethylene glycol-tetrahydrofuran, methanesulfonic acid; under these conditions ethyl 2-keto-L-gulonate was initially produced but on standing with the residual quantities of ethylene glycol and methanesulfonic acid this was converted to ascorbic acid

Example XVIII

The method of Example XVII may be repeated replacing 3,5:4,6-di-*O*-benzylidene-L-xylo-hexulosonate with the corresponding D-xylo-hexulosonate to obtain ethyl 2-keto-D-gulonate.

Claims

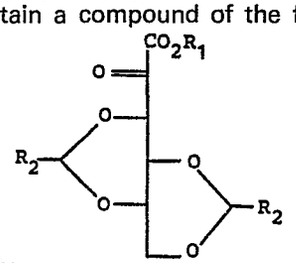
1. A process for preparing a 3,5:4,6-protected derivative of L- or D- gulonic acid chacterised by: contacting L-gulono-L-1,4-lactone or the D-isomer thereof with either at least two equivalents of an aldehyde dialkyl acetal of the formula $R_2CH(OR_1)_2$, or, at least two equivalents of an aldehyde of the formula R_2CHO and at least one equivalent of an alcohol of the formula R_1OH, in the presence of an acid having a pk_a less than 3 at a temperature of from 0° to 70°C to obtain a compound of the formula:



or the D-isomer thereof, respectively,

wherein R_1 is alkyl having 1 to 6 carbon atoms and R_2 is alkyl having 1 to 6 carbon atoms, phenyl or monosubstituted or disubstituted phenyl wherein said substituents are alkyl having 1 to 6 carbon atoms, alkoxy having 1 to 6 carbon atoms, chlorine, bromine, fluorine or nitro.

2. A process for preparing 2-keto-L- or D-gulonic acid or ester thereof, characterised by (a) oxidizing the product which has been prepared by the process of claim 1 with an agent which oxidizes secondary alcohols to ketones to obtain a compound of the formula:



or the D- isomer thereof, respectively,

*G. Drefahl and B. Gross, J. Prakt. Chem., *1*, 153 (1955).

and
(b) hydrolyzing the compound formed in step (a) under acid conditions at a temperature of from 35° to 150° to obtain 2-keto-L-gulonic acid or ester, or the D- isomer thereof, respectively.

3. A process as claimed in claim 2 wherein the hydrolysis in step (b) is carried out with either (i) a mixture of water and methanol in the presence of a sulfonic acid cation exchange resin, (ii) a mixture of isopropanol and water in the presence of a catalytic amount of concentrated sulfuric acid, (iii) a mixture of acetonitrile and methanol in the presence of a sulfonic acid cation exchange resin, (iv) a mixture of acetic acid and water, or (v) a mixture of ethylene glycol and tetrahydrofuran in the presence of methanesulfonic acid.

4. A process for preparing L- or D- ascorbic acid characterised in that 2-keto-L-gulonic acid or ester or D-isomer thereof which has been prepared by the process of claim 2 or 3 is converted by acid catalysed hydrolysis to L- or D- ascorbic acid, respectively.

5. A process as claimed in any one of claims 2 to 4 wherein the oxidizing agent in step (a) is a sulfoxonium salt.

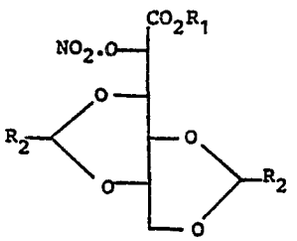
6. A process as claimed in any one of claims 2 to 4 wherein the oxidizing agent in step (a) is nitric acid.

7. A process as claimed in any one of the preceding claims wherein said acid of pKa less than 3 is present in an amount of from 0.05 to 1.5 moles per mole of gulono-1,4-lactone.

8. A process as claimed in any one of the preceding claims wherein said acid of pKa less than 3 is concentrated hydrochloric acid.

9. A process as claimed in any one of the preceding claims wherein R_1 is methyl, ethyl or isopropyl and R_2 is phenyl or methyl.

10. A compound of the formula:



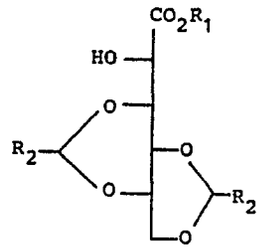
wherein R_1 and R_2 are as defined in claim 1; or the D- isomer thereof.

11. Ethyl 3,5:4,6-di-*O*-benzylidene-2-nitrato-L-gulonate.

Revendications

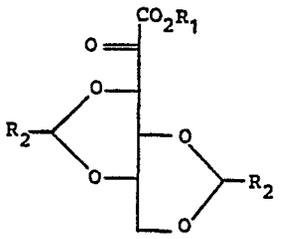
1. Procédé de production d'un dérivé protégé en 3,5:4,6 d'acide L- ou D-gulonique, caractérisé en ce qu'il consiste:

à faire entrer la L-gulono-4,4-lactone ou son isomère D en contact avec au moins deux équivalents d'un dialkylacétal d'aldéhyde de formule $R_2CH(OR_1)_2$ ou au moins deux équivalents d'un aldéhyde de formule R_2CHO et au moins un équivalent d'un alcool de formule R_1OH, en présence d'un acide de pK_a inférieur à 3 à une température de 0 à 70°C pour obtenir un composé de formule:



ou, respectivement, son isomère D,
formule dans laquelle R_1 est un groupe alkyle ayant 1 à 6 atomes de carbone et R_2 est un groupe alkyle ayant 1 à 6 atomes de carbone, phényle ou phényle monosubstitué ou disubstitué dont les substituants sont des radicaux alkyle ayant 1 à 6 atomes de carbone, alkoxy ayant 1 à 6 atomes de carbone, le chlore, le brome, le fluor ou le groupe nitro.

2. Procédé de production d'acide 2-céto-L- ou D-gulonique ou d'un ester de cet acide, caractérisé en ce qu'il consiste (a) à oxyder le produit qui a été préparé par le procédé suivant la revendication 1 avec un agent qui oxyde des alcools secondaires en cétones pour obtenir un composé de formule:



ou, respectivement son isomère D, et
(b) à hydrolyser le composé formé dans l'étape (a) dans des conditions acides à une température de 35 à 150° pour obtenir l'acide 2-céto-L-gulonique ou son ester ou, respectivement, son isomère D.

3. Procédé suivant la revendication 2, caractérisé en ce que l'hydrolyse dans l'étape (b) est conduite avec (1) un mélange d'eau et de méthanol en présence d'une résine d'échange cationique du type acide sulfonique, (2) un mélange d'isopropanol et d'eau en présence d'une quantité catalytique d'acide sulfurique concentré, (3) un mélange d'acétonitrile et de méthanol en présence d'une résine d'échange cationique du type acide sulfonique, (4) un mélange d'acide acétique de d'eau ou (5) un mélange d'éthylène-glycol et de tétrahydrofuranne en présence d'acide méthanesulfonique.

4. Procédé de production d'acide L- ou D-ascorbique, caractérisé en ce qu'il consiste à transformer de l'acide 2-céto-L-gulonique ou un ester de cet acide ou son isomère D qui a été préparé par le procédé suivant la revendication 2 ou 3, par hydrolyse catalysée par un acide, en acide L- ou, respectivement, D-ascorbique.

5. Procédé suivant l'une quelconque des revendications 2 à 4, caractérisé en ce que l'agent oxydant dans l'étape (a) est un sel de sulfoxonium.

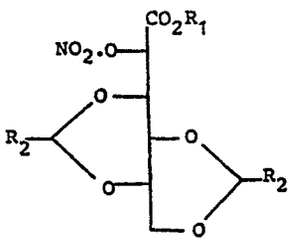
6. Procédé suivant l'une quelconque des revendications 2 à 4, caractérisé en ce que l'agent oxydant dans l'étape (a) est l'acide nitrique.

7. Procédé suivant l'une quelconque des revendications précédentes, caractérisé en ce que l'acide de pK_a inférieur à 3 est présent en une quantité de 0,05 à 1,5 mole par mole de gulono-1,4-lactone.

8. Procédé suivant l'une quelconque des revendications précédentes, caractérisé en ce que l'acide de pK_a inférieur à 3 est l'acide chlorhydrique concentré.

9. Procédé suivant l'une quelconque des revendications précédentes, caractérisé en ce que R_1 est le groupe méthyle, éthyle ou isopropyle et R_2 est le groupe phényle ou méthyle.

10. Un composé de formule:

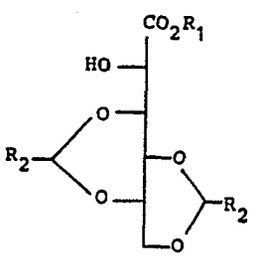


dans laquelle R_1 et R_2 ont les définitions données dans la revendication 1;
ou son isomère D.

11. Le 3,5:4,6-di-O-benzylidene-2-nitrato-L-gulonate d'éthyle.

Patentansprüche

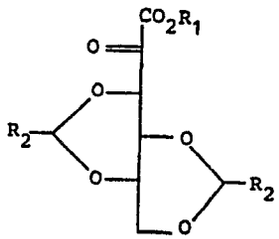
1. Verfahren zur Herstellung eines 3,5:4,6-geschützten Derivats der L- oder D-Gulonsäure, dadurch gekennzeichnet, daß L-Gulono-1,4-lacton oder dessen D-Isomeres entweder mit wenigstens 2 Äquivalenten eines Aldehyd-dialkylacetals der Formel $R_2CH(OR_1)_2$ oder wenigstens zwei Äquivalenten eines Aldehyds der Formel R_2CHO und wenigstens 1 Aquivalent eines Alkohols der Formel R_1OH in Gegenwart einer Säure mit einem pK_a-Wert unter 3 bei einer Temperatur von 0—70°C zusammengebracht werden, um eine Verbindung der Formel



bzw. deren D-Isomerem,

worin R_1 Alkyl mit 1 bis 6 Kohlenstoffatomen und R_2 Alkyl mit 1 bis 6 Kohlenstoffatomen, Phenyl oder monosubstituiertes oder disubstituiertes Phenyl ist, wobei die Substituenten Alkyl mit 1 bis 6 Kohlenstoffatomen, Alkoxy mit 1 bis 6 Kohlenstoffatomen, Chlor, Brom, Fluor oder Nitro sind, zu ergeben.

2. Verfahren zur Herstellung von 2-Keto-L- oder D-gulonsäure oder deren Ester, dadurch gekennzeichnet, daß a) das nach dem Verfahren gemäß Anspruch 1 hergestellte Produkt mit einem Mittel, das sekundäre Alkohole zu Ketonen oxidiert, zu einer Verbindung der Formel



bzw. deren D-Isomerem

oxidiert

und b) die in Stufe a) gebildete Verbindung unter sauren Bedingungen bei einer Temperatur von 35 bis 150°C zu 2-Keto-L-gulonsäure oder -ester bzw. deren D-Isomerem hydrolysiert wird.

3. Verfahren nach Anspruch 2, dadurch gekennzeichnet, daß die Hydrolyse in Stufe b) entweder mit (i) einem Gemisch aus Wasser und Methanol in Gegenwart eines Sulfonsäure-Kationenaustauscherharzes, (ii) einem Gemisch aus isopropanol und Wasser in Gegenwert einer katalytischen Menge konzentrierter Schwefelsäure, (iii) einem Gemisch aus Acetonitril und Methanol in Gegenwart eines Sulfonsäure-Kationenaustauscherharzes, (iv) einem Gemisch aus Essigsäure und Wasser oder (v) einem Gemisch aus Äthylenglykol und Tetrahydrofuran in Gegenwart von Methansulfonsäure durchgeführt wird.

4. Verfahren zur Herstellung von L- oder D-Ascorbinsäure, dadurch gekennzeichnet, daß 2-Keto-L-gulonsäure oder deren Ester oder D-Isomer, hergestellt nach dem Verfahren gemäß Anspruch 2 oder 3, durch säurekatalysierte Hydrolyse in L- oder D-Abscorbinsäure überführt wird.

5. Verfahren nach einem der Ansprüche 2 bis 4, dadurch gekennzeichnet, daß in Stufe a) als Oxidationsmittel ein Sulfoxoniumsalz verwendet wird.

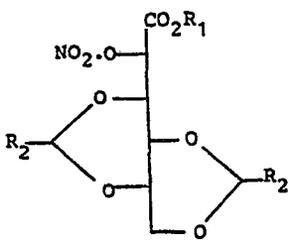
6. Verfahren nach einem der Ansprüche 2 bis 4, dadurch gekennzeichnet, daß in Stufe a) als Oxidationsmittel Salpetersäure verwendet wird.

7. Verfahren nach einem der vorhergehenden Ansprüche, dadurch gekennzeichnet, daß es mit einer Menge der Säure mit einem pK_a-Wert unter 3 von 0,05 bis 1,5 Mol/Mol Gulono-1,4-lacton durchgeführt wird.

8. Verfahren nach einem der vorhergehenden Ansprüche, dadurch gekennzeichnet, daß als Säure mit einem pK_a unter 3 konzentrierte Salzsäure verwendet wird.

9. Verfahren nach einem der vorhergehenden Ansprüche, dadurch gekennzeichnet, daß es für R_1 in der Bedeutung Methyl, Äthyl oder Isopropyl und für R_2 in der Bedeutung Phenyl oder Methyl durchgeführt wird.

10. Verbindung der Formel



worin R_1 und R_2 wie in Anspruch 1 definiert sind, oder deren D-Isomer.

11. Äthyl-3,5:4,6-di-O-benzyliden-2-nitrato-L-gulonat.