Stereospecificity of a New Reaction of L-Ascorbic Acid with Cis and Trans Olefinic 1,4-Dicarbonyl Compounds

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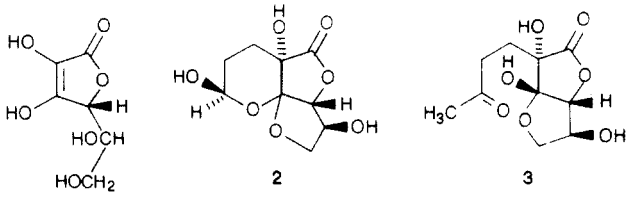
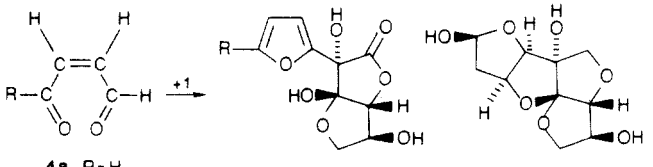
The Michael-type addition of the ascorbate carbanion upon α,β-unsaturated carbonyl compounds is compared with the aldol-like addition of the same carbanion to the related 1,4-dioxo olefins. In contrast to the behavior of maleic aldehyde and 3-acetylacrolein that leads to **4**, the primary aldol adduct of **1** to fumaric aldehyde is stabilized by internal Michael addition as a tetracyclic lactone–cycloketal hemiacetal (**6**). This structure is based on ^{13}C NMR, ^{1}H NMR, and ultimately X-ray crystallographic work.

L-Ascorbic acid (**1**) was found recently[1,2] to react as a Michael-type carbanion donor with α,β-unsaturated aldehydes and ketones, e.g., acrolein,[1,2] methylacrolein,[3] crotonic aldehyde,[3] and methyl vinyl ketone.[1,2] The way of stabilization of the primary adduct depended on whether an aldehyde or ketone was involved, leading to either **2** or **3**. In contrast, **1** reacted with 1,4-dicarbonyl



1 **2** **3**

2,3-ethenes primarily in an aldol-type reaction[4a] on the carbonyl carbon: e.g., with malealdehyde (**4a**) and 4-keto-*cis*-2-pentenal (*cis*-3-acetylacrolein) (**4b**). Those adducts gave rise to 2-furyl-3-ketogulonolactone (**5**) by elimination irrespective of whether the free dicarbonyl compounds or their cyclic acetals (ketals) were used.[4b] While



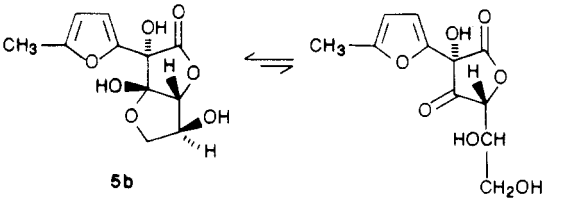
4a, R = H
b, R = CH_3 **5** **6**

the Michael products[1,2] were crystalline, the furylketogulonolactones withstood attempts to be crystallized. Finally, 2-(5-methyl-2-furyl)-3-keto-L-gulonolactone 3,6-hemiketal (**5b**) gave unusual crystalline molecular complexes[4a,b] with succinic anhydride, succinimide, and *N*-methylsuccinimide via H bonds. The succinic anhydride derivative formed single crystals, and its three-dimensional structure was established.[4b]

Results

Now we found that by decomposing the succinic anhydride complex of **5b** with water the crystalline furyl-3-ketogulonolactone could be obtained. The IR spectrum of **5b** in a KBr pellet shows the lactone carbonyl at 1780 cm^{-1} but no trace of a keto carbonyl band that would indicate even a trace of the 3,6-unbridged tautomer (Scheme I). However, the IR spectrum (methanol) shows a strong shoulder around 1710 cm^{-1}. Furthermore, in the ^{13}C NMR spectrum of **5b** (Me_2SO-d_6) a weak signal appeared at 204.09 ppm. This same resonance was present in amorphous **5b** and prompted us[4b] to assume tautomerism according to Scheme I. Both the IR and ^{13}C NMR spectra of the molecular complexes of **5b** where C-3 hydroxyl is hydrogen-bonded show complete absence of that carbonyl group, as expected. Thus, crystalline **5b** is entirely present as a cycloketal, while in solution there is evidence for a minor contribution by its tautomer.[4b]

Scheme I



5b

As the main objective, we planned to undertake a systematic study of the steric factors that are involved in the aldol type of ascorbic acid reaction. For the first approach we compared the behavior of ascorbic acid toward fumaraldehyde vs. malealdehyde. Next the influence of the chiral carbons of ascorbic acid upon the course of the reaction had to be established.

The reaction product from **1** and fumaraldehyde (**7**) was crystalline. We already indicated[4b] its molecular formula $C_{10}H_{12}O_8$, which is consistent with an addition and not with an elimination reaction that occurs with *cis*-olefins. There is a sharp band at 1780 cm^{-1} in the IR spectrum for the (saturated) lactone, a weak doublet at 2950 cm^{-1} for a C–H stretch, and a broad band (3600–3100 cm^{-1}) indicating the hydroxyl groups. The ^{1}H NMR spectrum (Me_2SO-d_6) shows a signal at δ 6.70, which is exchangeable by deuterium. A signal appears at δ 5.54 (t, 1 H) in the region where hemiacetal protons resonate, obviously next to a methylene group which appears as a multiplet at δ 2.4–1.6. The multiplet at δ 5.02 (1 H) is assigned to the proton at C-2′ whereas the proton at C-1′ appears as a doublet at δ 4.37. The rest of the signals show a similar pattern for ascorbic acid protons as in the furylketogulonolactone spectrum.[4b] Also, the chemical shifts do not show any olefinic proton unlike the aldol products.

The ^{13}C NMR spectrum is indicative of a lactone carbonyl (172.1 ppm), a ketal carbon (118.0 ppm), a hemi-

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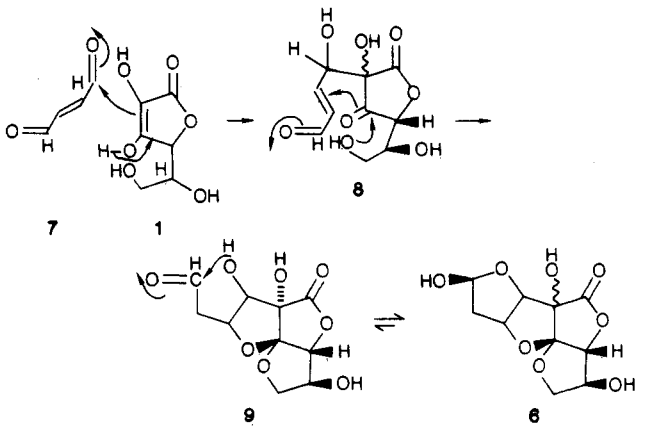
Scheme II



acetal carbon (99.7 ppm), one carbon that is bonded to a tertiary hydroxyl group (88.6 ppm), and a methylene carbon (40.6 ppm). In addition five more secondary (or primary) carbons linked to hydroxyls resonate in the range of 73–87 ppm. All these ^{13}C shifts are reminiscent of those of the Michael adduct (**2**) of ascorbic acid to acrolein;[2] some of them are quite different[4b] from those of the furan derivatives **5**. One could have speculated that fumaraldehyde reacted either as a Michael acceptor (unlike malealdehyde) or that an aldol-type addition occurred first, which was then followed by an internal Michael reaction. The absence of a free carbonyl (except the lactone) group was certainly indicative of one or more saturated, hemiacetal–ketal type structural elements. The mass spectrum shows the parent peak at *m/e* 260, which is also indicative of the addition product. The final decision was reached by X-ray crystallography.[5] Experimental details of this work are given in the present paper.

Discussion

The X-ray study proves structure **6** of 2-(1′,2′-dihydroxy-4′-oxobutyl)-3-keto-2′,3-anhydro-L-gulonolactone 1′,4′-cyclohemiacetal 3,6-cyclohemiketal. The absolute configuration is 2*S*,3*R*,4*R*,5*S*,1′*R*,2′*S*,4′*R*. The reaction mechanism logically follows from that structure. The first step is an acid-catalyzed addition of the ascorbate carbanion (**1**) to the carbonyl of fumaraldehyde (**7**) to form **8**, mechanistically the same way as the addition to acetylacrolein (**4b**). This is followed by a Michael addition of the C-3 oxygen upon the β-carbon of the α,β-unsaturated hydroxybutenal moiety which is attached to C-2 in **8**. Synchronous hemiketal ring closure between C-6 hydroxyl and C-3 of the ascorbate skeleton to lead to **9** is most likely (Scheme II). Finally, hemiacetal formation between the two, originally terminal, carbons of the fumaraldehyde moiety concludes the process to give **6**.

The second stereochemical problem of the new aldol-type reaction is the impact of chirality of the ascorbic acid carbons 4 and 5. Preliminary experiments showed that if C-5 has the D-glyceraldehyde configuration as in "D-isoascorbic acid" the course of the reaction is unaffected. Interestingly the immunopotentiating effect of the product is even more favorable according to Dr. R. Veltri[6] than that of **5b** while **6** shows no significant biological activity. Further studies involving synthesis of the antipode of **5b** and of its C-4 epimer are in progress.

Experimental Section

Melting points were determined on a Melt-Temp apparatus and are uncorrected. IR spectra were recorded on the Beckman IR-8 and Beckman IR-10 spectrophotometers. ^{13}C NMR spectra were taken on a Varian CFT-20 spectrometer at 20 MHz. ^1H NMR spectra were recorded on a Varian EM-360 (60 MHz) spectrometer. Mass spectra were obtained on a Finnigan 4021 mass spectrometer with an INCOS data system. Elemental analyses were performed by Galbraith Laboratories, Inc., Knoxville, TN. Optical rotations were measured on a Perkin-Elmer Model 141 Polarimeter. Fumaraldehyde was prepared as described by Alder, Betzing, and Heimbach.[7] L-Ascorbic acid USP (Mallinckrodt) was used as purchased.

2-(5-Methyl-2-furyl)-3-keto-L-gulonolactone 3,6-Hemiketal (5b). Colorless succinic anhydride molecular complex[4b] of **5b** (84.8 g) was suspended in water (200 mL) under nitrogen atmosphere for 3 h. The resulting pale yellow solution was frozen and freeze-dried on a Virtis Freezemobile 24 at 10–50 mtorr for 24 h. The solid residue was powdered, and ice-cold ethyl acetate (200 mL) was added. The slurry was filtered by suction and washed with 2 × 10 mL of cold ethyl acetate. The colorless solid (15.42 g, 95%) was identified as succinic acid, mp 185–186 °C.

The yellow ethyl acetate extract was shaken with decolorizing carbon (Norit) (3 × 5 g), filtered, and evaporated to partial dryness. The residue was treated with methylene chloride (3 × 150 mL), and upon removal of the solvent, a colorless solid (57.85 g, 82%) was obtained.

The solid (10 g) was recrystallized in hot chloroform (300 mL) to give long white needles (7.63 g): mp 89 °C, $[\alpha]^{20}_D$ +62.5° (*c* 1.025, ethyl acetate). Anal. Calcd for $C_{11}H_{12}O_7$: C, 51.57; H, 4.72; O, 43.71. Found: C, 51.38; H, 4.75; O, 43.69. IR (KBr) 3700–3000 (br, OH), 2970 (aliphatic CH), 1790 (lactone C=O), 1615 and 1550 cm^{-1} (furan C=C); ^1H NMR (acetone-d_6) δ 6.53 (d, 1 H), 6.17 (d, 1 H), 4.83 (s, 1 H), 4.60 (m, 1 H), 4.25 (m, 1 H), 2.25 (s, 3 H); ^{13}C NMR (Me_2SO-d_6) 173.06, 151.76, 148.38, 109.22, 107.04, 106.50, 87.53, 77.63, 74.70, 73.59, 13.18 ppm; mass spectrum; *m/e* 256, 239, 228, 155, 138, 109 (base peak), 95, 85, 71, 53.

Preparation of Fumaraldehyde–L-Ascorbic Acid Adduct 6. Fumaraldehyde[7] (16.8 g, 0.2 mol) and L-ascorbic acid (32.0 g, 0.18 mol) were suspended in 172 mL of freshly distilled tetrahydrofuran under nitrogen atmosphere in a 500-mL flask. The reaction mixture was stirred at room temperature for 5 days. The solid residue was filtered by suction and washed with 20 mL of THF. The filtrate was evaporated to dryness on a rotary evaporator to give 45.2 g (96.5%) of the crude product. The solid was dissolved in 188 mL of hot methanol and 47 mL of ethyl acetate was added until turbidity appeared. Upon cooling, white needles of the pure product separated: 25.0 g (53.3%); mp 168–170 °C; $[\alpha]^{25}_D$ −66.7° (*c* 1.088, methanol). Anal. Calcd. for $C_{10}H_{12}O_8$: C, 46.16; H, 4.64; O, 49.19. Found: C, 46.39; H, 4.51; O, 49.32. IR (KBr) 3600–3100 (s, br, OH), 1780 cm^{-1} (s, lactone CO); ^1H NMR (Me_2SO-d_6) δ 6.70 (HDO), 5.54 (t, 1 H), 5.02 (m, 1 H), 4.37 (d, 1 H), 4.30 (s, 1 H), 4.10 (m, 1 H), 3.83 (d, 2 H), 2.40–1.60 (m, 2 H); ^{13}C NMR (Me_2SO-d_6) 172.1, 118.0, 99.7, 88.6, 86.9, 85.0, 82.1, 73.7, 72.7, 40.6 ppm; mass spectrum, *m/e* 260, 243, 200, 158, 119, 97, 85 (base peak), 71.

X-ray Crystallography for 6. Compound **6** showed the following: $C_{10}H_{12}O_8$, monoclinic, space group $P2_1$, a = 6.142 (2) Å, b = 10.167 (2) Å, c = 18.369 (3) Å, β = 106.68 (2)°, Z = 4, d_{calcd} = 1.57 g cm^{-3}, μ = 11.6 cm^{-1}.

3410 independent reflections were measured out to $2\theta_{max}$ = 116° with a Nicolet R3 automatic diffractometer using Cu Kα radiation (λ = 1.54178 Å) with a graphite monochromator on the incident beam. Data were collected using the $\theta/2\theta$ scan technique with a variable scan rate related to the intensity of a reflection. The structure, which contained two molecules in the asymmetric unit, was solved by direct methods.[8,9] Full-matrix least-squares re-

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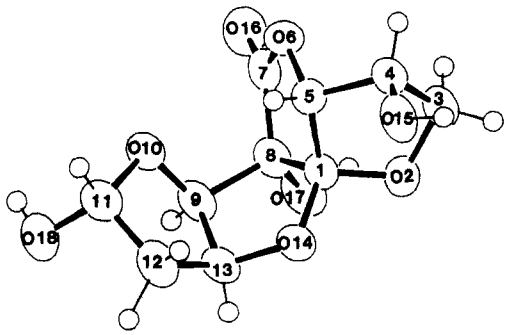

Figure 1. Diagram of **6** as determined by X-ray diffraction. The X-ray numbering scheme is also shown. Atoms in the second molecule in the asymmetric unit were numbered by adding 30 to the number of the equivalent atom shown here.

finement on 422 parameters (coordinates for all atoms, anisotropic thermal parameters for non-hydrogen atoms, and isotropic thermal parameters for the hydrogen atoms) using the 3157 reflections for which $|F_o| > 3\sigma|F_o|$ gave a final R factor of 4.3% (R_w = 6.4%). The absolute configuration of the molecule was determined from the anomalous scattering of the oxygen atoms. The goodness of fit parameter was 2.6, and the final difference map was featureless. All calculations were done using the SHELXTL system of computer programs.[10] Table I (supplementary material) lists the fractional coordinates and equivalent isotropic thermal parameters for the C and O atoms. Hydrogen coordinates and bond lengths and angles for **6** have been deposited with the Crystallographic Data Centre, Cambridge University Chemical Laboratory, Cambridge CB2 1EW, England. Anisotropic thermal parameters and a comparison of observed and calculated structure factors are available from us.

Discussion

The results of the X-ray study on **6** are illustrated in Figure 1, drawn by computer program ORTEP[11] using experimentally determined coordinates. Bond lengths and angles agree well within the two molecules in the asymmetric unit and do not indicate that any unusual characteristics or strains in the molecule caused by ring fusions. All of the five-membered rings have a flattened envelope conformation, and both molecules in the asymmetric unit have the same overall configuration. However, the two molecules do have different out of plane atoms in rings A and B. In molecule **6a**, O-10 and C-8 are the out of plane atoms in rings A and B, respectively, while in molecule **6b**, C-9 is the out of plane atom in both rings. Molecule **6a** is shown in Figure 1. This type of difference is not unusual in five-membered rings and is probably due to differences in the intermolecular environments of the two molecules. The crystal packing is influenced by hydrogen bonding. There are three possible donor hydrogens on each molecule, and they participate in a total of seven hydrogen bonds (see Table 2, supplementary material). In molecule **6a**, O-18 is the donor in a bifurcated hydrogen bond in which O-2 and O-17 of a symmetry related molecule share the role of the acceptor. The only other intermolecular approach less than van der Waals separations is O-46···O-43 at 3.13 Å.

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Registry No. **5b**, 93135-89-8; **6**, 102977-48-0; L-ascorbic acid, 50-81-7; fumaraldehyde, 3675-14-7; succinic anhydride, 108-30-5.

Supplementary Material Available: Tables of X-ray data (coordinates and bonding) for **6** (4 pages). Ordering information is given on any current masthead page.

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Organoboranes. 46. New Procedures for the Homologation of Boronic Esters: A Critical Examination of the Available Procedures To Achieve Convenient Homologation of Boronic Esters

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Two practical and more convenient procedures have been developed to achieve the one-carbon homologation of boronic esters: (1) in situ preparation of $LiCHCl_2$ by treatment of a mixture of methylene chloride and boronic ester with *sec*-butyllithium at −78 °C, followed by in situ reduction of the intermediate with potassium triisopropoxyborohydride, and (2) in situ preparation of (chloromethyl)lithium ($LiCH_2Cl$) by treatment of a mixture of bromochloromethane and boronic ester with *n*-butyllithium at −78 °C. These methods were compared with the previously known procedures: (3) treatment of the boronic ester with preformed $LiCHCl_2$ at −100 °C, followed by the in situ reduction of the intermediate with potassium triisopropoxyborohydride, (4) in situ preparation of $LiCHCl_2$ by treatment of a mixture of methylene chloride and boronic ester with lithium diisopropylamide (LDA) at 0 °C, followed by the reduction of the intermediate with KIPBH, and (5) in situ preparation of $LiCH_2Cl$ by treatment of a mixture of chloroiodomethane and boronic ester with *n*-butyllithium at −78 °C. A critical comparison of these procedures for the homologation of 2-(1-hexyl)- and 2-(3-hexyl)-1,3-dioxaborinane has led to the conclusion that the preferred procedures on the basis of convenience and economy are 2, followed by 4. These two preferred procedures are general, as shown by their applicability to the homologation of 11 different boronic esters.

The homologation of boronic esters[2] is assuming major importance in our efforts to develop a general synthesis of enantiomerically pure compounds via chiral hydroboration[3] (eq 1).

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