Synthesis of Allyl Ether Derivatives of L-Ascorbic Acid

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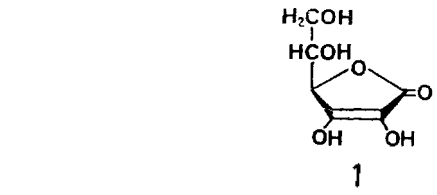
The biochemical activity of *L*-ascorbic acid (vitamin C) **(1)** has led to the synthesis of numerous analogs and derivatives of this compound. From a different viewpoint, **1** has been considered a useful synthetic precursor to many molecules of potential biological utility account of its inherent, varied chemical functionality. Thus, *L*-threonolactone[1] and 3-hexulose[2] have been prepared from **1**. Also, Jung *et al.*[3] have succeeded in transforming **1** into (−)-γ-amino-β-hydroxybutyric acid, and Brimacombe *et al.*[4] have attempted to synthesize spirolactones from **1**. The first step for the transformation of **1** into these biologically important molecules is usually the protection of 5,6-diol or of 2,3-endiol. Although two hydroxy groups at C-5 and C-6 can be easily protected with various hydroxy protecting groups, the methods for the protection of 2,3-endiol are scarce and are not always efficient. The most widely used protecting group for endiol of **1** has been methyl ether. However, the deprotection of the methyl ether is relatively difficult. Recntly, synthesis of 2,3,5,6-tertrakis (trimethylsilyl)-L-ascorbic acid has been reported[5], but trimethylsilyl group is stable under very limited conditions.

As part of a program directed toward the transformaton of **1** into complex carbohydrates, we report the synthesis of 2,3-diallyl ether derivatives of L-ascorbic acid. Allyl ether is very stable under various conditions and can be deprotected under mild conditions. Another purpose of the present study is to know which position of compound **1** can be allylated. Although O-allylation is expected to occur at O-3 of **1** on the basis of different acidities of the hydroxy grpuos on C-2 and C-3, the 2-O-derivatives of **1** have often called 3-O-derivatives in early studies.[6,7] Since ascorbate anion has ambident nucleophilic character and on the basis of canonical structures, I, II, and III shown in Figure 1, C-allylation of **1** is also expected.

Allylation of L-ascorbic acid using 2.1 molar equivalents of sodium hydride and 2.1 equivalents of allyl bromide in N,N-dimethylformamide afforded 2,3-di-O-allyl-L-ascorbic acid **(2a)** as a major product in 63% yield.[8] Since compound **2a** could not be obtained completely pure, **2a** was transformed into 5.6-di-O-acetyl-2,3-di-O-allyl-L-ascorbic acid **(2b)**[9] for the purpose of identification. The spectral and analytical data[9] of compound **2b** were consistent with the assinged structure. When one molar equivalent of sodium hydride and allyl bromide were used, compound **2a** was again one major product and negligible amounts of minor products were detected. Change of solvents or bases resulted in poor yields of compound **2a** but did not afford other products. Allylation of 5,6-O-isopropylidene-L-ascorbic acid **(3a)**[10] was also carried out under the same condition as that for compound **1**. 2,3-Di-O-allyl-5,6-O-isopropylidene-L-ascorbic acid **(3b)** was obtained in 65 % yield[11] but monoallyl ethers and C-allylated products were not detected. Hydrolysis of compound **3b** gave compound **2b** in 95 % yield. The fact that only di-O-allyl ethers, **2a** and **3b** were obtained in the present study is in contrast with the results reported before. Thus, it is well known that the controlled methylation of **1** or **3a** affords the 3-O-methyl ether. And it has also been reported that reaction of *L*-ascorbate anion with a glycosyl bromide afforded an only 3-O-glycosyl product and never gave di-O-glycosyl products even under forcing conditions.[12]



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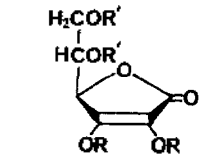
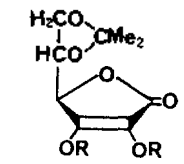


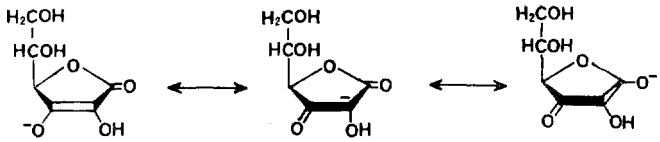
2a R = $CH_2CH{=}CH_2$, R′ = H



3a R = H

2b R = $CH_2CH{=}CH_2$, R′ = $COCH_3$

3b R = $CH_2CH{=}CH_2$



I II III

Figure 1. Resonance structures of L-ascorbate anion.

References and Notes

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(8) The compound **2a** was purified by a preparative TLC of sillica gel (ether–ethanol, 4:1 containing a small amount of triethylamine) to afford yellow syrup, R_f 0.24 (ether).
(9) The analytical sample of compound **2b** was purified by a preparative TLC of silica gel (ether) to afford a pale yellow syrup, R_f 0.60 (ether); IR (neat) ν_{max}: 1780, 1750, 1675 cm^{-1}; ^{1}HNMR ($CDCl_3$) δ: 2.01 (6H, **s**, 2 acetate Me), 4.23 —4.90 (7H, *m*, H–5, H–6, allylic H), 5.18 (1H, *d*, J=3.5Hz, H–4), 5.22–5.47 (4H, *m*, terminal vinylic H), 5.70–6.27 (2H, *m*, vinylic H). *Anal.* calcd. for $C_{16}H_{20}O_8$: C 56.47,H 5.92; found: C 56.32, H 6.39.
(10) The compound 3a was prepared using the method of Jackson–Jones (Ref. 2b and 3).
(11) The product mixture was fractionated on a column of silica gel (hexane–ethyl acetate, 7:3) to afford pure **3b** as a coloress syrup, R_f 0.24 (hexane–ethyl acetate, 8:2); IR (neat) ν_{max}: 1785, 1750, 1670cm^{-1}; ^{1}HNMR ($CDCl_3$) δ:1.38 (6H, *s*, isopropylidene Me), 3.97–5.03 (7H, *m*, H–5, H–6, allylic H), 5.20 (1H, *d*, J=3.5 Hz, H–4), 5.22–5.50(4H, *m*, terminal vinylic H), 5.65–6.25 (2H, *m*, vinylic H). *Anal.* calcd. for $C_{15}H_{20}O_6$: C60.80, H 6.80; found: C 59.96, H 6.89.
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Reactivity of 1, 1-Diphenyl-2-vinylcyclopropane to Singlet Oxygen

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In many ways the chemical properties of the cyclopropane ring resemble those of the carbon–carbon double bond. Cyclopropane compounds have been found to undergo addition reactions with electrophilic, nucleophilic and radical reagents.[1,2] Vinylcyclopropane compounds which exhibit bifunctionality, a vinyl group and a cyclopropyl ring, show much enhanced chemical reactivities and the homodienyl vinylcyclopropanes show extension of conjugative effects from the unsaturated double bond to the cyclopropane ring. As a result, in certain chemical reactions the double bond could be transmitted and the cyclopropane ring could be opened more readily.[3] However, cyclopropane compounds have aroused many controversial problems such as ring strains, ring structures, transmission of resonance effects, classical or nonclassical nature of cyclopropyl carbinyl species (cation, anion and radical), *etc*. Especially, there has been long standing controversies concerning the ability of cyclopropane ring to extend or transmit conjugation and its geometrical requirements, if any, for conjugation.[4,5]

For this reason, we undertook the study of the dye–sensitized photooxygenation of 1,1–diphenyl–2–vinylcyclopropane (VCP–DPh) and compared the results with those of previous observations.[6]

Dye–sensitized photooxygenation of 1,1–diphenyl–2–vinylcyclopropane (VCP–DPh) was carried out in pure acetone solution with 8×10^{-3} *M* VCP–DPh and 2×10^{-6} *M* Rose Bengal. The solution was irradiated at 10°C under oxygen with a 300–W sun lamp. The substrate was also irradiated with benzophenone sensitizer at 366 nm under oxygen. However, VCP–DPh was stable to singlet oxygen and the expected photoene product (cyclopropylidene derivative) or cycloaddition to vinyl group was not observed.

Singlet oxygen undergoes 1,4–cycloaddition with conjugated dienes to yield endoperoxides and the "ene" reaction with alkenes to give allylic hydroperoxides and 1,2–cycloaddition with electron–rich alkenes to form 1,2–dioxetanes. Depending on the nature of the substituents attached to the reaction centres and on the bulkiness of more distant parts of the molecule, stereoelectronic and steric effects determine the regiospecificity, the regioselectivity, the stereospecificity, and the stereoselectivity of the reactions and thus determine the product distributions observed with real systems.

Ene–product formation seems to be affected little by the nature of the solvent but is strongly dependent on the stereoelectronic and steric effects exerted by the olefin on the attacking electrophilic singlet oxygen. Substitution of olefinic hydrogens by electron–donating alkyl groups enhances the rate of ene–reactions with singlet oxygen. The reactivity of olefins toward singlet oxygen increases linearly with decreasing $\pi_{C=C}$–ionization potentials of the olefins, *i.e.*, with higher occupied $\pi_{C=C}$–orbitals.

The ene–mechanism requires that $^1O_2$ approaches the π system perpendicular to the double bond plane and, in addition, preferentially uses that allylic hydrogen which is oriented approximately orthogonal to the olefinic plane. Such