Synthesis of 2-Deoxy-2-halo-L-ascorbic Acids

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Received December 30, 1996[⊗]

2-Iodo- and 2-bromo-2-deoxy-L-ascorbic acids (**2** and **3**) were prepared by facile halogenation of 2-deoxy-L-ascorbic acid (**6**) with NIS and NBS, respectively. Likewise, chlorination with NCS produced 2-chloro-2-deoxy-L-ascorbic acid (**4**), but formation of **4** was accompanied by formation of the dichloro hemiketal **9**. Direct fluorination of **6** with 1-chloro-4-fluoro-1,4-diazoniabicyclo[2.2.2]-octane bis(tetrafluoroborate) (F-TEDA−BF_4) gave only the difluoro hemiketal **10**. A convenient synthesis of 2-deoxy-2-fluoro-L-ascorbic acid (**5**) was achieved by an indirect route. Fluorination of 2-bromo-2-deoxy-L-ascorbic acid (**3**) with F-TEDA−BF_4 produced the bromofluoro hemiketal **16** as a mixture of diastereoisomers. Debromination with tributyltin hydride gave **5** in good yield.

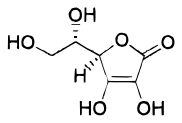
Introduction

The biological importance of ascorbic acid (vitamin C, **1**), a compound well known to the general public as a putative palliative against the common cold, was initially associated with scurvy, the symptoms of the vitamin deficiency. Recent research into the biochemistry of ascorbic acid has revealed a host of important physiological roles for the vitamin. For example, it functions as an antioxidant, serves as an electron donor for several enzymatic reactions, and is implicated in host defense mechanisms.[1] In addition to examination of functional roles of vitamin C, recent research has characterized efficient transport mechanisms that translocate vitamin C across cellular membranes, emphasizing the importance of the vitamin in biological processes.[2] The resurgent interest in ascorbic acid biochemistry has been accompanied by increased activity directed toward the synthesis of analogues. Among these analogues, the 6-deoxy-6-haloascorbic acids, synthesized along with 6-deoxyascorbic acid by Kiss and co-workers,[3] proved to be quite useful as competitive inhibitors for the study of ascorbate transport.[2] This and other work suggest that the 6-hydroxyl group of ascorbic acid is relatively unimportant in transport and function of the vitamin.

In contrast to the 6-hydroxy group, the 2-hydroxy group is at the locus of the reaction site in redox processes of ascorbic acid and is required for the reducing properties of the vitamin. Thus, chemical manipulation of the 2-position should have a marked influence on the biological properties of ascorbic acid. As part of an effort to explore this question, we had previously described the synthesis of 2-deoxy-L-ascorbic acid (**6**).[4] In this paper, we describe the synthesis of 2-deoxy-2-halo-L-ascorbic acids **2**−**5**.

Results and Discussion

2-Deoxy-L-ascorbic acid[4] (**6**) is a 4-substituted derivative of tetronic acid (**7**). On the basis of the previously reported facile electrophilic iodination of **7** to give 2-iodotetronic acid (**8**),[5] we reasoned that direct halogenation



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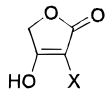


7: X = H
8: X = I

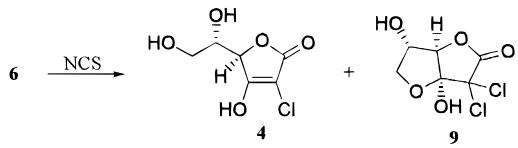
Figure 1.

of **6** should provide the 2-halo target compounds. Indeed, iodination of **6** with NIS gave 2-deoxy-2-iodo-L-ascorbic acid (**2**) in 81% yield (eq 1). Comparison of the ^{1}H NMR

6 **2:** X = I **3:** X = Br (1)

spectrum of **2** with that of **6** revealed a 0.2 ppm downfield shift of the 4-H that resulted from introduction of the iodine, whereas the chemical shifts and coupling patterns of protons in the side chain remain relatively unchanged. The absence of a 2-H signal in the spectrum of **2** is consistent with the enolic structure. In the crystalline state, **6** exists as the enol, as determined by X-ray analysis.[6] Halogenation of **6** with NBS also proceeded smoothly, and 2-bromo-2-deoxy-L-ascorbic acid (**3**) was obtained in 93% yield (eq 1).

The halogenations of **6** with NIS and NBS are very fast processes. TLC analysis of the reaction mixtures showed that iodination was completed almost instantaneously and bromination took only a few minutes to complete, with each procedure leading cleanly to the monohalogenated product. In contrast, chlorination of **6** with NCS was slower and gave a mixture of the starting material **6**, the desired 2-chloro-2-deoxy-L-ascorbic acid (**4**), and the dichlorobicyclic hemiketal **9** (eq 2). The ratio of **9** to



4 **9** (2)

[⊗] Abstract published in *Advance ACS Abstracts,* April 15, 1997.

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(2) Welch, R. W.; Wang, Y.; Crossman, A., Jr.; Park, J. B.; Kirk, K. L.; Levine, M. *J. Biol. Chem.* **1994**, *269*, 1041.

(3) Kiss, J.; Berg, K. P.; Dirscherl, A.; Oberhänsli, W. E.; Arnold, W. *Helv. Chim. Acta* **1980**, *63*, 1728.

(4) Ge, P.; Kirk, K. L. *J. Org. Chem.* **1996**, *61*, 8671.

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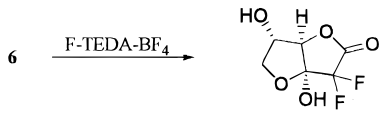
S0022-3263(96)02394-8

4 is about 2:1 as determined by NMR analysis of the reaction mixture. Formation of the hemiketal **9** resulted in a 0.2 ppm upfield shift of the 4-H due to the saturation of the double bond. In addition, the NMR signals of the two 6-protons appear as two sets of doublets of doublets at 3.94 and 4.32 ppm shifted downfield relative to the 6-H protons of **6** and **4**. It must be noted that saturation of the double bond during formation of **9** also introduces a new chiral center, and formation of two diastereomers is possible. However, the NMR data indicate that **9** is present as a single compound. Thus, the stereochemistry of hemiketal formation apparently is controlled by the configuration at C4. Indeed, molecular modeling revealed that the α-hydroxyl diastereomer (*cis*-ring junction) is much more favored thermodynamically ($\Delta E = 8$ kcal/mol), and a *cis*-ring assignment for **9** was later supported by NMR evidence derived from the bromofluoro bicyclic hemiketal **16** (see below).

On the basis of the above results, including the relative rates of halogenation of **6** observed (I > Br > Cl) and the facile hemiketal formation and dichlorination observed using NCS, we anticipated that electrophilic fluorination of **6** might be particularly challenging. Indeed, initial attempts to fluorinate **6** with 1-(chloromethyl)-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate) (F-TEDA−BF_4)[7] did not result in formation of 2-deoxy-2-fluoro-L-ascorbic acid (**5**) but gave instead a difluoro hemiketal **10** as the only product (eq 3). This result

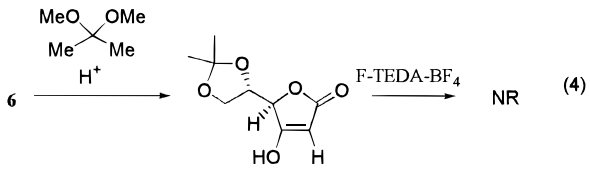


10 (3)

confirms that the course of halogenation of **6** is dependent on the reagents used. Thus, bromination or iodination of **6** did not give dihalogenated products, whereas chlorination gave monochlorinated and dichlorinated products and fluorination with F-TEDA−BF_4 resulted only in difluorination.

The isolation of the dichlorohemiketal **9** introduces the possiblity that cyclization of the monochlorinated product **4** precedes the introduction of the second chlorine. Hemiketal formation would be favored by the presence of the electronegative substituent at the 2-position. Enolization of the lactone carbonyl would provide a more nucleophilic site for the second chlorination. However, we have no direct evidence bearing on this detail of the mechanism of chlorination.

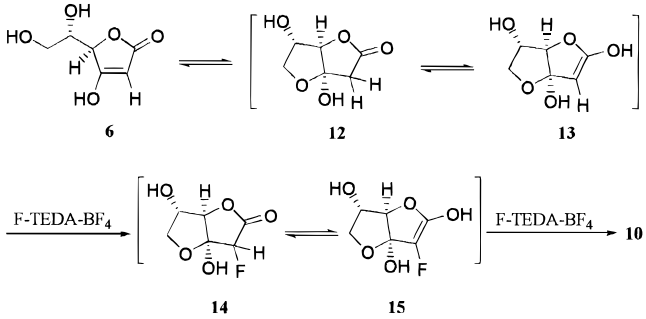
In further attempts to acheive fluorination, we found that the ketal **11** could not be fluorinated with F-TEDA−BF_4 in either neutral or basic conditions (eq 4). This



11 (4)

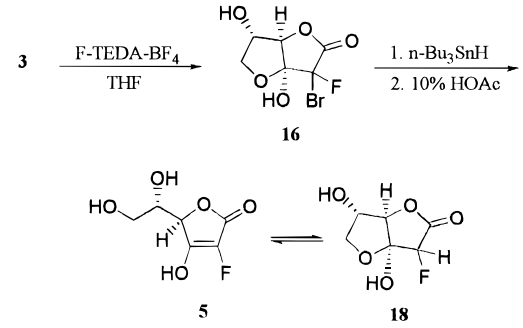
suggests that hemiketal formation *is* a prerequisite for the initial fluorination with this reagent. Since **6** is a

Scheme 1



4-substituted tetronic acid (tetronic acid p$K_a = 3.76$),[8] the C-2 position should be fairly unreactive toward electrophilic attack. As noted above, formation of the hemiketal **12** allows enolization at C-2 via the lactone carbonyl resulting in the more reactive enol **13** (Scheme 1), the species that we propose is the substrate for electrophilic fluorination. Rapid re-enolization of the monofluoro intermediate followed by a second fluorination step would result in the observed product **10**. In the simpler system, we found that fluorination of tetronic acid (**7**) by F-TEDA−BF_4 does not proceed in nonpolar solvents, but in ethanol a difluoro ethyl hemiketal is formed, a result that supports this mechanistic proposal.[9]

Mechanistic speculation aside, we were faced with the quandry that F-TEDA−BF_4 fluorination of 2-deoxyascorbic itself cannot be controlled to give the desired 2-deoxy-2-fluoro analogue **5**, possibly due to participation of the 6-OH in hemiketal formation. On the other hand, protection of the 6-OH as the acetonide blocks the reaction entirely. Fortunately, we were able to design a stepwise synthetic route to **5** that takes advantage of the facile bromination of **6** to give the 2-bromo-2-deoxy-L-ascorbic acid (**3**). Fluorination of **3** with F-TEDA−BF_4 gave **16** in 95% yield (eq 5). The NMR spectrum of the



(5)

product **16** indicated that a mixture of two diastereomers had been produced in a ratio of 4:1. As discussed above, the stereochemistry of hemiketal formation should be controlled by the side chain at C4 to produce only the *cis*-ring juncture. Although it is difficult to predict the stereochemistry of the fluorination at C2 by F-TEDA−BF_4, we were able to make stereochemical assignments on the basis of analysis of the NMR spectra. In the major isomer, the signal for one of the side-chain protons appears as two doublets of doublets centered at 3.91 ppm with coupling constants of 9.9, 4.5, and 1.5 Hz. This multiplicity indicates coupling with the fluorine. Molecular modeling shows that such an interaction is possible in **16a** between the 5-β-H (numbering for the furo[3,2-

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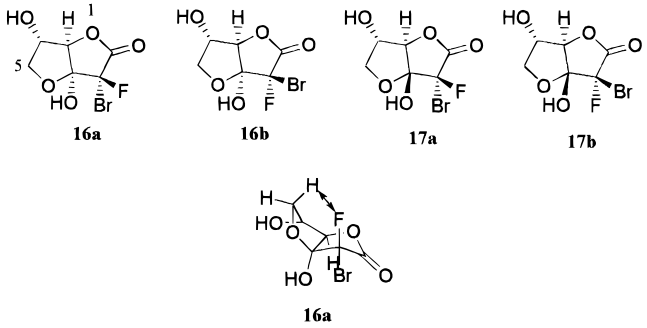

Figure 2.

b]furanone system) and fluorine (an interatomic distance of 2.3 Å was obtained), while no such interactions are present in **16b** having an α-fluorine or in either **17a** and **17b** having the *β*-hydroxy hemiketals (Figure 2). The assignment of the α-hydroxyl hemiketal stereochemistry based on thermodynamic considerations is supported by these NMR data.

Reductive debromination of **16** by tri-*n*-butyltin hydride,[10] followed by treatment with aqueous acid, gave 2-deoxy-2-fluoro-L-ascorbic acid (**5**) (eq 5). Unlike compounds **2**−**4**, which exist in solution as the enols, the strong electronegativity of the fluorine atom in **5** leads to facile tautomerization between the enol, characterized by a doublet of doublets at 4.89 ppm with coupling constants of 1.5 and 3.6 Hz (J_{FH}), and the hemiketal **18**, which has a doublet at 5.55 ppm with J_{FH} = 49.2 Hz.

We are currently examining the biological and physicochemical properties of the 2-deoxy-2-halo-L-ascorbic acids. We note that **2** and **3**, in particular, are potential halogenating agents by virtue of the stability of the anion produced by loss of positive halogen. Of additional interest is the fact that the replacement of the 2-OH of ascorbic acid with fluorine produces an analogue **5** that should closely resemble ascorbic acid sterically. In addition, the difluoro hemiketal **10** can be viewed as an analogue of the hemiketal form of dehydroascorbic acid, the product of oxidation of ascorbic acid.

Experimental Section

General Methods. Melting points were determined in open-end capillary tubes and are uncorrected. Proton NMR were recorded at 300 MHz, and chemical shifts are reported in ppm relative to tetramethylsilane. Molecular modeling was carried out on Alchemy III software, and standard parameters were applied. TLC analyses were performed on silica gel GHLF. Solvents and reagents were purchased from Aldrich or Fluka. F-TEDA−BF_4 was a gift from Air Products and Chemicals, Inc. Chromatographic separations were performed by flash column chromatography on silica gel. Analyses indicated by symbols of the elements were carried out by Atlantic Microlab, Inc., or Galbraith Laboratories, Inc.

2-Deoxy-2-iodo-L-ascorbic Acid (2). To a solution of **6** (90 mg, 0.56 mmol) in ethanol (3 mL) was added NIS (135 mg, 0.6 mmol) at rt. The resulting solution was stirred for 5 min and then evaporated to dryness. The residue was purified by column chromatography (silica gel, eluting with CH_2Cl_2:MeOH:HOAc 100:5:0.5) to afford **2** as white crystals (130 mg, 81%): mp 173−175 °C; ^{1}H NMR (DMSO-d_6) δ 3.37−3.48 (m, 2H, with a dd at 3.40, 1H, J = 8.1, 10.5 Hz and a dd at 3.45, 1H, J = 6.6, 10.5 Hz after D_2O exchange), 3.86−3.91 (m, 1H), 5.0 (d, 1H, J = 1.2 Hz); MS-EI *m/e* 286 (M^+); $[\alpha]^{25}_D$ = +76.4 (*c* 0.25, CH_3OH); Anal. Calcd for $C_6H_7O_5I$: C, 25.20; H, 2.47; I, 44.37. Found: C, 25.48; H, 2.50; I, 44.17.

2-Bromo-2-deoxy-L-ascorbic Acid (3). To a solution of **6** (225 mg, 1.4 mmol) in ethanol (6 mL) was added NBS (250 mg, 1.4 mmol) at rt. The resulting solution was stirred for 10 min and then evaporated to dryness. The residue was purified by column chromatography (silica gel, eluting with CH_2Cl_2:MeOH:HOAc 100:5:0.5) to afford **3** as white crystals (315 mg, 94%): mp 177−179 °C; ^{1}H NMR (DMSO-d_6) δ 3.38−3.49 (m, 2H), 3.85−3.91 (m, 1H), 4.99 (d, 1H, J = 1.2 Hz); MS-EI *m/e* 238 (M^+); $[\alpha]^{25}_D$ = +76.8 (*c* 0.25, CH_3OH). Anal. Calcd for $C_6H_7O_5Br$: C, 30.15; H, 2.95; Br, 33.43. Found: C, 30.23; H, 2.97; Br, 33.40.

2-Chloro-2-deoxy-L-ascorbic Acid (4). To a solution of **6** (160 mg, 1 mmol) in ethanol (6 mL) was added NCS (175 mg, 1.3 mmol) at rt. The resulting solution was stirred for 3 h and then evaporated to dryness. The residue was purified by column chromatography (silica gel, eluting with CH_2Cl_2:MeOH:HOAc 100:5:0.5) to give the product **4** as a light yellow hygroscopic powder (28 mg, 20%): ^{1}H NMR (DMSO-d_6) δ 3.38−3.48 (m, 2H), 3.82−3.87 (m, 1H), 4.93 (d, 1H, J = 1.5 Hz); MS-EI *m/e* 194 (M^+). Starting material **6** (45 mg) also was recovered, along with **9**, isolated in a separate experiment as described below.

(3a*S*,6*S*,6a*R*)-3,3-Dichloro-3a,6-dihydroxy-3a,5,6,6a-tetrahydrofuro[3,2-*b*]furan-2(3*H*)-one (9). To a solution of **6** (80 mg, 0.5 mmol) in ethanol (2.5 mL) was added NCS (75 mg, 0.5 mmol) at rt. The resulting solution was stirred for 3 h and then evaporated to dryness. The residue was dissolved in H_2O (2 mL) and EtOAc (3 mL). The EtOAc layer was separated, dried, and purified by column chromatography (silica gel, eluting with EtOAc:petroleum ether 1:2) to give the title compound **9** as a white solid (38 mg, 60%): mp 130−131 °C; ^{1}H NMR (DMSO-d_6) δ 3.94 (dd, 1H, J = 3.9, 9.6 Hz), 4.32 (dd, 1H, J = 6.3, 9.6 Hz), 4.41−4.44 (m, 1H), 4.72 (s, 1H), 5.82 (d, 1H, J = 4.2 Hz), 8.25 (s, 1H); MS-EI *m/e* 229 (M + 1). Anal. Calcd for $C_6H_6O_5Cl_2$: C, 31.46; H, 2.64. Found: C, 31.51; H, 2.62.

(3a*S*,6*S*,6a*R*)-3,3-Difluoro-3a,6-dihydroxy-3a,5,6,6a-tetrahydrofuro[3,2-*b*]furan-2(3*H*)-one (10). To a solution of **6** (80 mg, 0.5 mmol) in THF (4 mL) was added F-TEDA−BF_4 (390 mg, 1.1 mmol) at rt. The resulting mixture was stirred for 30 h. A white solid was removed by filtration, and the colorless filtrate was evaporated to give an oily residue. This was purified by column chromatography (silica gel, eluting with EtOAc:petroleum ether 1:2) to give the title compound **10** as white semisolid (65 mg, 66%): ^{1}H NMR (DMSO-d_6) δ 3.96 (ddd, 1H), 4.30 (dd, 1H), 4.38− 4.40 (m, 1H), 4.81 (s, 1H), 5.84 (br, 1H), 8.15 (s, 1H); MS-EI *m/e* 196 (M^+).

2-Deoxy-5,6-*O*-isopropylidene-L-ascorbic Acid (11). To a suspension of **6** (160 mg, 1.0 mmol) in acetone (1.5 mL) and 2,2-dimethoxypropane (3 mL) was added *p*-toluenesulfonic acid monohydrate (1 mg). A clear solution was obtained within 10 min. The reaction was stirred at rt for another 30 min. The solution was concentrated until white crystals appeared. The crystals were filtered and washed with 50% EtOAc in petroleum ether to give 135 mg of **11**, mp 138−139 °C. The filtrate was evaporated to dryness and purified by column chromatography (0.25% HOAc in EtOAc) to give another 35 mg of product (85% in total): ^{1}H NMR (DMSO-d_6) δ 1.25 (s, 6H), 3.89 (dd, 1H, J = 6.3, 8.4 Hz), 4.12 (dd, 1H, J = 6.9, 8.4 Hz), 4.31 (dt, 1H, J = 2.7, 6.6 Hz), 4.87 (dd, 1H, J = 1.2, 2.7 Hz), 4.94 (d, 1H, J = 1.2 Hz), 12.70 (s, 1H); MS-EI *m/e* 200 (M^+). Anal. Calcd for $C_9H_{12}O_5 \cdot 0.5H_2O$: C, 51.67; H, 6.25. Found: C, 51.44; H, 5.90.

(3a*S*,6*S*,6a*R*)-3-Bromo-3a,6-dihydroxy-3-fluoro-3a,5,6,-6a-tetrahydrofuro[3,2-*b*]furan-2(3*H*)-one (16). To a solution of **3** (320 mg, 1.34 mmol) in THF (5 mL) was added F-TEDA−BF_4 (570 mg, 1.6 mmol) at rt. The resulting mixture was stirred for 23 h. The white solid was removed by filtration, and the colorless filtrate was evaporated. The residue was purified by column chromatography (silica gel, eluting with EtOAc:petroleum ether 1:2) to give compound **16** as a white solid (328 mg, 95%): mp 155−158 °C; ^{1}H NMR (DMSO-d_6): major isomer **16a** δ 3.91 (ddd, 1H, J = 1.5, 4.5, 9.9 Hz), 4.27

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(dd, 1H, J = 6.3, 9.9 Hz), 4.41−4.46 (m, 1H), 4.83 (s, 1H), 5.85 (br, 1H), 8.07 (s, 1H); minor isomer **16b** δ 4.02 (dd, 1H, J = 2.7, 9.0 Hz), 4.31−4.36 (m, 1H), 4.41−4.46 (m, 1H), 4.60 (s, 1H), 5.82 (br, 1H), 8.29 (s, 1H); MS-EI *m/e* 256 (M^+). Anal. Calcd for $C_6H_6O_5BrF$: C, 28.04; H, 2.33; F, 7.39. Found: C, 27.80; H, 2.37; F, 7.33.

2-Deoxy-2-fluoro-L-ascorbic Acid (5). To a solution of **16** (160 mg, 0.62 mmol) in THF (2.5 mL) was added tri-*n*-butyltin hydride (0.34 mL, 1.2 mmol) under argon at rt. The resulting solution was stirred for 24 h and evaporated to remove THF. The residue was washed thoroughly with petroleum ether (3 mL × 5) to give the tin enol ether as a colorless thick oil (256 mg). The oil (90 mg) was subjected to acid hydrolysis in a mixture of 10% aqueous acetic acid (1.5 mL) and 50% EtOAc in petroleum ether (2 mL) at rt for 20 min. The aqueous layer was separated, washed with 50% EtOAc in petroleum ether (1.5 mL × 4), and evaporated to give **5** as a light yellow oil (34 mg, 87%): ^{1}H NMR (DMSO-d_6) enol form 3.35−3.42 (m, 2H), 3.87−3.92 (m, 1H), 4.89 (dd, 1H, J = 1.5, 3.6 Hz); hemiketal form δ 4.15−4.30 (m, 2H), 4.54 (s, 1H), 4.60−4.62 (m, 1H), 5.55 (d, 1H, J = 49.2 Hz), 7.49 (br, 1H); MS-EI *m/e* 178 (M^+).

JO962394B