

## Rational Approach to Selective and Direct 2-*O*-Alkylation of 5,6-*O*-Isopropylidene-L-ascorbic Acid

Ayodele O. Olabisi and Kandatege Wimalasena\*

Department of Chemistry, Wichita State University, Wichita, Kansas 67260-0051

kandatege.wimalasena@wichita.edu

Received April 22, 2004

L-Ascorbic acid is a versatile radical scavenger widely distributed in aerobic organisms that plays a central role in the protection of cellular components against oxidative damage by free radicals and oxidants. It also functions as a physiological reductant for key enzymatic transformations in catecholamine neurotransmitters, amidated peptide hormones, and collagen biosynthetic pathways. Simple derivatives of L-ascorbic acid have been shown to possess antioxidant, antitumor, and immunostimulant activities. The antioxidant and redox properties of L-ascorbic acid are closely associated with the electron-rich 2,3-enediol moiety of the molecule, and therefore, selective functionalization of the 2- and 3-OH groups is essential for the detailed structure–activity studies. Reactions of 5- and 6-OH-protected ascorbic acid with electrophilic reagents exclusively produce the corresponding 3-*O*-alkylated products under mild basic conditions due to the high nucleophilicity of the C-3-OH. Based on the density functional theory (B3LYP) electron density calculations, we have devised a novel and general method for the direct alkylation of the 2-OH group of ascorbic acid with complete regio- and chemoselectivity. We have also carried out a complete spectroscopic analysis of two complementary series of 2-*O*-acetyl-3-*O*-alkyl- and 2-*O*-alkyl-3-*O*-acetylascorbic acid derivatives to define their spectroscopic characteristics and to resolve common inconsistencies in the literature.

### Introduction

Ascorbic acid is a versatile water-soluble radical scavenger widely distributed in aerobic organisms that plays a central role in the protection of the cellular components against oxidative damage by free radicals and oxidants that are involved in the development and exacerbation of a multitude of chronic diseases such as cancer, heart disease, brain dysfunction, aging, rheumatism, inflammation, stroke, emphysema, and AIDS.<sup>1–9</sup> It also plays a critical role as a physiological reductant for key enzymatic transformations in catecholamine neurotransmitters, amidated peptide hormones, and collagen bio-

synthetic pathways. In addition, simple derivatives of L-ascorbic acid have been shown to possess important pharmacological properties. For example, (a) 5,6-*O*-modified ascorbic acid derivatives have been found to be effective antitumor agents for various human cancers and to induce apoptosis in tumor cells;<sup>10–17</sup> (b) C-2-alkylated derivatives have been shown to have immunostimulant activity;<sup>18–23</sup> (c) O-2- and O-3-alkylated derivatives are

\* To whom correspondence should be addressed. Phone: 316-978-7386. Fax: 316-978-3431.

(1) (a) Rose, R. C.; Bode, A. M. *FASEB J.* **1993**, *7*, 1135–42. (b) Ames, B. N.; Shigenaga, M. K.; Hagen, T. M. *Proc. Nat. Acad. Sci. U.S.A.* **1993**, *90*, 7915–22.

(2) Bielski, B. H. J.; Richter, H. W.; Chan, P. C. *Ann. N. Y. Acad. Sci.* **1975**, *258*, 231–7.

(3) Tolbert, B. M.; Downing, M.; Carlson, R. W.; Knight, M. K.; Baker, E. M. *Ann. N. Y. Acad. Sci.* **1975**, *258*, 48–69.

(4) Bielski, B. H. J. In *Ascorbic Acid: Chemistry, Metabolism, and Uses*; Seib, P. A., Tolbert, B. M., Eds.; American Chemical Society: Washington, D.C., 1982; pp 81–100.

(5) (a) Halliwell, B.; Gutteridge, J. M. *Trends Biochem. Sci. (Pers. Ed.)* **1986**, *11*, 372. (b) Youngman, R. Y. *Trends Biochem. Sci. (Pers. Ed.)* **1984**, *9*, 280.

(6) Clark, R. A.; Leidal, K. G.; Pearson, D. W.; Nauseef, W. M. *J. Biol. Chem.* **1987**, *262*, 4065–74.

(7) McCord, J. M. *N. Engl. J. Med.* **1985**, *312*, 159–63.

(8) (a) Hammond, B.; Kontos, H. A.; Hess, M. L. *Can. J. Physiol. Pharmacol.* **1985**, *63*, 173–87. (b) Fridovich, I. *Annu. Rev. Pharmacol. Toxicol.* **1983**, *23*, 239–57. (c) Burton, K. P.; McCord, J. M.; Ghai, G. *Am. J. Physiol.* **1984**, *246*, H776–83.

(9) (a) Wimalasena, K.; Herman, H. H.; May, S. W. *J. Biol. Chem.* **1989**, *264*, 124. (b) Wimalasena, K.; Wimalasena, D. S. *Biochem. Biophys. Res. Commun.* **1991**, *175*, 34. (c) Wimalasena, K.; Wimalasena, D. S. *Anal. Biochem.* **1991**, *197*, 353. (d) Wimalasena, K.; Dharmasena, S. *Anal. Biochem.* **1993**, *210*, 58. (e) Wimalasena, K.; Dharmasena, S.; Wimalasena, D. S. *Biochem. Biophys. Res. Commun.* **1994**, *200*, 113.

(10) Sauberlich, H. E. *Annu. Rev. Nutr.* **1994**, *14*, 371–91.

(11) Kochi, M.; Takeuchi, S.; Mitzutani, T.; Mochizuki, K.; Matsuoto, Y.; Saito, Y. *Cancer Treat Rep.* **1980**, *64*, 21–3.

(12) Kochi, M.; Isono, N.; Niwayama, M.; Shirakabe, K. *Cancer Treat Rep.* **1985**, *69*, 533–7.

(13) Kochi, M.; Ueda, S.; Hagiwara, T. *Prog. Cancer Res. Ther.* **1988**, *35*, 338.

(14) Osmak, M.; Eckert-Maksic, M.; Pavelic, k.; Maksic, Z. B.; Spaventi, R.; Beketic, L.; Kovacek, I.; Suskovic, B. *Res. Exp. Med.* **1990**, *190*, 443–9.

(15) Tsao, C. S.; Young, M. *In Vitro Cell Devel. Biol.* **1995**, *31*, 87–90.

(16) Osmak, M.; Kovacek, I.; Ljubenkov, I.; Spaventi, R.; Eckert-Maksic, M. *Neoplasia* **1997**, *44*, 101–7.

(17) Sakagami, H.; Asano, k.; Fukuchi, K.; Gomi, K.; Ota, H.; Kazama, k.; Tanuma, S.; Kochi, M. *Anticancer Res.* **1991**, *11*, 1533–8.

(18) Sakagami, H.; Takeda, M.; Utsumi, A.; Fujinaga, S.; Tsunoda, A.; Yasuda, N.; Shibusawa, M.; Koike, T.; Ota, H.; Kazama, K.; Shiokawa, D.; Tanuma, S.; Kochi, M. *Anticancer Res.* **1996**, *13*, 65.

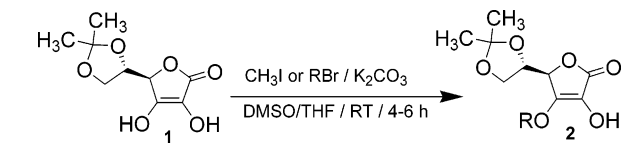
(19) Veltri, R. W.; Fodor, G.; Liu, C. M.; Woolverton, C. J.; Baseler, M. W. *J. Biol. Response Modifiers* **1986**, *5*, 444–61.

known to protect against peroxidation of lipids of the biomembrane.<sup>24,25</sup> Recently, the chemistry of ascorbic acid has also been exploited to develop strategies for central nervous system drug delivery.<sup>26</sup>

The antioxidant as well as redox and pharmacological properties of ascorbic acid are closely associated with the electron-rich 2,3-enediol moiety of the five-membered lactone ring.<sup>27</sup> Therefore, the selective modification of the 2- and 3-OH groups is essential for the detailed structure–activity studies of ascorbic acid. Reactions of 5- and 6-OH-protected ascorbic acid with electrophilic reagents under mild basic conditions exclusively takes place at the 3-OH due to its high nucleophilicity.<sup>27</sup> Preferential direct alkylation of 3-OH of the 5- and 6-OH unprotected ascorbic acid under the Mitsunobu conditions has been recently reported.<sup>28–30</sup> Therefore, the O-2-alkylated products could only be obtained after the protection of the 3-OH group with protecting groups such as acetyl, MOM, etc.<sup>31–33</sup> In the literature, the acetyl group has been commonly used as an O-3 protecting group in the alkylation of the 2-OH of ascorbic acid. However, the high instability of the 3-O-acetyl derivatives and facile migration of acyl groups from 3-O to 2-O, even under mild reaction conditions,<sup>34–37</sup> have led us<sup>32</sup> and others<sup>38,39</sup> in the misidentification and characterization of O-2- and O-3-substituted ascorbic acid derivatives. Although the products of these reactions were characterized as 3-O-acetyl-2-O-alkyl derivatives, in most cases they were 2-O-acetyl-3-O-alkyl derivatives which were predominantly formed due to the fast acetyl migration under the reaction conditions.<sup>32</sup> A detailed characterization of 2-O- and 3-O-acetyl esters of **1** has been previously reported.<sup>39</sup>

To resolve the discrepancies of the structure assignments of O-2- and O-3-substituted ascorbate derivatives, we sought to develop a specific and direct method to alkylate the O-2 position of 5,6-O-isopropylidene-L-

**TABLE 1.** 3-O-Alkylation of 5,6-O-Isopropylidene-L-ascorbic Acid



product	R	yield <sup>a</sup> (%)
<b>2a</b>	CH <sub>3</sub>	91
<b>2b</b>	CH <sub>2</sub> C <sub>6</sub> H <sub>5</sub>	86
<b>2c</b>	CH <sub>2</sub> CH=CHCH <sub>3</sub>	72
<b>2d</b>	CH <sub>2</sub> CH=CH <sub>2</sub>	80

<sup>a</sup> The yields are given for the purified products.

ascorbic acid (**1**), which has not been reported in the literature to our knowledge. We have used density functional theory (B3LYP) calculations to determine the electron density distributions and reactivities of the neutral, monoanion, and dianion of ascorbic acid and found that electrophilic reactions with the monoanion and dianion of ascorbic acid should preferentially occur at the O-3 and O-2 positions, respectively. Based on these findings, we have devised a novel and general method for the direct alkylation of 2-O of **1** in good yields with complete regio- and chemoselectivity with both activated and unactivated electrophiles. We have also carried out a complete spectroscopic analysis of two complementary series of 2-O-acetyl-3-O-alkyl- and 2-O-alkyl-3-O-acetyl-ascorbic acid derivatives in order to clearly define the spectroscopic characteristics of these derivatives for future studies.

## Results and Discussion

As mentioned above, the 3-OH group of L-ascorbic acid is more reactive toward electrophiles under mild basic conditions in comparison to 2-OH (Table 1). This is primarily due to the preferential deprotonation of 3-OH over 2-OH under mild basic conditions to produce primarily the monoanion (experimentally determined  $pK_a$ 's of 3-OH and 2-OH are 4.2 and 11.6, respectively).<sup>27</sup> The electron density distribution diagram of the monoanion of **1** clearly shows that the negative charge of the monoanion is distributed between the 3-O and C-1 carbonyl of the lactone ring with little electron density on 2-OH (Figure 1a). Therefore, the reactions of 5,6-OH-protected ascorbic acid with electrophilic reagents under mild basic conditions should predominantly occur at the O-3 position as experimentally observed. In addition, the electron density at the C-2 carbon of the monoanion is significantly higher than that of the 2-OH (Figure 1a), suggesting that the C-2 position of the monoanion may also be susceptible to electrophilic reactions. In agreement, C-2-alkylated products were also observed as minor products in the alkylation of **1** under mild alkaline conditions.<sup>32</sup> These analyses show that the reactions of **1** with simple electrophiles under mild basic conditions could be qualitatively predicted from the calculated electron density distribution of the monoanion. However, the kinetically controlled 3-O-acylated and 3-O-alkylated products must be thermodynamically relatively unstable due to the partial delocalization of the 3-O-alkyl or -acyl bonding electrons with the C-1 carbonyl group of the lactone ring, as mentioned above. Therefore, especially

(20) Woolverton, C. J.; Veltri, R. W.; Snyder, I. S. *J. Biol. Response Modifiers* **1986**, *5*, 527–38.

(21) Maxim, P. E.; Veltri, R. W.; Baseler, M. W.; Cameransi, B. G. *Fed. Proc.* **1986**, *45*, 628.

(22) Maxim, P. E.; Veltri, R. W. *FASEB J.* **1988**, *2*, A370.

(23) Maxim, P. E.; Veltri, R. W. *Proc. Am. Ass. Cancer Res.* **1988**, *29*, 374.

(24) Veltri, R. W.; Maxim, P. E.; Baseler, M. W.; Klinger, M. R. *Fed. Proc.* **1986**, *45*, 269.

(25) Nihro, Y.; Miyataka, H.; Sudo, T.; Matsumoto, H.; Satoh, T. *J. Med. Chem.* **1991**, *34*, 2152–7.

(26) Manfredini, S.; Pavan, B.; Vertuani, S.; Scaglianti, M.; Compagnone, D.; Biondi, C.; Scaturin, A.; Tanganelli, S.; Ferraro, L.; Prasad, P.; Dalpiaz, A. *J. Med. Chem.* **2002**, *45*, 559–562.

(27) Andrews, G. C.; Crawford, T. In *Ascorbic Acid: Chemistry, Metabolism, and Uses*; Seib, P. A., Tolbert, B. M., Eds.; American Chemical Society: Washington, D.C., 1982; pp 59–79.

(28) Tahir, H.; Hindsgaul, O. *J. Org. Chem.* **2000**, *65*, 911–913.

(29) Vilaca, G.; Rubio, C.; Susperregui, J.; Latxague, L.; Deleris, G. *Tetrahedron* **2002**, *58*, 9249–9256.

(30) Rubio, C.; Susperregui, J.; Latxague, L.; Deleris, G. *Synlett* **2002**, 1910–1912

(31) Kato, K.; Terao, S.; Shimamoto, N.; Hirata, M. *J. Med. Chem.* **1988**, *31*, 793–8.

(32) Wimalasena, K.; Mahindaratne, M. P. D. *J. Org. Chem.* **1994**, *59*, 3427–3432.

(33) Beifuss, U.; Kunz, O.; Aguado, G. P. *Synlett* **1999**, 147–49.

(34) Szarek, W. A.; Kim, K. S. *Carbohydr. Res.* **1978**, *67*, C13.

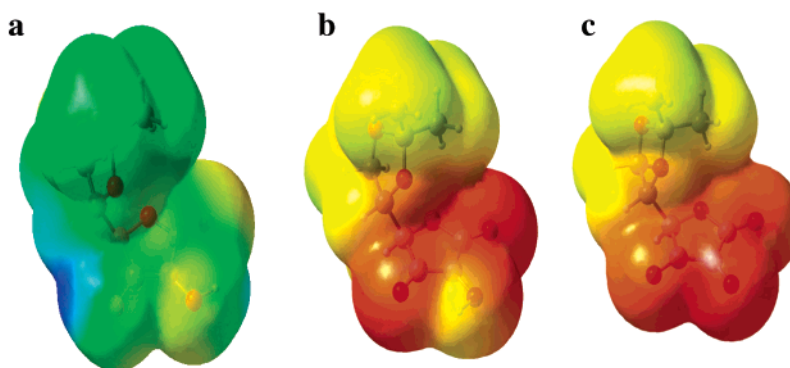
(35) Cabral, J.; Haake, P.; Kessler, K. *J. Carbohydr. Chem.* **1988**, *17*, 1321.

(36) Mumora, R.; Verlangieri, A.; Weber, W. *Carbohydr. Res.* **1971**, *19*, 127.

(37) Redford, T.; Sweeny, J.; Iacobucci, G. *J. Org. Chem.* **1979**, *44*, 658.

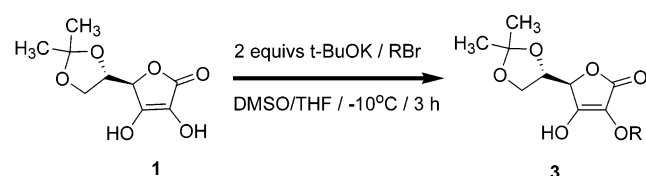
(38) Vestling, C.; Rebstock, M. *J. Biol. Chem.* **1944**, *152*, 585.

(39) Cabral, J.; Haake, P. *J. Org. Chem.* **1988**, *53*, 5742–5750.



**FIGURE 1.** Calculated electrostatic potential diagrams of the neutral, monoanionic, and dianionic forms of 5,6-*O*-isopropylidene-L-ascorbic acid (**1**). Calculated electron density diagrams of (a) neutral, (b) monoanionic, and (c) dianionic forms of **1**. Order of electron density: blue < green < yellow < red.

**TABLE 2.** 2-*O*-Alkylation of 5,6-*O*-Isopropylidene-L-ascorbic Acid



product	R	yield <sup>a</sup> (%)
<b>3a</b>	CH <sub>2</sub> CH=CH <sub>2</sub>	80
<b>3b</b>	CH <sub>3</sub>	91
<b>3c</b>	CH <sub>2</sub> CH=CHCH <sub>3</sub>	72
<b>3d</b>	CH <sub>2</sub> C <sub>6</sub> H <sub>5</sub>	83
<b>3e</b>	CH <sub>2</sub> CH=CHC <sub>6</sub> H <sub>5</sub>	87
<b>3f</b>	CH <sub>2</sub> (CH <sub>2</sub> ) <sub>5</sub> CH <sub>3</sub>	96

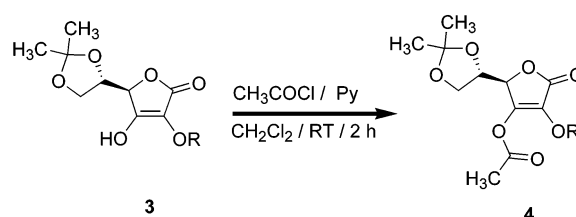
<sup>a</sup> The yields are given for the purified products.

the 3-*O*-acyl derivatives of ascorbic acid could undergo facile intramolecular acyl migration to produce the thermodynamically more stable 2-*O*-acyl derivatives, which is also in agreement with the previous experimental observations.<sup>32</sup>

Inspection of the electron density distribution of the dianion of **1** (Figure 1c) shows that the negative charge of the 3-*O*<sup>-</sup> is highly delocalized to the lactone carbonyl similar to that of the monoanion. However, the electron density of the 2-*O*<sup>-</sup> is highly localized in the dianion, suggesting that electrophilic reagents should preferentially react with the 2-*O*<sup>-</sup> rather than 3-*O*<sup>-</sup> of the dianion of **1**. In excellent agreement, the dianion of **1**, generated by reacting 2 equiv of potassium *tert*-butoxide (*t*-BuOK) in DMSO/THF (3:2) at -10 °C, reacts with 1 equiv of a number of activated and unactivated electrophilic alkylating agents (Table 2) to exclusively produce the corresponding *O*-2-alkylated products in good yields (80–90%). Furthermore, regardless of the nature of the electrophile, no detectable amounts of *O*-3- or *C*-2-substituted products were produced, under these experimental conditions. However, the addition of 2 equiv of the electrophile cleanly produces the corresponding 2-*O*- and 3-*O*-disubstituted derivative. In addition, both 3-*O*- and 2-*O*-alkylated ascorbic acid derivatives undergo clean 2-*O*- and 3-*O*-acetylations under standard reaction conditions, respectively (Tables 3 and 4).

**NMR Analysis.** As mentioned above, the literature on <sup>1</sup>H and <sup>13</sup>C NMR data of most *O*-2- and *O*-3-substituted

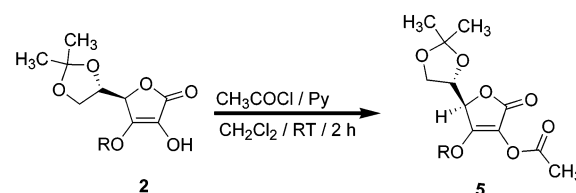
**TABLE 3.** 3-*O*-Acetylation of 5,6-*O*-Isopropylidene-2-*O*-alkylated-L-ascorbic Acid



product	R	yield <sup>a</sup> (%)
<b>4a</b>	CH <sub>2</sub> CH=CH <sub>2</sub>	70
<b>4b</b>	CH <sub>3</sub>	80
<b>4c</b>	CH <sub>2</sub> CH=CHCH <sub>3</sub>	84
<b>4d</b>	CH <sub>2</sub> C <sub>6</sub> H <sub>5</sub>	82
<b>4e</b>	CH <sub>2</sub> CH=CHC <sub>6</sub> H <sub>5</sub>	76

<sup>a</sup> The yields are given for the purified product.

**TABLE 4.** 2-*O*-Acetylation of 5,6-*O*-Isopropylidene-3-*O*-alkylated-L-ascorbic Acid

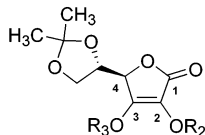


product	R	yield <sup>a</sup> (%)
<b>5a</b>	CH <sub>3</sub>	90
<b>5b</b>	CH <sub>2</sub> C <sub>6</sub> H <sub>5</sub>	90
<b>5c</b>	CH <sub>2</sub> CH=CHCH <sub>3</sub>	78
<b>5d</b>	CH <sub>2</sub> CH=CH <sub>2</sub>	70
<b>5e</b>	CH <sub>2</sub> CH=CHC <sub>6</sub> H <sub>5</sub>	76

<sup>a</sup> The yields are given for the purified products

derivatives of ascorbic acid were unavailable, incorrect, or misassigned.<sup>32</sup> Therefore, we have synthesized a complementary series of *O*-2- and *O*-3-substituted derivatives of **1** according to the above procedures, and their <sup>13</sup>C and <sup>1</sup>H NMR data were completely assigned and discussed for future reference. The data presented in Table 5 demonstrate that *O*-2- and *O*-3-monosubstituted derivatives of **1** display characteristic <sup>13</sup>C NMR chemical shifts for their *C*-2 and *C*-3 carbons and <sup>1</sup>H NMR chemical shifts for their *C*-4-H that could be used to unequivocally identify the *O*-2- and *O*-3-monosubstituted



**TABLE 5.**  $^1\text{H}$  NMR (C-4-H) and  $^{13}\text{C}$  NMR (C-2 and C-3) Chemical Shifts ( $\delta$ ) of 2-O-Alkyl-3-O-alkyl, 2-O-Alkyl-3-O-acetyl, and 3-O-Alkyl-2-O-acetyl Derivatives of 5,6-O-Isopropylidene-L-ascorbic Acid (**1**)

derivative	R <sub>2</sub>	R <sub>3</sub>	$\delta_{(\text{C}-2)}$	$\Delta_{(\text{C}-2)}^a$	$\delta_{(\text{C}-3)}$	$\Delta_{(\text{C}-3)}^a$	$\delta_{(\text{C}-4 \text{ 1H})}$
<b>1</b>	H	H	120.5	-	158.4	-	4.91
<b>2a</b>	H	CH <sub>3</sub>	119.5	-1.0	149.9	-8.5	4.53
<b>2c</b>	H	CH <sub>2</sub> CH=CHCH <sub>3</sub>	119.1	-1.4	148.6	-9.8	4.55
<b>2b</b>	H	CH <sub>2</sub> C <sub>6</sub> H <sub>5</sub>	119.5	-1.0	148.6	-9.8	4.57
<b>2d</b>	H	CH <sub>2</sub> CH=CH <sub>2</sub>	119.2	-1.3	148.2	-10.2	4.58
<b>3a</b>	CH <sub>2</sub> CH=CH <sub>2</sub>	H	121.4	+0.9	156.4	-2.0	4.72
<b>3b</b>	CH <sub>3</sub>	H	123.1	+2.6	155.8	-2.6	4.71
<b>3c</b>	CH <sub>2</sub> CH=CHCH <sub>3</sub>	H	120.8	+0.3	157.9	-0.5	4.69
<b>3d</b>	CH <sub>2</sub> C <sub>6</sub> H <sub>5</sub>	H	121.1	+0.6	157.5	-0.9	4.60
<b>4a</b>	CH <sub>2</sub> CH=CH <sub>2</sub>	O=CCH <sub>3</sub>	130.1	+9.6	143.8	-14.6	5.18
<b>4b</b>	CH <sub>3</sub>	O=CCH <sub>3</sub>	131.2	+10.7	142.3	-16.1	5.15
<b>4c</b>	CH <sub>2</sub> CH=CHCH <sub>3</sub>	O=CCH <sub>3</sub>	132.2	+11.7	143.8	-14.6	5.18
<b>4d</b>	CH <sub>2</sub> C <sub>6</sub> H <sub>5</sub>	O=CCH <sub>3</sub>	130.1	+9.6	144.6	-13.8	5.15
<b>4e</b>	CH <sub>2</sub> -CH=CHC <sub>6</sub> H <sub>5</sub>	O=CCH <sub>3</sub>	134.8	+14.3	144.6	-13.8	5.17
<b>5a</b>	O=CCH <sub>3</sub>	CH <sub>3</sub>	114.5	-6.0	160.7	+2.3	4.67
<b>5b</b>	O=CCH <sub>3</sub>	CH <sub>2</sub> C <sub>6</sub> H <sub>5</sub>	114.8	-5.7	159.8	+1.4	4.71
<b>5c</b>	O=CCH <sub>3</sub>	CH <sub>2</sub> CH=CHCH <sub>3</sub>	114.4	-6.1	159.7	+1.3	4.66
<b>5d</b>	O=CCH <sub>3</sub>	CH <sub>2</sub> CH=CH <sub>2</sub>	114.6	-5.9	159.5	+1.1	4.69
<b>5e</b>	O=CCH <sub>3</sub>	CH <sub>2</sub> CH=CHC <sub>6</sub> H <sub>5</sub>	114.7	-5.8	159.7	+1.3	4.70

<sup>a</sup> The difference in  $^{13}\text{C}$  chemical shifts of C-2 and C-3 ( $\Delta_{(\text{C}-2)}$  and  $\Delta_{(\text{C}-3)}$ ) were calculated by subtracting the chemical shifts of various derivatives from the corresponding values of compound **1**.

derivatives. The standard  $^{13}\text{C}$  chemical shifts of C-2 and C-3 of ascorbic acid and **1** are 118.8, 120.5, 156.3, and 158.4 ppm, respectively.<sup>32,40</sup> The  $^{13}\text{C}$  NMR signals of C-2 and C-3 are in the ranges of 119–120 ppm and 148–150 ppm for 3-O-alkylated derivatives and 121–123 ppm and 156–158 ppm for 2-O-alkylated derivatives, respectively (Table 5), and are in good agreement with the previously reported values.<sup>28–33</sup> The O-3 alkylation causes an upfield shift (8.5 to 10.2 ppm) of  $^{13}\text{C}$  signals of C-3 (**2a–d**) with respect to **1** depending on the nature of the alkyl substituent. On the other hand, the effects of the O-2-substitution (**3a–d**) on the  $^{13}\text{C}$  signals of C-2 are considerably smaller and in the range of 0.3–2.6 ppm (upfield). The large chemical shift difference in the  $^{13}\text{C}$  signals of C-3 in the 3-O-substituted derivatives (**2a–d**) in comparison to the C-2 in the 2-O-substituted derivatives (**3a–d**) must be due to the lack of efficient delocalization of the 3-O electron density into the C-1-carbonyl in 3-O-substituted derivatives (**2a–d**) in comparison to 2-O-substituted derivatives (**3a–d**). This effect is also clearly visible in  $^1\text{H}$  NMR chemical shifts of C-4-H, where 3-O-substitution (**2a–d**) caused an upfield shift of the C-4-H in comparison to the O-2-substituted derivatives (**3a–d**).

In the O-2- and O-3-disubstituted series, the C-2 and C-3 showed characteristic shifts of  $^{13}\text{C}$  signals with respect to **1** that could be used to distinguish the 3-O-acetyl-2-O-alkyl derivatives (**4a–e**) from the 2-O-acetyl-3-O-alkyl derivatives (**5a–e**). The  $^{13}\text{C}$  signals of C-3 of 3-O-acetyl-2-O-alkyl-substituted derivatives (**4a–e**) showed a large upfield shift in the range of 16–14 ppm with respect to **1**. On the other hand,  $^{13}\text{C}$  signals of C-2

of these derivatives showed large downfield shifts (in the range of 9–14 ppm) with respect to **1**. As discussed above for 3-O-alkylated derivatives (**2a–d**), these large  $^{13}\text{C}$  shifts of C-3 of 3-O-acetylated derivatives (**4a–e**) must be due to the significant perturbation of the native electronic structure of **1** by the electron withdrawing 3-O-acetate group. The inhibition of the delocalization of 3-O oxygen electron to the C-1 carbonyl by the 3-O-acetate group leads to the increase of the electron density at C-3 causing  $^{13}\text{C}$  signal to shift upfield, and a decrease of electron density at C-2 causing  $^{13}\text{C}$  signal to shift significantly downfield. A significant downfield shift of the  $^1\text{H}$  NMR signal of C-4-H of **4a–e**, in comparison to **1**, further confirms the significant perturbation of the native electronic structure of **1** by the electron-withdrawing nature of the 3-O-acetyl group. Interestingly, in 2-O-acetyl-3-O-alkyl-substituted derivatives (**5a–e**), the effects were more localized to the C-2 as expected. The  $^{13}\text{C}$  signals of the C-2 of these derivatives shifted upfield in comparison to **1**, which is in sharp contrast to the effects of C-3-O-acetyl substitution, suggesting that the direct electron-withdrawing effect of the C-2-O-acetate group primarily determines the  $^{13}\text{C}$  chemical shift of the C-2 of these derivatives. The C-4-H of 2-O-acetyl substituted derivatives (**5a–e**) showed a small but significant upfield shift, again demonstrating the electron withdrawing inductive effect of the 2-O-acetyl group.

## Experimental Section

General procedural information is reported on page 2 of the Supporting Information.

**5, 6-O-Isopropylidene-L-ascorbic Acid (1).** This was synthesized in 82% yield according to the procedure of Jung et al.<sup>42</sup> mp 204–206 °C (lit.<sup>25</sup> mp 201–203 °C);  $^1\text{H}$  NMR (400 MHz, D<sub>2</sub>O)  $\delta$  1.37 (6H, s), 4.17 (1H, dd,  $J = 9.1, 5.0$  Hz), 4.31 (1H, dd,  $J = 9.1, 7.3$  Hz), 4.59 (1H, ddd,  $J = 7.3, 5.0, 2.4$  Hz),

(40) Paukstelis, J. V.; Mueller, D. D.; Seib, P. A.; Lillard, D. W., Jr. In *Ascorbic Acid: Chemistry, Metabolism, and Uses*; Seib, P. A., Tolbert, B. M., Eds.; American Chemical Society: Washington, D.C., 1982; pp 125–151.

4.91 (1H, d,  $J = 2.4$  Hz);  $^{13}\text{C}$  NMR (100 MHz,  $\text{D}_2\text{O}$ )  $\delta$  26.70, 27.51, 67.75, 75.65, 78.54, 113.46, 120.54, 158.37, 176.08.

**5, 6-*O*-Isopropylidene-3-*O*-methyl-L-ascorbic Acid (2a).** This compound was synthesized according to the procedure of Wimalasena and Mahindaratne.<sup>32</sup> A mixture of **1** (1 g, 4.63 mmol) and 1.2 equiv of  $\text{K}_2\text{CO}_3$  (0.77 g, 5.56 mmol) in DMSO/THF (9:8) was stirred for 20 min at room temperature. Then 1.2 equiv of methyl iodide (0.79 g, 5.56 mmol) in the same solvent was added dropwise, and the mixture was vigorously stirred for 4–6 h at room temperature. The reaction mixture was diluted (4-fold) with water and extracted with ethyl acetate. The organic layer was thoroughly washed with water and dried over anhydrous  $\text{Na}_2\text{SO}_4$ , and the solvents were removed under reduced pressure. The product was purified by conventional silica gel column chromatography using 4:1 *n*-hexane/ethyl acetate to give 91% yield as a viscous oil:  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  1.37 (3H, s), 1.40 (3H, s), 4.02 (1H, dd,  $J = 8.5, 6.6$  Hz), 4.13 (1H, dd,  $J = 8.5, 6.7$  Hz), 4.18 (3H, s), 4.23 (1H, dt,  $J = 6.7, 3.8$  Hz), 4.53 (1H, d,  $J = 3.8$  Hz);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  25.2, 25.6, 59.4, 65.0, 73.9, 75.3, 110.0, 119.5, 149.9, 171.2.

**5,6-*O*-Isopropylidene-3-*O*-benzyl-L-ascorbic Acid (2b).** This was synthesized from **1** and benzyl bromide in 86% yield as a semisolid using the standard procedure for **2a**:  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  1.36 (3H, s), 1.39 (3H, s), 4.02 (1H, dd,  $J = 8.6, 6.7$  Hz), 4.10 (1H, dd,  $J = 8.6, 6.7$  Hz), 4.26 (1H, dt,  $J = 6.7, 3.8$  Hz), 4.57 (1H, d,  $J = 3.8$  Hz), 5.52 (2H, two d), 7.35–7.42 (5H, m);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ) 25.5, 25.9, 65.3, 73.5, 74.2, 75.7, 110.3, 119.5, 128.4, 128.6, 128.7, 135.7, 148.6, 171.1.

**5,6-*O*-Isopropylidene-3-*O*-trans-crotyl-L-ascorbic Acid (2c).** This was synthesized from **1** and *trans*-crotyl bromide in 72% yield as a light yellow oil using the standard procedure for **2a**:  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  1.37 (3H, s), 1.40 (3H, s), 1.75 (3H, dq,  $J = 6.5, 1.5$  Hz), 4.02 (1H, dd,  $J = 8.6, 6.7$  Hz), 4.13 (1H, dd,  $J = 8.6, 6.7$  Hz), 4.26 (1H, dt,  $J = 6.7, 3.9$  Hz), 4.55 (1H, d,  $J = 3.9$  Hz), 4.89 (2H, m), 5.68 (1H, dtq,  $J = 15.3, 6.6, 1.5$  Hz), 5.90 (1H, dtq,  $J = 15.3, 6.5, 1.5$  Hz);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  17.8, 25.6, 25.9, 65.3, 72.4, 74.4, 75.7, 110.3, 119.1, 125.2, 132.6, 148.6, 171.8.

**5,6-*O*-Isopropylidene-3-*O*-allyl-L-ascorbic Acid (2d).** This was synthesized from **1** and allyl bromide in 80% yield as a light transparent oil using the standard procedure for **2a**:  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  1.37 (3H, s), 1.40 (3H, s), 4.04 (1H, dd,  $J = 8.6, 6.7$  Hz), 4.15 (1H, dd,  $J = 8.6, 6.7$  Hz), 4.28 (1H, dt,  $J = 6.6, 3.8$  Hz), 4.58 (1H, d,  $J = 3.8$  Hz), 4.97 (2H, d,  $J = 5.7$  Hz), 5.31 (1H, dq,  $J = 10.4, 1.4$  Hz), 5.41 (1H, dq,  $J = 17.2, 1.4$  Hz), 6.01 (1H, ddt,  $J = 17.2, 10.4, 5.7$  Hz);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  25.5, 25.9, 65.3, 72.3, 74.3, 75.6, 110.3, 119.1, 119.2, 132.2, 148.2, 171.0.

**5,6-*O*-Isopropylidene-2-*O*-allyl-L-ascorbic Acid (3a).** A solution of 2 equiv of potassium *tert*-butoxide (*t*-BuOK) (1.04 g, 9.26 mmol) in dry DMSO/THF (3:2) was added dropwise to a solution of **1** (1 g, 4.63 mmol) in the same solvent at  $-10$  °C under nitrogen to produce a bright yellow solution with an orange tint. The stirring of the mixture was continued for about 2 min after which 1.1 equiv of allyl bromide (0.62 g, 5.09 mmol) in the same solvent was added dropwise over a period

of 3 min with stirring continued for an additional 5 min at  $-10$  °C. The cooling bath was removed, and the reddish orange reaction solution was stirred for 3 h at room temperature. The reaction mixture was quenched with a cold solution of 0.25 M HCl (20 mL) and extracted with ethyl acetate (3  $\times$  100 mL). The organic layer was dried over  $\text{Na}_2\text{SO}_4$ , and the solvents were removed under reduced pressure. The product was purified by conventional silica gel column chromatography using 3:1 *n*-hexane/ethyl acetate to give 80% yield as a white solid:  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  1.38 (3H, s), 1.43 (3H, s), 4.02 (1H, dd,  $J = 9.0, 6.8$  Hz), 4.16 (1H, dd,  $J = 9.0, 6.8$  Hz), 4.43 (1H, dt,  $J = 6.8, 3.6$  Hz), 4.62 (2H, dt,  $J = 6.3, 1.2$  Hz), 4.72 (1H, d,  $J = 3.6$  Hz), 5.28 (1H, dq,  $J = 10.2, 2.0$  Hz), 5.36 (1H, dq,  $J = 17.3, 2.0$  Hz), 5.98 (1H, ddt,  $J = 17.3, 10.2, 6.3$  Hz);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  25.2, 25.7, 64.9, 72.1, 73.8, 73.9, 110.6, 119.6, 121.4, 133.0, 156.4, 168.8. Anal. Calcd for  $\text{C}_{12}\text{H}_{16}\text{O}_6$ : C, 56.24; H, 6.29; O, 37.47. Found: C, 56.31; H, 6.21; O, 37.48.

**5,6-*O*-Isopropylidene-2-*O*-methyl-L-ascorbic Acid (3b).** This was synthesized from **1** and methyl iodide in 91% yield as a semisolid using the standard procedure for **3a**:  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  1.40 (3H, s), 1.45 (3H, s), 3.87 (3H, s), 4.07 (1H, dd,  $J = 9.0, 6.8$  Hz), 4.19 (1H, dd,  $J = 9.0, 6.8$  Hz), 4.46 (1H, dt,  $J = 6.8, 3.3$  Hz), 4.71 (1H, d,  $J = 3.3$  Hz);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  25.4, 25.8, 59.6, 65.1, 73.96, 74.2, 111.0, 123.1, 155.8, 169.3. Anal. Calcd for  $\text{C}_{10}\text{H}_{14}\text{O}_6$ : C, 52.17; H, 6.13; O, 41.70. Found: C, 52.43; H, 6.34; O, 41.23.

**5,6-*O*-Isopropylidene-2-*O*-trans-crotyl-L-ascorbic Acid (3c).** This was synthesized from **1** and *trans*-crotyl bromide in 72% yield as a light yellow oil using the standard procedure for **3a**:  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  1.37 (3H, s), 1.41 (3H, s), 1.71 (3H, dq,  $J = 6.9, 1.7$  Hz), 4.05 (1H, dd,  $J = 8.5, 6.8$  Hz), 4.17 (1H, dd,  $J = 8.5, 6.8$  Hz), 4.39 (1H, dt,  $J = 6.8, 3.6$  Hz), 4.49 (2H, dt,  $J = 6.6, 1.0$  Hz), 4.69 (1H, d,  $J = 3.6$  Hz), 5.64 (1H, dtq,  $J = 15.7, 6.9, 1.6$  Hz), 5.797 (1H, dtq,  $J = 15.7, 6.9, 1.6$  Hz);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  17.8, 25.3, 25.7, 64.99, 72.3, 73.9, 74.6, 110.4, 120.8, 125.8, 132.6, 157.9, 170.1; HRMS (FAB+)  $m/z$  exact mass calcd for  $\text{C}_{13}\text{H}_{19}\text{O}_6$  ( $M + 1$ ) 271.1180, found  $m/z$  271.1182.

**5,6-*O*-Isopropylidene-2-*O*-benzyl-L-ascorbic Acid (3d).** This was synthesized from **1** and benzyl bromide in 83% yield as a semisolid using the standard procedure for **3a**:  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  1.34 (3H, s), 1.37 (3H, s), 3.86 (1H, dd,  $J = 8.2, 6.7$  Hz), 4.04 (1H, dd,  $J = 8.2, 6.7$  Hz), 4.31 (1H, dt,  $J = 6.7, 3.6$  Hz), 4.60 (1H, d,  $J = 3.6$  Hz), 5.11 (2H, two d), 7.31–7.41 (5H, m);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  25.3, 25.8, 64.9, 73.3, 73.9, 74.2, 110.4, 121.1, 128.4, 128.5, 128.7, 136.4, 157.5, 169.3. Anal. Calcd for  $\text{C}_{16}\text{H}_{18}\text{O}_6$ : C, 62.74; H, 5.92; O, 31.34. Found: C, 62.95; H, 5.80; O, 31.25.

**5,6-*O*-Isopropylidene-2-*O*-trans-cinnamyl-L-ascorbic Acid (3e).** This was synthesized from **1** and *trans*-cinnamyl bromide in 87% yield as a semisolid using the standard procedure for **3a**:  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  1.30 (3H, s), 1.35 (3H, s), 3.99 (1H, dd,  $J = 8.8, 6.7$  Hz), 4.09 (1H, dd,  $J = 8.8, 6.7$  Hz), 4.36 (1H, dt,  $J = 6.7, 3.6$  Hz), 4.64 (1H, d,  $J = 3.6$  Hz), 4.74 (2H, d,  $J = 6.6$  Hz), 6.32 (1H, dt,  $J = 13.8, 6.6$  Hz), 6.36 (1H, d,  $J = 13.8$  Hz), 7.213–7.375 (5H, m), 8.667 (1H, s);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  25.13, 25.63, 64.85, 72.00, 73.73, 74.13, 110.59, 121.25, 123.77, 126.69, 128.15, 128.59, 135.09, 136.06, 157.11, 169.50. Anal. Calcd for  $\text{C}_{18}\text{H}_{20}\text{O}_6$ : C, 65.05; H, 6.07; O, 28.88. Found: C, 65.34; H, 5.75; O, 28.91.

**5,6-*O*-Isopropylidene-2-*O*-heptyl-L-ascorbic Acid (3f).** This was synthesized from **1** and 1-bromoheptane in 96% yield as a semisolid using the standard procedure for **3a**:  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  0.88 (3H, t), 1.28–1.35 (8H, m), 1.38 (3H, s), 1.42 (3H, s), 1.66 (2H, quin,  $J = 7.0$  Hz), 4.03–4.10 (2H, m), 4.18 (2H, dd,  $J = 8.8, 7.0$  Hz), 4.43 (1H, dt,  $J = 6.6, 3.4$  Hz), 4.71 (1H, d,  $J = 3.4$  Hz), 8.79 (1H, s);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  13.7, 22.51, 25.18, 25.46, 25.72, 29.00, 29.57, 31.69, 64.99, 72.04, 73.82, 74.47, 110.50, 121.78, 156.58, 170.01; HRMS (FAB+)  $m/z$  exact mass calcd for  $\text{C}_{16}\text{H}_{27}\text{O}_6$  ( $M + 1$ ) 315.1810, found  $m/z$  315.1808.

(41) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Zakrzewski, V. G.; Montgomery, J. A., Jr.; Stratmann, R. E.; Burant, J. C.; Dapprich, S.; Millam, J. M.; Daniels, A. D.; Kudin, K. N.; Strain, M. C.; Farkas, O.; Tomasi, J.; Barone, V.; Cossi, M.; Cammi, R.; Mennucci, B.; Pomelli, C.; Adamo, C.; Clifford, S.; Ochterski, J.; Petersson, G. A.; Ayala, P. Y.; Cui, Q.; Morokuma, K.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Cioslowski, J.; Ortiz, J. V.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Gonzalez, C.; Challacombe, M.; Gill, P. M. W.; Johnson, B. G.; Chen, W.; Wong, M. W.; Andres, J. L.; Head-Gordon, M.; Replogle, E. S.; Pople, J. A. *Gaussian 98*, revision A.7; Gaussian, Inc.: Pittsburgh, PA, 1998.

(42) Jung, M. E.; Shaw, T. J. *J. Am. Chem. Soc.* **1980**, *102*, 6304–6311.

**5,6-*O*-Isopropylidene-2-*O*-allyl-3-*O*-acetyl-*L*-ascorbic Acid (4a).** This was synthesized from **3a** (1 g, 3.90 mmol) and 1.4 equiv of pyridine (0.43 g, 5.46 mmol) in CH<sub>2</sub>Cl<sub>2</sub> and stirred for 20 min at room temperature. Then, 1.2 equiv of acetyl chloride (0.37 g, 4.68 mmol) was added dropwise under nitrogen. The mixture was vigorously stirred until the solution became homogeneous and was further stirred for 2 h at room temperature. The reaction mixture was diluted with water (4-fold) and extracted with ethyl acetate. The organic layer was dried over Na<sub>2</sub>SO<sub>4</sub>, and the solvents were removed under reduced pressure. The product was purified by conventional silica gel column chromatography using 7:1 *n*-hexane/ethyl acetate to give 70% yield as a light yellow oil: <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 1.36 (3H, s), 1.38 (3H, s), 2.31 (3H, s), 4.02 (1H, dd, *J* = 8.3, 6.6 Hz), 4.15 (1H, dd, *J* = 8.3, 6.6 Hz), 4.29 (1H, dt, *J* = 6.6, 2.5 Hz), 4.78 (2H, tt, *J* = 5.1, 1.5 Hz), 5.18 (1H, d, *J* = 2.5 Hz), 5.28 (1H, dq, *J* = 10.5, 2.1 Hz), 5.37 (1H, dq, *J* = 17.3, 2.1 Hz), 5.97 (1H, ddt, *J* = 17.3, 10.5, 5.1 Hz); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ 20.6, 25.3, 25.6, 65.1, 71.3, 72.8, 74.5, 110.5, 118.9, 130.1, 132.4, 143.8, 166.3, 166.4; HRMS (FAB+) *m/z* exact mass calcd for C<sub>14</sub>H<sub>19</sub>O<sub>7</sub> (M + 1) 299.1130, found *m/z* 299.1131.

**5,6-*O*-Isopropylidene-2-*O*-methyl-3-*O*-acetyl-*L*-ascorbic Acid (4b).** This was synthesized from **3b** and acetyl chloride in 80% yield as a transparent viscous oil using the standard procedure for **4a**: <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 1.36 (3H, s), 1.39 (3H, s), 2.32 (3H, s), 4.00 (3H, s), 4.04 (1H, dd, *J* = 9.0, 6.9 Hz), 4.16 (1H, dd, *J* = 9.0, 6.9 Hz), 4.30 (1H, dt, *J* = 6.9, 2.3 Hz), 5.15 (1H, d, *J* = 2.3 Hz); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ 20.5, 25.3, 25.6, 58.4, 65.1, 72.8, 74.4, 110.5, 131.2, 142.3, 166.2, 166.4; HRMS (FAB+) *m/z* exact mass calcd for C<sub>12</sub>H<sub>17</sub>O<sub>7</sub> (M + 1) 273.0970, found *m/z* 273.0974.

**5,6-*O*-Isopropylidene-2-*O*-trans-crotyl-3-*O*-acetyl-*L*-ascorbic Acid (4c).** This was synthesized from **3c** and acetyl chloride in 84% yield as a light yellow oil using the standard procedure for **4a**: <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 1.36 (3H, s), 1.38 (3H, s), 1.73 (3H, dq, *J* = 6.4, 1.8 Hz), 2.31 (3H, s), 4.01 (1H, dd, *J* = 8.5, 6.6 Hz), 4.14 (1H, dd, *J* = 8.5, 6.6 Hz), 4.28 (1H, dt, *J* = 6.6, 2.4 Hz), 4.70 (2H, dt, *J* = 6.4, 1.7 Hz), 5.18 (1H, d, *J* = 2.4 Hz), 5.64 (1H, dtq, *J* = 16.8, 6.4, 1.7 Hz), 5.83 (1H, dtq, *J* = 16.8, 6.4, 1.7 Hz); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 17.7, 20.5, 25.3, 25.6, 65.0, 71.4, 72.9, 74.4, 110.5, 125.4, 130.1, 132.2, 143.8, 166.3, 166.5. Anal. Calcd for C<sub>15</sub>H<sub>20</sub>O<sub>7</sub>: C, 57.69%; H, 6.45%; O, 35.86%. Found: C, 57.74%; H, 6.54%; O, 35.72%.

**5,6-*O*-Isopropylidene-2-*O*-benzyl-3-*O*-acetyl-*L*-ascorbic Acid (4d).** This was synthesized from **3d** and acetyl chloride in 82% yield as a light yellow oil using the standard procedure for **4a**: <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 1.33 (3H, s), 1.34 (3H, s), 2.21 (3H, s), 3.96 (1H, dd, *J* = 8.4, 6.8 Hz), 4.11 (1H, dd, *J* = 8.4, 6.8 Hz), 4.25 (1H, dt, *J* = 6.8, 2.4 Hz), 5.15 (1H, d, *J* = 2.4 Hz), 5.28 (1H, d, *J* = 11.6 Hz), 5.33 (1H, d, *J* = 11.6 Hz), 7.31–7.39 (5H, m); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 20.6, 25.3, 25.6, 65.0, 72.5, 72.8, 74.0, 110.5, 127.8, 128.4, 128.5, 130.1, 135.9, 144.6, 166.1, 166.5; HRMS (FAB+) *m/z* exact mass calcd for C<sub>18</sub>H<sub>21</sub>O<sub>7</sub> (M + 1) 349.1290, found *m/z* 349.1298.

**5,6-*O*-Isopropylidene-2-*O*-cinnamyl-3-*O*-acetyl-*L*-ascorbic Acid (4e).** This was synthesized from **3e** and acetyl chloride in 76% yield as viscous oil using the standard procedure for **4a**: <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 1.30 (3H, s), 1.32 (3H, s), 2.30 (3H, s), 4.02 (1H, dd, *J* = 8.4, 6.6 Hz), 4.13 (1H, dd, *J* = 8.4, 6.6 Hz), 4.29 (1H, dt, *J* = 6.6, 2.4 Hz), 4.89–5.00 (2H, m), 5.17 (1H, d, *J* = 2.4 Hz), 6.33 (1H, dt, *J* = 13.6, 6.5 Hz), 6.08 (1H, d, *J* = 13.6 Hz), 7.19–7.41 (5H, m); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ 25.3, 25.4, 25.6, 65.1, 71.3, 72.9, 74.5, 110.6, 123.4, 126.7, 128.3, 128.6, 128.8, 134.8, 136.0, 144.6, 166.3, 166.6; HRMS (FAB +) *m/z* exact mass calcd for C<sub>20</sub>H<sub>23</sub>O<sub>7</sub> (M + 1) 375.1440, found *m/z* 375.1444.

**5,6-*O*-Isopropylidene-3-*O*-methyl-2-*O*-acetyl-*L*-ascorbic Acid (5a).** This compound was synthesized according to the procedure of Wimalasena and Mahindaratne.<sup>32</sup> **2a** (1 g, 4.34 mmol) and 1.4 equiv of pyridine (0.481 g, 6.1 mmol) in

CH<sub>2</sub>Cl<sub>2</sub> was stirred for 20 min at room temperature, and 1.2 equiv of acetyl chloride (0.409 g, 5.21 mmol) was added dropwise. The mixture was vigorously stirred until the solution became homogeneous and was further stirred for 2 h at room temperature. The reaction mixture was diluted (4-fold) with water and extracted with ethyl acetate. The organic layer was thoroughly washed with water and dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, and the solvents were removed under reduced pressure. The product was isolated and purified with conventional silica gel column chromatography using 7:1 *n*-hexane/ethyl acetate to give 90% yield as a transparent oil: <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 1.36 (3H, s), 1.39 (3H, s), 2.31 (3H, s), 4.00 (3H, s), 4.02 (1H, dd, *J* = 8.5, 6.6 Hz), 4.15 (1H, dd, *J* = 8.5, 6.6 Hz), 4.29 (1H, dt, *J* = 6.6, 2.4 Hz), 5.14 (1H, d, *J* = 2.4 Hz); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ 20.5, 25.3, 25.6, 58.4, 65.1, 72.9, 74.4, 110.6, 131.3, 142.4, 166.3, 166.4.

**5,6-*O*-Isopropylidene-3-*O*-benzyl-2-*O*-acetyl-*L*-ascorbic Acid (5b).** This was synthesized from **2b** and acetyl chloride in 90% yield as a light yellow oil using the standard procedure for **5a**: <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 1.36 (3H, s), 1.39 (3H, s), 2.22 (3H, s), 4.07 (1H, dd, *J* = 8.6, 6.7 Hz), 4.14 (1H, dd, *J* = 8.6, 6.7 Hz), 4.38 (1H, dt, *J* = 6.7, 2.9 Hz), 4.71 (1H, d, *J* = 2.9 Hz), 5.31 (1H, d, *J* = 11.5 Hz), 5.37 (1H, d, *J* = 11.5 Hz), 7.30–7.50 (5H, m); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ 20.1, 25.5, 25.7, 65.1, 73.6, 73.9, 75.2, 110.5, 114.8, 127.5, 128.8, 129.0, 134.5, 159.8, 166.8, 167.5.

**5,6-*O*-Isopropylidene-3-*O*-trans-crotyl-2-*O*-acetyl-*L*-ascorbic Acid (5c).** This was synthesized from **2c** and acetyl chloride in 78% as a light yellow semisolid using the standard procedure for **5a**: <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 1.36 (3H, s), 1.40 (3H, s), 1.76 (3H, dq, *J* = 6.5, 1.6 Hz), 2.27 (3H, s), 4.07 (1H, dd, *J* = 8.6, 6.6 Hz), 4.15 (1H, dd, *J* = 8.6, 6.6 Hz), 4.36 (1H, dt, *J* = 6.6, 3.1 Hz), 4.66 (1H, d, *J* = 3.1 Hz), 4.73 (2H, m), 5.62 (1H, dtq, *J* = 15.4, 6.5, 1.6 Hz), 5.87 (1H, dtq, *J* = 15.4, 6.5, 1.6 Hz); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ 17.7, 20.2, 25.5, 25.7, 65.2, 72.6, 73.7, 75.3, 110.5, 114.4, 124.0, 133.2, 159.7, 167.0, 167.6.

**5,6-*O*-Isopropylidene-3-*O*-allyl-2-*O*-acetyl-*L*-ascorbic Acid (5d).** This was synthesized from **2d** and acetyl chloride in 70% yield as a colorless semisolid using the standard procedure for **5a**: <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 1.37 (3H, s), 1.41 (3H, s), 2.27 (3H, s), 4.08 (1H, dd, *J* = 8.6, 6.6 Hz), 4.16 (1H, dd, *J* = 8.6, 6.6 Hz), 4.38 (1H, dt, *J* = 6.6, 3.0 Hz), 4.69 (1H, d, *J* = 3.0 Hz), 4.81 (2H, two dtd), 5.35 (1H, dq, *J* = 10.6, 1.6 Hz), 5.40 (1H, dq, *J* = 17.7, 1.6 Hz), 5.95 (1H, ddt, *J* = 17.7, 10.6, 5.5 Hz); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ 20.3, 25.5, 25.8, 65.2, 72.5, 73.7, 75.3, 110.6, 114.6, 119.6, 131.0, 159.5, 166.8, 167.6.

**5,6-*O*-Isopropylidene-3-*O*-trans-cinnamyl-2-*O*-acetyl-*L*-ascorbic Acid (5e).** A mixture of **6** (1 g, 3.87 mmol) and 1.2 equiv of K<sub>2</sub>CO<sub>3</sub> (0.64 g, 4.65 mmol) in DMSO/THF (9:8) was stirred for 20 min at room temperature. Then 1.2 equiv of cinnamyl bromide (0.92 g, 4.65 mmol) in the same solvent was added dropwise, and the mixture was vigorously stirred for 4–6 h at room temperature. The reaction mixture was diluted (4-fold) with water and extracted with ethyl acetate. The organic layer was thoroughly washed with water and dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, and the solvents were removed under reduced pressure. The product was purified by conventional silica gel column chromatography using 7:1 *n*-hexane/ethyl acetate to give 76% yield as a colorless crystals: <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 1.36 (3H, s), 1.41 (3H, s), 2.28 (3H, s), 4.09 (1H, dd, *J* = 8.6, 6.6 Hz), 4.17 (1H, dd, *J* = 8.6, 6.6 Hz), 4.40 (1H, d, *J* = 6.6, 2.9 Hz), 4.70 (1H, d, *J* = 2.9 Hz), 4.90–5.03 (2H, m), 6.29 (1H, dt, *J* = 15.9, 6.3 Hz), 6.71 (1H, d, *J* = 15.9 Hz), 7.23–7.36 (3H, m), 7.37–7.42 (2H, m); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ 20.2, 25.5, 25.7, 65.2, 72.6, 73.6, 75.3, 110.6, 114.7, 121.6, 126.7, 128.6, 128.7, 129.3, 135.5, 159.7, 166.9, 167.6.

**5,6-*O*-Isopropylidene-2-*O*-acetyl-*L*-ascorbic Acid (6).** This was synthesized by stirring a suspension of **1** (1 g, 4.63 mmol) and 1.4 equiv of pyridine (0.51 g, 6.48 mmol) in CH<sub>2</sub>Cl<sub>2</sub> at room temperature for 10 min. Then 1.2 equiv of acetyl



chloride (0.44 g, 5.55 mmol) was added dropwise. The mixture was vigorously stirred until the solution became homogeneous and was further stirred for 2 h at room temperature. The reaction was diluted (4-fold) with water and extracted with ethyl acetate. The organic layer was thoroughly washed with water and dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, and the solvents were removed under reduced pressure. The product was purified with conventional silica gel column chromatography using 5:2 *n*-hexane/ethyl acetate to give 90% yield as a white solid: <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 1.38 (3H, s), 1.41 (3H, s), 2.36 (3H, s), 4.10 (1H, dd, *J* = 8.71, 6.74 Hz), 4.20 (1H, dd, *J* = 8.71, 6.74 Hz), 4.44 (1H, dt, *J* = 6.74, 2.81 Hz), 4.70 (1H, d, *J* = 2.81 Hz), 9.70–9.80 (1H, s); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ 20.68, 25.54, 25.72, 65.28, 73.40, 74.57, 110.72, 115.39, 155.13, 166.23, 171.29.

**Acknowledgment.** This work was supported by a grant from the National Institutes of Health (NS 39423). We thank Bob Drake and Lawrence Seib of the Mass Spectrometry laboratory at University of Kansas for the help in exact mass (FAB) analyses.

**Supporting Information Available:** <sup>1</sup>H, <sup>13</sup>C, and selected 2D NMR spectra for compounds **2a–d**, **3a–f**, **4a–e**, and **5a–e** and the calculated electrostatic potential diagram of the neutral, monoanionic, and dianionic forms of 5, 6-*O*-Isopropylidene-L-ascorbic acid (**1**). This material is available free of charge via the Internet at <http://pubs.acs.org>.

JO049319I