One-Pot 2-O-Alkylation of L-Ascorbic Acid

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Abstract: One-pot 2-O-alkylation of L-ascorbic acid involving an in situ 3-O-silylation and desilylation sequence was investigated. Initially the 3-OH group was masked with a *t*-butyldimethylsilyl (TBDMS) group followed by alkylation of the 2-OH group. Removal of the TBDMS group using 20% sulfuric acid also resulted in hydrolysis of the 5,6-*O*-isopropylidene to give 2-*O*-alkyl derivatives of L-ascorbic acid. Selective removal of the 3-*O*-TBDMS with tetrabutylammonium fluoride (TBAF) gave 5,6-*O*-isopropylidene-2-*O*-alkyl derivatives of L-ascorbic acid in good overall yields. Through the application of this protocol, 5,6-*O*-isopropylidene 2-*O*-alkyl derivatives of L-ascorbic acid as well as 2-*O*-alkyl derivatives of L-ascorbic acid may be easily accessed.

Key words: L-ascorbic acid, alkylation, one-pot synthesis, silylation, desilylation

L-Ascorbic acid (Vitamin C) exhibits an array of biological activities. It acts as an antioxidant, radical scavenger and protects cellular components against oxidative damage by free radicals and oxidants;[1] furthermore, the compound serves as a reductant in many important enzymatic transformations.[2,3] In addition, L-ascorbic acid appears to play preventive roles in chronic diseases such as cancer, cerebral apoplexy, diabetes, atopic dermatitis, myocardial infarction, and AIDS.[4] L-Ascorbic acid is susceptible to thermal and oxidative degradation and therefore considerable efforts have been made in recent years to develop more stable derivatives. For example, 5,6-O-modified L-ascorbic acid derivatives are known to be effective antitumor agents for various human cancers, and induce apoptosis in tumor cells,[5] 2-*C*-alkyl derivatives have immunostimulant activity,[6] and 2-O- and 3-O-alkylated derivatives are known to protect against peroxidation of lipids in biomembranes.[7]

Most reports of O-alkylation of L-ascorbic acid are centered on selective 3-O-alkylation because the 3-OH group is more reactive towards electrophiles under mildly basic conditions as compared to the 2-OH group. As a result, many reaction conditions have been developed for selective 3-O-alkylation of L-ascorbic acid.[8] We have recently shown that selective 3-O-alkylation of L-ascorbic acid can be achieved by using phase-transfer catalysis in aqueous medium.[8] 2-O-Alkylation of L-ascorbic acid has been achieved indirectly through a three-step sequence in which the 3-OH group is protected with either methoxymethyl (MOM) or benzyl (Bn) group, followed by alkylation of the 2-OH group and finally the MOM or benzyl group is removed to give 2-*O*-alkyl derivatives.[7b] However, there is only a single report on direct 2-O-alkylation of L-ascorbic acid using *t*-BuOK in DMSO–THF.[9] As part of an ongoing program to explore the utility of L-ascorbic acid in organic synthesis, we required both 5,6-O-protected as well as unprotected 2-*O*-alkyl derivatives of L-ascorbic acid. Our attempts to prepare these derivatives by a reported method[9] were unsuccessful. In our hands, methylation using *t*-BuOK (2.0 equiv) and methyl iodide (1.0 equiv) in DMSO–THF at –10 °C for more than ten hours, furnished the 2,3-di-*O*-methyl derivative of 5,6-*O*-isopropylidene L-ascorbic acid in low yield (25%) with recovery of starting material. An alternative route involving a three-step 3-OH protection, 2-OH alkylation, and 3-OH deprotection sequence is also available, however, this approach has drawbacks because it requires purification at each step, which makes it a somewhat tedious process. In this paper we wish to report an efficient one-pot synthesis of 2-O-alkyl derivatives of L-ascorbic acid.

The *tert*-butyldimethysilyl (TBDMS) group was chosen for 3-OH protection due to the ease of preparation of TBDMS ethers, their stability, and because they can be selectively deprotected under specific reaction conditions. It was conceived that treatment of L-ascorbic acid with TBDMSCl in the presence of an amine could give the 3-*O*-TBDMS derivative selectively, which, upon subsequent treatment with alkyl halides in the same reaction pot, could undergo 2-O-alkylation. The deprotection of both the TBDMS ether and 5,6-*O*-isopropylidene acetal under acidic conditions could thus deliver 5,6-O-unprotected, 2-*O*-alkyl derivatives of L-ascorbic acid. On the other hand, selective removal of the TBDMS group with tetrabutylammonium fluoride (TBAF) could yield 5,6-O-protected 2-*O*-alkyl derivatives of L-ascorbic acid.

Initially, 5,6-*O*-isopropylidene L-ascorbic acid **1** was treated with triethylamine (1.2 equiv) in anhydrous CH_2Cl_2 at 0 °C, followed by addition of TBDMSCl (1.1 equiv) and the reaction mixture was allowed to warm to room temperature. After completion of the reaction (reaction monitored by TLC; 2 h), triethylamine (1.2 equiv), and dimethyl sulfate (1.1 equiv) were added to the same reaction vessel, the mixture was stirred at room temperature for 1.5 h and then treated with 20% aq. H_2SO_4 to de-

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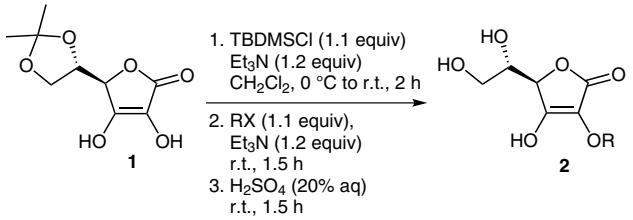
liver 2-*O*-methyl L-ascorbic acid (**2a**)[10] in an overall yield of 51% (over three steps).

Having established a successful one-pot 2-O-methylation, we next explored the scope of this methodology. A variety of alkyl halides underwent smooth alkylation under these reaction conditions and delivered 2-*O*-alkyl derivatives **2b**–**h**[10] in good yields (Table 1).[11] Minor modification of the above procedure provided an efficient synthesis of the 5,6-O-protected 2-*O*-alkyl derivatives. Thus, use of TBAF (1.00 equiv, 9.25 mmol) instead of H_2SO_4 in the last step of the sequence selectively removed the TBDMS group and gave various 2-*O*-alkyl derivatives of 5,6-*O*-isopropylidene L-ascorbic acid **3a**–**h**[10] in good overall yields (Table 2).[12]

Table 1 One-Pot Synthesis of 2-*O*-Alkyl Derivatives of L-Ascorbic Acid



Entry	**2**	R	Yield (%)[a]
1	**2a**	Me	51
2	**2b**	Et	48
3	**2c**	*i*-Pr	45
4	**2d**	Bn	48
5	**2e**	4-$ClC_6H_4CH_2$	50
6	**2f**	4-$BrC_6H_4CH_2$	52
7	**2g**	3-$O_2NC_6H_4CH_2$	40
8	**2h**	4-$O_2NC_6H_4CH_2$	43

[a] Isolated yields for the three-step, one-pot reaction.

To conclude, we report an efficient procedure for 2-O-alkylation of L-ascorbic acid through a three-step, one-pot protocol, using a 3-O-silylation and desilylation sequence, under mild reaction conditions. This strategy allowed a wide variety of both 5,6-O-protected and unprotected 2-*O*-alkyl derivatives of L-ascorbic acid to be synthesized in good yields. Further studies are in progress to expand the scope of this protocol.

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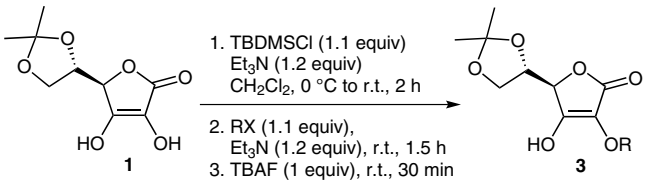
Table 2 Synthesis of 2-*O*-Alkyl Derivatives of 5,6-*O*-Isopropylidene L-Ascorbic Acid



Entry	**3**	R	Yield (%)[a]
1	**3a**	Me	55
2	**3b**	Et	50
3	**3c**	Bn	48
4	**3d**	2-$ClC_6H_4CH_2$	42
5	**3e**	4-$ClC_6H_4CH_2$	46
6	**3f**	4-$BrC_6H_4CH_2$	45
7	**3g**	3-$O_2NC_6H_4CH_2$	41
8	**3h**	4-$O_2NC_6H_4CH_2$	44

[a] Isolated yields for the three-step, one-pot reaction.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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(10) Selected analytical data of novel compounds:
Compound 2a: Viscous liquid; $[\alpha]_D^{25}$ +21.60 (*c* 0.5, MeOH); IR: 3400, 2951, 1770, 1675, 1352, 1145, 759 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ = 3.47–3.57 (m, 2 H), 3.71–3.76 (m, 1 H), 4.12 (s, 3 H), 4.73–4.85 (br m, 3 H); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 58.9, 61.9, 68.6, 74.6, 119.5, 150.8, 170.7; MS: *m*/*z* = 213.2 $[M + Na]^+$.
Compound 2b: Viscous liquid; ^1H NMR (400 MHz, DMSO-d_6): δ = 1.30 (t, *J* = 3.2 Hz, 3 H), 3.47–3.57 (m, 2 H), 3.72–3.76 (m, 1 H), 4.18 (m, 3 H), 4.43–4.49 (m, 3 H); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 15.2, 61.7, 66.5, 68.8, 74.70, 118.8, 150.0, 170.7.
Compound 2c: White solid; mp 100–102 °C; $[\alpha]_D^{25}$ +69.72 (*c* 0.5, MeOH); IR: 3423, 2987, 1749, 1681, 1373, 1074, 910 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 1.28 (m, 6 H), 2.90 (br s, 3 H), 3.79–3.85 (m, 2 H), 3.96 (dd, *J* = 6.2, 2.4 Hz, 1 H), 4.65 (d, *J* = 2.4 Hz, 1 H), 5.10–5.18 (m, *J* = 5.7 Hz, 1 H); ^{13}C NMR (75 MHz, DMSO-d_6): δ = 23.3, 23.4, 62.1, 68.7, 73.1, 74.8, 118.1, 149.2, 170.8.
Compound 2g: Viscous liquid; IR: 3332, 3155, 2949, 1739, 1681, 1537, 1340, 1161, 731 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ = 3.47 (m, 2 H), 3.75 (dd, *J* = 13, 6.4 Hz, 1 H), 4.86 (s, 2 H), 5.05 (d, *J* = 6.2 Hz, 1 H), 5.98 (AB q, *J* = 12.6 Hz, 2 H), 7.69 (t, *J* = 7.6 Hz, 1 H), 7.90 (d, *J* = 7.6 Hz, 1 H), 8.21 (d, *J* = 7.6, 1.5 Hz, 1 H), 8.31 (s, 1 H), 9.02 (br s, 1 H); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 61.7, 68.5, 70.5, 74.6, 119.9, 122.1, 122.9, 129.7, 134.0, 138.8, 147.8, 149.5, 170.2; MS: *m*/*z* = 333.8 $[M + Na]^+$.
Compound 2h: Yellow solid; mp 118–120 °C; IR: 3385, 3238, 2960, 1743, 1685, 1543, 1336, 1163, 732 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ = 3.50 (m, 2 H), 3.78 (m, 1 H), 4.20–4.35 (br s, 2 H), 4.73 (s, 1 H), 5.6 (m, 2 H), 7.72 (m, 2 H), 8.20–8.27 (m, 2 H), 9.04 (br s, 1 H); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 61.7, 68.5, 70.5, 74.6, 119.9, 122.9, 129.8, 138.8, 147.7, 149.4, 170.2; MS: *m*/*z* = 333.9 $[M + Na]^+$.
Compound 3b: White solid; mp 92–93 °C; $[\alpha]_D^{25}$ +15.52 (*c* 0.5, MeOH); IR: 3348, 2928, 1775, 1602, 1411, 1390, 707 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 1.35–1.40 (m, 9 H), 4.03 (dd, *J* = 8.5, 6.7 Hz, 1 H), 4.15 (dd, *J* = 8.5, 6.7 Hz, 1 H), 4.24–4.28 (m, 1 H), 4.51–4.58 (m, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 15.3, 25.5, 25.8, 65.2, 68.1, 74.2, 75.6, 110.7, 118.8, 148.8, 171.3.
Compound 3e: White solid; mp 122–124 °C; $[\alpha]_D^{25}$ +12.56 (*c* 0.5, MeOH); IR: 3289, 2988, 1757, 1697, 1757, 1697, 1372, 1117, 810 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 1.35 (s, 3 H), 1.37 (s, 3 H), 3.99–4.14 (m, 2 H), 4.27 (m, 1 H), 4.58 (d, *J* = 2.9 Hz, 1 H), 5.48 (s, 2 H), 6.51 (s, 1 H), 7.35 (m, 4 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 25.5, 25.8, 65.2, 72.5, 73.9, 75.6, 110.3, 119.7, 128.8, 129.5, 134.1, 134.6, 148.4, 171.2; MS: *m*/*z* = 341.3 $[M + H]^+$.
Compound 3f: White solid; mp 136–138 °C; $[\alpha]_D^{25}$ +82.84 (*c* 0.5, MeOH); IR: 3981, 2987, 1753, 1678, 1334, 1038, 806 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 1.29 (s, 3 H), 1.30 (s, 3 H), 3.93 (dd, *J* = 8.4, 6.4 Hz, 1 H), 4.08 (dd, *J* = 8.4, 6.4 Hz, 1 H), 4.22 (dt, *J* = 6.4, 3.3 Hz, 1 H), 4.64 (m, 1 H), 5.44 (s, 2 H), 7.32 (m, *J* = 8.2 Hz, 2 H), 7.51 (m, 2 H), 9.05 (br s, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 25.2, 25.6, 64.7, 71.2, 73.5, 74.4, 109.1, 120.1, 121.6, 129.4, 130.8, 135.5, 148.3, 169.7; MS: *m*/*z* = 385.0 $[M + H]^+$.
Compound 3g: Viscous liquid; IR: 3502, 2987, 1745, 1687, 1529, 1346, 1115, 729 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 1.32 (s, 3 H), 1.34 (s, 3 H), 4.03 (m, *J* = 8.6, 6.8 Hz, 1 H), 4.15 (dd, *J* = 8.6, 6.8 Hz, 1 H), 4.31–4.35 (m, 1 H), 4.61 (d, *J* = 3 Hz 1 H), 5.56–5.63 (AB q, *J* = 12.6 Hz, 2 H), 7.56 (m, 1 H), 7.73 (d, *J* = 7.6 Hz, 1 H), 8.20 (m, 1 H), 8.25 (d, *J* = 1.5 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 25.4, 25.8, 65.3, 71.8, 73.6, 75.5, 110.5, 120.1, 122.6, 123.5, 124.7, 129.7, 133.7, 137.9, 148.0, 171.0.
Compound 3h: Yellow solid; mp 152 °C; $[\alpha]_D^{25}$ +59.96 (*c* 0.5, MeOH); IR: 3266, 2996, 1758, 1701, 1523, 1339, 1164 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 1.36 (s, 3 H), 1.37 (s, 3 H), 4.06 (dd, *J* = 8.5, 6.7 Hz, 1 H), 4.14 (dd, *J* = 8.5, 6.7 Hz, 1 H), 4.33 (dt, *J* = 6.7, 3.3 Hz, 1 H), 4.64 (d, *J* = 3.3 Hz, 1 H), 5.60 (AB q, *J* = 13 Hz, 2 H), 6.37 (br s, 1 H), 7.58 (d, *J* = 8.6 Hz, 2 H), 8.25 (d, *J* = 8.6 Hz, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 25.5, 25.8, 65.2, 71.8, 73.7, 75.4, 110.4, 119.8, 123.8, 128.1, 142.9, 147.8, 147.9, 170.8; MS: *m*/*z* = 373.9 $[M + Na]^+$.

(11) **One-Pot Synthesis of 2-*O*-Alkyl Derivatives of L-Ascorbic Acid; General Procedure:** A solution of 5,6-*O*-isopropylidene-L-ascorbic acid (**1**; 2.00 g, 9.25 mmol) and Et_3N (1.2 equiv, 11.12 mmol) in anhydrous CH_2Cl_2 (10.0 mL) was cooled to 0 °C. To this reaction mixture was added a solution of TBDMSCl (1.53 g, 10.18 mmol) in anhydrous CH_2Cl_2 (5.0 mL). The reaction mixture was allowed to warm to r.t. and stirred for 2 h. After completion of the reaction (TLC), Et_3N (1.2 mL, 11.12 mmol) was added followed by the requisite alkylating agent (1.1 equiv 10.18 mmol) and the mixture was stirred for a further 1–2 h at r.t. The reaction mixture was then treated with 20% aq H_2SO_4 (10.0 mL) and stirred at r.t. for 1.5 h. After completion of the reaction as indicated by TLC, the reaction mixture was neutralized with solid $NaHCO_3$ and the product was extracted with EtOAc (3 × 10 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered, and the solvent was removed under vacuum. The crude product was purified by silica gel column chromatography (hexane–EtOAc).

(12) **One-Pot Synthesis of 2-*O*-Alkyl Derivatives of 5,6-*O*-Isopropylidene L-Ascorbic Acid; General Procedure:** The same experimental procedure as described in ref. 11 was employed with minor modifications. Selective deprotection of TBDMS group was achieved by the addition of TBAF (1.0 equiv, 9.25 mmol) instead of H_2SO_4. The reaction mixture was stirred at r.t. for 0.5 h. After completion of reaction (monitored by TLC), the mixture was diluted with H_2O (10 mL) and extracted with EtOAc (3 × 10 mL). The combined extracts were dried over anhydrous Na_2SO_4, filtered, and the solvent was removed under vacuum. The crude product was purified by silica gel column chromatography (hexane–EtOAc).

