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SYNTHESIS OF 3-*O*-ALKYLASCORBIC ACIDS FROM L-ASCORBIC ACID IN A SINGLE STEP

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Abstract- An efficient single step synthesis of 3-*O*-alkylascorbic acids from ascorbic acid is described.

L-Ascorbic acid (**1**) is a naturally occurring antioxidants and radical scavengers.[1] It has many important physiological roles as a cofactor in mammalian enzymatic reactions and provides a defense against oxidant readicals *in vivo*. The low solubility of **1** in lipophilic environments as well as the susceptibility to thermal and oxidative degeneration has stimulated considerable interest in the synthesis of lipophilic derivatives of ascorbic acid (**1**) with increased stability. For example, 3-*O*-alkylascorbic acids were found to be stable in ointments and to suppress intracellular melanin accumulation in the skin.[2] In light of the medicinal importance of 3-*O*-alkyl analogues, we undertook an investigation of shorter and more general routes to these derivatives.

Alkylation reactions of **1** are fairly sensitive to usual alkylation reagent, base, solvent and reaction conditions. The most general preparation of alkylated ascorbic acids was based on the regioselective alkylation of the 5,6-*O*-isopropylidene-L-ascorbic acid with alkyl halides in the presence of different bases.[2] Nihro and co-workers prepared a series of 3-*O*-alkyl analogues by regioselective alkylation of 5,6-*O*-isopropylidene-L-ascorbic acid.[3] Recently, 5,6-*O*-isopropylidene-L-ascorbic acid was also alkylated using various alkylating agents and bases to give both 3-*O* and 2-C substituted products.[4] However, these methods require 3 steps to obtain the final products.

A literature survey revealed two methods for the direct preparation of 3-*O*-alkylasocorbic acids from **1**. The first consists of treating the preformed adduct of Ph_3P and diethyl azodicarboxylate in THF at –78 ºC with a solution of ascorbic acid in DMF to give presumably the phosphonium intermediate. Reaction of this

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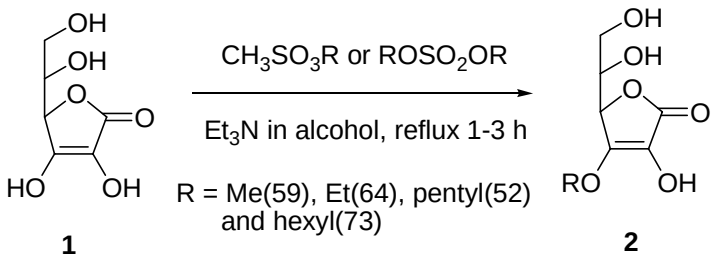
This paper is dedicated to the memory of the Emeritus Professor Kenji Koga of the University of Tokyo.

intermediate with an alcohol provides the 3-*O*-alkyl derivatives.[5] The other method consists of alkylation of 2.5 equiv. of **1** with 1.0 equiv. of alkyl mesylate in the presence of 3.5 equiv. of sodium bicarbonate in DMSO at 60 ºC for 15 h.[6]

Although these two procedures allow direct alkylation of the 3-hydroxly group of ascorbic acid, we saw disadvantages to each. Thus, for large scale production, simple reaction conditions are best and the use of ecologically harmful solvents such as DMSO should be avoided.

In the present study, we have been able to effect alkylation of **1** using simple and conventional reaction conditions without the use of protecting groups. The 3-*O*-selective alkylation of **1** can be achieved when **1** is treated with a slight excess of alkyl mesylates or alkyl sulfonates using triethylamine as a base in alcohols refluxing for 1-3 h (Scheme 1).

Scheme 1



Figures in parentheses show the yield (%) of the corresponding **2.**

Initially, **1** is not soluble in alcohols. However, addition of triethylamine and heating, if necessary, results in a clear solution, which indicates that the ammonium salt is formed with the more acidic 3-hydroxy group. Next, the alkylating agent is added and the reaction mixture is refluxed for few hours. After usual work-up, 3-*O*-alkylascorbic acids can be obtained in 52 – 73% yields. The alkylation was not successful in sodium bicarbonate or potassium carbonate due to the insolubility of **1** and these bases in alcohols.

In conclusion, we have shown that 3-*O*-alkylascorbic acids can be synthesized regioselectively in a single step from ascorbic acid without using environmentally harmful solvents and special reaction conditions.

EXPERIMENTAL

All melting points were determined with a Yanagimoto hot-stage melting point apparatus and are uncorrected. ^{1}H NMR (270 MHz) spectra and ^{13}C NMR spectra (68 MHz) were measured on a JEOL JNM-EX270 spectrometer with tetramethylsilane ($MeSi_4$) as an internal reference. ^{1}H NMR spectral data are reported in parts per million (δ) relative to $MeSi_4$. IR spectra were recorded on a JASCO IR 810 spectrophotometer. MS spectra were obtained with a JEOL JMX-DX 300 spectrometer with a direct inlet system at 70 eV. Optical rotations were taken on a JASCO DIP-181 digital polarimeter. Elemental analyses were performed in the Microanalytical Laboratory of this University.

General procedure for the preparation of 3-*O*-alkyl ascorbic acids (2)

To a solution of 1 equiv. of **1** and 1.1 equiv. of Et_3N in alcohol (MeOH or EtOH) was added 1.1 equiv. of the alkyl mesylate or dialkyl sulfate at rt. After the reaction mixture was refluxed for 1-3 h, the solvent was removed under reduced pressure. The resulting oil was chromatographed on a column of silica gel (AcOEt-MeOH 5:1) to give **2**.

3-*O*-Methyl-L-ascorbic acid (2a)

Reaction of **1** (352 mg, 2 mmol) with methyl mesylate (242 mg, 2.2 mmol) in the presence of Et_3N (223mg, 2.2 mmol) in MeOH (4 mL) for 2 h according to the General Procedure gave, after column chromatography, **2a** (226 mg, 59%). mp 125-127 ℃ (AcOEt) (lit.,[5] mp 121-122 ℃). $[\alpha]_D^{22}$ +27.9˚ (c=1.1, water). [lit.,[5] $[\alpha]_D$ +24.3˚ (c=1.1, water)]. IR (KBr) 3350, 3150, 1740, 1680 cm^{-1}. ^1H NMR (CD_3OD) δ3.64 (d, *J*=6.8 Hz, 2H), 3.80-3.85 (m, 1H), 4.18 (s, 3H), 4.77 (s, 1H). EI-MS *m/z* 190 (M^+, 8.35), 130 (100).

3-*O*-Ethyl-L-ascorbic acid (2b)

Reaction of **1** (352 mg, 2 mmol) with diethyl sulfate (339 mg, 2.2 mmol) in the presence of Et_3N (223mg, 2.2 mmol) in EtOH (4 mL) for 1 h according to the General Procedure gave, after column chromatography, **2b** (267 mg, 64%). mp 116-117.5 ℃ (AcOEt) (lit.,[3b] mp 113-114 ℃). $[\alpha]_D^{23}$ +41.6˚ (c=1.0, MeOH). IR (KBr) 3300, 1740, 1675 cm^{-1}. ^1H NMR (CD_3OD) δ 1.37 (t, *J*=7.3 Hz, 3H), 3.64 (d, *J*=6.8 Hz, 2H), 3.81-3.87 (m, 2H), 4.53 (m, 2H), 4.76 (s, 1H). EI-MS *m/z* 204 (M^+, 20.49), 144 (100). Anal. Calcd for $C_8H_{12}O_6$: C, 47.06; H, 5.92. Found: C, 46.87; H, 5.84.

Large scale preparation of 3-*O*-ethyl-L-ascorbic acid (2b)

To a solution of **1** (17.6 g, 0.1 mol) and Et_3N (11.1 g, 0.11 mol) in EtOH (140 mL) was added ethyl mesylate (13.9 g, 0.11 mol) at rt. After the reaction mixture was refluxed for 1 h, the solvent was removed under reduced pressure. To the residue was added H_2O (30 mL) and the aqueous layer was extracted with AcOEt (60 mL x 4). The collected organic phases were dried over Na_2SO_4 and the solvent was evaporated under reduced pressure. Compound (**2b**) was obtained as a solid (9.17 g, 45%). The aqueous layer was continuously extracted with AcOEt for 8 h using a continuous extraction device. The AcOEt layer was dried over Na_2SO_4 and was evaporated under reduced pressure to give **2b** (4.34 g, total yield, 66%).

3-*O*-Pentyl-L-ascorbic acid (2c)

Reaction of **1** (352 mg, 2 mmol) with pentyl mesylate (365 mg, 2.2 mmol) in the presence of Et_3N (223mg, 2.2 mmol) in EtOH (5 mL) for 3 h according to the General Procedure gave, after column chromatography, **2c** (257 mg, 52%). mp 82-83 ℃ (AcOEt/hexane) (lit.,[6] mp 81-83 ℃). $[\alpha]_D^{23}$ +41.7˚ (c=1.0, MeOH) [lit.,[6] $[\alpha]_D^{20}$ +41.5˚ (c=1.0, MeOH)]. IR (KBr) 3425, 3300, 3160, 1755, 1700 cm^{-1}. ^1H NMR (CD_3OD) δ0.93 (t, *J*=6.8 Hz, 3H), 1.37-1.43 (m, 4H), 1.75 (t, *J*=6.8 Hz, 2H), 3.65 (d, *J*=8.1 Hz, 2H), 3.84 (t, *J*=6.8 Hz, 1H), 4.44-4.53 (m, 2H), 4.76 (s, 1H). EI-MS *m/z* 246 (M^+, 9.08), 116 (100).

3-*O*-Heptyl-L-ascorbic acid (2d)

Reaction of **1** (352 mg, 2 mmol) with heptyl mesylate (427 mg, 2.2 mmol) in the presence of Et_3N (223mg, 2.2 mmol) in EtOH (4 mL) for 2 h according to the General Procedure gave, after column chromatography, **2d** (406 mg, 73%). mp 88-89 ℃ (AcOEt/hexane) (lit.,[6] mp 85-87 ℃). $[\alpha]_D^{22}$ +36.9˚ (c=1.0, MeOH) [lit.,[6] $[\alpha]_D^{20}$ +35.6˚ (c=1.0, MeOH)]. IR (KBr) 3430, 3300, 3170, 1760, 1700 cm^{-1}. ^1H NMR (CD_3OD) δ 0.80-0.95 (m, 3H), 1.25-1.50 (m, 8H), 1.70-1.80 (m, 2H), 3.66 (d, *J*=6.8Hz, 2H), 3.80-3.90 (m, 1H), 4.40-4.50 (m, 2H), 4.78 (s, 1H). EI-MS m/z 274 (M^+, 10.01), 116 (100).

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