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Chemoselective 3-*O*-alkylation of L-ascorbic acid under phase transfer catalysis

Shankar Ramchandra Thopate* and Santosh Rajaram Kote

Department of Chemistry, Dr. John Barnabas Post Graduate School for Biological Studies, Ahmednagar College, Ahmednagar, Maharashtra. 414001. India.

A detailed investigation for synthesis of chemo-selective 3-*O*-alkylation of L-ascorbic acid under phase transfer catalysis has been carried out. All the compounds were fully characterized by infra red (IR), NMR and microanalysis. Reaction of 5,6-*O*-isopropylidene-L-ascorbic acid with one equivalent of corresponding alkylating agent and tetrabutyl ammonium iodide as phase transfer catalyst in biphasic system (water:ethyl acetate, 1:1) afforded the 3-*O*-alkyl-5,6-*O*-isopropylidene-L-ascorbic acid derivatives (2a-f) in moderate to good yield as a sole product. Under this reaction condition formation of 2-*C*-alkylated and 2,3-di-*O*-alkylated product was not observed. Furthermore, present protocol allowed preparation of 2,3-di-*O*-alkyl and differentially protected 2,3-di-*O*-alkyl derivatives under mild reaction conditions at room temperature in a one-pot reaction.

Key words: 3-*O*-Alkylation, L-ascorbic acid, phase transfer catalysis, chemoselective alkylation.

INTRODUCTION

L-ascorbic acid, commonly known as Vitamin C, is widely distributed in aerobic organisms and is involved in several biological processes. The biological and pharmacological activity, as well as the therapeutic potential of L-ascorbic acid and its derivatives has been studied extensively (Tripathi et al., 2009). 2-*O* and 3-*O*-alkylated derivatives are known to protect against peroxidation of lipids of the bio-membrane (Kato et al., 1988; Nihro et al., 1991). In addition these derivatives have also been used as an inexpensive chiral synthon for the synthesis of a variety of natural products and pharmacologically active agents (Tripathi et al., 2009).

Many a times, while undertaking a natural product synthesis from L-ascorbic acid, selective preparation of its 2-*O* and 3-*O*-alkyl derivatives is a prerequisite and is a complex issue. The C3 OH is more reactive towards electrophiles under mild basic conditions as compaired to C2 OH group. However, attending the reaction conditions to selectively alkylate the C3 OH group is quite difficult, as the reaction is fairly sensitive to reaction conditions

leading to mixture of 3-*O*-alkyl, 2-*O*-alkyl, 2,3-di-*O*-alkyl and/or 2-*C*-alkyl derivatives. This is quite evident from reports in the literature; in solvents of high dielectric constant (Jackson and Jones, 1965; Fodor et al., 1984; Poss and Belter, 1988), for example, in water 2-*C*-alkylation is favored. Similarly 2-*C*-alkylation was also observed in Michael addition (Fodor et al., 1983; Arnold et al., 1987; Sussangkarn et al., 1988; Poss and Smyth, 1987), of L-ascorbic acid to conjugated carbonyls in highly polar solvents. So far only one method is reported for 2-*O*-alkylation of L-ascorbic acid using *t*-BuOk in DMSO/THF (Olabisi and Wimalasena, 2004). There exist few reports in the literature for selective 3-*O*-alkylation of L-ascorbic acid or 5,6-*O*-isopropylidene derivative (Wimalasena and Mahindaratne, 1994; Kulkarni and Thopate, 1996; Tahir and Hindsgaul, 2000; Beifuss et al., 2000; Kulkarni and Kate, 2004; Thierry et al., 2009), using various bases and solvents. All previous methods for selective 3-*O*-alkylation of L-ascorbic acid require anhydrous reaction conditions and gives mixture of products while in highly polar solvents like water 2-*C*-alkylation is favored. Phase transfer catalysis had been used for *O* and *C*-alkylations in literature (Kim et al., 2006; Yadav and Tekale, 2010; Bender et al., 2010). As a part of ongoing program to explore the utility of L-ascorbic

*Corresponding author. E-mail: srthopate@gmail.com. Tel: +91 241 2324754. Fax: +91 241 2322415.

acid in organic synthesis, we required to synthesize 3-*O*-alkyl derivatives of L-ascorbic acid. It has been reported that alkylation of L-ascorbic acid in aqueous medium affords mainly 2-*C*-alkylated compound. So it is interesting to study the alkylation of L-ascorbic acid in biphasic system (for example, water: ethyl acetate, 1:1) under phase transfer conditions.

MATERIALS AND METHODS

All solvents and reagents were used as obtained from commercial source. Melting points (M.P) (uncorrected) were determined in open capillary tubes using paraffin oil bath. Infra red (IR) spectra were recorded on Perkin Elmer Model 1600 series Fourier Transform (FT) instrument. Optical rotations were recorded on JASCO DIP Digital 181 Polarimeter. ^{1}H NMR and ^{13}C NMR were recorded on Varian Mercury 300 and 75 MHz respectively in CDCl$_3$ solution and tetramethylsilane (TMS) as internal reference (δ scale). The elemental analysis was obtained on Perkin-Elmer Series II 2400 CHNS/O elemental analyzer.

General procedure for 3-*O*-alkylation of 5,6-*O*-isopropylidene-L-ascorbic acid under phase transfer catalysis

To a magnetically stirred solution of 5,6-*O*-isopropylidene-L-ascorbic acid (1.00 g, 4.6 mmol) and tetrabutyl ammonium iodide (0.169 g, 0.4 mmol, 10 mol %) in water (5.00 ml), ethyl acetate (5.00 ml), potassium hydroxide (0.259 g, 4.6 mmol) was added (pH = 7.5 to 8.0) followed by addition of corresponding alkylating agent (4.6 mmol). Stirring was continued at room temperature for 17 to 24 h. Product was extracted in ethyl acetate (3 × 10.00 ml). Combined ethyl acetate extracts were dried over anhydrous sodium sulphate. Ethyl acetate was removed under reduced pressure and the crude product was purified on silica gel column chromatography using hexane-ethyl acetate solvent system.

General procedure for 2,3-di-*O*-alkylation of 5,6-*O*-isopropylidene-L-ascorbic acid under phase transfer catalysis

Method A

To a magnetically stirred solution of 5,6-*O*-isopropylidene-L-ascorbic acid 1 (1.00 g, 4.6 mmol) and tetrabutyl ammonium iodide (0.169 g, 0.46 mmol 10 mol %) in water (5.00 ml), ethyl acetate (5.00 ml), potassium hydroxide (0.544 g, 9.7 mmol) was added (pH = 7.5 to 8.0) followed by addition of corresponding alkylating agent (4.6 mmol). Stirring was continued at room temperature for 17 to 24 h. Product was extracted in ethyl acetate (3 × 10.00 ml). Combined ethyl acetate extracts were dried over anhydrous sodium sulphate. Ethyl acetate was removed under reduced pressure and the crude product was purified on silica gel column chromatography using hexane-ethyl acetate solvent system.

General procedure for differentially protected 2,3-di-*O*-alkyl derivatives in a one pot reaction

Method B

To a magnetically stirred solution of 5,6-*O*-isopropylidene-L-ascorbic acid 1 (1.00 g, 4.6 mmol) and tetrabutyl ammonium iodide (0.169 g, 0.4 mmol, 10 mol %) in water:ethyl acetate 1:1 (5.00 ml each), potassium hydroxide (0.259 g, 4.6 mmol) was added

(pH = 7.5 to 8.0) followed by addition of corresponding alkylating agent (4.6 mmol). Stirring was continued at room temperature for 17 to 24 h (TLC check). Then potassium hydroxide (0.259 g, 4.6 mmol) was added followed by addition of next alkylating agent (4.6 mmol). Stirring was continued at room temperature for another 24 h. Product was extracted in ethyl acetate (3 × 10.00 ml). Combined ethyl acetate extracts were dried over anhydrous sodium sulphate. Ethyl acetate was removed under reduced pressure and the crude product was purified on silica gel column chromatography using hexane-ethyl acetate solvent system.

RESULTS AND DISCUSSION

Initially, the methylation of 5,6-*O*-isopropylidene-L-ascorbic acid 1 in biphasic system (water:ethyl acetate, 1:1) using one equivalent of methyl iodide as alkylating agent and tetrabutyl ammonium iodide as phase transfer catalyst (PTC) was attempted. The reaction gave the 3-*O*-methyl-5,6-*O*-isopropylidene-L-ascorbic acid 2a in moderate yield as a sole product along with small amount of starting material. No trace of 2-*C*-alkylated product as well as 2,3-di-*O*-alkylated product was detected, either by thin layer or column chromatography. In order to obtain optimum reaction condition, further, we studied the effect of temperature and solvent system on product distribution and reaction time. At higher temperature (reflux) mixture of 2,3-di-*O*-alkylated and 3-*O*-alkylated products were detected. Replacing ethyl acetate by tetrahydrofuran as a solvent with water and changing ratio of water to ethyl acetate/tetrahydrofuran from 1:1 to 1:2, 1:3, 1:4 does not alter the product formation and/or reaction time. The results of alkylation with other alkyl halides are summarized in Table 1, which show that a variety of alkylating agents including activated as well as inactivated alkyl halides gave 3-*O*-alkyl-5,6-*O*-isopropylidene-L-ascorbic derivatives as sole product in moderate to good yields.

In order to test further scope of this methodology, 2,3-di-*O*-alkylation of 5,6-*O*-isopropylidene L-ascorbic acid was attempted under the PTC conditions using 2.1 equivalent alkylating agent. The 2,3-di-*O*-alkyl-5,6-*O*-isopropyldene L-ascorbic acids 3a-c were obtained in uniformly good yields (Table 2, Entry 1-3). Further, differentially protected 2,3-di-*O*-alkyl derivatives 3d-e were obtained in good yields (Table 2, Entry 4-6) in a single pot reaction by adding two different alkylating agents in a sequential manner. All the compounds synthesized were fully characterized by IR, NMR and Microanalysis (Tables 3 and 4).

Our protocol offers number of advantages over the existing methods (Wimalasena and Mahindaratne, 1994; Kulkarni and Thopate, 1996; Tahir and Hindsgaul, 2000; Beifuss et al., 2000; Kulkarni and Kate, 2004; Thierry et al., 2009). First, it gives exclusively 3-*O*-alkyl derivatives of 5,6-*O*-isopropylidene L-ascorbic acid without formation of 2,3-di-*O*-alkyl and/or 2-*C*-alkyl derivatives which makes purification process simple. The procedure does not need anhydrous reaction condition as water is used

Table 1. Chemoselective 3-*O*-alkylation of L-Ascorbic acid under phase transfer catalysis.

S/N	Product	R	Yield[a] (%)	M.P. (ºC)
1	2a	Methyl	75	115-116
2	2b	Ethyl	65	Viscous oil
3	2c	Benzyl	75	108-110
4	2d	Allyl	70	Viscous oil
5	2e	*p*-Nitrobenzyl	72	Viscous oil
6	2f	2(Bromo-methyl) Naphthalene	77	128-130

a. Isolated yield.

Table 2. Synthesis of 2,3-di-*O*-alkyl derivatives of 5,6-*O*-isopropylidene L-ascorbic.

S/N	Product	R	R[1]	Method	Yield[a] (%)	M.P. (ºC)
1	3a	Methyl	Methyl	A	94	100-102
2	3b	Benzyl	Benzyl	A	80	127-128
3	3c	Allyl	Allyl	A	85	Viscous oil
4	3d	Methyl	Benzyl	B	65	88-89
5	3e	Methyl	Allyl	B	65	Viscous oil
6	3f	Benzyl	Methyl	B	61	97-99

a. Isolated yield. Method A: 2.1eq. RX, KOH, 10 mol. % TBAI, H_2O:EtOAc (1:1), RT, 17-24 h. Method B: a) 1.1eq. RX, KOH, 10 mol. % TBAI, H_2O:EtOAc (1:1), RT, 17-24 h. b) 1.1eq. R[1]X, KOH, 10 mol. % TBAI, H_2O:EtOAc (1:1), RT, 17-24 h.

as solvent. Finally, reaction proceeds under mild reaction conditions at room temperature.

Conclusion

In conclusion, we have developed a user friendly methodology for preparation of 3-*O*-alkyl derivatives of 5,6-*O*-isopropylidene L-ascorbic acid using phase transfer catalyst in biphasic system (water:ethyl acetate 1:1) at room temperature. This procedure permits access to these biologically and synthetically important derivatives in good yield and with good regio- and chemo- selectivity. Furthermore, present protocol can be used for preparation of 2,3-di-*O*-alkyl and differentially protected 2,3-di-*O*-alkyl derivatives at room temperature in a one-pot reaction.

Table 3. Optical rotation, IR spectral data, molecular formula and elemental analysis of synthesized compounds.

S/N	Product	$[\alpha]^{25}_D$	IR (cm^{-1})	Molecular formula	Elemental analysis	
					Required	**Found**
1	2a	+ 11.3 (c 1 CHCl$_3$)	1765, 1700	$C_{10}H_{14}O_6$	C, 52.17; H, 6.13	C, 52.19; H, 6.42
2	2b	+ 36.70 (c 0.2 CHCl$_3$)	1765, 1700	$C_{11}H_{16}O_6$	C, 54.09; H, 6.60	C, 54.15; H, 6.72
3	2c	+ 36.3 (c 1 methanol)	1759, 1702	$C_{16}H_{18}O_6$	C, 62.74; H, 5.92	C, 62.45; H, 5.91
4	2d	+ 33.62 (c 2 methanol)	1763, 1686	$C_{12}H_{16}O_6$	C, 56.24; H, 6.29	C, 56.12; H, 6.41
5	2e	+ 36.70 (c 0.6 CHCl$_3$)	1760, 1695	$C_{16}H_{17}NO_8$	C, 54.70; H, 4.88; N, 3.99	C, 54.65; H, 4.68; N, 3.98
6	2f	+ 11.66 (c 0.3 CHCl$_3$)	1755, 1699	$C_{20}H_{20}O_6$	C, 67.41; H, 5.66	C, 67.35 H, 5.72
7	3a	+ 11.34 (c 0.7 CHCl$_3$)	1760, 1679	$C_{11}H_{16}O_6$	C, 54.09; H, 6.60	C, 54.30 H, 6.68
8	3b	+ 23.4 (c 2 CHCl$_3$)	1750, 1676	$C_{23}H_{24}O_6$	C, 69.70; H, 6.10	C, 69.54 H, 6.05
9	3c	+ 47.52 (c 2 methanol)	1763, 1677	$C_{15}H_{20}O_6$	C, 60.80; H, 6.80	C, 60.72 H, 6.91
10	3d	+ 39.33 (c 2 methanol)	1745, 1675	$C_{17}H_{20}O_8$	C, 63.74; H, 6.29	C, 63.87 H, 6.35
11	3e	+ 16.70 (c 2 methanol)	1770, 1670	$C_{13}H_{18}O_6$	C, 57.77; H, 6.71	C, 57.54; H, 6.95
12	3f	+ 37.23 (c 2 methanol)	1754, 1681	$C_{17}H_{20}O_8$	C, 63.74; H, 6.29	C, 63.91; H, 6.39

Table 4. ^{1}H NMR and ^{13}C NMR chemical shifts of synthesized compounds.

S/No.	Product	^{1}H NMR (300 MHz, CDCl$_3$)	^{13}C NMR (75 MHz, CDCl$_3$)
1	2a	1.35 (s, 3 H); 1.38 (s, 3 H); 3.98-4.31 (m, 3 H); 4.45 (s, 3 H); 4.60 (d, 1 H, J = 3 Hz); 5.90 (bs, 1H)	25.45, 25.70, 59.78, 65.30, 74.15, 75.60, 110.30, 119.71, 150.35, 171.49
2	2b	1.37 (m, 6 H); 1.40 (s, 3 H); 4.03 (m, 1 H); 4.14 (m, 1 H); 4.25 (m, 1 H); 4.54 (m, 3 H); 6.1 (s, 1 H)	15.30, 25.51, 25.86, 65.27, 68.04, 74.28, 75.63, 110.24, 118.88, 148.79, 171.29
3	2c	1.36 (s, 3 H); 1.41 (s, 3 H); 4.11-4.42 (m, 3 H); 4.71 (d, 1 H, J = 3.8 Hz); 5.85 (s, 2 H); 7.65 (s, 5 H)	25.52, 25.89, 65.30, 73.45, 74.27, 75.76, 110.23, 121.91, 128.13, 128.61, 135.86, 149.30, 171.51
4	2d	1.37(s, 3 H); 1.43 (s, 3 H); 4.14-4.51 (m, 3 H); 4.74 (d, 1 H, J = 3.8 Hz); 5.17 (d, 2H, J = 5.1 Hz); 5.57 (m, 2 H), 6.2 (m, 1 H)	25.60, 25.90, 65.31, 72.30, 74.29, 75.68, 110.32, 119.15, 119.25, 132.23, 148.40, 171.35
5	2e	1.35 (s, 3 H); 1.36 (s, 3 H); 4.02-4.19 (m, 2 H); 4.32-4.39 (m 1 H); 6.64 (d, 1 H, J = 2.7 Hz); 5.62 (AB q, 2 H, J = 13.1 Hz); 7.58 (d, 2 H, J = 8.7 Hz), 8.24 (d, 2 H, J = 8.7 Hz)	25.43, 25.72, 65.18, 71.76, 73.60, 75.40, 110.39, 119.88, 123.77, 128.09, 142.89, 147.84, 147.95, 170.88
6	2f	1.32 (s, 3 H); 1.37 (s, 3H); 3.95-4.15 (m, 2 H); 4.26 (m, 1 H); 4.56 (d, 1 H, J = 3.6 Hz); 5.65 (s, 2H); 7.44-7.51 (m, 3 H), 7.77-7.86 (m, 4 H)	25.46, 25.81, 64.60, 65.25, 73.57, 73.72, 74.10, 110.25, 111.02, 125.46, 126.36, 126.46, 127.33, 127.49, 127.61, 127.67, 127.83, 133.01, 133.25, 171.06
7	3a	1.36 (s, 3 H); 1.39 (s, 3 H); 3.85 (s, 3 H); 4.01-4.13 (m, 2 H); 4.15 (s, 3 H); 4.25-4.31 (m, 1 H); 4.51 (d, 1 H, J = 3 Hz)	25.46, 25.73, 59.39, 65.14, 73.77, 74.39, 110.28, 123.13, 156.66, 168.86
8	3b	1.36 (s, 3 H); 1.40 (s, 3 H); 4.07 (m, 2 H); 4.23 (m, 1 H); 4.52 (d, 1 H, J = 3.0 Hz); 5.04-5.21 (m, 4 H); 7.18-7.40 (m, 10 H)	25.59, 25.85, 65.20, 73.48, 73.76, 73.87, 74.64, 110.24, 121.11, 127.73, 128.28, 128.55, 128.60, 128.63, 129.09, 130.08, 135.29, 135.87, 156.59, 169.14
9	3c	1.37(s, 3 H); 1.42 (s, 3 H); 4.14-4.48 (m, 3 H); 4.71 (d, 1 H, J = 2.5 Hz); 4.88 (d, 2 H, J = 6.4 Hz); 5.17 (d, 2 H, J = 5.1 Hz), 5.57(m, 4 H); 6.17 (m, 2 H)	25.62, 25.95, 65.36, 72.44, 72.65, 74.08, 74.68, 110.43, 118.97, 119.25, 121.54, 132.89, 155.90, 168.96
10	3d	1.41(s, 3H); 1.45 (s, 3 H); 3.90 (s, 3 H); 4.05 (m, 2 H); 4.25 (m, 1 H); 4.50 (d, 1 H, J = 2.5 Hz); 5.15 (q, 2 H, J = 11 Hz); 7.40 (s, 5 H)	25.45, 25.78, 59.76, 65.21, 73.26, 73.85, 74.55, 110.09, 123.06, 127.70, 128.80, 135.28, 155.46, 168.76
11	3e	1.30(s, 3 H); 1.38 (s, 3 H); 4.01-4.28 (m, 3 H); 4.35 (s, 3 H); 4.52 (d, 1 H, J = 3.2 Hz); 4.64 (d, 2 H, J = 6.4 Hz); 5.48 (m, 2 H); 6.14 (m, 1 H)	25.00, 25.36, 59.76, 65.21, 72.26, 73.76, 74.15, 109.79, 118.76, 120.98, 132.47, 157.12, 168.64
12	3f	1.36 (s, 3 H); 1.40 (s, 3 H); 3.80 (s, 3 H); 4.08-4.40 (m, 3 H); 4.56 (d, 1 H, J = 3.2 Hz); 5.48 (s, 2 H); 7.44 (s, 5 H)	25.45, 25.94, 59.75, 65.28, 73.46, 74.35, 75.68, 110.28, 119.57, 128.50, 128.65, 128.76, 135.7, 148.68, 171.27;

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