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Chemoselective Alkylation Of L-Ascorbic Acid

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Abstract: A study on a general chemoselective method for the preparation of 3-O-alkyl and differentially protected 2,3-di-O-alkyl derivatives of 5,6-O-isopropylidene-L-ascorbic acid is described.

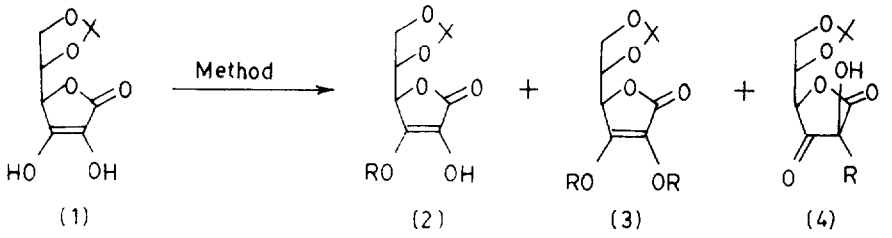
Ascorbic acid is widely distributed in aerobic organisms. It is involved in several biological processes e.g. it protects cellular components from free radicals and oxidants[1a], serves as a reductant in several important enzymatic biotransformations[1b,1c], plays a preventive role in a large number of diseases such as cancer[1d,1e,1f], heart ailments and AIDS[1f]. It is also known to protect the biomembrane from lipid peroxidations[1g]. Furthermore, several derivatives of ascorbic acid act as anti-tumour agents[1c]. Apart from these physiological and biochemical studies, ascorbic acid has been employed in the synthesis of natural products[2a-i] like delesserine, dilaspirolactone aglycon, leucodrin, leudrin, methylrhodomelol, reflexin and rhodomelol. However, the utility of this important compound does not appear to have been explored to a significant extent as one would have expected. This could be due to the complex chemical properties of ascorbic acid.

The literature survey showed that the acylation as well as alkylation of ascorbic acid is fairly sensitive to the reaction conditions[3-7]. It has been shown that alkylation of ascorbic acid in solvents of high dielectric constant favour 2-C-alkylation when powerful alkylating agents were employed[3]. Similarly 2-C-alkylation was observed in Michael addition of L-ascorbic acid to conjugated carbonyls in highly polar solvents[5]. A recent publication[6] reports that in THF-DMSO, 3-O-alkylation is favoured over 2-C-alkylation, no 2,3-di-O-alkylation was observed in this case. 2, 3-di-O-methylation of 1, in refluxing acetone using K_2CO_3 as a base and DMS as an alkylating agent has been reported[5g]. In the light of these varied results it became essential for us to optimise the reaction conditions for the preparation of the differentially protected 2,3-di-O-alkyl derivatives of 5,6-O-isopropylidene-L-ascorbic acid. This would ensure an uninterrupted supply of materials for the intended studies.

In the present study, the alkylations were carried out on 5,6-O-isopropylidene-L-ascorbic acid **1**. The reactions were performed using triethylamine or anhydrous potassium carbonate as a base and various alkylating agents[@] under different solvent and temperature conditions.

Initially the alkylations were carried out using triethylamine as a base in dry methanol at room temperature (Method A, Table I). With one mole equivalent of dimethyl sulphate or methoxymethyl chloride as an alkylating agent, a good yield of 5,6-O-isopropylidene-3-O-alkyl-L-ascorbic acid was obtained though a substantial amount of starting material was recovered. In case of benzyl bromide and allyl bromide 3-O-alkyl and 2-C-alkyl derivatives

@ 1.0 eq. of the alkylating agent was used unless otherwise mentioned.



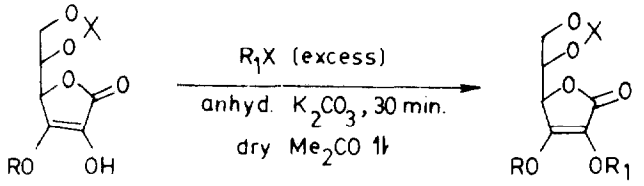
(1) (2) (3) (4)

Table I: Alkylation of 5,6-O-isopropylidene-L-ascorbic acid.

No.	Method	R	Products (% yield[7])		
			2	3	4
1	A	Me	**a**(56)	——	——
2	B	Me	**a**(60)	**a**(32)	——
3	C	Me	**a**(71)	**a**(19)	——
4	D	Me	**a**(69)	**a**(23)	——
5	E	Me	.....	**a**(96)	——
6	A	MOM	**b**(52)	——	——
7	B	MOM	**b**(63)	**b**(29)	——
8	C	MOM	**b**(68)	**b**(23)	——
9	D	MOM	**b**(73)	**b**(17)	——
10	E	MOM	.....	**b**(98)	——
11	A	Benzyl	**c**(40)	**c**(10)	**c**(36)
12	B	Benzyl	**c**(51)	**c**(35)	**c**(12)
13	C	Benzyl	**c**(61)	**c**(15)	**c**(<5)
14	D	Benzyl	**c**(17)	**c**(03)	**c**(02)
15	E	Benzyl		**c**(75)	——
16	A	Allyl	**d**(23)	**d**(05)	**d**(33)
17	B	Allyl	**d**(62)	**d**(17)	**d**(14)
18	C	Allyl	**d**(68)	**d**(10)	**d**(05)
19	D	Allyl	**d**(27)	**d**(28)	**d**(26)
20	E	Allyl	**d**(trace)	**d**(58)	**d**(trace)

were obtained in good yields. Small amount of 2,3-di-O-alkylated product was also isolated. However no starting material was detected in these reactions.

In THF:DMSO (1:1) using anhydrous potassium carbonate as a base at room temperature (Method B, Table I), 3-O- and 2,3-di-O-alkylation was observed to a large extent when one mole equivalent of dimethyl sulphate or methoxymethyl chloride was used as the alkylating agent (Table I). No 2-C-alkylation was detected. However, in case of benzyl bromide and allyl bromide (Table I) 3-O, 2,3-di-O and 2-C-alkylated products were isolated in more or less equal amounts. These results are at variance with the reported one[6] as 2,3-di-O-alkylation was observed to a significant level in the present study (Table I).



(2) (5)

Table II. Alkylation of 3-O-alkyl-5,6-O-isopropylidene-L-ascorbic acid.

No	Product	R	R_1	% yield[7]
1	**5a**	Me	MOM	72
2	**5b**	Me	Benzyl	90
3	**5c**	Me	Allyl	80
4	**5d**	MOM	Me	86
5	**5e**	MOM	Benzyl	77
6	**5f**	MOM	Allyl	91
7	**5g**	Benzyl	Me	83
8	**5h**	Benzyl	MOM	75
9	**5i**	Benzyl	Allyl	74

The reactions in dry acetone using anhydrous potassium carbonate as a base either at room temperature (Method C, Table I) or at reflux temperature of acetone (Method D, Table I) resulted mainly in 3-O-alkylation when one mole equivalent of dimethyl sulphate or methoxymethyl chloride was employed as alkylating agent. No 2-C-alkylation was observed in these cases. However, in case of benzyl bromide and allyl bromide 2-C-alkylation was also observed, albeit to a small extent.

On carrying out the reactions in dry acetone (Method E, Table I) using potassium carbonate as a base at reflux temperature and using excess of either dimethyl sulphate or methoxymethyl chloride or benzyl bromide or allyl bromide, 2,3-di-O-alkyl derivatives were isolated in good to excellent yields. No 2-C-alkylation was detected except in case of allyl bromide (Table I).

Reaction of 5,6-O-isopropylidene-3-O-alkyl-L-ascorbic acid **2** in refluxing acetone using anhydrous potassium carbonate as a base with excess of various alkylating agents furnished corresponding 2,3-di-O-alkyl products **5** in excellent yields (Table II).

In conclusion, alkylations of 5,6-O-isopropylidene-L-ascorbic acid **1** in dry acetone show better selectivity in favour of 3-O-alkylation than when conducted in THF DMSO (1:1) at ambient temperature or under triethylamine-methanol conditions. Further, the sequential alkylation of **1** with different alkylating agents in dry acetone constitutes a good method for the preparation of differentially protected 2,3-di-O-alkyl-5,6-O-isopropylidene -L-ascorbic acids **5** in good overall yields. These dialkyl derivatives are being utilised in exploring other reactions of L-ascorbic acid.

EXPERIMENTAL SECTION

All solvents were distilled and dried before use. All liquid reagents were distilled and stored under anhydrous conditions. Dry tetrahydrofuran was freshly prepared by distilling over benzophenone and sodium, under argon. Dry DMSO was obtained by refluxing over anhydrous K_2CO_3 and stored on molecular sieves. Anhydrous K_2CO_3 was prepared by heating to 230°C to 250°C for 30 min. and then cooled in desiccator before use. Dry acetone was obtained by refluxing over $KMnO_4$ till permanent pink colour persisted (2 days). Then it was refluxed over anhydrous K_2CO_3 for 4h and distilled and stored over anhydrous potassium carbonate. Triethylamine was refluxed on calcium hydride for 4 h and then distilled. It was stored over molecular sieves. Anhydrous methanol was prepared by distilling over calcium hydride and stored over molecular sieves. Silica gel (100-200 mesh) was used for column chromatography.

UV spectra were recorded on Perkin Elmer Lambda 3B, UV/VIS spectrophotometer. IR spectra were recorded on Perkin Elmer model 1600 series FTIR instrument. ^{1}HNMR spectra [ppm, TMS as internal standard] in $CDCl_3$ were recorded on a JEOL FX 90Q instrument. Optical rotations were measured on JASCO DIP 181 digital polarimeter. All melting points are uncorrected and obtained with paraffin oil bath.

General procedure for alkylation of 5,6-O-isopropylidene-L-ascorbic acid (1).

Method A. To a stirred mixture of **1** (3.0 mmol) and dry triethylamine (3.0 mmol) in dry methanol (10 ml), was added the corresponding alkylating agent (3.0 mmol, 1.0 eq.). The reaction mixture was stirred at room temperature for 3 to 6 hrs. Methanol was then removed under reduced pressure. Brine (10 ml) was added to the residue and products were extracted in ethyl acetate (3 x 20 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 using hexane-ethyl acetate solvent system.

Method B. A mixture of **1** (3.0 mmol) and anhydrous K_2CO_3 (3.0 mmol) in THF:DMSO (1:1, 15 ml) was stirred at room temperature. The corresponding alkylating agent (3.0 mmol, 1.0 eq.) was added to it. The reaction mixture was stirred for 1-3 hrs at room temperature and then brine (30 ml) was added to the mixture. It was extracted with ethyl acetate (3x25 ml). The combined organic layers were dried over anhydrous sodium sulphate and evaporated under reduced pressure. The crude products were purified on silica gel column using hexane-ethyl acetate solvent system.

Method C. A mixture of **1** (5.0 mmol) and anhyd. K_2CO_3 (5.0 mmol) in acetone (25ml) was stirred at room temperature and the alkylating agent (5.0 mmol, 1.0 eq.) was added to it in one lot. The stirring at room temperature was continued for 1h and then the reaction mixture was concentrated under reduced pressure. Brine (30 ml) was added to the residue and was extracted with ether (3x30 ml). The organic layer was dried over anhydrous sodium sulphate and ether was removed under reduced pressure. The crude products were separated on silica gel column using hexane-ethyl acetate solvent system.

Method D. To a stirred mixture of **1** (5.0 mmol) and anhyd. K_2CO_3 (5.0 mmol) in dry acetone (25ml) was added, in one lot, the corresponding alkylating agent (5.0 mmol, 1.0 eq.). The reaction mixture was stirred at reflux temperature for 1h and then acetone was removed under reduced pressure. Brine (25 ml) was added and the product was extracted in ether (3x30 ml). The organic layer was dried over anhydrous sodium sulphate, and ether was removed under reduced pressure. The crude products were separated on silica gel column using hexane-ethyl acetate solvent system.

Method E. A mixture of **1** (3.0 mmol) and K_2CO_3 (7.5 mmol) in acetone (30 ml) was heated to reflux while being

stirred. An excess of the alkylating agent (7.0 mmol, 2.3 eq.) was added to this mixture in one lot. Heating was continued for 10-30 min. Then it was cooled to room temperature and concentrated under reduced pressure. Brine (30 ml) was added and the product was extracted in diethyl ether (3x30 ml). Organic layer was dried over anhydrous sodium sulphate and ether was removed under reduced pressure. The crude product was purified on silica gel column using hexane-ethyl acetate solvent system.

5,6-O-isopropylidene-3-O-methyl-L-ascorbic acid (2a)
White solid. M.P. 116-117°C [lit [2b] 116-117°C]
$[\alpha]_D$ = +14.16 (c 2 methanol), +11.1 (c 1 $CHCl_3$) [lit [2b] +11.0 (c 1 $CHCl_3$)]
UV (methanol): λ_{max} 246 nm (ϵ 4934).
IR (CCl_4): 3350, 3000, 2965, 1770, 1700 cm^{-1}
^{1}HNMR ($CDCl_3$): δ 1.30 (s, 3H, C-**CH_3**,) 1.36 (s, 3H, C-**CH_3**), 3.96-4.48 (m, 6H, -O-**CH_3**, C-6-**H_2**, C-5-**H**), 4.56 (d, 1H, C-4-**H**, *J* = 3.2 Hz), 5.84 (bs, 1H, -**OH** exch. with D_2O).
Anal. Calcd. for $C_{10}H_{14}O_6$: C,52.17; H, 6.13. Found C,52.16; H, 6.47

5,6-O-isopropylidene-3-O-methoxymethyl-L-ascorbic acid (2b)
White solid. M.P. 95-96°C [lit [4b] 93-94°C]
$[\alpha]_D$ = +13.04 (c 2 methanol)
UV (methanol): λ_{max} 242 nm (ϵ 4753).
IR (CCl_4): 3400, 2900, 1770, 1700 cm^{-1}
^{1}HNMR ($CDCl_3$): δ 1.34 (s, 6H, C-**CH_3**), 3.71 (s, 3H, O-**CH_3**), 4.00-4.57 (m, 3H, C-6-**H_2**, C-5-**H**), 4.77 (d, 1H, *J* = 2.5 Hz, C-4-**H**), 5.54 (s, 2H, -O-**CH_2**-O-CH_3), 6.67 (bs, 1H,-**OH** exch. with D_2O).
Anal. Calcd. for $C_{11}H_{16}O_7$: C,50.76; H,6.19. Found C,50.57; H,6.30

5,6-O-isopropylidene-3-O-benzyl-L-ascorbic acid (2c)
White solid. M.P. 109-110°C [lit [4b] 105-106°C, lit [24] 109-111°C]
$[\alpha]_D$ = +36.4 (c 1 methanol). [lit [2a] +36 (c 1 methanol)]
UV (methanol): λ_{max} 247 nm (ϵ 2409)
IR (Nujol): 3447, 2976, 1759, 1702, 758 cm
^{1}HNMR ($CDCl_3$): δ 1.35 (s, 3H, C-**CH_3**), 1.41 (s, 3H,C-**CH_3**), 4.11-4.42 (m, 3H, C-6-**H_2**, C-5-**H**), 4.71 (d, 1H, *J* = 3.8 Hz, C-4-**H**), 5.71 (s, 2H, O-**CH_2**-Ph), 7.65 (s, 5H, Ar-**H**).
Anal. Calcd. for $C_{16}H_{18}O_6$: C,62.74; H,5.92. Found C,62.41; H,5.91

5,6-O-isopropylidene-3-O-allyl-L-ascorbic acid (2d)
Thick liquid
$[\alpha]_D$ = +33.46 (c 2 methanol)
UV (methanol): λ_{max} 247 nm (ϵ 5366)
IR (Neat): 3338, 2976, 1763, 1686 cm^{-1}.
^{1}HNMR ($CDCl_3$): δ 1.37 (s, 3H, C-**CH_3**), 1.43 (s, 3H, C-**CH_3**), 4.14-4.51 (m, 3H, C-6-**H_2**, C-5-**H**), 4.74 (d, 1H, *J* = 3.8 Hz, C-4-**H**), 5.17 (d, 2H, -O-**CH_2**-CH=CH_2), 5.57 (m, 2H, -O-CH_2-CH=**CH_2**), 6.2 (m, 1H, -O-CH_2-**CH**=CH_2).
Anal. Calcd. for $C_{12}H_{16}O_6$: C,56.24; H,6.29. Found C,56.12; H,6.41

5,6-O-isopropylidene-2-C-benzyl-L-ascorbic acid (4c).
White crystals. M.P. 125-126°C
$[\alpha]_D$ = - 62.18 (c 2 methanol)

UV (methanol): λ_{max} 224 nm (ε 3057)
IR (Nujol): 3385, 2923, 1743, 1655, 721 cm^{-1}
^{1}HNMR ($CDCl_3$): δ 1.31 (s, 3H, C-**CH_3**), 1.40 (s, 3H, C-**CH_3**), 2.6 (bs, 1H, **-OH**, exch. with D_2O), 3.62-4.33 (m, 6H, C-6-**H_2**, C-5-**H**, C-4-**H**, C-**CH_2**-Ph), 7.11 (s, 5H, Ar-**H**).
Anal. Calcd. for $C_{16}H_{18}O_6$: C,62.74; H,5.92. Found C,62.51; H,6.11.

5,6-O-isopropylidene-2-C-allyl-L-ascorbic acid (4d).
Undistillable liquid.
$[\alpha]_D$ = +50.40 (c 2 methanol).
UV (methanol): λ_{max} 227 nm (ε 2201)
IR (Neat): 3416, 2933, 1786, 1641 cm^{-1}.
^{1}HNMR ($CDCl_3$): δ 1.31 (s, 3H, C-**CH_3**), 1.38 (s, 3H, C-**CH_3**), 1.85 (bs, 1H, **-OH**, exch. with D_2O), 2.71 (d, 2H, *J* = 7.7 Hz, C-**CH_2**-CH=CH_2), 4.14-4.40 (m, 3H, C-6-**CH_2** C-5-**H**), 4.65 (d, 1H, *J* = 7.7 Hz, C-4-**H**), 5.42 (m, 2H, -C-CH=**CH_2**), 5.94 (m, 1H, -C-CH_2-**CH**=CH_2)
Anal. Calcd for $C_{12}H_{16}O_6$: C,56.64; H,6.29. Found C,56.30; H,6.47.

5,6-O-isopropylidene-2,3-di-O-methyl-L-ascorbic acid (3a).
Needle shaped crystals M.P. 100-101°C [lit.[5c] 83-87°C, lit.[2b] 98.5-99.5°C]
$[\alpha]_D$ = +13.35 (c 2 methanol), +11.4 (c 1 $CHCl_3$) [lit.[2b] +11.0 (c 1 $CHCl_3$)]
UV (methanol): λ_{max} 233 (ε 5352)
IR (CCl_4): 3005, 2960, 1790, 1700 cm^{-1}
^{1}HNMR ($CDCl_3$): δ 1.40 (s, 3H, C-**CH_3**), 1.45 (s, 3H, C-**CH_3**), 4.00 (s, 3H, -C-2-O-**CH_3**), 4.17-4.48 (m, 6H, C-6-**CH_2**, C-5-**H**, -C-3-O-**CH_3**), 4.65 (d, 1H, *J* = 3.8 Hz, C-4-**H**).
Anal. Calcd. for $C_{11}H_{16}O_6$: C,54.09; H,6.60. Found C,54.32; H,6.67.

5,6-O-isopropylidene-2,3-di-O-methoxymethyl-L-ascorbic acid (3b).
Undistillable oil.
$[\alpha]_D$ = +20.00 (c 2 methanol).
UV (methanol): λ_{max} 233 nm (ε 13823)
IR (Neat): 2950, 2880, 1750, 1670 cm^{-1}
^{1}HNMR ($CDCl_3$): δ 1.37 (s, 3H, C-**CH_3**), 1.42 (s, 3H, C-**CH_3**), 3.65 (s, 6H, -O-CH_2-O-**CH_3**), 4.14-4.34 (m, 3H, C-6-**CH_2**, C-5-**H**), 4.77 (d, 1H, *J* = 2.5 Hz, C-4-**H**), 5.40 (AB quartet, 2H, C-2-O-**CH_2**-O-CH_3), 5.68 (s, 2H, C-3-O-**CH_2**-O-CH_3).
Anal. Calcd. for $C_{13}H_{20}O_8$: C,51.31; H,6.62. Found C,51.00; H,6.88.

5,6-O-isopropylidene-2,3-di-O-benzyl-L-ascorbic acid (3c).
White solid. M.P. 126-127°C [lit.[2a] 125-126°C, lit.[4c] 128°C]
$[\alpha]_D$ = +22.00 (c 2 methanol), +23.3 (c 2 $CHCl_3$), +61.8 (c 0.58 acetone).
[lit.[2a] +23.0 ± 1 (c 1.15 $CHCl_3$), lit.[4c] +63 (c 0.58 acetone), lit.[4b] +59 acetone)].
UV (methanol): λ_{max} 237 nm (ε 2976)
IR (Nujol): 2923, 2853, 1750, 1676, 750 cm^{-1}
^{1}HNMR ($CDCl_3$): δ 1.37 (s, 3H, C-**CH_3**), 1.45 (s, 3H, C-**CH_3**), 4.05-4.48 (m, 3H, C-6-**H_2**, C-5-**H**), 4.65 (d, 1H, *J* = 3.8 Hz, C-4-**H**), 5.24 (m, 4H, O-**CH_2**-Ph), 7.57 (s, 10H, Ar-**H**).
Anal.Calcd. for $C_{22}H_{24}O_6$: C,69.70; H,6.10. Found C,69.49; H,6.31.

5,6-O-isopropylidene-2,3-di-O-allyl-L-ascorbic acid (3d).
Faint yellow oil.
$[\alpha]_D$ = +47.58 (c 2 methanol).
UV (methanol): λ_{max} 227 nm (ϵ 4748)
IR (Neat): 2937, 1763, 1677 cm^{-1}
^{1}HNMR ($CDCl_3$): δ 1.37 (s, 3H, C-**CH_3**), 1.42 (s, 3H, C-**CH_3**), 4.14-4.48 (m, 3H, C-6-**H_2**, C-5-**H**), 4.71 (d, 1H, *J*=2.5 Hz, C-4-**H**), 4.88 (d, 2H, J = 6.4 Hz, C-2-O-**CH_2**-CH=CH_2), 5.17 (d, 2H, *J* = 5.1 Hz, C-3-O-**CH_2**-CH=CH_2), 5.57 (m, 4H, C-2-O-CH_2-CH=**CH_2**, C-3-O-CH_2-CH=**CH_2**), 6.17 (m, 2H, C-2-O-CH_2-**CH**=CH_2, C-3-O-CH_2-**CH**=CH_2).
Anal. Calcd. for $C_{15}H_{20}O_6$: C,60.80, H,6.80. Found C,60.72, H,7.00.

General procedure for alkylation of 5,6-O-isopropylidene-3-O-alkyl-L- ascorbic acid (2).
To a refluxing mixture of **1** (3.0 mmol) and K_2CO_3 (4.0 mmol) in acetone corresponding alkylating agent (4.0 mmol) was added. Reaction mixture was refluxed for 10-30 min. and was cooled to room temperature. Acetone was removed under reduced pressure. Brine (30 ml) was added and product extracted in diethyl ether (3x30 ml). Combined organic layers were dried over anhydrous sodium sulphate and ether was removed under reduced pressure. Crude product was purified on silica gel column using hexane-ethyl acetate system.

5,6-O-isopropylidene-2-O-methoxymethyl- 3-O-methyl-L-ascorbic acid (5a).
White crystalline solid. M.P. 63-64°C.
$[\alpha]_D$ = +5.64 (c 2 methanol)
UV (methanol): λ_{max} 234 nm (ϵ 7895)
IR (CCl_4): 2950, 1750, 1670 cm^{-1}
^{1}HNMR ($CDCl_3$): δ 1.37 (s, 3H, C-**CH_3**), 1.42 (s, 3H, C-**CH_3**), 3.67 (s, 3H, O-CH_2-O-**CH_3**), 4.14-4.48 (m, 6H, O-**CH_3**, C-6-**H_2**, C-5-**H**), 4.68 (d, 1H, *J* = 2.5 Hz, C-4-**H**), 5.34 (q, 2H, O-**CH_2**-O-CH_3).
Anal. Calcd. for $C_{13}H_{18}O_7$: C,52.55, H,6.61. Found C,52.91, H,6.97.

5,6-O-isopropylidene-2-O-benzyl-3-O-methyl-L-ascorbic acid (5b).
White solid. M.P. 87-88°C [lit [20] 84-87°C]
$[\alpha]_D$ = +39.20 (c 2 methanol)
UV (methanol): λ_{max} 234 nm (ϵ 6156)
IR (CCl_4): 3000, 2950, 1750, 1675, 750 cm^{-1}
^{1}HNMR ($CDCl_3$): δ 1.37 (s, 3H, C-**CH_3**), 1.45 (s, 3H, C-**CH_3**), 4.02 (s, 3H, O-**CH_3**), 4.16-4.46 (m, 3H, C-6-**CH_2**, C-5-**H**), 4.65 (d, 1H, *J* = 2.5 Hz, C-4-**H**), 5.17 (s, 2H, O-**CH_2**-Ph), 7.65 (s, 5H, Ar-**H**).
Anal.Calcd. for $C_{17}H_{20}O_6$: C,63.74, H,6.29.Found C,63.97, H,6.39.

5,6-O-isopropylidene-2-O-allyl-3-O-methyl-L-ascorbic acid (5c).
Undistillable oil.
$[\alpha]_D$ = +16.76 (c 2 methanol).
UV (methanol): λ_{max} 235 nm (ϵ 13610).
IR (Neat): 3000, 2960, 1770, 1670 cm^{-1}
^{1}HNMR ($CDCl_3$): δ 1.28 (s, 3H, C-**CH_3**), 1.36 (s, 3H, C-**CH_3**), 4.00-4.28 (m, 6H, C-O**CH_3**, C-6-**H_2**, C-5-**H**), 4.52 (d, 1H, *J* = 3.2 Hz, C-4-**H**), 4.64 (d, 2H, *J* = 6.4 Hz, O-**CH_2**CH=CH_2), 5.48 (m, 2H, O-CH_2-CH=**CH_2**), 6.14 (m, 1H, O-CH_2-**CH**=CH_2).
Anal. Calcd. for $C_{13}H_{18}O_6$: C,57.77, H,6.71. Found C,57.51, H,6.92.

5,6-O-isopropylidene-2-O-methyl-3-O-methoxymethyl-L-ascorbic acid (5d).
Viscous oil.
$[\alpha]_D$ = +26.38 (c 2 methanol)
UV(methanol): λ_{max} 233 nm (ε 8542)
IR (Neat): 2980, 2925, 1760, 1675 cm^{-1}
^{1}HNMR ($CDCl_3$): δ 1.32 (s, 3H, C-**CH_3**), 1.40 (s, 3H, C-**CH_3**), 3.54 (s, 3H, O-CH_2-O-**CH_3**), 3.88 (s, 3H, O-**CH_3**), 4.12 (d, 2H, *J* = 3.2 Hz, C-6-**H_2**), 4.34 (m, 1H, C-5-**H**), 4.67 (d, 1H, *J* = 3.2 Hz, C-4-**H**), 5.48 (s, 2H, O-**CH_2**-O-CH_3)
Anal. Calcd. for $C_{13}H_{18}O_7$: C,52.53, H,6.61. Found C,52.19; H,6.63.

5,6-O-isopropylidene-2-O-benzyl-3-O-methoxymethyl-L-ascorbic acid (5e).
Undistillable oil.
$[\alpha]_D$ = +46.63 (c 2 methanol)
UV (methanol): λ_{max} 233 nm (ε 6723)
IR (Neat): 2990, 2940, 1770, 1670, 735 cm^{-1}
^{1}HNMR ($CDCl_3$): δ 1.37 (s, 3H, C-**CH_3**), 1.42 (s, 3H, C-**CH_3**), 3.57 (s, 3H, O-CH_2-O-**CH_3**), 4.11-4.54 (m, 3H, C-6-**H_2**, C-5-**H**), 4.71 (d, 1H, *J* = 2.5 Hz, C-4-**H**), 5.35 (s, 2H, O-**CH_2**-Ph), 5.48 (s, 2H, O-**CH_2**-O-CH_3), 7.65 (s, 5H, Ar-**H**)
Anal. Calcd. for $C_{18}H_{22}O_7$: C,61.70; H,6.32. Found C,61.82; H,6.60.

5,6-O-isopropylidene-2-O-allyl-3-O-methoxymethyl-L-ascorbic acid (5f).
Faint yellow oil.
$[\alpha]_D$ = +31.50 (c 2 methanol)
UV (methanol): λ_{max} 233 nm (ε 23424)
IR (Neat): 2990, 1770, 1690 cm^{-1}
^{1}HNMR ($CDCl_3$): δ 1.32 (s, 3H, C-**CH_3**), 1.40 (s, 3H, C-**CH_3**), 3.52 (s, 3H, O-CH_2-O-**CH_3**), 3.92 (d, 2H, *J* = 3.2Hz, C-6-**H_2**), 4.12 (m, 1H, C-5-**H**), 4.40 (d, 2H, *J* = 5.1 Hz, O-**CH_2**-CH=CH_2), 4.49 (d, 1H, *J* = 3.2 Hz, C-4-**H**), 5.28 (m, 2H, O-CH_2-CH=**CH_2**), 5.46 (s, 2H, O-**CH_2**-O-CH_3), 6.00 (m, 1H, O-CH_2-**CH**=CH_2).
Anal. Calcd. for $C_{12}H_{20}O_7$: C,55.99; H,6.71. Found C,55.77; H,6.79.

5,6-O-isopropylidene-2-O-methyl-3-O-benzyl-L-ascorbic-acid (5g).
White crystals M.P. 98-99°C. [lit [5] 99.5-100°C]
$[\alpha]_D$ = +37.25 (c 2 methanol)
UV (methanol): λ_{max} 235 nm (ε 8695)
IR (Nujol): 2922, 1754, 1681, 744 cm
^{1}HNMR ($CDCl_3$): δ 1.36 (s, 3H, C-**CH_3**), 1.40 (s, 3H, C-**CH_3**), 3.80 (s, 3H, O-**CH_3**), 4.08-4.40 (m, 3H, C-6-**H_2**, C-5-**H_2**), 4.56 (d, 1H, *J* = 3.2 Hz, C-4-**H**), 5.48 (s, 2H, O-**CH_2**-Ph), 7.44 (s, 5H, Ar-**H**).
Anal. Calcd. for $C_{17}H_{20}O_6$: C,63.74, H,6.29. Found C,63.92, H,6.64.

5,6-O-isopropylidene-2-O-methoxymethyl- 3-O-benzyl-L-ascorbic-acid (5h).
White solid M.P. 80-81°C
$[\alpha]_D$ = +31.93 (c 2 methanol).
UV (methanol): λ_{max} 236 nm (ε 5189).
IR (Nujol): 2923, 2858, 1751, 1678, 745 cm^{-1}
^{1}HNMR ($CDCl_3$): δ 1.34 (s, 3H, C-**CH_3**), 1.41 (s, 3H, C-**CH_3**), 3.62 (s, 3H, O-CH_2-O-**CH_3**), 4.11-4.48 (m, 3H, C-6-**H_2**, C-5-**H**), 4.71 (d, 1H, *J* = 2.5 Hz, C-4-**H**), 5.37 (AB quartet, 2H, *J* = 4.1 Hz, O-**CH_2**-O-CH_3), 5.71 (s, 2H,

O-**CH$_2$**-Ph), 7.64 (s, 5H, Ar-**H**).
Anal. Calcd. for $C_{18}H_{22}O_7$: C,61.70, H,6.32. Found C,61.82, H,6.17.

5,6-O-isopropylidene-2-O-allyl-3-O-benzyl-L-ascorbic-acid (5i).
Viscous oil.
$[\alpha]_D$ = +39.37 (c 2 methanol).
UV (methanol): λ_{max} 237 nm (ε 3324).
IR (Neat): 2986, 2936, 1766, 1681, 738 cm^{-1}.
^{1}HNMR ($CDCl_3$): δ 1.36 (s, 6H, C-**CH$_3$**), 3.92-4.28 (m, 3H, C-6-**H$_2$**, C-5-**H**), 4.56 (d, 3H, *J* = 4.8 Hz, C-4-**H**, O-**CH$_2$**-CH=CH$_2$), 5.20 (m, 2H, O-CH$_2$-CH=**CH$_2$**), 5.44 (s, 2H, O-**CH$_2$**-Ph), 5.84 (m, 1H, O-CH$_2$-**CH**=CH$_2$), 7.40 (s, 5H, Ar-**H**).
Anal. Calcd. for $C_{19}H_{22}O_6$: C,65.88, H,6.40. Found C,66.13, H,6.44.

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7. The product yields represent the yields by weighing the products after isolation & purification on silica gel column.

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