S 1

Rational Approach to Selective and Direct 2-O-Alkylation of 5, 6-O-Isopropylidene-L-Ascorbic Acid.

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Supporting Information

List of the Content:

S3...S54

- ^1H , ^{13}C NMR & Selected 2D NMR Spectra of Compounds:
2a-2d, 3a-3f, 4a-4e, & 5a-5e

S55...S57

- Calculated Electrostatic Potential Diagram of the Neutral,
Monoanionic and Dianionic forms of 5, 6-O-Isopropylidene-
L-Ascorbic Acid (1).

EXPERIMENTAL SECTION:

General: All reagents and chemicals were obtained from various commercial sources at the highest purity available and used without further purification. Chromatographic separations were carried out using normal phase silica gel and products were eluted with a mixture of ethyl acetate and n-hexane with varying ratios depending on the nature of the compound. The TLC analyses were performed on pre-coated silica gel GF plates and the compounds were observed under UV light and/or by exposure to iodine vapor. All solvents used were dried with appropriate drying agents and freshly distilled. All chemical shifts are reported on the δ (ppm) scale relative to TMS (0.00 ppm) for ^1H -NMR and to CDCl_3 (77.0 ppm) for ^{13}C -NMR. The elemental analyses were done at Desert Analytical, Tucson, Arizona. The exact mass FAB experiments were performed at the University of Kansas, Mass Spectrometry laboratory, Lawrence, Kansas.

Computational Modeling: The initial calculations were carried with AM1 semi-empirical method to obtain a reasonable initial model to serve as a foundation for the subsequent *ab initio* calculations. All the *ab initio* calculations were carried out by the density function B3LYP method and basis set 6-31G* using Gaussian 98 programs.⁴¹ The electrostatic potential diagrams of the isosurface electron densities were obtained from these calculations. The electron density distributions of the molecules are plotted as the electrostatic potential with the standard color-coding using the standard built in features of the Gaussian 98 programs⁴¹ (order of electron density: blue < green < yellow < red).

S 3

5,6-O-Isopropylidene-3-O-methyl-L-ascorbic Acid 1H (2a)

NMR2202A 5,6-O-Isopropylidene 3Methyl 2Hydroxyl L ascorbic acid

Pulse Sequence: zgpg30
Solvent: CDCl3
Ambient temperature
File: 2202A
Mercury-3000S "wau300"

Pulse 11.2 degrees
Acq. time 1.535 sec
Width 4566.5 Hz
64 repetitions
OBSERVE H1 300.1030102 MHz
DATA PROCESSING
FT size 32768
Total time 2 min, 51 sec

S 4

5,6-O-Isopropylidene-3-O-methyl-L-ascorbic Acid 13C (2a)

NMR22020 5,6-O-Isopropylidene-2Hydroxyl-3Methyl-L-Ascorbic Acid

Pulse Sequence: zgpg30

Solvent: CDCl3

Ambient temperature

File: 22020

Mercury-3000B "wss300"

Pulse 9.0 degrees

Acq. time 1.015 sec

Width 18761.7 Hz

38400 repetitions

OBSERVE C13, 75.4602813 MHz

DECOUPLE H1, 300.1045181 MHz

Power 35 dB

continuously on

WALTZ-16 modulated

DATA PROCESSING

Line broadening 1.0 Hz

FT size 131072

Total time 58 hr, 40 min, 11 sec

S 5

5,6-O-Isopropylidene-3-O-benzyl-L-ascorbic Acid 1H (2b)

HMR M1121010: 5,6-O-Isopropylidene-3-O-benzyl-L-ascorbic acid
Pulse Sequence: zgpg30
Solvent: CDCl3
Ambient temperature
INOVA-400 "nu400"

Pulse 52.5 degrees
Acq. time 3.744 sec
Width 6000.6 Hz
32 repetitions
OBSERVE H1, 399.8400423 MHz
DATA PROCESSING
FT size 65536
Total time 31 min, 15 sec

5,6-O-Isopropylidene-3-O-benzyl-L-ascorbic Acid 13C (2b)

S 7

5,6-O-Isopropylidene-3-O-trans-crotyl-L-ascorbic Acid 1H (2c)

S 8

5,6-O-Isopropylidene-3-O-trans-crotyl-L-ascorbic Acid 13C (2c)

S 9

5,6-O-Isopropylidene-3-O-allyl-L-ascorbic Acid 1H (2d)

5,6-O-Isopropylidene 3-Allyl L Ascorbic Acid t12004A

Pulse Sequence: zgpg30

Solvent: CDCl3

Acquire temperature

File: t12004A

Mercury-30000 "vnu3000"

Relax. delay 1.000 sec

Pulse 32.6 degrees

Acq. time 3.000 sec

Width 6506.5 Hz

200 repetitions

OBSERVE H1, 300.1453430 MHz

DATA PROCESSING

Line broadening 3.0 Hz

FT size 32768

Total time 14 min, 11 sec

S 10

5,6-O-Isopropylidene-3-O-allyl-L-ascorbic Acid ^{13}C (2d)

S 11

2Allyl3Hydroxyl of IAA
Pulse Sequence: zgpg30
Solvent: CDCl3
Ambient temperature
Mercury-3000B "wau300"

Relax. delay 1.000 sec
Pulse 11.2 degrees
Acq. time 1.335 sec
Width 4508.5 Hz
300 repetitions
OBSERVE H1: 300.1030347 MHz
DATA PROCESSING
FT size 32768
Total time 15 min, 32 sec

5,6-O-Isopropylidene-2-O-allyl-L-ascorbic Acid 1H (3a)

S 12

INDEX	FREQUENCY	PPM	HEIGHT
1	12738.781	188.813	4.7
2	11788.488	188.351	12.3
3	10997.747	121.388	16.4
4	9153.431	121.388	5.4
5	9025.621	119.806	23.2
6	8346.179	110.603	11.9
7	8842.854	77.422	52.8
8	8010.495	77.000	53.8
9	5778.800	76.573	58.2
10	5576.747	73.802	26.7
11	5570.710	73.802	29.5
12	5442.827	73.151	25.6
13	4894.283	64.658	31.5
14	1941.746	25.732	30.0
15	1898.149	25.154	27.3

5,6-O-Isopropylidene-2-O-allyl-L-ascorbic Acid ¹³C (3a)

S 13

5,6-O-Isopropylidene-2-O-methyl-L-ascorbic Acid 1H (3b)

S 14

5,6-O-Isopropylidene-2-O-methyl-L-ascorbic Acid 13C (3b)

NMR111501A 5,6-O-Isopropylidene-2-O-methyl-L-Ascorbic Acid

Pulse Sequence: zgpg30

Solvent: CDCl3

Ambient temperature

File: 111501A

INOVA-400 125.000 MHz

Pulse 9.0 degrees

Acq. time 1.015 sec

Width 18761.7 Hz

32712 repetitions

OBSERVE C13, 75.4600696 MHz

DECOUPLE H1, 399.1045181 MHz

Power 35 dB

continuously on

WALTZ-16 modulated

DATA PROCESSING

Line broadening 1.0 Hz

FT size 121072

Total time 50 hr, 35 min, 48 sec

S 15

5,6-O-Isopropylidene-2-O-trans-crotyl-L-ascorbic Acid 1H (3c)

Monday 7-28-02 2Crotyl5Hydroxyl of IAA 2CR030H
Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature
Mercury-30000 "vnu200"
Relax. delay 1.000 sec
Pulse 78.7 degree
Acq. time 1.305 sec
Width 4500.5 Hz
256 Repetitions
OBSERVE H1 300.1030290 MHz
DATA PROCESSING
F1 size 32768
Total time 12 min, 57 sec.

S 16

5,6-O-Isopropylidene-2-O-trans-crotyl-L-ascorbic Acid **(3c)**

Tuesday 7-20-02 SCRO30HC13
Pulse Sequence: zgpg30
Solvent: CDCl3
Ambient temperature
Mercury-3000B "nuu500"

Pulse 64.8 degrees
Acq. time 1.813 sec
Width 21378.0 Hz
20004 repetitions
OBSERVE C13, 75.4603718 MHz
DECUPLE R1, 200.1045181 MHz
Power 35 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
line broadening 1.0 Hz
FT size 131072
Total time 71 hr, 45 min, 46 sec

S 17

5,6-O-Isopropylidene-2-O-benzyl-L-ascorbic Acid 1H (3d)

NMR H130018 5,6-O-Isopropylidene 2benzyl 3Hydroxy L Ascorbic Acid

Pulse Sequence: s2pu1

Solvent: CDCl3

Ambient temperature

INOVA-400 "Wsu400"

Pulse S2.5 degrees

Acq. time 3.744 sec

Width 6000.6 Hz

S2 repetitions

OBSERVE H1 399.9449413 MHz

DATA PROCESSING

FT size 65536

Total time 31 min, 16 sec

S 18

5,6-O-Isopropylidene-2-O-benzyl-L-ascorbic Acid ^{13}C (3d)

S 19

5,6-O-Isopropylidene-2-O-trans-cinnamyl-L-ascorbic Acid 1H (3e)

5,6-O-Isopropylidene-2-O-~~trans~~^{cinnamyl}-L-Ascorbic acid 122004A
Pulse Sequence: zgpg30
Solvent: CDCl3
Ambient temperature
File: 122004A
Mercury-3000S "w60300"

Relax. delay 1.000 sec
Pulse 32.8 degrees
Acq. time 3.000 sec
Width 6506.5 Hz
128 repetitions
OBSERVE H1 300.1452494 MHz
DATA PROCESSING
Line broadening 1.0 Hz
FT size 32768
Total time 9 min, 5 sec

S 20

5,6-O-Isopropylidene-2-O-trans-cinnamyl-L-ascorbic Acid 13C (3e)

5,6-O-Isopropylidene 2-O-Cinnamyl L Ascorbic Acid svf=1220048
Pulse Sequence: zgpg30
Solvent: CDCl3
Ambient temperature
File: 1220048
Mercury=36000 "vau300"

Relax. delay 8.000 sec
Pulse 23.3 degree
Acq. time 3.000 sec
Width 10761.7 Hz
4720 repetitions
OBSERVE C13, 75.4715858 MHz
DECOUPLE H1, 300.1407838 MHz
Power 35 dB
Continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 5.0 Hz
FT size 32768
Total time 47 hr, 17 min, 30 sec

5,6-O-Isopropylidene-2-O-Heptane-L-Ascorbic Acid

S 21

Pulse Sequence: s2pu1

Solvent: CDCl₃

Ambient temperature

INOVA-400 "wsuino400"

Pulse 31.5 degrees

Acq. time 3.744 sec

Width 6000.6 Hz

144 repetitions

OBSERVE H1, 399.9371075 MHz

DATA PROCESSING

FT size 65536

Total time 12 min, 30 sec

5,6-O-Isopropylidene-2-O-heptane-L-ascorbic Acid 1H (3f)

S 22

5,6-O-Isopropylidene-2-O-Heptane-L-Ascorbic Acid

Pulse Sequence: s2pul

Solvent: CDCl₃

Ambient temperature

INOVA-400 "wspinova400"

Relax. delay 3.000 sec

Pulse 20.8 degrees

Acq. time 1.199 sec

Width 25000.0 Hz

9496 repetitions

OBSERVE C13, 100.5642703 MHz

DECOUPLE H1, 399.9391255 MHz

Power 45 dB

continuously on

WALTZ-16 modulated

DATA PROCESSING

Line broadening 1.0 Hz

FT size 65536

Total time 14 hr, 36 min, 42 sec

5,6-O-Isopropylidene-2-O-heptane-L-ascorbic Acid 13C (3f)

S 23

S 24

S 25

5,6-O-isopropylidene-2-O-allyl-3-O-acetyl-L-ascorbic Acid 1H (4a)

Monday 8-12-82 2Ay112Acetyl of IAA
Pulse Sequence: s2pu1
Solvent: CDCl3
Ambient temperature
Mercury-300SB "WuS00"

Relax. delay 1.000 sec
Pulse 11.2 degrees
Acq. time 1.895 sec
Width 4508.5 Hz
64 repetitions
OBSERVE H1 300.1030284 MHz
DATA PROCESSING
FT size 32768
Total time 8 min, 37 sec

S 26

5,6-O-Isopropylidene-2-O-allyl-3-O-acetyl-L-ascorbic Acid 13C (4a)

2allyl3acetyl1C13
Pulse Sequence: szpu1
Solvent: CDCl3
Ambient temperature
Mercury-300SB "wsu300"

Pulse 94.8 degrees
Acq. time 1.815 sec
Width 21378.0 Hz
22368 repetitions
OBSERVE C13, 75.4609726 MHz
DECOUPLE H1, 300.1045101 MHz
Power 25 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 1.0 Hz
FT size 131072
Total time 71 hr, 45 min, 46 sec

S 27

S 28

S 29

5,6-O-Isopropylidene-2-O-methyl-3-O-acetyl-L-ascorbic Acid 1H (4b)

S 30

5,6-O-Isopropylidene-2-O-methyl-3-O-acetyl-L-ascorbic Acid **4b**

HRH13102 5,6-O-Isopropylidene 2Methyl 3Acetyl L Ascorbic Acid
Pulse Sequence: g2pu1
Solvent: CDCl3
Ambient temperature
Mercury-300SB "wsu300"

Pulse 34.5 degrees
Acq. time 1.815 sec
Width 18761.7 Hz
34980 F010110105
OBSERVE C13, 75.4609724 MHz
DECOUPLE H1, 300.1945181 MHz
Power 35 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 1.0 Hz
FT size 131072
Total time 52 hr, 52 min, 19 sec

S 31

(4b)

Pg #1

S 32

(4b)

Pg #2

S 33

5,6-O-Isopropylidene-2-O-trans-crotyl-3-O-acetyl-L-ascorbic Acid 1H (4c)

S 34

5,6-O-Isopropylidene-2-O-trans-crotyl-3-O-acetyl-L-ascorbic Acid ¹³C (4c)

2CIN3ACETYL3
Pulse Sequence: zgpg30
Solvent: CDCl3
Ambient Temperature
F1: 2CIN3ACETYL3
INNOVA-400 "wau400"
Pulse 34.0 degrees
Acq. time 1.194 sec
Width 25000.0 Hz
8180 repetitions
OBSERVE: C13, 100.6252490 MHz
DECOUPLE: H1, 299.9450544 MHz
Power 45 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 1.0 Hz
FT size 65536
Total time 2 hr, 45 min, 2 sec

S 35

(4c)

Pg #1

S 36

(4c)

Pg #2

S 37

5,6-O-Isopropylidene-2-O-benzyl-3-O-acetyl-L-ascorbic Acid 1H (4d)

NMR12002C 2-Benzyl3Acetyl 5,6-O-Isopropylidene

Pulse Sequence: zgpg30

Solvent: CDCl3

Acidant: Temperature

INQVA-400 "usu400"

Pulse 52.5 degrees

Acq. time 3.749 sec

Width 6000.0 Hz

30 repetitions

OBSERVE F1, 399.3448432 MHz

DATA PROCESSING

FT 6520 65536

Total time 31 min, 15 sec

S 38

5,6-O-Isopropylidene-2-O-benzyl-3-O-acetyl-L-ascorbic Acid 13C (4d)

S 39

S 40

(4d)

Pg #2

S 41

5,6-O-Isopropylidene-2-O-trans-cinnamyl-3-O-acetyl-L-ascorbic Acid 1H (4e)

S 42

5,6-O-Isopropylidene-2-O-trans-cinnamyl-3-O-acetyl-L-ascorbic Acid 13C (4e)

NR124224 5,6-O-Isopropylidene-2-O-trans-cinnamyl-3-O-acetyl-L-Ascorbic Acid

Pulse Sequence: zgpg30
Solvent: CDCl3
Reagent Temperature: Mercury-300MS "H2O/50%
Pulse 81.8 degrees

RG-150 1.515 sec
Width 20701.7 Hz
32726 repetitions
OBSERVE CH: F3 4001000 MHz
DECOUPLE H1: 200.2045101 MHz
Power 35 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 1.0 Hz
GB 4000.151622
Total time 55 hr, 25 sec

S 43

S 44

S 45

5,6-O-Isopropylidene-3-O-methyl-2-O-acetyl-L-ascorbic Acid 1H (5a)

NMR M111401 5,6-O-Isopropylidene 3Methyl 2Acetyl L Ascorbic Acid

Pulse Sequence: zgpg30

Solvent: CDCl3

Ambient Temperature

INDV=400 "vsu400"

Pulse 52.5 degrees

Acq. time 3.744 sec

Width 6000.6 Hz

32 repetitions

OBSERVE H1 360.8440200 MHz

DATA PROCESSING

FT size 65536

Total time 31 min, 16 sec

S 46

5,6-O-Isopropylidene-3-O-methyl-2-O-acetyl-L-ascorbic Acid ¹³C (5a)

S 47

5,6-O-Isopropylidene-3-O-benzyl-2-O-acetyl-L-ascorbic Acid 1H (5b)

5,6-O-Isopropylidene-3-O-benzyl-2-O-acetyl-L-ascorbic Acid 13C (5b)

S 49

5,6-O-Isopropylidene-3-O-trans-crotyl-2-O-acetyl-L-ascorbic Acid 1H (5c)

5,6-Isopropylidene-3-O-trans-crotyl-2-O-acetyl-L-ascorbic Acid 13C (5c)

5. 5-D-ISOETHOXYHYDROXY-2-O-ACETYL-3-O-CROTYLASCORBIC ACID, C12 DECODED

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EXP# 14000 SEQUENCE: STD10
DATE 05-05-93
SOLVENT CDCl3
FILE 0

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S 51

5,6-O-Isopropylidene-3-O-allyl-2-O-acetyl-L-ascorbic Acid 1H (5d)

S 52

5,6-O-Isopropylidene-3-O-allyl-2-O-acetyl-L-ascorbic Acid 13C (5d)

S 53

5,6-O-Isopropylidene-3-O-trans-cinnamyl-2-O-acetyl-L-ascorbic Acid 1H (5e)

S 54

5,6-O-Isopropylidene-3-O-trans-cinnamyl-2-O-acetyl-L-ascorbic Acid 13C (5e)

S 55

Calculated Electrostatic Potential Diagram of the Neutral form of 1

Calculated Electrostatic Potential Diagram of the
Monoanionic form of 1

Calculated Electrostatic Potential Diagram of the
Dianionic form of 1