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# Vitamin C in Organic Synthesis. II. C-2 Methylation[1]

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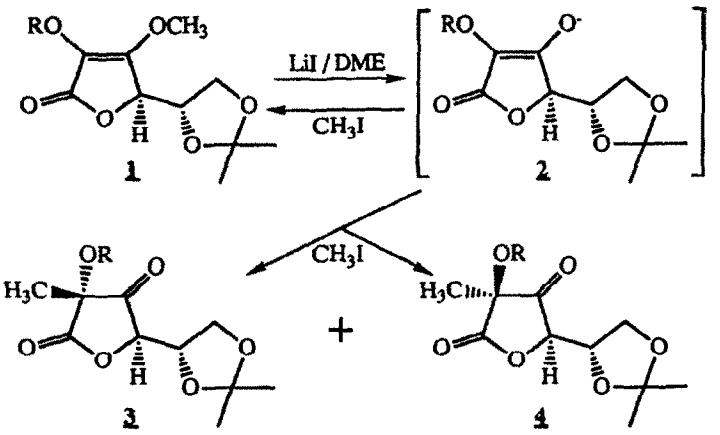
**Abstract:** An L-ascorbic acid (vitamin C) derivative was methylated at the 2 position via oxygen to carbon transfer in 61% yield to give the R configuration in 92% d.e.

As part of our investigation into the chemistry of vitamin C, we have reported that treatment of potassium ascorbate with allylic and propargylic halides in protic media yields the corresponding C-2 alkylation products. However, when this reaction was extended to the case of methyl iodide, it failed to give a displacement adduct.[2] Herein, we describe a method for the stereospecific C-2 methylation of L-ascorbic acid and various synthetic manipulations of the butenolide derived therefrom.

In 1975, Brimacombe observed that exposure of 2-O-(E)-cinnamoyl-5,6-O-isopropylidene-3-O-methyl ascorbic acid, **1a**, to LiI in polar aprotic solvents (DMF or DMSO) afforded a methylation product rather than the anticipated spirodilactone.[3] Our initial inquiry into this observation confirmed the product and showed that it was produced as a 1:1 mixture of stereoisomers, **3a** and **4a**. A survey of reaction solvents indicated a slight improvement in the isomeric ratio (3:1 of **3a** to **4a**) with DME.

Examination of various O-2 substituted vitamin C derivatives (Table I) led to the conclusion that a trimethylacetyl moiety affords the best stereoselectivity in this methylation process. Thus, treatment of 2-O-pivaloyl-5,6-O-isopropylidene-3-O-methyl ascorbic acid, **1d**, in DME with LiI and methyl iodide at 80°C gave a 23:1 ratio of **3d** to **4d** in 61% yield. The addition of iodomethane is necessary to ensure complete reaction at the elevated temperature. Mechanistically, the reaction proceeds by reversible dealkylation at oxygen, with C-2 methylation acting as the sink for the equilibrating mixture.[4] The methyl group adds from the same side as the 5,6-O-isopropylidene ethanediol sidechain in **2**, due to the steric encumberment of the trimethylacetyl group on the opposite face.

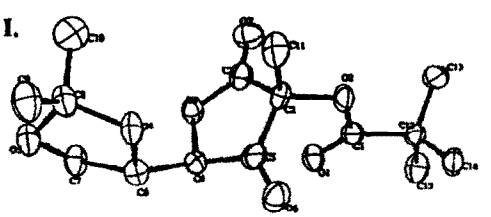
**Table I. The C-2 Methylation of Vitamin C Derivatives.**




| R | 3 : 4 | yield (%) |
|---|---|---|
| a COCH=CHPh | 3 : 1 | 25 |
| b $COCH_3$ | 2 : 1 | 37 |
| c COPh | 2 : 1 | 17 |
| d $COC(CH_3)_3$ | 23 : 1 | 61 |

The stereochemical assignment of the newly created center was based on the absence of an NOE between the C-2 methyl and the C-4 proton; whereas, the minor isomer, **4d**, showed a 5% enhancement. This assignment was verified by X-ray analysis of **3d** (Figure I).[5]

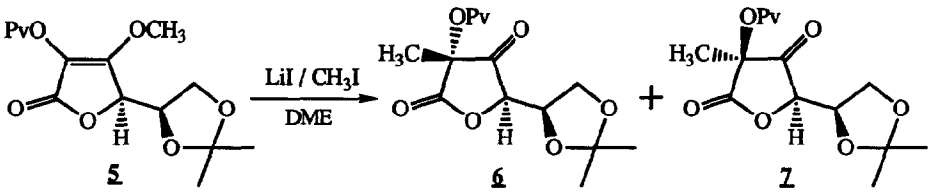
**Figure I.**



ORTEP drawing of **3d**

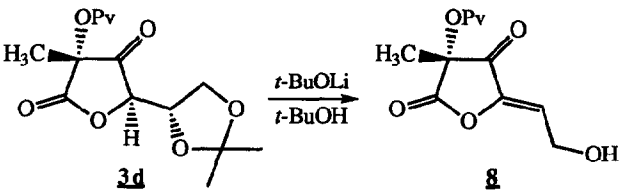
When 2-O-pivaloyl-5,6-O-isopropylidene-3-O-methyl isoascorbic acid, **5**, was reacted under the same conditions (Scheme I), the corresponding C-2 methylation products, **6** and **7**, were isolated as a 16:1 mixture of stereoisomers. As before, the minor isomer **7** displayed an NOE enhancement (4%) between the newly introduced methyl group and H-4.

**Scheme I.**




Exposure of **3d** to *t*-BuOLi in *t*-BuOH at room temperature leads to β-elimination of the 5,6-O-isopropylidene group to generate unsaturated ketone **8**. Only the Z-configuration of the 4,5-exomethylene was observed, as dictated by the antiperiplanar arrangement of H-4 and O-5 required for olefin formation.[6] Presumably, these highly functionalized synthons derived from vitamin C can serve as structural subunits for "chiron" based natural product synthesis.[7]

**Scheme II.**




**Spectroscopic Data**

5,6-O-isopropylidene-3-O-methyl-2-O-pivaloyl ascorbic acid, **1d**. mp 93-97°C (EtOAc/ hexanes); $[\alpha]_D$ +25.4 (c 1, $CHCl_3$). IR ($CHCl_3$): υ 3020-2860, 1786, 1772, 1699 $cm^{-1}$. $^1H$ NMR ($d_6$-DMSO): δ 1.22 (s, 15 H), 3.88 (dd, J = 5.6, 8.5 Hz, 1 H), 3.97 (s, 3 H), 4.09 (dd, J = 7.1, 8.5 Hz, 1 H), 4.30 (dq, J = 2.3, 5.6 Hz, 1 H), 5.05 (d, J = 2.3 Hz, 1 H). $^{13}C$ NMR ($d_6$-DMSO): δ 25.2, 25.7, 26.5, 38.4, 59.8, 65.0, 73.1, 75.0, 109.8, 113.9, 161.8, 167.3, 175.6. MS (CI), m/e (relative intensity): 315 (100), 257 (5.8), 230 ( 5.7).
Anal. Calcd for $C_{15}H_{22}O_7$: C, 57.31; H, 7.05. Found: C, 56.81; H, 6.89.

Compound **3d**: Rf 0.79 (1:1, EtOAc/hexanes); mp 125-128 °C (EtOAc/hexanes); $[\alpha]_D$ +114.3 (c 1, $CHCl_3$). IR ($CHCl_3$): υ 3030, 2995, 1817, 1777, 1732 $cm^{-1}$. $^1H$ NMR ($d_6$-DMSO): δ 1.12 (s, 9 H), 1.23 (s, 3 H), 1.27 (s, 3 H), 1.51 (s, 3 H), 3.94 (dd, J = 6.0, 8.7 Hz, 1 H), 4.13 (dd, J = 7.3, 8.7 Hz, 1 H), 4.48 (dq, J = 1.2, 5.7 Hz, 1 H), 5.35 (d, J = 1.2 Hz, 1 H). $^{13}C$ NMR ($d_6$-DMSO): δ 16.1, 24.8, 24.9, 26.3, 37.5, 65.0, 73.8, 83.5, 110.2, 171.5, 178.6, 203.9. MS (CI), m/e (relative intensity): 316 (15.6), 299 (100), 257 (69.7), 103 (12.9).
Anal. Calcd for $C_{15}H_{22}O_7$: C, 57.32; H, 7.05. Found: C, 57.22; H, 7.06.

Compound **4d**: Rf 0.76 (1:1, EtOAc/hexanes); $[\alpha]_D$ +34.9 (c 1, $CHCl_3$). IR ($CHCl_3$): υ 3030, 2998, 1820, 1777, 1732 $cm^{-1}$. $^1H$ NMR ($d_6$-DMSO): δ 1.11 (s, 9 H), 1.26 (s, 3H), 1.34 (s, 3 H), 1.57 (s, 3H), 3.91-4.14 (m, 3 H), 5.40 (d, J = 8.3 Hz, 1 H). $^{13}C$ NMR ($d_6$-DMSO): δ 17.3, 25.4, 26.9, 37.6, 64.9, 74.3, 83.6, 109.6, 171.0, 178.1, 202.9. MS (CI), m/e (relative intensity): 315 (100), 299 (32.4), 257 (32.1), 103 (7.9).
Anal. Calcd for $C_{15}H_{22}O_7$: C, 57.32; H, 7.05. Found: C, 57.20; H, 7.06.

2-O-pivaloyl-5,6-O-isopropylidene-3-O-methyl isoascorbic acid, **5**. $[\alpha]_D$ -8.0 (c 1, $CHCl_3$). IR ($CHCl_3$): υ 3020-2860, 1785, 1772, 1694 $cm^{-1}$. $^1H$ NMR ($d_6$-DMSO): δ 1.21 (s, 9 H),1.24 (s, 3 H), 1.30 (s, 3 H), 3.72 (dd, J = 5.6, 8.7 Hz, 1 H), 3.95 (s, 3 H), 3.96 (m, 1 H), 4.36 (m, 1 H), 5.13 (dd, J = 1.5, 3.0 Hz, 1 H). $^{13}C$ NMR ($d_6$-DMSO): δ 24.9, 25.9, 26.5, 38.4, 59.9, 63.4, 74.6, 75.1, 109.9, 114.0, 162.4, 167.0, 175.7. MS (CI), m/e (relative intensity): 315 (100), 257 (7.9), 230 ( 8.0).
Anal. Calcd for $C_{15}H_{22}O_7$: C, 57.31; H, 7.05. Found: C, 57.52; H, 7.11.

Compound **6**. Rf 0.78 (1:1, EtOAc/hexanes); mp 119-123 °C (EtOAc/hexanes); $[\alpha]_D$ -96.3 (c 1, $CHCl_3$). IR ($CHCl_3$): υ 3030, 2995, 1813, 1774, 1727 $cm^{-1}$. $^1H$ NMR ($d_6$-DMSO): δ 1.12 (s, 9 H), 1.23 (s, 3 H), 1.26 (s, 3 H), 1.51 (s, 3 H), 3.93 (dd, J = 5.6, 8.8 Hz, 1 H), 4.12 (dd, J = 7.7, 8.8 Hz, 1 H), 4.48 (dd, J = 5.6, 7.7 Hz, 1 H), 5.35 (d, J = 1.6 Hz, 1 H). $^{13}C$ NMR ($d_6$-DMSO): δ 16.1, 24.8, 25.1, 26.2, 37.5, 65.0, 73.8, 83.4, 110.2, 171.5, 178.6, 203.8. MS (CI), m/e (relative intensity): 315 (100), 299 (19.0), 257 (21.6), 215 (23.6), 213 (20.9).
Anal. Calcd for $C_{15}H_{22}O_7$: C, 57.32; H, 7.05. Found: C, 57.33; H, 7.09.

Compound **7**: Rf 0.77 (1:1, EtOAc/hexanes); $[\alpha]_D$ -28.7 (c 0.7, $CHCl_3$). IR ($CHCl_3$): υ 3030, 2998, 1819, 1776, 1731 $cm^{-1}$. $^1H$ NMR ($d_6$-DMSO): δ 1.13 (s, 9 H), 1.27 (s, 3H), 1.35 (s, 3 H), 1.58 (s, 3H), 3.92-4.13 (m, 3 H), 5.42 (d, J = 8.3 Hz, 1 H). $^{13}C$ NMR ($d_6$-DMSO): δ 17.3, 25.4, 26.4, 37.6, 64.9, 74.3, 83.6, 109.6, 171.0, 178 1, 202.9. MS (CI), m/e (relative intensity): 315 (84.7), 299 (15.1), 257 (20.3), 215 (25.8), 213 (35.9), 197 (6.1), 155 (9.6), 103 (100).
Anal. Calcd for $C_{15}H_{22}O_7$: C, 57.32; H, 7.05. Found: C, 57.43; H, 7.13.

Compound **8**. Rf 0.40 (1:1, EtOAc/hexanes); $[\alpha]_D$ -8.2 (c 1, $CHCl_3$). IR ($CHCl_3$): υ 3020-2860, 1822, 1767, 1728, 1675 $cm^{-1}$. $^1H$ NMR ($d_6$-DMSO): δ 1.13 (s, 9 H), 1.57 (s, 3 H), 4.22 (m, 2 H), 5.26 (t, J = 5.4 Hz, 1 H), 5.99 (t, J = 6.3 Hz, 1 H). $^{13}C$ NMR ($d_6$-DMSO): δ 17.2, 26.3, 37.6, 55.3, 72.5, 116.8, 142.5, 168.8, 178.4, 190.1. MS (CI), m/e (relative intensity): 256 (4.6), 239 (100), 154 (4.3).
Anal. Calcd for $C_{12}H_{16}O_6$: C, 56.25; H, 6.29. Found: C, 56.34; H, 6.37.

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