Tetrahedron Vol 44, No 23, pp 7047 to 7054, 1988
Printed in Great Britain

0040-4020/88 $3.00 + .00

Ascorbic Acid as a Michael Donor. Part II. Reaction with Alicyclic Enones.[1]

Kawporn Sussangkarn and Gabor Fodor
Department of Chemistry, West Virginia University, Morgantown, WV 26506-6045

Isabella Karle and Clifford George
Laboratory for the Structure of Matter, Naval Research Laboratory, Washington, DC 20375

(*Received in USA 2 May 1988*)

Abstract

The scope of the Michael reaction of L-ascorbic acid was explored by its application to 2-cyclohexen-1-one and 2-cyclopenten-1-one, respectively. Unexpected acid catalysis was discovered with the reaction.

The C-3' epimers of the 2-ketocycloalkyl-L-gulonolactones (3 and 4; 6 and 7) have been separated and their configurations on C-3' were determined. In the ketocyclohexyl epimers the absolute configurations of C-3' were assigned by applying the octant rule. These assignments ultimately were confirmed by X-ray diffractometry. The configurations of the ketocyclopentyl derivatives on C-3' were determined by X-ray crystallography. These compounds have been found to be biologically active.

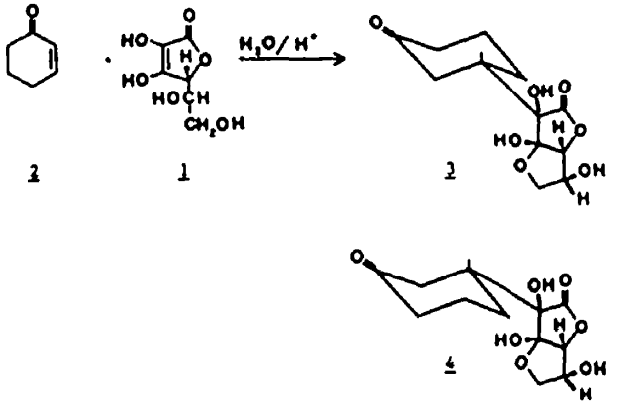
In the first paper[2] of this series we reported that L-ascorbic acid (1) is able to serve as a Michael donor to two simple aliphatic α,β-unsaturated carbonyl compounds: acrolein and methyl vinyl ketone. The addition of 1 to α-methyl acrolein and crotonaldehyde[3] proved the wide applicability of the new reaction to α,β-olefinic aldehydes.

Recently we decided to explore the Michael addition of 1 to the less reactive, cyclic enones[1]. As the first reaction partner, 2-cyclohexen-1-one (2) was chosen (Scheme 1). However, the reaction was very sluggish - when monitored by HPLC - even after 7 days no considerable amount of product was detected. One of us (KS) came to the conclusion that a strong acid shall be used as a catalyst by protonating the carbonyl of the ketone. Indeed, the addition of a few drops of concentrated hydrochloric acid caused a dramatic change: the reaction had started and became complete overnight. The two C-3' epimers (3 and 4) of 2-(1'-keto-3'-cyclohexyl)-3-keto-L-gulonolactone-(3,6)-cyclohemiketal were separated by fractional crystallization. After recrystallizations, the first crop had m.p. 155-156°C and the second crop had m.p. 170-171°C. They were further characterized by ^{1}H and ^{13}C NMR and IR spectra. The R_f values were 4.5 and 4.2 min, respectively in the HPLC using MCH-10 column, 80% water/methanol solvent and 1.0 ml/min flow rate. Measuring ORD in acetone, the lower melting epimer showed a negative Cotton effect while the higher melting compound had a positive Cotton effect. In order to apply the octant rule[4] we had constructed a "cage"[5] from three planes made of polyethylene with a cavity that was cut out in the middle so that the Dreyding models of the ketocyclohexyl 3'-epimers could be placed with the C=O group laying in the B plane[4] thus the groups around the new chiral center were positioned in one case (3) in the upper right octant and in the other case (4) in the upper left octant. Thus the sign of the contribution of the chiral center to the Cotton effect curve could be predicted. By applying the octant rule[4] the 3'S configuration was assigned to the levorotatory epimer (3) and the opposite, 3'R configuration to the dextrorotatory form (4).

Single crystals of 3 were obtained so the structure determination by X-ray crystallography became feasible and the result confirmed the optical rotatory dispersion data. Details of this X-ray study are described under a separate heading.

The second cyclic enone was 2-cyclopenten-1-one (5) a compound that is considered as a rather poor Michael acceptor. However, by using our new technique of acid catalysis, the reaction of L-ascorbic acid upon 5 gave the desired 2-(1'-keto-3'-cyclopentyl)-3-keto-L-gulono-lactone-(3,6)-cyclohemiketal. Again, two epimers, 6 and 7, were formed and were separated. The second crop gave single crystals and was subject to X-ray structure determination. Figure 2 shows the computer drawing that proves the compound 7 having the C-3'R configuration, hence the C-3'S configuration applies to the first crop 6. Details of the X-ray structure

Scheme 1



Scheme 2

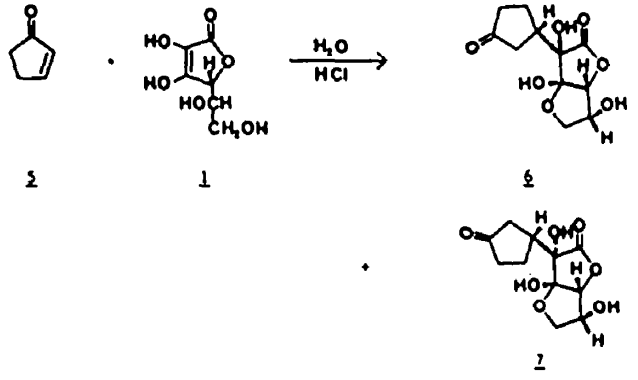


Table (3). Hydrogen Bond Parameters.

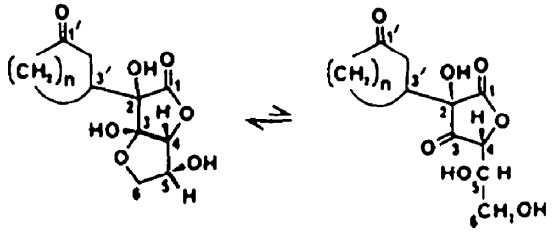
	3			3A			7		
	O(1')—O(3A)	O(1')—O(5A)	O(2)—O(3)	O(1'A)—O(2)	O(1'A)—O(2)	O(5A)—O(2A)	O(1)—O(2)	O(1')—O(3)	O(5)—O(2)
O--O Å	2.77	2.86	2.91	2.93	2.83	2.93	2.85	2.79	2.81
H--O Å	1.93	2.01	2.12	2.14	2.10	2.23	2.21	2.01	2.06
OH-O°	162	164	147	165	144	149	133	158	167

determination are given under a separate heading.

The acid catalysis technique has now been found to be of general value. The first enone–ascorbic acid adduct i.e. ascorbic acid–methylvinylketone[2], that was prepared in this laboratory caused serious problems of isolation. By using hydrochloric acid in catalytic amounts allowed the Michael addition to occur much faster and gave rise to the identical 2-(3'-ketobutyl)-3-ketogulonolactone <3,6>-cyclohemiketal in much better yields than before and in a high degree of purity. These compounds show a definite immunopotentiating effect[6,7] in that they amplified T-lymphocyte poliferation, lymphokine production and antibody production, often at low doses.

We reported earlier[8] the evidence for the tautomeric equilibrium between the bicyclic gulonolactone-<3,6>-cyclohemiketal and the corresponding monocyclic, 3-keto form of 2-(5'-methyl-2'-furyl)-3-keto-L-gulonolactone-<3,6>-cyclohemiketal. The four crystalline compounds (3, 4, 6, and 7) also showed the evidence of this equilibrium in the solution ^{13}C NMR spectra. In all cases, each carbon signal has associated with it a small satellite signal except the C-3 hemiketal peak that appears alone. An extra carbonyl peak above 200 ppm is also observed and can be assigned to the C-3 keto carbonyl carbon of the monocyclic form. Table 1 shows the ^{13}C assignments of the gulonolactone skeleton both in the major bicyclic cyclohemiketal form and in the monocyclic form, with a 4-(5,6-dihydroxy)ethyl side chain.

Table (1). ^{13}C NMR assignments of the gulonolactone skeletons in compounds 3, 4, 6, and 7: values in ppm from Me_4Si in Me_2SO.



n = 3 3a (3'S) 4a (3'R) ⇌ 3b (3'S) 4b (3'R)

n = 2 6a (3'S) 7a (3'R) ⇌ 6b (3'S) 7b (3'R)

Compound	C-1	C-2	C-3 hemiketal	C-3 keto	C-4	C-5	C-6	C-1'
3a	174.6	87.9	107.2	-	78.6	74.3	73.6	210.3
3b	172.8	82.8	-	208.6	75.1	69.8	61.0	208.8
4a	174.7	87.7	107.1	-	78.7	74.2	73.5	209.5
4b	173.1	82.8	-	208.3	75.2	69.8	61.0	208.9
6a	174.8	87.2	107.4	-	78.4	74.1	74.0	217.7
6b	173.3	82.7	-	208.7	74.2	69.9	60.7	216.0
7a	174.9	87.3	107.5	-	78.2	74.0	73.9	217.0
7b	173.3	82.7	-	208.3	74.0	69.7	61.1	216.0

X-ray Diffraction.

The X-ray diffraction data for compounds 3 and 7 are summarized in Table (2). Both structures were solved by direct methods[9] and refined using the program SHELXTL.[10] In each compound C and O atom coordinates were refined with anisotropic thermal parameters while the non-hydroxyl hydrogens were included using a Dreiding model (coordinate shifts of C atoms applied to the bonded hydrogens, C-H = 0.96 Å, U(H) = 1.1 Ueq(C) for 7. The coordinates of the

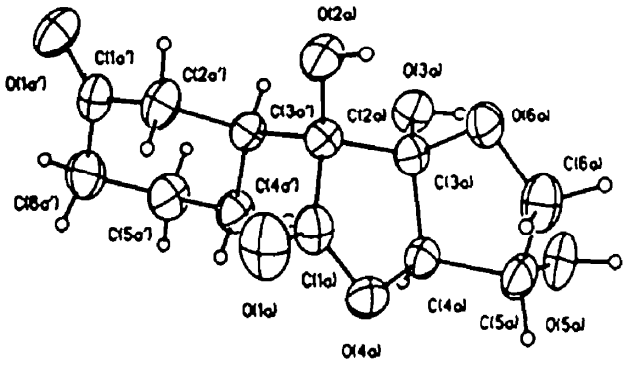


Figure (1). Thermal ellipsoid plot of 3 drawn with experimental coordinates. The second crystallographically unique molecule present has a nearly identical conformation and is not shown. Thermal ellipsoids are drawn at the 50% probability level.

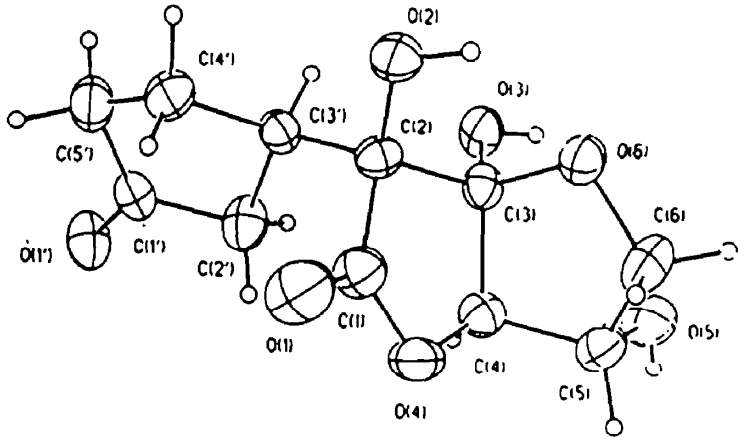


Figure (2). Thermal ellipsoid plot of 7 drawn with experimental coordinates. Thermal ellipsoids are drawn at the 50% probability level.

Table (2). Crystal and Refinement Data

formula	$C_{11}H_{14}O_7$ (7)	$C_{12}H_{16}O_7$ (3)
crystal system	orthorhombic	monoclinic
space group	$P2_12_12_1$	C2
a, Å	7.863(1)	20.091(11)
b, Å	10.674(2)	6.153(2)
c, Å	13.403(2)	24.632(14)
β, deg.		125.6(3)
V, $Å^3$	1124.9(3)	2474.0(17)
Z	4	8
formula weight	258.23	272.28
F(000)	544	1152
ρ(calc), g cm^{-3}	1.524	1.462
temp, C°	22	22
crystal dim., mm	0.18 x 0.21 x 0.20	0.65 x 0.22 x 0.15
λ, wavelength, Å	1.54184	1.54184
μ, absorption coef., cm^{-1}	10.6	9.93
2θ max., deg.	115	130
scan speed, deg./min.	variable 4 to 30	variable 4 to 30
2θ scan range, deg.	$2.0 + \Delta_{\alpha_1\alpha_2}$	$2.0 + \Delta_{\alpha_1\alpha_2}$
data collected, h k l	0 to 8, 0 to 11, 0 to 14	−15 to 23, −4 to 6, −28 to 23
unique data	918	3295*
unique data, $F_o > 3\sigma(F_o)$	867	2812
standard reflection	3% random variation	2.8% random variation
parameters refined	175	466
weighting function, g[a]	0.00050	0.00023
R[b], wR^2[c], S[d]	0.043, 0.054, 1.912	0.026, 0.034, 1.810
Fourier excursions, e $Å^{-3}$	0.52, −0.21	0.19, −0.20

*Friedels not merged

[a] $w^{-1} = \sigma^2(F_o) + g F_o^2$

[b] $\Sigma|\Delta|/\Sigma|F_o|$

[c] $\Sigma(|\Delta|w^{1/2})/\Sigma(|F_o|w^{1/2})$

[d] $[\Sigma w(\Delta^2)/(N_o-N_p)]^{1/2}$

non-hydroxyl hydrogens in 3 were refined with fixed isotropic thermal parameters; hydroxyl hydrogens were refined isotropically.

The geometry of 3 and 7 is shown in Figures (1) and (2). The absolute configuration of both is based on the chirality of L-ascorbic acid as referenced to the chiral centers of 3 and 7.

In each of the two molecules the bond distances and angles are normal. The fused furano-furanone rings common to both have nearly the same geometry with torsion angles about the rings common bond C(2)-C(3)-C(4)-C(5) and O(6)-C(3)-C(4)-O(4) of -138.2(3), 90.9(3)° respectively for 7, and -133.9(1), 95.9(1) and -136.4(1), 91.0(1)° respectively for the two crystallographically unique molecules of 3 in the asymmetric unit. The orientation of ketocyclopentyl ring in 7 with respect to the fused furan-furanone rings can be described by torsion angles C(1)-C(2)-C(3)'-C(2)' = 61.1(3)° and C(3)-C(2)-C(3)'-C(4)' = 177.1(3). The chair configured ketocyclohexyl ring in 3 may be likewise described by the same torsion angles of 72.8(1) and 73.9(1)°, and -51.9(1) and -51.6(1)° respectively for the two molecules of 3.

The two molecules of 3 differ only slightly and primarily with respect to hydrogen bonding. Both 3 and 7 are efficiently hydrogen bonded with relatively high densities for organic crystals of 1.462 and 1.524 g/cm^3 respectively. The parameters for the three intermolecular hydrogen bonds formed between neighboring molecules for each of the unique molecules in 3 and 7 are given in Table (3). Tables of coordinates, bond distances and angles, and anisotropic thermal parameters have been deposited with the Cambridge Crystallographic Data Centre.*

The primary reason for the crystal structure analysis was to establish the correct diastereoisomer, that is whether the ketone moiety was present at C(1') or at C(6') in Fig. (1) or at C(5') in Fig. (2). In the least squares analysis of 7 the data indicates that both diastereoisomers are present in the crystal. The largest peak in the final difference map corresponds to the oxygen position of the diastereoisomer 6. A least squares analysis with this peak included indicates an occupancy ratio of approximately 14:1 for the major (7), and minor (6) diastereoisomers, so that a minor amount of 6 may have co-crystallized with 7.

Experimental.

Melting points were determined on a Melt-Temp apparatus and on an Electrothermal melting point apparatus and were uncorrected. IR spectra were recorded on a Perkin-Elmer 1310 Infrared Spectrophotometer. ^{1}H and ^{13}C NMR spectra were recorded on a JEOL JNM-GX270 FTNMR spectrophotometer. A Varian Model 5000 Liquid Chromatograph equipped with a reverse-phase MCH-10 column was used for HPLC analyses. Mass spectra were obtained on a Finnigan 4021 mass spectrometer with an INCOS data system by Robert R. Smith (Biochemistry Department, West Virginia University). Elemental analyses were performed by Galbraith Laboratories, Inc., Knoxville, Tennessee. Optical rotation measurements were taken on a Perkin-Elmer Model 141 Polarimeter. L-Ascorbic acid (Mallinckrodt), 2-cyclohexen-1-one (Aldrich) and 2-cyclopenten-1-one (Aldrich) were used without further purification.

2-[1'-Keto-3'-cyclohexyl)-3-keto-L-gulonolactone-(3,6)-hemiketal (epimers 3 and 4).

Distilled water (704 mL) was purged for 1 hour with nitrogen and L-ascorbic acid (176.0 g, 1.0 mole) was added. To the resulting solution 2-cyclohexen-1-one (96.0 g, 1.0 mole) was added dropwise with stirring. One half hour after the addition of the 2-cyclohexen-1-one, concentrated hydrochloric acid (2.4 mL) was added. The solution was allowed to stand undisturbed at room temperature for 24 hours when the formation of a crystalline solid was observed. The mixture was cooled in ice-water bath and filtered by suction to give 88.95 g (33%) of a crude first crop. The filtrate was allowed to cool in a refrigerator overnight

whereupon more solid precipitated. The solid was filtered by suction to give 92.72 g (34%) of a crude second crop. High pressure liquid chromatography (HPLC) analysis (MCH-10 column with 80% water/methanol as eluent and 1.0 mL/min flow rate) indicated that the crude first crop consisted of 90% epimer 3 (retention time 4.5 min) and the crude second crop consisted of 55% epimer 4 (retention time 4.2 min).

The crude first crop was recrystallized in hot water (180 mL) yielding 58.90 g (22%) of pure epimer 3, mp 155–156°C, $[\alpha]^{22}$ = +7.1° (c = 2.1, methanol), $[\alpha]^{22}$ = −2.7° (c = 1, acetone).

The crude second crop was recrystallized three times in hot water (147 mL, 140 mL and 100 mL) yielding 28.75 g (11%) of pure epimer 4, mp. 170–171°C, $[\alpha]_D^{22}$ = +24.2° (c = 2.0, methanol), $[\alpha]_D^{22}$ = +6.5° (c = 1, acetone).

Epimer 3:

IR (KBr) 3600–3100 (s, broad, OH), 2940 (m, CH), 1770 (s, lactone CO), 1690 (s, CO) cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 6.9 (1H, HDO), 5.6 (2H, HDO), 4.4 (1H, s, 4-H), 4.2 (1H, m, 5-H), 4.1 (1H, m, 6-H), 3.9 (1H, m, 6H), 2.6–1.3 (9H, m, cyclohexyl-H); ^{13}C NMR (Me_2SO-d_6), 210.3 (C-1'), 174.6 (C-1), 107.2 (C-3), 87.9 (C-2), 78.6 (C-4), 74.3 (C-5), 73.6 (C-6), 41.4 (C-2'), 41.0 (C-6'), 40.5 (C-3'), 25.2 (C-4'), and 24.3 (C-5') ppm; mass spectrum, m/e 273 $(M+1)^+$, 255, 171, 98, 97 (base peak), 85, 69, 55; Anal. Calc. for $C_{12}H_{16}O_7$: C, 52.94; H, 5.92. Found: C, 53.08; H, 5.90.

Epimer 4:

IR (KBr) 3600–3100 (s, broad, OH), 2940 (m, CH), 1775 (s, lactone CO), 1690 (s, CO) cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 6.9 (1H, HDO), 5.6 (2H, HDO), 4.4 (1H, s, 4-H), 4.1 (1H, t, 5-H), 3.9 (2H, m, 6H), 2.5–1.5 (9H, m, cyclohexyl-H); ^{13}C NMR (Me_2SO-d_6) 209.5 (C-1'), 174.7 (C-1), 107.1 (C-3), 87.7 (C-2), 78.7 (C-4), 74.2 (C-5), 73.5 (C-6), 42.14 (C-2'), 42.09 (C-6'), 40.7 (C-3'), 24.2 (C-4') and 24.1 (C-5') ppm; mass spectrum, m/e 273 $(M+1)^+$, 255, 171, 98, 97, 85, 69 (base peak), 55; Anal. Calc. for $C_{12}H_{16}O_7$: C, 52.94; H, 5.92. Found: C, 52.85; H, 5.77.

2-(1'-Keto-3'-cyclopentyl)-3-keto-L-gulonolactone-(3,6)-hemiketal (epimers 6 and 7)

2-Cyclopenten-1-one (12.15 g, 0.148 mole) was added to a solution of L-ascorbic acid (25.05 g, 0.148 mole) in 104 ml water, followed by concentrated hydrochloric acid (1 ml). The solution was stirred at room temperature for 4 days when white solid precipitated. The solid was filtered by suction to give a crude first crop (7.02 g, 18.4%). The filtrate was concentrated to give a crude second crop (9.67 g, 25.3%).

The crude first crop was recrystallized from ethyl acetate/methanol (95:5%) to give 4.23 g (11%) pure epimer 6, mp 185–186°C, $[\alpha]_D^{20}$ = −49.1° (c = 2.0, methanol), HPLC R_f = 4.2 min (MCH-10 column - 80% water/methanol - 1.0 ml/min flow rate).

The crude second crop was recrystallized from absolute acetone to give 2.49 g (7%) pure epimer 7, mp 163–164°C, $[\alpha]_D^{23}$ = +92.5° (c = 2.0, methanol), HPLC R_f = 3.8 min (MCH-10 column - 80% water/methanol - 1.0 ml/min flow rate).

Epimer 6:

IR (KBr) 3600–3100 (s, broad, OH), 2940 and 2900 (m, CH), 1780 (s, lactone CO), 1720 (s, CO) cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 6.9 (1H, s, HDO), 5.7 (1H, s, HDO), 5.5 (1H, d, HDO), 4.4 (1H, s, 4-H), 4.27 (1H, m, 5-H), 4.15 (1H, m, 6-H), 3.86 (1H, m, 6-H), 2.6–1.7 (7H, m, cyclopentyl-H); ^{13}C NMR (Me^2SO-d^6) 217.7 (C-1'), 174.8 (C-1), 107.4 (C-3), 87.2 (C-2), 78.4 (C-4), 74.1 (C-5),

74.0 (C-6), 39.4 (C-2'), 38.9 (C-5'), 37.5 (C-3'), 23.7 (C-4') ppm; Anal. Calc. for $C_{11}H_{14}O_7$: C, 51.16; H, 5.46. Found: C, 51.01; H, 5.20.

Epimer 7:

IR (KBr) 3500-3100 (s, broad, OH), 2970 and 2940 (m, CH), 1770 (s, lactone CO), 1720 (s, CO) cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 6.9 (1H, s, HDO), 5.7 (1H, s, HDO), 5.5 (1H, d, HDO), 4.4 (1H, s, 4-H), 4.26 (1H, m, 5-H), 4.15 (1H, m, 6-H), 3.86 (1H, m, 6-H), 2.6-1.9 (7H, m, cyclopentyl-H); ^{13}C NMR (Me_2SO-d_6) 217.0 (C-1'), 174.9 (C-1), 107.5 (C-3), 87.3 (C-2), 78.2 (C-4), 74.0 (C-5), 73.9 (C-6), 39.7 (C-2'), 39.5 (C-5'), 37.5 (C-3'), 22.6 (C-4') ppm; Anal. Calc. for $C_{11}H_{14}O_7$: C, 51.16; H, 5.46. Found: C, 51.21; H, 5.37.

Conclusion

The Michael addition of ascorbic acid proved feasible for the synthesis of 2-ketocyclopentyl- and 2-keto-L-cyclohexyl-3-ketogulonolactones when a mineral acid was used as a catalyst. No reaction occurred when an aqueous solution of ascorbic acid or an aqueous solution of sodium ascorbate was added to 2-cyclohexen-1-one under the same conditions. Thus, for cyclic enones, the activation of the electrophilic acceptor is more important than the enrichment of the enolate anion. Unfortunately, cyclobutenone is not capable of existence at 20°, therefore it cannot be used under the same experimental conditions. 2-Cyclohepten-1-one on the other hand, reacts rather slowly with ascorbic acid, possibly because of poor solubility or for steric reasons. This calls for further studies.

In the next paper in this series we shall discuss the possibility of applying ascorbic acid as a Michael donor to cyclic enediones.

Acknowledgement. Thanks are due to American Biotechnology Company, Rockville, Maryland, for financial support.

References

1. Preliminary paper: K. Sussangkarn and G. Fodor, Abstracts ORGN 226, 191st ACS National Meeting, New York, NY, April 17, 1986. U.S. Pat. Appl. filed 1986.

2. G. Fodor, R. Arnold, T. Mohacsi, I. Karle and J. Flippen-Anderson, Tetrahedron, 1983, 39, 2137.

3. Regina Arnold, Ph.D. Dissertation to West Virginia University, Morgantown, WV, 1984.

4. W. Moffitt, R. B. Woodward, A. Moscowitz, W. Klyne and C. Djerassi, J. Am. Chem. Soc. 1961, 83, 4013; C. Djerassi and W. Klyne, J. Chem. Soc. 1962, 4929; D. A. Lightner and V. V. Toan, Tetrahedron, 1987, 43, 49.

5. Carl Wise of the Department of Chemistry, West Virginia University, constructed this cage according to G. Fodor's idea; this new research and educational tool shall be described in a paper submitted to J. Chem. Ed.

6. R. Veltri, G. Fodor, C-H. Liu, C. J. Woolverton and H. Baseler, J. Biol. Response Modifiers, 1986, 5, 494.

7. R. W. Veltri, H. W. Baseler, G. Fodor, K. Sussangkarn and P. E. Maxim, Federation of American Societies for Experimental Biology Proceedings, 1987, 46(3), 454; G. Fodor, K. Sussangkarn, R. Arnold, H. Mathelier, T. Mohacsi, R. Mujumder, J. Butterick and R. W. Veltri, Acta Biochim. Biophys. Hung. 1987, 22, 165.

8. a. G. Fodor, K. Sussangkarn, R. Arnold, I. Karle and C. George, J. Org. Chem. 1984, 49, 5064.
   b. G. Fodor, K. Sussangkarn, H. Mathelier, K. Fang, R. Arnold, J. Flippen-Anderson and I. Karle, J. Org. Chem. 1986, 51, 3148.

9. J. Karle and I. L. Karle, Acta Cryst., 1966, 21, 849.

10. G. M. Sheldrick, SHELXTL, Microcomputer programs for structure determination. University of Göttingen, West Germany, 1980.