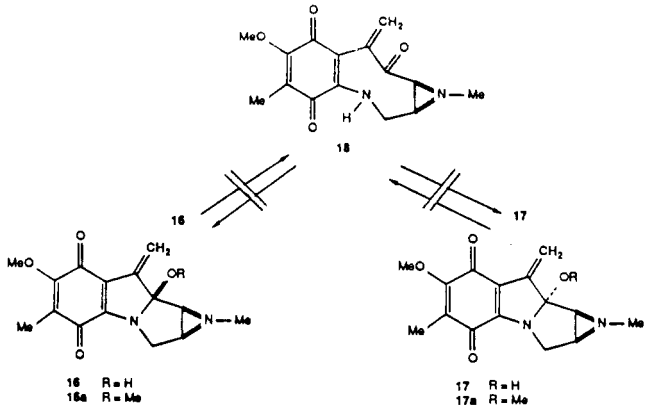

Figure 4.

adducts **15** and **15a** (Figure 3), which were surprisingly stable to spontaneous Peterson type elimination.[17] Cleavage of the silyl protecting group followed by oxidation (with DDQ–aqueous THF) and stirring for 30–40 min at room temperature led to the exocyclic methylene group in nearly quantitative yield. While the NMR spectra of **16** and **16a** indicate them to have the same gross structures as the corresponding natural products **17** and **17a**, there are small but clear differences in chemical shifts of various resonances.[18] The infrared and mass spectra of the two sets of stereoisomers are very similar. The TLC chromatographic properties of the two sets of compounds are also discernibly different. Given the previously derived 9a α-configuration of the oxygen functions of the natural products **17** and **17a**,[14,19] we are obliged to formulate the stereochemistry of the synthetic racemates as shown in **16** and **16a**.

Two features of this situation are most surprising. First, osmylation of **12** had occurred syn to the aziridino nitrogen, a result that stands in direct contrast to the previously described and rigorously proven α-osmylation of compound **7a**.[2] This difference may be a consequence of the much-reduced nucleophilicity of the indolic double bond of vinylogous formamide **13**. *Thus it might be that the only possibility for 13 to react at all with osmium tetraoxide is through a pathway where the osmylating species is directed by the cis proximal aziridino nitrogen.* In contrast, the indolic nitrogen atom of **7**, which is more basic than the corresponding center in **13**, may provide a ligating site for the oxidizing agent. Ligation by the indolic nitrogen could well occur anti to the aziridine for steric reasons, thus accounting for the observed results.

No less remarkable is the configurational stability of the hydroxy compounds **16** and **17**. A variety of attempts to effect interconversion of these compounds in either direction, under acidic or basic conditions, were unsuccessful. Starting with either substrate, there was no indication for interconversion, even at the very sensitive TLC level of analysis which would certainly have detected trace levels of crossover. We can only take these results to imply a very high barrier to opening of the carbinolamine, from either **16** or **17**, to what would have been the common ring chain tautomer **18** (Figure 4). This stands in sharp contrast to the reported accessibility of the corresponding system in the mitomycin B series.[20] Thus the exomethylene linkage seems to stabilize the carbinolamine relative to the amino ketone.[20]

Barring an enzymatically facilitated ring opening, it seems very unlikely that the in vivo bioactivity of **17** arises from its accession to the highly electrophilic **18**. Studies involving the mechanism of biological action of **17** (or **16**) are planned.

Acknowledgment. This work was supported by PHS Grant CA28824. NMR spectra were obtained through the auspices of the Northeast Regional NSF/NMR Facility at Yale University, which was supported by NSF Chemistry Division Grant CHE 7916210.

(16) Ager, D. J. *Synthesis* **1984**, 384.
(17) Peterson, D. J. *J. Org. Chem.* **1968**, *33*, 780.
(18) For instance: for compound **16** ($CDCl_3$), δ 5.94 and 5.33 (C_{10} olefinic protons); for **17**, δ 6.20 and 5.57 (C_{10} olefinic protons); for **16a**, δ 6.24 and 5.33 (C_{10} olefinic protons); for **17a**, δ 6.28 and 5.46 (C_{10} olefinic protons).
(19) The stereochemistry of the naturally derived compounds was inferred[14] from the interconversion of various carbamoyloxymitomycins into decarbamoyloxymitomycins. Thus, mitomycin B, upon direct elimination of the C-10 functionality, provided **17**. Base-induced methylation of **17** afforded **17a**. Compound **17a** could also be derived from the angular (C_{9a}) methoxy compound *N*-methylmitomycin A in a more circuitous sequence[20] which presumably could not have involved perturbation of the stereochemistry at C_{9a}.
(20) It had been concluded[14] that the barrier for carbinolamine → amino ketone conversion is accessible in the case of mitomycin B. The basis for the surmise was the finding that elimination of the 10-carbamoyloxy function occurs with mitomycin B in basic medium to produce **17**. By contrast, in the angular methoxy series (cf. *N*-methylmitomycin A), conversion to **17a** through elimination requires the use of a stronger leaving group (sulfonate) at C_{10}. The argument has been made that this difference is rationalized via the amino ketone form of mitomycin B, which is prone to eject carbamic acid to form **18** and thence **17**. Our data do not exclude this interpretation, but they would add the proviso that **18** must kinetically convert to **17** to the exclusion of **16**, since **16** does not suffer transformation to **17**. Similarly, the data per se do not rigorously exclude the possibility that either **16** (or **17**) does suffer transformation to **18** which kinetically returns to its precursor. They do exclude the possibility that **18** is accessible from both precursors, since in that case there would have been crossover between **16** and **17**.

Gregg B. Feigelson, Samuel J. Danishefsky*
Department of Chemistry
Yale University
New Haven, Connecticut 06511
Received January 25, 1988

Spontaneous Stepwise Reduction of an Organic Peroxide by Ascorbic Acid[1]

Summary: Ascorbic acid (**1**) reacts spontaneously with dilauroyl peroxide (**2**) to produce dehydroascorbic acid (**3**), carbon dioxide, lauric acid, and undecane.

Sir: The broad spectrum of physiological activity exhibited by vitamin C (L-(+)-ascorbic acid, **1**) may be attributed in part to the redox activity of the "reductone" functional group.[2] It is important that the reactivity of ascorbic acid toward simple organic functional groups be delineated.[3] We have begun exploring the chemistry of ascorbic acid and organic peroxides. In this paper we report the spontaneous, uncatalyzed, nonenzymatic reduction of dilauroyl

(1) A partial account of this work was presented to the 195th meeting of the American Chemical Society, New Orleans, LA, September 3, 1987.
(2) For a discussion of the nonenzymatic physiological effects of ascorbic acid, see: Brin, M. In *Ascorbic Acid: Chemistry, Metabolism, and Uses*; Seid, P. A.; Tolbert, B. M., Eds.; American Chemical Society: Washington, DC, 1982; pp 369–377.
(3) For reviews of ascorbic acid chemistry, see: (a) *Ascorbic Acid: Chemistry, Metabolism, and Uses*; Seid, P. A., Tolbert, B. M., Eds.; American Chemical Society: Washington, DC, 1982. (b) "Second Conference on Vitamin C" In *Annals of the New York Academy of Sciences*; King, C. G., Burns, J. J., Eds.; New York Academy of Sciences: New York, 1975; Vol. 258, pp 1–552. (c) "Vitamin C" In *Annals of the New York Academy of Sciences*; Burns, J. J., Ed.; New York Academy of Sciences: New York, 1961; Vol. 92, pp 1–332.

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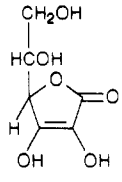
Table I. Stoichiometric Coefficients for Equation 1[a]

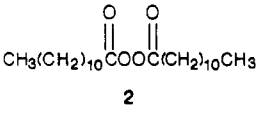
coefficient	moles (uncatalyzed)	moles (Cu^{2+} catalysis)[b]
a	1.1 ± 0.1	1.0 ± 0.1
b	2.0 ± 0.1	2.0 ± 0.1
c	1.1 ± 0.05	1.0 ± 0.1
d	2.7 ± 0.1	2.0 ± 0.1
e	1.24 ± 0.04	2.0 ± 0.1
f	0.2 ± 0.1	1.8 ± 0.1

[a] The stoichiometry was determined over an apparent pH range of ca. 5.0–8.4 and reactant concentrations ranging from 0.1 to 0.001 M. The stoichiometry was invariant over the pH and concentration ranges studied. T = 50 °C. [b] Observed when 1–5 mol % of cupric sulfate based upon the limiting reagent (1 or 2) was added.

peroxide (2). This is apparently the first report of an uncatalyzed reduction of an organic peroxide by ascorbic acid.



1



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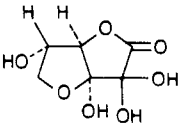


3

The reaction between 1 and 2 (eq 1) was conveniently performed in 85/15 (v/v) isopropyl alcohol/water under a nitrogen atmosphere. A constant pH (monitored as an

$$a(AH_2) + b((RCO_2)_2) \xrightarrow{H_2O} c(DA) + d(RCO_2H) + e(CO_2) + f(RH) \quad (1)$$

AH_2 = 1; $(RCO_2)_2$ = 2; DA = 3; RCO_2H = n-$C_{11}H_{23}CO_2H$; RH = n-$C_{11}H_{24}$

"apparent pH" with standard pH and calomel electrodes and a meter calibrated for aqueous solution) was maintained by a phosphate buffer. The stoichiometry of reactants was determined by iodimetry.[4,5] The products were dehydroascorbic acid (3) (drawn as the hemiketal hydrate[3a]) (determined by HPLC), lauric acid (determined by GLC as the methyl ester), CO_2 (determined by Patchornik's method[6]), and undecane (determined by GLC). The stoichiometric coefficients are reported in Table I. As can be seen, the stoichiometry is strongly affected by the presence of the redox catalyst, Cu^{2+}. The mass balance of the reaction is quite good, except for the loss of a portion of the undecyl moiety in the uncatalyzed reaction. It is noteworthy that the reaction stoichiometries are independent of the concentrations of the starting materials. Also, the diacyl peroxide is stable toward solvolysis and thermolysis under the conditions of the reaction.

Reproducible kinetics are observed when the reaction is performed with the rigorous exclusion of transition-metal ions. The rate law, determined as the rate of ascorbic acid disappearance under pseudo-first-order conditions, is cleanly first order in ascorbic acid and first order in lauroyl peroxide. The kinetics are pH dependent, the anionic form of ascorbic acid being more reactive than the neutral form.[7] The limiting rate constant for the ascorbate ion is 5.0 ± 0.1 M^{-1} s^{-1}. The kinetics were found to be independent of the buffer concentration at an apparent pH of 7.4. The kinetic behavior of ascorbic acid at low pH is complicated by the poor solubility of the buffer salts and is still under investigation.

The catalytic effect of certain transition metal salts is pronounced. The effect of Cu^{2+} is apparent even at micromolar levels of the ion. Nevertheless, we reject the hypothesis that the reaction under "uncatalyzed" conditions proceeds via catalysis by adventitious impurities. Reproducible stoichiometry and kinetics are observed when reagents and solvents of high purity are employed. Furthermore, the uncatalyzed reaction kinetics are insensitive to the addition of EDTA, a potent complexing agent.[8]

We propose that the mechanism described by eq 2–5 is operative for the Cu^{2+}-catalyzed reaction.[9] The appearance of CO_2 is diagnostic for the intermediacy of the lauryloxy radical[10] (eq 4). There is ample precedent for eq 2[11] and 3.[12] The alkane product is presumed to arise by hydrogen atom abstraction from a suitable donor to the alkyl radical (eq 5).

$$2Cu^{2+} + AH_2 \xrightarrow{H_2O} 2Cu^{+} + DA + 2H^{+} \quad (2)$$

$$Cu^{+} + (RCO_2)_2 \rightarrow Cu^{2+} + RCO_2^{-} + RCO_2^{\bullet} \quad (3)$$

$$RCO_2^{\bullet} \rightarrow R^{\bullet} + CO_2 \quad (4)$$

$$R^{\bullet} \xrightarrow{SH} RH \quad (5)$$

$$AH^{-} + (RCO_2)_2 \xrightarrow{k} AH^{\bullet} + RCO_2^{-} + RCO_2^{\bullet} \quad (6)$$

$$AH^{\bullet} + RCO_2^{\bullet} \xrightarrow{H_2O} RCO_2^{-} + DA + H^{+} \quad (7)$$

$$AH^{\bullet} + AH^{\bullet} \xrightarrow{H_2O} AH_2 + DA \quad (8)$$

$$AH^{\bullet} + (RCO_2)_2 \xrightarrow{H_2O} DA + RCO_2^{-} + RCO_2^{\bullet} + H^{+} \quad (9)$$

A mechanistic interpretation of the uncatalyzed reaction must adequately explain the noninteger values of the stoichiometric coefficients in Table I. A rate-limiting electron transfer between ascorbic acid and the peroxide provides an attractive rational for the formation of radical products (eq 6).[13] Free ascorbyl radicals may either disproportionate (eq 8) or react in a fast step with a molecule of peroxide (eq 9).[14] The fractional stoichiometry can be explained if the ascorbyl and carboxyl radicals are assumed to be formed in close proximity in eq 6.[15] A fast electron transfer between the ascorbyl and carboxyl radicals (eq 7) competes with diffusion of these radicals from the solvent

(4) See Roe, J. H., in ref 3c, pp 15–26, for a discussion of the iodimetric determination of ascorbic acid.

(5) Johnson, R. M.; Siddiqi, I. W. *The Determination of Organic Peroxides*; Pergamon: New York, 1970; pp 15–23.

(6) Patchornik, A.; Shalitin, Y. *Anal. Chem.* **1961**, *33*, 1887.

(7) Potentiometric titration of ascorbic acid with NaOH in 85/15 isopropyl alcohol/water showed that the anion form predominantes above an apparent pH of 6.5.

(8) The EDTA complexes of copper and iron are much less active catalysts for the autoxidation of ascorbic acid than are the free ions. See: Taqui-Khan, M. M.; Martell, A. E. *J. Am. Chem. Soc.* **1967**, *89*, 7104.

(9) A similar mechanism has been proposed for Ru(III)-catalyzed reduction of hydrogen peroxide with ascorbic acid. See: Taqui Khan, M. M.; Shukla, R. S. *J. Mol. Catal.* **1987**, *39*, 139.

(10) Braun, W.; Rabjenbach, L.; Eirich, F. R. *J. Phys. Chem.* **1962**, *66*, 1591.

(11) For a review of the reactions of Cu(I) with organic peroxides, see: Kochi, J. K. *Organometallic Mechanisms and Catalysis*; Academic: New York, 1978; pp 50–79.

(12) Unfortuantely, one-electron redox potentials for the oxidation of ascorbic acid and the reduction of lauroyl peroxide are unavailable. Thus, the energetics of a hypothetical electron transfer between 1 and 2 cannot be directly evaluated.

(13) See Martell, A. E., in ref 3a; pp 153–178.

(14) For a review of the chemistry of the ascorbyl radical, see Bielski, B. H. J., in ref 3a; pp 81–100.

(15) Similar cage efficiencies are known for the combination of carboxyl and alkyl radicals produced by thermolysis of diacyl peroxides. See Hiatt, R. In *Organic Peroxides* Swern, D., Ed.; Wiley-Interscience: New York, 1971; pp 822–828, 847–857.

cage. To satisfy the stoichiometry a cage efficiency of between 20% and 40% must be assumed.[15]

In conclusion, carboxyl radicals are certainly intermediates in both the catalyzed and uncatalyzed reactions of ascorbic acid with lauroyl peroxide. However, many mechanistic details of the uncatalyzed reaction are admittedly open to speculation.[16,17] Current research in these laboratories will shed light on the viability of eq 6–9.

Acknowledgment. This research was supported by the Goodyear Tire & Rubber Company, the donors of Petroleum Research Fund, administered by the American Chemical Society, and the Miami University Faculty Research Committee. We gratefully acknowledge the assistance of Professor Frederick Greene in the preparation of the revised manuscript.

(16) Electron-rich arenes are proposed to induce the decomposition of benzoyl peroxide by a rate-limiting electron transfer: Walling, C.; Zhao, C.; *Tetrahedron* **1982**, *38*, 1105.

(17) The decomposition of benzoyl peroxide with aniline produces free radicals but is believed not to proceed by a rate-limiting electron transfer: Pryor, W. A.; Hendrickson, W. H., Jr. *Tetrahedron Lett.* **1983**, *24*, 1459.

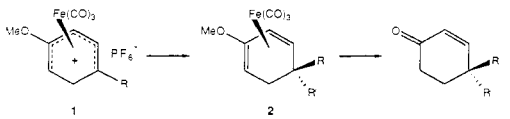
Karen F. Jenkins, Susan A. Hershberger
James W. Hershberger*
Chemistry Department
Miami University
Oxford, Ohio 45056

Richard Marshall
Chemical Research & Development
The Goodyear Tire & Rubber Company
Akron, Ohio 44305-3399
Received March 17, 1988

Construction of Quaternary Carbon Centers Using Organomolybdenum Chemistry. Synthesis of a Trichothecene Intermediate

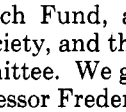
Summary: Dicarbonyl(1,4-dimethyl-1,3-cyclohexadiene)(η^5-indenyl)molybdenum(1+) tetrafluoroborate was shown to react with a variety of carbon nucleophiles, including Grignard reagents and "hard" enolates, to generate (π-allyl)molybdenum complexes containing quaternary carbon centers; this methodology was employed to prepare the lactone **8**, an intermediate for synthesis of trichodermin and trichodiene.

Sir: Development of methods for the construction of quaternary carbon centers remains an active area of research in contemporary organic chemistry, owing to the presence of such subunits in a diverse range of natural products.[1] Previous work in our laboratory was aimed at utilizing the reaction between dienyliron complexes, of general structure **1**, and carbon nucleophiles to generate



(1) For a review on this topic, see: Martin, S. F. *Tetrahedron* **1980**, *36*, 419. For some recent examples, see: Meyers, A. I.; Harre, M.; Garland, R. *J. Am. Chem. Soc.* **1984**, *106*, 1146. Meyers, A. I.; Warner, K. T. *Tetrahedron Lett.* **1985**, *26*, 2047. Meyers, A. I.; Hanreich, R.; Wanner, K. T. *J. Am. Chem. Soc.* **1985**, *107*, 7776.

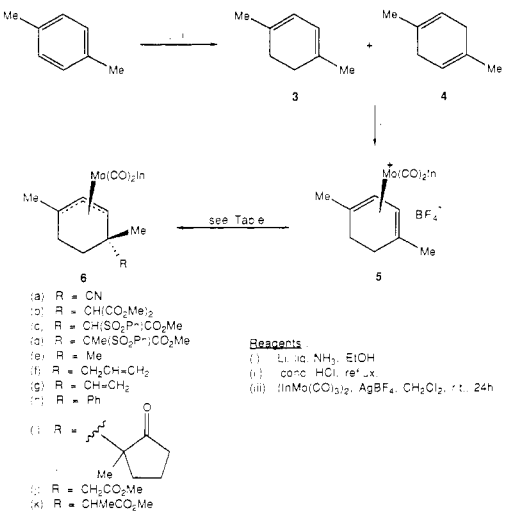
Table I. Reactions of Dicarbonyl(1,4-dimethyl-1,3-cyclohexadiene)(η^5-indenyl)molybdenum(1+) Cation (5) with Carbon Nucleophiles

entry	nucleophile[a]	product	yield, %
1	NaCN	**6a**	85
2	$NaCH(CO_2Me)_2$	**6b**	91
3	$NaCH(SO_2Ph)CO_2Me$	**6c**[b]	87
4	$NaCMe(SO_2Ph)CO_2Me$	**6d**[b]	81
5	MeMgBr	**6e**	92
6	CH_2=$CHCH_2MgBr$	**6f**	90
7	CH_2=CHMgBr	**6g**	37
8	PhMgBr	**6h**	30
9		**6i**[b]	83
10	CH_2=C(OLi)OMe	**6j**	81
11	CHMe=C(OLi)OMe	**6k**[b]	89

[a] All reactions were performed in tetrahydrofuran at −78 °C, except for entry 1, which was run in CH_3CN/H_2O (10:1) at 0 °C. [b] Obtained as an equimolar mixture of diastereomers.

diene complexes **2** which are then converted to 4,4-disubstituted cyclohexenones.[2] However, a number of shortcomings of this methodology, most notably the rather narrow range of carbon nucleophiles that can be used, led us to investigate other organometallic systems which might complement the dienyliron complexes.

The mixture of dienes **3** and **4** (3:1 ratio[3]) was readily converted by Green's method[4a] to the diene–molybdenum complex **5** (52% yield).[5] This reacts with a wide range of carbon nucleophiles to give (π-allyl)$Mo(CO)_2$In (In = η^5-indenyl) complexes of structure **6** (Table I). The



stereochemistry of **6** is assigned on the basis that nucleophile addition to previously prepared, but simpler, cyclohexadiene–molybdenum complexes occurs exclusively trans to the metal.[4b,6] Of direct relevance to the present work is the assignment of exo stereochemistry during nu-

(2) Pearson, A. J. In *Comprehensive Organometallic Chemistry*; Wilkinson, G., Stone, F. G. A., Abel, E. W., Ed.; Pergamon: New York, 1982; Vol. 8, Chapter 58.

(3) Brady, W. T.; Norton, S. J.; Ko, J. *Synthesis* **1985**, 704.

(4) (a) Bottrill, M.; Green, M. *J. Chem. Soc., Dalton Trans.* **1977**, 2365. (b) Green, M.; Greenfield, S.; Kersting, M. *J. Chem. Soc., Chem. Commun.* **1985**, 18.

(5) All new compounds were obtained in racemic form and purified by chromatography and/or recrystallization. Yields are quoted for purified products, which were fully characterized by 200-MHz ^{1}H NMR and IR spectra and gave satisfactory high-resolution mass spectra and/or combustion analyses.

(6) Faller, J. W.; Murray, H. H.; White, D. L.; Chao, K. H. *Organometallics* **1983**, *2*, 400. Pearson, A. J.; Khan, M. N. I.; Clardy, J. C.; Cun-heng, H. *J. Am. Chem. Soc.* **1985**, *107*, 2748.

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