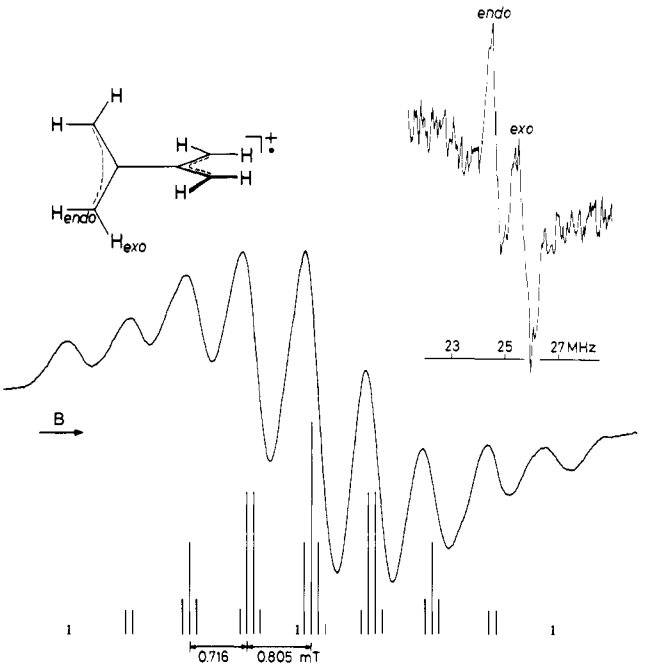

Figure 1. Center: ESR spectrum of $1^{\bullet+}$ in a CF_3CCl_3 matrix at 140 K. Top, right: proton ENDOR signals observed above the free proton frequency under the same conditions. Bottom: stick diagram of the ESR spectrum.

Considering the coupling constant of 1.72 mT for the 12 equivalent β-protons in the radical cation of tetramethylethene[8] and taking into account the $\cos^2\theta$ dependence of such values,[9] a hyperfine splitting as large as 2.5–3.0 mT is expected for the eight β-protons in $4^{\bullet+}$. On the other hand, the observed hyperfine data compare well with the halved coupling constants of the two exo (1.481 mT/2 = 0.741 mT) and the two endo protons (1.390 mT/2 = 0.695 mT) in the allyl radical.[10] This similarity strongly suggests that the ESR and ENDOR spectra in Figure 1 should be ascribed to the radical cation of tetramethyleneethane (**1**) which is a positively charged 2,2'-biallyl. We therefore assign the coupling constant of 0,805 mT to the four equivalent exo protons and that of 0.716 mT to the four likewise equivalent endo protons in $1^{\bullet+}$; both values are undoubtedly negative, The increase in the hyperfine splittings on going from a "neutral double allyl" (average 0.713 mT) to $1^{\bullet+}$ (average 0.761 mT) is in line with the charge dependence of the α-proton coupling constants.[11] It is noteworthy that the difference between the coupling constants of the exo and the endo protons could not be determined for the anion $1^{\bullet-}$ and the neutral $1^{\bullet\bullet}$, as no use was made of the ENDOR technique in those studies.[2,3]

The arguments presented above in favor of $1^{\bullet+}$ are corroborated by INDO calculations.[12] As anticipated, the singly occupied orbital of $1^{\bullet+}$ is a linear combination of two nonbonding allyl MO's, and it thus exhibits squared LCAO coefficients of 0.25 at the four methylene carbon atoms. The calculated coupling constants are −0.793 and −0.735 mT for the four exo and the four endo protons, respectively.

The conversion of the initially formed $4^{\bullet+}$ into $1^{\bullet+}$ implies opening of both cyclopropylidene rings which is likely to occur stepwise. According to recent ab inito calculations,[13] ring opening in the radical cation of methylenecyclopropane is exothermic and requires an activation energy of only 8 kJ/mol. This reaction, which yields the radical cation of trimethylenemethane, is fully analogous to that converting one ring in $4^{\bullet+}$ to an allyl moiety in $1^{\bullet+}$. However, a simultaneous opening of the two rings in $4^{\bullet+}$ cannot be excluded without further experimental and/or theoretical evidence.

In the formulas drawn in this paper and in the INDO calculations of the coupling constants, we have assumed that the two allyl moieties in $1^{\bullet+}$ are rotated by an angle ϕ of 90° about the essential single bond linking them. For the ground-state triplet $1^{\bullet\bullet}$, such a geometry is indicated by the absence of splitting between the x and y components in the ESR spectrum.[2] Moreover, in both INDO and AM1-UHF[14] approximations, a planar radical cation $1^{\bullet+}$ (ϕ = 0°) has higher energy than that with ϕ = 90°. Whereas for ϕ of either 0° or 90° the unpaired electron should be delocalized over both allyl moieties, localization on one moiety is predicted for an intermediate angle ϕ (ca. 45°). In this context, we note that the intensities and shape of some hyperfine components in the ESR spectrum of $1^{\bullet+}$ deviate significantly from those expected for an interaction with two sets of four equivalent protons (c.f. stick diagram in Figure 1). These deviations will be considered in a paper on structurally related radical cations.[15]

Acknowledgment. This work was supported by the Swiss National Science Foundation. We thank Prof. E. Haselbach, Université de Fribourg, for the permission to use his ^{60}Co source of γ-rays.

(8) Shida, T.; Egawa, Y.; Kubodera, H. *J. Chem. Phys.* **1980**, *73*, 5963.
(9) Heller, C.; McConnell, H. M. *J. Chem. Phys.* **1960**, *32*, 1535.
(10) Kochi, J. K.; Krusic, P. J. *J. Am. Chem. Soc.* **1968**, *90*, 7157.
(11) Colpa, J. P.; Bolton, J. R. *Mol. Phys.* **1963**, *6*, 273. See also, e.g.: Gerson, F. *High-Resolution ESR Spectroscopy*; Wiley: New York, and Verlag-Chemie: Weinheim, FRG, 1970; Chapter 2.1.
(12) Pople, J. A.; Beveridge, D. L. *Approximate Molecular Orbital Theory*; McGraw-Hill: New York, 1970. A factor of 54 mT was used to convert hydrogen 1s spin populations into proton-coupling constants.
(13) Du, P.; Borden, W. T. *J. Am. Chem. Soc.* **1987**, *108*, 5330.
(14) Dewar, M. J. S.; Zoebisch, E. G.; Healy, E. F.; Stewart, J. J. P. *J. Am. Chem. Soc.* **1985**, *107*, 3902.
(15) Gerson, F.; de Meijere, A.; Qin, X.-Z., manuscript in preparation.

p-Quinone Methide Initiated Cyclization Reactions

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Quinone methides are believed to play an important role in biosynthesis[1] and in the biological activity of many quinonoid antitumor compounds.[2,3] In spite of the major role these compounds are proposed to play in nature, the synthetic applications of quinone methides have been limited primarily to the use of in situ generated *o*-quinone methides as heterodienes in Diels–Alder reactions.[4,5] The use of *p*-quinone methides as synthetic inter-

(1) For leading references on quinone methides as intermediates in biosynthesis, see: (a) Gottlieb, O. R. *Fortsch. Chem. Org. Naturst.* **1978**, *35*, 1. (b) Erdtman, H. *Recent Advances in Phytochemistry, Vol. 1*; 1968. (c) Omura, S.; Tanaka, H.; Okada, Y.; Marumo, H. *J. Chem. Soc. Chem. Commun.* **1976**, 320. (d) St. Pyrek, J.; Achmatowicz, O., Jr.; Zamojski, A. *Tetrahedron* **1977**, *33*, 673. (e) Scott, A. I. *Quarterly Rev.* **1965**, 1.
(2) For leading references on quinone methides as the bioactive forms of various anti-tumor compounds, see: (a) Lin, A. J.; Sartorelli, A. C. *J. Med. Chem.* **1976**, *19*, 1336. (b) Lown, J. W. *Acc. Chem. Res.* **1982**, *15*, 381. (c) Boldt, M.; Gaudiano, G.; Haddadin, M. J.; Koch, T. H. *J. Am. Chem Soc.* **1988**, *110*, 3330.
(3) (a) Moore, H. W. *Science* **1977**, *197*, 527. (b) Moore, H. W.; Czerniak, R. *Med. Res. Rev.* **1981**, *1*, 249.
(4) For leading references, see: (a) Chapman, O. L.; Engel, M. R.; Springer, J. P.; Clardy, J. C. *J. Am. Chem. Soc.* **1971**, *93*, 6696. (b) Shelly, G. C. Ph.D. Dissertation, University of California, Los Angeles, CA, 1979. (c) Marino, J. P.; Dax, S. L. *J. Org. Chem.* **1984**, *49*, 3671.
(5) For reviews on the chemistry and preparation of quinone methides, see: (a) Turner, A. B. *Quart. Rev.* **1965**, *18*, 347. (b) Wagner, H.-U.; Gompper, R. Quinone Methides. In *The Chemistry of the Quinonoid Compounds*; Patai, S. Ed.; John Wiley and Sons: New York, 1974; pp 1145–1178. (c) Gruenanger, P. In *Houben-Weyl Methoden der Organischen Chemie*; Mueller, E., Bayer, O., Eds.; G. Thieme Verlag: Stuttgard, 1979; Vol. VII/3b, p 395.

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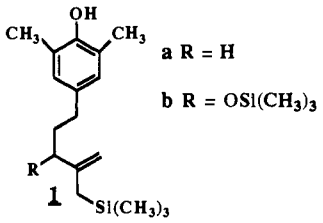
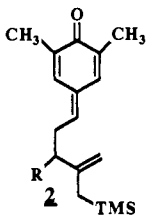
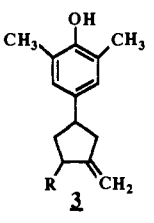
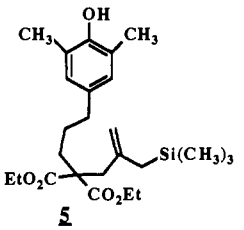
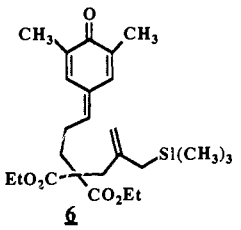
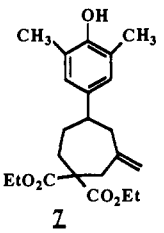
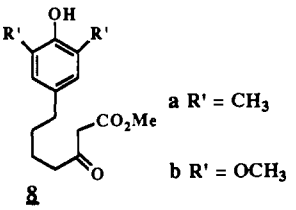
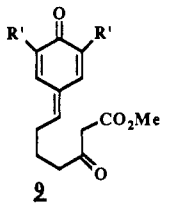
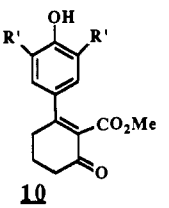
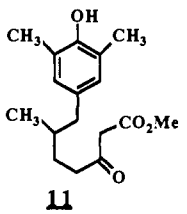
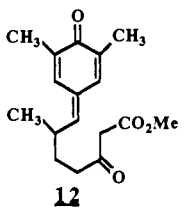
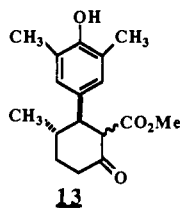
Table I. *p*-Quinone Methide Initiated Cyclization Reactions

entry	phenol	quinone methide[a]	product(s)[11]	yield,[b] %
1	 **a** R = H; **b** R = $OSi(CH_3)_3$			83[c]
2				82[d] (5:1)
3				98[c]
4	 **a** R' = CH_3; **b** R' = OCH_3			76
5				78
6				73[e]

[a] Oxidations were run in CH_2Cl_2 or $CDCl_3$ at 25 °C using the procedure of Dyall and Winstein (ref 8). Quinone methides 2, **6**, and **9b** were treated with $ZnCl_2$ to induce cyclization. [b] Yields refer to isolated material spectroscopically and chromatographically homogeneous unless otherwise noted. Numbers in parentheses indicate ratio of diastereomers determined by 300 MHz ^1H NMR and GC. [c] The crude product was treated with 1 equiv of n-Bu_4NF in THF (20 min, 25 °C). [d] Yield refers to chromatographed material >90% pure by ^1H NMR analysis. Phenol **3b** is unstable and decomposes upon purification; preparative TLC afforded a 37% yield of material >99% pure by capillary GC analysis. [e] The crude product was treated with 2.3 equiv of $ZnCl_2$ ($CDCl_3$, 25 °C) to equilibrate to a 1.8:1 ratio of α and β epimers of *13*.

mediates has been largely overlooked due to their purported instability.[5] Several groups have proposed *p*-quinone methides as transient intermediates,[6] but there are only a few examples where a reactive quinone methide has been unambiguously characterized.[7,8]

This communication describes the initial results of our program to better define the chemistry of quinone methides and exploit them as intermediates in synthesis. We have found *p*-quinone methides to be viable, well behaved, cyclization initiators. 2,6-Disubstitution imparts considerable stability to quinone methides and allows their observation by NMR.[8] Thus, all systems studied incorporate this substitution pattern, and the quinone methides were characterized by ^1H NMR spectroscopy. The results of our study can be used to make definitive conclusions about their reactivity and synthetic potential.

A quinone methide initiated cyclization requires an internal nucleophile (cyclization terminator) that is stable under the conditions used to generate the quinone methide and yet reactive enough to attack the carbon terminus. With this in mind, we have initially explored allyl silanes and β-keto esters as cyclization terminators.

Oxidation of readily available phenol **1a**[9] (Ag_2O, 10 equiv) afforded quinone methide **2a** as the sole product (Table I). The 300 MHz ^1H NMR spectrum of **2a** showed the new exocyclic alkene hydrogen as the expected triplet (J = 8 Hz) at δ 6.31 and the two cyclohexadiene hydrogens as singlets at δ 7.32 and δ 6.90.[11] Surprisingly, quinone methide **2a** proved to be quite stable, showing no sign of decomposition (^1H NMR analysis) upon storage (neat, −5 °C) for 3 days. Quinone methide **2a** was also characterized by IR and ^{13}C NMR.[11] Treatment of **2a** with $ZnCl_2$ (1.2 equiv, $CDCl_3$) followed by cleavage of the silyl ether [0.8 equiv (nBu)$_4$NF, THF/$CDCl_3$, 25 °C, 5 min] afforded methylenecyclopentane **3a** in 83% yield (see Table I).[11] Styrene **4**, a likely decomposition product, could not be detected in the 300 MHz ^1H NMR spectrum of crude **3a**.

Table I shows several examples of quinone methide initiated cyclization reactions for the formation of five-, six-, and seven-

(6) Cf.: (a) Poss, A. J.; Belter, R. K. *Tetrahedron Lett.* **1987**, *28*, 2555. (b) Kende, A. S.; Liebeskind, L. S.; Mills, J. E.; Rutledge, P. S.; Curran, D. P. *J. Am. Chem. Soc.* **1977**, *99*, 7082.

(7) This obviously excludes cases where the quinone methide derives stability from extensive substitution on the exocyclic methylene group and ortho to the carbonyl (e.g., 2,6-di-*tert*-butyl). For the direct observation of reactive *p*-quinone methides, see: (a) Zanarotti, A. *J. Org. Chem.* **1985**, *50*, 941. (b) Zanarotti, A. *Tetrahedron Lett.* **1982**, *23*, 3815.

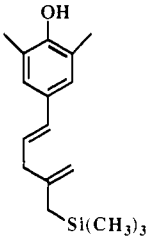
(8) Dyall, L. K.; Winstein, S. *J. Am. Chem. Soc.* **1972**, *94*, 2196.

(9) Prepared from readily available 2,6-dimethyl-4-(2-propenyl)phenol (Tarbell, D. S.; Kincaid, J. F. *J. Am. Chem. Soc.* **1940**, *62*, 728) in four steps, 55% yield: (i) BH_3·THF; H_2O_2, NaOH; (ii) PPh_3, CBr_4, Et_2O; (iii) cuprate derived from 2-lithio-2-(trimethylsilyl)-2-propene[10a] and lithium 2-thienylcyanocuprate,[10b] (1.5 equiv), THF, 40 °C, 36 h; (iv) 2 N NaOH, EtOH.

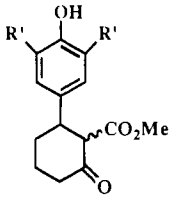
(10) (a) Trost, B. M.; Chan, D. M. T. *J. Am. Chem. Soc.* **1982**, *104*, 3733. (b) Lipshutz, B. H.; Koerner, M.; Parker, D. A. *Tetrahedron Lett.* **1987**, *28*, 945.

(11) All new compounds showed satisfactory 300 MHz ^1H NMR, ^{13}C NMR, IR, low resolution, and HRMS or elemental analysis. See Supplementary Material for details.

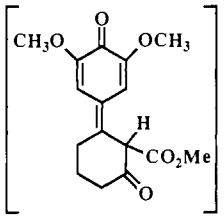
membered ring carbocycles. Entry 2 shows the tolerance of the cyclization to a protected alcohol (trimethylsilyl) adjacent to the allyl silane. Entries 4-6 show β-keto esters to be excellent cyclization terminators. In entries 4 and 5, the initially formed quinone methide **9** affords cyclohexenone **10**. Formation of **10** must occur via the oxidation of the initially formed product **14** to quinone methide **15** followed by loss of the acidic hydrogen, flanked by both a ketone and an ester, In support of this notion, cyclohexanone **14b** (1:1 mixture of diastereomers by ^{1}H NMR) was isolated, characterized,[11] and resubmitted to the oxidation conditions to afford **10b**. Entry 5 in Table I shows that even with two oxygen substituents a quinone methide is still an excellent cyclization initiator.[12]



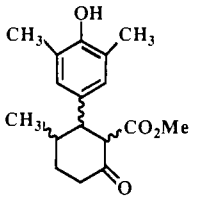
4



14a R' = CH_3
14b R' = OCH_3



15



16

Entry 6 shows that in the presence of a Lewis acid ($ZnCl_2$) the addition of a β-keto ester to a quinone methide is clearly reversible. The initial cyclization of **12** gives **16** as a mixture of three diastereomers (1:1:1 ratio in $CDCl_3$ by ^{1}H NMR spectroscopic analysis). Treating this mixture with $ZnCl_2$ (2.3 equiv, $CDCl_3$, 25 °C, 42 h) afforded cyclohexanone **13** as a 1.8:1 mixture of two diastereomers. This "epimerization", which undoubtedly occurs via a reversible addition of the β-keto ester to quinone methide **12**, allows *complete* control of the relative stereochemistry between the methyl and aryl substituents on the cyclohexanone. The 300 MHz ^{1}H NMR spectrum of the major α epimer of **13** shows the benzylic hydrogen as a triplet (δ 2.81, J = 12 Hz) indicative of the assigned stereochemistry.[11]

In conclusion, our work demonstrates the viability of quinone methide initiated cyclization reactions as a potentially general synthetic method, We are currently exploring the application of this methodology to the synthesis of natural products as well as investigating systems employing other terminators and highly reactive *o*- and *p*-quinone methides.[13]

Acknowledgment. This study was supported by grants from the UCR Committee on Research and National Institutes of Health (GM 39354). We thank Professors Tom Morton and Mark Midland for helpful comments on the manuscript,

Supplementary Material Available: A scheme showing the preparation of cyclization substrates and general experimental procedures for the preparation of **3**, **7**, **10**, and **13** along with full spectral data for all new compounds in Table I (8 pages). Ordering information is given on any current masthead page.

(12) The formation of **9b** could be observed by ^{1}H NMR spectroscopy; however, we were unable to get a pure sample for characterization as **9b** forms **10b** upon standing in solution.

(13) Preliminary experiments show a furan to be an efficient cyclization terminator: Angle, S. R.; Yang, W.-J., unpublished results.

Electron Spin Resonance Studies of Monoamine Oxidase B. First Direct Evidence for a Substrate Radical Intermediate

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Mitochondrial monoamine oxidase (MAO; E.C.1.4.3.4) is a flavoenzyme that has been known for 60 years to catalyze the oxidation of biogenic amines.[1] On the basis of the mechanism for chemical,[2] electrochemical,[3] and photochemical[4] amine oxidation, Silverman and co-workers[5] and Krantz and co-workers[6] proposed that MAO catalyzes amine oxidation by a single electron-transfer mechanism (Scheme I). Indirect evidence for radical intermediates has been obtained by Silverman and co-workers with the use of the *N*-cyclopropyl analogues, *N*-cyclopropylbenzylamine,[7] *N*-(1-methylcyclopropyl)benzylamine,[8] *N*-cyclopropyl-α-methylbenzylamine,[9] *trans*-2-phenylcyclopropylamine,[10] 1-phenylcyclopropylamine,[11] and 1-benzylcyclopropylamine.[12] All of these compounds are mechanism-based inactivators[13] of MAO and lead to the ring-opened adducts expected from cyclopropylaminyl radical intermediates,[14] 1-Phenylcyclobutylamine is metabolized by MAO to 2-phenyl-1-pyrroline,[15] the expected product of the amine radical cation-induced homolytic cleavage of the cyclobutyl ring, intramolecular radical capture by the incipient carbon-nitrogen double bond, and second-electron transfer.[16] All of these chemical probes for a radical intermediate support the single electron-transfer mechanism (Scheme I). Despite this strong indirect evidence, Tan et al.[17] found no ESR spectral support for radical intermediates in the MAO-catalyzed oxidation of benzylamine, even in the presence of spin traps. This inability to observe a radical intermediate may be based on kinetic or thermodynamic grounds. The oxidation of benzylamine may be so efficient that radical intermediates are processed rapidly

* Correspondence should be addressed to this author at the Department of Chemistry.

(1) Hare, M. L. C. *Biochem. J.* **1928**, *22*, 968-979.
(2) (a) Lindsay Smith, J. R.; Mead, L. A. V. *J. Chem. Soc., Perkin Trans. 2* **1973**, 206-210. (b) Smith, P. A. S.; Loeppky, R. N. *J. Am. Chem. Soc.* **1967**, *89*, 1147-1157.
(3) Mann, C. K.; Barnes, K. K. *Electrochemical Reactions in Nonaqueous Systems*; Marcel Dekker: New York, 1970; Chapter 9.
(4) (a) Cohen, S. G.; Parola, A.; Parsons, G. H. *Chem. Rev.* **1973**, *73*, 141-161. (b) Lewis, F. D.; Ho, T. *J. Am. Chem. Soc.* **1980**, *102*, 1751-1752.
(5) Silverman, R. B.; Hoffman, S. J.; Catus III, W. B. *J. Am. Chem. Soc.* **1980**, *102*, 7126-7128.
(6) (a) Krantz, A.; Kokel, B.; Sachdeva, Y. P.; Salach, J.; Detmer, K.; Claesson, A.; Sahlberg, C. In *Monoamine Oxidase: Structure, Function and Altered Functions*; Singer, T. P., Von Korff, R. W., Murphy, D. L., Eds.; Academic Press: New York, 1979; pp 51-70. (b) Simpson, J. T.; Krantz, A.; Lewis, F. D.; Kokel, B. *J. Am. Chem. Soc.* **1982**, *104*, 7155-7161.
(7) (a) Vazquez, M. L.; Silverman, R. B. *Biochemistry* **1985**, *24*, 6538-6543. (b) Yamasaki, R. B.; Silverman, R. B. *Biochemistry* **1985**, *24*, 6543-6550.
(8) (a) Silverman, R. B.; Yamasaki, R. B. *Biochemistry* **1984**, *23*, 1322-1332. (b) Silverman, R. B.; Hoffman, S. J. *Biochem. Biophys. Res. Commun.* **1981**, *101*, 1396-1401.
(9) Silverman, R. B. *Biochemistry* **1984**, *23*, 5206-5213.
(10) Silverman, R. B. *J. Biol. Chem.* **1983**, *258*, 14766-14769.
(11) (a) Silverman, R. B.; Zieske, P. A. *Biochemistry* **1985**, *24*, 2128-2138. (b) Silverman, R. B.; Zieske, P. A. *Biochem. Biophys. Res. Commun.* **1986**, *135*, 154-159.
(12) Silverman, R. B.; Zieske, P. A. *J. Med. Chem.* **1985**, *28*, 1953-1957.
(13) Silverman, R. B. *Mechanism-Based Enzyme Inactivation: Chemistry and Enzymology*; CRC Press: Boca Raton, FL, 1988; Vol. I and II.
(14) Maeda, Y.; Ingold, K. U. *J. Am. Chem. Soc.* **1980**, *102*, 328-331.
(15) Silverman, R. B.; Zieske, P. A. *Biochemistry* **1986**, *25*, 341-346.
(16) (a) Wilt, J. W.; Maravetz, L. L.; Zawadzki, J. F. *J. Org. Chem.* **1966**, *31*, 3018-3025. (b) Tanner, D. D.; Rahimi, R. M. *J. Org. Chem.* **1979**, *44*, 1674-1677.
(17) Tan, A.; Glantz, M. D.; Piette, L. H.; Yasunobu, K. T. *Biochem. Biophys. Res. Commun.* **1983**, *117*, 517-523.

0002-7863/89/1511-1138$01.50/0