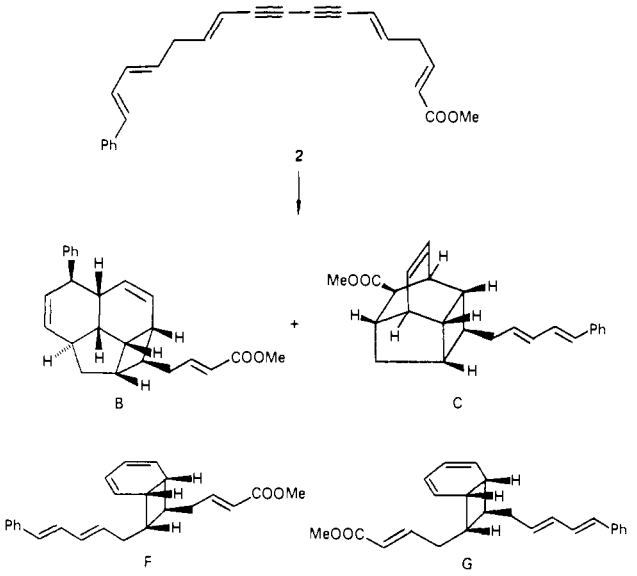
Scheme II. One-Step Generation of Endiandric Acids B, C, F, and G Methyl Esters from Acetylenic Precursor 2



spectrum at 250 MHz. The results were quite interesting and revealing and are graphically depicted in Figure 1. Thus, when endiandric acid E methyl ester (E) was maintained at 70 °C (toluene-d_8, NMR tube), it was observed to undergo (a) reversible isomerization to endiandric acid D methyl ester (D)[7] and (b) intramolecular $\pi 4s + \pi 2s$ cycloaddition (intramolecular Diels–Alder reaction) to endiandric acid A methyl ester (A)[7] with a half-life of disappearance $t_{1/2}$(70 °C) ca. 1.3 h (Figure 1a). Eventually, all the material was totally consumed, and endiandric acid A methyl ester (A) was formed in high yield. Endiandric acid D methyl ester (D) was observed (Figure 1b) under the same conditions and found to undergo a reversible isomerization to endiandric acid E methyl ester (E)[7] followed by an irreversible entry into the endiandric acid A skeleton (A)[7] by an intramolecular $\pi 4s + \pi 2s$ cycloaddition. Thus, endiandric acid D methyl ester (D) is converted to endiandric acid A methyl ester (A) in high yield with a half-life of disappearance $t_{1/2}$(70 °C) ca. 3.8 h. This observation explains the absence of endiandric acid D methyl ester in the hydrogenation–thermolysis experiment initiated with **1** (vide supra, Scheme I). The thermally induced chemical fates of endiandric acid F and G methyl esters (F) and (G) were monitored in a similar fashion (Figure 1c,d) and found to involve reversible equilibration of F[7] and G[7] and final conversion to both endiandric acids B[7] and C[7] methyl esters. Compound D disappeared with a half-life $t_{1/2}$(70 °C) ca. 1.7 h and produced endiandric acids B and C methyl esters (B and C) in a ratio of ca. 4.5:1, whereas compound F was consumed with a half-life $t_{1/2}$(70 °C) ca. 3.6 h and produced endiandric acid B and C methyl esters (B and C) in a ratio of ca. 3.7:1 in high yield (in both cases). The observed isomerizations E $\rightleftharpoons$ D and F $\rightleftharpoons$ G obviously proceed by a thermally allowed opening of the bicyclo[4.2.0] system to a cyclooctatriene systems, which after undergoing rapid conformational scrambling, reclose to a mixture of the bicyclo[4.2.0] compounds (see Scheme I, paper 3 in this series[1]). Extrapolation of these results to ambient temperatures makes it clear that these phenomena could take place in a natural environment, although at slower rates, and indeed such observations have been made on samples left standing at 25 °C for prolonged periods of time in these laboratories.

In conclusion, we have demonstrated in this series of papers the powerful nature of thermally allowed by the Woodward–Hoffmann rules $8\pi e$ and $6\pi e$ electrocyclizations in the stereospecific construction of polycyclic and complex systems. Our studies culminated in total syntheses of all endiandric acids A–G by both a stepwise stereocontrolled fashion and by a one-operation "biomimetic" approach from open-chain achiral precursors. Furthermore, these investigations provided an experimental test and final verification of Black's hypothesis postulating a possible nonenzymatic genesis of endiandric acids in nature from polyunsaturated achiral substrates.[8] It can also be deduced that endiandric acids E–G, which have not as yet been found in nature, should be stable enough for isolation from *Endiandra introrsa* (*Lauraceae*), particularly with the availability of synthetic samples. Questions still under investigation in this area concern whether these series of compounds originate from precursors with the E,Z,Z,E conjugated tetraene systems I and III or the Z,Z,Z,Z systems II and IV (Scheme I, paper 3 in this series[1]) or both, and the possible physiological role of endiandric acids in nature. Finally, the methodology described here should find numerous and novel applications in the construction of other polycyclic frameworks including both natural and unnatural products.

Acknowledgment. We express our many thanks to Professor D. St. C. Black, Monash University, Australia, for samples of the natural endiandric acids, spectral data, and many other helpful communications and exchanges. We also thank John Partridge of Hoffmann-LaRoche, Nutley, NJ, for the generous gifts of superior Lindlar catalyst. Our thanks are also due to Drs. George T. Furst, Mike Mitchell, and Tom Terwilliger of this department for their superb spectroscopic assistance and helpful discussions. Finally, we acknowledge generous financial support of our programs by Merck Sharp & Dohme, the A. P. Solan Foundation, and the Camille and Henry Dreyfus Foundation.

Registry No. 1, isomer 1, 82706-76-1; **2**, isomer 1, 82706-77-2; A, 74635-24-8; B, 82730-19-6; C, 81757-51-9; D, 82706-78-3; E, 82768-65-8; F, 82706-79-4; G, 82768-66-9; **1**, isomer 2, 82768-67-0; **2**, isomer 2, 82768-68-1.

(7) All compounds detected in these experiments were isolated chromatographically and characterized spectroscopically by comparisons with authentic samples.[4-6]

(8) These results taken together with the racemic nature of the natural endiandric acids strongly point to a nonenzymatic pathway to these compounds from the postulated achiral precursors although the participation of enzymes cannot be rigorously excluded at this point. Similar thermal changes were observed within the endiandric acid cascade utilizing free carboxylic acids in this series of compounds. It is possible that some of these changes may be somewhat solvent dependent, although such studies have not been done yet.

Extremely Facile Reaction between the Ultimate Carcinogen Benzo[*a*]pyrene-7,8-diol 9,10-Epoxide and Ellagic Acid

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Received June 1, 1982

Intensive efforts by several laboratories have led to tumor studies that have identified (+)-7β,8α-dihydroxy-9α-10α-epoxy-7,8,9,10-tetrahydrobenzo[*a*]pyrene as an ultimate carcinogenic metabolite of benzo[*a*]pyrene.[1] In accord with predictions of the bay region theory,[2] related diol epoxides either have been shown

† National Institutes of Health.
§ Hoffmann-La Roche Inc.

(1) Review: Levin, W.; Wood, A. W.; Wislocki, P. G.; Chang, R. L.; Kapitulnik, J.; Mah, H. D.; Yagi, H.; Jerina, D. M.; Conney, A. H. In "Polycyclic Hydrocarbons and Cancer: Environment, Chemistry, and Metabolism"; Gelboin, H. V., Ts'o, P. O. P., Eds.; Academic Press: New York, 1978; Vol. 1, pp 189–202.

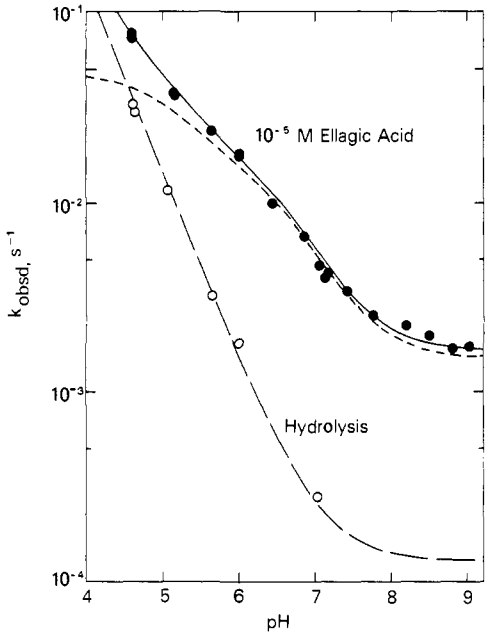
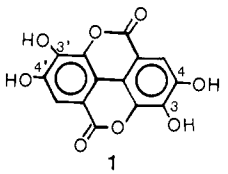


Figure 1. Dependence on pH of the observed pseudo-first-order rate constants for disappearance of 3.3×10^{-6} M **2** in the presence (●) and absence (○) of 10^{-5} M ellagic acid in 1:9 dioxane–water containing 2×10^{-3} M tris or acetate buffers, ionic strength 0.1 M ($NaClO_4$), 25 °C. The following rate and equilibrium constants were observed: pK_1 (5.07), pK_2 (6.55), k_1 (4.8×10^3 M^{-1} s^{-1}), k_2 (1.6×10^3 M^{-1} s^{-1}), k_3 (150 M^{-1} s^{-1}). The lower broken line (– – –) is based on values of k_{H^+} (1.4×10^3 M^{-1} s^{-1}) and k_0 (1.3×10^{-4} s^{-1}) for hydrolysis (ref 9). The solid line is a theoretical curve based on eq 1. The dashed line (- - -) represents the portion of the observed reaction that is due to ellagic acid. The pK values were determined by spectrophotometric titration in 1:9 dioxane–water containing 0.01 M buffers (μ 0.1) at 253 (pK_1) or 262 nm (pK_2).

to be or have been implicated as ultimate carcinogens from several other hydrocarbons.[3] Recently we have sought to identify compounds capable of blocking the biological activity of bay region diol epoxides by taking advantage of the susceptibility of epoxides to reaction with nucleophiles or of their high sensitivity to general-acid-catalyzed hydrolysis[4] to inactive tetraols. In addition to reactivity as a nucleophile and/or a general acid, the inactivating agent should have a high affinity for the diol epoxides through π–π interactions. Such affinity should ideally be greater in the transition state than the ground state. The naturally occurring plant phenol ellagic acid[5,6] (**1**) has exceptionally high activity in



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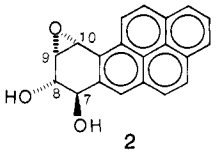


2

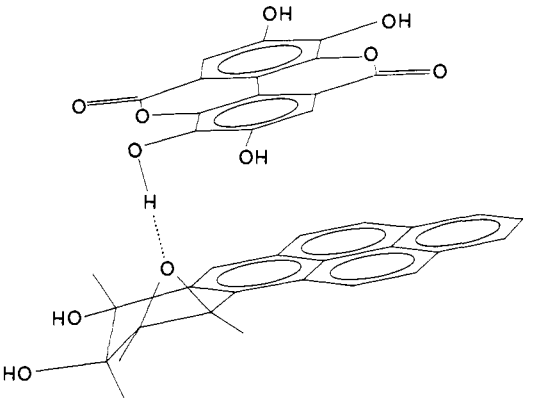


Figure 2. Computer-generated molecular models showing a possible orientation of **1** and **2** as they approach the transition state for epoxide ring opening. The planes of the ring systems are approximately parallel with a separation of ~3.5 Å. A linear hydrogen bond between the epoxide oxygen and the 3-hydroxyl group of **1** is shown with an O···O separation of 2.7 Å. This hydrogen bond makes an angle of 50° with the plane of the epoxide ring. The distance between C_{10} of **2** and the 4-hydroxyl of **1**, which will eventually attack at this position, is 3.7 Å. We thank Dr. Dennis P. Michaud for programming assistance in the construction of this model.

inhibiting mutagenesis by (±)-7β,8α-dihydroxy-9α,10α-epoxy-7,8,9,10-tetrahydrobenzo[a]pyrene (**2**).[7] In this communication we describe the extremely rapid reaction of **1** with **2** to form an adduct. The kinetics of the reaction indicate that this adduct must also be capable of further rapid reaction with the diol epoxide.

The disappearance of **2** from aqueous solution (1:9 dioxane: water, 0.1 M in $NaClO_4$, 25 °C), measured by a decrease in the absorbance of **2** at 346 nm, is markedly accelerated by low concentrations of ellagic acid (**1**) at pH 4.5–9.0 (Figure 1). At pH 7.5 the kinetics of this reaction are cleanly pseudo first order for >3 half-lives in the presence of an equimolar ratio of **1** to **2** (1.4×10^{-5} M).[8] Under these conditions, the major products of the reaction are adducts formed by nucleophilic addition of **1** to **2** (see below). The observation of pseudo-first-order kinetics, even though **1** is largely converted to adducts during the reaction, suggests that the adduct(s) must accelerate the disappearance of **2** at a rate similar to that caused by **1**. The observed pseudo-first-order rate constants, k_{obsd}, are linearly dependent on the concentration of **1** up to 2.5×10^{-4} M at pH 8.4 and up to 3.5×10^{-5} M (the highest concentration used) at pH 7.0. The pH dependence of k_{obsd} is described by the rate law of eq 1. In this

$$k_{obsd} = k_0 + k_{H^+}a_{H^+} + \frac{k_1a_{H^+}^2 + k_2K_1a_{H^+} + k_3K_1K_2}{a_{H^+}^2 + K_1a_{H^+} + K_1K_2}[\mathbf{1}] \quad (1)$$

equation, k_0 and k_{H^+} are rate constants for the hydrolysis[9] of **2** in the absence of **1** (Figure 1), K_1 and K_2 are the first and second ionization constants of **1**, and k_1, k_2, and k_3 are rate constants for the reaction of the fully protonated, monoanionic, and dianionic species of **1**, respectively.

Products of this reaction under kinetic conditions were determined by HPLC after ~6 half-lives of reaction. Results of product analyses at several pH values are given in the Supplementary Material. At pH 6.5–8.6, where >90% of the observed reaction of **2** in the presence of 10^{-5} M **1** proceeds by the ellagic acid dependent mechanism, only 15–27% of the products are accounted for by the cis and trans tetraols[10] derived from **2**. The

(2) Jerina, D. M.; Daly, J. W. In "Drug Metabolism from Microbe to Man"; Parke, D. V., Smith, R. L., Eds.; Taylor and Francis: London, 1976; pp 13–32. Jerina, D. M.; Lehr, R. E.; Yagi, H.; Hernandez, O.; Dansette, P. M.; Wislocki, P. G.; Wood, A. W.; Chang, R. L.; Levin, W.; Conney, A. H. In "In Vitro Metabolic Activation in Mutagenesis Testing"; de Serres, F. J., Fouts, J. R., Bend, J. R., Philpot, R. M., Eds.; Elsevier-North Holland Biomedical Press: Amsterdam, 1976; pp 159–177.

(3) Review: Nordqvist, M.; Thakker, D. R.; Yagi, H.; Lehr, R. E.; Wood, A. W.; Levin, W.; Conney, A. H.; Jerina, D. M. In "Molecular Basis of Environmental Toxicity"; Bhatnagar, R. S., Ed.; Ann Arbor Science Publishers: Ann Arbor, MI, 1980; pp 329–357.

(4) (a) Whalen, D. L.; Ross, A. M.; Montemarano, J. A.; Thakker, D. R.; Yagi, H.; Jerina, D. M. *J. Am. Chem. Soc.* **1979**, *101*, 5086–5088. (b) Rogers, D. Z.; Bruice, T. C. *Ibid.* **1979**, *101*, 4713–4719. Becker, A. R.; Janusz, J. M.; Bruice, T. C. *Ibid.* **1979**, *101*, 5679–5687. (c) Sayer, J. M.; Yagi, H.; Croisy-Delcey, M.; Jerina, D. M. *Ibid.* **1981**, *103*, 4970–4972. (d) Gupta, S. C.; Pohl, T. M.; Friedman, S. L.; Whalen, D. L.; Yagi, H.; Jerina, D. M. *Ibid.* **1982**, *104*, 3101–3104.

(5) Systematic name: 2,3,7,8-tetrahydroxy[1]benzopyrano[5,4,3-*cde*]-[1]benzopyran-5,10-dione.

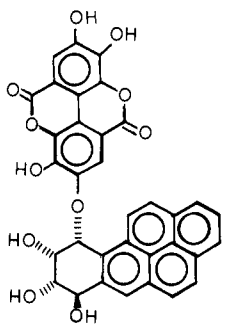
(6) Haslam, E. *Recent Adv. Phytochem.* **1979**, *12*, 475–523.

(7) Wood, A. W.; Huang, M.-T.; Chang, R. L.; Newmark, H. L.; Lehr, R. E.; Yagi, H.; Sayer, J. M.; Jerina, D. M.; Conney, A. H. *Proc. Natl. Acad. Sci. U.S.A.* **1982**, *79*, 5513–5517.

(8) In the presence of 5×10^{-6} M **1** and a 10-fold molar excess of **2**, the pseudo-first-order kinetic plot is linear for ~40% of the total absorbance change, with a rate constant that is consistent with rate constants measured in the presence of excess **1**.

(9) Whalen, D. L.; Montemarano, J. A.; Thakker, D. R.; Yagi, H.; Jerina, D. M. *J. Am. Chem. Soc.* **1977**, *99*, 5522–5524.

predominant products are a mixture of the cis and trans adducts **3** and **4**.[11] The yield of adducts decreases slightly with decreasing



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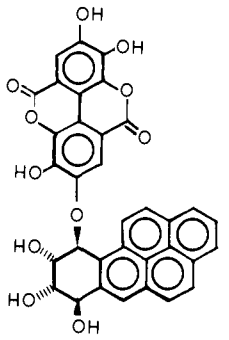

4

pH, possibly because of their partial hydrolysis during the course of reaction at the lower pH values.

Early attempts to characterize these products were complicated by the tendency of the initial product, the unstable cis-adduct **3**, to undergo hydrolysis to tetraols and reaction with excess **1** to yield the more stable trans-adduct **4**. In the absence of added **1**, a mixture of **3** and **4**, consisting predominantly of **3**, was ~50% hydrolyzed to tetraols and **1** after 6 h (pH 7.0, room temperature). In the presence of 10^{-5} M **1**, pH 7.25, the same mixture was converted largely to tetraols and additional trans-adduct **4** after ~7 h. Higher concentrations of **1** accelerated the disappearance of **3** and enhanced formation of **4** relative to tetraols.

To determine the position of substitution on the ellagic acid molecule, we treated adducts **3** and **4** with diazomethane and hydrolyzed the resultant methyl ethers to give trimethyl ethers of ellagic acid. Chromatographic and UV comparison of these esters with synthetic 3,4,4′- and 3,3′,4-tri-*O*-methylellagic acids[12] established that the 3,3′,4-tri-*O*-methyl derivative was produced from both adducts. Hence, the position of substitution is on the 4-hydroxyl of ellagic acid. Adducts involving the 3-position of **1** were not observed.

A change in dioxane concentration from 0.3% to 10% decelerates the reaction of **1** with **2** 12-fold at pH 7.45. This is consistent with an increase in charge separation in the transition state that would be expected for general acid catalysis.[4,13] of epoxide ring opening by a phenolic moiety. Although phenol accelerates the disappearance of **2**,[4a] the second-order rate constant for the reaction of the dianion of **1** (μ 0.1) is >3000 times the analogous rate constant for phenol (μ 0.2). The monoanion and neutral species of **1** are even more reactive and are comparable to hydronium ion. This extraordinary reactivity probably results from specific interactions between the aromatic ring systems[14] of **1** and **2**, although preequilibrium complexation between **1** and **2** in the ground state could not be demonstrated at experimentally practicable concentrations of **1**. In the transition state, a hypothetical complex (Figure 2) having the ellagic acid moiety directly above the aromatic rings of the diol epoxide and on the same side of the molecule as the epoxide oxygen is ideally arranged both for proton transfer to the epoxide oxygen and for cis attack on C_{10} of the benzo[*a*]pyrene moiety.

Ellagic acid is 10 times more potent as an inhibitor of mutagenesis induced by **2** than is riboflavin 5′-phosphate (FMN).[7] Correspondingly, ellagic acid is more effective in bringing about the chemical cleavage of the epoxide ring in **2** than is FMN, which is an extraordinarily effective catalyst for the hydrolysis of **2** to tetraols.[15] The second-order rate constants for the reaction of **2** with the fully protonated and monoanionic forms of **1** are 8–20-fold larger than the corresponding rate constant (204 M^{-1} s^{-1}) for the reaction of **2** with low concentrations of the catalytically active monoanion of FMN. Furthermore, the dianion of FMN is catalytically ineffective, whereas the dianion of **1** still retains two ionizable hydrogens and exhibits a high level of reactivity up to pH 9. Studies are in progess to determine whether ellagic acid can inhibit the tumorigenic activity of **2** in experimental animals.

Registry No. **1**, 58917-67-2; **2**, 476-66-4; **3**, 82933-08-2; **3-AC**, 82933-09-3; **4**, 82977-31-9; **4-Ac**, 82977-32-0.

Supplementary Material Available: Details of the product analyses and the separation and identification of the methylated and acetylated derivatives of **3** and **4** (4 pages). Ordering information is given on any current masthead page.

(10) (a) Yagi, H.; Thakker, D. R.; Hernandez, O.; Koreeda, M.; Jerina, D. M. *J. Am. Chem. Soc.* **1977**, *99*, 1604–1611. (b) Thakker, D. R.; Yagi, H.; Lu, A. Y. H.; Levin, W.; Conney, A. H.; Jerina, D. M. *Proc. Natl. Acad. Sci. U.S.A.* **1976**, *73*, 3381–3385.

(11) Adducts **3** and **4** were purified as their acetates, **3**-Ac and **4**-Ac, and the stereochemistry of these compounds was determined from their NMR spectra. The 100-MHz NMR spectrum of **3**-Ac ($CDCl_3$) is as follows: δ 6.17 (H_8), 5.74 (H_9), 6.80 and 6.84 (H_7 and H_{10}), with $J_{7,8}$ and $J_{9,10}$ = 4–5 and $J_{8,9}$ = 3 Hz; acetoxy protons δ 1.85–2.50 and aromatic protons δ 7.7–8.4. The assignments for the methine protons H_7–H_{10} are consistent with the corresponding chemical shifts and coupling constants for the acetate of the cis adduct of phenol and **2** (ref 10a). Satisfactory resolution of H_8 and H_9 of **4**-Ac could not be obtained even at 500 MHz in $CDCl_3$ but was obtained in acetone-d_6: δ 6.92 (H_7), 5.92 (H_8), 6.04 (H_9), 7.04 (H_{10}), with $J_{7,8}$ = 9, $J_{8,9}$ = 2, and $J_{9,10}$ = 3 Hz; acetoxy protons δ 2.0–2.35 and aromatic protons δ 7.95–8.30 and 8.6. The large value of $J_{7,8}$ for this compound requires that the acetoxy groups at C_7 and C_8 be diequatorial. Thus the axial ellagic acid substituent at C_{10} must be cis to the acetoxy group at C_7 and hence must have resulted from attack on the face of **2** that is opposite to the epoxide oxygen.

(12) The synthetic trimethylellagic acids were prepared by reaction of diazomethane with 4,4′ and 3,3′-di-*O*-methylellagic acids (Jurd, L. *J. Am. Chem. Soc.* **1959**, *81*, 4606–4610) followed by chromatographic purification (see Supplementary Material for details). Ultraviolet spectra observed by us for 3,3′,4-tri-*O*-methylellagic acid and its anion (in 1:9 dioxane–water) agree with previously reported spectra in ethanol (Jurd, L.; Palmer, K. J.; Stitt, F.; Shoolery, J. N. *J. Am. Chem. Soc.* **1959**, *81*, 4620–4623).

(13) The general acid-catalyzed hydrolyses of **2** by the monanions of phosphate and guanosine 5′-monophosphate are subject to similarly large solvent effects: see ref 4d.

(14) Enhanced stabilization of the cation-like transition state for epoxide cleavage by a π–π donor–acceptor interaction with the electron-rich ellagic acid molecule is an attractive possibility. Molecules capable of acting as π-electron donors have been shown to accelerate the acetolysis of 2,4,7-trinitro-9-fluorenyl-*p*-toluenesulfonate via complex formation: Colter, A. K.; Wang, S. S.; Megerle, G. H.; Ossip, P. S. *J. Am. Chem. Soc.* **1964**, *86*, 3106–3113. Colter, A. K.; Hui, S. H. *J. Org. Chem.* **1968**, *33*, 1935–1940.

(15) Wood, A. W.; Sayer, J. M.; Newmark, H. L.; Yagi, H.; Michaud, D. P.; Jerina, D. M.; Conney, A. H. *Proc. Natl. Acad. Sci. U.S.A.* **1982**, *79*, 5122–5126.

Homolytic Carbocyclization by Use of Heterogeneous Supported Organotin Catalyst. A New Synthetic Route to 2-Alkoxytetrahydrofurans and γ-Butyrolactones

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Received May 12, 1982

The synthesis or functionalization of γ-butyrolactones has been currently studied as a key synthetic reaction.[1] All such lactones have been prepared by polar reactions but not by radical ones.[2] Although radical reactions seem to be attractive in some aspects, their synthetic applications, especially to the C–C bond formations, are very restricted presumably due to the serious side reactions characteristic to them. For example, radical cyclization of 5-hexen-1-yl radical or its related species such as 3-oxa-5-hexen-1-yl radical has been investigated well, but only from the mechanistical viewpoint.[3]

(1) Wolfe, J. F.; Ogliaruso, M. A., "The Chemistry of Acid Derivatives"; Patai, S., Ed.; Wiley: New York, 1979; Part 2, Chapter 19.

(2) The only exceptional example is a free radical cyclization of *N*-iodoamides to lactones. Barton, D. H. R.; Beckwith, A. L. J., Goosen, A. *J. Chem. Soc.* **1965**, 181.

0002-7863/82/1504-5564$01.25/0