lowing instrumental parameters: spectral width, 4000 Hz; pulse width, 15 μs; delay between acquisitions, 500 μs; number of acquisitions, 800; size, 16K; acquisition time, 1.02 s; line broadening, 1.0 Hz; temperature, 25 °C.

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Ynenol Lactones: Synthesis and Investigation of Reactions Relevant to Their Inactivation of Serine Proteases†

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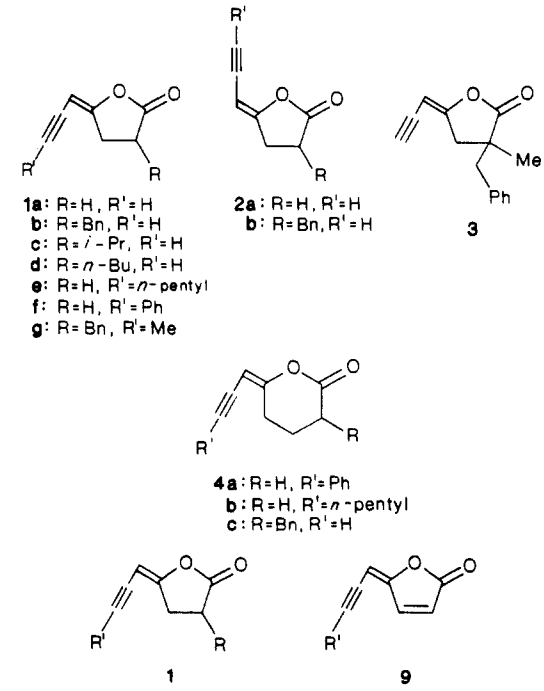
Abstract: The syntheses of ynenol lactones [5(*E* or *Z*)-(3-R′-2-propynylidene)-3-R-tetrahydro-2-furanones and 6(*E*)-(3-R′-2-propynylidene)-3-R-tetrahydro-2-pyrones; R = H, alkyl, benzyl; R′ = H, alkyl, phenyl] which are designed as serine protease suicide substrates have been accomplished. *E* ynenol lactones are prepared via iodolactonization of ω-hexynoic and ω-pentynoic acids, followed by the $CuI/Et_3N/PdCl_2(PPh_3)_2$-mediated coupling of the resulting *E* iodo enol lactones with appropriate alkynes. Isomerization of *E* iodo enol lactones gives the *Z* isomers, which can be separated and coupled to give the *Z* ynenol lactones. We have shown that the alkaline hydrolysis of ynenol lactones parallels the reaction sequence that has been proposed to account for ynenol lactone inactivation of serine proteases, namely, lactone ring cleavage, formation of the allenone, and conjugate addition of a nucleophile to the β-carbon of the allenone. When the acetylene terminus of the ynenol lactone is unsubstituted, alkaline hydrolysis leads to the allenone without a detectable intermediate. When the terminus is alkyl or phenyl substituted, an intermediate (which is probably the propargyl ketone resulting from α protonation) is apparent in the reaction kinetics. Base-catalyzed isomerization of 1-hexyn-4-one and 2-hexyn-5-one to allenones indicates a profound substituent effect of γ substitution ($k_{\gamma\text{-H}}/k_{\gamma\text{-Me}} = 300$). Nucleophilic attack on the allenones by hydroxide and *n*-butylamine gives, respectively, 1,3-dione monoanions and *Z*-β-amino enones. When the allenone is γ-phenyl substituted and is treated with hydroxide, an intermediate consistent with an ynenolate anion is apparent in the kinetics and ultraviolet spectra; the intermediate is formed with a pK_a of 13.4. Similar pK_a values are observed in the reaction kinetics of hydroxide with γ-methyl-substituted allenones.

A contemporary and intellectually appealing strategy in drug design involves the use of latent reactive substrates as enzyme inactivators.[1] This strategy features a relatively unreactive "suicide substrate" S (Scheme I) that is designed initially to bind to a specific target enzyme E and then to be transformed during the normal course of enzyme catalysis to a highly reactive species S*. Ideally, S*, before it can escape from the active site, is trapped by an amino acid side chain or coenzyme to give an irreversibly inactivated enzyme E-X.

Electrophilic allenes have played an important role in the development of this strategy as the demonstrable or putative intermediates that cause enzyme inactivation.[2] The success of inhibitors that are designed to generate these Michael acceptors has led us to explore the use of allenones as the latent functional group in a series of novel serine protease inhibitors.[3] In this paper we discuss the synthesis and nonenzymatic reactions of ynenol lactones **1–4**, which are designed to produce electrophilic allenones at protease active sites.

Scheme II outlines the reactions that must occur to achieve enzyme inactivation by this strategy. These are enzyme acylation (**1** → **5**), formation of the allenone (**5** → **7** or **5** → **6** → **7**), and capture of an enzyme nucleophile (**7** → **8**). Nonenzymatic models of each of these reactions will be presented herein to demonstrate the chemical and kinetic feasibility of this scheme. The characterization of these compounds as protease inhibitors will be presented elsewhere.[3]



The ynenol lactones in this study are prepared by coupling *E* or *Z* iodo enol lactones **10** and **11** with appropriate alkynes

Synthesis

To our knowledge the ynenol lactones **1** have not been previously characterized,[4] although their unsaturated analogues **9** have been frequently documented as natural products in the biosynthesis of polyacetylenes.[5]

† Contribution No. 241 from the Institute of Bioorganic Chemistry. This paper is dedicated to the memory of Dr. Howard J. Ringold.

(1) (a) Walsh, C. T. *Tetrahedon* **1982**, *38*, 871–909; *Trends Pharmacol. Sci.* **1983**, *5*, 254–257. (b) Abeles, R. H.; Maycock, A. L. *Acc. Chem. Res.* **1976**, *9*, 313–319. (c) Rando, R. R. *Science (Washington, D.C.)* **1974**, *185*, 320–324; *Acc. Chem. Res.* **1975**, *8*, 281–288; *Pharmacol. Rev.* **1984**, *36*, 111–142. (d) Silverman, R. B.; Hoffman, S. J. *Med. Res. Rev.* **1984**, *4*, 415–447.

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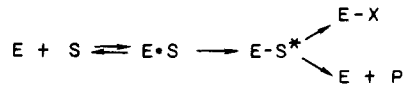
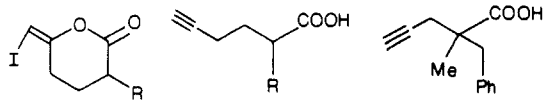
Scheme I



(Scheme III). The iodo enol lactones are obtained from the direct halolactonization of the corresponding ω-hexynoic and pentynoic acids[6] (**12**) with *N*-iodosuccinimide according to the procedure of Krafft and Katzenellenbogen.[7] This reaction is stereoselective and results in the exclusive formation of *E* olefins.[7] Treatment with elemental iodine causes slow isomerization of the *E* iodo enol lactones, providing access to the *Z* isomers **11**, which can in turn be converted to the *Z* ynenol lactones **2**. The latter isomers can also be synthesized independently via the mercury-mediated cyclization of ω-iodoacetylenic acids (**13**).[7]

The ynenol valerolactones **4** are similarly prepared from the iodo enol lactones **14** and the hexynoic acids **15**. The α,α-disubstituted ynenol lactone **3** is prepared from its corresponding acid **16**.



14a, R=H **b**, R=Bn **15a**, R=H **b**, R=Bn **16**

The coupling reaction between iodo enol lactones and alkynes is catalyzed by $PdCl_2(Ph_3P)_2$ in the presence of cuprous iodide and triethylamine. In acyclic systems this reaction has been reported to be stereoselective and to proceed with retention of configuration.[8] We observe that the coupling of all *E* iodo enol lactones and the simplest *Z* iodo enol lactone (**11a**) also proceeds with retention. However, in the reaction with **11b** a mixture of isomers [4:1, **2b**:**1b**] was obtained. Desilylation of the various ynenol lactones (**1a–d**, **2a,b**; R′ = trimethylsilyl) to the unsubstituted acetylenes (**1a–d**, **2a,b**; R′ = H) is achieved by treatment with silver nitrate and potassium cyanide.[9]

The assignments of configuration in both iodo enol and ynenol lactones were made with ^1H NMR, based on the chemical shift of the proton of the exo olefin. For example, the olefinic proton in the *E* isomer of methylenebutyrolactones and methylenebutenolides is consistently found downfield of its *Z* counterpart due to deshielding by the lactone oxygen.[10] For the unsilylated ynenol lactones this proton is found near δ 5.2 for *E* isomers and δ 4.8 for *Z* isomers. The assignment was confirmed by the proton nuclear Overhauser effect: the *Z* isomer **2** (R = H, R′ = trimethylsilyl) shows a strong enhancement of the olefinic proton signal when the methylene protons are irradiated, whereas the *E* isomer **1** (R = H, R′ = trimethylsilyl) shows no such enhancement.[11]

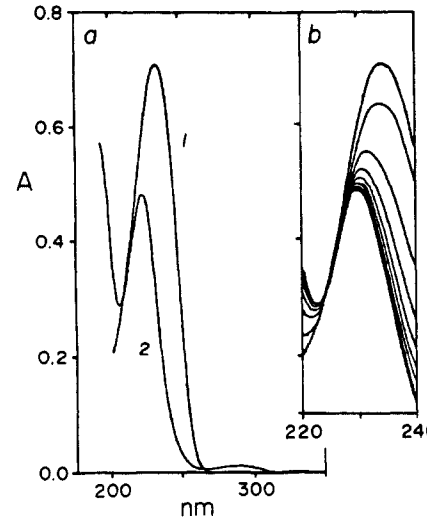


Figure 1. (a) Spectrum 1 is of 50 μM **1a** in 1.0 mL of water, 25 °C. The pH was raised by addition of 10 μL of 50 mM borate buffer, pH 10, and spectrum 2 was taken approximately 10 min later. (b) Time course of the same reaction recorded at 1-min intervals after the pH change.

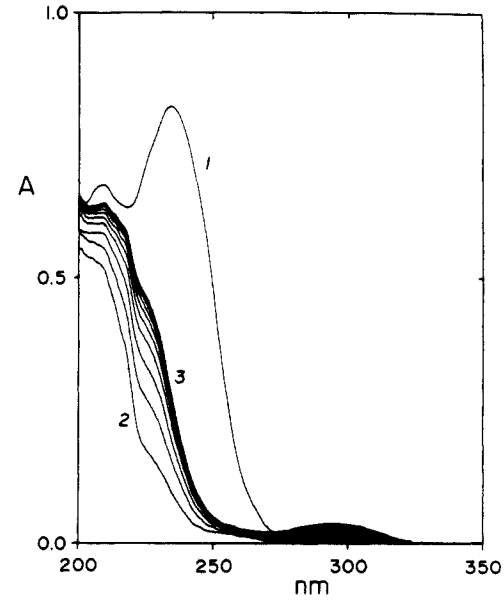


Figure 2. Spectrum 1 is of 50 μM **1g** in 1.0 mL of water, 25 °C. One microliter of 1 M NaOH was added, and spectra 2–3 were recorded at 2-min intervals.

Hydrolysis and Rearrangement

In the hypothetical mechanism for the inactivation of serine proteases by ynenol lactones depicted in Scheme II, opening of the lactone ring and formation of the allenone are prerequisites to enzyme inactivation. We have investigated the alkaline hydrolysis of ynenol lactones as a model for this transformation.

Alkaline hydrolysis of ynenol lactones can be measured by loss of absorbance at 230 nm (R′ ≠ Ph) or 280 nm (R′ = Ph). The rates are first order in hydroxide, ranging from 55 M^{-1} s^{-1} (**3**) to 300 M^{-1} s^{-1} (**2a**). The mechanism most likely proceeds by a

(2) (a) Helmkamp, G. M., Jr.; Bloch, K. *J. Biol. Chem.* **1969**, *244*, 604–6022. (b) Bloch, K. *Acc. Chem. Res.* **1969**, *2*, 193–202. (c) Morisaki, M.; Bloch, K. *Biochemistry* **1972**, *11*, 309–314. (d) White, R. L.; Smith, R. A.; Krantz, A. *Biochem. Pharmacol.* **1983**, *32*, 3661–3664. Krantz, A.; Kokel, B.; Sachdeva, J.; Salach, J.; Claesson, A.; Sahlberg, C, In *Drug Action and Design*: *Mechanism-Based Enzyme Inhibitors*; Kalman, T., Ed.; Elsevier-North Holland: New York, 1979; pp 145–174. Krantz, A.; Lipkowitz, G. S. *J. Am. Chem. Soc.* **1977**, *99*, 4156–4159. (e) See: Seiler, N., Jung, M. J., Koch-Weser, J., Eds.; *Enzyme-Activated Irreversible Inhibitors*; Elsevier: Amsterdam, 1978. (f) Kalman, T. I. *Drug Dev. Res.* **1981**, *1*, 311–328. (g) Alston, T. A. *Pharmacol. Ther.* **1981**, *12*, 1–41. (h) Jung, M. J.; Koch-Weser, J. In *Molecular Basis of Drug Action*; Singer, T. P.; Ondarza, R. N., Eds.; Elsevier-North Holland: New York, 1981; p 135. (i) Covey, D. F.; Robinson, C. H. *J. Am. Chem. Soc.* **1976**, *98*, 5038–5040. (j) Batzold, F. H.; Robinson, C. H. *J. Am. Chem. Soc.* **1975**, *97*, 2576–2578.

(3) (a) Tam, T. F.; Spencer, R. W.; Thomas, E. M.; Copp, L. J.; Krantz, A. *J. Am. Chem. Soc.* **1984**, *106*, 6849–6851. (b) Copp, L. C.; Krantz, A.; Spencer, R. W. *Biochemistry*, in press.

(4) An ynenol lactone is shown, however, in: Wat, C.-K.; Prasad, S. K.; Graham, E. A.; Partington, S.; Arnason, T.; Towers, G. H. N. *Biochem. Syst. Ecol.* **1981**, *9*, 59–62.

(5) (a) Bohlmann, F.; Burkhardt, T.; Zdero, C. *Naturally Occurring Acetylenes*; Academic: New York, 1973. (b) Reisch, J.; Mester, Z. *Monatsh. Chem.* **1983**, *114*, 635–637. (c) Nawamaki, T.; Sakakibara, T.; Ohta, K. *Agric. Biol. Chem.* **1979**, *43*, 1603–1604. (d) Lam, J. *Phytochemistry* **1971**, *10*, 647–653.

(6) Cologne, J.; Gelin, R. *Bull. Soc. Chim. Fr.* **1954**, *21*, 797–798.

(7) Krafft, G. A.; Katzenellenbogen, J. A. *J. Am. Chem Soc.* **1981**, *103*, 5459–5466.

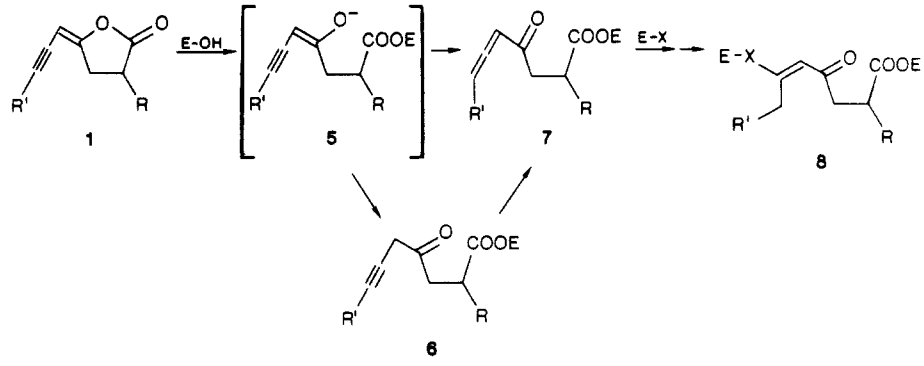
(8) (a) Ando, T.; Yu, M. H.; Yoshida, S.; Takahashi, N. *Agric. Biol. Chem.* **1982**, *46*, 717–722. (b) Robins, M.; Barr, P. J. *Tetrahedron Lett.* **1981**, 421–424. (c) Austin, W. B.; Billow, M.; Kelleghan, W. J.; Lau, K. S. Y. *J. Org. Chem.* **1981**, *46*, 2280–2286.

(9) Schmidt, H. M.; Arens, J. A. *Recl. Trav. Chim. Pays-Bas* **1967**, *86*, 1138–1142.

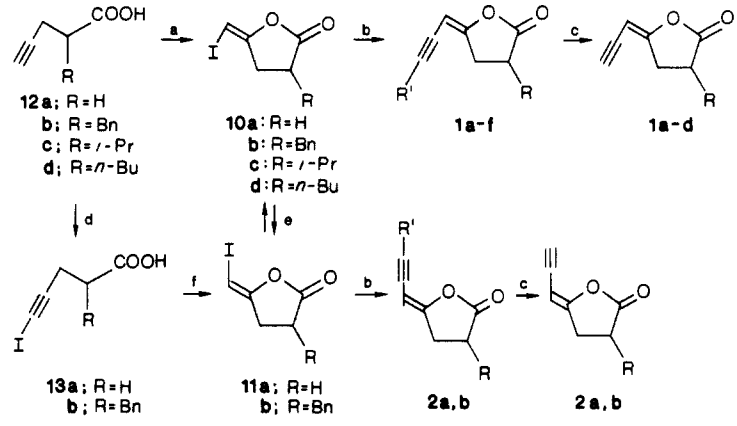
(10) (a) Yamamoto, M. *J. Chem. Soc., Perkin Trans. 1* **1981**, 582–587. (b) Bohlmann, F.; Reinecke, R. *Chem. Ber.* **1966**, *99*, 3437–3440.

(11) Inspection of Dreiding models shows that for the *Z* and *E* isomers these protons are approximately 2.6 and 3.8 Å apart, respectively.

Scheme II



Scheme III[a]

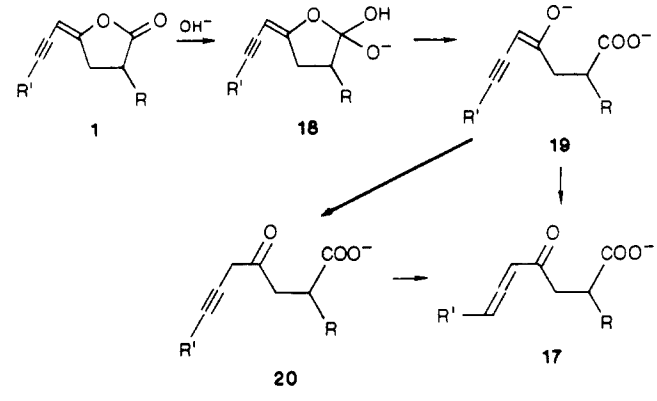


[a] (a) NIS, $NaHCO_3$, CH_2Cl_2, n-$Bu_4N^+OH^-$; (b) R'C≡CH, $PdCl_2(Ph_3P)_2$, CuI, Et_3N; (c) for R' = Me_3Si, $AgNO_3$, EtOH, KCN, H_2O; (d) I_2, NaOH; (e) I_2, CH_2Cl_2; (f) $Hg(O_2CCF_3)_2$, CH_2Cl_2.

$B_{AC}2$ pathway as in the cases of simple alkyl[12] and vinyl[13] esters. A carbanion-mediated pathway (E1cB) for hydrolysis seems unlikely, since **3** (which does not possess a hydrogen α to the carbonyl and therefore cannot follow an E1cB pathway) hydrolyzes only 5-fold more slowly than **1b** or **2b**.[14] The small value measured for imidazole catalysis of the hydrolysis of **1b** (k_{Im} = 0.018 ± 0.003 M^{-1} s^{-1}, 25 °C, μ = 0.25 M) is further support for a $B_{AC}2$ mechanism of hydrolysis of ynenol lactones.[14a]

If alkaline hydrolysis is a valid model for Scheme II, allenones must be the principal products of ring cleavage. Ultraviolet and proton NMR spectra provide the evidence for the high-yield conversion of ynenol lactones to allenones. As shown in Figure 1, ynenol lactone **1a** has a characteristic absorbance (λ_{max} 229 nm, ϵ 14 100 M^{-1} cm^{-1}). On addition of base this band disappears, and a new species (λ_{max} 220, ϵ 9600) is formed. Similar absorbance changes are observed in the hydrolyses of other ynenol lactones: for example, **1c** [232 (12 300) → 221 (8200)]; **1e** [236 (13 300) → 226 (≈8500)]; **1g**, [234 (16 400) → 228 sh (≈9000)] (Figure 2); **2a** (228 (15 000) → 220 (10 000)]; **4b** (240 (13 900) → 225 (9800)]. The new chromophore is consistent with those of allenones reported in the literature (λ_{max} 220–232, ϵ 7800–12 500).[15,2i] When the acetylene is phenyl substituted, these bands are observed at longer wavelengths: **1f** [278 (25 100) → 242 (24 500) (Figure 3a); **4a** [281 (22 500) → 240 (20 500)]. These spectra (λ_{max} 240–242 nm) are similar to those reported for 4-phenyl-2,3-butadienoic acids[15c] and thus are consistent with the production of γ-phenylallenones from **1f** and **4a**.

Scheme IV



The olefinic portion of the ^1H NMR spectrum of **1b** is shown in Figure 4a. Upon addition of a slight excess of aqueous KOH, the spectrum of Figure 4b was observed. This degenerate ABX pattern has $\delta_{A,B}(H_2C{=}C{=}CHCO$ = 5.26, $\delta_X(H_2C{=}C{=}CHCO)$ = 5.72, apparent $J_{A,X}$ = 5.9 Hz, and $J_{B,X}$ = 7.0 Hz and is in agreement with values reported for allenones.[2i,15]

With allenone **17** established as the first observable product in the alkaline hydrolysis of ynenol lactones **1** and **2**, the mechanism of this reaction can be addressed. Since the absorbance spectra recorded during the hydrolyses of **1a** and **2a** to **17** are isosbestic (Figure 1b), it is possible that when R' = H, protonation of enolate **19** occurs at the acetylenic terminus to give allenone **17** directly[16] (Scheme IV). Alternatively, propargyl ketone **20**

(12) (a) Lowry, T. H.; Richardson, K. S. *Mechanism and Theory in Organic Chemistry*, 2nd ed.; Harper and Row: New York, 1981; pp 648–658. (b) Balakrishnan, M.; Rao, G. V.; Venkatasubramanian, N. *J. Chem. Soc., Perkin Trans. 2* **1974**, 1093–1096. Huisgen, R.; Ott, H. *Tetrahedron* **1959**, *68* 253–267.

(13) Euranto, E. K. *Pure Appl. Chem.* **1977**, *49*, 1009–1020.

(14) (a) Holmquist, B.; Bruice, T. C. *J. Am. Chem. Soc.* **1969**, *91*, 2993–3002. (b) Bamford, C. H.; Tipper, C. F. H. *Comprehensive Chemical Kinetics*; Elsevier: Amsterdam, 1972; Vol. 10, pp 168–176.

(15) (a) Carlson, R.; Henton, D. *J. Chem. Soc., Chem. Commun.* **1969**, 674–675. (b) Meinwald, J.; Hendry, L. *Tetrahedron Lett.* **1969**, *21*, 1657–1660. (c) Kresze, G.; Runge, W.; Ruch, E. *Justus Liebigs Ann. Chem.* **1972**, *756*, 112–117.

(16) While tetrahedral intermediate **18** could be protonated to give **17** or **20** directly, the stability of ynenolate **19** does not demand such a concerted mechanism. The intermediacy of **19** is also supported by the reaction dependence on [OH^-] (vide infra).

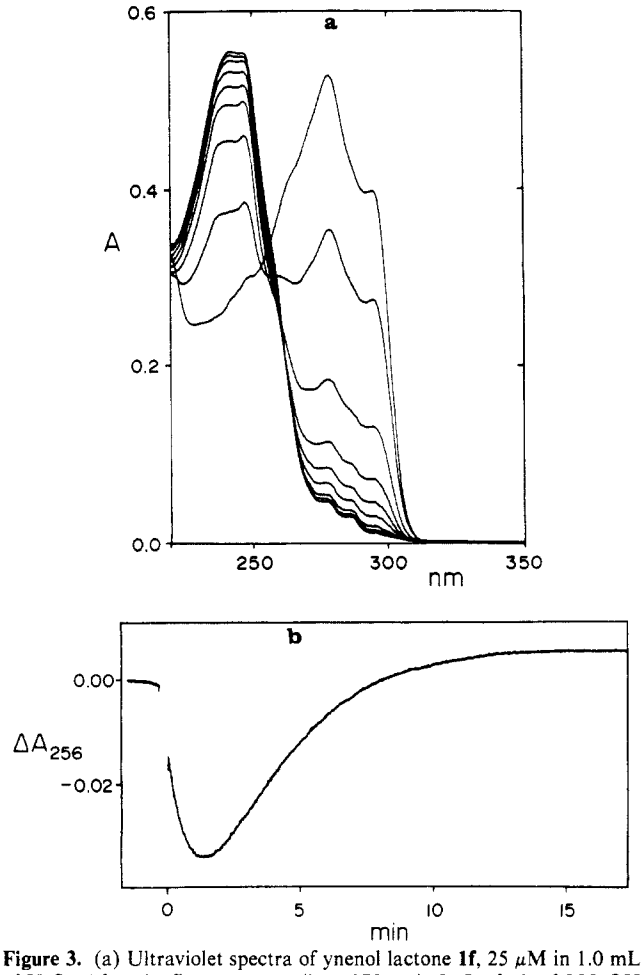


Figure 3. (a) Ultraviolet spectra of ynenol lactone **1f**, 25 μM in 1.0 mL of H_2O. After the first spectrum (λ_{max} 279 nm), 5 μL of 10 mM NaOH was added, and spectra were recorded at 2-min intervals. (b) Time course of the same reaction, monitored at 256 nm. NaOH (30 μL of 10 mM) was added at time zero.

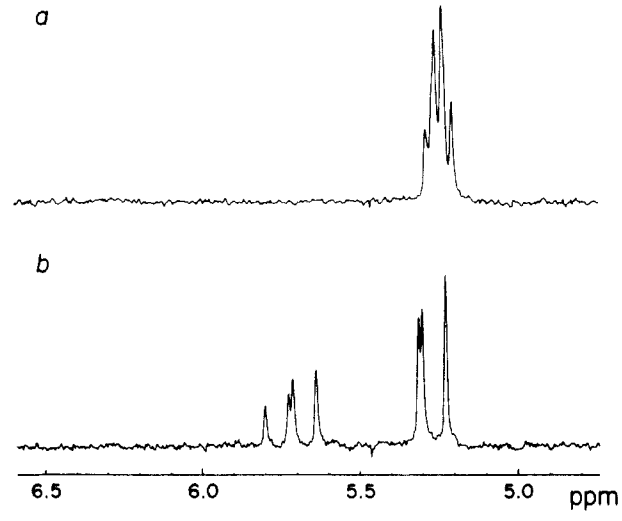
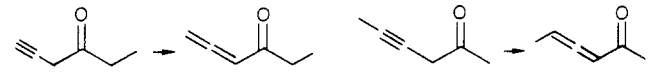


Figure 4. (a) Olefinic region of the 80-MHz ^1H NMR of **1b**, 3.8 mg in 0.54 mL of 10% (v/v) H_2O in CD_3CN, 30 C. The water signal at δ 3.2 was suppressed. (b) The same sample, immediately after the addition of 10 μL of 2 M KOH (=1.1 equiv). Integration of this region indicated approximately 70% yield of allenone; the allenic proton signals subsequently disappeared with a half-time of 50 min.

could be a distinct intermediate that is too short lived to be observed.

When R′ is alkyl, the spectra during hydrolysis are *not* isosbestic; the 230-nm absorbance of the ynenol lactone disappears, and the 220-nm allenone absorbance arises from a second, slower reaction. For example, Figure 2 shows the hydrolysis of **1g** in which these reactions have rates of 160 and 6 M^{-1} s^{-1}, respectively, a 27-fold difference. Similarly, when R′ is phenyl, the spectra are not isosbestic, but because the rates differ by a smaller factor (6.1-fold for **1f**), the intermediate is never more than a minor component (Figure 3). This lack of isosbesticity when R′ is alkyl or phenyl suggests that the propargyl ketone **20** is a UV-silent intermediate leading to the allenone **17**.

Although there have been numerous studies of propargylic rearrangements, there is very little kinetic data bearing on the interconversion of propargyl and propadienyl ketones. We have used a simple model system to investigate this rearrangement and obtain rate constants in an aqueous environment. Hexynones **21**



21 **22** **23** **24**

and **23** were prepared, and their hydroxide- and imidazole-catalyzed isomerizations to **22** and **24** were followed by the appearance of allenone absorbance at 220 nm.

Both isomerizations follow the rate equation

$$k_{obsd} = k_{OH^-}[OH^-] + k_{Im}[Im]$$

For **21** and **23** the values of k_{OH^-} are 3500 ± 300 and 11 ± 1 M^{-1} s^{-1}, respectively, and the values of k_{Im} are 0.223 ± 0.002 and (7.4 ± 0.5) × 10^{-4} M^{-1} s^{-1} (aqueous, μ = 0.25 M with KCl, 25 °C). Thus, for either catalyst, methyl substitution on the acetylene slows the isomerization 300-fold. The rate for hydroxide-catalyzed isomerization of **23** to **24** (11 M^{-1} s^{-1}) is close to that measured for the second phase of the hydrolysis of **1g** to its allenone (Figure 2): 6.0 ± 0.3 M^{-1} s^{-1}. This congruence in rates lends support to the suggestion that **20** is the UV-silent intermediate when R′ is methyl. If **20** were also formed when R′ = H and then rearranged at a rate comparable to that of hexynoate **21** (3500 M^{-1} s^{-1}), it should have been observable as a kinetic intermediate: in the sequence

$$\mathbf{1} \xrightarrow{k_1} \mathbf{20} \xrightarrow{k_2} \mathbf{17}$$

with k_2/k_1 = 3500/200, the maximum concentration of **20** would be 5% that of starting material,[17] which would be apparent in scanning spectra such as in Figure 1b. No such kinetic intermediate was observed for **1a** or **2a**.

Additional evidence that allenone **17** may be formed without the intervention of a propargyl ketone intermediate when R′ = H is provided by Bertrand and LeGras.[18] They have shown that the isomerization of **21** to **22** in alkaline D_2O occurs without incorporation of deuterium α to the carbonyl, demonstrating that in the unsubstituted propargyl system protonation at the γ terminus is significantly faster than α protonation. It is noteworthy that this preference is in contrast to the classical results of Ringold[19] with steroidal dienolates and recent reports involving acyclic dienolates, which protonate at the α carbon.[20]

Addition of Nucleophiles

The final requirement for suicide inactivation according to Scheme II is the capture of a nearby enzyme nucleophile (**7** → **8**). The conjugate additions of hydroxide and *n*-butylamine to

(17) Frost, A. A.; Pearson, R. G. *Kinetics and Mechanism*, 2nd ed.; Wiley: New York, 1961; pp 166–169.

(18) Bertrand, M.; LeGras, J. *C. R. Hebd. Seances Acad. Sci.* **1967**, *264*, 520–526 and references therein.

(19) Ringold, H. J.; Malhotra, S. K. *Tetrahedron Lett.* **1962**, *15*, 669–672. Malhotra, S. K.; Ringold, H. J. *J. Am. Chem. Soc.* **1963**, *85*, 1538–1539.

(20) (a) Duhaime, R. M.; Weedon, A. C. *J. Am. Chem. Soc.* **1985**, *107*, 6723–6724. Duhaime, R. M.; Lombardo, D. A.; Skinner, I. A.; Weedon, A. C. *J. Org. Chem.* **1985**, *50*, 873–879. Eng, S. L.; Roland, R.; Wan, C. S.; Weedon, A. C. *J. Chem. Soc., Chem. Commun.* **1983**, *5*, 236–238. (b) Note that the kinetically controlled products of conjugate additions to allenones appear to be the β,γ-olefinic species: Landor, S.R. In *Chemistry of the Allenes*; Landor, S. R., Ed.; Academic: New York, 1982; pp 373–387. Greaves, P. M; Landor, S. R. *J. Chem. Soc., Chem. Commun.* **1966**, 322–323. Landor, S. R.; Landor, P. D.; Fomum, Z. T.; Mbafor, J. T.; Mpango, G. W. B.; *Tetrahedron* **1984**, *40*, 2141–2149. Fomum, Z. T.; Greaves, P. M.; Landor, P. D.; Landor, S. R. *J. Chem. Soc. Perkin Trans. 1* **1973**, 1108–1111.

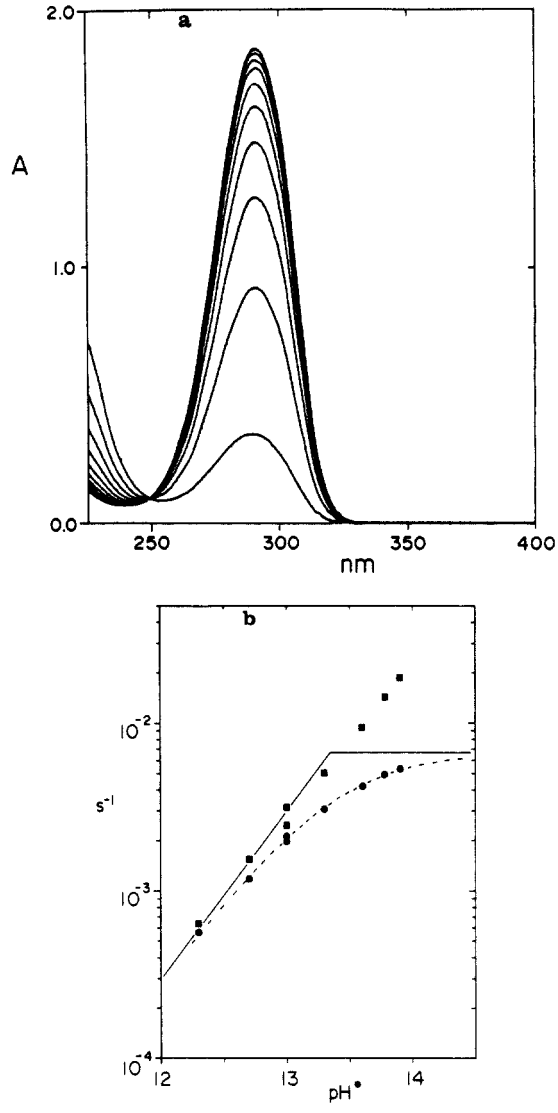
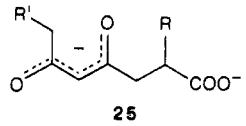


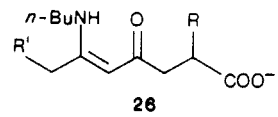
Figure 5. (a) Ultraviolet spectra at 3-min intervals after addition of propargyl ketone **21** (to approximately 90 μM) to 0.10 M NaOH, 25 °C. (b) pH–rate profiles for the hydration of **22** (■) and **24** (●) (formed in situ from **21** and **23**, respectively) to the keto enolate **27**. pH* = 14 + log [NaOH]. The dashed curve is calculated from $k = k_{max}/(1 + [H^+]/K_a)$, with $k_{max} = 0.0067\ s^{-1}$ and $pK_a = 13.35$. The solid lines are the asymptotes to this function.

allenones **17**, **22**, and **24** provide model reactions for this step.

Evidence that the final, stable products of alkaline hydrolysis of ynenol lactones are the 1,3-dione anions **25**[21] is as follows.



25



26

Hydrolysis of **1a** in 0.1 M KOH gives an absorbance with alkaline λ_{max} 293 nm, ϵ 23 600 (based on a 100% yield from **1a**), pK_a = 9.44, and a chromophore in acid at 273 nm ($\epsilon \approx 1500$), which is characteristic of the 1,3-dione system.[22] Ynenol lactone **1b** was similarly subjected to alkaline hydrolysis and the reaction mixture acidified, extracted, and esterified with diazomethane to give methyl 2-benzyl-4,6-dioxoheptanoate, as shown by its alkaline λ_{max}

Table I. Hydroxide and Butylamine Addition to Allenones **17**[a]

parent lactone	R	R′	k_{OH^-}	pK_a	$k_{n\text{-BuNH}_2}$[b]
1a	H	H	0.015	*c*	0.27
1f	H	Ph	0.014	13.3	0.27
1b	Bn	H	0.013	*c*	0.23
1g	Bn	Me	0.0070	13.9	0.10

[a] All rate constants in $M^{-1}\ s^{-1}$, 25 °C, measured under pseudo-first-order conditions by appearance of **25** at 290 nm or **26** at 318 nm. [b] Allenones **17** were formed in situ in 0.1 M Na_2CO_3, pH 10.5, followed by butylamine addition to 5–20 mM. [c] No pK_a was observed; the reaction was first order in $[OH^-]$.

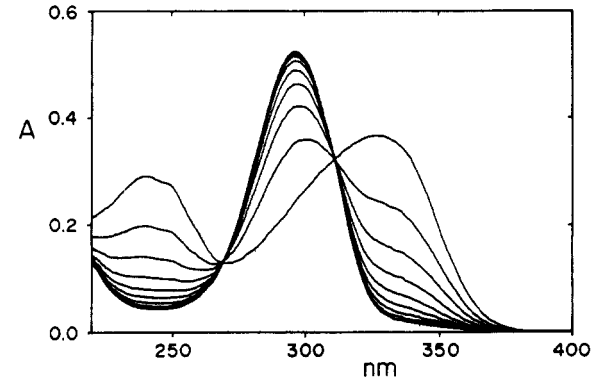
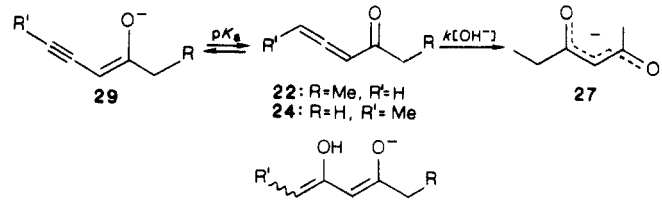


Figure 6. Ultraviolet spectra at 2-min intervals after the addition of **1f** (25 μM final) to 0.4 M NaOH, 25 °C. The first spectrum has maxima at 240 and 327 nm.

of 293 nm, pK_a = 8.69, and infrared, NMR, and mass spectra (see the Experimental Section). Treatment of **1a** with *n*-butylamine (10 mM, aqueous) gives a chromophore with λ_{max} 312 nm, ϵ 23 000, indicating the formation of cis amino enone **26**.[22c]

Substituent effects on these conjugate additions were probed first with the simpler allenones **22** and **24**, formed in situ from the propargyl ketones **21** and **23**. Figure 5a shows the time course of the alkaline hydration of **22** to **27**, and Figure 5b shows the



29 **22**: R=Me, R'=H; **24**: R=H, R'=Me **27**

28

OH^- concentration dependence of the reactions. When the allenone terminus is unsubstituted (**22**), the reaction is first order in hydroxide[23] with $k = 0.023\ M^{-1}\ s^{-1}$. However, when the allene has a γ-methyl substituent (**24**), the reaction has an apparent pK_a of 13.4 and a maximum rate of $0.0067\ s^{-1}$; this implies a second-order rate at pH $\ll pK_a$ (k in the above scheme) of 0.030 $M^{-1}\ s^{-1}$. Thus, the substituent effect at pH $\ll pK_a$ is small, but with γ-methyl substitution an intermediate is sufficiently stabilized that the reaction has an observable pK_a. As defined by the kinetics, this intermediate is formed by either proton abstraction from, or hydroxide addition to, allenone **24**. Hydroxide addition would be expected to give **28**, an isomer of the product **27**, whereas proton abstraction should give ynenolate **29**,[24] which is also an intermediate in the in situ production of allenones. Support for the latter assignment **29** is found when R′ = phenyl (vide infra).

(21) The precise configuration of these anions has not been established. They are shown in the *E,Z'* form in conformity with the results of: Raban, M.; Noe, E. A.; Yamamoto, G. *J. Am. Chem. Soc.* **1977**, *99*, 6527–6531.

(22) (a) Covey, D. F.; Albert, K. A.; Robinson, C. H. *J. Chem. Soc., Chem. Commun.* **1979**, 795–796. (b) Bell, R. P. *The Proton in Chemistry*, 2nd ed.; Cornell University Press: Ithaca, NY, 1973; p 105. (c) Kashima, C.; Yamamoto, M.; Sugiyama, N. *J. Chem. Soc. C* **1970**, 111–114.

(23) There is a slight curvature in Figure 5b for **22**; the data are equally well fit by $k = k_{max}/(1 + [H^+]/K_a)$ with $k_{max} = 0.064\ s^{-1}$ and $pK_a = 14.3$. In either case the apparent pK_a for **22** is at least 1 unit higher than that of **24**.

(24) The trienolate $R'CH{=}C{=}C{=}C(CH_2R)O^-$ is a less likely candidate than **29**, since it is more highly strained and should be more difficult to form by proton abstraction for stereoelectronic reasons.

Scheme V

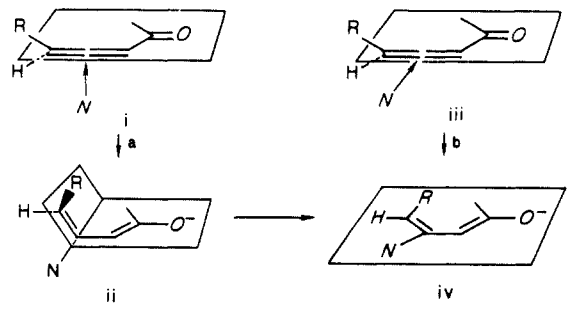


Table I presents the rates of conjugate addition of hydroxide and *n*-butylamine to allenones **17**. The reaction of butylamine with the allenone from **1a** was measured vs. pH; the data gave a kinetic pK_a of 10.4, showing as expected that the nucleophile is neutral butylamine. All other butylamine reactions were measured in buffer at pH 10.5. As in the hydration of **22** vs. **24**, γ-phenyl or γ-methyl substitution on the allenone results in stabilization of an intermediate that is manifested in a kinetic pK_a of 13.3 or 13.9, respectively. In the phenyl system (from **1f**) the intermediate has a strong ultraviolet absorbance (Figure 6). The chromophore at λ_{max} = 327 nm is formed immediately on the addition of **1f** to 0.02–0.40 M NaOH and disappears isosbestically with the formation of **25** (R = H, R′ = Ph) at λ_{max} 295 nm. When **1f** is treated first with dilute base to give the 242-nm species (allenone **17**; R = H, R′ = Ph, as in Figure 3a) and then NaOH is added to 0.2 M, the 327-nm species is formed immediately, followed by slow formation of **25**. If the mixture displaying the 327-nm absorption is rapidly acidified, this reaction is reversed: the 327-nm chromophore disappears with concomitant increase at 242 nm. Addition of more NaOH results in the return of the 327-nm species and eventual production of **25**. The apparent extinction at 327 nm increases with [OH^-] and is accurately fit by $\epsilon = \epsilon_{max}/(1 + [H^+]/K_a)$, with ϵ_{max} 26 900 and pK_a = 13.4. No such 327-nm species is seen when R′ = H or methyl (e.g., Figure 5a), suggesting that this intermediate has the phenyl in conjugation (e.g., **28** or **29**; R = H, R′ = Ph), unlike the final product **25** in which the phenyl is isolated from the 1,3-dione anion.

Because formation of the 327-nm species is freely reversible, it cannot be the compound of structure **28**. Even if **28** were slow to isomerize, neutralization would be expected[25] to result in ketonization to the 1,3-dione, not dehydration to the allenone (λ_{max} 242 nm). If the 327-nm intermediate is ynenolate **29** (R = H, R′ = Ph), it must be formed by abstraction of the γ-allenic hydrogen of **17** (R = H, R′ = Ph). Bushby and Whitham note the acidity of this hydrogen in related allenic acids and esters,[26] as indicated by its rapid exchange in alkaline D_2O. The acidity of allene protons is also manifest in the facile equilibration of methyl penta-2,3-dienoate and methyl pent-3-ynoate, which have an equilibrium constant near unity,[26a] and in the comparable gas-phase acidities of propyne and allene.[27] The stability of ynenolate **29** when R′ is alkyl (and therefore the acidity of **17** or **24**) may also be indicated by the profound suppression by γ-methyl substitution of the rate of formation of allenones from ynenolates (vide supra).

The small substituent effects on conjugate addition to allenones (Table I) are in contrast to the large effects recorded for such additions to conjugated olefins. Guthrie[28] has shown that the rates of hydroxide addition to acrolein, 3-methylacrolein, and 3,3-dimethylacrolein are in the ratio 90:10:1. The lack of a substituent effect in the case of allenones is readily understood upon analysis of the two extreme modes of nucleophilic attack on the terminally substituted allenone, as pictured in Scheme V.

First, since terminal substituents attached to allenic Michael acceptors are one bond further removed from the point of nucleophilic attack than are their olefinic counterparts, steric effects at the transition state should be less pronounced for allenes.

Second, for stereoelectronic reasons[29] the most favorable approach for nucleophilic attack is orthogonal to the plane defined by $C_\beta C_\alpha CO$, leading directly to enolate **ii** with overlap optimized along the reaction coordinate (path a).

In this mode of attack the terminal double bond is virtually orthogonal to the developing enolate in the transition state. Thus, the terminal double bond and the substituents attached to it cannot effectively interact by resonance with the developing negative charge. It follows that the effect of a substituent at the allenic terminus should not be significantly different in the ground and transition states and that the rate of conjugate addition should be insensitive to the nature of the substituent R. It is worth noting that **ii** is a metastable species that would be expected to relax to the completely delocalized dienolate **iv**. With more fully substituted allenes, steric effects may offset the gain in delocalization energy on going from species **ii** to **iv**.

A pathway b in which approach of the nucleophile N occurs within the $C_\beta C_\alpha CO$ plane (**iii**) and leads directly to **iv** is unlikely to be followed. This path is of higher energy than path a because of the considerable barrier to rotation[30] about C_α–C_β, which must be overcome in order to achieve significant stabilization of the developing negative charge by the carbonyl.[31]

Conclusion

We have shown that ynenol lactones **1–4** and their products are chemically competent in the reactions required to inactivate esterases or proteases according to Scheme II. Allenones **17** are rapidly formed following hydrolytic cleavage of the lactone by base. When the acetylene terminus of the ynenol lactone is unsubstituted, no intermediate can be detected in this reaction; when the terminus is alkyl or phenyl substituted, the propargyl ketone **20** is formed as an intermediate. The kinetics of isomerization of hexynones **21** and **23** to allenones **22** and **24** show that the substituent effect is profound; methyl at the terminus slows the base-catalyzed rearrangement 300-fold.

Once formed, allenones are subject to nucleophilic attack at the β-carbon as expected. Attack by hydroxide and butylamine give, respectively, 1,3-dione anions and cis amino enones as final products. When the allenone is γ substituted, an intermediate consistent with ynenolate **19** is apparent in the kinetics of hydroxide attack. A pK_a of 13.3–13.9 for γ deprotonation of such allenones is also suggested by the reaction kinetics.

All of these reactions have been investigated in aqueous systems at 25 °C, so there are no a priori barriers to this chemistry occurring at an enzyme active site. The success or failure of these compounds as suicide substrates will therefore depend on enzyme specificity and relative rates of release vs. rearrangement and conjugate addition, as will be reported in forthcoming papers.[3b]

Experimental Section

General Procedures. Analytical thin-layer chromatography (TLC) was performed with Merck silica gel 60 F-254 aluminum-backed plates. Compounds were visualized by ultraviolet light or phosphomolybdic acid spray reagent. Preparative TLC was carried out with 1-mm Whatman

(25) A similar argument can be made against the trans isomer of **28**, which also would be unlikely to possess the strong 327-nm chromophore.

(26) (a) Bushby, R. J.; Whitham, G. H. *J. Chem. Soc. B* **1969**, 67–73. (b) Runge, W. In *Chemistry of the Allenes*; Landor, S. R., Ed.; Academic: New York, 1982; Vol. 3, pp 650–652.

(27) Oakes, J. M; Ellison, G. B. *J. Am. Chem. Soc.* **1983**, *105*, 2969–2975.

(28) Guthrie, J. P.; Dawson, B. A. *Can. J. Chem.* **1983**, *61*, 171–178.

(29) (a) An analogous argument involving stereoelectronic control in enolization–ketonization reactions has been advanced by: Corey, E. J.; Sneen, R. A. *J. Am. Chem. Soc.* **1956**, *78*, 6269–6278. (b) Harvey, G. R.; Ratts, K. W. *J. Org. Chem.* **1966**, *31*, 3907–3910.

(30) (a) Roth, W. R.; Raf, G.; Ford, P. W. *Chem. Ber.* **1974**, *107*, 48–52. (b) Ample precedents point to the difficulty of generating a planar allylic intermediate from an allene in a single transition state: vinyl cations, rather than allyl cations, are formed when electrophiles add to simple allenes in solution (Jacobs, T. L. In *Chemistry of the Allenes*; Landor, S. R. Ed.; Academic: New York, 1982; Vol. 2, pp 417–510) and in the gas phase (Aue, D. H.; Davidson, W. R.; Bowers, M. T. *J. Am. Chem. Soc.* **1976**, *98*, 6700–6702). Also, hydrochlorination of phenylallene proceeds through a transition state that structurally resembles the perpendicularly twisted α-vinylbenzyl cation: Okuyama, T.; Izawa, K.; Fueno, T. *Ibid.* **1973**, *95*, 6749–6756.

(31) Interestingly, β,γ-olefinic ketones should be the kinetically controlled products of protonation of either **ii** or **iv**.[20b]

4861-480 precoated plates. Flash column chromatography was carried out with Whatman LPS-II silica gel.

Proton and ^{13}C NMR spectra were obtained at 80 and 20.1 MHz, respectively, on a Bruker WP-80 SY spectrometer, with $CDCl_3$ as solvent. Chemical shifts of both are given (ppm) from tetramethylsilane, and coupling constants are given in Hertz. Infrared (IR) spectra were recorded with a Perkin-Elmer Model 298 spectrometer and are presented (cm^{-1}) for key absorptions. Mass spectra were recorded with a Finnigan MAT-112S instrument in electron-impact mode at 80 eV, and high-resolution spectra were measured with a Finnigan MAT-311A. Ultraviolet absorption spectra and kinetics were recorded on a Perkin-Elmer 559A spectrophotometer at 25 ± 1 °C. All kinetics were run in water and measured under pseudo-first-order conditions, with compound at 10–100 μM and excess base. Rate constants were determined by nonlinear least-squares regression of the observed changes in absorbance vs. time to the first-order equation $A = A_0^{-kt} + B$. A Beckman 3560 meter was used to measure pH and was calibrated with commercial standards. Melting points were determined with a Buchi 510 melting point apparatus.

4-Pentynoic acid (**12a**) was purchased from Aldrich Chemical Co. 5-Hexynoic acid was prepared according to the literature[32] or by the oxidation of 5-hexynol with pyridinium dichromate[33] in DMF. Petroleum ether was a mixture of alkanes boiling at 30–60 °C.

All trimethylsilyl-protected ynenol lactones were prepared by the procedure described for **30**.

Preparation of Pentynoic and Hexynoic Acids. 2-Alkyl- or -benzyl-4-pentynoic acids were prepared by either one of two methods: (a) the alkylation of the corresponding substituted malonic ester with propargyl bromide in EtOH/NaOEt, followed by hydrolysis of the diester and thermal decarboxylation to the monoacid[6] or (b) the condensation of the corresponding alkyl or benzyl ester with 3-(trimethylsilyl)prop-2-ynyl bromide in the presence of LDA, followed by basic hydrolysis to the acid. 2-Substituted 5-hexynoic acids were prepared by method (b) from 6-(trimethylsilyl)hex-5-ynoate (vide infra).

2-Benzyl-4-pentynoic Acid (12b). The acid was prepared following to the procedure of Cologne and Gelin:[6] oil; IR 3290, 1710; ^1H NMR δ 2.1 (t, 1 H, C≡CH, J = 3), 2.4 (m, 2 H, C≡CCH_2), 2.8–3.2 (m, 3 H, PhCH_2, CHCO_2H), 7.3 (m, 5 H, Ph), 6.5–7.5 (br s, 1 H, COOH).

2-Isopropyl-4-pentynoic Acid (12c). In a procedure similar to that used in the preparation of **16**, ethyl 2-isopropyl-5-(trimethylsilyl)pent-4-ynoate was prepared by condensing ethyl 3-methylbutanoate with (trimethylsilyl)propargyl bromide: bp 84–85 °C (1 mmHg); ^1H NMR δ 0.12 (s, 9 H, Me_3Si), 0.9, 1.0 (2 d, 6 H, $2CH_3$), 1.3 (t, 3 H, CH_3), 1.95 [m, 1 H, $(CH_3)_2CH$], 2.4 (m, 3 H, C≡CCH_2, CHCO_2Et), 4.2 (q, 2 H, CH_2). Hydrolysis with aqueous NaOH yielded **12c**: bp 95–96 °C (1 mmHg); IR 3300, 2500–3500, 1700; ^1H NMR δ 1.0, 1.01 (2 d, 6 H, $2CH_3$), 2.0 (m, 1 H, C≡CH), 2.1 [m, 1 H, $(CH_3)_2CH$], 2.5 (m, 3 H, C≡CCH_2, CHCO_2H), 10.8–11.2 (br s, COOH).

2-Propargylhexanoic Acid (12d). This acid was prepared from propargyl bromide and diethyl butylmalonate according to the procedure of Cologne and Gelin;[6] bp 110–112 °C (1 mmHg).

6-(Trimethylsilyl)hex-5-ynol. To a three-neck flask equipped with a 500-mL pressure-equalizing funnel and an argon gas inlet/outlet was added 50 g (0.51 mol) of 5-hexynol (Farchan) in 100 mL of THF under argon. The flask and its contents were flushed with argon, and then n-BuLi (700 mL, 1.6 M, 2.2 equiv; Aldrich) was added dropwise over a period of 45 min at −40 °C. A white precipitate started to form after approximately 30 min. The solution was then warmed to −20 °C, and 130 mL of trimethylsilyl chloride was added dropwise over a 30-min period. The reaction mixture was left at room temperature overnight and then filtered, and the filtrate was evaporated to an oil. The oily residue was partitioned between ether and saturated ammonium chloride solution. The ether layer was washed with water, dried over $MgSO_4$, and then evaporated to give an oil. To this oil were added 80 mL of EtOH, 0.5 mL of concentrated HCl, and 5 mL of water. The mixture was stirred at room temperature for 1 h. Saturated brine solution was added, and the mixture was extracted with ether. The combined ethereal extracts were further washed with water and dried over $MgSO_4$. Solvent evaporation gave an oil that was distilled to give the title compound: 55 g (63%); bp 80 °C (0.1 mmHg); IR 3300–3400, 2160, 1250; ^1H NMR δ 1.7 (m, 4 H, H2, H3), 2.3 (m, 2 H, H4), 3.7 (m, 2 H, H1).

6-(Trimethylsilyl)hex-5-ynoic Acid. To a solution of 6-(trimethylsilyl)hex-5-ynol (10 g, 58.7 mmol) in 400 mL of dry DMF was added 98 g (0.26 mmol) of pyridinium dichromate. The solution was stirred in the dark for 24 h and then partitioned between ether and water. The ether extract was dried over $MgSO_4$ and evaporated to an oil. Distillation gave the title compound: 6.5 g (60%); bp 121–124 °C (1 mmHg); IR 3290, 2162, 1720; ^1H NMR δ 0.14 (s, 9 H, Me_3Si), 1.8 (m, 2 H, H3), 2.4–2.6 (m, 4 H, H2, H4).

Ethyl 6-(Trimethylsilyl)hex-5-ynoate. To a solution of 5.3 g (32.7 mmol) of 1,1-carbonyldiimidazole in 80 mL of dry THF under argon was added a solution of 5.03 g (27.3 mmole of 6-(trimethylsilyl)-5-hexynoic acid in 15 mL of dry THF. The mixture was stirred for 1 h. Absolute EtOH (80 mL) and pyridine (1 mL) were then added, and the resulting mixture was stirred at room temperature for 48 h. The solvent was evaporated, and the residual oil was extracted with ether and 1.5% HCl. The ethereal layer, which was washed with water and then dried, was evaporated to an oil (5.1 g, 88%). This material was purified by distillation: bp 70–75 °C (0.6 mmHg); IR 2170, 1735; ^1H NMR δ 0.15 (s, 9 H, Me_3Si), 1.3 (t, 3 H, CH_3), 1.85 (m, 2 H, H3), 2.2–2.5 (m, 4 H, H2, H4), 4.1 (q, 2 H, CH_2).

2-Benzylhex-5-ynoic Acid. To a three-neck flask equipped with septum and inert gas inlet and outlet were added 15 mL of dry THF and 1.6 mL (11.4 mmol) of diisopropylamine. n-Butyllithium (7 mL, 1.6 M) was added at 0 °C, and the resulting solution was stirred at 0 °C for 30 min. The solution was cooled to −78 °C. Ethyl 6-(trimethylsilyl)hex-5-ynoate (2 g, 9.4 mmol) in dry THF was added slowly. The resulting mixture was then stirred for 25 min. A solution of benzyl bromide (2 g, 11.6 mmol) in dry THF was added, and the reaction mixture was allowed to warm up to room temperature slowly. After the mixture stood for 2 days, the solvent was evaporated, and the residue was partitioned between ether and 5% HCl. The ethereal extract, which was washed with water and dried, was evaporated to an oil. To this oil were added NaOH (5%, 35 mL) and EtOH (60 mL). The mixture was refluxed for 75 min and then left at room temperatue overnight. Ethanol was removed under reduced pressure. The residue was partitioned between ether and 5% HCl. The ethereal layer was washed with 5% NaOH solution (2 × 75 mL), and the basic extract was acidified to pH 1 with dropwise addition of concentrated HCl. The acidified solution was extracted with ether. The ethereal extract, which was washed with water and dried, was evaporated to an oil. This oil was recrystallized from ether/hexane: 1.43 g (75%); mp 125–126 °C; IR 3290, 2110, 1700; ^1H NMR δ 1.8 (m, 2 H, H3), 2.0 (t, 1 H, C≡CH, J = 2.2), 2.2 (m, 2 H, H4), 2.7–3.1 (m, 3 H, H2, PhCH_2), 7.2 (m, 5 H, Ph), 9.8–10.6 (br s, 1 H, COOH); MS, m/z 220 (MNH_4^+), 203 (MH^+), 202 (M^+).

Ethyl 2-Methyl-3-phenylpropionate. A solution of 6.8 g (0.067 mmol) of diisopropylamine in 40 mL of dry THF was injected into a three-neck flask under argon. n-BuLi (42.2 mL, 1.6 M) was added slowly at 0 °C. The resulting mixture was stirred at 0 °C for 30 min and then cooled to −78°C. A solution of ethyl 3-phenylpropionate (11.1 g, 67 mmol) was added slowly. Following the addition, the mixture was stirred at −78 °C for 30 min. A solution of methyl iodide (10 g, 70.9 mmol) in 5 mL of dry THF was then added. The mixture was stirred at −78 °C for 1 h, warmed to room temperature for 1 h, and then partitioned between ether and water. The ethereal layer was washed with 5% HCl, brine solution, and water, dried over $MgSO_4$, and then evaporated to give an oil (11 g, 85%). The material was purified by distillation: bp 80–85 °C (0.6 mmHg); IR 3100–2800, 1732; ^1H NMR δ 1.1 (d, 3 H, CH_3), 1.2 (t, 3 H, CH_3CH_2O), 2.8 (m, 3 H, PhCH_2, CH), 4.1 (q, 2 H, CH_2), 7.2 (m, 5 H, Ph).

Ethyl 2-Benzyl-2-methyl-5-(trimethylsilyl)pent-4-ynoate. To a solution of 2.2 mL (1.58 g, 15.6 mmol) of diisopropylamine in 20 mL of dry THF was added dropwise a solution of n-BuLi (9.7 mL, 1.6 M) at 0 °C. The solution was stirred at 0 °C for 30 min and then cooled to −78 °C. A solution of ethyl 3-phenyl-2-methylpropionate (2.5 g, 14.9 mmol) in 10 mL of dry THF was added. After 30 min, 3 g (15.7 mmol) of (trimethylsilyl)propargyl bromide[34] in 10 mL of dry THF was added. The mixture was slowly warmed to 0 °C and maintained at 0 °C for 1.75 h. The reaction mixture was quenched with 5% HCl and partitioned between ether and 5% HCl. The ethereal layer, which was washed with brine solution and water, was dried and evaporated to an oil (3.5 g). The oil was chromatographed on silica gel (5% EtOAc in petroleum ether) to give the title compound: 2.7 g (67%); IR 2170, 1738; ^1H NMR δ 0.2 (s, 9 H, Me_3Si), 1.3 (t + s, 6 H, $2CH_3$), 2.5 (s, 2 H, C≡CCH_2), 3.0 (s, 2 H, PhCH_2), 4.15 (q, 2 H, CH_2), 7.2 (m, 5 H, Ph).

2-Benzyl-2-methylpent-4-ynoic Acid (16). To a solution of ethyl 2-benzyl-2-methyl-5-(trimethylsilyl)pent-4-ynoate (2.65 g, 7.43 mmol) in EtOH was added 30 mL of 5% NaOH. The mixture was refluxed overnight after which time the EtOH was removed under reduced pressure. The solution was acidified by dropwise addition of concentrated HCl and extracted with ether. The ethereal extract was washed with 5% NaOH. The basic wash was acidified with concentrated HCl and extracted with ether. The ethereal extract, which was washed with water and dried, was then evaporated to an oily solid that was chromatographed on silica gel (5% EtOAc in petroleum ether). The purified product was

(32) Holland, B. C.; Gilman, N. W. *Synth. Commun.* **1974**, *4*, 202.
(33) Corey, E. J.; Schmidt, G. *Tetrahedron Lett.* **1979**, 399–402.
(34) Miller, R. B. *Synth. Commun.* **1972**, *2*, 267.

recrystallized from petroleum ether: 1.25 g (87%); mp 87.5–91.5 °C; IR 3300, 2112, 1690; ^{1}H NMR δ 1.7 (s, 3 H, CH_3), 2.1 (t, 1 H, C≡CH, J = 2.65), 2.38 (d, 2 H, C≡CCH_2), 3.0 (s, 2 H, PhCH_2), 7.3 (s, 5 H, Ph); MS, m/z 202 (M^+), 187, 157, 111.

General Procedure for Iodolactonization. Iodo enol lactones were prepared according to the procedure of Krafft and Katzenellenbogen.[7] Typically, to a solution of 2 mmol of the acetylenic acid in 25 mL CH_2Cl_2 were added sequentially 2 mmol of *N*-iodosuccinimide, 2 mmol of $NaHCO_3$, and 0.5 mL of 0.4 M tetrabutylammonium hydroxide (40% in water; Aldrich). The reaction mixture was stirred vigorously for 30 min and then diluted with 50 mL of CH_2Cl_2. The resulting mixture was extracted with 5% sodium thiosulfate solution, brine, and water. The CH_2Cl_2 layer, which had been dried over Na_2SO_4, was evaporated to an oil, which was further purified by flash column chromatography (silica gel 60, 10% EtOAc and petroleum ether). Most iodo enol lactones were unstable and therefore were used immediately without any further purification. The following compounds were prepared by this procedure from the ω-acetylenic acids indicated in the text and Scheme III.

5(*E*)-(Iodomethylene)tetrahydro-2-furanone (10a): 89%; IR 1810, 1655; ^{1}H NMR δ 2.8 (m, 4 H, H3, H4), 5.8 (m, 1 H, C=CH).

3-Benzyl-5(*E*)-(iodomethylene)tetrahydro-2-furanone (10b): 72.4%; oil, IR 3020, 3080, 1800, 1655; ^{1}H NMR 2.6–3.3 (m, 5 H, H3, H4, PhCH_2), 5.8 (m, 1 H, C=CH), 7.3 (m, 5 H, Ph).

3-Isopropyl-5(*E*)-(iodomethylene)tetrahydro-2-furanone (10c): 81.5%; oil, IR 1800, 1650; ^{1}H NMR δ 0.95, 1.04 (2d, 6 H, $2CH_3$), 2.2 [m, 1 H, CH(CH_3)$_2$], 2.8 (m, 3 H, H3, H4), 5.8 (m, 1 H, C=CH).

3-Butyl-5(*E*)-(iodomethylene)tetrahydro-2-furanone (10d): 70%; oil; IR 3080, 1800, 1655; ^{1}H NMR δ 0.9 (m, 3 H, CH_3), 1.3 (m, 6 H, $CH_2CH_2CH_2$), 2.4–3.1 (m, 3 H, H3, H4), 5.8 (dd, 1 H, C=CH, J = 1.9, 2.3).

6(*E*)-(Iodomethylene)tetrahydro-2-pyrone (14a): 81%; IR 1750, 1610; ^{1}H NMR δ 1.63–1.95 (m, 2 H, H4), 2.40–2.78 (m, 4 H, H3, H5), 5.93 (t, 1 H, J= 1.9).

3-Benzyl-6(*E*)-(iodomethylene)tetrahydro-2-pyrone (14b): 73%; IR 1750, 1620; ^{1}H NMR δ 1.7 (m, 2 H, H.4), 2.5–2.8 (m, 4 H, PhCH_2, H5), 3.2 (m, 1 H, H3), 5.9 (dd, 1 H, C=CH, J = 1.5, 1.6), 7.2 (m, 5 H, Ph).

3-Benzyl-3-methyl-5(*E*)-(iodomethylene)tetrahydro-2-furanone (31): 80%; mp 75–78 °C; IR 1788, 1657; ^{1}H NMR δ 1.4 (s, 3 H, CH_3), 2.75, 3.1 (AB q, 2 H, PhCH_2, J_{AB} = 13.3), 2.5, 2.95 (ABX, 2 H, H4, J_{AB} = 17.7, $J_{CH_2,C=CH}$ = 1.9, 2.1), 5.6 (dd, 1 H, J = 1.9, 2.1), 7.3 (m, 5 H, Ph); MS, m/z 328 (M^+), 237 (M^+ – PhCH_2), 201 (M^+ – I).

5(*Z*)-(Iodomethylene)tetrahydro-2-furanone (11a). Iodine (1 g) was added to a solution of 5(*E*)-(iodomethylene)tetrahydro-2-furanone (**10a**; 500 mg, 2.2 mmol) in CH_2Cl_2 (50 mL). The mixture was protected from light and stirred at room temperature for 26 h, diluted with CH_2Cl_2 (100 mL), and washed with 5% sodium thiosulfate and the brine. TLC analysis of this solution showed two spots (R_f 0.2, 0.5; 20% EtOAc/petroleum ether). The solution was dried over $MgSO_4$ and evaporated to an oil. NMR analysis of this oil showed that this material contained a 4:1 mixture of *E*:*Z* isomers (based on integration of the olefinic protons at δ 5.8 and 5.2). The two isomers were separated by column chromatography (20% EtOAc/petroleum ether) to give 320 mg of the *E* isomer and 80 mg of the *Z* isomer. Alternatively, mercuric trifluoroacetate (1.43 g, 3.3 mmol) was added to a solution of 5-iodo-4-pentynoic acid[35] (300 mg, 1.3 mmol) in 25 mL of CH_2Cl_2. The reaction mixture, which was stirred in the dark for 52 h at room temperature in a stoppered flask, was then diluted with CH_2Cl_2 (25 mL), extracted with saturated $NaHCO_3$, and washed with brine. The organic layer was dried ($MgSO_4$) and evaporated to a solid (60 mg, 20%): mp 78–79 °C, IR 3080, 3000, 1810, 1660; ^{1}H NMR δ 2.8 (m, 4 H, H3, H4), 5.2 (m, 1 H, C=CH).

3-Benzyl-5(*Z*)-(iodomethylene)tetrahydro-2-furanone (11b). The title compound was generated from **10b** (4.53 g) by the isomerization procedure described for the preparation of **11a**. Workup after 90 h of reaction time gave the *E*:*Z* isomers (3:1, based on integration ratio of protons at δ 5.75 and 5.15). The isomers were separated by column chromatography (8% EtOAc/petroleum ether: *E* isomer, R_f 0.5, 1.99 g; *Z* isomer, R_f 0.75, 0.43 g. A column fraction that contained a mixture of *E*:*Z* isomers (0.4:1, 430 mg) was also isolated. **11b**: IR 1810, 1665; ^{1}H NMR δ 2.7–3.3 (m, 5 H, H3, H4, CH_2Ph), 5.2 (dd, 1 H, C=CH, J = 1.35, 2.0), 7.2 (m, 5 H, Ph); MS, m/z 314 (M^+), 223 (M^+ – PhCH_2) 187 (M^+ – I); exact mass calcd 313.9803, found 313.9794.

5(*E*)-[3-(Trimethylsilyl)prop-2-ynylidene]tetrahydro-2-furanone (30). A three-neck flask was equipped with argon gas inlet, outlet, and septum and was flushed with argon. A solution of 1.77 g (7.9 mmol) of 5-(*E*)-(iodomethylene)tetrahydro-2-furanone (**10a**) was added to the flask, followed by 109 mg (0.155 mmol) of bis(triphenylphosphine)palladium-(II) chloride and 106 mg (0.555 mmol) of cuprous chloride. (Trimethylsilyl)acetylene (1.08 mL, 9.25 mmol) was added, and the resulting mixture was stirred at 35 °C for 6 h. The reaction mixture was diluted with CH_2Cl_2, and then the solvent was evaporated, leaving a residue that was extracted with toluene and filtered. The toluene extract was evaporated to an oil, which was further purified by column chromatography on silica gel (elution gradient: hexane → 10% EtOAc/hexane). This procedure yielded the title compound after recrystallization from hexane: 680 mg (44%); mp 51.5–52 °C; IR ($CHCl_3$) 2130, 1800, 1662; ^{1}H NMR δ 0.2 (br s, 9 H, Me_3Si), 2.8, 3.1 (2 m, 4 H, H3, H4), 5.35 (t, 1 H, C=CH, J = 2.1); ^{13}C NMR δ 24.5, 26.8 (CH_2CH_2), 86.7 (*H*C=C), 98.8, 99.2 (C≡C), 162.3 (C5), 173.8 (CO).

5(*E*)-Prop-2-ynylidenetetrahydro-2-furanone (1a). To a solution of 5(*E*)-[(3-trimethylsilyl)prop-2-ynylidene]tetrahydro-2-furanone (250 mg, 1.29 mmol) in 5 mL of absolute EtOH under argon at 0 °C was added a solution of silver nitrate (0.879 g, 5.17 mmol) in 7 mL of water. A white suspension was formed immediately, which was stirred for 30 min at 0 °C in the dark. Meanwhile, a solution of 2 g (30.7 mmol) of potassium cyanide in 20 mL of water was prepared. The reaction mixture was mixed with 5 mL of CH_2Cl_2 and poured into the KCN solution with rapid stirring. The mixture was extracted with CH_2Cl_2 (2 × 25 mL). The CH_2Cl_2 layer was dried over Na_2SO_4 and then evaporated to a solid. The solid was recrystallized from CH_2Cl_2/hexane (9:1) to give the title compound: 70 mg (44.5%); mp 87–88 °C; IR ($CHCl_3$), 3300, 2100, 1810, 1660; ^{1}H NMR δ 2.8 (m, 2 H, H3), 3.1 (d, 1 H, C≡CH, J = 2.4), 3.1 (m, 2 H, H4), 5.4 (dt, 1 H, C=CH, J = 2.4); MS, m/z 122 (M^+), 94 (M^+ – CO).

3-Benzyl-5(*E*)-prop-2-ynylidenetetrahydro-2-furanone (1b). 3-Benzyl-5(*E*)-[3-(trimethylsilyl)prop-2-ynylidene]tetrahydro-2-furanone was prepared from **10b**: 41%; mp 68–69 °C (hexane); IR ($CHCl_3$) 2120, 1800, 1660; ^{1}H NMR δ 0.2 (s, 9 H, Me_3Si), 2.6–3.2 (m, 5 H, H3, H4, PhCH_2), 5.3 (m, 1 H, C=CH), 7.1–7.4 (m, 5 H, Ph); MS, m/z 284 (M^+), 269 (M^+ – CH_3), 194 (M^+ – PhCH_2). Desilylation with $AgNO_3$/KCN as above gave 3-benzyl-5(*E*)-prop-2-ynylidenetetrahydro-2-furanone (**1b**): 31%; mp 64–65 °C (ether/hexane, 1:10); IR ($CHCl_3$) 3300, 2100, 1800, 1600; ^{1}H NMR δ 2.9 (d, 1 H, C≡CH), 2.5–3.2 (m, 5 H, H3, H4, PhCH_2), 5.2 (m, 1 H, C=CH), 7.2 (m, 5 H, Ph); MS, m/z 212 (M^+), 145, 66, 91; exact mass (M^+) calcd 212.0837, found 212.0848, (M^+ – CO) calcd 184.0881, found 184.0879. Anal. Calcd for $C_{14}H_{12}O_2$: C, 79.22; H, 5.70. Found: C, 79.15; H, 5.87.

3-Isopropyl-5(*E*)-prop-2-ynylidenetetrahydro-2-furanone (1c). 3-Isopropyl-5(*E*)-[3-(trimethylsilyl)prop-2-ynylidene]tetrahydro-2-furanone, prepared from **10c**, was purified by vacuum distillation: 45%; bp 118–120 °C (1 mmHg); ^{1}H NMR δ 0.2 (s, 9 H, Me_3Si), 1.0 (t, 6 H, $2CH_3$), 2.2 [m, 1 H, CH(CH_3)$_2$], 2.6–3.1 (m, 3 H, H3, H4), 5.3 (dd, 1 H, C=CH, J = 2.1, 2.2); MS, m/z 236 (M^+), 215, 73. Desilylation with $AgNO_3$/KCN as above gave 3-isopropyl-5(*E*)-prop-2-ynylidenetetrahydro-2-furanone (**1c**): 75%, IR 3280, 1805, 1665; ^{1}H NMR δ 1.0 (t, 6 H, $2CH_3$), 2.1 [m, 1 H, CH(CH_3)$_2$], 2.8 (m, 3 H, H3, H4), 3.1 (d, 1 H, J = 2.1, C≡CH), 5.3 (m, 1 H, C=CH); MS, m/z 164 (M^+), 149 (M^+ – CH_3) 121 (M^+ – *i*-Pr); exact mass (M^+) calcd 164.0837, found 164.0844, (M^+ – CH_3) calcd 149.06025, found 149.0603, (M^+ – Pr) calcd 121.0290, found 121.0286.

3-Butyl-5(*E*)-prop-2-ynylidenetetrahydro-2-furanone (1d). 3-Butyl-5(*E*)-[3-(trimethylsilyl)prop-2-ynylidene]tetrahydro-2-furanone was prepared from **10d** and purified by vacuum distillation: 56%; bp 140–144 °C (1 mmHg); IR 2130, 1810, 1660; ^{1}H NMR δ 0.2 (s, 9 H, Me_3Si), 0.9 (m, 3 H, CH_3), 1.4 (m, 6 H, $CH_2CH_2CH_2$), 2.8 (m, 3 H, H3, H4), 5.3 (m, 1 H, C=CH); MS, m/z 250 (M^+), 193 (M^+ – Bu), 138, 111; exact mass (M^+) calcd 250.1389 found 250.1358, (M^+ – CH_3) calcd 235.1154, found 235.1117. Desilylation with $AgNO_3$/KCN gave **1d**, which was purified by vacuum distillation (the distillate turned red on standing at room temperature): 68.4%; bp 108–110 °C (1 mmHg); IR ($CHCl_3$) 3300, 2100, 1805, 1655; ^{1}H NMR δ 0.9 (br t, 3 H, CH_3), 1.4 (m, 6 H, $CH_2CH_2CH_2$), 2.8 (m, 3 H, H3, H4), 3.1 (d, 1 H, C≡CH, J = 2.2), 5.25 (m, 1 H, C=CH); MS, m/z 178 (M^+), 111, 66, 28; exact mass (M^+) calcd 178.0994, found 178.0999, (M^+ – Bu) calcd 121.0290, found 121.0286, (M^+ – COEt) calcd 121.0653, found 121.0649.

5(*E*)-2-Octynylidenetetrahydro-2-furanone (1e). This compound was prepared after **1f**. Cuprous heptyne[36] was used in place of cuprous phenylacetylide, and the product was isolated as an oil after workup and column chromatography (10% EtOAc in petroleum ether): 7.6%; IR 1815, 1665; ^{1}H NMR δ 0.9 (m, 3 H, CH_3), 1.5 (m, 6 H, $CH_2CH_2CH_2$), 2.3 (m, 2 H, C≡CCH_2), 2.8, 3.2 (2m, 4 H, H3, H4), 5.3 (m, 1 H, C=CH); MS, m/z 193 (MH^+).

5(*E*)-(3-Phenylprop-2-ynylidene)tetrahydro-2-furanone (1f). A mixture of cuprous phenylacetylide[36] (0.65 g, 4.0 mmol) and 5(*E*)-(iodomethylene)tetrahydro-2-furanone (0.809 g, 3.6 mmol) in 20 mL of dry

(35) Ueno, A.; Maeda, T. *Yakugaku Zasshi* **1970**, *90*, 1578–1580.

(36) Castro, C. E.; Gaughan, E. J.; Owsley, D. C. *J. Org. Chem.* **1966**, *31*, 4071–4078.

DMF was heated under argon at 110 °C for 1.5 days. The solution was cooled and partitioned between ether and water. The ether layer was dried over $MgSO_4$ and then evaporated to an oil. The oil was purified by repeated column chromatography on silica gel (elution gradient: 10% → 20% EtOAc in petroleum ether) to give **1f**: 0.4 g (64%); mp 90–91 °C; IR 1810, 1655; ^{1}H NMR δ 2.8, 3.2 (2 m, 4 H, H3, H4), 5.6 (t, 1 H, C=CH, J = 2.2), 7.3 (m, 5 H, Ph); MS, m/z 198 (M^+), 170 (M^+ − CO).

3-Benzyl-5(*E*)-but-2-ynylidenetetrahydro-2-furanone (1g). To a solution of **10b** (1.1 g, 3.2 mmol) in dry THF (6 mL) and anhydrous triethylamine (11 mL) under argon was added bis(triphenylphosphine)-palladium(II) chloride (0.1 g, 0.14 mmol) and cuprous iodide (0.09 g, 0.47 mmol). Propyne gas was bubbled into the reaction mixture slowly over a period of 30 min. The mixture was stirred at room temperature for 2 h and diluted with CH_2Cl_2. Insoluble material was removed by filtration through Celite and the filtrate evaporated to give an oil that was further purified by column chromatography (3% EtOAc in petroleum ether) to give a brownish solid: 0.4 g (50.5%); mp 74–76 °C; IR 1800, 1665; ^{1}H NMR δ 1.95 (d, 3 H, CH_3, J = 2.3), 2.8–3.1 (m, 5 H, H3, H4, $PhCH_2$), 5.2 (m, 1 H, C=CH), 7.2 (m, 5 H, Ph); MS, m/z 226 (M^+), 211.

5(*Z*)-Prop-2-ynylidenetetrahydro-2-furanone (2a). 5(*Z*)-[3-(Trimethylsilyl)prop-2-ynylidene]tetrahydro-2-furanone was prepared by a procedure analogous to that described for **30** using **11a** as substrate: 81% mp 114–115 °C (pentane/CH_2Cl_2, 9:1); IR ($CHCl_3$) 1810, 2110, 1670; ^{1}H NMR δ 0.2 (s, 9 H, Me_3Si), 2.8 (m, 4 H, H3, H4), 4.8 (t, 1 H, C=CH, J = 1.7). Anal. Calcd for $C_{10}H_{14}O_2Si$: C, 61.82; H, 7.26. Found: C, 61.68; H, 7.04. Desilylation with KCN/$AgNO_3$ gave **2a**: 68%; mp 84–85 °C; IR ($CHCl_3$) 3270, 1810, 1665; ^{1}H NMR δ 2.8 (m, 4 H, H3, H4), 3.1 (d, 1 H, J = 2.4, C≡CH), 4.8 (m, 1 H, C=CH). Anal. Calcd for $C_7H_6O_2$: C, 68.84; H, 4.95. Found: C, 68.83; H, 4.88.

3-Benzyl-5(*Z*)-prop-2-ynylidenetetrahydro-2-furanone (2b). 3-Benzyl-5(*Z*)-[3-(trimethylsilyl)prop-2-ynylidene]tetrahydro-2-furanone was prepared from **11b**. Workup and column chromatography (10% EtOAc in petroleum ether) gave 3-benzyl-5(*Z*)-[3-(trimethylsilyl)prop-2-ynylidene]tetrahydro-2-furanone (R_f 0.43) and 3-benzyl-5(*E*)-[3-(trimethylsilyl)prop-2-ynylidene]tetrahydrofuran-2-one (R_f 0.6) in a 4:1 ratio. 3-Benzyl-5(*Z*)-[3-(trimethylsilyl)prop-2-ynylidene]tetrahydrofuran-2-one: 32.5%; IR 2120, 1810, 1670; ^{1}H NMR δ 0.2 (br s, 9 H, Me_3Si), 2.8–3.2 (m, 5 H, H3, H4, $PhCH_2$), 4.8 (m, 1 H, C=CH), 7.2 (m, 5 H, Ph); MS, m/z 284 (M^+), 193 (M^+ − $PhCH_2$), 73. Desilylation with $AgNO_3$/KCN gave **2b**: 28%; IR ($CHCl_3$) 3300, 1805, 1670; ^{1}H NMR δ 2.8–3.2 (m, 5 H, H3, H4, $PhCH_2$), 3.1 (d, 1 H, C≡CH, J = 2.5), 4.8 (m, 1 H, C=CH), 7.2 (m, 5 H, Ph); MS, m/z 212 (M^+), 121 (M^+ − $PhCH_2$), 145; exact mass calcd 212.0837, found 212.0833.

3-Benzyl-3-methyl-5(*E*)-prop-2-ynylidenetetrahydro-2-furanone (3). 3-Benzyl-3-methyl-5(*E*)-[3-(trimethylsilyl)prop-2-ynylidene]tetrahydro-2-furanone was prepared from **31**: 66%; IR 1800, 1663; ^{1}H NMR δ 0.2 (s, 9 H, Me_3Si), 2.4 (s, 3 H, CH_3), 2.63, 3.08 (ABX, 2 H, H4, J_{AB} = 16, $J_{CH_2,C=CH}$ = 2.2), 2.75, 3.1 (AB q, 2 H, J_{AB} = 12, $PhCH_2$), 5.2 (dd, 1 H, C=CH, J = 2.2, 2.2), 7.3 (m, 5 H, Ph). Desilylation with $AgNO_3$/KCN gave **3**: 63%; mp 79–80 °C (hexane); IR ($CHCl_3$) 3280, 2102, 1795, 1660; ^{1}H NMR δ 1.38 (s, 3 H, CH_3), 3.1, 2.7 (ABX, 2 H, H4, J_{AB} = 18, $J_{CH_2,C=CH}$ = 2), 3.12, 2.75 (AB q, 2 H, $PhCH_2$, J_{AB} = 13.1), 3.0 (d, 1 H, C≡CH, J = 2), 5.14 (ddd, 1 H, C=CH, $J_{CH_2,C=CH}$ = 2); MS, m/z 226 (M^+), 91.

6(*E*)-(3-Phenylprop-2-ynylidene)tetrahydro-2-pyrone (4a). The lactone **4a** was prepared from **14a** in the manner employed for **1f**: 52% mp 79–80 °C (hexane/CH_2Cl_2, 4:1); IR 1760, 1640; ^{1}H NMR δ 2.0 (m, 2 H, H4), 2.6–3.0 (m, 4 H, H3, H5), 5.5 (m, 1 H, C=CH), 7.3 (m, 5 H, Ph); MS, m/z 212 (M^+).

6(*E*)-Oct-2-ynylidenetetrahydro-2-pyrone (4b). The lactone **4b** was prepared from **14a** and cuprous heptyne according to the procedure used for **1f**: oil, 13%; IR 1760, 1640; ^{1}H NMR δ 0.9 (m, 3 H, CH_3), 1.2–1.8 (m, 6 H, $CH_2CH_2CH_2$), 2.0 (m, 2 H, H4), 2.3 (m, 2 H, C≡CCH_2), 2.5–3.2 (m, 4 H, H3, H5), 5.2 (m, 1 H, C=CH); MS, m/z 206 (M^+), 149, 135.

3-Benzyl-6(*E*)-prop-2-ynylidenetetrahydro-2-pyrone (4c). 3-Benzyl-6(*E*)-[3-(trimethylsilyl)prop-2-ynylidene]tetrahydro-2-pyrone was prepared from **14b**: 91%; IR 2130, 1780, 1635; ^{1}H NMR δ 0.2 (s, 9 H, Me_3Si), 1.6 (m, 2 H, H4), 2.5–3.0 (m, 4 H, $PhCH_2$, H5), 3.2 (m, 1 H, H3), 5.2 (br s, 1 H, C=CH), 7.2 (m, 5 H, Ph). Desilylation with $AgNO_3$/KCN gave **4c**: 71%; mp 62–64 °C (hexane); IR ($CHCl_3$) 2178, 1755, 1636; ^{1}H NMR δ 1.4–2.0 (m, 2 H, H4), 2.5–3.0 (m, 3 H, $PhCH_2$, H3), 3.1 (d, 1 H, C≡CH, J = 2.4), 3.0–3.4 (m, 2 H, H5), 5.2 (m, 1 H, HC=C), 7.2–7.3 (m, 5 H, Ph); MS, m/z 226 (M^+), 91.

Alkaline Hydrolysis Product of 1b. To a suspension of 52 mg of **1b** in 2 mL of water was added 2 mL of 1 M NaOH. After being stirred at ambient temperature for 5 h, the yellow solution was acidified with 2.1 mL of 1 M HCl and extracted with EtOAc. The organic phase was dried with Na_2SO_4, treated with charcoal, filtered, taken to dryness, and redissolved in ether. Excess diazomethane in ether was added to this solution, the reaction was quenched with silica gel, and the major product (methyl-2-benzyl-4,6-dioxoheptanoate, mixture of diketo and enol tautomers) was isolated by preparative TLC (EtOAc/petroleum ether, 1:1): oil; IR 1780 (m), 1740 (s), 1610 (br), 1500 (m), 704 (s); ^{1}H NMR δ 2.00, 2.10, 2.19 (s, enol and keto CH_3), 2.2–3.3 (m), 3.63, 3.65 (s, enol and keto $COOCH_3$), 5.44 (s, enol H5), 7.1–7.4 (m, Ph); ^{13}C NMR δ 23.8 (enol CH_3), 51.7 (OCH_3), 58.0 (keto C5), 100.1 (enol C5), 128.3–129.3 (Ph), 174.8, 188.1, 193.8 (enol C1, C6, C4); MS, m/z 262 (M^+), 231, 220, 205, 163, 131, 91; exact mass (M^+) calcd 262.1205, found 262.1201.

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