methoxide in methanol solution (obtained from 0.5 g of Na and 10 mL of methanol). This addition was followed by 5 mL of THF and 6 mL of a 1 M solution of BH_3 in THF. After being stirred overnight at room temperature, the solvent was distilled off and the residue dissolved in 25 mL of benzene. Sodium chloride was decanted and the supernatant used for the reductions.

Reductions with Lanthanoid Tetrahydroborates. The keto compound (1 mmol) in 1 mL of THF or methanol under a nitrogen atmosphere was treated by 3 to 5 mL of the reagent solution, stirred for 5–30 min at room temperature, and then hydrolyzed, worked-up as usual, and analyzed by VPC. For example, in THF solution cyclohexenone yields 80% cyclohexanol and 20% cyclohexenol. Norcamphor gives 80% of the endo alcohol and 20 of the exo alcohol.

Methanolysis of $NaBH_4$ in the Presence of $CeCl_3$. A two-necked round-bottom flask (50 mL) was equipped with a magnetic stirring bar, a 20 mL equalized pressure dropping funnel, and a tube connected to a graduated cylinder filled with saturated aqueous NaCl. $NaBH_4$ (20 mg) is placed in the flask and 10 mL of a methanol solution of $CeCl_3$ in the funnel. The expected total H_2 volume is 47 mL. At t_0, the solution is added onto $NaBH_4$ with vigorous stirring. The gas volume evolved is measured by a direct reading. The estimated error is ca. 5 mL for rapid evolutions and 0.5 mL for slow evolutions. Reproducibility was found under the error limits and the curves result from at least three measurements.

Acknowledgment. The authors wish to thank G. Ullman and L. Rodriguez-Hahn for their participation to this work and C. A.P.E.S. (Brazil) for a fellowship (A.L.G.). Numerous and fruitful discussions with Dr. A. E. Greene, M. A. Teixeira, and C. Le Drian are acknowledged. Thanks are due to Mrs. A. Marquet and J. Seyden-Penne for their highly valuable comments and to R. O. Hutchins for his corrections and improvements of the manuscript.

Synthesis of Halo Enol Lactones. Mechanism-Based Inactivators of Serine Proteases[1]

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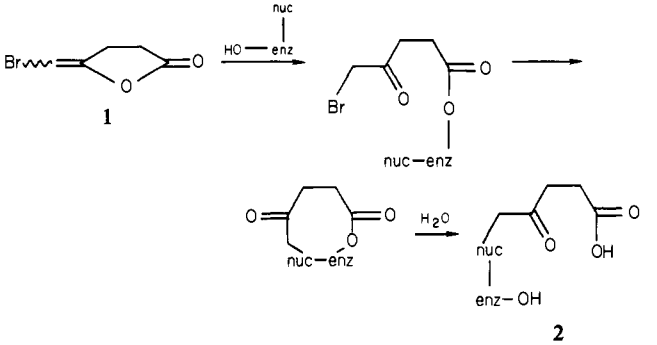
Contribution from the Roger Adams Laboratory, School of Chemical Sciences, University of Illinois, Urbana, Illinois 61801. *Received January 19, 1981*

Abstract: Enol lactones bearing a halogen at the vinylic position are potential mechanism-based inactivators (suicide inactivators) of serine hydrolases, since acyl transfer to the active-site serine releases an α-halo ketone that can react with nucleophilic sites in the active-site region. Efficient syntheses of such halo enol lactones needed for enzymatic studies are described. 5-Hexynoic acids can be cyclized with mercuric ion catalysis to γ-methylene butyrolactones. Cyclization of the 6-bromo and 6-chloro analogs leads stereospecifically to the *Z*-halo enol lactones (trans addition), but is quite slow. Cyclization of unsubstituted or 6-methyl- or 6-trimethylsilyl-substituted 5-hexynoic acids is more rapid, but olefin isomerization occurs during the reaction. Direct halogenation of γ-methylene butyrolactones leads to preferential elimination in an endocyclic sense, producing the undesired 5-bromomethylidene-2(3*H*)-furanones; however, the 5-trimethylsilylmethylene and the 5-mercuriomethylene butyrolactones can be converted with moderate efficiency into the desired 5-bromomethylene butyrolactones. The most efficient approach is direct halolactonization of the 5-hexynoic acids with bromine or iodine in a two-phase system with phase-transfer catalysis. This method was used to prepare various 5-halomethylene or 5-haloethylidene 2-phenylbutyrolactones and 6-bromo- and iodomethylene valerolactones. In certain cases where undesired enolization is blocked, γ-halomethylene butyrolactones can be prepared by cyclization of α-halo keto acids (e.g., *o*-(bromomacetyl)benzoic acid to 5-bromomethylidenebenzo-2(5*H*)-furanone), and certain endocyclic halo enol lactones can be prepared by Baeyer–Villiger oxidation of cyclic 3-halo 2-enones. Preliminary studies indicate that these halo enol lactones have reasonable hydrolytic stability, and, in studies presented elsewhere, selected compounds have been found to be efficient inactivators of chymotrypsin.

Introduction

Significant attention in recent years has been focused on mechanism-based enzyme inactivators, also known as suicide substrates.[2] Utilizing its catalytic machinery, the targeted enzyme plays the essential role of unmasking a latent reactive functional group contained in the suicide substrate molecule, revealing a reactive electrophilic species for alkylation of the enzyme. The potential for generating reactive species exclusively within the active site of the enzyme imparts a much higher degree of selectivity of these inactivators than that exhibited by conventional affinity reagents. Thus, suicide inactivators have found utility in in vitro enzyme studies and in in vivo biochemical investigations,[3] and several have shown promise as clinically useful drugs.[4]

Scheme I



In 1974, Rando[5] proposed that halo enol lactones such as **1**, which on hydrolysis form α-halo ketones (Scheme I), might function as suicide inactivators for serine proteases and estereases, by reaction with proximal active-site nucleophiles, ultimately forming the modified (inactivated) enzyme **2**. This has prompted us to develop efficient synthetic routes to **1** and to related structures

(1) Preliminary aspects of this work were presented at the 178th National Meeting of the American Chemical Society, Washington, D.C. Sept 1979.

(2) See, for instance: (a) Seiler, N.; Jung, M. J.; Koch-Weser, J.; Eds., "Enzyme-Activated Irreversible Inhibitors"; Elsevier/North Holland Biomedical Press; Amsterdam, 1978. (b) Rando, R. R. *Acc. Chem. Res.* **1975** *8*, 281. (c) Bloch, K. In "The Enzymes", (3rd ed.;) Boyer, P., Ed.; Academic Press: New York, 1971; Vol. 5, p 441. (d) Abeles, R. H. Maycock, A. L. *Acc. Chem. Res.* **1976**, **9**, 313. (e) Walsh, C. *Horiz. Biochem. Biophys.* **1977**, *3*; 36.

(3) (a) Fisher, J.; Charnias, R.; Knowles, J. R. *Biochemistry* **1978**, *17*, 36. Charnas, R.; Fischer, J.; Knowles, J. R. *Ibid.*, **1978**, *17*, 2185. (b) Wiseman, J.; Abeles, R. *Ibid.*, **1979**, *18*; 427. (c) Prakash, N. J.; Schechter, P. J.; Mamont, P. S.; Grove, J.; Koch-Weser, J.; Sjoerdsma, A. *Life Sci.* **1980**, *26*, 181.

(4) (a) Metcalf, B. W. *Biochem. Pharmacol.* **1979**, *28*, 1705. (b) Massey, V.; Kamai, H.; Palmer, G.; Elion, G. *J. Biol. Chem.* **1970**, *245*, 2387.

(5) Rando, R. R. *Science* **1974**, *185*, 320.

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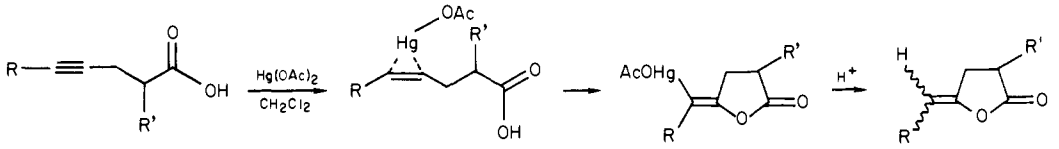
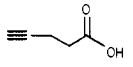
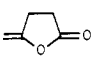
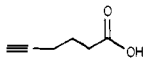
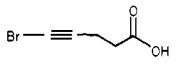
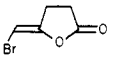
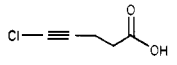
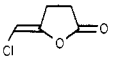
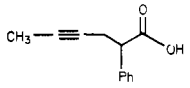
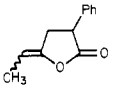
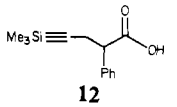
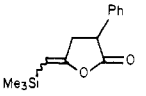
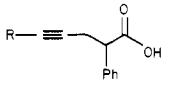
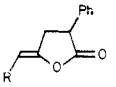
Table I. Mercury-Mediated Lactonizations[a]



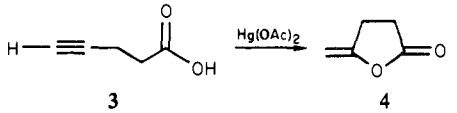
reactant	product	reaction time,[b] h		isolated yield, %	
		$Hg(OAc)_2$	$Hg(OTFA)_2$	$Hg(OAc)_2$	$Hg(OTFA)_2$
 **3**	 **4**	8	2.0	75	81
 **5**	 **8**	10	2.5	69	80
 **6**	 **1a**	48	40	60	62
 **7**	 **9**	>60	>60	49	55
 **10**	 **11**	18	4.5	76	86
 **12**	 **13**	5	0.5	51	62
 **14**, R = H **16**, R = D	 **15**, R = H **17**, R = D	10	2.0	70	84

[a] Reactions were run on 2.0 mmol scale in 20 mL of CH_2Cl_2 at 25 °C; 10 mol % catalysts was used. [b] Determined by TLC.

which contain reactive functional groups that are hydrolytically revealable. In this report we describe several synthetic approaches that lead to a variety of halo-enol lactones, the most efficient method being the direct halolactonization of acetylenic acids that is discussed near the end. Biochemical studies documenting that these lactones act as enzyme-activated irreversible inhibitors of chymotrypsin will be described elsewhere.[6]

Results and Discussion

Mercury-Mediated Lactonization. In an earlier publication,[7] we reported the mercury-catalyzed cyclization of acetylenic acids to give γ-methylene butyrolactones (eq 1). We have extended

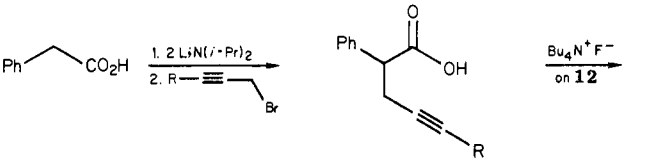


3 **4** (1)

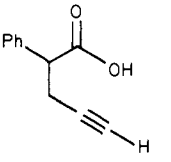
the investigation of this reaction in an effort to optimize reaction conditions and achieve an efficient synthesis of the desired halo enol lactones.

The simple acetylenic acid reactants for these cyclization reactions (cf. Table I, **3**, **5**, **6**, **7**) were prepared by standard techniques described in the Experimental Section. The synthesis of the 2-phenyl-substituted acids **10**, **12**, and **14** is shown in Scheme II.

Scheme II



10, R = CH_3 (90%)
12, R = $Si(CH_3)_3$ (84%)



14 (100%)

The mercury-catalyzed lactonization of the acetylenic acids was carried out in dichloromethane at room temperature; the rate and yield of cyclization were found to be dependent upon several factors (Table I). Mercury trifluoroacetate was substantially more effective than mercury acetate in catalyzing the lactonization of all compounds tested. Addition of 1 mol % methanesulfonic acid or trifluoroacetic acid to reactions catalyzed by mercury acetate resulted in rates comparable to those obtained with mercury trifluoroacetate (data not shown), suggesting that the rate-determining step involves protonation of the vinylic mercury intermediate to regenerate the catalyst. The yields in the reactions

(6) Krafft, G. A.; Katzenellenbogen, J. A.; Chakravarty, P. K. *J. Biol. Chem.*, submitted for publication.
(7) Amos, R. A.; Katzenellenbogen, J. A. *J. Org. Chem.* **1978**, *43*, 560.

Table II. Isomer Distribution in Mercury Lactonization[a]

reactant	product	time, h	isomer distribution Z : E
6, R = Br; R' = H	1	40	95 : 5
16, R = H; R' = Ph; -OD	17	2	30 : 70
10, R = CH_3; R' = Ph	11	4.5	64 : 36
12, R = TMS; R' = Ph	13	0.5	55 : 45

[a] Ratio determined by ^1H NMR at completion of the reaction.

with added acid were also comparable, with the exception of the trimethylsilyl derivative **12** and methanesulfonic acid, where significant desilylation occurred to give the unsubstituted lactone **15** (data not shown).

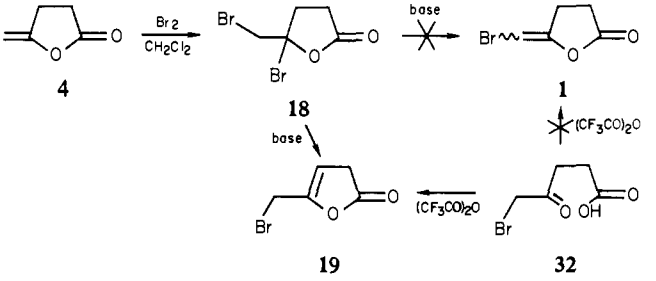
The ability of the acetylenic substitutents to stabilize developing positive charge of the mercuronium species in the transition state also influenced the reaction rate significantly. Thus, the trimethylsilyl group, which was most effective in providing positive charge stabilization at the β carbon, gave the most rapid cyclization (cf. **12**), while the bromine and chlorine substituents (cf. **6** and **7**) gave the slowest rate, owing to inductive destabilization of the developing cation. For these halogenated acetylenic acids, the addition of mercury to the alkyne appears to become the rate-limiting factor, as evidenced by the comparable reaction times for mercury acetate and mercury trifluoroacetate. The isolated yields for the methyl- and protio-substituted lactones **4**, **8**, **11**, and **15** were quite good; however, the trimethylsilyl and halogenated derivatives (**2**, **9**, and **13**) suffered significant desilylation and dehalogenation, respectively, substantially lowering yields.

The lactonization proceeds stereoselectively, with attack of the carboxylate on the mercuronium ion with inversion.[8] ^{13}C NMR was used to identify the initially formed isomer from **10** as the *Z* isomer **11a**. The resonance of the allylic methylene carbon in the initially formed isomer appears at 34.4 ppm, while that of the other isomer appears upfield at 27.3 ppm, because of the greater shielding effect of the adjacent (cis) methyl group in the latter isomer, relative to the adjacent proton in the former isomer. This is a well-established phenomenon for a variety of trisubstituted olefins.[9] However, during the reaction, the lactones undergo olefin isomerization, resulting in a mixture of geometric isomers (Table II). The isomerization presumably occurs via readdition of mercury to the olefin of the lactones. Thus, when the *Z* isomer **11a** was treated with mercury trifluoroacetate for 17 h, a 1:1 isomer ratio was obtained. The isomerization rate is enhanced for products with substituents which stabilize the developing carbocation upon readdition of mercury to the olefin. Thus, the trimethylsilyl derivative **13** isomerizes completely during the reaction time, while methyl and protio–deuterio derivatives **11** and **17**, respectively, isomerize more slowly. The halogenated derivatives undergo negligible isomerization, in spite of the substantially longer reaction times for cyclization.

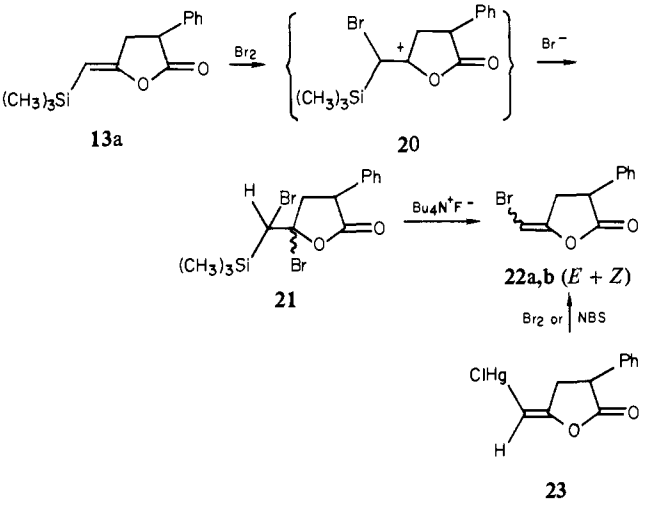
Ca. 5–15 mol % of mercury catalyst appears to be optimum in terms of the rate and efficiency of the lactonization; reaction times increased significantly with less catalyst, while the isolated yields of the lactones generally decreased with greater amounts of catalyst. As an example, stoichiometric reaction of **14** with mercury trifluoroacetate afforded the lactone **15** in 64% isolated yield, compared with an 84% yield with 10% catalyst.

Halogenation of Enol Lactones. The synthesis of the target halo enol lactones (e.g., **1**, **9**) by the direct mercury-mediated cyclization of the halo acetylenic acids proved to be less efficient then cyclization of the parent acids to the nonhalogenated enol lactones (e.g., **4**, **11**, **15**). Therefore, production of the halo enol lactones by direct halogenation of the enol lactones was explored.

Scheme III



Scheme IV



Bromination of the lactone **4** with bromine in dichloromethane (Scheme III) afforded the dibromide **18**, which was stable in solution for several hours at room temperature. Treatment of the dibromide with a large variety of bases (e.g., DBU, Et_3N, pyridine, NaOAc, NaH, sodium ethoxide, lithium diisopropylamide), silica gel, and alumina or heating did induce the elimination of HBr; however, the elimination invariably occurred with the undesired regiochemistry, affording the unstable allylic bromide **19**. None of the vinyl bromide **1** could be detected. A similar preference for endocyclic position of the double bond is related lactones has been noted previously.[10]

The regiochemical ambiguity in this type of elimination can be circumvented (Scheme IV) by bromination of a vinyl trimethylsilane. For example, treatment of the silyl enol lactone **13** with bromine, and subsequent treatment of the dibromide **21** with tetrabutylammonium fluoride afforded the desired bromo enol lactone **22**, in 72% yield after chromatography. An 85:15 mixture of the lactones **22a** and **22b** was obtained, suggesting that the bromination did not occur exclusively by a trans addition. This is not surprising, since the initially formed carbocation **21** (Scheme IV) derives significant stabilization from both a β-silicon and an α-oxygen, and therefore most probably does not exist as a stereodefined bromonium ion. The anti elmination[11] of trimethylsilyl bromide from the diastereomeric dibromides **21** results in the observed mixture of isomeric vinyl bromides, **22a,b**.

An attempt was made to prepare the halo enol lactone **19** by halogenation of the vinyl chloromercurial **23** (Scheme IV). Treatment of **23** with *N*-bromosuccinimide or bromide gave an isomeric mixture of the desired lactones (**22a,b**), but in only 32 and 41% yield, respectively. Reaction with bromine at 0 °C was rapid, but several other reaction products were formed; reaction with *N*-bromosuccinimide was much slower.

Halolactonizations. The most efficacious route to the halo enol lactones involved the halo lactonization of the acetylenic acids.

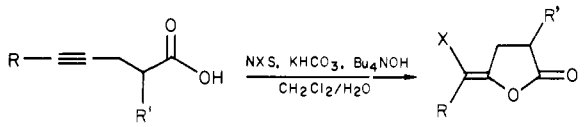
(8) (a) Larock, R. C.; Oertle, K.; Betty, K. M. *J. Am. Chem. Soc.* **1980**, *102*, 1966. (b) See, for instance: Larock, R. C. In "New Applications of Organometallic Reagents in Organic Synthesis"; Seyferth, D., Ed.; Elsevier Scientific Publishing Co.: Amsterdam, New York, 1976; Vol. 1, p 257.

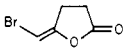
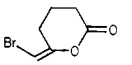
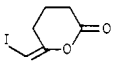
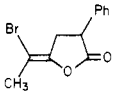
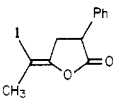
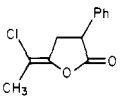
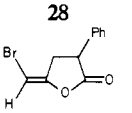
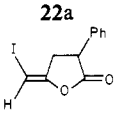
(9) Stothers, J. B. "Carbon-13 NMR Spectra"; Academic Press: New York, 1972; pp 80–85.

(10) Wineburg, J. P.; Abrams, C.; Swern, D. *J. Heterocycl. Chem.* **1975**, *12*, 749.

(11) Miller, R. B.; McGarvey, G. *J. Org. Chem.* **1978**, *43*, 4424.

Table III. Halolactonization of Acetylenic Acids[a]



reactant acid	halogenating agent	product	yield,[b] %
3	NBS	 1b	70
5	NBS	 24	85
5	NIS	 25	81
10	NBS	 26	93
10	NIS	 27	80
10	NCS	 28	82
14	NBS	 22a	89
14	NIS	 29	81

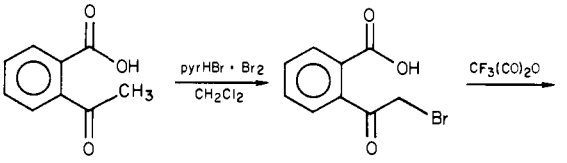
[a] Reactions were run at 25 °C for 30 min; concentration of *N*-halosuccinimide and reactant was 2.0 mmol in 25 mL of CH_2Cl_2 with 0.5 mL of 0.4 M Bu N^+ OH^-. [b] Isolated purified yield.

Initially, treatment of the cesium salts of the acids with iodine or bromine resulted in the formation of desired lactones, albeit in relatively poor yields. Modification of this procedure utilizing a two-phase system, with 2 mol % tetrabutylammonium hydroxide as a phase-transfer catalyst, potassium bicarbonate as the base, and the appropriate *N*-halosuccinimide, afforded the desired halo enol lactones in excellent yields of 80–93% (Table III). This method afforded nicely crystalline compounds which were easily purified further by recrystallization at low temperature.

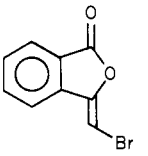
The halolactonization is completely stereoselective and results in exclusive formation of the *E* olefin. This implicates a discrete halonium ion intermediate which undergoes attack by the carboxylate exclusively with inversion. No Z isomer could be detected by ^1H NMR; however, exposure to acid or silica gel for prolonged periods did result in some isomerization.

It is interesting to note that the use of potassium carbonate, triethylamine, or pyridine, or the preformation of potassium or cesium carboxylate salts resulted in greatly decreased yields, longer reaction times, and the formation of several unidentified byproducts. In several attempts at iodolactonization of the acid **10** utilizing potassium carbonate as the base, none of the desired iodo enol lactone **27** was obtained. While the need for using bicarbonate as the base is not entirely understood, the pH of the reaction may be an important factor. Indeed, we[12] and others[13] have observed the bicarbonate-induced cyclization of acetylenic acids to the enol lactones with no other catalyst. When acid **14** was stirred in aqueous methanolic bicarbonate or 8 h, the lactone **15** was isolated in 72% yield. No reaction occurred in carbonate solution, or with triethylamine. Thus, the conversion of the acid to the lactone compound is favored at slightly basic pH, but not under acidic or more strongly basic conditions.

Scheme V

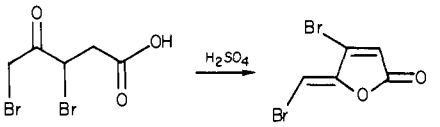


33 (94%)



34 (81%)

Dehydration of Halo Ketone Acids. It was reported in 1963[14] that, under strongly dehydrating conditions (fuming sulfuric acid), 3,5-dibromolevulinic acid (**30**) could be converted in 62% yield to the dibromo lactone **31** (eq 2). This reaction not only involved

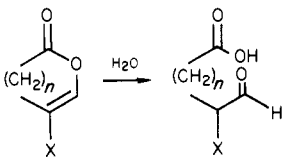


(2)

30 31

a dehydration, but also a dehydrogenation to give the α,β-unsaturated lactone. While these conditions were considered much too vigorous for our purposes, we briefly investigated the dehydration of two α-halo ketone acids, utilizing relatively milder conditions. When 5-bromolevulinic acid (**32**) was treated with trifluoroacetic anhydride or dicyclohexylcarbodiimide (Scheme III), dehydration did take place; however, the major product was the allylic bromide **19**. Small amounts (less than 10%) of the desired vinylic bromide, **1**, could be detected by ^1H NMR. However, its separation from the very unstable allylic bromide was not possible. Again, this conforms to the previously reported preference for the endocyclic position of a double bond in angelica lactones.[10] When *o*-(bromoacetyl)benzoic acid (**33**), obtained by bromination of acetylbenozic acid, was treated with trifluoroacetic anhydride, the desired bromo enol lactone **34** was obtained in 81% yield (Scheme V). Thus, when enolization in the undesired direction is blocked, dehydration provides a suitable route to halo enol lactones.

Baeyer–Villiger Oxidation of β-Halo Cycloenones. During the course of this investigation, the possibility of utilizing compounds with the general structure **35** as protease suicide substrates became apparent. Upon hydrolysis (eq 3) of these endocyclic halo enol



(3)

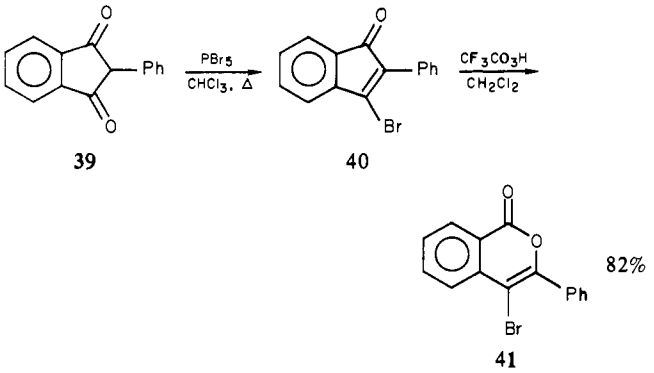
35 36

(12) Wells-Rollinson, S., Ph.D. Thesis, University of Illinois, Urbana, 1980.

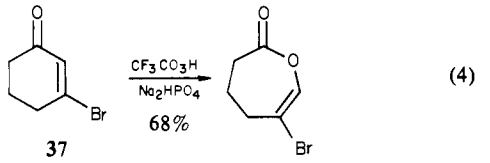
(13) (a) Christensen, P. K. *Acta Chem. Scand.* **1957**, *11*, 582. (b) Bell, I.; Jones, E. R. H.; Whiting, M. C. *J. Chem. Soc.* **1958**, 1313.

(14) Wells, D. R. *Aust. J. Chem.* **1963**, *16*, 165.

Scheme VI



lactones, an α-halo aldehyde **36** is revealed as the electrophilic alkylating agent.[5] While a synthetic approach involving the aforementioned dehydration methodology might have been feasible, the readily accessible β-halo cycloenones[15] such as **37** were envisioned as more suitable precursors to these endocyclic lactones, via Baeyer–Villiger oxidation (eq 4). The success of this strategy



(4)

depended upon the preferential migration of the vinyl group over the primary alkyl group. Several examples of such vinyl migration are known;[16] however, the presence of the electron-withdrawing halogen on the vinyl group was expected to decrease its migratory aptitude to some extent. Another anticipated difficulty with these substrates was the potential for competing epoxidation of the olefin; however, this reaction could be avoided under relatively acidic oxidation conditions.

Treatment of β-bromocyclohexenone (**37**) with pertrifluoroacetic acid in a buffered system afforded the desired lactone in 68% yield after chromatography on cyanopropyl functionalized silica gel. ^{1}H NMR analysis of the reaction products offered no evidence of competing alkyl migration. This method was also employed in the synthesis of the lactone **41**, obtained in 82% yield from 2-phenyl-1,3-indandione (**39**, Scheme VI). In this case, the vinylic–benzylic carbon migrated preferentially to the phenyl group, as anticipated. This method does provide an efficient route to these endocyclic lactones; however, the requirement for the vinylic migratory preference may limit potential substrate molecules to those with primary alkyl substituents at the α position.

Stability of Halo Enol Lactones. The hydrolytic stability of the halo enol ketones is an extremely important factor with regard to their intended use as suicide inactivators of proteases, since the spontaneous hydrolysis of these compounds prior to their interaction with the enzyme would generate conventional affinity reagents, which impart much lower selectivity to the inactivation process. Accurate monitoring of the rate of spontaneous hydrolysis was difficult for most lactones, owing to a lack of signficant absorbance changes at measurable wavelengths of the UV spectra during the hydrolysis. The benzo-phenyl derivative **41** did have a UV spectrum significantly different from its hydrolysis product, enabling accurate measurement of its hydrolysis. Its stability was pH dependent, with hydrolysis half-times increasing with pH and temperature (Table IV).

The stability of compound **22** was followed by ^{1}H NMR and TLC of $CDCl_3$ extracts of phosphate-buffered incubations, using

Table IV. Spontaneous Hydrolysis of Enol Lactone 41[a]

pH	reaction half-time, min	
	18 °C	30 °C
7.8	15.2	12.3
7.2	21.0	17.5
6.6	33.0	25.0

[a] Procedure: A 20.0-μL aliquot of a 20.0 mM solution of **41** in CH_3CN was added to a cuvette containing 1.0 mL of 0.1 M potassium phosphate buffer at the indicated pH; and the absorbance change at 243 nm, relative to a blank containing only buffer, was observed until no further absorbance change occurred.

levulinic acid as an internal standard. The hydrolysis half-time at pH 7.2, 25 °C, was approximately 95 min, and at lower pH's the half-times were much longer. Although they are somewhat labile at higher pH, compounds of this type should be sufficiently stable at neutral pH so that their spontaneous rate of hydrolysis will be slow relative to their enzymatic rate of hydrolysis.

Enzymatic Studies. In studies on chymotrypsin, we have found that several of the compounds whose preparation we have described here appear to be suicide inactivators. Details of these studies will be published elsewhere.[6]

Summary

We have explored a number of routes of halo enol lactones, and demonstrated the efficacy of several methods which provide access to a variety of protease suicide substrates. The methodology should allow for the synthesis of more complex molecules, which will be designed to act as highly specific suicide inactivators of other biologically important proteases. Efforts toward this goal are under way.

Experimental Section

General. Analytical thin-layer chromatography (TLC) was carried out using 0.25-mm Merck silica gel 60 F-254 or aluminum oxide/UV-254 glass-backed plates. Compounds were visualized by ultraviolet light (254 nm), iodine vapor, or phosphomolybdic acid spray reagent. Preparative layer chromatography was carried out using 2.0-mm Merck silica gel 60 F-254 precoated TLC plates. The plates were predeveloped with methanol and heat activated prior to use.

All column chromatography was performed on a medium-pressure liquid chromatograph (MPLC), designed and built in our laboratory. The basic system utilized a Milton-Roy Series D pump, stainless steel columns, an ISCO Model UA-5 ultraviolet detector, and ISCO fraction collector. Adsorbents used included Ventron silica gel sieved to include 45–63-μm particles, Waters ODS reversed-phase silica gel, cyanopropyl (CN) functionalized silica gel, or Ventron alumina.

Proton (^{1}H NMR) and carbon-13 magnetic resonance spectra were obtained on Varian Associates spectrometers, Models HR-220 (220 MHz), EM-390 (90 MHz), or XL-100, and are expressed as parts per million downfiled from tetramethylsilane as an internal standard (δ scale). Spectra were run in locked mode, with deuteriochloroform as solvent unless specified otherwise. The ^{1}H NMR data are presented in the form: δ value of signal (peak multiplicity, coupling constant (if applicable), integrated number of protons). Infrared (IR) spectra were obtained with a Beckman IR-12 or a Perkin-Elmer Model 137 spectrophotometer, and data are presented as cm^{-1}, for important diagnostic absorptions. Ultraviolet absorption spectra were recorded on a Varian Associates 635 UV-vis spectrophotometer. Mass spectra were obtained on a Varian Associates MAT CH-5 spectrometer at 10 or 70 eV. Data are reported in the form: m/e (intensity relative to base peak = 100). High-resolution electron-impact mass spectroscopy (HREIMS) for exact mass determination was performed on a Varian Associates MAT 731 mass spectrometer. Melting points were determined with a Thomas-Hoover capillary melting point appartus and are uncorrected. Elemental analyses were performed by the Microanalytical Service Laboratory of the Univeristy of Illinois School of Chemical Sciences.

n-Butyllithium as a hexane solution was purchased from Alfa (Ventron), 4-Å molecular sieves from Union Carbide (Linde Division). Other reagents and solvents were purchased as analytical reagent grade, or purified according to literature procedures as noted.

Solvents were used as purchased with the following exceptions: tetrahydrofuran (THF) was dried immediately prior to use by distillation from sodium benzophenone ketyl; dimethylformamide (DMF) and hexamethylphosphoric triamide (HMPT) were dried over calcium hydride,

(15) Piers, E.; Nagakura, I. *Synth. Commun.* **1975**, *5*, 193.
(16) Bosecken, M.; Jacobs, R. *Recl. Trav. Chim.* **1936**, *55*, 804.

distilled, and stored over 4-Å molecular sieves.

The organic base present in organolithium reagents was determined by the diphenylacetic acid method of Kofron,[17] the double titration method of Whitesides,[18] or the 1,10-phenanthroline method of Watson.[19]

Air- and moisture-sensitive reactions were carried out in oven-dried glassware under an atmosphere of dry nitrogen. Reaction progress was monitored by TLC, HPLC, or NMR. Unless otherwise stated, a standard proceure for product isolation was used: quenching with water or saturated salt solutions, exhaustive extraction with an organic solvent, washing of extracts with aqueous solutions, drying over magnesium sulfate, filtration (usually through a short bed of silica gel, alumina, or Florisil), and removal of solvent under reduced pressure with a rotary evaporator. The particular extraction solvents, aqueous washes, and filtration adsorbants are delineated in parentheses after the phrase "product isolation".

4-Pentynoic Acid (3). This was prepared in 74% yield by the method of Holland and Gilman.[20] Recrystallization from hexane–tetrahydrofuran gave colorless crystalline plates: mp 53–55 °C (lit.[20] 54.5–56.5 °C); ^{1}H NMR δ 11.30 (s, 1 H), 2.45–2.70 (m, 4 H), 1.99 (t, J = 2 Hz, 1 H).

5-Hexynoic Acid (5). This was also prepared by the method of Holland and Gilman[20] in 79% yield. Recrystallization from hexane–tetrahydrofuran gave colorless crystalline plates: mp 41–43.5 °C (lit.[21] liquid) ^{1}H NMR δ 11.16 (s, 1 H), 2.38–2.61 (m, 4 H), 1.97 (t, J = 2 Hz, 1 H), 1.88 (q, J = 7 Hz, 2 H).

5-Bromo-4-pentynoic Acid (6). To a solution of 3.84 g (24.0 mmol) of bromine in 40 mL of 10% aqueous NaOH was added a solution containing 2.2 g (22.4 mmol) of 4-pentynoic acid (3) in 10 mL of water. After stirring at 25 °C for 6 h, the reaction mixture was poured over ice and acidified with 6 N HCl. Product isolation (ether, satd NaCl, Florisil) afforded 3.88 g of the crude acid. Recrystallization (hexane–THF) yielded 3.53 g (88%) of **6**: mp 69–72 °C (lit.[22] 78–80 °C); ^{1}H NMR ($CDCl_3$) δ 9.20 (s, 1 H), 2.48–2.70 (m, 4 H).

Anal. Calcd for $C_5H_5BrO_2$: C, 33.93; H, 2.85; Br, 45.14. Found: C, 34.20; H, 2.91; Br, 44.70.

5-Chloro-4-pentynoic Acid (7). *n*-Butyllithium (1.82 mL of a 2.2 M solution in hexane, 4.0 mmol) was added dropwise to a solution of 0.41 g of diisopropylamine (4.0 mmol) in THF (20 mL) at −78 °C, and this solution was stirred for 30 min. A solution of 196 mg (2.0 mmol) of 3 in 5 mL of THF was added dropwise and the solution stirred for 1 h. *N*-Chlorosuccinimide (294 mg, 2.2 mmol) in 10 mL of THF was added dropwise and the solution stirred for 2 h at 0 °C. Following addition of satd NH_4Cl and acidification with 6 N HCl, product isolation (ether, water, satd NaCl, Florisil) gave 256 mg of a white solid, **7**. Crystallization (hexane–THF) afforded 209 mg (79%) of crystalline compound: mp 59–60 °C; ^{1}H NMR ($CDCl_3$) δ 9.84 (s, 1 H), 2.46–2.81 (m, 4 H).

Anal. Calcd for $C_5H_5ClO_2$: C, 45.31; H, 3.80; Cl, 26.75. Found: C, 45.10; H, 3.77; Cl, 26.66.

2-Phenyl-4-hexynoic Acid (10). *n*-Butyllium (9.1 mL of a 2.2 M solution in hexane, 20 mmol) was added dropwise to a solution of 2.02 g of diisopropylamine (20 mmol) in THF (20 mL) at 0 °C, and this solution was stirred for 30 min. 2-Phenylethanoic acid (1.36 g, 10.0 mmol) in 15 mL of THF was added dropwise to the lithium diisopropylamide solution while maintaining the solution at 0 °C, and this was stirred for 1 h. HMPT (2 mL) was added to effect diisolution of the dianion which had precipitated. To the resulting yellow homogeneous solution was added dropwise 1.33 g of 1-bromo-2-butyne (10.0 mmol) in THF (5 mL), and the reaction was allowed to warm to 25 °C. After stirring 4 h, the reaction mixture was quenched with cold 6 N HCl. Product isolation (ether, 1 N HCl, water, satd NaCl, silica gel) afforded 1.82 g of a light yellow oil, which solidified upon cooling. Recrystallization from THF–hexane yielded 1.68 g (90%) of the acid **10**, as white crystals: mp 101–103 °C; ^{1}H NMR ($CDCl_3$) δ 11.12 (s, 1 H), 7.33 (broad s, 5 H), 3.70 (dd, J_1 = 8 Hz, J_2 = 7 Hz, 1 H), 2.33–3.10 (m, 2 H), 1.68 (t, J = 2 Hz, 3 H); mass spectrum (10 eV) m/e (rel intensity) 188 (M^+, 20), 173 (11), 143 (100), 142 (13), 136 (38), 135 (21), 129 (21), 91 (27).

Anal. Calcd for $C_{12}H_{12}O_2$: C, 76.57; H, 6.43. Found: C, 76.44; H, 6.39.

2-Phenyl-5-trimethylsilyl-4-pentynoic Acid (12). In a procedure identical with that used in the preparation of **10**, 1.91 g (10.0 mmol) of 1-trimethylsilyl-3-bromopropyne[23] in 5 mL of THF was added to 10 mmol of the dianion. Product isolation gave 2.33 of a yellow oil which solidified upon cooling. Recrystallization from ether–hexane afforded **12** as a white solid (2.07 g, 84%): mp 88–91 °C; ^{1}H NMR ($CDCl_3$) δ 10.20 (s, 1 H), 7.30 (s, 5 H), 3.73 (t, J v 8 Hz, 1 H), 2.88 (AB quartet; $\Delta\nu$ = 0.26 ppm, J = 18 Hz, with additional doublet splitting, J = 8 Hz, 2 H), 0.08 (s, 9 H); mass spectrum (10 eV m/e (rel intensity), 247 (M^+ + 1, 0.81), 246 (M^+, 3.57), 231 (10, 203 (16), 75 (100), 73 (19).

Anal. Calcd for $C_{14}H_{18}O_2Si$: C, 68.25; H, 7.36. Found: C, 68.26; H, 7.29.

2-Phenyl-4-pentynoic Acid (14). To a solution of **12** (1.23 g, 5.0 mmol) in 20 mL of THF was added tetrabutylammonium fluoride (10 mL of a 1.0 M THF solution, 10 mmol). After stirring for 3 h at 25 °C, the solution was acidified with 1 N HCl. Product isolation (ether, satd NaCl) afforded 0.89 g of a white solid. Recrystallization from ether–hexane yielded 0.87 g (99%) of the pure acid **14**: mp 92–93.5 °C; ^{1}H NMR ($CDCl_3$) δ 10.27 (s, 1 H), 7.32 (s, 5 H), 3.77 (t, J = 7 Hz, 1 H), 2.74 (AB quartet, $\Delta\nu$ = 0.28 ppm, J = 17 Hz, with additional doublet of doublet splitting, J = 10, 2.3 Hz, 2 H), 1.92 (t, J = 2.3 Hz, 1 H); mass spectrum (10 eV) m/e (rel intensity) 174 (M^+, 0.50), 129 (31), 91 (11), 49 (27), 48 (18), 46 (198), 45 (100, 24 (37).

Anal. Calcd for $C_{11}H_{10}O_2$: C, 75.84; H, 5.79. Found: C, 75.69; H, 5.66.

General Procedure for Mercury-Catalyzed Cyclization (Method A). To a solution containing 2.0 mmol of the acetylenic acid in 25 mL of CH_2Cl_2 was added 0.3 mmol of mercury trifluoroacetate (85.2 mg). The reaction mixture was stirred at room temperature until the starting acid had disappeared (determined by TLC), at which time 25 mL of CH_2Cl_2 was added. Product isolation (5% $NaHCO_3$, satd NaCl, alumina) afforded the crude lactones, which were purified on silica gel or CN-silica gel by MPLC.

5-Methylidenetetrahydro-2-furanone (γ-Methylidene-γ-butyrolactone) (4). This product was obtained as an oil in 81% yield from the acid 3 by method A. Purification by gradient elution (hexene–20% ether/hexane) from silica gel ($^1/_2$ in. × 30 cm column) afforded the pure compound 4.[7]

6-Methylidenetetrahydro-2-pyrone (8). This material was prepared from the acid **5**, in 80% yield by method A. Gradient elution (hexane–20% ether/hexane) from silica gel ($^1/_2$ in. × 30 cm column) by MPLC gave the pure product as an oil: ^{1}H NMR ($CDCl_3$) δ 4.57 (s, 1 H), 4.15 (s, 1 H), 2.33–2.60 (m, 4 H), 1.70–2.05 (m, 2 H); IR 1795 (C=0).

Anal. Calcd for $C_6H_8O_2$: C, 64.27; H, 7.19. Found: C, 64.10; H, 7.11.

5(*Z*)-Bromomethylidenetetrahydro-2-furanone (1a). This compound was obtained from the acid **6** in 62% yield by method A. Gradient elution (hexane/20% ether–hexane) from CN-silica gel ($^1/_2$ in. × 30 cm) by MPLC gave the pure product as an oil: ^{1}H NMR ($CDCl_3$) δ 5.34 (t, J = 2 Hz, 1 H), 2.78–3.09 (m, 4 H); mass spectrum (10 eV) m/e (rel intensity) 178 (M + 2, 3.48), 176 (M, 3.55), 100 (11), 99 (100), 56 (27).

Anal. Calcd for $C_5H_5BrO_2$: C, 33.93; H, 1.85; Br, 44.68. Found: C, 34.02; H, 1.79; Br, 44.62.

5-(*Z*)-Chloromethylidenetetrahydro-2-furanone (9). This material, prepared from the acid **7** by method A, was isolated in 55% yield after graident elution (hexane/20% ether-hexane) from CN-silica gel ($^1/_2$ in. × 30 cm column): ^{1},H NMR ($CDCl_3$) δ 5.56 (t, J = 1 Hz, 1 H), 2.83–3.15 (m, 4 H).

Anal. Calcd for $C_5H_5ClO_2$: C, 45.31; H, 3.80; Cl, 26.75. Found: C, 45.40; H, 3.77; Cl, 26.55.

2-Phenyl-5(*E*,*Z*)-ethylidenetetrahydro-2-furanone (11a and 11b). Cyclization of the acid **10** by method A afforded a mixture of the isomeric lactones **11a** and **11b**, in 86% yield after purification by gradient elution (hexane/20% ether–hexane) from silica gel ($^1/_2$ in. × 30 cm) by MPLC. Elution with a shallower gradient (hexane/10% ether–hexane) afforded clean separation of the isomeric mixture: ^{1}H NMR ($CDCl_3$) δ 7.27 (s, 5 H), 5.29 (qt, J_1 = 7 Hz, J_2 = 2 Hz, 1 H (*Z* = isomer)), 5.03 (q, J = 2 Hz, 1 H (*E* isomer)), 3.63–4.07 (m, 1 H), 2.72–3.52 (m, 2 H (*Z* isomer)), 2.42–2.68 (m, 2 H (*E* isomer)), 1.90 (s–br, 3 H, (*E* isomer)), 1.60– (d, J = 7 Hz, 3 H (*Z* isomer)); ^{13}C NMR ($CDCl_3$) (*Z* isomer) δ 12.4 (1 C, allylic methyl), 34.4 (1 C, allylic methylene), 45.1 (α-carbon), 99.7 (1 C, vinyl), 127–129 (4 C, aromatic), 136.8 (1 C aromatic), 146.7 (1 C, vinyl), 175.1 (1 C, carbonyl); (*E* isomer) δ 16.9 (1 C, allylic methyl), 27.3 (allylic methylene).

Anal. Calcd for $C_{12}H_{12}O_2$: C, 76.57; H, 6.43. Found: C, 76.40; H, 6.38.

2-Phenyl-5(*E*,*Z*)-trimethylsilylmethylidenetetrahydro-2-furanone (13a and 13b). Cyclization of the acid **12** by method A gave a mixture of the isomeric lactones **13a** and **13b**, in 62% yield after purification by gradient elution (hexane/5% ether–hexane) from CN-silica gel ($^1/_2$ in. × 30 cm)

(17) Kofron, W. G.; Baclowski, M. *J. Org. Chem.* **1976**, 41; 1879.
(18) Whitesides, G. M.; Casey, C. P.; Krieger, J. K. *J. Am. Chem. Soc.* **1971**, *93*; 1279.
(19) Watson, S. C.; Eastham, J. R. *J. Organomet. Chem.* **1967**, *9*; 165.
(20) Holland, B. C.; Gilman, N. W. *Synth. Commun.* **1974**, *4*; 203.
(21) Eglinton, G.; Whiting, M. C. *J. Chem. Soc.* **1953**, 3052.
(22) Kobayashi, A.; Yamashita, K. *Agr. Biol. Chem.* **1975**, *39*; 2247.
(23) Miller, R. B. *Synth. Commun.* **1972**, *2*, 267.

by MPLC. An 18% yield of the desilylated lactone **15** was also obtained. The isomers were separated by preparative layer chromatography with three developments using 10% ether/hexane: ^{1}H NMR ($CDCl_3$) (isomer mixture) δ 7.32 (broad s, 5 H), 5.10 (t, J = 1.5 Hz, 1 H (Z isomer)), 4.63 (t, J = 1 Hz, 1 H (E isomer)), 3.94 (dd, J_1 = 7 Hz, J_2 = 8 Hz, 1 H), 3.10 (AB quartet, $\Delta\nu$ = 0.30 ppm, J = 17 Hz, upfield portion is a dd, J = 7, 1 Hz, downfield portion is a dd, J = 8, 1 Hz, 2 H), 0.20 (s, 9 H); mass spectrum (10 eV) m/e (rel intensity) 247 (M + 1, 1.86), 246 (M, 6.52), 174 (29), 147 (10), 59 (22), 53 (12)e, 39 (22), 36 (100), 28 (34).

Anal. Calcd for $C_{14}H_{18}O_2Si$: C, 68.25; H, 7.36. Found: C, 68.16; H, 7.33.

2-Phenyl-5-methylidenetetrahydro-2-furanone (15). This compound was obtained in 84% yield from the acid **14** by method A, after purification by gradient elution (hexane/10% ether–hexane) from silica gel $^1/_2$ in. × 30 cm column) by MPLC: ^{1}H NMR ($CDCl_3$) δ 7.31 (s, 5 H), 4.76 (m, 1 H), 4.34 (m, 1 H), 3.90 (dd, J_1 = 7 Hz, J_2 = 8 Hz, 1 H), 2.72–3.47 (m, 2 H).

Anal. Calcd for $C_{11}H_{10}O_2$: C, 75.84; H, 5.79. Found: C, 75.75; H, 5.61.

2-Phenyl-5(E)-chloromercuriomethylidenetetrahydro-2-furanone (23). To a solution of 348 mg (2.0 mmol) of **18** in 10 mL of aqueous methanol was added 357 mg (1.1 mmol) of $Cs(CO_3)_2$. The salt was suspended in THF (25 mL) and treated with 638 mg (2.0 mmol) of mercury acetate. After stirring for 17 h at 25 °C, the solution was poured into 50 mL of ice-cold saturated NaCl and stirred for 30 min; the THF was then removed.[8a] Product isolation (CH_2Cl_2, H_2O, Florisil) gave a beige solid. Purification by elution from a 2-in. bed of silica gel (8:1:1 hexane:ether:CH_2Cl_2) afforded 646 mg (79%) of a beige solid, **23**.

Anal. Calcd for $C_{11}H_9ClHgO_2$: C, 32.29; H, 2.22; Hg, 49.02. Found: C, 32.51; H, 2.44; Hz, 48.61.

2-Phenyl-5(E,Z)-bromomethylidenetetrahydro-2-furanone (22a and 22b) by Treatment of 23 with Bromine. To a solution of 409 mg (1.0 mmol) of **23** in 20 mL of CH_2Cl_2 at 0 °C was added 51 μL of bromine (1.0 mmol). The bromine color rapidly disappeared and the reaction mixture was allowed to stir for 30 min. Product isolation (CH_2Cl_2, 5% sodium thiosulfate, water, alumina) gave 320 mg of an oil containing three components. Gradient elution (hexane/8:1:1 hexane:ether:CH_2Cl_2) from CN-silica gel ($^1/_2$ in. × 30 cm column) by MPLC afforded an oil, which solidified on cooling. Recrystallization (hexane–ether) gave 105 mg (41%) of the white crystalline compound, which as an isomer mixture of **22a** and **22b**: ^{1}H NMR δ 7.30 (broad s, 5 H), 6.02 (t, J =v 2 Hz, 1 H (E isomer)), 5.28 (t, J = 1.5 Hz, 1 H (Z isomer)), 4.00 (dd, J_1 = 7 Hz, J_2 = 9 Hz), 3.20 (AB quartet, $\Delta\nu$ = 0.40 ppm, J = 17 Hz, upfield portion is a dd, J = 7, 1.5 Hz; downfield protion is a dd, J = 9, 1.5 Hz).

Anal. Calcd for $C_{11}H_9BrO_2$: C, 52.20; H, 3.58; Br, 31.57. Found: C, 52.41; H, 3.63; Br, 31.22.

By Bromination of 13a (Z isomer). To a solution of 246 mg (1.0 mmol) of **13a** in 10 mL of THF at 0 °C was added 51 μL (1.0 mmol) of bromine. After stirred for 30 min, 2 mmol (2 mL of a 1 M solution) of tetrabutylammonium fluoride was added. After the reaction mixture had stirred at 0 °C for 4 h, the solvent was removed and the oil dissolved in ether. Product isolation (water, saturated NaCl, florisil) gave 240 mg of an oil. Gradient elution (hexane/8:1:1 hexane:ether:CH_2Cl_2) from CN-silica gel ($^1/_2$ in. × 30 cm column) afforded 196 mg of a solid, which was recrystallized to give 182 mg (72%) of crystalline material **22a**(E) + **22b**(Z) in a ratio of 85:15. Spectral data are given above.

General Procedure for Halolactonizations (Method B). To a solution of 2 mmol of the acetylenic acid in 25 mL of CH_2Cl_2 were added sequentially 2 mmol of the N-halosuccinimide, 2 mmol of $KHCO_3$, and 0.5 mL of 0.4 tetrabutylammonium hydroxide. The reaction mixture was shaken or stirred vigorously for 30 min. Product isolation (CH_2Cl_2, 5% sodium thiosulfate, water, satd NaCl, Florisil) afforded the crude material which was recrystallized or purified by MPLC from CN-silica.

5(E)-Bromomethylidenetetrahydro-2-furanone (1b). This was material obtained as an oil from acid **3** by method B, in 70% yield after purification by gradient elution (hexane/12:1:1 hexane:ether:CH_2Cl_2) from CN-silica ($^1/_2$ in. × 30 cm column) by MPLC: ^{1}H NMR δ 6.02 (t, J = 2 Hz, 1 H) 2.78–3.07 (m, 4 H).

Anal. Calcd for $C_5H_5BrO_2$: C, 33.93; H, 1.85; Br, 44.68. Found: C, 34.10; H, 1.88; Br, 44.55.

6(E)-Bromomethylidenetetrahydro-2-pyrone (24). This compound was prepared in 35% yield from acid **5**, by method B, and purified by low-temperature recrystallization from hexane: ^{1}H NMR δ 6.11 (t, J = 1 Hz, 1 H), 2.43–2.85 (m, 4 H), 1.63–1.98 (q, J = 7 Hz, 2 H).

Anal. Calcd for $C_6H_7BrO_2$: C, 37.73; H, 3.69; Br, 41.83. Found: C, 37.91; H, 3.77; Br, 41.54.

6(E)-Iodomethylienetetrahydro-2-pyrone (25). This compound was prepared in 81% yield from acid **5** by method B and purified by recrystallization at low temperature from hexane: ^{1} H NMR ($CDCl_3$) δ 5.93 (t, J = 1 Hz, 1 H), 2.40–2.78 (m, 4 H), 1.63–1.95 (q, J = 7 Hz, 2 H).

Anal. Calcd for $C_6H_7IO_2$: C, 30.28; H, 2.96; I, 53.32. Found: C, 30.51; H, 3.11; I, 52.88.

2-Phentyl-5(E)-(1-bromoethylidene)tetrahydro-2-furanone (26). This material was prepared from acid **10** by method B in 93% yield after recrystallization from hexane: mp 57–58 °C; ^{1}H NMR δ 7.31 (broad s, 5 H), 3.98 (dd, J_1 v 10 Hz, J_2 = 7 Hz, 1 H), 3.18 (AB quartet, $\Delta\nu$ = 0.40 ppm, J = 17 Hz; upfield portion is a dq, J = 7, 2 Hz; downfield portion is a dq, J = 10, 2 Hz, 2 H), 2.34 (t, J = 2 Hz, 3 H).

anal. Calcd for $C_{12}C_{11}BrO_2$: C, 53.96; H, 4.15; Br, 29.92. Found: C, 53.96; H, 4.11; Br, 29.81.

2-Phenyl-5(E)-(1-iodoethylidene)tetrahydro-2-furanone (27). This compound was prepared from acid **10** by method B, in 80% yield after recrystallization from hexane: mp 75–77 °C dec; ^{1}H NMR δ 7.30 (m, 5 H), 3.98 (dd, J_1 = 10 Hz, J_2 = 8 Hz, 1 H), 3.17 (AB quartet, $\Delta\nu$ = 0.39 ppm, J = 17 Hz; upfield portion is a dq, J = 8, 1.5 hz; downfield portion is a dq, J = 10, 1.5 hz, 2 H), 2.48 (t, J = 1.5 Hz, 3 H).

Anal. Calcd for $C_{12}H_{11}IO_2$: C, 45.88; H, 3.53; I, 40.40. Found: C, 45.86; H, 3.39; I, 40.11.

2-Phenyl-5(E)-(1-chloroethylidene)tetrahydro-2-furanone (28). This compound was prepared from acid **10** by method B, in 82% yield after recrystallization from hexane: mp 53–54 °C; ^{1}H NMR δ 7.32 (m, 5 H), 3.98 (dd, J_1 = 10 Hz, J_2 = 9 Hz, 1 H), 3.14 (AB quartet, $\Delta\nu$ = 0.39 ppm, J = 19 Hz; upfield portion is a dq, J = 8, 1.5 Hz; downfield portion is a dq, J = 10, 1.5 Hz, 2 H), 2.40 (t, J = 1.5 Hz, 3 H).

Anal. Calcd. for $C_{12}H_{11}ClO_2$: C, 65.00; H, 5.00; Cl, 15.54. Found: C, 64.99; H, 4.90; Cl, 15.38.

2-Phenyl-5(E)-bromoethylidenetetrahydro-2-furanone (22a). This compound was prepared from acid **14** by method B, in 89% yield after recrystallization from hexane: mp 105–109.5 °C. Spectral properties are given above.

Anal. Calcd for $C_{11}H_9BrO_2$: C, 52.20; H, 3.58; Br, 31.57. Found: C, 52.49; H, 3.58; Br, 31.57.

2-Phenyl-5(E)-iodomethylidenetetrahydro-2-furanone (29). This compound was prepared from acid **14** by method B, in 81% yield after recrystallization from hexane: mp 67–69 °C dec; ^{1}H NMR δ 7.33 (m, 5 H), 5.83 (t, J = 2 Hz, 1 H), 4.02 (dd, J_1 = 10 Hz, J_2 = 7 Hz, 1 H), 3.16 (AB quartet, $\Delta\nu$ = 0.50 ppm, J = 16 Hz; upfield portion is a dd, J = 7, 2 Hz; downfield portion is a dd, J = 10, 2 Hz, 2 H).

Anal. Calcd for $C_{11}H_9IO_2$: C, 44.03; H, 3.02; I, 42.29. Found: C, 44.11; H, 2.91; I, 42.01.

***o*-(Bromoacetyl)benzoic Acid (33).** To a cold solution (0 °C) of 1.64 g (10.0 mmol) of acetylbenzoic acid in 50 mL of acetic acid was added 4.00 g (11 mmol) of pyridinium bromide perbromide (80+% tech). After stirring for 4 h, the solution was poured over ice and the solid collected by filtration. After dissolution in CH_2Cl_2 and washing with 5% sodium thiosulfate, water, and saturated NaCl, the solution was dried and evaporated to give 2.38 g of solid. Recrystallization from THF–hexane afforded 2.28 g of (93% yield) **33**: mp 141–143 °C dec; ^{1}H NMR ($CDCl_3$) δ 11.33 (broad s, 1 H), 7.40–7.92 (m, 4 H), 6.0–6.4 (broad s, 1 H, lactol form), 4.20–4.55 (m, 2 H, lactol form), 3.86 (s, 2 H, keto acid form).

Anal. Calcd for $C_9H_7BrO_3$: C, 44.47; H, 2.90; Br, 32.88. Found: C, 44.39; H, 2.95; Br, 32.79.

5-Bromoethylidenebenzo-2(5*H*)-furanone (34). To 15 mL of trifluoroacetic anhydride was added 1.23 g (5.0 mmol) of **33** in 10 mL of THF. After the solution was stirred for 17 h at 25 °C, the solvent, excess anhydride, and trifluoroacetic acid were evaporated. The residue was purified by gradient elution (10% ether–hexane/5:1:1 hexane: ether: CH_2Cl_2) from CN-silica ($^3/_4$ in. × 40 cm column) to afford 934 mg (82%) of **34**: mp 121–122.5 °C; ^{1}H NMR ($CDCl_3$) δ 7.62–8.06 (m, 4 H), 6.33 (s, 1 H).

Anal. Calcd for $C_9H_5BrO_2$: C, 48.03; H, 2.24; Br, 35.51. Found: C, 48.11; H, 2.31; Br, 35.40.

4-Bromo-2-oxacyclohept-3-en-1-one (38). To 630 mg (3 mmol, 425 μL) of trifluoroacetic anhydride in 5 mL of CH_2Cl_2 at 0 °C was added 80 μL of 90% H_2O_2 (2.5 mmol). After stirring for 1 h, the solution was transferred dropwise by cold syringe to a solution of 1-bromocyclohexen-2-one[15] (**37**,382 mg, 2.0 mmol) in mL of CH_2Cl_2 and stirred at 0 °C over 0.5 g of anhydrous powdered Na_2HPO_4. After 4 h at 0 °C, the reaction mixture was filtered and the salts were washed thoroughly with CH_2Cl_2. Product isolation (cold 5% $NaHCO_3$, satd NaCl, alumina) gave 355 mg of an oil. Gradient elution (10% ether–hexane/4:1:1 hexane: ether:CH_2Cl_2) from CN-silica ($^1/_2$ in. × 30 cm column) by MPLC afforded 285 mg (68%) of the oil, **38**: ^{1}H NMR δ 6.70 (s, 1 H), 2.60–2.83 (m, 4 H), 1.95–2.30 (q, J = 7 Hz, 2 H).

Anal. Calcd for $C_6H_7BrO_2$: C, 37.73; H, 3.69; Br, 41.83. Found: C, 37.66; H, 377; Br, 41.66.

4-Bromo-3-phenylisocoumarin (41). To a suspension of PBr_5 (0.864 g, 2.0 mmol) in 50 mL of chloroform was added dropwise 2-phenyl-1,3-indandione (1.12 g, 5.0 mmol) in 15 mL of chloroform. After refluxing for 6 h, the solution was cooled and filtered to remove residual PBr_5. Product isolation (ice water, cold 5% $NaHCO_3$ (2×)) afforded a yellow solid, 1-bromo-2-phenyl-inden-3-one (**40**). Owing to its instability no further purification was attempted: ^1H NMR δ 7.58–8.08 (m, 4 H), 7.10–7.38 (m, 5 H); IR 1820 cm^{-1} (C=O).

As described above for compound **38**, 2.84 g (10 mmol) of the solid, **40**, was dissolved in 50 mL of CH_2Cl_2 at 0 °C, and treated with 12.5 mmol of trifluoroperacetic acid in the presence of 2 g of Na_2HPO_4. After 3 h at 0 °C, the solution was filtered and salts were washed thoroughly with CH_2Cl_2. Product isolation (cold 5% $NaHCO_3$, water, satd NaCl, Florisil) gave 2.92 g of a solid. Recrystallization (hexane–chloroform) afforded **41** as white crystals, 2.46 g (82%): mp 100–101.5 °C; ^1H NMR δ 7.80–8.12 (m, 4 H), 7.60–7.77 (m, 2 H), 7.20–7.37 (m, 3 H); IR 1796 cm^{-1} (C=O).

Anal. Calcd for $C_{15}H_9BrO_2$: C, 59.83; H, 3.01; Br, 29.55. Found: C, 59.81; H, 2.94; Br, 29.50.

Acknowledgment. Support for this research through grants from the National Institutes of Health (AM 27526) and the National Science Foundation (PCM 76 10037) is gratefully acknowledged. G.A.K. has been supported with a fellowship from Proctor and Gamble.

The S_N2–S_N1 Spectrum. 3. Solvolyses of Secondary and Tertiary Alkyl Sulfonates in Fluorinated Alcohols. Further Evidence for the S_N2 (Intermediate) Mechanism[1,2]

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Received December 23, 1980

Abstract: Kinetic data are reported for solvolyses of secondary and tertiary alkyl tosylates in trifluoroethanol and hexafluoroisopropyl alcohol and also for 1-adamantylmethylcarbinyl (VI) and 1-bicyclo[2.2.2]octyl (VII) tosylates in a wide range of solvents. The relative solvolysis rates of 2-adamantyl (I), 1-adamantylmethylcarbinyl (VI), and 1-bicyclo[2.2.2]octyl (VII) tosylates are essentially independent of solvent (in ethanol, methanol, water, trifluoroethanol, hexafluoroisopropyl alcohol, acetic acid, formic acid, and trifluoroacetic acid). Thus these three substrates are good models for S_N1 (k_c or limiting) mechanistic behavior; they respond almost identically to changes in solvent ionizing power and are insensitive to changes in solvent nucleophilicity. In contrast relative solvolysis rates of 2-adamantyl and 2-propyl tosylates vary with solvent 10^5-fold from 134 in hexafluoroisopropyl alcohol to 0.0011 in ethanol. For straight-chain secondary alkyl tosylates, logarithms of solvolysis rate constants in hexafluoroisopropyl alcohol correlate with σ^* and give a large negative ρ^* value (−9.1). Other solvents give less negative ρ^* values (e.g., CF_3CO_2H, $\rho^* = -7.3$; CF_3CH_2OH, $\rho^* = -5.2$; H_2O, $\rho^* = -4.3$) and smaller 2-adamantyl/2-propyl (2-AdOTs/2-PrOTs) rate ratios. Increasing amounts of nucleophilic solvent assistance in the more nucleophilic solvents leads to decreased electron demand by the cationic center (i.e., less negative ρ^*), and solvolyses of 2-propyl become more rapid than 2-adamantyl. Solvent effects on the relative reactivity of secondary alkyl tosylates (ROTs) are correlated accurately by using the linear free energy relationship: $\log (k/k_0)_{ROTs} = Q' \log (k/k_0)_{2\text{-AdOTs}} (k/k_0)_{2\text{-AdOTs}} + (1 - Q') \log (k/k_0)_{2\text{-PrOTs}}$ where k refers to any solvent, k_0 refers to 80% ethanol/water (v/v), and Q' is an adjustable blending parameter. The high precision of correlations using this equation for 2-butyl, 2-pentyl, 3-pentyl, 4-heptyl, cyclopentyl, cyclohexyl, and cycloheptyl tosylates provides evidence for a gradual change of mechanism from S_N2 (one-stage) through S_N2 (intermediate) to S_N1 mechanisms. Solvolyses of 3-methyl-2-butyl tosylate show significant sensitivity to nucleophilic solvent assistance ($Q' = 0.42$). Solvolyses of pinacolyl (II), 2-*exo*-norbornyl (III), 2-*endo*-norbornyl (IV), menthyl (V), and cyclooctyl tosylates are either k_s or k_Δ (not k_c as proposed by others), since they respond less to changes in solvent ionizing power than the k_c mechanistic models (I, VI, VII).

S_N1 reactions proceed via transition states with high carbocation character to ion pair intermediates.[4] S_N2 reactions are accelerated relative to S_N1 reactions by rearside nucleophilic attack, and such nucleophilic assistance reduces the carbocation character in the transition state. S_N2 reactions occurring by a concerted mechanism will here be referred to as S_N2 (one-stage); they span a huge range of degrees of nucleophilic assistance, including classical S_N2 processes[4f] and some weakly assisted processes with relatively high carbocation character in the transition state.[2c,5] This variable character of the S_N2 process may be regarded as a "spectrum", implying a progressive series of changes or merging of character, and not a varying mixture of only two distinct processes (S_N2 and S_N1).[2a]

A further gradation of mechanism and reactivity between S_N1 and S_N2 (one-stage) processes can be achieved by using the S_N2 (intermediate) mechanism to account for relatively weakly nucleophilically assisted processes showing ion-pair characteristics.[2a] Thus, the S_N2 (intermediate) mechanism reconciles the evidence for both ion-pair intermediates and nucleophilic assistance.[4b] This

(1) Presented in part at the fourth international symposium on physical organic chemistry (York, Sept 1978) and abstracted in part from the M.Sc. Thesis of D.H.M. (1975) and the Ph.D. Thesis of C.T.B. (1980).

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