Stereoselective Z- and E-Bromo Enol Lactonization of Alkynoic Acids

Wei Dai and John A. Katzenellenbogen*

Department of Chemistry, Box 37, Roger Adams Laboratory, University of Illinois, 1209 W. California St., Urbana, Illinois 61801

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We have found that treatment of the silver salt of a 4- or 5-terminal alkynoic acid with bromine results in clean formation of the corresponding *Z*-bromo enol lactone, the result of a formal cis addition of carboxylate and bromine across the triple bond. This *Z*-bromo enol lactonization is highly stereoselective and gives good yields in systems that bear substituents on the internal methylene groups; yields with unsubstituted or terminally substituted alkynoic acids are modest. The *E*-bromo enol lactonization reaction, reported by us previously (Krafft, G. A.; Katzenellenbogen, J. A. *J. Am. Chem. Soc.* **1981**, *103*, 5459), has a broader scope and, with modifications, can be performed with high reliability. Mercury(II) salts equilibrate the *Z*- and *E*-bromo enol lactones, presumedly by a mercuric ion addition–elimination mechanism. These three reactions provide access to an array of stereoisomeric bromo enol lactone systems.

Introduction

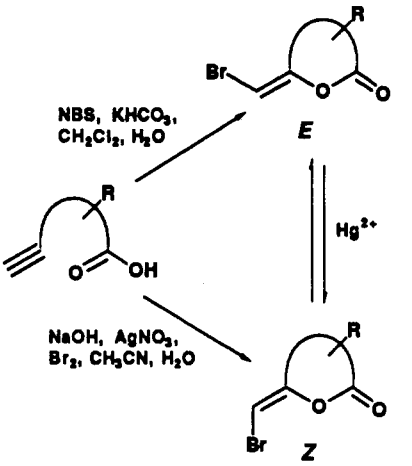
Halo enol lactones, which have been established as mechanism-based inhibitors of serine proteases,[1] are typically prepared by halo enol lactonization of the corresponding acetylenic acid. The reaction conditions for *E*-halo enol lactonization are well established:[1] (1) *N*-halosuccinimide (NBS, NCS, NIS), $KHCO_3$ in a phase-transfer system (CH_2Cl_2 with aqueous Bu_4NOH)[2] or CH_3CN;[1b] (2) I_2, $KHCO_3$ in CH_3CN or aqueous system;[4] and (3) iodosylbenzene (I^{III}) in CH_2Cl_2 in the presence of $BF_3{\cdot}Et_2O$.[5] However, to our knowledge *Z*-halo enol lactonization has not been reported.

In 1981, we found that *Z*-bromo enol lactones could be obtained by mercury-catalyzed lactonization of a bromo-substituted acetylenic acid.[2] However, under these conditions, isomerization and significant dehalogenation of the product were observed. Our recent efforts to develop more efficient inhibitors for human neutrophil elastase (HNE) have led us to a new method for stereoselective intramolecular *Z*-bromo enol lactonization. In addition, we have simplified our former *E*-bromo enol lactonization method, and we have found that an equilibrium is established between the *Z*- and *E*-halo enol lactones in CH_2Cl_2 under mercuric ion catalysis (Scheme I).

Results and Discussion

General. The configurations of the *Z*- and *E*-bromo enol lactones were determined by ^1H NMR and are based on the chemical shift of the vinyl proton of the lactone. For example, the vinyl proton in the *E* isomer is consistently found downfield of its *Z* counterpart, due to deshielding by the lactone ring oxygen. For the *E* isomer, this proton is found near δ 6.0, whereas for the *Z* isomer it is at approximately δ 5.4 (see Experimental Section). The methods to achieve selective *Z*- and *E*-bromo enol lactonization of acetylenic acids are summarized in Scheme I.

Scheme I. *E*- and *Z*-Bromo Enol Lactonization and Isomer Equilibration



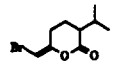
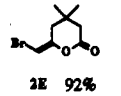
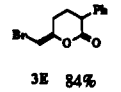
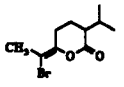
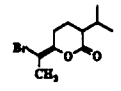
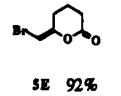
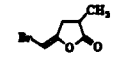
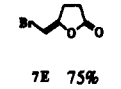
***Z*-Bromo Enol Lactonization.** *E*-Bromo enol lactonization results in an overall anti addition of bromine and carboxylate across the triple bond and is considered to involve initial electrophilic attack of Br^+ on the triple bond, followed by nucleophilic addition of the carboxylate.[2] The reaction takes the opposite stereochemical path—giving the *Z*-bromo enol lactone—when the silver carboxylate is used. While a silver carboxylate could react with bromine by a radical pathway to give Hunsdiecker-type decarboxylative bromination products,[6] the major course of reaction with these alkynoic acids appears to occur by an ionic mechanism to give the desired *Z*-bromo enol lactones. The mechanistic pathway may depend on the reaction medium, and the aqueous system used here would be expected to suppress the radical degradation and accelerate ionic lactonization.

In practice, the silver salt of the 4- or 5-alkynoic acid was prepared in situ by successive addition of aqueous solutions of NaOH (1 equiv) and $AgNO_3$ (1 equiv) to the acetylenic acid at room temperature (Scheme I). The salt suspension was stirred for 5 min, and a solution of Br_2 in CH_3CN was added in the dark. More CH_3CN was added in order to form a more completely dipersed suspension. Reaction times at 25 °C were typically about 12 h. Flash chromatography on silica gel provides only the *Z*-bromo enol lactone in low to excellent yields. The reaction conditions and results are summarized in Table I.

(1) (a) Rando, R. R. *Science* **1974**, *185*, 320. (b) Sofia, M. J.; Chakravarty, P. K.; Katzenellenbogen, J. A. *J. Org. Chem.* **1983**, *48*, 3318. (c) Daniels, S. B.; Katzenellenbogen, J. A. *Biochemistry* **1986**, *25*, 1436.
(2) Krafft, G. A.; Katzenellenbogen, J. A. *J. Am. Chem. Soc.* **1981**, *103*, 5459.
(3) Sofia, M. J.; Katzenellenbogen, J. A. *J. Org. Chem.* **1985**, *50*, 2331.
(4) (a) Doi, J. T.; Luehr, G. W.; Carmen, D. D. *J. Org. Chem.* **1989**, *54*, 2764. (b) Staninets, V. I.; Shilov, E. A. *Russ. Chem. Rev.* **1971**, *40*, 272. (c) Rengevich, E. N.; Staninets, V. I.; Shilov, E. A. *Dokl. Akad. Nauk. SSR* **1962**, *146*, 111.
(5) Ochiai, M.; Takaoka, Y.; Masaki, Y.; Inenaga, M.; Nagao, Y. *Tetrahedron Lett.* **1989**, *30*, 6701.
(6) Wilson, C. V. *Org. React.* **1957**, *9*, 335.

0022-3263/91/1956-6893$02.50/0

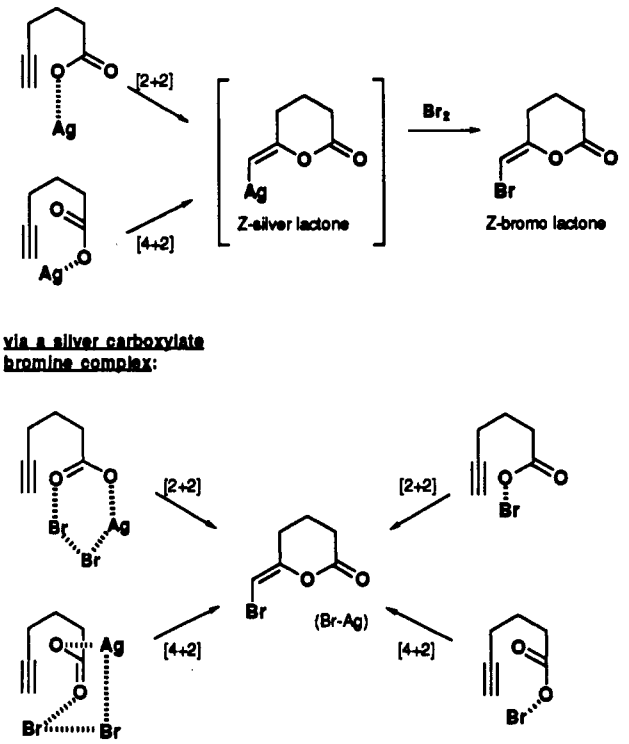
Table I. The Stereoselective *Z*- and *E*-Bromo Enol Lactonization

acetylenic acid	Z-lactone: solvent $CH_3CN:H_2O$	time (h)	yields (%)	E-lactone: base H_2O (eq)	time (min)	yields (%)
 1	1 : 4	10	 1Z 74%	$KHCO_3$ or K_2CO_3/(2)	20	 1E 93%
 2	1 : 1	3	 2Z 86%	$KHCO_3$ or K_2CO_3/(2)	20	 2E 92%
 3	1 : 1	15	 3Z 40%	$KHCO_3$/(3)	60	 3E 84%
 4	1 : 1	12	 4Z Trace	K_2CO_3/(3)	120	 4E 61%
 5	2 : 1	12	 5Z 5%	$KHCO_3$ or K_2CO_3/(3)	60	 5E 92%
 6	2 : 1	12	 6Z 34%	$KHCO_3$/(1)	45	 6E 81%
 7	2 : 1	12	 7Z 2%	$KHCO_3$/(1)	10	 7E 75%

The stereoselectivity of the lactonization was ascertained by ^1H NMR spectroscopy of the crude reaction mixtures (vide supra). Alkyl-substituted and unsubstituted terminal alkynoic acids (**1**, **2**, **5**, **6**, and **7**) showed exclusively *Z* stereoselectivity in the lactonization. However, the aryl-substituted acid **3** gave the *Z* isomer **3*Z*** in 40% yield, together with a trace amount of *E* isomer **3*E***, which was not isolated. The substituted alkynoic acids (**1**, **2**, **3**, **6**) gave much better yields than the unsubstituted compounds (**5**, **7**). This suggests that the substituent may be selectively stabilizing the cyclic transition state (Thorpe–Ingold effect). With acids **4**, **5**, and **7**, in which low yields were obtained, the starting acetylenic acid was still evident in the ^1H NMR spectra of the crude reaction product. Acids **2** and **3** also gave the protio enol lactone in about ~5% yield, but most of the unreacted acetylenic acids in the above reactions could be observed in the ^1H NMR. Alkynoic acid **4** with a disubstituted acetylene gave no reaction; this may be due to both steric and electronic effects of the methyl group on the end of the triple bond. These results indicate (a) that incomplete acyl hypobromite formation or its decomposition back to the starting acid can in some cases (acids **4**, **5**, and **7**) compete significantly with bromo enol lactonization, and (b) that bromine addition to the triple bond is not a serious side reaction.

The *Z*-bromo enol lactonization reported here is unprecedented and is a highly regio- and stereoselective method. The mechanism by which this cis addition of bromine and carboxylate takes place is not readily evident, since it is not certain from what species the cyclization occurs (Scheme II). The following additional observations

Scheme II. Proposed *Z* Lactonization Mechanisms

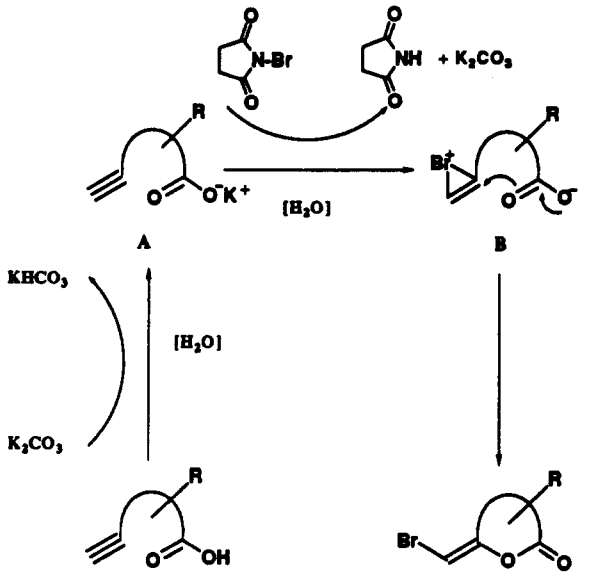


reveal some mechanistic features: (a) In the absence of Ag^+, lactonization does not occur at all; for example, when the sodium salt of acid **2** was treated with Br_2 under the similar conditions (H_2O/CH_3CN, 1:1), only acyclic addition products were obtained ($BrCH{=}CBrCH_2C(CH_3)_2CH_2CO_2H$ in 40% yield and $Br_2C{=}CBrCH_2C(CH_3)_2CH_2CO_2H$, trace amount), and acid **2** was recovered in 55% yield. (b) When bromo enol lactone **1*E*** was treated with $AgNO_3$, *E*–*Z* isomerization was not observed. (c) When I_2, a weaker electrophile, was used in place of Br_2, the silver salt of the acetylenic acid gave a mixture of *Z*- and *E*-iodo enol lactones in 20% yield (*Z*:*E* 1:10). (d) Olefinic acids under these reaction conditions gave only olefin bromohydrin products; this result is similar to that reported by Shilvo.[4b]

Silver carbonate catalyzed intermolecular addition of acetic acid to acetylenes has been reported; the mechanism proposed involved a vinylsilver intermediate that was protonolyzed to give the acetic acid adduct.[7] Silver salts of acetylenic acids have also been cyclized to enol lactones;[8,9] in the one case where the stereochemistry was evident, the addition proceeded in an anti fashion.[9] The formation of small amounts of protio enol lactones in the case of acids **2** and **3** would support a mechanism which involves a concerted syn addition of the silver carboxylate to the acetylene to form a *Z*-silver lactone and its subsequent bromolysis with retention of configuration at carbon to produce the *Z* isomer as the major course of reaction, and protonolysis to the protio enol lactone byproduct being the minor pathway (Scheme II). (Alternatively, the lactonization could give the *E*-silver lactone, and bromolysis could proceed with inversion.) A second possibility in-

(7) Ishino, Y.; Nishiguchi, I.; Nakao, S.; Hirashima, T. *Chem. Lett.* **1984**, 641.
(8) Castañer, J.; Pascual, J. *J. Chem. Soc.* **1958**, 3962.
(9) Jong, T.-T.; Williard, P. G.; Porwoll, J. P. *J. Org. Chem.* **1984**, *49*, 735.

Scheme III. Proposed Mechanism of E-Bromo Enol Lactonization



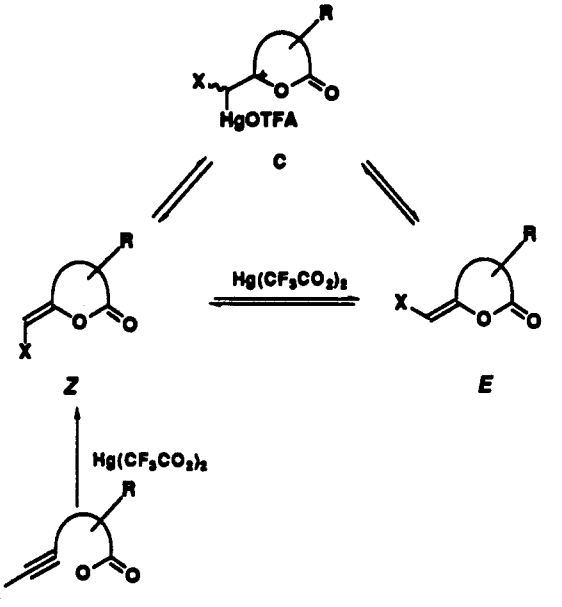
volves a complex between the silver carboxylate and bromine that undergoes a syn addition to give the Z-bromo enol lactone directly. Finally, the acyl hypobromite itself might be the species that undergoes cycloaddition to the Z-bromo enol lactone, with silver playing a role only in the formation of this intermediate.

***E*-Bromo Enol Lactonization.** Previously, we and Doi reported stereoselective E-halo enol lactonization of alkynoic acids in a buffered two-phase organic–aqueous systems with a phase-transfer catalyst (Bu_4NOH).[1b,2] We have simplified this E lactonization by using a CH_2Cl_2–H_2O solvent system. Reaction of 4- and 5-alkynoic acids with K_2CO_3 (or $KHCO_3$) and NBS in CH_2Cl_2, followed by addition of small amount of water (1–4 equiv) (Table I), gives results comparable with and in some cases better than our former phase-transfer procedure (using Bu_4NOH), in terms of reaction time, exclusive E stereochemistry and product yield. In the absence of water, the E-bromo enol lactonization is very slow. As water increases the solubilities of K_2CO_3, $KHCO_3$, and NBS, it may accelerate the deprotonation of the acid and protonation of NBS to release Br^+ in this system.

The E-bromo enol lactonization works well with all types of 4- and 5-alkynoic acids shown in Table I: substituted, unsubstituted, terminal, and internal alkynoic acids. These results suggest that a stepwise mechanism is being followed (Scheme III), without the strict geometric requirements that may be operating in the above Z lactonization mechanism.

Isomerization of *Z*- and *E*-Bromo Enol Lactones. The broader scope of the E-bromo enol lactonization of alkynoic acids led us to pursue a method to obtain the Z isomers from the E isomers (Scheme I). Mercury-catalyzed enol lactonization of certain terminally substituted (X = CH_3, Br, Cl, and Me_3Si) alkynoic acids was reported by us to give a mixture of Z- and E-enol lactones.[2] We proposed that the Z isomer was formed first, by an anti addition of mercuric ion and carboxylate, followed by stereoselective protio demercuration; the E isomer was produced from the Z isomer during the course of the reaction, presumably by a mercuric ion addition–elimination process (Scheme IV, C). Although the halo enol lactones were reported to be quite stereochemically stable,[2] we have found that treatment of E-bromo enol lactones with $Hg(CF_3CO_2)_2$ (0.5–1 equiv) in CH_2Cl_2 at room temperature

Scheme IV. Equilibrium of *E*- and *Z*-Enol Lactonization



X= CH_3, Me_3Si, Br, Cl

Table II. Mercury-Mediated Isomerization of *E*-Bromo Enol Lactones

entry	time (h)	ratio E/Z
1	2	1E/1Z 1/1.9
2	2	5E/5Z 1/6.5
3	2	7E/7Z 1/1.2
4	10	4E/4Z 2/1

results in equilibration between the E- and Z-enol lactone isomers. Several E-bromo enol lactones, prepared by the method above, have been treated with $Hg(CF_3CO_2)_2$ with the results are shown in Table II.

The equilibrium ratio of Z/E isomers was determined by ^1H NMR after TLC showed no further changes in isomer composition. The isolated yield of the mixture of both isomers was good ($Z + E \sim 70\%$), but was reduced somewhat during their separation by flash chromatography. The distribution of E- and Z-lactone isomers at equilibrium is consistent with steric considerations: With the 6-membered trisubstituted lactones 1 and 5 (Table II, entries 1 and 2), the predominant Z isomer achieves minimum steric interaction by placing the bulky bromine cis to the smaller lactone oxygen. As expected, the selectivity is lower in the 5-membered ring lactone 7 (entry 3), where the larger external bond angles reduce these steric interactions. Finally, with the tetrasubstituted system 4, the E isomer predominates (entry 4); since the steric interactions of bromine and methyl are more nearly similar, the dipole repulsion effect dominates, so bromine adopts a position anti to the lactone oxygen.

Conclusions

In summary, our new method for Z-bromo enol lactonization of alkynoic acids provides a unique, regio- and stereoselective approach to Z-bromo enol lactones. The yield of this reaction varies from 2 to 86% and appears to be improved by factors that stabilize a cyclic transition structure. An improved E-bromo enol lactonization method is carried out under milder conditions. As it usually gives good yields, regardless of alkynoic acid structure, this method may allow for the synthesis of more complex molecules for enzymatic study. An equilibration between Z- and E-bromo enol lactones can be achieved with mer-

cury(II) catalysis. The combination of the above synthetic methods, allowing *Z* and *E* stereoselective bromo enol lactonization and their isomerization, makes it possible to produce all stereoisomeric bromo enol lactones for further chemical or biochemical investigation.

Experimental Section

General Methods. All melting points are uncorrected. Analytical thin-layer chromatography (TLC) was performed using Merck silica gel 60 F-254 precoated (0.2 mm) glass-backed plates. Visualization methods included ultraviolet light or vanillin spray methods. Flash chromatography was performed according to Still,[10] using Woelm 32–63-μm silica gel. Deuterated chloroform ($CDCl_3$) was used for all ^1H NMR spectroscopy. The synthesis of acetylenic acids **3** and **5–7** have been described;[2,11] we are reporting the preparation of acids **1**, **2**, and **4** elsewhere (Dai, W.; Katzenellenbogen, J. A., manuscript in preparation).

General Procedure for *Z*-Bromo Enol Lactonization. To an acetylenic acid (1 mmol) were sequentially added solutions of NaOH (1 mmol in 5 mL of H_2O stirred about 10 min) and $AgNO_3$ (1 mmol in 5 mL of H_2O). After being stirred another 5 min, a solution of Br_2 (1 mmol in 2.5 mL of CH_3CN) was added with vigorous stirring. The reaction was followed by TLC (EtOAc–hexane, 2:3) and visualized by vanillin/H_2SO_4 spray. More CH_3CN was added to keep the mixture well dispersed. Extraction with CH_2Cl_2 (centrifugation used as needed), drying ($MgSO_4$), and solvent evaporation gave the crude products, which were purified by flash chromatography (EtOAc–hexane, 1:3) (Table I).

3-Isopropyl-6(*Z*)-(bromomethylidene)tetrahydro-2-pyranone (1*Z*): colorless oil; ^1H NMR ($CDCl_3$) δ 5.44 (br s, 1 H, C=CH), 2.66 (m, 1 H, COCH), 2.45 (C=CCH_2 and m, 3 H, (CH_3CH)), 1.80 (m, 2 H, CH_2); MS *m/z* 232 (38, M^+), 153 (11), 125 (100), 97 (24), 83 (10), 69 (12); HRMS (EI) calcd for $C_9H_{13}O_2Br$ (M^+) 232.0098, found (M^+) 232.0099.

4,4-Dimethyl-6(*Z*)-(bromomethylidene)tetrahydro-2-pyranone (2*Z*): colorless oil; ^1H NMR ($CDCl_3$) δ 5.35 (s, 1 H, C=CH), 2.49 (s, 2 H, CH_2CO), 2.33 (s, 2 H, CH_2), 1.07 (s, 6 H, 2 CH_3); MS *m/z* 218 (100, M^+), 189 (40), 161 (45), 138 (5), 120 (100), 82 (70); HRMS (EI) calcd for $C_8H_{11}O_2Br$ (M^+) 217.9943, found (M^+) 217.9942.

3-Phenyl-6(*Z*)-(bromomethylidene)tetrahydro-2-pyranone (3*Z*): colorless crystals; mp 100–101 °C; ^1H NMR ($CDCl_3$) δ 7.22–7.46 (m, 5 H, Ar), 5.42 (t, *J* = 1.1 Hz, 1 H, C=CH), 3.87 (dd, *J* = 10.1, 6.2 Hz, 1 H, CHPh), 2.02–2.74 (m, 4 H, CH_2CH_2); MS *m/z* 266 (4, M^+), 187 (82, 159 (100), 141 (21), 117 (65), 103 (41). Anal. Calcd for $C_{12}H_{11}BrO_2$: C, 53.96; H, 4.15; Br, 29.91. Found: C, 53.85; H, 4.21; Br, 29.76.

6(*Z*)-(Bromomethylidene)tetrahydro-2-pyranone (5*Z*): colorless crystals; mp 75–76 °C; ^1H NMR ($CDCl_3$) δ 5.37 (s, 1 H, C=CH), 2.71 (t, *J* = 6.8 Hz, 2 H, CH_2CO), 2.59 (t, *J* = 6.5 Hz, 2 H, C=CCH_2), 1.91 (tt, *J* = 6.5, 6.8 Hz, 2 H, CH_2); MS *m/z* 190 (14, M^+), 120 (35), 83 (83), 55 (100); HRMS (EI) calcd for $C_6H_7BrO_2$ (M^+) 189.9629, found (M^+) 189.9630. Anal. Calcd for $C_6H_7BrO_2$: C, 37.73; H, 3.69. Found: C, 38.08; H, 3.80.

3-Methyl-5(*Z*)-(bromomethylidene)tetrahydro-2-furanone (6*Z*): colorless oil; ^1H NMR δ 5.32 (dd, *J* = 1.2 Hz, 1 H, C=CH), 2.94 (ddq, *J* = 9.4, 7.6, 7.1 Hz, 1 H, CHCO), 2.80 (AB q, Δν = 0.58 ppm, *J* = 15 Hz; upfield, dd, *J* = 9.4, 1.2 Hz; downfield, dd, *J* = 8.6, 2.3 Hz), 1.36 (d, *J* = 7.1 Hz, 3 H, CH_3); MS *m/z* 190 (31, M^+), 120 (99), 111 (10), 83 (42), 56 (100), 41 (34). Anal. Calcd for $C_6H_7BrO_2$: C, 37.73; H, 3.69; Br, 41.83. Found: C, 37.75; H, 3.70; Br, 41.82.

5(*Z*)-(Bromomethylidene)tetrahydro-2-furanone (7*Z*):[2] colorless oil; ^1H NMR ($CDCl_3$) δ 5.34 (t, *J* = 2 Hz, 1 H, C=CH), 2.83 (m, 4 H, 1 CH_2).

General Procedure for *E*-Bromo Enol Lactonizations. To K_2CO_3 (or $KHCO_3$, 1 mmol) was added acetylenic acid (1 mmol) and CH_2Cl_2 (10 mL) with stirring. After 10 min, *N*-bromosuccinimide (1 mmol) was added, followed by addition of H_2O (1–4 mmol). The reaction was followed by TLC (EtOAc–hexane, 1:10) and visualized by vanillin/H_2SO_4 spray until the acetylenic acid almost totally disappeared. Dilution with additional CH_2Cl_2, drying over $MgSO_4$, and evaporation afforded the crude material, which was purified by flash chromatography (eluant EtOAc–hexane, 1:13) (Table I).

3-Isopropyl-6(*E*)-(bromomethylidene)tetrahydro-2-pyranone (1*E*): colorless oil; ^1H NMR δ 6.00 (t, *J* = 1.6 Hz, 1 H, C=CH), 2.90 (m, 1 H, COCH), 2.40 (m, 3 H, C=CCH_2 and Me_2CH), 1.87 (m, 2 H, CH_3), 1.00 (d, *J* = 6.6 Hz, 3 H, CH_3), 0.95 (d, *J* = 6.7 Hz, 3 H, CH_3); MS *m/z* 232 (6, M^+), 153 (4), 125 (51), 120 (5), 97 (34), 83 (120), 69 (100), 55 (76), 41 (100); HRMS (EI) calcd for $C_9H_{13}BrO_2$ (M^+) 232.0098, found (M^+) 232.0098.

4,4-Dimethyl-6(*E*)-(bromomethylidene)tetrahydro-2-pyranone (2*E*): colorless oil; ^1H NMR ($CDCl_3$) δ 6.08 (s, 1 H, C=CH), 2.51 (s, 2 H, $COCH_2$), 2.44 (s, 2 H, C=CCH_2), 1.10 (s, 6 H, 2 CH_3); MS *m/z* 218 (5, M^+), 120 (4), 111 (11), 83 (100), 55 (24), 41 (21); HRMS (EI) calcd for $C_8H_{11}BrO_2$ (M^+) 217.9942, found (M^+) 217.9942. Anal. Calcd for $C_8H_{11}BrO_2$: C, 43.86; H, 5.06. Found: C, 43.56; H, 4.90.

3-Phenyl-6(*E*)-(bromomethylidene)tetrahydro-2-pyranone (3*E*):[1b] colorless oil; ^1H NMR ($CDCl_3$) δ 7.33 (m, 5 H), 6.05 (t, *J* = 2 Hz, 1 H, C=CH), 3.80 (m, 1 H, PhCH), 2.75 (m, 2 H, C=CCH_2, 2.20 (m, 2 H, CH_2).

3-Isopropyl-6(*E*)-(1-bromoethylidene)tetrahydro-2-pyranone (4*E*): colorless oil; ^1H NMR ($CDCl_3$) δ 2.95 (m, 1 H, CHCO), 2.47 (m, 1 H, Me_2CH), 2.30 (t, *J* = 1.7 Hz, 3 H, C=CCH_3), 2.30 (m, 2 H, C=CCH_2), 1.80 (m, 2 H, CH_2), 1.01 (d, *J* = 6.5 Hz, 3 H, CH_3), 0.94 (d, *J* = 6.4 Hz, 3 H, CH_3); MS *m/z* 246 (94, M^+), 167 (59), 139 (74), 125 (20), 97 (87), 69 (239), 43 (20); HRMS (EI) calcd for $C_{10}H_{15}BrO_2$ (M^+) 246.0256, found (M^+) 246.0255.

6(*E*)-(Bromomethylidene)tetrahydro-2-pyranone (5*E*):[2] colorless oil; ^1H NMR δ 6.11 (t, *J* = 1 Hz, 1 H, C=CH), 2.43–2.85 (m, 4 H), 1.63–1.98 (q, *J* = 7 Hz, 2 H); δ 6.10 (br s, 1 H, C=CH), 2.69 (t, *J* = 6.3 Hz, 2 H, CH_2CO), 2.64 (t, *J* = 6.7 Hz, 2 H, C=CCH_2), 1.85 (tt, *J* = 6.7, 6.3 Hz, 2 H, CH_2).

3-Methyl-5(*E*)-(bromomethylidene)tetrahydro-2-furanone (6*E*): colorless oil; ^1H NMR δ 5.98 (dd, *J* = 2.7, 1.9 Hz, 1 H, C=CH), 2.90 (ddq, *J* = 10.1, 7.6, 7.3 Hz, 1 H, CHCO), 2.84 (AB q, Δν = 0.7 ppm, *J* = 17 Hz; upfield, dd, *J* = 7.6, 2.7 Hz; downfield, dd, *J* = 10.1, 1.9 Hz, 2 H, CH_2), 1.38 (d, *J* = 7.3 Hz, 3 H, CH_3); MS *m/z* 190 (30, M^+), 120 (100), 111 (7), 83 (32), 56 (81). Anal. Calcd for $C_6H_7BrO_2$: C, 37.73; H, 3.69; Br, 41.83. Found: C, 37.80; H, 3.75; Br, 42.18.

5(*E*)-(Bromomethylidene)tetrahydro-2-furanone (7*E*):[2] colorless oil; ^1H NMR ($CDCl_3$) δ 6.00 (t, *J* = 2.0 Hz, 1 H, C=CH), 2.83 (m, 4 H, 2 CH_2).

General Procedure for Mercury-Mediated Equilibration between *E*- and *Z*-Bromo Enol Lactones. A mixture of *E*-bromo enol lactone (0.5 mmol in 5 mL of CH_2Cl_2) and $Hg(CF_3CO_3)_2$ (0.5 mmol) was stirred at room temperature until TLC shows no further change. Addition of solutions of saturated $NaHCO_3$ and NaCl (to form insoluble HgO–3HgCl), stirring for 10 min, extraction with CH_2Cl_2, and drying over $MgSO_4$ afforded the crude mixture of *E* and *Z* isomers. The ratio of *E*/*Z* was determined by ^1H NMR (Table II). The two isomers could be separated by flash chromatography on silica gel (eluant hexane/CH_2Cl_2/Et_2O, 12:1:1).[2]

Registry No. 1, 136358-11-7; (*E*)-1 enol lactone, 136358-14-0; (*Z*)-1 enol lactone, 136358-13-9; 2, 92898-15-2; (*E*)-2 enol lactone, 136358-16-2; (*Z*)-2 enol lactone, 136358-15-1; 3, 88071-01-6; (*E*)-3 enol lactone, 88070-96-6; (*Z*)-3 enol lactone, 136457-92-6; 4, 136358-12-8; (*E*)-4 enol lactone, 136358-17-3; 5, 53293-00-8; (*E*)-5 enol lactone, 79054-08-3; (*Z*)-5 enol lactone, 136358-18-4; 6, 74064-82-7; (*E*)-6 enol lactone, 136408-11-2; (*Z*)-6 enol lactone, 136358-19-5; 7, 6089-09-4; (*E*)-7 enol lactone, 79054-09-4; (*Z*)-7 enol lactone, 79054-18-5.

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