New Approaches to the Synthesis of Alkyl-Substituted Enol Lactone Systems, Inhibitors of the Serine Protease Elastase

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We have synthesized a series of alkyl-substituted enol lactones designed to act as mechanism-based inhibitors of human neutrophil elastase (HLE). General methods were developed for the preparation of α- and β-alkyl-substituted 5-hexynoic acids by the bromoform reaction on the corresponding alkynoic methyl ketone, prepared by an Eschenmoser–Tanabe fragmentation sequence from a suitably substituted cyclohexenone. By this method, β-methyl- and β,β-dimethyl-5-hexynoic acids were synthesized from commercially available isophorone and 3,5-dimethyl-2-cyclohexen-1-one, respectively. α-Substituted 5-hexynoic acids were prepared from 3-ethoxy-2-cyclohexen-1-one, using a novel $ZnCl_2$-mediated alkylation that we developed; this method gives high yields of α'-alkylation products, even with secondary halides. The most efficient method for the preparation of α-substituted 5-hexynoic acids involved a four-reaction sequence—alkylation of the α-substituted ester with 1,4-dibromobutane, elimination, bromination and bisdehydrobromination—that proceeded in high overall yield. Protio enol lactonizations were performed with mercury(II) catalysis in CH_2Cl_2 or CH_2Cl_2–H_2O. Stereoselective *Z*-bromo enol lactonization was carried out by Br^+-induced lactonization in the presence of Ag^+. *E*-Bromo enol lactonization with *N*-bromosuccinimide in CH_2Cl_2 in the presence of a small amount of water gave better yields and shorter reaction times than the traditional anhydrous conditions. In studies of the inhibitory activity of these lactones toward several proteases (reported in full elsewhere), we found that the α-alkyl-substituted protio and bromo enol lactones **1–3** were very good inhibitors of HLE, with k_a/K_i values ranging from 14 500 to 37 500 M^{-1} s^{-1}; the β-alkyl-substituted enol lactones **5–8** showed only moderate inhibition of HLE.

Introduction

Serine proteases play important regulatory roles in protein processing and degradation, in both normal and pathological conditions.[1] Thus, the search for effective and selective inhibitors of serine proteases has been an active area of research, as such agents might have therapeutic utility or they might be useful at least in establishing the role played by specific proteases in vivo.

While inhibitors that have high selectivity for particular proteases must often consist of oligomeric structures of a peptidic or peptidomimetic nature, that resemble portions of the normal protease substrate,[2] it has been possible to achieve considerable selectivity with small molecule inhibitors. Examples of such small molecule inhibitors are peptidyl boronic acids,[3] peptide aldehydes and ketones,[4] or peptidyl derivatives of (α-aminoalkyl)phosphonates.[5] In addition, many interesting strategies have been taken in developing mechanism-based inhibitors of serine proteases, that is, those inhibitors whose latent reactivity is revealed by a protease-mediated process. There are examples of the generation of Michael acceptors,[7] acylating functions,[8] and diazonium ions (etc.).[9]

In our own work, we have developed enol lactones and halo enol lactones as inhibitors of serine proteases of the alternate substrate type and the enzyme-activated irreversible type, respectively.[10] The latter class, halo enol lactones, contains a reactive function that is latent in the lactone (as a vinyl halide) but is revealed as a reactive halomethyl ketone upon acyl transfer to the active site serine hydroxyl group. We have described a comprehensive investigation of aryl-substituted systems as inhibitors of chymotrypsin,[11] and more recently, we have described guanidino-aryl substituted enol lactone systems that are selective inhibitors of trypsin-like proteases.[12]

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(2) For a general review, see: Rich, D. H. In *Comprehensive Medicinal Chemistry, The Rational Design, Mechanistic Study and Therapeutic Application of Chemical Compounds*; Hansch, C., Sammes, P. G., Taylor, J. B., Eds.; Pergamon Press: New York, 1990, pp 391–439.

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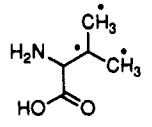
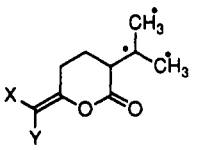
Scheme I. Enol Lactone Mimics of Valine, Leucine, Isoleucine, and Norleucine

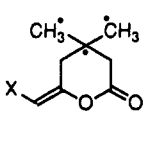


Valine

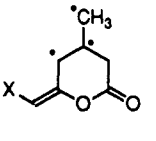
Valine Mimic Enol Lactones



	X	Y
1	H	H
2	Br	H
3	H	Br
4	Br	CH_3

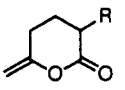


	X
5	H
6	Br



	X
7	H
8	Br

Mimics of Leucine, Isoleucine and Norleucine



9 R = $-CH_2CH(CH_3)CH_3$ (Leu)

10 R = $-CH(CH_3)CH_2CH_3$ (Ile)

11 R = $-CH_2CH_2CH_3$ (Nleu)

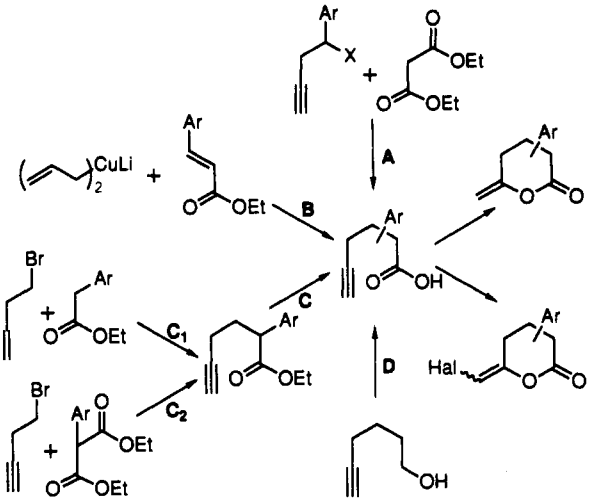
In this report, we present a variety of new approaches that have been used for the preparation of enol lactone systems substituted in a manner suitable for the inhibition of the serine protease elastase. Through these methods, we have prepared a number of inhibitors that mimic the small aliphatic residues (alanine, valine, and leucine) commonly found at the P_1 position of the substrates for elastase.[13] Elsewhere, we describe the enzyme inhibitory activity of these lactones toward elastase and related serine proteases.[14]

Results and Discussion

Synthetic Targets: Enol Lactones that Mimic Valine, Leucine, Isoleucine, and Norleucine. The structures of enol lactone systems whose preparation we describe in this paper are shown in Scheme I, together with the structure of valine. The three dots on the residue substituent of valine indicate in what way this isopropyl group is represented in the three valine mimic enol lactones: either fully external as in systems **1–4** (α-isopropyl-δ-methylenevalerolactone) or partially internal as in systems **5–8** (β,β-dimethyl-δ-methylenevalerolactone). For the purpose of comparison, we have also prepared δ-methylenevalerolactones bearing α-isobutyl (**9**), *sec*-butyl (**10**), and propyl (**11**) substituents as enol lactone mimics of leucine, isoleucine, and norleucine.

As we have described previously, both the enol lactones and the halo enol lactones can be prepared from the corresponding acetylenic acids, in this case 5-hexynoic acids, by a mercury-catalyzed enol lactonization or a halo enol lactonization, respectively. These processes are outlined in Scheme II.

Scheme II. Previously-Developed Routes to 5-Hexynoic Acids and Their Conversion into Enol Lactones and Halo Enol Lactones



This same scheme outlines the synthesis of α- and β-*aryl*-substituted or unsubstituted hexynoic acids that have been previously demonstrated by us[10] and by others.[15] The alkylation of diethyl malonate with an alkyl mesylate followed by saponification and decarboxylation provides β-aromatic hexynoic acids (path A).[10f] The β-aromatic hexynoic acids are also obtained by conjugate addition of lithium diallylcuprate to an aryl-substituted α,β-unsaturated ester, followed by a double bond to triple bond conversion (path B).[10g] α-*Aryl*-substituted hexynoic acids are synthesized by alkylation of an α-aryl-substituted ester with 1-bromo-3-butyne or 1-bromo-3-butene (path C_1, C_2).[10g] The oxidation of 5-hexyn-1-ol gives unsubstituted 5-alkynoic acid (path D).[15]

In some cases, the synthesis of α- or β-*alkyl*-substituted hexynoic acids by these methods is satisfactory. For example, the synthesis of 3-methyl-5-alkynoic acid **15b** can be achieved by the method shown in path A and 2-isopropyl-5-hexynoic acid **15a** by the method shown in path C_1, but these yields are quite often low. Furthermore, the conjugate addition pathway B and the alkylation pathway C_2 are often inefficient in alkyl-substituted systems. Therefore, we set out to develop some alternate synthetic strategies.

Synthesis of β-Alkyl- and β,β-Dialkyl-Substituted 5-Hexynoic Acids. Eschenmoser–Tanabe Fragmentation Approach. An alternate method for carboxyl group formation in a substituted 5-hexynoic acid is by a haloform cleavage of the corresponding acetylenic methyl ketone. The latter intermediate could be prepared by the Eschenmoser–Tanabe fragmentation method.[16] Both β-methyl- and β,β-dimethyl-5-hexynoic acids **15a** and **15b** were prepared by this approach (Scheme III). Commercially available isophorone (**12a**) and 3,5-dimethylcyclohexenone **12b** were subjected to epoxidation and fragmentation to give the acetylenic methyl ketones **14a** and

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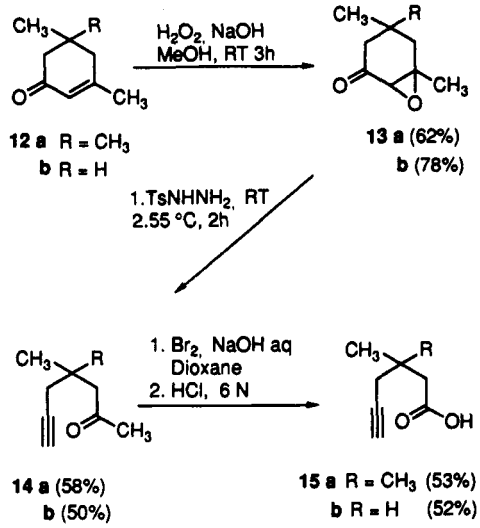
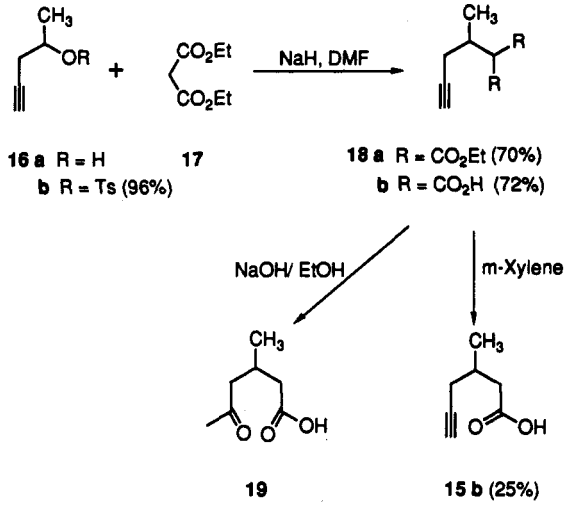
(16) (a) Wasson, R. L.; House, H. O. *Organic Syntheses*; Wiley: New York, 1963; Collect. Vol. IV, p 552. (b) Tanabe, M.; Crowe, D. F.; Dehn, R. L.; Detre, G. *Tetrahedron Lett.* **1967**, *40*, 3739 and 3943. (c) Langin-Lanteri, M. T.; Huet, J. *Synthesis* **1976**, 541.

Scheme III. Preparation of β-Substituted 5-Hexynoic Acids 15a,b



Scheme IV. Malonate Ester Approach to β-Alkyl-5-hexynoic Acids 15b



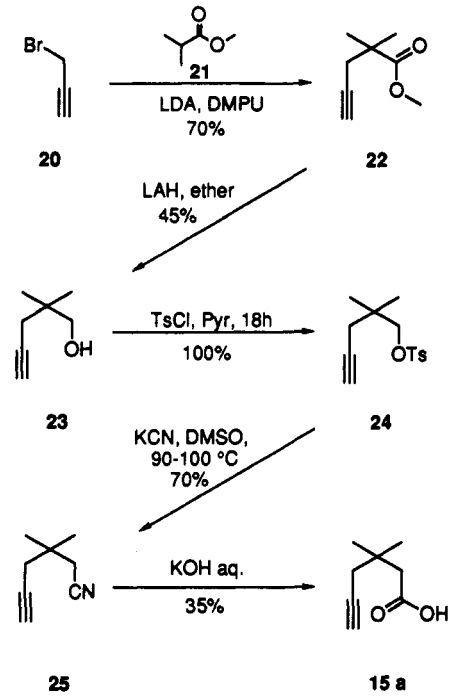
14b, respectively.[16b,c] A bromoform reaction in basic dioxane provided β-methyl- or β,β-dimethyl-5-hexynoic acids **15a** or **15b** in reasonable yields.

Malonate Ester Alkylation Approach. A similar procedure to that shown in Scheme II path A, was also used to prepare β-methyl-5-hexynoic acid **15b** (Scheme IV). The alkylation of diethyl malonate (**17**) with acetylenic tosylate **16b** in the presence of NaH in DMF gave diester **18a**. Hydrolysis in refluxing basic EtOH gave diacid **18b**. The decarboxylation of diacid **18b** under aqueous conditions caused hydration of the triple bond, affording methyl ketone acid **19**. However, when xylene was used as solvent for the decarboxylation of **18b**, the desired hexynoic acid **15b** was obtained.

Nitrile Homologation Approach. We investigated an approach to alkynoic acids **15a** and **15b** from the corresponding acetylenic nitriles respectively (Scheme V). Alkylation of methyl isobutyrate (**21**) with propargyl bromide (**20**) gave methyl 2,2-dimethyl-4-pentynoate (**22**) in 70% yield (Scheme V). Lithium aluminum hydride (LAH) reduction produced 2,2-dimethyl-4-pentyn-1-ol (**23**) in 45% yield.[17] Conversion to tosylate **24** and displacement

(17) Crimmins, M. T.; De Loach, J. A. *J. Am. Chem. Soc.* **1986**, *108*, 800.

Scheme V. Cyanide Homologation Approach to 5-Hexynoic Acid 15a



with KCN gave nitrile **25** in 70% yield. Basic hydrolysis of nitrile **25** produced acid **15a** in 35% yield.

A similar approach to 4-methyl-5-hexynoic acid (**15b**) via the corresponding nitrile proved to be less successful, as basic hydrolysis of the nitrile also caused hydration of the acetylene function, furnishing largely the keto acid.

Synthesis of α-Alkyl-5-hexynoic Acids. Eschenmoser–Tanabe Fragmentation Approach. We have explored the synthesis of α-alkyl-5-hexynoic acids by the Eschenmoser–Tanabe fragmentation. This approach requires a γ-alkyl-substituted cyclohexenone (e.g., **31a–d**), which we prepared by α′-alkylation of 3-ethoxy-2-cyclohexen-1-one (**26**). While the Stork–Danheiser kinetic alkylation with LDA in THF works well with allylic halides, and, upon the addition of HMPA, also with primary halides,[18] we were not successful in alkylating the kinetic enolate of **26** with secondary halides, and primary halides gave only low yields.

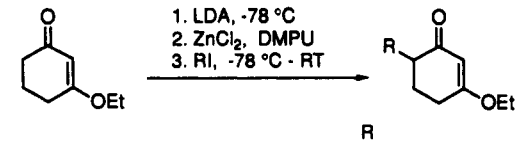
We are attracted to Noyori's recently described method for $Zn(CH_3)_2$-promoted alkylation of lithium enolates.[19] Much to our delight, we found that the expensive and explosive dimethylzinc reagent could be replaced simply by zinc chloride. The reaction was carried out as follows: the lithium enolate was generated from a solution of LDA (1.3 equiv) in THF at −78 °C. Freshly dried, anhydrous $ZnCl_2$ (1–2 equiv), an alkyl iodide (2 equiv), and HMPA were subsequently added. The reaction mixture was stirred at −78 °C for 2 h and then at room temperature for 15 h; HMPA can also be replaced by 1,3-dimethyl-3,4,5,6-tetrahydro-2*H*-pyrimidinone (DMPU) with similar results. The $ZnCl_2$-mediated alkylation was performed with both

(18) (a) Kende, S. A.; Fludzinski, P. *Org. Synth.* **1985**, *64*, 68. (b) Stork, G.; Danheiser, R. L.; Ganem, B. *J. Am. Chem. Soc.* **1973**, *95*, 3414. (c) Stork, G.; Danheiser, R. L. *J. Org. Chem.* **1973**, *38*, 1775.

(19) Noyori, R.; Morita, Y.; Suzuki, M. *J. Org. Chem.* **1989**, *54*, 1785.

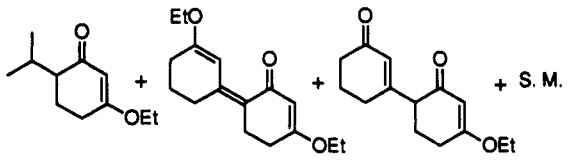
(20) (a) Yamamoto, M. *J. Chem. Soc., Perkin Trans. I* **1981**, 582. (b) Lambert, C.; Utimoto, K.; Nozaki, H. *Tetrahedron Lett.* **1984**, *25*, 5323. (c) Chan, D. M. T.; Marder, T. B.; Milstein, D.; Taylor, N. J. *J. Am. Chem. Soc.* **1987**, *109*, 6385.

Scheme VI. α'-Alkylation of 3-Ethoxy-2-cyclohexen-1-one (26). The Effect of $ZnCl_2$



	R	
26		
27 a	$CH_2CH_2CH_3$	100%
b	$CH_2CH(CH_3)_2$	96%
c	$CH_2CH_2CH(CH_3)_2$	97%

When R = $CH(CH_3)_2$



	27 d	28	29	26
$ZnCl_2$	50%	Trace	10%	30%
$MgCl_2$	30%	30%	Trace	30%
No Lewis Acid	0%	70%	Trace	30%

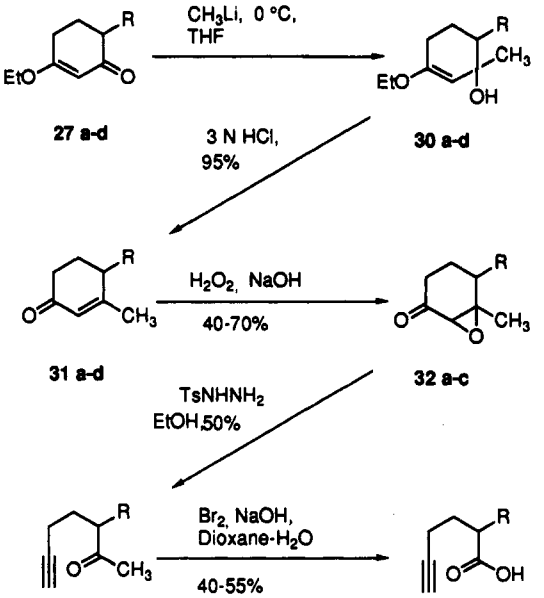
primary and secondary alkyl iodides, and the results are shown in Scheme VI.

The alkylation provided excellent yields of regioselective monoalkylation products, **27a–c**, with *n*-propyl, isobutyl, and isopentyl iodides (96–100%). With a secondary halide (isopropyl iodide), the yield of alkylation product (**27d**) was considerably lower (50%). With $MgCl_2$ in place of $ZnCl_2$, the alkylation yield with secondary halides fell to 30%, but in the absence of Lewis acid, the yield was zero. Two different dimers, **28** and **29**, were also formed under the reaction conditions. Dimer **28** was formed by an intermolecular aldol condensation; subsequent acid-catalyzed hydrolysis of enol ether ketone **28** gave dimer **29**.

As shown in Scheme VII, addition of MeLi to the α'-alkylated enones **27a–d** gave the allylic alcohols **30a–d**, which upon acidic workup gave the 3,4-substituted 2-cyclohex-1-ones **31a–d** in good yields. Epoxidation with alkaline hydrogen peroxide followed by treatment with tosylhydrazine to effect the Eschenmoser–Tanabe fragmentation gave the acetylenic methyl ketones **33a–c**. Finally, a bromoform reaction gave α-alkyl-5-hexynoic acids **34a–c**.

Ester Enolate Alkylation with 1,4-Dibromobutane. An alternate synthesis of α-alkyl-5-hexynoic acid was achieved by a modification of path C_1 in Scheme II. While the enolate alkylation approaches shown in pathway C_1 and C_2 of Scheme II appear to be direct, they suffer from low yield, as both the homoallylic and homopropargylic halides readily undergo elimination to the corresponding dienes or enynes. By contrast, we found that 1,4-dibromobutane (**35**), which is an inexpensive synthetic equivalent of 1-bromo-3-butene, gives a 98% yield of bromo ester **37**. This material was converted to the olefinic acid **38** by treatment with KOtBu and KOH in DMSO. A side product was acid **39**, which formed by intramolecular

Scheme VII. Eschenmoser–Tanabe Fragmentation of 3,4-Dialkyl-2-cyclohexen-1-ones



R:
a = Pr; b = iBu; c = iPen; d = iPr.

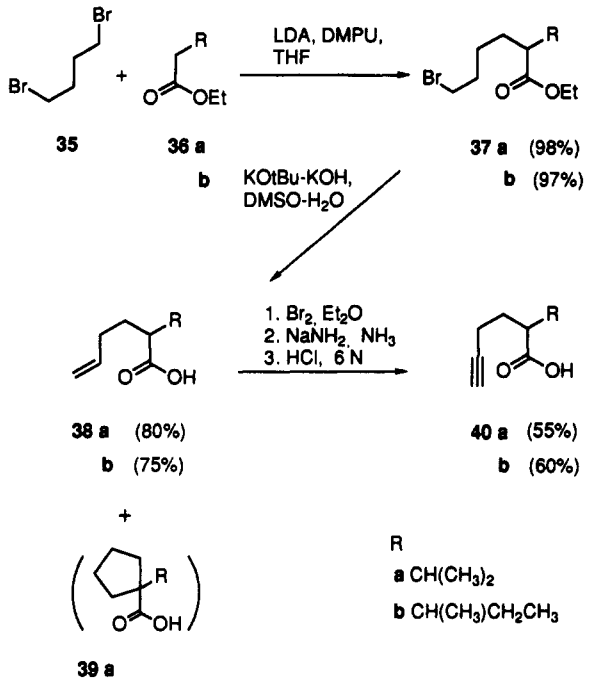
alkylation of **37**. Bromination followed by bis-dehydrobromination with $NaNH_2$[21] produced acetylenic acid **40** in 61% yield. While this route is longer than that in pathways C_1 and C_2 of Scheme II, it is much more efficient overall.

Synthesis of Internal Alkynoic Acids. In order to prepare 6-substituted bromo enol lactones, for example, **4**, the corresponding internal alkynoic acid **41** was required. We thought that regioselective alkylation of α-isopropyl-5-hexynoic acid (**40**) could be carried out by generation of the dianion of terminal acetylenic acid **40** and further reaction with 1 equiv of alkyl iodide. Therefore, acid **40** was treated with 2 equiv of LDA in THF at 0 °C, followed by the addition of CH_3I (or EtI, 1 equiv) and DMPU. Workup as usual gave the desired alkylated product **41** or **42**. When the more reactive methyl iodide was used, acid **41** was obtained in 80% yield; the less reactive ethyl iodide provided 20% of acid **42** (Scheme IX). In the latter case, no further optimization was made.

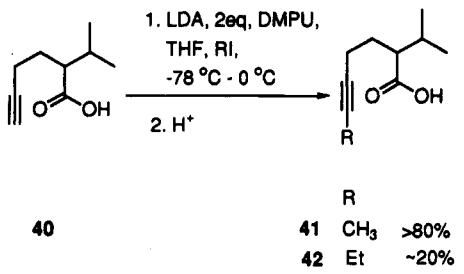
Preparation of the Protio Enol Lactones. Protio enol lactonization of acetylenic acids can be performed with different catalysts, Hg^{2+},[10] Pd^{2+}, and Rh.[20] In our hands, treatment of β-methyl- or β,β-dimethyl-5-hexynoic acids **15b**, **15a**, or **34a** with a catalytic amount (~5 mol %) of mercuric trifluoroacetate in anhydrous CH_2Cl_2 at room temperature gave enol lactones **7**, **5**, and **11** in very good yields (Scheme X). Under the same conditions, however, the bulkier α-substituted alkynoic acids such as **34b,c**, and **40a,b** (Scheme X) gave reduced yields of the corresponding lactones. Prolongation of the reaction time gives the desired exocyclic lactone contaminated with the endocyclic isomer **43**. With acid **40**, endo enol lactone **43** is the major product at longer reaction times (see Scheme X).

(21) Brandsma, L. in *Preparative Acetylenic Chemistry*; Brandsma, L., Ed.; Elsevier Science Publishers: Amsterdam-Oxford-New York-Tokyo, 1988; p 173.

Scheme VIII. An Efficient, Alternate Approach to α-Alkyl-5-hexynoic Acids 40a,b



Scheme IX. Regioselective Alkylation of 5-Hexynoic Acid 40



We found that the addition of 1–3 equiv of water reduced the reaction time (to within less than 0.5 h) and improved the yields of protio lactone **5** or **7** (Scheme X). In fact, the hindered lactone *sec*-Bu6H **10** and α-*i*-Pr6H **1** were isolated in over 92% yield, free from isomerization products under these reaction condition.

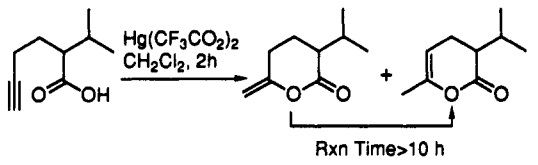
Mercury(II)-catalyzed enol lactonization of acid **40** was also performed in an aqueous acetonitrile solvent system (CH_3CN–H_2O, 1:2), but under these conditions the hydration of the triple bond became the predominate reaction.

Stereoselective *Z*- and *E*-Bromo Enol Lactonization of Alkynoic Acids. We have recently reported that alkyl-substituted 5-hexynoic acids can be stereoselectively cyclized to give either *Z*- or *E*-bromo enol lactones (Scheme XI).[22] *E*-Bromo enol lactones **2**, **4**, **6**, and **8** were obtained in very good yields (61–93%) by treatment of the corresponding alkynoic acid with NBS and $NaHCO_3$ in CH_2Cl_2–H_2O solvent systems. Reaction of silver salt of acid **40** with Br_2 in CH_3CN–H_2O gave the *Z*-bromo enol lactone in 74% yield.

Conclusions

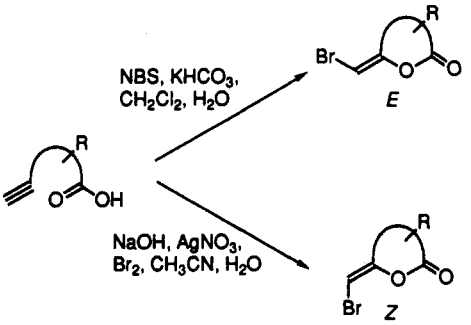
In summary, we have investigated synthetic approaches to α- and β-alkyl-substituted 5-hexynoic acids. The

Scheme X. Protio Enol Lactonization



	R	CH_2Cl_2–H_2O	CH_2Cl_2
1	iPr	92%	~ 30%
9	iBu	—	39%
10	secBu	95%	35%
11	Pr	—	85%
5	CH_3	93%	75%
7	H	85%	83%

Scheme XI. *E*- and *Z*-Bromo Enol Lactonization



Eschenmoser–Tanabe fragmentation pathway seems to be a general method for the synthesis of both α- and β-alkyl-substituted 5-hexynoic acids (Schemes III and VII). For β-alkyl-substituted alkynoic acids, the alkylation method (Scheme IV) is useful if the required starting alkyne, such as **16a**, is available. The nitrile hydrolysis method for β-substituted alkynoic acids occurs with a side reaction (triple bond hydrolysis); so, it is not very efficient. The Eschemoser–Tanabe fragmentation method for the synthesis of α-alkyl-substituted 5-alkynoic acids is novel. The $ZnCl_2$-mediated alkylation of 3-ethoxy-2-cyclohexen-1-one, developed by us in the course of this study, is very simple, giving excellent yields for primary alkyl iodides and reasonable yields for secondary alkyl iodide (Scheme VI). This alkylation may be generally useful in organic synthesis. The alkylation method for α-alkyl-substituted alkynoic acids shown in Scheme VIII, starting with 1,4-dibromobutane, is a very efficient method. We expect that this approach could be a generally useful synthetic method for α-substituted terminal alkynoic acids with longer carbon chains. The internal alkynoic acids **41** and **42** were obtained by regioselective alkylation of terminal alkynoic acid **40** with reasonable yields. We successfully

(22) Dai, W.; Katzenellenbogen, J. A. *J. Org. Chem.* **1991**, *56*, 6893.
(23) Still, W. C.; Kahn, M.; Mitra, A. P. *J. Org. Chem.* **1978**, *43*, 2923.

prepared protio enol lactones and *E*-bromo enol lactones in the CH_2Cl_2–H_2O solvent system with high yields and with short reaction times, and our new method for *Z*-bromo enol lactonization provides a unique, regio- and stereoselective approach to *Z*-bromo enol lactones.

The effectiveness of the α- and β-alkyl-substituted enol and halo enol lactone systems, described here as inhibitors of human neutrophil elastase and related serine proteases, will be described elsewhere.[14] In brief, we find that α-alkyl-substituted enol lactones **1–3** are much better inhibitors than β-alkyl substituted ones (**5–8**). The k_a/K_i values of α-alkyl-substituted enol lactones ranged from 14 500 to 37 500 M^{-1} s^{-1}. Some of the valine mimic enol lactones were found to have an inhibitory effect on other serine proteases, such as α-chymotrypsin, trypsin, urokinase, and plasmin, but their reaction is highest toward elastase.

Experimental Section

General Methods. Most chemicals and solvents were used as purchased from Aldrich except that mentioned below. Diethyl malonate was distilled before use and tetrahydrofuran (THF) was distilled from sodium benzophenone ketyl. Triethylamine was distilled from CaH_2. Melting points are uncorrected. Reactions were followed by analytical thin-layer chromatography (TLC) with Merck 0.25-mm silica gel glass-backed plates and a F-254 indicator. Visualization of TLC was done by UV light, iodine vapor, or vanillin spray reagent. In some cases, the reactions were followed by gas chromatography using a Hewlett-Packard Ultra 1 fused silica capillary column. The reaction products were purified by distillation at the indicated pressure and temperature, or by flash column chromatography,[21] using Woelm 32–63-μm silica gel. Deuterated chloroform ($CDCl_3$) was used for all ^1H NMR spectroscopy.

Small alkyl-substituted 5-hexynoic acids are quite polar, so special precautions are needed during their synthesis. For example, a minimum amount of water should be used in any aqueous workup, and the mobile phase used in flash chromatography should contain a small amount (1–5%) of acetic acid. The 5-hexynoic acids are also volatile; simple removal of acetic acid used above under vacuum results in almost total loss of the hexynoic acid products at the same time. Therefore, benzene azeotropic distillation was used to remove acetic acid efficiently.

3,5,5-Trimethyl-2,3-epoxycyclohexan-1-one (13a). This compound was prepared according to the method of House,[16a] on a 25-mmol scale, giving **13a** in 62% yield as a colorless oil, bp 81–83 °C/6 mmHg (lit. **16a** yield 70%, bp 70–73 °C/5 mmHg); ^1H NMR δ 3.06 (s, 1 H, COCH), 2.24 (AB q, $\Delta\nu$ = 0.8 ppm, J = 13 Hz, 2 H, CH_2), 1.87 (AB q, $\Delta\nu$ = 0.4 ppm, J = 15 Hz, 2 H, CH_2), 1.43 (s, 3 H, $COCH_3$), 0.92 and 1.02 (2 s, 6 H, 2 CH_3).

3,5-Dimethyl-2,3-epoxycyclohexan-1-one (13b). This compound was prepared according to the method of House,[16a] on a 25-mmol scale, giving **13b** in 78% yield as a colorless oil, bp 88–90 °C/16 mmHg (lit. **16a** yield 53%, bp 75–80 °C/14 mmHg); ^1H NMR δ 3.04 (s, 1 H, OCH), 1.50–2.57 (complex, 5 H, CH, 2 CH_2), 1.44 (s, 3 H, CH_3), 0.95 (d, J = 6.0 Hz, 3 H, CH_3).

4,4-Dimethyl-6-heptyn-2-one (14a). This compound was prepared according to the method of Tanabe,[16b] on a 20-mmol scale, giving **30a** in 58% yield as a colorless oil, bp 85–87 °C/16 mmHg. (lit. **16b** yield 40%, bp 75–80 °C/14 mmHg); ^1H NMR δ 2.51 (s, 2 H, $COCH_2$), 2.28 (d, J = 2.5 Hz, 2 H, $C{\equiv}CCH_2$), 2.16 (s, 3 H, CH3) 2.02 (t, J = 2.5 Hz, 1 H, C≡CH), 1.09 (s, 6 H, 2 CH_3).

4-Methyl-6-heptyn-2-one (14b). This compound was prepared according to the method of Tanabe,[16b] on a 20-mmol scale, giving crude **14b** in 50% yield as a colorless oil (97% pure): ^1H NMR δ 2.14 (s, 3 H, $COCH_3$), 2.14–2.70 (complex, 5 H, CH, 2 CH_2), 1.98 (t, J = 2.6 Hz, 1 H, C≡CH), 1.01 (d, J = 6 Hz, 3 H, CH_3).

General Procedure for Preparation of Acetylenic Acid by the Bromoform Reaction of γ-Acetylenic Methyl Ketones. To a stirred solution of sodium hydroxide (30 mmol) in water (10 mL) was added dropwise bromine (7.6 mmol) at −5 °C. The solution was stirred for 5 min and then diluted with dioxane (7 mL) at 0 °C. This cold hypobromite solution was added slowly to a solution of the γ-acetylenic methyl ketone (2.3 mmol) in a solution of dioxane (30 mL) and water (9 mL) below 5 °C. The resulting mixture was stirred for an additional 2 h at this temperature. Excess sodium hypobromite was destroyed by the addition of a solution of sodium thiosulfate (2.27 mmol) in water (3 mL). The mixture was heated under reflux for 15 min and then acidified with 6 N HCl, extracted with $CHCl_3$, and dried over $MgSO_4$. Purification by reduced pressure distillation or flash column chromatography gave the γ-acetylenic acid in 52–53% yield.

3,3-Dimethyl-5-hexynoic acid (15a): colorless oil; ^1H NMR δ 2.40 (s, 2 H, CH_2), 2.29 (d, J = 2.5 Hz, 2 H, CCH_2), 2.03 (t, J = 2.5, 1 H, C≡CH), 1.13 (s, 6 H, 2 CH_3); MS m/z 140 (2, M^+), 139 (7), 125 (8), 101 (34), 95 (8), 81 (52), 79 (26), 59 (100); HRMS (EI) calcd for $C_8H_{12}O_2$ (M^+ − 1) 139.0755, found 139.0757.

3-Methyl-5-hexynoic acid (15b): colorless oil; ^1H NMR δ 2.30–2.70 (complex, 3 H, CH and CH_2CO), 2.23 (m, 2 H, CCH_2), 2.01 (t, J = 2.4 Hz, 1 H, C≡CH), 1.08 (d, J = 6 Hz, 3 H, CH_3); MS m/z 126 (20, M^+), 111 (2), 101 (5), 98 (8), 87 (7), 84 (9), 69 (15), 59 (13), 43 (100). Anal. Calcd for $C_7H_{10}O_2$: C, 66.65; H, 7.99. Found: C, 66.67; H, 8.09.

4-Pentyn-2-yl Tosylate (16b). The alcohol **16a** (3.22 g, 38.2 mmol) and TsCl (14.2 g, 74.7 mmol) were dissolved in pyridine (10 mL). The reaction mixture was stirred at rt for 18 h. Then it was poured into ice water (10 mL) and extracted with benzene (3 × 30 mL). The organic layer was washed with HCl (1 N) and H_2O and dried over Na_2SO_4. The purification by flash chromatography (hexane–ether, 9:1) gave tosylate **16b** (6.6 g) in 94% yield as colorless oil: ^1H NMR δ 7.81 and 7.35 (2 d, J = 8 Hz, 4 H, ArH), 4.68 (m, 1 H, CH), 2.50 (m, 2 H, CH_2), 2.50 (m, 2 H, CH_2), 2.45 (s, 3 H, $ArCH_3$), 1.97 (t, J = 2.6 Hz, 1 H, C≡CH), 1.38 (d, J = 6 Hz, 3 H, CH_3); MS m/z 237 (2, M^+ − 1), 173 (8), 155 (39), 107 (5), 91 (100), 79 (49). Anal. Calcd for $C_{12}H_{14}O_2S$: C, 60.48; H, 5.92; S, 13.45. Found: C, 60.54; H, 6.00; S, 13.35.

Diethyl 2-(4-Pentynyl)malonate (18a). To a suspension of NaH (109 mg, 2.73 mmol, 60% dispersion in mineral oil, washed with hexane, 2 × 2 mL) in anhydrous DMF (5 mL) was added a solution of fresh distilled diethyl malonate (318 mL, 2.1 mmol) in DMF (5 mL) at room temperature, under N_2 and stirred for 20 min. Then a solution of 4-pentyn-2-yl tosylate (**16b**) (0.50 g, 2.1 mmol) in DMF (5 mL) was added. The reaction mixture was stirred at room temperature for 10 h and then at 100 °C for 20 h. It was cooled to room temperature, quenched with saturated NH_4Cl, extracted with EtOAc, washed with brine, and dried over $MgSO_4$. The crude product was purified by flash chromatography (hexane–EtOAc, 4:1) to give **18a** (0.32 g) in 70% yield as colorless oil: ^1H NMR (200 Hz) δ 4.21 (q, J = 7.0 Hz, 4 H, 2 OCH_2), 3.54 (d, J = 8.0 Hz, 1 H, $CHCO_2$), 2.46 (m, 1 H, CHMe), 2.35 (m, 2 H, CH_2), 2.02 (t, J = 2.6 Hz, 1 H, C≡CH), 1.27 (t, J = 7 Hz, 6 H, 2 CH_3), 1.12 (d, J = 7 Hz, 3 H, CH_3); MS m/z 226 (1, M^+), 181 (20), 160 (100), 141 (10), 133 (42), 132 (23), 104 (14), 97 (10), 85 (35), 81 (23), 65 (11), 44 (18). Anal. Calcd for $C_{12}H_{18}O_4$: C, 63.70; H, 8.02. Found: C, 63.52; H, 8.06.

2-(4-Pentynyl)malonic Acid (18b). Diester **18a** (0.40 g) was dissolved in 10% KOH aqueous MeOH (10 mL, MeOH–H_2O, 1:1), and the solution was stirred for 10 h at room temperature. The MeOH was removed by rotorary evaporation. The aqueous layer was acidified with 6 N HCl and extracted with EtOAc, and the extract was dried over $MgSO_4$. Recrystallization from EtOAc and hexane gave diacid **37** (0.22 g) in 72% yield as crystals, mp 145–146 °C: ^1H NMR (DMF-d_7) δ 3.40 (d, J = 7 Hz, 1 H, $CHCO_2$), 2.30–3.00 (complex, 3 H, C≡CH, $C{\equiv}CCH_2$), 1.12 (d, J = 6 Hz, 3 H, CH_3); MS m/z 170 (1, M^+), 155 (1), 126 (2), 113 (16), 100 (4), 87 (4), 85 (16), 69 (13), 58 (12), 43 (100). Anal. Calcd for $C_8H_{10}O_4$: C, 56.47; H, 5.92. Found: C, 56.48; H, 5.97.

3-Methyl-5-hexynoic Acid (15b). Diacid **18b** (0.20 g, 1.2 mmol) was refluxed in *m*-xylene (6 mL) for 4 h. The *m*-xylene was removed by flash chromatography with EtOAc–hexane, 3:7, containing 10% HOAc. The acetic acid was removed by azeotropic distillation with benzene. Acid **15b** (0.04 g) was obtained in 25% yield as colorless oil (for spectra data see above).

Methyl 2,2-Dimethyl-4-pentynoate (22). This compound was prepared according to the method of Crimmins[17] on a 100-mmol scale, giving **22** in 70% yield as colorless oil: bp 80–82

°C/16 mmHg (lit.[17] yield 80%, bp 48–50 °C/12 mmHg); ^{1}H NMR δ 3.68 (s, 3 H, OCH_3), 2.44 (d, J = 2.6 Hz, 2 H, $C{\equiv}CCH_2$), 2.02 (t, J = 2.6 Hz, 1 H, $C{\equiv}CH$), 1.27 (s, 6 H, CMe_2).

2,2-Dimethyl-4-pentyn-1-ol (23). To a slurry of $LiAlH_4$ (460 mg, 12 mmol) in dry ether (20 mL) was added slowly a solution of ester **22** (2.8 g, 20 mmol) in ether (10 mL) with vigorous stirring at such rate that the solvent refluxed gently. The reaction mixture was refluxed for 2 h and was poured into aqueous HCl (40 mL, 6 N) slowly, extracted with ether, washed with aqueous NaOH (6 N), and dried over K_2CO_3. The crude product was purified by distillation at 101–102 °C/14 mmHg, and the alcohol **23** (1.01 g) was obtained in 45% yield: ^{1}H NMR δ 3.43 (d, J = 6 Hz, 2 H, OCH_2), 2.17 (d, J = 3 Hz, 2 H, $C{\equiv}CCH_2$), 2.01 (t, J = 3 Hz, 1 H, $C{\equiv}CH$), 1.70 (b, 1 H, OH), 0.99 (s, 6 H, 2 CH_2); MS m/z 111 (2, $M^+ - 1$), 97 (24), 94 (2), 81 (44), 79 (76), 73 (100), 69 (23), 65 (161), 55 (100). Anal. Calcd for $C_7H_{12}O$: C, 74.96; H, 10.78. Found: C, 75.20; H, 11.06.

2,2-Dimethyl-4-pentyn-1-yl Tosylate (24). To dry pyridine (10 mL) were added alcohol **23** (1 g, 8.9 mmol) and tosyl chloride (3.31 g, 17.4 mmol). The reaction mixture was stirred at room temperature for 18 h and poured into ice water (10 mL). The mixture was extracted with benzene, washed with 1 N HCl, and water, and dried over Na_2SO_4. Flash chromatography of the crude product on silica gel (ether–hexane, 1:8) gave tosylate **24** (2.37 g) in 100% yield as a colorless oil: ^{1}H NMR δ 7.75 and 7.34 (2 d, J = 8.0 Hz, 4 H, ArH), 3.80 (s, 2 H, OCH_2), 2.45 (s, 3 H, $ArCH_3$), 2.12 (d, J = 2.5 Hz, 2 H, $C{\equiv}CCH_2$), 1.87 (t, J = 2.5 Hz, 1 H, $C{\equiv}CH$), 0.98 (s, 6 H, 2 CH_3); MS m/z 266 (13, M^+), 227 (18), 202 (100), 187 (29), 155 (68), 111 (23), 91 (57), 55 (19); HRMS (EI) calcd for $C_{14}H_{18}O_3S$ (M^+) 266.0977, found 266.0977.

5-Cyano-4,4-dimethylpentyne (25). To a solution of tosylate **24** (850 mg, 3.2 mmol) in dry DMSO (15 mL) was added KCN (311 mg, 4.7 mmol). The reaction mixture was stirred for 6 h at 90–100 °C under N_2 and then poured into 1:1 H_2O-saturated NH_4Cl in a well-ventilated hood. The mixture was extacted with CH_2Cl_2; the extracts were washed with H_2O and dried over Na_2SO_4. The crude product was purified by distillation at 170–172 °C/12 mmHg. Nitrile **25** was obtained in 70% yield: ^{1}H NMR δ 2.39 (s, 2 H, CH_2CN) 2.23 (d, J = 2.5 Hz, 2 H, CCH_2), 2.07 (t, J = 2.5 Hz, 1 H, $C{\equiv}CH$), 1.16 (s, 6 H, 2 CH_3); MS m/z 121 (6, M^+), 106 (4), 82 (100), 81 (56), 79 (20), 55 (52), 53 (18); HRMS (EI) calcd for $C_8H_{11}N$ (M^+) 121.0891, found 121.0891.

General Procedure for $ZnCl_2$-Mediated Alkylation of 3-Ethoxy-2-cyclohexenone with Primary and Secondary Alkyl Iodides. To a solution of LiN-*i*-Pr_2 (55.6 mmol, 1.3 equiv) in THF (prepared by addition of diisopropylamine (5.62 g, 55.6 mmol) and a solution of *n*-BuLi (1.5 M in hexane, 37.1 mL, 55.6 mmol) in THF (80 mL) at −78 °C under N_2) ws added slowly a solution of 3-ethoxy-2-cyclohexen-1-one (**26**) (6 g, 42.8 mmol, 1 equiv) in THF. After the solution was stirred for 2 h, anhydrous $ZnCl_2$ (5.8 g, 42.8 mmol, 1 equiv) was added with stirring. The addition of alkyl iodide (3 equiv) was followed by the addition of DMPU (10.97 g, 2 equiv), and the resulting reaction mixture was stirred at −78 °C for 2 h and then room temperature for 15–24 h. The reaction was followed by TLC (hexane–EtOAc, 3:1). The reaction mixture was quenched with H_2O and extracted with ether, and the extracts were dried over $MgSO_4$. Solvent removal and/or flash chromatography (hexane–EtOAc, 5:1) gave the alkylated products **27a–c** in 96–100% yields for primary iodide and 50% yield for **27d**. Two dimers **28** and **29** were isolated from alkylation reaction with isopropyl iodide.

3-Ethoxy-6-propyl-2-cyclohexen-1-one (27a): colorless oil; ^{1}H NMR δ 5.32 (s, 1 H, C═CH), 3.90 (q, J = 7.0 Hz, 2 H, OCH_2), 2.43 (t, J = 6.0 Hz, 2 H, $C{=}CH_2$), 1.24–2.26 (complex, 7 H, CH and 3 CH_2), 1.35 (t, J = 7 Hz, 3 H, CH_3), 0.92 (t, J = 7 Hz, 3 H, CH_3); MS m/z 182 (4, M^+), 153 (5), 140 (100), 112 (40), 96 (11), 84 (49), 68 (39), 55 (19), 42 (20). Anal. Calcd for $C_{11}H_{18}O_2$: C, 72.49; H, 9.95. Found: C, 72.46; H, 9.95.

6-Isobutyl-3-ethoxy-2-cyclohexenone (27b): colorless oil; ^{1}H NMR δ 5.30 (s, 1 H, C═CH), 3.88 (q, J = 7 Hz, 2 H, OCH_2), 2.40 (t, J = 6.0 Hz, 2 H, $C{=}CCH_2$), 1.35 (t, J = 7 Hz, 3 H, CH_3), 1.10–2.40 (complex, 6 H, 2 CH and 2 CH_2), 0.95 and 0.87 (2 d, J = 7 Hz, 6 H, 2 CH_3); MS m/z 196 (4, M^+), 181 (35), 168 (5), 154 (15), 153 (100), 141 (100), 140 (100), 112 (100), 85 (35), 68 (100); HRMS (EI) calcd for $C_{12}H_{20}O_2$ (M^+) 196.1463, found 196.1463.

3-Ethoxy-6-isopentyl-2-cyclohexan-1-one (27c): colorless oil; ^{1}H NMR δ 5.36 (s, 1 H, C═CH), 3.88 (q, J = 7 Hz, 2 H, OCH_3), 2.41 (t, J = 6.0 Hz, 2 H, $C{=}CCH_2$), 2.20 (m, 1 H, CHCO), 1.95 (AB q, upfield m, downfield m, 2 H, CH_2 ring methylene), 1.75 (m, 2 H, CH_2CMe_2), 1.60 (AB q, upfield m, 2 H, downfield m, 2 H, CH_2), 1.58 (m, 1 H, $CHMe_2$), 1.36 (t, J = 7 Hz, 2 H, CH_3), 0.89 (d, J = 7 Hz, 6 H, 2 CH_3); MS m/z 210 (12, M^+), 195 (3), 153 (20), 140 (100), 112 (50), 96 (15), 84 (49), 55 (37). Anal. Calcd for $C_{13}H_{22}O_2$: C, 74.24; H, 10.54. Found: C, 74.45; H, 10.67.

3-Ethoxy-6-isopropyl-2-cyclohexen-1-one (27d): colorless oil; ^{1}H NMR δ 5.32 (s, 1 H, C═CH), 3.87 (q, J = 7 Hz, 2 H, OCH_2), 2.40 (m, 3 H, $C{=}CCH_2$ and $CHMe_2$), 1.70–2.10 (complex, 3 H, CH and CH_2), 1.36 (t, J = 7 Hz, 3 H, CH_3), 0.91 and 0.84 (2 d, J = 7 Hz, 6 H, 2 CH_3); MS m/z 182 (16, M^+), 167 (17), 140 (84), 139 (12), 112 (34), 96 (9), 84 (52), 41 (100). Anal. Calcd for $C_{11}H_{18}O_2$: C, 72.49; H, 9.97. Found: C, 72.39; H, 9.96.

3-Ethoxy-6-(3-ethoxy-2-cyclohexen-1-ylidene)-2-cyclohexen-1-one (28): light yellow crystals, mp 90–91 °C; ^{1}H NMR δ 5.56 (s, 1 H, C═CH), 5.37 (s, 1 H, C═CH), 3.90 (m, 4 H, 2 OCH_2), 2.88, 2.70, 2.42, 2.25 (4 t, J = 7 Hz, 8 H, 4 $C{=}CCH_2$), 1.76 (m, 2 H, CH_2), 1.35 (t, J = 7 Hz, 6 H, 2 CH_3); MS m/z 262 (48, M^+), 234 (18), 233 (100), 217 (32), 189 (11), 177 (22), 161 (3), 150 (5), 135 (4), 121 (9), 112 (5), 107 (7), 84 (7), 69 (16), 55 (22); HRMS (EI) calcd for $C_{16}H_{22}O_3$ (M^+) 262.1571, found 262.1569.

3-Ethoxy-6-(3-oxo-1-cyclohexen-1-yl)-2-cyclohexen-1-one (29): light yellow crystals, mp 94–95 °C; ^{1}H NMR δ 5.90 (s, 1 H, C═CH), 5.40 (s, 1 H, C═CH), 3.92 (q, J = 7.0 Hz, 2 H, OCH_2), 3.11,(dd, J = 7 Hz, 7 Hz, 1 H, C═CCHCO), 2.40 (m, 6 H, 3 CH_2), 2.05 (m, 4 H, 2 CH_2), 1.39 (t, J = 7 Hz, 3 H, CH_3); MS m/z 234 (25, M^+), 206 (18), 205 (5), 178 (18), 160 (2), 150 (5), 140 (3), 122 (10), 112 (50), 97 (4), 84 (100), 72 (73), 55 (33), 39 (36); HRMS (EI) calcd for $C_{14}H_{18}O_3$ (M^+) 234.1526, found 234.1525.

General Procedure for Preparation of 4-Alkyl-Substituted 3-Methyl-2-cyclohexenones 31a–d. To a solution of 6-alkyl-substituted 3-ethoxy-2-cyclohexenone **64a–d** (2.5 mmol, 1 equiv) in anhydrous ether (15 mL) was added MeLi (as complex with lithium bromide, 1.4 M in ether, 2.2 mL, 1.3 equiv), with stirring at 0 °C. The solution was warmed up to room temperature with further stirring (~0.5 h) until the starting material disappeared. After the reaction mixture was quenched with H_2O (3 mL), a solvent (30% EtOAc in hexane) and aqueous HCl (1 N, 15 mL) were added with shaking. The crude addition product **30** readily underwent elimination of ethanol, giving the 4-substituted 3-ethoxy-2-cyclohexenone **31** in 95% yield after subsequent extraction and drying.

3-Methyl-4-propyl-2-cyclohexen-1-one (31a): colorless oil; ^{1}H NMR δ 5.83 (s, 1 H, C═CH), 1.25–2.53 (complex, 9 H, CH and 4 CH_2), 1.97 (s, 3 H, CH_3), 0.96 (t, J = 7 Hz, 3 H, CH_3); MS m/z 152 (16, M^+), 137 (1), 124 (24), 96 (18), 95 (100), 82 (23), 66 (21), 53 (11). Anal. Calcd for $C_{10}H_{16}O$: C, 78.90; H, 10.59. Found: C, 78.97; H, 10.64.

3-Methyl-4-isobutyl-2-cyclohexen-1-one (31b): colorless oil; ^{1}H NMR δ 5.81 (s, 1 H, C═CH), 1.95 (s, 3 H, $C{=}CCH_3$), 1.20–2.53 (complex, 8 H, 2 CH and 3 CH_2), 1.95 (s, 3 H, $C{=}CCH_3$), 0.95 (2 d, J = 7 Hz, 6 H, 2 CH_3); MS m/z 166 (2, M^+), 151 (1), 138 (10), 111 (10), 110 (46), 109 (11), 95 (100), 82 (28), 67 (21), 41 (36); HRMS (FAB) calcd for $C_{11}H_{19}O$ ($M^+ + 1$) 167.1439, found 167.1435.

3-Methyl-4-isopentyl-2-cyclohexen-1-one (31c): colorless oil; ^{1}H NMR δ 5.82 (s, 1 H, C═CH), 1.97 (s, 3 H, $C{=}CCH_3$), 1.20–2.50 (complex, 10 H, 2 CH and 4 CH_2), 0.91 (2 d, J = 6.0 Hz, 6 H, 2 CH_3); MS m/z 180 (25, M^+), 165 (2), 152 (6), 125 (11), 123 (13), 110 (74), 109 (40), 90 (91), 82 (100), 38 (28). Anal. Calcd for $C_{12}H_{20}O$: C, 79.95; H, 11.18. Found: C, 79.99; H, 11.21.

3-Methyl-4-isopropyl-2-cyclohexen-1-one (31d): colorless oil; ^{1}H NMR δ 5.93 (s, 1 H, C═CH), 1.85–2.57 (complex, 6 H, 2 CH and 2 CH_2), 1.98 (s, 3 H, CH_3), 1.05 and 0.84 (2 d, J = 7.0 Hz, 6 H, 2 CH_3); MS m/z 152 (39, M^+), 137 (2), 124 (50), 109 (81), 95 (99), 81 (34), 67 (17), 43 (76), 41 (66); HRMS (EI) calcd for $C_{10}H_{16}O$ 152.1200, found 152.1203. Anal. Calcd for $C_{10}H_{16}O$: C, 78.82; H, 10.59. Found: C, 78.33; H, 10.41.

General Procedure for Epoxidation of 4-Alkyl-Substituted 3-Methyl-2-cyclohexenones 31a–c. To a 4-alkyl-substituted 3-ethoxy-2-cyclohexen-1-one (**68a–c**) (10 mmol) was added a solution of H_2O_2 (30%, 2.8 g, 2.5 equiv) in MeOH (10 mL) at 15 °C, followed by the dropwise addition of a 6 N NaOH

solution (0.83 mL, 0.5 equiv) with stirring over 1 h. The resulting cloudy mixture was stirred for 3 h at 25 °C. Water (10 mL) was added, and the reaction mixture was extracted with EtOAc–$CHCl_3$ (2:1) and dried over $MgSO_4$. Purification by reduced pressure distillation gave epoxide ketones **32a–c** in 40–70% yield.

3-Methyl-4-propyl-2,3-epoxycyclohexan-1-one (32a): colorless oil; ^1H NMR δ 3.11 (s, 1 H, OCH), 2.05–2.40 (m, 3 H, CH and CH_2), 1.42 (s, 3 H, CH_3), 1.04–1.70 (m, 6 H, 3 CH_2), 0.92 (t, J = 7 Hz, 3 H, CH_3); MS m/z 168 (4, M^+), 153 (6), 140 (21), 126 (8), 112 (9), 96 (36), 81 (14), 71 (58), 69 (58), 54 (89). Anal. Calcd for $C_{10}H_{10}O_2$: C, 71.40; H, 9.59. Found: C, 71.34; H, 9.57.

3-Methyl-4-isobutyl-2,3-epoxycyclohexan-1-one (32b): colorless oil; ^1H NMR δ 3.11 (s, 1 H, CH), 2.46–2.10 (complex, 4 H, 2 CH and CH_2), 1.62 (m, 2 H, CH_2), 1.46 (s, 3 H, CH_3), 1.23 (m, 2 H, CH_2), 0.94 (2 d, J = 7.0 Hz, 6 H, 2 CH_3); MS m/z 182 (3, M^+), 167 (9), 154 (9), 139 (55), 126 (36), 111 (14), 97 (49), 83 (20), 69 (58), 43 (100); HRMS (EI) calcd for $C_{11}H_{18}O_2$ (M^+) 182.1307, found 182.1309.

3-Methyl-4-isopentyl-2,3-epoxycyclohexan-1-one (32c): colorless oil; ^1H NMR δ 3.10 (s, 1 H, OCH), 2.40–2.00 (complex, 3 H, CH and CH_2), 1.42 (s, 3 H, CH_3), 1.00–1.70 (complex, 7 H, CH and 3 CH_2), 0.86 (2 d, J = 7 Hz, 6 H, 2 CH_3); MS m/z 196 (5, M^+), 181 (5), 167 (2), 139 (45), 126 (25), 111 (14), 96 (56), 81 (29), 69 (75), 55 (61). Anal. Calcd for $C_{12}H_{20}O_2$: C, 73.43; H, 10.25. Found: C, 73.47; H, 10.35.

General Procedure for Preparation of γ-Acetylenic Methyl Ketones 33a–c. A solution of substituted epoxy cyclohexanone **32a–c** (25 mmol) in ethanol (200 mL) and (*p*-toluenesulfonyl)hydrazine (25 mmol) was stirred at room temperature for 2 h, and a light yellow precipitate was formed. The mixture was heated to 55 °C for 2 h. The resulting clear yellow solution was cooled to room temperature, diluted with water (50 mL), and extracted with chloroform. The organic layer was dried over $MgSO_4$. Reduced pressure distillation gave the γ-acetylenic methyl ketones in 50% yields.

3-Propyl-6-heptyn-2-one (33a): ^1H NMR δ 2.75 (m, 1 H, COCH), 2.17 (s, 3 H, $COCH_3$), 2.15 (m, 2 H, C≡CCH_2), 1.97 (t, 1 H, J = 2.5 Hz, C≡CH), 1.20–1.93 (complex, 6 H, 3 CH_2), 0.91 (t, J = 7 Hz, 3 H, CH_3); MS m/z 152 (3, M^+), 137 (6), 123 (14), 110 (100), 108 (18), 100 (100), 94 (38), 79 (83), 51 (35). Anal. Calcd for $C_{10}H_{16}O$: C, 78.90; H, 10.59. Found: C, 78.79; H, 10.52.

3-Isobutyl-6-heptyn-2-one (33b): colorless oil; ^1H NMR δ 2.75 (m, 1 H, COCH), 2.19 (s, 3 H, $COCH_3$), 2.15 (m, 2 H, CCH_2), 1.98 (t, J = 2.5 Hz, 1 H, C≡CH), 1.10–1.90 (complex, 5 H, CH and 2 CH_2), 0.90 (2 d, J = 7 Hz, 6 H, 2 CH_3); MS m/z 166 (3, M^+), 151 (4), 125 (12), 123 (32), 121 (33), 110 (100), 97 (14), 95 (76), 83 (47), 71 (100), 69 (86), 53 (99); HRMS (EI) calcd for $C_{11}H_{18}O$ (M^+) 166.1358, found 166.1349.

3-Isopentyl-6-heptyn-2-one (33c): colorless oil; ^1H NMR δ 2.76 (m, 1 H, COCH), 2.18 (s, 3 H, $COCH_3$), 2.15 (m, 2 H, C≡CCH_2), 1.98 (t, J = 2.6 Hz, 1 H, C≡CH), 1.85 (m, 1 H, $CHMe_2$), 1.04–1.80 (m, 6 H, 3 CH_2), 0.85 (d, J = 7 Hz, 6 H, 2 CH_3); MS m/z 180 (3, M^+), 165 (5), 137 (6), 128 (100), 110 (100), 95 (100), 63 (4), 39 (100). Anal. Calcd for $C_{12}H_{20}O$: C, 79.95; H, 11.18. Found: C, 79.95; H, 11.05.

General Procedure for Preparation of Acetylenic Acids 34a–c by Bromoform Reaction of γ-Acetylenic Methyl Ketones 33a–c. The following compounds were prepared from acetylenic ketones **33a–c** according to the method of preparation of acids **31** and **32**, on 2-mmol scale, in 40–55% yields.

2-Propyl-5-hexynoic acid (34a): colorless oil; ^1H NMR δ 2.56 (m, 1 H, CH), 2.25 (m, 2 H, C≡CH_2), 1.98 (t, J = 2.5 Hz, 1 H, C≡CH), 1.20–1.92 (complex, 6 H, 3 CH_2), 0.92 (t, J = 7 Hz, 3 H, CH_3); MS m/z 155 (16, M^+ + 1), 137 (1), 115 (11), 109 (21), 101 (11), 87 (100); HRMS (EI) calcd for $C_9H_{15}O_2$ (M^+ + 1) 155.1072, found 155.1074.

2-Isobutyl-5-hexynoic acid (34b): colorless oil; ^1H NMR δ 2.63 (m, 1 H, $CHCO_2$), 1.95 (t, J = 2.5 Hz, 1 H, C≡CH), 1.20–2.40 (complex, 7 H, CH and 3 CH_2), 0.95 (t, J = 5 Hz, 3 H, CH_3); MS m/z 168 (1, M^+), 167 (2), 153 (5), 139 (4), 129 (15), 116 (100), 98 (74), 74 (91), 69 (100), 57 (100); HRMS (EI) calcd for $C_{10}H_{16}O_2$ (M^+) 168.1149, found 168.1150.

2-Isopentyl-5-hexynoic acid (34c): ^1H NMR δ 2.54 (m, 1 H, CHCO), 2.27 (m, 2 H, CCH_2), 1.97 (t, J = 2.6 Hz, 1 H, C≡CH), 1.11–1.95 (complex, 7 H, CH and 3 CH_2), 0.89 (d, J = 6 Hz, 6 H, 2 CH_2); MS m/z 181 (5, M^+ – 1), 167 (30), 139 (70), 113 (54), 112 (100), 97 (100), 94 (98), 82 (42), 41 (100); HRMS (EI) calcd for $C_{11}H_{17}O_2$ (M^+ – 1) 181.1229, found 181.1228.

Ethyl 6-Bromo-2-isopropylhexanoate (37a). Diisopropylamine (19.1 g, 188.5 mmol) was added dropwise to a solution of *n*-BuLi (126 mL, 1.5 M, 88.5 mmol) in THF (250 mL) at –78 °C over 1 h. A solution of ethyl isovalerate (**36a**) (24.5 g, 188.5 mmol) in THF (25 mL) was added. After the solution was stirred for 2 h, 1,4-dibromobutane (**35**) (60.3 g, 282.7 mmol) was added, followed by the addition of DMPU (48 g, 377 mmol). The reaction mixture was slowly warmed up to room temperature over 3 h and then stirred overnight. Most of the THF was removed under reduced pressure, and the residue was extracted with ether (3 × 100 mL). The etheral layer was washed with brine and H_2O and then dried over $MgSO_4$. Distillation at 85–87 °C/0.35 mmHg gave **37a** (42.0 g) in 95 % yield: ^1H NMR δ 4.13 (q, J = 7 Hz, 2 H, CO_2CH_2), 3.38 (m, 2 H, $BrCH_2$), 2.08 (m, 1 H, $CHCO_2$), 1.30–2.00 (complex, 7 H, CH and 3 CH_2), 1.26 (t, J = 7 Hz, 3 H, CH_3), 0.97 (t, J = 6 Hz, 6 H, C $(CH_3)_2$); MS m/z 264 (1, M^+), 222 (53), 221 (34), 219 (16), 185 (10), 143 (100), 135 (10), 130 (100), 121 (3), 111 (60), 97 (60), 73 (100), 69 (100). Anal. Calcd for $C_{11}H_{21}O_2Br$: C, 49.92; H, 7.98; Br, 30.13. Found: C, 50.15; H, 7.89; Br, 30.09.

Ethyl 6-Bromo-2-isobutylhexanoate (37b). This compound was prepared from ester **36b** by the method for synthesis of **37a** in 97% yield, as a colorless oil: ^1H NMR δ 4.13 (q, J = 7 Hz, 2 H, CO_2CH_2), 3.39 (m, 2 H, $BrCH_2$), 2.24 (m, 1 H, $CHCO_2$), 1.05–1.97 (complex, 10 H, 2 CH, 4 CH_2), 1.27 (t, J = 7 Hz, 3 H, CH_3), 0.88 (d, J = 7 Hz, 3 H, CH_3), 0.88 (t, J = 7 Hz, 3 H, CH_3); MS m/z 278 (2, M^+), 251 (19), 249 (18), 235 (32), 233 (33), 224 (100), 222 (100), 199 (14), 73 (100); HRMS (EI) calcd for $C_{12}H_{23}BrO_2$ (M^+) 278.0883, found 278.0883.

2-Isopropyl-5-hexenoic Acid (38a). Potassium hydroxide (5.3 g, 94.6 mmol) was added to a solution of potassium *tert*-butoxide (95%, 11.3 g, 101.7 mmol) in DMSO (200 mL). To this suspension was added bromo ester **37a** at such a rate that the temperature of the reaction mixture remained at ~50 °C. The reaction was followed by TLC. After ester **37** disappeared, H_2O (10 mL) was added, and the resulting yellow solution was refluxed for 2 h. DMSO was removed under reduced pressure and the residue was dissolved in H_2O (15 mL). The aqueous layer was washed with ether, acidified with 6 N HCl to pH ~3 in an ice bath, saturated with NH_4Cl, and extracted with EtOAc (3 × 70 mL). The organic layer was washed with brine and H_2O and then dried over $MgSO_4$. The distillation through a Vigreux column (4 cm) at 95–96 °C/0.5 Torr gave alkenoic acid **38a**. This reaction has been repeated several times, with the yields ranging from 65% to 83%. The intramolecular alkylation product **39a** has also been isolated by flash chromatography in 17–35% yield (see below). For **38a**: ^1H NMR δ 5.90 (m, 1 H, C=CH), 5.20 (m, 2 H, C=CH_2), 1.90–2.30 (complex, 4 H, 2 CH and C=CCH_2), 1.70 (m, 2 H, CH_2), 1.00 (d, J = 7 Hz, 6 H, 2 CH_3); MS m/z 156 (4, M^+), 141 (15), 114 (53), 113 (96), 95 (45), 87 (100), 73 (100), 43 (100); HRMS (EI) calcd for $C_9H_{16}O_2$ (M^+) 156.1150, found 156.1150.

2-Isobutyl-5-hexenoic Acid (38b). This compound was prepared from ester **37b** by the method for synthesis of **38a** in 75% yield as a colorless oil: ^1H NMR δ 5.79 (m, 2 H, C=CH), 5.03 (m, 2 H, C=CH_2), 2.33 (m, 1 H, CHCO), 1.10–2.20 (complex, 7 H, 1 CH, 2 CH_2), 0.80–0.90 (complex, 6 H, 2 CH_3); MS m/z 170 (2, M^+), 169 (2), 141 (44), 116 (100), 114 (100), 87 (100), 69 (100), 55 (100). Anal. Calcd for $C_{10}H_{18}O_2$: C, 70.55; H, 10.66. Found: C, 70.47; H, 10.66.

1-Isopropyl-1-cyclopentanecarboxylic acid (39a): colorless oil. ^1H NMR δ 2.00 (m, 1 H, $CHMe_2$), 1.40–1.70 and 2.16 (complex, 8 H, 4 CH_2), 0.92 (d, J = 7 Hz, 6 H, 2 CH_3); MS m/z 156 (1, M^+), 155 (1), 141 (12), 114 (100), 113 (38), 111 (83), 96 (18), 95 (23), 87 (22), 86 (85), 69 (100), 55 (60); HRMS (EI) calcd for $C_9H_{16}O_2$ (M^+) 156.1150, found 156.1148.

General Procedure for Conversion of Alkenoic Acid to Alkynoic Acid. This conversion was performed according to Brandsma's general procedure.[21] Br_2 (1.98 mL, 38.5 mmol) was added dropwise to a solution of alkenoic acid **38a** (6 g, 38.5 mmol) in ether (150 mL) with stirring at –40 °C. The reaction was followed by GC. An additional amount of Br_2 was added until alkenoic acid **38a** disappeared. Nitrogen was bubbled through the reaction mixture to remove excess bromine and to concentrate

the solution to ~40 mL. This solution was transferred over 30 min to a suspension of sodium amide in liquid ammonia at −78 °C, which was prepared before use from Na (4.42 g, 192.2 mmol), $FeCl_3$ (0.62 g, 3.8 mmol), and ammonia (200 mL). The solvent was totally removed by evaporation at 40 °C and then under water aspirator vacuum. The solid residue was dissolved with H_2O (50 mL). The aqueous solution was acidified with 6 N HCl to pH ~3 at 0 °C and extracted with EtOAc (3 × 60 mL), and the extracts were dried over $MgSO_4$. Purification by flash chromatography (EtOAc–hexane, 1:9, 3% AcOH) and azeotropic distillation with benzene to remove AcOH yielded alkynoic acid.

2-Isopropyl-5-hexynoic Acid (40a). This compound was prepared from acid **38a** in 55% yield, as a colorless oil: ^{1}H NMR δ 2.35 (m, 1 H, CHCO), 2.22 (m, 2 H, CH_2), 1.60–2.00 (complex, 3 H, $CHMe_2$ and CH_2), 1.00 (2 d, J = 7 Hz, 6 H, 2 CH_3); MS m/z 154 (1, M^+), 153 (5), 139 (15), 129 (7), 113 (10), 112 (14), 111 (16), 102 (25), 95 (22), 73 (65), 53 (31), 42 (100); HRMS (EI) calcd for $C_9H_{14}O_2$ (M^+) 154.0994, found 154.0994.

2-*sec*-Butyl-5-hexynoic Acid (40b). This compound was prepared from acid **38b** in 60% yield, as a colorless oil: ^{1}H NMR δ 2.55 (m, 1 H, CHCO), 1.94 (t, J = 2.5 Hz, 1 H, C≡CH), 1.10–2.40 (complex, 7 H, CH and 3 CH_2), 1.85–1.00 (complex, 6 H, 2 CH_3); MS (FAB) 169 (49, M^+ + 1), 155 (100), 125 (25), 116 (2), 102 (100). Anal. Calcd for $C_{10}H_{16}O_2$: C, 71.40; H, 9.59. Found: C, 71.16; H, 9.77.

General Procedure for Alkylation of Terminal Alkynoic Acids. A solution of acid **40a** (225 mg, 1.63 mmol) in THF (2 mL) was added to a LiN-*i*-Pr_2 solution (3.26 mmol, 2 equiv) prepared by addition of diisopropylamine (445 mL, 3.26 mmol) to *n*-BuLi (2.16 mL, 3.26 mmol, 1.5 M in hexane) in THF (20 mL) at −78 °C, under N_2. The resulting light brown solution was stirred at −78 °C for 1 h. To this solution were added MeI (130 mL, 1.63 mmol) and DMPU (392 mL, 2 equiv), and the light brown color disappeared. The reaction mixture was slowly warmed up to room temperature and stirred for another 3 h, quenched with 6 N HCl (pH ~3) at 0 °C, extracted with EtOAc, and washed with brine. The crude acid was purified by flash chromatography on silica gel (3% AcOH in 3:1 hexane–EtOAc). The AcOH was removed by benzene azeotropic distillation.

2-Isopropyl-5-heptynoic Acid (41). This compound was prepared from acid **40a** in 80% yield, as a colorless oil: ^{1}H NMR δ 2.35 (m, 1 H, $CHCO_2$), 2.18 (m, 2 H, CCH_2), 1.78 (t, J = 2.6 Hz, 3 H, C≡CCH_3), 1.60–2.00 (complex, 3 H, CH and CH_2), 0.89 (d, J = 7 Hz, 6 H, 2 CH_3); MS m/z 168 (7, M^+), 126 (10), 112 (10), 102 (32), 101 (30), 87 (100), 84 (45), 81 (28), 68 (100), 67 (50), 39 (65); HRMS (EI) calcd for $C_{10}H_{16}O_2$ (M^+) 168.1155, found 168.1150.

2-Isopropyl-5-octynoic Acid (42). This compound was prepared from acid **40a** in 20% yield, as a colorless oil: ^{1}H NMR δ 2.35 (m, 1 H, CHCO), 2.08–2.30 (complex, 4 H, CH_2C≡CCH_2), 1.95 (m, 1 H, $CHMe_2$), 1.77 (m, 2 H, CH_2), 1.11 (t, J = 7 Hz, 3 H, CH_3), 0.98 (d, J = 7 Hz, 6 H, 2 CH_3); MS m/z 182 (3, M^+), 167 (6), 121 (22), 113 (27), 102 (79), 98 (96), 87 (100), 79 (89), 69 (93); HRMS (EI) calcd for $C_{11}H_{18}O_2$ (M^+) 182.1307, found 182.1309.

General Procedure for Mercury(II)-Catalyzed Protio Enol Lactonization in Aqueous CH_2Cl_2 (Method A). A solution of 5-alkynoic acid (100 mmol) in CH_2Cl_2 (5 mL) was added to $Hg(CF_3CO_2)_2$ (8.5 mg, 0.02–0.05 equiv). After the solution was stirred for 10 min, H_2O (1–3 equiv) was added at room temperature. The reaction was followed by TLC (EtOAc–hexane 1:2) and was completed in 0.5 h. A small amount of saturated brine and $KHCO_3$ was added, and the solution was stirred for another 10 min. Additional CH_2Cl_2 (30 mL) was added. The resulting mixture was dried over $MgSO_4$ and filtered through Celite. Flash chromatography on silica gel (EtOAc–hexane, 1:15–20) of this crude material gave the desired enol lactone in very good yield.

General Procedure for Mercury(II)-Catalyzed Protio Enol Lactonization in Anhydrous CH_2Cl_2 (Method B).[10a] This lactonization was performed as above in CH_2Cl_2.

3-Isopropyl-6-methylidenetetrahydro-2-pyranone (1). This compound was prepared from acid **40** by method A in 92% yield, and by method B in 30% yield, as a colorless oil: ^{1}H NMR δ 4.61 (s, 1 H, C=CCH), 4.26 (s, 1 H, C=CH), 2.62 (m, 1 H, CHCO), 2.45 (complex, 3 H, CH and C=CCH_2), 1.67 and 1.91 (2 m, 2 H, CH_2) 0.92 and 1.00 (2 d, J = 7 Hz, 6 H, 2 CH_3); MS m/z 154 (13, M^+), 126 (9), 112 (15), 111 (15), 97 (27), 83 (100), 69 (78), 41 (52). Anal. Calcd for $C_9H_{14}O_2$: C, 70.10; H, 9.15. Found: C, 70.22; H, 9.19.

2-Isopropyl-6-methyl-3,4-dihydropyran-2-one (43). This compound was prepared from acid **40** by method B (rt, 10 h) in 70% yield, as a colorless oil: ^{1}H NMR δ 4.98 (m, 1 H, C=CH), 2.10–2.45 (complex, 4 H, CHCO, $CHMe_2$, C=CCH_2), 1.85 (m, 3 H, C=CCH_3), 0.93 and 1.02 (2 d, J = 7 Hz, 6 H, 2 CH_3); MS m/z 154 (11, M^+), 126 (5), 111 (11), 84 (32), 69 (100), 55 (17), 43 (38); HRMS (EI) calcd for $C_9H_{14}O_2$ (M^+) 154.0994, found 154.0994.

4,4-Dimethyl-6-methylidenetetrahydro-2-pyranone (5). This compound was prepared from acid **15a** by method A in 93% yield, or by method B in 75% yield, as a colorless oil: ^{1}H NMR δ 4.72 (s, 1 H, C=CH), 4.30 (s, 1 H, C=CCH_2), 2.41 (s, 2 H, CH_2CO), 2.31 (s, 2 H, C=CCH_2), 1.05 (s, 6 H, 2 CH_3); MS m/z 140 (10, M^+), 125 (5), 112 (12), 111 (12), 83 (100), 79 (6), 69 (26), 56 (43), 55 (57), 39 (38). Anal. Calcd for $C_8H_{13}O_2$: C, 68.49; H, 8.77. Found: C, 68.22; H, 8.60.

4-Methyl-6-methylidenetetrahydro-2-pyranone (7). This compound was prepared from acid **15b** by method A in 85% yield, or by method B in 83% yield, as a colorless oil: ^{1}H NMR δ 4.66 (s, 1 H, C=CH), 4.28 (s, 1 H, C=CH), 2.68 (m, 2 H, CH_2-CO), 2.05–2.30 (complex, 3 H, CH and C=CCH_2), 1.05 (d, J = 6 Hz, 3 H, CH_3); MS m/z 126 (16, M^+), 98 (32), 97 (4), 83 (12), 69 (100), 43 (8), 41 (53), 39 (27); HMRS (EI) calcd for $C_7H_{10}O_2$ (M^+) 126.0681, found 126.0678.

3-Isobutyl-6-methylidenetetrahydro-2-pyranone (9). This compound was prepared from acid **34b** by method A in 39% yield, as a colorless oil: ^{1}H NMR δ 4.65 (s, 1 H, C=CH), 4.30 (s, 1 H, C=CH), 2.54 (complex, 3 H, CHCO and C=CCH_2), 1.30–2.10 (complex, 5 H, $CHMe_2$ and 2 CH_2), 0.90 and 0.96 (2 d, J = 7 Hz, 6 H, 2 CH_3); MS m/z 168 (18, M^+), 153 (3), 140 (67), 125 (100), 111 (18), 987 (90), 84 (54), 69 (39); HRMS (EI) calcd for $C_{10}H_{16}O_2$ (M^+) 168.1149, found 168.1150.

3-*sec*-Butyl-6-methylidenetetrahydro-2-pyranone (10). This compound was prepared from acid **40b** by method A in 95% yield, or by method B in 35% yield, as a colorless oil: ^{1}H NMR δ 4.60 (s, 1 H, C=CH), 4.24 (s, 1 H, C=CH), 2.60 (m, 1 H, CHCO) 2.42 (m, 2 H, C=CCH_2), 1.10–2.30 (complex, 5 H, CHMe and 2 CH_2), 0.90 (m, 6 H, 2 CH_3); MS (FAB) 169 (45, M^+ + 1), 155 (116), 141 (1), 121 (8), 119 (39), 112 (9), 103 (29). Anal. Calcd for $C_{10}H_{16}O_2$: C, 71.40; H, 9.59. Found: C, 71.38; H, 9.62.

3-Propyl-6-methylidenetetrahydro-2-pyranone (11). This compound was prepared from acid **34a** by method A in 85% yield, as a colorless oil: ^{1}H NMR δ 4.26 and 4.27 (2 s, 2 H, C=CH_2), 2.60 (m, 1 H, COCH), 2.50 (m, 2 H, C=CCH_2), 1.35–2.10 (m, 6 H, 3 CH_2), 0.94 (t, J = 6.5 Hz, 3 H, CH_3); MS m/z 154 (10, M^+), 126 (16), 98 (4), 97 (36), 84 (22), 83 (100), 69 (48), 55 (56); HRMS (EI) calcd for $C_9H_{14}O_2$ (M^+) 154.0994, found 154.0994.

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Supplementary Material Available: ^{1}H NMR spectra of compounds **7, 9, 11, 15a, 24, 25, 27b, 28, 29, 31b, 31d, 32b, 33b, 34a, 34b, 34c, 37b, 38a, 39a, 40a, 41, 42,** and **43** (12 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.