The Total Synthesis of Lauraceae Lactones: Obtusilactones, Litsenolides, and Mahubanolides[1]

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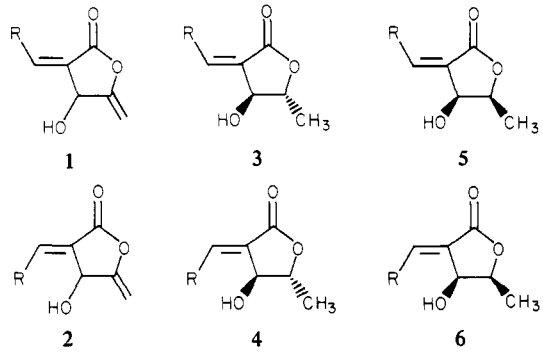
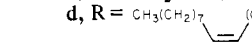
Abstract: The total synthesis of obtusilactones (**1a,b, 2a,b**), mahubanolides (**1c, 2c**), epilitsenolides (**5b, 6b**), and dihydromahubanolides (**4c, 5c, 6c**) is described. The enolates derived from the α-phenylselenenyl esters (**17a–c**) were used as acrylate α-anion synthons; aldol addition to propargylaldehyde, followed by oxidation to the selenoxide and elimination, furnished the isomeric acetylenic esters **20a–c** and **21a–c**. In a similar manner, aldol addition to acrolein followed by oxidation/elimination yielded olefinic esters **18b,c** and **19b,c**. The acetylenic esters were saponified, and the corresponding carboxylic acids were converted by either mercuric ion-catalyzed or bicarbonate-catalyzed lactonization to the obtusilactones (**1a,b, 2a,b**) and mahubanolides (**1c, 2c**). The olefinic esters were saponified, and the corresponding carboxylic acids lactonized to γ-substituted lactones (**30b,c, 32b,c, 32c**) by treatment with either phenylselenenyl chloride or iodine. The epilitsenolides (**5b, 6b**) and dihydromahubanolides (**5c, 6c**) were then obtained by treating the substituted γ-lactones with tri-*n*-butyltin hydride. Homogeneous catalytic hydrogenation ($Rh(PPh_3)_3Cl$) of isomahubanolide (**2c**) gave a mixture of dihydromahubanolides **4c** and **6c**.

A number of natural products containing the α-alkylidene-β-hydroxybutyrolactone unit have recently been isolated from three species of plants in the Lauraceae family.[2,3] Obtusilactones (**1a,b,d, 2a,b,d**)[2] and mahubanolides (**1c,f,g, 2c,f,g**)[3b] have a γ-



1 **3** **5**

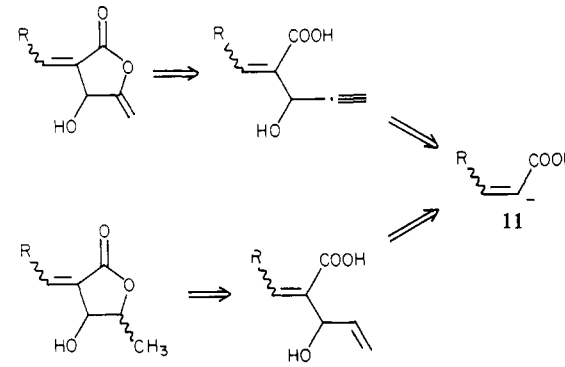
2 **4** **6**

a, $R = CH_2{=}CH(CH_2)_9$; b, $R = CH_3(CH_2)_{12}$; c, $R = CH_3(CH_2)_{14}$; d, R =  ; e, $R = HC{\equiv}CH(CH_2)_9$; f, $R = CH_2{=}CH(CH_2)_{13}$; g, $R = HC{\equiv}C(CH_2)_{13}$

methylene group, while litsenolides (**3a,b, 3e, 4a,b,e**)[3a] and dihydromahubanolides (**3–6** with R groups **c, f,** and **g**)[3b] have a γ-methyl group. Examples of all possible permutations of the stereochemistry exist: the α-alkylidene group may have either *E* or *Z* geometry, and saturated lactones may have the β-hydroxy group either cis or trans with respect to the γ-methyl group on the 5-membered lactone ring, although in the litsenolide series, only the trans configuration is found.

The Lauraceae lactones are interesting synthetic targets for several reasons. Biological interest stems from the reported cytotoxicity[2c] of obtusilactone, as well as from its close structural similarity to the α-methylene-γ-butyrolactone unit, which is present in many natural products having antitumor activity.[4] The lactones possess some unusual structural features, particularly the β-hydroxy and γ-methylene groups, that require the development of new synthetic methodology. Additionally, it would be desirable to devise a synthetic approach that would be sufficiently versatile to permit the preparation of all of the structural variants of this class. We wish to report a general method for the synthesis of α-alkylidene-β-hydroxy-γ-methylenebutyrolactones and its application to the synthesis of obtusilactone (**1a**), isoobtusilactone (**2a**), obtusilactone A (**1b**), isoobtusilactone A (**2b**), mahubanolide (**1c**), isomahubanolide (**2c**), isodihydromahubanolide A (**4c**), dihydromahubanolide B (**5c**), isodihydromahubanolide B (**6c**), and the "nonnatural products" epilitsenolide C_1 (**5b**) and epilitsenolide C_2 (**6b**).

Scheme I. Retrosynthetic Analysis of Lauraceae Lactones



Results and Discussion

Synthetic Analysis and Model Studies. The density of functional groups on the γ-lactone ring of the Lauraceae lactones make many of the methods available for the synthesis of α-methylene lactones[5] unsuitable. In particular, the β-hydroxy group presents special problems, and the sensitivity of the enol lactone requires the use

(1) Preliminary account of this work has been presented: 179th ACS National Meeting, Houston, Texas, March 1980, Abstract ORGN 66.

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(3) (a) Takeda, K.; Sakurawi, K.; Ishii, H. *Tetrahedron* **1972**, *28*, 3757–3766. (b) Martinez, J. C. V.; Yoshida, M.; Gottlieb, O. R. *Tetrahedron Lett.* **1979**, 1021–1024.

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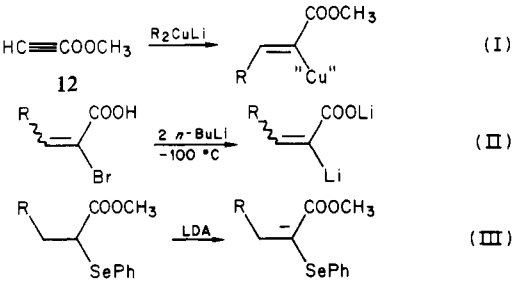
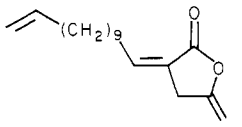
Scheme II. Approaches to the Acrylate α-Anion



of mild reaction conditions. An unsuccessful approach to obtusilactone (**1a**) has been reported[6] in which the failure resulted from the inability to hydroxylate the β position of deoxyobtusilactone (**7**).[6a,b] This is not entirely unexpected, since only one report of



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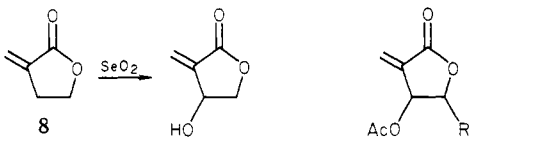
a related oxidation to Tulipalin B (**9**) exists (**8** → **9**),[7a] this being



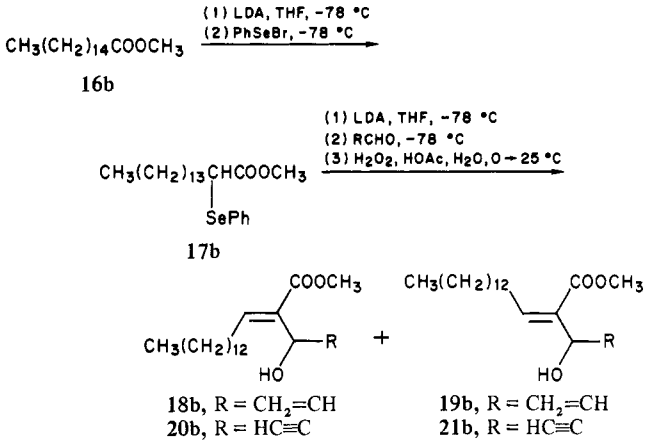
8 9 10, R = H, Me, Et, *i*-Pr, C_5H_{11}

a low yield process on a much simpler molecule. The synthesis of related β-acetoxy-α-methylene-γ-butyrolactones (**10**) has been reported in which an allylic sulfoxide rearrangement was used to generate the β-acetoxy group,[7b] and litsenolide C_1 has been synthesized by using an allylic selenoxide rearrangement to generate the β-hydroxy group.[7c] The applicability of this approach to the more sensitive enol lactone systems (**1** and **2**) is uncertain, however. Recently, Tanaka and Yamshita have reported the synthesis of optically active Tulipalin B (**9**) from glyceraldehyde[7d]—avoiding the oxidation problem completely.

The retrosynthetic analysis shown in Scheme I suggests an alternative approach to the lactones that would allow the synthesis of both the γ-methylene and the γ-methyl lactones from a common intermediate. The lactones can be perceived as being derived from the intramolecular Markownikow addition of the carboxylate group across a double or triple bond: the γ-methylene lactones from cyclization of an appropriate acetylenic acid and the γ-methyl lactones from cyclization of an appropriate olefinic acid. The existence of the β-hydroxy group in the precursor acids suggests formation of these intermediates by an unusual aldol addition. The addition of a β-substituted acrylate α-anion synthon **11** to either propargylaldehyde or acrolein would give the precursor needed for the γ-methylene or γ-methyl lactones, respectively.

Three approaches to synthon **11** were investigated, as outlined in Scheme II. Attention was first focused on the generation of an acrylate α-anion itself. One possible approach involves the conjugate addition of an appropriate carbon unit to methyl propiolate ((I), Scheme II).[8,9] This produces an enolate intermediate that might be trapped by an electrophile.[10]

Scheme III

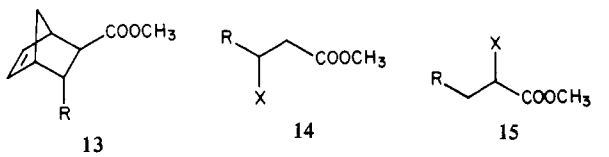


18b, R = CH_2=CH 19b, R = CH_2=CH
20b, R = HC≡C 21b, R = HC≡C

Although lithium di-*n*-butylcuprate in THF added cleanly to methyl propiolate (**12**) in a cis manner, only methyl (*Z*)-2-heptenoate could be isolated from the reaction, regardless of the electrophile (MeI, PhCHO, HC≡CCHO, CH_2=CHCHO, HCHO) or reaction conditions used (0.1 or 1 equiv of CuBr·SMe_2; conjugate addition adduct alone or with added $ZnCl_2$, $MgCl_2$, or *n*-BuLi). A further disadvantage of this approach is that only the *E* geometry would be available, since the addition of cuprates to acetylenes is known to proceed in a cis manner,[8,9,10f,g] which gives, in this system, the thermodynamically favored isomer.

Another possible approach is the low-temperature (−100 °C) lithium–halogen exchange on an α-bromo-α,β-unsaturated carboxylic acid ((II), Scheme II).[11] Again, in certain systems precedent exists for trapping the intermediate α-lithio acid with electrophiles. However, in our system, with an accessible β-hydrogen, elimination to the α,β-acetylenic acid was the predominant course of reaction.

An alternative to the direct generation of acrylate α-anion is the use of a synthetic equivalent in which the double bond can be introduced after aldol addition. Several such equivalents exist such as Diels–Alder adducts[12a,k] (**13**) and α- or β-heteroatom-



substituted esters[12b-j,13,14] (**14**, **15**). The use of α-phenylselenenyl

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esters (**15**, X = PhSe, see also (III), Scheme II) seems particularly attractive because of the mild conditions under which they can be oxidized to the selenoxide and subsequently undergo syn elimination. In addition, it is known that β-hydroxy selenoxides eliminate to allylic alcohols in preference to enols,[14] which is precisely the regioselectivity required for the synthesis of α-alkylidene-β-hydroxy compounds.

Preliminary work on this approach utilized methyl palmitate (**16b**, Scheme III). The enolate anion generated at −78 °C by treatment of **16b** with 2 equiv of lithium diisopropylamide in THF was quenched by the rapid addition of a THF solution of phenylselenenyl bromide (made immediately prior to use by adding bromine to a solution of diphenyl diselenide). The extra equivalent of lithium diisopropylamide was needed to deprotonate the resulting α-phenylselenenyl ester **17b**, which would otherwise be available for equilibration with any unreacted ester enolate. Column chromatography on silica gel gave the desired α-phenylselenenyl ester (**17b**) in greater than 95% yield. The enolate of this ester was easily generated in THF at −78 °C with lithium diisopropylamide and cleanly underwent addition to both acrolein and propargylaldehyde. Without isolation, the aldol product was oxidized with aqueous hydrogen peroxide in the presence of acetic acid to the selenoxide, which then underwent spontaneous elimination to an isomeric mixture of the desired enoates. Chromatographic separation furnished the *E* isomers (**18b**, **20b**) in ca. 40% yield and the *Z* isomers (**19b**, **21b**) in ca. 10% yield. The geometric isomers were readily distinguished by the chemical shift of their β-hydrogen in the ^{1}H NMR spectrum (**18b**, δ 6.71; **19b**, δ 6.11; **20b**, δ 6.67; **21b**, δ 6.36).

Synthesis of α-Phenylselenenyl Esters. The saturated α-phenylselenenyl esters **17b** and **17c** (Scheme IV) needed for the synthesis of obtusilactone A (**1b**), isoobutsilactone A (**2b**), mahubanolide (**1c**), and isomahubanolide (**2c**) were easily prepared from the methyl esters (**16b**, **16c**) of palmitic acid and stearic acid, respectively. The corresponding methyl ester **16a** required for the synthesis of obtusilactone (**1a**) and isoobtusilactone (**2a**) is not readily available.[15] Since various 1,11-difunctionalized 11-carbon compounds are known, ester **16a** could conceivably be synthesized by the addition of an appropriate 3-carbon fragment to an 11-carbon unit.

The first 3-carbon homologation attempted was conjugate addition of an organometallic to methyl acrylate.[8] 11-Bromo-1-undecene (**23**), prepared from 10-undecen-1-ol (**22**), was converted

$CH_2{=}CH(CH_2)_9{-}X$
22, X = OH
23, X = Br

$X{-}(CH_2)_{10}{-}Z$
24, Z = COOH, X = Br
25, Z = $COOCH_3$, X = Br
26, Z = $COOCH_3$, X = I
27, Z = $COOC(CH_3)_3$, X = Br
28, Z =  X = Br

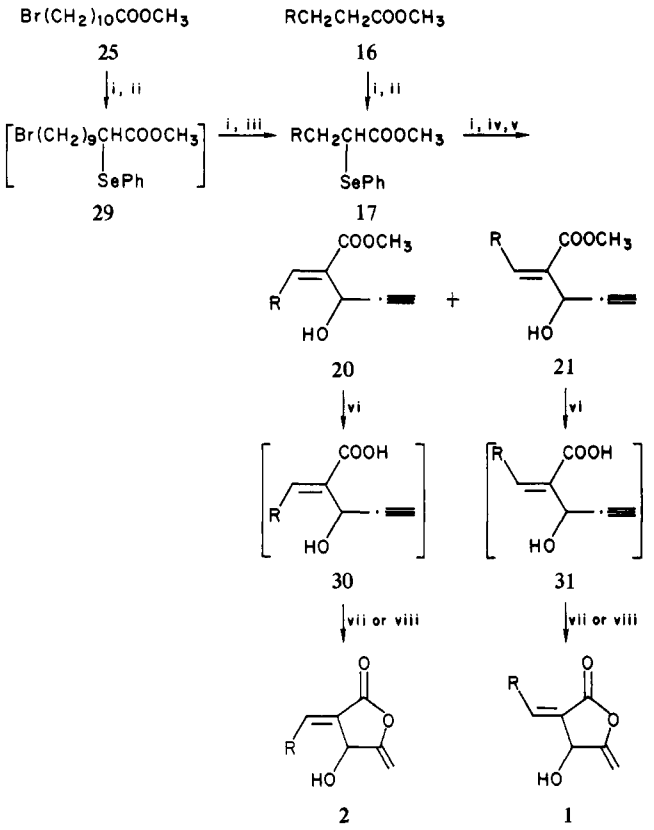
into the Grignard reagent in ether or THF and was treated with either 0.1 or 1 equiv $CuBr{\cdot}SMe_2$. Addition of this reagent to a solution of methyl acrylate produced a complex mixture of products, none of which was the desired ester **16a**. The major product appeared to result from subsequent addition of the desired intermediate enolate to at least one more acrylate unit, even when an excess of cuprate was used. This type of byproduct is well documented in cuprate addition to unhindered enones,[8] and further investigation of this approach was discontinued.

An alternative 3-carbon homologation involves displacement of a leaving group at C-11 of an undecanoic acid derivative by an allyl anion. On the basis of the literature precedent, the best method to displace a halogen with a carbon nucleophile while leaving an ester unscathed appeared to be the use of a cuprate.[16] Corey and Posner have reported such couplings of lithium dimethyl and di-*n*-butyl cuprates with 11-haloundecanoic acid and derivatives.[16] Lithium diallyl cuprate is a known species, and its coupling with alkyl halides has been reported.[17]

Lithium diallyl cuprate was generated from allyllithium and $CuBr{\cdot}SMe_2$, and coupling with several 11-haloundecanoic acid derivatives (**24**–**28**) was attempted, with the same results in all cases: when the reaction temperature was maintained at −20 °C or below, no reaction occurred, while at temperatures above −20 °C, the allyl cuprate decomposed, and complex product mixtures were obtained, including allyl carbinols resulting from bisaddition of the allyl group to the ester function. Allyllithium itself gave preferential attack at the ester. An attempt to protect the ester as an enolate anion resulted in a reaction between the enolate and the 11-halo function.

The needed precursor was finally prepared by the approach shown in Scheme IV, in which trishomologation was effected subsequent to introduction of the α-phenylselenenyl group. The enolate anion of bromo ester **25** was generated with LDA and then quenched with PhSeBr at low temperature (−78 °C) to prevent self-alkylation. The intermediate α-phenylselenenyl ester **29** could

Scheme IV[a, b]



[a] a, R = $CH_2{=}CH(CH_2)_9$; b, R = $CH_3(CH_2)_{12}$; c, R = $CH_3(CH_2)_{14}$. [b] (i) LDA, THF, −78 °C; (ii) PhSeBr, THF, −78 °C; (iii) $CH_2{=}CHCH_2Li$, THF, −78 → −10 °C, (iv) HC≡CCHO, THF, −78 °C; (v) H_2O_2, H_2O, 0 → 25 °C; (vi) KOH, H_2O, CH_3OH, 25 °C; (vii) $Hg(CF_3COO)_2$, CH_2Cl_2, 0 °C; (viii) $NaHCO_3$(aq), CH_2Cl_2, 25 °C.

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be either isolated or treated with another equivalent of lithium diisopropylamide (to protect the ester as the enolate anion), followed by addition of 3 equiv of allyllithium to effect displacement of the bromine. (Two equivalents of allyllithium were consumed by deprotonation of the diisopropylamine that originates from the lithium diisopropylamide used in making the enolates.) In this manner, phenylselenenyl ester **17a** was obtained in greater than 95% overall yield from the methyl ester **25**. An additional advantage of this approach is that the introduction of the PhSe group before the terminal double bond avoids the problem of the addition of PhSeBr to the double bond[14] that might have been encountered in the selenation of ester **16a**.

Synthesis of α-Alkylidene-β-hydroxy-γ-methylenebutyrolactones (Obtusilactones, Mahubanolides). With the α-phenylselenenyl esters in hand, the next transformations were the aldol addition to propargylaldehyde, followed by oxidation to the selenoxide and elimination (Scheme IV). A solution of ester **17a**, **17b**, or **17c** in THF was added to 2 equiv of lithium diisopropylamide in THF at −78 °C. The resulting enolate anion was quenched with propargylaldehyde, and, without isolation, the aldol product was oxidized with aqueous hydrogen peroxide and warmed to room temperature to ensure complete elimination of the selenoxide. The crude reaction mixture was separated by column chromatography into the *E* and *Z* isomers **20** and **21**. In general, the *E*:*Z* ratio was about 4:1, and the combined yields were on the order of 50%, the remainder of the reaction mixture consisting largely of nonvolatile material (by GC) having a higher R_f on TLC than those of the desired products.

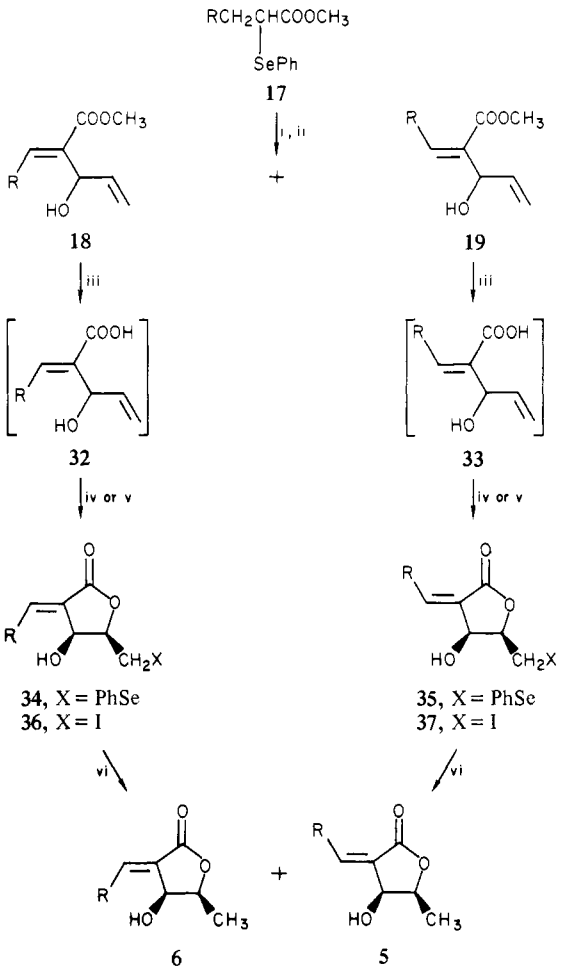
Each ester was hydrolyzed to the corresponding carboxylic acid (**30**, **31**) by treatment with Claisen's alkali[18] at room temperature. Without purification, the acetylenic acids were treated with mercuric trifluoroacetate in dichloromethane[6] at 0 °C to give the enol lactones (**1** and **2**) in 25–50% overall yield from the esters after preparative layer chromatography. Comparable yields of the enol lactones could be achieved by simply stirring a dichloromethane solution of the acetylenic acid with aqueous sodium bicarbonate. This latter reaction, though unusual, is a documented method of forming enol lactones from acetylenic acids.[5e,19] Its success depends critically upon the pH of the bicarbonate solution: strong base (e.g., KOH or Claisen's alkali) and solid sodium bicarbonate do not promote lactone formation, and strong acids (e.g., HCl or CF_3COOH) destroy the lactone. A small amount (<10%) of lactone formation occurs spontaneously when the acetylenic acids are allowed to stand neat at room temperature for several hours. The enol lactones had spectroscopic characteristics (^1H NMR, IR), identical with those reported for the natural products,[2,3] and the ^1H-NMR spectra were identical with those copies generously provided by Drs. Yamamura and Yoshida.[2,3b]

In general, the *E* esters and lactones were more well behaved than the *Z* isomers. The mass spectra of the *Z* isomers had either very weak or nonexistent (for ester **21a** and lactones **1a** and **1c**) molecular ions, although in all cases ions corresponding to loss of hydroxyl radical, water, and carbon dioxide were seen. The *Z* lactones also appeared to be less stable thermally than the *E* lactones, since the molar absorptivity of the *Z* lactones decreased rapidly when they were stored as neat oils at −20 °C.

Synthesis of α-Alkylidene-β-Hydroxy-γ-Methylbutyrolactones (Litsenolides, Dihydromahubanolides). As was mentioned earlier, the enolate anions of α-phenylselenenyl esters **17** add to acrolein (Scheme V) in a manner exactly analogous to the propargylaldehyde addition, yielding the olefinic esters **18** and **19** after oxidation and selenoxide elimination. Again, the geometric isomers, produced in a *E*:*Z* ratio of approximately 4:1, could be separated by column chromatography in a combined yield of 30–50%. Hydrolysis to the corresponding carboxylic acids (**32**, **33**) was accomplished by treatment with Claisen's alkali at room temperature.

Lactonization of γ,δ-unsaturated carboxylic acids is well-known, and the 5-membered γ-lactones are formed in preference to the 6-membered δ-lactones by addition in a Markownikow sense. While the olefinic acids (**32**, **33**) would not lactonize with mercuric

Scheme V[a, b]



[a] b, R = $CH_3(CH_2)_{12}$; c, R = $CH_3(CH_2)_{14}$. [b] (i) LDA, THF, −78 °C; (ii) CH_2=CHCHO, −78 °C; (iii) KOH, H_2O, CH_3OH; (iv) I_2 (2 equiv), CH_2Cl_2, 58 °C; (v) PhSeCl, CH_2Cl_2, 25 °C; (vi) *n*-Bu_3SnH, PhH, Δ.

ion catalysis under the same conditions used to synthesize the γ-methylene lactones, lactonization could be accomplished by two other methods. A recent method for cyclizing olefinic acids utilizes phenylselenenyl chloride.[14,20] When the olefinic *E* acids (**32**) were treated with 1 equiv of PhSeCl in dichloromethane, a rapid decolorization of the bright red-orange PhSeCl solution occurred, yielding the cis lactones **34** in approximately 75% yield after preparative layer chromatography. The IR and ^1H NMR spectra were consistent with the formation of a γ-lactone, and the cis orientation of the substituents was substantiated by their ^1H NMR spectra, particularly by the chemical shift of the β-proton,[21] as well as their subsequent hydrogenolysis to the cis lactones **5** and **6**.

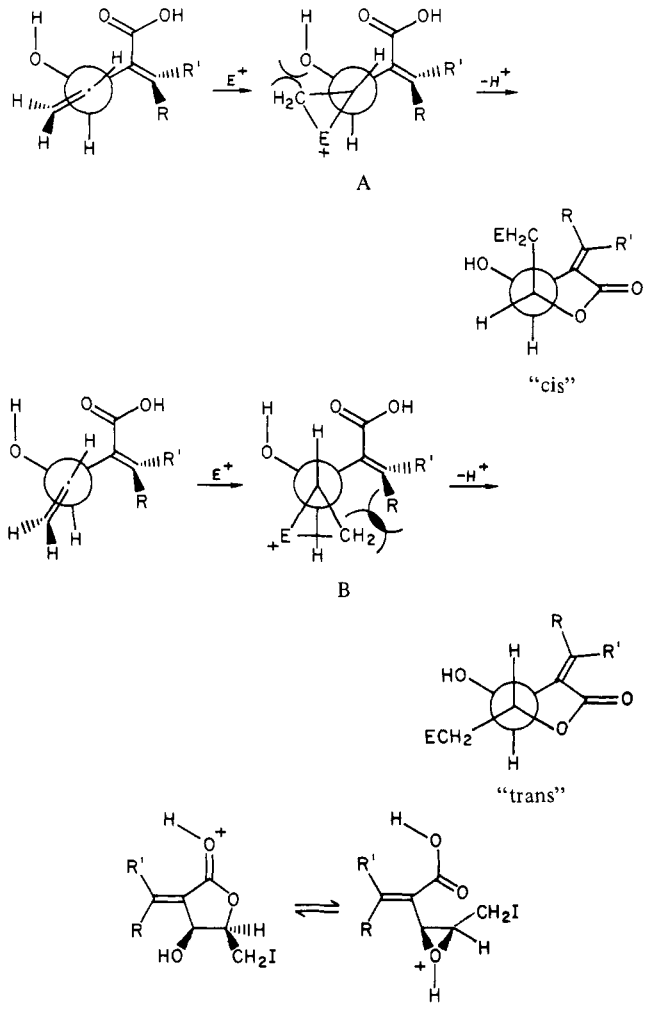
Another, well-known lactonization procedure is iodolactonization.[22] A particularly appealing aspect of this method is the report by Bartlett that, while the less stable lactone isomer is often the product of lactonization under kinetic control,[22c] the more stable isomer can be formed by conducting the lactonization

(20) (a) Nicolaou, K. C.; Seitz, S. P.; Sipio, W. J.; Blount, J. F. *J. Am. Chem. Soc.* **1979**, *101*, 3884–3893. (b) Clive, D. L. J.; Chittattu, G. J. *J. Chem. Soc., Chem. Commun.* **1977**, 484–485. (c) Clive, D. L. J.; Chittattu, G. J.; Farina, V.; Kiel, W. A.; Menchen, S. M.; Russell, C. G.; Singh, A.; Wong, C. K.; Curtis, N. J. *J. Am. Chem. Soc.* **1980**, *102*, 4438–4447.

(21) The chemical shifts given for the dihydromahubanolides are taken from Table III in the Ph.D. thesis of J. C. Martinez, V., Universidade de Sao Paulo, Brazil, which was kindly supplied by Dr. M. Yoshida.

(22) (a) Dowle, M. D.; Davies, D. I. *Chem. Soc. Rev.* **1979**, *8*, 171–197. (b) Bartlett, P. A.; Myerson, J. *J. Am. Chem. Soc.* **1978**, *100*, 3950–3952. (c) Jäger, V.; Günther, H. J. *Tetrahedron Lett.* **1977**, 2543–2546. (d) do Amaral, L.; Melo, S. C. *J. Org. Chem.* **1973**, *38*, 800–802.

Scheme VI. Lactonization of Olefinic Acids: Stereochemistry



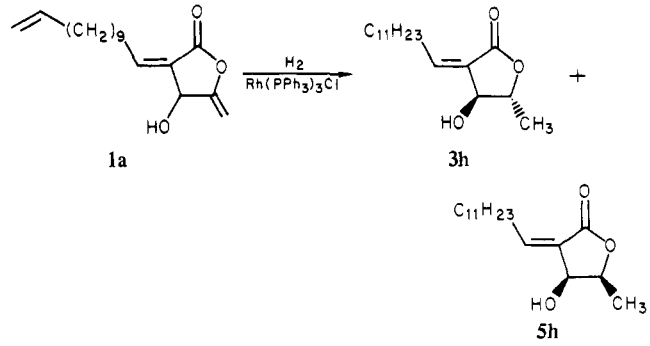
under equilibrating conditions.[22b] In the case at hand, it was expected that the lactone with the trans stereochemistry would be more stable and thus would be formed under equilibration conditions. However, under all lactonization conditions examined, only the cis isomers (**36**, **37**) were obtained when the olefinic acids (from esters **18** and **19**) were treated with 1–3 equiv of iodine[22d] in acetonitrile, ether, methanol, THF, or dichloromethane at temperatures from −78 to +82 °C. Yields range from 25 to 50% after purification by preparative layer chromatography. Again, the cis lactone structures were assigned on the basis of their ^{1}H NMR spectra, as well as their subsequent conversion to the cis lactones **5** and **6**.

This preference for formation of the cis lactones seemed unusual. The stereochemical requirements of lactonization are outlined in Scheme VI. The orientation of the α-alkylidene group is presumed to be determined by hydrogen bonding between the β-hydroxyl and the carboxylate groups. Under kinetic control, the stereochemistry is determined by a delicate balance in the energies of the transition states leading to the cyclic iodonium ions and the lactones. With the assumption that the electrophile approaches from the sterically least-hindered side of the γ,δ double bond and that the carboxylate group attacks with inversion at the γ-carbon, significant steric interactions are developed between the α-alkylidene group (especially when it bears a substituent trans to the carbonyl) and the γ-methylene group in the transition states leading to iodonium ion B and the trans lactone, while considerably less interaction is encountered with the β-hydrogen in the corresponding transition states leading to iodonium ion A and the cis lactone.

While the explanation above provides a satisfying rationalization for the predominant formation of the cis lactone under conditions of kinetic control, the continued predominance of the cis lactones under conditions that are generally effective in cis–trans isomerization of γ butyro-iodolactones (through elimination–readdition) is puzzling and is most likely due to nonequilibration. Instead of opening to the olefinic acid by elimination, it is possible that the neighboring hydroxyl group traps the incipient cation as the carboxylate group departs. This gives an epoxide that retains the original kinetically controlled stereochemistry when the lactone reforms (Scheme VI).

Treatment of both the phenylselenenyl and iodo lactones (**34**, **36**, **37**) with tri-*n*-butyltin hydride in the presence of a catalytic amount of *N*,*N*-azobis(isobutyronitrile) in refluxing benzene[14,20a,c,23] gave the cis-γ-methyl lactones **5** and **6** in 60% yield after preparative layer chromatography (SiO_2, 1:3 ethyl acetate–benzene). Although no evidence was seen for epimerization at the γ-carbon, the reduction did isomerize the α-alkylidene double bond. The *E*:*Z* ratio of the products (approximately 4:1) was the same regardless of whether pure *E* or pure *Z* iodo lactones were used. Recrystallization from hexane gave an approximately 25% yield of pure crystalline *E* cis lactones **6** and about 35% of a mixture of *E* and *Z* cis lactones **5** and **6** in the mother liquor. Triphenyltin hydride has been reported to be the preferred reagent for deselenation,[20a,23a] but the alcohol–lactones produced here were only marginally separated by chromatography from the tin products of Ph_3SnH reduction, while the corresponding products of *n*-Bu_3SnH reduction were readily removed. The lactones **6b** and **6c** displayed spectroscopic data (^{1}H NMR, IR), in agreement with those reported for the natural products,[3] and the ^{1}H NMR spectra matched in detail copies generously provided by Drs. Ishii and Yoshida.[3]

Hydrogenation of Enol Lactones. Since lactonization of olefinic acids provided only the cis lactones, an alternative route to the trans lactones was investigated. Yamamura et al. reported that homogeneous catalytic hydrogenation ($Rh(PPh_3)_3Cl$, benzene, room temperature, 30 min) of obtusilactone (**1a**) saturated only



1a **3h**

5h

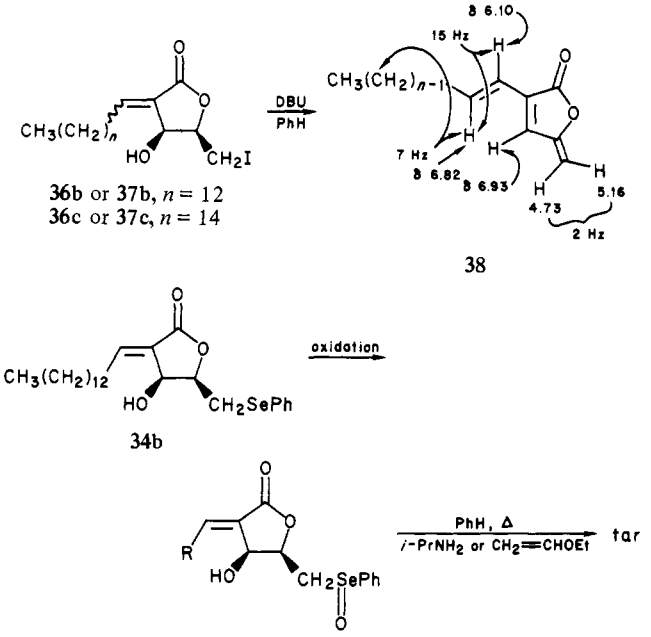
the terminal and enol lactone double bonds.[2a] Although they stated that the product was a mixture of isomers **3h** and **5h**, the chemical shift that they reported for the γ-methyl group in the ^{1}H NMR spectrum (δ 1.38) suggested that the trans lactone **3h** had been formed selectively since the γ-methyl group in the *Z* trans lactones has a chemical shift of δ 1.38, while in the *Z* cis lactones it has a chemical shift of δ 1.47. More forcing conditions (5% Pd/$BaSO_4$, EtOH, room temperature, 6 h) have been reported to effect hydrogenation of the α-alkylidene double bond as well.

Hydrogenation of isomahubanolide (**2c**) for 10 h at room temperature under 1 atm of hydrogen with $Rh(PPh_3)_3Cl$ catalyst gave a 50% yield of a mixture of isomers **4c** and **6c**, as indicated by the presence of two doublets (J = 6 Hz) at δ 1.44 and 1.36 in the ^{1}H NMR spectrum. While this provides evidence for the formation of the trans lactones, it is an impractical approach, since only minimal separation of the two isomers is effected by analytical thin-layer chromatography in a variety of solvent systems.

Attempts toward an Alternative Synthesis of Enol Lactones. Conceptually, the γ-methylene lactones should be available via the elimination of HX from lactones **34**–**37**. Attempts to effect

(23) (a) Clive, D. L. J.; Chittattu, G.; Wong, C. K. *J. Chem. Soc., Chem. Commun.* **1978**, 41–42. (b) For a review on organotin hydride reductions, see: Kuivila, H. G. *Synthesis* **1970**, 499–509.

Scheme VII



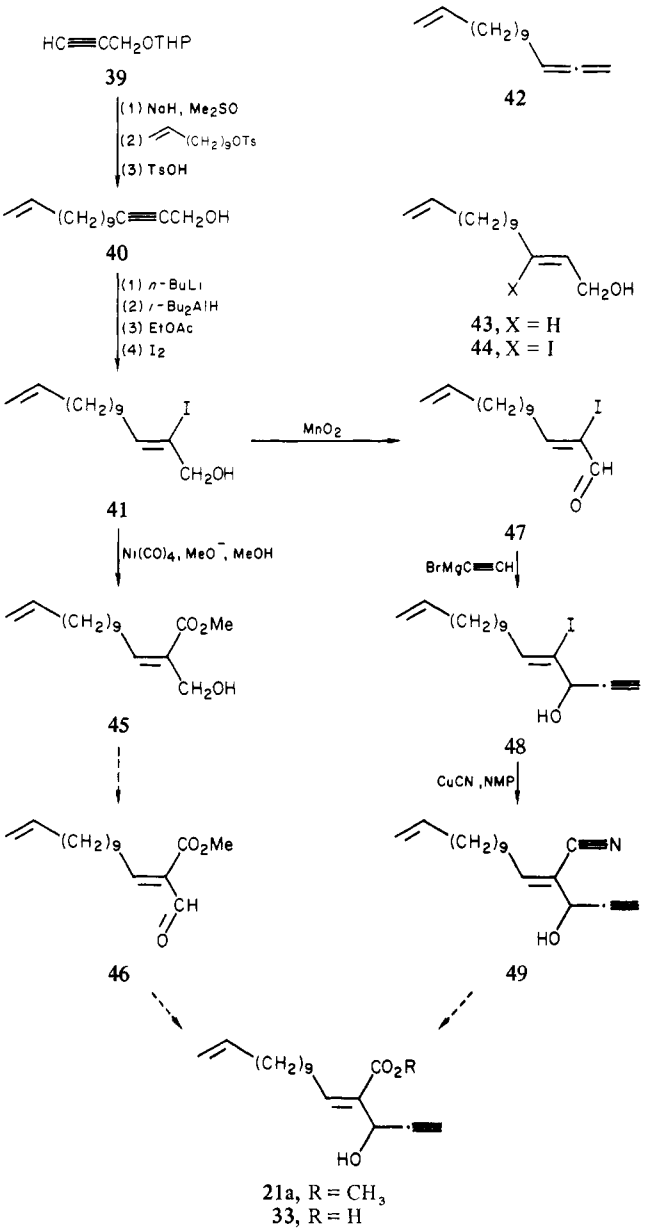
such an elimination are shown in Scheme VII. The conversion of γ-iodomethyl lactones to enol lactones by treatment with 1,8-diazabicyclo[5.4.0]undec-7-ene has been reported.[22c] However, treatment of lactone **36b** with 1,8-diazabicyclo[5.4.0]undec-7-ene gave a high yield (92%) of the fluorescent dehydrated enol lactone **38b**, characterized by a complex set of vinylic signals in the ^{1}H NMR spectrum (see Scheme VII), a molecular ion at *m/e* 290, and an IR spectrum showing a carbonyl frequency of 1775 cm^{-1} and lacking an OH stretch. The trienol lactone **38b** was unstable even when refrigerated. The lactones **36c** and **37c** gave a similar product, **38c** (by TLC and ^{1}H NMR). No evidence for the intermediacy of enol lactones **1** or **2** was seen when the reaction was stopped before completion, and the enol lactones themselves dehydrated in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene.

Although elimination of selenoxides bearing β-oxygen functions generally yields allyl alcohols, ethers, or esters rather than the corresponding enol compounds, enol generation has been reported when the allyl option is not available.[24] Phenylselenenyl lactones **34** are such a case. However, no elimination product was observed when lactone **34b** was treated with aqueous hydrogen peroxide in benzene at 25 °C in the presence of acetic acid and diisopropylamine. When the selenoxide was heated at reflux in benzene with diisopropylamine to scavenge PhSeOH, an intractable tar was formed. Low-temperature (−15 °C) oxidation to the selenoxide with *m*-chloroperbenzoic acid in dichloromethane,[14,25] followed by addition of the cold solution along with ethyl vinyl ether (to scavenge PhSeOH[26]) to refluxing hexane[14] again gave a complex mixture of products showing no evidence by ^{1}H NMR of enol lactone formation.

An Alternative Selective Approach to the *Z* Isomers of the Lauraceae Lactones. A disadvantage of the synthesis of obtusilactone via α-phenylselenenyl esters is the low yields obtained for the *Z* isomers. A stereospecific route to the *Z* ester **45** and the *Z* nitrile **49** (Scheme VIII) related to ester **21a** had been developed in early work on the synthesis of obtusilactone.[6b] Unfortunately, the ester **45** could not be oxidized selectively, and the nitrile **49** has resisted all efforts at hydrolysis to the corresponding carboxylic acid or amide.

The propargylic alcohol 3-tetradecen-2-yn-1-ol (**40**), produced efficiently by alkylation of the anion of propargyl tetrahydro-

Scheme VIII



pyranyl ether (**39**) with 10-undecen-1-yl toluenesulfonate followed by deprotection, could be hydroaluminated stereo- and regiospecifically by treatment with butyllithium, followed by diisobutylaluminum hydride;[27] the reaction was followed carefully to minimize formation of the allenic elimination product **42**. After the consumption of excess hydride with ethyl acetate, treatment of the vinyl alane intermediate with iodine furnished the 2-iodoallylic alcohol **41**, free from the isomeric 3-iodoallylic alcohol **44** but contaminated by small amounts of starting material and the unsubstituted allylic alcohol **43**,[27] which could be removed by careful column chromatography on basic alumina.

The alcohol **41** could be carbomethoxylated with nickel carbonyl and sodium methoxide,[28,29] but the resulting ester **45** could not be oxidized to the required aldehyde **46**. No reaction was observed with oxygen over a platinum catalyst nor with nickel peroxide. Oxidation of the alcohol with MnO_2, pyridinium chlorochromate, and Me_2SO-based oxidants gave rapid reaction but no evidence of **46**. Treatment of the mesylate of **45** with Me_2SO and $NaHCO_3$

(24) Petrizilka, M. *Helv. Chem. Acta* **1978**, *61*, 3075–3078.
(25) Reich, H. J.; Shah, S. *J. Am. Chem. Soc.* **1975**, *97*, 3250–3252. Reich, H. J.; Wollowitz, S.; Trend, J. E.; Chow, F.; Wendelborn, D. F. *J. Org. Chem.* **1978**, *43*, 1697–1705.
(26) Eaton, P. E.; Andrews, G. D.; Krebs, E.-P.; Kunai, A. *J. Org. Chem.* **1979**, *44*, 2824–2834.
(27) Corey, E. J.; Kirst, H. A.; Katzenellenbogen, J. A. *J. Am. Chem. Soc.* **1970**, *92*, 6314–6319.
(28) Corey, E. J.; Hegedus, L. S. *J. Am. Chem. Soc.* **1969**, *91*, 1233–1234.
(29) Semmelhack, M. F. *Org. React.* **1972**, *19*, 115–198 gives precautions in handling this reagent.

as well as the trimethylsilyl ether of **45** with trityl tetrafluoroborate gave no isolable aldehyde. As this compound would be a reactive Michael acceptor and might not survive standard aqueous workup, attempts were made to trap it by ethynylation after low temperature oxidation of **45**; however, no material corresponding to the ester **21a** could be isolated.

An alternative approach was also frustrated at the penultimate step. In contrast to the oxidation of **45**, the iodoallylic alcohol **41** is readily oxidized by manganese dioxide or nickel peroxide to the aldehyde **47** and this material is smoothly ethynylated to **48**. We were not able to carbomethoxylate this material by the nickel carbonyl procedure to give the ester **21a** (acetylenes themselves are known to react with nickel carbonyl[30]), but the corresponding nitrile **49** could be formed in 70% yield by reaction of **48** with cuprous cyanide in *N*-methyl-2-pyrrolidinone.[31] While in principle, this nitrile could be hydrolyzed to the acid **33**, all efforts to effect hydrolysis of **49** have led only to degradation products.[6b]

Conclusion

The use of α-phenylselenenyl esters as acrylate α-anion equivalents in aldol addition reactions provided a very direct and convenient synthesis of α-alkylidene-β-hydroxy-γ-methylene- and γ-methylbutyrolactones. A representative set of the Lauraceae lactones has been synthesized; the remaining compounds could be synthesized in an analogous manner by starting with the appropriate carboxylic acid.

Experimental Section

General Data. ^{1}H NMR spectra were recorded on a Varian EM 390 (90-MHz) or HR 220 (220-MHz) spectrometer in carbon tetrachloride or deuteriochloroform solution with tetramethylsilane as the internal standard. Spectra are 90 MHz in CCl_4 unless specified otherwise. Data, most of which is summarized in Table I, are reported in the form δ value of signal (peak multiplicity, coupling constant if appropriate, number of protons). When peak multiplicities are reported, the following abbreviations are used: s, singlet; d, doublet; t, triplet; q, quartet; quint, quintet; m, multiplet; br, broadened. Infrared spectra were obtained on a Beckman IR-12 spectrophotometer or Perkin-Elmer 137 sodium chloride spectrophotometer as a neat liquid or chloroform solution between sodium chloride plates or as a KBr pellet. Data, most of which is summarized in Table II, are given in cm^{-1} with only the important diagnostic bands being reported. Ultraviolet spectra were recorded on a Varian Technotron 635 UV-VIS spectrophotometer; UV data are summarized in Table 4. Mass spectra were obtained on a Varian-MAT CH-5 spectrometer with an ionization voltage of 10 or 70 eV. Data, most of which is summarized in Table III, are reported in the form m/e (intensity relative to base peak = 100). High-resolution electron impact mass spectroscopy (HREIMS) was performed on a Varian-MAT 731 mass spectrometer. Elemental analyses were performed by the University of Illinois microanalytical service laboratory. Melting points were obtained on a Thomas Hoover capillary melting point apparatus and are uncorrected.

Analytical thin-layer chromatography was performed by using 0.25-mm silica gel glass-backed plates with F-254 indicator (Merck). Visualization was accomplished by UV light, iodine, and/or phosphomolybdic acid. Preparative layer chromatography was performed on 20 × 20 cm glass plates coated to a thickness of about 2 mm with Merck Silica Gel 60 PF-254 or MN Silica Gel P/UV-254. The plates were predeveloped with methanol and heat activated prior to use. Column chromatography was performed by using 0.05–0.3-mm Brinkmann silica gel, usually in a weight ratio of 100:1 silica gel:crude product. Alumina chromatography was performed by using Brinkmann neutral alumina activity I. Analytical gas–liquid chromatography (GC) was performed on a Hewlett-Packard Model 5750 chromatograph (programmable temperature control) equipped with a flame ionization detector and nitrogen carrier gas. The column was 8 ft × $^1/_8$ in. 3% OV-17 on 80/100 Supelcoport.

Tetrahydrofuran (Aldrich Gold Label) was distilled from sodium benzophenone in a recirculating still, with a deep blue color maintained in the distilling pot. The in-house nitrogen supply was used to provide an inert atmosphere after being passed through a drying tower filled with Drierite. Reaction products were dried over magnesium sulfate unless otherwise specified. *n*-Butyllithium and *sec*-butyllithium were titrated by the single titration method.[32a] This method was unsuitable for the darkly colored phenyllithium and allyllithium solutions, which were titrated immediately prior to use by the double-titration method.[32b] Allyllithium[17] and propargylaldehyde (propynal)[33] were made by standard literature procedures. The dimethyl sulfide complex of cuprous bromide ($CuBr{\cdot}SMe_2$) was prepared as described by House.[34]

Chemicals were obtained from the following sources and used without purification unless specified: Aldrich, acrolein (distilled from magnesium sulfate), 2-amino-2-methyl-1-propanol, 11-bromoundecanoic acid, *m*-chloroperbenzoic acid, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), diisopropylamine (distilled from calcium hydride), diphenyl diselenide, ethyl vinyl ether, mercuric trifluoroacetate, palmitic acid, phenylselenenyl chloride, propargyl alcohol, stearic acid, 10-undecen-1-ol; Alfa/Ventron, *n*-butyllithium in hexane, *sec*-butyllithium in cyclohexane, nickel carbonyl, phenyllithium in benzene/ether, tetraallyltin, tri-*n*-butyltin hydride, triphenyltin hydride; J. T. Baker, mercuric acetate.

Methyl 2-Phenylselenenyl-13-tetradecenoate (17a).. To 25 mL of THF under nitrogen at −78 °C was added 1.5 mL (1.05 g, 10.4 mmol) of diisopropylamine and 3.90 mL of 2.54 M *n*-butyllithium (9.9 mmol). A second flask with half as much LDA was also prepared. Methyl 11-bromoundecanoate (**25**) (1.38 g, 4.95 mmol) was dissolved in 7 mL of THF, and the mixture was added dropwise over 15 min by using an addition funnel to the first LDA solution while it was being stirred at −78 °C. Diphenyl diselenide (0.93 g, 3 mmol) was dissolved in 4 mL of THF in the addition funnel, and 0.15 mL of bromine (0.47 g, 2.93 mmol) was added to this solution to generate phenylselenenyl bromide. One hour after the last of the bromo ester **25** had been added to the LDA, the PhSeBr solution was added rapidly. The dark orange color disappeared immediately. (At this point, the reaction could be quenched to give methyl 2-phenylselenenyl-11-bromoundecanoate (**29**), after preparative layer chromatography, SiO_2, hexane, and then 1:4 ether/hexane. ^{1}H NMR data are given in Table IA. IR data are given in the supplementary material.) The LDA solution in the second flask was siphoned into the first flask through Teflon tubing under nitrogen pressure. Allyllithium (0.82 M, 15.0 mL, 12.3 mmol) was then added by syringe, dropwise, over 5 min, while the solution was stirred at −78 °C. The reaction flask was allowed to warm to −10 °C over 2.5 h, and then the reaction was quenched by adding 30 mL of saturated aqueous ammonium chloride. The product was extracted into ether and then dried, and the solvents were removed on a rotary evaporator. Column chromatography (SiO_2, hexane to remove excess PhSeSePh and selenium-containing byproducts, and then 1:9 ether/hexane to elute product) gave 2.26 g (116% yield) of the α-phenylselenenyl ester **17a** as a yellow oil contaminated with substantial amounts of PhSeSePh. The product was used in its crude form: with the assumption of a 100% yield, the material was 86.5% desired ester **17a**. A small sample was subjected to preparative layer chromatography (SiO_2, hexane, and then 1:4 ether/hexane) to give a purer sample. ^{1}H NMR data are given in Table IA. IR and MS data are given in the supplementary material. HREIMS Calcd for $C_{21}H_{32}O_2Se$: 396.1567. Found: 396.1568.

α-Phenylselenenyl Esters 17b and 17c. A. General Procedure. To a dry flask containing 2 equiv of LDA (2.2 equiv of diisopropylamine, 2.0 equiv of *n*-butyllithium) in THF at −78 °C was added, with stirring, a solution of the desired methyl ester **16** in THF. After 1 h, a freshly prepared solution of 1.2 equiv of PhSeBr (1.2 equiv of PhSeSePh, 1.2 equiv of bromine) was added rapidly. The deep orange color immediately decolorized. After being warmed to room temperature over 30 min, the mixture was quenched by adding brine. The product was extracted into ether and then washed with 1 N hydrochloric acid (to remove diisopropylamine) and saturated aqueous bicarbonate. The ether extracts were then dried and solvents removed on a rotary evaporator. The resulting product, α-phenylselenenyl esters **17**, containing substantial amounts of PhSeSePh, could be used crude or further purified by column chromatography (SiO_2 and hexane followed by 1:9 ether/hexane).

B. Methyl 2-Phenylselenenylhexadecanoate (17b). A small scale reaction (2.3 g of ester **16b**) gave 3.94 g of **17b** (86% yield). A larger

(30) (a) Bird, C. W. *Chem. Rev.* **1962**, *62*, 283–302. (b) Eidus, Y. T.; Puzitskii, K. V.; Lapidus, A. L.; Nefedov, B. K. *Russ. Chem. Rev.* (*Engl. Transl.*) **1971**, *40*, 429–440. (c) Sternberg, H. W.; Markby, R.; Wender, I. *J. Am. Chem. Soc.* **1960**, *82*, 3638–3640 reports a reaction in alkaline media.

(31) (a) Friedman, L.; Schechter, H. *J. Org. Chem.* **1961**, *26*, 2522–2524. (b) Newman, M. S.; Boden, N. *Ibid.* **1961**, *26*, 2525.

(32) (a) Watson, S. C.; Eastham, J. F. *J. Organomet. Chem.* **1967**, *9*, 165–168. (b) Whitesides, G. M.; Casey, C. P.; Krieger, J. K. *J. Am. Chem. Soc.* **1971**, *93*, 1379–1389. (c) During the course of these studies a new single titration method was reported which is suitable for both types of organolithium reagents: Winkle, M. R.; Lansinger, J. M.; Ronald, R. C. *J. Chem. Soc., Chem. Commun.* **1980**, 87–88.

(33) Sauer, J. C. "Organic Syntheses"; Wiley: New York 1963; Coll. Vol. IV, pp 813–815.

(34) House, H. G.; Chu, C. Y.; Wilkins, J. M.; Umen, M. J. *J. Org. Chem.* **1975**, *40*, 1460–1469.

(35) Weast, R. C., Ed. "CRC Handbook of Chemistry and Physics", 51st ed.; CRC Press: Cleveland, OH, 1970–1971.

scale preparation (8.12 g of ester **16b**) gave a 74% yield (9.42 g) of **17b** as a yellow oil after column chromatography. ^{1}H NMR data are given in Table IA. IR and MS data are given in the supplementary material. HREIMS Calcd. for $C_{23}H_{38}O_3Se$: 426.2037. Found: 426.2037.

C. Methyl 2-Phenylselenenyloctadecanoate (17c). The enolate of ester **16c** was not soluble in the THF at −78 °C, so the temperature of the reaction was raised to −50 °C. A small scale reaction (2.97 g of methyl ester **16c**) gave 4.53 g of product (100% yield), while a larger scale reaction (8.96 g of **16c**) gave 10.52 g of **17c** (77% yield) as a yellow slush after column chromatography. ^{1}H NMR data are given in Table IA. IR and MS data are given in the supplementary material. HREIMS Calcd for $C_{25}H_{42}O_2Se$: 454.2350. Found: 454.2360.

Aldol Additions: Synthesis of Adducts 18–21. A. General Procedure. To a dry flask containing 2 equiv of LDA (2.2 equiv of diisopropylamine, 2.0 equiv of *n*-butyllithium) in THF was added a THF solution of the α-phenylselenenyl ester **17**, dropwise, while it was being stirred at −78 °C. After 30 min, the neat aldehyde (acrolein or propargylaldehyde) was added. Twenty minutes after addition of the aldehyde, the reaction mixture was warmed to 0 °C and 1 mL of glacial acetic acid and approximately 10 equiv of hydrogen peroxide (as a 30% aqueous solution) was added. After 30 min, the ice bath was removed and the mixture was allowed to stir at room temperature for 1–2 h, during which time the bright yellow color of the solution faded to pale yellow. The crude reaction mixture was partitioned between brine and ether, and the organic layer was washed with 1 N hydrochloric acid, then with saturated aqueous sodium bicarbonate, and finally once more with brine. The organic layer was dried and concentrated on a rotary evaporator. Column chromatography (SiO_2 and 1:9 and then 1:4 ether/hexane) separated the *E* and *Z* isomers of the aldol adducts. The *Z* adducts required further purification by preparative layer chromatography (SiO_2 and 3 × 1:9 ether/hexane or 3 × 1:100 ethanol/chloroform) to obtain an analytically pure sample.

B. Methyl (*E*)-2-(1-Hydroxy-2-propenyl)-2-hexadecenoate (18b) and Methyl (*Z*)-2-(1-Hydroxy-2-propenyl)-2-hexadecenoate (19b). Addition of 2.10 g (4.95 mmol) of ester **17b** to acrolein followed by selenoxide elimination yielded 0.69 g (43%) of *E* adduct **18b** and 0.18 g (11%) of *Z* adduct **19b** both as colorless oils after chromatography.

18b: ^{1}H NMR data are given in Table IB; IR and MS data are given in the supplementary material. Anal. Calcd for $C_{20}H_{36}O_3$: C, 74.03; H, 11.18. Found: C, 74.19; H, 11.19.

19b: ^{1}H NMR data are given in Table IC; IR and MS data are given in the supplementary material. Anal. Calcd for $C_{20}H_{36}O_3$: C, 74.03; H, 11.18. Found: C, 73.76; H, 11.28.

C. Methyl (*E*)-2-(1-Hydroxy-2-propenyl)-2-octadecenoate (18c) and Methyl (*Z*)-2-(1-Hydroxyl-2-propenyl)-2-octadeconoate (19c). Addition of 4.51 g (9.95 mmol) of ester **17c** to acrolein followed by selenoxide elimination yielded 0.78 g (22%) of *E* adduct **18c** and 0.20 g (6%) of *Z* adduct **19c**, both as colorless oils after chromatography.

18c: ^{1}H NMR data are given in Table IB; IR and MS data are given in the supplementary material. Anal. Calcd for $C_{22}H_{40}O_3$: C, 74.95; H, 11.44. Found, C, 74.70; H, 11.37.

19c: ^{1}H NMR data are given in Table IB; IR and MS data are given in the supplementary material. Anal. Calcd for $C_{22}H_{40}O_3$: C, 74.95; H, 11.44. Found: C, 74.62; H, 11.48.

D. Methyl (*E*)-2-(1-Hydroxy-2-propynyl)-2,13-tetradecadienoate (20a) and Methyl (*Z*)-2-(1-Hydroxy-2-propynyl)-2,13-tetradecadienoate (21a). Addition of 1.16 g (2.93 mmol) of ester **17a** to propargylaldehyde followed by selenoxide elimination yielded 0.16 g (18%) of *E* adduct **20a** and 40 mg of *Z* adduct **21a** (5%), both as pale yellow oils after chromatography.

20a: ^{1}H NMR data are given in Table IB; IR and MS data are given in the supplementary material. HREIMS Calcd for $C_{18}H_{28}O_3$: 292.2038. Found: 292.2042.

21a: ^{1}H NMR data are given in Table IB; IR (Table II) and MS (Table III) data are given in the supplementary material.

E. Methyl (*E*)-2-(1-Hydroxy-2-propynyl)-2-hexadecenoate (20b) and Methyl (*Z*)-2-(1-Hydroxy-2-propynyl)-2-hexadecenoate (21b). Addition of 2.15 g (5.06 mmol) of ester **17b** to propargylaldehyde followed by selenoxide elimination yielded 0.66 g (41%) of *E* adduct **20b** and 0.17 g (10%) of *Z* adduct **21b**, both as pale yellow oils after chromatography.

20b: ^{1}H NMR data are given in Table IB; IR and MS data are given in the supplementary material. Anal. Calcd for $C_{20}H_{34}O_3$: C, 74.49; H, 10.63. Found: C, 74.17, H, 10.68.

21b: ^{1}H NMR are given in Table IB; IR and MS data are given in the supplementary material. Anal. Calcd for $C_{20}H_{34}O_3$: C, 74.49; H, 10.63. Found: C, 74.41; H, 10.69.

F. Methyl (*E*)-2-(1-Hydroxy-2-propynyl)-2-octadecenoate (20c) and Methyl (*Z*)-2-(1-Hydroxy-2-propynyl)-2-octadecenoate (21c). Addition of 2.27 g (5.03 mmol) of ester **17c** to propargylaldehyde followed by selenoxide elimination yielded 0.59 g (34%) of *E* adduct **20c** as a colorless oil and 0.14 g (8%) of *Z* adduct **21c** as a white crystalline solid after chromatography.

20c: ^{1}H NMR data are given in Table IB; IR and MS data are given in the supplementary material. Anal. Calcd for $C_{22}H_{38}O_3$: C, 75.38; H, 10.93. Found: C, 75.26; H, 11.06.

21c: ^{1}H NMR data are given in Table IB. IR and MS data are given in the supplementary material. Anal. Calcd for $C_{22}H_{38}O_3$: C, 75.38; H, 10.93. Found: C, 75.27; H, 11.00.

Hydrolysis of Esters 18–21. The ester was dissolved in 1–2 mL of ether (to aid in transfer to flask) and 2–5 mL of Claisen's alkali[18] was added. The mixture was stirred vigorously (magnetically) at room temperature and kept under nitrogen to exclude atmospheric carbon dioxide. Hydrolysis was complete within 1–2 h, by which time most of the ether had evaporated. The reaction mixture was cooled to 0 °C, layered with approximately 5 mL of ether, then acidified to Congo Red with 6 N hydrochloric acid. Sufficient water was added to dissolve precipitated salts, and the product was extracted into ether. The ether layer was dried and concentrated on a rotary evaporator and then dried once more, and solvents were removed once again. The crude acids were obtained in 80–100% yields (typically 98%). The reaction was performed on a scale of 0.05–1.21 mmol (typically 0.3 mmol). The products were either oils or slushes. The esters that were hydrolyzed were **18b,c**, **19c**, **20a–21a** and **c**. ^{1}H NMR data are given in Table IC. IR data are given in the supplementary material.

Mercuric Ion Catalyzed Lactonization of Acetylenic Acids. Synthesis of Enol Lactones 1a–c and 2a–c. A. General Procedure. The acetylenic acid was dissolved in 1–5 mL of dichloromethane and cooled to 0 °C. Mercuric trifluoroacetate (0.1–0.2 equiv) was added and the mixture stirred for 1–2 h until TLC examination (SiO_2 and 1:3 ethyl acetate/benzene) showed complete conversion of the acid (R_f 0.2) to the lactone (R_f 0.5). The reaction mixture was chromatographed on a preparative layer plate (SiO_2 and 1:9 ethyl acetate/benzene) to yield the desired enol lactone. Yields ranged from 18 to 46% (typically 30%) and the scale ranged from 0.05 to 0.63 mmol (typically 0.15 mmol). Despite the low yields, no other materials could be isolated from the reaction mixture.

B. [±-(*Z*)]-3-(11-Dodecenylidene)-4-hydroxy-5-methylenetetrahydro-2-furanone (1a, Obtusilactone) as a Mixture with 2a. A 1:1 mixture of acetylenic acids **30a** and **31a** (15.1 mg, 0.052 mmol) yielded 5.1 mg (34%) of a 1:1 mixture of lactones **1a** and **2a**. The ^{1}H NMR spectrum confirmed the presence of both isomers, but characterization of lactone **1a** was completed in the next section (sodium bicarbonate lactonization).

C. [±-(*E*)-3-(11-Dodecenylidene)-4-hydroxy-5-methylenetetrahydro-2-furanone (2a, Isoobtusilactone). Acetylenic acid **30a** (40.4 mg, 0.15 mmol) yielded 10.7 mg (26%) of lactone **2a**. ^{1}H NMR data are given in Table IE. IR, MS, and UV data are given in the supplementary material. HREIMS Calcd for $C_{17}H_{26}O_3$: 278.1882. Found: 278.1885.

D. [±-(*Z*)]-4-Hydroxy-5-methylene-3-tetradecylidenetetrahydro-2-furanone (1b, Obtusilactone A). Acetylenic acid **31b** (42.7 mg, 0.138 mmol) yielded 7.7 mg (18%) of lactone **1b**. ^{1}H NMR data are given in Table IE. IR, MS, and UV data are given in the supplementary material. HREIMS Calcd for $C_{19}H_{32}O_3$: 308.2351. Found: 308.2351.

E. [±-(*E*)]-4-Hydroxy-5-methylene-3-tetradecylidenetetrahydro-2-furanone (2b, Isoobtusilactone A). Acetylenic acid **30b** (30 mg, 0.097 mmol) yielded 13.6 mg (46%) of lactone **2b**. ^{1}H NMR data are given in Table IE. IR, MS, and UV data are given in the supplementary material. HREIMS Calcd for $C_{19}H_{32}O_3$: 308.2351. Found: 308.2355.

F. [±-(*Z*)]-3-Hexadecylidene-4-hydroxy-5-methylenetetrahydro-2-furanone (1c, Mahubanolide). Acetylenic acid **31c** (44.7 mg, 0.13 mmol) yielded 13.7 mg (31%) of lactone **1c**. ^{1}H NMR data are given in Table IE. IR, MS, and UV data are given in the supplementary material.

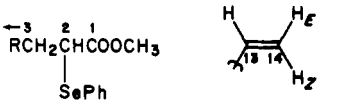
G. [±-(*E*)]-3-Hexadecylidene-4-hydroxy-5-methylenetetrahydro-2-furanone (2c, Isomahubanolide). Acetylenic acid **30c** (0.21 g, 0.63 mmol) yielded 75.4 mg (29%) of lactone **2c**. ^{1}H NMR data are given in Table IE. IR, MS, and UV data are given in the supplementary material. HREIMS Calcd for $C_{21}H_{36}O_3$: 336.2664. Found: 336.2661.

Bicarbonate-Catalyzed Lactonization of Acetylenic Acids. Synthesis of Enol Lactones 1a and 2b. A. General Procedure. The acetylenic acid was dissolved in 1–5 mL of dichloromethane, and approximately 0.1 mL of saturated aqueous sodium bicarbonate solution was added. The heterogeneous mixture was stirred vigorously (magnetically) for 30 min. Larger scale reactions (approximately 1 mmol) required the addition of solid sodium bicarbonate (approximately 10 mg) in addition to the aqueous solution. The reaction mixture was chromatographed on a preparative layer plate (SiO_2 and 1:9 ethyl acetate/benzene) to yield the enol lactones. Yields were comparable to the corresponding mercuric ion catalyzed lactonizations.

B. [±(*Z*)]-3-(11-Dodecenylidene)-4-hydroxy-5-methylenetetrahydro-2-furanone (1a, Obtusilactone). Acetylenic acid **31b** (16.3 mg, 0.058 mmol) yielded 4.1 mg (25%) of lactone **1a** after an additional preparative

Table I. ^{1}H NMR Data[a]

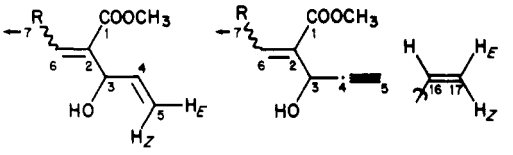
A. α-Phenylselenenyl Esters[a]



compd	MHz, solvent	H-2	H-3 (CH_2)	OCH_3	$(CH_2)_n$	Ph		H-16, 18 (CH_3)
29	90, CCl_4	3.5 (m)	1.77 (m)	3.57 (s)	1.28 (br s) (n = 6)	7.15–7.3 (m)	7.45–7.6 (m)	
17a	90, CCl_4	3.5 (m)	2.0 (m)	3.54 (s)	1.29 (br s) (n = 7)	7.15–7.3 (m)	7.45–7.6 (m)	
17b	90, CCl_4	3.5 (m)	1.8 (m)	3.53 (s)	1.25 (br s) (n = 12)	7.15–7.3 (m)	7.45–7.6 (m)	0.87 (t, 6)
17c	90, CCl_4	3.48 (t, 7)	1.75 (m)	3.57 (s)	1.33 (br s) (n = 14)	7.15–7.3 (m)	7.45–7.6 (m)	0.87 (t, 6)

compd	H-10 (CH_2)	H-11 (CH_2Br)	H-12 (CH_2)	H-13	H-14	
					E	*Z*
29	1.77 (m)	3.30 (t, 7)				
17a			2.0 (m)	5.7 (ddt, 17, 11, 7)	4.86 (dm, 11)	4.89 (dm, 17)

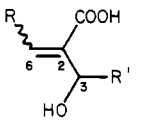
B. Aldol Adducts



compd	MHz, solvent	H-3	H-4	H-5 ≡CH	H-5 =CH, *E*	H-5 CH, *Z*	H-6	H-7 (CH_2)	H-8[b] (CH_2)	$(CH_2)_n$
18b	220, CCl_4	4.87 (m)	5.89 (ddd, 17, 10, 7)		5.02 (dd, 10, 1)	5.12 (dd, 17, 1)	6.71 (t, 8)	2.25 (m)	1.44 (m)	1.25 (br s) (n = 10)
18c	90, CCl_4	4.85 (m)	5.88 (ddd, 17, 10, 5)		4.91–5.17 (complex m)		6.67 (t, 7)	2.2 (m)		1.27 (br s) (n = 13)
19b	90, CCl_4	4.70 (m)	5.77 (ddd, 17, 10, 5)		4.99 (dt, 10, 2)	5.15 (dt, 17, 2)	6.11 (t, 8)	2.41 (q, 7)		1.33 (br s) (n = 11)
19c	90, CCl_4	4.68 (m)	5.81 (ddd, 17, 10, 6)		5.03 (d, 10)	5.18 (d, 17)	6.07 (t, 7)	2.4 (m)		1.27 (br s) (n = 13)
20a	220, CCl_4	5.13 (d, 2)		2.30 (d, 2)			6.73 (t, 7.5)	2.31 (m)	1.49 (m)	1.29 (br s) (n = 6)
20b	90, CCl_4	5.04 (dd, 10, 2)		2.26 (d, 2)			6.67 (t, 7)	2.3 (m)		1.28 (br s) (n = 11)
20c	90, CCl_4	5.10 (br s)		2.28 (d, 2)			6.71 (t, 7)	2.3 (m)		1.33 (br s) (n = 13)
21a	220, CCl_4	4.9 (br s)		2.39 (d, 2)			6.39 (t, 7)	2.48 (m)	1.41 (m)	1.29 (br s) (n = 6)
21b	90, CCl_4	4.92 (br s)		2.35 (d, 2)			6.36 (t, 7)	2.4 (m)		1.24 (br s) (n = 11)
21c	90, CCl_4	4.93 (br s)		2.38 (d, 2)			6.48 (t, 7)	2.47 (m)		1.30 (br s) (n = 13)

compd	OH	OCH_3	H-19, 21 (CH_3)	H-15	H-16	H-17	
						E	*Z*
18b	3.6 (br s)	3.72 (s)	0.89 (t, 7)				
18c	2.2 (br s)	3.68 (s)	0.87 (t, 5)				
19b	2.4 (br s)	3.70 (s)	0.88 (t, 6)				
19c	2.4 (m)	3.68 (s)	0.87 (t, 5)				
20a	3.8 (br s)	3.76 (s)		2.02 (q, 7)	5.70 (ddt, 17, 11, 7)	4.88 (d, 11)	4.98 (d, 17)
20b	3.58 (d, 10)	3.72 (s)	0.87 (t, 6)				
20c	3.7 (br s)	3.77 (s)	0.88 (t, 6)				
21a	2.7 (br s)	3.78 (s)		2.02 (q 7.5)	5.72 (ddt, 17, 11, 7)	4.88 (d, 11)	4.94 (d, 17)
21b	3.64 (s)	3.73 (s)	0.87 (t, 6)				
21c	2.8 (br s)	3.76 (s)	0.87 (t, 7)				

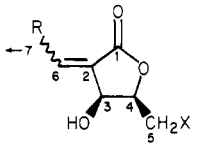
C. Carboxylic Acids



compd	MHz, solvent	H-6	OH	compd	MHz, solvent	H-6	OH
32b	90, CCl_4	6.82 (t, 8)	7.5 (br s)	**30c**	90, CCl_4	6.93 (t, 7)	
32c	90, CCl_4	6.88 (t, 8)	7.7 (br s)	**31a**	90, $CDCl_3$	6.65	
33c	90, CCl_4	6.27 (t, 7)	7.3 (br s)	**31b**	90, CCl_4	6.63	7.3 (br s)
30a	90, CCl_4	6.92 (t, 7)		**31c**	90, CCl_4	6.7	7.5 (br s)
30b	90, CCl_4	6.90 (t, 8)	7.9 (br s)				

Table I (*Continued*)

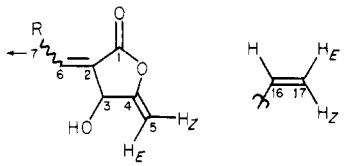
D. Phenylselenenyl and Iodo Lactones



X = I, PhSe

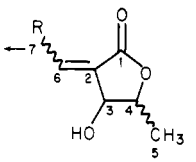
compd	MHz, solvent	H-3	H-4	H-5 (CH_2)	H-6	H-7 (CH_2)	H-8[b] (CH_2)	OH	$(CH_2)_n$	H-19, 21 (CH_3)	Ph	
34b	220, $CDCl_3$	5.03 (d, 4)	4.49 (m)		6.95 (td, 7, 1)	2.39 (m)	1.51 (m)	2.25 (br s)	1.26 (br s)	0.88 (t, 7)	7.28 (m)	7.57 (m)
34c	90, $CDCl_3$	4.98 (br d, 6)	4.44 (q, 6)		6.88 (br t, 8)	2.37 (q, 6)	2.37 (q, 6)	2.75 (br s)	1.28 (br s) (n = 13)	0.88 (t, 6)	7.2 (m)	7.5 (m)
36b	90, $CDCl_3$	5.01 (t, 6)	4.53 (q, 7)	3.42 (d, 8)	6.93 (t, 7)	2.38 (q, 7)		2.17 (d, 6)	1.28 (br s) (n = 11)	0.87 (t, 5)		
36c	90, $CDCl_3$	5.03 (m)	4.53 (m)	3.43 (d, 8)	6.96 (t, 7.5)	2.42 (m)		2.1 (br s)	1.31 (br s) (n = 13)	0.87 (t, 5)		
37c	90, $CDCl_3$	4.80 (m)	4.53 (m)	3.39 (d, 6) 3.41 (d, 8)	6.59 (t, 7)	2.75 (m)		4.20 (d)	1.32 (br s) (n = 13)	0.88 (t, 7)		

E. Enol Lactones



compd	MHz, solvent	H-3	H-5 *E*	H-5 *Z*	H-6	H-7 (CH_2)	H-8[b] (CH_2)	OH	$(CH_2)_n$	H-15 (CH_2)	H-16	H-17 *E*	H-17 *Z*	H-19 (CH_3)
1a	90, $CDCl_3$	*c*	4.65 (m)	*c*	6.65 (td, 8, 2)	2.75 (m)		1.43	1.28 (br s) (n = 6)	2.02 (m)	5.78 (m)	*c*	*c*	
1b	220, $CDCl_3$	5.11 (br s)	4.68 (m)	4.88 (m)	6.69 (td, 7, 2)	2.80 (m)	1.76 (m)		1.26 (br s) (n = 10)					0.88 (t, 7)
1c	90, $CDCl_3$	5.08 (br s)	4.63 (m)	4.82 (m)	6.65 (td, 8, 12)	2.72 (m)			1.30 (br s) (n = 13)					0.87 (t, 6)
2a	220, $CDCl_3$	5.27 (br s)	4.75 (m)	4.97 (m)	7.09 (td, 8, 2)	2.48 (q 8)	1.52 (m)		1.28 (br s) (n = 6)	2.04 (m)	5.84 (ddt, 17, 10, 8)	4.95 (d, 10)	5.01 (d, 17)	
2b	220, $CDCl_3$	5.26 (br s)	4.73 (br s)	4.95 (t, 2)	7.08 (td, 8, 2)	2.47 (2 q, 7)	1.51 (m)	2.5	1.26 (br s) (n = 10)					0.88 (t, 6)
2c	90, ($CDCl_3$	5.25 (br s)	4.70 (m)	4.91 (m)	7.05 (td, 8, 2)	2.47 (m)			1.30 (br s) (n = 13)					0.81 (t, 6)

F. γ-Methyl Lactones



compd	MHz, solvent	H-3	H-4	H-5 (CH_3)	H-6	H-7 (CH_2)	H-8[b] (CH_2)	OH	$(CH_2)_n$	H-19, 21
4c[d]	90, $CDCl_3$	*g*	*g*	1.36	6.99 (t, 8)	2.40 (2 q, 7)			1.26 (br s)	0.88 (t, 7)
5b[c]	220, $CDCl_3$	4.72 (m)	4.54 (m)	1.38 (d, 6)	6.56 7, 1)	2.70 (2 q, 6)			1.26 (br s)	0.88 (t, 7)
5c[f]	220, $CDCl_3$	4.65 (br s)	4.54 (m)	1.40 (d, 6)	6.57 (t, 7)	2.73 (m)	1.78 (m)		1.25 (br s)	0.88 (t, 7)
6b	220, $CDCl_3$	4.82 (t, 6)	4.53 (quint, 6)	1.46 (d 6.5)	6.95 (t, 8)	2.40 (2 q, 7)	1.55 (m)	1.71 (d, 6)	1.26 (br s) (n = 10)	0.87 (t, 6.5)
6c	220, $CDCl_3$	4.81 (br d, 6)	4.53 (quint, 6)	1.46 (d, 6.5)	6.94 (t, 7.5)	2.40 (2 q, 7.5)	1.52 (m)	2.04 (br s)	1.26 (br s) (n = 12)	0.88 (t, 6.5)

[a] Note in A–F that data are presented in the form δ (multiplicity, J (in Hz)). [b] 220 MHz. [c] δ 4.8–5.15 (complex, 4 H). [d] Data taken from spectrum containing a mixture of **4c** and **6c**. [e] Data taken from spectrum containing a mixture of **5b** and **6b**. [f] Data taken from spectrum containing a mixture of **5c** and **6c**. [g] δ 4.50–4.56 (complex m).

layer chromatography (SiO_2 and 3 × 1:100 ethanol/chloroform). ^1H NMR data are given in Table IE. IR, MS, and UV data are given in the supplementary material.

C. [±-(*E*)]-4-Hydroxy-5-methylene-3-tetradecylidenetetrahydro-2-furanone (2b, Isoobtusilactone A). Acetylenic acid **30b** (0.34 g, 1.1 mmol) yielded 0.136 g (40%) of lactone **2b**, identical with that synthesized by mercuric ion catalysis.

Phenylselenolactonization of Olefinic Acids. Synthesis of Lactones 34b and 34c. A. General Procedure. The olefinic acid was dissolved in 1–5 mL of dichloromethane. While the acid solution was magnetically stirred at room temperature, a solution of 1 equiv of phenylselenenyl chloride in 2–5 mL of dichloromethane was added dropwise until the yellow color of the PhSeCl persisted. The reaction mixture was concentrated on a rotary evaporator to yield the crude crystalline product (97–100%). Recrystallization from hexane yielded approximately 70% of the crystalline cis lactone. Preparative layer chromatography of the supernatant (SiO_2 and 1:3 ethyl acetate/benzene) gave additional product.

B. [±-(3*E*,4α,5α)]-4-Hydroxy-5-((phenylselenenyl)methyl)-3-tetradecylidenetetrahydro-2-furanone (34b). Olefinic ester **32b** (0.153 g, 0.493 mmol) yielded 0.108 g (70%) of crystalline lactone **34b** (mp 89.5–91.5 °C) after recrystallization from hexane. Preparative layer chromatography of the supernatant added an additional 33 mg (85% total) of lactone **34b**. ^1H NMR data are given in Table ID. IR and MS data are given in the supplementary material.

C. [±-(3*E*,4α,5α)-3-Hexadecylidene-4-hydroxy-5-((phenylselenyl)methyl)tetrahydro-2-furanone (34c). Olefinic ester **32c** (0.204 g, 0.602 mmol) yielded 0.132 g (44%) of crystalline lactone **34c** (mp 89–91 °C) after recrystallization from hexane. Preparative layer chromatography of the supernatant added an additional 12 mg (50% total) of lactone **34c**. ^1H NMR data are given in Table ID. IR and MS data are given in the supplementary material.

Iodolactonization of Olefinic Acids. Synthesis of Lactones 36b, 36c, and 37c. A. General Procedure. The olefinic acid was dissolved in dichloromethane and 2–3 equiv of iodine was added. After 4 h, the organic layer was washed with aqueous sodium thiosulfate to remove excess iodine. The organic layer was dried and concentrated on a rotary evaporator to yield crude iodo lactone **36** or **37** as a crystal solid (crude yields generally 75–90%). The crude lactone could be either recrystallized from hexane or, preferably, chromatographed on a preparative layer plate (SiO_2 and 1:3 ethyl acetate/benzene) to yield approximately 30% crystalline product. No explanation can be given for the dramatic decrease in yield upon purification: the crude product appears moderately clean (>90%) by ^1H NMR, yet no other lactone products can be recovered from the supernatant or chromatography.

B. [±-(3*E*,4α,5α)]-4-Hydroxy-5-(iodomethyl)-3-tetradecylidenetetrahydro-2-furanone (36b). Olefinic acid **32b** (33.4 mg, 0.108 mmol) yielded 37.1 mg (79%) of crude product. Chromatography yielded 13.4 mg (29%) of crystalline **36b** (mp 95–96.5 °C). ^1H NMR data are given in Table ID. IR and MS data are given in the supplementary material. Anal. Calcd for $C_{19}H_{33}O_3I$: C, 52.30; H, 7.62; I, 29.08. Found: C, 52.38; H, 7.31; I, 29.02.

C. [±-(3*E*,4α,5α)]-3-Hexadecylidene-4-hydroxy-5-(iodomethyl)-tetrahydro-2-furanone (36c). Olefinic acid **32c** (0.118 g, 0.348 mmol) yielded 0.129 g (79%) of crude product. Chromatography yielded 34.5 mg (21%) of crystalline **36c** (mp 100–101 °C). ^1H NMR data are given in Table ID. IR and MS data are given in the supplementary material.

D. [±-(3*Z*,4α,5α)]-3-Hexadecylidene-4-hydroxy-5-(iodomethyl)-tetrahydro-2-furanone (37c). Olefinic acid **33c** (88.8 mg, 0.262 mmol) yielded 0.108 (89%) of crude product. Chromatography yielded 36.3 g (30%) of crystalline **37c** (mp 84–85 °C). ^1H NMR data are given in Table ID. IR and MS data are given in the supplementary material.

Tri-*n*-butyltin Hydride Reductions. Synthesis of Lactones 5b,c and 6b,c. A. General Procedure. The phenylselenenyl lactone or iodo lactone was dissolved in 2–10 mL of benzene. Tri-*n*-butyltin hydride (3 equiv) and AIBN (1–3 equiv) were added, and the system was heated at reflux for 2 h. The reaction mixture was chromatographed on a preparative layer plate (SiO_2 and 1:3 ethyl acetate/benzene) to give approximately 60% yield of a mixture of isomeric lactones **5** and **6**. Recrystallization from hexane yielded pure crystalline **6** (approximately 20% yield) with the supernatant containing a mixture of **5** and **6**.

B. [γ-(3*E*,4α,5α)]-4-Hydroxy-5-methyl-3-tetradecylidenetetrahydro-2-furanone (6b, Epilitsenolide C_2) and [±-(3*Z*,4α,5α)]-4-Hydroxy-5-methyl-3-tetradecylidenetetrahydro-2-furanone (5b, Epilitsenolide C_1). Phenylselenenyl lactone **34b** (71.7 mg, 0.154 mmol) yielded 29.7 mg (62%) of a mixture of lactones **5b** and **6b**. Recrystallization yielded 11 mg (23%) of pure *E* lactone **6b** (mp 62.5–63.5 °C) and 19 mg (40%) of **5b** and **6b**, which was still a mixture. Iodo lactone **36b** (29.1 mg, 0.067 mmol) yielded 8.9 mg (43%) of a similar mixture.

5b: ^1H NMR data are given in Table IF.

6b: ^1H NMR data are given in Table IF; IR, MS, and UV data are given in the supplementary material. Anal. Calcd for $C_{19}H_{34}O_3$: C, 73.50; H, 11.04. Found: C, 73.08; H, 11.08. HREIMS Calcd for $C_{19}H_{34}O_3$: 310.2508. Found: 310.2508.

C. [±-(3*E*,4α,5α)]-3-Hexadecylidene-4-hydroxy-5-methyltetrahydro-2-furanone (6c, Isodihydromahubanolide B) and [±-(3*Z*,4α,5α)]-3-Hexadecylidene-4-hydroxy-5-methyltetrahydro-2-furanone (5c, Dihydromahubanolide B). Phenylselenenyl lactone **34c** (0.129 g, 0.262 mmol) yielded 50.2 mg (56%) of a mixture of lactones **5c** and **6c**. Recrystallization yielded 14.3 mg (16%) of pure *E* lactone **6c** (mp 70–70.5 °C) and 20 mg (23%) of **5c** and **6c**, which was still a mixture. Iodo lactone **37c** (*Z* isomer, 8.2 mg, 0.018 mmol) yielded 3.7 mg (62%) of a mixture of isomeric lactones (**5c**, **6c**) in which the *E* isomer (**6c**) predominated.

5c: ^1H NMR data are given in Table IF.

6c: ^1H NMR data are given in Table IF; IR, MS, and UV data are given in supplementary material. HREIMS Calcd for $C_{21}H_{38}O_3$: 338.2810. Found: 338.2815.

Hydrogenation of Enol Lactone 2c. Synthesis of Lactones 4c and 6c. [±-(3*E*,4α,5α)]-3-Hexadecylidene-4-hydroxy-5-methyltetrahydro-2-furanone (6c, Isodihydromahubanolide B) and [±-(3*E*,4α,5β)]-3-Hexadecylidene-4-hydroxy-5-methyltetrahydro-2-furanone (4c, Isodihydromahubanolide A). Isomahubanolide (**2c**) (24.7 mg, 0.073 mmol) was dissolved in 5 mL of benzene, and 6.8 mg (7.3 mol, 0.1 equiv) of $Rh(PPh_3)_3Cl$ was added. The homogeneous solution was stirred magnetically for 10 h at room temperature under hydrogen gas at 1 atm. The product was chromatographed on a preparative layer plate (SiO_2 and 1:9 ethyl acetate/benzene) to yield 12.3 mg (50%) of an approximately 1:1 mixture of isomeric lactones **4c** and **6c** identified by the location of their γ-methyl chemical shifts in the ^1H NMR spectrum. ^1H NMR data are given in Table IF.

[±-(*E*)]-3-(1-Tetradecenyl)-5-methylenedihydro-2(5*H*)-furanone (38b). Iodo lactone **36b** (73.3 mg, 0.168 mmol) was dissolved in benzene, and 26 μL (26 mg, 0.174 mmol) of DBU was added. The mixture was stirred at reflux for 2 h and then concentrated on a rotary evaporator. The residue was taken up in ether and then passed through a short column of silica gel to remove DBU. Removal of the ether on a rotary evaporator yielded 44.8 mg (92%) of lactone **38b**: ^1H NMR δ 0.87 (t, *J* = 6 Hz, 3 H), 1.28 (br s, 20 H), 2.18 (q, *J* = 7 Hz, 2 H), 4.73 (d, *J* = 2 Hz, 1 H), 5.16 (d, *J* = 2 Hz, 1 H), 6.10 (d, *J* = 15 Hz, 1 H), 6.82 (dt, *J* = 15 Hz, 1 H), 6.93 (s, 1 H); IR (neat) 1775 (C=O), 1645 (C=C); mass spectrum *m/e* (relative intensity) (10 eV) 290 (98, M^+), 291 (45, $M^+ + 1$), 180 (40), 177 (42), 136 (54), 122 (100), 123 (77), 110 (88), 96 (59), 82 (62).

13-Tetradecen-2-yn-1-ol (40). Sodium hydride, 0.58 g (12 mmol) of a 50% dispersion, was placed in a 100-mL flask with side arm. Dimethyl sulfoxide (40 mL) was then added rapidly by syringe, keeping the temperature at 20 °C by use of a water bath. After the hydrogen evolution ceased, propargyl alcohol tetrahydropyranyl ether (**39**) (1.68 g, 12 mmol) was added to the cloudy solution at room temperature. After the mixture was stirred for 15 min, 3.24 g (10 mmol) of 10-undecen-1-yl toluenesulfonate in 5 mL of Me_2SO was added, and after 16 h at room temperature, the product was poured into 150 mL of half-saturated ammonium chloride and was extracted with ether. The extract was washed with brine and dried. Silica gel chromatography (10% ether/hexane) gave 1.92 g (66%) of 13-tetradecen-2-yn-1-yl tetrahydropyranyl ether as a colorless liquid. This compound (4.04 g, 13.8 mmol) was added to 60 mL of methanol, followed by a dropwise addition of water until the solution just became cloudy. After 5 drops of 3 N hydrochloric acid was added, the mixture was stirred for 16 h at room temperature. The acid catalyst was then removed by the addition of saturated sodium bicarbonate. The methanol was removed under reduced pressure, and the product was extracted with ether and dried. Purification by silica gel chromatography (25% ether/hexane) gave 2.60 g (90%) of **40** as a colorless liquid: ^1H NMR (CCl_4) δ 5.78 (ddt, *J* = 17, 9, 6 Hz, 1 H), 4.70–5.15 (m, 2 H), 4.13 (t, *J* = 2 Hz, 2 H), 2.55 (br s, 1 H, D_2O exchangeable), 1.75–2.40 (m, 4 H), 1.15–1.75 (m, 14 H); IR 3360 (OH), 3080 (C=CH_2), 2290, 2220 (C≡C), 1640, 1015, 910 (C=C) cm^{-1}; mass spectrum (10 eV), *m/e* (relative intensity) 208 (M^+, 0.24), 177 (4.5), 147 (21), 133 (36), 119 (31), 105 (35), 81 (100). Anal. Calcd for $C_{14}H_{24}O$: C, 80.71; H, 11.61. Found: C, 80.46; H, 11.61.

(*Z*)-2-Iodo-2,13-tetradecadien-1-ol (41). Alcohol **40** (4.17 g, 20 mmol) was added to 30 mL of anhydrous ether and cooled to −20 °C. *n*-Butyllithium (8.51 mL of a 2.35 M hexane solution, 20 mmol) was then added, giving a viscous mixture which eventually appeared to freeze. The diisobutylaluminum hydride (8.53 g, 60 mmol) was then added at −20 °C from a precalibrated addition funnel. The mixture became fluid soon after the addition was started and was then heated at 30–35 °C for 48 h. The reaction must be monitored by GC to follow the disappearance of **40** and the appearance of the undesired allene elimination product

(**42**). The reaction must be quenched when the amount of **40** remaining is small compared to the amounts of allene being formed. After the mixture was cooled to 0 °C, 4.41 mL (3.96 g, 45 mmol) of dry ethyl acetate was added dropwise. After being stirred for 5 min, the mixture was cooled to −78 °C. A saturated iodine/ether solution (100 mL) was then added at a rapid rate, followed by stirring for 15 min at −78 °C. The product was poured into 100 mL of a solution 1 M in sodium hydroxide and 2.2 M in sodium thiosulfate. The ether layer was washed twice with the above solution, and the combined aqueous extracts were back-extracted with ether. The product was dried and then purified by chromatography on basic alumina, activity I (40% ether/hexane), to give the 2-iodoallylic alcohol (**41**) in 50% yield: ^{1}H NMR (CCl_4) δ 5.45–6.05 (m, 2 H), 4.75–5.15 (m, 2 H), 4.17 (br s, 2 H), 2.74 (br s, 1 H, D_2O exchangeable), 1.75–2.40 (m, 4 H), 1.20–1.75 (m, 14 H); IR 3350 (OH), 3080 (C=CH_2), 1640, 995, 910, 840 (C=C) cm^{-1}; mass spectrum (10 eV), *m/e* (relative intensity) 336 (M^+, 15), 209 (7), 196 (32), 191 (13), 184 (11), 135 (18), 127 (4), 121 (29), 70 (100).

Methyl (*Z*)-2-(Hydroxymethyl)-2,13-tetradecadienoate (45). Sodium methoxide (1.08 g, 20 mmol) was weighed under a nitrogen atmosphere and added to 30 mL of dry methanol in a 3-neck flask equipped with reflux condenser and addition funnel. The entire system was flushed with argon and cooled to 0 °C. Nickel carbonyl (3.88 mL, 5.12 g, 30 mmol) was transferred carefully (*Caution*: *This substance is very toxic and volatile. It must be used in an efficient hood with gloves and protective garments*, see ref 29 for details) to a precalibrated addition funnel and was then added to the methanol solution. The vinyl iodide **41** (3.35 g, 9.96 mmol) was added by syringe to give a pale yellow solution. The mixture was gradually warmed to 40 °C, at which point the solution began to turn dark brown and a vigorous reflux ensued. The heat source was removed immediately. After 15 min iodine in methanol was added until the iodine color persisted, and the mixture was stirred 45 min to ensure complete removal of all the nickel carbonyl. The methanol was removed under reduced pressure, and the mixture was poured into 175 mL of saturated brine containing 10 mL of 3 N hydrochloric acid. The product was extracted several times with ether, and the extracts were washed with saturated sodium bisulfite to remove excess iodine. After the product was dried, silica gel chromatography (50% ether:hexane) gave 2.00 g (75%) of pure product: ^{1}H NMR (CCl_4) δ 6.22 (t, J = 7 Hz, 1 H), 5.81 (ddt, J = 17, 10, 6 Hz, 1 H), 4.75–5.15 (m, 2 H), 4.15 (br s, 2 H), 3.72 (s, 3 H), 2.88 (br s, 1 H, D_2O exchangeable), 2.25–2.75 (m, 2 H), 1.75–2.25 (m, 2 H), and 1.15–1.70 (m, 14 H); IR 3450 (OH), 3080 (C=CH_2), 1730 (C=O), 1640, 995, 910, 820 (C=C) cm^{-1}; mass spectrum (10 eV), *m/e* (relative intensity) 268 (M^+, 2.3), 250 (25), 236 (11), 218 (15), 209 (2), 200 (12), 191 (48), 179 (11), 95 (100). Anal. Calcd for $C_{16}H_{28}O_3$: C, 71.60; H, 10.52. Found: C, 71.37; H, 10.49.

(*Z*)-2-Iodo-2,13-tetradecadienal (47). Alcohol **41** (1.01 g, 3 mmol) was added to 40 mL of hexane, followed by the addition of 3.91 g (45 mmol) of activated manganese dioxide, added in two portions 10 min apart. The reaction was kept on a water bath at 20 °C for the entire reaction. After the mixture was stirred 30 min, TLC showed a single UV active spot with an R_f above that of starting material. A small amount of magnesium sulfate was added to the mixture, followed by filtering and a very thorough washing with ether. The crude product (778 mg, 79%) was homogeneous by TLC and is sufficiently pure for further reactions: ^{1}H NMR (CCl_4) δ 8.58 (s, 1 H), 7.02 (t, J = 7 Hz, 1 H), 5.70 (ddt, J = 7, 10, 6 Hz, 1 H), 4.75–5.05 (m, 2 H), 2.35–2.65 (m, 2 H), 1.80–2.20 (m, 2 H), 1.15–1.80 (m, 14 H); IR 3090 (C=CH_2), 2740 (CHO), 1700 (C=O), 1645, 995, 910 (C=CH_2) cm^{-1}; mass spectrum, *m/e* (relative intensity) 334 (M^+, 9), 207 (18), 196 (42), 189 (20), 183 (23), 147 (12), 133 (16), 119 (15), 105 (11), 55 (100).

(*Z*)-3-Hydroxy-4-iodo-4,15-hexadecadiene-1-yne (48). The ethynylmagnesium bromide was prepared by the slow addition of ethylmagnesium bromide (2.48 mL of a 0.96 M solution in ether, 2.38 mmol) to 40 mL of dry tetrahydrofuran. A slow stream of purified acetylene was bubbled through the solvent for 5 min before the addition, throughout the addition and for 5 min afterward, maintaining a temperature of 15–20 °C throughout the procedure. The purified aldehyde **47** (666 mg, 1.99 mmol) was diluted with 3 mL of solvent and was added dropwise to the above solution at 0 °C. The reaction was complete within 10 min as indicated by TLC. After the reaction was quenched with saturated ammonium chloride, the solvent was removed under reduced pressure, and the product was taken up in ether and dried. Purification was achieved by a short basic alumina column (activity I) (40% ether/hexane), yielding 665 mg (93%) of product: ^{1}H NMR (CCl_4) δ 6.02 (t, J = 7 Hz, 1 H), 5.70 (ddt, J = 17, 10, 6 Hz, 1 H), 4.75–5.05 (m, 2 H), 4.58 (br s, 1 H), 2.47 (d, J = 2 Hz, 1 H), 1.70–2.35 (m, 5 H), 1.15–1.70 (m, 14 H); IR 3400 (OH), 3320 (C≡CH), 3080 (C=CH_2), 2120 (C≡C), 1643, 995, 910, 845 (C=C) cm^{-1}; mass spectrum (10 eV), *m/e* (relative intensity) 360 (M^+, 0.55), 261 (2), 247 (4), 235 (12), 233 (13), 220 (68), 173 (8), 159 (9), 81 (100).

(*E*)-3-Hydroxy-4-cyano-4,15-hexadecadien-1-yne (49). The vinyl iodide **48** (573 mg, 1.59 mmol) was added to 20 mL of dry *N*-methyl-2-pyrrolidinone, followed by dry cuprous cyanide (7.2 mg, 7.95 mmol). The mixture was heated under a nitrogen atmosphere at 130 ± 2 °C for 2.5 h. After being cooled, the mixture was poured into ether and was stirred vigorously with 40 mL of a solution containing 2–3 g of ferric chloride and 4–5 mL of 3 N hydrochloric acid to remove any cuprous ion complexes with the nitrile group. The aqueous layer was drawn off, and the organic extract was washed with brine to remove the remaining *N*-methyl-2-pyrrolidinone, dried, and concentrated to a black oil. Silica gel chromatography (30% ether/hexane) gave 290 mg (70%) of a yellow oil that was homogeneous by TLC and GC. The yellow coloration could not be removed by chromatographic means, but a bulb-to-bulb distillation gave a colorless product: ^{1}H NMR (CCl_4) δ 6.55 (t, J = 7 Hz, 1 H), 5.70 (ddt, J = 17, 9, 6 Hz, 1 H), 4.75–5.05 (m, 3 H), 3.17 (br d, J = 6 Hz, 1 H, D_2O exchangeable), 2.59 (d, J = 2 Hz, 1 H), 2.25–2.60 (m, 2 H), 1.80–2.20 (m, 2 H), 1.10–1.75 (m, 14 H); IR 3440 (OH), 3315 (C≡CH) 3080 (C=CH_2), 2230 (C≡N), 2125 (C≡C), 1645, 995, 910 (C=CH_2) cm^{-1}; mass spectrum (10 eV), *m/e* (relative intensity) 259 (M^+, 8), 258 (12), 242 (52), 230 (31), 216 (34), 202 (34), 188 (28), 174 (24), 55 (100). Anal. Calcd for $C_{17}H_{25}OH$: C, 78.72; H, 9.71; N, 5.40. Found: C, 78.48; H, 9.74; N, 5.55.

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Supplementary Material Available: IR (Table II), MS (Table III), and UV (Table IV) data on indicated compounds (7 pages). Ordering information is given on any current masthead page.