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A Total Synthesis of *dl*-Cerulenin

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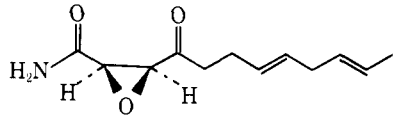
Abstract: A general route to endocyclic α,β-epoxy-γ-butyrolactones is described. The α,β-epoxylactones are potential protein cross-linking agents based upon the spectrum of reactivity displayed with amines and thiolate anion. The epoxylactone **8** is prepared from 1-bromo-2-butyne and serves as the key intermediate in a total synthesis of cerulenin (**1**), an important substance for the study of the enzyme systems involved in fatty acid biosynthesis.

The fungus *Cephalosporium caerulens* has proven to be a rich source of novel terpenoid metabolites, some of which possess antibiotic activity.[2] Among the nonterpenoid metabolites, a relatively minor component was isolated by Hata in 1960.[3,4] This substance, called cerulenin (**1**), possessed an



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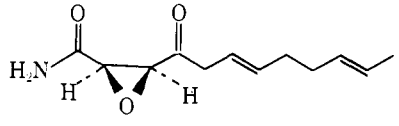
extremely interesting spectrum of biological activity. Cerulenin (**1**) was shown to have both antibiotic and antifungal activity, but the mechanism by which these effects were manifested has proven to be the most significant finding. It has been shown to be a potent inhibitor of fatty acid synthesis in a number of organisms,[5-8] and in *E. coli*, at least, the inhibition has been traced to reversible inactivation of the enzyme, β-keto-acyl-carrier-protein-synthetase.[9]

Originally, on the basis of spectroscopic and mass spectral studies, the novel fatty acid derived structure **2** was proposed



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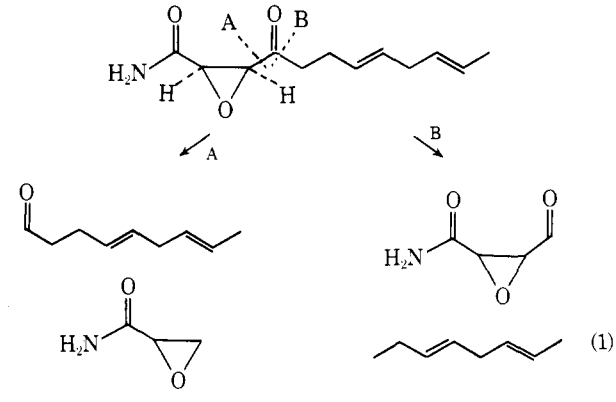
by Omura.[10] This initial assignment was subsequently revised to the double bond isomer **1** on the basis of high-resolution NMR measurements.[11] Recently the correct absolute configuration of (+)-cerulenin has been established by two groups as that shown.[12] This double bond arrangement is analogous to some naturally occurring fatty acids such as linelaidic acid (**3**),[13] but the cis epoxy amide grouping is unique among naturally occurring systems.

$$HOOC(CH_2)_7CH{=}CHCH_2CH{=}CHC_5H_{11}$$

3

In view of biosynthetic studies which established that cerulenin (**1**) was acetate derived,[14] and the value of this substance as a biochemical tool for study of the enzyme systems involved in fatty acid biosynthesis, especially the nature of substrate bonding at the active site, it was decided to undertake the total synthesis of **1**. Particular attention was paid to the feasibility of preparation of specifically labeled **1** for biochemical studies.

A number of plausible routes can be envisioned for the construction of cerulenin (**1**). Our efforts were focused on two convergent routes involving the retrosynthetic cleavage of the α carbonyl bonds illustrated in eq 1. In each case, the con-



(1)

struction of the olefinic side chain with labels in a variety of positions seems possible. Furthermore, labels could be incorporated in the synthon leading to the epoxy amide. The degree of flexibility inherent in these schemes also makes them particularly attractive by permitting the preparation of analogues with a variety of side-chain structures.

Acylation of Epoxymaleic Anhydride 4. Our initial approach utilized scheme B (eq 1) above in which the precursor of the epoxy amide was the known epoxymaleic anhydride **4**.[15] This

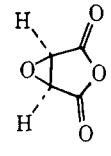


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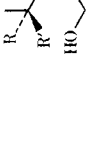
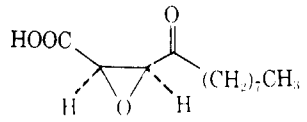
Table I

case	carbonyl compd	method of epoxidation	epoxy diol[a]	yield,[b] %
1	$C_7H_{15}CHO$	MCPBA	R = C_7H_{15}; R′ = H	54
		$VO(acac)_2$/*t*-BuOH		54
2	$(CH_3)_2C{=}CHCH_2CH_2CH(CH_3)CH_2CHO$	$VO(acac)_2$/*t*-BuOOH	R = $(CH_3)_2C{=}CHCH_2CH_2C(CH_3)CH_2$–; R′ = H	45
3	$CH_2{=}C(CH_3)CH_2CH_2CHO$	$VO(acac)_2$/*t*-BuOOH	R = $CH_2{=}C(CH_3)CH_2CH_2$–; R′ = H	45
4	PhCHO	MCPBA	R = Ph; R′ = H	55
5		MCPBA		22[c] (~40)
6		MCPBA		50

[a] Major isomer of a mixture (~7:1) is depicted. [b] Yields are reported for overall conversion from aldehyde to diol without intermediate purification. [c] A single diastereomer was separated chromatographically after the initial addition of the THP protected acetylide ion. Overall yield without separation given in parentheses.

route is extremely brief, requiring only treatment of **4** with a suitable organometallic followed by aminolysis of the keto acid/lactol intermediate, and provides complete control of stereochemistry by virtue of the cyclic nature of **4**.

Initial experiments involving treatment of **4**[14,16] with *n*-octyllithium (**6a**) or *n*-octylmagnesium bromide (**6b**) at −78 °C resulted in no acid **5** and spectral data suggested that



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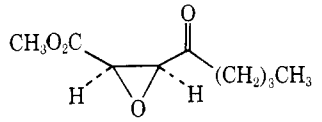
$CH_3(CH_2)_6CH_2M$

6a, M = Li^+
6b, M = $MgBr^{2+}$
6c, M = CdC_8H_{17}

multiple addition was occurring. Use of significantly less reactive cadmium reagent **6c**, surprisingly, afforded the same variety of products, in spite of the precedent that addition to isolated carbonyl groups is not facile.[17] Recent successful acylation of dioorganocuprates[18,19] led us to explore the reaction of lithium di-*n*-butylcuprate with **4**. Our preliminary studies were unsuccessful; however, upon reinvestigation of the reaction, we found that treatment of **4** with the dibutylcuprate in ether at −78 °C and warming to −20 °C afforded the desired keto ester **7** in low yield after esterification with ethereal



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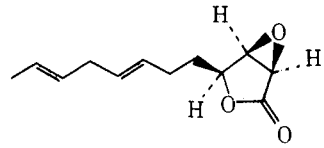
CH_2N_2. Subsequent to our preliminary studies, Corey and Williams have reported the successful application of this strategy to cerulenin (**1**).[20]

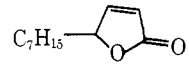
Consideration of the alternate bond disconnection scheme (eq 1) suggests that direct condensation of the indicated fragments might be difficult in practice. A related key intermediate **8** was identified which appeared to satisfy all the de-



8

sign criteria, especially control of stereochemistry. At the time this work was begun, few examples of endocyclic α,β-epoxy-γ-butyrolactones were known. Therefore, we set out to develop a general route for their preparation.[21]

Preparation of Endocyclic α,β-Epoxy-γ-butyrolactones. Our initial studies involved the attempted epoxidation of model butenolide **9** prepared by the method of Schlessinger[22] or via keto acid **10a**.[23,24]



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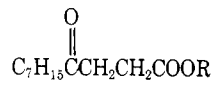
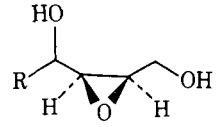


10a, R = H
10b, R = CH_3

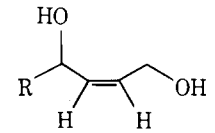
A number of electrophilic and nucleophilic epoxidizing agents were screened, including *m*-chloroperbenzoic acid,[25] pertrifluoroacetic acid, *t*-BuOOH/Triton B,[27] and basic H_2O_2.[26] Generally, no reaction was observed except with basic H_2O_2, which resulted in hydrolysis and double bond migration to afford **10b**. Recently, successful direct epoxidation of systems like **9** has been reported by Tishler utilizing NaOCl in pyridine.[28] This direct route to an epimeric epoxylactone related to **8** has resulted in a nice total synthesis of cerulenin.[28]

A second plausible sequence involves preparation of epoxy diols such as **11** and subsequent oxidation to the related lac-



11

tone. Stereochemical control is possible by this route, since the relative stereochemistry between hydroxyl and epoxide is ultimately eliminated. Diols of this type were conveniently prepared by condensation of lithiopropargyl alcohol tetrahydropyranyl ether and a variety of aldehydes. Removal of the protecting group (CH_3OH/p-TsOH, −20 °C) and semihydrogenation over 5% $Pd/BaSO_4$ in the presence of quinoline[29] afforded the cis diols of general structure **12** in good yields. In



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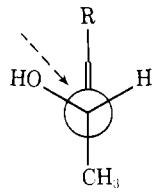
sensitive cases where hydrogenolysis was a problem, addition of sodium nitrite[30] successfully inhibited this side reaction. The results for a series of typical aldehydes and ketones are summarized in Table I.

Oxidation of the olefinic diols **12** to epoxides **11** was effected in the standard fashion ($MCPBA/CH_2Cl_2$, 0 °C) for all cases lacking unsaturation in the side chain. However, in spite of the known complexation of peracids by allylic hydroxyl groups,[31] the double bond is sufficiently deactivated by inductive effects to make selective oxidation of the allylic double bond unfeasible. To circumvent the problem, in these cases we employed the catalytic epoxidation system developed by Sharpless.[32] Treatment of the olefinic diols with *t*-BuOOH and $VO(acac)_2$ afforded the epoxy diols in yields of 50–60%.

The stereochemical control observed in these oxidations is of some interest. Asymmetric induction during epoxidation of allylic alcohols has been well documented[33,34] and a model for prediction of the major diastereomers in acyclic systems has been described by Chautemps and Pierre.[34] In their studies, highly stereoselective oxidation of *cis*- and *trans*-3-penten-2-ol occurred with MCPBA (90–98%) with the major isomer predicted on the basis that (1) in the major conformer, the olefinic group and methyl are anti, and (2) the approach of the reagent occurs cis to the hydroxyl (cf. **13**). The "gauche" methyl double bond interaction in the alternate conformer **14** is maximized when the olefin is cis, leading to the increased stereoselectivity observed for cis vs. trans (98 vs. 90). Applying



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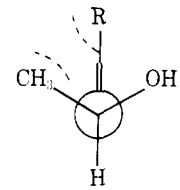

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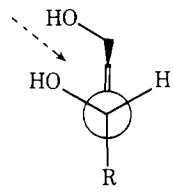

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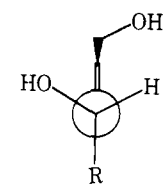

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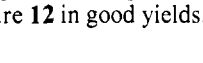
Table II

case	diol	lactone yield,[a] % Ag_2CO_3/Celite[b]	lactone yield,[a] % Pt/O_2[c]
1	R = C_7H_{15}; R′ = H	60	57
	R = H; R′ = C_7H_{15}		10
2	R = $(CH_3)_2C{=}CHCH_2CH_2C(H)(CH_3)CH_2$-	50	30–50
3	R = $CH_2{=}C(CH_3)CH_2CH_2$-	20[e]	
4	R = Ph; R′ = H	33	50
5	R, R′ = 	80	90
6	R, R′ =	70	40–50

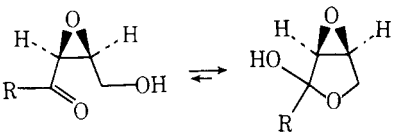
[a] Yields are reported for distilled or chromatographically purified materials. [b] The remaining material is primarily ketol which can be recycled by reduction and reoxidation. [c] Reactions run in aqueous acetone by use of prereduced Pt catalyst. [d] Only the major lactone was isolated in this case. [e] Lactone is volatile and difficultly isolable.

this model to **12** suggests that the major isomer should result from conformer **15** in which both hydroxyls assist the approaching reagent. However, one would expect less selectivity since conformer **16** is of nearly comparable energy and the directing effect of the primary OH opposes the secondary OH. The experimental results for both MCPBA and $VO(acac)_2/t$-BuOOH reagents are in accord with this prediction, affording a ~7:1 mixture of diastereomers (by NMR) in all cases examined. Since the mode of association of the incoming reagents differs, it is surprising that essentially the same stereoselectivity occurs.[35] In the case of $VO(acac)_2$, association presumably occurs by incorporation of the hydroxyl into the coordination sphere of the active vanadium species. It appears that preferential incorporation of the less hindered primary OH leads to a larger than expected proportion of the oxidation occuring via a conformer resembling **16.** Assignments of stereochemistry were confirmed upon oxidation of the epoxy diols **11** to the epoxylactones as described below.

With the epoxy diols **11** in hand, methods were investigated for oxidation of **11** to the lactone. Two reagent systems were studied in detail. Platinum/oxygen, well established in the area of carbohydrate chemistry as a reagent system for selective oxidation of primary alcohols,[36] had been utilized for production of a lactone in one case.[37] Furthermore, Fetizon had demonstrated the utility of silver carbonate on Celite for lactone formation in some cases.[38] Generally, the oxidations were conducted on the mixture of diastereomers resulting from epoxidation. The results of these studies are indicated in Table II. As can be seen, it was found that the platinum/oxygen procedure was very satisfactory for systems devoid of unsaturation. The presence of unsaturation led to diminished yields and generally inferior results. Most oxidations were conducted in aqueous acetone, which was the preferred medium. Oxidation in the presence of sodium bicarbonate was found to enhance the rate in some cases; however, byproducts resulting from hydrolysis were encountered if excessively long reaction periods (≥48 h) were required to consume the starting material. The oxidation could be conducted in a nonpolar solvent such as octane; however, solubility problems make the use of octane impossible in some cases. The problem posed by unsaturated systems was never fully identified, although no evi-

dence of unselective oxidation of the side chain was observed. The problem seemed to be at least partially a surface phenomenon. The catalyst, which remained finely dispersed in the case of saturated systems, aggregated during oxidation of the unsaturated systems and the oxidation was sluggish or did not occur at all. Attempts to use surfactants to overcome the problem were unsuccessful.

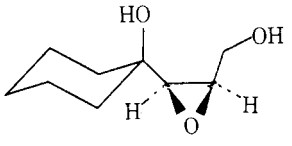
Silver carbonate on Celite, on the other hand, proved to be a general reagent (Table II). Oxidation to the lactone occurred in good to excellent yields in all cases except the low molecular weight diol (case 3). The difficulty in that case proved to be isolation of the volatile products. In all systems (e.g., case 1) where selectivity of primary over secondary alcohol was required, the yields were generally in the 40–60% range accompanied by 30–40% of the corresponding keto alcohols **17**, which exist almost exclusively in the hemiketal forms **18**,



17 **18**

precluding further oxidation. However, efficient overall conversion could be effected by reduction of **17** with $NaBH_4$ in ethanol and reoxidation. This general level of selectivity is expected based upon the studies of Fetizon.[38] In our cases, however, the significant solvent dependence ($CHCl_3$ vs. benzene) reported by Fetizon was not observed and the ratio of lactone to ketol was generally insensitive to solvent in the cases examined.[39]

Both oxidations are presumed to proceed via the aldehyde which undergoes intramolecular hydration and further oxidation.[40] This pathway could be confirmed in the case of the platinum/oxygen oxidation. Oxidation of diol **19** (case 6, Table II) in the absence of $NaHCO_3$ gives spirolactol **20** as the major



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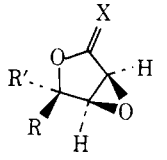
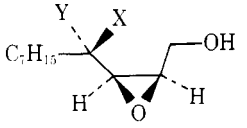


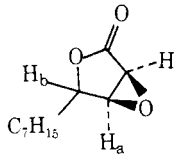
20, R, R′ = $(CH_2)_5$; X = H, OH
21, R, R′ = $(CH_2)_5$; X = O

product (40%). Lactol **20** could be oxidized to **21** obtained directly by oxidation in the presence of $NaHCO_3$.

The stereochemistry of the epoxylactones (and therefore the precursor epoxy diols **11**) were assigned on the basis of a Karplus correlation. The simplest alkyl side chain diols **22** and **23** (~7:1) were studied in detail (case 1, Tables I and II).



22, X = OH; Y = H
23, X = H; Y = OH

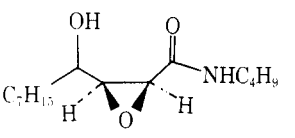


24, H_b = αH
25, H_b = βH

Oxidation of the mixture afforded crystalline lactone **24** (mp 43–44 °C) and epimeric lactone **25**. The stereochemical assignment was clear on the basis of the magnitude of the coupling between the β epoxide proton (H_a) and α oxygen proton (H_b). In **24**, H_a–H_b has a coupling of 2–3 Hz, whereas in isomer **25** H_a–H_b is small (< 1 Hz). Examination of models of **24** and **25** shows that the dihedral angle between H_a and H_b in **25** (but not **24**) is very nearly 90° and in accord with the very small coupling constant observed. Further confirmation of this assignment is provided by the data reported by Tishler for similar systems.[28] The major isomer of the nucleophilic epoxidation by NaOCl is the minor isomer obtained via oxidation of diols such as **22** and **23**. This result is expected since nucleophilic attack on the butenolide should be more favorable trans to the adjacent side chain affording lactones of the stereochemical series **25**.

Reaction of Nucleophiles with α,β-Epoxy-γ-butyrolactones. Since it was reasonably well established that one of the modes of reactivity of cerulenin in vivo involved cleavage of the epoxide, we felt that the strain inherent in the lactones might make them good candidates for protein cross-linking agents. If the spectrum of reactivity shows selectivity for certain biological nucleophiles, information about the tertiary structure in the protein could become available.

Lactone **24** was utilized to screen reactivity with various nucleophiles. Methanol under neutral conditions failed to attack **24** at 25 °C and methoxide ion was nonspecific. Exposure to *n*-butylamine for 18 h at 25 °C afforded the amide **26** in nearly quantitative yield. Even at reflux in benzene the epoxide was attacked only very slowly (~5% after 12 h). **24** was also unaffected by neutral *n*-heptanethiol at room temperature and 70 °C; however, thiolate anion cleaved the epoxide selectively at −65 → 25 °C over 2 h, providing **27** in 90% yield. Most in-



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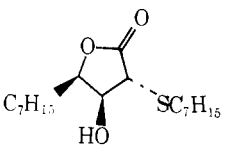

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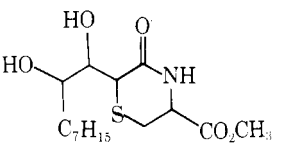
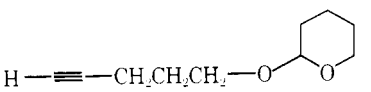


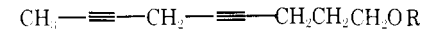
28

terestingly, **24** reacted with cysteine methyl ester, a bidentate nucleophile, to provide the thialactam **28** in which selective cleavage of the lactone by nitrogen and the epoxide by thiol had occurred (60%).

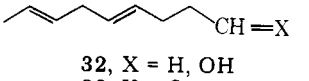
Preparation of the Side-Chain Component for Cerulenin (1). With the successful development of a route to epoxylactones, we set out to prepare the key epoxylactone **8** required for cerulenin (**1**). The following route was developed to the required trans,trans dienal **33**. The THP ether of 4-pentyn-1-ol (**29**) was converted to the magnesium salt by treatment with ethylmagnesium bromide (1.2 equiv) in THF at 65 °C (2 h). Successive treatment of this solution with anhydrous $(CuCl)_2$ and 1-bromo-2-butyne (1.0 equiv) afforded crude diiynol THP ether **30**.[40] The unstable and oxygen-sensitive diiynol THP



29

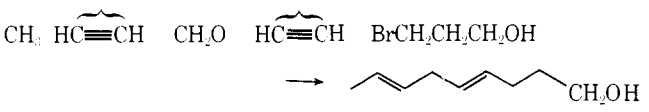


30, R = THP
31, R = H



32, X = H, OH
33, X = O

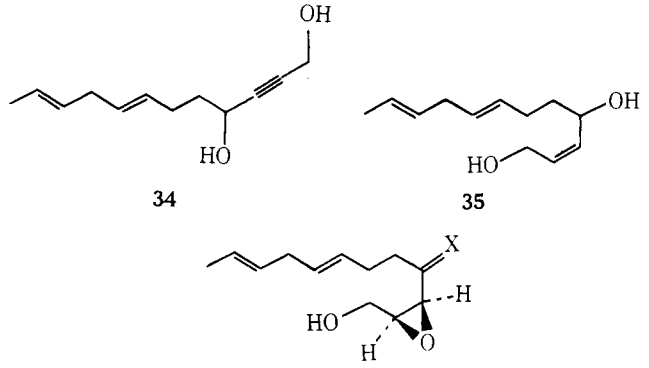
Scheme I



ether **30** was immediately hydrolyzed (CH_3OH/*p*-TsOH, −20 °C) to sensitive (O_2) diiynol **31** (bp 95–105 °C, 0.3 mm) in 70% overall yield. Reduction of the diiynol **31** to trans,trans dienol **32** was accomplished by treatment of **31** in anhydrous NH_3(l) containing $(NH_4)_2SO_4$ (10 equiv) and *t*-BuOH (1.0 equiv) with lithium metal (6 equiv) using a slow addition apparatus. Workup afforded dienol **32** (~100%), which was directly oxidized with pyridinium chlorochromate[42] (1.4 equiv) in CH_2Cl_2 (25 °C, 3 h) to provide the desired dienal **33** (bp 40–45 °C, 0.4 mm) in 55% overall yield.

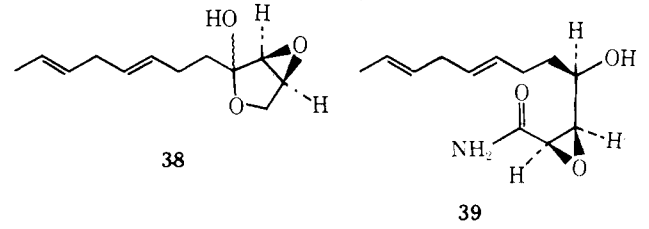
Adaptation of the sequence to the preparation of labeled (^{14}C) cerulenin (**1**) appears straightforward as indicated in Scheme I, in which labeled acetylene, formaldehyde, methyl iodide, and 3-bromo-1-propanol could be utilized to incorporate ^{14}C labels in a variety of positions in the side chain.

Elaboration of Cerulenin (1). Preparation of the key epoxylactone **8** was accomplished via the general route described earlier. Reaction of dienal **33** with lithiopropargyl alcohol tetrahydropyranyl ether (1.06 equiv) at −78 °C in THF for 2 h and direct hydrolysis (*p*-TsOH/CH_3OH–H_2O (20:1), 25 °C, 48 h) afforded the desired alcohol **34** in ~90% yield. Semihydrogenation of alcohol **34** over 5% Pd/$BaSO_4$ and quinoline (1 atm, 25 °C) followed by direct epoxidation of the resulting trienediol **35** with *t*-BuOOH (1.5 equiv) and VO-



$(acac)_2$ (cat)[32] in benzene (25 °C, 5 h) gave after chromatographic purification the cis epoxy diols (**36**) in 56% overall yield from **33.**

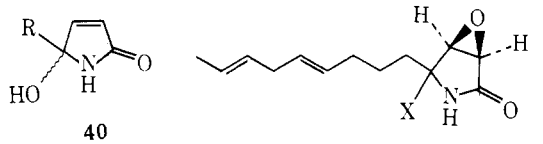
Oxidation of diol **36** with Ag_2CO_3 on Celite (15 equiv) in benzene (78 °C, 3 h) gave, after workup and chromatographic separation, epoxylactone **8** (40–50%) and ketol **37** (30%) which was in equilibrium with the corresponding hemiketal (**38**). The



overall conversion could be increased to ~60–70% by recycling the recovered ketol **37** by reduction ($NaBH_4$/EtOH) and resubmission to oxidation with Ag_2CO_3/Celite.

Lactone **8** was initially subjected to aminolysis by treatment with 28% NH_4OH (excess) in ether (25 °C, 3.5 h) affording primary amide **39** in essentially quantitative yield as a gummy solid. Oxidation of **39** to cerulenin (**1**) was accomplished smoothly by treatment of **39** with pyridinium chlorochromate (1.39 equiv) in CH_2Cl_2 at 25 °C for 3 h. *dl*-Cerulenin (**1**) was obtained after chromatography on Florisil in 55% yield. Analysis of the product by TLC (SiO_2) indicated the presence of three components, one of which was identical with a sample of authentic natural cerulenin (**1**).[43] Spectral data indicated minor differences from the spectra of crystalline natural cerulenin (**1**) in $CHCl_3$ and an identical mass spectral fragmentation pattern. It was noted that natural cerulenin after a time at room temperature and exposure to the atmosphere showed the same TLC behavior (three spots). It was initially thought that this resulted from decomposition. Isolation by chromatography of the mixture provided *dl*-cerulenin (**1**) (mp 42–44 °C) identical in every respect with natural crystalline cerulenin. However, on standing the original synthetic mixture was observed to crystallize slowly. Analysis of this crystalline material indicated that it was now identical by TLC (one spot) and spectral comparison with natural cerulenin (**1**).

We initially suggested that in spite of the precedent for closure of pyrrole photooxidation products such as **40** to hemiaminol structures, we had not observed this behavior in cerulenin (in $CHCl_3$).[44] Clearly, however, the behavior of the synthetic mixture of cerulenin upon crystallization is consistent with the equilibration of cerulenin (**1**) in the presence of acid,



or in protic solvents, or upon chromatography to an equilibrium mixture of the two aminol epimers **41** and **42** and the open form **1**. Redissolving the crystalline synthetic material in protic solvent regenerates the equilibrium mixture observed originally. Omura had observed such behavior earlier (unpublished), and it was also subsequently described by Tishler and Corey.[20,28]

Experimental Section

Infrared spectra were recorded on a Perkin-Elmer Model 137 spectrometer. NMR spectra were determined on a Varian T-60 spectrometer, and chemical shifts are reported in δ units relative to Me_4Si. The mass spectra, both high and low resolution, were determined on an AEI MS-9. Tetrahydrofuran (THF) and ether (Et_2O) were freshly distilled from $LiAlH_4$ before use. Other solvents were purified by literature methods.[45] Reactions were conducted in flame-dried glassware under argon. Compounds were purified by column chromatography on Baker 60–200 mesh silica gel unless otherwise specified. Florisil (Fisher Scientific Co.) was 100–200 mesh. Solutions were dried with anhydrous $MgSO_4$. Melting points were taken on a Thomas-Hoover apparatus and are reported uncorrected. Boiling points are uncorrected for changes in barometric pressure. LC was performed on a Waters A-6000 liquid chromatograph utilizing a 30-cm μ-Porasil column. Microanalyses were conducted by Midwest Microlab, Inc., Indianapolis, Ind.

All compounds are racemic and *R**, *S** only serves to indicate relative stereochemistry.

1-(2-Tetrahydropyranyloxy)-4-pentyne (29).[46] A mixture of 4-pentyn-1-ol (58.8 g, 0.7 mol), dihydropyran (58.8 g, 0.7 mol), and *p*-TsOH (1.0 g) was maintained at −20 °C for 4 days, then fractionally distilled to afford **29**: 105.0 g (90%); bp 65 °C (0.3 mm); IR (film) 3300, 2900, 1450, 1140, 1130, 1040 cm^{-1}.

1-Bromo-2-butyne.[47] A solution of triphenylphosphine (262.0 g, 1.0 mol) and 2-butyn-1-ol (68.0 g, 0.97 mol) in 500 mL of dry DMF was treated with 52 mL (1.0 mol) of bromine according to the procedure of Wiley[48] to give 1-bromo-2-butyne: 64.0 g (50%); bp 35 °C (20 mm); ^1H NMR ($CDCl_3$) δ 1.92 (t, 3 H), 3.95 (q, 2 H); IR (film) 2900, 2200, 1420, 1210 cm^{-1}.

4,7-Nonadiyn-1-ol (31). A solution of ethylmagnesium bromide was prepared from 12.9 g (0.54 g-atom) of Mg and 58.5 g (0.54 mol) of ethyl bromide in 220 mL of THF. Compound **29** (75.6 g, 0.45 mol) in 66 mL of THF was added to the above solution at a rate sufficient to maintain a gentle reflux; after the addition was completed, heating was continued for 1 h. After 10 min of cooling, CuCl (3.0 g) was added followed by dropwise addition of 1-bromo-2-butyne (**1**, 60.0 g, 0.45 mol) in 100 mL of THF over 1 h. The mixture was heated at reflux for 3 h, quenched with 200 mL of 10% NH_4Cl, and washed twice with 100-mL portions of 10% NH_4Cl and then with saturated aqueous NaCl. The aqueous layers were then extracted three times with 250-mL portions of Et_2O. The organic portions were combined, dried, and concentrated to crude **30,** 97.0 g: ^1H NMR ($CHCl_3$) δ 1.4–2.6 (m, 13 H), 3.06 (dd, 2 H), 3.3–4.2 (m, 4 H), 4.7 (s, 1 H).

Crude **30** was hydrolyzed in a mixture of 250 mL of MeOH, 30 mL of H_2O, and 2 g of *p*-TsOH for 5 days at −20 °C, The resulting solution was diluted with 150 mL of Et_2O and extracted twice with 100-mL portions of saturated $NaHCO_3$. The organic layer was dried, concentrated, and then distilled to afford **31:** 42.0 g (70%); bp 95–105 °C (0.3 mm); ^1H NMR ($CDCl_3$) δ 1.75 (m, 5 H), 2.32 (m, 3 H), 3.06 (dd, 2 H), 3.72 (t, 2 H); IR (film) 3400, 2900, 1440, 1310, 1060, 940 cm^{-1}.

Anal. ($C_9H_{12}O$) C, H.

(4*E*,7*E*)-4,7-Nonadien-1-ol (31). A 5-L flask equipped with an overhead stirrer, a slow addition apparatus, and a dry ice condenser was charged with $(NH_4)_2SO_4$ (409 g, 3.0 mol), 3 L of NH_3 (distilled from Na), *t*-BuOH (22.9 g, 0.31 mol), and **31** (42.0 g, 0.31 mol) in 20 mL of Et_2O. Lithium ribbon (13.0 g, 1.86 g-atoms), cut into small pieces, was added via a slow addition apparatus. During the addition a vigorous reaction ensued, and after 1 h the dark blue color disappeared indicating that the reaction was complete. The NH_3 was then allowed to evaporate and 1.5 L of H_2O was added to dissolve the residue. The resulting solution was extracted with five 300-mL portions of Et_2O. The organic layer was dried and concentrated to yield **32** (42.0 g, 100%): ^1H NMR ($CDCl_3$) δ 1.6–2.3 (m, 7 H), 2.75 (m, 2 H), 3.3 (t, 2 H), 5.6 (m, 4 H); IR (film) 3350, 2900, 1440, 1060, 970 cm^{-1}; mass spectrum *m/e* 140 (parent ion).

Anal. ($C_9H_{16}O$) C, H.

(4*E*,7*E*)-4,7-Nonadienal (33). A solution of **32** (42.0 g, 0.3 mol) in 60 mL of CH_2Cl_2 was added in one portion to a red slurry of pyridinium chlorochromate (109.0 g, 0.51 mol) in 600 mL of CH_2Cl_2. The reaction mixture was stirred for 3 h at 25 °C, diluted with 600 mL of dry Et_2O, and then filtered through a plug of Florisil to afford a clear eluent. The solid residue in the flask was also washed three times with 150-mL portions of Et_2O and this solution was also filtered through Florisil. Concentration of the Et_2O solutions, followed by distillation, afforded **33:** 22.6 g (55%); bp 40–45 °C (0.4 mm); ^1H NMR ($CDCl_3$) δ 1.65 (m, 3 H), 2.5 (m, 4 H), 2.7 (m, 2 H), 5.5 (m, 4 H), 9.8 (m, 1 H); IR (film) 2890, 2700, 1740, 1450, 975 cm^{-1}.

Anal. ($C_9H_{14}O$) C, H.

(7*E*,10*E*)-7,10-Dodecadien-2-yne-1,3-diol (34). To a solution of 2-propyn-1-ol tetrahydropyranyl ether (26.8 g, 0.19 mol) in 250 mL of THF, cooled to −78 °C, was added dropwise *n*-butyllithium (0.17 mol of 1.5 M hexane solution). The solution was warmed to −20 °C over 1 h and recooled to −78 °C. A solution of aldehyde **33** (22.0 g, 0.16 mol) in 150 mL of THF was added over 0.5 h and the reaction was kept at −78 °C for 2 h. After the reaction mixture was allowed to warm to 25 °C over a 2-h period, it was quenched with 70 mL of H_2O. The organic layer was decanted and the aqueous layer was extracted with three 25-mL portions of Et_2O. The organic layers were combined and concentrated to furnish the crude adduct, 76.0 g: IR (film) 3320, 2850, 1450, 1225, 1020, 900, 870, 820 cm^{-1}. Upon treatment with *p*-TsOH (0.5 g) in 95% aqueous MeOH (300 mL) for 48 h, the crude adduct was hydrolyzed. Evaporation of the MeOH left a yellow syrup which was dissolved in 500 mL of Et_2O and washed five times with 100-mL portions of H_2O. The Et_2O layer was dried and evaporated to produce **34,** 30.0 g (90%). This material was sufficiently pure to be utilized directly in the next step: ^1H NMR ($CDCl_3$) δ 1.6–2.4 (m, 7 H), 2.72 (m, 2 H), 3.74 (s, 2 H), 4.33 (m, 3 H), 5.5 (m, 4 H).

(2*Z*,7*E*,10*E*)-2,7,10-Dodecatriene-1,3-diol (35). A solution of **34** (28.0 g, 0.144 mol) in 300 mL of MeOH was hydrogenated at 1 atm and 25 °C with 0.5 g of 5% Pd-$BuSO_4$ and 0.56 mL of quinoline. After 3.46 L (1 equiv) of H_2 had been taken up, the reaction was terminated and the mixture was filtered. The mixture was concentrated and then dissolved in 500 mL of Et_2O. This solution was washed twice with 100-mL portions of saturated aqueous $NaHCO_3$ followed by 100 mL of saturated brine. The organic layer was dried and stripped of all solvents leaving **35,** 26.0 g (90%). This material was sufficiently pure to be utilized directly in the next step: ^1H NMR ($CDCl_3$) δ 1.6–2.4 (m, 7 H), 2.72 (m, 4 H), 4.6 (m, 3 H), 5.6 (m, 6 H); IR (film) 3300, 2850, 1450, 1020, 970 cm^{-1}.

(2*S,3*R**,4*S**,7*E*,10*E*)-2,3-Epoxy-7,10-dodecadiene-1,3-diol (36).** A solution of **35** (26.0 g, 0.13 mol) and $VO(acac)_2$[32] (265 mg, 1 mmol) in benzene (200 mL) was cooled to 0 °C and 90% *t*-BuOOH (22.0 g, 0.22 mol) in 50 mL of benzene was added dropwise over 0.5 h. The solution was warmed to 25 °C and stirred for 5 h. The mixture was concentrated and subjected to a vacuum (0.3 mm) overnight. The crude material was chromatographed (benzene/Et_2O), and the desired fractions were isolated and concentrated to yield **30:** 15.9 g (56%); ^1H NMR ($CDCl_3$) δ 1.6–2.4 (m, 7 H), 2.7 (m, 2 H), 3.0–4.0 (m, 7 H), 5.5 (m, 4 H); IR (film) 3320, 2850, 1450, 1040, 970 cm^{-1}.

Exact mass. Calcd for $C_{12}H_{20}O_3$: 212.1412. Found: 212.1421.

(2*R,3*R**,4*S**,7*E*,10*E*)-2,3-Epoxy-4-hydroxy-7,10-dodecanoic Lactone (8).** A solution of **36** (2.12 g, 10 mmol) in 100 mL of benzene was added to a mechanically stirred suspension of Ag_2CO_3 on Celite[38] (85.5 g, 150 mmol) in benzene (500 mL). After azeotropic distillation of 150 mL of solvent, the reaction mixture was heated at reflux for 3 h. The mixture was cooled and filtered, and the solid was washed with a total of 1.5 L of CH_2Cl_2. The combined organic fractions were concentrated to afford 2.0 g of crude material. Column chromatography (C_6H_6/Et_2O, 9:1) yielded epoxylactone **8**: 850 mg (40%); bp 120 °C (0.5 mm); ^1H NMR ($CDCl_3$) δ 1.6–2.4 (m, 7 H), 2.75 (m, 2 H), 3.8 (d, J = 3 Hz, 1 H), 4.13 (dd, J_{AB} = 3 Hz, 1 H), 4.5 (m, 1 H), 5.5 (m, 4 H); IR (neat) 2850, 1790, 1450, 1190, 970, 870, 830 cm^{-1}.

Exact mass. Calcd for $C_{12}H_{16}O_3$: 208.1099. Found: 208.1084.

Further elution afforded a second component, **37,** 600 mg (30%): ^1H NMR ($CDCl_3$) δ 1.6–2.8 (m, 10 H), 3.6–4.0 (m, 4 H), 5.5 (m, 4 H); IR (film) 4350, 2900, 1720, 1450, 1060 cm^{-1}.

Exact mass. Calcd for $C_{12}H_{18}O_3$: 210.1256. Found: 210.1243.

2*R,3*R**,4*S**,7*E*,10*E*)-2,3-Epoxy-4-hydroxy-7,10-dodecadienamide (39).** A solution of epoxy amide **8** (650 mg, 3.1 mmol) and 28% NH_4OH (3 mL) in 30 mL of Et_2O was stirred for 3.5 h at 25 °C. The aqueous layer was extracted three times with 10-mL portions of Et_2O and the organic layers were combined and evaporated to give semisolid **39** (720 mg, 100%): ^1H NMR ($CDCl_3$) δ 1.6–2.4 (m, 7 H), 2.65 (m, 2 H), 3.0–3.6 (m, 4 H), 5.5 (m, 4 H), 6.2 (d, 2 H); IR (Nujol) 3350, 3200, 2900, 1690, 1620, 1445, 960, 930, 840, 810 cm^{-1}.

Anal. ($C_{12}H_{17}NO_3$) C, H, N.

***dl*-Cerulenin (1).** To a solution of **39** (720 mg, 3.1 mmol) in 20 mL of CH_2Cl_2 was added pyridinium chlorochromate[42] (1.3 g, 6.0 mmol). After stirring for 3.5 h at 25 °C, the mixture was diluted with dry ether (20 mL) and filtered through a short column of Florisil. The residue in the reaction flask was washed with three 10-mL portions of ether and these combined solutions were also passed through the Florisil column. Concentration of the combined eluent afforded *dl*-cerulenin (**1**, 370 mg, 55%) as an oil which crystallized slowly on standing at room temperature. TLC analysis of the oil indicated a mixture of three materials, the two lactamols **41** and **42** and the keto amide form **1**. Isolation of the keto amide form by column chromatography (ether/benzene, 4:1) afforded *dl*-cerulenin (**1**) (mp 42–44 °C) which was identical in all respects (IR, NMR, TLC, MS) with authentic natural cerulenin (**1**) (keto amide form). Reanalysis of the material after it had crystallized (by TLC) indicated only a single component identical in R_f with the open form. Apparently, cerulenin exists in the open form in the crystal and is converted to an equilibrium mixture of open and closed forms in alcohol solution or upon chromatography.

General Procedures for the Preparation of Epoxy Diols. 2-Undecyne-1,4-diol. To a solution of 2-propyn-1-ol tetrahydropyranyl ether (5.6 g, 40 mmol) in 30 mL of THF, cooled to −78 °C, was added dropwise *n*-butyllithium (34 mmol of a 1.7 M hexane solution). The reaction mixture was warmed to −20 °C over 1 h and recooled to −78 °C. A solution of octanol (4.35 g, 34 mmol) in 25 mL of THF was added over 20 min and the mixture was allowed to warm to 25 °C over a 2-h period. After an additional 4 h of stirring, the reaction was quenched with 10 mL of H_2O, the organic layer was decanted, and the aqueous layer was washed three times with 10-mL portions of Et_2O. The organic extracts were combined, dried, and evaporated, affording the crude adduct (10.0 g): IR (film) 3350, 2850, 1450, 1120,

1040, 905, 870, 820 cm^{-1}.

The crude adduct was hydrolyzed in 95% aqueous MeOH (130 mL) and *p*-TsOH (0.5 g) for 5 h at 25 °C. The solution was then concentrated to 75 mL, and 75 mL of cold 10% Na_2CO_3 was added. The mixture was extracted five times with 75-mL portions of Et_2O; the organic portions were combined and washed twice with 50-mL portions of saturated brine. The solution was dried and concentrated to produce the title diol, 5.7 g (90%): ^1H NMR ($CDCl_3$) δ 0.8–0.2 (m, 15 H), 3.4 (m, 2 H), 4.35 (m, 3 H); IR (film) 3340, 2850, 1460, 1140, 1020 cm^{-1}.

This material was sufficiently pure to be utilized directly in the next step below.

(*Z*)-2-Undecene-1,4-diol. A solution of 2-undecyne-1,4-diol (5.6 g, 30.4 mmol) in 50 mL of MeOH was hydrogenated at 1 atm and 25 °C with 0.1 g of 5% Pd–$BaSO_4$ and 100 μL of quinoline. After 740 mL (1.02 equiv) of H_2 had been taken up the reaction was stopped. The mixture was filtered and concentrated to afford (*Z*)-2-undecene-1,4-diol, 5.6 g (~100%): ^1H NMR ($CDCl_3$) δ 0.8–2.0 (m, 15 H), 3.7 (m, 2 H), 4.19 (m, 3 H), 5.6 (m, 2 H). This material was utilized directly in the next step below.

(2*S,3*R**,4*S**)-2,3-Epoxyundecane-1,4-diol.** A solution of (*Z*)-2-undecene-1,4-diol (5.0 g, 26 mmol) in CH_2Cl_2 (100 mL) was cooled to 0 °C and 85% *m*-chloroperoxybenzoic acid (MCPBA, 5.27 g, 26 mmol) was added in one portion. The solution was stirred for 1 h at 25 °C and then quenched with saturated $Na_2S_2O_3$ until a negative starch–iodine test was achieved. The solution was washed with 10% Na_2CO_3 to a pH of 9. The organic layer was dried, concentrated, and chromatographed (Et_2O/C_6H_6, 2:1) to yield the title diol, 3.0 g (60%): ^1H NMR ($CDCl_3$) δ 0.8–2.0 (m, 15 H), 3.0–4.0 (m, 5 H), 4.2 (m, 2 H).

Exact mass. Calcd for $C_{11}H_{22}O_3$: 202.1569. Found: 202.1568.

Oxidation of (*Z*)-2-Undecene-1,4-diol by VO(acac)$_2$/*t*-BuOOH. To a green solution of (*Z*)-2-undecene-1,4-diol (5.6 g, 30 mmol) and $VO(acac)_2$[32] (70 mg, 0.3 mmol) in 30 mL of benzene was added 90% *t*-BuOOH (5.0 g, 50 mmol) in 10 mL of benzene over 15 min. The solution was stirred for 3 h and evaporated, and the crude material was chromatographed (Et_2O/C_6H_6, 2:1) to produce (2*S**,3*R**,4*S**)-2,3-epoxyundecene-1,4-diol, 3.7 g (60%): ^1H NMR ($CDCl_3$) δ 0.8–2.0 (m, 15 H), 3.0–4.0 (m, 7 H); IR (neat) 3300, 2850, 1560, 1040 cm^{-1}.

General Procedures for the Preparation of Epoxylactones. (2*R,3*R**,4*S**)-2,3-Epoxy-4-hydroxyundecanoic Lactone (24).** A solution of (2*S**,3*R**,4*S**)-2,3-epoxyundecane-1,4-diol (100 mg, 0.5 mmol) and Ag_2CO_3/Celite (4.2 g, 7.5 mmol) in 40 mL of benzene were heated to azeotrope off 10 mL of solvent and heating at reflux was continued for 6 h. The solution was filtered and the solid residue was washed with CH_2Cl_2. The filtrate was concentrated and chromatographed (C_6H_6/Et_2O, 19:1) affording **24** (mp 43–44 °C), 60 mg (60%): ^1H NMR ($CDCl_3$) δ 0.9–1.8 (m, 15 H), 3.8 (d, J_{AB} = 2.5 Hz, 1 H), 4.15 (dd, J_{AB} = 2.5, J_{BC} = 2.0 Hz, 1 H), 4.6 (m, 1 H); IR (film) 2850, 1780, 1460, 1200, 1050, 870, 830 cm^{-1}.

Exact mass. Calcd for $C_{11}H_{18}O_3$: 198.1256. Found: 198.1274.

Oxidation of (2*S,3*R**,4*S**)-2,3-Epoxyundecane-1,4-diol with Platinum/Oxygen.** Platinum oxide (1.0 g) suspended in 100 mL of distilled H_2O was hydrogenated with the uptake of 200 mL of H_2 and then a stream of argon was used to purge the system of residual hydrogen. Epoxy diol **15** (1.0 g, 5 mmol) in 10 mL of H_2O was added to the platinum catalyst and the entire mixture was heated to 60 °C while O_2 bubbled through for 14.5 h. The cooled mixture was filtered and the filtrate was extracted three times with 100-mL portions of $CHCl_3$. After the organic portion was dried, it was concentrated to afford a semisolid (700 mg, 79%) which showed two spots by TLC. The two diastereomers were separated by column chromatography (C_6H_6/Et_2O, 19:1). The first isomer eluted proved to be epimeric lactone **25**, 100 mg (10%): ^1H NMR ($CDCl_3$) δ 0.9–1.7 (m, 15 H), 3.8 (d, J = 2.5 Hz, 1 H), 4.0 (d, J = 2.5 Hz, 1 H), 4.6 (t, 1 H); IR (film) 2850, 1780, 1460, 1200, 1050, 870, 830 cm^{-1}. The second fraction eluted provided **24**, 570 mg (57%).

By use of the general procedures described above the following compounds listed in Tables I and II were prepared. In each case, the intermediates were fully characterized after oxidation to the lactone.

4-Phenyl-2-butyne-1,4-diol: mp 83–85 °C (70%); ^1H NMR ($CDCl_3/Me_2SO$) δ 7.5 (m, 5 H), 5.5 (s, 1 H), 4.3 (m, 2 H), 4.3 (d, 2 H).

(*Z*)-4-Phenyl-2-butene-1,4-diol (hydrogenation conducted in the presence of $NaNO_2$ to inhibit hydrogenolysis): mp 73–75 °C (95%); ^1H NMR ($CDCl_3$) δ 7.4 (s, 5 H), 5.70 (m, 3 H), 4.30 (m, 2 H), 2.5 (m, 2 H).

(2*S*,3*R,4*S**)-2,3-Epoxy-4-phenylbutane-1,4-diol** (epoxidation conducted with MCPBA buffered with $NaHCO_3$) (60%): ^1H NMR ($CDCl_3$) δ 7.4 (s, 5 H), 4.65 (m, 1 H), 3.9 (m, 4 H), 3.2 (m, 2 H).

(2*R,3*R**,4*S**)-2,3-Epoxy-4-hydroxy-4-phenylbutanoic lactone** (oxidation by PtO_2 in 20% aqueous acetone buffered with $NaHCO_3$): mp 62–64 °C; ^1H NMR ($CDCl_3$) δ 7.5 (s, 5 H), 5.57 (d, 1 H), 4.95 (d, 1 H), 4.33 (m, 1 H); IR (Nujol) 2900, 1780, 1200, 1050, 870, 840, 830 cm^{-1}.

Exact mass. Calcd for $C_{10}H_8O_3$: 176.0473. Found: 176.0480.

Oxidation of (2*S**,3*R**,4*S**)-2,3-epoxy-4-phenylbutane-1,4-diol with Ag_2CO_3 afforded an inseparable mixture of the above-described lactone (60%) and the corresponding ketol (**18**, *R* = phenyl) assayed by ^1H NMR.

6,10-Dimethyl-9-undec-2-yne-1,4-diol. (90%): ^1H NMR ($CDCl_3$) δ 5.18 (t, 1 H), 4.4–4.3 (m, 3 H), 2.8 (m, 2 H), 1.7 (s, 3 H), 1.6 (s, 3 H), 2.4–1.0 (m, 7 H), 0.95 (d, 3 H).

(*Z*)-6,10-Dimethyl-2,9-undecadiene-1,4-diol (~100%): ^1H NMR ($CDCl_3$) δ 5.7 (m, 2 H), 5.12 (t, 1 H), 4.4 (m, 3 H), 3.4 (m, 2 H), 1.7 (s, 3 H), 2.4–1.0 (m, 7 H), 0.95 (d, 3 H).

(2*S,3*R**,4*S**)-2,3-Epoxy-6,10-dimethyl-9-undecene-1,4-diol.** Epoxidation was conducted with $VO(acac)_2$/*t*-BuOOH and the product purified by chromatography (50%): ^1H NMR ($CDCl_3$) δ 5.1 (t, 3 H), 4.0–2.6 (m, 7 H), 1.7 (s, 3 H), 1.6 (s, 3 H), 2.4–1.0 (m, 7 H), 0.91 (d, 3 H).

(2*R,3*R**,4*S**)-2,3-Epoxy-4-hydroxy-6,10-dimethyl-9-undecenoic Lactone.** Oxidation by Pt/O_2 in 24% aqueous acetone afforded two components separated by chromatography. The first was the title lactone (20%): ^1H NMR ($CDCl_3$) δ 5.2 (t, 1 H), 4.6 (m, 1 H), 4.1 (m, 1 H), 3.8 (d, 1 H), 1.7 (s, 3 H), 1.6 (s, 3 H), 2.2–0.9 (m, 7 H), 0.97 (d, 3 H); IR (film) 2850, 1780, 1450, 1200, 1040, 870, 830 cm^{-1}.

Exact mass. Calcd for $C_{13}H_{20}O_3$: 224.1412. Found: 224.1390.

The second component (30%) was the lactol **20** (R = $CH_2CH(CH_3)CH_2CH_2CH{=}C(CH_3)_2$; R^1 = H): ^1H NMR ($CDCl_3$) δ 5.5 (s, 1 H), 5.2 (t, 1 H), 4.3 (t, 1 H), 3.75 (s, 2 H), 3.3 (m, 1 H), 1.7 (s, 3 H), 1.6 (s, 3 H), 2.2–0.9 (m, 7 H), 0.97 (d, 3 H); IR (film) 3360, 2960, 1440, 1420, 1050, 870, 830 cm^{-1}. The title lactone was also obtained by oxidation with Ag_2CO_3/Celite (45%) along with the corresponding ketol (**17**, R = $CH_2CH(CH_3)CH_2CH_2CH{=}C(CH_3)_2$) (45%): ^1H NMR ($CDCl_3$) δ 5.18 (m, 1 H), 4.0–3.6 (m, 5 H), 1.7 (s, 3 H), 1.6 (s, 3 H), 2.4–0.9 (m, 10 H).

4-*tert*-Butyl-1-(3-hydroxy-1-butynyl)cyclohexan-1-ol (30%); one diastereomer separated at the THP-protected stage): mp 91–94 °C; IR (Nujol) 3250, 2850, 1450, 1360, 1070, 980 cm^{-1}.

4-*tert*-Butyl-1-((*Z*)-3-hydroxy-1-butenyl)cyclohexan-1-ol (~100%): ^1H NMR ($CDCl_3$) δ 5.7 (m, 2 H), 4.2 (m, 4 H), 2.0–0.9 (m, 9 H), 0.85 (s, 9 H).

4-*tert*-Butyl-1-((1*R,2*R**)-1,2-epoxy-3-hydroxybutyl)cyclohexan-1-ol.** Epoxidation with MCPBA afforded the title compound (mp 163 °C) (53%): ^1H NMR (Me_2SO-d_6) δ 4.82 (t, 1 H), 4.30 (s, 1 H), 3.90 (m, 2 H), 3.1 (m, 2 H), 2.0–0.85 (m, 9 H), 0.90 (s, 9 H).

(2*S,3*R**)-3-(4-*tert*-Butyl-1-hydroxy-1-cyclohexyl)propanoic Lactone.** Oxidation by Pt/O_2 in 20% aqueous acetone afforded the title lactone (mp 78–80 °C) (90%): ^1H NMR ($CDCl_3$) δ 4.1 (d, 1 H), 3.75 (d, 1 H), 2.0–0.9 (m, 9 H), 0.90 (s, 9 H); IR (film) 2890, 1770, 1230, 1050, 950 cm^{-1}.

Exact mass. Calcd for $C_{13}H_{20}O_3$: 224.1412. Found: 224.1395.

The title lactone was also obtained by oxidation with Ag_2CO_3/Celite (78%).

7-Methyl-7-octen-2-yne-1,4-diol (93%): ^1H NMR ($CDCl_3$) δ 4.8 (s, 2 H), 4.5–4.0 (m, 5 H), 2.2 (m, 4 H), 1.78 (s, 3 H).

(*Z*)-7-Methyl-2,7-octadiene-1,4-diol (90%): ^1H NMR ($CDCl_3$) δ 5.7 (m, 2 H), 4.8 (s, 2 H), 4.3 (m, 5 H), 2.2 (m, 4 H), 1.78 (s, 3 H); IR (film) 3450, 2900, 1660, 1440, 1040, 880 cm^{-1}.

(2*S,4*R**,4*S**)-2,3-Epoxy-7-methyl-7-octene-1,4-diol.** Epoxidation with $VO(acac)_2$/*t*-BuOOH afforded , after chromatography, the title diol (50%): ^1H NMR ($CDCl_3$) δ 4.8 (s, 2 H), 4.0–3.0 (m, 7 H), 2.2 (m, 4 H), 1.78 (s, 3 H); IR (film) 3420, 2900, 1660, 1460, 1040, 880, 790 cm^{-1}.

(2*R,3*R**,4*S**)-2,3-Epoxy-4-hydroxy-7-methyl-7-octenoic Lactone.** Oxidation with silver carbonate on Celite afforded after chromatography the volatile and difficulty isolable title lactone (mp 29–32 °C) in 20% yield: ^1H NMR ($CDCl_3$) δ 4.6 (s, 2 H), 4.45 (m, 1 H), 4.1 (m, 1 H), 2.77 (d, 1 H), 2.1 (m, 4 H), 1.75 (s, 3 H); IR (film) 2900,

1785, 1650, 1200, 1060, 1010 cm^{-1}.

Exact mass. Calcd for $C_9H_{12}O_3$: 168.0786. Found: 168.0774.

The corresponding ketol (**17**, R = $CH_2CH_2C(CH_3)=CH_2$) was obtained (50%): IR (film) 3300, 2900, 1720, 1450 cm^{-1}.

Attempted oxidation with platinum and oxygen resulted in recovery of unchanged starting diol (75%).

1-(3-Hydroxy-1-butynyl)cyclohexan-1-ol (80%): ^1H NMR ($CDCl_3$) δ 4.2 (m, 4 H), 1.6 (m, 10 H).

1-((*Z*)-3-Hydroxy-1-butenyl)cyclohexane-1-ol (95%): ^1H NMR ($CDCl_3$) δ 5.6 (s, 2 H), 4.3 (m, 2 H), 3.65 (m, 2 H), 1.55 (m, 10 H).

1-((2*R*,3*R)-1,2-Epoxy-3-hydroxybutyl)cyclohexan-1-ol.** Oxidation was conducted with MCPBA in the presence of NaOAc as a buffer affording the title epoxy diol (65%): ^1H NMR ($CDCl_3$) δ 4.2–3.0 (m, 6 H), 1.55 (m, 10 H).

(2S*,3*R)-3-(1-Hydroxy-1-cyclohexyl)propanoic Lactone.** Oxidation with Pt/O_2 in 60% aqueous acetone containing $NaHCO_3$ afforded after chromatography (benzene/ether) the title lactone (40%): ^1H NMR ($CDCl_3$) δ 3.95 (d, 1 H), 3.7 (d, 1 H), 1.65 (m, 10 H); IR (film) 2980, 1780, 1450, 1290, 1220, 950, 870 cm^{-1}.

Exact mass. Calcd for $C_9H_{12}O_3$: 168.0786. Found: 168.0776.

If the oxidation was conducted in the absence of $NaHCO_3$ the yield of the title lactone decreased to 10% and a second component, lactol **20** (R = R′ = $-(CH_2)_5-$), could be isolated by chromatography (40%): ^1H NMR ($CDCl_3$) δ 5.4 (s, 1 H), 3.65 (m, 2 H), 1.65 (m, 10 H); IR (film) 3300, 2900, 1710 (w), 1450 cm^{-1}. Lactol **20** (R = R′ = $-(CH_2)_5-$) gave the title lactone upon treatment with Jones reagent[49] in acetone.

Oxidation with Ag_2CO_3 gave the title lactone (70%).

Reaction of 24 with 1-Butanamine. Lactone **24** (50 mg, 0.25 mmol) and 1-butanamine (18 mg, 0.25 mmol) were stirred in 2 mL of Et_2O at 25 °C for 16 h. The solution was evaporated to yield amide **26**, 70 mg (100%): ^1H NMR ($CDCl_3$) δ 0.8–2.0 (m, 24 H), 3.0–4.0 (m, 6 H), 6.7(m, 1 H); IR (film) 3300, 2900, 1650, 1540, 1430 cm^{-1}; mass spectrum *m/e* 271 (parent ion).

Reaction of 24 with Lithium *n*-Heptanethiolate. A solution of 1-heptanethiol (70 μL, 0.5 mmol) in 4 mL of Et_2O/THF (1:1) was cooled to −65 °C and 200 μL (0.3 mmol) of 1.7 M *n*-butyllithium was then added. To this solution was added **24** (50 mg, 0.25 mmol) in 2 mL of THF, and the entire mixture was allowed to warm to 25 °C over 1 h. The reaction mixture was quenched with H_2O and extracted with Et_2O. The combined extracts were dried and concentrated to afford **27**, 80 mg (90%): ^1H NMR ($CDCl_3$) δ 0.8–2.0 (m, 28 H), 2.0–3.0 (m, 6 H); IR (film) 3300, 2900, 1770, 1620, 1430 cm^{-1}; mass spectrum *m/e* 330 (parent ion).

Reaction of 24 with L-Cysteine Methyl Ester. A solution of lactone **24** (50 mg, 0.25 mmol) and L-cysteine methyl ester[50] (33 mg, 0.25 mmol) in 5 mL of Et_2O was stirred at 25 °C for 1.5 h. A solution of 5 drops of Et_3N in 2 mL of Et_2O was added and the mixture was stirred for 16 h. The mixture was concentrated and purified by chromatography to produce **28**, 50 mg (60%): ^1H NMR ($CDCl_3$) δ 0.8–1.8 (m, 15 H), 1.8–3.0 (m, 4 H), 3.0–3.4 (m, 2 H), 3.6–4.0 (m, 5 H), 5.0 (m, 1 H); IR (neat) 3300, 2900, 1740, 1660, 1510, 1440, 1200 cm^{-1}; mass spectrum *m/e* 333 (parent ion).

Addition of Organometallic Reagents to 2. 2,3-Epoxybutanedioic Anhydride (4). A solution of (*Z*)-2,3-epoxybutanedioic acid disodium salt (2.0 g, 11.3 mmol) in excess trifluoroacetic anhydride was treated according to the literature procedure to afford **2**: 800 mg (66%); mp 63–64 °C; ^1H NMR ($CDCl_3$) δ 4.33 (s) (lit.[14] mp 63–64 °C).

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