Total Syntheses of (±)-Cerulenin, (±)-Tetrahydrocerulenin, and Related Compounds

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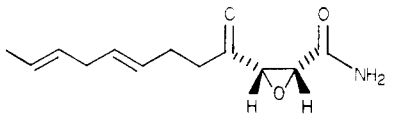
The total synthesis of the microbial metabolite (±)-cerulenin (1) is described. Detailed evidence for the cyclization of cerulenin to a mixture of hydroxy lactams 2 is presented. The successful synthetic approach to cerulenin uses butenolide 3 as a key intermediate. Sodium hypochlorite in pyridine was found to epoxidize the butenolide system nicely; all other methods investigated failed. The syntheses of (±)-tetrahydrocerulenin 25 and a number of related compounds are also described.

Cerulenin, an antibiotic first isolated from *Cephalosporium caerulens* in 1960,[1] has attracted considerable attention. This compound was shown to be a potent inhibitor of fatty acid biosynthesis in a variety of yeast cells[2] but without effect on sterol formation.[3] Cerulenin was also found to be inhibitory for a number of bacteria, fungi, and yeasts.[4] While the basis chemical structure has been known for some time,[5] the absolute configuration of cerulenin has only recently been established as (2*R*,3*S*)-2,3-epoxy-4-oxo-7,10-*trans*,*trans*-dodecadienamide (1).[6-8] The



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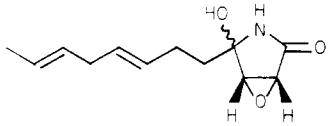

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unique structural features of cerulenin as well as its interesting biological properties have made this molecule a challenging synthetic goal.

Two structural features of cerulenin deserve noting. The keto *cis*-epoxy amide moiety appears to be unique among natural products. The *trans*,*trans*-1,4-diene system is quite rare, occuring elsewhere only in linelaidic acid.[9] No general synthetic methods existed for the preparation of either of these groupings.

There is a significant complication when considering synthetic approaches to cerulenin. While cerulenin in chloroform-*d* exhibits a clean NMR spectrum (see Experimental Section), its spectrum in a polar medium is more complex. In methanol-d_4, the doublets at 3.70 and 3.86 ppm for the epoxy protons in cerulenin gradually diminish with time, and a new pair of complex doublets develop at 3.57 and 3.80 ppm. Moreover, the multiplet at 2.65 ppm reduces from four to two protons when a new multiplet that integrates for two protons appears at 1.85 ppm, due to a shift of the C-5 methylene protons. These observations suggest that rapid equilibration occurs in methanol between cerulenin and its diastereomeric hydroxy lactam forms (2), which were characterized by careful preparative thin-layer chromatography of the isomeric mixture. In addition, a reduction in the NH_2 bending frequency occurs with concomitant appearance of a hydroxy absorption in the infrared spectrum. Both isomeric compounds generate the same molecular ion in the mass spectrum as does cerulenin. Chromatographic purification conditions on silica also cause the equilibration to occur. Finally, cerulenin is slowly regenerated from 2 under polar conditions.

Three reports on the total synthesis of (±)-cerulenin have appeared, the first by Boeckman and Thomas.[10] In that publication and in the preliminary report from this laboratory,[11] the carbon skeleton was obtained by condensing a C-9 chain with a propiolic acid derived moiety while in the third synthesis, that of Corey and Williams,[12] a maleic acid derived C-4 fragment was combined with a C-8 chain. Four syntheses of the microbiologically active tetrahydrocerulenin have been published;[6a,7,8,11] the latter three references described chiral syntheses of (+)-tetrahydrocerulenin previously made from (+)-cerulenin.[5] Finally, a stereoselective synthesis of the natural (+)-cerulenin was reported recently by Ohrui and co-workers.[6b]

This paper presents in detail our synthesis of (±)-cerulenin and its tetrahydro derivative as well as a number of related compounds which were synthesized for the purpose of gaining insight into the salient chemical structures essential for biological activity.

The key intermediate in our synthesis is the 12-carbon butenolide 3 (Scheme I). The 12-carbon keto triene amide 4 (Scheme III), also considered by us as a key intermediate, was synthesized, but we were unable to convert it into cerulenin. Compound 3 was prepared by a sequence of reactions (Scheme I) beginning with *trans*-crotyl chloride and the Grignard reagent derived from 4-pentynoic acid

(1) Hata, T.; Sano, Y.; Matsumae, A.; Kanio, Y.; Nomura, S.; Sugawara, R. *Nippon Saikingoku Zasshi* **1960**, *15*, 1075.
(2) Nomura, S.; Horiuchi, T.; Ōmura, S.; Hata, T. *J. Biochem.* **1972**, *71*, 783. Vance, D.; Goldberg, I.; Mitsuhashi, O.; Block, K.; Ōmura, S.; Nomura, S. *Biochem. Biophys. Res. Commun.* **1973**, *48*, 649. D'Agnolo, G.; Rosengold, I. S.; Awaya, J.; Ōmura, S.; Vagelos, P. R. *Biochem. Biophys. Acta* **1973**, *326*, 155.
(3) Greenspan, M. D.; Mackow, R. C.; Ōmura, S. *Lipids* **1977**, 729.
(4) Matsumae, A.; Nomura, S.; Hata, T. *J. Antibiot.* **1964**, *17*, 1.
(5) Ōmura, S.; Katagiri; Nakagawa, A.; Sano, Y.; Nomura, S.; Hata, T. *J. Antibiot.* **1967**, 349. Ōmura, S.; Nakagawa, A.; Sekikawa, K.; Otani, M.; Hata, T. *Chem. Pharm. Bull.* **1969**, 2361. Arison, B.; Ōmura, S. *J. Antibiot.* **1974**, 28.
(6) (a) Ohrui, H.; Emoto, S. *Tetrahedron Lett.* **1978**, 2095. (b) Sveta, N.; Ohrui, H.; Kuzuhara, H. *Ibid.*, **1979**, 2039.
(7) Poughny, J. R.; Sinary, P. *Tetrahedron Lett.* **1978**, 3301.
(8) Vigneron, J. P.; Blanchard, J. M. *Tetrahedron Lett.* **1980**, 1739.
(9) Chisholm, M. J.; Hopkins, C. Y. *Can. J. Chem.* **1963**, *41*, 1888.
(10) Boeckman, R. K.; Thomas, E. W. *J. Am. Chem. Soc.* **1977**, *99*, 2805; **1979**, *101*, 897.
(11) Jakubowski, A. A.; Guziec, F. S., Jr.; Tishler, M. *Tetrahedron Lett.* **1977**, 2399.
(12) Corey, E. J.; Williams, D. R. *Tetrahedron Lett.* **1977**, 3847.

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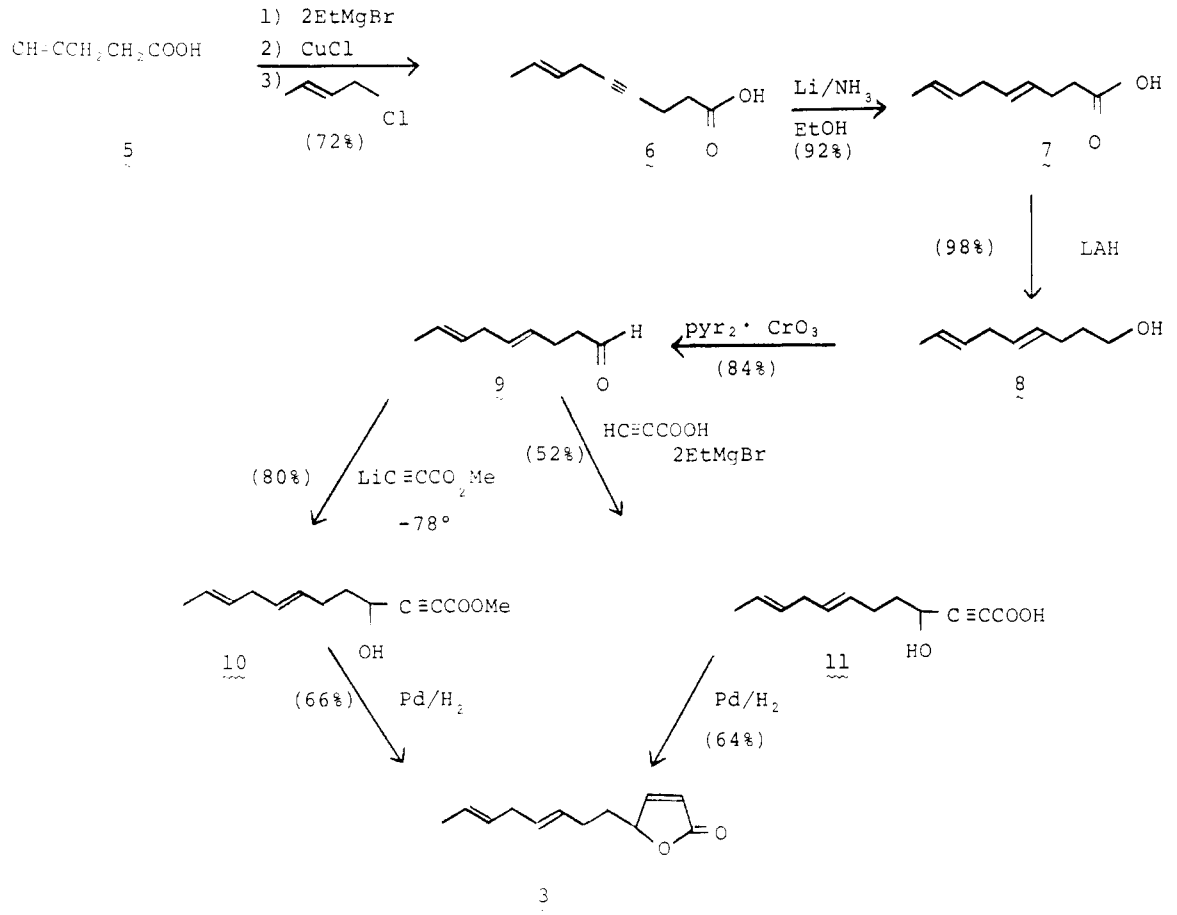
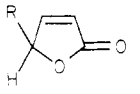
Scheme I



(5) and ethylmagnesium bromide. The resulting crystalline *trans*-7-nonen-4-ynoic acid (6) obtained in 65–72% yield was reduced with lithium–ethanol in liquid ammonia to *trans,trans*-4,7-diene acid 7 in 92% yield without isomerization. Attempted reduction of the acetylenic acid by lithium–liquid ammonia without addition of a proton source led to a complex mixture probably due to lithamide-catalyzed isomerization of the diene system. Reduction of the diene acid with lithium aluminum hydride followed by chromium trioxide–pyridine oxidation of the intermediate alcohol 8 cleanly afforded diene aldehyde 9 in 82% overall yield from 7.

The diene aldehyde was condensed at −78 °C with the lithium salt of methyl propiolate in dry tetrahydrofuran, affording methyl 4-hydroxy-*trans,trans*-7,10-dodecadien-2-ynoate (10) in 80% yield. The latter was hydrogenated by using the Lindlar catalyst presumably to a hydroxy olefinic ester which spontaneously cyclized upon warming to 35 °C to butenolide 3 in 66% yield. Alternative preparations of 3 proved to be much less satisfactory. Thus, the condensation of 9 with the magnesium dianion of propiolic acid in dry tetrahydrofuran afforded oily hydroxyacetylenic acid 11 in only 52% yield. Use of the dilithium salt of propiolic acid in the condensation drastically lowered yields of 11 to 10–20%, probably due to self-condensation of the aldehyde. When HMPT was added as a cosolvent in the condensation reactions, crude condensation yields increased; but since 11 could not be readily purified, traces of HMPT in the crude product significantly lowered yields in the subsequent hydrogenation of 11 to 3. A significant side reaction in the hydrogenation of 11 was the isomerization of the intermediate hydroxyethylenic acid to the corresponding keto acid. This isomerization was most pronounced when hydrogenations proceeded very slowly—especially when impure 11 was reduced—leading to irreproducible and low yields of 3.

Butenolides such as 12 have proved very difficult to



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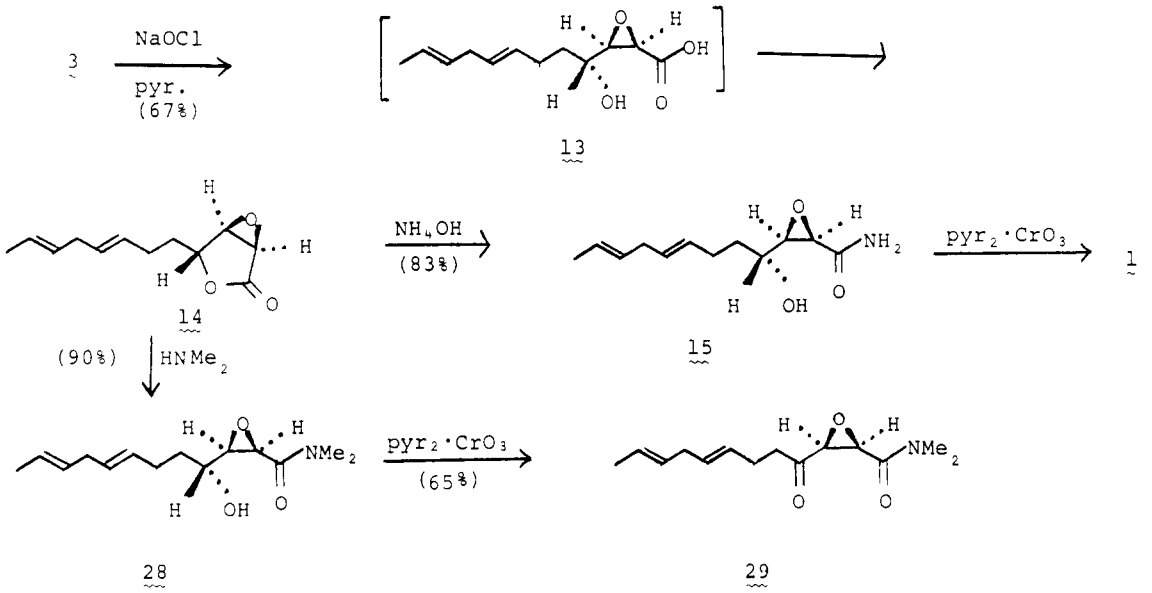
epoxidize. They are inert to peracids and are rapidly isomerized by alkaline hydrogen peroxide to the corresponding γ-keto acid. All the published chemical epoxidation methods we tried failed to achieve our objective. However, treatment of 3 with excess sodium hypochlorite (Scheme II) in pyridine[13] solution at 0 °C rapidly and cleanly epoxidized the butenolide double bond grouping and opened the intermediate epoxy lactone to the corresponding hydroxyepoxy acid (13). Unreacted butenolide appeared to be inert to ring opening under the conditions of these experiments. Warming 13 to 65 °C regenerated epoxy lactone 14 in 84% yield.

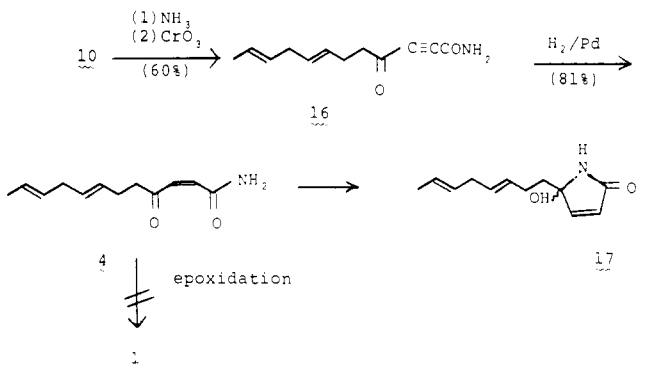
Only one isomeric epoxy lactone is formed in the hypochlorite epoxidation. From the Karplus equation and the observed coupling constants of J = 2.5 Hz for the epoxide protons and J < 0.5 Hz for the protons on C-3 and C-4, the stereochemical relationship between the alkyl group and the epoxide has been assigned as trans. The cis stereochemistry would require that the coupling constants be $J \approx 3$ Hz for the epoxide protons and $J \approx 2$ Hz for the coupling of protons on C-3 and C-4.[14] Trans

(13) Alkaline hypochlorite has been used in the epoxidation of α,β-unsaturated ketones: Reamonn, L. S. L.; O'Sullivan, W. I. *J. Chem. Soc., Chem. Commun.* **1976**, 1012. Marmor, S. *J. Org. Chem.* **1963**, *28* 250.

Scheme II



Scheme III



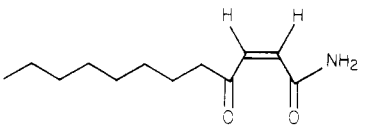
stereochemistry is consistent with attack of hypochlorite from the less hindered side of the molecule.

Ammonolysis of **14** with ammonium hydroxide in methanol cleanly opened the lactone to a single isomer of hydroxyepoxy amide **15**, in 83% yield. Collins oxidation[15] of **15** afforded crystalline *dl*-cerulenin (**1**) in 90% yield. Attempted oxidation of **15** with pyridinium chlorochromate,[16] with or without added sodium acetate, and normal chromatographic workup afforded only an oily mixture of *dl*-cerulenin and its isomeric hydroxy lactams.

The 12-carbon keto triene amide **4**, considered to be a useful intermediate for the synthesis of cerulenin, was also prepared from **10** by the sequence in Scheme III. Ammonolysis of **10** followed by chromic acid oxidation afforded keto acetylenic amide **16** in 60% yield. Hydrogenation of **16** to **4** was carried out by using Lindlar catalyst and stopping the reduction when 1 equiv of hydrogen was absorbed. In general, the hydrogenation was rapid and would not stop or slow down at the ethylene stage. The same catalyst behaved extremely well in the model hydrogenation of 2,5-dimethyl-3-hexyne-2,5-diol to the corresponding ethylene.

The crude keto olefinic amide **4** proved to be quite unstable. Attempted purification of **4** by silica column chromatography led to complete cyclization of **4** to the unstable hydroxy lactam **17**. Simply warming **4** in pentane–benzene caused this isomerization. No uncyclized compound could be detected in either case. This observation is consistent with the findings of Lutz and coworkers on the rapid cyclizations of keto ethylenic amides.[17]

In model reactions, reduced derivatives of **4** and **17**, namely, compounds **18** and **19** were subjected to ep-



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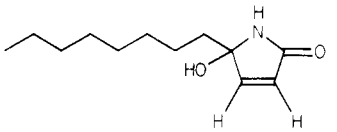

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oxidation conditions by using sodium hypochlorite in pyridine, alkaline hydrogen peroxide, alkaline hydrogen peroxide–sodium tungstate,[18] bis(2,4-dioxopentanato)vanadium(IV) oxide–*tert*-butyl hydrogen peroxide,[19] and *m*-chloroperbenzoic acid. All experiments were unsuccessful, affording either intractable mixtures or recovered starting materials.

The synthesis of (±)-tetrahydrocerulenin was carried out according to Scheme IV, and as a whole this sequence proceeded with very little complications. Thus, the reaction between nonanal and propiolic acid magnesium dianion went nicely as did the catalytic Lindlar hydrogenations of the crystalline 4-hydroxy-2-dodecynoic acid (**21**) to butenolide (**22**, 90% yield). Sodium hypochlorite oxidation of the latter gave the epoxy lactone **23** in almost quantitative yield. Ammonlysis of **23** followed by oxidation of **24** with Collins reagent gave (±)-tetrahydrocerulenin (**25**) in 92% yield.

(14) Boeckman and Thomas[10] generated the epoxy lactone with alkyl groups and epoxide cis. The reported coupling constants for this isomer are as expected from the Karplus equation.

(15) Collins, J. C.; Hess, W. W.; Frank, F. J. *Tetrahedron Lett.* **1968**, 3363.

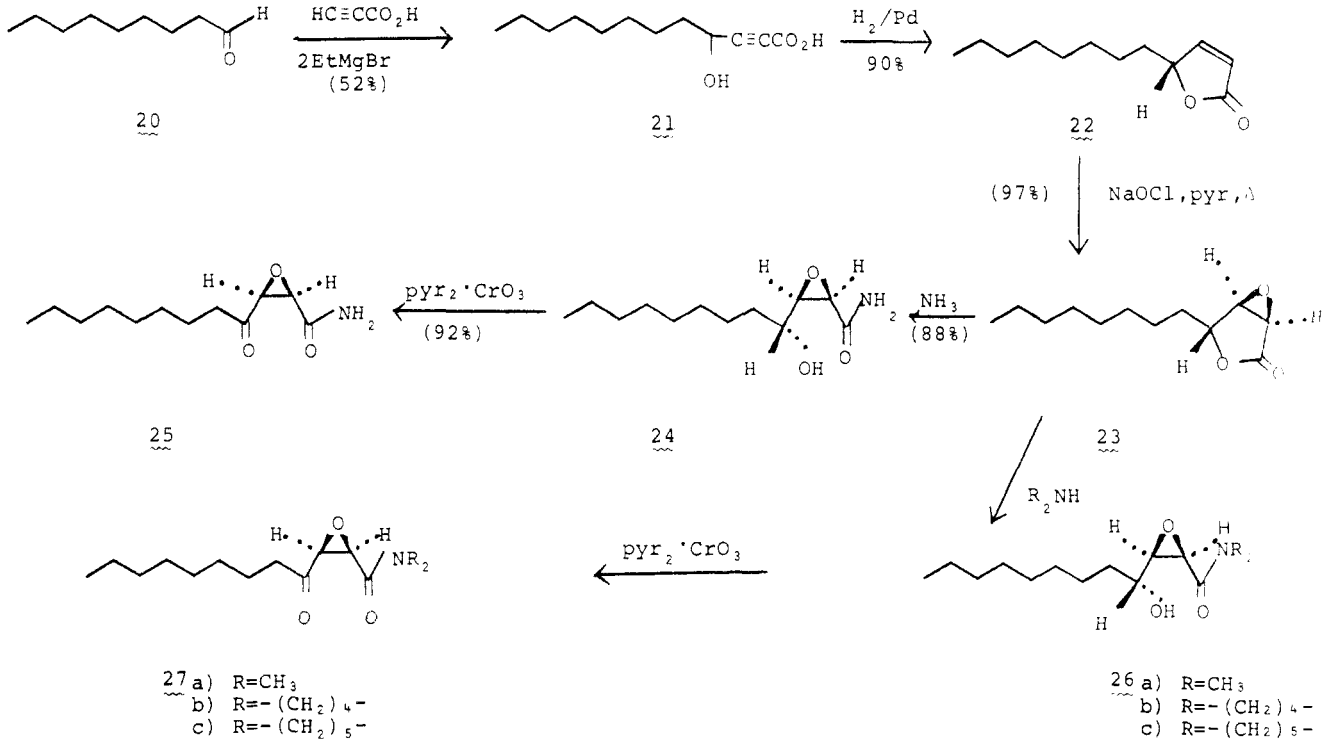
(16) Corey, E. J.; Suggs, J. W. *Tetrahedron Lett.* **1975**, 2647.

(17) Lutz, R. E.; Clark, C. T.; Feifer, J. P. *J. Org. Chem.* **1960**, *25*, 346 and references therein.

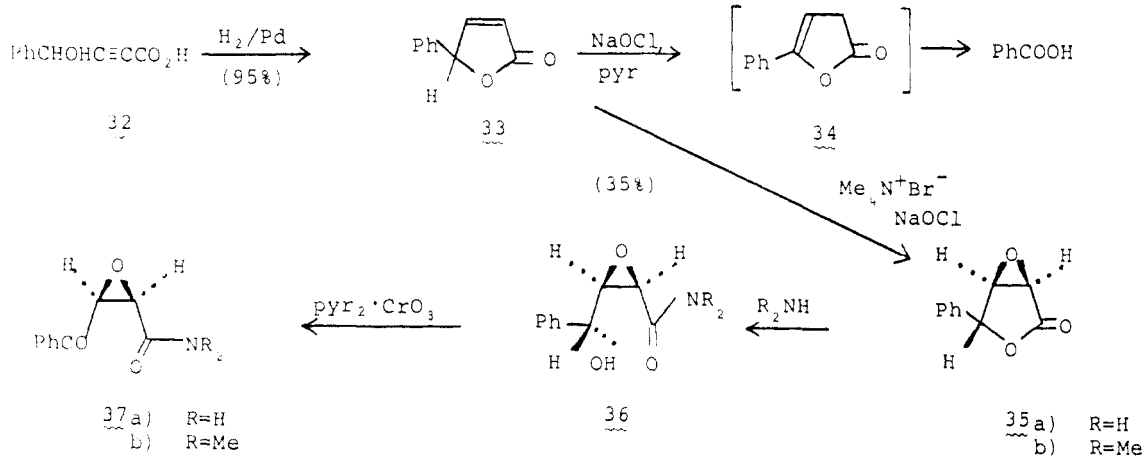
(18) Payne, G. B.; Williams, D. H. *J. Org. Chem.* **1959**, *24*, 54.

(19) Gould, E. S.; Hiatt, R. R.; Irwin, K. C. *J. Am. Chem. Soc.* **1968**, *90*, 4573. Sharpless, K. B.; Michaelson, R. C. *Ibid.* **1973**, *95*, 6136.

Scheme IV

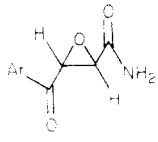


Scheme V



Inasmuch as cerulenin and its tetrahydro derivative lose biological activity rather quickly under the conditions favoring their cyclization to lactam forms, we synthesized a few related compounds in which cyclization cannot occur. *N,N*-Dimethyl-(±)-cerulenin (**29**) was prepared in 59% yield from the epoxy lactone **14** by treatment with dimethylamine to **28** followed by oxidation. In the tetrahydrocerulenin series, *N,N*-dimethyltetrahydrocerulenin **27a** and the corresponding pyrrolidine and piperidine derivatives **27b** and **27c** were synthesized in respective yields of 72%, 81%, and 81%.

Aromatic analogues of cerulenin with a trans orientation of the keto epoxy amide moiety, **30**, have been reported



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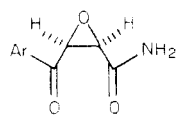

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to be active antilipogenic agents.[20] The corresponding cis analogues were prepared by using the general synthetic scheme for cerulenin (Scheme V). The known 4-hydroxy-4-phenylbutynoic acid (**32**) was converted in 95% yield to butenolide **33** by Lindlar reduction. Under the previously used epoxidation conditions of sodium hypochlorite in pyridine no significant epoxide formed, and only aromatic carboxylic acids could be isolated from the reaction. Apparently the increased acidity of the benzylic proton causes isomerization of **33** to the β,γ-unsaturated derivative **34** which is further cleaved under the reaction conditions. Use of sodium hypochlorite with tetramethylammonium bromide as a phase-transfer reagent allowed the epoxidation to **35** to occur in moderate yield. Reaction of **35** with ammonia or dimethylamine followed by oxidation afforded the desired aromatic cis epoxy amides **37a,b**.

The antimicrobial activities of synthetic cerulenin and its derived (±)-tetrahydrocerulenin were found to be about

(20) Carr, J. G.; Durham, H. G. U.S. Patent 4 091 221, 1978. While **30** (where Ar is phenyl) is reported to be active microbiologically, we found essentially no activity with the corresponding cis isomer, **31**.

half the activities of the natural compounds against certain sensitive microorganisms such as *Bacillus subtilis* PCI 210, *Mycobacterium smegmatis* ATCC 607, *Piricularia oryzae* KB 888, and *Candida albicans* KF 1, suggesting that the unnatural isomers have no microbial action. Of the remaining compounds tested, the 4-keto compounds (**4**, **27a**, **29**, **37a**) retained some modest activities whereas the precursors, the corresponding 4-hydroxy compounds, were without any microbial activities. None of these compounds exhibited significant inhibitory activity against fatty acid synthetase from *Brevibacterium ammoniagenes*.[21] These results indicate the high degree of specificity of chemical structure of the cerulenin molecule essential for microbiological activity.

Experimental Section

Infrared spectra were recorded on a Perkin-Elmer Model 137 spectrophotometer. Nuclear magnetic resonance spectra were recorded on a Varian XL-200 or a EM-360A NMR spectrometer, and chemical shifts are reported in δ units with tetramethylsilane as an internal reference. Low-resolution mass spectra were recorded on a Hitachi RMU-6 instrument operated at 70 eV, and high-resolution mass spectra were recorded by Merck Sharp & Dohme Research Laboratories. Melting points were taken on a Fisher-Johns melting point apparatus and are corrected. Boiling points were determined by using a standard McLeod gauge and are uncorrected. Microanalyses were conducted by Merck Sharp & Dohme Research Laboratories or Olin Research Laboratories.

Tetrahydrofuran (THF) and ether were distilled from sodium benzophenone ketyl under nitrogen immediately before use. *n*-Butyllithium was titrated according to the method described by Kofron and Baclawski.[22] Reactions that require anhydrous conditions were conducted in flame-dried glassware under nitrogen. Flash chromatography was performed according to the method described by Still et al.[23]

***trans*-Non-7-en-4-ynoic Acid (6).** Ethylmagnesium bromide (1.90 M in THF, 525 mL, 1.00 mol) was carefully added via cannula under positive nitrogen pressure to a mechanically stirred, ice-cooled solution of 4-pentynoic acid[24] (49.0 g, 0.50 mol) in dry THF (125 mL). After the addition was completed and ethane evolution ceased, the mixture was allowed to rise to room temperature, at which time freshly prepared cuprous chloride[25] (6.8 g, 0.07 mol) was added in one portion. The mixture was heated to reflux, and freshly purified *trans*-crotyl chloride[26] (47.6 g, 0.52 mol) was added dropwise. The mixture was kept under reflux for 6 h, and a second addition of cuprous chloride (3.4 g, 0.03 mol) was then made. After an additional 1 h at reflux, the reaction mixture was cooled in an ice bath. Sulfuric acid (2 M, 400 mL) was slowly added to the mixture, the organic layer separated, and the aqueous layer extracted with ether. The combined organic phases were washed twice with NH_4Cl solution (2%, 200 mL) and then with brine solution, dried over anhydrous $MgSO_4$, and concentrated. The greenish oily residue was flash distilled [bp 87 °C (0.25 mm)] whereupon the distillate crystallized. The crystals were recrystallized twice from hexanes, affording colorless crystals: 65–72%; mp 59–60 °C; IR ($CHCl_3$) 3450–2500, 1710, 965 cm^{-1}; NMR ($CDCl_3$) δ 1.68 (m, 3 H), 2.56 (s, 4 H), 2.87 (m, 2 H), 5.50 (m, 1 H), 5.73 (m, 1 H), 11.30 (br s, 1 H); mass spectrum, *m/e* 152 (M^+), 135, 111, 93; exact mass calcd *m/e* 152.0836, found *m/e* 152.0831.

Anal. Calcd for $C_9H_{12}O_2$: C, 71.02; H, 7.95. Found: C, 70.64; H, 8.23.

***trans,trans*-Nona-4,7-dienoic Acid (7).** Freshly scraped lithium (2.8 g, 0.40 mol) was added in small portions to a stirred solution of **6** (20.0 g, 0.13 mol) in liquid ammonia (150 mL previously dried by distillation from sodium) containing absolute ethanol (12.6 mL, 0.26 mol) and maintained under nitrogen at −78 °C. After the addition was complete and a blue color persisted for 30 min, dry NH_4Cl was added, and the mixture was allowed to reach room temperature with evaporation of the ammonia. Water (300 mL) was added to the dried residue, and the resulting solution was extracted with ether (3 × 50 mL). The aqueous solution was acidified with hydrochloric acid and extracted with ethyl acetate (3 × 70 mL), and the combined extracts were dried over anhyd sodium sulfate and concentrated to an oily residue. The latter on distillation afforded **7**: 18.7 g (0.12 mol, 92%); bp 87–88 °C (0.55 mm); IR ($CHCl_3$) 3450–2450, 1710, 970 cm^{-1}; NMR ($CDCl_3$) δ 1.67 (m, 3 H), 2.42 (m, 4 H), 2.70 (m, 2 H), 5.50 (m, 4 H), 10.41 (br s, 1 H); mass spectrum, *m/e* 154 (M^+), 109, 95, 94, 81.

Anal. Calcd for $C_9H_{14}O_2$: C, 70.10; H, 9.15. Found: C, 70.07; H, 9.26.

***trans,trans*-Nona-4,7-dienol (8).** Distilled diene acid **7** (20 g, 0.13 mol) in anhydrous ether (60 mL) was added dropwise over 20 min to a stirred suspension of $LiAlH_4$ (4.96 g, 0.13 mol) in 140 mL of absolute ether (140 mL) under gentle reflux. After the mixture cooled to room temperature, water (5 mL) was carefully added dropwise, followed by NaOH solution (15% NaOH, 5 mL) and finally water. The separated white solid was removed by filtration and washed with ether, and the combined ether layers were dried over $MgSO_4$ and concentrated under vacuum. The colorless liquid residue **8** distilled entirely: 17.8 (0.127 mol, 98%); bp 64–65 °C (1.4 mm); IR (neat) 3300, 965 cm^{-1}; NMR ($CDCl_3$) δ 1.33 (br s, 1 H), 1.66 (m, 5 H), 2.12 (m, 2 H), 2.68 (m, 2 H), 3.68 (t, J = 7 Hz, 2 H), 5.48 (m, 4 H); mass spectrum, *m/e* 140 (M^+), 122, 95, 81, 79.

Anal. Calcd for $C_9H_{16}O$: C, 77.09; H, 11.42. Found: C, 76.69; H, 11.44.

***trans,trans*-Nona-4,7-dienal (9).** Chromium trioxide (6.05 g, 0.06 mol) was added in small portions to a stirred solution of pyridine (9.8 mL, 0.12 mol) in dichloromethane (150 mL) kept at 0 °C. After 15 min at 20 °C a solution of dienol **8** (1.07 g, 7.1 mmol) in dichloromethane (5 mL) was added in one portion, and the mixture stirred at 0 °C for 15 min and then allowed to come to room temperature. The mixture was filtered through glass wool, and the organic layer was washed with water and then with dilute HCl and dried over anhydrous sodium sulfate. Concentration followed by distillation of the residue gave a colorless liquid, **9**: 0.82 g (5.9 mmol, 83%); bp 50 °C (1.34 mm); IR (neat) 2820 (sh), 2720, 1715, 970 cm^{-1}; NMR ($CDCl_3$) δ 1.66 (m, 3 H), 2.39 (m, 2 H), 2.52 (m, 2 H), 2.69 (m, 2 H), 5.47 (m, 4 H), 9.73 (m, 1 H); mass spectrum, *m/e* 138 (M^+), 123, 109, 95, 94, 81, 79.

Anal. Calcd for $C_9H_{14}O$: C, 78.21; H, 10.21. Found: C, 78.24; H, 10.16. The 2,4-DNP derivative of **9** was prepared; mp 91–93 °C.

Methyl 4-Hydroxy-*trans,trans*-7,10-dodecadien-2-ynoate (10). To a solution of diisopropylamine (1.20 mL, 9.5 mmol) in dry THF (14 mL) at 0 °C was added dropwise *n*-butyllithium (3.5 mL, 8.4 mmol, 2.4 M in hexane). The solution was then cooled to −78 °C, and methyl propiolate (0.75 mL, 8.4 mmol) was added dropwise to the mixture. After 30 min, a solution of aldehyde **9** (1.06 g, 7.6 mmol) in THF (1 mL) was added. The mixture was stirred at −78 °C for 1.5 h after which time a solution of acetic acid (2 mL) in THF (10 mL) was added, and the mixture was allowed to come to 25 °C over 2 h. The mixture was diluted with ether, washed successively with saturated bicarbonate solution, water, and brine solution, and dried. Concentration in vacuo followed by flash chromatography (silica gel, 15% ethyl acetate/petroleum ether) afforded the hydroxy ester (1.25 g, 6.1 mmol, 80%) as a light yellow liquid. The product was either used as such or distilled on a Kugelrohr apparatus to give analytically pure **10**: 92%; bp 100 ± 10 °C (oven temperature; 3 μm); IR (neat) 3400, 2250, 1725, 970 cm^{-1}; NMR ($CDCl_3$) δ 1.67 (m, 3 H), 1.87 (m, 2 H), 2.09 (br m, 1 H), 2.22 (m, 2 H), 2.70 (m, 2 H), 3.85 (s, 3 H), 5.51 (4 H); mass spectrum, *m/e* 222 (M^+), 138, 123, 111, 109.

(21) Kawaguchi, A.; Okuda, S. *Proc. Natl. Acad. Sci.* **1977**, *74*, 3180.
(22) Kofron, W. C.; Baclawski, L. M. *J. Org. Chem.* **1976**, *41*, 1879.
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(24) Cologne, J.; Gellin, R. *Bull. Soc. Chim. Fr.* **1954**, *23*, 797. The first step in the synthesis sequence of 4-pentynoic acid (**5**), the reaction between sodio ethyl malonate and propargyl bromide, gave poor yields in our hands (ca. 35%) due to dialkylation of the malonic ester. We found that a 1-equiv excess of ethyl malonate inhibits dialkylation and almost doubles the yield of ethyl 2-propylmalonate, the intermediate to **5**. The excess ethyl malonate is readily recovered by distillation.
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(26) Commercial crotyl chloride (Aldrich) was dried over anhydrous calcium sulfate overnight, filtered, and distilled from 2% tri-*n*-butylamine by using a Teflon spinning-band column. The fraction boiling at 84–86 °C was collected and used immediately.

Anal. Calcd for $C_{13}H_{18}O_3$: C, 70.24; H, 8.16. Found: C, 70.36; H, 8.24.

4-Hydroxy-*trans*,*trans*-7,10-dodecadien-2-ynoic Acid (11). Ethylmagnesium bromide (1.9 M, 19.6 mL, 35 mmol) in dry THF was added at 0 °C to a mechanically stirred solution of distilled propiolic acid (1.23 g, 17.5 mmol) in dry THF (75 mL) under nitrogen. After 2 h at 0 °C dry hexamethylphosphoramide (20 mL) was added. When the mixture became homogeneous, the aldehyde **9** (2.49 g, 18.0 mmol) in dry THF (10 mL) was added at 0 °C, and the mixture was stirred at 0° for 1 h and then allowed to come to room temperature over 1 h. Sulfuric acid (2 M, 20 mL) was added in one portion, followed by water (30 mL). The mixture was diluted with ethyl acetate (50 mL), and the organic phase washed with sulfuric acid (2 M, 2 × 30 mL), followed by sodium bicarbonate solution (30 mL). The aqueous phase was washed with dichloromethane (3 × 10 mL), acidified to pH ~1 with sulfuric acid (2 M), and extracted with CH_2Cl_2 (3 × 20 mL). The combined extracts were washed with distilled water until the pH of the washings was 4, dried, and concentrated. The residue was **11**, an air-sensitive yellow oil: 1.89 g (9.1 mmol, 52%); IR (CCl_4) 3600–2400, 2250, 1700, 965 cm^{-1}; NMR ($CDCl_3$) δ 1.68 (m, 3 H), 2.05 (m, 4 H), 2.66 (m, 2 H), 4.55 (t, J = 6.5 Hz, 1 H), 5.43 (m, 4 H), 7.78 (s, 2 H); mass spectrum, m/e 208 (M^+).

Anal. Calcd for $C_{12}H_{16}O_3$: C, 69.23; H, 7.69. Found: C, 68.91; H, 7.81.

***cis*,*trans*,*trans*-Dodeca-2,7,10-trienoic Acid γ-Lactone (3).** A mixture of hydroxy ester **10** (2.22 g, 10.0 mmol), methanol (7 mL), pyridine (0.8 mL), and Lindlar catalyst (0.27 g) was hydrogenated under atmospheric pressure over 7.5 h, whereby a total of 246 mL of hydrogen had been taken up. The reaction mixture was filtered, diluted with ether, and washed successively with dilute HCl solution, water, and saturated bicarbonate solution. The ether layer was subsequently stirred with a pinch of *p*-toluenesulfonic acid over 10 h. The mixture was then washed with bicarbonate solution and brine solution, dried, and concentrated in vacuo to give a yellow-red liquid (1.92 g). Flash chromatography (silica gel, 25% ethyl acetate/petroleum ether) afforded butenolide **3** as a very pale yellow oil: 1.26 g (6.6 mmol, 66%); bp 90 °C (5 μm, Kugelrohr); IR (neat) 1750, 1600, 965 cm^{-1}; NMR ($CDCl_3$) δ 1.68 (m, 3 H), 1.80 (m, 2 H), 2.20 (m, 2 H), 2.70 (m, 2 H), 5.10 (m, 1 H), 5.46 (m, 4 H), 6.17 (dd, J = 7, 2 Hz, 1 H), 7.56 (dd, J = 7, 2 Hz, 1 H); mass spectrum, m/e 192 (M^+), 147, 137, 95.

Anal. Calcd for $C_{12}H_{16}O_2$: C, 75.00; H, 8.38. Found: C, 74.81; H, 8.55.

The trienol γ-lactone **3** was obtained from **11** by Lindlar hydrogenation in the same way as **10** was converted into **3**. The product **3** was again isolated as an oil (64%) which was identical in all aspects with the product obtained from **10**.

***cis*-2,3-Epoxydodeca-7,10-dienoic Acid γ-Lactone (14).** To the lactone **3** (476 mg, 2.5 mmol) in pyridine (25 mL) at 0 °C was added sodium hypochlorite solution (5%, 15 mL, 10 mmol). The mixture was stirred at 0 °C for 1 h and allowed to reach room temperature over an additional hour. The mixture was poured onto CH_2Cl_2–water (30–10 mL) and $NaHCO_3$ solution added (1 M, 10 mL). The bicarbonate extract was washed with ethyl acetate, acidified to pH 1, and extracted with ethyl acetate (3 × 20 mL). The acid extracts were combined, dried, concentrated, and distilled, affording analytically pure epoxy lactone **14**: 280 mg (1.35 mmol, 59%); bp 120–121 °C (0.35 mm); IR ($CHCl_3$) 1780, 975, 855 cm^{-1}; NMR ($CDCl_3$) δ 1.67 (m, 3 H), 1.78 (m, 2 H), 2.20 (m, 2 H), 2.70 (m, 2 H), 3.79 (dd, J = 3, 1 Hz, 1 H), 3.99 (d, J = 3 Hz, 1 H), 4.62 (t, J = 7 Hz, 1 H), 5.45 (m, 4 H); mass spectrum, m/e 208 (M^+).

Anal. Calcd for $C_{12}H_{16}O_3$: C, 69.23; H, 7.69. Found: C, 68.91; H, 7.43.

***cis*-2,3-Epoxy-4-hydroxy-*trans*,*trans*-7,10-dodecadienamide (15).** The epoxy lactone **14** (200 mg, 1 mmol) in methanol (2 mL) was treated with ammonium hydroxide (15 M, 0.20 mL) at 0 °C. After being stirred at 0 °C for 25 min, the mixture was diluted with CH_2Cl_2 (20 mL) and 0.5 N HCl (5 mL), and the organic phase was dried and concentrated, affording a yellow oil (180 mg, 0.8 mmol, 83%) which crystallized at 0 °C. Recrystallization from $CHCl_3$–hexanes gave a colorless solid which melted upon warming to room temperature. Crude **15** was sufficiently pure for subsequent oxidation to (±)-cerulenin: IR ($CHCl_3$) 3550–3200, 1690, 1580, 970 cm^{-1}; NMR ($CDCl_3$) δ 1.66 (m, 3 H), 1.78 (m, 2 H), 2.10 (m, 2 H), 2.71 (m, 2 H), 3.10 (m, 1 H), 3.53 (m, 2 H), 4.73 (br s, 1 H), 5.45 (m, 4 H), 6.57 (br s, 1 H), 6.98 (br s, 1 H).

(±)-Cerulenin (1). The hydroxy amide **15** (40 mg, 0.22 mmol) in CH_2Cl_2 (3 mL) was added at room temperature to a stirred solution of the pyridine–chromic anhydride complex (355 mg) in CH_2Cl_2 (9 mL). After 15 min the mixture was diluted with ether (10 mL), filtered through Celite, washed with water and then dilute acid, dried, and concentrated, affording a colorless oil (45 mg, 0.20 mmol, 90%), which crystallized at −20 °C from benzene–hexanes: mp 40–43 °C dec; IR ($CHCl_3$) 3540, 3410, 1720, 1690, 1585, 970 cm^{-1}; NMR ($CDCl_3$) δ 1.68 (m, 3 H), 2.35 (m, 2 H), 2.65 (m, 4 H), 370 (d, J = 5 Hz, 1 H), 3.86 (d, J = 5 Hz, 1 H), 5.47 (m, 4 H), 6.40 (br, 2 H); mass spectrum, m/e 223 (M^+).

Anal. Calcd for $C_{12}H_{17}NO_3$: C, 64.55; H, 7.68; N, 6.27. Found: C, 64.71; H, 7.85; N, 6.14.

These spectral data are identical with those obtained from the natural product.

4-Oxo-*trans*,*trans*-7,10-dodecadien-2-ynamide (16). Treatment of the acetylenic ester **10** (0.5 g, 2.3 mmol) in dry methanol (2 mL) with ammonia in methanol (7.5 M, 4 mL, 30 mmol) for 24 h, concentration, and column chromatography on silica (1:4 ether/benzene) afforded colorless hydroxy amide: 0.32 g (1.54 mmol, 67%); mp 63–65 °C; IR ($CHCl_3$) 3250, 2210, 1660, 965 cm^{-1}; NMR ($CDCl_3$) δ 1.66 (dd, 3 H), 1.72, 2.37 (m, 4 H), 2.50–2.82 (m, 2 H), 3.83–4.16 (br s, 1 H), 4.25–4.74 (m, 1 H), 5.25–5.57 (m, 4 H), 6.33–6.82 (br s, 2 H); mass spectrum, m/e 207 (M^+).

To the cooled (0 °C), stirred hydroxy amide (230 mg, 1.1 mmol) dissolved in acetone (2 mL) was added freshly prepared 6 N chromic acid (0.75 mL). After 1 h at 0 °C, dilution with water (7 mL), extraction with ether (3 × 25 mL), decolorization with charcoal, drying, and concentrating afforded **16** as a yellowish solid (203 mg, 0.99 mmol, 90%) which could be recrystallized from petroleum ether–benzene: mp 51–52 °C; IR ($CHCl_3$) 3300, 2220, 1660, 965 cm^{-1}; NMR ($CDCl_3$) δ 1.67 (m, 3 H), 2.18–2.6 (m, 2 H), 2.6–2.95 (m, 4 H), 5.35–5.65 (m, 4 H), 6.91 (br s, 2 H); mass spectrum, m/e 205 (M^+).

Anal. Calcd for $C_{12}H_{15}NO_2$: C, 70.24; H, 7.31; N, 6.83. Found: C, 70.37; H, 7.52; N, 6.74.

4-Oxo-*cis*,*trans*,*trans*-2,7,10-dodecatrienamide (4) and Cyclization to 17. The keto acetylenic amide **16** (0.25 g, 1.2 mmol) in ethyl acetate (25 mL) was hydrogenated in a Parr apparatus over Lindlar catalyst (25 mg) with added quinoline (7 drops). Washing with 2% HCl and water and drying afforded crude **4** as a yellow semisolid: 0.20 g (0.97 mmol, 81%); IR (KBr) 3250, 1625, 960, 812 cm^{-1}; NMR ($CDCl_3$) δ 1.65 (m, 3 H), 2.0–30 (m, 6 H), 5.4 (m, 4 H), 6.10 (d, 1 H), 6.50 (d, 1 H); mass spectrum, m/e 207 (M^+).

Attempted purification of **4** by silica chromatography or by recrystallization afforded the unstable hydroxy lactam **17** as an oil: IR ($CHCl_3$) 3300, 1700, 965 cm^{-1}; NMR ($CDCl_3$) δ 1.65 (m, 3 H), 2.0–2.9 (m, 6 H), 5.4 (m, 4 H), 6.00 (d, 1 H), 6.95 (d, 1 H); mass spectrum, m/e 207 (M^+).

4-Hydroxydodec-2-ynoic Acid (21). Methylmagnesium bromide (3.0 M, 33 mL, 0.1 mol) in THF was added at 0 °C via syringe to a mechanically stirred solution of the propiolic acid (3.5 g, 0.05 mol) in dry THF (100 mL), kept under nitrogen. After the mixture was stirred for 2 h at 0 °C, nonanal (**20**; 7.1 g, 0.05 mol) was added via syringe in one portion at 0 °C, and the mixture was stirred at 0 °C for 1 h and allowed to warm to room temperature over 1 h. The mixture was diluted with ether (50 mL) and acidified (with cooling at 0 °C) to pH 1 with 2 M H_2SO_4. The organic phase was extracted with 5% $NaHCO_3$ solution, and the bicarbonate solution was acidified to pH 1 and extracted with CH_2Cl_2 (3 × 25 mL). Drying and concentrating afforded a pale yellow oil which crystallized at −20 °C from hexanes, affording colorless crystals of **21**: 7.7 g (0.036 mol 73%); mp 68–69 °C; IR (CCl_4) 2230, 1690, cm^{-1}; NMR ($CDCl_3$) δ 0.8–1.8 (m, 17 H), 4.08 (m, 1 H), 4.42 (m, 1 H), 8.12 (br s, 1 H); mass spectrum, m/e 212 (M^+).

Anal. Calcd for $C_{12}H_{20}O_3$: C, 67.89; H, 9.50. Found: C, 67.81; H, 9.81.

Dodec-2-enoic Acid γ-Lactone (22). The acetylenic acid **21** (6.36 g, 30 mmol) in ethyl acetate (150 mL) was hydrogenated

over Lindlar catalyst (150 mg). Hydrogen uptake stopped when ~95% of the theoretical amount was consumed. The mixture was filtered through Celite and washed with ethyl acetate (2 × 20 mL). The solution was warmed to 35 °C for 10 min, washed with 5% $NaHCO_3$, dried, concentrated, and distilled, affording colorless butenolide **22**: 5.3 g (27 mmol, 90%); bp 90–92 °C (0.4 mm) [lit.[26] bp 152–153 °C (6 mm)]. This crystallized upon standing: mp 34–36 °C; IR (CCl_4) 1755, 1600 cm^{-1}; NMR (CCl_4) δ 0.80–1.80 (m, 17 H), 5.00 (m, 1 H), 6.00 (dd, J = 6, 2 Hz, 1 H), 7.50 (dd, J = 6, 1.5 Hz, 1 H); mass spectrum, m/e 196 (M^+), 97, 85.

Anal. Calcd for $C_{12}H_{20}O_2$: C, 73.47; H, 10.21. Found: C, 73.21; H, 10.27.

***cis*-2,3-Epoxydodecanoic Acid γ-Lactone (23).** Sodium hypochlorite (5%, 35 mL, 23 mmol) was added to a cooled (0 °C), stirred solution of **22** (2.00 g, 10 mmol) in pyridine (40 mL). The mixture was stirred at 0 °C for 1 h and allowed to come to room temperature over 1 h. NaOCl consumption was monitored by NaI–starch paper and the reaction monitored by TLC (silica, Et_2O). When no butenolide was observed on TLC, the mixture was diluted with ether (50 mL) and washed with 5% $NaHCO_3$ solution. The bicarbonate solution was washed with an additional portion of ether (25 mL). Acidification to pH ~1, extraction with CH_2Cl_2 (3 × 25 mL), and concentration led to a yellow oil which was heated at 65 °C under reduced pressure on the rotary evaporator for 1 h. Bulb-to-bulb distillation afforded colorless **23**: 2.05 g (9.7 mmol, 97%); bp 134 °C (1.35 mm); mp 29.5–31 °C; IR ($CHCl_3$) 1775, 1160, 855 cm^{-1}; NMR ($CDCl_3$) δ 0.8–1.8 (m, 17 H), 3.76 (dd, J = 2.5, 0.5 Hz, 1 H), 3.98 (d, J = 2.5 Hz, 1 H), 4.56 (m, 1 H); mass spectrum, m/e 212 (M^+).

Anal. Calcd for $C_{12}H_{20}O_2$: C, 73.47; H, 10.21. Found: C, 73.66; H, 10.31.

Attempts to epoxidize the butenolide **22** in methanol with *tert*-butyl hydroperoxide and sodium hydroxide at room temperature left **22** unchanged. With alkaline hydrogen peroxide in methanol, **22** was transformed into 4-oxododecanoic acid (mp 78.5–79 °C), identified spectroscopically.

***cis*-2,3-Epoxy-4-hydroxydodecanamide (24).** Ammonium hydroxide (15 M, 0.50 mL) was added at 0 °C to a solution of **23** (500 mg, 2.4 mmol) in methanol (5 mL) whereupon crystals separated within 2 min. The mixture was stirred 15 min at 0 °C, diluted with water (5 mL), acidified, and extracted with CH_2Cl_2 (25 mL, 3 × 10 mL). The combined organic phases were dried and concentrated, affording colorless crystals of **24** which were recrystallized from $CHCl_3$–hexanes: 460 mg (2.1 mmol, 88%); mp 106–107 °C (two recrystallizations from CCl_4 raised the melting point to 108–108.5 °C); IR ($CHCl_3$) 3600–3200, 1690, 1565 cm^{-1}; NMR ($CDCl_3$) δ 0.8–1.8 (m, 17 H), 3.15 (m, 1 H), 3.50 (m, 2 H), 4.90 (br s, 1 H), 5.8 (br s, 1 H), 6.50 (br s, 1 H); mass spectrum, m/e 230 (M^+), 185, exact mass calcd m/e 229.1676, found m/e 229.1675.

Anal. Calcd for $C_{12}H_{23}NO_2$: C, 62.85; H, 10.11; N, 6.11. Found: C, 62.86; H, 10.62; N, 6.29.

(±)-Tetrahydrocerulenin (25). The hydroxy amide **24** (115 mg, 0.53 mmol) in warm CH_2Cl_2 (7 mL) was added to a stirred solution of Collins reagent (1.55 g, 6 mmol) in CH_2Cl_2 (20 mL). The mixture was stirred 15 min at room temperature, filtered through Celite, and then washed with water until the washes became colorless. Drying and concentration of the organic layer gave **25** as a light tan solid (105 mg, 0.49 mmol, 92%) which was recrystallized from CH_2Cl_2–hexanes or CCl_4; mp 79–80 °C. Spectral characteristics of **25** were identical with those of an authentic sample prepared from cerulenin: IR ($CHCl_3$) 3500–3350, 1730, 1685, 1580 cm^{-1}; NMR ($CDCl_3$) δ 0.8–1.8 (m, 15 H), 2.61 (t, J = 6.5 Hz, 2 H), 3.82 (AB q, J = 5.5 Hz, 2 H), 6.2 (br s, 1 H), 6.45 (br s, 1 H); mass spectrum, m/e 227 (M^+), 226, 183, 141, 129, 114; exact mass calcd m/e 227.1519, found m/e 227.1518.

Anal. Calcd for $C_{12}H_{21}NO_3$: C, 63.41; H, 9.31; N, 6.16. Found: C, 63.20; H, 9.61; N, 6.41.

***N,N*-Dimethyl-*cis*-2,3-epoxy-4-hydroxydodecanamide (26a).** Dimethylamine (0.96 g, 213 mmol) in absolute methanol (70 mL) was added to a solution of the *cis*-epoxy γ-lactone **23** (1.6 g, 7.6 mmol) in methanol (30 mL) at 0 °C. The reaction mixture, after being allowed to stand at 0 °C for 2 h and overnight at room temperature, was diluted with water (20–40 mL), acidified (pH 3–4), and extracted with CH_2Cl_2 (3 × 25 mL). The organic layer was dried and concentrated, yielding **26a** as a crystalline residue (1.67 g, 6.5 mmol, 86%) which on recrystallization from hexanes had the following: mp 64–65 °C; IR (Nujol) 3450, 1640, 1100, 1075, 880 cm^{-1}; NMR ($CDCl_3$) δ 0.7–1.80 (m, 17 H), 2.97 (s, 3 H), 3.08 (m, 2 H), 3.17 (s, 3 H), 3.57 (m, 1 H), 3.90 (br s, 1 H); mass spectrum, m/e 257 (M^+).

Anal. Calcd for $C_{14}H_{27}NO_3$: C, 65.33; H, 10.58; N, 5.44. Found: C, 65.75; H, 10.98; N, 5.39.

The pyrrolidine and piperidine analogues **26b** and **26c** were made in a similar manner: **26b**, mp 51–52 °C; **26c**, mp 80–81 °C. Satisfactory spectral and analytical data were obtained for each compound.

***N,N*-Dimethyl-*cis*-2,3-epoxy-4-oxododecanamide (27a).** A solution of **26a** (1.5 g, 5.8 mmol) in CH_2Cl_2 (50 mL) was oxidized with Collins reagent in essentially the manner described for tetrahydrocerulenin (**25**). It was obtained as an oil which, after a CH_2Cl_2 solution of the oil was passed through a small bed of Florisil, fave pure **27a**: 1.25 g (4.9 mmol, 84%); mp 23–24 °C; IR (Nujol) 1710, 1660, 1500, 1460, 1400, 1270, 1155 cm^{-1}; NMR ($CDCl_3$) δ 0.7–1.7 (m, 15 H), 2.53 (m, 2 H), 2.91 (s, 3 H), 3.12 (s, 3 H), 3.75 (AB q, J = 5.0 Hz, 2 H); mass spectrum, m/e 255 (M^+).

Anal. Calcd for $C_{14}H_{25}NO_3$: C, 65.85; H, 9.86; N, 5.48. Found: C, 65.81; H, 10.10; N, 5.51.

The pyrrolidine and piperidine analogues **27b** and **27c** were made similarly.

***N,N*-Dimethyl-*cis*-2,3-epoxy-4-hydroxy-*trans,trans*-7,10-dodecadienamide (28).** To epoxy lactone **14** (500 mg, 2.4 mmol) at 0 °C was added dropwise aqueous dimethylamine (40%, 5 mL, 44 mmol). After being stirred for 1.5 h at 0 °C, the mixture was diluted with CH_2Cl_2, washed with water and brine solution, dried, and concentrated to give epoxy amide **28** (541 mg, 2.1 mmol, 90%) as a viscous yellow oil. Attempted chromatography (silica gel) led to decomposition of the epoxy amide, and the crude product was oxidized without further purification: IR ($CHCl_3$) 3400, 1650, 970 cm^{-1}; NMR ($CDCl_3$) δ 1.68 (m, 3 H), 1.77 (m, 2 H), 2.20 (m, 2 H), 2.69 (m, 2 H), 3.00 (s, 3 H), 3.14 (m, 1 H), 3.21 (s, 3 H), 3.25 (m, 1 H), 3.62 (d, J = 4 Hz, 1 H), 3.88 (m, 1 H), 5.48 (m, 4 H).

(±)-*N,N*-Dimethylcerulenin (29). To a suspension of Collins reagent (5.2 g, 20.0 mmol) in CH_2Cl_2 (90 mL) at 25 °C was added a solution of hydroxyepoxy amide **28** (0.52 g, 2.07 mmol) in CH_2Cl_2 (1 mL). The mixture was stirred for 3 h, diluted with ether, and filtered. The filtrate was concentrated, taken up in ether, washed successively with water and brine solution, dried, and concentrated, affording crude dimethylcerulenin **29** (0.34 g, 1.35 mmol, 65%) as a yellow oil. Flash chromatography (silica gel, 4/1 ether/benzene) provided pure **29** (0.18 g) as a very pale yellow oil: IR ($CHCl_3$) 1740, 1660, 970 cm^{-1}; NMR ($CDCl_3$) δ 1.66 (m, 3 H), 2.30 (m, 2 H), 2.65 (m, 4 H), 2.96 (s, 3 H), 3.16 (s, 3 H), 3.72 (d, J = 5 Hz, 1 H), 3.88 (d, J = 5 Hz, 1 H), 5.50 (m, 4 H); exact mass calcd m/e 251.1521, found m/e 251.1516.

4-Hydroxy-4-phenylbut-2-ynoic Acid (32). Methylmagnesium bromide (2.0 M, 200 mL, 0.6 mol) in dry THF was added at 0 °C to a mechanically stirred solution of propiolic acid (21.0 g, 0.3 mol) in dry THF (500 mL). After the mixture was stirred for 2 h at 0 °C, freshly distilled benzaldehyde (31.8 g, 0.3 mol) was added in one portion. The mixture was stirred for an additional hour and then allowed to warm to room temperature. The reaction mixture was diluted with ether (300 mL) and acidified (with cooling) to pH ~1 with 2 M H_2SO_4. The organic phase was extracted with excess 5% $NaHCO_3$, and the aqueous layer was acidified (pH ~1), extracted with CH_2Cl_2, dried, and concentrated to afford **32** as a white solid:[27] 45.0 g (0.26 mol, 85%); mp 88–90 °C; IR (Nujol) 2240, 1670 cm^{-1}; NMR ($CDCl_3$–Me_2SO-d_6) δ 5.53 (s, 1 H), 7.22–7.70 (m, 5 H), 8.43 (br s, 2 H); mass spectrum, m/e 176 (M^+), 132, 131.

4-Phenyl-2-butenoic Acid γ-Lactone (33). The acetylenic acid **32** (17.0 g, 96.6 mmol) in ethyl acetate (150 mL) was hydrogenated by using 5% Lindlar catalyst. After 15–30 min the reaction mixture was filtered through Celite and washed with ethyl acetate. The filtrate was concentrated at 50 °C and afforded **33** as an oily material:[28] 15.0 g (93.8 mmol, 97%); IR (neat) 1780,

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1750 cm^{-1}; NMR ($CDCl_3$) δ 5.92 (m, 1 H), 6.12 (dd, J = 6, 2 Hz, 1 H), 7.20–7.40 (m, 5 H), 7.48 (d, J = 2 Hz, 1 H); mass spectrum, m/e 160 (M^+) 131, 104, 77.

***cis*-2,3-Epoxy-4-phenylbutanoic Acid γ-Lactone (35).** To a suspension of tetramethylammonium bromide (1.7 g) in benzene (350 mL) containing butenolide **33** (17.35 g, 0.108 mol) was added aqueous NaOCl (5%, 455 mL, 0.03 mol). The progress of the reaction was monitored by ^{1}H NMR (the reaction was considered essentially complete when the two quartets for compounds **33** and **35** were approximately 1:2 by integration). The mixture was diluted with benzene (50–100 mL), washed several times with water, dried, and concentrated, yielding an oily product (10 g). Trituration with ether–hexane (2:1) gave the epoxy lactone **35** as a white solid: 6.40 g (0.037 mol, 35%); mp 70–71 °C. Some starting butenolide **33** was recovered from the mother liquor (~20%): IR (Nujol) 1770, 1180, 1060, 965, 870, 845 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.88 (m, 1 H), 4.12 (d, 1 H), 5.55 (d, J = 0.59 Hz, 1 H) 7.24–7.52 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 49.76 (C-3), 59.25 (C-2), 80.52 (C-4), 125.96, 129.30, 129.63, 134.64 (aromatic), 170.37 (C-1); mass spectrum, m/e 176 (M^+), 160, 147, 131, 105, 77, 51.

Anal. Calcd for $C_{10}H_8O_3$: C, 68.18; H, 4.58. Found: C, 68.06; H, 4.41.

***cis*-2,3-Epoxy-4-hydroxy-4-phenylbutyramide (36a).** Ammonium hydroxide (15% aqueous, 2.0 mL) was added to a mixture of **35** (0.1 g, 0.57 mmol) and tetramethylammonium bromide (10 mg) in $CHCl_3$ (20 mL) at 0 °C. The mixture was stirred for 30 min at 0 °C and 20 h at room temperature and then diluted with $CHCl_3$. The organic layer was dried and concentrated to give essentially pure **36a**: 0.1 g (0.52 mmol, 91%); mp 150–151 °C; IR (Nujol) 3400, 3240, 1670, 1050, 950, 850 cm^{-1}; NMR ($CDCl_3$–Me_2SO-d_6) δ 3.23 (dd, J_{ba} = 4.0 Hz, J_{bc} = 8.0 Hz, 1 H), 3.53 (d, J_{ab} = 4.0 Hz, 1 H), 4.53 (d, J_{cb} = 8.0 Hz, 1 H), 5.50 (br s, 1 H), 7.0–7.67 (m, 7 H); mass spectrum, m/e 193 (M^+) 140, 131, 120, 105, 77, 71, 59.

Anal. Calcd for $C_{10}H_{11}NO_3$: C, 62.16; H, 5.74; N, 7.25. Found: C, 62.08; H, 5.74; N, 6.99.

***cis*-2,3-Epoxy-4-oxo-4-phenylbutyramide (37a).** A solution of **36a** (0.1 g, 0.52 mmol) in CH_2Cl_2 (20 mL) was added in one portion to a red slurry of chromium trioxide–pyridine complex (1.14 g, 3.89 mmol) in CH_2Cl_2 (50 mL). The reaction mixture was stirred for 40 min at 25 °C, diluted with ether (50 mL), and filtered through Celite. The filtrate was washed with water, dried, and concentrated to afford **37a** as a light brown solid, 90 mg (0.47 mmol, 91%). Recrystallization from $CHCl_3$–hexance gave pure **37a**: 39 mg; mp 181–183 °C; IR (Nujol) 3420, 3170, 1680, 1235, 1000, 950 cm^{-1}; NMR ($CDCl_3$) δ 4.22 (AB q, J = 5.5 Hz, 2 H), 7.30–7.70 (m, 5 H), 7.82–8.10 (m, 2 H); mass spectrum, m/e 191 (M^+), 147, 105, 77.

Anal. Calcd for $C_{10}H_9NO_3$: C, 62.82; H, 4.75; N, 7.33. Found: C, 62.56; H, 5.72; N, 7.17.

(28) Nineham, A. W.; Raphael, R. A. *J. Chem. Soc.* **1949**, 118. Rao, Y. S. *Chem. Rev.* **1976**, *76*, 625.

***N,N*-Dimethyl-*cis*-2,3-epoxy-4-hydroxy-4-phenylbutyramide (36b).** Dimethylamine (1.06 g, 23.6 mmol) in $CHCl_3$–ether (1:1, 10 mL) was added to a solution of epoxybutyrolactone **35** (2.0 g, 10.8 mmol) in $CHCl_3$ (200 mL) at 0 °C. The reaction mixture was stirred for 90 min at 0 °C and 5 h at room temperature, diluted with water (50 mL), and extracted with $CHCl_3$. The organic layer was dried and concentrated, and the light yellow solid obtained was recrystallized from $CHCl_3$–ether–hexane, giving pure **36b**: 1.77 g (8.0 mmol, 74%); mp 97–98 °C; IR (Nujol) 3380, 1650, 1065, 990, 750 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.96 (s, 3 H), 3.12 (s, 3 H), 3.28 (dd, J_{ab} = 4.0 Hz, J_{bc} = 7.6 Hz, 1 H), 3.60 (d, J_{ab} = 4.0 Hz, 1 H), 4.07 (br s, 1 H), 4.33 (d, J_{cb} = 7.6 Hz, 1 H), 7.13–7.57 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 35.24, 36.70 ($N(CH_3)_2$), 54.29 (C-2), 6066 (C-3), 73.07 (OH carbon), 125.90, 127.90, 128.55, 140.85 (aromatic), 167.24 (amide); mass spectrum, m/e 221 (M^+), 204, 149, 77.

Anal. Calcd for $C_{12}H_{15}NO_3$: C, 65.14; H, 6.83; N, 6.33. Found: C, 65.25; H, 7.07; N, 6.27.

***N,N*-Dimethyl-*cis*-2,3-epoxy-4-oxo-4-phenylbutyramide (37b).** The 4-keto analogue **37b** was made from **36b** in 95% yield by essentially the same method as described for **37a**: mp 93–94 °C; IR (Nujol) 1690, 1650, 1600, 1235, 1140, 1070, 1000, 965, 920, 840 cm^{-1}; NMR ($CDCl_3$) δ 2.83 (s, 3 H), 3.2 (s, 3 H), 4.17 (AB q, J = 5.5 Hz, 2 H), 7.27–7.63 (m, 3 H), 7.83–8.13 (m, 2 H); CI mass spectrum (isobutane), m/e 220 (M^+H^+).

Anal. Calcd for $C_{12}H_{13}NO_3$: C, 65.74; H, 5.98; N, 6.39. Found: C, 65.28; H, 6.01; N, 6.08.

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Registry No. 1, 62964-96-9; 3, 64807-39-2; 4, 80663-04-3; 5, 6089-09-4; 6, 64807-32-5; 7, 64807-33-6; 8, 62964-98-1; 9, 62499-92-7; 9 2,4-DNP, 80663-05-4; 10, 80663-06-5; 11, 64807-38-1; 14, 80734-31-2; 15, 69854-91-7; 16, 80663-07-6; 17, 80663-08-7; 20, 124-19-6; 21, 64807-34-7; 22, 58949-91-0; 23, 80734-32-3; 24, 80734-33-4; 25, 64838-72-8; 26a, 80663-09-8; 26b, 80663-10-1; 26c, 80663-11-2; 27a, 80663-12-3; 27b, 80663-13-4; 27c, 80663-14-5; 28, 80663-15-6; 29, 80663-16-7; 32, 80663-17-8; 33, 70404-21-6; 35, 80734-34-5; 36a, 80663-18-9; 36b, 80663-19-0; 37a, 80663-20-3; 37b, 80663-21-4; *trans*-crotyl chloride, 4894-61-5; methyl propiolate, 922-67-8; propiolic acid, 471-25-0; (±)-(*E*,*E*)-4-hydroxy-7,10-dodecadien-2-ynamide, 80663-22-5; 4-oxododecanoic acid, 4144-55-2; benzaldehyde, 100-52-7; dimethylamine, 124-40-3; pyrrolidine, 123-75-1; piperidine, 110-89-4.