A Concise Synthesis of (+)-Cerulenin from a Chiral Oxiranyllithium

Neelakandha S. Mani and Craig A. Townsend*

Department of Chemistry, The Johns Hopkins University, Baltimore, Maryland 21218

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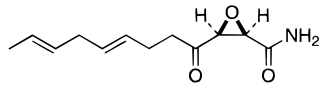
(+)-Cerulenin, a potent fungal inactivator of fatty acid synthases, has been prepared in optically pure form by a sequence involving reaction of a chiral oxiranyllithium with (4*E*,7*E*)-nonadienal. Synthesis of the former takes advantage of a particularly favorable Sharpless epoxidation and metalation to a configurationally stable organolithium, while the latter is available in quantity by a direct and improved route.

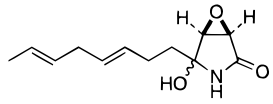
Introduction

Cerulenin (**1**) was discovered as an antimicrobial agent and is produced by the fungus *Cephalosporium caerulens*.[1] It is a low micromolar inactivator of the broad physical range of fatty acid synthases from the Type II particulate enzyme systems of bacteria[2,3] to the highly evolved Type I polyproteins of yeast, fungi, and animals.[3,4] Similarly, it inhibits the biosynthesis of polyketide-derived natural products in fermentation as, for example, leucomycin,[5] candicidin,[6] 6-methylsalicylic acid,[7] and alternariol.[8] Curiously, however, it has been reported to greatly stimulate the formation of aflatoxin, a potent acetogenic mycotoxin.[9] The mode of action of cerulenin has been determined with yeast fatty acid synthase, a mechanism thought to be general for this class of enzymes. Specific covalent reaction at the catalytic peripheral thiol in the β-ketoacyl synthase domain, a highly nucleophilic cysteine residue, has been shown to take place to form adduct **2** and prevent further chain elongation.[10] This catalytic locus carries out the characteristic two-carbon homologation of the growing fatty acid acyl chain bound to this reactive cysteine by decarboxylative Claisen condensation with malonyl-ACP.[11]

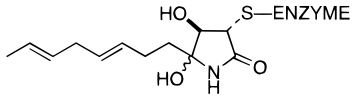
Among the distinguishing structural features of cerulenin are the *trans,trans*-1,4-diene-containing side chain, which plays an important role in favorable hydrophobic interaction within the enzyme active site,[12] and the unique keto *cis*-epoxy amide terminus. A striking property of this latter arrangement of functional groups is that in protic solvents cerulenin exists principally as a mixture of diasteromeric hydroxy lactams **1b**. Which of these possible open or closed forms is responsible for binding and adduct formation has been a matter of continued speculation.[13]



1a



1b



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Cerulenin has been the target of several racemic and enantioselective total syntheses.[14] A key intermediate in almost all of these is the epoxy lactone **3** from which cerulenin can be prepared in two steps, namely, ammonolysis to the hydroxy amide followed by oxidation of the secondary hydroxyl group (eq 1, Scheme 1). The linear syntheses, notably those of Boeckman[15] and Tishler,[16] focused on the construction of the lactone from an acetylenic precursor. Though efficient, these racemic syntheses are not well-suited for preparing structural analogues and also suffer from a difficult epoxidation

* Address correspondence to this author: Department of Chemistry, The Johns Hopkins University, Charles & 34th Streets, Baltimore, MD 21218. tel: 410-516-7444. fax: 410-516-8420. email: Townsend@jhunix.hcf.jhu.edu.

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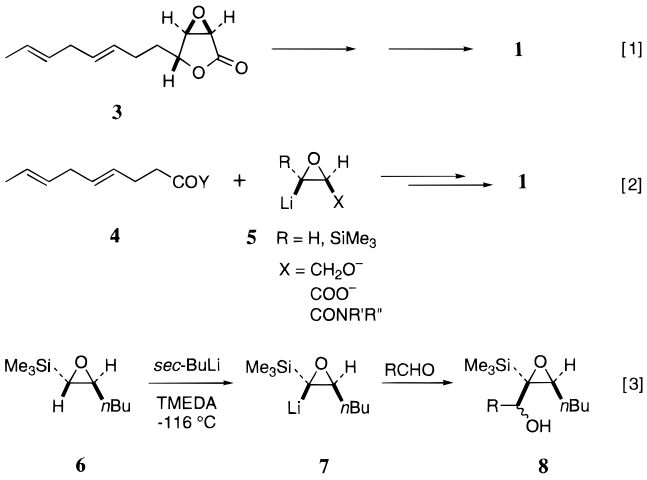
Scheme 1



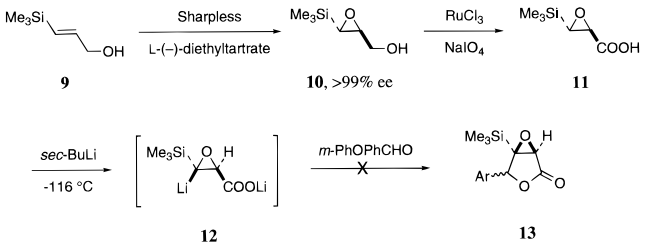
step. Natural cerulenin has been synthesized from glucose,[17] tartaric acid,[18] and using a Sharpless epoxidation to obtain a four-carbon synthon.[19] These lengthy approaches, however, suffer from poor overall yields.

A conceptually simpler and more efficient route to cerulenin would be direct addition of an elaborated electrophile **4** and a chiral oxiranyllithium derivative **5** (X = CH_2OR, CO_2H, $CONR_2$) as outlined in eqn 2 (Scheme 1). This approach moreover allows easy access to a variety of cerulenin structural analogues bearing modified side chains. Metalated oxiranes, considered once as fleetingly unstable intermediates, are emerging as useful synthons. Their potential was first demonstrated by Eisch and Galle[20] who showed that epoxides α-substituted with anion-stabilizing groups (silyl, carboxy, phenyl, *etc.*) can be metalated at low temperature (−110 to −78 °C) and trapped by electrophiles. Molander and Mautner[21] optimized conditions for metalation of trimethylsilyl-substituted epoxides at low temperature using *sec*-butyllithium in ether in the presence of TMEDA (eq 3, Scheme 1). They also showed that the silyl group subsequently can be removed with complete retention of configuration and in very good yield using the procedure of Chan.[22] We describe a synthesis of (+)-cerulenin stimulated by these developments, which, so far as we are aware, represents the first example in which a metalated oxirane intermediate is used in a natural product synthesis.

Results and Discussion

It was first thought that a glycidic acid **11** with a β-silyl substituent could be used to generate a dianion **12**, which upon treatment with an aldehyde would give the desired cerulenin skeleton at a synthetically useful oxidation state as outlined in Scheme 2. The starting material (*E*)-3-(trimethylsilyl)-2-propen-1-ol (**9**) was prepared in two

Scheme 2



steps from propargyl alcohol in high configurational purity (100% *E*) as reported.[23] Sharpless epoxidation using diethyl L-tartrate[24] furnished the silyl glycidol **10** in 85% yield. The enantiomeric purity of the product was estimated to be >99% based on comparison of its optical rotation with reported values of known optical purity.[24] Ruthenium tetraoxide-catalyzed oxidation[25] of the alcohol **10** furnished the corresponding carboxylic acid **11** in nearly quantitative yield. Treatment of this acid with 2 equiv of *sec*-butyllithium followed by *m*-phenoxybenzaldehyde, however, failed to give the hoped for condensation product **13**. Various solvent conditions such as ether, ether−THF, and Trapp mixture (hexane:ether:THF)[26] were tried without marked success. Considerable amounts of starting material were isolated in most trials, indicating that the desired dianion either had not formed or was not reactive. In light of these observations it was decided to carry out the condensation with a protected glycidol.

Protection of the hydroxyl group of **10** as the corresponding ethoxyethyl ethers was accomplished easily and in good yield using pyridinium *p*-toluenesulfonate (PPTS) as the catalyst.[27] The ethoxyethyl ether was selected because of the ease with which it can be removed and as a metalation stabilizing and directing group. As expected, the proton and carbon NMR spectra of the ether **14** clearly showed it to be a 1:1 mixture of the two possible diastereomers. Deprotonation of **14** by treatment with *sec*-butyllithium in presence of TMEDA at −116 °C generated the oxiranyllithium reagent, which was then reacted with (*E*,*E*)-4,7-nonadienal (**25**) to give the adduct **15** in 77% yield. The product thus obtained was found to be a mixture of all four possible diastereomers, indicating poor enantiofacial selectivity during the addition reaction in keeping with similar observations reported by Molander and Mautner.[21] Desilylation of the adduct **15** using Chan's method[22] cleanly furnished the desilylated product in 85% yield. Subsequent deprotection of the ethoxyethyl ether using PPTS in MeOH furnished the diol **16** in 77% overall yield as a mixture of diastereomers. The two diastereomers (2*S*,3*R*,4*R*)-**16** and (2*S*,3*R*,4*S*)-**16** were readily separated by flash column chromatography in a 55:45 ratio, respectively.

Oxidation of the diastereomeric diols **16** to the corresponding lactones **17** and **19** has been reported by Boeckman using Fetizon's reagent,[15] but heating either of the diols to reflux in benzene with Ag_2CO_3 on Celite

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(24) (2*S*,3*S*)-2,3-Epoxy-3-(trimethylsilyl)propan-1-ol (**10**) was prepared in high enantiomeric purity (99% ee) by the Sharpless asymmetric epoxidation of (*E*)-3-(trimethylsilyl)-2-propen-1-ol. For details on the preparation of **10** see: Kobayashi, Y.; Ito, T.; Yamakawa, I.; Urabe, H.; Sato, F. *Synlett.* **1991**, 811−812. Katsuki, T. *Tetrahedron Lett.* **1984**, 2821−2822.
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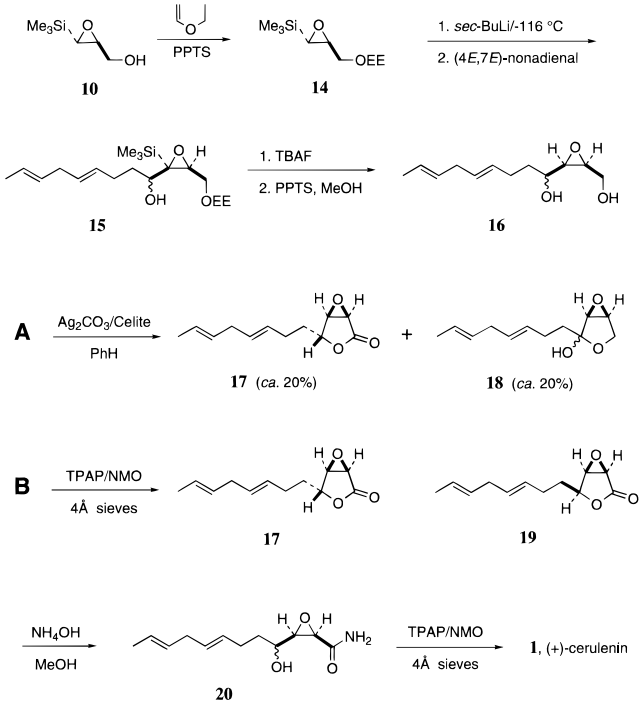
Scheme 3



afforded poor yields of the lactones in our hands (*ca*. 20%). A considerable amount of the product **18** arising from oxidation of the secondary alcohol was also observed (*ca*. 20%; reaction **A**, Scheme 3). Tetrapropylammonium perruthenate (TPAP)-catalyzed oxidation[28] proved most efficient in the oxidation of the diols to the corresponding lactones in very good yields. Thus, oxidation of (2*S*,3*R*,4*R*)-**16** by treatment with NMO and catalytic TPAP in CH_2Cl_2 at room temperature furnished the lactone **17** in 90% yield (reaction **B**, Scheme 3). Similarly, oxidation of the diastereomeric (2*S*,3*R*,4*S*)-**16** diol furnished **19** in 88% yield. Both of the diastereomeric lactones **17** and **19** have been synthesized previously, and the optical rotations and all spectral data were in agreement with the reported values.[29]

Conversion of the lactones **17** and **19** to cerulenin is well-precedented[29] and involves two steps: ammonolysis of the lactone to the hydroxy amide followed by oxidation. Treatment of the lactones **17** and **19** with aqueous ammonia furnished the hydroxy amides **20**. TPAP was found to be a better oxidizing agent for the final transformation to cerulenin compared to reported Collins oxidation.[16] Treatment with TPAP/NMO in CH_2Cl_2 at room temperature furnished cerulenin as a white solid in 80% yield. Analysis of the proton NMR spectrum showed the product to be an equilibrium mixture of the open and the closed hydroxy lactam structures, **1a** and **1b**, respectively. Crystallization from benzene−hexane at −20 °C furnished cerulenin in the open form as thin needles, mp 92−93 °C. Comparison of melting point, TLC mobility, optical rotation, and IR and NMR spectra with an authentic sample showed the synthetic product to be identical in all respects to natural (+)-cerulenin.

The skipped diene side chain of cerulenin was prepared by a conventional acetylene route outlined in Scheme 4 and is effective on a multigram scale. Alkylation of (trimethylsilyl)acetylene **21** with 2-(2-bromoethyl)-1,3-dioxolane furnished **22** in 78% yield. Coupling with crotyl bromide was carried out in one step by treatment with TBAF in the presence of Cu(I) as catalyst. Thus, treatment of a mixture of the acetylene **22** and crotyl bromide with TBAF (1 equiv) and $CuBr{\cdot}Me_2S$ (10 mol %) furnished the substituted acetylene **23** in 63% yield. Metal−ammonia reduction[16] of **23** using *tert*-butyl alcohol as proton donor furnished the (*E*,*E*)-diene **24** in excellent yield. Capillary GC analysis (methyl silicone, 12 m) of the skipped diene showed high isomeric purity (92% *E*,*E*). Deprotection of the cyclic acetal using 70% trifluoroacetic acid[22] furnished the desired aldehyde **25** in 83% yield.

In conclusion, an efficient synthesis of (+)-cerulenin has been developed employing a chiral oxiranyllithium reagent readily accessible on a large scale and in high enantiomeric purity. Beginning with readily available starting materials, the synthesis was completed in 12 steps with a longest linear sequence of 8 steps from **9** in 26% overall yield. The synthesis illustrates for the first time the utility of a chiral, metalated oxirane in natural product synthesis, an optically pure intermediate whose wider applicability is apparent.

Experimental Section

Melting points were determined in open capillaries using a Thomas-Hoover apparatus and are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded using a Varian Unity^{Plus} instrument (^{1}H at 400 MHz and ^{13}C at 100 MHz). Flash column chromatography was conducted using silica gel 60 (EM Science, 230−400 mesh ASTM).

(2*S*,3*S*)-2,3-Epoxy-3-(trimethylsilyl)propan-1-ol Ethoxyethyl Ether (14). To a solution of (2*S*,3*S*)-2,3-epoxy-3-(trimethylsilyl)propan-1-ol[24] (**10**; 0.76 g, 5.2 mmol) in dry CH_2Cl_2 (10 mL) was added ethyl vinyl ether (0.5 g, 5.9 mmol) followed by pyridinium *p*-toluenesulfonate (PPTS; 0.13 g, 0.5 mmol), and the resulting solution was stirred at rt. After 3 h, the reaction mixture was diluted with CH_2Cl_2 and washed successively with saturated aqueous $NaHCO_3$, water, and brine. The CH_2Cl_2 solution was dried over anhydrous $MgSO_4$, filtered, and evaporated under reduced pressure. The residue was purified by flash column chromatography (silica gel, ethyl acetate:hexanes 4:96) to yield the ethoxyethyl ether **14** (0.96 g, 4.4 mmol, 80.6%) as a colorless oil: IR (neat) 1250, 1134, 1085, 1058, 861, 841 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.00 (s, 9H), 1.12 (tt, 3H, J = 7.2 Hz), 1.25 (d, 1.5H, J = 5.6 Hz), 1.26 (d, 1.5H, J = 5.6 Hz), 2.02 (d, 0.5H, J = 3.6 Hz), 2.06 (d, 0.5H, J = 3.2 Hz), 2.93 (m, 1H), 3.28 (dd, 0.5H, J = 11.2 Hz), 3.39−3.47 (m, 1.5H), 3.56−3.64 (m, 1H), 3.67−3.83 (m, 1H), 4.74 (m, 1H); ^{13}C NMR ($CDCl_3$) δ −3.6, 15.2, 19.6, 19.8, 48.2, 48.4, 54.4, 54.6, 60.6, 60.9, 66.7, 67.4, 99.5, 99.6; exact mass calcd for $C_{10}H_{26}NO_3Si$ (M + NH_4^+) 236.1682, found 236.1687.

2-[4-(Trimethylsilyl)-3-butynyl]-1,3-dioxolane (22). To acetylene **21** (6 g, 61.2 mmol) in 100 mL of dry THF under an argon atmosphere at −78 °C was added in drops 2.5 M *n*-butyllithium (25 mL, 62.5 mmol) over 30 min. After stirring for 1.5 h at −78 °C, 25 mL of HMPA was added. To this reaction mixture was then added 7.4 mL (11.4 g, 63.0 mmol) of 2-(2-bromoethyl)-1,3-dioxolane over 15 min. The reaction mixture was allowed to warm slowly to rt, stirred overnight, and then quenched with saturated aqueous NH_4Cl (50 mL) and extracted with ether. The combined ethereal extracts were dried over anhydrous $MgSO_4$, filtered, and evaporated under reduced pressure. The crude product was purified by flash column chromatography (silica gel, ethyl acetate:hexanes 2:98) to obtain the dioxolane **22** (9.5 g, 0.048 mol, 78%) as a colorless oil: IR (neat) 2176, 1249, 1140, 842 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.06 (s, 9H), 1.78 (dt, 2H, J = 4.4, 7.2 Hz), 2.27 (t, 2H, J = 7.6 Hz), 3.78−3.91 (m, 4H), 4.89 (t, 1H, J = 4.8 Hz); ^{13}C NMR ($CDCl_3$) δ 0.08, 14.6, 32.8, 64.8, 84.5, 103.0, 106.1; exact mass calcd for $C_{10}H_{18}O_2Si$ 198.1076, found 198.1078.

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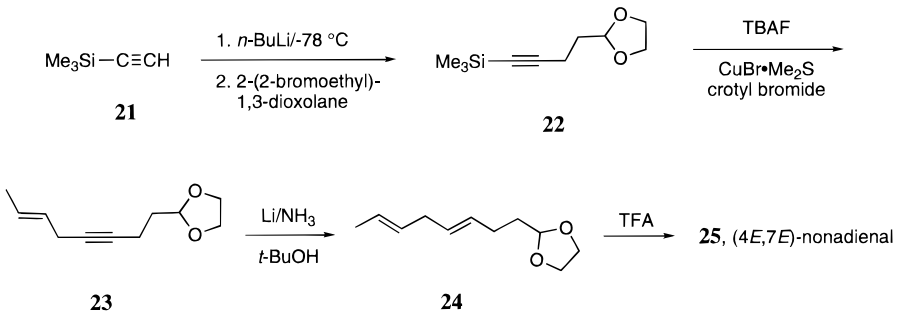
Scheme 4



Anal. Calcd for $C_{10}H_{18}O_2Si$: C, 60.57; H, 9.15. Found: C, 60.53; H, 9.37.

(6*E*)-2-(Oct-3-yn-6-enyl)-1,3-dioxolane (23). To a solution of dioxolane **22** (3 g, 15 mmol) in dry THF (75 mL) was added CuBr·Me_2S (0.3 g, 1.5 mmol) followed by freshly distilled crotyl bromide (1.9 mL, 18 mmol). The solution was cooled to −78 °C under argon and 1 M tetrabutylammonium fluoride in THF (16 mL, 16 mmol, freshly dried over neutral alumina for 30 min) was added dropwise over 30 min. After stirring for 1 h at −78 °C, the reaction mixture was allowed to warm to rt and left overnight. The reaction was quenched with saturated aqueous NH_4Cl and extracted with ether. The combined organic layers were then washed with brine and dried over anhydrous $MgSO_4$. After filtration, the solvents were removed under reduced pressure and the residue was purified by flash column chromatography (silica gel, ethyl acetate:hexanes 1:9) followed by distillation under reduced pressure to furnish **23** (1.71 g, 9.4 mmol, 63%) as a colorless liquid: bp 75−77 °C (0.35 mm); IR (neat) 2214, 1131, 1043 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.63 (dd, 3H, J = 1.6, 5.2 Hz), 1.81 (m, 2H), 2.26−2.30 (m, 2H), 2.78 (m, 2H), 3.78 (m, 2H), 3.85 (m, 2H), 4.95 (t, 1H, J = 5.2 Hz), 5.32 (m, 1H), 5.56 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 13.7, 17.6, 21.9, 33.3, 64.9, 77.9, 80.7, 103.31, 103.33, 125.7, 126.3; exact mass calcd for $C_{11}H_{17}O_2$ (M + H^+) 181.1229, found 181.1231.

(3*E*,6*E*)-2-(3,6-Octadienyl)-1,3-dioxolane (24). To ammonia (175 mL, freshly distilled over sodium) in a 500 mL, three-necked round-bottomed flask fitted with a cold-finger condenser was added in small portions ammonium sulfate (5 g) followed by *tert*-butyl alcohol (5 mL) and the alkyne **23** (3 g, 16.6 mmol). Lithium (wire, freshly cut, 0.35 g, 50 mmol) was cautiously added in small portions to the reaction mixture. After complete addition of the lithium, the reaction mixture was stirred for 15 min. The reaction was quenched by cautious addition of solid NH_4Cl (5 g), and the ammonia was allowed to evaporate. The residue was treated with water and then extracted with ether. The organic extracts were combined, washed with water and brine, and dried over anhydrous $MgSO_4$. After filtration, the solvents were removed under reduced pressure, and the residue was purified by distillation under reduced pressure to obtain the skipped diene **24** (2.9 g, 15.9 mmol, 95.6%) as a colorless liquid: bp 79−81 °C (0.6 mm); IR (neat) 1637, 1456, 1377, 1178, 1147 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.58 (dd, 3H, J = 1.2, 3.2 Hz), 1.63 (m, 2H), 2.02 (m, 2H), 2.60 (m, 2H), 3.78 (m, 2H), 3.95 (m, 2H), 4.80 (t, 1H, J = 5.2 Hz), 5.36−5.55 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 17.8, 26.9, 33.6, 35.4, 64.7, 104.0, 125.3, 129.0, 129.5, 129.6; exact mass calcd for $C_{11}H_{18}O_2$ 182.1307, found 182.1309. Capillary GC analysis (methyl silicone, 12 m; gradient 50 °C to 200 °C at 10 °C/min): >92% 3*E*,6*E*; the other three possible stereoisomers are present in roughly equal amounts totaling <8% of the mixture.

(4*E*,7*E*)-4,7-Nonadienal (25). To **24** (0.9 g, 4.94 mmol) cooled at 5 °C was added 70% aqueous trifluoroacetic acid (8 mL, precooled at 5 °C). The reaction flask was then stored at 5 °C for 1 day and then poured into a stirred mixture of saturated aqueous $NaHCO_3$ solution (25 mL) and ether. The layers were separated and the aqueous layer was further extracted with ether. The combined organic layers were washed with water and brine and dried over anhydrous $MgSO_4$. After filtration, the solvents were removed under reduced pressure, and the residue was purified by flash column chromatography (silica gel, ether:pentane 4:96) followed by distillation under reduced pressure to furnish the pure aldehyde **25** (0.61 g, 4.4 mmol, 89.4%) as a colorless liquid (unstable on storage at 4 °C): bp 85 °C (4.5 mm) [lit.[21] bp 50 °C (1.3 mm)]; IR (neat) 2959, 2718, 1727, 969 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.59 (brd, 3H, J = 4.8 Hz), 2.27 (m, 2H), 2.43 (m, 2H), 2.60 (m, 2H), 5.32−5.55 (m, 4H), 9.69 (t, 1H, J = 1.6 Hz); ^{13}C NMR ($CDCl_3$) δ 17.8, 25.0, 35.4, 43.3, 125.6, 128.2, 129.1, 130.1, 202.1; exact mass calcd for $C_9H_{18}NO$ (M + NH_4^+) 156.1388, found 156.1389.

(2*S*,3*R*,4*R*,7*E*,10*E*)-2,3-Epoxy-7,10-dodecadiene-1,4-diol and (2*S*,3*R*,4*S*,7*E*,10*E*)-2,3-Epoxy-7,10-dodecadiene-1,4-diol (16). A solution of silyl epoxide **14** (218 mg, 1 mmol) and TMEDA (0.18 mL, 1.2 mmol) in 24 mL of dry ether was cooled under an atmosphere of argon to −116 °C. To this was added dropwise *sec*-butyllithium (0.92 mL, 1.3 M, 1.2 mmol). After stirring at −116 °C for 4 h, a solution of aldehyde **25** (180 mg, 1.3 mmol) in 3 mL of ether was added through a cannula cooled at −78 °C. The reaction mixture was stirred at −116 °C for 1.5 h and then allowed to warm to rt. The reaction was quenched by the addition of 25 mL of saturated aqueous NH_4Cl and then extracted with ether. The combined extracts were washed with brine and dried over anhydrous $MgSO_4$. After filtration, the solvents were removed under reduced pressure, and the residue was purified by flash column chromatography (silica gel, ethyl acetate:hexanes 1:9) to afford the required epoxy alcohol **15** (0.274 g, 0.77 mmol, 77%) as a pale yellow oil. The epoxy alcohol was found to be a mixture of all four possible diastereoisomers and was not chromatographically separable. This mixture was, therefore, submitted to the desilylation reaction without further characterization.

A solution of epoxy alcohol **15** (150 mg, 0.421 mmol; diastereomeric mixture obtained as described above) in 5 mL of anhydrous DMSO was treated with TBAF (1 M in THF, 0.5 mL, 0.5 mmol) at rt. After stirring for 3 h, the reaction mixture was quenched with 10 mL of water and extracted with ether. The combined ethereal extracts were dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. The crude desilylated product was dissolved in 20 mL of dry methanol and then treated with PPTS (15 mg, 0.06 mmol). The solution was stirred at rt for 3 h and then concentrated under reduced pressure. The residue was dissolved in ethyl acetate, and this solution was washed with saturated aqueous $NaHCO_3$, water and brine and dried over anhydrous $MgSO_4$. After filtration, the solvents were removed under reduced pressure and the residue was purified by flash column chromatography (silica gel, 20 g; ether:hexanes 9:1, ether) to furnish the diastereomeric diols (2*S*,3*R*,4*R*)-**16** (38.35 mg, 0.18 mmol, 42.9%) and (2*S*,3*R*,4*S*)-**16** (30.45 mg, 0.14 mmol, 34.1%) (77% overall from **15**) as colorless oils. (2*S*,3*R*,4*R*)-**16**: $[\alpha]_D$ +33.8° (*c* 0.13, CH_2Cl_2); IR (neat) 3342, 1601, 1096, 1032, 961, 849 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.55−1.78 (m, 5H), 2.05−2.22 (m, 2H), 2.65 (m, 2H), 2.90 (dd, 1H, J = 4.4, 7.6 Hz), 3.16 (m, 1H), 3.55 (ddd, 1H, J = 4.4, 4.8, 8.0 Hz), 3.65 (dd, 1H, J = 6.8, 12.4 Hz), 3.97 (dd, 1H, J = 5.6, 12.0 Hz), 5.34−5.50 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 17.9, 28.2, 35.1, 35.5, 55.5, 58.8, 60.9, 69.5, 125.6, 129.4, 129.6, 129.8; exact mass calcd for $C_{12}H_{20}O_3Na$ (M + Na^+) 235.1310, found 235.1306. (2*S*,3*R*,4*R*)-**16**: $[\alpha]_D$ −14.6° (*c* 0.45, CH_2Cl_2); IR (neat) 3386, 1594, 1041, 967, 849 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.45−1.55 (m, 2H), 1.60 (m, 3H), 2.01 (m, 4H), 2.60 (m, 2H),

2.99 (dd, 1H, J = 4.4 Hz, 7.6 Hz), 3.22 (m, 1H), 3.54 (m, 1H), 3.64 (dd, 1H, J = 7.2, 12.4 Hz), 3.81 (dd, 1H, J = 3.2, 12.4 Hz), 5.34−5.55 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 17.8, 27.9, 33.7, 35.5, 57.9, 60.6, 60.8, 69.0, 125.6, 129.3, 129.4, 129.8; exact mass calcd for $C_{12}H_{24}O_3N$ ($M + NH_4^+$) 230.1756, found 230.1758.

(2*R*,3*R*,4*R*,7*E*,10*E*)-2,3-Epoxy-4-hydroxy-7,10,-dodecadienoic Lactone (17) and (2*R*,3*R*,4*S*,7*E*,10*E*)-2,3-Epoxy-4-hydroxy-7,10-dodecadienoic Lactone (19). A mixture of diol (2*S*,3*R*,4*R*)-**16** (70 mg, 0.33 mmol), *N*-methylmorpholine *N*-oxide (NMO; 120 mg, 1.02 mmol), and powdered molecular sieves (4 Å, 250 mg) in 15 mL of dry CH_2Cl_2 was stirred under argon at rt. Solid tetrapropylammonium perruthenate (TPAP; 11.5 mg, 0.1 mol %) was added to the reaction in one portion. The dark reaction mixture was stirred for 15 min when TLC showed complete conversion. The reaction was diluted with ether and filtered through a plug of silica gel. After removal of the solvents under reduced pressure, the crude product was purified by flash column chromatography (silica gel, 25 g; ethyl acetate:hexanes 14:86) to yield the desired lactone **17** (62 mg, 0.298 mmol, 90%) as a colorless oil: $[\alpha]_D$ +56.7° (*c* 0.025, $CHCl_3$), [lit.[17] $[\alpha]_D$ +56.5° (*c* 0.8, $CHCl_3$)]; IR (neat) 1789, 1191, 967, 855 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.65 (brd, 3H, J = 4.8 Hz), 1.71−1.78 (m, 2H), 2.11−2.35 (m, 2H), 2.62 (m, 2H), 3.76 (dd, 1H, J = 0.8, 2.4 Hz), 3.96 (d, 1H, J = 2.4 Hz), 4.57 (dd, 1H, J = 6.0, 7.2 Hz), 5.32−5.55 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 17.9, 27.2, 31.8, 35.5, 49.8, 58.0, 79.1, 125.9, 128.0, 129.0, 131.0, 170.2; exact mass calcd for $C_{12}H_{16}O_3$ 208.1099, found 208.1101.

In a similar fashion, TPAP oxidation of the (2*S*,3*R*,4*S*)-diastereoisomer (13.5 mg, 0.063 mmol) using NMO (24 mg, 2 mmol), molecular sieves (40 mg), and TPAP, (2.3 mg, 0.1 mol %) in CH_2Cl_2 (5 mL) furnished the lactone **19** (11.6 mg, 0.055 mmol, 88%) as colorless oil: $[\alpha]_D$ +33.5° (*c* 0.35, $CHCl_3$), [lit.[29] $[\alpha]_D$ +29.7° (*c* 0.175, $CHCl_3$)]; IR (neat) 1789, 1191, 967, 825 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.62 (m, 3H), 1.76−1.92 (m, 2H), 2.11−2.24 (m, 2H), 2.62 (m, 2H), 3.77 (d, 1H, J = 2.4 Hz), 4.06 (dd, 1H, J = 1.6, 2.4 Hz), 4.46 (ddd, 1H, J = 1.2, 6.4, 7.2 Hz), 5.32−5.55 (m, 4H); ^{13}C ($CDCl_3$) δ 17.9, 28.1, 29.4, 35.5, 50.7, 56.5, 78.5, 125.8, 128.4, 129.1, 130.7, and 170.2; exact mass calcd for $C_{12}H_{16}O_3$ 208.1099, found 208.1099.

(2*R*,3*R*,4*R*,7*E*,10*E*)-2,3-Epoxy-4-hydroxy-7,10-dodecadienamide (20). A solution of the lactone **17** (30 mg, 0.144 mmol) in methanol (0.6 mL) cooled to 0 °C was treated with 27% aqueous ammonium hydroxide (0.06 mL). After stirring for 3 h at 0 °C, the solution was diluted with CH_2Cl_2 and was washed with dilute HCl (0.5 N, 2 mL) and then distilled water. The solution was dried over anhydrous $MgSO_4$, filtered, and evaporated under reduced pressure. The crude product was purified by flash column chromatography (silica gel, 15 g; ethyl acetate:hexanes 1:1) to afford the known amide **20** (29.1 mg, 0.129 mmol, 90%) as white sticky solid: $[\alpha]_D$ +67.4° (*c* 0.24, $CHCl_3$) [lit.[22] $[\alpha]_D$ +65° (*c* 1.03, $CHCl_3$)]; IR (film) 3386, 1678, 1595, 1426, 1119, 1072, 1037, 967, 931 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.61 (m, 3H), 1.71 (m, 2H), 2.05−2.25 (m, 2H), 2.62 (m, 2H), 2.70 (brs, ^{1}H), 3.13 (dd, 1H, J = 4.8, 8.1 Hz), 3.42−3.50 (m, 2H), 5.30−5.55 (m, 4H), 6.27 (brs, 1H), 6.51 (brd, 1H); ^{13}C NMR ($CDCl_3$) δ 17.9, 27.8, 34.6, 35.5, 54.2, 60.0, 67.9, 125.5, 129.4, 129.5, 129.7, 170.5.

(+)-Cerulenin (1). To a mixture of amide **20** (20 mg, 0.088 mmol), powdered molecular sieves (4 Å, 200 mg), and NMO (31.2 mg, 0.27 mmol) in 2 mL of anhydrous CH_2Cl_2 was added solid TPAP (3.1 mg, 0.1 mol %) in one portion. After stirring at rt under argon for 1 h, the dark suspension was diluted with ether and filtered through a plug of silica gel. Evaporation of the solvents under reduced pressure followed by flash column chromatography (silica gel, 10 g; ethyl acetate:hexanes 2:3) furnished cerulenin (**1**, 15.7 mg, 0.07 mmol, 80%) as a white solid. Recrystallization from benzene−hexanes furnished thin needles: mp 92−93 °C (lit.[17] mp 93−94 °C). TLC mobility, optical rotation, melting point, and NMR analysis of the crystalline product was found to be identical to that of an authentic sample natural cerulenin (**1**): $[\alpha]_D$ +62.3° (*c* 0.14, MeOH), [lit.[11] $[\alpha]_D$ + 62.0° (*c* 0.15, MeOH)]; ^{1}H NMR ($CDCl_3$) δ 1.65 (dd, 3H, J = 1.2, 4.8 Hz), 2.30 (m, 2H), 2.58−2.73 (m, 4H), 3.71 (d, 1H, J = 5.2 Hz), 3.85 (d, 1H, J = 5.2 Hz), 5.31−5.52 (m, 5H), 6.28 (b, 1H); exact mass calcd for $C_{12}H_{21}N_2O_3$ ($M + NH_4^+$) 241.1552, found 241.1555.

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Supporting Information Available: ^{13}C{^{1}H}NMR spectra of **14**, **16** (each diastereomer), **23**, and **24** are provided as well as a capillary GC trace of **24** (6 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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