# Synthesis of 4-Alkyl-4-alkoxybutenolides Having Unsaturated Side Chains via Chromium Carbene Complex Photochemistry: (+)-Cerulenin

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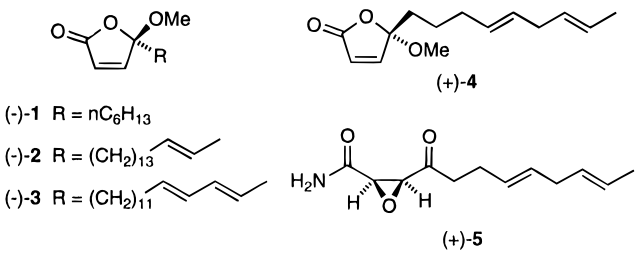
*Received April 9, 1996*[⊗]

The photochemical reaction between optically active ene carbamates and chromium alkoxycarbene complexes containing unsaturated aliphatic side chains was further developed. Although remote olefinic groups, including conjugated dienes, were tolerated, a homoallylic side chain underwent intramolecular reaction to give a strained cyclobutanone. (+)-Cerulenin was synthesized utilizing the photochemical reaction of an alkynylcarbene complex with an optically active ene carbamate and the bis($\pi$-crotyl)nickel halide alkylation of a vinyl bromide as key steps.

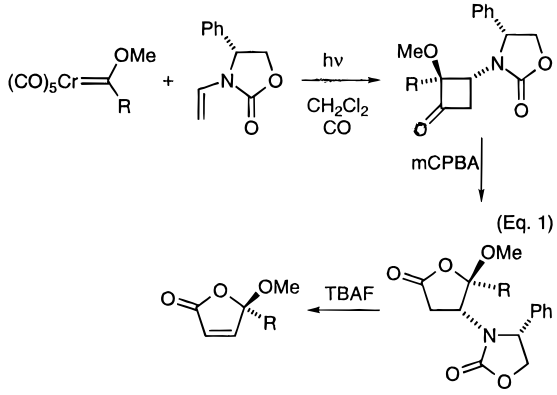
## Introduction

Optically active butenolides **1**−**3** having a 5-alkoxy substituent in addition to a long saturated or unsaturated aliphatic side chain at the same position have been isolated from the marine sponge *Plakortis lita*.[1] The related (racemic) butenolide **4** was used as a key intermediate in the synthesis of (racemic) cerulenin **5**,[2] an antifungal antibiotic. Synthetic approaches to optically active 4-alkoxy-4-alkylbutenolides are somewhat limited and involve either a resolution at some stage[3] or the oxidation of carbohydrate-derived furan derivatives.[4] We have recently developed a quite different approach to this class of compounds[5] and have used it to synthesize optically active butenolides (−)-**1** and (−)-**2**, as well as (+)-tetrahydrocerulenin.[6] Below we describe its use in an approach to diene-containing butenolide (−)-**3** and in the total synthesis of (+)-cerulenin **5**.




## Results and Discussion

The general approach to optically active 4-alkoxy-4-alkylbutenolides involves the photochemical reaction of chromium alkoxycarbene complexes with optically active ene carbamates, followed by Baeyer−Villiger oxidation of the resulting cyclobutanones and oxazolidine elimination (eq 1). The reaction is highly diastereoselective, giving cyclobutanones having the large R group and the oxazolidinone group *syn*,[7] with the absolute configuration being determined by the oxazolidinone chiral auxilliary. Since the successful synthesis of (−)-**2** by this methodology had demonstrated that remote olefinic groups were tolerated, the approach appeared applicable to the synthesis of (−)-**3** as well.




(Eq. 1)

The conjugate diene side chain required for (−)-**3** was synthesized as shown in Scheme 1. (*E*,*E*)-2,4-Hexadienal was complexed to iron carbonyl[8] to allow clean reaction at the aldehyde center, and the resulting complex **6** was alkylated with the THP ether of 10-lithiodecanol (from lithiation of the corresponding iodide). Reduction of the allylic alcohol **7** followed by decomplexation gave the free (*E*,*E*)-12,14-hexadienol **9**. The requisite organolithium reagent was prepared by mesylation followed by displacement with iodide and halogen metal exchange with *tert*-butyllithium. Reaction with chromium hexacarbonyl followed by trimethyloxonium tetrafluoroborate produced carbene complex **11**. Photolysis of **11** in the presence of (*R*)-ene carbamate **12** produced cyclobutanone **13** in fair yield with ≥95% de. However, all attempts to effect a Baeyer−Villiger oxidation to the lactone (*m*-CPBA, $^t$BuOOH/NaOH, $H_2O_2/CF_3CH_2OH$) resulted in competitive to exclusive oxidation of the diene unit. Thus, synthesis of (−)-**3** was abandoned.

Since previous studies[6] had shown that nonconjugate alkenes in the side chain tolerated Baeyer−Villiger oxidation, attention was turned to the synthesis of (+)-

[⊗] Abstract published in *Advance ACS Abstracts,* August 1, 1996.

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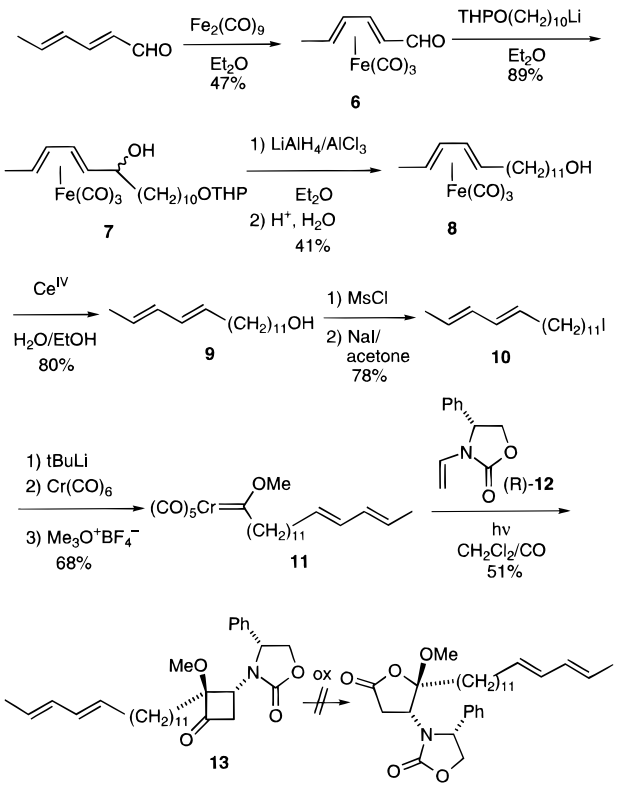
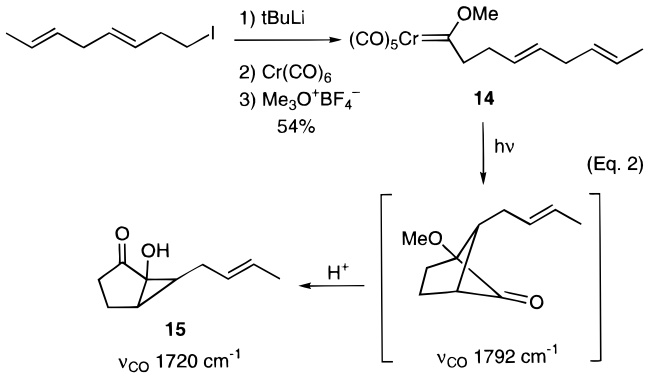
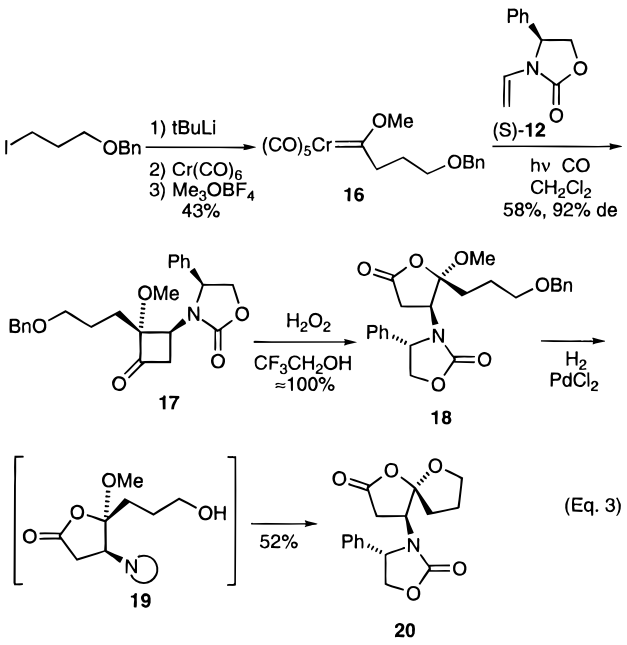
S0022-3263(96)00664-0 CCC: $12.00 

**Scheme 1. Attempted Synthesis of (−)-3**




cerulenin (**5**) via butenolide (+)-**4**. The requisite carbene complex **14** was synthesized in the usual manner (eq 2).[9] Photolysis of **14** in both the presence and absence of ene carbamate **12** led to the *same* product, which was very unstable and rearranged upon acid workup to give cyclopentanone **15**.[10] This product resulted from the internal alkene being close enough to intramolecularly trap the photochemically generated ketene, producing the unstable cyclobutanone, which subsequently underwent an acid-catalyzed pinacol rearrangement, producing cyclopentanone **15**. Thus, although remote olefinic groups were tolerated by the photochemical reaction, those within "striking distance" of the photogenerated ketene were not, necessitating the installation of the requisite alkene after the photochemical reaction. To that end, carbene complex **16** was photolyzed with ene carbamate (*S*)-**12** to give cyclobutanone **17** in fair yield and with good diastereoselectivity (eq 3). Baeyer−Villiger oxidation cleanly afforded butyrolactone **18**. The *O*-benzyl group was removed hydrogenolytically, preparatory to oxidation to provide an aldehyde for the introduction of the side chain by a Wittig reaction. However, upon deprotection, the alcohol **19** spontaneously cyclized to a single diastereoisomer of spiroketal **20**, a process which precluded further use.




Finally, a successful route to (+)-cerulenin was devised and carried out (Scheme 2), utilizing an alkynyl group as a masked aldehyde. Although many of the steps are straightforward, some warrant comment. Previous studies[11] had shown that alkynes did not undergo photocycloaddition with chromium carbene complexes, either inter- or intramolecularly, and, as expected, the conversion of alkynylcarbene complex **21** to cyclobutanone **22** went without interference from side chain reactivity. Clean reduction of the alkyne **24** to the alkene **25** was problematic, with overreduction occurring readily. The use of Mn(II)-modified Lindlar's catalyst[12] provided the best results. Ozonolysis was uneventful, and the chromous chloride promoted iodomethylenation (**26** → **27**) provided excellent yields of pure trans vinyl iodide. The final olefinic portion of the side chain was appended using ($\pi$-crotyl)nickel bromide complex chemistry.[13] This little used reagent is almost unique among crotyl metal reagents in that coupling occurs almost exclusively at the *less* substituted terminus, giving the required connectivity for cerulenin. As previously observed,[2,6] epoxidation of the butenolide was highly stereoselective (only a single isomer was detected in the crude reaction mixture) but proceeded in only modest yield and conversion. Treatment of butenolide **29** with gaseous ammonia produced (+)-cerulenin,[14] in overall 11% yield from carbene complex **21** (8% from butynol). This is comparable to three of the four other published syntheses of (+)-cerulenin, two from an intermediate (no yield or procedure reported)

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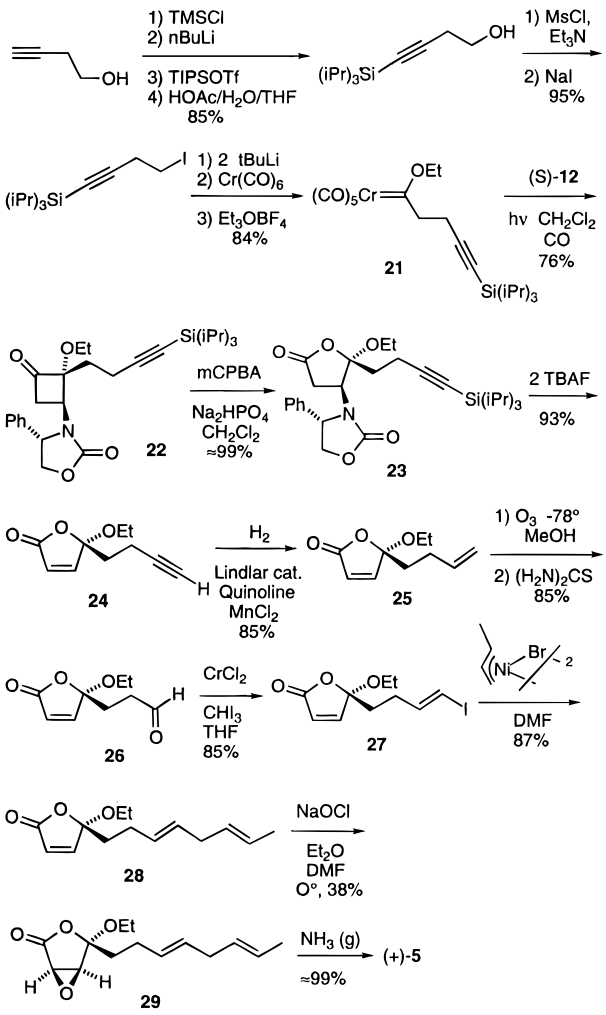
**Scheme 2. Synthesis of (+)-Cerulenin**




derived from *d*-glucose in 6.7%[15] and 8%[16] yields, respectively, and one from Sharpless epoxidation of *cis*-2-butene-1,4-diol in 3.3% yield.[17] The most efficient synthesis remains that of Yoda[18] from D-tartaric acid, in overall 12.3% yield.

## Experimental Section

**General Methods.** Optical rotations were obtained on a Perkin-Elmer 24 polarimeter at a wavelength of 589 nm (Na D line) with a 1.0 dm cell with a total volume of 1 mL. Specific rotation ($[\alpha]_D$) was reported in degrees per decimeter at the specified temperature and the concentration (c) given in grams per 100 mL in the specified solvent. Photolysis reactions were carried out in pressure tubes with size 15 Ace-Thread placed at a distance of 10 cm from a Conrad-Hanovia 7825 medium pressure mercury lamp operating at 450 W, which was placed in a water-cooled immersion well (Pyrex). A Conrad-Hanovia 7830-C power supply was used for the mercury lamp. Reactions which were run under CO pressure were saturated with CO (three cycles, 50−80 psi) and were photolyzed under 60−70 psi of CO. NMR spectra (300 MHz for $^1$H and 75 MHz for $^{13}$C) were recorded in $CDCl_3$, and chemical shifts are reported in $\delta$ relative to $CDCl_3$ ($\delta$ 7.24 for $^1$H and $\delta$ 77.0 for $^{13}$C) unless otherwise noted.

**Materials.** The following compounds were prepared according to literature methods: (*S*)-phenylglycinol,[21] [(methoxy)(methyl)carbene]pentacarbonyl chromium(0),[22] 3-vinyl-(*S*)-4-phenyl-2-oxazolidinone (**43**),[23] nickel bis(cyclooctadiene),[24] and ($\eta^3$-crotyl)nickel bromide.[25]

**((*E*,*E*)-2,4-Hexadienal)iron Tricarbonyl (6).**[8] (*E*,*E*)-2,4-Hexadienal (1.9 g, 20 mmol) and $Fe_2(CO)_9$ (8.7 g, 24 mmol) in $Et_2O$ (100 mL, degassed) were heated at 40 °C under argon for 16 h, cooled, and filtered through basic $Al_2O_3$, and the solvent was removed under reduced pressure. Purification via Kugelrohr distillation gave 2.2 g (47%) of **6** as an orange oil: $^1$H NMR $\delta$ 1.23 (m, 1H), 1.48 (d, 3H, $J$ = 6.3 Hz), 1.67 (m, 1H), 5.27 (dd, 1H, $J$ = 5.0, 8.9 Hz), 5.74 (ddd, 1H, $J$ = 1.1, 4.9, 6.0 Hz), 9.23 (d, 1H, $J$ = 4.4 Hz).

**Tetrahydro-2-[(10-bromodecanyl)oxy]-2*H*-pyran.** 10-Bromodecanol (5.0 g, 21 mmol), dihydropyran (2.3 mL, 25 mmol), and $CH_2Cl_2$ (50 mL) were cooled to 0 °C, and TsOH (5 mg) was added at 0 °C. The reaction mixture was stirred at 0 °C (15 min) and then warmed to 25 °C and stirred at 25 °C for 1 h. The reaction mixture was washed with saturated $NaHCO_3$(aq), dried over $MgSO_4$, filtered, and concentrated under reduced pressure to give the crude bromide. Purification via Kugelrohr distillation gave 6.7 g (100%) of the bromide as a colorless oil, bp = 120 °C (0.45 mmHg): $^1$H NMR $\delta$ 1.2−1.9 (m, 22H), 3.37 (m, 1H), 3.38 (t, 2H, $J$ = 6.5 Hz), 3.50 (m, 1H), 3.70 (m, 1H), 3.85 (m, 1H), 4.55 (t, 1H, $J$ = 2.8 Hz).

**Alkylation of Dienal Complex 6 To Produce Complex 7.** *tert*-Butyllithium (12 mL, 1.7 M in pentane) was added to tetrahydro-2-[(10-bromodecanyl)oxy]-2*H*-pyran (3.4 g, 9.3 mmol) and $Et_2O$ (90 mL) at −78 °C, and the mixture was stirred at −78 °C (5 min) and then warmed to 25 °C and stirred at 25 °C (1 h). The resulting solution was transferred via a cannula to a 200 mL Airless flask containing the Fe−dienal complex **6** (2.2 g, 9.3 mmol) in $Et_2O$ (30 mL) at −78 °C. The mixture was stirred at −78 °C (0.5 h), warmed to 0 °C, and stirred at that temperature (0.5 h). The mixture was partitioned between $NH_4Cl$(aq) (100 mL) and $Et_2O$ (100 mL), and the organic layer was washed with brine and dried over $MgSO_4$. Filtration and concentration under reduced pressure gave the crude complex. Purification via flash chromatography (3/1 hexanes/EtOAc, $SiO_2$) gave 3.4 g (89%) of the complex **7** as an orange oil: $^1$H NMR $\delta$ 1.1−1.9 (m, 27H), 1.38 (d, 3H, $J$ = 6.2 Hz), 3.4−3.5 (m, 3H), 3.69 (dt, 1H, $J$ = 6.9, 9.5 Hz), 3.85 (m, 1H), 4.55 (d, 1H, $J$ = 2.8 Hz), 5.02 (dd, 1H, $J$ = 5.0, 8.8 Hz), 5.19 (dd, 1H, $J$ = 4.9, 8.4 Hz).

**((*E*,*E*)-12,14-Hexadien-1-ol)iron Tricarbonyl (8).**[19] Lithium aluminum hydride (320 mg, 8.4 mmol) was added in portions to $AlCl_3$ (4.5 g, 33 mmol) in 150 mL of ether at 0 °C in a 500 mL Airless flask. The grey mixture was stirred at 0 °C (15 min), and complex **7** (4.0 g, 8.3 mmol) in $Et_2O$ (30 mL) was added to the reaction mixture and stirred at 0 °C (10 min). The reaction was quenched with slow addition of $H_2O$ (10 mL) at 0 °C. The organic layer was washed with saturated $NH_4Cl$(aq) and brine and then dried over $MgSO_4$. Filtration and concentration under reduced pressure gave a dark orange oil. Purification via flash chromatography (3/1 hexanes/EtOAc, $SiO_2$) gave 1.3 g (41%) of **8** as an orange oil: $^1$H NMR $\delta$ 1.0−1.6 (m, 25H), 3.61 (q, 3H, $J$ = 4.8 Hz), 4.96 (d, 2H, $J$ = 7.6 Hz); $^{13}$C NMR $\delta$ 19.08, 25.69, 29.19, 29.37, 29.48, 29.52, 31.84, 32.10, 32.73, 34.16, 56.92, 62.92, 63.96, 83.68, 84.83, 212.79; IR (film) $\nu$ 3361, 2039, 1964 cm$^{-1}$.

**(*E*,*E*)-12,14-Hexadien-1-ol (9).** Complex **8** (1.3 g, 3.4 mmol) was taken up in EtOH (30 mL) and cooled to −40 °C, and ceric ammonium nitrate (7.50 g, 13.6 mmol) in $H_2O$/EtOH (30 mL, 1/1) was added to the mixture in portions at −40 °C. When the color persisted, no more oxidant was added. The

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reaction mixture was stirred for an additional 10 min and then partitioned between saturated $NaHCO_3$(aq) (100 mL) and $Et_2O$ (100 mL), the aqueous layer was extracted with $Et_2O$ (2 × 100 mL), and the combined $Et_2O$ layers were washed with saturated $NaHCO_3$(aq) and brine and then dried over $MgSO_4$. Filtration and concentration under reduced pressure gave a white solid. Purification via flash chromatography (2/1 hexanes/EtOAc, $SiO_2$) gave 650 mg (80%) of **9** as a white solid: $^1$H NMR $\delta$ 1.24 (m, 16H), 1.55 (m, 2H),1 .71 (d, 3H, $J$ = 6.2 Hz), 2.00 (q, 2H, $J$ = 7.0 Hz), 3.62 (bt, 3H, $J$ = 5.4 Hz), 5.55 (m, 2H), 6.00 (m, 2H); $^{13}$C NMR $\delta$ 17.95, 25.71, 29.17, 29.40, 29.47, 29.54, 32.53, 32.78, 63.06, 126.60, 130.15, 131.70, 132.18; IR (film) $\nu$ 3330 cm$^{-1}$.

**(*E*,*E*)-1-Iodo-12,14-hexadiene (10).** Alcohol **9** (650 mg, 2.7 mmol) and $Et_3N$ (0.43 mL, 3 mmol) in $CH_2Cl_2$ (50 mL), cooled to 0 °C, and methanesulfonyl chloride (0.23 mL, 3.0 mmol) were added. The mixture was warmed to 25 °C and stirred at that temperature (2 h), washed with saturated $NH_4Cl$(aq), and dried over $MgSO_4$. Filtration and concentration under reduced pressure gave 780 mg (91%) of the mesylate as a white solid: $^1$H NMR $\delta$ 1.24 (m, 16H), 1.72 (d, 3H, $J$ = 9.1 Hz), 1.75 (m, 2H), 2.01 (q, 2H, $J$ = 6.6 Hz), 2.97 (s, 3H), 4.19 (t, 2H, $J$ = 6.6 Hz), 5.55 (m, 2H), 6.00 (m, 2H); $^{13}$C NMR $\delta$ 17.87, 25.29, 28.89, 29.00, 29.04, 29.13, 29.30, 29.35, 29.39, 32.43, 37.18, 70.13, 126.47, 130.09, 131.62, 132.03. This material was used without further purification.

The mesylate (780 mg, 2.50 mmol) and NaI (4.0 g, 27 mmol) were heated at reflux (14 h) in acetone. The mixture was partitioned between hexanes and $H_2O$, the aqueous layer was extracted with hexanes, and the combined hexane layers were washed with 10% $Na_2S_2O_3$(aq) and brine and then dried over $MgSO_4$. Filtration and concentration under reduced pressure gave 810 mg (86% from the alcohol) of **10** as a yellow oil: $^1$H NMR $\delta$ 1.24 (m, 16H), 1.70 (d, 3H, $J$ = 6.3 Hz), 1.79 (quint, 2H, $J$ = 6.9 Hz), 2.01 (q, 2H, $J$ = 6.9 Hz), 3.16 (t, 2H, $J$ = 7.1 Hz), 5.55 (m, 2H), 5.95 (m, 2H); $^{13}$C NMR $\delta$ 7.16, 17.96, 28.49, 29.13, 29.37, 29.44, 29.48, 29.61, 30.46, 32.51, 33.52, 126.49, 130.15, 131.68, 132.07. This material was used without further purification.

**Dienyl Carbene Complex 11.** *tert*-Butyllithium (2.8 mL, 1.7 M in pentanes) was added to iodide **10** (0.81 g, 2.33 mmol) at −78 °C in 25 mL of $Et_2O$, and the resulting homogeneous, yellow solution was stirred at −78 °C (0.5 h). The mixture was warmed to 25 °C, stirred at that temperature (1 h), and then added via a cannula to $Cr(CO)_6$ (506 mg, 2.33 mmol) in $Et_2O$ (40 mL). The yellow-brown solution was stirred at 25 °C (16 h). The solvent was removed under reduced pressure, the residue was taken up in $H_2O$ (50 mL), and $Me_3OBF_4$ was added until the solution was acidic (pH = 2). The aqueous layer was extracted with $Et_2O$ (3 × 50 mL), and the combined $Et_2O$ layers were washed with brine and dried over $MgSO_4$. Filtration and concentration under reduced pressure gave an orange oil. Purification via flash chromatography (9/1 hexanes/$Et_2O$, $SiO_2$) gave 720 mg (68%) of **11** as an orange oil: $^1$H NMR $\delta$ 1.21 (m, 16H), 1.4 (m, 2H), 1.70 (d, 3H, $J$ = 6.3 Hz), 2.01 (q, 2H, $J$ = 6.9 Hz), 3.27 (t, 2H, $J$ = 7.5 Hz), 4.74 (s, 3H), 5.55 (m, 2H), 5.95 (m, 2H); $^{13}$C NMR $\delta$ 17.92, 26.31, 29.19, 29.23, 29.38, 29.44, 29.53, 29.66, 32.55, 63.08, 67.48, 126.51, 130.23, 131.77, 132.10, 216.41, 223.13, 363.78; IR (film) $\nu$ 2062, 1930 cm$^{-1}$.

**Dienyl Cyclobutanone 13.** The dienyl carbene complex **11** (722 mg, 1.58 mmol) and (*R*)-ene carbamate **12** (150 mg, 0.79 mmol) in $CH_2Cl_2$ (15 mL) were placed in an Ace pressure tube which was charged with CO (60 psi) and irradiated at 25 °C for 16.5 h. The solvent was removed under reduced pressure, and $Cr(CO)_6$ was recovered by sublimation from the crude reaction mixture. Purification via flash chromatography (4/1, 2/1 hexanes/EtOAc, $SiO_2$) gave 190 mg (51%) of **13** as a colorless oil which solidified upon standing: $^1$H NMR $\delta$ 1.24 (m, 18H), 1.70 (d, 3H, $J$ = 6.5 Hz), 1.82 (m, 2H), 2.02 (q, 2H, $J$ = 6.9 Hz), 2.51 (dd, 1H, $J$ = 10.1, 17.9 Hz), 3.15 (s, 3H), 3.21 (dd, 1H, $J$ = 9.6, 18.1 Hz), 4.19 (dd, 1H, $J$ = 4.8, 8.7 Hz), 4.34 (t, 1H, $J$ = 9.7 Hz), 4.67 (t, 1H, $J$ = 8.6 Hz), 4.87 (dd, 1H, $J$ = 4.9, 8.4 Hz), 5.54 (m, 2H), 5.98 (m, 2H), 7.25 (m, 2H), 7.39 (m, 3H); $^{13}$C NMR $\delta$ 17.92, 23.04, 29.13, 29.38, 29.44, 29.51, 29.76, 29.90, 32.49, 42.57, 47.30, 52.38, 61.55, 70.03, 98.75, 126.38, 126.53, 129.32, 129.49, 130.13, 131.68, 132.15, 138.73, 157.81, 205.67; IR (film) $\nu$ 1788, 1751 cm$^{-1}$. Anal. Calcd for $C_{30}H_{43}NO_4$: C, 74.84; H, 8.93; N, 2.91. Found: C, 74.56; H, 9.02; N, 3.10.

**[(Methoxy)(1-(*E*,*E*)-3,6-octadienyl)carbene]pentacarbonyl Chromium(0) (14) and Photolysis To Produce 15.** *tert*-Butyllithium (1.2 mL, 1.7 M in pentanes) was added dropwise to (*E*,*E*)-1-iodo-3,6-octadiene[9] (0.24 g, 1.00 mmol) in 1 mL of $Et_2O$ at −78 °C, and the yellow solution was stirred at −78 °C for 40 min, warmed to room temperature, and stirred at that temperature for 1 h. This solution was added via a cannula to $Cr(CO)_6$ (0.22 g, 1.00 mmol) and $Et_2O$ (5 mL). The dark brown solution was stirred at room temperature for 3 h, and the volatiles were removed under reduced pressure. The brown residue was taken up in $H_2O$ (15 mL), and $Me_3OBF_4$ was added until the solution was acidic (pH = 2). The mixture was extracted with $Et_2O$ (5 × 10 mL), the combined $Et_2O$ layers were dried over $MgSO_4$, and filtration and concentration under reduced pressure gave the crude carbene complex. Purification via flash chromatography (9/1 hexanes/EtOAc, $SiO_2$) gave 190 mg (54%) of **14** as an orange oil: $^1$H NMR $\delta$ 1.63 (d, 3H, $J$ = 5.0 Hz), 2.16 (app q, 2H, $J$ = 6.4, 14.4 Hz), 2.63 (m, 2H), 3.35 (t, 2H, $J$ = 7.6 Hz), 4.76 (s, 3H), 5.5 (m, 4H); $^{13}$C NMR $\delta$ 17.84, 29.34, 35.43, 62.52, 67.58, 125.75, 128.16, 129.21, 130.38, 216.32, 223.13, 362.95; IR (film) $\nu$ 2062, 1920 cm$^{-1}$. Photolysis of this complex, both in the presence and absence of substrate, led to the same unstable compound with an absorption in the infrared spectrum at $\nu$ 1792 cm$^{-1}$, characteristic of cyclobutanones. Stirring an ether solution of a small portion of this material with 5% aqueous HCl converted it to a new compound (crude yield ≈ 80%), assigned as **15** on the basis of spectral data and subsequent studies:[10] $^1$H NMR $\delta$ 5.50 (m, 2H), 2.88 (br s, 1H), 2.26−2.11 (m, 4H), 1.87 (m, 2H), 1.65 (d, 3H, $J$ = 4.0 Hz), 1.62 (m, 1H), 1.34 (dt, 1H, $J$ = 4.1, 7.0 Hz); $^{13}$C NMR $\delta$ 213.4, 129.2, 125.9, 70.3, 32.7, 30.9, 30.3, 29.9, 21.6, 17.9; IR (film) $\nu$ 3366, 1718 cm$^{-1}$; MS $m/e$ 166 ($M^+$).

**[(Methoxy)(3-(benzyloxy)propyl)carbene]pentacarbonyl Chromium(0) (16).** *tert*-Butyllithium (4.4 mL, 1.7 M in pentanes) was added to 3-(benzyloxy)iodopropane (1.0 g, 3.6 mmol) in 10 mL of ether at −78 °C, and the resulting homogeneous, yellow solution was stirred at −78 °C (10 min) and then warmed to 25 °C and stirred at that temperature (1 h). This solution was added via a cannula to $Cr(CO)_6$ (0.79 g, 3.60 mmol) in $Et_2O$ (20 mL), and the yellow-brown solution was stirred at 25 °C (16.5 h). $H_2O$ (10 mL) was added to the mixture, and $Me_3OBF_4$ was added until the solution was acidic (pH = 2). The $Et_2O$ layer was separated, and the aqueous layer was extracted with $Et_2O$ (2 × 10 mL). The combined $Et_2O$ layers were washed with brine and dried over $MgSO_4$. Filtration and concentration under reduced pressure gave an orange oil. Purification via flash chromatography (9/1 hexanes/$Et_2O$, $SiO_2$) gave 590 mg (43%) of **16** as an orange oil: $^1$H NMR (270 MHz, $CDCl_3$) $\delta$ 1.79 (q, 2H, $J$ = 7.5 Hz), 3.42 (m, 4H), 4.47 (s, 2H), 4.73 (s, 3H), 7.30 (m, 5H). This material was relatively unstable and was used immediately.

**Cyclobutanone 17.** The carbene complex **16** (0.59 g, 1.53 mmol) and (*S*)-ene carbamate **12** (0.19 g, 1.00 mmol) in $CH_2Cl_2$ (20 mL) were photolyzed as above (19.75 h). Purification via radial chromatography (2/1, hexanes/EtOAc, 2 mm $SiO_2$) gave 0.22 g (54%) of cyclobutanone **17**: $^1$H NMR $\delta$ 1.4−2.0 (m, 4H), 2.47 (dd, 1H, $J$ = 10.2, 18.0 Hz), 3.03 (dd, 1H, $J$ = 9.5, 17.9 Hz), 3.22 (s, 3H), 3.50 (t, 2H, $J$ = 5.8 Hz), 4.10 (dd, 1H, $J$ = 4.4, 8.7 Hz), 4.45 (t, 1H, $J$ = 9.9 Hz), 4.47 (s, 2H), 4.61 (t, 1H, $J$ = 8.6 Hz), 4.87 (dd, 1H, $J$ = 4.4, 8.4 Hz), 7.2−7.4 (m, 10H). This was used without further purification.

**Lactone 18.** Cyclobutanone **17** (140 mg, 0.35 mmol) and $H_2O_2$ (30%, 90 $\mu$L) in $CF_3CH_2OH$ (20 mL)[20] were stirred for 24 h, followed by removal of the solvent under vacuum, to give 150 mg (100%) of **17** as a colorless solid: $^1$H NMR $\delta$ 1.5−1.7 (m, 2H), 1.83 (d, 1H, $J$ = 18.3 Hz), 1.89 (m, 1H), 2.28 (m, 1H), 2.73 (dd, 1H, $J$ = 8.2, 18.3 Hz), 3.28 (s, 3H), 3.52 (m, 2H), 3.97 (dd, 1H, $J$ = 2.5, 8.5 Hz), 4.33 (t, 1H, $J$ = 8.5 Hz), 4.46 (d, 1H, $J$ = 11.7 Hz), 4.51 (d, 1H, $J$ = 11.7 Hz), 4.55 (dd, 1H, $J$ = 2.5, 8.3 Hz), 4.72 (d, 1H, $J$ = 8.0 Hz), 7.2−7.4 (m, 10H).

**Spirolactone 20.** Lactone **18** (37 mg, 0.09 mmol) was

taken up in THF (5 mL). $PdCl_2$ (5 mg, 0.03 mmol) was added, and the mixture was stirred at 25 °C under 1 atm $H_2$ (16 h). The palladium black was removed via filtration through Celite, and the solvent was removed under reduced pressure. Purification via flash chromatography (1/1 hexanes/EtOAc, $SiO_2$) gave 14 mg (52%) of a single diastereoisomer of **20** as a colorless oil which solidified upon standing: $^1$H NMR $\delta$ 1.9−2.4 (m, 6H), 4.04 (dd, $J$ = 7.6, 7.6 Hz), 4.12 (dd, 1H, $J$ = 3.8, 8.5 Hz), 4.17 (ddd, $J$ = 4.3, 8.3, 8.3 Hz), 4.61 (t, 1H, $J$ = 8.6 Hz), 4.85 (dd, 1H, $J$ = 8.6, 11.3 Hz), 5.18 (dd, 1H, $J$ = 3.8, 8.7 Hz), 7.25 (m, 2H), 7.36 (m, 3H); $^{13}$C NMR $\delta$ 23.62, 31.64, 34.00, 53.33, 58.32, 70.18, 71.02, 115.92, 126.08, 129.30, 129.65, 140.94, 158.65, 171.65; IR (film) $\nu$ 1786, 1750 cm$^{-1}$. Anal. Calcd for $C_{10}H_{17}NO_9$: C, 63.36; H, 5.65; N, 4.62. Found: C, 63.26; H, 5.69; N, 4.61.

**1-(Trimethylsiloxy)-3-butyne.** Trimethylsilyl chloride (13.0 mL, 100 mmol) was added to 3-butyn-1-ol (6.7 g, 95 mmol) and triethylamine (15 mL, 105 mmol) in 150 mL of $CH_2Cl_2$, at 0 °C. The resulting slurry was warmed to 25 °C and stirred at that temperature for 1 h. The mixture was washed with saturated $NaHCO_3$(aq) and $H_2O$ and then dried over $MgSO_4$. Filtration and purification via distillation (ambient pressure) gave 11 g (85%) of the silyl ether as a colorless oil, bp = 125−128 °C: $^1$H NMR $\delta$ 0.11 (s, 9H), 1.95 (t, 1H, $J$ = 2.7 Hz), 2.39 (dt, 2H, $J$ = 2.7, 7.1 Hz), 3.69 (t, 2H, $J$ = 7.2 Hz); $^{13}$C NMR $\delta$ −0.59, 22.64, 61.04, 69.34, 81.28. This was used without further purification.

**4-(Triisopropylsilyl)-3-butynol.** *n*-Butyllithium (32.7 mL, 1.6 M in hexanes) was added to 1-(triisopropylsiloxy)silyl-3-butyne (6.96 g, 49.0 mmol) in 200 mL of $Et_2O$ at −40 °C, and the mixture was stirred at −40 °C for 0.5 h. Triisopropylsilyl trifluoromethanesulfonate (16.51 mL, 53.9 mmol) was added, and the reaction was allowed to warm to 25 °C and stirred at that temperature (7 h). The reaction mixture was washed with $H_2O$, the aqueous layer was extracted with $Et_2O$, and the combined $Et_2O$ layers were washed with 5% $NaHCO_3$(aq) and brine. Filtration and concentration under reduced pressure gave the crude alkynol. This was taken up in THF (50 mL), $H_2O$ (30 mL), and glacial acetic acid (30 mL), and the mixture was stirred at 25 °C (6 h) and then neutralized with $NH_4OH$-(aq). The aqueous layer was extracted with $Et_2O$ (3 × 50 mL), and the combined $Et_2O$ layers were washed with saturated $NH_4Cl$(aq) and brine and then dried over $MgSO_4$. Filtration and concentration under reduced pressure gave a yellow oil. Purification via flash chromatography (5/1 hexanes/EtOAc, $SiO_2$) gave 10.05 g (91% from 1-(trimethylsiloxy)-3-butyne) of the product as a colorless oil: $^1$H NMR $\delta$ 1.03 (m, 21H), 1.72 (bs, 1H), 2.52 (t, 2H, $J$ = 6.2 Hz), 3.70 (t, 2H, $J$ = 6.2 Hz); IR (film) $\nu$ 3329 cm$^{-1}$. This was used without further purification.

**1-Iodo-4-(triisopropylsilyl)-3-butyne.** Methanesulfonyl chloride (1.00 mL, 12.9 mmol) was added to 2.66 g (11.8 mmol) of 4-(triisopropylsilyl)-3-butynol and 1.8 mL (12.9 mmol) of triethylamine in 200 mL of $CH_2Cl_2$ at 0 °C. The mixture was warmed to 25 °C and stirred at that temperature for 17 h and then washed with saturated $NH_4Cl$(aq) dried over $MgSO_4$, and the solvent was removed under vacuum to give 3.60 g (≈100%) of the desired mesylate as a yellow oil: $^1$H NMR $\delta$ 1.04 (m, 21H), 2.71 (t, 2H, $J$ = 6.9 Hz), 3.02 (s, 3H), 4.28 (t, 2H, $J$ = 7.0 Hz). This material (3.6 g) was heated at reflux in 60 mL of acetone containing 18 g of NaI for 24 h, cooled, and partitioned between hexanes and water. The combined hexane layers were washed with 10% $Na_2S_2O_3$(aq) and brine and then dried over $MgSO_4$. Filtration and concentration under reduced pressure gave 3.6 g (91% from the alcohol) of the product as a yellow oil: $^1$ H NMR $\delta$ 1.04 (m, 21H), 2.80 (t, 2H, $J$ = 7.3 Hz), 3.20 (t, 2H, $J$ = 7.3 Hz); $^{13}$C NMR $\delta$ 1.61, 11.15, 18.56, 25.09, 82.75, 106.55; IR (film) $\nu$ 2173 cm$^{-1}$. This material was used without further purification.

**[(Ethoxy)(4-(triisopropylsilyl)-3-butynyl)carbene]pentacarbonyl Chromium(0) (21).** A flame-dried 100 mL Airless flask was charged with iodide **55** (1.68 g, 5.00 mmol) and $Et_2O$ (50 mL), flushed with argon, and then cooled to −78 °C. *tert*-Butyllithium (6.20 mL, 10.5 mmol, 2.1 equiv 1.7 M solution in pentanes) was added dropwise to the cooled mixture, and the resulting solution was stirred at −78 °C for 0.5 h and then gradually warmed to 25 °C. This solution was transferred to an Airless flask containing $Cr(CO)_6$ (1.10 g, 5.00 mmol) in $Et_2O$ (20 mL), via a cannula, resulting in an orange/brown solution. This was stirred at 25 °C for 14 h, and then $H_2O$ (15 mL) was added. Ethyl Meerwein salt ($Et_3O^+BF_4^-$) was added to the solution until a pH of 2 was reached. The aqueous layer was extracted with $Et_2O$ (3 × 50 mL), and the organic layers were combined and washed with brine and then dried over $MgSO_4$. Filtration and concentration under reduced pressure and then purification via flash chromatography (hexanes, $SiO_2$) gave 1.93 g (84%) of carbene **56** as an orange oil: $^1$H NMR $\delta$ 1.02 (m, 21 H), 1.65 (t, 3 H, $J$ = 7.1 Hz), 2.41 (t, 2 H, $J$ = 6.9 Hz), 3.60 (t, 2 H, $J$ = 6.8 Hz), 5.11 (q, 2 H, $J$ = 7.1 Hz); $^{13}$C NMR $\delta$ 11.2, 14.8, 16.2, 18.5, 60.9, 78.2, 80.7, 106.6, 216.2, 223.0, 355.6; IR (film) $\nu$ 2063, 1938 cm$^{-1}$. This carbene was unstable and thus was used immediately upon purification.

**Alkynylcyclobutanone 22.** Carbene complex **21** (2.49 g, 5.34 mmol, 1.5 equiv) and (*S*)-ene carbamate **12** (0.68 g, 3.62 mmol) were placed into an Ace pressure tube, dissolved in degassed $CH_2Cl_2$ (15mL) and charged to 50−80 psi of CO (3 cycles), and then irradiated at 25 °C (20−25 h) at 60−70 psi. The solvent was removed under reduced pressure, and the $Cr(CO)_6$ was recovered via sublimation. Purification via flash chromatography (4/1 hexanes/EtOAc, $SiO_2$) gave 1.32 g of **22** (76%) as a colorless viscous oil. Only a single diastereomer was detected by NMR analysis: $^1$H NMR $\delta$ 1.06 (m, 24 H), 2.1−2.3 and 2.4−2.5 (m, 4 H), 2.56 (dd, 1 H, $J$ = 10.2, 18.0 Hz), 3.30 (dd, 1 H, $J$ = 9.5, 18.0 Hz), 3.32 (q, 2 H, $J$ = 6.9 Hz), 4.20 (dd, 1 H, $J$ = 5.1, 9.7 Hz), 4.35 (t, 1 H, $J$ = 9.8 Hz), 4.66 (t, 1 H, $J$ = 8.6 Hz), 4.90 (dd, 1 H, $J$ = 5.0, 8.4 Hz), 7.27 (m, 2 H), 7.42 (m, 3 H); $^{13}$C NMR $\delta$ 11.2, 14.4, 15.2, 18.6, 30.3, 42.4, 47.6, 60.6, 61.7, 70.1, 80.8, 97.5, 108.0, 126.5, 129.4, 129.6, 138.6, 157.9, 205.4; IR (film) $\nu$ 1790, 1732 cm$^{-1}$; $[\alpha]_D$ = +51.8° ($c$ = 0.714, $CH_2Cl_2$); MS (FAB) $m/e$ 483.3 (M) 484.3 (M + 1).

**Alkynyl Lactone 23.** Cyclobutanone **22** (1.32 g, 2.73 mmol) was dissolved in $CH_2Cl_2$ (100 mL). *m*-Chloroperbenzoic acid (0.85 g, 4.10 mmol, 1.5 equiv) and $Na_2HPO_4$ (0.78 g, 5.47 mmol, 2 equiv) were added to the mixture which was allowed to stir at 25 °C for 8 h. A solution of 10% $Na_2S_2O_3$(aq) was then added to the mixture which was stirred for a further 0.5 h. The organic layer was washed with saturated $NaHCO_3$-(aq) (2 × 80 mL) and then dried over $MgSO_4$. Filtration and concentration under reduced pressure and then purification via flash chromatography (3/1 hexanes/EtOAc, $SiO_2$) gave 1.35 g (99%) of **23** as a white, sticky solid: $^1$H NMR $\delta$ 1.05 (m, 21 H), 1.10 (t, 3 H, $J$ = 6.9 Hz), 1.98 (m, 2H), 2.27 (m, 2H), 2.45 (m, 1H), 2.75 (dd, 1 H, $J$ = 8.2, 18.2 Hz), 3.57 (m, 2 H), 4.22 (dd, 1 H, $J$ = 2.2, 7.7 Hz), 4.60 (m, 3 H), 7.24 (m, 2 H), 7.39 (m, 3 H); $^{13}$C NMR $\delta$ 11.1, 13.8, 15.0, 18.5, 30.5, 32.0, 56.3, 58.3, 58.9, 70.8, 81.2, 106.8, 110.6, 126.5, 129.6, 139.0, 157.8, 173.8; IR (film) $\nu$ 1751, 1755 cm$^{-1}$; $[\alpha]_D$ = +26.5° ($c$ = 1.16, $CH_2Cl_2$); MS (FAB) $m/e$ 499.3 (M) 500.2 (M + 1).

**Alkynylbutenolide 24.** Lactone **23** (0.19 g, 0.39 mmol) was dissolved in THF (50 mL) and cooled to 0 °C. Tetrabutylammomium fluoride (TBAF) (0.98 mL, 0.97 mmol, 2.5 equiv, 1 M soln in THF) was added dropwise to the solution which instantly turned an orange color. This was stirred at 0 °C for 3 h. The mixture was partitioned between $Et_2O$ (60 mL) and saturated $NH_4Cl$(aq) (60 mL), the layers were separated, and the aqueous layer was washed with $Et_2O$ (2 × 60 mL). The organic layers were combined, washed with brine, and then dried over $MgSO_4$. Purification via flash chromatography (3/1 hexanes/EtOAc, $SiO_2$) gave 0.065 g (93%) of **24** as a colorless oil: $^1$H NMR $\delta$ 1.14 (t, 3 H, $J$ = 7.0 Hz), 1.93 (t, 1 H, $J$ = 2.6 Hz), 2.11 (t, 2 H, $J$ = 7.6 Hz), 2.35 (m, 2 H), 3.29 (dq, 1 H, $J$ = 7.2, 9.0 Hz), 3.44 (dq, 1 H, $J$ = 7.2, 9.0 Hz), 6.16 (d, 1 H, $J$ = 5.7 Hz), 7.23 (d, 1 H, $J$ = 5.8 Hz); $^{13}$C NMR $\delta$ 13.0, 15.0, 36.6, 59.5, 69.3, 83.1, 109.8, 124.5, 153.5, 169.6; IR (film) $\nu$ 3290, 1771 cm$^{-1}$; $[\alpha]_D$ = +76.8° ($c$ = 1.12, $CH_2Cl_2$). Anal. Calcd for $C_{10}H_{12}O_3$: C, 66.65; H, 6.71. Found: C, 66.80; H, 6.51.

**Alkenylbutenolide 25.** Alkynylbutenolide **24** (0.280 g, 1.56 mmol), Lindlar's catalyst poisoned with $MnCl_2$[12] (0.012 g), and quinoline (3 drops) were taken up in EtOAc (25 mL) and stirred under an atmosphere of hydrogen for 1 h. The mixture was filtered through Celite, washed with 1 M HCl (2

× 20 mL) and $H_2O$ (2 × 20 mL), and then dried over $Na_2SO_4$. Purification via flash chromatography (2/1 hexanes/EtOAc, $SiO_2$) gave 0.264 g (93%) of **25** as a colorless oil: $^1$H NMR $\delta$ 1.16 (t, 3H, $J$ = 7.0 Hz), 1.97 (m, 2H), 2.15 (m, 2H), 3.32 (dq, 1H, $J$ = 7.0, 9.0 Hz), 3.47 (dq, 1H, $J$ = 7.0, 9.0 Hz), 4.95 (dd, 1H, $J$ = 1.0, 10.2 Hz), 5.02 (dd, 1 H, $J$ = 1.0, 17.4 Hz), 5.77 (ddt, 1H, $J$ = 6.4, 10.3, 17.1 Hz), 6.16 (d, 1H, $J$ = 5.7 Hz), 7.14 (d, 1H, $J$ = 5.6 Hz); $^{13}$C NMR $\delta$ 15.0, 27.4, 36.3, 59.3, 110.6, 115.2, 124.3, 137.0, 153.8, 169.8; IR (film) $\nu$ 3082, 1770 cm$^{-1}$; $[\alpha]_D$ = +68.1° ($c$ = 1.16, $CH_2Cl_2$); MS (EI) $m/e$ 182.1 ($M^+$).

**Aldehyde 26.** Alkene **25** (0.20 g, 1.10 mmol) in methanol (20 mL) was cooled to −78 °C, and ozone was bubbled through the solution at −78 °C until a blue color persisted (∼5 min). Then argon was bubbled through the solution until the blue color disappeared. A mixture of thiourea (0.04 g, 0.55 mmol, 0.5 equiv) in methanol (2 mL) was added, and the resulting mixture was stirred at −78 °C for 15 min and then warmed to 0 °C and stirred for a further 1 h. The mixture was concentrated under reduced pressure, and the resulting white slurry was diluted with $CH_2Cl_2$ (10 mL), washed with 1% $NaHCO_3$(aq) (1 × 10 mL) and $H_2O$ (3 × 10 mL), and then dried over $Na_2SO_4$. Filtration and concentration under reduced pressure gave 0.19 g (94%) of **26** as a colorless oil. Purification via flash chromatography (1/1 hexanes/EtOAc, $SiO_2$) gave 0.17g (85%) of pure **26**: $^1$H NMR $\delta$ 1.10 (t, 3H, $J$ = 7.0 Hz), 2.07 (ddd, 1H, $J$ = 6.6, 7.8, 14.4 Hz), 2.23 (ddd, 1H, $J$ = 6.6, 7.8, 14.4 Hz), 2.61 (m, 2H), 3.26 (dq, 1H, $J$ = 7.0, 9.0 Hz), 3.40 (dq, 1H, $J$ = 7.0, 9.0 Hz), 6.15 (d, 1H, $J$ = 5.7 Hz), 7.12 (d, 1H, $J$ = 5.7 Hz), 9.71 (s, 1H); $^{13}$C NMR $\delta$ 14.8, 29.9, 37.6, 59.4, 109.6, 124.5, 153.4, 169.3, 200.4; IR (film) $\nu$ 1769, 1723 cm$^{-1}$; $[\alpha]_D$ = +26.3° ($c$ = 0.72, $CH_2Cl_2$); MS (FAB) $m/e$ 184.1 (M), 185.1 (M + 1).

**Vinyl Iodide 27.** Chromous (II) chloride (0.69 g, 5.36 mmol, 6 equiv) was weighed out in a glovebag, under an atmosphere of argon, and suspended in freshly distilled THF (10 mL). The green suspension was cooled to 0 °C under argon, and to this was added dropwise a solution of aldehyde **26** (0.16 g, 0.89 mmol, 1 equiv) and iodoform (0.70 g , 1.79 mmol, 2 equiv) in THF (10 mL). The solution went from pale green to deep orange. This was stirred at 0 °C for 3 h, after which the mixture was poured into $H_2O$ (15 mL) and extracted with $Et_2O$ (3 × 15 mL). The organic layers were combined and dried over $Na_2SO_4$. Filtration and concentration under reduced pressure and then purification via flash chromatography (1/1 hexanes/EtOAc, $SiO_2$) gave 0.23 g (85%) of **27** as a pale yellow oil: $^1$H NMR $\delta$ 1.15 (t, 3H, $J$ = 7.0 Hz), 1.98 (m, 2H), 2.21 (m, 2H), 3.31 (dq, 1H, $J$ = 7.0, 9.0 Hz), 3.46 (dq, 1H, $J$ = 7.0, 9.0 Hz), 6.04 (d, 1H, $J$ = 14.8 Hz), 6.18 (d, 1H, $J$ = 5.6 Hz), 6.46 (dt, 1H, $J$ = 7.1, 14.3 Hz), 7.12 (d, 1H, $J$ = 5.6 Hz); $^{13}$C NMR $\delta$ 15.1, 29.9, 36.0, 59.4, 109.5, 124.6, 139.6, 144.6, 153.5, 169.4; IR (film) $\nu$ 3085, 1769 cm$^{-1}$; $[\alpha]_D$ = +28.3° ($c$ = 0.6, $CH_2Cl_2$); MS (EI) $m/e$ 308.0 ($M^+$).

**Butenolide 28.** Bis($\pi$-crotyl)nickel bromide (0.09 g, 0.71 mmol, 1.1 equiv) was dissolved in degassed DMF (10 mL). To this was added a solution of vinyl iodide **27** (0.20 g, 0.65 mmol)-in DMF (1 mL). The mixture was stirred at 25 °C until the solution turned emerald green. This was washed with hexanes (3 × 10 mL). The organic layers were combined and dried over $Na_2SO_4$. Filtration and concentration under reduced pressure gave 0.136 g (89%) of a 10/1 mixture of butenolide **28** and its regioisomer. These were separated via flash chromatography (10/1 hexanes/EtOAc) on $SiO_2$ impregnated with 10% $AgNO_3$: $^1$H NMR $\delta$ 1.16 (t, 3H, $J$ = 7.0 Hz), 1.62 (d, 3H, $J$ = 4.1 Hz), 1.88−2.14 (m, 4H), 2.63 (m, 2H), 3.32 (dq, 1H, $J$ = 7.0, 9.0 Hz), 3.47 (dq, 1H, $J$ = 7.0, 9.0 Hz), 5.38 (m, 4H), 6.15 (d, 1H, $J$ = 5.7 Hz), 7.12 (d, 1H, $J$ = 5.7 Hz); $^{13}$C NMR $\delta$ 15.1, 17.8, 26.3, 35.4, 37.0, 59.4, 110.7, 124.3, 125.6, 128.9, 129.3, 129.8, 153.8, 169.9; IR (film) $\nu$ 3084, 3022, 1772 cm$^{-1}$; $[\alpha]_D$ = +48.2° ($c$ = 1.10, $CH_2Cl_2$); MS (EI) $m/e$ 236.1 ($M^+$); EI cald for $C_{14}H_{20}O_3$ 236.1412, found 236.1408.

The $AgNO_3$-impregnated silica gel was prepared by dissolving $AgNO_3$ (10% w/w of $SiO_2$) in water and adding this to $SiO_2$. The mixture was thoroughly shaken and then the water removed under reduced pressure. The silica gel was dried overnight at 110 °C.

**Epoxide 29.** Butenolide **28** (0.05 g, 0.21 mmol) was dissolved in a solution of $Et_2O$/DMF (5 mL/5 mL) and cooled to 0 °C. Sodium hypochlorite (0.31 mL, 0.72 mmol, 2 equiv, 10% solution in $H_2O$) was added dropwise to the cooled solution and after complete addition the mixture was stirred for 1 h at 0 °C. The reaction mixture was quenched with 10% $Na_2S_2O_3$ (aq), and the aqueous layer was extracted with $Et_2O$ (2 × 10 mL). The combined organic layers were washed with brine and dried over $MgSO_4$. Filtration and concentration under reduced pressure and purification via flash chromatography (5/1 hexanes/$Et_2O$, $SiO_2$) gave 11 mg (21%) of the epoxide and 33 mg of recovered starting material which was resubjected to the reaction conditions. Recycling the starting material twice gave 20 mg (38%) of epoxide **29** as a colorless oil: $^1$H NMR $\delta$ 1.20 (t, 3 H, $J$ = 7.0 Hz), 1.64 (d, 3 H, $J$ = 4.4 Hz), 1.82−2.21 (m, 4 H), 2.65 (m, 2 H), 3.62 (dq, 1 H, $J$ = 7.0, 8.9 Hz), 3.69 (dq, 1 H, $J$ = 7.0, 8.9 Hz), 3.77 (d, 1 H, $J$ = 2.5 Hz), 3.94 (d, 1 H, $J$ = 2.3 Hz), 5.43 (m, 4 H); $^{13}$C NMR $\delta$ 15.1, 17.9, 26.4, 31.0, 35.5, 50.1, 57.3, 58.7, 107.8, 125.8, 128.7, 129.2, 130.2, 169.1; IR (film) $\nu$ 1781 cm$^{-1}$; $[\alpha]_D$ = +62.6° ($c$ = 0.8, $CH_2Cl_2$).

**(+)-Cerulenin (5).** Epoxide **29** (8 mg, 0.03 mmol) was dissolved in dry $Et_2O$ (4 mL) and cooled to 0 °C. Ammonia gas was bubbled into the mixture for 25 min at 0 °C after which the solution was allowed to stir for 2 h at 0 °C. The solvent was removed under reduced pressure. The crude mixture contained a 1/1 ratio of the linear and cyclic isomers. Only partial equilibration was observed after 24 h in either $CD_3OD$ or $CDCl_3$. In $CD_3OD$ the cyclic isomer **5** was favored and a mixture of 90% of this and 10% of **(+)-5** was obtained. The linear isomer **(+)-5** was dominant in $CDCl_3$, and purification via flash chromatography (1/1 $Et_2O/CH_2Cl_2$, $SiO_2$) gave 6 mg of a mixture of 90% of **(+)-5** and 10% of the cyclic isomer. These were not able to be separated completely.

**(+)-5**: $^1$H NMR $\delta$ 1.66 (d, 3H), 2.31 (q, 2H, $J$ = 7.0 Hz), 2.64 (m, 4H), 3.72 (d, 1H, $J$ = 5.0 Hz), 3.85 (d, 1H, $J$ = 5.0 Hz), 5.30−5.51 (m, 5H), 6.28 (bs, 1H); $^{13}$C NMR $\delta$ 17.9, 25.9, 29.7, 35.4, 40.8, 55.3, 58.4, 125.8, 127.7, 129.2, 130.7, 167.2, 202.0; IR (film) $\nu$ 3382, 3202, 1720, 1663, 967 cm$^{-1}$; $[\alpha]_D$ = +63.3° (natural (+)-cerulenin, mixture of isomers +63°) ($c$ = 2.62, MeOH for 24 h). Spectroscopic data are identical with reported values.[26]

**Cyclic isomer**: $^1$H NMR (300 MHz, $CD_3OD$) $\delta$ 1.63 (d, 3H, $J$ = 7.0 Hz), 1.78 (m, 2H), 2.21 (m, 2H), 2.64 (m, 2H), 3.58 (d, 1H, $J$ = 3.0 Hz), 3.81 (d, 1H, $J$ = 3.0 Hz), 5.42 (m, 4H); $^{13}$C NMR (75.5 MHz, $CD_3OD$) $\delta$ 18.2, 28.1, 36.7, 53.3, 59.1, 87.1, 126.5, 130.7, 130.9, 131.2, 186.8.

**Acknowledgment.** Support for this research by National Science Foundation Grant CHE-9224489 is gratefully acknowledged. Mass spectra were obtained on instruments supported by the National Institutes of Health shared instrumentation grant GM49631.

**Supporting Information Available:** $^1$H and $^{13}$C NMR spectra (60 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.

JO960664K

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