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Zinc Carbenoid-Mediated Chain Extension: Preparation of α,β-Unsaturated-γ-keto Esters and Amides

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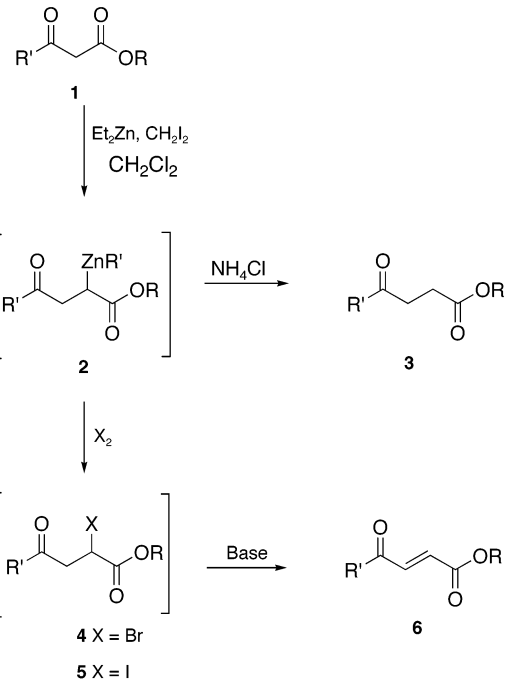
Abstract: An efficient one-pot preparation of α,β-unsaturated-γ-keto esters and amides has been developed. A zinc carbenoid-mediated chain extension of a β-dicarbonyl substrate provides access to an intermediate zinc enolate, which is treated sequentially with a halogen and amine base. This method has been applied to a variety of ester and amide starting materials, as well as to amino acid-derived substrates and to a formal synthesis of (*R*,*R*)-(−)-pyrenophorin.

The appearance of α,β-unsaturated-γ-keto ester functionalities in a variety of natural products[1] coupled with the rich reactivity of this functional group have stimulated interest in the preparation of this functionality. Methods reported for the preparation of α,β-unsaturated-γ-keto esters include the conversion of γ-keto esters to the α,β-unsaturated systems via selenium dioxide oxidation,[2] bromination of γ-keto esters, followed by elimination with base,[3] Horner−Emmons chemistry between α-formyl esters and β-keto phosphonates,[4] oxidation of furan skeletons,[5] and laborious multistep syntheses.[6] Herein we present a rapid one-pot conversion of readily available β-keto carbonyl compounds to the corresponding α,β-unsaturated-γ-keto carbonyl systems utilizing a one-pot chain extension followed by halogenation and elimination.

The facile conversion of readily available β-keto esters (**1**),[7] amides,[8] and phosphonates[9] to the corresponding γ-keto carbonyl system (**3**) through application of a zinc carbenoid has been a recent focus of our research efforts. We demonstrated that exposure of β-keto esters (**1**), as well as amides and phosphonates, to a mixture of diethyl zinc and methylene iodide facilitates chain extension of the system in which an intermediate zinc enolate (**2**) is generated.[10] Addition of a proton completes the chain extension process in which the new methylene is incorporated adjacent to the ketone functionality. A variety of alternative electrophiles have been used to trap this intermediate enolate, namely aldehydes,[10] ketones,[11] iminium ions,[11] and carbenoids.[12] We envisioned a modification of this procedure in which the intermediate zinc enolate (**2**) is trapped with an electrophile that could be subsequently eliminated to form an α,β-unsaturated-γ-dicarbonyl **6** (Scheme 1). Herein we report the results of a study in which halogens were used to quench the intermediate zinc enolate and the resulting halide eliminated through treatment with base. Rapid and efficient diastereoselective formation of an unsaturated system results.

SCHEME 1



Initial attempts to capture the zinc enolate intermediate (**2**) utilized bromine as the electrophile and triethylamine as the base. Formation of the α-bromo-γ-keto carbonyl (**4**) was assumed and in situ elimination of the halide provided the unsaturated system (**6**); however, the yield of the olefin-containing compound was poor and a product (**5**) resulting from iodination at the α-carbon and incomplete elimination was observed. The source of the iodine is likely the zinc iodide salts[13] that are byproducts of carbenoid formation and reaction; however, the details of iodination are unclear. The ratio of products formed

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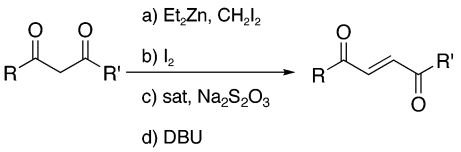
TABLE 1. Chain Extension−Oxidation−Elimination of Esters and Amides

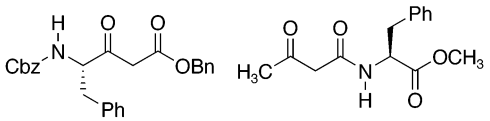


SM	R	R′	prod	yield, %
7	$C(CH_3)_3$	OCH_3	**8**	86
9	CH_3	$OC(CH_3)_3$	**10**	73
11	CH_3	OCH_3	**12**	67
13	CH_3	OCH_2CH_3	**14**	70
15	CH_3	$OCH_2C_6H_5$	**16**	73
17	C_6H_5	OCH_2CH_3	**18**	59
19	CH_3	$CH_2CH{=}CH_2$	**20**	71
21	CH_3	$N(C_6H_5)CH_3$	**22**	63

under this initial set of reaction conditions was inconsistent and suitable yields of the desired α,*β*-unsaturated-*γ*-keto ester were not obtained. Further attempts to form the bromide intermediate **4** with *N*-bromosuccinimide (NBS) or 1,2-dibromoethane were unsuccessful and resulted in the formation of the saturated *γ*-keto ester **3**.

To ensure that a single intermediate is being formed in the halogenation reaction, molecular iodine was utilized as the electrophile. Efficient, reproducible, and exclusive iodination of the intermediate zinc enolate resulted. All subsequent reactions were performed with a 5-fold excess of iodine. Destruction of excess iodine with saturated aqueous $Na_2S_2O_3$, followed by treatment with triethylamine provided mixtures of the α-iodo ester (**5**) and the desired unsaturated ester (**6**). However, efficient elimination was facilitated by treatment with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU, 10 equiv) and resulted in the formation of the α,*β*-unsaturated-*γ*-keto ester (**6**) or amide in good yield (Table 1). Isolation of the intermediate iodide (**5**) is possible when DBU is not added to the reaction; however, chromatographic purification of the iodinated species is challenging and typically results in partial elimination and the formation of several products.

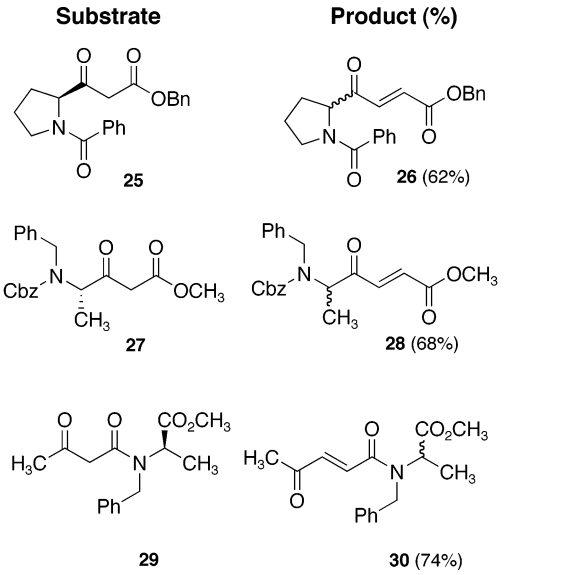
The formation of the α,*β*-unsaturated compounds proceeds efficiently with complete *E* selectivity in the formation of the new alkene. No evidence of *Z*-olefin formation was observed in any of the reactions. In addition, we have demonstrated that oxidation of the enolate is efficient even in the presence of reactive olefins. For example, conversion of **19** to **20** proceeds cleanly, without cyclopropanation or halogenation of the olefin.

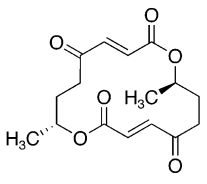


23 **24**

In addition to performing this transformation on simple *β*-keto carbonyl compounds, we have also applied this methodology to the formation of amino acid-derived α,*β*-unsaturated-*γ*-keto carbonyl systems. These conjugated olefins have been used in the preparation of ketomethylene isosteric replacements for peptide bonds through conjugate addition of malonate anion derivatives[14] and aromatic and aliphatic cuprates.[15] Although the simple chain extension of monoprotected amino acid derivatives proceeds smoothly,[9,16] we found that exposure of amino acid derivatives **23** and **24** to the chain extension−oxidation−elimination reaction resulted in a very complex reaction mixture and afforded the desired product in very low yield. However, simple benzyl protection of the nitrogen was sufficient to provide the desired iodinated species, which is readily eliminated to the α,*β*-unsaturated system (Table 2). HPLC analysis with a chiral stationary phase revealed that complete racemization of the amino acids occurred under the elimination reaction conditions. Since loss of stereochemical integrity is not observed in the simple chain extension of amino acid-derived *β*-keto esters,[17] the epimerization is apparently occurring in the elimination step. We have recently reported[18] a procedure in which an intermediate iodide is isolated and, without purification, subjected to 1.2 equiv of DBU in cold diethyl ether to facilitate a kinetically controlled elimination. A similar avoidance of excess DBU in the reaction of amino acid-derived *β*-keto esters would be expected to minimize potential epimerization in the elimination reaction. Efforts are presently underway to develop conditions in which the stereochemical integrity of the amino acid-derived substrates is maintained.

TABLE 2. Chain Extension−Oxidation−Elimination of Amino Acids Substrates





31 (-)-Pyrenophorin

We have further demonstrated the utility of this transformation in a two-pot formal synthesis of the 16-

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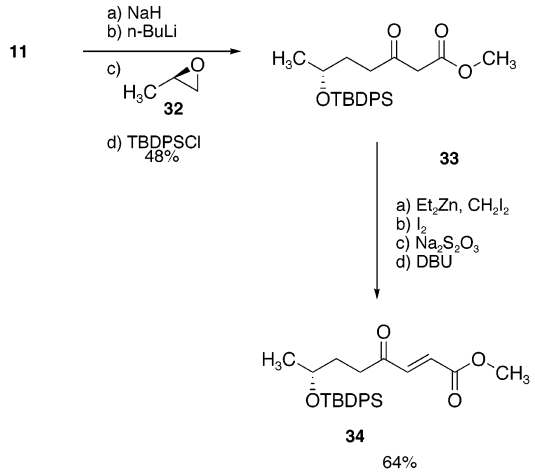
SCHEME 2



membered dilactone natural product pyrenophorin **31**.[19] Reaction of the dianion of methyl acetoacetate (**11**) with *R*-propylene oxide (**32**) followed by capture of the resulting alkoxide with TBDPSCl produced the hydroxy-protected β-keto ester **33** in 47% yield.[20] Exposure of **33** to the chain extension/iodination/elimination reaction conditions produced the desired α,β-unsaturated-γ-keto ester **34** in 64% yield (Scheme 2). The enantiomer of **34** has been reported as a synthetic intermediate in the total synthesis of (*R*,*R*)-(−)-pyrenophorin **31**.[21]

We have developed an efficient method for the formation of α,β-unsaturated-γ-keto esters and amides from readily available β-keto esters and amides. In addition, we applied this methodology to the synthesis of amino acid-derived compounds that offer potential utility as precursors to ketomethylene isosteres. A short formal synthesis of optically active pyrenophorin **31** was accomplished.

Experimental Section

General Methods. All reactions were run in oven-dried glassware under a nitrogen atmosphere. Methylene chloride was distilled from phosphorus pentoxide (P_2O_5). The reactions were monitored by thin-layer chromatography (TLC) on EM Science F254 glass plates that were visualized by short-wavelength UV and anisaldehyde stain. Column chromatography was performed on Baker 40 μm silica gel, using the indicated mobile phase. The R_f value refers to the use of the identical mobile phase in TLC analysis. Starting materials were purchased from commercial sources and used as received. HPLC analysis was performed through use of a Diacel Chiralpak AD-RH reverse-phase column.

General Procedure: Methyl *E*-5,5-Dimethyl-4-oxo-hex-2-enoate[22] **(8).** A 100-mL round-bottom flask was equipped with a stir bar and charged with 15 mL of methylene chloride and diethyl zinc (1.0 M in hexanes, 5.0 mL, 5.0 mmol) under an atmosphere of N_2 at 0 °C. Methylene iodide (0.42 mL, 5.2 mmol) was added and the resulting white suspension was stirred for 10 min. Methyl pivaloylacetate (**7**) (0.16 mL, 1.0 mmol) was added rapidly by syringe and allowed to stir at 0 °C for 30 min. Iodine (1.27 g, 5 mmol) was added to the reaction mixture in a single portion and the solution was allowed to stir until a pink color persisted for 30 s. Saturated aqueous sodium thiosulfate (10 mL) was added and the biphasic mixture was stirred until the pink color had disappeared. 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU) (1.5 mL, 10 mmol) was added and the mixture was stirred vigorously for 1 min. Saturated aqueous ammonium chloride was added and the solution was extracted three times with diethyl ether. The combined organic layers were dried with anhydrous sodium sulfate and concentrated in vacuo. The residue was chromatographed on silica (15:1, hexanes/ethyl acetate; R_f 0.23) to yield 147 mg (86%) of **8** as a yellow oil. Spectroscopic data were identical with those reported in the literature.[18] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 (d, 1H, J = 15.6 Hz), 6.75 (d, 1H, J = 15.6 Hz), 3.79 (s, 3H), 1.74 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 203.8, 166.3, 135.8, 131.1, 52.4, 43.8, 25.9.

1,1-Dimethylethyl *E*-4-Oxo-pent-2-enoate[23] **(10).** Chromatography on silica (20:1, hexanes/EtOAc; R_f 0.20) yielded 170 mg (73%) of a yellow oil that possessed spectroscopic data identical with that reported in the literature. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.92 (d, 1H, J = 16.4 Hz), 6.58 (d, 1H, J = 16.4 Hz), 2.35 (s, 3H), 1.51 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.2, 164.9, 139.4, 133.9, 82.3, 28.2, 28.1.

Methyl *E*-4-Oxo-pent-2-enoate[24] **(12).** Chromatography on silica (10:1, hexanes/EtOAc; R_f 0.25) yielded 86 mg (67%) of a white solid that possessed spectroscopic data identical with that reported in the literature. Mp 58.5−60.0 °C (lit.[25] mp 59−60 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.03, (d, 1H, J = 16.4 Hz), 6.66 (d, 1H, J = 16.4 Hz), 3.83 (s, 3H), 2.37 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.7, 166.1, 140.3, 131.3, 52.6, 28.4.

Ethyl *E*-4-Oxo-pent-2-enoate[26] **(14).** Chromatography on silica (10:1, hexanes/EtOAc; R_f 0.25) yielded 100 mg (70%) of a yellow oil that possessed spectroscopic data identical with that reported in the literature. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.04 (d, 1H, J = 16.0 Hz), 6.65 (d, 1H, J = 16.0 Hz), 4.28 (q, 2H, J = 7.0 Hz), 2.36 (s, 3H), 1.33 (t, 3H, J = 7.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 197.9, 185.7, 140.2, 131.8, 61.7, 28.3, 14.3.

Phenylmethyl *E*-4-Oxo-pent-2-enoate[2] **(16).** Chromatography on silica (15:1, hexanes/EtOAc; R_f 0.19) yielded 148 mg (73%) of a yellow oil that possessed spectroscopic data identical with that reported in the literature. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39−7.36 (m, 5H), 7.05 (d, 1H, J = 16.0 Hz), 6.69 (d, 1H, J = 16.4 Hz), 5.25 (s, 2H), 2.35 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.7, 165.5, 140.6, 135.4, 131.4, 128.9, 128.8, 128.6, 67.4, 28.3.

Ethyl *E*-4-Oxo-4-phenyl-but-2-enoate[18] **(18).** Chromatography on silica (15:1, hexanes/EtOAc; R_f 0.21) yielded 120 mg (59%) of a yellow oil that possessed spectroscopic data identical with that reported in the literature. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01−7.99 (m, 2H), 7.91 (d, 1H, J = 15.6 Hz), 7.63−7.60 (m, 1H), 7.53−7.49 (m, 2H), 6.89 (d, 1H, J = 15.6 Hz), 4.30 (t, 2H, J = 7.2 Hz), 1.35 (q, 3H, J = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 189.8, 165.8, 136.8, 136.6, 134.0, 132.8, 129.1, 129.0, 61.6, 14.4.

Prop-2-enyl *E*-4-Oxo-pent-2-enoate (20). Chromatography on silica (10:1, hexanes/EtOAc; R_f 0.23) yielded 110 mg (71%) of a yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.05 (d, 1H, J = 16.1 Hz), 6.70 (d, 1H, J = 16.1 Hz), 5.94 (tdd, 1H, J = 5.9, 10.7, 16.1 Hz), 5.39−5.28 (m, 2H), 4.71 (td, 2H, J = 1.5, 5.9), 2.37 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 194.2, 161.8, 136.9, 128.1, 127.9, 115.7, 62.7, 24.8.

***N*-Methyl-*N*-phenyl *E*-4-Oxo-pent-2-enoamide (22).** Chromatography on silica (3:1, hexanes/EtOAc; R_f 0.20) yielded 104 mg (60%) of a yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.47−7.27 (m, 3H), 7.18−7.17 (m, 2H), 7.07 (d, 1H, J = 15.5 Hz), 6.64 (d, 1H, J = 15.5 Hz), 3.40 (s, 3H), 2.19 (s, 3H); ^{13}C NMR (125

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MHz, $CDCl_3$) δ 197.7, 164.5, 142.7, 137.2, 131.9, 129.9, 128.2, 127.0, 37.7, 28.8.

Phenylmethyl *E*-4-(1-Benzoyl-pyrrolidin-2-yl)-4-oxo-but-2-enoate (26). Chromatography on silica (2:1, hexanes/EtOAc; R_f 0.21) yielded 65 mg (62%) of a yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.60−7.22 (m, 11H), 6.90 (d, 1H, J = 16.1 Hz), 5.24 (s, 2H), 4.96 (dd, 1H, J = 6.4, 8.8 Hz), 3.70−3.56 (m, 2H), 2.34−2.25 (m, 1H), 2.05−1.88 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 197.3, 169.8, 165.4, 137.3, 135.9, 135.5, 131.9, 130.6, 128.9, 128.7, 128.6, 128.5, 127.6, 67.4, 64.5, 50.4, 28.6, 25.7. HRMS (CI, NH_3) $[M + H]^+$ calcd for $C_{22}H_{22}NO_4$ 364.1544, found 364.1546.

Methyl *E*-5-[*N*-Benzyl-*N*-(benzyloxycarbonyl)amino]-4-oxo-hex-2-enoate (28). Chromatography on silica (2:1, hexanes/EtOAc; R_f 0.21) yielded a yellow oil (65 mg, 62%) as a mixture (55:45) of rotomers. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40−7.15 (m, 10H), 7.08 (d, 0.55H, J = 15.6 Hz), 6.90 (d, 0.45H, J = 15.6 Hz), 6.65 (d, 0.55H, J = 15.6 Hz), 6.41 (d, 0.45H, J = 15.6 Hz), 5.25−5.09 (m, 2H), 4.76 (d, 0.45H, J = 13.0 Hz), 4.68 (d, 0.55H, J = 13.0 Hz), 4.46−4.31 (m, 1.55H), 4.02 (m, 0.45H), 3.75 (s, 3H), 1.33−1.21 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 196.8, 196.4, 166.0, 165.8, 156.2, 137.6, 137.4, 136.7, 136.3, 135.9, 130.8, 128.9, 128.7, 128.5, 128.4, 128.3, 128.1, 128.0, 68.2, 61.3, 60.9, 52.4, 51.6, 49.9, 13.8, 13.3. HRMS (CI, NH_3) $[M + NH_4]^+$ calcd for $C_{22}H_{27}N_2O_5$ 399.1914, found 399.1898.

Methyl *E*-2-[Benzyl(4-oxo-pent-2-enoyl)amino]propionate (30). Chromatography on silica (2:1, hexanes/EtOAc; R_f 0.18) yielded 120 mg (74%) of a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39−7.26 (m, 5H), 7.15 (d, 1H, J = 15.2 Hz), 7.08 (d, 1H, J = 15.6), 4.79−4.59 (m, 3H), 3.70 (s, 2.5H), 3.56 (s, 0.50H), 2.36 (s, 052H), 2.24 (s, 2.4H), 1.45−1.39 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.6, 171.9, 166.2, 138.8, 136.9, 131.4, 129.2, 128.2, 126.6, 54.8, 52.6, 50.6, 29.2, 15.0. HRMS (CI, NH_3) $[M + H]^+$ calcd for $C_{16}H_{20}NO_4$ 290.1387, found 290.1395.

Methyl 6*R*-(*tert*-Butyldiphenylsilyloxy)-3-oxo-heptanoate (33). Into a 100-mL round-bottom flask containing a 60% suspension of sodium hydride in mineral oil (221 mg, 5.5 mmol) under an atmosphere of N_2 was added THF (20 mL). The resulting gray suspension was brought to 0 °C and methyl acetoacetate (**11**) (0.54 mL, 5 mmol) was added slowly. The resulting yellow solution was allowed to stir at this temperature for 0.5 h. The temperature of the yellow solution was lowered to −15 °C and a 2.5 M solution of *n*-BuLi (2.2 mL, 5.5 mL) was added. The resulting red solution was allowed to stir for 15 min and *R*-propylene oxide (**32**) (0.39 mL, 5.5 mmol) was added. The solution was then stirred for 4 h at this temperature and TBDPSCl (1.17 mL, 5 mmol) was added. The solution was allowed to slowly warm to room temperature and stirred for an additional 8 h. The reaction was quenched with NH_4Cl (25 mL), and the solution was extracted with ether (3 × 25 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated in vacuo. Chromatography on silica (15:1, hexanes/EtOAc; R_f 0.18) yielded 823 mg (48%) of **33** as a clear oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.70−7.67 (m, 3H), 7.46−7.38 (m, 7H), 3.96−3.90 (m, 1H), 3.72 (s, 3H), 3.38 (d, 1H, J = 15.6 Hz), 3.35 (d, 1H, J = 15.6 Hz), 2.59 (ddd, 2H, J = 5.9, 9.3, 15.1 Hz), 1.82−1.69 (m, 2H), 1.10−1.07 (m, 12H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 202.5, 167.6, 135.8, 135.8, 134.8, 129.6, 129.5, 127.6, 127.5, 68.4, 52.2, 48.9, 38.7, 32.5, 27.0, 23.1, 19.2. $[\alpha]^{20}_D$ +10.25 (*c* 0.0122 g/mL, benzene).

Methyl 7*R*-(*tert*-Butyl-diphenyl-silanyloxy)-4-oxo-oct-2-enoate[18] (34). A 100-mL round-bottom flask was equipped with a stir bar and charged with 15 mL of methylene chloride and diethyl zinc (1.0 M in hexanes, 1.95 mL, 1.95 mmol) under an atmosphere of N_2 at 0 °C. Methylene iodide (0.16 mL, 2.03 mmol) was added and the resulting white suspension was stirred for 10 min. Compound **33** (146 mg, 0.39 mmol) was added rapidly by syringe and allowed to stir at 0 °C for 30 min. Iodine (516 mg, 2.03 mmol) was added in a single portion to the reaction mixture and allowed to stir until a pink color persisted for 30 s. Saturated aqueous sodium thiosulfate (10 mL) was added and the biphasic mixture was stirred until the pink color had disappeared. DBU (0.58 mL, 3.9 mmol) was added and the mixture was stirred vigorously for 1 min. Saturated aqueous ammonium chloride was added and the solution was extracted three times with diethyl ether. The combined organic layers were dried with anhydrous sodium sulfate and concentrated in vacuo. The residue was chromatographed on silica (15:1, hexanes/ethyl acetate; R_f 0.19) to yield 96 mg (64%) of **34** as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.65−7.62 (m, 3H), 7.43−7.36 (m, 7H), 6.98 (d, 1H, J = 16.1 Hz), 6.58 (d, 1H, J = 16.1 Hz), 3.96−3.90 (m, 1H), 3.82 (s, 3H), 2.64 (ddd, 2H, J = 5.9, 9.3, 15.1 Hz), 1.82−1.69 (m, 2H), 1.08 (d, 3H, J = 8.3 Hz), 1.05 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 199.5, 166.0, 139.5, 135.9, 135.8, 134.8, 130.1, 129.7, 129.6, 127.6, 127.5, 68.7, 52.5, 37.5, 33.0, 27.3, 23.5, 19.5; $[\alpha]^{25}_D$ +19.1 (*c* 0.0045 g/mL, methanol).[18] Optical purity was assessed to be >95% by HPLC, using a chiral stationary phase.

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Supporting Information Available: ^{1}H and ^{13}C NMR spectra for **8**, **10**, **12**, **14**, **16**, **18**, **20**, **22**, **26**, **28**, **30**, **33**, and **34**. This material is available free of charge via the Internet at http://pubs.acs.org.

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