Tandem Chain Extension-Homoenolate Formation: The Formation of α-Methylated-γ-Keto Esters

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Supporting Information

General Experimental

All reactions were run in oven-dried glassware under nitrogen atmosphere and stirred with teflon-coated magnetic stir-bars. The terms concentrated *in vacuo* or under reduced pressure refer to the use of a rotary-evaporator. Methylene chloride was distilled from phosphorous pentoxide. Ethyl acetate and hexanes were distilled prior to use. Reagents were purchased from commercial suppliers and used without further purification. Diethyl zinc was used as a 1.0 M solution in hexanes. Methylene iodide (CH_2I_2) was purchased from commercial suppliers and non-oxidized copper wire was added as a stabilizer. Column chromatography was performed on EM Science flash silica gel (35-75μm). Mobile phases were used as noted. Thin Layer Chromatography (TLC) was carried out on EM Science F254 glass plates and visualized by UV and anisaldehyde or phosphomolybdic acid stains. The R_f values were determined with the same solvent used for column chromatography. Low Resolution Mass Spectroscopy were performed by the University of New Hampshire Instrumentation Center on a Perkin-Elmer 2400 Analyzer. High Resolution Mass Spectroscopy was performed at the University of California Riverside Mass Spectrometry Facility.

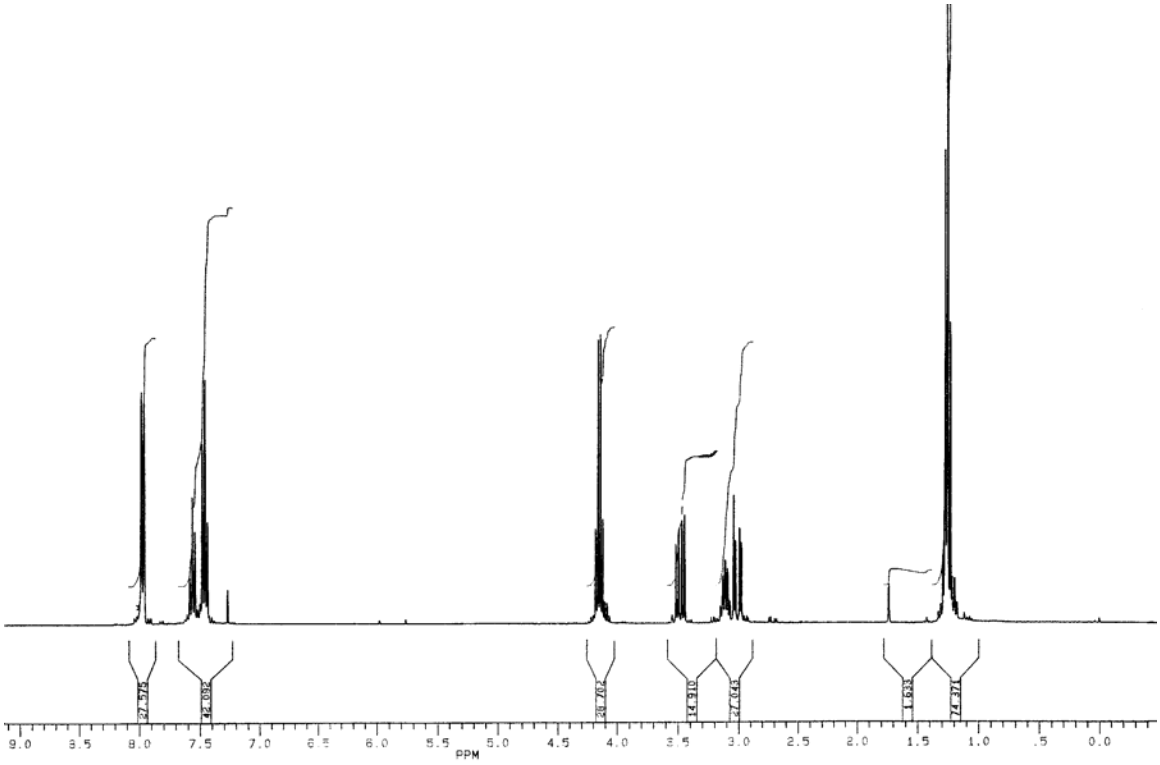
Ethyl 2-methyl-4-oxo-4-phenyl-butanoate (6)

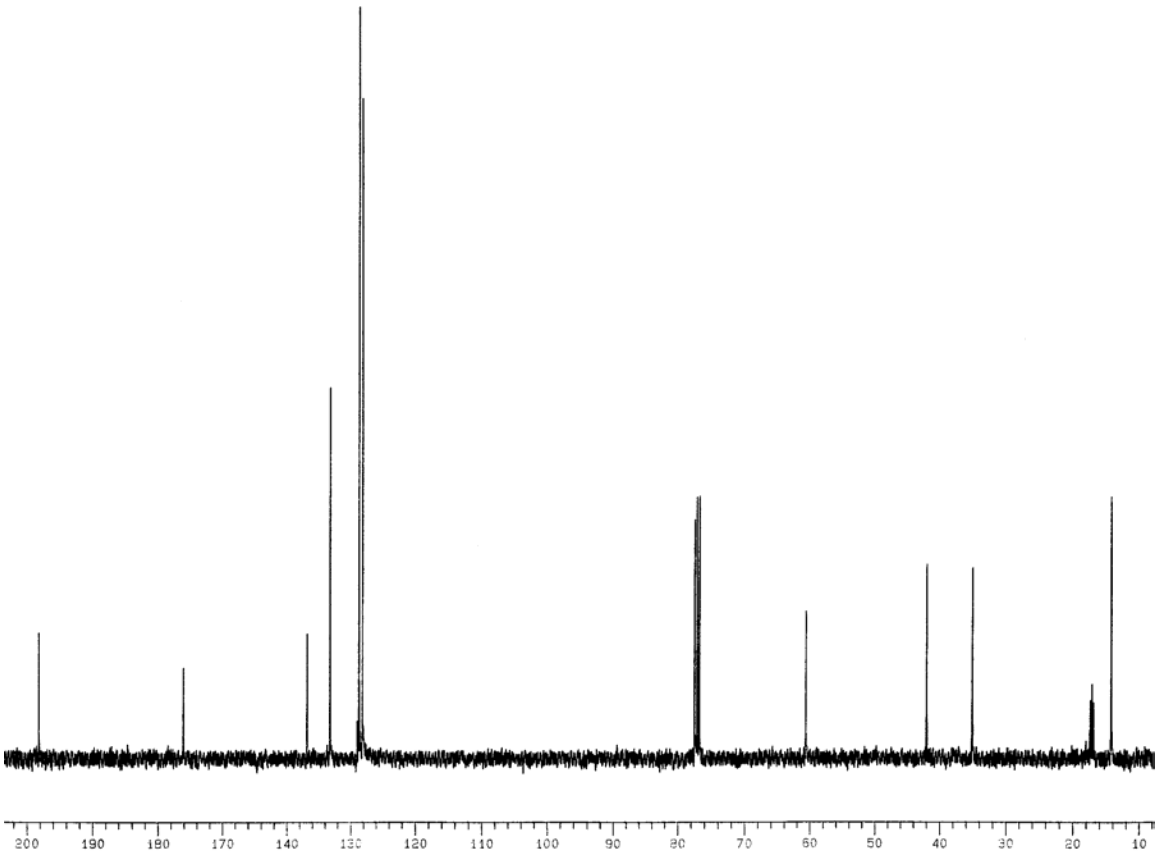
A 50 mL round-bottom flask was equipped with a stir bar and charged with 15 mL of methylene chloride and diethyl zinc (1.0 M in hexanes, 4.0 mL, 4.0 mmol) under an inert atmosphere. The solution was cooled to 0 °C and methylene iodide (0.32 mL, 4.0 mmol) in methylene chloride (2.5 mL) was added dropwise. The resulting white suspension was stirred for 10 minutes, then ethyl benzoylacetate (192 mg, 1.0 mmol) was added rapidly by syringe. Trimethylsilyl chloride (25 μL, 0.2 mmol) was added by micro-syringe after 30 seconds. The mixture was stirred for 30 minutes at 0 °C, quenched with saturated aqueous ammonium chloride, and extracted three times with diethyl ether. The combined

organic extracts were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was chromatographed on silica (12:1, hexanes: ethyl acetate; R_f = 0.2) to yield 155 mg (70%) of α-methyl γ-keto ester **6** as a clear colorless liquid that provided spectra consistent with those reported in the literature.[1] ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.94-7.99 (m, 2H), 7.56 (m, 1H), 7.43-7.49 (m, 2H), 4.15 (q, 2H, *J* = 7.1 Hz), 3.48 (dd, 1H, *J* = 17.5, 7.7 Hz), 3.11 (m, 1H), 3.01 (dd, 1H, *J* = 17.5, 5.5 Hz), 1.22-1.29 (m, 6H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 198.1, 176.0, 136.7, 133.2, 128.6, 128.0, 60.6, 41.9, 35.0, 17.3, 14.2; IR (film) 3100-2850, 1734, 1685, 1215, 1180.

Ethyl 2-deuteriomethyl-4-oxo-4-phenyl-butanoate (10)

The same procedure as described for the preparation of **10** was performed, with the exception that D_2O was used for the quench instead of aqueous ammonium chloride. The relevant features of the spectra that indicate incorporation of deuterium on the methyl group include (a) the multiplet at 1.25 ppm in the ^{1}H-NMR spectrum that integrates for five protons rather than six; and (b) the triplet at 17.0 ppm in the ^{13}C-NMR for the α-methyl carbon.





Methyl 2-methyl-4-oxo-pentanoate (12)

A 50 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 inert atmosphere. The solution was cooled to 0 °C and methylene iodide (0.40 mL, 5.0 mmol) in methylene chloride (2.5 mL) was added dropwise. The resulting white suspension was stirred for 10 minutes, then methyl acetoacetate (116 mg, 1.0 mmol) was added rapidly by syringe. Trimethylsilyl chloride (25 μL, 0.2 mmol) was added by micro-syringe after 30 seconds. The mixture was stirred for 30 minutes at 0 °C, quenched with saturated aqueous ammonium chloride, and extracted three times with diethyl ether. The combined organic extracts were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was chromatographed on silica (5:1, hexanes: ethyl acetate; R_f = 0.3) to yield 89 mg (62%) of α-methyl γ-keto ester **12** as a clear colorless liquid that provided spectra consistent with those reported in the literature.[6] ^{1}H NMR (360 MHz, $CDCl_3$) δ 3.69 (s, 3H), 2.88-2.99 (m, 2H), 2.48 (dd, 1H, J = 20.7, 8.2 Hz), 2.16 (s, 3H), 1.18 (d, 3H, J = 6.8 Hz); ^{13}C NMR (90 MHz, $CDCl_3$) δ 207.0, 176.5, 52.0, 46.6, 34.6, 30.1, 17.0; IR (film) 2950-2800, 1737, 1718.

***tert*-Butyl 2-methyl-4-oxo-pentanoate (14)**

A 50 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 inert

atmosphere. The solution was cooled to 0 °C and methylene iodide (0.40 mL, 5.0 mmol) in methylene chloride (2.5 mL) was added dropwise. The resulting white suspension was stirred for 10 minutes, then *tert*-butyl acetoacetate (158 mg, 1.0 mmol) was added rapidly by syringe. Trimethylsilyl chloride (12.5 μL, 0.1 mmol) was added by micro-syringe after 30 seconds. The mixture was stirred for 30 minutes at 0 °C, quenched with saturated aqueous ammonium chloride, and extracted three times with diethyl ether. The combined organic extracts were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was chromatographed on silica (10:1, hexanes: ethyl acetate; R_f = 0.2) to yield 135 mg (73%) of α-methyl γ-keto ester **14** as a clear colorless liquid. ^{1}H NMR (360 MHz, $CDCl_3$) δ 2.77-2.90 (m, 2H), 2.42 (dd, 1H, *J* = 20.7, 8.6 Hz), 2.16 (s, 3H), 1.44 (s, 9H), 1.14 (d, 3H, *J* = 6.5 Hz); ^{13}C NMR (90 MHz, $CDCl_3$) δ 206.5, 174.7, 80.0, 46.4, 35.4, 29.7, 27.6, 16.8; IR (film) 3000-2850, 1719 (broad), 1368, 1155. HRMS (CI/CH_4) MH^+ Calcd. for $C_{10}H_{219}O_3$: 187.1334, found: 187.1338.

Benzyl 2-methyl-4-oxo-pentanoate (16)

A 50 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, 4.0 mL, 4.0 mmol) under an inert atmosphere. The solution was cooled to 0 °C and methylene iodide (0.32 mL, 4.0 mmol) in methylene chloride (2.5 mL) was added dropwise. The resulting white suspension was stirred for 10 minutes, then benzyl acetoacetate (144 mg, 0.75 mmol) was added rapidly by syringe. Trimethylsilyl chloride (25 μL, 0.2 mmol) was added by micro-syringe after 30 seconds. The mixture was stirred for 30 minutes at 0 °C, quenched with saturated aqueous ammonium chloride, and extracted three times with diethyl ether. The combined organic extracts were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was chromatographed on silica (10:1, hexanes: ethyl acetate; R_f = 0.15) to yield 94 mg (57%) of α-methyl γ-keto ester **16** as a clear colorless liquid. ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.32-7.37 (m, 5H), 5.13 (d, 1H, *J* = 12.4 Hz), 5.10 (d, 1H, *J* = 12.4 Hz), 2.89-3.06 (m, 2H), 2.49 (dd, 1H, *J* = 17.2, 4.9 Hz), 2.14 (s, 3H), 1.20 (d, 3H, *J* = 7.0 Hz); ^{13}C NMR (90 MHz, $CDCl_3$) δ 207.0, 175.6, 136.0, 128.5, 128.2, 128.0, 66.4, 46.6, 34.8, 30.1, 17.0; IR (film) 3100-2850, 1734, 1718, 1161. HRMS (CI/CH_4) MH^+ Calcd. for $C_{13}H_{17}O_3$: 221.1178, found: 221.1175.

N,N-Dimethyl 2-methyl-4-oxo-4-phenyl-butanamide (18)

A 50 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 inert atmosphere. The solution was cooled to 0 °C and methylene iodide (0.40 mL, 5.0 mmol) in methylene chloride (2.5 mL) was added dropwise. The resulting white suspension was stirred for 10 minutes, then N,N-dimethyl 3-oxo-3-phenyl-propanamide (**17**)[2] (191 mg, 1.0 mmol) was dissolved in 1 mL of methylene chloride and added rapidly by syringe. Trimethylsilyl chloride (100 μL, 0.8 mmol) was added by micro-syringe after 10 minutes. The mixture was stirred for 30 minutes at 0 °C, quenched with saturated aqueous ammonium chloride, and extracted three times with ethyl acetate. The combined organic

extracts were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was chromatographed on silica (1:1, hexanes: ethyl acetate; R_f = 0.25) to yield 115 mg (53%) of α-methyl γ-keto amide **18** as a white solid (mp = 79.8-81.3 °C). ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.96-8.00 (m, 2H), 7.55 (m, 1H), 7.41-7.47 (m, 2H), 3.66 (dd, 1H, *J* = 18.0, 8.8 Hz), 3.38-3.49 (m, 1H), 3.19 (s, 3H), 2.89-2.97 (m, 4H), 1.21 (d, 3H, *J* = 7.0 Hz); ^{13}C NMR (90 MHz, $CDCl_3$) δ 199.2, 175.8. 136.8, 133.0, 128.5, 128.1, 43.0, 37.8, 36.0, 31.3, 17.5; IR (film) 3100-3000, 2975-2850, 1685, 1643, 1450, 1400. HRMS (EI) M^+ Calcd. for $C_{13}H_{17}NO_2$: 219.1259, found: 219.1255.

N-Cyclohexyl 4-oxo-pentanamide (20) and N-Cyclohexyl 2-methyl-4-oxo-pentanamide (21)

A 50 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 inert atmosphere. The solution was cooled to 0 °C and methylene iodide (0.40 mL, 5.0 mmol) in methylene chloride (2.5 mL) was added dropwise. The resulting white suspension was stirred for 10 minutes, then N-cyclohexyl 3-oxo-butanamide **19**[3] (183 mg, 1.0 mmol) was dissolved in 1 mL of methylene chloride and added rapidly by syringe. Trimethylsilyl chloride (50 μL, 0.4 mmol) was added by micro-syringe after 30 seconds. The mixture was stirred for 30 minutes at 0 °C, quenched with saturated aqueous ammonium chloride, and extracted three times with ethyl acetate. The combined organic extracts were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was chromatographed on silica (1:1, hexanes: ethyl acetate; R_f = 0.2) to yield 30 mg (14%) of α-methyl γ-keto amide **21** as a white solid (mp = 91.9-93.5 °C). ^{1}H NMR (360 MHz, $CDCl_3$) δ 5.65 (s, 1H), 3.70 (m, 1H), 2.95 (dd, 1H, *J* = 18.0, 9.0 Hz), 2.68 (m, 1H), 2.43 (dd, 1H, *J* = 18.0, 4.4 Hz), 2.15 (s, 3H), 1.05-1.90 (m, 10H), 1.14 (d, 3H, *J* = 7.0 Hz); ^{13}C NMR (90 MHz, $CDCl_3$) δ 207.9, 174.5, 48.0, 47.4, 36.0, 33.0, 30.2, 25.5, 24.8, 17.9; IR (film) 2935, 1714, 1654. HRMS (EI) M^+ Calcd. for $C_{12}H_{21}NO_2$: 211.1572, found: 221.1581.Also isolated was 101 mg (48%) of N-cyclohexyl 4-oxo-pentanamide **20** as a white solid (mp = 105.7-106.5 °C).[4] ^{1}H NMR (360 MHz, $CDCl_3$) δ 5.57 (s, 1H), 3.67-3.78 (m, 1H), 2.79 (t, 2H, *J* = 6.5 Hz), 2.39 (t, 2H, *J* = 6.5 Hz), 2.18 (s, 3H), 1.85-1.94 (m, 2H), 1.65-1.74 (m, 2H), 1.56-1.65 (m, 1H), 1.28-1.41 (m, 2H), 1.06-1.22 (m, 3H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 207.5, 171.0, 48.2, 38.7, 33.1, 30.2, 30.0, 25.5, 24.8; IR (KBr) 3295, 2934, 2854, 1709, 1632, 1558, 1436.

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