

**Addition of Organocerium Reagents to
Morpholine Amides: Synthesis of Important
Pheromone Components of *Achaea janata*.**

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General Methods. Most solvents and reagents were used without purification unless mentioned otherwise. Solvents (EtOAc and hexane) for flash chromatography were distilled. Dry THF was prepared by distillation from sodium/benzophenone under a nitrogen atmosphere immediately before use. Pyridine was dried over CaH₂ and distilled under nitrogen. Benzene was distilled from sodium and kept under nitrogen. Reactions with compounds sensitive to air or moisture were performed under nitrogen. TLC was run on silica gel 60 F₂₅₄ plates (0.25 mm thick), and visualized by UV light or Iodine or a Ce-Mo staining solution (phosphomolybdate, 25 g; Ce(SO₄)₂·4H₂O, 10 g; H₂SO₄ 60 mL, concentrated; water, 940 mL) with heating. Flash chromatography³⁸ was performed using a silica gel 60 (mesh size 0.040-0.063 mm) using a silica gel:crude compound weight ratio of ca. 30:1. Analytical GC was performed using a Carlo Erba Fractovap 4160, with a capillary fused silica column (0.32 mm x 25 m), stationary phase OV1 (film thickness 0.40-0.45 nm). Infrared spectra were measured on a Perkin-Elmer Paragon 500 FT-IR Fourier Transform spectrophotometer using thin films on NaCl plates. Only the characteristic peaks are reported. Nuclear magnetic resonance (NMR) spectra were recorded on a Varian Gemini 200 spectrometer. ¹H NMR (200 MHz) spectra were taken in CDCl₃ with residual signals of CHCl₃ (7.26 ppm) as an internal standard. ¹³C NMR (75.5 MHz) spectra were recorded in CDCl₃ and chemical shifts are reported relative to the center line of the triplet at 77.00 ppm for deuteriochloroform. Mass spectra were determined with an HP5890 Series II capillary GC operating in split mode with helium as the carrier gas and fitted with mass-selective (MSD) HP5790 MS by means of the EI technique (70 eV).

Preparation of Morpholine Amides. Typical Procedure. To a mixture containing 5.0 mmol of fatty acid and 25 mL of dry benzene was added thionyl chloride (30 mL) and the mixture was stirred for 24 h at 50°C. The solvent and excess of thionyl chloride were evaporated off under reduced pressure and the residual acid chloride was used in the next stage of preparation without purification.

To a stirred solution of the acid chloride in 60 mL of EtOH-free CHCl₃ was added dry morpholine (0.48 g, 5.5 mmol) in EtOH-free CHCl₃ (1 mL). The mixture was cooled at 0°C, and pyridine (0.43 g, 5.5 mmol) was added dropwise *via* syringe. Stirring was continued for 20 h at room temperature, and then the mixture was evaporated under reduced pressure. The residue was diluted with a 1:1 mixture of Et₂O and CH₂Cl₂, washed with brine containing sufficient 2N HCl to remove the amines, washed with saturated aqueous NaHCO₃, and dried over Na₂SO₄. After evaporation of solvent the crude product was purified by flash chromatography (30% EtOAc/hexane), affording the pure morpholine amide.

1-Morpholin-4-yldecan-1-one (12a): colorless oil; IR (neat, cm⁻¹) 1651; ¹H NMR δ 0.86 (t, 3H, J = 6.23 Hz), 1.24-1.40 (m, 12H), 1.56-1.64 (m, 2H), 2.29 (t, 2H, J = 7.25 Hz), 3.42-3.50 (m, 2H), 3.57-3.67 (m, 6H); ¹³C NMR δ 14.17, 23.30, 24.82, 29.20, 29.41, 29.60, 30.04, 32.58, 32.76, 42.00, 44.90, 66.25, 170.01; EI-MS *m/z* 241[M⁺], 142, 129, 114, 85, 57 (100), 43, 41. Anal. Calcd for C₁₄H₂₇NO₂: C, 69.66; H, 11.27; N, 5.80. Found: C, 69.69; H, 11.25; N, 5.82.

1-Morpholin-4-ylhexan-1-one (12b): colorless oil; IR (neat, cm^{-1}) 1672; ^1H NMR δ 0.86 (t, 3H, $J = 6.85$ Hz), 1.35-1.60 (m, 6H), 3.01 (t, 2H, $J = 7.20$ Hz), 3.50-3.70 (m, 2H), 3.85-3.94 (m, 6H); ^{13}C NMR δ 13.85, 22.45, 26.05, 30.94, 33.05, 41.90, 44.81, 66.25, 177.76; EI-MS m/z 185 $[\text{M}^+]$, 129 (100), 114, 86, 70, 43, 41. Anal. Calcd for $\text{C}_{10}\text{H}_{19}\text{NO}_2$: C, 64.83; H, 10.34; N, 7.56. Found: C, 64.84; H, 10.35; N, 7.50.

2-Methyl-1-morpholin-4-ylbutan-1-one (12c): colorless oil; IR (neat, cm^{-1}) 1643; ^1H NMR δ 0.88 (t, 3H, $J = 7.41$ Hz), 1.10 (d, 3H, $J = 6.79$ Hz), 1.34-1.48 (m, 1H), 1.62-1.76 (m, 1H), 2.51-2.62 (m, 1H), 3.51-3.59 (m, 2H), 3.64-3.68 (m, 6H); ^{13}C NMR δ 13.75, 17.60, 27.90, 36.70, 41.67, 45.04, 66.10, 171.65; EI-MS m/z 171 $[\text{M}^+]$, 156, 143, 114, 86, 57 (100), 43, 41. Anal. Calcd for $\text{C}_9\text{H}_{17}\text{NO}_2$: C, 63.13; H, 10.01; N, 8.18. Found: C, 63.10; H, 10.05; N, 8.17.

1-Morpholin-4-yl-2-phenylpropan-1-one (12d): colorless oil; IR (neat, cm^{-1}) 3172, 1612, 1540; ^1H NMR δ 1.17 (d, 3H, $J = 7.02$ Hz), 3.72-3.84 (m, 3H), 3.88-3.97 (m, 6H), 7.26-7.35 (m, 3H, Arom.), 7.56-7.60 (m, 2H, Arom.); ^{13}C NMR δ 16.98, 42.15, 45.06, 48.76, 66.10, 127.04, 127.96, 128.44, 140.78, 169.01; EI-MS m/z 219 $[\text{M}^+]$, 114 (100), 105, 86, 77, 70, 51. Anal. Calcd for $\text{C}_{13}\text{H}_{17}\text{NO}_2$: C, 71.21; H, 7.81; N, 6.39. Found: C, 71.18; H, 7.78; N, 6.40.

(E)-1-Morpholin-4-yl-3-phenylprop-2-en-1-one (12e): pale yellow oil; IR (neat, cm^{-1}) 3106, 3009, 1605, 1453; ^1H NMR δ 3.70 (bs, 8H), 6.84 (d, 1H, $J = 15.43$ Hz), 7.26-7.38 (m, 3H, Arom.), 7.50-7.55 (m, 2H, Arom.), 7.70 (d, 1H, $J = 15.47$ Hz); ^{13}C NMR δ 42.60, 44.26, 66.57, 115.30, 125.65, 127.10, 128.30, 144.17, 145.20, 164.76; EI-MS m/z 217 $[\text{M}^+]$, 131 (100), 103, 86, 77, 51. Anal. Calcd for $\text{C}_{13}\text{H}_{15}\text{NO}_2$: C, 71.87; H, 6.96; N, 6.45. Found: C, 71.88; H, 6.92; N, 6.40.

(E)-1-Morpholin-4-yl-octadec-9-en-1-one (12f): colorless oil; IR (neat, cm^{-1}) 1675, 1590; ^1H NMR δ 0.86 (t, 3H, $J = 7.01$ Hz), 1.24-1.39 (m, 22H), 1.57-1.65 (m, 2H), 1.98-2.07 (m, 2H), 2.30 (t, 2H, $J = 7.29$ Hz), 3.42-3.47 (m, 2H), 3.58-3.67 (m, 6H), 5.29-5.35 (m, 2H); ^{13}C NMR δ 14.06, 20.54, 21.64, 22.76, 24.60, 24.86, 25.98, 26.30, 26.76, 27.09, 27.96, 29.75, 30.50, 31.24, 34.20, 44.65, 45.69, 66.85, 128.15, 134.06, 170.17; EI-MS m/z 351 $[\text{M}^+]$, 198, 142, 129 (100), 114, 88, 86, 70, 55. Anal. Calcd for $\text{C}_{22}\text{H}_{41}\text{NO}_2$: C, 75.16; H, 11.75; N, 3.98. Found: C, 75.20; H, 11.68; N, 4.00.

(9Z,12Z,15Z)-1-Morpholin-4-yl-octadeca-9,12,15-trien-1-one (17b): pale yellow oil (84%); IR (neat, cm^{-1}) 3018, 1673, 1545; ^1H NMR δ 0.97 (t, 3H, $J = 7.50$ Hz), 1.26-1.34 (m, 8H), 1.58-1.66 (m, 2H), 2.00-2.11 (m, 4H), 2.30 (t, 2H, $J = 7.65$ Hz), 2.77-2.83 (m, 4H), 3.45-3.49 (m, 2H), 3.64-3.74 (m, 6H), 5.32-5.40 (m, 6H); ^{13}C NMR δ 14.76, 21.03, 25.72, 26.01, 26.10, 27.69, 29.63, 29.81, 29.92, 30.07, 33.60, 42.33, 46.52, 67.31, 127.59, 128.21, 128.72, 128.86, 130.74, 132.44, 172.33. Anal. Calcd for $\text{C}_{22}\text{H}_{37}\text{NO}_2$: C, 76.03; H, 10.73; N, 4.03. Found: C, 76.06; H, 10.87; N, 4.02.

1-Morpholin-4-yl-octadecan-1-one (17c): colorless oil (89%); IR (neat, cm^{-1}) 1689; ^1H NMR δ 0.97 (t, 3H, $J = 6.19$ Hz), 1.25-1.40 (m, 28H), 1.58-1.65 (m, 2H), 2.40 (t, 2H, $J = 7.33$ Hz), 3.50-3.55 (m, 2H), 3.68-3.75 (m, 6H); ^{13}C NMR δ 14.05, 21.06, 22.68, 24.05, 24.82, 25.76, 29.25, 29.65, 29.81, 29.95, 30.04, 30.76, 31.15, 31.76, 31.96, 32.54, 32.87, 41.36, 44.65, 66.08, 170.15. Anal. Calcd for $\text{C}_{22}\text{H}_{43}\text{NO}_2$: Found: C, 74.73; H, 12.26; N, 3.96. Found: C, 74.59; H, 12.35; N, 4.02.

Reaction between morpholine and organocerium reagents. A 250 mL three-neck flask fitted

with septum and gas inlet was charged with $\text{CeCl}_3 \cdot 7\text{H}_2\text{O}$ (4.46 g, 12 mmol), which as dried by heating to 140°C at 0.2 Torr for 2 h. The flask was allowed to cool at room temperature and vented to dry nitrogen, and THF (40 mL) was added from a syringe. This slurry was stirred overnight at room temperature and cooled to -78°C . To this white suspension organomagnesium or organolithium compound (12 mmol) was added slowly from a syringe, and the reaction mixture was stirred for 2 h at -78°C . A solution of morpholine amides **12** (4 mmol) in THF (25 mL) was added dropwise and the reaction mixture was stirred for 1.5 h at -78°C . Then, it was quenched by addition of 10% aqueous acetic acid (90 mL) and extract with Et_2O (5 x 75 mL). The combined organic layers were washed with NaHCO_3 sat and brine, dried over anhydrous Na_2SO_4 and concentrated to afford an oil. Purification by flash chromatography on a silica gel column by a mixture of hexane-ethyl acetate (8:2) as eluent afforded ketone in good yield.

Tridecan-4-one (15aa): colorless oil; IR (neat, cm^{-1}) 1715; ^1H NMR δ 0.75 (t, 3H, $J = 7.24$ Hz), 0.89 (t, 3H, $J = 7.15$ Hz), 1.08-1.15 (m, 2H), 1.25-1.35 (m, 8H), 1.45-1.70 (m, 6H), 2.10 (t, 2H, $J = 7.05$ Hz), 2.45 (t, 2H, $J = 7.05$ Hz); ^{13}C NMR δ 13.95, 14.24, 17.00, 23.05, 23.60, 29.35, 29.60, 29.62, 29.70, 31.85, 42.05, 44.85, 210.64; EI-MS m/z 198 $[\text{M}^+]$, 155, 99, 86, 71, 57, 43 (100), 41. Anal. Calcd for $\text{C}_{13}\text{H}_{26}\text{O}$: C, 78.72; H, 13.21. Found: C, 78.69; H, 13.25.

2-Methyldodecan-3-one (15ab): oil; IR (neat, cm^{-1}) 1745; ^1H NMR δ 0.87 (t, 3H, $J = 6.95$ Hz), 1.12 (d, 6H, $J = 7.25$ Hz), 1.20-1.27 (m, 10H), 1.45-1.62 (m, 4H), 2.04 (hept, 1H, $J = 7.20$ Hz), 2.30 (t, 2H, $J = 7.05$ Hz); ^{13}C NMR δ 14.05, 18.20, 22.55, 23.68, 29.55, 29.70, 29.84, 39.75, 41.04, 212.69; EI-MS m/z 183, 155, 99, 85, 71, 55, 43 (100), 41. Anal. Calcd for $\text{C}_{13}\text{H}_{26}\text{O}$: C, 78.72; H, 13.21. Found: C, 78.74; H, 13.20.

Octan-3-one (15bc): colorless oil; IR (neat, cm^{-1}) 1716; ^1H NMR δ 0.94 (t, 3H, $J = 7.15$ Hz), 1.05 (t, 3H, $J = 7.01$ Hz), 1.20-1.45 (m, 4H), 1.60-1.68 (m, 2H), 2.36 (t, 2H, $J = 6.95$ Hz), 2.39 (t, 2H, $J = 6.85$ Hz); ^{13}C NMR δ 1 $^{\text{S}}$ 3.96, 14.12, 22.60, 23.78, 31.86, 36.03, 42.76, 213.61; EI-MS m/z 128 $[\text{M}^+]$, 99, 72, 71, 57, 43 (100), 41. Anal. Calcd for $\text{C}_8\text{H}_{16}\text{O}$: C, 74.94; H, 12.58. Found: C, 74.90; H, 12.55.

3-Methyloctan-4-one (15cd): colorless oil; IR (neat, cm^{-1}) 1730; ^1H NMR δ 0.92 (t, 6H, $J = 7.02$ Hz), 1.12 (d, 3H, $J = 6.85$ Hz), 1.25-1.56 (m, 6H), 2.20-2.24 (m, 1H), 2.25 (t, 2H, $J = 7.28$ Hz); ^{13}C NMR δ 12.05, 13.94, 14.50, 22.37, 26.00, 26.09, 42.10, 43.94, 212.00; EI-MS m/z 142 $[\text{M}^+]$, 127, 113, 99, 72, 71, 57 (100), 43, 41. Anal. Calcd for $\text{C}_9\text{H}_{18}\text{O}$: C, 76.00; H, 12.76. Found: C, 75.96; H, 12.75.

3-Methyltetradecan-4-one (15ce): colorless oil; IR (neat, cm^{-1}) 1728; ^1H NMR δ 0.88 (t, 3H, $J = 7.03$ Hz), 1.09 (d, 3H, $J = 6.95$ Hz), 1.20-1.30 (m, 6H), 1.34-1.65 (m, 12H), 2.22-2.27 (m, 1H), 2.25 (t, 2H, $J = 7.32$ Hz); ^{13}C NMR δ 12.10, 14.15, 15.25, 22.49, 23.63, 25.84, 28.36, 29.56, 29.82, 32.10, 39.01, 42.05, 44.63, 212.74; EI-MS m/z 197, 142, 126, 99, 71, 57 (100), 43, 41. Anal. Calcd for $\text{C}_{15}\text{H}_{30}\text{O}$: C, 79.58; H, 13.36. Found: C, 79.59; H, 13.35.

2-Phenyltridecan-3-one (15de): colorless oil; IR (neat, cm^{-1}) 3013, 1715, 1600; ^1H NMR δ 0.93

(t, 3H, $J = 7.16$ Hz), 1.14 (d, 3H, $J = 7.02$ Hz), 1.24-1.35 (m, 6H), 1.40-1.65 (m, 10H), 2.36 (t, 2H, $J = 6.66$ Hz), 3.95 (q, 1H, $J = 7.00$ Hz), 7.04-7.12 (m, 3H, Arom.), 7.15-7.21 (m, 2H, Arom.); ^{13}C NMR δ 14.12, 19.00, 22.70, 23.85, 29.05, 29.40, 29.75, 31.00, 40.76, 52.01, 126.04, 127.43, 127.94, 136.99, 214.05; EI-MS m/z 274[M^+], 169 (100), 105, 95, 85, 71, 57, 43, 41. Anal. Calcd for $\text{C}_{19}\text{H}_{30}\text{O}$: C, 83.15; H, 11.02. Found: C, 83.19; H, 11.05.

(E)-1-Phenylhept-1-en-3-one (15ed): colorless oil; IR (neat, cm^{-1}) 3020, 1695, 1612; ^1H NMR δ 0.92 (t, 3H, $J = 7.24$ Hz), 1.35-1.43 (m, 2H), 1.60-1.65 (m, 2H), 2.56 (t, 2H, $J = 7.30$ Hz), 6.75 (d, 1H, $J = 16.20$ Hz), 7.32-7.40 (m, 3H, Arom.), 7.48-7.52 (m, 2H, Arom.), 7.56 (d, 1H, $J = 16.00$ Hz); ^{13}C NMR δ 14.06, 22.46, 26.52, 41.03, 126.35, 128.64, 128.98, 130.64, 134.26, 143.05, 200.64; EI-MS m/z 188[M^+], 146, 131 (100), 103, 77, 65, 51. Anal. Calcd for $\text{C}_{13}\text{H}_{14}\text{O}$: C, 82.94; H, 8.57. Found: C, 82.88; H, 8.62.

(E)-1,4-Diphenylbut-3-en-2-one (15ef): pale yellow oil; IR (neat, cm^{-1}) 3010, 1690, 1585; ^1H NMR δ 3.77 (s, 2H), 6.76 (d, 1H, $J = 15.75$ Hz), 7.05-7.22 (m, 6H, Arom.), 7.30-7.48 (m, 4H, Arom.), 7.54 (d, 1H, $J = 16.01$ Hz); ^{13}C NMR δ 48.65, 126.65, 127.64, 129.30, 129.64, 135.75, 138.36, 150.26, 197.39; EI-MS m/z 222[M^+], 131 (100), 103, 91, 77, 65, 51. Anal. Calcd for $\text{C}_{16}\text{H}_{14}\text{O}$: C, 86.45; H, 6.35. Found: C, 86.48; H, 6.32.

(Z)-Henicos-11-en-4-one (15fa): colorless oil; IR (neat, cm^{-1}) 3012, 1718, 1621; ^1H NMR δ 0.84-0.95 (m, 6H), 1.16-1.42 (m, 18H), 1.52-1.64 (m, 6H), 1.89-2.02 (m, 4H), 2.36 (t, 4H, $J = 7.33$ Hz), 5.30-5.36 (m, 2H). Anal. Calcd for $\text{C}_{21}\text{H}_{40}\text{O}$: C, 81.75; H, 13.07. Found: C, 81.79; H, 13.05.

Synthesis of Ketones 5a-c by Reaction of Amides with n-Propylmagnesium Chloride in the Presence of CeCl_3 . Typical Procedure. A 250 mL three-necked flask fitted with septum and gas inlet was charged with $\text{CeCl}_3 \cdot 7\text{H}_2\text{O}$ (4.46 g, 12 mmol), which was dried by heating to 140°C at 0.2 Torr for 2 h. The flask was allowed to cool at room temperature and vented to dry nitrogen, and THF (40 mL) was added from a syringe. This slurry was stirred overnight at room temperature and cooled to -78°C . To this white suspension n-propylmagnesium chloride (12 mL, 12 mmol) was added slowly from a syringe, and the reaction mixture was stirred for 2 h at -78°C . A solution of morpholine amides **17a-c** (4 mmol) in THF (25 mL) was added dropwise and the reaction mixture was stirred for 1.5 h at -78°C . Then, it was quenched by addition of 10% aqueous acetic acid (90 mL) and be extracted with Et_2O (5 x 75 mL). The combined organic layers were washed with sat NaHCO_3 and brine, dried over anhydrous Na_2SO_4 and concentrated to afford an oil. Purification by flash chromatography on a silica gel column by a mixture of hexane-ethyl acetate (8:2) as eluent afforded ketone in good yield.

(12Z,15Z)-Henicos-12,15-dien-4-one (5a): pale yellow oil (92%); IR (neat, cm^{-1}) 3019, 1719, 1459; ^1H NMR δ 0.88 (t, 3H, $J = 6.59$ Hz), 0.94 (t, 3H, $J = 7.45$ Hz), 1.24-1.42 (m, 14H), 1.53-1.64 (m, 4H), 2.01-2.05 (m, 4H), 2.32-2.40 (m, 4H), 2.73-2.78 (m, 2H), 5.30-5.38 (m, 4H); ^{13}C NMR δ 13.96, 14.69, 17.26, 19.05, 21.36, 23.64, 25.35, 24.44, 26.48, 27.40, 29.04, 29.15, 29.35, 42.98, 44.80, 122.36, 128.10, 128.60, 129.71, 211.76, 170.96. Anal. Calcd for $\text{C}_{21}\text{H}_{38}\text{O}$: C, 82.28; H, 12.50. Found: C, 82.29; H, 12.55.

(12Z,15Z,18Z)-Henicosa-12,15,18-trien-4-one (5b): pale yellow oil (89%); IR (neat, cm^{-1}) 3018, 1722, 1540; ^1H NMR δ 0.75 (t, 3H, $J = 7.35$ Hz), 0.84 (t, 3H, $J = 7.32$ Hz), 1.10-1.60 (m, 12H), 1.98-2.15 (m, 4H), 2.54 (t, 4H, $J = 7.35$ Hz), 2.70-2.82 (m, 4H), 5.25-5.40 (m, 6H); ^{13}C NMR δ 13.96, 14.90, 18.09, 21.96, 23.64, 25.36, 25.64, 26.42, 27.20, 29.25, 29.37, 29.75, 43.26, 44.82, 122.65, 123.04, 128.15, 128.35, 128.90, 130.17, 214.00. Anal. Calcd for $\text{C}_{21}\text{H}_{36}\text{O}$: C, 82.83; H, 11.92. Found: C, 82.85; H, 11.87.

Henicosan-4-one (5c): colorless oil (90%); IR (neat, cm^{-1}) 1735; ^1H NMR δ 0.87-0.95 (m, 6H), 1.21-1.32 (m, 28H), 1.54-1.62 (m, 4H), 2.38 (t, 4H, $J = 7.26$ Hz); ^{13}C NMR δ 13.61, 14.19, 17.20, 22.67, 23.54, 26.20, 27.29, 29.42, 29.65, 29.99, 30.44, 31.97, 42.65, 44.81, 211.55; EI-MS m/z 310 $[\text{M}^+]$, 267, 126, 99, 85, 71, 57 (100), 43, 41. Anal. Calcd for $\text{C}_{21}\text{H}_{42}\text{O}$: C, 81.22; H, 13.63. Found: C, 81.23; H, 13.66.