

The Supporting Information published June 29, 2006 contained an incorrect procedural step on page S6. The corrected version was published December 7, 2006.

Synthesis of *N*-Methoxy-*N*-methyl- β -enaminoketoesters: New Synthetic Precursors for the Regioselective Synthesis of Heterocyclic Compounds

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General experimental information

Commercially available reagents (Aldrich) were used without further purification unless otherwise noted. Solvents used for the synthesis were of analytical grade, dried over activated 4 Å molecular sieves when necessary (all solvents used under dry conditions had a water content < 25 ppm measured by Karl-Fischer titration). All reactions employing ethyl propynoate as starting material were performed under dry conditions in an atmosphere of argon (dried by passage through phosphorus pentoxide). MilliQ water was used for RP-HPLC. Analytical TLC was performed using pre-coated silica gel 60 F₂₅₄ plates and visualized using either UV light, phosphomolybdic acid or potassium permanganate stain. Flash chromatography was performed automatically on a Biotage Quad 3+ Parallel Flash Purification™ system with pre-packed columns (KP-SIL, 32-63 µm, 60 Å). Reactions requiring microwave heating were performed in sealed pressure-rated reaction tubes on an Emrys™ Creator from Personal Chemistry. Corrected melting points were measured in open capillary tubes on a Gallenkamp electrothermal melting point apparatus (**3g**, **7a** and **7g**) or on a Reichert melting point microscope, number N254-1R (**2h**, **2j**, **3a**, **3h**, **7b**, **7d**, **7f** and **7h**). ¹H and ¹³C NMR spectral data were recorded on a Bruker Avance 300 using the deuterated solvent as lock. Chemical shifts are reported in ppm relative to the residual solvent peak (¹H NMR) or the solvent peak (¹³C NMR) as the internal standard. Accurate mass determinations were performed on a Micromass LCT apparatus equipped with an AP-ESI probe calibrated with Leu-Enkephalin (556.2771 g/mol). HPLC was performed on a Waters 2525 system equipped with a Waters 2996 photodiode array detector and Xterra C18 Columns (anal.: 4.6 x 100 mm, 5 µm; prep.: 19 x 100 mm, 5 µm) with a flow of 1.0 mL/min. (anal.) or 15 mL/min. (prep.) 35% → 25% A 1-7 minutes (A: H₂O; B: CH₃CN). Purity determinations of all

substances stable in water were made by anal. HPLC (220 nm) and products of >98% purity were considered homogeneous.

Synthesis of acetylenic ketoesters

Ethyl 4-oxo-4-phenylbut-2-ynoate

During 15 minutes a 1.0 M THF-solution of LHMDs (5.0 mL, 5.0 mmol) was added to a THF-solution (5 mL) of ethyl propynoate (4.5 mmol, 460 μ L) cooled at -78 $^{\circ}$ C. The mixture was stirred for another half hour before addition of benzoyl chloride (590 μ L, 5.0 mmol). After stirring for 3 h at the same temperature the reaction was quenched by addition of water (25 mL). The water phase was extracted with ether (3 \times 25 mL) and the combined organic phases dried (MgSO_4), filtered and evaporated to dryness. Flash chromatography (1:99 EtOAc/hexane) provided ethyl 4-oxo-4-phenyl-but-2-ynoate as an oil in 7% (67 mg, 0.33 mmol) yield. ^1H NMR and ^{13}C NMR spectral data were in agreement with those previously reported.¹

Ethyl 4-oxo-pent-2-ynoate

During 15 minutes a 1.0 M THF-solution of LHMDs (5.0 mL, 5.0 mmol) was added to a THF-solution (5 mL) of ethyl propynoate (4.5 mmol, 460 μ L) cooled at -78 $^{\circ}$ C. The mixture was stirred for another half hour before transfer via cannula to a THF-solution (10 mL) of acetyl chloride (2.4 mL, 22.5 mmol) cooled at -78 $^{\circ}$ C. After stirring for 1 h at the same temperature the reaction was quenched by addition of water (25 mL). The water phase was extracted with ether (3 \times 25 mL) and the combined organic phases dried (MgSO_4), filtered and evaporated to dryness. Flash chromatography (EtOAc/hexane 1:99) provided ethyl 4-oxo-pent-2-ynoate as an oil in 9% (58 mg, 0.41 mmol) yield. ^1H NMR and ^{13}C NMR spectral data were in agreement with those previously reported.²

Synthesis of Weinreb amides according to Li *et al.*³



Compound **2b** was synthesized from propionyl chloride and isolated as a colorless oil in 51% yield (UV purity: 98%) by distillation. ¹H NMR and ¹³C NMR spectral data were in agreement with those previously reported.⁴



Compound **2c** was synthesized from phenylacetyl chloride and isolated as a colorless oil in 65% yield (UV purity: 98%) after purification by flash chromatography (EtOAc/hexane 10:90): ¹H NMR and ¹³C NMR spectral data were in agreement with those previously reported.⁵



Compound **2d** was synthesized from hydrocinnamoyl chloride and isolated as a colorless oil in 84% yield (UV purity: 85%) after purification by flash chromatography (EtOAc/hexane 10:90): ¹H NMR and ¹³C NMR spectral data were in agreement with those previously reported.⁶



Compound **2e** was synthesized from isobutyryl chloride and isolated as a colorless oil in 13% yield (UV purity: 96%) after purification by flash chromatography (EtOAc/heptane 10:90): ¹H NMR (300 MHz, CDCl₃) δ 3.69 (s, 3 H), 3.18 (s, 3 H), 2.96 (heptet, ³*J*_(H,H) = 6.8, 1 H), 2.76 (d, ³*J*_(H,H) = 6.8, 6 H); ¹³C NMR (75 MHz, CDCl₃) δ 178.2, 61.4, 33.5, 29.8, 19.1



Compound **2f** was synthesized from pivaloyl chloride and isolated as a yellow oil in 36% yield (UV purity: 93%) after purification by flash chromatography (EtOAc/heptane 10:90): ^1H NMR and ^{13}C NMR spectral data were in agreement with those previously reported.⁵



Compound **2h** was synthesized from *p*-nitrobenzoyl chloride and isolated as yellow crystals in 85% yield (UV purity: 98%) after recrystallization from ether: Mp 70-72 °C (lit.⁷ mp 72-74 °C); ^1H NMR (300 MHz, CDCl_3) δ 8.26 (d, $^3J_{\text{(H,H)}} = 8.9$, 2 H), 7.84 (d, $^3J_{\text{(H,H)}} = 8.9$, 2 H), 3.52 (s, 3 H), 3.39 (s, 3 H); ^{13}C NMR (75 MHz, CDCl_3) δ 167.6, 148.8, 140.0, 129.2, 123.2, 61.3, 33.1; HRMS ($\text{M} + \text{H}$)⁺ calcd. for $\text{C}_9\text{H}_{11}\text{N}_2\text{O}_4$ 211.0719, found 211.0701.



Compound **2i** was synthesized from *p*-anisoyl chloride and isolated as a colorless oil in 63% yield (UV purity: 90%) after purification by flash chromatography (EtOAc/heptane 10:90): ^1H NMR and ^{13}C NMR spectral data were in agreement with those previously reported.⁸



Compound **2j** was synthesized from 2,4-dimethoxybenzoyl chloride and isolated as a colorless solid in 73% yield (UV purity: 92%) after purification by flash chromatography (EtOAc/heptane 5:95 and then EtOAc/heptane 20:80): Mp 60-61 °C; ^1H NMR (300 MHz, CDCl_3) δ 7.24-7.21 (m, 1 H) 6.51-6.47 (m, 2 H), 3.82 (s, 3 H), 3.59 (s, 3 H), 3.27 (s, 3 H); ^{13}C NMR (75 MHz, CDCl_3) δ

167.9, 161.7, 157.2, 128.8, 117.6, 104.3, 98.5, 60.8, 55.5, 55.3, 33.4; HRMS ($M + H$)⁺ calcd. for C₁₁H₁₆NO₄ 226.1079, found 226.1053.

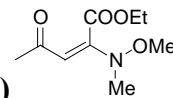


Compound **2k** was synthesized from 2,4-dichlorobenzoyl chloride and isolated as a colorless oil in 81% yield (UV purity: 98%) after purification by flash chromatography (EtOAc/hexane 10:90): ¹H NMR (300 MHz, CDCl₃) δ 7.43-7.28 (m, 5 H), 3.48 (s, 3 H), 3.35 (s, 3 H); ¹³C NMR (75 MHz, CDCl₃) δ 167.4, 135.6, 133.7, 131.8, 129.5, 128.6, 126.9, 61.4, 32.3; HRMS ($M + H$)⁺ calcd. for C₉H₁₀NO₂Cl₂ 234.0089, found 234.0075.

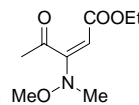
General procedure for the synthesis of *N*-methoxy-*N*-methyl-β-enaminoketoesters **3a/4a, **3b/4b**, **3c/4c**, **3d/4d**, **3e/4e**, **3g**, **3h**, **3i** and **3k****

Under anhydrous conditions a 1.0 M THF-solution of sodium hexamethyldisilazide (2.0 mL, 2.0 mmol) was added to a THF-solution (2.0 mL) of ethyl propynoate (2.0 mmol, 205 μL) cooled at -78 °C. The addition was made dropwise during a period of 15 minutes followed by an additional half hour of stirring and addition of Weinreb amide (1.0 mmol **2**). The mixture was heated to -40 °C during one hour and kept constant at that temp. until the reaction was quenched half an hour later by addition of 1M aq HCl (2mL). Stirring was continued while the mixture heated to ambient temp. Extraction with ether (3×25 mL), drying (MgSO₄) of the comb. org. phases, filtration and evaporation to dryness by rotovap afforded the crude product (**3a/4a**, **3b/4b**, **3c/4c**, **3d/4d**, **3e/4e**, **3g**, **3h**, **3i** and **3k**). The products were isolated by flash chromatography (EtOAc/heptane 5:95) unless otherwise noted.

(E)-2-(N-Methoxy-N-methyl-amino)-4-oxo-2-pentenoic acid ethyl ester (3a)

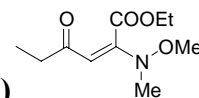


and (E)-3-(N-methoxy-N-methyl-amino)-4-oxo-2-pentenoic acid ethyl ester (4a)

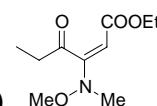


N-Methoxy-*N*-methylacetamide (**2a**, 106 μ L, 1.0 mmol) yielded **3a** as colorless crystals (63 mg, 31%): Mp 44-46 $^{\circ}$ C; ^1H NMR (300 MHz, CDCl_3) δ 5.32 (s, 1 H), 4.35 (q, $^3J_{\text{H,H}} = 7.2$, 2 H), 3.64 (s, 3 H), 3.01 (s, 3 H), 2.11 (s, 3 H), 1.34 (t, $^3J_{\text{H,H}} = 7.2$, 3 H); ^{13}C NMR (75 MHz, CDCl_3) δ 194.6, 164.1, 152.4, 97.0, 62.2, 60.8, 37.5, 30.0, 13.7 and **4a** as a colorless oil (66 mg, 33%): ^1H NMR (300 MHz, CDCl_3) δ 4.71 (s, 1 H), 4.03 (q, $^3J_{\text{H,H}} = 7.1$, 2 H), 3.50 (s, 3 H), 2.90 (s, 3 H), 2.36 (s, 3 H), 1.17 (t, $^3J_{\text{H,H}} = 7.1$, 3 H); ^{13}C NMR (75 MHz, CDCl_3) δ 198.8, 166.7, 162.1, 87.7, 61.0, 59.7, 37.6, 30.3, 14.1. Purification by flash chromatography was performed with EtOAc/heptane 5:95 (**4a**) and then EtOAc/heptane 10:90 (**3a**) as eluent. The isolated crystals of **3a** were used to define its structure by crystallography

(E)-2-(N-Methoxy-N-methyl-amino)-4-oxo-2-hexenoic acid ethyl ester (3b)



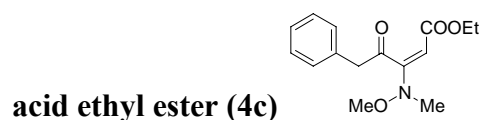
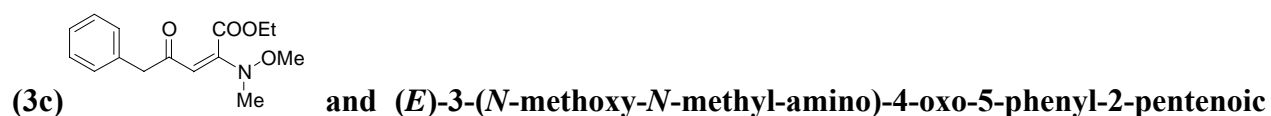
and (E)-3-(N-methoxy-N-methyl-amino)-4-oxo-2-hexenoic acid ethyl ester (4b)



Compound **2b** (117 mg, 1.0 mmol) yielded **3b** as a colorless oil (88 mg, 41%): ^1H NMR (300 MHz, CDCl_3) δ 5.29 (s, 1 H), 4.33 (q, $^3J_{\text{H,H}} = 7.2$, 2 H), 3.61 (s, 3 H), 2.97 (s, 3 H), 2.36 (q, $^3J_{\text{H,H}} = 7.4$, 2 H), 1.30 (t, $^3J_{\text{H,H}} = 7.2$, 3 H), 1.01 (t, $^3J_{\text{H,H}} = 7.4$, 3 H); ^{13}C NMR (75 MHz, CDCl_3) δ 197.7, 164.1, 152.1, 96.6, 62.0, 60.7, 37.5, 35.8, 13.7, 8.3; HRMS ($\text{M} + \text{H}$) $^{+}$ calcd. for $\text{C}_{10}\text{H}_{18}\text{NO}_4$ 216.1236, found 216.1217 and **4b** as a colorless oil (73 mg, 34%): ^1H NMR (300 MHz, CDCl_3) δ 4.76 (s, 1 H), 4.05 (q, $^3J_{\text{H,H}} = 7.1$, 2 H), 3.52 (s, 3 H), 2.91 (s, 3 H), 2.67 (q, $^3J_{\text{H,H}} = 7.2$, 2 H), 1.19 (t, $^3J_{\text{H,H}} = 7.1$, 3 H), 1.14 (t, $^3J_{\text{H,H}} = 7.2$, 3 H); ^{13}C NMR (75 MHz,

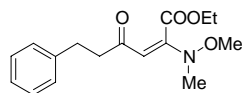
CDCl₃) δ 201.8, 166.8, 162.1, 87.9, 60.9, 59.6, 37.6, 36.1, 14.2, 7.2; HRMS (M + H)⁺ calcd. for C₁₀H₁₈NO₄ 216.1236, found 216.1211. Purification by flash chromatography was performed with EtOAc/heptane 5:95 (**4b**) and then EtOAc/heptane 10:90 (**3b**) as eluent.

(E)-2-(N-Methoxy-N-methyl-amino)-4-oxo-5-phenyl-2-pentenoic acid ethyl ester



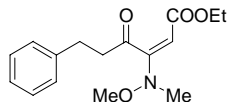
Compound **2c** (179 mg, 1.0 mmol) yielded **3c** as a colorless oil (121 mg, 44%): ¹H NMR (300 MHz, CDCl₃) δ 7.21-7.12 (m, 5 H), 5.20 (s, 1 H), 4.29 (q, ³J_(H,H) = 7.1, 2 H), 3.57 (s, 2 H), 3.52 (s, 3 H), 2.90 (s, 3 H), 1.26 (t, ³J_(H,H) = 7.1, 3 H); ¹³C NMR (75 MHz, CDCl₃) δ 194.1, 163.9, 152.7, 135.3, 129.3, 128.4, 126.5, 95.7, 62.1, 60.6, 49.8, 37.3, 13.6; HRMS (M + H)⁺ calcd. for C₁₅H₂₀NO₄ 278.1392, found 278.1400 and **4c** as a colorless oil (82 mg, 30%): ¹H NMR (300 MHz, CDCl₃) δ 7.33-7.26 (m, 5 H), 4.83 (s, 1 H), 4.14 (q, ³J_(H,H) = 7.1, 2 H), 4.03 (s, 2 H), 3.49 (s, 3 H), 2.85 (s, 3 H), 1.25 (t, ³J_(H,H) = 7.1, 3 H); ¹³C NMR (75 MHz, CDCl₃) δ 198.5, 166.9, 161.5, 133.1, 130.1, 128.2, 126.9, 88.1, 60.9, 59.8, 49.4, 37.6, 14.3; HRMS (M + H)⁺ calcd. for C₁₅H₂₀NO₄ 278.1392, found 278.1377. Purification by flash chromatography was performed with EtOAc/heptane 5:95 (**4c**) and then EtOAc/heptane 10:90 (**3c**) as eluent.

(E)-2-(N-Methoxy-N-methyl-amino)-4-oxo-6-phenyl-2-hexenoic acid ethyl ester (3d)



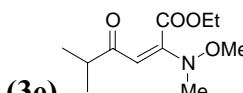
and (E)-3-(N-methoxy-N-methyl-amino)-4-oxo-6-phenyl -2-hexenoic acid

ethyl ester (4d)



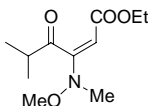
Compound **2d** (483 mg, 2.5 mmol) yielded **3d** as a colorless oil (98 mg, 34%): ^1H NMR (300 MHz, CDCl_3) δ 7.29-7.17 (m, 5 H), 5.31 (s, 1 H), 4.40 (q, $^3J_{(\text{H,H})} = 7.2$, 2 H), 3.65 (s, 3 H), 3.02 (s, 3 H), 2.92 (t, $^3J_{(\text{H,H})} = 7.8$, 2 H), 2.71 (t, $^3J_{(\text{H,H})} = 8.2$, 2 H), 1.34 (t, $^3J_{(\text{H,H})} = 7.2$, 3 H); ^{13}C NMR (75 MHz, CDCl_3) δ 196.2, 164.2, 152.4, 141.4, 128.3, 128.3, 125.9, 96.6, 62.3, 60.8, 44.5, 37.6, 30.6, 13.8; HRMS ($\text{M} + \text{H}$) $^+$ calcd. for $\text{C}_{16}\text{H}_{22}\text{NO}_4$ 229.1549, found 229.1522 and **4d** as a colorless oil (96 mg, 33%): ^1H NMR (300 MHz, CDCl_3) δ 7.31-7.18 (m, 5 H), 4.81 (s, 1 H), 4.12 (q, $^3J_{(\text{H,H})} = 7.1$, 2 H), 3.48 (s, 3 H), 3.05 (s, 4 H), 2.91 (s, 3 H), 1.25 (t, $^3J_{(\text{H,H})} = 7.1$, 3 H); ^{13}C NMR (75 MHz, CDCl_3) δ 200.2, 166.9, 162.0, 141.1, 128.5, 128.3, 125.9, 88.2, 61.1, 59.9, 44.4, 37.7, 29.2, 14.3; HRMS ($\text{M} + \text{H}$) $^+$ calcd. for $\text{C}_{16}\text{H}_{22}\text{NO}_4$ 229.1549, found 229.1563

(E)-2-(N-Methoxy-N-methyl-amino)-5-methyl-4-oxo-2-hexenoic acid ethyl ester (3e)



and (E)-3-(N-methoxy-N-methyl-amino)-5-methyl-4-oxo-2-hexenoic acid

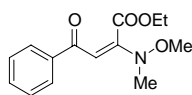
ethyl ester (4e)



Compound **2e** (131 mg, 1.0 mmol) yielded **3e** as a colorless oil (120 mg, 52%): ^1H NMR (300 MHz, CDCl_3) δ 5.32 (s, 1 H), 4.31 (q, $^3J_{(\text{H,H})} = 7.2$, 2 H), 3.59 (s, 3 H), 2.97 (s, 3 H), 2.49 (heptet, $^3J_{(\text{H,H})} = 6.9$, 1 H), 1.28 (t, $^3J_{(\text{H,H})} = 7.2$, 3 H), 1.02 (d, $^3J_{(\text{H,H})} = 6.9$, 6 H); ^{13}C NMR (75 MHz, CDCl_3) δ 200.9, 164.1, 152.6, 95.8, 61.9, 60.6, 40.3, 37.5, 18.5, 13.6; HRMS ($\text{M} + \text{H}$) $^+$ calcd. for

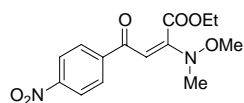
C₁₁H₂₀NO₄ 230.1392, found 230.1366 and **4e** as a colorless oil (83 mg, 36%): ¹H NMR (300 MHz, CDCl₃) δ 4.83 (s, 1 H), 4.04 (q, ³J_(H,H) = 7.1, 2 H), 3.52 (s, 3 H), 2.91 (s, 3 H), 2.83 (heptet, ³J_(H,H) = 7.0, 1 H), 1.19 (t, ³J_(H,H) = 7.1, 3 H), 1.17 (d, ³J_(H,H) = 7.0, 6 H); ¹³C NMR (75 MHz, CDCl₃) δ 205.2, 166.9, 161.1, 88.4, 60.5, 59.6, 40.8, 37.8, 17.5, 14.2; HRMS (M + H)⁺ calcd. for C₁₁H₂₀NO₄ 230.1392, found 230.1344

(E)-2-(N-Methoxy-N-methyl-amino)-4-oxo-4-phenyl-2-butenic acid ethyl ester (3g)



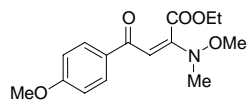
N-Methoxy-*N*-methylbenzamide (**2g**, 155 μL, 1.0 mmol) yielded **3g** as a colorless oil (253 mg, 96%): ¹H NMR (300 MHz, CDCl₃) δ 7.92-7.88 (m, 2 H), 7.52-7.39 (m, 3 H), 6.01 (s, 1 H), 4.44 (q, ³J_(H,H) = 7.2, 2 H), 3.72 (s, 3 H), 3.14 (s, 3 H), 1.38 (t, ³J_(H,H) = 7.2, 3 H); ¹³C NMR (75 MHz, CDCl₃) δ 187.7, 164.3, 154.0, 138.9, 131.9, 128.3, 127.8, 93.9, 62.4, 60.8, 37.8, 13.9; HRMS (M + H)⁺ calcd. for C₁₄H₁₈NO₄ 264.1236, found 264.1261

(E)-2-(N-Methoxy-N-methyl-amino)-4-oxo-4-(4-nitrophenyl)-2-butenic acid ethyl ester (3h)



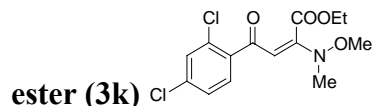
Compound **2h** (210 mg, 1.0 mmol) yielded **3h** as a beige powder (231 mg, 75%) after washing the crude product with heptane: Mp 81-83 °C; ¹H NMR (300 MHz, CDCl₃) δ 8.26 (d, ³J_(H,H) = 8.6, 2 H), 8.03 (d, ³J_(H,H) = 8.6, 2 H), 5.97 (s, 1 H), 4.47 (q, ³J_(H,H) = 7.1, 2 H), 3.76 (s, 3 H), 3.21 (s, 3 H), 1.41 (t, ³J_(H,H) = 7.1, 3 H); ¹³C NMR (75 MHz, CDCl₃) δ 185.4, 163.6, 154.5, 149.5, 144.2, 128.6, 123.5, 91.7, 62.7, 60.8, 37.5, 13.8; HRMS (M + H)⁺ calcd. for C₁₄H₁₇N₂O₆ 309.1087, found 309.1055

(E)-2-(N-Methoxy-N-methyl-amino)-4-oxo-4-(4-anisoyl)-2-butenic acid ethyl ester (3i)

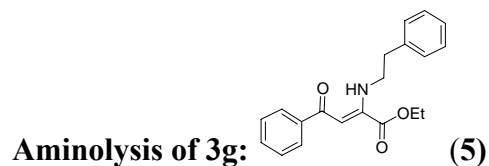


Compound **2i** (195 mg, 1.0 mmol) yielded **3i** as an orange oil (210 mg, 72%) after flash chromatography (EtOAc/heptane 10:90): ^1H NMR (300 MHz, CDCl_3) δ 7.87-7.83 (m, 2 H), 6.87-6.83 (m, 2 H), 6.00 (s, 1 H), 4.38 (q, $^3J_{(\text{H,H})} = 7.1$, 2 H), 3.77 (s, 3 H), 3.65 (s, 3 H), 3.06 (s, 3 H), 1.32 (t, $^3J_{(\text{H,H})} = 7.1$, 3 H); ^{13}C NMR (75 MHz, CDCl_3) δ 186.2, 164.3, 162.5, 153.5, 131.4, 129.7, 113.2, 94.0, 61.9, 60.6, 55.1, 37.6, 13.6; HRMS ($\text{M} + \text{H}$) $^+$ calcd. for $\text{C}_{15}\text{H}_{20}\text{NO}_5$ 294.1342, found 294.1313

(E)-2-(N-Methoxy-N-methyl-amino)-4-oxo-4-(2,4-dichlorophenyl)-2-butenic acid ethyl ester (3k)

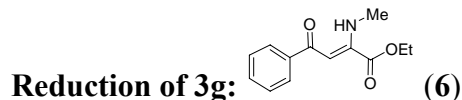


Compound **2k** (234 mg, 1.0 mmol) yielded **3k** as a white solid (199 mg, 60%): Mp 72-73 °C; ^1H NMR (300 MHz, CDCl_3) δ 7.47-7.24 (m, 3 H), 5.70 (s, 1 H), 4.42 (q, $^3J_{(\text{H,H})} = 7.2$, 2 H), 3.71 (s, 3 H), 3.14 (s, 3 H), 1.38 (t, $^3J_{(\text{H,H})} = 7.2$, 3 H); ^{13}C NMR (75 MHz, CDCl_3) δ 187.4, 163.6, 153.2, 138.8, 136.3, 132.0, 130.6, 129.9, 127.1, 96.2, 62.6, 60.9, 37.5, 13.8; HRMS ($\text{M} + \text{H}$) $^+$ calcd. for $\text{C}_{14}\text{H}_{16}\text{NO}_4\text{Cl}_2$ 332.0456, found 332.0426



An EtOH-solution (1 mL) of **3g** (26 mg, 0.10 mmol) and phenethylamine (14 μL , 0.11 mmol) was stirred at ambient temperature for 13 hours. The solvent was then removed at reduced pressure by evaporation and the crude purified by flash chromatography (EtOAc/hexane 10:90). **5**

was isolated as a colorless oil (24 mg, 75%): ^1H NMR (300 MHz, CDCl_3) δ 10.88 (br s, 1 H), 7.90-7.87 (m, 2 H), 7.50-7.21 (m, 8 H), 6.16 (s, 1 H), 4.40 (q, $^3J_{(\text{H,H})} = 7.1$, 2 H), 3.72 (dt, $^3J_{(\text{H,H})} = 6.9$, 2 H), 2.95 (t, $^3J_{(\text{H,H})} = 7.4$, 2 H), 1.34 (t, $^3J_{(\text{H,H})} = 7.1$, 3 H); ^{13}C NMR (75 MHz, CDCl_3) δ 190.4, 163.5, 153.2, 139.5, 138.2, 131.4, 128.9, 128.6, 128.3, 127.2, 126.6, 92.4, 62.1, 46.7, 37.6, 14.1; HRMS ($\text{M} + \text{H}$) $^+$ calcd. for $\text{C}_{20}\text{H}_{22}\text{NO}_3$ 324.1600, found 324.1568

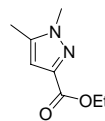


Compound **3g** (9.9 mg, 0.030 mmol) was heated by microwaves at 150 °C in abs. EtOH (0.6 mL) for an hour. The product was isolated as a colorless oil (1.9 mg, 27%) by removal of the solvent at reduced pressure and purification by flash chromatography (EtOAc/heptane 10:90): ^1H NMR (300 MHz, CDCl_3) δ 10.74 (br s, 1 H), 7.89-7.39 (m, 5 H), 6.19 (s, 1 H), 4.37 (q, $^3J_{(\text{H,H})} = 7.1$, 2 H), 3.14 (d, $^3J_{(\text{H,H})} = 5.5$, 3 H), 1.40 (t, $^3J_{(\text{H,H})} = 7.1$, 3 H); ^{13}C NMR (75 MHz, CDCl_3) δ 190.4, 163.4, 154.0, 139.5, 131.3, 128.3, 127.1, 92.1, 62.1, 31.7, 14.1; HRMS ($\text{M} + \text{H}$) $^+$ calcd. for $\text{C}_{13}\text{H}_{16}\text{NO}_3$ 234.1130, found 234.1102

General procedure for the synthesis of pyrazoles 7a-h

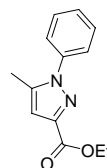
A mixture of *N*-methoxy-*N*-methyl- β -enaminoketoester (**3a**, **d**, **g** and **k**) and methyl/phenylhydrazine was heated by microwaves at 100 °C in dry CDCl_3 (0.6 mL) for 1 (**7c**, **7d**, **7e**, **7g** and **7h**) or 2 (**7a**, **b**, and **f**) hours. The progression of the reaction was followed by ^1H NMR spectroscopy after one hour and completed by an additional hour of heating if the analysis was unsatisfactory. The product was isolated by removal of the solvent at reduced pressure by evaporation and purification by prep. HPLC. The physical data for **7a**, **7b**, **7e** and **7f** were in agreement with those previously reported.⁹

1,5-Dimethyl-pyrazole-3-carboxylic acid ethyl ester (7a)



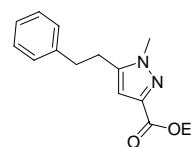
Compound **3a** (6.0 mg, 0.030 mmol) and methylhydrazine (2.0 μ L, 0.036 mmol) yielded **7a** (2.1 mg, 42%, UV purity: 94%) as colorless crystals: Mp 41-42 $^{\circ}$ C (lit.¹⁰ mp 42 $^{\circ}$ C).

5-Methyl-1-phenyl-pyrazole-3-carboxylic acid ethyl ester (7b)



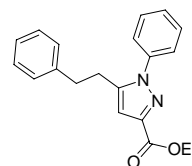
Compound **3a** (6.0 mg, 0.030 mmol) and phenylhydrazine (3.7 μ L, 0.036 mmol) yielded **7b** (5.0 mg, 72%, UV purity: 93%) as a white solid: Mp 31-32 $^{\circ}$ C (lit.⁹ mp 37 $^{\circ}$ C); HRMS ($M + H$)⁺ calcd. for $C_{13}H_{15}N_2O_2$ 231.1134, found 231.1155

1-Methyl-5-phenylethyl-pyrazole-3-carboxylic acid ethyl ester (7c)



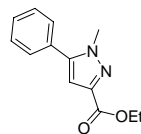
Compound **3d** (8.7 mg, 0.030 mmol) and methylhydrazine (2.0 μ L, 0.036 mmol) yielded **7c** (4.6 mg, 59%, UV purity: 85%) as a colorless oil: 1H NMR (300 MHz, $CDCl_3$) δ 7.32-7.13 (m, 5 H), 6.63 (s, 1 H), 4.41 (q, $^3J_{(H,H)} = 7.1$, 2 H), 3.68 (s, 3 H), 2.99-2.87 (m, 4 H), 1.25 (t, $^3J_{(H,H)} = 7.1$, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.5, 143.8, 142.3, 140.1, 128.6, 128.3, 126.5, 107.4, 60.8, 36.8, 34.9, 27.6, 14.4; HRMS ($M + H$)⁺ calcd. for $C_{15}H_{19}N_2O_2$ 259.1447, found 259.1429

1-Phenyl-5-phenylethyl-pyrazole-3-carboxylic acid ethyl ester (7d)



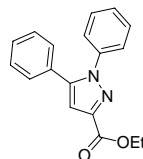
Compound **3d** (8.7 mg, 0.030 mmol) and phenylhydrazine (3.7 μ L, 0.036 mmol) yielded **7d** (5.4 mg, 54%, UV purity: 94%) as a white solid: Mp 64-66 $^{\circ}$ C; 1H NMR (300 MHz, $CDCl_3$) δ 7.45-7.04 (m, 10 H), 6.81 (s, 1 H), 4.42 (q, $^3J_{(H,H)} = 7.1$, 2 H), 2.96-2.87 (m, 4 H), 1.40 (t, $^3J_{(H,H)} = 7.1$,

3 H); ^{13}C NMR (75 MHz, CDCl_3) δ 162.6, 144.7, 143.9, 140.1, 139.0, 129.1, 128.8, 128.5, 128.2, 126.4, 126.0, 108.0, 61.0, 34.9, 28.0, 14.1; HRMS ($\text{M} + \text{H}$) $^+$ calcd. for $\text{C}_{20}\text{H}_{21}\text{N}_2\text{O}_2$ 321.1603, found 321.1586



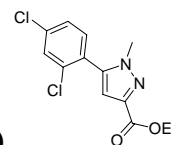
1-Methyl-5-phenyl-pyrazole-3-carboxylic acid ethyl ester (7e)

Compound **3g** (7.9 mg, 0.030 mmol) and methylhydrazine (2.0 μL , 0.036 mmol) yielded **7e** (15.9 mg, 69%, UV purity: 95%) as a colorless oil: HRMS ($\text{M} + \text{H}$) $^+$ calcd. for $\text{C}_{13}\text{H}_{15}\text{N}_2\text{O}_2$ 231.1134, found 231.1125



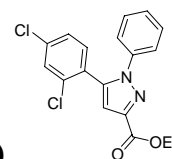
1,5-Diphenyl-pyrazole-3-carboxylic acid ethyl ester (7f)

Compound **3g** (7.9 mg, 0.030 mmol) and phenylhydrazine (3.7 μL , 0.036 mmol) yielded **7f** (8.2 mg, 94%, UV purity: 90%) as a yellow solid: Mp 58-60 $^{\circ}\text{C}$ (lit.⁹ mp 56-58 $^{\circ}\text{C}$); HRMS ($\text{M} + \text{H}$) $^+$ calcd. for $\text{C}_{18}\text{H}_{17}\text{N}_2\text{O}_2$ 293.1290, found 293.1270



1-Methyl-5-(2,4-dichlorophenyl)-pyrazole-3-carboxylic acid ethyl ester (7g)

Compound **3k** (9.9 mg, 0.030 mmol) and methylhydrazine (2.0 μL , 0.036 mmol) yielded **7g** (6.8 mg, 76%, UV purity: 98%) as a white solid: Mp 81-82 $^{\circ}\text{C}$; ^1H NMR (300 MHz, CDCl_3) δ 7.55-7.25 (m, 3 H), 6.82 (s, 1 H), 4.42 (q, $^3J_{(\text{H,H})} = 7.1$, 2 H), 3.78 (s, 3 H), 1.41 (t, $^3J_{(\text{H,H})} = 7.1$, 3 H); ^{13}C NMR (75 MHz, CDCl_3) δ 162.1, 142.8, 140.8, 136.5, 135.2, 132.6, 130.0, 127.5, 127.4, 110.2, 61.0, 37.8, 14.4; HRMS ($\text{M} + \text{H}$) $^+$ calcd. for $\text{C}_{13}\text{H}_{13}\text{N}_2\text{O}_2\text{Cl}_2$ 299.0354, found 299.0338



1-Phenyl-(2, 4-dichlorophenyl)-pyrazole-3-carboxylic acid ethyl ester (7h)

Compound **3k** (9.9 mg, 0.030 mmol) and phenylhydrazine (3.7 μ L, 0.036 mmol) yielded **7h** (7.2 mg, 67%, UV purity: 98%) as a brown solid: Mp 29-31 $^{\circ}$ C; ^1H NMR (300 MHz, CDCl_3) δ 7.43-7.15 (m, 8 H), 7.04 (s, 1 H), 4.46 (q, $^3J_{(\text{H,H})} = 7.1$, 2 H), 1.43 (t, $^3J_{(\text{H,H})} = 7.1$, 3 H); ^{13}C NMR (75 MHz, CDCl_3) δ 162.2, 144.3, 140.2, 139.2, 136.1, 134.8, 132.7, 130.0, 129.0, 128.3, 127.8, 127.3, 124.7, 111.9, 61.2, 14.4; HRMS ($\text{M} + \text{H}$) $^{+}$ calcd. for $\text{C}_{18}\text{H}_{15}\text{N}_2\text{O}_2\text{Cl}_2$ 361.0511, found 361.0481

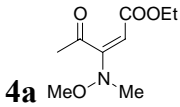
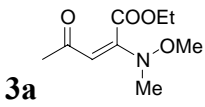
HMBC Crosspeaks	 4a	 3a
-OCH ₂ CH ₃ (3a and 4a)	-OCH ₂ CH ₃	-OCH ₂ CH ₃
-OCH ₂ CH ₃ (3a and 4a)	-OCH ₂ CH ₃ and C-1	-OCH ₂ CH ₃ and C-1
H-2 (4a)	C-3 and C-4	-
H-3 (3a)	-	C-1, C-2 and C-4
H-5 (3a and 4a)	C-3 and C-4	C-2, C-3 and C-4
-N(OCH ₃)CH ₃ (3c and 4a)	C-2 and C-3	C-2 and C-3

Figure S1. ^1H - ^{13}C COSY Spectrum (HMBC) of compound **4a**

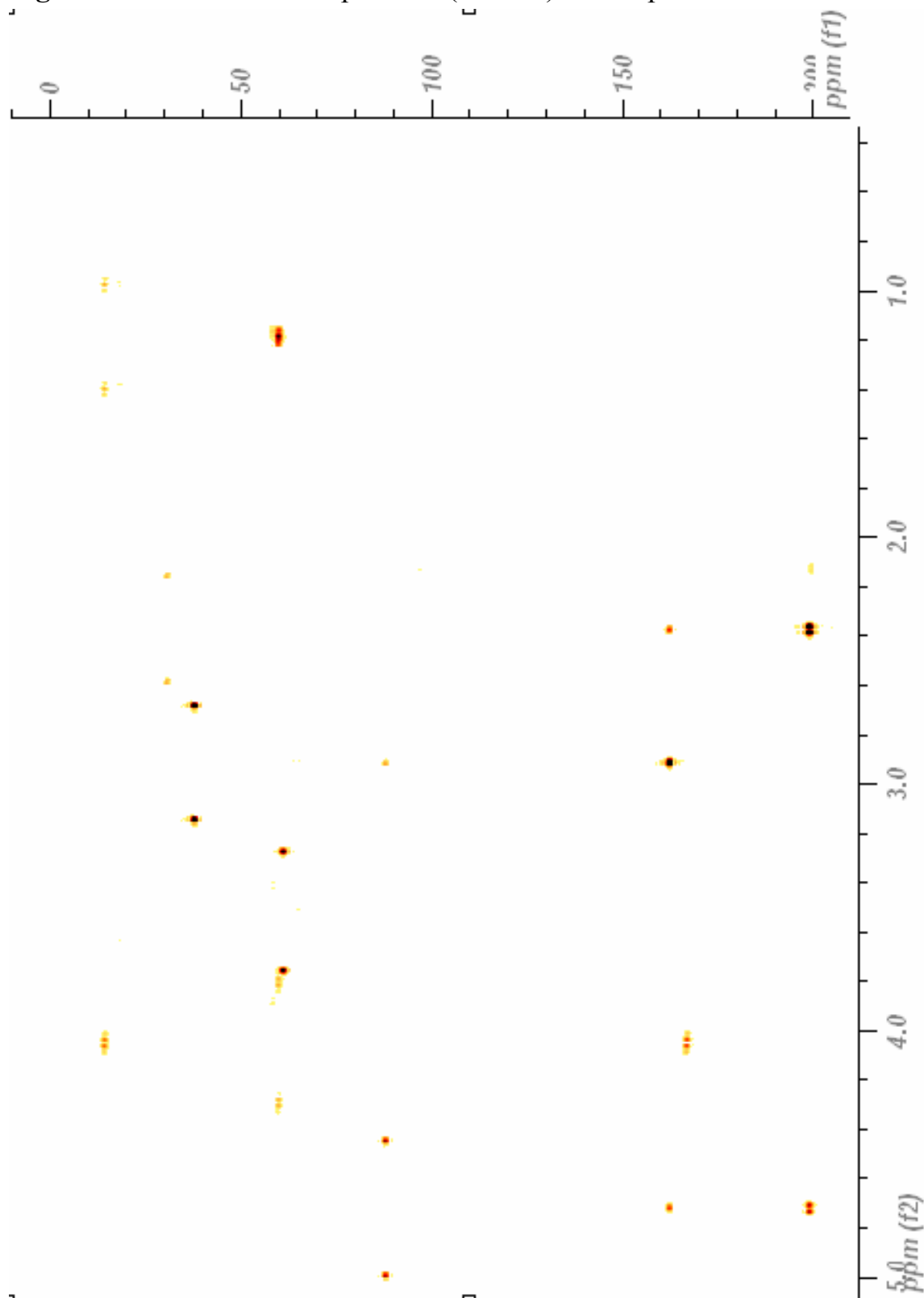
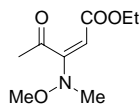


Figure S2. ^1H - ^1H COSY (NOESY) Spectrum of compound **4a**

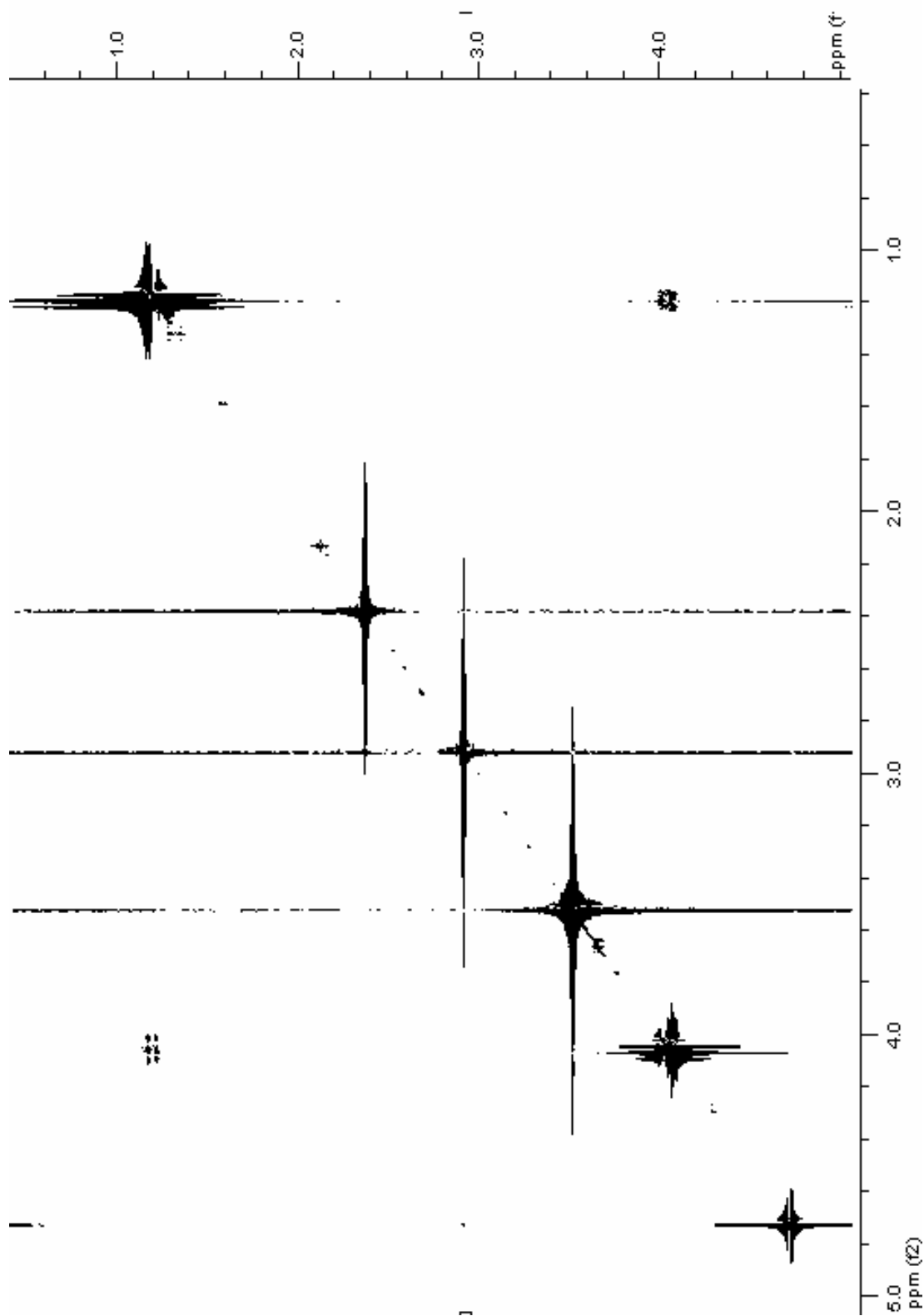
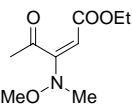
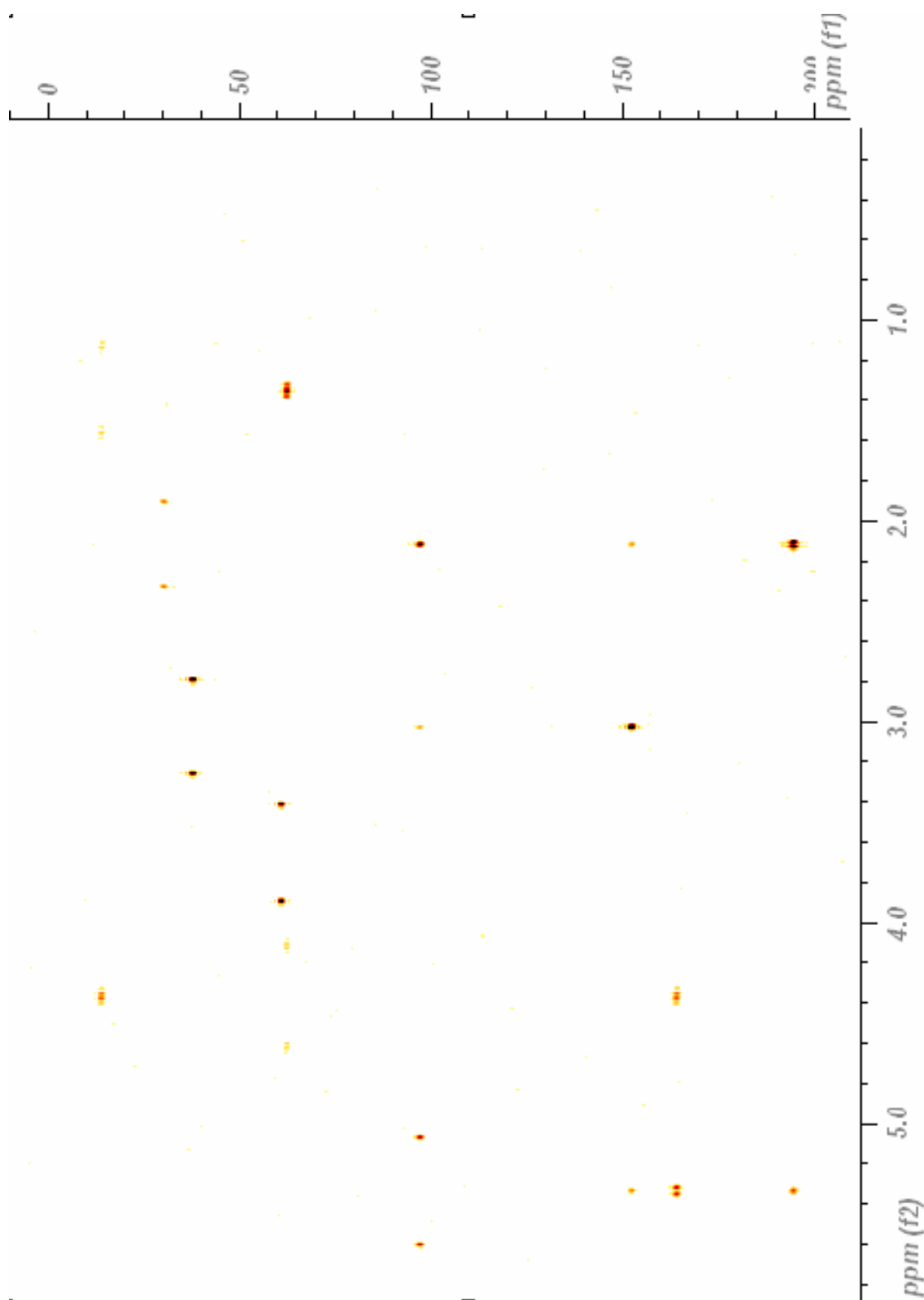
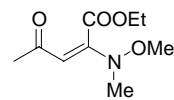


Figure S3. ^1H - ^{13}C COSY Spectrum (HMBC) of compound **4b**



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