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Supporting Information

Experimental Section

All experiments were run under an argon atmosphere. IR spectra were performed in CCl_4 (NaCl cells). ^1H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ at 300 MHz and 75 MHz respectively. Chemical shifts are reported as δ values in ppm relative to internal tetramethylsilane. Uncorrected melting points were taken using a Kofler bank. Flash column chromatography was accomplished on Merck Kieselgel 60 (230-400 mesh). Solvents such as dichloromethane or 1,2-dichloroethane were distilled from CaH_2, THF was distilled from Na/benzophenone and ethanol from Mg.

2,2-Dimethyl-5-phenylpent-4-ynal (2). A mixture of 30% $NaOH/H_2O$ (5.31 g NaOH, 132.8 mmol), NaI (1 g, 6.64 mmol), n-Bu_4NI (0.49 g, 1.328 mmol) and toluene (10 mL) was heated at 50 °C. To this vigorously stirred mixture was added dropwise (ca. 1 h) a solution of 1-chloro-3-phenyl-2-propyne **1** (10 g, 66.4 mmol) and isobutyraldehyde (7.18 g, 9 mL, 99.6 mmol) in toluene (5 mL). After 24 h at 50 °C, the reaction mixture was cooled, diluted with water (100 mL) and extracted with ether (3x50 mL). The organic phase was dried over $MgSO_4$ and filtered. The solvent was removed in *vacuo* and the residue was purified by flash column chromatography on silica gel (95/5 petroleum ether/EtOAc) to give **2** as a colorless oil (11.13 g, 90% yield): IR 2700, 2240, 2220, 1730, 1460, 1440, 885, 690 cm^{-1}; ^1H NMR δ 1.22 (s, 6H), 2.56 (s, 2H), 7.25-7.30 (m, 3H), 7.35-7.45 (m, 2H), 9.60 (s, 1H); EI MS *m/z* (relative intensity) 186 (M^+, 4), 171 (100), 143 (44), 128 (40), 115 (93), 102 (48), 63 (20); HRMS Calcd for $C_{13}H_{14}O$: 186.1044. Found: 186.1044.

Methyl *N*-(2,2-dimethyl-5-phenylpent-4-ynyl) glycinate (3). To a solution of **2** (6 g, 32.21 mmol) in dry dichloromethane or dry 1,2-dichloroethane (100 mL) at room temperature were added powdered glycine methyl ester hydrochloride (4.25 g, 33.82 mmol) and dry Et_3N (6.52 g, 9 mL, 64.43 mmol). The resulting suspension was vigorously stirred for 15 mn and powdered

$NaBH(OAc)_3$ (10.24 g, 48.32 mmol) was then added by small portions. The reaction mixture was vigorously stirred for an additional 12 h, quenched by addition of saturated $NaHCO_3/H_2O$ (100 mL) and, after 15 mn, extracted with dichloromethane (3x100 mL). The organic phase was dried over $MgSO_4$ and filtered. The solvent was removed in *vacuo* and the residue was purified by flash column chromatography on silica gel (95/5 CH_2Cl_2/EtOAc) to furnish **3** as a colorless oil (6.7 g, 80% yield): IR 2240, 2220, 1740, 1715, 1470, 1435, 1360, 1200, 1175, 690 cm^{-1}; ^1H NMR δ 1.04 (s, 6H), 1.60 (broad s, 1H), 2.38 (s, 2H), 2.53 (s, 2H), 3.44 (s, 2H), 3.71 (s, 3H), 7.25-7.30 (m, 3H), 7.35-7.45 (m, 2H); ^{13}C NMR δ 25.3 (q, 2C), 30.5 (t), 35.1 (s), 51.6 (q), 51.9 (t), 59.3 (t), 82.4 (s), 88.1 (s), 124.1 (s), 127.5 (d), 128.2 (d, 2C), 131.5 (d, 2C), 173.2 (s); EI MS *m z* (relative intensity) 259 (M^+, 28), 200 (76), 115 (56), 102 (100), 74 (55); HRMS Calcd for $C_{16}H_{21}NO_2$: 259.1572. Found: 259.1571.

2,2-Dimethyl-7-phenyl-2,3,5,6-tetrahydro-1*H*-pyrrolizin-6-one (4). A stirred mixture of **3** (2 g, 7.71 mmol) and pivalic acid (0.787 g, 7.71 mmol) was heated at 150 °C for 5 h. Methanol was distilled during the reaction. After cooling to room temperature, the crude product was purified by flash column chromatography on silica gel (50/50 CH_2Cl_2/EtOAc) to give **4** as a yellow-orange solid (1.2 g, 68% yield): IR 1665, 1600, 1465, 1365, 1310, 1170, 1130, 935, 695 cm^{-1}; ^1H NMR δ 1.25 (s, 6H), 2.85 (t, J = 2.2 Hz, 2H), 3.20 (s, 2H), 3.80 (t, J = 2.2 Hz, 2H), 7.10 (t, J = 7.5 Hz, 1H), 7.30 (t, J = 7.5 Hz, 2H), 7.63 (d, J = 7.5 Hz, 2H); ^{13}C NMR δ 27.9 (q, 2C), 40.1 (s), 43.9 (t), 56.7 (t), 61.3 (t), 106.5 (s), 124.5 (d), 124.9 (d, 2C), 128.3 (d, 2C), 133.1 (s), 181.0 (s), 197.2 (s); EI MS *m z* (relative intensity) 227 (M^+, 100), 198 (54), 115 (30); HRMS Calcd for $C_{15}H_{17}NO$: 227.1310. Found: 227.1310.

Ethyl 2-(2,2-dimethyl-6-hydroxy-7-phenyl-2,3-dihydro-1*H*-pyrrolizin-5-yl)-2-oxoacetate (5). Small pieces of sodium metal (0.394 g, 17.16 mmol) were carefully added to dry ethanol (10 mL) stirred at 0 °C. After disappearance of the sodium, a solution of **4** (1.3 g, 5.72 mmol) and diethyl oxalate (0.919 g, 0,854 mL, 6.29 mmol) in dry ethanol (10 mL) was added dropwise. The resulting solution was stirred at room temperature for 15 h. The reaction was stopped by addition of acetic acid (2.5 mL), followed by addition of water (2.5 mL). Solvents were removed in *vacuo* and the residue was taken up with water (50 mL) and extracted with EtOAc (50

mL, then 2x25 mL). The organic phase was washed with brine (10 mL), dried over $MgSO_4$ and filtered. The solvent was removed in *vacuo* and the residue was purified by flash column chromatography on silica gel (80/20 petroleum ether/EtOAc) to give **5** as a yellow-green solid (1.436 g, 77% yield): mp 123-125 °C; IR 3100(broad), 1730, 1690, 1600, 1570(broad), 1270, 1040, 695 cm^{-1}; ^1H NMR δ 1.27 (s, 6H), 1.46 (t, J = 7.2 Hz, 3H), 2.87 (s, 2H), 4.13 (s, 2H), 4.48 (q, J = 7.2 Hz, 2H), 7.20 (t, J = 7.5 Hz, 1H), 7.38 (t, J = 7.5 Hz, 2H), 7.62 (d, J = 7.5 Hz, 2H), 11.33 (s, 1H); ^{13}C NMR δ 13.9 (q), 27.9 (q, 2C), 41.2 (s), 41.9 (t), 62.6 (t), 63.8 (t), 106.2 (s), 116.7 (s), 125.7 (d), 126.8 (d, 2C), 128.4 (d, 2C), 133.0 (s), 148.5 (s), 154.7 (s), 165.8 (s), 166.7 (s); EI MS *m/z* (relative intensity) 327 (M^+, 43), 254 (100), 115 (14); HRMS Calcd for $C_{19}H_{21}NO_4$: 327.1470. Found: 327.1454.

Ethyl 2-(2,2-dimethyl-7-phenyl-6-trifluoromethanesulfonyloxy-2,3-dihydro-1*H*-pyrrolizin-5-yl)-2-oxoacetate (6). To a stirred suspension of NaH (60% in mineral oil) (0.183 g, i.e. 0.109 g NaH, 4.582 mmol) in dry THF (10 mL) at room temperature was added dropwise a solution of **5** (1 g, 3.054 mmol) in dry THF (10 mL). The resulting orange suspension was stirred at room temperature for 1 h. *N*-Phenyltrifluoromethanesulfonimide (1.31 g, 3.665 mmol) was then added in one portion. After 12 h at room temperature, the resulting solution was dilute with brine (20 mL) and water (20 mL), and extracted with EtOAc (50 mL, then 2x25 mL). The organic phase was washed with brine (10 mL), dried over $MgSO_4$ and filtered. The solvent was removed in *vacuo* and the residue was purified by flash column chromatography on silica gel (85/15 petroleum ether/EtOAc) to furnish **6** as a colorless oil (1.12 g, 80% yield): IR 1740, 1650, 1460, 1430, 1385, 1210, 1140, 1035, 940, 695 cm^{-1}; ^1H NMR δ 1.29 (s, 6H), 1.42 (t, J = 7.2 Hz, 3H), 2.87 (s, 2H), 4.16 (s, 2H), 4.42 (q, J = 7.2 Hz, 2H), 7.25-7.45 (m, 5H); ^{13}C NMR δ 13.8 (q), 27.8 (q, 2C), 40.9 (t), 41.7 (s), 62.9 (t), 63.0 (t), 113.1 (s), 117.5 (s), 118.3 (q, J = 320 Hz, OSO_2CF_3), 127.5 (d), 128.1 (d, 2C), 128.8 (d, 2C), 130.4 (s), 136.9 (s), 142.1 (s), 162.6 (s), 173.4 (s); EI MS *m/z* (relative intensity) 327 ($M^+ + H - SO_2CF_3$, 40), 254 (100), 115 (20).

Ethyl 2-(6-(4-chlorophenyl)-2,2-dimethyl-7-phenyl-2,3-dihydro-1*H*-pyrrolizin-5-yl)-2-oxoacetate (7). A solution of **6** (0.6 g, 1.3 mmol) and 4-chlorophenylboronic acid (0.224 g, 1.43 mmol) in dry THF (10 mL) was degased with argon for 15 mn. To this solution were added

$Pd(PPh_3)_4$ (0.075 g, 0.065 mmol) and Na_2CO_3 (0.35 g) solubilized in a minimum water (1 mL). The resulting mixture was vigorously stirred at room temperature for 1 h and then refluxed for an additional 1 h. After cooling to room temperature, the suspension was diluted with ether (25 mL) and filtered through a plug of Celite, which was washed by additional ether (20 mL). The filtrate was washed with brine (10 mL), dried over $MgSO_4$ and filtered. The solvent was removed in *vacuo* and the residue was purified by flash column chromatography on silica gel (90/10 petroleum ether/EtOAc) to give **7** as a slightly yellow solid (0.51 g, 92% yield): mp 84-86 °C; IR 1740, 1625, 1600, 1425, 1380, 1185, 1065, 700 cm^{-1}; ^1H NMR δ 1.05 (t, J = 7.2 Hz, 3H), 1.32 (s, 6H), 2.85 (s, 2H), 3.60 (q, J = 7.2 Hz, 2H), 4.23 (s, 2H), 6.95-7.40 (m, 9H); ^{13}C NMR δ 13.5 (q), 28.0 (q, 2C), 40.2 (t), 42.9 (s), 61.8 (t), 62.1 (t), 119.4 (s), 121.8 (s), 126.2 (d), 128.1 (d, 2C), 128.3 (d, 2C), 128.5 (d, 2C), 132.2 (d, 2C), 132.3 (s), 133.4 (s), 133.8 (s), 136.0 (s), 145.6 (s), 164.8 (s), 176.5 (s); EI MS m/z (relative intensity) 423 (7), 421 (M^+, 20), 350 (35), 348 (100); HRMS Calcd for $C_{25}H_{24}ClNO_3$: 421.1444. Found: 421.1445.

Ethyl 2-(6-(4-chlorophenyl)-2,2-dimethyl-7-phenyl-2,3-dihydro-1*H*-pyrrolizin-5-yl)acetate (8). A stirred suspension of 7 (0.97 g, 2.3 mmol), *p*-toluenesulfonhydrazide (0.471 g, 2.53 mmol) and *p*-TsOH.H_2O (0.115 g) in dry ethanol (9 mL) was refluxed for 7 h. After cooling to room temperature, a solution of $NaBH_3CN$ (0.578 g, 9.2 mmol) in dry ethanol (6 mL) was added dropwise to the yellow suspension, which was then refluxed for an additional 4 h. The resulting solution was cooled to room temperature and ethanol was removed in *vacuo*. The residue was taken up with water (30 mL) and extracted with EtOAc (3x20 mL). The organic phase was washed with brine (10 mL), dried over $MgSO_4$ and filtered. The solvent was removed in *vacuo* and the residue was purified by flash column chromatography on silica gel (95/5 petroleum ether/EtOAc) to give **8** as a slightly yellowish solid (0.84 g, 90% yield): mp 87-89 °C; IR 1735, 1600, 1485, 1450, 1370, 1175, 1100, 1030, 700 cm^{-1}; ^1H NMR δ 1.28 (t, J = 7.2 Hz, 3H), 1.30 (s, 6H), 2.85 (s, 2H), 3.51 (s, 2H), 3.75 (s, 2H), 4.18 (q, J = 7.2 Hz, 2H), 7.00-7.27 (m, 9H); ^{13}C NMR δ 14.2 (q), 28.0 (q, 2C), 31.6 (t), 40.6 (t), 43.3 (s), 58.4 (t), 61.0 (t), 114.8 (s), 117.7 (s), 123.6 (s), 124.7 (d), 128.0 (d, 2C), 128.2 (d, 2C), 128.3 (d, 2C), 131.6 (s), 131.7 (d, 2C), 134.1 (s), 134.7 (s), 136.0 (s), 170.8 (s); EI MS m/z (relative intensity) 409 (12), 407 (M^+, 36), 336 (33), 334 (100), 299 (14), 242 (14); HRMS Calcd for $C_{25}H_{26}ClNO_2$: 407.1652. Found: 407.1653.

2-(6-(4-Chlorophenyl)-2,2-dimethyl-7-phenyl-2,3-dihydro-1*H*-pyrrolizin-5-yl)acetic acid (ML-3000). To a stirred solution of **8** (0.408 g, 1 mmol) in absolute ethanol (3 mL), heated at 80 °C, was added a solution of 10% aqueous NaOH (0.55 mL). After an additionnal 15 mn at 80 °C, the solution was cooled to 0 °C, diluted with water (5 mL) and acidified to pH 6-7 with a 1M aqueous phosphoric acid solution. The mixture was extracted with Et_2O/CH_2Cl_2 (3/1, 3x20 mL), the organic phase was dried over $MgSO_4$ and filtered. The solvent was removed in *vacuo* and the solid residue was washed with isopropyl ether, filtered off and dried in *vacuo* to give **ML-3000** as a slightly yellowish solid (0.292 g, 77% yield): mp 162-163 °C; IR 3520(broad), 1710(broad), 1600, 1485, 1090, 910, 700 cm^{-1}; ^1H NMR δ 1.30 (s, 6H), 2.86 (s, 2H), 3.59 (s, 2H), 3.76 (s, 2H), 7.00-7.30 (m, 9H), 9.30 (s, CO_2H); ^{13}C NMR δ 28.0 (q, 2C), 31.1 (t), 40.5 (t), 43.3 (s), 58.4 (t), 114.9 (s), 116.8 (s), 124.0 (s), 124.7 (d), 128.0 (d, 2C), 128.2 (d, 2C), 128.4 (d, 2C), 131.6 (d, 2C), 131.8 (s), 134.4 (s), 134.5 (s), 135.8 (s), 176.1 (s); EI MS $C_{23}H_{22}ClNO_2$ *m/z* (relative intensity) 337(35), 335($M^+ - CO_2$, 100), 278 (12), 264 (15), 244 (14), 202(27).