Synthesis of ω -(Hetero)arylalkynylated α -Amino Acid by Sonogashira-type Reactions in Aqueous Media

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SUPPORTING INFORMATION

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1. General Methods, Instrument Details and Materials

Dichloromethane (DCM) was dried and distilled over calcium hydride.^{1,2} Dioxane was dried and distilled over sodium^{1,2}. DIEA was dried and distilled over calcium hydride, and then redistilled over nynhidrin^{1,2}. DMF used in coupling and cyclization steps was dried over 4 Å molecular sieves. Analytical thin-layer chromatography was performed on silica gel 60 F₂₅₄ plates. Compounds, which were not UV active, were visualized by dipping the plates in a nynhidrin, *p*-anisaldehyde or cerium ammonium molybdate solution and heating. Silica gel flash chromatography was performed using silica gel (type 60SDS, 230-400 mesh). Solvent mixtures for chromatography are reported as v/v ratios. Reversed-phase HPLC purification was carried out on C-18 column with *Solvent A/Solvent B* gradients between 5:95 and 95:5 (*Solvent A*: 1 % CH₃CN in H₂O with 0.1 % TFA; *Solvent B*: 10 % H₂O in CH₃CN with 0.1 % TFA). Nuclear magnetic resonance (¹H NMR and ¹³C NMR³) spectra were recorded on 300 MHz, 500 MHz or 250 MHz spectrometers. Chemical shifts were reported in parts per million (ppm, δ) relative to tetramethylsilane (δ 0.00). ¹H NMR splitting patterns are designated as singlet (s), doublet (d), triplet (t), quartet (q) or pentuplet (p). All first-order splitting patterns were assigned on the basis of the appearance of the multiplet. Splitting patterns that could not be easily interpreted are designated as multiplet (m) or broad (br). Carbon resonances were assigned using distortionless enhancement by polarization transfer (DEPT) spectra obtained with phase angles of 135.

2. Experimental Section

Diethyl α-acetamido-α-propargylmalonate (3). A solution of diethyl acetamidomalonate (1.05 g, 4.75 mmol) in dry dioxane (30 mL) was treated with potassium tert-butoxide (0.59 g, 5.23 mmol). The resulting mixture was vigorously stirred at 60 °C for 2 h, and then propargyl bromide (0.53 mL, 4.75 mmol) was added. After 48 h refluxing, the suspension was filtered, rinsed with Et₂O (3 x 10 mL) and concentrated, affording a yellow oil that when purified by flash chromatography (10-30 % EtOAc in hexanes) gave 1.08 g of **3** as a white crystals [89 %, R_f = 0.54 (40 % EtOAc in hexanes)]. ¹H NMR (CDCl₃, 250.13 MHz, δ): 6.97 (s, 1H), 4.17 (dq, *J*₁ = 1.1 Hz, *J*₂ = 7.1 Hz, 4H), 3.17 (d, *J* = 2.6 Hz, 2H), 1.97 (s, 3H), 1.92 (t, *J* = 2.6 Hz, 1H), 1.17 (t, *J* = 7.1 Hz, 6H). ¹³C NMR (CDCl₃, 62.90 MHz, δ): 169.7 (CO), 166.9 (CO), 78.6 (C), 71.8 (CH), 65.6 (C), 63.2 (CH₂), 24.1 (CH₂), 23.2 (CH₃), 14.3 (CH₃). **MS (CI)** [*m/z* (%): 256 ([MH]⁺, 81), 214 (100), 182 (76), 140 (87)]. **HRMS (CI) calculated** for C₁₂H₁₈NO₅ ([MH]⁺) 256.118498, **found** 256.118463.

Diethyl α-acetamido-α-homopropargylmalonate (4). Using the conditions described for preparation of **3**, 5.40 g of acetamidomalonate **4** was obtained as pale yellow crystals [70 %, R_f = 0.58 (40 % EtOAc in hexanes)]. ¹H NMR (CDCl₃, 250.13 MHz, δ): 6.82 (s, 1H), 4.19 (dq, *J*₁ = 2.7 Hz, *J*₂ = 7.1 Hz, 4H), 2.57

¹ Brown, H. C. “*Organic Synthesis via Boranes*”, Ed. John Wiley & Sons, **1975**.

² Perrin, D. D.; Armarego, W. I. F. “*Purification of Laboratory Chemicals*”, Ed. Pergamon Press, **1988**.

³ Some of the peaks appears at two different resonance shifts because of the *cis-trans* conformation.

(t, $J = 7.4$ Hz, 2H), 2.10 (dt, $J_1 = 2.6$ Hz, $J_2 = 7.3$ Hz, 2H), 2.01 (s, 3H), 1.90 (t, $J = 2.6$ Hz, 1H), 1.21 (t, $J = 7.1$ Hz, 6H). ^{13}C NMR (CDCl_3 , 62.90 MHz, δ): 169.2 (CO), 167.6 (CO), 82.5 (C), 68.9 (CH), 65.6 (C), 62.6 (CH_2), 30.7 (CH_2), 22.9 (CH_3), 13.8 (CH_3), 13.2 (CH_2). **MS (CI)** [m/z (%): 270 ($[\text{MH}]^+$, 100), 228 (42), 154 (27). **HRMS (CI) calculated** for $\text{C}_{13}\text{H}_{20}\text{NO}_5$ ($[\text{MH}]^+$) 270.134148, **found** 270.134373. **m.p.**: 55-59 °C.

N-Acetyl-2-aminopent-4-ynoic acid (5a). Diethyl α -acetamido- α -propargylmalonate (**3**, 5.00 g, 19.58 mmol) was dissolved in 10% NaOH (40 mL) and the mixture was refluxed for 5 h. The solution was cooled, acidified to pH 2 with 6 M HCl and concentrated, affording a yellow solid that was dissolved in H_2O (80 mL). After 5 h refluxing, this solution was filtered through a layer of active carbon in Celite and the yellow filtrate was acidified to pH 3 with 10 % HCl and extracted with EtOAc (5 x 100 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated, affording 2.78 g of **5a** as a white solid [91 %, $R_f = 0.66$ (70 % MeOH in DCM with 0.5 % AcOH)]. ^1H NMR (CD_3OD , 250.13 MHz, δ): 4.54 (t, $J = 6.1$ Hz, 1H), 2.70 (m, 2H), 2.37 (t, $J = 2.6$ Hz, 1H), 2.01 (s, 3H). ^{13}C NMR (CD_3OD , 62.90 MHz, δ): 173.4 (CO), 173.3 (CO), 80.1 (C), 72.2 (CH), 52.7 (CH), 22.4 (CH_2), 22.4 (CH_3). **MS (CI)** [m/z (%): 156 ($[\text{MH}]^+$, 86), 114 (100), 86 (48). **HRMS (CI) calculated** for $\text{C}_7\text{H}_{10}\text{NO}_3$ ($[\text{MH}]^+$) 156.066068, **found** 156.066316.

N-Boc-Propargylglycine (5c).⁴ A solution of N-acetyl-2-aminopent-4-ynoic acid (**5a**, 1.00 g, 6.45 mmol) in 20 mL of HCl 2 N was stirring for 2 h at reflux, and then concentrated *in vacuo*. Addition of acetone to the yellow residue gave a white solid that was filtered and washed with acetone to give 2-aminopent-4-ynoic acid hydrochloride [0.89 g, 91 %, $R_f = 0.52$ (70 % MeOH in DCM with 1 % AcOH)] and used without further purification. ^1H NMR (D_2O , 250.13 MHz, δ): 3.43 (t, $J = 5.5$ Hz, 1H), 2.52 (d, $J = 4.8$ Hz, 1H), 2.30 (s, 1H). **MS (CI)** [m/z (%): 114 ($[\text{MH}]^+$, 58), 74 (26), 68 (59). **HRMS (CI) calculated** for $\text{C}_5\text{H}_8\text{NO}_2$ ($[\text{MH}]^+$) 114.055504, **found** 114.055674.

To a solution of 2-aminopent-4-ynoic acid hydrochloride (400 mg, 2.65 mmol) in water (10 mL) and dioxane (10 mL) was added Boc_2O (868 mg, 3.98 mmol) and DIEA (1.39 mL, 7.97 mmol). After stirring at rt for 3 h, the solution was acidified to pH=3 by addition of HCl (10 %), and extracted with CH_2Cl_2 . The combined organic layers were dried (Na_2SO_4), filtered and concentrated, providing a yellow oil, which was purified by flash chromatography (0-3 % MeOH in DCM), affording 547 mg of **5c** as a white foam [97 %, $R_f = 0.73$ (70 % MeOH in DCM with 1 % AcOH)]. ^1H NMR (CDCl_3 , 250.13 MHz, δ): 10.53 (br s, 1H), 6.52 (d, $J = 6.3$ Hz, 0.25H), 5.41 (d, $J = 8.3$ Hz, 0.75H), 4.68-4.15 (m, 1H), 2.77 (m, 2H), 2.07 (t, $J = 2.5$ Hz, 1H), 1.45 (s, 9H). ^{13}C NMR (CDCl_3 , 62.90 MHz, δ): 175.2 (CO), 155.4 (CO), 80.6 (C), 78.3 (C), 71.9 (CH), 51.7 (CH), 28.2 (CH_3), 22.5 (CH_2). **MS (CI)** [m/z (%): 214 ($[\text{MH}]^+$, 65), 158 (100), 142 (38), 114 ($[\text{MH} - \text{Boc}]^+$, 91). **HRMS (CI) calculated** for $\text{C}_{10}\text{H}_{16}\text{NO}_4$ ($[\text{MH}]^+$) 214.107933, **found** 214.107925.

⁴ a) Van Hest, J. C. M.; Kiick, K. L.; Tirrell, D. A. *J. Am. Chem. Soc.* **1989**, *111*, 1282-1288. b) Baldwin, J. E.; Bradley, M.; Abbott, S. D.; Adlington, R. M. *Tetrahedron* **1991**, *47*, 5309-5328. c) Leukart, O.; Caviezel, M.; Eberle, A.; Escher, E.; Tun-Kyi, A.; Schwyzer, R. *Helv. Chim. Acta* **1976**, *59*, 2181-2183. d) Coulter, A. W.; Talalay, P. *J. Biol. Chem.* **1968**, *243*, 3238-3247.

N-Acetyl-2-aminohept-5-ynoic acid (6a). Using the conditions described for preparation of **5a**, 890 mg of amino acid **6a** was obtained as white crystals [71 %, R_f = 0.72 (70 % MeOH in DCM with 0.5 % AcOH)]. $^1\text{H NMR}$ (DMSO- d_6 , 250.13 MHz, δ): 12.63 (br s, 1H), 8.13 (d, J = 7.3 Hz, 1H), 4.23 (dd, J_1 = 8.8 Hz, J_2 = 12.3 Hz, 1H), 2.81 (s, 1H), 2.21 (m, 2H), 1.84 (s, 3H), 1.72 (m, 2H). $^{13}\text{C NMR}$ (DMSO- d_6 , 62.90 MHz, δ): 173.7 (CO), 169.4 (CO), 83.2 (C), 71.8 (CH), 50.9 (CH), 30.2 (CH₂), 22.3 (CH₃), 14.8 (CH₂). **MS (CI)** [m/z (%): 170 ([MH]⁺, 100), 128 (96). **HRMS (CI) calculated** for C₈H₁₂NO₃ ([MH]⁺) 170.081718, **found** 170.081476. **m.p.**: 127-130 °C.

Preparation of L-Propargylglycine. Representative procedure for kinetic resolutions.⁵ Racemic N-acetyl-2-aminopent-4-ynoic acid (**5a**, 1.00 g, 6.45 mmol) in distilled water (70 mL) was treated with enough lithium hydroxide to make the final solution pH 7.5-8.0. Then Acylase I (5.2 mg; 8.3 U of enzyme by mmol of acyl L-amino acid) was added and the mixture was incubated at 37 °C during 24 h. After this time, the reaction was adjusted to pH 5.0 with HCl (10%) and filtered through a layer of activated carbon. The filtrate was acidified to pH 1.5 with HCl (10%) and extracted with ethyl acetate (5 x 25 mL). The aqueous layer was concentrated to a reduced volume (~1 mL) and then applied to a column of Dowex-50 (H⁺), and the column was rinsed with water until neutral and then eluted with aqueous ammonia (10%). The resulting solution was evaporated to dryness by rotary evaporation and the residue was treated with acetone to give 259 mg of the corresponding free L-Propargylglycine, whose spectroscopic and physical properties match with previously reported [71%, R_f = 0.47 (70% MeOH in CH₂Cl₂), ee > 99%].⁴

Otherwise, the ethyl acetate layer was dried with Na₂SO₄, filtered, and evaporated *in vacuo*, obtaining the corresponding N-acetyl D-Propargylglycine as a white solid, which was hydrolyzed by refluxing for 2 h in HCl (10%). The free D-Propargylglycine was recovered from the hydrolysis mixture by cation-exchange chromatography as shown before for the L-derivative, to provide 196 mg as a white solid [54%, R_f = 0.47 (70% MeOH in CH₂Cl₂), ee > 99%].⁴

The enantiomeric purities of amino acids were determined by the test of Marfey.⁶ L-propargylglycine (1 mg) was dissolved in water (100 μ L) and then treated with a solution of 1-fluoro-2,4-dinitrophenyl-5-L-alanine amide (2 mg) in acetone (200 μ L). The resulting mixture was treated with NaHCO₃ (1 M, 40 μ L) and heated at 40 °C during 1 h. After this time, the solution was cooled at rt and treated with HCl (2 M, 20 μ L). Finally, the mixture was injected in the HPLC (C18 column, 10-40% B in 45 min) and enantiomeric excess was estimated by area ratio of peaks corresponding to the *D*- and *L*-diastereomers.

Preparation of 7a. Representative procedure for Sonogashira cross-coupling with propargylglycine or homopropargylglycine derivatives. 3-Bromopyridine (102 μ L, 1.06 mmol), Cs₂CO₃ (788 mg, 2.42 mmol), CuI (37 mg, 0.19 mmol), 4-DPPBA (59 mg, 0.19 mmol) and 10% Pd/C (52 mg, 0.05 mmol) were mixed in 9 mL of 1:1 DMF/H₂O. The resulting suspension was degassed and stirred at rt for 30 min, and then amino acid **5a** (150 mg, 0.97 mmol) was added. The mixture was heated at 80 °C for 4 h, allowed to

⁵ a) Chenault, H. K.; Dahmer, J.; Whitesides, G. M. *J. Am. Chem. Soc.* **1989**, *111*, 6354-6364. b) Wolf, L. B.; Tjen, K. C. M. F.; Rutjes, F. P. J. T.; Hiemstra, H.; Schoemaker, H. E. *Tetrahedron Lett.* **1998**, *39*, 5081-5084.

⁶ Marfey, P. *Carlsberg Res. Commun.* **1984**, *49*, 591-596.

cool to rt, filtered through Celite and concentrated, and this crude product was purified by flash chromatography (0-8 % MeOH in EtOAc with 0.5 % AcOH), giving 215 mg of **7a** as a yellow foam [96 %, R_f = 0.61 (50 % MeOH in DCM with 1 % AcOH)]. **¹H NMR** (CD₃OD, 250.13 MHz, δ): 8.62-8.30 (m, 2H), 7.79 (dd, J_1 = 1.6 Hz, J_2 = 7.9 Hz, 1H), 7.34 (dd, J_1 = 4.9 Hz, J_2 = 7.8 Hz, 1H), 4.46 (t, J = 5.7 Hz, 1H), 2.93 (dd, J_1 = 5.8 Hz, J_2 = 8.4 Hz, 2H), 1.99 (s, 3H). **¹³C NMR** (CD₃OD, 62.90 MHz, δ): 179.4 (CO), 172.8 (CO), 152.6 (CH), 148.6 (CH), 140.7 (CH), 124.9 (CH), 123.0 (C), 92.1 (C), 79.3 (C), 50.0 (CH), 24.3 (CH₂), 22.9 (CH₃). **MS (CI)** [m/z (%]): 233 ([MH]⁺, 7), 215 (17), 174 (61). **HRMS (CI) calculated** for C₁₂H₁₃N₂O₃ ([MH]⁺) 233.092617, **found** 233.092474.

Preparation of 7c. Using the conditions described for preparation of **7a**, 253 mg of **7c** was obtained from **5c** [93 %, R_f = 0.52 (10 % MeOH in DCM with 1 % AcOH), yellow foam]. **¹H NMR** (MeOD, 250.13 MHz, δ): 9.65-8.02 (m, 2H), 8.01-7.18 (m, 2H), 4.39 (m, 1H), 3.00 (m, 2H), 1.45 (s, 9H). **¹³C NMR** (CD₃OD, 62.90 MHz, δ): 175.7 (CO), 157.5 (CO), 152.3 (CH), 148.5 (CH), 140.7 (CH), 124.9 (CH), 122.4 (C), 91.3 (C), 79.7 (C), 49.9 (CH), 28.7 (CH₃), 24.3 (CH₂). **MS (ESI)** [m/z (%]): 291 ([MH]⁺, 44), 235 (100). **HRMS (ESI) calculated** for C₁₅H₁₉N₂O₄ ([MH]⁺) 291.1345, **found** 291.1351.

Preparation of 8a. Using the conditions described for preparation of **7a**, 68 mg of **8a** was obtained from **6a** [86 %, R_f = 0.68 (70 % MeOH in DCM with 1 % AcOH), yellow solid]. **¹H NMR** (CD₃OD, 250.13 MHz, δ): 8.47 (dd, J_1 = 7.0 Hz, J_2 = 18.7 Hz, 2H), 7.81 (d, J = 7.8 Hz, 1H), 7.36 (dd, J_1 = 5.0 Hz, J_2 = 7.4 Hz, 1H), 4.42 (m, 1H), 2.54 (t, J = 7.2 Hz, 2H), 2.19 (m, 2H), 2.00 (s, 3H). **¹³C NMR** (CD₃OD, 62.90 MHz, δ): 179.0 (CO), 173.1 (CO), 152.5 (CH), 148.5 (CH), 140.6 (CH), 124.9 (CH), 123.0 (C), 94.7 (C), 78.2 (C), 49.3 (CH), 32.6 (CH₂), 22.9 (CH₃), 17.1 (CH₂). **MS (FAB)** [m/z (%]): 247 ([MH]⁺, 7), 223 (12), 207 (11), 131 (5), 115 (15). **HRMS (FAB) calculated** for C₁₃H₁₅N₂O₃ ([MH]⁺) 247.108268, **found** 247.108988.

Compound 9a. Using the conditions described for preparation of **7a**, 67 mg of **9a** was obtained from **5a** [88 %, R_f = 0.79 (50 % MeOH in DCM with 1 % AcOH), yellow oil]. **¹H NMR** (MeOD, 250.13 MHz, δ): 7.35 (m, 1H), 7.07 (m, 1H), 6.89 (m, 1H), 4.55 (m, 1H), 2.71 (m, 2H), 2.01 (s, 3H). **¹³C NMR** (MeOD, 62.90 MHz, δ): 173.4 (CO), 173.3 (CO), 131.1 (CH), 128.9 (CH), 128.5 (CH), 122.7 (C), 92.1 (C), 77.7 (C), 52.6 (CH), 24.6 (CH₃), 22.4 (CH₃). **MS (CI)** [m/z (%]): 238 ([MH]⁺, 9), 220 (23), 183 (46). **HRMS (CI) calculated** for C₁₁H₁₂NO₃S ([MH]⁺) 238.053795, **found** 238.053664.

Compound 10a. Using the conditions described for preparation of **7a**, 78 mg of **10a** was obtained from **5a** [94 %, R_f = 0.50 (50 % MeOH in DCM with 1 % AcOH), orange foam]. **¹H NMR** (CD₃OD, 250.13 MHz, δ): 10.42 (s, 1H), 7.52 (m, 1H), 7.44-7.10 (m, 3H), 4.56 (t, J = 5.8 Hz, 1H), 2.98 (m, 2H), 2.02 (s, 3H). **¹³C NMR** (CD₃OD, 62.90 MHz, δ): 193.7 (CO), 173.1 (CO), 173.0 (CO), 140.7 (C), 133.2 (CH), 129.5 (CH), 128.8 (CH), 127.5 (CH), 123.6 (C), 92.0 (C), 81.0 (C), 49.9 (CH), 24.2 (CH₂), 22.8 (CH₃). **MS (CI)** [m/z (%]): 260 ([MH]⁺, 7), 204 (28). **HRMS (CI) calculated** for C₁₄H₁₄NO₄ ([MH]⁺) 260.092281, **found** 260.092734.

Compound 11a. Using the conditions described for preparation of **7a**, 73 mg of **11a** was obtained from **5a** [92 %, R_f = 0.65 (50 % MeOH in DCM with 1 % AcOH), yellow oil]. ^1H NMR (CD_3OD , 250.13 MHz, δ): 7.41 (dd, J_1 = 2.1 Hz, J_2 = 6.5 Hz, 1H), 7.33 (d, J = 7.5 Hz, 1H), 7.20-7.04 (m, 2H), 6.51 (s, 1H), 4.75 (dd, J_1 = 4.1 Hz, J_2 = 7.4 Hz, 1H), 3.43-3.06 (m, 2H), 1.89 (s, 3H). ^{13}C NMR (CD_3OD , 62.90 MHz, δ): 175.6 (CO), 173.2 (CO), 156.2 (C), 130.1 (C), 127.7 (CH), 124.6 (CH), 123.6 (CH), 121.5 (CH), 102.9 (C), 78.8 (C), 49.9 (CH), 31.8 (CH_2), 22.5 (CH_3). **MS (CI)** [m/z (%)]: 248 ($[\text{MH}]^+$, 66), 206 (82), 188 (59), 160 (88), 131 (59). **HRMS (CI) calculated** for $\text{C}_{13}\text{H}_{14}\text{NO}_4$ ($[\text{MH}]^+$) 248.092283, **found** 248.092419.

Compound 12a. Using the conditions described for preparation of **7a**, 147 mg of **12a** was obtained from **5a** [93 %, R_f = 0.63 (50 % MeOH in DCM with 1 % AcOH), yellow oil]. **MS (CI)** [m/z (%)]: 248 ($[\text{MH}]^+$, 24), 193 (69), 133 (78). **HRMS (CI) calculated** for $\text{C}_{13}\text{H}_{14}\text{NO}_4$ ($[\text{MH}]^+$) 248.092283, **found** 248.091962.

Compound 12c. Using the conditions described for preparation of **7a**, 195 mg of **12c** was obtained from **5c** [91 %, R_f = 0.58 (10 % MeOH in DCM with 1 % AcOH), brownish oil]. **MS (ESI)** [m/z (%)]: 306 ($[\text{MH}]^+$, 4), 251 (100), 205 ($[\text{MH} - \text{Boc}]^+$, 18). **HRMS (ESI) calculated** for $\text{C}_{16}\text{H}_{20}\text{NO}_5$ ($[\text{MH}]^+$) 306.1341, **found** 306.1348.

Compound 13a. Using the conditions described for preparation of **7a**, 59 mg of **13a** was obtained from **6a** [82 %, R_f = 0.59 (70 % MeOH in DCM with 1 % AcOH), white solid]. **MS (CI)** [m/z (%)]: 248 ($[\text{MH}]^+$, 12), 205 (72), 189 (27), 160 (91). **HRMS (CI) calculated** for $\text{C}_{12}\text{H}_{14}\text{N}_3\text{O}_3$ ($[\text{MH}]^+$) 248.103522, **found** 248.104134.

Compound 14a. Using the conditions described for preparation of **7a**, 69 mg of **14a** was obtained from **6a** [90 %, R_f = 0.73 (70 % MeOH in DCM with 1 % AcOH), brownish oil]. ^1H NMR (CD_3OD , 250.13 MHz, δ): 7.43 (m, 1H), 7.33 (m, 1H), 7.12 (ddd, J_1 = 1.6 Hz, J_2 = 4.7 Hz, J_3 = 6.5 Hz, 2H), 6.52 (d, J = 0.8 Hz, 1H), 4.39 (dd, J_1 = 4.7 Hz, J_2 = 9.0 Hz, 1H), 2.88-2.79 (m, 2H), 2.36-1.97 (m, 2H), 1.94 (s, 3H). **MS (CI)** [m/z (%)]: 262 ($[\text{MH}]^+$, 27), 207 (46), 147 (79). **HRMS (CI) calculated** for $\text{C}_{14}\text{H}_{16}\text{NO}_4$ ($[\text{MH}]^+$) 262.107932, **found** 262.107963.

Compound 15a. Using the conditions described for preparation of **7a**, 88 mg of **15a** was obtained from **6a** [88 mg, 87 %, R_f = 0.76 (70 % MeOH in DCM with 1 % AcOH), yellow solid]. ^1H NMR ($\text{DMSO}-d_6$, 250.13 MHz, δ): 12.66 (br s, 1H), 8.71 (s, 1H), 8.40 (d, J = 8.9 Hz, 2H), 8.18-8.12 (m, 3H), 7.75-7.55 (m, 4H), 4.26 (ddd, J_1 = 4.7 Hz, J_2 = 7.9 Hz, J_3 = 9.4 Hz, 1H), 2.23 (dt, J_1 = 2.5 Hz, J_2 = 7.1 Hz, J_3 = 7.3 Hz, 2H), 2.00-1.65 (m, 5H). ^{13}C NMR ($\text{DMSO}-d_6$, 62.90 MHz, δ): 173.4 (CO), 169.5 (CO), 131.7 (C), 129.8 (C), 128.8 (CH), 128.0 (CH), 127.5 (CH), 126.6 (CH), 125.9 (CH), 120.9 (C), 96.0 (C), 80.2 (C), 50.9 (CH), 29.0 (CH_2), 22.3 (CH_3), 12.9 (CH_2). **MS (CI)** [m/z (%)]: 346 ($[\text{MH}]^+$, 6), 287 (32), 258 (36), 229 (65). **HRMS (CI) calculated** for $\text{C}_{22}\text{H}_{20}\text{NO}_3$ ($[\text{MH}]^+$) 346.144327, **found** 346.144682.

Preparation of 16c. A solution of **7c** (50 mg, 0.17 mmol) in MeOH (2 mL) was treated with 10 % Pd/C (37 mg, 0.03 mmol) and hydrogenated at balloon pressure for 2 h. The insolubles were separated by filtration through Celite and rinsed with MeOH (3 x 2 mL). Concentration of the filtrate provided 50 mg of **16c** as a white foam [98 %, R_f = 0.54 (10 % MeOH in DCM with 1 % AcOH)]. **¹H NMR** (CDCl₃, 250.13 MHz, δ): 10.71 (br s, 1H), 9.53-7.35 (m, 4H), 5.53 (m, 1H), 4.38 (m, 1H), 3.71 (m, 1H), 3.41-2.47 (m, 3H), 1.77 (m, 2H), 1.43 (s, 9H). **¹³C NMR** (MeOD, 62.90 MHz, δ): 175.5 (CO), 157.3 (CO), 149.6 (CH), 148.1 (CH), 137.9 (C), 136.7 (CH), 124.5 (CH), 79.7 (C), 49.9 (CH), 34.9 (CH₂), 30.7 (CH₂), 28.7 (CH₃), 25.2 (CH₂). **MS (ESI)** [m/z (%): 295 ([MH]⁺, 100). **HRMS (ESI) calculated** for C₁₅H₂₃N₂O₄ ([MH]⁺) 295.1652, **found** 295.1656.

Compound 17c. 48 mg, [Using the conditions described for preparation of **16c**, 48 mg of **17c** was obtained from **12c** [96 %, R_f = 0.56 (10 % MeOH in DCM with 1 % AcOH), brownish oil]. **MS (ESI)** [m/z (%): 310 ([MH]⁺, 100), 332 ([M + Na]⁺, 47), 349 ([M + K]⁺, 8). **HRMS (ESI) calculated** for C₁₆H₂₄NO₅ ([MH]⁺) 310.1654, **found** 310.1643.

Compound 16a by one-pot Sonogashira cross-coupling and hydrogenation. 3-Bromopyridine (35 μ L, 0.36 mmol), Cs₂CO₃ (115 mg, 0.83 mmol), CuI (5 mg, 0.02 mmol), PPh₃ (9 mg, 0.03 mmol) and 10% Pd/C (18 mg, 0.015 mmol) were mixed in 20 mL of 1:1 DMF/H₂O. The resulting suspension was degassed and stirred at rt for 30 min, and then **7a** (50 mg, 0.33 mmol) was added. The mixture was heated at 80 °C for 12 h, allowed to cool to rt, and hydrogenated at balloon pressure for 8 h. The resulting suspension was filtered through Celite, rinsed with EtOAc (3 x 20 mL) and concentrated. This crude product was purified by flash chromatography (0-3 % MeOH in DCM with 0.5 % AcOH), giving 66 mg of **16a** as a white solid. [87 %, R_f = 0.66 (50 % MeOH in DCM with 1 % AcOH), yellow foam. **MS (CI)** [m/z (%): 237 ([MH]⁺, 12), 211 (22), 169 (52). **HRMS (CI) calculated** for C₁₂H₁₇N₂O₃ ([MH]⁺) 237.123921, **found** 237.124724.

Preparation of 18c. A solution of **7c** (60 mg, 0.21 mmol) and quinoline (50 μ L, 0.42 mmol) in MeOH (2 mL) was treated with Lindlar's catalyst (50 mg), and hydrogenated at balloon pressure for 8 h. After removal of the insolubles by filtration through Celite and addition of more Lindlar's catalyst (100 mg), the resulting mixture was hydrogenated at balloon pressure for additional 3 h. The suspension was filtered through Celite and concentrated, and the crude was purified by flash chromatography (0-8 % MeOH in DCM with 0.5 % AcOH), providing 49 mg of **18c** as a brownish foam [82 %, R_f = 0.20 (5 % MeOH in DCM with 1 % AcOH)]. **¹H NMR** (CDCl₃, 250.13 MHz, δ): 8.82-8.23 (m, 2H), 7.68 (d, J = 7.7 Hz, 1H), 7.34 (m, 1H), 6.46 (d, J = 11.6 Hz, 1H), 5.92 (ddd, J_1 = 7.2 Hz, J_2 = 9.8 Hz, J_3 = 11.7 Hz, 1H), 5.59 (br s, 1H), 4.40 (m, 1H), 2.82 (m, 2H), 1.42 (s, 9H). **¹³C NMR** (CDCl₃, 62.90 MHz, δ): 175.2 (CO), 155.5 (CO), 147.5 (CH), 145.5 (CH), 137.7 (CH), 133.8 (C), 130.8 (CH), 127.0 (CH), 123.9 (CH), 79.6 (C), 53.7 (CH), 29.7 (CH₂), 28.3 (CH₃). **MS (ESI)** [m/z (%): 293 ([MH]⁺, 100), 316 ([M + Na]⁺, 72), 332 ([M + K]⁺, 8). **HRMS (ESI) calculated** for C₁₅H₂₁N₂O₄ ([MH]⁺) 293.1496, **found** 293.1484.

Compound 19c. Using the conditions described for preparation of **18c**, 43 mg of **19c** was obtained from **12c** [86 %, $R_f = 0.50$ (10 % MeOH in DCM with 1 % AcOH), brownish oil]. **MS (ESI)** [m/z (%): 308 ($[MH]^+$, 100), 331 ($[M + Na]^+$, 32). **HRMS (ESI) calculated** for $C_{16}H_{22}NO_5$ ($[MH]^+$) 308.1498, **found** 308.1422.