Copper-Mediated Synthesis of *N*-Acyl Vinylogous Carbamic Acids and Derivatives: Synthesis of the Antibiotic CJ-15,801

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Supporting Information

General Information: ^1H NMR spectra were recorded on a 400 MHz spectrometer at ambient temperature. ^{13}C NMR spectra were recorded on a 75.0 MHz spectrometer at ambient temperature with complete proton decoupling. Chemical shifts are reported in parts per million relative to CDCl_3 (^1H , δ 7.27; ^{13}C , δ 77.23) unless otherwise stated. Data for ^1H NMR are reported as follows: chemical shift, integration, multiplicity (app = apparent, br = broad, ovrlp = overlapping, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet) and coupling constants. Infrared spectra were recorded on a Nicolet Nexus 670 FT-IR spectrophotometer and a Nicolet Nexus 470 FT-IR + Continuum microscope. Optical rotations were recorded on an AUTOPOL III digital polarimeter at 589 nm, and are reported as $[\alpha]_{\text{D}}$ (concentration in grams/100 mL solvent). HPLC analysis was performed on an Agilent 1100 series HPLC (column: Agilent, Eclipse XDB-C18, 5 μm , 4.6 $\times$ 150 mm). HPLC-ELSD analysis was performed on an Agilent 1100 series LC/ELSD (Column: Waters, Xterra MS C₁₈ 5 μm 4.6 $\times$ 100 mm). High-resolution mass spectra were obtained in the Boston University Mass Spectrometry Laboratory using a Finnegan MAT-90 spectrometer. HR-TOFMS spectra were obtained using a Micromass LCT spectrometer by Ms. Qing Liao (Department of Chemistry and Chemical Biology, Harvard University). Analytical thin layer chromatography was performed on 0.25 mm silica gel 60-F plates. Flash chromatography was performed using 200~400 mesh silica gel (Scientific Absorbent Incorporated) or neutral aluminum oxide (Sigma-Aldrich). Sep-Pak Vac 12cc C-18 cartridges (Part NO. WAT036915) were obtained from Waters, Inc. Yields refer to chromatographically and spectroscopically pure materials, unless otherwise stated. Tetrahydrofuran was freshly distilled under argon from sodium/benzophenone ketyl. Copper (I) thiophene-2-carboxylate (CuTC) was prepared according the procedure of Allred and

Liebeskind.¹ Copper (I) tetrakis (acetonitrile) hexafluorophosphate ($\text{Cu}(\text{CH}_3\text{CN})_4\text{PF}_6$) was prepared according the procedure of Kubas.² 2,6-Hexadienamide (sorbamide) was prepared according to the method reported by Pellegata.³ Dimethylacetamide (DMA) was distilled from barium oxide and stored over 4Å molecular sieves prior to use. PS-NH₂, PS-HOBt, and chloro-1,1,3,3-tetramethyluronium hexachloro-antimonate (ACTU) were obtained from Argonaut Technologies (Foster City, CA.). All other reagents were used as supplied by Sigma-Aldrich, Lancaster, Fluka, Strem, and Bachem Chemicals. Solid-phase synthesis reactions were conducted on the Quest 205 and 210 parallel synthesizers (Argonaut Technologies). All other reactions were performed in oven-dried glassware under an argon atmosphere unless otherwise noted.

(*E*)-allyl-3-iodo acrylate **4**: To a 250 mL flask were added β -iodo acrylic acid⁴ (11.88 g, 60.0 mmol), DMAP (0.44 g, 3.6 mmol), and DMAP·HCl (1.33 g, 8.4 mmol). Allyl alcohol (20.4 mL, 300 mmol) and CH_2Cl_2 (40 mL) were added to the flask using oven-dried syringes. The solution was cooled to 0 °C and 1,3-diisopropylcarbodiimide (DIC) (9.86 mL, 63.0 mmol) was added dropwise. The reaction was warmed to rt and stirred for 1 h. The reaction mixture was filtered through Celite and concentrated. After dilution with EtOAc, the organic layer was washed with saturated NaHCO_3 (2×), brine (2×) and the aqueous layer extracted 2× with EtOAc. The organic layers were combined, dried over Na_2SO_4 , and concentrated. Purification on silica gel (hexane: EtOAc= 20:1) provided 13.02 g (54.8 mmol, 92 %) of (*E*)-allyl- β -iodo acrylate **4** as a pale yellow oil. IR (neat): 3072, 2943, 1722, 1591, 1298, 1250, 1212, 1145, 991, 947 cm^{-1} ; ¹H NMR: δ 7.92 (1H, d, *J* = 15.2 Hz), 6.91 (1H, d, *J* = 15.2 Hz), 5.96 (1H, ddt, *J* = 17.2, 10.4, 5.6 Hz), 5.35 (1H, d, *J* = 17.2 Hz), 5.26 (1H, d, *J* = 10.4 Hz), 4.64 (2H, d, *J* = 5.6 Hz) ppm; ¹³C NMR: δ 164.0, 136.4, 131.9, 119.0, 100.1, 65.7 ppm; CI-HRMS calcd. for $\text{C}_6\text{H}_7\text{IO}_2$: 237.9491, found 237.9520.

(*E*)-allyl-3-iodo acrylamide **8**: To a 100 mL flask were added β -iodo acrylic acid⁴ (989.8 mg, 5.0 mmol) and DMAP (122.2 mg, 1.0 mmol). Benzylamine (819 μL , 7.5 mmol) and CH_2Cl_2 (10 mL) were added to the flask using oven-dried syringes. The solution was cooled to 0 °C and DIC (861 μL , 5.5 mmol) was added dropwise. The reaction was warmed to rt, stirred for 6 h, filtered through Celite, and concentrated. After dilution with ethyl acetate, the organic layer was washed with saturated NaHCO_3 (2×), brine (2×) and the aqueous layer extracted with EtOAc (2×). The organic layers were combined, dried over Na_2SO_4 , and concentrated. Purification on silica gel (hexane: EtOAc= 3:1) provided 718 mg (2.5 mmol, 50 %) of 3-iodo-*N*-benzyl-2-propenamide **8** as pale yellow needles. mp. 165~167 °C; IR (neat): 3291, 3055, 1631, 1592, 1546, 1452, 1309, 1234, 1151, 1024, 1009, 958 cm^{-1} ; ¹H NMR: δ 7.70 (1H, br s), 7.66 (1H, d, *J* = 14.4 Hz), 7.30~7.21 (5H, m), 7.11 (1H, d, *J* = 14.4 Hz), 4.44 (2H, d, *J* = 6.0 Hz) ppm; ¹³C

¹ Allred, G. D.; Liebeskind, L. S. *J. Am. Chem. Soc.* **1996**, *118*, 2748.

² Kubas, G. J. *Inorg. Synth.* **1979**, *19*, 90.

³ Pellegata, R.; Italia, A.; Villa, M. *Synthesis*, **1985**, 517

⁴ Takeuchi, R.; Tanabe, K.; Tanaka S. *J. Org. Chem.* **2000**, *65*, 1558

NMR: δ 164.5, 141.0, 140.2, 129.5 (2C), 128.7 (2C), 128.1, 93.6, 43.6 ppm; CI-HRMS calcd. for $C_{10}H_{11}INO$ $[M+H]^+$: 287.9885, found 287.9894.

General Procedure for the Preparation of *N*-Acyl Vinyllogous Carbamates and Ureas:

Benzamide (90.9 mg, 0.75 mmol), Rb_2CO_3 (173.2 mg, 0.75 mmol), $Cu(CH_3CN)_4PF_6$ (9.3 mg, 0.025 mmol), and 3,4,7,8-tetramethyl-1,10-phenanthroline (11.8 mg, 0.05 mmol) were placed in a flame-dried 10 mL Schlenk tube equipped with a stir bar. β -Iodo-acrylate **4** (59.5 mg, 0.25 mmol, 36 μ L) and anhydrous DMA (1 mL) were added to the Schlenk tube. The mixture was degassed under high vacuum until no further gas evolution was observed. The suspension was stirred at 45 $^{\circ}C$ for 12 h under argon. The brown slurry was cooled to room temperature and diluted with 4 mL EtOAc and 1 mL pH 7 buffer. The EtOAc extract was then filtered through neutral alumina. The water layer was further extracted with a total of 20 mL EtOAc until the product was removed from the aqueous layer (monitored by TLC). The EtOAc extracts were washed with pH 7 buffer (1 $\times$) and brine (1 $\times$) to remove DMA and the aqueous layer was further extracted with EtOAc (2 $\times$) (this step is not necessary when using DME as solvent). The organic layers were combined, dried over anhydrous Na_2SO_4 , and concentrated. Pure *N*-acyl vinyllogous carbamate **5a** was obtained as a white solid (32.0 mg, 54 % yield; 41.2 mg, 71 % yield using DME as solvent) after flash chromatography on silica gel (hexane: EtOAc = 3:1). mp. 111~113 $^{\circ}C$; IR (neat): 3314, 3084, 2935, 1678, 1634, 1518, 1488, 1448, 1361, 1302, 1212, 1143, 1030, 990 cm^{-1} ; ^1H NMR: δ 9.66 (1H, br d, J = 11.2 Hz), 8.27 (1H, dd, J = 14.0, 11.2 Hz), 7.84 (2H, d, J = 7.6 Hz), 7.49 (1H, dd, J = 7.6, 7.6 Hz), 7.38 (2H, dd, J = 7.6, 7.6 Hz), 5.91 (1H, ddt, J = 17.2, 10.4, 5.6 Hz), 5.72 (1H, d, J = 14.0 Hz), 5.27 (1H, d, J = 17.2 Hz), 5.18 (1H, d, J = 10.4 Hz), 4.57 (2H, d, J = 5.6 Hz) ppm; ^{13}C NMR: δ 167.8, 166.0, 139.2, 133.0, 132.4 (2C, overlap), 128.9 (2C), 127.9 (2C), 118.2, 102.2, 65.0 ppm; CI-HRMS calcd. for $C_{13}H_{14}NO_3$ $[M+H]^+$: 232.0974, found 232.0993.

N-acyl vinyllogous carbamate **5b**: Prepared according to the general procedure as a pale yellow solid (43 % yield) after flash chromatography on silica gel (hexane: EtOAc = 3:1). mp. 114~116 $^{\circ}C$; IR (neat): 3279, 3084, 2938, 1695, 1631, 1503, 1358, 1315, 1294, 1272, 1213, 1142, 991 cm^{-1} ; ^1H NMR: δ 10.07 (1H, br d, J = 12.4 Hz), 8.59 (1H, d, J = 4.8 Hz), 8.22 (1H, d, J = 8.0 Hz), 8.22 (1H, dd, J = 14.0, 12.4 Hz), 7.91 (1H, dd, J = 8.0, 6.4 Hz), 7.51 (1H, dd, J = 6.4, 4.8 Hz), 5.99 (1H, ddt, J = 17.2, 10.4, 5.6 Hz), 5.76 (1H, d, J = 14.0 Hz), 5.34 (1H, d, J = 17.2 Hz), 5.23 (1H, d, J = 10.4 Hz), 4.66 (2H, d, J = 5.6 Hz) ppm; ^{13}C NMR: δ 167.3, 162.5, 148.7, 148.2, 138.1, 137.5, 132.7, 127.7, 123.4, 118.3, 103.1, 65.1 ppm; CI-HRMS calcd. for $C_{12}H_{13}N_2O_3$ $[M+H]^+$: 233.0926, found 233.0901.

N-acyl vinyllogous carbamate **5c**: Prepared according to the general procedure as a white crystalline solid (90 % yield) after flash chromatography on neutral Al_2O_3 (hexane: EtOAc = 5:1). mp. 69~71 $^{\circ}C$; IR (neat): 3331, 3085, 2992, 2959, 2874, 1720, 1639, 1495, 1393, 1378, 1361, 1301, 1260, 1200, 1137, 1098, 1052, 1021, 994 cm^{-1} ; ^1H NMR: δ 8.43 (1H, d, J = 11.6 Hz), 8.00 (1H, dd, J = 14.4, 11.6 Hz), 5.95 (1H, ddt, J = 17.2, 10.4, 5.6 Hz), 5.61 (1H, d, J = 14.4 Hz), 5.31 (1H, d, J = 17.2 Hz), 5.20 (1H, d, J = 10.4 Hz), 4.61 (2H, d, J = 5.6 Hz), 4.16 (1H, s),

3.69 (1H, d, $J = 12.0$ Hz), 3.29 (1H, d, $J = 12.0$ Hz), 1.47 (3H, s), 1.41 (3H, s), 1.01 (3H, s), 0.97 (3H, s) ppm; ^{13}C NMR: δ 168.3, 167.1, 136.6, 132.7, 118.2, 102.8, 99.7, 77.4, 71.4, 65.0, 33.5, 29.5, 21.9, 18.9, 18.7 ppm; CI-HRMS calcd. for $\text{C}_{15}\text{H}_{24}\text{NO}_5$ $[\text{M}+\text{H}]^+$: 298.1654, found 298.1667. $[\alpha]_{\text{D}}^{25} = +32.3$ ($c = 0.13$, CHCl_3)

5d

N-acyl vinylogous carbamate **5d**: Prepared according to the general procedure as a colorless oil (61 % yield) after flash chromatography on silica gel (hexane: EtOAc= 3:1). IR (neat): 3301, 2984, 2881, 1683, 1625, 1496, 1361, 1254, 1212, 1129, 1074, 1035, 991, 936, 851 cm^{-1} ; ^1H NMR: δ 8.67 (1H, d, $J = 12.0$ Hz), 7.98 (1H, dd, $J = 14.0, 12.0$ Hz), 5.96 (1H, ddt, $J = 17.2, 10.4, 5.6$ Hz), 5.59 (1H, d, $J = 14.0$ Hz), 5.31 (1H, d, $J = 17.2$ Hz), 5.21 (1H, d, $J = 10.4$ Hz), 4.62 (2H, d, $J = 5.6$ Hz), 4.42 (1H, dd, $J = 8.4, 6.0$ Hz), 3.99~3.86 (2H, m), 2.35~2.26 (1H, m), 2.11~2.01 (1H, m), 1.98~1.82 (2H, m) ppm; ^{13}C NMR: δ 172.1, 167.1, 136.9, 132.7, 118.3, 102.9, 78.3, 69.9, 65.1, 30.2, 25.6 ppm; CI-HRMS calcd. for $\text{C}_{11}\text{H}_{16}\text{NO}_4$ $[\text{M}+\text{H}]^+$: 226.1080, found 226.1078.

5e

N-acyl vinylogous carbamate **5e**: Prepared according to the general procedure as a colorless oil (6 % yield) after flash chromatography on silica gel (hexane: EtOAc= 3:1). IR (neat): 3292, 2959, 2871, 1717, 1690, 1633, 1514, 1452, 1377, 1306, 1247, 1218, 1145, 988, 928, 845, 724 cm^{-1} ; ^1H NMR: δ 8.08 (1H, dd, $J = 14.4, 12.0$ Hz), 7.71 (1H, br d, $J = 12.0$ Hz), 5.96 (1H, ddt, $J = 17.2, 10.4, 5.6$ Hz), 5.46 (1H, d, $J = 14.4$ Hz), 5.32 (1H, d, $J = 17.2$ Hz), 5.22 (1H, d, $J = 10.4$ Hz), 4.62 (2H, d, $J = 5.6$ Hz), 2.63 (1H, tt, $J = 7.6, 7.6$ Hz), 1.90~1.57 (8H, m) ppm; ^{13}C NMR: δ 175.0, 167.6, 138.6, 132.6, 118.3, 100.8, 65.0, 45.8, 30.3, 26.1 ppm; CI-HRMS calcd. for $\text{C}_{12}\text{H}_{18}\text{NO}_3$ $[\text{M}+\text{H}]^+$: 224.1287, found 224.1285.

5f

N-acyl vinylogous carbamate **5f**: Prepared according to the general procedure (DME as solvent) as a pale yellow solid (58 % yield) after flash chromatography on silica gel (hexane: EtOAc= 3:1). mp. >250 $^{\circ}\text{C}$; IR (neat): 3273, 3080, 3012, 2953, 1714, 1683, 1635, 1559, 1540, 1507, 1457, 1342, 1295, 1256, 1130, 986 cm^{-1} ; ^1H NMR: δ 8.66 (1H, br d, $J = 12.0$ Hz), 8.17 (1H, dd, $J = 14.4, 12.0$ Hz), 7.35 (1H, dd, $J = 15.2, 10.4$ Hz), 6.18~6.16 (2H, m), 5.96 (1H, ddt, $J = 17.2, 10.4, 5.6$ Hz), 5.87 (1H, d, $J = 15.2$ Hz), 5.49 (1H, d, $J = 14.4$ Hz), 5.32 (1H, d, $J = 17.2$ Hz), 5.21 (1H, d, $J = 10.4$ Hz), 4.62 (2H, d, $J = 5.6$ Hz), 1.84 (3H, d, $J = 4.8$ Hz) ppm; ^{13}C NMR: δ 167.3, 162.5, 148.7, 138.1, 137.5, 132.7, 127.7, 123.4, 118.3, 103.1, 65.2, 19.0 ppm; CI-HRMS calcd. for $\text{C}_{12}\text{H}_{16}\text{NO}_3$ $[\text{M}+\text{H}]^+$: 222.1131, found 222.1145.

5g

N-acyl vinylogous carbamate **5g**: Prepared according to the general procedure as a pale yellow oil (77 % yield) after flash chromatography on silica gel (hexane: EtOAc= 3:1). IR (neat): 3400, 3099, 2946, 1712, 1626, 1434, 1242, 1071 cm^{-1} ; ^1H NMR: (major rotamers) δ 8.45 (1H, s), 7.82 (1H, d, $J = 13.6$ Hz), 5.98 (1H, ddt, $J = 17.2, 10.4, 5.6$ Hz), 5.45 (1H, d, $J = 13.6$ Hz), 5.34 (1H, d, $J = 17.2$ Hz), 5.25 (1H, d, $J = 10.4$ Hz), 4.65 (2H, d, $J = 5.6$ Hz).

Hz), 3.06 (3H, s) ppm; ^{13}C NMR: (major rotamor) δ 167.0, 163.4, 144.1, 132.5, 118.5, 99.8, 65.2, 27.8 ppm; CI-HRMS calcd. for $\text{C}_8\text{H}_{12}\text{NO}_3$ $[\text{M}+\text{H}]^+$: 170.0817, found 170.0806.

5h *N*-acyl vinylogous carbamate **5h**: Prepared according to the general procedure as a pale yellow oil (92 % yield) after flash chromatography on silica gel (hexane: EtOAc= 3:1). IR (neat): 3084, 2944, 2894, 1731, 1629, 1483, 1461, 1401, 1359, 1327, 1217, 1153 cm^{-1} ; ^1H NMR: δ 8.08 (1H, d, J = 14.0 Hz), 5.94 (1H, ddt, J = 17.2, 10.4, 5.6 Hz), 5.29 (1H, d, J = 17.2 Hz), 5.19 (1H, d, J = 14.0 Hz), 5.19 (1H, d, J = 10.4 Hz), 4.60 (2H, d, J = 5.6 Hz), 3.53 (2H, t, J = 7.2 Hz), 2.52 (2H, t, J = 8.0 Hz), 2.17 (2H, tt, J = 8.0, 7.2 Hz) ppm; ^{13}C NMR: δ 174.5, 167.1, 137.8, 132.6, 118.2, 100.4, 64.9, 45.0, 30.9, 17.4 ppm; CI-HRMS calcd. for $\text{C}_{10}\text{H}_{14}\text{NO}_3$ $[\text{M}+\text{H}]^+$: 196.0974, found 196.0987.

5i *N*-acyl vinylogous carbamate **5i**: Prepared according to the general procedure as a white foam (72 % yield) after flash chromatography on silica gel (hexane: EtOAc= 3:1). IR (neat): 3375, 2993, 2942, 1740, 1635, 1376, 1222, 992, 940 cm^{-1} ; ^1H NMR: δ 7.56 (1H, d, J = 14.8 Hz), 6.00 (1H, d, J = 14.8 Hz), 5.94 (1H, ddt, J = 17.2, 10.4, 5.6 Hz), 5.30 (1H, d, J = 17.2 Hz), 5.20 (1H, d, J = 10.4 Hz), 4.61 (2H, d, J = 5.6 Hz), 4.38 (1H, q, J = 6.8 Hz), 1.59 (3H, s), 1.50 (3H, s), 1.39 (3H, d, J = 6.8 Hz) ppm; ^{13}C NMR: δ 172.3, 167.2, 134.5, 132.5, 118.4, 103.4, 94.0, 71.6, 65.2, 27.6, 25.1, 17.6 ppm; CI-HRMS calcd. for $\text{C}_{12}\text{H}_{18}\text{NO}_4$ $[\text{M}+\text{H}]^+$: 240.1236, found 240.1253.

7a *N*-acyl vinylogous urea **7a**: Prepared according to the general procedure as a white solid (70 % yield) after flash chromatography on silica gel (hexane: EtOAc= 1:1). IR (neat): 3301, 1657, 1617, 1498, 1425, 1327, 1285, 1257, 1198, 1175, 1102, 1045 cm^{-1} ; ^1H NMR (acetone- d_6 , 2.05): δ 9.48 (1H, br d, J = 10.8 Hz), 7.91 (1H, dd, J = 14.0, 10.8 Hz), 7.52 (1H, br t, J = 5.6 Hz), 7.29~7.28 (4H, m), 7.23~7.20 (1H, m), 6.03 (1H, d, J = 14.0 Hz), 4.44 (2H, d, J = 5.6 Hz), 4.27 (1H, s), 3.77 (1H, d, J = 12.0 Hz), 3.28 (1H, d, J = 12.0 Hz), 1.45 (3H, s), 1.38 (3H, s), 1.01 (3H, s), 0.99 (3H, s) ppm; ^{13}C NMR (CD_3OD , 49.15): δ 169.6, 167.2, 141.0, 134.2, 129.4 (2C), 128.6 (2C), 127.9, 106.9, 100.1, 78.0, 71.7, 43.5, 33.9, 30.4, 22.1, 19.3, 19.0 ppm; CI-HRMS calcd. for $\text{C}_{19}\text{H}_{27}\text{N}_2\text{O}_4$ $[\text{M}+\text{H}]^+$: 347.1971, found 347.1985. $[\alpha]_{\text{D}}^{25}$ = +61.4 (c = 0.22, MeCN)

7b *N*-acyl vinylogous urea **7b**: Prepared according to the general procedure as a white solid (72 % yield) after flash chromatography on silica gel (hexane: EtOAc: MeOH= 20:80:5). mp. 173~174 $^{\circ}\text{C}$; IR (neat): 3276, 3096, 2961, 2932, 1717, 1665, 1653, 1602, 1558, 1407, 1330, 1249 cm^{-1} ; ^1H NMR (CD_3OD , 3.31): δ 8.03 (1H, d, J = 14.0 Hz), 7.32~7.24 (5H, m), 5.91 (1H, br t, J = 5.6 Hz), 5.28 (1H, d, J = 14.0 Hz), 4.49 (2H, d, J = 5.6 Hz), 3.51 (2H, t, J = 7.2 Hz), 2.51 (2H, t, J = 8.4 Hz), 2.14 (2H, tt, J = 8.4, 7.2 Hz) ppm; ^{13}C NMR (acetone- d_6 , 29.92): δ 175.0, 166.9, 141.1, 134.8, 129.4 (2C), 128.6 (2C), 127.9, 104.2, 45.8, 43.6, 31.4, 18.2 ppm; CI-HRMS calcd. for $\text{C}_{14}\text{H}_{16}\text{N}_2\text{O}_2$ $[\text{M}]^+$: 244.1212, found 244.1212.

N-acyl vinyllogous urea 11a: Prepared according to the general procedure as a yellow solid (25 % yield) after flash chromatography on silica gel (CH₂Cl₂: MeOH= 20: 1). mp. 151~154 °C; IR (neat): 3295, 2925, 1649, 1613, 1454, 1389, 1225 cm⁻¹; ¹H NMR (CD₃OD, 3.31): δ 7.95 (2H, d, *J* = 6.8 Hz), 7.64 (1H, dd, *J* = 6.8, 6.8 Hz), 7.60 (2H, dd, *J* = 6.8, 6.8 Hz), 7.55 (1H, d, *J* = 8.8 Hz), 7.33~7.24 (5H, m), 5.44 (1H, d, *J* = 8.8 Hz), 4.50 (2H, s) ppm; ¹³C NMR (acetone-*d*₆, 29.92): δ 170.1, 164.7, 140.4, 136.3, 134.0, 133.7, 130.1 (2C), 129.5 (2C), 128.7 (2C), 128.5 (2C), 128.1, 101.2, 43.3 ppm; CI-HRMS calcd. for C₁₇H₁₆N₂O₂ [M]⁺: 280.1212, found 280.1210.

N-acyl vinyllogous urea 11b: Prepared according to the general procedure as a yellow solid (18 % yield) after flash chromatography on silica gel (CH₂Cl₂: CH₃OH= 20: 1). mp. °C; IR (neat): 3300, 3088, 3030, 2964, 2931, 1657, 1612, 1556, 1464, 1394, 1358, 1238, 1147, 1100, 1081, 999 cm⁻¹; ¹H NMR (acetone-*d*₆, 2.05): δ 11.46 (1H, d, *J* = 10.4 Hz), 7.77 (1H, br s), 7.39 (1H, dd, *J* = 10.4, 8.8 Hz), 7.31~7.27 (5H, m), 7.27 (1H, dd, *J* = 14.8, 10.4 Hz), 6.36 (1H, dd, *J* = 14.8, 10.4 Hz), 6.27 (1H, dq, *J* = 14.8, 6.4 Hz), 6.10 (1H, d, *J* = 14.8 Hz), 5.28 (1H, d, *J* = 8.8 Hz), 4.45 (1H, d, *J* = 6.0 Hz), 1.85 (1H, d, *J* = 6.4 Hz) ppm; ¹³C NMR (acetone-*d*₆, 29.92): δ 169.7, 164.4, 144.3, 140.6, 140.2, 135.9, 131.1, 129.5, 128.6, 128.1, 122.5, 100.2, 43.2, 18.8 ppm; CI-HRMS calcd. for C₁₆H₁₈N₂O₂ [M]⁺: 270.1368, found 270.1381.

N-acyl vinyllogous carbamate 12: To a test tube were added acetoneide **5c** (80.1 mg, 0.269 mmol) and BiCl₃ (17.0 mg, 0.0539 mmol), followed by distilled H₂O (96.9 mg, 5.38 mmol, 96.9 uL) and MeCN (1.1 mL). The reaction was stirred at room temperature for 8 h, then filtered and concentrated. After dilution with EtOAc, the reaction mixture was washed with sat. NaHCO₃ (2×) and the aqueous layer was extracted with EtOAc (2×). The organic layers were combined, dried over Na₂SO₄, and concentrated. Purification using a Sep-Pak C18 cartridge (20 % MeCN/H₂O) provided 52.0 mg (75 %) of **12** as a pale yellow solid. mp. 62~64 °C; IR (neat): 3295, 2969, 2879, 1697, 1634, 1504, 1366, 1305, 1262, 1212, 1146, 1079, 1037, 989 cm⁻¹; ¹H NMR (CD₃OD, 3.31): δ 7.99 (1H, d, *J* = 14.4 Hz), 6.01 (1H, ddt, *J* = 17.2, 10.4, 5.6 Hz), 5.78 (1H, d, *J* = 14.4 Hz), 5.34 (1H, d, *J* = 17.2 Hz), 5.22 (1H, d, *J* = 10.4 Hz), 4.63 (2H, d, *J* = 5.6 Hz), 4.02 (1H, s), 3.50 (1H, d, *J* = 10.8 Hz), 3.39 (1H, d, *J* = 10.8 Hz), 0.93 (3H, s), 0.92 (3H, s) ppm; ¹³C NMR (CD₃OD, 49.15): δ 175.3, 169.6, 139.3, 134.2, 118.4, 102.7, 77.2, 69.9, 66.0, 40.9, 21.6, 20.6 ppm; CI-HRMS calcd. for C₁₂H₂₀NO₅ [M+H]⁺: 258.1341, found 258.1322. [α]_D²⁵ = + 80.0 (*c* = 0.12, MeCN)

N-hydroxylphthalimide resin 14: Pre-swelled PS-NH₂ resin (5.0 g, 6.50 mmol, loading: 1.30 mmol/g,) was mixed with 40 mL CH₂Cl₂ in an 80 mL reaction vessel on the Quest 205 parallel synthesizer. After addition of 8.1 mL HCl in dioxane (4.0 M, 32.4 mmol), the mixture was agitated for 1 h. Upon filtration,

the PS-NH₂·HCl resin was washed with CH₂Cl₂ (3×30 mL) and transferred to a pre-silylated 250 mL two-neck flask equipped with a mechanical stirrer. Trimellitic anhydride chloride (6.80 g, 32.4 mmol) was added followed by 30 mL CH₂Cl₂ and the reaction was cooled to 0 °C using an ice bath. A solution of Et₃N (6.22 mL, 45.5 mmol) in 20 mL CH₂Cl₂ was added to the reaction mixture over 2 h *via* syringe pump. The reaction was stirred at 0 °C for an additional 3 h, warmed to rt, and stirred for an additional 2 h. After the reaction mixture was transferred to a reaction vessel on the Quest 205 synthesizer and the resulting anhydride resin was washed with CH₂Cl₂ (2×20 mL), DMF (2×20 mL), THF (2×20 mL), and CH₂Cl₂ (2×20 mL). Following washing, NH₂OH·HCl (2.24 g, 32.5 mmol, 5.0 equiv.) and 40 mL 3:1 pyridine: 1,2-dichloroethane were added and the reaction was agitated for 24 h at 75 °C. The reaction was cooled to rt, the resin **14** filtered, washed with MeOH (2×20 mL), DMF (2×20 mL), DMF: H₂O=1: 1 (2×30 mL), DMF (1×20 mL), THF (3×20 mL), CH₂Cl₂ (2×20 mL), Et₂O (2×20 mL), and dried under high vacuum at 50 °C for 12 h. IR (single bead): 3385, 3060, 3027, 2925, 1788, 1728, 1669, 1601, 1514, 1494, 1453, 1374, 1299, 1194, 1141, 1115, 1021, 998, 913, 827, 761, 709 cm⁻¹

Loading determination: Resin **14** (100 mg) was pre-swelled with CH₂Cl₂ in a 5 mL reaction vessel on the Quest-210 synthesizer and 4-biphenylmethanol (55.2 mg, 0.30 mmol) and azodicarboxylic acid bis[*N*-dimethylamide]⁵ (51.6 mg, 0.30 mmol) were added as solids under N₂ followed by 2 mL 1:1 THF: CH₂Cl₂. After mixing to dissolve the reagents, P(*n*-Bu)₃ (43.2 μL, 0.30 mmol) was added and reaction mixture was agitated for 6 h. After filtering the reaction mixture, the resulting resin was washed with DMF (2×3 mL), MeOH (2×3 mL), THF (3×3 mL), CH₂Cl₂ (3×3 mL). Following the addition of 2 mL CH₂Cl₂, NH₂NH₂ (6.3 μL, 0.20 mmol) was added and the reaction was agitated for 1 h. The filtration was collected and treated with 2 mL acetone. After concentration, the resulting sample was subjected to an HPLC analysis using an Agilent 1100 with diodearray detector (DAD) and an Agilent Zorbax C₁₈ (3.5 μm, 4.6 × 75 mm) column (4-Biphenylmethanol as internal standard). The loading was determined to be 75% (0.77 mmol/g).

CJ-15,801 **3**: To a Teflon vial were added allyl ester **12** (13.2 mg, 0.0513 mmol), polymer supported *N*-hydroxyphthalimide **14** (200 mg, 0.154 mmol, loading: 0.77 mmol/g), and THF (1.5 mL). After stirring for 5 minutes, Pd(PPh₃)₄ (11.9 mg, 0.0103 mmol) was added. The reaction was stirred in the dark at 35 °C

for 12 h, then filtered and concentrated to provide crude product **3**. Purification using a Sep-Pak C₁₈ cartridge (10 % MeCN/deionized H₂O) afforded 8.9 mg (80 %) of acid **3** as a white amorphous solid. IR (neat): 3307, 2968, 2936, 2880, 1776, 1685, 1639, 1508, 1477, 1377, 1265, 1210, 1166, 1080, 1042, 988, 915, 859 cm⁻¹; ¹H NMR (CD₃OD, 3.31): δ 7.96 (1H, d, *J* = 14.4 Hz), 5.70 (1H, d, *J* = 14.4 Hz), 4.02 (1H, s), 3.50 (1H, d, *J* = 10.8 Hz), 3.39 (1H, d, *J* = 10.8 Hz), 0.93 (3H, s), 0.92 (3H, s) ppm; ¹³C NMR (CD₃OD, 49.15): δ 175.3, 172.0, 139.3, 103.5, 77.3, 70.0, 40.9, 21.6, 20.5 ppm; FAB-HRMS calcd. for C₉H₁₆NO₅ [M+H]⁺: 218.1028, found 218.1029; [α]_D²⁵ = + 54.3 (*c* = 0.44, MeOH).

ent-CJ-15,801 *ent*-**3**: Prepared according to the procedure reported for **3**. IR (neat): 3337, 2967, 2935, 2880, 1775, 1686,

reaction on solid phase, see: Rano, T. A.; Chapman, K. T. *Tetrahedron Lett.*

1640, 1510, 1478, 1380, 1265, 1211, 1165, 1079, 1042, 987, 859 cm^{-1} ; ^1H NMR (CD_3OD , 3.31): δ 7.96 (1H, d, $J = 14.4$ Hz), 5.70 (1H, d, $J = 14.4$ Hz), 4.02 (1H, s), 3.50 (1H, d, $J = 10.8$ Hz), 3.39 (1H, d, $J = 10.8$ Hz), 0.93 (3H, s), 0.92 (3H, s) ppm; ^{13}C NMR (CD_3OD , 49.15): δ 175.3, 172.0, 139.3, 103.5, 77.3, 70.0, 40.9, 21.6, 20.5 ppm; CI-HRMS calcd. for $\text{C}_9\text{H}_{15}\text{NO}_5$ $[\text{M}]^+$: 217.0950, found 217.0960; $[\alpha]_{\text{D}}^{25} = -49.3$ ($c = 0.28$, MeOH).

N-acyl vinyllogous carbamic acid 6a: Prepared from **5a** in 78 % yield according to the procedure reported for **3**. IR (neat): 3332, 1670, 1640, 1554, 1524, 1411, 1198, 1142, 988, 965, 843, 804, 723 cm^{-1} ; ^1H NMR (CD_3OD , 3.31): δ 8.21 (1H, d, $J = 14.0$ Hz), 7.95 (2H, d, $J = 7.2$ Hz), 7.61 (1H, dd, $J = 7.2, 7.2$ Hz), 7.54 (2H, dd, $J = 7.2, 7.2$ Hz), 5.76 (1H, d, $J = 14.0$ Hz) ppm; ^{13}C NMR (CD_3OD , 49.15): δ 172.06, 168.2, 140.5, 134.3, 134.2, 130.1, 129.3, 103.9 ppm; CI-HRMS calcd. for $\text{C}_{10}\text{H}_{10}\text{NO}_3$ $[\text{M}+\text{H}]^+$: 192.0661, found 192.0640.

N-acyl vinyllogous carbamic acid 6b: Prepared from **5c** in 82 % yield according to the procedure reported for **3**. IR (neat): 3397, 2992, 2958, 2875, 1693, 1639, 1504, 1440, 1381, 1262, 1200, 1161, 1097, 1051, 1021, 990, 948, 870 cm^{-1} ; ^1H NMR (CD_3OD , 3.31): δ 7.89 (1H, d, $J = 14.0$ Hz), 5.83 (1H, d, $J = 14.0$ Hz), 4.25 (1H, s), 3.76 (1H, d, $J = 11.2$ Hz), 3.28 (1H, d, $J = 11.2$ Hz), 1.48 (3H, s), 1.44 (3H, s), 0.99 (3H, s), 0.98 (3H, s) ppm; ^{13}C NMR (CD_3OD , 49.15): δ 172.7, 171.2, 138.1, 105.5, 101.0, 78.8, 72.4, 34.4, 29.6, 22.3, 19.4, 19.1 ppm; CI-HRMS calcd. for $\text{C}_{12}\text{H}_{19}\text{NO}_5$ $[\text{M}+\text{H}]^+$: 257.1263, found 257.1251; $[\alpha]_{\text{D}}^{25} = +63.4$ ($c = 0.41$, MeCN)

N-acyl vinyllogous urea 15: Prepared from **7a** according to the procedure reported for **12**. Purification using a Sep-Pak C18 cartridge (20-40 % MeCN/ H_2O) provided **15** (75 %) as a pale yellow foam. IR (neat): 3300, 2965, 2931, 1710, 1660, 1605, 1496, 1328, 1255, 1211, 1082, 1042 cm^{-1} ; ^1H NMR (acetone- d_6 , 2.05): δ 9.65 (1H, d, $J = 10.8$ Hz), 7.94 (1H, dd, $J = 14.0, 10.8$ Hz), 7.63 (1H, br s), 7.29 (4H, m), 7.22 (1H, m), 6.08 (1H, d, $J = 14.0$ Hz), 4.44 (2H, d, $J = 6.0$ Hz), 4.08 (1H, s), 3.49 (1H, d, $J = 10.8$ Hz), 3.40 (1H, d, $J = 10.8$ Hz), 0.92 (3H, s), 0.91 (3H, s) ppm; ^{13}C NMR (acetone- d_6 , 29.92): δ 173.4, 167.6, 141.0, 134.6, 129.4 (2C), 128.6 (2C), 127.9, 106.3, 77.4, 70.3, 43.5, 40.3, 21.4, 20.7 ppm; CI-HRMS calcd. for $\text{C}_{16}\text{H}_{23}\text{N}_2\text{O}_4$ $[\text{M}+\text{H}]^+$: 307.1658, found 307.1639; $[\alpha]_{\text{D}}^{25} = +43.8$ ($c = 0.24$, MeOH)

N-acyl vinyllogous urea 7c: To a Teflon vial were added carbamic acid **6a** (17.3 mg, 0.09 mmol), PS-HOBt resin (53.6 mg, 0.6 mmol, loading: 1.12 mmol/g), chloro-1,1,3,3-tetramethyluronium hexachloro-antimonate (ACTU) (28.2 mg, 0.06 mmol), and DMF (0.9 mL). After stirring for 5 minutes at 0°C , 2,6-lutidine (32.1 mg, 0.30 mmol, 35 μL) was added. The mixture was stirred at rt for 4 h. The product resin **16** was then washed with DMF (2 $\times$ 2 mL), THF (2 $\times$ 2 mL), CH_2Cl_2 (2 $\times$ 2 mL), and then used immediately in the next step. A solution of benzylamine (3.2 mg, 0.03 mmol, 3.3 μL in 0.6 mL THF) was added to the activated resin **16** and the reaction stirred for 2 h. The

mixture was filtered and the resin was washed with DMF. Removal of solvent using high vacuum afforded 6.8 mg (81 %) of urea **7c** as a white solid (Purity: 93 % by HPLC-ELSD analysis). IR (neat): 3301, 1649, 1605, 1514, 1328, 1291, 1184 cm^{-1} ; ^1H NMR (CD_3OD , 3.31): δ 8.12 (1H, d, $J = 14.0$ Hz), 7.91 (2H, d, $J = 8.0$ Hz), 7.60 (1H, dd, $J = 8.0, 8.0$ Hz), 7.51 (2H, dd, $J = 8.0, 8.0$ Hz), 7.30~7.28 (4H, m), 7.23 (1H, dd, $J = 7.2, 7.2$ Hz), 6.02 (1H, d, $J = 14.0$ Hz), 4.43 (2H, s) ppm; ^{13}C NMR ($\text{DMSO}-d_6$, 39.51): δ 166.1, 165.3, 140.0, 134.7, 133.0, 132.6, 128.8 (2C), 128.5 (2C), 128.1 (2C), 127.5 (2C), 126.9, 105.7, 42.1; CI-HRMS calcd. for $\text{C}_{17}\text{H}_{16}\text{N}_2\text{O}_2$ $[\text{M}+\text{H}]^+$: 280.1212, found 280.1205.

NMR data (in CD₃OD) comparison of natural and synthetic CJ-15,801

¹ H NMR (ppm)		¹³ C NMR (ppm)	
Natural	Synthetic (400 MHz)	Natural	Synthetic (75.0 MHz)
(CD ₃ OD at 3.30 ppm)	(CD ₃ OD at 3.31 ppm)	(CD ₃ OD at 49.8 ppm)	(CD ₃ OD at 49.2 ppm)
7.94 (1H, d, <i>J</i> = 14.3 Hz)	7.96 (1H, d, <i>J</i> = 14.4 Hz)	175.8	175.3
5.69 (1H, d, <i>J</i> = 14.3 Hz)	5.70 (1H, d, <i>J</i> = 14.4 Hz)	172.4	172.0
4.02 (1H, s)	4.02 (1H, s)	139.8	139.3
3.48 (1H, d, <i>J</i> = 11.1 Hz)	3.50 (1H, d, <i>J</i> = 10.8 Hz)	104.0	103.5
3.37 (1H, d, <i>J</i> = 11.1 Hz)	3.39 (1H, d, <i>J</i> = 10.8 Hz)	77.9	77.3
0.93 (3H, s)	0.93 (3H, s)	70.6	70.0
0.93 (3H, s)	0.92 (3H, s)	41.6	40.9
		22.3	21.6
		21.3	20.5

[α]_D of Natural and synthetic CJ-15,801:

	Natural CJ-15,801	Synthetic CJ-15,801
[α] _D	+47.7° (<i>c</i> 0.44, MeOH)	+54.3° (<i>c</i> 0.44, MeOH)

^1H NMR (300 MHz, CD_3OD) of natural CJ-15,801

^1H NMR (400 MHz, CD_3OD) of synthetic CJ-15,801

^{13}C NMR (67.5 MHz, CD_3OD) of natural CJ-15,801

^{13}C NMR (75 MHz, CD_3OD) of synthetic CJ-15,801

HPLC data for natural and synthetic CJ-15,801^a

Natural:

Synthetic:

Natural + Synthetic:

^a HPLC analysis was performed on an Agilent 1100 series HPLC (column: Agilent, Eclipse XDB-C18, 5 μ m, 4.6 $\times$ 150 mm). Conditions: 5 % CH₃CN in H₂O, flow rate: 1 mL/ min

^1H NMR (400 MHz, CDCl_3)

^{13}C NMR (75 MHz, CDCl_3)

^1H NMR (400 MHz, CDCl_3)

^{13}C NMR (75 MHz, CDCl_3)

^1H NMR (400 MHz, CDCl_3)

^{13}C NMR (75 MHz, CDCl_3)

¹H NMR (400 MHz, CD₃OD)

¹³C NMR (75 MHz, DMSO-*d*₆)

¹H NMR (400 MHz, acetone-*d*₆)

^{13}C NMR (75 MHz, acetone- d_6)

¹H NMR (400 MHz, CD₃OD)

¹³C NMR (75 MHz, CD₃OD)

¹H NMR (400 MHz, acetone-*d*₆)

¹³C NMR (75 MHz, acetone-*d*₆)