Supporting Information

for

Three Component Synthesis of β-Aminoxy Amides

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1. General Information

Reactions were monitored by thin layer chromatography (TLC) using silicycle precoated silica gel plates. Column chromatography was performed over silica gel (200– 300mesh).

Melting points were measured with X-4 micro melting point apparatus.

HRMS were performed on Agilent Technologies 6546-LC/Q-TOF mass spectrometer (ESI-TOF) (Pharmaceutical Informatics Institute, Zhejiang University).

¹H NMR spectra and ¹³C NMR spectra were recorded on a Bruker AV-600 spectrometer (College of Life Sciences, Zhejiang University), a Bruker AV-500 spectrometer (Pharmaceutical Informatics Institute, Zhejiang University) or a WNMR-I-400 spectrometer (Department of Chemistry, Zhejiang University) in chloroform-*d* (CDCl₃, contain internal TMS). Chemical shifts of ¹H NMR spectra were reported in ppm with the internal TMS signal at 0 ppm as a standard, and chemical shifts of ¹³C NMR spectra were reported in ppm with the chloroform signal at 77.16 ppm as a standard.¹ The data is being reported as (s = singlet, d = doublet, t = triplet, q = quartet, quint = quintet, hept = heptet, dd = double doublet, dt = double of triplet, m = multiplet or unresolved, br = broad singlet, coupling constant(s) in Hz, integration).

Solvents, such as ethyl acetate (EA), petroleum ether (PE) were obtained commercially and used without further purification unless otherwise noted. Methanol (MeOH) purified by distillation after treating with magnesium rod; toluene (PhMe), 1,4-dioxane (dioxane) and tetrahydrofuran (THF) were purified by distillation after treating with sodium; dichloromethane (CH₂Cl₂), acetonitrile (MeCN), 1,2dichloroethane (DCE) were purified by distillation after treating with CaH₂.

2. Starting Materials



Figure S1. Starting materials

All starting materials are listed as Figure S1. *N*-hydroxamic acids **1a** and **2a** were commercially available; Ynamides were prepared according to the reported methods (Figure S2). Ynamides **2a-2h** were synthesized via the **method A**,² and ynamide **2i** was obtained by the **method B**.³ Aldehydes **3a-3k** were commercially available, and **3l** was synthesized according to the reported procedure.⁴



Figure S2. Synthesis of ynamides

3. Typical Procedure for The Synthesis of 4a



An oven-dried Schlenk tube equipped with a magnetic stirrer bar was charged with *N*-hydroxysuccinimide **1a** (23 mg, 0.2 mmol), ynamide **2a** (42 mg, 0.2 mmol) and *p*-nitrobenzaldehyde **3a** (31 mg, 0.2 mmol), and then purged with argon three times. Anhydrous CH₂Cl₂ (2 mL) was added as solvent and the mixture was stirred for 3 h until **1a** and **2a** were completely consumed. BF₃·Et₂O (5 μ L, 20 mol%) was added and the reaction was stirred for another 5 mins. TLC analysis showed that the completion of the reaction. The reaction mixture was concentrated to obtain the residue, which was purified by silica gel column chromatography eluting with PE/EA = 3/1 to give the desired product 3-((2,5-dioxopyrrolidin-1-yl)oxy)-*N*-methyl-3-(4-nitrophenyl)-*N*-tosylpropanamide **4a** (58 mg, 61% yield) as a white solid.

4. Gram-Scale Reaction



An oven-dried flask tube equipped with a magnetic stirrer bar was charged with *N*-hydroxysuccinimide **1a** (576 mg, 5 mmol), ynamide **2a** (1.05 g, 5 mmol) and *p*-nitrobenzaldehyde **3a** (775 mg, 5 mmol), and then purged with argon three times. Anhydrous CH₂Cl₂ (50 mL) was added as solvent and the mixture was stirred for 3 h until **1a** and **2a** were completely consumed. BF₃·Et₂O (120 μ L, 20 mol%) was added and the reaction was stirred until TLC analysis showed the completion of the reaction. The reaction mixture was concentrated to obtain the residue, which was purified by silica gel column chromatography eluting with PE/EA = 3/1 to give the desired product 3-((2,5-dioxopyrrolidin-1-yl)oxy)-*N*-methyl-3-(4-nitrophenyl)-*N*-tosylpropanamide **4a** (1.35 g, 57% yield) as a white solid.



5. Step-wise Reaction

An oven-dried Schlenk tube equipped with a magnetic stirrer bar was charged with *N*-hydroxysuccinimide **1a** (23 mg, 0.2 mmol) and ynamide **2a** (42 mg, 0.2 mmol), and then purged with argon three times. Anhydrous CH₂Cl₂ (2 mL) was added as solvent and the mixture was stirred for 3 h until **1a** and **2a** were completely consumed. The mixture was concentrated to obtain the residue, which was further purified by silica gel column chromatography eluting with PE/EA = 5/1 to give **5a** (64 mg, 98% yield).

An oven-dried Schlenk tube equipped with a magnetic stirrer bar was charged with **5a** (64 mg, 0.2 mmol) and *p*-nitrobenzaldehyde **3a** (31 mg, 0.2 mmol), and then purged with argon three times. Anhydrous CH₂Cl₂ (2 mL) was added as solvent. BF₃·Et₂O (5 μ L, 20 mol%) was added and the reaction was stirred for another 5 mins. TLC analysis showed that the completion of the reaction. The reaction mixture was concentrated to obtain the residue, which was purified by silica gel column chromatography eluting with PE/EA = 3/1 to give the desired product 3-((2,5-dioxopyrrolidin-1-yl)oxy)-*N*-methyl-3-(4-nitrophenyl)-*N*-tosylpropanamide **4a** (59 mg, 63% yield) as a white solid.

6. Crossover reaction



An oven-dried Schlenk tube equipped with a magnetic stirrer bar was charged with **5b** (38 mg, 0.1 mmol), **5c** (39 mg, 0.1 mmol) and *p*-nitrobenzaldehyde **3a** (31 mg, 0.2 mmol), and then purged with argon three times. Anhydrous CH_2Cl_2 (2 mL) was added as solvent. BF₃·Et₂O (5 µL, 20 mol%) was added and the reaction was stirred for another 10 mins. TLC analysis showed the formation of **4m** and **4u**. The crossover products were not detected (See the TLC analysis). **4m** and **4u** were isolated in 61% and 66% yields, respectively.

7. Characterization of Products



3-((2,5-dioxopyrrolidin-1-yl)oxy)-N-methyl-3-(4-nitrophenyl)-N-

tosylpropanamide

4a: White solid (58 mg, 61% yield), m. p. 162.4-164.2 °C.

¹**H NMR (600 MHz, CDCl₃)** δ 8.17 (d, *J* = 7.8 Hz, 2H), 7.77 (d, *J* = 7.2 Hz, 2H), 7.63 (d, *J* = 7.8 Hz, 2H), 7.36 (d, *J* = 7.2 Hz, 2H), 5.87 (t, *J* = 6.0 Hz, 1H), 3.69 (dd, *J*₁ = 17.4 Hz, *J*₂ = 6.0 Hz, 1H), 3.31 (dd, *J*₁ = 17.4 Hz, *J*₂ = 4.8 Hz, 1H), 3.21 (s, 3H), 2.58 (s, 4H), 2.46 (s, 3H).

¹³C NMR (150 MHz, CDCl₃) δ 171.0, 169.1, 148.3, 145.4, 144.0, 135.6, 130.1, 128.7, 127.6, 123.7, 82.3, 42.7, 33.0, 25.3, 21.7.

HRMS (ESI-TOF) m/z: (M+H)⁺ calcd. For C₂₁H₂₂N₃O₈S, 476.1128; found, 476.1130.



3-((2,5-dioxopyrrolidin-1-yl)oxy)-N-methyl-3-phenyl-N-tosylpropanamide

4b: White solid (52 mg, 61% yield), m. p. 162.3-164.1 °C.

¹**H NMR (600 MHz, CDCl₃)** δ 7.81 – 7.76 (m, 2H), 7.45 – 7.38 (m, 2H), 7.36 – 7.30 (m, 5H), 5.84 (dd, J_1 = 7.2 Hz, J_2 = 5.4 Hz, 1H), 3.68 (dd, J_1 = 18.0 Hz, J_2 = 7.2 Hz, 1H), 3.27 (dd, J_1 = 17.4 Hz, J_2 = 4.8 Hz, 1H), 3.23 (s, 3H), 2.49 (s, 4H), 2.44 (s, 3H). ¹³**C NMR (150 MHz, CDCl₃)** δ 171.4, 169.9, 145.2, 136.6, 135.9, 130.0, 129.4, 128.6, 128.0, 127.8, 83.2, 42.4, 33.1, 25.3, 21.7.

HRMS (ESI-TOF) m/z: (M+H)⁺ calcd. For C₂₁H₂₃N₂O₆S, 431.1277; found, 431.1273.



3-(4-chlorophenyl)-3-((2,5-dioxopyrrolidin-1-yl)oxy)-N-methyl-N-

tosylpropanamide

4c: White solid (53 mg, 57% yield), m. p. 177.0-178.5 °C.

¹H NMR (600 MHz, CDCl₃) δ 7.78 – 7.73 (m, 2H), 7.38 – 7.32 (m, 4H), 7.30 – 7.27

(m, 2H), 5.79 (t, J = 6.0 Hz, 1H), 3.64 (dd, $J_1 = 17.4$ Hz, $J_2 = 6.6$ Hz, 1H), 3.27 (dd, $J_1 = 17.4$ Hz, $J_2 = 6.0$ Hz, 1H), 3.22 (s, 3H), 2.52 (s, 4H), 2.45 (s, 3H).

¹³C NMR (150 MHz, CDCl₃) δ 171.3, 169.6, 145.3, 135.9, 135.4, 135.3, 130.1, 129.4, 128.9, 127.7, 82.6, 42.4, 33.1, 25.4, 21.8.

HRMS (ESI-TOF) m/z: (M+H)⁺ calcd. For C₂₁H₂₂ClN₂O₆S, 465.0887; found, 465.0892.



3-((2,5-dioxopyrrolidin-1-yl)oxy)-N-methyl-N-tosyl-3-(4-

(trifluoromethyl)phenyl)propenamide

4d: White solid (51 mg, 51% yield), m. p. 115.7-117.6 °C.

¹**H NMR (600 MHz, CDCl₃)** δ 7.79 – 7.73 (m, 2H), 7.61 – 7.53 (m, 4H), 7.34 (d, J = 7.8 Hz, 2H), 5.86 (dd, $J_I = 6.6$ Hz, $J_2 = 6.0$ Hz 1H), 3.67 (dd, $J_I = 17.4$ Hz, $J_2 = 7.2$ Hz, 1H), 3.28 (dd, $J_I = 18.0$ Hz, $J_2 = 5.4$ Hz, 1H), 3.22 (s, 3H), 2.55 (s, 4H), 2.45 (s, 3H). ¹³**C NMR (150 MHz, CDCl₃)** δ 171.3, 169.5, 145.4, 140.9, 135.8, 131.4 (q, J = 33.0 Hz), 130.1, 128.2, 127.7, 125.6 (q, J = 3.0 Hz), 124.0 (q, J = 270.0 Hz), 82.7, 42.8, 33.2, 25.4, 21.8.

¹⁹F NMR (565 MHz, CDCl₃) δ -62.76.

HRMS (ESI-TOF) m/z: (M+H)⁺ calcd. For C₂₂H₂₂F₃N₂O₆S, 499.1151; found, 499.1145.



3-(4-cyanophenyl)-3-((2,5-dioxopyrrolidin-1-yl)oxy)-N-methyl-N-

tosylpropanamide

4e: White solid (52 mg, 57% yield), m. p. 122.6-124.2 °C.

¹**H NMR (600 MHz, CDCl₃)** δ 7.78 – 7.72 (m, 2H), 7.64 – 7.59 (m, 2H), 7.58 – 7.54 (m, 2H), 7.35 (d, *J* = 8.4 Hz, 2H), 5.81 (t, *J* = 6.0 Hz, 1H), 3.65 (dd, *J*₁ = 17.4 Hz, *J*₂ = 6.6 Hz, 1H), 3.27 (dd, *J*₁ = 17.4 Hz, *J*₂ = 5.4 Hz, 1H), 3.20 (s, 3H), 2.55 (s, 4H), 2.45 (s, 3H).

¹³C NMR (150 MHz, CDCl₃) δ 171.1, 169.2, 145.4, 142.0, 135.6, 132.3, 130.0, 128.5, 127.6, 118.3, 113.0, 82.5, 42.5, 33.0, 25.3, 21.7.

HRMS (ESI-TOF) m/z: (M+H)⁺ calcd. For C₂₂H₂₂N₃O₆S, 456.1229; found, 456.1230.



3-((2,5-dioxopyrrolidin-1-yl)oxy)-*N*-methyl-**3-(***o*-tolyl)-*N*-tosylpropanamide **4f:** White solid (56 mg, 63% yield), m. p. 144.0-146.0 °C.

¹**H NMR (600 MHz, CDCl₃)** δ 7.80 (d, J = 7.8 Hz, 2H), 7.41 (dd, J_1 = 7.8 Hz, J_2 = 1.2 Hz, 1H), 7.34 (d, J = 8.4 Hz, 2H), 7.21 (td, J_1 = 7.2 Hz, J_2 = 1.8 Hz, 1H), 7.17 (td, J_1 = 7.8 Hz, J_2 = 1.8 Hz, 1H), 7.17 (td, J_1 = 7.8 Hz, J_2 = 1.8 Hz, 1H), 7.13 (dd, J_1 = 7.8 Hz, J_2 = 1.8 Hz, 1H), 6.11 (dd, J_1 = 7.2 Hz, J_2 = 4.2 Hz, 1H), 3.69 (dd, J_1 = 17.4 Hz, J_2 = 7.2 Hz, 1H), 3.25 (s, 3H), 3.15 (dd, J_1 = 18.0 Hz, J_2 = 4.2 Hz, 1H), 2.55 – 2.45 (m, 4H), 2.44 (s, 3H), 2.41 (s, 3H).

¹³C NMR (150 MHz, CDCl₃) δ 171.6, 170.2, 145.1, 136.7, 135.9, 135.1, 130.7, 129.9, 129.0, 127.8, 127.1, 126.2, 79.6, 42.4, 33.1, 25.3, 21.7, 19.2.

HRMS (ESI-TOF) m/z: (M+H)⁺ calcd. For C₂₂H₂₅N₂O₆S, 445.1433; found, 445.1433.



3-((2,5-dioxopyrrolidin-1-yl)oxy)-N-methyl-3-(3-nitrophenyl)-N-

tosylpropanamide

4g: White solid (51 mg, 54% yield), m. p. 159.6-160.4 °C.

¹**H NMR (600 MHz, CDCl₃)** δ 8.27 (t, *J* = 1.8 Hz, 1H), 8.18 (dd, *J*₁ = 8.4 Hz, *J*₂ = 1.8 Hz, 1H), 7.82 (dt, *J*₁ = 7.8 Hz, *J*₂ = 1.2 Hz, 1H), 7.80 – 7.75 (m, 2H), 7.53 (t, *J* = 7.8 Hz, 1H), 7.36 (d, *J* = 7.8 Hz, 2H), 5.83 (t, *J* = 6.0 Hz, 1H), 3.71 (dd, *J*₁ = 17.4 Hz, *J*₂ = 6.6 Hz, 1H), 3.32 (dd, *J*₁ = 17.4 Hz, *J*₂ = 6.0 Hz, 1H), 3.23 (s, 3H), 2.58 (s, 4H), 2.45 (s, 3H).

¹³C NMR (150 MHz, CDCl₃) δ 171.1, 169.2, 148.2, 145.4, 139.1, 135.6, 134.0, 130.1, 129.6, 127.6, 124.1, 122.7, 82.3, 42.5, 33.0, 25.3, 21.7.

HRMS (ESI-TOF) m/z: (M+H)⁺ calcd. For C₂₁H₂₂N₃O₈S, 476.1128; found, 476.1126.



3-(3-bromo-4-fluorophenyl)-3-((2,5-dioxopyrrolidin-1-yl)oxy)-*N*-methyl-*N*-tosylpropanamide

4h: White solid (58 mg, 55% yield), m. p. 143.7-144.9 °C.

¹**H NMR (600 MHz, CDCl₃)** δ 7.77 (d, *J* = 7.8 Hz, 2H), 7.62 (dd, *J*₁ = 6.6 Hz, *J*₂ = 2.4 Hz, 1H), 7.42 - 7.32 (m, 3H), 7.07 (t, *J* = 8.4 Hz, 1H), 5.74 (t, *J* = 6.0 Hz, 1H), 3.63 (dd, *J*₁ = 17.4 Hz, *J*₂ = 6.6 Hz, 1H), 3.28 - 3.21 (m, 4H), 2.56 (s, 4H), 2.45 (s, 3H).

¹³C NMR (150 MHz, CDCl₃) δ 171.3, 169.4, 159.5 (d, *J* = 247.5 Hz), 145.4, 135.8, 134.4 (d, *J* = 4.5 Hz), 133.2, 130.1, 128.8 (d, *J* = 7.5 Hz), 127.7, 116.7 (d, *J* = 22.5 Hz), 109.2 (d, *J* = 22.5 Hz), 82.0, 42.6, 33.1, 25.4, 21.8.

¹⁹F NMR (565 MHz, CDCl₃) δ -105.90.

HRMS (ESI-TOF) m/z: (M+H)⁺ calcd. For C₂₁H₂₁BrFN₂O₆S, 527.0288; found, 527.0291.



3-((2,5-dioxopyrrolidin-1-yl)oxy)-N-methyl-3-(naphthalen-1-yl)-N-

tosylpropanamide

4i: Yellow solid (47 mg, 49% yield), m. p. 145.2-146.1 °C.

¹**H NMR (600 MHz, CDCl₃)** δ 8.23 (d, J = 8.4 Hz, 1H), 7.87 – 7.81 (m, 2H), 7.82 – 7.77 (m, 2H), 7.69 (dd, J_1 = 7.2 Hz, J_2 = 1.2 Hz, 1H), 7.54 (ddd, J_1 = 8.4 Hz, J_2 = 6.6 Hz, J_3 = 1.2 Hz, 1H), 7.49 (ddd, J_1 = 7.8 Hz, J_2 = 6.6 Hz, J_3 = 1.2 Hz, 1H), 7.45 (dd, J_1 = 8.4 Hz, J_2 = 7.2 Hz, 1H), 7.32 (d, J = 7.8 Hz, 2H), 6.67 (dd, J_1 = 7.2 Hz, J_1 = 3.6 Hz, 1H), 3.87 (dd, J_1 = 18.0 Hz, J_2 = 7.8 Hz, 1H), 3.29 – 3.24 (m, 4H), 2.55 – 2.45 (m, 4H), 2.44 (s, 3H).

¹³C NMR (150 MHz, CDCl₃) δ 171.7, 170.4, 145.2, 136.0, 133.8, 133.0, 130.8, 129.9, 129.8, 129.0, 128.0, 126.9, 126.0, 125.5, 125.3, 123.4, 79.7, 42.8, 33.2, 25.4, 21.8.
HRMS (ESI-TOF) *m/z*: (M+H)⁺ calcd. For C₂₅H₂₅N₂O₆S, 481.1433; found, 481.1434.



3-((2,5-dioxopyrrolidin-1-yl)oxy)-N-methyl-3-(thiophen-2-yl)-N-

tosylpropanamide

4j: White solid (33 mg, 38% yield), m. p. 144.6-145.7 °C.

¹**H NMR (600 MHz, CDCl₃)** δ 7.81 (d, *J* = 7.8 Hz, 2H), 7.39 – 7.32 (m, 3H), 7.14 (d, *J* = 3.6 Hz, 1H), 6.98 – 6.94 (m, 1H), 6.05 (t, *J* = 6.0 Hz, 1H), 3.77 (dd, *J*₁ = 17.4 Hz, *J*₂ = 6.6 Hz, 1H), 3.45 (dd, *J*₁ = 17.4 Hz, *J*₂ = 4.8 Hz, 1H), 3.25 (s, 3H), 2.55 (s, 4H), 2.45 (s, 3H).

¹³C NMR (150 MHz, CDCl₃) δ 171.3, 169.4, 145.3, 138.9, 135.9, 130.1, 128.3, 127.8, 127.5, 127.0, 78.3, 42.7, 33.2, 25.4, 21.8.

HRMS (ESI-TOF) m/z: (M+H)⁺ calcd. For C₁₉H₂₁N₂O₆S₂, 437.0841; found, 437.0844.



(*E*)-3-((2,5-dioxopyrrolidin-1-yl)oxy)-*N*-methyl-5-phenyl-*N*-tosylpent-4-enamide 4k: White solid (30 mg, 33% yield), m. p. 122.0-123.3 °C.

¹**H NMR (600 MHz, CDCl₃)** δ 7.79 (d, *J* = 7.8 Hz, 2H), 7.37 – 7.26 (m, 7H), 6.64 (d, *J* = 15.6 Hz, 1H), 6.13 (dd, *J*₁ = 15.6 Hz, *J*₂ = 9.0 Hz, 1H), 5.37 (dt, *J*₁ = 9.0 Hz, *J*₂ = 6.0 Hz, 1H), 3.48 (dd, *J*₁ = 17.4 Hz, *J*₂ = 6.0 Hz, 1H), 3.27 – 3.20 (m, 4H), 2.58 (s, 4H), 2.43 (s, 3H).

¹³C NMR (150 MHz, CDCl₃) δ 171.6, 169.4, 145.2, 136.9, 136.0, 135.6, 130.1, 128.81, 128.77, 127.7, 127.1, 124.7, 83.4, 41.2, 33.2, 25.4, 21.8.

HRMS (ESI-TOF) m/z: (M+H)⁺ calcd. For C₂₃H₂₅N₂O₆S, 457.1433; found, 457.1430.



3-((2,5-dioxopyrrolidin-1-yl)oxy)-*N***-methyl-5-phenyl-***N***-tosylpent-4-ynamide 41:** Yellow solid (36 mg, 40% yield), m. p. 56.0-58.0 °C.

¹**H NMR (600 MHz, CDCl₃)** δ 7.85 – 7.80 (m, 2H), 7.42 – 7.37 (m, 2H), 7.38 – 7.27 (m, 5H), 5.75 (dd, J_I = 7.2 Hz, J_2 = 5.4 Hz, 1H), 3.65 (dd, J_I = 18.0 Hz, J_2 = 7.2 Hz, 1H), 3.43 (dd, J_I = 18.0 Hz, J_2 = 5.4 Hz, 1H), 3.28 (s, 3H), 2.67 (s, 4H), 2.42 (s, 3H). ¹³C NMR (150 MHz, CDCl₃) δ 171.3, 168.9, 145.3, 135.8, 132.0, 130.2, 129.3, 128.5, 127.8, 121.6, 89.1, 83.6, 72.8, 42.3, 33.2, 25.5, 21.8.



N-benzyl-3-((2,5-dioxopyrrolidin-1-yl)oxy)-3-(4-nitrophenyl)-N-

(phenylsulfonyl)propenamide

4m: Yellow solid (61 mg, 57% yield), m. p. 45.9-47.4 °C.

¹**H NMR (500 MHz, CDCl₃)** δ 8.11 – 8.04 (m, 2H), 7.80 – 7.73 (m, 2H), 7.68 – 7.61 (m, 1H), 7.54 – 7.47 (m, 2H), 7.48 – 7.41 (m, 2H), 7.29 – 7.23 (m, 3H), 7.24 – 7.16 (m, 2H), 5.78 (t, J_1 = 6.5 Hz, 1H), 5.08 (d, J = 16.0 Hz, 1H), 4.92 (d, J = 16.0 Hz, 1H), 3.57 (dd, J_1 = 17.0 Hz, J_2 = 6.0 Hz, 1H), 3.23 (dd, J_1 = 17.5 Hz, J_2 = 6.5 Hz, 1H), 2.57 – 2.43 (m, 4H).

¹³C NMR (125 MHz, CDCl₃) δ 171.0, 169.3, 148.3, 143.7, 139.2, 136.0, 134.2, 129.4, 128.8, 128.03, 127.99, 127.8, 123.7, 82.4, 49.8, 42.5, 25.3.

HRMS (ESI-TOF) m/z: (M+H)⁺ calcd. For C₂₆H₂₄N₃O₈S, 538.1284; found, 538.1280.



N-benzyl-3-((2,5-dioxopyrrolidin-1-yl)oxy)-*N*-(naphthalen-1-ylsulfonyl)-3-(4nitrophenyl)propenamide

4n: White solid (59 mg, 50% yield), m. p. 81.6-83.8 °C.

¹**H NMR (600 MHz, CDCl₃)** δ 8.21 (s, 1H), 7.97 – 7.81 (m, 5H), 7.71 (t, *J* = 7.2 Hz, 1H), 7.64 (t, *J* = 7.8 Hz, 2H), 7.39 – 7.17 (m, 7H), 5.74 (t, *J* = 6.0 Hz, 1H), 5.17 (d, *J* =

15.6 Hz, 1H), 4.98 (d, J = 15.6 Hz, 1H), 3.58 (dd, $J_1 = 17.4$ Hz, $J_2 = 5.4$ Hz, 1H), 3.28 (dd, $J_1 = 17.4$ Hz, $J_2 = 6.6$ Hz, 1H), 2.52 – 2.36 (m, 4H).

¹³C NMR (150 MHz, CDCl₃) δ 171.0, 169.2, 148.1, 143.6, 136.1, 135.9, 135.3, 131.9, 130.01, 129.99, 129.7, 129.6, 128.8, 128.6, 128.2, 128.13, 128.09, 128.0, 123.5, 122.2, 82.5, 49.6, 42.5, 25.3.

HRMS (ESI-TOF) m/z: (M+H)⁺ calcd. For C₃₀H₂₆N₃O₈S, 588.1441; found, 588.1440.



N-benzyl-3-((2,5-dioxopyrrolidin-1-yl)oxy)-N-(methylsulfonyl)-3-(4-

nitrophenyl)propenamide

40: Yellow solid (35 mg, 37% yield), m. p. 54.6-55.1 °C.

¹**H NMR (400 MHz, CDCl₃)** δ 8.24 – 8.15 (m, 2H), 7.67 – 7.58 (m, 2H), 7.38 – 7.25 (m, 5H), 5.89 (dd, J_1 = 7.6 Hz, J_2 = 4.4 Hz, 1H), 5.02 (d, J = 16.0 Hz, 1H), 4.95 (d, J = 16.0 Hz, 1H), 3.66 (dd, J_1 = 17.6 Hz, J_1 = 7.6 Hz, 1H), 3.20 (s, 3H), 3.12 (dd, J_1 = 17.6 Hz, J_2 = 4.8 Hz, 1H), 2.65 – 2.58 (m, 4H).

¹³C NMR (100 MHz, CDCl₃) δ 171.2, 170.2, 148.4, 143.8, 135.8, 129.1, 128.7, 128.3, 127.7, 123.9, 82.7, 49.4, 43.04, 42.99, 25.4.

HRMS (ESI-TOF) m/z: (M+H)⁺ calcd. For C₂₁H₂₂N₃O₈S, 476.1128; found, 476.1133.



N-benzyl-3-((2,5-dioxopyrrolidin-1-yl)oxy)-3-(4-nitrophenyl)-N-

tosylpropanamide

4p: White solid (50 mg, 45% yield), m. p. 68.0-69.4 °C.

¹**H NMR (600 MHz, CDCl₃)** δ 8.10 – 8.05 (m, 2H), 7.65 – 7.60 (m, 2H), 7.48 – 7.43 (m, 2H), 7.31 – 7.24 (m, 5H), 7.24 – 7.17 (m, 2H), 5.79 (t, *J* = 6.6 Hz, 1H), 5.06 (d, *J* = 16.2 Hz, 1H), 4.90 (d, *J* = 15.6 Hz, 1H), 3.56 (dd, *J*₁ = 17.4 Hz, *J*₂ = 6.0 Hz, 1H), 3.24 (dd, *J*₁ = 17.4 Hz, *J*₁ = 6.6 Hz, 1H), 2.58 – 2.46 (m, 4H), 2.45 (s, 3H).

¹³C NMR (100 MHz, CDCl₃) δ 171.1, 169.2, 148.2, 145.5, 143.6, 136.1, 136.0, 130.0, 128.8, 128.7, 128.0, 127.8, 123.6, 82.4, 49.6, 42.4, 25.3, 21.7.

HRMS (ESI-TOF) m/z: (M+H)⁺ calcd. For C₂₇H₂₆N₃O₈S, 552.1441; found, 552.1437.



3-((2,5-dioxopyrrolidin-1-yl)oxy)-N-isopropyl-3-(4-nitrophenyl)-N-

tosylpropanamide

4q: Yellow solid (54 mg, 54% yield), m. p. 109.2-111.0 °C.

¹**H** NMR (600 MHz, CDCl₃) δ 8.16 (d, J = 8.4 Hz, 2H), 7.78 (d, J = 7.8 Hz, 2H), 7.61 (d, J = 8.4 Hz, 2H), 7.37 (d, J = 7.8 Hz, 2H), 5.87 (t, J = 6.0 Hz, 1H), 4.30 (hept, J = 6.6 Hz, 1H), 3.70 (dd, J_I = 17.4 Hz, J_2 = 6.6 Hz, 1H), 3.36 (dd, J_I = 17.4 Hz, J_2 = 6.0 Hz, 1H), 2.60 (s, 4H), 2.47 (s, 3H), 1.31 (d, J = 7.2 Hz, 3H), 1.28 (d, J = 6.6 Hz, 3H). ¹³C NMR (150 MHz, CDCl₃) δ 171.1, 169.3, 148.3, 145.3, 144.2, 136.7, 130.2, 128.9, 127.6, 123.7, 82.6, 53.6, 44.2, 25.4, 21.8, 20.4.

HRMS (ESI-TOF) m/z: (M+H)⁺ calcd. For C₂₃H₂₆N₃O₈S, 504.1441; found, 504.1445.



3-((2,5-dioxopyrrolidin-1-yl)oxy)-*N*-(2-methylallyl)-3-(4-nitrophenyl)-*N*tosylpropanamide 4r: White solid (46 mg, 45% yield), m. p. 146.6-147.9 °C.

¹**H NMR (600 MHz, CDCl₃)** δ 8.13 (d, J = 8.4 Hz, 2H), 7.80 (d, J = 7.8 Hz, 2H), 7.54 (d, J = 8.4 Hz, 2H), 7.32 (d, J = 7.8 Hz, 2H), 5.82 (t, J = 5.4 Hz, 1H), 4.87 (s, 1H), 4.66 (s, 1H), 4.44 (d, J = 17.4 Hz, 1H), 4.27 (d, J = 17.4 Hz, 1H), 3.51 (dd, J_I = 17.4 Hz, J_2 = 6.0 Hz, 1H), 3.13 (dd, J_I = 17.4 Hz, J_2 = 5.4 Hz, 1H), 2.61 – 2.48 (m, 4H), 2.45 (s, 3H), 1.70 (s, 3H).

¹³C NMR (150 MHz, CDCl₃) δ 171.2, 169.2, 148.3, 145.4, 143.8, 139.8, 136.1, 129.7, 128.7, 128.6, 123.7, 112.1, 82.1, 51.5, 41.9, 25.4, 21.8, 20.2.

HRMS (ESI-TOF) m/z: (M+H)⁺ calcd. For C₂₄H₂₆N₃O₈S, 516.1441; found, 516.1440.



N-(2-((*tert*-butyldimethylsilyl)oxy)ethyl)-3-((2,5-dioxopyrrolidin-1-yl)oxy)-3-(4nitrophenyl)-*N*-tosylpropanamide

4s: White solid (74 mg, 60% yield), m. p. 138.6-140.0 °C.

¹**H NMR (600 MHz, CDCl₃)** δ 8.17 – 8.12 (m, 2H), 7.84 – 7.78 (m, 2H), 7.60 – 7.55 (m, 2H), 7.32 (d, *J* = 7.8 Hz, 2H), 5.83 (dd, *J*₁ = 6.6 Hz, *J*₂ = 5.4 Hz, 1H), 3.96 (dt, *J*₁ = 15.0 Hz, *J*₂ = 5.4 Hz, 1H), 3.87 (dt, *J*₁ = 15.0 Hz, *J*₂ = 6.6 Hz, 1H), 3.83 – 3.73 (m, 2H), 3.59 (dd, *J*₁ = 18.0 Hz, *J*₂ = 6.6 Hz, 1H), 3.24 (dd, *J*₁ = 18.0 Hz, *J*₂ = 5.4 Hz, 1H), 2.58 – 2.49 (m, 4H), 2.45 (s, 3H), 0.77 (s, 9H), -0.01 – -0.05 (m, 6H).

¹³C NMR (100 MHz, CDCl₃) δ 171.2, 169.8, 148.3, 145.2, 144.0, 136.5, 129.8, 128.7, 128.2, 123.8, 81.9, 61.7, 48.4, 42.6, 25.8, 25.4, 21.8, 18.3, -5.4.

HRMS (ESI-TOF) m/z: (M+H)⁺ calcd. For C₂₈H₃₈N₃O₉SSi, 620.2098; found, 620.2095.



methyl *N*-(3-((2,5-dioxopyrrolidin-1-yl)oxy)-3-(4-nitrophenyl)propanoyl)-*N*-tosyl-*L*-alaninate

4t: White solid (22 mg, 20% yield), m. p. 83.6-84.9 °C.

¹**H NMR (600 MHz, CDCl₃)** δ 8.20 – 8.14 and 8.14 – 8.06 (m, 2H), 7.90 – 7.86 and 7.85 – 7.80 (m, 2H), 7.65 – 7.57 and 7.50 – 7.44 (m, 2H), [7.41 (d, *J* = 7.8 Hz) and 7.40 – 7.36 (m)] (2H), [5.82 (dd, *J*₁ = 7.2 Hz, *J*₂ = 6.0 Hz) and 5.76 (dd, *J*₁ = 7.8 Hz, *J*₂ = 5.4 Hz)] (1H), 4.88 – 4.81 (m, 1H), [3.73 (dd, *J*₁ = 18.0 Hz, *J*₂ = 5.4 Hz) and 3.59 (dd, *J*₁ = 17.4 Hz, *J*₂ = 6.6 Hz)] (1H), 3.65 and 3.45 (s, 3H), [3.41 (dd, *J*₁ = 17.4 Hz, *J*₂ = 6.0 Hz) and 3.28 (dd, *J*₁ = 17.4 Hz, *J*₂ = 7.8 Hz)] (1H), 2.63 – 2.56 (m, 4H), 2.49 (s, 3H), 1.54 and 1.44 (d, *J* = 7.2 Hz, 3H).

¹³C NMR (150 MHz, CDCl₃) δ 170.9, 170.8, 169.8, 169.7, 168.3, 148.2, 145.8, 143.7, 136.0, 130.2, 130.1, 129.0, 128.9, 127.9, 127.8, 123.6, 123.4, 82.4, 82.1, 56.1, 56.0, 52.6, 52.4, 42.4, 42.2, 25.3, 25.3, 21.8, 21.7, 16.04, 15.97.

HRMS (ESI-TOF) *m/z*: (M+H)⁺ calcd. For C₂₄H₂₆N₃O₁₀S, 548.1339; found, 548.1342.



3-((1,3-dioxoisoindolin-2-yl)oxy)-N-methyl-3-(4-nitrophenyl)-N-

tosylpropanamide

4u: White solid (68 mg, 65% yield), m. p. 133.2-135.1 °C.

¹**H NMR (600 MHz, CDCl₃)** δ 8.19 – 8.13 (m, 2H), 7.78 – 7.72 (m, 4H), 7.75 – 7.69 (m, 2H), 7.70 – 7.65 (m, 2H), 7.35 (d, *J* = 8.4 Hz, 2H), 5.90 (t, *J* = 6.6 Hz, 1H), 3.74 (dd, *J*₁ = 17.4 Hz, *J*₂ = 6.0 Hz, 1H), 3.52 (dd, *J*₁ = 17.4 Hz, *J*₂ = 7.2 Hz, 1H), 3.21 (s, 3H), 2.46 (s, 3H).

¹³C NMR (150 MHz, CDCl₃) δ 169.0, 163.5, 148.4, 145.5, 144.4, 135.8, 134.8, 130.3, 129.2, 128.7, 127.5, 123.8, 123.7, 84.2, 42.6, 33.2, 21.8.

HRMS (ESI-TOF) m/z: (M+H)⁺ calcd. For C₂₅H₂₂N₃O₈S, 524.1128; found, 524.1127.



3-(4-chlorophenyl)-3-((1,3-dioxoisoindolin-2-yl)oxy)-N-methyl-N-

tosylpropanamide

4v: White solid (57 mg, 56% yield), m. p. 126.3-127.6 °C.

¹**H NMR (600 MHz, CDCl₃)** δ 7.77 – 7.69 (m, 6H), 7.42 – 7.38 (m, 2H), 7.36 – 7.32 (m, 2H), 7.29 – 7.25 (m, 2H), 5.82 (t, *J* = 6.6 Hz, 1H), 3.69 (dd, *J*₁ = 17.4 Hz, *J*₂ = 6.0 Hz, 1H), 3.48 (dd, *J*₁ = 17.4 Hz, *J*₂ = 6.6 Hz, 1H), 3.21 (s, 3H), 2.45 (s, 3H).

¹³C NMR (150 MHz, CDCl₃) δ 169.3, 163.6, 145.3, 135.9, 135.6, 135.3, 134.6, 130.2, 129.6, 128.8, 127.6, 127.5, 127.2, 123.6, 84.4, 42.3, 33.2, 21.8.

HRMS (ESI-TOF) m/z: (M+H)⁺ calcd. For C₂₅H₂₂ClN₂O₆S, 513.0887; found, 513.0889.



3-((1,3-dioxoisoindolin-2-yl)oxy)-N-methyl-3-(o-tolyl)-N-tosylpropanamide

4w: White solid (45 mg, 46% yield), m. p. 115.0-116.5 °C.

¹**H NMR (600 MHz, CDCl₃)** δ 7.80 – 7.75 (m, 2H), 7.76 – 7.70 (m, 2H), 7.72 – 7.67 (m, 2H), 7.45 (dd, J_1 = 7.8 Hz, J_2 = 1.2 Hz, 1H), 7.33 (d, J = 7.8 Hz, 2H), 7.23 – 7.14 (m, 2H), 7.12 (dd, J_1 = 7.8 Hz, J_2 = 1.8 Hz, 1H), 6.16 (t, J = 6.6 Hz, 1H), 3.73 (dd, J_1 = 17.4 Hz, J_2 = 6.6 Hz, 1H), 3.48 (dd, J_1 = 17.4 Hz, J_2 = 6.0 Hz, 1H), 3.21 (s, 3H), 2.45 (s, 3H), 2.43 (s, 3H).

¹³C NMR (150 MHz, CDCl₃) δ 169.8, 163.7, 145.0, 137.4, 135.9, 135.1, 134.4, 130.6, 130.0, 129.0, 128.8, 127.5, 127.3, 126.1, 123.4, 81.4, 42.0, 33.0, 21.7, 19.2.

HRMS (ESI-TOF) m/z: (M+H)⁺ calcd. For C₂₆H₂₅N₂O₆S, 493.1433; found, 493.1430.



N-(1-((2,5-dioxopyrrolidin-1-yl)oxy)vinyl)-*N*,4-dimethylbenzenesulfonamide 5a: White solid (64 mg, 98% yield), m. p. 132.9-133.7 °C.

¹H NMR (600 MHz, CDCl₃) δ 7.84 – 7.79 (m, 2H), 7.32 (d, J = 8.4 Hz, 2H), 4.61 (d, J = 3.6 Hz, 1H), 4.54 (d, J = 3.6 Hz, 1H), 3.15 (s, 3H), 2.76 (s, 4H), 2.43 (s, 3H).
¹³C NMR (150 MHz, CDCl₃) δ 169.7, 152.5, 144.3, 134.8, 129.8, 128.2, 92.0, 36.6, 25.7, 21.7.

HRMS (ESI-TOF) m/z: (M+H)⁺ calcd. For C₁₄H₁₇N₂O₅S, 325.0858; found, 325.0855.



N-(1-((1,3-dioxoisoindolin-2-yl)oxy)vinyl)-*N*,4-dimethylbenzenesulfonamide **5b:** White solid, m. p. 118.6-119.5 °C.

¹H NMR (600 MHz, CDCl₃) δ 7.89 – 7.83 (m, 4H), 7.81 – 7.77 (m, 2H), 7.30 (d, J = 7.8 Hz, 2H), 4.72 (d, J = 4.2 Hz, 1H), 4.67 (d, J = 3.6 Hz, 1H), 3.23 (s, 3H), 2.39 (s,

3H).

¹³C NMR (150 MHz, CDCl₃) δ 162.2, 153.5, 144.2, 135.0, 129.7, 128.9, 128.3, 124.0, 90.6, 36.3, 21.7.

HRMS (ESI-TOF) m/z: (M+H)⁺ calcd. For C₁₈H₁₇N₂O₅S, 373.0858; found, 373.0855.



N-benzyl-*N*-(1-((2,5-dioxopyrrolidin-1-yl)oxy)vinyl)benzenesulfonamide

5c: White solid, m. p. 121.7-122.9 °C.

¹**H NMR (600 MHz, CDCl**₃) δ 7.93 – 7.88 (m, 2H), 7.61 – 7.54 (m, 1H), 7.48 (t, *J* = 7.8 Hz, 2H), 7.41 – 7.35 (m, 2H), 7.33 – 7.26 (m, 3H), 4.73 (s, 2H), 4.62 (d, *J* = 3.0 Hz, 1H), 4.38 (d, *J* = 3.6 Hz, 1H), 2.71 (s, 4H).

¹³C NMR (150 MHz, CDCl₃) δ 169.7, 149.8, 139.4, 135.5, 133.2, 129.4, 129.1, 128.5, 128.2, 128.1, 95.8, 52.1, 25.7.

HRMS (ESI-TOF) *m/z*: (M+H)⁺ calcd. For C₁₈H₁₇N₂O₅S, 387.1015; found, 387.1015.

8. X- Ray Crystallographic Data

Compound **4b** was crystallized from petroleum ether / dichloromethane. Intensity data for **4b** was collected on Bruker D8 Venture Ims3.0. The details of crystal data collection and refinement of **4b** is summarized in Table **S1**.





Figure S3. X-ray crystallographic structure **4b** (ORTEP view with 50% thermal ellipsoid contour probability)

CCDC code	1883882	
Empirical formula	$C_{21}H_{22}N_2O_6S$	
Formula weight	430.46	
Temperature/K	170	
Crystal system	triclinic	
Space group	P-1	
a / Å	8.9610(3)	
b / Å	10.1919(3)	
c / Å	11.3979(3)	
α/°	89.228(1)	
β/ °	84.590(1)	
$\gamma/^{\circ}$	89.609(1)	
Volume/Å ³	1036.22(5)	
Z	2	
$ ho \ { m calc} \ g \ / \ cm^3$	1.380	
μ / mm ⁻¹	0.197	
F(000)	452.0	
Crystal size / mm ³	0.362 × 0.299 × 0.226	
Radiation	MoKa ($\lambda = 0.71073$)	
2θ range for data collection / °	2.28 to 35.4	
Index ranges	$-15 \le h \le 13,$ $-18 \le k \le 18,$ $-20 \le 1 \le 20$	
Reflections collected	33755	
Independent reflections	12284 [$R_{int} = 0.1011$, $R_{sigma} = 0.0572$]	
Data / restraints / parameters	12284/0/273	
Goodness-of-fit on F ²	1.035	
Final R indexes [I>=2 σ (I)]	$R_1 = 0.0572, wR_2 = 0.0587$	
Final R indexes [all data]	$R_1 = 0.1011, wR_2 = 0.0794$	
Largest diff. peak / hole / e Å ⁻³	0.581/-0.406	

Table S1. Crystal data and structure refinements for 4b.

9. References

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- Mansfield, S. J.; Campbell, C. D.; Jones, M. W.; Anderson, E. A. *Chem. Commun.* 2015, *51*, 3316.
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10.Copies of NMR Spectra









¹H NMR: 600 MHz in CDCl₃





fl (ppm)









S31


































¹H NMR: 600 MHz in CDCl₃







S48







¹H NMR: 500 MHz in CDCl₃









¹H NMR: 600 MHz in CDCl₃













¹H NMR: 600 MHz in CDCl₃







S58























S66









¹³C NMR: 150 MHz in CDCl₃



42.33

-33.15

-21.79










0 100 f1 (ppm)





--2.395

3.230



¹H NMR: 600 MHz in CDCl₃









¹H NMR: 600 MHz in CDCl₃

5c





0 100 f1 (ppm)