Supplementary Materials

Article

Traceless Solid-Phase Synthesis of Ketones via Acid-Labile Enol Ethers: Application in the Synthesis of Natural Products and Derivatives

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**Table S1:** Base-catalyzed Wittig olefination to compounds 7.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Cmpd</th>
<th>Route</th>
<th>R&lt;sup&gt;1&lt;/sup&gt;</th>
<th>R&lt;sup&gt;2&lt;/sup&gt;</th>
<th>Base</th>
<th>Conditions</th>
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<tbody>
<tr>
<td>1</td>
<td>{1,1}</td>
<td>I</td>
<td>H</td>
<td>Me</td>
<td>0.1 M DBU</td>
<td>60 °C, 16 h</td>
</tr>
<tr>
<td>2</td>
<td>{1,2}</td>
<td>II</td>
<td>H</td>
<td>PhthN(CH&lt;sub&gt;2&lt;/sub&gt;)&lt;sub&gt;2&lt;/sub&gt;</td>
<td>0.1 M TEA</td>
<td>rt, 48 h</td>
</tr>
<tr>
<td>3</td>
<td>{2,-}</td>
<td>I</td>
<td>Hyp(BzI)&lt;sup&gt;a&lt;/sup&gt;</td>
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<td>60 °C, 48 h</td>
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<tr>
<td>4</td>
<td>{3,-}</td>
<td>I</td>
<td>Idc&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.1 M TEA</td>
<td>rt, 48 h</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>{4,1}</td>
<td>I</td>
<td>CH&lt;sub&gt;2&lt;/sub&gt;C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;OH</td>
<td>Me</td>
<td>0.1 M TEA</td>
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<tr>
<td>6</td>
<td>{5,3}</td>
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<td>Me</td>
<td>Bn</td>
<td>0.1 M TEA</td>
<td>rt, 2 h</td>
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<td>7</td>
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<td>Bn</td>
<td>PhthN(CH&lt;sub&gt;2&lt;/sub&gt;)&lt;sub&gt;2&lt;/sub&gt;</td>
<td>0.1 M TEA</td>
<td>rt, 48 h</td>
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<tr>
<td>8</td>
<td>{6,4}</td>
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<td>Bn</td>
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<td>9</td>
<td>{7,2}</td>
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<td>CH&lt;sub&gt;2&lt;/sub&gt;OH</td>
<td>PhthN(CH&lt;sub&gt;2&lt;/sub&gt;)&lt;sub&gt;2&lt;/sub&gt;</td>
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<td>rt, 48 h</td>
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<td>10</td>
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<td>II</td>
<td>(CH&lt;sub&gt;2&lt;/sub&gt;)&lt;sub&gt;2&lt;/sub&gt;CO&lt;sub&gt;2&lt;/sub&gt;H</td>
<td>PhthN(CH&lt;sub&gt;2&lt;/sub&gt;)&lt;sub&gt;2&lt;/sub&gt;</td>
<td>0.1 M TEA</td>
<td>rt, 48 h</td>
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</table>

Note: <sup>a</sup>cyclic amino acids

**Table S2:** Self-condensation of purified compounds 8 to 9 in ammonium acetate buffer.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Cmpd</th>
<th>R&lt;sup&gt;1&lt;/sup&gt;</th>
<th>R&lt;sup&gt;2&lt;/sup&gt;</th>
<th>Purity 8 [%]</th>
<th>Yield of 8 [%]&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Purity 9 [%]&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Yield 9 [%]</th>
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<tbody>
<tr>
<td>1</td>
<td>{1,2}</td>
<td>H</td>
<td>PhthN(CH&lt;sub&gt;2&lt;/sub&gt;)&lt;sub&gt;2&lt;/sub&gt;</td>
<td>81</td>
<td>70</td>
<td>97</td>
<td>80</td>
</tr>
<tr>
<td>2</td>
<td>{6,2}</td>
<td>Bn</td>
<td>PhthN(CH&lt;sub&gt;2&lt;/sub&gt;)&lt;sub&gt;2&lt;/sub&gt;</td>
<td>72</td>
<td>30</td>
<td>95</td>
<td>53</td>
</tr>
</tbody>
</table>

Note: <sup>a</sup>Crude compounds 8 were purified by RP HPLC in MeCN/aqueous 0.1% TFA or formic acid; <sup>b</sup>Procedure for self-condensation: solution of compounds 8 (14.1 mg for {1,2}, 11.9 mg for {6,2}) in 600 μL of DMSO was added to 5 mL of 10 mM aqueous ammonium acetate and left at rt overnight, then compounds 9 were purified in MeCN/10 mM aqueous ammonium acetate.
General Information

Solvents were used without further purification. The Wang linker (100-200 mesh, 1% DVB, 0.9 mmol/g) was used. Synthesis was carried out on Domino Blocks (www.torviq.com) in disposable polypropylene reaction vessels.

The volume of wash solvent was 10 mL per 1 g of resin. For washing, resin slurry was shaken with the fresh solvent for at least 1 min before changing the solvent. After adding a reagent solution, the resin slurry was manually vigorously shaken to break any potential resin clumps. Resin-bound intermediates were dried by a stream of nitrogen for prolonged storage and/or quantitative analysis.

For the LC/MS analysis a sample of resin (~5 mg) was treated by 50% TFA in DCM, the cleavage cocktail was evaporated by a stream of nitrogen, and cleaved compounds extracted into 1 mL of MeOH.

The LC/MS analyses were carried out using two instruments. The first one comprised a 3 x 50 mm C18 reverse phase column, 5 µm particles. Mobile phases: 10 mM ammonium acetate in HPLC grade water (A) and HPLC grade acetonitrile (B). A gradient was formed from 5% to 80% of B in 10 minutes, flow rate of 0.7 mL/min. The MS electrospray source operated at capillary voltage 3.5 kV and a desolvation temperature 300 °C. The second instrument comprised a 2.1 x 50 mm C18 reverse phase column, 2.6 um particles, at 30°C and flow rate of 800 µL/min. Mobile phases: 10 mM ammonium acetate in HPLC grade water (A) and HPLC grade acetonitrile (B). A gradient was formed from 10% to 80% of B in 2.5 minutes; kept for 1.5 minute, flow rate of 0.8 mL/min. The column was re-equilibrated with 10% solution B for 1 minute. The APCI source operated at discharge current of 5 µA, vaporizer temperature of 400 °C and capillary temperature of 200 °C.

Purification was carried out on C18 reverse phase column 19 x 100 mm, 5 µm particles, gradient was formed from 10 mM aqueous ammonium acetate (acidic mobile phase: 0.1% aqueous TFA or formic acid) and acetonitrile, flow rate 20 mL/min.

All ¹H and ¹³C NMR experiments were performed at magnetic field strengths of 9.39 T (with operating frequencies 399.78 MHz for ¹H and 100.53 MHz for ¹³C) at ambient temperature (20 °C). ¹H spectra and ¹³C spectra were referenced relative to the signal of DMSO (¹H δ = 2.49 ppm, ¹³C δ = 39.50 ppm).

HRMS analysis was performed using LC-MS on an Orbitrap Elite high-resolution mass spectrometer (Dionex Ultimate 3000, Thermo Exactive plus, MA, USA) operating at positive full scan mode (120,000 FWMH) in the range of 100–1000 m/z. The settings for electrospray ionization were as follows: oven temperature of 150 °C and source voltage of 3.6 kV. The
acquired data were internally calibrated with diisooctyl phthalate as a contaminant in CH$_3$OH ($m/z$ 391.2843). Samples were diluted to a final concentration of 0.1 mg/mL in H$_2$O and CH$_3$OH (50:50, v/v). Before HPLC separation (column Phenomenex Gemini, 50 × 2.00 mm, 3 μm particles, C18), the samples were injected by direct infusion into the mass spectrometer using an autosampler. The mobile phase was isocratic CH$_3$CN/IPA/0.01 M ammonium acetate (40:5:55) and flow 0.3 mL/min.
Analytical Data of Synthetic Compounds

2-(2-(2,4-Dioxopyrrolidin-1-yl)ethyl)isoindoline-1,3-dione 8a\{1,2\} and 2-(2-(4-hydroxy-2-oxo-2,5-dihydro-1H-pyrrol-1-yl)ethyl)isoindoline-1,3-dione 8b\{1,2\}

Yield 18.6 mg (70 %) of amorphous solid. Mixture of tautomers 8a\{1,2\} and 8b\{1,2\} in DMSO: 

\(^1^H\) NMR (400 MHz, DMSO-\(d_6\)) \(\delta = 11.33\ (s, \ 1 \ H), \ 7.92 - 7.77\ (m, \ 8 \ H), \ 4.62\ (s, \ 1 \ H), \ 4.00\ (s, \ 2 \ H), \ 3.89\ (s, \ 2 \ H), \ 3.79\ (t, \ J = 5.5 \ Hz, \ 2 \ H), \ 3.69\ (t, \ J = 5.3 \ Hz, \ 2 \ H), \ 3.65 - 3.57\ (m, \ 2 \ H), \ 3.55 - 3.47\ (m, \ 2 \ H), \ 2.91\ (s, \ 2 \ H).

\(^1^3^C\) NMR (101 MHz, DMSO-\(d_6\)) \(\delta = 205.2, \ 172.4, \ 172.2, \ 169.7, \ 168.0, \ 167.7, \ 134.4, \ 134.3, \ 131.6, \ 131.6, \ 123.1, \ 123.0, \ 93.4, \ 56.8, \ 50.1, \ 41.3, \ 36.0, \ 34.6\). Only tautomer 8a\{1,2\} in CDCl\(_3\): 

\(^1^H\) NMR (400 MHz, CDCl\(_3\)) \(\delta = 7.87 - 7.82\ (m, \ 2 \ H), \ 7.75 - 7.71\ (m, \ 2 \ H), \ 4.13 - 3.99\ (m, \ 2 \ H), \ 3.95 - 3.90\ (m, \ 2 \ H), \ 3.83 - 3.72\ (m, \ 2 \ H), \ 2.92\ (s, \ 2 \ H).

\(^1^3^C\) NMR (101 MHz, CDCl\(_3\)) \(\delta = 203.0, \ 169.7, \ 168.4, \ 134.2, \ 131.9, \ 123.5, \ 57.2, \ 41.3, \ 41.1, \ 34.8\). HRMS (ESI-Orbitrap) \(m/z\) calcd for C\(_{14}\)H\(_{12}\)N\(_2\)O\(_4\) [M+H\(^+\)] 273.0870, found 273.0870.

\((S)-9,9a\text{-dihydro-1H-pyrrolo[1,2-a]}\text{-indole-1,3(2H)-dione 8a}\{3,-\}\) and \((S)-1\text{-hydroxy-9,9a-dihydro-3H-pyrrolo[1,2-a]}\text{-indol-3-one 8b}\{3,-\}\)

Yield 15.8 mg (31 %) of amorphous solid. Mixture of tautomers 8a\{3,-\} and 8b\{3,-\} in DMSO: \(^1^H\) NMR (400 MHz, DMSO-\(d_6\)) \(\delta = 12.34\ (br.\ s., \ 1 \ H), \ 7.43\ (d, \ J = 7.8 \ Hz, \ 1 \ H), \ 7.31 - 7.13\ (m, \ 5 \ H), \ 7.12 - 7.05\ (m, \ 1 \ H), \ 7.00\ (dt, \ J = 1.1, \ 7.4 \ Hz, \ 1 \ H), \ 5.11 - 5.05\ (m, \ 1 \ H), \ 5.02\ (t, \ J = 9.4 \ Hz, \ 1 \ H), \ 4.86\ (s, \ 1 \ H), \ 3.79 - 3.69\ (m, \ 1 \ H), \ 3.28 - 3.17\ (m, \ 2 \ H), \ 3.15 - 2.97\ (m, \ 3 \ H). \(^1^3^C\) NMR (101 MHz, DMSO-\(d_6\)) \(\delta = 206.0, \ 179.5, \ 175.7, \ 169.7, \ 142.1, \ 140.6, \ 134.6, \ 133.3, \ 127.4, \ 125.4, \ 124.7, \ 123.6, \ 116.3, \ 116.0, \ 94.2, \ 70.0, \ 64.4, \ 46.1, \ 31.4, \ 29.9\). HRMS (ESI-Orbitrap) \(m/z\) calcd for C\(_{11}\)H\(_9\)NO\(_2\) [M+H\(^+\)] 188.0706, found 188.0706.

\((S)-5\text{-}(4\text{-Hydroxybenzyl)}\text{-1-methylpyrrolidine-2,4-dione and 8a}\{4,1\}\) and \((S)-4\text{-hydroxy-5-(4-hydroxybenzyl)}\text{-1-methyl-1,5-dihydro-2H-pyrrol-2-one 8b}\{4,1\}\)
Yield 21.6 mg (25%) of amorphous solid. Mixture of tautomers 8a(4,1) and 8b(4,1) in DMSO:

$^1$H NMR (400 MHz, DMSO-$d_6$) δ = 11.39 (br. s., 1 H), 9.31 (s, 1 H), 9.18 (s, 1 H), 6.93 - 6.88 (m, 2 H), 6.88 - 6.83 (m, 2 H), 6.68 - 6.63 (m, 2 H), 6.62 - 6.58 (m, 1 H), 4.62 (s, 1 H), 4.15 (dt, $J = 1.4$, 4.6 Hz, 1 H), 4.06 (s, 3 H), 2.85 (d, $J = 21.0$ Hz, 1 H), 3.04 - 2.79 (m, 5 H), 2.71 (s, 3 H), 2.32 (d, $J = 22.0$ Hz, 1 H). $^{13}$C NMR (101 MHz, DMSO-$d_6$) δ = 207.9, 173.4, 171.9, 168.7, 156.1, 155.8, 130.4, 130.3, 125.8, 125.5, 115.2, 114.7, 94.4, 69.2, 62.3, 40.9, 33.7, 33.4, 27.4, 26.8. The NMR spectra in CDCl$_3$ were not collected due to insolubility.

HRMS (ESI-Orbitrap) m/z calcd for C$_{12}$H$_{13}$NO$_3$ [M+H]$^+$ 220.0968, found 220.0967.

(S)-2-(2-Benzyl-3,5-dioxopyrrolidin-1-yl)ethylisoindoline-1,3-dione 8a(6,2) and (S)-2-(2-benzyl-3-hydroxy-5-oxo-2,5-dihydro-1H-pyrrol-1-yl)ethylisoindoline-1,3-dione 8b(6,2)

Yield 32.3 mg (30%) of amorphous solid. Mixture of tautomers 8a(6,2) and 8b(6,2) in DMSO:

$^1$H NMR (400 MHz, DMSO-$d_6$) δ = 11.52 (s, 1 H), 7.88 - 7.76 (m, 8 H), 7.30 - 7.05 (m, 10 H), 4.53 (t, $J = 4.1$ Hz, 1 H), 4.44 (s, 1 H), 4.39 (t, $J = 4.1$ Hz, 1 H), 4.09 (ddd, $J = 4.6$, 10.1, 14.2 Hz, 1 H), 4.01 - 3.84 (m, 2 H), 3.80 - 3.65 (m, 2 H), 3.55 (td, $J = 3.5$, 14.1 Hz, 1 H), 3.28 (td, $J = 3.7$, 14.2 Hz, 1 H), 3.21 - 3.03 (m, 4 H), 2.97 (dd, $J = 3.9$, 14.4 Hz, 1 H), 2.66 (d, $J = 22.0$ Hz, 1 H), 2.35 (d, $J = 21.5$ Hz, 1 H). $^{13}$C NMR (126 MHz, DMSO-$d_6$) δ = 206.9, 173.6, 171.8, 169.1, 168.0, 167.6, 135.6, 135.4, 134.3, 134.2, 131.6, 131.5, 129.3, 129.3, 128.3, 127.8, 126.8, 126.3, 123.0, 122.9, 93.8, 66.1, 58.9, 40.5, 37.9, 36.8, 35.8, 34.5, 34.3, 33.5. Only tautomer 8a(6,2) in CDCl$_3$:

$^1$H NMR (400 MHz, CDCl$_3$) δ = 7.86 - 7.78 (m, 2 H), 7.75 - 7.68 (m, 2 H), 7.29 - 7.22 (m, 3 H, overlap with CDCl$_3$), 7.07 (dd, $J = 1.4$, 7.8 Hz, 2 H), 4.52 (dt, $J = 1.4$, 4.4 Hz, 1 H), 4.45 - 4.36 (m, 1 H), 3.84 (dd, $J = 3.9$, 6.6 Hz, 2 H), 3.21 - 3.06 (m, 3 H), 2.74 - 2.62 (m, 1 H), 2.34 - 2.22 (m, 1 H). $^{13}$C NMR (101 MHz, CDCl$_3$) δ = 205.9, 169.8, 168.4, 134.7, 134.2, 131.8, 129.3, 128.9, 127.4, 123.4, 66.9, 40.7, 38.9, 35.3, 34.7. HRMS (ESI-Orbitrap) m/z calcd for C$_{21}$H$_{18}$N$_2$O$_4$ [M+H]$^+$ 363.1339, found 363.1338.
(S)-5-Benzyl-1-(prop-2-yn-1-yl)pyrrolidine-2,4-dione 8a{6,4} and (S)-5-benzyl-4-hydroxy-1-(prop-2-yn-1-yl)-1,5-dihydro-2H-pyrrol-2-one 8b{6,4}

Yield 18.8 mg (21 %) of amorphous solid. Mixture of tautomers 8a{7,4} and 8b{7,4} in DMSO:  
\(^1\)H NMR (400 MHz, DMSO-\(d_6\)) \(\delta = 11.75 \text{ (s, 1 H)}, 7.32 - 7.11 \text{ (m, 10 H)}, 4.66 \text{ (s, 1 H)}, 4.56 \text{ (dd, } J = 2.5, 17.6 \text{ Hz, 1 H)}, 4.40 - 4.31 \text{ (m, 2 H)}, 4.25 \text{ (t, } J = 4.4 \text{ Hz, 1 H)}, 4.01 \text{ (dd, } J = 2.1, 17.2 \text{ Hz, 1 H)}, 3.75 \text{ (dd, } J = 2.5, 17.6 \text{ Hz, 1 H)}, 3.32 \text{ (t, } J = 2.5 \text{ Hz, 1 H)}, 3.22 - 3.14 \text{ (m, 3 H)}, 3.11 \text{ (dd, } J = 2.1, 4.8 \text{ Hz, 1 H)}, 3.03 - 2.92 \text{ (m, 2 H)}. \(^{13}\)C NMR (101 MHz, DMSO-\(d_6\)) \(\delta = 206.3, 174.5, 172.1, 168.4, 135.6, 135.6, 129.5, 128.4, 127.9, 126.8, 126.4, 124.0, 79.7, 78.1, 75.3, 74.1, 66.7, 59.7, 40.9, 34.4, 34.0, 29.5, 29.1. Only tautomer 8a{6,4} in CDCl\(_3\):  
\(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta = 7.35 - 7.22 \text{ (m, 3 H, overlap with CDCl\(_3\))}, 7.13 - 7.03 \text{ (m, 2 H)}, 4.91 \text{ (dd, } J = 2.3, 17.9 \text{ Hz, 1 H)}, 4.46 \text{ (dt, } J = 1.4, 4.4 \text{ Hz, 1 H)}, 3.82 \text{ (d, } J = 17.4 \text{ Hz, 1 H)}, 3.25 - 3.12 \text{ (m, 2 H)}, 2.83 \text{ (d, } J = 22.4 \text{ Hz, 1 H)}, 2.35 \text{ (t, } J = 2.5 \text{ Hz, 1 H)}, 2.35 \text{ (d, } J = 22.4 \text{ Hz, 1 H}). \(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \(\delta = 205.6, 168.4, 134.2, 129.5, 128.9, 127.5, 76.3, 73.7, 66.9, 41.2, 35.3, 30.0. HRMS (ESI-Orbitrap) \(m/z\) calcld for C\(_{14}\)H\(_{13}\)NO\(_2\) [M+H]\(^+\) 228.1019, found 228.1019.

(S)-2-(2-(2-(Hydroxymethyl)-3,5-dioxopyrrolidin-1-yl)ethyl)isoindoline-1,3-dione 8a{7,2} and (S)-2-(2-(3-hydroxy-2-(hydroxymethyl)-5-oxo-2,5-dihydro-1H-pyrrol-1-yl)ethyl)isoindoline-1,3-dione 8b{7,2}

Yield 34.7 mg (52 %) of amorphous solid. Mixture of tautomers 8a{7,2} and 8b{7,2} in DMSO:  
\(^1\)H NMR (400 MHz, DMSO-\(d_6\)) \(\delta = 11.44 \text{ (br. s., 1 H)}, 7.90 - 7.77 \text{ (m, 8 H)}, 5.15 \text{ (br. s., 1 H)}, 4.61 \text{ (s, 1 H)}, 4.17 \text{ (br. s., 1 H)}, 4.11 - 3.97 \text{ (m, 2 H)}, 3.94 - 3.77 \text{ (m, 4 H)}, 3.76 - 3.62 \text{ (m, 4 H)}, 3.34 - 3.18 \text{ (m, 3 H)}, 2.87 \text{ (d, } J = 22.0 \text{ Hz, 1 H)}, 2.79 \text{ (d, } J = 22.0 \text{ Hz, 1 H}). \(^{13}\)C NMR (101 MHz, DMSO-\(d_6\)) \(\delta = 207.2, 172.5, 172.4, 169.8, 168.1, 167.8, 134.4, 134.3, 131.7, 131.6, 123.1, 123.0, 93.9, 68.1, 61.8, 59.2, 58.1, 41.3, 37.9, 37.5, 36.4, 34.7. Only tautomer 8a{7,2} in CDCl\(_3\):  
\(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta = 7.82 - 7.70 \text{ (m, 2 H)}, 7.69 - 7.58 \text{ (m, 2 H)}, 5.30 - 4.59 \text{ (m, 1 H)}, 4.07 \text{ (br. s., 1 H)}, 4.02 - 3.93 \text{ (m, 1 H)}, 3.91 \text{ (br. s., 2 H)}, 3.87 - 3.79 \text{ (m, 2 H)}, 3.51 \text{ (td, } J = 4.5,
14.3 Hz, 1 H), 2.91 - 2.79 (m, 1 H), 2.79 - 2.69 (m, 1 H). $^{13}$C NMR (101 MHz, CDCl$_3$) δ = 205.3, 170.4, 168.4, 134.0, 131.7, 123.2, 69.3, 59.3, 41.3, 39.5, 35.5. HRMS (ESI-Orbitrap) m/z calcd for C$_{15}$H$_{14}$N$_2$O$_5$ [M+H]$^+$ 303.0975, found 303.0976.

(S)-3-(1-(2,1,3-Dioxoisindolin-2-yl)ethyl)-3,5-dioxopyrrolidin-2-yl)propanoic acid 8a$^{[8,2]}$ and (S)-3-(1-(2-(1,3-dioxoisindolin-2-yl)ethyl)-3-hydroxy-5-oxo-2,5-dihydro-1H-pyrrol-2-yl)propanoic acid 8b$^{[8,2]}$

Yield 14.8 mg (21%) of amorphous solid. Mixture of tautomers 8a$^{[8,2]}$ and 8b$^{[8,2]}$ in DMSO: $^1$H NMR (400 MHz, DMSO-$d_6$) δ = 12.22 (br. s., 1 H), 11.50 (br. s., 1 H), 7.90 - 7.76 (m, 8 H), 4.64 (s, 1 H), 4.29 - 4.21 (m, 1 H), 4.19 (s, 1 H), 3.99 (ddd, $J$ = 4.4, 9.5, 14.1 Hz, 1 H), 3.93 - 3.80 (m, 2 H), 3.79 - 3.65 (m, 3 H), 3.58 (td, $J$ = 3.9, 13.7 Hz, 2 H), 3.21 (td, $J$ = 3.9, 14.2 Hz, 1 H), 3.13 (d, $J$ = 22.0 Hz, 1 H), 3.10 - 3.04 (m, 1 H), 2.79 (d, $J$ = 22.0 Hz, 1 H), 2.36 - 2.12 (m, 2 H), 2.11 - 1.91 (m, 5 H). $^{13}$C NMR (101 MHz, DMSO-$d_6$) δ = 207.8, 174.0, 173.9, 173.6, 172.1, 169.6, 168.1, 167.8, 134.4, 134.3, 131.7, 131.6, 123.1, 123.0, 93.6, 64.4, 57.7, 40.8, 37.9, 36.7, 36.1, 34.7, 28.4, 27.0, 23.8, 22.6. Only tautomer 8a$^{[8,2]}$ in CDCl$_3$: $^1$H NMR (400 MHz, CDCl$_3$) δ = 10.05 (br. s., 1 H), 7.86 - 7.76 (m, 2 H), 7.75 - 7.65 (m, 2 H), 4.40 - 4.22 (m, 2 H), 3.99 - 3.80 (m, 2 H), 3.18 (td, $J$ = 3.3, 14.5 Hz, 1 H), 2.91 (d, $J$ = 22.0 Hz, 1 H), 2.84 (d, $J$ = 22.0 Hz, 1 H), 2.43 - 2.31 (m, 2 H), 2.23 (dtd, $J$ = 2.7, 7.4, 14.5 Hz, 1 H), 2.07 - 1.93 (m, 1 H). $^{13}$C NMR (101 MHz, CDCl$_3$) δ = 206.0, 174.6, 169.9, 168.4, 134.1, 131.8, 123.3, 64.5, 40.8, 38.6, 34.7, 28.4, 23.7. HRMS (ESI-Orbitrap) m/z calcd for C$_{17}$H$_{16}$N$_2$O$_6$ [M+H]$^+$ 345.1081, found 345.1081.

Ammonium 1,1'-dimethyl-2,5'-dioxo-2',5',5'-tetrahydro-1H,1'H-[3,3'-bipyrrl]-4-olate 9b$^{[1,1]}$

Crude product was purified in MeCN/10 mM aqueous ammonium acetate and left overnight at room temperature for quantitative self-condensation: 9.6 mg (47%) of amorphous solid. $^1$H NMR (400 MHz, DMSO-$d_6$) δ = 6.26 (s, 1 H), 4.27 (s, 2 H), 3.95 (s, 2 H), 2.88 (s, 3 H), 2.82 (s, 3
**H).** ¹³C NMR (101 MHz, DMSO-₅) δ = 171.5, 171.4, 169.8, 146.7, 115.9, 99.1, 54.8, 51.4, 28.3, 28.1. HRMS (ESI-Orbitrap) m/z calcd for C₁₀H₁₂N₂O₃ [M+H]^+ 209.0921, found 209.0921.

**Ammonium 1,1'-bis(2-(1,3-dioxoisindolin-2-yl)ethyl)-2,5'-dioxo-2',5,5'-tetrahydro-1H,1'H-[3,3'-bipyrrul]-4-olate 9b{1,2}**

![Ammonium 1,1'-bis(2-(1,3-dioxoisindolin-2-yl)ethyl)-2,5'-dioxo-2',5,5'-tetrahydro-1H,1'H-[3,3'-bipyrrul]-4-olate 9b](image)

Crude product was purified in MeCN/10 mM aqueous ammonium acetate: 27.4 mg (53 %), and by self-condensation of 8{1,2} exposed to 10 mM aqueous ammonium acetate for 24 h at room temperature and purified by MeCN/10 mM aqueous ammonium acetate: 10.9 mg (80%) of amorphous solid. ¹H NMR (400 MHz, DMSO-₅) δ = 7.87 - 7.78 (m, 8 H), 5.90 (s, 1 H), 4.21 (s, 2 H), 4.04 (br. s., 2 H), 3.78 - 3.71 (m, 2 H), 3.71 - 3.65 (m, 2 H), 3.61 - 3.51 (m, 4 H). ¹³C NMR (101 MHz, DMSO-₅) δ = 171.8, 171.3, 169.9, 167.8, 167.7, 146.9, 134.3, 134.3, 131.6, 131.6, 123.1, 123.0, 115.5, 52.4, 49.5, 36.1, 35.9. HRMS (ESI-Orbitrap) m/z calcd for C₂₈H₂₄N₄O₇ [M+H]^+ 527.1561, found 527.1564.

**Ammonium (6S,6'R,7aS,7'aS)-6,6'-bis(benzyloxy)-3,3'-dioxo-5,5',6,6',7,7'a,7',7'a-octahydro-3H,3'H-[1,2'-bipyrrrolizin]-1'-olate 9b{2,-}**

![Ammonium (6S,6'R,7aS,7'aS)-6,6'-bis(benzyloxy)-3,3'-dioxo-5,5',6,6',7,7'a,7',7'a-octahydro-3H,3'H-[1,2'-bipyrrrolizin]-1'-olate 9b](image)

Crude product was purified in MeCN/10 mM aqueous ammonium acetate: 31.9 mg (37 %) of amorphous solid. ¹H NMR (400 MHz, DMSO-₅) δ = 7.39 - 7.25 (m, 10 H), 6.00 (s, 1 H), 4.77 (dd, J = 6.0, 10.1 Hz, 1 H), 4.56 - 4.44 (m, 5 H), 4.36 (t, J = 5.0 Hz, 1 H), 4.29 (t, J = 5.0 Hz, 1 H), 4.07 (dd, J = 6.6, 9.8 Hz, 1 H), 3.67 (dd, J = 5.5, 11.9 Hz, 1 H), 3.59 (dd, J = 5.5, 12.4 Hz, 1 H), 3.03 (dd, J = 12.6, 16.7 Hz, 2 H), 2.67 (dd, J = 5.7, 13.1 Hz, 1 H), 2.24 (dd, J = 6.4, 12.8 Hz, 1 H), 1.47 (ddd, J = 5.0, 10.1, 12.8 Hz, 1 H), 1.17 (ddd, J = 5.0, 10.4, 12.9 Hz, 1 H). ¹³C NMR (101 MHz, DMSO-₅) δ = 184.3, 177.8, 176.9, 156.0, 138.4, 128.3, 127.6, 127.4, 110.2, 95.8, 82.6, 81.2, 70.1, 70.0, 65.7, 63.3, 50.1, 49.5, 36.3, 34.6. HRMS (ESI-Orbitrap) m/z calcd for C₂₈H₂₆N₂O₅ [M+H]^+ 473.2071, found 473.2074.
Ammonium (2'S,5S)-1,1'-dibenzyl-2',5-dimethyl-2,5'-dioxo-2,2',5,5'-tetrahydro-1H,1'H-[3,3'-bipyrrol]-4-olate 9b{5,3}

Crude product was purified in MeCN/10 mM aqueous ammonium acetate: 7.9 mg (22 %) of amorphous solid. 1H NMR (400 MHz, DMSO-d6) δ = 7.37 - 7.26 (m, 5 H), 7.26 - 7.17 (m, 5 H), 6.27 (s, 1 H), 4.91 (d, J = 15.6 Hz, 1 H), 4.77 (d, J = 15.6 Hz, 1 H), 4.39 (q, J = 6.4 Hz, 1 H), 4.16 (d, J = 15.6 Hz, 1 H), 4.14 (d, J = 15.6 Hz, 1 H), 3.68 (q, J = 6.4 Hz, 1 H), 1.22 (d, J = 6.4 Hz, 3 H), 1.19 (d, J = 6.4 Hz, 3 H). 13C NMR (101 MHz, DMSO-d6) δ = 178.4, 170.7, 169.7, 154.2, 138.6, 138.5, 128.53, 128.50, 127.54, 127.48 127.03, 126.99, 113.8, 67.8, 56.9, 55.2, 42.5, 42.3, 17.7, 16.2. HRMS (ESI-Orbitrap) m/z calcd for C24H24N2O3 [M+H]+ 389.1860, found 389.1861.

Ammonium (2'S,5S)-2',5-dibenzyl-1,1'-bis(2-(1,3-dioxoisindolin-2-yl)ethyl)-2,5'-dioxo-2,2',5,5'-tetrahydro-1H,1'H-[3,3'-bipyrrol]-4-olate 9b{6,2}

Crude product was purified in MeCN/10 mM aqueous ammonium acetate: 3.9 mg (49 %) of amorphous solid and by spontaneous self-condensation of 8{6,2} and purified by MeCN/10 mM aqueous ammonium acetate: 6.1 mg (53%). 1H NMR (400 MHz, DMSO-d6) δ = 7.87 - 7.77 (m, 8 H), 7.28 - 7.20 (m, 2 H), 7.19 - 7.10 (m, 3 H), 7.08 - 7.01 (m, 1 H), 7.01 - 6.94 (m, 2 H), 6.63 (d, J = 7.3 Hz, 2 H), 5.66 (s, 1 H), 4.82 (t, J = 3.9 Hz, 1 H), 4.63 (t, J = 3.7 Hz, 1 H), 4.00 (dd, J = 4.6, 9.4, 14.4 Hz, 1 H), 3.86 - 3.71 (m, 2 H), 3.70 - 3.52 (m, 2 H), 3.45 (d, J = 4.6 Hz, 2 H, overlap with the water), 3.33 - 3.25 (m, 1 H, overlap with the water), 3.23 - 3.08 (m, 2 H), 2.97 (dd, J = 4.1, 14.2 Hz, 1 H), 2.63 (dd, J = 4.1, 14.2 Hz, 1 H). 13C NMR (101 MHz, DMSO-d6) δ = 173.0, 170.8, 169.3, 167.9, 167.5, 149.9, 135.8, 135.1, 134.4, 134.3, 131.6, 129.2, 129.1, 128.1, 127.7, 126.7, 126.0, 123.1, 122.9, 117.8, 99.8, 60.6, 58.6, 37.6, 37.3, 36.0, 35.8, 35.4, 33.8. HRMS (ESI-Orbitrap) m/z calcd for C42H34N4O7 [M-H]+ 705.2344, found 705.2349.
\(^1\text{H}\) and \(^{13}\text{C}\) NMR spectra (\(d_6\)-DMSO) of \(2-(2,4\text{-dioxopyrrolidin-1-yl})\text{ethyl}\)isoindoline-1,3-dione 8a\(^{1,2}\) and \(2-(2\text{-}(4\text{-hydroxy-2-oxo-2,5\text{-dihydro}-1H\text{-pyrrol-1-yl})\text{ethyl}\)isoindoline-1,3-dione 8b\(^{1,2}\)
$^1$H and $^{13}$C NMR spectra (CDCl$_3$) of 2-(2-(2,4-dioxopyrrolidin-1-yl)ethyl)isoindoline-1,3-dione 8a{$^{1,2}$}
$^1$H and $^{13}$C NMR spectra ($d_6$-DMSO) of (S)-9,9a-dihydro-1H-pyrrolo[1,2-a]indole-1,3(2H)-dione 8a\{3,\} and (S)-1-hydroxy-9,9a-dihydro-3H-pyrrolo[1,2-a]indol-3-one and 8b\{3,\}

![NMR Spectra Diagram]
\(^1\)H and \(^{13}\)C NMR spectra (\(d_6\)-DMSO) of (S)-5-(4-hydroxybenzyl)-1-methylpyrrolidine-2,4-dione and 8a\([4,1]\) and (S)-4-hydroxy-5-(4-hydroxybenzyl)-1-methyl-1,5-dihydro-2H-pyrrol-2-one 8b\([4,1]\)
$^{1}$H and $^{13}$C NMR spectra ($d_6$-DMSO) of (S)-2-(2-(2-benzyl-3,5-dioxopyrrolidin-1-yl)ethyl)isoindoline-1,3-dione 8a(6,2) and (S)-2-(2-(2-benzyl-3-hydroxy-5-oxo-2,5-dihydro-1H-pyrrol-1-yl)ethyl)isoindoline-1,3-dione 8b(6,2)
$^1$H and $^{13}$C NMR spectra (CDCl$_3$) of (S)-2-(2-benzyl-3,5-dioxopyrrolidin-1-yI)ethyl)isoindoline-1,3-dione 8a$^{(6,2)}$
\(^1\text{H} \text{ and } ^{13}\text{C} \text{ NMR spectra (}\text{\textit{d}_6}\text{-DMSO}) \text{ of } (S)-5\text{-benzyl-1-(prop-2-yn-1-yl)pyrrolidine-2,4-dione 8a(6,4)} \text{ and } (S)-5\text{-benzyl-4-hydroxy-1-(prop-2-yn-1-yl)-1,5-dihydro-2H-pyrrol-2-one 8b(6,4)}}
$^1$H and $^{13}$C NMR spectra (CDCl$_3$) of (S)-5-benzyl-1-(prop-2-yn-1-yl)pyrrolidine-2,4-dione

8a(6,4)
$^1$H and $^{13}$C NMR spectra (d$_6$-DMSO) of (S)-2-(2-(hydroxymethyl)-3,5-dioxopyrrolidin-1-yl)ethyl)isoindoline-1,3-dione 8a[7,2] and (S)-2-(2-(3-hydroxy-2-(hydroxymethyl)-5-oxo-2,5-dihydro-1H-pyrrol-1-yl)ethyl)isoindoline-1,3-dione 8b[7,2]
$^{1}\text{H} \text{ and } ^{13}\text{C NMR spectra (CDCl}_3\text{) of (S)-2-(2-((\text{hydroxymethyl})-3,5-\text{dioxopyrroldin-1-yl})\text{ethyl})\text{isoindoline-1,3-dione 8a}}$\text{(7,2)}}
$^1$H and $^{13}$C NMR spectra ($d_6$-DMSO) of (S)-3-(1-(2-(1,3-dioxoisooindolin-2-yl)ethyl)-3,5-dioxopyrrolidin-2-yl)propanoic acid 8a[8,2] and (S)-3-(1-(2-(1,3-dioxoisooindolin-2-yl)ethyl)-3-hydroxy-5-oxo-2,5-dihydro-1H-pyrrol-2-yl)propanoic acid 8b[8,2]
\(^1\)H and \(^{13}\)C NMR spectra (CDCl\(_3\)) of \((S)-3-(1-(2-(1,3-dioxoisindolin-2-yl)ethyl)-3,5-dioxopyrrolidin-2-yl)propanoic acid 8a\(\{8,2\}\)
$^1\text{H}$ and $^{13}\text{C}$ NMR spectra ($d_6$-DMSO) of ammonium 1,1'-dimethyl-2,5'-dioxo-2,2',5,5'-tetrahydro-1$H$,1'$H$-[3,3'-bipyrol]-4-olate 9b{1,1}
$^1$H and $^{13}$C NMR spectra ($d_6$-DMSO) of ammonium 1,1'-bis(2-(1,3-dioxoisindolin-2-yl)ethyl)-2,5'-dioxo-2',5,5'-tetrahydro-1$H,1'$-$H$-[3,3'-bipyrol]-4-olate 9b{1,2}
$^{1}H$ and $^{13}C$ NMR spectra ($d_{6}$-DMSO) of ammonium (6$S$,6'$R$,7$a$S,7'a$S$)-6,6'$-bis(benzyloxy)-3,3'-dioxo-5,5',6,6',7,7a,7',7'a-octahydro-3$H$,3'$H$-[1,2'-bipyrrrolizin]-1'-olate 9b/2, -
$^1$H and $^{13}$C NMR spectra (d$_6$-DMSO) of ammonium (2'S,5S)-1,1'-dibenzyl-2',5-dimethyl-2,5'-dioxo-2,2',5,5'-tetrahydro-1H,1'H-[3,3'-bipyrrol]-4-olate 9b$^{(5,3)}$
$^1$H and $^{13}$C NMR spectra ($d_6$-DMSO) of ammonium (2'$S,5S$)-2',5-dibenzyl-1,1'-bis(2-(1,3-dioxoisindolin-2-yl)ethyl)-2,5'-dioxo-2',2',5,5'-tetrahydro-1$H,1'H$-[3,3'-bipyrrrol]-4olate

9b(6,2)