Site Isolated Base and Acid Mediated Michael Initiated Cyclization Cascades

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General Experimental

Acrolein and crotonaldehyde were distilled prior to use. Methyl vinyl ketone, Amberlyst® A15 and polymer supported BEMP were used as sold. Organic solutions were concentrated under reduced pressure on a Büchi rotary evaporator. Chromatographic purification of products was carried out using Merck Kiesegel 60 silica gel (230-400 mesh). Thin-layer chromatography was carried out using Merck Kiesegel 60 F₂₅₄ (230-400 mesh) fluorescent treated silica which were visualized under UV light (250 nm) or by staining with aqueous potassium permanganate solutions.

¹H and ¹³C spectra were recorded on a Bruker 500 MHz spectrometer and are using ppm for measurement against a TMS internal standard. Data for ¹H are reported as follows: chemical shift (δ ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), integration and coupling constants (Hz). Data for ¹³C are reported in terms of chemical shift. IR spectra were recorded on an ATI Mattson: Genesis Series FTIR spectrometer from a thin film deposited on a sodium chloride plate and only selected absorbances (λmax) are reported. Low resolution mass spectra were recorded on a Fissions VG Trio 2000 quadrupole mass spectrometer. High resolution mass spectra were recorded on a Thermo Finnigan Mat 95XP mass spectrometer.

Proof of Principle Reactions

Amide 5 (50.0 mg, 0.23 mmol) and polymer supported BEMP (10.0 mg, 0.023 mmol) were stirred in dichloromethane (2 mL) at room temperature. Methyl vinyl ketone (22.5 µL, 0.27 mmol) was added via syringe and the mixture was stirred at room temperature for 2 hours. The polymer was
removed by filtration and the filtrate passed through a 2 cm plug of silica. The solution was concentrated to dryness to give adduct 7 (65.3 mg, 100%) as a colourless oil.

Amide 5 (44.0 mg, 0.20 mmol) and Amberlyst® A15 (84.0 mg, 0.40 mmol) were stirred in dichloromethane (2 mL) at room temperature. Methyl vinyl ketone (100 µL, 1.20 mmol) was added \textit{via} syringe and the mixture was stirred at room temperature for 36 hours. The polymers were removed by filtration and the filtrate was concentrated to dryness. Purification \textit{via} flash chromatography, eluting with neat diethyl ether, gave adduct 8 (45.9 mg, 68 %) as a colourless oil.

Amide 5 (44.0 mg, 0.20 mmol), BEMP (5.6 µL, 0.02 mmol) and Amberlyst® A15 (84.0 mg, 0.40 mmol) were stirred in dichloromethane (2 mL) at room temperature. Methyl vinyl ketone (100 µL, 1.20 mmol) was added \textit{via} syringe and the mixture was stirred at room temperature for 36 hours. The polymers were removed by filtration and the filtrate was concentrated to dryness. Purification \textit{via} flash chromatography, eluting with neat diethyl ether, gave adduct 8 (46.2 mg, 68 %) as a colourless oil.

\textbf{N-(2-(1H-Pyrrol-1-yl)ethyl)-2-oxo-1-(3-oxobutyl)cyclopentanecarboxamide 7}

\begin{center}
\includegraphics[width=0.2\textwidth]{image.png}
\end{center}

IR (film) 1729, 1663, 1626 cm\textsuperscript{-1}; \textsuperscript{1}H NMR (500 MHz, CDCl\textsubscript{3}) \(\delta\) 1.74-1.96 (m, 5H), 2.09 (s, 3H, CH\textsubscript{3}), 2.22-2.34 (m, 4H), 2.49-2.54 (m, 1H), 3.48 (dq, 1H, CONHCH\textsubscript{2}\textsuperscript{a}, J 15.3 Hz, 5.4 Hz.), 3.62 (tt, 1H, CONHCH\textsubscript{2}\textsuperscript{b}, J 15.3 Hz, 5.4 Hz), 3.94-4.04 (m, 2H), 6.13 (t, 2H, NCH=CH, J 2.1 Hz), 6.61 (t, 2H, NCH=CH, J 2.1 Hz), 6.79 (t, 1H, NH, J 5.4 Hz); \textsuperscript{13}C NMR (125 MHz, CDCl\textsubscript{3}) \(\delta\) 18.8, 30.0, 30.1, 31.8, 38.3, 38.6, 40.7, 48.5, 59.3, 108.7, 120.6, 169.4, 207.2, 220.2; MS (Cl+) 291 ([M+H]\textsuperscript{+}, 100%); HRMS (ES+) exact mass calculated for [M+H]\textsuperscript{+} (C\textsubscript{16}H\textsubscript{23}N\textsubscript{2}O\textsubscript{3}) requires \(m/z\) 291.1703, found \(m/z\) 291.1696.

\textbf{N-(2-(2,5-Bis(3-oxobutyl)-1H-pyrrol-1-yl)ethyl)-2-oxocyclopentanecarboxamide 8}
IR (film) 1741, 1712, 1657 cm\(^{-1}\); \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 1.79-1.87 (m, 1H), 2.04-2.11 (m, 1H), 2.18 (s, 6H, CH\(_3\)), 2.23-2.38 (m, 4H), 2.80-2.82 (m, 8H), 3.01 (t, 1H, COCH(\(\text{CH}_2\))CO, J 9.5 Hz), 3.47 (ddd, 2H, NHCH\(_2\)CH\(_2\), J 13.5 Hz, 7.0 Hz, 3.3 Hz), 3.94 (t, 2H, NHCH\(_2\)CH\(_2\), J 7.0 Hz), 5.74 (s, 2H, C=CH), 7.02 (br t, 1H, NH, J 3.3 Hz); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \(\delta\) 20.3, 20.4, 25.9, 30.1, 38.9, 40.1, 42.1, 42.4, 54.2, 104.4, 131.2, 167.5, 207.9, 216.4; MS (Cl\(^+\)) 361 ([M+H]\(^+\), 100 %); HRMS (ES\(^+\)) exact mass calculated for [M+H]\(^+\) (C\(_{20}\)H\(_{29}\)N\(_2\)O\(_4\)) requires m/z 361.2122, found m/z 361.2133.

**General Method for Cascade Reactions**

Starting material (0.20 mmol), polymer supported BEMP (9.0 mg, 0.02 mmol) and Amberlyst® A15 (85.0 mg, 0.40 mmol) were stirred in dichloromethane (2 mL) at room temperature. Michael acceptor (0.22 mmol) was added via syringe and the mixture was stirred at room temperature for 24 hours. The polymers were removed via filtration and the filtrate was passed through a 2 cm plug of silica and concentrated to dryness to give an essentially pure mixture of diastereomers. Further chromatography allowed isolation of a small amount of the major diastereomer for characterisation where possible.

**11a'-Methyl-5',6',11',11a'-tetrahydrospiro[cyclopentane-1,9'-pyrido[1,2-a]pyrrolo[2,1-c]pyrazine]-2,8'(10'H)-dione 9**

The title compound was isolated as a colourless gum (45.2 mg, 83 %) as a 1:1 mixture of diastereomers (R\(_f\) 0.27 and 0.30 in neat diethyl ether). Characterisation data of the least polar diastereomer is given.
IR (film) 1740, 1625 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 1.59-1.63 (m, 1H), 1.68 (s, 3H, CH₃), 1.83-1.90 (m, 1H), 1.93-1.98 (m, 1H), 2.03 (td, 1H, J 14.3 Hz, 4.2 Hz), 2.14-2.20 (m, 1H), 2.25 (td, 1H, J 11.4 Hz, 2.4 Hz), 2.29-2.34 (m, 1H), 2.35-2.38 (m, 1H), 2.47 (dt, 1H, J 12.8 Hz, 7.9 Hz), 2.55 (quintet, 1H, J 14.0 Hz), 3.21 (ddd, 1H, CONCH₂ᵃ, J 14.0 Hz, 12.4 Hz, 4.5 Hz), 3.88 (td, 1H, CONCH₂CH₂O, J 12.4 Hz, 4.5 Hz), 3.95 (ddd, 1H, CONCH₂CH₂O, J 12.4 Hz, 4.5 Hz, 1.5 Hz), 4.91 (ddd, 1H, CONCH₂CH₂O, J 14.0 Hz, 4.5 Hz, 1.5 Hz), 5.87 (dd, 1H, J 3.5 Hz, 1.5 Hz), 6.16 (dd, 1H, J 3.5 Hz, 2.5 Hz), 6.51 (dd, 1H, J 2.5 Hz, J 1.5 Hz); ¹³C NMR (125 MHz, CDCl₃) δ 19.9, 26.3, 28.4, 34.1, 35.8, 37.2, 39.1, 44.4, 56.5, 57.1, 102.1, 108.5, 118.5, 134.6, 170.3, 218.1; MS (CI⁺) 273 ([M+H]⁺, 100%); HRMS (ES⁺) exact mass calculated for [M+H]⁺ (C₁₆H₂₁N₂O₂) requires m/z 273.1598, found m/z 273.1604.

Ethyl 12b-methyl-4-oxo-3-(3-oxobutyl)-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-a]quinolizine-3-carboxylate 10

[Chemical structure image]

After further purification by flash chromatography (eluting with neat diethyl ether), the title compound was isolated as a colourless oil (45.3 mg, 57 %) as a 3:1 mixture of diastereomers (Rf 0.20 and 0.27 in neat diethyl ether). Characterisation data of the major diastereomer is given.

IR (film) 1735, 1720, 1610 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 1.29 (t, 3H, CH₃CH₂O, J 7.0 Hz), 1.73 (s, 3H, CCH₃), 1.78 (ddd, 1H, J 13.1 Hz, J 5.2 Hz, J 3.8 Hz), 2.07-2.13 (m, 1H), 2.11 (s, 3H, COCH₃), 2.15-2.21 (m, 3H), 2.43-2.48 (ddd, 1H, J 13.3 Hz, J 11.5 Hz, J 4.5 Hz), 2.54-2.61 (ddd, 1H, J 17.9 Hz, J 11.5 Hz, J 4.5 Hz), 2.73-2.85 (m, 3H), 3.05 (dd, 1H, CONCH₂ᵃ, J 13.3 Hz, 9.0 Hz, 4.2 Hz), 4.18 (dq, 1H, CH₃CH₂O, J 11.0 Hz, 7.0 Hz), 4.30 (dq, 1H, CH₃CH₂O, J 11.0 Hz, 7.0 Hz), 5.00 (dd, 1H, CONCH₂ᵇ, J 13.3 Hz, 4.0 Hz, 0.8 Hz), 7.13 (td, 1H, J 7.8 Hz, J 0.8 Hz), 7.19 (td, 1H, J 7.8 Hz, J 0.8 Hz), 7.34 (d, 1H, J 8.0 Hz), 7.50 (d, 1H, J 8.0 Hz), 7.85 (br s, 1H, NH); ¹³C NMR (125 MHz, CDCl₃) δ 14.5, 21.7, 27.0, 27.6, 29.8, 32.5, 37.4, 40.0, 53.7, 57.6, 61.9, 83.6, 109.1, 111.3, 118.9, 120.3, 122.7, 127.1, 136.4, 137.9, 168.5, 173.3, 208.7; MS (Cl⁺) 397 ([M+H]⁺, 100%); HRMS (ES⁺) exact mass calculated for [M+H]⁺ (C₂₃H₂₉N₂O₄) requires m/z 397.2122, found m/z 397.2111.
12b'-Ethyl-6',7',12',12b'-tetrahydro-1'H-spiro[cyclopentane-1,3'-indolo[2,3-a]quinolizine]-
2,4'(2'H)-dione 11

The title compound was isolated as a colourless gum (65.2 mg, 97 %) as a 3:1 mixture of
diastereomers (R_f 0.26 and 0.33 in neat diethyl ether). Characterisation data of the major diastereomer
is given.

IR (film) 1738, 1603 cm\(^{-1}\); \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 1.09 (t, 3H, CH\(_3\), J 9.5 Hz), 1.59 (m, 1H), 1.85 (m, 3H), 2.11-2.36 (m, 5H), 2.47-2.61 (m, 3H), 2.72-2.86 (m, 2H), 3.13 (ddd, 1H, CONCH\(_a\), J 16.6 Hz, 14.5 Hz, 6.2 Hz), 5.02 (ddd, 1H, CONCH\(_b\), J 17.0 Hz, 6.8 Hz, 2.2 Hz), 7.13 (t, 1H, J 8.5 Hz), 7.20 (td, 1H, J 8.5 Hz, 1.5 Hz), 7.34 (d, 1H, J 10.0 Hz), 7.51 (d, 1H, J 10.0 Hz), 7.82 (br s, 1H, NH); \(^1^3\)C NMR (125 MHz, CDCl\(_3\)) \(\delta\) 9.87, 19.9, 21.1, 25.8, 28.7, 29.7, 32.0, 37.5, 39.1, 56.5, 59.9, 108.8, 110.9, 118.5, 119.9, 122.2, 126.6, 135.9, 137.0, 170.2, 218.1; MS (Cl+) 337 ([M+H]\(^+\), 100%); HRMS (ES+) exact mass calculated for [M+H]\(^+\) \((\text{C}_{21}\text{H}_{25}\text{N}_2\text{O}_2)\) requires m/z 337.1911, found m/z 337.1911.

12b'-Methyl-6',7',12',12b'-tetrahydro-1'H-spiro[cyclohexane-1,3'-indolo[2,3-a]quinolizine]-
2,4'(2'H)-dione 12

The title compound was isolated as a white powder (67.2 mg, 100 %) as a 3:1 mixture of
diastereomers (R_f 0.37 and 0.42 in neat diethyl ether). Characterisation data of the major diastereomer
is given.

mp 226-228 °C; IR (film) 1739, 1602 cm\(^{-1}\); \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 0.83-0.90 (m, 1H), 1.67 (m, 1H), 1.70 (s, 3H, CH\(_3\)), 1.76 (ddd, 1H, J 13.8 Hz, 4.9 Hz, 3.0 Hz), 1.82-1.87 (m, 1H), 1.93-2.01 (m, 2H), 2.07 (td, 1H, J 13.6 Hz, 3.5 Hz), 2.13-2.19 (m, 1H), 2.40-2.50 (m, 3H), 2.75 (td, 1H, J 15.1 Hz, 3.0 Hz), 2.80-2.86 (m, 2H), 3.05 (dt, 1H, CONCH\(_a\), J 12.7 Hz, 4.5 Hz), 5.04 (dd, 1H, CONCH\(_b\), J 12.7 Hz, 4.5 Hz), 7.13 (t, 1H, J 7.0 Hz), 7.20 (t, 1H, J 7.0 Hz), 7.34 (d, 1H, J 8.7 Hz),
7.50 (d, 1H, J 7.7 Hz), 7.85 (br s, 1H, NH); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 20.6, 21.2, 25.3, 26.0, 26.4, 31.6, 36.2, 37.1, 39.8, 56.7, 56.7, 108.6, 110.9, 118.5, 119.9, 122.2, 126.7, 136.0, 138.0, 169.6, 210.7; MS (Cl+) 354 ([M+NH$_4^+$], 100%); HRMS (ES+) exact mass calculated for [M+H]$^+$ (C$_{21}$H$_{25}$N$_2$O$_2$) requires m/z 337.1911, found m/z 337.1919.

12b'-Methyl-6',7',12',12b'-tetrahydro-1'H-spiro[cycloheptane-1,3'-indolo[2,3-a]quinolizine]-2,4'(2'H)-dione 13

![Chemical structure](image)

The title compound was isolated as a colourless crystalline solid (64.0 mg, 91 %) as a 3:1 mixture of diastereomers (R$_f$ 0.61 and 0.66 in neat diethyl ether). Characterisation data of the major diastereomer is given.

mp 242-243 $^\circ$C; IR (film) 1699, 1603 cm$^{-1}$; $^1$H NMR (500 MHz, CDCl$_3$) δ 1.39-1.46 (m, 2H), 1.53-1.63 (m, 2H), 1.77 (s, 3H, CH$_3$), 1.82-2.05 (m, 5H), 2.19 (dt, 1H, J 16.8 Hz, 4.9 Hz), 2.30-2.41 (m, 1H), 2.62 (ddd, 1H, J 14.5 Hz, 10.0 Hz, 2.1 Hz), 2.73-2.88 (m, 3H), 3.06 (ddd, 1H, J 19.7 Hz, 14.0 Hz, 6.5 Hz), 3.37 (td, 1H, CONC$_{\text{a}}$, J 16.0 Hz, 3.0 Hz), 4.96 (ddd, 1H, CONC$_{\text{b}}$, J 16.0 Hz, 5.5 Hz, 2.0 Hz), 7.15 (t, 1H, J 9.2 Hz), 7.22 (t, 1H, J 9.2 Hz), 7.36 (d, 1H, J 10.4 Hz) 7.52 (d, 1H, J 10.4 Hz), 7.81 (br s, 1H, NH); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 21.2, 22.8, 24.8, 25.8, 26.6, 30.6, 31.9, 34.3, 37.1, 43.3, 56.7, 59.1, 108.2, 110.9, 118.5, 119.9, 122.2, 126.6, 136.0, 138.3, 169.9, 212.8; MS (Cl+) 351 ([M+H]$^+$, 100%); HRMS (ES+) exact mass calculated for [M+H]$^+$ (C$_{22}$H$_{27}$N$_2$O$_2$) requires m/z 351.2067, found m/z 351.2059.

tert-Butyl 8a'-methyl-2,5'-dioxohexahydro-1'H-spiro[cyclopentane-1,6'-imidazo[1,2-a]pyridine]-1'-carboxylate 14

![Chemical structure](image)

The title compound was isolated as an off-white crystalline solid (50.1 mg, 78 %) as a 1:1 mixture of diastereomers (R$_f$ 0.08 and 0.11 in neat diethyl ether). Characterisation data of the least
polar diastereomer is given. NMR signals are broadened due to contributions from different rotameric forms.

mp 98-100 °C; IR (film) 1741, 1696, 1638 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 1.48 (s, 9H, C(CH₃)₃), 1.49 (m, 1H), 1.65-1.73 (m, 3H), 1.84-2.00 (m, 3H), 2.16 (td, 1H, J 15.1 Hz, 3.3 Hz), 2.20-2.33 (m, 1H), 2.34 (dq, 1H, J 18.5 Hz, 4.2 Hz), 2.36-2.56 (m, 2H), 2.65-2.92 (br m, 1H), 3.28 (dt 1H, J 12.0 Hz, 9.0 Hz), 3.40 (q, 1H, J 9.0 Hz), 3.53-3.62 (m, 1H), 4.29 (m, 1H, CONC₄H₂a); ¹³C NMR (125 MHz, CDCl₃) δ 19.6, 20.0, 22.5, 27.9, 28.5, 36.8, 37.0, 37.4, 38.9, 43.5, 80.1, 80.8, 152.5, 168.4, 216.5; MS (CI⁺) 323 ([M+H]⁺, 100%); HRMS (ES+) exact mass calculated for [M+H]⁺ (C₁₇H₂₇N₂O₄) requires m/z 323.1965, found m/z 323.1959.

11a'-Methyl-5',6',11',11a'-tetrahydrospirocyclopentane-1,9'-pyrido[1,2-a]indolo[2,1-c]pyrazine-2,8'(10'H)-dione 15

In a slight modification to the general procedure, starting material, polymer supported BEMP and methyl vinyl ketone (in the quantities indicated above) were stirred in dichloromethane for 2 hours before the addition of Amberlyst® A15. The title compound was isolated as an off-white crystalline solid (61.9 mg, 97 %) as a 3:1 mixture of diastereomers (Rf 0.46 and 0.51 in neat diethyl ether). Characterisation data of the major diastereomer is given.

mp 130-134 °C; IR (film) 1740, 1629 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 1.67 (ddd, 1H, J 13.5 Hz, 4.5 Hz, 3.0 Hz), 1.80 (s, 3H, CH₃), 1.83-1.96 (m, 2H), 2.13-2.22 (m, 2H), 2.27-2.60 (m, 5H), 3.23 (ddd, 1H, CONCH₂CH₂a, 14.1 Hz, 12.4 Hz, 4.5 Hz), 3.91 (td, 1H, CONCH₂a, J 12.4 Hz, 4.5 Hz), 4.21 (ddd, 1H, CONCH₂b, J 12.4 Hz, 4.5 Hz, 1.5 Hz), 5.08 (ddd, 1H, J 14.1 Hz, 4.5 Hz, 1.5 Hz), 6.26 (s, 1H), 7.13 (td, 1H, J 6.9 Hz, J 0.8 Hz), 7.21 (td, 1H, J 6.9 Hz, J 0.8 Hz), 7.29 (d, 1H, J 8.0 Hz), 7.57 (d, 1H, J 8.0 Hz); ¹³C NMR (125 MHz, CDCl₃) δ 19.8, 26.3, 28.6, 34.0, 35.5, 37.1, 37.1, 39.0, 41.5, 56.4, 57.3, 95.7, 108.9, 120.4, 121.4, 128.0, 135.3, 141.7, 170.3, 217.8; MS (Cl⁺) 323 ([M+H]⁺, 100%); HRMS (ES+) exact mass calculated for [M+H]⁺ (C₂₀H₂₃N₂O₂) requires m/z 323.1754, found m/z 323.1750.
11b'-Methyl-1',6',7',8',9',10',11' octahydrospiro[cyclopentane-1,3'-pyrido[2,1-alisoquinoline]-2,4'(2'H)-dione 16

The title compound was isolated as a colourless oil (49.0 mg, 85 %) as a mixture of isomers (R_f 0.45 in neat diethyl ether).

IR (film) 1741, 1621 cm

^-1; ^1H NMR (500 MHz, CDCl_3) δ 0.84-2.73 (br m, 24H), 3.32 (m, 1H, CONCH_2a''), 4.55-4.76 (br m, 1H, CONCH_2b', CONCH_2b'', CONCH_2b'''), 5.33 (m, 1H, CH'=C), 5.62 (br s, CH'''=C); ^13C NMR (125 MHz, CDCl_3) δ 14.1, 19.6, 19.7, 19.7, 19.8, 19.9, 20.5, 22.0, 22.2, 22.5, 23.2, 23.4, 24.4, 24.6, 25.0, 25.5, 25.7, 26.2, 29.7, 29.9, 30.1, 30.4, 30.9, 31.9, 33.7, 34.0, 34.8, 36.5, 36.8, 36.9, 37.3, 37.5, 37.6, 38.6, 38.8, 39.2, 45.5, 48.1, 55.9, 56.2, 56.3, 58.7, 59.9, 60.1, 124.2, 124.4, 127.4, 133.2, 133.7, 134.2, 169.6, 169.6, 170.1, 217.7, 218.0; MS (CI+) 288 ([M+H]^+, 100%); HRMS (ES+) exact mass calculated for [M+H]^+ (C_{18}H_{26}NO_2) requires m/z 288.1958, found m/z 288.1964.

9',10'-Dimethoxy-2'-methyl-1',6',7',11b'-tetrahydrospiro[cyclopentane-1,3'-pyrido[2,1-alisoquinoline]-2,4'(2'H)-dione 17

The title compound was synthesized on 0.10 mmol scale (half that indicated above) and isolated as a colourless gum (29.2 mg, 85 %) as a 7:5:5:3 mixture of inseparable diastereomers (R_f 0.37-0.46 in neat diethyl ether).

IR (film) 1738, 1622 cm

^-1; ^1H NMR (500 MHz, CDCl_3) δ 0.92 (d, 3H, CHCH_3', J 7.2 Hz), 1.04 (d, 3H, CHCH_3'', J 3.5 Hz), 1.05 (d, 3H, CHCH_3''', J 3.5 Hz), 1.15 (d, 3H, CHCH_3''''', J 7.2 Hz), 1.50-1.98 (m, 11H), 3.41-3.54 (m, 1H, CONCH_2a'''''), 3.78-3.92 (5 x s, 24H, 2 x OMe', OMe''', OMe''''', OMe'''''''), 4.61-4.80 (br m, 8H, CONCH_2b', CONCH_2b'', CONCH_2b''', CONCH_2b'''''', CONCH_2b''''''', CONCH_2b'''''''', CONCH_2b''''''''', CONCH_2b'''''''''', CONCH_2b''''''''''', CONCH_2b'''''''''''', CONCH_2b''''''''''''', CONCH_2b'''''''''''''', CONCH_2b''''''''''''''', CONCH_2b''''''''''''''''), 6.61-6.66 (br m, 8H, 2 x Ar-H', Ar-H'', Ar-H''', Ar-H'''', Ar-H''''', Ar-H''''''); ^13C NMR (125 MHz, CDCl_3) δ 16.1, 16.4, 16.7, 19.6, 19.9, 20.2, 21.0, 28.3, 28.5, 28.6, 29.2, 30.2, 31.2, 31.3, 32.1, 32.1, 33.0, 35.1, 35.2, 35.3, 35.7, 38.5, 39.8, 40.2, 40.2, 40.6, 41.0, 41.1, 53.4,
55.9, 56.1, 56.2, 58.6, 59.6, 59.7, 107.5, 107.7, 107.8, 108.2, 111.4, 111.4, 111.8, 111.8, 111.9, 126.8, 127.2, 127.6, 128.7, 128.8, 128.9, 129.0, 147.6, 147.7, 147.7, 147.9, 147.9, 169.5, 169.9, 171.0, 216.8, 217.6; MS (CI+) 344 ([M+H]+, 100%); HRMS (ES+) exact mass calculated for [M+H]+ (C_{20}H_{26}NO_{4}) requires m/z 344.1856, found m/z 344.1861.

9',10'-Dimethoxy-11b'-methyl-1',6',7',11b'-tetrahydrospiro[cyclopentane-1,3'-pyrido[2,1-a]isoquinoline]-2,4'(2'H)-dione 18

![Chemical structure of 9',10'-Dimethoxy-11b'-methyl-1',6',7',11b'-tetrahydrospiro[cyclopentane-1,3'-pyrido[2,1-a]isoquinoline]-2,4'(2'H)-dione 18](image)

The title compound was isolated as a white powder (68.6 mg, 100 %) as a 2:1 mixture of inseparable diastereomers (R_f 0.23 in neat diethyl ether).

mp 148-150 °C; IR (film) 1740, 1619 cm\(^{-1}\); \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 1.57-1.61 (m, 2H), 1.68 (s, CCH\(_3\), CCH\(_3\)'), 1.79-1.95 (m, 7H), 2.08-2.61 (m, 13H), 2.80-2.91 (m, 4H), 3.84, 3.79 (2 x s, 12H, OCH\(_3\), OCH\(_3\)'), 4.80-4.92 (m, 2H, CONCH\(_a\), CONCH\(_a\)'), 6.60 (d, 2H, Ar-H), 6.57 (s, 2H, Ar-H); \(^13\)C NMR (125 MHz, CDCl\(_3\)) \(\delta\) 18.6, 18.8, 25.2, 25.5, 26.8, 27.8, 28.1, 32.3, 33.4, 34.8, 35.5, 36.2, 36.5, 38.2, 53.7, 54.8, 55.1, 55.2, 57.7, 82.0, 82.2, 107.2, 107.3, 110.3, 110.4, 124.8, 125.5, 133.3, 133.6, 146.6, 146.6, 146.7, 168.0, 169.0, 215.7, 217.4; MS (CI+) 344 ([M+H]+, 100%); HRMS (ES+) exact mass calculated for [M+H]+ (C_{20}H_{26}NO_{4}) requires m/z 344.1856, found m/z 344.1857.

9',10'-Dimethoxy-1',6',7',11b'-tetrahydrospiro[cyclopentane-1,3'-pyrido[2,1-a]isoquinoline]-2,4'(2'H)-dione 19

![Chemical structure of 9',10'-Dimethoxy-1',6',7',11b'-tetrahydrospiro[cyclopentane-1,3'-pyrido[2,1-a]isoquinoline]-2,4'(2'H)-dione 19](image)

The title compound was synthesized on 0.10 mmol scale (half that indicated above) and isolated as a white powder (30.9 mg, 94 %) as a 1:1 mixture of inseparable diastereomers (R_f 0.43 in neat diethyl ether).

mp 62-65 °C; IR (film) 1738, 1622 cm\(^{-1}\); \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 1.66-1.76 (m, 3H), 1.83-1.94 (m, 5H), 2.06 (ddd, 1H, J 13.3 Hz, 4.8 Hz, 3.1 Hz), 2.15-2.23 (m, 3H), 2.25-2.43 (m, 5H), 2.54-2.64 (m, 4H), 2.77-2.95 (m, 5H), 3.84, 3.86 (2 x s, 12H, OCH\(_3\), OCH\(_3\)'), 4.62 (dd, 1H, NCH, J...
11.5 Hz, 4.5 Hz), 4.69 (dd, 1H, NCH', J 11.5 Hz, 4.5 Hz), 4.76-4.83 (m, 2H, CONCHa, CONCHa'), 6.61 (s, 2H, Ar-H), 6.65 (d, 2H, Ar-H); δ (125 MHz, CDCl₃) δ 19.6, 19.8, 26.8, 27.8, 28.4, 28.6, 29.0, 36.7, 36.9, 37.8, 39.2, 39.8, 40.3, 55.2, 55.9, 56.1, 56.3, 56.6, 56.7, 108.0, 108.1, 111.4, 111.5, 127.0, 127.5, 128.6, 128.7, 147.7, 147.7, 147.8, 147.9, 169.1, 170.0, 216.8; MS (CI+) 330 ([M+H]⁺, 100%); HRMS (ES+) exact mass calculated for [M+H]⁺ (C₁₉H₂₄N₂O₄) requires m/z 330.1700, found m/z 300.1695.

3-Acetyl-3-benzyl-12b-methyl-1,2,3,6,7,12b-hexahydroindolo[2,3-a]quinolizin-4(12H)-one 20

![3-Acetyl-3-Benzyl-12b-Methyl-1,2,3,6,7,12b-Hexahydroindolo[2,3-a]Quinolizin-4(12H)-One 20](image)

In a slight modification to the general procedure, starting material, polymer supported BEMP and methyl vinyl ketone (in the quantities indicated above) were stirred in dichloromethane for 2 hours before the addition of Amberlyst® A15. The title compound was isolated as a colourless crystalline solid (98.9 mg, 99 %) as a 2:1 mixture of diastereomers (Rᶠ 0.37 and 0.61 in neat diethyl ether). Characterisation data of the major diastereomer is given.

mp 220-223 °C; IR (film) 1705, 1604 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 1.09 (s, 3H, CCH₃), 1.82-1.91 (m, 2H), 1.96-2.05 (m, 1H), 2.09-2.17 (m, 1H), 2.32 (s, 3H, COCH₃), 2.74-2.85 (m, 3H), 2.91-2.97 (ddd, 1H, J 13.3 Hz, 11.0 Hz, 5.2 Hz), 3.72 (d, 1H, PhCH₂a, J 13.3 Hz), 5.16 (ddd, 1H, CONCH₂a, J 12.5 Hz, 5.2 Hz, 2.0 Hz), 7.11 (td, 1H, J 7.5 Hz, 0.8 Hz), 7.17 (td, 1H, J 8.5 Hz, 0.8 Hz), 7.21-7.31 (m, 6H), 7.48 (d, 1H, J 8.0 Hz), 7.77 (br s, 1H, NH); ¹³C NMR (125 MHz, CDCl₃) δ 21.3, 23.2, 25.2, 28.1, 33.0, 37.1, 41.9, 56.8, 61.3, 107.9, 110.9, 118.5, 119.9, 122.2, 126.5, 126.9, 128.3, 130.7, 136.0, 136.8, 138.2, 168.9, 208.0; MS (Cl+) 387 ([M+H]⁺, 100%); HRMS (ES+) exact mass calculated for [M+H]⁺ (C₂₅H₂₇N₂O₂) requires m/z 387.2067, found m/z 387.2073.

12b'-Methyl-6',7',12',12b'-tetrahydro-1'H-spiro[cyclopentane-1,3'-indolo[2,3-a]quinolizine]-2,4'(2'H)-dione 21

![12b'-Methyl-6',7',12',12b'-Tetrahydro-1'H-Spiro[cyclopentane-1,3'-Indolo[2,3-a]Quinolizine]-2,4'(2'H)-Dione 21](image)

The title compound was isolated as a colourless crystalline solid (58.0 mg, 90 %) as a 3:1 mixture of diastereomers (Rᶠ 0.32 and 0.28 in neat diethyl ether). Characterisation data of the major diastereomer is given.
mp 257 °C; IR (film) 1735, 1602 cm⁻¹; ¹H NMR (500 MHz, DMSO) δ 0.73 (s, 3H), 0.76 (t, 1H, J 3.5 Hz), 0.83-0.93 (m, 2H), 1.02 (quintet, 1H, J 5.9 Hz), 1.07-1.18 (m, 2H), 1.27-1.46 (m, 3H), 1.53-1.66 (m, 2H), 1.74 (dd, 1H, J 15.2 Hz, 3.1 Hz), 2.04 (dt, 1H, CONCH₂, J 12.8 Hz, 3.9 Hz), 3.84 (dd, 1H, CONCH₂, J 12.8 Hz, 5.0 Hz), 6.06 (t, 1H, J 7.5 Hz), 6.15 (t, 1H, J 7.5 Hz), 6.40 (d, 1H, J 8.4 Hz), 6.47 (d, 1H, J 7.0 Hz), 10.06 (br s, 1H, NH); ¹³C NMR (125 MHz, DMSO) δ 19.4, 20.8, 25.1, 25.1, 31.6, 35.8, 38.8, 56.2, 56.4, 105.6, 111.0, 117.9, 118.6, 121.0, 126.0, 136.0, 139.2, 169.6, 218.1; MS (Cl⁺) 323 ([M+H]⁺, 100%); HRMS (ES⁺) exact mass calculated for [M+H]⁺ (C₂₀H₂₃N₂O₂) requires m/z 323.1754, found m/z 323.1748.

**Flow Reactor Procedure**

1.20 g of polymer supported BEMP and 2.20 g of Amberlyst® A15 were placed separately inside a 10 x 0.46 cm and a 15 x 0.46 cm steel cylinder respectively. Starting material 22 (500 mg, 1.64 mmol) and methyl vinyl ketone (163 µL, 1.97 mmol) were dissolved in dichloromethane (10 mL) and passed through the cylinders in series at 0.1 ml/min. After all the solution has been passed through, another 10 mL of dichloromethane was passed through to wash the resins. The solvent was removed in vacuo and the crude material was passed through a 2 cm plug of silica to give 550 mg of an off-white foam of which approximately 85 % was product. Further chromatography allowed the title compound to be isolated as a colourless gum (442 mg, 75 %) as a 1:1 mixture of diastereomers (R₉ 0.25 and 0.28 in neat diethyl ether). Characterisation data of the most polar diastereomer is given.

9',10'-Dimethoxy-11b'-methyl-1',6',7',11b'-tetrahydrospiro[cyclohexane-1,3'-pyrido[2,1-alisoquinoline]-2,4'(2'H)-dione 23

![Chemical Structure](image)

IR (film) 1706, 1621 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 1.61 (s, 3H, CCH₃), 1.63-1.68 (m, 2H), 1.70 (ddd, 1H, J 14.2 Hz, 5.0 Hz, 3.5 Hz), 1.77-1.93 (m, 4H), 2.19 (ddd, 1H, J 13.3 Hz, 4.5 Hz, 3.1 Hz), 2.33-2.44 (m, 3H), 2.57 (d, 1H, J 16.3 Hz), 2.77-2.88 (m, 2H), 2.89 (td, 1H, J 12.5 Hz, 3.1 Hz), 3.83 (s, 3H, OMe), 3.84 (s, 3H, OMe), 4.85 (m, 1H, CONCH₂), 6.56 (s, 1H, Ar-H), 6.59 (s, 1H, Ar-H); ¹³C NMR (125 MHz, MeOD) δ 21.3, 26.1, 27.2, 27.8, 29.7, 34.2, 35.9, 37.8, 40.3, 56.4, 56.8, 58.4, 60.4, 110.3, 113.1, 127.4, 135.9, 149.3, 149.3, 172.2, 212.6; MS (Cl⁺) 358 ([M+H]⁺, 100%); HRMS (ES⁺) exact mass calculated for [M+H]⁺ (C₂₁H₂₈NO₄) requires m/z 358.2013, found m/z 358.2018.