Expedient Diels-Alder Cycloadditions with ortho-Quinodimethanes in a High Temperature/Pressure Flow Reactor

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Supporting information

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General Information

All reagents were purchased from Sigma-Aldrich, Enamine or Alfa Aesar and used without further purification. 2-(1,3-dihydrobenzo[c]thiophen-1-yl)acetic acid was ordered from WuXi AppTec and used without further purification. Flash chromatography was performed using a Teledyne ISCO CombiFlash® Rf automated purification system and RediSep® Rf Gold silica columns. Preparative HPLC was performed on either an Agilent automated preparative-scale purification system equipped with a Waters Sunfire C8 5m column (150 x 30 mm) or on a Phenomenex Luna C8 5m 100Å AXIA column (50mm x 21.2mm). A gradient of acetonitrile (A) and 0.1% trifluoroacetic acid in water (B) was used, at a flow rate of 30 mL/min (0-0.5 min 5% A, 0.5-6.5 min linear gradient 5-100% A, 6.5-8.5 min 100% A, 8.5-9.0 min linear gradient 100-5% A, 9.0-10 min 5% A). Proton nuclear magnetic resonance spectra (1H NMR, 500 or 400 MHz) and proton decoupled carbon nuclear magnetic resonance spectra (13C NMR, 126 or 100 MHz) were obtained in deuterochloroform (CDCl₃), deuterodimethylsulfoxide (DMSO-d₆) or deuteropyridine (pyridine-d₅) with residual solvent as the internal standard unless otherwise noted. Data for NMR are reported as follows: chemical shift as parts per million (ppm), coupling constants as scalar values in Hz and integration. Mass spectra (MS) were obtained by ionizing samples via positive electron spray ionization (ESI+) or desorption chemical ionization (DCI+).
General Instrumentation:

We used a commercially available high-temperature and high-pressure Phoenix™ flow reactor from ThalesNano, designed to allow reactions at up to 450°C and at high pressure. The reactor coil consists of a stainless steel tubing (1.0 mm in diameter) of 2 mL volume, which is wrapped around a metallic housing tube and placed inside the Phoenix. Our flow platform consisted of four components: a JASCO PU-2085 plus HPLC pump, a JASCO BP-2080 Plus back pressure regulator, a Tecan MiniPrep Automated Sample Processor and a 10-port Valco Injector valve in addition to the Phoenix Flow Reactor™. The HPLC pump allowed for a range of flow rates from 0.01 to 4.00 mL/min and along with the variable back pressure regulator, a wide array of residence times, pressures and temperatures could readily be assessed. Equilibration of the reactor was achieved by flushing with tetrahydrofuran (THF) at 0.5 mL/min and pressurized to desired pressure (100 - 120 bar). The temperature on the Phoenix was set to desired temperature (300 °C) and allowed to equilibrate. Equilibration of the reactor temperature was only required for the first run each day. The configuration allowed for automatically increasing temperature
with successive runs. The 10-port injector valve was fitted with a pair of stainless steel 5mL loops configured in a last-in-first-out flow mode. With this configuration, we were able to inject variable substrate volumes without having to fill the entire loop.
Optimization studies

1) Batch studies

\[
\text{1a} + \text{2a, 2 equiv} \xrightarrow{1,2 \text{ DCB (0.2 M)}} \text{Reflux, 6h}} \quad \text{3a, 100% conv, 1.3:1 cis/trans}
\]

2) Biotage Microwave reactor

\[
\text{1a} + \text{2a, 2 equiv} \xrightarrow{\text{THF (0.2M)}} \mu w, 180^\circ C, 1h} \quad \text{3a, 7% conv, 1:1 cis/trans}
\]

3) Phoenix Flow reactor

\[
\text{1a} \xrightarrow{\text{Phoenix}} \text{2 mL stainless steel loop}} \quad \text{3a, dimer}
\]

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<th>Solvent (conc)</th>
<th>Temp.(°C)</th>
<th>Pressure (bar)</th>
<th>Flow rate (mL/s)</th>
<th>3a (%)(^a), cis/trans ratio</th>
<th>Dimer (%)(^a)</th>
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*Yields based on ¹H NMR spectroscopic analysis using p-nitroacetophenone as an internal standard. |  
| Isolated in 85% yield. |  
| 2 equiv of pTsOH as additive. |  

**Experimental Procedure 1 (Table 1)**

The flow rate on the Phoenix reactor was set to 4.0 mL/min, the back-pressure regulator set to 120 bar, and the temperature set to 300 °C. A 4 mL vial was charged with 1-benzocyclobutanecarbonitrile (0.15 mmol, 19 mg), imine dienophile (2 equiv, 0.3 mmol) and 750 μL of THF, and the reaction mixture then injected into the Phoenix using the autosampler. The crude reaction mixtures were collected in 20 mL scintillation vials, concentrated, and purified by column chromatography unless otherwise indicated.

6,8,13,13a-tetrahydro-5H-isoquinolino[3,2-a]isoquinoline-13-carbonitrile (3a)

Following experimental procedure 1 with 3,4-dihydroisoquinoline (2 equiv, 0.3 mmol, 39 mg), product 3a was formed in a 1.3:1 cis/trans ratio based on ¹H NMR spectroscopic analysis of the crude material. The title compound was isolated in 85% yield (0.13 mmol, 33 mg) as a white powder. Crystallization of the evaporated mixture from dichloromethane/ether affords the cis product.

¹H NMR (500 MHz, CDCl₃) δ 7.34 – 7.15 (m, 8H), 4.37 (d, J = 3.2 Hz, 1H), 4.17 (d, J = 15.2 Hz, 1H), 4.03 – 3.92 (m, 1H), 3.79 (d, J = 15.2 Hz, 1H), 3.32 (ddd, J = 17.3, 12.2, 5.2 Hz, 1H), 3.22 (ddd, J = 10.9, 5.2, 4.4 Hz, 1H).

¹³C NMR (126 MHz, CDCl₃) δ 136.1, 134.8, 133.4, 129.3, 129.3, 128.4, 128.4, 127.2, 127.1, 126.8, 126.6, 125.3, 119.1, 61.3, 57.7, 50.3, 39.3, 29.3.


(11R,11aR)-2,3,4,6,11,11a-hexahydro-1H-pyrido[1,2-b]isoquinoline-11-carbonitrile (3b)

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Following experimental procedure 1 with 2,3,4,5-tetrahydropyridine (2 equiv, 0.3 mmol, 25 mg), product 3b was formed in a 1.9:1 cis/trans ratio based on $^1$H NMR spectroscopic analysis of the crude material. Both endo and exo products of the title compound were isolated using prep-HPLC (15-45% NH$_4$OAc/ACN method).

Isolated in 28% yield (0.04 mmol, 9 mg) as a white powder.

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.30 – 7.31 (m, 3H), 7.10 (d, $J$ = 7.4 Hz, 1H), 4.05 (d, $J$ = 15.8 Hz, 1H), 3.82 (d, $J$ = 3.4 Hz, 1H), 3.40 (d, $J$ = 15.8 Hz, 1H), 3.18 (d, $J$ = 11.5 Hz, 1H), 2.45 (dt, $J$ = 10.8, 3.7 Hz, 1H), 2.30 – 2.08 (m, 1H), 2.01 – 1.83 (m, 3H), 1.81 – 1.65 (m, 2H), 1.49 – 1.23 (m, 1H).

Similarly, isolated in 13% yield (0.02 mmol, 4 mg) as a white powder.

$^1$H NMR (400 MHz, Pyridine-$_d_5$) $\delta$ 7.54 (dd, $J$ = 5.4, 3.6 Hz, 1H), 7.24 (dt, $J$ = 7.2, 2.6 Hz, 2H), 7.05 (dd, $J$ = 5.5, 3.6 Hz, 1H), 4.12 (d, $J$ = 10.1 Hz, 1H), 3.73 (d, $J$ = 15.6 Hz, 1H), 3.25 (d, $J$ = 15.6 Hz, 1H), 2.86 (d, $J$ = 11.5 Hz, 1H), 2.36 (td, $J$ = 10.3, 3.2 Hz, 1H), 2.21 (dd, $J$ = 12.9, 3.2 Hz, 1H), 2.03 – 1.89 (m, 1H), 1.62 (dtd, $J$ = 12.9, 3.4, 1.7 Hz, 1H), 1.49 (ddt, $J$ = 10.1, 4.9, 3.4 Hz, 2H), 1.34 (tdd, $J$ = 13.8, 10.4, 3.7 Hz, 1H), 1.25 – 1.08 (m, 1H).

$^{13}$C NMR (100 MHz, Pyridine-$_d_5$) $\delta$ 135.0, 129.1, 128.5, 128.2, 127.7, 127.2, 121.2, 61.0, 58.0, 55.9, 39.4, 32.6, 26.0, 24.2.

HRMS (ESI/TOF-Q) m/z: [M+H]$^+$ calcd for C$_{14}$H$_{17}$N$_2$: 213.1386; found: 213.1395.

**13a-phenyl-6,8,13,13a-tetrahydro-5H-isoquinolino[3,2-a]isoquinoline-13-carbonitrile (3c)**

This compound was prepared from 1-phenyl-3,4-dihydroisoquinoline (0.15 mmol, 62 mg) according to procedure 1 and was formed in a 3:1 diastereomeric ratio based on LC-MS analysis of the crude material. The title compound was isolated as a 3:1 mixture of diastereomers (major product depicted above). Stereochemistry was confirmed by 2D NMR experiments.
$^1\text{H NMR}$ (400 MHz, CDCl$_3$) major stereoisomer: $\delta$ 7.46 (d, $J = 7.6$ Hz, 1H), 7.39 – 7.03 (m, 8H), 7.01 (d, $J = 7.4$ Hz, 1H), 6.96 – 6.91 (m, 2H), 6.86 (d, $J = 7.9$ Hz, 1H), 4.79 (s, 1H), 3.81 (d, $J = 16.3$ Hz, 1H), 3.39 (d, $J = 16.7$ Hz, 1H), 3.35 – 3.24 (m, 2H), 3.15 (dd, $J = 12.5$, 5.7, 3.6 Hz, 1H), 3.01 (dt, $J = 14.4$, 3.6 Hz, 1H); minor stereoisomer (selected peaks): $\delta$ 7.68 (d, $J = 7.8$ Hz, 1H), 4.69 (s, 1H), 3.76 (d, $J = 17.3$ Hz, 1H), 3.58 (d, $J = 17.3$ Hz, 1H), 2.97 (dt, $J = 14.4$, 3.6 Hz, 1H).

$^{13}\text{C NMR}$ (100 MHz, CDCl$_3$) major stereoisomer: $\delta$ 140.9, 139.7, 135.0, 134.8, 130.0, 129.0, 128.7, 124.8, 128.4, 128.1, 127.6, 127.6, 127.5, 127.4, 127.1, 126.7, 126.6, 120.0, 64.4, 52.7, 45.8, 42.5, 29.2.

HRMS (ESI/TOF-Q) m/z: [M+H]$^+$ calcd for C$_{24}$H$_{21}$N$_2$: 337.1699; found: 337.1708.

$\text{N-allyl-N-(bicyclo[4.2.0]octa-1,3,5-trien-7-ylmethyl)prop-2-en-1-amine (4a)}$

![Structure of 4a]

To a slurry of Raney Nickel in H$_2$O (45% wt in H$_2$O, 1.67 equiv, 448 mg, 3.43 mmol) in a 20 mL Barstead Hast. C reactor was added a solution of 1-benzocyclobutanecarbonitrile (1 equiv, 2.07 mmol, 267 mg) in 7M NH$_3$/MeOH (5 mL). The reactor was purged with Ar, then the reaction mixture stirred under 135 psi of H$_2$ at room temperature until complete uptake was observed. The crude reaction mixture was then filtered over Celite using CH$_2$Cl$_2$ and the organic layer concentrated. $^1\text{H NMR}$ spectrum of the crude product matched reported literature values$^2$ for (benzocyclobutenyl)methylamine and was taken directly to the next step. $^1\text{H NMR}$ (500 MHz, CDCl$_3$) $\delta$ 7.23 – 7.18 (m, 2H), 7.11 (dd, $J = 16.7$, 6.7 Hz, 2H), 3.73 – 2.74 (m, 5H).

A 20 mL scintillation vial was charged with CsOH (2 equiv, 1.05 mmol, 176 mg), (benzocyclobutenyl)methylamine (1 equiv, 0.526 mmol, 70 mg) and DMF (5 mL). The reaction mixture was stirred at room temperature for 30 minutes, then allyl bromide (2.2 equiv, 1.16 mmol, 100 μL) was added to the suspension and the reaction allowed to stir overnight. The reaction mixture was then filtered over celite, the filtrate concentrated and the residue purified by column chromatography. Product 4a was isolated in 56% as a colourless oil.

$^1\text{H NMR}$ (500 MHz, CDCl$_3$) $\delta$ 7.21 – 7.14 (m, 2H), 7.12 – 7.05 (m, 2H), 5.88 (ddt, $J = 16.8$, 10.2, 6.4 Hz, 2H), 5.18 (dq, $J = 17.1$, 1.6 Hz, 2H), 5.12 (ddt, $J = 10.2$, 2.2, 1.2 Hz, 2H), 3.67 (dt, $J = 8.3$, 5.8, 2.5 Hz, 1H), 3.32 (dd, $J = 14.0$, 5.2 Hz, 1H), 3.27 – 3.08 (m, 4H), 2.89 – 2.76 (m, 2H), 2.70 (dd, $J = 12.9$, 8.4 Hz, 1H).
**C NMR** (100 MHz, CDCl$_3$) $\delta$ 148.2, 144.2, 135.8, 127.2, 126.6, 122.9, 122.2, 117.3, 57.4, 57.2, 41.7, 35.6.

**HRMS** (ESI/TOF-Q) m/z: [M+H]$^+$ calcd for C$_{15}$H$_{20}$N: 214.1590; found: 214.1593.

**Experimental Procedure 2 (Synthesis of starting material 4)**

A 20 mL scintillation vial was charged with 1-benzocyclobutanecarboxylic acid, HATU (1.1 equiv) and DMF (0.1 M). The reaction mixture was stirred at room temperature for 15 minutes, then treated with DIPEA (3 equiv), followed by amine (1.5 equiv). The resulting reaction mixture was allowed stir at room temperature until complete, then diluted with EtOAc, washed with sat. NH$_4$Cl, water and brine. The organic layer was dried over MgSO$_4$, filtered and concentrated under reduced pressure. Resulting residues were purified by column chromatography.

**N-methyl-N-(prop-2-yn-1-yl)bicyclo[4.2.0]octa-1,3,5-triene-7-carboxamide (4b)**

Following experimental procedure 2 with N-methylprop-2-yn-1-amine (1.5 equiv, 0.9 mmol, 76 µL), product 4b was isolated in 63% yield (0.38 mmol, 76 mg) as a

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.28 – 7.13 (m, 3H), 7.12 – 7.02 (m, 1H), 4.46 (dd, $J = 5.7$, 3.0 Hz, 1H), 4.25 (dd, $J = 8.5$, 2.5 Hz, 2H), 3.58 (ddd, $J = 16.8$, 13.7, 2.9 Hz, 1H), 3.44 (ddd, $J = 13.8$, 5.7, 3.2 Hz, 1H), 3.23 (s, 3H, 2.22 (t, $J = 2.5$ Hz, 1H); *Selected rotamer peaks*: $\delta$ 4.49 (dd, $J = 5.5$, 2.8 Hz, 1H), 3.03 (s, 3H), 2.37 (t, $J = 2.5$ Hz, 1H).

$^{13}$C NMR (100 MHz, CDCl$_3$) (mixture of rotamers) $\delta$ 171.0, 143.9, 143.8, 143.3, 143.2, 128.1, 127.2, 122.9, 122.8, 78.7, 78.1, 73.2, 72.0, 45.5, 45.2, 39.1, 36.4, 34.1, 34.1, 34.0, 33.1.

**HRMS** (ESI/TOF-Q) m/z: [M+H]$^+$ calcd for C$_{13}$H$_{13}$NO: 200.1070; found: 200.1063.

**Experimental Procedure 3 (Synthesis of starting material 4)**

Borane in THF (1M, 1.25 equiv, 1.62 mL) was added dropwise to a solution of bicyclo[4.2.0]octa-1,3,5-triene-7-carboxylic acid (1 equiv, 1.3 mmol, 192 mg) in THF (6.5 mL) at 0 °C. The reaction mixture was warmed to room temperature and stirred overnight. The reaction was then quenched with water, extracted with EtOAc (x3), and the organic layers dried over MgSO$_4$ then concentrated to yield a colourless oily solid in 99% yield (1.29 mmol, 173 mg). $^1$H NMR spectrum of the crude product matched...
reported literature values\(^3\) for bicyclo[4.2.0]octa-1,3,5-trien-7-ylmethanol and was taken directly to the next step.  \(^{1}\text{H} \text{NMR}\) (500 MHz, CDCl\(_3\)) \(\delta 7.24 - 7.15\) (m, 2H), 7.18 - 7.04 (m, 2H), 3.94 - 3.82 (m, 2H), 3.73 - 3.65 (m, 1H), 3.30 (dd, \(J = 14.1, 5.3\) Hz, 1H), 2.92 (dd, \(J = 14.1, 2.5\) Hz, 1H).

**(bicyclo[4.2.0]octa-1,3,5-trien-7-ylmethoxy)dimethyl(vinyl)silane (4c)**

Following experimental procedure 3, a 4 mL vial was charged with bicyclo[4.2.0]octa-1,3,5-trien-7-ylmethanol (0.932 mmol, 125 mg), imidazole (2 equiv, 1.86 mmol, 127 mg), and DMAP (0.2 equiv., 0.19 mmol, 23 mg) and CH\(_2\)Cl\(_2\) (0.9 mL). The resulting reaction mixture was cooled to 0\(^\circ\)C and treated with the desired chlorodimethylvinylsilane (1.5 equiv, 1.38 mmol, 191 \(\mu\)L). The reaction was allowed to warm to room temperature and stirred until completion. The reaction mixture was then filtered through celite and concentrated. Purification by column chromatography yielded product 4c as a colourless oil in 52\% yield (0.48 mmol, 105.8 mg).

\(^{1}\text{H} \text{NMR}\) (400 MHz, CDCl\(_3\)) \(\delta 7.24 - 7.13\) (m, 2H), 7.08 (dd, \(J = 8.3, 6.6\) Hz, 2H), 6.14 (dd, \(J = 20.0, 14.9\) Hz, 1H), 6.01 (dd, \(J = 14.9, 4.3\) Hz, 1H), 5.78 (dd, \(J = 20.0, 4.3\) Hz, 1H), 3.87 (dd, \(J = 10.1, 7.1\) Hz, 1H), 3.79 (dd, \(J = 10.1, 7.7\) Hz, 1H), 3.75 - 3.62 (m, 1H), 3.29 (dd, \(J = 14.2, 5.2\) Hz, 1H), 2.83 (dd, \(J = 14.2, 2.3\) Hz, 1H), 0.20 (s, 3H), 0.19 (s, 3H).

\(^{13}\text{C} \text{NMR}\) (100 MHz, CDCl\(_3\)) \(\delta 147.0, 144.4, 137.6, 133.4, 127.6, 126.8, 123.1, 122.5, 66.0, 45.4, 33.8, -1.9, -1.9.

\(\text{MS} \) (DCI/NH\(_3\)) \(m/z: \left[\text{M+NH}_4\right]^+\) calcd for C\(_{13}\)H\(_{22}\)NOSi: 236.15; found: 236.11

**(bicyclo[4.2.0]octa-1,3,5-trien-7-ylmethoxy)dimethyl(vinyl)silane (4d)**

Following experimental procedure 3, a 4 mL vial was charged with bicyclo[4.2.0]octa-1,3,5-trien-7-ylmethanol (0.8 mmol, 107 mg), Et\(_3\)N (1.2 equiv, 0.96 mmol, 124 \(\mu\)L) and CH\(_2\)Cl\(_2\) (0.8 mL). The resulting reaction mixture was cooled to 0\(^\circ\)C and treated with chloro(ethynyl)dimethylsilane\(^4\) (1.15 equiv, 109 mg). The reaction was allowed to warm to room temperature and stirred until completion. The reaction mixture was then filtered through celite with
Et₂O and concentrated. Crude product 4d was isolated as a light yellow oil in 92% yield (0.74 mmol, 159 mg) and used as is. Caution: product is highly moisture- and acid-sensitive.

**1H NMR** (400 MHz, CDCl₃) δ 7.27 – 7.14 (m, 2H), 7.16 – 7.01 (m, 2H), 4.00 (dd, J = 10.2, 6.9 Hz, 1H), 3.92 (dd, J = 10.2, 7.8 Hz, 1H), 3.73 (qd, J = 6.7, 5.9, 2.0 Hz, 1H), 3.32 (dd, J = 14.2, 5.2 Hz, 1H), 2.90 (dd, J = 14.2, 2.5 Hz, 1H), 2.45 (s, 1H), 0.33 – 0.22 (m, 6H).

**13C NMR** (100 MHz, CDCl₃) δ 146.8, 144.4, 127.6, 126.8, 123.1, 122.5, 93.5, 87.8, 66.6, 45.1, 33.8, 0.1.

**MS** (DCI/NH₃) m/z: [M+NH₄]+ calcd for C₁₃H₂₀NOSi: 234.13; found: 234.19

**N-methyl-N-(2-oxoethyl)bicyclo[4.2.0]octa-1,3,5-triene-7-carboxamide (4e)**

Following experimental procedure 2 with 2-(methylamino)ethanol (2 equiv, 3.0 mmol, 225 mg), N-(2-hydroxyethyl)-N-methylbicyclo[4.2.0]octa-1,3,5-triene-7-carboxamide was isolated in 86% yield (1.3 mmol, 266 mg) as a colourless oil. **1H NMR** (400 MHz, CDCl₃) δ 7.26 – 7.14 (m, 3H), 7.11 – 7.02 (m, 1H), 4.51 (dd, J = 5.5, 3.0 Hz, 1H), 3.80 (app q, J = 5.1 Hz, 2H), 3.64 – 3.40 (m, 2H), 3.25 (s, 3H), 3.10 – 2.92 (m, 2H). To DMSO (4 equiv, 4.8 mmol, 0.34 mL) in CH₂Cl₂ (3 mL) at -78 °C was added a solution of oxalyl chloride in CH₂Cl₂ (0.2M, 2 equiv, 2.4 mmol) and the reaction mixture stirred for 15 minutes. A solution of N-(2-hydroxyethyl)-N-methylbicyclo[4.2.0]octa-1,3,5-triene-7-carboxamide (1.2 mmol, 246 mg) in CH₂Cl₂ (1.7 mL) was added dropwise to the reaction at -78 °C, and then resulting mixture stirred for 3h. Reaction was then quenched with Et₃N (0.85 mL) and warmed slowly to 0°C, diluted with H₂O and extracted with CH₂Cl₂ (x3). The combined organic layers were washed with brine, dried with MgSO₄ and concentrated. Purification by column chromatography gave product 4e in 65% yield (0.77 mmol, 157 mg) as a colourless oil.

**1H NMR** (400 MHz, CDCl₃) δ 9.60 (s, 1H), 7.26 – 7.14 (m, 3H), 7.15 – 7.07 (m, 1H), 4.58 (dd, J = 5.5, 3.0 Hz, 1H), 4.28 (d, J = 18.2 Hz, 1H), 4.17 (d, J = 18.2 Hz, 1H), 3.60 (dd, J = 13.8, 3.1 Hz, 1H), 3.49 (dd, J = 13.8, 5.5 Hz, 1H), 3.26 (s, 3H).

**13C NMR** (100 MHz, CDCl₃) δ 197.1, 172.2, 143.8, 143.1, 128.2, 127.3, 122.9, 122.8, 58.0, 45.1, 36.5, 34.1.

**HRMS** (ESI/TOF-Q) m/z: [M+H]+ calcd for C₁₂H₁₃NO₂: 204.1019; found: 204.1019.
N-(cyanomethyl)bicyclo[4.2.0]octa-1,3,5-triene-7-carboxamide (4f)

Following experimental procedure 2 with 2-aminoacetonitrile (1.5 equiv, 1.5 mmol, 84 mg), product 4f was isolated in 95% yield (0.95 mmol, 177 mg) as a white powder.

$^1$H NMR (400 MHz, CDCl$_3$) δ 7.39 – 7.24 (m, 2H), 7.21 – 7.06 (m, 2H), 6.21 (br s, 1H), 4.26 (dd, $J = 5.9$, 2.7 Hz, 1H), 4.24 – 4.11 (m, 2H), 3.61 (dd, $J = 14.4$, 6.0 Hz, 1H), 3.33 (dd, $J = 14.3$, 2.7 Hz, 1H).

$^{13}$C NMR (100 MHz, CDCl$_3$) δ 172.0, 144.6, 141.5, 129.0, 128.0, 123.7, 122.4, 115.9, 47.3, 35.5, 27.5.

HRMS (ESI/TOF-Q) m/z: [M+H]$^+$ calcd for C$_{11}$H$_{11}$N$_2$O: 187.0866; found: 187.0869.

(E)-7-((cinnamyloxy)methyl)bicyclo[4.2.0]octa-1,3,5-triene (4g)

Following experimental procedure 3, a 4 mL vial was charged with bicyclo[4.2.0]octa-1,3,5-trien-7-ylmethanol (0.8 mmol, 107 mg), (E)-(3-bromoprop-1-en-1-yl)benzene (2 equiv, 1.6 mmol, 315 mg), NaOH (10 equiv, 8.0 mmol, 320 mg) and TBAI (0.1 equiv, 0.08 mmol, 30 mg), H$_2$O (0.3 mL) and CH$_2$Cl$_2$ (3 mL). The reaction mixture was allowed to stir for 15h at room temperature, then diluted with additional CH$_2$Cl$_2$. Organic layer was washed with brine, dried over MgSO$_4$, filtered and concentrated. Purification by column chromatography gave product 4g in 57% yield (0.46 mmol, 115 mg) as a colourless oil.

$^1$H NMR (400 MHz, CDCl$_3$) δ 7.43 – 7.34 (m, 2H), 7.34 – 7.24 (m, 2H), 7.24 – 7.14 (m, 3H), 7.14 – 7.08 (m, 1H), 7.09 – 7.04 (m, 1H), 6.60 (dt, 15.9, 1.6 Hz, 1H), 6.31 (dt, $J = 15.9$, 6.0 Hz, 1H), 4.20 (dd, $J = 6.0$, 1.6 Hz, 2H), 3.79 – 3.74 (m, 2H), 3.74 – 3.66 (m, 1H), 3.40 – 3.32 (m, 1H), 2.90 (ddd, $J = 13.4$, 2.0, 1.1 Hz, 1H).

$^{13}$C NMR (100 MHz, CDCl$_3$) δ 146.8, 144.2, 136.7, 132.3, 128.6, 127.7, 127.5, 126.8, 126.5, 126.3, 123.0, 122.4, 73.2, 71.8, 43.1, 34.0.

MS (DCI/NH$_3$) m/z: [M+NH$_4$]$^+$ calcd for C$_{18}$H$_{22}$NO: 268.17; found: 268.14

N-((5-methylfuran-2-yl)methyl)bicyclo[4.2.0]octa-1,3,5-triene-7-carboxamide (4h)
Following experimental procedure 2 with (5-methylfuran-2-yl)methanamine (1.5 equiv, 1.5 mmol, 167 µL), product 4h was isolated in 80% yield (0.8 mmol, 193 mg) as a white, fluffy powder.

\[ ^1H \text{ NMR (400 MHz, CDCl}_3 \delta 7.32 - 7.19 (m, 2H), 7.17 - 7.03 (m, 2H), 6.06 (d, J = 3.1 Hz, 1H), 5.96 (br s, 1H), 5.87 (dd, J = 3.1, 1.3 Hz, 1H), 4.43 (dd, J = 15.5, 5.7 Hz, 1H), 4.34 (dd, J = 15.5, 5.4 Hz, 1H), 4.23 (dd, J = 5.9, 2.7 Hz, 1H), 3.57 (dd, J = 14.2, 5.9 Hz, 1H), 3.33 (dd, J = 14.2, 2.8 Hz, 1H), 2.25 (s, 3H). \]

\[ ^13C \text{ NMR (100 MHz, CDCl}_3 \delta 172.0, 152.4, 149.7, 145.2, 143.0, 128.9, 128.1, 123.9, 122.7, 108.7, 106.7, 48.3, 37.2, 35.9, 14.0. \]

HRMS (ESI/TOF-Q) m/z: [M+H]+ calcd for C_{15}H_{15}NO_2: 241.1112; found: 241.1103.

N-(furan-3-ylmethyl)bicyclo[4.2.0]octa-1,3,5-triene-7-carboxamide (4i)

Following experimental procedure 2 with furan-3-ylmethanamine (1.5 equiv, 1.5 mmol, 146 µL), product 4i was isolated in 67% yield (0.67 mmol, 152 mg) as a white powder.

\[ ^1H \text{ NMR (500 MHz, CDCl}_3 \delta 7.36 (t, J = 1.7 Hz, 1H), 7.32 (s, 1H), 7.26 (dq, J = 9.1, 7.1 Hz, 2H), 7.18 - 7.02 (m, 2H), 6.33 (s, 1H), 5.94 (br s, 1H), 4.32 (dd, J = 14.9, 5.8 Hz, 1H), 4.26 (dd, J = 14.9, 5.5 Hz, 1H), 4.22 (dd, J = 6.0, 2.8 Hz, 1H), 3.57 (dd, J = 14.2, 5.9 Hz, 1H), 3.31 (dd, J = 14.2, 2.8 Hz, 1H). \]

\[ ^13C \text{ NMR (126 MHz, CDCl}_3 \delta 171.9, 144.9, 143.6, 142.7, 140.1, 128.6, 127.8, 123.6, 122.4, 122.3, 110.2, 47.9, 35.6, 34.6. \]

HRMS (ESI/TOF-Q) m/z: [M+H]+ calcd for C_{14}H_{13}NO_2: 227.0949; found: 227.0946.

Experimental procedure 4 (IMDA; Table 2 and Scheme 3)

The flow rate on the Phoenix reactor was set to 4.0 mL/min, the back-pressure regulator set to 100 bar, and the temperature set to 300 °C. A 4 mL vial was charged with ortho-quinodimethane precursor 4 (0.15 mmol) and 3 mL of THF, and the reaction mixture then injected into the Phoenix (2 mL stainless
steel loop) using the autosampler. The crude reaction mixtures were collected in 20 mL scintillation vials, concentrated, and purified by column chromatography or prep-HPLC as indicated.

2-allyl-2,3,3a,4,5,9b-hexahydro-1H-benzo[e]isoindole (5a)

This compound was prepared from 4a (0.15 mmol, 32 mg) according to procedure 4. The product was purified by column chromatography to give the title compound as a colourless oil in 64% yield (20 mg). Cis-conformation confirmed by ROESY experiments.

\[ \text{H NMR (500 MHz, CDCl}_3\text{)} \delta 7.18 - 7.07 \text{ (m, 3H), 6.95 (dt, } J = 7.3, 1.1 \text{ Hz, 1H), 5.96 (ddt, } J = 16.8, 10.2, 6.5 \text{ Hz, 1H), 5.28 (dq, } J = 17.1, 1.6 \text{ Hz, 1H), 5.22 (dq, } J = 10.2, 1.2 \text{ Hz, 1H), 3.51 (dd, } J = 8.7, 6.4 \text{ Hz, 1H), 3.42 (ddt, } J = 9.6, 6.6, 1.3 \text{ Hz, 2H), 3.12 (dd, } J = 9.8, 7.1 \text{ Hz, 1H), 3.10 - 2.78 \text{ (m, 4H), 2.72 (dd, } J = 11.0, 9.8 \text{ Hz, 1H), 2.11 (ddddd, } J = 12.8, 7.1, 3.4, 2.4 \text{ Hz, 1H), 2.05 - 1.92 \text{ (m, 1H), 1.65 (tddd, } J = 12.4, 10.3, 7.7 \text{ Hz, 1H).} \]

\[ \text{C NMR (100 MHz, CDCl}_3\text{)} \delta 137.8, 136.4, 134.0, 128.8, 126.3, 125.6, 125.4, 118.7, 59.6, 57.3, 55.6, 45.6, 42.1, 29.1, 25.4. \]

HRMS (ESI/TOF-Q) m/z: [M+H]^+ calcd for C_{15}H_{20}N: 214.1590; found: 214.1590

2-methyl-2,3,4,5-tetrahydro-1H-benzo[e]isoindol-1-one (5b)

This compound was prepared from 4b (0.15 mmol, 30 mg) according to procedure 4. The product was purified by prep-HPLC (15-45% NH₄OAc/ACN method) to give the title compound as a white powder in 79% yield (0.12 mmol, 24 mg).

\[ \text{H NMR (400 MHz, CDCl}_3\text{)} \delta 8.30 (d, J = 7.8 \text{ Hz, 1H), 7.30 - 7.13 \text{ (m, 3H), 3.97 (s, 2H), 3.11 (s, 3H), 2.98 (t, } J = 8.2 \text{ Hz, 2H), 2.61 (t, } J = 8.2 \text{ Hz, 2H).} \]

\[ \text{C NMR (100 MHz, CDCl}_3\text{)} \delta 169.9, 149.9, 134.4, 129.2, 129.2, 127.7, 127.5, 126.9, 123.6, 54.0, 29.0, 27.9, 22.9. \]

HRMS (ESI/TOF-Q) m/z: [M+Na]^+ calcd for C_{13}H_{13}NNaO: 222.0889; found: 222.0896.
(3aS,9bS)-3,3-dimethyl-1,3,3a,4,5,9b-hexahydronaphtho[2,1-c][1,2]oxasilole (5c)

This compound was prepared from 4b (0.2 mmol, 44 mg) according to procedure 4. The product was purified by column chromatography to give the title compound as a grey crystalline solid in 75% yield (0.15 mmol, 33 mg).

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.23 – 7.00 (m, 4H), 3.92 (dd, $J = 11.0$, 4.5 Hz, 1H), 3.68 (t, $J = 10.6$ Hz, 1H), 3.28 (dd, $J = 9.1$, 5.0 Hz, 1H), 2.84 – 2.59 (m, 2H), 2.20 – 1.99 (m, 1H), 1.88 (td, $J = 6.7$, 5.8, 3.3 Hz, 1H), 1.69 – 1.52 (m, 1H), 0.30 (s, 3H), -0.13 (s, 3H).

$^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 138.7, 136.9, 129.3, 126.2, 125.4, 124.5, 69.8, 44.4, 30.2, 29.3, 22.1, -1.2, -2.6.

MS$^5$ (DCI/NH$_3$) m/z: [M+NH$_4$]$^+$ calcd for C$_{13}$H$_{22}$NOSi: 236.15; found: 236.12

3,3-dimethyl-1,3,5,9b-tetrahydronaphtho[2,1-c][1,2]oxasilole (5d)

This compound was prepared from 4c (0.15 mmol, 33 mg) according to procedure 4. The product was purified by column chromatography to give the title compound as a colourless oil in 21% yield (0.03 mmol, 7 mg).

$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.24 – 7.15 (m, 4H), 6.54 (ddd, $J = 7.9$, 4.8, 2.8 Hz, 1H), 3.83 – 3.63 (m, 2H), 3.52 – 3.42 (m, 1H), 3.40 – 3.35 (m, 2H), 0.28 (d, $J = 4.5$ Hz, 3H), 0.24 (d, $J = 1.2$ Hz, 3H).

$^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 139.0, 138.9, 137.3, 135.4, 128.4, 128.2, 126.5, 126.3, 66.6, 46.2, 31.8, 0.7, 0.7.

MS$^5$ (DCI/NH$_3$) m/z: [M+NH$_4$]$^+$ calcd for C$_{13}$H$_{20}$NOSi: 234.13; found: 234.10

2-methyl-3,3a,5,9b-tetrahydroisochromeno[3,4-c]pyrrol-1(2H)-one (5e)
This compound was prepared from 4e (0.15 mmol, 30 mg) according to procedure 4 and was formed in a 1.7:1 cis/trans ratio based on $^1$H NMR spectroscopic analysis of the crude material. The two diastereomeric products were separated by column chromatography.

Isolated as a white powder in 19% yield (0.03 mmol, 6 mg).

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.69 (d, $J = 7.7$ Hz, 1H), 7.32 (t, $J = 7.5$ Hz, 1H), 7.24 (t, $J = 7.4$ Hz, 1H), 7.02 (d, $J = 7.5$ Hz 1H), 4.72 (s, 2H), 4.52 (t, $J = 5.0$ Hz, 1H), 3.76 (dd, $J = 11.3$, 4.9 Hz, 1H), 3.47 (d, $J = 11.2$ Hz, 1H), 3.42 (d, $J = 5.1$ Hz, 1H), 2.93 (s, 1H).

$^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 171.8, 134.1, 130.4, 128.4, 127.4, 127.0, 124.1, 71.3, 67.0, 54.7, 43.7, 30.1.

Isolated as a white powder in 32% yield (0.05 mmol, 10 mg)

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.10 (d, $J = 6.1$ Hz, 1H), 7.34 – 7.18 (m, 2H), 7.13 – 6.92 (m, 1H), 5.07 (s, 2H), 4.05 (ddd, $J = 10.8$, 9.2, 6.8 Hz, 1H), 3.72 – 3.38 (m, 3H), 2.93 (s, 3H).

$^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 170.5, 133.6, 132.8, 127.2, 126.8, 125.3, 124.3, 74.8, 69.9, 51.8, 45.0, 29.8.

HRMS (ESI/TOF-Q) m/z: [M+Na]$^+$ calcd for C$_{12}$H$_{13}$NNaO$_2$: 226.0838; found: 223.0838

2,3-dihydro-1H-pyrrolo[3,4-c]isoquinolin-1-one (5f)

This compound was prepared from 4f (0.15 mmol, 28 mg) according to procedure 4. The product was purified by column chromatography to give the title compound as a pale yellow powder in 58% yield (0.09 mmol, 16 mg).

$^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 9.49 (s, 1H), 8.85 (d, $J = 8.4$ Hz, 1H), 8.29 (d, $J = 8.2$ Hz, 1H), 7.95 (t, $J = 7.5$ Hz, 1H), 7.77 (t, $J = 7.6$ Hz, 1H), 4.53 (s, 2H).
$^{13}$C NMR (100 MHz, DMSO-$d_6$) δ 170.0, 160.6, 156.5, 132.4, 131.4, 128.8, 127.7, 127.6, 121.8, 117.9, 46.6.

HRMS (ESI/TOF-Q) m/z: [M+H]$^+$ calcd for C$_{11}$H$_8$N$_2$O: 185.0709; found: 185.0711.

4-phenyl-1,3,3a,4,5,9b-hexahydronaphtho[1,2-c]furan (5g)

Title compound was prepared from 4g (0.15 mmol, 38 mg) according to procedure 4 and was formed in a 2:1 cis/trans ratio based on $^1$H NMR spectroscopic analysis of the crude material. The products were purified by column chromatography in 80% yield (0.12 mmol, 30 mg) as white fluffy powders. The two diastereomers were separated by re-submission to column chromatography to yield samples for 2D NMR spectroscopic analysis. Relative stereochemistry assignments based on ROESY experiments.

$^1$H NMR (500 MHz, Pyridine-$d_5$) δ 7.39 (dd, $J = 8.0$, 7.0 Hz, 2H), 7.33 – 7.27 (m, 3H), 7.18 – 7.14 (m, 1H), 7.13 (d, $J = 7.4$ Hz, 1H), 4.41 (dd, $J = 8.6$, 7.9 Hz, 1H), 3.92 (dd, $J = 8.8$, 6.2 Hz, 1H), 3.73 – 3.65 (m, 2H), 3.55 (q, $J = 8.8$ Hz, 1H), 2.88 (dd, $J = 16.7$, 12.6 Hz, 1H), 2.83 – 2.73 (m, 2H), 2.69 (dddd, $J = 11.1$, 8.0, 6.2, 2.9 Hz, 1H).

MS (DCI/NH$_3$) m/z: [M+NH$_4$]$^+$ calcd for C$_{18}$H$_{22}$NO: 268.17; found: 268.15

5-methyl-2,3,6a,7-tetrahydrobenzo[g]furo[2,3-d]isoindol-1(11bH)-one (5h)
This compound was prepared from 4h (0.15 mmol, 36 mg) according to procedure 4. The product was purified by column chromatography to give the title compound as a white powder in 55% yield (0.08 mmol, 19.9 mg). Note: upon standing, product 5h slowly degraded to 5h'.

\(^1\)H NMR (500 MHz, DMSO-\(d_6\)) \(\delta\) 7.92 (d, \(J = 7.6\) Hz, 1H), 7.83 (br s, 1H), 7.32 – 7.01 (m, 3H), 4.48 (dd, \(J = 2.8, 1.4\) Hz, 1H), 3.74 (s, 1H), 3.51 (d, \(J = 10.1\) Hz, 1H), 3.33 (dd, \(J = 10.1, 2.0\) Hz, 1H), 3.30 – 3.23 (m, 1H), 2.74 (dd, \(J = 14.5, 7.1\) Hz, 1H), 2.47 (d, \(J = 14.5\) Hz, 1H), 1.35 (s, 3H).

\(^13\)C NMR (126 MHz, DMSO-\(d_6\)) \(\delta\) 173.3, 153.4, 137.7, 133.5, 128.4, 125.8, 125.6, 124.2, 99.1, 93.2, 51.6, 45.9, 42.0, 35.0, 13.1.

HRMS (ESI/TOF-Q) \(m/z\): \([\text{M+H}]^+\) calcd for C\(_{15}\)H\(_{15}\)NO\(_2\): 242.1176; found: 242.1174.

4-(2-oxopropyl)-2,3,4,5-tetrahydro-1H-benzo[e]isoindol-1-one (5h')

The flow rate on the Phoenix reactor was set to 4.0 mL/min, the back-pressure regulator set to 100 bar, and the temperature set to 300 \(^\circ\)C. A 4 mL vial was charged with compound 4h (0.15 mmol, 36 mg), 2 equiv of pTsOH (2 equiv, 0.3 mmol, 57 mg) and 3 mL of THF, and the reaction mixture then injected into the Phoenix using the autosampler. The crude reaction mixture was collected in a 20 mL scintillation vial, concentrated, and purified by column chromatography to give the title compound as a white powder in 64% yield (0.1 mmol, 23.2 mg).

\(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 8.21 (dd, \(J = 7.5, 1.4\) Hz, 1H), 7.68 (br s, 1H), 7.30 – 7.21 (m, 1H), 7.20 (td, \(J = 7.4, 1.6\) Hz, 1H), 7.15 (dd, \(J = 7.3, 1.5\) Hz, 1H), 4.04 (s, 2H), 3.27 (p, \(J = 6.8\) Hz, 1H), 3.08 (dd, \(J = 15.7, 6.7\) Hz, 1H), 2.68 (dd, \(J = 15.7, 6.7\) Hz, 1H), 2.60 (dd, \(J = 6.9, 1.4\) Hz, 2H), 2.13 (s, 3H).

\(^13\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 206.7, 173.6, 156.8, 133.5, 128.5, 128.2, 128.2, 127.9, 127.1, 123.7, 47.4, 45.8, 34.3, 30.5, 29.2.

HRMS (ESI/TOF-Q) \(m/z\): \([\text{M+H}]^+\) calcd for C\(_{15}\)H\(_{15}\)NO\(_2\): 242.1176; found: 242.1189.

2,3,6a,7-tetrahydrobenzo[g]furo[3,2-d]isoindol-1(11bH)-one (5i)
This compound was prepared from 4i (0.15 mmol, 36 mg) according to procedure 4. The product was purified by column chromatography to give the title compound as a white powder in 24% yield.

\(^1\text{H NMR}\) (400 MHz, CDCl\(_3\)) \(\delta\) 7.36 – 7.24 (m, 3H), 7.20 – 7.13 (m, 1H), 6.24 (d, \(J = 2.7\) Hz, 1H), 6.05 (br s, 1H), 4.87 (d, \(J = 2.7\) Hz, 1H), 4.85 (t, \(J = 3.6\) Hz, 1H), 3.73 (d, \(J = 10.0\) Hz, 1H), 3.46 (s, 1H), 3.38 (dd, \(J = 10.0, 1.2\) Hz, 1H), 3.19 (dd, \(J = 15.8, 3.6\) Hz, 1H), 2.98 (dd, \(J = 15.7, 3.8\) Hz, 1H).

\(^{13}\text{C NMR}\) (100 MHz, CDCl\(_3\)) \(\delta\) 175.7, 148.0, 133.5, 132.1, 130.2, 129.0, 128.3, 127.3, 104.5, 87.5, 55.0, 53.6, 52.5, 34.3.

HRMS (ESI/TOF-Q) m/z: [M+H]\(^+\) calcd for C\(_{14}\)H\(_{13}\)NO\(_2\): 228.1019; found: 228.1024.

(1S,2S)-1-(hydroxymethyl)-1,2,3,4-tetrahydronaphthalen-2-ol (6)

Compound 5c was dissolved in 1:1 THF/MeOH (0.5 mL) in a 4 mL vial. KF (2 equiv, 0.09 mmol, 5.3 mg), NaHCO\(_3\) (1 equiv, 0.05 mmol, 3.9 mg) and H\(_2\)O\(_2\) (12 equiv, 0.55 mmol, 56 \(\mu\)L) were added sequentially, and the vial sealed and stirred at 60 °C for 15 hours. Upon cooling, the reaction mixture was diluted with EtOAc, and washed with water and brine. The organic layer was then dried over MgSO\(_4\), filtered and concentrated to yield the title compound as a white crystalline solid in 75% yield (0.03 mmol, 6 mg).

\(^1\text{H NMR}\) (500 MHz, DMSO-\(d_6\)) \(\delta\) 7.20 (dd, \(J = 7.1, 1.8\) Hz, 1H), 7.12 – 6.96 (m, 3H), 4.72 (t, \(J = 5.3\) Hz, 1H), 4.60 (d, \(J = 3.7\) Hz, 1H), 4.07 (dt, \(J = 6.8, 3.5\) Hz, 1H), 3.62 (dt, \(J = 10.1, 4.9\) Hz, 1H), 3.49 (ddd, \(J = 10.9, 7.9, 5.4\) Hz, 1H), 2.82 (ddd, \(J = 15.9, 9.7, 5.8\) Hz, 1H), 2.71 (dt, \(J = 8.0, 4.3\) Hz, 1H), 2.58 (dt, \(J = 16.7, 5.5\) Hz, 1H), 1.85 (ddddd, \(J = 12.5, 9.7, 5.6, 2.6\) Hz, 1H), 1.69 (dt, \(J = 12.9, 6.0\) Hz, 1H).

\(^{13}\text{C NMR}\) (126 MHz, DMSO-\(d_6\)) \(\delta\) 136.8, 136.4, 129.4, 128.2, 125.4, 125.4, 65.1, 64.7, 48.7, 26.9, 24.9.

MS (DCI/NH\(_3\)) m/z: [M+NH\(_4\)]\(^+\) calcd for for C\(_{11}\)H\(_{16}\)NO\(_2\): 196.13; found: 196.08

Experimental procedure 5 (synthesis of starting material 7)
A 20 mL scintillation vial was charged with 2-(2,2-dioxido-1,3-dihydrobenzo[c]thiophen-1-yl)acetic acid, HATU (1.5 equiv) and DMF (0.1 M). The reaction mixture was stirred at room temperature for 15 minutes, then treated with DIPEA (3 equiv), followed by amine (2 equiv). The resulting reaction mixture was allowed stir at room temperature until complete, then diluted with EtOAc, washed with sat. NH₄Cl, water and brine. The organic layer was dried over MgSO₄, filtered and concentrated under reduced pressure. Resulting residues were purified by column chromatography.

**N-allyl-N-benzyl-2-(2,2-dioxido-1,3-dihydrobenzo[c]thiophen-1-yl)acetamide (7a)**

Following experimental procedure 5 with N-benzylprop-2-en-1-amine (2 equiv, 8.8 mmol, 1.38 mL), product 7a was isolated in 47% yield (0.87 mmol, 310 mg) as a colourless oil.

**1H NMR** (400 MHz, CDCl₃) δ 7.40 – 7.20 (m, 8H), 7.12 (d, J = 7.0 Hz, 1H), 5.69 (dddd, J = 15.4, 9.6, 5.5, 4.1 Hz, 1H), 5.19 – 5.15 (m, 2H), 5.05 (t, J = 6.4 Hz, 1H), 4.71 (d, J = 14.8 Hz, 1H), 4.61 (d, J = 14.8 Hz, 1H), 4.40 (d, J = 16.0 Hz, 1H), 4.34 (d, J = 16.0 Hz, 1H), 3.90 (dd, J = 17.8, 4.6 Hz, 1H), 3.80 (dd, J = 17.8, 3.2 Hz, 1H), 3.25 (dd, J = 5.5, 3.9, 1.3 Hz, 1H), 2.87 (ddd, J = 6.2, 4.8, 1.3 Hz, 1H); **Selected rotamer peaks:** δ 5.87 – 5.75 (m, 1H), 5.23 – 5.19 (m, 1H), 5.12 (dt, J = 4.3, 1.4 Hz, 1H), 5.03 (t, J = 6.6 Hz, 1H), 4.57 (d, J = 17.2 Hz, 1H), 4.49 (d, J = 17.2 Hz, 1H), 4.35 (d, J = 15.8 Hz, 1H), 4.28 (d, J = 15.8 Hz, 1H), 4.13 (dd, J = 15.2, 5.9 Hz, 1H), 4.03 (dd, J = 15.2, 6.2 Hz, 1H), 3.29 (d, J = 5.5, 3.9, 1.3 Hz, 1H), 2.83 (ddd, J = 6.1, 4.6, 1.4 Hz, 1H).

**13C NMR** (100 MHz, CDCl₃) (mixture of rotamers) δ 169.1, 168.8, 137.1, 136.1, 136.0, 136.0, 132.6, 132.1, 130.2, 129.1, 129.1, 129.0, 128.9, 128.8, 128.7, 128.4, 127.8, 127.7, 126.4, 125.9, 125.9, 118.1, 117.3, 62.2, 62.2, 55.8, 55.8, 50.2, 49.2, 49.1, 48.6, 34.6, 34.2.

**HRMS** (ESI/TOF-Q) m/z: [M+H]+ calcd for C₂₀H₂₂NO₃S: 356.1315; found: 356.1315.

**N-allyl-2-(2,2-dioxido-1,3-dihydrobenzo[c]thiophen-1-yl)acetamide (7b)**
Following experimental procedure 5 with prop-2-en-1-amine (2 equiv, 0.88 mmol, 66 μL), product 7b was isolated in 86% yield (0.38 mmol, 101 mg) as a colourless oil.

\[ ^1H\text{ NMR (500 MHz, CDCl}_3 \] δ 7.39 – 7.32 (m, 3H), 7.30 – 7.26 (m, 1H), 6.05 (s, 1H), 5.83 (ddt, \( J = 17.2, 10.3, 5.7 \) Hz, 1H), 5.20 (dq, \( J = 17.1, 1.7 \) Hz, 1H), 5.14 (dq, \( J = 10.3, 1.4 \) Hz, 1H), 4.83 (t, \( J = 6.8 \) Hz, 1H), 4.52 – 4.19 (m, 2H), 3.92 (tq, \( J = 5.7, 1.5 \) Hz, 2H), 3.05 (dd, \( J = 15.6, 7.0 \) Hz, 1H), 2.75 (dd, \( J = 15.6, 6.7 \) Hz, 1H).

\[ ^{13}C\text{ NMR (126 MHz, CDCl}_3 \] δ 168.3, 135.5, 133.8, 130.0, 129.2, 129.1, 126.0, 125.8, 116.9, 62.2, 55.6, 42.4, 36.6.

HRMS (ESI/TOF-Q) m/z: [M+H]^+ calcd for C_{13}H_{15}NO_3S: 266.0845; found: 266.0849.

1-(2,2-dioxidobenzo[c]isothiazol-1(3H)-yl)pent-4-en-1-one (7c)

A 20 mL scintillation vial was charged with 1,3-dihydrobenzocisothiazole 2,2-dioxide (0.8 mmol, 135 mg), EDC-HCl (1.2 equiv, 0.96 mmol, 184 mg), DMAP (0.2 equiv, 0.16 mmol, 19.5 mg) and DMF (4 mL). The reaction mixture was stirred at room temperature for 14 hours, then diluted with EtOAc, and washed with water and brine. The organic layer was dried over MgSO_4, filtered and concentrated under reduced pressure. Purification by column chromatography gave product 7c in 46% yield (0.37 mmol, 93 mg) as a beige powder.

\[ ^1H\text{ NMR (400 MHz, CDCl}_3 \] δ 8.12 (d, \( J = 8.4 \) Hz, 1H), 7.38 (td, \( J = 7.9, 1.5 \) Hz, 1H), 7.26 (dd, \( J = 7.6, 1.5 \) Hz, 1H), 7.20 (td, \( J = 7.5, 1.1 \) Hz, 1H), 5.90 (ddt, \( J = 16.8, 10.3, 6.5 \) Hz, 1H), 5.14 (dd, \( J = 17.1, 1.7 \) Hz, 1H), 5.05 (dd, \( J = 10.2, 1.5 \) Hz, 1H), 4.53 (s, 2H), 3.05 (t, \( J = 7.3 \) Hz, 2H), 2.69 – 2.38 (m, 2H).

\[ ^{13}C\text{ NMR (100 MHz, CDCl}_3 \] δ 170.0, 136.8, 136.4, 129.9, 125.4, 125.3, 118.1, 116.8, 116.1, 52.9, 35.7, 28.3.

MS (DCI/NH_3) m/z: [M+NH_4]^+ calcd for for C_{12}H_{17}N_2O_3S: 269.10; found: 269.06.
1-(pent-4-en-1-yl)-1,3-dihydrobenzo[c]isothiazole 2,2-dioxide (7d)

A 20 mL scintillation vial was charged with 1,3-dihydrobenzo[c]isothiazole 2,2-dioxide (1 mmol, 169 mg), 5-bromopent-1-ene (1.5 equiv, 1.5 mmol, 224 mg), K$_2$CO$_3$ (2 equiv, 2 mmol, 276 mg) and CH$_2$Cl$_2$ (10 mL). Reaction mixture was allowed to stir at room temperature for 15 hours, then washed with water, sat. NH$_4$Cl solution, brine and dried over MgSO$_4$. Purification by column chromatography gave product 7d in 61% yield (0.6 mmol, 146 mg) as a yellow oil.

$^1$H NMR (400 MHz, CDCl$_3$) δ 7.31 (t, $J = 7.9$ Hz, 1H), 7.23 (dd, $J = 7.6, 1.3$ Hz, 1H), 6.98 (t, $J = 7.6$ Hz, 1H), 6.73 (d, $J = 8.0$ Hz, 1H), 5.84 (ddt, $J = 16.9, 10.1, 6.6$ Hz, 1H), 5.09 (dq, $J = 17.1, 1.7$ Hz, 1H), 5.04 (dq, $J = 10.2, 1.4$ Hz, 1H), 4.32 (s, 2H), 3.68 – 3.53 (m, 2H), 2.32 – 2.10 (m, 2H), 1.90 (app. p, $J = 7.4$ Hz, 2H).

$^{13}$C NMR (100 MHz, Chloroform-d) δ 141.2, 137.2, 129.5, 125.7, 121.6, 117.4, 115.9, 109.2, 51.2, 41.2, 31.0, 27.1.

HRMS (ESI/TOF-Q) m/z: [M+Na]$^+$ calcd for C$_{12}$H$_{15}$NNaO$_2$S: 260.0716; found: 260.0723.

Experimental procedure 6 (IMDA; Table 3)

The flow rate on the Phoenix reactor was set to 0.5 mL/min, the back-pressure regulator set to 100 bar, and the temperature set to 300 °C. A 4 mL vial was charged with ortho-quinodimethane precursor 7 (0.15 mmol) and 3 mL of THF, and the reaction mixture then injected into the Phoenix (2 mL stainless steel loop) using the autosampler. The crude reaction mixtures were collected in 20 mL scintillation vials, concentrated, and purified by column chromatography or prep-HPLC as indicated.

3-benzyl-1,4,4a,5,6,10b-hexahydrobenzo[f]isoquinolin-2(3H)-one (8a)

This compound was prepared from 7a (0.15 mmol, 53 mg) according to procedure 6. $^1$H NMR and ROESY spectroscopic analysis of the crude product showed a 2.9:1 cis/trans ratio. Purification by column chromatography gave the two diastereomeric products as colourless oils in 93% total yield.
\[ ^1H \text{NMR} \ (500 \text{ MHz, CDCl}_3 \delta \ 7.34 - 7.26 \ (m, 3H), 7.26 - 7.20 \ (m, 2H), 7.18 - 7.12 \ (m, 2H), 7.13 - 7.06 \ (m, 2H), 4.74 \ (d, J = 14.6 \text{ Hz, 1H}), 4.50 \ (d, J = 14.6 \text{ Hz, 1H}), 3.49 \ (dd, J = 12.7, 5.4 \text{ Hz, 1H}), 3.22 \ (dt, J = 11.1, 5.7 \text{ Hz, 1H}), 3.07 \ (dd, J = 12.7, 3.7 \text{ Hz, 1H}), 2.94 - 2.81 \ (m, 2H), 2.79 \ (dd, J = 17.9, 6.5 \text{ Hz, 1H}), 2.54 \ (dd, J = 17.9, 10.8 \text{ Hz, 1H}), 2.24 \ (dt, J = 9.9, 4.5 \text{ Hz, 1H}), 1.97 - 1.79 \ (m, 1H), 1.71 - 1.61 \ (m, 1H). \]

\[ ^{13}C \text{NMR} \ (126 \text{ MHz, CDCl}_3 \delta \ 169.0, 138.9, 137.1, 135.2, 129.2, 128.6, 128.0, 128.0, 128.0, 128.0, 128.0, 127.4, 126.5, 126.1, 51.4, 49.9, 37.5, 35.9, 31.9, 28.3, 23.1. \]

\[ ^1H \text{NMR} \ (400 \text{ MHz, CDCl}_3 \delta \ 7.40 - 7.28 \ (m, 4H), 7.26 - 7.09 \ (m, 5H), 4.79 \ (d, J = 14.6 \text{ Hz, 1H}), 4.56 \ (d, J = 14.7 \text{ Hz, 1H}), 3.50 - 3.21 \ (m, 2H), 3.06 \ (t, J = 11.6 \text{ Hz, 1H}), 2.99 - 2.76 \ (m, 3H), 2.43 \ (dd, J = 17.3, 12.5 \text{ Hz, 1H}), 1.93 - 1.78 \ (m, 2H), 1.49 \ (qd, J = 12.2, 6.7 \text{ Hz, 1H}). \]

\[ ^{13}C \text{NMR} \ (100 \text{ MHz, CDCl}_3 \delta \ 169.6, 137.5, 137.3, 136.1, 129.3, 128.7, 128.7, 128.1, 128.1, 127.6, 126.5, 126.5, 126.1, 53.0, 50.2, 38.3, 38.3, 36.7, 29.1, 26.3. \]

\[ \text{HRMS (ESI/TOF-Q) m/z: } [M+H]^+ \text{ calcd for C}_{20}H_{22}NO: 292.1696; \text{ found: 292.1701.} \]

\[1,4,4a,5,6,10b\text{-hexahydrobenzo[f]isoquinolin-2(3H)-one (8b)}\]

This compound was prepared from \(7a\) (0.15 mmol, 53 mg) according to procedure 6. \(^1H\) NMR and ROESY spectroscopic analysis of the crude product showed a 1:1 cis/trans ratio. Purification by column chromatography gave the two diastereomeric products as light yellow oils in 69% total yield.
**1H NMR** (500 MHz, CDCl$_3$) δ 7.28 – 7.10 (m, 3H), 7.12 – 7.02 (m, 1H), 5.91 (br s, 1H), 3.64 (ddd, $J = 12.4$, 5.1, 1.3 Hz, 1H), 3.29 – 3.11 (m, 2H), 2.99 – 2.85 (m, 2H), 2.67 (dd, $J = 18.1$, 6.6 Hz, 1H), 2.41 (dd, $J = 18.1$, 10.9 Hz, 1H), 2.27 (dp, $J = 12.1$, 4.3 Hz, 1H), 2.04 – 1.89 (m, 1H), 1.85 – 1.74 (m, 1H).

**13C NMR** (100 MHz, CDCl$_3$) δ 171.4, 139.3, 135.2, 129.4, 128.1, 126.7, 126.3, 46.9, 37.0, 35.8, 31.4, 28.6, 23.0.

**3,3a,4,5-tetrahydropyrrolo[1,2-a]quinolin-1(2H)-one (8c)**

This compound was prepared from 7c (0.15 mmol, 38 mg) according to procedure 6. Purification by column chromatography gave the title compound in 55% yield (0.08 mmol, 15 mg).

**1H NMR** (500 MHz, CDCl$_3$) δ 8.70 (dd, $J = 8.5$, 1.2 Hz, 1H), 7.24 – 7.14 (m, 1H), 7.13 (dt, $J = 7.5$, 1.3 Hz, 1H), 5.95 (br s, 1H), 3.44 (ddd, $J = 11.5$, 4.9, 3.9 Hz, 1H), 3.25 – 3.09 (m, 2H), 3.00 – 2.86 (m, 2H), 2.33 (dd, $J = 17.3$, 12.4 Hz, 1H), 1.95 (ddt, $J = 12.9$, 5.4, 2.7 Hz, 1H), 1.87 (qdd, $J = 11.5$, 4.9, 2.8 Hz, 1H), 1.59 – 1.39 (m, 2H).

**13C NMR** (100 MHz, CDCl$_3$) δ 172.0, 137.5, 136.2, 129.3, 126.6, 126.5, 126.0, 48.1, 38.0, 37.5, 36.1, 29.2, 26.4.

**HRMS** (ESI/TOF-Q) m/z: [M+H]$^+$ calcd for C$_{13}$H$_{16}$NO: 202.1226; found: 202.1232.

**3,3a,4,5-tetrahydropyrrolo[1,2-a]quinolin-1(2H)-one (8c)**
1,2,3,3a,4,5-hexahydropyrrolo[1,2-a]quinoline (8d)

This compound was prepared from 7d (0.15 mmol, 36 mg) according to procedure 6. Purification by prep-HPLC (15-45% NH₄OAc/ACN method) gave the title compound in 14% yield (0.02 mmol, 4 mg) as a pale yellow oil. Characterization data was fully concordant with that already reported in the literature.

**^1H NMR** (400 MHz, CDCl₃) δ 7.07 (dd, J = 8.3, 6.8 Hz, 1H), 6.99 (d, J = 7.3 Hz, 1H), 6.55 (t, J = 7.3 Hz, 1H), 6.40 (d, J = 8.0 Hz, 1H), 3.43 (tdd, J = 10.6, 5.1, 3.1 Hz, 1H), 3.33 (td, J = 9.0, 2.3 Hz, 1H), 3.23 (td, J = 9.1, 7.3 Hz, 1H), 2.94 – 2.81 (m, 1H), 2.76 (ddd, J = 16.0, 4.7, 2.3 Hz, 1H), 2.14 (dtd, J = 11.0, 5.5, 2.5 Hz, 2H), 2.12 – 2.01 (m, 1H), 2.02 – 1.87 (m, 1H), 1.54 – 1.33 (m, 2H).

**MS** (ESI/TFA) m/z: [M+H]^+ calcd for C_{12}H_{16}N: 173.25; found: 174.00

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5. No HRMS could be provided as no ions were observed through ESI method.