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

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Supporting information

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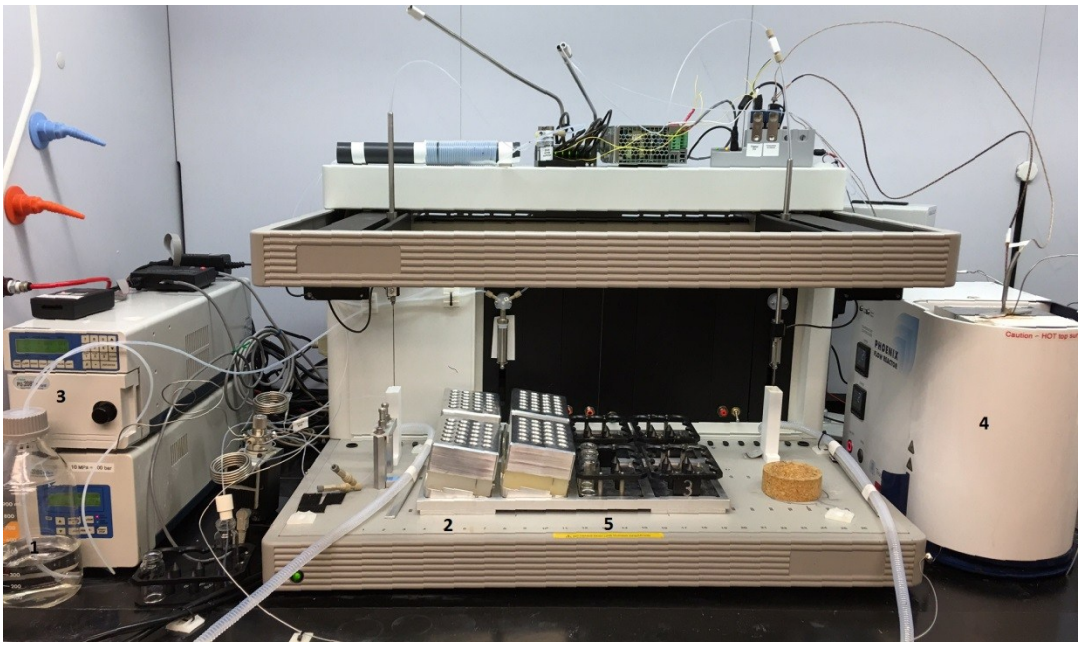
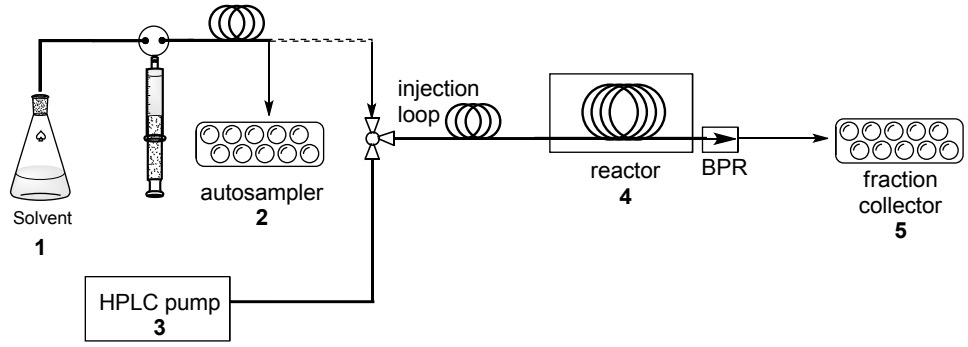
General Information

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 Combi*flash*® Rf automated purification system and Redi*Sep*® 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 × 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 (^{1}H NMR, 500 or 400 MHz) and proton decoupled carbon nuclear magnetic resonance spectra (^{13}C NMR, 126 or 100 MHz) were obtained in deuterochloroform ($CDCl_3$), deuterodimethylsulfoxide (DMSO-d_6) or deuteropyridine (pyridine-d_5) 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:



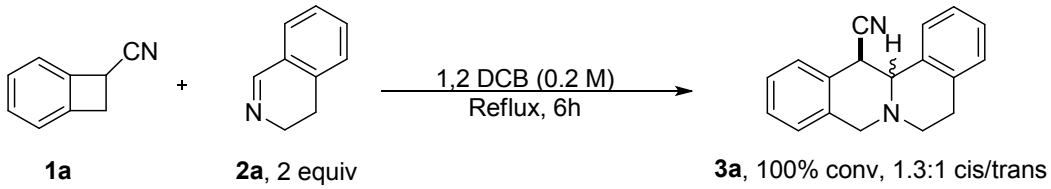


We used a commercially available high-temperature and high-pressure Phoenix™ flow reactor from ThalesNano, designed to allow reactions at up to 450° C and at high pressure. The reactor coil consists of a stainless steel tubing (1.0 mm in diameter) of 2 mL volume, which is wrapped around a metallic housing 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.

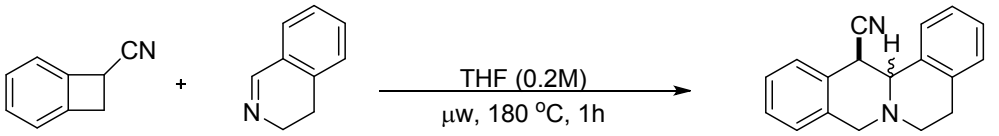
Optimization studies

1) Batch studies



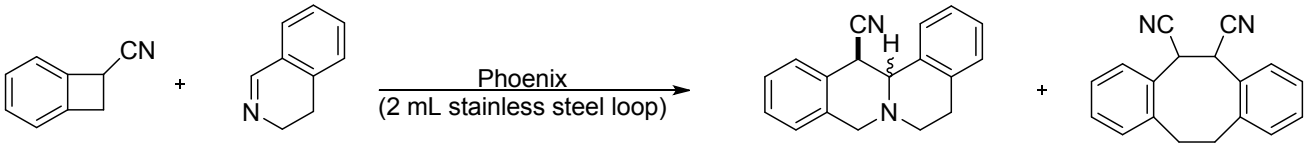
1a **2a**, 2 equiv **3a**, 100% conv, 1.3:1 cis/trans

2) Biotage Microwave reactor



1a **2a**, 2 equiv **3a**, 7% conv, 1:1 cis/trans

3) Phoenix Flow reactor



1a **2a** **3a** dimer

Entry	2a (equiv)	Solvent (conc)	Temp.(°C)	Pressure (bar)	Flow rate (mL/s)	3a (%),[a] cis/trans ratio	Dimer (%)[a]
1	2	THF(0.2M)	350	120	0.5	89 (1.3:1)	-
2	2	THF (0.2M)	250	120	0.5	100 (1.5:1)	-
3	2	THF (0.2M)	200	120	0.5	15 (1:1)	-
4[b]	2	THF(0.2M)	300	120	0.5	100 (1.3:1)	-
5	2	THF(0.2M)	300	120	4	100 (1.3:1)	-
6	1	THF(0.2M)	300	120	4	78 (1.2:1)	-
7	2	ACN (0.2M)	300	120	4	72 (1.7:1)	17
8	2	Toluene (0.2M)	300	120	4	80 (1:1)	-
9	2	1,2-DCB (0.2M)	300	120	4	82 (1:1)	13
10	2	100:1 THF/H_2O (0.2M)	300	120	4	69 (1:1.4)	-
11[c]	2	THF (0.2M)	300	120	4	69 (1:1)	27

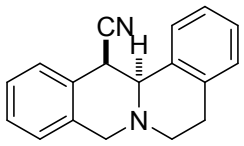
12	2	THF(0.05M)	300	120	4	100 (1.2:1)	-
13	2	THF(0.4M)	300	120	4	99 (1.4:1)	-
14	2	THF (0.2M)	300	80	4	85 (1.4:1)	-
15	2	THF (0.2M)	300	140	4	77 (1.3:1)	-

[a] Yields based on ^{1}H NMR spectroscopic analysis using *p*-nitroacetophenone as an internal standard. [b] Isolated in 85% yield. [c] 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 ^{1}H 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.

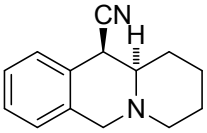
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34 – 7.15 (m, 8H), 4.37 (d, *J* = 3.2 Hz, 1H), 4.17 (d, *J* = 15.2 Hz, 1H), 4.03 – 3.92 (m, 1H), 3.79 (d, *J* = 15.2 Hz, 1H), 3.32 (ddd, *J* = 17.3, 12.2, 5.2 Hz, 1H), 3.22 (ddd, *J* = 10.9, 5.2, 2.4 Hz, 1H).

^{13}C NMR (126 MHz, $CDCl_3$) 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.

HRMS (ESI/TOF-Q) m/z: $[M+H]^+$ calcd for $C_{18}H_{17}N_2$: 261.1386; found: 261.1393.

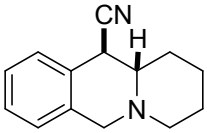
(11R,11aR)-2,3,4,6,11,11a-hexahydro-1H-pyrido[1,2-b]isoquinoline-11-carbonitrile (3b)[1]

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_4OAc/ACN method).



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

^{1}H NMR (400 MHz, $CDCl_3$) δ 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).



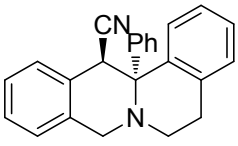
Isolated in 13% yield (0.02 mmol, 4 mg) as a white powder.

^{1}H NMR (400 MHz, Pyridine-d_5) δ 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) δ 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)



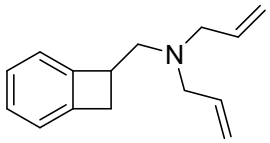
This compound was prepared from 1-phenyl-3,4-dihydroisoquinoline (0.15 mmol, 62 mg) according to procedure 1 and was formed in a 3:1 diastereomeric ratio based on LC-MS analysis of the crude material. The title compound was isolated as a 3:1 mixture of diastereomers (major product depicted above). Stereochemistry was confirmed by 2D NMR experiments.

^{1}H NMR (400 MHz, $CDCl_3$) *major stereoisomer*: δ 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 (ddd, *J* = 12.5, 5.7, 3.6 Hz, 1H), 3.01 (dt, *J* = 14.4, 3.6 Hz, 1H); *minor stereoisomer* (selected peaks): δ 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}C NMR (100 MHz, $CDCl_3$) *major stereoisomer:* δ 140.9, 139.7, 135.0, 134.8, 130.0, 129.0, 128.7, 128.4, 128.4, 128.1, 127.6, 127.6, 127.5, 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.

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



To a slurry of Raney Nickel in H_2O (45% wt in H_2O, 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_2Cl_2 and the organic layer concentrated. ^{1}H NMR spectrum of the crude product matched reported literature values[2] for (benzocyclobutenyl)methylamine and was taken directly to the next step. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 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}H NMR (500 MHz, $CDCl_3$) δ 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 (dtd, *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).

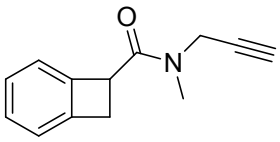
^{13}C NMR (100 MHz, $CDCl_3$) δ 148.2, 144.2, 135.8, 127.2, 126.6, 122.9, 122.2, 117.3, 57.4, 57.2, 41.7, 35.6.

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_4Cl, 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, $CDCl_3$) δ 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*: δ 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) δ 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.

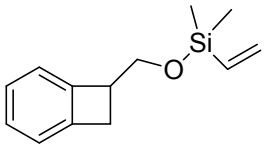
HRMS (ESI/TOF-Q) m/z: $[M+H]^+$ calcd for $C_{13}H_{13}NO$: 200.1070; found: 200.1063.

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}H NMR** (500 MHz, $CDCl_3$) δ 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)



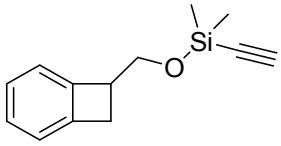
Following experimental procedure 3, a 4 mL vial was charged with bicyclo[4.2.0]octa-1,3,5-trien-7-ylmethanol (0.932 mmol, 125 mg), imidazole (2 equiv, 1.86 mmol, 127 mg), and DMAP (0.2 equiv., 0.19 mmol, 23 mg) and CH_2Cl_2 (0.9 mL). The resulting reaction mixture was cooled to 0^{O}C and treated with the desired chlorodimethylvinylsilane (1.5 equiv, 1.38 mmol, 191 µL). 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}H NMR (400 MHz, $CDCl_3$) δ 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}C NMR (100 MHz, $CDCl_3$) δ 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.

MS (DCI/NH_3) m/z: $[M+NH_4]^+$ 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_3N (1.2 equiv, 0.96 mmol, 124 µL) and CH_2Cl_2 (0.8 mL). The resulting reaction mixture was cooled to 0^{O}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

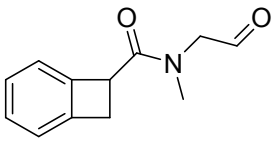
Et_2O and concentrated. Crude product **4d** was isolated as a light yellow oil in 92% yield (0.74 mmol, 159 mg) and used as is. *Caution:* product is highly moisture- and acid-sensitive.

^{1}H NMR (400 MHz, $CDCl_3$) 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).

^{13}C NMR (100 MHz, $CDCl_3$) 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/NH_3) m/z: $[M+NH_4]^+$ calcd for $C_{13}H_{20}NOSi$: 234.13; found: 234.19

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



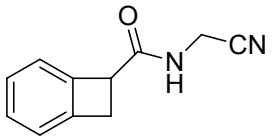
Following experimental procedure 2 with 2-(methylamino)ethanol (2 equiv, 3.0 mmol, 225 mg), N-(2-hydroxyethyl)-N-methylbicyclo[4.2.0]octa-1,3,5-triene-7-carboxamide was isolated in 86% yield (1.3 mmol, 266 mg) as a colourless oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.26 – 7.14 (m, 3H), 7.11 – 7.02 (m, 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 CH_2Cl_2 (3 mL) at -78 °C was added a solution of oxalyl chloride in CH_2Cl_2 (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 CH_2Cl_2 (1.7 mL) was added dropwise to the reaction at -78 °C, and then resulting mixture stirred for 3h. Reaction was then quenched with Et_3N (0.85 mL) and warmed slowly to 0°C, diluted with H_2O and extracted with CH_2Cl_2 (x3). The combined organic layers were washed with brine, dried with $MgSO_4$ and concentrated. Purification by column chromatography gave product **4e** in 65% yield (0.77 mmol, 157 mg) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) 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).

^{13}C NMR (100 MHz, $CDCl_3$) 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 $C_{12}H_{13}NO_2$: 204.1019; found: 204.1019.

N-(cyanomethyl)bicyclo[4.2.0]octa-1,3,5-triene-7-carboxamide (4f)



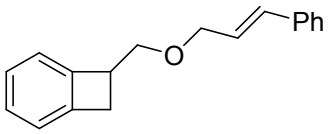
Following experimental procedure 2 with 2-aminoacetonitrile (1.5 equiv, 1.5 mmol, 84 mg), product **4f** was isolated in 95% yield (0.95 mmol, 177 mg) as a white powder.

^{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 $C_{11}H_{11}N_2O$: 187.0866; found: 187.0869.

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



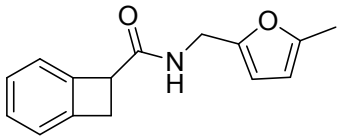
Following experimental procedure 3, a 4 mL vial was charged with bicyclo[4.2.0]octa-1,3,5-trien-7-ylmethanol (0.8 mmol, 107 mg), (*E*)-(3-bromoprop-1-en-1-yl)benzene (2 equiv, 1.6 mmol, 315 mg), NaOH (10 equiv, 8.0 mmol, 320 mg) and TBAI (0.1 equiv, 0.08 mmol, 30 mg), H_2O (0.3 mL) and CH_2Cl_2 (3 mL). The reaction mixture was allowed to stir for 15h at room temperature, then diluted with additional CH_2Cl_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)



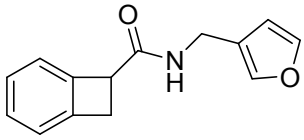
Following experimental procedure 2 with (5-methylfuran-2-yl)methanamine (1.5 equiv, 1.5 mmol, 167 µL), product **4h** was isolated in 80% yield (0.8 mmol, 193 mg) as a white, fluffy powder.

^{1}H NMR (400 MHz, $CDCl_3$) δ 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).

^{13}C NMR (100 MHz, $CDCl_3$) δ 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.

^{1}H NMR (500 MHz, $CDCl_3$) δ 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).

^{13}C NMR (126 MHz, $CDCl_3$) δ 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.

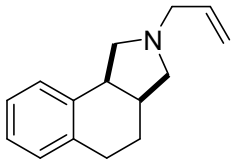
HRMS (ESI/TOF-Q) m/z: $[M+H]^+$ calcd for $C_{14}H_{13}NO_2$: 227.0949; found: 227.0946.

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)



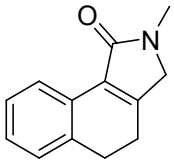
This compound was prepared from **4a** (0.15 mmol, 32 mg) according to procedure 4. The product was purified by column chromatography to give the title compound as a colourless oil in 64% yield (20 mg). *Cis*-conformation confirmed by ROESY experiments.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.18 – 7.07 (m, 3H), 6.95 (dt, *J* = 7.3, 1.1 Hz, 1H), 5.96 (ddt, *J* = 16.8, 10.2, 6.5 Hz, 1H), 5.28 (dq, *J* = 17.1, 1.6 Hz, 1H), 5.22 (dq, *J* = 10.2, 1.2 Hz, 1H), 3.51 (dd, *J* = 8.7, 6.4 Hz, 1H), 3.42 (ddt, *J* = 9.6, 6.6, 1.3 Hz, 2H), 3.12 (dd, *J* = 9.8, 7.1 Hz, 1H), 3.10 – 2.78 (m, 4H), 2.72 (dd, *J* = 11.0, 9.8 Hz, 1H), 2.11 (dddd, *J* = 12.8, 7.1, 3.4, 2.4 Hz, 1H), 2.05 – 1.92 (m, 1H), 1.65 (tdd, *J* = 12.4, 10.3, 7.7 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_{3k}$) δ 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)



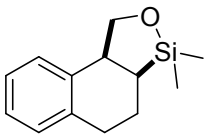
This compound was prepared from **4b** (0.15 mmol, 30 mg) according to procedure 4. The product was purified by prep-HPLC (15-45% NH_4OAc/ACN method) to give the title compound as a white powder in 79% yield (0.12 mmol, 24 mg).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.30 (d, *J* = 7.8 Hz, 1H), 7.30 – 7.13 (m, 3H), 3.97 (s, 2H), 3.11 (s, 3H), 2.98 (t, *J* = 8.2 Hz, 2H), 2.61 (t, *J* = 8.2 Hz, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 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)



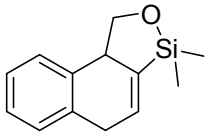
This compound was prepared from **4b** (0.2 mmol, 44 mg) according to procedure 4. The product was purified by column chromatography to give the title compound as a grey crystalline solid in 75% yield (0.15 mmol, 33 mg).

^{1}H NMR (400 MHz, $CDCl_3$) δ 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, $CDCl_3$) δ 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).

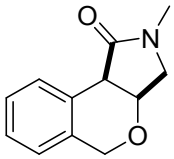
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.24 – 7.15 (m, 4H), 6.54 (ddd, *J* = 7.9, 4.8, 2.8 Hz, 1H), 3.83 – 3.63 (m, 2H), 3.52 – 3.42 (m, 1H), 3.40 – 3.35 (m, 2H), 0.28 (d, *J* = 4.5 Hz, 3H), 0.24 (d, *J* = 1.2 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 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)

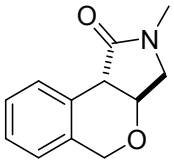
This compound was prepared from **4e** (0.15 mmol, 30 mg) according to procedure 4 and was formed in a 1.7:1 *cis/trans* ratio based on ^{1}H NMR spectroscopic analysis of the crude material. The two diastereomeric products were separated by column chromatography.



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

^{1}H NMR (400 MHz, $CDCl_3$) δ 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, $CDCl_3$) δ 171.8, 134.1, 130.4, 128.4, 127.4, 127.0, 124.1, 71.3, 67.0, 54.7, 43.7, 30.1.



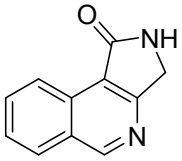
Isolated as a white powder in 32% yield (0.05 mmol, 10 mg)

^{1}H NMR (400 MHz, $CDCl_3$) δ 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, $CDCl_3$) δ 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).

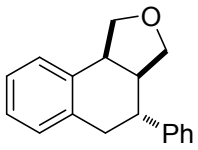
^{1}H NMR (400 MHz, DMSO-d_6) δ 9.49 (s, 1H), 8.85 (d, *J* = 8.4 Hz, 1H), 8.29 (d, *J* = 8.2 Hz, 1H), 7.95 (t, *J* = 7.5 Hz, 1H), 7.77 (t, *J* = 7.6 Hz, 1H), 4.53 (s, 2H).

^{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.

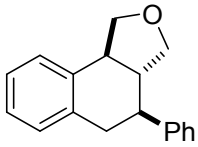
HRMS (ESI/TOF-Q) m/z: $[M+H]^+$ calcd for $C_{11}H_8N_2O$: 185.0709; found: 185.0711.

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).

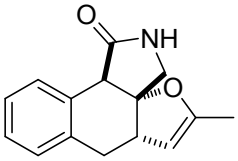


^{1}H NMR (500 MHz, Pyridine-d_5) δ 7.39 (td, *J* = 7.4, 1.4 Hz, 2H), 7.33 – 7.21 (m, 5H), 7.18 – 7.12 (m, 1H), 6.98 (dd, *J* = 7.3, 1.3 Hz, 1H), 4.57 (t, *J* = 7.3 Hz, 1H), 3.93 (t, *J* = 7.3 Hz, 1H), 3.81 (dd, *J* = 10.8, 7.1 Hz, 1H), 3.47 (dd, *J* = 10.9, 7.6 Hz, 1H), 3.22 – 3.09 (m, 2H), 3.00 (td, *J* = 10.9, 6.2 Hz, 1H), 2.91 (dd, *J* = 16.5, 10.6 Hz, 2H), 2.37 (qd, *J* = 11.2, 7.0 Hz, 1H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 144.1, 136.9, 135.3, 128.8, 128.7, 128.6, 127.8, 127.0, 126.7, 126.7, 126.4, 126.2, 125.7, 125.1, 124.2, 74.6, 73.7, 73.0, 69.8, 51.7, 44.8, 43.6, 43.0, 42.1, 38.5, 29.7.

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)



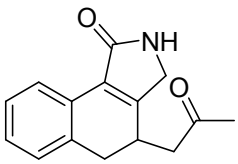
This compound was prepared from **4h** (0.15 mmol, 36 mg) according to procedure 4. The product was purified by column chromatography to give the title compound as a white powder in 55% yield (0.08 mmol, 19.9 mg). *Note:* upon standing, product **5h** slowly degraded to **5h'**.

^{1}H NMR (500 MHz, DMSO-d_6) δ 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) δ 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: $[M+H]^+$ 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')



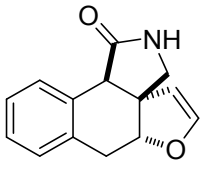
The flow rate on the Phoenix reactor was set to 4.0 mL/min, the back-pressure regulator set to 100 bar, and the temperature set to 300 °C. A 4 mL vial was charged with compound **4h** (0.15 mmol, 36 mg), 2 equiv of pTsOH (2 equiv, 0.3 mmol, 57 mg) and 3 mL of THF, and the reaction mixture then injected 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, $CDCl_3$) δ 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, $CDCl_3$) δ 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: $[M+H]^+$ 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)



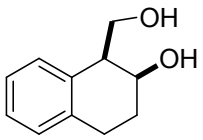
This compound was prepared from **4i** (0.15 mmol, 36 mg) according to procedure 4. The product was purified by column chromatography to give the title compound as a white powder in 24% yield.

^{1}H NMR (400 MHz, $CDCl_3$) δ 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}C NMR (100 MHz, $CDCl_3$) δ 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_2O_2 (12 equiv, 0.55 mmol, 56 µL) 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}H NMR (500 MHz, DMSO-d_6) δ 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 (dddd, *J* = 12.5, 9.7, 5.6, 2.6 Hz, 1H), 1.69 (dt, *J* = 12.9, 6.0 Hz, 1H).

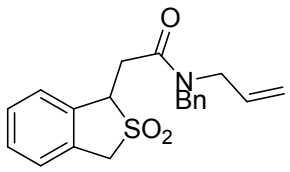
^{13}C NMR (126 MHz, DMSO-d_6) δ 136.8, 136.4, 129.4, 128.2, 125.4, 125.4, 65.1, 64.7, 48.7, 26.9, 24.9.

MS (DCI/NH_3) m/z: $[M+NH_4]^+$ calcd for for $C_{11}H_{18}NO_2$: 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. NH_4Cl, 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-allyl-N-benzyl-2-(2,2-dioxido-1,3-dihydrobenzo[c]thiophen-1-yl)acetamide (7a)



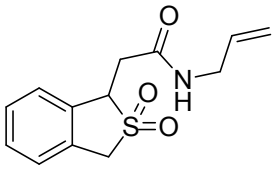
Following experimental procedure 5 with *N*-benzylprop-2-en-1-amine (2 equiv, 8.8 mmol, 1.38 mL), product **7a** was isolated in 47% yield (0.87 mmol, 310 mg) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) 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 (ddd, *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 (ddd, *J* = 5.5, 3.9, 1.3 Hz, 1H), 2.83 (ddd, *J* = 6.1, 4.6, 1.4 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) (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 $C_{20}H_{22}NO_3S$: 356.1315; found: 356.1315.

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



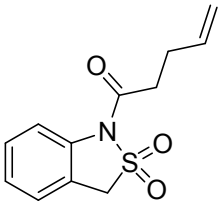
Following experimental procedure 5 with prop-2-en-1-amine (2 equiv, 0.88 mmol, 66 µL), product **7b** was isolated in 86% yield (0.38 mmol, 101 mg) as a colourless oil.

^{1}H 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 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)



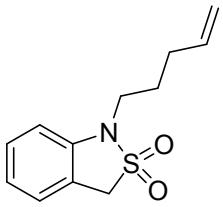
A 20 mL scintillation vial was charged with 1,3-dihydrobenzo[c]isothiazole 2,2-dioxide (0.8 mmol, 135 mg), EDC-HCl (1.2 equiv, 0.96 mmol, 184 mg), DMAP (0.2 equiv, 0.16 mmol, 19.5 mg) and DMF (4 mL). The reaction mixture was stirred at room temperature for 14 hours, then diluted with EtOAc, and washed 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.

^{1}H 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 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_2CO_3 (2 equiv, 2 mmol, 276 mg) and CH_2Cl_2 (10 mL). Reaction mixture was allowed to stir at room temperature for 15 hours, then washed with water, sat. NH_4Cl 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.

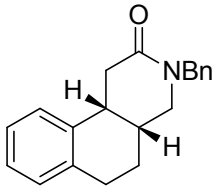
HRMS (ESI/TOF-Q) m/z: $[M+Na]^+$ calcd for $C_{12}H_{15}NNaO_2S$: 260.0716; found: 260.0723.

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.

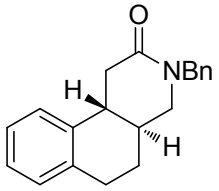
3-benzyl-1,4,4a,5,6,10b-hexahydrobenzo[f]isoquinolin-2(3H)-one (8a)

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.



^{1}H NMR (500 MHz, $CDCl_3$) δ 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 Hz, 1H), 4.50 (d, *J* = 14.6 Hz, 1H), 3.49 (dd, *J* = 12.7, 5.4 Hz, 1H), 3.22 (dt, *J* = 11.1, 5.7 Hz, 1H), 3.07 (dd, *J* = 12.7, 3.7 Hz, 1H), 2.94 – 2.81 (m, 2H), 2.79 (dd, *J* = 17.9, 6.5 Hz, 1H), 2.54 (dd, *J* = 17.9, 10.8 Hz, 1H), 2.24 (dt, *J* = 9.9, 4.5 Hz, 1H), 1.97 – 1.79 (m, 1H), 1.71 – 1.61 (m, 1H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 169.0, 138.9, 137.1, 135.2, 129.2, 128.6, 128.6, 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.



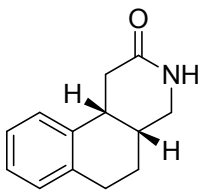
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 – 7.28 (m, 4H), 7.26 – 7.09 (m, 5H), 4.79 (d, *J* = 14.6 Hz, 1H), 4.56 (d, *J* = 14.7 Hz, 1H), 3.50 – 3.21 (m, 2H), 3.06 (t, *J* = 11.6 Hz, 1H), 2.99 – 2.76 (m, 3H), 2.43 (dd, *J* = 17.3, 12.5 Hz, 1H), 1.93 – 1.78 (m, 2H), 1.49 (qd, *J* = 12.2, 6.7 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 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.

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

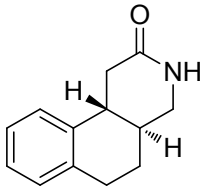
1,4,4a,5,6,10b-hexahydrobenzo[f]isoquinolin-2(3H)-one (8b)

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 1:1 *cis/trans* ratio. Purification by column chromatography gave the two diastereomeric products as light yellow oils in 69% total yield



^{1}H 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).

^{13}C 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.

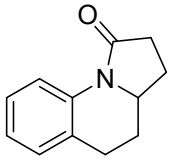


^{1}H NMR (500 MHz, $CDCl_3$) δ 7.22 – 7.19 (m, 2H), 7.19 – 7.15 (m, 1H), 7.13 (dt, *J* = 7.5, 1.3 Hz, 1H), 5.95 (br s, 1H), 3.44 (ddd, *J* = 11.5, 4.9, 3.9 Hz, 1H), 3.25 – 3.09 (m, 2H), 3.00 – 2.86 (m, 2H), 2.33 (dd, *J* = 17.3, 12.4 Hz, 1H), 1.95 (ddt, *J* = 12.9, 5.4, 2.7 Hz, 1H), 1.87 (qdd, *J* = 11.5, 4.9, 2.8 Hz, 1H), 1.59 – 1.39 (m, 2H).

^{13}C 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)



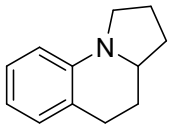
This compound was prepared from **7c** (0.15 mmol, 38 mg) according to procedure 6. Purification by column chromatography gave the title compound in 55% yield (0.08 mmol, 15 mg).

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.70 (dd, *J* = 8.5, 1.2 Hz, 1H), 7.24 – 7.14 (m, 1H), 7.13 (dd, *J* = 7.8, 1.7 Hz, 1H), 7.02 (td, *J* = 7.4, 1.3 Hz, 1H), 3.91 (dddd, *J* = 11.7, 9.2, 6.6, 2.7 Hz, 1H), 2.95 (dd, *J* = 12.6, 5.6 Hz, 1H), 2.88 (dd, *J* = 5.4, 2.0 Hz, 1H), 2.62 (ddd, *J* = 16.9, 11.3, 9.3 Hz, 2H), 2.50 (ddd, *J* = 17.0, 9.6, 2.1 Hz, 2H), 2.30 (dddd, *J* = 12.6, 9.1, 6.7, 2.1 Hz, 2H), 2.18 (ddt, *J* = 13.1, 5.8, 2.3 Hz, 1H), 1.84 – 1.61 (m, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 173.7, 136.9, 129.2, 127.0, 125.9, 123.7, 119.3, 58.3, 32.4, 29.6, 27.9, 25.7.

HRMS (ESI/TOF-Q) m/z: $[M+H]^+$ calcd for $C_{12}H_{14}NO$: 188.1070; found: 188.1069.

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% NH_4OAc/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.

^{1}H NMR (400 MHz, $CDCl_3$) 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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[1] Cis/trans isomers assigned by ^{1}H NMR spectroscopic analysis and comparison to analogous examples, see: S. Zhao, M. J. Totleben, J. P. Freeman, C. L. Bacon, G. B. Fox, E. O'Driscoll, A. G. Foley, J. Kelly, U. Farrell, C. Regan, S. A. Mizsak and J. Szmuszkovicz, *Bioorganic & Medicinal Chemistry*, 1999, **7**, 1637-1646.

[2] 1. G. L. B. Carlson, F. H. Quina, B. M. Zarnegar and D. G. Whitten, *Journal of the American Chemical Society*, 1975, **97**, 347-354.

[3] 2. W. F. Berkowitz and T. V. John, *The Journal of Organic Chemistry*, 1984, **49**, 5269-5271.

[4] Chloro(ethynyl)dimethylsilane was prepared according to literature procedures: M. Sukeda, S. Ichikawa, A. Matsuda and S. Shuto, *The Journal of Organic Chemistry*, 2003, **68**, 3465-3475.

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