Hypervalent iodine mediated cyclization of bishomoallylamides to prolinols

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**General information**

Chemicals were purchased from Sigma Aldrich, Fisher Scientific, or Fluorochem and were used as received without purification or drying. Solvents were used as received without drying. Thin layer chromatography (TLC) was performed on precoated aluminum sheets of Merck silica gel 60 F254 (0.20 mm) and visualized by UV radiation (254 nm). Automated column chromatography was performed on a Biotage® Isolera Four using Biotage® SNAP Ultra cartridges. Melting points were obtained by DSC analysis. 1H NMR and 13C NMR spectra were measured on Bruker AV III 400 or Bruker Neo 600 apparatus and were referenced to the solvent peak. Chemical shifts δ are given in ppm and the multiplicity of the signals are reported as: s = singlet, sbr = broad singlet, d = doublet, t = triplet, q = quartet, sept = septet, dd = doublet of doublets, dt = doublet of triplets, dq = doublet of quartets, qd = quartet of doublets, m = multiplet. The coupling constants (*J*) are given in Hertz. Mass spectrometric measurements were performed at Innovative Physical Organic Solutions (IPOS), University of Huddersfield on Agilent 1290 HPLC + 6530 QTOF instrument. Ions were generated by electrospray ionisation (ESI) and only the mass ions are reported. Spectral data for previously reported compounds are in good agreement with the literature values.

**Preparation of cyclization substrates 3**

Substrates were prepared in three steps using the strategy below:



**General procedure for STEP 1. Synthesis of 2-(pent-4-en-1-yl)-1*H*-isoindole-1,3(2*H*)-dione (S2a).**



Prepared using a modified version of the procedure reported by White *et al.*[[1]](#endnote-1)PPh3 (17.5 g, 67 mmol, 1.0 equiv) was added to an oven dried flask and purged with N2. THF (180 mL) was added and the mixture cooled to 0 °C. DIAD (14.5 mL, 74 mmol, 1.1 equiv) was added dropwise followed by the addition of 4-penten-1-ol (6.9 mL, 67 mmol, 1.0 equiv). After 5 minutes, phthalimide (9.83 g, 67 mmol, 1.0 equiv) was added. The reaction vessel was raised out of the cooling bath and left stirring at rt overnight. All volatiles were removed under vacuum and a mixture of petroleum ether/EtOAc (10:1, 125 mL) was added. The suspension was filtered, and the filtrate was concentrated under vacuum. The crude was purified using flash chromatography (silica gel, 95:5 petrol/EtOAc) to afford the product **S2a** as a pale-yellow oil (12.12 g, 84% yield). Data matched the literature values.1

IR: 716 (s), 884 (m), 1047 (w), 1071 (w), 1335 (m), 1367 (m), 1393 (s), 1437 (m), 1467 (w), 1640 (w), 1703 (s), 2937 (w) cm-1.

1H NMR (CDCl3, 600 MHz): δ 1.77 (2H, quint, *J* = 7.4 Hz, CH2), 2.10 (2H, q, *J* = 7.3 Hz, CH2), 3.68 (2H, t, *J* = 7.3 Hz, CH2), 4.96 (1H, dq, *J* = 10.3, 1.5 Hz, Hb), 5.04 (1H, dq, *J* = 17.1, 1.7 Hz, Ha), 5.80 (1H, ddt, *J* = 17.2, 10.4, 6.6 Hz, CH), 7.69 (2H, dd, *J* = 5.5, 3.0 Hz, Ar), 7.82 (2H, dd, *J* = 5.5, 3.0 Hz, Ar).

13C NMR (CDCl3, 150 MHz): δ 27.7, 31.1, 37.7, 115.4, 123.3, 132.3, 134.0, 137.4, 168.5.

HRMS (ESI-TOF) m/z: [M+H]+ Cald for C13H14NO2+ 216.1019; Found 216.1024.

**Synthesis of 2-((4*Z*)-hex-4-en-1-yl)-1*H*-isoindole-1,3(2*H*)-dione (S2o).[[2]](#endnote-2)**



Prepared according to the general procedure for step 1, at half the scale, using *cis*-4-hexen-1-ol (3.9 mL, 33 mmol, 1.0 equiv). The crude was purified using flash chromatography (silica gel, 95:5 petrol/EtOAc) to afford the product **S2o** as a pale-yellow oil (6.26 g, 82% yield).

IR: 712 (s), 883 (w), 1017 (m), 1072 (m), 1334 (m), 1365 (m), 1392 (s), 1436 (m), 1466 (w), 1614 (w), 1703 (s), 2937 (w) cm-1.

1H NMR (CDCl3, 400 MHz): δ 1.59 (3H, d, *J* = 6.5 Hz, Me), 1.75 (2H, quint, *J* = 7.5 Hz, CH2), 2.11 (2H, q, *J* = 7.4 Hz, CH2), 3.69 (2H, t, *J* = 7.5 Hz, CH2), 5.34-5.52 (2H, m, Ha+Hb), 7.70 (2H, dd, *J* = 5.6, 3.1 Hz, Ar), 7.84 (2H, dd, *J* = 5.5, 3.1 Hz, Ar).

13C NMR (CDCl3, 100 MHz): δ 12.9, 24.4, 28.5, 37.9, 123.3, 125.0, 129.2, 132.3, 134.0, 168.6.

HRMS (ESI-TOF) m/z: [M+H]+ Cald for C14H16NO2+ 230.1176; Found 230.1181.

**Synthesis of 2-(6-methylhept-5-en-2-yl)-1*H*-isoindole-1,3(2*H*)-dione (S2p).**



Prepared according to the general procedure for step 1, at half the scale, using 6-methyl-5-hepten-2-ol (5.1 mL, 33 mmol, 1.0 equiv). The crude was purified using flash chromatography (silica gel, 98:2 petrol/EtOAc) to afford the product **S2p** as a colorless oil (6.48 g, 75% yield).

IR: 717 (s), 879 (m), 1039 (m), 1085 (w), 1332 (m), 1355 (s), 1392 (m), 1451 (w), 1466 (w), 1613 (w), 1702 (s), 2929 (w) cm-1.

1H NMR (CDCl3, 400 MHz): δ 1.46 (3H, d, *J* = 6.9 Hz, Me), 1.49 (3H, s, Mea), 1.54 (3H, d, *J* = 1.0 Hz, Meb), 1.75 (1H, ddt, *J* = 13.8, 7.5, 6.0 Hz, CH2), 1.97 (2H, q, *J* = 7.3 Hz, CH2), 2.16 (1H, ddt, *J* = 14.7, 9.6, 7.3 Hz, CH2), 4.36 (1H, ddt, *J* = 14.6, 9.6, 6.9 Hz, Ha), 5.04 (1H, tt, *J* = 7.1, 1.4 Hz, CH), 7.69 (2H, dd, *J* = 5.6, 3.0 Hz, Ar), 7.81 (2H, dd, *J* = 5.6, 3.0 Hz, Ar).

13C NMR (CDCl3, 100 MHz): δ 17.8, 19.0, 25.6, 25.7, 33.6, 47.4, 123.1, 123.5, 132.2, 132.3, 133.9, 168.7.

HRMS (ESI-TOF) m/z: [M+H]+ Cald for C16H20NO2+ 258.1489; Found 258.1494.

**General procedure for STEP 2. Synthesis of** **pent-4-en-1-amine (S3a).**



Prepared using a modified version of the procedure reported by Xu *et al*.[[3]](#endnote-3) Phthalimide **S2a** (3.0 g, 14 mmol, 1.0 equiv), hydrazine monohydrate (1.0 mL, 21 mmol, 1.5 equiv) and styrene (3.2 mL, 28 mmol, 2.0 equiv) were all dissolved in ethanol (70 mL) and stirred at reflux for 4 hours. The suspension was cooled down to rt and filtered. The filtrate was acidified using HCl (1 M, 20 mL), filtered and transferred to a separating funnel. The organic layer was extracted with Et2O (50 mL) and then discarded. The aqueous layer was basified using NaOH (4 M, 20 mL) and extracted three times with DCM (3 x 50 mL). The organic extracts were combined, dried using Na2SO4 and filtered. The filtrate was reduced under vacuum (20 °C, 500 mbar) to ~30 mL and immediately used in the next step.

**Synthesis of (*Z*)-hex-4-en-1-amine (S3o).**



Prepared according to the general procedure for step 2 using phthalimide **S2o** (3.19 g, 14 mmol, 1.0 equiv). The crude amine was used directly in the next step.

**Synthesis of 6-methylhept-5-en-2-amine (S3p).**



Prepared according to the general procedure for step 2 using phthalimide **S29** (2.99 g, 12 mmol, 1.0 equiv). The crude amine was used directly in the next step.

**General procedure for STEP 3. Synthesis of *N*-(pent-4-en-1-yl)benzamide (3a)**



Prepared using the procedure reported by Gilmour *et al*.3 Pent-4-en-1-amine (**S3a**) (2.6 g, 14 mmol, 1.0 equiv) was dissolved in DCM (30 mL), purged with N2, and cooled to 0 °C. Et3N (3.9 mL, 28 mmol, 2.0 equiv) was added followed by dropwise addition of benzoyl chloride (1.6 mL, 14 mmol, 1.0 equiv). The reaction vessel was raised out of the cooling bath and left stirring at rt overnight. All volatiles were removed under vacuum and Et2O (50 mL) was added. The suspension was filtered and the filtrate was basified using NaOH (2 M, 10 mL). The resulting mixture was transferred to a separating funnel and extracted three times with Et2O (3 x 50 mL). The organic extracts were combined, dried using Na2SO4, filtered and reduced under vacuum. The crude was purified by flash chromatography (silica gel, 85:15 petrol/EtOAc) to afford the product **3a** as a colorless oil (1.74 g, 66% yield). Data matched literature values.3

IR: 692 (s, b), 910 (m), 1204 (w), 1366 (w), 1435 (m), 1489 (m), 1603 (m), 1634 (s), 2931 (w), 3074 (w), 3307 (w, b) cm-1.

1H NMR (CDCl3, 400 MHz): δ 1.72 (2H, quint, *J* = 7.4 Hz, CH2), 2.16 (2H, q, *J* = 7.2 Hz, CH2), 3.47 (2H, q, *J* = 6.7 Hz, CH2), 5.00 (1H, dd, *J* = 10.2, 1.0 Hz, Hb), 5.06 (1H, dd, *J* = 17.2, 1.5 Hz, Ha), 5.83 (1H, ddt, *J* = 17.2, 10.4, 6.6 Hz, CH), 6.28 (1H, br s, NH), 7.41 (2H, t, *J* = 7.4 Hz, Ar), 7.48 (1H, t, *J* = 7.2 Hz, Ar), 7.75 (2H, d, *J* = 8.0 Hz, Ar).

13C NMR (CDCl3, 100 MHz): δ 28.9, 31.4, 39.8, 115.4, 126.9, 128.7, 131.5, 134.9, 138.0, 167.6.

HRMS (ESI-TOF) m/z: [M+H]+ Cald for C12H16NO+ 190.1226; Found 190.1238.

**Synthesis of 4-chloro-*N*-(pent-4-en-1-yl)benzamide(3b)**



Prepared according to the general procedure for step 3 using pent-4-en-1-amine (**S3a**) (12 mmol, 1.0 equiv) in DCM (30 mL). Et3N (3.4 mL, 24 mmol, 2.0 equiv). 4-Chlorobenzoyl chloride (1.6 mL, 12 mmol, 1.0 equiv). The crude was purified using flash chromatography (silica gel, 90:10 petrol/EtOAc) to afford the product **3b** as a white powder (1.28 g, 47% yield).

M.p.: 48-51 °C.

IR: 664 (s, b), 758 (m), 917 (s), 1210 (m), 1374 (m), 1435 (m), 1460 (m), 1483 (m), 1595 (m), 1630 (s), 2979 (m), 3074 (w), 3301 (m, br) cm-1.

1H NMR (CDCl3, 400 MHz): δ 1.72 (2H, quint, *J* = 7.4 Hz, CH2), 2.15 (2H, q, *J* = 7.2 Hz, CH2), 3.46 (2H, q, *J* = 6.7 Hz, CH2), 5.01 (1H, dd, *J* = 10.2, 1.0 Hz, Hb), 5.06 (1H, dd, *J* = 17.2, 1.5 Hz, Ha), 5.83 (1H, ddt, *J* = 17.2, 10.3, 6.6 Hz, CH), 6.23 (1H, br s, NH), 7.39 (2H, d, *J* = 8.5 Hz, Ar), 7.69 (2H, d, *J* = 8.5 Hz, Ar).

13C NMR (CDCl3, 100 MHz): δ 28.8, 31.4, 39.9, 115.5, 128.4, 128.9, 133.2, 137.7, 137.9, 166.6.

HRMS (ESI-TOF) m/z: [M+H]+ Cald for C12H15ClNO+ 224.0837; Found 224.0846.

**Synthesis of 4-bromo-*N*-(pent-4-en-1-yl)benzamide (3c)**



Prepared according to the general procedure for step 3 using pent-4-en-1-amine (**S3a**) (14 mmol, 1.0 equiv) in DCM (30 mL). Et3N (3.9 mL, 28 mmol, 2.0 equiv) and 4-bromobenzoyl chloride (3.05 g, 14 mmol, 1.0 equiv). The crude was purified using flash chromatography (silica gel, 89:11 petrol/EtOAc) to afford the product as a white solid (0.45 g, 12% yield).

M.p.: 67-70 °C.

IR: 641 (m, b), 756 (m), 919 (s), 1263 (m), 1333 (m), 1436 (m), 1479 (m), 1589 (m), 1630 (s), 2979 (s), 3077 (w), 3301 (m, b) cm-1.

1H NMR (CDCl3, 400 MHz): δ 1.73 (2H, quint, *J* = 7.3 Hz, CH2), 2.16 (2H, q, *J* = 7.1 Hz, CH2), 3.46 (2H, q, *J* = 6.7 Hz, CH2), 5.01 (1H, dd, *J* = 10.2, 1.5 Hz, Hb), 5.07 (1H, dq, *J* = 17.2, 1.7 Hz, Ha), 5.84 (1H, ddt, *J* = 17.2, 10.3, 6.7 Hz, CH), 6.16 (1H, br s, NH), 7.56 (2H, d, *J* = 8.7 Hz, Ar), 7.62 (2H, d, *J* = 8.7 Hz, Ar).

13C NMR (CDCl3, 100 MHz): δ 28.8, 31.4, 39.9, 115.5, 126.1, 128.6, 131.9, 133.7, 137.9, 166.6.

HRMS (ESI-TOF) m/z: [M+H]+ Cald for C12H15BrNO+ 268.0346; Found 268.0336.

**Synthesis of** ***N*-(pent-4-en-1-yl)[1,1'-biphenyl]-4-carboxamide (3d)**



Prepared according to the general procedure for step 3 using pent-4-en-1-amine (**S3a**) (14 mmol, 1.0 equiv) in DCM (30 mL). Et3N (3.9 mL, 28 mmol, 2.0 equiv). Biphenyl-4-carbonyl chloride (3.01 g, 13.9 mmol, 1.0 equiv). The crude was purified using flash chromatography (silica gel, 85:15 petrol/EtOAc) to afford the product as a white powder (0.46 g, 12% yield).

M.p.: 141-144 °C.

IR: 654 (m, b), 742 (s), 912 (m), 1448 (m), 1483 (m), 1608 (w), 1630 (s), 2979 (w), 3325 (w, b) cm-1.

1H NMR (CDCl3, 400 MHz): δ 1.76 (2H, quint, *J* = 7.3 Hz, CH2), 2.19 (2H, q, *J* = 7.2 Hz, CH2), 3.51 (2H, q, *J* = 6.7 Hz, CH2), 5.02 (1H, dd, *J* = 10.2, 1.5 Hz, Hb), 5.09 (1H, dq, *J* = 17.2, 1.7 Hz, Ha), 5.86 (1H, ddt, *J* = 17.2, 10.3, 6.6 Hz, CH), 6.21 (1H, br s, NH), 7.38 (1H, t, *J* = 7.3 Hz, Ar), 7.46 (2H, t, *J* = 7.5 Hz, Ar), 7.61 (2H, d, *J* = 7.8 Hz, Ar), 7.65 (2H, d, *J* = 8.3 Hz, Ar), 7.83 (2H, d, *J* = 8.3 Hz, Ar).

13C NMR (CDCl3, 100 MHz): δ 29.0, 31.4, 39.8, 115.5, 127.3, 127.4, 127.5, 128.1, 129.1, 133.6, 138.0, 140.2, 144.3, 167.3.

HRMS (ESI-TOF) m/z: [M+H]+ Cald for C18H20NO+ 266.1539; Found 266.1551.

**Synthesis of 4-methoxy-*N*-(pent-4-en-1-yl)benzamide (3e)**



Prepared according to the general procedure for step 3 using pent-4-en-1-amine (**S3a**) (14 mmol, 1.0 equiv) in DCM (30 mL). Et3N (3.9 mL, 28 mmol, 2.0 equiv) and 4-methoxybenzoyl chloride (1.9 mL, 14 mmol, 1.0 equiv). The crude was purified using flash chromatography (silica gel, 80:20 petrol/EtOAc) to afford the product as a white solid (0.92 g, 30% yield). Data matches the literature values.[[4]](#endnote-4)

M.p.: 48-51 °C.

IR: 652 (m, b), 762 (s), 911 (m), 1250 (m), 1366 (w), 1440 (m), 1452 (m), 1462 (m), 1603 (s), 1628 (s), 2924 (w), 3079 (w), 3323 (m, b) cm-1.

1H NMR (CDCl3, 400 MHz): δ 1.64 (2H, quint, *J* = 7.3 Hz, CH2), 2.06 (2H, q, *J* = 7.3 Hz, CH2), 3.36 (2H, q, *J* = 6.6 Hz, CH2), 3.76 (3H, s, OMe), 4.92 (1H, dd, *J* = 10.2, 1.5 Hz, Hb), 4.98 (1H, dq, *J* = 17.2, 1.7 Hz, Ha), 5.75 (1H, ddt, *J* = 17.2, 10.3, 6.6 Hz, CH), 6.82 (2H, d, *J* = 8.9 Hz, Ar), 6.85 (1H, br s, NH), 7.73 (2H, d, *J* = 8.9 Hz, Ar).

13C NMR (CDCl3, 100 MHz): δ 28.8, 31.2, 39.6, 55.3, 113.5, 115.0, 127.0, 128.0, 137.9, 161.9, 167.2.

HRMS (ESI-TOF) m/z: [M+H]+ Cald for C13H18O2+ 220.1332; Found 220.1341.

**Synthesis of 2-methyl-N-(pent-4-en-1-yl)benzamide (3f)**



Prepared according to the general procedure for step 3 using pent-4-en-1-amine (**S3a**) (12 mmol, 1.0 equiv) in DCM (30 mL). Et3N (3.4 mL, 24 mmol, 2.0 equiv) and *o*-toluoyl chloride (1.6 mL, 12 mmol, 1.0 equiv). The crude was purified using flash chromatography (silica gel, 90:10 petrol/EtOAc to afford the product as a colorless oil (0.84 g, 34% yield).

IR: 693 (m, b), 727 (m), 909 (m), 1205 (w), 1378 (w), 1435 (m), 1486 (m), 1600 (m), 1634 (s), 2927 (w), 3073 (w), 3271 (w, b) cm-1.

1H NMR (CDCl3, 400 MHz): δ 1.71 (2H, quint, *J* = 7.3 Hz, CH2), 2.16 (2H, q, *J* = 7.3 Hz, CH2), 2.43 (3H, s, Me), 3.44 (2H, q, *J* = 6.7 Hz, CH2), 5.00 (1H, dd, *J* = 10.2, 1.5 Hz, Hb), 5.06 (1H, dq, *J* = 17.2, 1.7 Hz, Ha), 5.77-5.89 (2H, m, CH+NH), 7.15-7.22 (2H, m, Ar), 7.25-7.35 (2H, m, Ar).

13C NMR (CDCl3, 100 MHz): δ 19.8, 29.0, 31.3, 39.4, 115.5, 125.8, 126.7, 129.8, 131.1, 136.0, 136.8, 137.8, 170.2.

HRMS (ESI-TOF) m/z: [M+H]+ Cald for C13H18NO+ 204.1383; Found 204.1374.

**Synthesis of 2-fluoro-*N*-(pent-4-en-1-yl)benzamide (3g)**



Prepared according to the general procedure for step 3 using pent-4-en-1-amine (**S3a**) (14 mmol, 1.0 equiv) in DCM (30 mL). Et3N (3.9 mL, 28 mmol, 2.0 equivand 2-fluorobenzoyl chloride (1.7 mL, 14mmol, 1.0 equiv. The crude was purified using flash chromatography (silica gel, 90:10 petrol/EtOAc) to afford the product as a yellow oil (1.76 g, 61% yield).

IR: 912 (m), 1223 (m), 1366 (w), 1451 (m), 1480 (m), 1614 (m), 1639 (s), 2932 (w), 3078 (w), 3297 (w, b) cm-1.

1H NMR (CDCl3, 400 MHz): δ 1.72 (2H, quint, *J* = 7.3 Hz, CH2), 2.15 (2H, q, *J* = 7.3 Hz, CH2), 3.48 (2H, q, *J* = 6.7 Hz, CH2), 4.99 (1H, dq, *J* = 10.2, 1.5 Hz, Hb), 5.05 (1H, dq, *J* = 17.2, 1.7 Hz, Ha), 5.82 (1H, ddt, *J* = 17.2, 10.3, 6.7 Hz, CH), 6.78 (1H, br s, NH), 7.08 (1H, ddd, *J* = 12.3, 8.3, 1.0 Hz, Ar), 7.23 (1H, td, *J* = 7.6, 1.1 Hz, Ar), 7.39-7.47 (1H, m, Ar), 8.06 (1H, td, *J* = 7.9, 1.9 Hz, Ar).

13C NMR (CDCl3, 100 MHz): δ 28.7, 31.3, 39.6, 115.5, 116.1 (d, *J* = 24.9 Hz), 121.3 (d, *J* = 11.8 Hz), 124.9 (d, *J* = 3.4 Hz), 132.2 (d, *J* = 2.2 Hz), 133.3 (d, *J* = 9.2 Hz), 137.8, 160.7 (d, *J* = 247 Hz), 163.4 (d, *J* = 3.2 Hz).

19F (CDCl3, 376 MHz): -114.0.

HRMS (ESI-TOF) m/z: [M+H]+ Cald for C12H15FNO+ 208.1132; Found 208.1132.

**Synthesis of** **2-methoxy-*N*-(pent-4-en-1-yl)benzamide(3h)**



Prepared according to the general procedure for step 3 using pent-4-en-1-amine (**S3a**) (14 mmol, 1.0 equiv) in DCM (30 mL). Et3N (3.9 mL, 28 mmol, 2.0 equiv) and *o*-methoxybenzoyl chloride (2.0 mL, 14 mmol, 1.0 equiv). The crude was purified using flash chromatography (silica gel, 80:20 petrol/EtOAc) to afford the product as a yellow oil (1.07 g, 35% yield).

IR: 655 (m, b), 753 (s), 909 (m), 1236 (s), 1435 (m), 1464 (m), 1482 (m), 1598 (m), 1642 (s), 2931 (w), 3075 (w), 3404 (w, b) cm-1.

1H NMR (CDCl3, 400 MHz): δ 1.72 (2H, quint, *J* = 7.2 Hz, CH2), 2.16 (2H, q, *J* = 7.2 Hz, CH2), 3.48 (2H, q, *J* = 6.6 Hz, CH2), 3.96 (3H, s, OMe), 4.99 (1H, dq, *J* = 10.3, 1.5 Hz, Hb), 5.06 (1H, dq, *J* = 17.1, 1.7 Hz, Ha), 5.84 (1H, ddt, *J* = 17.2, 10.3, 6.7 Hz, CH), 6.96 (1H, d, *J* = 8.5 Hz, Ar), 7.07 (1H, td, *J* = 7.6, 0.8 Hz, Ar), 7.40-7.45 (1H, m, Ar), 7.87 (1H, br s, NH), 8.21 (1H, dd, *J* = 7.8, 1.8 Hz, Ar).

13C NMR (CDCl3, 100 MHz): δ 28.9, 31.4, 39.3, 56.0, 111.4, 115.2, 121.4, 121.8, 132.4, 132.7, 138.0, 157.5, 165.3.

HRMS (ESI-TOF) m/z: [M+Na]+ Cald for C13H18NO2+ 242.1151; Found 242.1157.

**Synthesis of *N*-(pent-4-en-1-yl)acetamide (3i)**



Prepared according to the general procedure for step 3 using pent-4-en-1-amine (**S3a**) (14 mmol, 1.0 equiv) in DCM (30 mL). Et3N (3.9 mL, 28 mmol, 2.0 equiv) and acetyl chloride (1.0 mL, 14 mmol, 1.0 equiv). The crude was purified using flash chromatography (silica gel, 80:20 petrol/EtOAc) to afford the product as a yellow oil (0.60 g, 34% yield). Data matched the literature values.4

IR: 604 (m, b), 724 (w), 910 (m), 1289 (m), 1366 (m), 1640 (m), 2929 (w), 3079 (w), 3287 (w, b) cm-1.

1H NMR (CDCl3, 400 MHz): δ 1.58 (2H, quint, *J* = 7.3 Hz, CH2), 1.94 (3H, s, Me), 2.06 (2H, q, *J* = 7.3 Hz, CH2), 3.22 (2H, q, *J* = 6.6 Hz, CH2), 4.95 (1H, dq, *J* = 10.3, 1.4 Hz, Hb), 5.00 (1H, dq, *J* = 17.2, 1.7 Hz, Ha), 5.77 (1H, ddt, *J* = 17.0, 10.2, 6.7 Hz, CH), 5.86 (1H, br s, NH).

13C NMR (CDCl3, 100 MHz): δ 23.4, 28.8, 31.2, 39.3, 115.3, 137.9, 170.2.

HRMS (ESI-TOF) m/z: [M+H]+ Cald for C7H14NO+ 128.1070; Found 128.1076.

**Synthesis of** **2,2-dimethyl-I-(pent-4-en-1-yl)propanamide (3j)**



Prepared according to the general procedure for step 3 using pent-4-en-1-amine (**S3a**) (12 mmol, 1.0 equiv) in DCM (30 mL). Et3N (3.4 mL, 24 mmol, 2.0 equiv) and trimethylacetyl chloride (1.5 mL, 12 mmol, 1.0 equiv). The crude was purified using flash chromatography (silica gel, 85:15 petrol/EtOAc) to afford the product as a pale-brown oil (0.64 g, 31% yield).

IR: 640 (w, b), 908 (m), 1210 (m), 1366 (w), 1480 (w), 1635 (s), 2963 (w), 3077 (w), 3342 (w, b) cm-1.

1H NMR (CDCl3, 400 MHz): δ 1.18 (9H, s, Me), 1.60 (2H, quint, *J* = 7.2 Hz, CH2), 2.08 (2H, q, *J* = 7.2 Hz, CH2), 3.25 (2H, q, *J* = 6.7 Hz, CH2), 4.98 (1H, dd, *J* = 10.3, 1.0 Hz, Hb), 5.03 (1H, dq, *J* = 17.2, 1.7 Hz, Ha), 5.67 (1H, br s, NH), 5.80 (1H, ddt, *J* = 17.1, 10.3, 6.7 Hz, CH).

13C NMR (CDCl3, 100 MHz): δ 27.7, 28.8, 31.3, 38.8, 39.2, 115.3, 138.1, 178.5.

HRMS (ESI-TOF) m/z: [M+H]+ Cald for C10H20NO+ 170.1539; Found 170.1547.

**Synthesis of *N*-(pent-4-en-1-yl)(phenyl)acetamide(3k)**



Prepared according to the general procedure for step 3 using pent-4-en-1-amine (**S3a**) (14 mmol, 1.0 equiv) in DCM (30 mL). Et3N (3.9 mL, 28 mmol, 2.0 equiv) and phenylacetyl chloride (1.8 mL, 14 mmol, 1.0 equiv). The crude was purified using flash chromatography (silica gel, 83:17 petrol/EtOAc) to afford the product as a yellow solid (1.07 g, 38% yield).

M.p.: 39-42 °C.

IR: 692 (s), 754 (m), 909 (m), 1270 (m), 1346 (m), 1453 (m), 1472 (m), 1491 (m), 1626 (m), 1655 (m), 2932 (m), 3063 (m), 3242 (m, b) cm-1.

1H NMR (CDCl3, 400 MHz): δ 1.52 (2H, quint, *J* = 7.2 Hz, CH2), 1.99 (2H, q, *J* = 7.2 Hz, CH2), 3.21 (2H, q, *J* = 6.5 Hz, CH2), 3.56 (2H, s, ArCH2), 4.88-4.97 (2H, m, Ha+Hb), 5.45 (1H, br s, NH), 5.72 (1H, ddt, *J* = 17.1, 10.2, 6.7 Hz, CH), 7.23-7.39 (5H, m, Ar).

13C NMR (CDCl3, 100 MHz): δ 28.6, 31.2, 39.2, 44.0, 115.3, 127.5, 129.1, 129.6, 135.1, 137.8, 171.0.

HRMS (ESI-TOF) m/z: [M+H]+ Cald for C13H18NO+ 204.1383; Found 204.1388.

**Synthesis of *N*-(pent-4-en-1-yl)prop-2-enamide (3l)**



Prepared according to the general procedure for step 3 using pent-4-en-1-amine (**S3a**) (14mmol, 1.0 equiv) in DCM (30 mL). Et3N (3.9 mL, 28 mmol, 2.0 equiv) and acryloyl chloride (1.1 mL, 14 mmol, 1.0 equiv). The crude was purified using flash chromatography (silica gel, 75:25 petrol/EtOAc) to afford the product as a pale-yellow oil (0.47 g, 24% yield). Data matched the literature values.[[5]](#endnote-5)

IR: 648 (w, b), 710 (w), 911 (m), 1242 (m), 1655 (m), 2931 (w), 3078 (w), 3284 (w, b) cm-1.

1H NMR (CDCl3, 400 MHz): δ 1.64 (2H, quint, *J* = 7.3 Hz, CH2), 2.10 (2H, q, *J* = 7.3 Hz, CH2), 3.34 (2H, q, *J* = 6.7 Hz, CH2), 4.98 (1H, dd, *J* = 10.3, 1.1 Hz, He), 5.03 (1H, dq, *J* = 17.2, 1.7 Hz, Hd), 5.61 (1H, dd, *J* = 10.3, 1.4 Hz, Hb), 5.74-5.85 (2H, m, CH+NH), 6.08 (1H, dd, *J* = 16.9, 10.3 Hz, Hc), 6.26 (1H, dd, *J* = 17.1, 1.5 Hz, Ha).

13C NMR (CDCl3, 100 MHz): δ 28.8, 31.2, 39.3, 115.4, 126.3, 131.1, 137.8, 165.7.

HRMS (ESI-TOF) m/z: [M+H]+ Cald for C8H14NO+ 140.1070; Found 140.1073.

**Synthesis of *N*-(pent-4-en-1-yl)cyclopropanecarboxamide (3m)**



Prepared according to the general procedure for step 3 using pent-4-en-1-amine (**S3a**) (14 mmol, 1.0 equiv) in DCM (30 mL). Et3N (3.9 mL, 28 mmol, 2.0 equiv) and cyclopropanecarbonyl chloride (1.3 mL, 14 mmol, 1.0 equiv). The crude was purified using flash chromatography (silica gel, 85:15 petrol/EtOAc) to afford the product as a pale-yellow oil (0.93 g, 44% yield).

1H NMR (CDCl3, 400 MHz): δ 0.65-0.73 (2H, m, cycloprop), 0.88-0.95 (2H, m, cycloprop), 1.28-1.37 (1H, m, cyclopropCH), 1.59 (2H, quint, *J* = 7.2 Hz, CH2), 2.07 (2H, q, *J* = 7.3 Hz, CH2), 3.25 (2H, q, *J* = 6.8 Hz, CH2), 4.96 (1H, dd, *J* = 10.3, 1.1 Hz, Hb), 5.01 (1H, dd, *J* = 17.0, 1.6, Hz Ha), 5.79 (1H, ddt, *J* = 17.2, 10.4, 6.5 Hz, CH), 5.94 (1H, br s, NH).

13C NMR (CDCl3, 100 MHz): δ 7.0, 14.8, 29.0, 31.2, 39.3, 115.2, 137.9, 173.6.

IR: 640 (w, b), 910 (m), 1242 (m), 1364 (w), 1640 (s), 2932 (w), 3080 (w), 3290 (w, b) cm-1.

HRMS (ESI-TOF) m/z: [M+H]+ Cald for C9H20NO+ 154.1226; Found 154.1229.

**Synthesis of** ***N*-(pent-4-en-1-yl)cyclohexanecarboxamide** **(3n)**



Prepared according to the general procedure for step 3 using pent-4-en-1-amine (**S3a**) (14 mmol, 1.0 equiv) in DCM (30 mL). Et3N (3.9 mL, 28 mmol, 2.0 equiv) and cyclohexanecarbonyl chloride (1.9 mL, 14 mmol, 1.0 equiv). The crude was purified using flash chromatography (silica gel, 86:14 petrol/EtOAc) to afford the product as a white solid (0.77 g, 28% yield).

M.p.: 39-42 °C.

IR: 697 (m, b), 747 (w), 911 (m), 1256 (m), 1392 (m), 1636 (s), 2928 (s), 3093 (w), 3286 (m, b) cm-1.

1H NMR (CDCl3, 400 MHz): δ 1.19-1.31 (3H, m, cyclohex), 1.34-1.47 (2H, m, cyclohex), 1.53-1.68 (3H, m, cyclohexCH+CH2), 1.72-1.87 (4H, m, cyclohex), 2.03-2.10 (3H, m, CH2), 3.23 (2H, q, *J* = 6.7 Hz, CH2), 4.95 (1H, dd, *J* = 10.2, 1.5, Hz, Hb), 5.01 (1H, dq, *J* = 17.2, 1.7 Hz, Ha), 5.63 (1H, br s, NH), 5.78 (1H, ddt, *J* = 17.1, 10.2, 6.7 Hz, CH).

13C NMR (CDCl3, 100 MHz): δ 25.9, 28.9, 29.8, 31.2, 38.9, 45.7, 115.2, 138.0, 176.2.

HRMS (ESI-TOF) m/z: [M+H]+ Cald for C12H22NO+ 196.1696; Found 196.1702.

**Synthesis of** ***N*-(pent-4-en-1-yl)furan-2-carboxamide (3o)**



Prepared according to the general procedure for step 3 using pent-4-en-1-amine (**S3a**) (12 mmol, 1.0 equiv) in DCM (30 mL). Et3N (3.4 mL, 24 mmol, 2.0 equiv). 2-Furoyl chloride (1.2 mL, 12 mmol, 1.0 equiv). The crude was purified using flash chromatography (silica gel, 85:15 petrol/EtOAc) to afford the product as a yellow oil (0.80 g, 36% yield).

IR: 678 (w, b), 749 (s), 911 (m), 1242 (w), 1376 (w), 1475 (m), 1639 (s), 2932 (m), 3076 (w), 3297 (m, b) cm-1.

1H NMR (CDCl3, 400 MHz): δ 1.70 (2H, quint, *J* = 7.3 Hz, CH2), 2.14 (2H, q, *J* = 7.2 Hz, CH2), 3.43 (2H, q, *J* = 6.7 Hz, CH2), 5.00 (1H, dd, *J* = 10.2, 1.5 Hz, Hb), 5.06 (1H, dq, *J* = 17.2, 1.7 Hz, Ha), 5.82 (1H, ddt, *J* = 17.2, 10.3, 6.6 Hz, CH), 6.40 (1H, br s, NH), 6.48 (1H, dd, *J* = 3.5, 1.7 Hz, furan), 7.09 (1H, d, *J* = 3.5 Hz, furan), 7.41 (1H, d, *J* = 1.0 Hz, furan).

13C NMR (CDCl3, 100 MHz): δ 28.9, 31.2, 38.8, 112.2, 114.1, 115.4, 137.8, 143.8, 148.3, 158.5.

HRMS (ESI-TOF) m/z: [M+H]+ Cald for C10H14NO2+ 180.1019; Found 180.1024.

**Synthesis of *N*-(2,2-dimethylpent-4-en-1-yl)benzamide (3p)**



Prepared according to the general procedure for step 3 using 2,2-dimethylpent-4-en-1-amine[[6]](#endnote-6) (20 mmol, 1.0 equiv) in DCM (50 mL). Et3N (5.6 mL, 40 mmol, 2.0 equiv) and benzoyl chloride (2.3 mL, 20 mmol, 1.0 equiv). The crude was purified using flash chromatography (silica gel, 90:10 petrol/EtOAc) to afford the product as a yellow oil (0.14 g, 3% yield). Data matched the literature values.[[7]](#endnote-7)

IR: 913 (m), 1204 (w), 1367 (m), 1431 (w), 1489 (w), 1579 (w), 1639 (m), 2913 (w), 3328 (m, b) cm-1.

1H NMR (CDCl3, 400 MHz): δ 0.97 (6H, s, Me), 2.06 (2H, d, *J* = 7.5 Hz, CH2), 3.31 (2H, d, *J* = 6.4 Hz, CH2), 5.05-5.12 (2H, m, Ha+Hb), 5.89 (1H, ddt, *J* = 16.7, 7.5, 7.4, Hz, CH), 6.23 (1H, br s, NH), 7.43 (2H, t, *J* = 7.3 Hz, Ar), 7.49 (1H, t, *J* = 7.3 Hz, Ar), 7.75 (2H, d, *J* = 7.8 Hz, Ar).

13C NMR (CDCl3, 100 MHz): δ 25.2, 35.2, 45.0, 49.5, 117.7, 126.9, 128.7, 131.5, 135.1, 135.2, 167.7.

HRMS (ESI-TOF) m/z: [M+H]+ Cald for C14H19NO 218.1539; Found 218.1547.

**Synthesis of *N*-((4*Z*)-hex-4-en-1-yl)benzamide (3q)**



Prepared according to the general procedure for step 3 using (*Z*)-hex-4-en-1-amine (**S3o**) (14 mmol, 1.0 equiv) in DCM (30 mL). Et3N (3.9 mL, 28 mmol, 2.0 equiv) and benzoyl chloride (1.6 mL, 14 mmol, 1.0 equiv). The crude was purified using flash chromatography (silica gel, 90:10 petrol/EtOAc) to afford the product as a pale-yellow oil (1.46 g, 52% yield).

IR: 691 (s, b), 1369 (w), 1435 (w), 1489 (m), 1602 (m), 1634 (m), 2932 (w), 3310 (w, b) cm-1.

1H NMR (CDCl3, 400 MHz): δ 1.61 (3H, d, *J* = 6.7 Hz, Me), 1.68 (2H, quint, *J* = 7.3 Hz, CH2), 2.14 (2H, q, *J* = 7.2 Hz, CH2), 3.45 (2H, q, *J* = 6.7 Hz, CH2), 5.36-5.55 (2H, m, Ha+Hb), 6.35 (1H, br s, NH), 7.40 (2H, t, *J* = 7.4 Hz, Ar), 7.47 (1H, t, *J* = 7.3 Hz, Ar), 7.75 (2H, d, *J* = 8.0 Hz, Ar).

13C NMR (CDCl3, 100 MHz): δ 12.9, 24.5, 29.5, 39.9, 125.0, 126.9, 128.6, 129.6, 131.4, 134.9, 167.6.

HRMS (ESI-TOF) m/z: [M+H]+ Cald for C13H18NO+ 204.1383; Found 204.1384.

**Synthesis of *N*-(6-methylhept-5-en-2-yl)benzamide(3r)**



Prepared according to the general procedure for step 3 using 6-methylhept-5-en-2-amine (**S3p**) (12 mmol, 1.0 equiv) in DCM (30 mL). Et3N (3.2 mL, 23 mmol, 2.0 equiv) and benzoyl chloride (1.3 mL, 11.6 mmol, 1.0 equiv). The crude was purified using flash chromatography (silica gel, 90:10 petrol/EtOAc) to afford the product as an orange powder (0.18 g, 7% yield).

M.p.: 84-87 °C.

IR: 664 (m, b), 746 (w), 893 (w), 1278 (w), 1352 (m), 1450 (m), 1492 (m), 1602 (m), 1629 (m), 2922 (m), 3302 (w, b) cm-1.

1H NMR (CDCl3, 400 MHz): δ 1.24 (3H, d, *J* = 6.6 Hz, Me), 1.56-1.66 (6H, m, Mea+CH2), 1.68 (3H, d, *J* = 0.9 Hz, Meb), 2.05-2.13 (2H, m, CH2), 4.21 (1H, ddt, *J* = 13.3, 12.7, 6.7 Hz, Ha), 5.14 (1H, tt, *J* = 7.2, 1.4 Hz, CH), 5.96 (1H, br d, *J* = 7.2 Hz, NH), 7.42 (2H, t, *J* = 7.4 Hz, Ar), 7.48 (1H, t, 7.3 Hz, Ar), 7.74 (1H, d, *J* = 7.8 Hz, Ar).

13C NMR (CDCl3, 100 MHz): δ 17.8, 21.1, 24.8, 25.9, 37.0, 45.8, 123.9, 126.9, 128.7, 131.4, 132.4, 135.2, 166.9.

HRMS (ESI-TOF) m/z: [M+H]+ Cald for C15H22NO+ 232.1696; Found 232.1703.

**General procedure for the cyclization reaction: synthesis of (2-(hydroxymethyl)pyrrolidin-1-yl)(phenyl)methanone (7a)**



*N*-(Pent-4-en-1-yl)benzamide **(3a)** (69.4 mg, 0.37 mmol, 1.0 equiv) was dissolved in MeCN (3.0 mL) at room temperature. TFA (42 µL, 0.55 mmol, 1.5 equiv) was added followed by Selectfluor (260 mg, 0.73 mmol, 2.0 equiv). After 5 minutes, 1-iodo-2,4-dimethoxybenzene (145 mg, 0.55 mmol, 1.5 equiv) was added and the mixture was left stirring for 48 hours. The resulting mixture was basified with aqueous NaOH solution (2 M, 2.0 mL), stirred for 10 minutes, then transferred to a separating funnel containing a saturated aqueous solution of sodium thiosulfate pentahydrate (5.0 mL). After vigorous shaking, the organic layer was extracted three times with EtOAc (3 x 10 mL). The organic extracts were combined, dried using Na2SO4, filtered and concentrated under vacuum. The crude was purified by flash chromatography (silica gel, 35:65 petrol/EtOAc) to afford the product as a brown oil (51.3 mg, 68% yield). Data matched the literature values.[[8]](#endnote-8)

IR: 700 (s), 1027 (m), 1421 (s), 1598 (s), 2970 (m), 3378 (w, b) cm-1.

1H NMR (CDCl3, 400 MHz): δ 1.58-1.78 (2H, m, CH2), 1.80-1.90 (1H, m, CH2), 2.08-2.18 (1H, m, CH2), 3.40-3.52 (2H, m, CH2), 3.67-3.81 (2H, m, CH2OH), 4.32-4.41 (1H, m, CH), 4.94 (1H, br s, OH), 7.35-7.42 (3H, m, Ar), 7.48 (2H, d, *J* = 6.5 Hz, Ar).

13C NMR (CDCl3, 100 MHz): δ 25.0, 28.5, 51.2, 61.4, 67.0, 127.1, 128.4, 130.2, 136.7, 172.2.

HRMS (ESI-TOF) m/z: [M+H]+ Cald for C12H16NO2+ 206.1176; Found 206.1175.

**Synthesis of (4-chlorophenyl)(2-(hydroxymethyl)pyrrolidin-1-yl)methanone (7b)**



Prepared according to the general procedure for the cyclization reaction using 4-chloro-*N*-(pent-4-en-1-yl)benzamide (**3b**) (83 mg, 0.37 mmol, 1.0 equiv). The crude was purified using flash chromatography (silica gel, 40:60 petrol/EtOAc) to afford the product as a brown oil (49 mg, 55% yield). Data matched the literature values.[[9]](#endnote-9)

IR: 756 (m), 1014 (m), 1422 (s), 1595 (s), 2969 (w), 3398 (w, b) cm-1.

1H NMR (CDCl3, 400 MHz): δ 1.60-1.80 (2H, m, CH2), 1.83-1.92 (1H, m, CH2), 2.08-2.19 (1H, m, CH2), 3.38-3.52 (2H, m, CH2), 3.64-3.84 (2H, m, CH2OH), 4.29-4.39 (1H, m, CH), 4.73 (1H, br s, OH), 7.36 (2H, d, *J* = 8.4 Hz, Ar), 7.44 (2H, d, *J* = 8.4 Hz, Ar).

13C NMR (CDCl3, 150 MHz): δ 25.1, 28.4, 51.2, 61.5, 66.8, 128.7, 135.0, 136.3, 171.0.

HRMS (ESI-TOF) m/z: [M+H]+ Cald for C12H15ClNO2+ 240.0786; Found 240.0783.

**Synthesis of (4-bromophenyl)(2-(hydroxymethyl)pyrrolidin-1-yl)methanone (7c)**



Prepared according to the general procedure for the cyclization reaction using 4-bromo-*N*-(pent-4-en-1-yl)benzamide(**3c**) (81 mg, 0.30 mmol, 1.0 equiv). The crude was purified using flash chromatography (silica gel, 40:60 petrol/EtOAc) to afford the product as a brown oil (47 mg, 55% yield).Data matched the literature values.7

IR: 754 (m), 1047 (m), 1422 (s), 1589 (s), 2970 (w), 3362 (w, b) cm-1.

1H NMR (CDCl3, 400 MHz): δ 1.60-1.79 (2H, m, CH2), 1.82-1.91 (1H, m, CH2), 2.08-2.17 (1H, m, CH2), 3.40-3.47 (1H, m, CH2), 3.65-3.73 (1H, m, CH2OH), 3.73-3.80 (1H, m, CH2OH), 4.29-4.38 (1H, m, CH), 4.73 (1H, br s, OH), 7.36 (2H, d, *J* = 8.2 Hz, Ar), 7.52 (2H, d, *J* = 8.2 Hz, Ar).

13C NMR (CDCl3, 100 MHz): δ 25.0, 28.4, 51.2, 61.4, 66.6, 124.6, 128.8, 131.6, 135.5, 171.0.

HRMS (ESI-TOF) m/z: [M+H]+ Cald for C12H15NO2+ 284.0281; Found 284.0290.

**Synthesis of [1,1'-biphenyl]-4-yl(2-(hydroxymethyl)pyrrolidin-1-yl)methanone (7d)**



Prepared according to the general procedure for the cyclization reaction using *N*-(pent-4-en-1-yl)[1,1'-biphenyl]-4-carboxamide (**3d**) (71 mg, 0.27 mmol, 1.0 equiv). The crude was purified using flash chromatography (silica gel, 40:60 petrol/EtOAc) to afford the product as a brown oil (43 mg, 57% yield). Data matched the literature values.7

IR: 747 (s), 1031 (m), 1426 (s), 1599 (s), 2970 (w), 3346 (w, b) cm-1.

1H NMR (CDCl3, 400 MHz): δ 1.61-1.82 (2H, m, CH2), 1.84-1.95 (1H, m, CH2), 2.10-2.25 (1H, m, CH2), 3.48-3.63 (2H, m, CH2), 3.70-3.89 (2H, m, CH2OH), 4.35-4.50 (1H, m, CH), 4.95 (1H, br d, *J* = 5.0 Hz, OH), 7.37 (1H, t, *J* = 7.3 Hz, Ar), 7.45 (2H, t, *J* = 7.5 Hz, Ar), 7.54-7.66 (6H, m, Ar).

13C NMR (CDCl3, 100 MHz): δ 25.2, 28.6, 51.3, 61.7 67.3, 127.1, 127.2, 127.7, 128.0, 129.0, 135.4, 140.2, 143.2, 172.1.

HRMS (ESI-TOF) m/z: [M+H]+ Cald for C18H20NO2+ 282.1489; Found 282.1498.

**Synthesis of (2-(hydroxymethyl)pyrrolidin-1-yl)(4-methoxyphenyl)methanone (7e)**



Prepared according to the general procedure for the cyclization reaction using 4-methoxy-*N*-(pent-4-en-1-yl)benzamide (**3e**) (75 mg, 0.34 mmol, 1.0 equiv). The crude was purified using flash chromatography (silica gel, 35:65 petrol/EtOAc) to afford the product as a brown oil (36 mg, 45% yield). Data matched the literature values.7

IR: 727 (m), 1026 (s), 1422 (s), 1600 (s), 2970 (w), 3394 (w, b) cm-1.

1H NMR (CDCl3, 400 MHz): δ 1.55-1.78 (2H, m, CH2), 1.80-1.90 (1H, m, CH2), 2.06-2.18 (1H, m, CH2), 3.45-3.60 (2H, m, CH2), 3.65-3.83 (5H, m, CH2OH+OMe), 4.32-4.41 (1H, m, CH), 4.98 (1H, br s, OH), 6.88 (2H, d, *J* = 8.5 Hz, Ar), 7.47 (2H, d, *J* = 8.5 Hz, Ar).

13C NMR (CDCl3, 100 MHz): δ 25.2, 28.5, 51.4, 55.4, 61.5, 67.2, 113.6, 128.7, 129.2, 161.1, 172.0.

HRMS (ESI-TOF) m/z: [M+H]+ Cald for C13H18NO3+ 236.1281; Found 236.1290.

**Synthesis of (2-(hydroxymethyl)pyrrolidin-1-yl)(2-methylphenyl)methanone (7f)**



Prepared according to the general procedure for the cyclization reaction using *N*-(pent-4-en-1-yl)[1,1'-biphenyl]-4-carboxamide (**3f**) (72 mg, 0.35 mmol, 1.0 equiv). The crude was purified using flash chromatography (silica gel, 35:65 petrol/EtOAc) to afford the product as a brown oil (24 mg, 32% yield). Data matched the literature values.[[10]](#endnote-10)

IR: 728 (s), 1030 (m), 1421 (s), 1595 (s), 2980 (m), 3367 (w, b) cm-1.

1H NMR (CDCl3, 400 MHz): δ 1.58-1.90 (3H, m, CH2), 2.11-2.21 (1H, m, CH2), 2.32 (3H, s, Me), 3.13-3.26 (2H, m, CH2), 3.70-3.81 (2H, m, CH2OH), 4.34-4.42 (1H, m, CH), 5.11 (1H, br s, OH), 7.16-7.30 (4H, m, Ar).

13C NMR (CDCl3, 100 MHz): δ 18.9, 24.7, 28.7, 50.0, 61.2, 67.4, 125.4, 126.1, 129.2, 130.6, 133.6, 137.3, 172.5.

HRMS (ESI-TOF) m/z: [M+H]+ Cald for C13H18NO2+ 220.1332; Found 220.1331.

**Synthesis of (2-fluorophenyl)(2-(hydroxymethyl)pyrrolidin-1-yl)methanone (7g)**



Prepared according to the general procedure for the cyclization reaction using 2-fluoro-*N*-(pent-4-en-1-yl)benzamide(**3g**) (83 mg, 0.40 mmol, 1.0 equiv). The crude was purified using flash chromatography (silica gel, 40:60 petrol/EtOAc) to afford the product as a brown oil (37 mg, 42% yield).

IR: 754 (m), 1050 (m), 1425 (s), 1608 (s), 2958 (w), 3382 (w, b) cm-1.

1H NMR (CDCl3, 400 MHz): δ 1.62-1.81 (2H, m, CH2), 1.82-1.91 (1H, m, CH2), 2.11-2.20 (1H, m, CH2), 3.31-3.42 (2H, m, CH2), 3.70-3.81 (2H, m, CH2OH), 4.30-4.39 (1H, m, CH), 4.76 (1H, br s, OH), 7.09 (1H, t, *J* = 9.2 Hz, Ar), 7.19 (1H, t, *J* = 7.4 Hz, Ar), 7.35-7.43 (2H, m, Ar).

13C NMR (CDCl3, 100 MHz): δ 24.6, 28.6, 49.5 (d, *J* = 3.7 Hz), 61.6, 66.7, 116.1 (d, *J* = 21.4 Hz), 124.7 (d, *J* = 3.4 Hz), 125.2 (d, *J* = 17.4 Hz), 128.8 (d, *J* = 3.6 Hz), 131.7 (d, *J* = 8.1 Hz), 158.2 (d, *J* = 248 Hz), 167.6.

19F (CDCl3, 376 MHz): -114.9.

HRMS (ESI-TOF) m/z: [M+H]+ Cald for C12H15FNO2+ 224.1081; Found 224.1090.

**Synthesis of (2-(hydroxymethyl)pyrrolidin-1-yl)(2-methoxyphenyl)methanone (7h)**



Prepared according to the general procedure for the cyclization reaction using 2-methoxy-*N*-(pent-4-en-1-yl)benzamide (**3h**) (68 mg, 0.31 mmol, 1.0 equiv). The crude was purified using flash chromatography (silica gel, 35:65 petrol/EtOAc) to afford the product as a brown oil (39 mg, 53% yield).

IR: 726 (s), 1021 (m), 1437 (s), 1597 (s), 2979 (m), 3398 (w, b) cm-1.

1H NMR (CDCl3, 400 MHz): δ 1.59-1.87 (3H, m, CH2), 2.09-2.19 (1H, m, CH2), 3.19-3.31 (2H, m, CH2), 3.65-3.73 (1H, m, CH2OH), 3.77-3.85 (4H, m, CH2OH+OMe), 4.28-4.37 (1H, m, CH), 4.97 (1H, br s, OH), 6.91 (1H, d, *J* = 8.4 Hz, Ar), 6.97 (1H, t, *J* = 7.4 Hz, Ar), 7.25 (1H, t, *J* = 7.7 Hz, Ar), 7.34 (1H, t, *J* = 7.9 Hz, Ar).

13C NMR (CDCl3, 100 MHz): δ 24.5, 28.7, 49.4, 55.8, 61.2, 66.8, 111.2, 121.0, 126.8, 127.7, 130.8, 155.1.

HRMS (ESI-TOF) m/z: [M+H]+ Cald for C13H18NO3+ 236.1281; Found 236.1292.

**Synthesis of 1-(2-(hydroxymethyl)pyrrolidin-1-yl)-2-phenylethan-1-one (7k)**



Prepared according to the general procedure for the cyclization reaction using *N*-(pent-4-en-1-yl)(phenyl)acetamide (**3k**) (83 mg, 0.41 mmol, 1.0 equiv). The crude was purified using flash chromatography (silica gel, 35:65 petrol/EtOAc) to afford the product as a brown oil (19 mg, 22% yield).

IR: 720 (m), 1029 (m), 1427 (m), 1614 (m), 2979 (w), 3362 (w, b) cm-1.

1H NMR (CDCl3, 400 MHz): δ 1.52-1.62 (1H, m, CH2), 1.76-1.96 (3H, m, CH2), 1.97-2.08 (1H, m, CH2), 3.39-3.47 (1H, m, CH2), 3.52-3.68 (3H, m, CH2+CH2OH), 3.69 (2H, s, ArCH2), 4.19-4.27 (1H, m, CH), 5.03 (1H, br s, OH), 7.23-7.28 (3H, m, Ar), 7.30-7.36 (2H, m, Ar).

13C NMR (CDCl3, 100 MHz): δ 24.5, 28.4, 42.5, 48.5, 61.6, 67.4, 127.1, 128.8, 129.0, 134.4, 172.5.

HRMS (ESI-TOF) m/z: [M+H]+ Cald for C13H18NO2+ 220.1332; Found 220.1341.

**Synthesis of cyclopropyl(2-(hydroxymethyl)pyrrolidin-1-yl)methanone (7m)**



Prepared according to the general procedure for the cyclization reaction using *N*-(pent-4-en-1-yl)cyclopropanecarboxamide(**3m**) (71 mg, 0.47 mmol, 1.0 equiv). The crude was purified using flash chromatography (silica gel, 40:60 petrol/EtOAc) to afford the product as a brown oil (40 mg, 50% yield).

IR: 739 (m), 1030 (m), 1438 (s), 1602 (s), 2950 (w), 3374 (w, b) cm-1.

1H NMR (CDCl3, 400 MHz): δ 0.78-0.85 (2H, m, cycloprop), 0.98-1.08 (2H, m, cycloprop), 1.58-1.68 (2H, m, CH2), 1.86-2.08 (3H, m, CH2+Ha), 3.52-3.79 (4H, m, CH2+CH2OH), 4.18-4.27 (1H, m, CH), 5.21 (1H, dd, *J* = 7.4, 1.6 Hz, OH).

13C NMR (CDCl3, 100 MHz): δ 8.0, 8.5, 12.9, 24.5, 28.5, 48.3, 61.6, 68.0, 175.2.

HRMS (ESI-TOF) m/z: [M+H]+ Cald for C9H16NO2+ 170.1176; Found 170.1183.

**Synthesis of cyclohexyl(2-(hydroxymethyl)pyrrolidin-1-yl)methanone (7n)**



Prepared according to the general procedure for the cyclization reaction using *N*-(pent-4-en-1-yl)cyclohexanecarboxamide (**3n**) (76 mg, 0.39 mmol, 1.0 equiv). The crude was purified using flash chromatography (silica gel, 50:50 petrol/EtOAc) to afford the product as a yellow oil (22 mg, 26% yield).

IR: 1050 (m), 1435 (m), 1606 (m), 2924 (m), 3363 (w, b) cm-1.

1H NMR (CDCl3, 400 MHz): δ 1.17-1.31 (4H, m, cyclohex), 1.43-1.60 (3H, m, cyclohex+CH2), 1.63-1.70 (1H, m, CH2), 1.73-1.82 (2H, m, cyclohex+CH2), 1.82-2.07 (4H, m, cyclohex), 2.34 (1H, tt, *J* = 3.1, 11.7 Hz, cyclohexCH), 3.43-3.64 (4H, m, CH2+CH2OH), 4.15-4.23 (1H, m, CH), 5.24 (1H, br s, OH).

13C NMR (CDCl3, 100 MHz): δ 24.6, 25.81, 25.83, 25.9, 28.3, 28.6, 29.4, 43.2, 47.8, 61.2, 67.8, 177.8.

HRMS (ESI-TOF) m/z: [M+H]+ Cald for C12H22NO2+ 212.1645; Found 212.1653.

**Synthesis of furan-2-yl(2-(hydroxymethyl)pyrrolidin-1-yl)methanone (7o)**



Prepared according to the general procedure for the cyclization reaction using *N*-(pent-4-en-1-yl)furan-2-carboxamide (**3o**) (73 mg, 0.41 mmol, 1.0 equiv). The crude was purified using flash chromatography (silica gel, 35:65 petrol/EtOAc) to afford the product as a brown oil (50 mg, 63% yield).

IR: 750 (s), 1027 (s), 1422 (s), 1594 (s), 2947 (w), 3351 (w, b) cm-1.

1H NMR (CDCl3, 400 MHz): δ 1.61-1.72 (1H, m, CH2), 1.81-1.92 (1H, m, CH2), 1.92-2.09 (2H, m, CH2), 3.64-3.73 (2H, m, CH2), 3.77-3.85 (1H, m, CH2OH), 3.91-4.00 (1H, m, CH2OH), 4.36-4.44 (1H, m, CH), 4.78 (1H, br s, OH), 6.47 (1H, d, *J* = 1.6 Hz, furan), 7.07 (1H, d, *J* = 3.0 Hz, furan), 7.50 (1H, s, furan).

13C NMR (CDCl3, 100 MHz): δ 25.0, 27.8, 49.2, 62.3, 66.9, 111.6, 117.0, 144.7, 148.2, 160.4.

HRMS (ESI-TOF) m/z: [M+H]+ Cald for C10H14NO3+ 196.0968; Found 196.0966.

**Synthesis of (2-(hydroxymethyl)-4,4-dimethylpyrrolidin-1-yl)(phenyl)methanone (7p)**



Prepared according to the general procedure for the cyclization reaction using *N*-(2,2-dimethylpent-4-en-1-yl)benzamide (**3p**) (198 mg, 0.91 mmol, 1.0 equiv). The crude was purified using flash chromatography (silica gel, 40:60 petrol/EtOAc) to afford the product as a brown oil (20 mg, 10% yield).

IR: 698 (m), 1028 (m), 1426 (m), 1600 (m), 2959 (w), 3347 (w, b) cm-1.

1H NMR (CDCl3, 400 MHz): δ 0.96 (3H, s, Me), 1.05 (3H, s, Me), 1.43 (1H, t, *J* = 11.6 Hz, CH2), 1.89 (1H, ddd, *J* = 12.6, 7.4, 1.8Hz, CH2), 3.18 (1H, dd, *J* = 10.7, 1.5 Hz, CH2), 3.27 (1H, d, *J* = 10.7 Hz, CH2), 3.69-3.81 (2H, m, CH2OH), 4.45-4.54 (1H, m, CH), 4.98 (1H, br s, OH), 7.38-7.44 (3H, m, Ar), 7.46-7.50 (2H, m, Ar).

13C NMR (CDCl3, 100 MHz): δ 25.4, 25.6, 37.7, 42.2, 61.3, 63.4, 67.5, 127.2, 128.5, 130.3, 136.6, 172.7.

HRMS (ESI-TOF) m/z: [M+H]+ Cald for C14H20NO2+ 234.1489; Found 234.1499.

**Synthesis of (2-(1-hydroxyethyl)pyrrolidin-1-yl)(phenyl)methanone (7q)**



Prepared according to the general procedure for the cyclization reaction using *N*-((4*Z*)-hex-4-en-1-yl)benzamide (**3q**) (72 mg, 0.35 mmol, 1.0 equiv). The crude was purified using flash chromatography (silica gel, 40:60 petrol/EtOAc) to afford the product as a brown oil (26 mg, 34% yield). Only one diastereomer observed.

IR: 699 (m), 1026 (m), 1420 (s), 1599 (s), 2970 (w), 3381 (w, b) cm-1.

1H NMR (CDCl3, 400 MHz): δ 1.17 (3H, d, *J* = 6.3 Hz, Me), 1.61-1.77 (2H, m, CH2), 1.81-1.90 (1H, m, CH2), 2.09-2.20 (1H, m, CH2), 3.38-3.47 (1H, m, CH2), 3.49-3.57 (1H, m, CH2), 4.06 (1H, d, *J* = 5.7 Hz, CH), 4.39 (1H, t, *J* = 7.8 Hz, CHOH), 4.79 (1H, br s, OH), 7.37-7.43 (3H, H, Ar), 7.50 (2H, *J* = 6.6 Hz, Ar).

13C NMR (CDCl3, 100 MHz): δ 17.5, 25.2, 28.0, 52.1, 64.8, 69.3, 127.2, 128.4, 130.3, 136.8, 171.9.

HRMS (ESI-TOF) m/z: [M+H]+ Cald for C13H18NO2+ 220.1332; Found 220.1340.

**Synthesis of *N*-(6-(acetylamino)-5-fluoro-6-methylheptan-2-yl)benzamide (15)**



Prepared according to the general procedure for the cyclization reaction using *N*-(6-methylhept-5-en-2-yl)benzamide (**3r**) (75 mg, 0.32 mmol, 1.0 equiv). The crude was purified using flash chromatography (silica gel, 35:65 petrol/EtOAc) to afford the product as a brown oil (56 mg, 56% yield). The product is a 1:1 mixture of diastereomers.

IR: 1028 (m), 1451 (m), 1634 (m), 2972 (w), 3305 (w, b) cm-1.

1H NMR (CDCl3, 400 MHz): δ 1.22 (3H, d, *J* = 5.6 Hz, Me), 1.22 (3H, d, *J* = 5.6 Hz, Me), 4.27 (2x3H, d, *J* = 5.6 Hz, Me), 1.29 (3H, s, Me), 1.32 (3H, s, Me), 1.50-1.73 (2x4H, m, CH2), 1.83 (3H, s, Me), 1.86 (3H, s, Me), 4.10-4.30 (2x1H, m, C*H*N), 4.68-4.77 (1H, m, C*H*F), 4.80-4.89 (1H, m, C*H*F), 5.76 (1H, s, NH), 5.91 (1H, s, NH), 6.33-6.41 (2x1H, m, NH), 7.34-7.41 (2x2H, m, Ar), 7.41-7.50 (2x1H, m, Ar), 7.70-7.77 (2x2H, m, Ar).

13C NMR (CDCl3, 100 MHz): δ 21.4, 21.6, 22.0 (d, *J* = 3.3 Hz), 22.5 (d, *J* = 3.0 Hz), 22.6 (d, *J* = 3.5 Hz), 22.8 (d, *J* = 4.1 Hz), 24.37, 24.44, 26.1 (d, *J* = 21 Hz), 26.5 (d, *J* = 21 Hz), 33.6 (d, *J* = 1.7 Hz), 34.0 (d, *J* = 2.2 Hz), 45.1, 45.9, 56.2 (d, *J* = 21 Hz), 56.3 (d, *J* = 20 Hz), 96.0 (d, *J* = 175 Hz), 96.7 (d, *J* = 175 Hz), 126.9 (2x2C), 128.6, 128.7, 131.5, 131.6, 134.7, 134.9, 167.2, 167.4, 170.07, 170.12.

19F (CDCl3, 376 MHz): -193.8, -193.2.

HRMS (ESI-TOF) m/z: [M+H]+ Cald for C17H26FN2O2+ 309.1973; Found 309.1968.

**Cartesian coordinates and energies of calculated structures**

**8**

**A chemical formula with letters and numbers

Description automatically generated**

C -0.000004 1.568477 -0.539663

C -0.000022 2.465623 0.543921

C 0.000005 2.000779 -1.862347

C -0.000031 3.838184 0.254964

C -0.000003 3.370447 -2.132954

H 0.000020 1.281853 -2.674148

C -0.000021 4.275885 -1.071080

H -0.000043 4.562876 1.059898

H 0.000003 3.718646 -3.160003

H -0.000027 5.343182 -1.270565

O 2.201147 -0.222484 -0.184127

C 2.803245 -1.359379 0.020475

C 4.352072 -1.199825 0.007068

O 2.277486 -2.443260 0.203918

F 4.747053 -0.324951 0.958231

F 4.769709 -0.731585 -1.189615

F 4.963552 -2.368315 0.235023

I 0.000007 -0.498674 -0.137704

O -2.201133 -0.222507 -0.184159

C -4.352055 -1.199853 0.007054

F -4.963531 -2.368358 0.234943

F -4.769695 -0.731546 -1.189600

F -4.747037 -0.325035 0.958269

C -2.803227 -1.359400 0.020462

O -2.277464 -2.443276 0.203927

O -0.000032 1.938191 1.788154

C -0.000063 2.812646 2.919788

H -0.898601 3.439108 2.929620

H -0.000078 2.158193 3.790738

H 0.898465 3.439122 2.929658

Zero-point correction = 0.178345 (Hartree/Particle)

Thermal correction to Energy = 0.202063

Thermal correction to Enthalpy = 0.203007

Thermal correction to Gibbs Free Energy = 0.117439

SCF Done: E(RB3LYP) = -1409.97140056 Hartree

**3a**

A chemical formula of a molecule

Description automatically generated

C 0.49522 -0.92112 0.09276

C -1.6235 -1.40535 -1.1189

C -5.31559 -0.12613 -1.2968

C -2.81342 -0.43586 -1.04999

C -4.15804 -1.07594 -1.44093

H -5.48708 0.26706 -0.29266

H -1.6813 -2.14181 -0.31356

H -2.60338 0.40868 -1.71902

H -1.64432 -1.94808 -2.07194

H -2.88348 -0.01498 -0.03643

H -4.32787 -1.9537 -0.80223

H -4.10375 -1.44659 -2.47157

N -0.32717 -0.74602 -0.98744

H 0.03694 -0.25644 -1.79108

O 0.62702 -2.01025 0.65197

C -6.12421 0.26498 -2.28661

H -6.94444 0.95584 -2.11369

H -5.99542 -0.09876 -3.30391

C 1.24665 0.29615 0.56691

C 2.41155 0.08095 1.31766

C 0.82919 1.61283 0.31784

C 3.15845 1.16022 1.78893

H 2.71029 -0.94142 1.52316

C 1.57274 2.69365 0.79757

H -0.09441 1.81034 -0.21918

C 2.74222 2.46972 1.52849

H 4.06308 0.98079 2.3626

H 1.2333 3.70781 0.60814

H 3.32091 3.31055 1.89987

Zero-point correction = 0.245807 (Hartree/Particle)

Thermal correction to Energy = 0.259812

Thermal correction to Enthalpy = 0.260756

Thermal correction to Gibbs Free Energy = 0.202185

SCF(Done): E(RB3LYP): -596.331553629 Hartree

**TS[8-9]**

A chemical structure with letters and numbers

Description automatically generated

C -1.71301 2.06039 1.60314

H -2.61314 1.4932 1.367

C -1.49709 3.33669 0.83413

H -2.29361 4.05089 1.09662

H -0.55125 3.77893 1.15807

C -0.88434 1.58866 2.54814

H 0.02313 2.12049 2.82129

H -1.11105 0.67268 3.087

C -0.19931 -1.50337 0.82227

C 0.05606 -2.31956 1.94932

C -2.30384 -2.6202 0.43144

C -0.88322 -3.30379 2.28959

C -2.04775 -3.4442 1.53133

H -3.21571 -2.73127 -0.14483

H -0.71406 -3.95132 3.14141

H -2.76657 -4.20831 1.81295

O 2.07699 -1.48591 -1.15492

C 3.13476 -2.17159 -0.75138

C 3.60463 -3.11411 -1.9073

O 3.68289 -2.16477 0.32215

F 2.71489 -4.12325 -2.05275

F 4.79778 -3.64796 -1.61967

F 3.70019 -2.46352 -3.0781

C -1.37495 -1.643 0.07585

H -1.01199 2.19946 -0.96419

H -0.81815 3.93109 -1.13161

C -1.46802 3.15824 -0.7037

N -3.86618 2.35933 -0.97986

H -4.72522 2.75806 -0.63197

C -3.87408 1.04191 -1.32781

O -2.93813 0.52078 -1.94316

C -5.08536 0.24474 -0.92387

C -5.86984 0.55446 0.19783

C -5.42083 -0.86922 -1.70794

C -6.97748 -0.23226 0.52327

H -5.60556 1.38766 0.84324

C -6.53379 -1.64698 -1.38866

H -4.79994 -1.10592 -2.56587

C -7.31502 -1.33021 -0.27224

H -7.57091 0.00899 1.4002

H -6.79354 -2.49869 -2.01062

H -8.17965 -1.93788 -0.02175

H -2.65722 3.13697 -2.49957

H -3.21841 4.2932 -1.28183

C -2.81651 3.28483 -1.42522

I 1.24508 -0.08035 0.22003

O 1.67682 2.44417 0.86679

C 2.66576 2.53947 0.08416

C 3.3534 3.93774 0.05727

F 4.44187 3.96411 -0.72838

F 2.48834 4.87673 -0.40749

F 3.73126 4.31716 1.3002

O 3.11874 1.64381 -0.65937

H -1.57678 -0.9919 -0.77043

O 1.19822 -2.08625 2.62904

C 1.58117 -2.95769 3.69345

H 2.55568 -2.59929 4.02283

H 1.66956 -3.99056 3.33968

H 0.8669 -2.90297 4.52284

Zero-point correction = 0.424395 (Hartree/Particle)

Thermal correction to Energy = 0.463471

Thermal correction to Enthalpy = 0.464416

Thermal correction to Gibbs Free Energy = 0.338895

SCF Done: E(RB3LYP) = -2006.27254238 Hartree

Imaginary frequency= -51.06 cm-1

**9**

A chemical structure with black text

Description automatically generated

C 1.29369 -1.33116 0.10995

H 1.59497 -0.65708 -0.68765

C 1.51879 -2.79165 -0.11672

H 1.20066 -3.36601 0.76147

C 0.7389 -0.78786 1.24173

H 0.52486 -1.40642 2.11015

H 0.74647 0.28635 1.39205

C -1.44919 1.2283 -0.42502

C -1.59216 2.18695 0.6014

C -1.15046 2.91892 -2.1015

C -1.5211 3.5385 0.22811

C -1.30552 3.8889 -1.10467

H -0.98295 3.20606 -3.1335

H -1.63036 4.31173 0.9788

H -1.2544 4.941 -1.36683

O -3.72194 -0.75241 -0.72123

C -4.6835 -0.57585 0.17177

C -6.07597 -0.60382 -0.54039

O -4.56953 -0.42603 1.36452

F -6.15725 0.41159 -1.42291

F -7.0578 -0.47497 0.35252

F -6.23857 -1.76326 -1.20227

C -1.22334 1.57084 -1.76055

I -1.69964 -0.7988 0.07391

H -1.11791 0.80276 -2.51833

O -1.76478 1.73333 1.85495

C -2.09436 2.65777 2.90927

H -2.27144 2.0377 3.78628

H -3.00226 3.21396 2.65957

H -1.2612 3.34173 3.09711

C 2.98844 -3.12614 -0.47829

H 3.01867 -4.16735 -0.81384

H 3.29917 -2.51641 -1.33203

C 3.98889 -2.91385 0.6913

H 3.47193 -2.46865 1.54874

H 4.4013 -3.8697 1.0208

N 5.11742 -2.05711 0.3419

H 6.05013 -2.42901 0.4351

C 4.94632 -0.71494 0.18607

O 3.80659 -0.22304 0.24371

C 6.15503 0.12735 -0.07123

C 7.39359 -0.40268 -0.46977

C 6.0261 1.51535 0.09402

C 8.48359 0.44037 -0.68654

H 7.51934 -1.46631 -0.65245

C 7.11804 2.35555 -0.11691

H 5.06407 1.91561 0.39403

C 8.34975 1.82 -0.50528

H 9.43347 0.02084 -1.00238

H 7.00996 3.42682 0.02194

H 9.20028 2.47391 -0.6713

H 0.89094 -3.11547 -0.96057

Zero-point correction = 0.398225 (Hartree/Particle)

Thermal correction to Energy = 0.429813

Thermal correction to Enthalpy = 0.430758

Thermal correction to Gibbs Free Energy = 0.325847

SCF Done: E(RB3LYP) = -1479.83351702 Hartree

**TS[9-10]**

A chemical formula of a molecule

Description automatically generated

C 4.85643 0.08058 -0.5201

C 3.86485 1.58585 -2.25404

C 1.6285 0.18542 -0.63183

C 2.93605 2.32447 -1.2681

C 1.57919 1.63735 -0.98225

H 1.92727 -0.50581 -1.41387

H 3.29662 0.89371 -2.89038

H 2.7078 3.3151 -1.6734

H 4.33072 2.3086 -2.92731

H 3.46231 2.48555 -0.32407

H 0.96436 1.71552 -1.89279

H 1.0598 2.19399 -0.19683

N 4.97214 0.87516 -1.60546

H 5.872 0.90961 -2.06267

O 3.74958 -0.14682 0.0245

C 1.00725 -0.35611 0.50093

H 1.23471 -1.38972 0.74891

H 0.79963 0.29092 1.34915

I -1.32184 -0.76923 -0.31962

C -1.90739 1.21908 0.0879

C -2.30322 2.03506 -0.9718

C -1.99404 1.61647 1.43573

C -2.81115 3.30238 -0.68691

C -2.51443 2.89382 1.69639

C -2.91567 3.71754 0.64427

H -3.13639 3.94676 -1.49618

H -2.60934 3.23863 2.71905

H -3.31982 4.69892 0.87186

C 6.10203 -0.52516 0.03396

C 5.98912 -1.71713 0.76664

C 7.36647 0.06357 -0.13976

C 7.12674 -2.32519 1.29443

H 5.00868 -2.15725 0.91042

C 8.50099 -0.54373 0.39816

H 7.47429 1.01406 -0.65483

C 8.3837 -1.74135 1.10953

H 7.03411 -3.25269 1.85055

H 9.47289 -0.07781 0.27066

H 9.26862 -2.21348 1.52486

O -3.42417 -1.19891 -0.97407

C -4.3029 -1.23182 -0.00278

O -4.11492 -1.03411 1.18076

C -5.72916 -1.54716 -0.55862

F -6.61576 -1.65298 0.43528

F -6.12799 -0.55339 -1.38219

F -5.7254 -2.69945 -1.25471

H -2.25009 1.68052 -1.99538

O -1.54971 0.75419 2.37115

C -1.92673 0.95367 3.74692

H -3.01376 1.03154 3.83333

H -1.57731 0.06584 4.27165

H -1.43863 1.84236 4.15878

Zero-point correction = 0.398904 (Hartree/Particle)

Thermal correction to Energy = 0.429287

Thermal correction to Enthalpy = 0.430231

Thermal correction to Gibbs Free Energy = 0.329718

SCF Done: E(RB3LYP) = -1479.82962603 Hartree

Imaginary frequency= -64.42 cm-1

**TS[9-11]**

A chemical structure with letters and numbers

Description automatically generated

C -1.74335 -1.43442 -0.57096

H -1.99244 -1.64832 0.46795

C -1.39823 -2.63693 -1.3983

H -1.08385 -2.33162 -2.40323

H -0.54063 -3.13737 -0.92402

C -1.20576 -0.1412 -0.83862

H -1.03895 0.12522 -1.88078

H -1.54849 0.6758 -0.20839

I 1.14792 -0.29757 -0.06924

C 1.20577 1.81398 0.02362

C 1.42985 2.53012 -1.16732

C 1.19662 3.82749 1.33494

C 1.53616 3.92586 -1.07392

C 1.42076 4.55784 0.16549

H 1.11957 4.32642 2.29462

H 1.71341 4.51724 -1.96394

H 1.51185 5.63845 0.21309

O 3.33659 -0.13121 0.57107

C 4.04054 -0.21322 -0.51505

C 5.57115 -0.08709 -0.24215

O 3.61036 -0.36484 -1.65132

F 6.27515 -0.2182 -1.37001

F 5.97217 -1.03737 0.62596

F 5.84391 1.1203 0.29507

C 1.09082 2.43807 1.26477

H 0.94387 1.85356 2.16638

H -2.76151 -4.05207 -0.4684

H -2.40812 -4.41617 -2.16151

C -2.58839 -3.60489 -1.45133

N -3.7922 -1.50341 -1.0992

H -3.93148 -0.68306 -1.68051

C -4.53467 -1.46431 0.1349

O -4.70633 -2.51072 0.73196

C -4.98434 -0.1386 0.62896

C -4.85003 1.06305 -0.09258

C -5.60008 -0.11411 1.8948

C -5.31859 2.2616 0.44412

H -4.39678 1.09318 -1.07959

C -6.06513 1.08499 2.42699

H -5.7076 -1.04509 2.44044

C -5.92541 2.27434 1.70355

H -5.21921 3.18162 -0.12279

H -6.54051 1.09322 3.40249

H -6.29401 3.20815 2.11666

H -4.74334 -3.31136 -1.66072

H -3.76887 -2.51971 -2.92378

C -3.81113 -2.77934 -1.86254

O 1.51577 1.82256 -2.31738

C 1.9362 2.48923 -3.51908

H 2.91083 2.96496 -3.37476

H 2.01761 1.70534 -4.27087

H 1.19416 3.22937 -3.83553

Zero-point correction = 0.399081 (Hartree/Particle)

Thermal correction to Energy = 0.429286

Thermal correction to Enthalpy = 0.430230

Thermal correction to Gibbs Free Energy = 0.329111

SCF Done: E(RB3LYP) = -1479.82658287 Hartree

Imaginary frequency= -170.91 cm-1

**10**

A chemical structure with black text

Description automatically generated

C 5.02142 0.16231 -0.49328

C 4.03556 1.6686 -2.23236

C 1.81006 0.26428 -0.60402

C 3.10888 2.40807 -1.24582

C 1.75659 1.71746 -0.94958

H 2.10695 -0.42351 -1.38991

H 3.46517 0.98294 -2.87379

H 2.8756 3.39572 -1.65551

H 4.50759 2.39206 -2.90065

H 3.63956 2.57642 -0.30542

H 1.13317 1.79598 -1.85441

H 1.24213 2.27094 -0.1587

N 5.13743 0.94852 -1.58411

H 6.03683 0.97501 -2.04298

O 3.91555 -0.05724 0.05825

C 1.17994 -0.28214 0.5233

H 1.40784 -1.31643 0.76826

H 0.9749 0.36166 1.37468

I -1.14666 -0.69019 -0.29346

C -1.73246 1.29836 0.11384

C -2.12902 2.11389 -0.94588

C -1.81967 1.69582 1.46153

C -2.63785 3.38094 -0.6612

C -2.34098 2.97282 1.72207

C -2.74272 3.79622 0.66989

H -2.96368 4.02489 -1.47057

H -2.43632 3.31758 2.74472

H -3.14767 4.77729 0.89737

C 6.26656 -0.44469 0.06037

C 6.15389 -1.63604 0.79412

C 7.53116 0.14346 -0.11515

C 7.29197 -2.24427 1.32081

H 5.17353 -2.0758 0.93961

C 8.66601 -0.46396 0.4219

H 7.63854 1.09369 -0.63079

C 8.54899 -1.66112 1.1341

H 7.19958 -3.17139 1.8776

H 9.63795 0.00156 0.29314

H 9.43415 -2.13341 1.54874

O -3.25185 -1.1172 -0.94927

C -4.13004 -1.15076 0.02197

O -3.94202 -0.95354 1.20579

C -5.55651 -1.46656 -0.53303

F -6.44294 -1.57247 0.46115

F -5.95624 -0.47322 -1.3568

F -5.55293 -2.61911 -1.22889

H -2.07606 1.75907 -1.96938

O -1.37501 0.83385 2.3972

C -1.75405 1.03241 3.7725

H -2.84128 1.1092 3.85748

H -1.40452 0.14471 4.29738

H -1.26736 1.9214 4.18543

Zero-point correction = 0.402266 (Hartree/Particle)

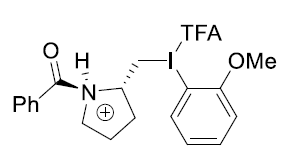
Thermal correction to Energy = 0.432218

Thermal correction to Enthalpy = 0.433162

Thermal correction to Gibbs Free Energy = 0.333758

SCF Done: E(RB3LYP) = -1479.84721816 Hartree

**11**



C 2.08785 -1.76064 0.00492

H 2.03411 -1.21267 -0.93854

C 1.90146 -3.26004 -0.21203

H 1.706 -3.75745 0.74613

H 1.03645 -3.43538 -0.8576

C 1.26336 -1.11347 1.07524

H 1.2659 -1.66387 2.0198

H 1.46575 -0.05458 1.23391

I -1.06553 -1.05659 0.56201

C -0.74639 0.50729 -0.83302

C -0.44803 1.78326 -0.32635

C -0.83733 1.32538 -3.08821

C -0.35836 2.83999 -1.24468

C -0.55211 2.60535 -2.60692

H -0.99947 1.15411 -4.14675

H -0.14688 3.84309 -0.89337

H -0.4853 3.43921 -3.29872

O -3.30334 -0.92456 -0.01655

C -3.90466 0.14412 0.40552

C -5.41217 0.13801 0.0078

O -3.42789 1.08863 1.01764

F -6.05745 1.20503 0.49719

F -6.02768 -0.97266 0.46448

F -5.53111 0.15806 -1.34091

C -0.94427 0.26152 -2.18956

H -1.21471 -0.72861 -2.53977

H 3.29188 -3.44019 -1.87604

H 3.28662 -4.85691 -0.81343

C 3.20237 -3.76777 -0.83618

N 3.767 -1.70282 0.2986

H 3.88747 -1.46932 1.28429

C 4.45429 -0.66504 -0.57712

O 4.68423 -1.00276 -1.71177

C 4.73229 0.65474 0.00667

C 4.61294 0.9669 1.37563

C 5.14999 1.65436 -0.89867

C 4.89605 2.25505 1.82472

H 4.31593 0.22617 2.11296

C 5.42058 2.93975 -0.44427

H 5.248 1.40376 -1.94905

C 5.29226 3.24242 0.91655

H 4.81186 2.48777 2.88105

H 5.73418 3.70521 -1.14641

H 5.50848 4.24533 1.27149

H 5.25648 -3.03986 -0.47647

H 4.3978 -3.60869 0.98104

C 4.28667 -3.11195 0.01417

O -0.23773 1.8967 1.00517

C -0.40918 3.18257 1.62607

H -1.38047 3.60549 1.35627

H -0.37767 2.99275 2.69833

H 0.40219 3.86351 1.34814

Zero-point correction = 0.401673 (Hartree/Particle)

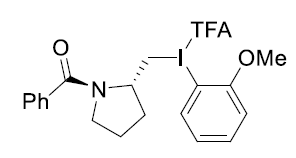
Thermal correction to Energy = 0.431988

Thermal correction to Enthalpy = 0.432932

Thermal correction to Gibbs Free Energy = 0.330865

SCF Done: E(RB3LYP) = -1479.83676517 Hartree

**12**



C -1.51763 -1.40908 0.44972

H -1.41329 -0.68666 1.26171

C -1.0716 -2.79757 0.9141

H -0.99126 -3.48418 0.06134

H -0.09173 -2.75074 1.39467

C -0.9324 -0.8748 -0.8352

H -1.00033 -1.59119 -1.66009

H -1.34784 0.08882 -1.13479

I 1.31732 -0.48546 -0.63028

C 0.94985 1.55649 -0.16531

C 1.16002 2.51112 -1.15588

C 0.42048 3.26386 1.44074

C 0.98738 3.86229 -0.8464

C 0.62086 4.22697 0.4494

H 0.14282 3.5732 2.44109

H 1.15774 4.61522 -1.6081

H 0.49481 5.27506 0.70215

O 3.55552 0.2749 -0.36008

C 4.29346 -0.76739 -0.51662

C 5.81388 -0.4681 -0.35428

O 3.91446 -1.91168 -0.76623

F 6.21474 0.45545 -1.25676

F 6.56119 -1.56694 -0.52503

F 6.06815 0.02224 0.88153

C 0.58777 1.90335 1.14627

H -2.06597 -2.73488 2.84459

H -2.17951 -4.31623 2.06374

C -2.17683 -3.23944 1.88019

N -3.07135 -1.60036 0.30611

C -3.86724 -0.33228 0.65313

O -3.52601 0.23761 1.65642

C -4.96159 0.03177 -0.25114

C -5.37026 -0.74295 -1.35698

C -5.64037 1.23472 0.04199

C -6.43121 -0.31905 -2.15238

H -4.89719 -1.68774 -1.61055

C -6.69539 1.65297 -0.75997

H -5.32447 1.82256 0.89669

C -7.09135 0.87848 -1.85714

H -6.74509 -0.92097 -2.99849

H -7.21155 2.57973 -0.53242

H -7.91692 1.20598 -2.48125

H -4.25292 -2.46784 1.88801

H -3.88617 -3.55908 0.53377

C -3.47578 -2.79544 1.19723

H 1.48064 2.21405 -2.14826

O 0.4083 0.89462 2.04277

C 0.33323 1.22328 3.43898

H 0.34481 0.26891 3.96489

H 1.20029 1.81777 3.74192

H -0.59413 1.75859 3.66763

Zero-point correction = 0.388844 (Hartree/Particle)

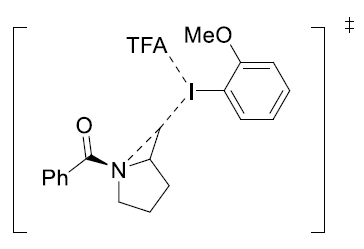
Thermal correction to Energy = 0.418807

Thermal correction to Enthalpy = 0.419751

Thermal correction to Gibbs Free Energy = 0.319675

SCF Done: E(RB3LYP) = -1479.49475645 Hartree

**TS[12-13]**



C 0.96983 -0.75281 -1.83137

H 0.97099 0.27727 -2.19043

C 0.9439 -1.87153 -2.88845

H 0.09767 -2.54331 -2.70963

H 0.83142 -1.46089 -3.89429

I -2.49507 -0.69937 -1.14688

C -3.05617 -1.21904 0.85261

C -3.82769 -2.36188 1.06882

C -3.04192 -0.71273 3.19286

C -4.20689 -2.67208 2.37885

C -3.81518 -1.84977 3.43892

H -2.73654 -0.06852 4.01198

H -4.81045 -3.55606 2.56319

H -4.11537 -2.09397 4.45356

O -0.42511 1.63143 0.75073

C -0.51481 2.38133 -0.26373

C -0.8976 3.85852 0.08623

O -0.37117 2.10508 -1.46748

F -0.89839 4.68458 -0.98068

F -0.0522 4.39661 1.00259

F -2.15073 3.9132 0.62642

C -2.65354 -0.37782 1.88988

H -2.04479 0.50362 1.69722

H 3.06244 -2.14909 -3.32578

H 2.23072 -3.6712 -2.97576

C 2.28739 -2.61271 -2.70653

N 2.13164 -1.03285 -0.94277

C 3.01582 0.04278 -0.58978

O 2.92682 1.11881 -1.14339

C 4.01237 -0.24116 0.48329

C 3.78397 -1.17939 1.502

C 5.18864 0.52537 0.49669

C 4.72683 -1.35442 2.51558

H 2.8589 -1.74618 1.52312

C 6.13507 0.33669 1.50181

H 5.33873 1.26761 -0.28027

C 5.90582 -0.60337 2.51215

H 4.53722 -2.06771 3.31192

H 7.0457 0.92783 1.504

H 6.63959 -0.74303 3.30057

H 3.6938 -2.46529 -1.00071

H 2.11091 -3.13474 -0.58584

C 2.62799 -2.40828 -1.22301

C 0.17319 -0.90353 -0.59432

H 0.04819 -0.01482 0.05128

H 0.01668 -1.90501 -0.2033

O -4.22749 -3.17368 0.09162

C -4.97656 -4.29598 0.42634

H -5.22806 -4.87523 -0.43744

H -5.87327 -3.97085 0.91122

H -4.40244 -4.89453 1.10237

Zero-point correction = 0.386878 (Hartree/Particle)

Thermal correction to Energy = 0.416760

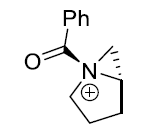
Thermal correction to Enthalpy = 0.417704

Thermal correction to Gibbs Free Energy = 0.318013

SCF Done: E(RB3LYP) = -1479.46950749 Hartree

Imaginary frequency= -254.56 cm-1

**13**



C 2.38567 0.15507 -1.06911

H 2.26113 1.04283 -1.70149

C 3.65486 -0.10833 -0.27013

H 4.09952 -1.06684 -0.55991

H 4.39602 0.67151 -0.45635

H 3.22446 0.89415 1.61387

H 3.8228 -0.75642 1.84435

C 3.19905 -0.12178 1.20868

N 1.20912 -0.10535 -0.14729

C 0.06022 0.89351 -0.03776

O 0.37453 2.04542 0.09112

C -1.29718 0.32219 -0.00944

C -1.53903 -1.05935 0.0656

C -2.378 1.22121 -0.03022

C -2.84815 -1.53585 0.12789

H -0.71807 -1.7674 0.07205

C -3.68137 0.73894 0.02249

H -2.17725 2.2838 -0.10955

C -3.91862 -0.63825 0.10227

H -3.03271 -2.60392 0.18299

H -4.51442 1.434 -0.01083

H -4.93763 -1.01187 0.13803

H 1.1242 -0.21088 1.97194

H 1.66294 -1.70282 1.17394

C 1.74561 -0.6125 1.17014

C 1.43871 -0.946 -1.37228

H 0.71321 -0.70303 -2.14942

H 1.68514 -1.98212 -1.15627

Zero-point correction = 0.238493 (Hartree/Particle)

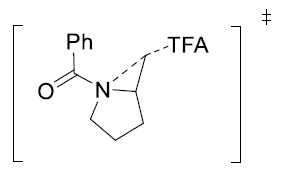
Thermal correction to Energy = 0.250232

Thermal correction to Enthalpy = 0.251177

Thermal correction to Gibbs Free Energy = 0.199739

SCF Done: E(RB3LYP) = -595.452695757 Hartree

**TS[13-14]**



C 0.21166 1.93727 0.50731

H 0.24422 2.01994 1.59437

C 0.0869 3.24009 -0.30183

H -0.78257 3.19271 -0.9658

H -0.04768 4.10089 0.35685

O -2.72712 0.54701 0.41535

C -3.10817 -0.56942 -0.03832

C -4.65438 -0.7914 0.07018

O -2.43806 -1.50133 -0.51788

F -5.07944 -1.93112 -0.51468

F -5.35458 0.22641 -0.49359

F -5.0377 -0.85555 1.37947

H 2.1716 3.83796 -0.52991

H 1.28405 3.85295 -2.06112

C 1.40006 3.32267 -1.11166

N 1.27537 1.16138 -0.03811

C 2.23014 0.58905 0.8722

O 2.31091 0.99354 2.0129

C 3.07909 -0.51285 0.33376

C 2.65323 -1.36116 -0.70032

C 4.32194 -0.73656 0.94753

C 3.46652 -2.41397 -1.12087

H 1.67665 -1.22142 -1.152

C 5.13819 -1.77952 0.51427

H 4.62597 -0.0908 1.76462

C 4.712 -2.61929 -0.52025

H 3.12468 -3.07893 -1.9082

H 6.10106 -1.94429 0.98801

H 5.34473 -3.43783 -0.85066

H 2.87523 1.7081 -1.46737

H 1.27586 1.40123 -2.15649

C 1.80623 1.85554 -1.31198

C -0.31866 0.53468 -0.05712

H -0.3819 -0.31175 0.65094

H -0.50827 0.39942 -1.11762

Zero-point correction = 0.264695 (Hartree/Particle)

Thermal correction to Energy = 0.283716

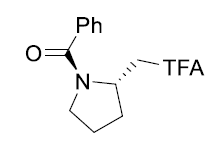
Thermal correction to Enthalpy = 0.284660

Thermal correction to Gibbs Free Energy = 0.212184

SCF Done: E(RB3LYP) = -1121.88063434 Hartree

Imaginary frequency= -54.28 cm-1

**14**



C 0.21993 0.83048 -0.43067

H 0.31488 0.57367 -1.4921

C 0.55422 2.31378 -0.17637

H 0.95439 2.43977 0.83744

H 1.3035 2.68679 -0.87776

O 2.44023 0.00696 -0.07866

C 3.35885 -0.71191 0.55436

C 4.75653 -0.44933 -0.06867

O 3.1872 -1.4715 1.47584

F 5.6926 -1.17674 0.5502

F 5.0935 0.8552 0.04429

F 4.76638 -0.77033 -1.37975

H -1.0687 3.17147 -1.34942

H -0.82265 3.9983 0.19828

C -0.80279 3.0229 -0.29653

N -1.206 0.70902 -0.04023

C -1.9205 -0.36442 -0.52299

O -1.37714 -1.22774 -1.21633

C -3.37284 -0.48197 -0.15671

C -3.85993 -0.18509 1.12398

C -4.24933 -1.00281 -1.12141

C -5.20767 -0.39052 1.4305

H -3.18661 0.18235 1.89207

C -5.59809 -1.18656 -0.82095

H -3.85424 -1.26592 -2.09723

C -6.08047 -0.88119 0.45652

H -5.5719 -0.17262 2.4302

H -6.27215 -1.57735 -1.57751

H -7.12923 -1.0355 0.69324

H -2.79446 2.12134 -0.00016

H -1.76517 2.13347 1.44295

C -1.76626 2.02224 0.35079

C 1.06502 -0.15521 0.37328

H 0.75906 -1.18538 0.1846

H 1.02052 0.04906 1.44671

Zero-point correction = 0.268103 (Hartree/Particle)

Thermal correction to Energy = 0.287045

Thermal correction to Enthalpy = 0.287989

Thermal correction to Gibbs Free Energy = 0.216407

SCF Done: E(RB3LYP) = -1121.95686024 Hartree

A black background with blue lines

Description automatically generated

A screen shot of a black screen

Description automatically generated

A black screen with blue text

Description automatically generated

A screen shot of a computer

Description automatically generated

A black screen with blue text

Description automatically generated

A screen shot of a computer

Description automatically generated

A black screen with blue lines

Description automatically generated

A screen shot of a computer

Description automatically generated

A screen shot of a computer

Description automatically generated

 A screen shot of a computer

Description automatically generated

A screen shot of a game

Description automatically generated

A screen shot of a computer

Description automatically generated

A black screen with blue lines and numbers

Description automatically generated

A screen shot of a black background

Description automatically generated

A screen shot of a black background

Description automatically generated

A black screen with blue text

Description automatically generated

A screen shot of a black screen

Description automatically generated

A screen shot of a computer

Description automatically generated

A screen shot of a computer

Description automatically generated

A black screen with blue text

Description automatically generated

A screen shot of a black screen

Description automatically generated

A screen shot of a computer

Description automatically generated

A screen shot of a black background

Description automatically generated

A screen shot of a computer

Description automatically generated

A screen shot of a black screen

Description automatically generated

A black screen with blue text

Description automatically generated

A screen shot of a black background

Description automatically generated

A black screen with blue lines and numbers

Description automatically generated

A screen shot of a computer

Description automatically generated

A black screen with blue text

Description automatically generated

A screen shot of a black background

Description automatically generated

A screen shot of a computer

Description automatically generated

A screen shot of a computer

Description automatically generated

A screen shot of a computer

Description automatically generated

A graph of a test

Description automatically generated with medium confidence

A screen shot of a computer

Description automatically generated

A screen shot of a black background

Description automatically generated

A screen shot of a game

Description automatically generated

 A screen shot of a black screen

Description automatically generated

A screen shot of a computer

Description automatically generated

A screen shot of a black background

Description automatically generated

A black background with blue lines

Description automatically generated

A screen shot of a computer

Description automatically generated

A black background with blue lines

Description automatically generated

A screen shot of a black screen

Description automatically generated

A screen shot of a black background

Description automatically generated

A screen shot of a computer

Description automatically generated

A screen shot of a black screen

Description automatically generated

A black background with blue lines

Description automatically generated

A screen shot of a black screen

Description automatically generated

A screen shot of a computer

Description automatically generated

A screen shot of a black screen

Description automatically generated

A screen shot of a black screen

Description automatically generated

A screen shot of a black background

Description automatically generated

A screen shot of a computer

Description automatically generated

A screen shot of a black background

Description automatically generated

A screen shot of a computer

Description automatically generated

A screen shot of a black screen

Description automatically generated

A screen shot of a computer

Description automatically generated

A screenshot of a computer

Description automatically generated

A screen shot of a computer

Description automatically generated

 A screen shot of a black background

Description automatically generated

A screen shot of a black background

Description automatically generated

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