Electronic Supplementary Material (ESI) for ChemComm.

Modular Synthesis of Bicyclic Twisted Amides and Anilines

Supporting Information

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Contents

1. General Experimental

Commercially available starting materials were obtained from Sigma−Aldrich, Fluorochem, Alfa Aesar and Acros. All non-aqueous reactions were performed under a nitrogen atmosphere unless otherwise stated. Water-sensitive reactions were performed in anhydrous solvents in oven-dried glassware cooled under nitrogen before use. Anhydrous dichloromethane (DCM), anhydrous tetrahydrofuran (THF), anhydrous toluene, anhydrous diethyl ether, anhydrous ethanol, anhydrous methanol and anhydrous acetonitrile were obtained from a PureSolv MD5 Purification System. Anhydrous dimethyl sulfoxide (DMSO) was obtained from SureSeal bottles from Sigma−Aldrich. All other solvents used were of chromatography or analytical grade. An IKA RV 10 rotary evaporator was used to remove the solvents under reduced pressure.

Thin layer chromatography (TLC) was performed using aluminium backed silica (Merck silica gel 60 F254) plates obtained from Merck. Ultraviolet lamp (λ_{max} = 254 nm) and $KMnO_4$ were used for visualization. Flash column chromatography was performed using silica gel 60 (35-70 µm particles) supplied by Merck. A Bruker Daltonics micrOTOF spectrometer with electrospray (ES) ionisation source was used for high-resolution mass spectrometry (HRMS). Perkin-Elmer One FT-IR spectrometer was used to analyse the infrared spectra. Melting points (m.p.) were determined using Stuart melting point apparatus SMP3. Mass directed auto-purification (MDAP) was performed using an Agilent 1290 Infinity II Preparative HPLC system with mass spectrometer (LC/MSD XT) and fraction collector. The system ran in positive mode with an Agilent Technologies PLRP-S, 300Å, 8 µM particle size, 150x25 mM column at ambient temperature with a binary solvent system: MeCN and H_2O with 0.1% formic acid.

Proton (^{1}H), carbon (^{13}C) and fluorine (^{19}F) NMR data was collected on a Bruker 300, 400 or 500 MHz spectrometer. Data was collected at 300 K unless otherwise stated. Chemical shifts (δ) are given in parts per million (ppm) and they are referenced to the residual solvent peak. Coupling constants (*J*) are reported in Hertz (Hz) and splitting patterns are reported in an abbreviated manner: app. (apparent), s (singlet), d (doublet), t (triplet), q (quartet), p (pentet), m (multiplet), br. (broad). Assignments were made using COSY, DEPT, HMQC, HMBC and NOESY experiments.

X-ray measurements were carried out at 120 K on an Agilent SuperNova diffractometer equipped with an Atlas CCD detector and connected to an Oxford Cryostream low temperature device using mirror monochromated Cu K_{α} radiation (λ = 1.54184 Å) from a Microfocus X-ray source. The structure was solved by intrinsic phasing using SHELXT[1] and refined by a full matrix least squares technique based on F^2 using SHELXL2014.[2]

2. General Methods

General method A: Synthesis of enecarbamates *via* Shono oxidation and Brønsted acid-mediated elimination**:**[3,4]

An Electrasyn vial (10 or 20 mL) fitted swith a stir bar was charged with the Boc-protected amine in anhydrous methanol (10 or 20 mL) containing tetraethylammonium tosylate and was electrolysed with graphite electrodes at a constant current of 65 mA at 25 °C. After the passage of 2.5 $Fmol^{-1}$ of electricity, the mixture was concentrated *in vacuo*. The residue was taken up in toluene, NH_4Cl (20 mol%) was added and the mixture stirred at reflux for 1-4 h. Then, the mixture was allowed to cool to rt and the solvent evaporated under reduced pressure to give a crude product. The crude product was purified by flash column chromatography to yield the corresponding enecarbamate as a mixture of rotamers.

General method B: Hydroamination of enecarbamates with amino esters**:**[5]

To a 7 mL vial were added $[Ir(dF(Me)ppy)_2(dtbbpy)PF_6]$ (5.1 mg, 2 mol%), TRIP thiol (27 mg, 50 mol%), amino ester hydrochloride (0.50 mmol), enecarbamate (0.25 mmol) and lithium hydroxide monohydrate (21.0 mg, 0.50 mmol). The vial was flushed with N_2 and toluene (5 mL) was then added and the resultant mixture was stirred for 16 h under irradiation with a blue LED and fan cooling. The reaction was scaled out by repetition in additional vials as specified. The solvent was evaporated under reduced pressure to give a crude product. The crude product was purified by flash column chromatography to yield the resulting amine as a mixture of rotamers.

General method C: Cbz/POC protection of amino esters and benzylamines:[6]

Benzyl or propargyl chloroformate (1.1 eq.) was slowly added to a mixture of amine (1.0 eq.) and $NaHCO_3$ (6.0 eq.) in DCM. The mixture was stirred for 16-96 h at room temperature, and then water was added (10 mL). The two layers were separated, and the organic layer was dried ($MgSO_4$) and the solvent evaporated under reduced pressure to give a crude product. The crude product was purified by flash column chromatography to yield the resulting carbamate as a mixture of rotamers.

General method D: Tin-mediated cyclisation of protected amino esters:[6]

NaOH (1.1 eq.) was added to a solution of amino ester (1.0 eq.) in 1:1 MeOH:water (0.059 M) and stirred at 70 °C for 2 h or until complete by TLC and the solvent then evaporated under reduced pressure. To the resultant residue was added HCl (6 N) (0.089 M) and EtOAc (0.071 M) and the mixture stirred for 3 h or until complete by TLC and the solvent then evaporated under reduced pressure. To a suspension of the crude amino acid in toluene (0.075 M) was added *n*-Bu_2SnO (1.01 eq.) and the mixture refluxed under Dean-Stark for 16 h. The solvent was then evaporated under reduced pressure and the residue partitioned between DCM (10 mL) and water (10 mL). The organic layer was then washed with water (3 × 10 mL) and dried ($MgSO_4$) and the solvent then evaporated under reduced pressure to give the crude product. The crude product was purified by flash column chromatography to yield the resulting bicyclic lactam as a mixture of rotamers.

General method E: Hydroamination of enecarbamates with benzylamines**:**[5]

To a 7 mL vial were added $[Ir(dF(Me)ppy)_2(dtbbpy)PF_6]$ (5.1 mg, 2 mol%), TRIP thiol (27 mg, 50 mol%), 2-bromobenzylamine (186 mg, 1.00 mmol) and enecarbamate (0.25 mmol). Toluene (5 mL) was then added under N_2 and the resultant mixture was stirred for 16 h under irradiation with a blue LED and fan cooling. The reaction

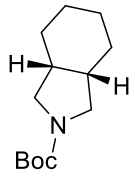
was scaled out by repetition in additional vials as specified. Then, the solvent was evaporated under reduced pressure to give a crude product. The crude product was purified by flash column chromatography to yield the resulting amine as a mixture of rotamers.

General method F: Buchwald-Hartwig cyclisations of protected benzylamines**:**[7]

HCl (6 N) (0.089 M) was added to a solution of protected amine (1 eq.) in EtOAc (0.071 M) and stirred for 3 h or until complete by TLC. The solvent was then removed under reduced pressure to give the corresponding NH amine. $Pd_2(dba)_3$ (4 mol%) and BINAP (8 mol%) were dissolved in toluene and stirred at 110 °C for 30 min and then cooled to rt. This solution was then added to NaOtBu (1.9 eq.) and the NH amine and the resulting mixture stirred at reflux for 16-96 h. The mixture was then allowed to cool to rt, filtered through celite, and washed with DCM (20 mL). The solvent was then removed under reduced pressure to give a crude product. The crude product was purified by flash column chromatography to yield the corresponding bicyclic aniline as a mixture of rotamers.

3. Synthesis of Enecarbamates

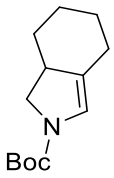
cis-_tert_-Butyl octahydro-2_H_-isoindole-2-carboxylate S1



S1

Boc_2O (2.7 mL, 11.8 mmol) was added to a solution of *cis*-octahydro-1*H*-isoindole hydrochloride (1.59 g, 9.84 mmol) and Et_3N (2.7 mL, 19.7 mmol) in DCM (30 mL) and stirred at rt for 72 h. The solvent was then evaporated under reduced pressure to give a crude product. The crude product was purified by flash column chromatography eluting with 90:10 hexane−EtOAc to yield slightly impure *carbamate* **S1** as a 1:1 mixture of rotamers (2.17 g, 97%) as a colourless oil, R_f 0.31 (80:20 hexane−EtOAc); ν_{max}/cm^{-1} 2975, 2926, 2856, 1693 (C=O), 1392, 1304, 1136, 1092, 875 and 771; δ_H (400 MHz, $CDCl_3$) 3.36–3.25 (2H, m, 2-H, 9-H), 3.22 (1H, dd, *J* 10.6, 5.4, m, 2-H, 9-H), 3.14 (1H, dd, *J* 10.5, 5.7, m, 2-H, 9-H), 2.21–2.09 (2H, m, 3-H, 8-H), 1.59–1.42 (15H, m, Boc CMe_3, 4-H_2, 5-H_A, 6-H_A, 7-H_2), 1.38–1.39 (2H, m, 5-H_B, 6-H_B); δ_C (100 MHz, $CDCl_3$) 155.4 (Boc C=O), 80.0 (Boc *C*Me_3), 50.1 (C-2, C-9), 49.7 (C-2, C-9), 37.5 (C-3, C-8), 36.8 (C-3, C-8), 28.7 (Boc C*Me*$_3$), 26.0 (C-4, C-7), 23.02 (C-5, C-6), 22.96 (C-5, C-6) (10 out of 14 signals present); HRMS found MNa^+, 248.1618. $C_{13}H_{23}NO_2Na$ requires 248.1621.

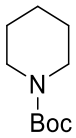
***tert*-Butyl 1,4,5,6,7,7a-hexahydro-2H-isoindole-2-carboxylate 5b**



5b

Compound **5b** was synthesised using general method A using Boc protected amine **S1** (2.00 g, 8.88 mmol), anhydrous methanol (20 mL), tetraethylammonium tosylate (166 mg, 0.56 mmol), toluene (20 mL) and NH_4Cl (95.0 mg, 20 mol%)). Reflux was carried out for 1 h. The crude product was purified by flash column chromatography eluting with 95:5 hexane−EtOAc to yield the *enecarbamate* **5b** as a 60:40 mixture of rotamers (1.45 g, 70%) as a pale yellow oil, R_f 0.68 (80:20 hexane−EtOAc); ν_{max}/cm^{-1} 2976, 2931, 2858, 1687 (C=O), 1385, 1365, 1164, 1109, 892 and 773; δ_H (500 MHz, $CDCl_3$) 6.24 (0.4H, br s, 2-H), 6.12 (0.6H, br s, 2-H), 3.90 (0.6H, app. t, *J* 10.9, 9-H_A), 3.84 (0.4H, app. t, *J* 11.3, 9-H_A), 3.24 (0.6H, dd, *J* 11.4, 7.1, m, 9-H_B), 3.19 (0.4H, dd, *J* 11.3, 7.2, m, 9-H_B), 2.79–2.66 (1H, 8-H), 2.38 (1H, app. t, *J* 15.3, 4-H_A), 2.00–1.87 (2H, m, 4-H_B, 7-H_A), 1.84–1.72 (2H, m, 5-H_A, 6-H_A), 1.46 (9H, s, Boc CMe_3), 1.31 (1H, app. qt, *J* 13.1, 3.0, 6-H_B), 1.22 (1H, app. qt, *J* 12.8, 3.2, 5-H_B), 1.16 (1H, app. dq, *J* 12.5, 3.1, 7-H_B); δ_C (125 MHz, $CDCl_3$) 152.3 (Boc C=O), 151.7 (Boc C=O), 125.5 (C-3), 125.4 (C-3), 120.5 (C-2), 120.4 (C-2), 79.8 (Boc *C*Me_3), 79.6 (Boc *C*Me_3), 52.2 (C-9), 51.7 (C-9), 43.3 (C-8), 42.2 (C-8), 34.6 (C-7), 28.6 (Boc C*Me*$_3$), 27.6 (C-5), 25.8 (C-4), 25.5 (C-6) (17 out of 22 signals present); HRMS found MNa^+, 246.1464. $C_{13}H_{21}NO_2Na$ requires 246.1465.

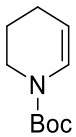
***tert*-Butyl piperidine-1-carboxylate S2**



S2

Boc_2O (14 mL, 60 mmol) was added to piperidine (6.5 mL, 66 mmol) in DCM (210 mL) and stirred at rt for 72 h. The solvent was then evaporated under reduced pressure to yield carbamate **S2** as a mixture of rotamers (11.0 g, 99%) as a colourless oil, ν_{max}/cm^{-1} 2976, 2934, 2855, 1687 (C=O), 1446, 1416, 1257, 1237, 1175, 1083 and 868; δ_H (400 MHz, $CDCl_3$) 3.38–3.31 (4H, m, 2-H_2, 6-H_2), 1.59–1.53 (2H, m, 4-H_2), 1.53–1.47 (4H, m, 3-H_2, 5-H_2), 1.45 (9H, s, Boc CMe_3); δ_C (100 MHz, $CDCl_3$) 155.1 (Boc C=O), 79.2 (Boc *C*Me_3), 44.8 (C-2, C-6), 28.6 (Boc C*Me*$_3$), 25.9 (C-4), 24.7 (C-3, C-5); HRMS found MNa^+, 208.1308. $C_{10}H_{19}NO_2Na$ requires 208.1308. Spectroscopic data are consistent with those reported in the literature.[8]

***tert*-Butyl 3,4-dihydropyridine-1(2H)-carboxylate 5c**

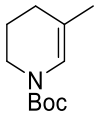


5c

Compound **5c** was synthesised using general method A using Boc protected amine **S1** (1.02 g, 4.56 mmol), anhydrous methanol (10 mL), tetraethylammonium tosylate (83 mg, 0.28 mmol), toluene (10 mL) and NH_4Cl (57.8 mg, 20 mol%). Reflux was carried out for 4 h. The crude product was purified by flash column chromatography eluting with 95:5 hexane−Et_2O to yield the enecarbamate **5c** as a 60:40 mixture of rotamers (464 mg, 47%) as a colourless oil, R_f 0.44 (80:20 hexane−Et_2O); ν_{max}/cm^{-1} 2976, 2934, 1688 (C=O), 1365, 1253, 1150, 990, 918, 876

and 729; δ_H (500 MHz, $CDCl_3$) 6.85 (0.4H, d, *J* 8.5, 2-H), 6.71 (0.6H, d, *J* 8.4, 2-H), 4.90 (0.4H, m, 3-H), 4.79 (0.6H, dt, *J* 8.1 and 3.8, 3-H), 3.63–3.43 (2H, m, 6-H_2), 2.09–1.95 (2H, m, 4-H_2), 1.86–1.72 (2H, m, 5-H_2), 1.48 (9H, s, Boc CMe_3); δ_C (125 MHz, $CDCl_3$) 152.9 (Boc C=O), 152.5 (Boc C=O), 125.8 (C-2), 125.4 (C-2), 105.8 (C-3), 105.3 (C-3), 80.6 (Boc *C*Me_3), 80.5 (Boc *C*Me_3), 42.7 (C-6), 41.6 (C-6), 28.5 (Boc C*Me*$_3$), 21.9, 21.6, 21.5 (C-4 and C-5) (15 out of 16 signals present); HRMS found $2MNa^+$, 389.2399. $C_{20}H_{34}N_2O_4Na$ requires 389.2411. Spectroscopic data are consistent with those reported in the literature.[4]

tert-Butyl 3-((2-ethoxy-2-oxoethyl)amino)-3-methylpiperidine-1-carboxylate 5d[9,10]

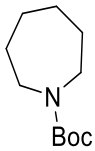


5d

To a stirred solution of DIPA (1.5 mL, 11.0 mmol) in Et_2O (20 mL) was added *n*-BuLi (6.9 mL of a 1.6 M solution in hexanes, 11.0 mmol) dropwise at 0 °C to 5 °C under N_2. The solution was stirred for 15 min and then cooled to –78 °C whereupon addition of *tert*-butyl 2-oxopiperidine-1-carboxylate (2.00 g, 10.0 mmol) in Et_2O (20 mL) was performed by syringe addition. The solution was stirred at –78 °C for 1 h before iodomethane (0.93 mL, 15.0 mmol) was added dropwise at –50 °C. The solution was then slowly warmed to –20 °C and stirred for 30 min. Sat. $NH_4Cl_{(aq)}$ (20 mL) was then added and the layers separated. The aqueous layer was then extracted with Et_2O (3 × 20 mL), and the organics washed with sat. $NH_4Cl_{(aq)}$ (2 × 20 mL), dried ($MgSO_4$) and the solvent then evaporated under reduced pressure to give the crude product. The crude product was purified by flash column chromatography eluting with 9:1 hexane−EtOAc to yield impure *lactam* (562 mg) as a yellow oil. Super-Hydride® (2.7 mL of a 1 M solution in THF, 2.67 mmol) was added dropwise to a solution of the lactam (541 mg, 2.54 mmol) in toluene (9.4 mL) at –78 °C and the mixture stirred for 30 min at –78 °C. Then, DIPEA (2.5 mL, 14.5

mmol), DMAP (6.2 mg, 2 mol%) and TFAA (0.42 mL, 3.05 mmol) were added and the resultant mixture was allowed to warm to room temperature and stirred for 16 h at room temperature. Then, water (10 mL) was added and the two layers were separated and the aqueous layer was extracted with DCM (2 × 10 mL). The organic layers were combined and washed with water (2 × 20 mL), dried ($MgSO_4$) and the solvent evaporated under reduced pressure to give a crude product. The crude product was purified by flash column chromatography eluting with 95:5 hexane−EtOAc to yield the enecarbamate **5d** as a 60:40 mixture of rotamers (297 mg, 15% over two steps) as a yellow oil, R_f 0.46 (80:20 hexane−EtOAc); ν_{max}/cm^{-1} 2975, 2928, 2877, 1695 (C=O), 1674 (C=O), 1452, 1393, 1253, 1154, 1110, 981 and 764; δ_H (500 MHz, $CDCl_3$) 6.59 (0.4H, br s, 2-H), 6.43 (0.6H, br s, 2-H), 3.46–3.34 (2H, m, 6-H_2), 1.91–1.84 (2H, m, 4-H_2), 1.77–1.69 (2H, br m, 5-H_2), 1.60 (3H, br s, Me), 1.41 (9H, s, Boc CMe_3); δ_C (125 MHz, $CDCl_3$) 152.9 (Boc C=O), 152.5 (Boc C=O), 120.5 (C-2), 120.2 (C-2), 114.7 (C-3), 114.2 (C-3), 80.4 (Boc *C*Me_3), 80.2 (Boc *C*Me_3), 42.1 (C-6), 41.0 (C-6), 28.5 (Boc C*Me*$_3$), 27.2 (C-4), 26.9 (C-4), 22.1 (C-5), 21.0 (C-5), 21.14 (Me), 21.09 (Me) (17 out of 18 signals present); Spectroscopic data are consistent with those reported in the literature.[9]

tert-Butyl azepane-1-carboxylate S3

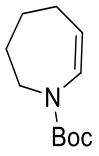


S3

Boc_2O (4.6 mL, 20 mmol) was added to a solution of azepane (2.3 mL, 20 mmol) in DCM (70 mL) and stirred at rt for 72 h. The solvent was then evaporated under reduced pressure to yield carbamate **S3** as a 1:1 mixture of rotamers (3.98 g, 100%) as a yellow oil; ν_{max}/cm^{-1} 2974, 2927, 2857, 1687 (C=O), 1413, 1160, 1115, 964 and 770; δ_H (400 MHz, $CDCl_3$) 3.37 (2H, app. t, *J* 6.1, 2-H_2, 7-H_2), 3.31 (2H, app. t, *J* 6.1, 2-

H_2, 7-H_2), 1.71–1.58 (4H, br m, 3-H_2, 6-H_2), 1.57–1.48 (4H, br m, 4-H_2, 5-H_2), 1.45 (9H, s, Boc CMe_3); δ_C (100 MHz, $CDCl_3$) 155.8 (Boc C=O), 79.0 (Boc *C*Me_3), 47.1 (C-2, C-7), 46.7 (C-2, C-7), 28.7 (Boc C*Me*$_3$), 28.6 (Boc C*Me*$_3$), 27.6 (C-3, C-6), 27.0 (C-4, C-5), (8 out of 12 signals present); HRMS found MNa^+, 221.1461. $C_{11}H_{21}NO_2Na$ requires 221.1465. Spectroscopic data are consistent with those reported in the literature.[11]

tert-Butyl 2,3,4,5-tetrahydro-1H-azepine-1-carboxylate 5e

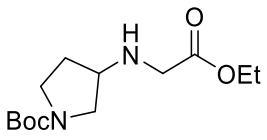


5e

Compound **5e** was synthesised using general method A using Boc protected amine **S2** (3.00 g, 15.1 mmol), anhydrous methanol (20 mL), tetraethylammonium tosylate (249 mg, 0.42 mmol), toluene (20 mL) and NH_4Cl (161 mg, 20 mol%). Reflux was carried out for 4 h. The crude product was purified by flash column chromatography eluting with 95:5 hexane−EtOAc to yield the enecarbamate **5e** as an undetermined mixture of rotamers (2.05 g, 69%) as a colourless oil, R_f 0.69 (80:20 hexane−EtOAc); ν_{max}/cm^{-1} 2976, 2930, 2863, 1698 (C=O), 1650, 1365, 1217, 1115, 1073, 1012, 858, 768 and 721; δ_H (400 MHz, $CDCl_3$) 6.60–6.37 (1H, m, 2-H), 5.07–4.86 (1H, m, 3-H), 3.69–3.58 (2H, m, 7-H_2), 2.17 (2H, app. ddd, *J* 11.6, 5.4, 1.5, 4-H_2), 1.82–1.63 (4H, m, 5-H_2, 6-H_2), 1.48 (9H, s, Boc CMe_3); δ_C (100 MHz, $CDCl_3$) 152.1 (Boc C=O), 130.8 (C-2), 114.2 (C-3), 80.4 (Boc *C*Me_3), 47.1 (C-7), 47.0 (C-7), 28.5 (Boc C*Me*$_3$), 28.2 (6), 26.4 (C-4), 25.4 (5) (10 out of 18 signals present); HRMS found MNa^+, 220.1304. $C_{11}H_{19}NO_2Na$ requires 220.1308. Spectroscopic data are consistent with those reported in the literature.[4]

4. Synthesis of Bicyclic Lactams

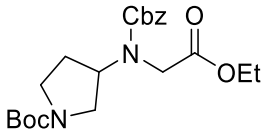
***tert*-Butyl 3-((2-ethoxy-2-oxoethyl)amino)pyrrolidine-1-carboxylate S4**



S4

S4 was synthesised using general method B using *N*-Boc-2,3-dihydro-1H-pyrrole (42.3 mg, 0.25 mmol, supplier: Sigma Aldrich) and glycine ethyl ester hydrochloride (70.0 mg, 0.50 mmol). Reaction was performed in duplicate and the contents of the two vials combined before work-up. The crude product was purified by flash column chromatography eluting with 1:1 hexane−EtOAc to yield amino ester **S4** as a 1:1 mixture of rotamers (77.2 mg, 57%) as a yellow oil, R_f 0.27 (EtOAc); ν_{max}/cm^{-1} 2976, 2934, 2879, 1738 (C=O), 1693 (C=O), 1404, 1168, 1114 and 772; δ_H (500 MHz, $CDCl_3$) 4.19 (2H, q, *J* 7.1 Hz, 10-H_2), 3.54–3.42 (2H, m, 2-H_A, 5-H_A), 3.42–3.38 (2H, m, 7-H_2), 3.38–3.33 (1H, m, 5-H_B), 3.32–3.28 (1H, m, 3-H), 3.15 (0.5H, dd, *J* 10.9, 4.3, 2-H_B), 3.08 (0.5H, dd, *J* 10.8, 5.0, 2-H_B), 2.01 (1H, app. td, *J* 12.9, 6.2, 4-H_A), 1.73 (1H, app. dd, *J* 11.7, 5.4, 4-H_B), 1.66 (1H, br s, NH), 1.45 (9H, s, C(Me)$_3$), 1.28 (3H, t, *J* 7.1 Hz, 11-H_3); δ_C (125 MHz, $CDCl_3$) 172.5 (C=O C-8), 154.8 (C=O Boc), 154.7 (C=O Boc), 79.3 (*C*(Me)$_3$), 61.1 (C-10), 57.4 (C-3), 56.6 (C-3), 52.0 (C-2), 51.4 (C-2), 49.4 (C-7), 49.3 (C-7), 44.5 (C-5), 44.1 (C-5), 32.1 (C-4), 31.4 (C-4), 28.7 (C(*Me*)$_3$), 14.4 (C-11) (17 out of 22 signals present); HRMS found MH^+, 273.1809. $C_{13}H_{25}N_2O_4$ requires 273.1809. Spectroscopic data are consistent with those reported in the literature.[12]

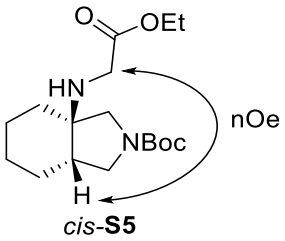
***tert*-Butyl 3-(((benzyloxy)carbonyl)(2-ethoxy-2-oxoethyl)amino)pyrrolidine-1-carboxylate 9a**



9a

9a was synthesised using general method C using benzyl chloroformate (43 µL, 0.304 mmol), amino ester **S4** (75.0 mg, 0.276 mmol) and $NaHCO_3$ (139 mg, 1.66 mmol) in DCM (3 mL) for 16 h. The crude product was purified by flash column chromatography, eluting with 1:1 hexane−EtOAc to yield *carbamate* **9a** as a 60:40 mixture of rotamers (105 mg, 94%) as a colourless oil, R_f 0.37 (1:1 hexane-EtOAc); ν_{max}/cm^{-1} 2977, 2877, 1750 (C=O), 1694 (C=O), 1404, 1365, 1198, 1169, 1135, 771 and 643; δ_H (500 MHz, $CDCl_3$) 7.40–7.27 (5H, m, Ph), 5.17 (0.8H, br s, Cbz CH_2), 5.13 (1.2H, br s, Cbz CH_2), 4.86–4.75 (0.6H, br m, 3-H), 4.70–4.59 (0.4H, br m, 3-H), 4.26–4.15 (0.8H, br m, 10-H_2), 4.15–4.06 (1.2H, br m, 10-H_2), 4.04–3.81 (2H, m, 7-H_2), 3.61 (1H, dd, *J* 11.3, 7.9, 2-H_A), 3.53–3.36 (1H, br m, 5-H_A), 3.35–3.21 (1H, br m, 5-H_B), 3.20–3.09 (1H, dd, br m, 2-H_B), 2.16–2.04 (1H, br m, 4-H_B), 1.95–1.83 (1H, br m, 4-H_B), 1.44 (9H, s, $C(Me)_3$), 1.30–1.22 (1.2H, br m, 11-H_3), 1.22–1.13 (1.8H, br m, 11-H_3); δ_C (125 MHz, $CDCl_3$) 170.0 (C=O C-8), 154.8 (C=O Cbz), 154.5 (C=O Boc), 136.3 (*ipso*-Ph), 128.7 (Ph), 128.6 (Ph), 128.4 (Ph), 128.3 (Ph), 128.2 (Ph), 128.0 (Ph), 79.8 ($C(Me)_3$), 68.0 (Cbz CH_2), 67.8 (Cbz CH_2), 61.5 (C-10), 55.3 (C-3), 54.6 (C-3), 55.3 (C-2), 54.6 (C-2), 45.5 (C-7), 45.2 (C-7), 44.5 (C-5), 43.9 (C-5), 28.6 ($C(Me)_3$), 28.5 (C-4), 14.2 (C-11) (25 out of 34 signals present); HRMS found MH^+, 407.2172. $C_{21}H_{31}N_2O_6$ requires 407.2177.

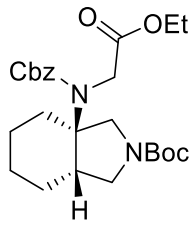
***tert*-Butyl 3a-((2-ethoxy-2-oxoethyl)amino)octahydro-2H-isoindole-2-carboxylate *cis*-S5**



cis-**S5**

Cis-**S5** was synthesised using general method B using enecarbamate **5b** (55.8 mg, 0.25 mmol) and glycine ethyl ester hydrochloride (70.0 mg, 0.50 mmol). Reaction was performed in triplicate and the contents of the three vials combined before work-up. The crude product was purified by flash column chromatography eluting with 1:1 hexane−EtOAc to yield *amino ester cis*-**S5** as a 1:1 mixture of rotamers (138 mg, 56%) as a yellow oil, R_f 0.34 (1:1 hexane-EtOAc); ν_{max}/cm^{-1} 2975, 2929, 2857, 1738 (C=O), 1694 (C=O), 1392, 1365, 1172, 1097, 881 and 772; δ_H (500 MHz, $CDCl_3$) 4.19 (1H, q, *J* 7.1 Hz, 14-H_2), 4.18 (1H, q, *J* 7.1 Hz, 14-H_2), 3.54–3.46 (1H, m, 9-H_A), 3.40 (1H, d, *J* 16.9, 11-H_A), 3.35–3.28 (1.5H, m, 2-H_A, 11-H_B), 3.27–3.21 (1H, m, 2-H_A, 9-H_B), 3.19–3.12 (1H, m, 2,-H_B, 9-H_B), 3.09 (0.5H, d, *J* 10.8, 2-H_B), 1.98 (1H, app. q, *J* 6.8, 8-H), 1.80 (1H, br s, NH), 1.68 (1H, app. dt, *J* 12.7, 8.5, 4-H_A), 1.61–1.49 (4H, m, 5-H_2, 6-H_2), 1.45 (4.5H, s, C(Me)$_3$), 1.45 (4.5H, s, C(Me)$_3$), 1.40–1.31 (3H, m, 4-H_B, 7-H_2), 1.27 (1.5H, t, *J* 7.1 Hz, 15-H_3), 1.27 (1.5H, t, *J* 7.1 Hz, 15-H_3); δ_C (125 MHz, $CDCl_3$) 172.9 (C=O C-12), 172.8 (C=O C-12), 155.4 (C=O Boc), 155.3 (C=O Boc), 79.34 (*C*(Me)$_3$), 79.32 (*C*(Me)$_3$), 61.2 (C-14), 60.5 (C-3), 59.9 (C-3), 54.6 (C-2), 53.4 (C-2), 49.7 (C-9), 48.9 (C-9), 44.8 (C-11), 44.7 (C-11), 42.5 (C-8), 41.2 (C-8), 29.71 (C-4), 29.68 (C-4), 28.7 (C(*Me*)$_3$), 25.7 (C-7), 25.1 (C-7), 22.5, 22.2, 22.02, 21.96 (C-5, C-6), 14.3 (C-15) (27 out of 30 signals present); HRMS found MNa^+, 349.2098. $C_{17}H_{30}N_2O_4Na$ requires 349.2098. The stereochemistry was assigned through positive NOESY interaction between 8-H and 11-H_2.

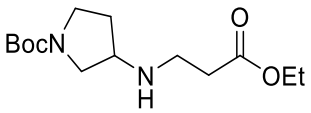
***tert*-Butyl 3a-(((benzyloxy)carbonyl)(2-ethoxy-2-oxoethyl)amino)octahydro-2H-isoindole-2-carboxylate *cis*-9b**



cis-**9b**

Cis-**9b** was synthesised using general method C using benzyl chloroformate (66 µL, 0.465 mmol), amino ester *cis*-**S5** (138 mg, 0.423 mmol) and $NaHCO_3$ (212 mg, 2.54 mmol) in DCM (4 mL) for 72 h. The crude product was purified by flash column chromatography, eluting with 8:2 hexane–EtOAc to yield *carbamate cis*-**9b** as a 60:40 mixture of rotamers (133 mg, 68%) as a pale yellow oil, R_f 0.50 (1:1 hexane-EtOAc); ν_{max}/cm^{-1} 2976, 2931, 2863, 1749, 1691 (C=O), 1393, 1365, 1174, 1128, 1100, 774 and 698; δ_H (500 MHz, $CDCl_3$) 7.39–7.28 (5H, m, Ph), 5.22–4.98 (2H, m, Cbz CH_2), 4.45–4.19 (1H, m, 2-H_A), 4.07–4.15 (2H, m 14-H_2), 4.00–3.72 (2H, m, 2-H_B, 11-H_A), 3.57 (1H, d, *J* 15.8, 11-H_B), 3.49–3.40 (1H, m, 9-H_A), 3.25 (0.6H, dd, *J* 10.8, 7.3, 9-H_B), 3.14 (0.4H, dd, *J* 10.7, 5.0, 9-H_B), 2.70–2.54 (0.4H, m, 8-H), 2.52–2.41 (0.6H, m, 8-H), 1.75–1.61 (2H, m, 4-H_2 or 5-H_2, 6-H_2 or 7H_2), 1.53–1.47 (2H, m, 4-H_2 or 5-H_2, 6-H_2 or 7H_2), 1.45 (4.5H, s, $C(Me)_3$), 1.44 (4.5H s, $C(Me)_3$), 1.40–1.33 (2H, m, 4-H_2 or 5-H_2, 6-H_2 or 7H_2), 1.33–1.24 (2H, m, 4-H_2 or 5-H_2, 6-H_2 or 7H_2), 1.24–1.12 (3H, m, 15-H_3); δ_C (125 MHz, $CDCl_3$) 170.9 (C=O C-12), 170.7 (C=O C-12), 154.8 (C=O Boc or Cbz), 128.6 (Ph), 128.1 (Ph), 128.0 (Ph), 79.64 (*C*$(Me)_3$), 79.57 (*C*$(Me)_3$), 67.4 (Cbz CH_2), 67.3 (Cbz CH_2), 61.4 (C-14), 61.3 (C-14), 60.6 (C-3), 50.2 (C-9), 48.8 (C-9), 47.0 (C-11), 38.9 (C-8), 28.4 (C-4), 28.6 (C(*Me*)$_3$), 26.2 (C-7), 22.3, 21.6 (C-5, C-6), 14.4 (C-15), 14.3 (C-15) (24 out of 42 signals present); HRMS found MNa^+, 483.2478. $C_{25}H_{36}N_2O_6Na$ requires 483.2466.

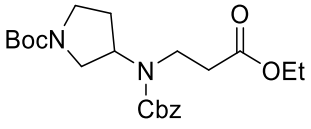
***tert*-Butyl 3-((3-ethoxy-3-oxopropyl)amino)pyrrolidine-1-carboxylate S6**



S6

S6 was synthesised using general method B using *N*-Boc-2,3-dihydro-1H-pyrrole (42.3 mg, 0.25 mmol, supplier: Sigma Aldrich) and ethyl 3-aminopropionate hydrochloride (75.0 mg, 0.50 mmol). Reaction was performed in duplicate and the contents of the two vials combined before work-up. The crude product was purified by flash column chromatography eluting with EtOAc to yield *amino ester* **S6** as a 1:1 mixture of rotamers (89.5 mg, 63%) as a yellow oil, R_f 0.10 (EtOAc); ν_{max}/cm^{-1} 2976, 2932, 2873, 1733 (C=O), 1692 (C=O), 1405, 1167 and 771; δ_H (500 MHz, $CDCl_3$) 4.14 (2H, q, *J* 7.1 Hz, 11-H_2), 3.56 (0.5H, dd, *J* 10.7, 6.1, 2-H_A), 3.52 (0.5H, dd, *J* 11.2, 4.8, 2-H_A), 3.50–3.38 (1H, m, 5-H_A), 3.38–3.31 (1H, m, 5-H_B), 3.31–3.26 (1H, m, 3-H), 3.10 (0.5H, dd, *J* 10.7, 5.0, 2-H_B), 3.02 (0.5H, dd, *J* 10.6, 5.7, 2-H_B), 2.93–2.82 (2H, m, 7-H_2), 2.50 (2H, t, *J* 6.4, 8-H_2), 2.04 (1H, app. td, *J* 13.0, 5.9, 4-H_A), 1.73 (1H, app. d5, *J* 15.2, 7.3, 4-H_B), 1.49 (1H, br s, NH), 1.45 (9H, s, C$(Me)_3$), 1.26 (3H, t, *J* 7.1 Hz, 12-H_3); δ_C (125 MHz, $CDCl_3$) 172.8 (C=O C-9), 154.8 (C=O Boc), 79.3 (*C*$(Me)_3$), 60.7 (C-11), 57.8 (C-3), 57.0 (C-3), 52.1 (C-2), 51.7 (C-2), 44.6 (C-5), 44.2 (C-5), 43.5 (C-7), 35.0 (C-8), 32.2 (C-4), 31.5 (C-4), 28.7 (C(*Me*)$_3$), 14.4 (C-12) (16 out of 24 signals present); HRMS found MH^+, 287.1969. $C_{14}H_{27}N_2O_4$ requires 287.1965.

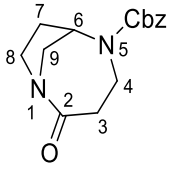
***tert*-Butyl 3-((3-ethoxy-3-oxopropyl)amino)pyrrolidine-1-carboxylate 9c**



9c

9c was synthesised using general method C using benzyl chloroformate (47 µL, 0.327 mmol), amino ester **S6** (85.0 mg, 0.297 mmol) and $NaHCO_3$ (149 mg, 1.78 mmol) in DCM (3 mL) for 16 h. The crude product was purified by flash column chromatography, eluting with 1:1 hexane−EtOAc to yield *carbamate* **9c** as a mixture of rotamers (112 mg, 89%) as a colourless oil, R_f 0.37 (1:1 hexane-EtOAc); ν_{max}/cm^{-1} 2978, 2894, 1733 (C=O), 1694 (C=O), 1404, 1168, 1132 and 771; δ_H (500 MHz, $CDCl_3$) 7.39–7.30 (5H, m, Ph), 5.15 (2H, s, Cbz CH_2), 4.66–4.49 (1H, br m, 3-H), 4.11 (2H, q, *J* 7.0, 11-H_2), 3.64–3.41 (4H, m, 2-H_A, 5-H_A, 7-H_2), 3.31–3.09 (2H, m, 2-H_B, 5-H_B), 2.66–2.47 (2H, br m, 8-H_2), 2.05–1.97 (2H, br m, 4-H_2), 1.45 (9H, s, $C(Me)_3$), 1.24 (3H, t, *J* 6.9 Hz, 12-H_3); δ_C (125 MHz, $CDCl_3$) 171.5 (C=O C-9), 155.9 (C=O Cbz), 154.8 (C=O Boc), 136.5 (*ipso*-Ph), 128.7 (Ph), 128.3 (Ph), 128.1 (Ph), 79.7 ($C(Me)_3$), 67.6 (Cbz CH_2), 60.8 (C-11), 55.9 (C-3), 55.1 (C-3), 47.5 (C-2), 44.4 (C-5), 43.9 (C-5), 40.3 (C-7), 34.9 (C-8), 29.1 (C-4), 28.6 ($C(Me)_3$), 14.3 (C-12) (20 out of 36 signals present); HRMS found MH^+, 421.2331. $C_{22}H_{33}N_2O_6$ requires 421.2333.

Benzyl 2-oxo-1,5-diazabicyclo[4.2.1]nonane-5-carboxylate 6c

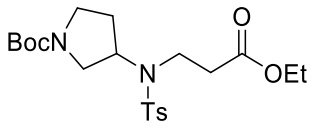


6c

6c was synthesised using general method D using NaOH (11.5 mg, 0.288 mmol), amino ester **9c** (110 mg, 0.262 mmol), 1:1 MeOH:water (4.4 mL), HCl (2.9 mL, 6 N), EtOAc (0.4 mL), toluene (3.5 mL) and *n*-Bu_2SnO (65.7 mg). The crude product was purified by flash column chromatography, eluting with EtOAc to yield *bicyclic carbamate* **6c** as a 1:1 mixture of rotamers (22.4 mg, 31%) as a colourless oil, R_f 0.31 (EtOAc); ν_{max}/cm^{-1} 2928, 1680 (C=O), 1406, 1262, 1217, 1098, 1008, 771 and 699; δ_H (500 MHz, $CDCl_3$) 7.39–7.30 (5H, m, Ph), 5.18–5.01 (2H, s, Cbz CH_2), 4.73–4.50 (1H, m, 6-H), 4.22 (0.5H, dt, *J* 9.0, 2.8 8-H_A), 4.20 (0.5H, dt, *J* 9.0, 2.8 8-H_A), 3.99–3.86

(2H, m, 4-H_A, 9-H_A), 3.74–3.60 (1H, m, 4-H_B), 3.09 (1H, ddd, *J* 14.6, 8.1, 6.9, 3-H_A), 2.89–2.73 (2H, m, 5-H_B, 9-H_B), 2.61–2.45 (1H, m, 3-H_B), 2.20–2.10 (1H, m, 7-H_2), 2.09–1.55 (1H, m, 7-H_2); δ_C (125 MHz, $CDCl_3$) 182.1 (C=O C-2), 182.0 (C=O C-2), 156.4 (C=O Cbz), 156.2 (C=O Cbz), 136.3 (*ipso*-Ph), 128.7 (Ph), 128.4 (Ph), 128.2 (Ph), 67.8 (CH_2 Cbz), 54.3 (C-6), 54.0 (C-6), 53.5 (C-9), 49.5 (C-8), 40.1 (C-4), 36.6 (C-3), 33.0 (C-7), 32.1 (C-7) (17 out of 26 signals present); HRMS found MH^+, 275.1389. $C_{15}H_{19}N_2O_3$ requires 275.1390.

tert-Butyl 3-((_N_-(3-ethoxy-3-oxopropyl)-4-methylphenyl)sulfonamido)pyrrolidine-1-carboxylate 9d

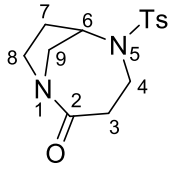


9d

Tosyl chloride (195 mg, 0.341 mmol), DIPEA (169 µL, 0.341 mmol) and DMAP (4.1 mg, 5 mol%) were added in sequence to a mixture of amino ester **S6** (195 mg, 0.681 mmol) in DCM (7 mL). The mixture was stirred for 16 h at room temperature, and the solvent evaporated under reduced pressure to give a crude product. The crude product was purified by flash column chromatography, eluting with 1:1 hexane−EtOAc to yield *carbamate* **9d** as a 1:1 mixture of rotamers (287 mg, 96%) as a yellow oil, R_f 0.31 (6:4 hexane-EtOAc); ν_{max}/cm^{-1} 2978, 2933, 2884, 1731 (C=O), 1694 (C=O), 1402, 1344, 1157, 1108, 663 and 548; δ_H (500 MHz, $CDCl_3$) 7.75–7.66 (2H, m, Ar), 7.35–7.27 (2H, m, Ar), 4.52–4.42 (0.5H, br m, 3-H), 4.42–4.32 (0.5H, br m, 3-H), 4.14 (2H, q, *J* 7.1, 11-H_2), 3.52–3.26 (4H, m, 2-H_A, 5-H_A, 7-H_2), 3.21–3.11 (1H, m, 5-H_B), 2.96–2.85 (1H, m, 2-H_B), 2.85–2.67 (2H, br m, 8-H_2), 2.44 (3H, s, Me), 2.05–1.95 (0.5H, br m, 4-H_2), 1.91–1.80 (1H, br m, 4-H_2), 1.80–1.71 (0.5H, br m, 4-H_2), 1.42 (9H, s, $C(Me)_3$), 1.26 (3H, t, *J* 7.1, 12-H_3); δ_C (125 MHz, $CDCl_3$) 171.4 (C=O C-9), 144.0 (*ipso*-Ar), 135.7 (*ipso*-Ar), 135.6 (*ipso*-Ar), 130.1 (Ar), 127.8 (Ar), 79.9 ($C(Me)_3$), 60.9 (C-11), 56.7 (C-3), 56.1 (C-3), 47.6 (C-2), 46.4 (C-2), 43.9 (C-5), 43.5 (C-

5), 39.84 (C-7), 39.75 (C-7), 36.72 (C-8), 36.65 (C-8), 29.4 (C-4), 27.9 (C-4), 28.5 (C(*Me*)$_3$), 21.7 (Me), 14.3 (C-12) (23 out of 34 signals present); HRMS found MNa^+, 463.1877. $C_{21}H_{32}N_2O_6SNa$ requires 463.1873.

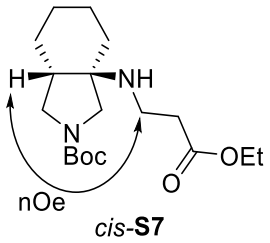
5-Tosyl-1,5-diazabicyclo[4.2.1]nonan-2-one 6d



6d

6d was synthesised using general method D using NaOH (27.9 mg, 0.700 mmol), amino ester **9d** (280 mg, 0.636 mmol), 1:1 MeOH:water (10 mL), HCl (7 mL, 6 N), EtOAc (1 mL), toluene (8 mL) and *n*-Bu_2SnO (159 mg). The crude product was purified by flash column chromatography, eluting with EtOAc to yield *bicyclic sulfonamide* **6d** (39.4 mg, 21%) as a colourless oil, R_f 0.38 (EtOAc); ν_{max}/cm^{-1} 3061, 2925, 1682, 1639 (C=O), 1598, 1442, 1338, 1158, 1091, 662 and 549; δ_H (500 MHz, $CDCl_3$) 7.62 (2H, d, *J* 8.3, Ar), 7.31 (2H, d, *J* 8.0, Ar), 4.69–4.60 (1H, m, 6-H), 4.05 (1H, ddt, *J* 11.7, 9.0, 2.5, 8-H_A), 2.92 (1H, app. dt, *J* 13.8, 4.6, 4-H_B), 3.76 (1H, d, *J* 14.2, 9-H_A), 3.15 (1H, ddd, *J* 13.9, 11.1, 3.9, 3-H_A), 2.88 (1H, ddd, *J* 13.9, 11.1, 2.9, 4-H_B), 2.81–2.71 (2H, m, 8-H_B, 9-H_B), 2.46–2.42 (1H, m, 3-H_B), 2.42 (3H, s, Me), 1.91 (1H, app. dtd, *J* 14.6, 8.3, 2.3, 7-H_2), 1.44 (1H, app. dtt, *J* 14.5, 8.9, 1.7, 7-H_2); δ_C (125 MHz, $CDCl_3$) 183.1 (C=O C-2), 144.1 (*ipso*-Ar), 135.7 (*ipso*-Ar), 130.1 (Ar), 127.3 (Ar), 54.8 (C-9), 54.5 (C-6), 51.1 (C-8), 41.7 (C-4), 37.7 (C-3), 29.5 (C-7) 21.7 (Me); HRMS found MNa^+, 317.0939. $C_{14}H_{18}N_2O_3SNa$ requires 317.0930.

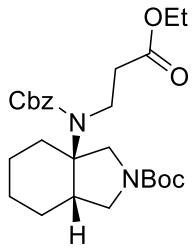
***tert*-Butyl 3a-((3-ethoxy-3-oxopropyl)amino)octahydro-2H-isoindole-2-carboxylate *cis*-S7**



cis-**S7**

Cis-**S7** was synthesised using general method B using enecarbamate **5b** (55.8 mg, 0.25 mmol) and ethyl 3-aminopropionate hydrochloride (75.0 mg, 0.50 mmol). The crude product was purified by flash column chromatography eluting with EtOAc to yield *amino ester cis*-**S7** as a 1:1 mixture of rotamers (37.9 mg, 45%) as a yellow oil, R_f 0.20 (1:1 hexane-EtOAc); ν_{max}/cm^{-1} 2976, 2931, 2858, 1733 (C=O), 1694 (C=O), 1042, 1366, 1174, 1155, 1101, 844 and 769; δ_H (500 MHz, $CDCl_3$) 4.13 (1H, q, *J* 7.1 Hz, 15-H_2), 4.12 (1H, q, *J* 7.1 Hz, 15-H_2), 3.50–3.41 (1H, m, 9-H_A), 3.32 (0.5H, d, *J* 10.8, 2-H_A), 3.26–3.20 (1H, m, 2-H_A, 9-H_B), 3.19–3.08 (1.5H, m, 2-H_B, 9-H_B), 2.86 (1H, dt, *J* 11.4, 5.3, 11-H_A), 2.69 (1H, dt, *J* 11.4, 5.3, 11-H_B), 2.45 (2H, app. td, *J* 6.3, 4.1, 12-H_2), 1.98 (1H, app. dd, *J* 12.7, 6.3, 8-H), 1.67–1.56 (2H, m, 4-H_A, 7-H_A), 1.56–1.47 (3H, m, NH, 5-H/6-H), 1.46–1.42 (9H, m, 5-H/6-H, C$(Me)_3$), 1.40–1.30 (3H, m, 5-H/6-H, 7-H_B), 1.25 (1.5H, t, *J* 7.1 Hz, 16-H_3), 1.25 (1.5H, t, *J* 7.1 Hz, 16-H_3); δ_C (125 MHz, $CDCl_3$) 172.99 (C=O C-13), 172.95 (C=O C-13), 155.39 (C=O Boc), 155.38 (C=O Boc), 79.22 (*C*$(Me)_3$), 79.19 (*C*$(Me)_3$), 60.6 (C-15), 60.5 (C-15), 60.4 (C-3), 59.8 (C-3), 55.1 (C-2), 54.2 (C-2), 49.4 (C-9), 48.7 (C-9), 42.1 (C-8), 41.1 (C-8), 38.1 (C-11), 38.0 (C-11), 35.83 (C-12), 35.82 (C-12), 29.5 (C-4), 29.4 (C-4), 28.7 (C(*Me*)$_3$), 25.2 (C-7), 24.9 (C-7), 22.3, 22.1, 22.0, 21.9 (C-5, C-6), 14.4 (C-16) (30 out of 32 signals present); HRMS found MH^+, 341.2437. $C_{18}H_{33}N_2O_4$ requires 341.2435. The stereochemistry was assigned through positive NOESY interaction between 8-H and 11-H_2.

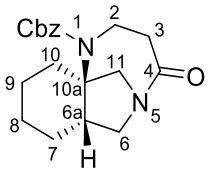
***tert*-Butyl 3a-(((benzyloxy)carbonyl)(3-ethoxy-3-oxopropyl)amino)octahydro-2H-isoindole-2-carboxylate *cis*-9e**



cis-**9e**

Cis-**9e** was synthesised using general method C using benzyl chloroformate (16 µL, 0.109 mmol), amino ester *cis*-**S7** (33.6 mg, 99.0 µmol) and $NaHCO_3$ (50.0 mg, 0.594 mmol) in DCM (1 mL) for 72 h. The crude product was purified by flash column chromatography, eluting with 8:2 hexane−EtOAc to yield *carbamate cis*-**9e** as a 60:40 mixture of rotamers (43.0 mg, 92%) as a pale yellow oil, R_f 0.56 (1:1 hexane-EtOAc); ν_{max}/cm^{-1} 2975, 2930, 1733, 1691 (C=O), 1397, 1365, 1165, 1126, 1097, 774 and 698; δ_H (500 MHz, $CDCl_3$) 7.38–7.28 (5H, m, Ph), 5.18–5.07 (2H, Cbz CH_2), 4.10 (1.2H, q, *J* 7.1 Hz, 15-H_2), 4.08 (0.8H, q, *J* 7.1 Hz, 15-H_2), 3.84–3.75 (1H, m, 11-H_A), 3.73 (0.4H, d, *J* 12.5, 2-H_A), 3.72 (0.6H, d, *J* 12.5, 2-H_A), 3.59–3.46 (2H, m, 2-H_B, 11-H_B), 3.43 (0.6H, dd, *J* 10.8, 7.2, 9-H_A), 3.39 (0.4H, dd, *J* 10.7, 6.7, 9-H_A), 3.21 (0.6H, dd, *J* 10.8, 5.3, 9-H_B), 3.11 (0.4H, dd, *J* 10.7, 4.1, 9-H_B), 3.00–2.92 (0.4H, m, 8-H), 2.89–2.80 (0.6H, m, 8-H), 2.64–2.46 (2H, m, 12-H_2), 2.35–2.25 (1H, m, 4-H_A), 1.79–1.69 (1H, m, 7-H_A), 1.64–1.49 (3H, m, 4-H_B, 5-H/6-H), 1.48–1.43 (12H, m, 5-H/6-H, 7-H_B $C(Me)_3$), 1.23 (1.8H, t, *J* 7.1 Hz, 16-H_3), 1.22 (1.2H, t, *J* 7.1 Hz, 16-H_3); δ_C (125 MHz, $CDCl_3$) 171.4 (C=O C-13), 155.61 (C=O Cbz), 155.56 (C=O Cbz), 154.9 (C=O Boc), 154.8 (C=O Boc), 128.66 (Ph), 128.65 (Ph), 128.14 (Ph), 128.10 (Ph), 127.91 (Ph), 127.86 (Ph), 79.7 (*C*$(Me)_3$), 79.6 (*C*$(Me)_3$), 67.14 (Cbz CH_2), 67.08 (Cbz CH_2), 65.9 (C-3), 65.7 (C-3), 60.70 (C-15), 60.66 (C-15), 54.0 (C-2), 52.4 (C-2), 50.4 (C-9), 49.5 (C-9), 40.8 (C-11), 40.7 (C-11), 39.8 (C-8), 38.9 (C-8), 35.7 (C-12), 35.5 (C-12), 29.19 (C-4), 29.16 (C-4), 28.6 (C(*Me*)$_3$), 28.1 (C-7), 27.4 (C-7), 22.9, 22.72, 22.65, 22.3 (C-5, C-6), 14.29 (C-16), 14.25 (C-16) (40 out of 44 signals present); HRMS found MNa^+, 497.2631. $C_{26}H_{38}N_2O_6Na$ requires 497.2622.

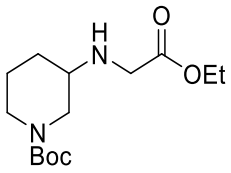
Benzyl (6aS*,10aR*)-4-oxooctahydro-5,10a-methanobenzo[b][1,5]diazocine-1(2H)-carboxylate 6e



6e

6e was synthesised using general method D using NaOH (3.7 mg, 92.7 μmol), amino ester **9e** (40.0 mg, 84.3 μmol), 1:1 MeOH:water (2 mL), HCl (1 mL, 6 N), EtOAc (0.2 mL), toluene (1.5 mL) and *n*-Bu_2SnO (21.1 mg). The crude product was purified by flash column chromatography, eluting with 1:1 EtOAc-hexane to yield *bicyclic carbamate* **6e** as a 75:25 mixture of rotamers (6.8 mg, 25%) as a pale yellow oil, R_f 0.38 (EtOAc); ν_{max}/cm^{-1} 2925, 2858, 1680 (C=O), 1400, 1359, 1248, 1101, 1047, 1023, 797 and 697; δ_H (500 MHz, $CDCl_3$) 7.40–7.28 (5H, m, Ph), 5.14 (1.5H, d, *J* 11.6, Cbz CH_2), 4.98 (0.5H, d, *J* 12.2, Cbz CH_2), 4.64–4.40 (0.25H, m, 2-H_A), 4.39–4.23 (1.75H, m, 2-H_A, 11-H_A), 3.68 (1H, app. d, *J* 13.9, 6-H_A), 3.44–3.28 (1.75H, m, 2-H_A, 6a-H), 3.23 (1H, app. d, *J* 13.8, 6-H_B), 3.13–3.02 (0.25H, m, 6a-H), 2.94 (1H, ddd, *J* 14.8, 10.2, 2.8, 3-H_A), 2.77–2.66 (1H, m, 3-H_B), 2.61 (1H, d, *J* 12.2, 11-H_B), 2.25–2.11 (1H, m, 10-H_A), 2.05–1.90 (2H, m, 7-H_A, 10-H_B), 1.81–1.70 (1H, m, 8-H/9-H_A), 1.65–1.57 (1H, m, 8-H/9-H_A), 1.49–1.40 (1H, m, 8-H/9-H_A), 1.21–1.09 (2H, m, 7-H_B, 9-H_B); δ_C (125 MHz, $CDCl_3$) 179.9 (C=O C-4), 155.6 (C=O Cbz), 155.0 (C=O Cbz), 128.8 (Ph), 128.7 (Ph), 128.6 (Ph), 128.5 (Ph), 128.1 (Ph), 127.8 (Ph), 67.0 (Cbz CH_2), 66.7 (C-10a), 56.1 (C-11), 52.5 (C-6), 39.7 (C-6a), 38.5 (C-2), 35.1 (C-3), 33.4 (C-7), 25.7 (C-10), 23.6 (C-8, C-9) (19 out of 32 signals present); HRMS found MNa^+, 351.1681. $C_{18}H_{24}N_2O_3Na$ requires 351.1679.

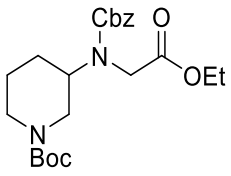
***tert*-Butyl 3-((2-ethoxy-2-oxoethyl)amino)piperidine-1-carboxylate S8**



S8

Compound **S8** was synthesised using general method B using enecarbamate **5c** (45.8 mg, 0.25 mmol) and glycine ethyl ester hydrochloride (70.0 mg, 0.50 mmol). The crude product was purified by flash column chromatography eluting with 1:1 hexane−EtOAc to yield amino ester **S8** as a 1:1 mixture of rotamers (59.0 mg, 82%) as a yellow oil, R_f 0.31 (EtOAc); ν_{max}/cm^{-1} 2967, 2932, 2859, 1738 (C=O), 1688 (C=O), 1420, 1365, 1238, 1153, 1026, 844 and 768; δ_H (500 MHz, $CDCl_3$) 4.16 (2H, q, *J* 7.1 Hz, 11-H_2), 4.07–3.78 (1H, m, 2-H_A), 3.74 (1H, app. dt, *J* 13.1, 4.2, 6-H_A), 3.43 (1H, d, *J* 17.3, 8-H_A), 3.39 (1H, d, *J* 17.3, 8-H_B), 2.91–2.79 (1H, m, 6-H_B), 2.78–2.56 (1H, m, 2-H_B), 2.56–2.46 (1H, m, 3-H), 1.92–1.84 (1H, m, 4-H_A), 1.73 (1H, br s, NH), 1.70–1.62 (1H, m, 5-H_A), 1.46–1.37 (10H, m, 5-H_B, C(Me)$_3$), 1.33–1.27 (1H, m, 4-H_B), 1.25 (3H, t, *J* 7.1 Hz, 12-H_3); δ_C (125 MHz, $CDCl_3$) 172.6 (C=O C-9), 154.9 (C=O Boc), 79.6 (*C*(Me)$_3$), 61.0 (C-11), 53.6 (C-3), 49.4 (C-2), 48.7 (C-2), 48.5 (C-8), 44.7 (C-6), 43.9 (C-6), 31.4 (C-4), 28.5 (C(*Me*)$_3$), 23.8 (C-5), 23.4 (C-5), 14.3 (C-12) (15 out of 24 signals present); HRMS found MH^+, 287.1965. $C_{14}H_{27}N_2O_4$ requires 287.1965. Spectroscopic data are consistent with those reported in the literature.[6]

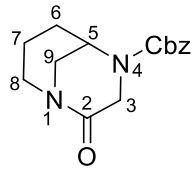
***tert*-Butyl 3-(((benzyloxy)carbonyl)(2-ethoxy-2-oxoethyl)amino)piperidine-1-carboxylate 9f**



9f

9f was synthesised using general method C using benzyl chloroformate (55.0 µL, 0.385 mmol), amino ester **S8** (100 mg, 0.35 mmol) and $NaHCO_3$ (175 mg, 2.1 mmol) in DCM (3 mL) for 16 h. The crude product was purified by flash column chromatography, eluting with 1:1 hexane−EtOAc to yield *carbamate* **9f** as a 60:40 mixture of rotamers (120 mg, 82%) as a pale yellow oil, R_f 0.55 (1:1 hexane-EtOAc); ν_{max}/cm^{-1} 2976, 2936, 2860, 1752, 1687 (C=O), 1409, 1364, 1238, 1177, 1149, 1113, 1028, 992, 771 and 698; δ_H (500 MHz, $CDCl_3$) 7.40–7.27 (5H, m, Ph), 5.20 (0.8H, s, Cbz CH_2), 5.12 (1.2H, s, Cbz CH_2), 4.23–3.84 (7H, m, 2-H_A, 6-H_A, 3-H, 8-H_2, 11-H_2), 2.72 (0.6H, app. t, *J* 11.8, 6-H_B), 2.65 (0.4H, app. t, *J* 11.8, 6-H_B), 2.60–2.45 (1H, m, 2-H_B), 2.02–1.89 (1H, m, 4-H_A), 1.77–1.69 (1H, m, 5-H_A), 1.59–1.47 (2H, m, 4-H_B, 5-H_B), 1.45 (5.4H, m, $C(Me)_3$), 1.40 (3.6H, m, $C(Me)_3$), 1.28 (1.8H, t, *J* 7.1, 12-H_3), 1.17 (1.2H, t, *J* 7.1 Hz, 12-H_3); δ_C (125 MHz, $CDCl_3$) 170.1 (C=O C-9), 156.3 (C=O Cbz), 155.5 (C=O Cbz), 154.9 (C=O Boc), 154.8 (C=O Boc), 136.5 (*ipso*-Ph), 128.7 (Ph), 128.6 (Ph), 128.2 (Ph), 128.0 (Ph), 127.9 (Ph), 79.9 ($C(Me)_3$), 67.9 (CH_2 Cbz), 67.5 (CH_2 Cbz), 61.4 (C-11), 53.3 (C-3), 47.3 (C-6), 45.7 (C-8), 43.4 (C-2), 29.1 (C-4), 28.5 ($C(Me)_3$), 24.8 (C-5), 14.3 (C-12), 14.2 (C-12) (24 out of 36 signals present); HRMS found MNa^+, 443.2157. $C_{22}H_{32}N_2O_6Na$ requires 443.2153. Spectroscopic data are consistent with those reported in the literature.[13]

Benzyl 2-oxo-1,4-diazabicyclo[3.3.1]nonane-4-carboxylate 6f

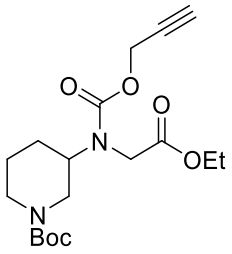


6f

6f was synthesised using general method D using NaOH (11.5 mg, 0.288 mmol), amino ester **9f** (110 mg, 0.262 mmol), 1:1 MeOH:water (4.4 mL), HCl (2.9 mL, 6 N), EtOAc (0.4 mL), toluene (3.5 mL) and *n*-Bu_2SnO (65.7 mg). The crude product was purified by flash column chromatography, eluting with 1:1 hexane−EtOAc to yield

bicyclic carbamate **6f** as a 55:45 mixture of rotamers (41.7 mg, 58%) as a colourless oil, R_f 0.35 (EtOAc); ν_{max}/cm^{-1} 2927, 2859, 1686 (C=O), 1407, 1156, 1090, 1008, 765 and 698; δ_H (500 MHz, $CDCl_3$) 7.39–7.29 (5H, m, Ph), 5.22–5.06 (2H, s, Cbz CH_2), 4.50 (0.45H, d, *J* 15.5, 3-H_A), 4.41 (0.55H, d, *J* 15.3, 3-H_A), 4.15–4.04 (2H, m, 8-H_A, 5-H), 3.55 (1H, app. d, *J* 14.3, 9-H_A), 3.82 (0.55H, d, *J* 15.3, 3-H_B), 3.77 (0.45H, d, *J* 15.3, 3-H_B), 3.21 (1H, app. t, *J* 15.0, 9-H_B), 2.94 (1H, app. qd, *J* 13.1, 3.2, 8-H_B), 2.27–2.19 (0.55H, m, 6-H_B), 2.13–2.04 (0.45H, m, 6-H_A), 1.89–1.76 (1H, m, 7-H_A), 1.72–1.66 (1H, m, 6-H_B), 1.45–1.35 (1H, m, 7-H_B); δ_C (125 MHz, $CDCl_3$) 180.2 (C=O C-2), 155.4 (C=O Cbz), 154.9 (C=O Cbz), 136.4 (*ipso*-Ph), 136.3 (*ipso*-Ph), 128.70 (Ph), 128.69 (Ph), 128.4 (Ph), 128.3 (Ph), 128.2 (Ph), 128.1 (Ph), 67.63 (CH_2 Cbz), 67.56 (CH_2 Cbz), 52.1 (C-8), 51.9 (C-8), 51.2 (C-9), 51.1 (C-9), 50.2 (C-5), 49.7 (C-5), 48.8 (C-3), 48.7 (C-3), 28.8 (C-6), 27.7 (C-6), 21.1 (C-7), 21.0 (C-7) (21 out of 26 signals present); HRMS found MNa^+, 297.1209. $C_{15}H_{18}N_2O_3Na$ requires 297.1210.

tert-Butyl 3-((2-ethoxy-2-oxoethyl)((prop-2-yn-1-yloxy)carbonyl)amino)piperidine-1-carboxylate 9g

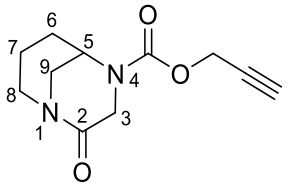


9g

9g was synthesised using general method C using propargyl chloroformate (40 µL, 0.322 mmol), amino ester **S8** (83.9 mg, 0.293 mmol) and $NaHCO_3$ (145 mg, 1.76 mmol) in DCM (3 mL) for 16 h. The crude product was purified by flash column chromatography, eluting with 1:1 hexane−EtOAc to yield *carbamate* **9g** as a 55:45 mixture of rotamers (96.9 mg, 91%) as a colourless oil, R_f 0.30 (1:1 hexane-EtOAc); ν_{max}/cm^{-1} 3250 (C≡C-H), 2978, 2941, 2864, 1750 (C=O), 1684 (C=O), 1409, 1366, 1299, 1264, 1238, 1176, 1147, 1108, 1026, 991 and 769; δ_H (500 MHz, $CDCl_3$) 4.81–

4.65 (2H, m, POC 3-H_2), 4.21 (0.9H, q, *J* 7.1, 11-H_2), 4.19 (1.1H, q, *J* 7.1, 11-H_2), 4.16–3.79 (5H, m, 2-H_A, 3-H, 6-H_A, 8-H_2), 2.72 (0.55H, app. t, *J* 11.9, 6-H_B), 2.66 (0.45H, app. t, *J* 11.9, 6-H_B), 2.61–2.49 (1H, m, 2-H_B), 2.47 (0.45H, t, *J* 2.2, POC 5-H), 2.43 (0.55H, t, *J* 2.1, POC 5-H), 2.01–1.90 (1H, m, 4-H_A), 1.76–1.67 (1H, m, 5-H_A), 1.59–1.50 (2H, m, 4-H_B, 5-H_B), 1.46 (4.05H, s, C$(Me)_3$), 1.45 (4.95H, m, C$(Me)_3$), 1.27 (3H, t, *J* 7.3, 12-H_3); δ_C (125 MHz, $CDCl_3$) 169.9 (C=O C-9), 155.5, 154.9, 154.8, 154.7 (C=O POC/Boc), 80.0 (*C*$(Me)_3$), 78.2 (POC C-4), 75.0 (POC C-5), 74.7 (POC C-5), 61.51 (C-11), 61.47 (C-11), 53.6 (C-3), 53.4 (POC C-3), 53.3 (POC C-3), 45.8 (br, C-6/C-8), 43.4 (br, C-2), 29.0 (C-4), 28.5 (C(*Me*)$_3$), 28.4 (C-4), 24.8 (C-5), 14.31 (C-12), 14.28 (C-12) (22 out of 32 signals present); HRMS found MH^+, 369.2019. $C_{18}H_{29}N_2O_6$ requires 369.2020.

Prop-2-yn-1-yl 2-oxo-1,4-diazabicyclo[3.3.1]nonane-4-carboxylate 6g

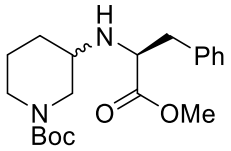


6g

6g was synthesised using general method D using NaOH (7.0 mg, 0.175 mmol), amino ester **9g** (58.5 mg, 0.159 mmol), 1:1 MeOH:water (2.4 mL), HCl (1.5 mL, 6 N), EtOAc (0.2 mL), toluene (2 mL) and *n*-Bu_2SnO (39.5 mg). The crude product was purified by flash column chromatography, eluting with 1:1 hexane−EtOAc to yield *bicyclic carbamate* **6g** as a 55:45 mixture of rotamers (18.7 mg, 53%) as a colourless oil, R_f 0.49 (EtOAc); ν_{max}/cm^{-1} 3247, 2953, 2867, 1691 (C=O), 1409, 1382, 1159, 1093, 1009 and 764; δ_H (500 MHz, $CDCl_3$) 4.78–4.72 (1.45H, m, POC 3-H_2), 4.68 (0.55, dd, *J* 15.6, 2.4, POC 3-H_2), 4.48 (0.45H, d, *J* 15.5, 3-H_A), 4.39 (0.55H, d, *J* 15.3, 3-H_A), 4.14–4.04 (2H, m, 8-H_A, 5-H), 3.84 (0.55H, d, *J* 15.3, 3-H_B), 3.77 (0.45H, d, *J* 15.3, 3-H_B), 3.56 (1H, app. d, *J* 14.3, 9-H_A), 3.23 (1H, dd, *J* 14.3, 4.4, 9-H_B), 3.00–2.89

(1H, m, 8-H_B), 2.48 (0.55H, t, *J* 2.4, POC 5-H), 2.46 (0.45H, t, *J* 2.4, POC 5-H), 2.22 (0.55H, app. d, *J* 14.0, 6-H_A), 2.13 (0.45H, app. d, *J* 14.0, 6-H_B), 1.88–1.76 (1H, m, 7-H_A), 1.75–1.66 (1H, m, 6-H_B), 1.41 (1H, app. d, *J* 14.1, 7-H_B); δ_C (125 MHz, $CDCl_3$) 179.9 (C=O C-2), 154.6 (C=O POC), 154.0 (C=O POC), 78.2 (POC C-4), 78.2 (POC C-4), 75.0 (POC C-5), 74.9 (POC C-5), 53.31 (POC C-3), 53.27 (POC C-3), 52.0 (C-8), 51.9 (C-8), 51.2 (C-9), 51.1 (C-9), 50.4 (C-5), 49.7 (C-5), 48.74 (C-3), 48.72 (C-3), 28.7 (C-6), 27.5 (C-6), 21.1 (C-7), 21.0 (C-7) (21 out of 22 signals present); HRMS found MNa^+, 245.0897. $C_{11}H_{14}N_2O_3Na$ requires 245.0897.

tert-Butyl 3-(((S)-1-methoxy-1-oxo-3-phenylpropan-2-yl)amino)piperidine-1-carboxylate _(S)_-S9

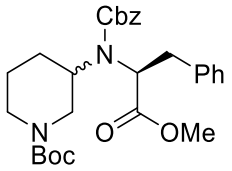


(S)-**S9**

(S)-**S9** was synthesised using general method B using enecarbamate **5c** (45.8 mg, 0.25 mmol) and L-phenylalanine methyl ester hydrochloride (70.0 mg, 0.50 mmol). Reaction was performed in duplicate and the contents of the two vials combined before work-up. The crude product was purified by flash column chromatography eluting with 2:1 hexane−EtOAc to yield *amino ester (S)*-**S9** as an unresolved mixture of rotamers and diastereomers (139 mg, 51%) as a yellow oil, R_f 0.64 (EtOAc); ν_{max}/cm^{-1} 2975, 2931, 2857, 1736 (C=O), 1688 (C=O), 1422, 1365, 1261, 1239, 1172, 1151, 766 and 700; δ_H (500 MHz, $CDCl_3$) 7.30–7.26 (2H, m, Ph), 7.24–7.20 (1H, m, Ph), 7.18–7.14 (2H, m, Ph), 3.94–3.68 (2H, m, 2-H_A, 6-H_A), 3.69–3.58 (4H, m, OMe, 8-H), 2.97–2.86 (2H, m, 9-H_2), 2.80 (1H, ddd, *J* 13.5, 12.1, 6.7, 6-H_B), 2.66 (0.5H, dd, *J* 12.6, 9.1, 2-H_B), 2.57–2.46 (1H, m, 3-H, 2-H_B), 2.45–2.36 (0.5H, m, 3-H), 1.85–1.74 (1H, m, 4-H_A), 1.68–1.60 (1H, m, 5-H_A), 1.56 (1H, br s, NH), 1.44 (9H, m, $C(Me)_3$), 1.42–1.30 (1H, m, 5-H_B), 1.30–1.21 (0.5H, m, 4-H_B), 1.16 (0.5H, ddd, *J* 13.1, 12.1, 3.8, 4-H_B); δ_C (125 MHz, $CDCl_3$) 172.6 (C=O CO_2Me), 175.3 (C=O CO_2Me), 155.0 (C=O

Boc), 137.4 (*ipso*-Ph), 137.3 (*ipso*-Ph), 130.4 (Ph), 129.3 (Ph), 128.6 (Ph), 128.5 (Ph), 126.8 (Ph), 79.6 (C(Me)$_3$), 79.1 (C(Me)$_3$), 60.4 (C-8), 52.7 (C-3), 51.9 (OMe), 51.8 (OMe), 49.4 (C-2), 48.6 (C-2), 44.6 (C-6), 43.8 (C-6), 40.3 (C-9), 40.1 (C-9), 32.1 (C-4), 30.7 (C-4), 28.58 (C(Me)$_3$), 28.57 (C(Me)$_3$), 23.8 (C-5), 23.4 (C-5) (28 out of 32 signals present); HRMS found MNa^+, 385.2103. $C_{20}H_{30}N_2O_4Na$ requires 385.2098.

tert-Butyl 3-(((benzyloxy)carbonyl)((S)-1-methoxy-1-oxo-3-phenylpropan-2-yl)amino)piperidine-1-carboxylate _(S)_-9h

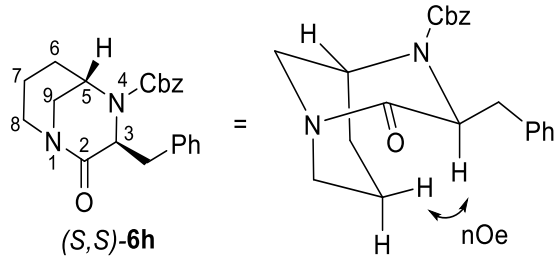


(S)-**9h**

(S)-**9h** was synthesised using general method C using benzyl chloroformate (52 µL, 0.364 mmol), amino ester *(S)*-**S9** (120 mg, 0.331 mmol) and $NaHCO_3$ (167 mg, 1.99 mmol) in DCM (5 mL) for 96 h. The crude product was purified by flash column chromatography, eluting with 75:25 hexane–EtOAc to yield *impure carbamate (S)*-**9h** as an unknown mixture of diastereomers and rotamers (53.3 mg, ~32%) as a colourless oil, R_f 0.67 (1:1 hexane-EtOAc); ν_{max}/cm^{-1} 2950, 2859, 1743 (C=O), 1688 (C=O), 1420, 1268, 1238, 1174, 1149, 754 and 700; δ_H (500 MHz, $CDCl_3$) 7.41–7.32 (6H, m, Ph), 7.25–7.17 (2H, m, Ph), 7.13–7.06 (2H, m, Ph), 5.34–5.03 (2H, m, Cbz CH_2), 4.31–3.83 (3H, m, 2-H_A, 6-H_A, 8-H), 3.80–3.48 (4H, m, OMe, 3-H), 3.45–3.37 (1H, m, CH_2Ph), 3.34–3.04 (1H, m, CH_2Ph), 2.82–2.54 (1H, m, 2-H_B), 2.47–2.24 (1H, m, 6-H_B), 1.66–1.52 (1H, m, 5-H_A), 1.59–1.34 (9H, m, C(Me)$_3$), 1.35–1.22 (1H, m, 5-H_B), 1.21–0.78 (2H, m, 4-H_2); δ_C (125 MHz, $CDCl_3$) 171.6 (C=O CO_2Me), 171.4 (C=O CO_2Me), 155.6, 155.3, 154.8, 154.6 (C=O Cbz/Boc), 138.4 (*ipso*-Ph), 138.1 (*ipso*-Ph), 136.6 (*ipso*-Ph), 136.2 (*ipso*-Ph), 129.8 (Ph), 129.6 (Ph), 128.7 (Ph), 128.4 (Ph), 128.2 (Ph), 128.0 (Ph), 127.7 (Ph), 127.1 (Ph), 79.7 (C(Me)$_3$), 79.6 (C(Me)$_3$), 67.6 (Cbz CH_2), 67.4 (Cbz CH_2), 59.4 (C-8), 54.1 (C-3), 53.7 (C-3), 52.5 (OMe), 52.4 (OMe), 47.3 (C-2),

43.5 (C-6), 37.2 (CH_2Ph), 35.9 (CH_2Ph), 28.9 (C-4), 28.53 (C(*Me*)$_3$), 28.50 (C(*Me*)$_3$), 25.0 (C-5) (35 out of 44 signals present); HRMS found MH^+, 497.2656. $C_{28}H_{37}N_2O_6$ requires *MH*, 497.2646.

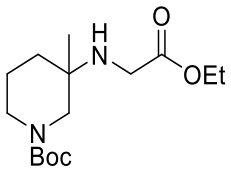
Benzyl (3S,5S)-3-benzyl-2-oxo-1,4-diazabicyclo[3.3.1]nonane-4-carboxylate *(S,S)*-6h



(S,S)-**6h** was synthesised using general method D using NaOH (4.4 mg, 0.111 mmol), amino ester *(S,S)*-**9h** (50.0 mg, 0.101 mmol), 1:1 MeOH:water (2 mL), HCl (1.1 mL, 6 N), EtOAc (0.2 mL), toluene (1.3 mL) and *n*-Bu_2SnO (25.3 mg). The crude product was purified by flash column chromatography, eluting with 1:1 hexane−EtOAc to yield *bicyclic carbamate (S,S)*-**6h** as a single diastereomer and as a 60:40 mixture of rotamers (4.4 mg, 12%) as a colourless oil, R_f 0.62 (EtOAc); ν_{max}/cm^{-1} 2956, 2869, 1684 (C=O), 1404, 1266, 1160, 1108 and 699; δ_H (500 MHz, $CDCl_3$) 7.40–7.31 (5H, m, Ph), 7.31–7.26 (1H, m, Ph), 7.25–7.16 (3H, m, Ph), 7.06–7.02 (1H, m, Ph), 5.19 (0.4H, d, *J* 12.4, Cbz CH_2), 5.16 (0.4H, d, *J* 12.4, Cbz CH_2), 5.08 (0.6H, d, *J* 12.0, Cbz CH_2), 4.99 (0.6H, d, *J* 12.0, Cbz CH_2), 4.90 (0.4H, dd, *J* 9.8, 5.3, 5-H), 4.77 (0.6H, dd, *J* 9.2, 5.9, 5-H), 4.20 (0.6H, app. br s, 2-H), 4.10 (0.4H, app. br s, 2-H), 4.08–4.01 (1H, m, 8-H_A), 3.71 (0.6H, app. d, *J* 14.5, 9-H_A), 3.55 (0.4H, app. d, *J* 14.5, 9-H_A), 3.28 (0.4H, dd, *J* 13.4, 5.3, CH_2Ph), 3.22 (0.6H, dd, *J* 14.5, 1.5, 9-H_B), 3.14–3.19 (1H, m, 9-H_B, CH_2Ph), 3.09–3.02 (1H, m, CH_2Ph), 3.02–2.89 (1H, m, 8-H_B), 2.20 (0.6H, app. d, *J* 13.3, 7-H_A), 2.03 (0.4H, app. d, *J* 13.3, 6-H_A), 1.86–1.65 (2H, m, 6-H_B, 7-H_A), 1.47–1.35 (1H, m, 7-H_B); δ_C (125 MHz, $CDCl_3$) 181.4 (C=O C-2), 179.9 (C=O C-2), 136.8 (*ipso*-Ph), 136.7 (*ipso*-Ph), 129.4 (Ph), 129.2 (Ph), 128.8 (Ph), 128.48 (Ph), 128.45 (Ph), 128.3 (Ph),

128.1 (Ph), 127.1 (Ph), 67.7 (CH_2 Cbz), 67.5 (CH_2 Cbz), 62.8 (C-3), 53.6 (C-8), 53.5 (C-8), 49.8 (C-9), 49.7 (C-5), 49.1 (C-5), 40.4 (CH_2Ph), 39.4 (CH_2Ph), 29.0 (C-6), 27.8 (C-6), 21.52 (C-7), 21.45 (C-7) (26 out of 36 signals present); HRMS found MH^+, 365.1871. $C_{22}H_{25}N_2O_3$ requires 365.1860. Stereochemistry of *(S,S)*-**6h** assigned by a positive nOe observed between 3-H and 7-H_A.

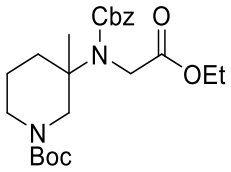
***tert*-Butyl 3-((2-ethoxy-2-oxoethyl)amino)-3-methylpiperidine-1-carboxylate S10**



S10

S10 was synthesised using general method B using enecarbamate **5d** (45.8 mg, 0.25 mmol) and glycine ethyl ester hydrochloride (70.0 mg, 0.50 mmol). Reaction was performed in duplicate and the contents of the two vials combined before work-up. The crude product was purified by flash column chromatography eluting with 1:1 hexane−EtOAc to yield *amino ester* **S10** as an undetermined mixture of rotamers (69.3 mg, 46%) as a yellow oil, R_f 0.33 (EtOAc); ν_{max}/cm^{-1} 2974, 2933, 2862, 1740 (C=O), 1692 (C=O), 1424, 1366, 1276, 1165 and 765; δ_H (500 MHz, $CDCl_3$) 4.18 (2H, q, *J* 6.9 Hz, 11-H_2), 3.59–3.50 (1H, m, 6-H_A), 3.48–3.32 (3H, m, 2-H_A, 8-H_2), 3.18–3.09 (1H, m, 6-H_B), 3.00 (1H, d, *J* 13.0, 2-H_B), 1.68–1.58 (3H, m, NH, 4-H_B, 5-H_B), 1.54–1.46 (2H, m, 4-H_B, 5-H_B), 1.45 (9H, s, $C(Me)_3$), 1.27 (3H, t, *J* 7.1, 12-H_3), 1.03 (3H, s, 13-Me); δ_C (125 MHz, $CDCl_3$) 172.6 (C=O C-9), 155.1 (C=O Boc), 79.7 ($C(Me)_3$), 61.0 (C-11), 51.2 (C-2), 44.2 (C-8), 43.6 (C-6), 36.3 (C-4), 28.6 ($C(Me)_3$), 23.0 (Me-13), 21.6 (C-5), 14.4 (C-12) (12 out of 13 signals present); HRMS found MH^+, 301.2206. $C_{15}H_{29}N_2O_4$ requires 301.2207.

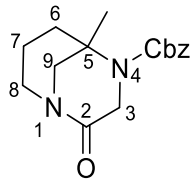
***tert*-Butyl 3-(((benzyloxy)carbonyl)(2-ethoxy-2-oxoethyl)amino)-3-methylpiperidine-1-carboxylate 9i**



9i

9i was synthesised using general method C using benzyl chloroformate (34 µL, 0.239 mmol), amino ester **S10** (65.0 mg, 0.217 mmol) and $NaHCO_3$ (109 mg, 1.30 mmol) in DCM (2 mL) for 16 h. The crude product was purified by flash column chromatography, eluting with 80:20 hexane−EtOAc to yield *carbamate* **9i** as an undetermined mixture of rotamers (73.7 mg, 78%) as a colourless oil, R_f 0.54 (1:1 hexane-EtOAc); ν_{max}/cm^{-1} 2977, 2934, 2868, 1750 (C=O), 1699 (C=O), 1425, 1227, 1189, 1156, 1114, 775 and 698; δ_H (500 MHz, $CDCl_3$) 7.38–7.26 (5H, m, Ph), 5.12 (2H, br s, Cbz CH_2), 4.25–3.99 (4H, br m, 11-H_2, 8-H_2), 3.97–3.75 (1H, br m, 2-H_A), 3.66–3.44 (1H, br m, 6-H_A), 3.42–3.01 (2H, br m, 2-H_B, 6-H_B), 2.95–2.37 (1H, br m, 4-H_A), 1.73–1.50 (3H, br m, 4-H_B, 5-H_2), 1.44 (9H, s, $C(Me)_3$), 1.42 (3H, br s, 13-Me), 1.23–1.13 (3H, br m, 12-H_3); δ_C (125 MHz, $CDCl_3$) 171.2 (C=O C-9), 154.7 (C=O Boc/Cbz), 136.6 (*ipso*-Ph), 128.7 (Ph), 128.6 (Ph), 128.1 (Ph), 127.9 (Ph), 127.8 (Ph), 127.1 (Ph), 80.1 ($C(Me)_3$), 67.2 (Cbz CH_2), 61.1 (C-11), 57.7 (C-3), 52.8 (C-2), 46.7 (C-8), 43.4 (C-6), 34.6 (C-4), 28.5 ($C(Me)_3$), 22.8 (C-5), 21.8 (Me-13), 14.2 (C-12); HRMS found MH^+, 435.2490. $C_{23}H_{35}N_2O_6$ requires 435.2490.

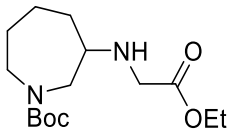
Benzyl 5-methyl-2-oxo-1,4-diazabicyclo[3.3.1]nonane-4-carboxylate 6i



6i

6i was synthesised using general method D using NaOH (7.1 mg, 0.177 mmol), amino ester **9i** (70.0 mg, 0.161 mmol), 1:1 MeOH:water (2.8 mL), HCl (1.8 mL, 6 N), EtOAc (0.2 mL), toluene (2.1 mL) and *n*-Bu_2SnO (40.4 mg). The crude product was purified by flash column chromatography, eluting with 1:1 hexane−EtOAc to yield *bicyclic carbamate* **6i** as a 65:35 mixture of rotamers (35.9 mg, 77%) as a colourless oil, R_f 0.47 (EtOAc); ν_{max}/cm^{-1} 2935, 1684 (C=O), 1401, 1378, 1349, 1313, 1200, 1117, 766 and 698; δ_H (500 MHz, $CDCl_3$) 7.39–7.28 (5H, m, Ph), 5.20–5.17 (0.7H, m, Cbz CH_2), 5.15 (0.65H, d, *J* 12.4, Cbz, CH_2), 5.05 (0.65H, d, *J* 12.4, Cbz, CH_2), 4.67 (0.35H, d, *J* 15.2, 3-H_A), 4.52 (0.65H, d, *J* 15.2, 3-H_A), 4.09–4.01 (1H, m, 8-H_A), 3.80 (0.65H, d, *J* 15.2, 3-H_B), 3.75 (0.35H, d, *J* 15.2, 3-H_B), 3.49–3.42 (1H, m, 9-H_A), 2.95–2.75 (2.65H, m, 8-H_B, 9-H_B, 6-H_A), 2.51–2.44 (0.35H, m, 6-H_A), 1.73–1.64 (1H, m, 7-H_A), 1.43 (1.95H, s, Me), 1.40–1.31 (3.05H, m, 6-H_B, 7-H_B, Me); δ_C (125 MHz, $CDCl_3$) 179.7 (C=O C-2), 156.1 (C=O Cbz), 153.8 (C=O Cbz), 136.4 (*ipso*-Ph), 136.2 (*ipso*-Ph), 128.72 (Ph), 128.67 (Ph), 128.37 (Ph), 128.35 (Ph), 128.2 (Ph), 128.0 (Ph), 67.9 (CH_2 Cbz), 67.1 (CH_2 Cbz), 58.7 (C-8), 58.3 (C-8), 56.2 (C-5), 55.6 (C-5), 50.8 (C-9), 50.6 (C-9), 48.9 (C-3), 48.7 (C-3), 34.2 (C-6), 32.5 (C-6), 24.2 (C-7), 22.9 (C-7), 21.8 (Me), 21.7 (Me) (27 out of 28 signals present); HRMS found MH^+, 289.1548. $C_{16}H_{21}N_2O_3$ requires 289.1547.

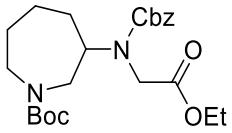
***tert*-Butyl 3-((2-ethoxy-2-oxoethyl)amino)azepane-1-carboxylate S11**



S11

S11 was synthesised using general method B using enecarbamate **5e** (49.3 mg, 0.25 mmol) and glycine ethyl ester hydrochloride (70.0 mg, 0.50 mmol). Reaction was performed in duplicate and the contents of the two vials combined before work-up. The crude product was purified by flash column chromatography eluting with 1:1 hexane−EtOAc to yield amino ester **S11** as a 60:40 mixture of rotamers (68.2 mg, 42%) as a yellow oil, R_f 0.25 (EtOAc); ν_{max}/cm^{-1} 2975, 2929, 2864, 1738 (C=O), 1687 (C=O), 1365, 1298, 1162, 842 and 771; δ_H (500 MHz, $CDCl_3$) 4.20 (1.2H, q, *J* 7.1 Hz, 12-H_2), 4.17 (0.8H, q, *J* 7.1 Hz, 12-H_2), 3.76 (0.4H, dd, *J* 14.0, 3.9, 2-H_A), 3.70–3.62 (1.2H, m, 2-H_A, 7-H_A), 3.55–3.49 (0.4H, m, 7-H_B), 3.48 (0.8H, m, 9-H_2), 3.45 (1.2H, m, 9-H_2), 3.22–3.09 (1H, m, 7-H_A, 7-H_B), 2.89 (0.4H, dd, *J* 14.0, 8.5, 2-H_B), 2.84–2.72 (1H, m, 2-H_B, 3-H), 2.66–2.58 (0.6H, m, 3-H), 1.90–1.79 (1.6H, m, 4-H_A, 6-H_A), 1.79–1.42 (1.4H, m, 5-H_A, 6-H_A) 1.64 (1H, br s, NH), 1.61–1.55 (1H, m, 6-H_B), 1.47 (5.4H, s, C(Me)$_3$), 1.45 (3.6H, s, C(Me)$_3$), 1.41–1.31 (2H, m, 4-H_B, 5-H_B), 1.27 (1.8H, t, *J* 7.0, 13-H_3), 1.26 (1.2H, t, *J* 7.0, 13-H_3); δ_C (125 MHz, $CDCl_3$) 172.8 (C=O C-10), 156.0 (C=O Boc), 155.7 (C=O Boc), 79.6 (*C*(Me)$_3$), 79.4 (*C*(Me)$_3$), 61.0 (C-12), 60.9 (C-12), 58.5 (C-3), 58.0 (C-3), 50.7 (C-2), 50.2 (C-2), 49.2 (C-9), 48.9 (C-9), 47.9 (C-7), 46.8 (C-7), 35.3 (C-4), 34.3 (C-4), 28.6 (C(*Me*)$_3$), 27.9 (C-6), 27.5 (C-6), 22.8 (C-5), 22.7 (C-5), 14.4 (C-13), 14.3 (C-13) (24 out of 26 signals present); HRMS found MH^+, 301.2133. $C_{15}H_{29}N_2O_4$ requires 301.2122. Spectroscopic data are consistent with those reported in the literature.[12]

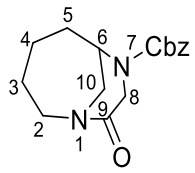
***tert*-Butyl 3-(((benzyloxy)carbonyl)(2-ethoxy-2-oxoethyl)amino)azepane-1-carboxylate 9j**



9j

9j was synthesised using general method C using benzyl chloroformate (34 µL, 0.239 mmol), amino ester **S11** (65.0 mg, 0.217 mmol) and $NaHCO_3$ (109 mg, 1.30 mmol) in DCM (2 mL) for 16 h. The crude product was purified by flash column chromatography, eluting with 75:25 hexane−EtOAc to yield *carbamate* **9j** as a 65:35 mixture of rotamers (65.5 mg, 70%) as a colourless oil, R_f 0.64 (1:1 hexane-EtOAc); ν_{max}/cm^{-1} 2975, 2930, 1691 (C=O), 1394, 1365, 1156, 981 and 768; δ_H (500 MHz, $CDCl_3$) 7.42–7.27 (5H, m, Ph), 5.23–5.14 (0.7H, m, Cbz CH_2), 5.14–5.04 (1.3H, m, Cbz CH_2), 4.19 (0.7H, q, *J* 7.1 Hz, 12-H_2), 4.15–4.02 (1.95H, m, 3-H, 12-H_2), 4.01–3.86 (2.35H, m, 3-H, 9-H_2), 3.81–3.68 (0.65H, m, 2-H_A), 3.66–3.43 (1.35H, m, 2-H_A, 7-H_A), 3.38–3.02 (2H, m, 2-H_B, 7-H_B), 2.01–1.72 (3H, m, 4-H_A, 5-H_A, 6-H_A), 1.70–1.51 (3H, m, 4-H_B, 5-H_B, 6-H_B), 1.50–1.42 (7.5H, m, $C(Me)_3$), 1.38 (1.5H, s, $C(Me)_3$), 1.27 (1.05H, t, *J* 6.8, 13-H_3), 1.17 (1.95H, t, *J* 6.8, 13-H_3); δ_C (125 MHz, $CDCl_3$) 170.2 (C=O C-10), 170.3 (C=O C-10), 156.1 (C=O Boc), 155.5 (C=O Cbz), 136.6 (*ipso*-Ph), 128.7 (Ph), 128.6 (Ph), 128.5 (Ph), 128.1 (Ph), 127.91 (Ph), 127.87 (Ph), 79.9 ($C(Me)_3$), 79.6 ($C(Me)_3$), 67.4 (Cbz CH_2), 61.3 (C-12), 61.2 (C-12), 58.5 (C-3), 58.0 (C-3), 49.5 (C-2), 49.0 (C-2), 47.6 (C-7), 47.2 (C-7), 46.9 (C-9), 46.5 (C-9), 31.8 (C-4), 31.0 (C-4), 28.6 ($C(Me)_3$), 28.5 ($C(Me)_3$), 28.1 (C-6), 27.5 (C-6), 23.8 (C-5), 23.6 (C-5), 14.3 (C-13), 14.2 (C-13) (34 out of 38 signals present); HRMS found MH^+, 435.2494. $C_{23}H_{35}N_2O_6$ requires 435.2490.

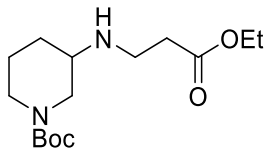
Benzyl 9-oxo-1,7-diazabicyclo[4.3.1]decane-7-carboxylate 6j



6j

6j was synthesised using general method D using NaOH (6.06 mg, 0.152 mmol), amino ester **9j** (60 mg, 0.138 mmol), 1:1 MeOH:water (2.4 mL), HCl (1.5 mL, 6 N), EtOAc (0.2 mL), toluene (1.8 mL) and *n*-Bu_2SnO (34.6 mg). The crude product was purified by flash column chromatography, eluting with EtOAc to yield *bicyclic carbamate* **6j** as a 60:40 mixture of rotamers (28.9 mg, 73%) as a colourless oil, R_f 0.30 (EtOAc); ν_{max}/cm^{-1} 2928, 2860, 1667 (C=O), 1403, 1331, 1191, 1126, 1072, 765 and 699; δ_H (500 MHz, $CDCl_3$) 7.39–7.29 (5H, m, Ph), 5.21–5.07 (2H, m, Cbz CH_2), 4.46 (0.4H, d, *J* 15.6, 8-H_A), 4.41 (0.6H, d, *J* 15.4, 8-H_A), 4.35–4.24 (1H, m, 2-H_A), 4.20 (0.6H, m, 6-H), 4.13 (0.4H, m, 6-H), 3.82 (0.6H, d, *J* 15.4, 8-H_B), 3.77 (0.4H, d, *J* 15.6, 8-H_B), 2.93–2.84 (1H, m, 2-H_B), 3.64 (1H, dd, *J* 14.6, 2.2, 10-H_A), 3.26 (0.6H, dd, *J* 14.6, 1.0, 10-H_B), 3.21 (0.4H, app. d, *J* 14.6, 10-H_B), 2.25 (0.6H, app. dd, *J* 15.1, 2.8, 5-H_A), 2.14 (0.4H, app. dd, *J* 14.8, 3.3, 5-H_A), 2.05–1.93 (1H, m, 3-H_A), 1.65–1.52 (2H, m, 3-H_B, 4-H_A), 1.50–1.41 (1H, m, 5-H_B), 1.29–1.14 (1H, m, 4-H_B); δ_C (125 MHz, $CDCl_3$) 170.9 (C=O C-9), 155.2 (C=O Cbz), 155.0 (C=O Cbz), 136.5 (*ipso*-Ph), 136.3 (*ipso*-Ph), 128.7 (Ph), 128.3 (Ph), 128.2 (Ph), 128.1 (Ph), 67.6 (CH_2 Cbz), 67.5 (CH_2 Cbz), 51.8 (C-6), 51.3 (C-6), 47.9 (C-8), 47.8 (C-8), 47.7 (C-10), 47.5 (C-10), 44.01 (C-2), 43.97 (C-2), 35.8 (C-5), 34.8 (C-5), 27.3 (C-3), 27.1 (C-3), 20.5 (C-4) (24 out of 28 signals present); HRMS found MH^+, 289.1544. $C_{16}H_{21}N_2O_3$ requires 289.1547.

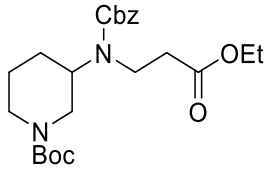
***tert*-Butyl 3-((3-ethoxy-3-oxopropyl)amino)piperidine-1-carboxylate S12**



S12

S12 was synthesised using general method B using enecarbamate **5c** (45.8 mg, 0.25 mmol) and ethyl 3-aminopropionate hydrochloride (75.0 mg, 0.50 mmol). The crude product was purified by flash column chromatography eluting with EtOAc to yield *amino ester* **S12** as a 1:1 mixture of rotamers (59.8 mg, 80%) as a yellow oil, R_f 0.11 (EtOAc); ν_{max}/cm^{-1} 2976, 2932, 2856, 1731 (C=O), 1687 (C=O), 1466, 1392, 1238, 1150 and 767; δ_H (500 MHz, $CDCl_3$) 4.11 (2H, q, *J* 7.1 Hz, 12-H_2), 4.07–3.80 (1H, m, 2-H_A), 3.79–3.75 (0.5H, m, 6-H_A), 3.75–3.72 (0.5H, m, 6-H_A), 2.96–2.77 (3H, m, 6-H_B, 8-H_2), 2.76–2.49 (2H, m, 2-H_B, 3-H), 2.45 (2H, app. dd, *J* 14.6, 8.2, 9-H_2), 1.92–1.83 (1H, m, 4-H_A), 1.69–1.60 (1H, m, 5-H_A), 1.49–1.35 (11H, m, NH, 5-H_B, C(Me)$_3$), 1.29–1.16 (4H, m, 4-H_B, 13-H_3); δ_C (125 MHz, $CDCl_3$) 172.8 (C=O C-10), 155.0 (C=O Boc), 79.5 (*C*(Me)$_3$), 60.5 (C-11), 53.7 (C-3), 49.5 (C-2), 49.1 (C-2), 44.7 (C-6), 43.9 (C-6), 42.4 (C-8), 35.2 (C-9), 31.6 (C-4), 28.5 (C(*Me*)$_3$), 23.9 (C-5), 23.5 (C-5), 14.3 (C-13) (16 out of 26 signals present); HRMS found MH^+, 301.2131. $C_{15}H_{29}N_2O_4$ requires 301.2122. Spectroscopic data are consistent with those reported in the literature.[6]

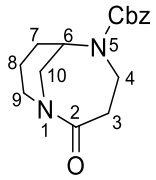
***tert*-Butyl 3-(((benzyloxy)carbonyl)(3-ethoxy-3-oxopropyl)amino)piperidine-1-carboxylate 9k**



9k

9k was synthesised using general method C using benzyl chloroformate (22.0 µL, 0.169 mmol), amino ester **S12** (46.2 mg, 0.154 mmol) and $NaHCO_3$ (77.0 mg, 0.924 mmol) in DCM (2 mL) for 72 h. The crude product was purified by flash column chromatography, eluting with 1:1 hexane−EtOAc to yield *carbamate* **9k** as a 55:45 mixture of rotamers (66.9 mg, 100%) as a colourless oil, R_f 0.42 (1:1 hexane-EtOAc); ν_{max}/cm^{-1} 2976, 2937, 2867, 1732, 1688 (C=O), 1416, 1264, 1239, 1149, 1112, 770 and 698; δ_H (500 MHz, $CDCl_3$) 7.38–7.27 (5H, m, Ph), 5.12 (2H, s, Cbz CH_2), 4.17–3.93 (4H, m, 2-H_A, 6-H_A, 12-H_2), 3.72 (1H, app. t, *J* 10.8, 3-H), 3.59–3.40 (2H, m, 8-H_2), 2.92–2.81 (0.55H, m, 2-H_B), 2.80–2.69 (0.45H, m, 2-H_B), 2.67–2.43 (3H, m, 6-H_B, 9-H_2), 1.85–1.65 (3H, m, 4-H_2, 5-H_A), 1.57–1.33 (10H, m, 5-H_B, $C(Me)_3$), 1.24 (3H, t, *J* 7.1 Hz, 13-H_3); δ_C (125 MHz, $CDCl_3$) 171.6 (C=O C-10), 171.2 (C=O C-10), 155.8 (C=O Boc), 155.6 (C=O Boc), 154.8 (C=O Cbz), 136.6 (*ipso*-Ph), 128.6 (Ph), 128.1 (Ph), 127.9 (Ph), 79.9 ($C(Me)_3$), 67.3 (CH_2 Cbz), 60.7 (C-12), 60.5 (C-12), 54.5 (C-3), 54.1 (C-3), 47.0 (C-2), 44.0 (C-6), 43.2 (C-6), 40.9 (C-8), 35.4 (C-9), 34.7 (C-9), 29.2 (C-4), 28.5 ($C(Me)_3$), 25.0 (C-5), 14.29 (C-13), 14.27 (C-13) (25 out of 38 signals present); HRMS found MNa^+, 457.2319. $C_{23}H_{34}N_2O_6Na$ requires 457.2309.

Benzyl 2-oxo-1,5-diazabicyclo[4.3.1]decane-5-carboxylate 6k

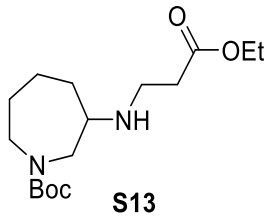


6k

6k was synthesised using general method D using NaOH (50.9 mg, 0.127 mmol), amino ester **9k** (50.0 mg, 0.115 mmol), 1:1 MeOH:water (2 mL), HCl (1.3 mL, 6 N), EtOAc (0.2 mL), toluene (2 mL) and *n*-Bu_2SnO (29.0 mg). The crude product was purified by flash column chromatography, eluting with 3:1 EtOAc-hexane to yield bicyclic carbamate **6k** as a 1:1 mixture of rotamers (25.4 mg, 77%) as a colourless oil, R_f 0.30 (EtOAc); ν_{max}/cm^{-1} 2931, 1688 (C=O), 1657 (C=O), 1409, 1223, 1093,

1067, 1008, 735 and 698; δ_H (500 MHz, $CDCl_3$) 7.40–7.29 (5H, m, Ph), 5.15 (1H, d, *J* 12.3, Cbz CH_2), 5.11 (1H, d, *J* 12.3, Cbz CH_2), 4.48 (1H, app. dd, *J* 11.6, 5.8, 6-H), 4.35 (1H, ddd, *J* 14.0, 7.7, 6.0, 9-H_A), 4.28 (1H, app. d, *J* 11.6, 4-H_A), 3.72 (1H, app. d, *J* 15.6, 10-H_A), 3.36 (1H, app. t, *J* 11.6, 4-H_B), 3.25 (1H, app. dd, *J* 15.1, 5.0, 10-H_B), 3.05 (1H, app. dt, *J* 14.2, 3.6, 3-H_A), 2.95 (1H, app. dt, *J* 12.8, 5.7, 9-H_B), 2.49 (1H, ddd, *J* 14.3, 5.4, 2.2, 3-H_B), 1.88–1.79 (1H, m, 7-H_A), 1.78–1.65 (2H, m, 8-H_A, 7-H_B), 1.56–1.49 (1H, m, 8-H_B); δ_C (125 MHz, $CDCl_3$) 176.8 (C=O C-2), 156.2 (C=O Cbz), 136.5 (*ipso*-Ph), 128.7 (Ph), 128.3 (Ph), 128.2 (Ph), 67.8 (CH_2 Cbz), 50.0 (C-6), 49.4 (C-10), 45.6 (C-9), 39.8 (C-4), 36.9 (C-3), 24.0 (C-7), 20.6 (C-8); HRMS found MNa^+, 311.1374. $C_{16}H_{20}N_2O_3Na$ requires 311.1366. Spectroscopic data are consistent with those reported in the literature.[6]

***tert*-Butyl 3-((3-ethoxy-3-oxopropyl)amino)azepane-1-carboxylate S13**

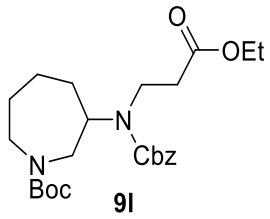


S13

S13 was synthesised using general method B using enecarbamate **5e** (49.3 mg, 0.25 mmol) and ethyl 3-aminopropionate hydrochloride (75.0 mg, 0.50 mmol). Reaction was performed in duplicate and the contents of the two vials combined before work-up. The crude product was purified by flash column chromatography eluting with EtOAc to yield *amino ester* **S13** as a 55:45 mixture of rotamers (56.6 mg, 36%) as a yellow oil, R_f 0.11 (EtOAc); ν_{max}/cm^{-1} 2975, 2929, 2859, 1732 (C=O), 1689 (C=O), 1468, 1413, 1365, 1299, 1164 and 772; δ_H (500 MHz, $CDCl_3$) 4.14 (1.1H, q, *J* 7.0 Hz, 13-H_2), 4.12 (0.9 H, q, *J* 7.0 Hz, 13-H_2), 3.80 (0.45H, dd, *J* 13.7, 4.0, 2-H_A), 3.73 (0.55H, dd, *J* 13.8, 3.1, 2-H_A), 3.69 (0.55H, ddd, *J* 14.5, 8.3, 3.0, 7-H_A), 3.50 (0.45H, ddd, *J* 14.5, 8.3, 3.0, 7-H_A), 3.20–3.09 (1H, m, 7-H_B), 2.94 (1.1H, t, *J* 6.0, 9-H_2), 2.93 (0.9H, t, *J* 6.0, 9-H_2), 2.85 (0.45H, dd, *J* 13.7, 8.6, 2-H_B), 2.81–2.72 (1H, m, 2-H_B, 3-H),

2.72–2.65 (0.55H, m, 3-H), 2.48 (2H, t, *J* 5.9, 10-H_2), 1.89–1.78 (1.55H, m, 4-H_A, 6-H_A), 1.78–1.69 (1.45H, m, 5-H_A, 6-H_A) 1.62–1.51 (2H, m, NH, 6-H_B), 1.47 (4.95H, s, $C(Me)_3$), 1.45 (4.05H, s, $C(Me)_3$), 1.41–1.29 (2H, m, 4-H_B, 5-H_B), 1.26 (1.65H, t, *J* 7.1, 14-H_3), 1.25 (1.35H, t, *J* 7.1, 14-H_3); δ_C (125 MHz, $CDCl_3$) 173.0 (C=O C-11), 172.8 (C=O C-11), 156.0 (C=O Boc), 155.7 (C=O Boc), 79.5 ($C(Me)_3$),79.3 ($C(Me)_3$), 60.6 (C-13), 60.5 (C-13), 58.4 (C-3), 57.9 (C-3), 51.2 (C-2), 50.7 (C-2), 48.0 (C-7), 46.9 (C-7), 42.9 (C-9), 35.31 (C-10), 35.27 (C-10), 35.2 (C-4), 34.2 (C-4), 28.7 ($C(Me)_3$), 28.6 ($C(Me)_3$), 28.0 (C-6), 27.6 (C-6), 22.9 (C-5), 22.8 (C-5), 14.4 (C-14) (21 out of 28 signals present); HRMS found MNa^+, 337.2099. $C_{16}H_{30}N_2O_4Na$ requires 337.2098.

tert-Butyl 3-(((benzyloxy)carbonyl)(3-ethoxy-3-oxopropyl)amino)azepane-1-carboxylate 9l

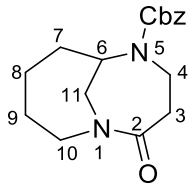


9l

9l was synthesised using general method C using benzyl chloroformate (27.5 µL, 0.193 mmol), amino ester **S13** (55.0 mg, 0.175 mmol) and $NaHCO_3$ (87.9 mg, 1.05 mmol) in DCM (2 mL) for 16 h. The crude product was purified by flash column chromatography, eluting with 75:25 hexane–EtOAc to yield *carbamate* **9l** as an undetermined mixture of rotamers (72.7 mg, 93%) as a colourless oil, R_f 0.52 (1:1 hexane-EtOAc); ν_{max}/cm^{-1} 2974, 2933, 2869, 1731 (C=O), 1692 (C=O), 1657 (C=O), 1416, 1213, 1162, 1115, 770 and 699; δ_H (500 MHz, $CDCl_3$) 7.40–7.27 (5H, m , Ph), 5.19–5.06 (2H, br m, Cbz CH_2), 4.19–4.03 (2H, br m, 13-H_2), 3.81–2.95 (7H, m, 2-H_2, 3-H, 7-H_2, 9-H_2), 2.72–2.49 (2H, m, 10-H_2), 2.01–1.68 (4H, br m, 4-H_2, 5-H_A, 6-H_A) 1.63–1.58 (1H, m, 6-H_B), 1.52–1.37 (9H, br m, $C(Me)_3$), 1.33–1.18 (4H, br m, 5-H_B, 14-H_3); δ_C (125 MHz, $CDCl_3$) 171.7 (C=O C-11), 171.6 (C=O C-11), 155.7, 155.4 (C=O Boc, Cbz), 136.8 (*ipso*-Ph), 128.71 (Ph), 128.67 (Ph), 128.6 (Ph), 128.1 (Ph), 127.8

(Ph), 127.1 (Ph), 80.0 (*C*(Me)$_3$), 79.6 (*C*(Me)$_3$), 67.4 (Cbz CH_2), 67.1 (Cbz CH_2), 60.7 (C-13), 60.6 (C-13), 59.6 (C-3), 49.5 (C-2), 48.9 (C-2), 46.7 (C-7), 46.1 (C-7), 43.2 (C-9), 42.7 (C-9), 35.0 (C-10), 34.4 (C-10), 32.1 (C-4), 31.6 (C-4), 28.6 (C(*Me*)$_3$), 27.5 (C-6), 27.2 (C-6), 24.1 (C-5), 23.5 (C-5), 14.3 (C-14) (28 out of 40 signals present); HRMS found MH^+, 449.2652. $C_{24}H_{37}N_2O_6$ requires 449.2646.

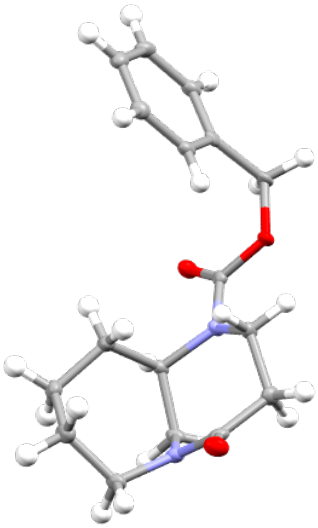
Benzyl 2-oxo-1,5-diazabicyclo[4.4.1]undecane-5-carboxylate 6l



6l

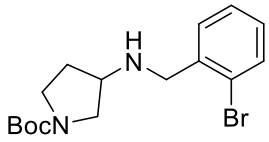
6l was synthesised using general method D using NaOH (6.85 mg, 0.172 mmol), amino ester **9l** (70 mg, 0.156 mmol), 1:1 MeOH:water (2.8 mL), HCl (1.7 mL, 6 N), EtOAc (0.2 mL), toluene (2 mL) and *n*-Bu_2SnO (39.1 mg). The crude product was purified by flash column chromatography, eluting with EtOAc to yield *bicyclic carbamate* **6l** as a 55:45 mixture of rotamers (35.8 mg, 75%) as a white solid, R_f 0.20 (EtOAc); ν_{max}/cm^{-1} 2931, 2858, 1689 (C=O), 1647 (C=O), 1418, 1312, 1236, 1210, 1158 and 658; δ_H (500 MHz, $CDCl_3$) 7.40–7.30 (5H, m, Ph), 5.13 (2H, s, Cbz CH_2), 4.76–4.65 (0.55H, m, 6-H), 4.62–4.51 (0.45H, m, 6-H), 4.44 (1H, app. d, *J* 12.7, 10-H_A), 4.38 (0.45H, app. d, *J* 11.7, 4-H_A), 4.24 (0.55H, app. d, *J* 11.7, 4-H_A), 3.85 (1H, app. d, *J* 16.1, 11-H_A), 3.41 (1H, app. t, *J* 16.7, 11-H_B), 3.31-3.14 (1H, m, 4-H_B), 2.87–2.74 (1H, m, 3-H_B), 2.54–2.51 (2H, m, 5-H_A, 3-H_B), 2.02–1.89 (1H, m, 7-H_A), 1,89–1.79 (1H, m, 8-H_A), 1.79–1.67 (2H, m, 9-H_2), 1.56–1.30 (2H, m, 7-H_B, 8-H_B); δ_C (125 MHz, $CDCl_3$) 172.80 (C=O C-2), 172.75 (C=O C-4), 155.5 (C=O Cbz), 136.6 (*ipso*-Ph), 136.5 (*ipso*-Ph), 128.7 (Ph), 128.3 (Ph), 128.2 (Ph), 67.7 (CH_2 Cbz), 53.6 (C-11), 53.5 (C-11), 53.0 (C-6), 52.7 (C-6), 48.6 (C-10), 38.2 (C-3), 38.0 (C-3), 36.9 (C-4), 29.8 (C-9), 29.7 (C-9), 28.2 (C-7), 27.5 (C-7), 23.2 (C-8) (22 out of 30 signals present); HRMS

found MH^+, 303.1702. $C_{17}H_{23}N_2O_3$ requires 303.1703. X-ray crystallographic data was collected. CCDC deposition number 2192693:



5. Synthesis of Bicyclic Anilines

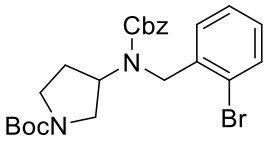
***tert*-Butyl 3-((2-bromobenzyl)amino)pyrrolidine-1-carboxylate S14**



S14

S14 was synthesised using general method E using *N*-Boc-2,3-dihydro-1H-pyrrole (42.3 mg, 0.25 mmol, supplier: Sigma Aldrich). Reaction was performed in quadruplicate and the contents of the four vials combined before work-up. The crude product was purified by flash column chromatography eluting with 2:1 hexane−EtOAc to yield *amine* **S14** as a 1:1 mixture of rotamers (242 mg, 68%) as a pale yellow oil, R_f 0.34 (EtOAc); ν_{max}/cm^{-1} 2974, 2931, 2876, 1699 (C=O), 1404, 1365, 1168, 1119, 1025 and 752; δ_H (500 MHz, $CDCl_3$) 7.54 (1H, d, *J* 7.9, 3-Ar), 7.38 (1H, app. t, *J* 7.4, 6-Ar), 7.28 (1H, t, *J* 6.8, 5-Ar), 7.13 (1H, t, *J* 7.3, 4-Ar), 3.88 (1H, s, benzyl CH_2), 3.85 (1H, s, benzyl CH_2), 3.60–3.41 (1H, m, 2-H_A, 5-H_A), 3.41–3.28 (2H, br m, 3-H, 5-H_B), 3.20 (0.5H, dd, *J* 10.9, 4.7, 2-H_B), 3.12 (0.5H, dd, *J* 10.7, 5.1, 2-H_B), 2.08–1.98 (1H, br m, 4-H_A), 1.82–1.70 (1H, br m, 4-H_B), 1.58 (1H, br s, NH), 1.45 (9H, s, $C(Me)_3$); δ_C (125 MHz, $CDCl_3$) 154.8 (C=O Boc), 139.2 (*ipso*-Ar-2), 139.1 (*ipso*-Ar-2), 133.0 (Ar-3), 130.6 (Ar-6), 130.5 (Ar-6), 129.0 (Ar-5), 127.7 (Ar-4), 124.1 (*ipso*-Ar-1), 79.3 ($C(Me)_3$), 57.3 (C-3), 56.2 (C-3), 52.3 (benzyl CH_2), 52.1 (C-2), 51.6 (C-2), 44.5 (C-5), 44.2 (C-5), 31.5 (C-4), 31.3 (C-4), 28.7 ($C(Me)_3$) (20 out of 28 signals present); HRMS found MH^+, 355.1021. $C_{16}H_{24}{}^{79}BrN_2O_2$ requires 355.1016.

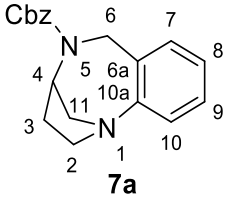
***tert*-Butyl 3-(((benzyloxy)carbonyl)(2-bromobenzyl)amino)pyrrolidine-1-carboxylate 11a**



11a

11a was synthesised using general method C using benzyl chloroformate (104 µL, 0.730 mmol), amine **S14** (235 mg, 0.664 mmol) and $NaHCO_3$ (334 mg, 3.98 mmol) in DCM (6 mL) for 72 h. The crude product was purified by flash column chromatography, eluting with 80:20 hexane−EtOAc to yield *carbamate* **11a** as 1:1 mixture of rotamers (313 mg, 97%) as a colourless oil, R_f 0.53 (1:1 hexane-EtOAc); ν_{max}/cm^{-1} 2974, 2882, 1695 (C=O), 1442, 1169, 1135 and 749; δ_H (500 MHz, $CDCl_3$) 7.53 (1H, app. t, *J* 7.3, 3-Ar), 7.44–7.01 (8H, br m, 4,5,6-Ar, Ph), 5.30–5.02 (2H, br m, Cbz CH_2), 4.87–4.64 (1H, br m, 3-H), 4.62–4.39 (2H, s, benzyl CH_2), 3.64–3.53 (1H, m, 2-H_A), 3.51–3.44 (0.5H, br m, 5-H_A), 3.44–3.35 (0.5H, br m, 5-H_A), 3.28–3.17 (1H, br m, 5-H_B), 3.14 (1H, dd, *J* 9.6, 5.1, 2-H_B), 2.06–1.78 (2H, br m, 4-H_2), 1.42 (9H, s, $C(Me)_3$); δ_C (125 MHz, $CDCl_3$) 156.5 (C=O Cbz), 154.5 (C=O Boc), 137.4 (*ipso*-Ar-2), 136.4 (*ipso*-Ph), 132.9 (Ar-3), 128.7, 128.6, 128.2, 128.1, 127.7, 127.1 (Ar-4,5,6, Ph), 122.2 (*ipso*-Ar-1), 79.7 ($C(Me)_3$), 67.6 (Cbz CH_2), 55.6 (C-3), 54.9 (C-3), 47.7 (benzyl CH_2), 47.1 (C-2), 44.3 (C-5), 43.9 (C-5), 29.0 (C-4), 28.6 ($C(Me)_3$) (22 out of 40 signals present); HRMS found MH^+, 489.1390. $C_{24}H_{30}{}^{79}BrN_2O_4$ requires 489.1383.

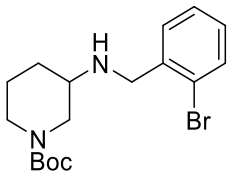
Benzyl 3,4-dihydro-2H-1,4-methanobenzo[b][1,5]diazocine-5(6H)-carboxylate 7a



7a

7a was synthesised using general method F using carbamate **11a** (299 mg, 0.612 mmol), HCl (6.8 mL, 6 N), EtOAc (1 mL), $Pd_2(dba)_3$ (22.5 mg), BINAP (30.5 mg), NaO*t*Bu (118 mg, 1.16 mmol) and toluene (5 mL). Heated at reflux for 16 h. The crude product was purified by flash column chromatography, eluting with 1:1 hexane−EtOAc to yield *carbamate* **7a** as a 55:45 mixture of rotamers (120 mg, 64%) as a brown oil, R_f 0.28 (EtOAc); ν_{max}/cm^{-1} 2948, 2877, 1687 (C=O), 1485, 1449, 1408, 1346, 1332, 1222, 1123, 1093, 763, 735 and 697; δ_H (500 MHz, $CDCl_3$) 7.39–7.28 (5H, m, Ph), 7.23–7.14 (1H, br m, Ar), 7.13–7.09 (1H, br m, Ar), 7.05–6.97 (2H, br m, 7-Ar, Ar), 5.19–5.05 (2H, br m, Cbz CH_2), 4.58 (0.45H, app. t, *J* 4.0, 4-H), 4.51 (0.55H, app. t, *J* 4.9, 4-H), 4.93 (0.55H, d, *J* 16.4, 6-H_A), 4.77 (0.45H, d, *J* 16.6, 6-H_A), 4.74–4.68 (1H, m, 6-H_B), 3.42 (0.45H, ddd, *J* 12.2, 9.7, 6.7, 2-H_A), 3.35 (0.55H, ddd, *J* 12.1, 9.9, 6.8, 2-H_A), 3.27–3.18 (1H, br m, 3-H_B), 3.84 (0.55H, app. d, *J* 14.0, 11-H_A), 3.76 (0.45H, app. d, *J* 13.9, 11-H_A), 2.93 (0.45H, dd, *J* 13.9, 3.9, 11-H_B), 2.87 (0.55H, dd, *J* 14.0, 4.2, 11-H_B), 2.23–2.13 (1.45H, br m, 3-H_2), 2.13–2.05 (0.55H, br m, 3-H_2); δ_C (125 MHz, $CDCl_3$) 155.9 (C=O Cbz), 155.4 (C=O Cbz), 152.6 (C-10a), 152.0 (C-10a), 132.2 (C-6a), 131.5 (C-6a), 136.8 (*ipso*-Ph), 130.4, 130.0, 128.7, 128.63, 128.61, 128.1, 128.0, 127.6 (Ar-8/9/10, Ph), 124.3 (C-7), 124.2 (C-7), 67.5 (Cbz CH_2), 67.3 (Cbz CH_2), 58.3 (C-4), 57.8 (C-4), 56.8 (C-2), 56.7 (C-2), 55.5 (C-11), 54.9 (C-11), 47.1 (C-6), 46.9 (C-6), 34.9 (C-3), 33.5 (C-3) (29 out of 34 signals present); HRMS found MNa^+, 331.1416. $C_{19}H_{20}N_2O_2Na$ requires 331.1417.

tert-Butyl 3-((2-bromobenzyl)amino)piperidine-1-carboxylate S15

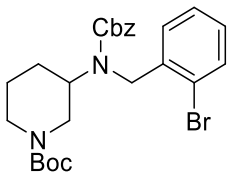


S15

S15 was synthesised using general method E using enecarbamate **5c** (45.8 mg, 0.25 mmol). Reaction was performed in quadruplicate and the contents of the four vials

combined before work-up. The crude product was purified by flash column chromatography eluting with 2:1 hexane−EtOAc to yield *amine* **S15** as a 1:1 mixture of rotamers (255 mg, 69%) as a colourless oil, R_f 0.39 (EtOAc); ν_{max}/cm^{-1} 2974, 2930, 2856, 1686 (C=O), 1420, 1364, 1260, 1238, 1174, 1150, 1024 and 750; δ_H (500 MHz, $CDCl_3$) 7.53 (1H, d, *J* 5.5, 3-Ar), 7.41 (1H, dd, *J* 7.6, 1.6, 6-Ar), 7.28 (1H, td, *J* 7.5, 0.9, 5-Ar), 7.12 (1H, td, *J* 7.8, 1.5, 4-Ar), 4.25–3.93 (1H, m, 2-H_A), 3.93 (1H, d, *J* 13.8, benzyl CH_2), 3.86 (1H, d, *J* 13.8, benzyl CH_2), 3.86–3.74 (1H, br m, 6-H_A), 3.00–2.65 (2H, m, 2-H_B, 6-H_B), 2.64–2.52 (1H, m, 3-H), 1.97–1.86 (1H, br m, 4-H_A), 1.74–1.64 (1H, br m, 5-H_A), 1.63–1.48 (2H, m, NH, 5-H_A), 1.46 (9H, s, $C(Me)_3$), 1.40–1.29 (1H, br m, 4-H_B); δ_C (125 MHz, $CDCl_3$) 155.1 (C=O Boc), 139.5 (*ipso*-Ar-2), 133.0 (Ar-3), 130.4 (Ar-6), 128.8 (Ar-5), 127.6 (Ar-4), 124.1 (*ipso*-Ar-1), 79.6 ($C(Me)_3$), 53.2 (C-3), 51.2 (benzyl CH_2), 49.5 (C-2), 48.9 (C-2), 44.9 (C-6), 44.1 (C-6), 31.7 (C-4), 28.6 ($C(Me)_3$), 23.7 (C-5) (17 out of 30 signals present); HRMS found MNa^+, 391.0994. $C_{17}H_{25}{}^{79}BrN_2O_2Na$ requires 391.0992.

tert-Butyl 3-(((benzyloxy)carbonyl)(2-bromobenzyl)amino)piperidine-1-carboxylate 11b

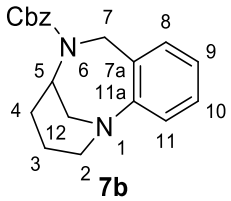


11b

11b was synthesised using general method C using benzyl chloroformate (103 µL, 0.721 mmol), amine **S15** (241 mg, 0.655 mmol) and $NaHCO_3$ (329 mg, 3.93 mmol) in DCM (6 mL) for 72 h. The crude product was purified by flash column chromatography, eluting with 75:25 hexane−EtOAc to yield *carbamate* **11b** as an undetermined mixture of rotamers (243 mg, 74%) as a colourless oil, R_f 0.65 (1:1 hexane-EtOAc); ν_{max}/cm^{-1} 3055, 2978, 2861, 1686 (C=O), 1413, 1264, 1240, 1149, 731 and 699; δ_H (500 MHz, $CDCl_3$) 7.52 (1H, d, *J* 7.9, 3-Ar), 7.46–7.14 (7H, br m, 5-Ar,

6-Ar, Ph), 7.1 (1H, t, *J* 7.5, 4-Ar), 4.29–5.04 (2H, br m, Cbz CH_2), 4.68–4.40 (2H, br m, benzyl CH_2), 4.22–3.79 (3H, br m, 2-H_A, 3-H, 6-H_A), 2.93–2.62 (1H, br m, 2-H_B), 2.59–2.41 (1H, m, 6-H_B), 1.89–1.75 (1H, br m, 4-H_A), 1.73–1.59 (2H, br m, 4-H_B, 5-H_A), 1.56–1.31 (10H, br m, $C(Me)_3$, 5-H_B); δ_C (125 MHz, $CDCl_3$) 154.8 (C=O Boc), 137.7 (*ipso*-Ar-2), 136.6 (*ipso*-Ph), 132.8 (Ar-3), 128.64, 128.57, 128.1, 128.0, 127.6 (Ar-4,5,6, Ph), 122.3 (*ipso*-Ar-1), 79.8 ($C(Me)_3$), 67.9 (Cbz CH_2), 67.4 (Cbz CH_2), 54.2 (C-3), 48.4 (benzyl CH_2), 47.0 (C-2), 44.1 (C-6), 43.4 (C-6), 29.1 (C-4), 28.5 ($C(Me)_3$), 25.0 (C-5) (21 out of 42 signals present); HRMS found MH^+, 503.1555. $C_{25}H_{32}{}^{79}BrN_2O_4$ requires 503.1540.

Benzyl 2,3,4,5-tetrahydro-1,5-methanobenzo[b][1,5]diazonine-6(7H)-carboxylate 7b

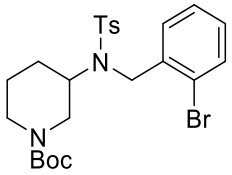


7b

7b was synthesised using general method F using carbamate **11b** (120 mg, 0.239 mmol), HCl (2.6 mL, 6 N), EtOAc (0.4 mL), $Pd_2(dba)_3$ (8.8 mg), BINAP (11.9 mg), NaO*t*Bu (46.0 mg, 0.454 mmol) and toluene (4 mL). Heated at reflux for 16 h. The crude product was purified by flash column chromatography, eluting with 2:1 hexane−EtOAc to yield *carbamate* **7b** as a 60:40 mixture of rotamers (28.1 mg, 37%) as a yellow oil, R_f 0.65 (1:1 hexane-EtOAc); ν_{max}/cm^{-1} 3061, 3060, 2924, 2860, 1689 (C=O), 1490, 1400, 1346, 1177, 1074, 747 and 697; δ_H (500 MHz, $CDCl_3$) 7.40–7.29 (5H, m, Ph), 7.16 (1H, app. td, *J* 7.5, 1.0, 10-H), 7.07–7.00 (1H, br m, 8-H), 6.97 (1H, d, *J* 8.0, 11-H), 6.84 (1H, app. td, *J* 7.5, 1.0, 9-H), 5.27–4.98 (3H, br m, 7-H_A, Cbz CH_2), 4.81 (1H, d, *J* 16.6, 7-H_B), 4.04 (1H, dd, *J* 15.7, 2.2, 12-H_A), 3.84 (1H, app. s, 5-H), 3.65 (1H, dd, *J* 13.6, 1.6, 2-H_A), 3.29–3.15 (2H, m, *J* 2-H_B, 12-H_B), 3.00–2.47 (1H, br m, 4-H_A), 1.80 (0.4H, dt, *J* 6.6, 3.6, 3-H_A), 1.64 (1H, app. tt, *J* 13.9, 3.3, 4-H_B), 1.73 (0.6H,

dt, *J* 6.6, 3.6, 3-H_A), 1.23–1.12 (1H, br m, 3-H_B); δ_C (125 MHz, $CDCl_3$) 149.3 (C-11a), 136.8 (*ipso*-Ph), 130.4 (Ar-8), 129.1 (C-7a), 128.7 (Ar-10), 128.5 (Ph), 128.1 (Ph), 128.0 (Ph), 124.5 (C-11), 121.4 (C-9), 67.4 (Cbz CH_2), 53.5 (C-5), 52.6 (C-5), 57.2 (C-2), 50.8 (C-12), 49.8 (C-7), 28.6 (C-4), 30.3 (C-4), 18.0 (C-3) (19 out of 36 signals present); HRMS found MH^+, 323.1756. $C_{20}H_{23}N_2O_2$ requires 323.1754.

tert-Butyl 3-((*N*-(2-bromobenzyl)-4-methylphenyl)sulfonamido)piperidine-1-carboxylate 11c

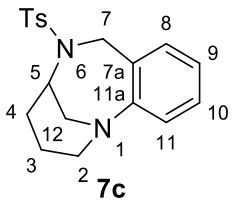


11c

Tosyl chloride (179 mg, 0.937 mmol), DIPEA (155 µL, 0.937 mmol) and DMAP (3.8 mg, 5 mol%) were added in sequence to a mixture of amino ester **S15** (230 mg, 0.625 mmol) in DCM (6 mL). The mixture was stirred for 16 h at room temperature, and the solvent evaporated under reduced pressure to give a crude product. The crude product was purified by flash column chromatography, eluting with 75:25 hexane−EtOAc to yield *carbamate* **11c** as an undetermined mixture of rotamers (210 mg, 64%) as a colourless oil, R_f 0.24 (8:2 hexane-EtOAc); ν_{max}/cm^{-1} 2974, 2930, 2862, 1689 (C=O), 1419, 1341, 1265, 1241, 1091, 856, 753 and 656; δ_H (500 MHz, $CDCl_3$) 7.76 (2H, d, *J* 8.3 Ts Ar), 7.68 (1H, d, *J* 7.7, 6-Ar), 7.48 (1H, d, *J* 7.9, 3-Ar), 7.35–7.29 (3H, m, 5-Ar, Ts Ar), 7.12 (1H, t, *J* 7.4, 4-Ar), 4.56–4.39 (2H, br m, benzyl CH_2), 4.05–3.86 (2H, br m, 2-H_A, 6-H_A), 3.84–3.64 (1H, m, 3-H), 2.58–2.29 (5H, m, 2-H_B, 6-H_B, Me), 1.67–1.53 (2H, br m, 4-H_A, 5-H_A), 1.44–1.32 (11H, m, 4-H_B, 5-H_B, $C(Me)_3$); δ_C (125 MHz, $CDCl_3$) 154.5 (C=O Boc), 143.6 (Ts *ipso*-Ar), 137.9 (*ipso*-Ar-2), 137.4 (Ts *ipso*-Ar), 132.5 (Ar-3), 130.0 (Ts Ar), 129.9 (Ar-6), 129.0 (Ar-5), 127.8 (Ar-4), 127.1 (Ts Ar), 122.0 (*ipso*-Ar-1), 79.9 ($C(Me)_3$), 53.5 (C-3), 48.2 (C-2), 47.8 (benzyl CH_2), 47.0 (C-2), 43.9 (C-6), 43.1 (C-6), 29.3 (C-4), 28.4 ($C(Me)_3$), 25.0 (C-5), 21.6

(Me) (22 out of 40 signals present); HRMS found MH^+, 523.1274. $C_{24}H_{32}{}^{79}BrN_2O_4S$ requires 523.1261.

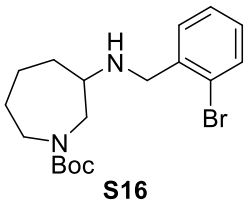
6-Tosyl-2,3,4,5,6,7-hexahydro-1,5-methanobenzo[b][1,5]diazonine 7c



7c

7c was synthesised using general method F using carbamate **11c** (200 mg, 0.383 mmol), HCl (4.2 mL, 6 N), EtOAc (0.5 mL), $Pd_2(dba)_3$ (14.1 mg), BINAP (19.1 mg), NaO*t*Bu (73.8 mg, 0.723 mmol) and toluene (5 mL). Heated at reflux for 16 h. The crude product was purified by flash column chromatography, eluting with 1:1 hexane−EtOAc to yield *carbamate* **7c** (59.2 mg, 45%) as a brown oil, R_f 0.40 (1:1 hexane-EtOAc); ν_{max}/cm^{-1} 3054, 2921, 2860, 1491, 1336, 1189, 1101, 729 and 679; δ_H (500 MHz, $CDCl_3$) δ_H (500 MHz, $CDCl_3$) 7.72 (2H, d, *J* 8.3, Ts Ar), 7.31 (2H, d, *J* 8.0, Ts Ar), 7.15 (1H, app. t, *J* 7.2, 10-H), 6.98 (1H, dd, *J* 7.7, 1.4, 8-H), 6.93 (1H, dd, *J* 8.2, 0.9, 11-H), 6.82 (1H, app. td, *J* 7.5, 1.1, 9-H), 4.67 (1H, d, *J* 15.7, 7-H_A), 4.46 (1H, d, *J* 15.6, 7-H_B), 3.78 (1H, dd, *J* 15.7, 2.2, 12-H_A), 3.64 (1H, dd, *J* 13.8, 1.9, 2-H_A), 3.56–3.51 (1H, br m, 5-H), 3.23–3.12 (2H, m, 2-H_B, 12-H_B), 2.79 (1H, ddq, *J* 14.1, 5.5, 3.0, 4-H_A), 2.43 (3H, s, Me), 1.93 (1H, app. qt, *J* 13.3, 3.8, 3-H_A), 1.71 (1H, app. tt, *J* 13.8, 3.3, 4-H_B), 1.24–1.17 (1H, br m, 3-H_B); δ_C (125 MHz, $CDCl_3$) 149.2 (C-11a), 143.6 (*ipso*-Ar Ts), 135.1 (*ipso*-Ar Ts), 130.6 (C-8), 129.8 (Ar Ts), 128.7 (C-10), 128.0 (C-7a), 127.7 (Ar Ts), 124.2 (Ar-11), 121.4 (C-9), 56.6 (C-2), 54.3 (C-5), 51.8 (C-7), 50.9 (C-12), 31.6 (C-4), 21.7 (Me), 17.9 (C-3); HRMS found MNa^+, 365.1296. $C_{19}H_{22}N_2O_2SNa$ requires 365.1294.

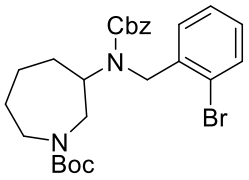
***tert*-Butyl 3-((2-bromobenzyl)amino)azepane-1-*carboxylate* S16**



S16

S16 was synthesised using general method E using enecarbamate **5e** (49.3 mg, 0.25 mmol). Reaction was performed in quadruplicate and the contents of the four vials combined before work-up. The crude product was purified by flash column chromatography eluting with 2:1 hexane−EtOAc to yield *amine* **S16** as a 55:45 mixture of rotamers (94.6 mg, 25%) as a yellow oil, R_f 0.39 (EtOAc); ν_{max}/cm^{-1} 2973, 2926, 2858, 1684 (C=O), 1466, 1412, 1364, 1160, 1044 and 750; δ_H (500 MHz, $CDCl_3$) 7.54 (0.55H, d, *J* 8.0, 3-Ar), 7.52 (0.45H, d, *J* 8.0, 3-Ar), 7.47 (0.45H, d, *J* 7.5, 6-Ar), 7.41 (0.55H, d, *J* 7.5, 6-Ar), 7.31–7.26 (1H, m, 5-Ar), 7.15–7.07 (1H, m, 4-Ar), 3.86 (0.45H, dd, *J* 14.1, 3.6, 2-H_A), 3.78 (0.55H, dd, *J* 14.1, 3.6, 2-H_A), 3.91 (0.9H, s, benzyl CH_2), 3.89 (1.1H, s, benzyl CH_2), 3.68 (0.55H, ddd, *J* 13.2, 7.6, 5.1, 7-H_A), 3.48 (0.45H, ddd, *J* 13.1, 7.6, 5.1, 7-H_A), 3.23 (0.45H, app. td, *J* 13.9, 5.9, 7-H_B), 3.16 (0.55H, app. td, *J* 13.6, 5.5, 7-H_B), 3.00 (0.45H, dd, *J* 13.9, 8.3, 2-H_B), 2.88 (0.55H, dd, *J* 14.1, 8.9, 2-H_B), 2.87–2.81 (0.45H, m, 3-H), 2.74–2.81 (0.55H, m, 3-H), 1.93–1.71 (3H, m, 4-H_A, 5-H_A, 6-H_A), 1.61–1.54 (2H, br m, NH, 6-H_B), 1.47 (4.05H, s, $C(Me)_3$), 1.45 (4.95H, s, $C(Me)_3$), 1.43–1.33 (2H, m, 4-H_B, 5-H_B); δ_C (125 MHz, $CDCl_3$) 156.0 (C=O Boc), 155.7 (C=O Boc), 139.6 (*ipso*-Ar-2), 133.0 (Ar-3), 132.8 (Ar-3), 130.8 (Ar-6), 130.2 (Ar-6), 128.8 (Ar-5), 128.7 (Ar-5), 127.7 (Ar-4), 127.6 (Ar-4), 124.13 (*ipso*-Ar-1), 124.05 (*ipso*-Ar-1), 78.0 ($C(Me)_3$), 79.3 ($C(Me)_3$), 57.9 (C-3), 57.5 (C-3), 51.7 (benzyl CH_2), 51.6 (benzyl CH_2), 51.1 (C-2), 50.9 (C-2), 48.1 (C-7), 47.1 (C-7), 35.1 (C-4), 34.1 (C-4), 28.7 ($C(Me)_3$), 28.6 ($C(Me)_3$), 28.0 (C-6), 27.7 (C-6), 23.0 (C-5), 22.7 (C-5) (31 out of 32 signals present); HRMS found MH^+, 383.1339. $C_{18}H_{28}{}^{79}BrN_2O_2$ requires 383.1329.

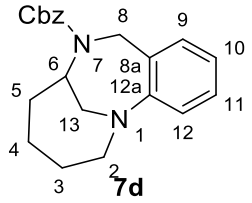
***tert*-Butyl 3-(((benzyloxy)carbonyl)(2-bromobenzyl)amino)azepane-1-carboxylate 11d**



11d

11d was synthesised using general method C using benzyl chloroformate (38 µL, 0.266 mmol), amine **S16** (92.3 mg, 0.242 mmol) and $NaHCO_3$ (122 mg, 1.45 mmol) in DCM (2 mL) for 72 h. The crude product was purified by flash column chromatography, eluting with 80:20 hexane−EtOAc to yield *carbamate* **11d** as 60:40 mixture of rotamers (101 mg, 81%) as a colourless oil, R_f 0.67 (1:1 hexane-EtOAc); ν_{max}/cm^{-1} 2973, 2930, 2864, 1691 (C=O), 1414, 1365, 1249, 1162 and 749; δ_H (500 MHz, $CDCl_3$) 7.52 (1H, app. t, *J* 8.6, 3-Ar), 7.47–7.05 (8H, br m, Ar), 5.22 (0.8H, br s, Cbz CH_2), 5.11 (1.2H, br s, Cbz CH_2), 4.72–4.41 (2H, br m, benzyl CH_2), 4.00–3.81 (1H, m, 3-H), 3.82–3.73 (0.4H, br m, 2-H_A), 3.72–3.64 (0.6H, br m, 2-H_A), 3.58 (0.6H, ddd, *J* 14.4, 8.8, 5.8, 7-H_A), 3.54–3.20 (1.4H, br m, 7-H_B, 2-H_B), 3.19–2.99 (1H, br m, 7-H_A, 2-H_B), 1.92–1.62 (4H, m, 4-H_2, 5-H_A, 6-H_A), 1.60–1.33 (10H, s, $C(Me)_3$, 6-H_B), 1.33–1.16 (1H, m, 5-H_B); δ_C (125 MHz, $CDCl_3$) 156.6, 156.0, 155.8, 155.5 (C=O Boc/Cbz), 137.8 (*ipso*-Ar-2), 137.6 (*ipso*-Ar-2), 136.7 (*ipso*-Ph), 136.5 (*ipso*-Ph), 132.8 (Ar-3), 132.7 (Ar-3), 128.6, 128.5, 128.2, 128.0, 127.9, 127.8, 127.7, 127.5, 127.0 (Ar-4,5,6, Ph), 122.6 (*ipso*-Ar-1), 122.4 (*ipso*-Ar-1), 79.8 ($C(Me)_3$), 79.5 ($C(Me)_3$), 67.8 (Cbz CH_2), 67.1 (Cbz CH_2), 59.0 (C-3), 58.7 (C-3), 49.8 (benzyl CH_2), 49.7 (benzyl CH_2), 49.4 (C-2), 49.2 (C-2), 47.0 (C-7), 46.1 (C-7), 31.9 (C-4), 31.3 (C-4), 28.6 ($C(Me)_3$), 28.5 ($C(Me)_3$), 27.7 (C-6), 27.3 (C-6), 24.3 (C-5), 23.6 (C-5) (41 out of 44 signals present); HRMS found MH^+, 517.1705. $C_{26}H_{34}{}^{79}BrN_2O_4$ requires 517.1696.

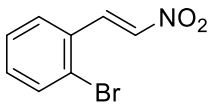
Benzyl 3,4,5,6-tetrahydro-2H-1,6-methanobenzo[b][1,5]diazecine-7(8H)-carboxylate 7d



7d

HCl (0.7 mL of a 6 M solution) was added to a solution of *N*-Boc amine **11d** (33.2 mg, 0.0659 mmol) in EtOAc (0.2 mL) and stirred for 3 h. The solvent was then removed under reduced pressure to give the NH amine. $Pd(OAc)_2$ (1.3 mg, 10 mol%), BINAP (8.1 mg, 2 mol%), Cs_2CO_3 (23.8 mg, 0.0725 mmol) and toluene (3 mL) were then added and the resulting mixture stirred at 110 °C for 96 h. The mixture was then allowed to cool to rt, filtered through celite, and washed with DCM (20 mL). The solvent was then removed under reduced pressure to give a crude product. The crude product was purified by flash column chromatography, eluting with 2:1 hexane−EtOAc to yield *carbamate* **7d** (7.4 mg, 33%) as a colourless oil, R_f 0.57 (1:1 hexane-EtOAc); ν_{max}/cm^{-1} 3064, 3031, 2925, 2855, 1690 (C=O), 1599, 1493, 1414, 1303, 1244, 1157, 748 and 698; δ_H (500 MHz, $CDCl_3$) 7.39–7.28 (5H, m, Ph), 7.14–7.09 (1H, m, 11-H), 7.03 (1H, d, *J* 6.7, 9-H), 6.78 (1H, d, *J* 8.3, 12-H), 6.63, (1H, td, *J* 7.4, 1.0, 10-H), 5.16 (1H, d, *J* 12.4, Cbz CH_2), 5.13 (1H, d, *J* 12.4, Cbz CH_2), 5.08 (1H, d, *J* 15.5, 8-H_A), 4.77–4.62 (1H, br m, 8-H_B), 4.43–4.17 (2H, br m, 6-H, 13-H_A), 4.07 (1H, app. d, *J* 14.2, 2-H_A), 3.33 (1H, dd, *J* 16.4, 5.0, 13-H_B), 2.92 (1H, app. t, *J* 12.1, 2-H_A), 2.44–2.34 (1H, m, 5-H_A), 1.83–1.70 (2H, br m, 3-H_A, 4-H_A), 1.68–1.59 (1H, br m, 3-H_B), 1.53–1.36 (2H, br m, 4-H_B, 5-H_B); δ_C (125 MHz, $CDCl_3$) 155.1 (C=O Cbz), 149.0 (C-12a), 137.0 (*ipso*-Ph), 132.4 (C-9), 129.0 (C-11), 128.5 (Ph), 127.94 (Ph), 127.88 (Ph), 123.5 (8a), 118.1 (C-10), 115.6 (C-12), 67.1 (Cbz CH_2), 57.6 (C-3), 54.8 (C-2), 53.9 (C-13), 48.7 (C-8), 32.2 (C-5), 28.2 (C-3), 25.5 (C-4); HRMS found MH^+, 337.1914. $C_{21}H_{25}N_2O_2$ requires 337.1911.

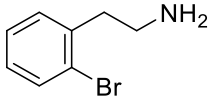
(*E*)-1-Bromo-2-(2-nitrovinyl)benzene S17[14]



S17

2-Bromobenzaldehyde (5.84 mL, 50.0 mmol) was added to a mixture of NH_4OAc (6.76 g) in AcOH (140 mL). Nitromethane (9.25 mL) was slowly added with stirring over 5 min. The mixture was heated at reflux for 4h and then ice-cold water (100 mL) added. The organics were extracted with DCM (100 mL), dried ($MgSO_4$) and the solvent evaporated under reduced pressure to give a crude product. The crude product was purified by flash column chromatography, eluting with 80:20 hexane−Et_2O to yield *alkene* **S17** (10.4 g, 92%) as a yellow amorphous solid, R_f 0.54 (1:1 hexane-Et_2O); ν_{max}/cm^{-1} 3110, 3055, 2974, 2850, 1663, 1512, 1466, 1337, 1284, 1046, 1027, 960, 758 and 744; δ_H (400 MHz, $CDCl_3$) 8.40 (1H, d, *J* 13.7, C*H*Ar), 7.69 (1H, dd, *J* 7.8, 1.4, 6-Ar), 7.57 (1H, dd, *J* 7.6, 1.8, 3-Ar), 7.42–7.31 (2H, m, 4,5-Ar), 7.54 (1H, d, *J* 13.6, C*H*NO_2); δ_C (100 MHz, $CDCl_3$) 139.0 ($CHNO_2$), 137.7 (CHAr), 134.2 (Ar-6), 133.1 (Ar-4/5), 130.5 (*ipso*-2-Ar), 128.6 (Ar-4/5), 128.2 (Ar-3), 126.5 (*ispo*-1-Ar); Spectroscopic data are consistent with those reported in the literature.[14]

2-(2-Bromophenyl)ethan-1-amine 10b[15]

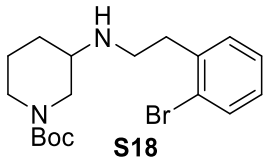


10b

$LiAlH_4$ (33.3 mL of a 2.4M solution in THF, 80.0 mmol) was added dropwise to a solution of alkene **S17** (4.54 g, 20.0 mmol) in THF (120 mL) at 0 °C and the mixture was stirred at 0 °C for 5h. Then, water (15 mL), 20% NaOH (15 mL) and water (32 mL) were added in sequence. The resulting precipitate was filtered and washed

with Et_2O (100 mL). The filtrate was then dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was purified by flash column chromatography, eluting with 90:10 EtOAc–MeOH to yield slightly impure *amine* **10b** (1.40 g, ~35%) as a brown oil, R_f 0.13 (9:1 EtOAc-MeOH); ν_{max}/cm^{-1} 3057 (NH), 2930, 2855, 1566, 1470, 1439, 1023, 749 and 658; δ_H (500 MHz, $CDCl_3$) 7.54 (1H, d, *J* 8.6, 6-Ar), 7.25–7.22 (1H, m, 3,4-Ar), 7.10–7.05 (2H, m, 5-Ar), 3.00–2.96 (2H, m, C*H*$_2$NH$_2$), 2.92–2.88 (2H, m, C*H*$_2$Ar), 1.78 (2H, br s, NH_2); δ_C (125 MHz, $CDCl_3$) 139.2 (*ipso*-2-Ar), 133.1 (Ar-6), 131.2 (Ar-3/4), 128.1 (Ar-5), 127.6 (Ar-3/4), 124.8 (*ispo*-1-Ar), 42.2 (CH_2NH_2), 40.3 (*C*H$_2$Ar); Spectroscopic data are consistent with those reported in the literature.[15]

***tert*-Butyl 3-((2-bromophenethyl)amino)piperidine-1-carboxylate S18**

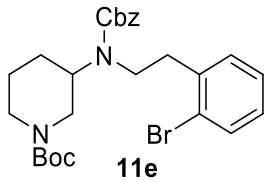


S18

To a 7 mL vial were added [Ir(dF(Me)ppy)$_2$(dtbbpy)PF_6] (5.1 mg, 2 mol%), TRIP thiol (27 mg, 50 mol%), 2-(2-Bromophenyl)ethan-1-amine (99.5 mg, 0.5 mmol) and enecarbamate **5e** (45.8 mg, 0.25 mmol). Toluene (5 mL) was then added under N_2 and the resultant mixture was stirred for 16 h under irradiation with a blue LED and fan cooling. Reaction was performed in quadruplicate and the contents of the four vials combined before work-up. Then, the solvent was evaporated under reduced pressure to give a crude product. The crude product was purified by flash column chromatography eluting with EtOAc to yield *amine* **S18** as an undetermined mixture of rotamers (207 mg, 54%) as a yellow oil, R_f 0.19 (EtOAc); ν_{max}/cm^{-1} 2974, 2932, 2857, 1687 (C=O), 1421, 1365, 1239, 1174, 1151 and 752; δ_H (500 MHz, $CDCl_3$) 7.53 (1H, d, *J* 7.9, 3-Ar), 7.25–7.22 (2H, m, 5-Ar, 6-Ar), 7.14–7.10 (1H, m, 4-Ar), 4.23–3.82 (1H, br m, 2-H_A), 3.79 (1H, app. d, *J* 13.1, 6-H_A), 2.96–2.88 (4H, m, benzylamine CH_2), 2.88–2.77 (1H, m, 6-H_B), 2.77–2.49 (1H, br m, 2-H_B, 3-H), 1.96–1.87 (1H, br m, 4-H_A), 1.66 (1H, app. ddt, 12.4, 8.1, 3.9, 5-H_A), 1.48–1.42 (11H, m, NH, 5-H_A, C(Me)$_3$), 1.31–

1.22 (1H, br m, 4-H_B); δ_C (125 MHz, $CDCl_3$) 155.1 (C=O Boc), 139.4 (*ipso*-Ar-2), 133.0 (Ar-3), 130.9 (Ar-6), 128.1 (Ar-5), 127.6 (Ar-4), 124.7 (*ipso*-Ar-1), 79.6 (*C*$(Me)_3$), 53.8 (C-3), 49.7 (C-2), 49.0 (C-2), 46.8 (benzyl NCH_2), 44.6 (C-6), 43.9 (C-6), 37.1 (benzyl CH_2Ar), 31.7 (C-4), 28.6 (C(*Me*)$_3$), 24.0 (C-5), 23.5 (C-5) (19 out of 32 signals present); HRMS found MH^+, 383.1335. $C_{18}H_{28}{}^{79}BrN_2O_2$ requires 383.1329.

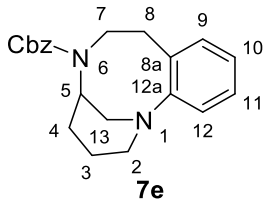
tert-Butyl 3-(((benzyloxy)carbonyl)(2-bromophenethyl)amino)piperidine-1-carboxylate 11e



11e

11e was synthesised using general method C using benzyl chloroformate (82 µL, 0.576 mmol), amine **S18** (200 mg, 0.524 mmol) and $NaHCO_3$ (200 mg, 0.524 mmol) in DCM (5 mL) for 72 h. The crude product was purified by flash column chromatography, eluting with 75:25 hexane−EtOAc to yield *carbamate* **11e** as 60:40 mixture of rotamers (263 mg, 87%) as a colourless oil, R_f 0.64 (1:1 hexane-EtOAc); ν_{max}/cm^{-1} 2936, 2862, 1692 (C=O), 1471, 1416, 1365, 1265, 1242, 1170, 1150, 752 and 698; δ_H (500 MHz, $CDCl_3$) 7.58–7.46 (1H, br m, 3-Ar), 7.44–7.30 (5H, m, Ar, Ph), 7.25–6.94 (3H, m, Ar, Ph), 5.27–5.04 (2H, br m, CH_2 Cbz), 4.27–3.87 (2H, br m, 2-H_A, 6-H_A), 3.79 (1H, app. ddd, *J* 15.3, 10.9, 4.2, 3-H), 3.49–3.29 (2H, br m, benzylamine NCH_2), 3.08–2.90 (2H, br m, benzylamine CH_2Ar), 2.89–2.80 (0.6H, m, 2-H_B), 2.79–2.66 (0.4H, m, 2-H_B), 2.64–2.40 (1H, br m, 6-H_B), 1.85–1.64 (3H, br m, 4-H_2, 5-H_A), 1.57–1.32 (10H, br m, 4-H_B, C$(Me)_3$); δ_C (125 MHz, $CDCl_3$) 155.9, 154.9 (C=O Boc/Cbz), 138.5 (*ipso*-Ar-2), 136.7 (*ipso*-Ph), 132.9 (Ar-3), 131.2 (Ar-6), 128.7 (Ar), 128.4 (Ar), 128.3 (Ar), 127.8 (Ar), 124.6 (*ipso*-Ar-1), 79.9 (*C*$(Me)_3$), 67.4 (CH_2 Cbz), 54.4 (C-3), 47.1 (C-2), 44.9 (benzyl NCH_2), 43.3 (C-6), 37.2 (benzyl CH_2Ar), 29.2 (C-4), 28.6 (C(*Me*)$_3$), 25.1 (C-5) (21 out of 22 signals present); HRMS found MH^+, 517.1714. $C_{26}H_{34}{}^{79}BrN_2O_4$ requires 517.1696.

Benzyl 2,3,4,5,7,8-hexahydro-6H-1,5-methanobenzo[b][1,6]diazecine-6-carboxylate 7e

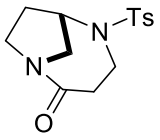
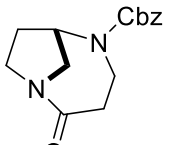
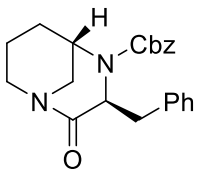
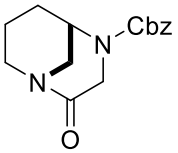
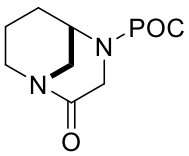


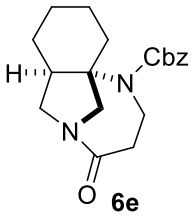
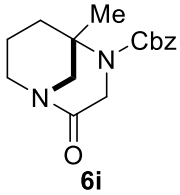
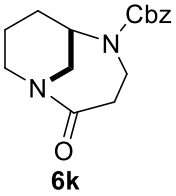
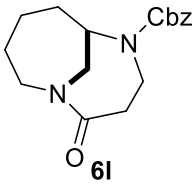
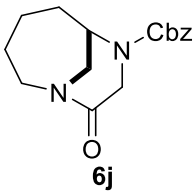
7e

7e was synthesised using general method F using carbamate **11e** (110 mg, 0.213 mmol), HCl (2.3 mL, 6 N), EtOAc (0.4 mL), $Pd_2(dba)_3$ (7.8 mg), BINAP (10.6 mg), NaO*t*Bu (41.0 mg, 0.405 mmol) and toluene (4 mL). Heated at reflux for 96 h. The crude product was purified by flash column chromatography, eluting with 9:1 hexane−EtOAc to yield *carbamate* **7e** as a 55:45 mixture of rotamers (1.3 mg, 2%) as an orange oil, R_f 0.48 (7:3 hexane-EtOAc); ν_{max}/cm^{-1} 2924, 2852, 1690 (C=O), 1497, 1455, 1420, 1226, 1174, 753 and 698; δ_H (500 MHz, $CDCl_3$) 7.34–7.24 (5H, br m, Ph), 7.05 (1H, td, *J* 7.7, 0.8, 11-H), 6.97 (0.55H, d, *J* 7.5, 9-H), 6.93 (0.45H, d, *J* 7.3, 9-H), 6.74 (1H, d, *J* 8.0, 12-H), 6.67 (0.55H, t, *J* 7.4, C-10), 6.66 (0.45H, t, *J* 7.4, C-10), 5.15–5.07 (2H, br m, Cbz CH_2), 4.68 (0.55H, dd, *J* 14.8, 10.3, 7-H_A), 4.42 (0.45H, dd, *J* 15.2, 10.2, 7-H_A), 4.37–4.32 (0.45H, br m, 5-H), 4.20–4.16 (0.55H, br m, 5-H), 3.58–3.48 (2H, br m, 2-H_A, 13-H_A), 3.48–3.38 (1H, m, 7-H_B), 3.38–3.21 (2H, m, 2-H_B, 13-H_B), 3.21–3.10 (1H, m, 8-H_A), 2.82 (1H, app. dd, *J* 17.9, 6.1, 8-H_B), 1.92–1.68 (3H, br m, 4-H_2, 5-H_A), 1.40–1.46 (1H, br m, 5-H_B); δ_C (125 MHz, $CDCl_3$) 156.6 (C=O Cbz), 156.0 (C=O Cbz), 148.8 (C-12a), 148.7 (C-12a), 137.2 (*ipso*-Ph), 137.1 (*ipso*-Ph), 132.2 (C-9), 132.1 (C-9), 129.7 (C-8a), 129.3 (C-8a), 128.7 (Ph), 128.1 (Ph), 128.0 (Ph), 127.5 (C-11), 127.4 (C-11), 119.5 (C-12), 119.4 (C-12), 119.3 (C-10), 119.2 (C-10), 67.4 (Cbz CH_2), 67.3 (Cbz CH_2), 50.22, 50.18, 49.8 (C-2/13), 49.3 (C-5), 49.0 (C-5), 42.5 (C-7), 41.7 (C-7), 38.0 (C-8), 37.6 (C-8), 30.2 (C-4), 29.9 (C-4), 21.9 (C-5) (33 out of 38 signals present); HRMS found MNa^+, 359.1727. $C_{21}H_{24}N_2O_2Na$ requires 359.1730.

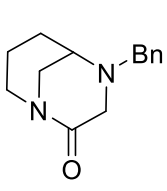
6. NMR, IR, Distortion Parameters and X-ray data[6,16]

Summary of C=O ^{13}C NMR and IR data for all bicyclic lactams:

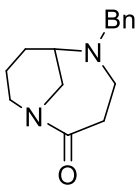
Entry	Lactam	^{13}C NMR C=O δ (ppm)	IR C=O (cm^{-1})
1	 **6d**	183.1	1682
2	 **6c**	182.1, 182.0	1680
3	 *(S,S)*-**6h**	181.4	1684
4	 **6f**	180.2	1686
5	 **6g**	179.9	1691

6	 **6e**	179.9	1680
7	 **6i**	179.7	1684
8	 **6k**	176.8	1657
9	 **6l**	172.80, 172.75	1647
10	 **6j**	170.9	1667

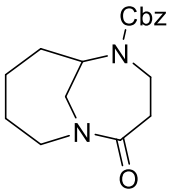
X-ray crystallographic data:



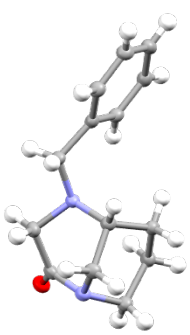
6f'



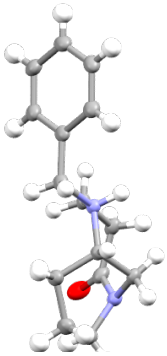
6k'



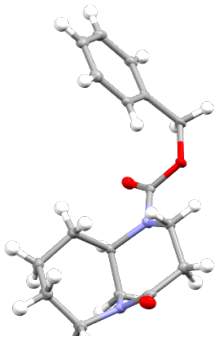
6l



CCDC 1588303



CCDC 1588304



CCDC 2192693

Crystallographic data for compounds **6f'** and **6k'** previously reported.[6]

Data for **6l** (CCDC 2192693):

Empirical formula	$C_{17}H_{22}N_2O_3$
Formula weight	302.36
Temperature/K	100.01(10)
Crystal system	monoclinic
Space group	P21/c
a/Å	12.1041(10)
b/Å	11.5162(9)
c/Å	10.8177(8)
α/°	90
β/°	95.407(7)
γ/°	90
Volume/Å^3	1501.2(2)
Z	4
ρ_{calc}g/cm^3	1.338
μ/mm^{-1}	0.092
F(000)	648

Crystal size/mm^3	0.25 × 0.15 × 0.09
Radiation	Mo Kα (λ = 0.71073)
2Θ range for data collection/°	5.178 to 59.002
Index ranges	-16 ≤ h ≤ 12, -12 ≤ k ≤ 15, -14 ≤ l ≤ 14
Reflections collected	8357
Independent reflections	3554 [R_{int} = 0.0392, R_{sigma} = 0.0672]
Data/restraints/parameters	3554/0/199
Goodness-of-fit on F^2	1.087
Final R indexes [I>=2σ (I)]	R_1 = 0.0628, wR_2 = 0.1184
Final R indexes [all data]	R_1 = 0.0913, wR_2 = 0.1305
Largest diff. peak/hole / e $Å^{-3}$	0.29/-0.27

Entry	Distortion parameters (°)							Bond lengths (Å)		^{13}C NMR (δ)	Sum of bond angles at N (°)
	ω_1	ω_2	ω_3	ω_4	χ_C	χ_N	τ	N-C(O)	C=O		
6f'[a]	0.06	46.86	173.98	-127.06	6.08	52.88	23.5	1.380	1.233	182.9	333.7
6k'[a]	8.61	-26.54	-168.55	150.62	2.84	37.99	8.9	1.361	1.218	179.6	348.8
6l	-4.22	11.36	173.82	-166.68	1.96	17.54	3.57	1.355	1.233	172.80, 172.75	357.8

[a]Compounds and associated data published previously.[6]

7. pK_a Determinations of Bicyclic Anilines

Experimental details:

Non-aqueous (DMSO) pK_a determinations were performed using the method published by Iggo *et. al*.[17]

Experiments were performed in Norell Sample Vault NMR tubes on a Bruker AV-I 400 spectrometer operating at 400.053 MHz for ^{1}H. CSI experiments were carried out using the gradient phase encoding sequence of Schenck *et al*.[17] This is based on the sequences of Trigo-Mourino *et al*[18] and Wallace *et al*.[19]

The phase encoding gradient pulse **g** was 267.52220 µs and varied from -27 to 27 Gcm^{-1} in 128 slices. Typically, 16 dummy scans preceded signal acquisition, with 8 scans acquired for each gradient increment, with an acquisition time of 1.278 s. A spoil gradient of 27 Gcm^{-1} was included after the acquisition period to destroy any remaining transverse magnetisation. Time domain data files were transformed without zero-filling using sine bell apodization. A 128 slice CSI experiment had a total acquisition time of 32 minutes with a theoretical spatial resolution of 0.15 mm.

All indicator 0.6 mol/L stock solutions were prepared with dry DMSO-d_6 as 2 mL stock solutions in a N_2 purged glovebox. Volatile reagents deleterious to the glovebox were added in air. A 33 mmol / L stock solution of hexamethyldisilane in dry DMSO-d_6 was prepared to act as a pH independent internal chemical shift reference.

Benzyl 3,4-dihydro-2H-1,4-methanobenzo[b][1,5]diazocine-5(6H)-carboxylate **7a**:

The analyte was dissolved in 1144 µL of dry DMSO-d_6. The following volumes of stock solutions were then added: 15 µL of pyridine solution; 15 µL of 2,6-lutidine solution; 10 µL of 1-methylimidazole solution; 10 µL of *N,N*-dimethylbenzylamine solution and 6 µL of HMDS solution. The resulting concentrations of analyte and indicators in the measured sample were: Analyte **7a** 5.40 mmol / L; pyridine = 7.5

mmol / L; 2,6-lutidine = 7.5 mmol / L; 1-methylimidazole = 5 mmol / L; *N,N*-dimethylbenzylamine = 5 mmol / L; HMDS = 165 µmol / L.

Benzyl 2,3,4,5-tetrahydro-1,5-methanobenzo[b][1,5]diazonine-6(7H)-carboxylate **7b**:

The analyte was dissolved in 1140 µL of anhydrous DMSO-d_6. The following volumes of stock solutions were then added: 15 µL of *N,N*-dimethylaniline solution; 15 µL of pyridine solution; 10 µL of 2,6-lutidine solution; 10 µL of 1-methylimidazole solution and 10 µL of HMDS solution. The resulting concentrations of analyte and indicators in the measured sample were: Analyte **7b=** 5.17 mmol / L; *N,N*-dimethylaniline = 7.5 mmol / L; pyridine = 7.5 mmol / L; 2,6-lutidine = 7.5 mmol / L; 1-methylimidazole = 5 mmol / L; HMDS = 275 µmol / L.

Benzyl 3,4,5,6-tetrahydro-2H-1,6-methanobenzo[b][1,5]diazecine-7(8H)-carboxylate **7d**:

The analyte was dissolved in 1140 µL of anhydrous DMSO-d_6. The following volumes of stock solutions were then added: 15 µL of *N,N*-dimethylaniline solution; 15 µL of pyridine solution; 10 µL of 2,6-lutidine solution; 10 µL of 1-methylimidazole solution and 10 µL of HMDS solution. The resulting concentrations of analyte and indicators in the measured sample were: Analyte **7d=** 5.20 mmol / L; *N,N*-dimethylaniline = 7.5 mmol / L; pyridine = 7.5 mmol / L; 2,6-lutidine = 7.5 mmol / L; 1-methylimidazole = 5 mmol / L; HMDS = 275 µmol / L.

To establish a pH gradient, solid acid was weighed directly into the NMR tube using a Mettler AE101 balance with a stated precision of ± 0.01 mg. Four 2 mm glass beads were placed on top of the solid acid in the NMR tube to prevent rapid mixing. 550 µL of basic solution was then gently layered on top of the glass beads and the tube left to stand vertically at ambient laboratory temperature (20°C) until analysis. Basic analytes were investigated by titrating a solid acid of known pK_a (*p*-toluenesulfonic acid) against a solution containing the analyte and several basic

indicators as specified. Limiting shifts of indicators were determined independently from the imaging experiments. An excess of strong acid or base was used to measure limiting shifts of all reagents.

Water content across the samples was assessed by NMR and established to be below 1.0 v% and as such low it would not have an impact on pK_a value.[17]

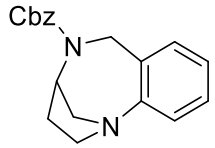
Electronic Structure and *p*K_a Calculations

Geometries of **7a**, **7b** and **7d** were optimised using Density-Functional Theory (DFT). A conformational search was performed, and only conformers with the lowest energy were used for further calculations. M06-2x functional and 6-31G** basis set were used within the Schrodinger optimisation tool.[21,22,23] The tool performed quantum mechanical Hessian matrix analysis to avoid convergence at a local minimum. Pseudospectral methods were turned off. Geometries were optimised in the gas phase and also in the parallel runs in both DMSO and water using Poisson Boltzmann Finite (PBF) solvation model.

Jaguar Prediction Method was used to calculate *p*K_a in water of **7a**, **7b** and **7d**.[20,21,22,23,24] It calculates a reference value from the gas and water-solvated phase energies. The conformational search was performed, and only conformers with the lowest energy were used for further calculations. Gas phase and water-solvated geometries were optimised using B3LYP/6-31G* density functional theory (DFT). Pseudospectral methods were turned off. Energies of each optimised geometry were obtained using single spot B3LYP/cc-pVTZ(+) DFT calculations. The solvation-free energy of the protonated and deprotonated species with empirical parameterisation being applied. The results were collected, and raw *p*K_a was calculated. The final *p*K_a is obtained after applying empirical corrections.[20,21,22,23,24]

Results:

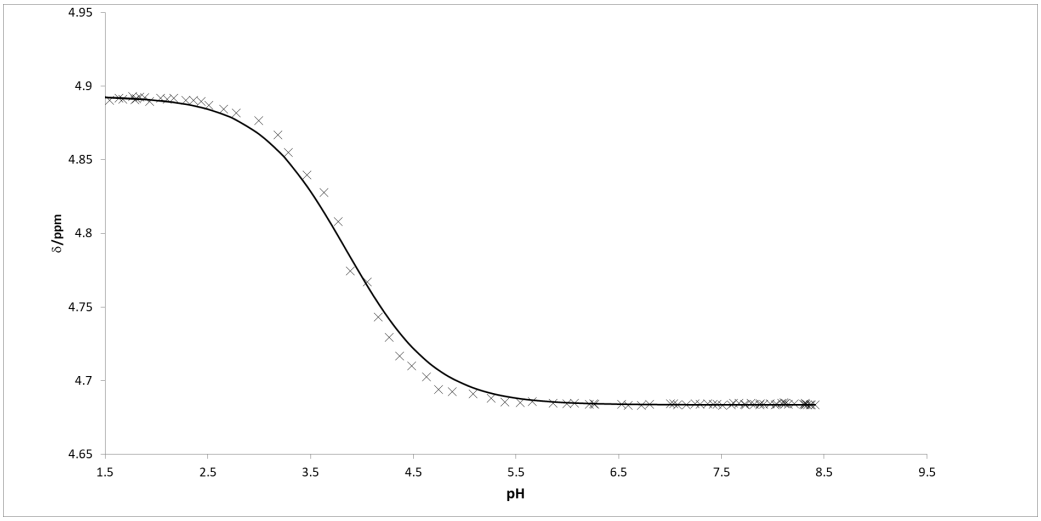
Benzyl 3,4-dihydro-2H-1,4-methanobenzo[b][1,5]diazocine-5(6H)-carboxylate **7a**:



7a

Basic indicators: pyridine (pK_a = 3.4), 2,6-lutidine (pK_a = 4.46), 1-methylimidazole (pK_a = 6.15), *N*,*N*-dimethylbenzylamine (pK_a = 7.60).

Titration curve:

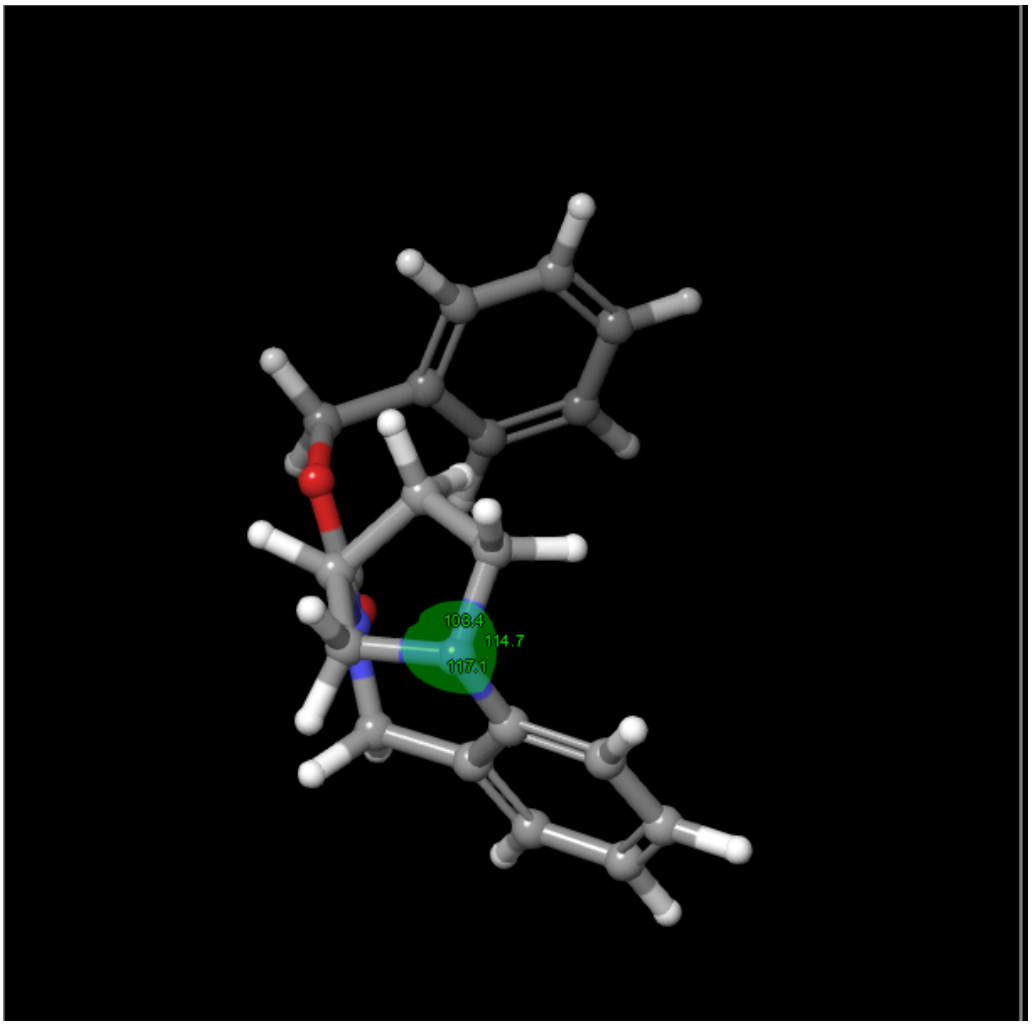


83 data points

R^2 = 0.999999504

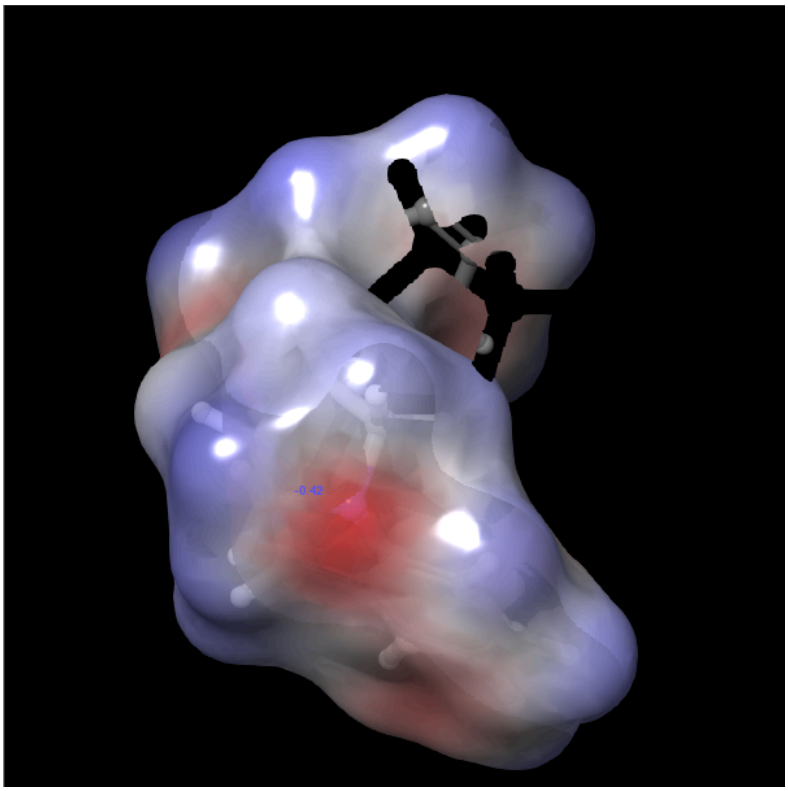
p$K_{a\ (dmso)}$ = 3.85 (+/-0.1)

Geometry optimised in gas phase for **7a**:

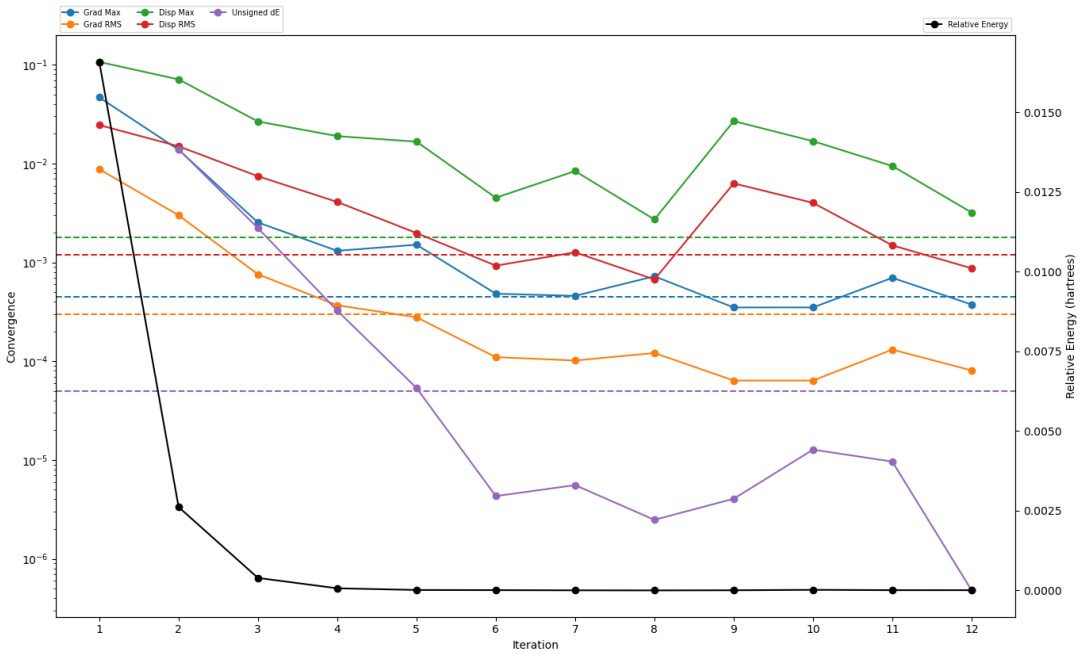


Sum of bond angles at nitrogen: Σ_{angles} = 335.2

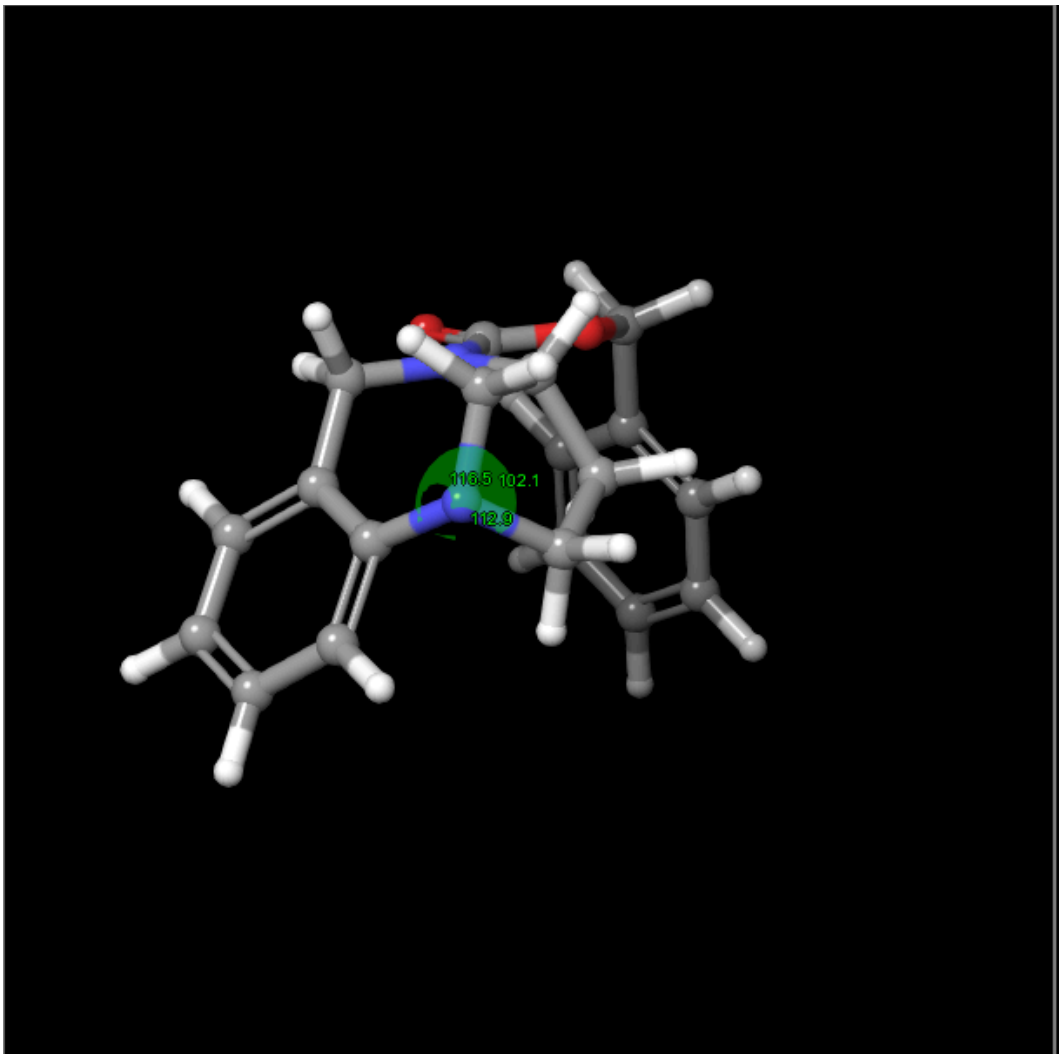
Electrostatic potential map in gas phase for **7a**:



Convergence parameters in gas phase for **7a**:

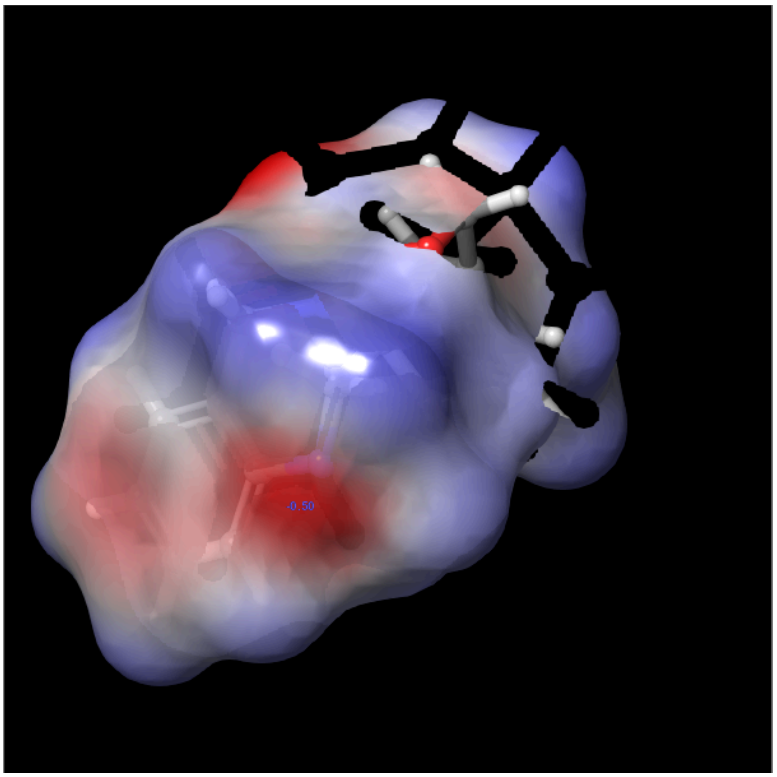


Geometry optimised in DMSO for **7a**:

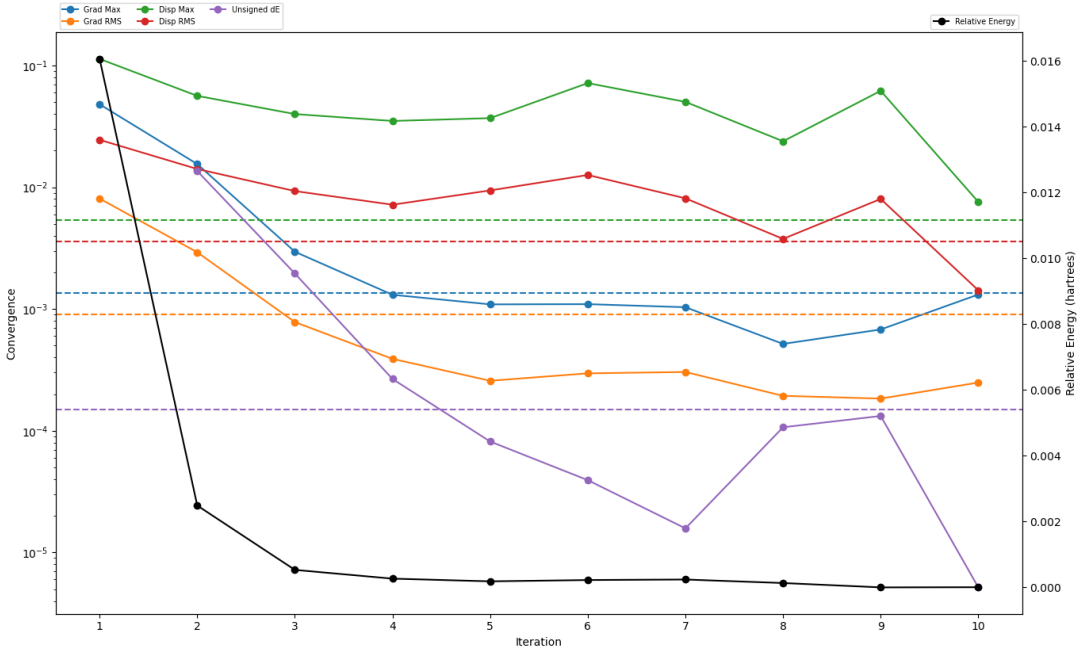


Sum of bond angles at nitrogen: $\Sigma_{angles} = 331.5^{o}$

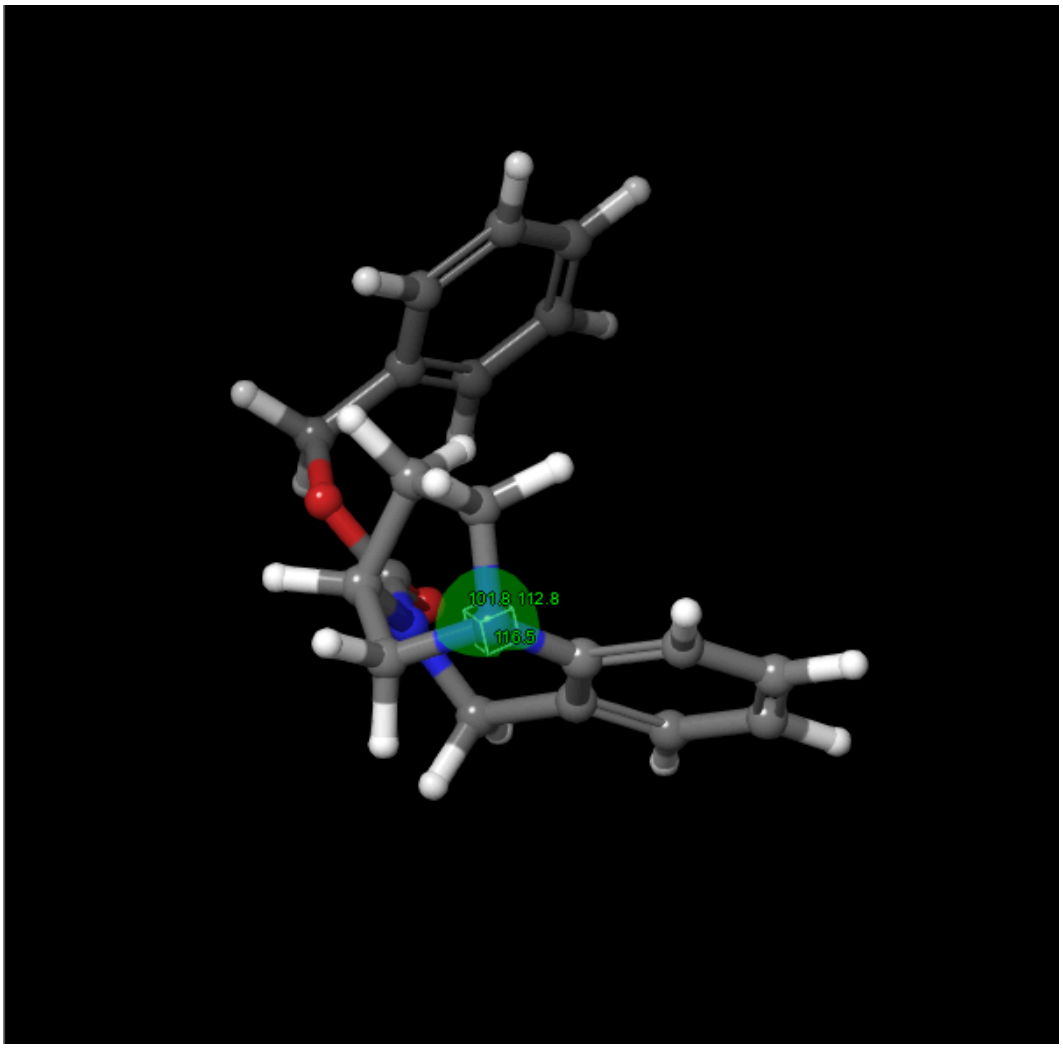
Electrostatic potential map in DMSO for **7a**:



Convergence parameters in DMSO for **7a**:

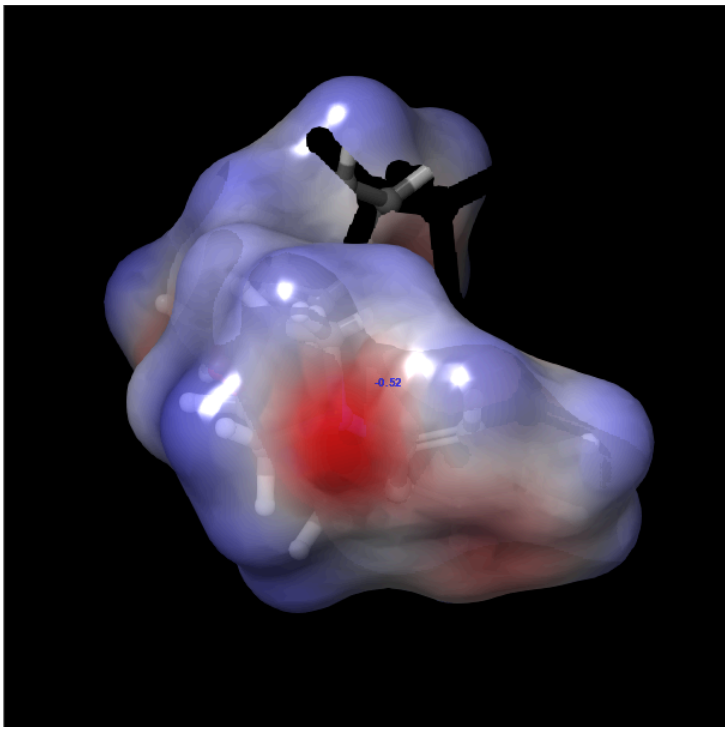


Geometry optimised in water for **7a**:

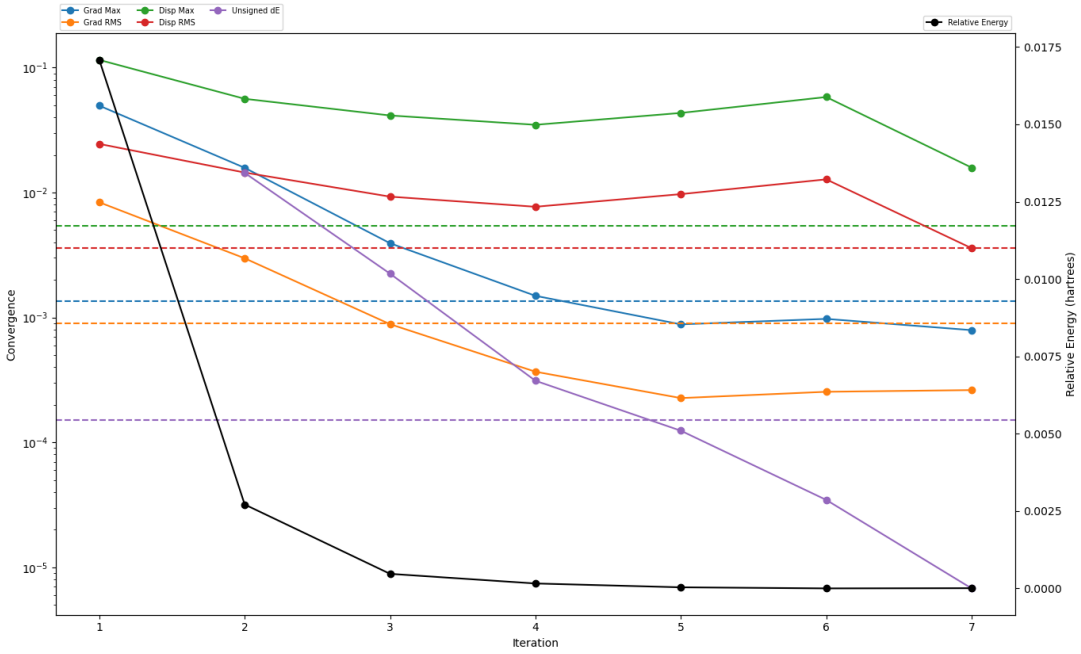


Sum of bond angles at nitrogen: Σ_{angles} = 331.1

Electrostatic potential map in water for **7a**:

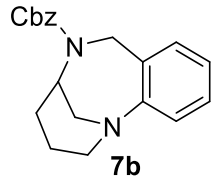


Convergence parameters in water for **7a**:



p$K_{a\ (water\ JPM)}$ = 5.64 (+/-0.5)

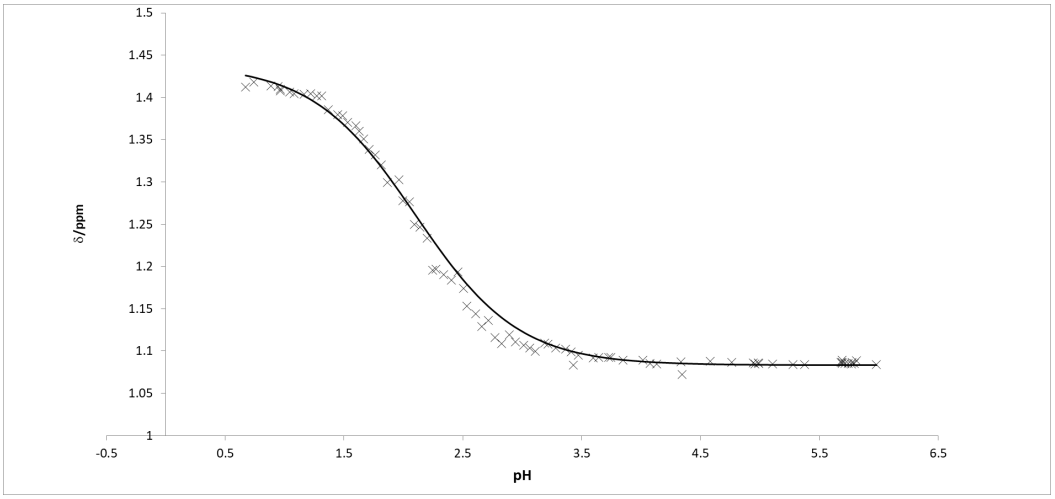
Benzyl 2,3,4,5-tetrahydro-1,5-methanobenzo[b][1,5]diazonine-6(7H)-carboxylate **7b**:



7b

Basic indicators: pyridine (pK_a = 3.4), *N*,*N*-dimethylaniline (pK_a = 2.51).

Titration curve:

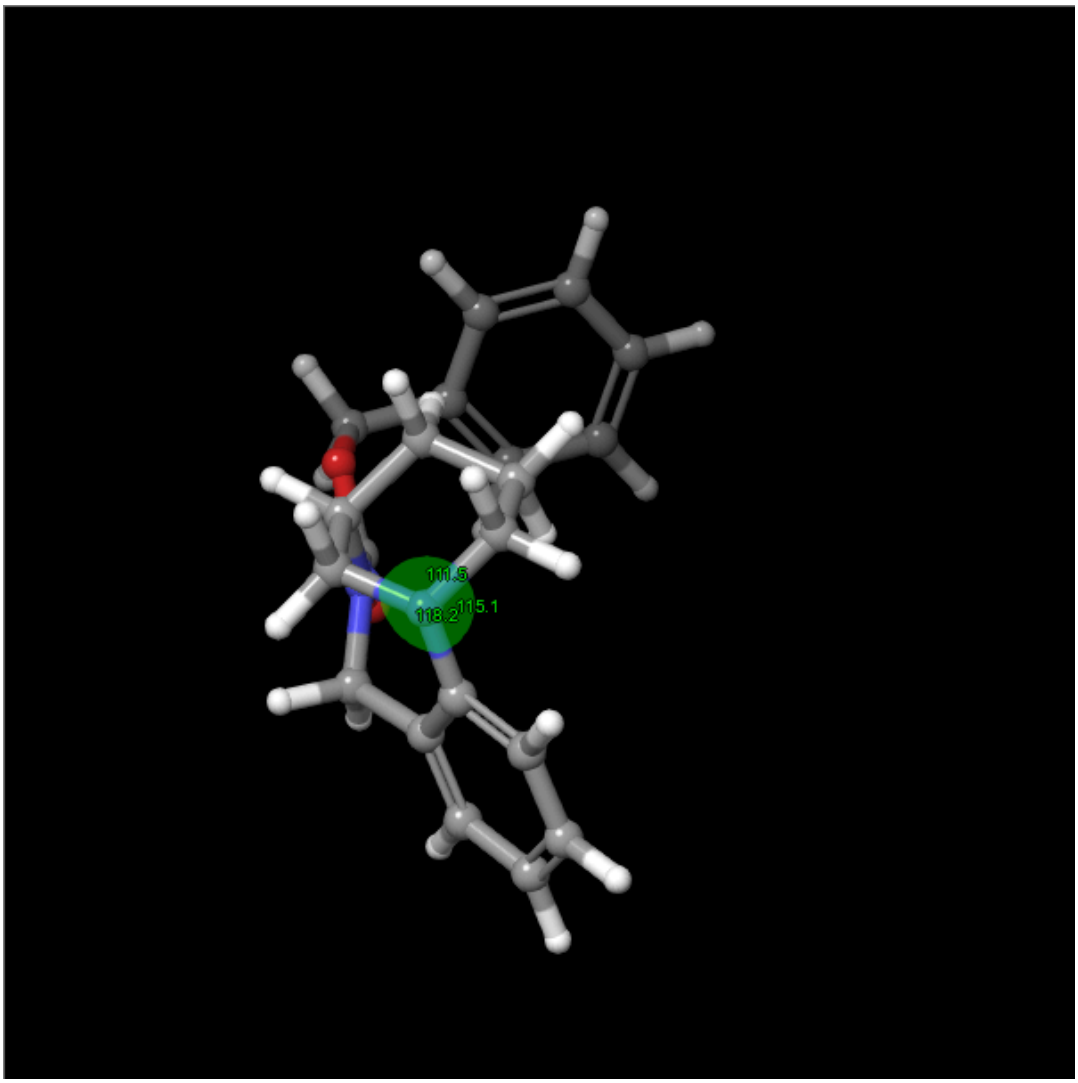


79 data points

R^2 = 0.999955198

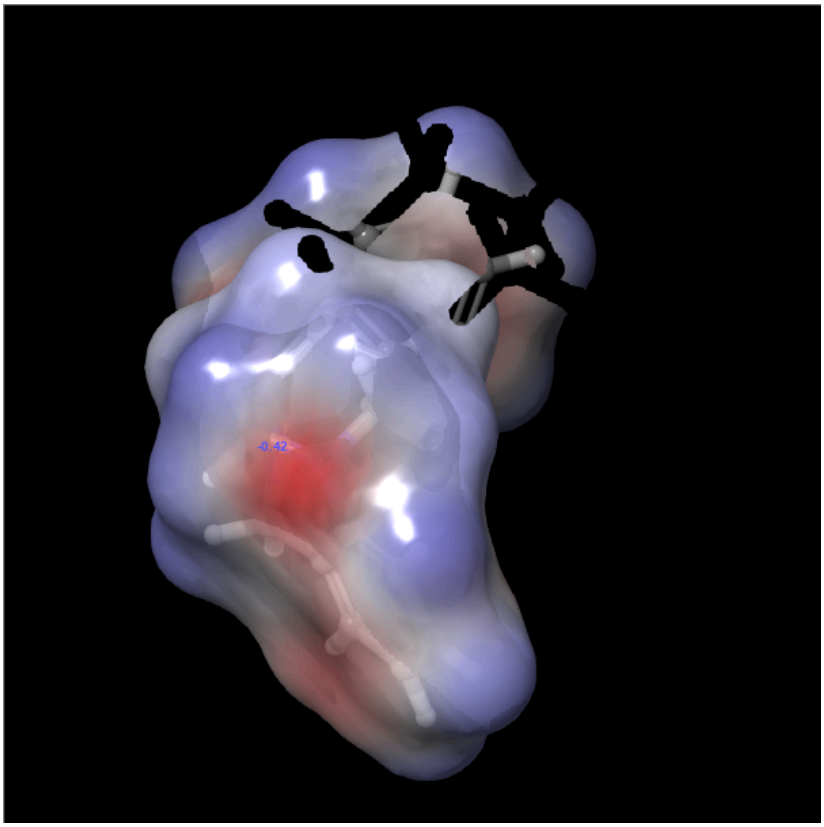
pK_a = 2.10 (+/-0.1)

Geometry optimised in gas phase for **7b**:

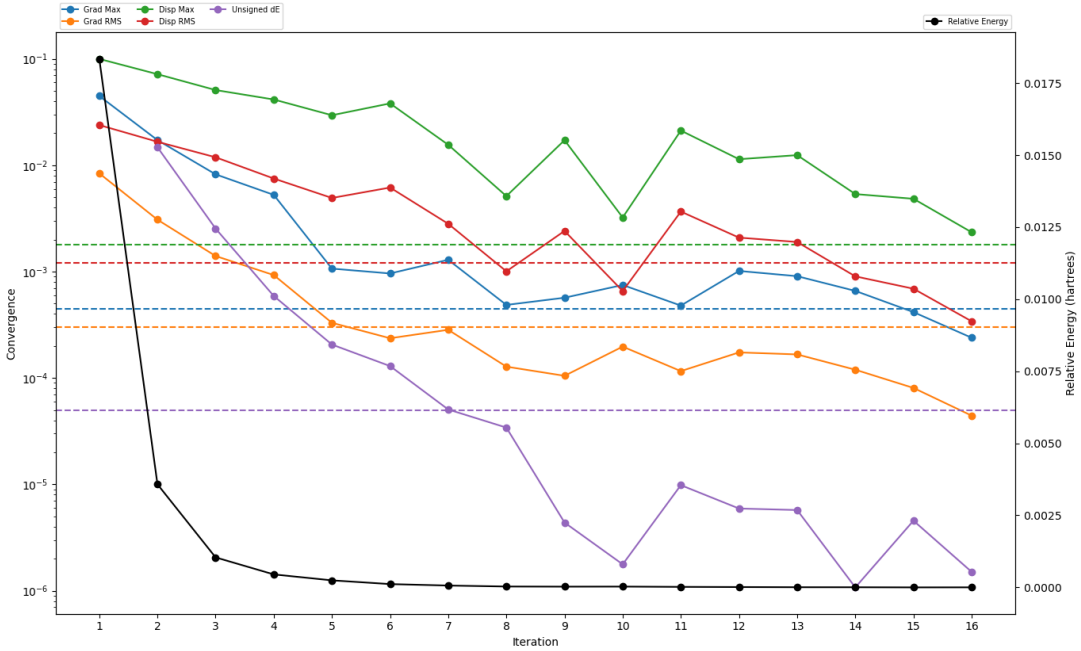


Sum of bond angles at nitrogen: Σ_{angles} = 344.8

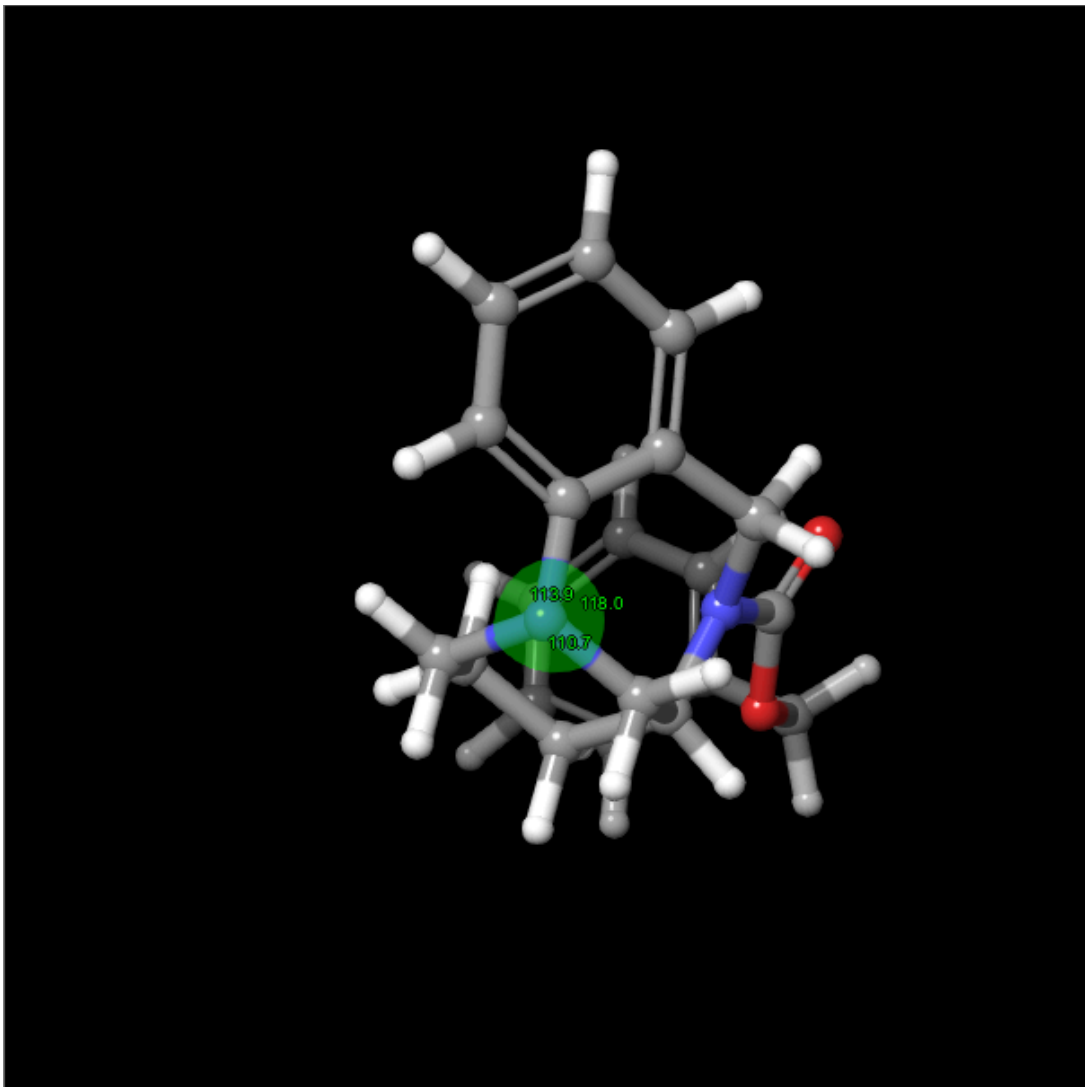
Electrostatic potential map in gas phase for **7b**:



Convergence parameters in gas phase for **7b**:

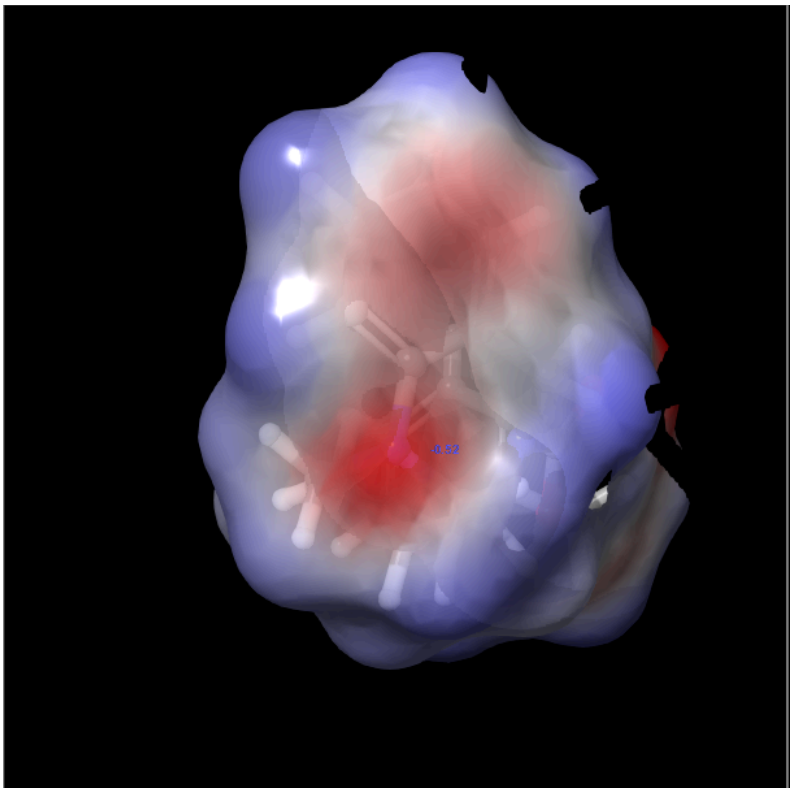


Geometry optimised in DMSO for **7b**:

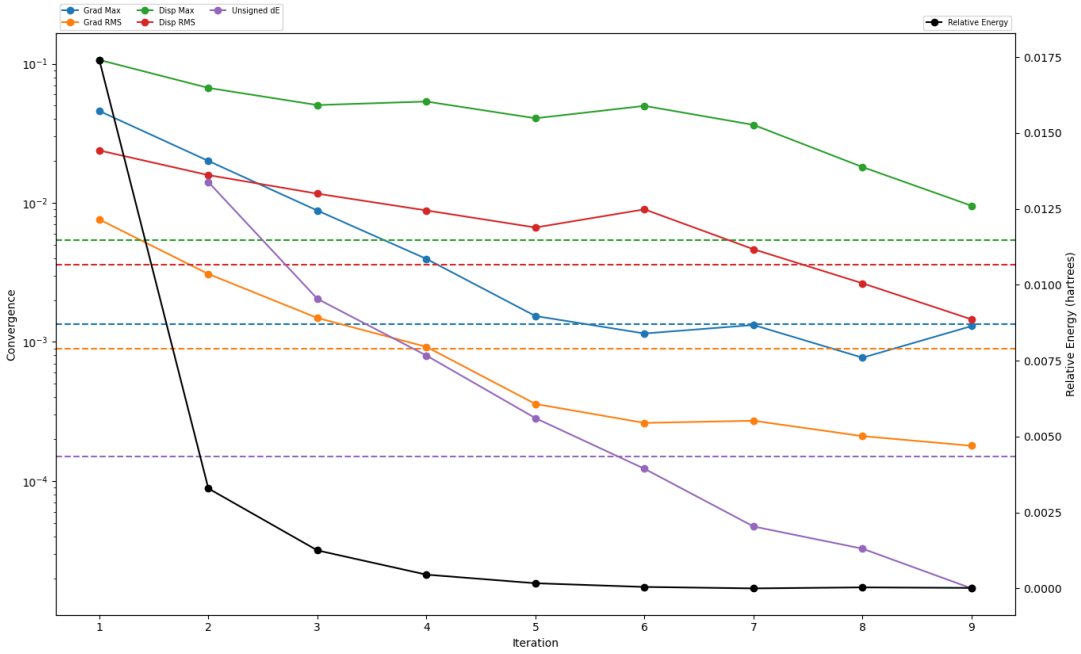


Sum of bond angles at nitrogen: Σ_{angles} = 342.6

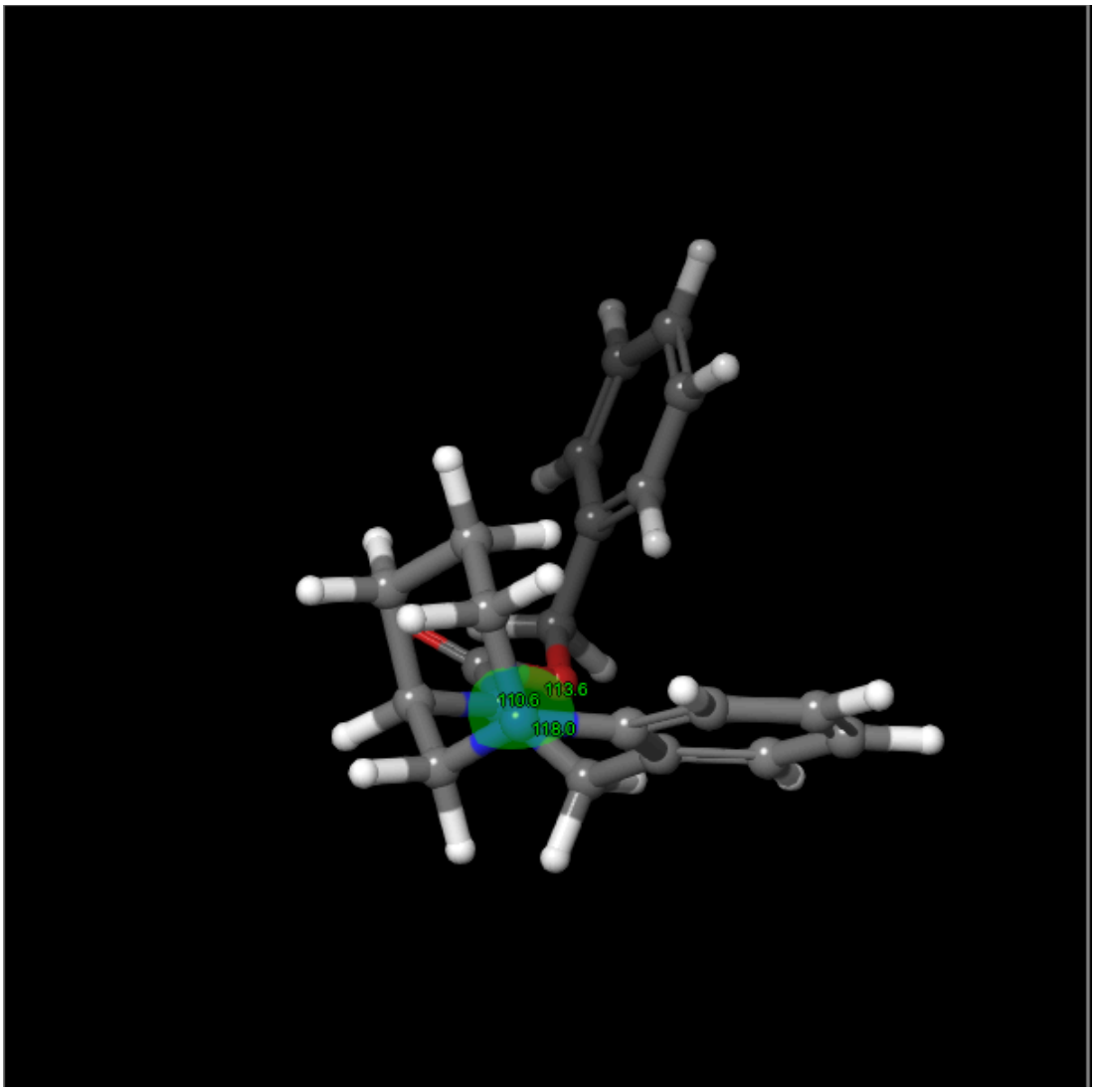
Electrostatic potential map in DMSO for **7b**:



Convergence parameters in DMSO for **7b**:

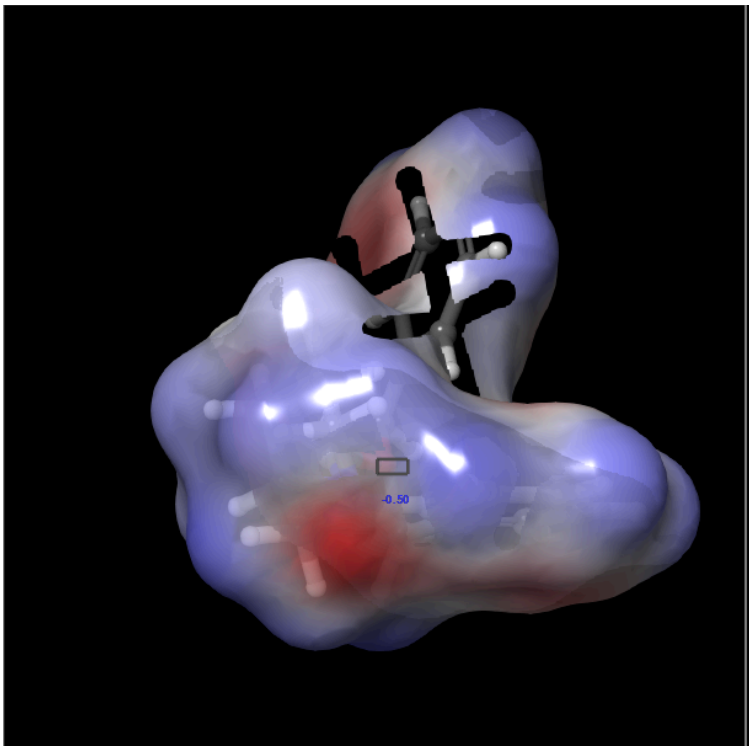


Geometry optimised in water for **7b**:

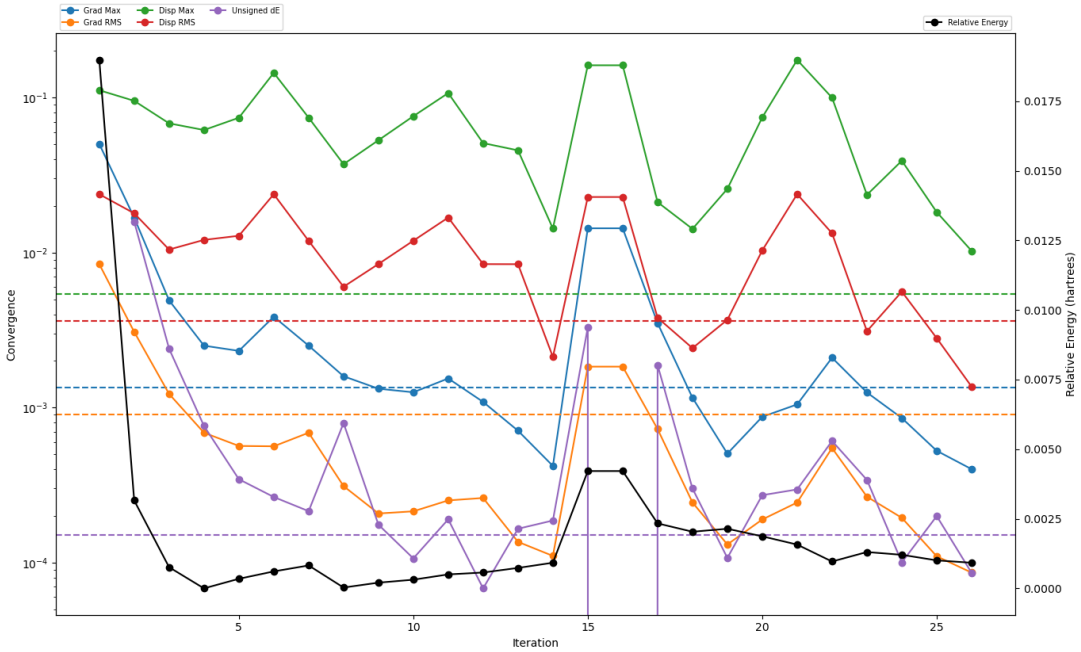


Sum of bond angles at nitrogen: $\Sigma_{angles} = 342.2^{o}$

Electrostatic potential map in water for **7b**:

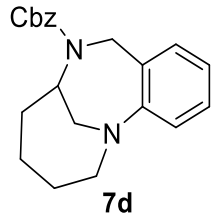


Convergence parameters in water for **7b**:



p$K_{a\ (water\ JPM)}$ = 3.56 (+/-0.5)

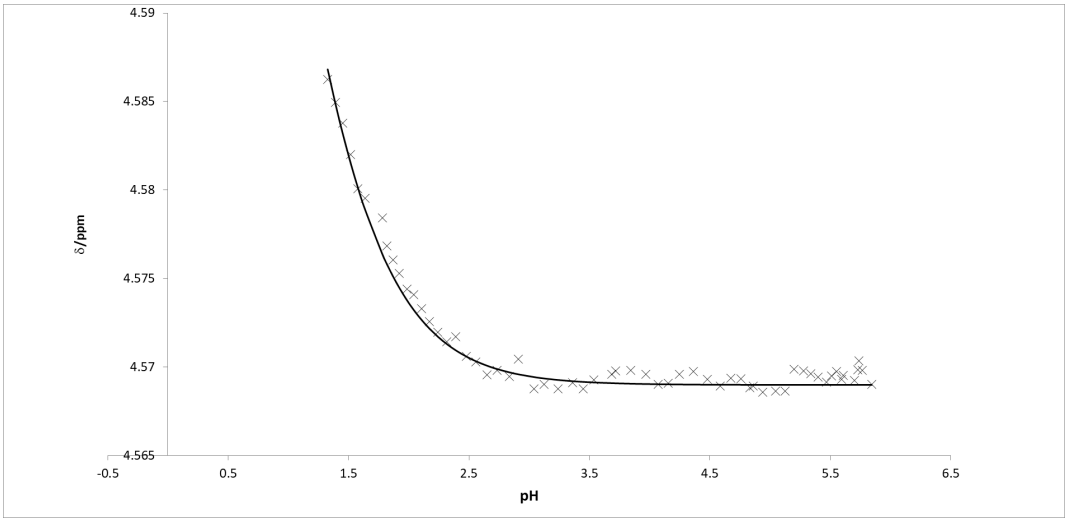
Benzyl 3,4,5,6-tetrahydro-2H-1,6-methanobenzo[b][1,5]diazecine-7(8H)-carboxylate **7d**:



7d

Basic indicators: pyridine (pK_a = 3.4), 2,6-lutidine (pK_a = 4.46), 1-methylimidazole (pK_a = 6.15), *N*,*N*-dimethylaniline (pK_a = 2.51).

Titration curve:

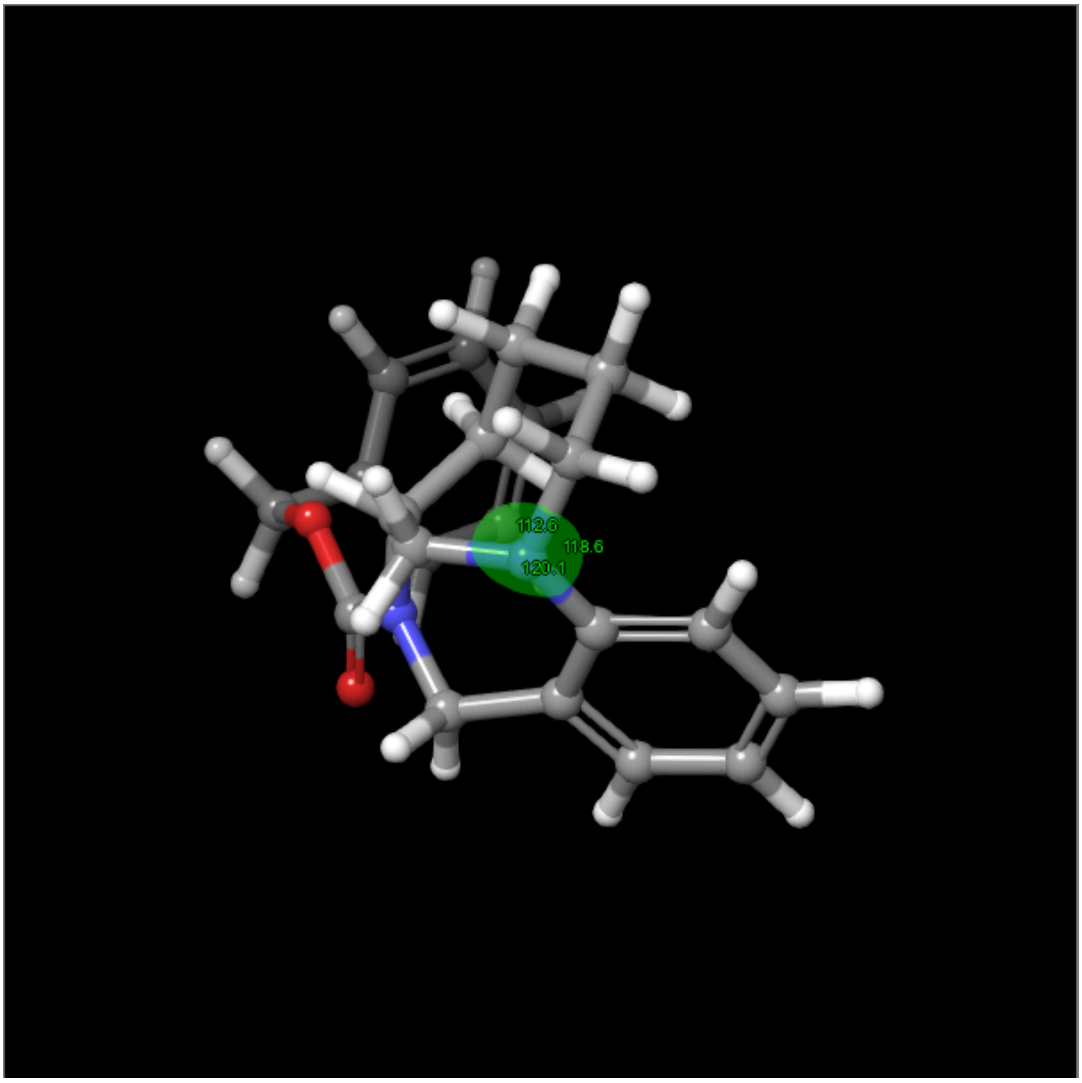


59 data points

R^2 = 0.999999641

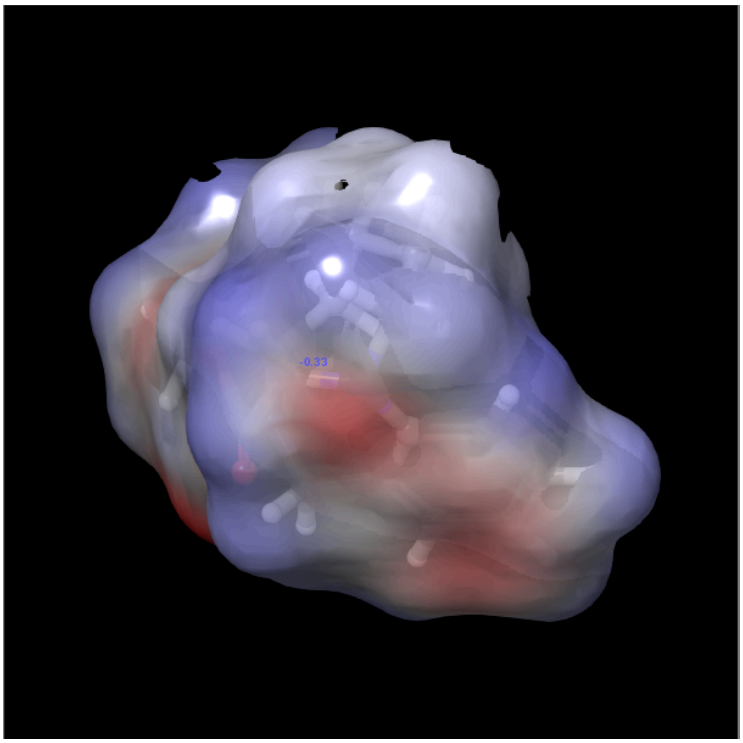
pK_a = 0.81 (+/-0.1)

Optimised Geometry in gas phase for **7d**:

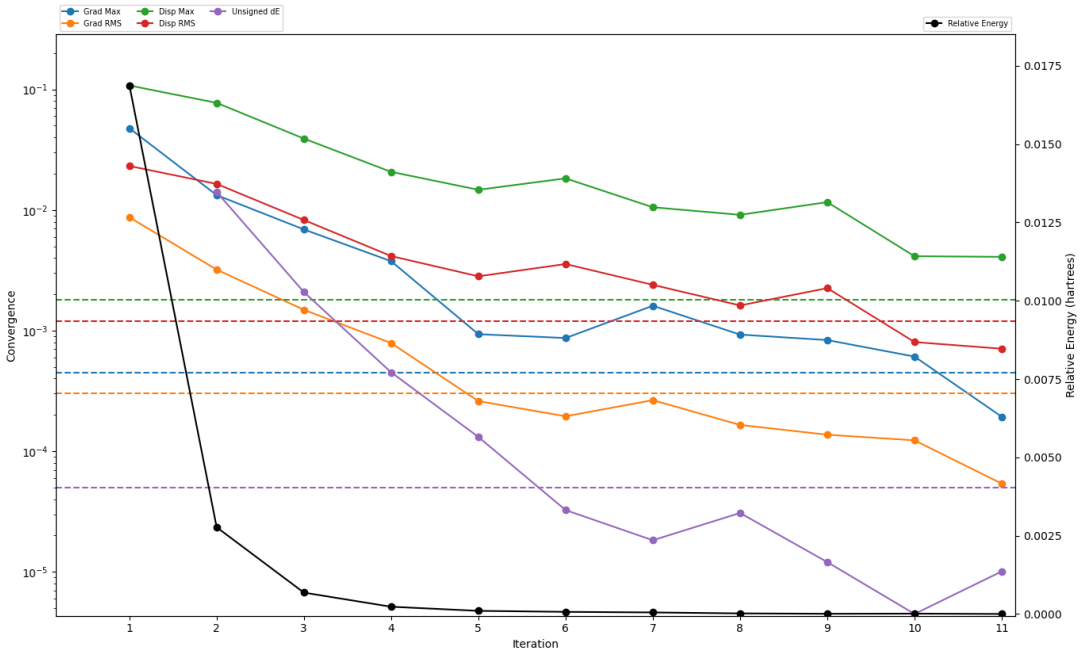


Sum of bond angles at nitrogen: $\Sigma_{angles} = 351.3^{o}$

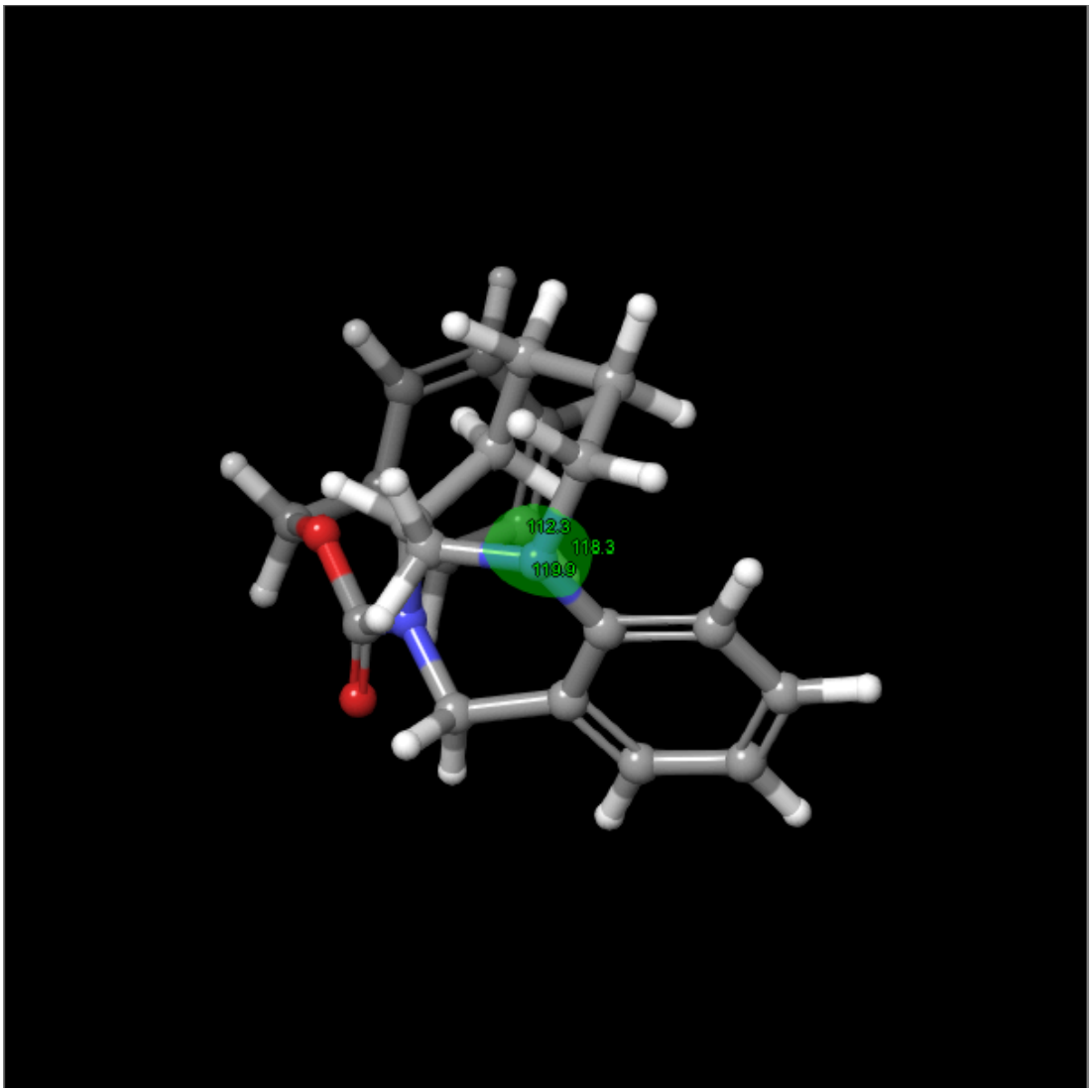
Electrostatic potential map in gas phase for **7d**:



Convergence parameters in gas phase for 7d:

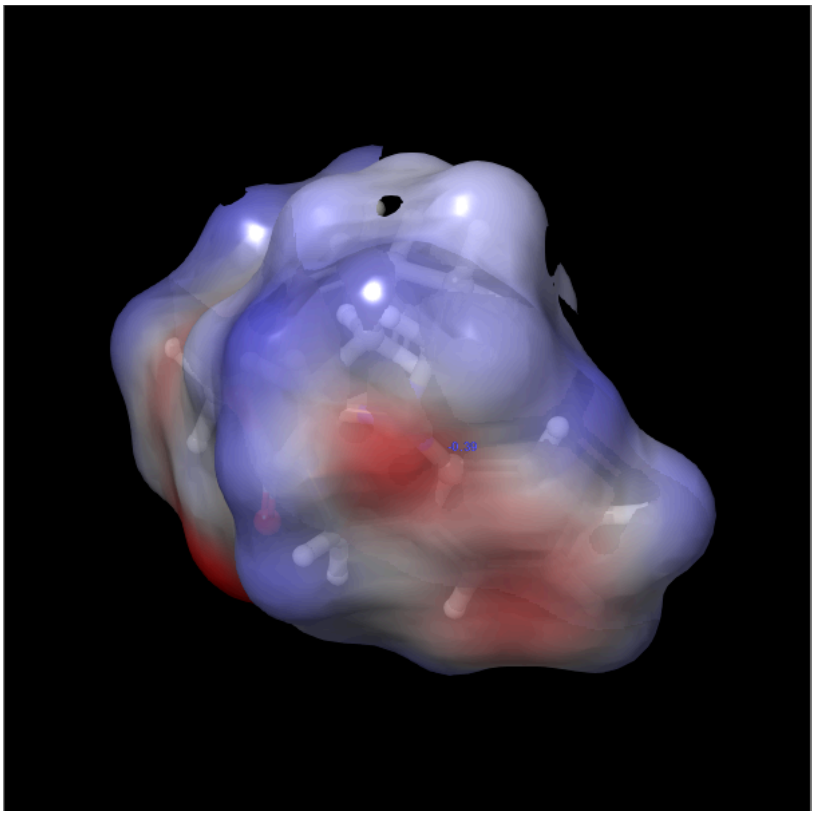


Optimised Geometry in DMSO for **7d**:

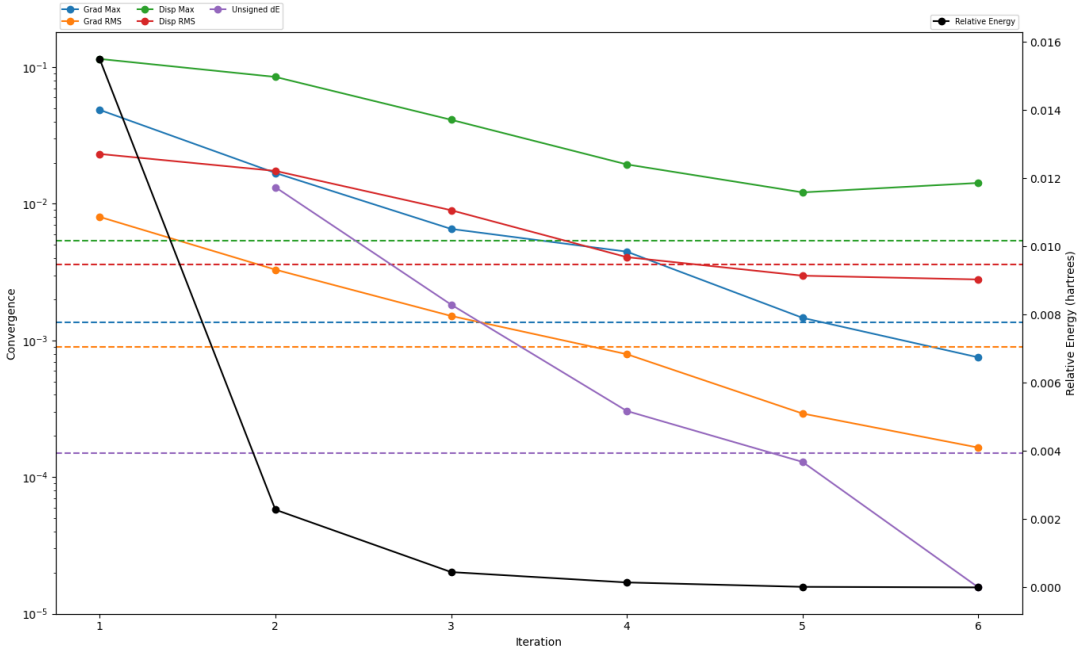


Sum of bond angles at nitrogen: $\Sigma_{angles} = 350.5^{o}$

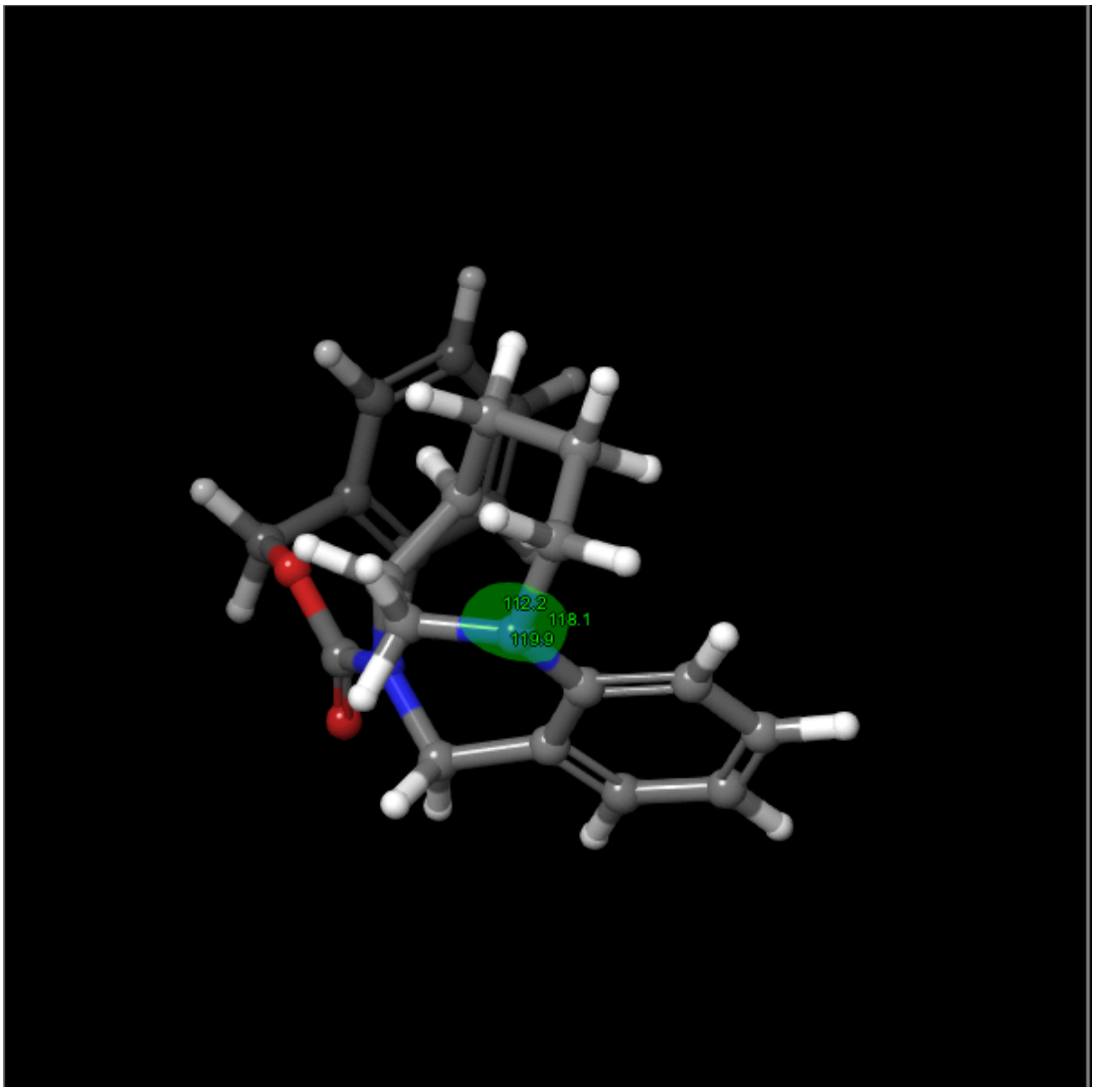
Electrostatic potential map in DMSO for **7d**:



Convergence parameters in DMSO for **7d**:

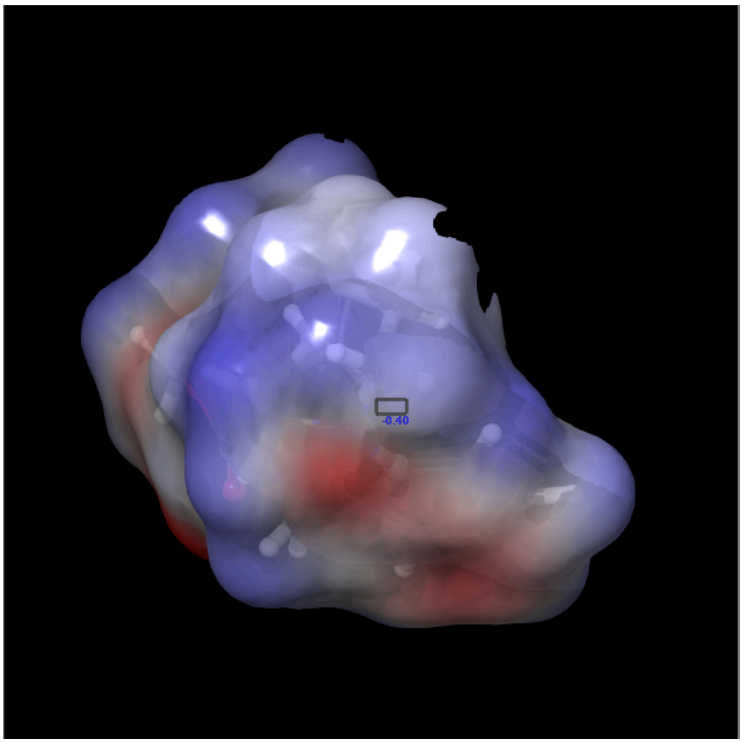


Geometry optimised in water for **7d**:

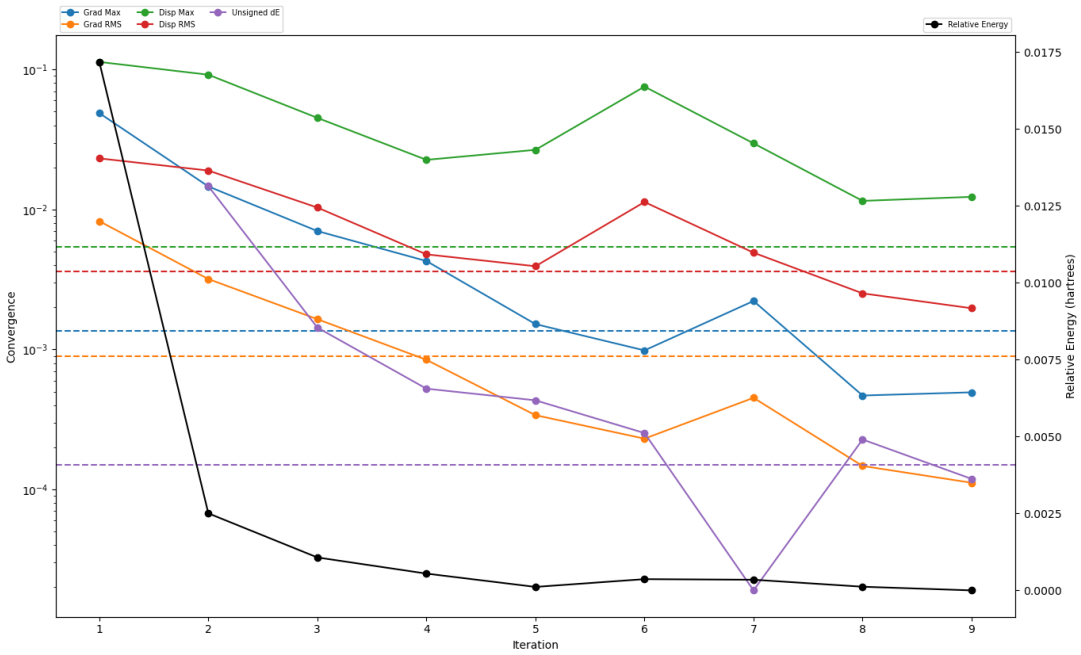


Sum of bond angles at nitrogen: $\Sigma_{angles} = 350.2^{o}$

Electrostatic potential map in water for **7d**:



Convergence parameters in water for 7d:



p$K_{a\ (water\ JPM)}$ = 1.27 (+/-0.5)

8. Antimicrobial Assays of Twisted Lactams

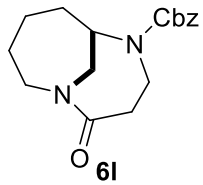
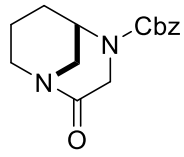
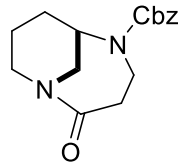
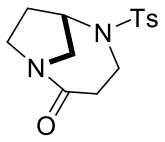
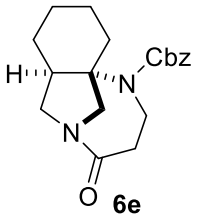
General Experimental:

All antibacterial screening was performed by Julian Chesti (University of Leeds). Minimum inhibitory concentration (MIC) values for selected compounds were determined by broth microdilution against *S. aureus* strain $ATCC_{29213}$[25] according to CLSI guidelines for low solubility compounds except for using Iso-Sensitest Broth (ISB) in place of cation-adjusted Mueller-Hinton Broth (MHB-II).[26]

A 2-fold dilution series of the isolated compounds in DMSO was prepared, ranging from 6400–12.5 μg mL^{-1}. Each dilution was transferred into a 96-well format at a final volume of 1 μL and 99 μL of the standardised culture was added to each well to give final antibiotic concentrations of 64–0.125 μg mL-1 (1% DMSO in ISB). Plates were incubated for 16 h at 37 °C (Inkubator 1000, Heidolph) and the minimum inhibitory concentration (MIC) was determined visually as the lowest concentration at which growth was inhibited.

Raw Data:

Table 8.1: Plate reader raw data for the twisted lactam series.

Sample	Replicate	Measured absorbance values as optical density for each concentration of sample				
		32 µg/mL	4 µg/mL	0.5 µg/mL	0.0625 µg/mL	0 µg/mL
 **6l**	1	3.918	3.36	1.971	1.667	3.408
	2	5.466	4.247	3.204	2.95	5.054
 **6f**	1	4.054	3.472	3.154	5.736	4.271
	2	4.886	5.404	4.934	2.102	2.582
 **6k**	1	4.87	3.682	2.845	3.177	5.371
	2	5.583	4.146	4.798	3.664	4.019
 **6d**	1	4.867	5.643	4.623	4.357	5.841
	2	4.879	4.466	5.67	4.125	5.663
 **6e**	1	0.187	4.827	3.078	2.705	2.67
	2	0.188	4.796	2.356	2.308	3.376

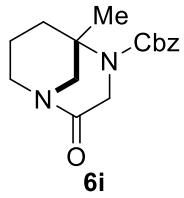
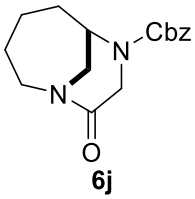
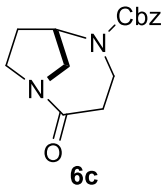
 **6i**	1	3.445	2.639	2.841	3.343	3.103
	2	3.101	3.363	2.775	2.76	3.421
 **6j**	1	3.268	3.237	3.317	3.095	2.819
	2	5.384	5.183	2.661	2.9	3.545
 **6c**	1	3.825	3.511	3.327	2.991	3.393
	2	4.369	5.291	3.289	5.222	3.571

Table 8.2: Plate reader raw data for active twisted lactam **6e** against control **6f**. MIC = 32 µg/mL

Concentration (µg/mL)	Measured absorbance values as optical density for each concentration of sample							
	Colony 1		Colony 2		Colony 3		Colony 1 (Control, **6f**)	
64	0.139	0.157	0.145	0.156	0.87	0.157	5.717	5.237
32	0.122	4.638	3.687	0.171	0.16	0.165	4.494	4.652
16	3.978	5.883	6.027	6.091	5.813	5.158	5.197	4.331
8	5.239	5.654	4.97	4.961	5.417	5.738	5.24	5.45

4	5.447	6.968	6.727	5.822	6.456	5.725	5.253	5.391
2	5.212	5.572	5.745	4.688	4.976	4.86	5.072	5.165
1	5.42	5.817	5.272	5.404	5.435	5.152	3.984	4.966
0.5	5.422	5.224	5.511	4.987	5.49	5.591	4.905	5.146
0.25	5.295	5.167	4.935	4.813	4.992	5.222	4.672	4.968
0.125	5.32	5.055	5.341	5.036	4.98	5.099	5.231	5.513

Growth inhibition:

Growth inhibition values were calculated for lactam **6e** within excel using the optical density (OD) data obtained from the plate reader presented in table 8.2, using equation 1. Duplicates and colonies were averaged. Outlining values were excluded. Growth inhibition was calculated at 97.247% (64 µg/mL) and 96.621 (32 µg/mL).

$$Growth\ inhibition\ (\%) = \frac{\left(OD_{control} - OD_{sample}\right)}{OD_{control}} \times 100\ \#(1)$$

9. References

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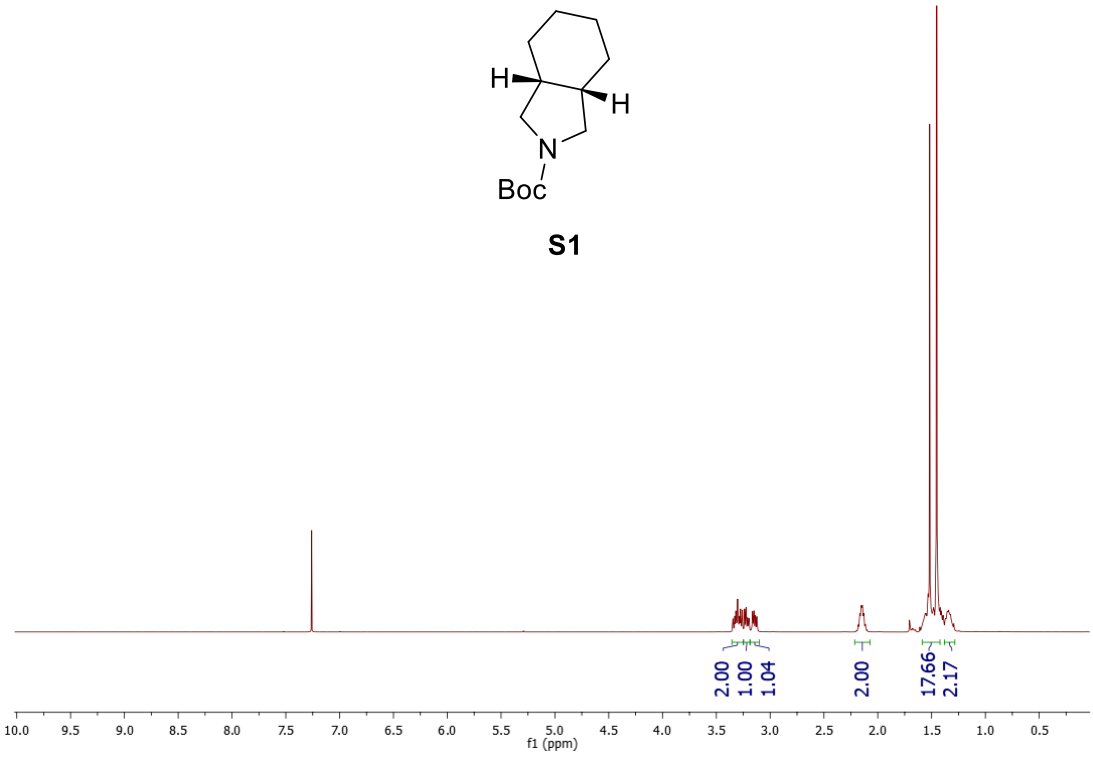
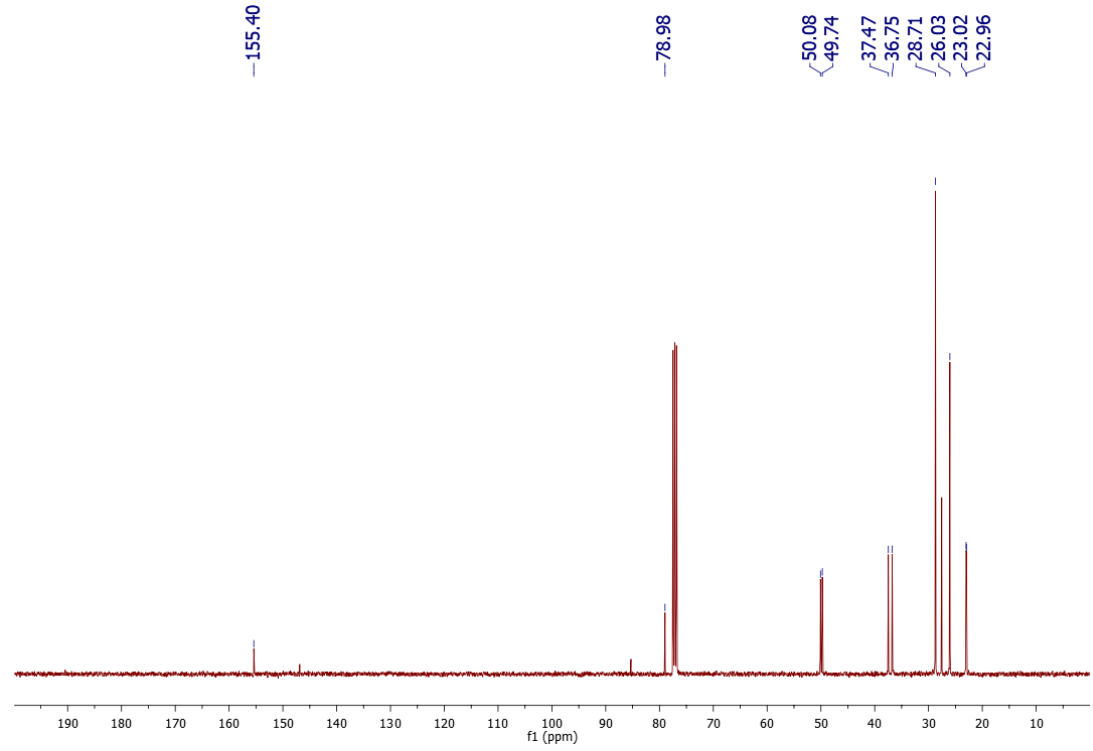
10. Spectra

cis-_tert_-Butyl octahydro-2_H_-isoindole-2-carboxylate S1



S1



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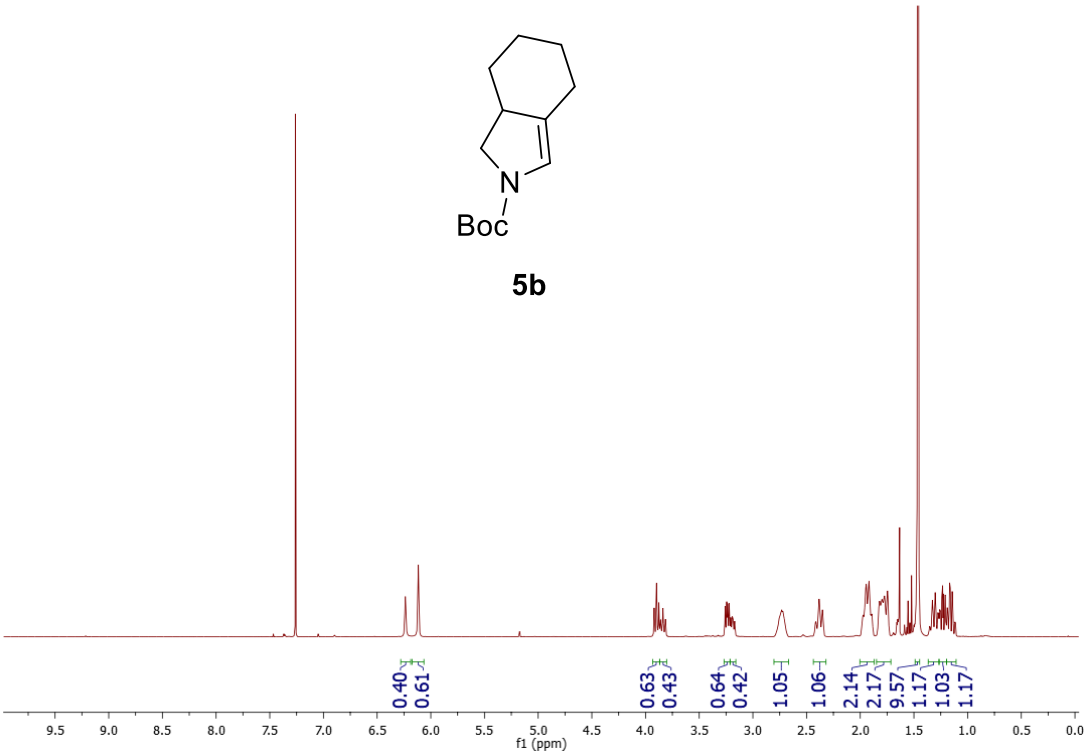

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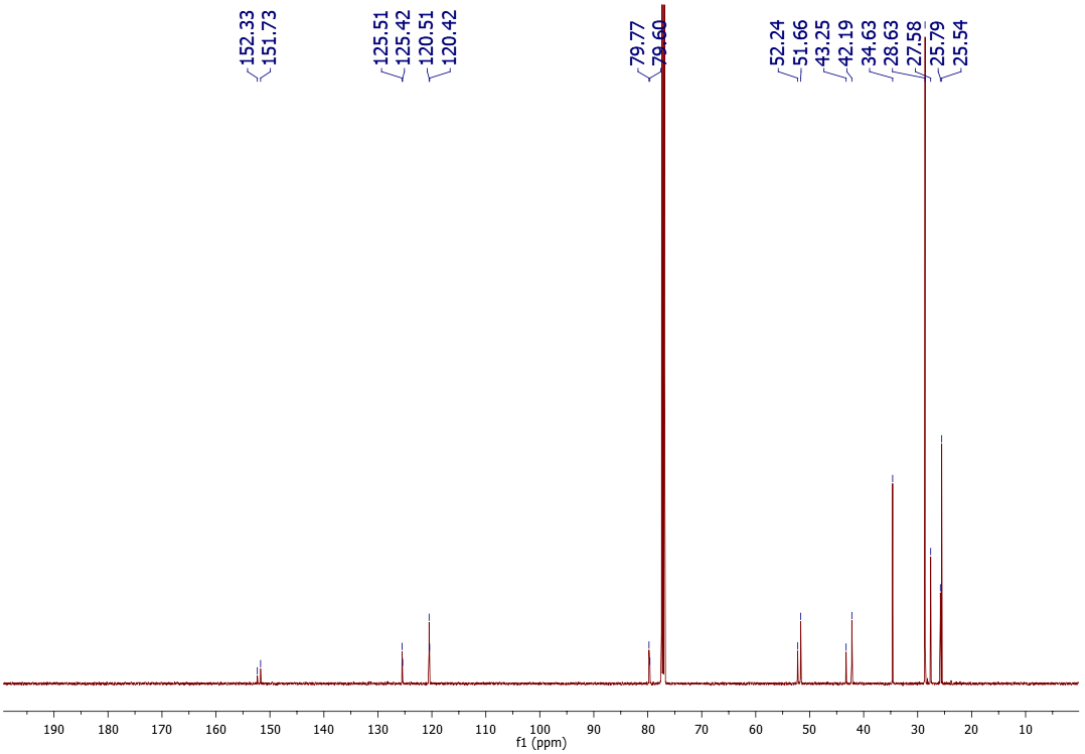

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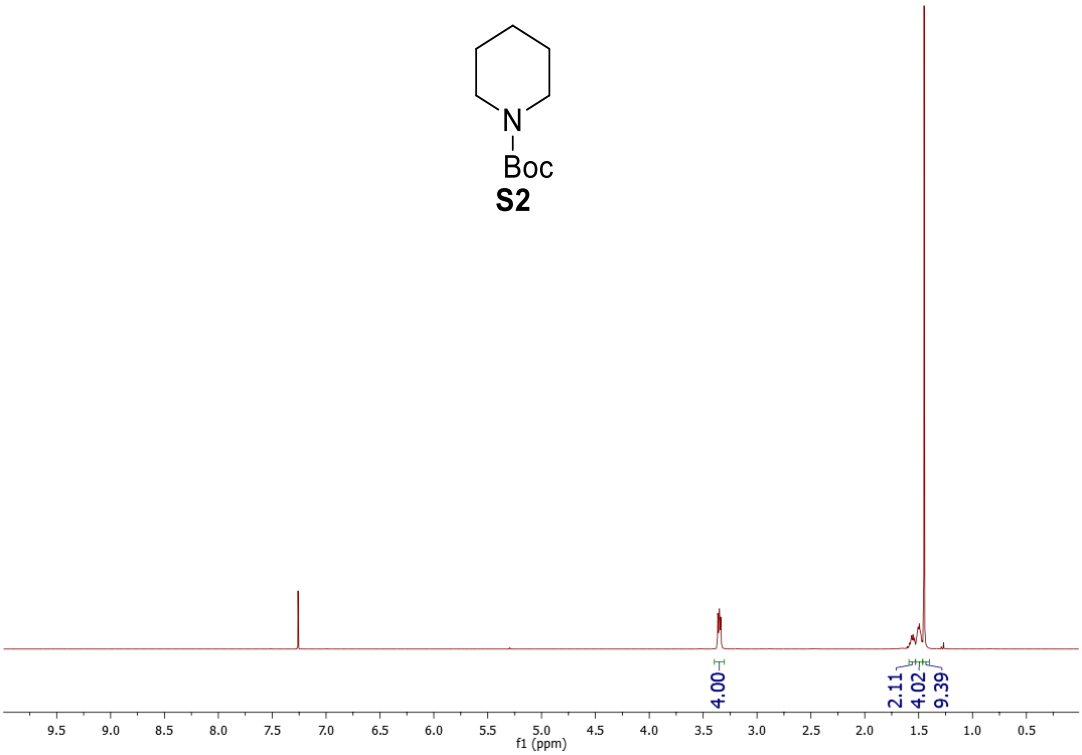
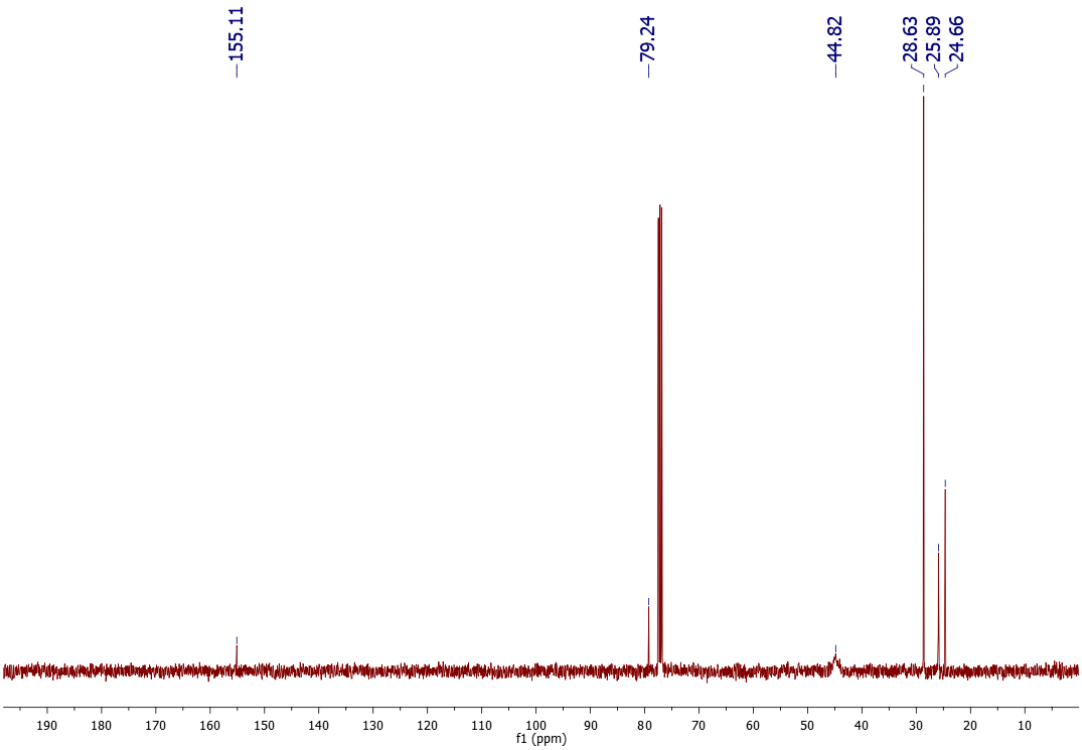
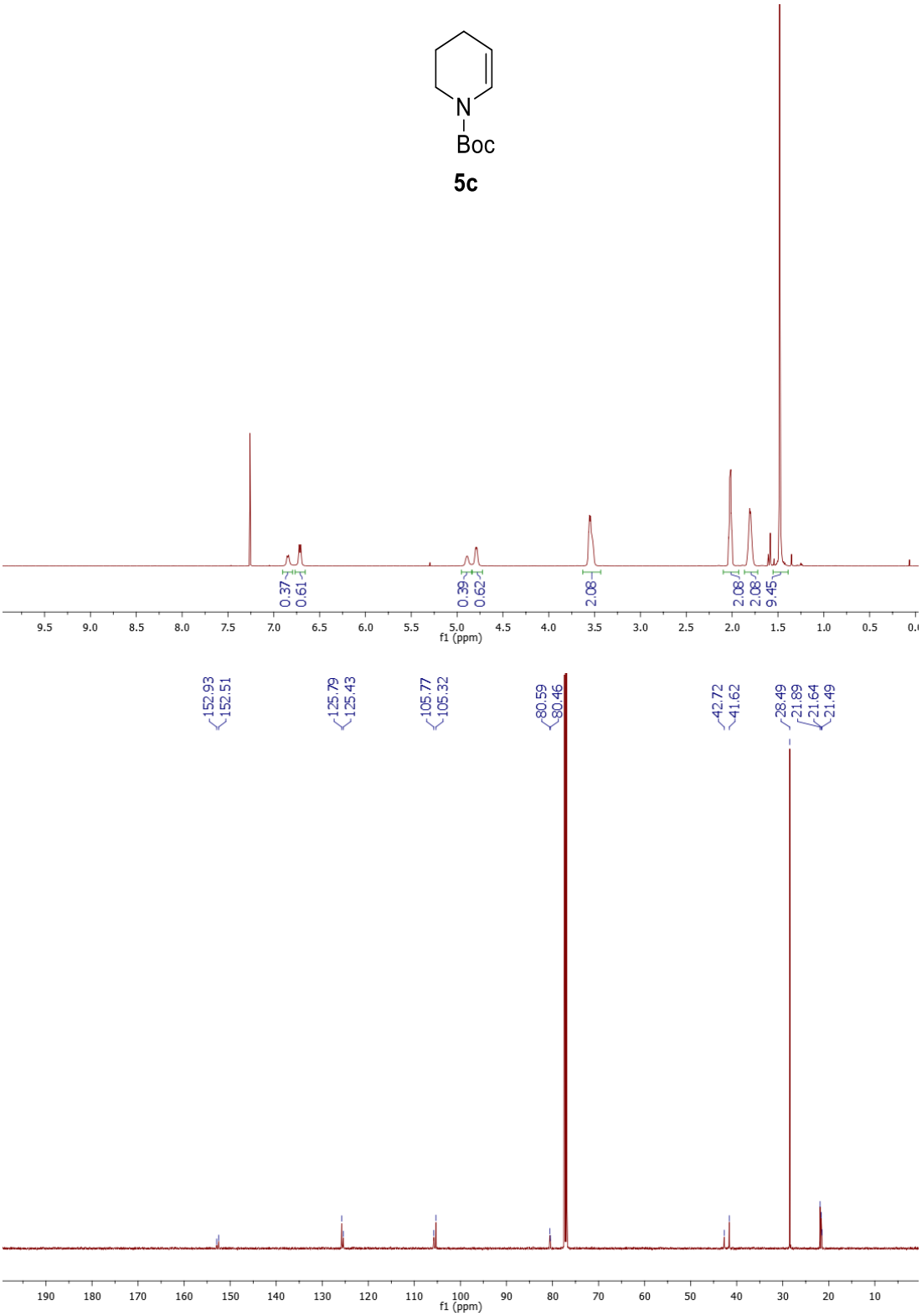
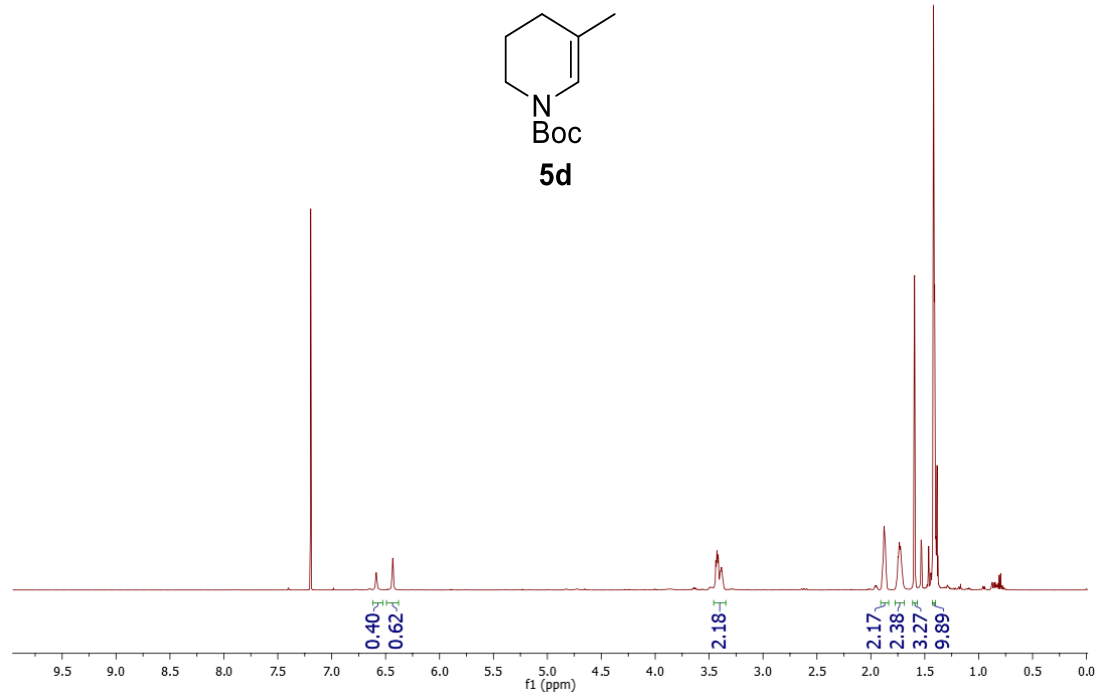




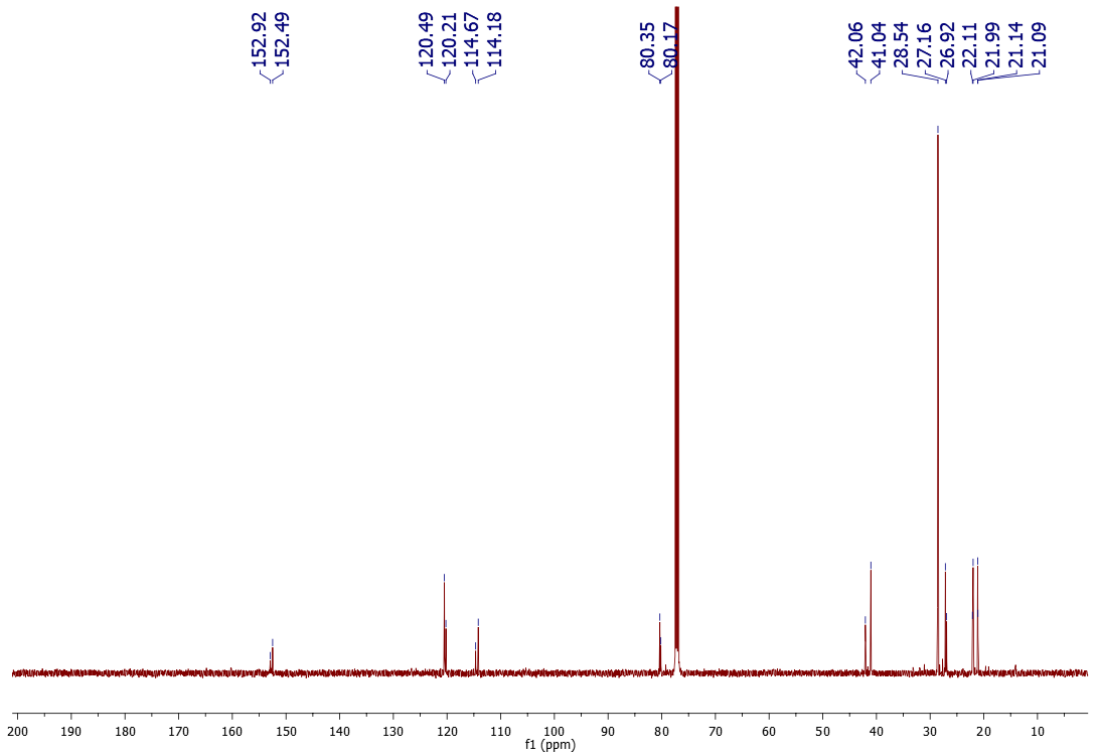
tert-Butyl 3,4-dihydropyridine-1(2*H*)-carboxylate 5c



tert-Butyl 3-((2-ethoxy-2-oxoethyl)amino)-3-methylpiperidine-1-carboxylate 5d



5d



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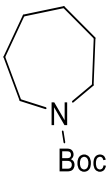
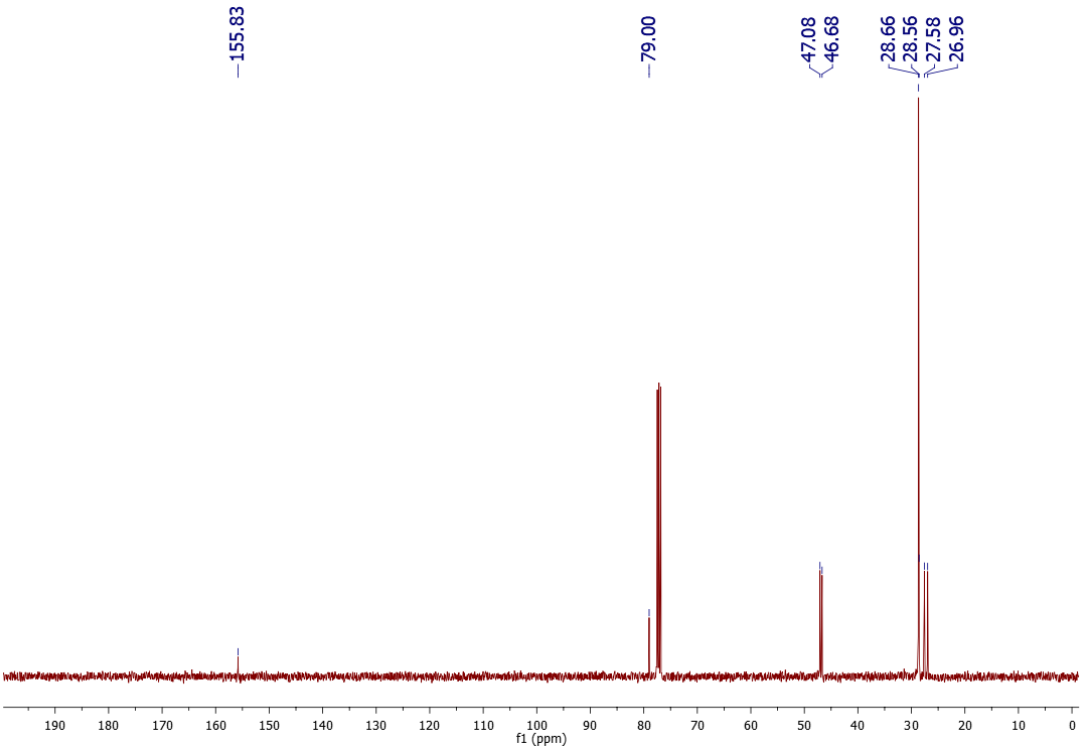


S3



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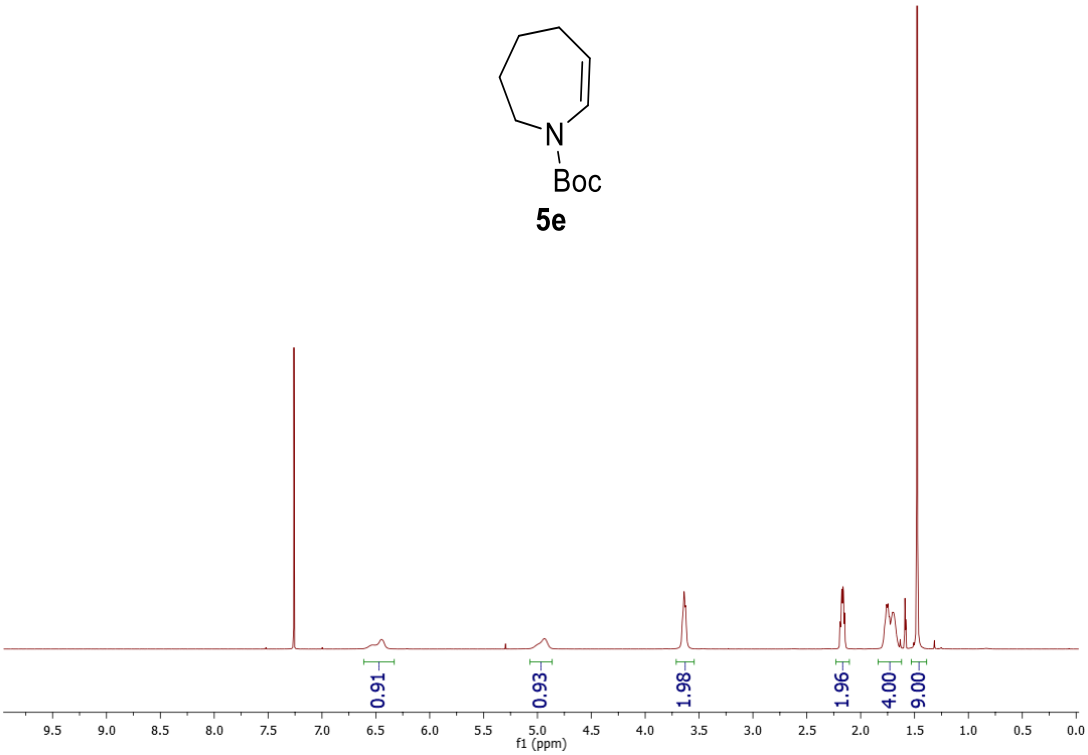

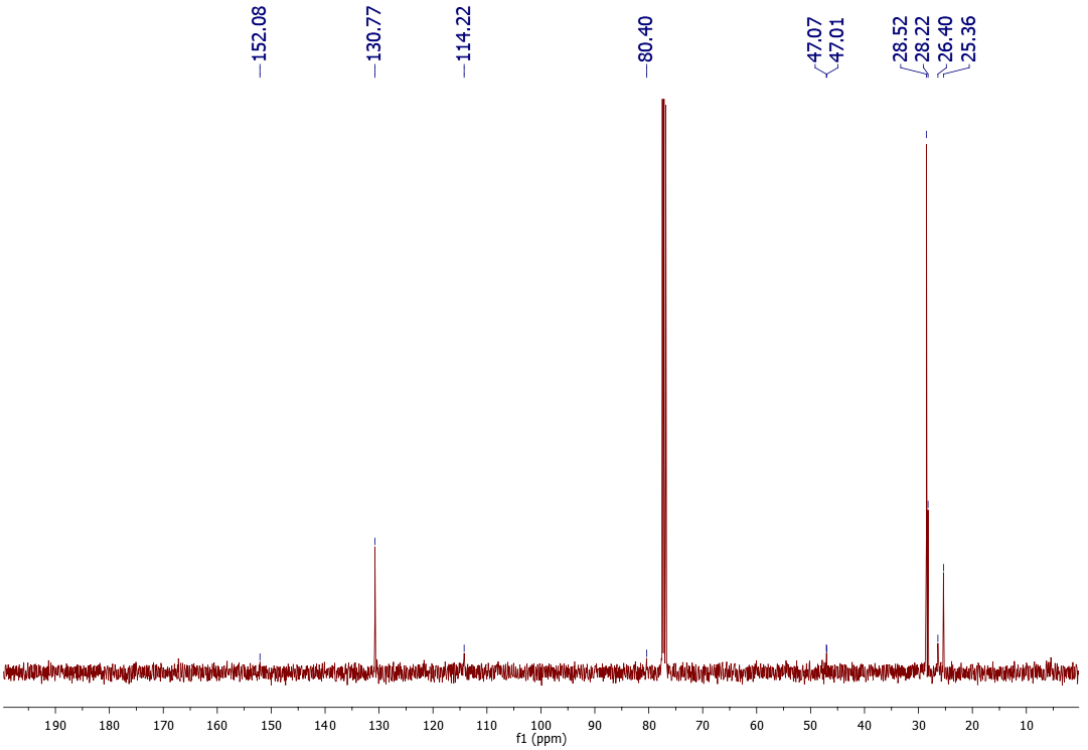

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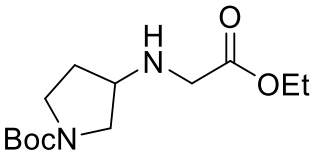
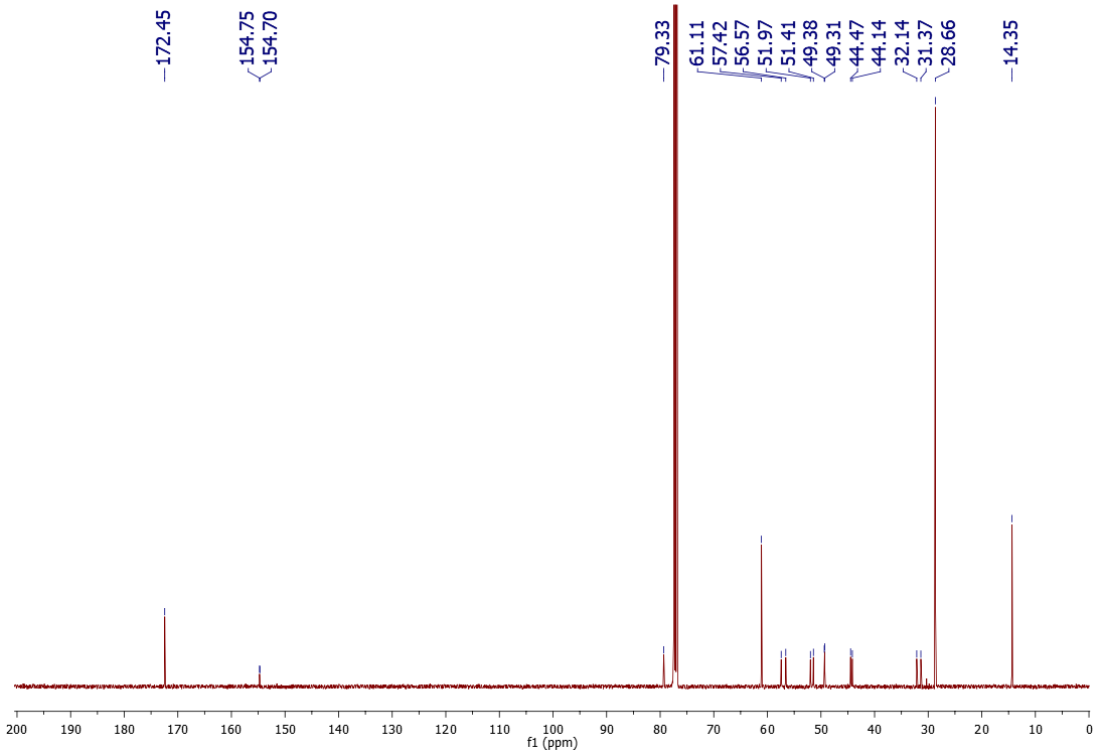


S4



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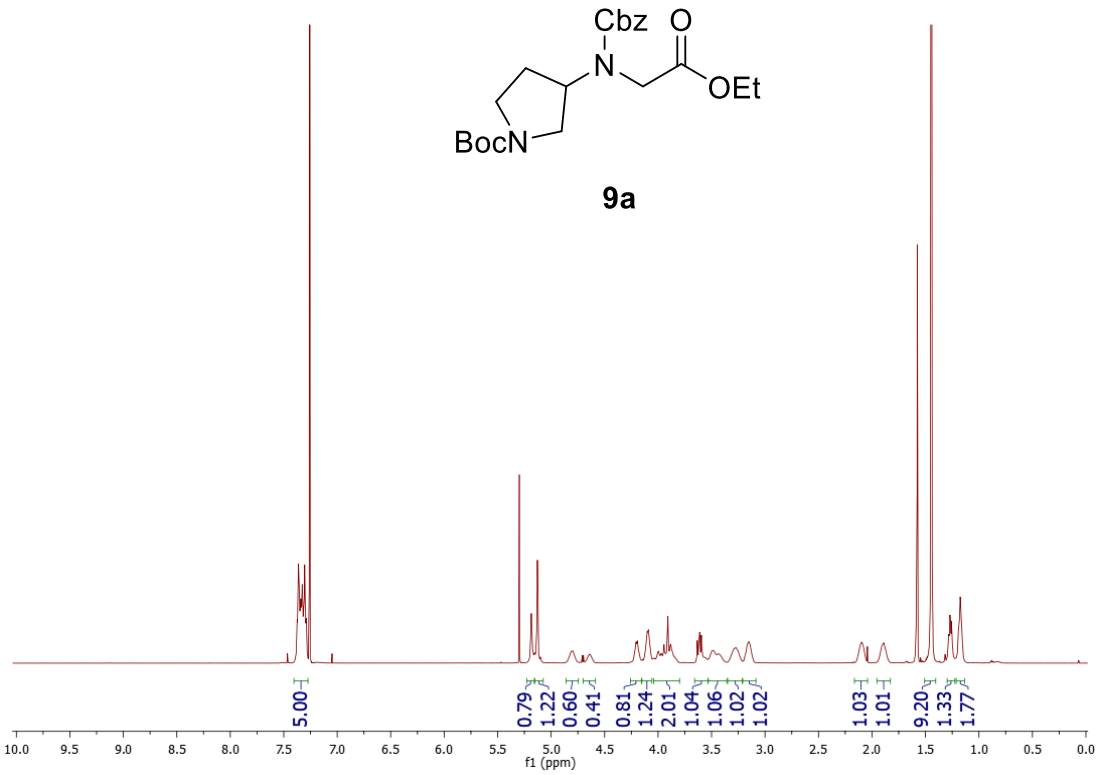

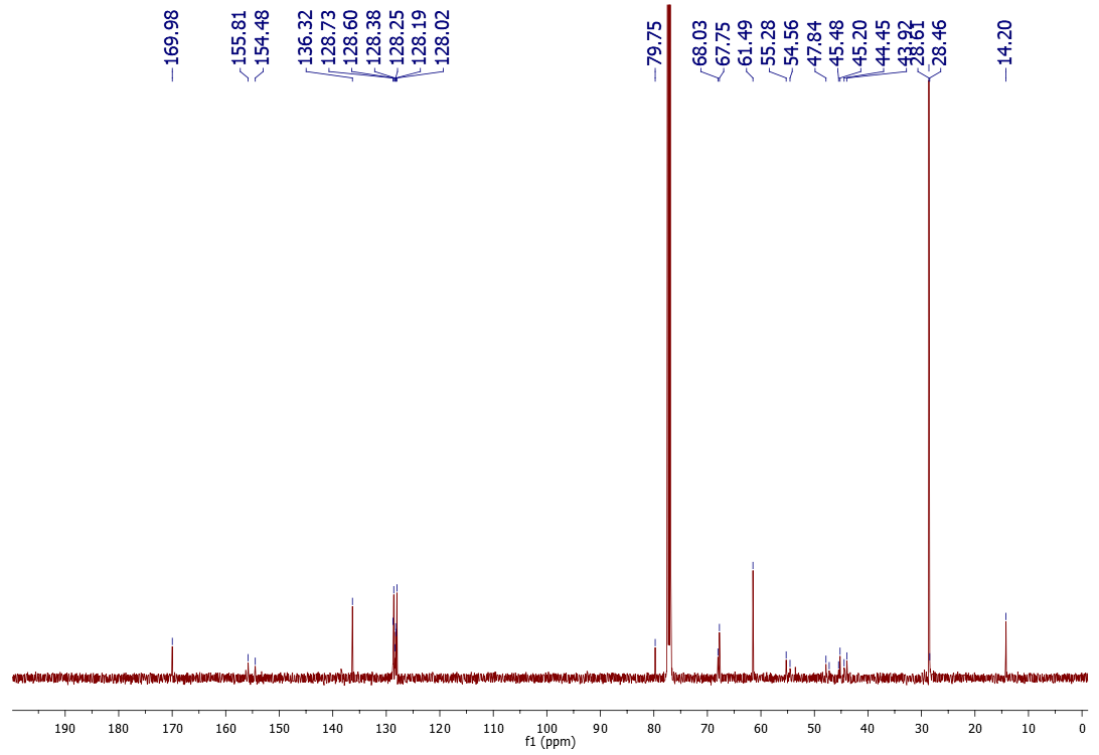

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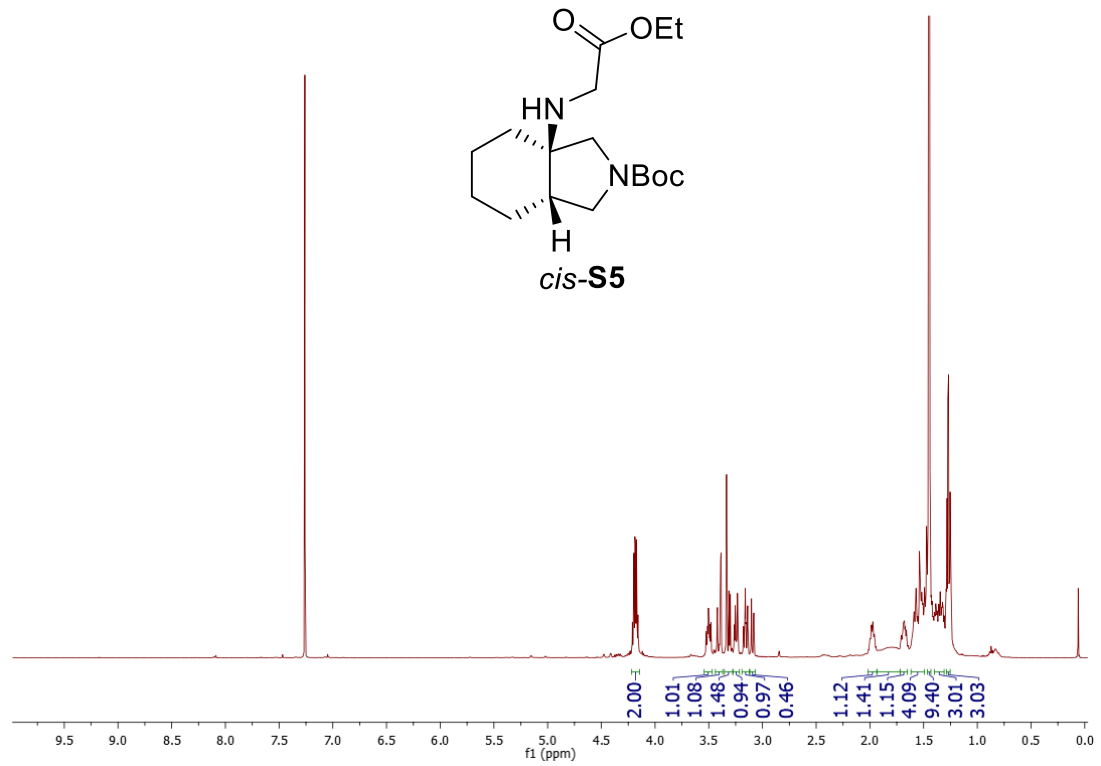
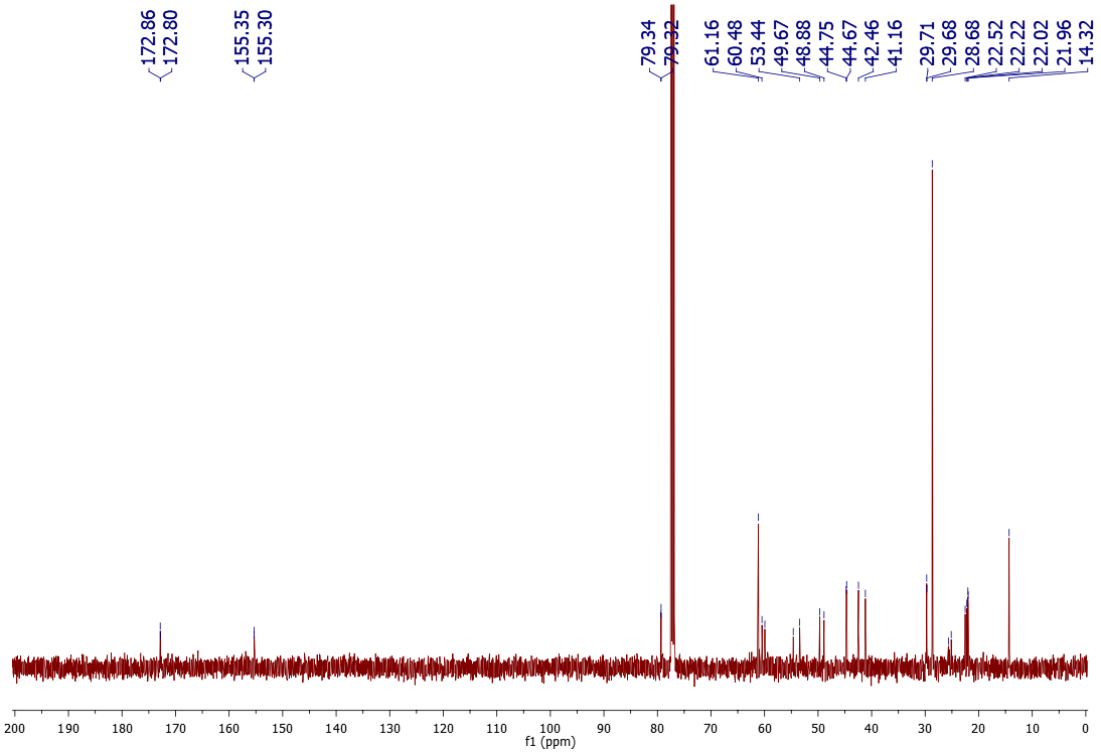
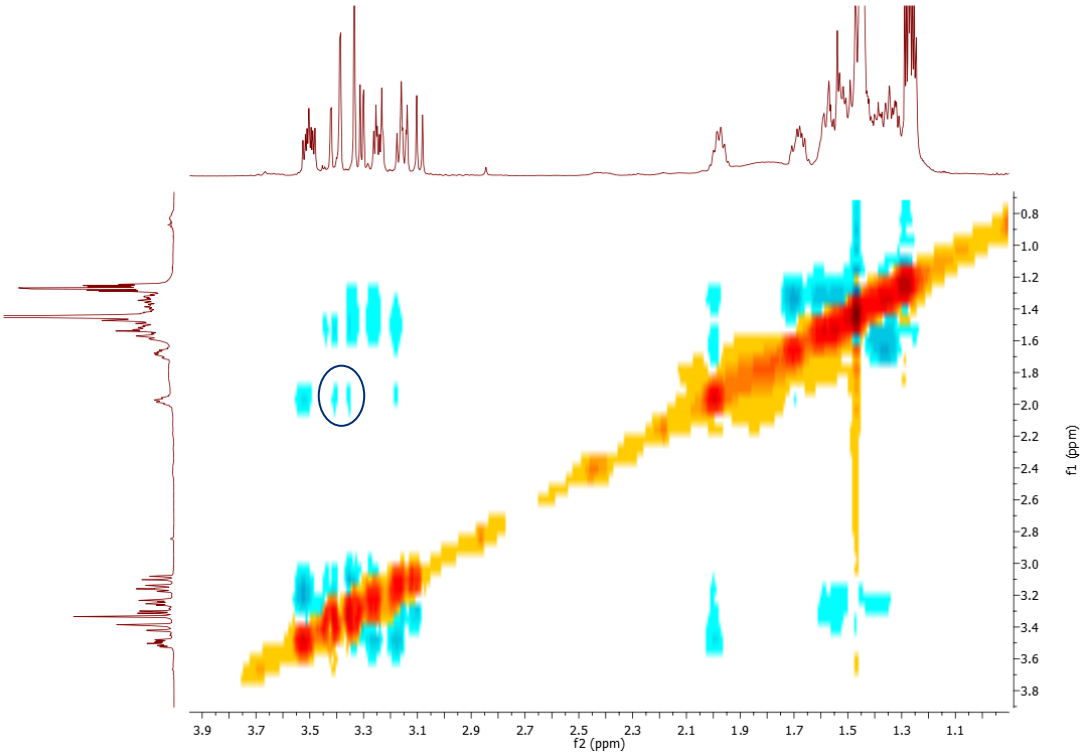


cis-**S5**

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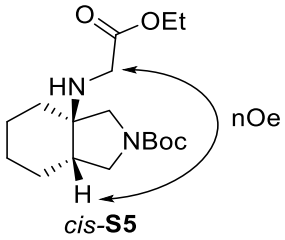
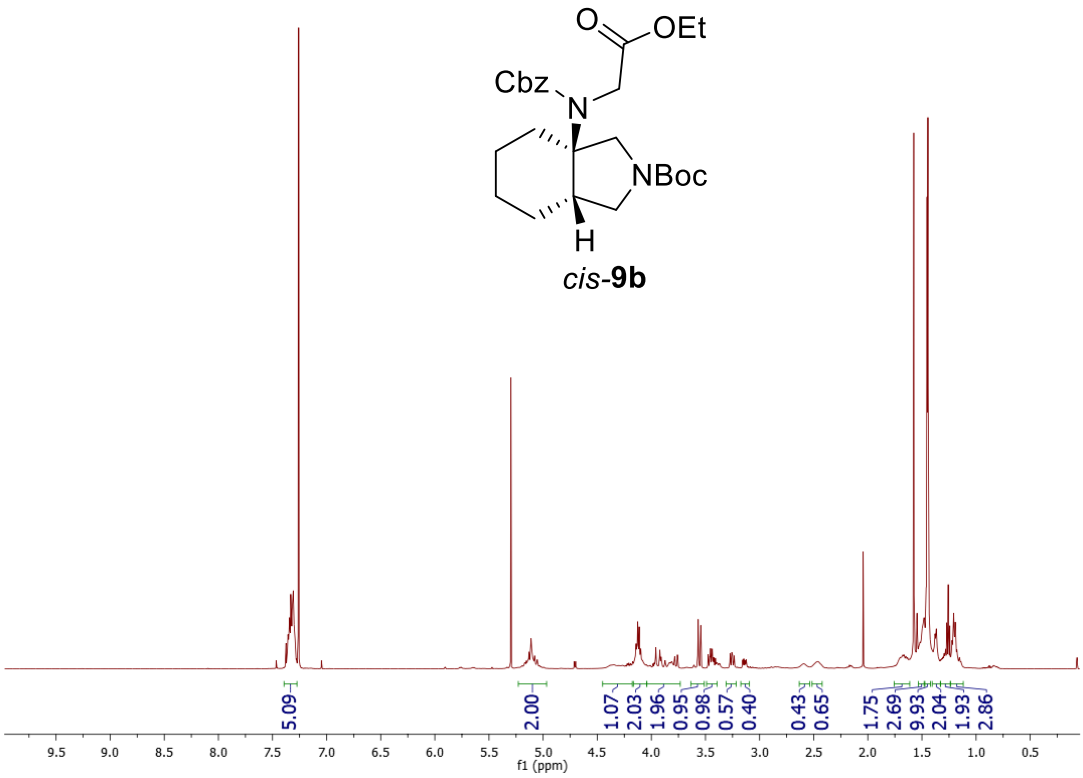
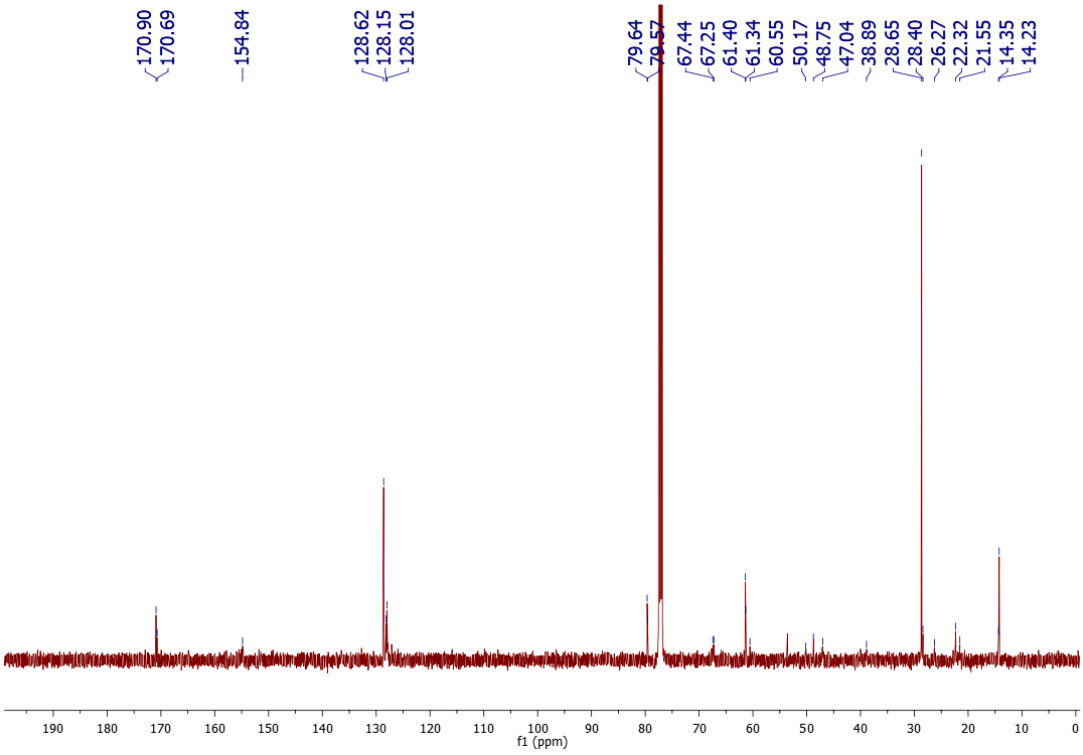
1.2
1.4
1.6
1.8
2.0
2.2
2.4
2.6
2.8
3.0
3.2
3.4
3.6
3.8
f1 (ppm)
3.9
3.7
3.5
3.3
3.1
2.9
2.7
2.5
2.3
2.1
1.9
1.7
1.5
1.3
1.1
f2 (ppm)


O
OEt
HN
NBoc
H
nOe

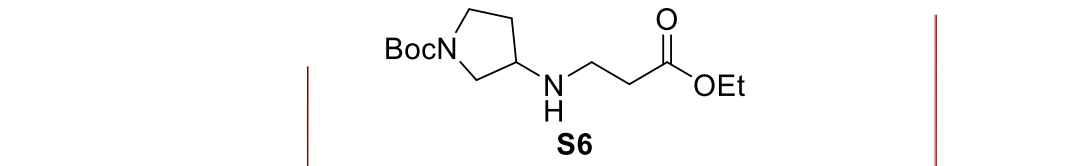
cis-**S5**

***tert*-Butyl 3a-(((benzyloxy)carbonyl)(2-ethoxy-2-oxoethyl)amino)octahydro-2H-isoindole-2-carboxylate *cis*-9b**

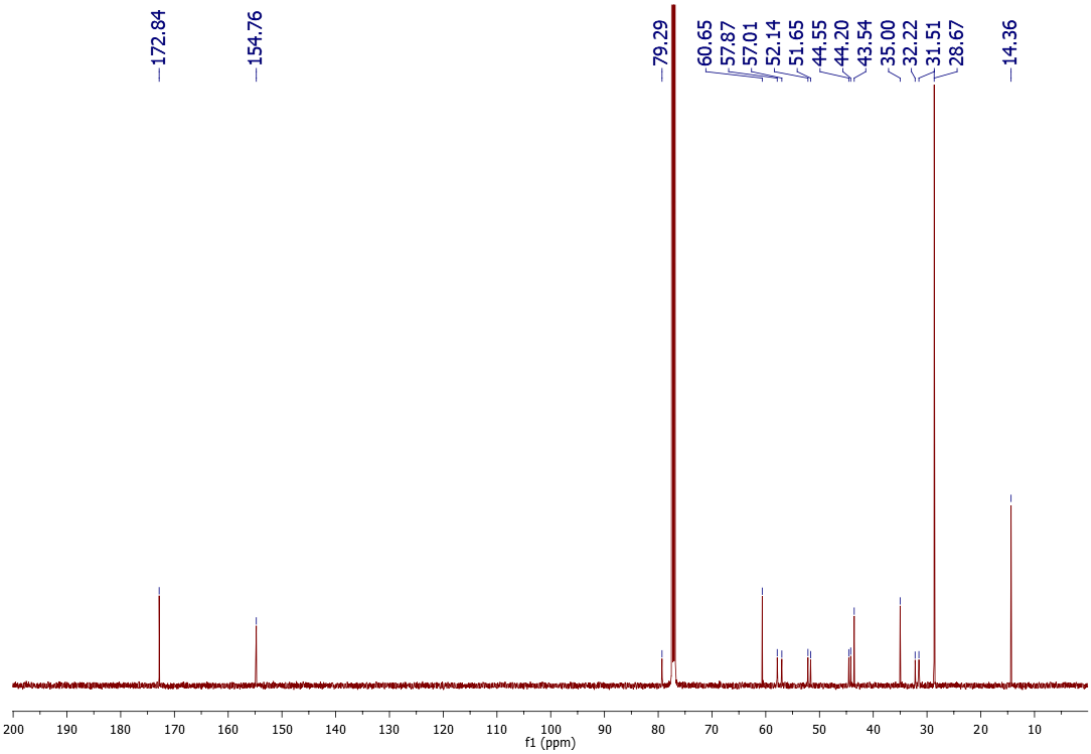




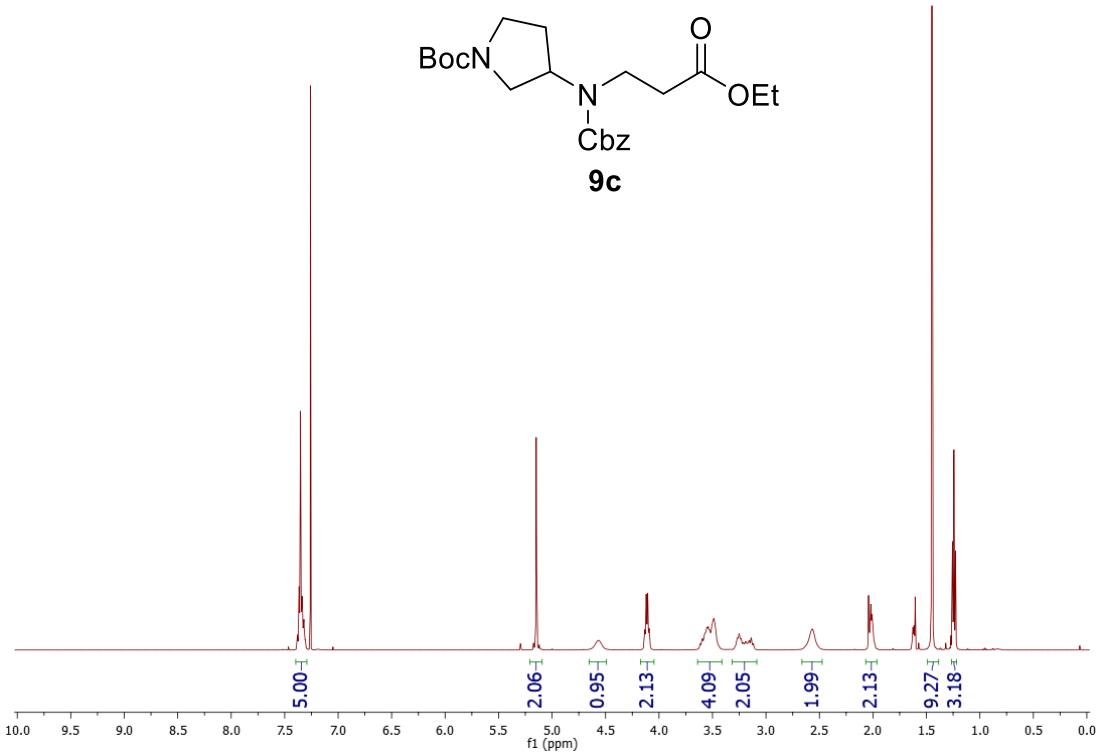
***tert*-Butyl 3-((3-ethoxy-3-oxopropyl)amino)pyrrolidine-1-carboxylate S6**

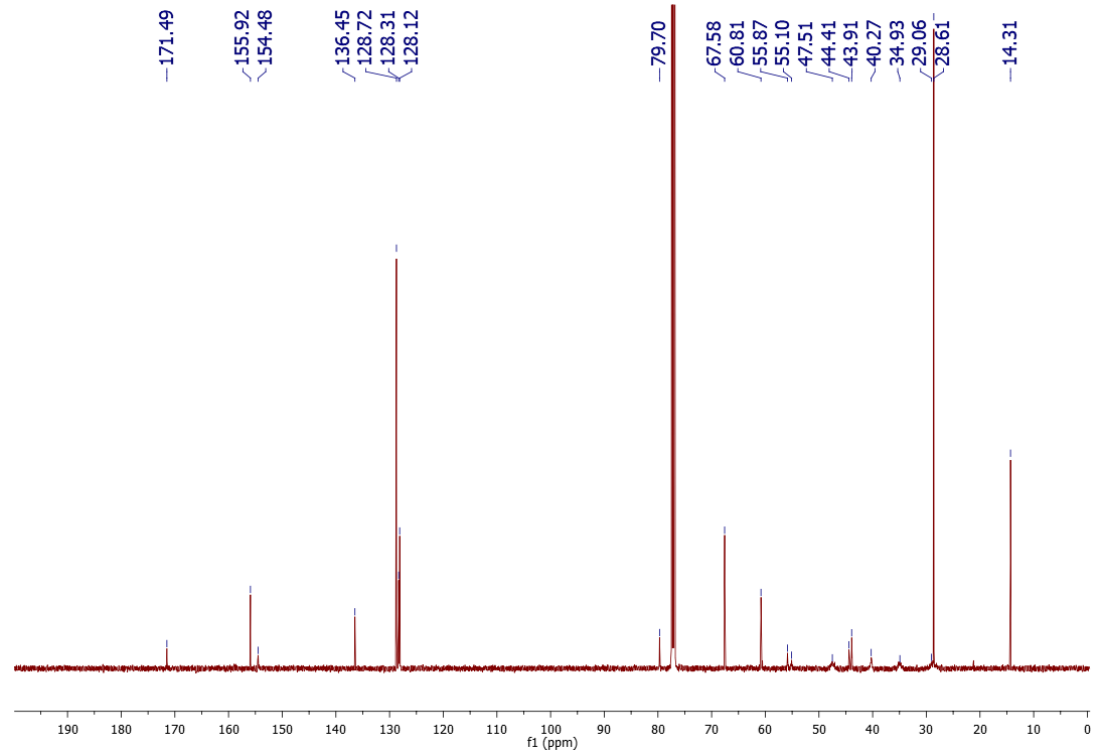


S6

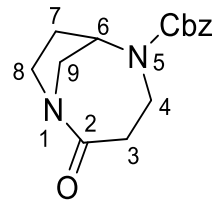


***tert*-Butyl 3-((3-ethoxy-3-oxopropyl)amino)pyrrolidine-1-carboxylate 9c**

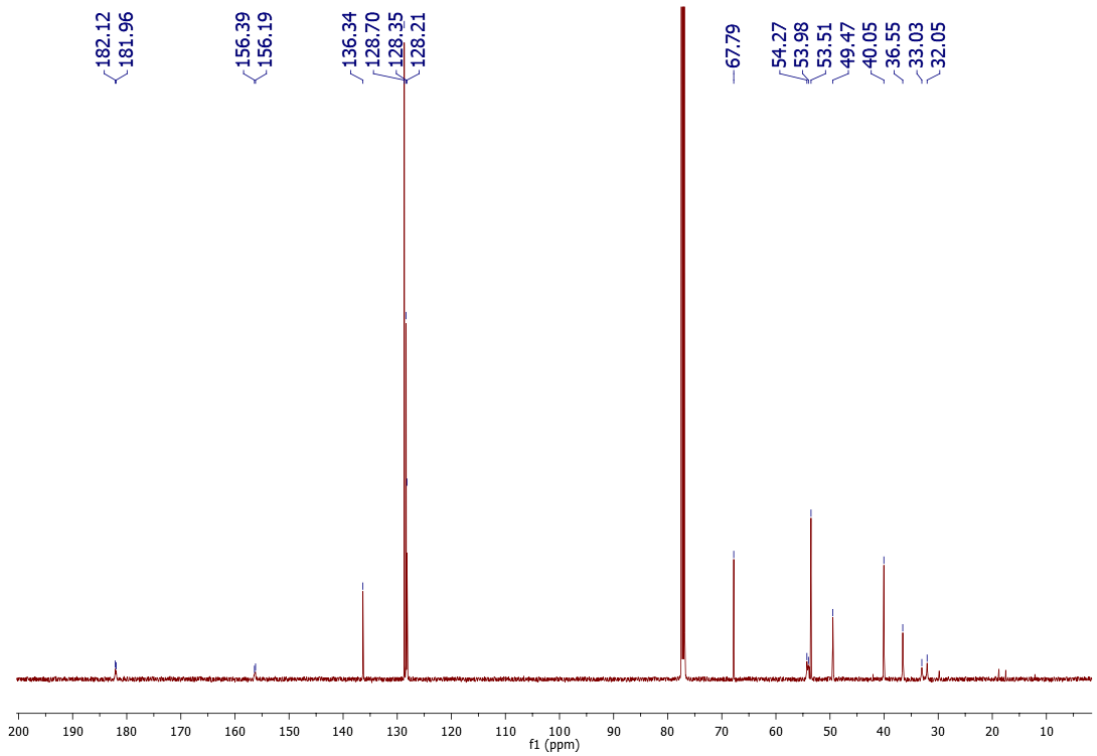




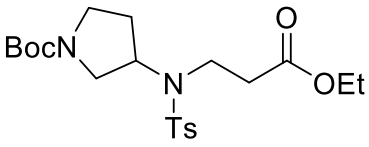
Benzyl 2-oxo-1,5-diazabicyclo[4.2.1]nonane-5-carboxylate 6c



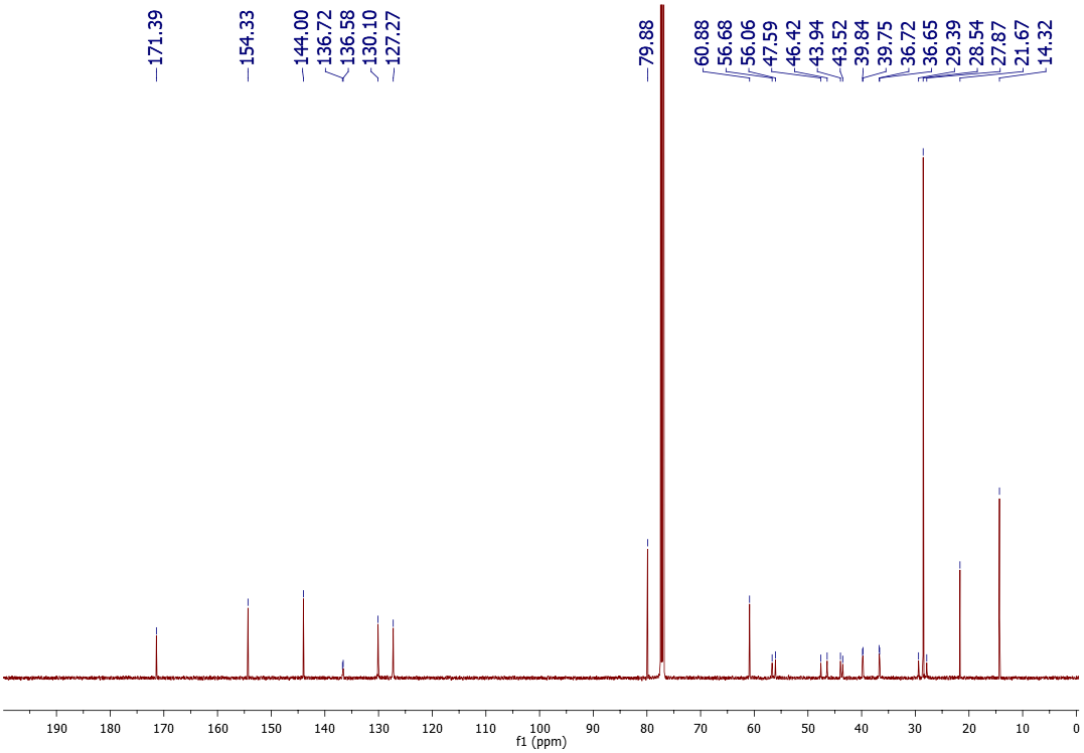
6c



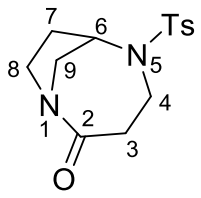
***tert*-Butyl 3-((*N*-(3-ethoxy-3-oxopropyl)-4-methylphenyl)sulfonamido)pyrrolidine-1-carboxylate 9d**



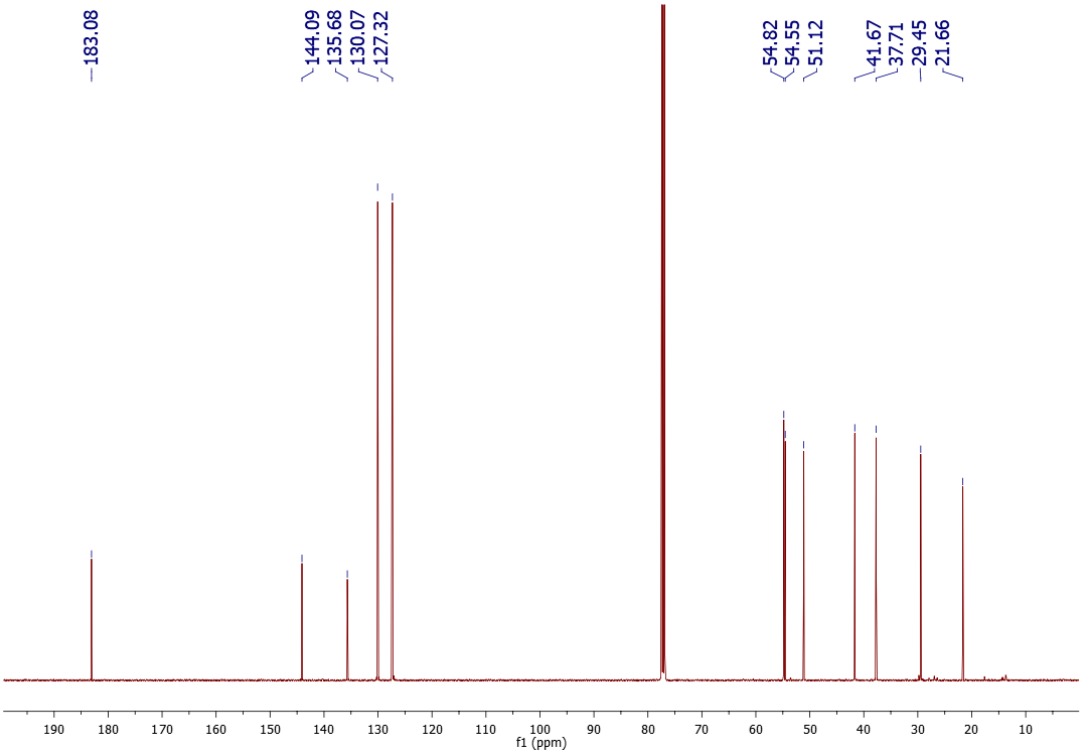
9d



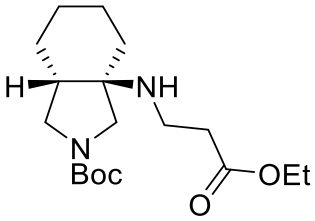
5-Tosyl-1,5-diazabicyclo[4.2.1]nonan-2-one 6d



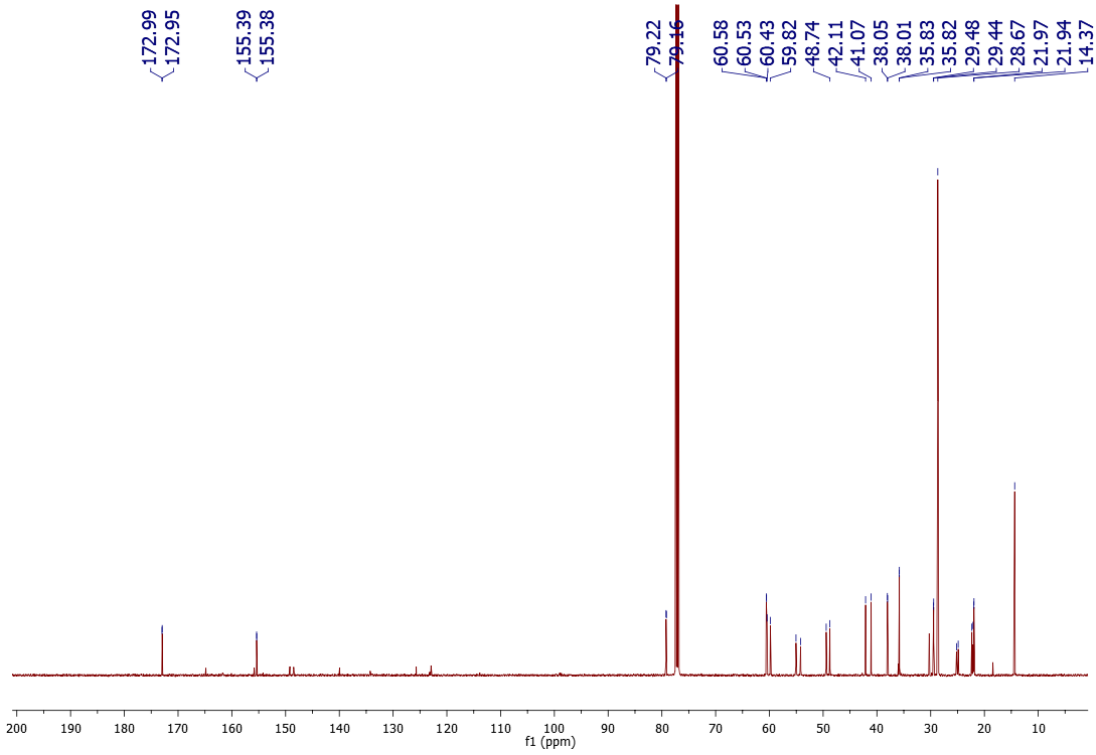
6d

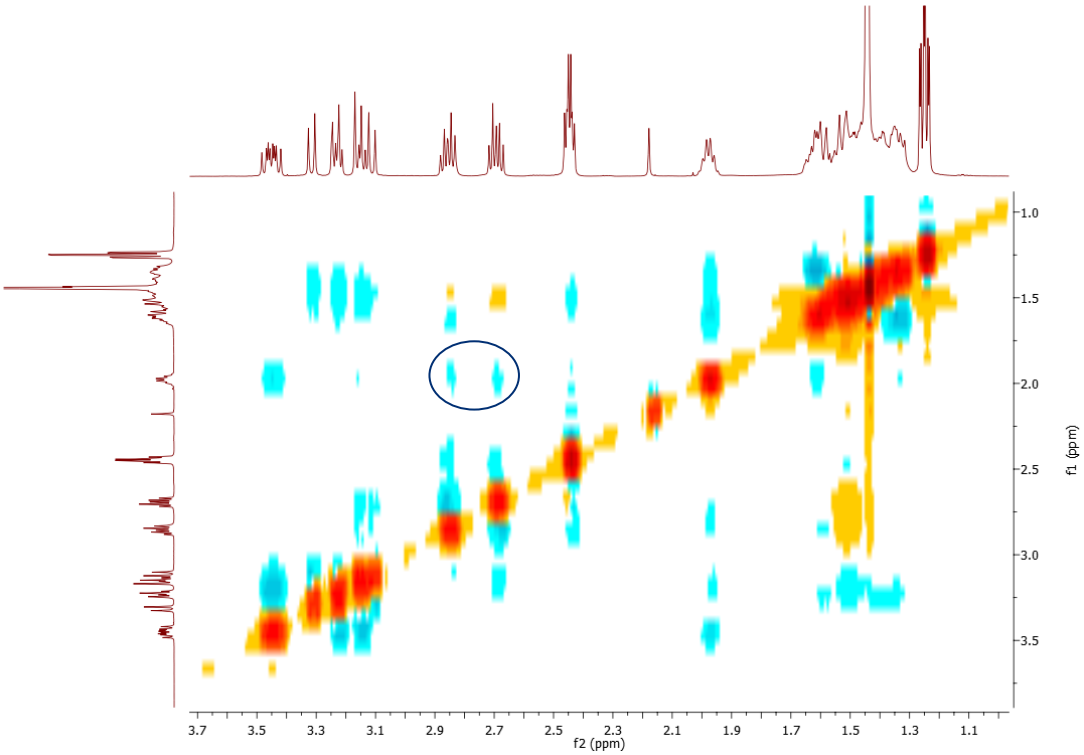


***tert*-Butyl 3a-((3-ethoxy-3-oxopropyl)amino)octahydro-2H-isoindole-2-carboxylate *cis*-S7**



cis-**S7**

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1.5
2.0
2.5
3.0
3.5
f1 (ppm)
3.7
3.5
3.3
3.1
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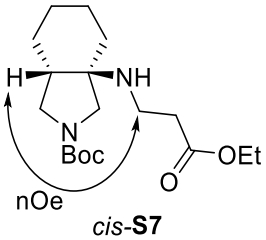
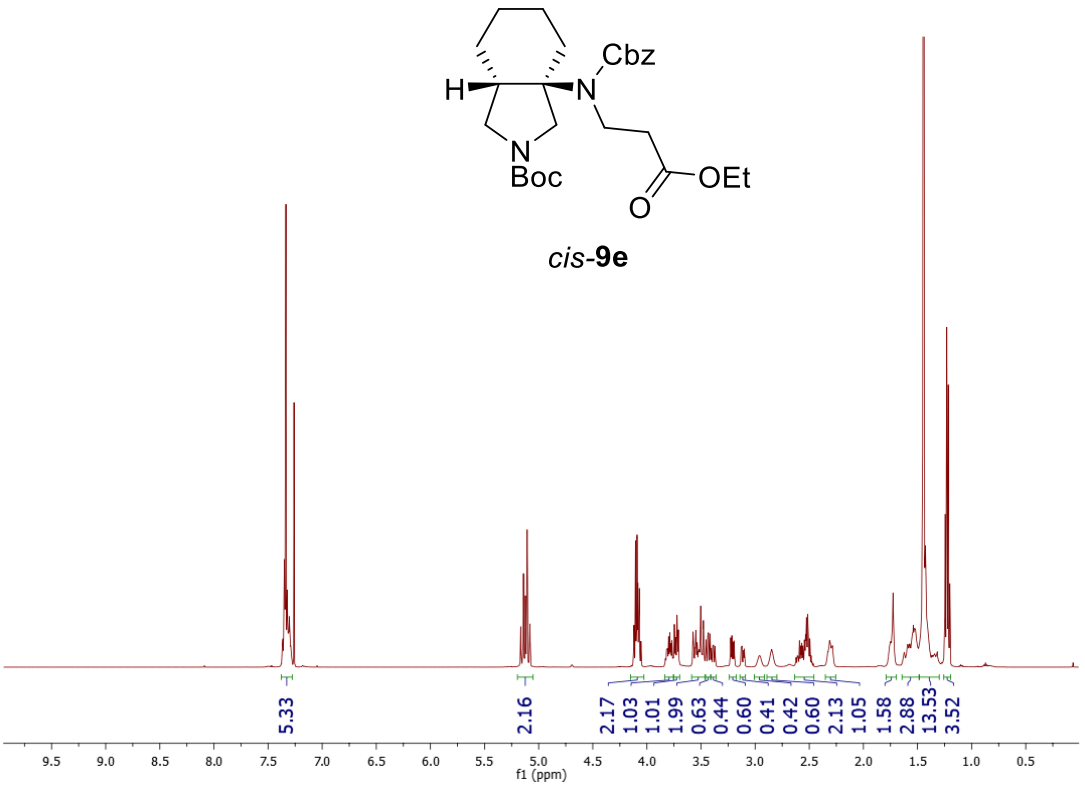
1.7
1.5
1.3
1.1
f2 (ppm)

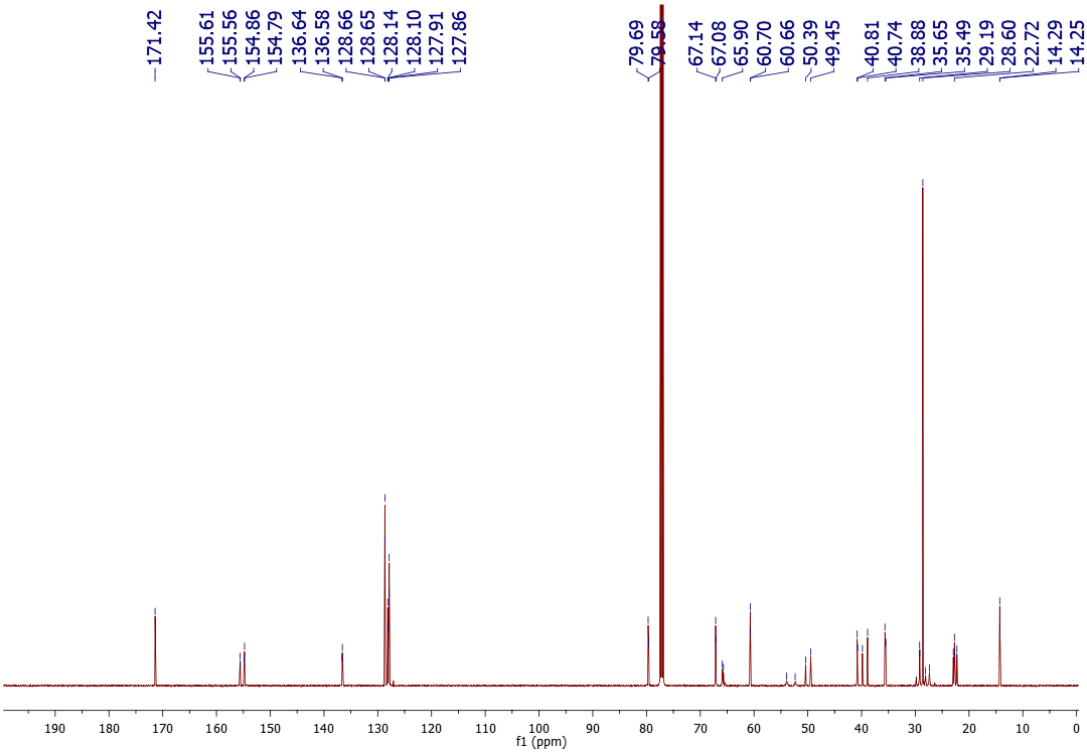

H
NH
N
Boc
OEt
O
nOe

cis-**S7**

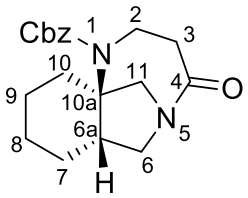
tert-Butyl 3a-(((benzyloxy)carbonyl)(3-ethoxy-3-oxopropyl)amino)octahydro-2H-isoindole-2-carboxylate _cis_-9e



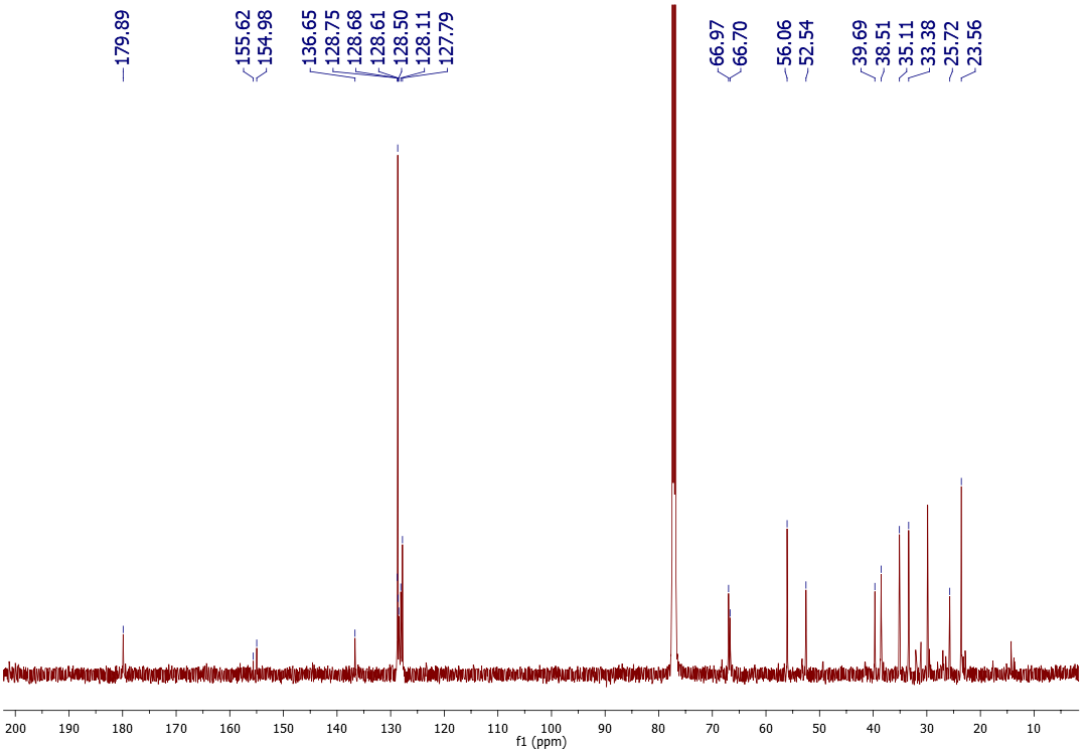
cis-**9e**



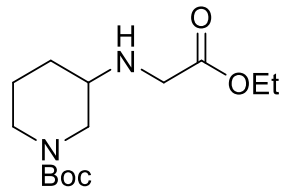
Benzyl (6aS*,10aR*)-4-oxooctahydro-5,10a-methanobenzo[b][1,5]diazocine-1(2H)-carboxylate 6e



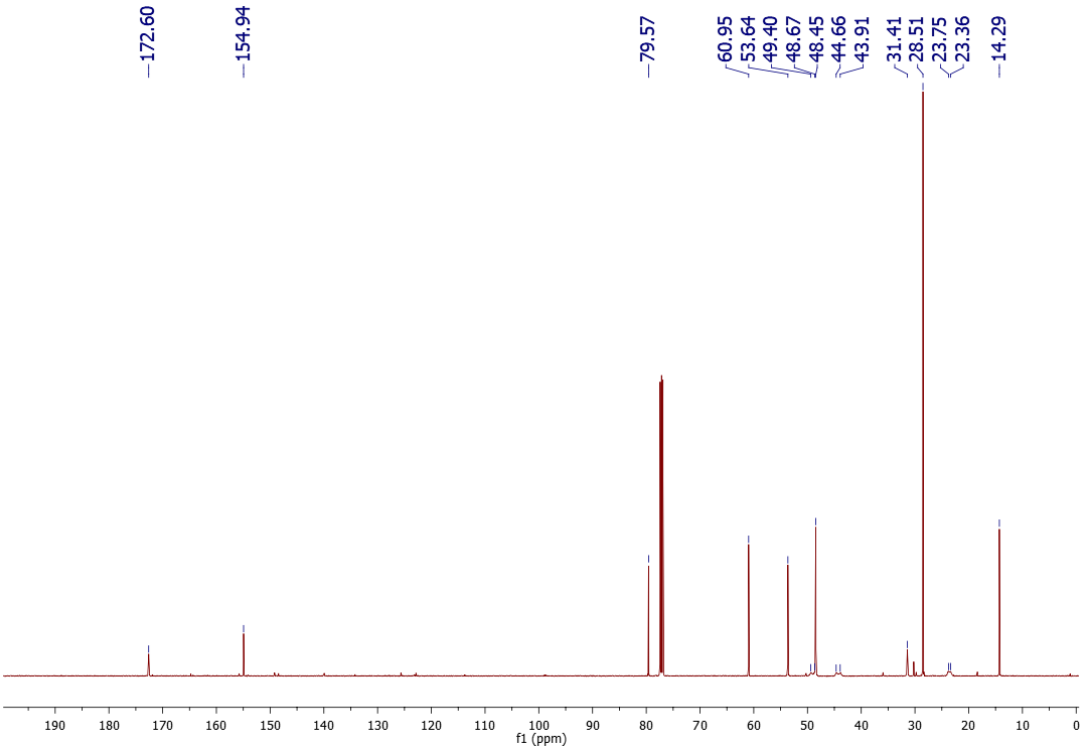
6e



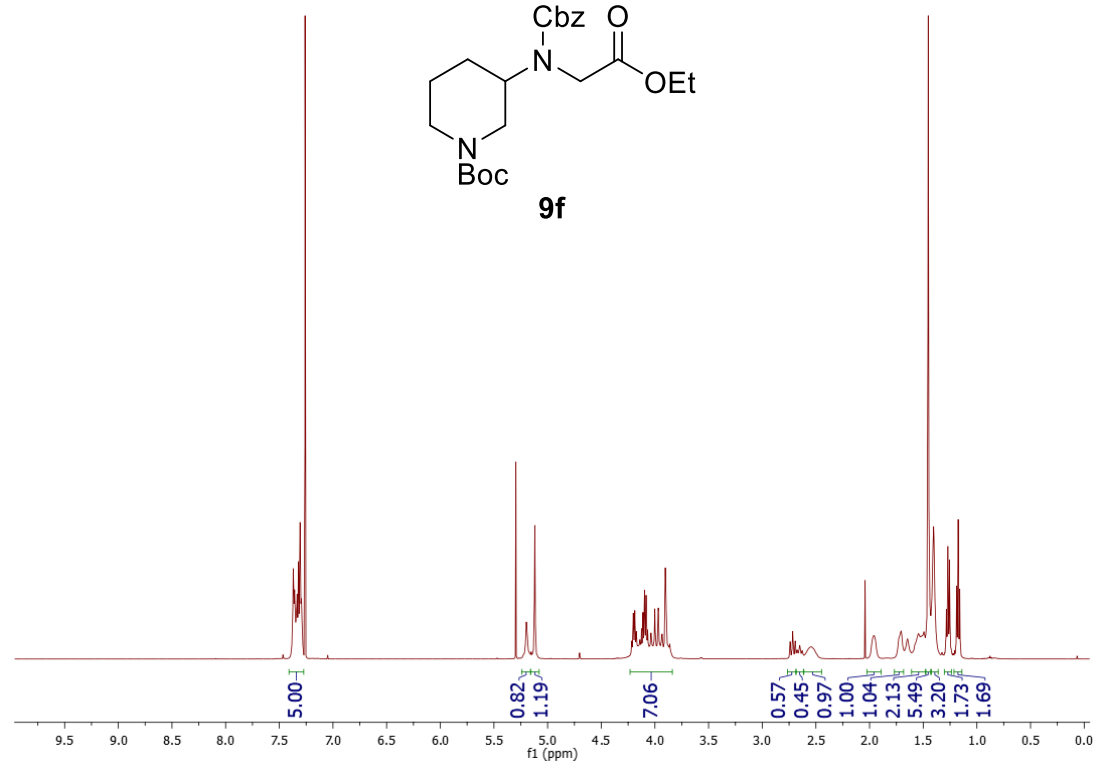
tert-Butyl 3-((2-ethoxy-2-oxoethyl)amino)piperidine-1-carboxylate S8



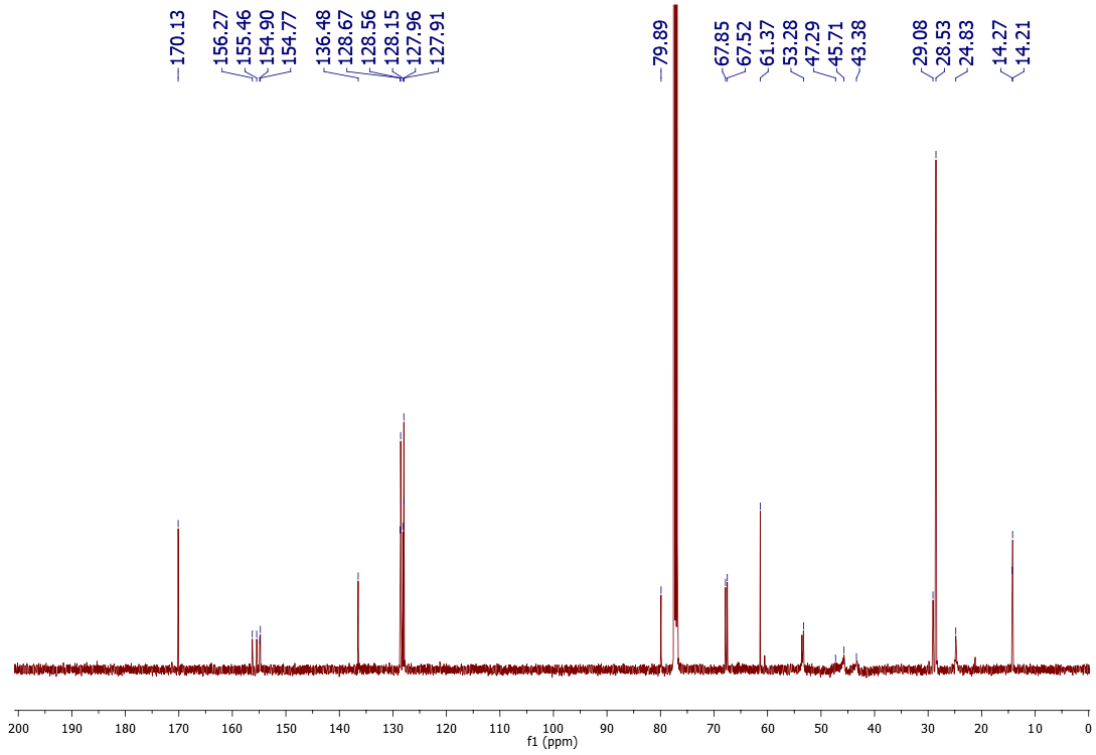
S8



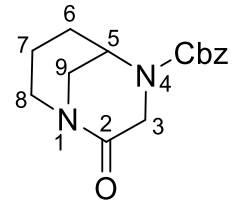
***tert*-Butyl 3-(((benzyloxy)carbonyl)(2-ethoxy-2-oxoethyl)amino)piperidine-1-carboxylate 9f**



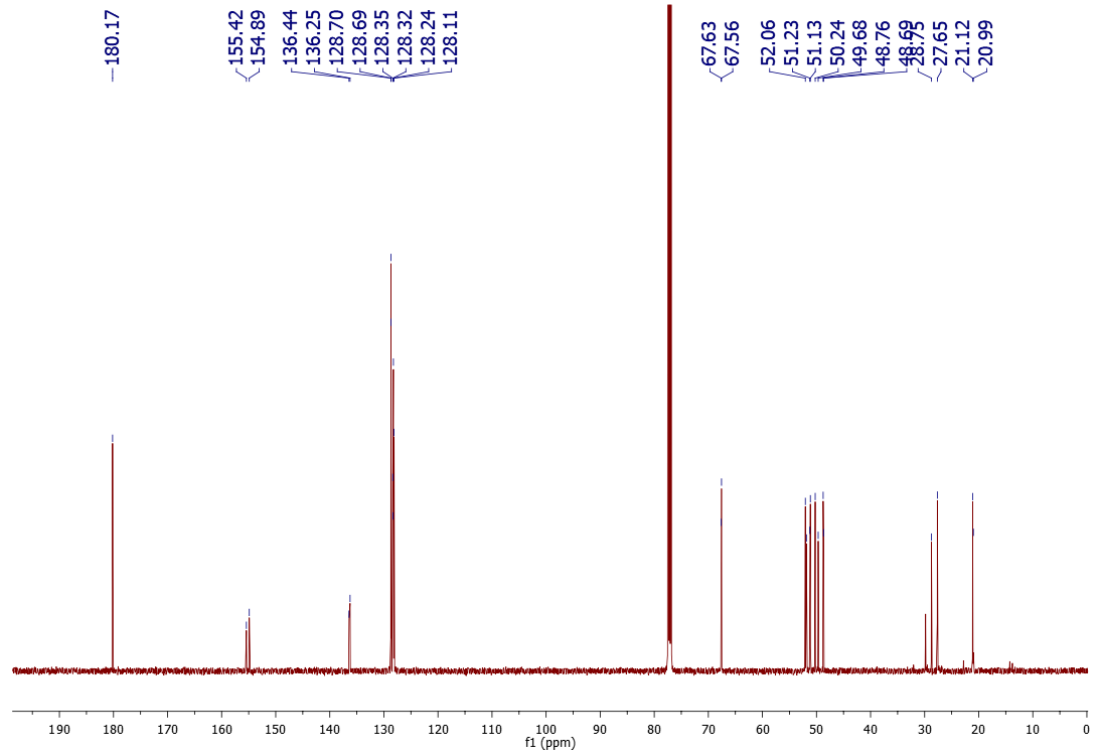
9f



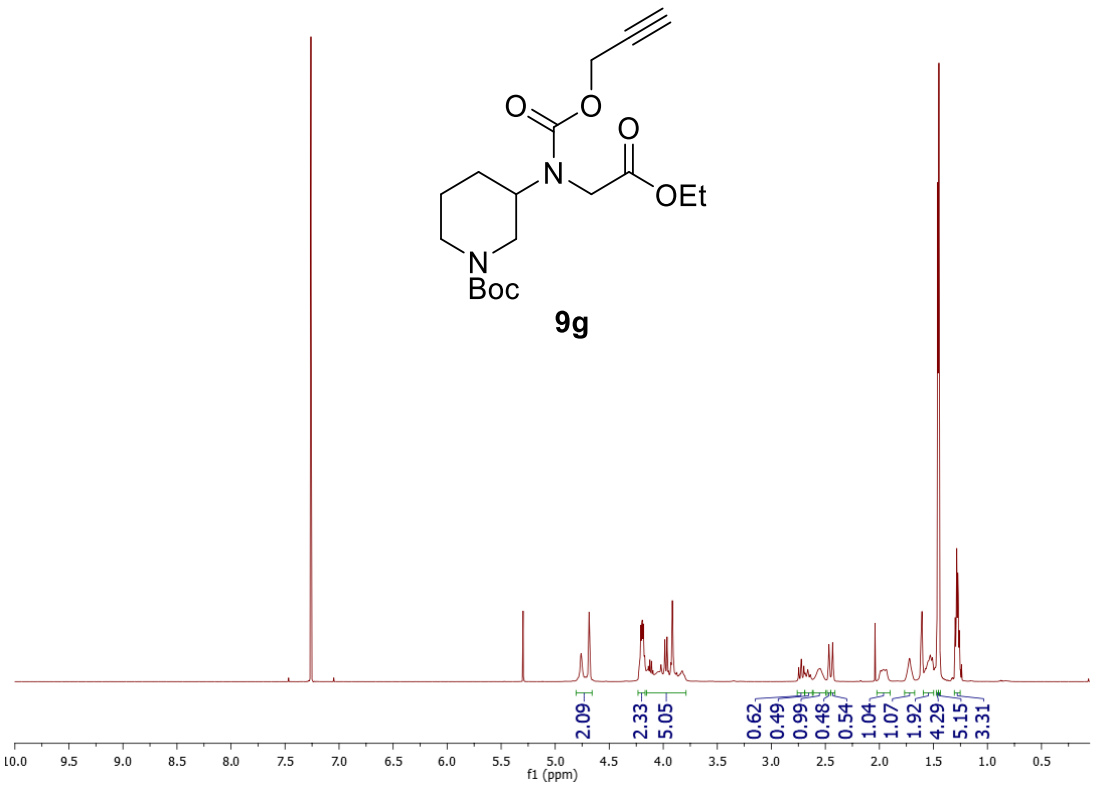
Benzyl 2-oxo-1,4-diazabicyclo[3.3.1]nonane-4-carboxylate 6f

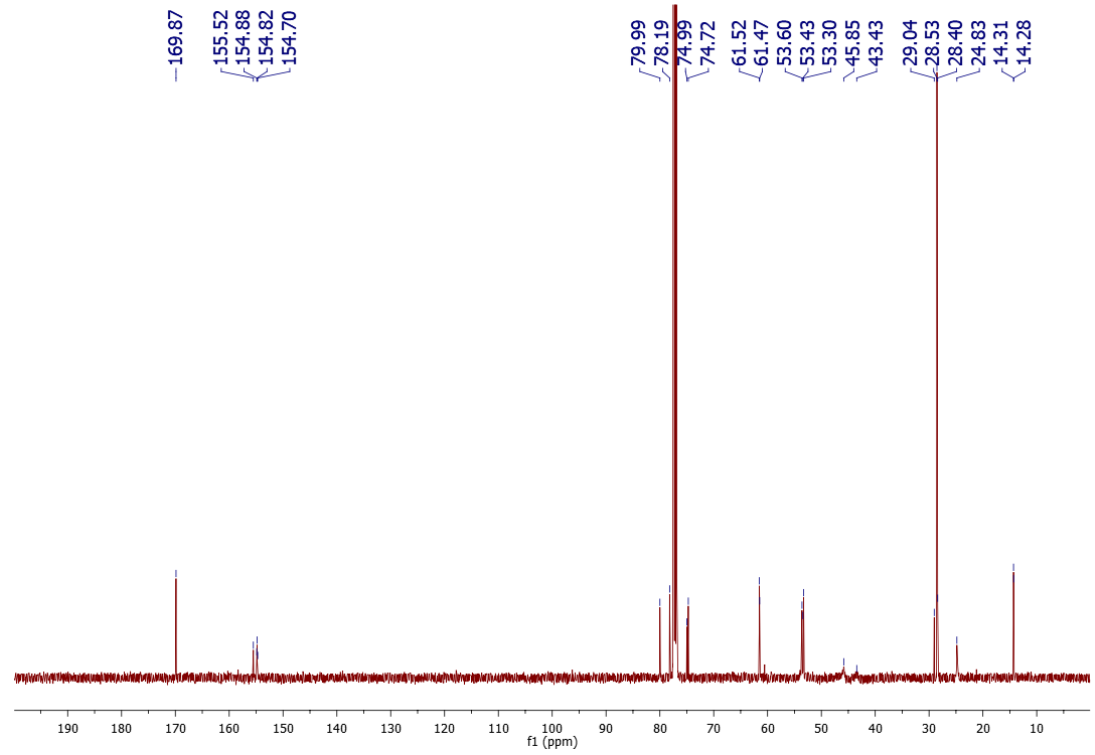


6f

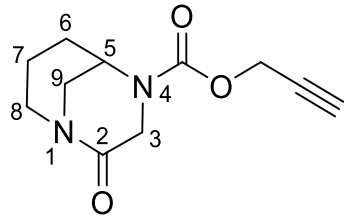


***tert*-Butyl 3-((2-ethoxy-2-oxoethyl)((prop-2-yn-1-yloxy)carbonyl)amino)piperidine-1-carboxylate 9g**

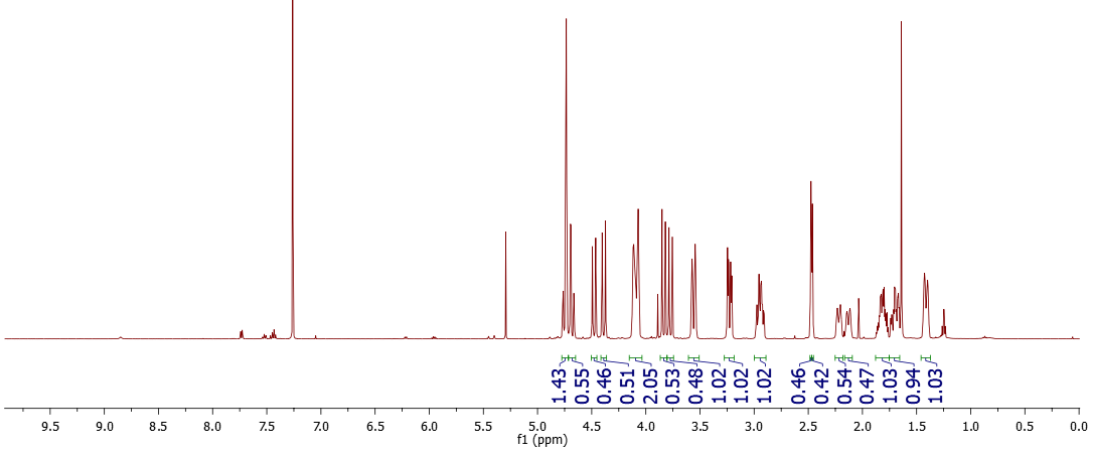


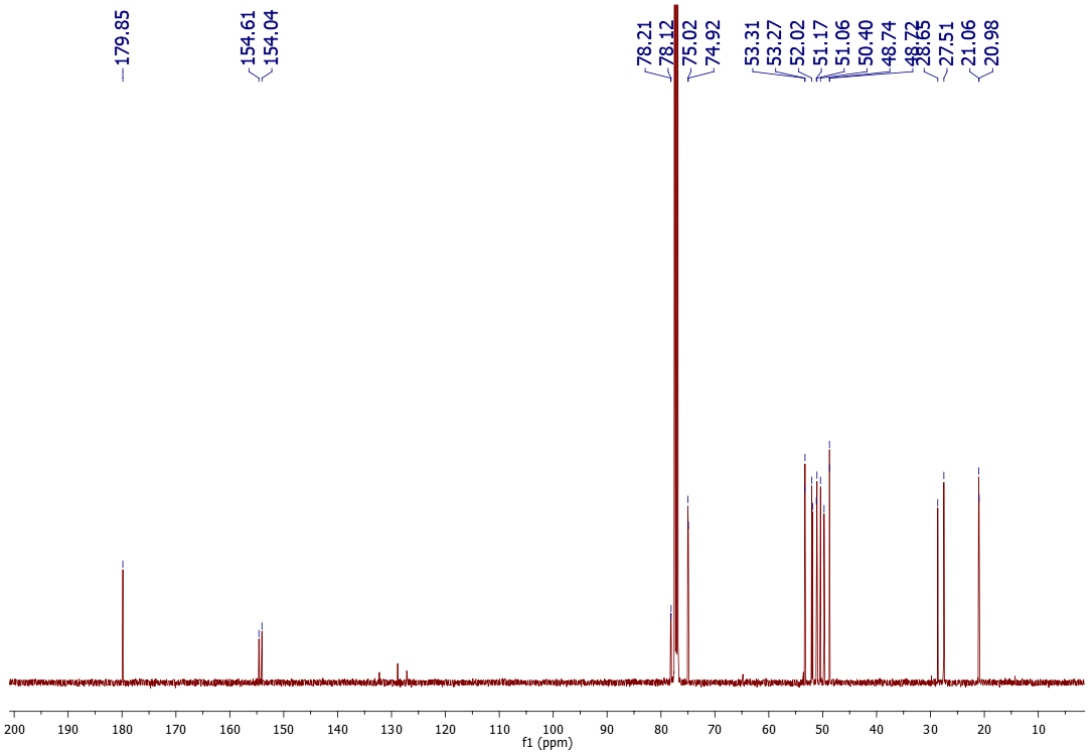


Prop-2-yn-1-yl 2-oxo-1,4-diazabicyclo[3.3.1]nonane-4-carboxylate 6g

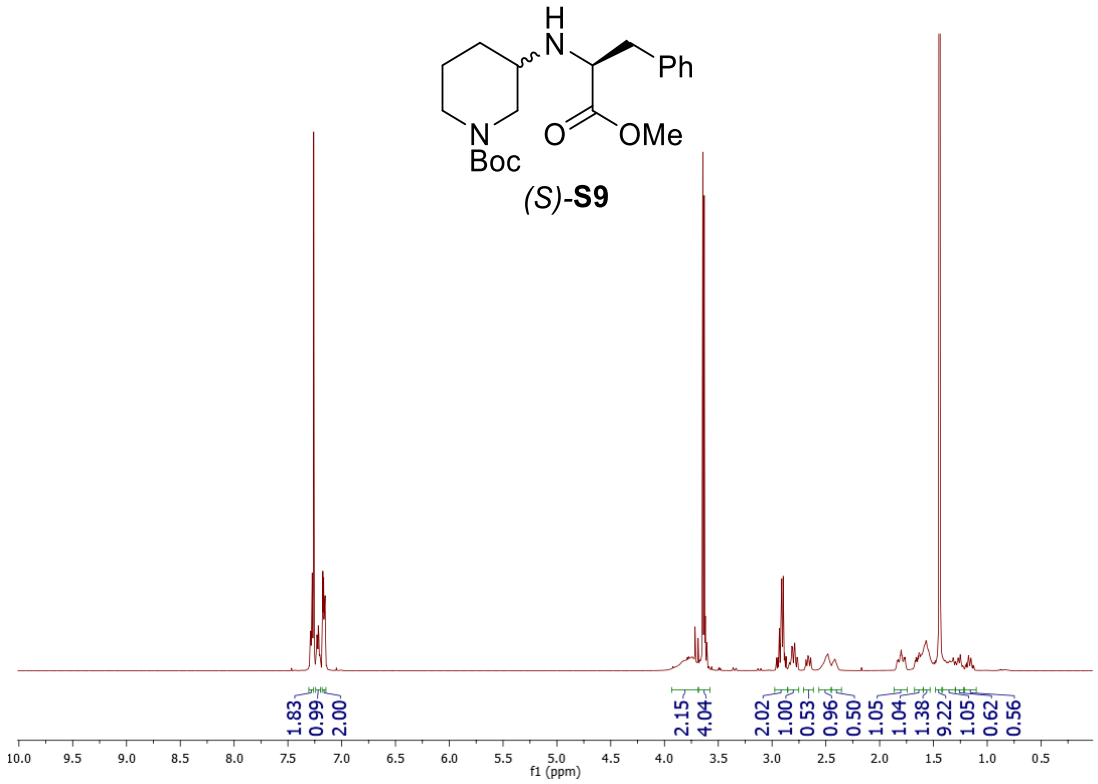


6g

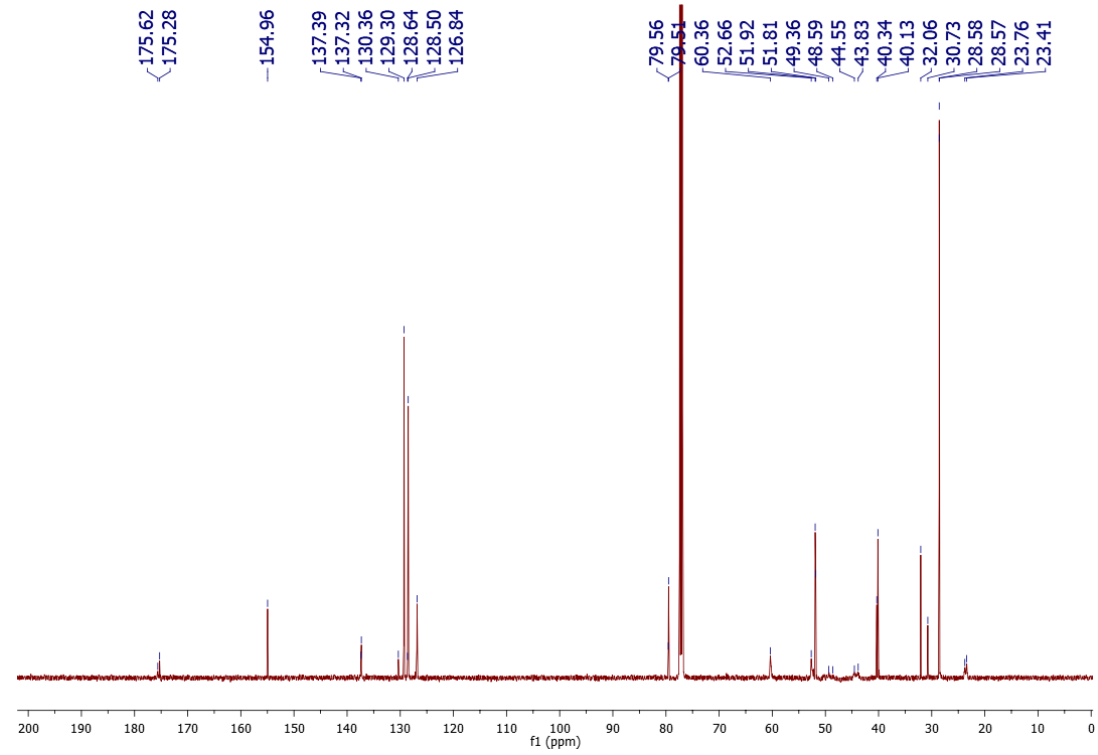




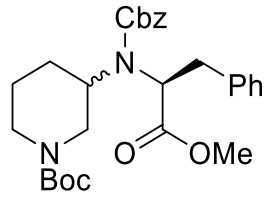
***tert*-Butyl 3-(((S)-1-methoxy-1-oxo-3-phenylpropan-2-yl)amino)piperidine-1-carboxylate *(S)*-S9**



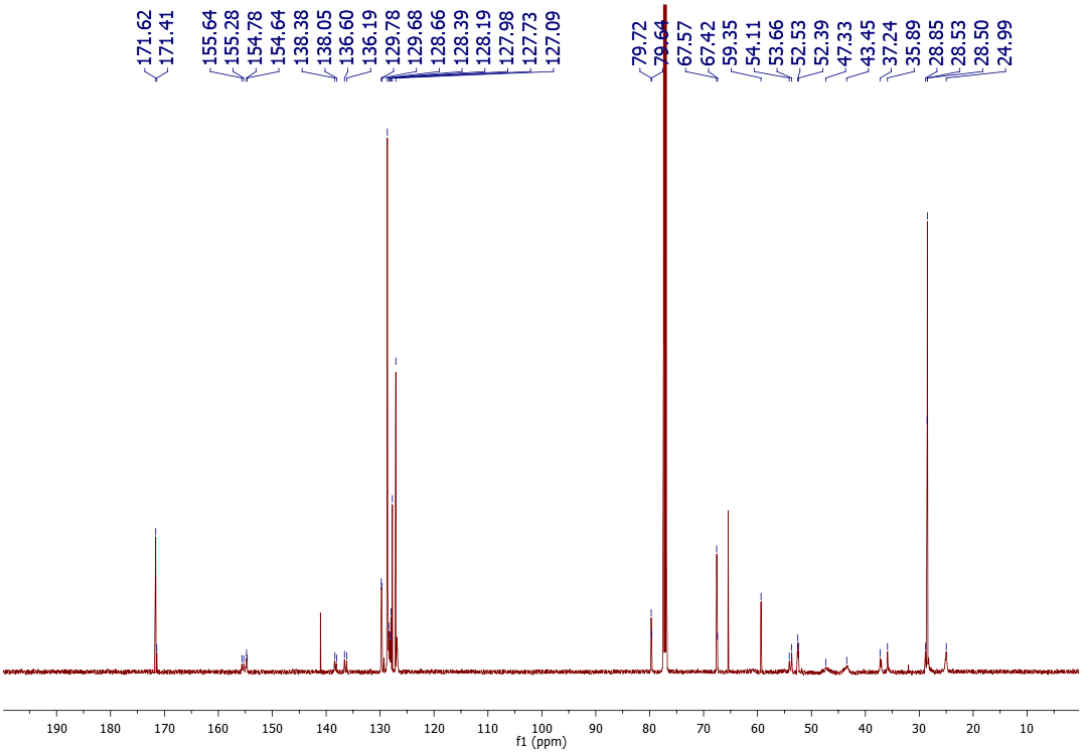
(S)-**S9**



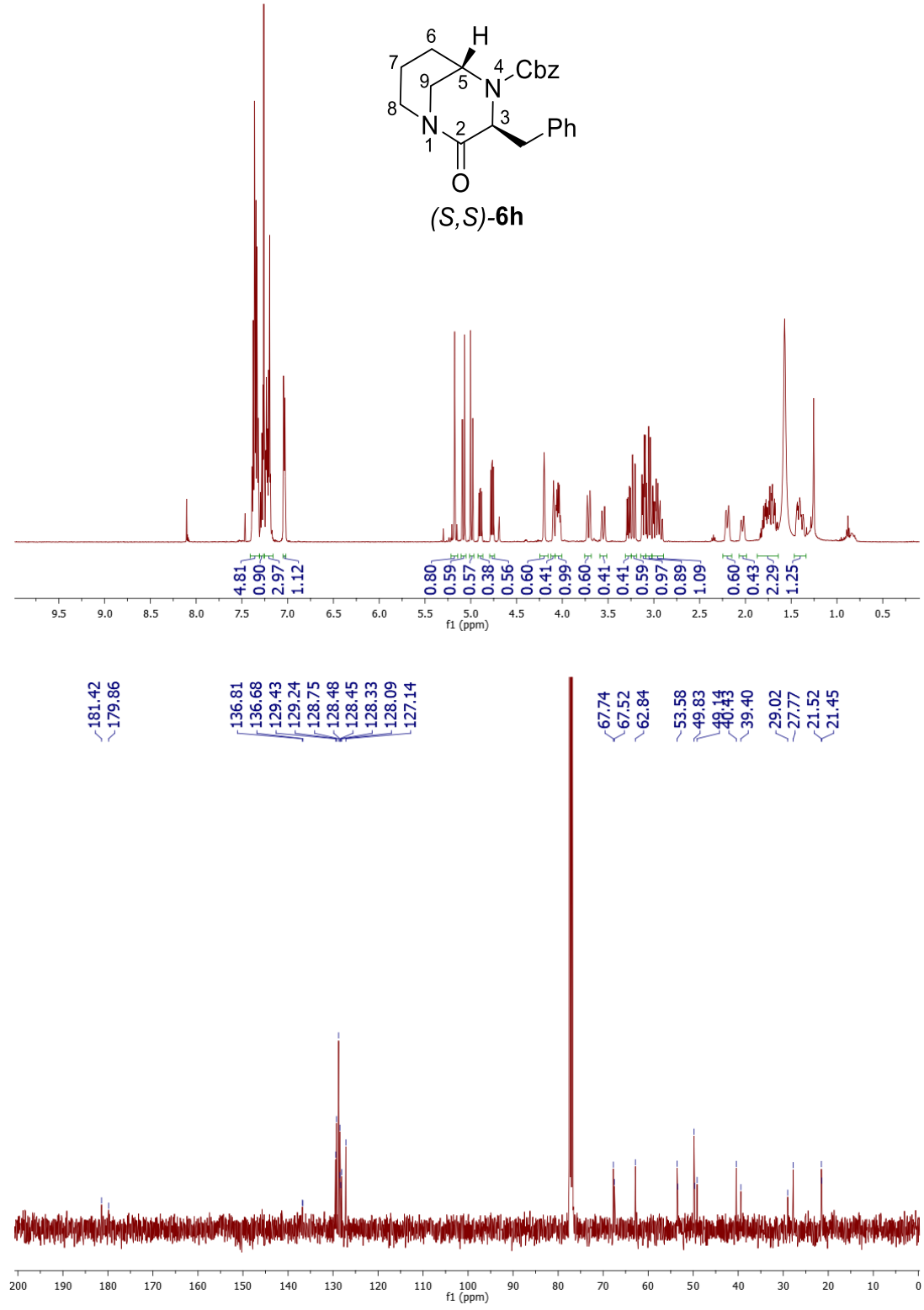
***tert*-Butyl 3-(((benzyloxy)carbonyl)((S)-1-methoxy-1-oxo-3-phenylpropan-2-yl)amino)piperidine-1-carboxylate *(S)*-9h**

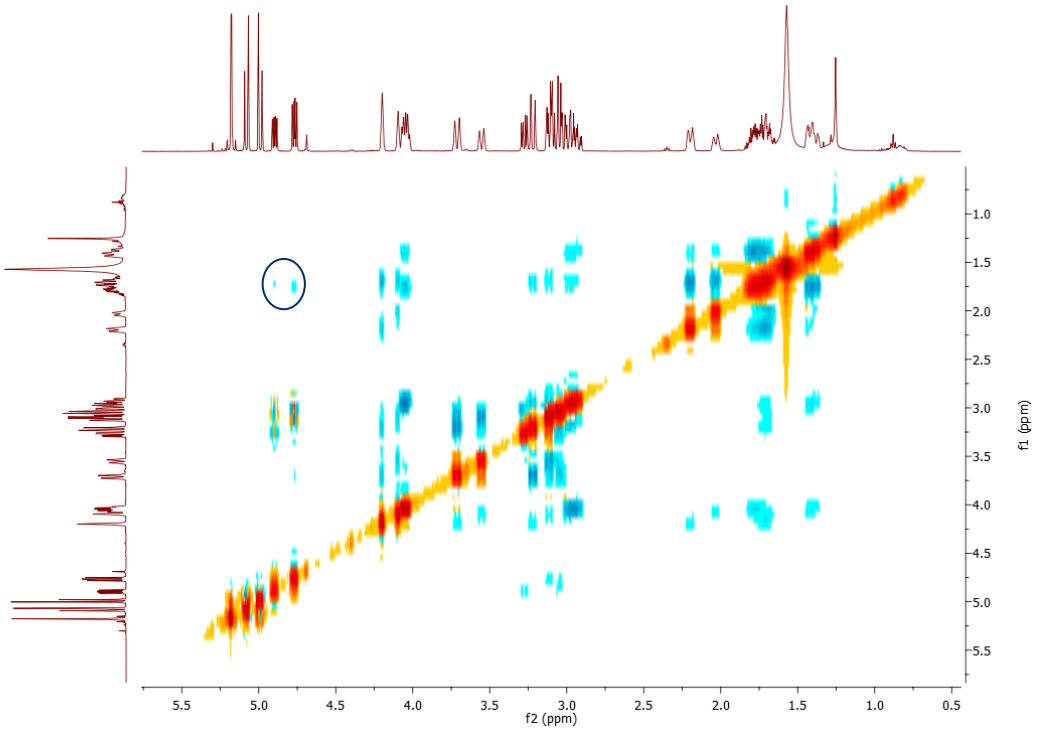


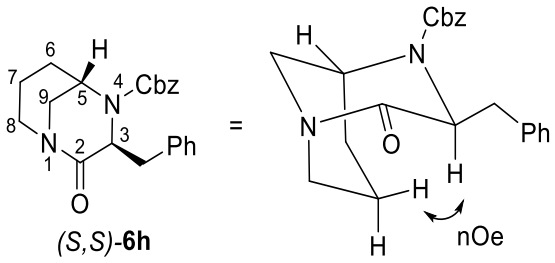
(S)-**9h**



Benzyl (3S,5S)-3-benzyl-2-oxo-1,4-diazabicyclo[3.3.1]nonane-4-carboxylate *(S,S)*-6h

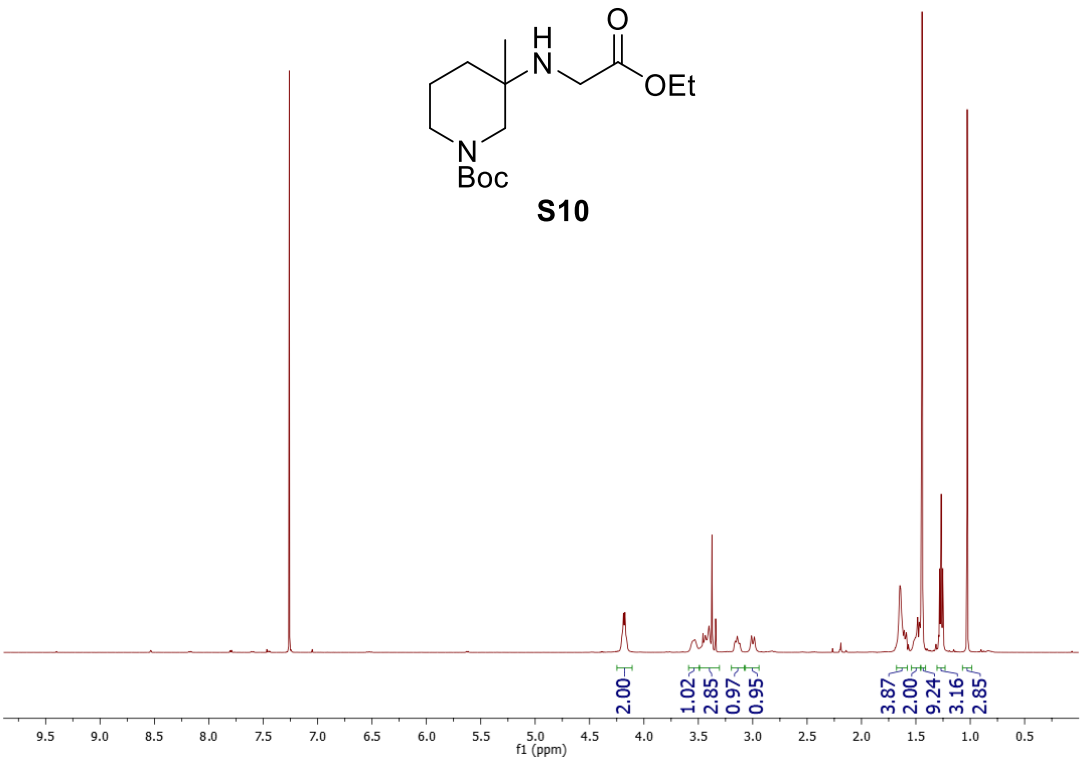


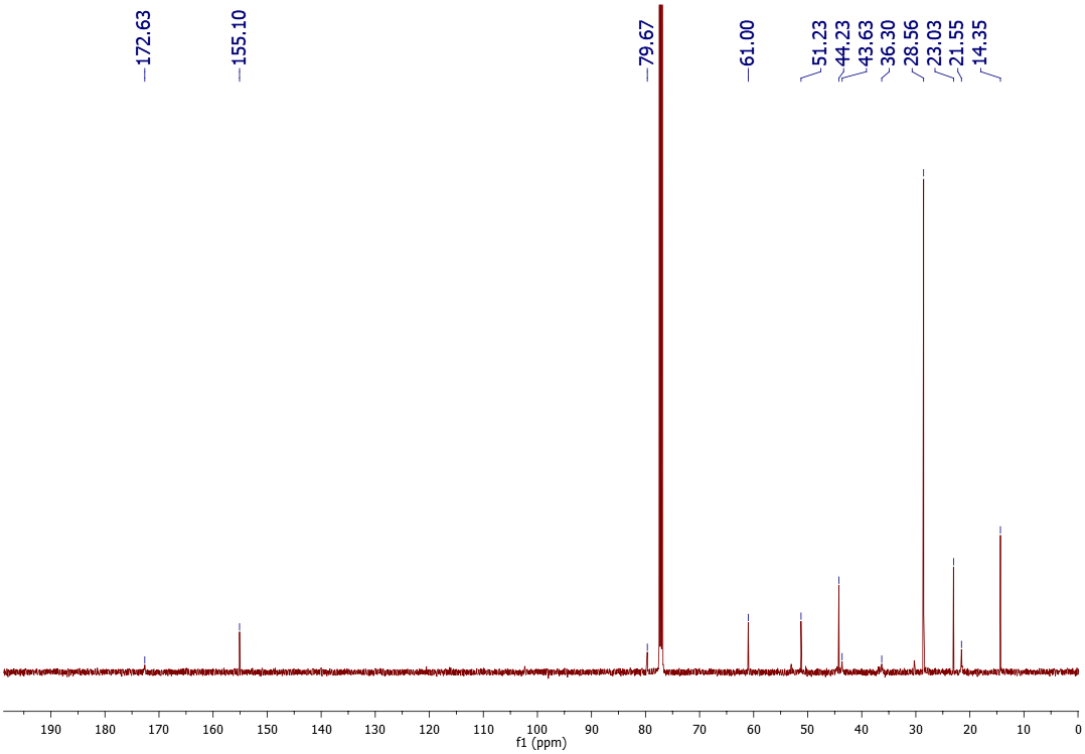

5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f2 (ppm)
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
f1 (ppm)


6
H
7
9
5
4
Cbz
N
8
N
2
3
Ph
1
O
=
H
Cbz
N
N
O
Ph
H
H
H
nOe

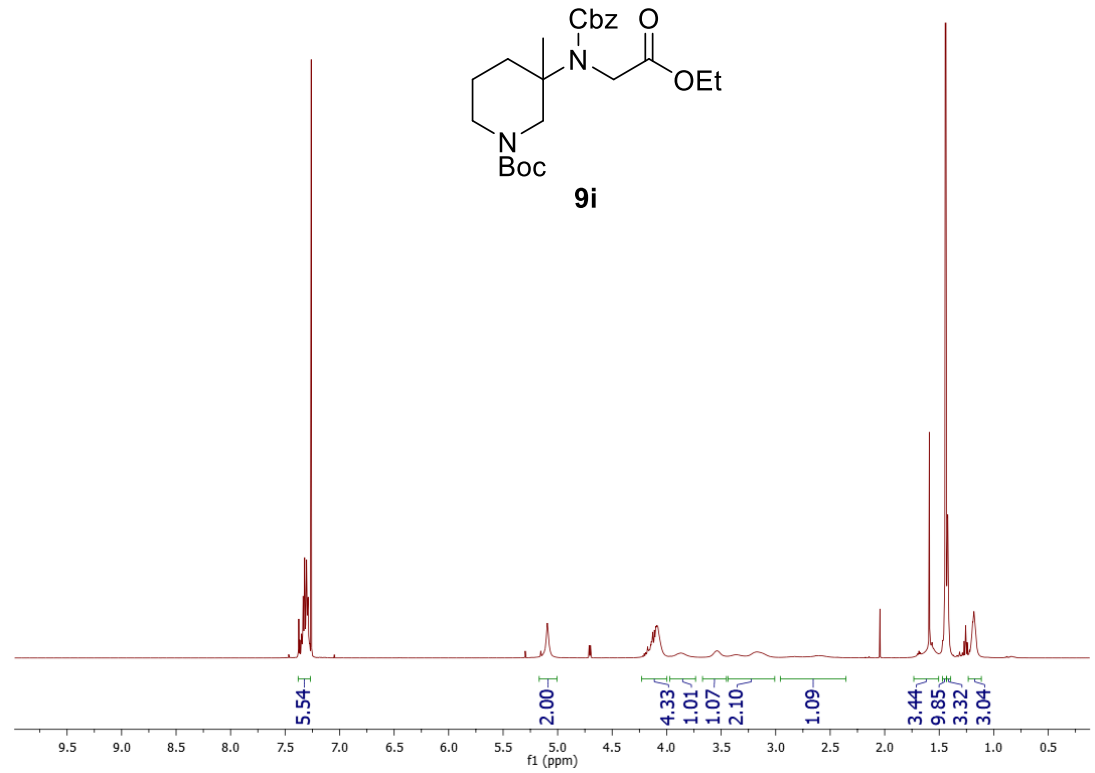
(S,S)-**6h**

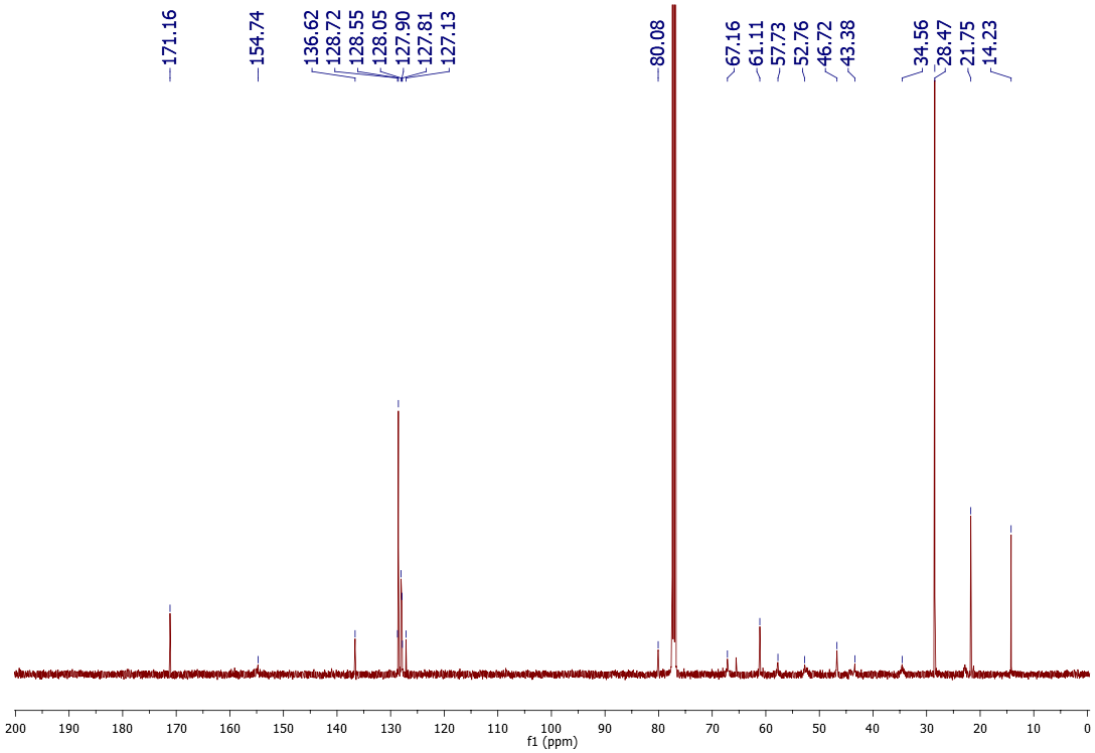
tert-Butyl 3-((2-ethoxy-2-oxoethyl)amino)-3-methylpiperidine-1-carboxylate S10



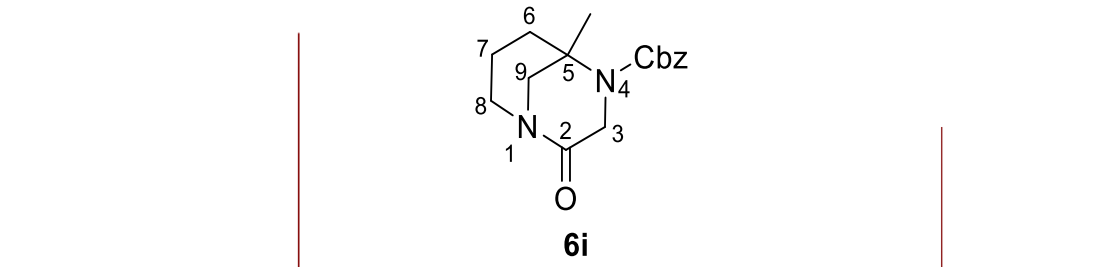


***tert*-Butyl 3-(((benzyloxy)carbonyl)(2-ethoxy-2-oxoethyl)amino)-3-methylpiperidine-1-carboxylate 9i**

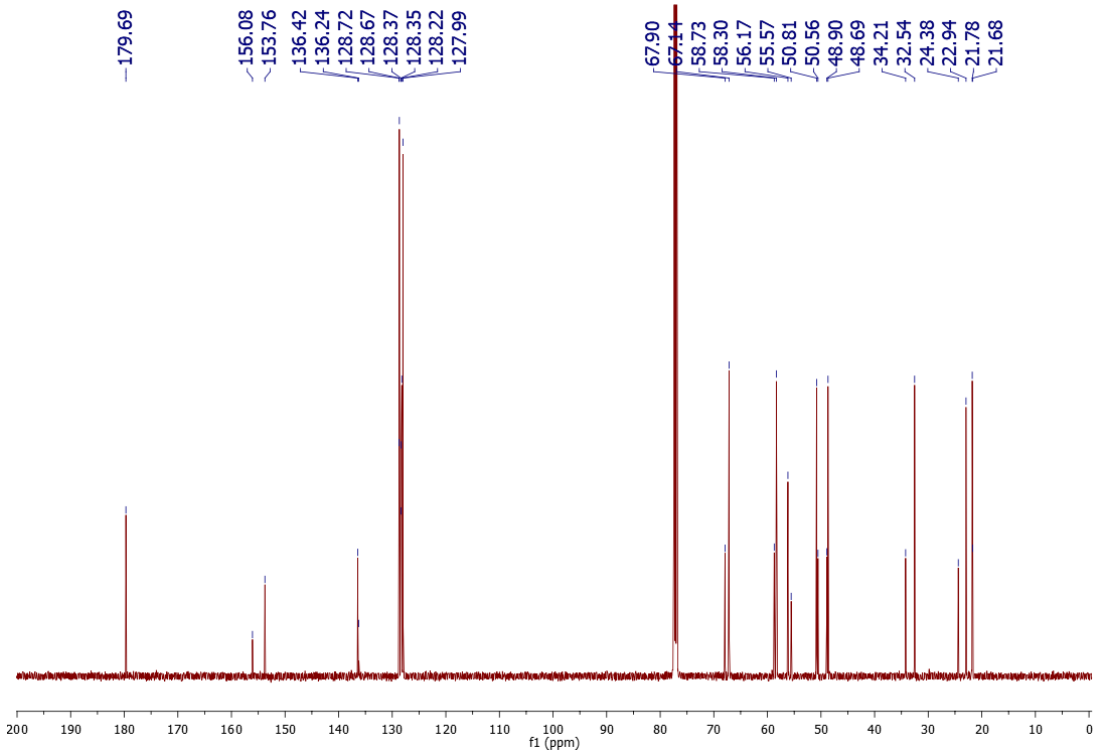




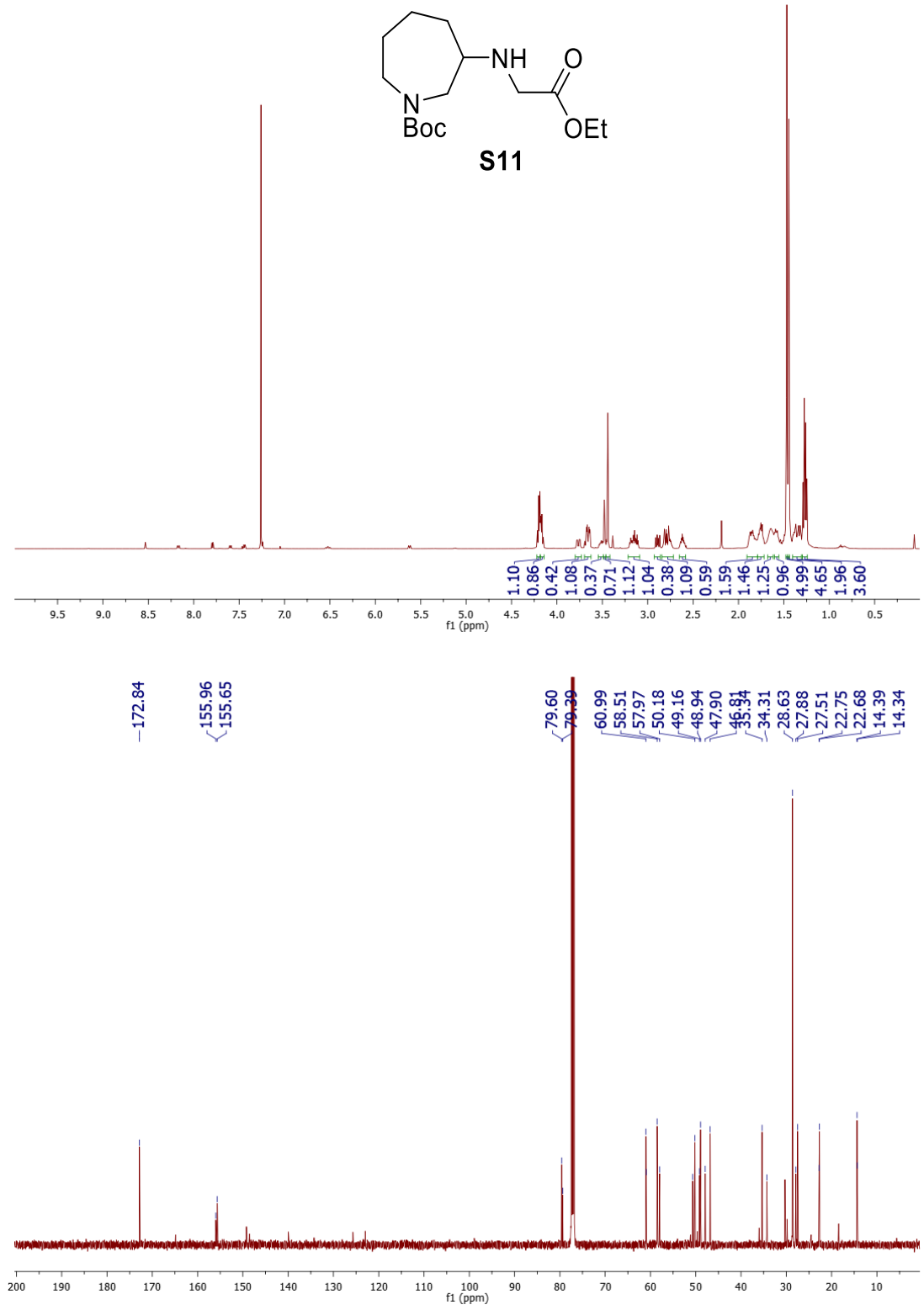
Benzyl 5-methyl-2-oxo-1,4-diazabicyclo[3.3.1]nonane-4-carboxylate 6i



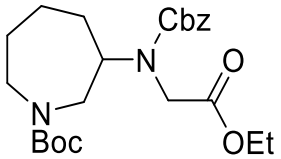
6i



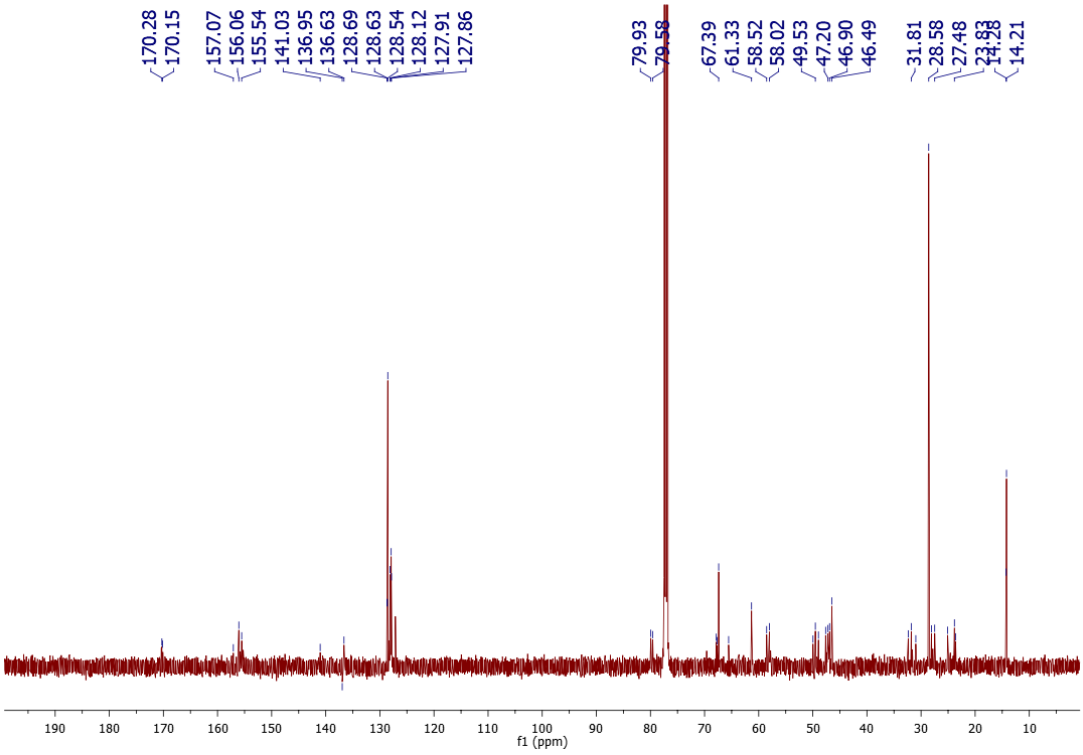
***tert*-Butyl 3-((2-ethoxy-2-oxoethyl)amino)azepane-1-carboxylate S11**



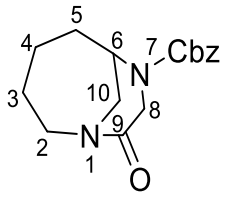
***tert*-Butyl 3-(((benzyloxy)carbonyl)(2-ethoxy-2-oxoethyl)amino)azepane-1-carboxylate 9j**



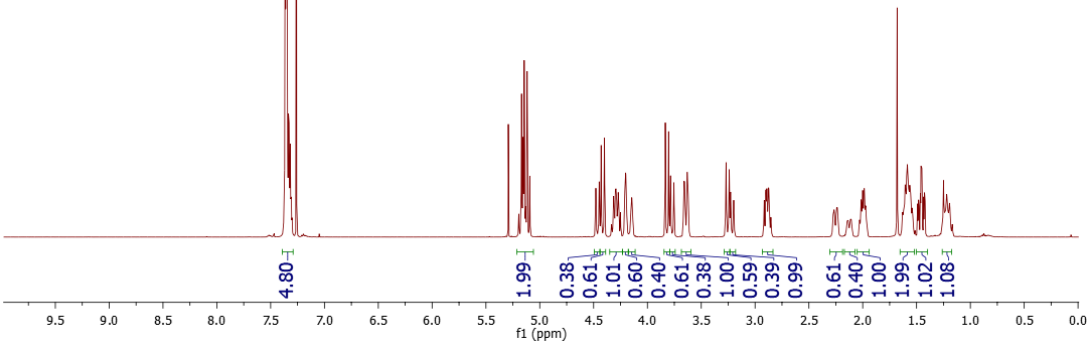
9j

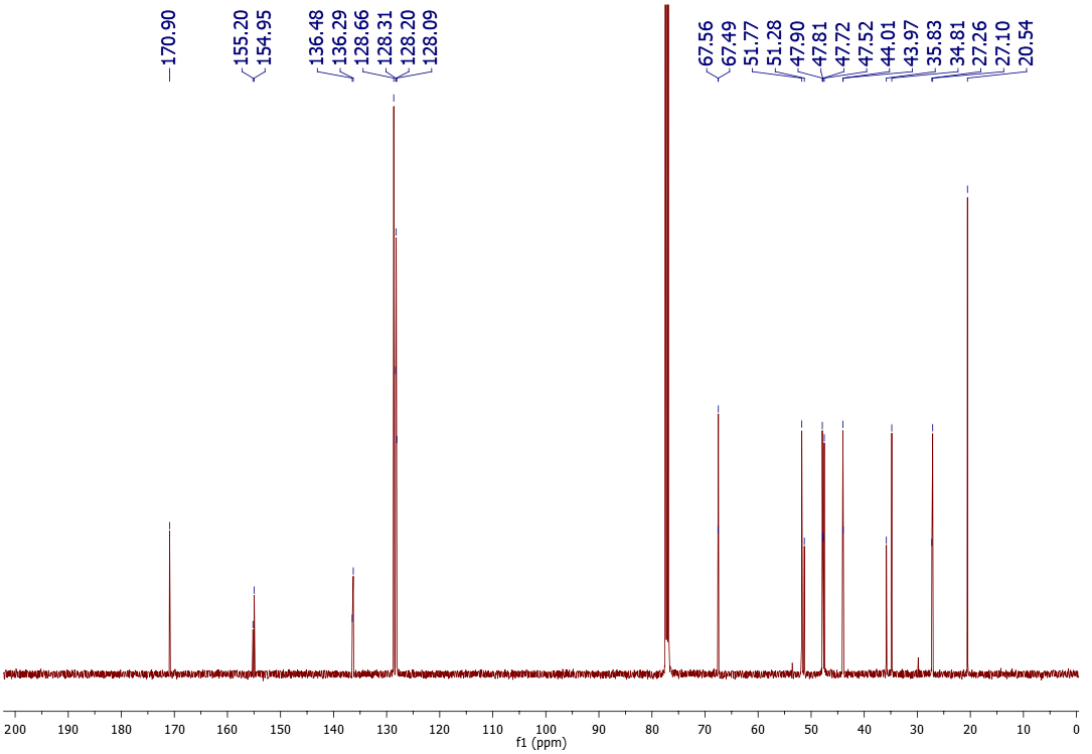


Benzyl 9-oxo-1,7-diazabicyclo[4.3.1]decane-7-carboxylate 6j

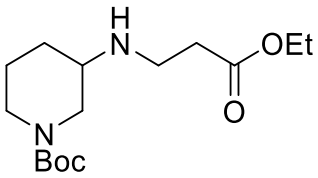


6j

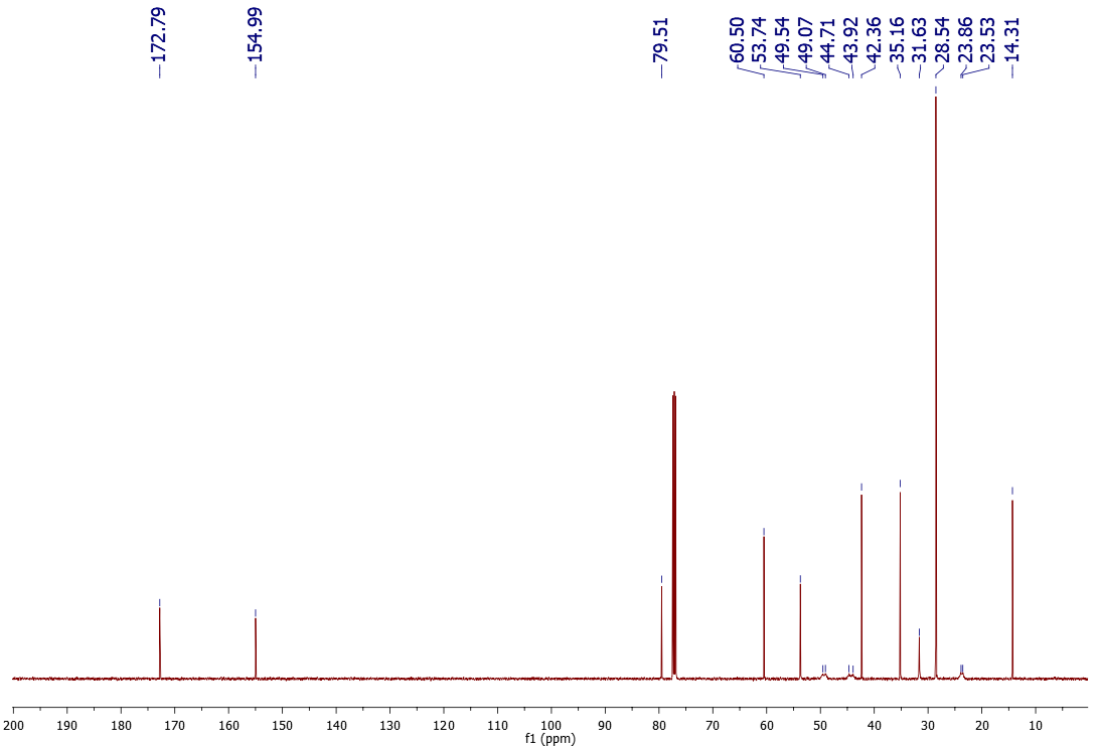




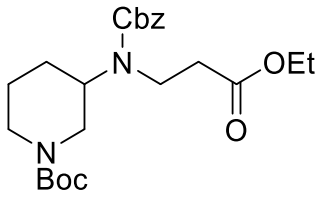
tert-Butyl 3-((3-ethoxy-3-oxopropyl)amino)piperidine-1-carboxylate S12



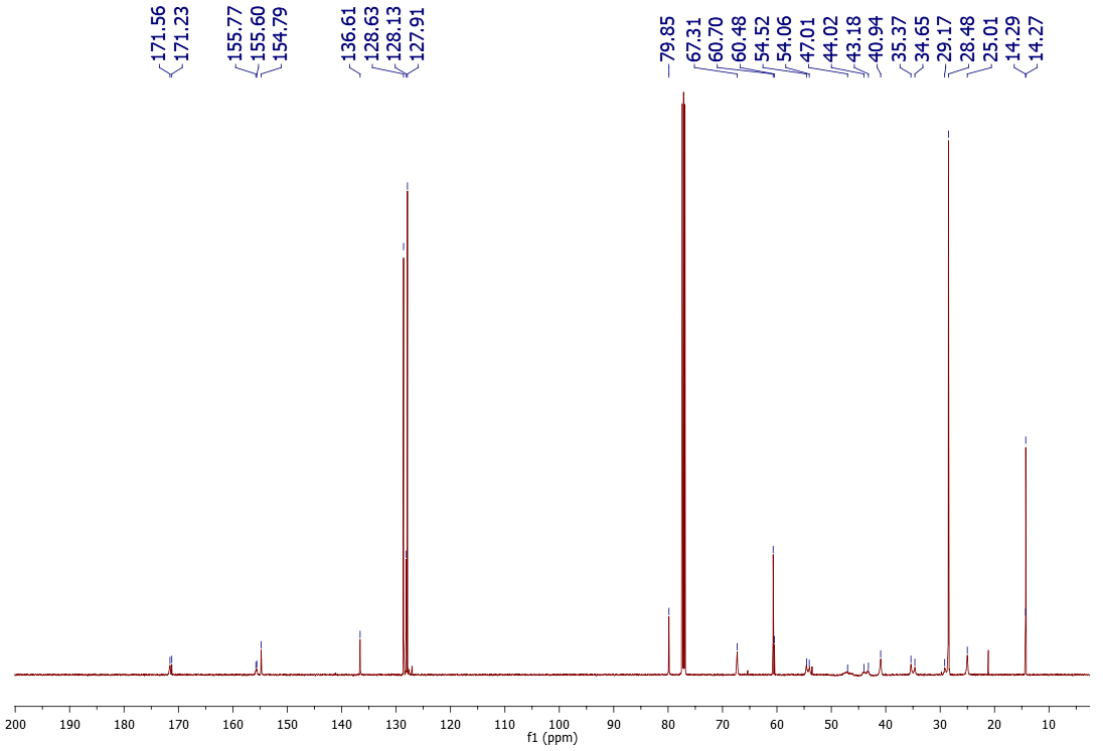
S12



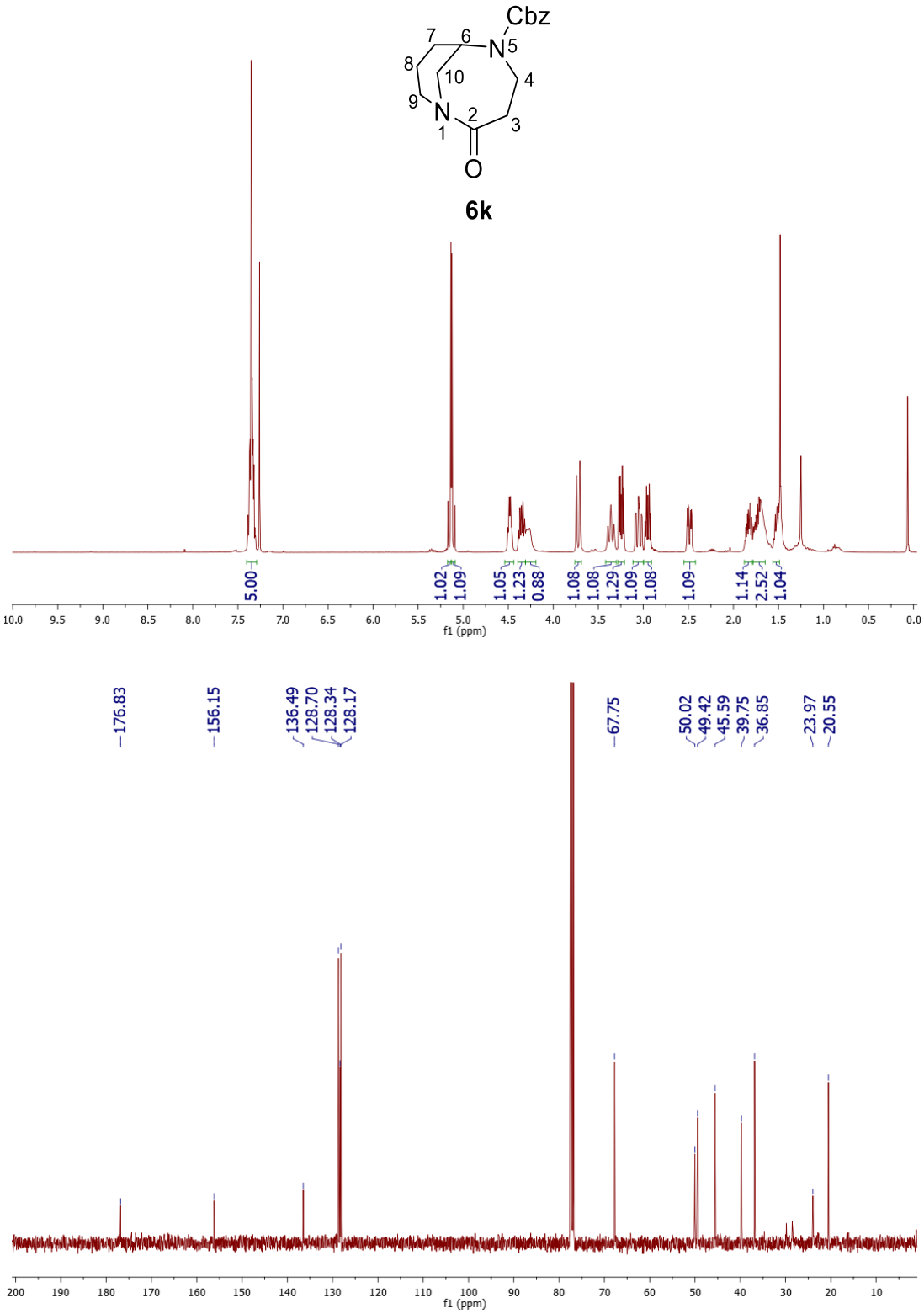
***tert*-Butyl 3-(((benzyloxy)carbonyl)(3-ethoxy-3-oxopropyl)amino)piperidine-1-carboxylate 9k**



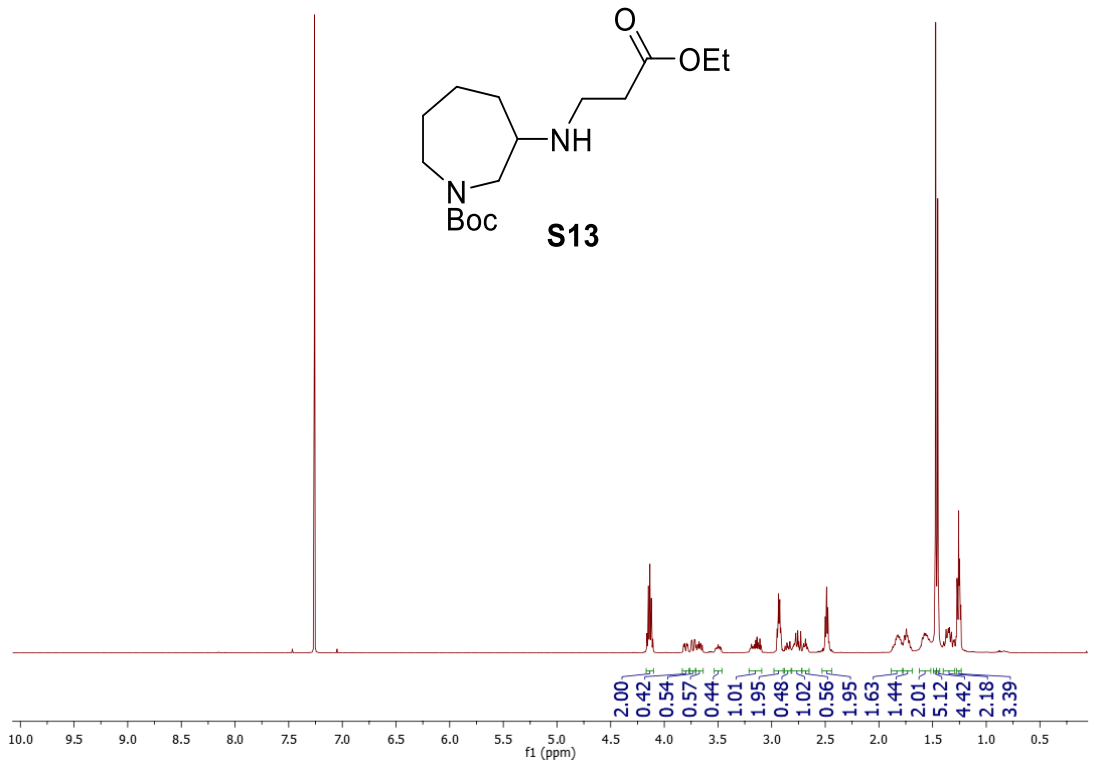
9k

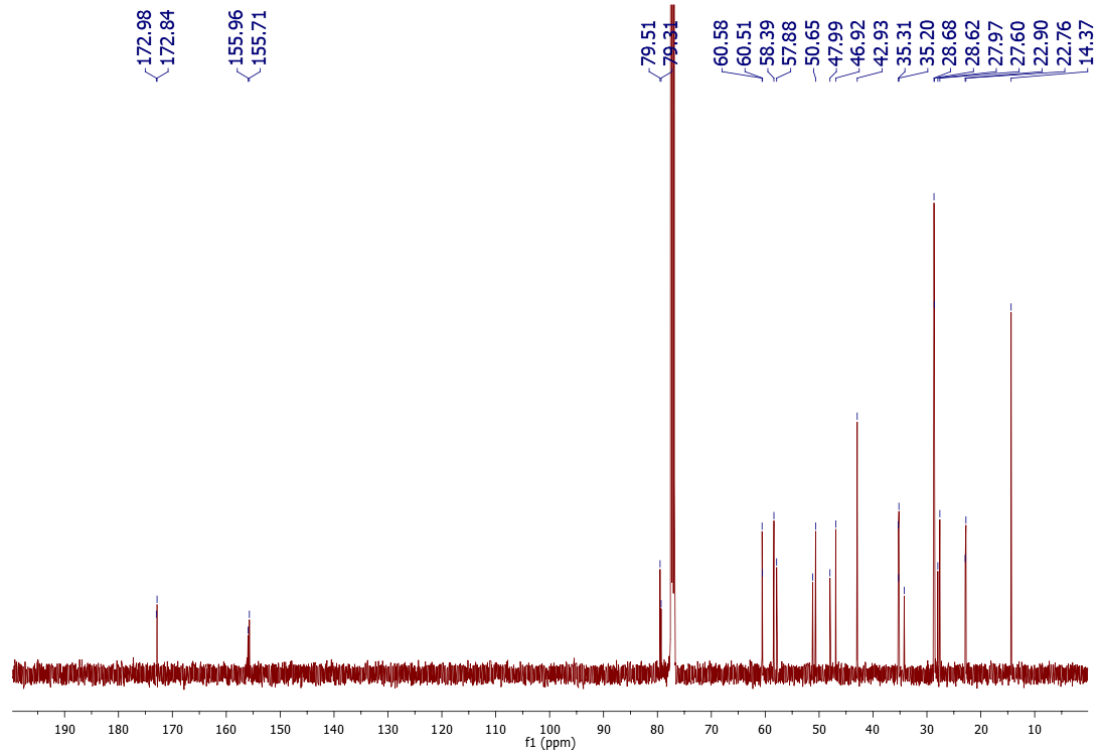


Benzyl 2-oxo-1,5-diazabicyclo[4.3.1]decane-5-carboxylate 6k

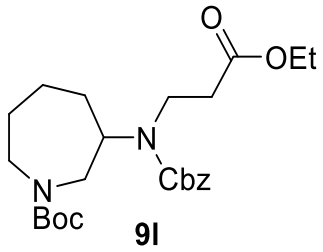


tert-Butyl 3-((3-ethoxy-3-oxopropyl)amino)azepane-1-carboxylate S13

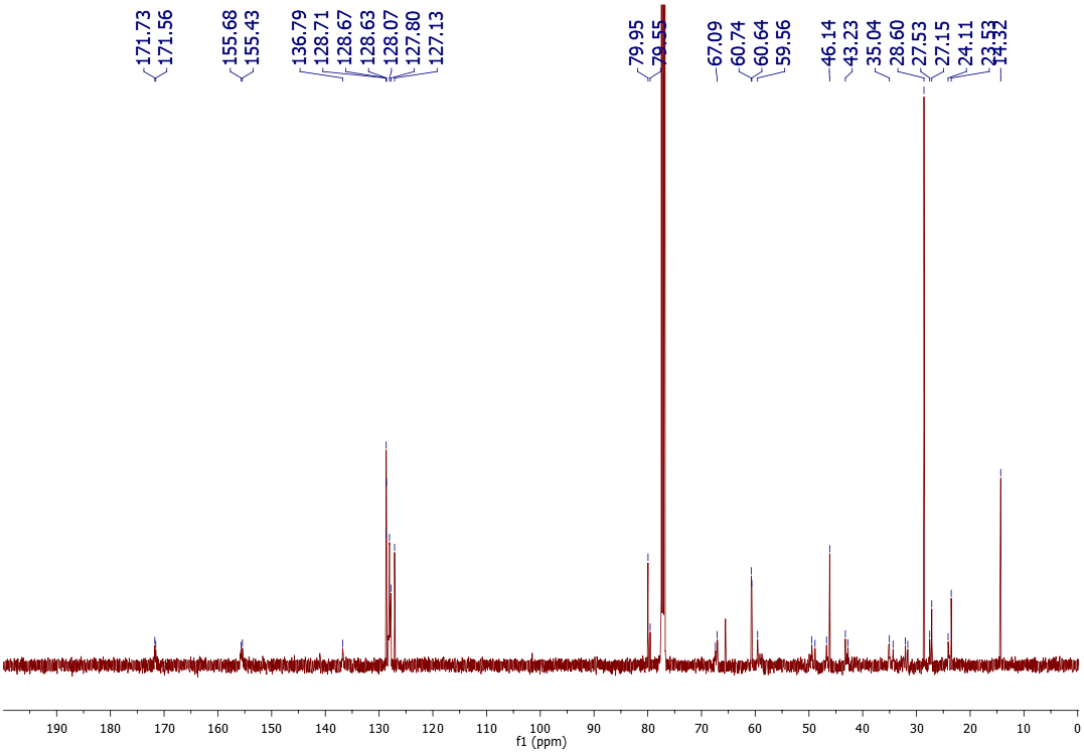




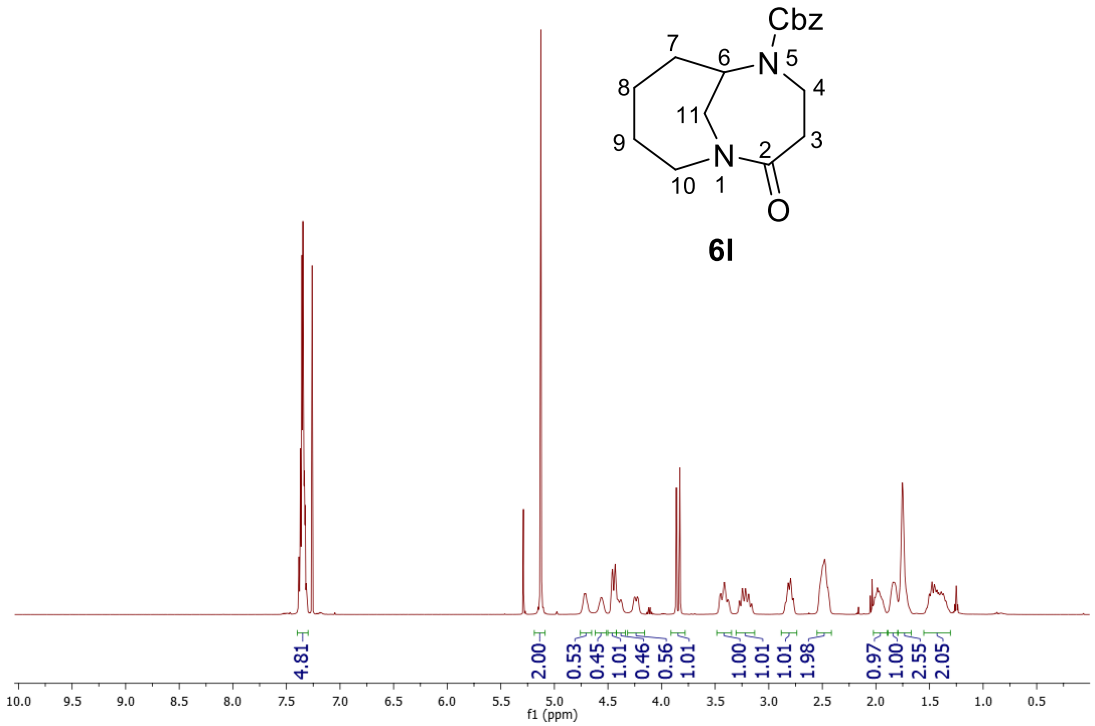
***tert*-Butyl 3-(((benzyloxy)carbonyl)(3-ethoxy-3-oxopropyl)amino)azepane-1-carboxylate 9l**



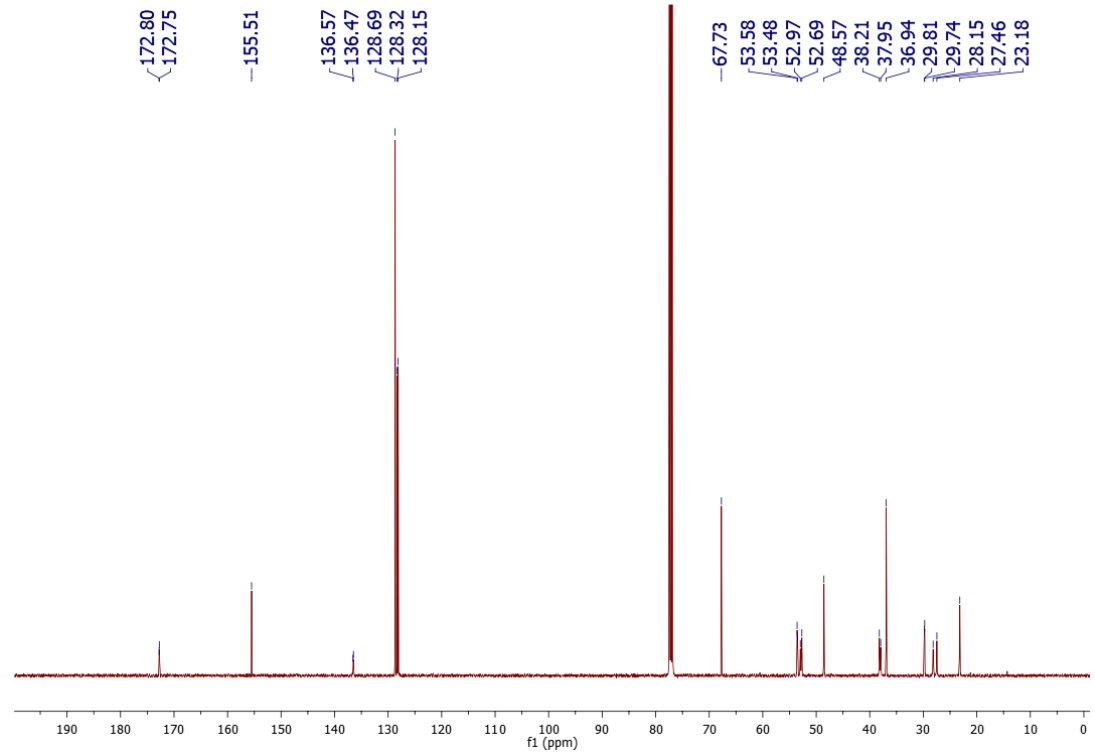
9l



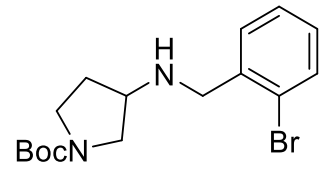
Benzyl 2-oxo-1,5-diazabicyclo[4.4.1]undecane-5-carboxylate 6l



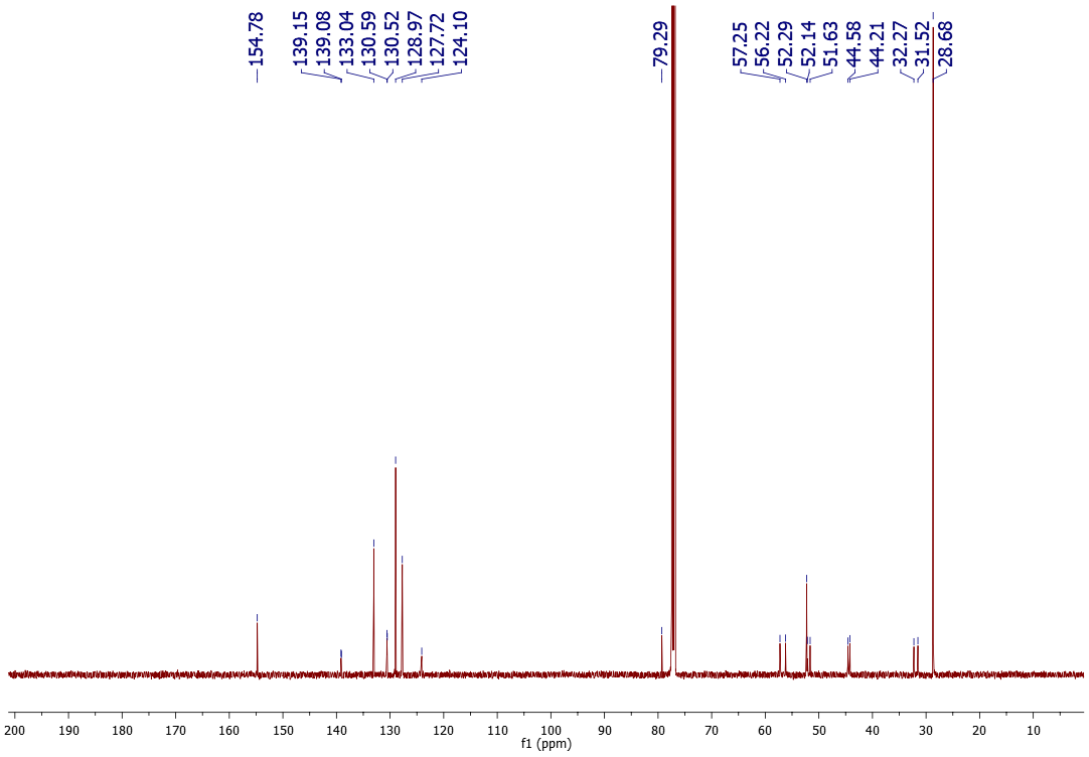
6l



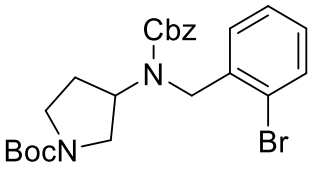
***tert*-Butyl 3-((2-bromobenzyl)amino)pyrrolidine-1-carboxylate S14**



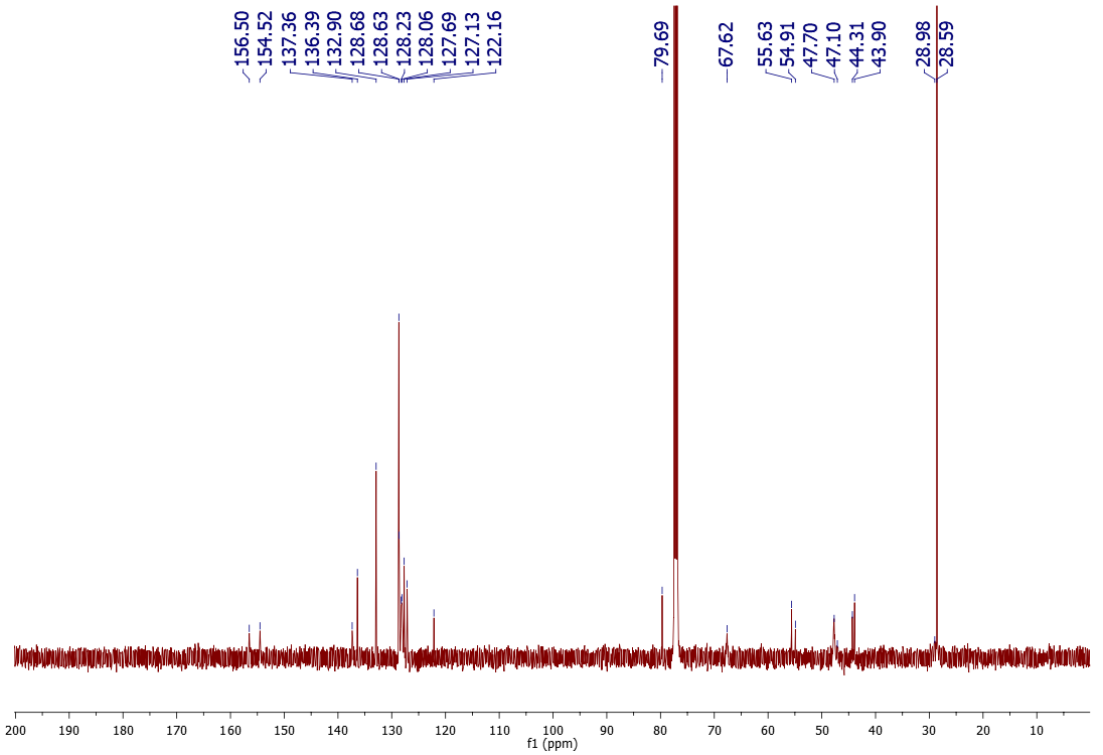
S14



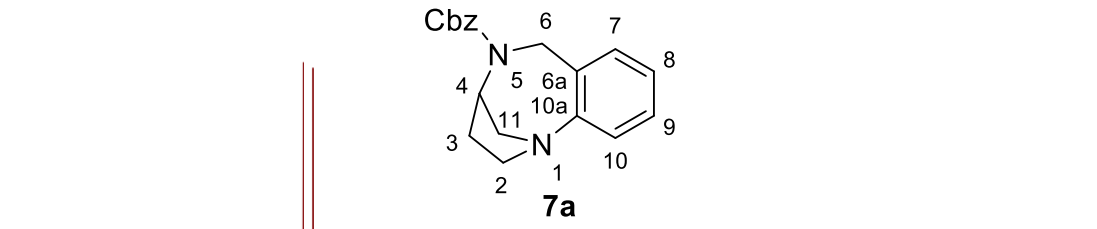
***tert*-Butyl 3-(((benzyloxy)carbonyl)(2-bromobenzyl)amino)pyrrolidine-1-carboxylate 11a**



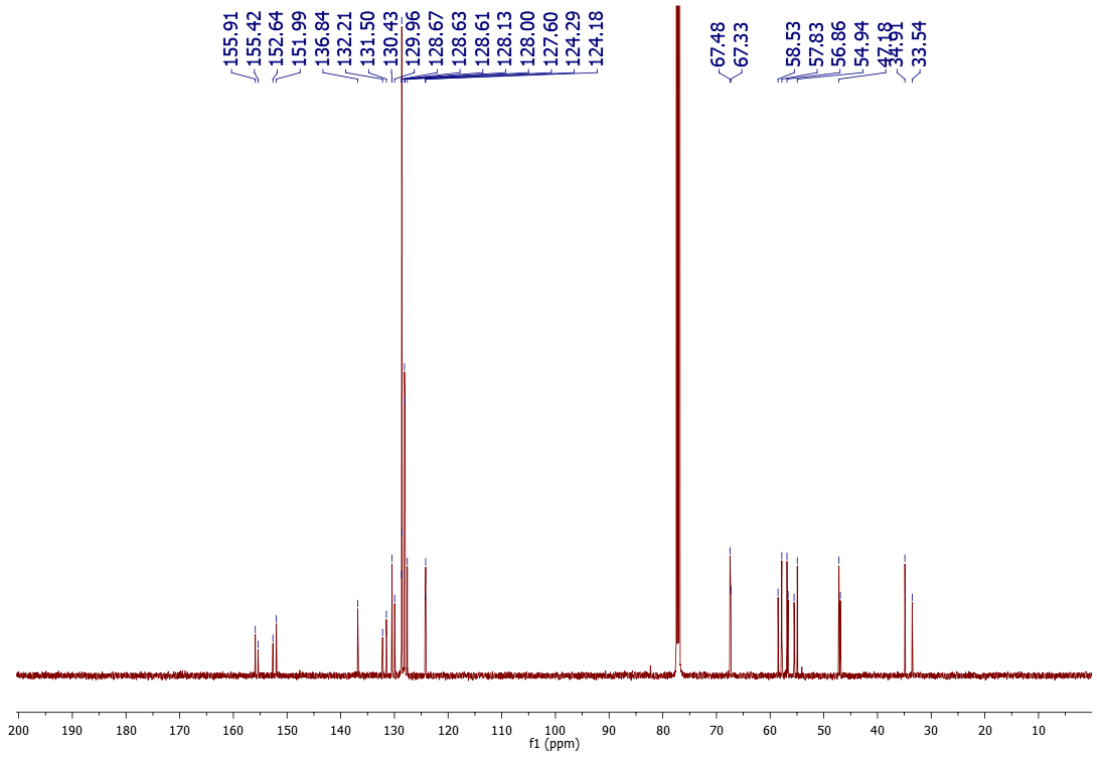
11a



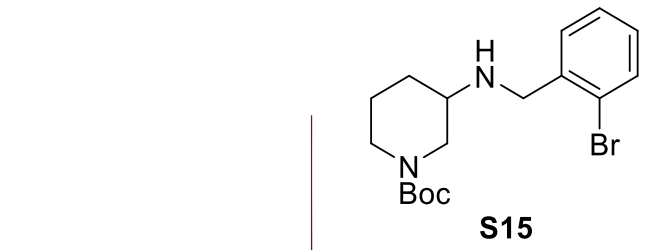
Benzyl 3,4-dihydro-2H-1,4-methanobenzo[b][1,5]diazocine-5(6H)-carboxylate 7a



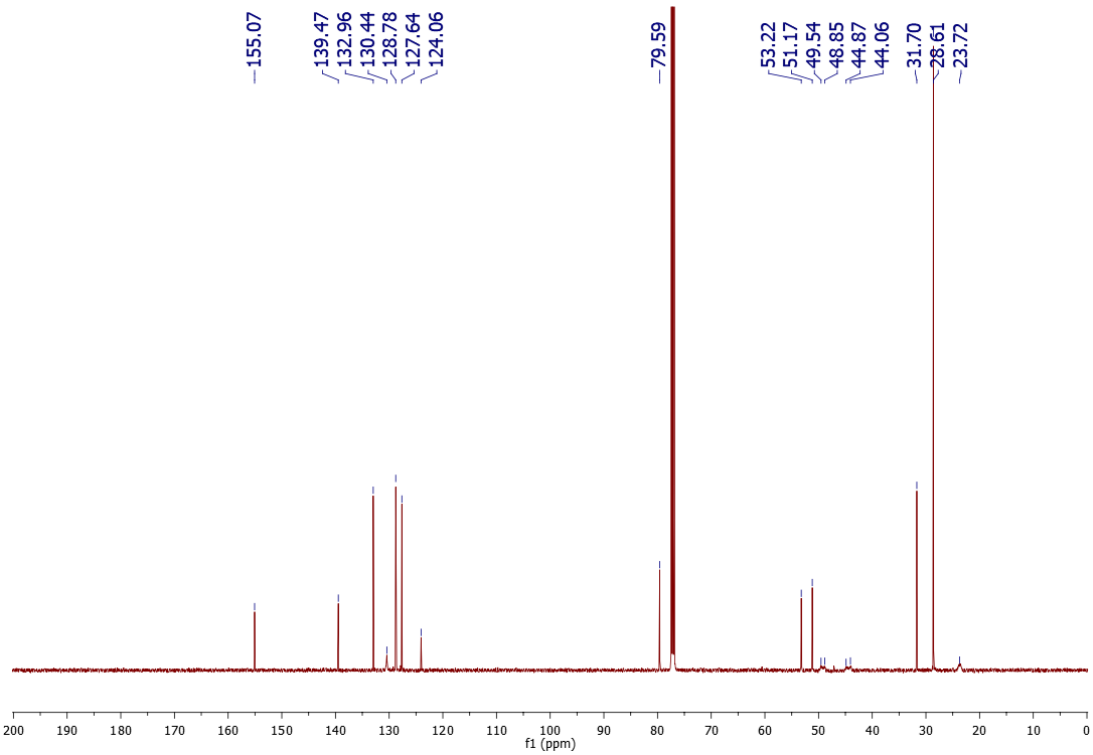
7a



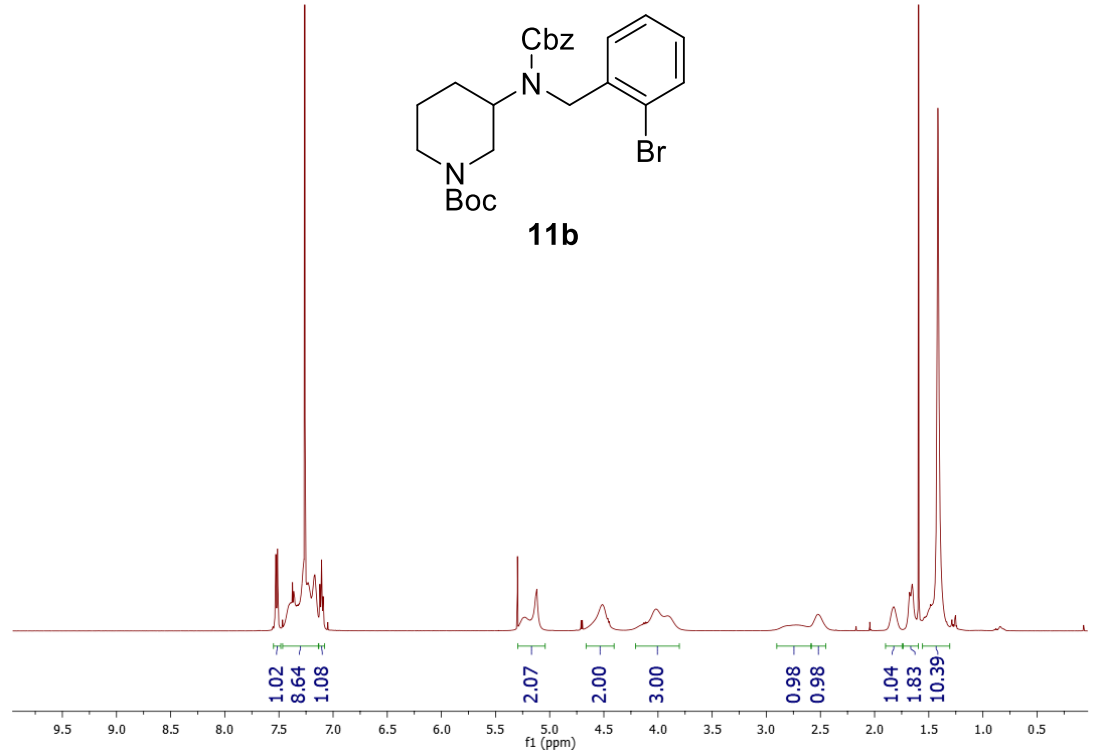
tert-Butyl 3-((2-bromobenzyl)amino)piperidine-1-carboxylate S15

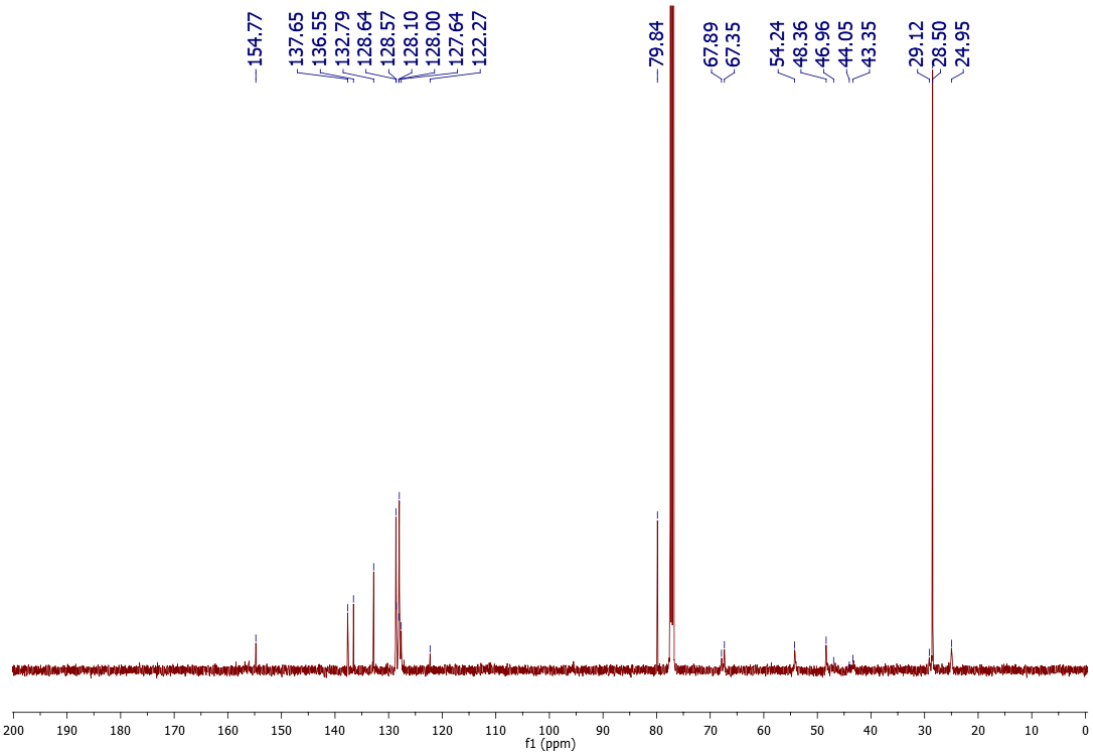


S15

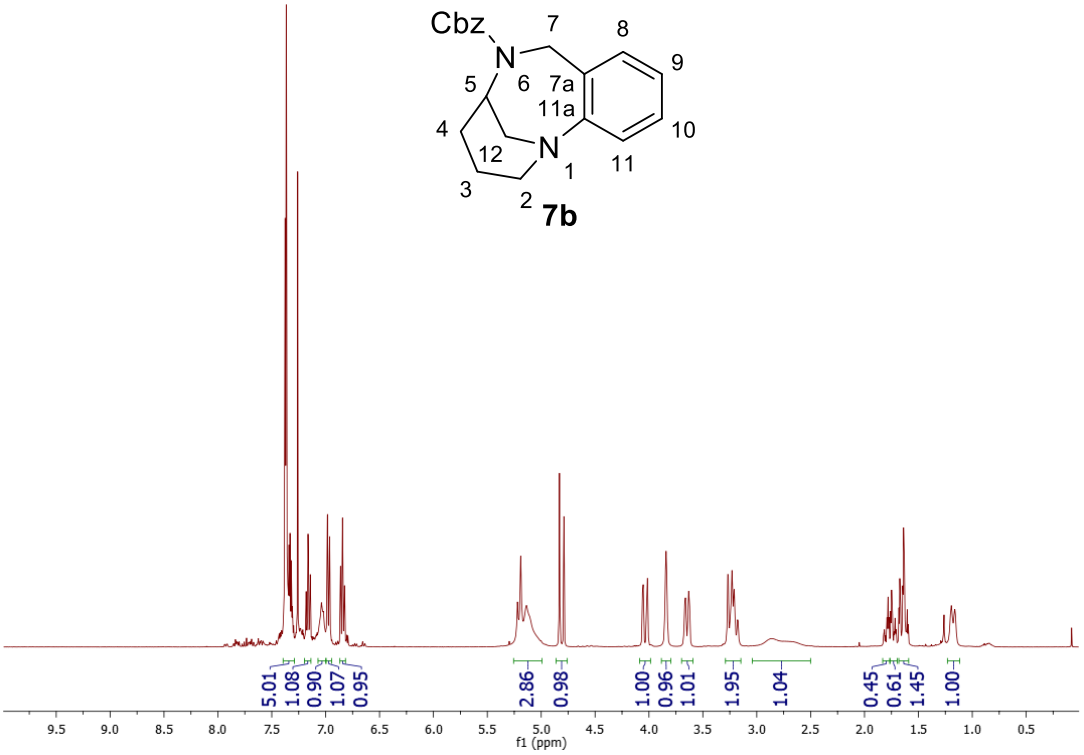


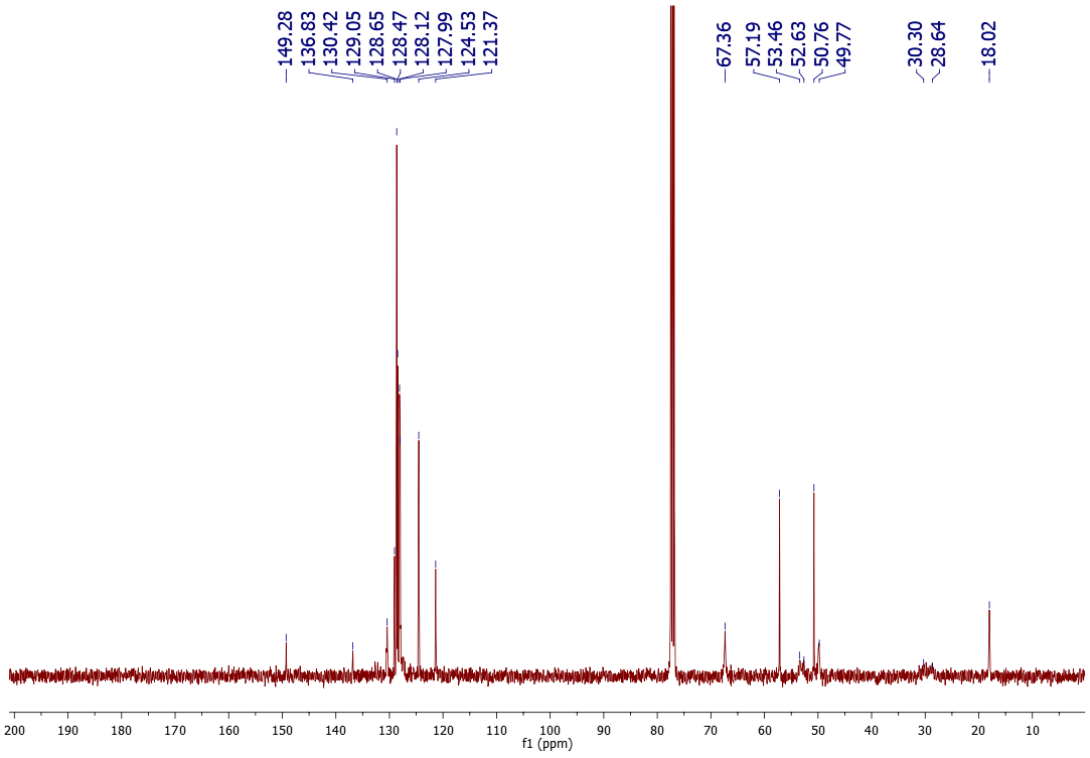
***tert*-Butyl 3-(((benzyloxy)carbonyl)(2-bromobenzyl)amino)piperidine-1-carboxylate 11b**



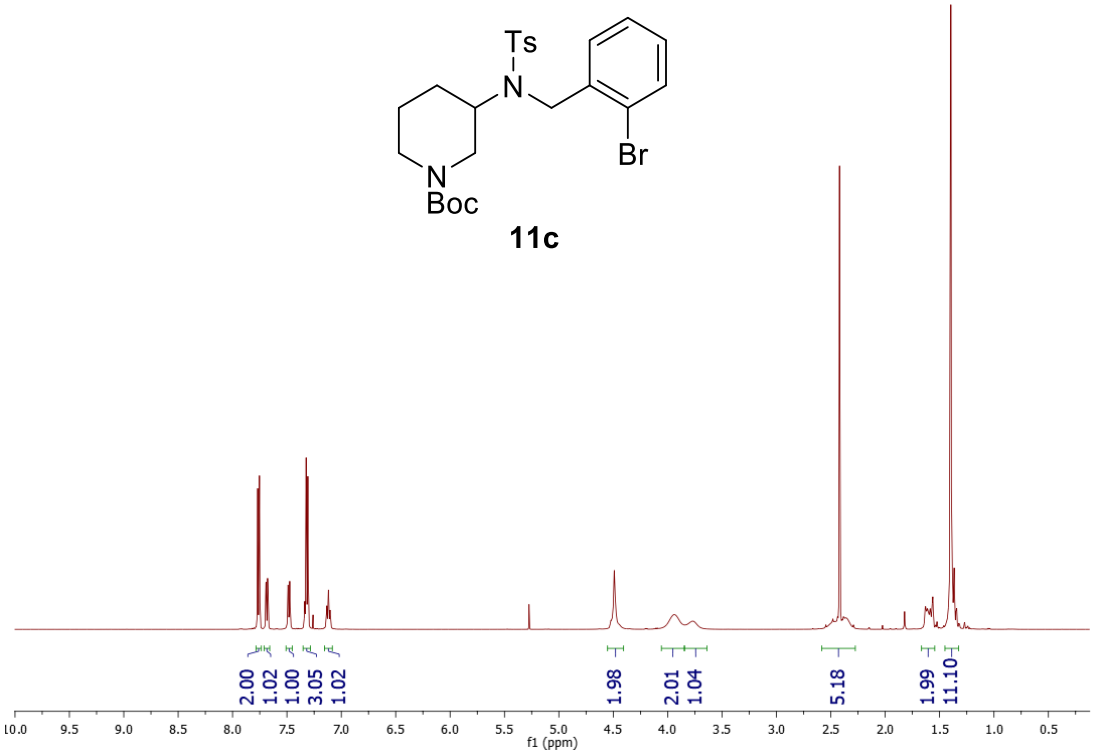


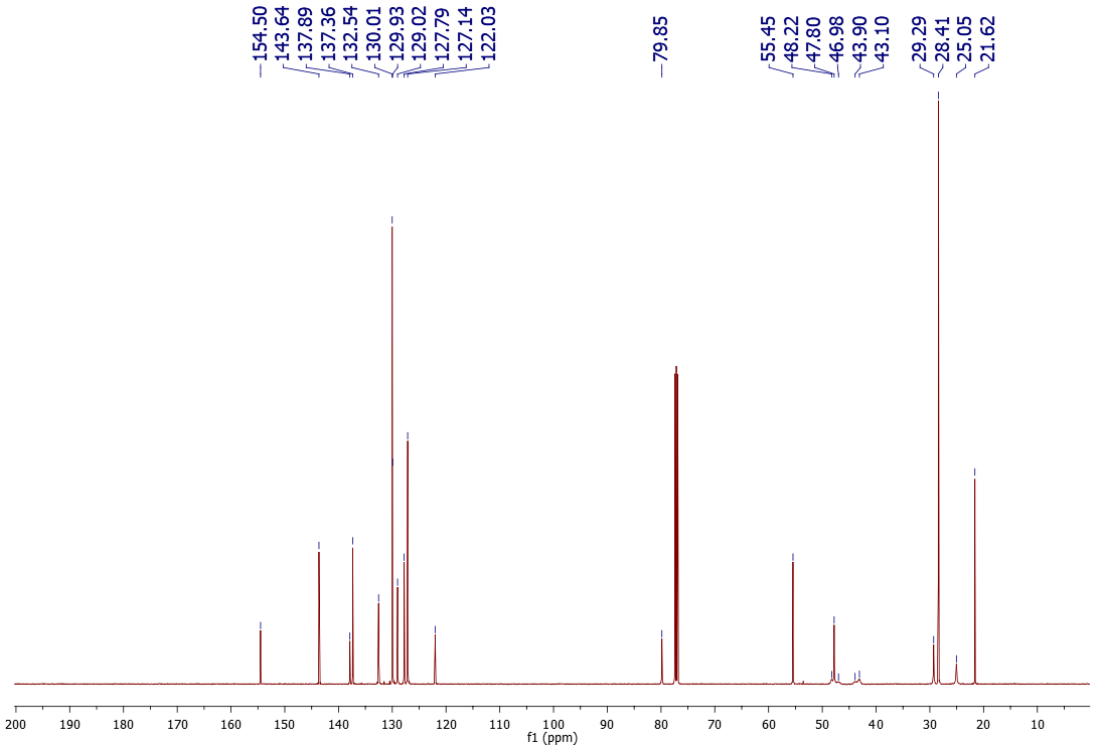
Benzyl 2,3,4,5-tetrahydro-1,5-methanobenzo[b][1,5]diazonine-6(7H)-carboxylate 7b



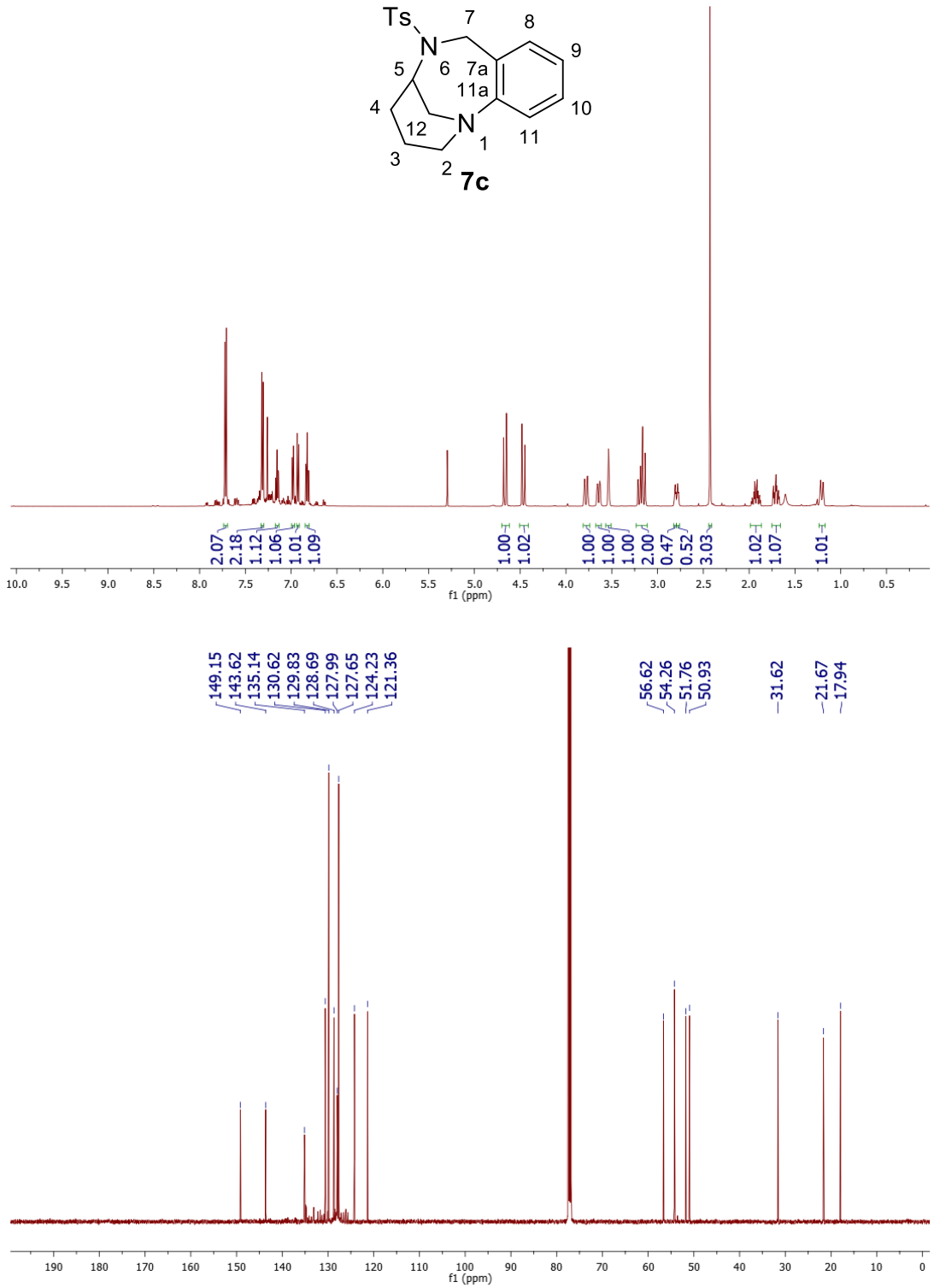


***tert*-Butyl 3-((N-(2-bromobenzyl)-4-methylphenyl)sulfonamido)piperidine-1-carboxylate 11c**

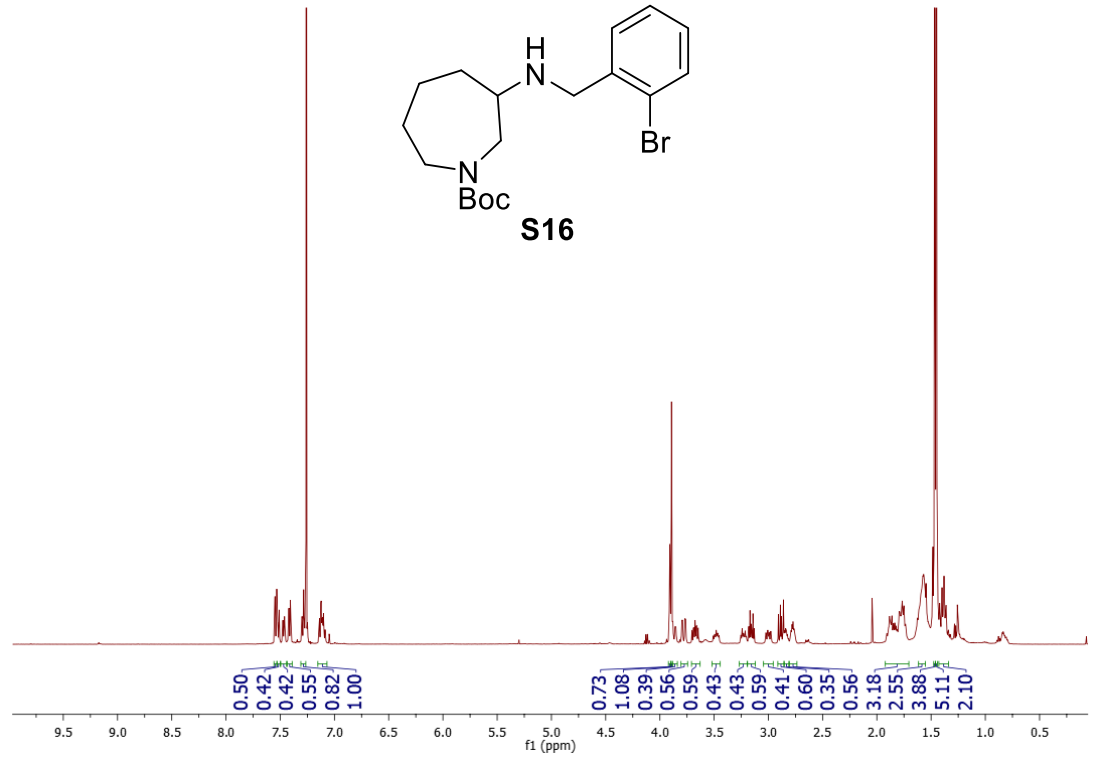




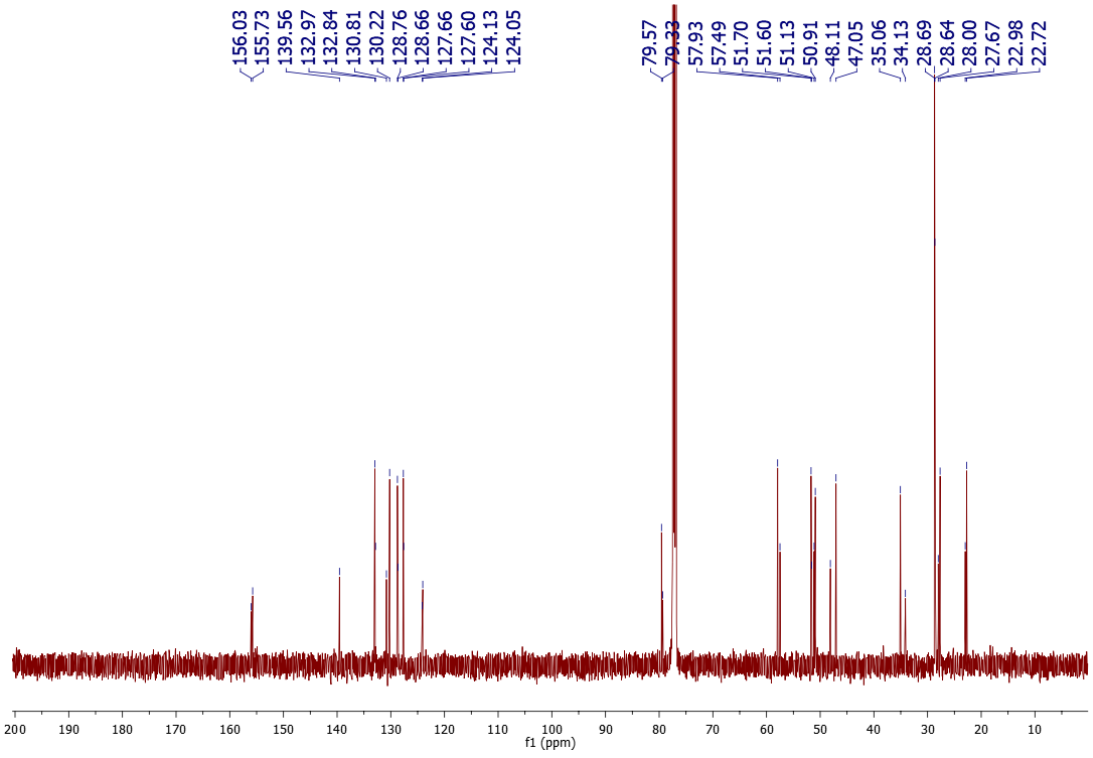
6-Tosyl-2,3,4,5,6,7-hexahydro-1,5-methanobenzo[b][1,5]diazonine 7c



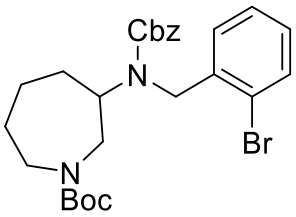
tert-Butyl 3-((2-bromobenzyl)amino)azepane-1-_carboxylate_ S16



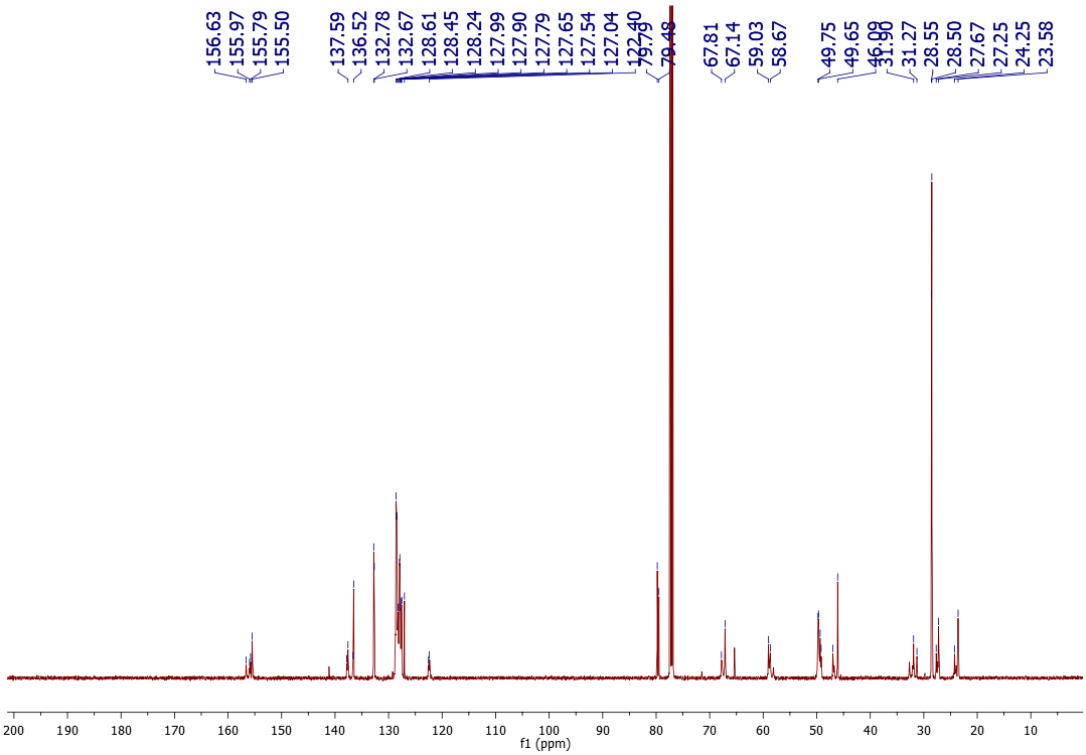
S16



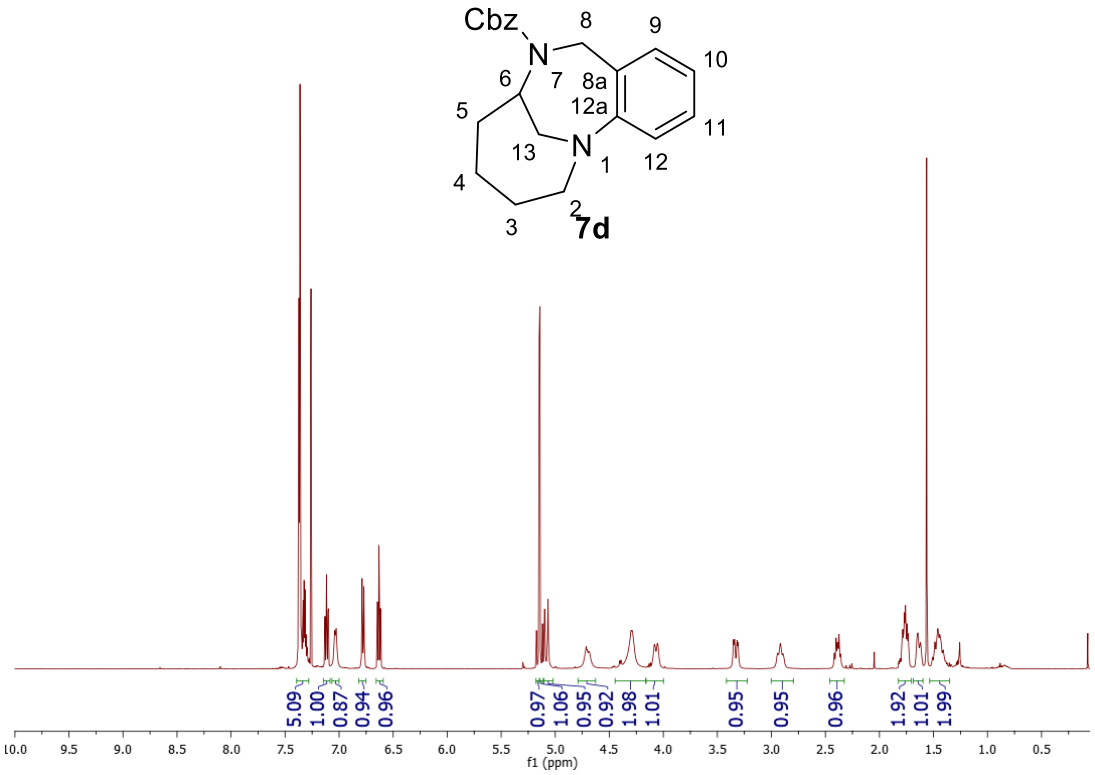
***tert*-Butyl 3-(((benzyloxy)carbonyl)(2-bromobenzyl)amino)azepane-1-carboxylate 11d**

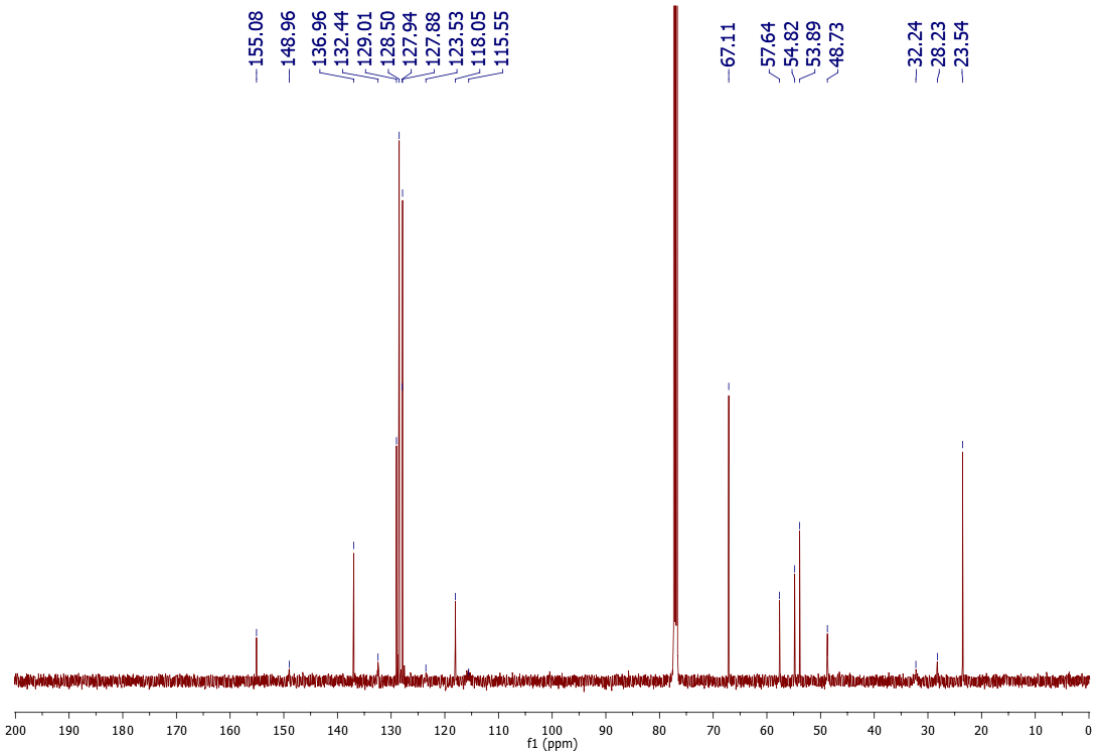


11d

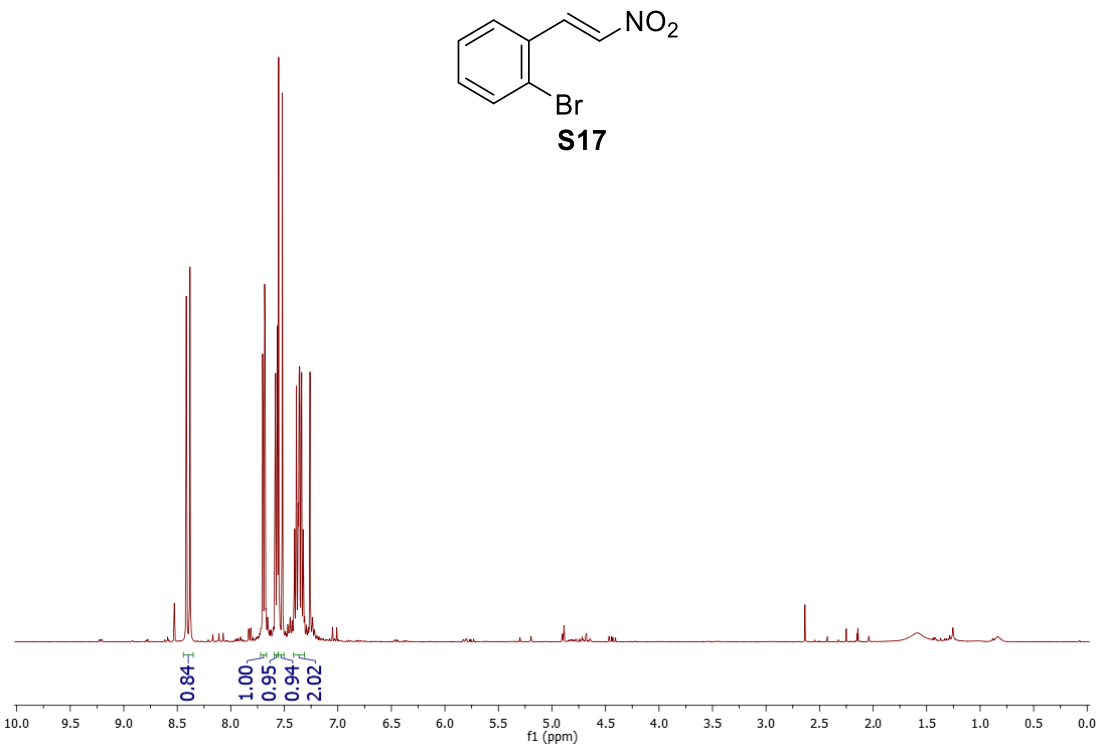


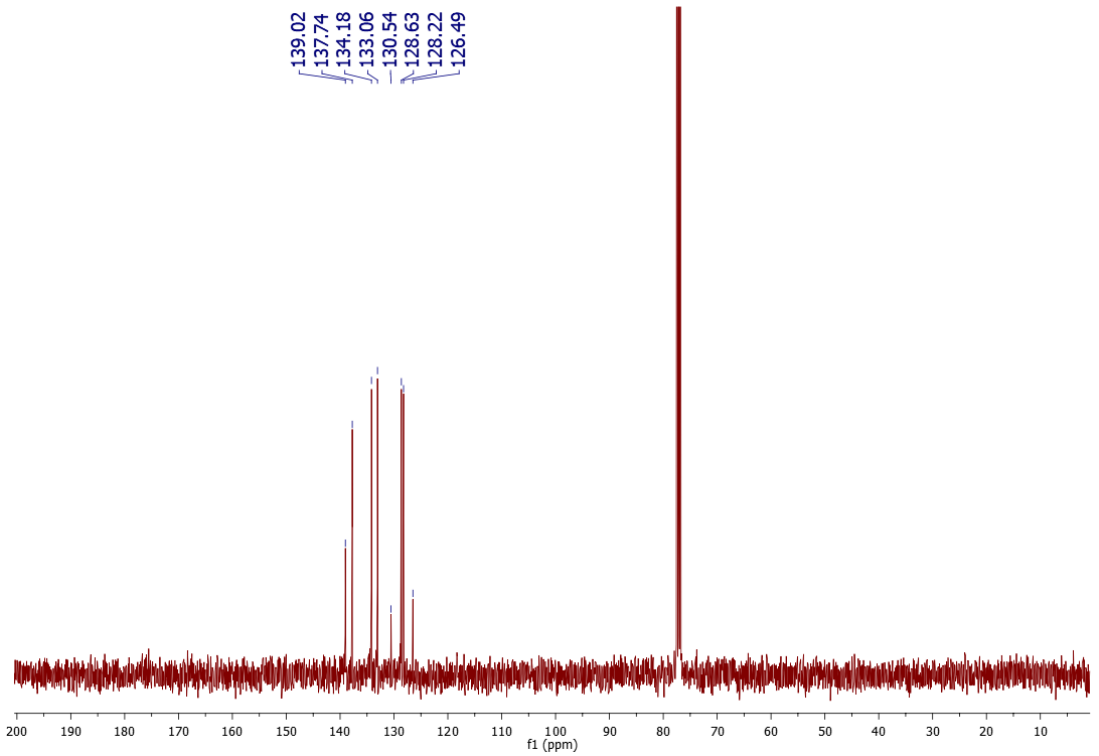
Benzyl 3,4,5,6-tetrahydro-2H-1,6-methanobenzo[b][1,5]diazecine-7(8H)-carboxylate 7d



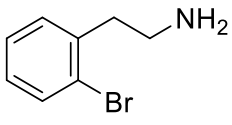


(*E*)-1-Bromo-2-(2-nitrovinyl)benzene S17

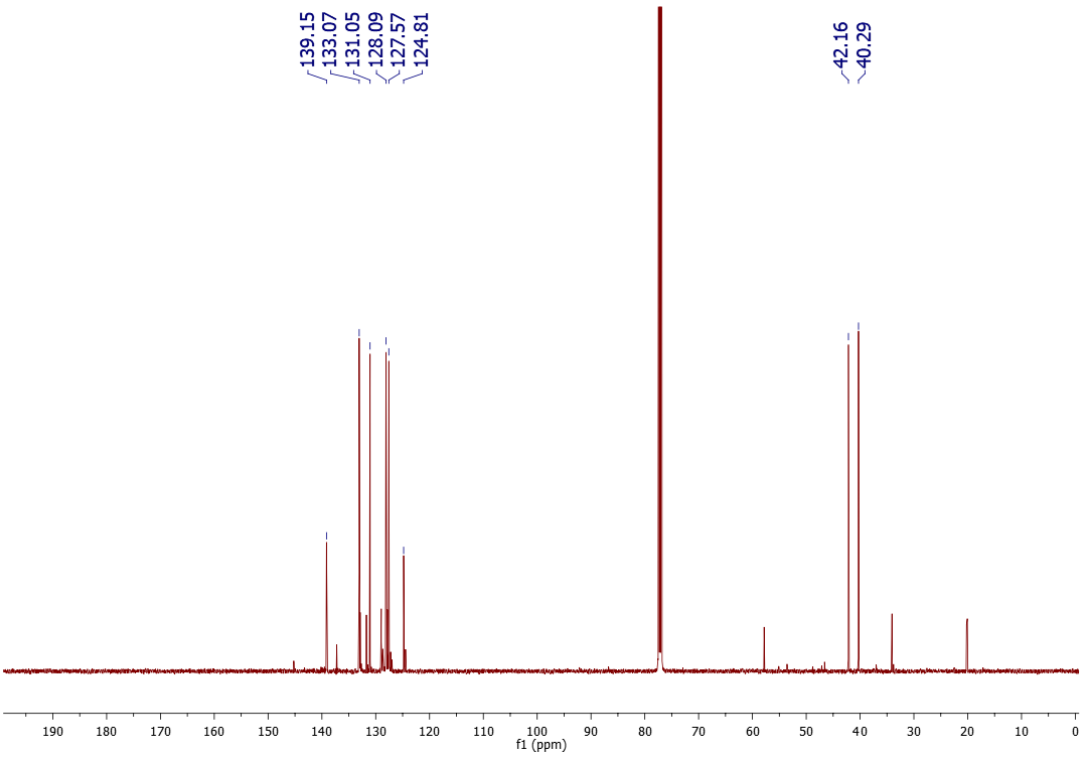




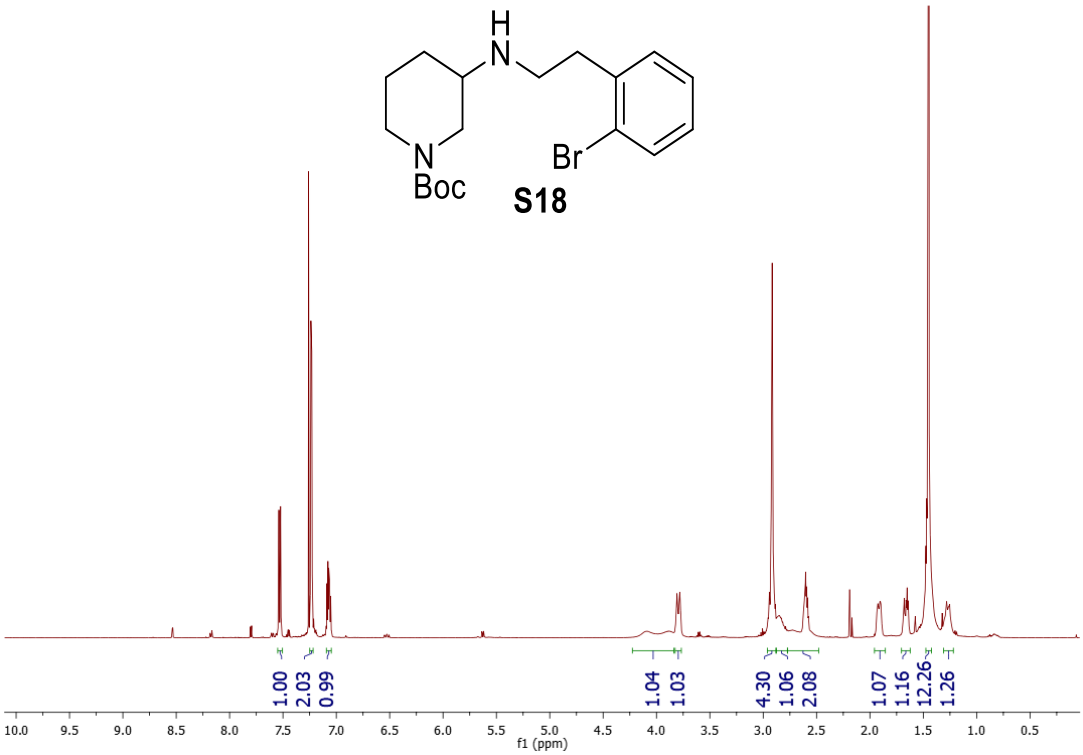
2-(2-Bromophenyl)ethan-1-amine 10b

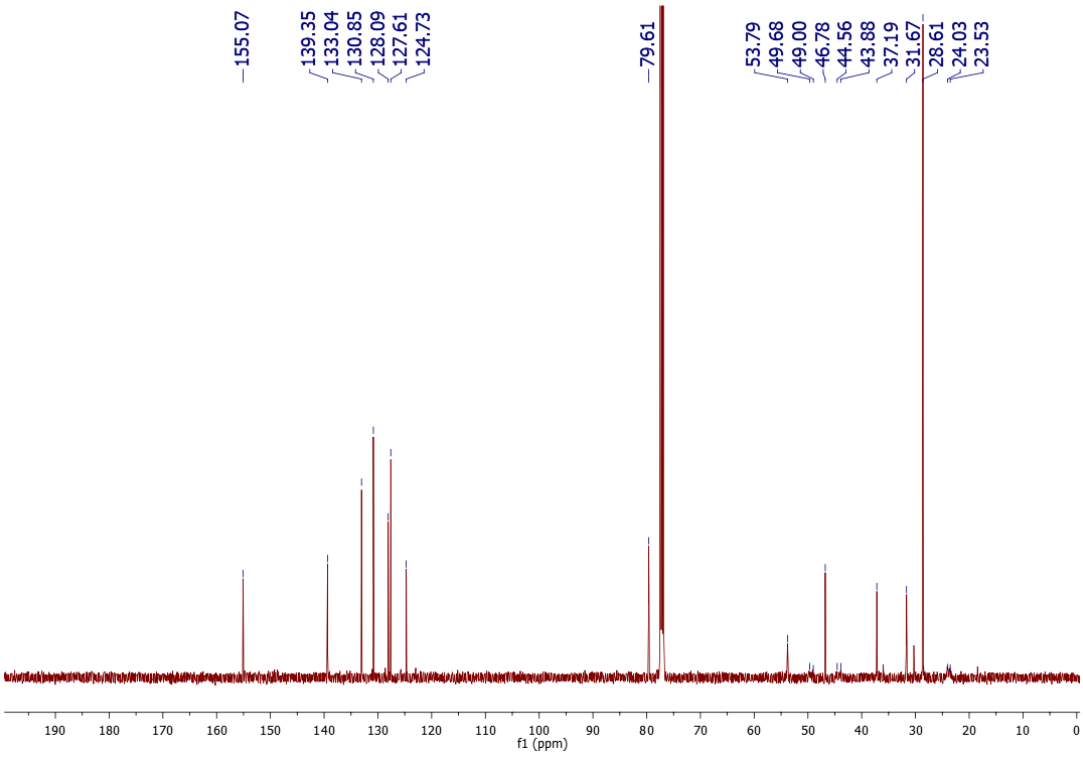


10b

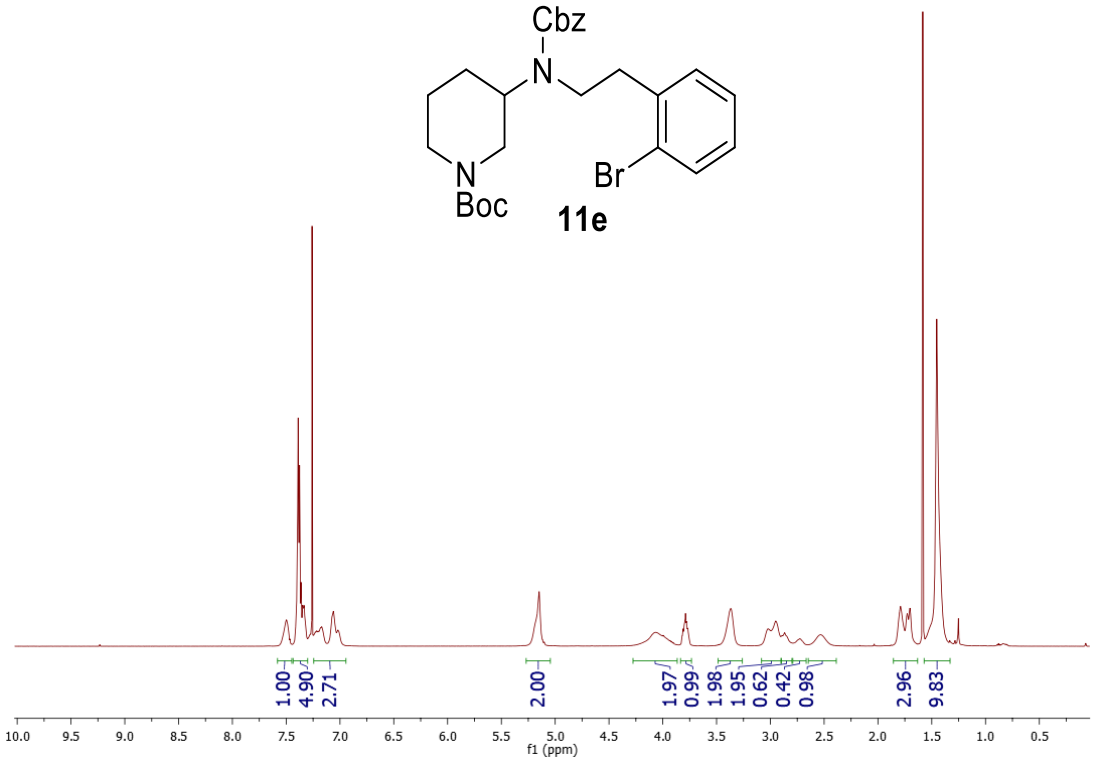


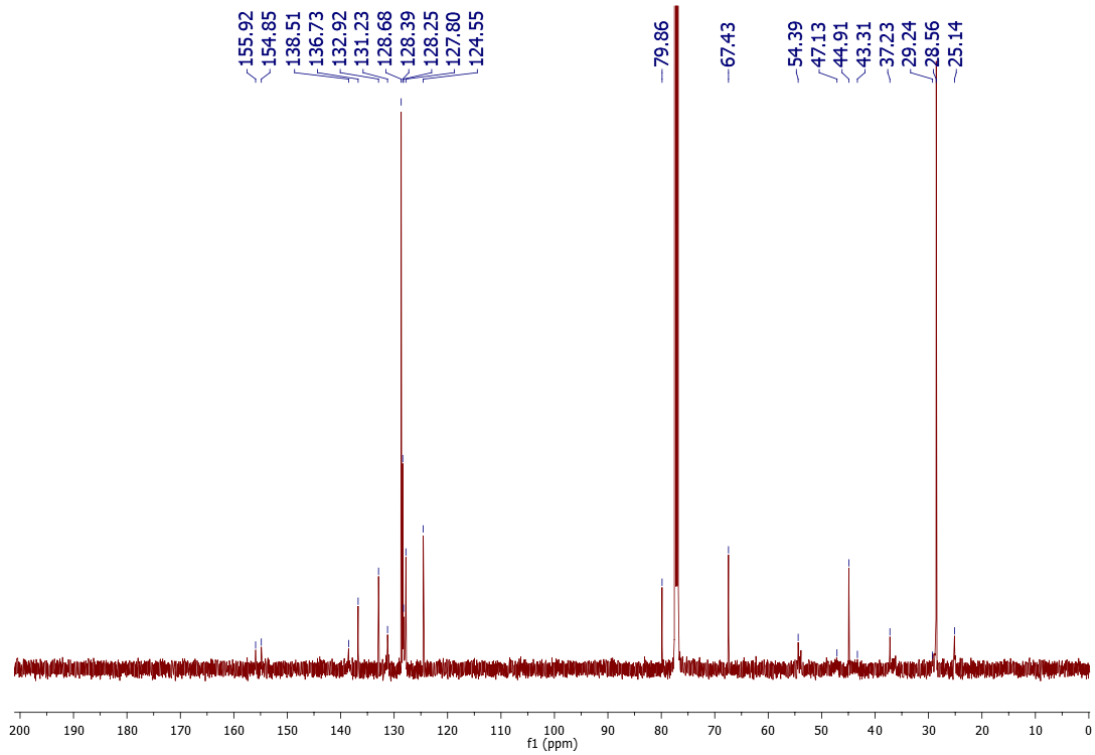
***tert*-Butyl 3-((2-bromophenethyl)amino)piperidine-1-carboxylate S18**





***tert*-Butyl 3-(((benzyloxy)carbonyl)(2-bromophenethyl)amino)piperidine-1-carboxylate 11e**





Benzyl 2,3,4,5,7,8-hexahydro-6H-1,5-methanobenzo[b][1,6]diazecine-6-carboxylate 7e