Electronic Supplementary Material (ESI) for Organic & Biomolecular Chemistry.

(–)-Cytisine: Access to a Stereochemically Defined and Functionally Flexible Piperidine Scaffold

SUPPLEMENTARY INFORMATION

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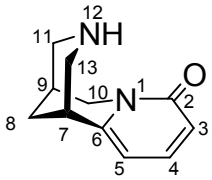
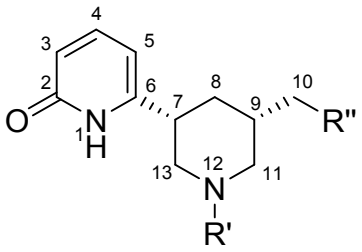
1. General Information

All reagents were purchase from commercial suppliers and used without further purification unless otherwise stated. Anhydrous solvents were obtained by distillation using standard procedures or by using the Anhydrous Engineering Ltd. double alumina and alumina-copper catalysed drying columns. Reactions requiring anhydrous conditions were run under an atmosphere of dry nitrogen; glassware and needles were flamed-dried prior to use or placed in the oven (150 °C) for at least 2 h and allowed to cool either in a desiccator. Thin layer chromatography was performed using aluminium backed 60 F254 silica plates. Visualisation was achieved by UV fluorescence or a basic $KMnO_4$ solution and heat. Flash column chromatography was performed on silica gel (Aldrich 40-63 μm, 230-400 mesh). Infrared spectra were recorded using a Perkin Elmer Spectrum One FT-IR Spectrometer as solids or neat films in the range of 600-4000 cm^{-1}. NMR spectra were recorded using either a Varian 400 MHz or 500 MHz, or JEOL ECP 400 MHz spectrometer. Chemical shifts are quoted in parts per million, coupling constants are given in Hz to the nearest 0.5 Hz. ^{1}H and ^{13}C NMR spectra are referenced to the appropriate residual peak. DEPT 135, COSY, HSQC and HMBC were used where necessary in assigning NMR spectra. Melting points were determined using Reichert melting point apparatus. Mass spectra were determined by the University of Bristol mass spectroscopy service by electrospray ionization (ESI^+) using a Bruker Daltonics micrOTOF II spectrometer.

2a. Numbering systems used in the Supplementary Information for NMR assignment



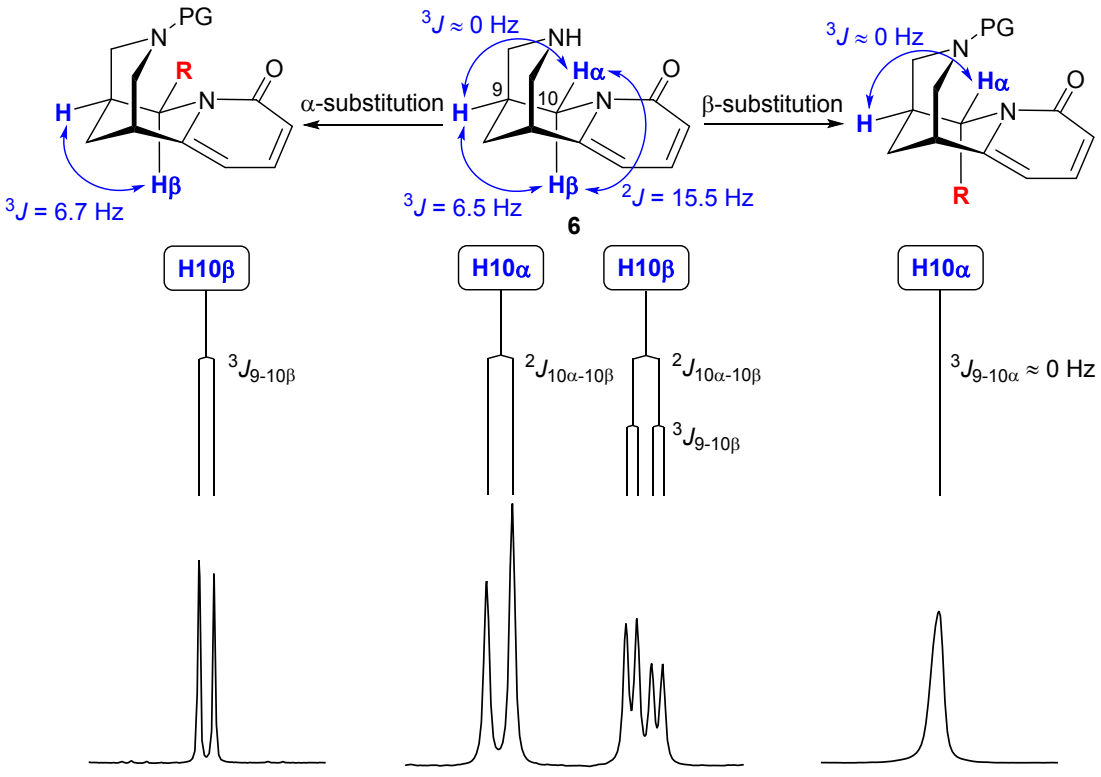
(–)-Cytisine



Piperidine derivatives

2b. ^{1}H NMR Characteristics of cytisine derivatives; H10α vs H10β assignment

Assignment of stereochemistry at C(10) is linked directly to the ^{2}J and ^{3}J values observed for the H10α and H10β. This methodology was used to assign the stereochemistry of C(10) adducts such as **6**.



3. Crystallography

X-ray diffraction experiments on alcohol **20** were carried out at 100(2) K on a Bruker APEX II diffractometer using Mo-Kα radiation (λ = 0.71073 Å), while acid **31** and PNB ester **44** were carried out at 100(2) K on a Bruker Microstar rotating anode diffractometer using Cu-Kα (λ = 1.54178 Å). Intensities were integrated in SAINT[1] and absorption corrections based on equivalent reflections were applied using SADABS.[2]

All structures were solved using Superflip[3,4] and refined against F^2 in SHELXL[5,6] using Olex2[7]. All non-hydrogen atoms were refined anisotropically. While all hydrogen atoms were located geometrically and refined using a riding model, apart from the O-H protons in **20** which were located in the difference map and refined freely.

Crystal structure and refinement data are given in Table 1. Crystallographic data for compounds **20, 31** and **44** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication CCDC 1840054-1840056. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax(+44) 1223 336033, e-mail: deposit@ccdc.cam.ac.uk.

Structural images are shown for each compound following the relevant synthetic procedure.

Crystallography references:

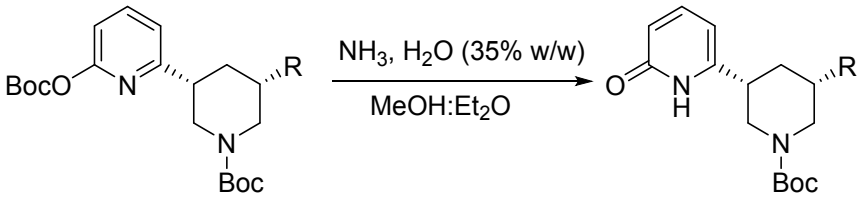
1. Bruker, *SAINT+ Integration Engine, Data Reduction Software, Bruker Analytical X-ray Instruments Inc., Madison, WI, USA*, 2007.
2. Bruker, *SADABS, Bruker AXS area detector scaling and absorption correction, Bruker Analytical X-ray Instruments Inc., Madison, Wisconsin, USA*, 2001.
3. L. Palatinus and G. Chapuis, *J. Appl. Crystallogr.*, 2007, **40**, 786-790.
4. L. Palatinus, S. J. Prathapa and S. van Smaalen, *J. Appl. Crystallogr.*, 2012, **45**, 575-580.
5. G. M. Sheldrick, *Acta Crystallogr., Sect. A: Found. Crystallogr.*, 2008, **64**, 112-122.
6. G. M. Sheldrick, *Acta Crystallogr. C*, 2015, **71**, 3-8.
7. O. V. Dolomanov, L. J. Bourhis, R. J. Gildea, J. A. K. Howard and H. Puschmann, *J. Appl. Crystallogr.*, 2009, **42**, 339-341.

Table 1. Crystal data and structure refinement for **20, 31** and **44**.

Identification code	**Alcohol 20**	**Acid 31**	**PBN ester 44**
Empirical formula	$C_{21}H_{32}N_2O_6$	$C_{21}H_{30}N_2O_7$	$C_{26}H_{25}N_3O_5$
Formula weight	408.48	422.47	459.49
Temperature/K	100(2)	100(2)	100(2)
Crystal system	tetragonal	orthorhombic	monoclinic
Space group	$P4_2$	$P2_12_12_1$	$P2_1$
a/Å	27.1192(8)	8.5893(15)	7.1313(16)
b/Å	27.1192(8)	11.638(2)	8.764(2)
c/Å	6.0742(2)	22.452(4)	17.546(4)
β/°	90	90	91.710(5)
Volume/Å^3	4467.3(3)	2244.4(7)	1096.1(4)
Z	8	4	2
ρ_{calc}g/cm^3	1.215	1.250	1.392
μ/mm^1	0.089	0.781	0.802
F(000)	1760.0	904.0	484.0
Crystal size/mm^3	0.618 × 0.176 × 0.166	0.34 × 0.24 × 0.17	0.576 × 0.422 × 0.11
Radiation	MoKα (λ = 0.71073)	CuKα (λ = 1.54178)	CuKα (λ = 1.54178)
2θ range for data collection/°	1.502 to 52.74	7.876 to 133.184	10.086 to 133.578
Index ranges	$-33 \le h \le 33$, $-33 \le k \le 33$, $-6 \le l \le 7$	$-10 \le h \le 9$, $-13 \le k \le 13$, $-26 \le l \le 25$	$-8 \le h \le 6$, $-10 \le k \le 10$, $-20 \le l \le 20$
Reflections collected	37067	40771	13480
R_{int} / R_{sigma}	0.0711 / 0.0640	0.0753 / 0.0351	0.0526 / 0.0465
Data/restraints/parameters	8969/1/543	3943/0/278	3827/1/307
Goodness-of-fit on F^2	1.024	1.059	1.027
Final R indexes [I>=2σ (I)]	R_1 = 0.0442, wR_2 = 0.0809	R_1 = 0.0341, wR_2 = 0.0892	R_1 = 0.0517, wR_2 = 0.1368
Final R indexes [all data]	R_1 = 0.0649, wR_2 = 0.0889	R_1 = 0.0349, wR_2 = 0.0899	R_1 = 0.0517, wR_2 = 0.1368
Largest diff. peak/hole / e Å^{-3}	0.18/-0.18	0.23/-0.21	0.29/-0.33

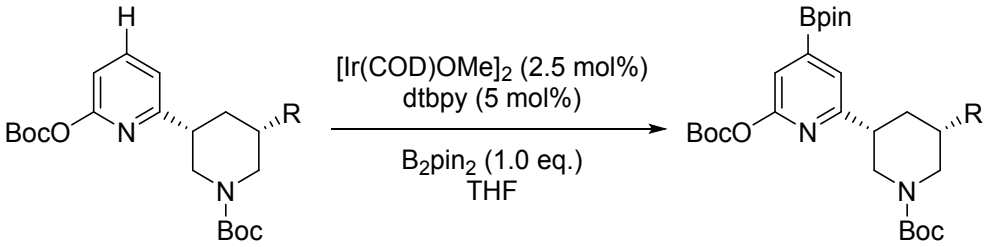
4. General Procedures

General Procedure A: O-Boc pyridone deprotection **(e.g. 23 to 24)**



To a solution of the corresponding *O*-Boc pyridone derivative (1.0 equiv) in an equimolar mixture of Et_2O and MeOH (20 mL/equiv of starting material) was added NH_3,H_2O (35% w/w, 2 mL/equiv of starting material). The reaction mixture was stirred at room temperature for 2 – 20 h (followed by TLC) and the solvent was removed *in vacuo*. The resulting residue was dissolved within DCM and water was added. The aqueous phase was extracted twice with DCM, dried (Na_2SO_4), filtered and concentrated *in vacuo*. The product was purified by flash column chromatography.

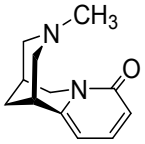
General Procedure B: O-Boc pyridine borylation **(e.g. 23 to 37)**



A Schlenk tube was charged with the corresponding pyridine derivative (1.0 equiv), (1,5-cyclooctadiene)(methoxy) iridium (I) dimer (2.5 mol%), 4,4',-di-*tert*-butyl-2,2'-dipyridyl (5 mol%) and bis(pinacolato)diboron (1.0 equiv). The flask was placed under vacuum and backfilled with nitrogen for three times, THF (0.50 mL/equiv of starting material) was added and the reaction mixture was heated at reflux for 3 – 20 h (followed by TLC). The solvent was removed *in vacuo* and the product was purified by flash column chromatography.

5. Experimental procedures

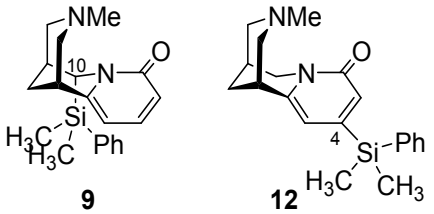
N-Methylcytisine 7



7

To a solution of (–)-cytisine **6** (100 mg, 0.52 mmol) in an equimolar mixture of MeOH and THF (6.0 mL) were succesively added formaldehyde (0.23 mL, 3.11 mmol, 37% aq. sol.) and $NaCNBH_3$ (117 mg, 1.87 mmol) and the reaction mixture was stirred at room temperature for 1.5 h. The solvent was removed *in vacuo,* the crude was partitioned between DCM and water and the aqueous phase was extracted with DCM (3 × 10 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated *in vacuo*. Purification by flash column chromatography [DCM:MeOH (99:1 to 95:5)] gave **7** (92 mg, 85%) as colourless solid. R_f = 0.20 [DCM:MeOH (95:5)]; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 1.63 (m, 1H), 1.75 (m, 1H), 2.03 (s, 3H), 2.12 – 2.19 (m, 2H), 2.34 (m, 1H), 2.73 – 2.86 (m, 3H), 3.78 (dd, *J* = 15.5, 7.0 Hz, 1H), 3.93 (d, *J* = 15.5 Hz, 1H), 5.93 (dd, *J* = 7.0, 1.0 Hz, 1H), 6.35 (dd, *J* = 9.0, 1.5 Hz, 1H), 7.20 (dd, *J* = 9.0, 7.0 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ_C 25.4, 28.0, 35.5, 46.3, 50.0, 62.2, 62.6, 104.8, 116.7, 138.7, 151.6, 163.7. Spectroscopic data were consistent with those reported earlier.[3]

N-Methyl 10-[(dimethyl)phenylsilyl]cytisine 9 and **N-methyl 4-[(dimethyl)phenylsilyl]cytisine 12**



9 **12**

(a) No TMEDA: leads to formation of the C(4)-silyated adduct **12**.

To a solution of N-methylcytisine **7** (100 mg, 0.48 mmol) and chloro(dimethyl)phenylsilane (0.40 mL, 2.40 mmol) in THF (16 mL) at -78 °C was added a solution of LDA [prepared from *n*-BuLi (0.90 mL, 1.44 mmol, 1.6 M in hexanes) and diisopropylamine (0.20 mL, 1.44 mmol) in dry THF (2.7 mL) at -20 °C]. The reaction mixture was stirred for 2 h at -78 °C and then at room temperature overnight. HCl (10 mL, 1 M aq. sol.) was added and the aqueous layer was washed with Et_2O (3 × 10 mL). The aqueous phase was basified with aqueous Na_2CO_3 (sat. sol.) to pH = 9 and extracted with DCM (3 × 10 mL). The combined organic phases were dried

(Na_2SO_4), filtered and concentrated *in vacuo.* Purification by flash column chromatography [DCM:MeOH (100:0 to 95:5)] gave **12** (21 mg, 13%) as a pale yellow oil; followed by **9** (20 mg, 13%) as a colourless oil.

Characterisation data for both compounds shown below.

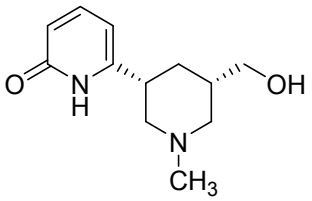
*(b) Optimal conditions involving use of TMEDA; Adduct **12** not observed.*

To a solution of *N*-methylcytisine **7** (100 mg, 0.48 mmol), chloro(dimethyl)phenylsilane (0.20 mL, 0.96 mmol), and TMEDA (0.07 mL, 0.48 mmol) in THF (34 mL) at -78 °C was added a solution of LDA [prepared from *n*-BuLi (0.90 mL, 1.44 mmol, 1.6 M in hexanes) and diisopropylamine (0.20 mL, 1.44 mmol) in THF (13.3 mL) at -20 °C] over *ca.* 5 h. The reaction mixture was stirred at -78 °C for 2 h and then at room temperature overnight. HCl (10 mL, 1 M aq. sol.) was added and the aqueous layer was washed with Et_2O (3 × 10 mL). The aqueous phase was basified with aqueous Na_2CO_3 (to pH = 9) and extracted with DCM (3 × 10 mL). The combined organic phases were dried (Na_2SO_4), filtered and concentrated *in vacuo*. Purification by flash column chromatography [DCM:MeOH (100:0) to (95:5)] afforded **9** (135 mg, 83%) as a colourless oil.

Data for 9 : R_f = 0.34 [DCM:MeOH (95:5)]; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 0.31 (s, 3H), 0.46 (s, 3H), 1.44 (m, 1H), 1.77 (m, 1H), 2.01 (s, 3H), 2.13 (m, 2H), 2.23 (m, 1H), 2.68 (m, 1H), 2.85 (m, 2H), 4.33 (s, 1H), 5.92 (dd, *J* = 7.0, 1.5 Hz, 1H), 6.27 (dd, *J* = 9.0, 1.5 Hz, 1H), 7.15 (dd, *J* = 9.0, 7.0 Hz, 1H), 7.28-7.32 (m, 3H), 7.48-7.52 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ_C -3.09, -1.24, 24.9, 30.7, 35.4, 46.1, 54.2, 63.5, 64.2, 105.0, 115.9, 127.5 (2C), 128.8, 134.3 (2C), 137.6, 138.4, 150.9, 163.4. HRMS (ESI$^+$) calcd for $C_{20}H_{27}N_2OSi$ $[M+H]^+$: 339.1887, found 339.1892.
Spectroscopic data were consistent with those reported earlier.[3]

Data for 12: $[\alpha]_D^{23}$ = –110 (c 1.0, $CHCl_3$); R_f = 0.40 [DCM:MeOH (95:5)]; FTIR ν_{max}/cm^{-1} (neat): 2934, 2778, 1644, 1558, 1427, 1247, 1112, 827, 804, 774; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 0.49 (s, 6H), 1.69 (m, 1H), 1.80 (m, 1H), 2.11 (s, 3H), 2.20 (m, 2H), 2.40 (m, 1H), 2.72 – 2.86 (m, 3H), 3.87 (ddd, *J* = 15.5, 7.0, 1.0 Hz, 1H), 4.00 (d, *J* = 15.5 Hz, 1H), 5.96 (d, *J* = 1.5 Hz, 1H), 6.62 (d, *J* = 1.5 Hz, 1H), 7.32 – 7.37 (m, 3H), 7.49 – 7.52 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ_C -3.14 (2C), 25.6, 28.1, 35.4, 46.4, 49.9, 62.4, 62.7, 108.5, 123.5, 128.1 (2C), 129.6, 134.3 (2C), 136.5, 149.8, 151.2, 162.6; HRMS (ESI$^+$) calcd for $C_{20}H_{27}N_2OSi$ $[M+H]^+$: 339.1887, found 339.1892.

(+)-Kuraramine 11

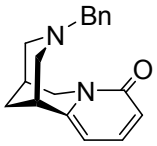


11

To a solution of N-methylcytisine **7** (102 mg, 0.50 mmol), B(O*i*Pr)pin (0.15 mL, 0.75 mmol) and TMEDA (75 µL, 0.50 mmol) in THF (17 mL) was added a solution of LDA (6.0 mL, 0.1 M in THF, 0.60 mmol) dropwise over 2 h and the reaction mixture was stirred at -78 °C overnight. Water (20 mL) and DCM (20 mL) were added, and the aqueous phase was extracted with DCM (2 × 20 mL). The combined organic phases were dried (Na_2SO_4), filtered and concentrated *in vacuo*. The residue was dissolved in THF (2.5 mL) and water (2.5 mL), $NaBO_3 \cdot 4H_2O$ (231 mg, 1.50 mmol) was added and the reaction mixture was stirred under air at room temperature for 6 h. The solution was cooled to 0 °C, $NaBH_4$ (93 mg, 2.50 mmol) was slowly added and the reaction mixture was stirred for 3 h. The crude reaction mixture was distributed between DCM (10 mL) and water (10 mL), and the aqueous phase was extracted with DCM (4 × 10 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated *in vacuo*. Purification by flash column chromatography [DCM:MeOH:NH_4OH (96.7:3.0:0.3 to 94.5:5.0:0.5)] yielded **11** (36 mg, 32% overall yield from **7**) as a yellow solid.

$[\alpha]_D^{23}$ = +4.1 (c 1.0, EtOH) (lit. value: $[\alpha]_D^{20}$ = +9.5 (c 2.1, EtOH)[3]; $[\alpha]_D^{29}$ = +8.4 (c 0.52, EtOH))[4]; R_f = 0.05 [DCM:MeOH (85:15)]; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 1.12 – 1.34 (m, 1H), 1.76 (t, *J* = 11.0 Hz, 1H), 2.05 (m, 3H), 2.31 (s, 3H), 2.88 (s, 1H), 3.02 – 3.11 (m, 2H), 3.46 – 3.59 (m, 2H), 6.03 (d, *J* = 7.0 Hz, 1H), 6.40 (dd, *J* = 7.0, 9.0 Hz, 1H), 7.33 (dd, *J* = 9.0, 7.0 Hz, 1H), *O<u>H</u> and N<u>H</u> signals have not been detected*; ^{13}C NMR (101 MHz, $CDCl_3$) δ_C 31.6, 38.9, 40.2, 46.3, 58.4, 60.4, 65.8, 103.6, 118.0, 141.7, 150.9, 165.2; HRMS (ESI$^+$) calcd for $C_{12}H_{19}N_2O_2$ $[M+H]^+$: 223.1441, found 223.1438. Data for **11** were matched to those reported earlier[3] and to those described for the natural product.[4]

N-Benzylcytisine 14



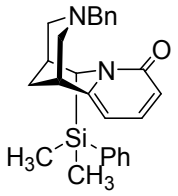
14

To a solution of (–)-cytisine **6** (1.00 g, 5.2 mmol) and K_2CO_3 (3.63 g, 26.2 mmol) in CH_3CN (30 mL) was added benzyl bromide (1.2 mL, 10.5 mmol) and the reaction mixture was heated at reflux for 20 h, cooled to room temperature, and diluted with DCM (100 mL). The suspension was filtered through Celite® and concentrated *in vacuo*. Purification of the crude by flash column chromatography [DCM:MeOH (95:5)] gave **14** (1.41 g, 99%) as a pale yellow solid.

R_f = 0.36 [DCM:MeOH (95:5)]; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 1.77 (d, *J* = 12.5 Hz, 1H), 1.90 (d, *J* = 12.5 Hz, 1H), 2.29 (d, *J* = 10.5 Hz, 1H), 2.34 (d, *J* = 11.0 Hz, 1H), 2.40 (s, 1H), 2.82 (d, *J* = 10.5 Hz, 1H), 2.92 (m, 2H), 3.36 (d, *J* = 13.5 Hz, 1H), 3.44 (d, *J* = 13.5 Hz, 1H), 3.86 (dd, *J* = 15.5, 6.5 Hz, 1H), 4.08 (d, *J* = 15.5 Hz, 1H), 5.88 (d, *J* = 7.0 Hz, 1H), 6.47 (d, *J* = 9.0 Hz, 1H), 6.95 – 7.0 (m, 2H), 7.13 – 7.19 (m, 3H), 7.27 (dd, *J* = 9.0, 7.0 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ_C 25.9, 28.1, 35.5, 49.9, 59.9, 60.0, 62.0, 104.5, 116.5, 126.8, 128.1 (2C), 128.2 (2C), 138.0, 138.5, 151.4, 163.6.

Spectroscopic data were consistent with those reported in the literature for (+)-N-Benzylcytisine.[5]

N-Benzyl 10-[(dimethyl)phenylsilyl]lcytisine 15

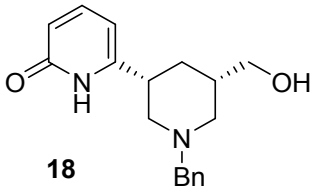


15

To a solution of *N*-benzylcytisine **14** (460 mg, 2.0 mmol), chloro(dimethyl)phenylsilane (0.84 mL, 4.0 mmol) and TMEDA (0.28 mL, 2.0 mmol) in THF (67 mL) at -78 °C, was added a solution of LDA (60 mL, 0.1 M in THF, 6.0 mmol) over 4 h. The reaction mixture was stirred for 2 h at -78 °C and then at room temperature overnight. HCl (50 mL, 1 M) was added and the aqueous layer was extracted with Et_2O (3 × 50 mL). The aqueous phase was basified with Na_2CO_3 (sat. sol) to pH = 9 and extracted with DCM (3 × 50 mL). The combined organic phases were dried (Na_2SO_4), filtered, and concentrated *in vacuo.* Purification of the crude by flash column chromatography [*n*-Hexane:DCM:triethylamine (20:80:1)] gave **15** (643 mg, 78%) as a yellow oil.

R_f = 0.50 [DCM:MeOH (95:5)]; FTIR ν_{max}/cm^{-1} (neat): 2953, 2800, 1648, 1544, 1427, 1252, 1056, 828, 789, 698; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H ppm 0.30 (s, 3H), 0.47 (s, 3H), 1.49 (m, 1H), 1.82 (m, 1H), 2.11 (dd, *J* = 10.5, 1.5 Hz, 1H), 2.25 (s, 1H), 2.40 (dd, *J* = 10.5, 2.5 Hz, 1H), 2.66 (dt, *J* = 10.5, 1.5 Hz, 1H), 2.85 (s, 1H), 2.95 (d, *J* = 10.5 Hz, 1H), 3.22 (d, *J* = 14.0 Hz, 1H), 3.44 (d, *J* = 14.0 Hz, 1H), 4.41 (s, 1H), 5.82 (dd, *J* = 7.0, 1.0 Hz, 1H), 6.40 (dd, *J* = 9.0, 1.0 Hz, 1H), 6.85 – 6.90 (m, 2H), 7.11 – 7.14 (m, 3H), 7.16 (dd, *J* = 9.0, 7.0 Hz, 1H), 7.29 (m, 3H), 7.49 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ_C ppm -3.22, -1.26, 25.4, 31.0, 35.5, 54.2, 60.5, 62.0, 62.6, 105.1, 115.7, 126.8, 127.6 (2C), 128.1 (2C), 128.2 (2C), 128.9, 134.4 (2C), 137.6, 138.3, 138.4, 150.8, 163.4; HRMS (ESI$^+$) calcd for $C_{26}H_{31}N_2OSi$ $[M+H]^+$: 415.2200, found 415.2206.

6-((3*R*,5*S*)-1-Benzyl-5-[(hydroxymethyl)piperidin-3-yl]pyridin-2(1*H*)-one 18



18

To a solution of N-benzylcytisine **14** (460 mg, 2.00 mmol), B(O*i*Pr)pin (0.60 mL, 3.00 mmol) and TMEDA (0.30 mL, 2.00 mmol) in THF (68 mL) was added LDA (24.0 mL, 0.1 M in THF, 2.40 mmol) dropwise over 2 h and the reaction mixture was stirred at -78 °C overnight. Water (30 mL) and DCM (100 mL) were added, and the aqueous phase was extracted with DCM (2 × 50 mL).[**]

After the organic phases were concentrated *in vacuo*, the resulting residue was dissolved in THF (10 mL) and water (10 mL), followed by $NaBO_3 \cdot 4H_2O$ (923 mg, 6.00 mmol). The reaction mixture was stirred under air at room temperature for 6 h. After cooled to 0 °C, $NaBH_4$ (374 mg, 10.0 mmol) was slowly added and the reaction mixture was stirred for 3 h. The crude mixture was distributed between DCM (25 mL) and water (25 mL), and the aqueous phase was extracted with DCM (4 × 25 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated *in vacuo*. Purification by flash column chromatography [DCM:MeOH:NH_4OH (96.7:3.0:0.3 to 94.5:5.0:0.5)] gave piperidine **18** (312 mg, 52% from **14**) as a yellow solid.

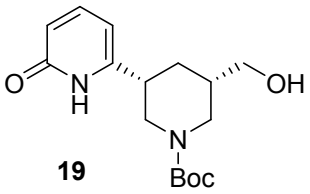
Data for **18:** R_f = 0.24 [DCM:MeOH:NH_4OH (89:10:1)]; m.p. 83 °C (DCM/*n*-Hexane); FTIR ν_{max}/cm^{-1} (neat): 3290, 2911, 2812, 1644, 1611, 1452, 1061, 1008, 733, 698; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 1.22 – 1.27 (m, 1H), 1.86 (t, *J* = 11.0 Hz, 1H), 2.02 – 2.09 (m, 3H), 2.89 (m, 1H), 3.00 – 3.08 (m, 2H), 3.48 – 3.52 (m, 2H), 3.55 – 3.60 (m, 2H), 6.02 (d, *J* = 7.0 Hz, 1H), 6.39 (d, *J* = 9.0 Hz, 1H), 7.21 – 7.27 (m, 5H), 7.33 (dd, *J* = 9.0, 7.0 Hz, 1H)*; O<u>H</u> and N<u>H</u> signals have not been detected*; ^{13}C NMR (101 MHz, $CDCl_3$) δ_C 32.4, 38.6, 40.2, 56.2, 58.0,

63.1, 65.9, 103.7, 117.9, 127.2, 128.4 (2C), 129.2 (2C), 137.9, 141.7, 151.2, 165.2; HRMS (ESI$^+$) calcd for $C_{18}H_{23}N_2O_2$ [M+H]$^+$: 299.1754, found 299.1764.

** Isolation of **17** could be done at this stage following solvent removal and purification of the crude product by rapid flash chromatography [EtOAc:Et_3N (99:1 to 98:2)] to give **17** as a colourless oil. Generally, however, **17** was not purified but used directly in the next step.

Data for **17**: $[\alpha]_D^{23}$ = –180 (c 1.0, $CHCl_3$); R_f = 0.20 [EtOAc:Et_3N (99:1)]; FTIR ν_{max}/cm^{-1} (neat): 2968, 2926, 2799, 2762, 2225, 1635, 1560, 1513, 1127, 727, 698; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H 1.25 (s, 12H), 1.65 (m, 1H), 1.77 (dt, *J* = 13.0, 3.0 Hz, 1H), 2.33 (d, *J* = 10.5 Hz, 1H), 2.40 (dd, *J* = 11.0, 3.0 Hz, 1H), 2.64 (s, 1H), 2.90 – 2.96 (m, 2H), 3.08 (d, *J* = 11.0 Hz, 1H), 3.42 (d, *J* = 13.5 Hz, 1H), 3.52 (s, 1H), 3.58 (d, *J* = 13.5 Hz, 1H), 6.40 (d, *J* = 7.0 Hz, 1H), 6.72 (dd, *J* = 9.0, 1.0 Hz, 1H), 7.07 – 7.12 (m, 2H), 7.18 – 7.25 (m, 3H), 7.52 (dd, *J* = 9.0, 7.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 25.3 (2C), 25.5 (2C), 27.5, 27.9, 35.4, 55.0, 57.8, 61.6, 62.6, 79.9 (2C), 110.2, 110.5, 127.0, 128.2 (2C), 128.5 (2C), 138.0, 140.9, 155.0, 164.2; ^{11}B NMR (160 MHz, $CDCl_3$) δ_B 13.7; HRMS (ESI$^+$) calcd for $C_{24}H_{32}BN_2O_3$ [M+H]$^+$: 407.2500, found 407.2483.

***tert*-Butyl (3*S*,5*R*)-3-(hydroxymethyl)-5-(6-oxo-1,6-dihydropyridin-2-yl)piperidine-1-carboxylate 19**



19

To a solution of alcohol **18** (290 mg, 0.97 mmol) in MeOH (10 mL) was added HCl (1.9 mL, 0.50 M in MeOH, 0.97 mmol) and the resulting solution was stirred for 10 min at room temperature. $Pd(OH)_2$/C (58 mg, 20% w/w) was added, and the reaction mixture was stirred under hydrogen atmosphere (1 atm) for 18 h. The solution was filtered through Celite®, the solvent was removed *in vacuo*, NH_4OH (3 mL) was added and then evaporated *in vacuo*. The crude reaction was dissolved in THF (3.8 mL) and H_2O (0.3 mL), followed by the addition of Na_2CO_3 (102 mg, 2.91 mmol) and Boc_2O (0.2 mL, 0.97 mmol). The reaction mixture was stirred at room temperature for 3 days. The solution was distributed between DCM (10 mL) and water (10 mL), and the aqueous phase was extracted with DCM (3 × 10 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated. Purification of the

crude by flash column chromatography [DCM:MeOH:NH_4OH (94.5:5:0.5)] gave alcohol **19** (225 mg, 75%) as a colourless solid.

$[\alpha]_D^{24}$ = –13 (c 3.8, MeOH); R_f = 0.77 [DCM:MeOH (95:5)]; m.p. 119-122 °C (DCM/*n*-Hexane); FTIR ν_{max}/cm^{-1} (neat): 2925, 1650, 1613, 1425, 1171, 1142, 1009, 880, 729; ^{1}H NMR (500 MHz, MeOD, 52 °C) δ_H 1.33-1.50 (m, 10H), 1.75 (m, 1H), 2.05 (d, *J* = 12.5 Hz, 1H), 2.53 (d, *J* = 12.5 Hz, 1H), 2.66 (tt, *J* = 3.5, 15.5 Hz, 1H), 2.77 (t, *J* = 12.5 Hz, 1H), 3.43 (m, 1H), 3.49 (dd, *J* = 5.5, 11.0 Hz, 1H), 4.24 (m, 2H), 6.25 (d, *J* = 6.5 Hz, 1H), 6.40 (d, *J* = 9.0 Hz, 1H), 7.51 (dd, *J* = 6.5, 9.0 Hz, 1H), *OH and NH signals have not been detected*; ^{13}C NMR (125 MHz, MeOD, 52 °C) δ_C 27.7, 32.8, 38.6, 39.9, 63.9, 80.1, 103.8, 117.2, 142.2, 150.3, 155.0, 164.9; HRMS (ESI^+) calcd for $C_{16}H_{24}N_2O_4$ $[M+H]^+$: 309.1809, found: 309.1809.

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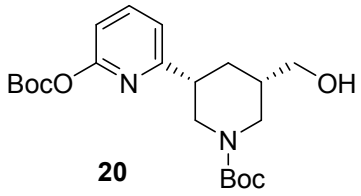
tert-Butyl (3*R*,5*S*)-7-(2-((_tert_-butoxycarbonyl)oxy)-1,2-dihydropyridin-6-yl)-9-(hydroxymethyl)piperidine-12-carboxylate 20



20

To a solution of alcohol **18** (290 mg, 0.97 mmol) in MeOH (10 mL) was added HCl (1.9 mL, 0.50 M in MeOH, 0.97 mmol) and the resulting solution was stirred for 10 min at room temperature. $Pd(OH)_2$/C (58 mg, 20% w/w) was added, and the reaction mixture was stirred under hydrogen (1 atm) for 18 h. The solution was filtered through Celite®, the solvent was removed *in vacuo*, NH_4OH (3 mL) was added and then evaporated *in vacuo.* The residue was dissolved in THF (3.8 mL) and H_2O (0.3 mL), followed by the addition of Na_2CO_3 (736 mg, 6.98 mmol) and Boc_2O (0.5 mL, 2.33 mmol) and the reaction mixture was stirred at room temperature for 3 days. The solution was distributed between DCM (10 mL) and water (10 mL) and the aqueous phase was extracted with DCM (3 × 10 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated *in vacuo*. Purification by flash column chromatography [DCM:MeOH:NH_4OH (94.5:5:0.5)] gave alcohol **20** (297 mg, 75%) as a colourless solid.

$[\alpha]_D^{23}$ = –41 (c 1.0, $CHCl_3$); R_f = 0.30 [DCM:MeOH (93:7)]; m.p. 105 °C (DCM/*n*-Hexane); FTIR ν_{max}/cm^{-1} (neat): 3422, 2926, 1752, 1665, 1424, 1250, 1140, 1057, 860; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 1.43 (s, 9H), 1.53 (s, 9H), 1.55 (s, 1H), 1.83 (m, 2H), 2.03 (d, *J* = 12.0 Hz, 1H), 2.45 (m, 1H), 2.85 (m, 2H), 3.52 (m, 2H), 4.26 (s, 2H), 6.96 (d, *J* = 8.0 Hz, 1H), 7.07 (d, *J* = 7.5 Hz, 1H), 7.68 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ_C 27.7 (3C), 28.5 (3C), 33.5, 38.3, 43.5, 48.7, 55.8, 65.6, 79.8, 84.0, 113.7, 120.1, 140.0, 151.1, 154.9, 157.5, 161.8; HRMS (ESI^+) calcd for

$C_{21}H_{33}N_2O_6$ $[M+H]^+$: 409.2333, found: 409.2345, $C_{21}H_{32}N_2NaO_6$ $[M+Na]^+$: 431.2153, found: 431.2168.

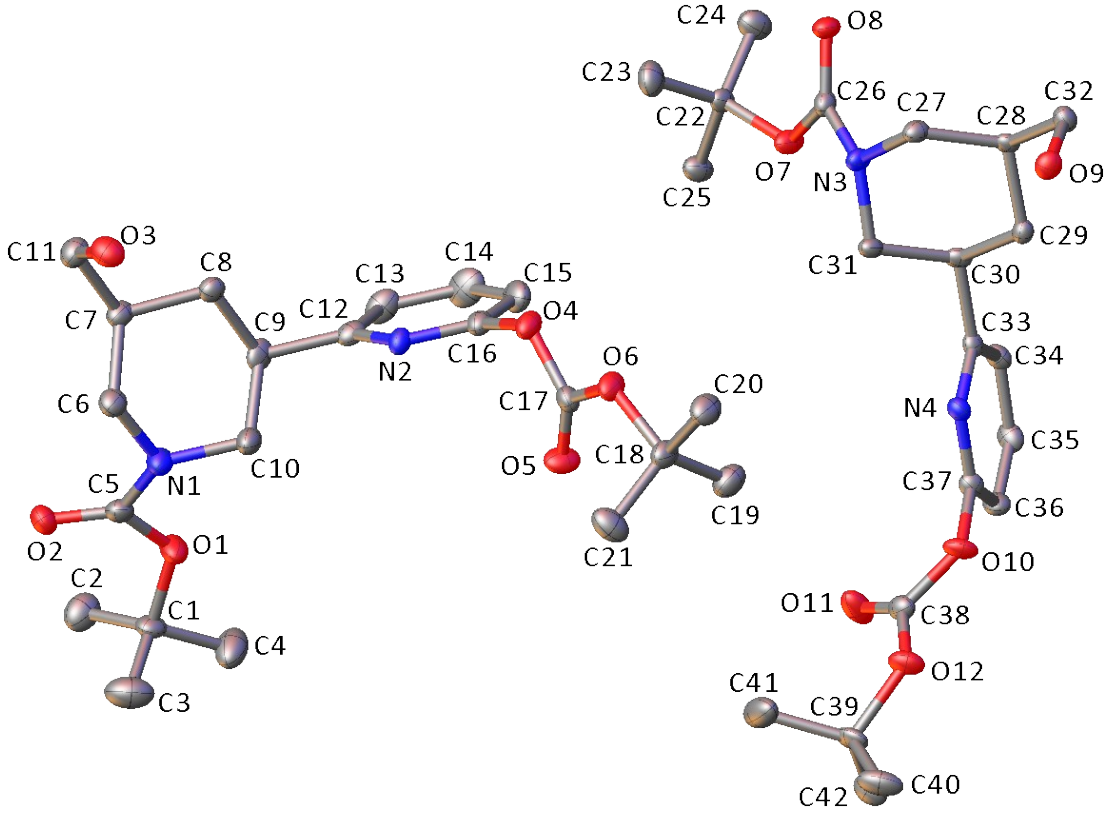
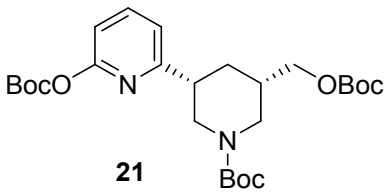


Illustration of the structure of **20** with atomic numbering scheme depicted. Ellipsoids are depicted at the 50% probability level and hydrogen atoms are omitted for clarity.

***tert*-Butyl (3*S*,5*R*)-3-(((*tert*-butoxycarbonyl)oxy)methyl)-5-(6-((*tert*-butoxycarbonyl)oxy) pyridin-2-yl)piperidine-1-carboxylate 21**



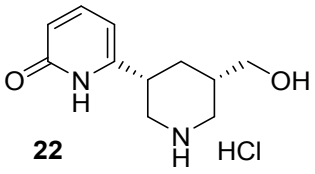
21

To a solution of alcohol **18** (66 mg, 0.22 mmol) in MeOH (2 mL) was added HCl (0.44 mL, 0.50 M in MeOH, 0.22 mmol) and the solution was stirred for 10 min at room temperature. $Pd(OH)_2/C$ (14 mg, 20% w/w) was added, and the reaction mixture was stirred under hydrogen atmosphere (1 atm) for 18 h. The solution was filtered through Celite®, the solvent was removed *in vacuo*, NH_4OH (3 mL) was added and then evaporated *in vacuo*. The crude product was suspended in DCM (1.5 mL) and triethylamine (0.13 mL, 0.92 mmol), DMAP (7 mg, 10% w/w) and Boc_2O (0.16 mL, 0.70 mmol) were added. The reaction mixture was

stirred for 18 h at room temperature. The solution was diluted with DCM (10 mL) and the organic phase was washed with NH_4Cl (10 mL, aq. sat. sol.), dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash column chromatography [Et_2O:*n*-Hexane (1:4 to 1:1)] gave piperidine **21** (56 mg, 50%) as a colourless oil.

R_f = 0.63 [DCM:MeOH, 2% MeOH)]; FTIR ν_{max}/cm^{-1} (neat): 2922, 2852, 1760, 1742, 1693, 1281, 1254, 1145, 858, 753; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H 1.35-1.60 (m, 28H), 1.93-2.15 (m, 2H), 2.49 (s, 1H), 2.88 (s, 2H), 3.88-4.09 (m, 2H), 4.27 (s, 2H), 6.99 (d, *J* = 8.5 Hz, 1H), 7.08 (dd, *J* = 8.5, 5.0 Hz, 1H), 7.70 (t, *J* = 7.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 27.6 (3C), 27.7 (3C), 28.4 (3C), 32.8-34.1 (rotamers), 38.2-39.3 (conformers), 43.0-43.9 (conformers), 47.2-48.3 (conformers), 48.4-49.3 (conformers), 68.9, 69.9, 79.8, 82.0, 83.8, 113.7, 120.1, 139.9, 150.9, 153.5, 154.6, 155.1, 157.4, 161.2; HRMS (ESI$^+$) calcd for $C_{26}H_{41}N_2O_8$ $[M+H]^+$: 509.2857, found: 509.2834.

6-((3R, 5S)-5-(hydroxymethyl)piperidin-3-yl)pyridine-2(1H)-one hydrochloride salt 22

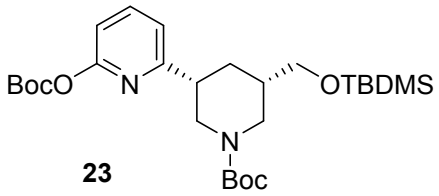


22

To a solution of piperidine**18** (20 mg, 0.07 mmol) in MeOH (1 mL) was added palladium on activated charcoal 10% (0.9 mg) and the reaction mixture was stirred under hydrogen atmosphere for 24 h. The solution was filtered through Celite® and concentrated. The residue was dissolved in a solution of HCl in MeOH (0.5 M, 5 mL) and concentrated in vacuo. The crude was dissolved in the minimal amount of MeOH (ca 0.1 mL), acetone was added slowly (ca 10 mL) and the solid product was collected by filtration *a*ffording **22** (10 mg, 70%) as a colourless solid.

$[\alpha]_D^{23}$ = -20 (c 3.5, MeOH); m.p. >200 °C (acetone); FTIR ν_{max}/cm^{-1} (neat): 2950, 2806, 1645, 1610, 1444, 1198, 1127, 1006, 833, 797; ^{1}H NMR (500 MHz, MeOD) δ_H 1.60 (m, 1H), 2.13 (m, 2H), 2.85 (t, *J* = 13.5 Hz, 1H), 3.15 (m, 2H), 3.37 (s, 1H), 3.48-3.64 (m, 4H), 6.35 (d, *J* = 7.5 Hz, 1H), 6.48 (d, *J* = 9.5 Hz, 1H), 7.58 (dd, *J* = 9.5, 7.5 Hz, 1H); ^{13}C NMR (125 MHz, MeOD) δ_C 30.9, 36.3, 37.0, 45.8, 46.1, 63.0, 104.6, 117.8, 142.4, 148.2, 164.9; HRMS (ESI$^+$) calcd for $C_{11}H_{17}N_2O_2$ $[M+H]^+$: 209.1285, found 209.1288.

***tert*-Butyl (3*R*,5*S*)-3-(6-((*tert*-butoxycarbonyl)oxy)pyridin-2-yl)-5-(((*tert*-butyldimethyl silyl)oxy)methyl)piperidine-1-carboxylate 23.**

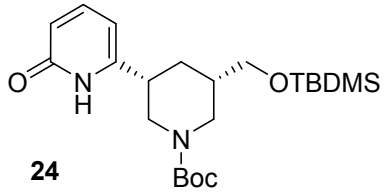


23

To a solution of alcohol **20** (102 mg, 0.25 mmol) in DCM (2.5 mL) at 0 °C were added triethylamine (52 µL, 0.37 mmol) and TBDMSCl (56 mg, 0.37 mmol), and the reaction mixture was warmed to room temperature and stirred for 18 h. The solution was diluted with EtOAc (10 mL) and the organic phase was washed with NH_4Cl (10 mL, aq. sat. sol.), water (10 mL) and brine (10 mL). The organic phase was dried (Na_2SO_4), filtered and concentrated *in vacuo.* Purification by flash column chromatography [Et_2O:*n*-Hexane (10:90 to 50:50)] gave **23** (126 mg, 97%) as a colourless oil.

R_f = 0.20 [Et_2O:*n*-Hexane (1:4)]; FTIR ν_{max}/cm^{-1} (neat): 2954, 2929, 2856, 1760, 1692, 1249, 1219, 1141, 835, 775; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H ^{1}H NMR (500 MHz, $CDCl_3$) δ_H 0.06 (s, 6H), 0.91 (s, 9H), 1.48 (s, 10H), 1.58 (s, 9H), 1.84 (s, 1H), 1.99 (s, 1H), 2.44 (t, *J* = 12.0 Hz, 1H), 2.87 (m, 2H), 3.44-3.54 (m, 2H), 4.32 (m, 2H), 7.01 (d, *J* = 7.5 Hz, 1H), 7.10 (d, *J* = 7.5 Hz, 1H), 7.72 (dd, *J* = 7.5, 7.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C -5.43 (2C), 18.3, 25.9 (3C), 27.7 (3C), 28.5 (3C), 33.3, 38.4, 43.3, 47.8, 49.0, 65.8, 79.5, 83.9, 113.5, 120.2, 139.8, 151.0, 154.8, 157.3, 162.4; HRMS (ESI$^+$) calcd for $C_{27}H_{47}N_2O_6Si$ [M+H]$^+$: 523.3198, found 523.3196, calcd for $C_{27}H_{46}N_2NaO_6Si$ [M+Na]$^+$: 545.3017, found 545.3015.

***tert*-Butyl (3*S*,5*R*)-3-(((*tert*-butyldimethylsilyl)oxy)methyl)-5-(6-oxo-1,6-dihydropyridin-2-yl)piperidine-1-carboxylate 24**



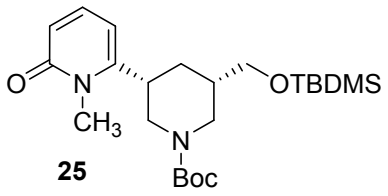
24

Silyl ether **23** (131 mg, 0.25 mmol) was deprotected according to the **General Procedure A.** Purification by flash chromatography [EtOAc:*n*-Hexane (3:1) to EtOAc] gave pyridone **24** (105 mg, 90%) as a colourless oil.

$[\alpha]_D^{22}$ = -6 (c 9.8, MeOH); R_f = 0.12 [EtOAc:*n*-Hexane (3:1)]; FTIR ν_{max}/cm^{-1} (neat): 2928, 2852, 1693, 1650, 1616, 1250, 1145, 834, 774; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H 0.06 (s, 6H), 0.91 (s, 9H), 1.48 (s, 9H), 1.73 – 1.94 (m, 2H), 2.02 (m, 1H), 2.51 (m, 1H), 2.72 (m, 1H), 2.84 (m, 1H), , 3.36 – 3.61 (m, 2H), 4.15 – 4.44 (m, 2H), 6.06 (d, *J* = 7.0 Hz, 1H), 6.42 (d, *J* = 8.5 Hz,

1H), 7.39 (dd, *J* = 7.0, 8.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C -5.45 (2C), 18.3, 25.9 (3C), 28.4 (3C), 32.9, 37.7-39.9 (rotamers), 40.3, 45.6-46.6 (rotamers), 47.0-48.6 (rotamers), 65.5, 79.8, 103.7, 118.1, 145.5, 150.4, 154.6, 165.4; HRMS (ESI$^+$) calcd for $C_{22}H_{39}N_2O_4Si$ $[M+H]^+$: 423.2674, found 423.2673, calcd for $C_{22}H_{38}N_2NaO_4Si$ $[M+Na]^+$: 445.2493, found 445.2496.

***tert*-Butyl (3*S*,5*R*)-3-(((*tert*-butyldimethylsilyl)oxy)methyl)-5-(1-methyl-6-oxo-1,6-dihydropyridin-2-yl)piperidine-1-carboxylate 25**

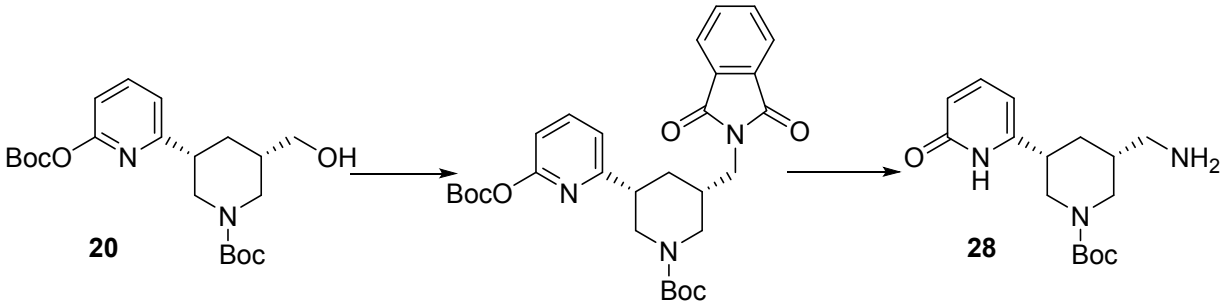


25

To a solution of pyridone **24** (42 mg, 0.10 mmol) and Cs_2CO_3 (98 mg, 0.30 mmol) in THF (0.50 mL) was added CH_3I (12 µL, 0.20 mmol), and the reaction mixture was stirred for 18 h at room temperature (using a sealed tube). The solution was diluted with EtOAc (10 mL), the aqueous phase was washed with water (10 mL), brine (10 mL), and then dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash column chromatography [EtOAc:*n*-Hexane (3:1 to 1:0)] gave **25** (30 mg, 70%) as a colourless oil.

R_f = 0.12 [EtOAc:*n*-Hexane (3:1)]; FTIR ν_{max}/cm^{-1} (neat): 2953, 2927, 2855, 1691, 1662, 1551, 1251, 1148, 835, 776; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H 0.08 (s, 6H), 0.93 (s, 9H), 1.50 (m, 10H), 1.86 (m, 1H), 2.04 (m, 1H), 2.45 – 2.58 (m, 2H), 2.82 (m, 1H), 3.46 – 3.61 (m, 2H), 3.66 (s, 3H), 4.20 – 4.51 (m, 2H), 6.06 (d, *J* = 6.0 Hz, 1H), 6.52 (d, *J* = 9.0 Hz, 1H), 7.28 (app t, *J* = 9.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C -5.44 (2C), 18.3, 25.9 (3C), 28.4 (3C), 30.5, 33.4, 38.8, 39.2, 65.3, 80.2, 103.3, 118.4, 138.4, 150.4, 154.2, 164.0; *C11 and C13 not observed*; HRMS (ESI$^+$) calcd for $C_{23}H_{41}N_2O_4Si$ $[M+H]^+$: 437.2830, found 437.2816, calcd for $C_{23}H_{40}N_2NaO_4Si$ $[M+Na]^+$: 459.2650, found 459.2638.

***tert*-Butyl (3*R*,5*R*)-3-(aminomethyl)-5-(6-oxo-1,6-dihydropyridin-2-yl)piperidine-1-carboxylate 28**



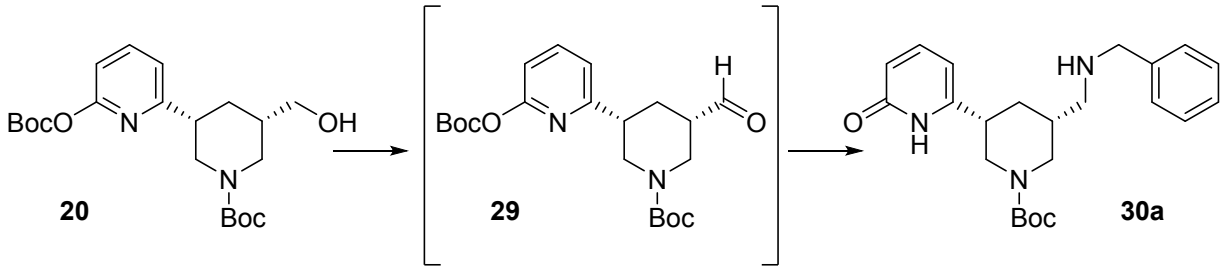
A solution of alcohol **20** (204 mg, 0.50 mmol), PPh_3 (262 mg, 1.00 mmol) and phthalimide (147 mg, 1.00 mmol) in THF (3.0 mL) was cooled at 0 °C and DEAD (0.16 mL, neat, 1.00 mmol) was added dropwise over 3 min. The reaction mixture was allowed to warm up to room temperature and stirred for 16 h. The solvent was removed *in vacuo.* Purification by flash column chromatography [Et_2O:*n*-Hexane (1:1)] gave the phthalimide adduct (237 mg, 88%) as a colourless solid.

R_f = 0.20 [Et_2O:*n*-Hexane (1:1)]; m.p. 107 °C (DCM/*n*-Hexane); FTIR ν_{max}/cm^{-1} (neat): 2984, 2933, 1758, 1710, 1366, 1250, 1138, 723; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 1.36 (s, 9H), 1.53 - 1.56 (m, 10H), 1.98 – 2.21 (m, 2H), 2.44 – 2.54 (m 1H), 2.80 – 2.86 (m, 2H), 3.55 – 3.60 (m, 2H), 4.20 – 4.30 (m, 2H), 6.97 (dd, *J* = 8.0, 0.5 Hz, 1H), 7.02 (dd, *J* = 7.5, 0.5 Hz, 1H), 7.65 – 7.69 (m, 3H), 7.78 – 7.84 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ_C 27.7 (3C), 28.5 (3C), 35.0, 35.9, 41.0, 43.6, 62.3, 64.2, 79.8, 84.0, 113.8, 120.0, 123.4 (2C), 132.0 (2C), 134.1 (2C), 140.0 (2C), 151.0, 154.6, 157.5, 161.4, 168.6; HRMS (ESI$^+$) calcd for $C_{29}H_{36}N_3O_7$ $[M+H]^+$: 538.2548, found 538.2558, calcd for $C_{29}H_{35}N_3NaO_7$ $[M+Na]^+$: 560.2367, found 560.2369.

To a solution of phthalimide adduct (described above) (87 mg, 0.16 mmol) in EtOH (1.0 mL) was added hydrazine hydrate (26 mg, 0.80 mmol) and the reaction mixture was stirred for 18 h at room temperature. The solution was filtered through Celite®, washed with EtOH and concentrated *in vacuo*. Purification by flash column chromatography [DCM:MeOH:NH_4OH (95:5:0.5 to 90:10:1)] gave **28** (22 mg, 44%) as a colourless solid.

R_f = 0.06 [DCM:MeOH:NH_4OH (90:9:1)]; m.p. 132 °C (DCM/*n*-Hexane); FTIR ν_{max}/cm^{-1} (neat): 3367, 2922, 2852, 1727, 1462, 1268, 1146, 726; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H 1.41 – 1.53 (m, 10H), 1.73 (m, 1H), 2.20 (m, 1H), 2.47 (m, 1H), 2.59 – 2.77 (m, 3H), 2.87 (m, 1H), 4.03 – 4.50 (m, 3H), 6.07 (d, *J* = 7.0 Hz, 1H), 6.43 (d, *J* = 8.5 Hz, 1H), 7.39 (dd, *J* = 8.5, 7.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 28.4 (3C), 34.2, 38.7, 40.3, 45.3, 46.4 and 48.4, (2C, *conformers*), 80.1, 103.8, 118.1, 141.7, 150.2, 154.6, 165.2; HRMS (ESI$^+$) calcd for $C_{16}H_{26}N_3O_3$ $[M+H]^+$: 308.1969, found 308.1976.

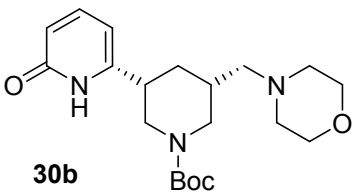
***tert*-Butyl (3*R*,5*R*)-3-((benzylamino)methyl)-5-(6-oxo-1,6-dihydropyridin-2-yl)piperidine-1-carboxylate 30a**



A solution of $(COCl)_2$ (22 µL, 0.26 mmol) in DCM (0.80 mL) was cooled to -78 °C, and a solution of DMSO (36 µL, 0.52 mmol) in DCM (1.0 mL) was added dropwise over 5 min. A solution of alcohol **20** (82 mg, 0.20 mmol) in DCM (0.80 mL) was added over the mixture and the solution was stirred at -78 °C for 15 min. Triethylamine (0.14 mL, 1.00 mmol) was added, and the reaction mixture was stirred at room temperature for 2 h. The solvent was removed *in vacuo*. The crude aldehyde **29** was immediately dissolved in MeOH (10 mL), benzylamine (28 µL, 0.26 mmol) and glacial acetic acid (48 µL, 0.84 mmol) were added and the reaction mixture was stirred for 18 h. $NaCNBH_3$ (9 mg, 0.14 mmol) was added and the solution was stirred for 18 h. Water (10 mL) was added and the pH adjusted to pH = 9 with Na_2CO_3 (aq.sat. sol). The aqueous phase was extracted with DCM (3 × 10 mL) and the combined organic phases were dried (Na_2SO_4), filtered and concentrated *in vacuo*. Purification by flash column chromatography [DCM:MeOH:NH_4OH (94.5:5:0.5)] gave **30a** (58 mg, 73%) as a colourless solid.

R_f = 0.28 [DCM:MeOH (93:7)]; m.p. 147 °C (DCM/*n*-Hexane); FTIR ν_{max}/cm^{-1} (neat): 2926, 2849, 1645, 1613, 1422, 1142, 729, 698 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H 1.38 – 1.56 (m, 9H), 1.87 (m, 1H), 2.20 (m, 1H), 2.48 (m, 1H), 2.52 – 2.64 (m, 2H), 2.72 (m, 1H), 2.89 (m, 1H), 3.74 – 3.90 (m, 2H), 4.13 – 4.46 (m, 2H), 6.05 (d, *J* = 7.0 Hz, 1H), 6.35 (d, *J* = 9.0 Hz, 1H), 7.26 (m, 1H), 7.30 – 7.38 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 28.4 (3C), 34.9, 36.2, 40.3, 47.3, 48.2, 52.5, 54.0, 79.9, 103.8, 118.0, 126.9, 128.1 (2C), 128.4 (2C), 140.3, 141.6, 150.4, 154.6, 165.5; HRMS (ESI$^+$) calcd for $C_{23}H_{32}N_3O_3$ $[M+H]^+$: 398.2438, found 398.2436.

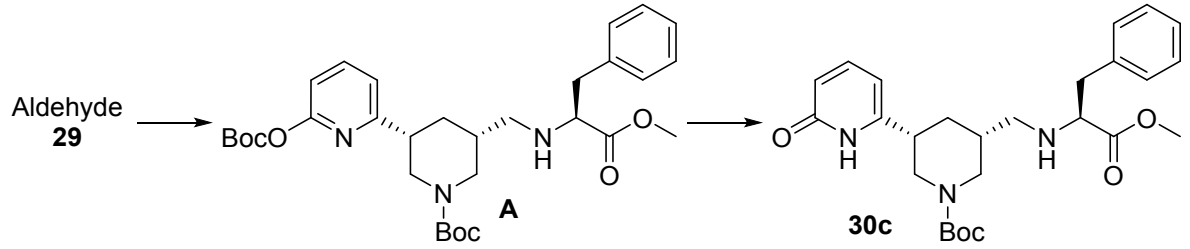
***tert*-Butyl (3*R*,5*R*)-3-(morpholinomethyl)-5-(6-oxo-1,6-dihydropyridin-2-yl)piperidine-1-carboxylate 30b**



A solution of $(COCl)_2$ (22 µL, 0.26 mmol) in DCM (0.80 mL) was cooled to -78 °C, and a solution of DMSO (36 µL, 0.52 mmol) in DCM (1.0 mL) was added dropwise over 5 min. A solution of alcohol **20** (82 mg, 0.20 mmol) in DCM (0.80 mL) was added over the mixture and the solution was stirred at -78 °C for 15 min. Triethylamine (0.14 mL, 1.00 mmol) was added, and the reaction mixture was stirred at room temperature for 2 h. The solvent was removed *in vacuo*. To a solution of the crude aldehyde **29** in MeOH (10.0 mL) were added morpholine (23 µL, 0.26 mmol) and glacial acetic acid (48 µL, 0.84 mmol) and the reaction mixture was stirred for 19 h. $NaCNBH_3$ (9 mg, 0.14 mmol) was added and the reaction mixture was stirred for 5 h. The solution was diluted with DCM (10 mL) and water (10 mL), and the organic phase was washed with $NaHCO_3$ (10 mL, aq. sat. sol.) and brine (10 mL). The organic phase was dried (Na_2SO_4), filtered and concentrated *in vacuo*. Purification by flash column chromatography [DCM:MeOH:NH_4OH (97.25:2.5:0.25 to 94.5:5:0.5)] gave amine **30b** (67 mg, 70%) as a colourless solid.

$[\alpha]_D^{22}$ = -16 (c 2.0, MeOH); R_f = 0.18 [DCM:MeOH (95:5)]; m.p. 147 °C (DCM/*n*-Hexane); FTIR ν_{max}/cm^{-1} (neat): 2922, 2852, 1693, 1654, 1462, 1269, 1120 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H 1.30 – 1.59 (m, 10H), 1.91 (m, 1H), 2.13 – 2.26 (m, 3H), 2.31 – 2.56 (br s, 5H), 2.72 (t, *J* = 12.0 Hz, 1H), 2.90 (t, *J* = 12.0 Hz, 1H), 3.61 – 3.78 (m, 4H), 4.13 – 4.46 (m, 2H), 6.07 (d, *J* = 7.0 Hz, 1H), 6.39 (d, *J* = 9.0 Hz, 1H), 7.39 (m, 1H), 13.2 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 28.4 (3C), 32.7, 35.4, 40.3, 37.5, 48.2, 53.9 (2C), 62.1, 66.9 (2C), 79.9, 103.7, 117.8, 141.7, 150.6, 154.4, 165.5; HRMS (ESI$^+$) calcd for $C_{20}H_{32}N_3O_4$ $[M+H]^+$: 378.2387, found 378.2389.

***tert*-Butyl (3*R*,5*R*)-3-((((*S*)-1-methoxy-1-oxo-3-phenylpropan-2-yl)amino)methyl)-5-(6-oxo-1,6-dihydropyridin-2-yl)piperidine-1-carboxylate 30c**

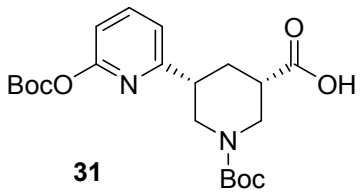


Following the same oxidation procedure as described above, to the solution of the crude aldehyde **29** in MeOH (10.0 mL) was added L-phenylalanine methyl ester hydrochloride (56 mg, 0.26 mmol) and the reaction mixture was stirred for 18 h. $NaCNBH_3$ (9 mg, 0.14 mmol) was added and the reaction mixture was stirred for 5 h. The crude reaction mixture was distributed between DCM (10 mL) and water (10 mL), and the aqueous phase was washed with $NaHCO_3$ (10 mL, aq. sat. sol.) and brine (10 mL). The organic phase was dried (Na_2SO_4), filtered, and concentrated *in vacuo*. Purification by flash column chromatography

[EtOAc:*n*-Hexane (1:4) to EtOAc] gave **the O-Boc protected pyridine A** (52 mg, 46%) as a colourless oil, together with some impurities. However, further purification was not required. R_f = 0.30 [EtOAc:*n*-Hexane (1:1)]; FTIR ν_{max}/cm^{-1} (neat): 2978, 2930, 2856, 1759, 1735, 1687, 1454, 1250, 1218, 1137, 747, 700; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H 1.47 – 1.50 (s, 10H), 1.60 (s, 9H), 1.72 (m, 1H), 2.10 (m, 1H), 2.46 – 2.30 (m, 2H), 2.35 (m, 1H), 2.79 – 2.91 (m, 2H), 2.95 (m, 2H), 3.49 (m, 1H), 3.65 (s, 3H), 4.04 – 4.47 (m, 2H), 7.02 (d, *J* = 8.0 Hz, 1H), 7.08 (d, *J* = 7.5 Hz, 1H), 7.16 – 7.31 (m, 5H), 7.73 (m, 1H); HRMS (ESI$^+$) calcd for $C_{31}H_{44}N_3O_7$ [M+H]$^+$: 570.3174 found 570.3176.

The O-Boc pyridine **A** (prepared above) (28 mg, 0.05 mmol) was deprotected according to the **General Procedure A**. Purification by flash column chromatography [DCM:MeOH:NH_4OH (94.5:5:0.5)] gave **30c** (17 mg, 73%) as a colourless solid.
$[\alpha]_D^{23}$ = –5 (c 0.2, $CHCl_3$); R_f = 0.40 [DCM:MeOH (95:5)]; m.p. 68 °C (DCM/*n*-Hexane); FTIR ν_{max}/cm^{-1} (neat): 2922, 2852, 1735, 1692, 1653, 1463, 1145, 761; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H 1.35 (m, 1H), 1.47 (s, 9H), 1.71 (m, 1H), 2.12 (m, 1H), 2.30 (dd, *J* = 7.0, 12.0 Hz, 1H), 2.42 (m, 1H), 2.58 – 2.70 (m, 2H), 2.82 (m, 1H), 2.90 – 2.99 (m, 2H), 3.48 (t, *J* = 7.0 Hz, 1H), 3.65 (s, 3H), 4.04 – 4.45 (m, 2H), 6.04 (d, *J* = 7.0 Hz, 1H), 6.42 (d, *J* = 9.0 Hz, 1H), 7.14 – 7.33 (m, 5H), 7.38 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 28.4 (3C), 34.6, 36.6, 39.8, 40.4, 45.8 - 48.9 (2C), 51.4, 51.6, 63.3, 80.0, 103.7, 118.2, 126.7, 128.4 (2C), 129.2 (2C), 137.2, 141.6, 150.1, 154.5, 165.1, 175.0; HRMS (ESI$^+$) calcd for $C_{26}H_{36}N_3O_5$ [M+H]$^+$: 470.2649, found 470.2640, calcd for $C_{26}H_{35}N_3NaO_5$ [M+Na]$^+$: 492.2469, found 492.2453.

(3*S*,5*R*)-1-(*tert*-Butoxycarbonyl)-5-(6-((*tert*-butoxycarbonyl)oxy)-1,6-dihydropyridin-2-yl)piperidine-3-carboxylic acid 31



31

A solution of $(COCl)_2$ (29 µL, 0.65 mmol) in DCM (2.5 mL) was cooled to -78 °C, and a solution of DMSO (92 µL, 1.30 mmol) in DCM (2.0 mL) was added dropwise over 5 min. A solution of alcohol **20** (204 mg, 0.50 mmol) in DCM (2.0 mL) was added over the mixture and the solution was stirred at -78 °C for 15 min. Triethylamine (0.35 mL, 2.50 mmol) was added, and the reaction mixture was stirred at room temperature for 2 h. The solvent was removed *in vacuo*. To a solution of the crude aldehyde **29** and 2-methyl-2-butene (1.0 mL, 10.0 mmol) in *t*BuOH (5.0 mL) was added a solution of $NaClO_2$ (407 mg, 4.5 mmol) and $NaH_2PO_4 \cdot H_2O$ (420 mg,

3.5 mmol) in H_2O (5.0 mL), and the reaction mixture was stirred for 3 h at room temperature. The resulting solution was acidified to pH ≈ 3 (HCl, conc. aq. sol.) and the aqueous phase was extracted with EtOAc (5 × 20 mL). The combined organic layers were washed with brine (20 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash column chromatography [DCM:MeOH (95:5)] gave **31** (200 mg, 94%) as a colourless solid.

$[\alpha]_D^{24}$ = –27 (c 1.0, $CHCl_3$); R_f = 0.22 [DCM:MeOH (95:5)]; m.p. 166 °C (DCM/*n*-Hexane); FTIR ν_{max}/cm^{-1} (neat): 3071, 2986, 2929, 1762, 1732, 1639, 1252, 1222, 1132, 862; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H 1.45 (s, 9H), 1.54 (s, 9H), 2.00 (m, 1H), 2.35 (m, 1H), 2.60 (m, 1H), 2.78 – 3.01 (m, 3H), 4.22 – 4.62 (m, 2H), 6.99 (d, *J* = 8.0 Hz, 1H), 7.08 (d, *J* = 7.4 Hz, 1H), 7.74 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 27.7 (3C), 28.4 (3C), 33.2, 41.2, 42.9, 44.6 and 45.4 (conformers), 47.9 and 48.7 (conformers), 80.3, 84.0, 113.9, 120.1, 140.0, 151.0, 154.6, 157.4, 160.7, 178.1; HRMS (ESI$^+$) calcd for $C_{21}H_{29}N_2O_7$ [M-H]$^-$: 421.1980, found 421.1979.

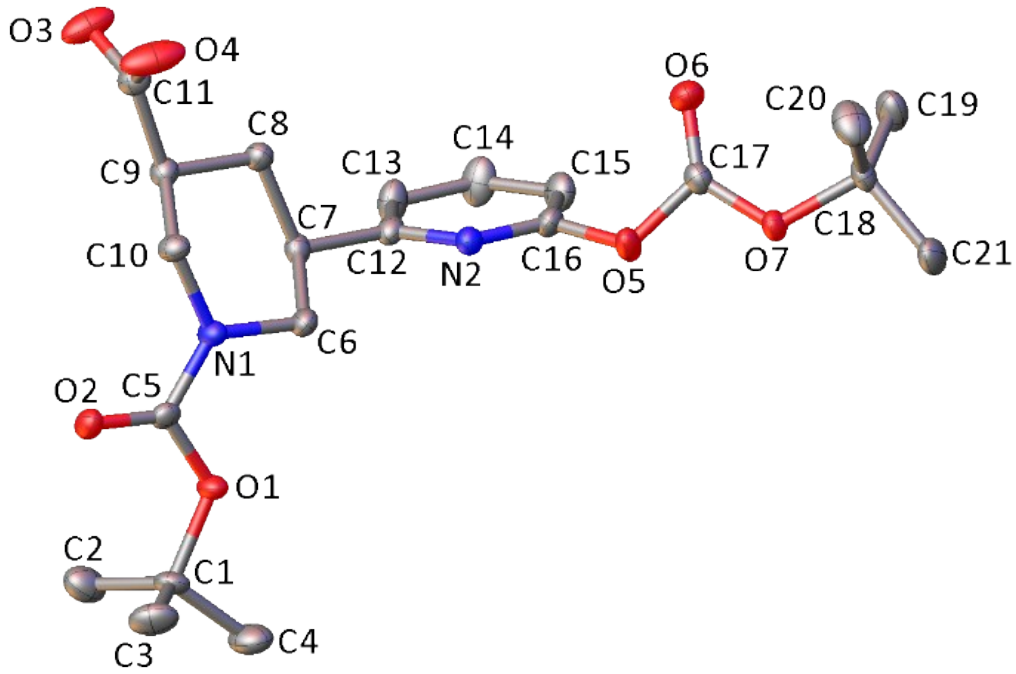
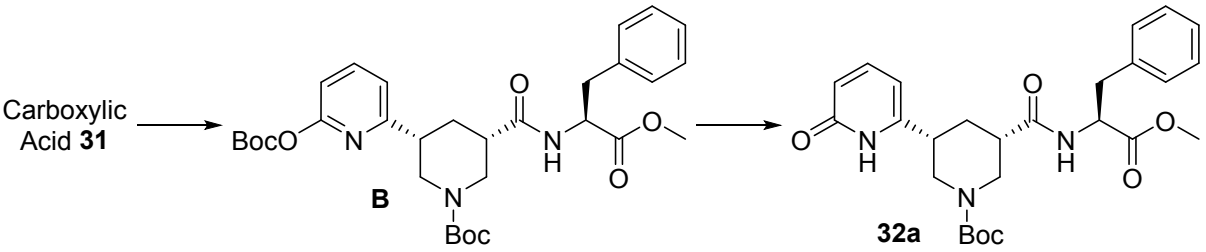


Illustration of the structure of acid **31** with atomic numbering scheme depicted. Ellipsoids are depicted at the 50% probability level and hydrogen atoms are omitted for clarity.

***Tert*-Butyl (3*S*,5*R*)-3-(((*S*)-1-methoxy-1-oxo-3-phenylpropan-2-yl)carbamoyl)-5-(6-oxo-1,6-dihydropyridin-2-yl)piperidine-1-carboxylate 32a**



To a solution of carboxylic acid **31** (84 mg, 0.20 mmol) and L-phenylalanine methyl ester hydrochloride (43 mg, 0.20 mmol) in DCM (2.0 mL) at 0 °C, were added N(3dimethylaminopropyl)-N'-ethylcabodiimide hydrochloride (42 mg, 0.22 mmol), 1hydroxybenzotriazole (34 mg, 0.22 mmol) and triethylamine (70 µL, 0.50 mmol), and the reaction mixture was stirred at 0 °C for 1 h. The solution was allowed to warm to room temperature and stirred for 18 h. The solvent was removed *in vacuo*, and citric acid (10 mL, 15% aq. sol.) was added. The aqueous phase was extracted with DCM (3 × 30 mL), and the combined organic layers were washed with $NaHCO_3$ (10 mL, aq. sat. sol.), water (10 mL), brine (10 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo*. Purification by flash column chromatography [EtOAc:*n*-Hexane (1:1)] gave the **O-Boc protected amide B** (59 mg, 45%) as a colourless solid.

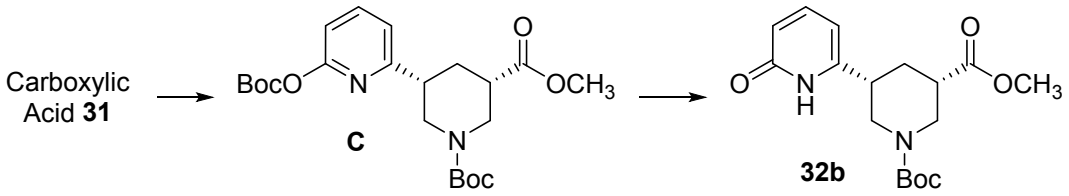
R_f = 0.30 [EtOAc:*n*-Hexane (1:1)]; m.p. > 200 °C (DCM/*n*-Hexane); FTIR ν_{max}/cm^{-1} (neat): 3307, 2979, 2932, 1750, 1660, 1251, 1217, 1138, 747, 700; ^1H NMR (500 MHz, $CDCl_3$) δ_H 1.47 (s, 9H), 1.59 (s, 9H), 1.97 (m, 1H), 2.11 (m, 1H), 2.39 (m, 1H), 2.76 – 2.97 (m, 3H), 3.08 (dd, *J* = 6.0, 14.0 Hz, 1H), 3.18 (dd, *J* = 6.0, 14.0 Hz, 1H), 3.75 (s, 3H), 4.17 – 4.45 (m, 2H), 4.90 (dd, *J* = 6.0, 14.0 Hz, 1H), 6.00 (br s, 1H), 7.03 (d, *J* = 8.0 Hz, 1H), 7.06 – 7.10 (m, 3H), 7.19 – 7.30 (m, 3H), 7.75 (t, *J* = 7.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 27.7 (3C), 28.4 (3C), 34.0, 37.8, 43.1, 45.8-48.7 (3C), 52.4, 52.9, 80.1, 84.0, 113.9, 119.6, 127.2, 128.5 (2C), 129.3 (2C), 135.7, 140.0, 151.0, 154.6, 157.4, 160.9, 171.8, 172.1; HRMS (ESI^+) calcd for $C_{31}H_{42}N_3O_8$ $[M+H]^+$: 584.2966, found 584.2957, calcd for $C_{31}H_{41}N_3NaO_8$ $[M+Na]^+$: 606.2786, found 606.2781.

The amide **B** (prepared above) (30 mg, 0.05 mmol) was deprotected according to the **General Procedure A**. Purification by flash column chromatography [DCM:MeOH:NH_4OH (94.5:5:0.5)] gave **32a** (20 mg, 83%) as a colourless soild.

$[\alpha]_D^{22}$ = +2 (c 0.03, $CHCl_3$); R_f = 0.40 [DCM:MeOH (95:5)]; m.p. 93 °C (DCM/*n*-Hexane); FTIR ν_{max}/cm^{-1} (neat): 2922, 2852, 1747, 1652, 1613, 1455, 1380, 1149, 779; ^1H NMR (500 MHz, $CDCl_3$) δ_H 1.48 (s, 9H), 1.86 (m, 1H), 2.19 (m, 1H), 2.47 (m, 1H), 2.68 (m, 1H), 2.73 – 3.00 (m, 2H), 3.06 (dd, *J* = 6.5, 14.0 Hz, 1H), 3.19 (dd, *J* = 6.5, 14.0 Hz, 1H), 3.76 (s, 3H), 4.09 – 4.60

(m, 3H), 4.92 (m, 1H), 6.07 (d, *J* = 6.5 Hz, 1H), 6.19 – 6.50 (m, 2H), 7.08 (d, *J* = 7.5 Hz, 2H), 7.18 (m, 1H), 7.20 – 7.27 (m, 2H), 7.42 (dd, *J* = 6.5, 6.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 28.3 (3C), 29.7, 37.8, 39.3, 42.8, 45.4, 48.0, 52.4, 52.9, 80.5, 103.6, 118.3, 127.1, 128.5 (2C), 129.3 (2C), 135.7, 141.7, 149.3, 154.4, 156.2, 165.2, 171.9; HRMS (ESI$^+$) calcd for $C_{26}H_{34}N_3O_6$ [M+H]$^+$: 484.2442, found 484.2427, calcd for $C_{26}H_{33}N_3NaO_6$ [M+Na]$^+$: 506.2262, found 506.2266.

1-(*Tert*-Butyl) 3-methyl (3*S*,5*R*)-5-(6-oxo-1,6-dihydropyridin-2-yl)piperidine-1,3-dicarboxylate 32b

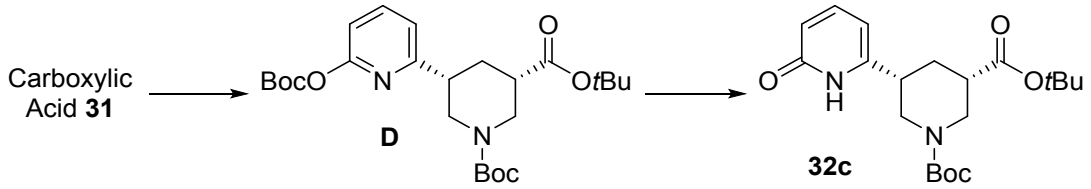


A solution of carboxylic acid **31** (127 mg, 0.30 mmol) and K_2CO_3 (124 mg, 0.90 mmol) in DMF (3.0 mL) was placed under nitrogen, iodomethane (45 µL, 0.72 mmol) was added and the reaction mixture was stirred at room temperature for 5 h. The solution was concentrated, the residue was distributed between water (10 mL) and EtOAc (10 mL) and the aqueous phase was extracted with EtOAc (2 × 10 mL). The combined organic phases were dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash column chromatography [EtOAc:*n*-Hexane (1:4)] gave **O-Boc methy ester C** (129 mg, 99%) as an colourless oil.
R_f = 0.23 [EtOAc:*n*-Hexane (1:4)]; FTIR ν_{max}/cm^{-1} (neat): 2979, 2933, 1759, 1733, 1688, 1250, 1220, 1134, 859, 749; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H 1.48 (s, 9H), 1.57 (s, 9H), 1.97 (s, 1H), 2.36 (d, *J* = 13.0 Hz, 1H), 2.61 (t, *J* = 13.0 Hz, 1H), 2.69 – 3.05 (m, 3H), 3.70 (s, 3H), 4.16 – 4.57 (m, 2H), 7.02 (d, *J* = 7.5 Hz, 1H), 7.11 (d, *J* = 7.5 Hz, 1H), 7.73 (app t, *J* = 7.5, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 27.7 (3C), 28.4 (3C), 33.3, 41.4, 43.1, 44.9 – 45.6, (conformers), 47.8 – 48.7, (conformers), 51.8, 80.1, 84.0, 113.9, 120.1, 140.0, 151.0, 154.6, 157.4, 160.1, 173.4; HRMS (ESI$^+$) calcd for $C_{22}H_{32}N_2NaO_7$ [M+Na]$^+$: 459.2102, found 459.2115.

Methyl ester **C** (prepared above) (22 mg, 0.05 mmol) was deprotected according to the **General Procedure A**. Purification by flash column chromatography [DCM:MeOH (90:10)] gave **32b** (15 mg, 87%) as a colourless oil.
$[\alpha]_D^{22}$ = -11 (c 0.4, MeOH); R_f = 0.32 [DCM:MeOH (95:5)]; m.p. 192 °C (DCM/*n*-Hexane); FTIR ν_{max}/cm^{-1} (neat): 2923, 2852, 1735, 1694, 1653, 1617, 1464, 1146; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H 1.48 (s, 9H), 1.88 (q, *J* = 12.5 Hz, 1H), 2.39 (d, *J* = 13.5 Hz, 1H), 2.66 (m, 1H), 2.40 (m, 1H), 2.78 – 3.05 (m, 2H), 3.71 (s, 3H), 4.14 – 4.62 (m, 2H), 6.08 (d, *J* = 7.0 Hz, 1H), 6.46 (d,

J = 8.5 Hz, 1H), 7.40 (dd, *J* = 8.5, 7.0 Hz, 1H), 12.89 (1H, br s, NH); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 28.4 (3C), 32.6, 39.7, 41.1, 44.1 – 48.7 (2C, conformers), 52.0, 80.4, 103.9, 118.4, 141.6, 149.4, 154.4, 165.5, 173.0; HRMS (ESI$^+$) calcd for $C_{17}H_{25}N_2O_5$ $[M+H]^+$: 337.1758, found 337.1744.

Di-*tert*-butyl (3*S*,5*R*)-5-(6-oxo-1,6-dihydropyridin-2-yl)piperidine-1,3-dicarboxylate 32c



A solution of carboxylic acid **31** (84 mg, 0.20 mmol), benzyltriethylammonium bromide (57 mg, 0.21 mmol) and K_2CO_3 (760 mg, 5.50 mmol) in DMA (1.60 mL) was cooled to 0 °C in a resealable tube, and *tert*-butyl bromide was added (1.2 mL, 10.5 mmol) dropwise over 1 min. The reaction mixture was stirred at 55 °C for 23 h. The solution was cooled to room temperature, the reaction mixture was distributed between EtOAc (10 mL) and water (10 mL), and the aqueous phase was extracted with EtOAc (3 × 10 mL). The combined organic phases were washed with water (10 mL), brine (10 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash column chromatography [Et_2O:*n*-Hexane (1:4 to 1:1)] gave **O-Boc tert-butyl ester D** (40 mg, 42%) as an colourless oil.

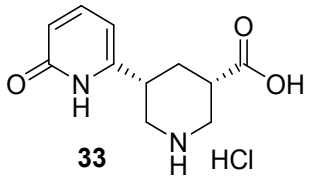
R_f = 0.26 [EtOAc:*n*-Hexane (1:1)]; FTIR ν_{max}/cm^{-1} (neat): 2979, 2928, 1762, 1728, 1694, 1369, 1252, 1223, 1144, 897, 732; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H 1.46 (s, 9H), 1.49 (s, 9H) 1.58 (s, 9H), 1.89 (m, 1H), 2.32 (d, *J* = 13.5 Hz, 1H), 2.51 (m, 1H), 2.68 – 3.06 (m, 3H), 4.16 – 4.54 (m, 2H), 7.03 (d, *J* = 7.5 Hz, 1H), 7.11 (d, *J* = 7.5 Hz, 1H), 7.74 (app t, *J* = 7.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 27.7 (3C), 28.0 (3C), 28.4 (3C), 33.6, 42.4, 43.2, 80.0, 80.8, 84.0, 113.8, 120.1, 140.0, 151.0, 154.7, 157.4, 161.1, 172.3, *C11 and C13 were not observed*; HRMS (ESI$^+$) calcd for $C_{25}H_{39}N_2O_7$ $[M+H]^+$: 479.2752, found 479.2724.

tert-Butyl ester **D** (prepared above) (24 mg, 0.05 mmol) was deprotected according to the **General Procedure A**. Purification by flash chromatography [DCM:MeOH (90:10)] gave **32c** (17 mg, 87%) as a colourless oil.

R_f = 0.32 [DCM:MeOH (95:5)]; m.p. 95 °C (DCM/*n*-Hexane); FTIR ν_{max}/cm^{-1} (neat): 2922, 2852, 1725, 1701, 1654, 1619, 1463, 1147; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H 1.46 (s, 9H), 1.49 (s, 9H), 1.83 (q, *J* = 12.5 Hz, 1H), 2.33 (d, *J* = 12.5 Hz, 1H), 2.54 (m, 1H), 2.69 (m, 1H), 2.76 – 2.97 (m, 2H), 4.17 – 4.58 (m, 2H), 6.09 (d, *J* = 7.5 Hz, 1H), 6.46 (d, *J* = 8.5 Hz, 1H), 7.40 (dd t, *J* = 8.5, 7.5 Hz, 1H), 12.38 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 28.0 (3C), 28.4

(3C), 32.7, 39.8, 42.0, 44.1- 48.0 (conformers), 51.9, 80.4, 81.1, 103.8, 118.4, 141.6, 149.5, 154.4, 165.2, 171.8; HRMS (ESI$^+$) calcd for $C_{20}H_{31}N_2O_5$ [M+H]$^+$: 379.2227, found 379.2213.

(3*S*,5*R*)-5-(6-Oxo-1,6-dihydropyridin-2-yl)piperidine-3-carboxylic acid hydrochloride salt 33

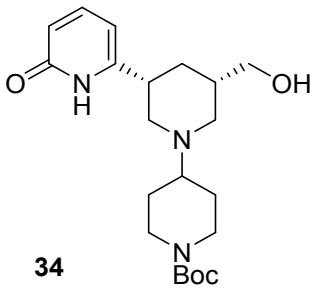


33

A solution of carboxylic acid **31** (211 mg, 0.50 mmol) in a mixture of TFA:DCM (1:19) was stirred at room temperature for 18 h. The reaction mixture was concentrated *in vacuo*. Purification by flash column chromatography [0.05 M HCl:CH_3CN (5:95 to 20:80)] gave acid **33** (93 mg, 84%) as a colourless solid.

$[\alpha]_D^{22.1}$ = –15 (c 0.6, MeOH); R_f = 0.20 [0.05 M HCl:CH_3CN (20:80)]; m.p. >200 °C (DCM/*n*-Hexane); FTIR ν_{max}/cm^{-1} (neat): 3231, 2987, 2971, 2901, 1717, 1633, 1614, 1545, 1394, 1007, 808, 728; ^{1}H NMR (500 MHz, D_2O) δ_H 1.85 (m, 1H), 2.45 (m, 1H), 2.96 (m, 1H), 3.02 – 3.14 (m, 3H), 3.59 (m, 1H), 3.65 (m, 1H), 6.41 (d, *J* = 7.0 Hz, 1H), 6.50 (d, *J* = 9.0 Hz, 1H), 7.63 (dd, *J* = 7.0, 9.0 Hz, 1H); ^{13}C NMR (125 MHz, D_2O) δ_C 30.3, 36.4, 38.6, 43.9, 45.8, 48.8, 106.6, 117.8, 143.9, 146.8, 165.3, 174.7; HRMS (ESI$^+$) calcd for $C_{11}H_{13}N_2O_3$ [M-H]$^+$: 221.0932, found: 221.0933.

Tert-butyl (3S, 5R)-3-(hydroxymethyl)-(6-oxo-1,6-dihydropyridin-2-yl)-[1,4'-bipiperidine]-1'- carboxylate 34



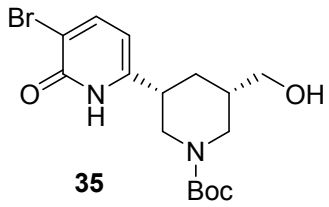
34

A solution of piperidine **22** (150 mg, 0.61 mmol) and trimethylamine (0.09 mL, 1 equiv) in THF (5 mL) was stirred for 5 min before being concentrated *in vacuo*. To the residue was added N-Boc-4-piperidone (121 mg, 1 equiv), palladium on activated charcoal 10% (60 mg) and MeOH (3.0 mL). The mixture was flushed and stirred under an atmosphere of hydrogen for 18 h. The solution was filtered through Celite® and concentrated *in vacuo*. Purification by flash column

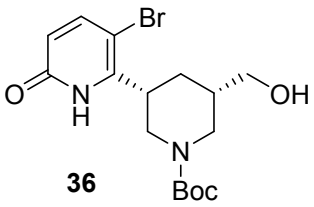
chromatography [DCM:MeOH (98:2 to 90:10)] afforded **34** (181 mg, 75%) as a colourless solid.

$[\alpha]_D^{25}$ = -10 (c 4.0, MeOH); m.p. 134-136 °C (DCM/*n*-Hexane); FTIR ν_{max}/cm^{-1} (neat): 2928, 1651, 1598, 1423, 1355, 1242, 1160, 799; ^{1}H NMR (500 MHz, MeOD) δ_H 1.35 (m, 2H), 1.47 (s, 9H), 1.57 (m, 2H), 1.98 (m, 4H), 2.37 (s, 1H), 2.51-3.00 (m, 5H), 3.33 (s, 1H), 3.49 (m, 1H), 3.56 (m, 1H), 4.22 (d, *J* = 13.0 Hz, 2H), 6.32 (s, 1H), 6.45 (s, 1H), 7.56 (s, 1H); ^{13}C NMR (125 MHz, MeOD) δ_C 27.0, 27.2, 31.9, 37.9, 38.9, 42.4, 51.7, 52.9, 63.0, 63.9, 79.9, 104.4, 117.5, 142.4, 149.9, 154.8, 164.9; HRMS (ESI$^+$) calcd for $C_{21}H_{34}N_3O_4$ $[M+H]^+$: 392.2543, found 392.2545.

3-Bromopyridone isomer 35 and 5-bromopyridone isomer 36



35



36

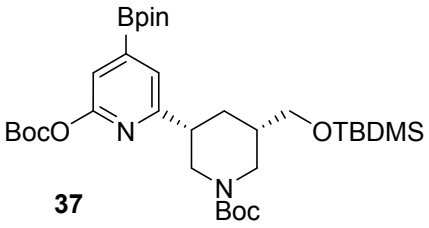
To a solution of pyridone **19** (31 mg, 0.10 mmol) in THF (1.0 mL) was added NBS (20 mg, 0.11 mmol) and the mixture was stirred at room temperature for 1.5 h. The solution was diluted with water (5 mL) and the aqueous phase was extracted with DCM (3 × 5 mL). The combined organic phases were dried (Na_2SO_4), filtered and concentrated *in vacuo*. Purification by flash column chromatography [DCM:MeOH:NH_4OH (97.25:2.5:0.25 to 94.5:5.0:0.5)] gave **35** (20 mg, 52%) as a colourless solid and **36** (9 mg, 23%) as a colourless solid.

Data for 35: $[\alpha]_D^{22}$ = –24 (c 4.0, MeOH); R_f = 0.28 [DCM:MeOH (95:5)]; m.p. 125 – 128 °C (DCM/*n*-Hexane); FTIR ν_{max}/cm^{-1} (neat): 2927, 1638, 1611, 1423, 1365, 1253, 1144, 1025, 877; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H 1.47 (s, 9H), 1.70-1.80 (m, 1H), 1.81-.190 (m, 1H), 2.06-2.32 (m, 2H), 2.58-2.75 (m, 2H), 2.78-3.10 (m, 1H), 3.58-3.67 (m, 2H), 4.07-4.37 (m, 2H), 6.06 (d, *J* = 7.5 Hz, 1H), 7.75 (d, *J* = 7.5 Hz, 1H), 13.17 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 28.4 (3C), 32.3, 38.5, 40.5, 46.4, 47.5, 65.2, 80.0, 105.1, 113.1, 143.5, 150.1, 154.6, 161.4; HRMS (ESI$^+$) calcd for $C_{16}H_{23}{}^{79}BrN_2NaO_4$ $[M+Na]^+$: 409.0733, found 409.0734.

Data for 36: $[\alpha]_D^{22}$ = –23 (c 3.1, MeOH); R_f = 0.22 [DCM:MeOH (95:5)]; m.p. 112 – 115 °C (DCM/MeOH/NH_4OH); FTIR ν_{max}/cm^{-1} (neat): 2928, 1645, 1587, 1423, 1365, 1254, 1170, 1145, 1066, 880, 826; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H 1.47 (s, 9H), 1.79 – 2.11 (m, 3H), 2.63 – 2.80 (t, *J* = 11.5 Hz, 1H), 2.87 – 3.06 (t, *J* = 11.5 Hz, 1H), 3.17 – 3.33 (m, 1H), 3.56 – 3.65 (m, 2H), 4.00 – 4.37 (m, 2H), 6.34 (d, *J* = 9.5 Hz, 1H), 7.51 (d, *J* = 9.5 Hz, 1H); ^{13}C NMR (125 MHz,

$CDCl_3$) δ_C 28.4 (3C), 30.0, 37.8, 40.3, 45.7, 47.0, 65.2, 80.0, 100.2, 119.1, 145.6, 147.3, 154.7, 164.2; HRMS (ESI$^+$) calcd for $C_{16}H_{23}{}^{79}BrN_2NaO_4$ $[M+H]^+$: 409.0733, found 409.0739.

***Tert*-butyl (3*R*,5*S*)-3-(6-((*tert*-butoxycarbonyl)oxy)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-yl)-5-(((*tert*-butyldimethylsilyl)oxy)methyl)piperidine-1-carboxylate 37**

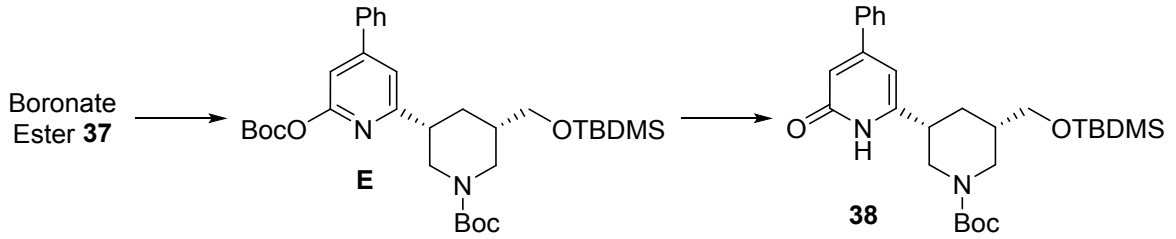


37

Silyl ether **23** (104 mg, 0.20 mmol) was borylated according to the **General Procedure B**. Purification by flash column chromatography [Et_2O:*n*-Hexane (1:1)] gave **37** (117 mg, 91%) as a colourless oil.

R_f = 0.26 [Et_2O:*n*-Hexane (1:1)]; FTIR ν_{max}/cm^{-1} (neat): 2978, 2930, 2857, 1760, 1695, 1368, 1256, 1144, 837; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H 0.05 (s, 6H), 0.91 (s, 9H), 1.36 (s, 12H), 1.44 – 1.51 (m, 10H), 1.57 (s, 9H), 1.82 (m, 1H), 2.00 (m, 1H), 2.43 (m, 1H), 2.77 – 2.98 (m, 2H), 3.37 – 3.61 (m, 2H), 4.20 – 4.45 (m, 2H), 7.33 (s, 1H), 7.46 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C -5.45 (2C), 18.3, 24.9 (4C), 25.9 (3C), 27.7 (3C), 28.5 (3C), 33.0-34.2 (conformers), 38.5-39.0 (conformers), 43.4-43.8 (conformers), 46.1, 47.9-48.6 (conformers), 65.9, 79.5, 83.7, 84.7 (2C), 118.6, 125.4, 142.0, 151.2, 154.8, 157.2, 161.4; HRMS (ESI$^+$) calcd for $C_{33}H_{58}BN_2O_8Si$ $[M+H]^+$: 649.4056, found 649.4033, calcd for $C_{33}H_{57}BN_2NaO_8Si$ $[M+Na]^+$: 671.3876, found 671.3890.

***Tert*-butyl (3*S*,5*R*)-3-(((*tert*-butyldimethylsilyl)oxy)methyl)-5-(6-oxo-4-phenyl-1,6-dihydropyridin-2-yl)piperidine-1-carboxylate 38**



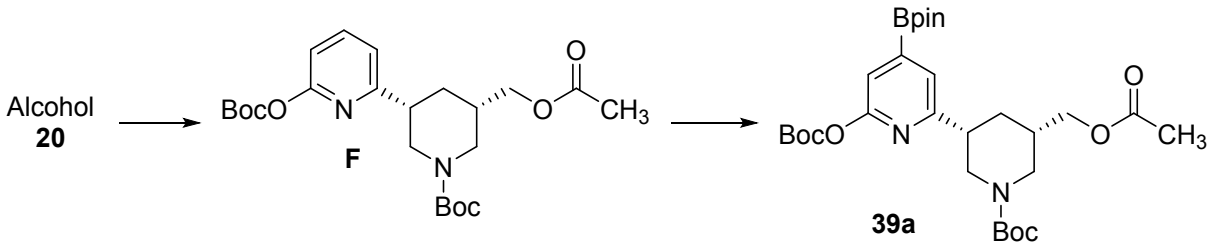
E **38**

A Schlenk tube was charged with boronic ester **37** (65 mg, 0.10 mmol), bromobenzene (10 µL, 0.10 mmol), bis(triphenylphosphine)palladium (II) dichloride (1.4 mg, 2 mol%) and K_2CO_3 (28 mg, 0.20 mmol). After purging with nitrogen, DMF (1.0 mL) was added and the reaction mixture was heated at 80 °C for 19 h. The solvent was removed *in vacuo*. Purification by flash column chromatography [Et_2O:*n*-Hexane (1:4)] gave **Suzuki adduct E** (36 mg, 60%) as a colourless oil, which was converted to **38** immediately.

Adduct **E** (prepared above) (12 mg, 0.025 mmol) was deprotected according to the **General Procedure A**. Purification by flash column chromatography [DCM:MeOH:NH_4OH (94.5:5:0.5)] yielded **38** (7 mg, 70%) as a colourless solid.

R_f = 0.30 [DCM:MeOH (95:5)]; m.p. 92-94 °C (DCM/*n*-Hexane); FTIR ν_{max}/cm^{-1} (neat): 2929, 1690, 1646, 1422, 1364, 1250, 1141, 1079, 834; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H 0.07 (s, 6H), 0.91 (s, 9H), 1.49 (s, 10H), 1.88 (s, 1H), 2.12 (s, 1H), 2.51 (t, *J* = 11.5 Hz, 1H), 2.81 (t, *J* = 11.5 Hz, 1H), 2.91, (s, 1H), 3.36-3.64 (m, 2H), 4.17-4.52 (m, 2H), 6.34 (s, 1H), 6.66 (s, 1H), 7.47 (m, 3H), 7.59 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C -5.44, -5.39, 25.9 (3C), 28.4 (3C), 29.3, 29.7, 32.9, 38.7, 40.6, 47.4, 65.5, 79.9, 103.6, 114.9, 126.8 (2C), 128.9 (2C), 129.4, 138.1, 149.8, 153.9, 154.5, 165.2; HRMS (ESI$^+$) calcd for $C_{28}H_{43}N_2O_4Si$ $[M+H]^+$: 499.2987, found 499.3000, calcd for $C_{28}H_{42}N_2NaO_4Si$ $[M+Na]^+$: 521.2806, found 521.2846.

Tert-butyl (3S,5R)-3-(acetoxymethyl)-5-(6-((*tert*-butoxycarbonyl)oxy)-4-(4,4,5,5-tetra methyl-1,3,2-dioxaborolan-2-yl)pyridin-2-yl)piperidine-1-carboxylate 39a



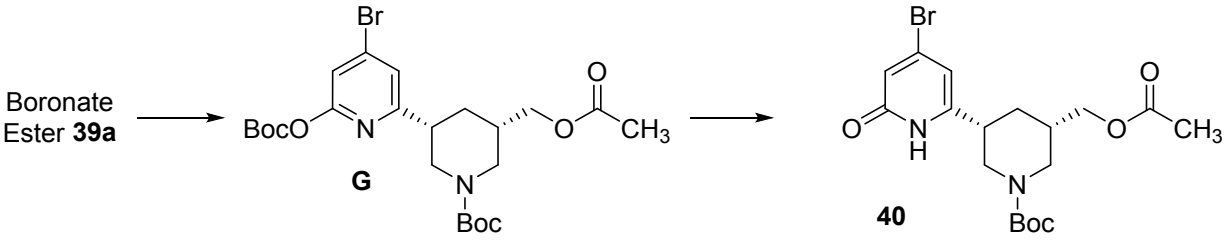
A solution of alcohol **20** (102 mg, 0.25 mmol) and triethylamine (70 µL, 0.50 mmol) in DCM (2.5 mL) was cooled to 0 °C, acetic anhydride (36 µL, 0.38 mmol) was added dropwise over 5 min, and the reaction mixture was stirred at room temperature for 18 h. The solvent was removed *in vacuo*, and the residue was diluted with EtOAc (10 mL). The organic phase was washed with $NaHCO_3$ (2 × 10 mL, aq. sat. sol.), water (10 mL), brine (10 mL), and then dried (Na_2SO_4), filtered and concentrated *in vacuo*. Purification by flash column chromatography [Et_2O:*n*-Hexane (1:1)] gave the **acetate F** (121 mg, 99%.) as a colourless oil.

R_f = 0.20 [Et_2O:*n*-Hexane (1:1)]; FTIR ν_{max}/cm^{-1} (neat): 2978, 2933, 1759, 1740, 1689, 1247, 1220, 1140, 751; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H 1.48 (s, 9H), 1.52 – 1.64 (m, 10H), 1.93 – 2.11 (m, 5H), 2.47 (m, 1H), 2.80 – 3.04 (m, 2H), 3.93 (m, 1H), 4.02 (dd, *J* = 5.5, 11.0 Hz, 1H), 4.10 – 4.48 (m, 2H), 7.02 (d, *J* = 8.0 Hz, 1H), 7.10 (d, *J* = 7.5 Hz, 1H), 7.73 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 20.8, 27.7 (3C), 28.4 (3C), 33.6, 35.5, 43.5, 46.2-47.0 (conformers), 48.2-48.9 (conformers), 66.5, 79.8, 83.9, 113.7, 120.1, 139.9, 151.0, 154.7, 157.4, 161.3, 171.0; HRMS (ESI$^+$) calcd for $C_{23}H_{35}N_2O_7$ $[M+H]^+$: 451.2439, found 451.2452, calcd for $C_{23}H_{34}N_2NaO_7$ $[M+Na]^+$: 473.2258, found 473.2270.

Acetate **F** (prepared above) (90 mg, 0.20 mmol) was borylated according to the **General Procedure B**. Purification by flash column chromatography [EtOAc:*n*-Hexane (1:1 to 3:1)] yielded **39a** (89 mg, 77%) as a colourless oil.

R_f = 0.22 [Et_2O:*n*-Hexane (1:1)]; FTIR ν_{max}/cm^{-1} (neat): 2973, 2923, 2854, 1765, 1713, 1393, 1236, 1146, 848, 747; ^1H NMR (500 MHz, $CDCl_3$) δ_H 1.37 (s, 12H), 1.49 (s, 9H), 1.53 – 1.65 (s, 10H), 1.96 – 2.11 (m, 5H), 2.46 (m, 1H), 2.78 – 3.10 (m, 2H), 3.94 (m, 1H), 4.02 (dd, *J* = 5.5, 11.0 Hz, 1H), 4.13 – 4.50 (m, 2H), 7.36 (s, 1H), 7.46 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$, 52 °C) δ_C 20.6, 28.4, 33.7, 35.7, 43.4, 46.5, 48.6, 66.4, 76.7, 79.7, 83.6, 84.6, 118.6, 124.9, 139.7, 151.0, 154.7, 160.7, 170.7; HRMS (ESI$^+$) calcd for $C_{29}H_{46}BN_2O_9$ $[M+H]^+$: 577.3296, found 577.3279, calcd for $C_{29}H_{45}BN_2NaO_9$ $[M+Na]^+$: 599.3116, found 599.3104.

***Tert*-butyl (3*R*,5*S*)-3-(4-bromo-6-oxo-1,6-dihydropyridin-2-yl)-5-(((*tert*-butyldimethyl silyl)oxy)methyl)piperidine-1-carboxylate 40**

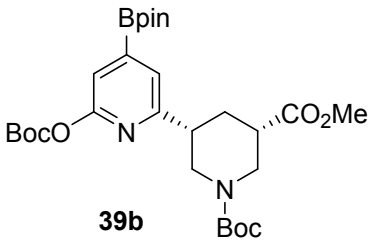


To a solution of boronate ester **39a** in MeOH (2.0 mL) was added a solution of copper (II) bromide (100 mg, 0.45 mmol) in water (1.0 mL). The reaction mixture was stirred at room temperature for 3 days under air. NH_4OH (2.0 mL, 15% aq. sol.) was added and the aqueous phase was extracted with DCM (3 × 10 mL). The combined organic phases were dried (Na_2SO_4), filtered and concentrated *in vacuo*. Purification by flash column chromatography [Et_2O:*n*-Hexane (1:4 to 1:1)] gave **bromide G** (20 mg, 25%) as a colourless oil. R_f = 0.26 [Et_2O:*n*-Hexane (1:1)]; FTIR ν_{max}/cm^{-1} (neat): 2978, 2933, 2862, 1762, 1741, 1689, 1242, 1225, 1139, 730; ^1H NMR (500 MHz, $CDCl_3$) δ_H 1.49 (s, 9H), 1.58 (s, 9H), 1.61 (m, 1H), 1.93 – 2.10 (m, 5H), 2.49 (m, 1H), 2.79 – 2.96 (m, 2H), 3.92 (m, 1H), 4.02 (dd, *J* = 5.5, 11.0 Hz, 1H), 4.10 – 4.50 (m, 2H), 7.25 (s, 1H), 7.28 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 20.8, 27.6 (3C), 28.4 (3C), 33.5, 35.6, 43.2, 46.1, 48.7, 66.4, 80.0, 84.5, 117.2, 123.5, 134.9, 150.4, 154.6, 157.7, 162.2, 171.0; HRMS (ESI$^+$) calcd for $C_{23}H_{34}{}^{79}BrN_2O_7$ $[M+H]^+$: 529.1544, found 529.1548, calcd for $C_{23}H_{33}{}^{79}BrN_2NaO_7$ $[M+Na]^+$: 551.1363, found 551.1366.

Bromide **G** (prepared above) (26 mg, 0.05 mmol) was deprotected according to the **General Procedure A**. Purification by flash column chromatography [DCM:MeOH:NH_4OH (94.5:5:0.5)] gave **40** (14 mg, 65%) as a colourless solid.

$[\alpha]_D^{22}$ = -9 (c 2.3, MeOH); R_f = 0.48 [DCM:MeOH (95:5)]; m.p. 175 – 180 °C (DCM/*n*-Hexane); FTIR ν_{max}/cm^{-1} (neat): 2924, 2852, 1741, 1695, 1647, 1607, 1249, 1148; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H 1.45 – 1.53 (m, 10H), 1.95 – 2.13 (m, 5H), 2.53 (m, 1H), 2.69 (dt, *J* = 12.0, 4.5 Hz, 1H), 2.88 (m, 1H), 3.92 – 4.07 (m, 2H), 4.09 – 4.44 (m, 2H), 6.28 (s, 1H), 6.69 (s, 1H), 12.77 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 20.8, 28.4 (3C), 32.6, 35.3, 40.1, 44.4 – 48.6 (2C, conformers), 66.0, 80.3, 108.7, 120.6, 138.0, 150.0, 154.4, 164.3, 171.0; HRMS (ESI$^+$) calcd for $C_{18}H_{26}{}^{79}BrN_2O_5$ $[M+H]^+$: 429.1020, found 429.1021.

1-(*tert*-Butyl) 3-methyl (3*S*,5*R*)-5-(6-((*tert*-butoxycarbonyl)oxy)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-yl)piperidine-1,3-dicarboxylate 39b

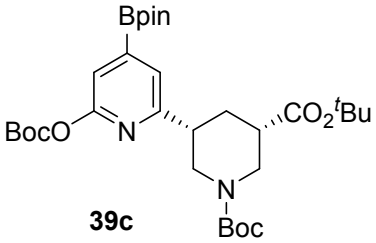


39b

Methyl ester **32b** (44 mg, 0.10 mmol) was borylated according to the **General Procedure B**. Purification by preparative thin layer chromatography [EtOAc:*n*-Hexane (3:7)] gave **39b** (44 mg, 77%) as a colourless oil.

R_f = 0.45 [EtOAc:*n*-Hexane (3:7)]; FTIR ν_{max}/cm^{-1} (neat): 2921, 2852, 1761, 1737, 1714, 1455, 1371, 1252, 1145, 849; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H 1.37 (s, 12H), 1.49 (s, 9H), 1.58 (s, 9H), 1.98 (m, 1H), 2.36 (m, 1H), 2.63 (m, 1H), 2.72 – 3.05 (m, 3H), 3.71 (s, 3H), 4.15 – 4.60 (m, 2H), 7.36 (s, 1H), 7.47 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 24.9 (4C), 27.7 (3C), 28.4 (3C), 41.5, 43.0, 51.8, 80.0, 83.8, 84.7 (2C), 119.0, 125.5, 151.2, 154.6, 157.2, 160.3, 173.4; *C4, C8, C11 and C13 were not detected*; HRMS (ESI$^+$) calcd for $C_{28}H_{44}BN_2O_9$ $[M+H]^+$: 563.3139, found 563.3139, $C_{28}H_{43}BN_2NaO_9$ $[M+Na]^+$: 585.2959, found 585.2956.

Di-*tert*-butyl (3*S*,5*R*)-5-(6-((*tert*-butoxycarbonyl)oxy)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-yl)piperidine-1,3-dicarboxylate 39c

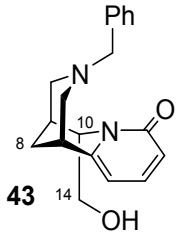


39c

Tert-butyl ester **32c** (48 mg, 0.10 mmol) was borylated according to the **General Procedure B**. Purification by flash column chromatography [Et_2O:*n*-Hexane (1:1) to Et_2O] gave **39c** (50 mg, 91%) as a colourless oil.

R_f = 0.20 [Et_2O:*n*-Hexane (1:1)]; FTIR ν_{max}/cm^{-1} (neat): 2977, 2926, 1761, 1725, 1697, 1405, 1393, 1252, 1145, 1062, 848; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H 1.37 (s, 12H), 1.48 (s, 9H), 1.53 – 1.62 (m, 9H), 1.58 (s, 9H), 1.88 (m, 1H), 2.32 (m, 1H), 2.49 (m, 1H), 2.69 – 3.06 (m, 3H), 4.11 – 4.57 (m, 2H), 7.36 (s, 1H), 7.47 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 24.9 (4C), 27.7 (3C), 28.0 (3C), 28.4 (3C), 33.8, 42.4, 43.2, 79.9, 80.8, 83.8, 84.7 (2C), 118.9, 125.1, 151.2, 154.7, 157.2, 160.1, 172.3; *C4, C11 and C13 were not detected;* HRMS (ESI$^+$) calcd for $C_{31}H_{50}BN_2O_9$ $[M+H]^+$: 605.3609, found 605.3621.

(6*S*)-3-Benzyl-6-(hydroxymethyl)-1,2,3,4,5,6-hexahydro-8*H*-1,5-methanopyrido[1,2-a][1,5]diazocin-8-one 43



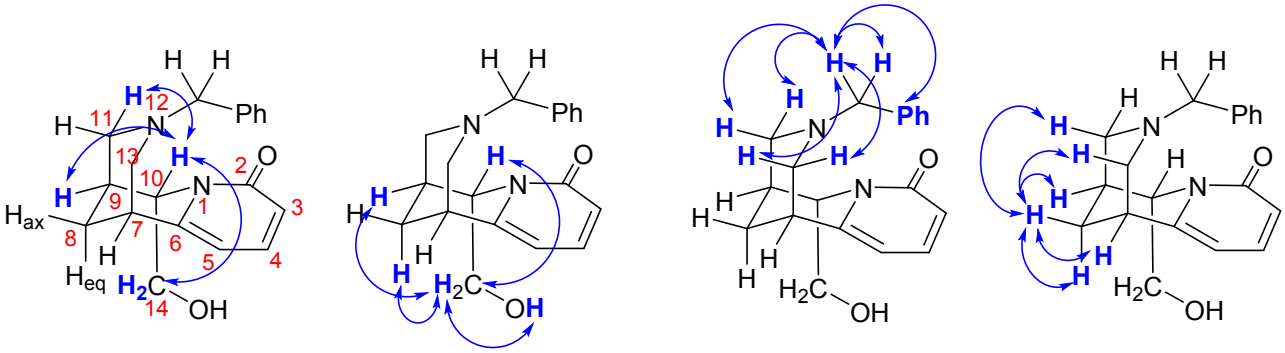
43

To a solution of boronate **17** (64 mg, 0.16 mmol) and bromochloromethane (61 mg, 0.47 mmol) in MTBE (0.6 mL) at -78 °C was added *n*-BuLi (0.25 mL, 1.6 M in hexanes, 0.40 mmol) dropwise over 15 min. The reaction mixture was stirred at -78 °C for 30 min, then allowed to warm to room temperature and stirred for an additional 1 h. The reaction mixture was cooled to 0 °C, and a solution of NaOH (1.0 mL, 2 M aq. sol.) and H_2O_2 (0.5 mL, 30% aq. sol.) were added. The reaction mixture was warmed to room temperature and stirred for an additional 2 h. The solution was diluted with water (5 mL) and the aqueous phase was extracted with EtOAc (3 × 10 mL), the combined organic layers were washed with brine (10 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash column chromatography [DCM:MeOH:NH_4OH (97.5:2:0.5 to 95:4.5:0.5)] gave **43** (42 mg, 86% overall yield from **17**) as a colourless solid.

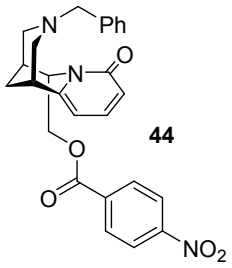
$[\alpha]_D^{23}$ = –36 (c 0.2, $CHCl_3$); R_f = 0.12 [EtOAc]; m.p. 170 °C (DCM/*n*-Hexane); FTIR ν_{max}/cm^{-1} (neat): 3320, 2933, 2797, 1646, 1545, 1137, 1062, 803, 737, 698; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H 1.69 (dt, *J* = 13.0, 3.0, Hz, 1H), 2.07 (d, *J* = 13.0 Hz, 1H), 2.26 (dd, *J* = 10.5, 1.5 Hz, 1H), 2.42 – 2.50 (m, 2H), 2.69 (dt, *J* = 10.5, 1.5 Hz, 1H), 2.94 (s, 1H), 3.04 (d, *J* = 11.0 Hz, 1H), 3.29 (d, *J* = 10.5 Hz, 1H), 3.46 (d, *J* = 10.5 Hz, 1H), 3.62 (s, 1H), 3.90 (m, 1H), 3.95 (m, 1H), 4.74 (t, *J* = 5.0 Hz, 1H), 5.93 (d, *J* = 7.0 Hz, 1H), 6.53 (d, *J* = 9.0 Hz, 1H), 6.87 – 6.93 (m, 2H), 7.12 – 7.19 (m, 3H), 7.28 (dd, *J* = 9.0, 7.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 23.7, 31.6,

36.0, 59.9, 60.7, 61.7, 62.0, 67.4, 105.7, 117.2, 126.9, 128.0 (2C), 128.1 (2C), 138.1, 139.0, 151.2, 164.5; HRMS (ESI$^+$) calcd for $C_{19}H_{23}N_2O_2$ [M+H]$^+$: 311.1754, found 311.1754, calcd for $C_{19}H_{22}N_2NaO_2$ [M+Na]$^+$: 333.1573, found 333.1578.

Details of NOESY correlations observed for the alcohol 43, which was irradiated at (from left) H10, H14, C<u>H</u>$_2$Ph, and H8 (axial).



((6S)-3-Benzyl-8-oxo-1,3,4,5,6,8-hexahydro-2*H*-1,5-methanopyrido[1,2-a][1,5]diazocin-6-yl)methyl 4-nitrobenzoate 44



44

To a solution of alcohol **43** (49 mg, 0.16 mmol), DMAP (2 mg, 2 mol%) and triethylamine (33 µL, 0.24 mmol) in DCM (1.0 mL) at room temperature was added *p*-nitrobenzoyl chloride (41 mg, 0.22 mmol). The reaction mixture was stirred for 48 h, and the crude reaction mixture was diluted with DCM (10 mL), washed with $NaHCO_3$ (10 mL, aq. sat. sol.), dried (Na_2SO_4), filtered, and concentrated *in vacuo*. Purification by flash column chromatography [EtOAc:*n*-Hexane (1:1) to EtOAc)] gave a yellow solid. The resulting solid was recrystallised from DCM/*n*-Hexane to give **44** (23 mg, 32%) as pale yellow needles.

$[\alpha]_D^{23}$ = –6 (c 0.3, $CHCl_3$); R_f = 0.10 [EtOAc:*n*-Hexane (1:1)]; m.p. 187 °C (DCM/*n*-Hexane); FTIR ν_{max}/cm^{-1} (neat): 2987, 2970, 2901, 1727, 1656, 1576, 1406, 1393, 1266, 1065, 1056, 891, 719; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H 1.75 (ddd, *J* = 13.0, 3.0, 3.0 Hz, 1H), 2.26 (m, 1H), 2.35 (dd, *J* = 10.5, 2.0 Hz, 1H), 2.40 (m, 1H), 2.53 (dd, *J* = 11.0, 2.5 Hz, 1H), 2.76 (m, 1H), 3.01 (m, 1H), 3.10 (m, 1H), 3.37 (d, *J* = 10.5 Hz, 1H), 3.50 (d, *J*, 10.5 Hz, 1H), 4.55 (dd, *J* = 10.5, 9.0 Hz, 1H), 4.64 (dd, *J* = 10.5, 3.0 Hz, 1H), 5.06 (dd, *J* = 9.0, 3.0 Hz, 1H), 5.97 (dd, *J* = 7.0, 1.0 Hz, 1H), 6.56 (dd, *J* = 9.0, 1.0 Hz, 1H), 6.93 – 7.03 (m, 2H), 7.17 – 7.25 (m, 3H),

7.31 (dd, *J* = 9.1, 6.9 Hz, 1H), 8.17 – 8.23 (m, 2H), 8.28 – 8.34 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 23.7, 30.4, 35.9, 56.6, 59.7, 60.9, 61.8, 64.6, 105.2, 117.8, 123.6 (2C), 127.0 (2C), 128.1 (2C), 128.3, 130.8 (2C), 135.2, 138.0, 139.0, 150.6, 151.0, 163.0, 164.3; HRMS (ESI$^+$) calcd for $C_{26}H_{26}N_3O_5$ $[M+H]^+$: 460.1867, found 460.1854, calcd for $C_{26}H_{25}N_3NaO_5$ $[M+Na]^+$: 482.1686, found 482.1671.

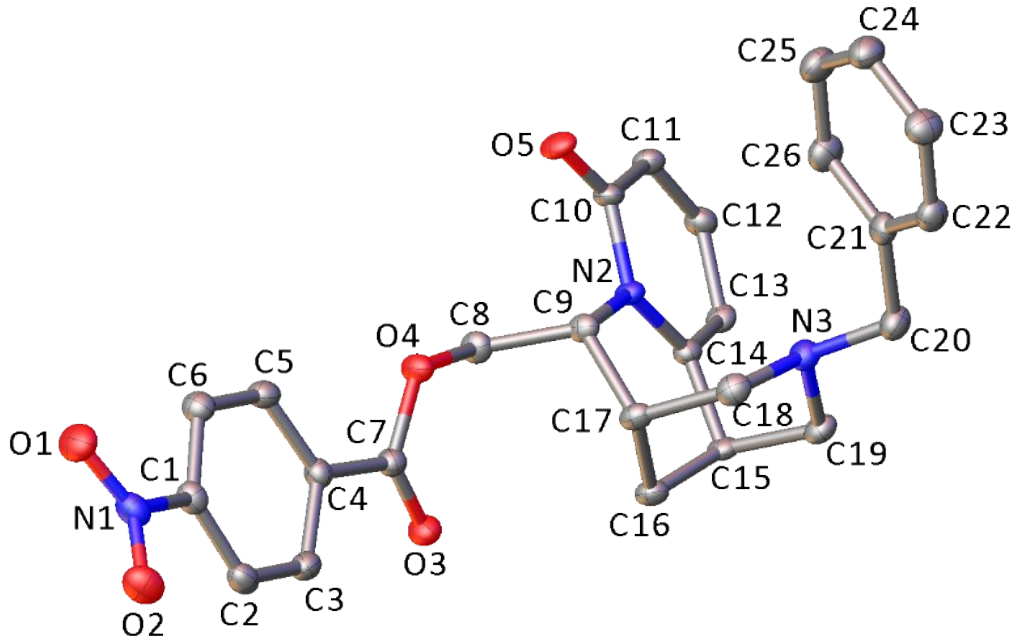
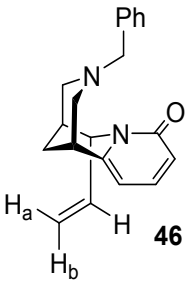


Illustration of the structure of **44** with atomic numbering scheme depicted. Ellipsoids are depicted at the 50% probability level and hydrogen atoms are omitted for clarity.

(6*R*)-3-Benzyl-6-vinyl-1,2,3,4,5,6-hexahydro-8*H*-1,5-methanopyrido[1,2-a][1,5]diazocin-8-one 46



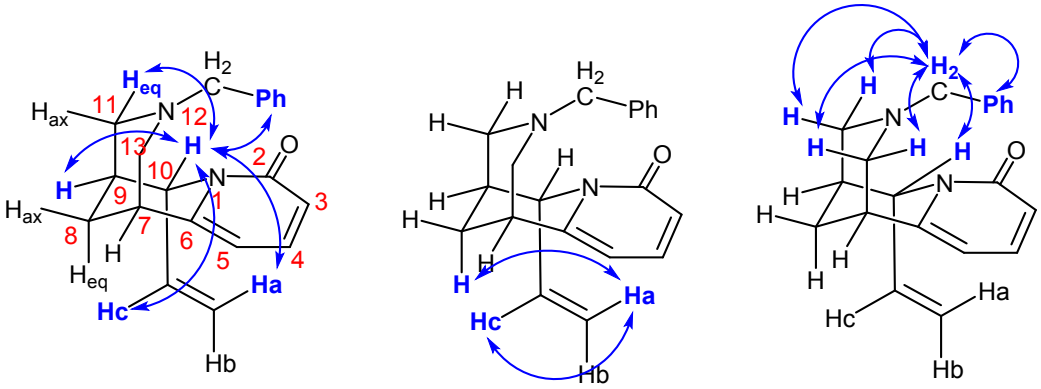
46

To a solution of boronic ester **17** (61 mg, 0.15 mmol) in THF (1.5 mL) at room temperature, was added vinyl magnesium bromide (1.0 M in THF, 0.60 mL, 0.60 mmol) dropwise over 5 min. The reaction mixture was stirred at room temperature for 2 h and cooled to -78 °C. A solution of iodine in MeOH (1.0 M, 0.60 mL, 0.60 mmol) was added dropwise over 5 min, and the reaction mixture was stirred at -78 °C for 30 min. A solution of sodium methoxide in MeOH (0.50 M, 2.40 mL, 1.20 mmol) was added in a single portion. The reaction mixture was then allowed to warm to room temperature and stirred for an additional 1 h. The crude reaction

mixture was diluted with DCM (5 mL) and quenched with $Na_2S_2O_3$ (5 mL, aq. sat. sol.) and water (5 mL). The aqueous layer was extracted with DCM (3 × 10 mL) and the combined organic layers were dried (Na_2SO_4), filtered, and concentrated *in vacuo*. Purification by flash column chromatography [EtOAc:*n*-Hexane: triethylamine (49:50:1 to 99:0:1)] gave **46** (36 mg, 94%) as a colourless solid.

$[\alpha]_D^{23}$ = –24 (c 0.3, $CHCl_3$); R_f = 0.34 [EtOAc]; m.p. 160 °C (DCM/*n*-Hexane); FTIR ν_{max}/cm^{-1} (neat): 3059, 2936, 2809, 1650, 1568, 1542, 1141, 809, 736; ^1H NMR (400 MHz, $CDCl_3$) δ_H 1.59 (ddd, *J* = 4.0, 2.5, 1.0 Hz, 1H), 2.07 – 2.16 (m, 2H), 2.24 (dd, *J* = 10.5, 2.0 Hz, 1H), 2.48 (dd, *J* = 11.0, 2.5 Hz, 1H), 2.70 (ddd, *J* = 10.5, 2.0, 2.0 Hz, 1H), 2.91 (m, 1H), 3.08 (m, 1H), 3.29 (d, *J* = 13.5 Hz, 1H), 3.46 (d, *J* = 13.5 Hz, 1H), 4.67 (ddd, *J* = 17.0, 1.5, 1.0 Hz, 1H), 5.10 (ddd, *J* = 10.5, 1.5, 1.0 Hz, 1H), 5.25 (ddd, *J* = 5.0, 1.5, 1.5 Hz, 1H), 5.88 (dd, *J* = 7.0, 1.5 Hz, 1H), 5.92 (ddd, *J* = 17.0, 10.5, 5.0 Hz, 1H), 6.49 (dd, *J* = 9.0, 1.5 Hz, 1H), 6.90 – 6.95 (m, 2H), 7.12 – 7.19 (m, 3H), 7.24 (dd, *J* = 9.0, 7.0 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ_C 22.8, 33.2, 36.0, 59.5, 59.7, 60.7, 61.9, 104.6, 114.0, 117.7, 127.0, 128.2 (2C), 128.3 (2C), 138.3, 138.4, 138.6, 151.1, 162.9; HRMS (ESI^+) calcd for $C_{20}H_{23}N_2O$ $[M+H]^+$: 307.1805, found 307.1801.

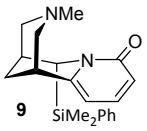
Details of NOESY correlations observed for alkene 46, which was irradiated at (from left) H10, Ha, and C<u>H</u>$_2$Ph.



Synthesis references

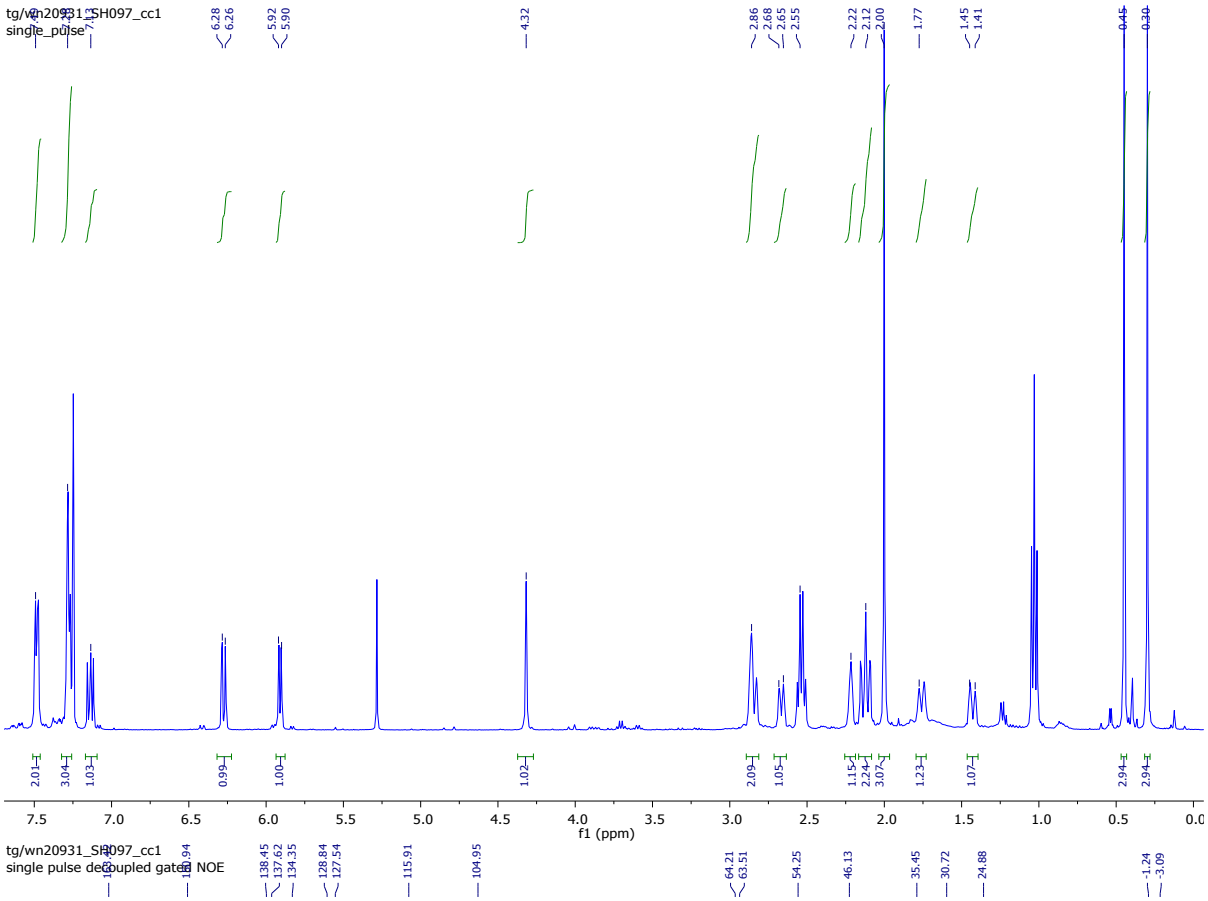
(1) A. J. Dixon, M. J. McGrath and P. O'Brien, *Org. Synth.,* 2006, **83**, 141-154.
(2) B. Danieli, G. Lesma, D. Passarella, A. Sacchetti, A. Silvani and A. Virdis, *Org. Lett.,* 2004, **6**, 493-496.
(3) F. Frigerio, C. A. Haseler, and T. Gallagher, *Synlett,* **2010**, 729-730.
(4) I. Murakoshi, E. Kidoguchi, J. Haginiwa, S. Ohmiya, K. Higashiyama and H. Otomasu, *Phytochemistry*, 1981, **20**, 1407-1409.
(5) T. Honda, R. Takahashi and H. Namiki, *J. Org. Chem.*, 2005, **70**, 499-504.

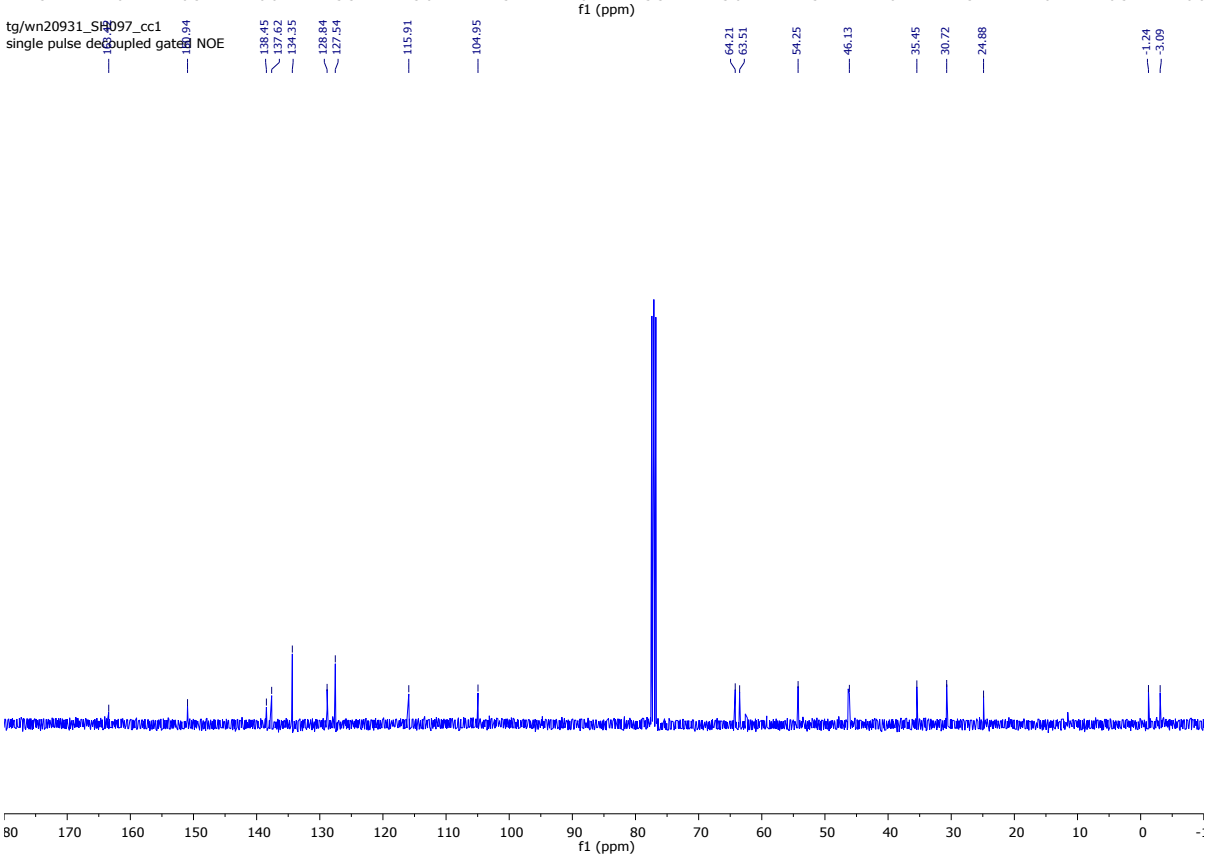
5. NMR Spectra



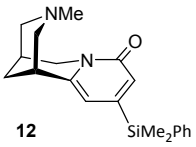
9

^{1}H NMR (400 MHz), ^{13}C NMR (101 MHz): $CDCl_3$

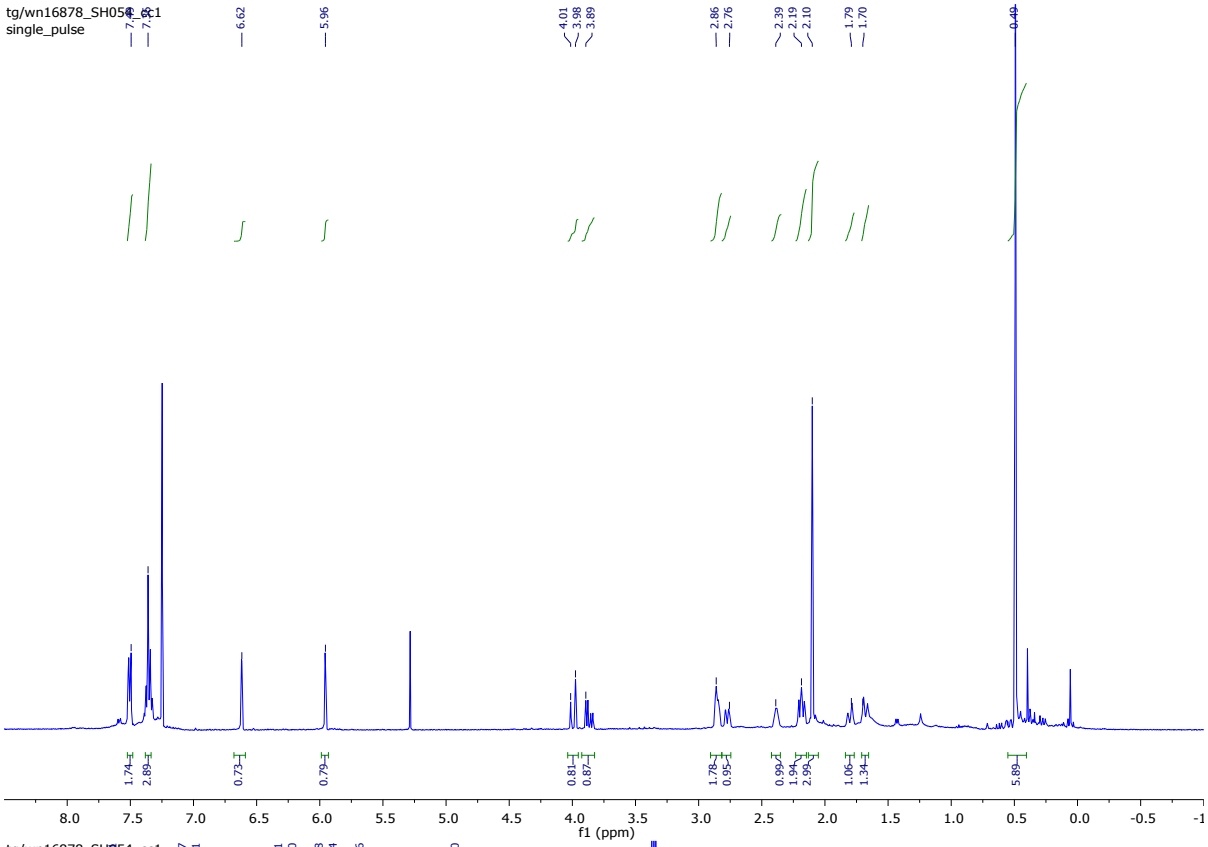


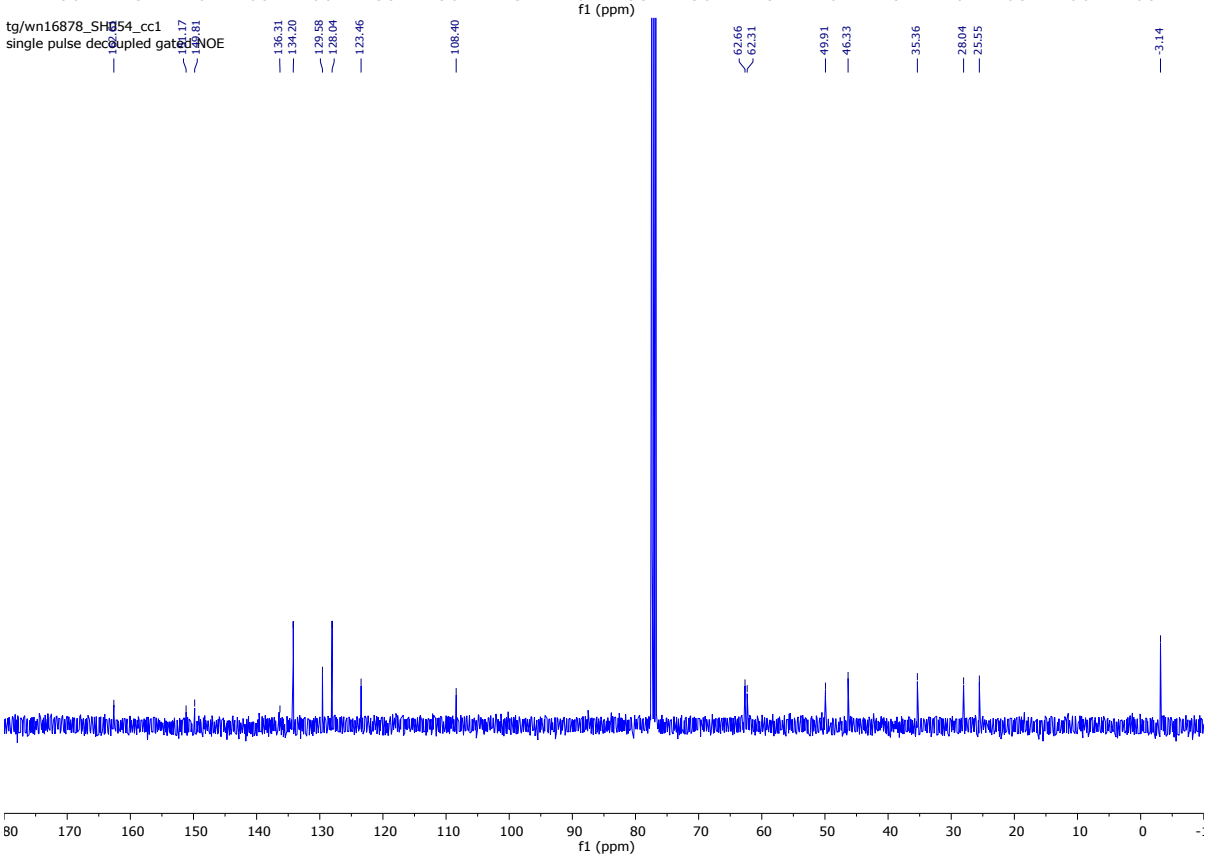


^{1}H NMR (400 MHz), ^{13}C NMR (101 MHz): $CDCl_3$

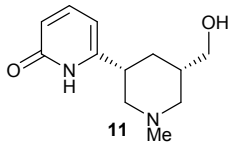


12

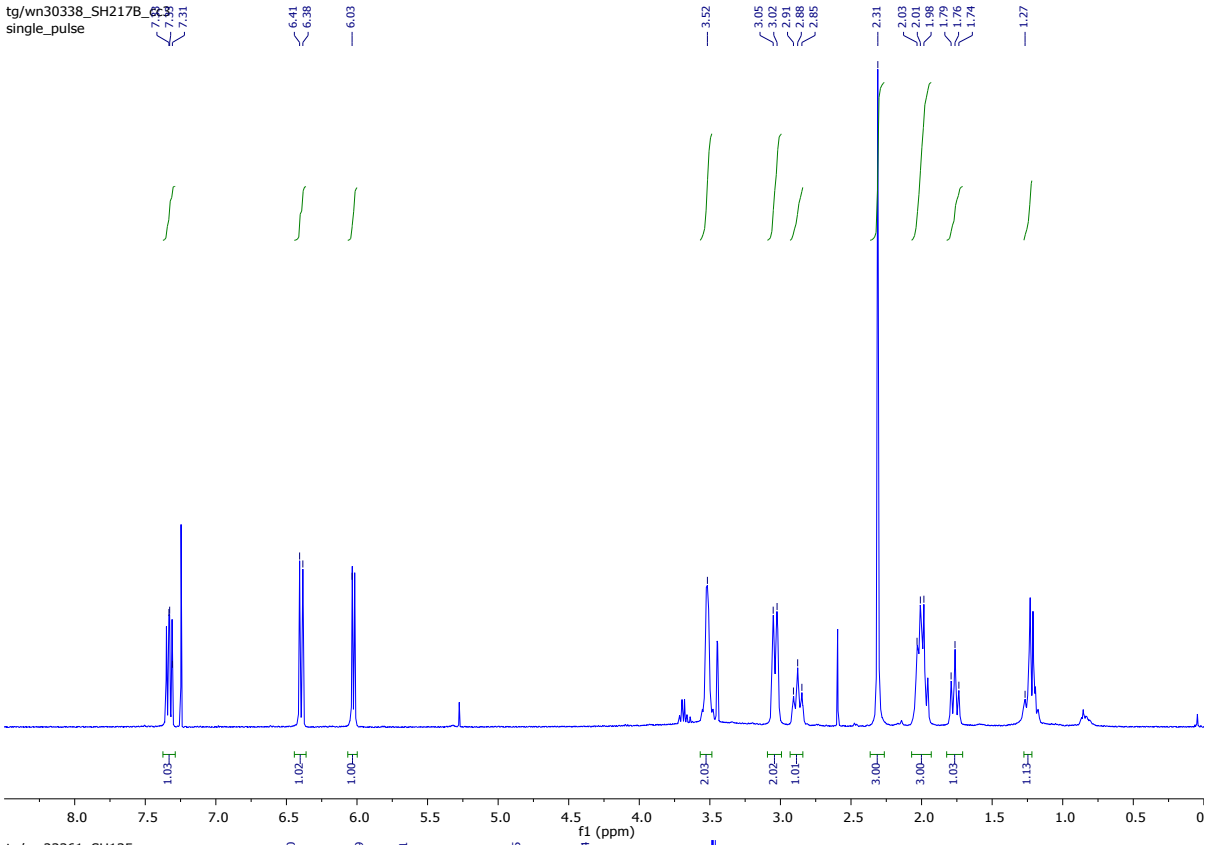


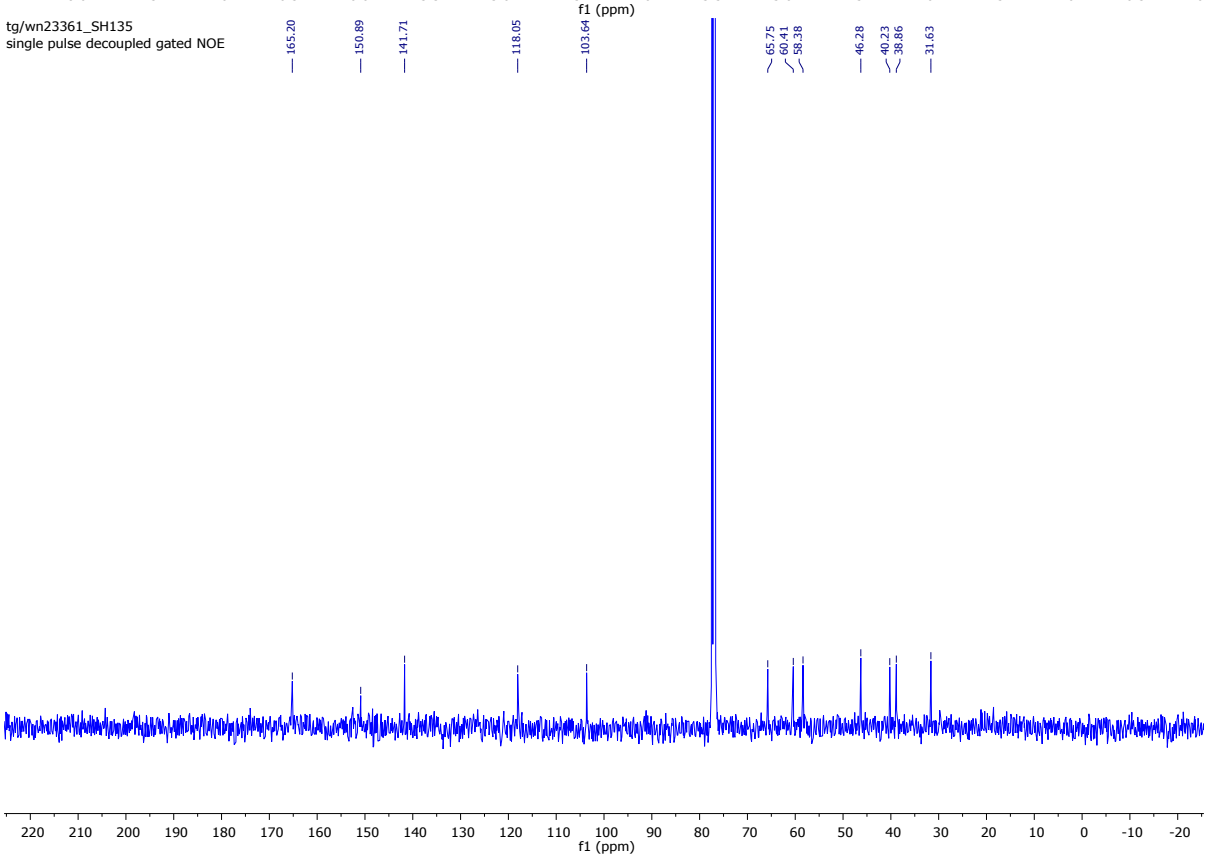


^{1}H NMR (400 MHz), ^{13}C NMR (101 MHz): $CDCl_3$

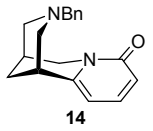


11

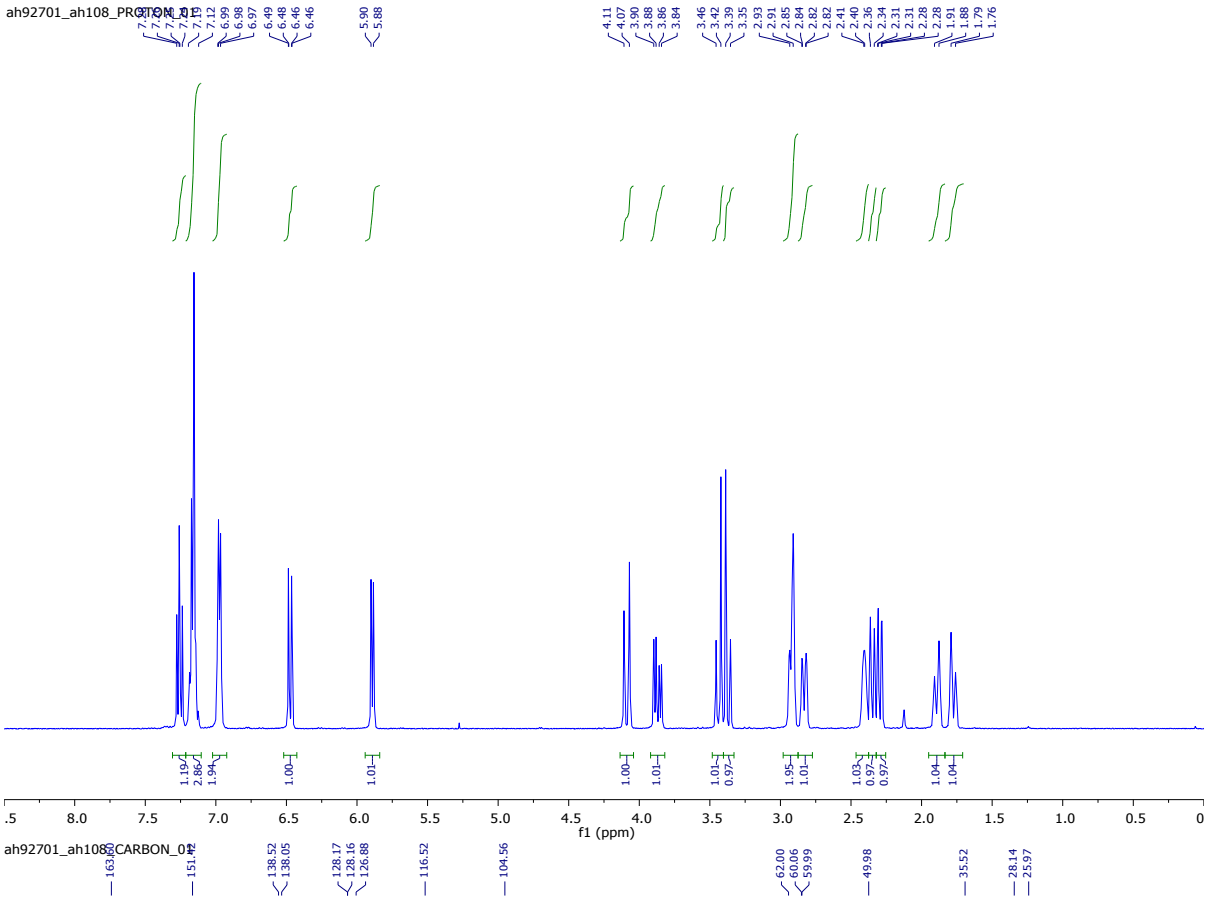


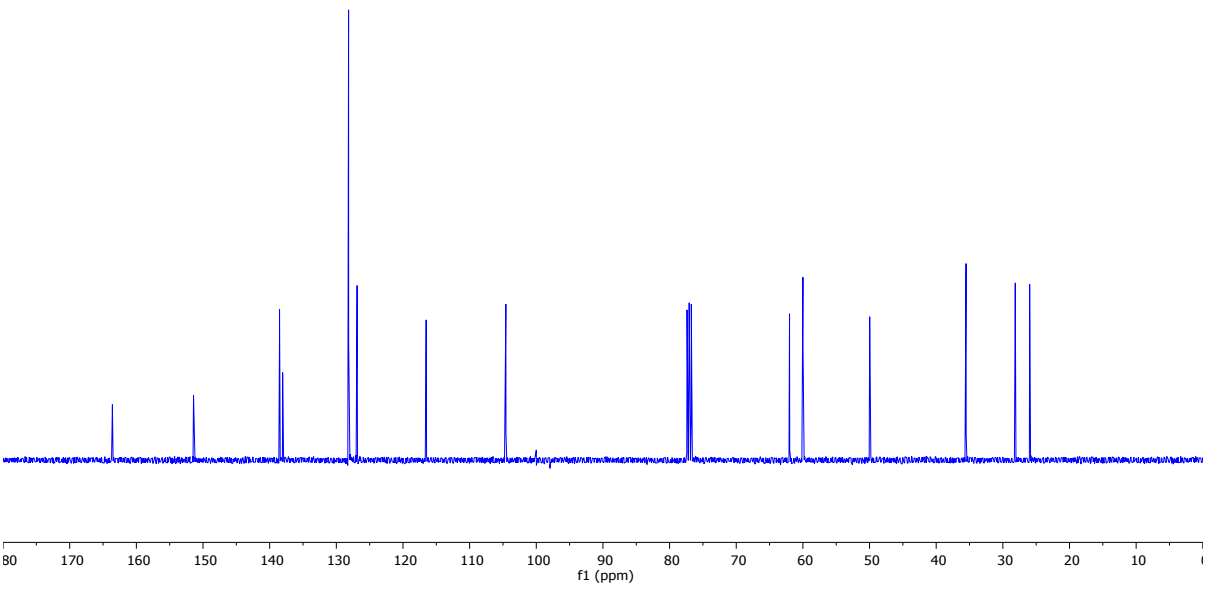


^{1}H NMR (400 MHz), ^{13}C NMR (101 MHz): $CDCl_3$

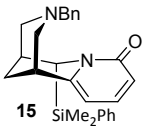


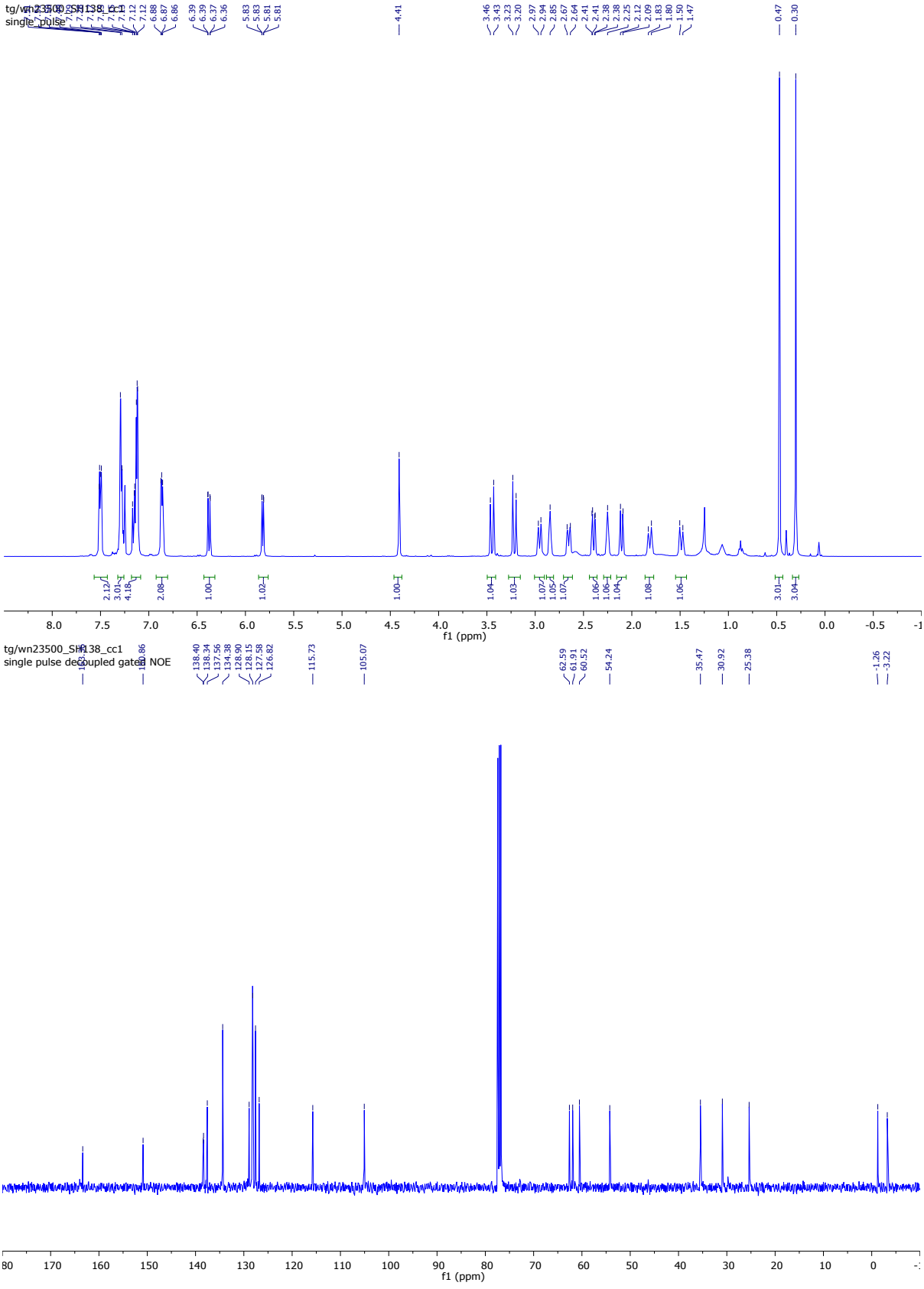
14



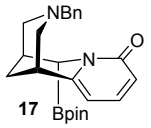


^{1}H NMR (400 MHz), ^{13}C NMR (101 MHz): $CDCl_3$





^{1}H NMR (500 MHz), ^{13}C NMR (125 MHz): $CDCl_3$



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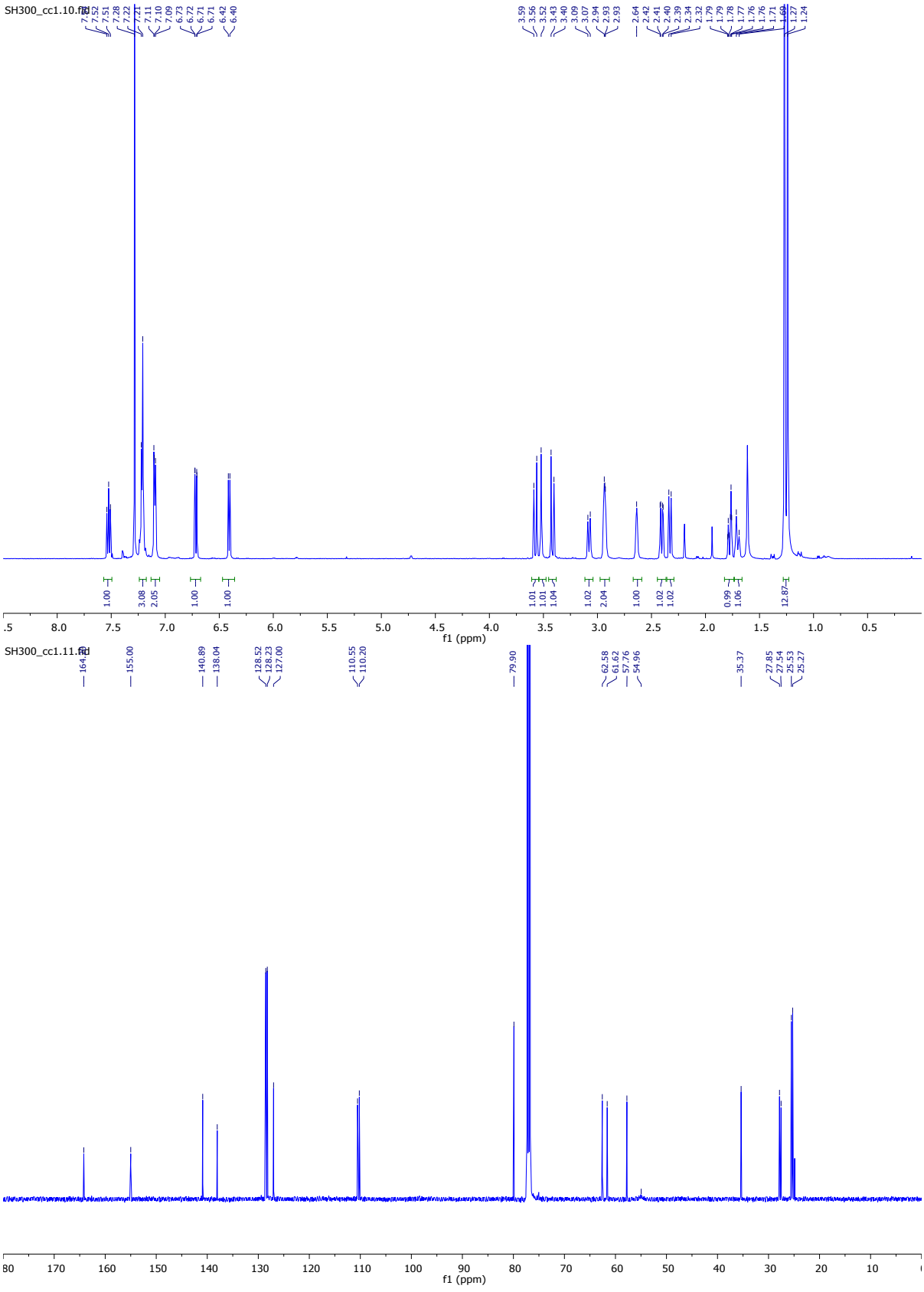
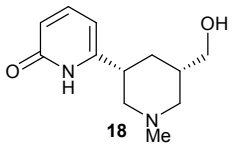


^{1}H NMR (400 MHz), ^{13}C NMR (101 MHz): $CDCl_3$



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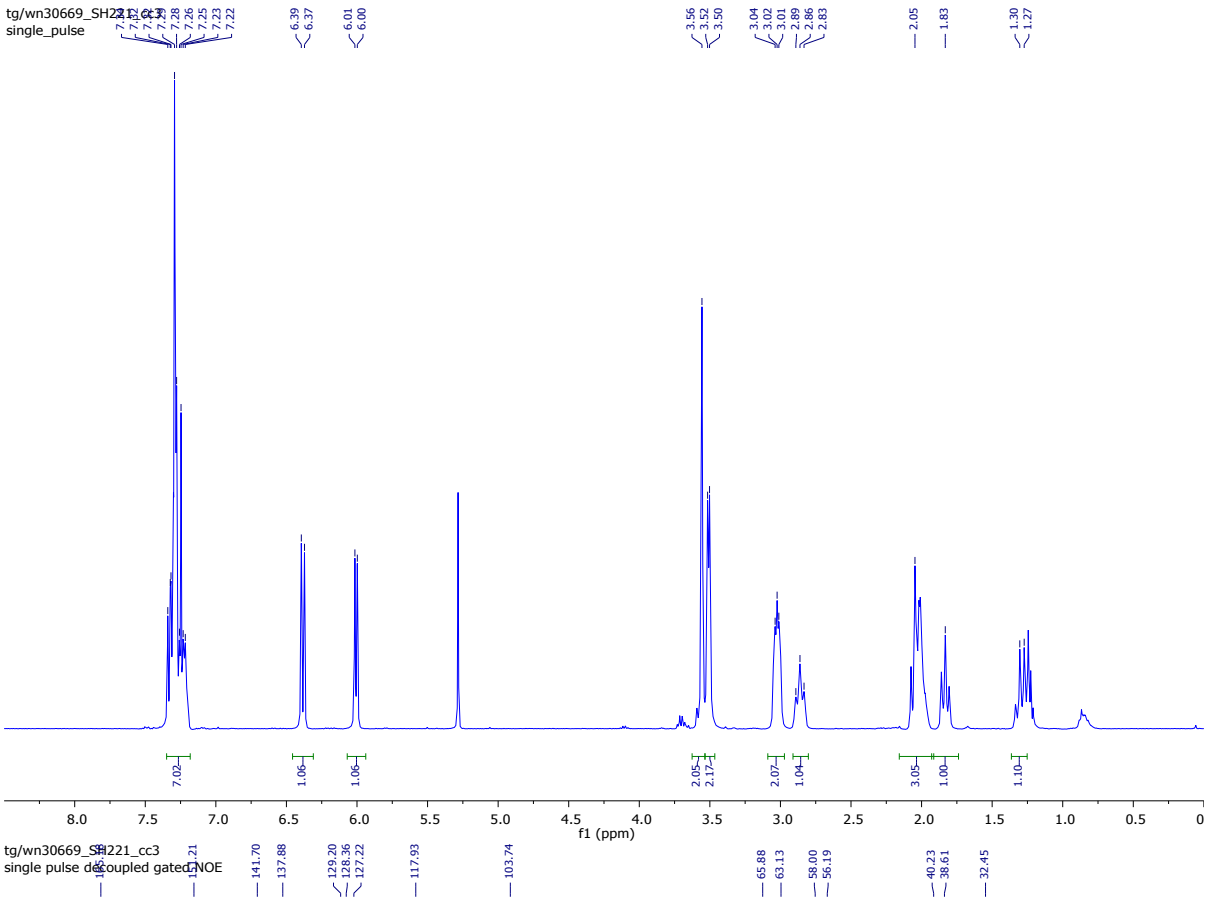
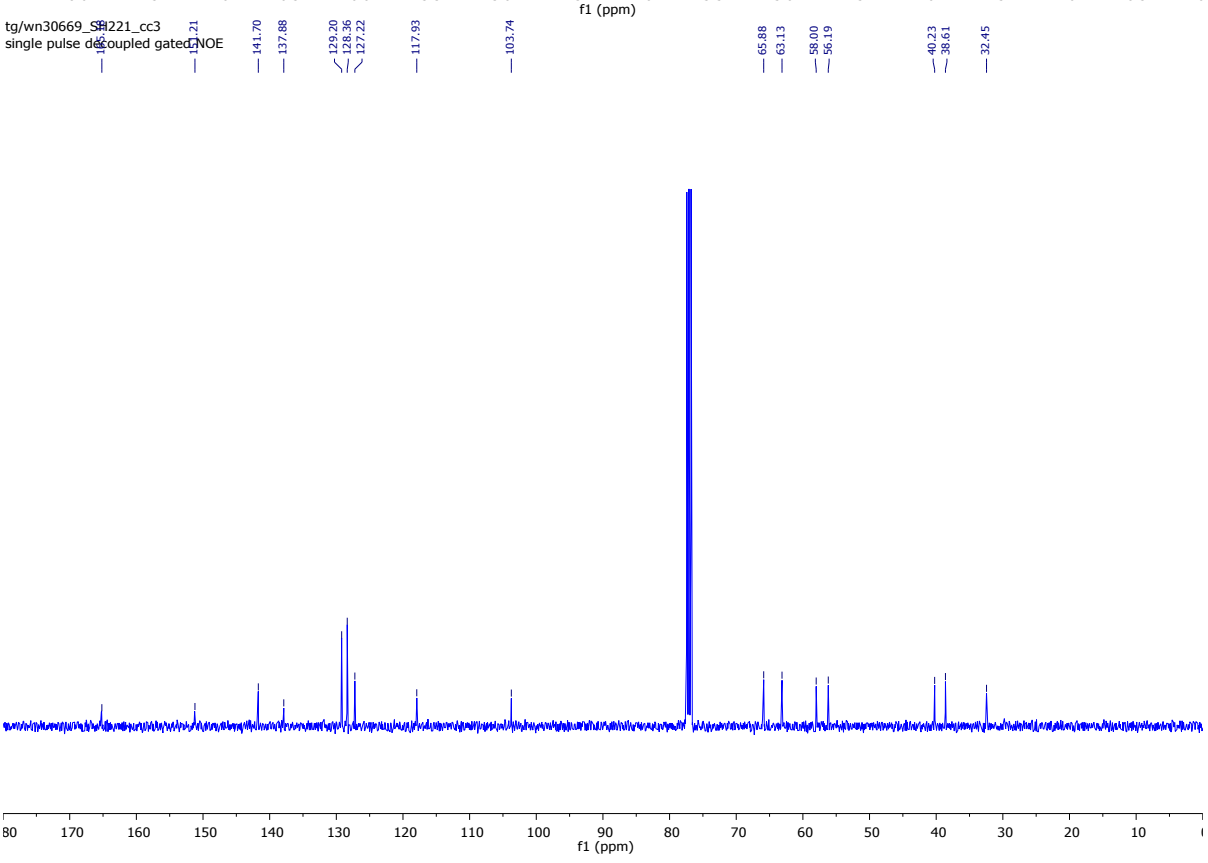
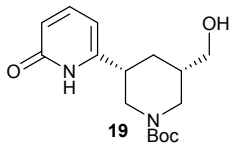




^{1}H NMR (500 MHz, 52 °C), ^{13}C NMR (125 MHz, 52 °C): MeOD



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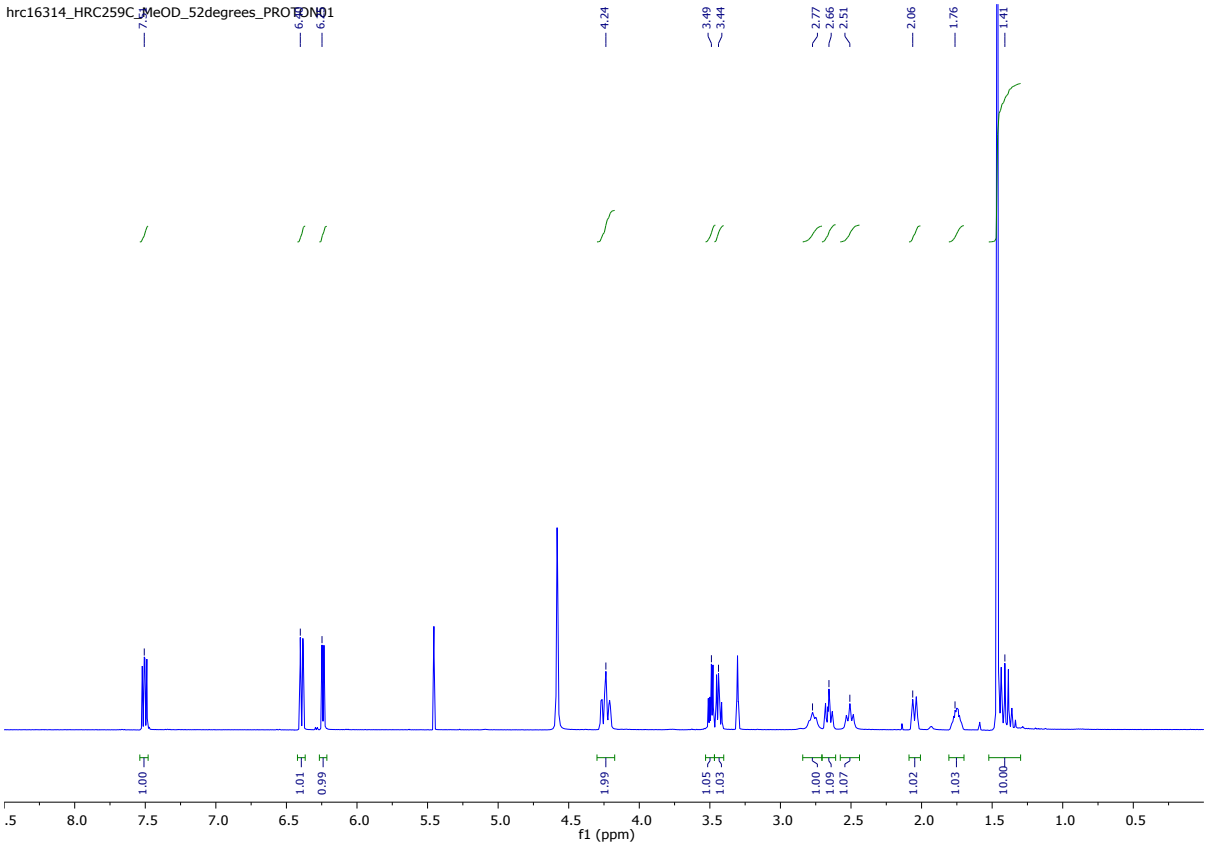
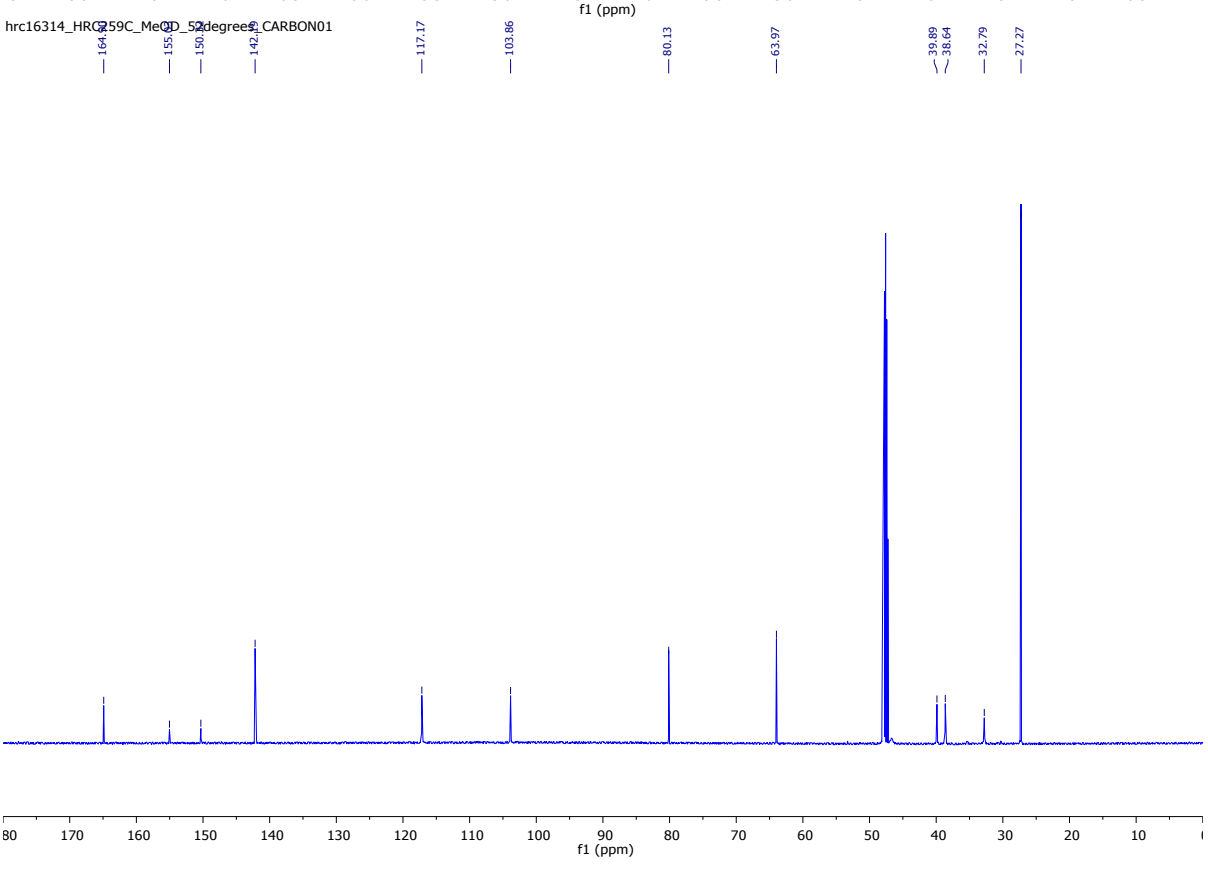
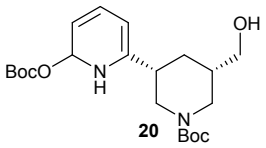




^{1}H NMR (400 MHz), ^{13}C NMR (101 MHz): $CDCl_3$



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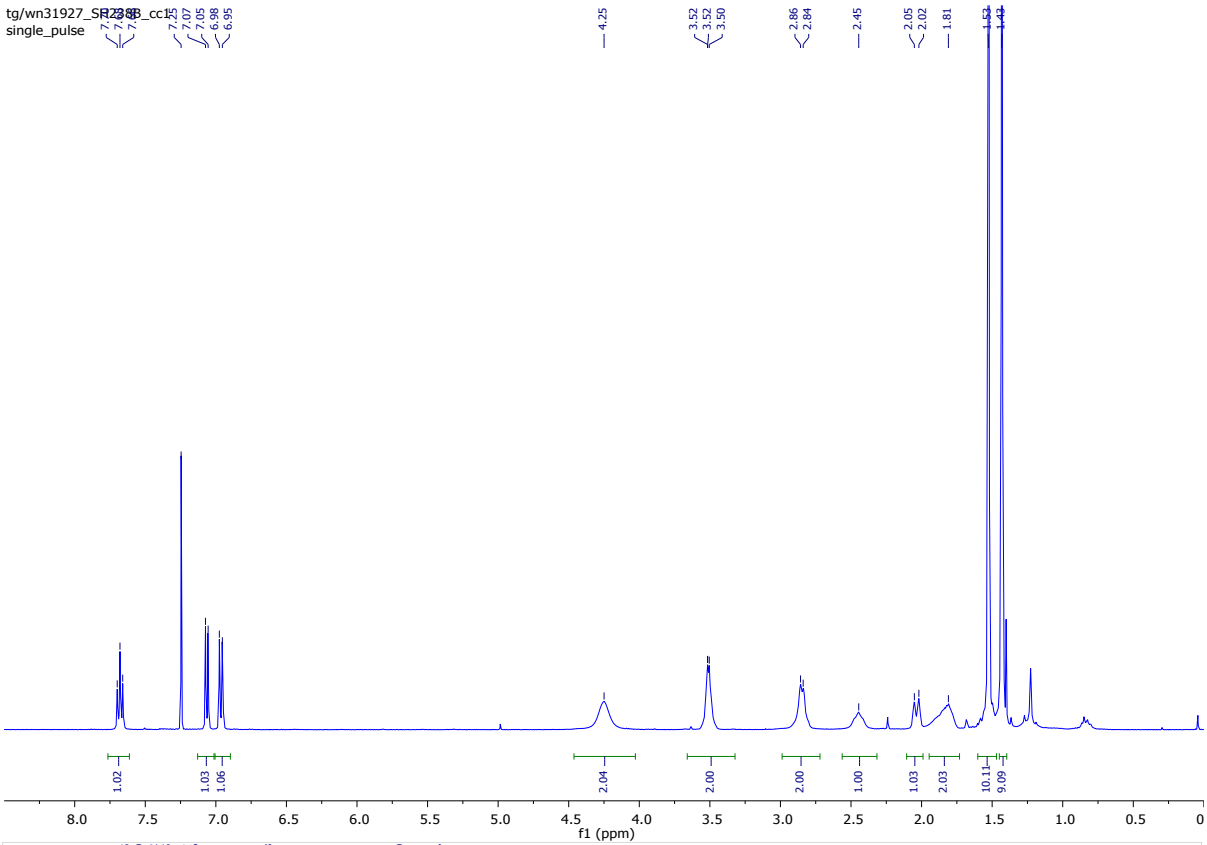
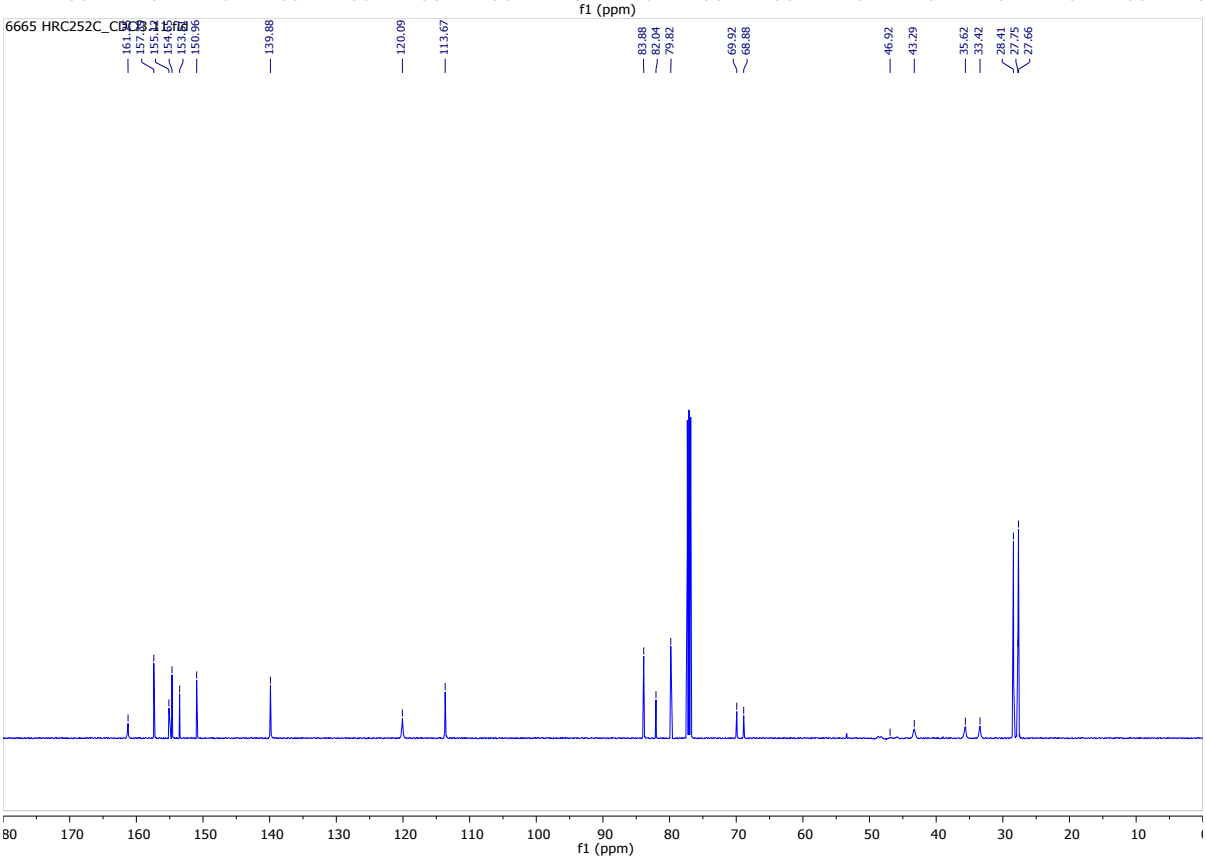
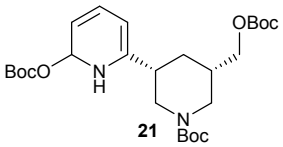




^{1}H NMR (500 MHz), ^{13}C NMR (125 MHz): $CDCl_3$



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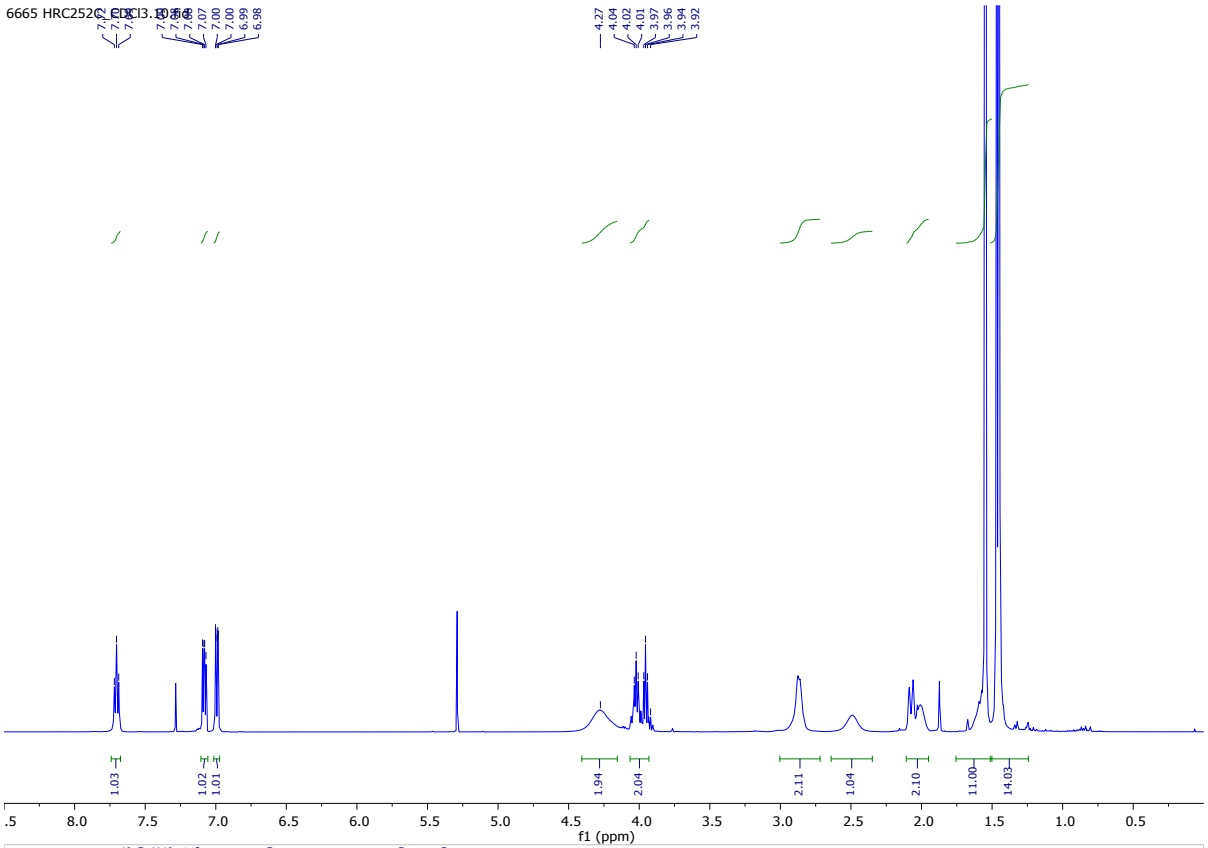
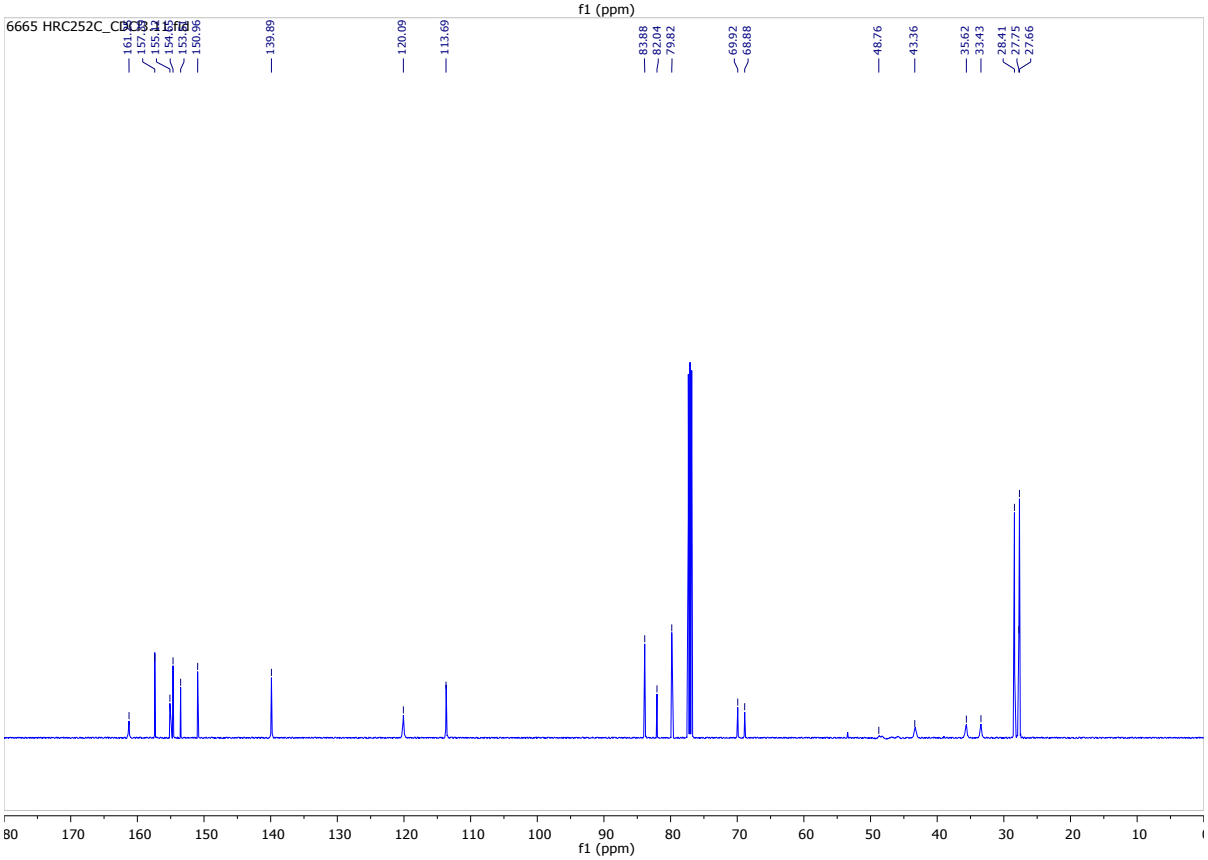
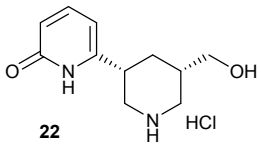




^{1}H NMR (500 MHz), ^{13}C NMR (125 MHz): MeOD



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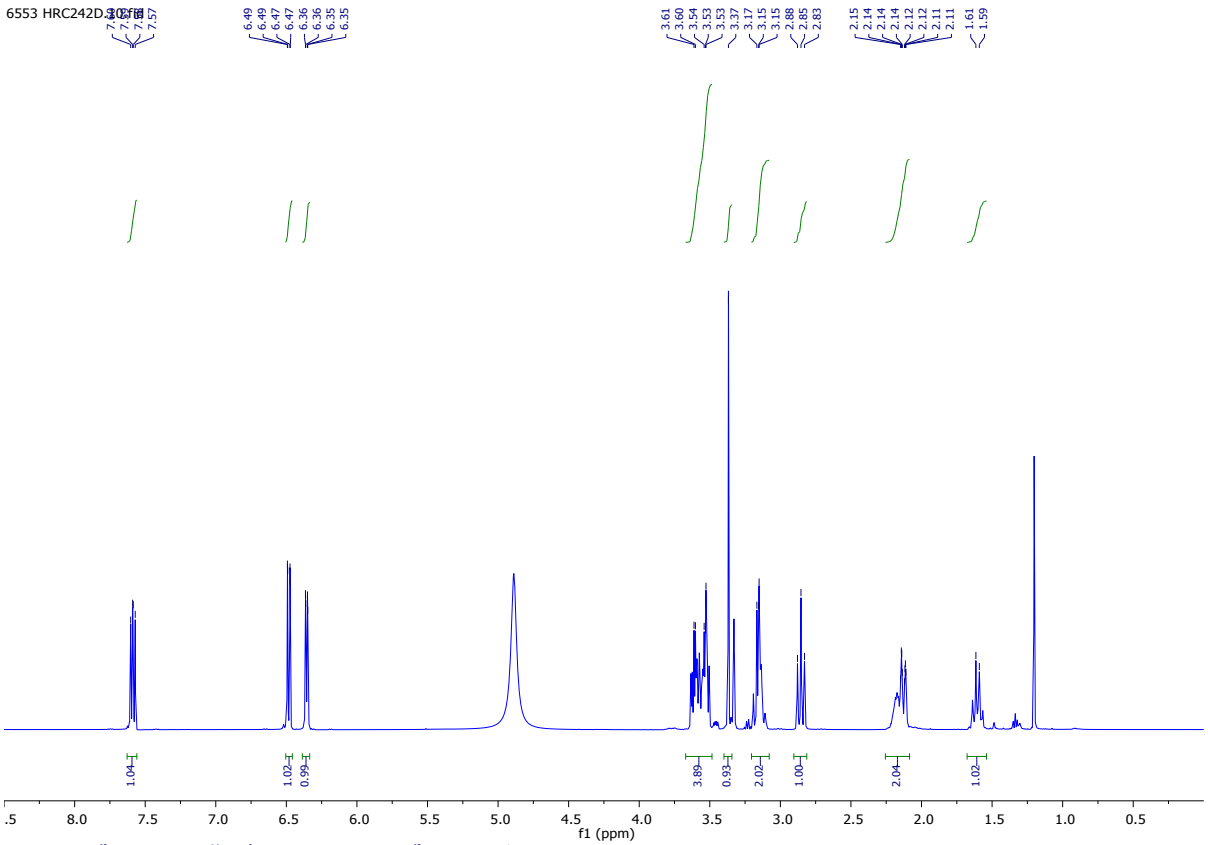
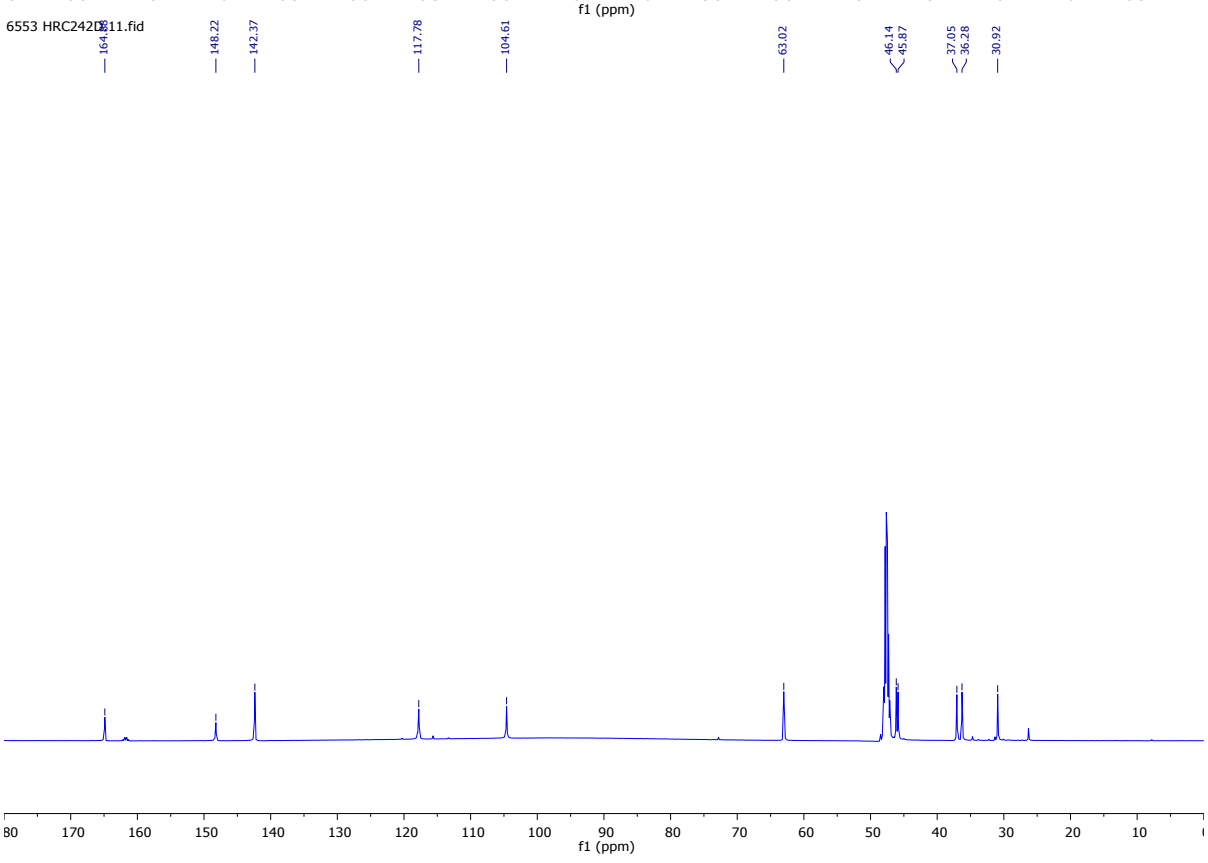
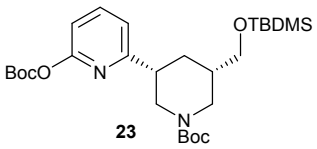




^{1}H NMR (500 MHz), ^{13}C NMR (125 MHz): $CDCl_3$



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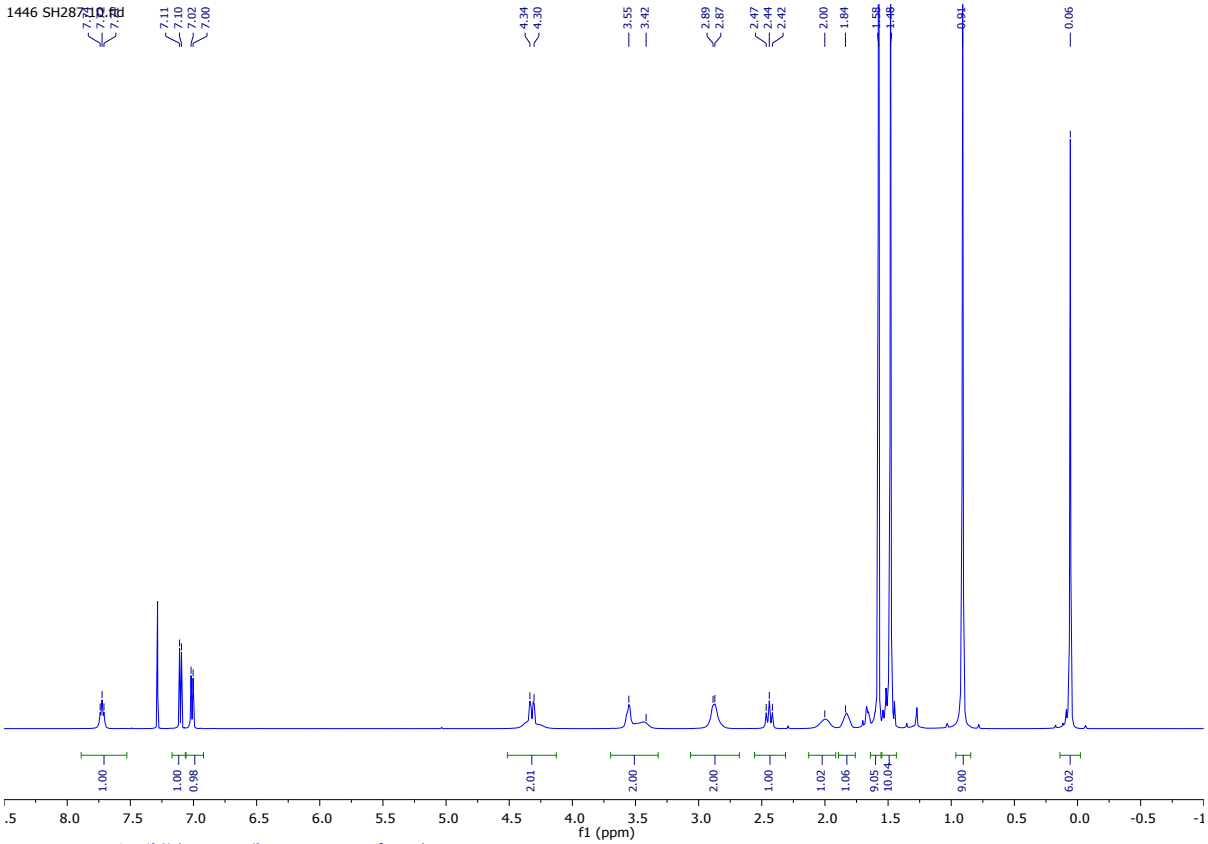
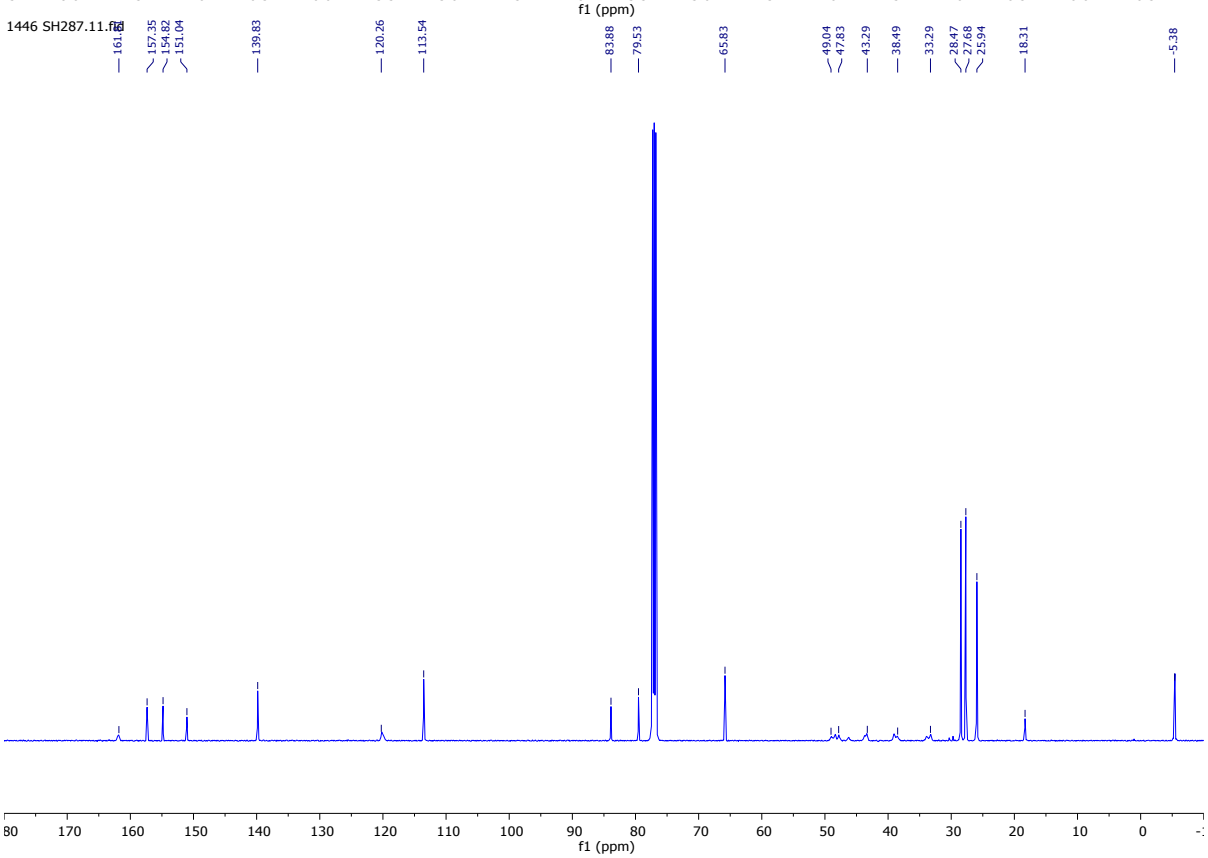
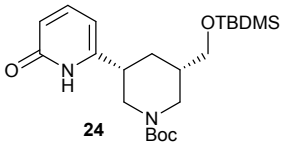




^{1}H NMR (500 MHz), ^{13}C NMR (125 MHz): $CDCl_3$



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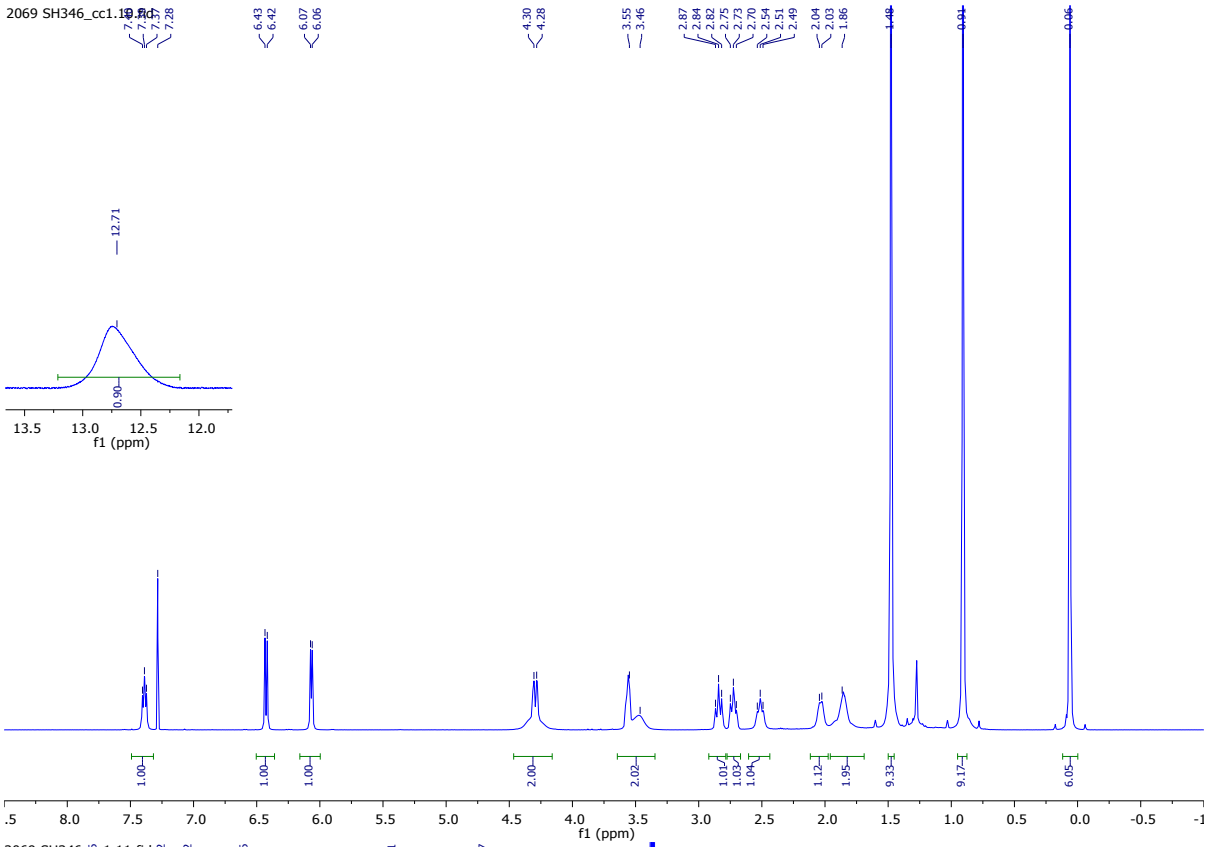
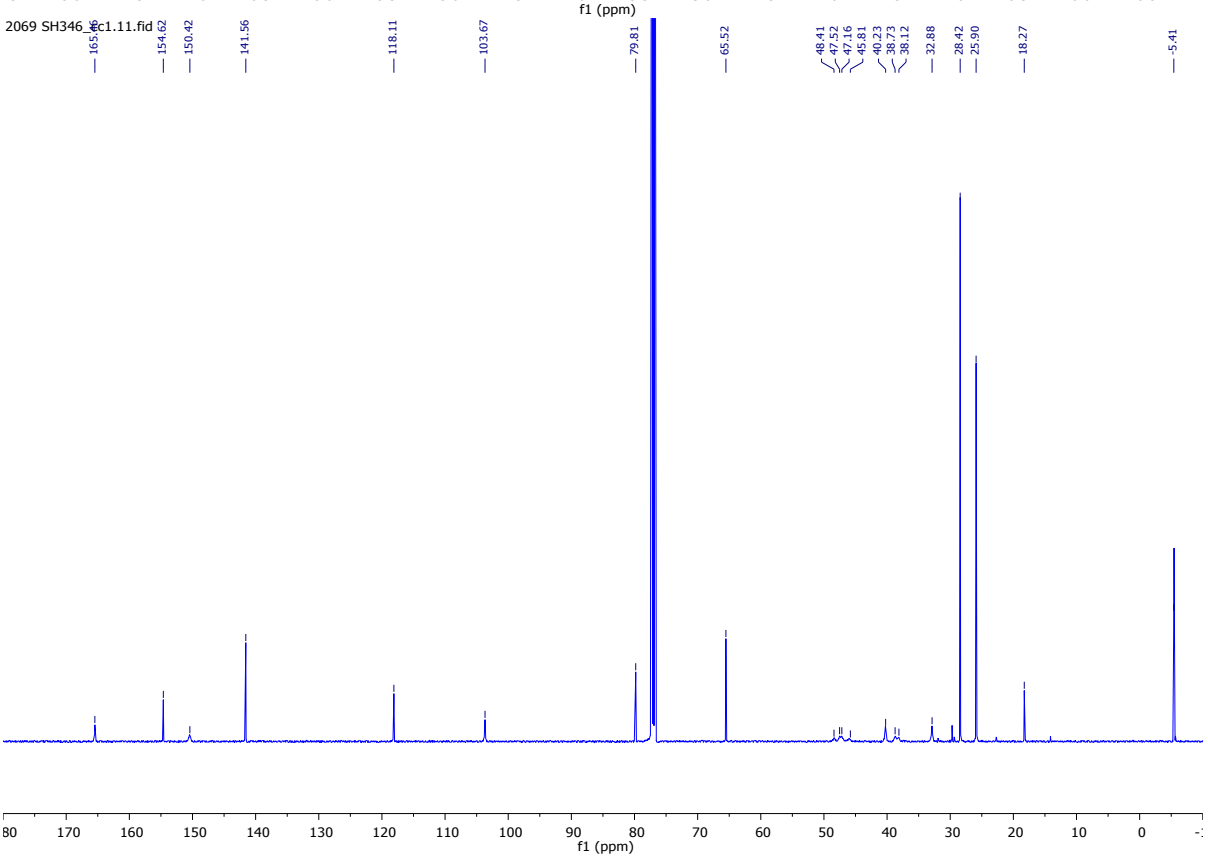
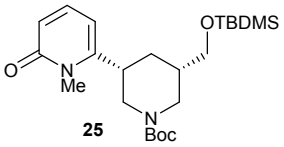




^{1}H NMR (500 MHz), ^{13}C NMR (125 MHz): $CDCl_3$



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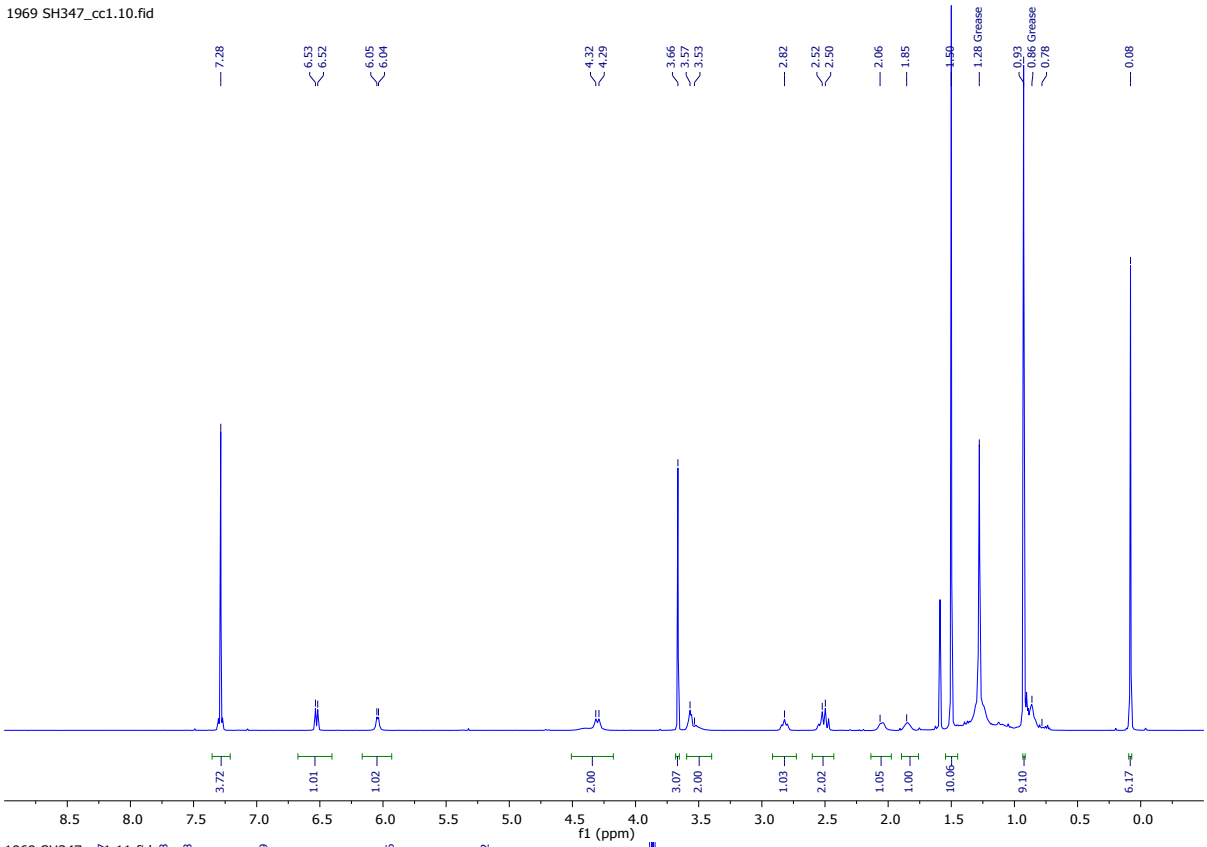
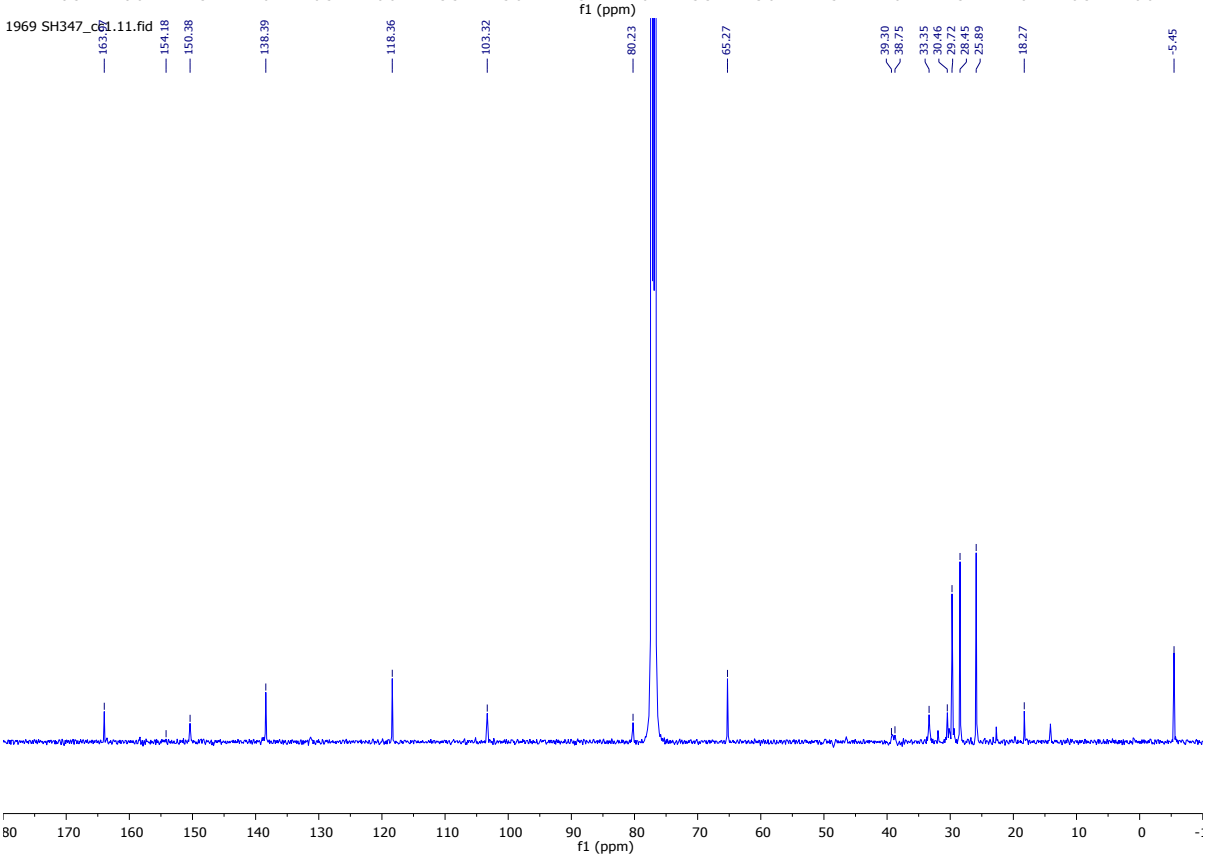
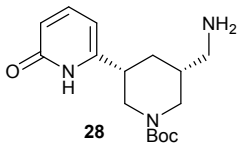




^{1}H NMR (500 MHz), ^{13}C NMR (125 MHz): $CDCl_3$



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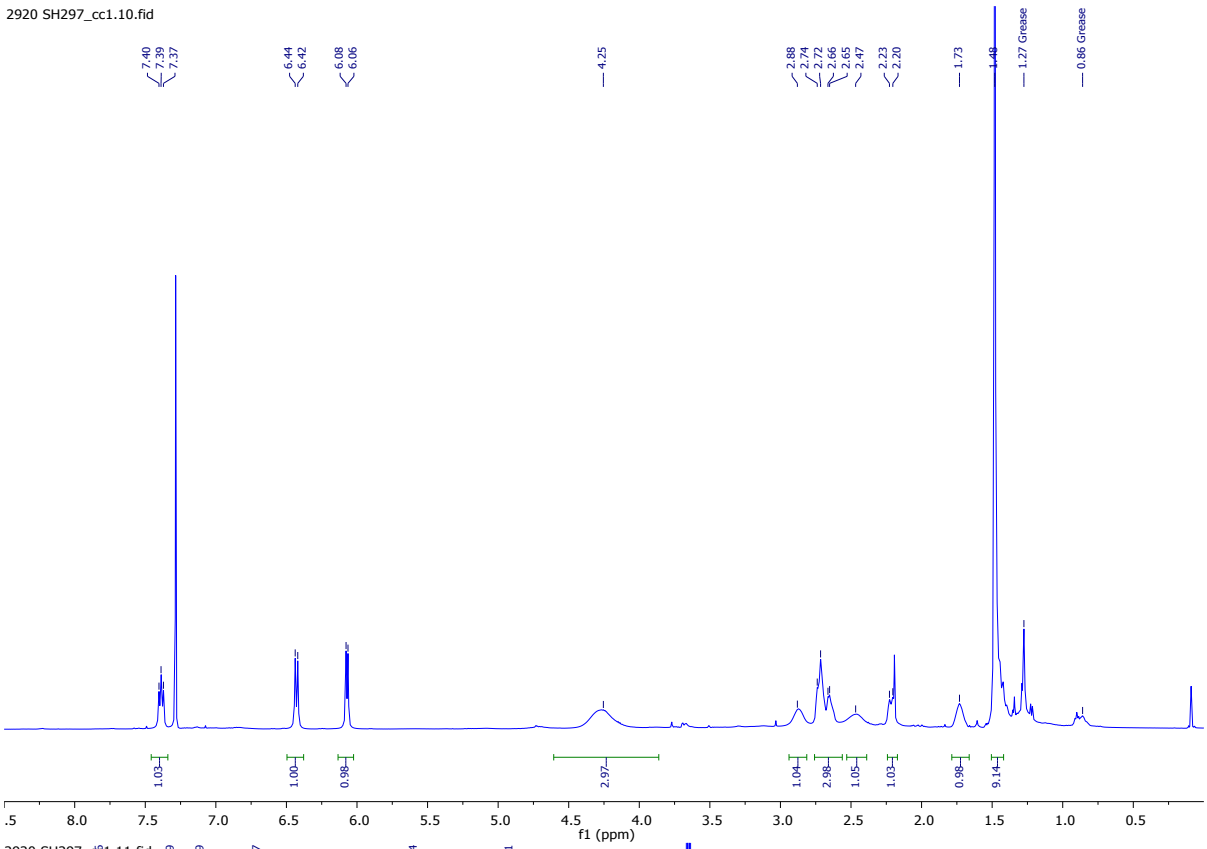
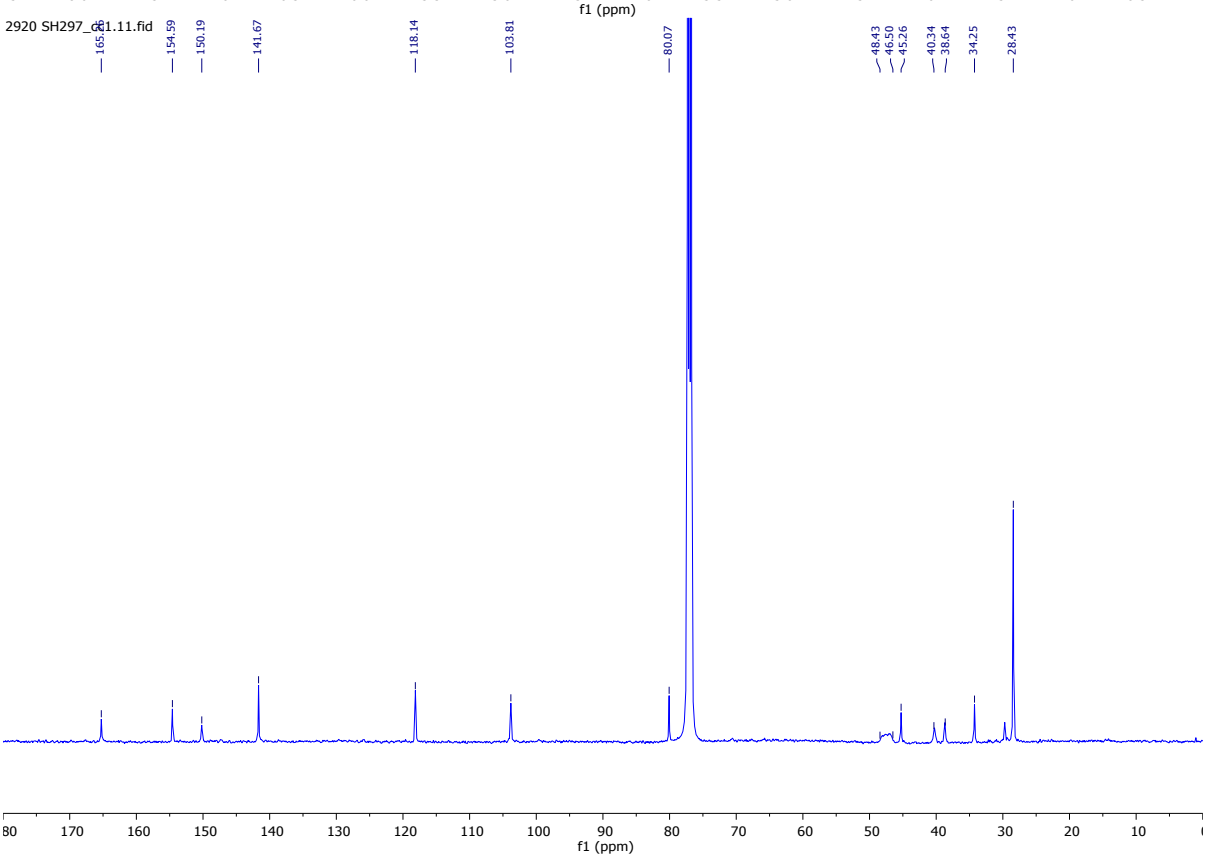
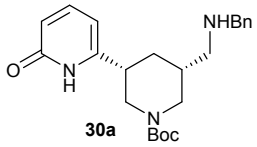
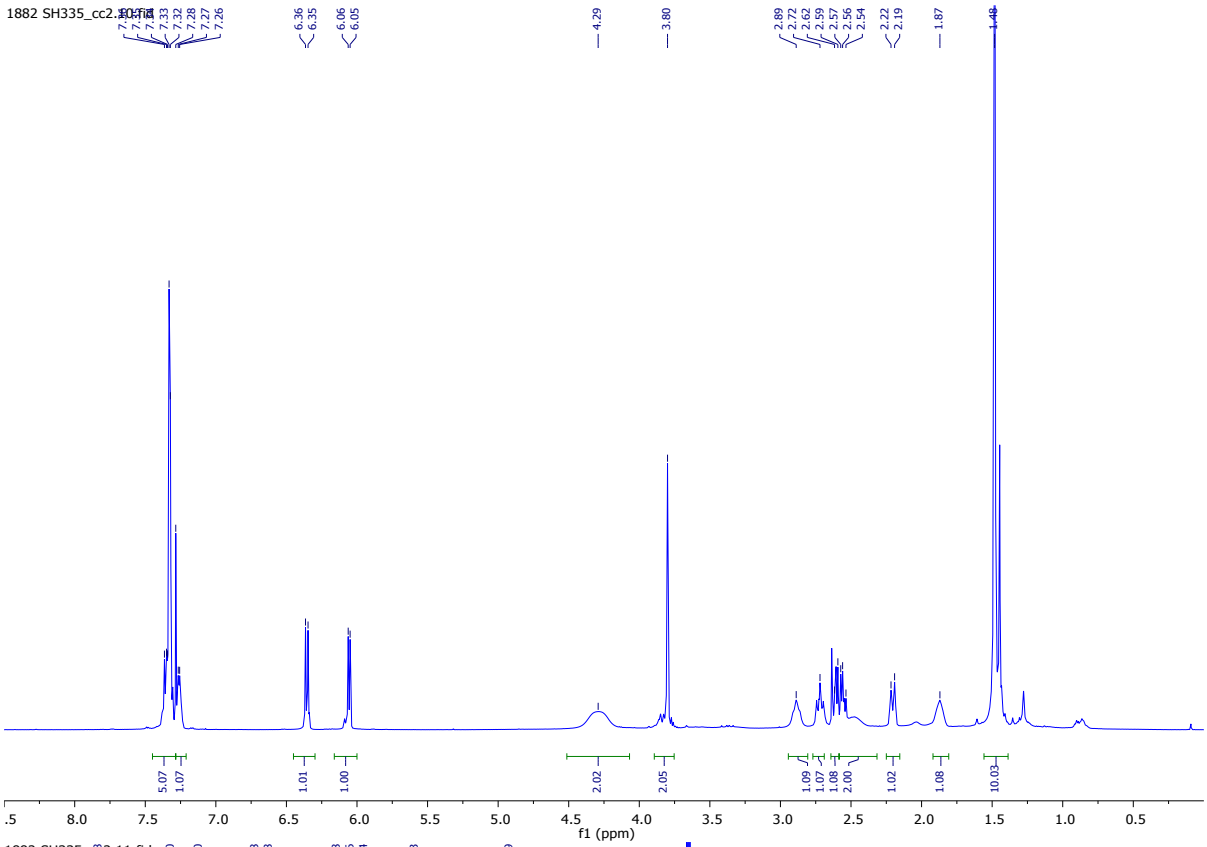


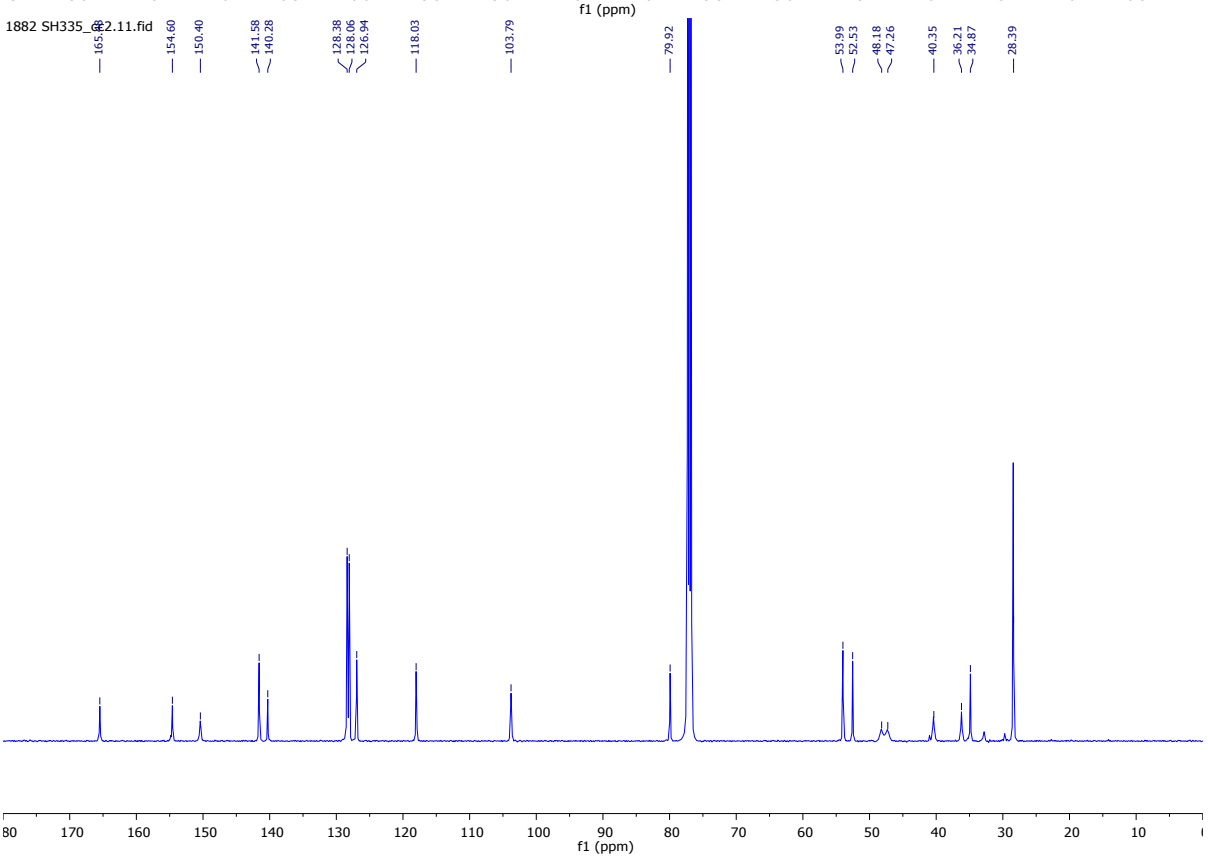


^{1}H NMR (500 MHz), ^{13}C NMR (125 MHz): $CDCl_3$

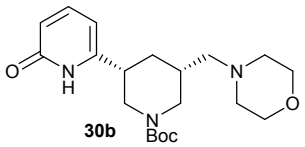


30a

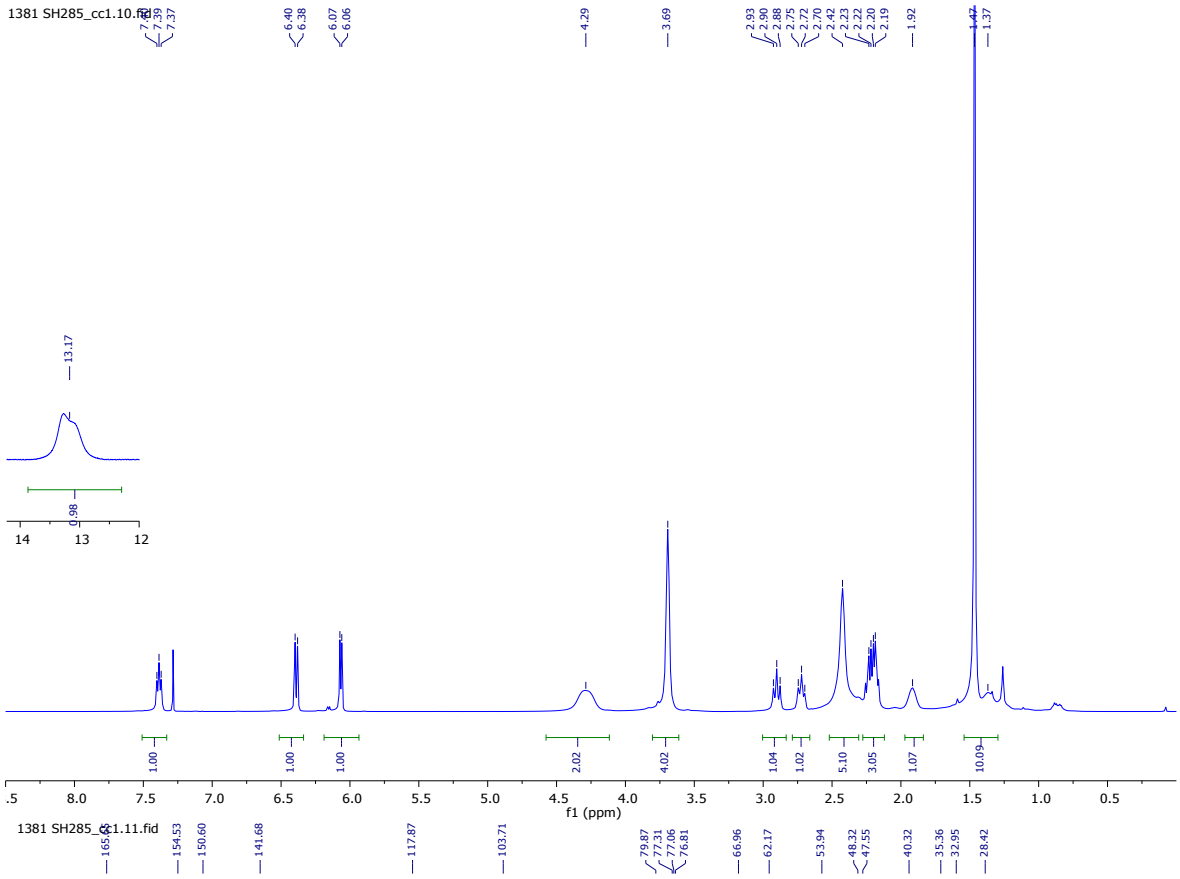


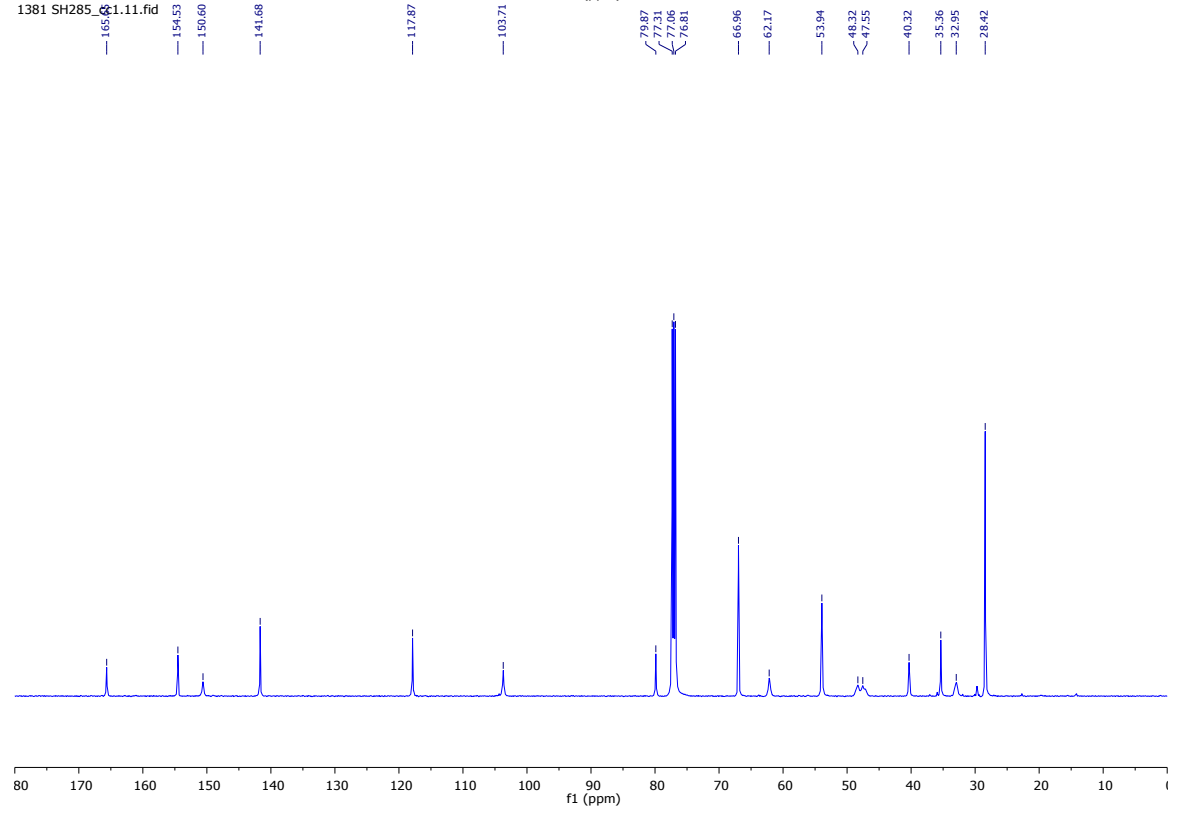


^{1}H NMR (500 MHz), ^{13}C NMR (125 MHz): $CDCl_3$

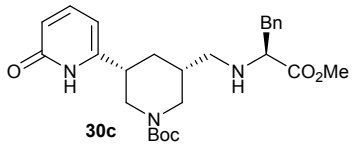


30b

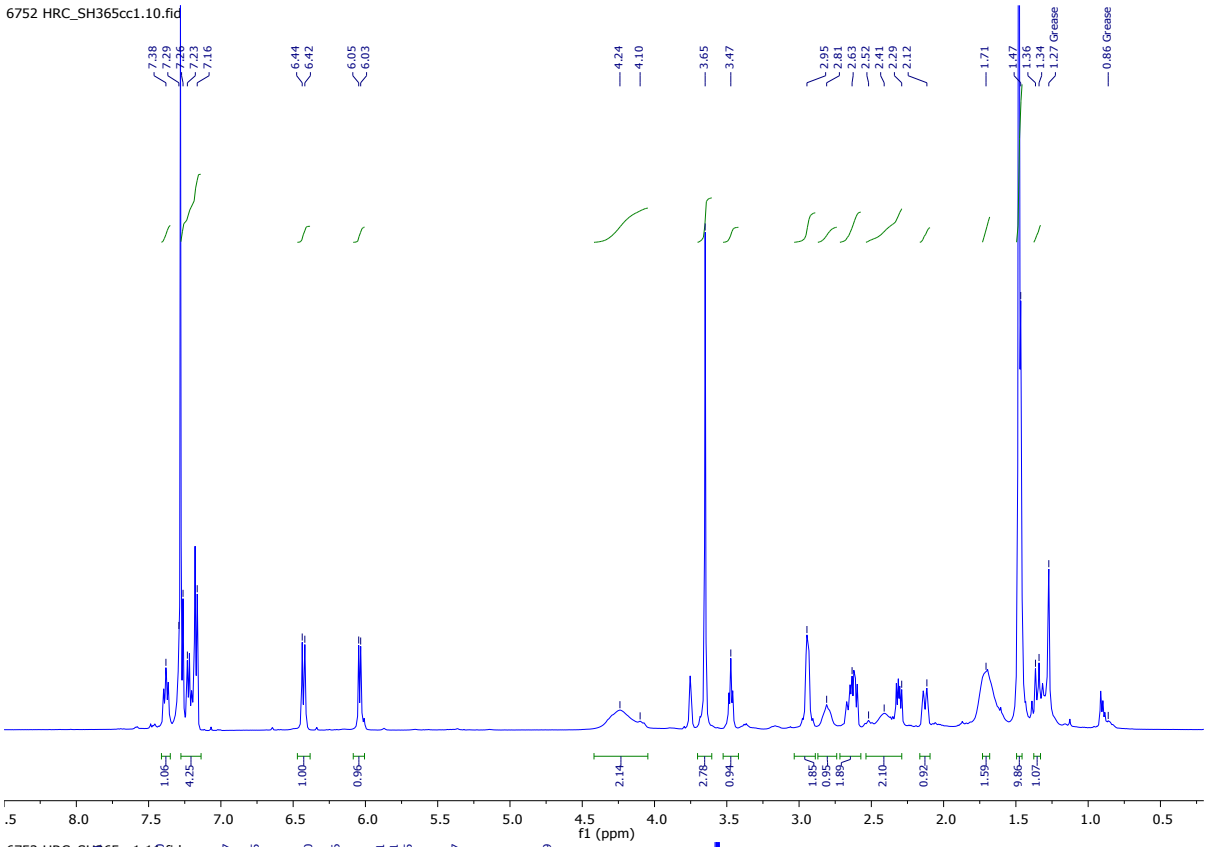


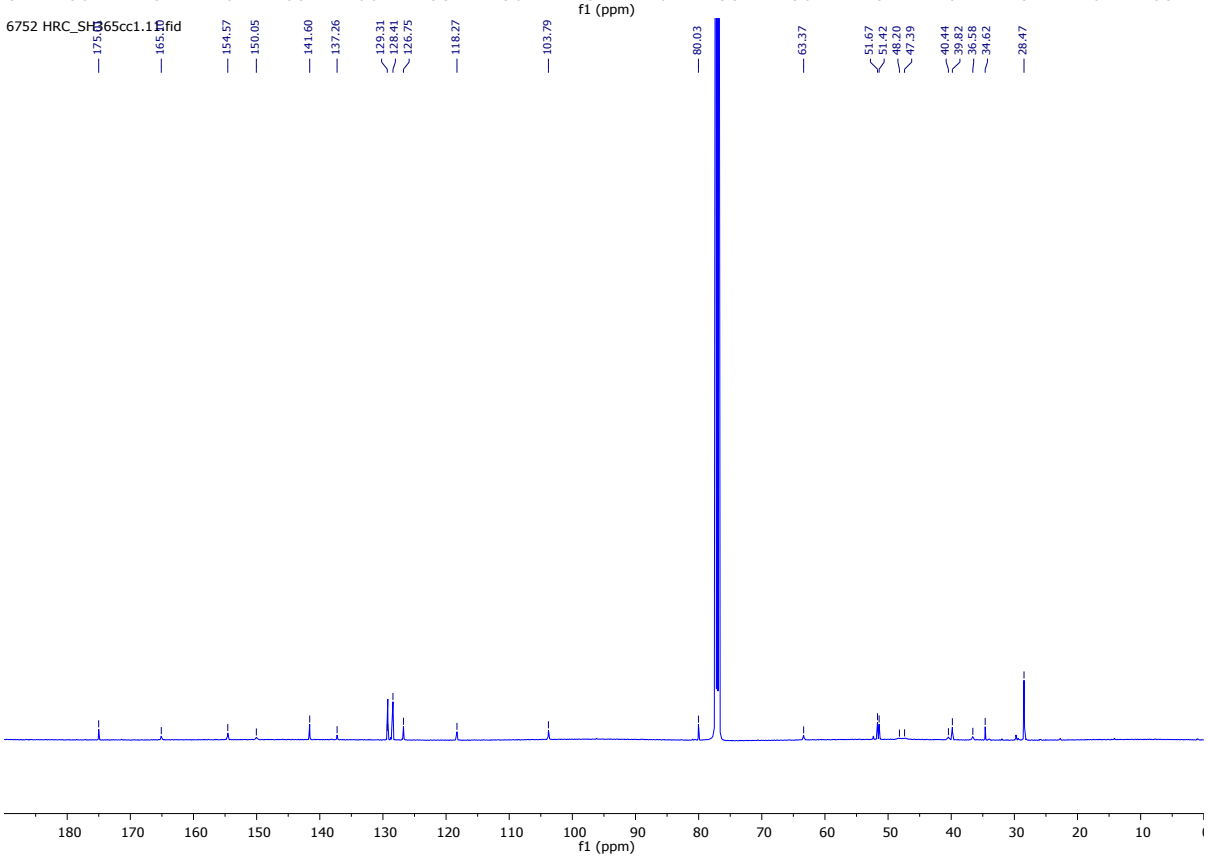


^{1}H NMR (500 MHz), ^{13}C NMR (125 MHz): $CDCl_3$

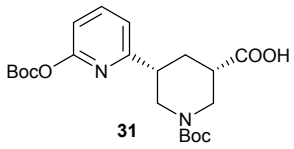


30c

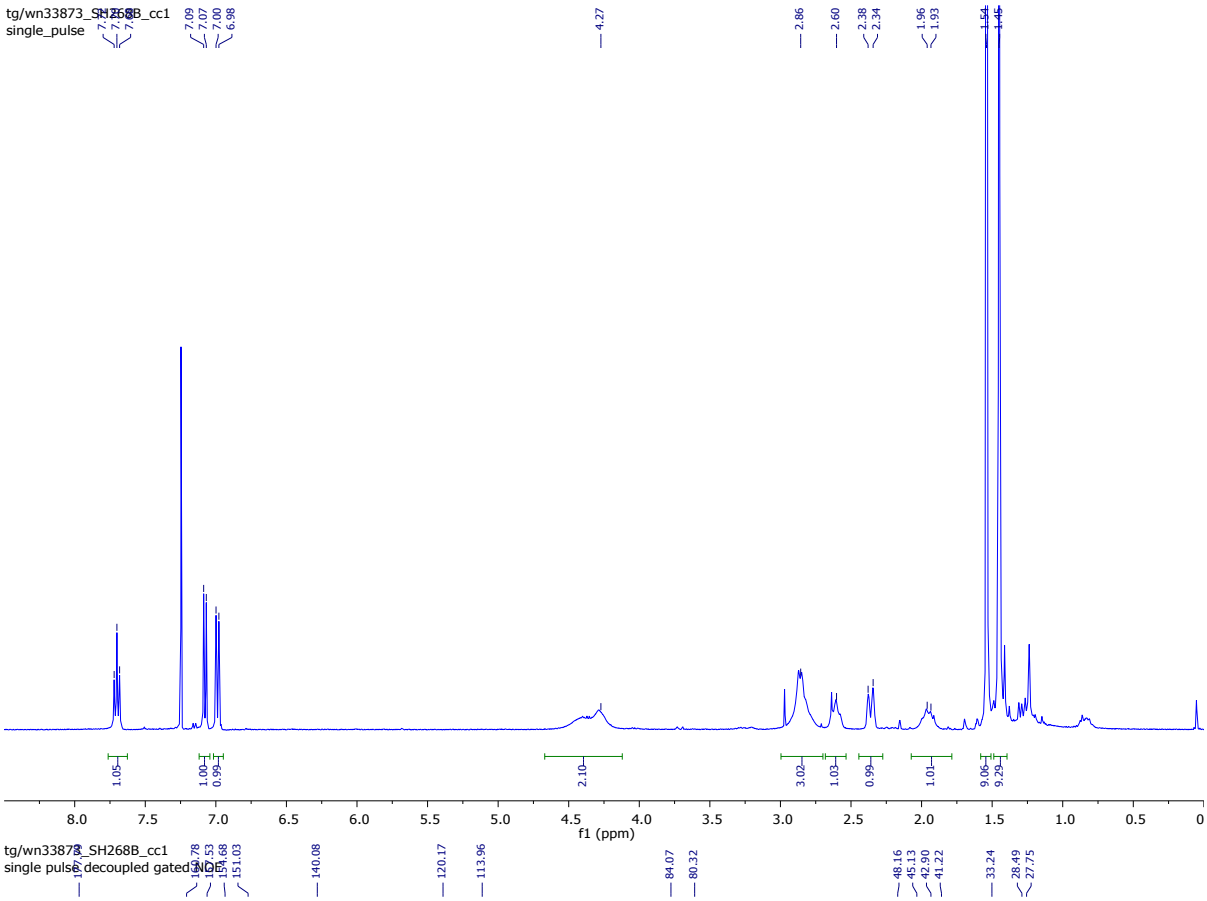


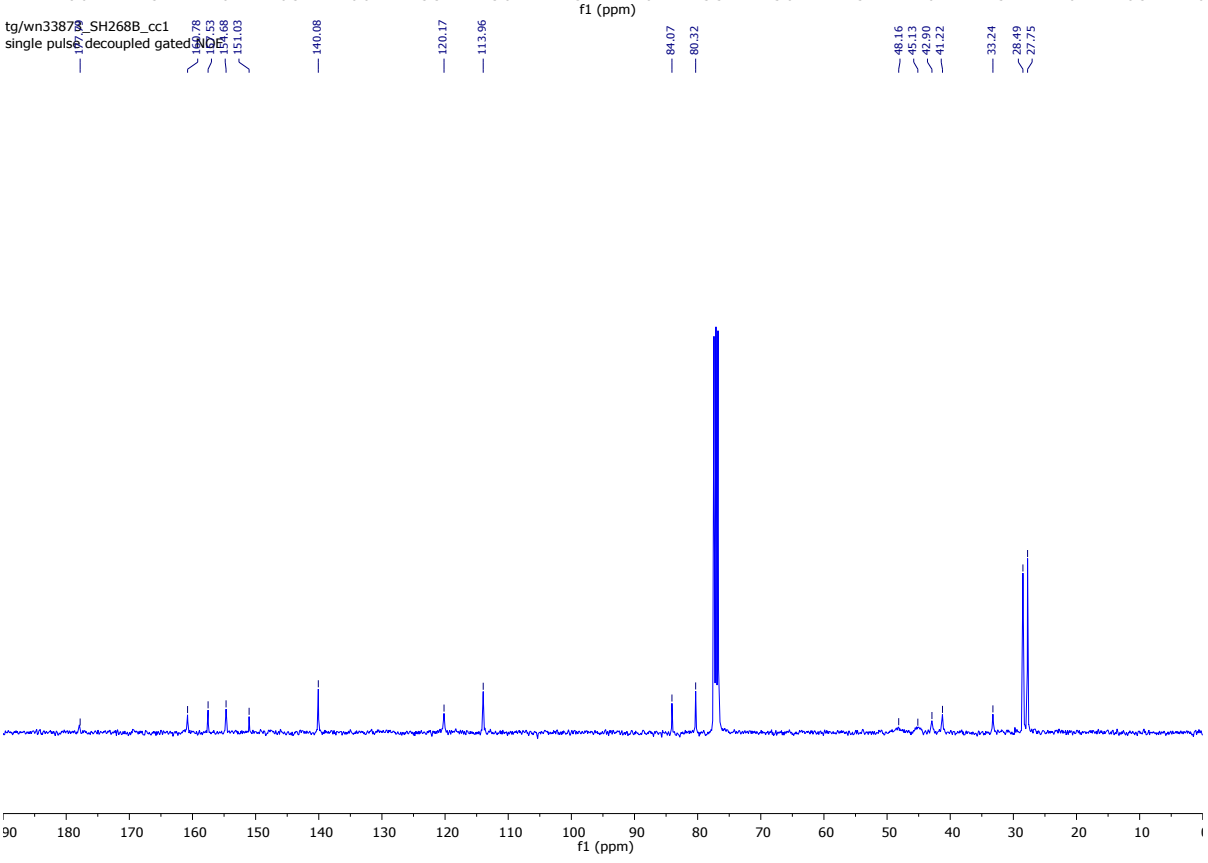


^{1}H NMR (500 MHz), ^{13}C NMR (125 MHz): $CDCl_3$

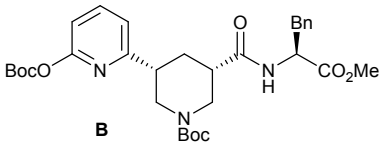


31

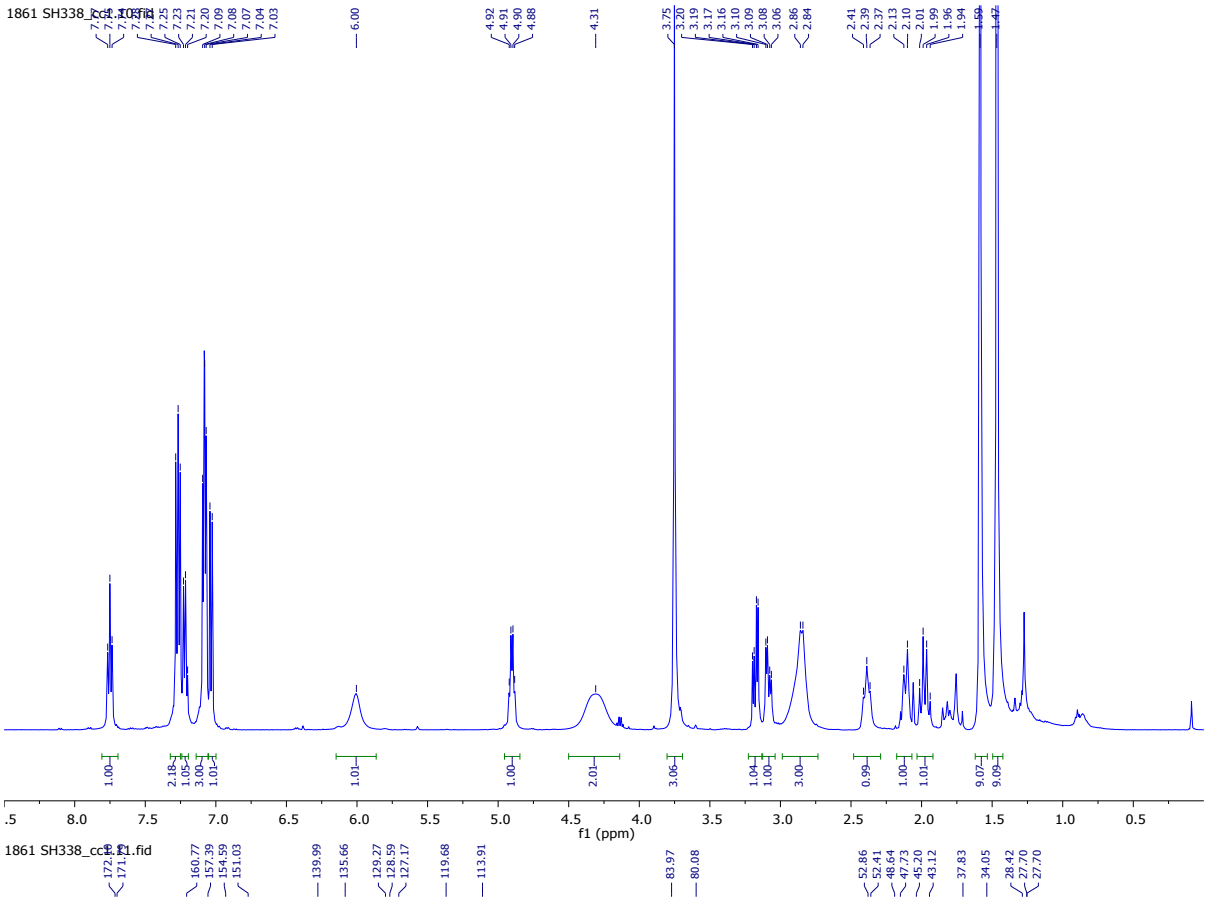


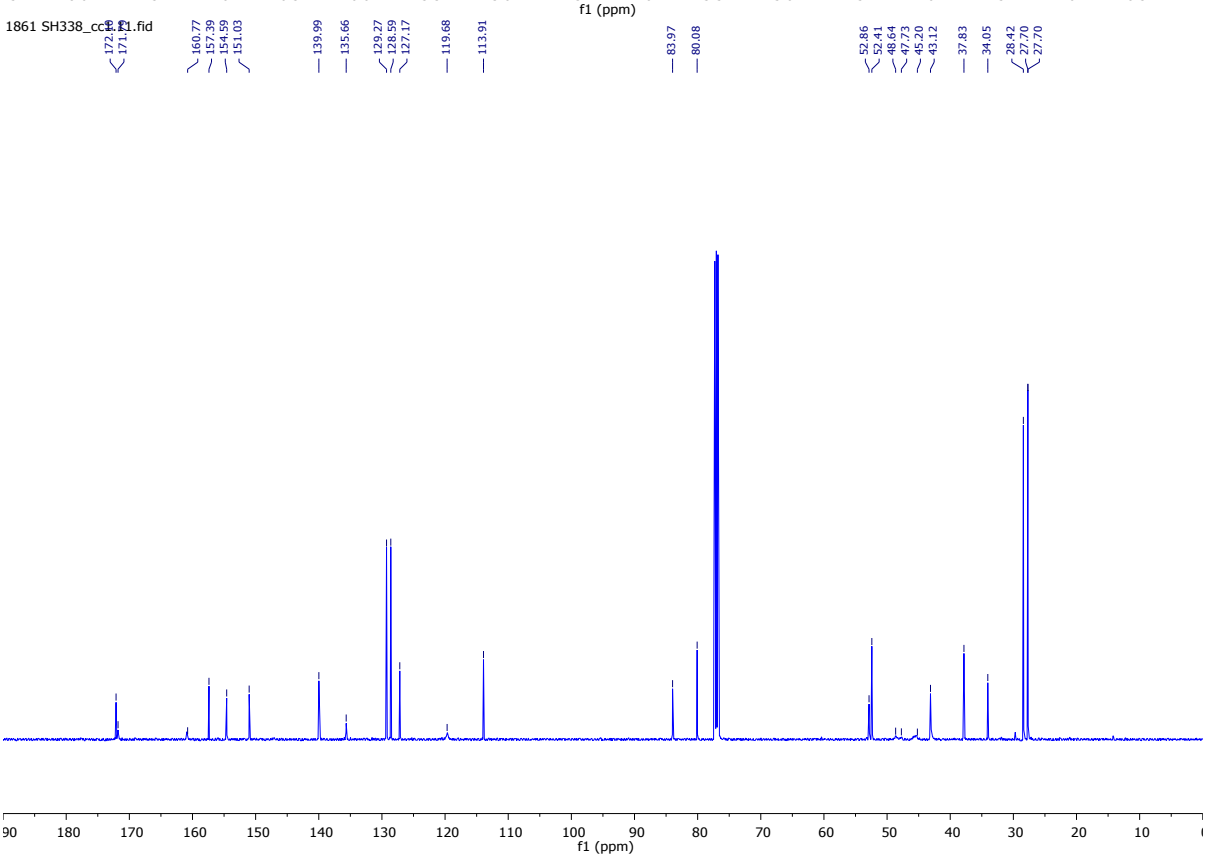


^{1}H NMR (500 MHz), ^{13}C NMR (125 MHz): $CDCl_3$

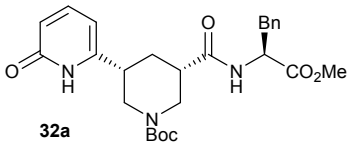


B

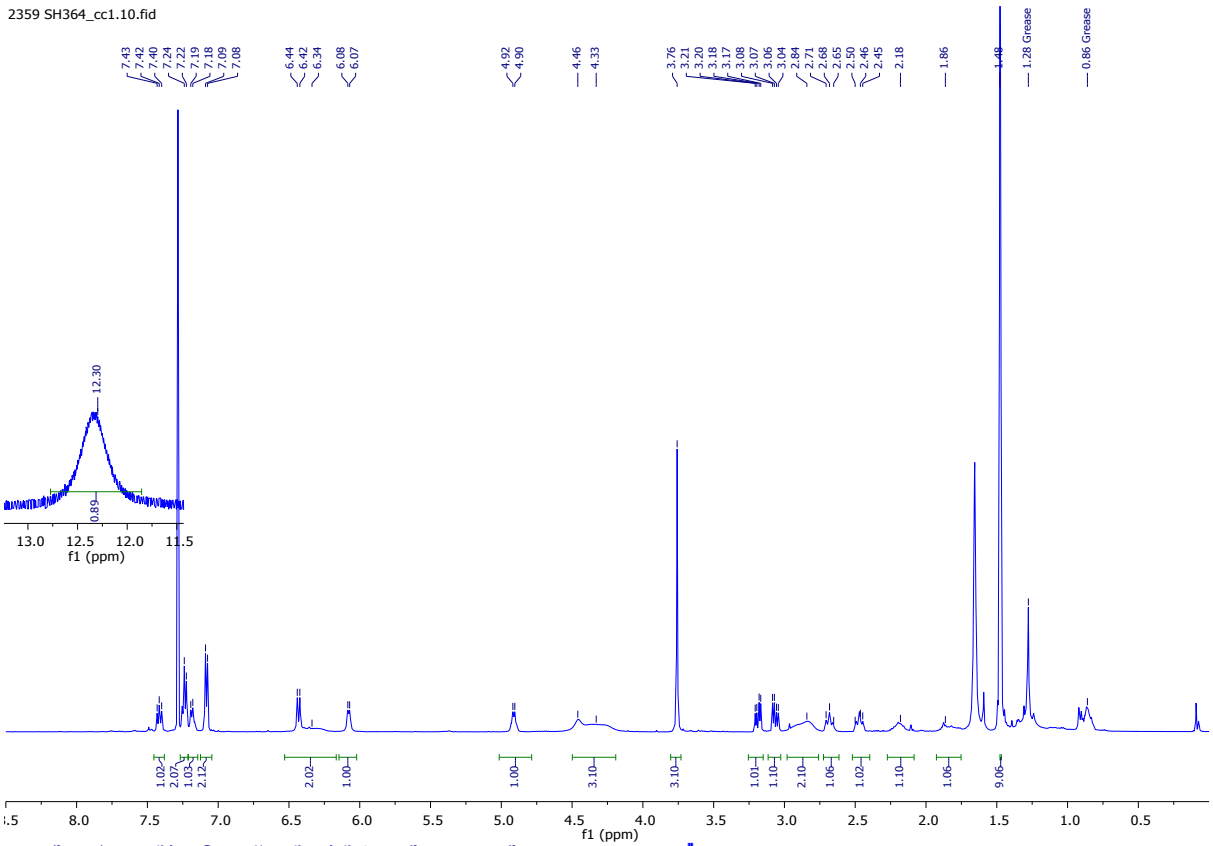


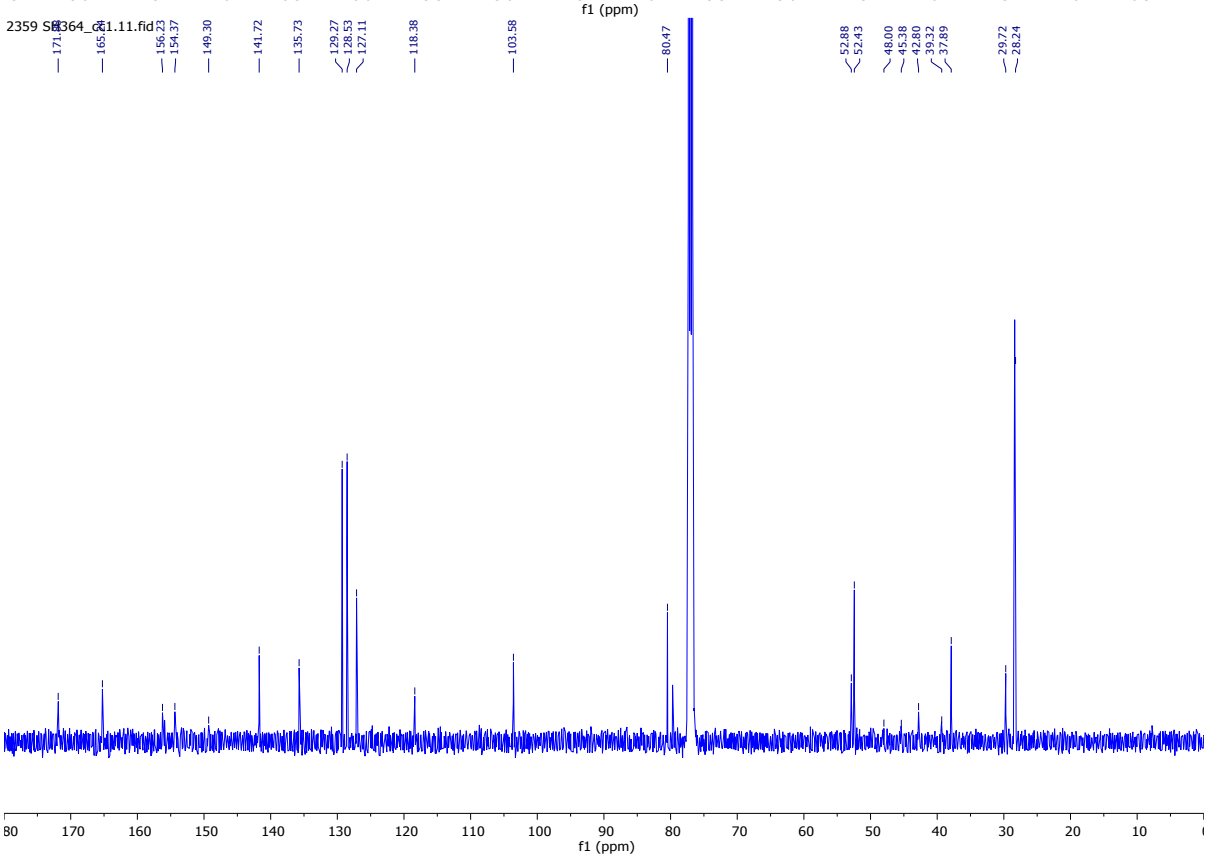


^{1}H NMR (500 MHz), ^{13}C NMR (125 MHz): $CDCl_3$

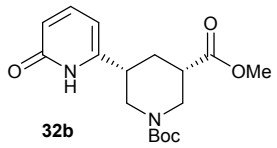


32a

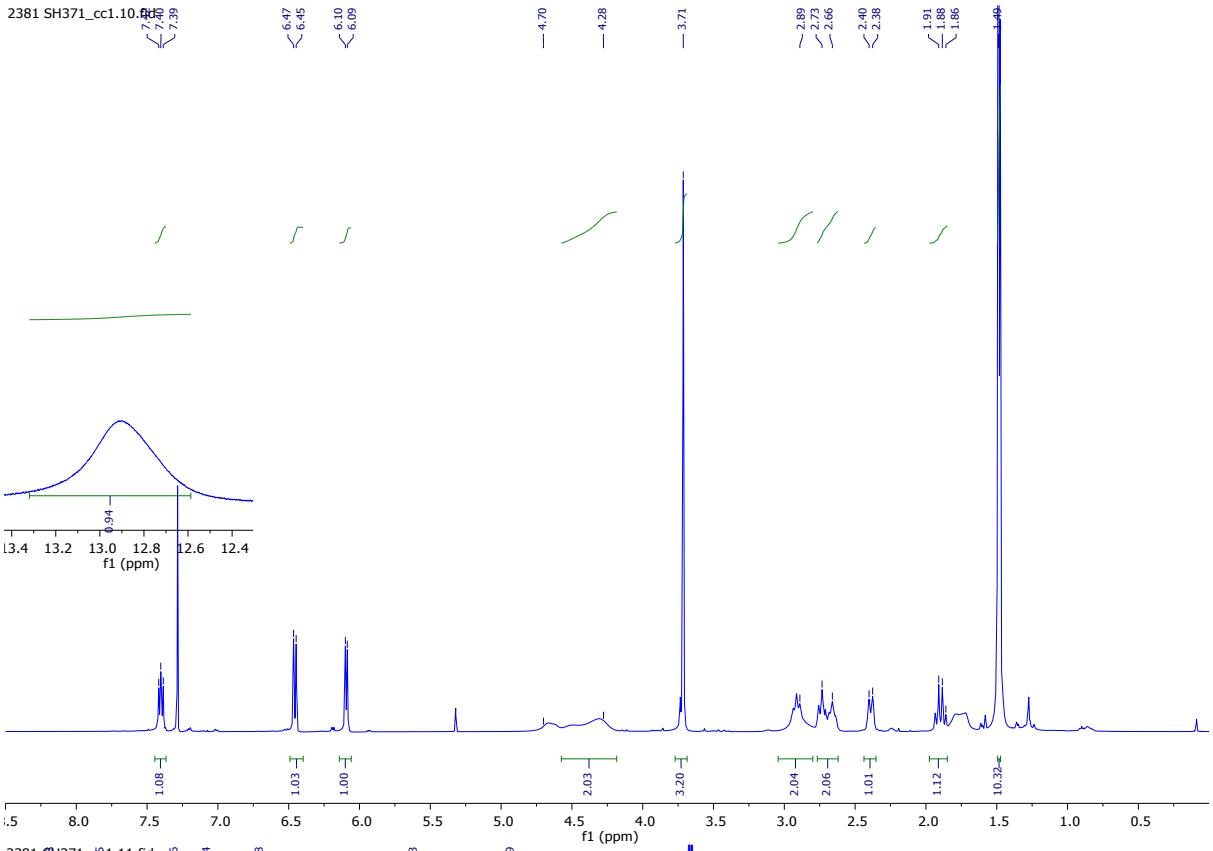


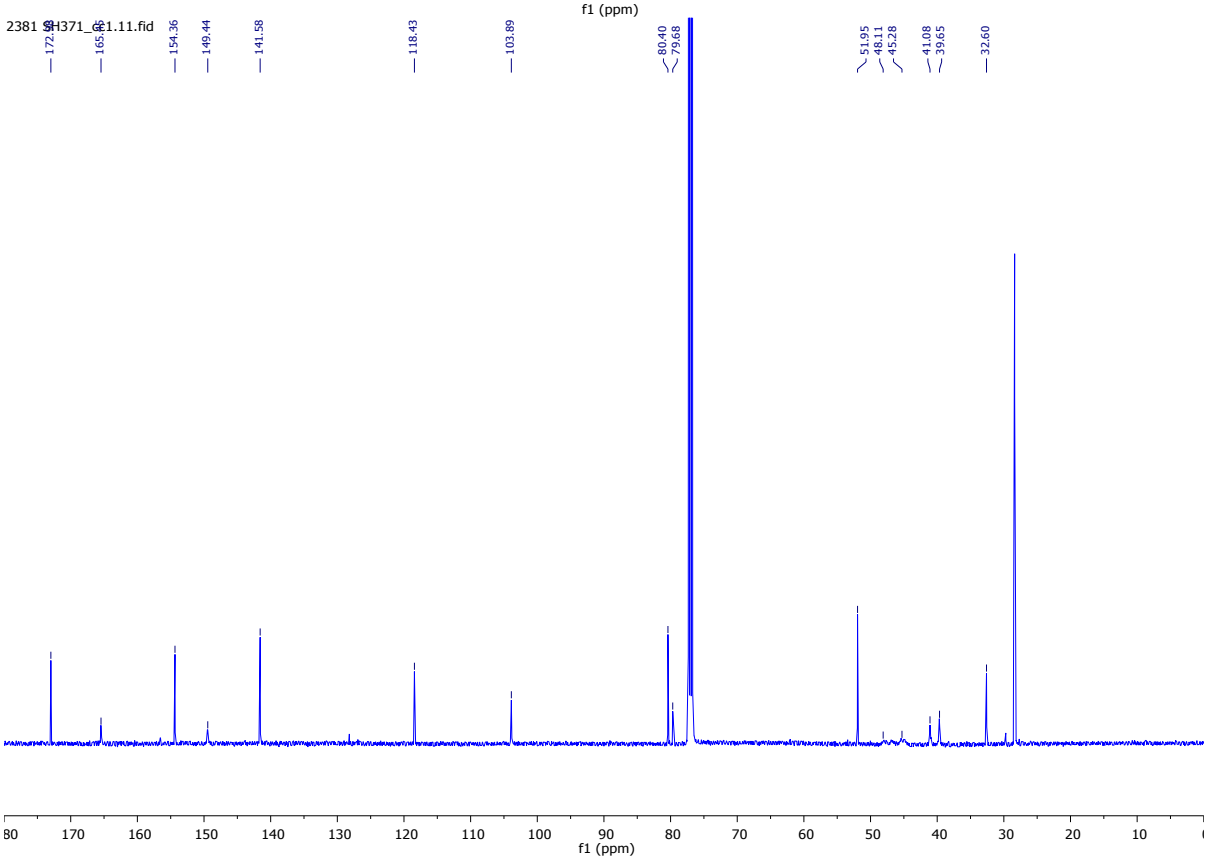


^{1}H NMR (500 MHz), ^{13}C NMR (125 MHz): $CDCl_3$

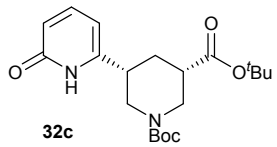


32b

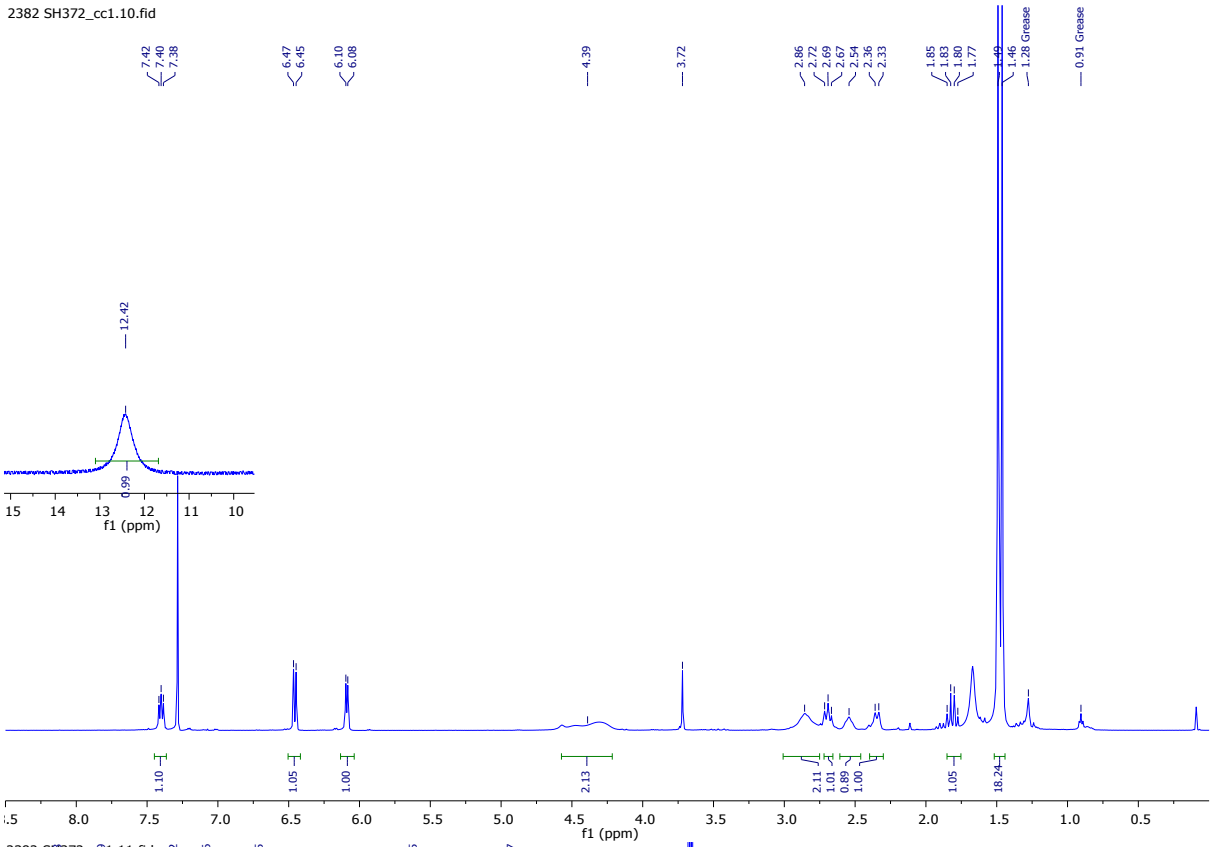


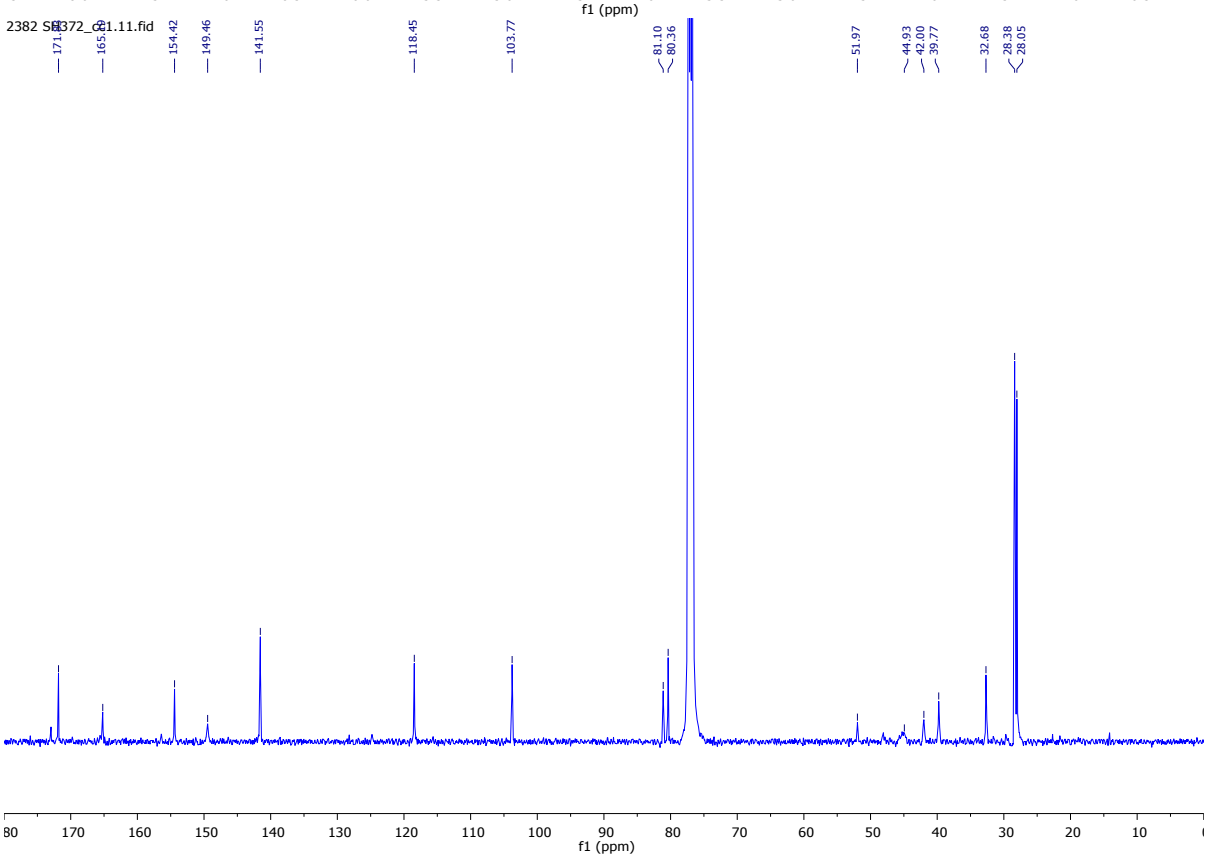


^{1}H NMR (500 MHz), ^{13}C NMR (125 MHz): $CDCl_3$

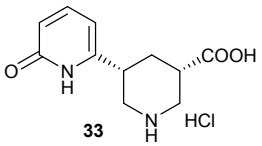


32c





^{1}H NMR (500 MHz), ^{13}C NMR (125 MHz): D_2O



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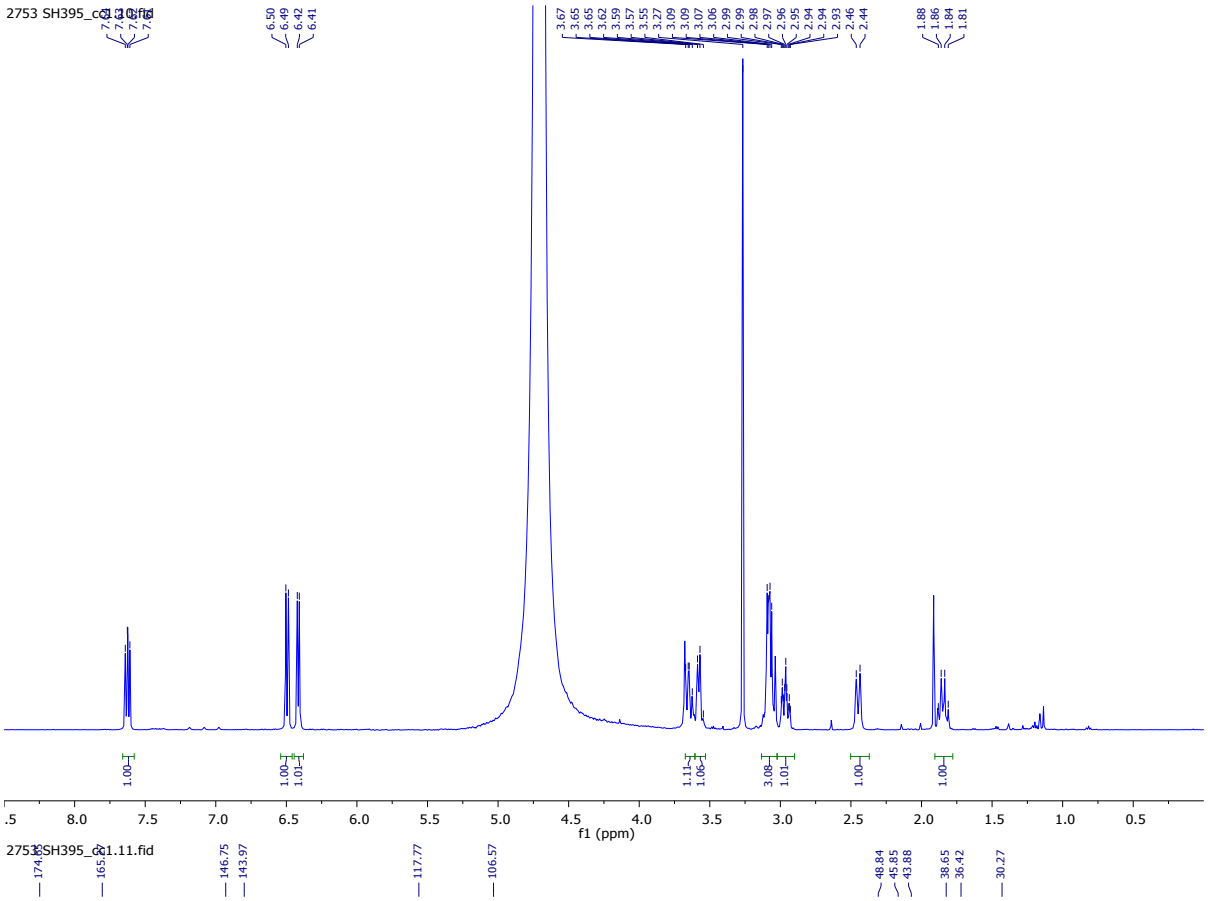
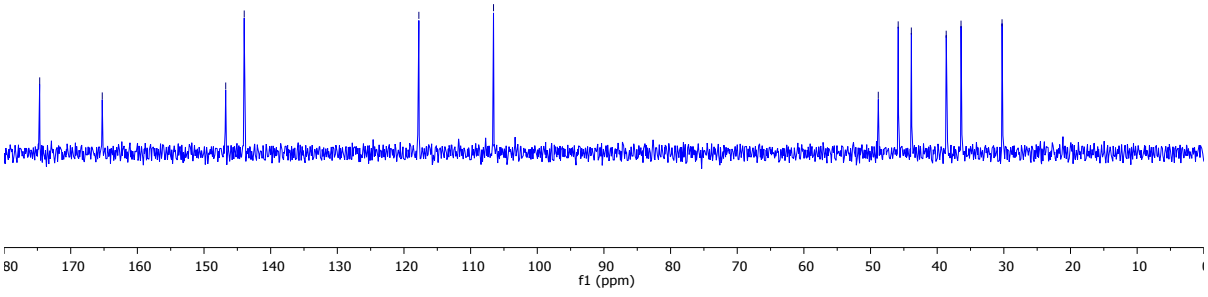
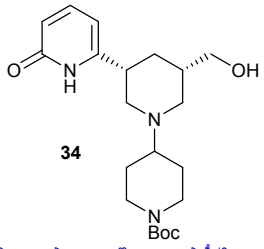




^{1}H NMR (500 MHz), ^{13}C NMR (125 MHz): MeOD



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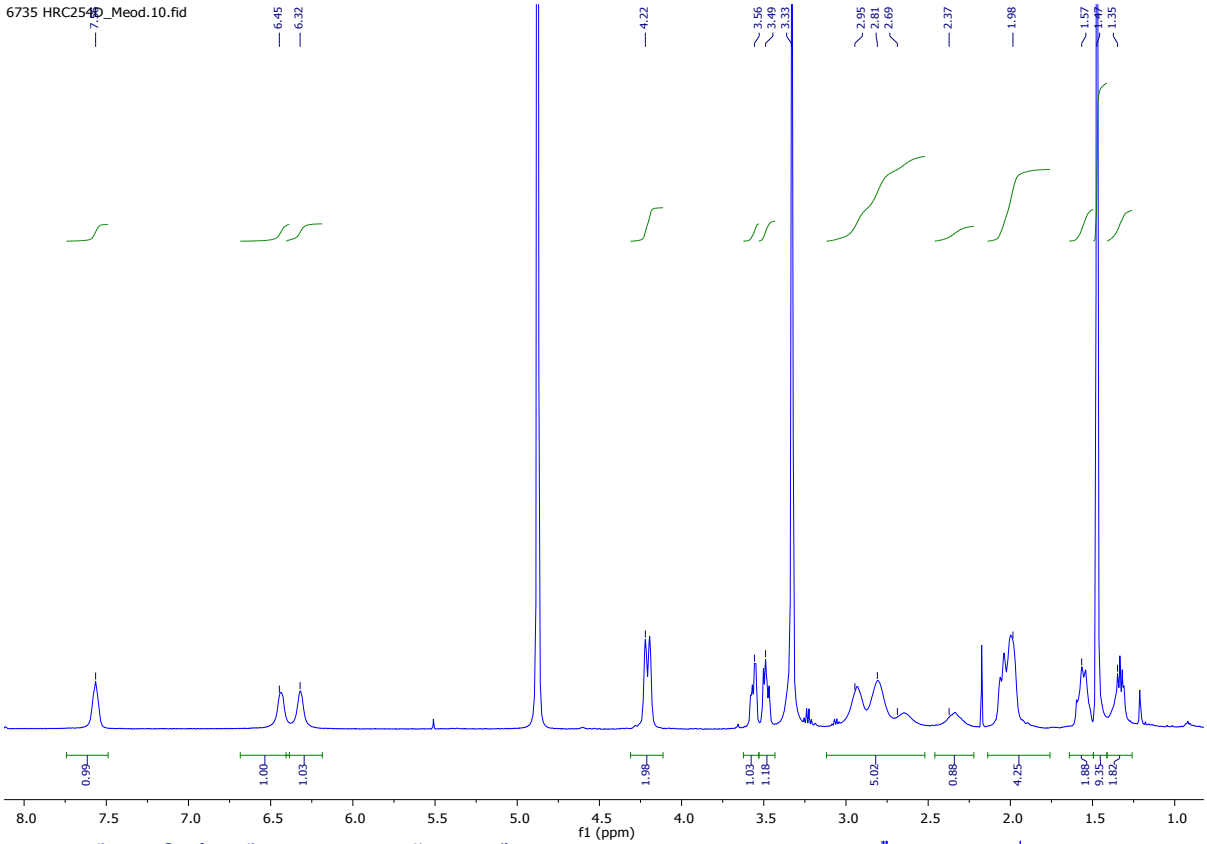
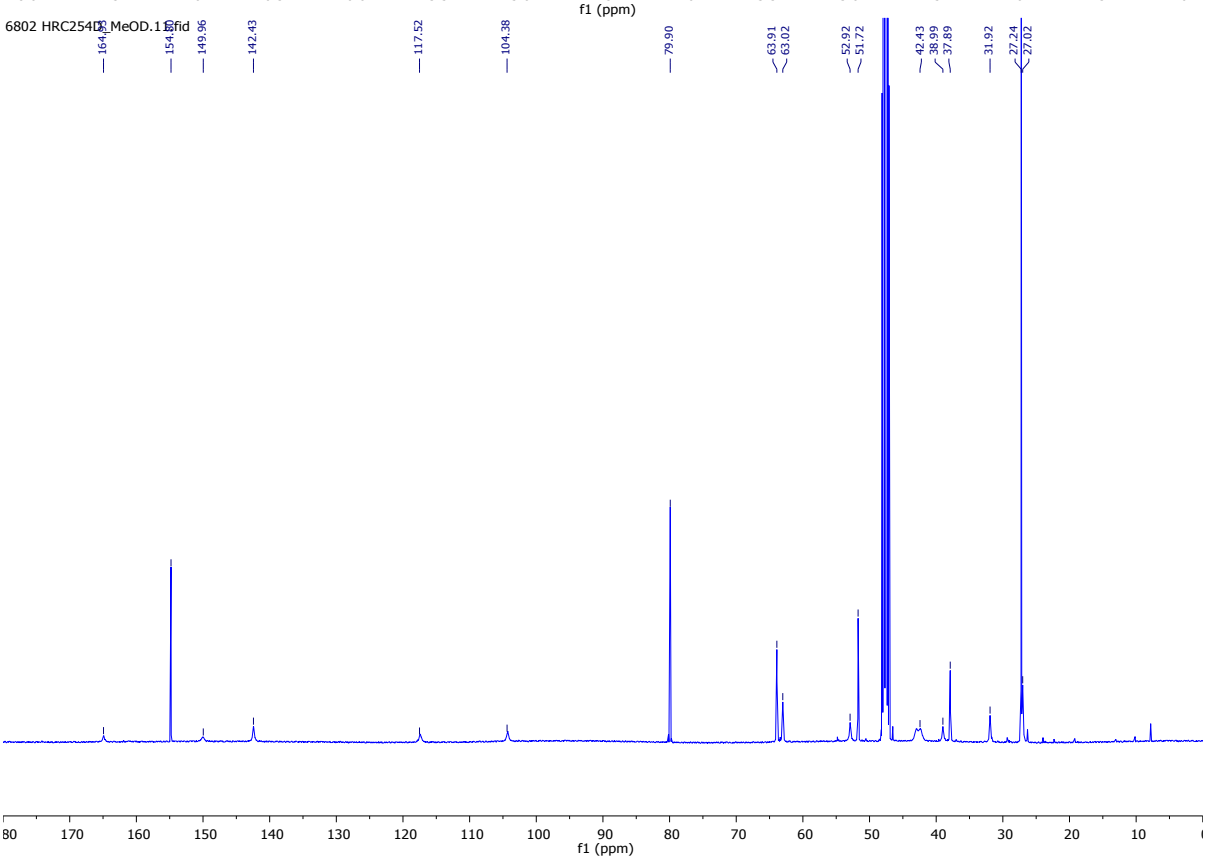
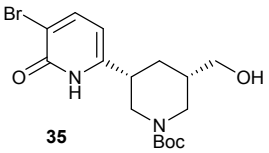




^{1}H NMR (500 MHz), ^{13}C NMR (125 MHz): $CDCl_3$



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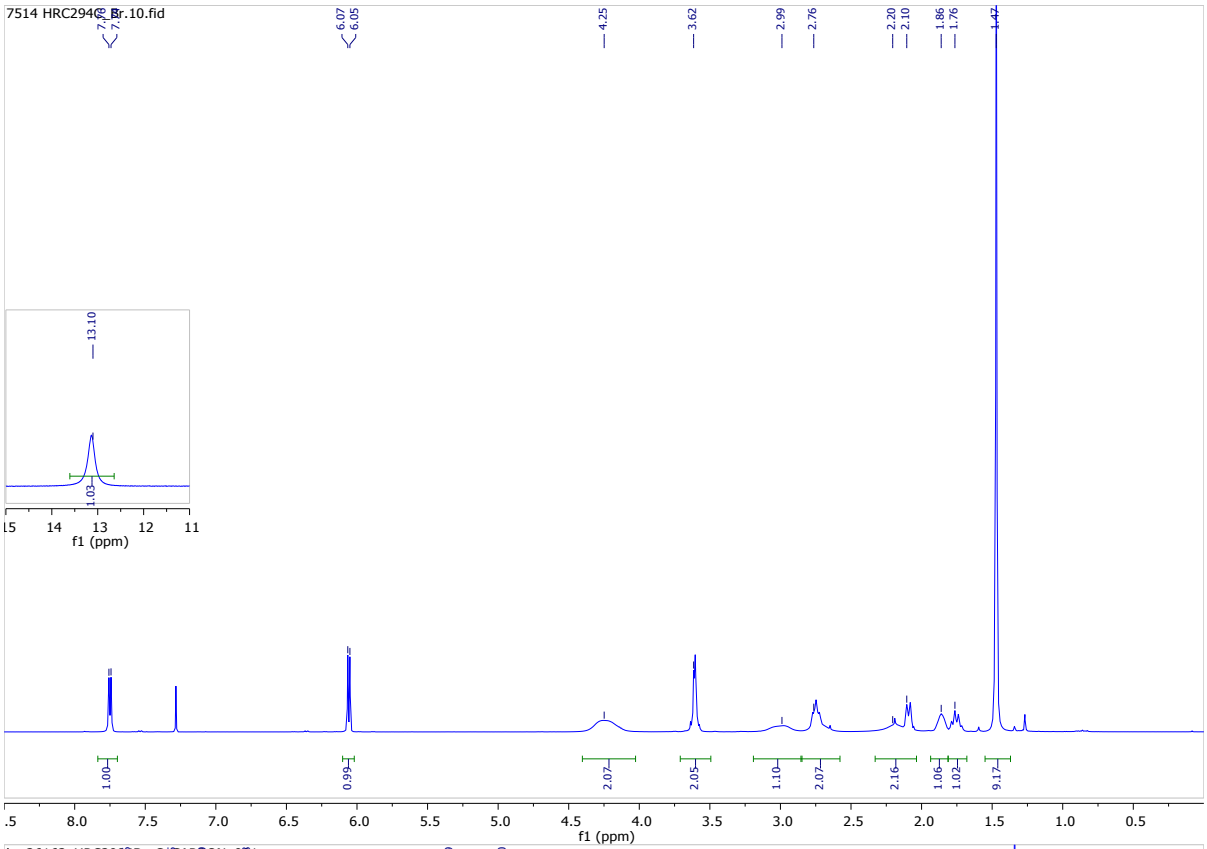
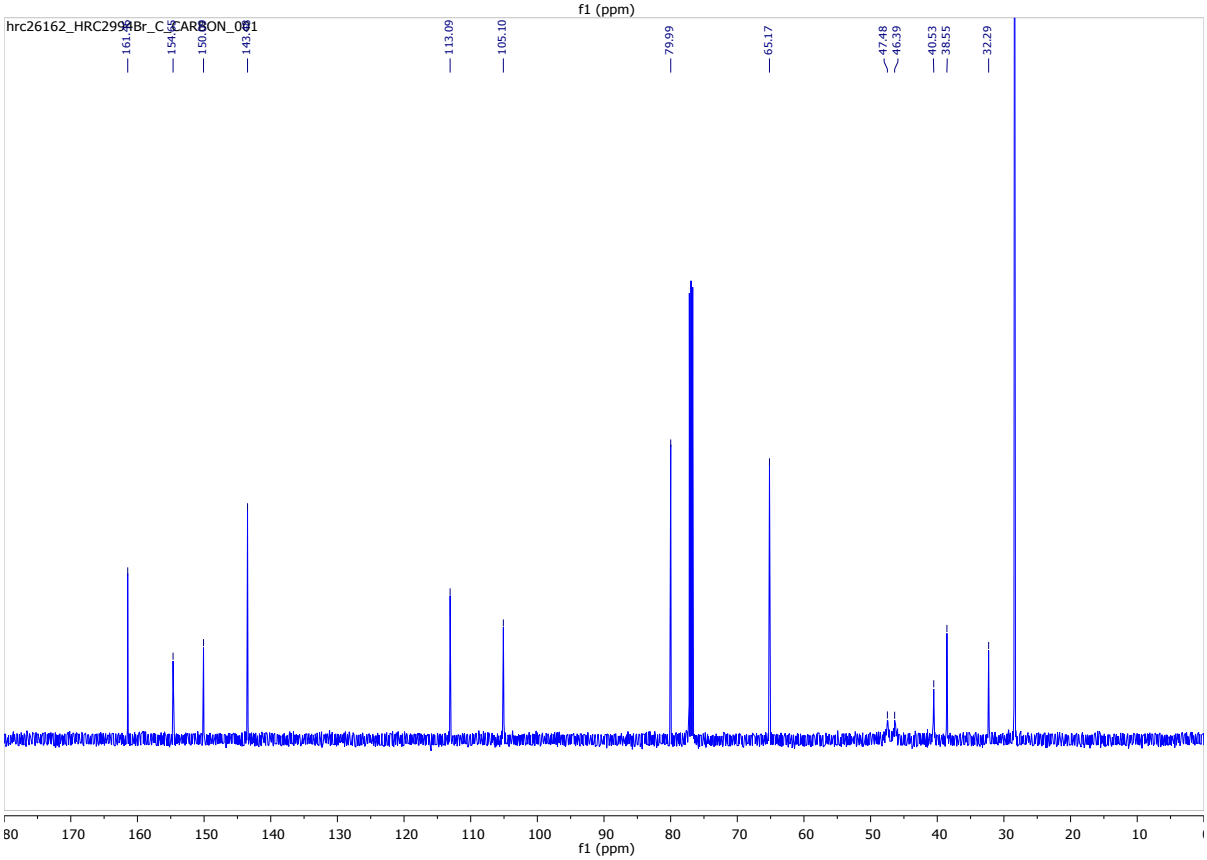
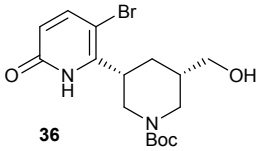




^{1}H NMR (500 MHz), ^{13}C NMR (125 MHz): $CDCl_3$



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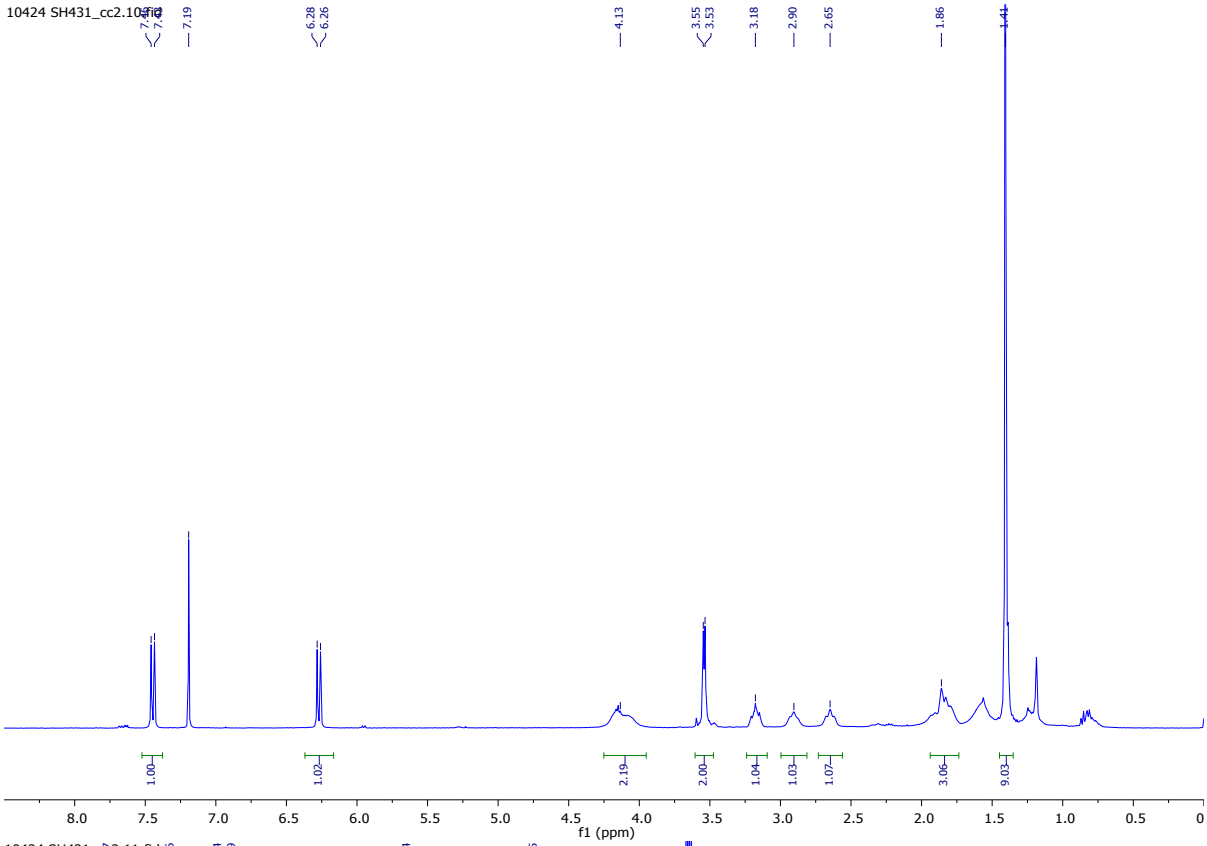
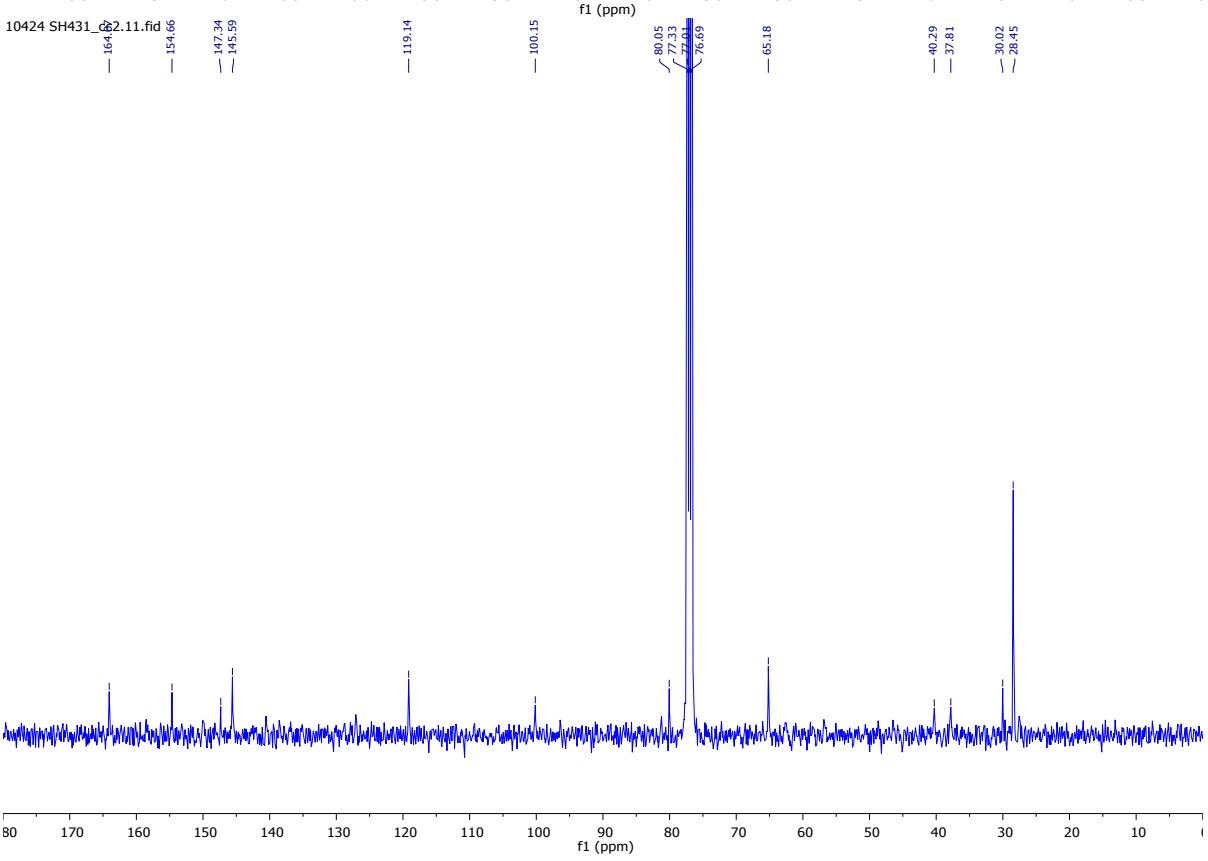
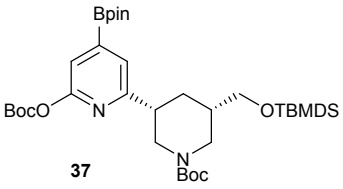




^{1}H NMR (500 MHz), ^{13}C NMR (125 MHz): $CDCl_3$



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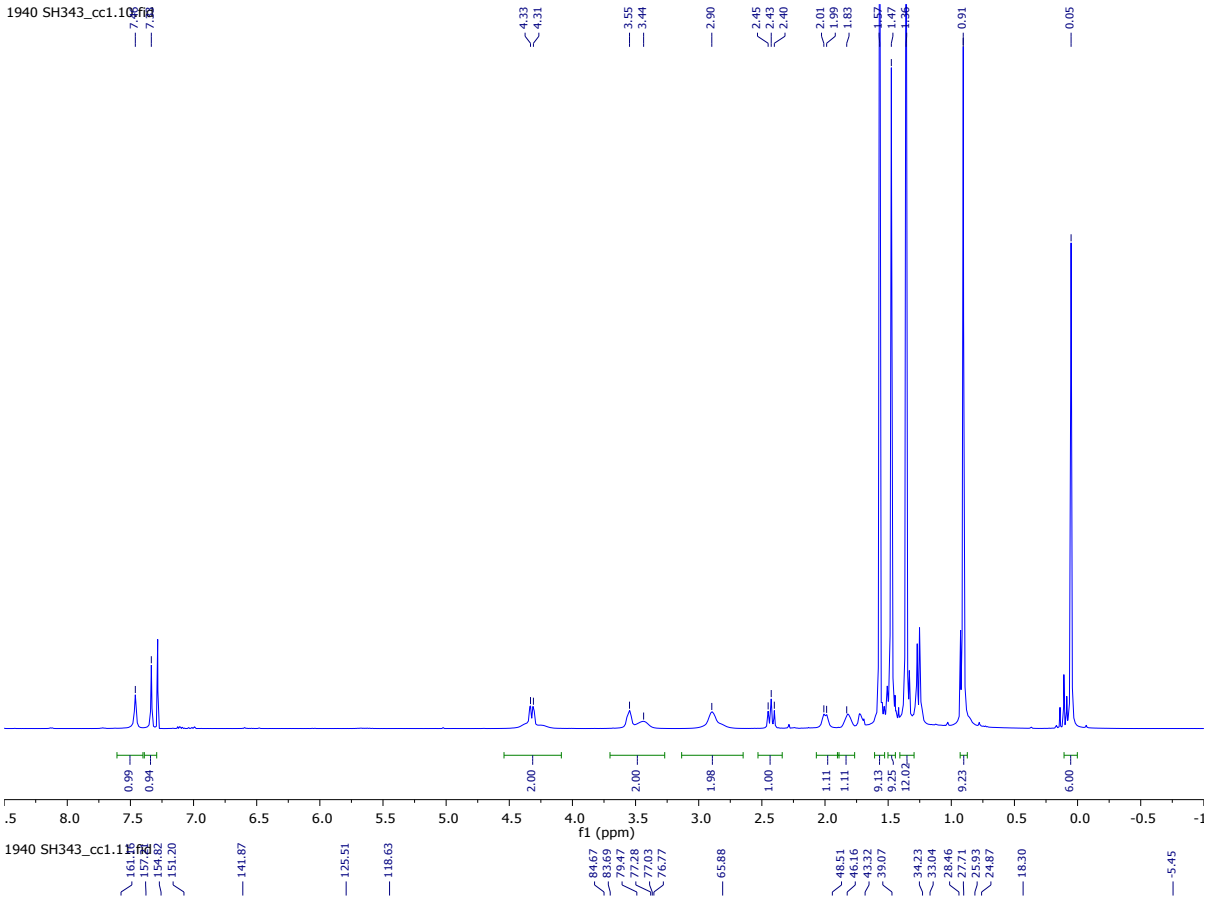
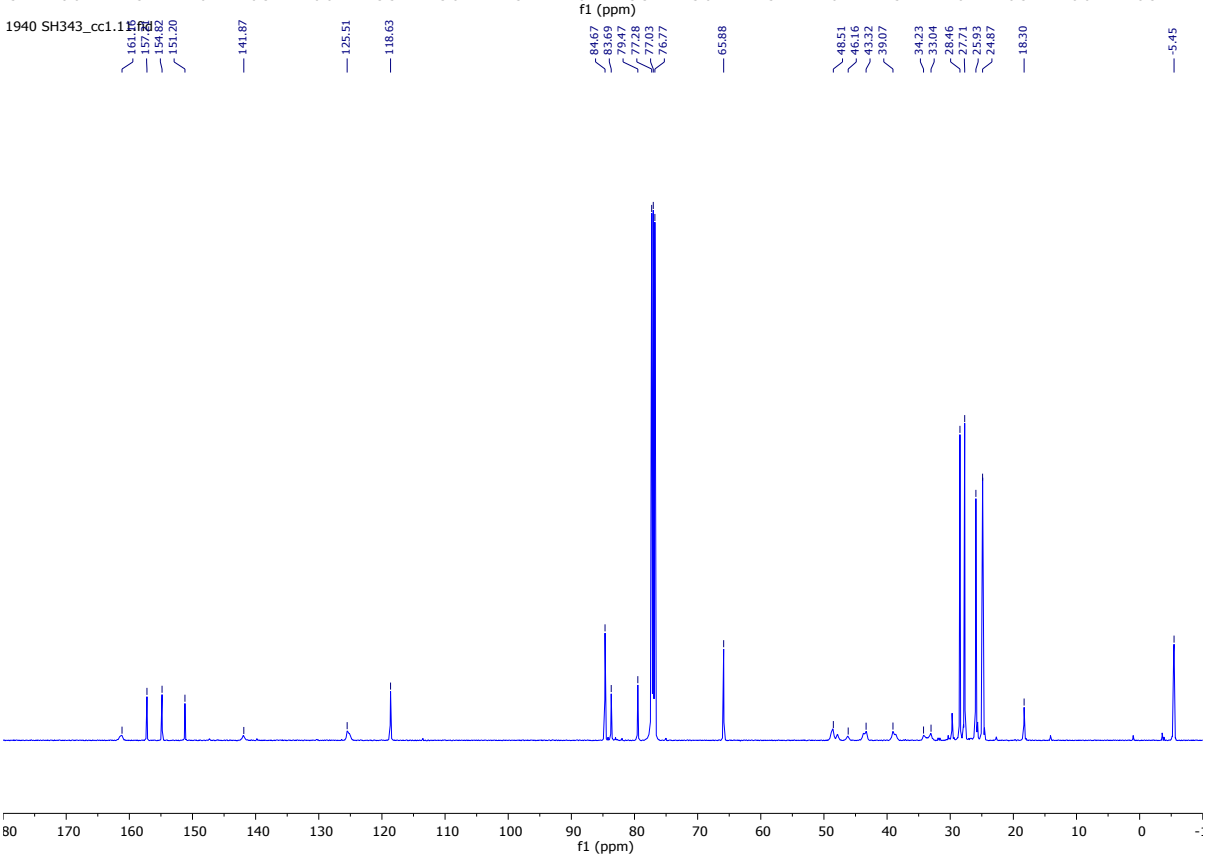
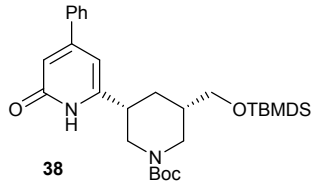




^{1}H NMR (500 MHz), ^{13}C NMR (125 MHz): $CDCl_3$



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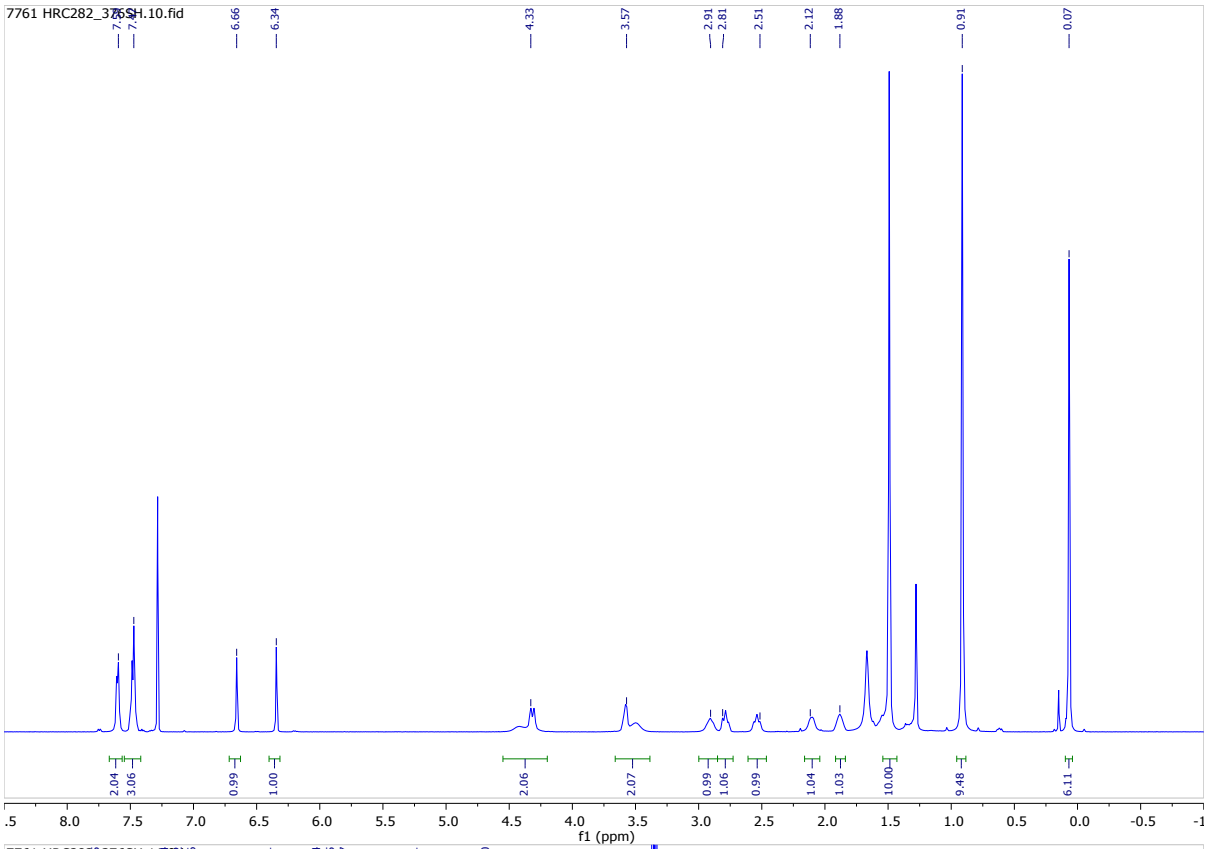
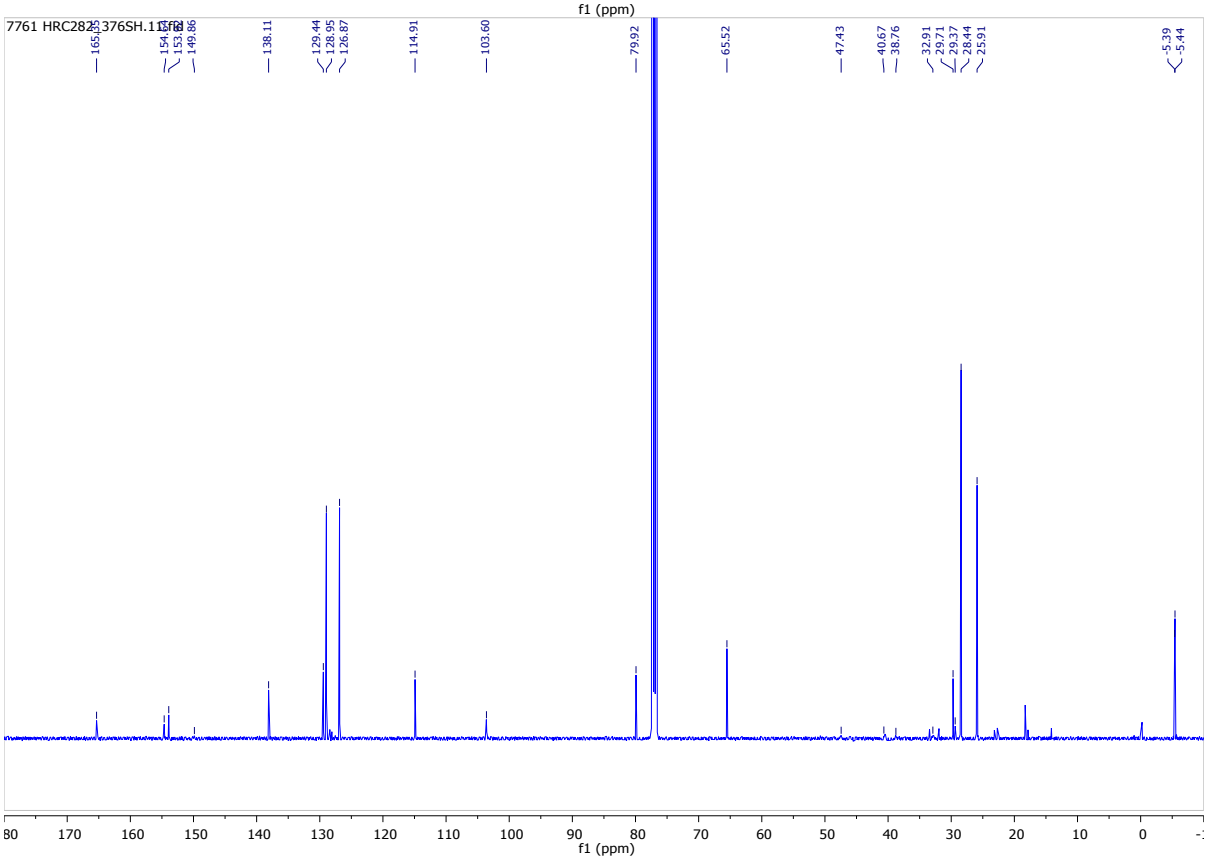
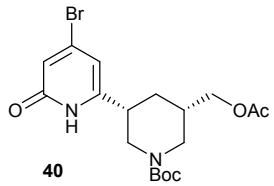




^{1}H NMR (500 MHz), ^{13}C NMR (125 MHz): $CDCl_3$



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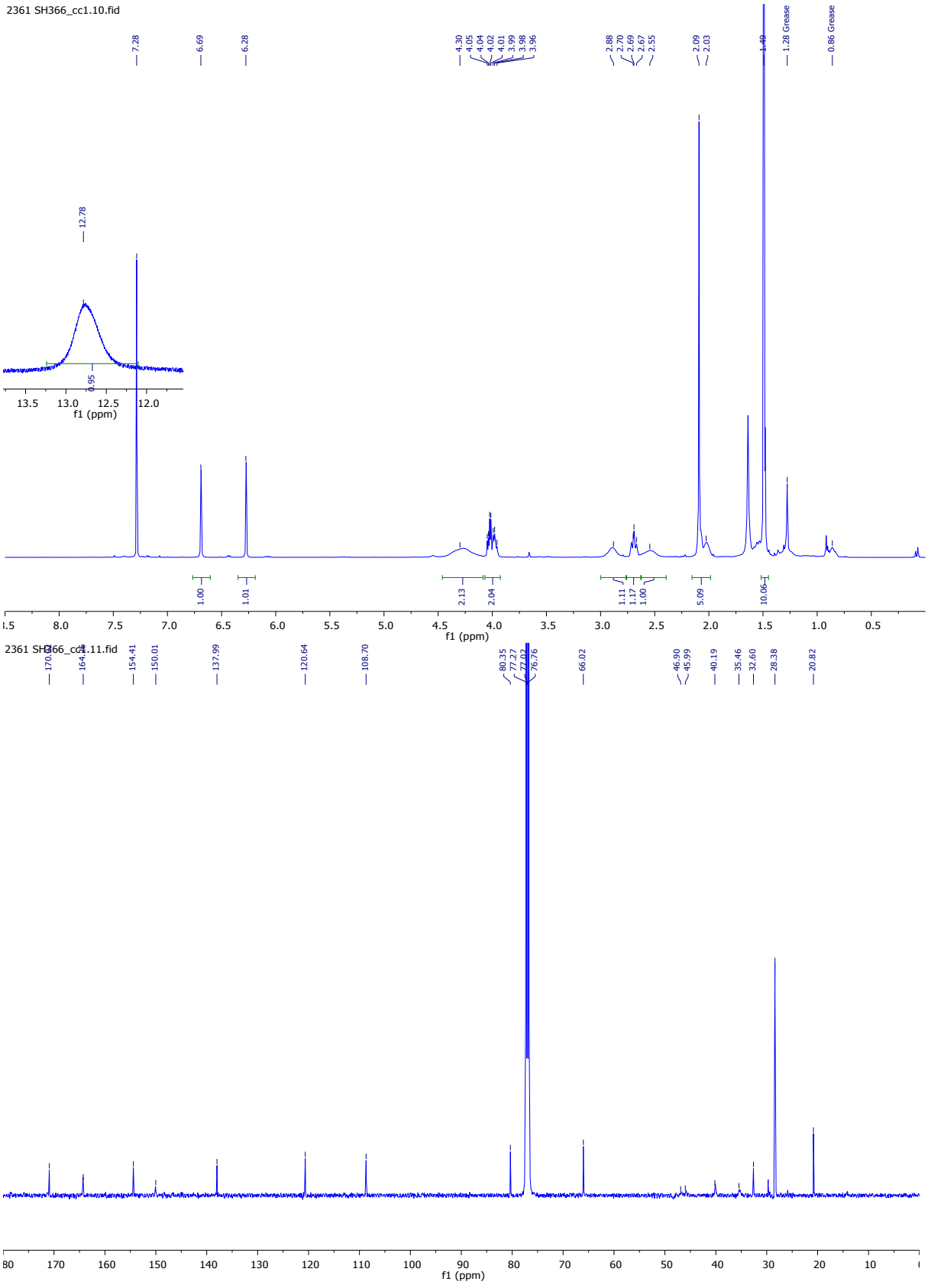
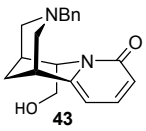


^{1}H NMR (500 MHz), ^{13}C NMR (125 MHz): $CDCl_3$



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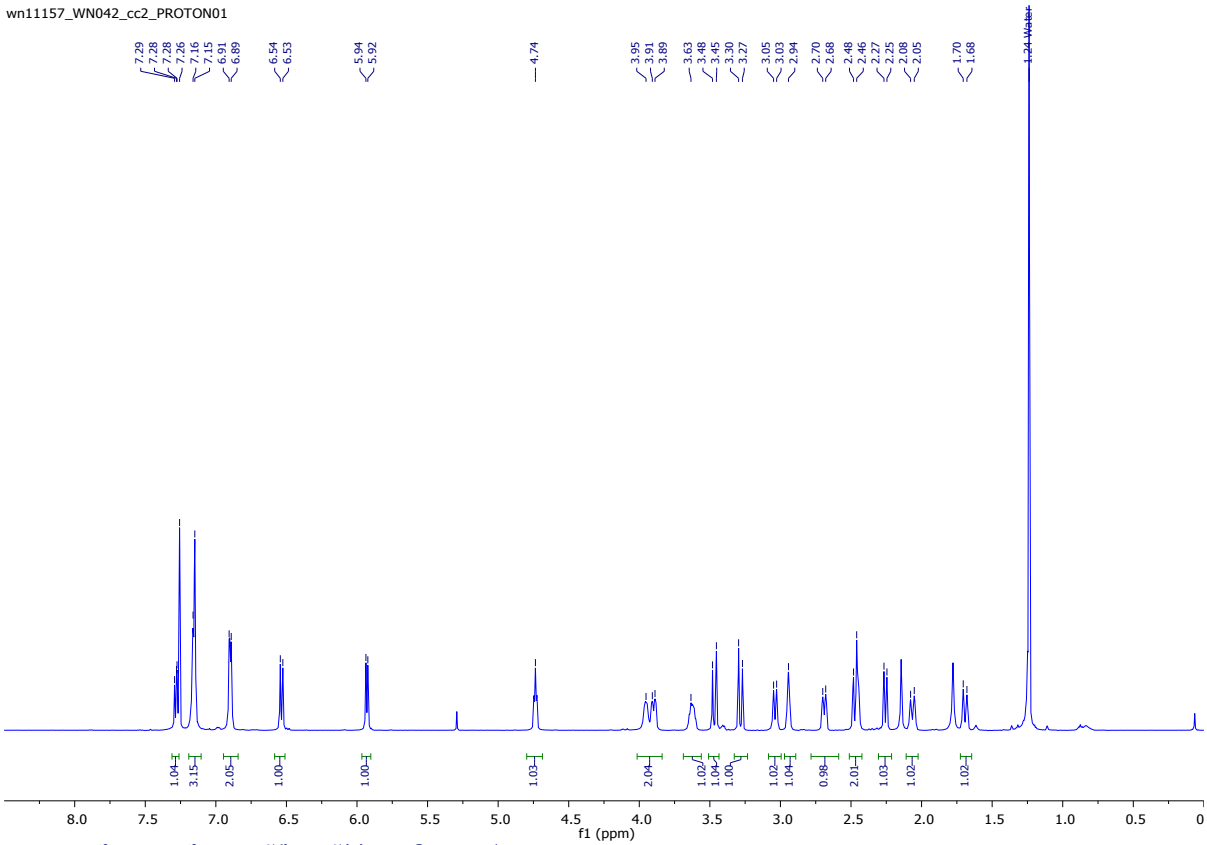
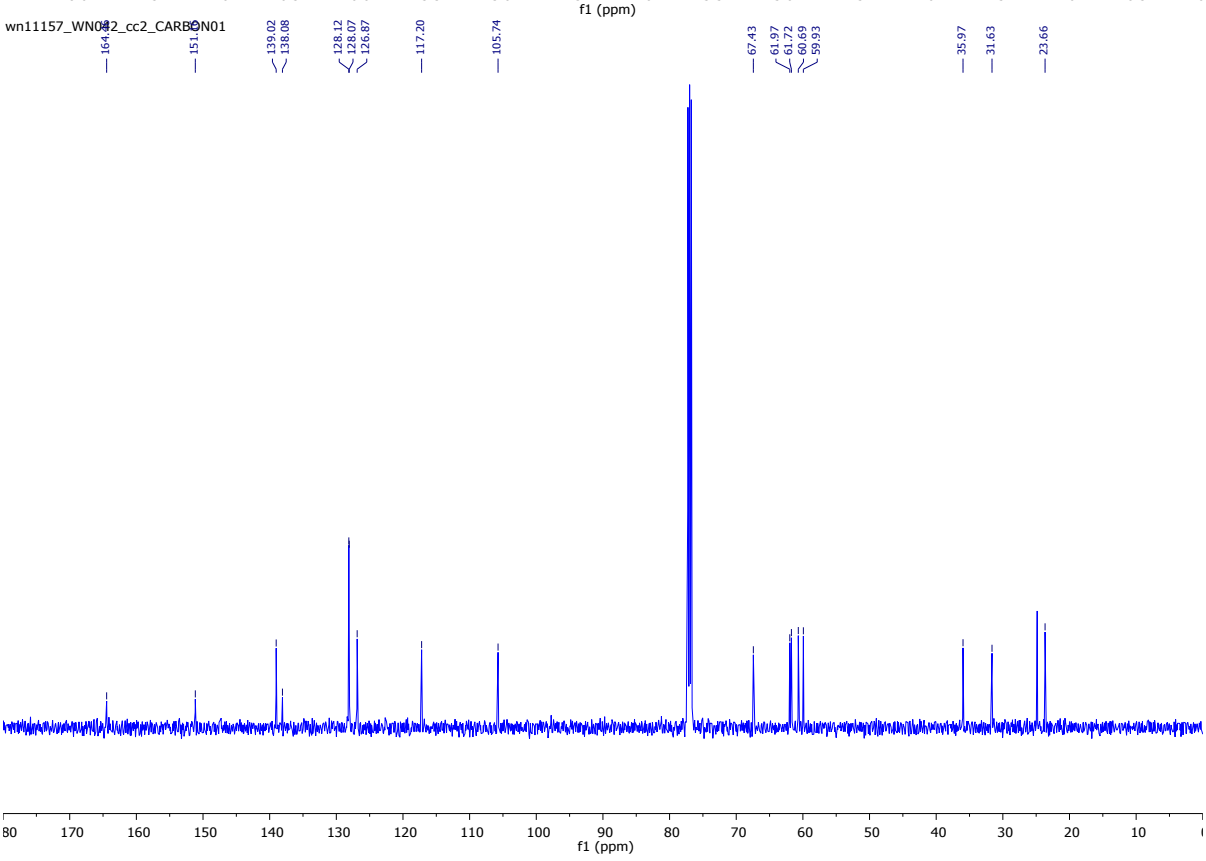
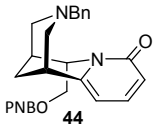




^{1}H NMR (500 MHz), ^{13}C NMR (125 MHz): $CDCl_3$



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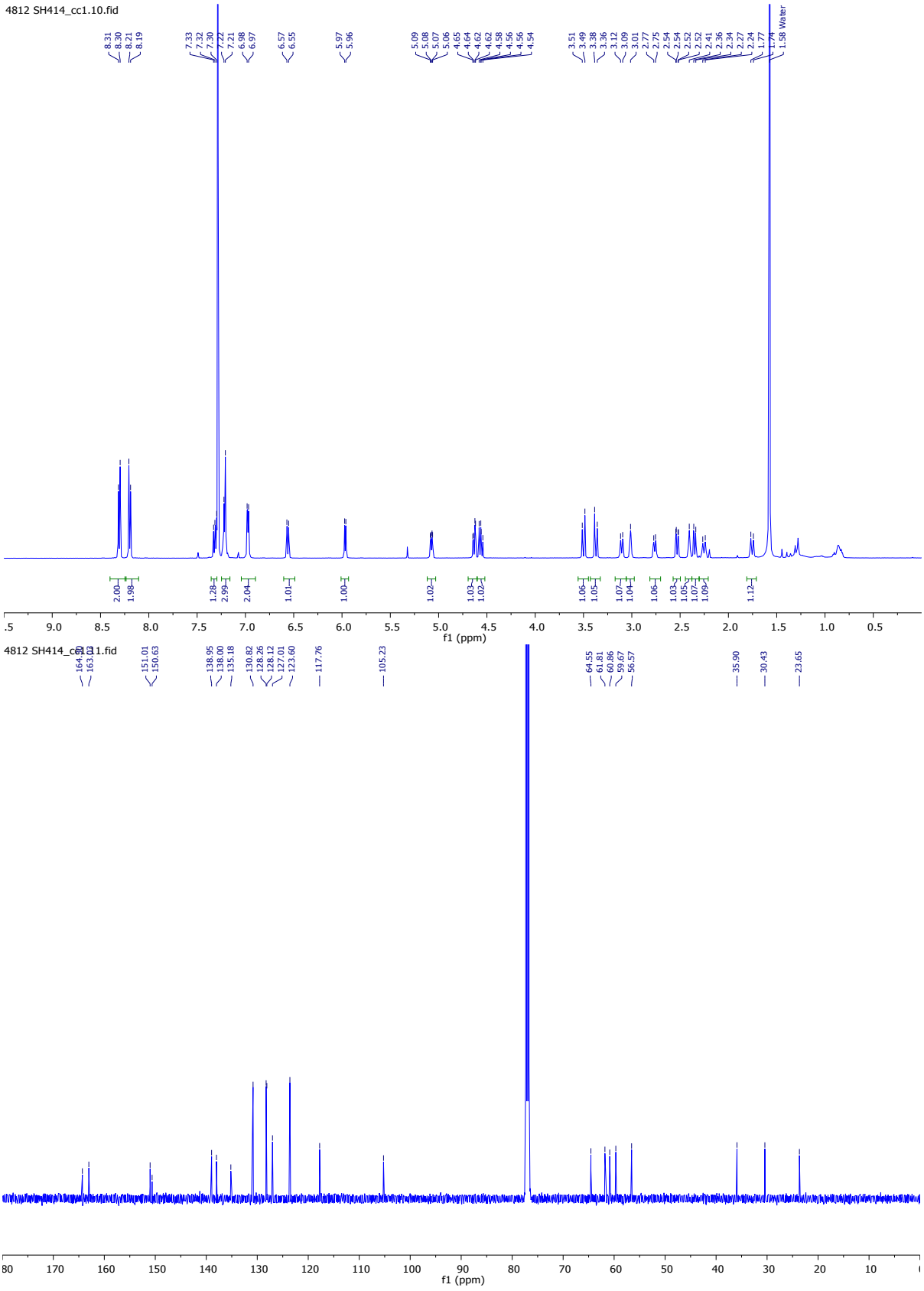
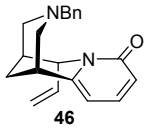


^{1}H NMR (500 MHz), ^{13}C NMR (125 MHz): $CDCl_3$



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