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Diastereoselective Synthesis of Novel Heterocyclic Scaffolds through Tandem Petasis 3-Component/Intramolecular Diels-Alder and ROM-RCM Reactions

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Supporting Information

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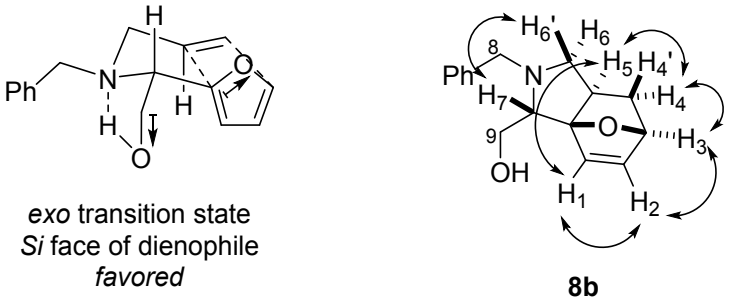
Stereochemical Assignment of Petasis 3-CR/IMDA Products

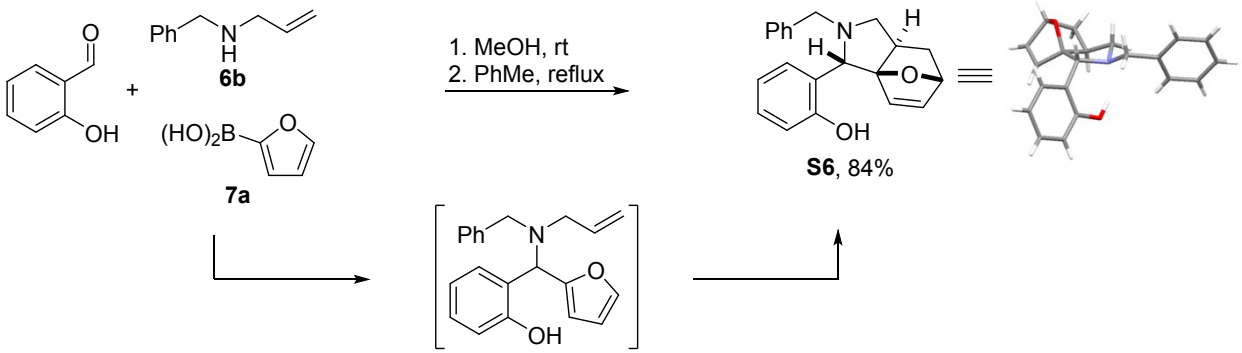
The proposed *exo* transition states leading to **8** were supported by NOESY correlations observed between H_1 and H_5. Furthermore, through H_4 the connection between H_3 and H_5 was established. Although not conclusive, the missing correlation between H_5 and H_7 supported that the dienophile had reacted from the Si face (Scheme S1).



Scheme S1: Transition state model and selected NOESY correlations supporting the stereochemical assignment of *exo* products **8** from the Petasis 3-CR/IMDA reaction. See page 51-55 for NMR spectra.

Introduction of Additional Scaffold Diversity

The use of salicylaldehyde in the Petasis 3-CR had previously been reported,[1] nonetheless, we were delighted to observe, that its use was also well-tolerated in the Petasis 3-CR/IMDA cascade reaction to afford the product **S6** in 84% yield. We were furthermore able to unambiguously confirm the diastereomeric outcome of the reaction sequence by X-ray crystallography (Scheme S1). NOE correlations of **S6** were also in accordance with those of **8b**, see page 68-71 for NMR spectra.



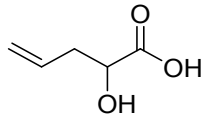
Scheme S2: The Petasis 3-CR/IMDA reaction employing salicylaldehyde, allylamine and 2-furylboronic acid provides a single diastereomer, as confirmed by X-ray crystallography.

General Methods

Commercially available reagents were used without further purification. All solvents were of HPLC quality. Reactions were monitored by thin-layer chromatography (TLC), reversed-phase ultra-performance liquid chromatography mass spectrometry (RP-UPLC-MS) and/or reversed-phase high-performance liquid chromatography (RP-HPLC). Analytical TLC was conducted on Merck aluminium sheets covered with silica (C60). The plates were either visualized under UV-light or stained by dipping in a developing agent followed by heating. $KMnO_4$ (3 g in water (300 mL) along with K_2CO_3 (20 g) and 5% aqueous NaOH (5 mL)) was used as developing agent. Flash column chromatography was performed using Matrex 60 Å, 35–70 μm silica gel. Analytical HPLC was conducted on a Waters Alliance 2695 RP-HPLC system using a Symmetry® C18 column (*d* 3.5 μm, 4.6x75 mm; column temp: 25 °C; flow: 1 mL/min.) with detection at 215 nm and 254 nm. Eluents A (0.1% TFA in H2O) and B (0.1% TFA in MeCN) were used in a linear gradient (100% A to 100% B) in a total run time of 13 min. Analytical RP-UPLC-MS (ESI) analysis was performed on a Waters AQUITY RP-UPLC system equipped with a diode array detector using a Kinetex XB-C18 column (*d* 1.7 μm, 2.1x50 mm; column temp: 50 °C; flow: 0.6 mL/min). Eluents A (0.1% HCO_2H in H_2O) and B (0.1% HCO_2H in MeCN) were used in a linear gradient (5% B to 100% B) in a total run time of 2.6 min. For more apolar compounds the total run time was 5 min. The LC system was coupled to a SQD mass spectrometer.
For the recording of ^{1}H NMR and ^{13}C NMR either a Varian Mercury spectrometer (operating at 300 MHz for proton and 75 MHz for carbon), a Varian Unity Inova spectrometer (operating at 500MHz for proton) or a 400 Bruker Ascend with a Prodigy cryoprobe (operating at 400 MHz for proton and 100 MHz for carbon) were used. The chemical shifts (δ) are reported in parts per million (ppm) and the coupling constants (*J*) in Hz. DMSO-d_6 or $CDCl_3$ were used as the solvents and signal positions were measured relative to the signal for DMSO (δ 2.50 ppm for ^{1}H NMR and δ 39.43 ppm for ^{13}C NMR) or for $CHCl_3$ (δ 7.26 ppm for ^{1}H NMR and δ 77.0 ppm for ^{13}C NMR), respectively. IR analysis was performed on a Bruker Alpha FT-IR spectrometer. Analytical LC-HRMS (ESI) analysis was performed on an Agilent 1100 RPLC system equipped with a diode array detector using a Phenomenex Luna C18 column (*d* 3 μm, 2.1x50 mm; column temp: 40 °C; flow: 0.4 mL/min.). Eluents A (0.1% HCO_2H in H_2O) and B (0.1% HCO_2H in MeCN) were used in a linear gradient (20% B to 100% B) in a total run time of 15 min. The LC system was coupled to a Micromass LCT orthogonal time-of-flight mass spectrometer equipped with a Lock Mass probe operating in positive electrospray mode. Melting points were measured using a Stuart® SMP30 melting point apparatus and are given in degrees Celcius, uncorrected.

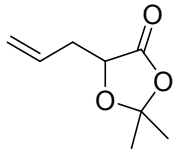
Synthesis of Alkene-Containing Building Blocks

2-hydroxypent-4-enoic acid (S1)



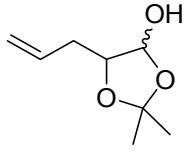
Glyoxylic acid (15.9 g, 0.172 mol) was suspended in a mixture of allyl bromide (23.3 mL, 0.276 mol) and THF:H2O (2:1) (300 mL) at room temperature. Fine flakes of freshly cut indium (20.0 g, 0.174 mol) were added under vigorous stirring. After 24 h the turbid reaction mixture was quenched with aqueous 1 M HCl (300 mL) and the aqueous phase was extracted with CH_2Cl_2 (4x300 mL). The combined organic layers were dried over $MgSO_4$, and the volatiles were removed *in vacuo* to give the title compound as a white solid (16.2 g, 81%), that was used in the next step without further purification. ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.44 (bs, 1H), 5.87–5.73 (m, 1H), 5.10–5.00 (m, 2H), 3.99 (dd, J = 7.0, 5.1 Hz, 1H), 2.44–2.23 (m, 2H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 175.2, 134.5, 117.3, 69.7, 38.6. Spectroscopic data were in accordance with the previously reported.[2]

5-allyl-2,2-dimethyl-1,3-dioxolan-4-one (S2)



2-Hydroxypent-4-enoic acid (6.70 g, 0.0577 mol) was dissolved in acetone (124 mL). 2,2-Dimethoxypropane (56.8 mL, 0.462 mol) and pyridine *p*-toluenesulfonate (2.90 g, 0.0115 mol) were added and the reaction was heated to reflux for 4 h. The reaction mixture was kept in the freezer overnight, and then filtered through a pad of celite. The volatiles were removed *in vacuo* at 0 °C and the residue was purified by flash column chromatography on silica gel (CH_2Cl_2, R_f = 0.4 (heptane:EtOAc (3:1), $KMnO_4$ stain) to afford the title compound as a colorless oil (6.51 g, 72%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.82 (ddt, J = 17.1, 10.2, 6.9 Hz, 1H), 5.33 – 5.14 (m, 2H), 4.47 (dd, J = 6.7, 4.3 Hz, 1H), 2.71 – 2.59 (m, 1H), 2.56 – 2.43 (m, 1H), 1.61 (s, 2H), 1.54 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.7, 132.0, 119.3, 110.8, 73.9, 35.9, 27.3, 26.1; IR (neat) cm^{-1}: 3056, 2944, 1790, 1386, 240, 1106, 993, 914. Spectroscopic data were in accordance with the previously reported.[3]

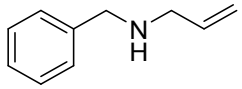
5-allyl-2,2-dimethyl-1,3-dioxolan-4-ol (1)



A solution of 5-allyl-2,2-dimethyl-1,3-dioxolan-4-one (2.32 g, 14.9 mmol) in toluene (59 mL) was stirred at -78 °C. DIBALH (17.8 mL, 17.8 mmol, 1 M in toluene) was added dropwise and after 30 min the reaction was cautiously quenched with 1 M HCl (aq) (23 mL) at -78 °C. The reaction mixture was allowed to reach room temperature and stirred for another 30 min, whereupon the reaction was diluted with water (180 mL) and extracted with CH_2Cl_2 (3x200 mL). The combined organic layers were dried over $MgSO_4$, and the volatiles were removed *in vacuo* to give the title compound as a colorless oil (2.15 g, 91%, *d.r.* 2:1), that was used immediately without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.94–5.76 (m, 1H), 5.30 (dd, J = 6.3, 3.4 Hz, 0.33H), 5.25–5.09 (m, 2.66H), 4.09 (td, J = 6.4, 3.2 Hz, 0.66H), 4.03 (dt, J = 6.9, 3.4 Hz, 0.33H), 3.00 (d, J = 3.9 Hz, 0.66H), 2.53 (d, J = 6.3 Hz,

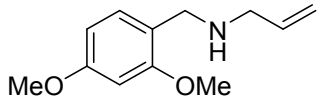
0.33H), 2.50–2.45 (m, 0.66H), 2.42–2.35 (m, 1.33H), 1.54 (s, 1H), 1.52 (s, 2H), 1.45 (s,2H), 1.35 (s, 1H), diastereoisomers; ^{13}C NMR (100 MHz, $CDCl_3$) δ 133.9, 133.4, 118.1, 117.8, 110.8, 109.7, 99.6, 95.4, 82.3, 79.2, 37.2, 33.2, 29.1, 28.0, 27.2, 26.0, diastereomers; IR (neat) cm^{-1}: 3422, 2988, 2938, 1371, 1214, 1166, 1014, 918, 844.[4]

_N_-benzylprop-2-en-1-amine (6b)



A solution of benzaldehyde (1.50 mL, 14.7 mmol) and allylamine (1.25 mL, 16.2 mmol) in MeOH (75 mL) was stirred overnight at room temperature with molecular sieves (3 Å). $NaBH_4$ (556 mg, 14.7 mmol) was slowly added and the reaction mixture was allowed to stand at room temperature for 1 h whereupon it was filtered through a pad of celite. The filtrate was evaporated *in vacuo*, and the residue was taken up in CH_2Cl_2 (150 mL) and water (100 mL). The aqueous phase was extracted with CH_2Cl_2 (2x100 mL), and the combined organic layers were dried over Na_2SO_4. The volatiles were removed *in vacuo* to give the title compound as a colorless oil (1.89 g, 86%), that was used without further purification. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.33–7.27 (m, 4H), 7.25–7.18 (m, 1H), 5.86 (ddt, J = 17.2, 10.3, 5.7 Hz, 1H), 5.15 (ddt, J = 17.2, 1.6, 1.6 Hz, 1H), 5.06–5.03 (m, 1H), 3.66 (s, 2H), 3.12 (ddd, J = 5.7, 1.6, 1.6 Hz, 2H), 2.20 (bs, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 140.9, 137.6, 128.0, 127.9, 126.4, 115.1, 52.2, 51.0; MS (ESI) calcd for $C_{10}H_{14}N$ $[M + H]^+$ 148.1 found 148.1. NMR data are in accordance with the previously reported.[5]

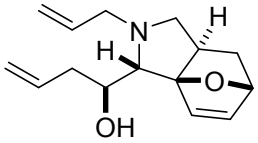
_N_-(2,4-Dimethoxybenzyl)prop-2-en-1-amine (6c)



A solution of 2,4-dimethoxybenzaldehyde (2.51 g, 15.1 mmol) and allylamine (1.29 mL, 16.6 mmol) in MeOH (76 mL) was stirred overnight at room temperature with molecular sieves (3 Å). $NaBH_4$ (572 mg, 15.1 mmol) was slowly added and the reaction mixture was allowed to stand at room temperature for 1 h whereupon it was filtered through a pad of celite. The filtrate was evaporated *in vacuo*, and the residue was taken up in EtOAc (150 mL) and water (100 mL). The aqueous phase was extracted with EtOAc (2x100 mL), and the combined organic layers were dried over Na_2SO_4. The volatiles were removed *in vacuo* to give the title compound as a slightly yellow oil (2.92 g, 93%), that was used without further purification. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.16 (d, J = 8.2 Hz, 1H), 6.52 (d, J = 2.4 Hz, 1H), 6.46 (dd, J = 8.2, 2.4 Hz, 1H), 5.85 (ddt, J = 16.0, 10.4, 5.7 Hz, 1H), 5.18–5.11 (m, 1H), 5.06–5.01 (m, 1H), 3.75 (s, 3H), 3.74 (s, 3H), 3.56 (s, 2H), 3.12 (ddd, J = 5.7, 1.4, 1.4 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 159.4, 158.1, 137.8, 129.6, 120.7, 115.1, 104.1, 98.2, 55.3, 55.1, 51.0, 46.7; MS (ESI) calcd for $C_{12}H_{18}NO_2$ $[M + H]^+$ 208.1 found 208.1; IR (neat) cm^{-1} 3322, 2936, 2834, 1612, 1587, 1505, 1455, 1287, 1206, 1154, 1034, 917, 823. NMR data are in accordance with the previously reported.[6]

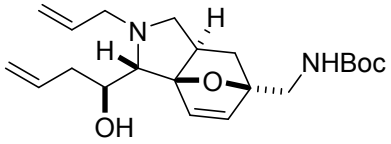
Initial Synthesis of P3-CR/IMDA and ROM-RCM Products

(*S*)-1-((3*S*,3a*R*,6*R*,7a*R*)-2-allyl-1,2,3,6,7,7a-hexahydro-3a,6-epoxyisoindol-3-yl)but-3-en-1-ol (*rac.*) (2)



A solution of **1** (295 mg, 1.87 mmol) and diallylamine (230 μL, 1.87 mmol) in dry CH_2Cl_2 (10 mL) was stirred at room temperature. 2-furylboronic acid (209 mg, 1.87 mmol) and HFIP (2 mL) were added and the reaction mixture was heated to reflux for 24 h. The volatiles were removed *in vacuo*, and the residue was purified by flash column chromatography on silica gel (heptane:EtOAc:Et_3N (14:7:1), R_f = 0.3, $KMnO_4$ stain) to give the title compound as a pale orange solid (315 mg, 68%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.73 (d, J = 5.8 Hz, 1H), 6.21 (dd, J = 5.8, 1.6 Hz, 1H), 5.95–5.81 (m, 2H), 5.22–5.08 (m, 4H), 4.95 (dd, J = 4.4, 1.6 Hz, 1H), 3.92–3.86 (m, 1H), 3.48–3.42 (m, 1H), 3.30 (dd, J = 8.6, 6.8 Hz, 1H), 3.04 (dd, J = 13.8, 7.7 Hz, 1H), 2.88 (s, 1H), 2.76 (d, J = 2.1 Hz, 1H), 2.62–2.53 (m, 1H), 2.42–2.34 (m, 1H), 2.13 (dd, J = 10.5, 8.6 Hz, 1H), 1.90–1.82 (m, 1H), 1.66–1.60 (m, 1H), 1.30 (dd, J = 11.4, 7.7 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.2, 135.7, 135.2, 134.1, 117.5, 117.3, 97.6, 79.0, 69.8, 68.6, 58.1, 56.8, 43.2, 37.0, 29.8; MS (ESI) calcd for $C_{15}H_{22}NO_2$ [M + H]+ 248.2, found 248.2; HRMS (ESI) calcd for $C_{15}H_{22}NO_2$ $[M + H]^+$ 248.1645 found 248.1644; IR (neat) cm^{-1}: 3451, 3075, 2941, 1641, 1419, 1318, 993, 913; m.p. (EtOAc) 40–42 ^{o}C.

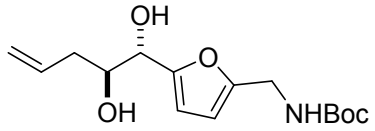
***tert*-butyl (((3*S*,3a*R*,6*R*,7a*R*)-2-allyl-3-((*S*)-1-hydroxybut-3-en-1-yl)-2,3,7,7a-tetrahydro-3a,6-epoxyisoindol-6(1*H*)-yl)methyl)carbamate (*rac.*) (8d)**



A solution of **1** (100 mg, 0.632 mmol) and diallylamine (78 μL, 0.632 mmol) in dry CH_2Cl_2 (3.5 mL) was stirred at room temperature. 5-((Boc-amino)methyl)furan-2-boronic acid (152 mg, 0.632 mmol) and HFIP (1 mL) were added and the reaction mixture was heated to reflux for 24 h. The volatiles were removed in vacuo, and the residue was purified by flash column chromatography on silica gel (heptane:EtOAc:Et_3N (40:10:1) to heptane:EtOAc:Et_3N (10:10:1), R_f = 0.3 (heptane:EtOAc:Et_3N (40:10:1)), $KMnO_4$ stain) to give the title compound as a slightly brown oil (116 mg, 74%).[1] ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.75 (d, J = 5.7 Hz, 1H), 6.11 (d, J = 5.7 Hz, 1H), 5.97–5.78 (m, 2H), 5.24–5.06 (m, 4H), 4.82 (bs, 1H), 3.89–3.83 (m, 1H), 3.77 (dd, J = 14.4, 6.8 Hz, 1H), 3.54–3.37 (m, 2H), 3.29 (dd, J = 8.5, 6.8 Hz, 1H), 3.03 (dd, J = 13.6, 7.6 Hz, 1H), 2.87 (bs, 1H), 2.69 (d, J = 2.2 Hz, 1H), 2.62–2.47 (m, 1H), 2.44–2.29 (m, 1H), 2.11 (dd, J = 10.5, 8.5 Hz, 1H), 2.04–1.91 (m, 1H), 1.44 (s, 9H), 1.43–1.32 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.3, 137.9, 135.6, 135.2, 134.6, 117.5, 117.3, 97.8, 89.8, 79.5, 69.8, 68.7, 58.0, 56.9, 45.8, 42.6, 37.0, 32.2, 28.5; MS (ESI) calcd for $C_{21}H_{33}N_2O_4$ $[M+H]^+$ 377.2, found 377.4; HRMS (ESI) calcd for $C_{21}H_{33}N_2O_4$ $[M+H]^+$ 377.2435 found 377.2443; IR (neat) cm^{-1}: 3351, 2976, 2930, 1702, 1509, 1248, 1164, 915.

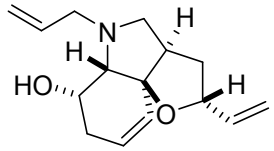
[1]Along with the desired product **8d**, the side-product **S3** was isolated in 18% yield.

***tert*-butyl ((5-((1*S*,2*S*)-1,2-dihydroxypent-4-en-1-yl)furan-2-yl)methyl)carbamate (*rac.*) (MI-7-16-F2) (S3)**



Isolated as a by-product from the synthesis of **8d**, as a colorless oil (33 mg, 18%, R_f = 0.2 (heptane:EtOAc:Et_3N (10:10:1)), $KMnO_4$ stain). ^1H NMR (400 MHz, $CDCl_3$)δ 6.23 (d, J = 3.1 Hz, 1H), 6.14 (d, J = 3.1 Hz, 1H), 5.90–5.65 (m, 1H), 5.19–5.09 (m, 2H), 5.07 (bs, 1H), 4.59 (d, J = 4.6 Hz, 1H), 4.26–4.15 (m, 2H), 3.93 (ddd, J = 8.5, 8.5, 4.6 Hz, 1H), 3.08–2.80 (m, 2H), 2.35–2.12 (m, 2H), 1.42 (s, 9H); ^{13}C NMR (101 MHz, CDCl3) δ 155.9, 153.3, 151.9, 134.5, 118.1, 108.8, 107.7, 80.0, 73.0, 70.5, 37.8, 37.1, 28.5; MS (ESI) calcd for $C_{15}H_{23}NNaO_5$ $[M + Na]^+$ 320.1 found 320.3; HRMS (ESI) calcd for $C_{15}H_{23}NNaO_5$ $[M + Na]^+$ 320.1468 found 320.1463; IR (neat) cm^{-1}: 3338, 2978, 1688, 1513, 1366, 1249, 1163, 1012, 911, 783.

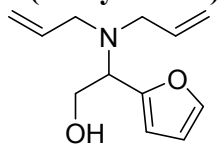
(2*R*,3a*R*,5a*S*,6*S*,9a*R*)-5-allyl-2-vinyl-2,3,3a,4,5,5a,6,7-octahydrofuro[3,2-c]indol-6-ol (*rac.*) (4)



A stirred solution of **2** (100 mg, 0.404 mmol) in dry CH_2Cl_2 (40 mL) was added HCl (404 µL, 0.404 mmol, 1M in Et_2O) followed by the Grubbs II catalyst (34 mg, 0.0404 mmol). The reaction mixture was stirred at room temperature for 3 h, whereupon the volatiles were removed *in vacuo*. The residue was taken up in CH_2Cl_2 (20 mL) and satd. $NaHCO_3$ (aq) (15 mL). The organic layer was separated and washed with water (20 mL), and then dried over Na_2SO_4. The volatiles were removed *in vacuo* and the residue purified by flash column chromatography on silica gel (heptane:EtOAc:Et_3N (10:10:1), R_f = 0.4 (heptane:EtOAc (1:3)), $KMnO_4$ stain) to give the title compound as a white solid (66 mg, 66%). ^1H NMR (400 MHz, $CDCl_3$) δ 5.96–5.78 (m, 2H), 5.73–5.65 (m, 1H), 5.60 (dd, J = 10.0, 2.2 Hz, 1H), 5.27–5.18 (m, 2H), 5.15–5.07 (m, 2H), 4.58 (dt, J = 9.4, 6.2 Hz, 1H), 3.98–3.93 (m, 1H), 3.48 (dd, J = 13.6, 5.9 Hz, 1H), 3.26 (dd, J = 8.5, 7.6 Hz, 1H), 3.18 (dd, J = 13.6, 7.2 Hz, 1H), 2.99 (d, J = 4.0 Hz, 1H), 2.54–2.46 (m, 1H), 2.45–2.36 (m, 2H), 2.21 (ddd, J = 17.5, 5.7, 2.8 Hz, 1H), 2.03 (dd, J = 13.0, 6.2 Hz, 1H), 1.86 (ddd, J = 13.0, 9.8, 6.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.9, 135.5, 128.9, 124.5, 117.6, 115.9, 89.6, 78.3, 70.6, 65.4, 57.0, 56.6, 48.4, 35.5, 28.5; MS (ESI) calcd for $C_{15}H_{22}NO_2$ $[M + H]^+$ 248.2, found 248.2; HRMS (ESI) calcd for $C_{15}H_{22}NO_2$ $[M+H]^+$ 248.1645 found 248.1646; IR (neat) cm^{-1}: 3332, 2933, 2784, 1466, 1422, 1344, 1257, 1123, 1072, 1051, 1033, 1013, 991, 927; m.p. (EtOAc) 64–66 ^oC.

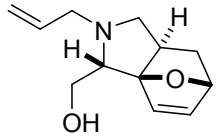
Sequential P3-CR/IMDA Reactions

2-(diallylamino)-2-(furan-2-yl)ethan-1-ol (S4)



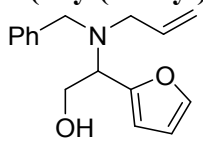
A solution of glycolaldehyde dimer (50 mg, 0.416 mmol) and diallylamine (106 μL, 0.833 mmol) in MeOH (2.1 mL) was stirred at room temperature. 2-furylboronic acid (93 mg, 0.833 mmol) was added and the reaction mixture was stirred at room temperature for 14 h. The volatiles were removed *in vacuo*, and the residue was purified by flash column chromatography on silica gel (heptane:EtOAc:Et_3N (40:10:1), R_f = 0.3, $KMnO_4$ stain) to give the title compound as a colorless oil (131 mg, 76%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 (d, J = 1.6 Hz, 1H), 6.34 (dd, J = 3.2, 1.6 Hz, 1H), 6.14 (d, J = 3.2 Hz, 1H), 5.84–5.69 (m, 2H), 5.26–5.11 (m, 4H), 4.12 (dd, J = 10.8, 5.3 Hz, 1H), 3.85 (t, J = 10.7 Hz, 1H), 3.64 (dd, J = 10.6, 5.3 Hz, 1H), 3.43–3.32 (m, 2H), 2.80 (dd, J = 14.2, 8.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.8, 142.3, 136.3, 118.0, 110.0, 108.5, 59.3, 57.3, 53.3; MS (ESI) calcd for $C_{12}H_{18}NO_2$ $[M+H]^+$ 208.1 found 208.2; HRMS (ESI) calcd for $C_{12}H_{18}NO_2$ $[M+H]^+$ 208.1332 found 208.1334.

((3*S*,3a*R*,6*R*,7a*R*)-2-allyl-1,2,3,6,7,7a-hexahydro-3a,6-epoxyisoindol-3-yl)methanol (*rac.*) (8a)



A solution of **S4** (131 mg, 0.633 mmol) in toluene (2.6 mL) was heated to reflux for two days, whereupon the volatiles were removed *in vacuo*. The residue was purified by flash column chromatography on silica gel (heptane:EtOAc (1:2), R_f = 0.4, $KMnO_4$ stain) to give the title compound as slightly yellow oil (111 mg, 85%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.51 (d, J = 5.8 Hz, 1H), 6.30 (dd, J = 5.8, 1.6 Hz, 1H), 5.87 (dddd, J = 17.3, 10.1, 7.3, 5.8 Hz, 1H), 5.19 (dd, J = 17.1, 1.6 Hz, 1H), 5.11 (dd, J = 10.1, 1.6 Hz, 1H), 4.98 (dd, J = 4.4, 1.6 Hz, 1H), 3.76 (d, J = 2.5 Hz, 2H), 3.39 (ddt, J = 13.7, 5.8, 1.6 Hz, 1H), 3.31 (dd, J = 8.5, 6.9 Hz, 1H), 3.21–3.11 (m, 1H), 3.03 (bs, 1H), 2.90 (t, J = 2.5 Hz, 1H), 2.22 (dd, J = 10.5, 8.6 Hz, 1H), 1.95–1.81 (m, 1H), 1.68 (ddd, J = 11.4, 4.3, 3.1 Hz, 1H), 1.33 (dd, J = 11.5, 7.7 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.8, 135.6, 135.3, 117.4, 99.0, 79.7, 64.8, 60.0, 58.3, 56.8, 42.8, 29.9; MS (ESI) calcd for $C_{12}H_{18}NO_2$ $[M + H]^+$ 208.1 found 208.3; HRMS (ESI) calcd for $C_{12}H_{18}NO_2$ $[M+ H]^+$ 208.1332 found 208.1362.

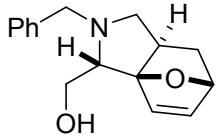
2-(allyl(benzyl)amino)-2-(furan-2-yl)ethan-1-ol (S5)



A solution of glycolaldehyde dimer (75 mg, 0.624 mmol) and *N*-benzylprop-2-en-1-amine (184 mg, 1.25 mmol) in MeOH (5.5 mL) was stirred at room temperature. 2-furylboronic acid (140 mg, 1.25 mmol) was added and the reaction mixture was stirred at room temperature for 14 h. The volatiles were removed *in vacuo*, and the residue was purified by flash column chromatography on silica gel (heptane:EtOAc:Et_3N (40:10:1), R_f = 0.3, $KMnO_4$ stain) to give the title compound as a colorless oil (288 mg, 90%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 (dd,

J = 1.8, 0.7 Hz, 1H), 7.37–7.31 (m, 4H), 7.30–7.24 (m, 1H), 6.38 (dd, J = 3.2, 1.8 Hz, 1H), 6.18 (dd, J = 3.2, 0.7 Hz, 1H), 5.79 (dddd, J = 17.2, 10.1, 8.4, 4.5 Hz, 1H), 5.29–5.12 (m, 2H), 4.08 (dd, J = 10.8, 5.2 Hz, 1H), 3.97–3.86 (m, 2H), 3.63 (dd, J = 10.6, 5.2 Hz, 1H), 3.41–3.34 (m, 1H), 3.22 (d, J = 13.6 Hz, 1H), 2.85 (dd, J = 14.1, 8.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.7, 142.4, 139.2, 136.3, 129.2, 128.6, 127.4, 118.3, 110.0, 108.7, 59.3, 57.1, 54.4, 53.3; MS (ESI) calcd for $C_{16}H_{20}NO_2$ $[M+H]^+$ 258.1 found 258.2; HRMS (ESI) calcd for $C_{16}H_{20}NO_2$ $[M+H]^+$ 258.1489 found 258.1492; IR (neat) cm^{-1}: 3448, 2941, 2819, 1496, 1453, 1064, 1029, 1009, 920, 733, 697.

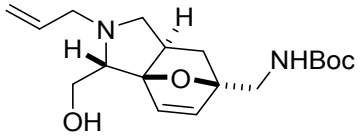
((3*S*,3a*R*,6*R*,7a*R*)-2-benzyl-1,2,3,6,7,7a-hexahydro-3a,6-epoxyisoindol-3-yl) (*rac.*) (8b)



A solution of **S5** (110 mg, 0.427 mmol) in toluene (2.6 mL) was heated to reflux for two days, whereupon the volatiles were removed *in vacuo*. The residue was purified by flash column chromatography on silica gel (heptane:EtOAc (1:2), R_f = 0.3, $KMnO_4$ stain) to give the title compound as an orange solid (95 mg, 86%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44–7.12 (m, 5H), 6.54 (d, J = 5.8 Hz, 1H), 6.31 (dd, J = 5.8, 1.7 Hz, 1H), 5.00 (dd, J = 4.4, 1.7 Hz, 1H), 3.96 (d, J = 12.9 Hz, 1H), 3.80 (dd, J = 11.2, 0.4 Hz, 1H), 3.69 (dd, J = 11.2, 3.4 Hz, 1H), 3.61 (d, J = 12.9 Hz, 1H), 3.20 (dd, J = 8.6, 6.8 Hz, 1H), 3.02 (d, J = 2.7 Hz, 1H), 2.22 (dd, J = 10.5, 8.6 Hz, 1H), 1.93–1.80 (m, 1H), 1.67 (ddd, J = 11.5, 4.4, 3.1 Hz, 1H), 1.32 (dd, J = 11.5, 7.7 Hz, 1H); ^{13}C NMR (100 MHz, CDCl3) δ 139.0, 135.9, 135.3, 128.9, 128.6, 127.4, 99.1, 79.8, 65.5, 59.9, 58.6, 58.4, 42.9, 29.9; MS (ESI) calcd for $C_{16}H_{20}NO_2$ $[M+H]^+$ 258.1, found 258.3; HRMS (ESI) calcd for $C_{16}H_{20}NO_2$ $[M+ H]^+$ 258.1489 found 258.1502; IR (neat) cm^{-1}: 3448, 2941, 2867, 2811, 1453, 1320, 1051, 1028, 961, 692; m.p. (EtOAc) 49–51 ^{o}C.

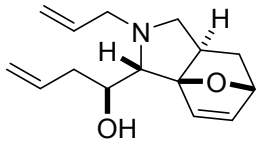
Sequential One-Pot Synthesis of Petasis 3-CR/IMDA Products

***tert*-butyl (((3*S*,3a*R*,6*R*,7a*R*)-2-allyl-3-(hydroxymethyl)-2,3,7,7a-tetrahydro3a,6-epoxyisoindol-6-(1*H*)yl)methyl)carbamate (*rac.*) (8c)**



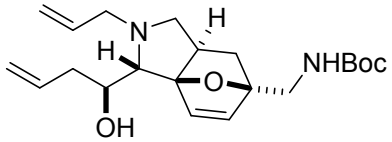
General procedure I: A solution of glycolaldehyde dimer (1.0 g, 8.4 mmol, 1 equiv) and diallylamine (2.1 mL, 17 mmol, 1 equiv) in MeOH (112 mL, 0.15 M) was stirred at room temperature. 5-((Boc-amino)methyl)furan-2-boronic acid (4.1 g, 17 mmol, 1 equiv) was added and the reaction mixture was stirred at room temperature for 21 h. The volatiles were removed *in vacuo*, and the residue was re-dissolved in acetonitrile (2.1 mL). The reaction mixture was heated to reflux for 24 h, whereupon the volatiles were removed *in vacuo*. The residue was purified by flash column chromatography on silica gel (EtOAc:Et_3N (95:5), R_f = 0.4, $KMnO_4$ stain) to give the title compound as a pale yellow solid (5.4 g, 97%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.56 (d, J = 5.8 Hz, 1H), 6.23 (d, J = 5.7 Hz, 1H), 5.87 (dddd, J = 17.2, 10.1, 7.3, 5.8 Hz, 1H), 5.20 (ddd, J = 17.2, 2.8, 1.3 Hz, 1H), 5.12 (ddd, J = 10.0, 2.2, 1.0 Hz, 1H), 4.81 (m, 1H), 3.82 (dd, J = 14.5, 7.0 Hz, 1H), 3.75 (d, J = 2.4 Hz, 2H), 3.45 (dd, J = 14.6, 4.5 Hz, 1H), 3.39 (dd, J = 13.7, 5.8 Hz, 1H), 3.31 (dd, J = 8.4, 6.8 Hz, 1H), 3.15 (dd, J = 13.6, 7.3 Hz, 1H), 2.97 (bs, 1H), 2.85 (t, J = 2.3 Hz, 1H), 2.22 (dd, J = 10.5, 8.6 Hz, 1H), 2.00 (m, 1H), 1.47 (dd, J = 11.8, 3.1 Hz, 1H), 1.44 (s, 9H), 1.40 (dd, J = 11.5, 7.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.1, 136.8, 136.2, 135.5, 117.3, 99.0, 90.7, 79.4, 64.8, 59.7, 58.0, 56.7, 45.4, 42.6, 32.3, 28.4; MS (ESI) calcd for $C_{18}H_{29}N_2O_4$ [M+ H]$^+$ 337.2 found 337.3; HRMS (ESI) calcd for $C_{18}H_{29}N_2O_4$ [M+ H]$^+$ 337.2122 found 337.2132; IR (neat) cm^{-1}: 3276, 2932, 1686, 1533, 1390, 1365, 1254, 1160, 1042, 966, 921, 875, 728; m.p. (EtOAc) 70–75 ^{o}C.

(*S*)-1-((3*S*,3a*R*,6*R*,7a*R*)-2-allyl-1,2,3,6,7,7a-hexahydro-3a,6-epoxyisoindol-3-yl)but-3-en-1-ol (*rac.*) (2)



General procedure I was followed using **1** (160 mg, 1.01 mmol), diallylamine (125 μL, 1.01 mmol) and 2-furylboronic acid (113 mg, 1.01 mmol) with reaction times of 19 h and 23 h, respectively, to give the title compound as a pale orange solid (227 mg, 91%) after flash column chromatography on silica gel (heptane:EtOAc:Et_3N (10:20:1), R_f = 0.3, $KMnO_4$ stain). Spectroscopic data for **2** were in accordance with those reported using the initially used reaction conditions, see page 6.

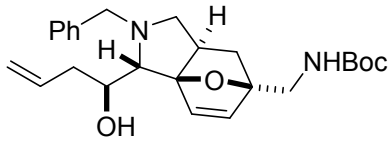
***tert*-butyl (((3*S*,3a*R*,6*R*,7a*R*)-2-allyl-3-((*S*)-1-hydroxybut-3-en-1-yl)-2,3,7,7a-tetrahydro-3a,6-epoxyisoindol-6(1*H*)-yl)methyl)carbamate (*rac.*) (8d)**



General procedure I was followed using **1** (400 mg, 2.53 mmol), diallylamine (312 μL, 2.53 mmol) and 5-((Boc-amino)methyl)furan-2- boronic acid (610 mg, 2.53 mmol) with reaction times of 20 h and 23 h, respectively, to give the title compound as a slightly brown oil (833

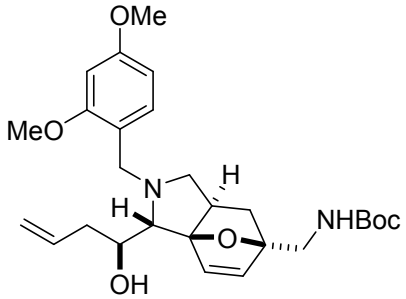
mg, 88%) after flash column chromatography on silica gel (heptane:EtOAc:Et_3N (10:20:1), R_f = 0.3, $KMnO_4$ stain). ^1H NMR (400 MHz, $CDCl_3$) δ 6.75 (d, J = 5.7 Hz, 1H), 6.11 (d, J = 5.7 Hz, 1H), 5.97–5.78 (m, 2H), 5.24–5.06 (m, 4H), 4.82 (bs, 1H), 3.89–3.83 (m, 1H), 3.77 (dd, J = 14.4, 6.8 Hz, 1H), 3.54–3.37 (m, 2H), 3.29 (dd, J = 8.5, 6.8 Hz, 1H), 3.03 (dd, J = 13.6, 7.6 Hz, 1H), 2.87 (bs, 1H), 2.69 (d, J = 2.2 Hz, 1H), 2.62–2.47 (m, 1H), 2.44–2.29 (m, 1H), 2.11 (dd, J = 10.5, 8.5 Hz, 1H), 2.04–1.91 (m, 1H), 1.44 (s, 9H), 1.43–1.32 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.3, 137.9, 135.6, 135.2, 134.6, 117.5, 117.3, 97.8, 89.8, 79.5, 69.8, 68.7, 58.0, 56.9, 45.8, 42.6, 37.0, 32.2, 28.5; MS (ESI) calcd for $C_{21}H_{33}N_2O_4$ $[M+H]^+$ 377.2, found 377.4; HRMS (ESI) calcd for $C_{21}H_{33}N_2O_4$ $[M+H]^+$ 377.2435 found 377.2443; IR (neat) cm^{-1}: 3351, 2976, 2930, 1702, 1509, 1248, 1164, 915.

***tert*-butyl (((3*S*,3a*R*,6*R*,7a*R*)-2-benzyl-3-((*S*)-1-hydroxybut-3-en-1-yl)-2,3,7,7a-tetrahydro-3a,6-epoxyisoindol-6(1*H*)-yl)methyl)carbamate (*rac.*) (8e)**



General procedure I was followed using **1** (200 mg, 1.26 mmol), *N*-benzylprop-2-en-1-amine (186 mg, 1.26 mmol) and 5-((Boc-amino) methyl)furan-2-boronic acid (305 mg, 1.26 mmol) with reaction times of 23 h and 17 h, respectively, to give the title compound as a slightly yellow solid (451 mg, 84%) after flash column chromatography on silica gel (heptane:EtOAc:Et_3N (30:10:2), R_f = 0.4 (heptane:EtOAc:Et_3N (40:10:1)), $KMnO_4$ stain). ^1H NMR (400 MHz, $CDCl_3$) δ 7.35–7.23 (m, 5H), 6.78 (d, J = 5.8 Hz, 1H), 6.12 (d, J = 5.8 Hz, 1H), 5.97–5.85 (m, 1H), 5.20–5.10 (m, 2H), 4.81 (bs, 1H), 4.03 (d, J = 13.0 Hz, 1H), 3.96–3.89 (m, 1H), 3.86–3.72 (m, 1H), 3.54–3.43 (m, 2H), 3.14 (dd, J = 8.6, 6.8 Hz, 1H), 2.93 (bs, 1H), 2.83 (d, J = 2.1 Hz, 1H), 2.68–2.54 (m, 1H), 2.47–2.35 (m, 1H), 2.11 (dd, J = 10.5, 8.6 Hz, 1H), 2.02–1.89 (m, 1H), 1.45 (s, 9H), 1.42–1.20 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.3, 139.1, 137.8, 135.2, 134.6, 128.8, 128.6, 127.3, 117.6, 97.8, 89.9, 79.6, 69.9, 69.3, 58.7, 58.1, 46.0, 42.6, 36.9, 32.2, 28.5; MS (ESI) calcd for $C_{25}H_{35}N_2O_4$ $[M+H]^+$ 427.3 found 427.4; HRMS (ESI) calcd for $C_{25}H_{35}N_2O_4$ $[M+H]^+$ 427.2591 found 427.2590; IR (neat) cm^{-1}: 3500, 3343, 2923, 1706, 1522, 1367, 1247, 1154, 877, 700; m.p. (EtOAc) 131–133 ^oC.

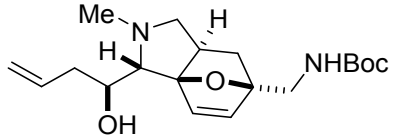
***tert*-butyl (((3*S*,3a*R*,6*R*,7a*R*)-2-(2,4-dimethoxybenzyl)-3-((*S*)-1-hydroxybut-3-en-1-yl)-2,3,7,7a-tetrahydro-3a,6-epoxyisoindol-6(1*H*)-yl)methyl)-carbamate (*rac.*) (8f)**



General procedure I was followed using **1** (275 mg, 1.74 mmol), *N*-(2,4-dimethoxybenzyl)-prop-2-en-1-amine (360 mg, 1.74 mmol) and 5-((Boc-amino) methyl)furan-2-boronic acid (419 mg, 1.74 mmol) with reaction times of 19 h and 24 h, respectively, to give the title compound as a pale yellow oil (606 mg, 72%) after flash column chromatography on silica gel (heptane:EtOAc:Et_3N (20:10:1), R_f = 0.3, $KMnO_4$ stain). ^1H NMR (400 MHz, $CDCl_3$) δ 7.09 (d, J = 8.1 Hz, 1H), 6.76 (d, J = 5.7 Hz, 1H), 6.47–6.40 (m, 2H), 6.09 (d, J = 5.7 Hz, 1H), 6.01–5.89 (m, 1H), 5.21–5.06 (m, 2H), 4.85–4.78 (m, 1H), 4.10–4.04 (m, 1H), 4.00 (d, J = 12.8 Hz, 1H), 3.81 (s, 3H), 3.80 (s, 3H), 3.80–3.74 (m, 1H), 3.48 (dd, J = 14.3, 4.6 Hz,

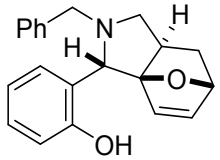
1H), 3.36 (d, J = 12.8 Hz, 1H), 3.24 (bs, 1H), 3.13 (dd, J = 8.4, 7.0 Hz, 1H), 2.78 (d, J = 1.8 Hz, 1H), 2.65–2.56 (m, 1H), 2.42–2.34 (m, 1H), 2.12 (dd, J = 10.5, 8.4 Hz, 1H), 1.93–1.85 (m, 1H), 1.45 (s, 9H), 1.44–1.37 (m, 1H), 1.30 (m, J = 11.3, 7.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.4, 158.8, 156.3, 138.1, 135.7, 134.3, 131.2, 119.6, 117.0, 103.7, 98.7, 97.9, 89.8, 79.5, 69.4, 68.8, 57.7, 55.5, 55.4, 52.2, 45.9, 42.7, 36.8, 32.0, 28.5; MS (ESI) calcd for $C_{27}H_{39}N_2O_6$ [M+ H]$^+$ 487.3 found 487.7; HRMS (ESI) calcd $C_{27}H_{39}N_2O_6$ [M + H]$^+$ 487.2803 found 487.2821; IR (neat) cm^{-1}: 3356, 2965, 2935, 1710, 1612, 1587, 1506, 1455, 1365, 1288, 1208, 1155, 1035, 876, 833.

tert-butyl (((3*S*,3a*R*,6*R*,7a*R*)-3-((*S*)-1-hydroxybut-3-en-1-yl)-2-methyl-2,3,7,7a-tetrahydro-3a,6-epoxyisoindol-6(1*H*)-yl)methyl)carbamate (*rac.*) (8g)



General procedure I was followed using **1** (275 mg, 1.74 mmol), *N*-methylprop-2-en-1-amine (167 µL, 1.74 mmol) and 5-((Boc-amino) methyl)furan-2-boronic acid (419 mg, 1.74 mmol) with reaction times of 19 h and 24 h, respectively, to give the title compound as a colorless oil (281 mg, 47%) after flash column chromatography on silica gel (heptane:EtOAc:Et_3N (20:20:1) to heptane:EtOAc:Et_3N (13:27:1), R_f = 0.2 heptane:EtOAc:Et_3N (20:20:1)), $KMnO_4$ stain). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.77 (d, J = 5.7 Hz, 1H), 6.10 (d, J = 5.7 Hz, 1H), 5.97–5.84 (m, 1H), 5.19–5.08 (m, 2H), 4.86–4.78 (m, 1H), 3.88–3.83 (m, 1H), 3.77 (dd, J = 14.4, 6.7 Hz, 1H), 3.49 (dd, J = 14.4, 4.7 Hz, 1H), 3.23 (dd, J = 8.5, 6.7 Hz, 1H), 2.60–2.49 (m, 1H), 2.49 (d, J = 2.1 Hz, 1H), 2.39 (s, 3H), 2.38–2.32 (m, 1H), 2.17 (dd, J = 10.6, 8.5 Hz, 1H), 2.03–1.95 (m, 1H), 1.44 (s, 9H), 1.44–1.40 (m, 1H), 1.34 (dd, J = 11.3, 7.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.8, 138.0, 135.2, 134.4, 117.5, 98.3, 89.9, 79.5, 70.8, 69.3, 61.0, 46.3, 42.6, 40.5, 37.2, 31.9, 28.5; MS (ESI) calcd for $C_{19}H_{31}N_2O_4$ [M+ H]$^+$ 351.2 found 351.3; HRMS (ESI) calcd for $C_{19}H_{31}N_2O_4$ [M+ H]$^+$ 351.2278 found 351.2286; IR (neat) cm^{-1}: 3350, 2974, 2939, 1711, 1509, 1365, 1247, 1166, 998, 877, 779.

2-((3*S*,3a*S*,6*S*,7a*S*)-2-benzyl-1,2,3,6,7,7a-hexahydro-3a,6-epoxyisoindol-3-yl)phenol (*rac.*) (S6)



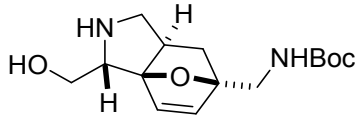
General procedure I was followed using salicylaldehyde (109 µL, 1.02 mmol), *N*-benzylprop-2-en-1-amine (151 mg, 1.02 mmol) and 2-furylboronic acid (114 mg, 1.02 mmol) with reaction times of 16 h and 4 h, respectively, to give the title compound as a white solid (274 mg, 84%) after flash column chromatography on silica gel (heptane:EtOAc (5:1), R_f = 0.3, $KMnO_4$ stain). ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.21 (bs, 1H), 7.36–7.20 (m, 6H), 7.09 (dd, J = 7.4, 1.6 Hz, 1H), 6.91 (dd, J = 8.1, 1.1 Hz, 1H), 6.85 (ddd, J = 7.4, 7.4, 1.2 Hz, 1H), 6.17 (dd, J = 5.8, 1.7 Hz, 1H), 5.79 (d, J = 5.8 Hz, 1H), 5.03 (dd, J = 4.4, 1.7 Hz, 1H), 4.14 (d, J = 12.5 Hz, 1H), 4.06 (s, 1H), 3.52 (d, J = 12.5 Hz, 1H), 3.23 (dd, J = 8.7, 6.1 Hz, 1H), 2.25 (dd, J = 10.9, 8.7 Hz, 1H), 2.15 (dddd, J = 10.9, 7.6, 6.1, 3.2 Hz, 1H), 1.72 (ddd, J = 11.5, 4.3, 3.2 Hz, 1H), 1.35 (dd, J = 11.5, 7.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.9, 136.9, 135.3, 135.3, 129.6, 129.5, 129.3, 128.7, 127.8, 121.4, 119.6, 117.2, 100.2, 80.1, 70.9, 58.5, 56.7, 43.5, 29.3; MS (ESI) calcd for $C_{21}H_{22}NO_2$ [M+ H]$^+$ 320.2 found 320.3; HRMS

(ESI) calcd for $C_{21}H_{22}NO_2$ $[M + H]^+$ 320.1645 found 320.1650; IR (neat) cm^{-1}: 2941, 2829, 1586, 1478, 1255, 1140, 1049, 1032, 962, 897, 751, 698; m.p. (EtOAc) 99–102 °C.

Diversification of Petasis 3-CR/IMDA Products

Deallylation of Petasis 3-CR/IMDA Products

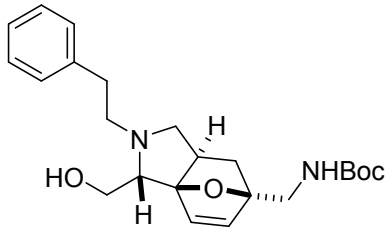
***tert*-butyl (((3*S*,3a*R*,6*R*,7a*R*)-3-(hydroxymethyl)-2,3,7,7a-tetrahydro-3a,6-epoxyisoindol-6(1*H*)-yl)-methyl)carbamate (*rac.*) (9)**



General procedure II: A solution of **8c** (1.5 g, 4.4 mmol, 1 equiv) in $CHCl_3$ (44 mL, 0.1 M) was added 2,2,5-trimethyl-1,3-dioxane-4,6-dione (0.70 g, 4.4 mmol, 1 equiv) and $Pd(PPh3)_4$ (0.51 g, 0.44 mmol, 0.1 equiv). The reaction mixture was heated to reflux for 1 h, whereupon it was cooled to room temperature. The volatiles were removed *in vacuo*, and the residue was purified by flash column chromatography on silica gel (CH_2Cl_2:MeOH:NH_4OH (25% w/w, aq) (45:5:1), R_f = 0.4 (CH_2Cl_2:MeOH:NH_4OH (25% w/w, aq) (15:4:1)), $KMnO_4$ stain) to give the title compound as a yellow solid (0.6 g, 51%). ^1H NMR (400 MHz, $CDCl_3$) δ 6.50 (d, J = 5.7 Hz, 1H), 6.28 (d, J = 5.7 Hz, 1H), 4.90 (bs, 1H), 3.82 (dd, J = 14.4, 6.9 Hz, 1H), 3.69 (dd, J = 10.9, 4.2 Hz, 1H), 3.66 (dd, J = 10.9, 4.2 Hz, 1H), 3.46 (m, 1H), 3.46 (m, 1H), 3.32 (t, J = 8.3 Hz, 1H), 2.91 (bs, 2H), 2.70 (t, J = 9.5 Hz, 1H), 2.05 (m, 1H), 1.47 (m, 2H), 1.43 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.1, 136.9, 135.8, 98.6, 90.7, 79.4, 62.3, 58.5, 51.3, 46.3, 42.5, 33.3, 28.3; MS (ESI) calcd for $C_{15}H_{25}N_2O_4$ $[M + H]^+$ 297.2, found 297.2; HRMS (ESI) calcd for $C_{15}H_{25}N_2O_4$ [M+ H]$^+$ 297.1809 found 297.1837.

Reductive Amination of Secondary Amines

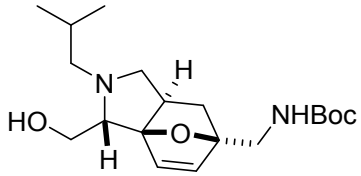
***tert*-butyl (((3*S*,3a*R*,6*R*,7a*R*)-3-(hydroxymethyl)-2-phenethyl-2,3,7,7a-tetrahydro-3a,6-epoxyisoindol-6(1*H*)-yl)methyl)carbamate (*rac.*) (10a)**



General procedure III: A solution of **9** (92 mg, 0.31 mmol) in CH_2Cl_2 (1.0 mL, 0.3 M) was added molecular sieves (4 Å), phenylacetaldehyde (73 μL, 0.62 mmol, 2 equiv) and $NaBH(OAc)_3$ (131 mg, 0.62 mmol, 2 equiv). The reaction mixture was stirred at room temperature for 20 h, whereupon the volatiles were removed *in vacuo*. The residue was purified by flash column chromatography on silica gel (hexanes:EtOAc:Et_3N (15:4:1), R_f = 0.1, $KMnO_4$ stain) to give the title compound as a pale yellow oil (79 mg, 63%). ^1H NMR (400 MHz, $CDCl_3$) δ 7.29 (t, J = 7.3 Hz, 2H), 7.20 (m, 1H), 7.18 (d, J = 6.9 Hz, 2H), 6.51 (d, J = 5.8 Hz, 1H), 6.21 (d, J = 5.7 Hz, 1H), 4.88 (m, 1H), 3.81 (dd, J = 14.4, 7.0 Hz, 1H), 3.67 (dd, J = 11.3, 0.8 Hz, 1H), 3.59 (dd, J = 11.3, 3.4 Hz, 1H), 3.46 (m, 1H), 3.45 (m, 1H), 2.95 (m, 1H), 2.81 (m, 1H), 2.80 (m, 1H), 2.79 (m, 2H), 2.24 (dd, J = 10.4, 8.4 Hz, 1H), 1.99 (m, 1H), 1.49 (dd, J = 11.5, 2.8 Hz, 1H), 1.44 (s, 9H), 1.40 (dd, J = 11.6, 7.7 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.0, 140.1, 136.7, 136.1, 128.40, 128.4, 126.1, 98.5, 90.7, 79.3, 65.4,

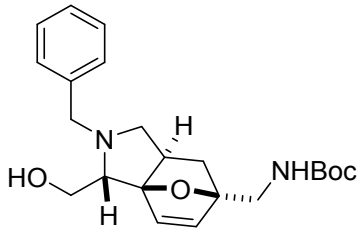
59.5, 57.4, 55.1, 45.5, 42.5, 35.0, 32.3, 28.3; MS (ESI) calcd for $C_{23}H_{33}N_2O_4$ [M+ H]$^+$ 401.2, found 401.3.

***tert*-butyl (((3*S*,3a*R*,6*R*,7a*R*)-3-(hydroxymethyl)-2-isobutyl-2,3,7,7a-tetrahydro-3a,6-epoxyisoindol-6-(1*H*)-yl)methyl)carbamate (*rac.*) (10b)**



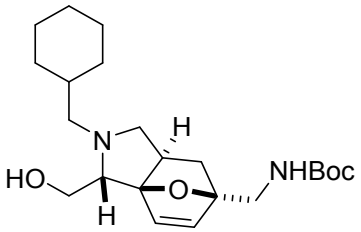
General procedure III was followed using **9** (95 mg, 0.32 mmol), isobutyraldehyde (58 μL, 0.64 mmol) and $NaBH(OAc)_3$ (136 mg, 0.64 mmol) to give the title compound as a white solid (82 mg, 72%) after purification by flash column chromatography on silica gel (hexanes:EtOAc:Et_3N (15:4:1), R_f = 0.3, $KMnO_4$ stain). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.55 (d, J = 5.8 Hz, 1H), 6.22 (d, J = 5.7 Hz, 1H), 4.82 (m, 1H), 3.81 (dd, J = 14.5, 7.0 Hz, 1H), 3.75 (d, J = 10.7 Hz, 1H), 3.70 (dd, J = 11.1, 3.2 Hz, 1H), 3.45 (dd, J = 14.4, 4.6 Hz, 1H), 3.35 (dd, J = 7.9, 6.8 Hz, 1H), 3.07 (bs, 1H), 2.75 (d, J = 2.1 Hz, 1H), 2.44 (dd, J = 12.0, 4.6 Hz, 1H), 2.31 (dd, J = 11.8, 10.4 Hz, 1H), 2.11 (dd, J = 10.5, 8.2 Hz, 1H), 2.00 (m, 1H), 1.77 (m, 1H), 1.48 (dd, J = 11.4, 2.9 Hz, 1H), 1.43 (s, 9H), 1.40 (dd, J = 11.7, 7.8 Hz, 1H), 0.92 (d, J = 6.5 Hz, 3H), 0.88 (d, J = 6.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.1, 136.9, 136.2, 98.7, 90.7, 79.4, 66.0, 62.5, 59.4, 57.8, 45.8, 42.6, 32.3, 28.3, 27.1, 21.1, 20.3; MS (ESI) calcd for $C_{19}H_{33}N_2O_4$ [M+ H]$^+$ 353.2, found 353.2; m.p. (EtOAc) 96–97 ^{o}C.

***tert*-butyl (((3*S*,3a*R*,6*R*,7a*R*)-2-benzyl-3-(hydroxymethyl)-2,3,7,7a-tetrahydro-3a,6-epoxyisoindol-6(1*H*)-yl)-methyl)carbamate (*rac.*) (10c)**



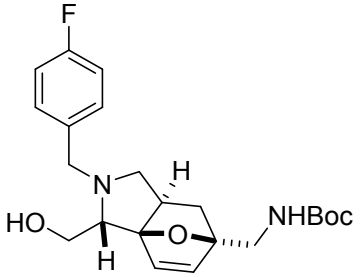
General procedure III was followed using **9** (68 mg, 0.23 mmol), benzaldehyde (47 μL, 0.46 mmol) and $NaBH(OAc)_3$ (98 mg, 0.46 mmol) to give the title compound as a transparent oil (58 mg, 65%) after purification by flash column chromatography on silica gel (hexanes:EtOAc:Et3N (15:4:1), R_f = 0.2, $KMnO_4$ stain). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35–7.24 (m, 5H), 6.58 (d, J = 5.8 Hz, 1H), 6.23 (d, J = 5.7 Hz, 1H), 4.85 (m, 1H), 3.95 (d, J = 12.9 Hz, 1H), 3.82 (dd, J = 14.7, 7.3 Hz, 1H), 3.77 (d, J = 11.4 Hz, 1H), 3.66 (dd, J = 11.3, 3.4 Hz, 1H), 3.60 (d, J = 12.9 Hz, 1H), 3.45 (dd, J = 14.4, 4.6 Hz, 1H), 3.19 (dd, J = 8.3, 6.9 Hz, 1H), 2.96 (d, J = 2.6 Hz, 1H), 2.22 (dd, J = 10.5, 8.6 Hz, 1H), 1.98 (m, 1H), 1.45 (m, 1H), 1.44 (s, 9H), 1.37 (dd, J = 11.4, 7.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.1, 138.8, 136.8, 136.2, 128.6, 128.4, 127.3, 99.0, 90.8, 79.4, 65.4, 59.6, 58.4, 58.1, 45.5, 42.5, 32.2, 28.3; MS (ESI) calcd for $C_{22}H_{31}N_2O_4$ [M+ H]$^+$ 387.2, found 387.3.

***tert*-butyl (((3*S*,3a*R*,6*R*,7a*R*)-2-(cyclohexylmethyl)-3-(hydroxymethyl)-2,3,7,7a-tetrahydro-3a,6-epoxyisoindol-6(1*H*)-yl)methyl)carbamate (*rac.*) (10e)**



General procedure III was followed using **9** (95 mg, 0.32 mmol), cyclohexanecarboxaldehyde (78 μL, 0.64 mmol) and $NaBH(OAc)_3$ (136 mg, 0.64 mmol) to give the title compound as a transparent oil (69 mg, 56%) after purification by flash column chromatography on silica gel (hexanes:EtOAc:Et_3N (15:4:1), R_f = 0.3, $KMnO_4$ stain). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.52 (d, J = 5.8 Hz, 1H), 6.19 (d, J = 5.7 Hz, 1H), 4.86 (m, 1H), 3.78 (dd, J = 14.5, 7.0 Hz, 1H), 3.71 (d, J = 11.1 Hz, 1H), 3.66 (dd, J = 11.1, 3.3 Hz, 1H), 3.42 (dd, J = 14.5, 4.6 Hz, 1H), 3.32 (dd, J = 7.9, 6.9 Hz, 1H), 2.71 (d, J = 2.1 Hz, 1H), 2.38 (d, J = 7.2 Hz, 2H), 2.08 (dd, J = 10.5, 8.3 Hz, 1H), 1.97 (m, 1H), 1.87 (m, 1H), 1.67 (m, 2H), 1.64 (m, 1H), 1.61 (m, 1H), 1.45 (dd, J = 11.3, 3.1 Hz, 1H), 1.44 (m, 1H), 1.41 (s, 9H), 1.36 (dd, J = 11.5, 7.5 Hz, 1H), 1.21 (m, 2H), 1.14 (m, 1H), 0.84 (m, 1H), 0.79 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.0, 136.8, 136.1, 98.6, 90.7, 79.3, 65.9, 61.1, 59.4, 57.9, 45.8, 42.5, 36.5, 32.2, 31.9, 31.2, 28.3, 26.7, 26.0, 25.8; MS (ESI) calcd for $C_{22}H_{37}N_2O_4$ $[M+H]^+$ 393.3, found 393.3.

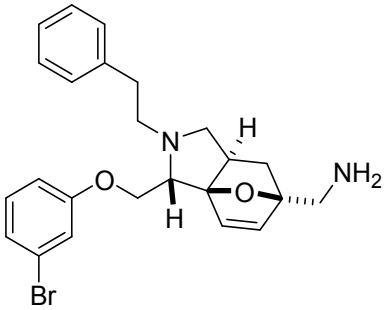
***tert*-butyl (((3*S*,3a*R*,6*R*,7a*R*)-2-(4-fluorobenzyl)-3-(hydroxymethyl)-2,3,7,7a-tetrahydro-3a,6-epoxyisoindol-6(1*H*)-yl)methyl)carbamate (*rac.*) (10f)**



General procedure III was followed using **9** (92 mg, 0.31 mmol), 4-fluorobenzaldehyde (67 μL, 0.62 mmol) and $NaBH(OAc)_3$ (131 mg, 0.62 mmol) to give the title compound as a transparent oil (73 mg, 57%) after purification by flash column chromatography on silica gel (hexanes:EtOAc:Et_3N (15:4:1), R_f = 0.3, $KMnO_4$ stain). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 (dd, J = 8.5, 5.5 Hz, 2H), 7.00 (t, J = 8.7 Hz, 2H), 6.56 (d, J = 5.8 Hz, 1H), 6.23 (d, J = 5.7 Hz, 1H), 4.84 (m, 1H), 3.90 (d, J = 12.9 Hz, 1H), 3.81 (dd, J = 14.7, 7.2 Hz, 1H), 3.77 (d, J = 11.6 Hz, 1H), 3.64 (dd, J = 11.3, 3.4 Hz, 1H), 3.57 (d, J = 12.9 Hz, 1H), 3.45 (dd, J = 14.4, 4.6 Hz, 1H), 3.16 (dd, J = 8.2, 7.0 Hz, 1H), 2.94 (d, J = 2.7 Hz, 1H), 2.19 (dd, J = 10.5, 8.6 Hz, 1H), 1.97 (m, 1H), 1.45 (m, 1H), 1.44 (s, 9H), 1.37 (dd, J = 11.4, 7.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.0 (d, J_{CF} = 245.4 Hz), 156.1, 136.7, 136.3, 134.5 (d, J_{CF} = 3.2 Hz), 130.1 (d, J_{CF} = 8.0 Hz), 115.3 (d, J_{CF} = 21.3 Hz), 98.9, 90.8, 79.4, 65.4, 59.6, 58.0, 57.7, 45.4, 42.5, 32.2, 28.3; MS (ESI) calcd for $C_{22}H_{30}FN_2O_4$ $[M+H]^+$ 405.2, found 405.3.

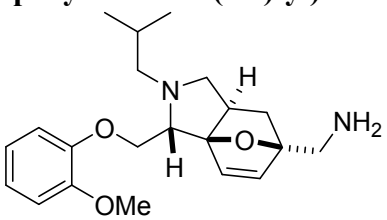
Mitsunobu Reaction and Boc-Deprotection

((3*S*,3a*R*,6*R*,7a*R*)-3-((3-bromophenoxy)methyl)-2-phenethyl-2,3,7,7a-tetrahydro-3a,6-epoxyisoindol-6(1*H*)-yl)methanamine (*rac.*) (11a)



General procedure IV: A stirred solution of **10a** (92 mg, 0.23 mmol, 1 equiv) in dry THF (2.1 mL, 0.11 M) as added 3-bromophenol (48 mg, 0.28 mmol, 1.2 equiv), PPh_3 (73 mg, 0.28 mmol, 1.2 equiv). DEAD (54 μL, 0.35 mmol, 1.5 equiv) in dry THF (309 μL, 0.94 M) was added dropwise and the reaction mixture was stirred at room temperature for 20 h, whereupon the volatiles were removed *in vacuo*. The residue was semi-purified by flash column chromatography on silica gel (hexanes:EtOAc:Et_3N (17:2:1)). The resulting residue was dissolved in CH_2Cl_2 (1.15 mL, 0.2 M) and the reaction mixture was cooled to 0 °C. TFA (1.15 μL, 0.1 M final concentration) was added and the reaction mixture was allowed to heat to room temperature and stirred for 1 h. The volatiles were removed *in vacuo*, and the residue was taken up in EtOAc (15 mL) and washed with satd. $NaHCO_3$ (aq) (10 mL). The organic layer was isolated and the aqueous phase was extracted with EtOAc (3x15 mL). The combined organic layers were dried over Na_2SO_4 and the volatiles were removed *in vacuo*. The residue was purified by flash column chromatography on silica gel (CH_2Cl_2:MeOH:NH_4OH (25% w/w, aq) (94:5:1), R_f = 0.1, $KMnO_4$ stain) to give the title compound as a transparent oil (59 mg, 57% over 2 steps). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24 (m, 2H), 7.17 (m, 2H), 7.17 (m, 1H), 7.10 (t, J = 7.8 Hz, 1H), 7.06 (m, 1H), 7.04 (m, 1H), 6.81 (ddd, J = 8.0, 2.2, 1.4 Hz, 1H), 6.36 (d, J = 5.8 Hz, 1H), 6.22 (d, J = 5.8 Hz, 1H), 3.95 (dd, J = 9.6, 4.5 Hz, 1H), 3.92 (dd, J = 9.6, 6.7 Hz, 1H), 3.43 (dd, J = 7.7, 7.1 Hz, 1H), 3.20 (d, J = 13.9 Hz, 1H), 3.16 (dd, J = 6.6, 4.6 Hz, 1H), 3.11 (d, J = 13.9 Hz, 1H), 3.03 (ddd, J = 11.7, 9.6, 6.9 Hz, 1H), 2.86 (ddd, J = 17.4, 12.1, 4.8 Hz, 1H), 2.79 (m, 2H), 2.30 (dd, J = 10.3, 8.2 Hz, 1H), 2.20 (m, 1H), 1.54 (dd, J = 11.4, 2.7 Hz, 1H), 1.39 (bs, 2H), 1.36 (dd, J = 11.3, 7.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.4, 140.2, 136.5, 135.7, 130.5, 128.6, 128.3, 126.0, 124.0, 122.7, 117.8, 113.5, 97.7, 92.3, 68.4, 63.7, 58.4, 57.2, 44.7, 44.2, 35.1, 32.1; MS (ESI) calcd for $C_{24}H_{28}BrN_2O_2$ $[M+H]^+$ 455.1, 457.1 found 455.2, 457.2.

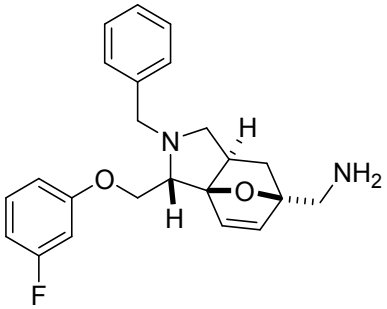
((3*S*,3a*R*,6*R*,7a*R*)-2-isobutyl-3-((2-methoxyphenoxy) methyl)-2,3,7,7a-tetrahydro-3a,6-epoxyisoindol-6(1*H*)-yl)methanamine (*rac.*) (11b)



General procedure IV was followed using **10b** (95 mg, 0.32 mmol), 2-methoxyphenol (29 mg, 0.23 mmol), PPh_3 (60 mg, 0.23 mmol) and DEAD (45 μL, 0.29 mmol) to give the title compound as a transparent oil (27 mg, 60% over 2 steps) after purification by flash column chromatography on silica gel (CH_2Cl_2:MeOH:NH_4OH (25% w/w, aq) (94:5:1), R_f = 0.4 (CH_2Cl_2:MeOH:NH_4OH (25% w/w, aq) (88:10:1)), $KMnO_4$ stain). ^{1}H NMR (400 MHz,

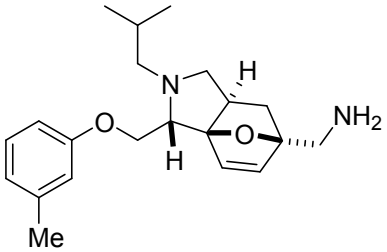
$CDCl_3$) δ 6.97 (m, 1H), 6.94 (m, 1H), 6.90 (m, 1H), 6.901 (m, 1H), 6.60 (d, J = 5.8 Hz, 1H), 6.22 (d, J = 5.8 Hz, 1H), 4.07 (dd, J = 9.9, 4.8 Hz, 1H), 4.04 (dd, J = 9.8, 7.0 Hz, 1H), 3.82 (s, 3H), 3.33 (dd, J = 7.4, 6.6 Hz, 1H), 3.23 (d, J = 13.9 Hz, 1H), 3.14 (dd, J = 6.9, 4.8 Hz, 1H), 3.12 (d, J = 13.6 Hz, 1H), 2.48 (m, 2H), 2.21 (m, 1H), 2.13 (dd, J = 10.3, 7.8 Hz, 1H), 1.85 (bs, 2H), 1.73 (m, 1H), 1.51 (dd, J = 11.3, 2.6 Hz, 1H), 1.36 (dd, J = 11.3, 7.3 Hz, 1H), 0.89 (d, J = 6.7 Hz, 3H), 0.88 (d, J = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.0, 148.6, 136.5, 135.7, 121.6, 120.9, 114.8, 112.6, 98.0, 92.0, 70.0, 64.5, 64.4, 58.8, 56.0, 44.7, 44.2, 32.3, 27.4, 21.1, 20.4; MS (ESI) calcd for $C_{21}H_{31}N_2O_3$ $[M+H]^+$ 359.2, found 359.2.

((3*S*,3a*R*,6*R*,7a*R*)-2-benzyl-3-((3-fluorophenoxy)-methyl)-2,3,7,7a-tetrahydro-3a,6-epoxyisoindol-6-(1*H*)-yl)methanamine (*rac.*) (11c)



General procedure IV was followed using **10c** (58 mg, 0.15 mmol), 3-fluorophenol (16 μL, 0.18 mmol), PPh_3 (47 mg, 0.18 mmol) and DEAD (35 μL, 0.23 mmol) to give the title compound as a transparent oil (19 mg, 34% over 2 steps) after purification by flash column chromatography on silica gel (CH_2Cl_2:MeOH:NH_4OH (25% w/w, aq) (94:5:1), R_f = 0.5 (CH_2Cl_2:MeOH:NH_4OH (25% w/w, aq) (88:10:1)), $KMnO_4$ stain). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37–7.21 (m, 5H), 7.20 (m, 1H), 6.66 (m, 2H), 6.60 (dt, J = 10.9, 2.3 Hz, 1H), 6.44 (d, J = 5.8 Hz, 1H), 6.25 (d, J = 5.8 Hz, 1H), 4.03 (d, J = 13.2 Hz, 1H), 3.99 (dd, J = 10.0, 4.5 Hz, 1H), 3.93 (dd, J = 9.7, 7.1 Hz, 1H), 3.74 (d, J = 13.0 Hz, 1H), 3.28 (dd, J = 7.1, 4.2 Hz, 1H), 3.24 (dd, J = 8.1, 6.8 Hz, 1H), 3.24 (d, J = 13.9 Hz, 1H), 3.14 (d, J = 13.9 Hz, 1H), 2.27 (dd, J = 10.4, 8.2 Hz, 1H), 2.19 (m, 1H), 1.53 (bs, 2H), 1.52 (dd, J = 11.3, 2.6 Hz, 1H), 1.35 (dd, J = 11.3, 7.3 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.6 (d, J_{CF} = 245.2 Hz), 160.0 (d, J_{CF} = 10.9 Hz), 139.2, 136.4, 135.9, 130.1 (d, J_{CF} = 10.1 Hz), 128.8, 128.3, 127.1, 110.4 (d, J_{CF} = 2.8 Hz), 107.7 (d, J_{CF} = 21.3 Hz), 102.4 (d, J_{CF} = 24.8 Hz), 98.2, 92.3, 68.6, 63.6, 59.9, 58.9, 44.6, 44.2, 32.0; MS (ESI) calcd for $C_{23}H_{26}FN_2O_2$ $[M+ H]^+$ 381.2, found 381.2.

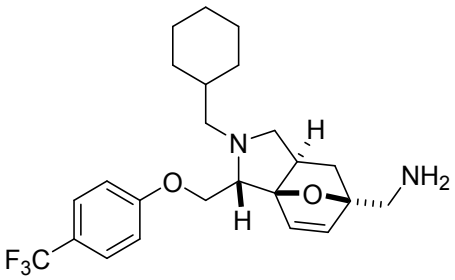
((3*S*,3a*R*,6*R*,7a*R*)-2-isobutyl-3-((*m*-tolyloxy)methyl)-2,3,7,7a-tetrahydro-3a,6-epoxyisoindol-6-(1*H*)-yl)methanamine (*rac.*) (11d)



General procedure IV was followed using **10b** (67 mg, 0.19 mmol), 3-methylphenol (24 μL, 0.23 mmol), PPh_3 (60 mg, 0.23 mmol) and DEAD (45 μL, 0.29 mmol) to give the title compound as a transparent oil (42 mg, 64% over 2 steps) after purification by flash column chromatography on silica gel (CH_2Cl_2:MeOH:NH_4OH (25% w/w, aq) (94:5:1), R_f = 0.1, $KMnO_4$ stain). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.16 (t, J = 7.9 Hz, 1H), 6.77 (s, 1H), 6.77 (m,

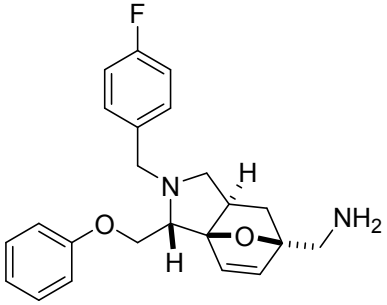
1H), 6.75 (m, 1H), 6.44 (d, *J* = 5.8 Hz, 1H), 6.21 (d, *J* = 5.8 Hz, 1H), 4.03 (dd, *J* = 9.6, 3.9 Hz, 1H), 3.95 (dd, *J* = 9.6, 7.9 Hz, 1H), 3.34 (dd, *J* = 6.4, 5.5 Hz, 1H), 3.22 (d, *J* = 13.9 Hz, 1H), 3.12 (d, *J* = 13.5 Hz, 1H), 3.09 (dd, *J* = 7.5, 3.5 Hz, 1H), 2.50 (dd, *J* = 12.2, 5.8 Hz, 1H), 2.45 (dd, *J* = 12.1, 9.2 Hz, 1H), 2.33 (s, 3H), 2.18 (m, 1H), 2.16 (m, 1H), 1.74 (m, 1H), 1.53 (dd, *J* = 11.2, 2.2 Hz, 1H), 1.42 (bs, 2H), 1.35 (dd, *J* = 11.3, 7.2 Hz, 1H), 0.91 (d, *J* = 6.5 Hz, 3H), 0.89 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.8, 139.4, 136.3, 136.0, 129.1, 121.6, 115.5, 111.3, 98.0, 92.2, 68.2, 64.6, 64.4, 58.6, 44.7, 44.3, 32.1, 27.4, 21.5, 21.1, 20.5; MS (ESI) calcd for $C_{21}H_{31}N_2O_2$ $[M+H]^+$ 343.2, found 343.3.

((3*S*,3a*R*,6*R*,7a*R*)-2-(cyclohexylmethyl)-3-((4-(trifluoromethyl)phenoxy)methyl)-2,3,7,7a-tetrahydro-3a,6-epoxyisoindol-6(1*H*)-yl)methanamine (*rac.*) (11e)



General procedure IV was followed using **10e** (90 mg, 0.23 mmol), 4-(trifluoromethyl)phenol (45 mg, 0.28 mmol), PPh_3 (73 mg, 0.28 mmol) and DEAD (54 μL, 0.35 mmol) to give the title compound as a transparent oil (70 mg, 71% over 2 steps) after purification by flash column chromatography on silica gel (CH_2Cl_2:MeOH:NH_4OH (25% w/w, aq) (94:5:1), R_f = 0.2, $KMnO_4$ stain). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (d, *J* = 8.6 Hz, 2H), 6.99 (d, *J* = 8.6 Hz, 2H), 6.38 (d, *J* = 5.8 Hz, 1H), 6.22 (d, *J* = 5.8 Hz, 1H), 4.06 (dd, *J* = 9.6, 4.0 Hz, 1H), 3.99 (dd, *J* = 9.6, 7.8 Hz, 1H), 3.33 (m, 1H), 3.21 (d, *J* = 13.9 Hz, 1H), 3.12 (d, *J* = 13.7 Hz, 1H), 3.09 (dd, *J* = 7.8, 4.0 Hz, 1H), 2.53 (dd, *J* = 12.1, 9.2 Hz, 1H), 2.47 (dd, *J* = 12.1, 5.2 Hz, 1H), 2.16 (m, 1H), 2.15 (m, 1H), 1.90 (m, 1H), 1.672 (m, 2H), 1.666 (m, 1H), 1.64 (m, 1H), 1.52 (dd, *J* = 11.3, 1.9 Hz, 1H), 1.44 (bs, 2H), 1.43 (m, 1H), 1.34 (dd, *J* = 11.3, 7.1 Hz, 1H), 1.22 (m, 2H), 1.14 (m, 1H), 0.86 (m, 1H), 0.78 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.2 (m), 136.3, 135.8, 126.8 (q, J_{CF} = 3.8 Hz), 124.4 (q, J_{CF} = 271.1 Hz), 122.9 (q, J_{CF} = 32.7 Hz), 114.5, 97.8, 92.3, 68.5, 64.4, 63.0, 58.7, 44.8, 44.2, 36.9, 31.9, 31.5, 26.8, 26.1, 25.9; MS (ESI) calcd for $C_{24}H_{32}F_3N_2O_2$ $[M+H]^+$ 437.2 found 437.4.

((3*S*,3a*R*,6*R*,7a*R*)-2-(4-fluorobenzyl)-3-(phenoxymethyl)-2,3,7,7a-tetrahydro-3a,6-epoxyisoindol-6-(1*H*)-yl)methanamine (*rac.*) (11f)

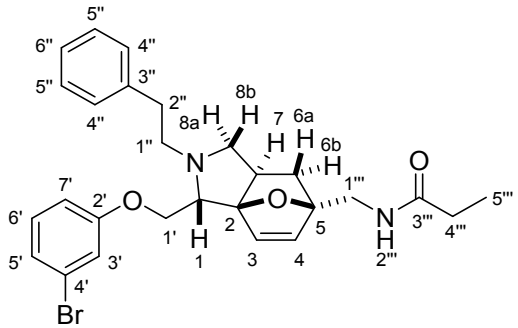


General procedure IV was followed using **10f** (73 mg, 0.15 mmol), phenol (20 mg, 0.22 mmol), PPh_3 (58 mg, 0.22 mmol) and DEAD (42 μL, 0.27 mmol) to give the title compound as a transparent oil (38 mg, 56% over 2 steps) after purification by flash column chromatography on silica gel (CH_2Cl_2:MeOH:NH_4OH (25% w/w, aq) (94:5:1), R_f = 0.5 (CH_2Cl_2:MeOH:NH_4OH (25% w/w, aq) (88:10:1)), $KMnO_4$ stain). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 (m, 2H), 7.25 (m, 2H), 6.96 (t, *J* = 7.8 Hz, 2H), 6.93 (dd, *J* = 7.0, 1.4 Hz, 1H),

6.88 (dd, J = 8.6, 0.9 Hz, 2H), 6.44 (d, J = 5.8 Hz, 1H), 6.22 (d, J = 5.8 Hz, 1H), 4.02 (dd, J = 9.6, 4.4 Hz, 1H), 4.01 (d, J = 13.3 Hz, 1H), 3.97 (dd, J = 9.7, 6.9 Hz, 1H), 3.67 (d, J = 13.0 Hz, 1H), 3.26 (dd, J = 6.8, 4.4 Hz, 1H), 3.21 (d, J = 13.9 Hz, 1H), 3.18 (dd, J = 6.1, 4.7 Hz, 1H), 3.12 (d, J = 13.9 Hz, 1H), 2.21 (m, 1H), 2.18 (m, 1H), 1.49 (dd, J = 11.4, 2.3 Hz, 1H), 1.33 (dd, J = 11.3, 7.2 Hz, 1H), 1.52 (bs, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.9 (d, J_{CF} = 244.8 Hz), 158.7, 136.3, 136.0, 135.0 (d, J_{CF} = 3.1 Hz), 130.2 (d, J_{CF} = 7.9 Hz), 129.4, 120.9, 115.0 (d, J_{CF} = 21.2 Hz), 114.6, 98.1, 92.3, 68.3, 63.7, 59.0, 58.7, 44.6, 44.2, 32.0; MS (ESI) calcd for $C_{23}H_{26}FN_2O_2$ $[M+H]^+$ 381.2, found 381.2.

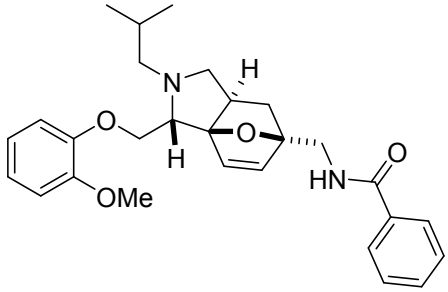
Functionalization of Primary Amines

_N_-(((3_S_,3a_R_,6_R_,7a_R_)-3-((3-bromophenoxy)-methyl)-2-phenethyl-2,3,7,7a-tetrahydro-3a,6- epoxyisoindol-6(1_H_)-yl)methyl)propionamide (_rac._) (12a)



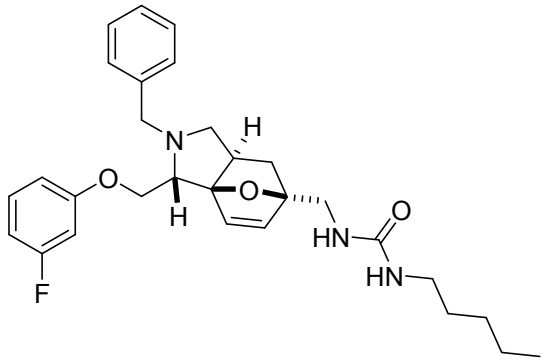
General procedure V: A stirred solution of **11a** (59 mg, 0.13 mmol, 1 equiv) in dry CH_2Cl_2 (2.6 mL, 0.05 M) was added propanoic acid (11 μL, 0.14 mmol, 1.1 equiv), DIPEA (25 μL, 0.14 mmol, 1.1 equiv) and PyBOP (73 mg, 0.14 mmol, 1.1 equiv). The reaction mixture was stirred at room temperature for 21 h, whereupon the volatiles were removed *in vacuo*. The residue was purified by flash column chromatography on silica gel (hexanes:EtOAc:Et_3N (10:10:1), R_f = 0.4, $KMnO_4$ stain) to give the title compound as a transparent oil (47 mg, 71%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24 (m, 2H, 5''), 7.17 (m, 2H, 4''), 7.16 (m, 1H, 6''), 7.11 (t, J = 7.9 Hz, 1H, 6'), 7.06 (dt, J = 7.9, 1.3 Hz, 1H, 5'), 7.03 (m, 1H, 3'), 6.80 (ddd, J = 8.0, 2.3, 1.2 Hz, 1H, 7'), 6.34 (d, J = 5.8 Hz, 1H, 3), 6.17 (d, J = 5.8 Hz, 1H, 4), 5.79 (dd, J = 5.9, 4.4 Hz, 1H, 2'''), 4.05 (dd, J = 14.5, 7.0 Hz, 1H, 1'''a), 3.93 (dd, J = 9.7, 4.3 Hz, 1H. 1'a), 3.89 (dd, J = 9.7, 7.3 Hz, 1H, 1'b), 3.50 (dd, J = 14.6, 4.2 Hz, 1H, 1'''b), 3.43 (t, J = 7.1 Hz, 1H, 8a), 3.12 (dd, J = 7.1, 4.2 Hz, 1H, 1), 3.02 (ddd, J = 12.2, 9.8, 7.0 Hz, 1H, 1''a), 2.83 (m, 1H, 1''b), 2.78 (m, 2H, 2''), 2.26 (m, 1H, 8b), 2.20 (q, J = 7.6 Hz, 2H, 4'''), 2.18 (m, 1H, 7), 1.50 (dd, J = 11.6, 2.6 Hz, 1H, 6a), 1.42 (dd, J = 11.5, 7.2 Hz, 1H, 6b), 1.13 (t, J = 7.5 Hz, 3H, 5'''); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.9 (1C, 3''), 159.3 (1C, 2'), 140.1 (1C, 3''), 136.3 (1C, 4), 135.9 (1C, 3), 130.5 (1C, 6'), 128.6 (2C, 4''), 128.3 (2C, 5''), 126.0 (1C, 6''), 124.1 (1C, 5'), 122.8 (1C, 4'), 117.8 (1C, 3'), 113.4 (1C, 7'), 98.0 (1C, 2), 90.5 (1C, 5), 68.3 (1C, 1'), 63.7 (1C, 1), 58.3 (1C, 8), 57.1 (1C, 1''), 44.6 (1C, 7), 41.0 (1C, 1'''), 35.1 (1C, 2''), 32.4 (1C, 6), 29.6 (1C, 4'''), 9.9 (1C, 5''')MS (ESI) calcd for $C_{27}H_{32}BrN_2O_3$ $[M+ H]^+$ 511.2, 513.2, found 511.2, 513.2.

***N*-(((3*S*,3a*R*,6*R*,7a*R*)-2-isobutyl-3-((2-methoxyphenoxy)methyl)-2,3,7,7a-tetrahydro-3a,6-epoxyisoindol-6(1*H*)-yl)methyl)benzamide (*rac.*) (12b)**



General procedure V was followed using **11b** (27 mg, 0.075 mmol), benzoic acid (10 mg, 0.083 mmol), DIPEA (14 μL, 0.083 mmol) and PyBOP (43 mg, 0.083 mmol) to give the title compound as a transparent oil (23 mg, 66%) after purification by flash column chromatography on silica gel (hexanes:EtOAc:Et_3N (10:10:1), R_f = 0.4, $KMnO_4$ stain). ^1H NMR (400 MHz, $CDCl_3$) δ 7.79 (m, 2H), 7.54–7.36 (m, 3H), 6.98 (m, 1H), 6.94 (m, 1H), 6.91 (m, 1H), 6.90 (m, 1H), 6.62 (d, J = 5.8 Hz, 1H), 6.52 (m, 1H), 6.23 (d, J = 5.8 Hz, 1H), 4.30 (dd, J = 14.5, 7.1 Hz, 1H), 4.08 (dd, J = 9.8, 4.3 Hz, 1H), 4.03 (dd, J = 9.7, 7.9 Hz, 1H), 3.80 (s, 3H), 3.72 (dd, J = 14.5, 4.0 Hz, 1H), 3.35 (dd, J = 7.6, 7.0 Hz, 1H), 3.16 (dd, J = 7.8, 4.2 Hz, 1H), 2.49 (d, J = 7.3 Hz, 2H), 2.23 (m, 1H), 2.14 (dd, J = 10.3, 8.1 Hz, 1H), 1.74 (m, 1H), 1.58 (dd, J = 11.4, 2.7 Hz, 1H), 1.49 (dd, J = 11.4, 7.3 Hz, 1H), 0.90 (d, J = 6.5 Hz, 3H), 0.89 (d, J = 6.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.7, 150.0, 148.5, 136.8, 135.5, 134.3, 131.5, 128.5, 127.0, 121.8, 121.0, 114.9, 112.6, 98.3, 90.3, 70.0, 64.5, 64.4, 58.8, 56.0, 44.6, 41.7, 32.6, 27.4, 21.1, 20.4; MS (ESI) calcd for $C_{28}H_{35}N_2O_4$ $[M+H]^+$ 463.3 found 463.4.

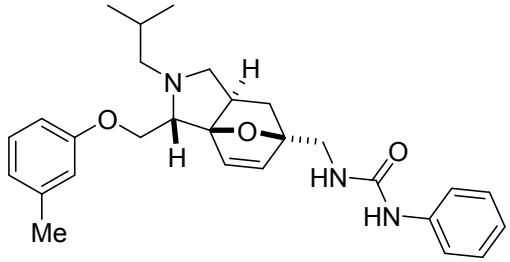
1-(((3*S*,3a*R*,6*R*,7a*R*)-2-benzyl-3-((3-fluorophenoxy)methyl)-2,3,7,7a-tetrahydro-3a,-6-epoxyisoindol-6(1*H*)-yl)methyl)-3-pentylurea (*rac.*) (12c)



General procedure VI: A stirred solution of **11c** (17 mg, 0.050 mmol, 1 equiv) in dry CH_2Cl_2 (1.0 mL, 0.05 M) was added pentyl isocyanate (7 μL, 0.055 mmol, 1.1 equiv) and DIPEA (10 μL, 0.055 mmol, 1.1 equiv). The reaction mixture was stirred at room temperature for 21 h, whereupon the volatiles were removed *in vacuo*. The residue was purified by flash column chromatography on silica gel (hexanes:EtOAc:Et_3N (10:10:1), R_f = 0.2, $KMnO_4$ stain) to give the title compound as a transparent oil (19 mg, 79%). ^1H NMR (400 MHz, $CDCl_3$) δ 7.35–7.24 (m, 5H), 7.20 (m, 1H), 6.66 (m, 1H), 6.65 (m, 1H), 6.58 (dt, J = 10.9, 2.3 Hz, 1H), 6.40 (d, J = 5.8 Hz, 1H), 6.24 (d, J = 5.8 Hz, 1H), 4.68 (m, 1H), 4.54 (bs, 1H), 4.02 (d, J = 12.9 Hz, 1H), 3.98 (dd, J = 9.8, 4.0 Hz, 1H), 3.95 (dd, J = 14.6, 7.3 Hz, 1H), 3.92 (dd, J = 9.3, 7.5 Hz, 1H), 3.72 (d, J = 13.0 Hz, 1H), 3.51 (dd, J = 14.6, 4.5 Hz, 1H), 3.24 (dd, J = 7.2, 5.0 Hz, 2H), 3.16 (dd, J = 12.9, 7.0 Hz, 2H), 2.24 (dd, J = 10.2, 7.8 Hz, 1H), 2.18 (m, 1H), 1.53 (dd, J = 11.7, 2.5 Hz, 1H), 1.49 (m, 2H), 1.39 (dd, J = 11.5, 7.1 Hz, 1H), 1.32 (m, 2H), 1.30 (m, 2H), 0.89 (dd, J = 8.3, 5.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.6 (d, J_{CF} = 245.3

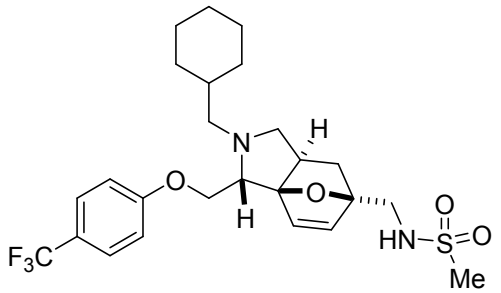
Hz), 159.9 (d, J_{CF} = 10.8 Hz), 158.3, 139.0, 136.5, 135.7, 130.2 (d, J_{CF} = 10.0 Hz), 128.8, 128.4, 127.2, 110.3 (d, JCF = 2.8 Hz), 107.8 (d, J_{CF} = 21.3 Hz), 102.4 (d, J_{CF} = 24.8 Hz), 98.4, 91.3, 68.5, 63.6, 59.9, 58.9, 44.5, 42.3, 40.6, 32.0, 29.8, 29.0, 22.4, 14.0; MS (ESI) calcd for $C_{29}H_{37}FN_3O_3$ $[M+H]^+$ 494.3 found 494.4.

1-(((3*S*,3a*R*,6*R*,7a*R*)-2-isobutyl-3-((*m*-tolyloxy)methyl)-2,3,7,7a-tetrahydro-3a,6-epoxy-isoindol-6(1*H*)-yl)methyl)-3-phenylurea (*rac.*) (12d)



General procedure VI was followed using **11d** (41 mg, 0.12 mmol), phenyl isocyanate (14 μL, 0.13 mmol) and DIPEA (23 μL, 0.13 mmol) to give the title compound as a transparent oil (49 mg, 86%) after purification by flash column chromatography on silica gel (hexanes:EtOAc:Et_3N (11:8:1), R_f = 0.3, $KMnO_4$ stain). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 (dd, J = 8.4, 0.9 Hz, 1H), 7.24 (m, 2H), 7.16 (td, J = 7.6, 1.5 Hz, 1H), 7.01 (t, J = 7.3 Hz, 1H), 6.78 (d, J = 7.4 Hz, 1H), 6.72 (s, 1H), 6.71 (m, 1H), 6.44 (d, J = 5.8 Hz, 1H), 6.28 (d, J = 5.8 Hz, 1H), 5.73 (t, J = 5.5 Hz, 1H), 4.02 (dd, J = 14.4, 6.1 Hz, 1H), 3.99 (dd, J = 9.7, 4.2 Hz, 1H), 3.91 (dd, J = 9.4, 8.6 Hz, 1H), 3.60 (dd, J = 14.8, 4.7 Hz, 1H), 3.32 (dd, J = 7.4, 6.7 Hz, 1H), 3.04 (dd, J = 8.3, 3.8 Hz, 1H), 2.43 (dd, J = 11.9, 5.8 Hz, 1H), 2.39 (dd, J = 11.7, 9.1 Hz, 1H), 2.32 (s, 3H), 2.17 (m, 1H), 2.11 (m, 1H), 1.71 (m, 1H), 1.58 (dd, J = 11.5, 2.4 Hz, 1H), 1.42 (dd, J = 11.4, 7.3 Hz, 1H), 0.91 (d, J = 6.5 Hz, 1H), 0.88 (d, J = 6.6 Hz, 1H); 13C NMR (100 MHz, CDCl3) δ 158.5, 156.2, 139.5, 138.8, 136.24, 136.19, 129.2, 129.0, 123.1, 121.7, 120.3, 115.4, 111.3, 98.3, 91.2, 68.0, 64.6, 64.4, 58.6, 44.6, 42.1, 32.1, 27.4, 21.5, 21.1, 20.4; MS (ESI) calcd for $C_{28}H_{36}N_3O_3$ $[M+H]^+$ 462.3 found 462.4.

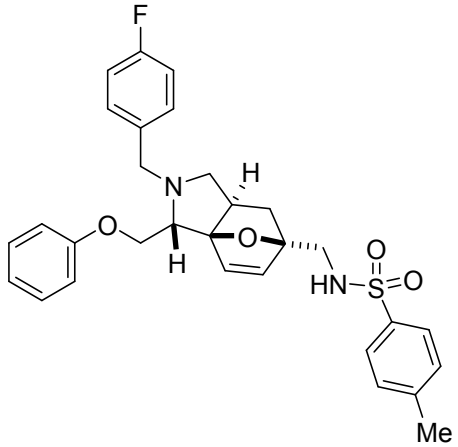
***N*-(((3*S*,3a*R*,6*R*,7a*R*)-2-(cyclohexylmethyl)-3-((4-(trifluoromethyl)phenoxy)methyl)-2,3,-7,7a-tetrahydro-3a,6-epoxyisoindol-6(1*H*)-yl)-methyl)methanesulfonamide (*rac.*) (12e)**



General procedure VII: A stirred solution of **11e** (74 mg, 0.16 mmol, 1 equiv) in dry CH_2Cl_2 (3.2 mL, 0.05 M) was added methanesulfonyl chloride (14 μL, 0.18 mmol, 1.1 equiv) and DIPEA (31 μL, 0.18 mmol, 1.1 equiv). The reaction mixture was stirred at room temperature for 21 h, whereupon the volatiles were removed *in vacuo*. The residue was purified by flash column chromatography on silica gel (hexanes:EtOAc:Et_3N (11:8:1), R_f = 0.4, $KMnO_4$ stain) to give the title compound as a transparent oil (65 mg, 78%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 (d, J = 8.6 Hz, 2H), 6.99 (d, J = 8.6 Hz, 2H), 6.40 (d, J = 5.8 Hz, 1H), 6.23 (d, J = 5.8 Hz, 1H), 4.79 (bs, 1H), 4.07 (dd, J = 9.7, 3.8 Hz, 1H), 3.98 (dd, J = 9.5, 8.1 Hz, 1H), 3.74 (d, J = 13.6 Hz, 1H), 3.57 (d, J = 13.6 Hz, 1H), 3.34 (dd, J = 7.4, 6.6 Hz, 1H), 3.05 (dd, J = 7.9, 3.8 Hz, 1H), 3.00 (s, 3H), 2.52 (dd, J = 11.9, 9.4 Hz, 1H), 2.45 (dd, J = 12.1, 5.0 Hz, 1H), 2.18 (m, 1H), 2.12 (dd, J = 10.3, 7.9 Hz, 1H), 1.90 (m, 1H), 1.69 (m, 2H), 1.67 (m, 1H), 1.66

(m, 1H), 1.62 (dd, J = 11.6, 2.5 Hz, 1H), 1.44 (m, 1H), 1.41 (dd, J = 11.4, 7.3 Hz, 1H), 1.23 (m, 2H), 1.16 (m, 1H), 0.87 (m, 1H), 0.80 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.0 (m), 136.2, 135.5, 126.9 (q, J_{CF} = 3.8 Hz), 124.3 (q, J_{CF} = 271.1Hz), 123.1 (q, J_{CF} = 32.7 Hz), 114.5, 98.2, 89.6, 68.3, 64.3, 62.9, 58.6, 44.9, 44.7, 40.5, 36.9, 32.0, 31.9, 31.4, 26.7, 26.1, 25.9; MS (ESI) calcd for $C_{25}H_{34}F_3N_2O_4S$ $[M+H]^+$ 515.2 found 515.3.

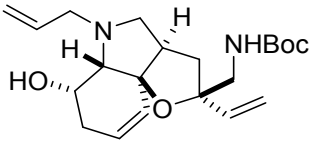
_N_-(((3_S_,3a_R_,6_R_,7a_R_)-2-(4-fluorobenzyl)-3-(phenoxymethyl)-2,3,7,7a-tetrahydro-3a,6-epoxyisoindol-6(1_H_)-yl)methyl)-4-methylbenzenesulfonamide (_rac._) (12f)



General procedure VII was followed using **11f** (38 mg, 0.10 mmol), _p_-toluenesulfonyl chloride (21 mg, 0.11 mmol) and DIPEA (19 μL, 0.11 mmol) to give the title compound as a transparent oil (42 mg, 78%) after purification by flash column chromatography on silica gel (hexanes:EtOAc:Et_3N (10:10:1), R_f = 0.3, $KMnO_4$ stain). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (d, J = 8.2 Hz, 2H), 7.32 (d, J = 8.1 Hz, 2H), 7.29 (m, 2H), 7.28 (m, 2H), 6.98 (t, J = 8.7 Hz, 2H), 6.96 (m, 1H), 6.89 (dd, J = 8.7, 0.9 Hz, 2H), 6.42 (d, J = 5.8 Hz, 1H), 6.11 (d, J = 5.8 Hz, 1H), 4.85 (bs, 1H), 4.02 (dd, J = 9.7, 4.1 Hz, 1H), 3.99 (d, J = 13.7 Hz, 1H), 3.95 (dd, J = 9.9, 7.5 Hz, 1H), 3.64 (d, J = 13.1 Hz, 1H), 3.52 (d, J = 13.0 Hz, 1H), 3.37 (d, J = 13.0 Hz, 1H), 3.19 (dd, J = 7.2, 4.3 Hz, 1H), 3.16 (d, J = 1.1 Hz, 1H), 2.44 (s, 3H), 2.17 (m, 2H), 1.57 (dd, J = 11.6, 1.7 Hz, 1H), 1.35 (dd, J = 11.4, 6.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.9 (d, JCF = 244.9 Hz), 158.5, 143.5, 136.6, 136.0, 135.6, 134.8 (d, J_{CF} = 3.1 Hz), 130.2 (d, J_{CF} = 7.9 Hz), 129.7, 129.4, 127.1, 121.0, 115.1 (d, J_{CF} = 21.2 Hz), 114.5, 98.5, 89.3, 68.0, 63.5, 58.8, 58.4, 44.9, 44.4, 31.9, 21.5; MS (ESI) calcd for $C_{30}H_{32}FN_2O_4S$ $[M+H]^+$ 535.2 found 535.3.

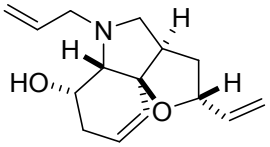
Synthesis of ROM-RCM Cascade Products

***tert*-butyl (((2*R*,3a*R*,5a*S*,6*S*,9a*R*)-5-allyl-6-hydroxy-2-vinyl-2,3,3a,4,5,5a,6,7-octahydrofuro[3,2-*c*]indol-2- yl)methyl)carbamate (*rac.*) (13a)**



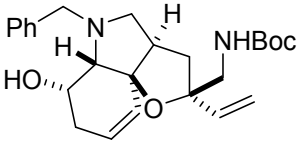
General procedure VIII: A stirred solution of **8d** (499 mg, 1.33 mmol, 1 equiv) in CH_2Cl_2 (133 mL, 0.01 M) was added 1 M HCl (1325 µL, 1.33 mmol, 1M in Et_2O, 1 equiv) followed by the Grubbs II catalyst (113 mg, 0.0133 mmol, 0.1 equiv). The reaction mixture was heated to reflux for 15 h, whereupon it was cooled to room temperature and satd. $NaHCO_3$ (aq) (60 mL) was added under stirring. The organic layer was separated and the aqueous phase was extracted with CH_2Cl_2 (3×25 mL). The combined organic layers were dried over Na_2SO_4 and the volatiles were removed *in vacuo*. The residue was purified by flash column chromatography on silica gel (heptane:EtOAc:Et_3N (30:30:15), R_f= 0.4 (heptane:EtOAc (1:3)), $KMnO_4$ stain) to give the title compound as a slightly brown solid (217 mg, 62%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.96–5.82 (m, 2H), 5.73–5.60 (m, 2H), 5.30–5.17 (m, 3H), 5.16–5.04 (m, 2H), 4.04–3.98 (m, 1H), 3.49 (dd, J = 13.8, 5.5 Hz, 1H), 3.31–3.17 (m, 4H), 3.06 (d, J = 3.5 Hz, 1H), 2.57 (t, J = 8.5 Hz, 1H), 2.52–2.44 (m, 1H), 2.34 (dt, J = 17.3, 4.6 Hz, 1H), 2.27–2.15 (m, 2H), 1.93 (dd, J = 13.4, 2.7 Hz, 1H), 1.42 (s, 9H); ^{13}C NMR (100 MHz, CDCl3) δ 156.4, 143.2, 135.4, 129.4, 124.3, 117.3, 114.0, 91.6, 86.5, 79.2, 69.8, 65.8, 58.1, 56.3, 49.4, 47.8, 38.1, 29.1, 28.5; MS (ESI) calcd for $C_{21}H_{33}N_2O_4$ $[M + H]^+$ 377.2, found 377.3; HRMS (ESI) calcd for $C_{21}H_{33}N_2O_4$ $[M + H]^+$ 377.2435 found 377.2438; IR (neat) cm^{-1}: 3260, 2970, 1703, 1547, 1389, 1363, 1273, 1136, 1082, 1042, 975, 907, 735; m.p. (EtOAc) 107–109 °C.

(2*R*,3a*R*,5a*S*,6*S*,9a*R*)-5-allyl-2-vinyl-2,3,3a,4,5,5a,6,7-octahydrofuro[3,2-*c*]indol 6-ol (*rac.*) (4)



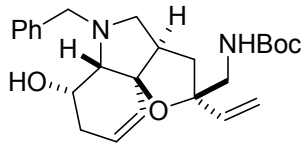
General procedure VIII was followed using **2** (267 mg, 1.08 mmol), 1 M HCl (1100 µL, 1.10 mmol, 1M in Et_2O) and the Grubbs II catalyst (46 mg, 0.0540 mmol) with a reaction time of 30 min to give the title compound as a white solid (180 mg, 76%) after purification by flash column chromatography on silica gel (heptane:EtOAc:Et_3N (30:30:1), R_f = 0.4 (heptane:EtOAc (1:3)), $KMnO_4$ stain. Spectroscopic data for **4** were in accordance with those reported using the initially used reaction conditions, see page 7.

***tert*-butyl(((2*R*,3a*R*,5a*S*,6*S*,9a*R*)-5-benzyl-6-hydroxy-2-vinyl-2,3,3a,4,5,5a,6,7-octahydro-furo[3,2-*c*]indol- 2-yl)methyl)carbamate (*rac.*) (13b)**



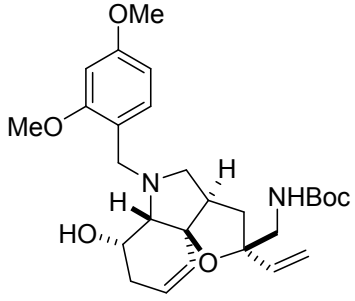
General procedure VIII was followed using **8e** (200 mg, 0.469 mmol), 1 M HCl (470 μL, 0.470 mmol, 1M in Et_2O) and the Grubbs II catalyst (20 mg, 0.0234 mmol) with a reaction time of 18 h to give the title compound as a white solid (144 mg, 72%) after aqueous work-up and flash column chromatography on silica gel (heptane:EtOAc:Et_3N (15:5:2), R_f = 0.5 (heptane:EtOAc (1:1)), $KMnO_4$ stain). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29–7.22 (m, 4H), 7.21–7.16 (m, 1H), 5.81 (dd, J = 17.3, 10.8 Hz, 1H), 5.67–5.56 (m, 2H), 5.26–5.15 (m, 2H), 5.04 (d, J = 10.8 Hz, 1H), 4.07 (d, J = 13.0 Hz, 1H), 3.94–3.89 (m, 1H), 3.59 (d, J = 13.1 Hz, 1H), 3.22–3.10 (m, 3H), 3.07 (d, J = 3.6 Hz, 1H), 2.58–2.47 (m, 1H), 2.46–2.37 (m, 1H), 2.30 (dt, J = 17.3, 4.6 Hz, 1H), 2.20–2.08 (m, 2H), 1.86 (dd, J = 13.4, 2.4 Hz, 1H), 1.37 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.4, 143.2, 138.7, 129.4, 128.9, 128.5, 127.3, 124.3, 114.0, 91.6, 86.4, 79.3, 70.1, 66.0, 58.4, 58.2, 49.5, 47.8, 38.2, 29.3, 28.6; MS (ESI) calcd for $C_{25}H_{35}N_2O_4$ $[M+H]^+$ 427.3, found 427.4; HRMS (ESI) calcd for $C_{25}H_{35}N_2O_4$ $[M+H]^+$ 427.2591 found 427.2610; IR (neat) cm^{-1}: 3297, 2922, 1702, 1536, 1389, 1365, 1253, 1157, 1083, 1039, 976, 931, 898, 729; m.p. (EtOAc) 178–181 ^{o}C.

***tert*-butyl (((2*R*,3a*R*,5a*S*,6*S*,9a*R*)-5-benzyl-6-hydroxy-2-vinyl-2,3,3a,4,5,5a,6,7-octahydrofuro[3,2-*c*]indol-2-yl)methyl)carbamate (*rac.*) (13b)**



General procedure IX: A stirred solution of **8e** (90 mg, 0.211 mmol, 1 equiv) in toluene (21 mL, 0.01 M) was added the Grubbs II catalyst (18 mg, 0.0211 mmol. 0.1 equiv). The reaction mixture was heated to reflux for 1 h, whereupon the volatiles were removed *in vacuo*. The residue was purified by flash column chromatography on silica gel (heptane:EtOAc:Et_3N (10:10:1), R_f = 0.2), $KMnO_4$ stain) to give the title compound as a slightly brown solid (72 mg, 80%). Spectroscopic data were in accordance with those reported using general procedure VIII, see page 23.

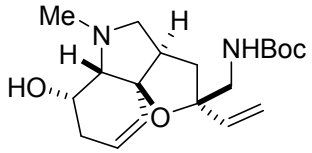
***tert*-butyl (((2*R*,3a*R*,5a*S*,6*S*,9a*R*)-5-(2,4-dimethoxybenzyl)-6-hydroxy-2-vinyl-2,3,3a,4,5,5a,6,7-octahydrofuro[3,2-*c*]indol-2-yl)methyl)carbamate (*rac.*) (13c)**



General procedure IX was followed using **8f** (200 mg, 0.411 mmol) and the Grubbs II catalyst (18 mg, 0.0210 mmol) with a reaction time of 1 h to give the title compound as a white semi-solid (151 mg, 76%) after purification by flash column chromatography on silica gel (heptane:EtOAc:Et_3N (10:10:1), R_f = 0.3, $KMnO_4$ stain). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.14 (d, J = 8.1 Hz, 1H), 6.46–6.40 (m, 2H), 5.86 (dd, J = 17.3, 10.8 Hz, 1H), 5.72–5.65 (m, 2H), 5.24 (dd, J = 17.3, 1.0 Hz, 1H), 5.10 (dd, J = 10.8, 1.0 Hz, 1H), 4.99–4.92 (m, 1H), 4.07 (d, J = 12.7 Hz, 1H), 4.01–3.95 (m, 1H), 3.80 (s, 3H), 3.80 (s, 3H), 3.53 (d, J = 12.7 Hz, 1H), 3.35–3.21 (m, 2H), 3.11 (d, J = 3.7 Hz, 1H), 3.07–3.00 (m, 1H), 2.60–2.53 (m, 1H), 2.44–2.34 (m, 2H), 2.23–2.15 (m, 2H), 1.90 (dd, J = 13.3, 2.8 Hz, 1H), 1.44 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.5, 158.8, 156.3, 143.2, 131.3, 129.2, 124.8, 119.5, 114.1, 103.7,

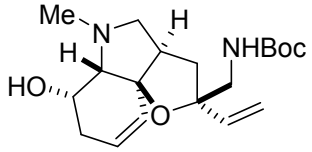
98.7, 91.6, 86.2, 79.3, 70.8, 65.5, 57.2, 55.5, 55.3, 53.6, 49.6, 48.0, 37.3, 28.7, 28.6; MS (ESI) calcd for $C_{27}H_{39}N_2O_6$ $[M+H]^+$ 487.3, found 487.4; HRMS (ESI) calcd for $C_{27}H_{39}N_2O_6$ $[M+ H]^+$ 487.2803 found 487.2842; IR (neat) cm^{-1}: 3434, 2932, 1710, 1611, 1505, 1365, 1248, 1207, 1154, 1033, 930, 834, 731, 642.

***tert*-butyl (((2*R*,3a*R*,5a*S*,6*S*,9a*R*)-6-hydroxy-5-methyl-2-vinyl-2,3,3a,4,5,5a,6,7-octahydrofuro[3,2-*c*]indol-2-yl)methyl)carbamate (*rac.*) (13d)**



General procedure VIII was followed using **8g** (100 mg, 0.285 mmol), 1 M HCl (290 μL, 0.290 mmol, 1M in Et_2O) and the Grubbs II catalyst (17 mg, 0.0200 mmol) with a reaction time of 18 h to give the title compound as a colorless semi-solid (65 mg, 65%) after aqueous work-up and flash column chromatography on silica gel (EtOAc:Et_3N (95:5), R_f = 0.2, $KMnO_4$ stain). ^1H NMR (400 MHz, $CDCl_3$) δ 5.84 (dd, J = 17.3, 10.8 Hz, 1H), 5.69–5.61 (m, 2H), 5.28–5.19 (m, 2H), 5.09 (d, J = 10.8 Hz, 1H), 4.11–4.01 (m, 1H), 3.31–3.18 (m, 3H), 2.80 (d, J = 2.9 Hz, 1H), 2.53–2.42 (m, 2H), 2.47 (s, 3H), 2.40–2.28 (m, 2H), 2.27–2.13 (m, 2H), 1.89 (dd, J = 13.2, 3.2 Hz, 1H), 1.41 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.4, 142.9, 129.7, 124.5, 114.1, 92.1, 87.3, 79.3, 72.5, 66.1, 61.4, 49.1, 47.8, 40.8, 38.6, 29.1, 28.5; MS (ESI) calcd for $C_{19}H_{31}N_2O_4$ $[M + H]^+$ 351.2, found 351.3; HRMS (ESI) calcd for $C_{19}H_{31}N_2O_4$ $[M+H]^+$ 351.2278 found 351.2321; IR (neat) cm^{-1}: 3351, 2975, 1697, 1633, 1507, 1365, 1247, 1164, 1018, 922, 729.

***tert*-butyl (((2*R*,3a*R*,5a*S*,6*S*,9a*R*)-6-hydroxy-5-methyl-2-vinyl-2,3,3a,4,5,5a,6,7-octahydrofuro[3,2-*c*]indol-2-yl)methyl)carbamate (*rac.*) (13d)**

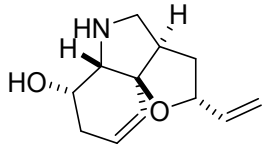


General procedure IX was followed using **8g** (147 mg, 0.419 mmol) and the Grubbs II catalyst (18 mg, 0.0210 mmol) with a reaction time of 1 h to give the title compound as a colorless semi-solid (82 mg, 56%) after purification by flash column chromatography on silica gel (EtOAc:Et_3N (95:5), R_f = 0.2, $KMnO_4$ stain). Spectroscopic data were in accordance with those reported using general procedure VIII, see page 25.

Diversification of ROM-RCM Cascade Products

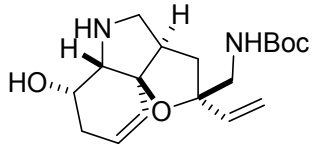
Deallylation of ROM-RCM Cascade Products

(2*R*,3a*R*,5a*S*,6*S*,9a*R*)-2-vinyl-2,3,3a,4,5,5a,6,7-octahydrofuro[3,2-*c*]indol-6-ol (*rac.*) (14a)



General procedure II was followed using **2** (50 mg, 0.202 mmol), 2,2,5-trimethyl- 1,3-dioxane-4,6-dione (32 mg, 0.202 mmol) and $Pd(PPh_3)_4$ (23 mg, 0.0202 mmol) with a reaction time of 2 h to give the title compound as a thick colorless oil (27 mg, 65%)[2] after purification by flash column chromatography on silica gel (CH_2Cl_2:MeOH:NH_4OH (25% w/w, aq) (181:15:4), R_f = 0.5 (CH_2Cl_2:MeOH:NH_4OH (25% w/w, aq) (90:5:1)), $KMnO_4$ stain). ^1H NMR (400 MHz, $CDCl_3$) δ 5.85 (ddd, J = 17.1, 10.3, 6.7 Hz, 1H), 5.68–5.56 (m, 2H), 5.30–5.23 (m, 1H), 5.15–5.09 (m, 1H), 4.52–4.44 (m, 1H), 4.03–3.95 (m, 1H), 3.37 (dd, J = 10.1, 8.4 Hz, 1H), 3.28 (d, J = 4.0 Hz, 1H), 2.96 (s, 1H), 2.67 (dd, J = 10.2, 8.4 Hz, 1H), 2.55–2.45 (m, 1H), 2.27–2.11 (m, 2H), 1.90–1.73 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.0, 129.9, 124.6, 116.6, 91.2, 79.7, 67.5, 66.0, 51.3, 50.5, 37.8, 28.9; MS (ESI) calcd for $C_{12}H_{18}NO_2$ $[M+H]^+$ 208.1, found 208.2; HRMS (ESI) calcd for $C_{12}H_{18}NO_2$ $[M+ H]^+$ 208.1332 found 208.1335; IR (neat) cm^{-1}: 3327, 2926, 1425, 1057, 1023, 921, 713.

***tert*-butyl (((2*R*,3a*R*,5a*S*,6*S*,9a*R*)-6-hydroxy-2-vinyl-2,3,3a,4,5,5a,6,7-octahydrofuro[3,2-*c*]indol-2-yl)methyl)carbamate (*rac.*) (14b)**



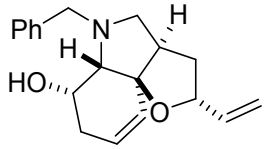
General procedure II was followed using **13a** (51 mg, 0.136 mmol), 2,2,5-trimethyl-1,3-dioxane-4,6-dione (22 mg, 0.136 mmol) and $Pd(PPh_3)_4$ (16 mg, 0.0136 mmol) with a reaction time of 3 h to give the title compound as a thick pale yellow oil (32 mg, 70%)[3] after purification by flash column chromatography on silica gel (CH_2Cl_2:MeOH:NH_4OH (25% w/w, aq) (181:15:4), R_f = 0.5 (CH_2Cl_2:MeOH:NH_4OH (25% w/w, aq) (90:5:1)), $KMnO_4$ stain). ^1H NMR (400 MHz, $CDCl_3$) δ 5.80 (dd, J = 17.2, 10.7 Hz, 1H), 5.72–5.61 (m, 2H), 5.32 (dd, J = 17.2, 1.2 Hz, 1H), 5.14 (dd, J = 10.7, 1.3 Hz, 1H), 5.02–4.95 (m, 1H), 3.97 (dt, J = 8.8, 4.6 Hz, 1H), 3.52–3.37 (m, 3H), 3.31–3.15 (m, 3H), 2.88 (dd, J = 11.3, 3.4 Hz, 1H), 2.64–2.52 (m, 1H), 2.29–2.19 (m, 1H), 2.18–2.01 (m, 2H), 1.90 (dd, J = 12.7, 8.8 Hz, 1H), 1.41 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.5, 141.5, 123.0, 125.8, 114.8, 92.9, 88.9, 79.5, 66.9, 66.7, 50.8, 50.2, 48.4, 39.3, 29.2, 28.5; MS (ESI) calcd for $C_{18}H_{29}N_2O_4$ $[M + H]^+$ 337.2, found 337.2; HRMS (ESI) calcd for $C_{18}H_{29}N_2O_4$ $[M+ H]^+$ 337.2122 found 337.2121; IR (neat) cm^{-1}: 3322, 2975, 1698, 1634, 1507, 1365, 1246, 1163, 1024, 921, 748.

[2] On 0.0972 mmol and 0.352 mmol reaction scales, the yields were 52% and 58%, respectively.

[3] On 0.0585 mmol and 0.205 mmol reaction scales, the yields were 81% and 60%, respectively.

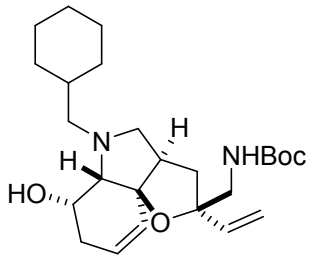
Functionalization of Secondary Amines

(2*R*,3a*R*,5a*S*,6*S*,9a*R*)-5-benzyl-2-vinyl-2,3,3a,4,5,5a,6,7-octahydrofuro[3,2-*c*]indol-6-ol (*rac.*) (15a)



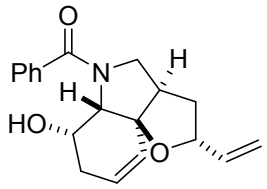
General procedure III was followed using **14a** (10 mg, 0.048 mmol), benzaldehyde (10 μL, 0.097 mmol) and $NaBH(OAc)_3$ (20 mg, 0.097 mmol) with a reaction time of 21 h to give the title compound as a colorless oil (10.4 mg, 91%) after purification by flash column chromatography on silica gel (hexanes:EtOAc:Et_3N (11:8:1), R_f = 0.3, $KMnO_4$ stain). ^1H NMR (400 MHz, $CDCl_3$) δ 7.36–7.24 (m, 5H), 5.85 (ddd, J = 17.1, 10.2, 6.9 Hz, 1H), 5.72 (ddd, J = 9.2, 5.4, 1.8 Hz, 1H), 5.61 (dd, J = 10.0, 2.3 Hz, 1H), 5.25 (d, J = 17.0 Hz, 1H), 5.11 (d, J = 10.2 Hz, 1H), 4.60 (dt, J = 9.3, 6.6 Hz, 1H), 4.09 (d, J = 12.8 Hz, 1H), 3.90 (q, J = 3.4 Hz, 1H), 3.75 (bs, 1H), 3.60 (d, J = 12.8 Hz, 1H), 3.15–3.08 (m, 2H), 2.51–2.35 (m, 3H), 2.22 (ddd, J = 17.5, 5.5, 2.8 Hz, 1H), 2.01 (dd, J = 13.0, 6.2 Hz, 1H), 1.85 (ddd, J = 13.0, 9.8, 6.2 Hz, 1H); ^{13}C NMR (100 MHz, CDCl3) δ 139.9, 138.9, 128.9, 128.9, 128.6, 127.4, 124.5, 116.0, 89.7, 78.3, 71.3, 65.4, 58.9, 56.8, 48.4, 35.5, 28.6; MS (ESI) calcd for $C_{19}H_{24}NO_2$ $[M + H]^+$ 298.2, found 298.3; HRMS (ESI) calcd for $C_{19}H_{23}NNaO_2$ $[M + Na]^+$ 320.1621 found 320.2614.

***tert*-butyl (((2*R*,3a*R*,5a*S*,6*S*,9a*R*)-5-(cyclohexylmethyl)-6-hydroxy-2-vinyl-2,3,3a,4,5,5a,6,7-octahydrofuro[3,2-*c*]indol-2-yl)methyl)carbamate (*rac.*) (15b)**



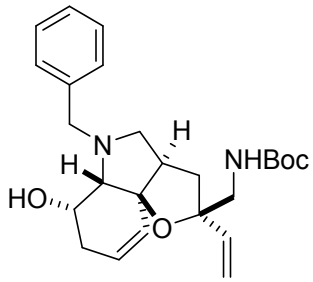
General procedure III was followed using **14b** (53 mg, 0.158 mmol), cyclohexanecarboxaldehyde (38 μL, 0.315 mmol) and $NaBH(OAc)_3$ (67 mg, 0.315 mmol) with a reaction time of 18 h to give the title compound as a colorless film (64 mg, 94%) after purification by flash column chromatography on silica gel (heptane:EtOAc:Et_3N (10:10:1), R_f = 0.3, $KMnO_4$ stain). ^1H NMR (400 MHz, $CDCl_3$) δ 5.88 (dd, J = 17.3, 10.8 Hz, 1H), 5.74–5.61 (m, 2H), 5.23 (d, J = 17.3 Hz, 1H), 5.09 (d, J = 10.9 Hz, 1H), 5.06–5.02 (m, 1H), 3.96 (s, 1H), 3.61–3.53 (m, 1H), 3.35–3.19 (m, 3H), 2.96 (d, J = 2.3 Hz, 1H), 2.58–2.42 (m, 3H), 2.42–2.32 (m, 1H), 2.27–2.14 (m, 2H), 2.00–1.84 (m, 2H), 1.77–1.56 (m, 4H), 1.42 (s, 9H), 1.31–1.09 (m, 4H), 0.96–0.79 (m, 2H); ^{13}C NMR (100 MHz, CDCl3) δ 156.3, 143.5, 129.1, 124.3, 114.0, 91.0, 86.0, 79.3, 71.3, 65.2, 61.4, 58.0, 49.6, 48.2, 37.4, 36.8, 32.1, 31.2, 28.8, 28.5, 26.9, 26.2, 26.0; MS (ESI) calcd for $C_{25}H_{41}N_2O_4$ $[M+ H]^+$ 433.3, found 433.4; HRMS (ESI) calcd for $C_{25}H_{41}N_2O_4$ $[M+ H]^+$ 433.3061 found 433.3142; IR (neat) cm^{-1}: 3451, 2922, 2851, 1710, 1507, 1449, 1365, 1247, 1164, 1024.

((2*R*,3a*R*,5a*S*,6*S*,9a*R*)-6-hydroxy-2-vinyl-2,3,3a,4,6,7-hexahydrofuro[3,2-*c*]indol-5(5a*H*)-yl)(phenyl)methanone (*rac.*) (15c)



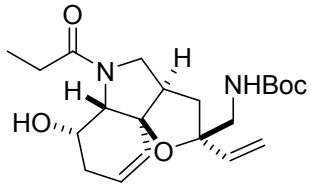
General procedure V was followed using **14a** (42 mg, 0.203 mmol), Et_3N (283 μL, 2.03 mmol), PyBOP (116 mg, 0.223 mmol) and benzoic acid (27 mg, 0.223 mmol) with a reaction time of 3 days to give the title compound as an off-white semi-solid solid (50 mg, 79%) after purification by flash column chromatography on silica gel (CH_2Cl_2:MeOH (25:1), R_f = 0.3, $KMnO_4$ stain). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56–7.31 (m, 5H), 5.91–5.74 (m, 1.75H), 5.68–5.51 (m, 1.25H), 5.37–5.18 (m, 1H), 5.20–5.04 (m, 1H), 4.65–4.51 (m, 1.75H), 4.41–4.26 (m, 0.75H), 4.09–3.98 (m, 0.5H), 3.90–3.75 (m, 1H), 3.70–3.63 (m, 0.25H), 3.26 (dd, *J* = 11.1, 2.8 Hz, 0.75H), 2.96–2.84 (m, 0.25H), 2.69–2.56 (m, 0.75H), 2.43– 2.29 (m, 1.5H), 2.20–1.82 (m, 1.75H), rotamers; ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.1, 170.7, 138.7, 136.3, 130.2, 129.8, 129.7, 128.9, 128.8, 128.6, 128.5, 128.3, 127.1, 126.7, 123.7, 116.5, 115.9, 89.7, 89.5, 79.8, 79.6, 69.0, 68.1, 67.8, 65.6, 54.8, 53.0, 47.8, 47.5, 39.5, 37.4, 31.6, 30.3, rotamers; MS (ESI) calcd for $C_{19}H_{22}NO_3$ $[M+H]^+$ 312.2, found 312.2; HRMS (ESI) calcd for $C_{19}H_{22}NO_3$ $[M+H]^+$ 312.1594 found 312.1620; IR (neat) cm^{-1}: 3374, 2929, 1599, 1419, 1073, 904, 700.

***tert*-butyl (((2*R*,3a*R*,5a*S*,6*S*,9a*R*)-5-benzyl-6-hydroxy-2-vinyl-2,3,3a,4,5,5a,6,7-octahydrofuro[3,2-*c*]indol-2-yl)methyl)carbamate (*rac.*) (15d)**



General procedure III was followed using **14b** (16 mg, 0.048 mmol), benzaldehyde (10 μL, 0.096 mmol) and $NaBH(OAc)_3$ (20 mg, 0.096 mmol) with a reaction time of 21 h to give the title compound as a white solid (14.2 mg, 69%) after purification by flash column chromatography on silica gel (hexanes:EtOAc:Et_3N (11:8:1), R_f = 0.1, $KMnO_4$ stain). Spectroscopic data for **15d** were in accordance with those for **13b** reported using general procedure VIII, see page 23.

***tert*-butyl (((2*R*,3a*R*,5a*S*,6*S*,9a*R*)-6-hydroxy-5-propionyl-2-vinyl-2,3,3a,4,5,5a,6,7-octahydrofuro[3,2-*c*]indol-2-yl)methyl)carbamate (*rac.*) (15e)**

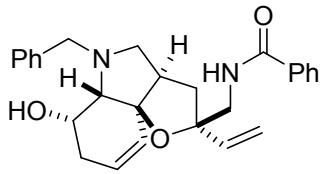


General procedure V was followed using **14b** (50 mg, 0.149 mmol), Et_3N (23 μL, 0.163 mmol), PyBOP (85 mg, 0.163 mmol) and propanoic acid (13 μL, 0.163 mmol) with a reaction time of 23 h to give the title compound as a white amorphous solid (45 mg, 70%) after purification by flash column chromatography on silica gel (heptane:EtOAc:Et_3N

(100:200:15), R_f = 0.2, $KMnO_4$ stain). ^1H NMR (400 MHz, $CDCl_3$) δ 6.29–6.19 (m, 1H), 5.87–5.74 (m, 2H), 5.54 (d, J = 10.0 Hz, 1H), 5.37 (dd, J = 17.1, 1.3 Hz, 1H), 5.17 (dd, J = 10.7, 1.2 Hz, 1H), 4.93 (bs, 1H), 4.22 (s, 1H), 4.14–4.01 (m, 1H), 3.55–3.44 (m, 2H), 3.32–3.19 (m, 2H), 2.54–2.43 (m, 1H), 2.40–2.19 (m, 3H), 2.09 (dd, J = 12.5, 7.3 Hz, 1H), 2.02–1.79 (m, 2H), 1.40 (s, 9H), 1.13 (t, J = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 75.8, 156.3, 140.7, 129.1, 128.2, 115.1, 91.2, 88.8, 79.5, 67.9, 67.7, 50.2, 47.9, 45.8, 37.7, 29.5, 28.3, 28.2, 9.0; MS (ESI) calcd for $C_{21}H_{33}N_2O_5$ $[M + H]^+$ 393.2, found 393.3; HRMS (ESI) calcd for $C_{21}H_{33}N_2O_5$ $[M+H]^+$ 393.2384 found 393.2439; IR (neat) cm^{-1}: 3266, 2979, 1691, 1621, 1551, 1437, 1364, 1276, 1156, 1039, 980, 908, 730.

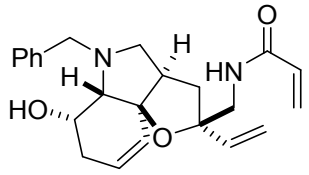
Boc-Deprotection and Primary Amine Functionalization

_N_-(((2_R_,3a_R_,5a_S_,6_S_,9a_R_)-5-benzyl-6-hydroxy-2-vinyl-2,3,3a,4,5,5a,6,7-octahydrofuro[3,2-_c_]indol-2-yl)methyl)benzamide (_rac._) (16a)



A stirred solution of **13b** (43 mg, 0.100 mmol) in CH_2Cl_2 (530 µL) was added TFA (530 µL). The reaction mixture was stirred at room temperature for 1 h, whereupon the reaction mixture was concentrated *in vacuo*. The residue was dissolved in CH_2Cl_2 (2.1 mL) and Et_3N (150 µL, 1.08 mmol), PyBOP (57 mg, 0.110 mmol) and benzoic acid (13 mg, 0.110 mmol) were added. The reaction mixture was stirred at room temperature for 25 h, whereupon the volatiles were removed *in vacuo*. The residue was purified by flash column chromatography on silica gel (heptane:EtOAc:Et_3N (200:200:15), R_f = 0.2, $KMnO_4$ stain) to give the title compound as a white semi-solid (39 mg, 91%). ^1H NMR (400 MHz, $CDCl_3$) δ 7.80–7.72 (m, 2H), 7.55–7.40 (m, 3H), 7.32–7.18 (m, 5H), 6.52–6.39 (m, 1H), 5.93 (dd, J = 17.2, 10.7 Hz, 1H), 5.75–5.66 (m, 2H), 5.32 (d, J = 17.2 Hz, 1H), 5.16 (d, J = 10.7 Hz, 1H), 4.10–3.95 (m, 1H), 3.72 (dd, J = 13.4, 6.6 Hz, 1H), 3.62–3.50 (m, 2H), 3.23–3.10 (m, 1H), 2.59–2.38 (m, 3H), 2.34–2.16 (m, 2H), 2.01–1.89 (m, 1H), 1.64 (bs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.7, 143.0, 138.5, 134.8, 131.7, 129.1, 128.9, 128.7, 128.6, 127.4, 127.1, 124.7, 114.4, 91.7, 85.9, 70.5, 65.6, 58.5, 57.9, 48.8, 47.7, 38.2, 28.9; MS (ESI) calcd for $C_{27}H_{31}N_2O_3$ $[M+H]^+$ 431.2, found 431.3; HRMS (ESI) calcd for $C_{27}H_{31}N_2O_3$ $[M+ H]^+$ 431.2329 found 431.2410; IR (neat) cm^{-1}: 3335, 2926, 1644, 1526, 1488, 1452, 1303, 1025, 908, 696.

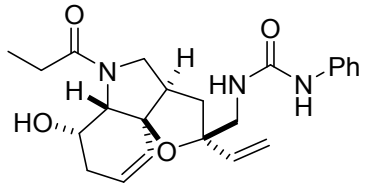
_N_-(((2_R_,3a_R_,5a_S_,6_S_,9a_R_)-5-benzyl-6-hydroxy-2-vinyl-2,3,3a,4,5,5a,6,7-octahydrofuro-[3,2-_c_]indol-2-yl)-methyl)acrylamide (_rac._) (16b)



A stirred solution of **13b** (49 mg, 0.115 mmol) in CH_2Cl_2 (575 µL) was added TFA (575 µL). The reaction mixture was stirred at room temperature for 1 h, whereupon CH_2Cl_2 (5 mL) and toluene (5 mL) were added, and the reaction mixture was concentrated *in vacuo*. The residue was dissolved in CH_2Cl_2 (2.3 mL), Et_3N (160 µL, 1.15 mmol) was added and the resulting solution was cooled to -78 °C. Acryloyl chloride (10 µL, 0.126 mmol) in CH_2Cl_2 (500 µL) was added dropwise. The reaction was stirred at -78 °C for 30 min, whereupon CH_2Cl_2 (15 mL) and satd. $NaHCO_3$ (aq) (10 mL) were added and the quenched reaction mixture was

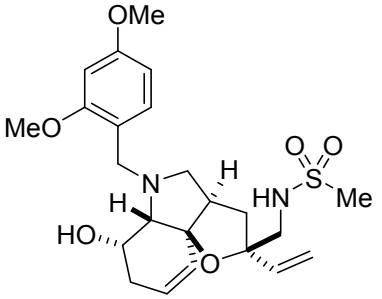
allowed to reach room temperature. The organic layer was isolated, and the aqueous phase was extracted with CH_2Cl_2 (3x15 mL). The combined organic layers were dried over $MgSO_4$ and the volatiles were removed *in vacuo*. The residue was purified by flash column chromatography on silica gel (EtOAc, R_f = 0.3, $KMnO_4$ stain) to give the title compound as a colorless film (31 mg, 70%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37–7.22 (m, 5H), 6.29 (dd, J = 17.0, 1.4 Hz, 1H), 6.17 (bs, 1H), 6.07 (dd, J = 17.0, 10.3 Hz, 1H), 5.87 (dd, J = 17.3, 10.8 Hz, 1H), 5.73–5.66 (m, 2H), 5.63 (dd, J = 10.3, 1.3 Hz, 1H), 5.27 (d, J = 17.4 Hz, 1H), 5.12 (dd, J = 10.8, 1.1 Hz, 1H), 4.19–4.07 (m, 1H), 4.06–3.97 (m, 1H), 3.77–3.65 (m, 1H), 3.65–3.52 (m, 1H), 3.45 (dd, J = 13.6, 5.3 Hz, 1H), 3.30–3.15 (m, 2H), 2.63–2.50 (m, 2H), 2.44–2.34 (m, 1H), 2.28–2.16 (m, 2H), 1.99–1.88 (m, 1H); ^{13}C NMR (100 MHz, CDCl3) δ 165.7, 142.7, 130.8, 129.1, 128.8, 128.6, 127.3, 126.8, 124.6, 114.3, 91.9, 86.1, 70.0, 66.0, 58.3, 48.3, 47.6, 38.8, 29.3; MS (ESI) calcd for $C_{23}H_{29}N_2O_3$ $[M + H]^+$ 381.2, found 381.3; HRMS (ESI) calcd for $C_{23}H_{29}N_2O_3$ $[M+H]^+$ 381.2173 found 381.2233 ; IR (neat) cm^{-1}: 3291, 3027, 2925, 1658, 1625, 1538, 1406, 1240, 1025, 926, 729, 698.

1-(((2*R*,3a*R*,5a*S*,6*S*,9a*R*)-6-hydroxy-5-propionyl-2-vinyl-2,3,3a,4,5,5a,6,7-octahydro-furo[3,2-*c*]indol-2-yl)methyl)-3-phenylurea (*rac.*) (16c)



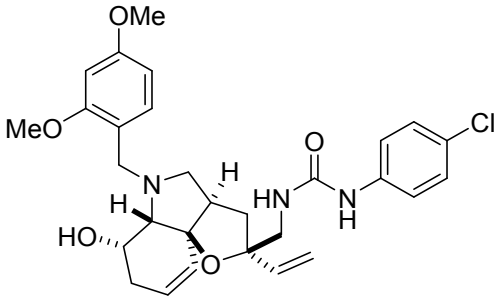
A stirred solution of **15e** (46 mg, 0.117 mmol) in CH_2Cl_2 (590 µL) was added TFA (590 µL). The reaction mixture was stirred at room temperature for 1 h, whereupon CH_2Cl_2 (15 mL) and satd. $NaHCO_3$ (aq) (10 mL) were added and the quenched reaction mixture was stirred at room temperature for 10 min. The aqueous phase was basified with NaOH (2M, aq) (2 mL) and the organic layer was isolated. The aqueous phase was extracted with CH_2Cl_2 (10x15 mL), the combined organic layers were dried over $MgSO_4$ and the volatiles were removed *in vacuo*. The residue was re-dissolved in CH_2Cl_2 (2.7 mL) and Et_3N (76 µL, 0.545 mmol) and phenyl isocyanate (16 µL, 0.149 mmol) were added. The reaction mixture was stirred at room temperature for 3 days, whereupon it was concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (CH_2Cl_2:MeOH (25:1), R_f = 0.2, $KMnO_4$ stain) to give the title compound as a slightly yellow film (38 mg, 83%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (bs, 1H), 7.44–7.38 (m, 2H), 7.29–7.22 (m, 3H), 7.05–6.94 (m, 1H), 5.99–5.90 (m, 1H), 5.88–5.78 (m, 2H), 5.54 (d, J = 9.9 Hz, 1H), 5.38 (dd, J = 17.1, 1.4 Hz, 1H), 5.18 (dd, J = 10.7, 1.4 Hz, 1H), 4.29–4.25 (m, 1H), 4.17–4.11 (m, 1H), 3.71 (dd, J = 14.5, 6.7 Hz, 1H), 3.53–3.44 (m, 2H), 3.07 (d, J = 14.1 Hz, 1H), 2.53 (ddt, J = 11.6, 7.8, 4.1 Hz, 1H), 2.37–2.20 (m, 3H), 2.12–1.90 (m, 3H), 1.09 (t, J = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.1, 156.5, 141.2, 139.5, 129.2, 129.1, 128.2, 122.8, 119.8, 115.1, 90.9, 89.7, 67.6, 67.5, 50.3, 45.7, 45.4, 36.9, 29.5, 28.2, 9.0; MS (ESI) calcd for $C_{23}H_{30}N_3O_4$ $[M+H]^+$ 412.2, found 412.3; HRMS (ESI) calcd for $C_{23}H_{30}N_3O_4$ $[M+ H]^+$ 412.2231 found 412.2218.

***N*-(((2*R*,3a*R*,5a*S*,6*S*,9a*R*)-5-(2,4-dimethoxybenzyl)-6-hydroxy-2-vinyl-2,3,3a,4,5,5a,6,7-octahydrofuro-[3,2-*c*]-indol-2-yl)methyl)methanesulfonamide (*rac.*) (16d)**



A stirred solution of **13c** (50 mg, 0.103 mmol) in CH_2Cl_2 (515 µL) was added TFA (515 µL). The reaction mixture was stirred at room temperature for 1 h, whereupon CH_2Cl_2 (15 mL) and satd. $NaHCO_3$ (aq) (10 mL) were added and the quenched reaction mixture was stirred at room temperature for 10 min. The aqueous phase was basified with NaOH (2M, aq) (2 mL) and the organic layer was isolated. The aqueous phase was extracted with CH_2Cl_2 (5x20 mL), the combined organic layers were dried over Na_2SO_4 and the volatiles were removed *in vacuo*. The residue was re-dissolved in CH_2Cl_2 (2.0 mL) and Et_3N (50 µL, 0.359 mmol) was added. The reaction mixture was cooled to 0 ^oC, and methanesulfonyl chloride (9 µL, 0.113 mmol) was added slowly. The reaction mixture stirred at 0 ^oC for 1 h, whereupon it was diluted with CH_2Cl_2 (15 mL) and satd. $NaHCO_3$ (aq) (10 mL). The organic layer was isolated and the aqueous phase was extracted with CH_2Cl_2 (3x15 mL). The combined organic layers were dried over $MgSO_4$ and the volatiles were removed *in vacuo*. The residue was purified by flash column chromatography on silica gel (CH_2Cl_2:MeOH (25:1), R_f = 0.2, $KMnO_4$ stain) to give the title compound as a slightly brown film (25 mg, 52%). ^1H NMR (400 MHz, $CDCl_3$) δ 7.15 (d, J = 7.9 Hz, 1H), 6.47–6.41 (m, 2H), 5.87 (dd, J = 17.3, 10.7 Hz, 1H), 5.72–5.64 (m, 2H), 5.30 (dd, J = 17.3, 1.1 Hz, 1H), 5.17 (dd, J = 10.8, 1.0 Hz, 1H), 4.95 (t, J = 5.7 Hz, 1H), 4.07–4.00 (m, 2H), 3.85 (s, 1H), 3.80 (s, 3H), 3.80 (s, 3H), 3.58 (d, J = 12.8 Hz, 1H), 3.31 (dd, J = 12.9, 6.2 Hz, 1H), 3.17 (dd, J = 12.9, 5.5 Hz, 1H), 3.13–3.07 (m, 3H), 2.96 (s, 3H), 2.61 (t, J = 8.9 Hz, 1H), 2.49–2.39 (m, 1H), 2.37 (t, J = 3.9 Hz, 1H), 2.27–2.15 (m, 2H), 1.99 (dd, J = 13.4, 2.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.5, 158.8, 142.8, 131.4, 128.9, 124.9, 119.1, 115.1, 103.9, 98.7, 92.1, 85.3, 70.1, 65.3, 57.4, 55.5, 55.3, 52.4, 52.2, 47.7, 41.0, 37.7, 28.8; MS (ESI) calcd for $C_{23}H_{33}N_2O_6S$ $[M+H]^+$ 465.2, found 465.3; HRMS (ESI) calcd for $C_{23}H_{33}N_2O_6S$ $[M+H]^+$ 465.2054 found 465.2134; IR (neat) cm^{-1}: 3290, 2933, 1612, 1587, 1506, 1456, 1318, 1207, 1152, 1032, 913, 833, 727.

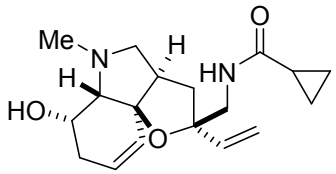
1-(4-chlorophenyl)-3-(((2*R*,3a*R*,5a*S*,6*S*,9a*R*)-5-(2,4-dimethoxybenzyl)-6-hydroxy-2-vinyl-2,3,3a,4,5,5a,6,7-octahydrofuro[3,2-*c*]indol-2-yl)methyl)urea (*rac.*) (16e)



A stirred solution of **13c** (50 mg, 0.103 mmol) in CH_2Cl_2 (515 µL) was added TFA (515 µL). The reaction mixture was stirred at room temperature for 1 h, whereupon CH_2Cl_2 (15 mL) and satd. $NaHCO_3$ (aq) (10 mL) were added and the quenched reaction mixture was stirred at room temperature for 10 min. The aqueous phase was basified with NaOH (2M, aq) (2 mL)

and the organic layer was isolated. The aqueous phase was extracted with CH_2Cl_2 (3x15 mL), the combined organic layers were dried over $MgSO_4$ and the volatiles were removed *in vacuo*. The residue was re-dissolved in CH_2Cl_2 (2.0 mL) and Et_3N (58 μL, 0.416 mmol) and 4-chlorophenyl isocyanate (20 mg, 0.130 mmol) were added. The reaction mixture was stirred at room temperature for 3 days, whereupon it was concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (CH_2Cl_2:MeOH (25:1), R_f = 0.2, $KMnO_4$ stain) to give the title compound as a brown film (20 mg, 36%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.50–7.38 (m, 2H), 7.36–7.13 (m, 3H), 6.5–6.39 (m, 2H), 6.19–6.06 (m, 1H), 5.83 (dd, J = 17.2, 10.7 Hz, 1H), 5.67–5.59 (m, 1H), 5.42 (d, J = 9.5 Hz, 1H), 5.26 (dd, J = 17.3, 1.6 Hz, 1H), 5.10 (d, J = 10.6 Hz, 1H), 4.83 (bs, 1H), 4.42 (d, J = 13.9 Hz, 1H), 3.97–3.88 (m, 1H), 3.70 (s, 6H), 3.40–3.18 (m, 3H), 3.06–2.97 (m, 2H), 2.38–2.34 (m, 2H), 2.20–1.96 (m, 2H), 1.81–1.72 (m, 1H); 13C NMR (100 MHz, DMSO-d_6) δ 159.1, 157.8, 155.0, 152.4, 142.2, 139.5, 138.6, 130.3, 129.8, 128.6, 128.5, 126.0, 119.7, 118.9, 113.9, 104.2, 98.1, 92.3, 88.5, 70.0, 67.8, 58.1, 55.2, 55.0, 52.9, 47.2, 45.4, 40.7, 29.0; MS (ESI) calcd for $C_{29}H_{35}ClN_3O_5$ $[M + H]^+$ 540.2, found 540.3; HRMS (ESI) calcd for $C_{29}H_{35}ClN_3O_5$ $[M+ H]^+$ 540.2260 found 540.2243.

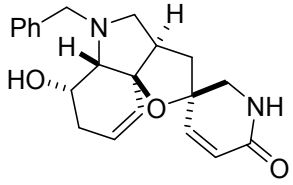
_N_-(((2_R_,3a_R_,5a_S_,6_S_,9a_R_)-6-hydroxy-5-methyl-2-vinyl-2,3,3a,4,5,5a,6,7-octahydro-furo[3,2-_c_]indol-2-yl) methyl)cyclopropanecarboxamide (_rac._) (16f)



A stirred solution of **13d** (43 mg, 0.123 mmol) in CH_2Cl_2 (610 μL) was added TFA (610 μL). The reaction mixture was stirred at room temperature for 1 h, whereupon CH_2Cl_2 (15 mL) and satd. $NaHCO_3$ (aq) (10 mL) were added and the quenched reaction mixture was stirred at room temperature for 10 min. The aqueous phase was basified with NaOH (2 M, aq) (2 mL) and the organic layer was isolated. The aqueous phase was extracted with CH_2Cl_2 (5x20 mL), the combined organic layers were dried over Na_2SO_4 and the volatiles were removed *in vacuo*. The residue was re-dissolved in CH_2Cl_2 (2.2 mL) and Et_3N (30 mL, 0.216 mmol) was added. The reaction mixture was cooled to 0 °C, and cyclopropanecarbonyl chloride (12 μL, 0.135 mmol) was added slowly. The reaction mixture was allowed to reach room temperature overnight, and was then diluted with CH_2Cl_2 (15 mL) and satd. $NaHCO_3$ (aq) (10 mL). The organic layer was isolated and the aqueous phase was extracted with CH_2Cl_2 (3x10 mL). The combined organic layers were dried over Na_2SO_4 and the volatiles were removed *in vacuo*. The residue was purified by flash column chromatography on silica gel (CH_2Cl_2:MeOH (9:1), R_f = 0.3, $KMnO_4$ stain) to give the title compound as an off-white semi-solid (17 mg, 50%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.89 (dd, J = 17.3, 10.8 Hz, 1H), 5.74–5.65 (m, 2H), 5.29 (dd, J = 17.3, 1.0 Hz, 1H), 5.14 (dd, J = 10.8, 1.0 Hz, 1H), 4.25–4.07 (m, 1H), 3.53–3.28 (m, 3H), 3.03–2.85 (m, 1H), 2.56 (s, 3H), 2.67–2.49 (m, 1H), 2.45–2.33 (m, 1H), 2.33–2.21 (m, 2H), 2.00–1.90 (m, 1H), 1.48–1.31 (m, 1H), 1.33–1.18 (m, 2H), 1.04–0.91 (m, 2H), 0.7–0.65 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.8, 142.7, 129.4, 124.5, 114.2, 92.1, 86.9, 72.5, 65.7, 61.4, 47.9, 38.8, 29.7, 14.8, 7.2, 7.1; MS (ESI) calcd for $C_{18}H_{27}N_2O_3$ $[M+H]^+$ 319.2, found 319.2; HRMS (ESI) calcd for $C_{18}H_{27}N_2O_3$ $[M+H]^+$ 319.2016 found 319.2046; IR (neat) cm^{-1}: 3306, 2925, 1647, 1544, 1401, 1239, 1028, 924, 727.

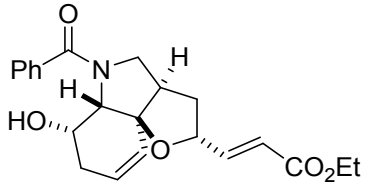
ROM-RCM-CM and CM Reactions

(2*R*,3a*R*,5a*S*,6*S*,9a*R*)-5-benzyl-6-hydroxy-1',2',3a,4,5,5a,6,7-octahydro-3H,6'*H*-spiro-[furo[3,2-*c*]indole-2,3'-pyridin]-6'-one (*rac.*) (17)



A stirred solution of **16b** (30 mg, 0.0788 mmol) in dry CH_2Cl_2 (7.9 mL) was added the Grubbs II catalyst (7 mg, 0.00788 mmol). The reaction mixture was heated to reflux for for 5 h, whereupon the volatiles were removed *in vacuo*. The residue was purified by flash column chromatography on silica gel (CH_2Cl_2:MeOH (19:1), R_f = 0.5 (CH_2Cl_2:MeOH (18:2)), $KMnO_4$ stain) to give the title compound as a brown semi-solid (21 mg, 78%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39–7.23 (m, 5H), 6.52 (d, J = 10.1 Hz, 1H), 6.44 (bs, 1H), 5.85–5.73 (m, 2H), 5.69 (dd, J = 10.0, 2.6 Hz, 1H), 4.04 (d, J = 12.9 Hz, 1H), 3.94 (d, J = 2.3 Hz, 1H), 3.74–3.64 (m, 1H), 3.64 (d, J = 12.5 Hz, 1H), 3.41 (dd, J = 12.5, 2.7 Hz, 1H), 3.23–3.12 (m, 2H), 2.60–2.49 (m, 1H), 2.50–2.36 (m, 2H), 2.28–2.11 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.7, 149.1, 138.2, 128.9, 128.7, 127.8, 127.6, 126.1, 122.9, 91.8, 79.0, 70.6, 64.9, 58.2, 57.6, 51.9, 47.8, 38.1, 28.7; MS (ESI) calcd for $C_{21}H_{25}N_2O_3$ $[M+ H]^+$ 353.2, found 353.2; HRMS (ESI) calcd for $C_{21}H_{25}N_2O_3$ $[M + H]^+$ 353.1860 found 353.1901; IR (neat) cm^{-1}: 3268, 2896, 1674, 1608, 1451, 1072, 1025, 819, 726.

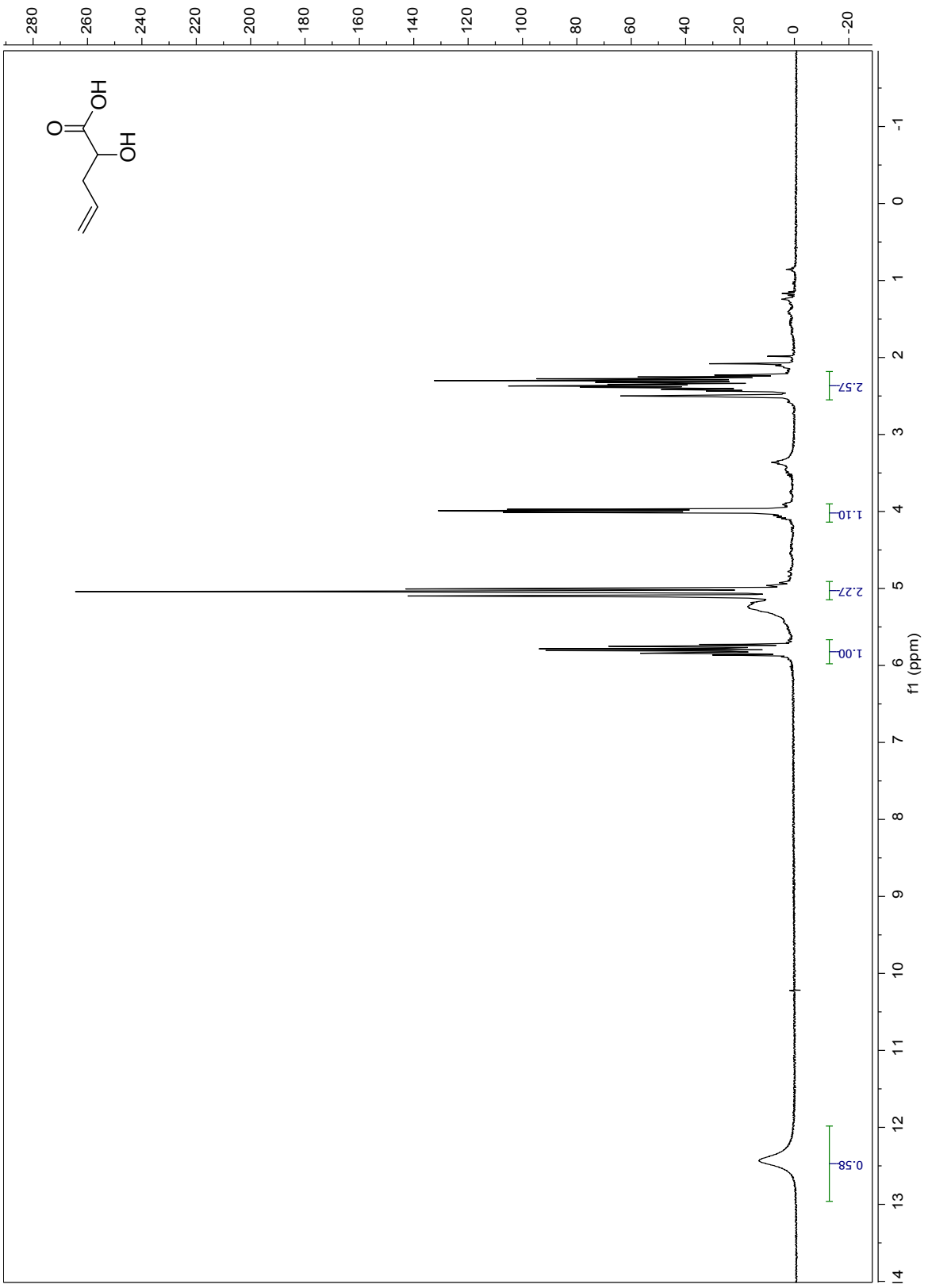
Ethyl (*E*)-3-((2*R*,3a*R*,5a*S*,6*S*,9a*R*)-5-benzoyl-6-hydroxy-2,3,3a,4,5,5a,6,7-octahydrofuro-[3,2-*c*]indol-2-yl)acrylate (*rac.*) (18)



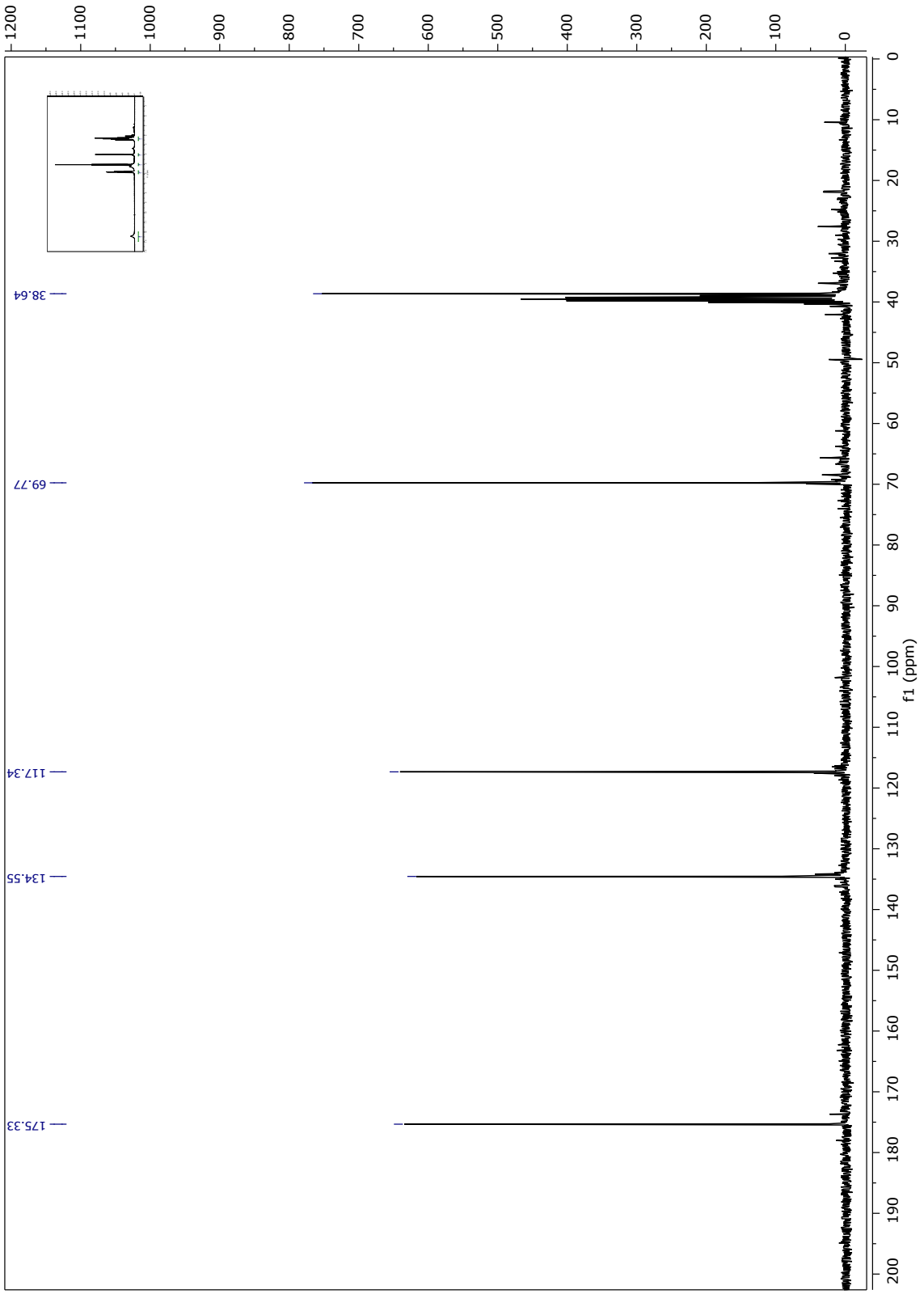
A solution of **15c** (33 mg, 0.106 mmol) in CH_2Cl_2 (11 mL) was added ethyl acrylate (116 μL, 1.06 mmol), CuI (2.0 mg, 0.0106 mmol) and the Hoveyda-Grubbs II catalyst (7 mg, 0.0106 mmol). The reaction mixture was heated to reflux for 18 h, whereupon it was concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (EtOAc, R_f = 0.3, $KMnO_4$ stain) to give the title compound as a slightly brown film (30 mg, 74%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54–7.33 (m, 5H), 6.99–6.83 (m, 1H), 6.12–6.01 (m, 1H), 5.89–5.80 (m, 0.7H), 5.68–5.59 (m, 1.3H), 4.78–4.68 (m, 1H), 4.62 (d, J = 2.0 Hz, 0.7H), 4.41–4.33 (m, 0.7H), 4.18 (q, J = 6.9 Hz, 2H), 4.10–4.01 (m, 0.6H), 3.91–3.77 (m, 1H), 3.68–3.60 (m, 0.3H), 3.32–3.21 (m, 0.7H), 3.00–2.91 (m, 0.3H), 2.71–2.58 (m, 0.7H), 2.45–2.34 (m, 0.7H), 2.25–2.13 (m, 1H), 2.10–1.99 (m, 1.3H), 1.98–1.89 (m, 1H), 1.27 (t, J = 7.1 Hz, 3H), rotamers; ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.3, 170.9, 166.4, 147.7, 136.8, 136.2, 130.4, 129.9, 128.6, 128.6, 128.4, 128.3, 127.2, 127.2, 126.7, 121.0, 120.9, 90.4, 77.4, 69.0, 68.0, 67.8, 65.6, 60.6, 54.6, 52.9, 47.6, 47.4, 39.2, 37.0, 31.7, 30.4, 14.3, rotamers; MS (ESI) calcd for $C_{22}H_{26}NO_5$ $[M + H]^+$ 384.2, found 384.3; IR (neat) cm^{-1}: 3380, 2925, 1713, 1600, 1417, 1264, 1170, 1041, 910, 702.

NMR Spectra for Alkene-Containing Building Blocks

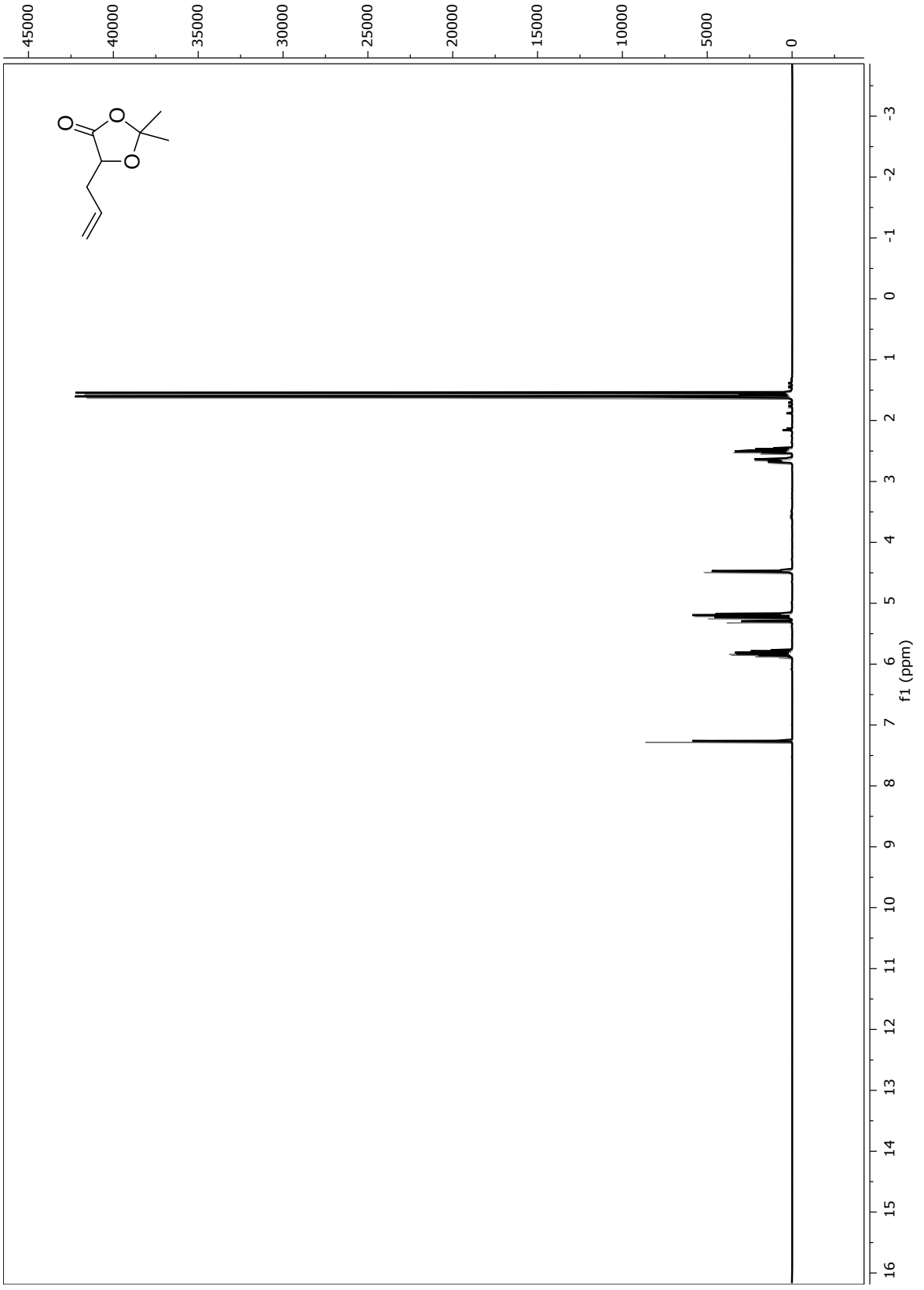
^{1}H NMR (300 MHz, DMSO-d_6) of compound **S1**



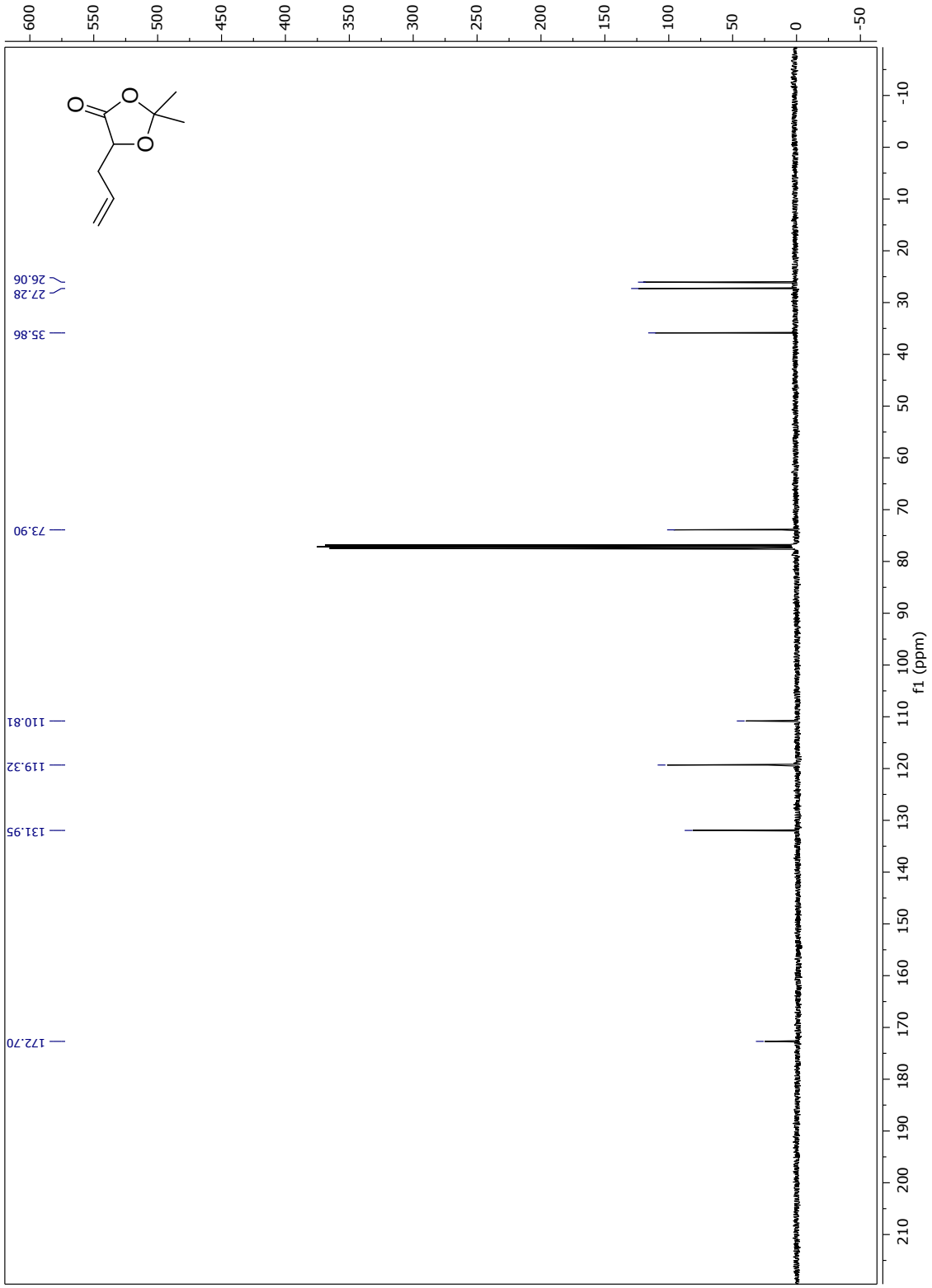
^{13}C NMR (75 MHz, DMSO-d_6) of compound **S1**



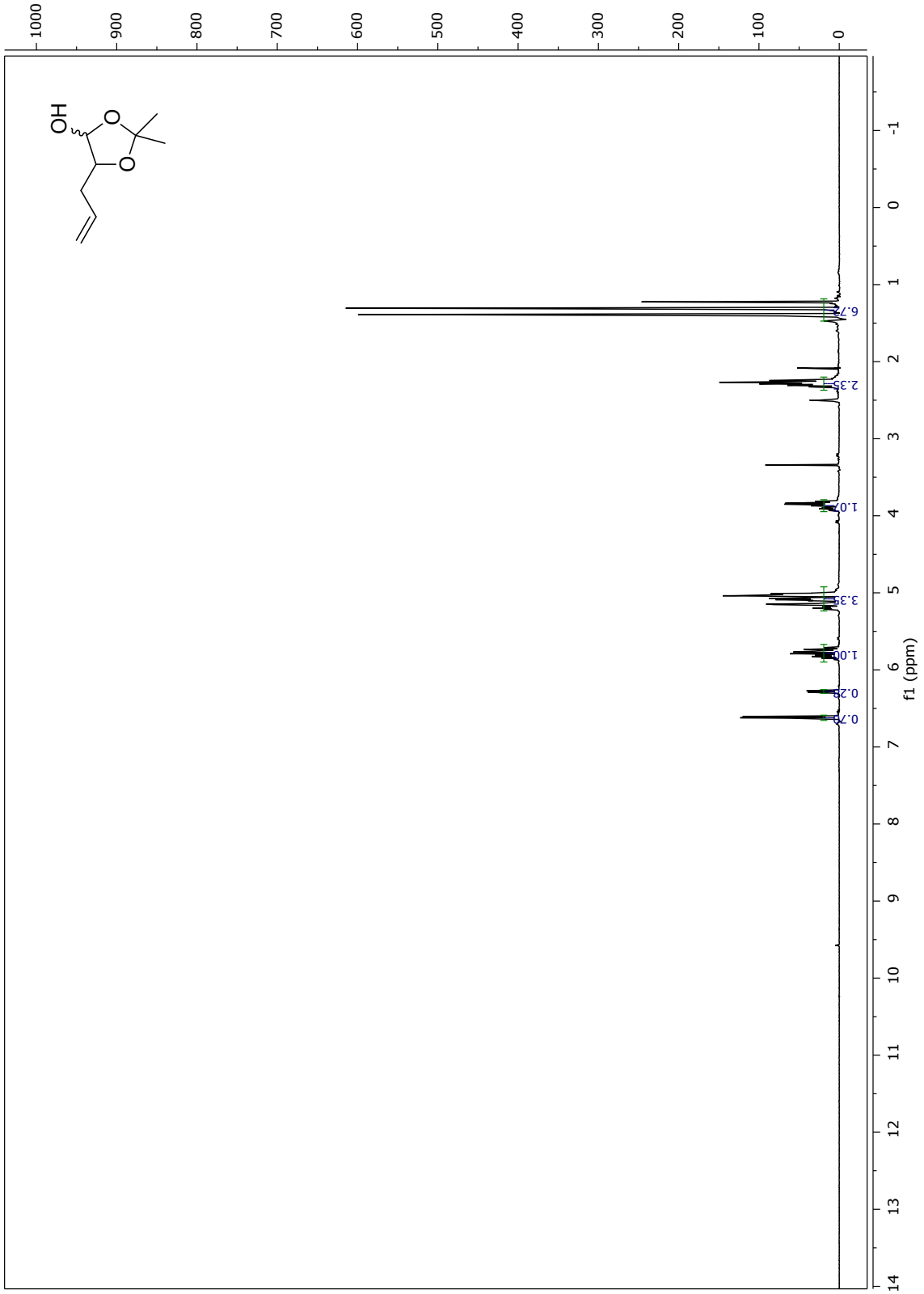
^{1}H NMR (400 MHz, $CDCl_3$) of compound **S2**



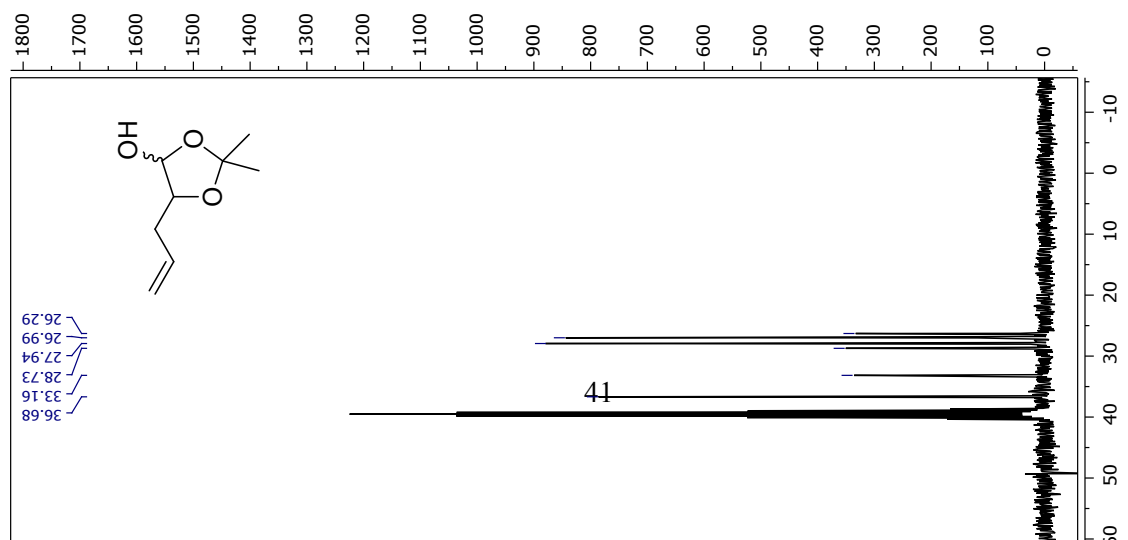
^{13}C NMR (100 MHz, $CDCl_3$) of compound **S2**



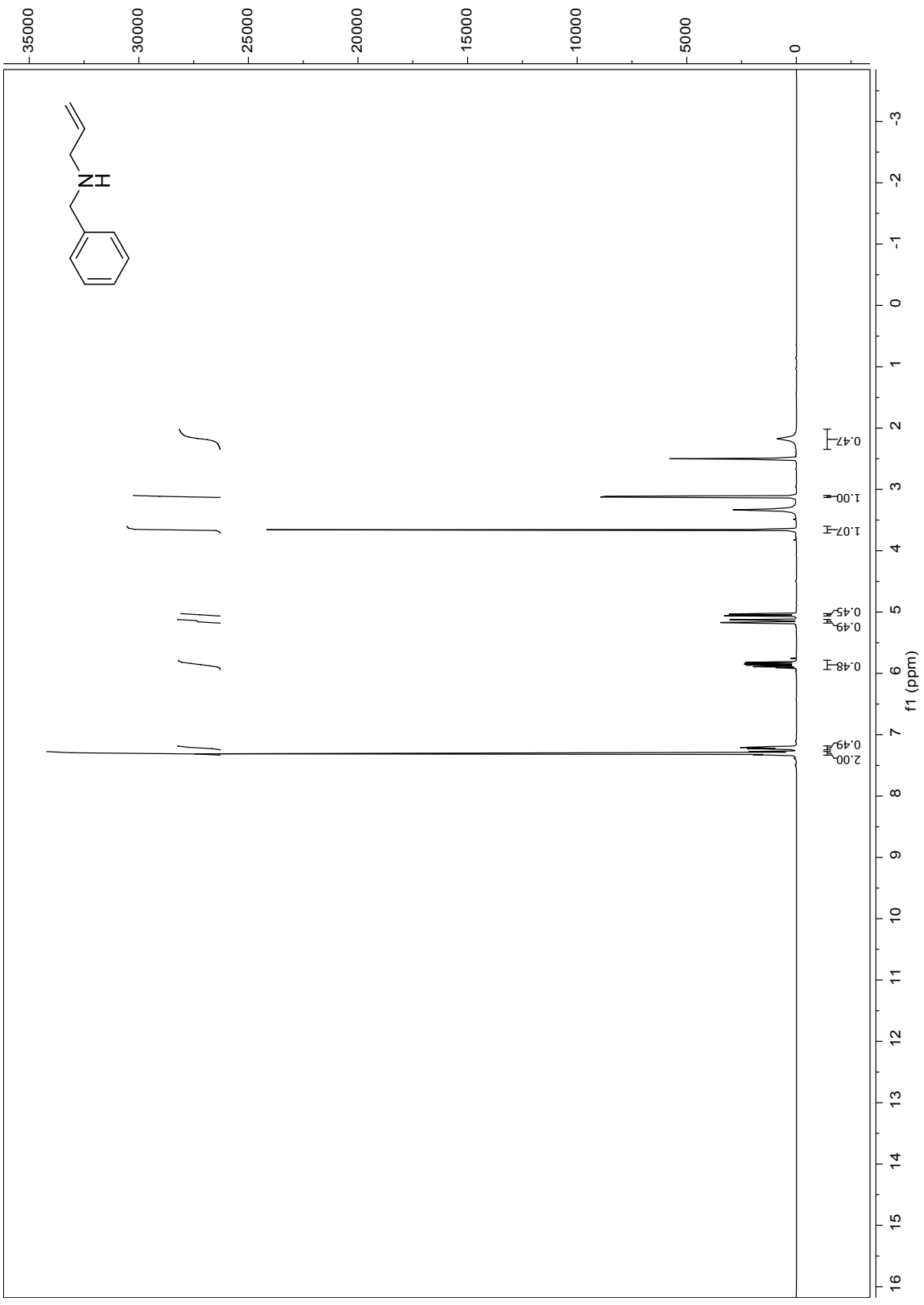
^{1}H NMR (400 MHz, $CDCl_3$) of **1**



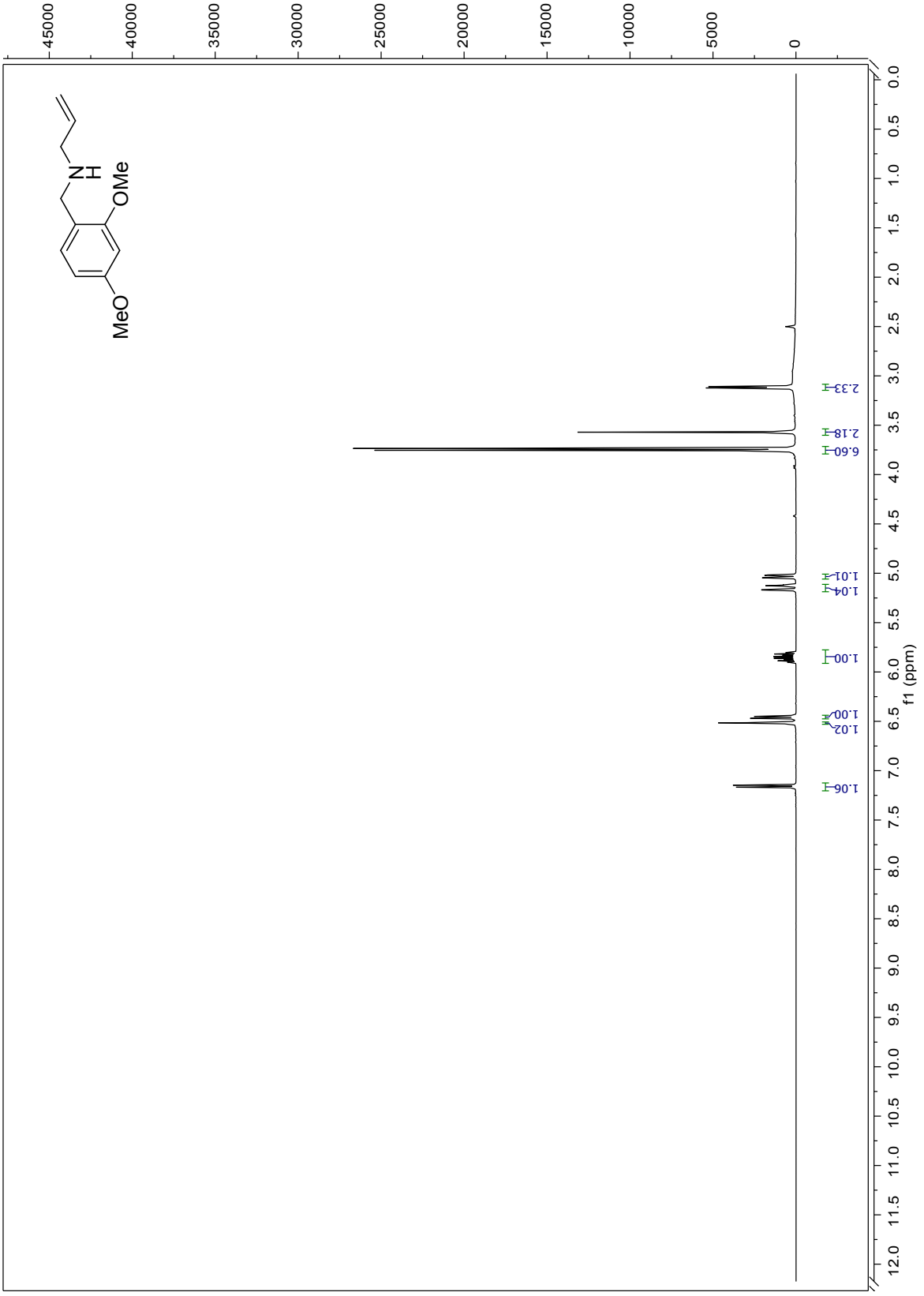
^{13}C NMR (100 MHz, $CDCl_3$) of **1**



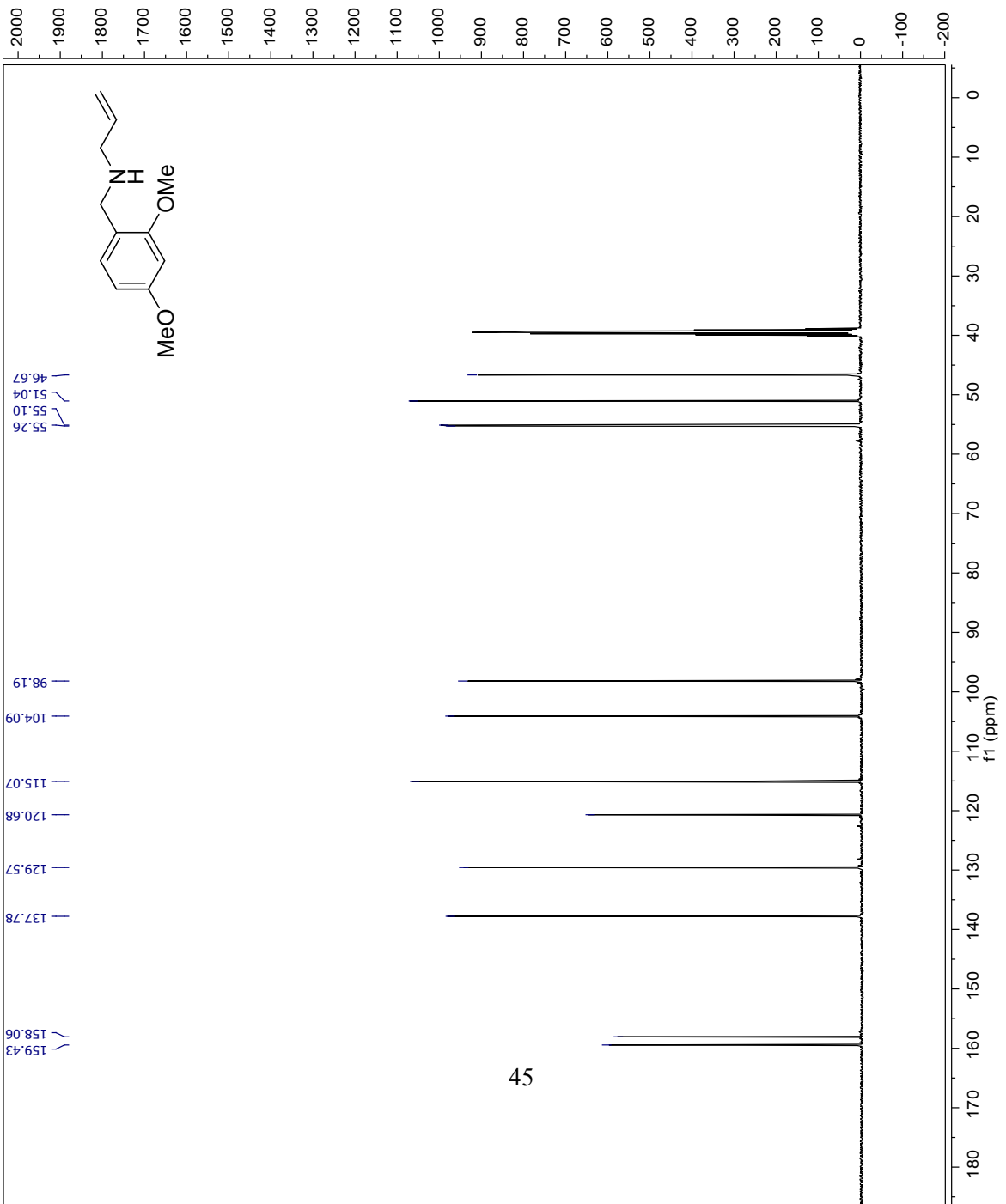
^{1}H NMR (400 MHz, DMSO-d_6) of **6b**



^{1}H NMR (400 MHz, DMSO-d_6) of **6c**

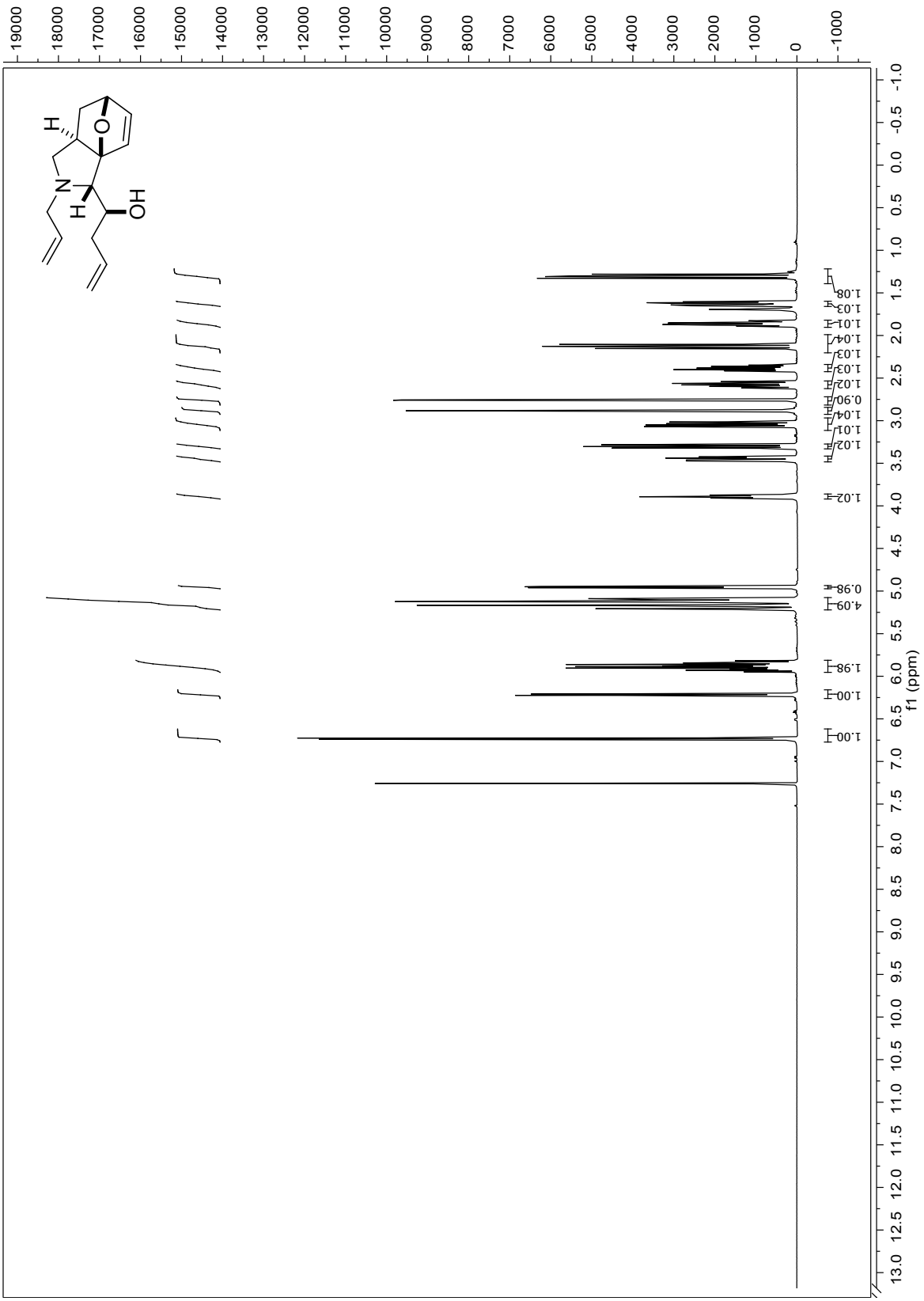


^{13}C NMR (100 MHz, DMSO-d_6) of **6c**

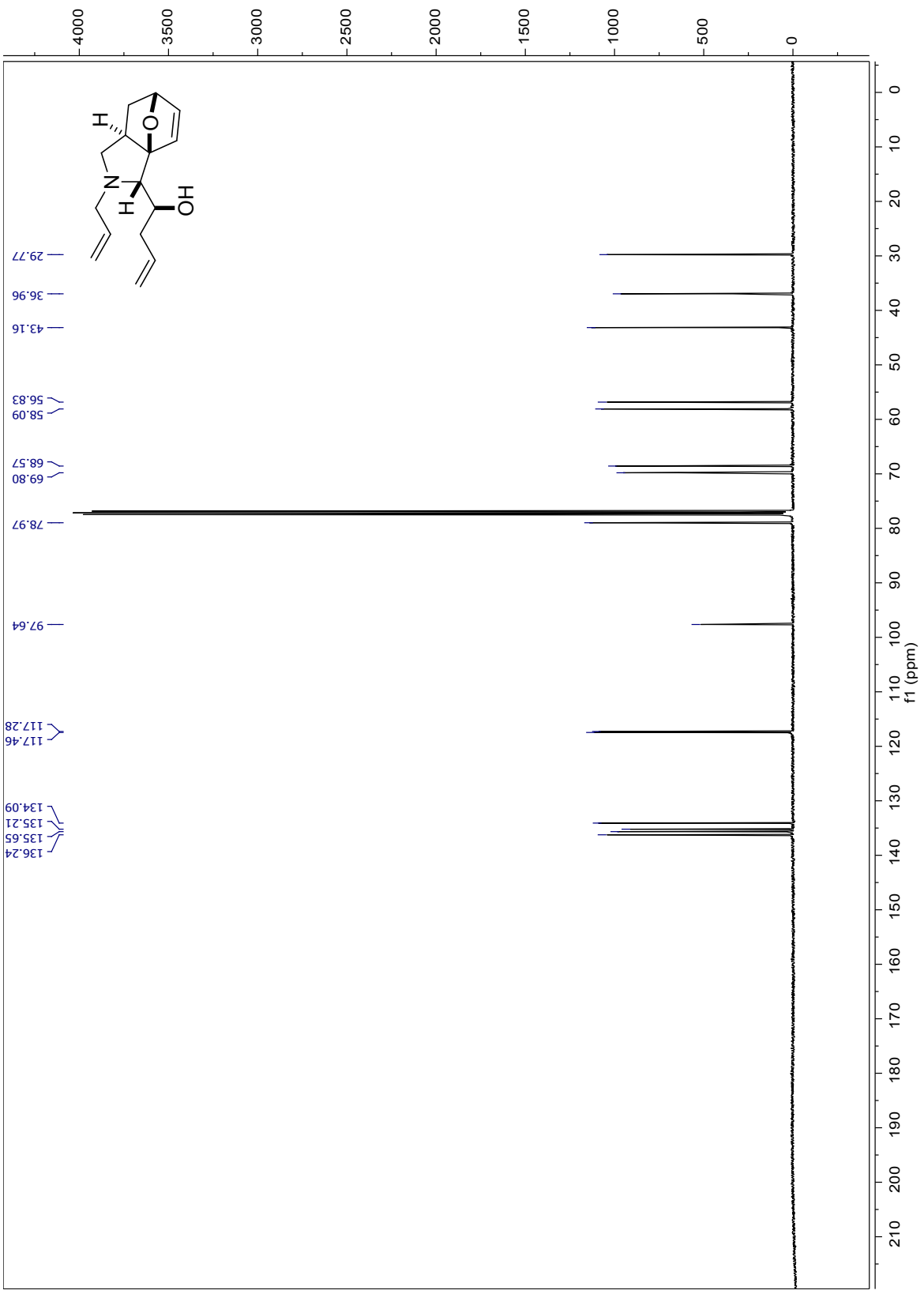


NMR Spectra for Petasis 3-CR/IMDA Products

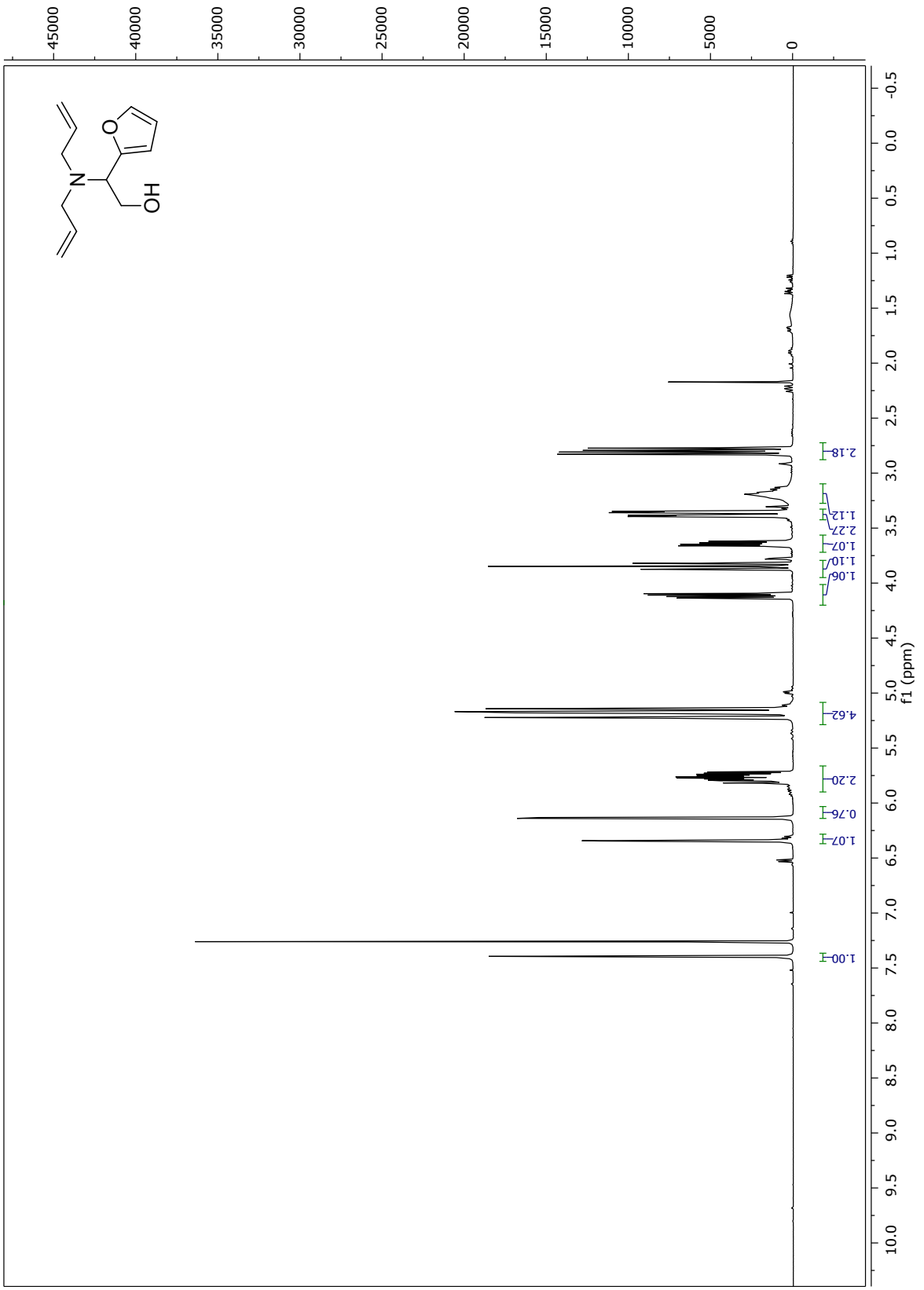
^{1}H NMR (400 MHz, $CDCl_3$) of **2**



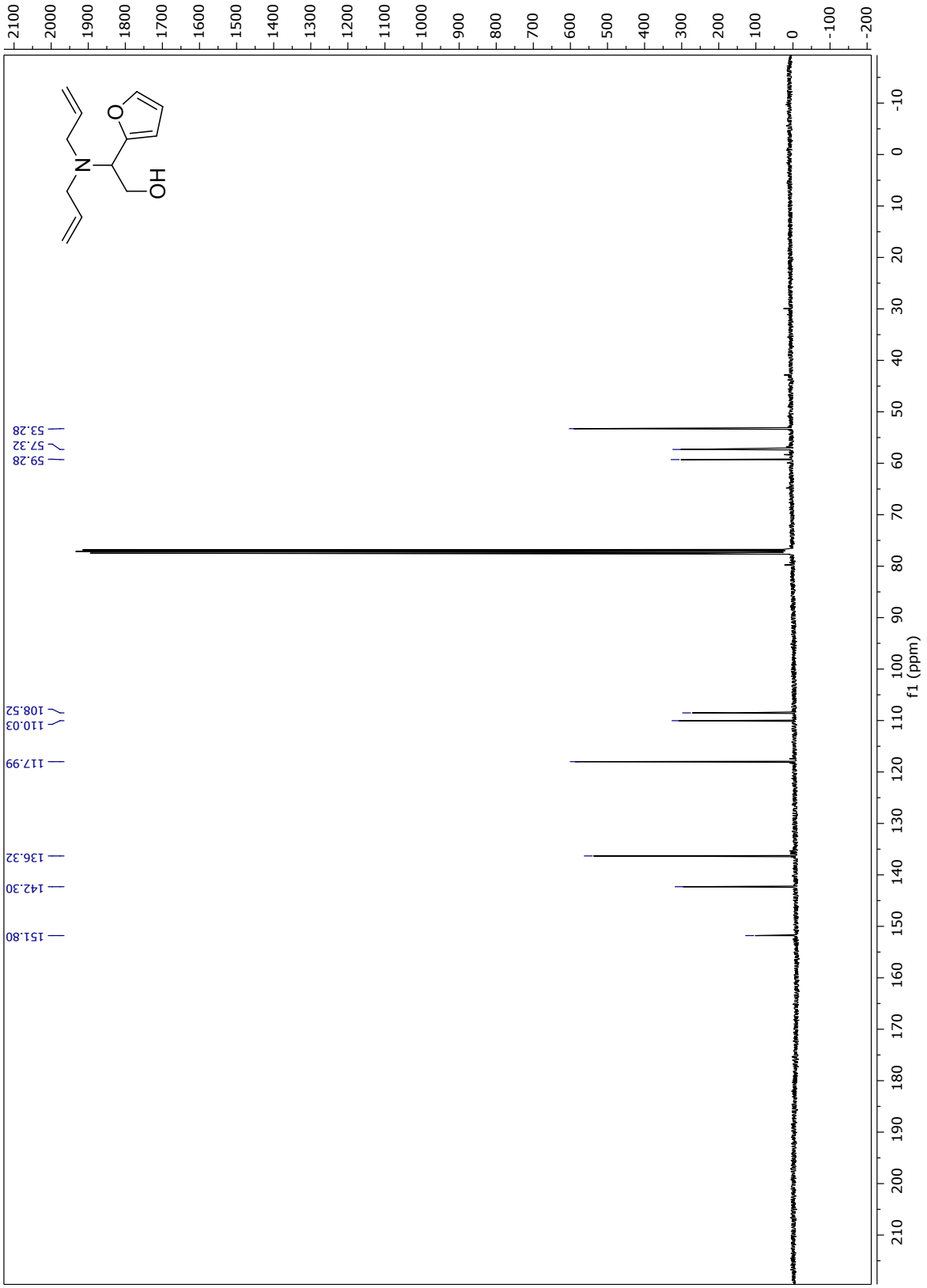
^{13}C NMR (100 MHz, $CDCl_3$) of **2**



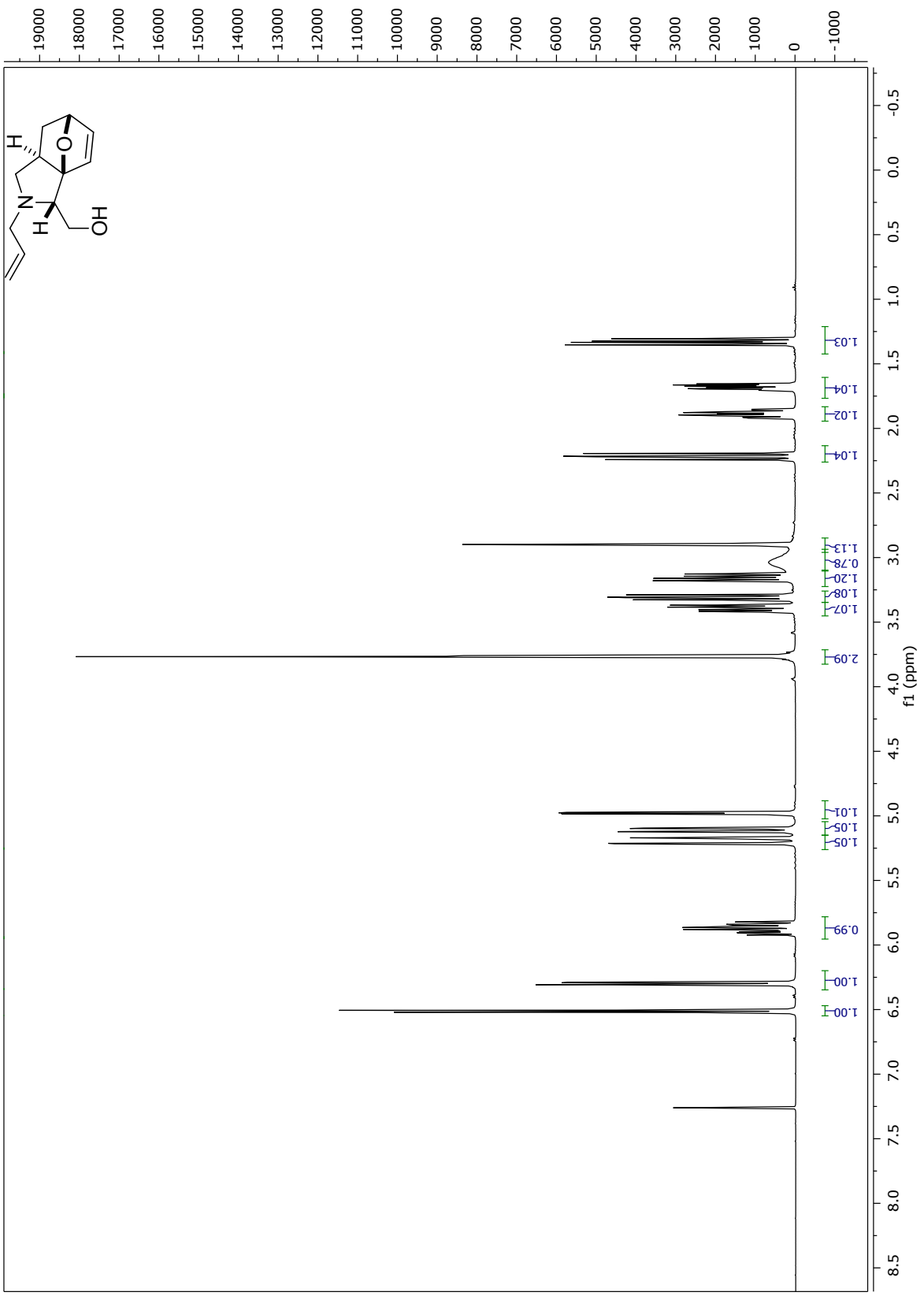
^{1}H NMR (400 MHz, $CDCl_3$) of **S4**



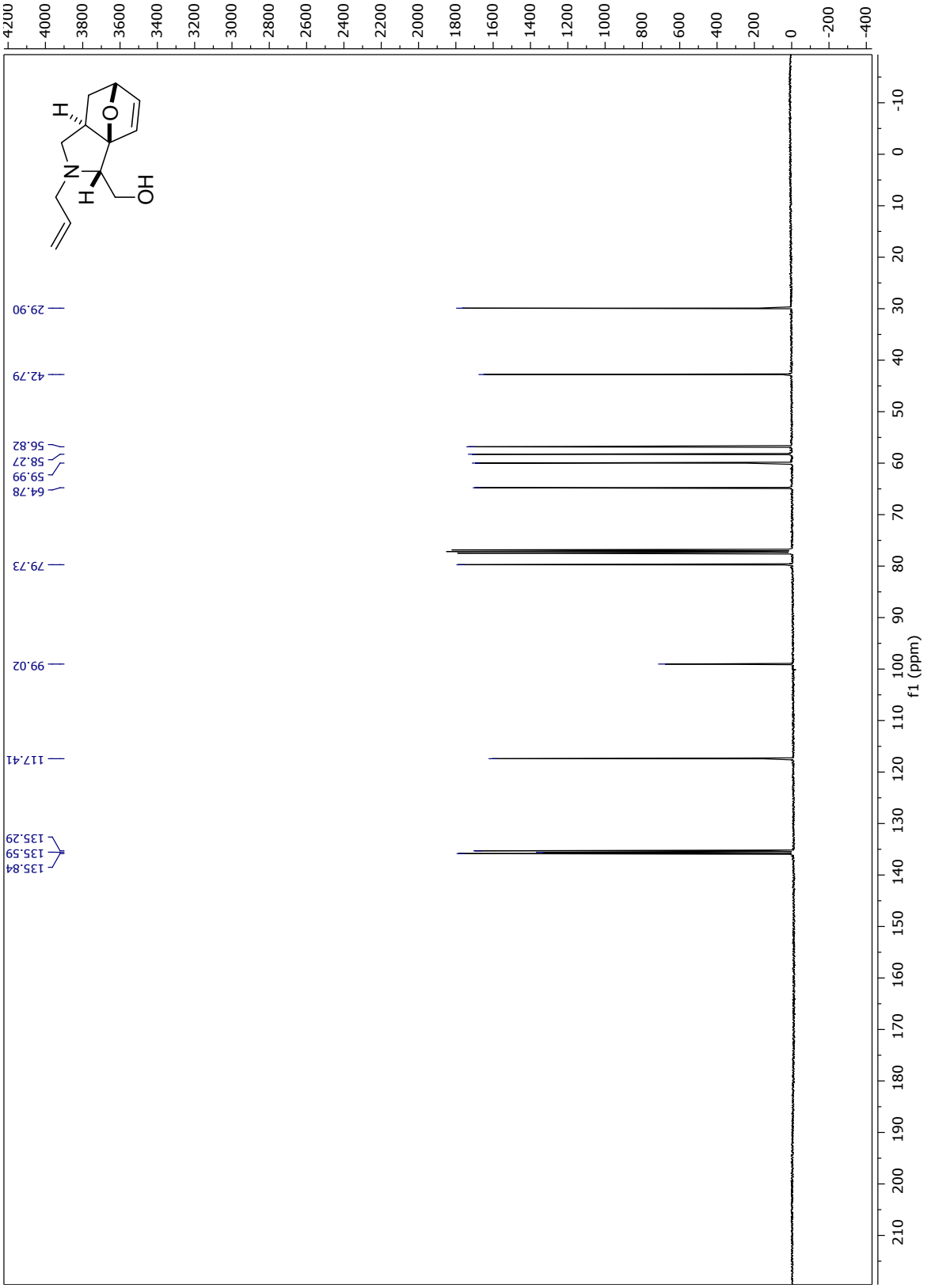
^{13}C NMR (100 MHz, $CDCl_3$) of **S4**



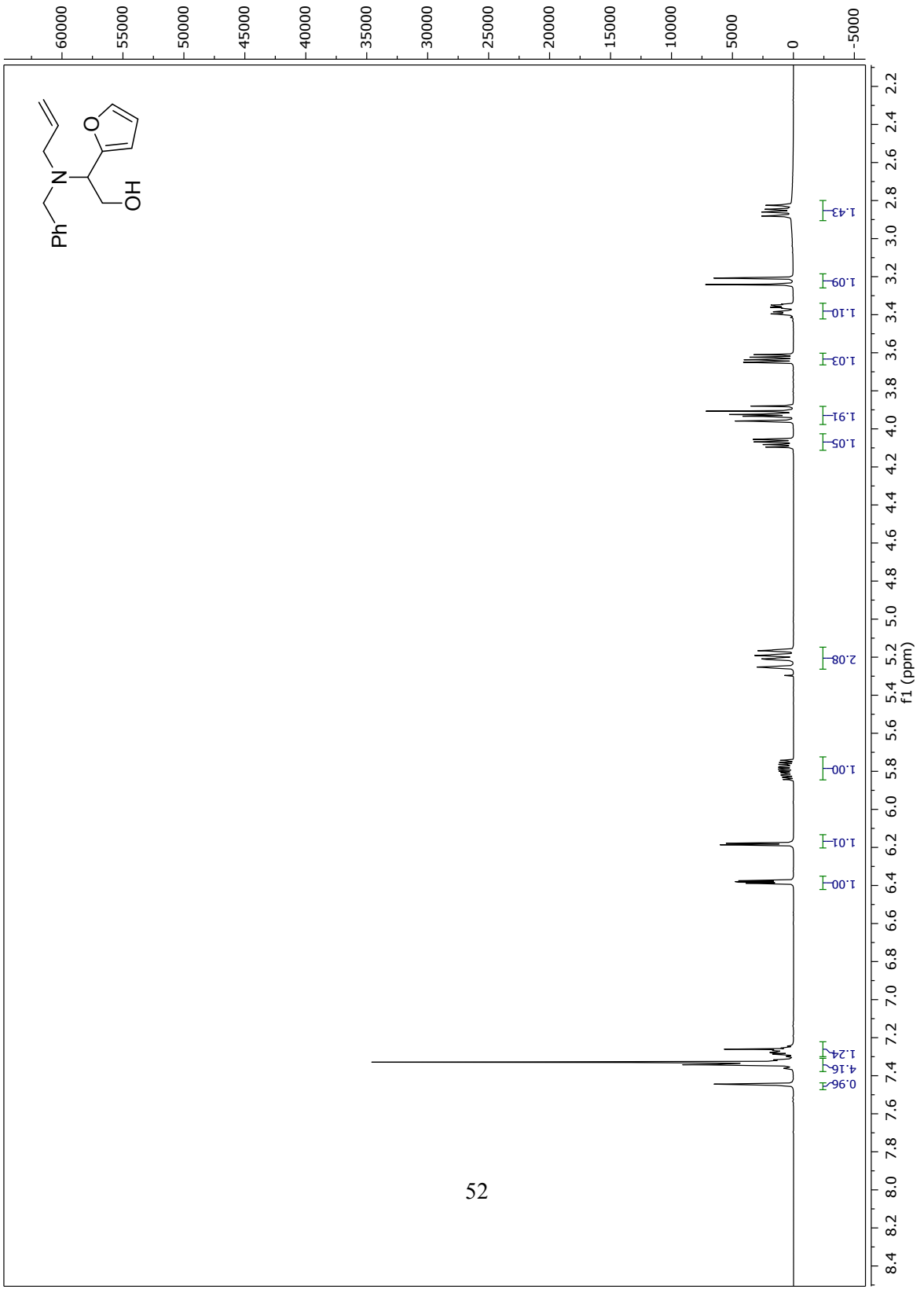
^{1}H NMR (400 MHz, $CDCl_3$) of **8a**

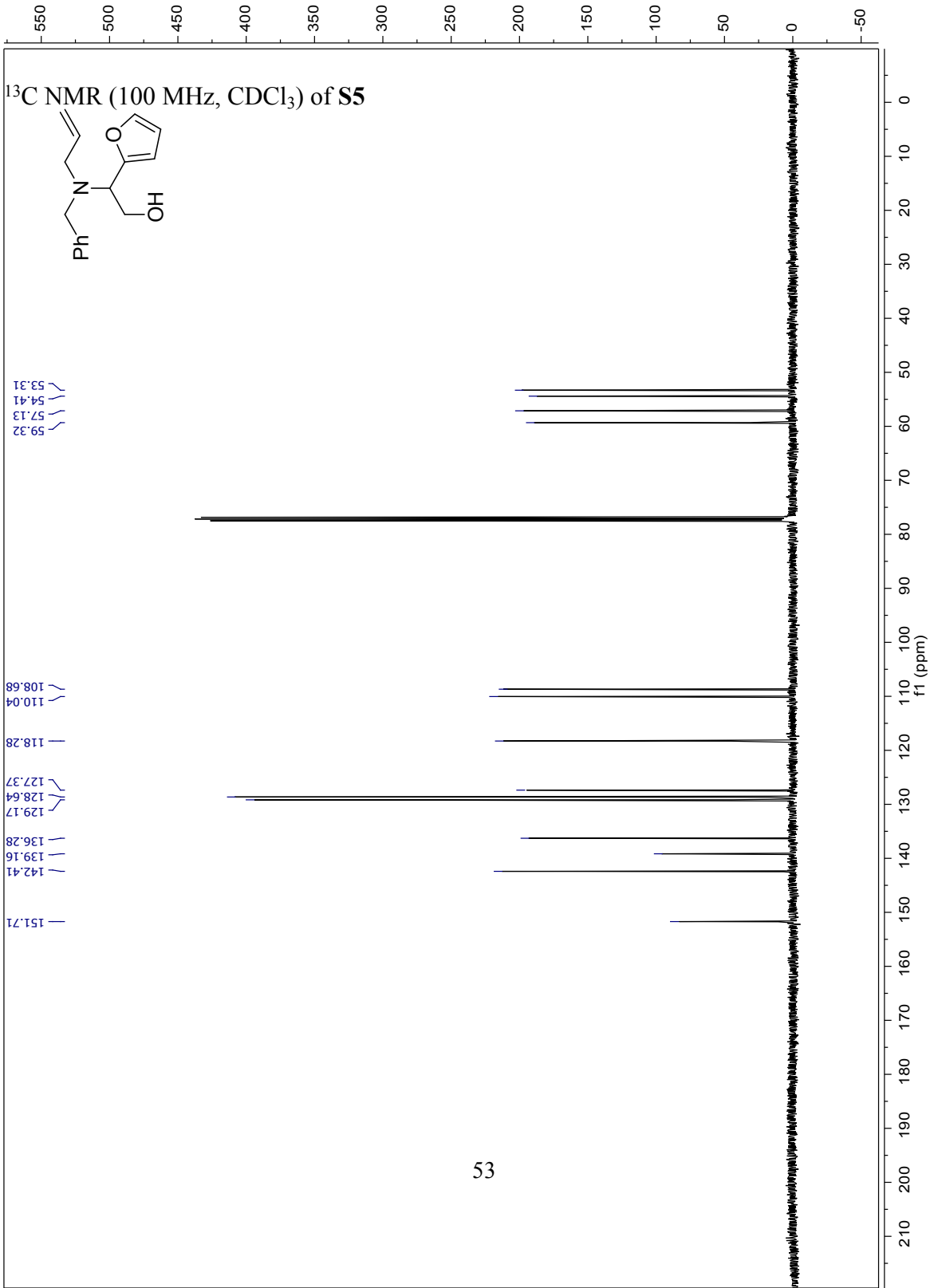


^{13}C NMR (100 MHz, $CDCl_3$) of **8a**

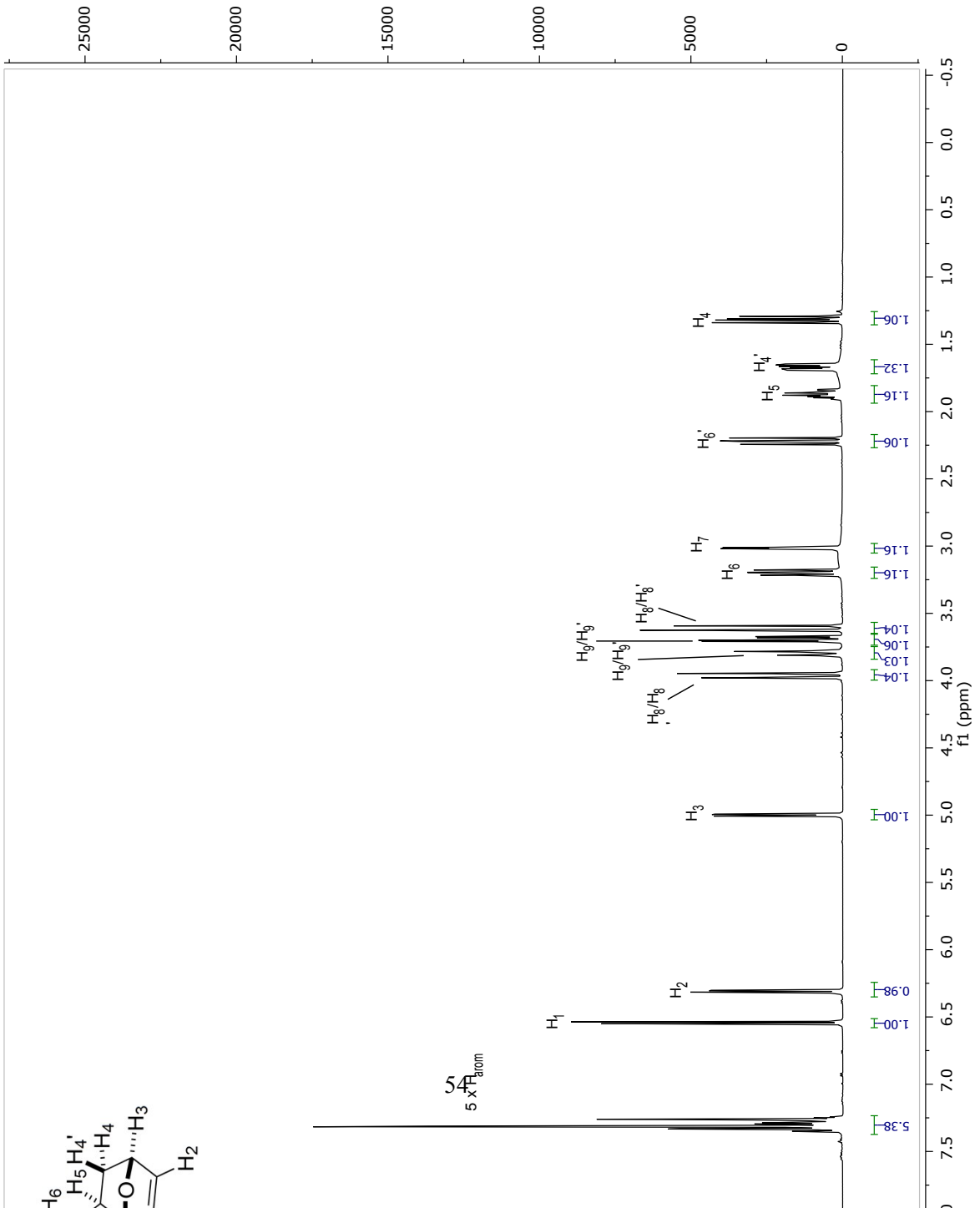


^{1}H NMR (400 MHz, $CDCl_3$) of **S5**

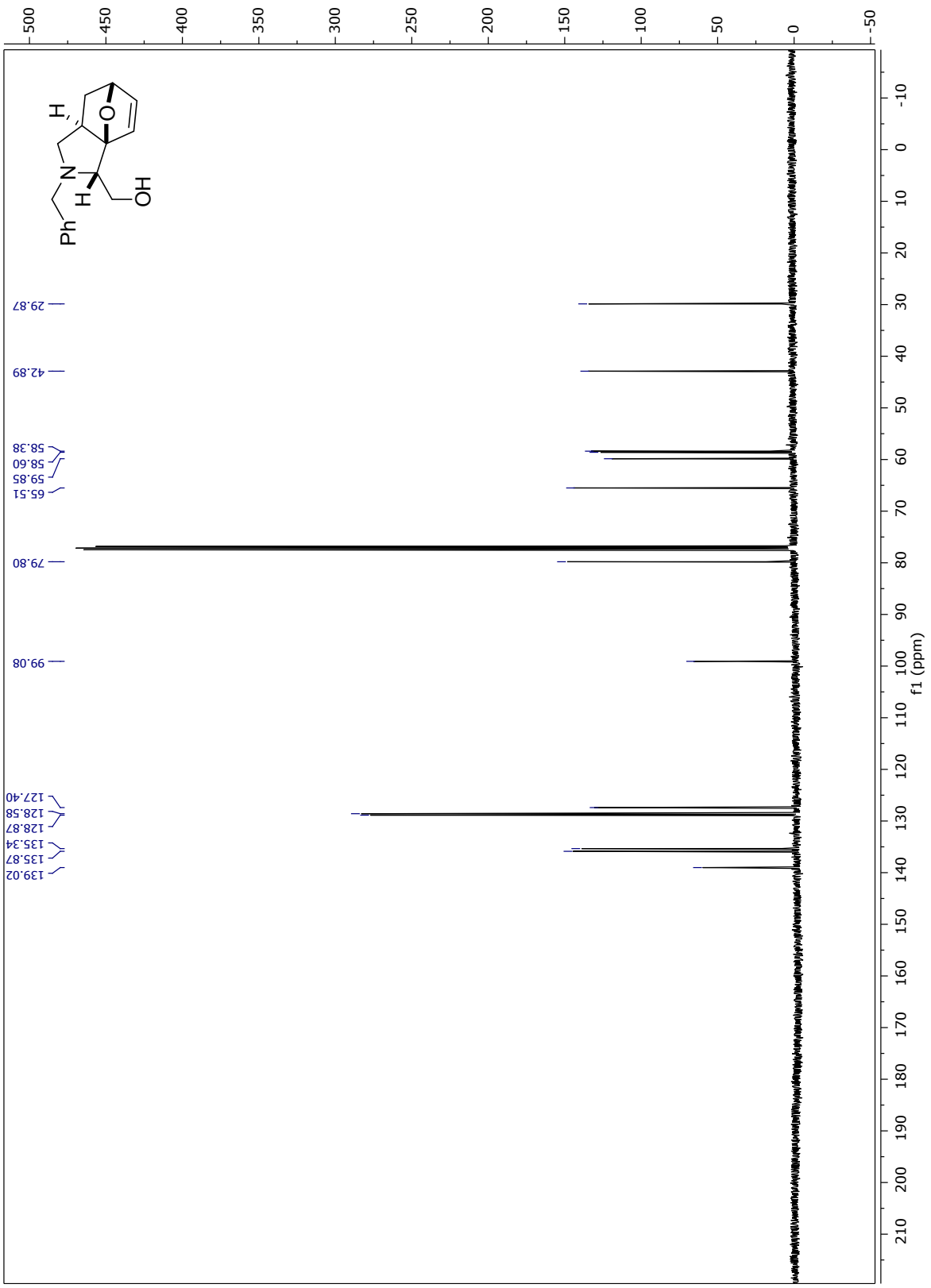



^{13}C NMR (100 MHz, $CDCl_3$) of **S5**
Ph
N
O
OH
59.32
57.13
54.41
53.31
110.04
108.68
118.28
127.37
128.64
129.17
136.28
139.16
142.41
151.71
f1 (ppm)

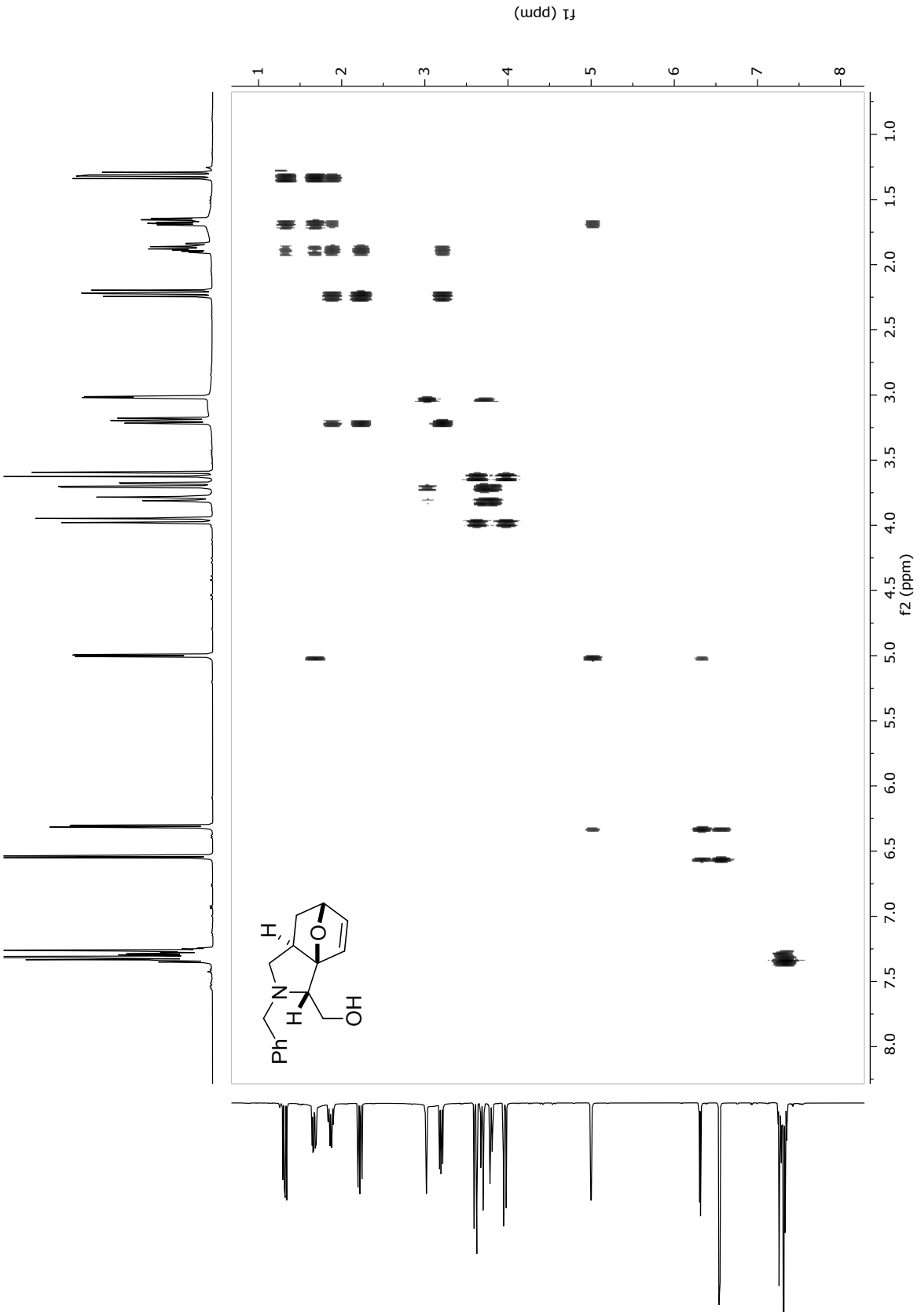
^{1}H NMR (400 MHz, $CDCl_3$) of **8b**



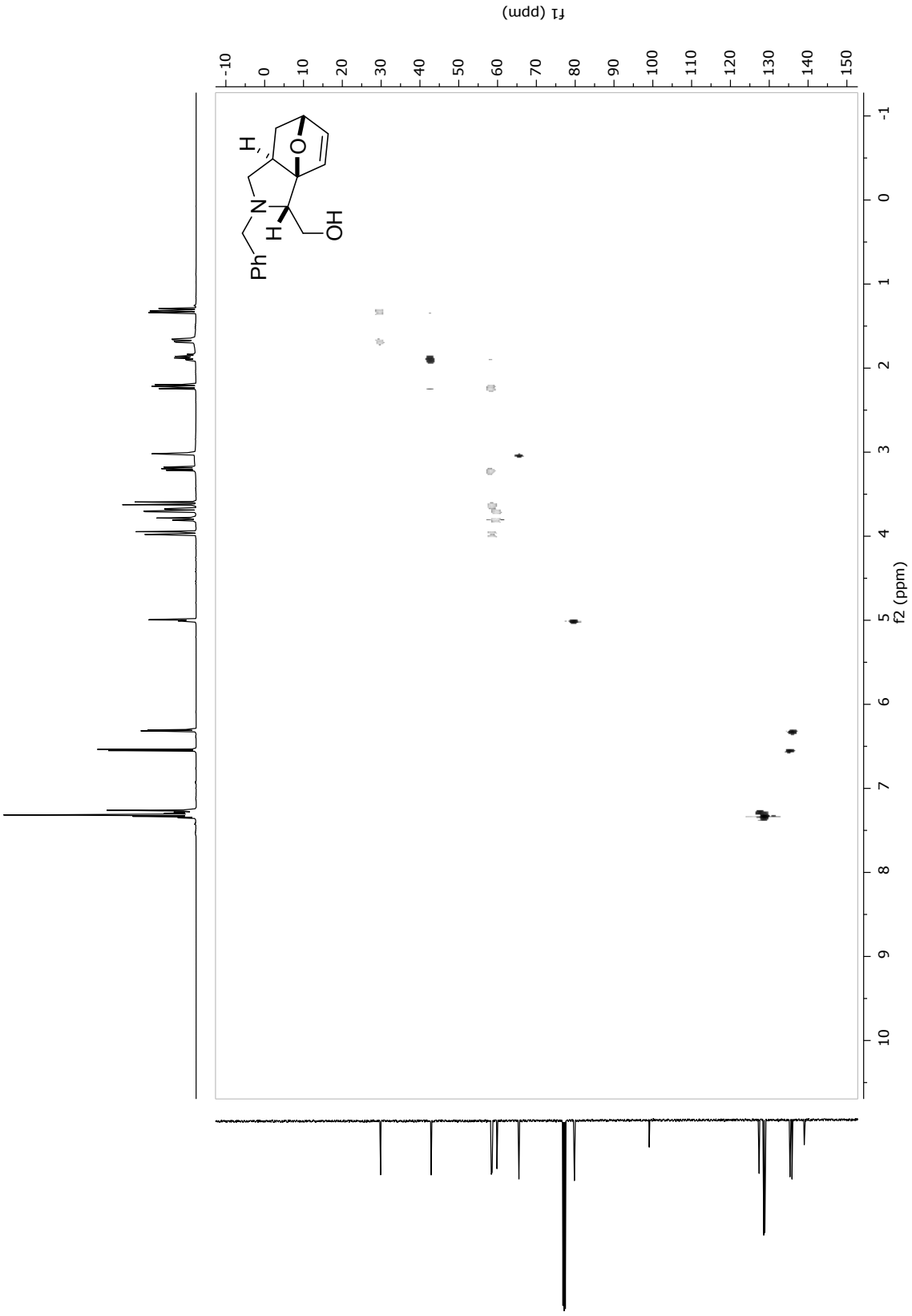
^{13}C NMR (100 MHz, $CDCl_3$) of **8b**



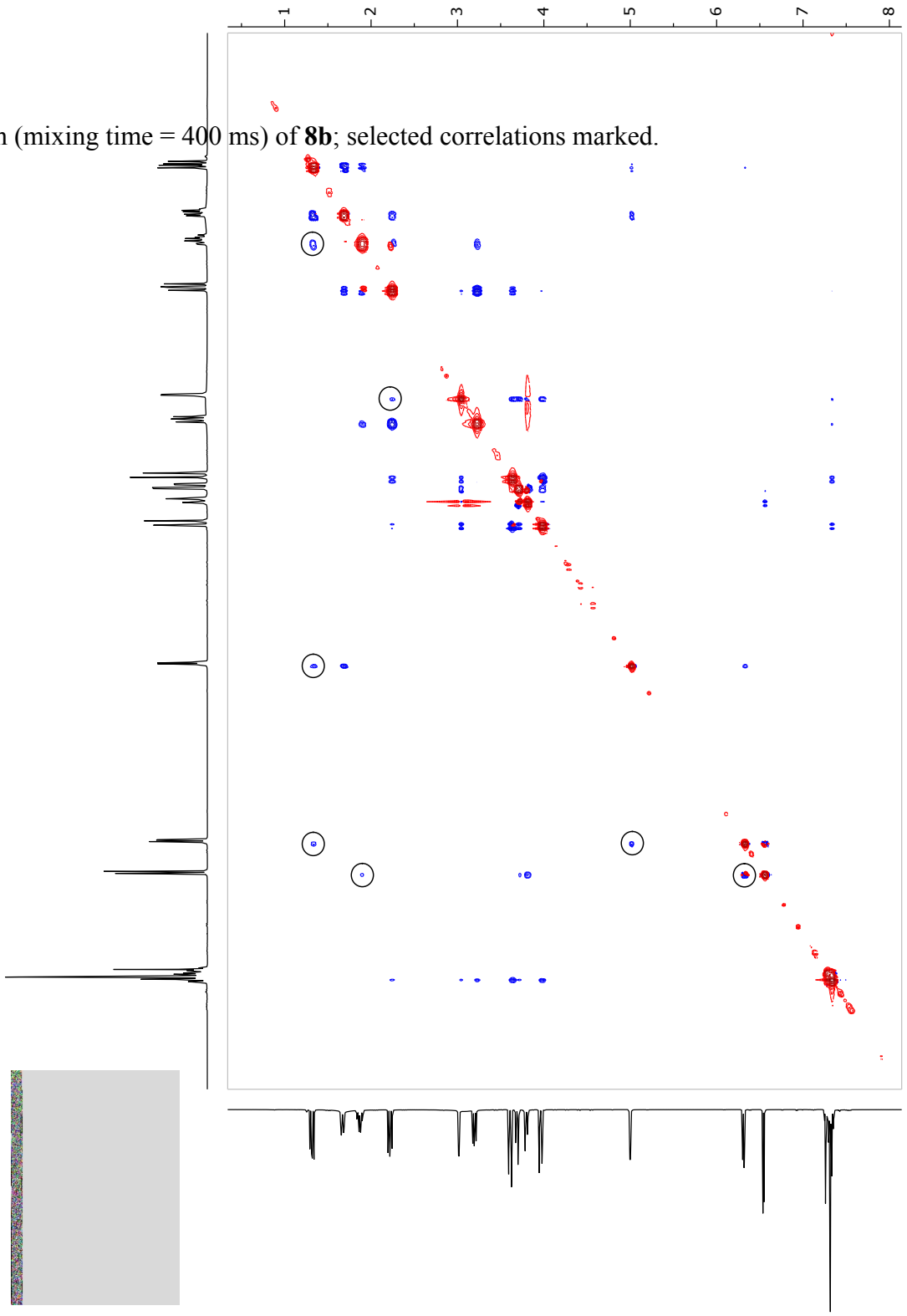
gCOSY (400 MHz, $CDCl_3$) of **8b**



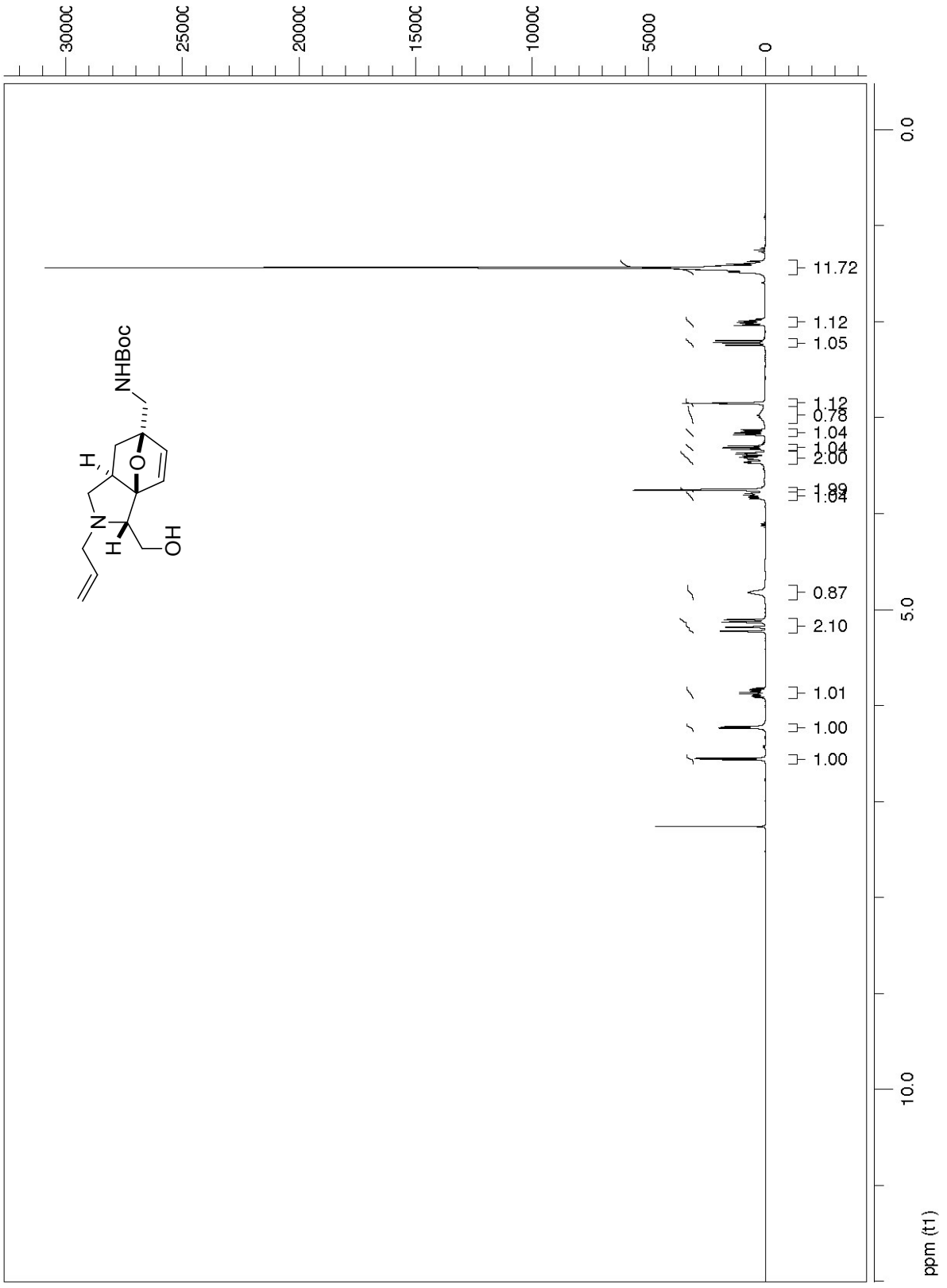
HSQC (400 MHz, $CDCl_3$) of **8b**



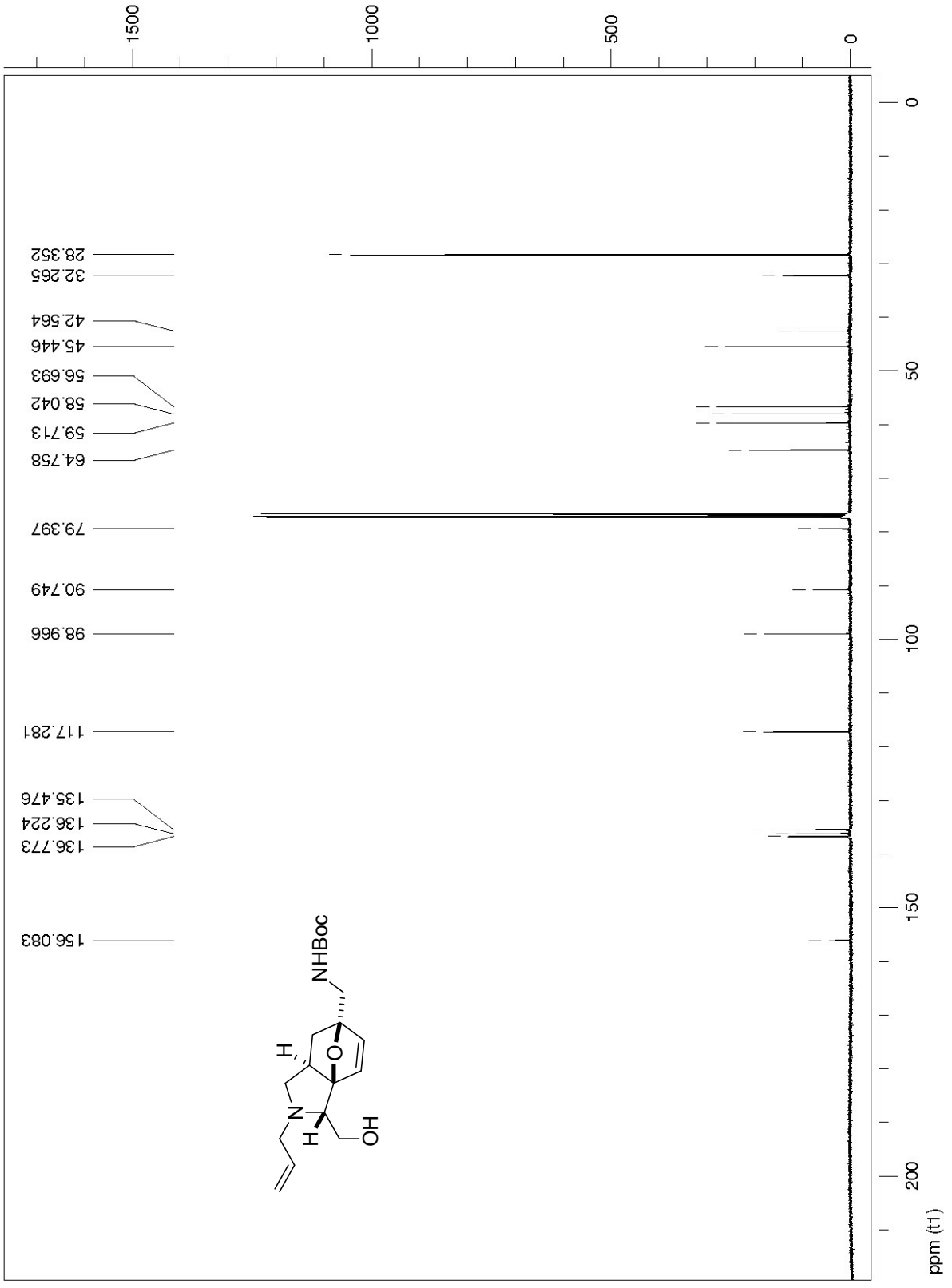
2D NOESY spectrum (mixing time = 400 ms) of **8b**; selected correlations marked.



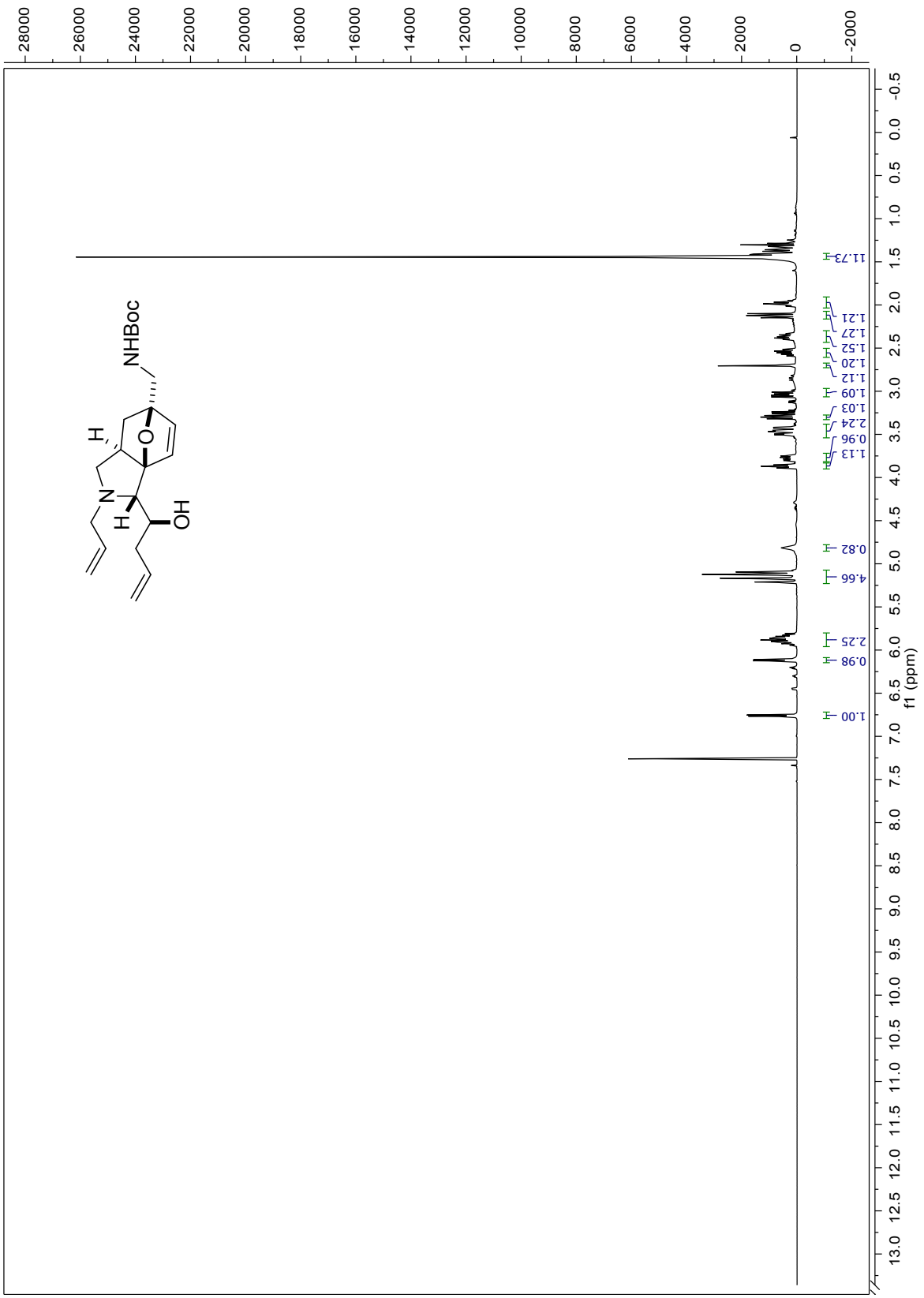
^{1}H NMR (400 MHz, $CDCl_3$) of **8c**



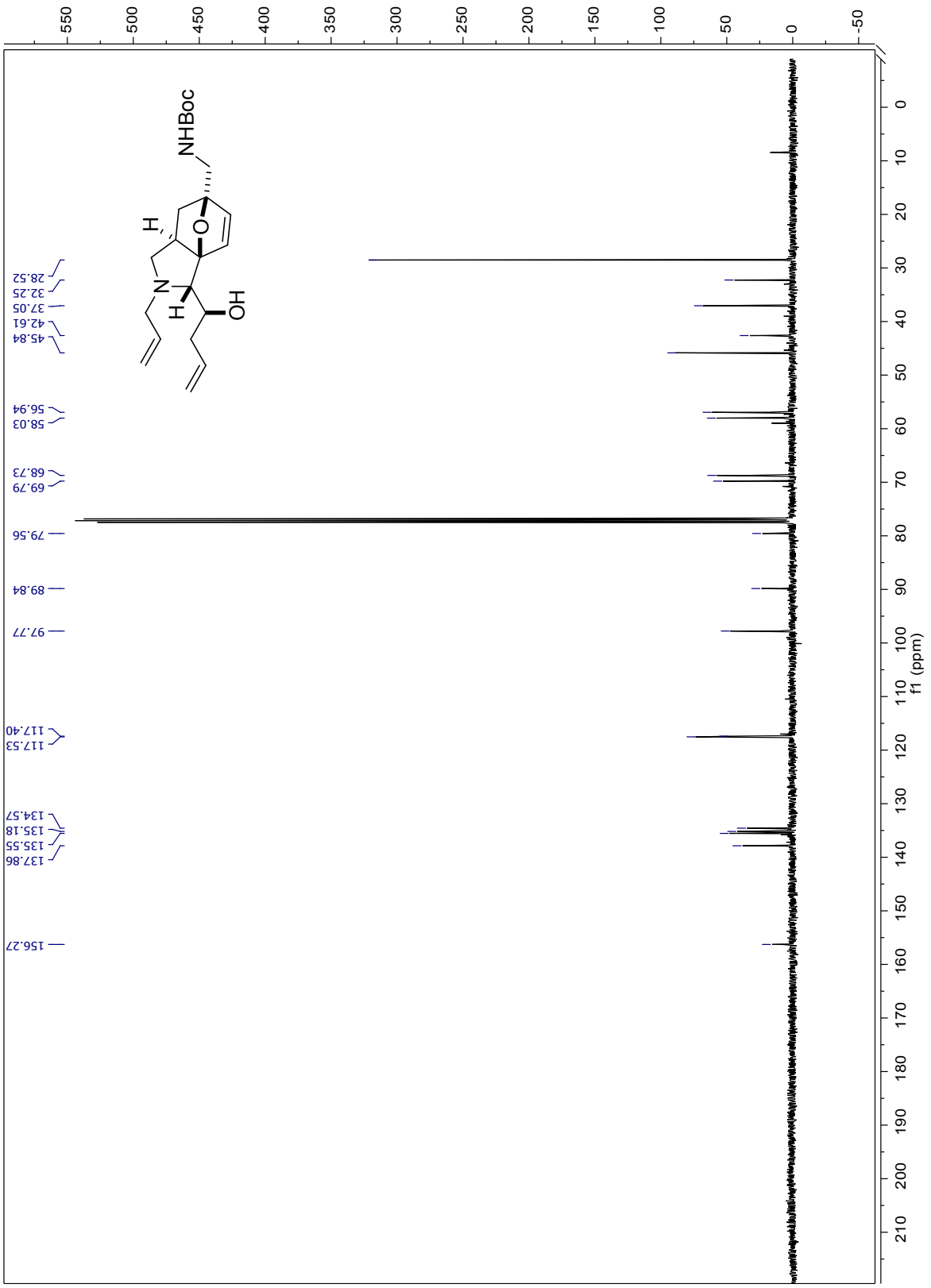
^{13}C NMR (100 MHz, $CDCl_3$) of **8c**



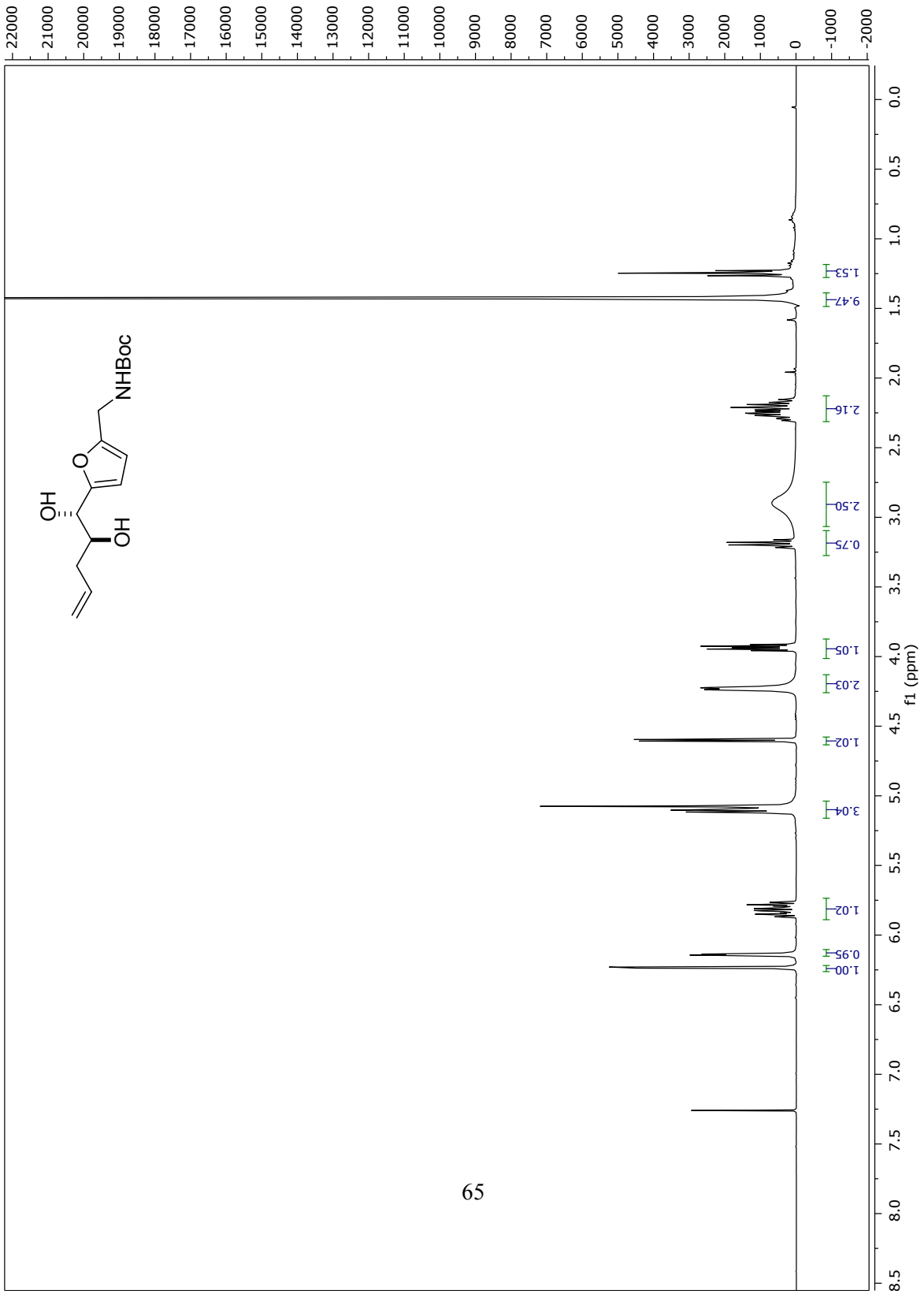
^{1}H NMR (400 MHz, $CDCl_3$) of **8d**



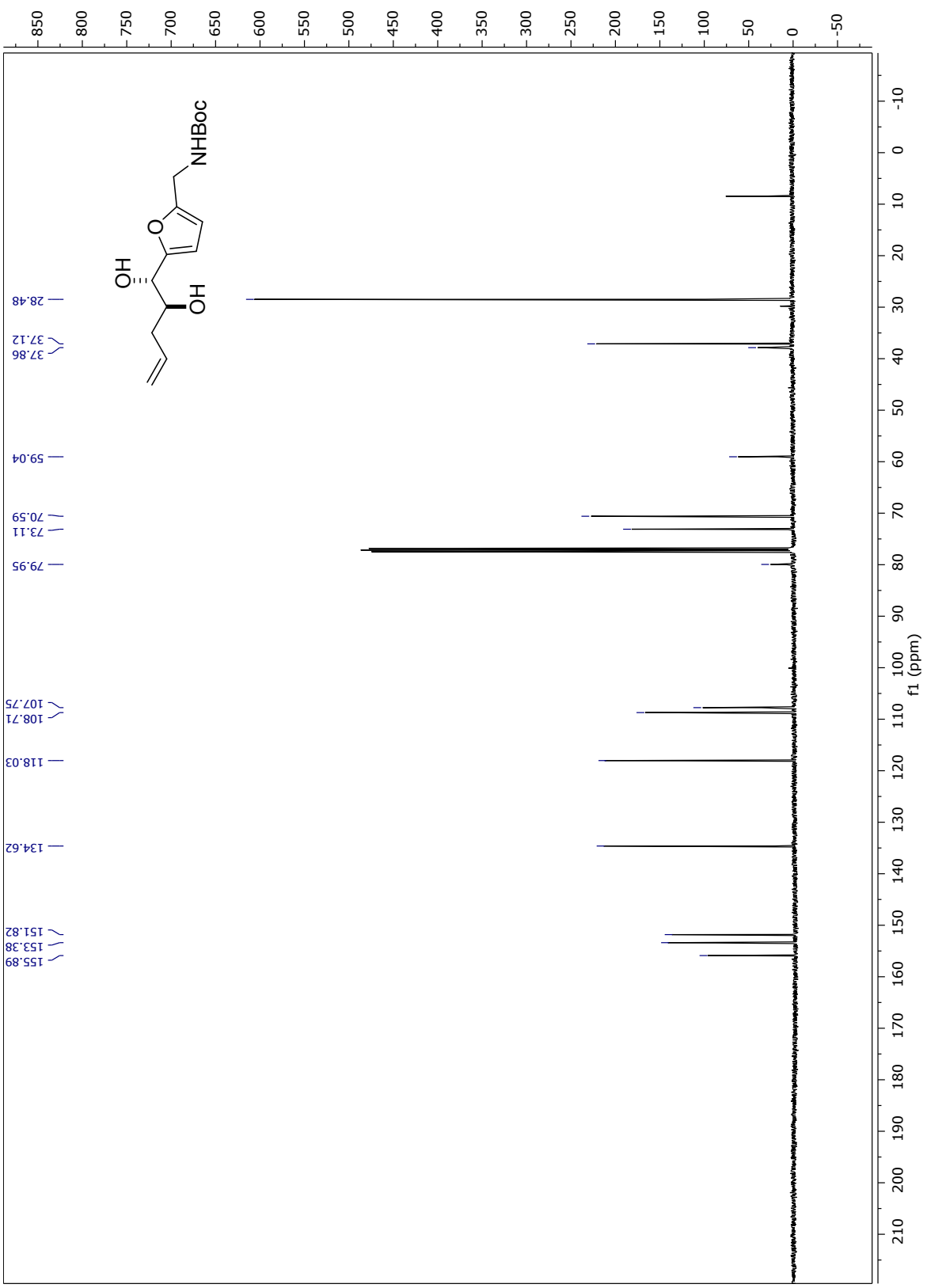
^{13}C NMR (100 MHz, $CDCl_3$) of **8d**



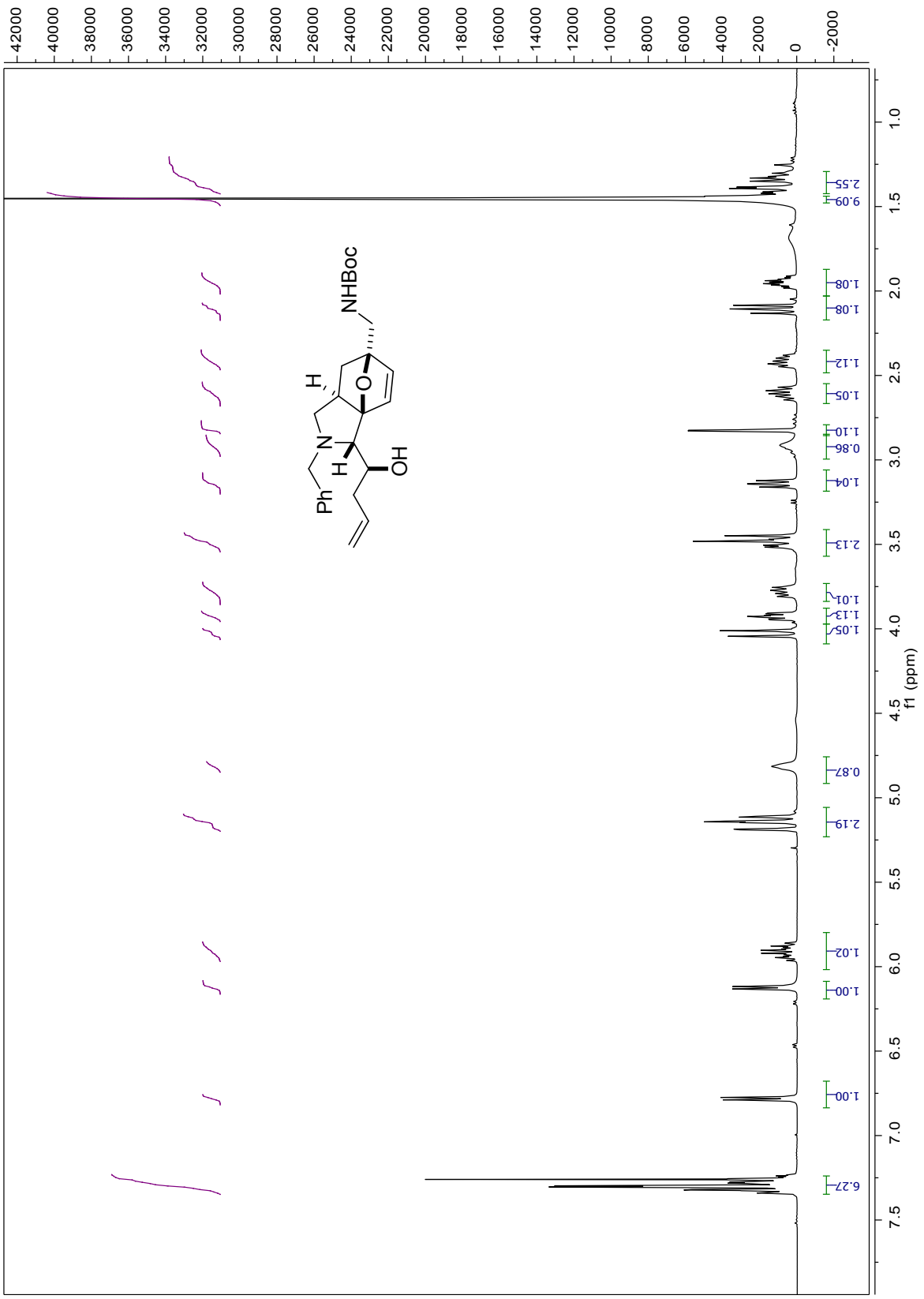
^{1}H NMR (400 MHz, $CDCl_3$) of **S3**



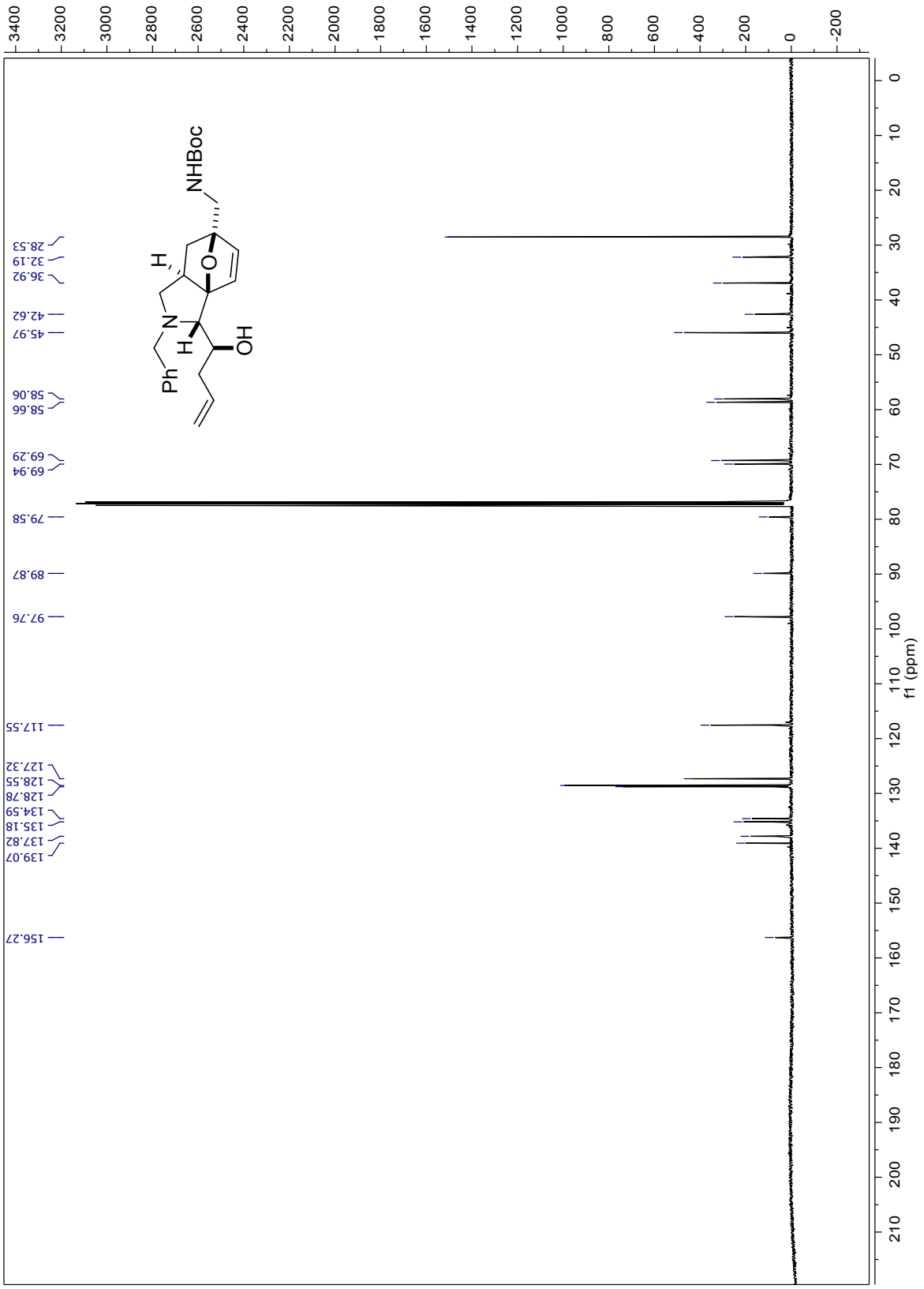
^{13}C NMR (100 MHz, $CDCl_3$) of **S3**



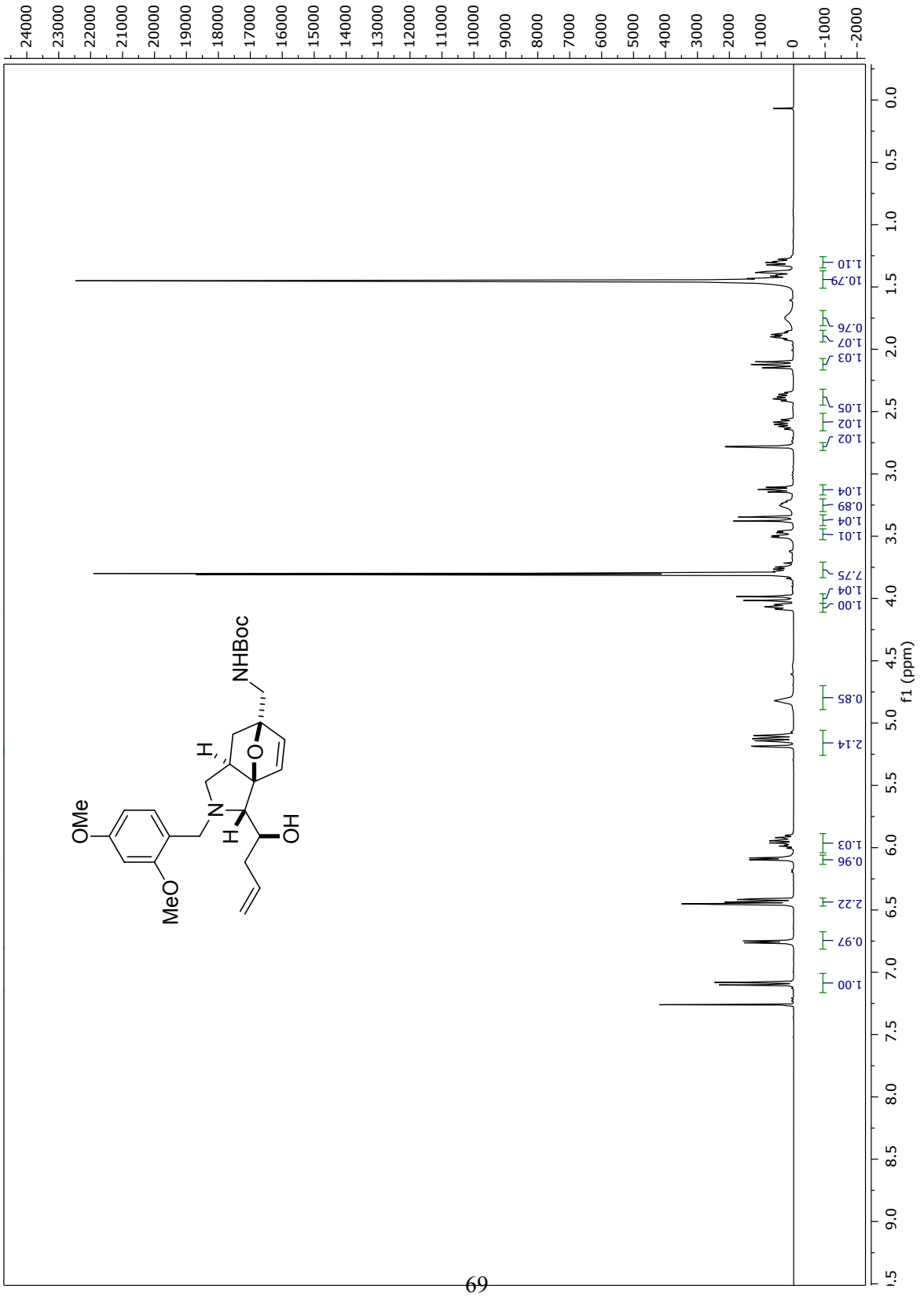
^{1}H NMR (400 MHz, $CDCl_3$) of **8e**



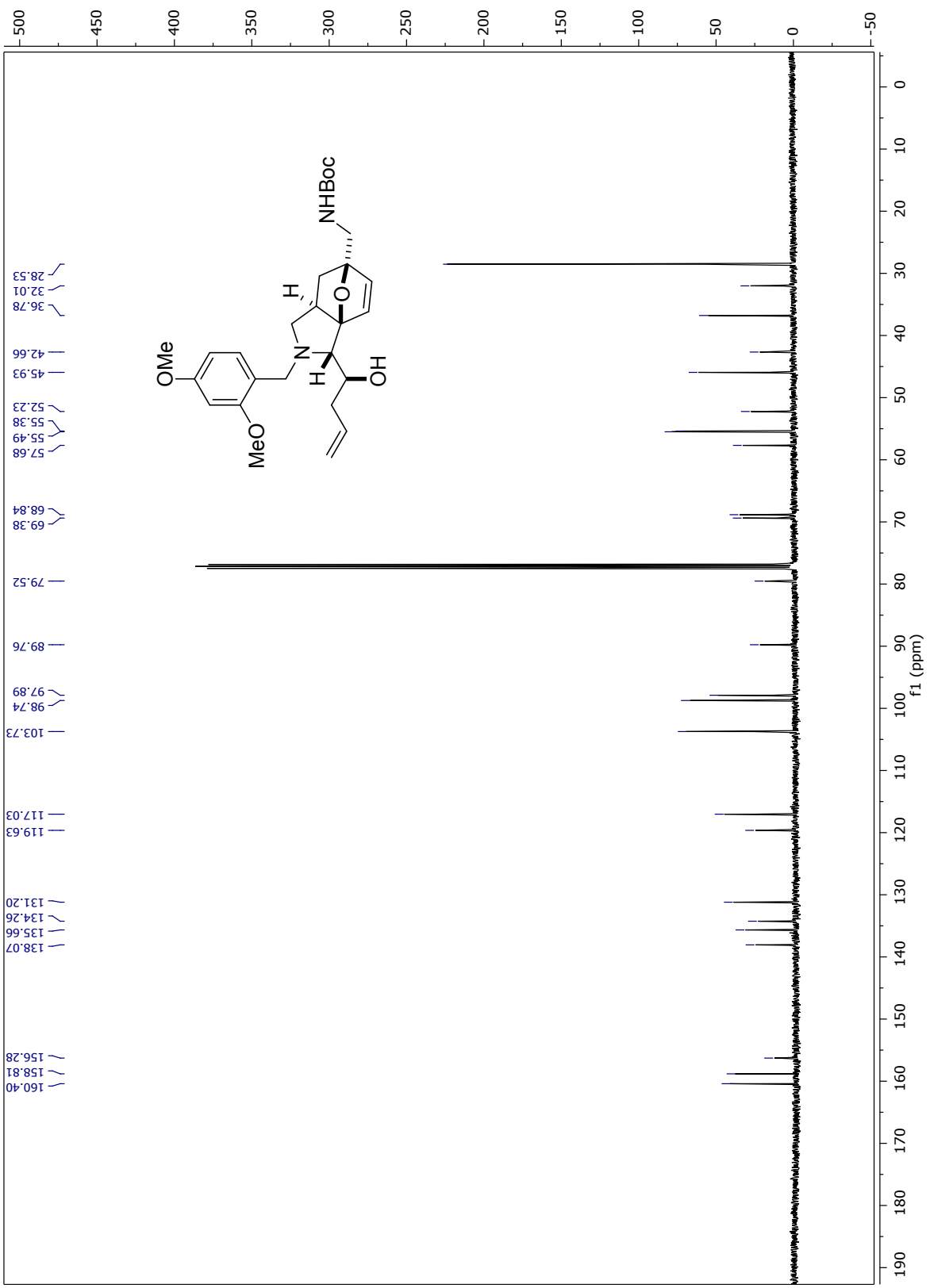
^{13}C NMR (100 MHz, $CDCl_3$) of **8e**



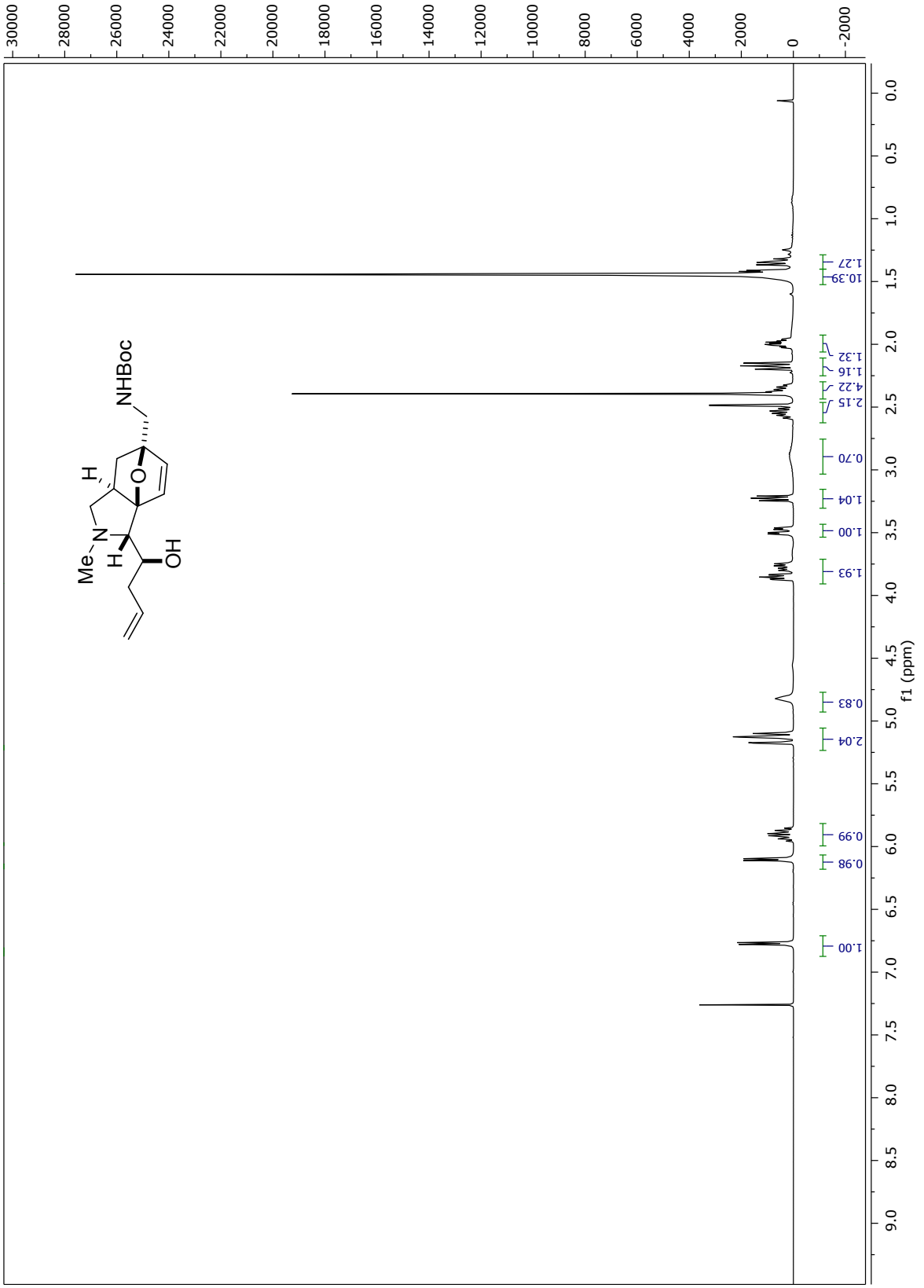
^{1}H NMR (400 MHz, $CDCl_3$) of **8f**



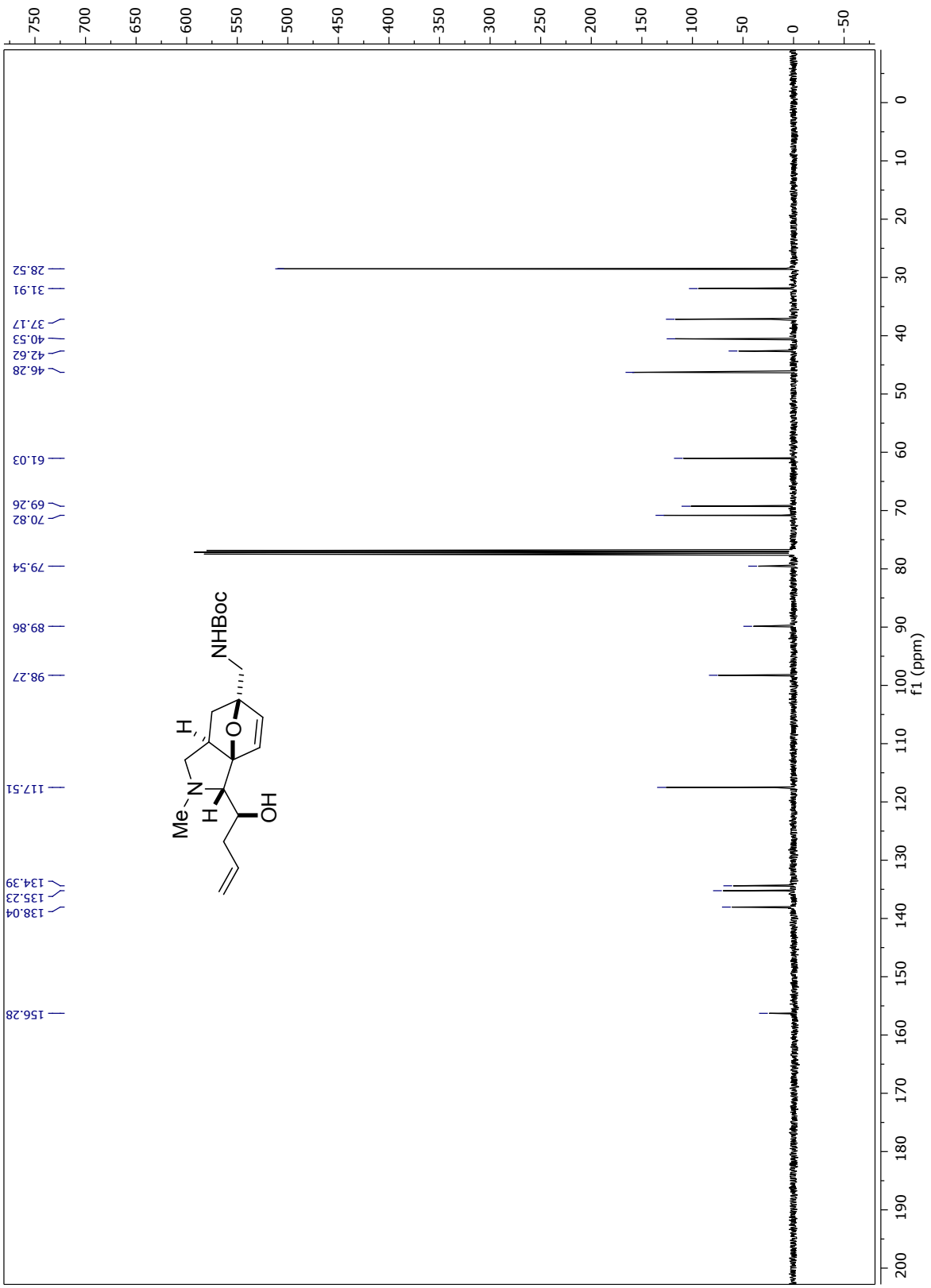
^{13}C NMR (100 MHz, $CDCl_3$) of **8f**



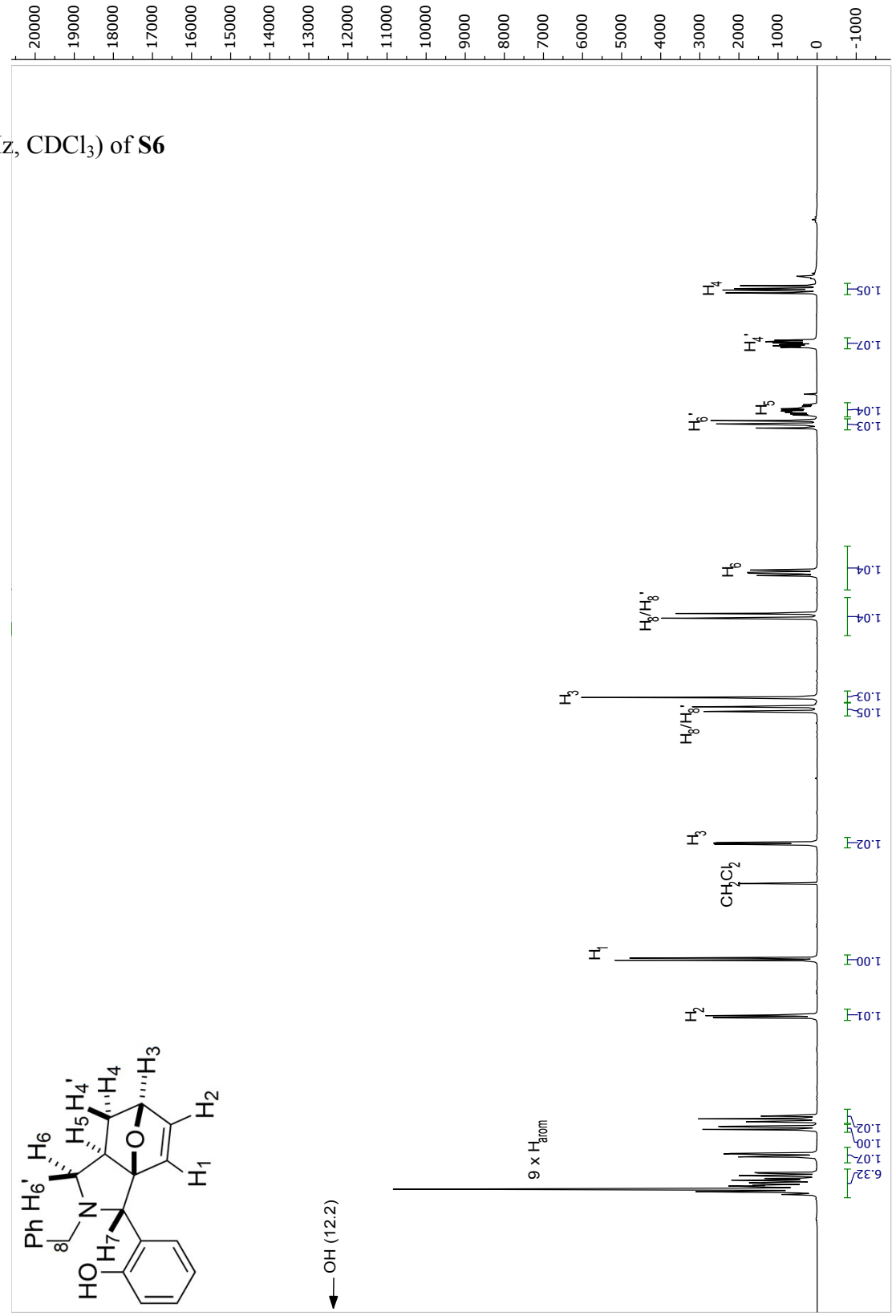
^{1}H NMR (400 MHz, $CDCl_3$) of **8g**



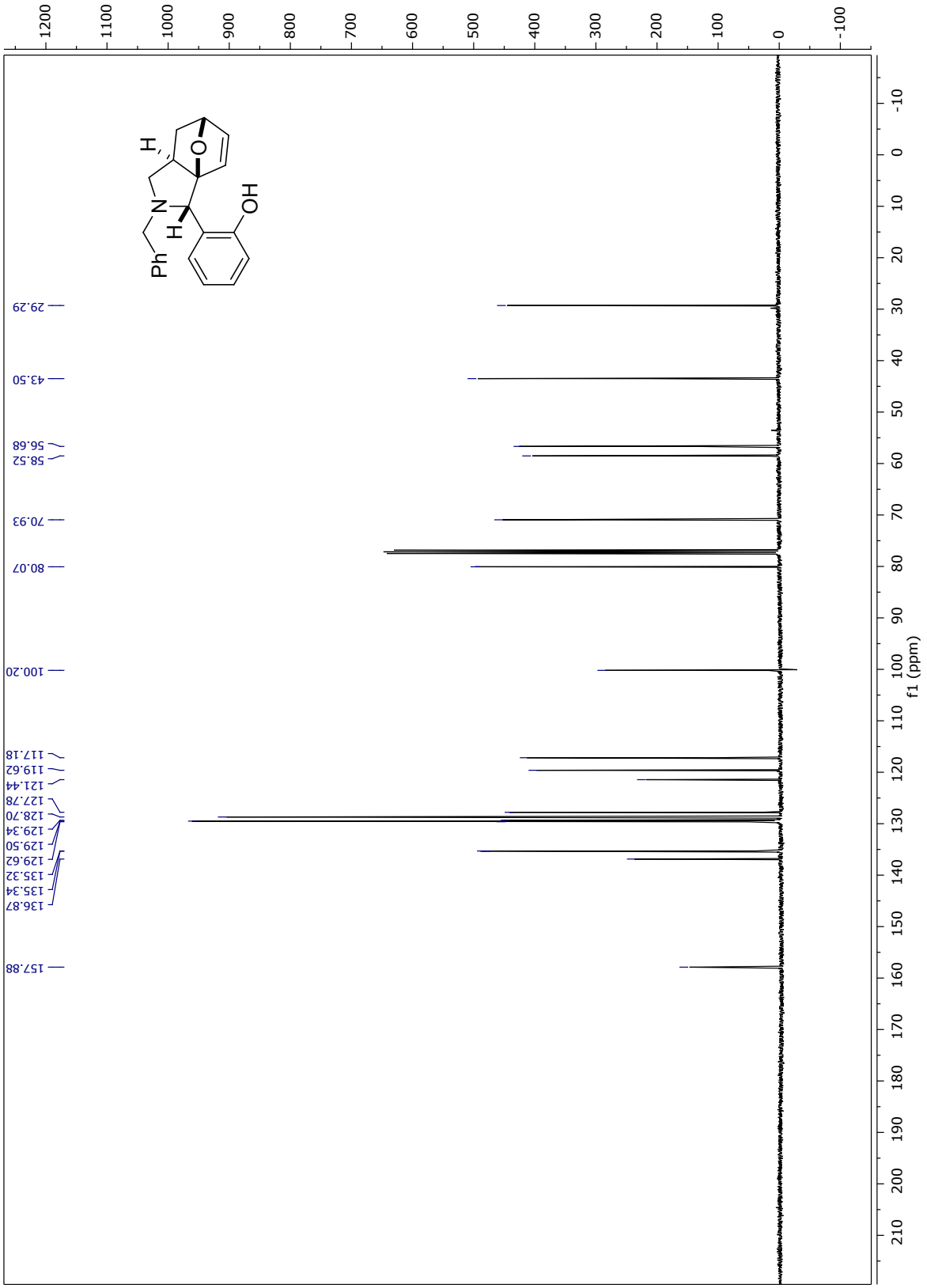
^{13}C NMR (100 MHz, $CDCl_3$) of **8g**



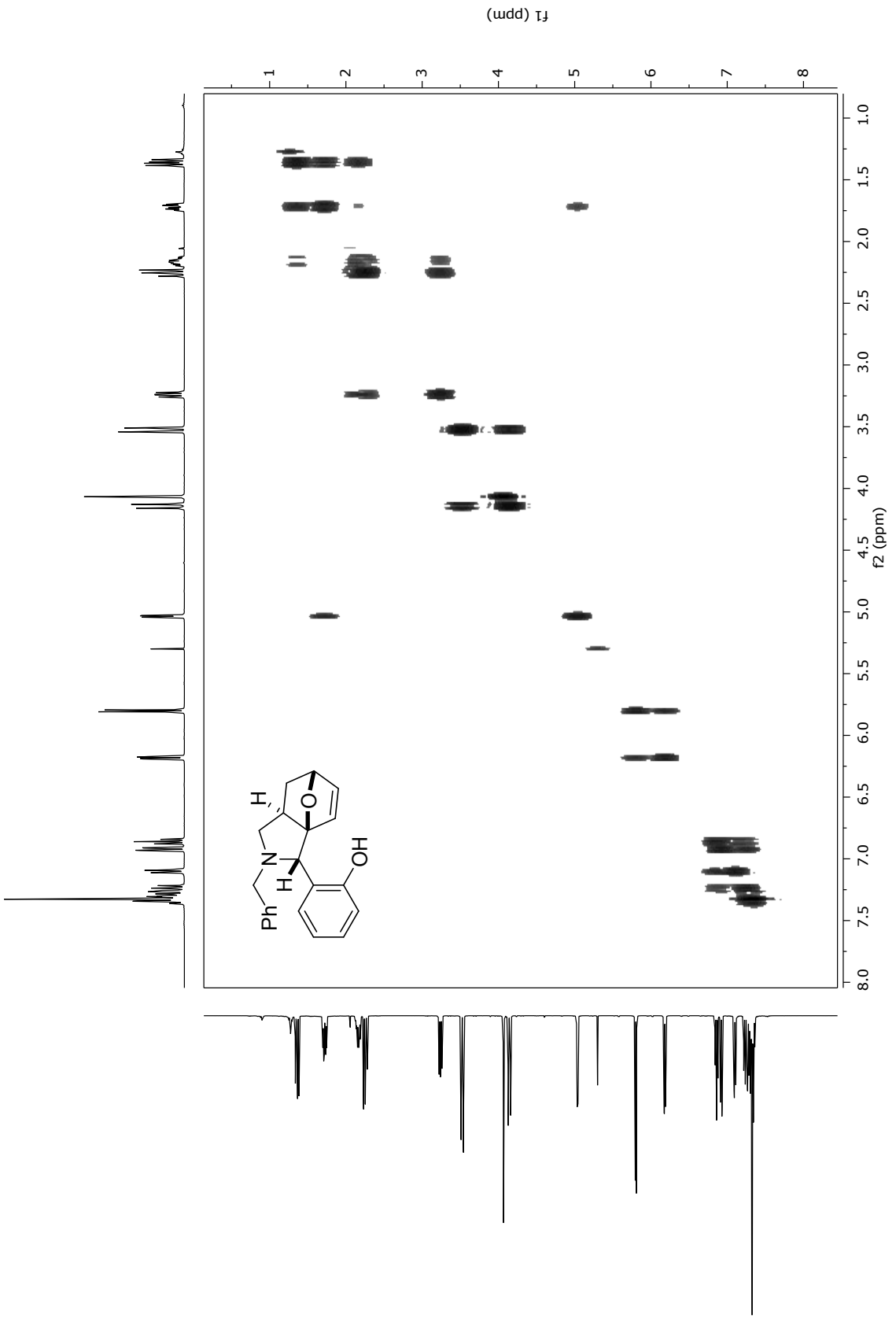
^{1}H NMR (400 MHz, $CDCl_3$) of **S6**



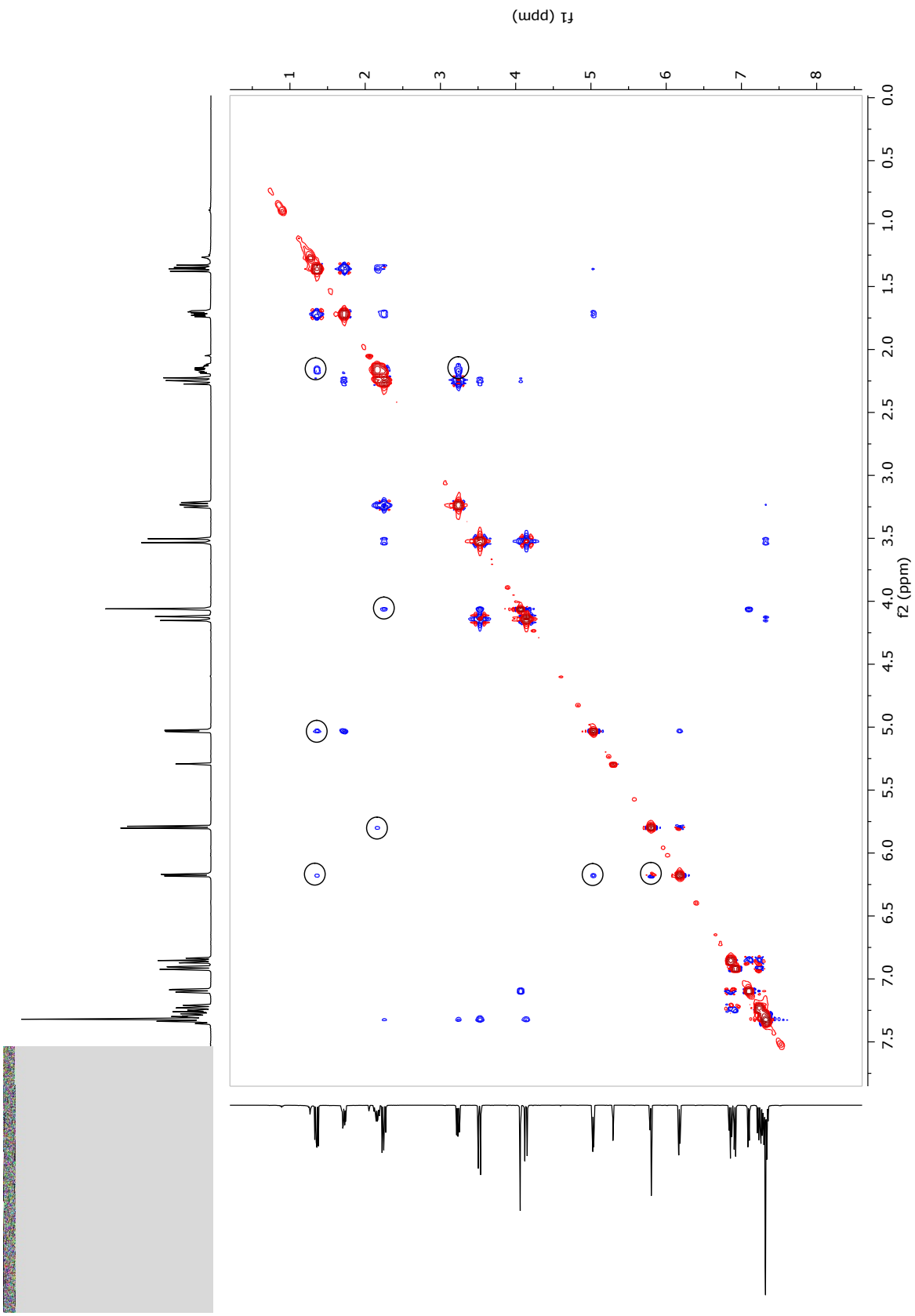
^{13}C NMR (100 MHz, $CDCl_3$) of **S6**



gCOSY (400 MHz, $CDCl_3$) of **S6**

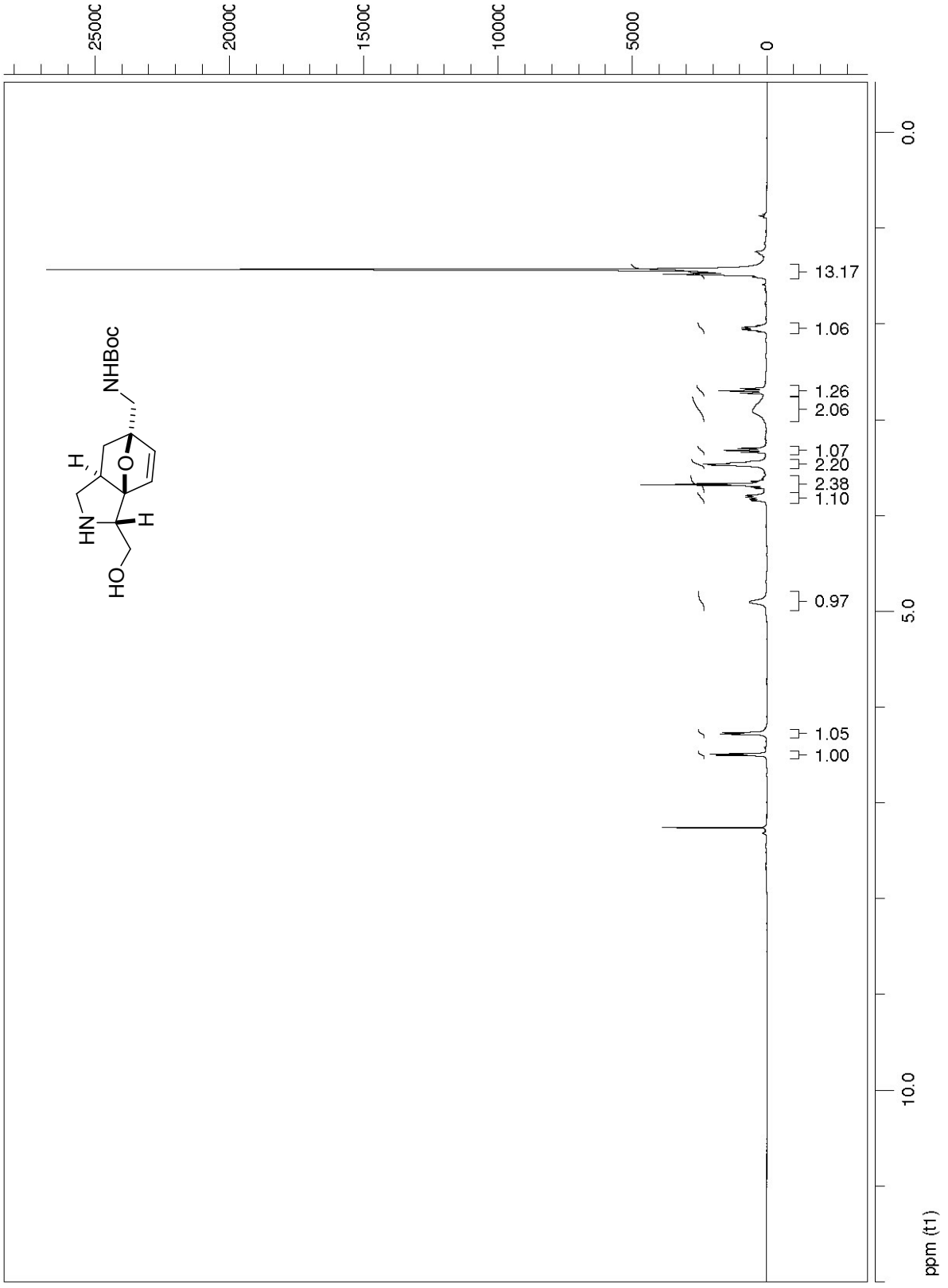


2D NOESY spectrum (mixing time = 400 ms) of **S6**; selected correlations marked.

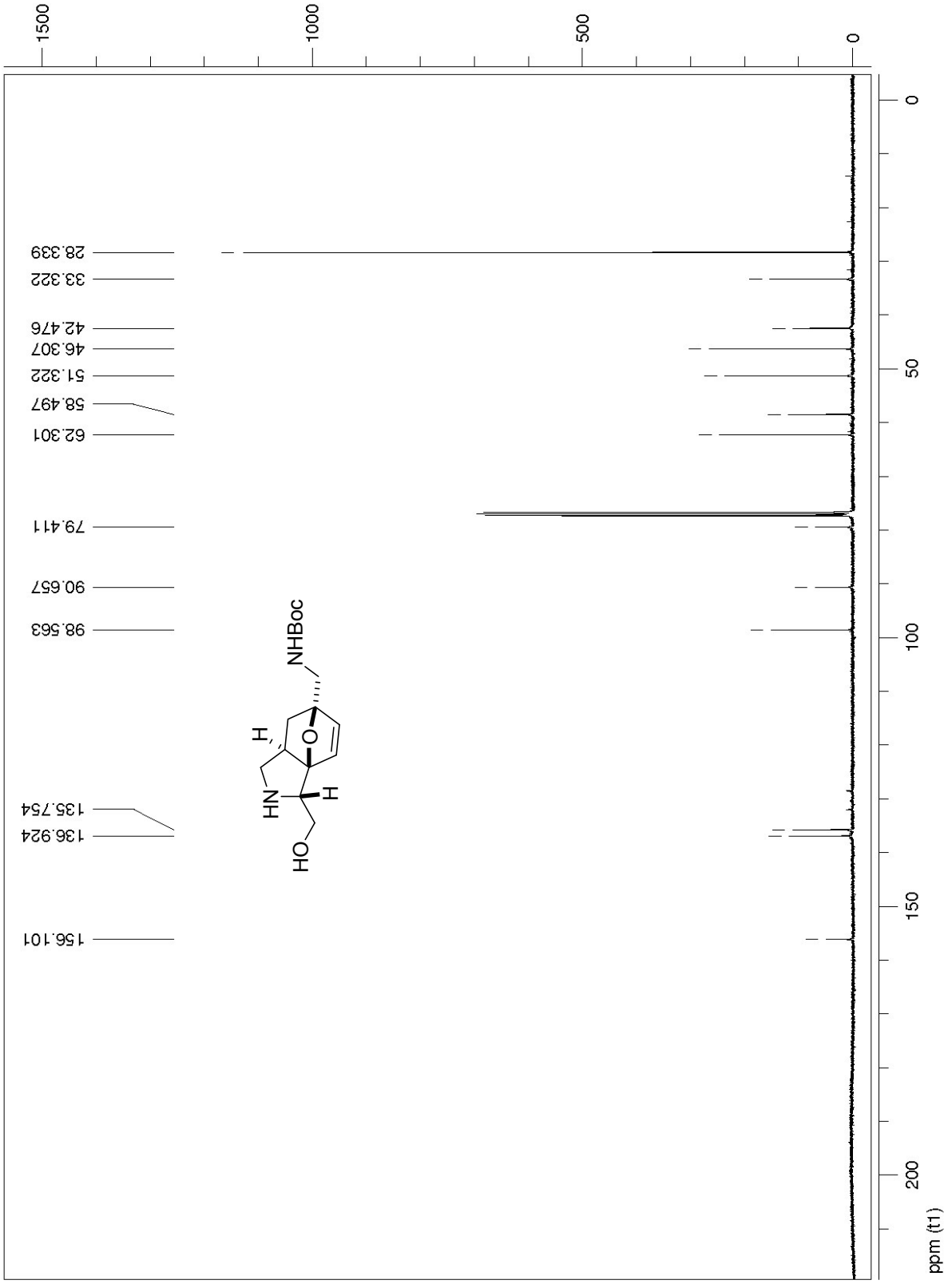


NMR Spectra for Diversified Petasis 3-CR/IMDA Products

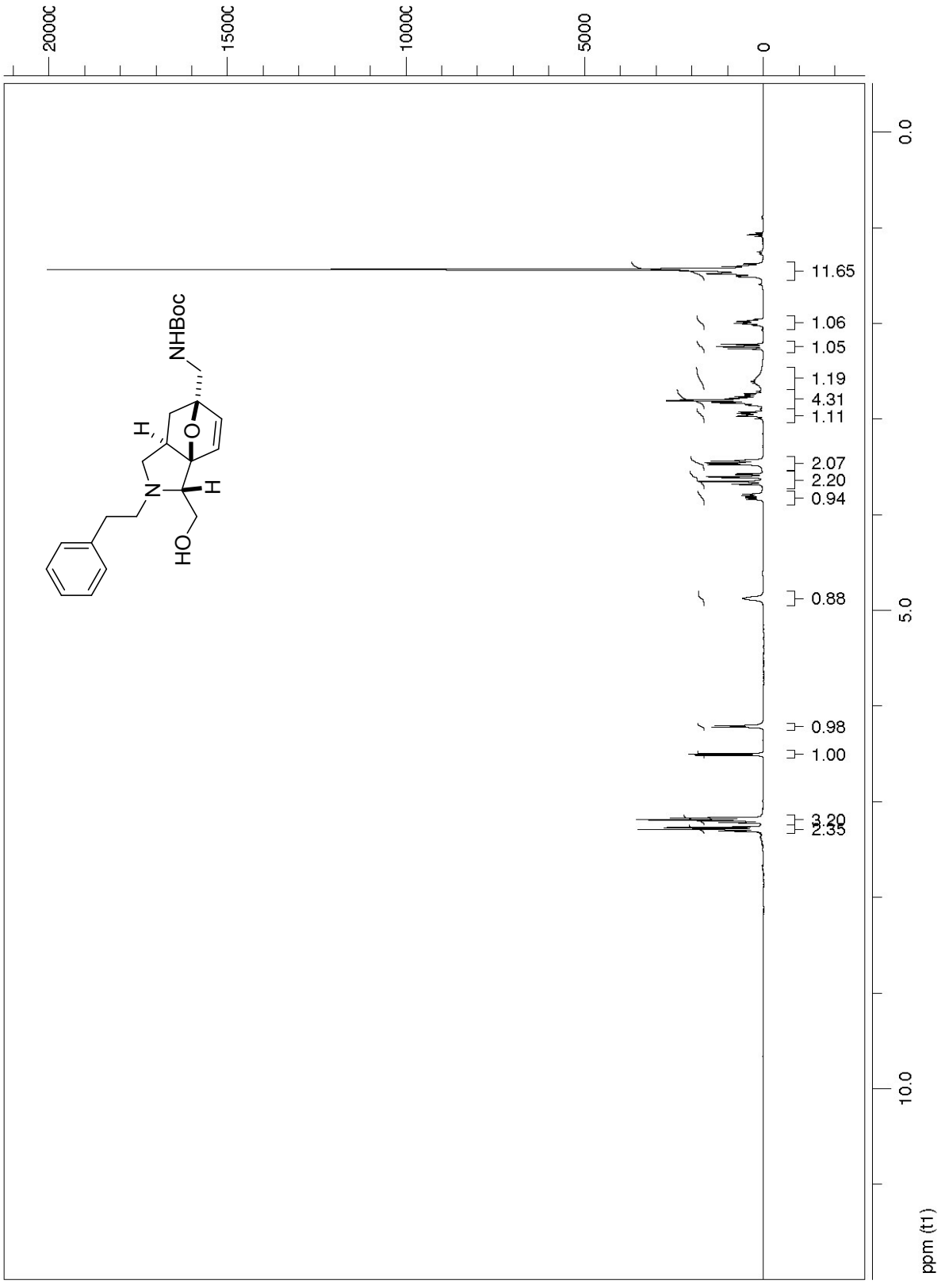
^{1}H NMR (400 MHz, $CDCl_3$) of **9**



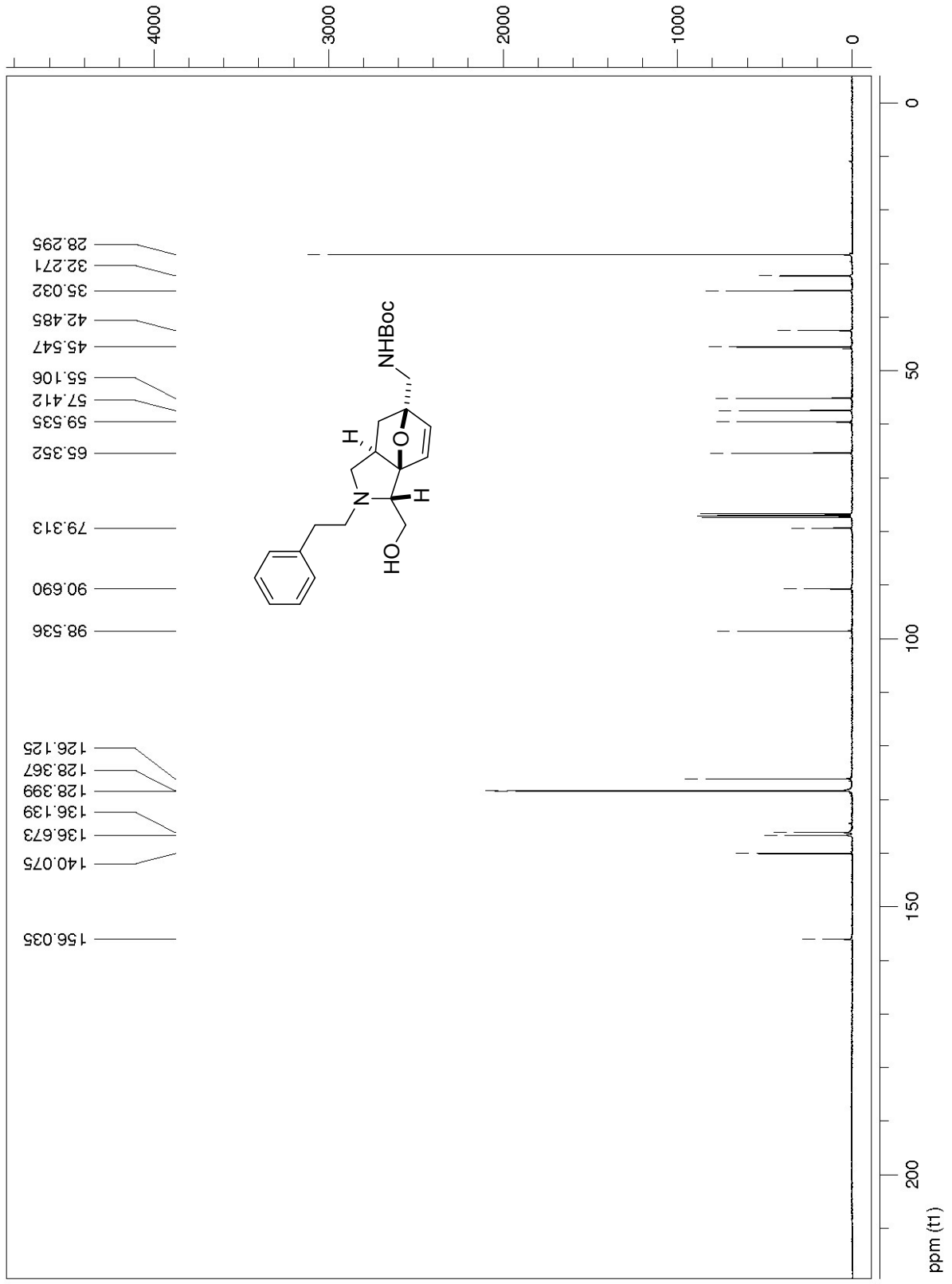
^{13}C NMR (100 MHz, $CDCl_3$) of **9**



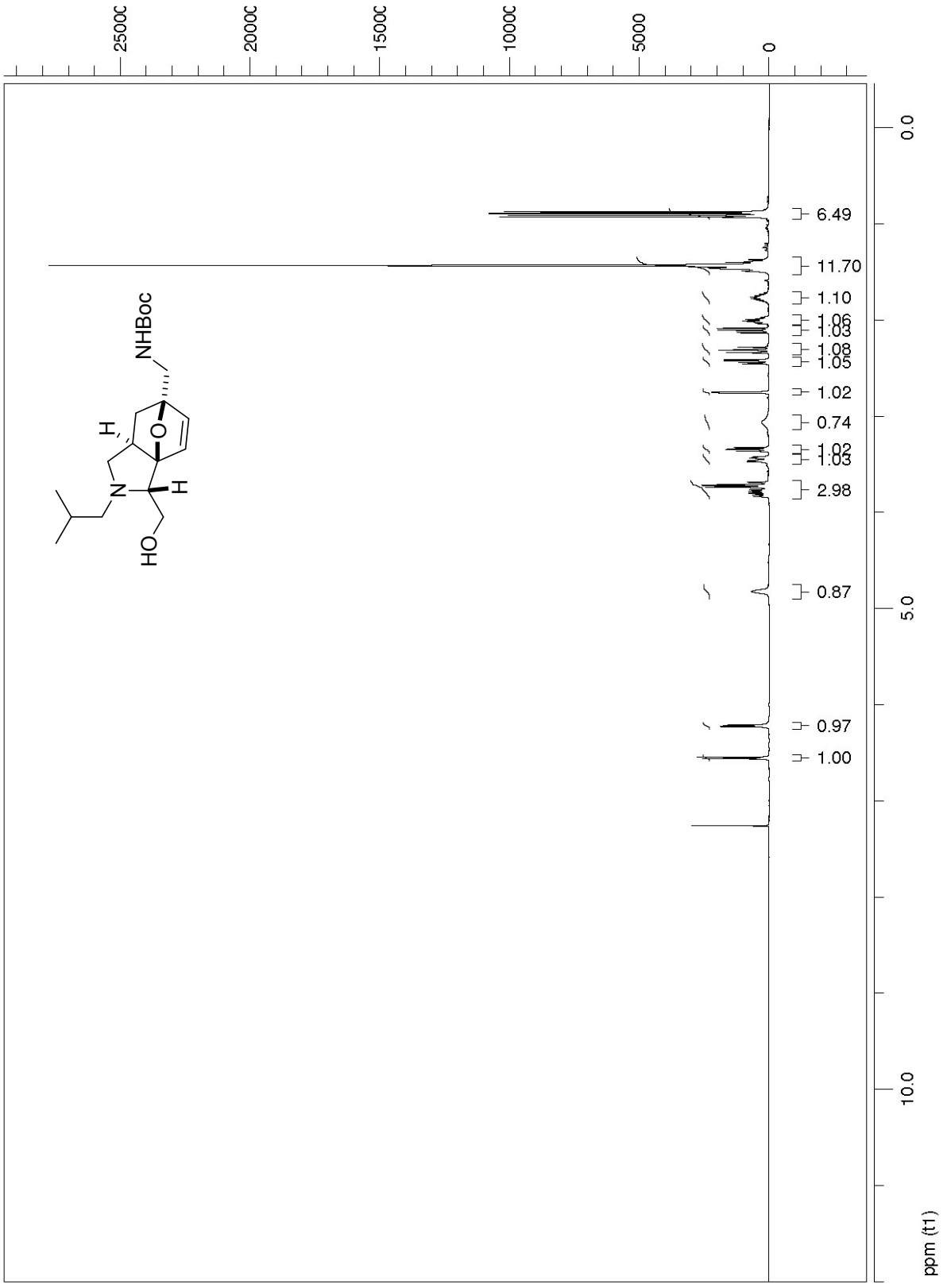
^{1}H NMR (400 MHz, $CDCl_3$) of **10a**



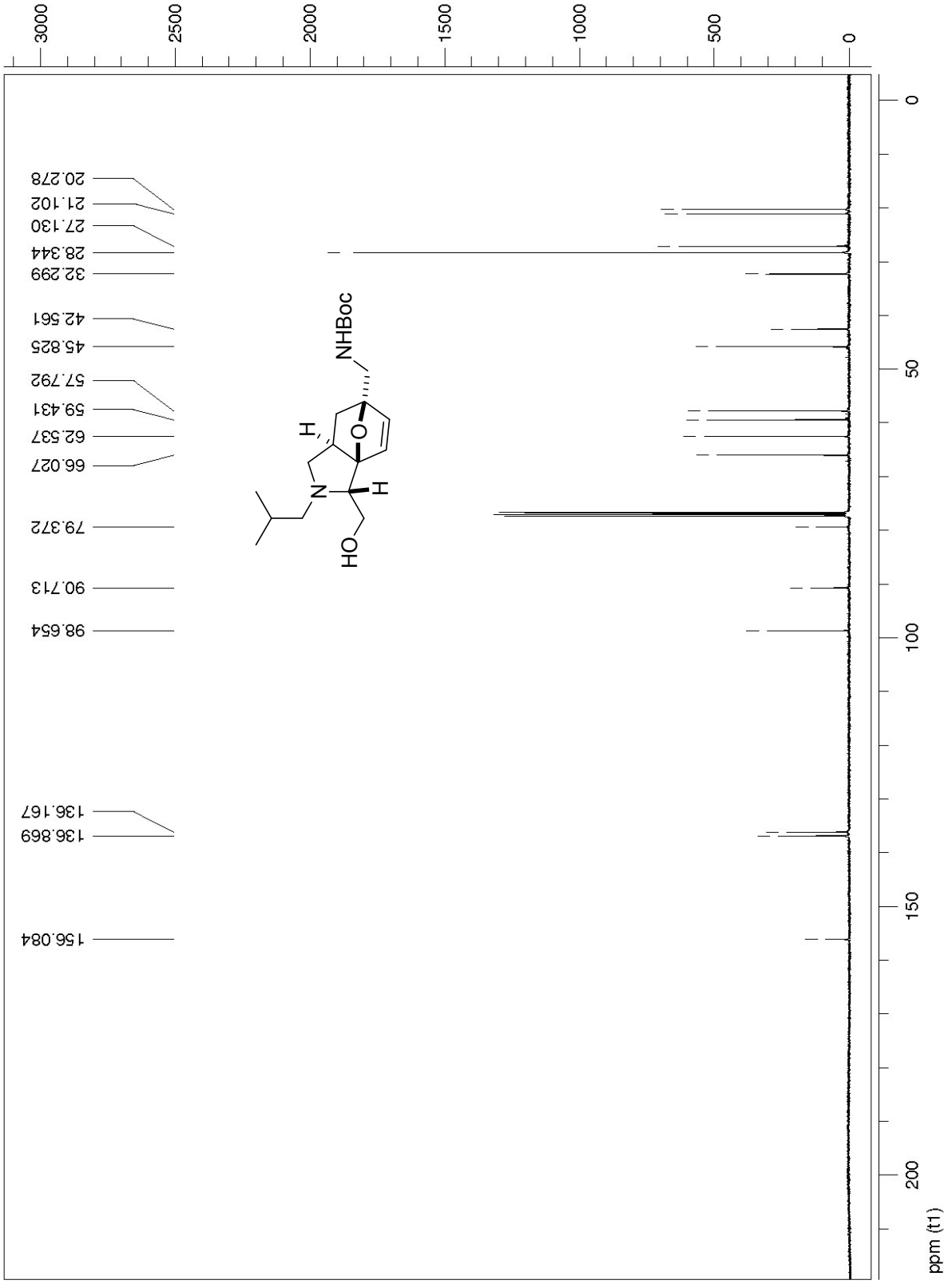
^{13}C NMR (100 MHz, $CDCl_3$) of **10a**



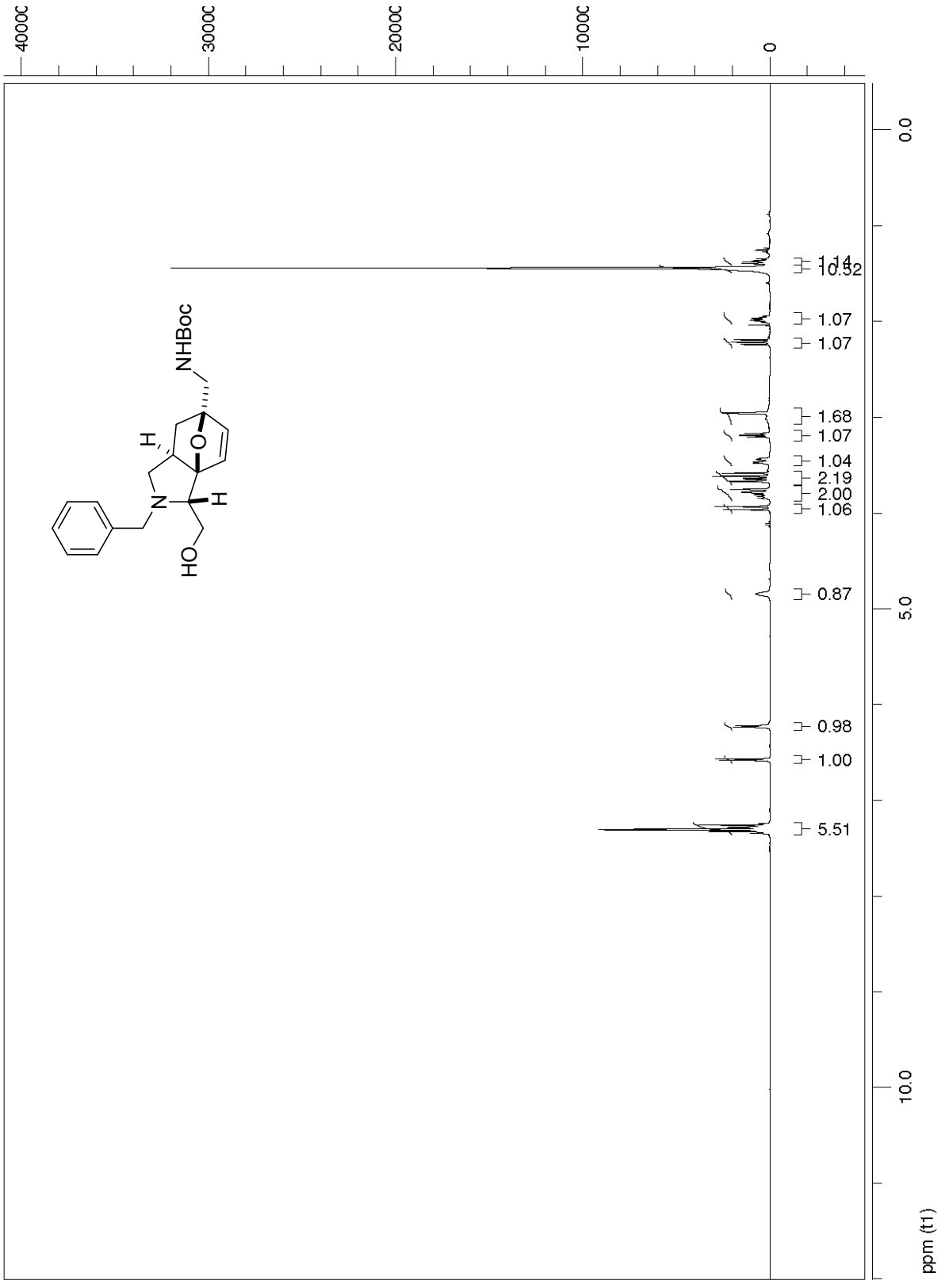
^{1}H NMR (400 MHz, $CDCl_3$) of **10b**



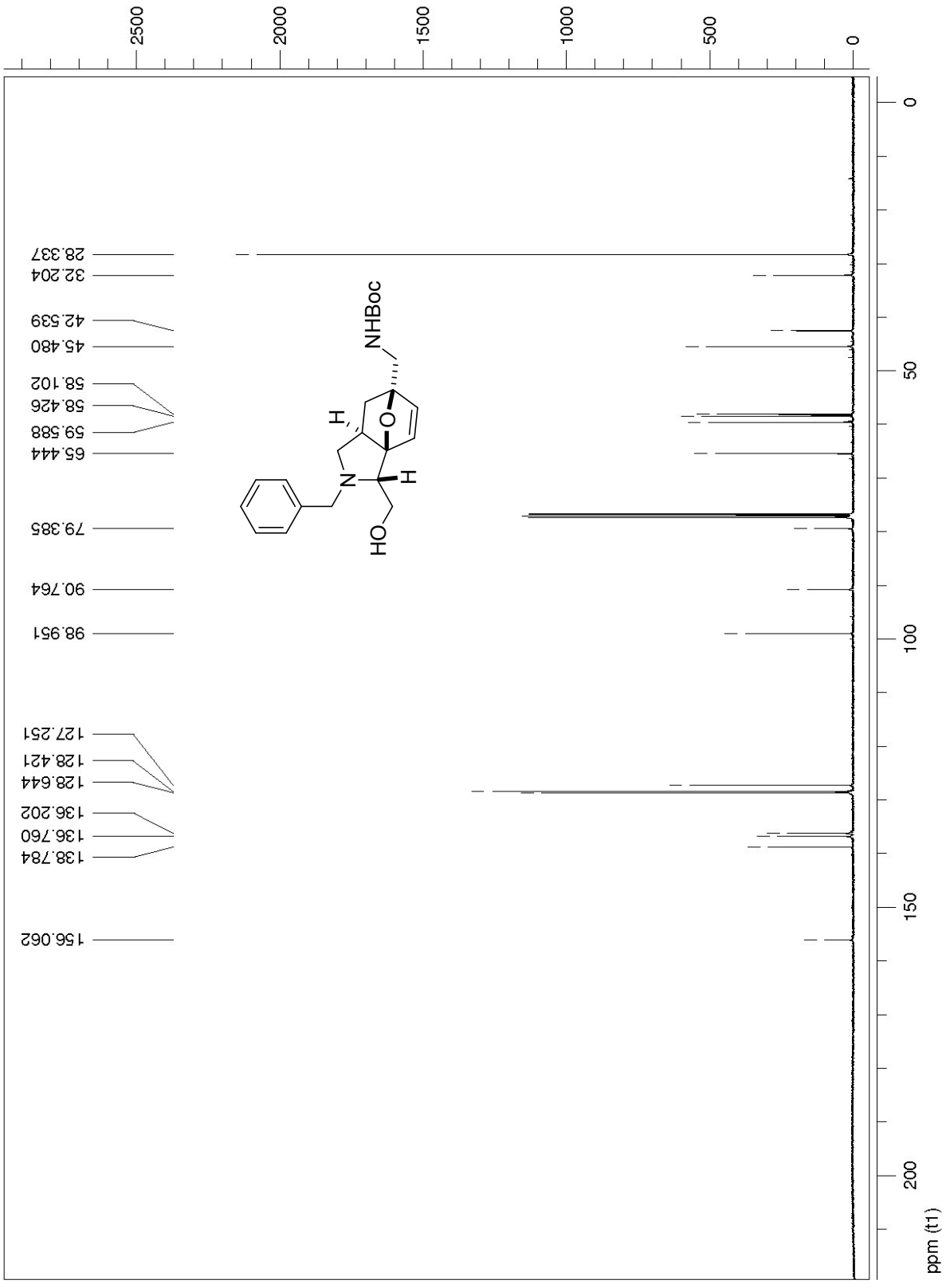
^{13}C NMR (100 MHz, $CDCl_3$) of **10b**



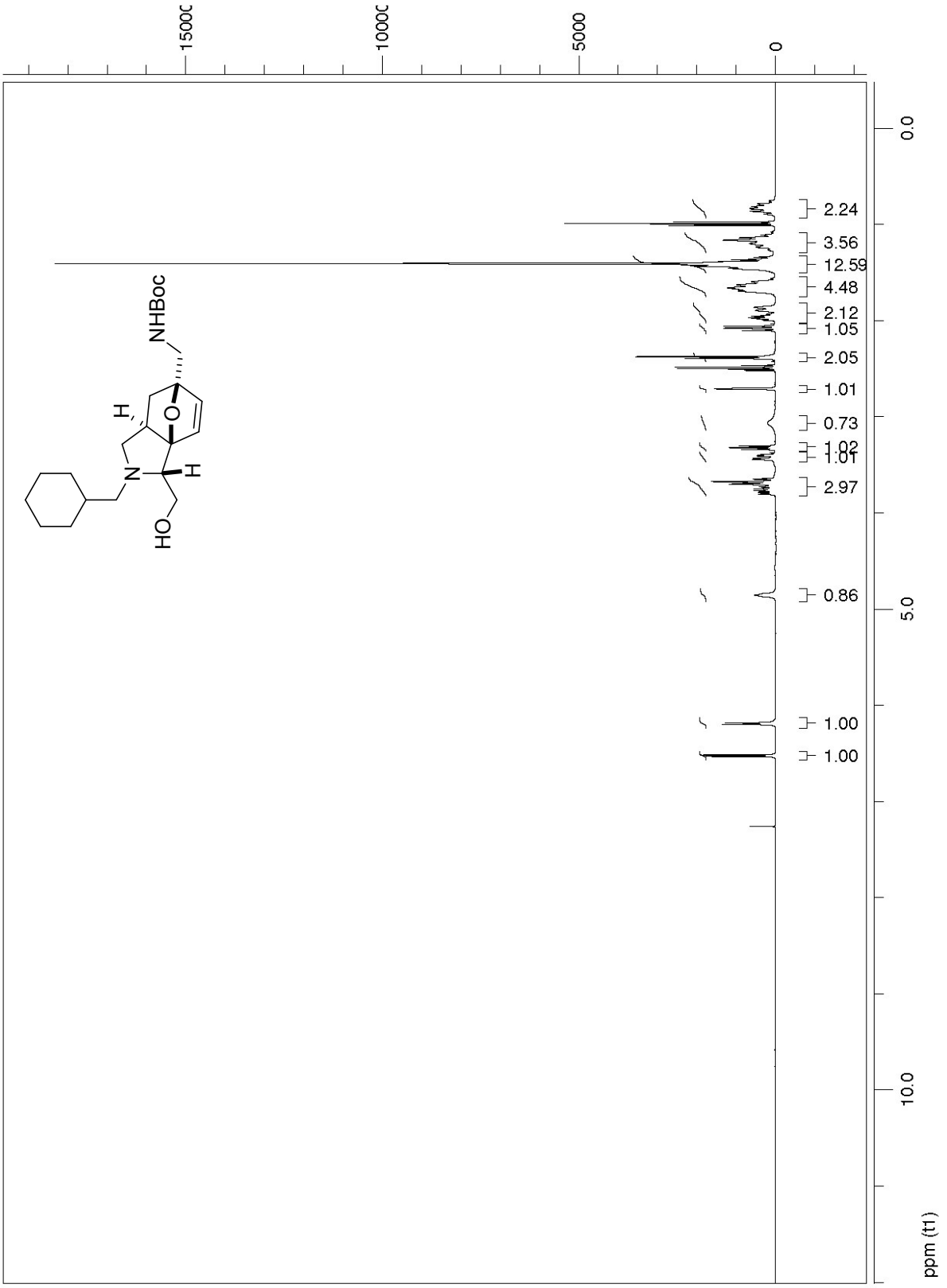
^{1}H NMR (400 MHz, $CDCl_3$) of **10c**



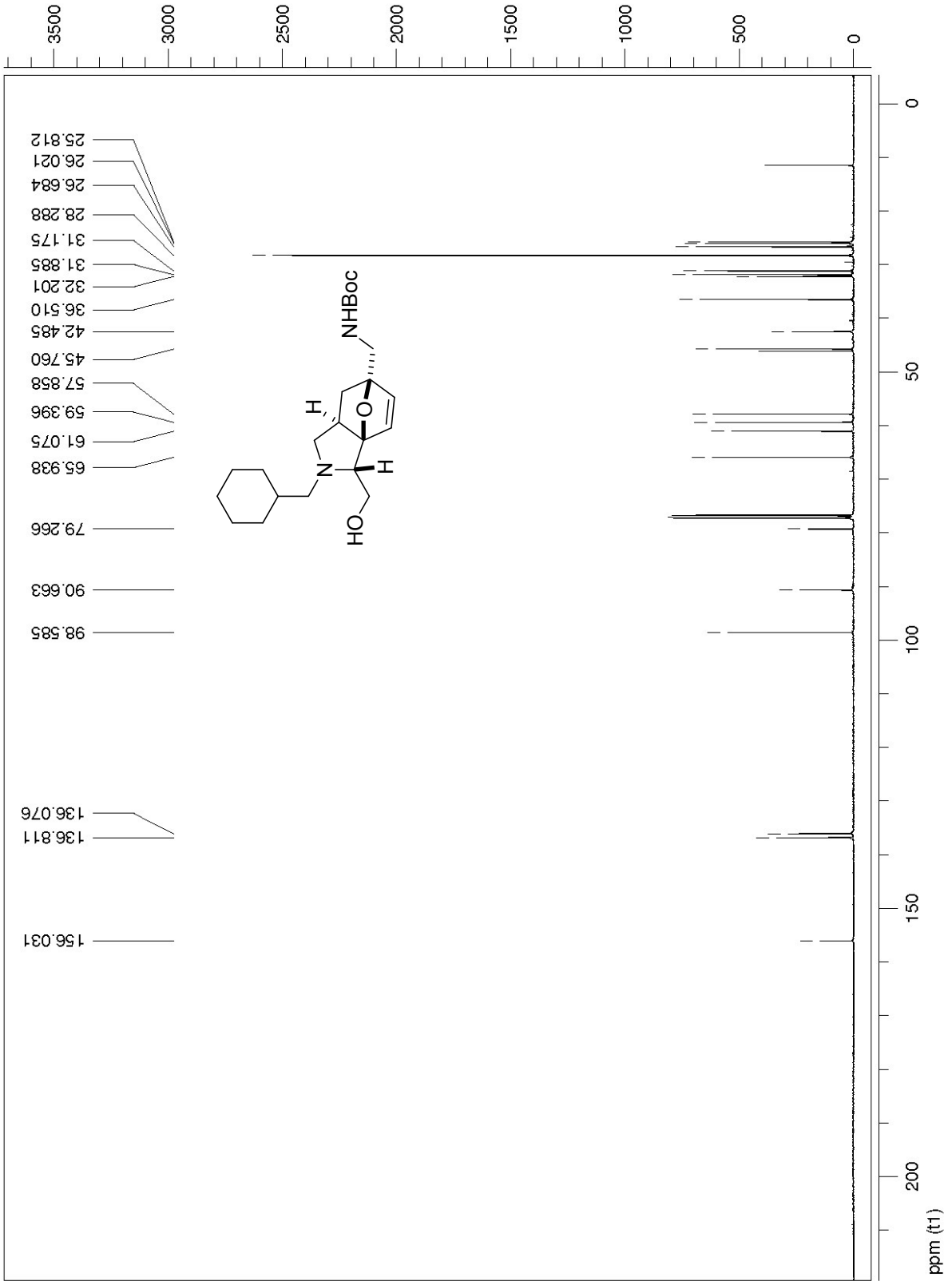
^{13}C NMR (100 MHz, $CDCl_3$) of **10c**



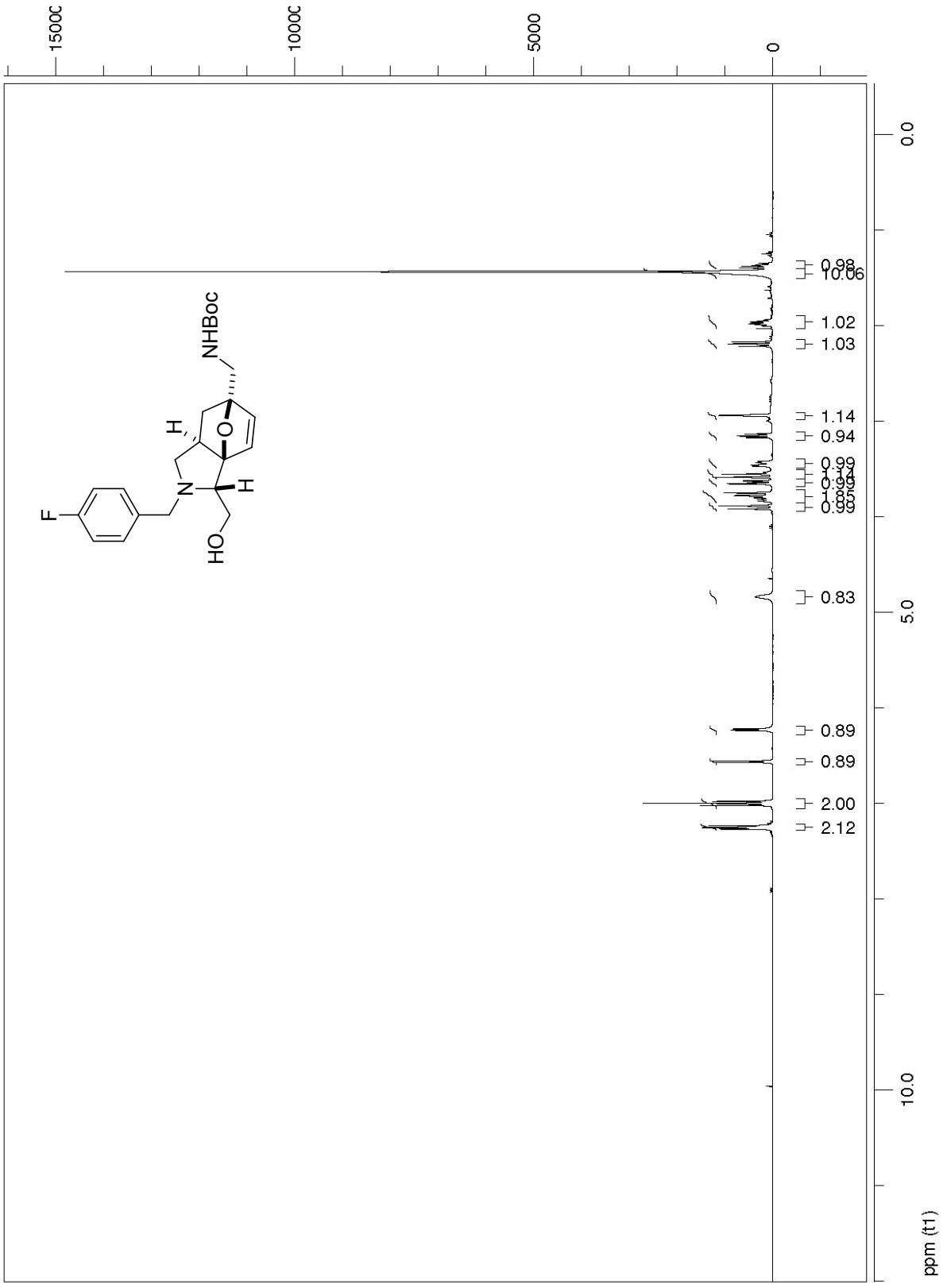
^{1}H NMR (400 MHz, $CDCl_3$) of **10e**



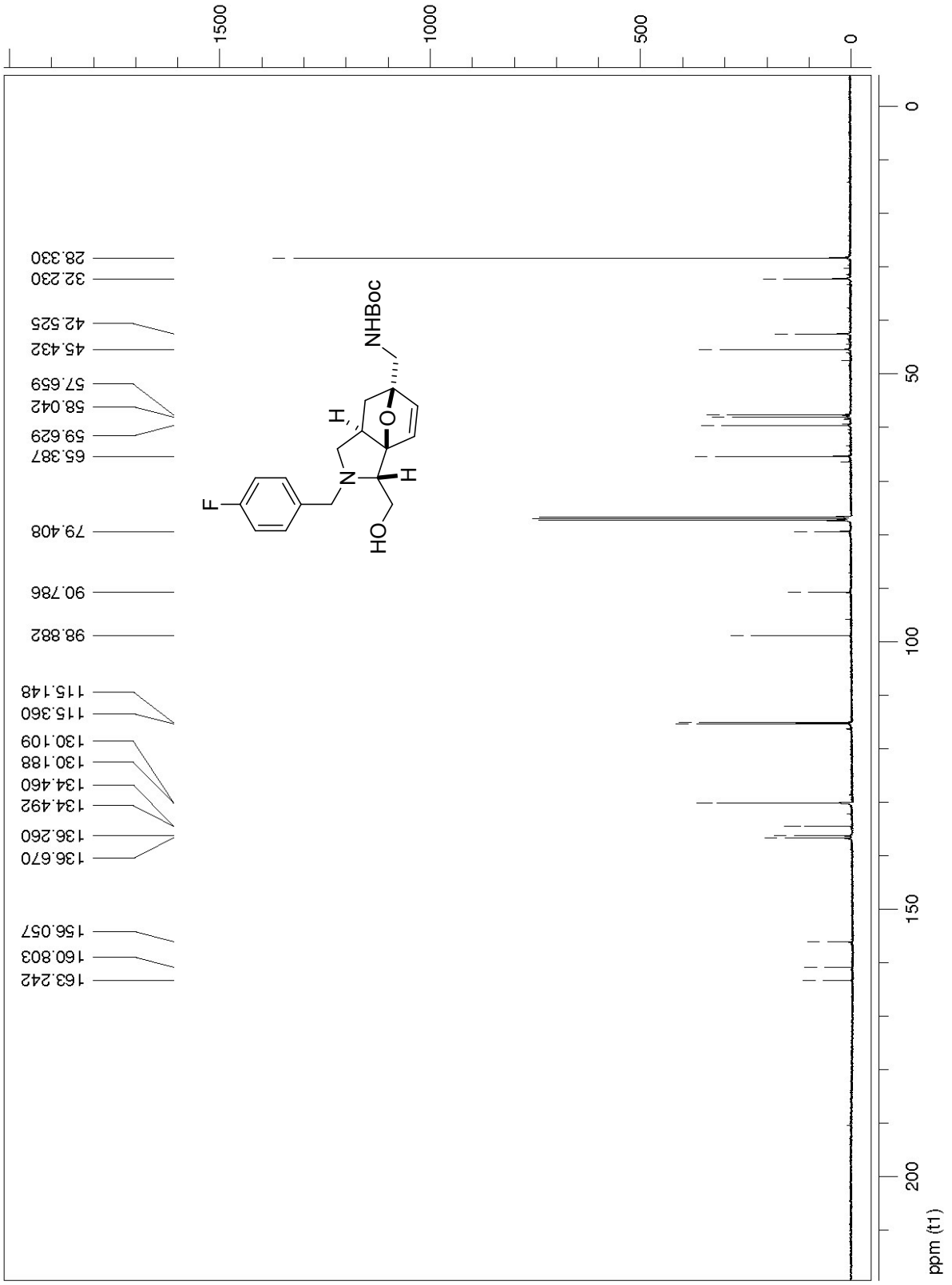
^{13}C NMR (100 MHz, $CDCl_3$) of **10e**



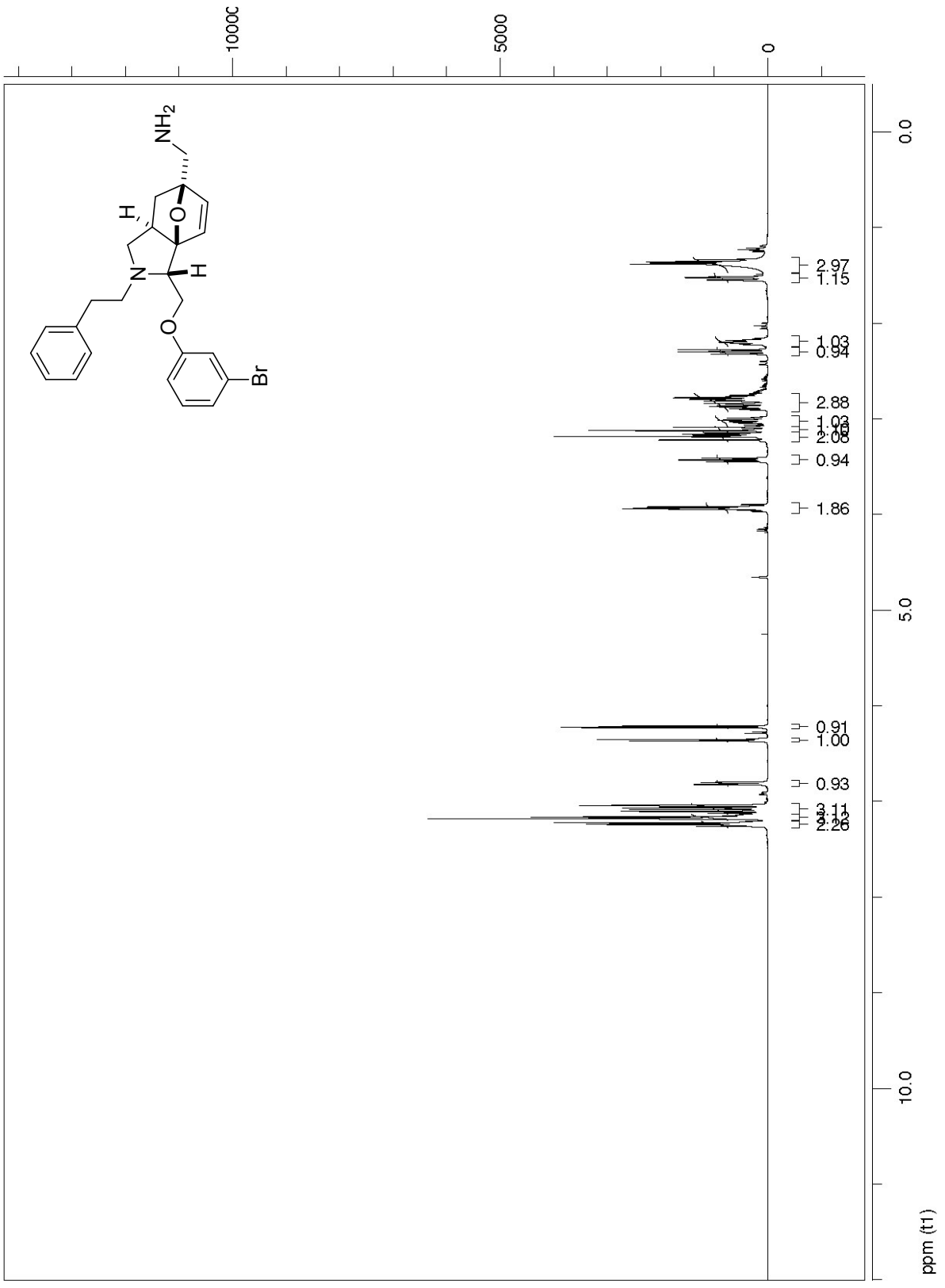
^{1}H NMR (400 MHz, $CDCl_3$) of **10f**



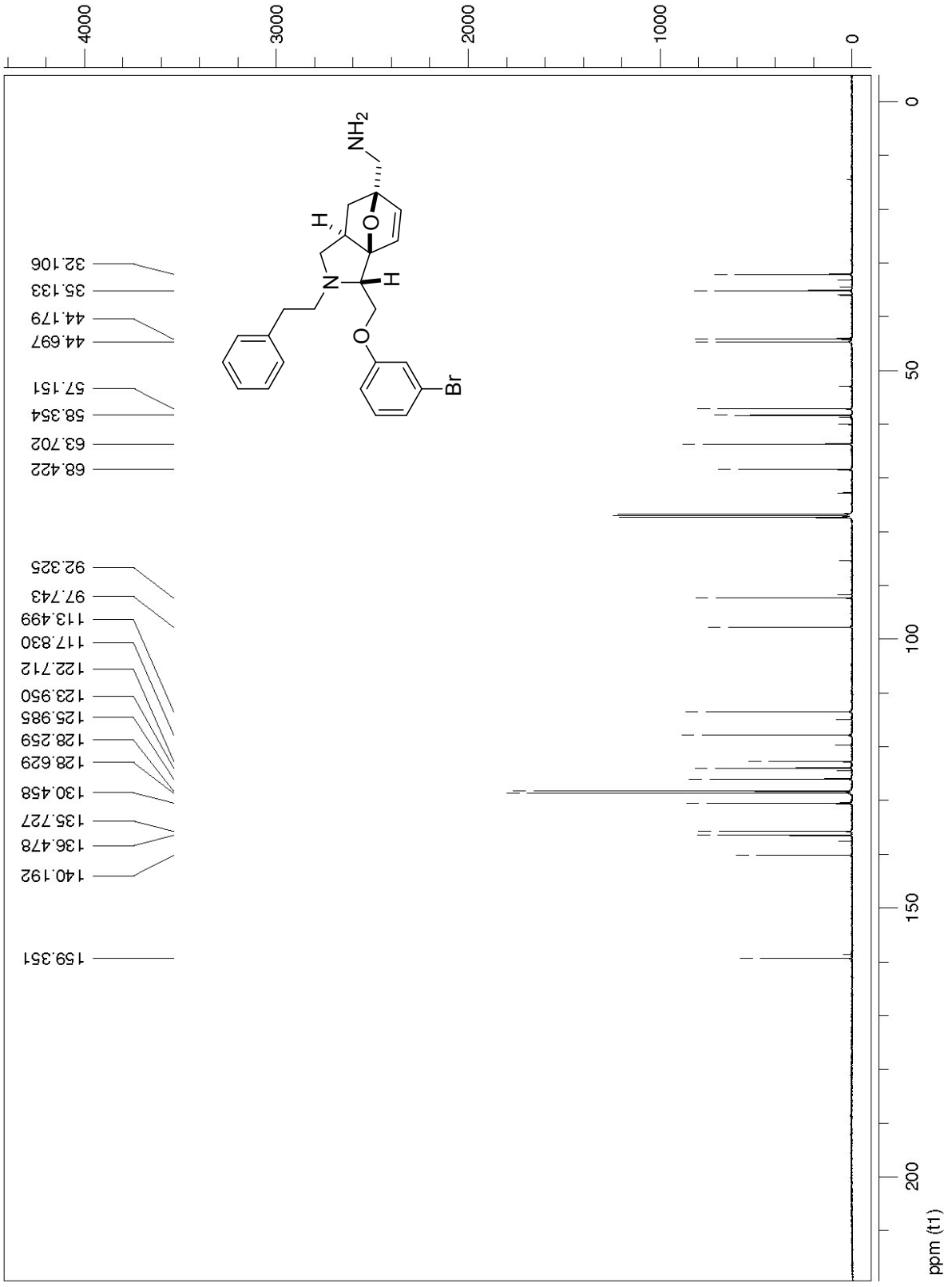
^{13}C NMR (100 MHz, $CDCl_3$) of **10f**



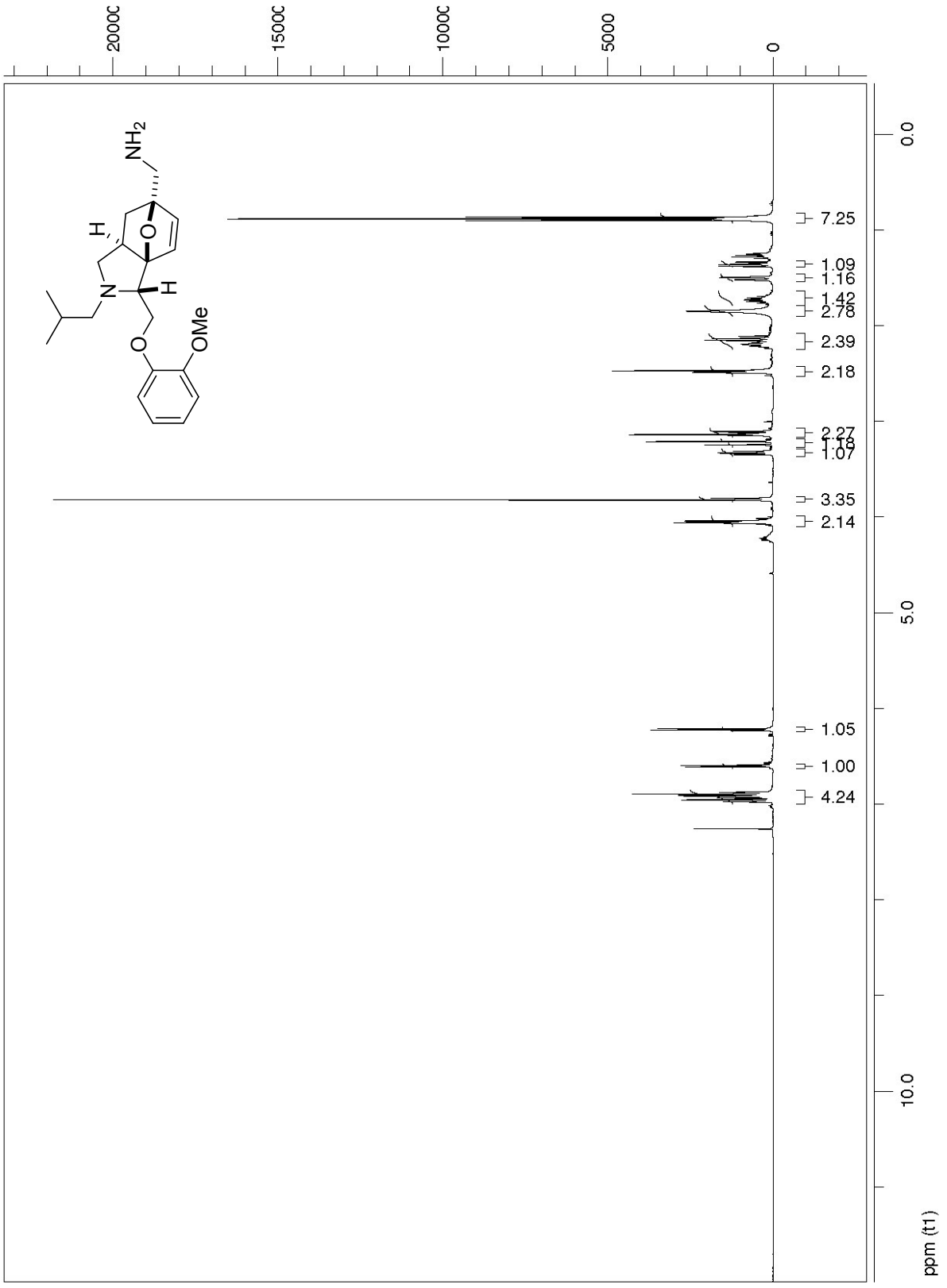
^{1}H NMR (400 MHz, $CDCl_3$) of **11a**



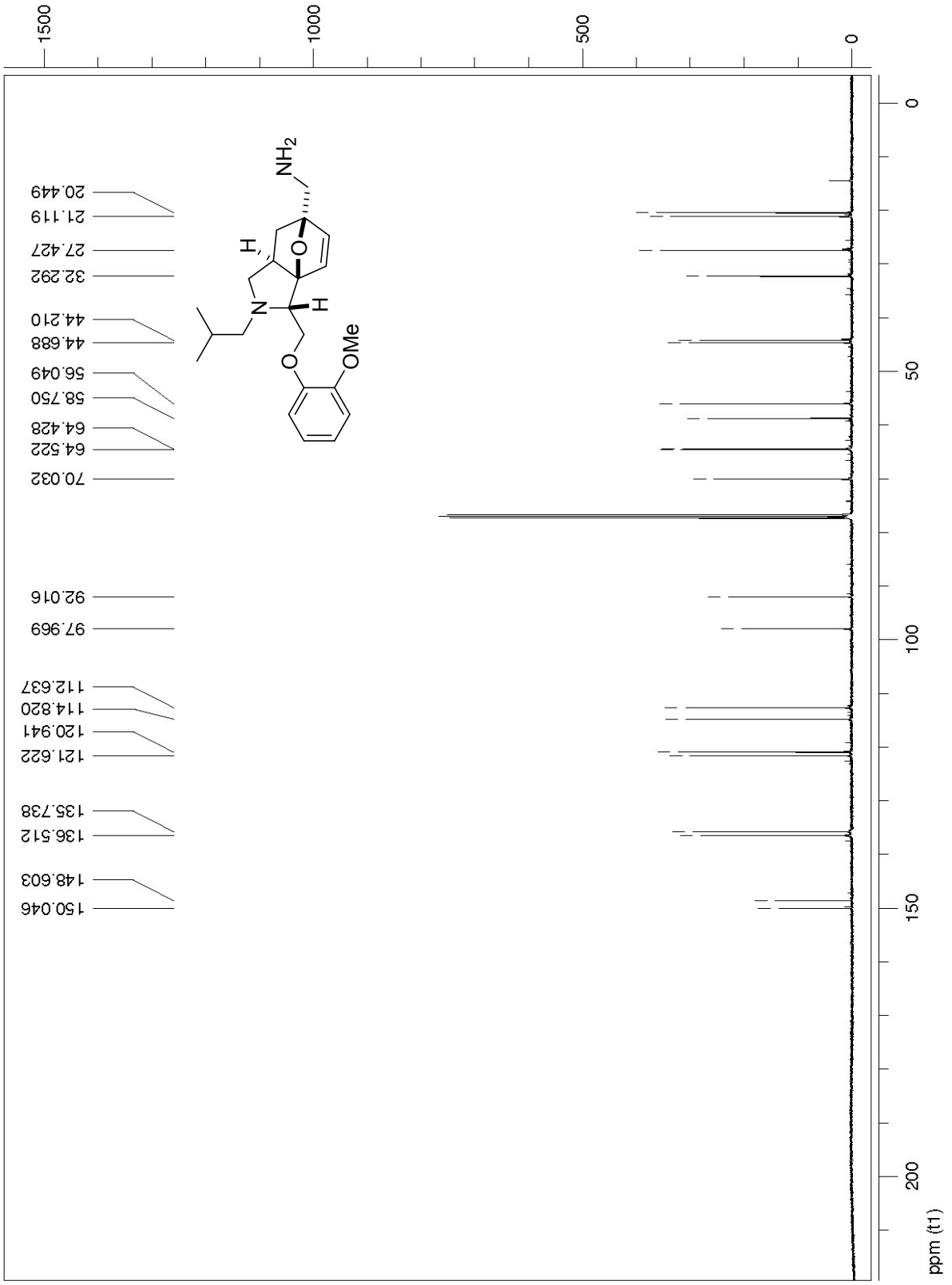
^{13}C NMR (100 MHz, $CDCl_3$) of **11a**



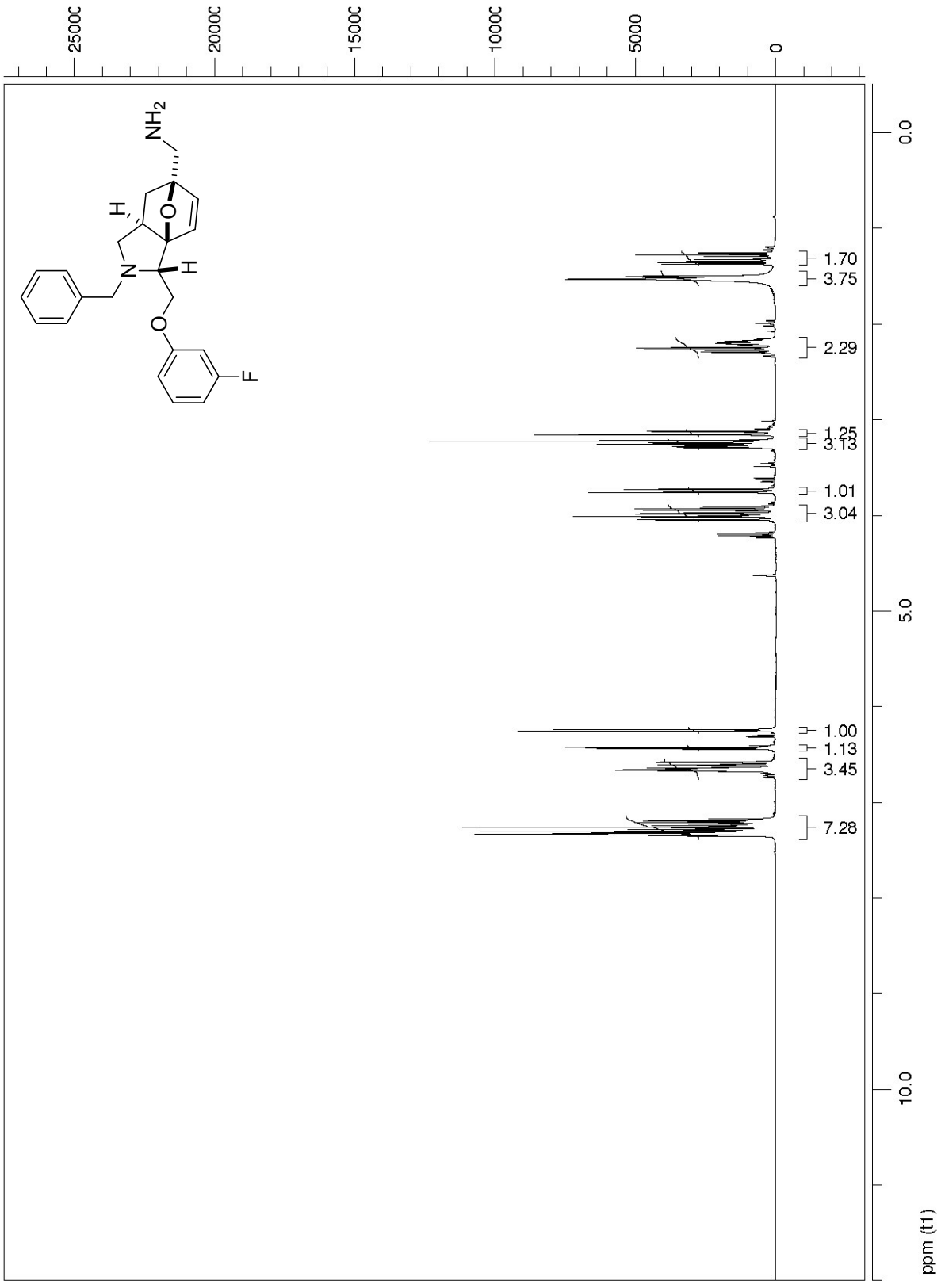
^{1}H NMR (400 MHz, $CDCl_3$) of **11b**



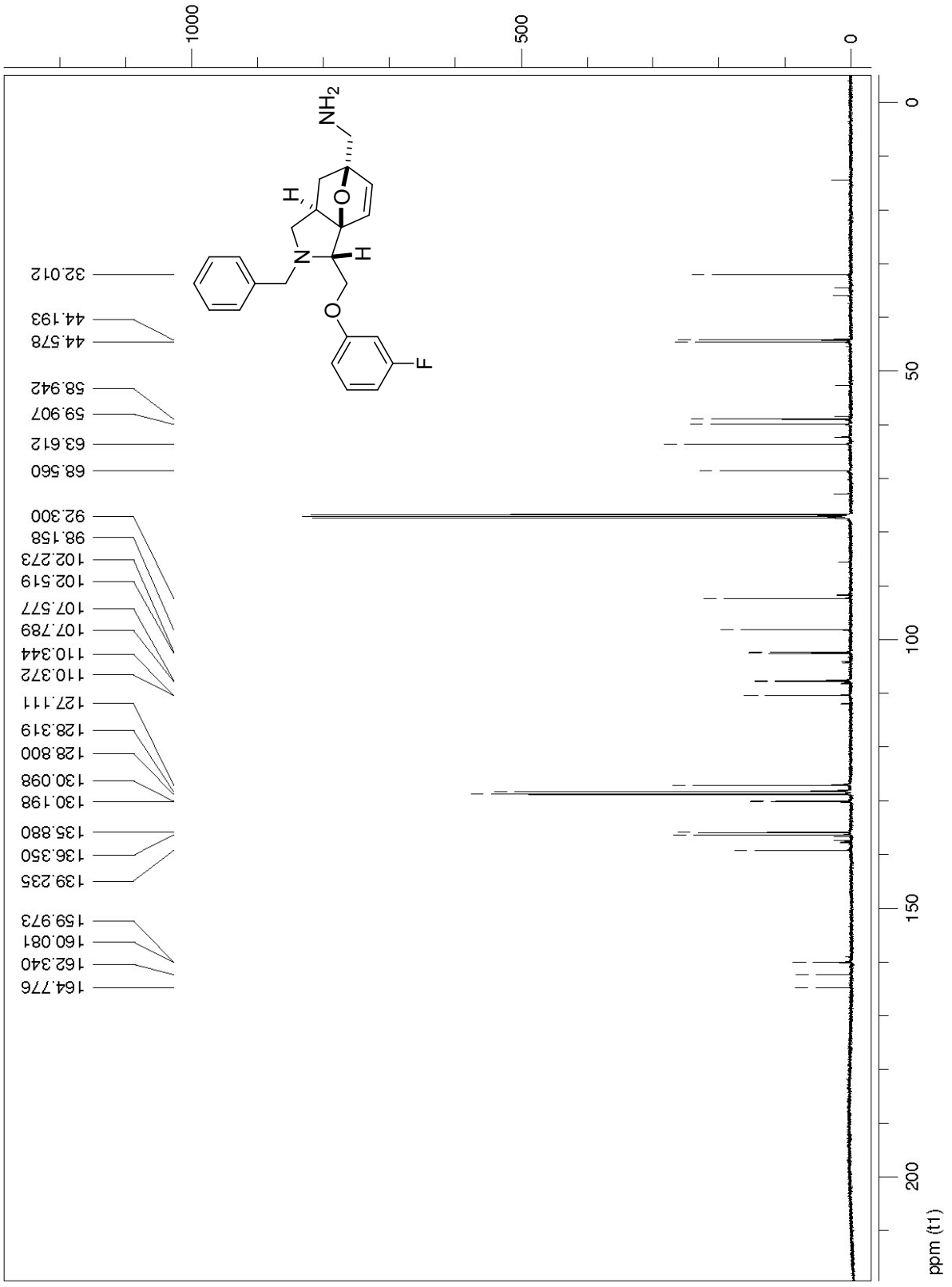
^{13}C NMR (100 MHz, $CDCl_3$) of **11b**



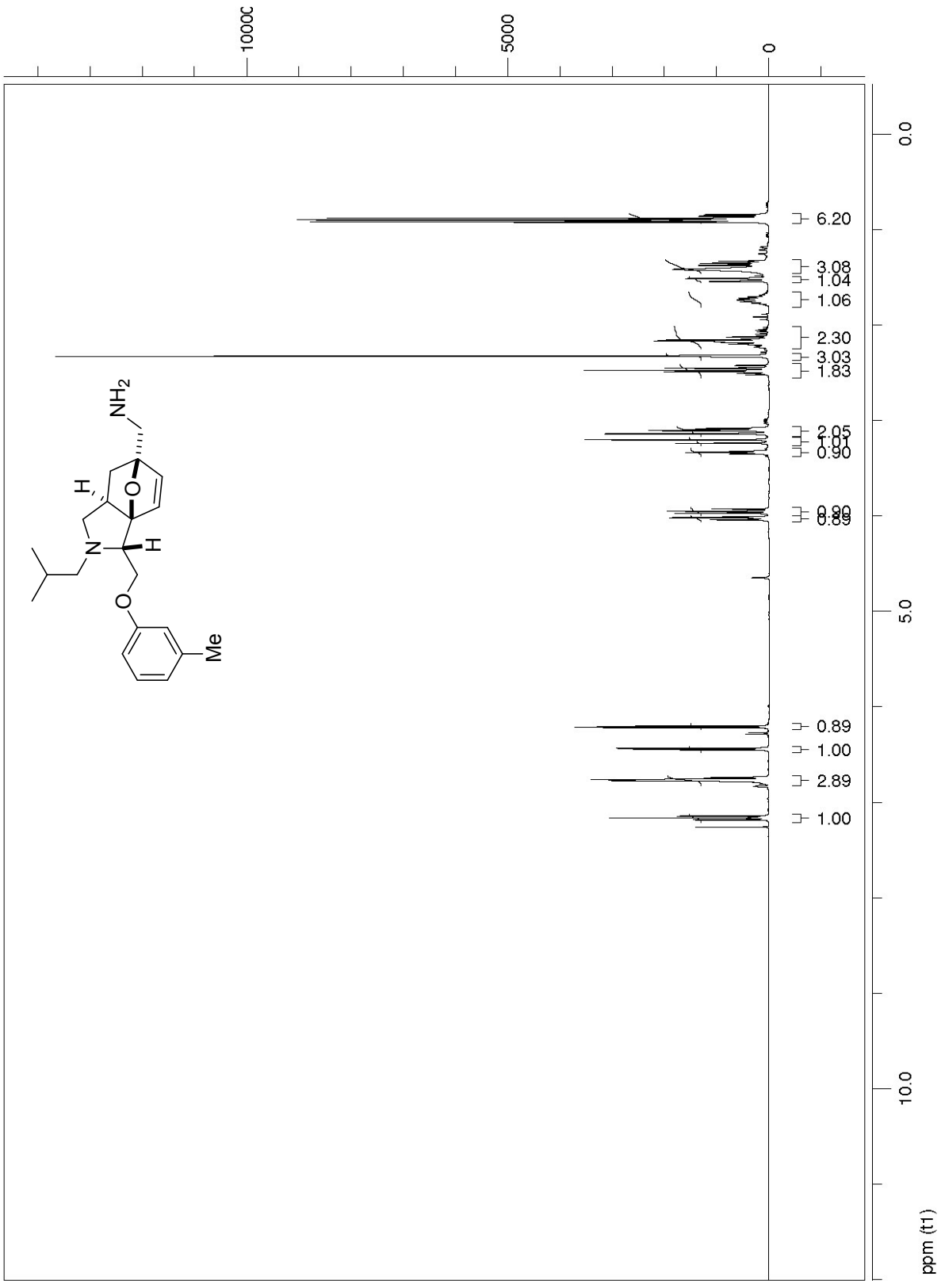
^{1}H NMR (400 MHz, $CDCl_3$) of **11c**



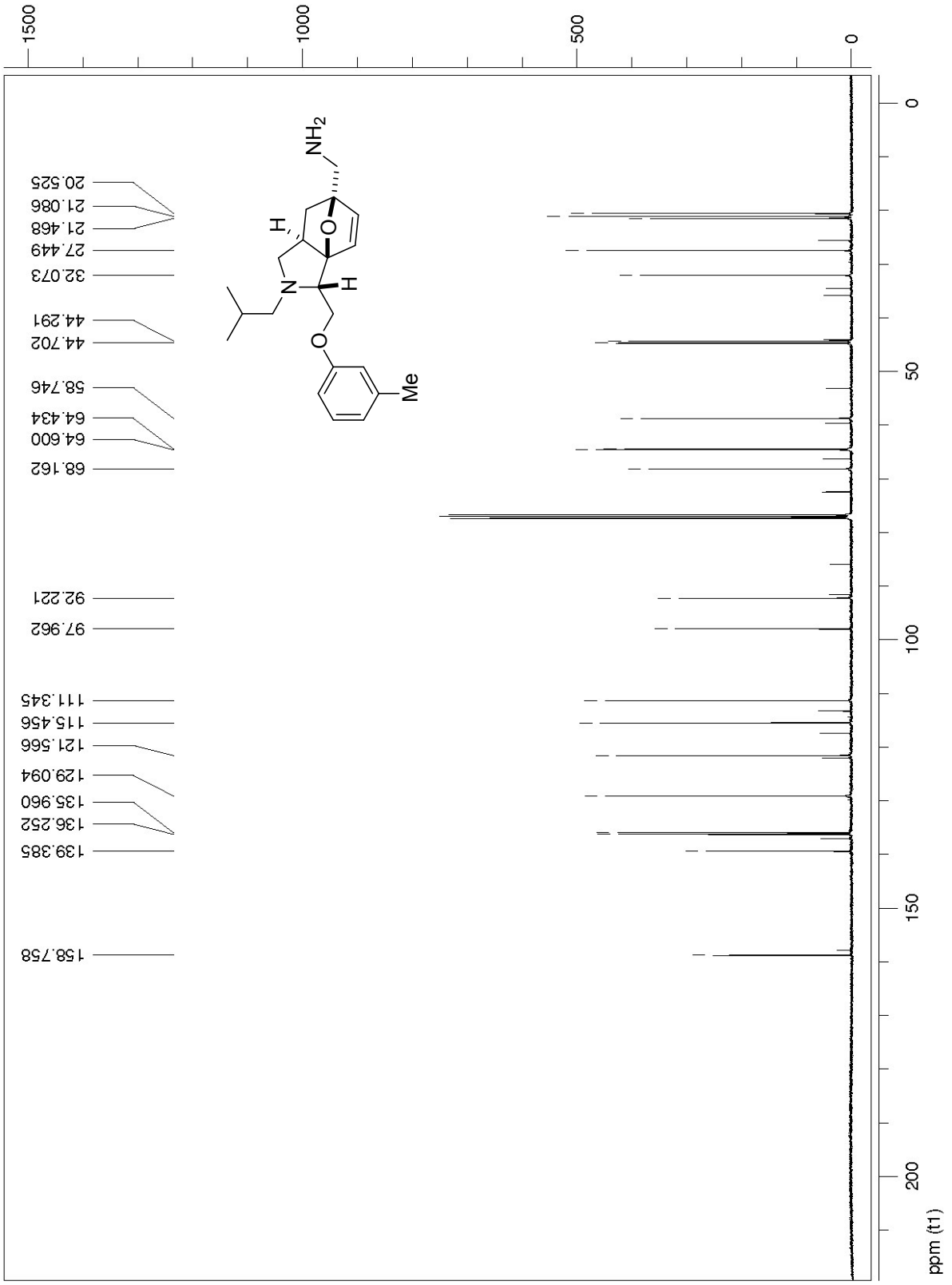
^{13}C NMR (100 MHz, $CDCl_3$) of **11c**



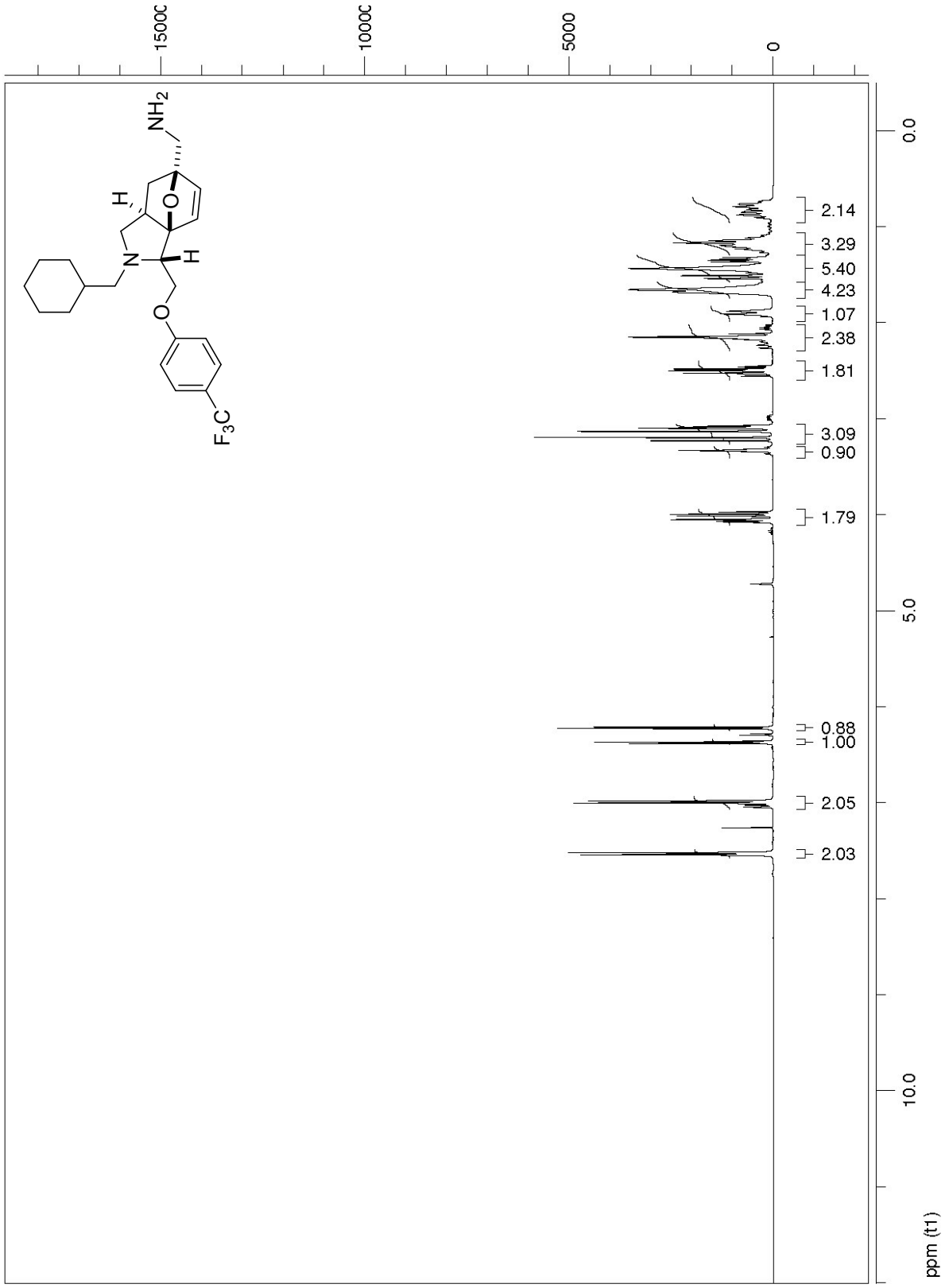
^{1}H NMR (400 MHz, $CDCl_3$) of **11d**



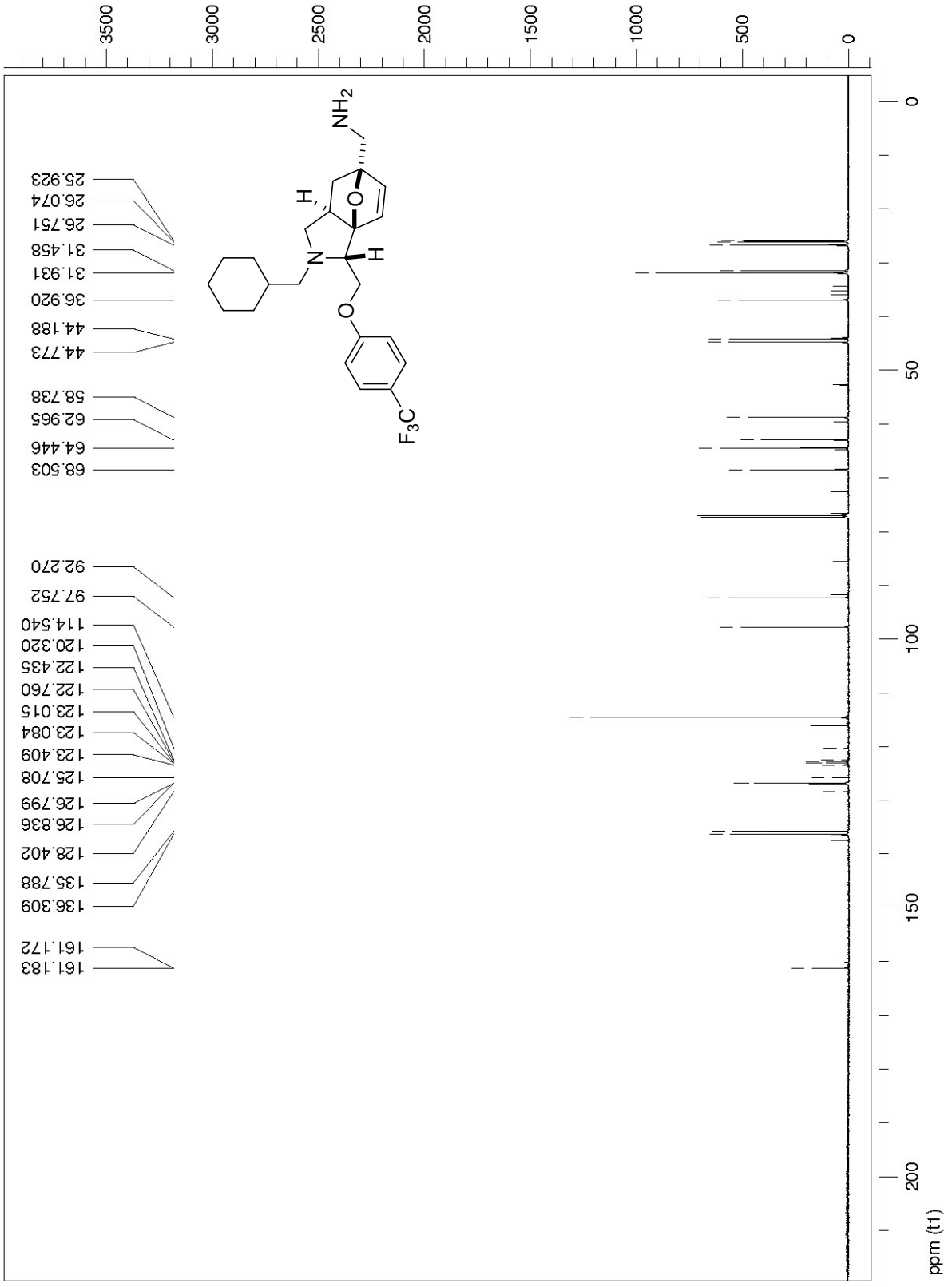
^{13}C NMR (100 MHz, $CDCl_3$) of **11d**



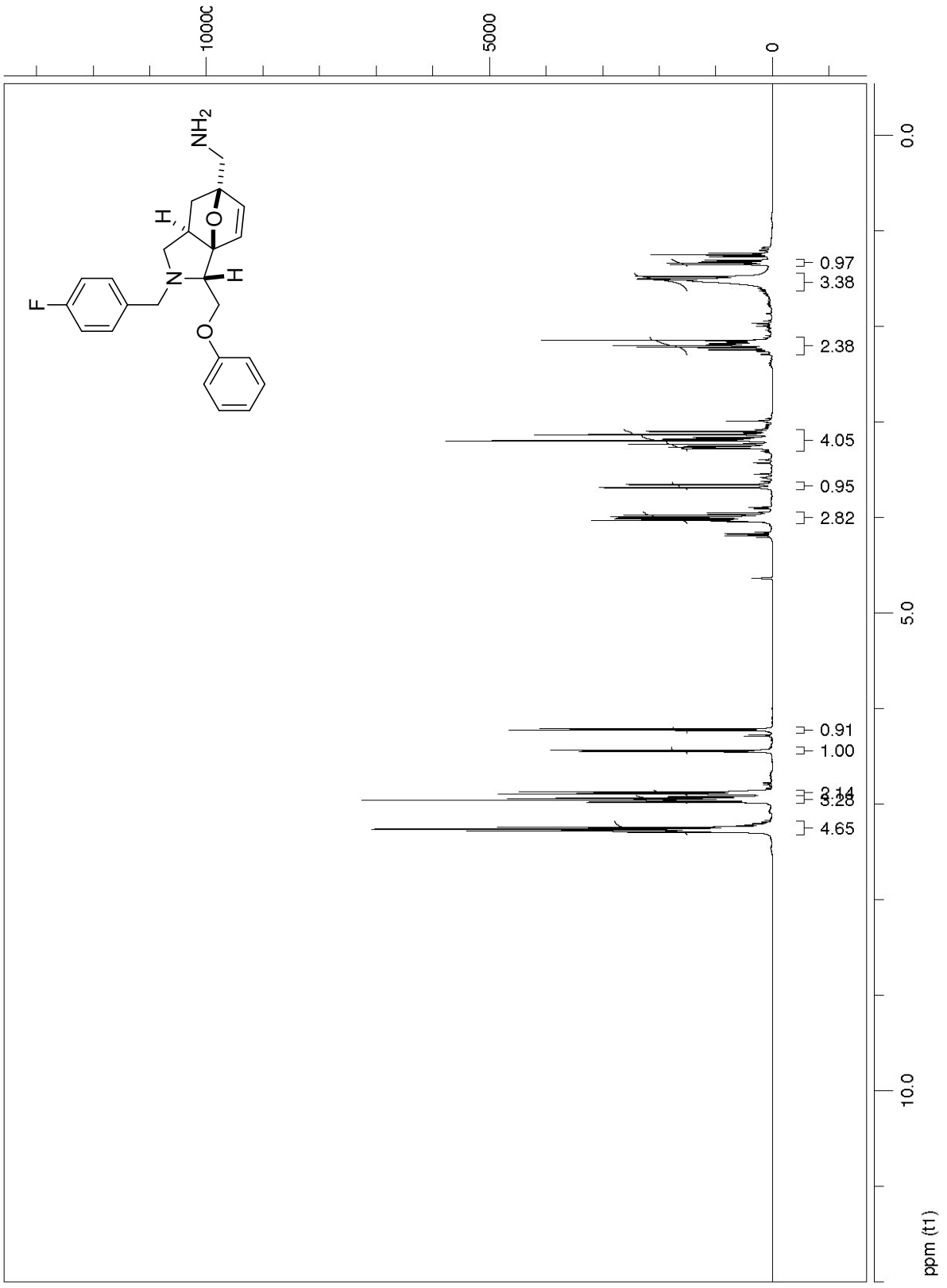
^{1}H NMR (400 MHz, $CDCl_3$) of **11e**



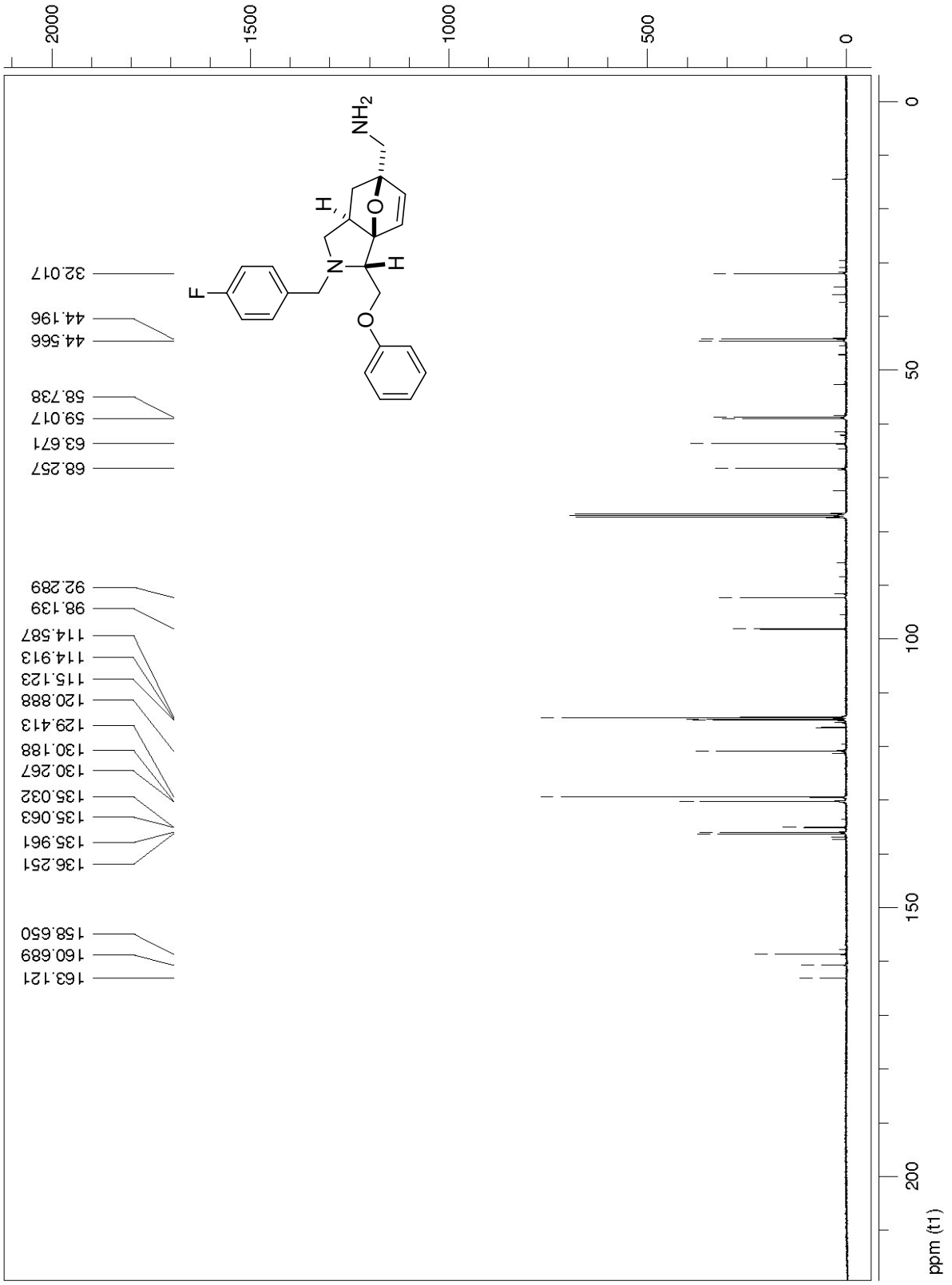
^{13}C NMR (100 MHz, $CDCl_3$) of **11e**



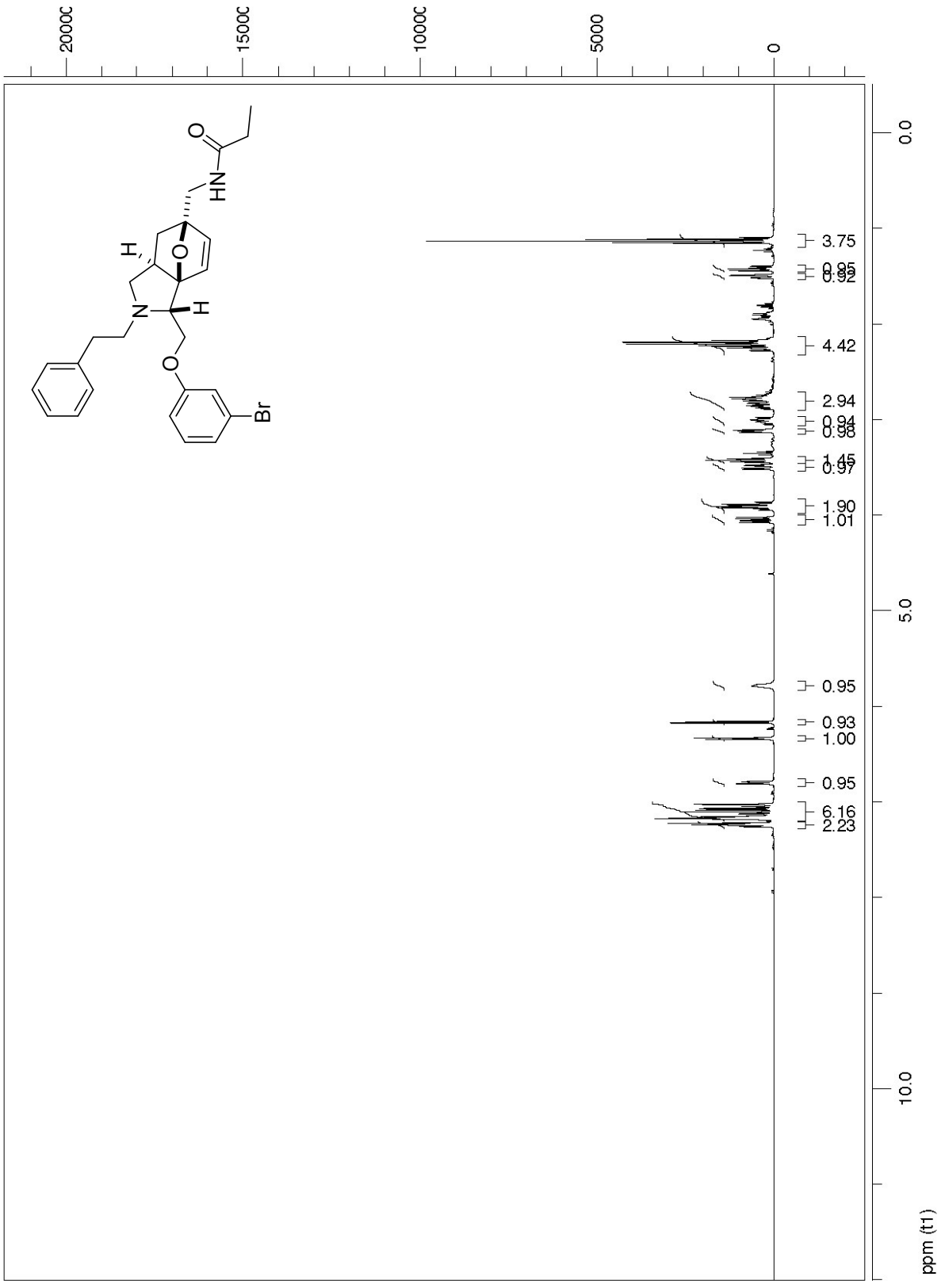
^{1}H NMR (400 MHz, $CDCl_3$) of **11f**



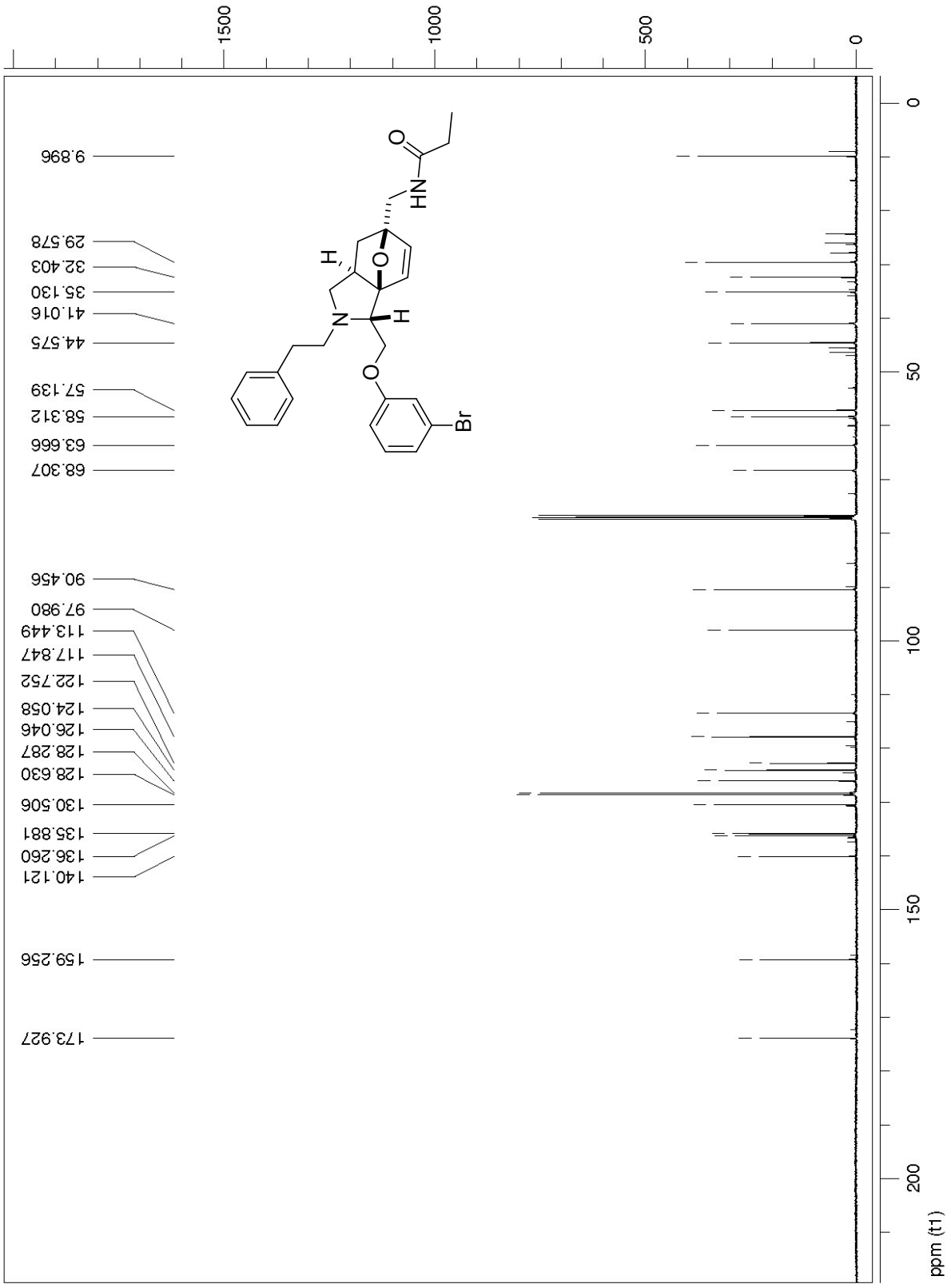
^{13}C NMR (100 MHz, $CDCl_3$) of **11f**



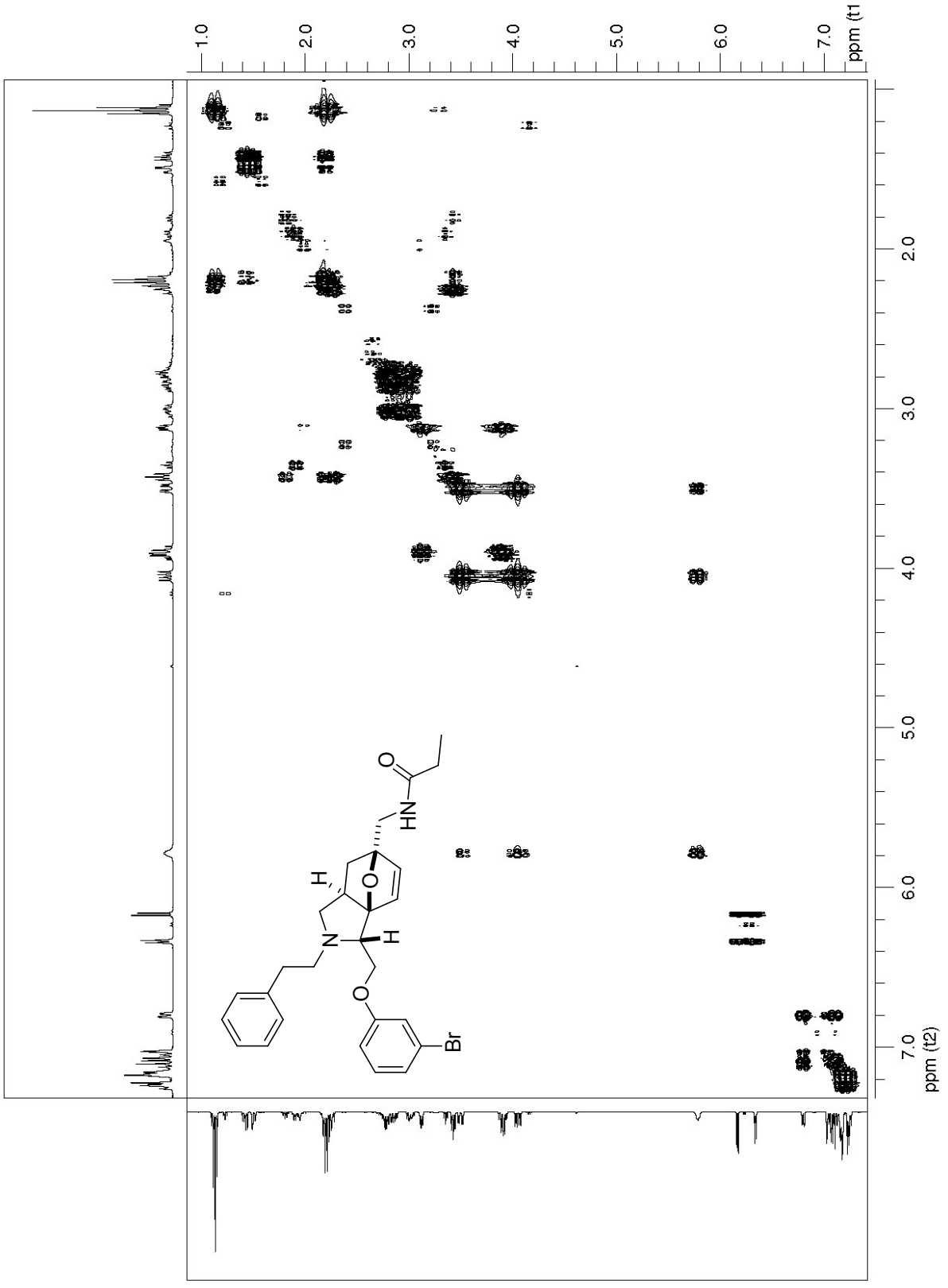
^{1}H NMR (400 MHz, $CDCl_3$) of **12a**



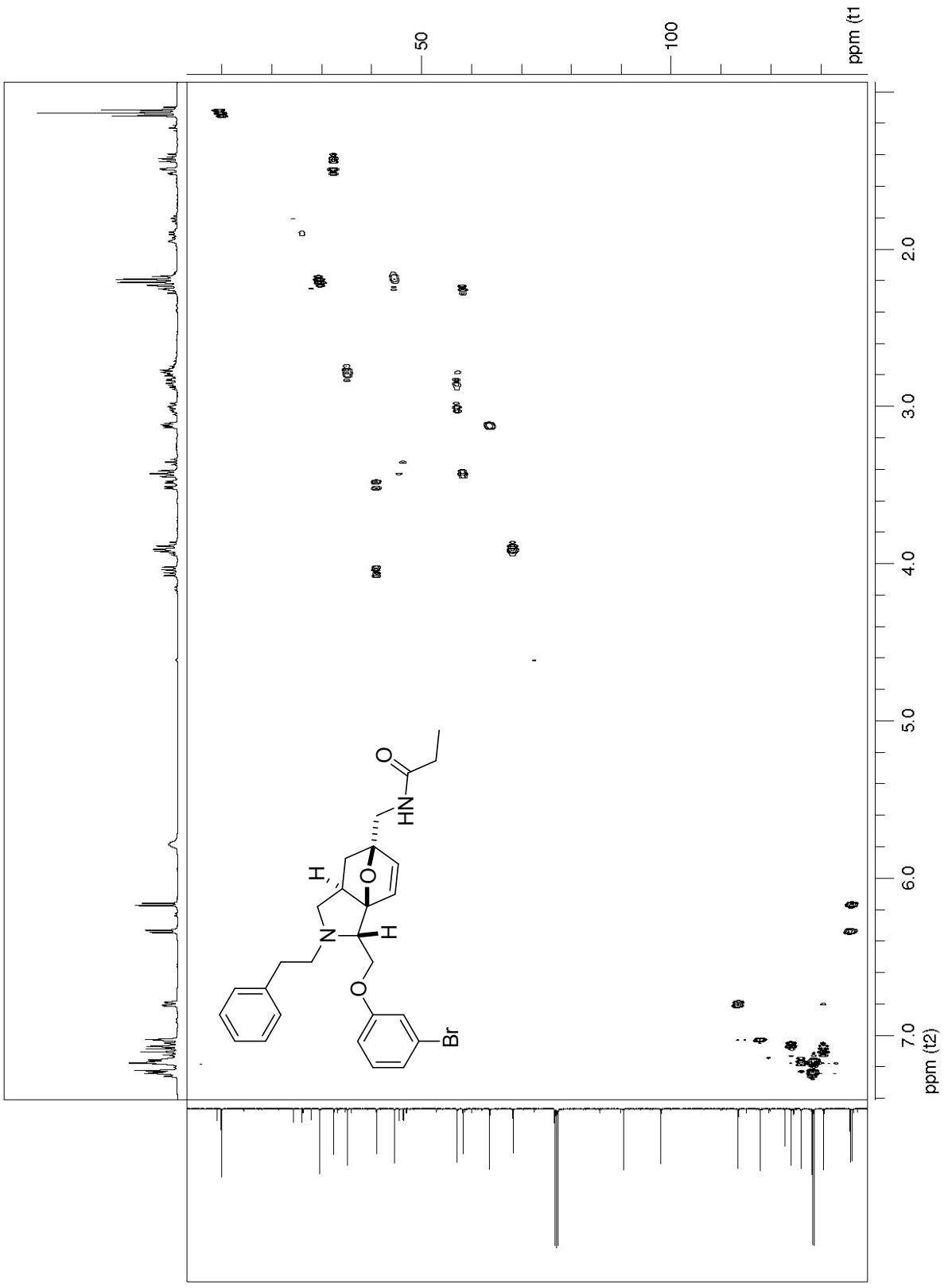
^{13}C NMR (100 MHz, $CDCl_3$) of **12a**



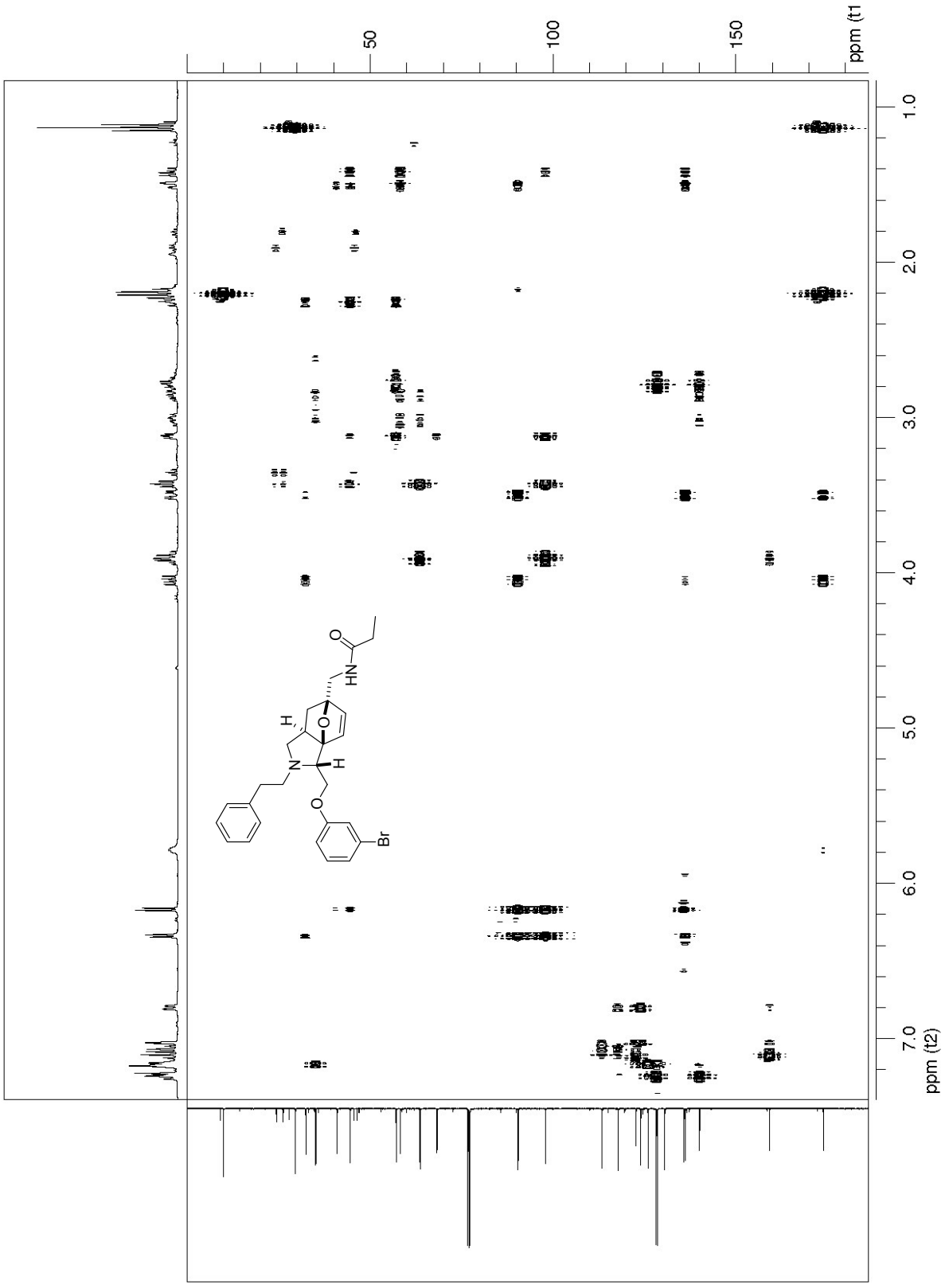
DQF-COSY (400 MHz, $CDCl_3$) of **12a**



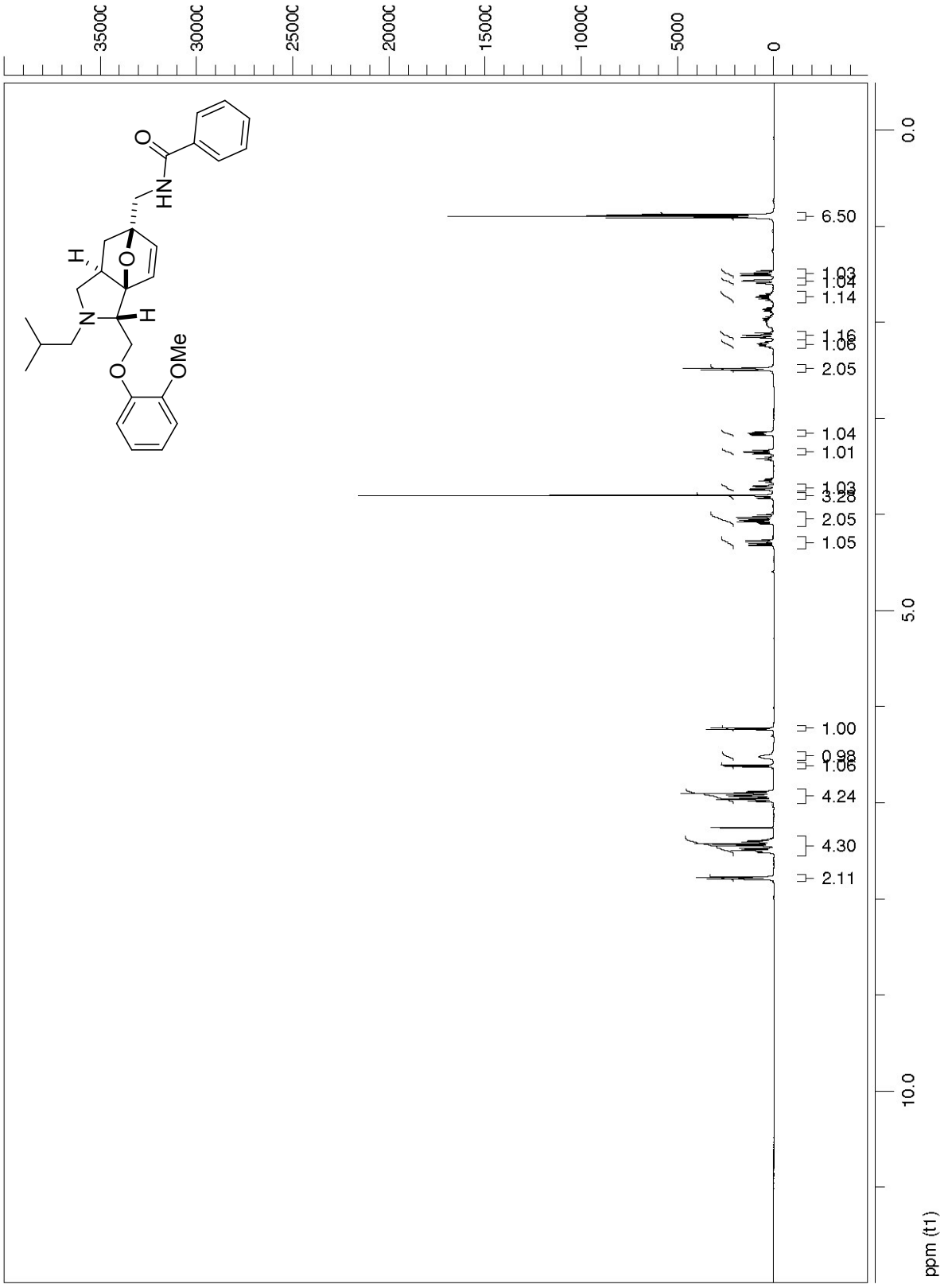
gHSQC (400 MHz, $CDCl_3$) of **12a**



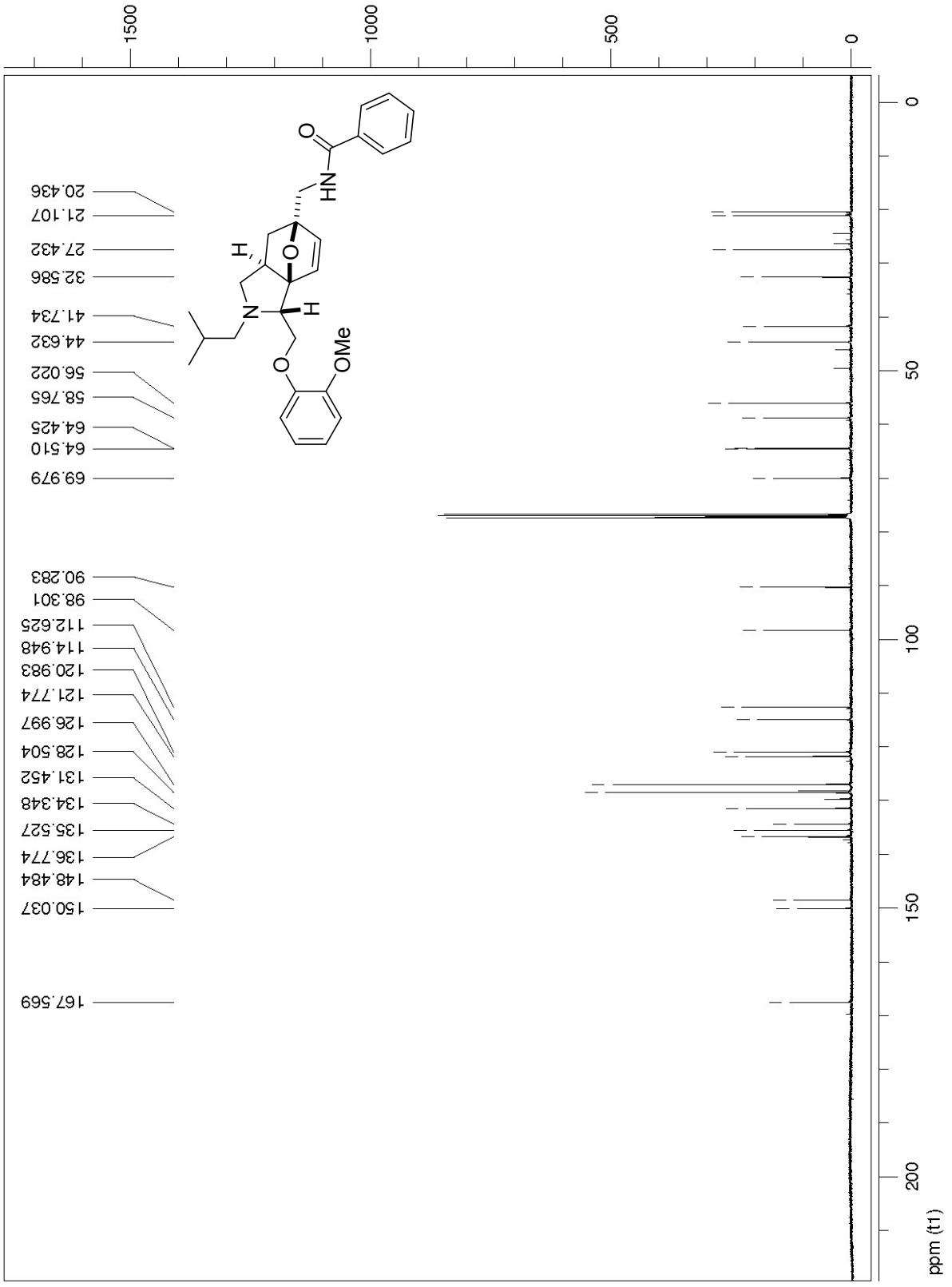
HMBC (400 MHz, $CDCl_3$) of **12a**



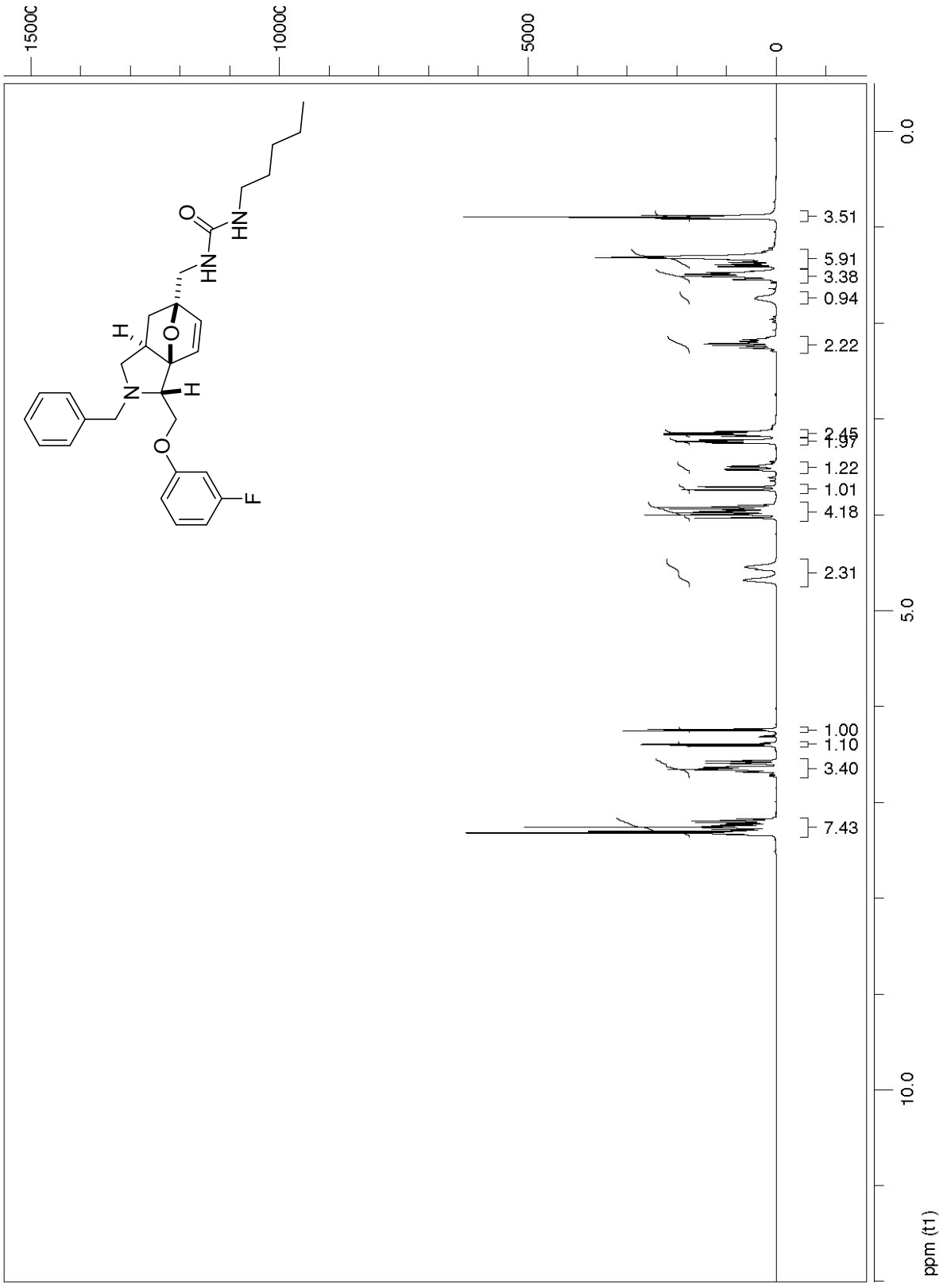
^{1}H NMR (400 MHz, $CDCl_3$) of **12b**



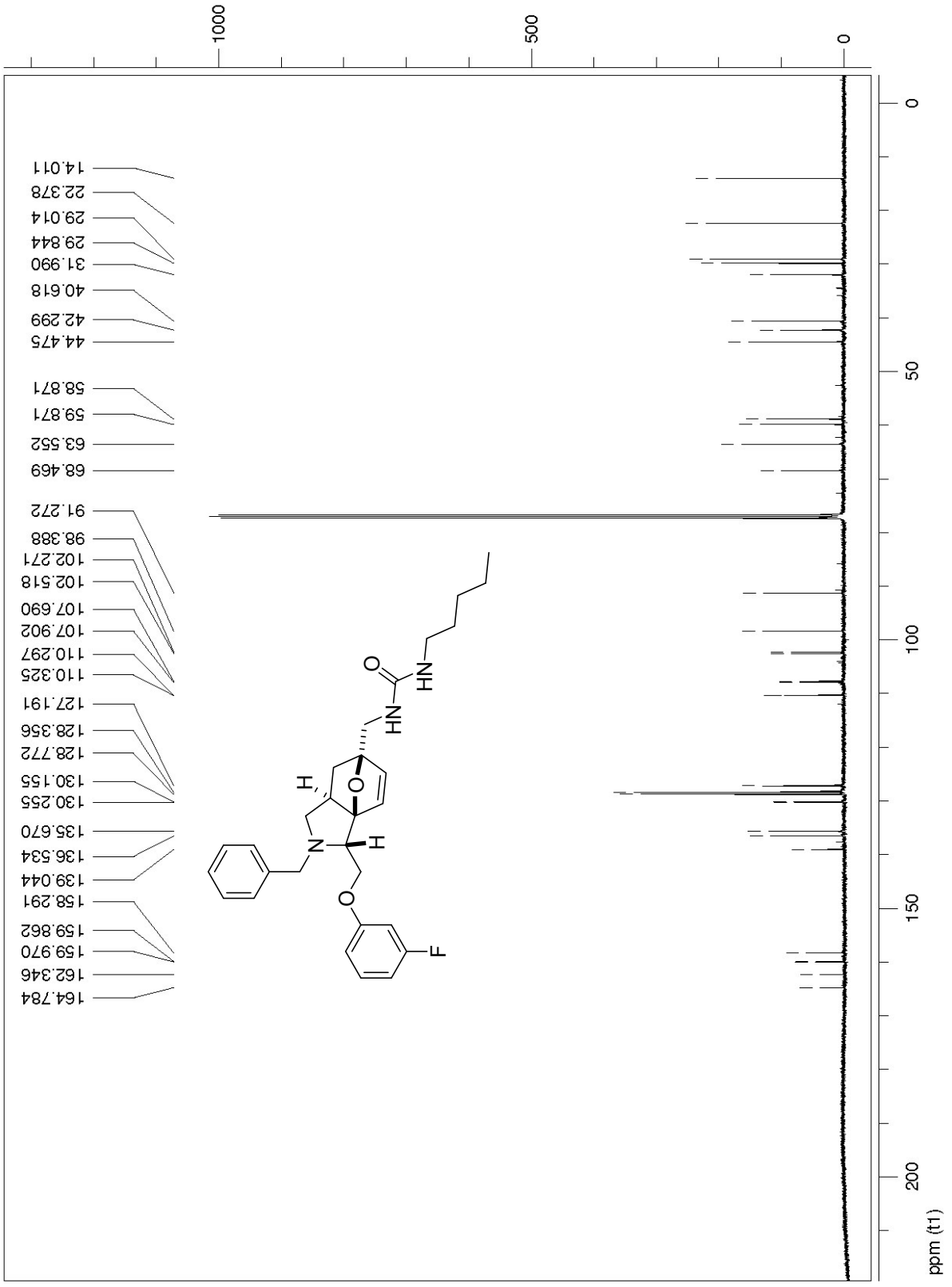
^{13}C NMR (100 MHz, $CDCl_3$) of **12b**



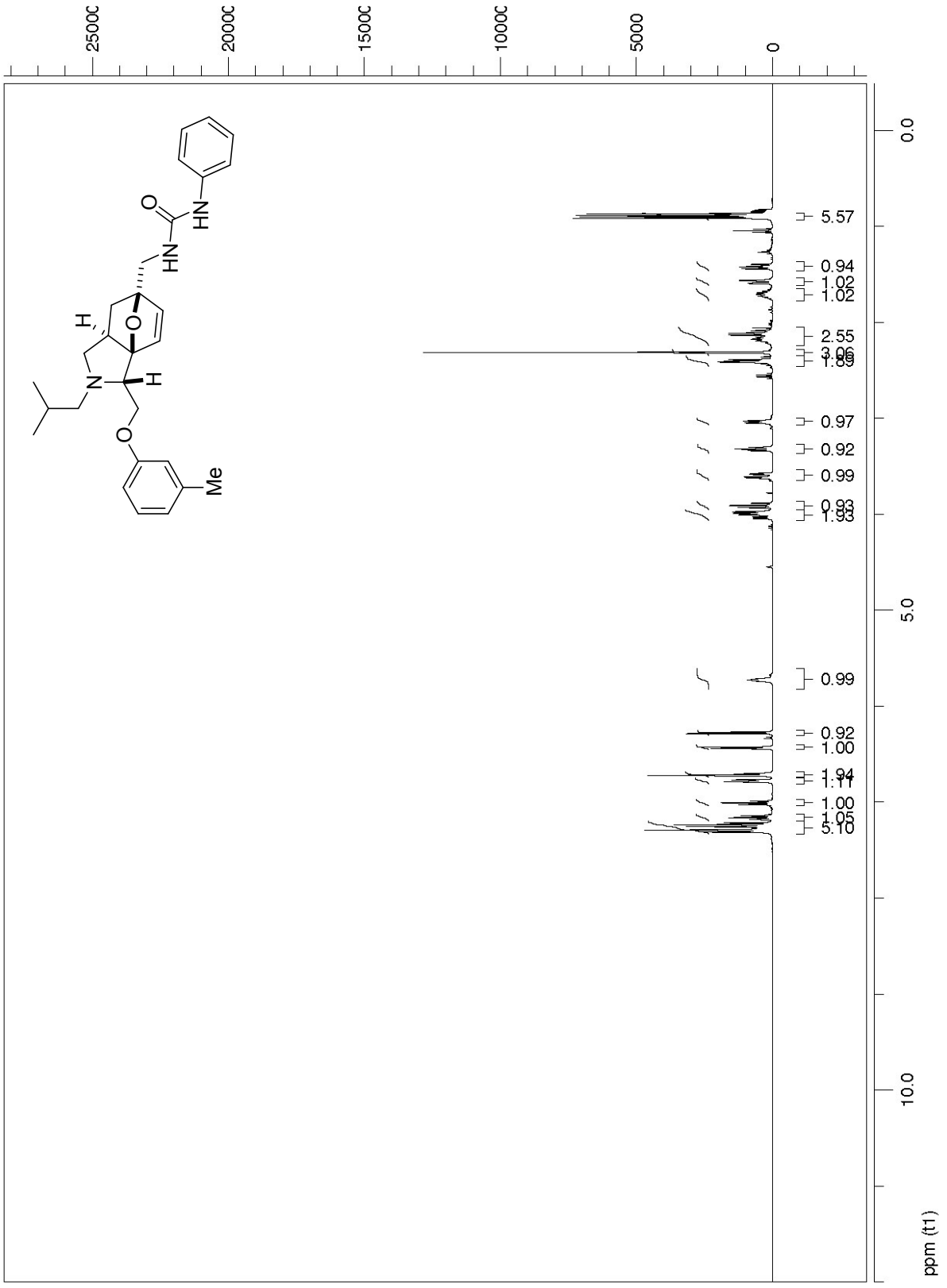
^{1}H NMR (400 MHz, $CDCl_3$) of **12c**



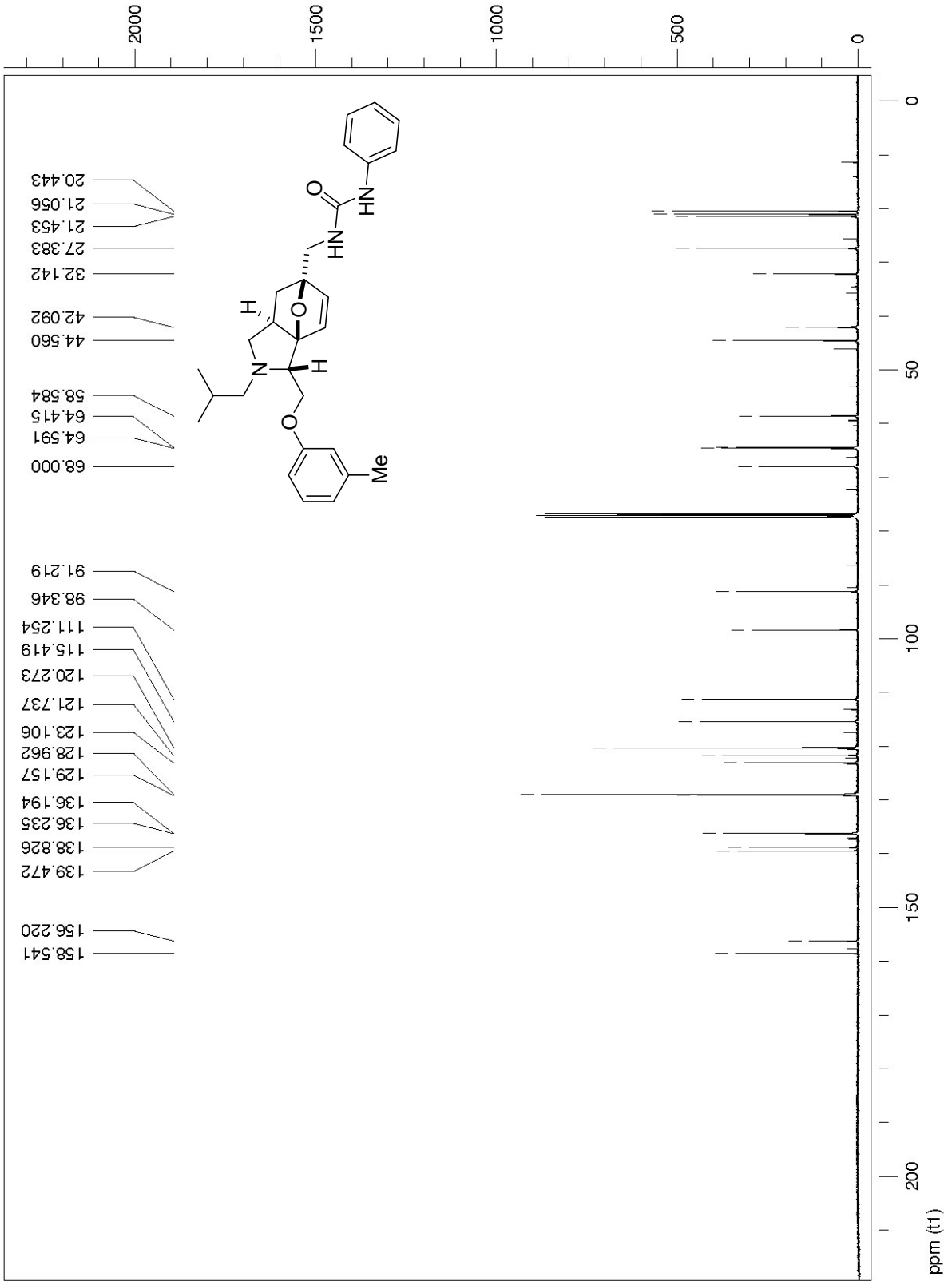
^{13}C NMR (100 MHz, $CDCl_3$) of **12c**



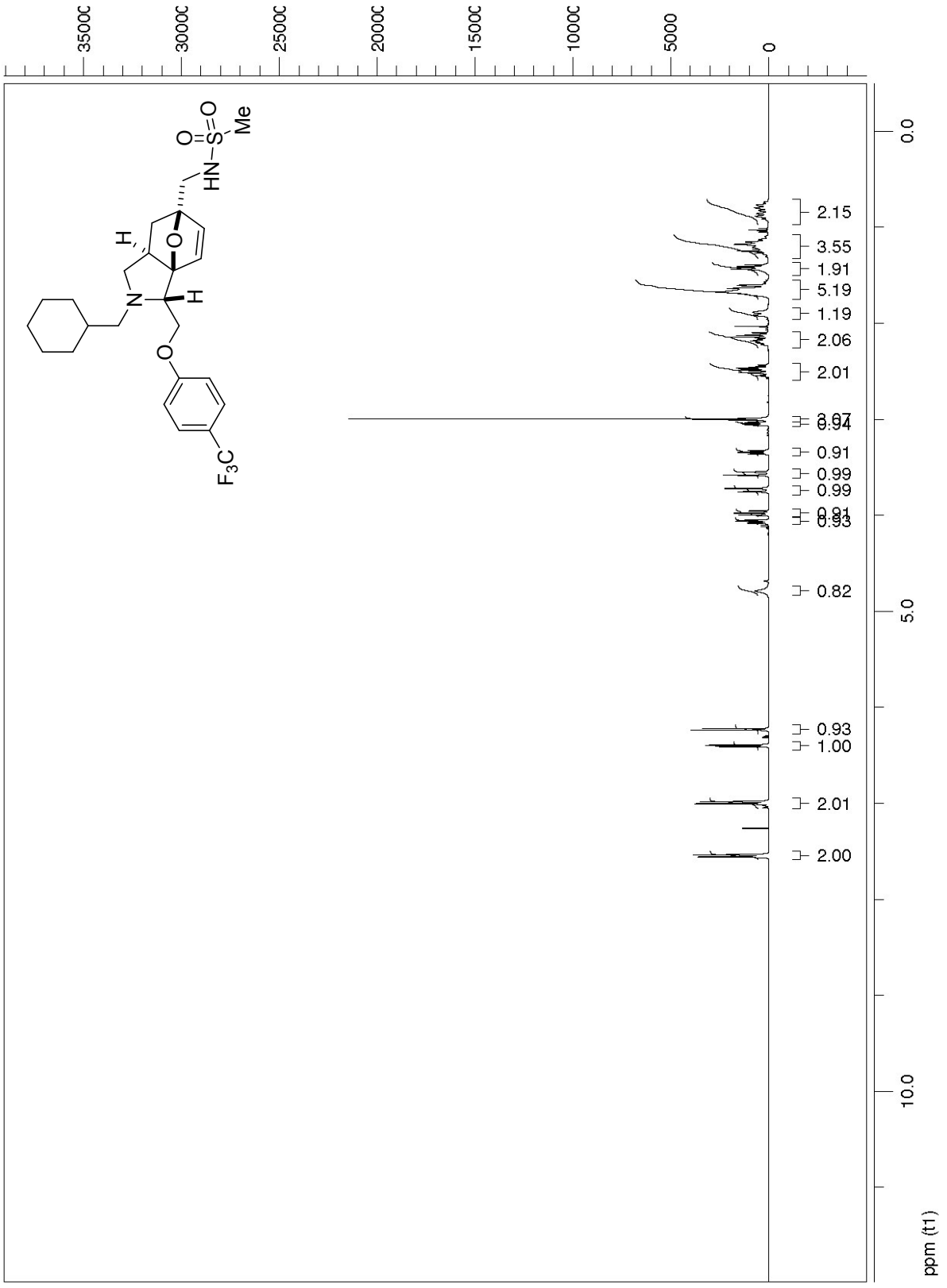
^{1}H NMR (400 MHz, $CDCl_3$) of **12d**



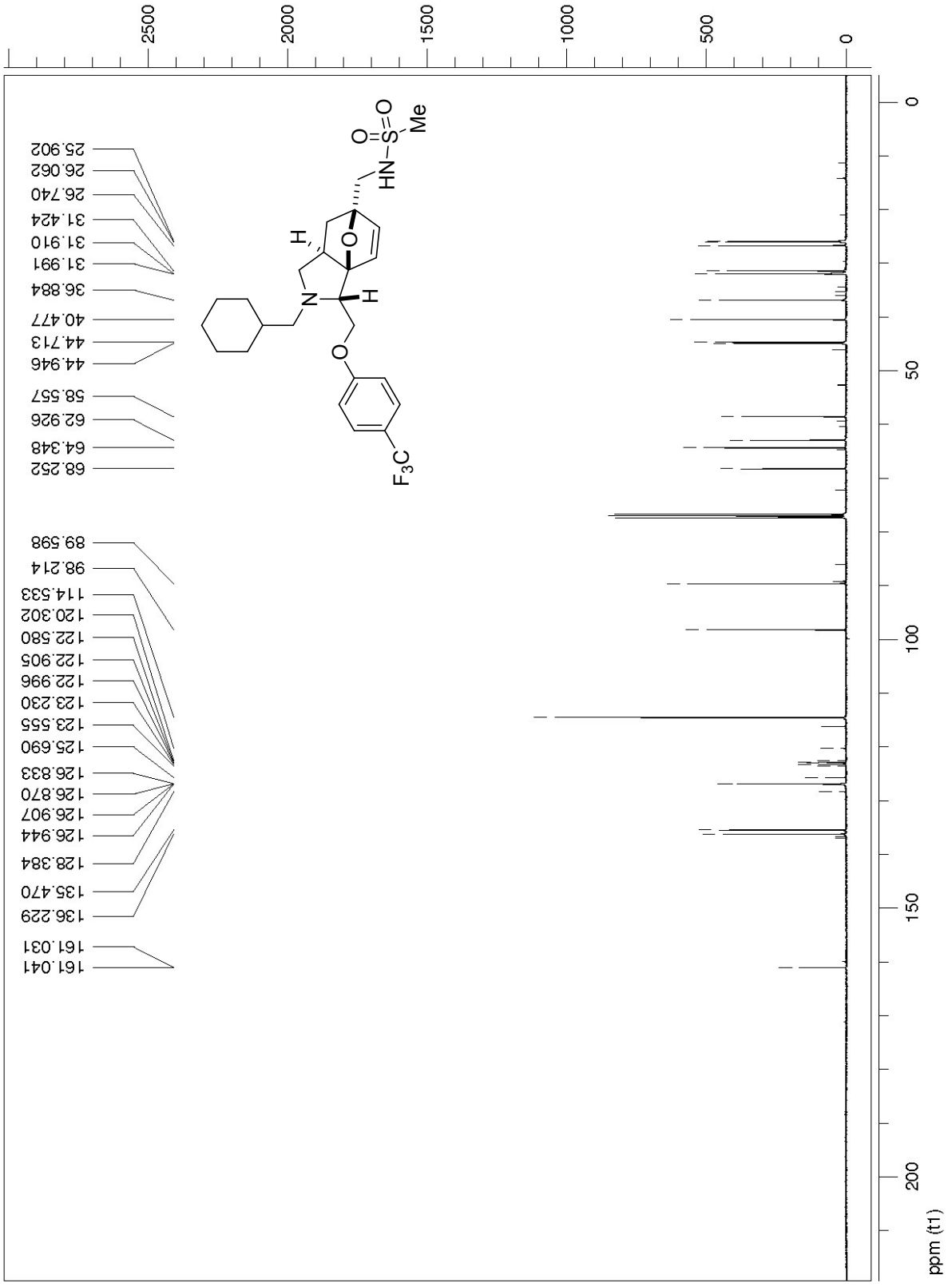
^{13}C NMR (100 MHz, $CDCl_3$) of **12d**



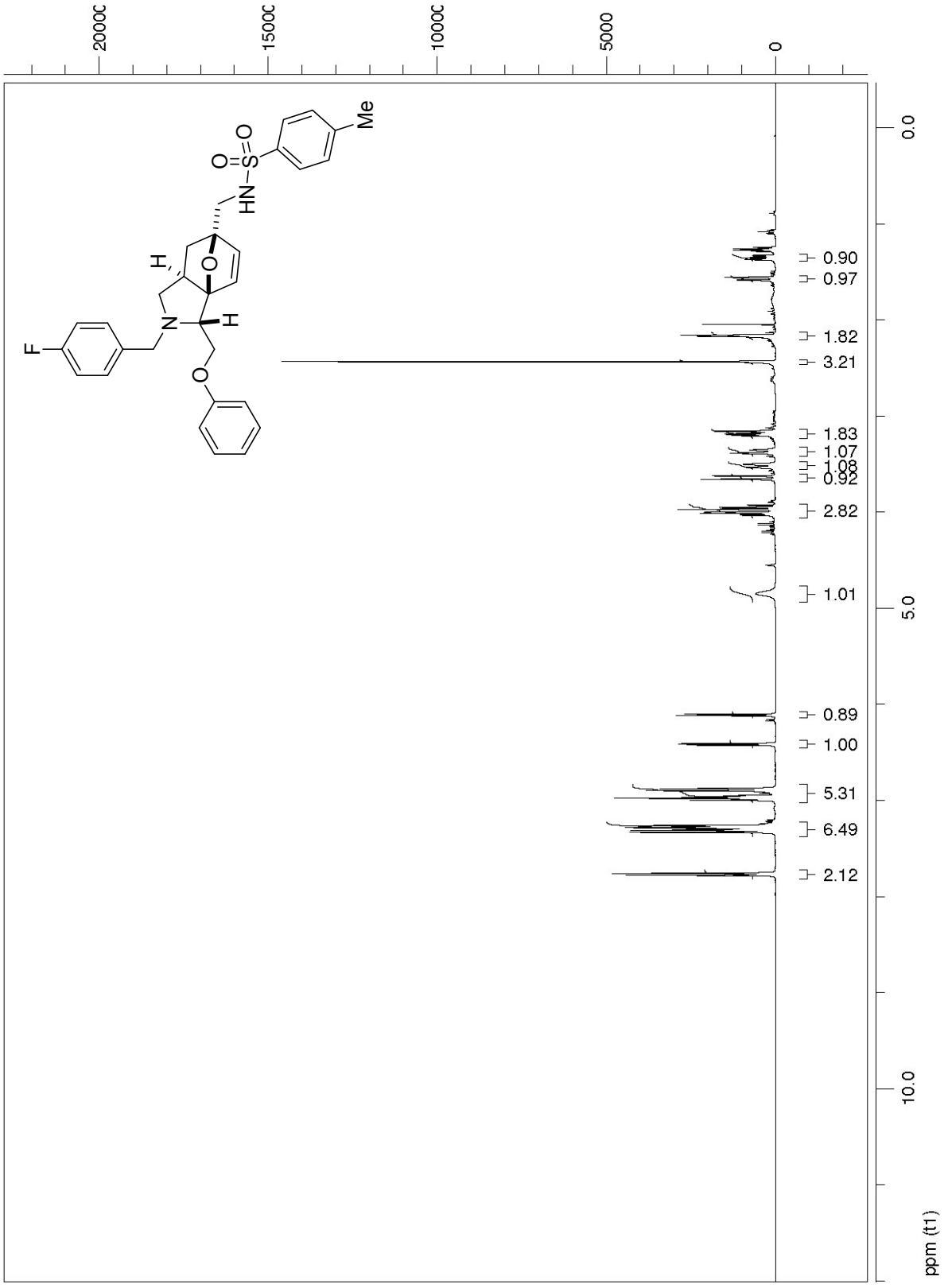
^{1}H NMR (400 MHz, $CDCl_3$) of **12e**



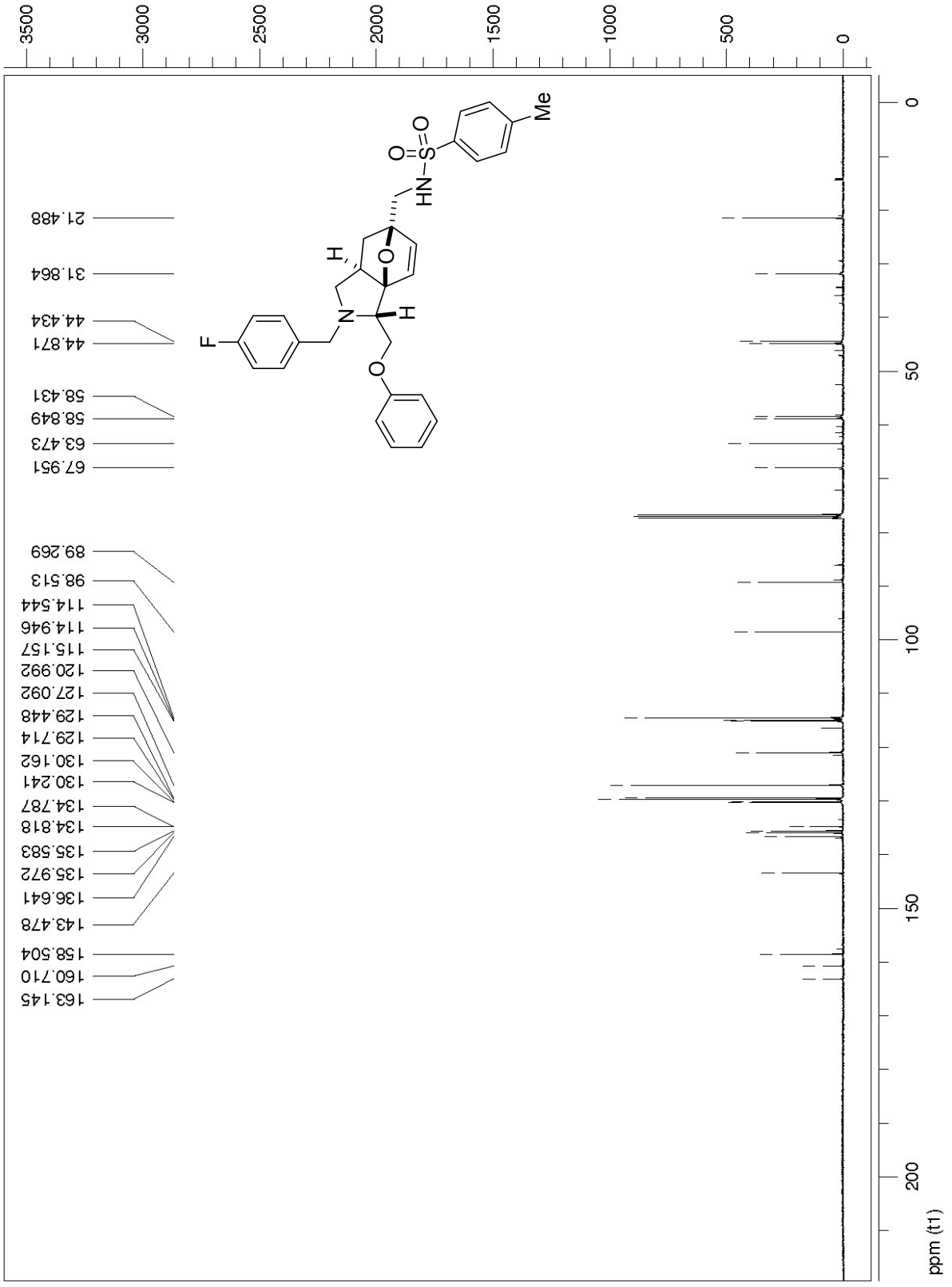
^{13}C NMR (100 MHz, $CDCl_3$) of **12e**



^{1}H NMR (400 MHz, $CDCl_3$) of **12f**

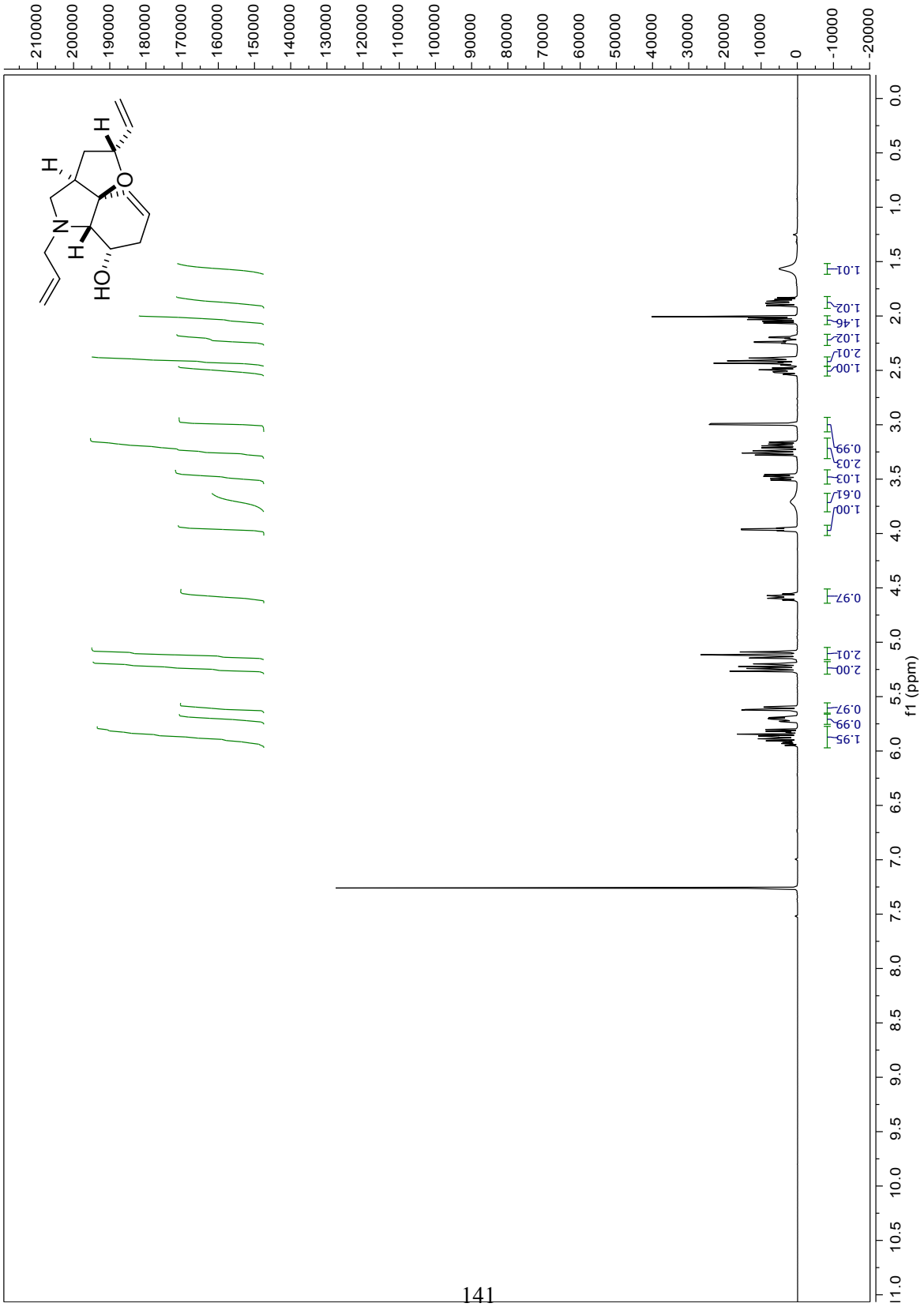


^{13}C NMR (100 MHz, $CDCl_3$) of **12f**

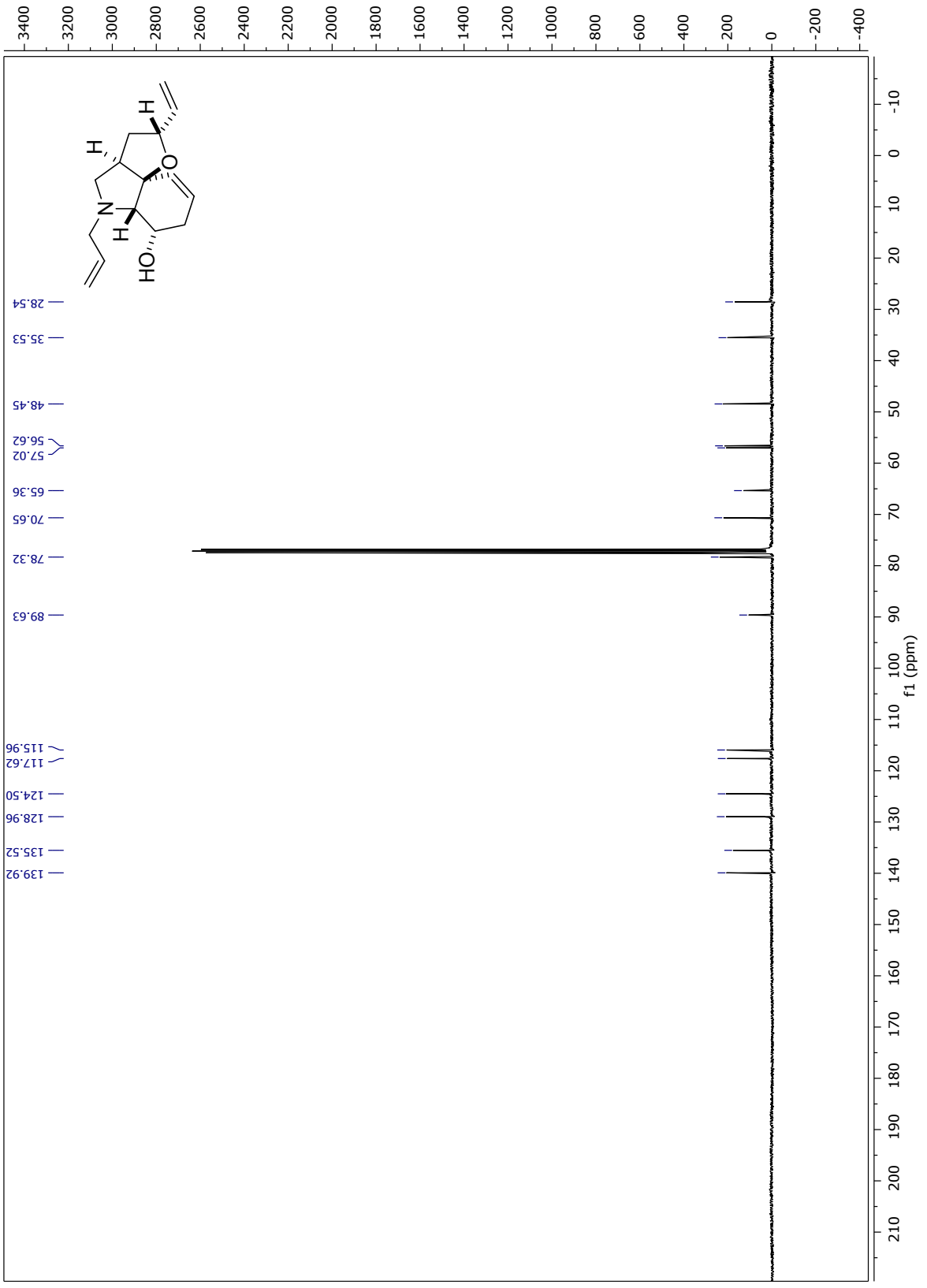


NMR Spectra for ROM-RCM Cascade Products

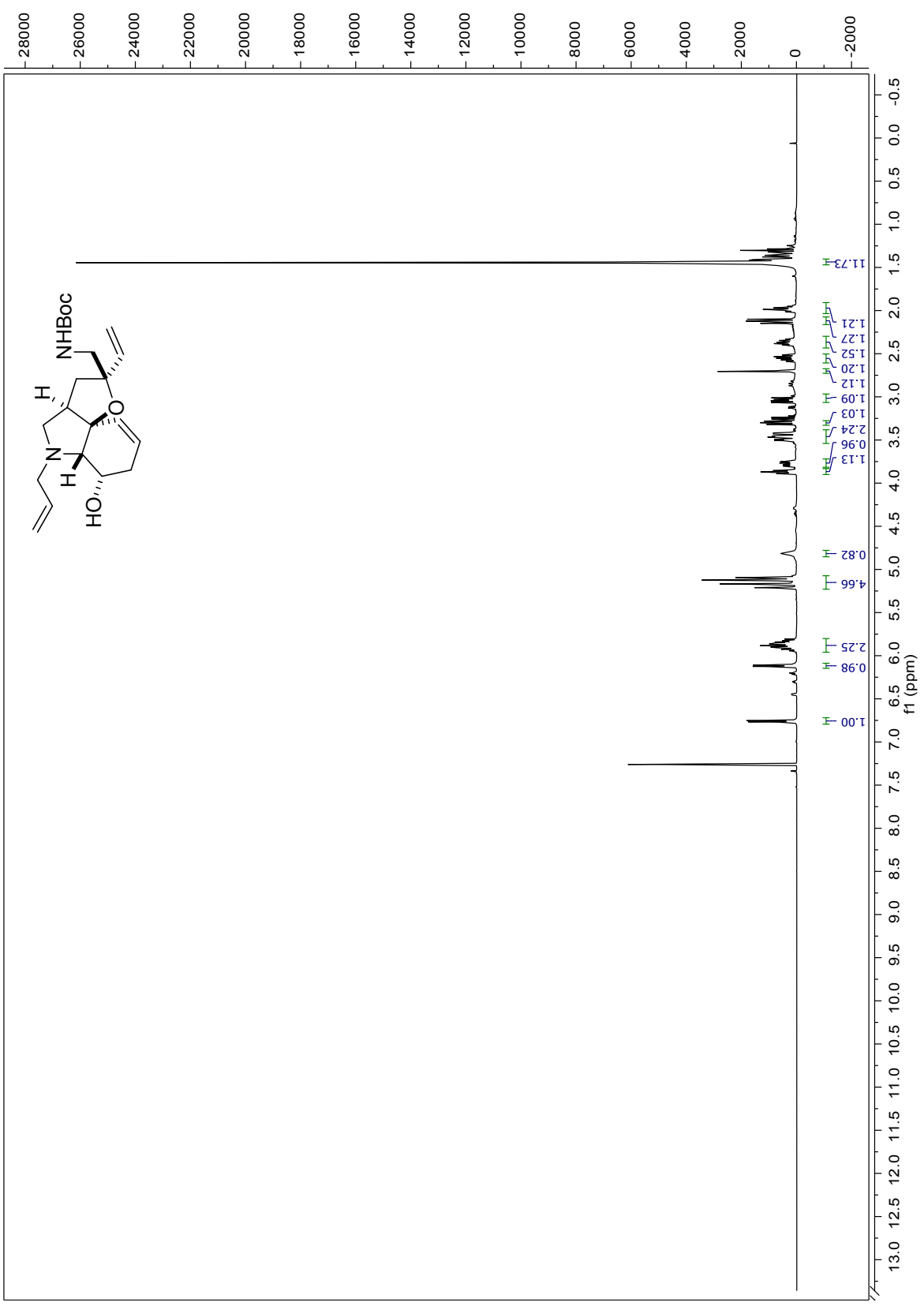
^{1}H NMR (400 MHz, $CDCl_3$) of **4**



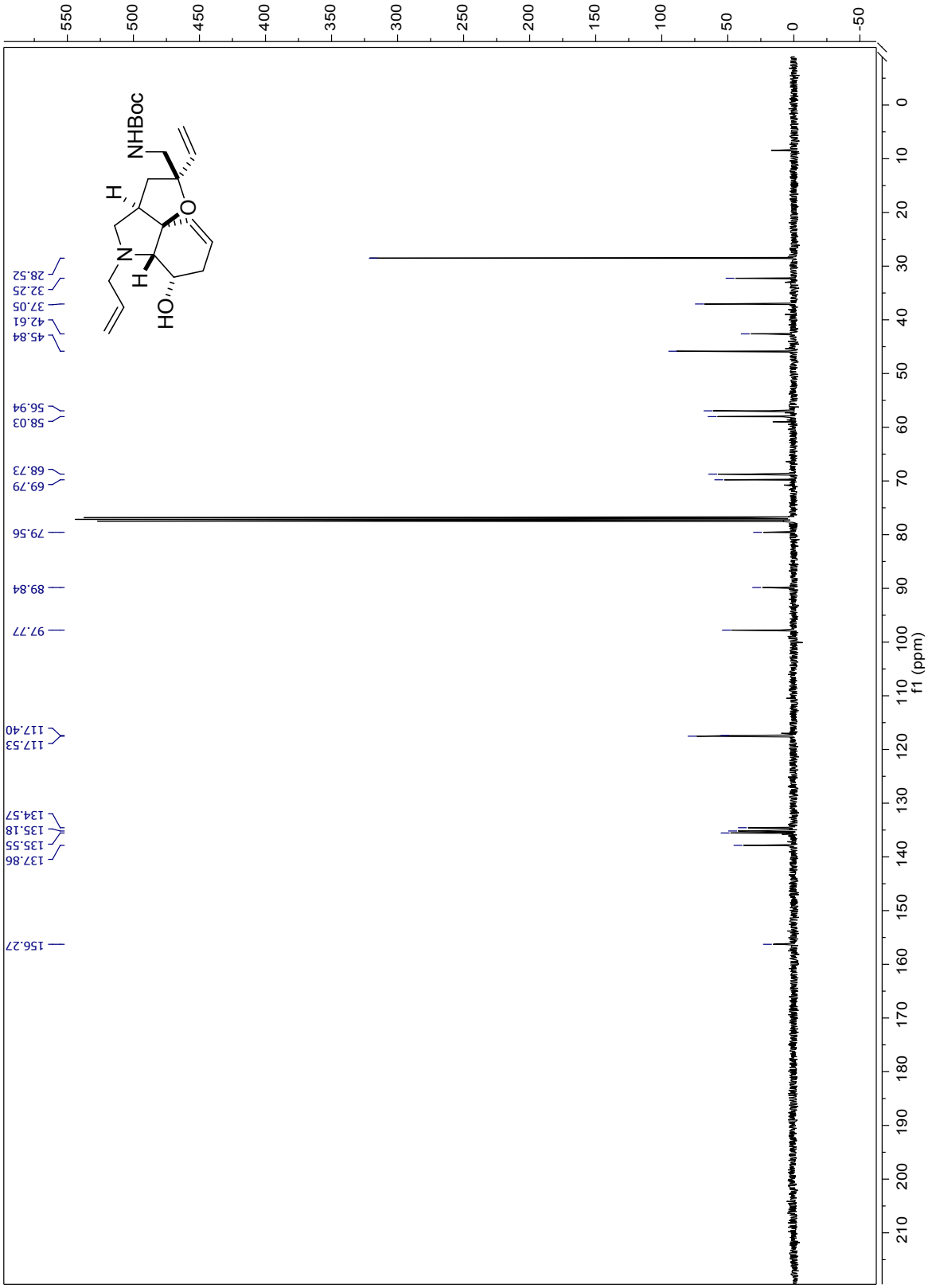
^{13}C NMR (100 MHz, $CDCl_3$) of **4**



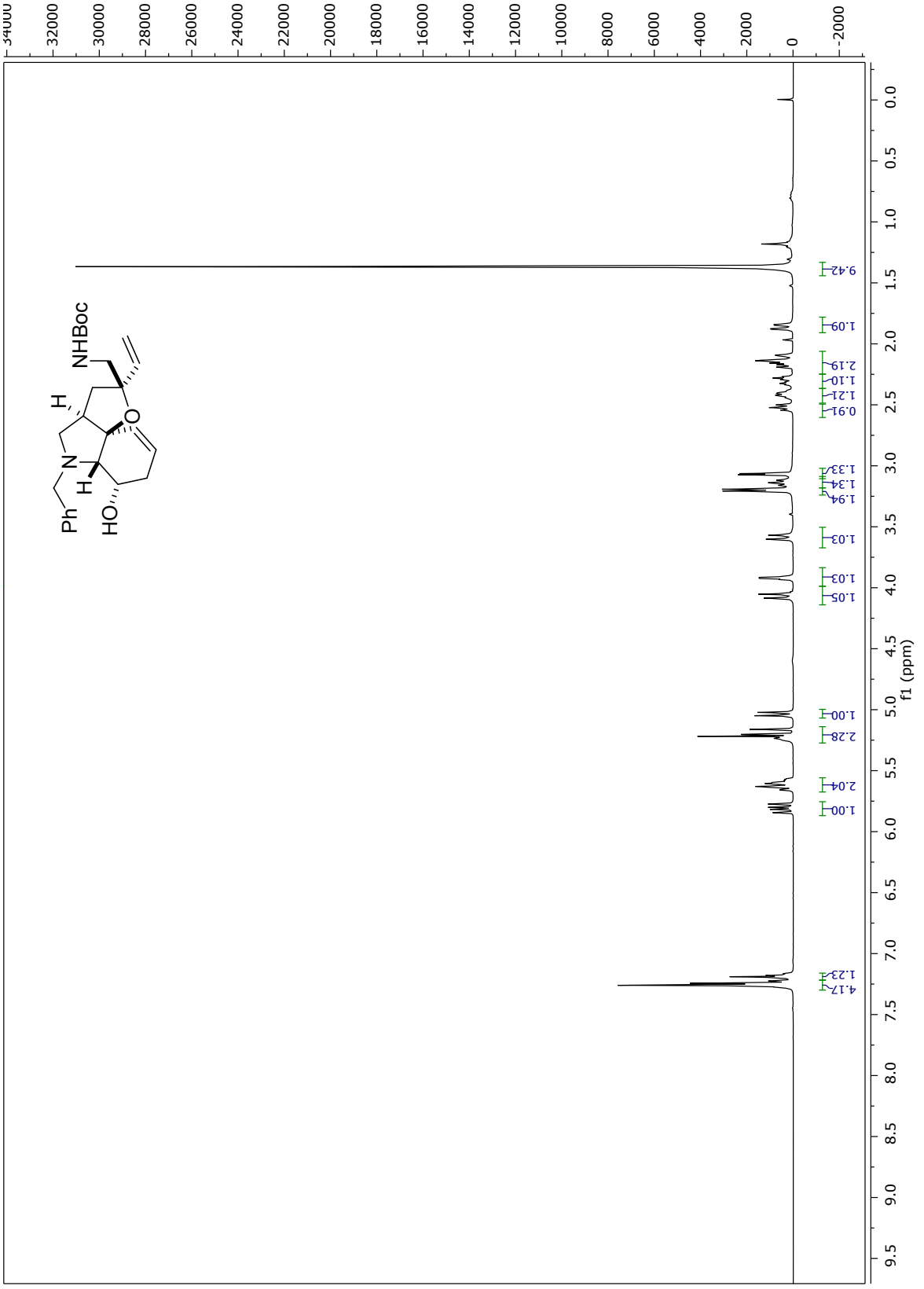
^{1}H NMR (400 MHz, $CDCl_3$) of **13a**



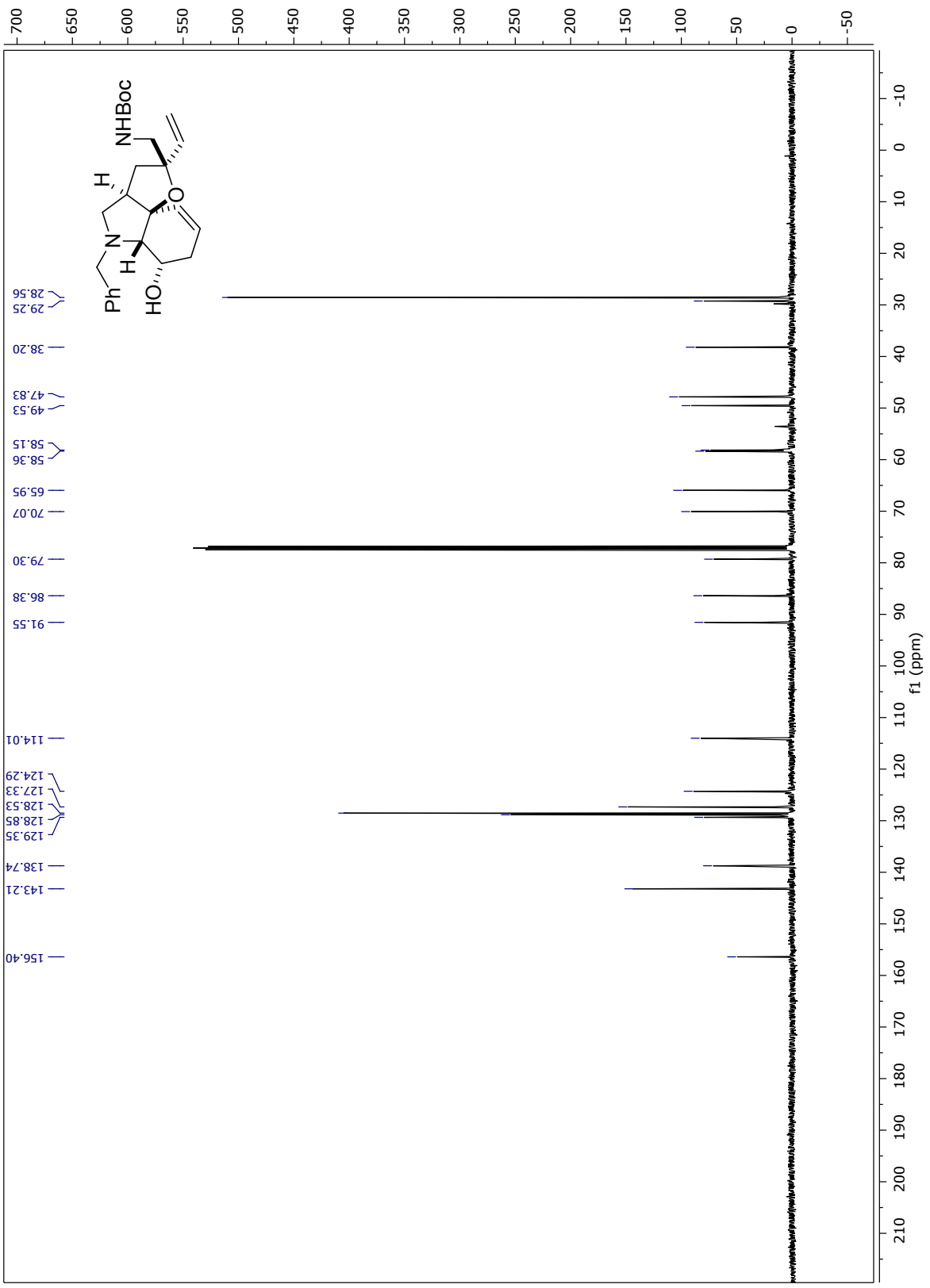
^{13}C NMR (100 MHz, $CDCl_3$) of **13a**



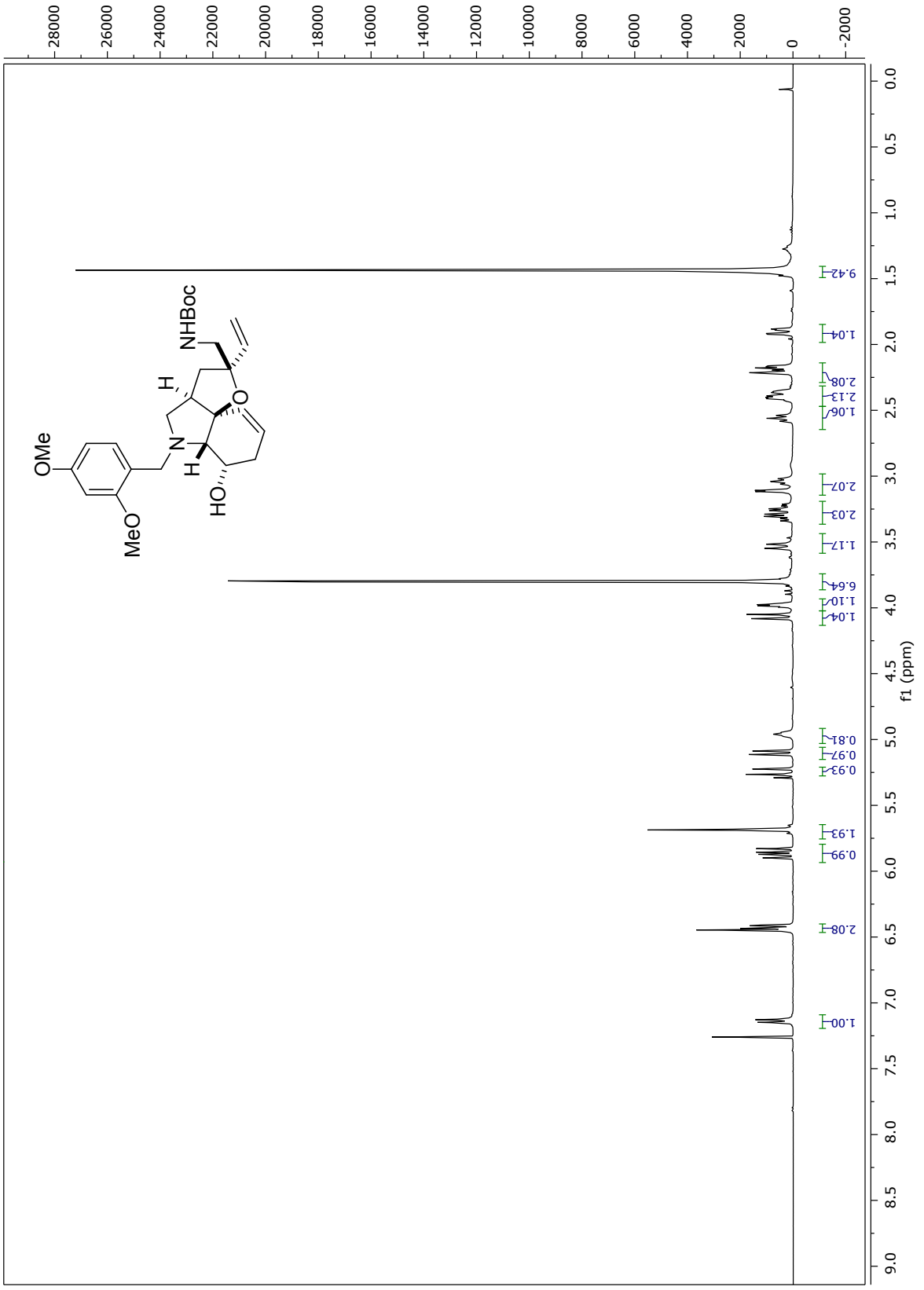
^{1}H NMR (400 MHz, $CDCl_3$) of **13b**



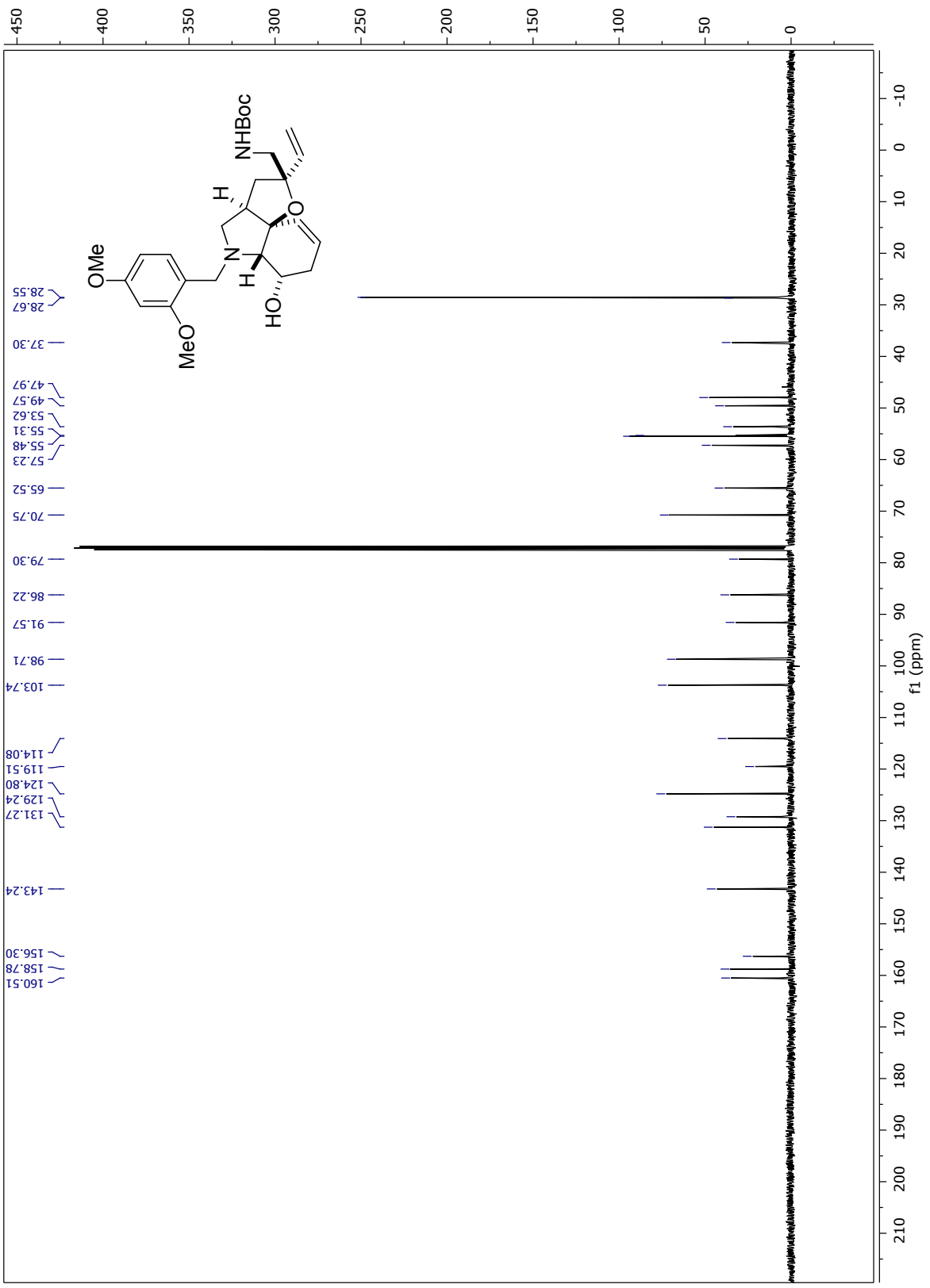
^{13}C NMR (100 MHz, $CDCl_3$) of **13b**



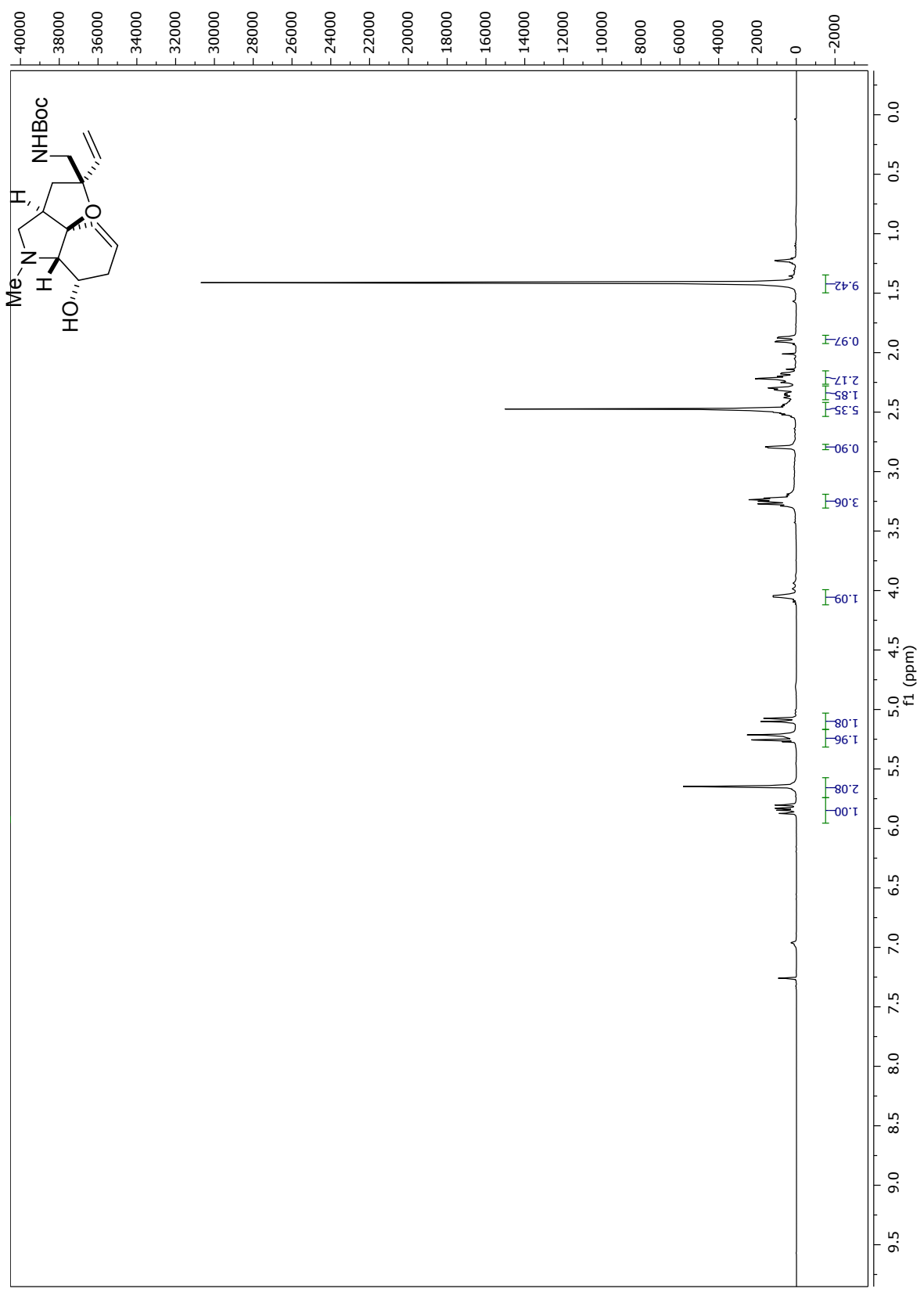
^{1}H NMR (400 MHz, $CDCl_3$) of **13c**



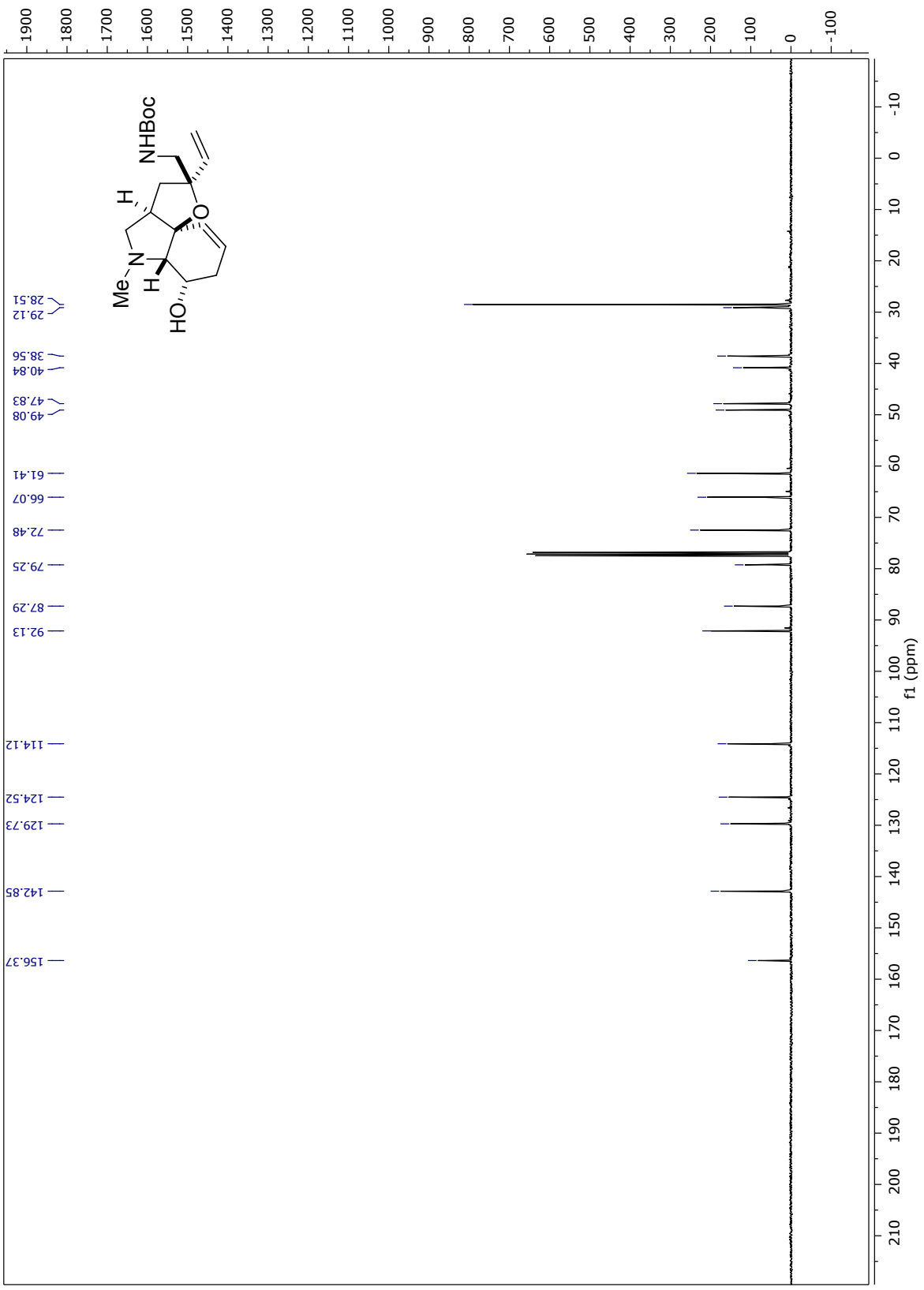
^{13}C NMR (100 MHz, $CDCl_3$) of **13c**



^{1}H NMR (400 MHz, $CDCl_3$) of **13d**

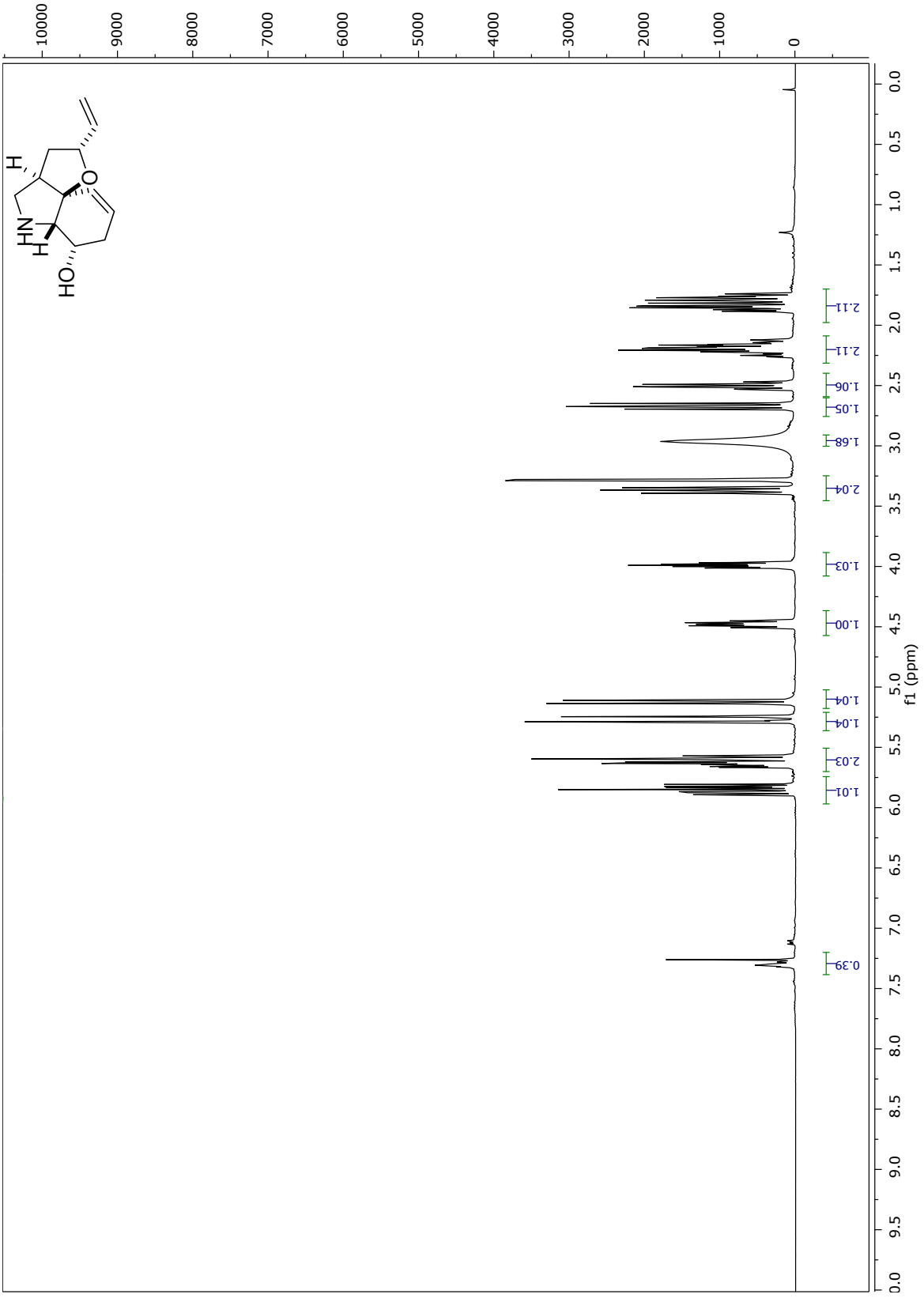


^{13}C NMR (100 MHz, $CDCl_3$) of **13d**

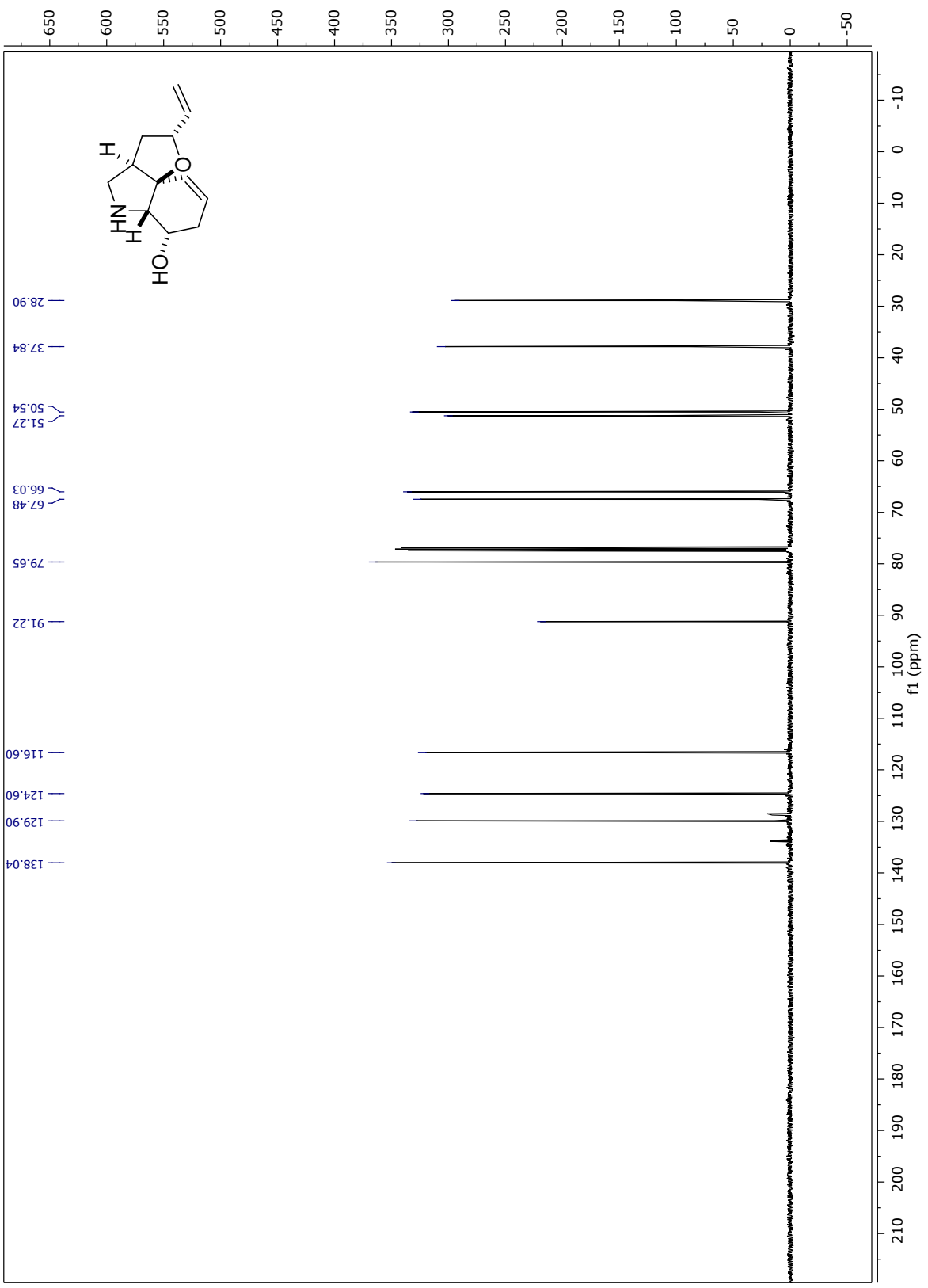


NMR Spectra for Diversified ROM-RCM Cascade Products

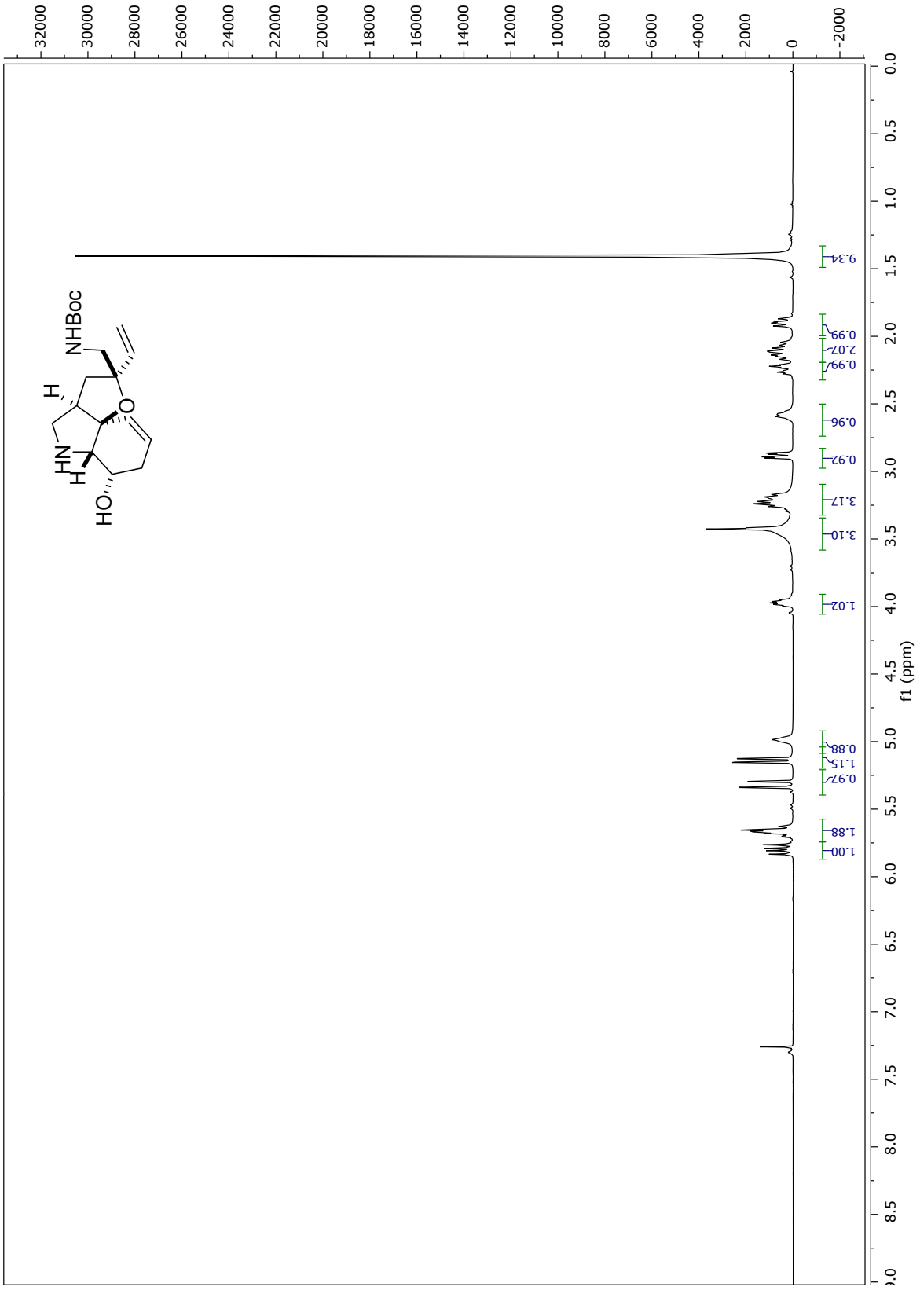
^{1}H NMR (400 MHz, $CDCl_3$) of **14a**



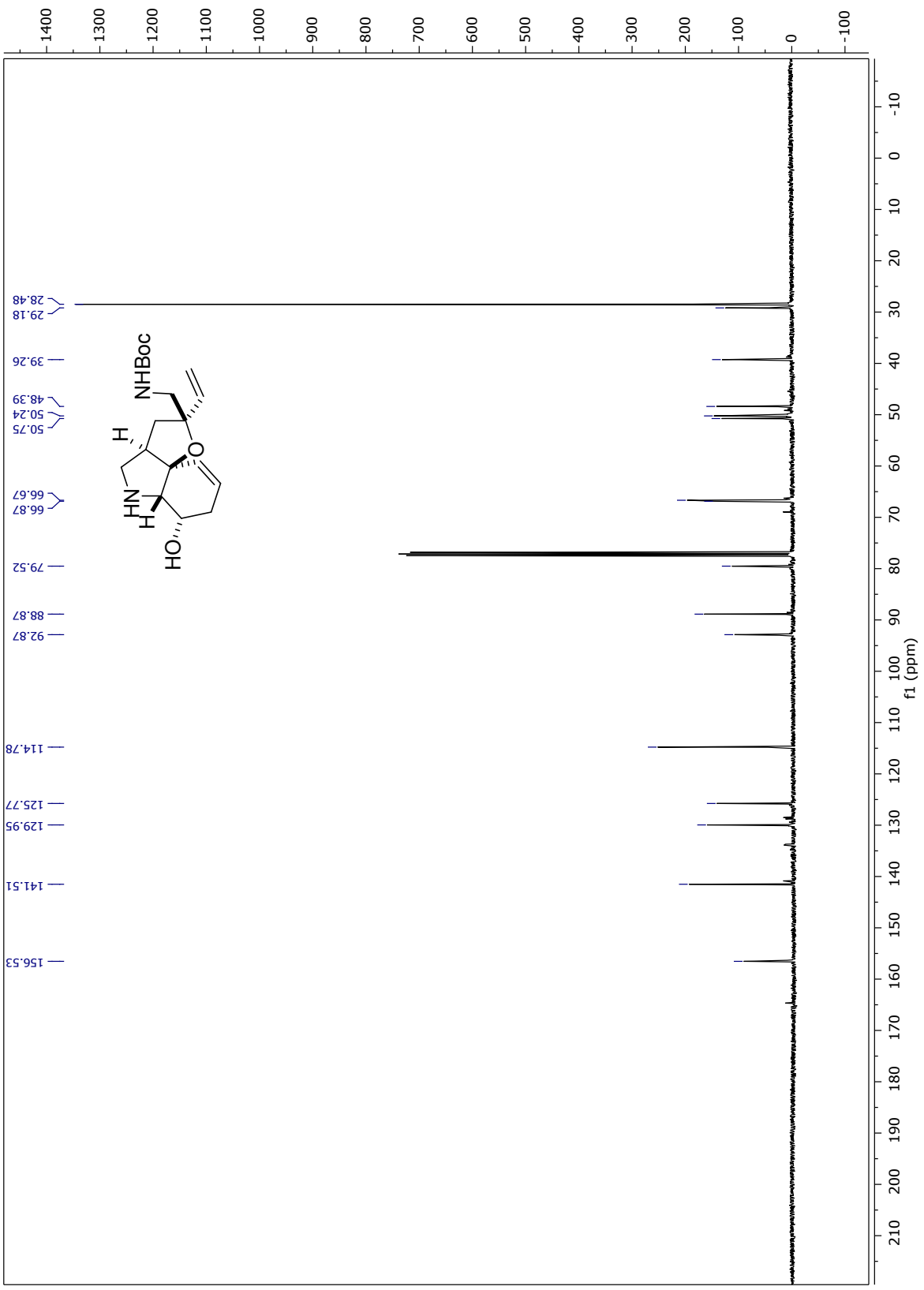
^{13}C NMR (100 MHz, $CDCl_3$) of **14a**



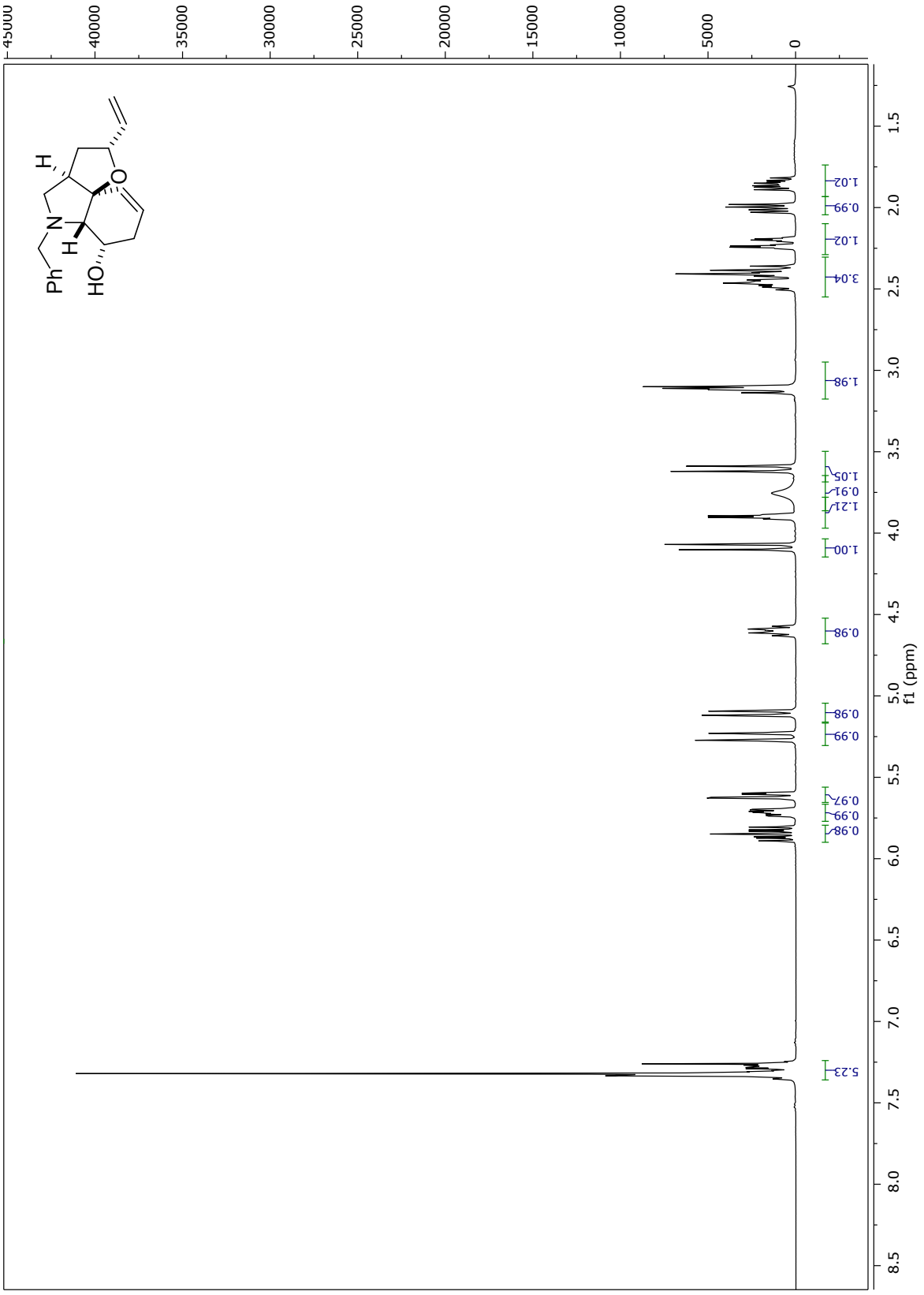
^{1}H NMR (400 MHz, $CDCl_3$) of **14b**



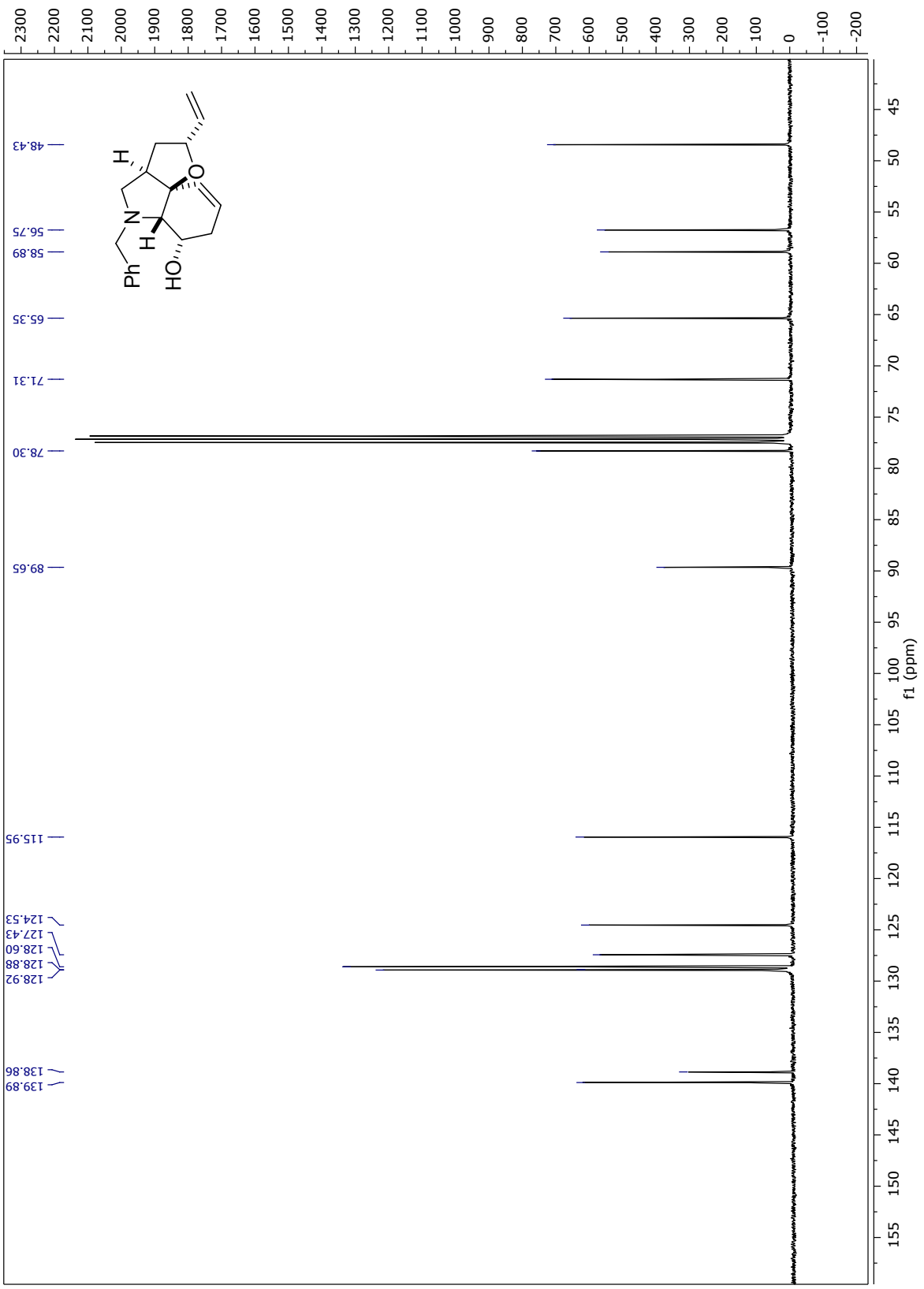
^{13}C NMR (100 MHz, $CDCl_3$) of **14b**



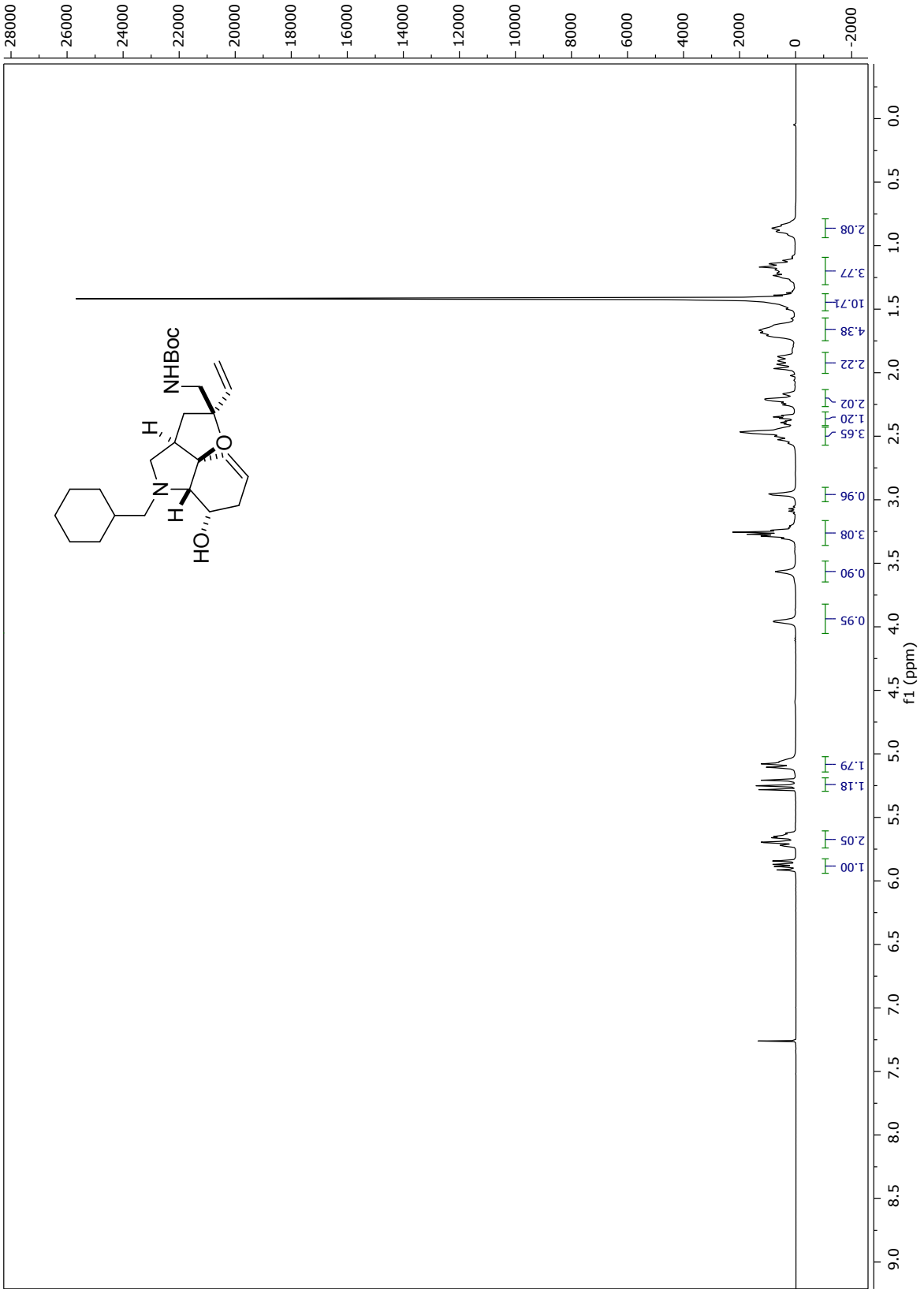
^{1}H NMR (400 MHz, $CDCl_3$) of **15a**



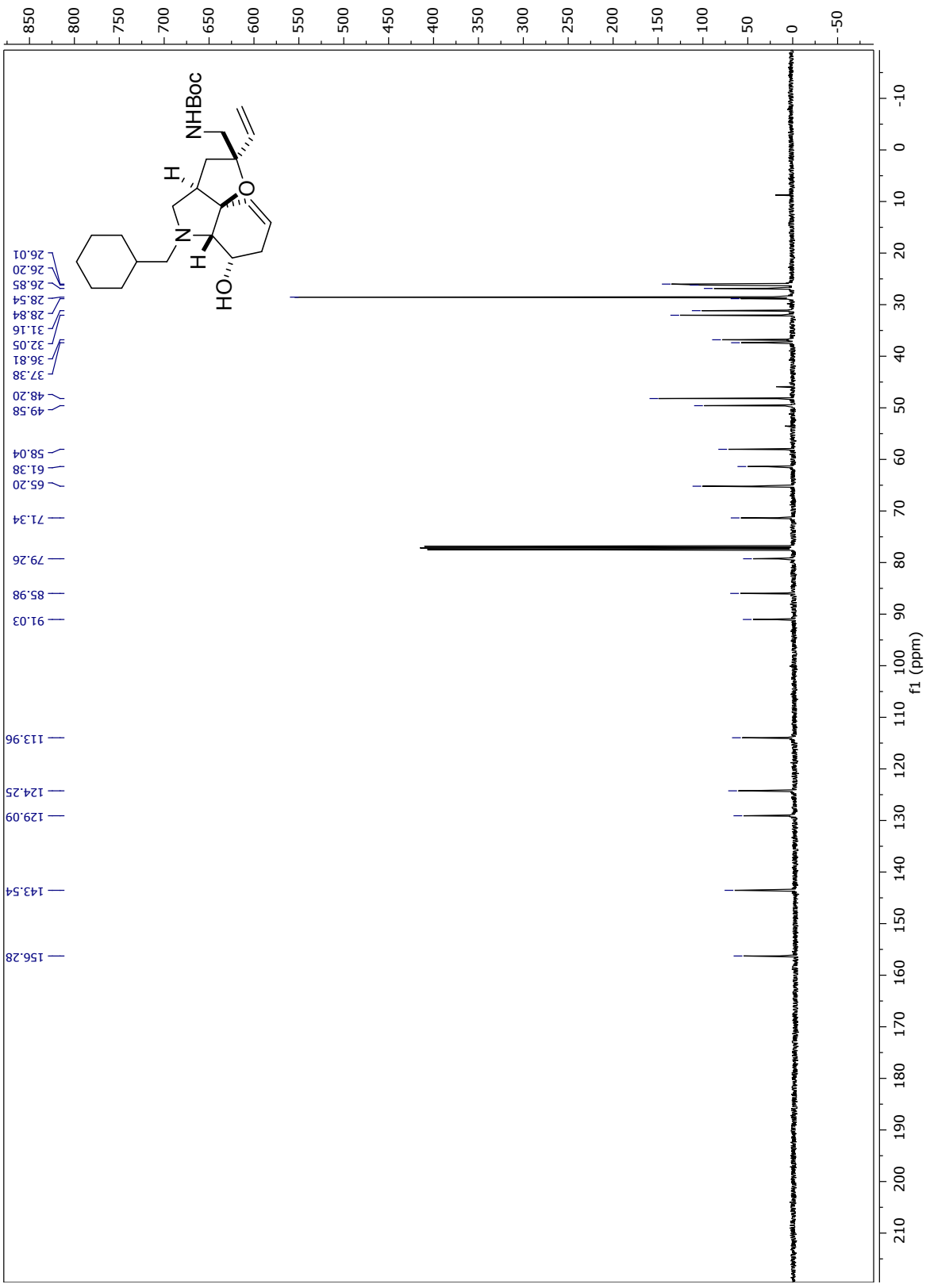
^{13}C NMR (100 MHz, $CDCl_3$) of **15a**



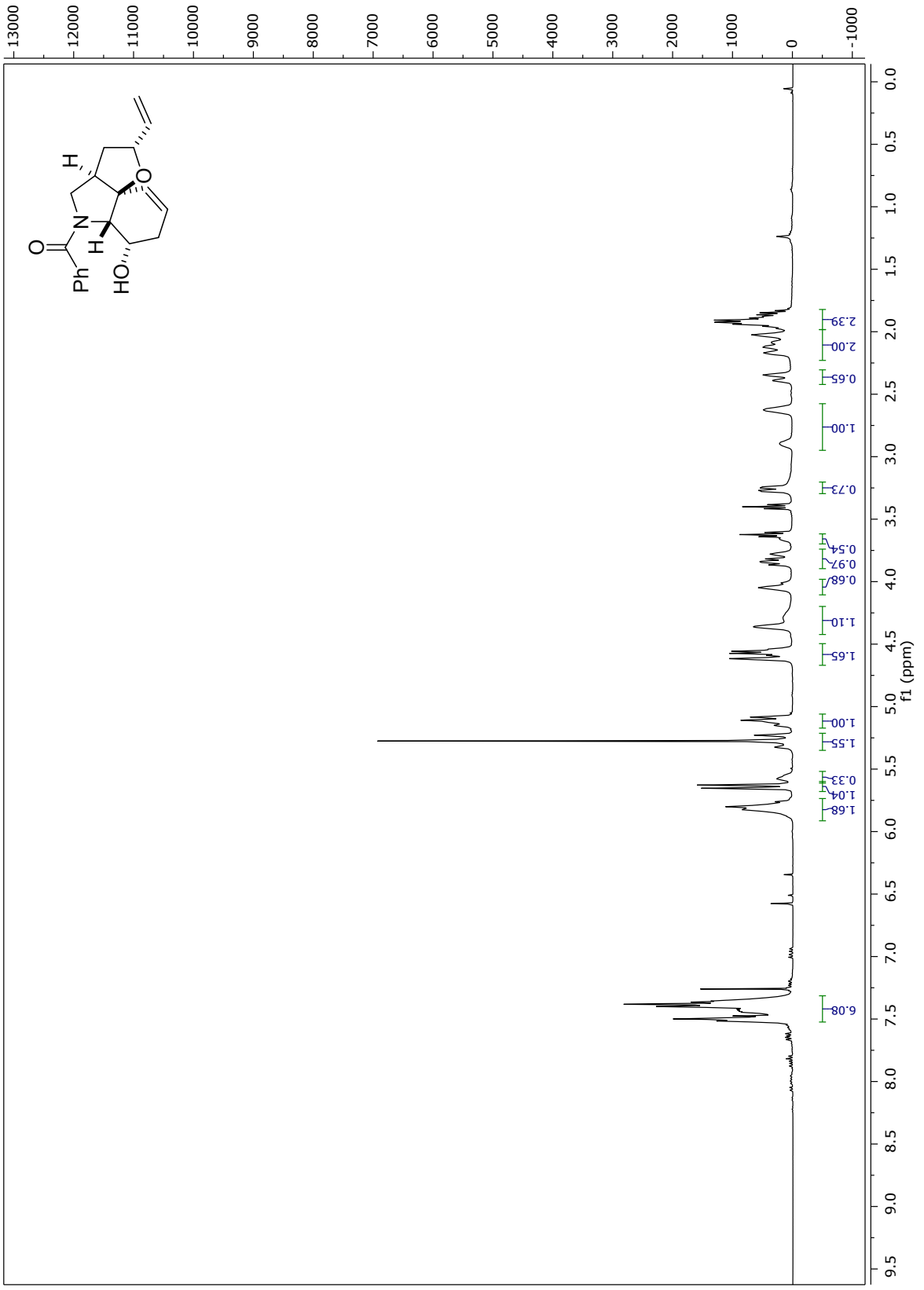
^{1}H NMR (400 MHz, $CDCl_3$) of **15b**



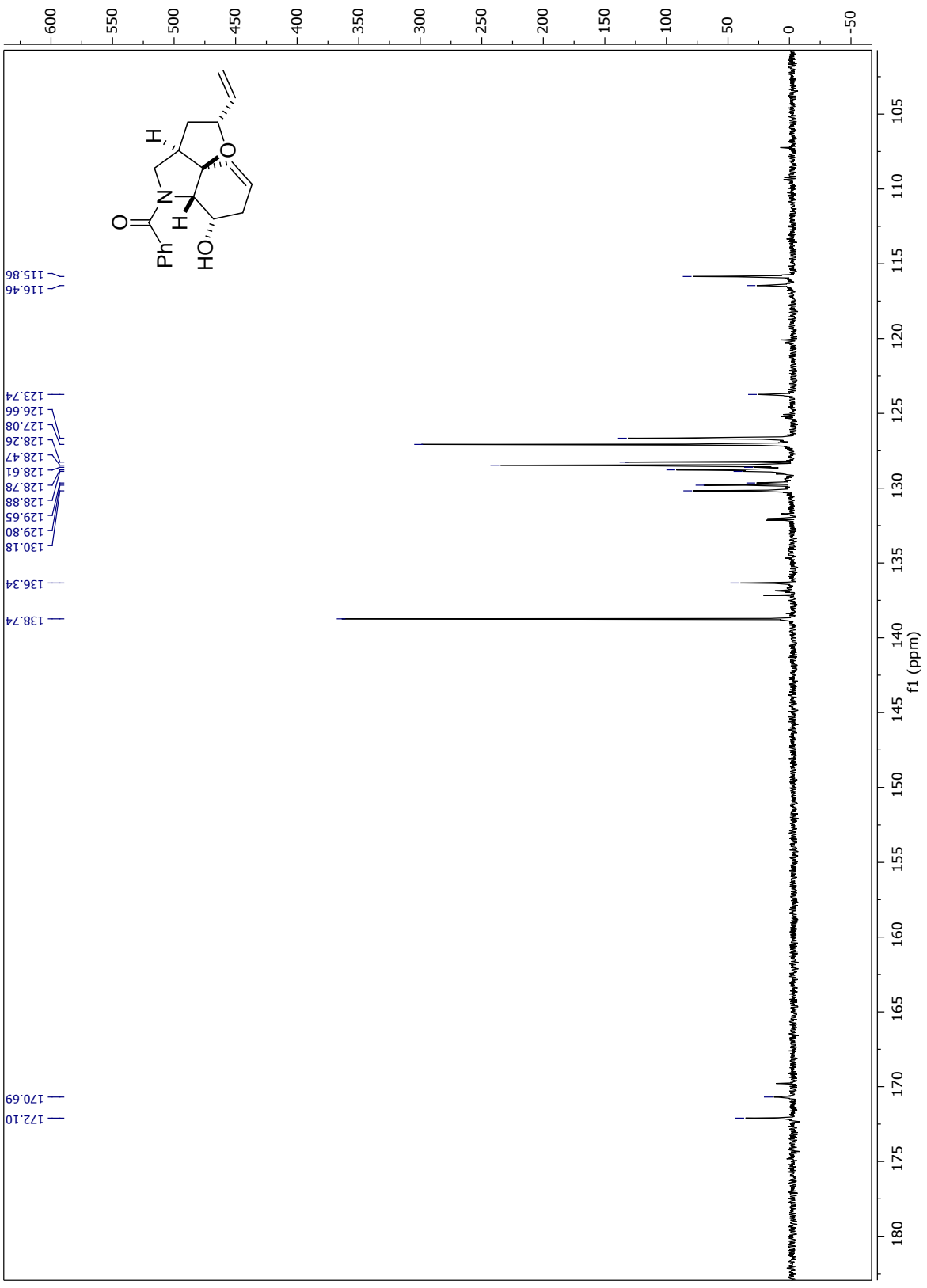
^{13}C NMR (100 MHz, $CDCl_3$) of **15b**



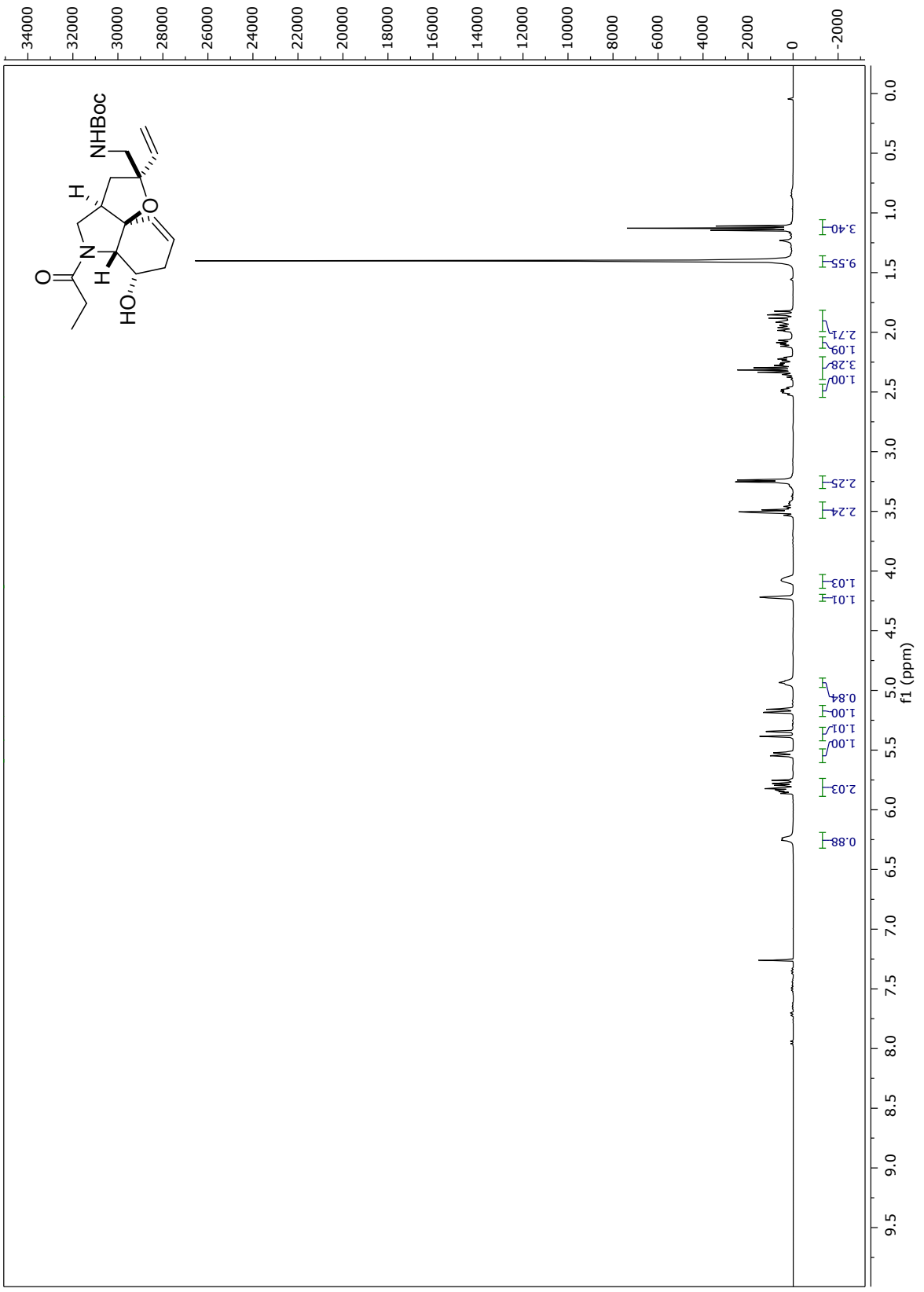
^{1}H NMR (400 MHz, $CDCl_3$) of **15c**



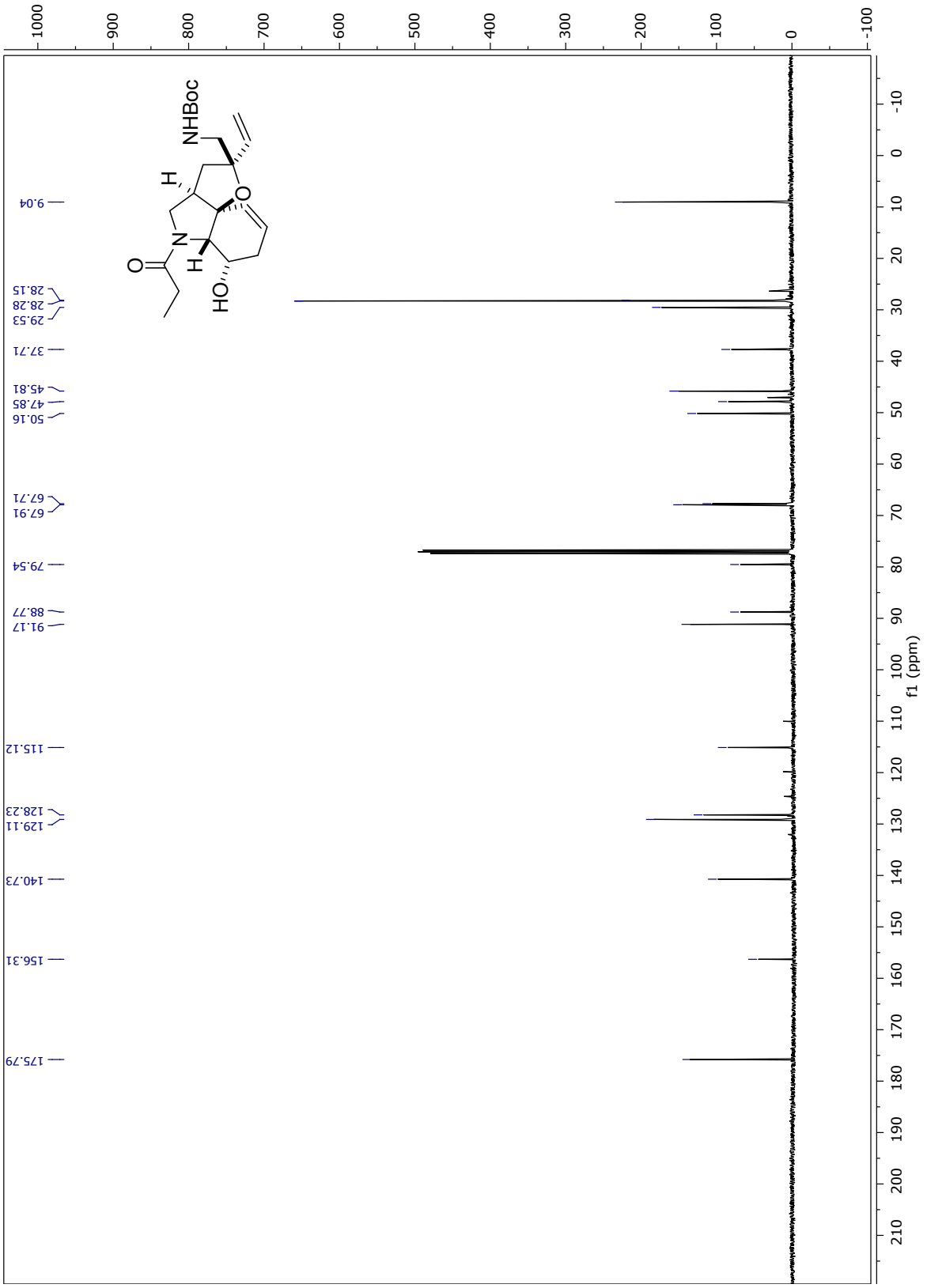
^{13}C NMR (100 MHz, $CDCl_3$) of **15c**



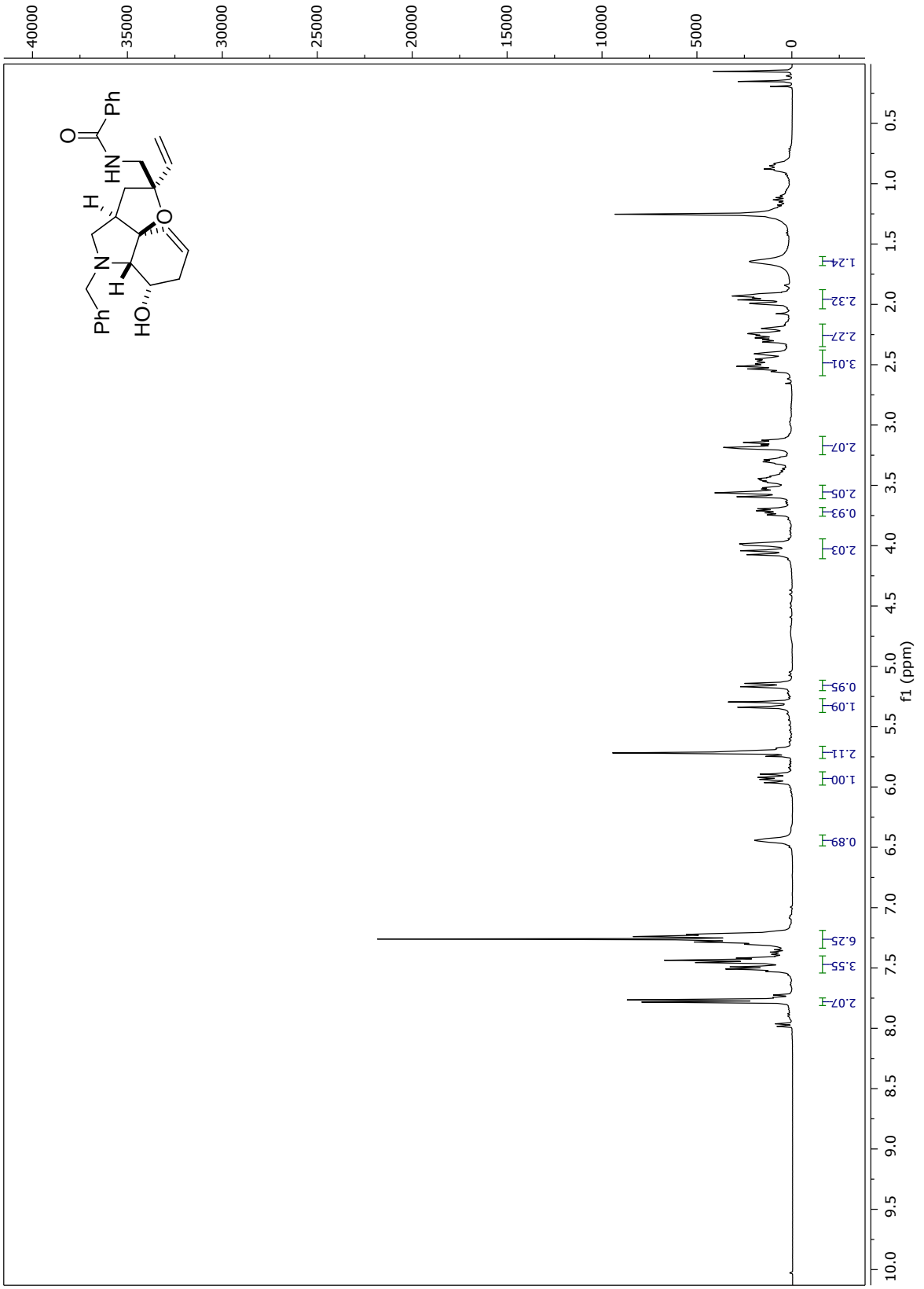
^{1}H NMR (400 MHz, $CDCl_3$) of **15e**



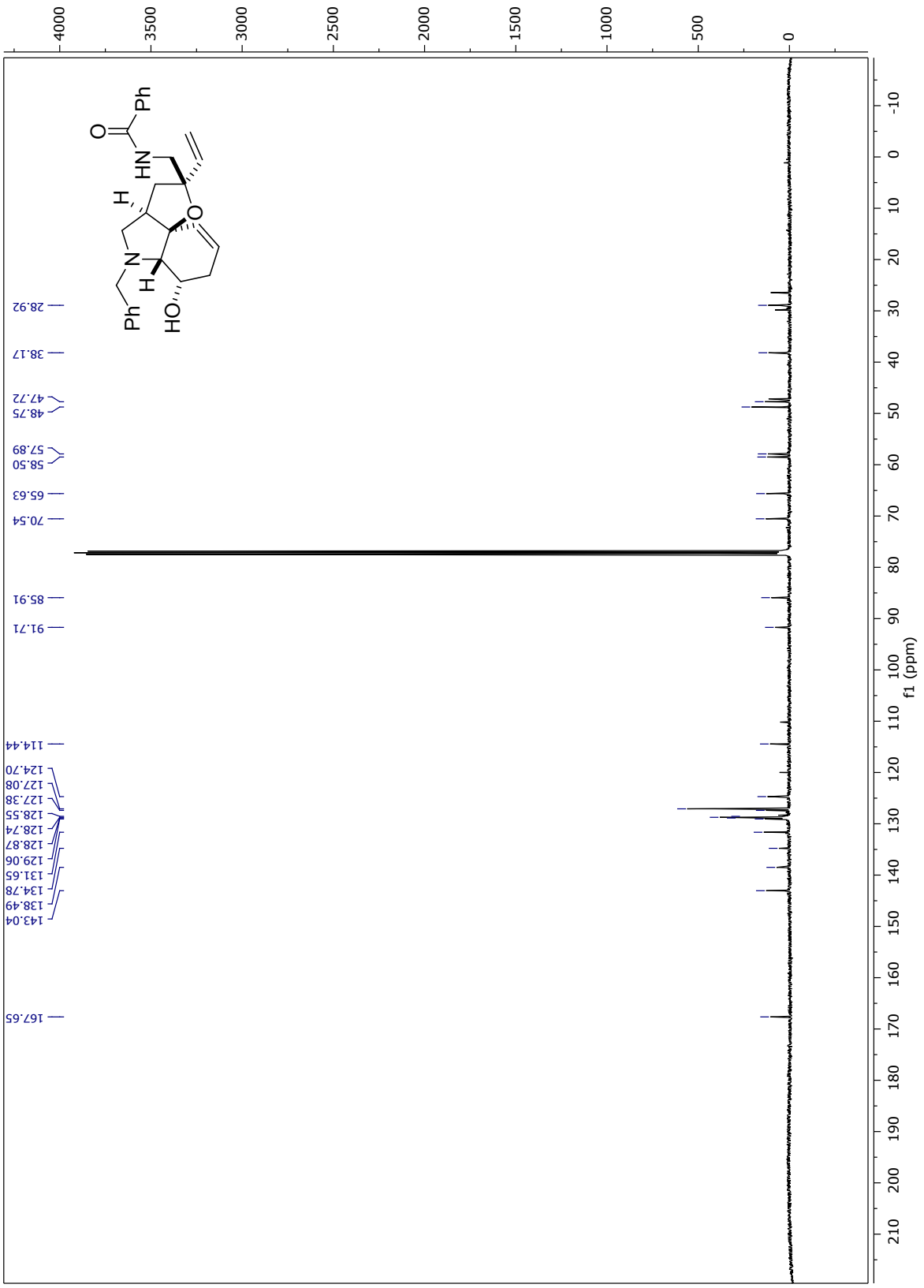
^{13}C NMR (100 MHz, $CDCl_3$) of **15e**



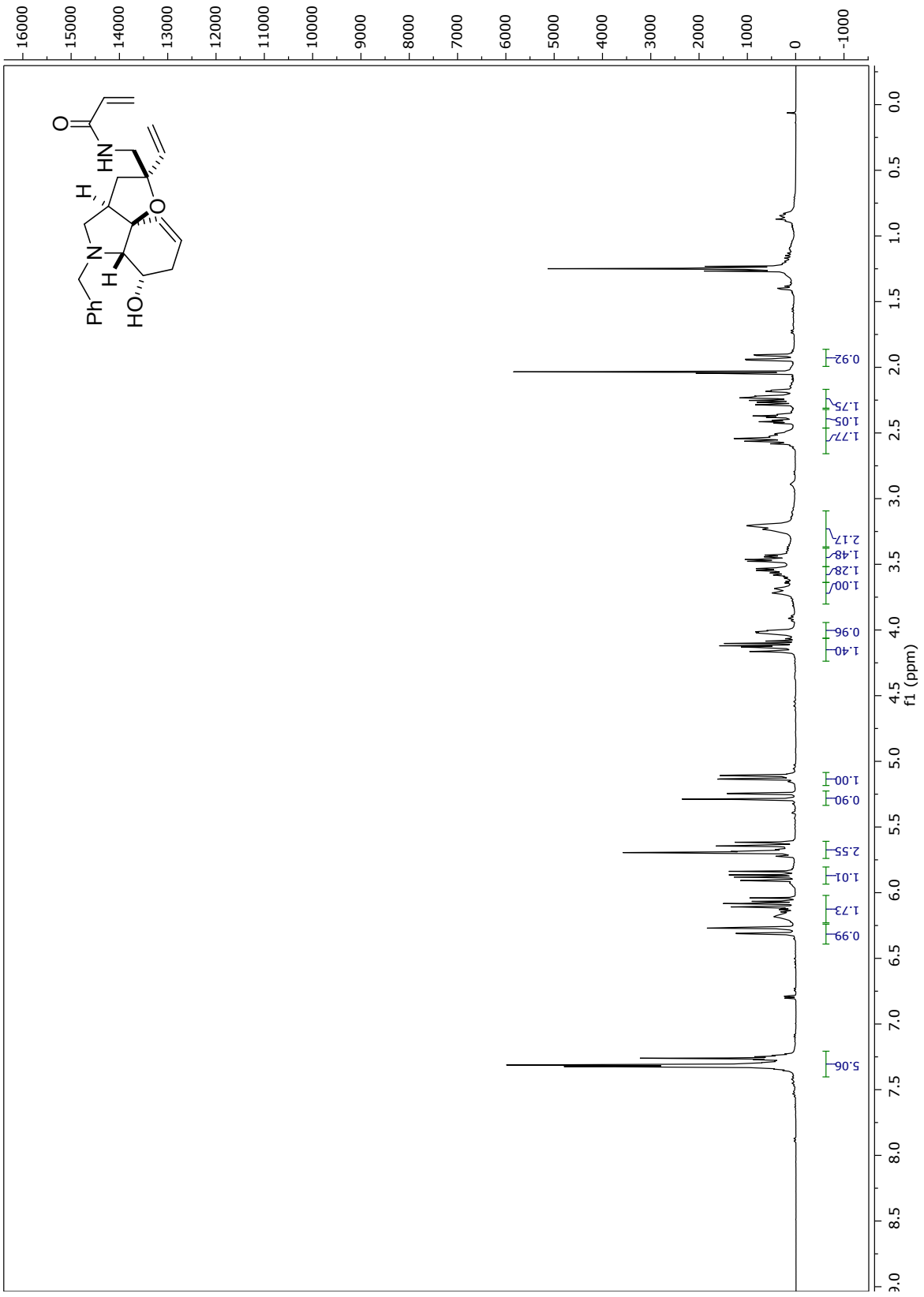
^{1}H NMR (400 MHz, $CDCl_3$) of **16a**



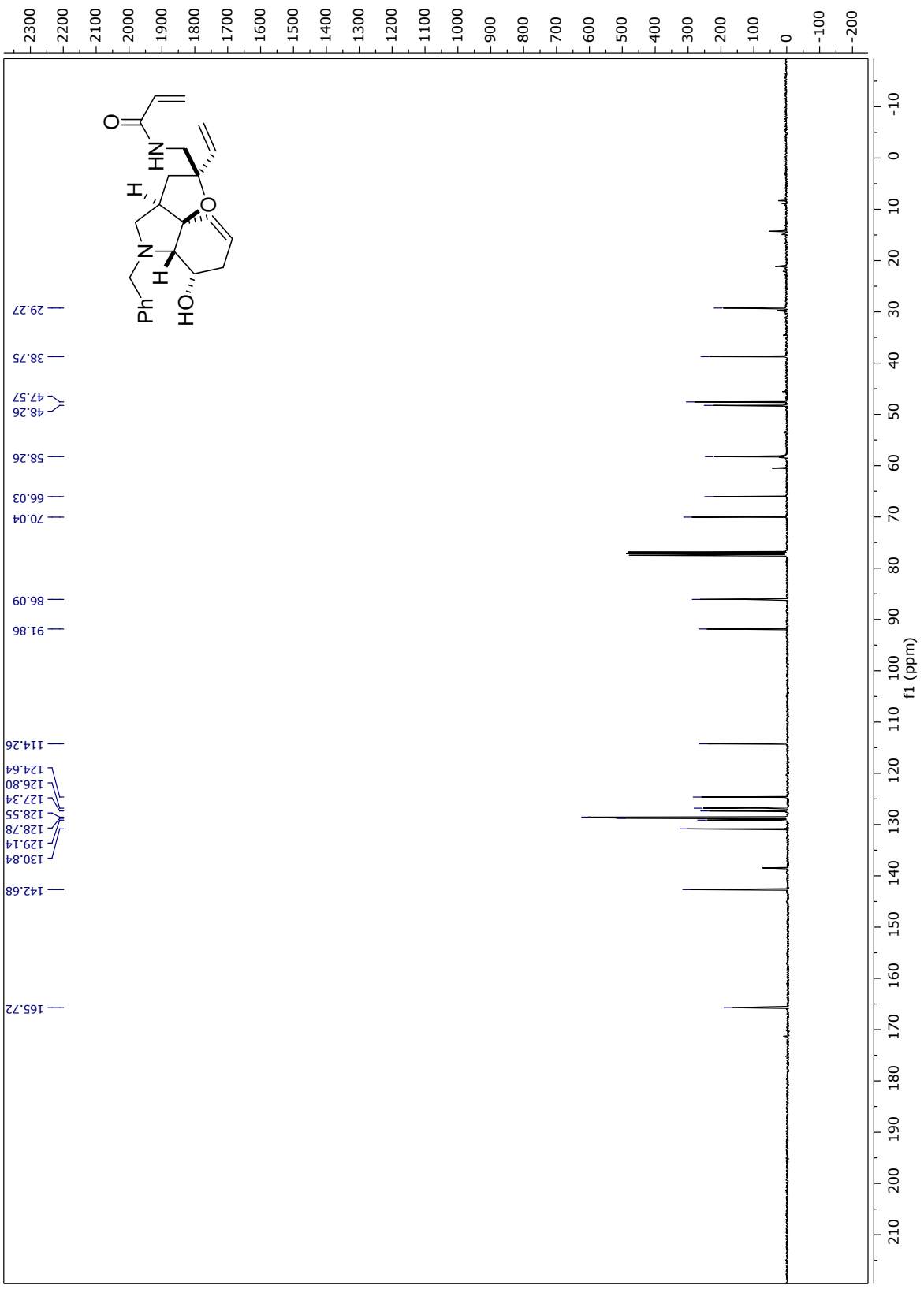
^{13}C NMR (100 MHz, $CDCl_3$) of **16a**



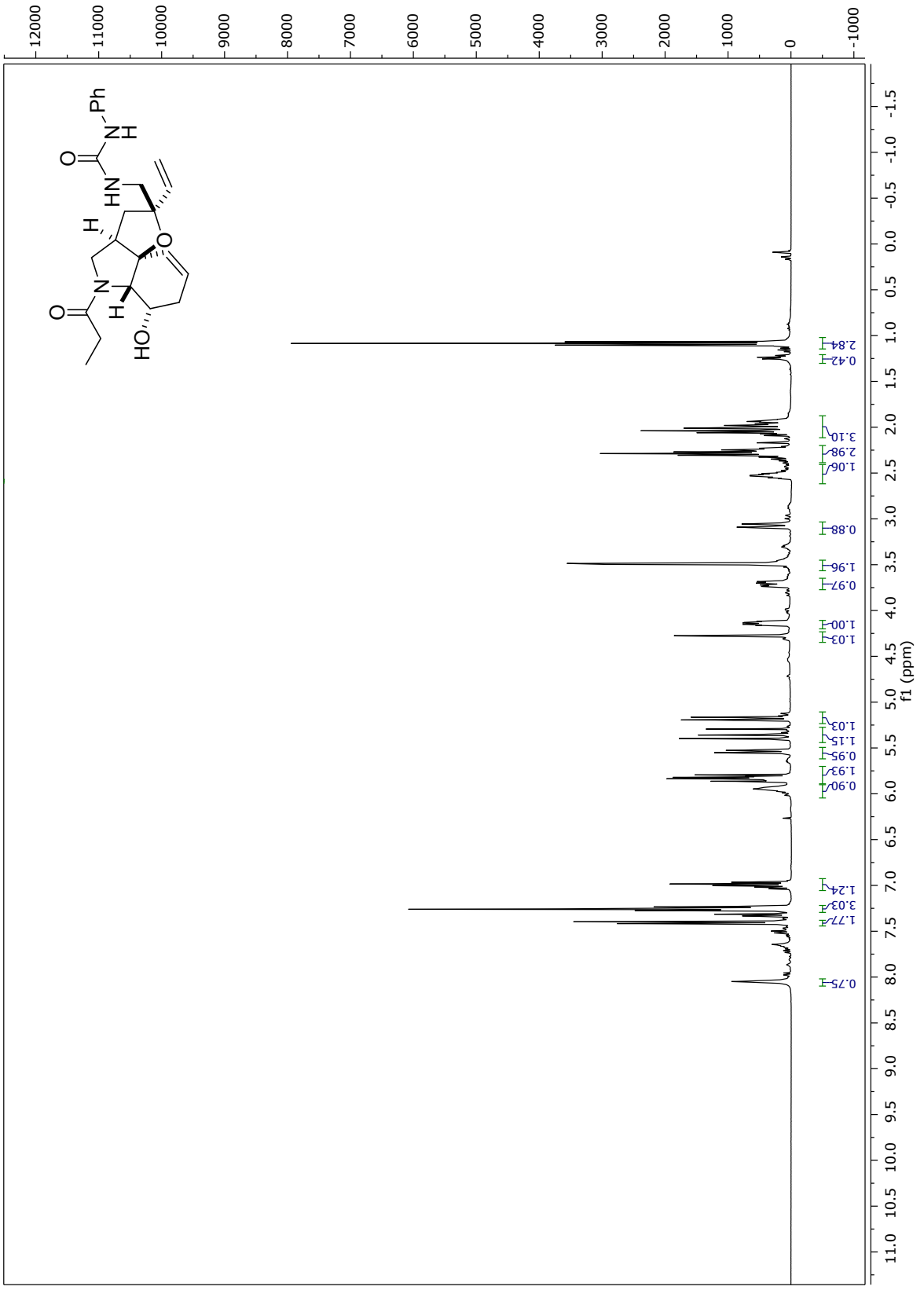
^{1}H NMR (400 MHz, $CDCl_3$) of **16b**



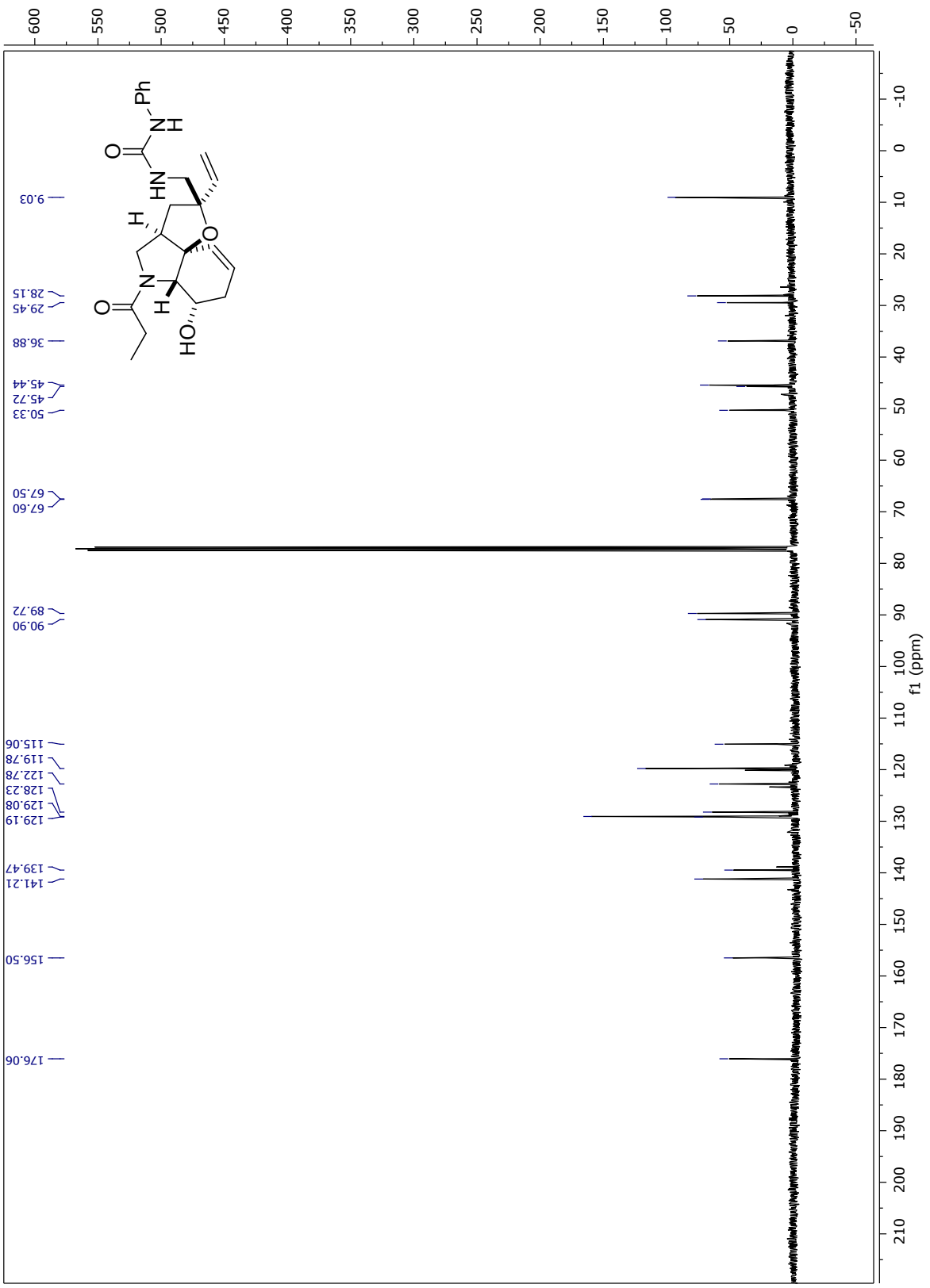
^{13}C NMR (100 MHz, $CDCl_3$) of **16b**



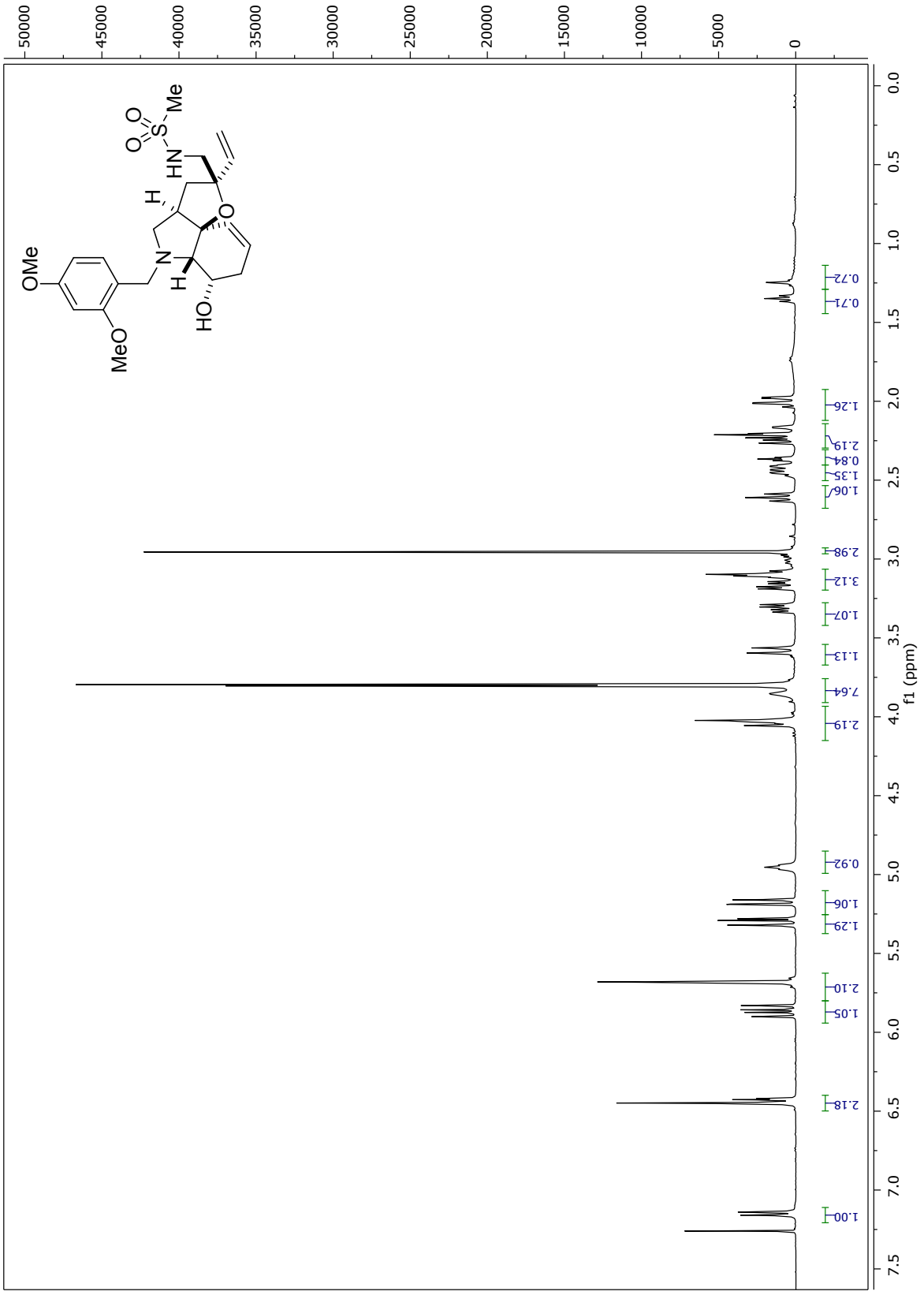
^{1}H NMR (400 MHz, $CDCl_3$) of **16c**



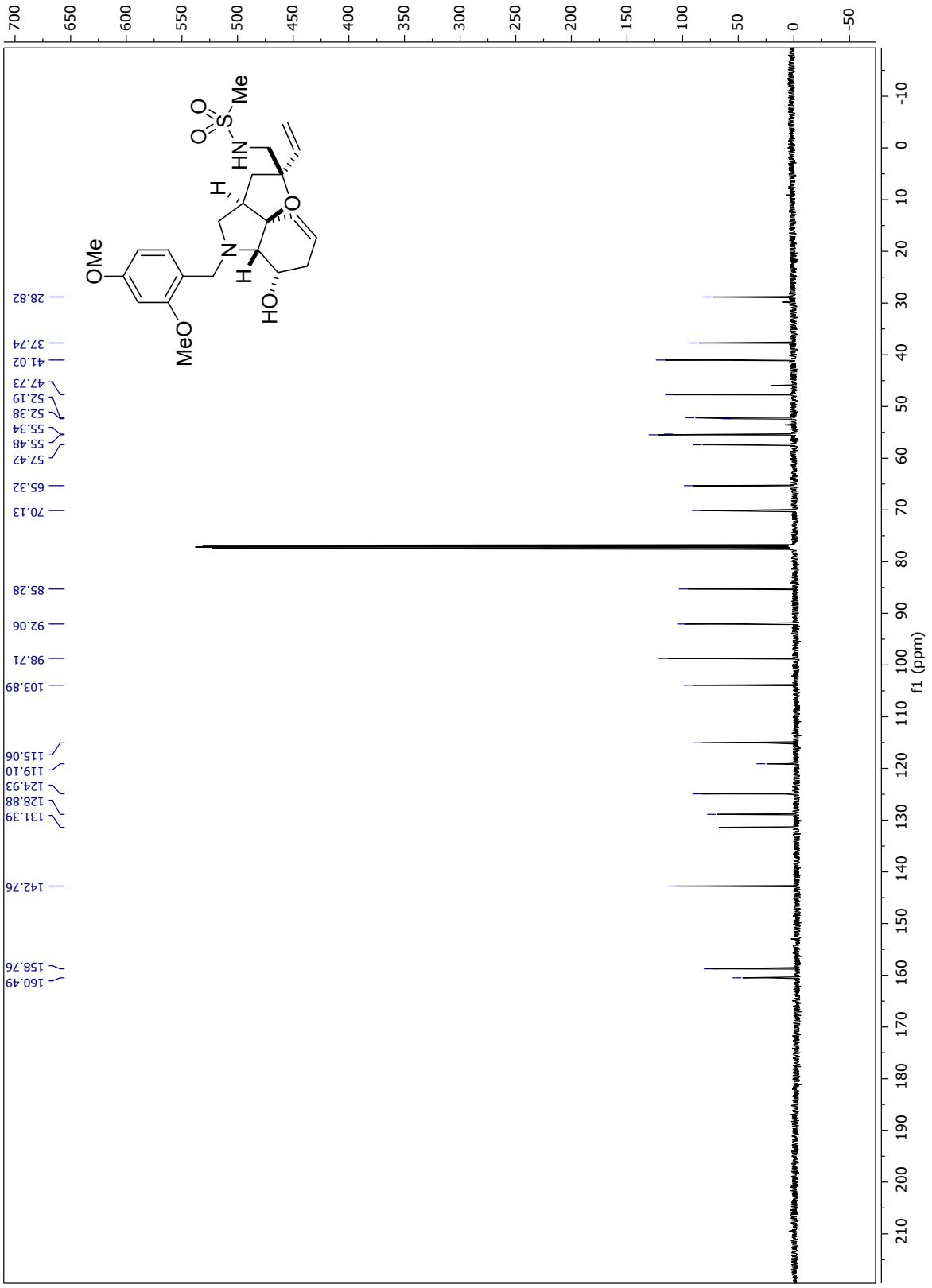
^{13}C NMR (100 MHz, $CDCl_3$) of **16c**



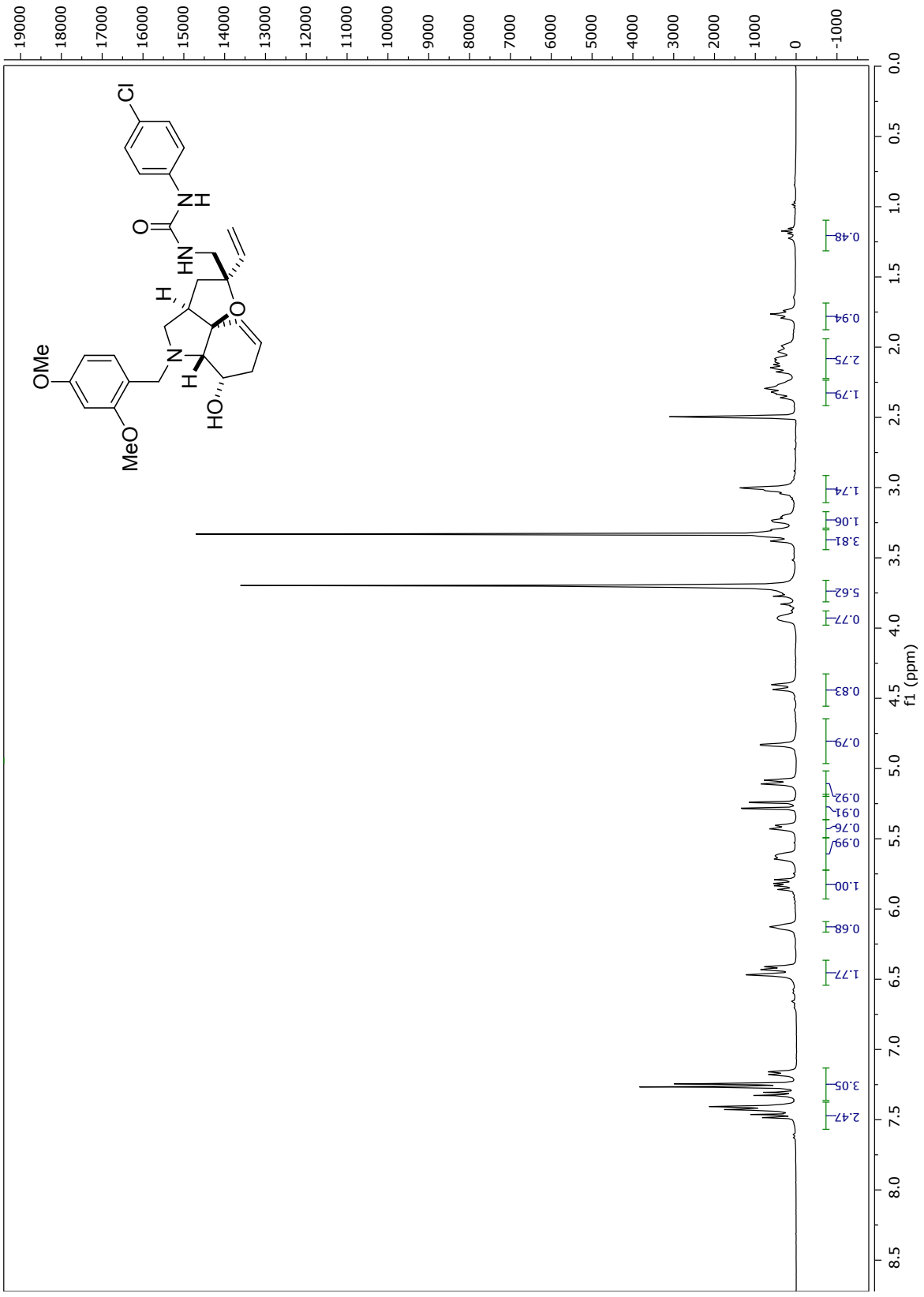
^{1}H NMR (400 MHz, $CDCl_3$) of **16d**



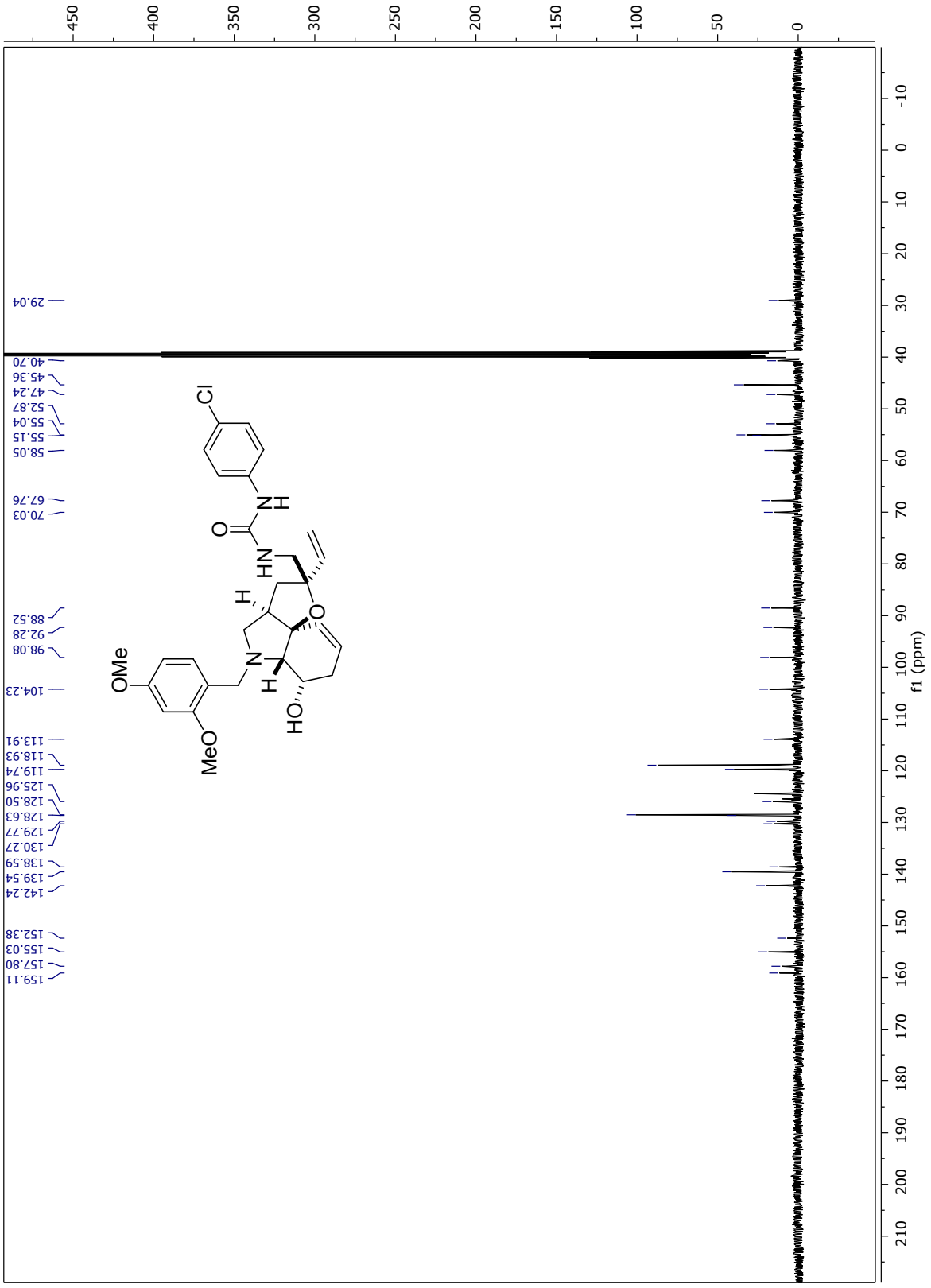
^{13}C NMR (100 MHz, $CDCl_3$) of **16d**



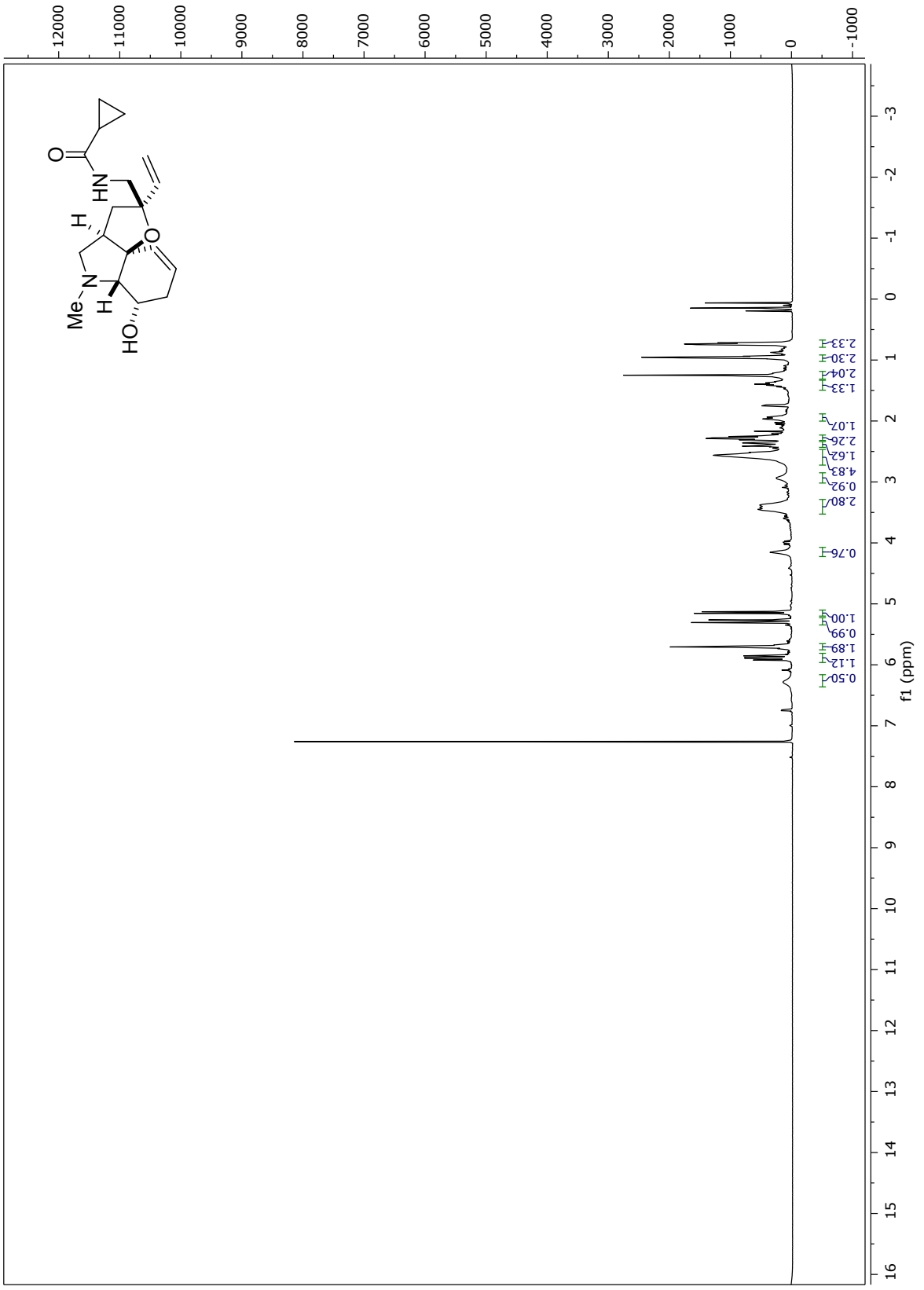
^{1}H NMR (400 MHz, $CDCl_3$) of **16e**



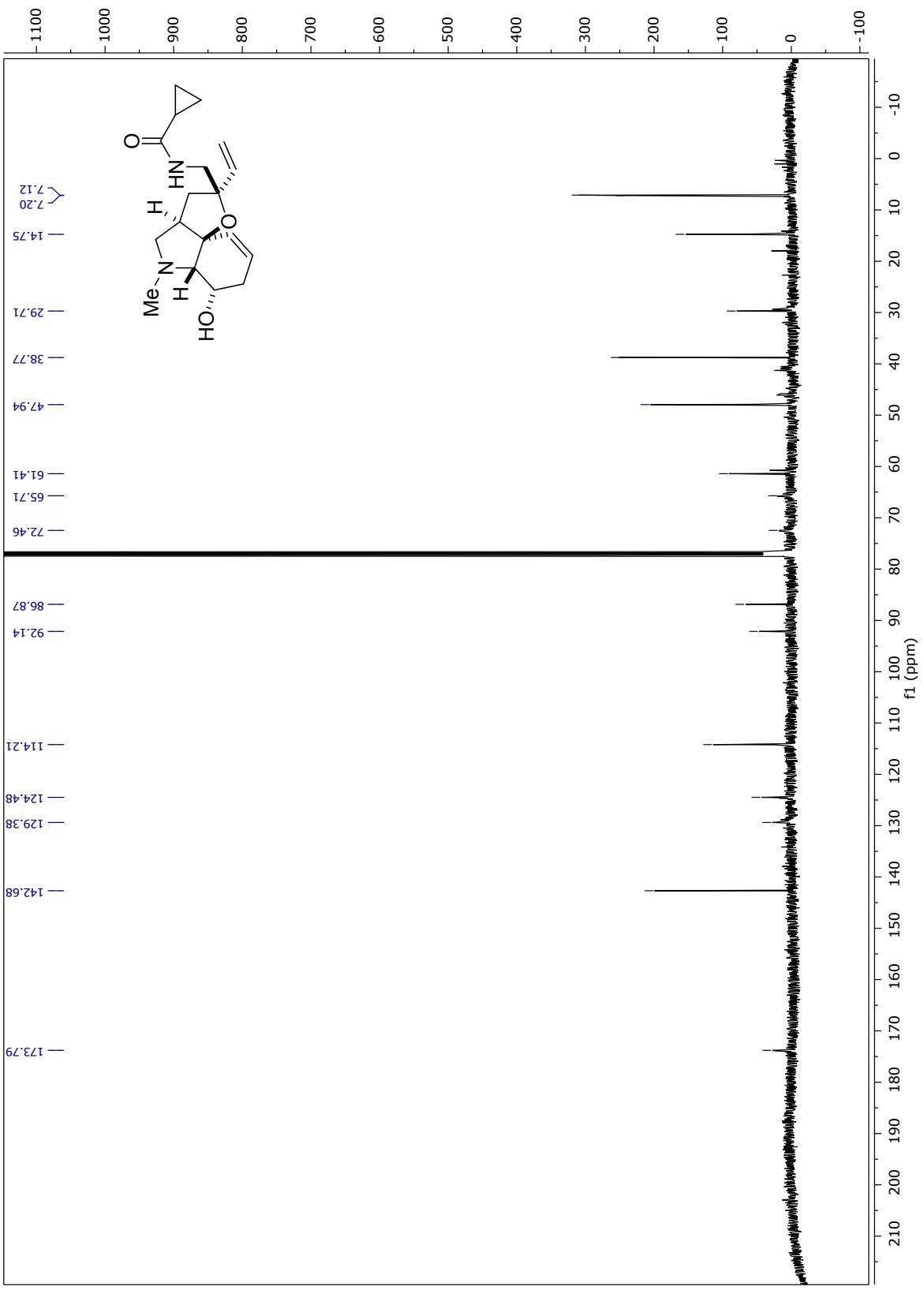
^{13}C NMR (100 MHz, $CDCl_3$) of **16e**



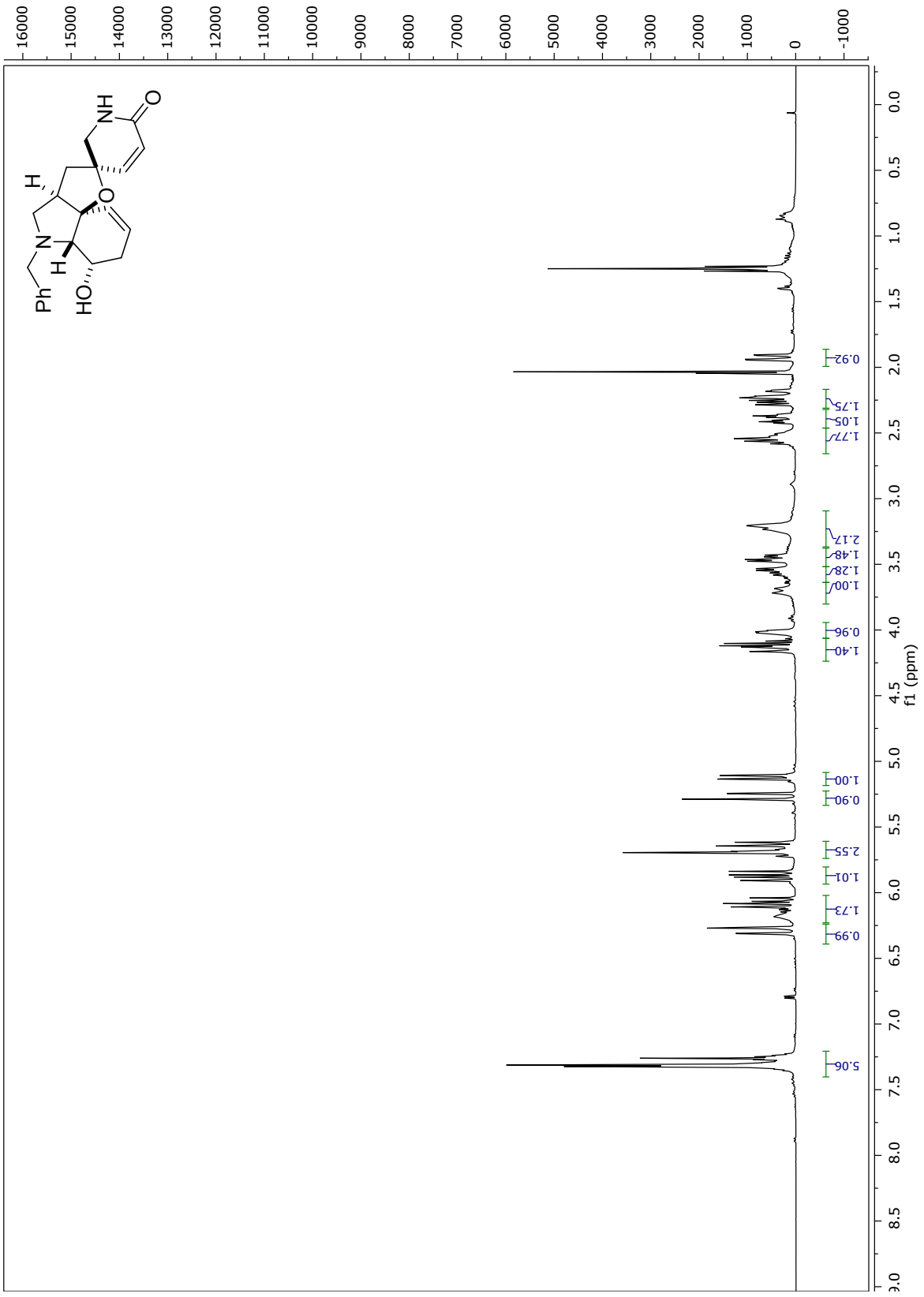
^{1}H NMR (400 MHz, $CDCl_3$) of **16f**



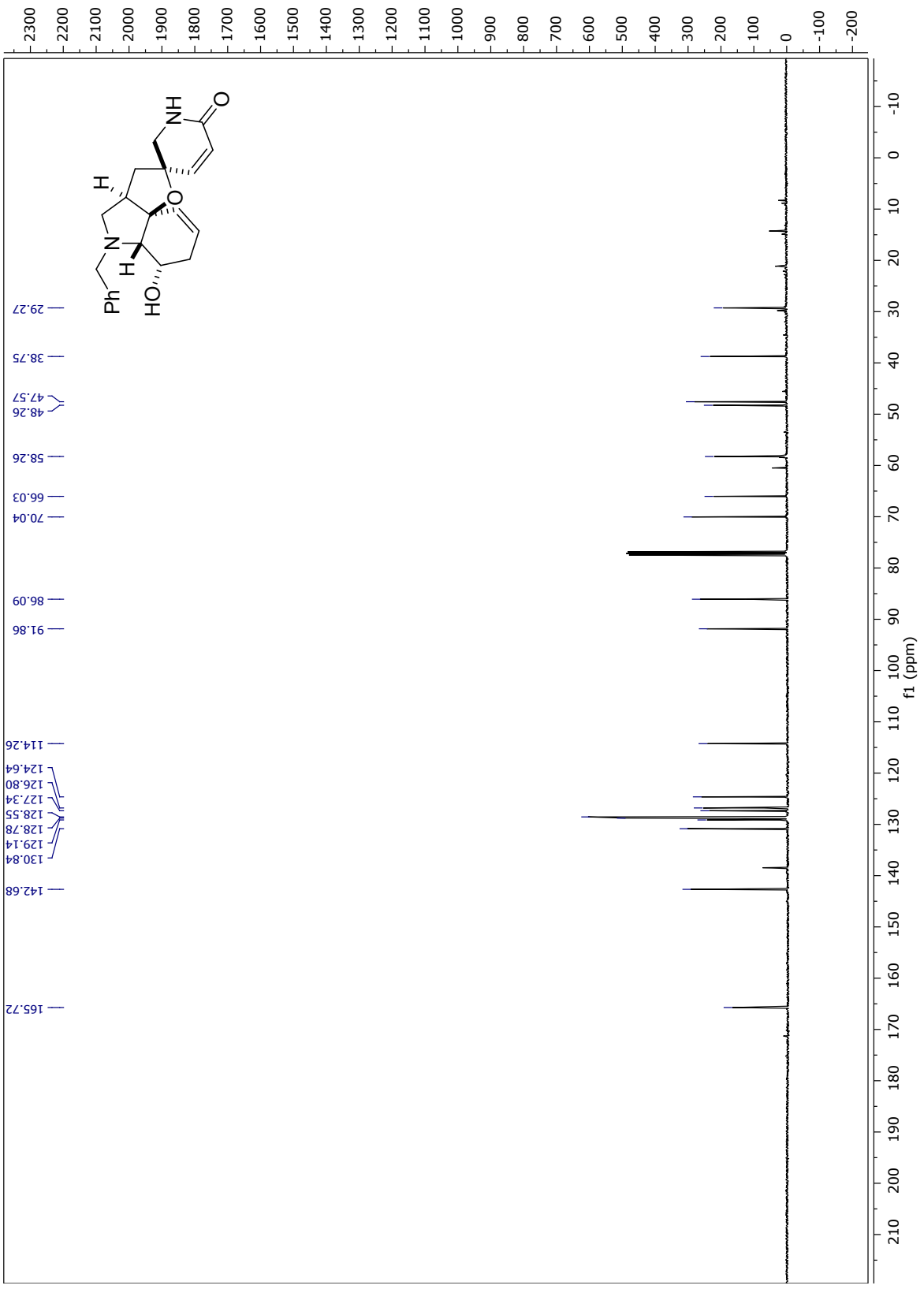
^{13}C NMR (100 MHz, $CDCl_3$) of **16f**



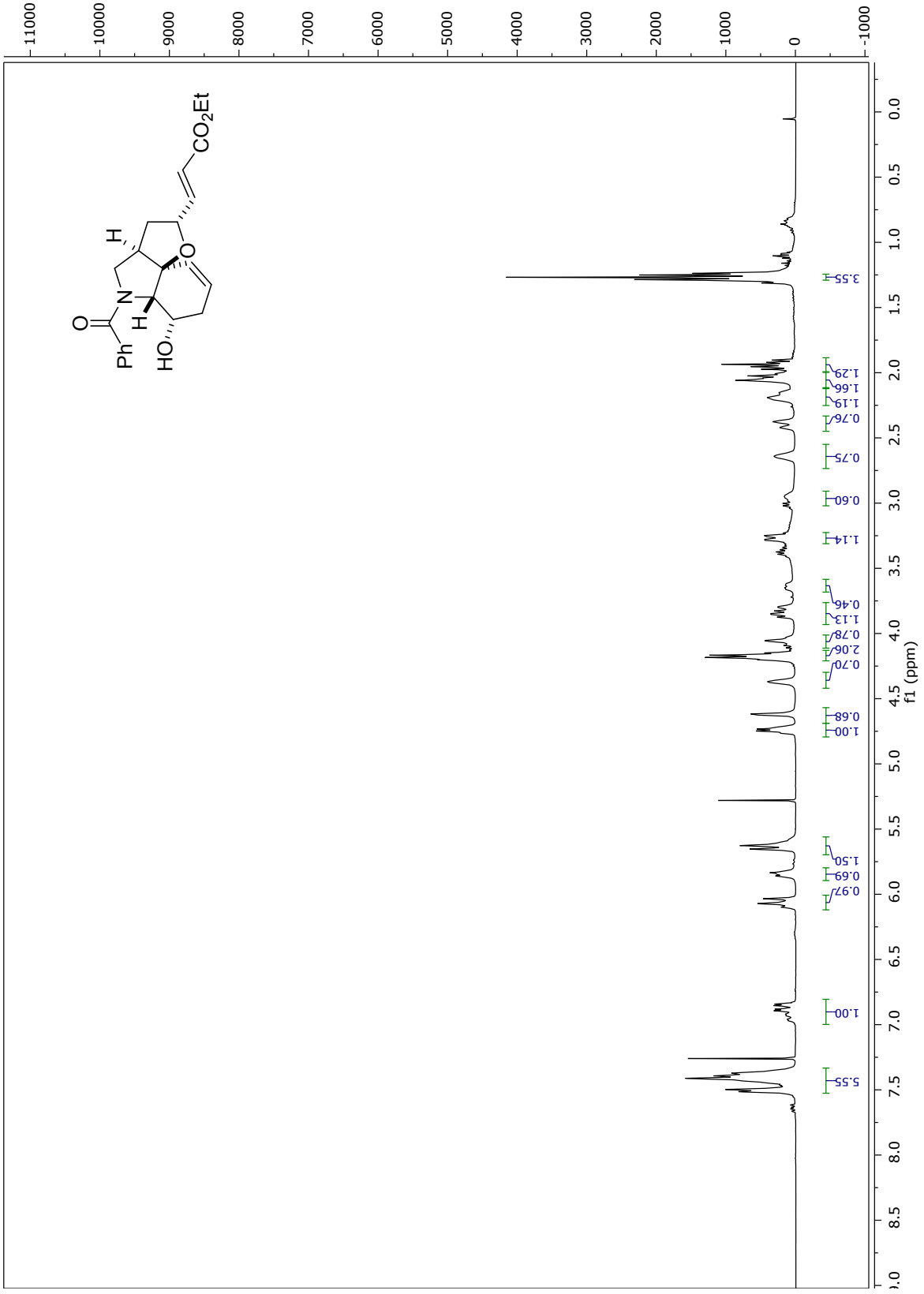
^{1}H NMR (400 MHz, $CDCl_3$) of **17**



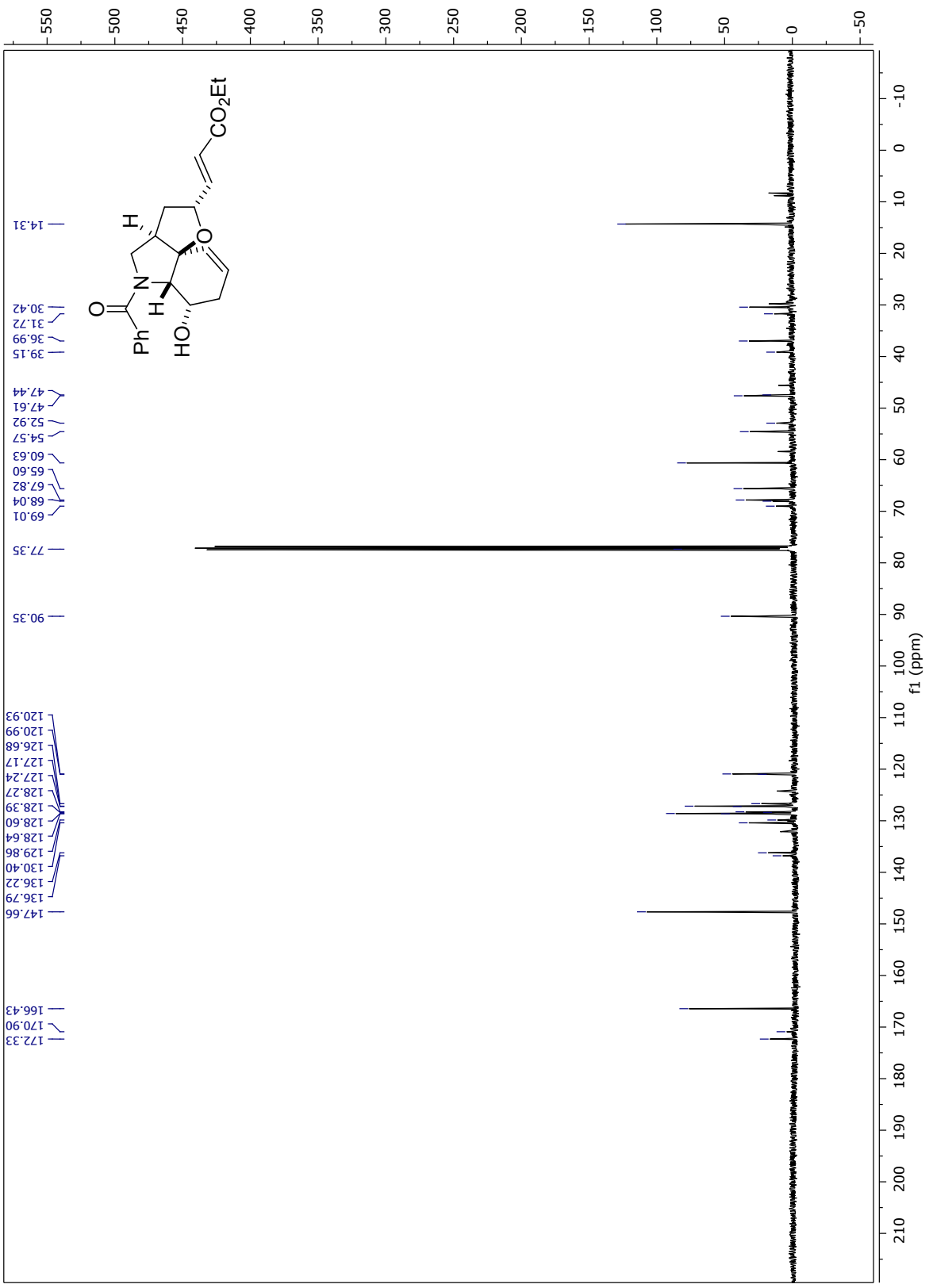
^{13}C NMR (100 MHz, $CDCl_3$) of **17**



^{1}H NMR (400 MHz, $CDCl_3$) of **18**



^{13}C NMR (100 MHz, $CDCl_3$) of **18**



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