Remodeling of Fumagillol: Discovery of an Oxygen-Directed Oxidative Mannich Reaction.

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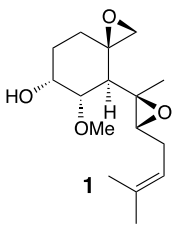
1. General Methods

Chemical Materials: Fumagillol was prepared from the crude fumagillin extract (60% fumagillin) which was obtained as a gift from Sinova Inc. All reagents, including anilines and nucleophilic coupling partners, were commercially available. All commercially available reagents were used without further purification. Anhydrous THF and toluene were purified using the Pure Solv™ solvent system. Flash chromatography was performed on silica gel-60 (43-60 μm).

Structure Analysis: ^{1}H, ^{13}C NMR, COSY, and NOE spectra were obtained at one of two field strengths as indicated: (1) 93.94 kG (400 MHz for ^{1}H; 100 MHz for ^{13}C) (2) 117.42 kG (500 MHz for ^{1}H; 125 MHz for ^{13}C) at ambient temperature. Hydrogen chemical shifts are expressed in parts per million (ppm) relative to the residual protio solvent resonance: $CDCl_3$ δ 7.26. For ^{13}C spectra, the center line of the solvent resonance was used as internal reference: $CDCl_3$ δ 77.16, Unless otherwise noted, each carbon resonance represents a single carbon (relative intensity). UPLC-MS analysis was performed on a C_{18} column (1.7 μm, 2.1 X 50 mm) with CH_3CN:H_2O gradient as eluent (10% CH_3CN – to 99% CH_3CN over 2 min, hold 1 min at 99% CH_3CN, 0.1% formic acid) with electrospray ionization (ESI) positive ion detection, and high resolution mass spectra (HRMS) were obtained on a QToF (hybrid quadrupolar/time-of-flight) API US system by electrospray ionization (ESI) in positive ion mode. Mass correction was done by an external reference using a lockspray accessory. Mobile phases (direct flow analysis) were water and acetonitrile gradient with 0.1% formic acid. The MS settings were: capillary voltage = 3kV, cone voltage = 35, source temperature = 120 °C and desolvation temperature = 350 °C.

2. Preparation and Characterization of Fumagillol (1)



1

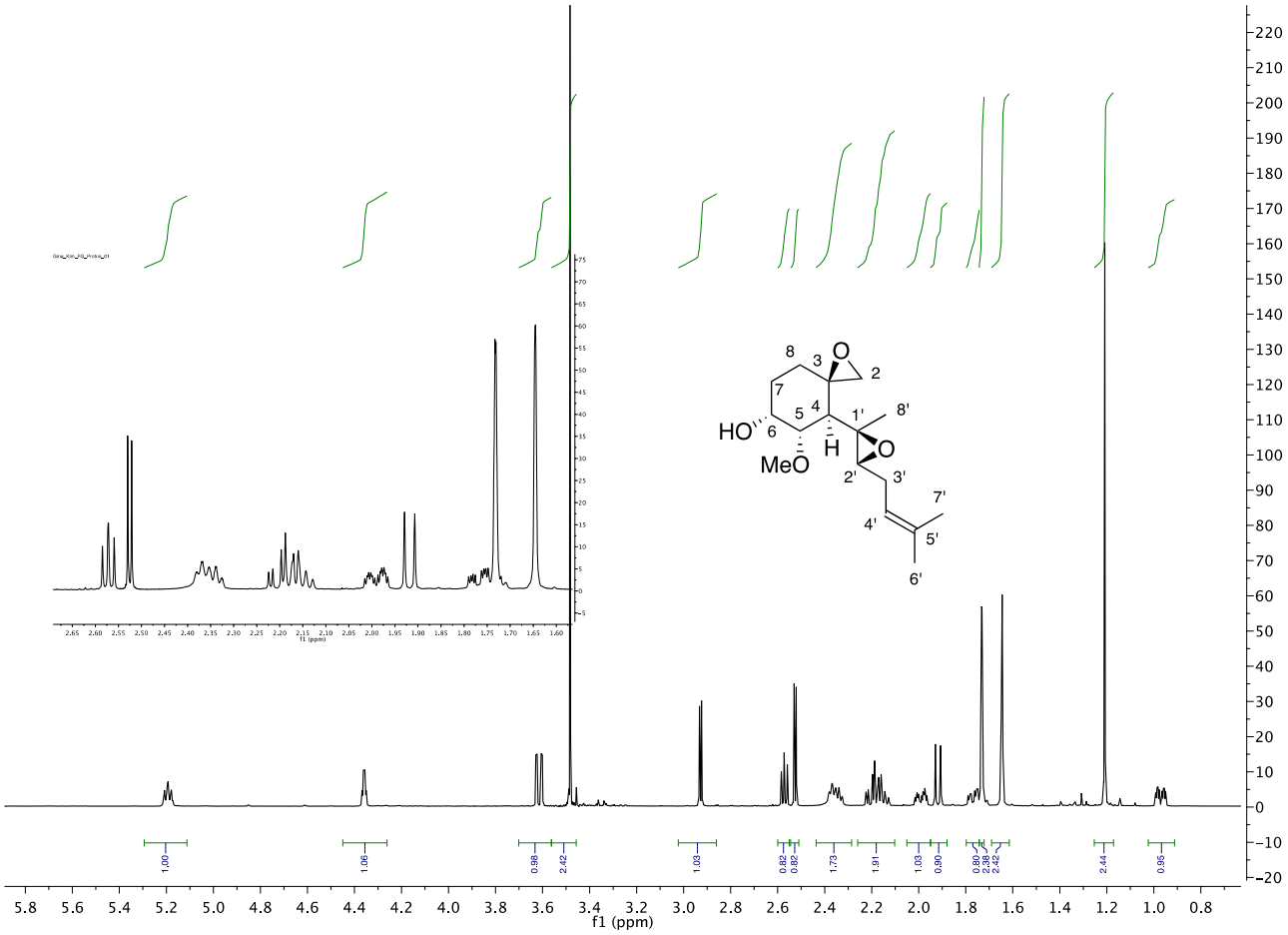
Fumagillol was prepared in two steps from a crude fumagillin extract (~60% fumagillin) supplied by Sinova Inc. (Bethesda, MD).

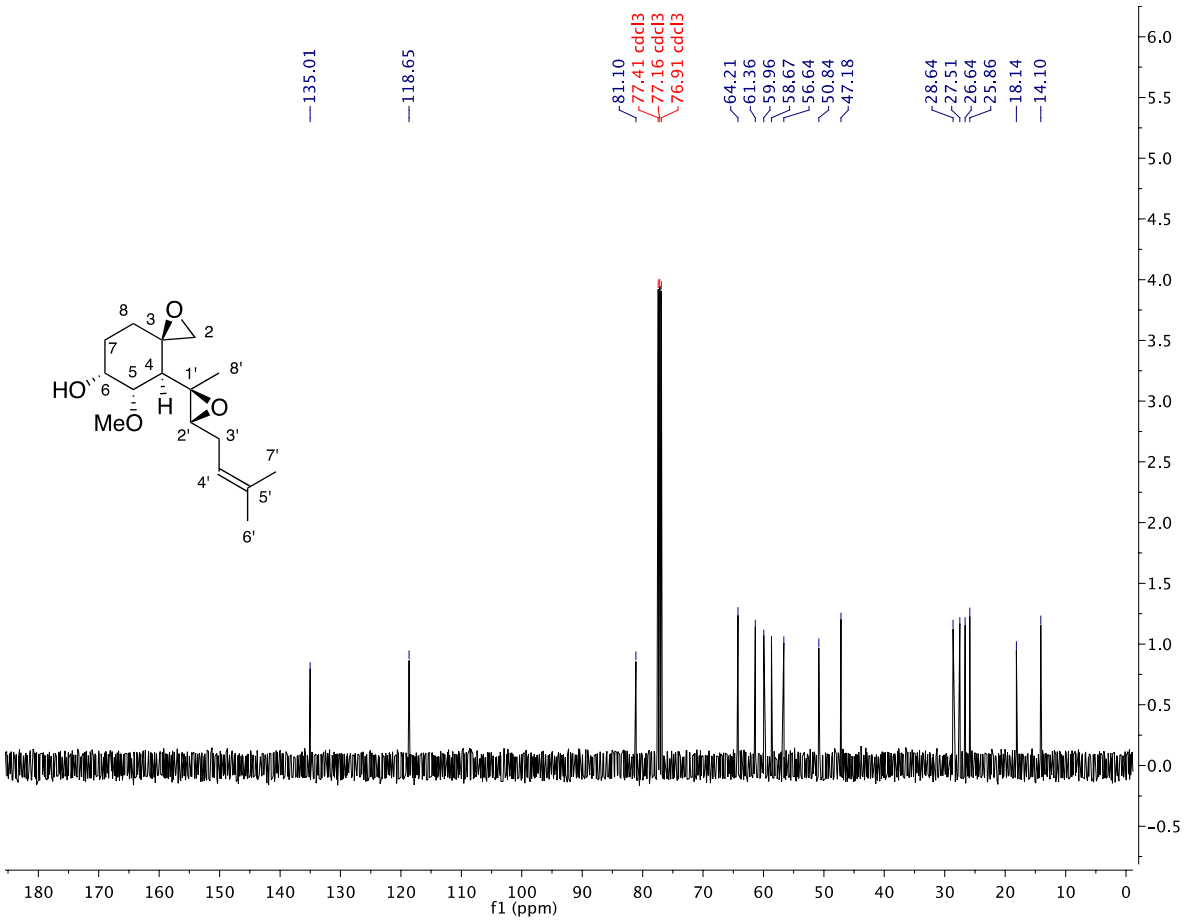
Step 1: Purification of Fumagillin:. Crude fumagillin (50 g, ~60% fumagillin) was dissolved in a minimal amount of 1% MeOH in CH_2Cl_2 (~30 mL), then purified by flash chromatography (5% MeOH in CH_2Cl_2, ~2L).

Step 2: Hydrolysis of fumagillin. Purified fumagillin (20 g, 43.7 mmol) was dissolved in MeOH (100 mL) and water (100 mL) was added. The reaction mixture was cooled to 0 °C in an ice bath, then an aqueous solution of NaOH (2 equiv., 88 mmol, 3.5 grams in 20 mL water) was added dropwise with stirring over 5 min. Once the addition was complete, the reaction mixture was removed from the ice bath

and allowed to warm to rt, then further warmed to 40 °C. The reaction was kept at 40 °C until the starting material was completely consumed as monitored by TLC analysis (~3 h). The reaction mixture was then allowed to cool to rt and was transferred to a 2L separatory funnel and diluted with EtOAc (600 mL). Water (1 L) was added and the organic layer was separated and extracted with EtOAc (500 mL). The organic layers were combined, washed with saturated brine (200 mL), and dried over Na_2SO_4. After filtering, the solvent was removed *in vacuo* and the residue purified by flash chromatography (1:1 EtOAc:hexanes) to afford pure fumagillol (12.5 g, 90% yield).

Fumagillol Characterization Assignments of all proton and carbon resonances followed from extensive experiments including gCOSY, HSQC, HMBC, and 1D-NOESY analysis. **^{1}H NMR (500 MHz, $CDCl_3$)**[1] δ 5.19 (ddqq, *J* = 8.0, 6.8, 1.6, 1.2 Hz, H4'), 4.36 (ddd, *J* = 2.8, 2.7, 2.6 Hz, H6), 3.62 (dd, *J* = 11.1, 2.7 Hz, H5), 3.49 (s, 3H, OMe), 2.93 (d, *J* = 4.4 Hz, H2), 2.57 (dd, *J* = 6.7, 6.6 Hz, H2'), 2.52 (d, *J* = 4.4 Hz, H2), 2.40 – 2.30 (overlap, O*H*), 2.35 (ddd, *J* = 14.4, 8.0, 6.6 Hz, H3'), 2.20 (ddd, *J* = 13.7, 13.6, 4.4 Hz, H8α), 2.17 (ddd, 14.4, 8.0, 6.6 Hz, H3'), 2.00 (dddd, *J* = 14.1, 4.4, 2.8, 2.5 Hz, H7α), 1.92 (d, *J* = 11.1 Hz, H4), 1.77 (ddd, *J* = 14.1, 13.6, 4.6, 2.6 Hz, H7β), 1.73 (br s, 3H, H6'), 1.65 (br s, 3H, H7'), 1.21 (s, 3H, H8'), 0.97 (ddd, *J* = 13.7, 4.6, 2.5 Hz, H8α). **^{13}C NMR (125 MHz, $CDCl_3$)** δ 135.0 (C5'), 118.7 (C4'), 81.1 (C5), 64.2 (C6), 61.4 (C2'), 60.0 (C2), 58.7 (C1'), 56.6 (OMe), 50.8 (C3), 47.2 (C4), 28.6 (C8), 27.5 (C3'), 26.6 (C7), 25.9 (C6'), 18.1 (C7'), 14.0 (C8').

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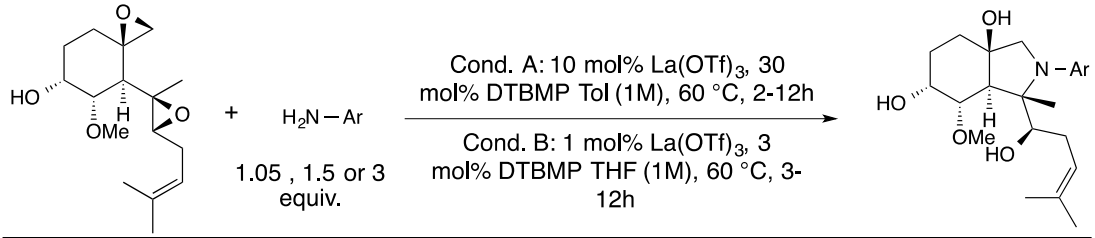
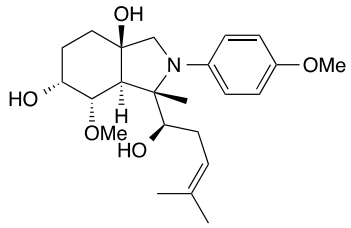
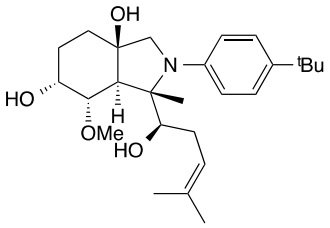
118.65
81.10
77.41 cdcl3
77.16 cdcl3
76.91 cdcl3
64.21
61.36
59.96
58.67
56.64
50.84
47.18
28.64
27.51
26.64
25.86
18.14
14.10
HO
MeO
H
O
f1 (ppm)

3. *Bis*-Epoxide Opening of Fumagillol with Anilines

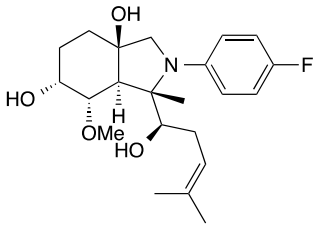




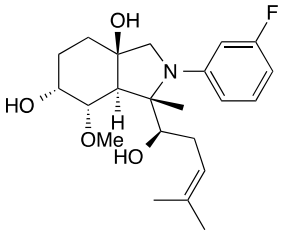
2a
Cond. B, 1.05 equiv., 3h, NH_2Ar, multiple runs, 91-99%



2b
Cond. A, 1.05 equiv. NH_2Ar, 6h
99% yield



2c
Cond. B, 1.50 equiv. NH_2Ar, 12h
93% yield



2d
Cond. A, 3 equiv. NH_2Ar, 12h
90% yield

General Procedure A (Condition A, Scheme 1). A 5-mL vial equipped with a stir bar was charged with fumagillol **1** (564 mg, 2 mmol), aniline (2.1 mmol), 2,6-di-*tert*-butyl methyl pyridine (DTBMP) (123 mg, 30 mol%), and $La(OTf)_3$ (117 mg**,** 10 mol%). Toluene was added to a concentration of 1M fumagillol (2 mL) and the vial was capped and heated at 60 °C until the reaction was complete as monitored by UPLC-MS analysis. Upon complete conversion, the reaction was diluted with CH_2Cl_2 (2 mL) and directly purified by silica gel flash chromatography (30 ➔60% EtOAc in hexanes) to yield the pure perhydroisoindole **2**.

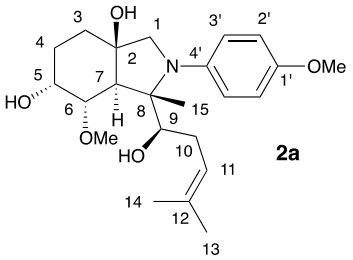
NOTE 1: In the case of sluggish reactions (electron-poor anilines), an excess of the aniline (1.5-3 equiv) was used as noted below.

NOTE 2: Compounds **2** were often isolated as sticky solids. In order to obtain powders, the chromatographed compounds were dissolved in a small amount of CH_2Cl_2 (~0.5 mL) and hexanes added (~10 mL). The volatiles were then evaporated to afford the target compounds as fluffy powders.

General Procedure B (Condition B, Scheme 1) A 5-mL vial equipped with a stir bar was charged with fumagillol **1** (564 mg, 2 mmol), aniline (2.1 mmol), DTBMP (12.3 mg, 3 mol%), and $La(OTf)_3$ (11.7 mg**,** 10 mol%). Next, THF was added to a concentration of 1M fumagillol (2 mL) and the vial was capped and heated at 60 °C until the reaction was complete as monitored by UPLC-MS analysis (3 – 12 h). Upon complete conversion, the reaction was diluted with CH_2Cl_2 (2 mL) and directly purified by flash chromatography (30 ➔60% EtOAc in hexanes) to yield the perhydroisoindole compound **2**.

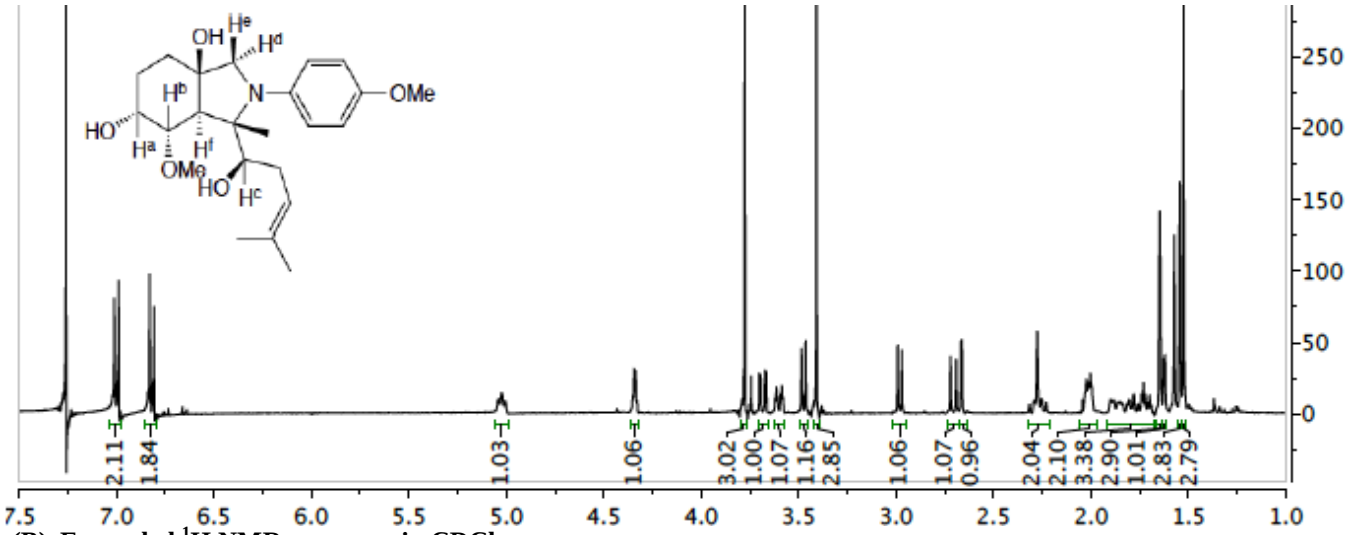
4. Fumagillol-Aniline Adduct Characterizations

Compounds **2a, 2b** were previously reported [2] A full ^{1}H-NMR assignment for compound **2a** is provided below.

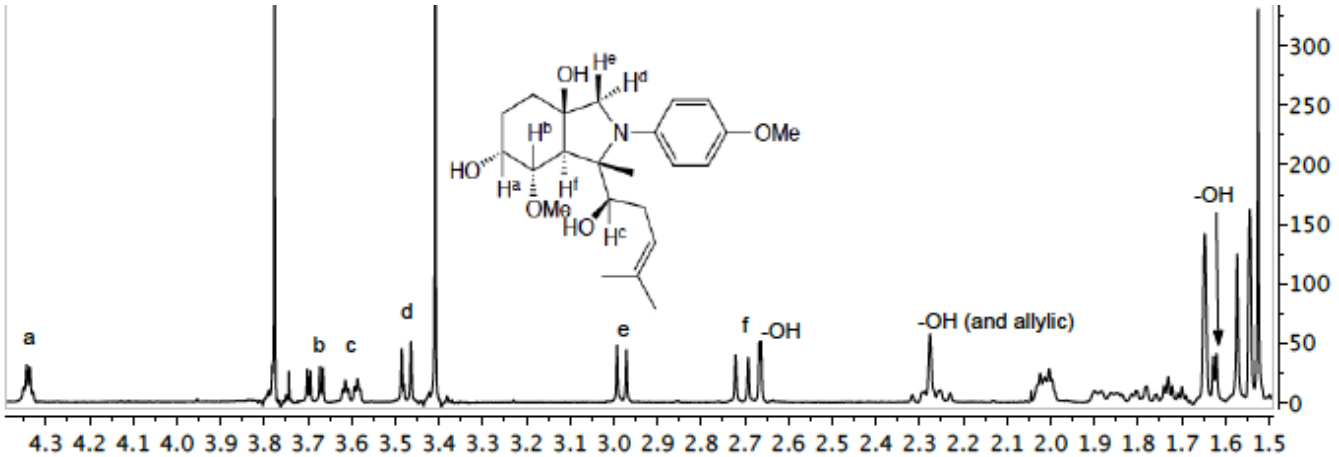


2a: Prepared according to General Procedure B in 91-99% yield. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.00 (d, *J* = 9.1 Hz, H2'/6'), 6.82 (d, *J* = 9.1 Hz, H3'/5'), 5.02 (ddqq, *J* = 8.5, 5.9, 1.5, 1.2 Hz, H11), 4.34 (br ddd, *J* = 3.2, 3.1, 2.9, Hz, 1H' H5), 3.78 (s, 3H, ArOCH_3), 3.68 (dd, *J* = 11.5, 2.9 Hz, 1H, H6), 3.60 (ddd, *J* = 11.1, 3.0, 2.7 Hz, 1H, H9), 3.47 (d, *J* = 8.7 Hz, 1H, H1α), 3.41 (s, 3H, 5-OCH_3), 2.98 (d, *J* = 8.7 Hz, 1H, H1β), 2.71 (d, *J* = 11.5 Hz, 1H, H7), 2.66 (d, *J* = 1.7 Hz, 1H, C5-O*H*), 2.28 (br s, C2-O*H*) 2.26 (br ddd, *J* = 15.1, 11.1, 8.5 Hz, H10), 2.05 – 1.98 (overlap, 2H), 1.88 (br dd, *J* = 15.1, 5.9 Hz, H10'), 1.91 – 1.68 (overlap m, 1H), 1.71 (ddd, *J* = 12.6, 3.7, 3.6 Hz, 1H) 1.65 (s, 3H, H14), 1.62 (d, *J* = 3.0 Hz, 1H,C9-O*H*), 1.54 (s, 3H, H13), 1.52 (s, 3H,H15).

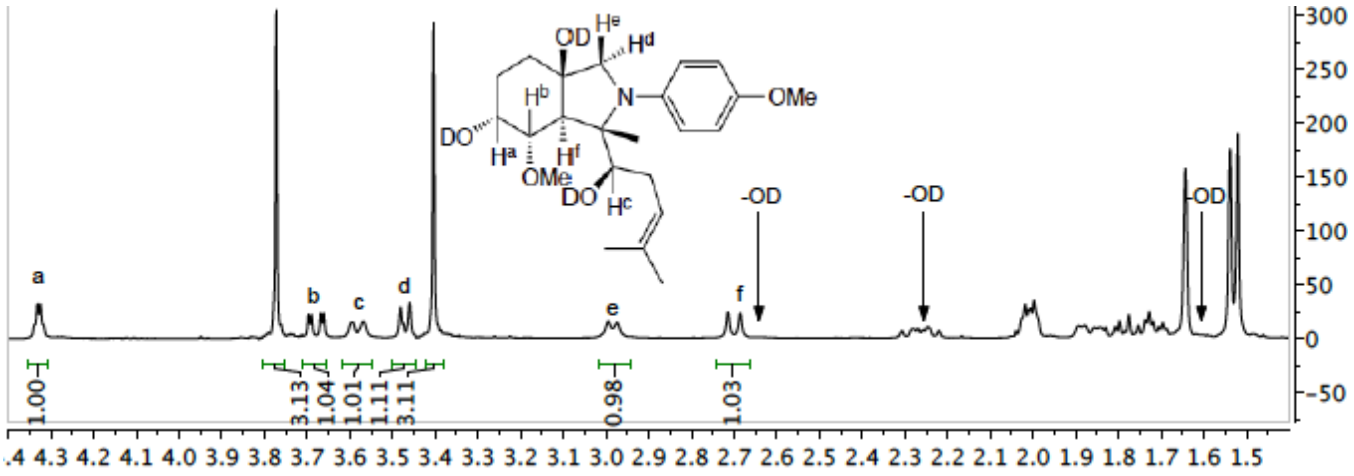
(A) ^{1}H NMR Full Spectrum in $CDCl_3$



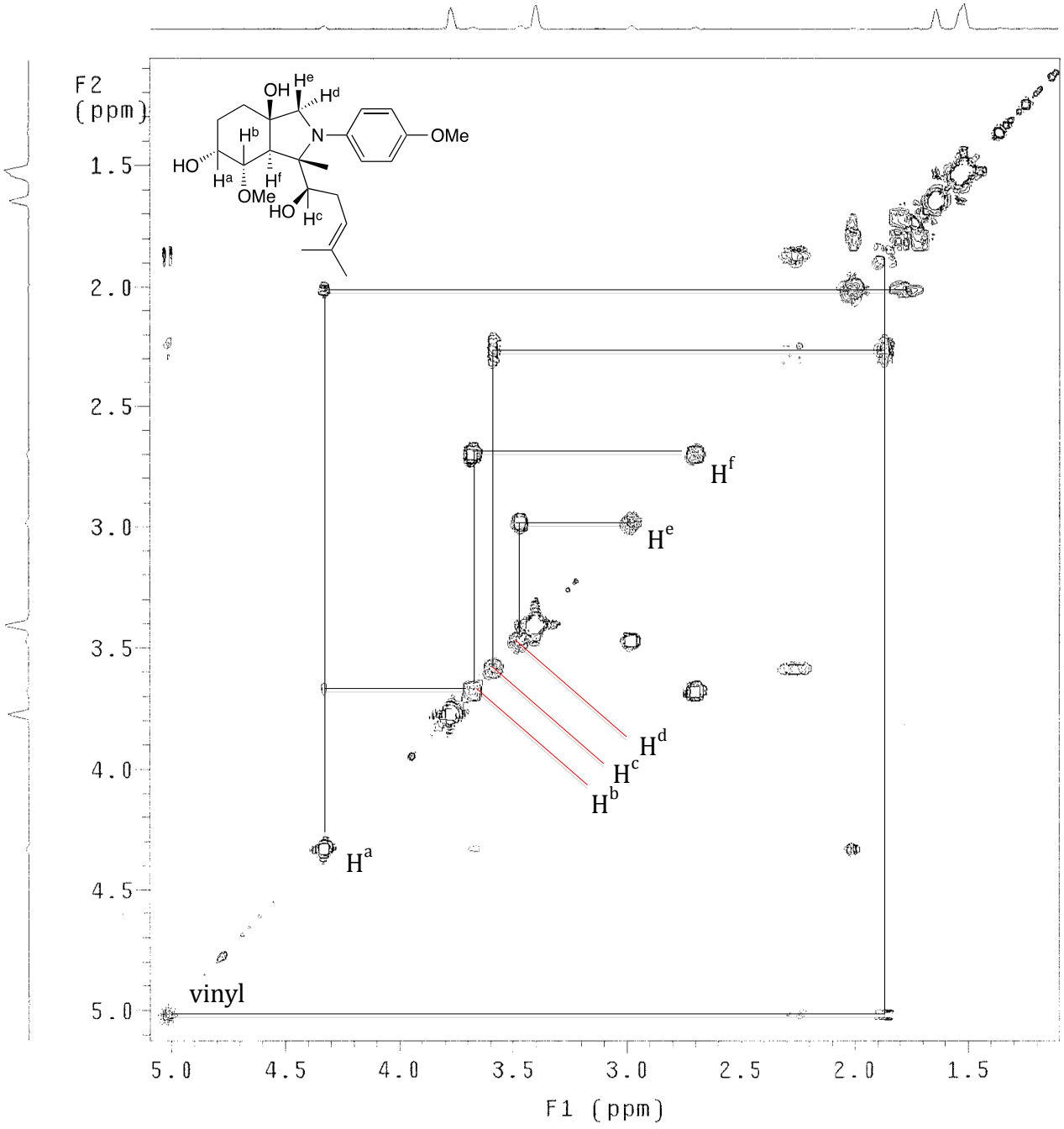
(B) Expanded ^{1}H NMR spectrum in $CDCl_3$



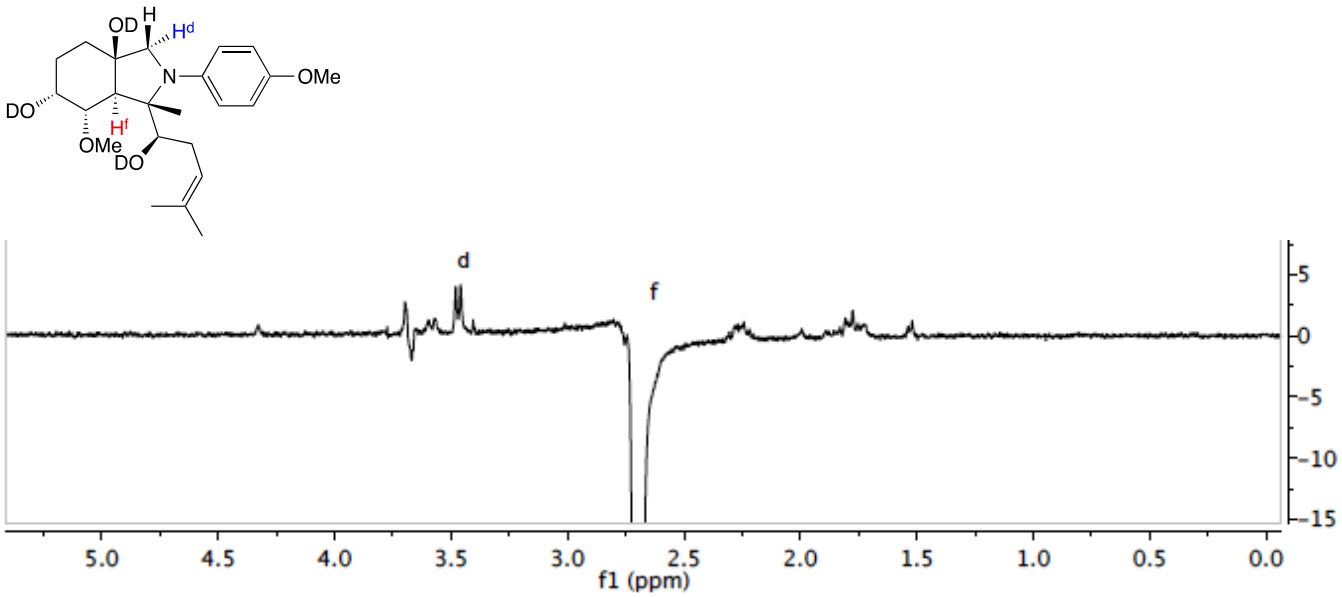
(C) ^{1}H NMR spectrum after D_2O exchange ($CDCl_3$).

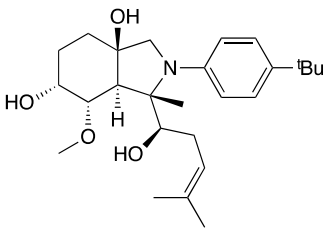


(D) COSY spectrum in $CDCl_3$.

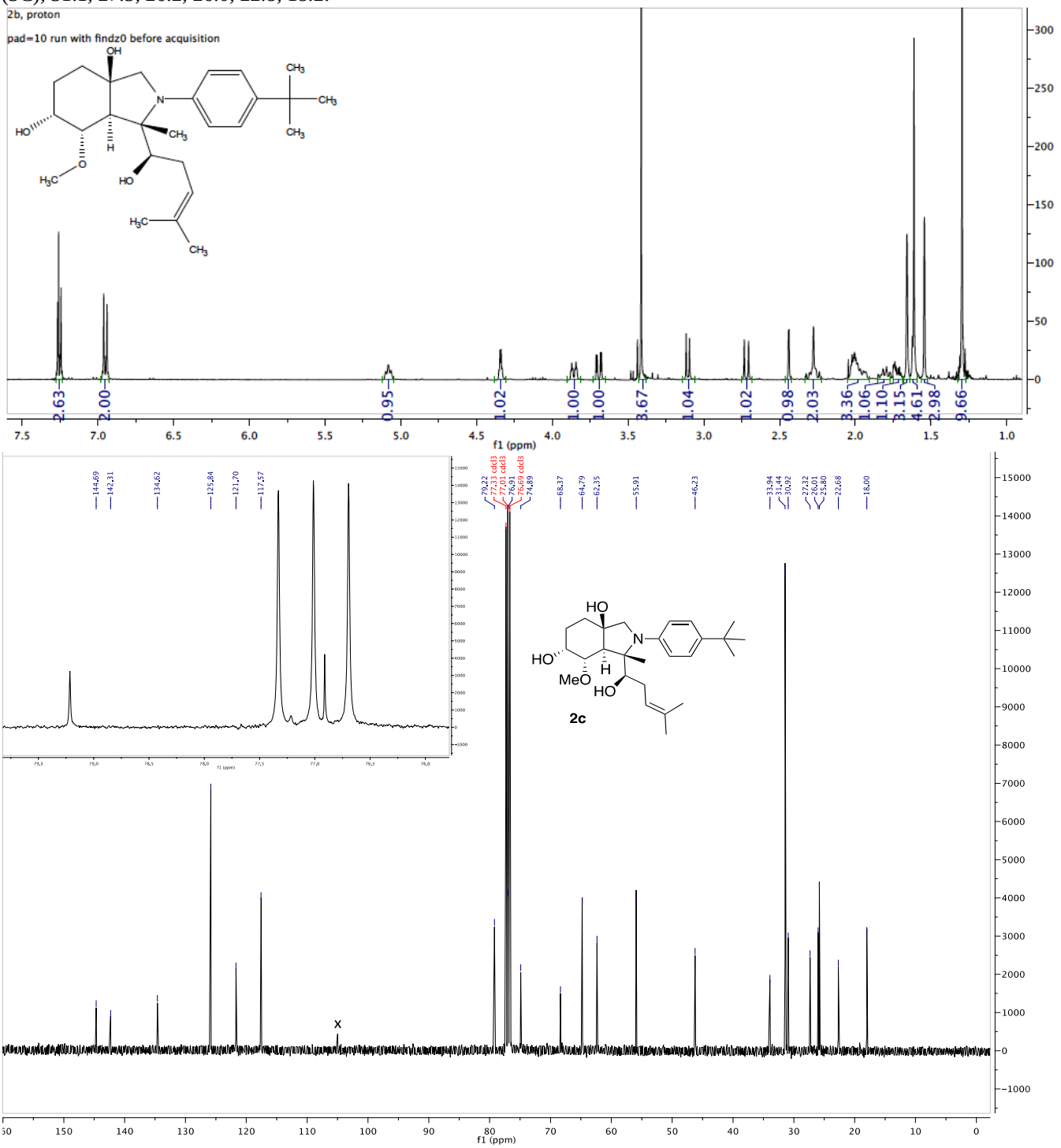


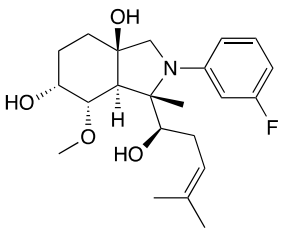
(E) NOE upon irradiation of H^f (δ 2.71 ppm) RED = irradiated signal; BLUE = observed NOE.



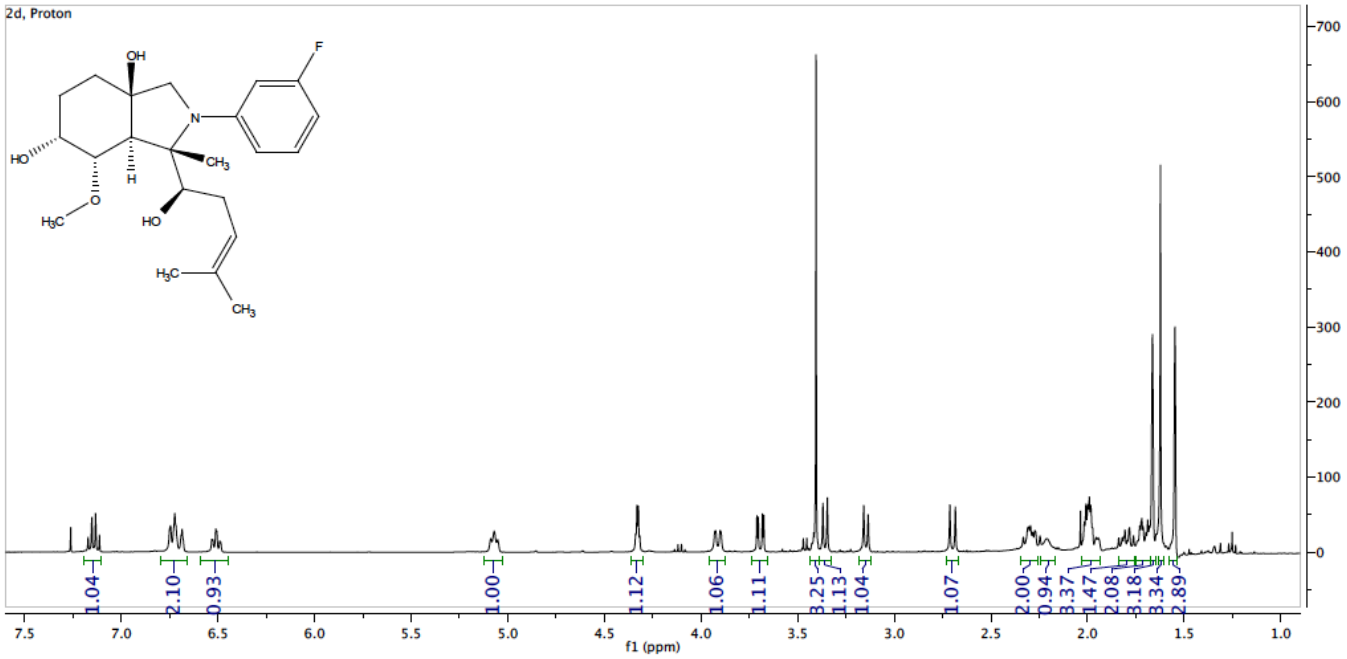


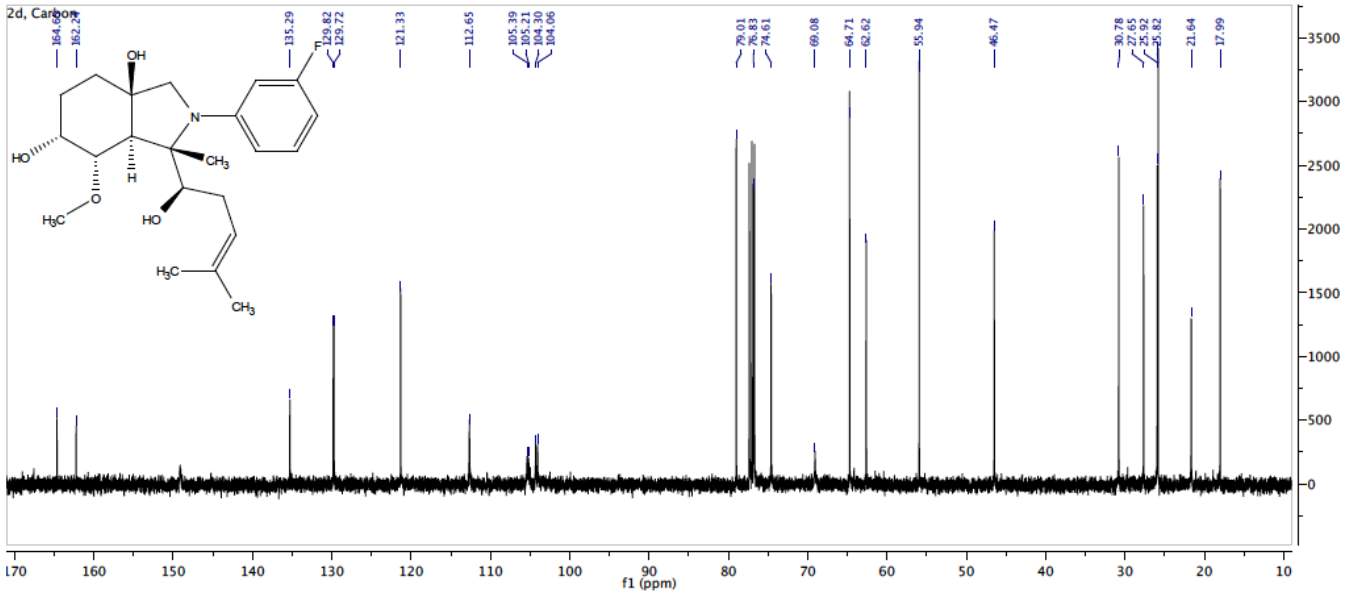
2c: Prepared according to General Procedure A in 99% yield. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.26 (d, *J* = 8.8 Hz, 2H), 6.95 (d, *J* = 8.8 Hz, 2H), 5.08 (br dd, *J* = 8.2, 6.4 Hz, 1H), 4.34 (ddd, *J* = 3.2, 2.9, 2.6 Hz, 1H), 3.86 (ddd, *J* = 11.0, 2.7, 2.7 Hz, 1H), 3.69 (dd, *J* = 11.5, 2.9 Hz, 1H), 3.43 (overlapped d, J = 8.8 Hz, 1H), 3.41 (s, 3H), 3.11 (d, *J* = 8.8 Hz, 1H), 2.72 (d, *J* = 11.5 Hz, 1H), 2.44 (d, *J* = 1.6 Hz,1H), 2.32 – 2.24 (overlapped, 2H), 2.05 - 1.91 (overlapped, 3H), 1.81 (m, 1H), 1.73 (ddd, *J* = 12.9, 3.7, 3.2 Hz, 1H), 1.66 (s, 3H), 1.62 (s, 1H), 1.61 (s, 3H), 1.54 (s, 3H), 1.30 (s, 9H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 144.8, 142.5, 134.8, 126.0 (2C), 121.8, 117.7 (2C), 79.4, 77.1, 75.0, 68.5, 64.9, 62.5, 56.1, 46.4, 34.1, 31.6 (3C), 31.1, 27.5, 26.2, 26.0, 22.8, 18.2.



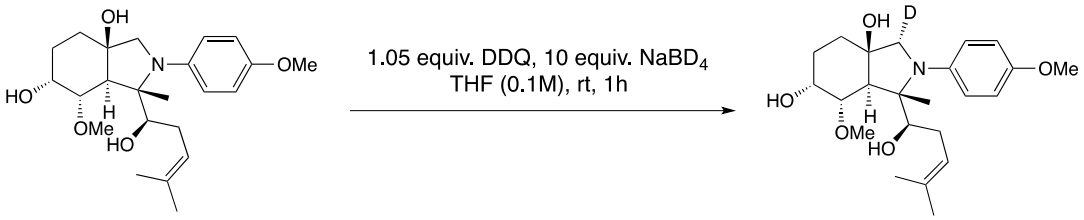


2d: Prepared according to General Procedure A in 90% yield. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.15 (ddd,, J = 8.1, 8.1, 7.7 Hz, 1H), 6.74 (br d, J = 8.6 Hz, 1H), 6.71 (br d, J = 12.8 Hz, 1H), 6.51 (ddd, J = 8.3, 8.1, 2.4 Hz, 1H), 5.07 (br dd, J = 7.3, 7.3 Hz, 1H), 4.33 (ddd, J = 2.8, 2.8, 2.7 Hz, 1H), 3.91 (dd, J = 10.6, 1.2 Hz, 1H), 3.69 (dd, J = 11.4, 2.8 Hz, 1H), 3.41 (s, 3H), 3.36 (d, J = 9.2 Hz, 1H), 3.15 (d, J = 9.1 Hz, 1H), 2.70 (d, J = 11.4 Hz, 1H), 2.35 – 2.22 (overlapped, 2H),,2.21 (br s, 1H), 2.03 - 1.94 (overlapped, 3H), 1.81 (m, 1H), 1.72 (ddd, J = 13.0, 3.7, 2.7 Hz, 1H), 1.66 (s, 3H), 1.65 (overlapped, 1H), 1.62 (s, 3H), 1.55 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 163.6 (d, $J_{C\text{-}F}$ = 242.8 Hz), 149.1 (br s) 135.9, 129.9 (d, $J_{C\text{-}F}$ = 10.1 Hz) 121.5, 112.7 (br s), 105.4 (d, $J_{C\text{-}F}$ = 17.8 Hz), 104.4 (d, $J_{C\text{-}F}$ = 25.0 Hz), 79.1, 76.9, 74.8, 69.2, 64.8, 62.7, 56.0, 46.6, 30.9, 27.8, 26.0, 25.9, 21.7, 18.1.



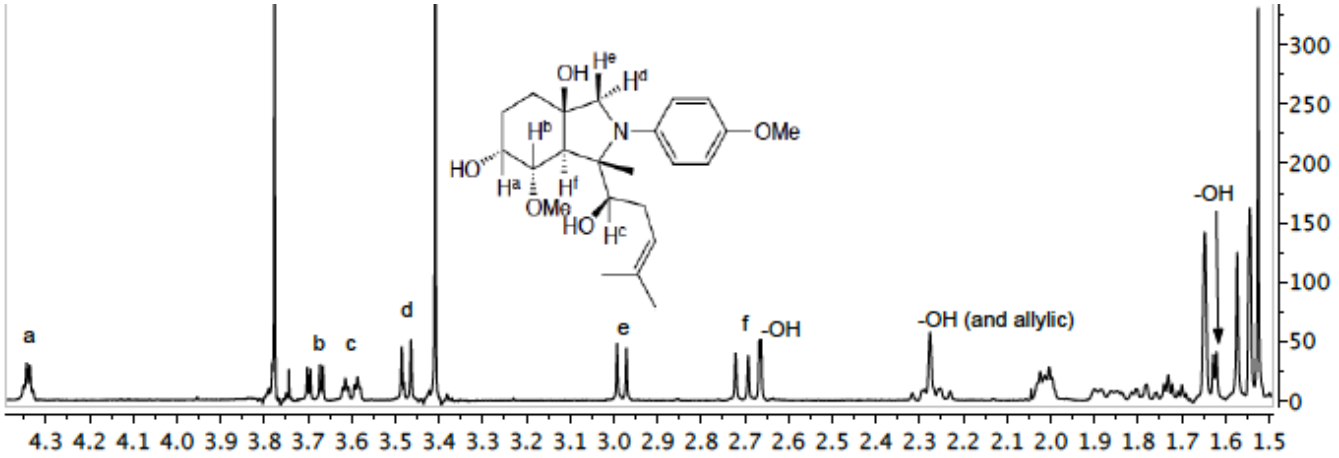


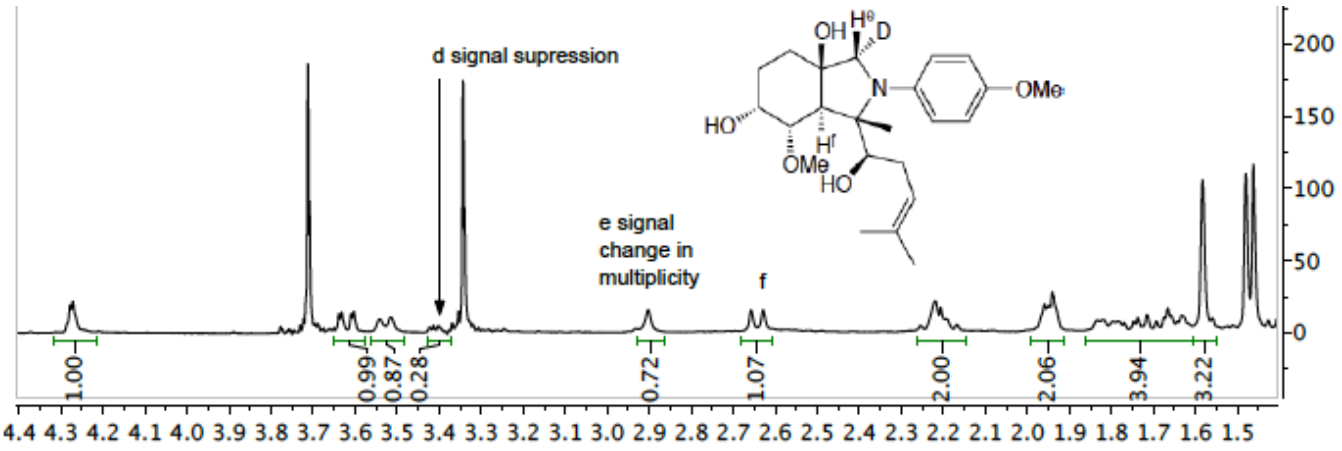
5. Oxidation of 2a and Stereoselective Deuteride Addition: *deutero*-2a



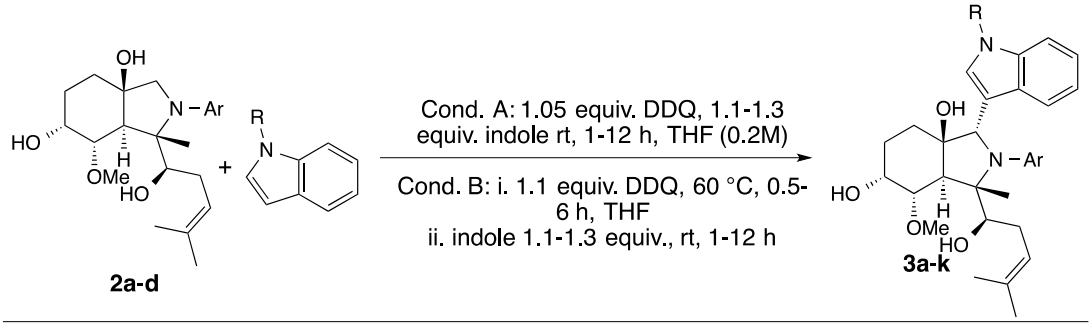
2a *deutero*-**2a**

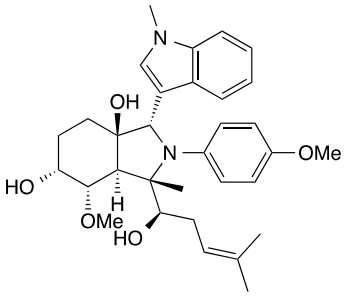
Synthesis of deutero-**2a:** A 2 mL vial equipped with a stir bar was charged with **2a** (36 mg, 0.089 mmol). 1 mL of THF was added followed by the addition of DDQ (21 mg, 0.09 mmol). Directly after DDQ addition, the vessel was cooled to 0 °C and blanketed with a stream of nitrogen. Next, $NaBD_4$ (41 mg, 1 mmol, ~10 equiv.) was added and the vessel was allowed to slowly warm to rt and was stirred for 1h. The reaction mixture was then transferred to a separatory funnel with 25 mL of EtOAc. The organic layer was extracted with aqueous Na_2CO_3 (0.5 M, 2 x 20 mL), followed by saturated brine (20 mL). The organic layer was dried over Na_2SO_4 and evaporated yielding crude *deuterio*-**2a.** Pure product was obtained by flash chromatography (30 mg, 0.074 mmol, 83%). The ^{1}H NMR spectrum was identical to **2a** with the exception of the loss of intensity of the doublet of 1-αH (δ 3.47) and loss of H,H-coupling to 1-βH (δ br s, 2.98) which appeared as a broad singlet due to ^{2}H,^{1}H-coupling.



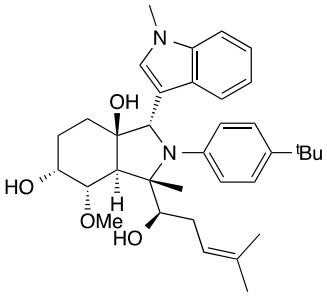


6. Oxidative Coupling of Fumagillol-Aniline Adducts 2a-e with Indole Nucleophiles

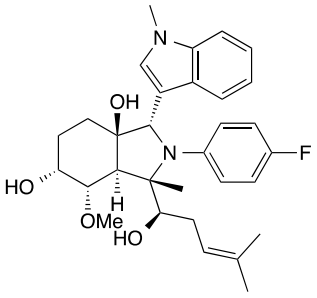




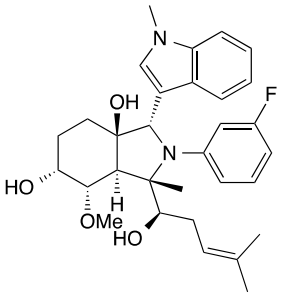
4a R = 4-OMe, 87-95%
Cond. A



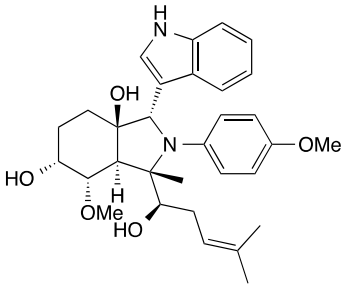
4b R = 4-^{t}Bu, 88%
Cond. A



4c R = 4-F, 76%
Cond. B



4d R = H, 81%
Cond. B

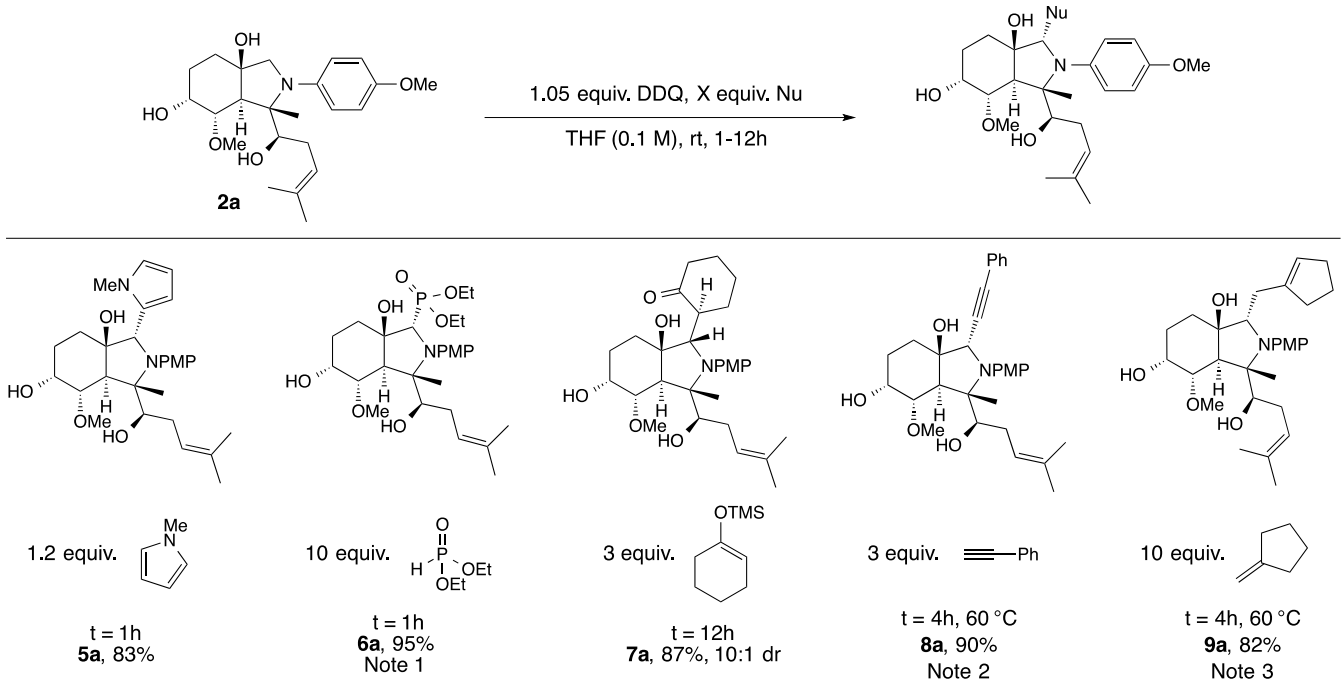


4e R = H, 95%
Cond. A

General Procedure C (Condition A, Scheme 3) for Electron-Rich Fumagillol-Aniline Adducts. A 2 mL vial equipped with a stir bar was charged with fumagillol-aniline adduct **2a,b** (0.1 mmol), then THF was added to a concentration of 0.1M (1 mL), followed by DDQ (1.05 equiv) with stirring over 0.5 min. Once the oxidation was complete as monitored by UPLC-MS analysis (< 1 min), the indole derivative (1.2 equiv) was added and the reaction was stirred at rt until the reaction was complete as monitored by UPLC-MS (1-12 h). The reaction mixture was then transferred to a separatory funnel with EtOAc (30 mL). The organic layer was extracted with aqueous Na_2CO_3 (0.5 M, 2 x 20 mL), followed by saturated brine (20 mL). The solvent was removed *in vacuo* which afforded the crude product. Products were purified by flash chromatography (1:1 EtOAc:hexanes).

General Procedure D (Condition B, Scheme 3) for Electron-Poor Fumagillol-Aniline Adducts. A 2 mL vial equipped with a stir bar was charged with fumagillol-aniline adduct **2c-e** (0.1 mmol), and THF was added to a concentration of 0.1M (1 mL). Then, DDQ (1.05 equiv.) was added with stirring over 0.5 min, and the reaction mixture heated to 60 ^{o}C. Once the oxidation was complete as monitored by UPLC-MS analysis (< 0.5 – 6 h), the reaction mixture was allowed to cool to rt, then the indole derivative (1.2 equiv) was added and the reaction was stirred until the reaction was complete as monitored by UPLC-MS analysis (1 - 12 h). The reaction mixture was then transferred to a separatory funnel with EtOAc (30 mL). The organic layer was extracted with aqueous Na_2CO_3 (0.5 M, 2 x 20 mL), followed by saturated brine (20 mL). The solvent was removed *in vacuo* to afford the crude product. Products were purified by flash chromatography (1:1 EtOAc:hexanes).

7. Oxidative Coupling of Fumagillol-Anisidine Adduct 2a with Nucleophiles Other Than Indoles

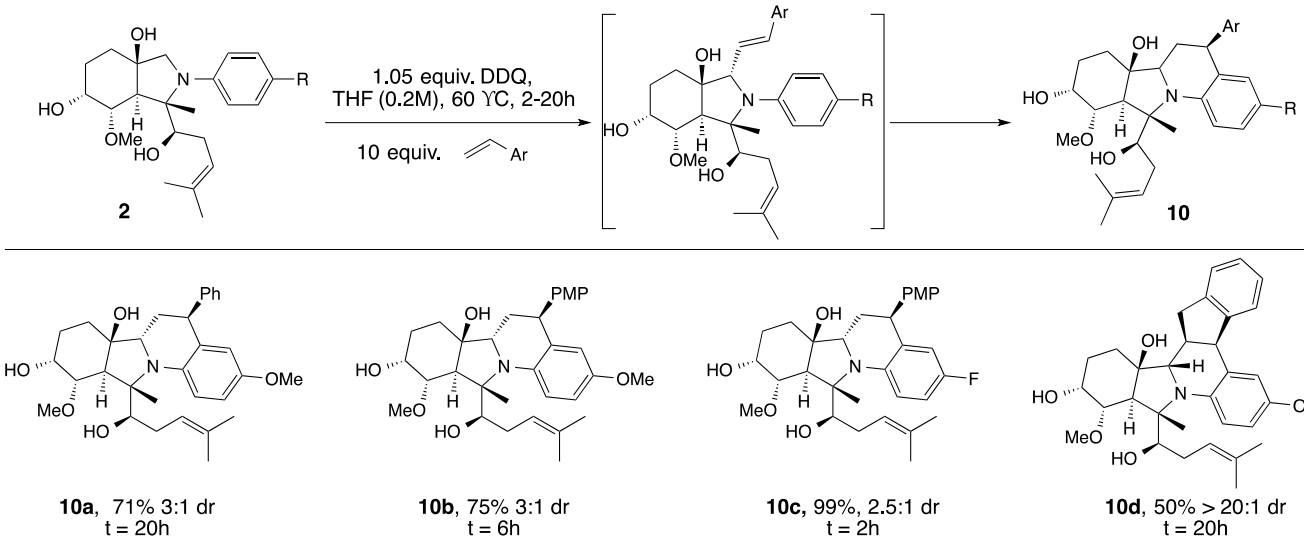


General Procedure E (Scheme 4): A 2 mL vial equipped with a stir bar was charged with fumagillol-anisidine adduct **2a** (101 mg, 0.25 mmol, 1 equiv.), then THF (1 mL) was added, followed by DDQ (59 mg, 0.26 mmol, 1.05 equiv.). After stirring 1 min, the nucleophile was added and the reaction was stirred at rt until the reaction was complete as monitored by UPLC-MS analysis (1-12 h). The reaction mixture was then transferred to a separatory funnel with EtOAc (30 mL), and the organic layer was extracted with aqueous Na_2CO_3 (0.5 M, 2 x 30 mL) followed by saturated brine (30 mL). The organic layer was dried over Na_2SO_4, and the solvent was removed *in vacuo* to yield the crude product. Products were purified by flash chromatography (1:1, EtOAc:hexanes, with the exception of **5a**, see Note 1).

NOTE 1: Compound **5a** was >95% pure following extraction and evaporation of volatiles. Furthermore, this compound was found to be unstable to SiO_2 gel chromatography. The product was recrystallized by dissolving the residue in a small amount of CH_2Cl_2 and adding cold hexanes at -78 °C to induce precipitation.

NOTE 2: For the coupling of phenylacetylene to oxidized **2a**, 10 mol% CuI and 1.1 equiv. Et_3N were added in sequence following the addition of phenylacetylene.

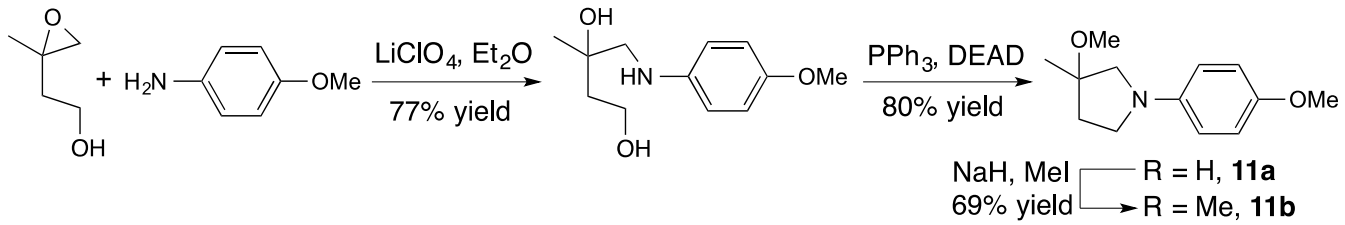
8. Oxidative Coupling of Fumagillol-Aniline Adducts with Styrenes



General Procedure G (Scheme 6): A 2 mL vial equipped with a stir bar was charged with fumagillol-anisidine adduct **2a** (101 mg, 0.25 mmol, 1.0 equiv.). Then, THF (1 mL, 0.25 M) was added, followed by addition of DDQ (59 mg, 0.26 mmol, 1.05 equiv). After stirring for one min, the styrene derivative (10 equiv.) was added and the reaction mixture was heated at 60 °C until the reaction was complete as monitored by UPLC-MS analysis. The reaction mixture was then transferred to a separatory funnel with EtOAc (30 mL). The organic layer was extracted with aqueous Na_2CO_3 (0.5 M, 2 x 30 mL), washed with saturated brine (30 mL), and dried over Na_2SO_4. The solvent and volatiles were removed *in vacuo* yielding the crude product **10**. Pure products (as mixtures of diastereomers) were isolated by flash chromatography (1:2 EtOAc:hexanes).

NOTE: Single diastereomers were separated by recrystallization upon dissolving the diastereomeric mixture in a minimal amount of EtOAc (1 mL, in 20 mL vial) and adding hexanes (20 mL), heating with a heat gun to effect dissolution. Upon standing at rt for 12 - 24 h, a pure sample of the major diastereomer could be isolated in the case of compounds **10b** and **10c**; **10d** was isolated as a single diastereomer; **10a** is reported as a mixture (3:1**)** as diastereomeric separation was challenging *via* chromatography and recrystallization.

9. Synthesis of Simplified Substrates

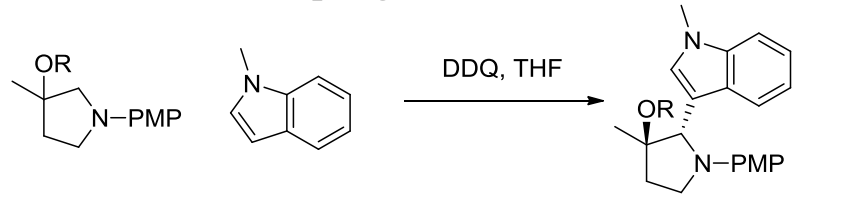


4-((4-Methoxyphenyl)amino)-3-methylbutane-1,3,-diol. Lithium perchlorate (4 g) and p-anisidine (2.5 g, 20 mmol) were dissolved in ether (12 mL) in a 50 mL round bottom flask equipped with a stir bar. 2-Methyl 2-oxiraneethanol (prenyl alcohol epoxide), (1.021 g, 10 mmol) was added and the reaction mixture stirred for 20 min. The mixture was then transferred to a separatory funnel with EtOAc (60 mL). The organic layer was extracted with aq. Na_2CO_3 (0.5 M, 2 x 25 mL) and saturated brine (1 x 25 mL), then dried over Na_2SO_4. After the solvent was removed *in vacuo*, the product was purified by flash chromatography (50% EtOAc in hexanes until p-anisidine was eluted, then 75% EtOAc in hexanes) yielding pure 4-((4-methoxyphenyl)amino)-3-methylbutane-1,3-diol (1.75 g, 7.7 mmol, 77 %). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.78 (d, J_{AB} = 8.9 Hz, 2H), 6.66 (d, J_{AB} = 8.9 Hz, 2H), 3.97 (ddd, J = 11.2, 8.7, 3.5 Hz, 1H), 3.85 (ddd, J = 11.2, 6.1, 4.1 Hz, 1H), 3.75 (s, 3H), 3.39 (br s, 2H), 3.14 (d, J_{AB} = 12.3 Hz, 1H), 3.04 (d, J_{AB} = 12.3 Hz, 1H), 2.96 (br s, 1H), 1.95 (ddd, J = 14.7, 8.7, 4.1 Hz, 1H), 1.71 (ddd, J = 14.7, 6.1, 3.5 Hz, 1H), 1.33 (s, 3H).

1-(4-Methoxyphenyl)-3-methylpyrrolidin-3-ol (11a). To a 20 mL screw cap vial equipped with a stir bar was added 4-((4-methoxyphenyl)amino)-3-methylbutane-1,3-diol (4.88 mmol, 1.1 g), triphenylphosphine (5 mmol, 1.31 g), and THF (10 mL). The reaction mixture was cooled in an ice bath under a stream of nitrogen, then DEAD (5 mmol, 40% in toluene , ~2.176 grams, total mass of DEAD and toluene) was then added dropwise over 1 min. The vessel was capped and removed from the ice bath and allowed to warm to rt. The reaction volume was then reduced *in vacuo* over 30 min. The solid residue was redissolved in a small amount of CH_2Cl_2 (~3 mL) and was subjected to flash chromatography (15-30% EtOAc in hexanes) to yield amino alcohol **12a** (810 mg, 3.9 mmol, 80% yield. See below for NMR spectra and characterization).

3-Methoxy-1-(4-methoxyphenyl)-3-methylpyrrolidine (11b). To a 2 mL screw cap vial equipped with a stir bar was added **12a** (62 mg, 0.30 mmol) and DMSO (1 mL) followed by sodium hydride (60% dispersion with mineral oil, 0.5 mmol, 20 mg total weight) which was followed by rapid effervescence. Methyl iodide (43 mg, 19 µL, 0.30 mmol) was then added with stirring and the reaction mixture was capped and stirred at 40 °C for 2h. The reaction mixture was then transferred to a separatory funnel with EtOAc (30 mL) and extracted with aq. Na_2CO_3 (0.5 M, 3 x 50 mL) followed by saturated brine (1 x 30 mL). The organic layer was dried over Na_2SO_4, then the solvent removed *in vacuo*. The residue was purified by flash chromatography (25% EtOAc in hexanes) to yield amino ether **11b** (45 mg, 0.207 mmol, 69% yield. See below for NMR spectra and characterization).

10. Oxidative Couplings of 11a and 11b with Indoles

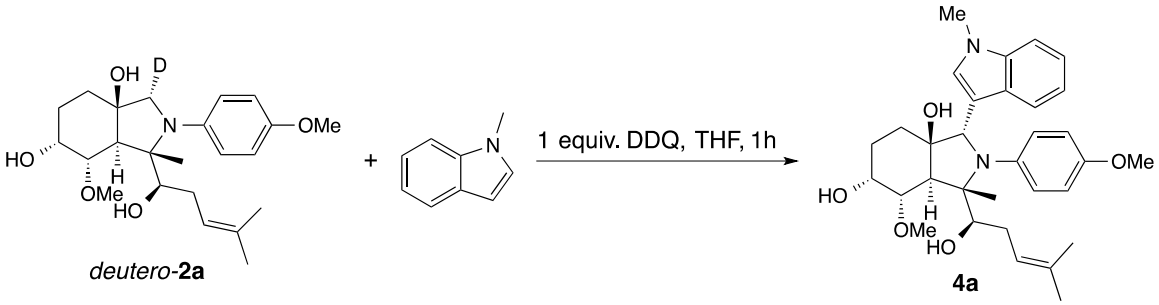


(±)-**11a**, R = H — **12a**, R = H 91% yield, >20:1 dr
(±)-**11b**, R = Me — **12b**, R = Me, 81% yield, >20:1 dr

[a] Standard conditions: 1 equiv. DDQ, THF (0.5M), 5 equiv. indole derivative, 12h, rt.

A 2 mL vial equipped with a stir bar was charged with substrate **11** (0.2 mmol), then 0.5 mL of THF was added and the vessel was cooled to 0 °C in an ice bath under a slow stream of nitrogen. Subsequently, DDQ (46 mg, 0.2 mmol, 1 equiv.) was then added as a solid and the vial was capped under nitrogen and removed from the ice bath. Once at room temperature *N*-methylindole was added (131 mg, 1 mmol, 125 µL). The reaction volume was then reduced *in vacuo* until the mixture became viscous (approximately half of the THF volume was removed). Stirring was continued until the reaction was complete as monitored by UPLC-MS analysis. The mixture was transferred to a separatory funnel with EtOAc (30 mL) and the organic layer extracted with aqueous Na_2CO_3 (0.5 M, 2 x 30 mL), then saturated brine (1 x 30 mL). The organic layer was dried over Na_2SO_4, the solvent removed *in vacuo*, and the residue purified by flash chromatography (30-40% EtOAc in hexanes) yielding the pure products **12.**

11. Stereoselective Oxidative Coupling of *deutero*-2a with *N*-Methylindole

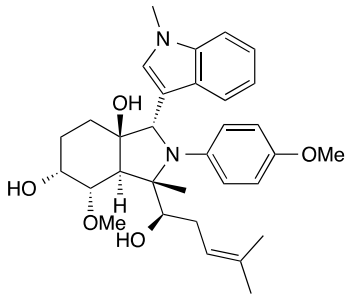


deutero-**2a** — **4a**

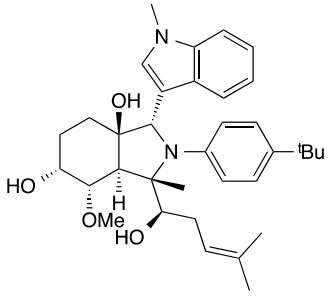
A 2 mL screw cap vial equipped with a stir bar was charged with a solution of *deutero*-**2a** (30 mg, 0.075 mmol, see Scheme 2 of the SI) and dissolved in THF (1 mL). Next, DDQ (18 mg, 0.08 mmol) was added as a solid and the oxidation

was monitored by UPLC-MS analysis. The oxidation took ~20 min for completion noticeably slower than the hydrogen analogue **2a** (complete conversion in 1 min). Once the oxidation was complete, *N*-methylindole (30 μL, 0.25 mmol, 3 equiv.) was added and the reaction was stirred for an additional 30 min. The reaction mixture was then transferred to a separatory funnel with EtOAc (30 mL) and the organic layer extracted with aqueous Na_2CO_3 (0.5 M, 2 x 30 mL) followed by saturated brine (1 x 30 mL). The organic layer was then dried over Na_2SO_4, then the solvent removed *in vacuo* The residue was purified by flash chromatography (40 – 60% EtOAc in hexanes) yielding pure product **4a** (34 mg, 0.064 mmol, 84% yield).

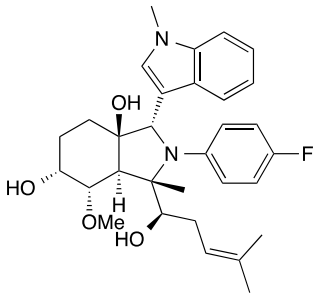
12. Characterization of Products 4-13



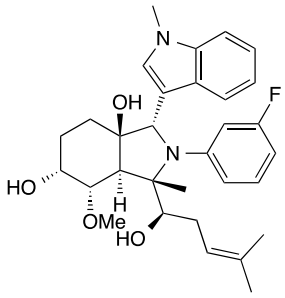
4a: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 (d, *J* = 7.9 Hz, 1H), 7.27 (d, overlapped with $CHCl_3$, 1H), 7.26 (d overlapped, with $CHCl_3$, 1H, 7.19 (ddd, *J* = 8.1, 7.5, 0.8 Hz, 1H, 1H), 7.05 (ddd, *J* = 7.9, 7.5, 0.9 Hz, 1H), 7.02 (d, *J* = 9.0 Hz, 2H), 6.69 (d, *J* = 9.0 Hz, 2H), 5.35 (br dd, *J* = 7.1, 6.1 Hz, 1H), 4.82 (s, 1H), 4.25 (ddd, *J* = 2.9, 2.9, 2.8 Hz, 1H), 4.11 (s, 1H), 3.88 (br d, J = 10.4 Hz, 1H), 3.79 (dd, *J* = 11.4, 2.9 Hz, 1H), 3.71 (s, 3H), 3.70 (s, 3H), 3.48 (s, 3H), 2.85 (d, *J* = 11.4 Hz, 1H), 2.40 (dd, *J* = 14.6, 6.1 Hz, 1H), 2.25 (br ddd, *J* = 14.6, 10.4, 7.1 Hz, 1H), 2.17 (br s, 1H*)*, 1.89 – 1.75 (overlap, 2H), 1.75 (s, 3H), 1.65 (br s, 1H), 1.63 (s, 3H), 1.54 (s, 3H) 1.45 – 1.35 (overlap, 2H). **^{13}C NMR (100 MHz, $CDCl_3$)** 154.3, 141.2, 137.2, 133.0, 127.6, 127.3, 124.7 (2C), 123.2, 121.6, 119.0, 118.8, 115.8, 114.1 (2C), 109.5, 83.3, 79.6, 79.1, 74.6, 70.5, 64.6, 56.3, 55.6, 47.6, 33.1, 31.4, 28.9, 26.0, 25.9, 18.3, 16.8. **HRMS (ESI):** Calc'd for $C_{32}H_{43}N_2O_5$ ([M+H]$^+$): 535.3172, Found: *m/z* 535.3179



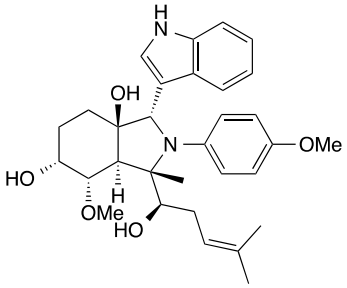
4b: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 (d, *J* = 7.8 Hz, 1H), 7.31 (s, 1H), 7.29 (d, *J* = 8.2 Hz, 1H), 7.23 (dd, *J* = 8.2, 7.6 Hz, 1H), 7.12 (dd, *J* = 7.8, 7.6 Hz, 1H), 7.08 (d, *J* = 8.9 Hz, 2H), 6.79 (d, *J* = 8.9 Hz, 2H), 5.36 (dd, *J* = 7.4, 6.2 Hz, 1H), 4.93 (s, 1H), 4.31 – 4.24 (overlapped, 2H), 3.77 (dd, *J* = 11.4, 2.8 Hz, 1H), 3.69 (s, 3H), 3.50 (s, 3H), 3.26 (br s, 1H), 3.08 (d, *J* = 11.4 Hz, 1H), 2.50 (br dd, *J* = 14.3, 6.2 Hz, 1H), 2.41 (m, 1H), 2.09 (s, 1H), 1.85 – 1.75 (overlapped, 2H), 1.77 (s, 3H), 1.74 (s, 3H), 1.66 (s, 3H), 1.44 (m, 1H), 1.37 (m, 1H), 1.21 (s, 9H). **^{13}C NMR (100 MHz, $CDCl_3$)** 144.1, 139.7, 137.3, 133.7, 127.8, 127.4, 125.6 (2C), 122.9, 121.6, 118.92, 118.89, 116.6 (2C), 114.5, 109.6, 82.6, 79.4, 77.3, 72.3, 70.2, 64.5, 56.2, 46.9, 33.8, 33.1, 32.3, 31.6 (3C), 28.5, 26.1, 25.8, 18.3, 17.5. **HRMS (ESI):** Calc'd for $C_{35}H_{49}N_2O_4$ ([M+H]$^+$): 561.3692, Found: *m/z* 561.3699



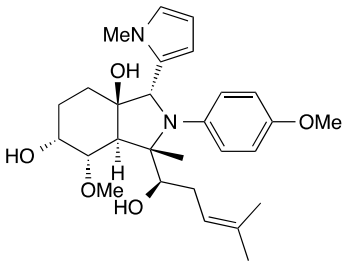
4c: **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.55 (d, *J* = 7.9 Hz, 1H), 7.28 (d, *J* = 8.2 Hz, 1H), 7.24 (s, 1H), 7.21 (dd, *J* = 8.2, 7.5 Hz, 1H), 7.09 (dd, *J* = 7.9, 7.5 Hz, 1H), 6.91 (dd, *J* = 8.9, 4.7 Hz, 2H), 6.78 (dd, *J* = 8.9, 8.6 Hz, 2H), 5.34 (br dd, *J* = 7.1, 6.1 Hz, 1H), 4.85 (s, 1H), 4.25 (ddd, *J* = 2.9, 2.9, 2.8 Hz, 1H), 4.05 (d, *J* = 10.5 Hz, 1H), 3.79 (dd, *J* = 11.3, 2.8 Hz, 1H), 3.70 (s, 3H), 3.64 (br s, 1H), 3.49 (s, 3H), 2.92 (d, *J* = 11.3 Hz, 1H), 2.42 (dd, *J* = 14.0, 6.1 Hz, 1H), 2.31 (m, 1H), 2.14 (br s, 1H), 1.90 – 1.75 (overlapped, 2H), 1.76 (s, 3H), 1.67 (br s, 1H), 1.633 (s, 3H), 1.629 (s, 3H), 1.48 – 1.34 (overlapped, 2H). **^{13}C NMR (100 MHz, $CDCl_3$)** 156.7 (d, $J_{C,F}$ = 238.1 Hz), 143.5 (d, $J_{C,F}$ = 2.3 Hz),137.3, 133.7, 127.41, 127.37, 122.8, 121.7, 121.1 (d, $J_{C,F}$ = 7.2 Hz, 2C) 118.97, 118.95, 115.0 (d, $J_{C,F}$ = 21.7 Hz, 2C), 114.8, 109.6, 82.7, 79.4, 78.2, 73.7, 70.5, 64.5, 56.3, 47.5, 33.1, 31.8, 28.8, 26.0, 25.8, 18.3, 16.8. **HRMS (ESI):** Calc'd for $C_{31}H_{40}FN_2O_4$ ([M+H]$^+$): 523.2972, Found, *m/z* 523.2985



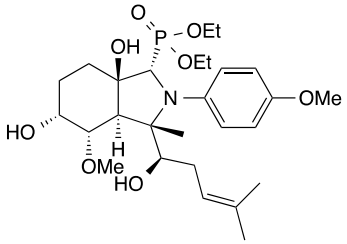
4d: **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.64 (d, *J* = 8.0 Hz, 1H), 7.30 (d, *J* = 8.0 Hz, 1H), 7.28 (s, 1H, overlapped with $CHCl_3$), 7.24 (dd, J =8.0, 7.2 Hz, 1H), 7.14 (dd, *J* = 8.0, 7.2 Hz, 1H), 6.94 (ddd, *J* = 8.3, 8.1, 8.0 Hz, 1H), 6.60 (ddd, *J* = 13.8, 2.3, 2.2 Hz, 1H), 6.49 (dd, *J* = 8.3, 2.3 Hz, 1H), 6.30 (ddd, *J* = 8.1,8.0, 2.2 Hz, 1H), 5.36 (br dd, *J* = 7.6, 6.5 Hz, 1H), 4.92 (s, 1H), 4.35 (br dd, *J* = 10.8, 1.9 Hz, 1H), 4.26 (ddd, *J* = 2.9, 2.8, 2.6 Hz, 1H), 3.78 (dd, *J* = 11.4, 2.9 Hz, 1H), 3.68 (s, 3H), 3.49 (s, 3H), 3.11 (d, *J* = 11.4 Hz, 1H), 2.96 (br s, 1H), 2.53 (br dd, *J* = 13.9, 6.5 Hz, 1H), 2.42 (ddd, *J* = 13.9, 10.8, 7.6 Hz, 1H), 2.09 (br s, 1H), 1.78 (s, 3H), 1.76 (s, 3H), 1.68 (s, 3H), 1.39 (m, 3H), 1.29 (m, 1H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 163.3 (d, $J_{C,F}$ = 240.5 Hz), 147.8 (d, $J_{C,F}$ = 10.7 Hz), 137.4, 134.4, 129.6 (d, $J_{C,F}$ = 10.3 Hz) 127.7, 127.2, 122.3, 121.7, 119.1, 118.9, 113.5, 111.4 (d, $J_{C,F}$ = 2.1 Hz), 109.7, 102.9 (d, $J_{C,F}$ = 19.3 Hz), 102.6 (d, $J_{C,F}$ = 24.5 Hz), 82.3, 79.2, 76.5, 72.2, 70.6, 64.4, 56.3, 46.6, 33.1, 32.4, 28.7, 26.1, 25.8, 18.3, 16.9. **HRMS (ESI):** Calc'd for $C_{31}H_{40}FN_2O_4$ ([M+H]$^+$): 523.2972, Found *m/z* 523.2988



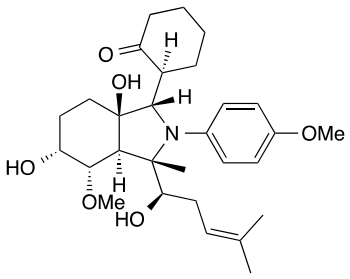
4e: **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.17 (br s, 1H), 7.50 (d, *J* = 8.0 Hz, 1H), 7.42 (d, *J* = 2.4 Hz, 1H), 7.33 (d, *J* = 8.0 Hz, 1H), 7.16 (ddd, *J* = 8.0, 7.5, 0.8 Hz, 1H), 7.06 (ddd, *J* = 8.0, 7.5, 0.8 Hz, 1H), 7.01 (d, *J* = 9.1 Hz, 2H), 6.69 (d, *J* = 9.1 Hz, 2H), 5.33 (br dd, *J* = 7.3, 6.4 Hz, 1H), 4.82 (s, 1H), 4.25 (ddd, *J* = 2.9, 2.8, 2.6 Hz, 1H), 3.88 (dd, *J* = 11.0, 2.1 Hz, 1H), 3.79 (dd, *J* = 11.3, 2.9 Hz, 1H), 3.70 (s, 3H), 3.48 (s, 3H), 2.88 (d, *J* = 11.3 Hz, 1H), 2.39 (dd, *J* = 14.9, 6.4 Hz, 1H), 2.23 (br ddd, *J* = 14.9, 11.0, 7.3 Hz, 1H), 2.10 (br s, 1H), 2.08 (br s, 1H) 1.90 – 1.75 (overlapped, 3H), 1.73 (s, 3H), 1.60 (s, 3H), 1.55 (s, 3H), 1.44 – 1.37 (overlapped , 2H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 154.3, 141.1, 136.5, 133.1, 127.1, 124.7 (2C), 123.1, 122.8, 122.0, 119.4, 119.0, 117.3, 114.1 (2C), 111.4, 83.2, 79.6, 79.0, 74.4, 70.5, 64.6, 56.4, 55.6, 47.6, 31.5, 28.8, 26.0, 25.9, 18.3, 16.9. **HRMS (ESI):** Calc'd for $C_{31}H_{41}N_2O_5$ ($[M+H]^+$): 521.3015, *m/z* 521.3016



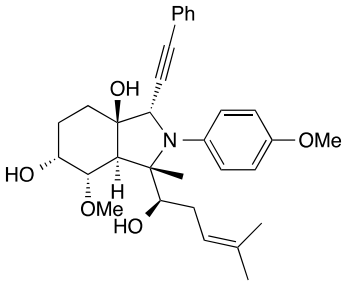
5a: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.05 (d, *J* = 8.8 Hz, 2H), 6.74 (d, *J* = 8.8 Hz, 2H), 6.43 (dd, *J* = 2.7, 1.7 Hz, 1H), 6.28 (dd, *J* = 3.8, 1.7 Hz, 1H), 6.04 (dd, *J* = 3.8, 2.7 Hz, 1H), 5.28 (br dd, *J* = 6.6, 6.5 Hz, 1H), 4.44 (s, 1H), 4.27 (ddd, *J* = 2.8, 2.6, 2.5 Hz, 1H), 3.78 – 3.72 (overlapping m, 1H), 3.74 (s, 3H), 3.51 (dd, *J* = 9.6, 3.5 Hz, 1H), 3.45 (s, 3H), 3.28 (s, 3H), 2.86 (d, *J* = 11.2 Hz, 1H), 2.20 – 2.08 (overlapped, 3H), 1.93 – 1.86 (overlapped, 2H), 1.83 (br ddd, *J* = 14.0, 3.5, 2.8 Hz, 1H), 1.72 – 1.64 (overlapped, 2H), 1.68 (s, 3H), 1.53 (s, 3H), 1.33 (s, 3H), 1.22 (d, *J* = 13.3 Hz, 1H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 156.4, 140.5, 133.1, 132.3, 129.3 (2C), 123.4, 122.1, 114.1 (2C), 107.53, 107.51, 83.5, 79.5, 78.9, 74.1, 70.8, 64.5, 56.4, 55.5, 47.2, 34.3, 30.7, 28.4, 25.98, 25.95, 18.2, 17.4. **HRMS (ESI):** Calc'd for $C_{28}H_{41}N_2O_5$ ($[M+H]^+$): 484.3015, *m/z* 485.3005



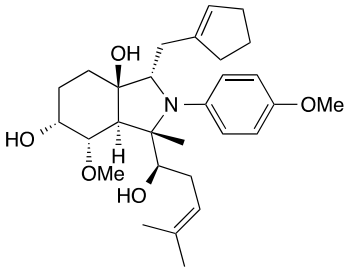
6a ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.19 (d, *J* = 8.8 Hz, 2H), 6.75 (d, *J* = 98.8 Hz, 2H), 5.31 (br dd, *J* = 6.6, 6.5 Hz, 1H), 4.27 (br ddd, *J* = 3.2, 2.8, 2.6 Hz, 1H), 4.24 (br s), 4.09 (qd, *J* = 7.0, 7.1 Hz, 2H), 3.87 (qdd, *J* = 7.0, 9.0, 7.2 Hz, 1H), 3.80 (d, *J* = 7.0 Hz, 1H), 3.77 (s, 3H), 3.67 (dd, *J* = 11.2, 2.8 Hz, 1H), 3.57 (qdd, *J* = 7.0, 9.8, 7.2 Hz, 1H), 3.44 (dd, *J* = 10.6, 1.8 Hz, 1H), 3.37 (s, 3H), 2.82 (d, *J* = 11.2 Hz, 1H), 2.54 (br s, 1H), 2.37 (br ddd, *J* = 15.0, 10.6, 7.0 Hz,, 1H), 2.16 (overlapped, 2H), 2.07 – 1.97 (overlapped, 3H), 1.94 (br d, *J* = 13.1 Hz, 1H), 1.81 (br d, *J* = 12/7 Hz, 1H), 1.70 (s, 3H), 1.58 (s, 3H), 1.26 (t, *J* = 7.0 Hz, 3H), 1.03 (t, *J* = 7.0 Hz, 3H), 1.00 (s, 3H).**^{13}C NMR (101 MHz, $CDCl_3$)** δ 157.3, 139.9 (d, *J* = 3.2 Hz) 132.0, 131.5 (2C), 124.2, 113.6 (2C), 81.7 (d, *J* = 13.5 Hz) 79.0, 78.0, 74.8 (d, *J* = 151.5 Hz) 72.5 (d, *J* = 4.2 Hz), 64.5, 62.6 (d, *J* = 7.6 Hz) 61.7 (d, *J* = 6.5 Hz), 56.0, 55.5, 45.3, 30.4, 29.5, 26.2, 26.0, 18.1, 17.5 (d, *J* = 1.5 Hz) 16.5 (d, *J* = 5.5 Hz), 16.2 (d, *J* = 6.3 Hz). **HRMS (ESI):** Calc'd for $C_{27}H_{45}NO_8P$ ($[M+H]^+$): 542.2883, *m/z* 542.2885



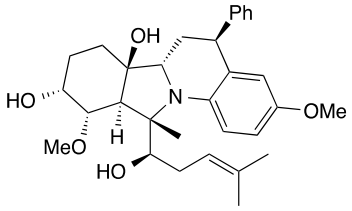
7a: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.11 (d, *J* = 8.9 Hz, 2H), 6.77 (d, *J* = 8.9 Hz, 2H) 5.36 (br dd, *J* = 6.5, 6.5 Hz, 1H), 4.74 (br s, 1H), 4.26 (br ddd, *J* = 2.8, 2.5, 2.5 Hz, 1H), 3.96 (d, *J* = 9.8 Hz, 1H), 3.78 (s, 3H), 3.60 (dd, *J* = 11.2, 2.8 Hz, 1H), 3.41 (br dd, 11.0, 1.6 Hz, 1H), 3.37 (s, 3H), 2.79 (d, 11.2 Hz, 1H), 2.58 (ddd, *J* = 9.8, 9.8, 3.8 Hz, 1H), 2.23 (m, 1H), 2.00 – 1.87 (overlapped, 4H), 1.90 – 1.80 (overlapped, 2H), 1.75 – 1.64 (overlapped, 3H), 1.64 (s, 3H), 1.60 – 1.42 (overlapped, 6H), 1.51 (s, 3H), 0.82 (s, 3H). **^{13}C NMR (100 MHz, $CDCl_3$)** □ 215.4, 156.9, 140.6, 131.5, 131.3 (2C), 124.7, 114.0 (2C), 83.8, 79.1, 78.8, 75.5, 71.9, 64.4, 56.0, 55.4, 54.4, 43.3, 41.6, 30.5, 29.4, 28.2, 26.5, 26.1, 25.9, 21.1, 18.15, 18.09. **HRMS (ESI):** Calc'd for $C_{29}H_{44}NO_6$ ($[M+H]^+$): 502.3169, *m/z* 502.3159



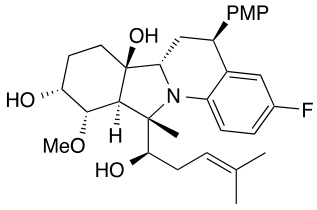
8a: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 (AA'm, 2H), 7.32 (d, *J* = 9.0 Hz, 2H), 7.28 (overlapped, 3H), 6.83 (d, *J* = 9.0 Hz, 2H), 5.22 (dd, *J* = 6.9, 6.8 Hz, 1H), 4.34 (dd, *J* = 2.8, 2.7, 2.5 Hz, 1H), 4.23 (s, 1H), 3.88 (br dd, *J* = 7.1, 5.9 Hz, 1H), 3.77 (s, 3H), 3.70 (dd, *J* = 11.3, 2.8 Hz, 1H), 3.46 (s, 3H), 3.36 (br s, 1H), 2.92 (d, *J* = 11.3 Hz, 1H), 2.37 – 2.25 (overlapped, 3H), 2.10 – 1.90 (overlapped, 4H), 1.69 (overlapped, 1H), 1.66 (s, 3H), 1.51 (s, 3H), 1.46 (s, 3H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 133.0, 131.8, 128.5, 128.4, 123.2, 122.7, 122.6, 114.5, 87.6, 87.4, 79.3, 77.1, 65.7, 64.5, 56.3, 55.7, 48.0, 30.7, 29.9, 26.9, 25.9 19.3, 18.1. **HRMS (ESI):):** Calc'd for $C_{31}H_{40}NO_5$ ($[M+H]^+$): 506.2906, *m/z* 506.2908



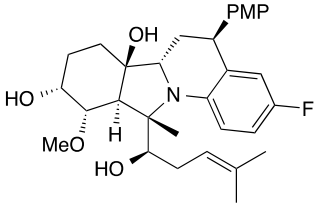
9a: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.08 (d, *J* = 8.8 Hz, 2H), 6.76 (d, *J* = 8.8 Hz, 2H), 5.52 (br s, 1H), 5.35 (br dd, *J* = 6.6, 6.1 Hz, 1H), 4.35 (br s, 1H), 4.28 (ddd, *J* = 2.7, 2.5, 2.5 Hz, 1H), 3.77 (s, 3H), 3.68 (dd, *J* = 11.2, 2.7 Hz, 1H), 3.65 (dd, *J* = 10.8, 4.2 Hz, 1H), 3.39 (s, 3H), 3.25 (dd, *J* = 10.8, 1.5 Hz, 1H), 2.59 (d, *J* = 11.2 Hz, 1H), 2.38 – 2.28 (overlapped, 2H), 2.28 – 2.04 (overlapped, 6H), 2.04 - 1.77 (overlapped, 5H), 1.72 (s, 3H), 1.60 (s, 3H), 0.99 (s, 3H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 156.4, 141.8, 140.7, 132.3, 130.2, 127.7, 124.0, 113.7, 82.9, 79.2, 77.6, 73.9, 72.2, 64.7, 56.1, 55.5, 43.6, 36.4, 34.1, 32.3, 30.6, 28.2, 26.02, 25.95 23.5, 18.03, 17.5. **HRMS (ESI):** Calc'd for $C_{29}H_{44}NO_5$ ($[M+H]^+$): 486.3219, *m/z* 486.3199



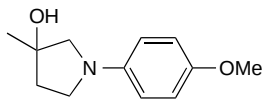
10a Major Diastereomer Reported (see spectra for all signals) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22 (d, *J* = 7.7 Hz, 2H), 7.15 (dd, *J* = 7.7, 7.1 Hz, 1H), 7.08 (d, *J* = 8.9 Hz, 1H), 6.99 (d, *J* = 7.1 Hz, 2H), 6.71 (dd, *J* = 8.9, 3.0 Hz, 1H), 6.46 (d, *J* = 3.0 Hz, 1H), 5.06 (br dd, *J* = 7.2, 7.1 Hz, 1H), 4.29 (ddd, *J* = 2.7, 2.7, 2.7 Hz, 1H), 4.17 (d, *J* = 7.2 Hz, 1H), 3.75 (dd, *J* = 11.2, 2.9 Hz, 1H), 3.80 – 3.73 (overlapped, 1H), 3.65 (s, 3H), 3.41 (s, 3H), 3.20 (dd, *J* = 12.7, 2.2 Hz, 1H), 2.70 (d, *J* = 11.2 Hz, 1H), 2.45 (m, 1H), 2.38 (m, 1H), 2.27 (br s, 1H), 2.05 – 1.85 (overlapped, 4H), 1.75 – 1.62 (overlapped, 3H), 1.66 (s, 3H), 1.59 (s, 3H), 1.57 (s, 3H), 1.36 (ddd, *J* = 12.9, 3.2, 3.0 Hz, 1H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 153.50, 148.75, 138.24, 134.29, 129.03, 128.70, 128.17, 125.84, 122.55, 122.46, 115.61, 113.39, 80.62, 79.47, 72.36, 70.98, 64.86, 64.24, 55.90, 55.35, 43.41, 42.00, 31.28, 30.16, 26.34, 25.78, 25.62, 24.77, 18.02. **HRMS (ESI):** Calc'd for $C_{31}H_{42}NO_5$ ($[M+H]^+$): 508.3063, *m/z* 508.3053



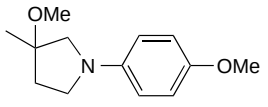
10b: ^{1}H **NMR (400 MHz, $CDCl_3$)** δ 7.07 (d, *J* = 8.9 Hz, 1H), 6.90 (d, *J* = 8.6 Hz, 2H), 6.77 (d, *J* = 8.6 Hz, 2H), 6.72 (dd, *J* = 8.9, 2.6 Hz, 1H), 6.46 (d, *J* = 2.6 Hz, 1H), 5.05 (br dd, *J* = 7.1, 6.5 Hz, 1H), 4.29 (br ddd, *J* = 2.8, 2.7, 2.7 Hz, 1H), 4.14 (d, *J* = 7.1 Hz, 1H), 3.76 (s, 3H), 3.73 (br s, 1H), 3.66 (s, 3H), 3.40 (s, 3H), 3.18 (d, *J* = 11.5 Hz, 1H), 2.70 (d, *J* = 10.9 Hz, 1H), 2.43 (m, 1H), 2.31 (ddd, *J* = 13.4, 12.4, 7.0 Hz, 1H), 2.26 (br s, 1H), 2.02 - 1.89 (overlapped, 4H), 1.69 (ddd, *J* = 6.4, 3.2, 3.2 Hz, 1H) 1.66 (s, 3H), 1.59 (s, 3H), 1.56 (s, 3H), 1.60 – 1.60 (overlapped, 3H), 1.37 (br d, *J* = 13.4 Hz, 1H). **^{13}C NMR (100 MHz, $CDCl_3$)** 157.8, 153.6, 141.1, 138.3, 134.4, 129.5 (2C), 129.5, 122.69, 122.60, 115.7, 113.7 (2C), 113.5, 80.8, 79.5, 72.5, 71.1, 65.0, 64.4, 56.1, 55.5, 55.4, 43.6, 41.3, 31.4, 30.5, 26.5, 25.9, 24.9, 182.. **HRMS (ESI):** Calc'd for $C_{32}H_{44}NO_6$ ($[M+H]^+$): 538.3169, *m/z* 538.3177



10c: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.07 (dd, *J* = 8.9, 5.1 Hz, 1H), 6.90 (d, *J* = 8.7 Hz, 2H), 6.83 (ddd, *J* = 8.9, 8.3, 3.0 Hz, 1H), 6.78 (d, *J* = 8.9 Hz, 2H), 6.63 (dd, *J* = 9.6, 3.0 Hz, 1H), 5.05 (br dd, *J* = 7.2, 7.1 Hz, 1H), 4.29 (br ddd, *J* = 2.8, 2.8, 2.6 Hz, 1H), 4.12 (d, *J* = 7.1 Hz, 1H), 3.77 (s, 4H), 3.78 – 3.75 (overlapped, 1H), 3.75 (overlapped dd, *J* = 11.3, 2.8 Hz, 1H), 3.41 (s, 3H), 3.18 (dd, *J* = 12.7, 2.3 Hz, 1H), 2.71 (d, *J* = 11.3 Hz, 1H), 2.49 (ddd, *J* = 14.9, 10.8, 9.1 Hz, 1H), 2.31 (ddd, *J* = 12.7, 12.6, 7.3 Hz, 1H), 2.27 (br s, 1H), 2.03 – 1.90 (overlapped, 3H), 1.88 (s, 1H), 1.74 – 1.65 (overlapped Hz, 1H), 1.66 (s, 3H), 1.66 – 1.62 (overlapped, 1H), 1.61 (s, 3H), 1.57 (s, 3H), 1.51 (d, *J* = 3.2 Hz, 1H), 1.37 (ddd, *J* = 12.7, 3.3, 3.3 Hz, 1H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 158.0, 157.1 (d, J_{CF} = 239.2 Hz), 141.0 (br s), 140.8, 135.1, 130.3 (d, J_{CF} = 6.3 Hz), 129.7 (2C), 122.3 122.2 (d, J_{CF} = 7.5 Hz),, 117.6 (d, J_{CF} = 21.3 Hz), 113.8 (2C), 113.4 (d, J_{CF} = 22.4 Hz) 80.7, 79.5, 72.1, 71.3, 65.0, 64.5, 56.1, 55.4, 43.6, 41.2, 31.4, 30.4, 26.7, 25.9, 25.8, 24.7, 18.2. **HRMS (ESI):** Calc'd for $C_{31}H_{41}FNO_5$ ($[M+H]^+$): 526.2968, *m/z* 526.2970

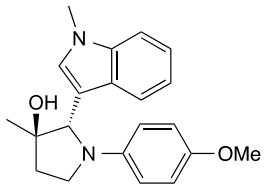


11a: **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.85 (d, *J* = 9.0 Hz, 2H), 6.52 (d, *J* = 9.0 Hz, 2H), 3.76 (s, 3H), 3.53 (ddd, *J* = 14.9, 7.5, 7.4 Hz, 1H), 3.34 – 3.24 (overlapped, 2H), 3.20 (d *J* = 9.7 Hz, 1H), 2.10 – 1.95 (overlapped, 2H), 1.86 (s, 1H), 1.48 (s, 3H).**^{13}C NMR (100 MHz, $CDCl_3$)** δ 151.3, 143.0, 115.1 (2C), 112.8 (2C), 61.8, 56.1, 47.4, 39.8, 25.5.

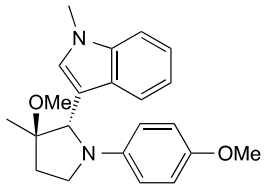


11b ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.84 (d, *J* = 8.8 Hz, 2H), 6.50 (d, *J* = 8.8 Hz, 2H), 3.75 (s, 3H), 3.45 – 3.38 (overlapped, 1H), 3.40 (overlapped d, *J* = 9.8 Hz, 1H), 3.37 – 3.25 (overlapped, 1H), 3.27 (s, 3H), 3.14 (d, *J* = 9.8 Hz, 1H), 2.21 (ddd, *J* = 12.7, 7.4, 4.7 Hz, 1H), 1.90 (ddd, *J* = 12.8, 8.0, 7.8 Hz, 1H), 1.42 (s, 3H). ^{13}C NMR and HRMS not taken.

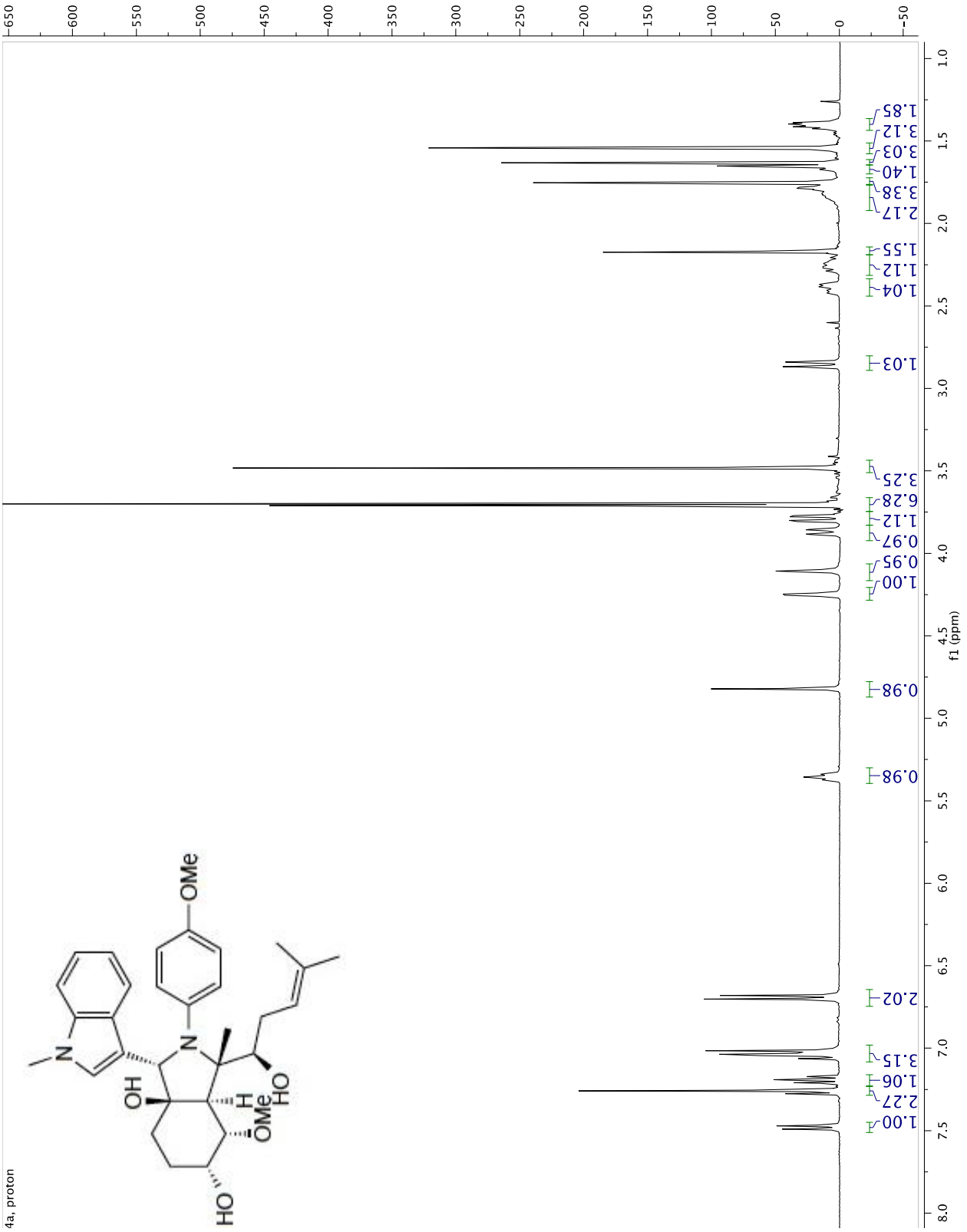
12a: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (d, *J* = 8.0, Hz, 1H), 7.34 (d, *J* = 8.2, Hz, 1H), 7.28 (dd, *J* = 8.2, 7.1 Hz, 1H), 7.17 (dd, *J* = 8.2, 7.1 Hz, 1H), 6.95 (s, 1H), 6.70 (d, *J* = 9.1 Hz, 2H), 6.46 (d, *J* = 9.1 Hz, 2H), 4.75 (s, 1H), 3.84 (ddd, *J* = 14.4, 7.4, 6.6 Hz, 1H), 3.73 (s, 3H), 3.68 (s, 3H), 3.40 (ddd, *J* = 14.4, 7.7, 6.2 Hz, 1H), 2.21 (ddd, *J* = 12.9, 7.4, 6.2 Hz, 1H), 2.07 (ddd, *J* = 12.9, 7.7, 6.6 Hz, 1H), 1.78 (s, 1H), 1.47 (s, 3H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 151.0, 142.6, 137.7, 128.4, 127.2, 122.1, 120.0, 119.6, 114.6 (2C), 113.6 (2C), 111.4, 110.0, 77.9, 66.0, 55.9, 48.3, 37.9, 33.1, 26.0. **HRMS (ESI):** Calc'd for $C_{21}H_{25}N_2O_2$ ($[M+H]^+$), 337.1916, *m/z* 337.1918

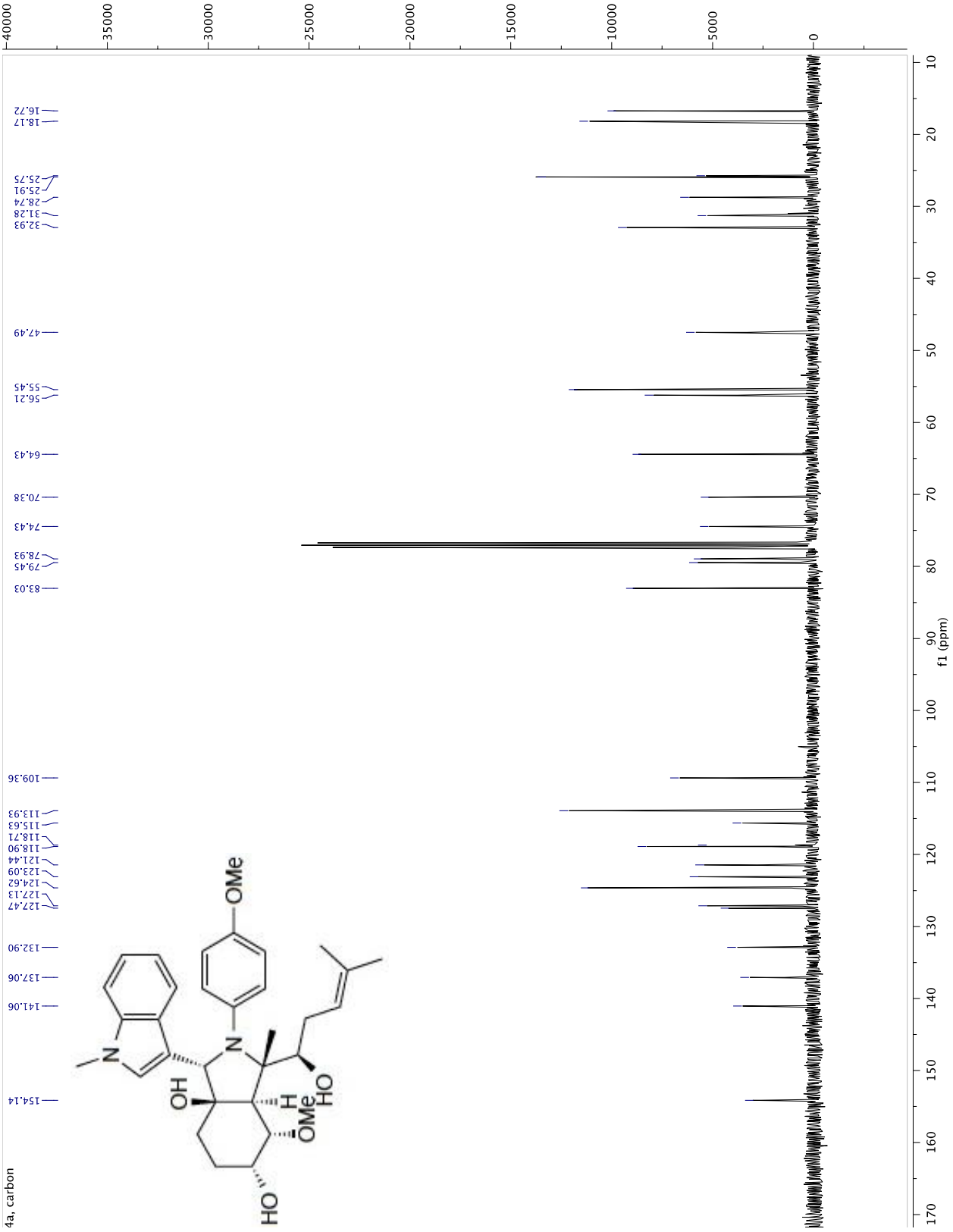


12b: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (dd, *J* = 7.9, 0.9 Hz, 1H), 7.30 (dd, *J* = 8.2, 0.7 Hz, 1H), 7.23 (ddd, *J* = 8.2, 7.2, 0.9 Hz, 1H), 7.14 (ddd, *J* = 8.0, 6.9, 0.7 Hz, 1H), 6.86 (s, 1H), 6.72 (d, *J* = 9.1 Hz, 2H), 6.47 (d, J = 9.1 Hz, 2H), 4.72 (s, 1H), 3.76 (ddd, *J* = 8.5, 8.3, 3.9 Hz, 1H), 3.70 (s, 3H), 3.69 (s, 3H), 3.37 (ddd, *J* = 8.5, 8.1, 7.7 Hz, 1H), 3.10 (s, 3H), 2.38 (ddd, *J* = 12.1, 8.3, 8.1 Hz, 1H), 2.00 (ddd, *J* = 12.1, 7.7, 3.9 Hz, 1H), 1.47 (s, 3H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 150.7, 142.5, 137.1, 127.9, 127.8, 121.1, 119.8, 118.7, 114.6 (2C), 113.2, 113.0 (2C), 109.3, 82.3, 65.5, 55.8, 51.4, 47.2, 33.6, 32.9, 22.1. **HRMS (ESI):** Calc'd for $C_{21}H_{25}N_2O_2$ ($[M+H]^+$), 337.1916, *m/z* 337.1918

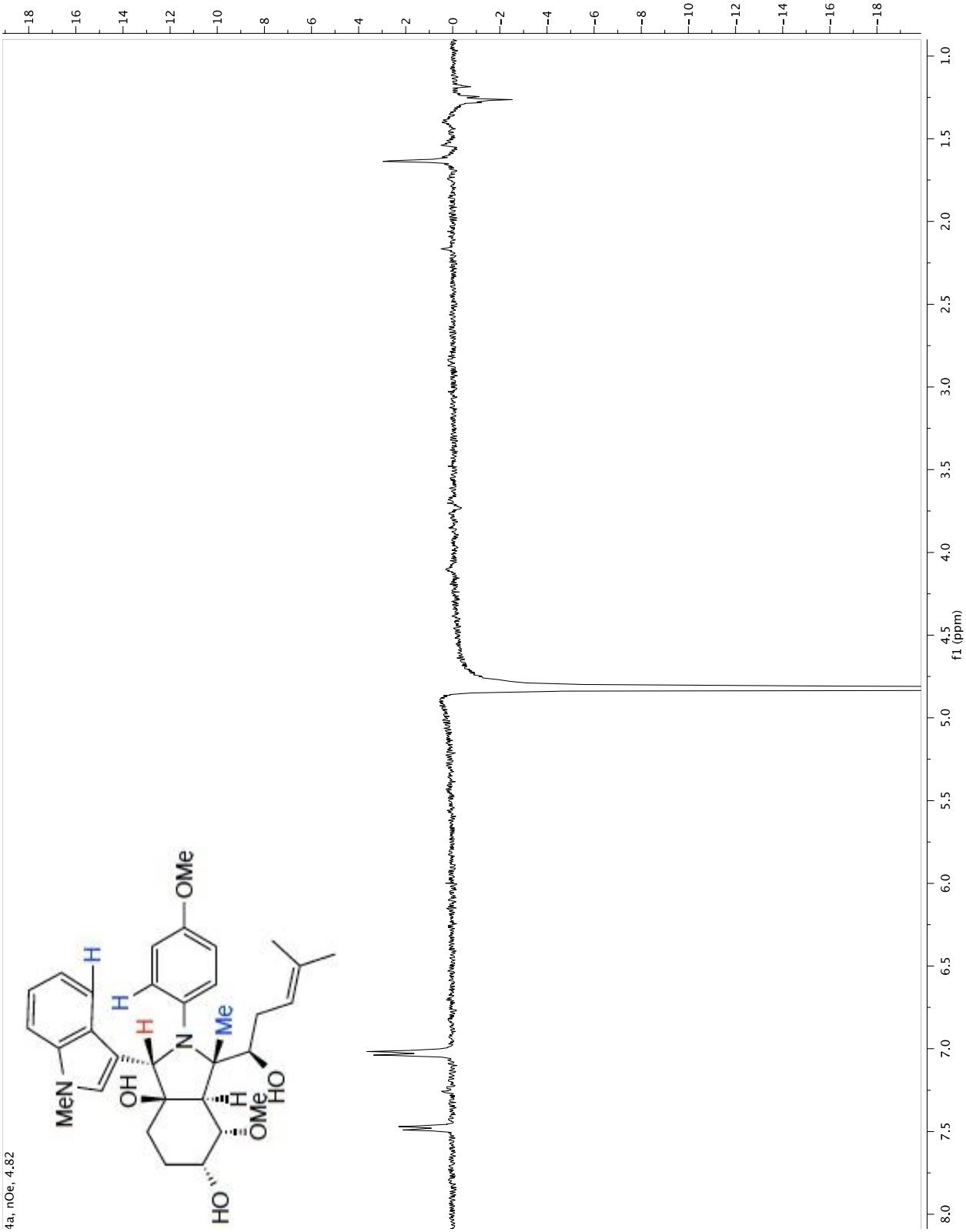


13. ^{1}H and ^{13}C NMR Reprints of 4-13

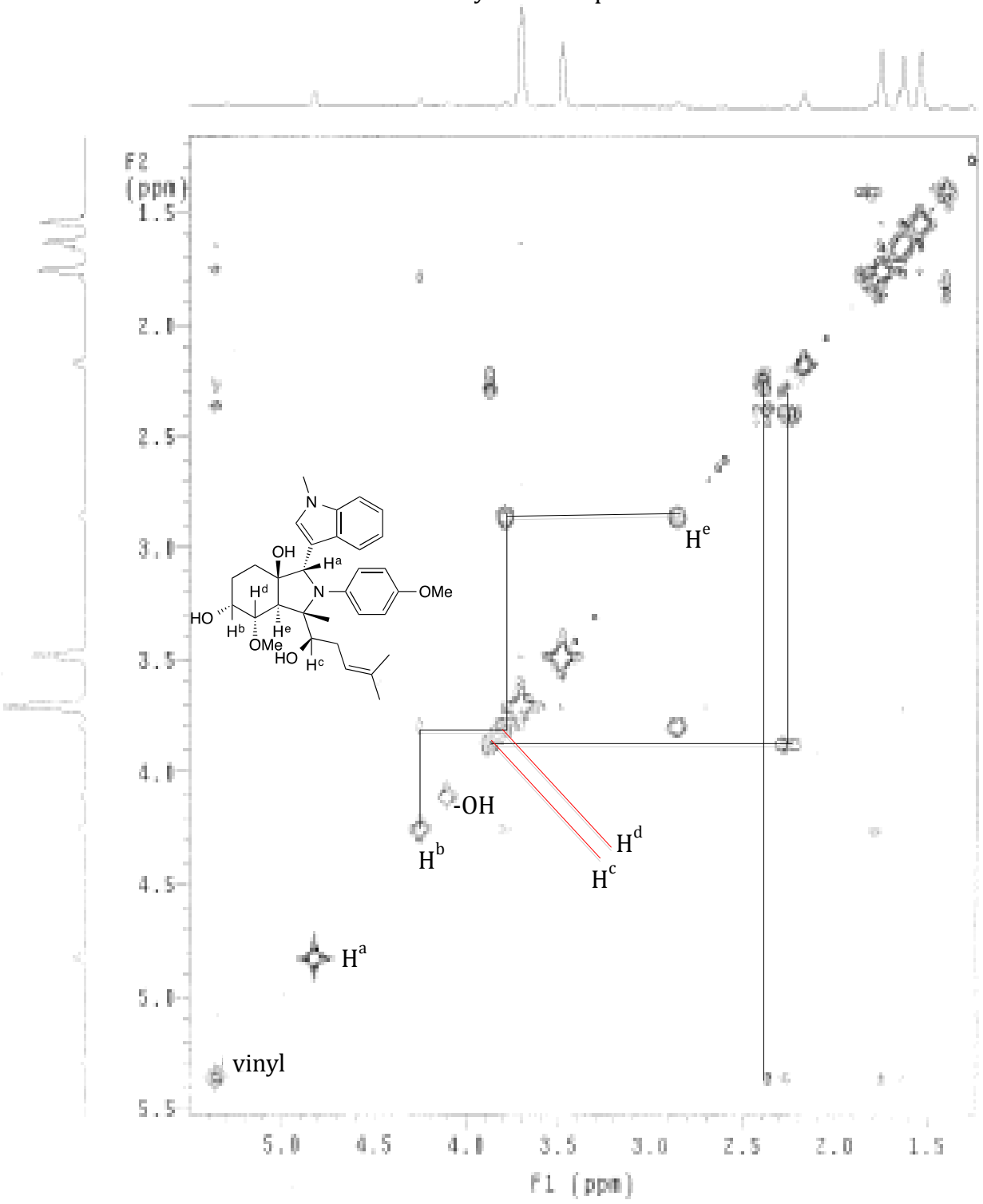


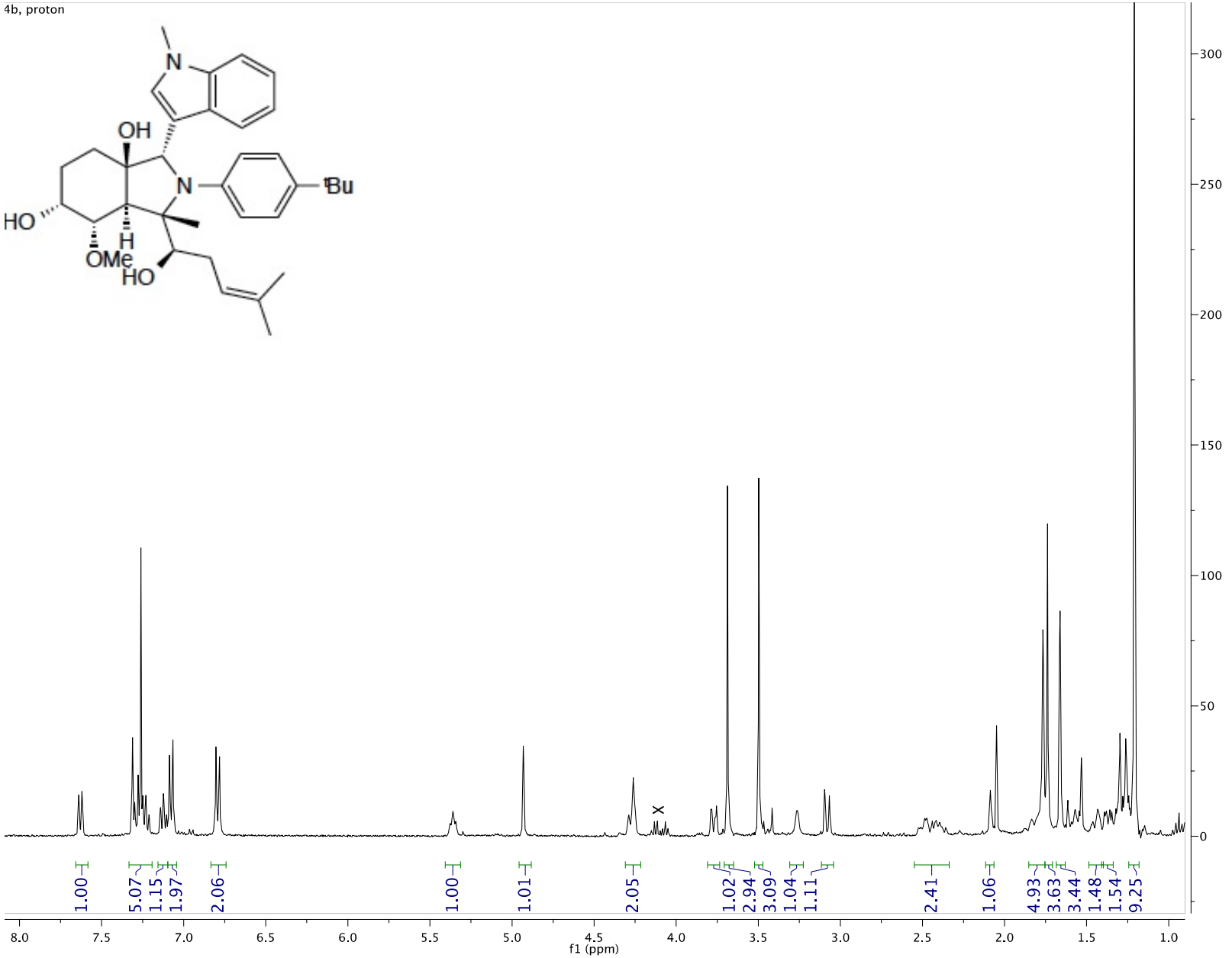

4a, carbon
f1 (ppm)
16.72
18.17
25.75
25.91
28.74
31.28
32.93
47.49
55.45
56.21
64.43
70.38
74.43
78.93
79.45
83.03
109.36
113.93
115.63
118.71
118.90
121.44
123.09
124.62
127.13
127.47
132.90
137.06
141.06
154.14
OMe
OH
H
OMe
HO
HO
N
N

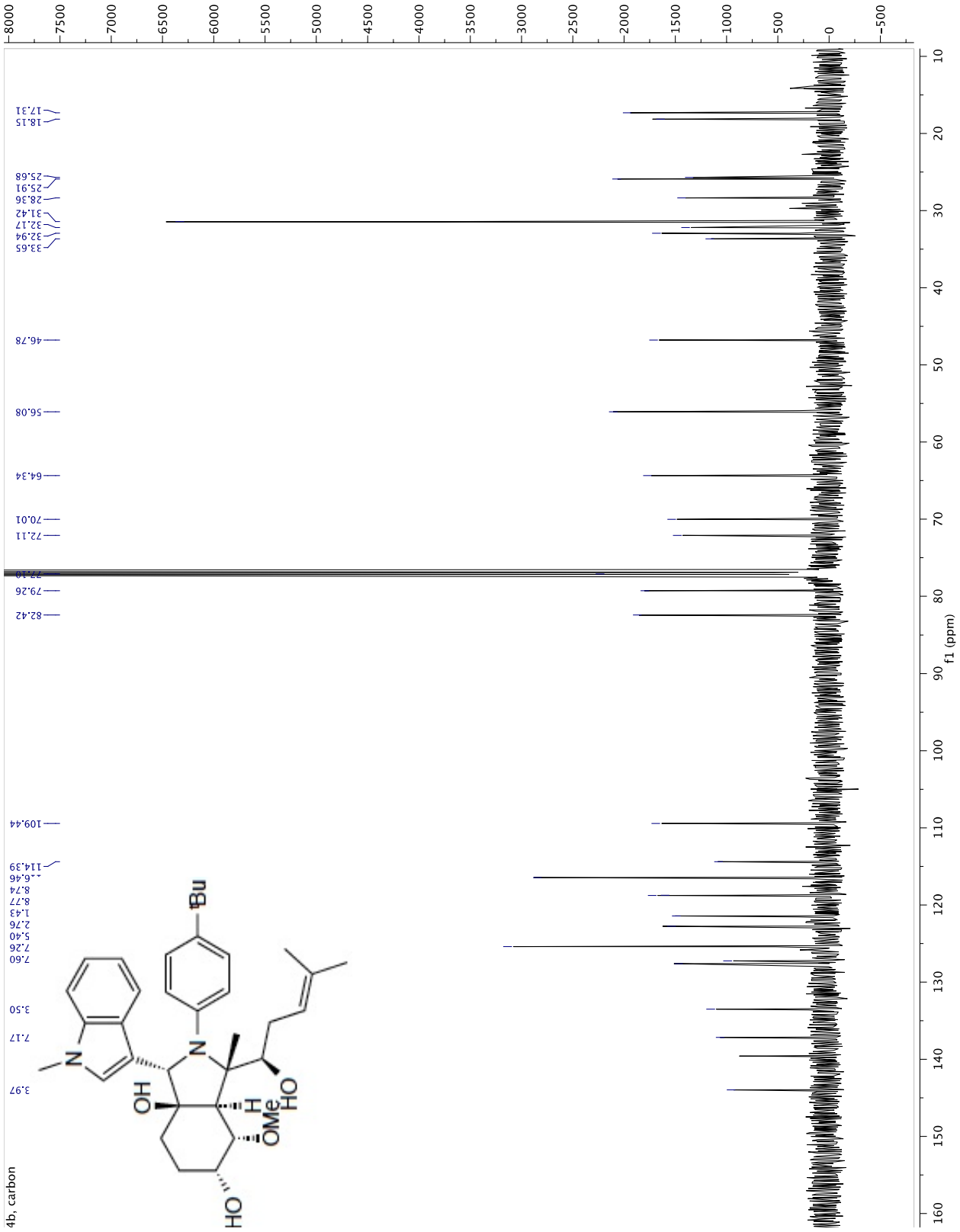
Irradiated Signal, Observed NOEs

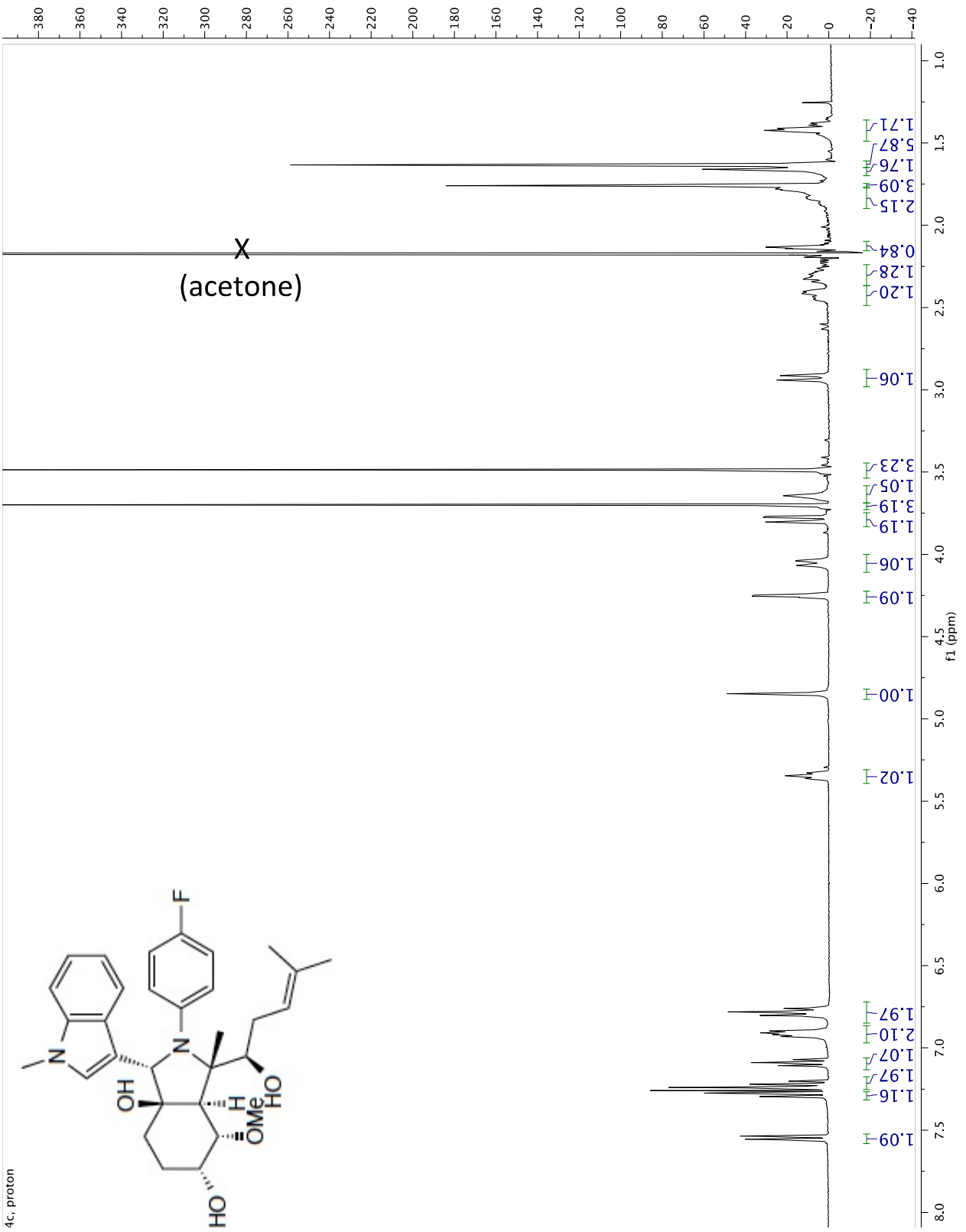


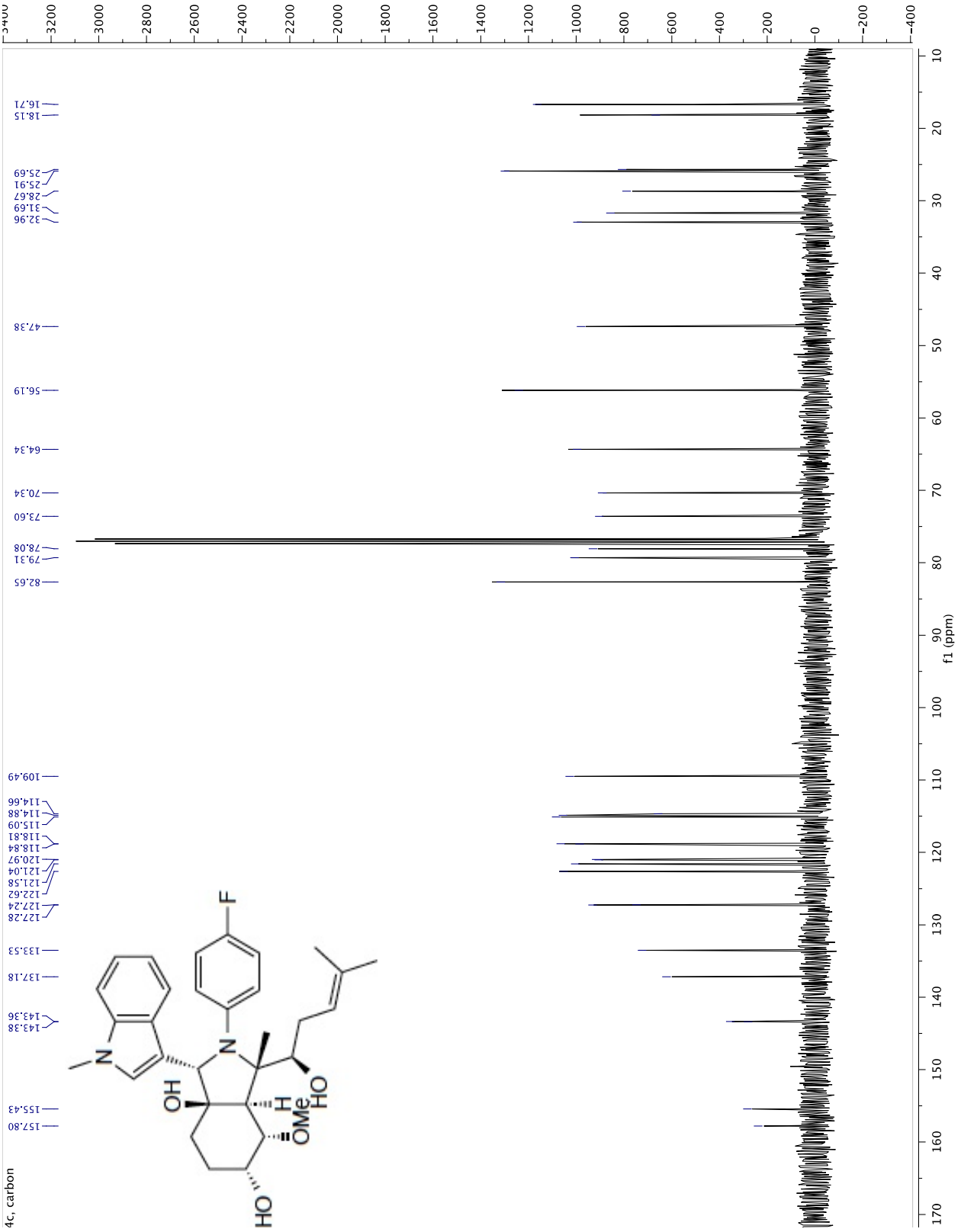
COSY analysis of compound **4a**

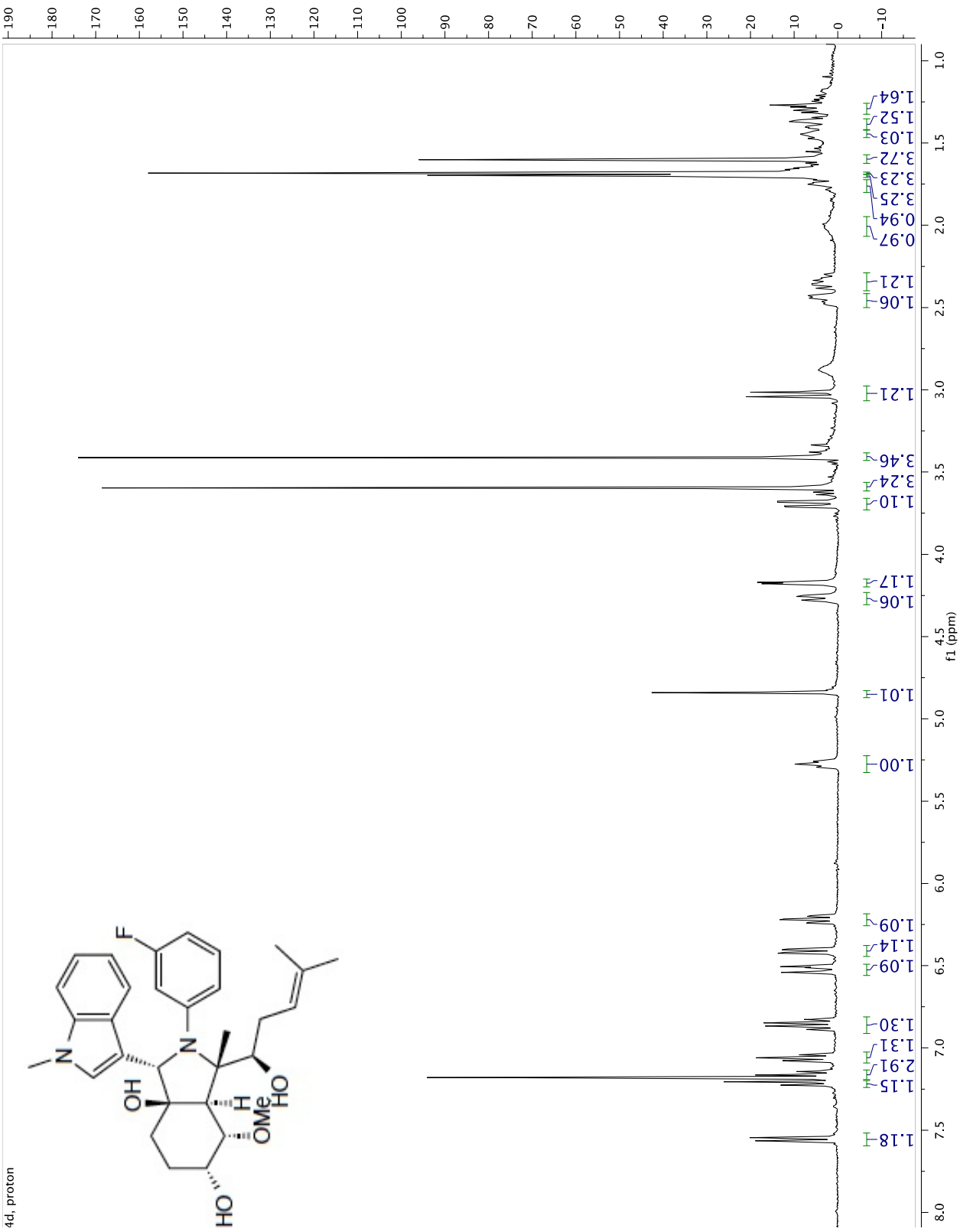


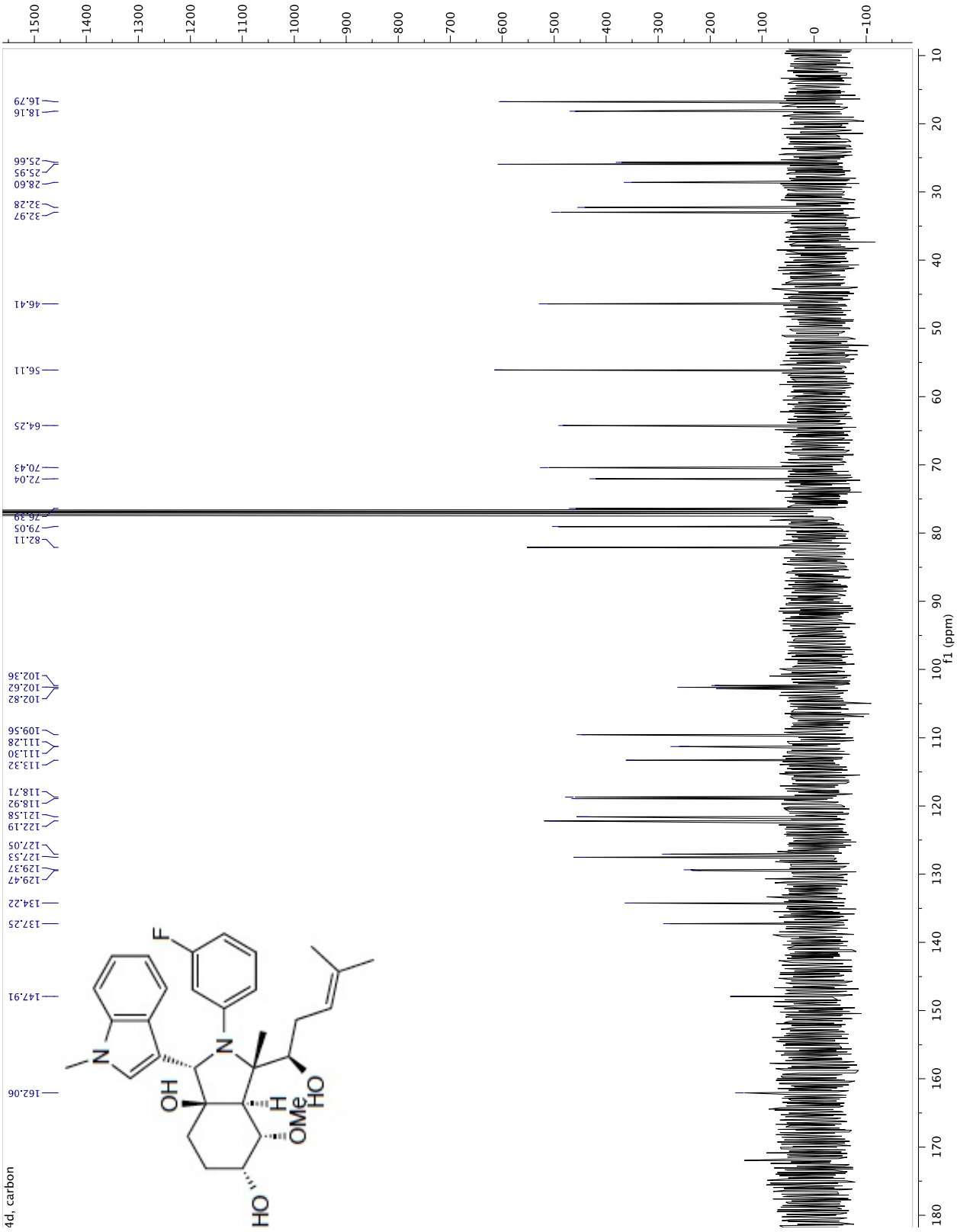

4b, proton
N
OH
N
tBu
HO
H
OMe
HO
X
1.00
5.07
1.15
1.97
2.06
1.00
1.01
2.05
1.02
2.94
3.09
1.04
1.11
2.41
1.06
4.93
3.63
3.44
1.48
1.54
9.25
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
f1 (ppm)
300
250
200
150
100
50
0

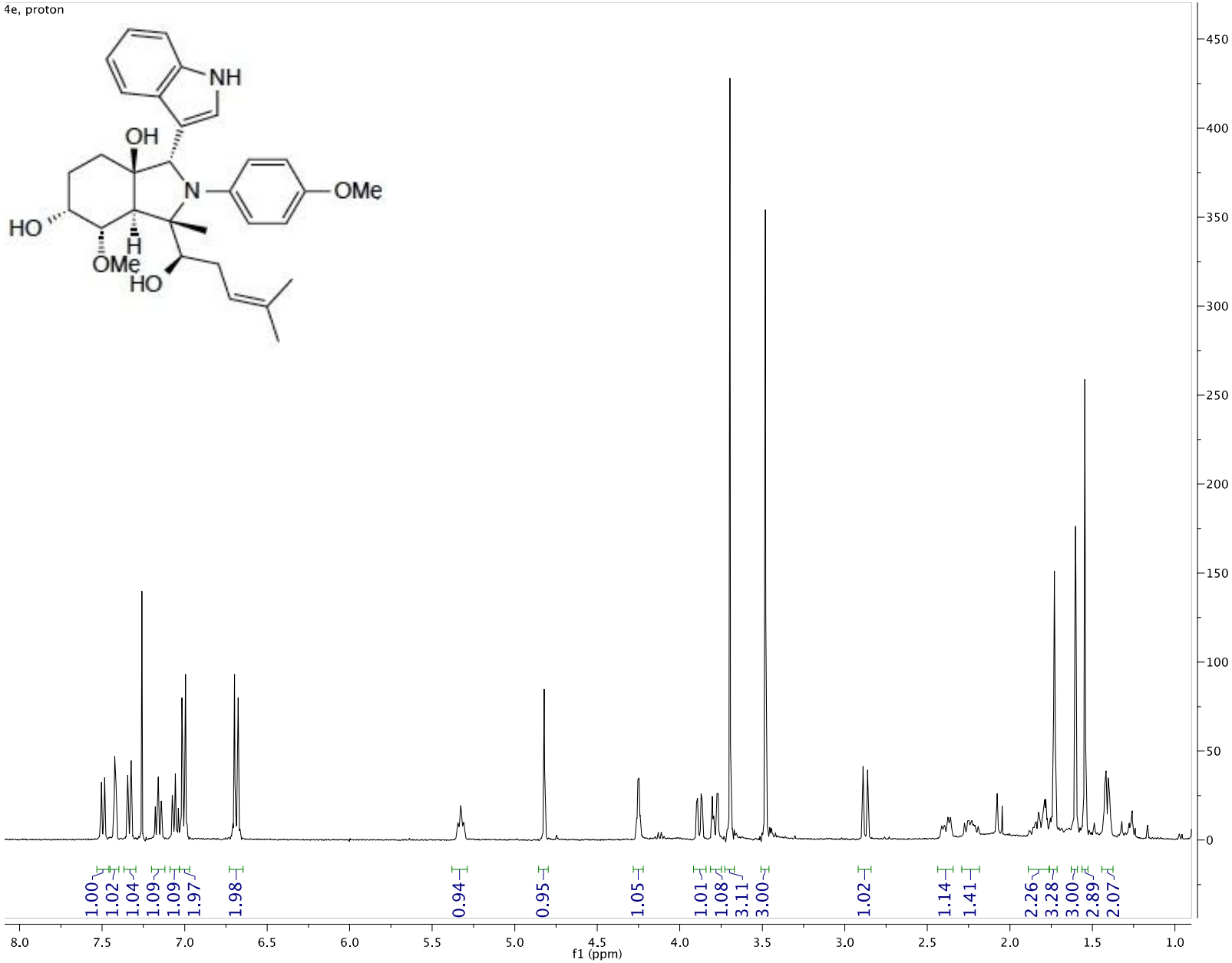

4b, carbon
f1 (ppm)
tBu
OH
OMe
HO
HO
N
N

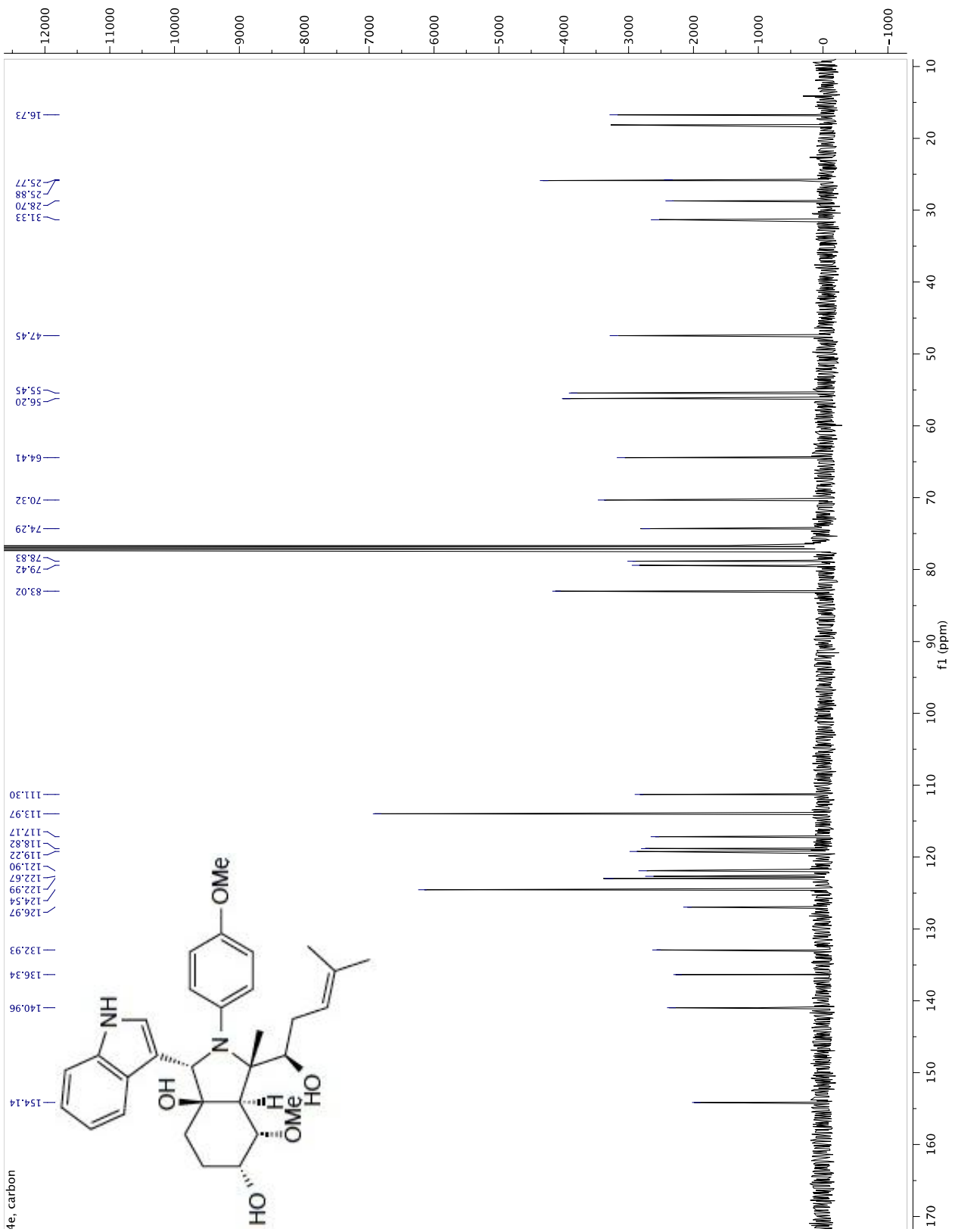

X
(acetone)
4c, proton
f1 (ppm)

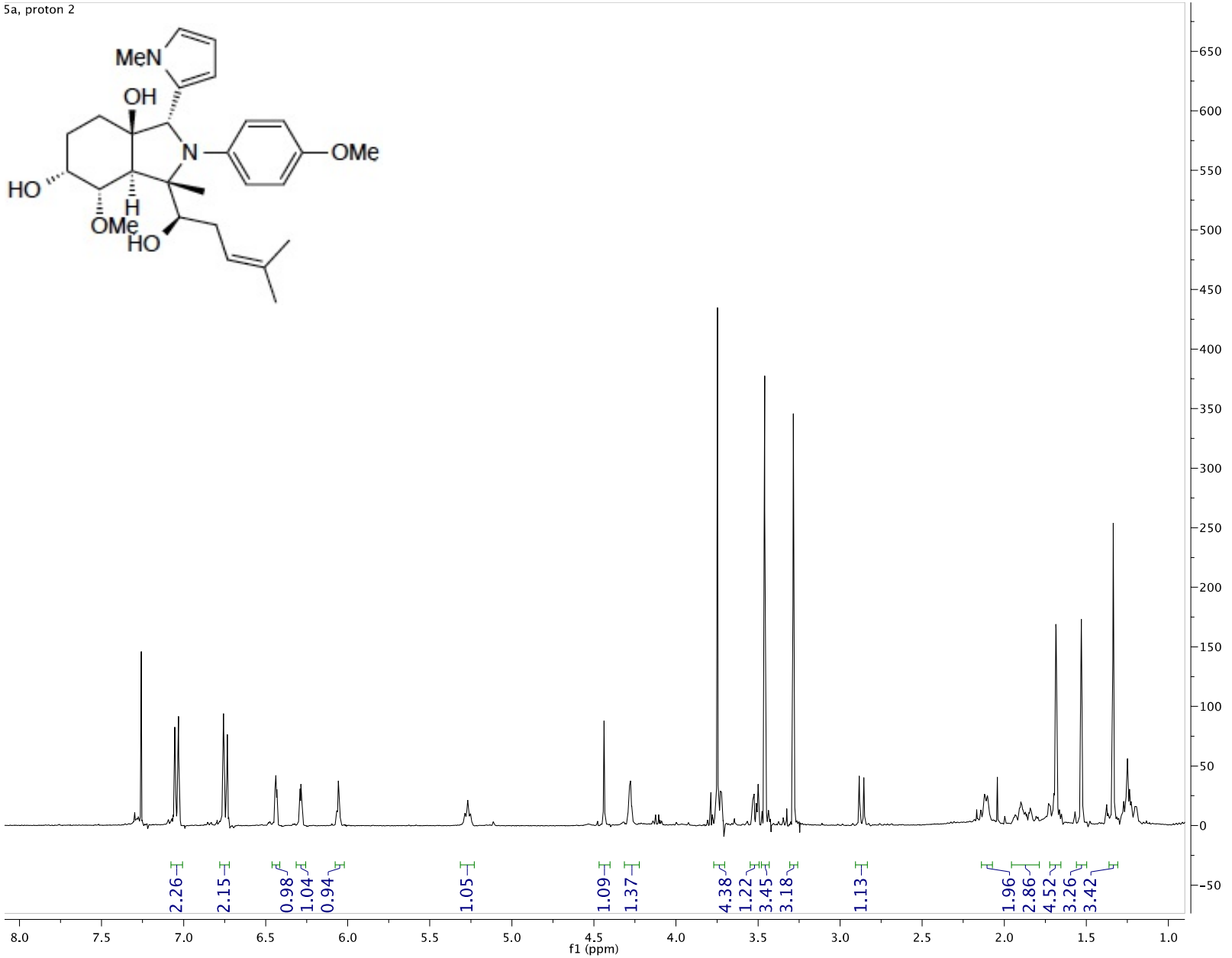

4c, carbon
f1 (ppm)
16.71
18.15
25.69
25.91
28.67
31.69
32.96
47.38
56.19
64.34
70.34
73.60
78.08
79.31
82.65
109.49
114.66
114.88
115.09
118.81
118.84
120.97
121.04
121.58
122.62
127.24
127.28
133.53
137.18
143.36
143.38
155.43
157.80
F
N
N
OH
H
OMe
HO
HO

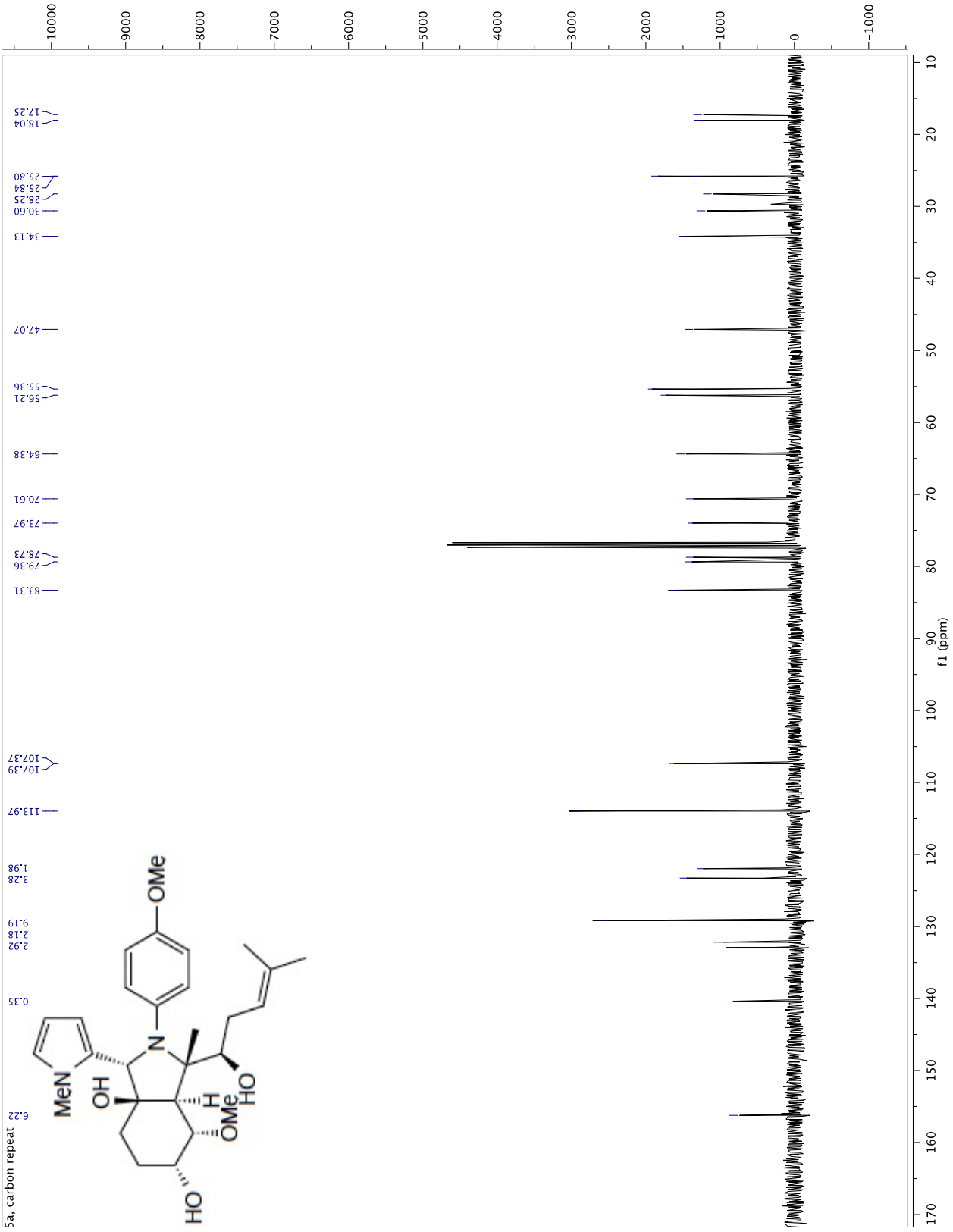

4d, proton
F
N
N
OH
H
OMe
HO
HO
1.64
1.52
1.03
3.72
3.23
3.25
0.94
0.97
1.21
1.06
1.21
3.46
3.24
1.10
1.17
1.06
1.01
1.00
1.09
1.14
1.09
1.30
1.31
2.91
1.15
1.18
f1 (ppm)

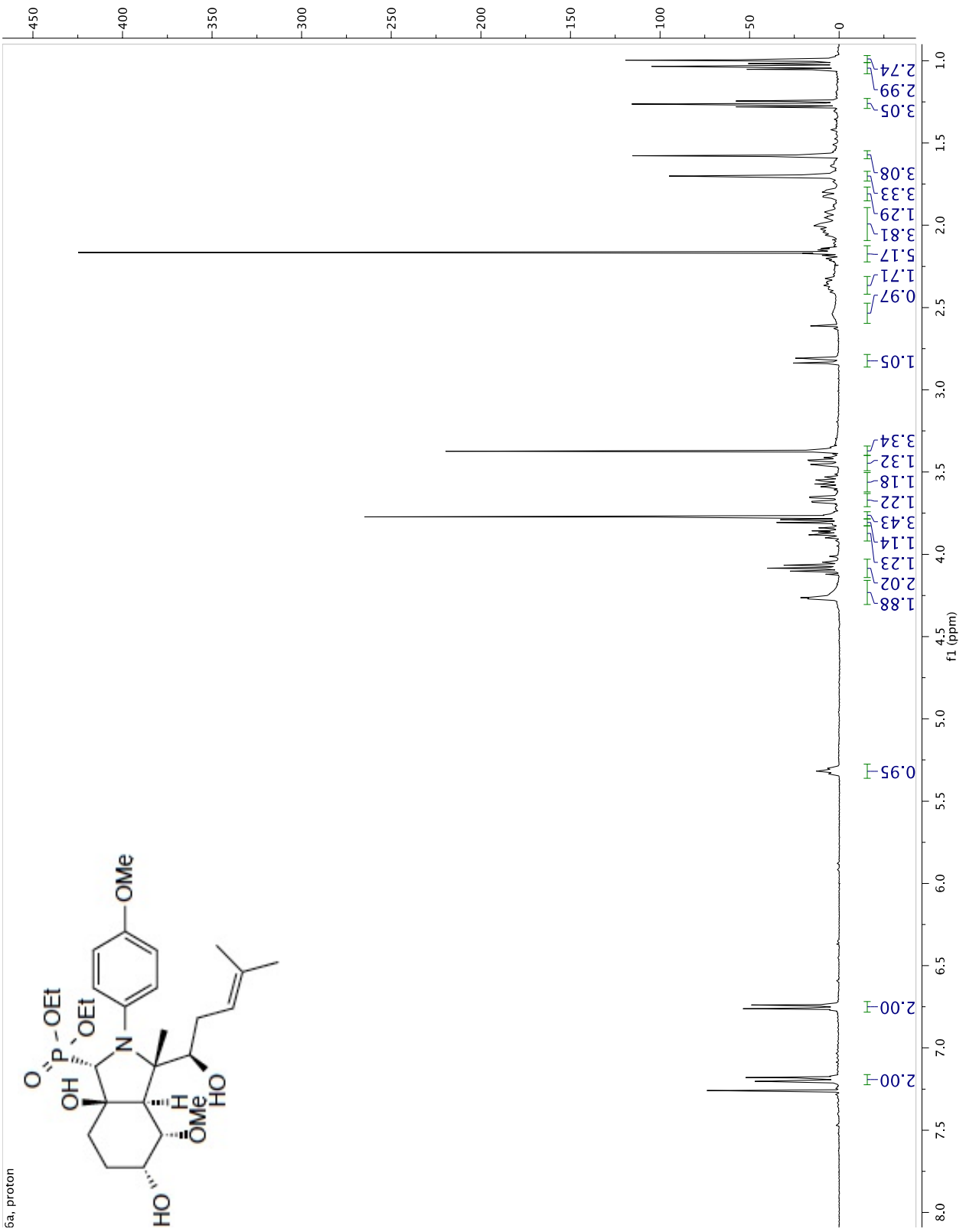

4d, carbon
f1 (ppm)
16.79
18.16
25.66
25.95
28.60
32.28
32.97
46.41
56.11
64.25
70.43
72.04
76.39
79.05
82.11
102.36
102.62
102.82
109.56
111.28
111.30
113.32
118.71
118.92
121.58
122.19
127.05
127.53
129.37
129.47
134.22
137.25
147.91
162.06
F
N
N
OH
H
OMe
HO
HO

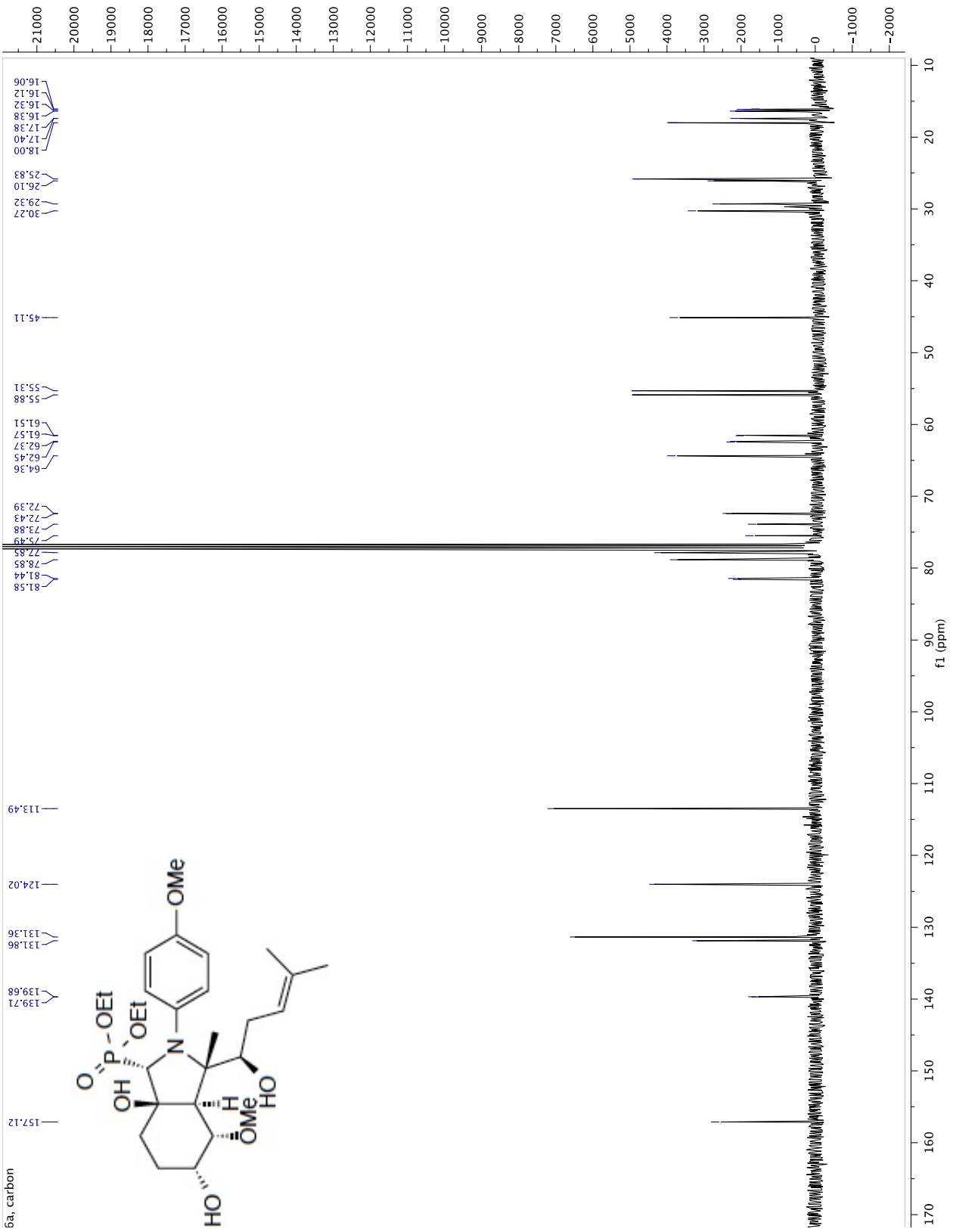

4e, proton
NH
OH
N
OMe
HO
H
OMe
HO
1.00
1.02
1.04
1.09
1.09
1.97
1.98
0.94
0.95
1.05
1.01
1.08
3.11
3.00
1.02
1.14
1.41
2.26
3.28
3.00
2.89
2.07
f1 (ppm)


4e, carbon
16.73
25.77
25.88
28.70
31.33
47.45
55.45
56.20
64.41
70.32
74.29
78.83
79.42
83.02
111.30
113.97
117.17
118.82
119.22
121.90
122.67
122.99
124.54
126.97
132.93
136.34
140.96
154.14
f1 (ppm)

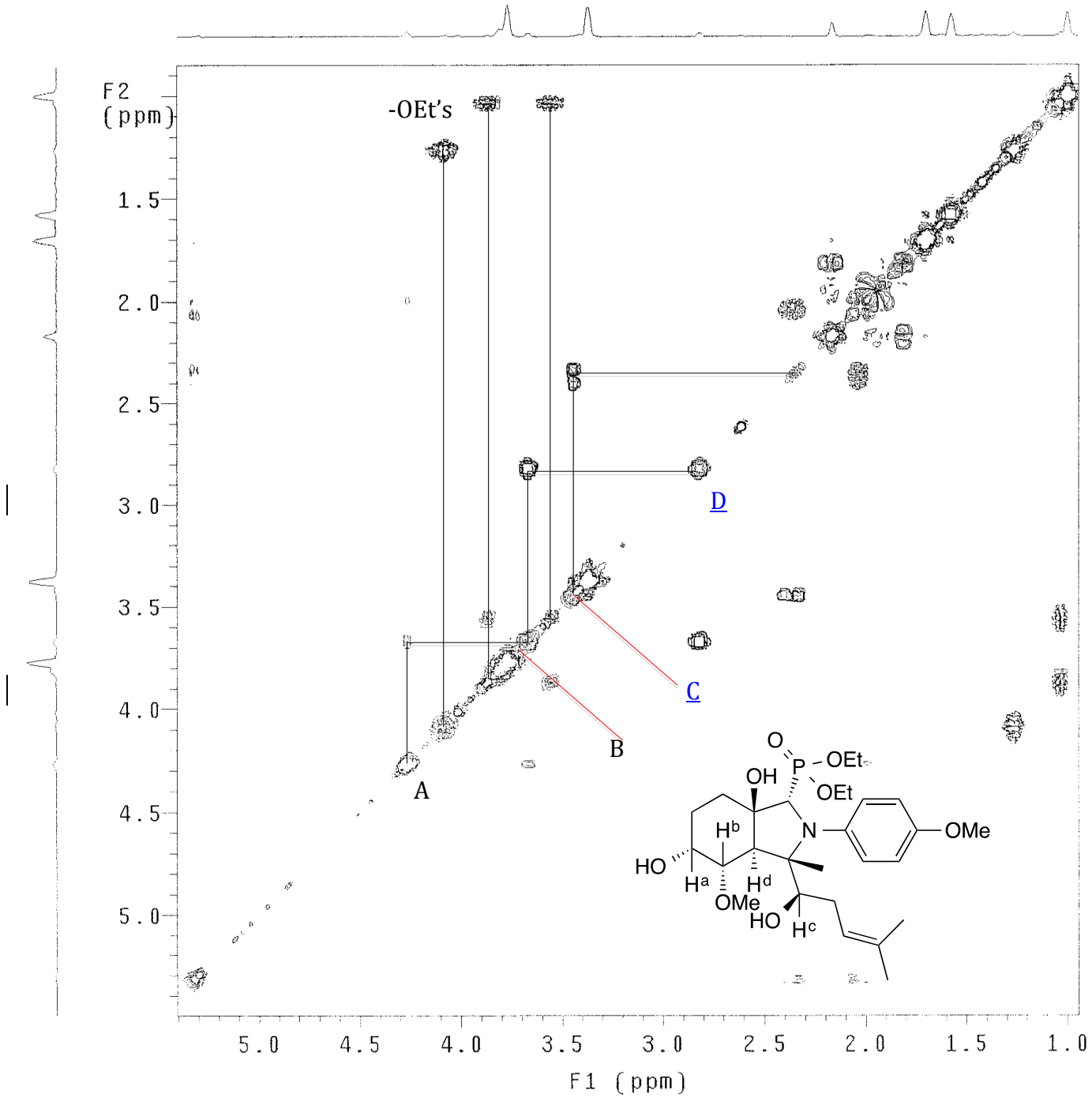

5a, proton 2
MeN
OH
N
OMe
HO
H
OMe
HO
650
600
550
500
450
400
350
300
250
200
150
100
50
0
-50
2.26
2.15
0.98
1.04
0.94
1.05
1.09
1.37
4.38
1.22
3.45
3.18
1.13
1.96
2.86
4.52
3.26
3.42
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
f1 (ppm)


5a, carbon repeat
f1 (ppm)
17.25
18.04
25.80
25.84
28.25
30.60
34.13
47.07
55.36
56.21
64.38
70.61
73.97
78.73
79.36
83.31
107.37
107.39
113.97
0.35
2.92
2.18
9.19
1.98
3.28
6.22
MeN
OH
OMe
HO
H
OMe
HO

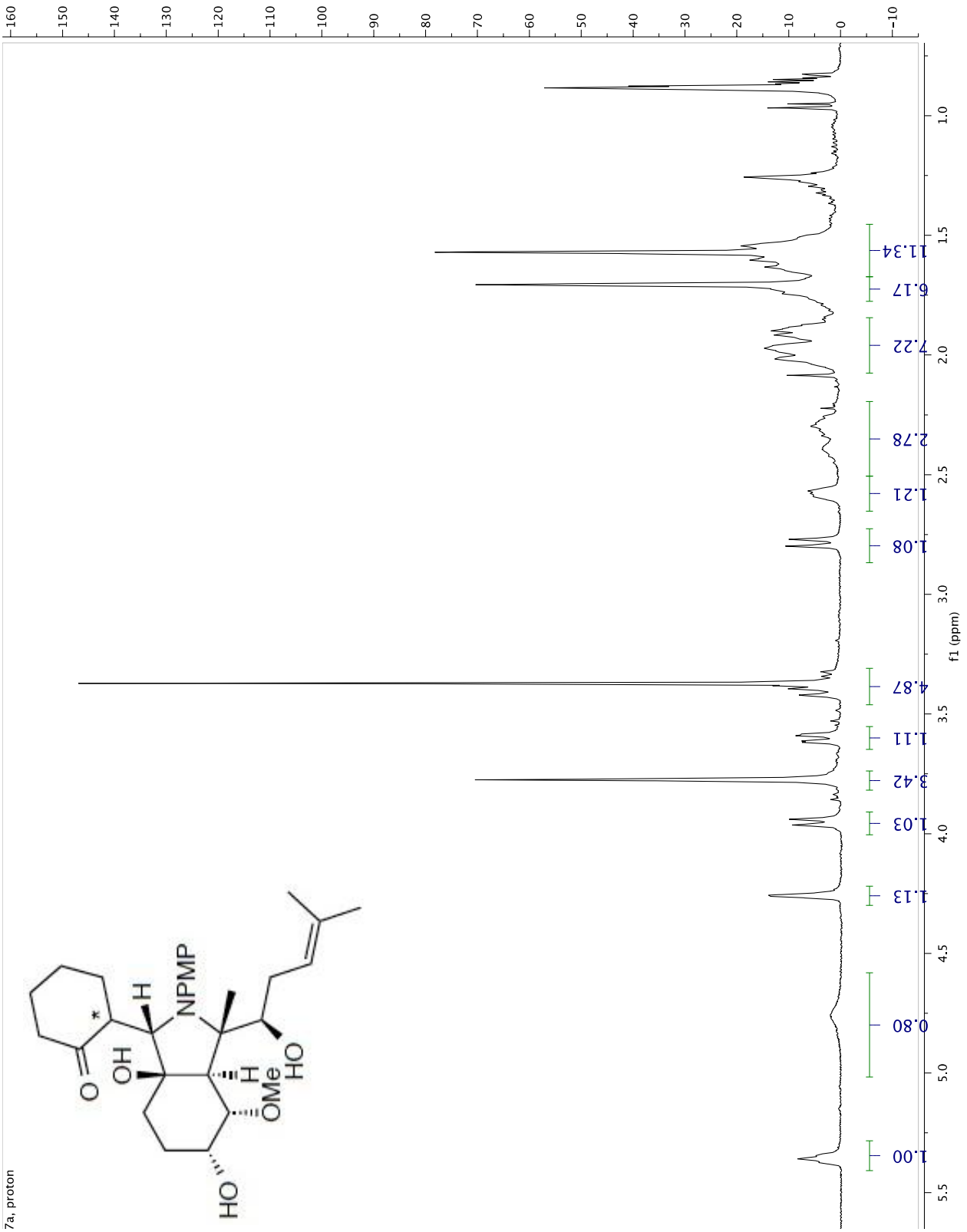

6a, proton
f1 (ppm)
1.88
2.02
1.23
1.14
3.43
1.22
1.18
1.32
3.34
1.05
0.97
1.71
5.17
3.81
1.29
3.33
3.08
3.05
2.99
2.74
0.95
2.00
2.00

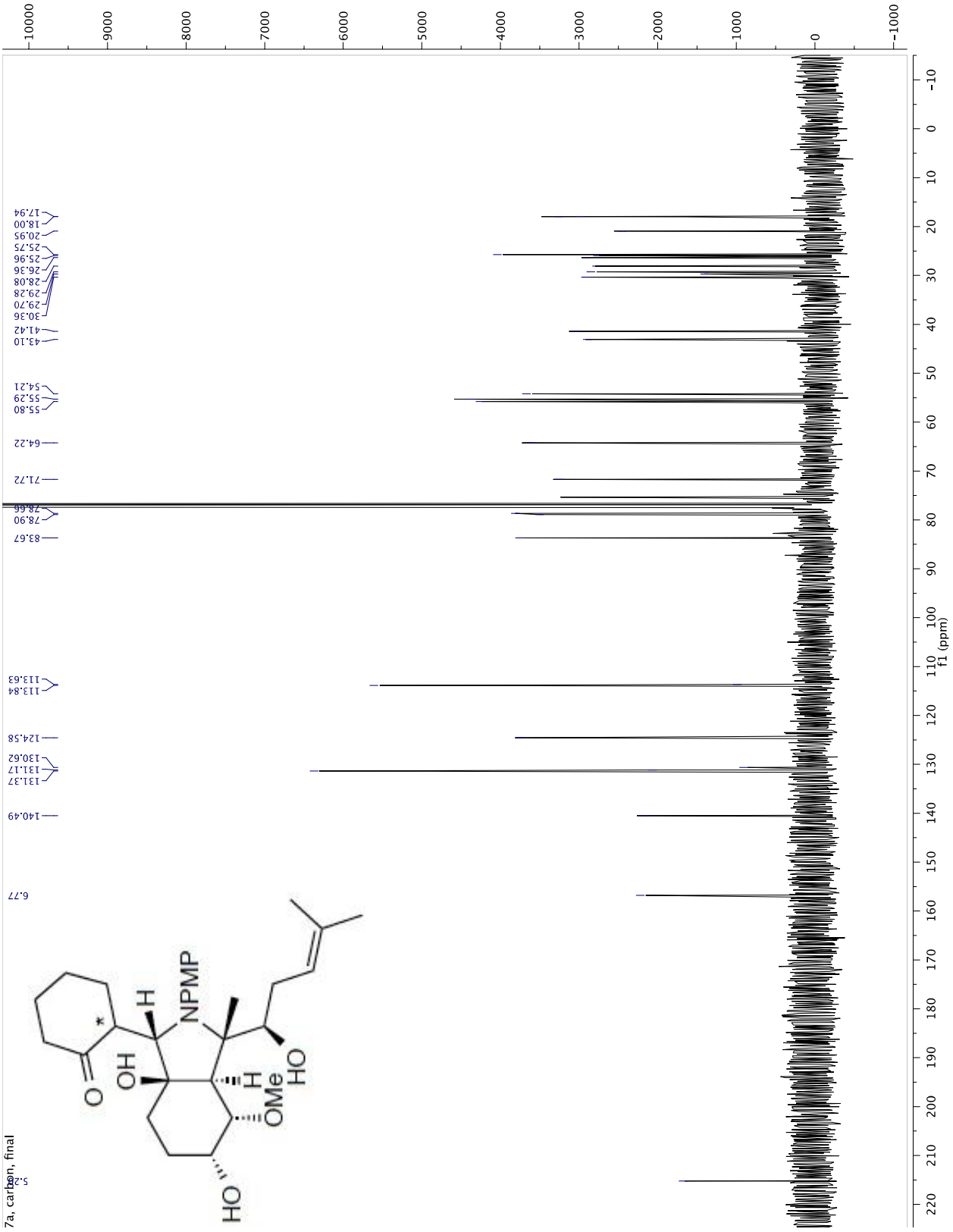

6a, carbon
f1 (ppm)
16.06
16.12
16.32
16.38
17.38
17.40
18.00
25.83
26.10
29.32
30.27
45.11
55.31
55.88
61.51
61.57
62.37
62.45
64.36
72.39
72.43
73.88
75.49
77.85
78.85
81.44
81.58
113.49
124.02
131.36
131.86
139.68
139.71
157.12
OMe
OEt
OEt
O
P
OH
N
H
OMe
HO
HO

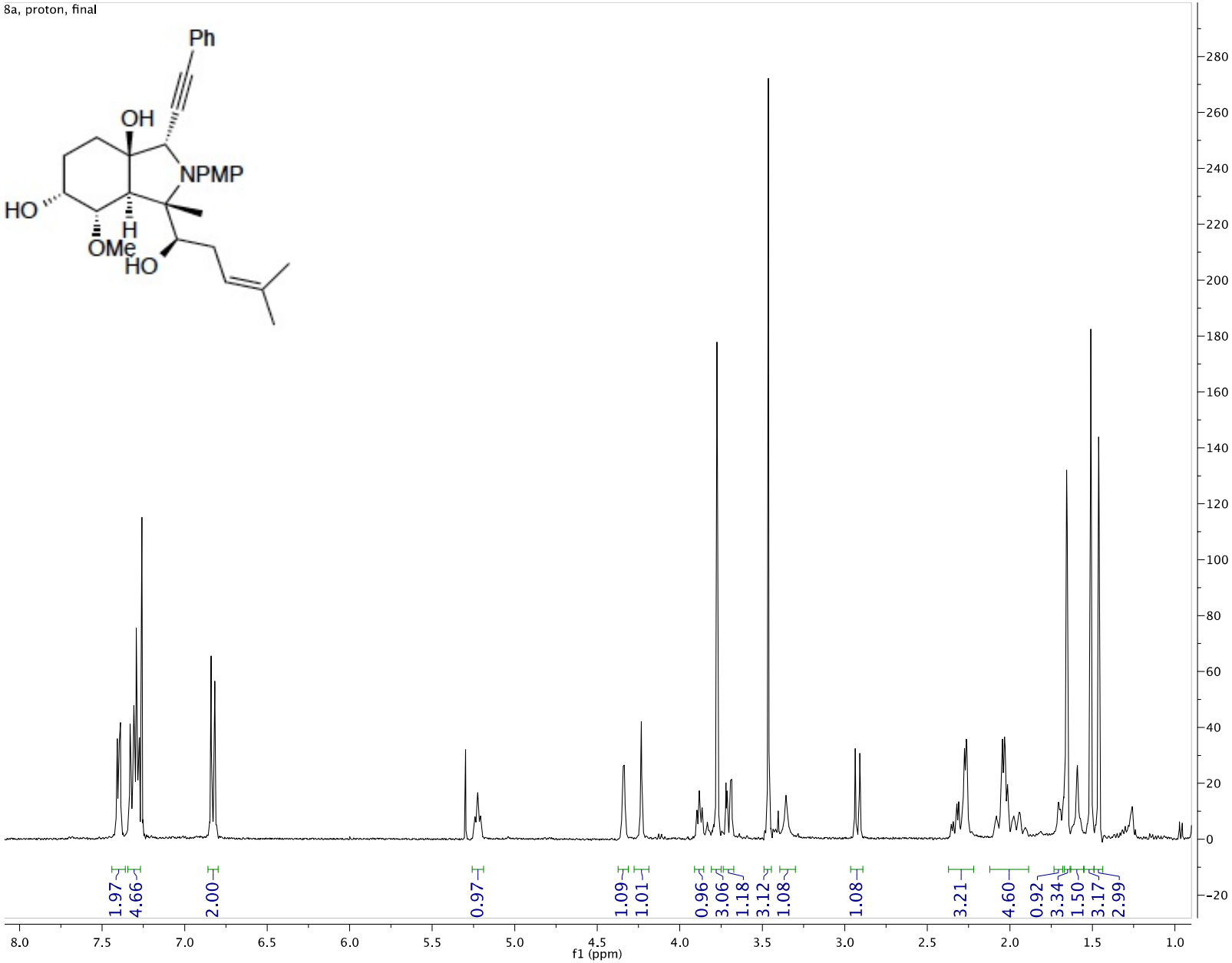
COSY analysis of **6a**

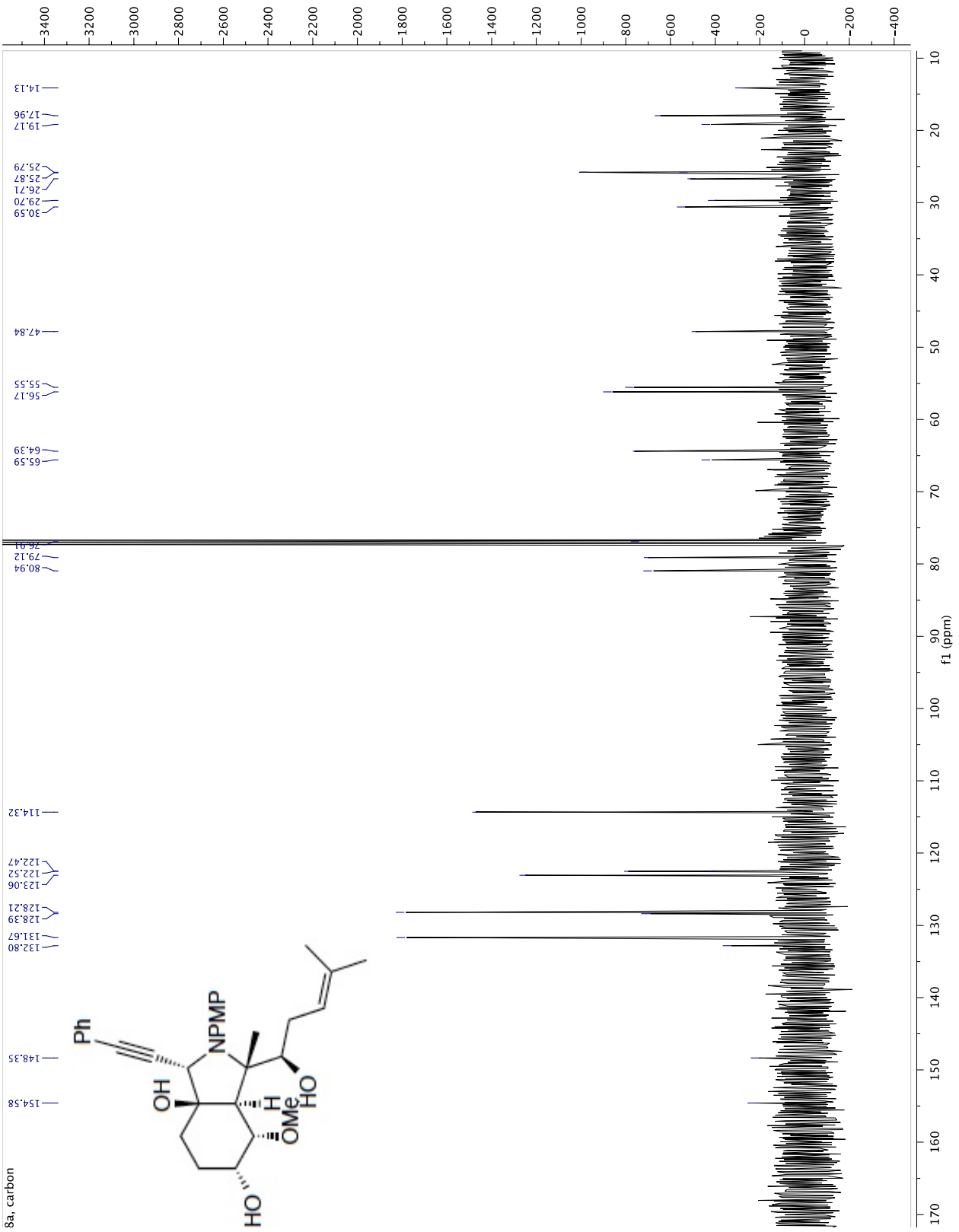


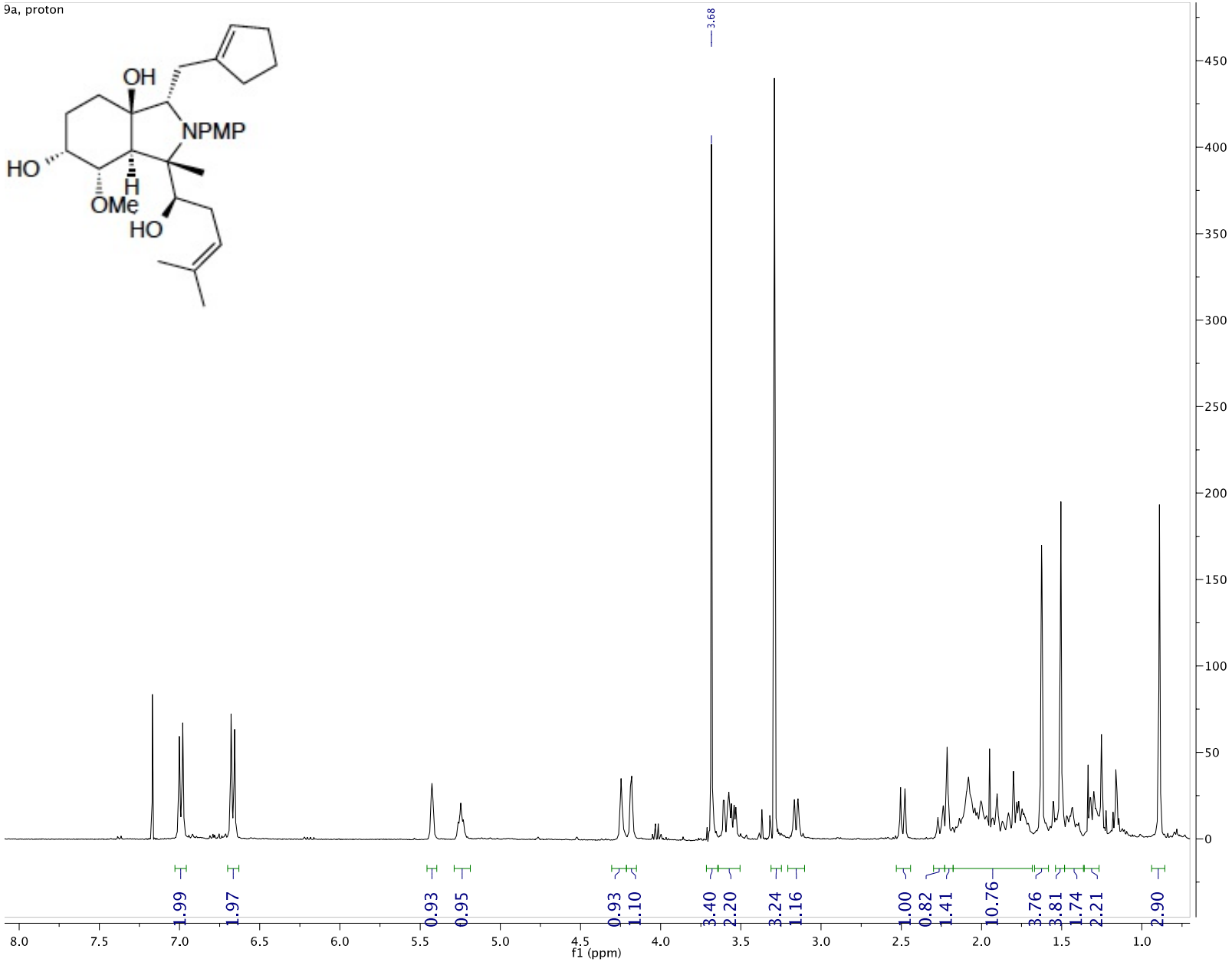
7a: The α-ketone stereocenter could not be unambiguously assigned by ^{1}H NMR and NOE analysis due to free rotation.

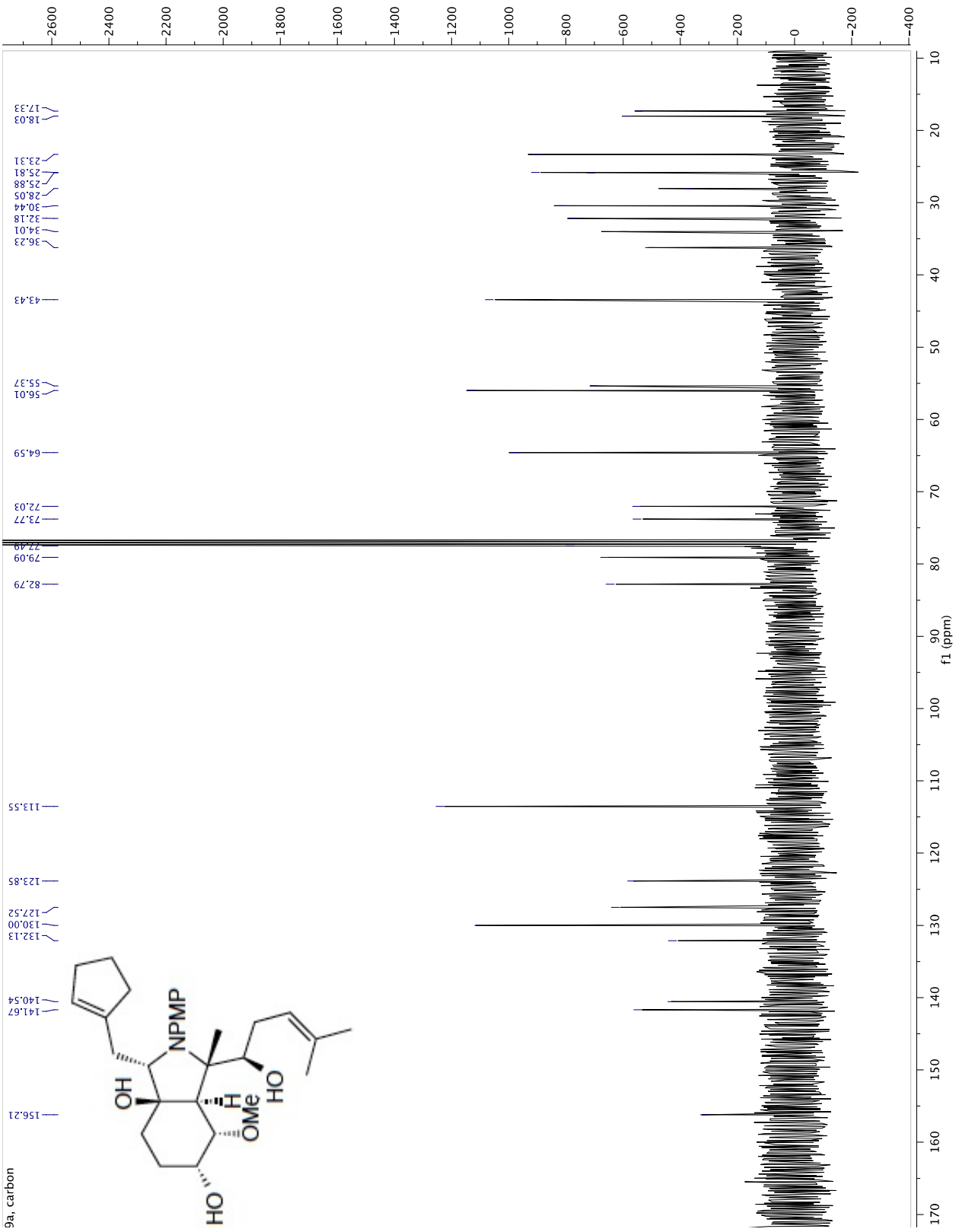



7a, carbon, final
f1 (ppm)
NPMP
OH
H
OMe
HO
O
HO

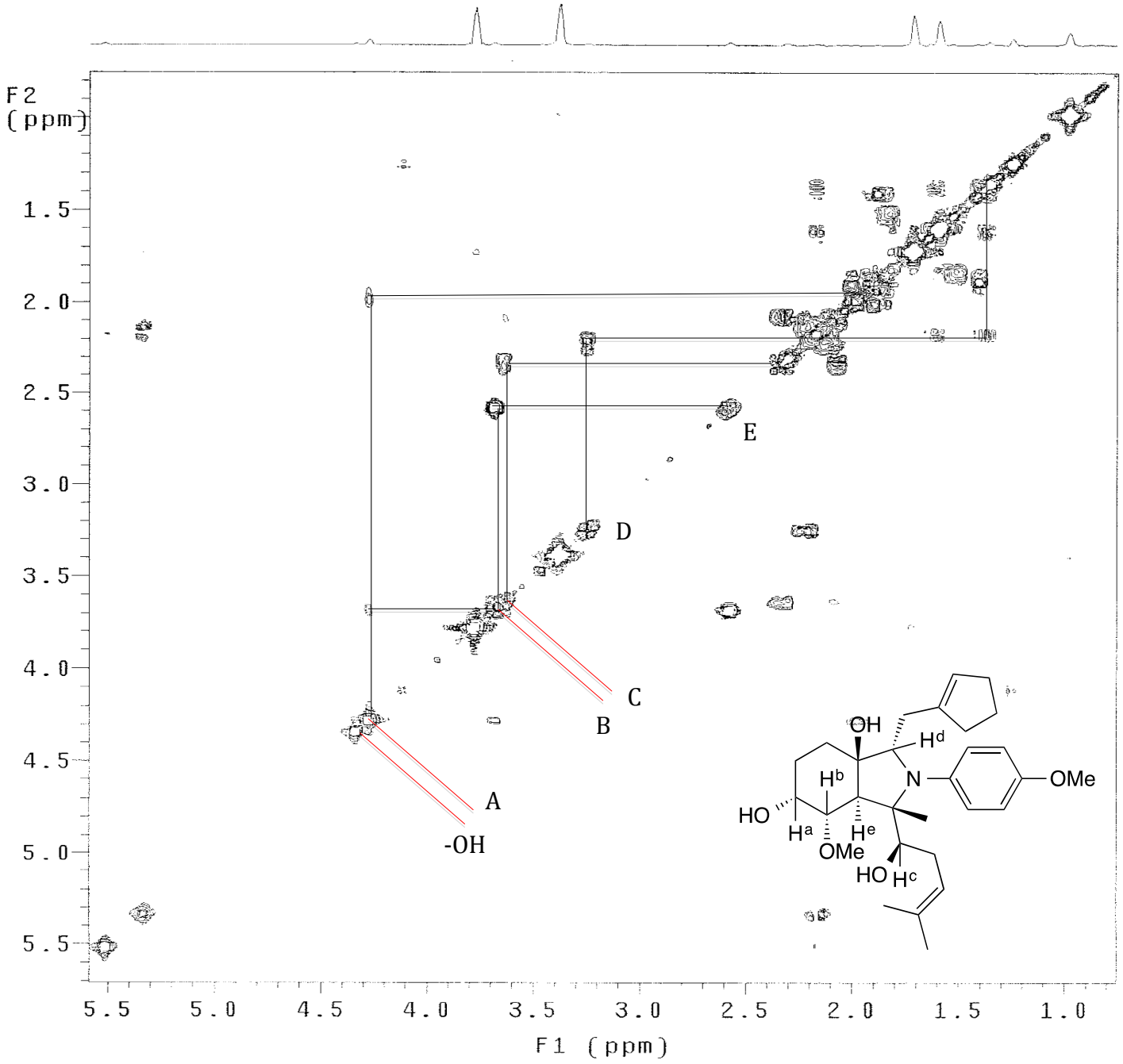

8a, proton, final
Ph
OH
NPMP
HO
H
OMe
HO
1.97
4.66
2.00
0.97
1.09
1.01
0.96
3.06
1.18
3.12
1.08
1.08
3.21
4.60
0.92
3.34
1.50
3.17
2.99
f1 (ppm)

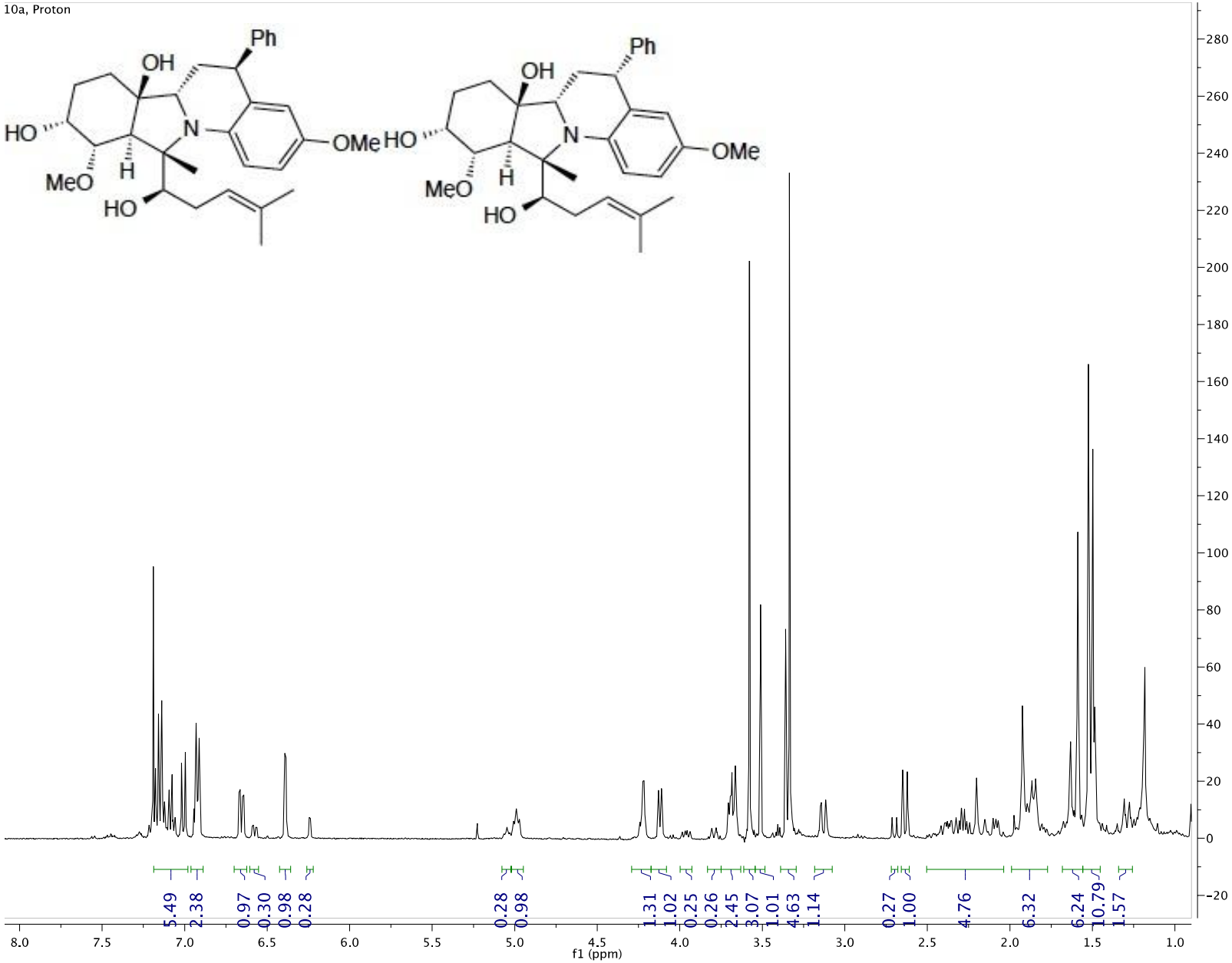

8a, carbon
f1 (ppm)
Ph
NPMP
OH
HO
H
OMe
HO
14.13
17.96
19.17
25.79
25.87
26.71
29.70
30.59
47.84
55.55
56.17
64.39
65.59
76.91
79.12
80.94
114.32
122.47
122.52
123.06
128.21
128.39
131.67
132.80
148.35
154.58

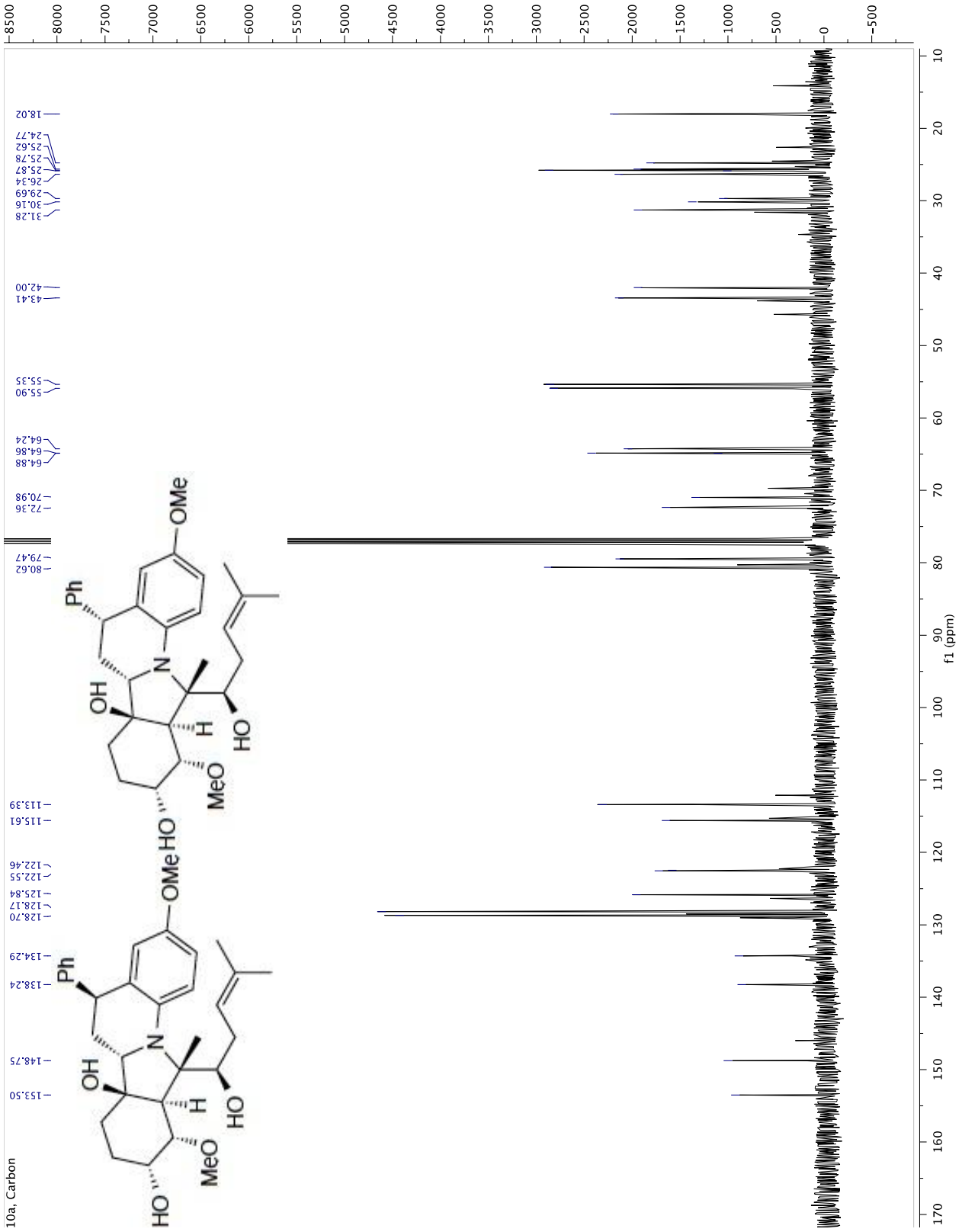

9a, proton
OH
NPMP
HO
H
OMe
HO
3.68
450
400
350
300
250
200
150
100
50
0
1.99
1.97
0.93
0.95
0.93
1.10
3.40
2.20
3.24
1.16
1.00
0.82
1.41
10.76
3.76
3.81
1.74
2.21
2.90
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
f1 (ppm)

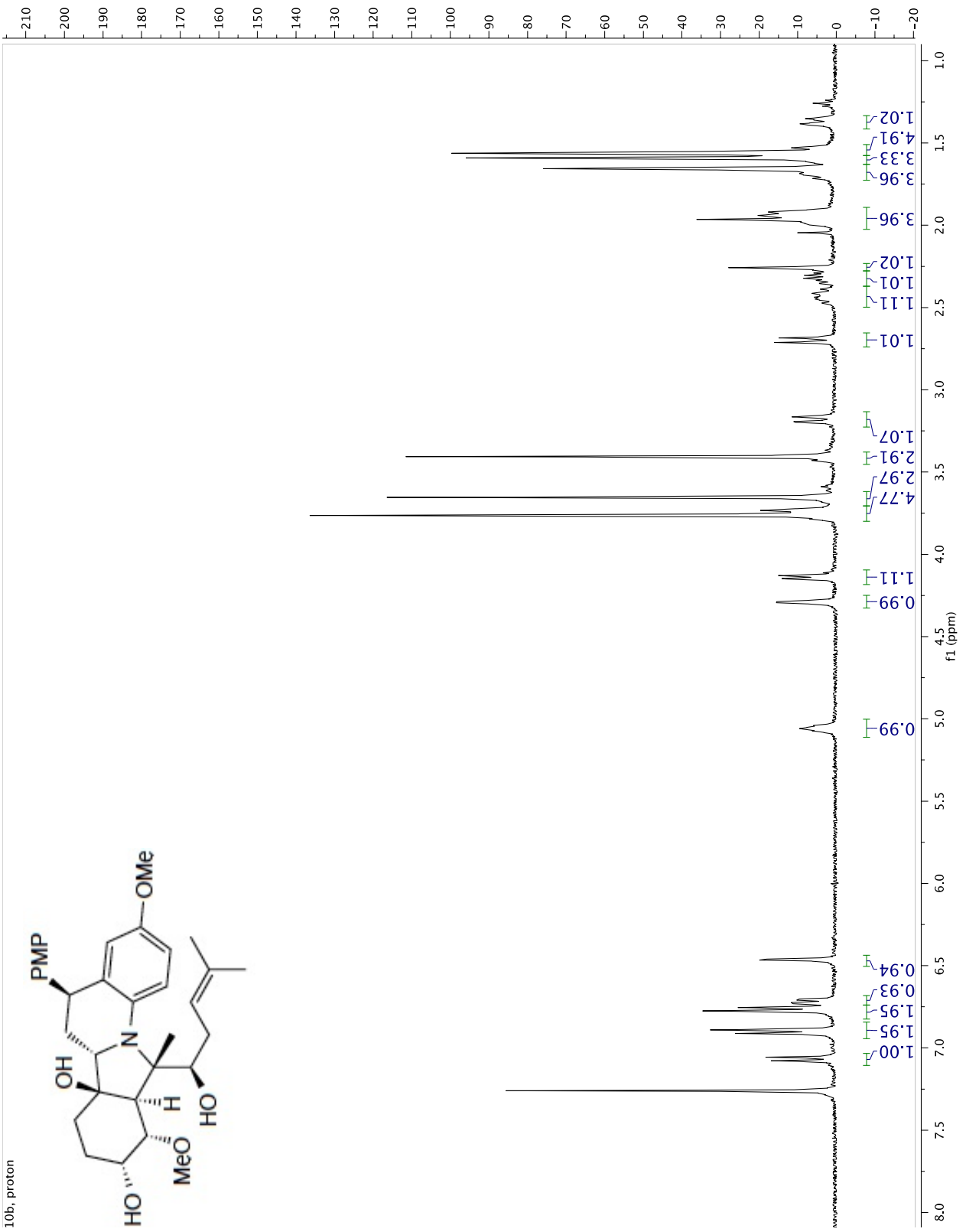

17.33
18.03
23.31
25.81
25.88
28.05
30.44
32.18
34.01
36.23
43.43
55.37
56.01
64.59
72.03
73.77
77.49
79.09
82.79
113.55
123.85
127.52
130.00
132.13
140.54
141.67
156.21
NPMP
OH
H
OMe
HO
HO
f1 (ppm)
9a, carbon

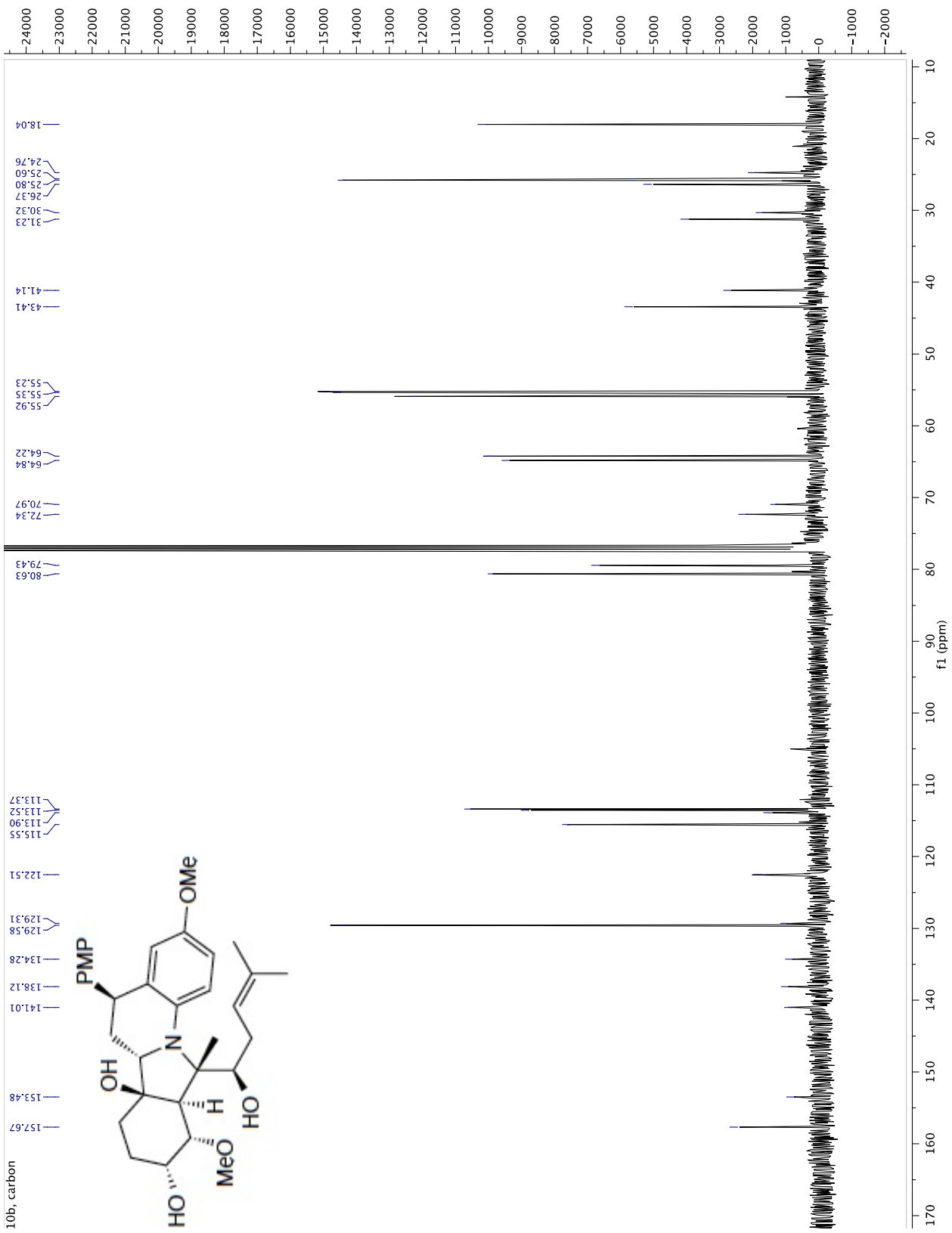
COSY analysis of **9a**

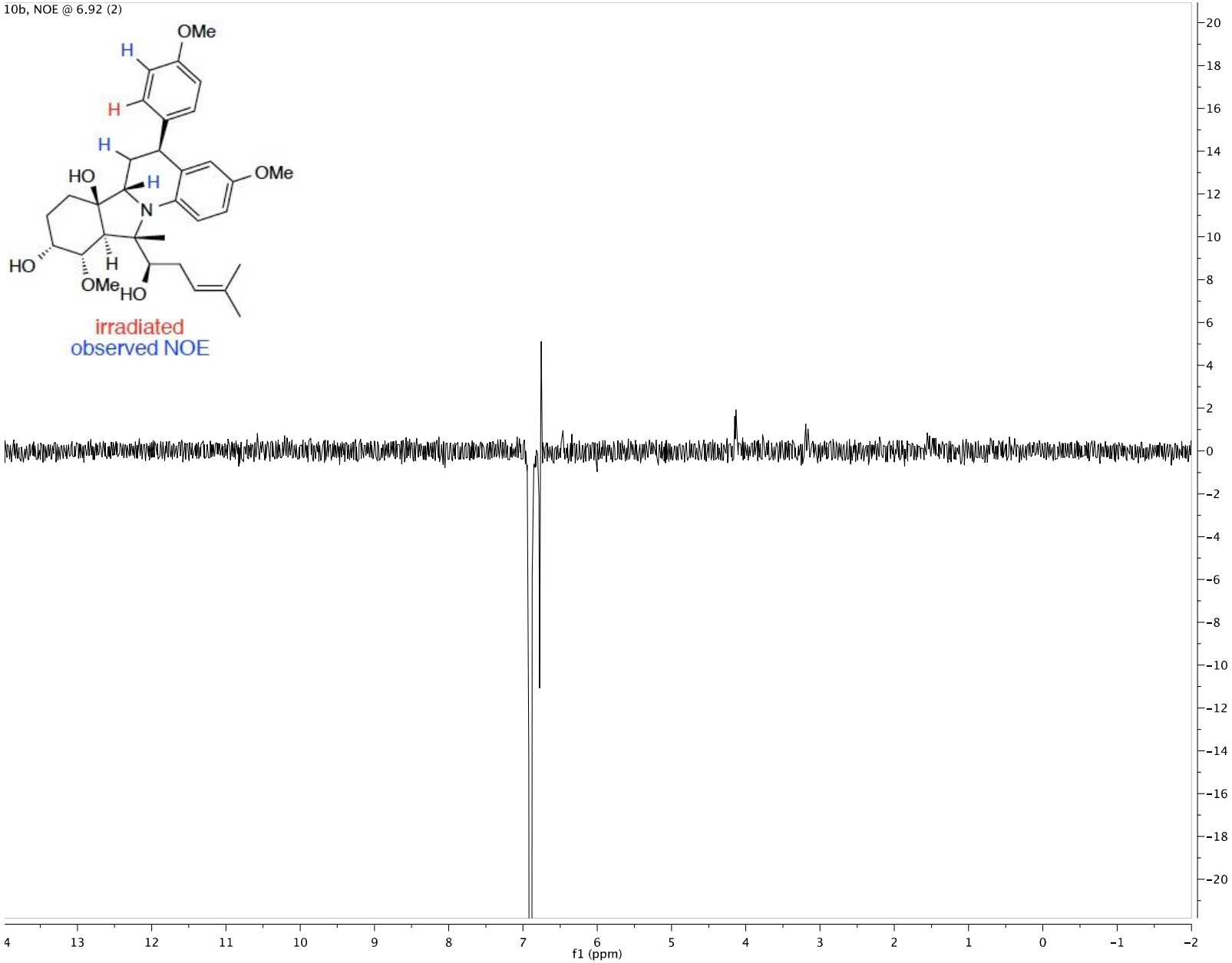


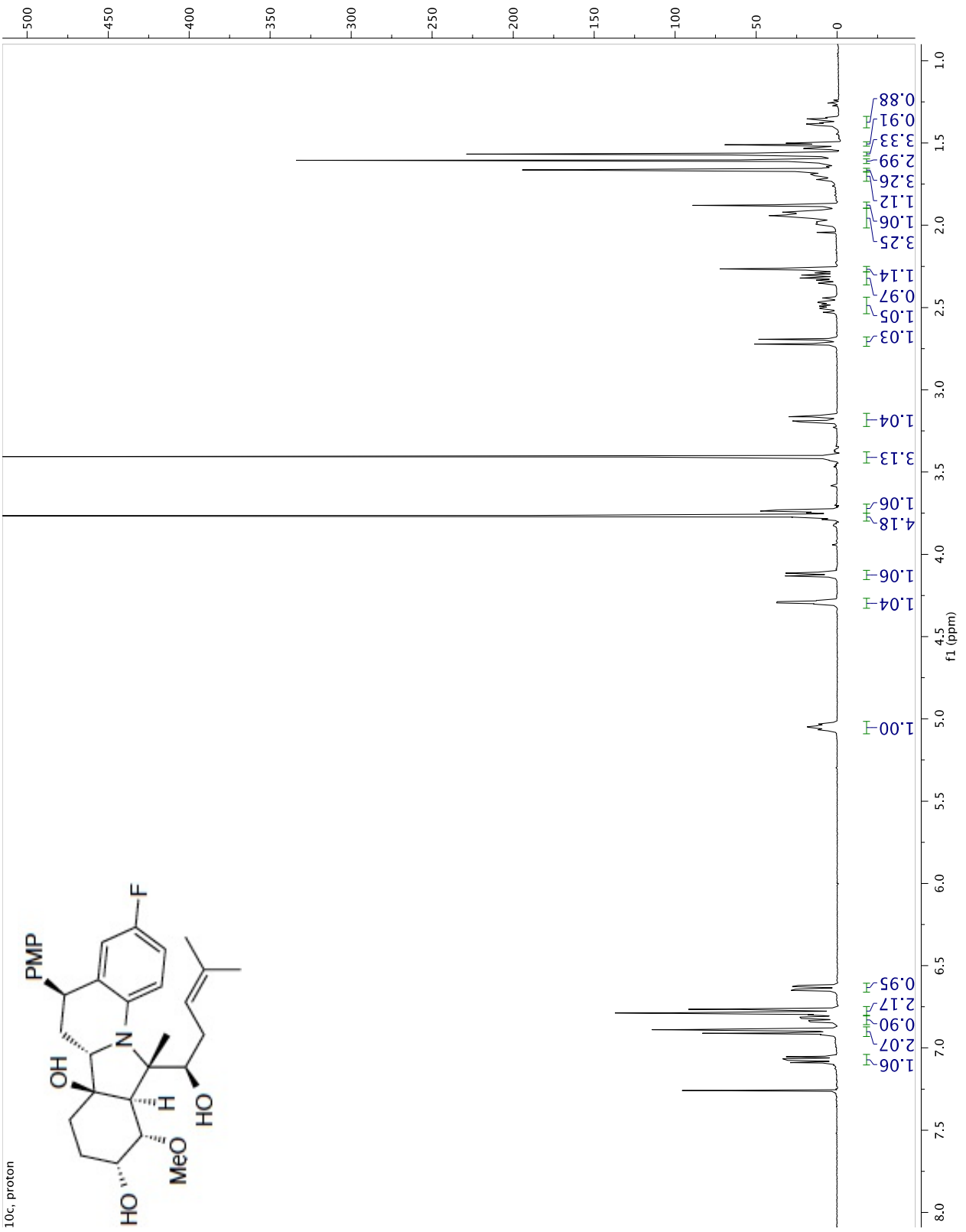

10a, Proton
Ph
OH
HO
N
OMe
MeO
H
HO
Ph
OH
HO
N
OMe
MeO
H
HO
5.49
2.38
0.97
0.30
0.98
0.28
0.28
0.98
1.31
1.02
0.25
0.26
2.45
3.07
1.01
4.63
1.14
0.27
1.00
4.76
6.32
6.24
10.79
1.57
f1 (ppm)

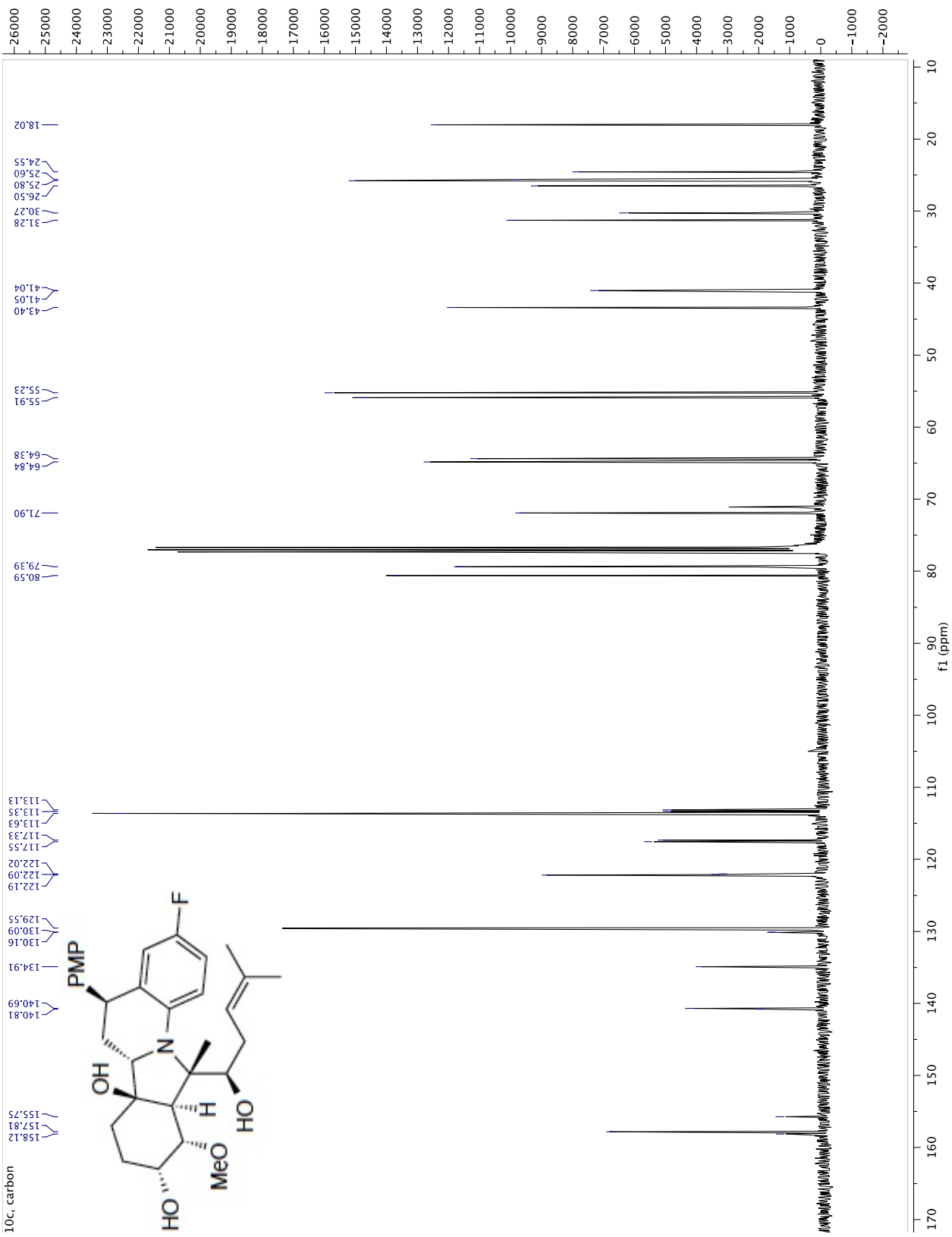

10a, Carbon
f1 (ppm)
18.02
24.77
25.62
25.78
25.87
26.34
29.69
30.16
31.28
42.00
43.41
55.35
55.90
64.24
64.86
64.88
70.98
72.36
79.47
80.62
113.39
115.61
122.46
122.55
125.84
128.17
128.70
134.29
138.24
148.75
153.50
OMe
HO
MeO
OH
N
H
Ph


10b, proton
PMP
OMe
N
OH
H
HO
MeO
HO
f1 (ppm)

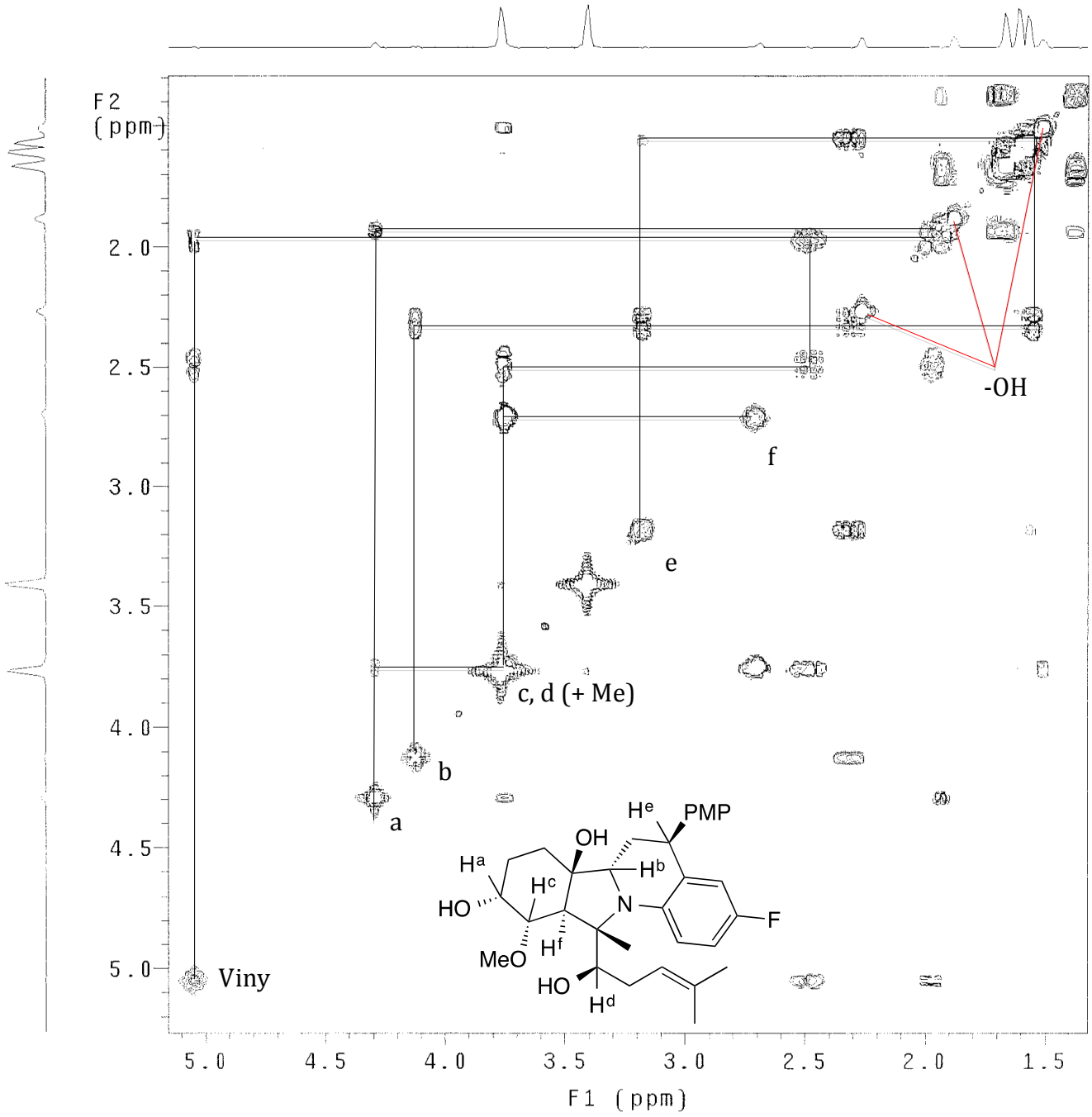

10b, carbon
18.04
24.76
25.60
25.80
26.37
30.32
31.23
41.14
43.41
55.23
55.35
55.92
64.22
64.84
70.97
72.34
79.43
80.63
113.37
113.52
113.90
115.55
122.51
129.31
129.58
134.28
138.12
141.01
153.48
157.67
PMP
OMe
OH
N
H
HO
MeO
HO
f1 (ppm)

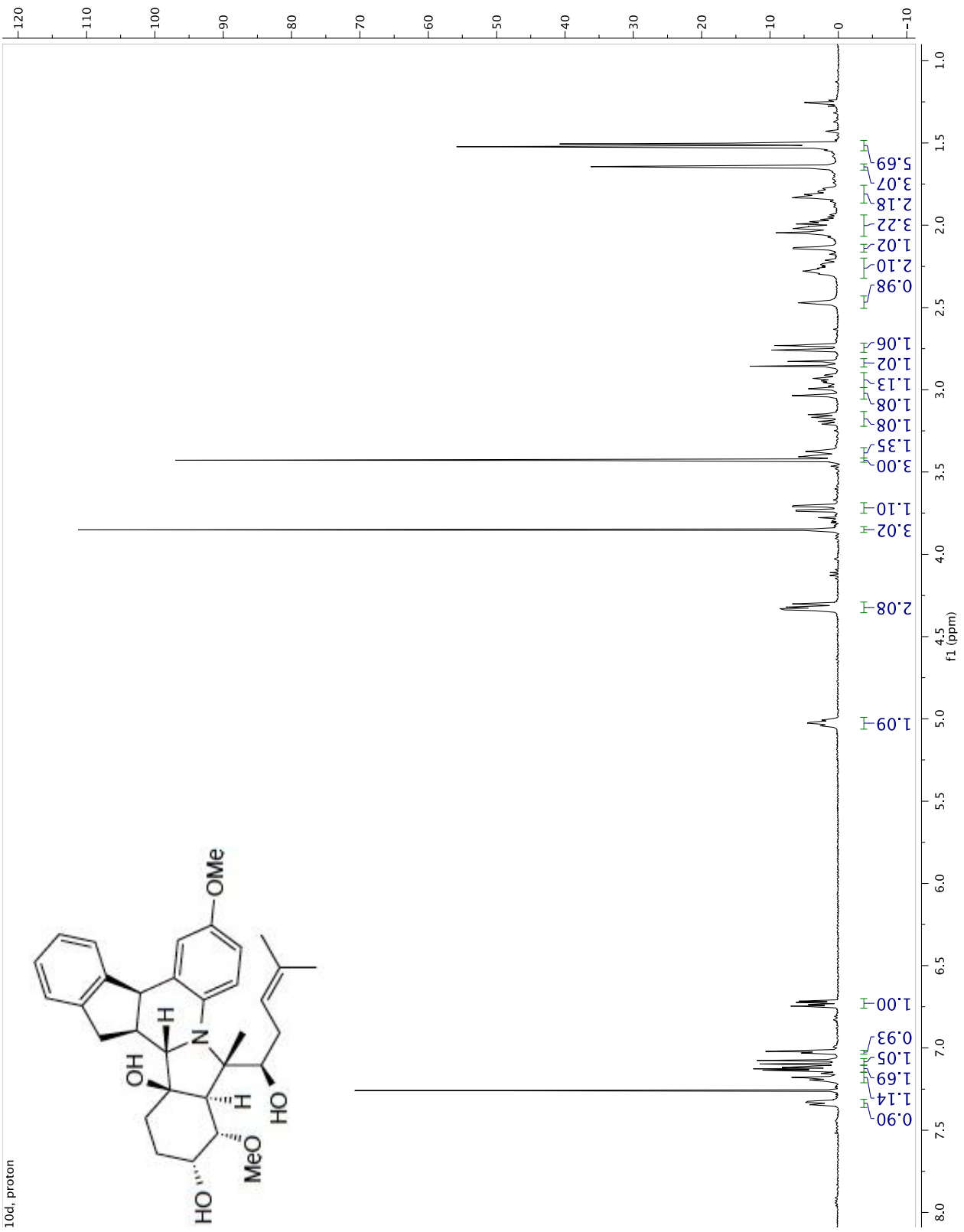

10b, NOE @ 6.92 (2)
OMe
H
H
H
HO
H
N
OMe
HO
H
OMe
HO
irradiated
observed NOE
20
18
16
14
12
10
8
6
4
2
0
-2
-4
-6
-8
-10
-12
-14
-16
-18
-20
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
-2
f1 (ppm)

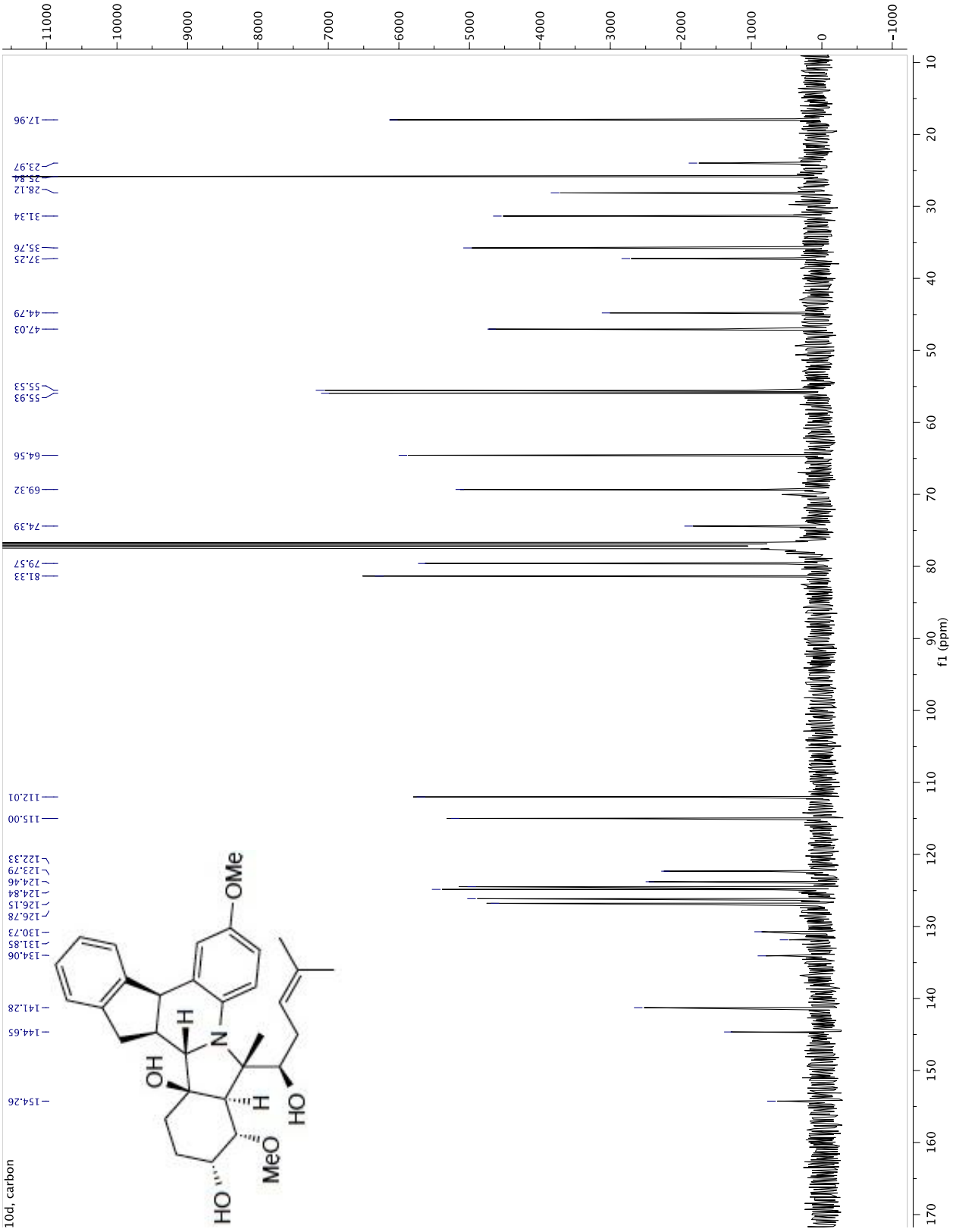

10c, proton
PMP
F
N
OH
H
HO
MeO
HO
f1 (ppm)
0.88
0.91
3.33
2.99
3.26
1.12
1.06
3.25
1.14
0.97
1.05
1.03
1.04
3.13
1.06
4.18
1.06
1.04
1.00
0.95
2.17
0.90
2.07
1.06


10c, carbon
18.02
24.55
25.60
25.80
26.50
30.27
31.28
41.04
41.05
43.40
55.23
55.91
64.38
64.84
71.90
79.39
80.59
113.13
113.35
113.63
117.33
117.55
122.02
122.09
122.19
129.55
130.09
130.16
134.91
140.69
140.81
155.75
157.81
158.12
PMP
F
OH
N
H
HO
MeO
HO
f1 (ppm)

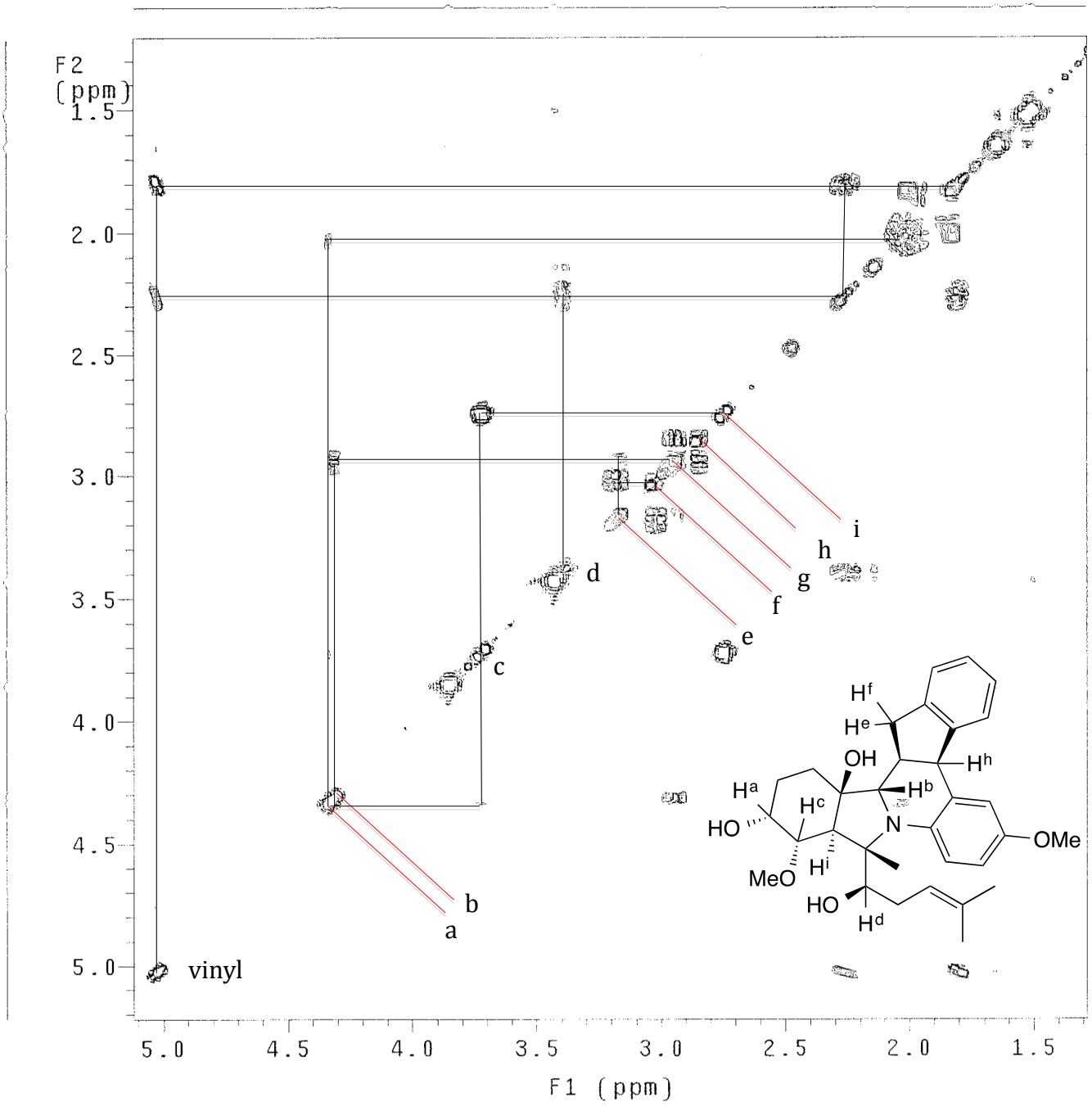
COSY analysis of **10c**

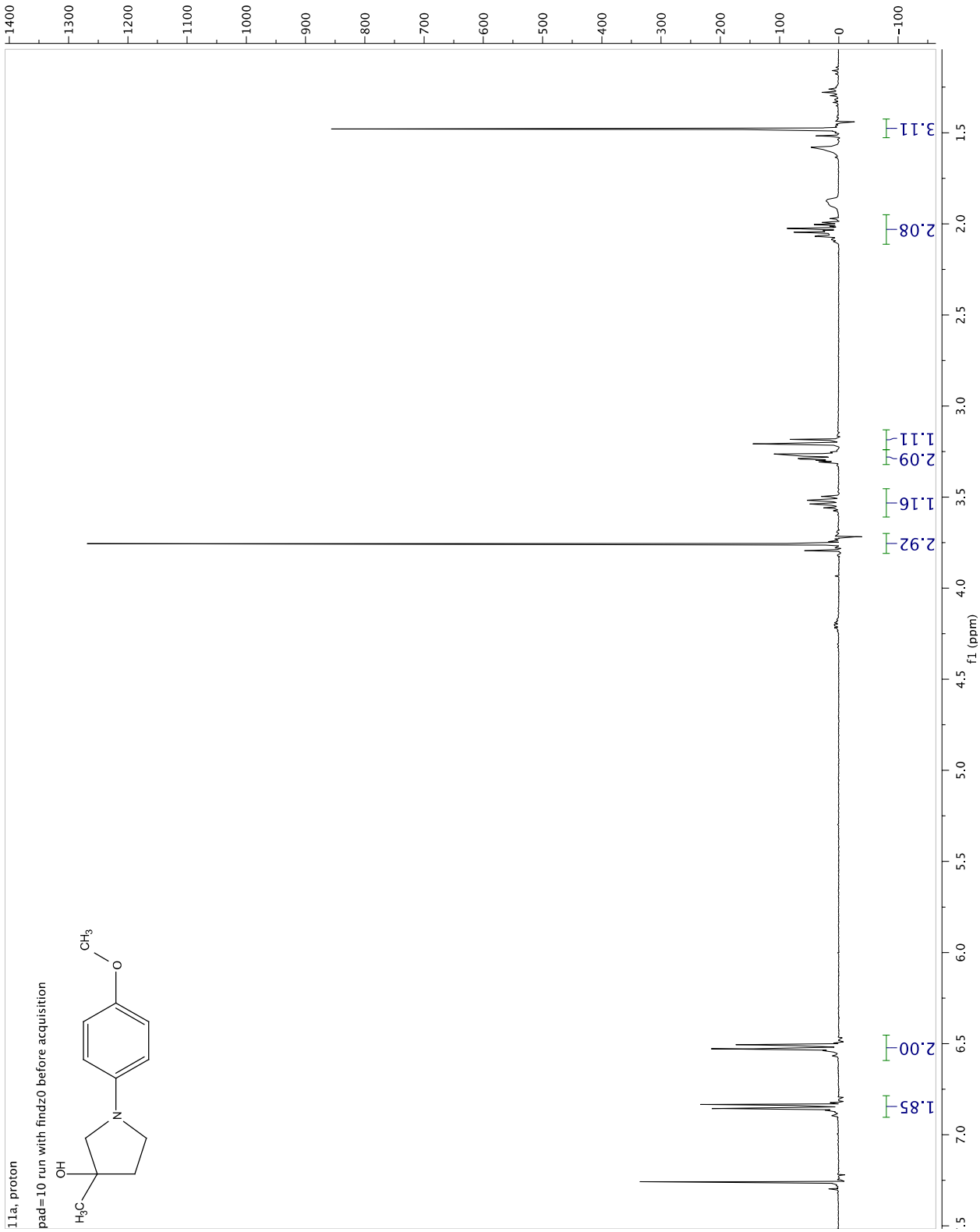


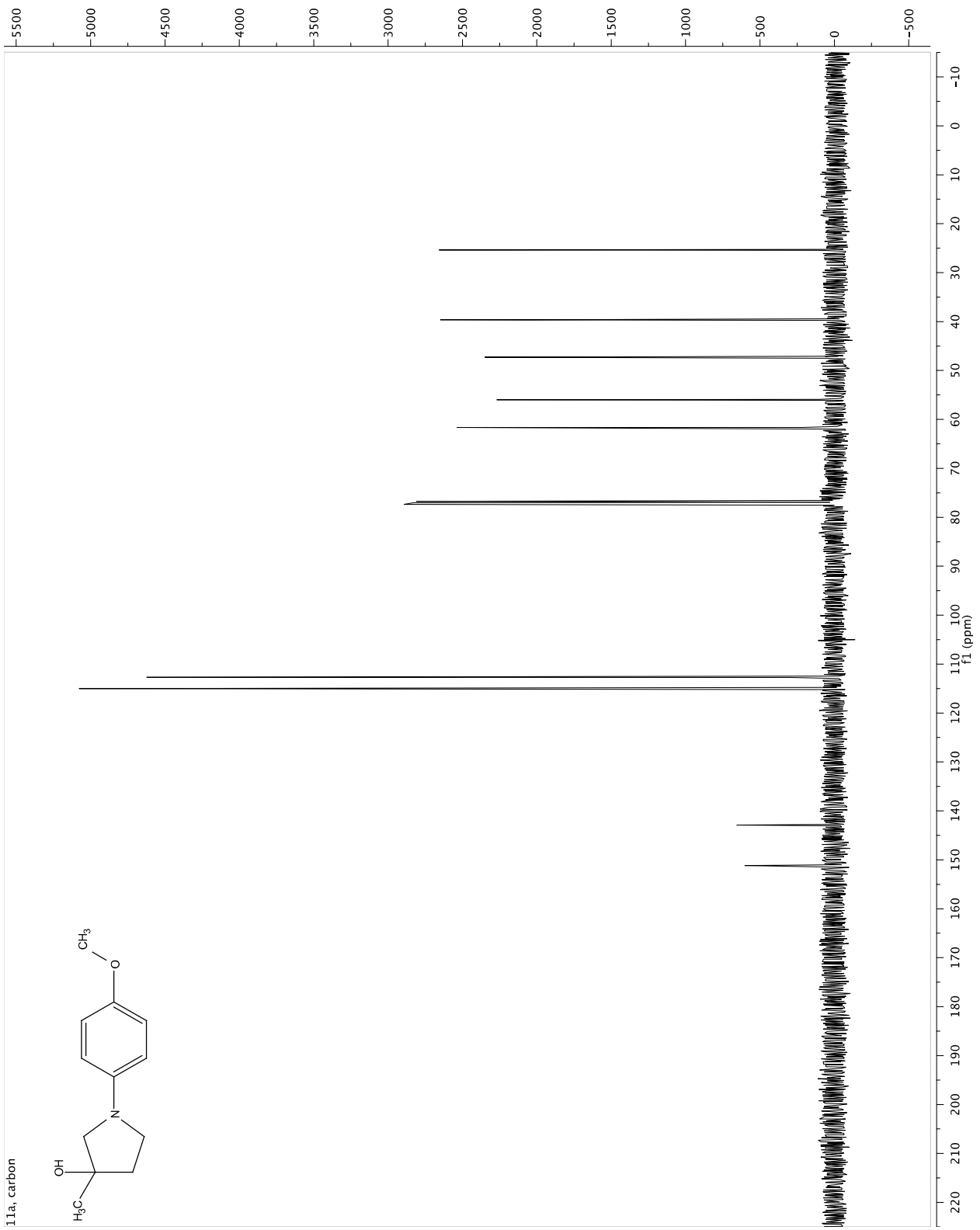

10d, proton
OMe
OH
H
N
H
HO
MeO
HO
0.90
1.14
1.69
1.05
0.93
1.00
2.08
1.09
3.02
1.10
3.00
1.35
1.08
1.08
1.13
1.02
1.06
0.98
2.10
1.02
3.22
2.18
3.07
5.69
f1 (ppm)

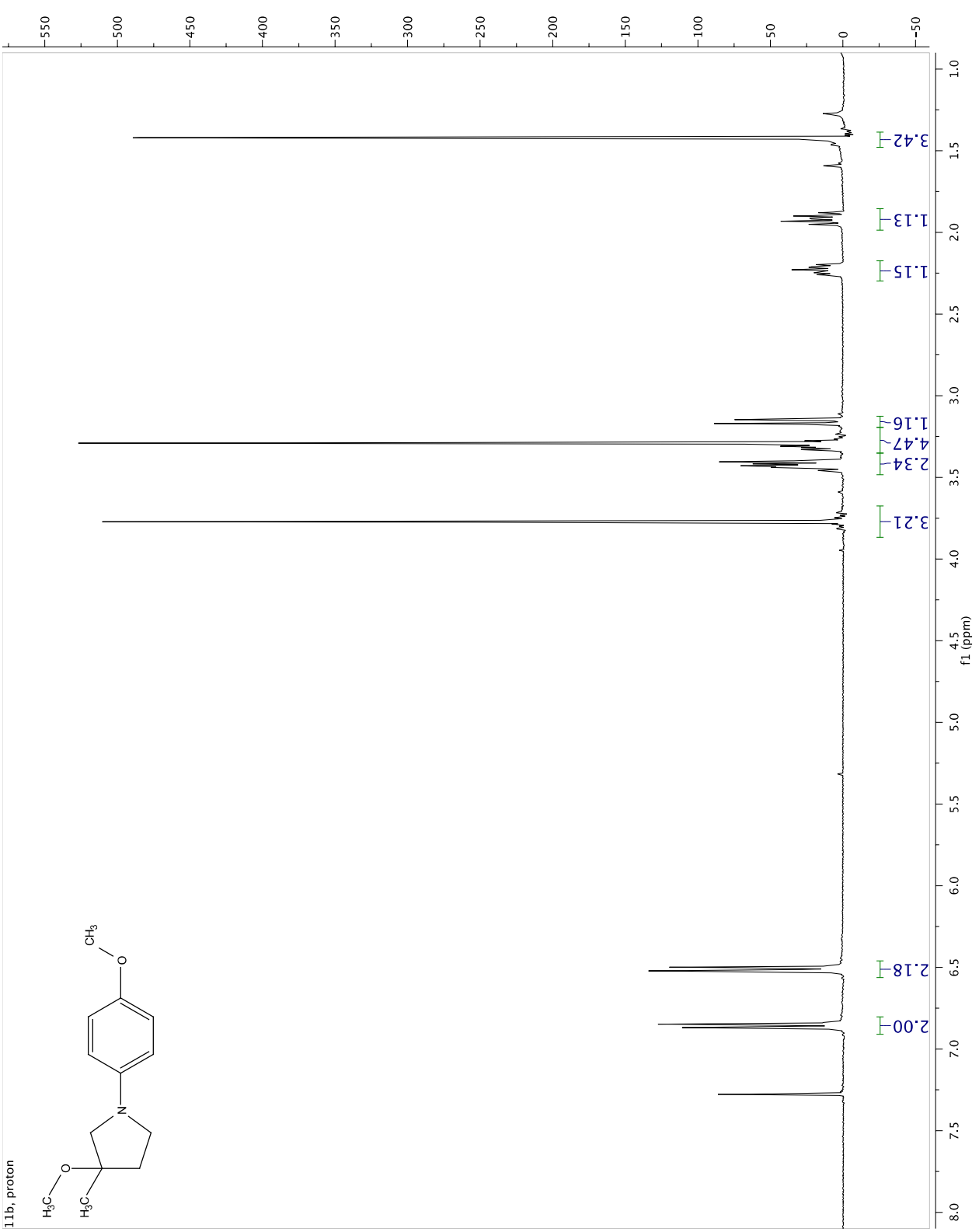

10d, carbon
17.96
23.97
25.84
28.12
31.34
35.76
37.25
44.79
47.03
55.53
55.93
64.56
69.32
74.39
79.57
81.33
112.01
115.00
122.33
123.79
124.46
124.84
126.15
126.78
130.73
131.85
134.06
141.28
144.65
154.26
OMe
OH
H
N
HO
H
HO
MeO
HO
f1 (ppm)

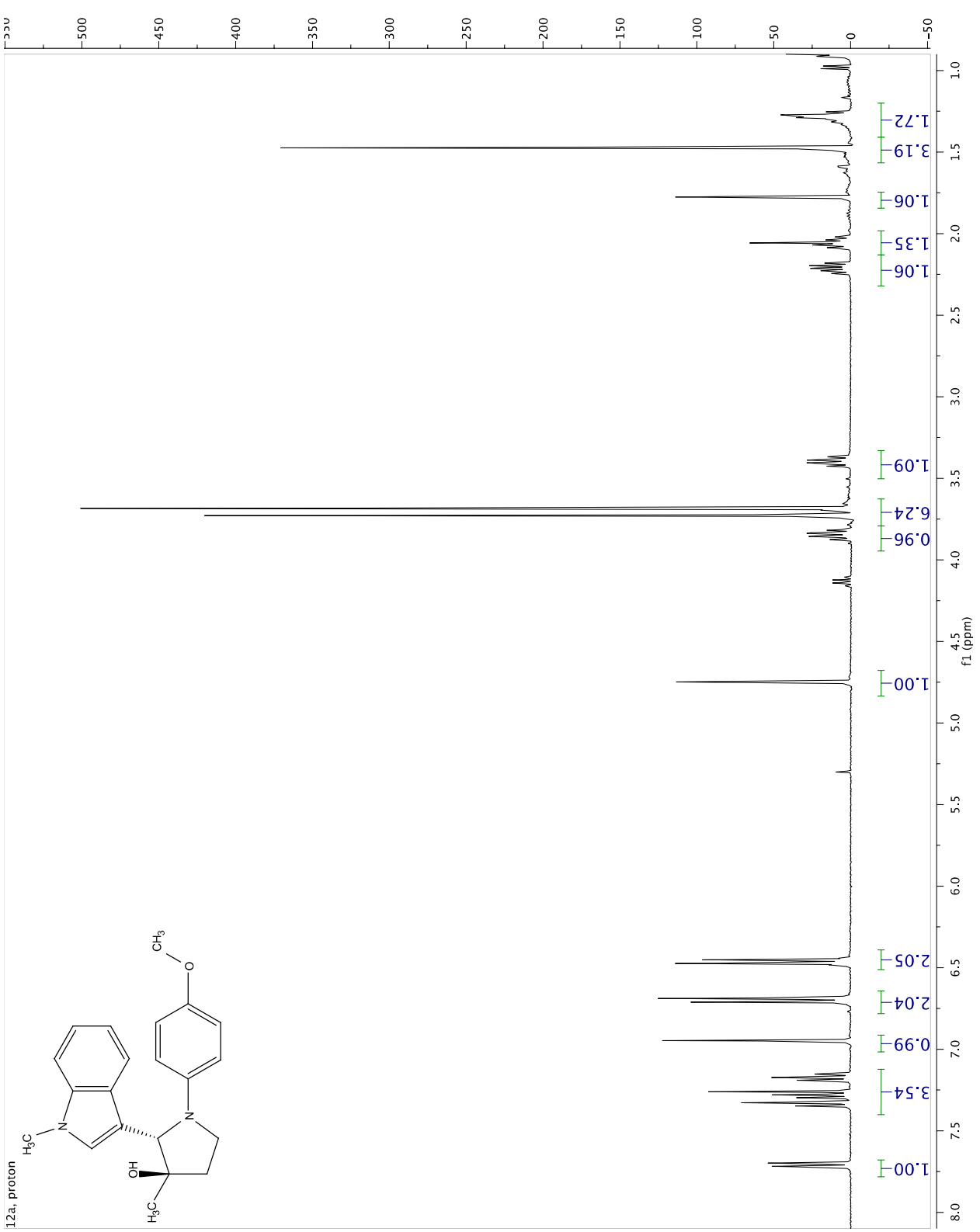
COSY analysis of **10d**

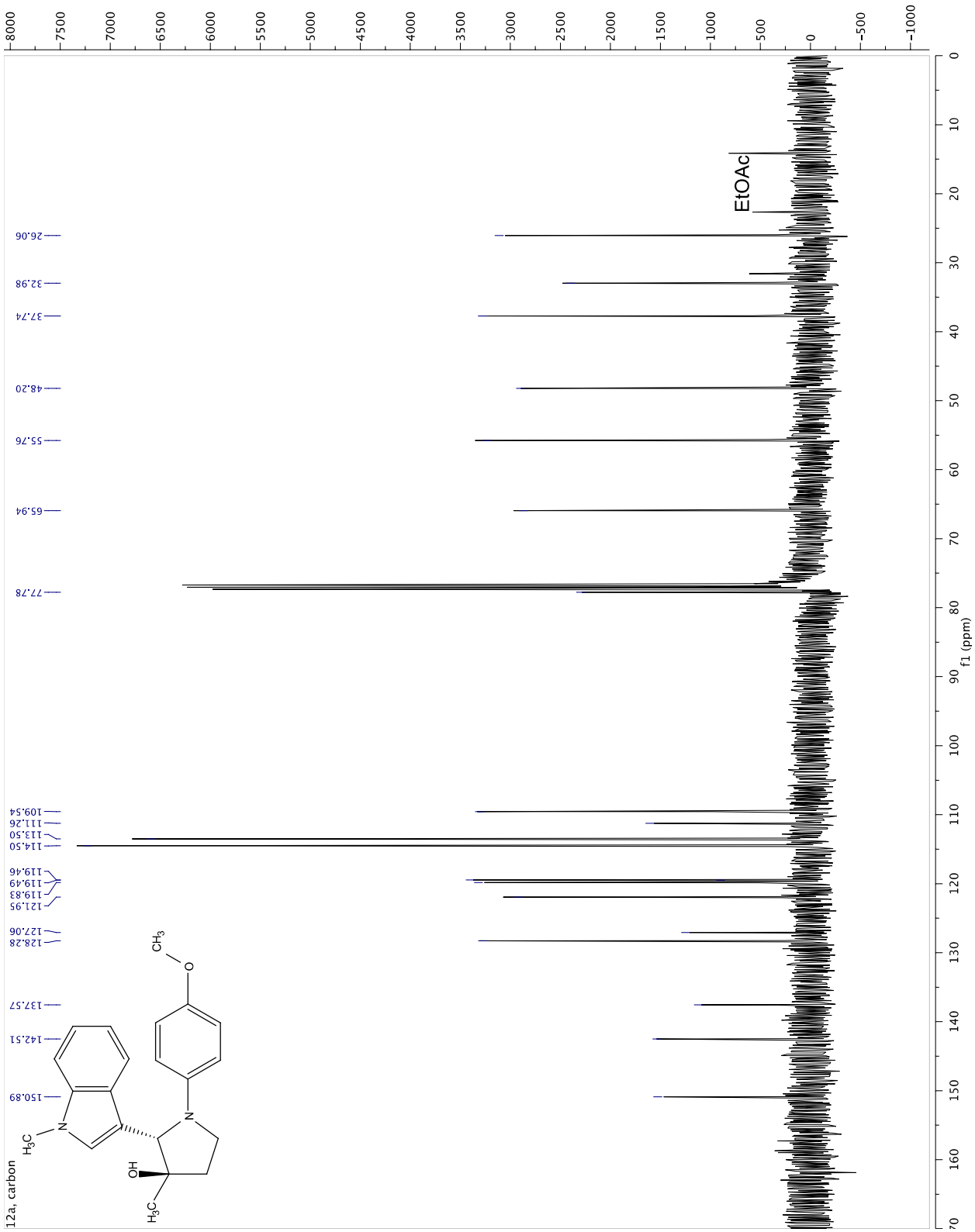



11a, proton
pad=10 run with findz0 before acquisition
f1 (ppm)
3.11
2.08
1.11
2.09
1.16
2.92
2.00
1.85

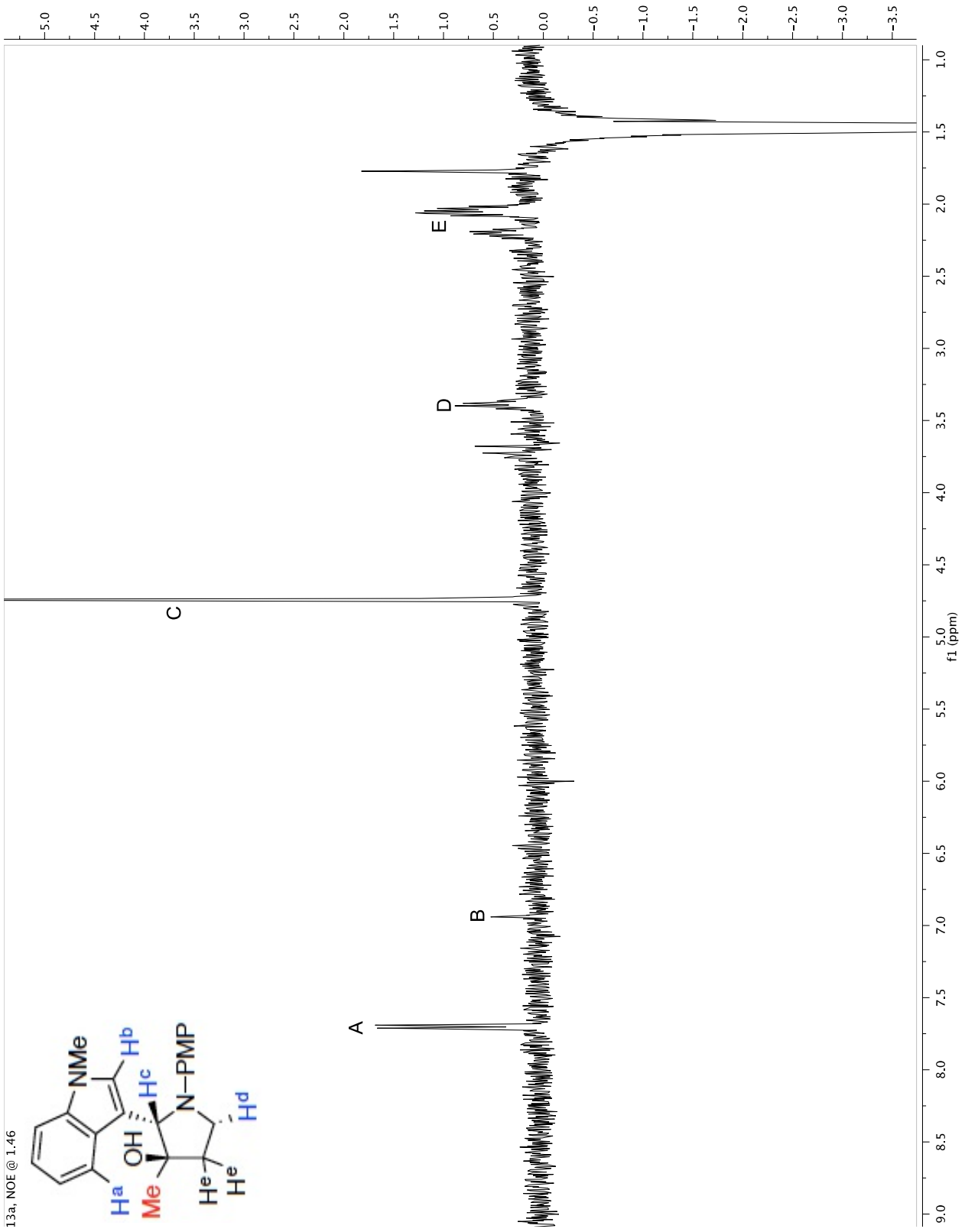

11a, carbon
f1 (ppm)


11b, proton
f1 (ppm)
3.42
1.13
1.15
1.16
4.47
2.34
3.21
2.18
2.00

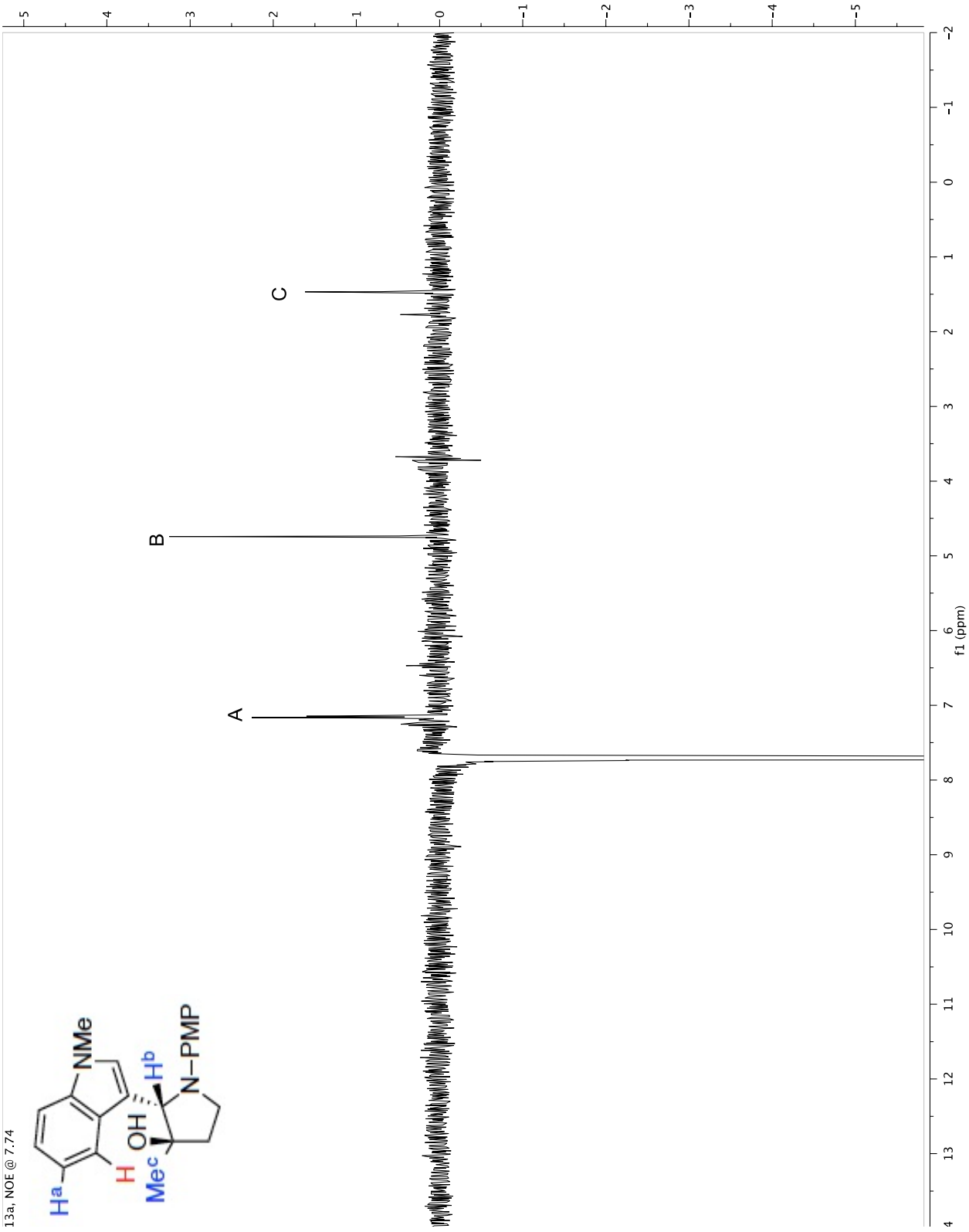

12a, proton
f1 (ppm)
1.72
3.19
1.06
1.35
1.06
1.09
6.24
0.96
1.00
2.05
2.04
0.99
3.54
1.00

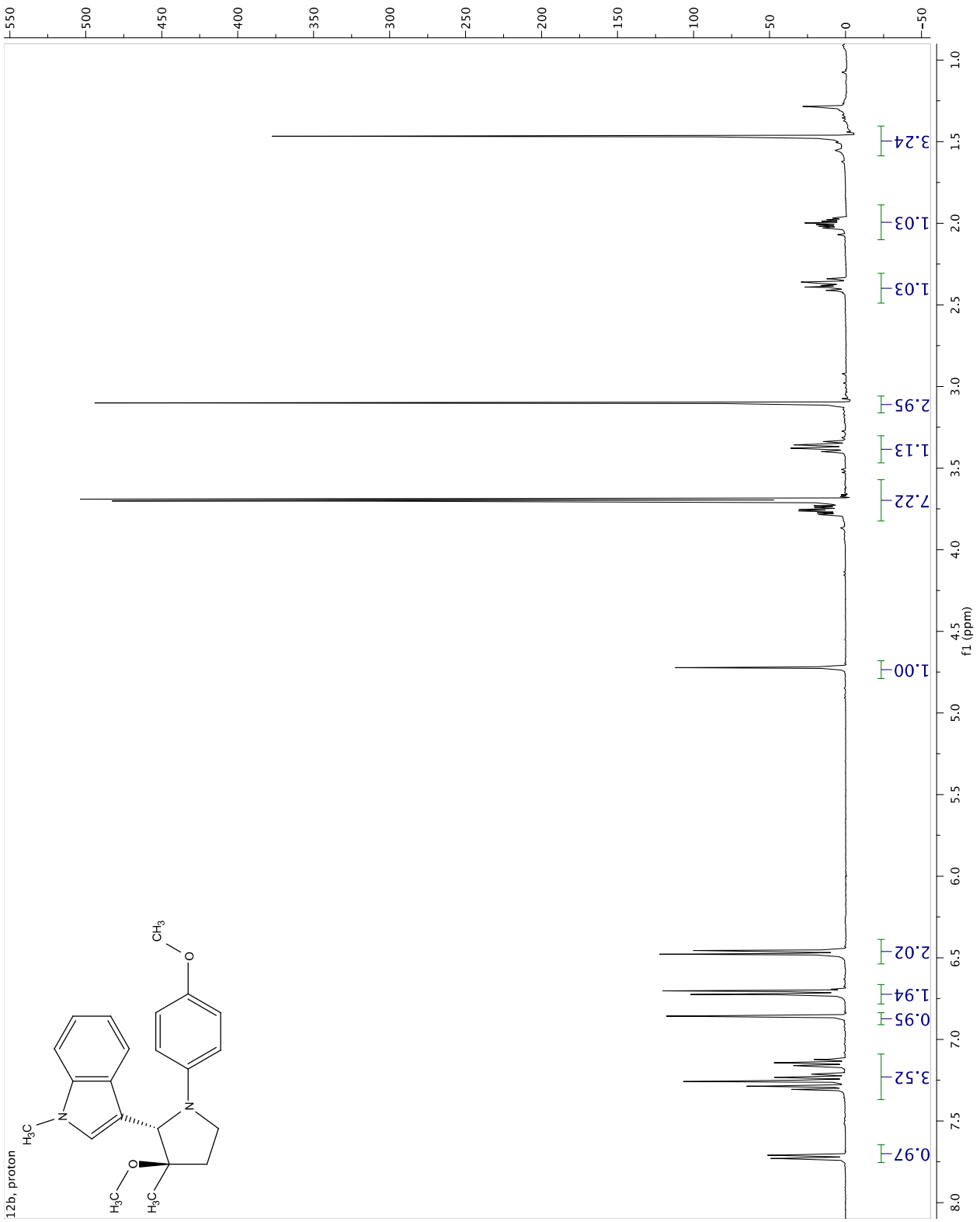

12a, carbon
EtOAc
f1 (ppm)
26.06
32.98
37.74
48.20
55.76
65.94
77.78
109.54
111.26
113.50
114.50
119.46
119.49
119.83
121.95
127.06
128.28
137.57
142.51
150.89

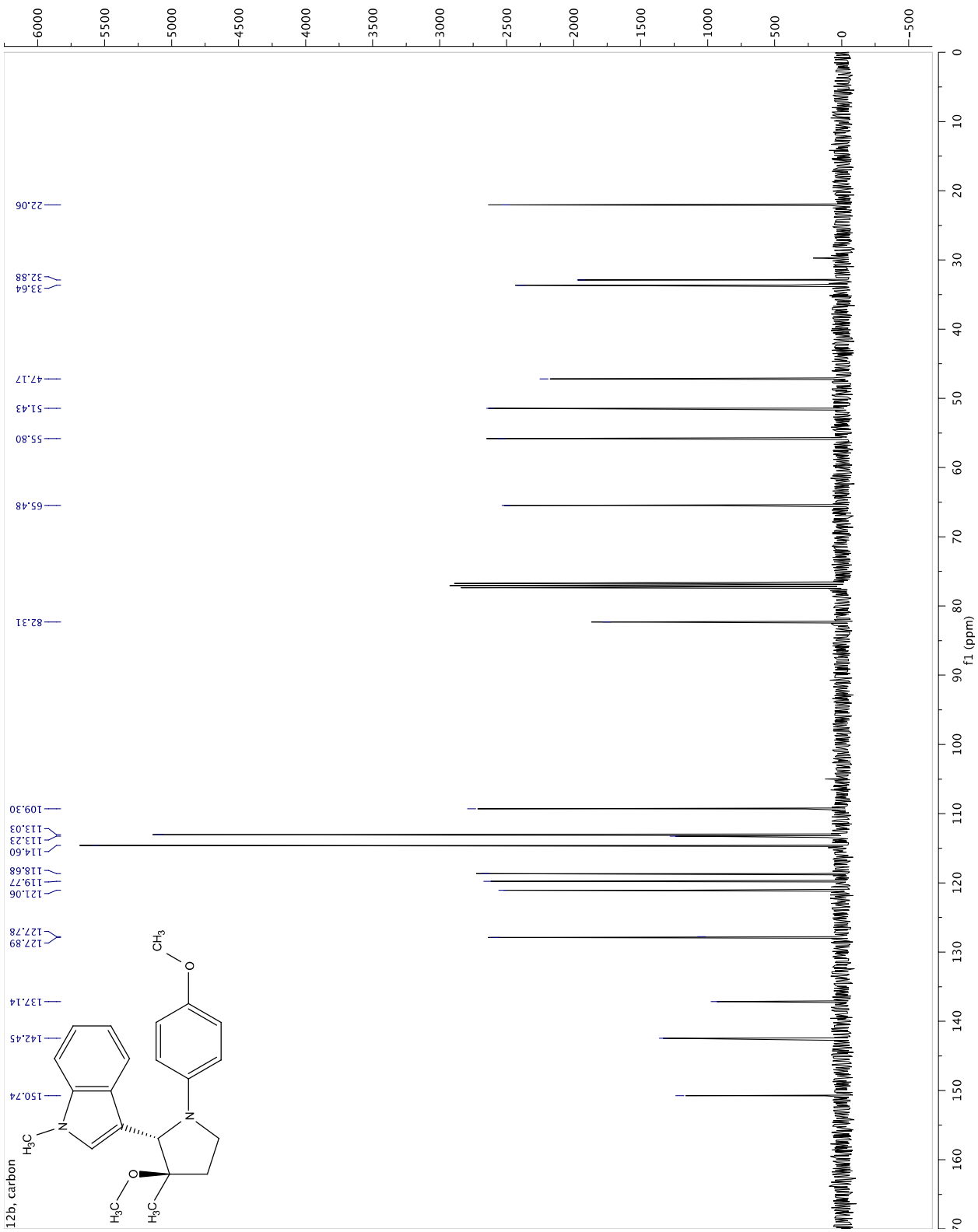
12a, NOE analysis



12a, NOE analysis




12b, proton
f1 (ppm)
3.24
1.03
1.03
2.95
1.13
7.22
1.00
2.02
1.94
0.95
3.52
0.97


22.06
32.88
33.64
47.17
51.43
55.80
65.48
82.31
109.30
113.03
113.23
114.60
118.68
119.77
121.06
127.78
127.89
137.14
142.45
150.74
f1 (ppm)

References Cited

[1] For previously reported ^{1}H NMR data for fumagillol, see: Chamni, S.; He, Q.-L.; Dang, Y.; Bhat, S.; Liu, J. O.; Romo, D. *ACS Chem. Bio.* **2011**, *6*, 1175–1181, and references therein.
[2] Balthaser, B. R.; Maloney, M.; Beeler, A. B.; Porco, J. A., Jr.; Snyder, J. K. *Nature-Chem.* **2011**, *3*, 969.