Total Synthesis of (+)-Scyphostatin Featuring an Enantioselective and Highly Efficient Route to the Side-Chain via Zr-Catalyzed Asymmetric Carboalumination of Alkenes (ZACA)

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Supporting Information

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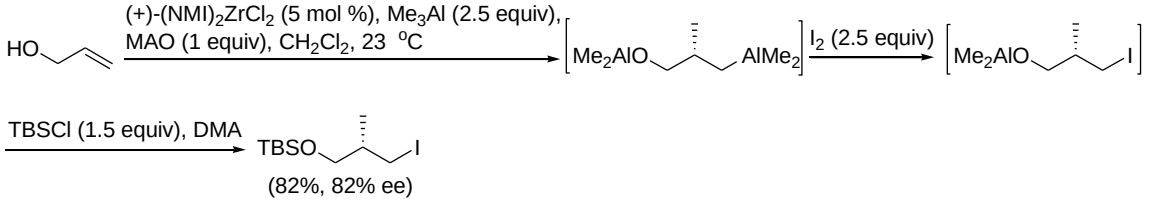
General Procedures. All reactions were run under a dry Ar atmosphere. Reactions were monitored by thin layer chromatography (TLC) carried out on 0.25-mm E.Merck silica gel plates (60F-254) or by GC analysis of reaction aliquots. GC analysis was performed on an HP6890 Gas Chromatograph using an HP-5 capillary column (30 m x 0.32 mm, 0.5 μM film) packed with SE-30 on Chromosorb W. Column chromatography was carried out on 230-400 mesh silica gel. ^{1}H and ^{13}C NMR spectra were recorded on Varian-Inova-300, Bruker Advance DRX-500, or a Bruker ARX400 instrument

spectrometer. Optical rotations were measured on an Autopol III automatic polarimeter or on a Perkin Elmer 341 instrument. THF was distilled from sodium/benzophenone. CH_2Cl_2 was distilled from CaH. $ZnBr_2$ was flame-dried under vacuum. (+)-(NMI)$ZrCl_2$ were prepared as reported in the literature[a]. The starting materials were purchased from commercial sources and used as received. Chemical shifts are measured in parts per million (δ) relative to the deuterated solvent used in the experiment. Multiplicities are designated as singlet (s), doublet (d), triplet (t), or multiplet (m). Broad peaks are indicated as "b".

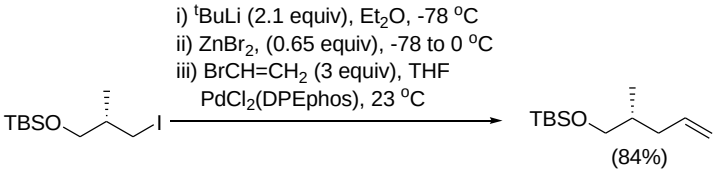
(*R*)-3-(*tert*-Butyldimethylsilyloxy)-2-methyl-1-propyl Iodide.[b]



To allyl alcohol (0.68 mL, 10 mmol) in CH_2Cl_2 (5 mL) was added Me_3Al (1.5 mL, 15 mmol) at –78 ℃, and the mixture was warmed to 23 °C and stirred for 1 h. In another flask (+)-(NMI)$_2ZrCl_2$ (334 mg, 0.5 mmol) was dissolved in CH_2Cl_2 (5 mL) and treated consecutively with Me_3Al (1 mL, 10 mmol), methylaluminoxane (MAO) (10 mmol in CH_2Cl_2 (5 mL), and the pretreated allyl alcohol solution prepared as described above at 0 ℃. After stirring overnight, the solvent and excess Me_3Al were evaporated in vacuo at 40 ℃. The residue was dissolved in 10 mL of THF and treated with I_2 (6.35 g, 25 mmol) in THF (10 mL) for 2 h at 0 ℃. The resultant mixture was treated with *tert*-BuMe_2SiCl (2.25 g, 15 mmol) in dimethyl acetamide (25 mL) at 0 ℃, stirred for 12 h at 23 °C, quenched with water, extracted with Et_2O, washed with brine, dried, filtered, concentrated, and purified by column chromatography (silica gel, hexanes) to give 2.57 g (82%) of the title compound as a colorless oil: optical purity by Mosher ester analysis, 82%; $[\alpha]_D^{23}$= +8.0 (*c* 1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.20 (s, 6 H), 1.04 (s, 9 H), 1.09 (d, *J* = 6.6 Hz, 3 H), 1.7-1.85 (m, 1 H), 3.3-3.5 (m, 2 H), 3.53 (dd, *J* = 9.9, 7.2 Hz 1 H), 3.67 (dd, *J* = 9.9, 5.1 Hz 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 5.18 (2 C), 13.76,

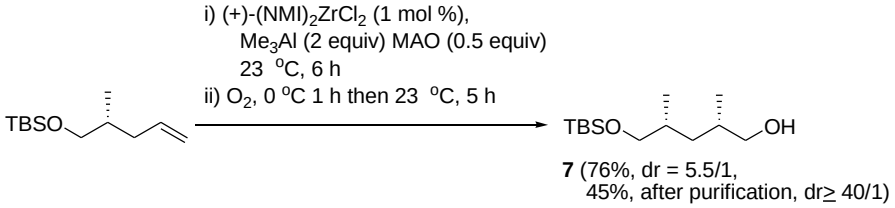
17.42, 18.40, 26.08 (3 C), 37.54, 66.85.

(*R*)-5-(*tert*-Butyldimethylsilyloxy)-4-methyl-1-pentene. [c]



A solution of (2*S*)-3-*tert*-butyldimethylsilyloxy-2-methyl-1-propyl iodide (3.14 g, 10.0 mmol) in Et_2O (10 mL) was cooled to –78 °C. To this was added *tert*-BuLi (12.4 mL, 21.0 mmol, 1.7 M in pentane) and after 30 min, an ice-cold solution of $ZnBr_2$ (1.46 g, 6.5 mmol) in THF (20 mL). The mixture was stirred for 30 min at –78 °C and warmed to 0 °C for 10 min. In another flask $PdCl_2$(DPEphos) (72 mg, 0.1 mmol) was suspended in THF (5 mL), treated with vinyl bromide (1.7 mL, 30.0 mmol, condensed at –78 °C), and transferred to the organozinc compound at 0 °C. After stirring for 6 h at 0 °C and 12 h at 23 °C, the reaction mixture was quenched with water, filtered through Celite, extracted with Et_2O, washed with brine, dried, filtered, concentrated, and purified by column chromatography (silica gel, 99/1 hexanes–EtOAc) to give 1.80 g (84% yield) of the title product as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.04 (s, 6 H), 0.87 (d, *J* = 6.6 Hz, 3 H), 0.90 (s, 9 H), 1.6-1.75 (m, 1 H), 1.8-1.95 (m, 1 H), 2.1-2.3 (m, 1 H), 3.3-3.5 (m, 2 H), 4.97 (s, 1 H), 5.02 (d, *J* = 10.8 Hz, 1 H), 5.7-5.9 (m, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ -5.49 (2 C), 16.23, 18.21, 25.82 (3 C), 35.56, 37.53, 67.63, 115.55, 137.21.

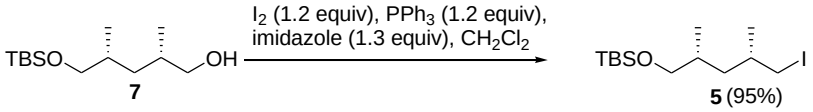
(2*S*,4*R*)-5-(*tert*-Butyldiphenylsilyloxy)-2,4-dimethyl-1-pentanol (7) [b,d]



To (+)-$(NMI)_2ZrCl_2$ (67 mg, 0.1 mmol) in CH_2Cl_2 (30 mL) was added Me_3Al (2.0 mL, 20.0 mmol) and MAO (5.0 mmol). This orange mixture was treated with a solution of (*R*)-5-(*tert*-butyldimethylsilyloxy)-4-methyl-1-pentene (2.14 g, 10.0 mmol) in CH_2Cl_2 (20

mL). After 6 h at 23 ℃, the mixture was treated with a vigorous stream of oxygen bubbled through it for 1 h at 0 ℃, then stirred further for 5 h under oxygen atmosphere at 23 ℃. The resultant mixture was diluted with Et_2O, washed with 2 N NaOH, NH_4Cl and $NaHCO_3$, dried, concentrated, and purified by column chromatography (silica gel, 5/1 hexanes–EtOAc) to give 1.87 g (76%) of the crude product (dr = 5.5/1 by ^{13}C NMR). The product was further purified by column chromatography (silica gel, 98/2 hexane–EtOAc) to give 1.11 g (45% from (*R*)-5-(*tert*-butyldimethylsilyloxy)-4-methyl-1-pentene) of the title compound as a colorless oil: dr by ^{13}C NMR, ≥40/1. $[\alpha]_D^{23} = -1.5^o$ (*c* 1, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$) δ -0.02 (s, 6 H), 0.82 (s, 9 H), 0.83 (d, *J* = 6.6 Hz, 3 H), 0.87 (d, *J* = 6.3 Hz, 3 H), 1.14 (t, *J* = 6.3 Hz, 1 H), 1.35-1.45 (m, 1 H), 1.55-1.7 (m, 1 H), 1.17 (s, 9 H), 1.26 (t, *J* = 6.9 Hz, 1 H), 1.4-1.55 (m, 1H), 1.6-1.85 (m, 2 H), 3.25-3.45 (m, 4 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ -5.25 (2 C), 17.84, 17.93, 26.08 (3 C), 33.36(2 C), 37.43(2 C), 68.18, 68.45.

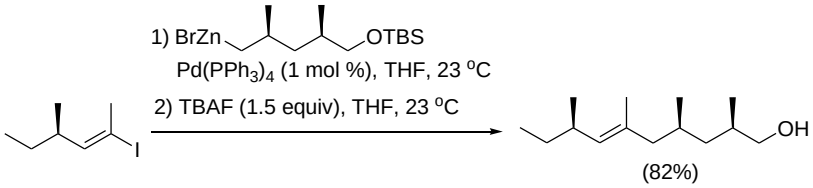
(2*S*,4*R*)-5-(*tert*-Butyldimethylsilyloxy)-2,4-dimethyl-1-pentanyl iodide (5). [c]



Imidazole (0.44 g, 6.5 mmol) and iodine (1.52 g, 6.0 mmol) were added sequentially to a solution of PPh_3 (1.57 g, 6.0 mmol) in CH_2Cl_2 (30 mL) at 23 ^oC. The reaction mixture was cooled to 0 ^oC and stirred for 15 min. A solution of the **7** (1.23 g, 5.0 mmol) in CH_2Cl_2 (10 mL) was then added and the mixture was warmed to room temperature and stirred for 2 h. Then, the solvent was removed *in vacuo* and the resulting solid residue was suspended in a minimal amount of CH_2Cl_2 (2 mL), and loaded on to a column of silica gel. Eluting with hexane-ethyl acetate (98/2) afforded a red solution that was washed with saturated sodium bisulfite and brine, dried over $MgSO_4$, filtered, and concentrated to give 1.69 g (95%) of the title compound as a colorless oil. $[\alpha]_D^{23} = +7.5^o$ (*c* 1, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$) δ -0.19 (s, 6 H), 1.03 (d, *J* = 5.7 Hz, 3 H), 1.05 (s, 9 H), 1.13 (d, *J* = 6.6 Hz, 3 H), 1.5-1.6 (m, 1 H), 1.35-1.45 (m, 1 H), 1.65-1.85 (m, 2 H), 3.27 (dd, *J* = 9.9, 6.3 Hz, 1 H), 3.40 (dd, *J* = 9.6, 3.9 Hz, 1 H), 3.45-3.65 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ -5.19 (2 C), 17.33, 18.21, 18.43, 21.67, 26.12 (3 C), 32.06,

33.32, 40.54, 68.33.

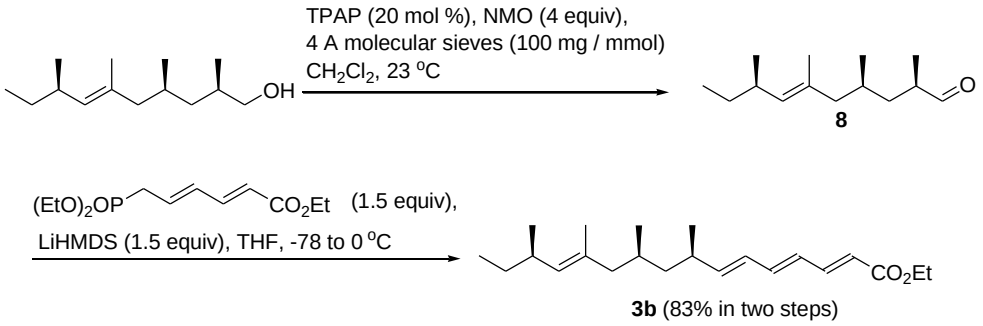
(2*R*,4*S*,8*R*,*E*)-2,4,6,8-Tetramethyl-6-decen-1-ol. [c]



A solution of **5** (1.28 g, 3.6 mmol) in Et_2O (5 mL) was cooled to –78 °C. To this was added *tert*-BuLi (4.3 mL, 7.3 mmol, 1.7 M in pentane) and after 30 min, an ice-cold solution of $ZnBr_2$ (0.53 g, 0.24 mmol) in THF(10 mL). The mixture was stirred for 30 min at –78 °C and warmed to 0 °C for 10 min. In another flask $Pd(PPh_3)_4$ (35 mg, 0.03 mmol) was suspended in THF (5 mL), treated with (*R*,*E*)-2-iodo-4-methyl-2-hexene [c] (0.67 g, 3.0 mmol) and transferred to the organozinc compound. After stirring for 6 h at 23 °C, the reaction mixture was quenched with water, filtered through Celite, extracted with Et_2O, washed with brine, dried, filtered, concentrated, and used directly for the next reaction without purification.

To a solution of above product in THF (20 mL) was added dropwise TBAF (3.6 mL, 3.6 mmol, 1 M in THF) at 0 °C, and the resultant mixture was stirred for 3 h at 23 °C. The reaction was quenched with water, extracted with Et_2O, washed with brine, dried, concentrated, and purified by column chromatography (silica gel, 90/10 hexanes–EtOAc) to give 0.53 g (82% from (*R*,*E*)-2-iodo-4-methyl-2-hexene) of the title compound as colorless oil. $[\alpha]_D^{23} = -14.7^o$ (*c* 1, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.81 (t, *J* = 7.2 Hz, 6 H), 0.89 (t, *J* = 6.6 Hz, 3 H), 0.90 (t, *J* = 6.6 Hz, 3 H), 1.1-1.4 (m, 4 H), 1.54 (s, 3 H), 1.6-1.8 (m, 3H), 1.98 (dd. *J* = 10.5, 7.5 Hz, 1 H), 2.03 (brs, 1 H), 2.15-2.3 (m, 1 H), 3.31 (dd, *J* = 10.2, 6.9 Hz, 1 H), 3.50 (dd, *J* = 10.2, 4.8 Hz, 1 H), 4.83 (d, *J* = 9.0, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 11.94, 16.03, 17.36, 19.99, 20.95, 27.94, 30.39, 32.95, 33.99, 40.81, 47.51, 68.06, 132.06, 132.89.

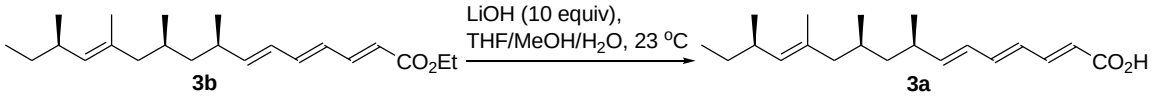
(2*E*,4*E*,6*E*,12*E*)-(8*R*,10*S*,14*R*)-8,10,12,14-(Tetramethyl)hexadeca-2,4,6,12-tetraenoic acid ethyl ester (3b). [c]



To a stirred solution of (2*R*,4*S*,8*R*,*E*)-2,4,6,8-tetramethyl-6-decen-1-ol (318 mg, 1.5 mmol) in CH_2Cl_2 (10 mL) was added powdered 4Å molecular sieves (150 mg), TPAP (105 mg, 0.3 mmol), and NMO (703 mg, 6.0 mmol). After 15 min the reaction mixture was filtered through a short pad of silica gel, and the filtrate was concentrated *in vacuo* to give the **8** as a colorless oil, which was used immediately for the next reaction without further purification.

To a solution of triethyl (2*E*,4*E*)-6-phosphono-2,4-hexadienoate[e] (621 mg, 2.3 mmol) in dry THF (10 ml) was added dropwise LiHDMS (2.23 mL, 2.3 mmol, 1 M in hexanes) at –78 ℃. After stirring for 30 min, a solution of the above crude aldehyde in dry THF (5 mL) was added slowly and the resulting mixture was stirred at –78 ℃ for 30 min and at 0 ℃ for 30 min. Then, it was quenched with water, extracted with Et_2O, washed with brine, dried, concentrated, and purified by column chromatography (silica gel, 90/10 hexanes–EtOAc) to give 414 mg (83% from (2*R*,4*S*,8*R*,*E*)-2,4,6,8-tetramethyl-6-decen-1-ol) of the title compound as colorless oil. $[\alpha]_D^{23} = -1.7^o$ (*c* 1, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.81 (t, *J* = 6.6 Hz, 6 H), 0.83 (t, *J* = 6.9 Hz, 3 H), 0.90 (t, *J* = 6.6 Hz, 3 H), 0.93 (d, *J* = 6.3 Hz, 3 H), 0.99 (d, *J* = 7.5 Hz, 3 H), 0.95-1.05 (m, 1H), 1.27 (t, *J* = 4.5 Hz, 1 H), 1.1-1.4 (m, 4 H), 1.52 (s, 3 H), 1.78 (dd. *J* = 9.9, 6 Hz, 1 H), 1.88 (dd. *J* = 13.2, 6.9 Hz, 1 H), 2.1-2.4 (m, 2 H), 4.19 (dd, *J* = 14.8, 7.2 Hz, 2 H), 4.83 (d, *J* = 9.0, 1 H), 5.71 (dd, *J* = 15.3, 8.4 Hz, 1 H), 5.83 (d, *J* = 15.3, 1 H), 6.05-6.3 (m, 2 H), 6.52 (dd, *J* = 15.0, 8.4 Hz, 1 H), 7.29 (dd, *J* = 15.0, 11.1 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 11.94, 14.21, 16.06, 19.60, 19.84, 20.96, 28.14, 30.39, 34.00, 34.57, 43.83, 47.69, 60.08, 119.81, 127.58, 127.69, 132.01, 133.02, 141.29, 144.74, 146.75, 167.17.

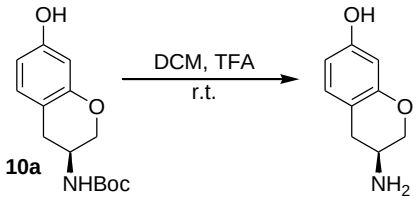
(2*E*,4*E*,6*E*,12*E*)-(8*R*,10*S*,14*R*)-8,10,12,14-(Tetramethyl)hexadeca-2,4,6,12-tetraenoic acid (3a)



3b **3a**

To a solution of **3b** (167 mg, 0.5 mmol) in THF (5 mL) was added LiOH (120 mg (5 mmol) in THF-methanol (2 ml, 1/1)) and stirred at 23 ^{o}C for 8 h. The reaction mixture was washed with 1 M HCl (2 ml), extracted with Et_2O, washed with brine, dried, concentrated to give **3a** (153 mg, 100%), which was used for the next reaction without further purification.

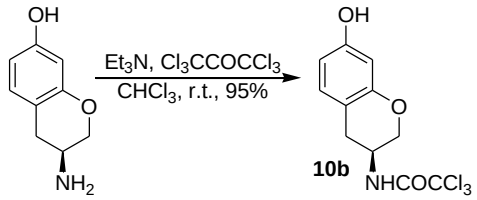
(*S*)-3-Amino-3,4-dihydro-2*H*-chromen-7-ol.



10a

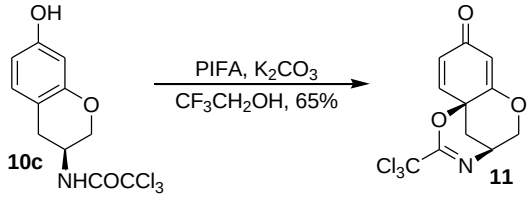
To a stirred solution of (*S*)-3,4-dihydro-7-hydroxy-2H-chromen-3-ylcarbamate (**10**a)[f] (325 mg, 1.23 mmol) in DCM (6 mL) was, added dropwise and at ambient temperature, TFA (1.8 mL) and the mixture was stirred until TLC analysis indicated complete consumption of the starting material (ca. 45 min). Solvent and excess reagent were removed under reduced pressure and the oil thus obtained was dissolved in toluene (10 mL) and then reconcentrated under reduced pressure. Repetition of this process (× 2) yielded a hydroscopic white amorphous solid (0.2 g) which was used without further purification in the next step. ^{1}H NMR (250 MHz, CD_3OD) δ 6.76 (bd, *J* = 8 Hz, 1 H), 6.26 (bd, *J* = 8 Hz, 1 H), 6.15 (bs, 1 H), 4.02 (bd, *J* = 10 Hz, 1 H), 3.64 (bdd, *J* = 10, 9 Hz, 1 H), 3.18–3.04 (bm, 1 H), 2.84 (bdd, *J* = 15, 4 Hz, 1 H), 2.40 (bdd, *J* = 15, 8 Hz, 1 H); ^{13}C NMR (62.5 MHz, CD_3OD) δ 157.8, 155.9, 131.6, 112.3, 109.6, 103.8, 71.7, 45.4, 34.0; HR-ESI: *m/*z: 188.06818, [*M*+Na^+] for the compound $C_9H_{11}NO_2$ requires 188.06820.

2,2,2-Trichloro-*N*-((*S*)-3,4-dihydro-7-hydroxy-2*H*-chromen-3-yl)acetamide (10b).



To a stirred solution of the above amine (0.2 g) in chloroform (15 mL) were added at ambient temperature triethylamine (0.6 mL, 4.3 mmol) and hexachloroacetone (1.9 mL, 12.7 mmol). The mixture was stirred at ambient temperature for 12 h and was then and concentrated under reduced pressure. The residue thus obtained was dissolved in methanol (6 mL) and potassium carbonate (60 mg) was added. The mixture was stirred for 1 h and was then poured into a 0.1 N aqueous HCl solution (15 mL) and extracted with ethyl acetate (3 × 10 mL). The combined organic phases were washed with water (20 mL) and brine (20 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The residue thus obtained was purified by flash column chromatography (7:3 hexane-ethyl acetate) to produce 2,2,2-trichloro-*N*-((*S*)-3,4-dihydro-7-hydroxy-2H-chromen-3-yl)acetamide (**10b**) (361 mg, 95% over two steps) as amorphous white solid: R_f 0.27 (7:3 hexane-ethyl acetate); $[\alpha]_D^{21}$ = +10.9 (*c* 0.49, acetone); ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.04 (bd, *J* = 7.0 Hz, 1 H), 6.90 (d, *J* = 8.3 Hz, 1 H), 6.48 (dd, *J* = 8.3, 2.4 Hz, 1 H), 6.42 (d, *J* = 2.4 Hz, 1 H), 5.71 (bs, 1 H), 4.45–4.41 (m, 1 H), 4.22 (ddd, *J* = 11.2, 3.8, 2.2 Hz, 1 H), 4.11 (dd, *J* = 11.2, 1.6 Hz), 3.12 (dd, *J* = 16.6, 5.2 Hz, 1 H), 2.78 (bd, *J* = 16.6 Hz, 1 H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 162.0, 155.6, 154.2, 131.1, 110.1, 109.6, 103.6, 92.1, 67.1, 44.8, 29.4; HR-ESI: *m/z*: 331.96173, [M+Na^+] for the compound $C_{11}H_{10}Cl_3NO_3$ requires 331.96185.

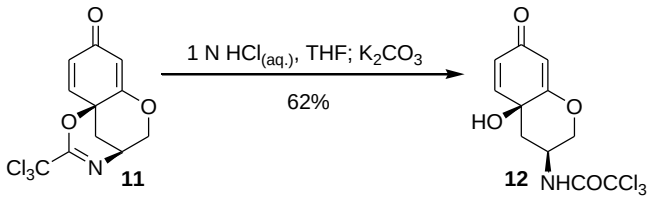
Oxazine (11).



Trichloroacetamide **10b** (100 mg, 0.32 mmol) was suspended in trifluoroethanol (10 mL)

and the mixture was heated with stirring at 60°C until complete dissolution of the solids and then allowed to cool at ambient temperature. This clear solution was then added dropwise (over 20 min) to a stirred mixture of PIFA (150 mg, 0.35 mmol) and anhydrous K_2CO_3 (150 mg, 1.1 mmol) in trifluoroethanol (2 mL). The deep orange reaction mixture was allowed to stirr for 30 min and then the reaction was quenced by addition of water (5 mL). The mixture was extracted with DCM (2 × 10 mL) and the combined organic extracts were washed with brine (10 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The residue thus obtained was purified by flash column chromatography (8:2 to 6:4 hexane-ethyl acetate) to produce oxazine **11** (64 mg, 65%) as off-white amorphous solid: R_f 0.19 (6:4 hexane-ethyl acetate); $[\alpha]_D^{21}$ = -237 (*c* 1.56, acetone); ^{1}H NMR (250 MHz, $CDCl_3$) δ 6.59 (d, *J* = 9.9 Hz, 1 H), 6.32 (dd, *J* = 9.9, 1.6 Hz, 1 H), 5.85 (d, *J* = 1.6 Hz, 1 H), 4.50 (bd, *J* = 11.2 Hz, 1 H), 4.22–4.18 (m, 1 H), 4.10 (dd, *J* = 11.2, 1.9 Hz, 1 H), 2.22 (dd, *J* = 13.7, 1.8 Hz, 1 H), 2.17–2.07 (m, 1 H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 186.3, 166.6, 155.4, 139.9, 131.3, 110.9, 91.1, 73.5, 70.6, 48.4, 28.9; HR-ESI: *m/*z: 329.94624, [*M*+Na^+] for the compound $C_{11}H_8Cl_3NO_3$ requires 329.94620.

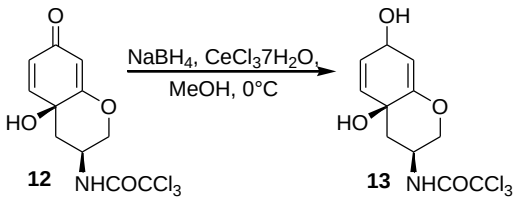
2,2,2-Trichloro-*N*-((3*S*,4a*S*)-3,4,4a,7-tetrahydro-4a-hydroxy-7-oxo-2*H*-chromen-3-yl) acetamide (12).



To a solution of oxazine **11** (64 mg, 0.21 mmol) in THF (3 mL) was added dropwise (over 15 min) 1 N aqueous HCl solution (0.2 mL) and the mixture was stirred at ambient temperature for 30 min. The mixture was diluted with THF (9 mL), solid K_2CO_3 (0.5 g) was added and stirring was continued for 2 h. Water (10 mL) was added and the mixture was neutralized by careful addition of 1 N aqueous HCl solution. The mixture was extracted with DCM (3 × 10 mL) and the combined organic phases were washed with brine (10 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash column chromatography (8:2 to 6:4 hexane-ethyl acetate) to

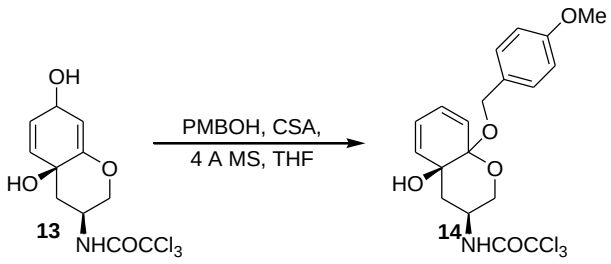
produce *p*-quinol **12** (43 mg, 62%) as light yellow amorphous solid: R_f 0.36 (1:1 hexane-ethyl acetate); $[\alpha]_D^{21}$ = -221 (*c* 2.50, acetone); ^{1}H NMR (500 MHz, acetone-d_6) δ 9.20 (bs, 1 H), 6.77 (d, *J* = 9.9 Hz, 1 H), 6.03 (dd, *J* = 9.9, 1.7 Hz, 1 H), 5.94 (bs, 1 H), 5.63 (d, *J* = 1.7 Hz, 1 H), 4.43 (bd, *J* = 11.4 Hz, 1 H), 4.37–4.28 (m, 1 H), 4.16 (dd, *J* = 11.4, 3.0 Hz), 2.36 (bd, *J* = 14.5 Hz, 1 H), 2.26 (dd, *J* = 14.5, 5.0 Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 188.6, 173.7, 162.8, 147.6, 129.0, 111.6, 74.2, 67.0, 47.8, 37.2; HR-ESI: *m*/z: 347.95692, [*M*+Na^+] for the compound $C_{11}H_{10}Cl_3NO_4$ requires 347.95676.

2,2,2-Trichloro-*N*-((3*S*,4a*S*)-3,4,4a,7-tetrahydro-4a,7-dihydroxy-2*H*-chromen-3-yl)acetamide (13).



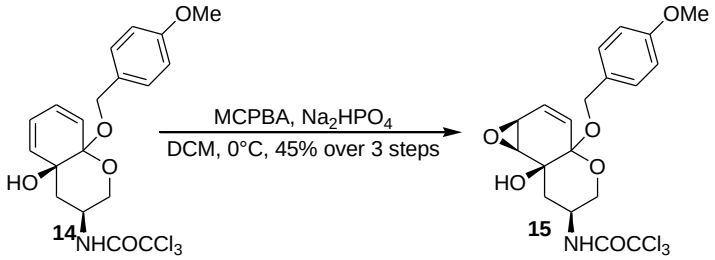
To a stirred solution of quinol **12** (98 mg, 0.30 mmol) and $CeCl_3 \cdot 7H_2O$ (223 mg, 0.60 mmol) in methanol (20 mL) was added, at 0 ℃ and in small portions, sodium borohydride (12 mg, 0.32 mmol). Upon reaction completion, excess reagent was quenched by addition of acetone (2 mL). The mixture was stirred at ambient temperature for 30 min and was then poured in water (20 mL) and extracted with ethyl acetate (4 × 15 mL). The combined organic phases were washed sequentially with water (2 × 10 mL) and brine (2 × 10 mL), dried over Na_2SO_4 and concentrated under reduced pressure to produce diol **13** (97 mg) as light yellow oil. Further purification of this sensitive intermediate is neither necessary nor advisable: R_f 0.12 (1:1 hexane-ethyl acetate); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.96 (bs, 1 H), 6.02 (ddd, *J* = 9.9, 2.9, 2.0 Hz, 1 H), 5.83 (dd, *J* = 9.9, 1.6 Hz, 1 H), 5.61 (dd, *J* = 3.0, 2.0 Hz, 1 H), 4.76–4.72 (m, 1 H), 4.29–4.25 (m, 1 H), 4.24–4.20 (m, 1 H), 3.81 (dd, *J* = 11.8, 2.1 Hz, 1 H), 2.23 (ddd, *J* = 14.5, 2.5, 2.4 Hz, 1 H), 1.97 (ddd, *J* = 14.5, 4.5, 2.5 Hz, 1 H).

***N*-((3*S*,4a*S*)-8a-(4-Methoxybenzyloxy)-3,4,4a,8a-tetrahydro-4a-hydroxy-2*H*-chromen-3-yl)-2,2,2-trichloroacetamide (14).**



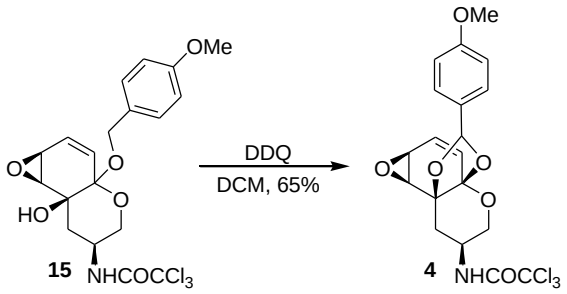
To a stirred solution of the above diol (**13**, 97 mg) in THF (6 mL) were added powdered molecular sieves 4 Å (200 mg), 4-methoxybenzyl alcohol (210 mg, 1.5 mmol) and (±)-CSA (60 mg, 0.26 mmol). The mixture was stirred at ambient temperature for 24 h. The reaction was quenched by addition of solid sodium bicarbonate (100 mg). The mixture was diluted with ethyl acetate (20 mL) and filtered with the aid of Celite®. The filtrate was poured in saturated aqueous solution of sodium bicarbonate (10 mL) and the mixture was extracted with ethyl acetate (2 × 15 mL). The combined organic phases were washed sequentially with water (2 × 10 mL) and brine (2 × 10 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The residue thus obtained was partially purified by a fast flash column chromatography (1:9 to 2:8 ethyl acetate/hexane) to produce ketal **9** contaminated with 4-methoxybenzyl alcohol (105 mg) as colorless oil. Taking into account the sensitivity of the ketal and the fact that 4-methoxybenzyl alcohol does not interfere with the subsequent transformation (epoxidation) and is then readily separated from the desired product, it was deemed safer and more convenient to proceed with the synthesis without further purification. Data for ketal **14**: R_f 0.64 (1:1 ethyl acetate-hexane); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.76 (bd, *J* = 6.7 Hz, 1 H), 7.22 (d, *J* = 8.3 Hz, 2 H), 6.86 (d, *J* = 8.3 Hz, 2 H), 6.23 (ddd, *J* = 9.9, 4.5, 1.6 Hz, 1 H), 6.03 (d, *J* = 9.9 Hz, 1 H), 5.89–5.84 (m, 2 H), 4.59 (AB_q, *J* = 10.7 Hz, Δν = 111 Hz, 2 H), 4.06 (bd, *J* = 12.2 Hz, 1 H), 4.03–3.99 (m, 1 H), 3.83 (dd, *J* = 12.2, 1.9 Hz, 1 H), 3.80 (s, 3 H), 2.10 (ddd, *J* = 14.8, 2.5, 2.4 Hz, 1 H), 1.94 (ddd, *J* = 14.8, 4.2, 2.4 Hz, 1 H).

***N*-((1a*S*,1b*S*,3*S*,7a*S*)-5a-(4-Methoxybenzyloxy)-1b,2,3,4,5a,7a-hexahydro-1b-hydroxy-1a*H*-oxireno[2,3-f]chromen-3-yl)-2,2,2-trichloroacetamide (15).**



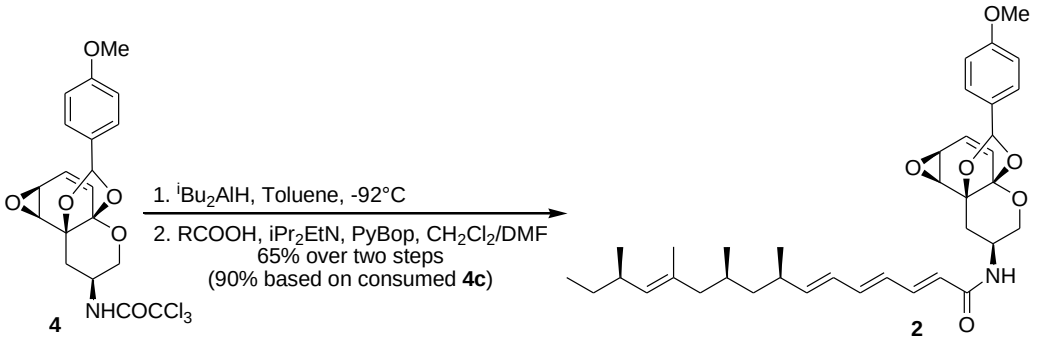
To a stirred solution of the above ketal (**14**, 105 mg) in dichloromethane (12 mL) at 0 ℃ were added solid Na_2HPO_4 (300 mg) and *m*-chloroperbenzoic acid (200 mg). The mixture was stirred at 0 ℃ for 12 h. The reaction was quenched by addition of 0.5 N aqueous NaOH solution (6 mL) and was then poured in water (10 mL). The mixture was extracted with ethyl acetate (2 × 15 mL), the combined organic phases were washed with brine (2 × 10 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The residue thus obtained was purified by flash column chromatography (2:8 to 4:6 ethyl acetate/hexane) to produce epoxide **15** (63 mg, 45% from **12**) as amorphous white solid: R_f 0.48 (1:1 ethyl acetate-hexane); $[\alpha]_D^{21}$ = -207 (*c* 0.53, acetone) ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.61 (bd, *J* = 7.6 Hz, 1 H), 7.30 (d, *J* = 8.6 Hz, 2 H), 6.87 (d, *J* = 8.6 Hz, 2 H), 6.39 (dd, *J* = 10.1, 3.9 Hz, 1 H), 6.02 (dd, *J* = 10.1, 1.7 Hz, 1 H), 4.59 (AB_q, *J* = 10.4 Hz, Δν = 80 Hz, 2 H), 4.11–4.07 (m, 1 H), 3.97 (dt, *J* = 12.3, 2.5 Hz, 1 H), 3.91 (d, *J* = 2.3 Hz, 1 H), 3.80 (s, 3 H), 3.64 (dd, *J* = 12.3, 2.6 Hz, 1 H), 3.43 (dt, *J* = 3.9, 1.8 Hz, 1 H), 3.32 (d, *J* = 3.9 Hz, 1 H), 2.11 (dt, *J* = 14.7, 2.3 Hz, 1 H), 1.73 (ddd, *J* = 14.7, 4.7, 2.4 Hz, 1 H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 161.5, 159.2, 133.3, 131.3, 129.9, 129.5, 113.7, 96.2, 70.8, 65.4, 65.2, 58.0, 55.2, 48.0, 44.2, 32.5; HR-ESI: *m/z*: 486.02447, [M+Na^+] for the compound $C_{19}H_{20}Cl_3NO_6$ requires 486.02484.

Bisketal (4).



To a stirred solution of compound **15** (111 mg, 0.24 mmol) in dichloromethane (12 mL) was added DDQ (82 mg, 0.36 mmol). The mixture was stirred at ambient temperature for 24 h and then the reaction was quenched by addition of saturated aqueous $NaHCO_3$ solution (12 mL) and ascorbic acid (65 mg, 0.37 mmol). The mixture was extracted with ethyl acetate (2 X 15 mL). The combined organic phases were washed sequentially with water (2 X 10 mL) and brine (2 X 10 mL) and were then dried over Na_2SO_4. Evaporation under reduced pressure and further chromatographic purification (3:7 ethyl acetate-hexane) of the residue produced unreacted starting material (37.3 mg) and compound **4** as white foam (47.5 mg, 65% based on consumed **15**): R_f 0.39 (1:1 ethyl acetate-hexane); $[\alpha]_D^{21}$ = -70.4 (*c* 5.61, dichloromethane); IR (thin film) 3385, 2934, 1713, 1613, 1516, 1460, 1432, 1390, 1305, 1252, 1174, 1106, 1044, 1013 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.61 (bd, *J* = 5.6 Hz, 1 H), 7.56 (d, *J* = 8.6 Hz, 2 H), 6.92 (d, *J* = 8.6 Hz, 2 H), 6.58 (dd, *J* = 10.0, 3.8 Hz, 1 H), 6.33 (s, 1 H), 6.07 (d, *J* = 10.0 Hz, 1 H), 4.16 (dt, *J* = 12.5, 2.3 Hz, 1 H), 4.03–3.99 (m, 1 H), 3.81 (s, 3 H), 3.58 (dt, *J* = 3.5, 1.3 Hz, 1 H), 3.53 (d, *J* = 12.4 Hz, 1 H), 3.47 (d, *J* = 3.8 Hz, 1 H), 2.51 (dt, *J* = 15.3, 2.1 Hz, 1 H), 1.82 (dd, *J* = 15.3, 4.5 Hz, 1 H, CH*H*); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 161.4, 160.9, 133.1, 130.9, 129.0, 127.7, 113.9, 101.8, 99.5, 92.5, 78.1, 64.9, 57.2, 55.3, 49.0, 44.3, 31.0; HR-ESI: m/z: 484.00903, [*M*+Na^+] for the compound $C_{19}H_{18}Cl_3NO_6$ requires 484.00919.

Fully protected scyphostatin (2).



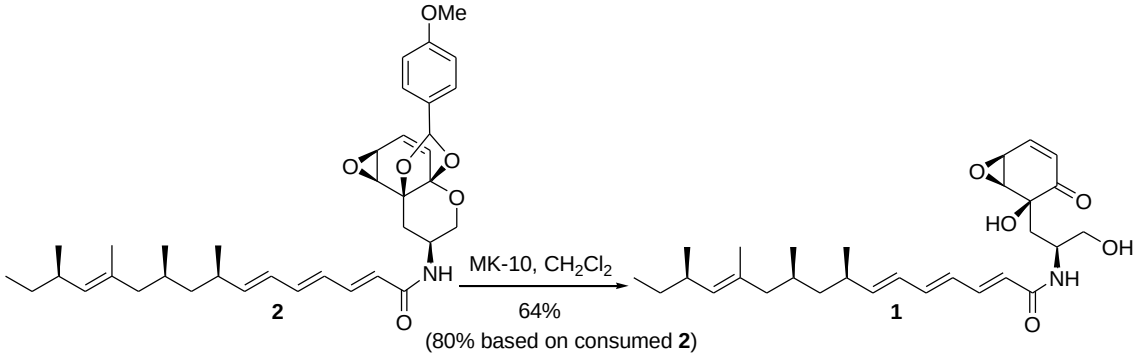
A solution of trichloroacetamide **4** (15 mg, 32 μmol) in toluene (3 mL) was cooled to

–92 ℃ and *i*-Bu_2AlH (0.1 M solution in toluene; 600 μL, 60 μmol) was added dropwise. The mixture was stirred at the same temperature for10 min and then the reaction was quenched by careful addition of cooled acetone (2 mL). To the resulting solution was added solid $Na_2SO_4 \cdot 10H_2O$ (large excess) at 0 ℃. After stirring for 30 min at 0 ℃, the mixture was allowed to warm up to ambient temperature, the insoluble materials were filtered off, washed with dichloromethane (3 × 5 mL) and the combined filtrate and washings were concentrated under reduced pressure to give crude amine.

To a solution of the crude amine and side-chain acid **3a** (16 mg, 53 μmol) in a mixture of dichloromethane (2 mL) and DMF (0.2 mL) cooled to 0 ℃ were added *i*Pr_2EtN (30 μL, 172 μmol), and PyBop (31 mg, 60 μmol). The mixture was stirred at 0 ℃ for 3 h and was then allowed to gradually warm up to ambient temperature. After 8 h, the reaction mixture was poured in water (10 mL) and extracted with dichloromethane (3 × 15 mL). The combined organic phases were washed with brine (10 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The residue thus obtained was purified by flash column chromatography (1:1 ethyl acetate/hexanes) to produce amide **2** as colorless oil (13 mg, 65% over two steps; 90% based on consumed **4**): R_f 0.23 (6:4 ethyl acetate-hexane); $[\alpha]_D^{21}$ = -70.6 (*c* 1.26, dichloromethane); IR (thin film) 3421, 2957, 2924, 2868, 1655, 1613, 1517, 1458, 1388, 1376, 1305, 1251, 1173, 1154, 1105, 1045, 1004 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.62–7.59 (m, 2 H), 7.25 (dd, *J* = 14.8, 12.3 Hz, 1 H), 6.95–6.91 (m, 2 H), 6.59 (bd, *J* = 7.5 Hz, 1 H), 6.53 (dd, *J* = 10.0, 3.8 Hz, 1 H), 6.49 (dd, *J* = 14.9, 10.7 Hz, 1 H), 6.29 (s, 1 H), 6.21 (dd, *J* = 14.8, 11.2 Hz, 1 H), 6.09 (dd, *J* = 15.2, 10.7 Hz, 1 H), 6.05 (dd, *J* = 10.0, 1.7 Hz, 1 H), 5.83 (d, *J* = 14.9 Hz, 1 H), 5.70 (dd, *J* = 15.1, 8.4 Hz, 1 H), 4.84 (dd, *J* = 9.4, 1.1 Hz, 1 H), 4.18–4.14 (m, 1 H), 4.08 (ddd, *J* = 12.2, 2.5, 2.2 Hz, 1 H), 3.81 (s, 3 H), 3.55 (dt, *J* = 3.9, 1.7 Hz, 1 H), 3.50 (dd, *J* = 12.2, 1.6 Hz, 1 H), 3.47 (d, *J* = 3.9 Hz, 1 H), 2.40 (dt, *J* = 15.3, 2.4 Hz, 1 H), 2.37–2.29 (m, 1 H), 2.27–2.18 (m, 1 H), 1.88 (dd, *J* = 13.1, 7.1 Hz, 1 H), 1.81–1.73 (m, 2 H), 1.60–1.49 (m, 1 H), 1.52 (d, *J* = 1.3 Hz, 3 H), 1.35–1.13 (m, 3 H), 1.04–0.97 (m, 1 H), 1.00 (d, *J* = 6.7 Hz, 3 H), 0.90 (d, *J* = 6.7 Hz, 3 H), 0.83 (t, *J* = 7.4 Hz, 3 H), 0.80 (d, *J* = 6.5 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) 165.7, 160.8, 145.6, 141.6, 140.5, 133.0, 132.7, 132.1, 131.4, 129.0, 128.2, 127.7, 122.2, 113.8, 101.7, 99.4, 78.3, 66.0, 57.6, 55.3, 49.1, 48.3, 44.0, 41.9, 34.9, 34.1, 31.7, 30.5, 28.2, 21.4, 21.0, 19.5, 16.1, 12.0; HR-ESI: m/z:

626.3465, [*M*+Na^+] for the compound $C_{37}H_{49}NO_6$ requires 626.3458.

(+)-Scyphostatin (1).



To a solution of **2** (11 mg, 18 μmol) in dichloromethane (9 mL) was added montmorillonite K 10 (27 mg). The mixture was stirred at ambient temperature for 15 min and was then filtered. The clay was washed on the filter with acetone (4 × 5 mL) and the combined filtrates were evaporated under reduced pressure. The residue thus obtained was purified by flash column chromatography (10:1 CH_2Cl_2:MeOH) to produce scyphostatin as colourless wax (4.1 mg). A mixture of unreacted starting material and *p*-methoxybenzaldehyde was also obtained (6.6 mg). Resubmission of this mixture to the above reaction conditions provided additional scyphostatin (1.6 mg) and unreacted starting material (2.2 mg): R_f 0.09 (20:1 CH_2Cl_2/MeOH); $[\alpha]_D^{21}$ = +61.0 (*c* 0.48, MeOH); IR (thin film) 3294, 2959, 2925, 1685, 1648, 1609, 1542, 1458, 1376, 1272, 1087, 1004 cm^{-1}; ^{1}H NMR (400 MHz, CD_3OD) δ 7.18–7.11 (m, 2 H), 6.53 (dd, *J* = 14.6, 10.6 Hz, 1 H), 6.26 (dd, *J* = 14.7, 11.1 Hz, 1 H), 6.15 (dd, *J* = 15.1, 10.7 Hz, 1 H), 6.08 (dd, *J* = 9.9, 1.6 Hz, 1 H), 5.90 (d, *J* = 15.0 Hz, 1 H), 5.71 (dd, *J* = 15.1, 8.6 Hz, 1 H), 4.85–4.82 (m, 1 H), 4.08–4.02 (m, 1 H), 3.67 (d, *J* = 3.9 Hz, 1 H), 3.59 (dt, *J* = 3.9, 1.6 Hz, 1 H), 3.52 (dd, *J* = 11.0, 5.1 Hz, 1 H), 3.45 (dd, *J* = 11.0, 5.9 Hz, 1 H), 2.41–2.22 (m, 2 H), 2.09 (dd, *J* = 14.7, 3.4 Hz, 1 H), 1.93–1.85 (m, 2 H), 1.80 (dd, *J* = 13.3, 7.2 Hz, 1 H), 1.63–1.55 (m, 1 H), 1.54 (d, *J* = 1.3 Hz, 3 H), 1.41–1.31 (m, 2 H), 1.26–1.14 (m, 1 H), 1.06–0.96 (m, 1 H), 1.00 (d, *J* = 6.7 Hz, 3 H), 0.91 (d, *J* = 6.6 Hz, 3 H), 0.86 (t, *J* = 7.4 Hz, 3 H), 0.83 (d, *J* = 6.4 Hz, 3 H); ^{13}C NMR (100 MHz, CD_3OD) 199.6, 168.6, 146.2, 145.9, 142.5, 141.5, 134.3, 133.6, 132.1, 130.0, 129.5, 123.8, 77.6, 65.6, 58.3, 49.9, 49.4, 48.0, 45.3, 39.9,

36.3, 35.5, 31.7, 29.6, 22.0, 21.6, 20.0, 16.4, 12.6; HR-ESI: m/z: 508.3043, [M+Na^+] for the compound $C_{29}H_{43}NO_5$ requires 508.3039.

References:

(a) Erker, G.; Aulbach, M.; Knickmeier, M.; Wingbermuhle, D.; Kruger, C.; Nolte, M.; Werner, S. *J. Am. Chem. Soc*. **1993**, *115*, 4590.

(b) Liang, B.; Novak, T.; Tan, Z.; Negishi, E. *J. Am. Chem. Soc.* **2006**, *128*, 2770.

(c) Tan, Z.; Negishi, E. *Angew. Chem. Int. Ed.* **2004**, *43*, 2911.

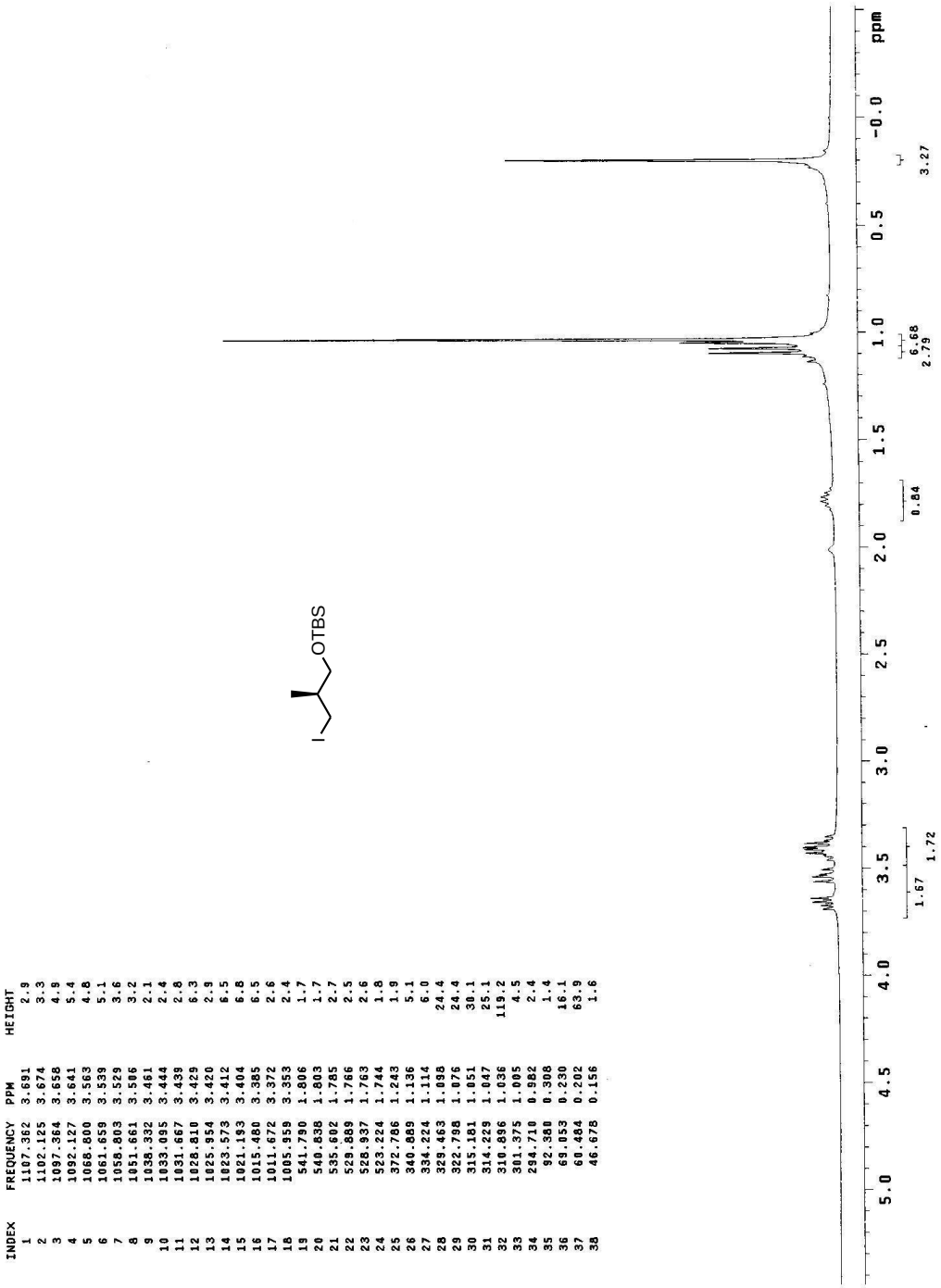
(d) Zhu, G.; Negishi, E. *Org. Lett.* **2007**, *9*, 2771.

(e) Wang, G.; Huang, Z.; Negishi, E. *Tetrahedron Lett.* **2009**, *50*, 3220.

(f) Pitsinos, E. N.; Moutsos, V. I.; Vageli, O. *Tetrahedron Lett.* **2007**, *48*, 1523.

Total Synthesis of (+)-Scyphostatin Featuring a Fully Enantioselective and Highly Efficient Route to the Side-Chain via Zr-Catalyzed Asymmetric Carboalumination of Alkenes (ZACA)

E. Pitsinos,* N. Athinaios, Z. Xu, G. Wang, and E. Negishi*



INDEX	FREQUENCY	PPM	HEIGHT
1	1107.362	3.691	2.9
2	1102.125	3.674	3.3
3	1097.364	3.658	4.9
4	1092.127	3.641	5.4
5	1068.800	3.563	4.8
6	1061.659	3.539	5.1
7	1058.803	3.529	3.6
8	1051.661	3.506	3.2
9	1038.332	3.461	2.1
10	1033.095	3.444	2.4
11	1031.667	3.439	2.8
12	1028.810	3.429	6.3
13	1025.954	3.420	2.9
14	1023.573	3.412	6.5
15	1021.193	3.404	6.8
16	1015.480	3.385	6.5
17	1011.672	3.372	2.6
18	1005.959	3.353	2.4
19	541.790	1.806	1.7
20	540.838	1.803	1.7
21	535.602	1.785	2.7
22	529.889	1.766	2.5
23	528.937	1.763	2.6
24	523.224	1.744	1.8
25	372.786	1.243	1.9
26	340.889	1.136	5.1
27	334.224	1.114	6.0
28	329.463	1.098	24.4
29	322.798	1.076	24.4
30	315.181	1.051	30.1
31	314.229	1.047	25.1
32	310.896	1.036	119.2
33	301.375	1.005	4.5
34	294.710	0.982	2.4
35	92.380	0.308	1.4
36	69.053	0.230	16.1
37	60.484	0.202	63.9
38	46.678	0.156	1.6

Total Synthesis of (+)-Scyphostatin Featuring a Fully Enantioselective and Highly Efficient Route to the Side-Chain via Zr-Catalyzed Asymmetric Carboalumination of Alkenes (ZACA)

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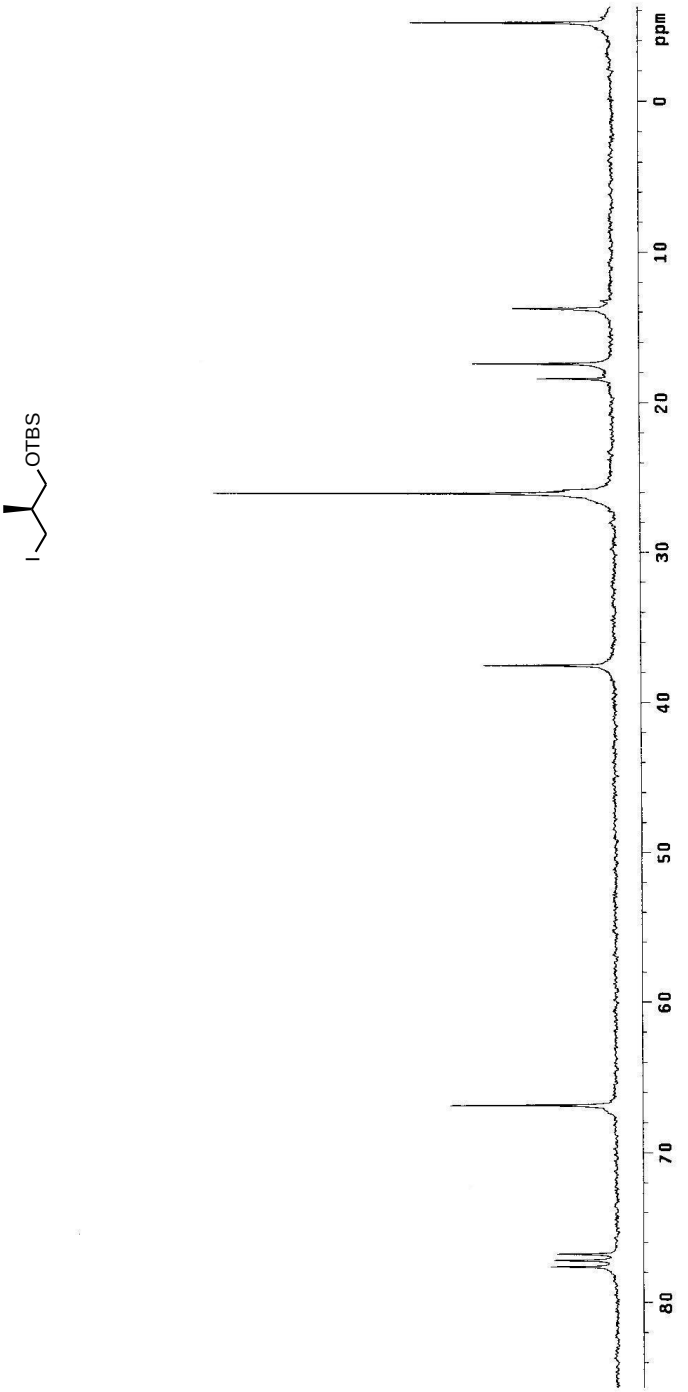

INDEX	FREQUENCY	PPM	HEIGHT
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3	5792.826	76.794	10.9
4	5042.946	66.853	30.0
5	2831.983	37.543	23.6
6	1967.151	26.078	72.3
7	1388.089	18.402	13.7
8	1313.960	17.418	25.4
9	1037.858	13.759	18.1
10	-390.995	-5.183	36.3

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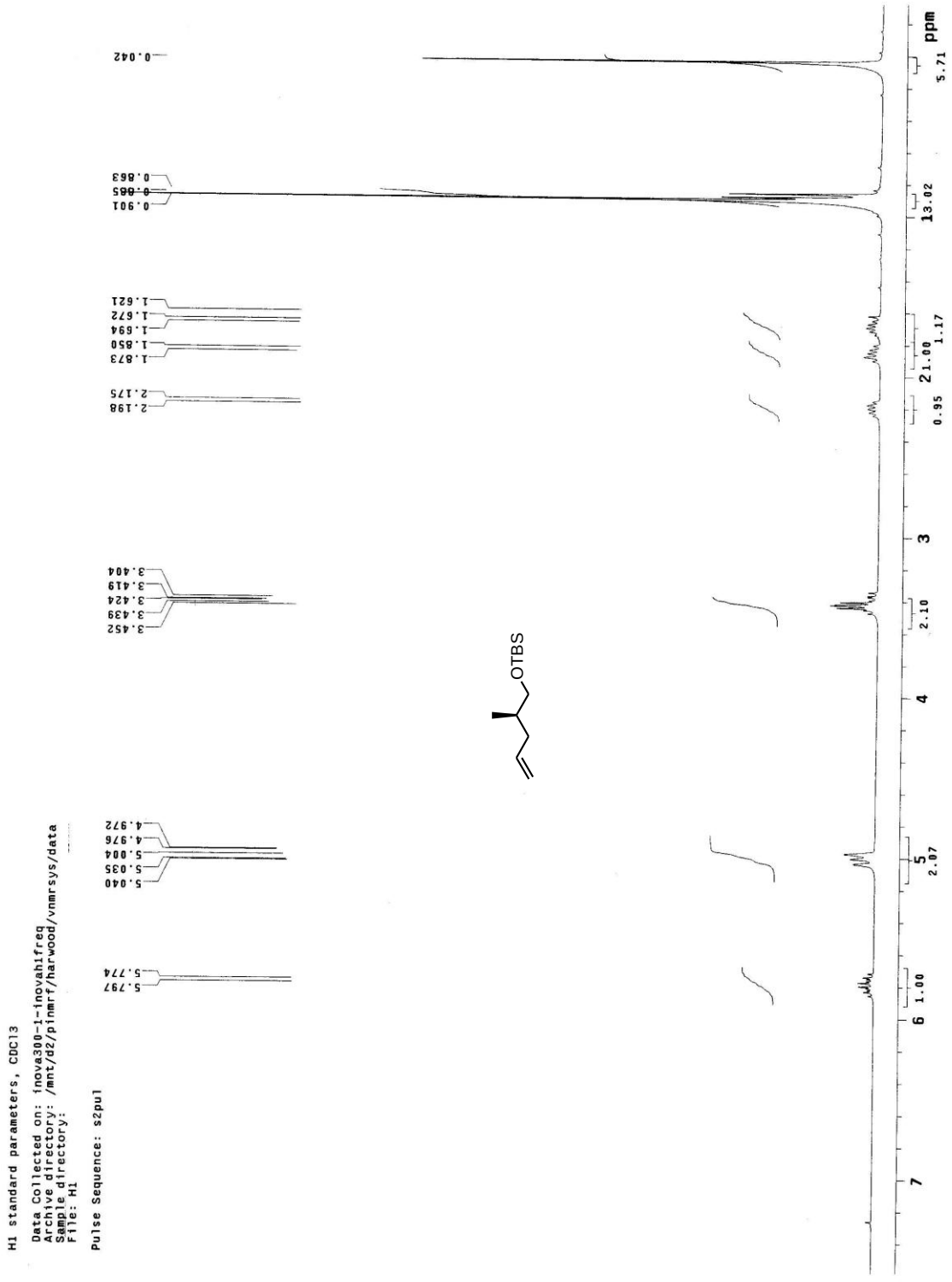

Total Synthesis of (+)-Scyphostatin Featuring a Fully Enantioselective and Highly Efficient Route to the Side-Chain via Zr-Catalyzed Asymmetric Carboalumination of Alkenes (ZACA)

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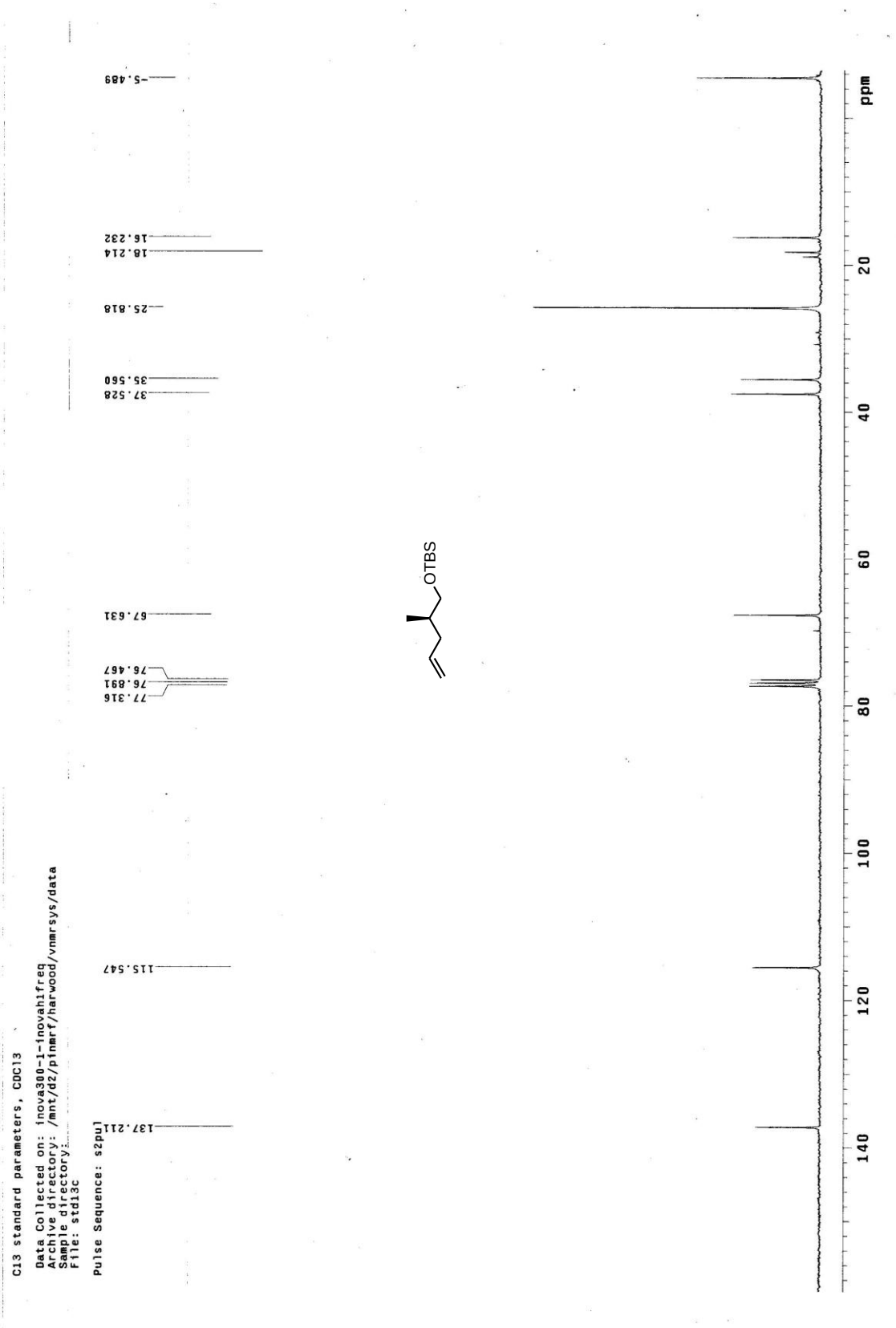

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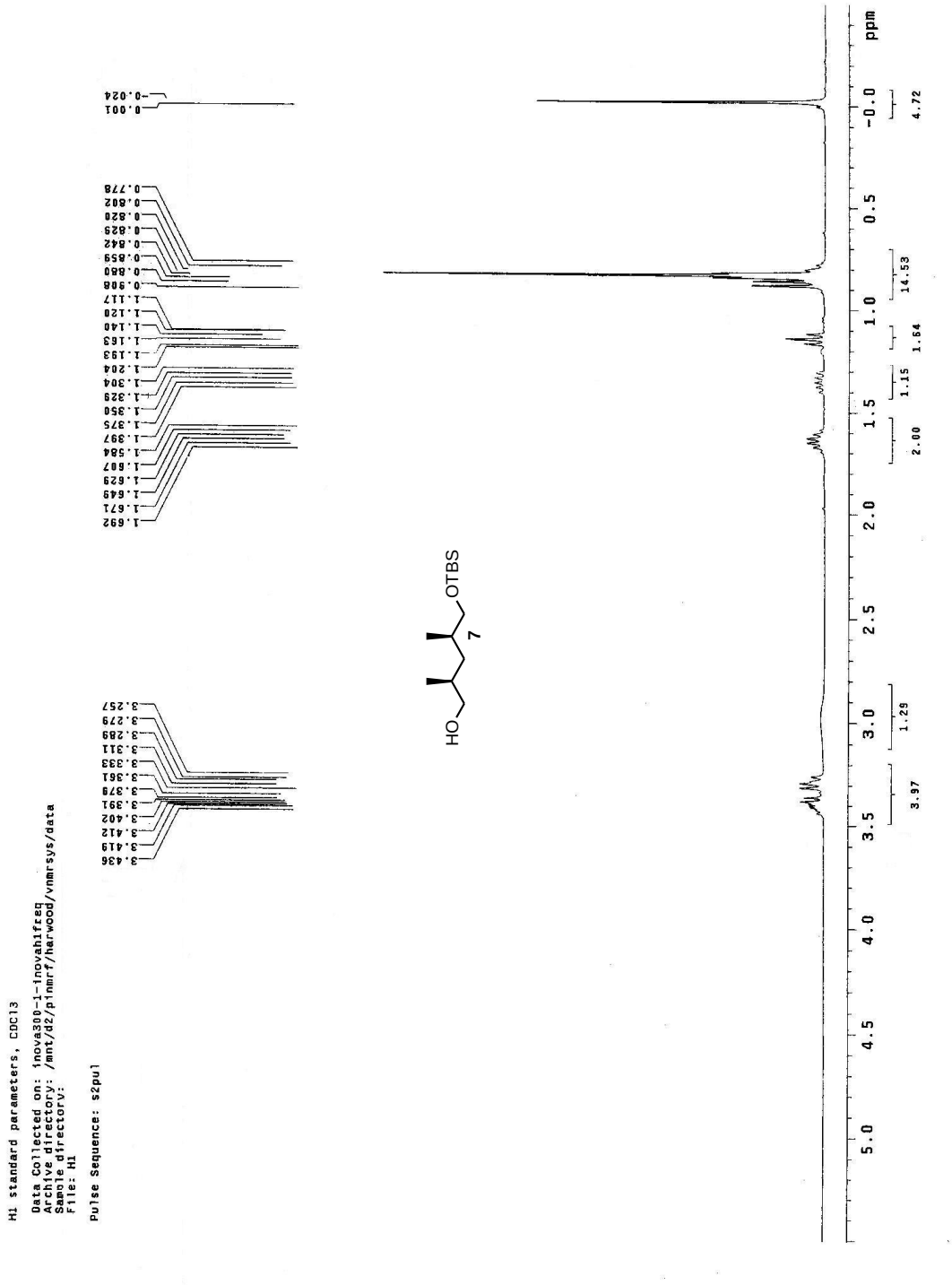

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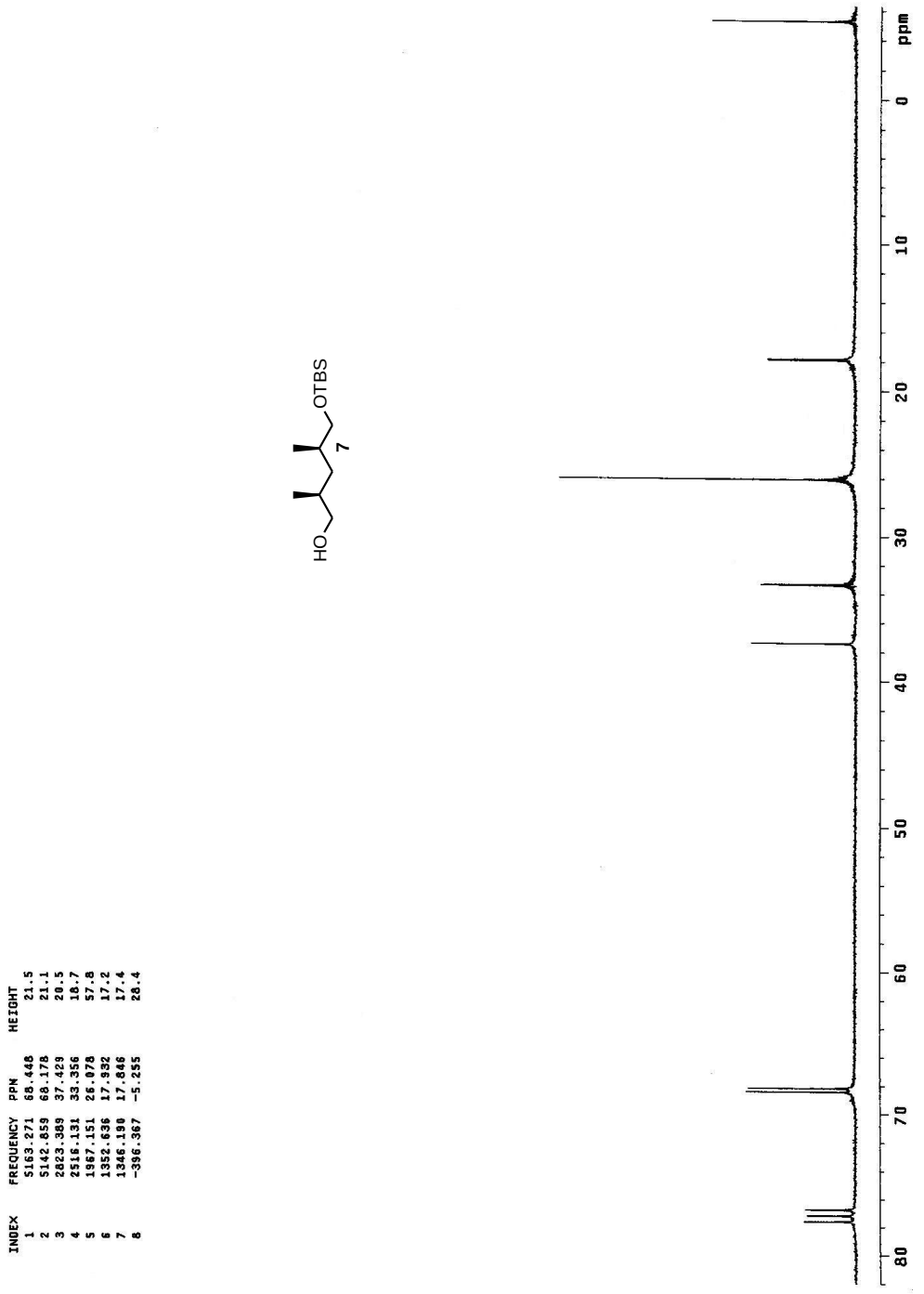

INDEX	FREQUENCY	PPM	HEIGHT
1	5163.271	68.448	21.5
2	5142.859	68.178	21.1
3	2823.389	37.429	20.5
4	2516.131	33.356	18.7
5	1967.151	26.078	57.8
6	1352.636	17.932	17.2
7	1346.190	17.846	17.4
8	-396.367	-5.255	28.4

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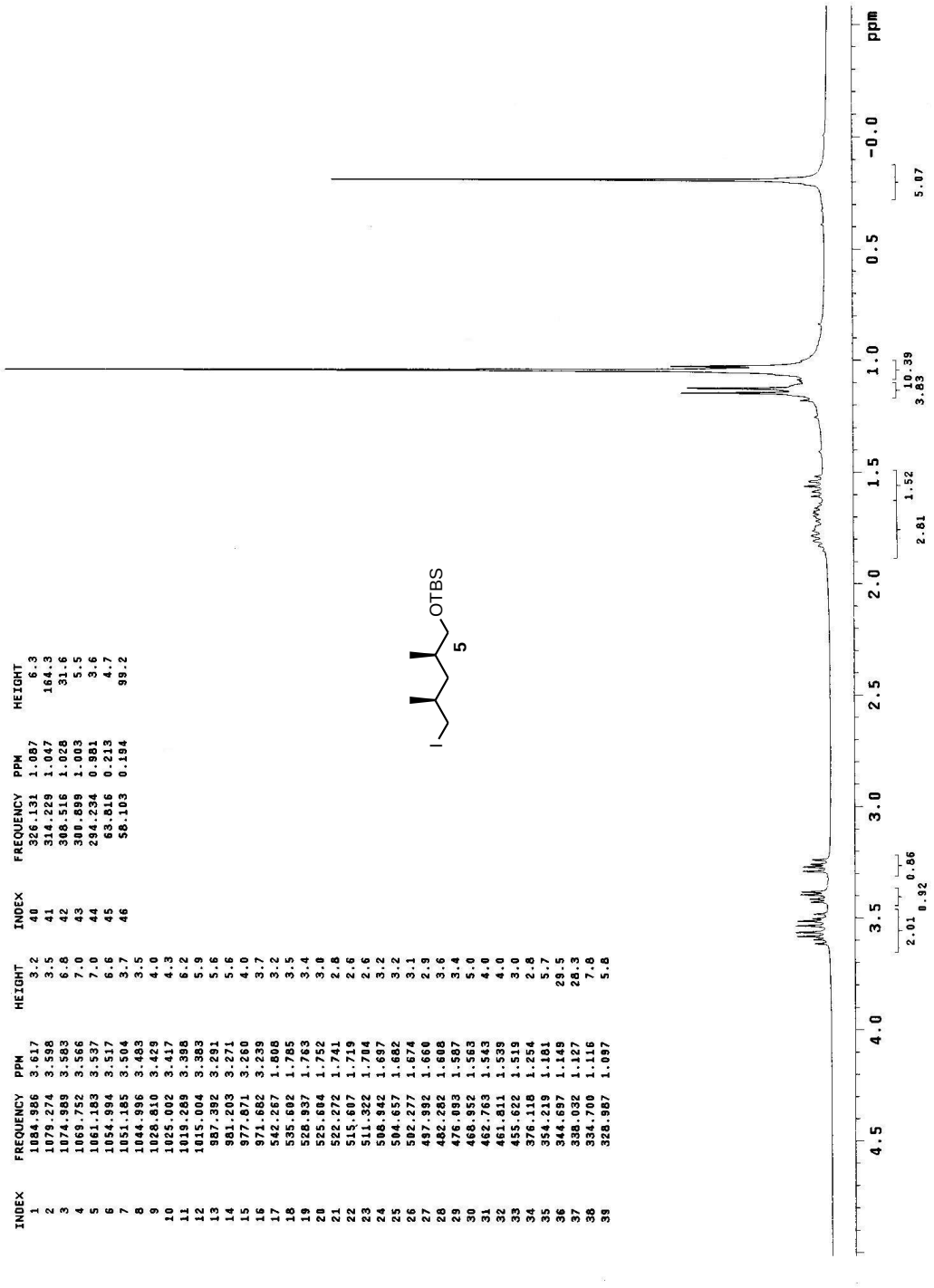

INDEX	FREQUENCY	PPM	HEIGHT
1	1084.986	3.617	3.2
2	1079.274	3.598	3.5
3	1074.989	3.583	6.8
4	1069.752	3.566	7.0
5	1061.183	3.537	7.0
6	1054.994	3.517	6.6
7	1051.185	3.504	3.7
8	1044.996	3.483	3.5
9	1028.810	3.429	4.0
10	1025.002	3.417	4.3
11	1019.289	3.398	6.2
12	1015.004	3.383	5.9
13	987.392	3.291	5.6
14	981.203	3.271	5.6
15	977.871	3.260	4.0
16	971.682	3.239	3.7
17	542.267	1.808	3.2
18	535.602	1.785	3.5
19	528.937	1.763	3.4
20	525.604	1.752	3.0
21	522.272	1.741	2.8
22	515.607	1.719	2.6
23	511.322	1.704	2.6
24	508.942	1.697	3.2
25	504.657	1.682	3.2
26	502.277	1.674	3.1
27	497.992	1.660	2.9
28	482.282	1.608	3.6
29	476.093	1.587	3.4
30	468.952	1.563	5.0
31	462.763	1.543	4.0
32	461.811	1.539	4.0
33	455.622	1.519	3.0
34	376.118	1.254	2.8
35	354.219	1.181	5.7
36	344.697	1.149	29.5
37	338.032	1.127	28.3
38	334.700	1.116	7.8
39	328.987	1.097	5.8

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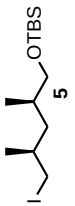
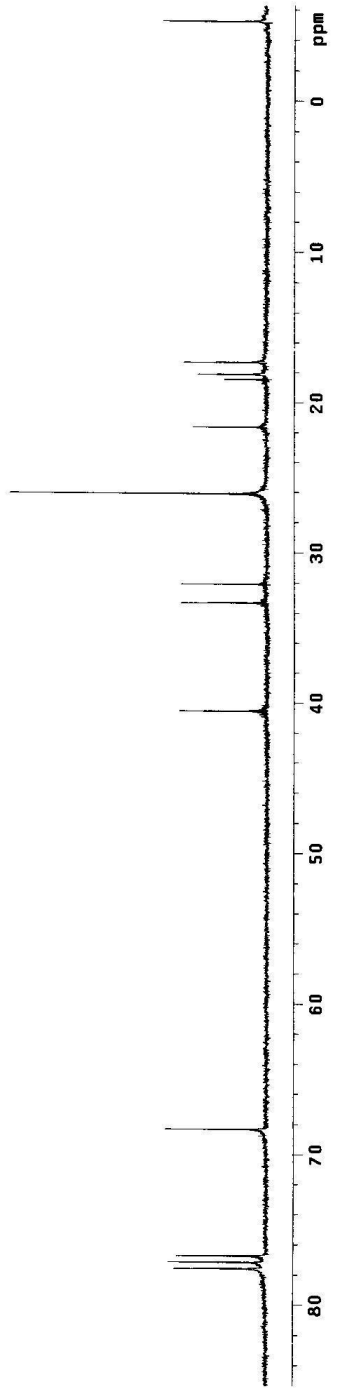


INDEX	FREQUENCY	PPM	HEIGHT
1	5854.063	77.686	16.9
2	5821.833	77.179	17.9
3	5789.603	76.752	16.5
4	5154.676	68.335	18.6
5	3059.740	40.562	16.1
6	2515.057	33.342	15.8
7	2421.591	32.103	15.8
8	1970.374	26.121	46.6
9	1967.151	26.078	7.2
10	1633.035	21.649	13.6
11	1393.460	18.473	7.9
12	1367.677	18.131	12.8
13	1307.514	17.333	15.3
14	-393.144	-5.212	19.2



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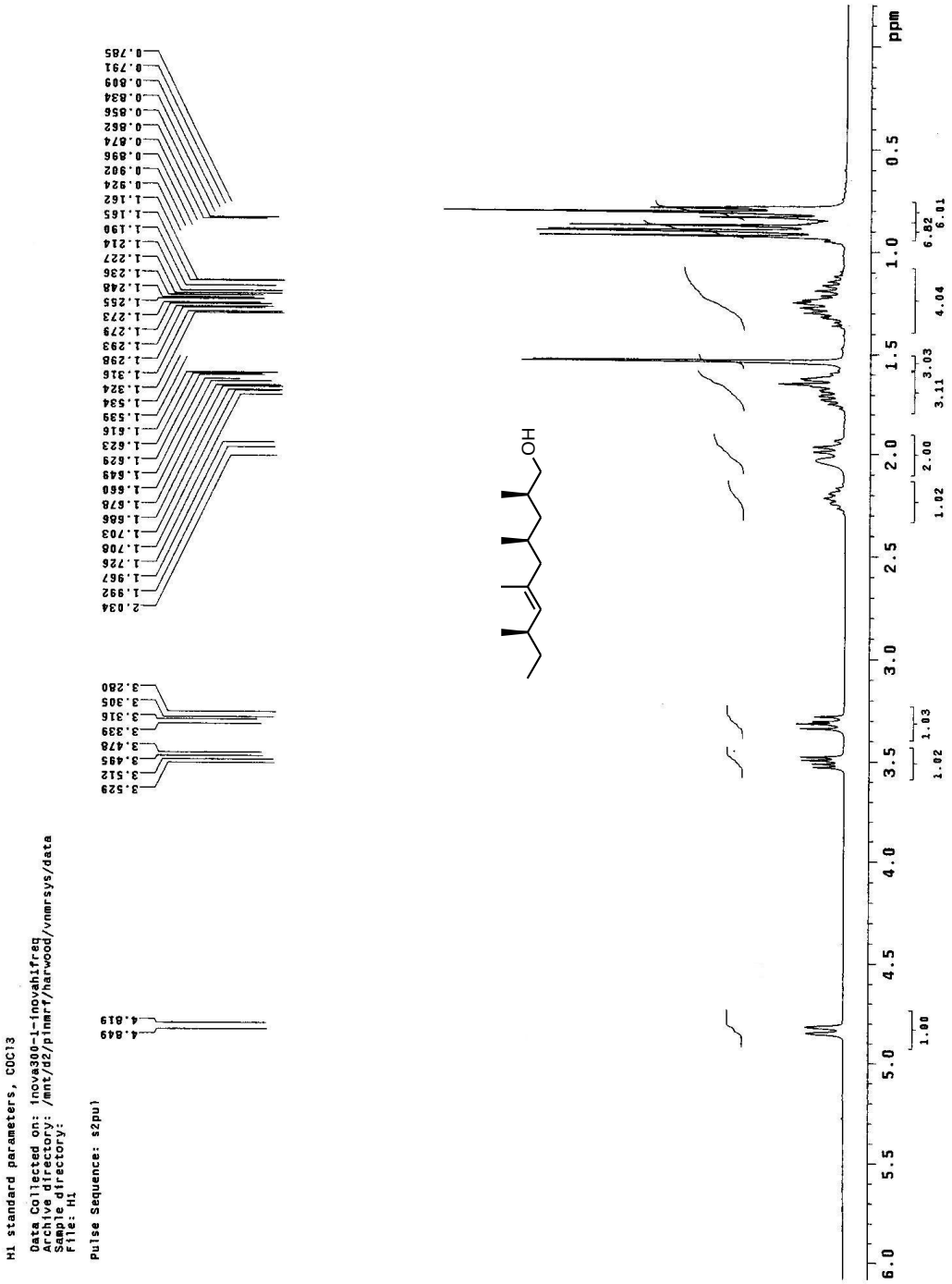

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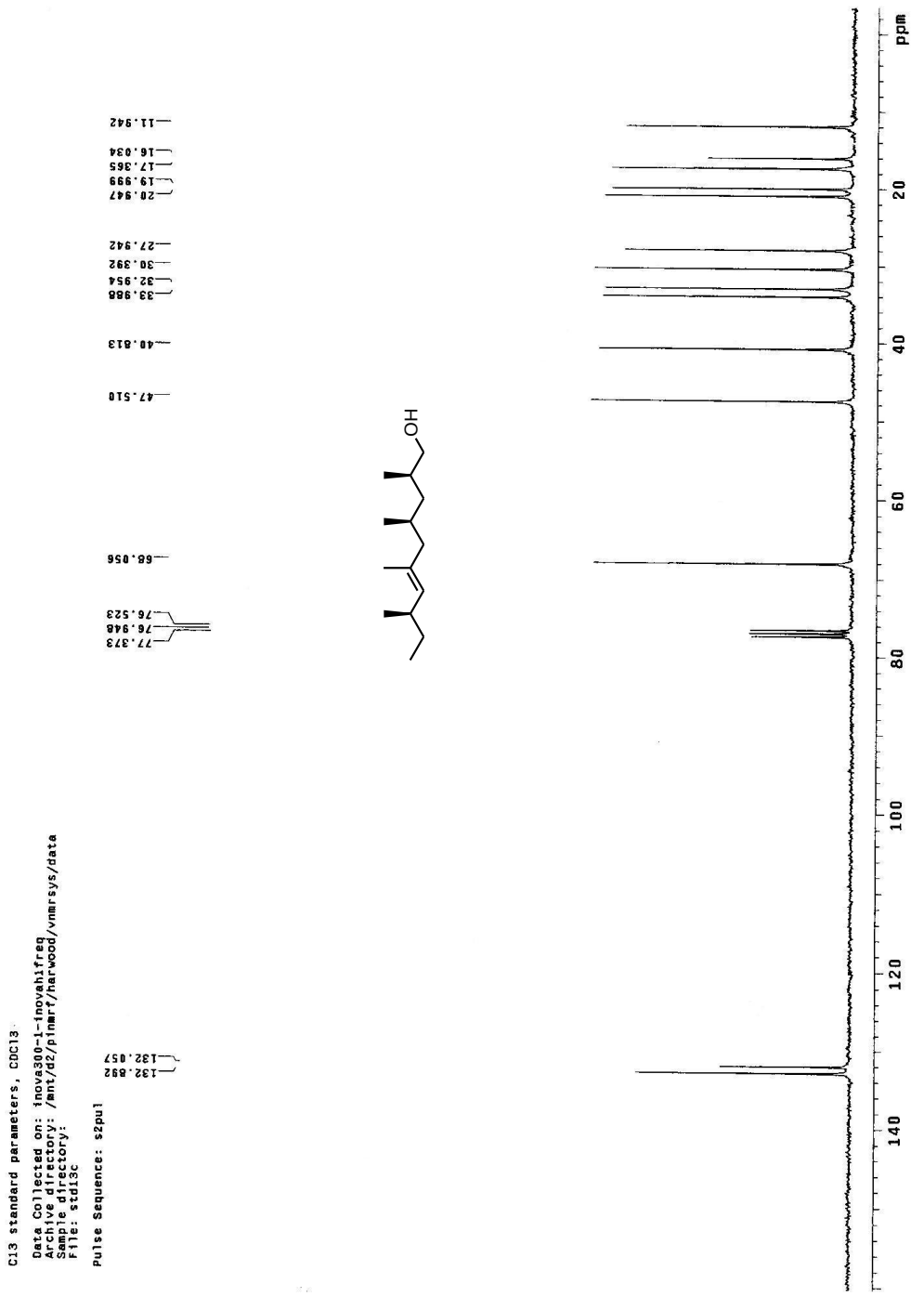

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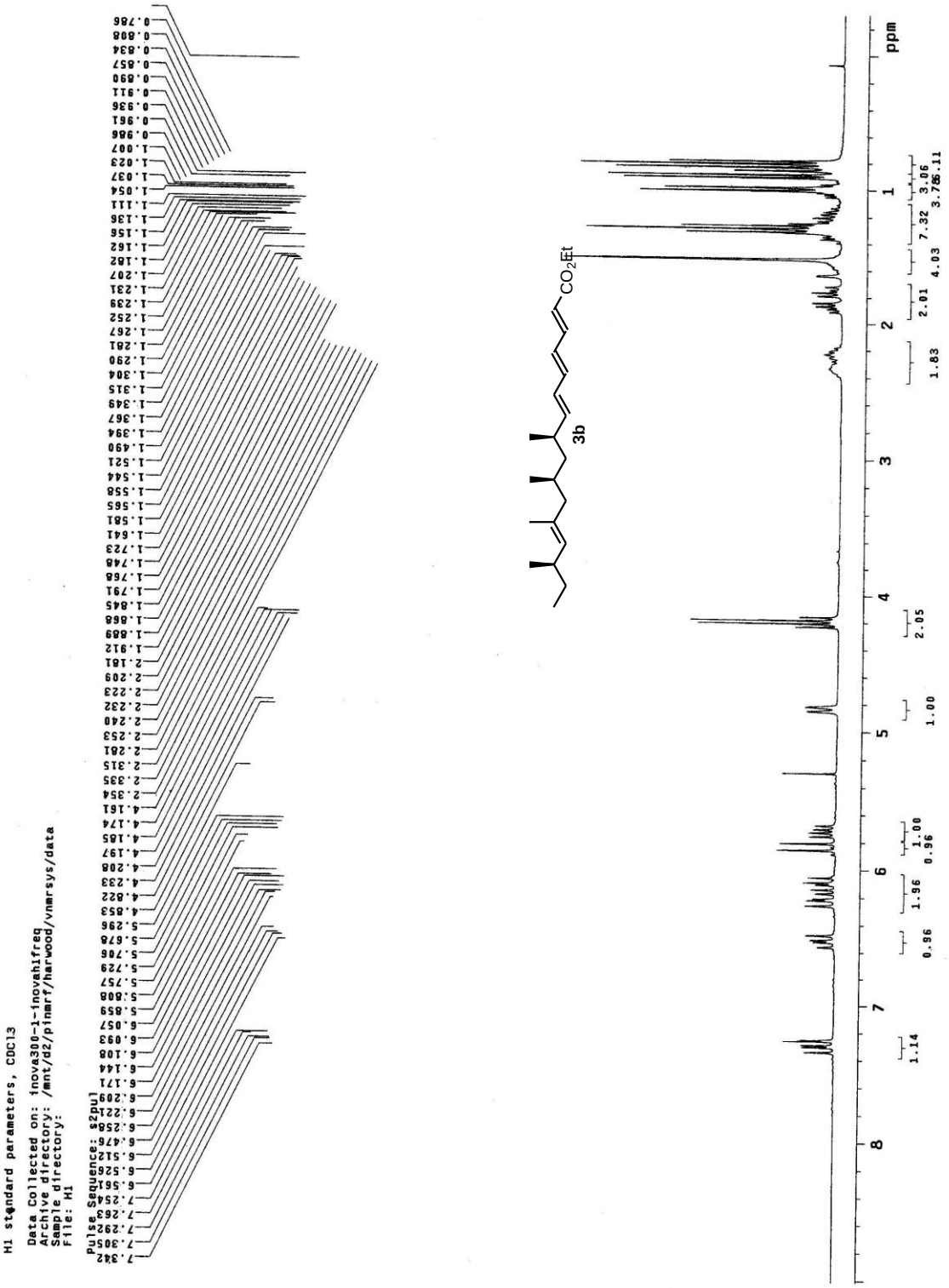

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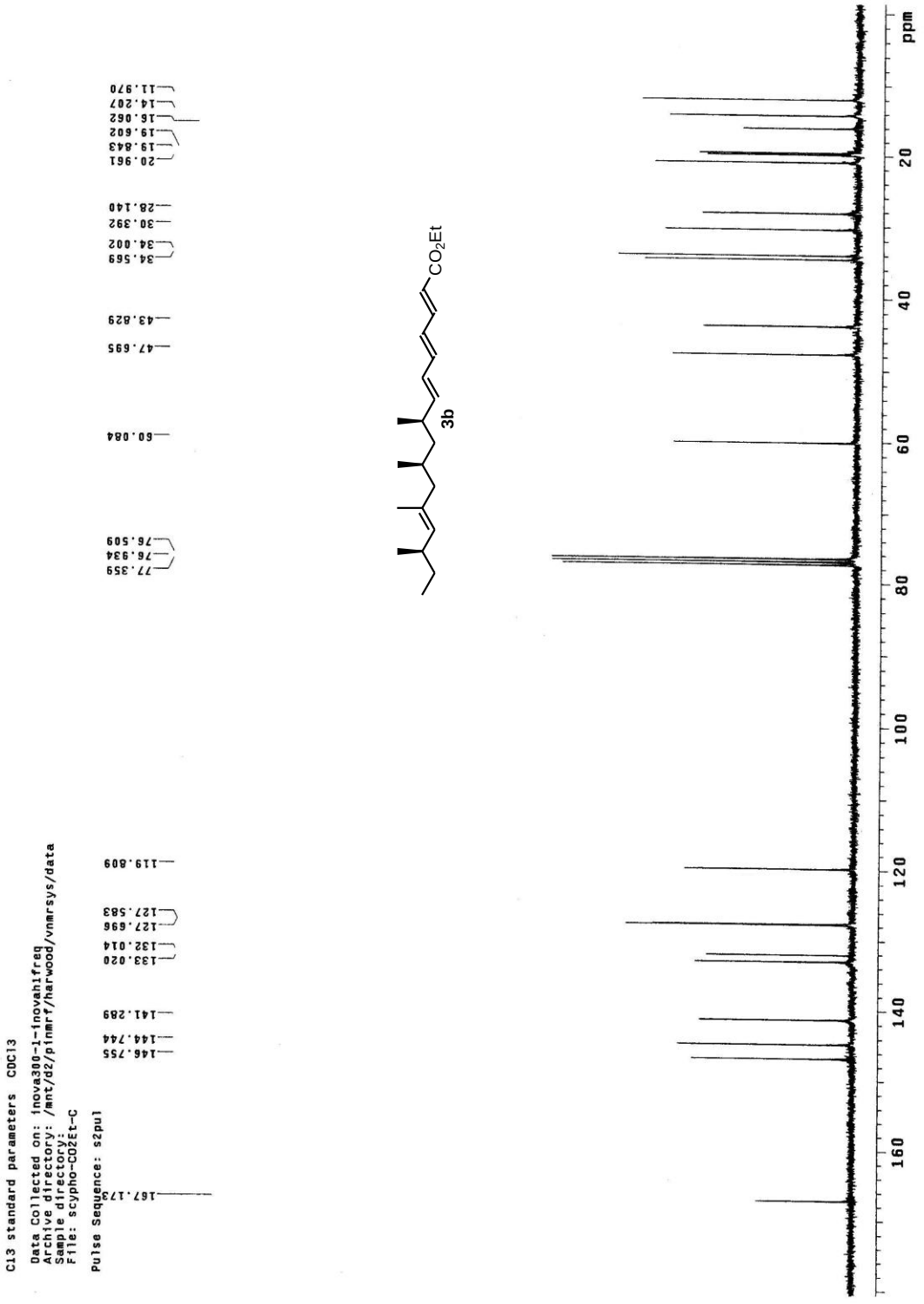

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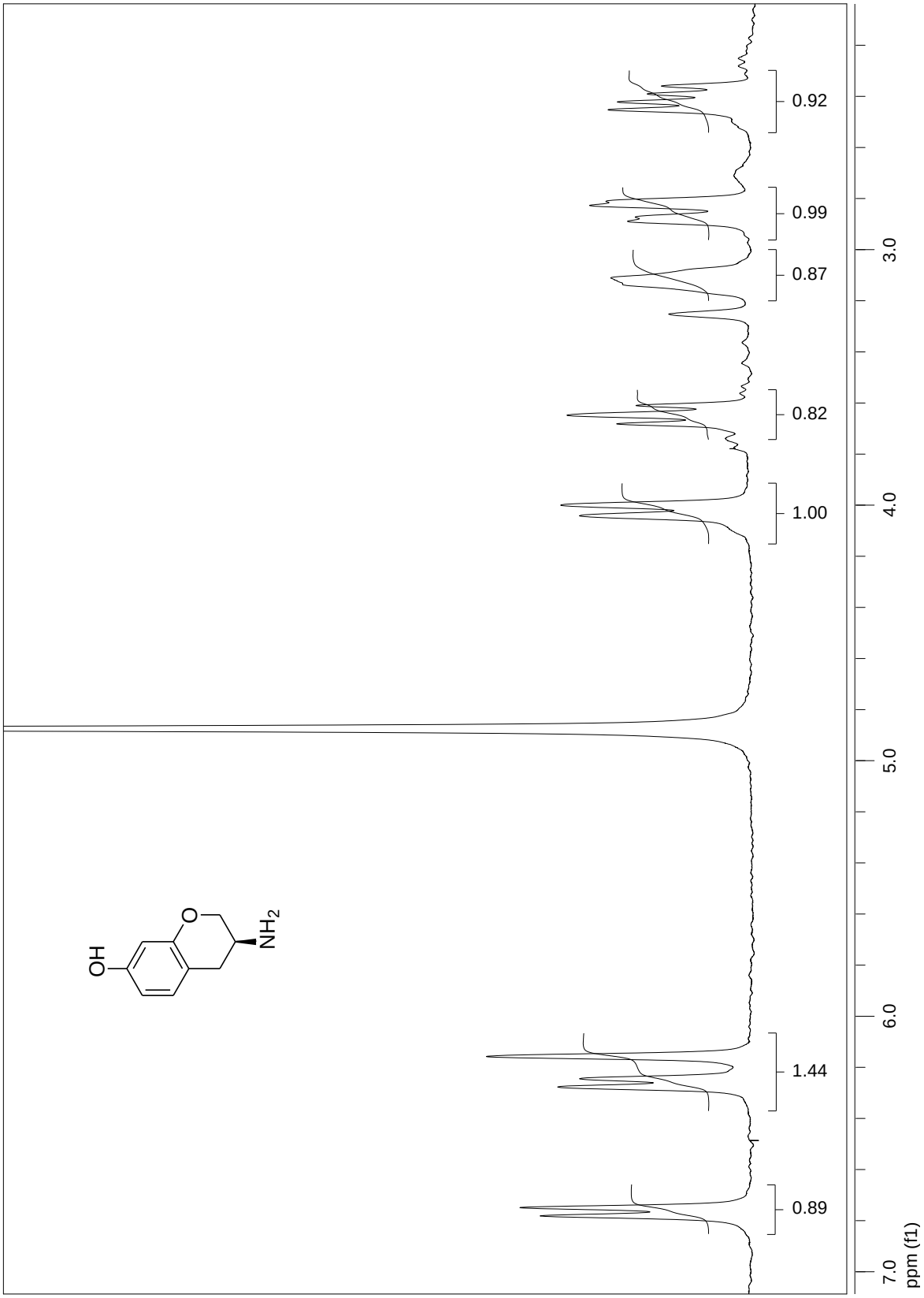

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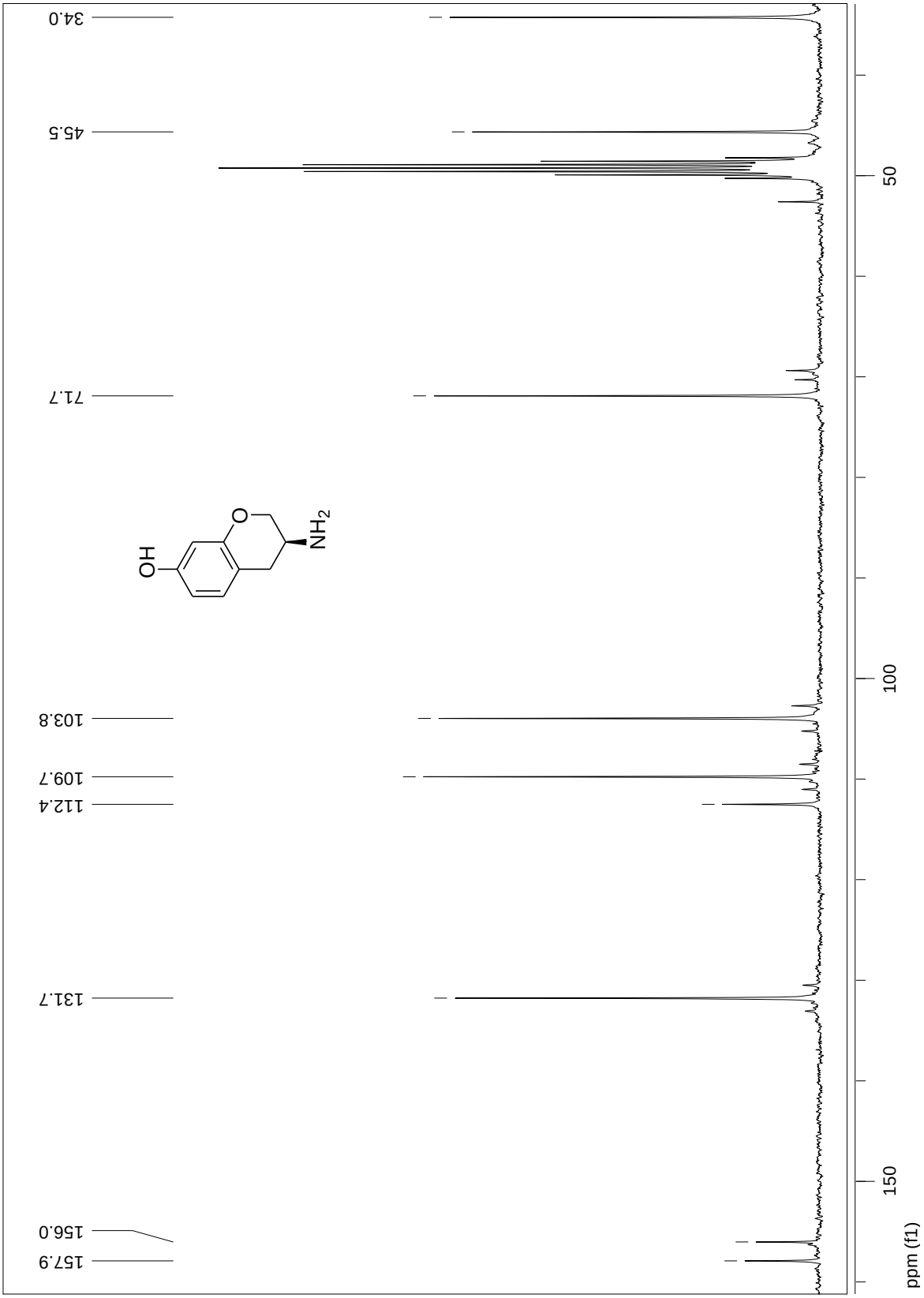

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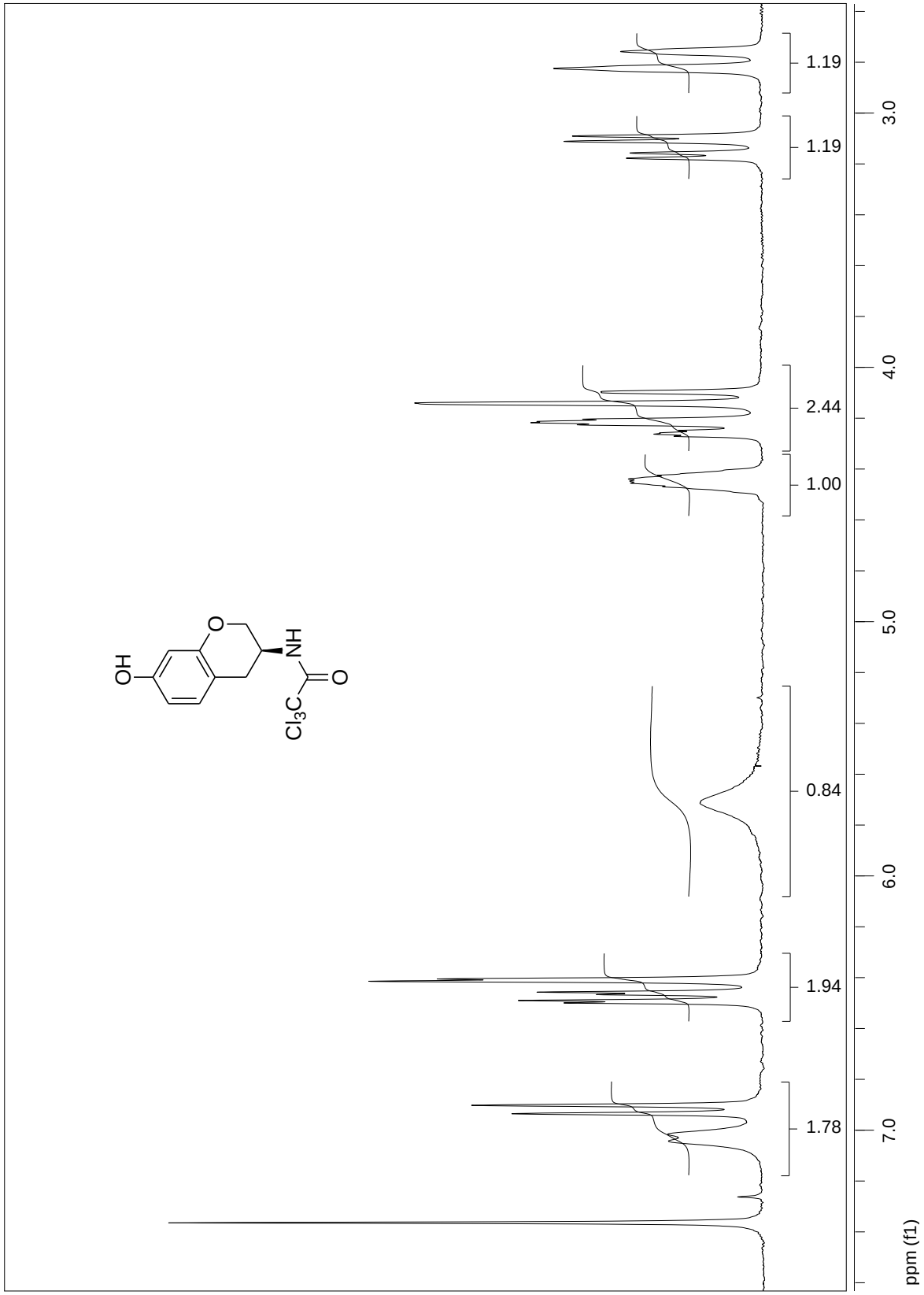

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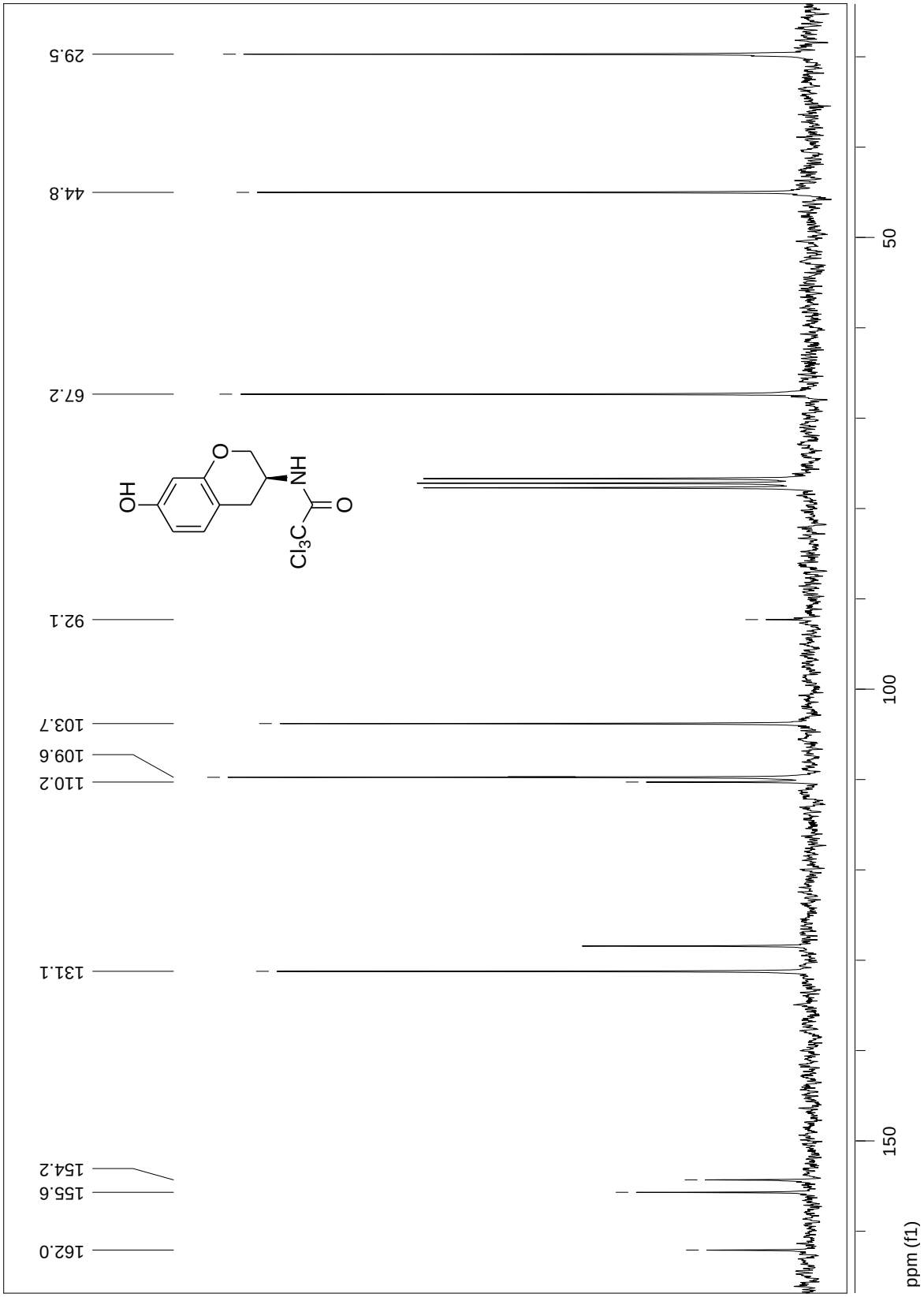

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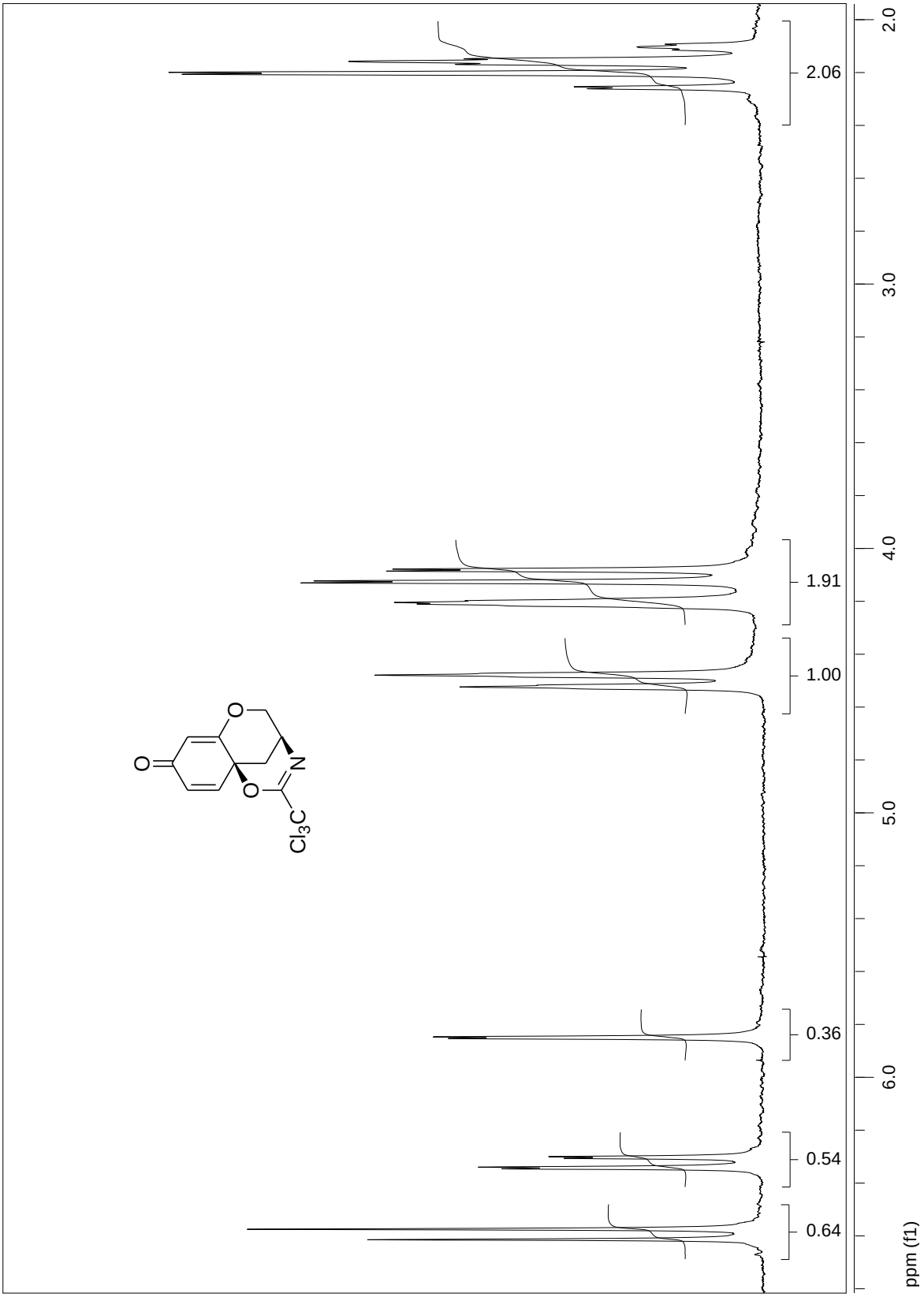

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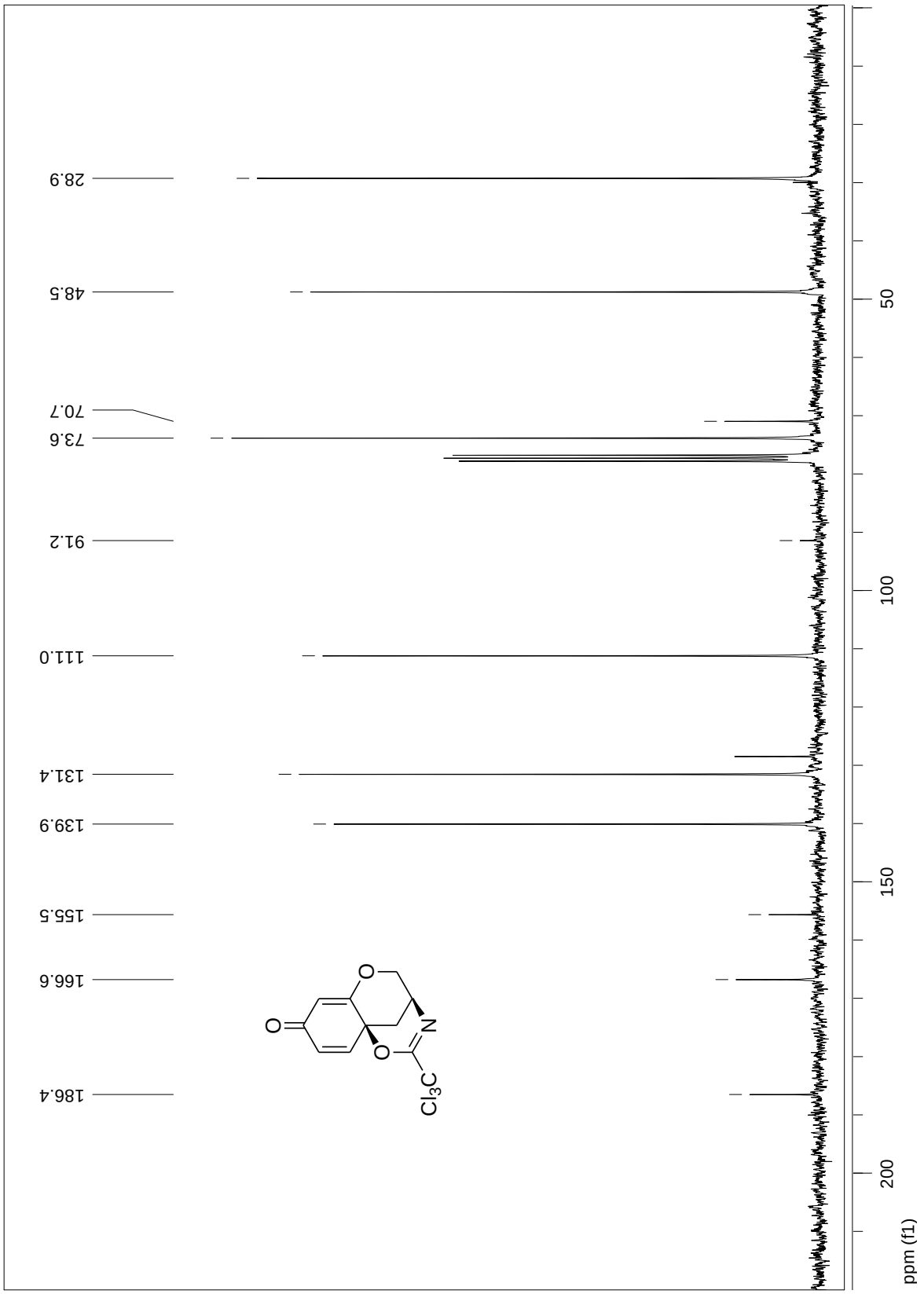

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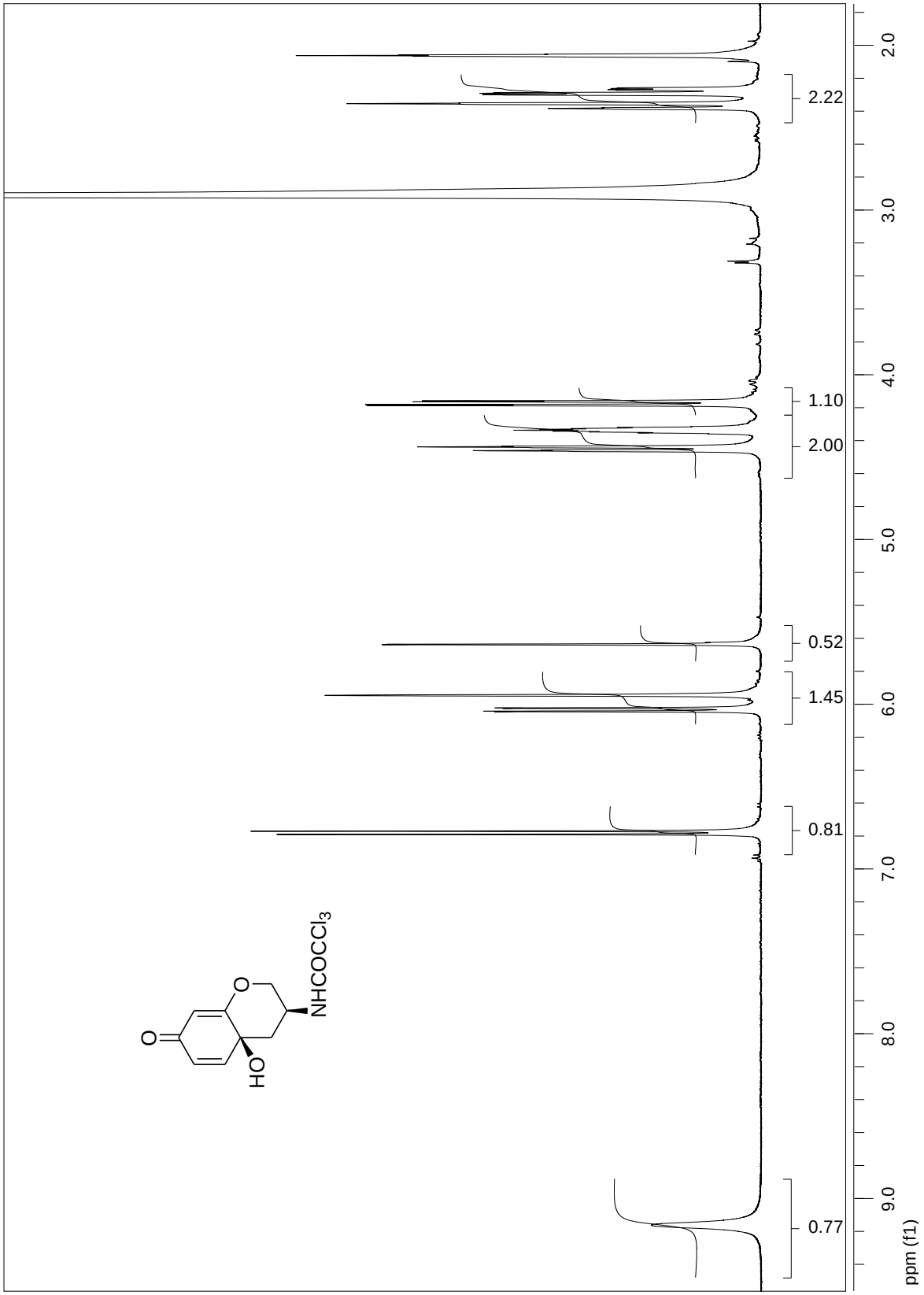

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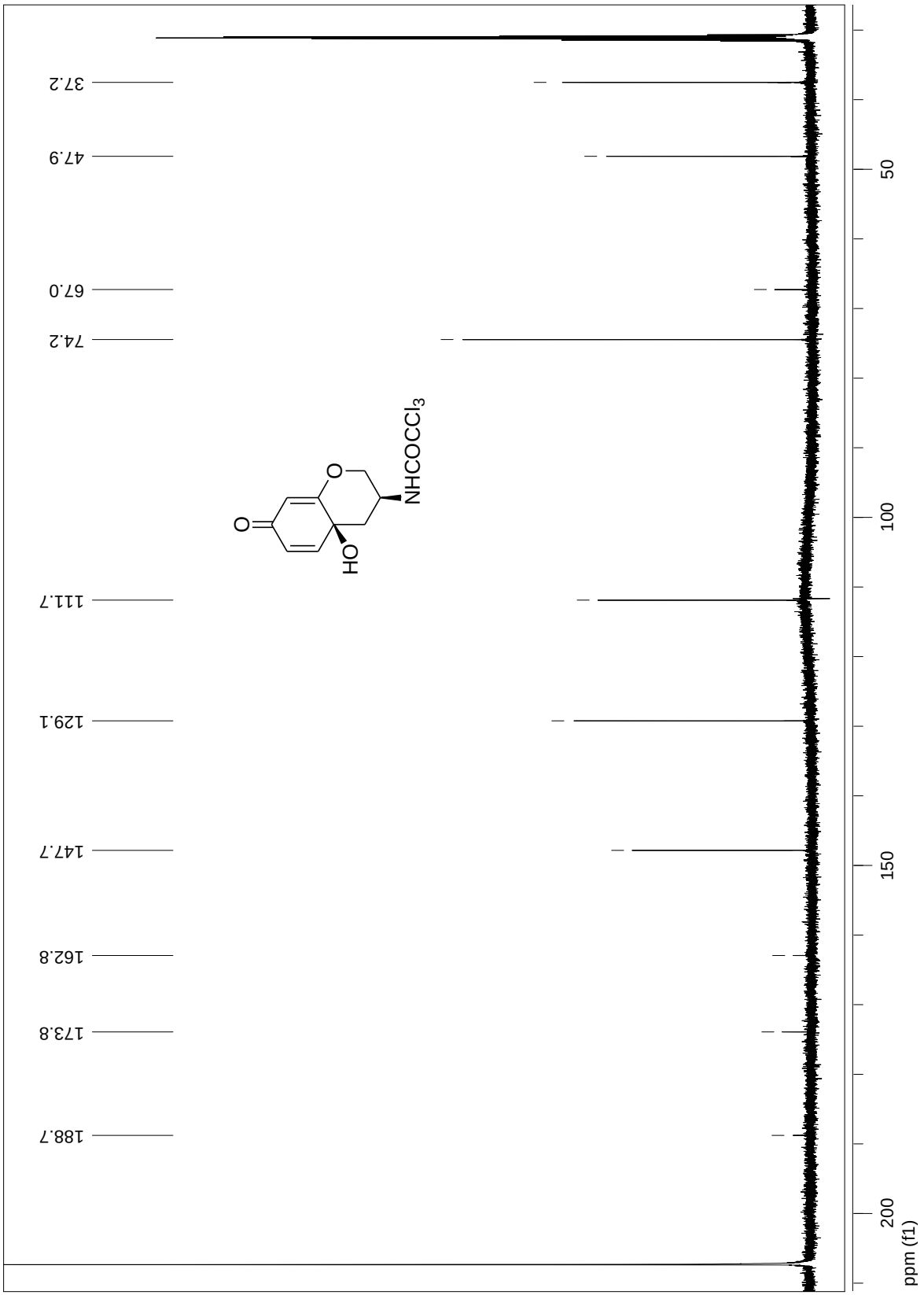

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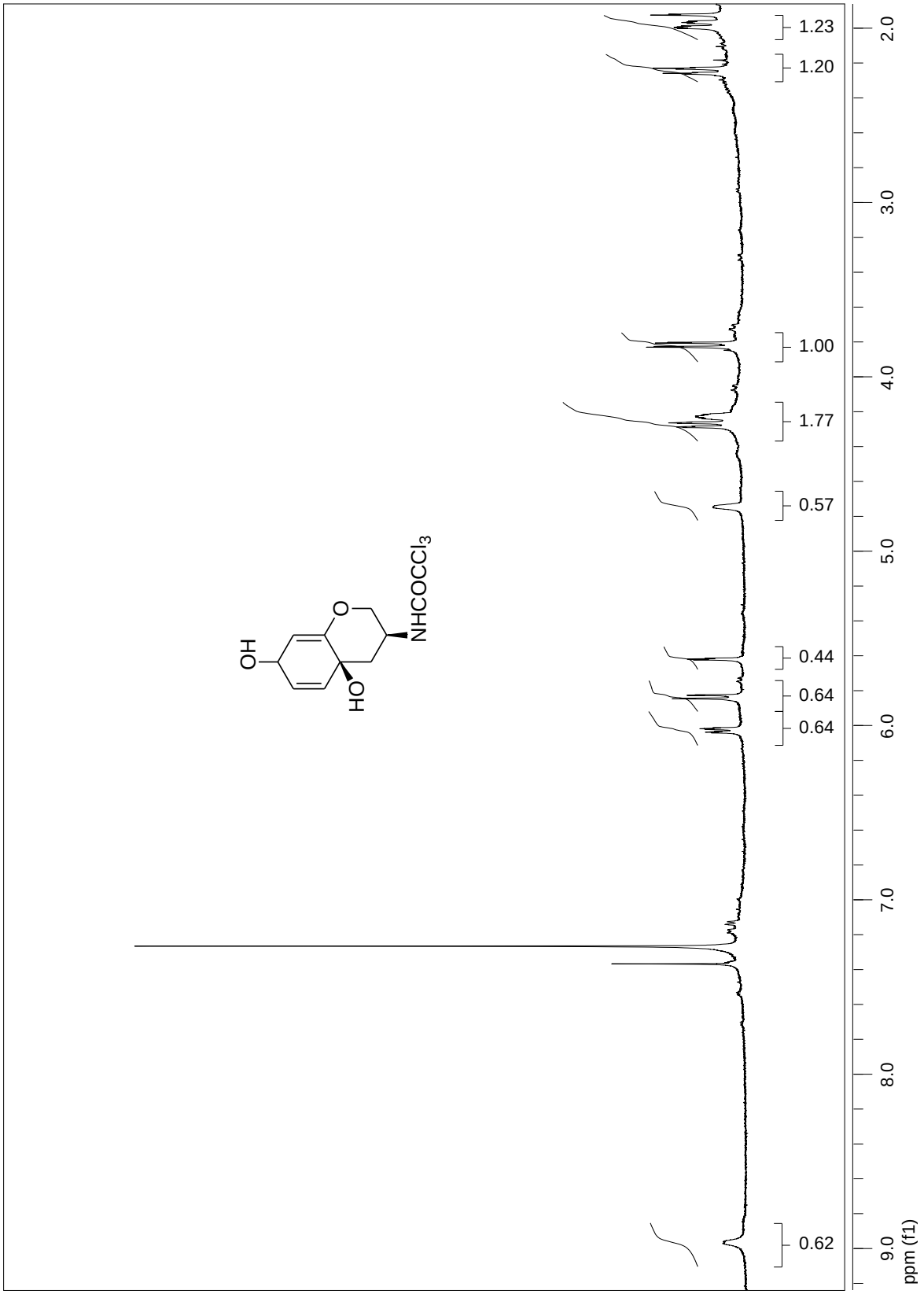

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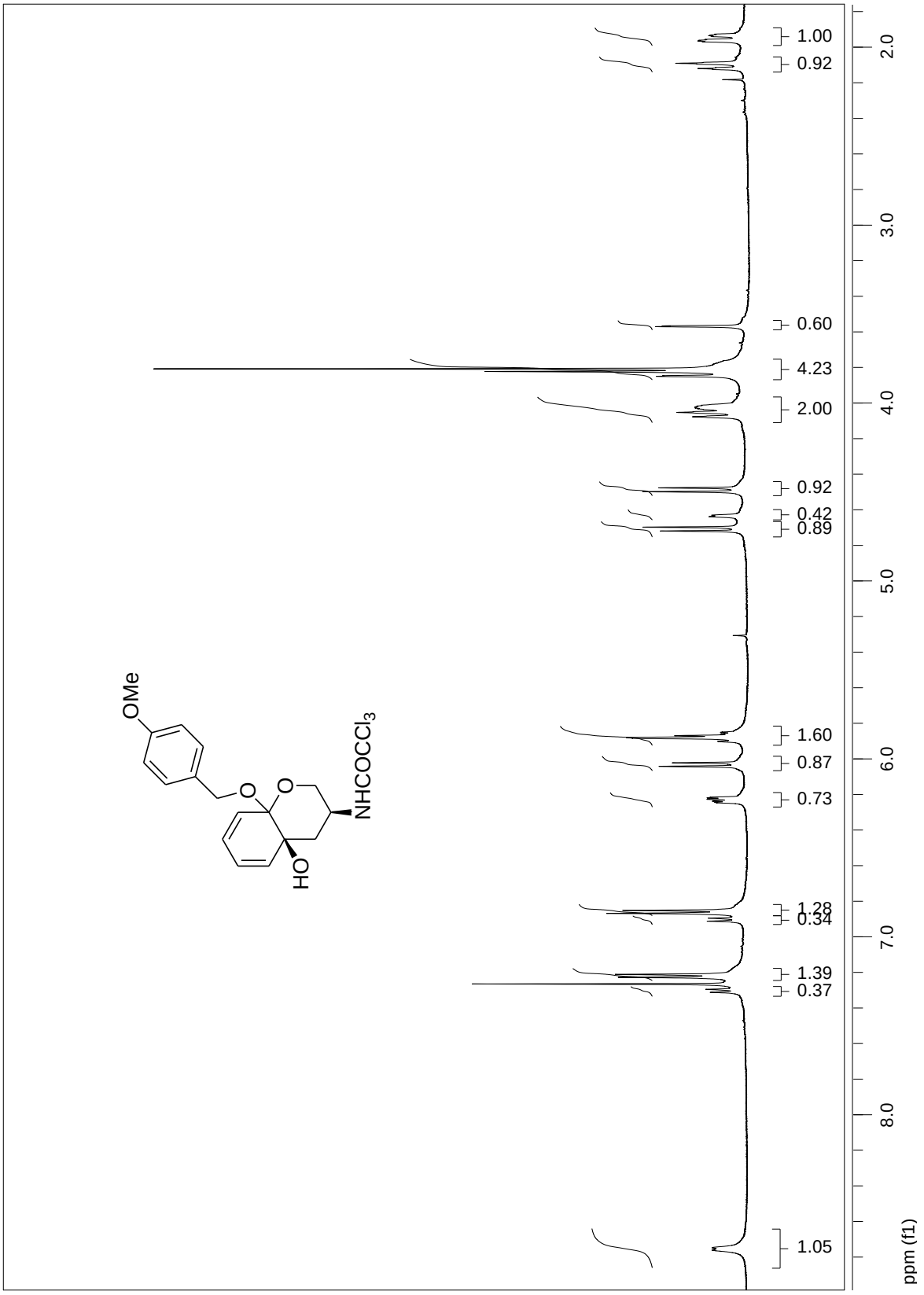

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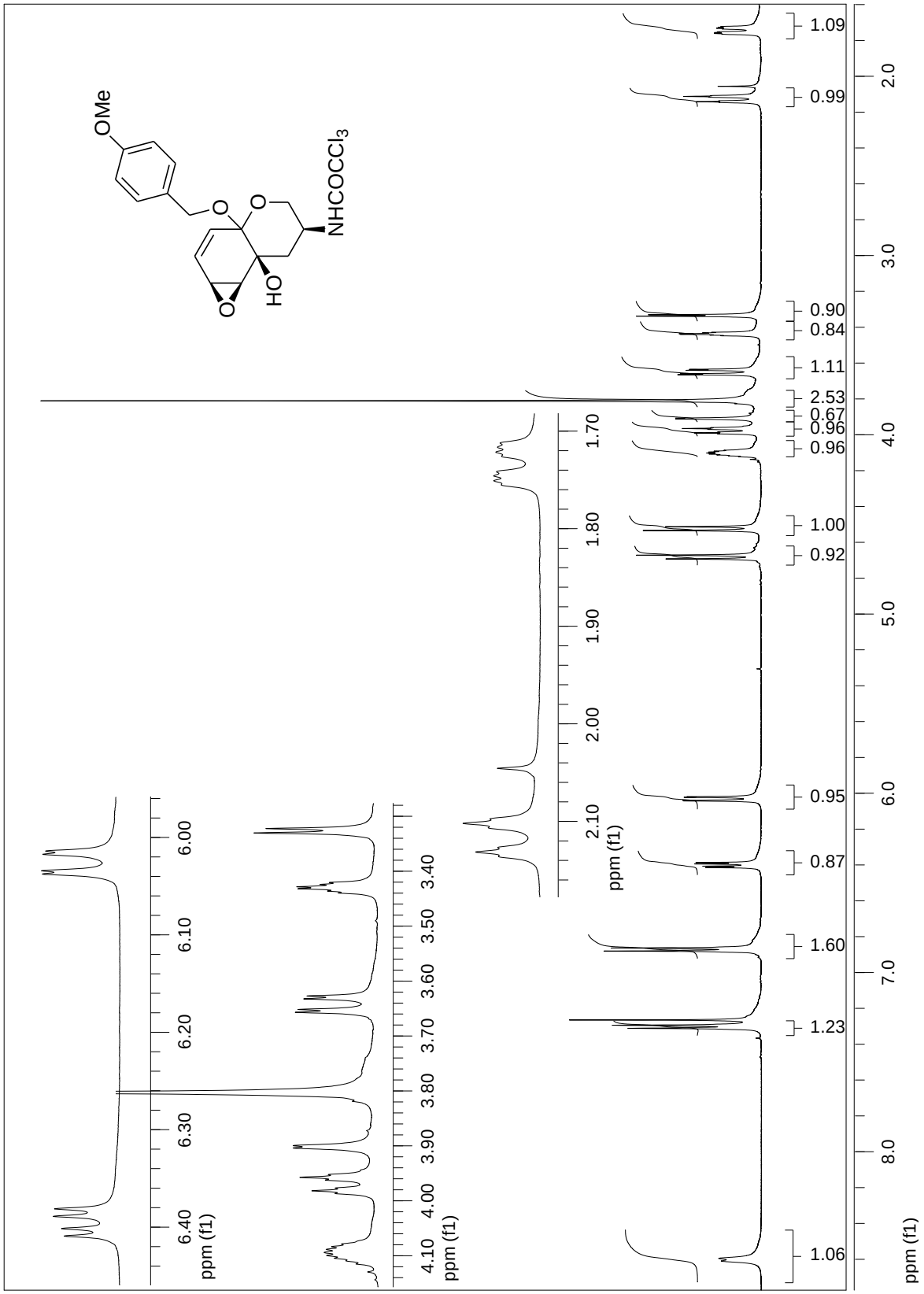

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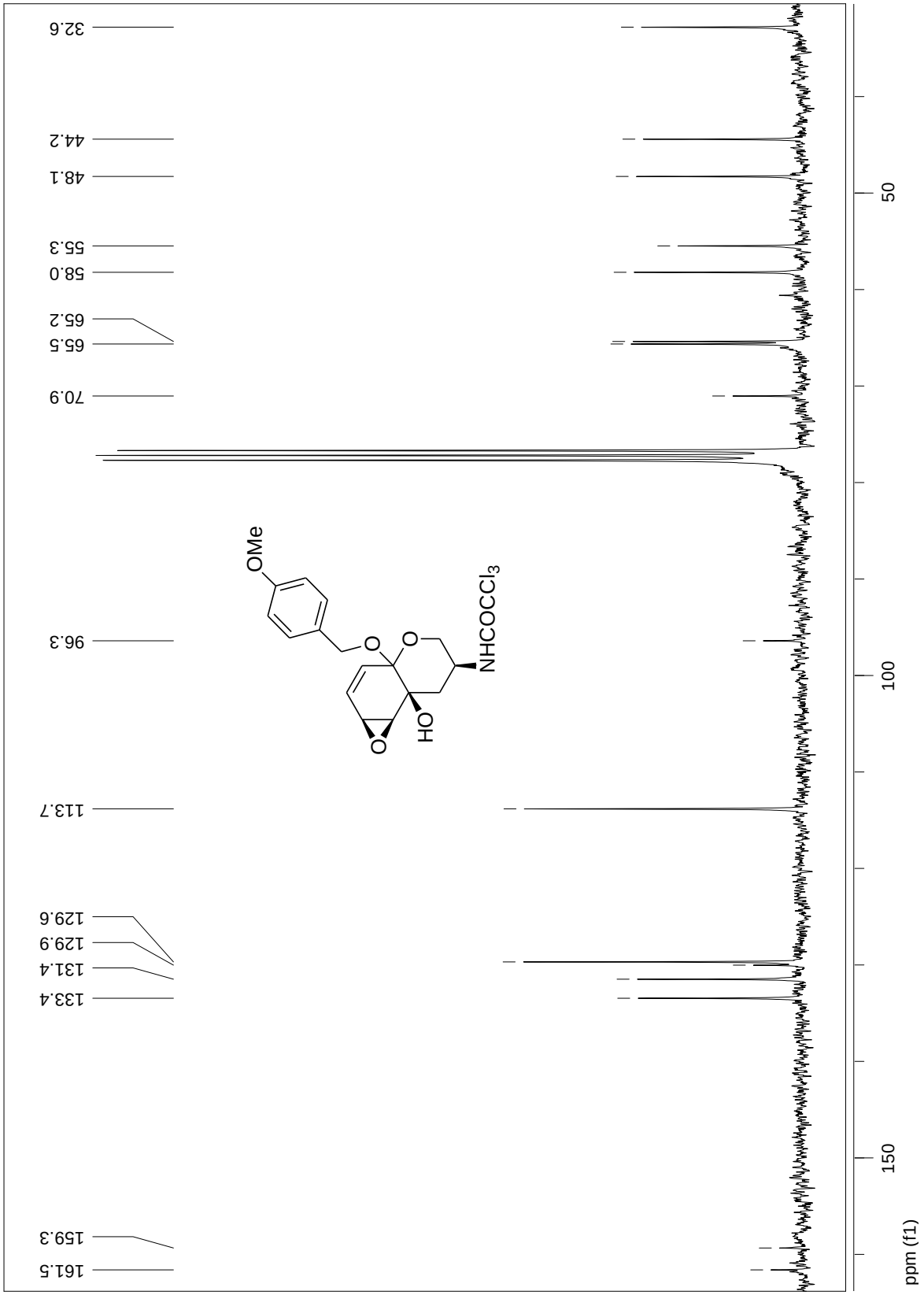

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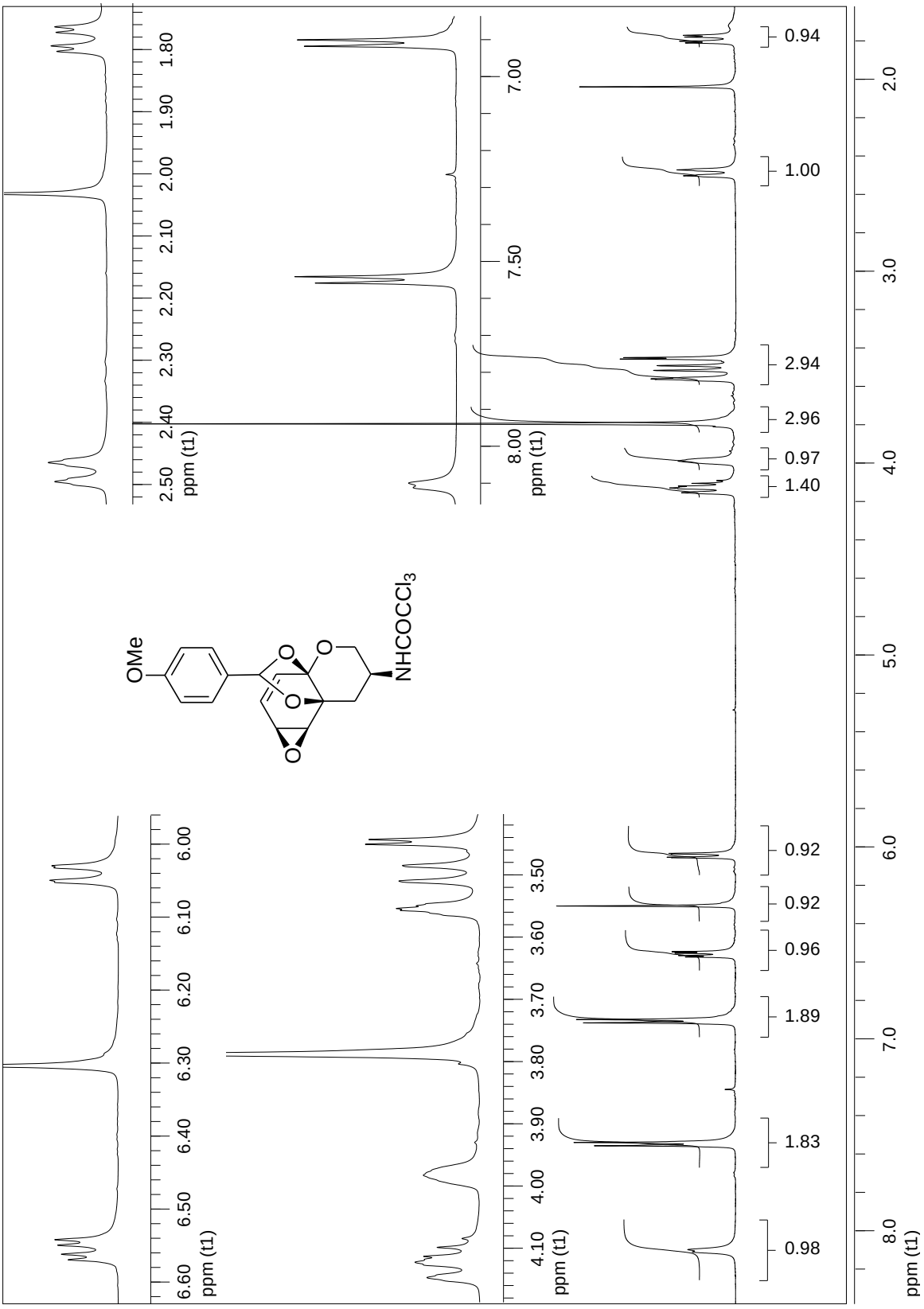

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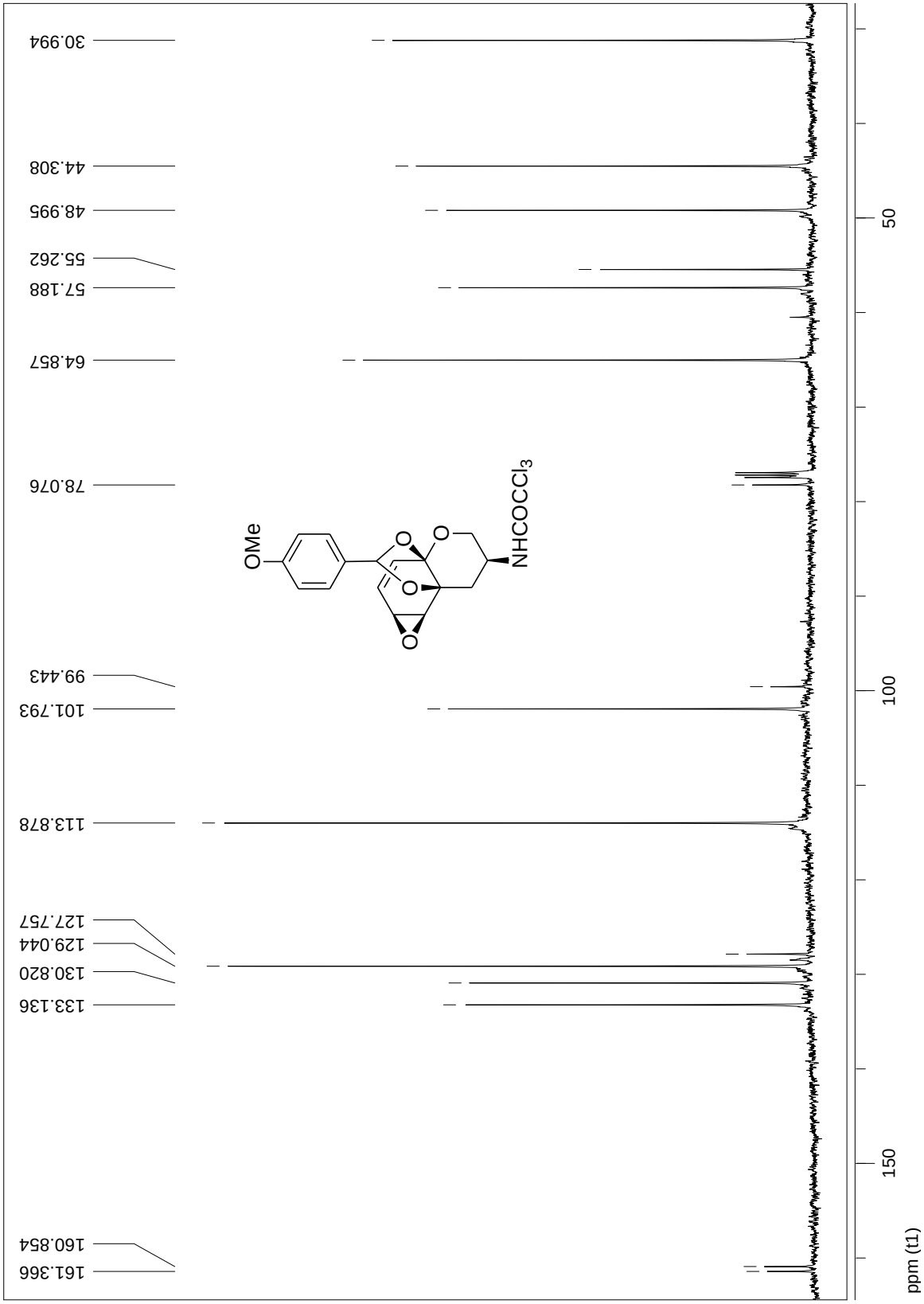

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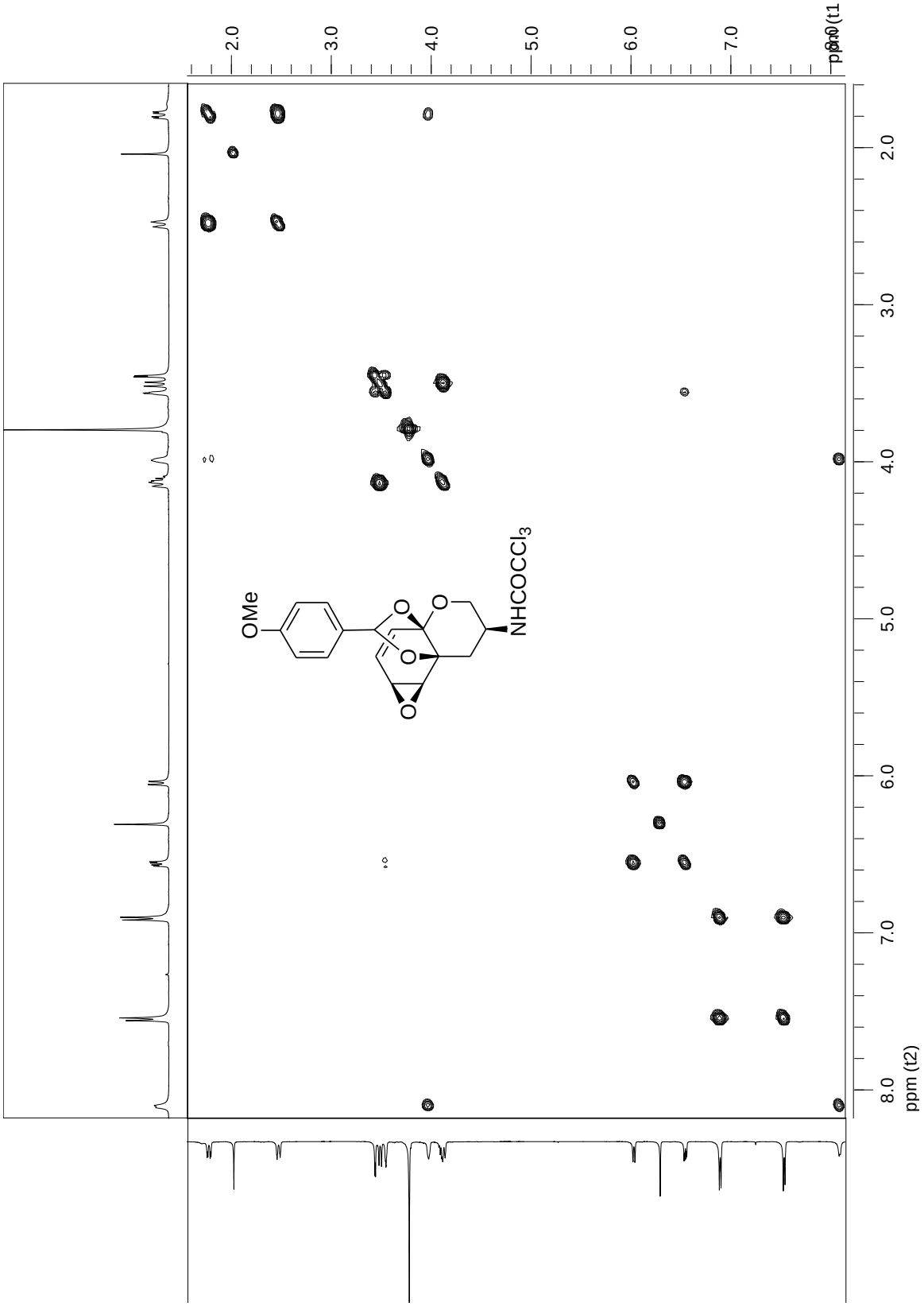

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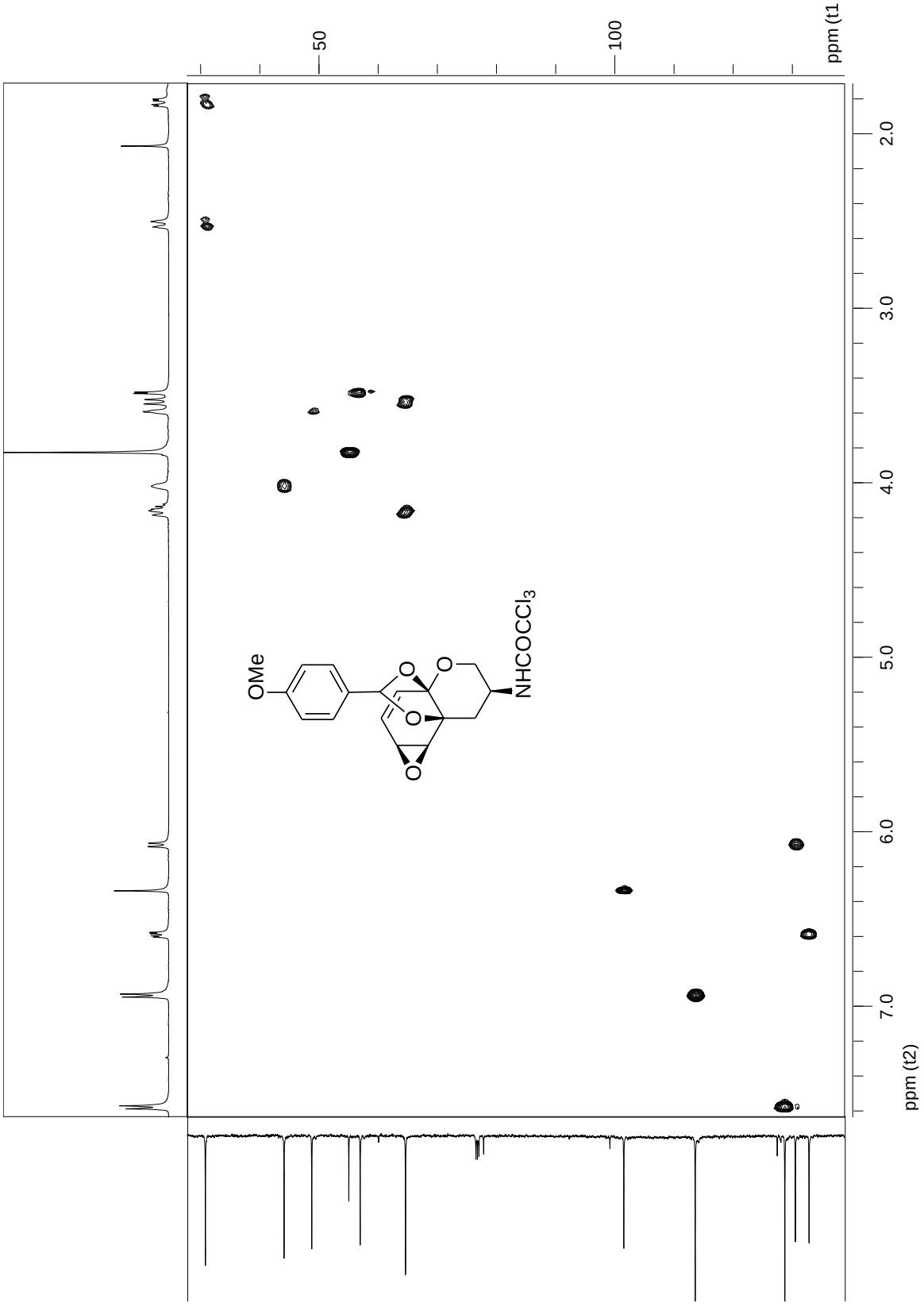

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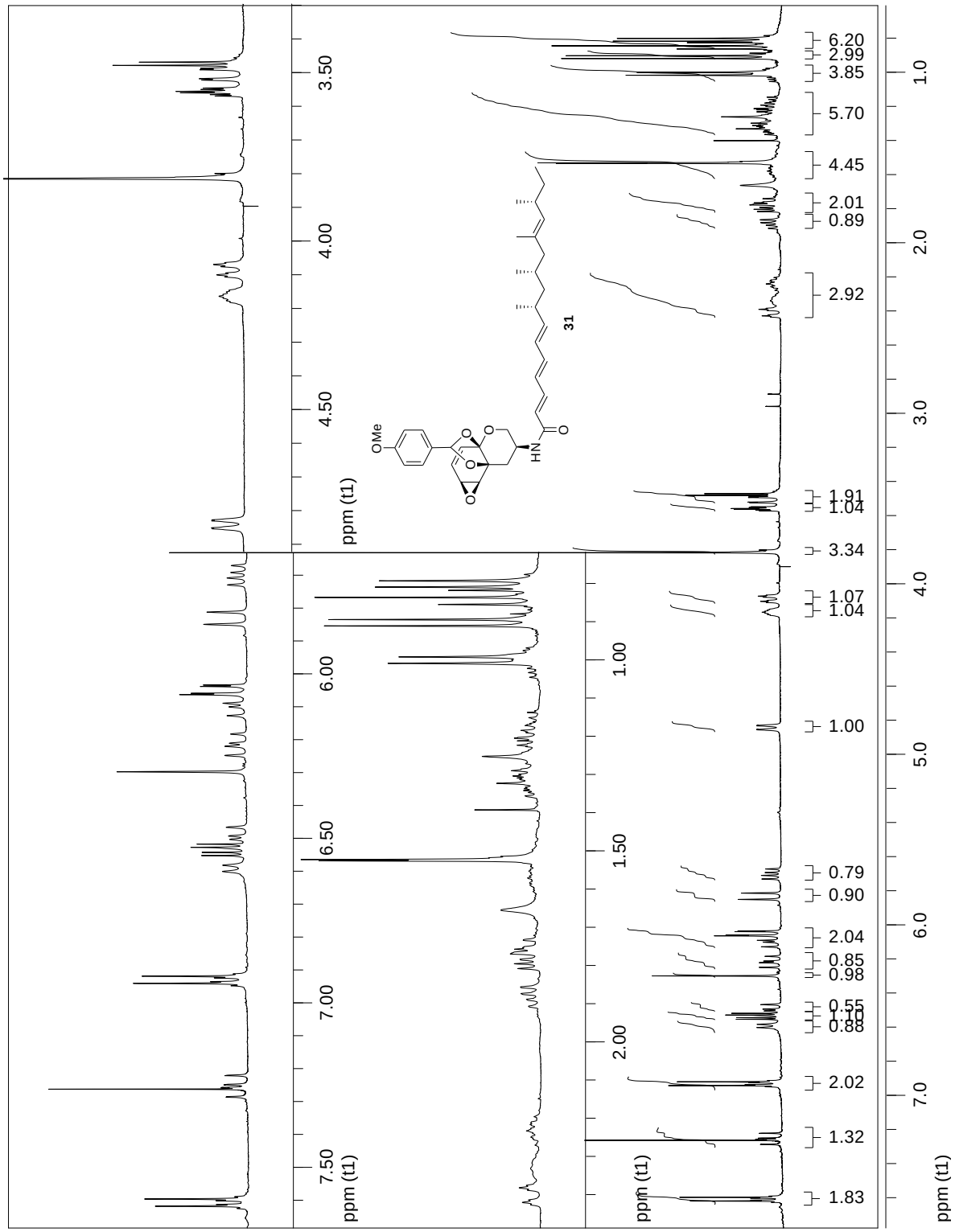

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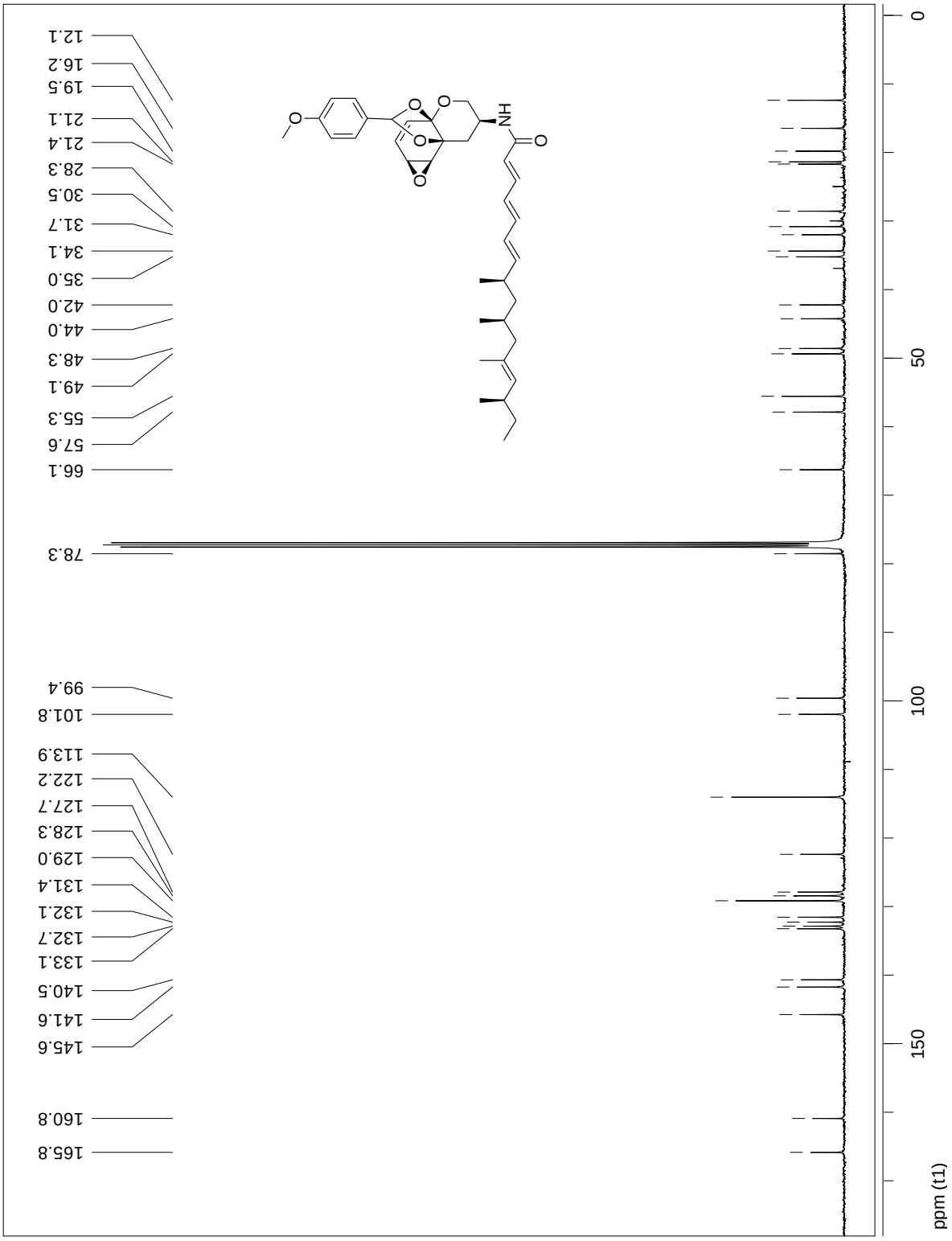

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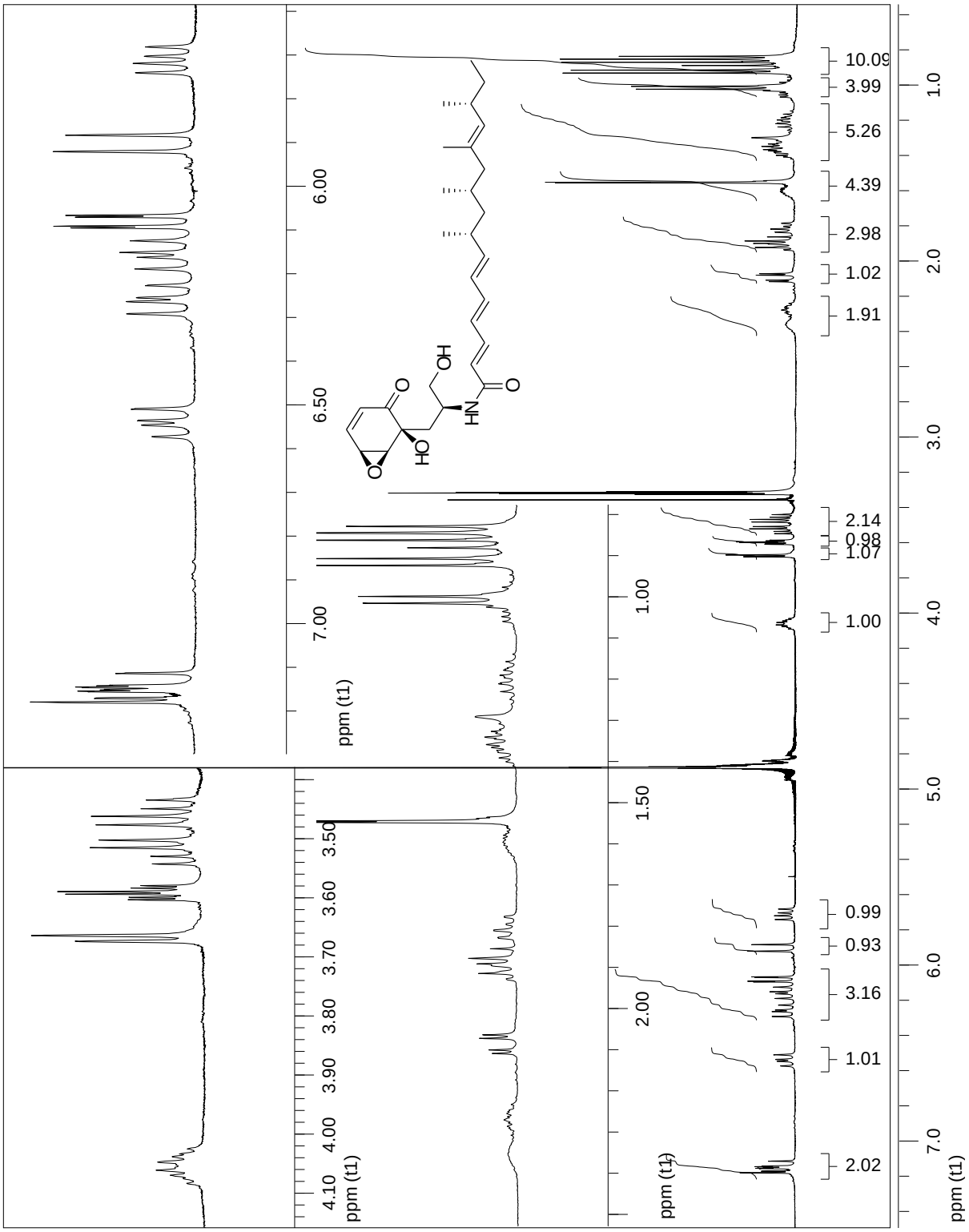

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