Electronic Supplementary Material (ESI) for Organic & Biomolecular Chemistry
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Synthesis of *anti* and *syn* Hydroxy-*iso*-Evoninic Acids

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SUPPORTING INFORMATION

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General Directions

All reactions were performed under anhydrous conditions, in oven-dried glassware and under a nitrogen atmosphere. *Anhydrous Solvents:* MeCN, Et_2O, CH_2Cl_2 and THF were used directly following passage under nitrogen through Al_2O_3 columns in a Grubbs dry-solvent system (Innovative Technology Inc.). MeOH was used after distillation over CaH_2. *Reagents:* These were purchased from commercial sources and handled according to COSHH regulations. *Chromatography:* Flash chromatography (FC) was performed on silica gel (Merck Kieselgel 60 F_{254} 230-400 mesh) and reverse phase chromatography on C18 silica gel (Fluka Kieselgel 90 F_{254} 230-400 mesh). Thin Layer Chromatography (TLC) was performed on Merck aluminium-backed plates pre-coated with silica (0.2 mm, 60 F254) which were visualized either by quenching of ultraviolet fluorescence (λmax = 254 nm) or by charring with $KMnO_4$ TLC dip. *Melting points:* were determined on a Khofler hot stage. *Infra red spectra:* were recorded as neat liquids on Perkin-Elmer Paragon 1000 Fourier transform spectrometer. Only selected absorbances (ν_{max}) are reported. *^{1}H NMR spectra:* These were recorded at 400 MHz on a Bruker AMX-400 instrument. Chemical shifts (δ_H) are quoted in parts per million (ppm) and referenced to to the residual solvent peaks ($CHCl_3$ or HOD). Coupling constants (*J*) are reported to the nearest 2 significant figures. *^{13}C NMR spectra:* These were recorded at 100 MHz on a Bruker AMX-400 instrument. Chemical shifts (δ_C) are quoted in ppm and referenced to the residual solvent peaks ($CHCl_3$ or HOD). *Mass spectra:* Low resolution mass spectra (*m/z*) were recorded on either a VG platform II or VG AutoSpec spectrometers, with only molecular ions (M^+, MH^+, MNH_4^+) and major peaks being reported with intensities quoted as percentages of the base peak. High Resolution Mass Spectrometry (HRMS) measurements are valid to ± 5ppm.

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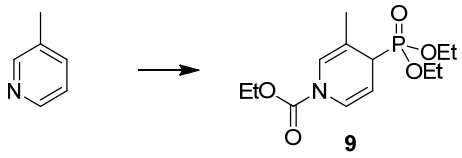
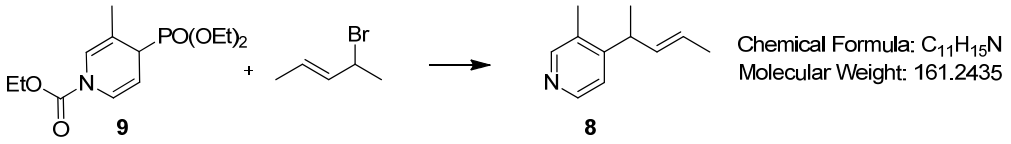
Diethyl 1-ethoxycarbonyl-1,4-dihydroxy-3-methylpyridine-4-phosphonate, 9



Chemical Formula: $C_{13}H_{22}NO_5P$
Molecular Weight: 303.2912

3-Picoline (3 mL, 30.8 mmol, 1 eq.) was dissolved in MeCN (23 mL) and cooled to 0 °C. Ethyl chloroformate (2.95 mL, 30.8 mmol, 1 eq.) was added dropwise and the red solution was stirred at 0 °C for 40 min. $P(OEt)_3$ (4.96 mL, 30.8 mmol, 1 eq.) was added dropwise and the solution was allowed to warm to room temperature and stirred for a further 17 h, after which time, a colour change to yellow was observed. The mixture was concentrated *in vacuo* to afford *phosphonate* **9** (9.25 g, 30.5 mmol, 99%) as a yellow oil. R_f 0.21 (MeOH/CH_2Cl_2, 1:19); ν_{max}/cm^{-1} 2982 (CH_3), 1716 (C=O), 1312 (C-N), 1018 (C-O), 958 (phosphonate), 746 (P-O-C); δ_H ($CDCl_3$, 400 MHz) 6.72 (1H, bd, *J* 42 Hz, NCH), 6.53 (1H, bd, *J* 46 Hz, NCH), 4.78 (1H, bd *J* 24 Hz, NCHC*H*), 4.08 (2H, q, *J* 7.2 Hz, NCO_2CH_2), 3.95 (4H, m, $P(O)OCH_2$), 3.14 (1H, dd, *J* 27 and 4.7 Hz, PCH), 1.69 (3H, d, *J* 2.1 Hz, NCHCCH_3), 1.17-1.11 (9H, OCH_2CH_3); δ_c ($CDCl_3$, 100 MHz) 170.73 (s), 124.74 (d, *J* 27 Hz), 120.73 (d), 110.48 (d, *J* 46 Hz), 101.24 (d, *J* 46 Hz), 62.30 (t), 60.06 (t), 39.31 (d, *J* 145 Hz), 20.66 (q), 14.17 (q), 13.92 (q); δ_P ($CDCl_3$, 160 MHz) 21.20 (d, *J* 26 Hz); MS (ESI) *m/z* 230 ([M-COOEt]$^+$), 180 (9), 162 (12); HRMS (ESI) 230.0941 calcd for $C_{10}H_{17}NO_3P^+$ ([M-COOEt]$^+$), found 230.0940, Δ = -0.4 ppm.

(±)-3-Methyl-4-[(*E*)-pent-2-en-4-yl]pyridine, 8

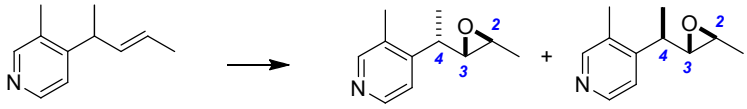


Chemical Formula: $C_{11}H_{15}N$
Molecular Weight: 161.2435

Phosphonate **9** (9.74 g, 30.45 mmol, 1 eq.) was dissolved in THF (60 mL) and cooled to -78 ˚C. ^{n}BuLi (1.6 M in THF, 20.9 mL, 33.5 mmol, 1.1 eq.) was added dropwise and the brown solution was stirred at -78 ˚C for 40 min. *4-Bromo-2-pentene*[1] (5 g, 33.5 mmol, 1.1 eq.) in THF (5 mL) was added dropwise and after 30 min the reaction mixture was allowed to warm to 0 ˚C and stirred for another 40 min. The mixture was cooled down to -78 ˚C again and ^{n}BuLi (1.6 M in THF, 41.8 mL, 67.0 mmol, 2.2 eq.) was added. After addition the solution was allowed to warm to 0 ˚C and stirred for another 45 min. Et_2O (20 mL) was added, followed by water (15 mL). The mixture was concentrated *in vacuo* to leave a orange/yellow liquid. Purification by FC (1:9 to 1:3, EtOAc/hexane) afforded *alkene* **8** (2.60 g, 16.1 mmol, 53%) as a pale yellow liquid. R_f 0.18 (EtOAc/hexane, 3:7); ν_{max}/cm^{-1} (neat) 2965 (CH_3), 2929 (CH_3), 2874 (CH_3), 1593 (C=C), 1451 (pyridine), 1404 (pyridyl), 966 (CH), 834 (CH); δ_H ($CDCl_3$, 400 MHz) 8.36 (1H, d, *J* 5.1 Hz, NC*H*CH), 8.31 (1H, s, NC*H*), 7.07 (1H, d, *J* 5.1 Hz, NCHC*H*), 5.33-5.38 (2H, C*H*C*H*CH_3), 3.58 (1H, p, *J* 6.9 Hz, ArC*H*), 2.27 (3H, s, ArCH_3), 1.66 (3H,

dt, *J* 6.1 and 1.2 Hz, CHCHCH_3), 1.29 (3H, d, *J* 7.1 Hz, ArCHCH_3); δ_c ($CDCl_3$, 100 MHz) 152.97 (s), 150.81 (d), 147.81 (d), 133.78 (d), 130.99 (s), 125.02 (d), 120.92 (d), 37.52 (d), 20.01 (q), 17.88 (q), 16.08 (q); MS (ESI) *m/z* 162 (MH^+, 100), 155 (4), 150 (4), 147 (4); HRMS (ESI) 162.1277 calcd for $C_{11}H_{16}N^+$ (MH^+), found 162.1275, Δ = -1.2 ppm.

3-Methyl-4-[(2*S,3*S**,4*S**)-2,3-epoxypentan-4-yl]pyridine** and **Methyl-4-[(2*S**,3*S**,4*R**)-2,3-epoxypentan-4-yl]pyridine, 11**

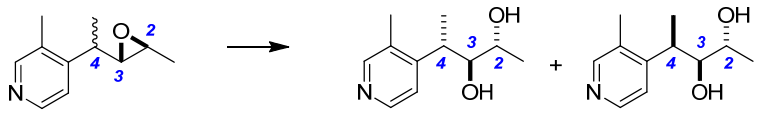


8 **11** *dr* 52:48

Chemical Formula: $C_{11}H_{15}NO$
Molecular Weight: 177.2429

Alkene **8** (2.60 g, 16.1 mmol, 1 eq.) was dissolved in a mixture of THF (25 mL) and water (25 mL) and cooled to 0 ˚C. NBS (2.77 g, 16.1 mmol, 1 eq.) was added turning the solution yellow. After stirring at 0 ˚C for 1 h, $NaHCO_3$ (sat. aq., 30 mL) was added. The aqueous solution was extracted with CH_2Cl_2 (5 × 20 mL) and the combined extracts dried over $MgSO_4$ and then concentrated *in vacuo* to leave a crude mixture of bromohydrins **10** as a cream colored solid. MeCN (20 mL) was added, followed by 1M NaOH (20 mL) and the solution was heated at 65 ˚C for 1 h. MeCN was removed *in vacuo* and the remaining aqueous solution was extracted with CH_2Cl_2 (4 × 60 mL). The combined organic extracts were dried over $MgSO_4$ then concentrated *in vacuo* to afford *epoxide* **11** (2.40 g, 13.6 mmol, 84%, *dr* 52:48) as a clear oil. R_f 0.49 (MeOH/CH_2Cl_2, 1:9); ν_{max}/cm^{-1} (neat) 2970 (CH), 1594 (pyridyl), 1404 (CH_3), 1381 (CH_3), 902 (epoxide), 834 (epoxide). ***(2S*,3S*,4S*)-epoxide* 11 (major component):** δ_H ($CDCl_3$, 400 MHz) 8.43 (1H, d, *J* 5.2 Hz, NC*H*CH), 8.38 (1H, s, NCH), 7.20 (1H, d, *J* 5.1 Hz, NCHC*H*), 2.97 (1H, p, *J* 6.8 Hz, ArCH), 2.87-2.79 (2H, CHO), 2.31 (3H, s, $ArCH_3$), 1.35-1.28 (6H, CHCH_3); δ_c ($CDCl_3$, 100 MHz) 150.94 (d), 150.09 (s), 147.83 (d), 131.49 (s), 120.92 (d), 62.46 (d), 53.47 (d), 36.21 (d), 17.52 (q), 16.73 (q), 16.34 (q). ***(2S*,3S*,4R*)-epoxide* 11 (minor component):** δ_H ($CDCl_3$, 400 MHz) 8.42 (1H, d, *J* 5.1 Hz, NC*H*CH), 8.39 (1H, s, NCH), 7.16 (1H, d, *J* 5.1 Hz, NCHC*H*), 3.06 (1H, p, *J* 7.1 Hz, ArCH), 2.87-2.79 (2H, CHO), 2.32 (3H, s, $ArCH_3$), 1.35-1.28 (6H, CHCH_3); δ_c ($CDCl_3$, 100 MHz) 151.03 (d), 150.45 (s), 147.90 (d), 131.04 (s), 121.16 (d), 62.74 (d), 53.47 (d), 36.54 (d), 17.47 (q), 16.73 (q), 16.31 (q). MS (ESI) *m/z* 178 (MH^+, 100), 155 (3), 150 (3); HRMS (ESI) 178.1226 calcd for $C_{11}H_{16}NO^+$ (MH^+), found 178.1228, Δ = +1.1 ppm.

(2*R,3*S**,4*S**)-** and **(2*R**,3*S**,4*R**)-4-(3-Methylpyridin-4-yl)pentane-2,3-diol, 12**



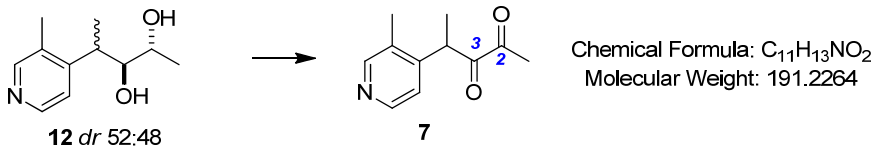
11 *dr* 52:48 **12** *dr* 52:48

Chemical Formula: $C_{11}H_{17}NO_2$
Molecular Weight: 195.2582

Epoxide **11** (1.60 g, 9.02 mmol, 1 eq., *dr* 52:48) was dissolved in MeCN (19 mL) and water (9.6 mL). $HClO_4$ (60% aq., 1.6 mL) was added dropwise and the solution was stirred at room temperature for 40

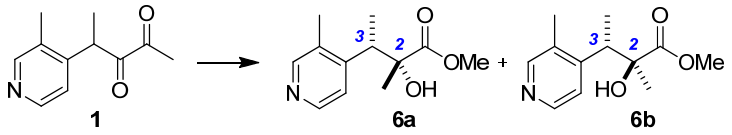
h. The solution was neutralised with sat. $NaHCO_3$ (sat. aq.) then concentrated *in vacuo* to remove all MeCN. The remaining aqueous solution was extracted with CH_2Cl_2 (4 × 30 mL) and the combined organic extracts were dried over $MgSO_4$, then concentrated *in vacuo* to leave a pale yellow oil. Purification by FC (MeOH/CH_2Cl_2, 1:19) afforded *1,2-diol* **12** (1.469 g, 7.52 mmol, 83%, *dr* 52:48) as a clear oil. R_f 0.34 (MeOH/CH_2Cl_2), 1:9); ν_{max}/cm^{-1} (neat) 3331 (OH), 2969 (CH_3), 2926 (CH_3), 1600 (pyridyl), 1074 (C-O), 734 (pyridyl). ***(2R*,3S*, 4S*)-diol* 11 (major component):** δ_H ($CDCl_3$, 400 MHz) 8.40-8.30 (2H, NCH), 7.16 (1H, d, *J* 5.2 Hz, NCHC*H*), 4.00 (1H, qd, *J* 6.4 and 3.7 Hz, C*H*OHCH$_3$), 3.87 (1H, dd, *J* 9.0 and 3.6 Hz, ArCHC*H*OH), 3.19-3.07 (1H, ArCH), 2.37 (3H, s, ArCH$_3$), 1.19 (3H, d, *J* 7.0 Hz, ArCHC*H*$_3$), 1.16 (3H, d, *J* 6.3 Hz, CHOHC*H*$_3$); δ_C ($CDCl_3$, 100 MHz) 152.42 (s), 150.49 (d), 147.35 (d), 132.43 (s), 121.06 (d), 78.61 (d), 68.00 (d), 37.05 (d), 16.99 (q), 16.64 (q), 16.01 (q). ***(2R*,3S*, 4R*)-diol* 11 (minor component):** δ_H ($CDCl_3$, 400 MHz) 8.40-8.30 (2H, NCH), 7.21 (1H, d, *J* 5.1 Hz, NCHC*H*), 3.81 (1H, dd, *J* 7.2 and 4.4 Hz, ArCHC*H*OH), 3.71 (1H, qd, *J* 6.3 and 4.5 Hz, C*H*OHCH$_3$), 3.19-3.07 (1H, ArCH), 2.33 (3H, s, ArCH$_3$), 1.34 (3H, d, *J* 6.9 Hz, ArCHC*H*$_3$), 1.30 (3H, d, *J* 6.3 Hz, CHOHC*H*$_3$); δ_C ($CDCl_3$, 100 MHz) 152.09 (s), 150.90 (d), 147.42 (d), 130.86 (s), 121.69 (d), 77.46 (d), 68.17 (d), 36.47 (d), 17.56 (q), 16.62 (q), 16.28 (q). MS (ESI) *m/z* 196 (MH^+, 100), 179 (4), 178 (7), 150 (3); HRMS (ESI) 196.1332 calcd for $C_{11}H_{18}NO_2$ (MH^+), found 196.1336, Δ = +2.4 ppm.

(±)-4-(3-Methylpyridin-4-yl)pentane-2,3-dione, 7



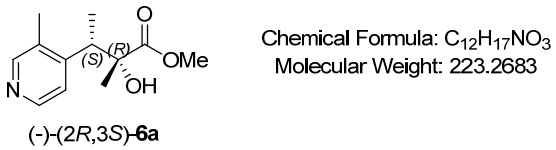
Oxalyl chloride (464 µL, 3.21 mmol, 2.2 eq.) in CH_2Cl_2 (2 mL) was cooled to –78 ˚C. DMSO (278 µL, 6.42 mmol, 4.4 eq) was added and the solution stirred for 5 min. 1,2-Diol **12** (290 mg, 1.49 mmol, 1 eq., *dr* 52:48) in CH_2Cl_2 (1.5 mL) was added dropwise and the solution was stirred for a further 15 min. Triethylamine (1.24 mL, 8.94 mmol, 6 eq.) was added dropwise and after 5 min the reaction mixture was quickly transferred to a short silica column and eluted with CH_2Cl_2. Purification by FC (CH_2Cl_2 to 1:99, MeOH/CH_2Cl_2) afforded *1,2-diketone* **7** (270 mg, 1.41 mmol, 95%) as a bright yellow liquid. R_f 0.45 (MeOH/CH_2Cl_2, 1:19); ν_{max}/cm^{-1} (neat) 2982 (CH_3), 2930 (CH_3), 1716 (C=O), 1594 (pyr); δ_H ($CDCl_3$, 400 MHz) 8.59 (1H, s, NCH), 8.52 (1H, d, *J* 5.6 Hz, NC*H*CH), 7.31 (1H, d, *J* 5.6 Hz, NCHC*H*), 4.84 (1H, q, *J* 7.0 Hz, ArCH), 2.54 (3H, s, ArCH$_3$), 2.34 (3H, s, COCH$_3$), 1.45 (3H, d, *J* 7.0 Hz, ArCHC*H*$_3$); δ_C ($CDCl_3$, 100 MHz) 197.72 (s), 196.89 (s), 151.56 (d), 147.90 (d), 146.13 (s), 131.68 (s), 121.19 (d), 40.43 (d), 24.34 (q), 16.22 (q), 15.94 (q); MS (ESI) 192 (MH^+, 100), 193 (16), 233 (7), 251 (6); HRMS (ESI) 192.1019 calcd for $C_{11}H_{14}NO_2^+$ (MH^+), found 192.1020, Δ = +0.5 ppm.

(2*R,3*S**)-** and **(2*S**,3*S**)-Methyl 2-hydroxy-2-methyl-3-(3-methylpyridin-4-yl)butanoate, 6a** and **6b (Table 1, entry 3)**



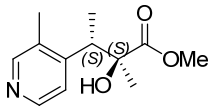
Freshly prepared 1,2-diketone **7** (223 mg, 1.17 mmol, 1 eq.) was dissolved in MeOH (25 mL) and $ZnCl_2$ (203 mg, 1.23 mmol, 1 eq.) was added. The mixture was stirred at 40 ˚C for 18 h then concentrated *in vacuo* to leave a yellow oil. CH_2Cl_2 (20 mL) was added followed by $NaHCO_3$ (sat. aq., 15 mL). The organic layer was extracted and the aqueous layer was further extracted with CH_2Cl_2 (3 x 15 mL) and the combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo* to leave a pale yellow oil. Purification by FC ($MeOH/CH_2Cl_2$, 1:49) afforded *esters* **6a** and **6b** (235 mg, 1.05 mmol, 90%, *dr* 35:65) as a pale yellow oil. R_f 0.47 ($MeOH/CH_2Cl_2$, 1:9); ν_{max}/cm^{-1} (neat) 3505 (OH), 1730 (C=O), 1596 (pyr), 1452 (CH_3), 1255 (CH), 1175 (C-O), 1116 (C-O), 840 (C-O-C); ***(2R*,3S*)-ester* 6a (minor component):** δ_H ($CDCl_3$, 400 MHz) 8.40-8.35 (2H, NCH), 7.49 (1H, d, *J* 5.2 Hz, NCHC*H*), 3.89 (3H, s, OCH_3), 3.43 (1H, q, *J* 7.0 Hz, ArCH), 2.38 (3H, s, $ArCH_3$), 1.20 (3H, s, $COHCH_3$), 1.18 (3H, d, *J* 7.0 Hz, $ArCHCH_3$); δ_C ($CDCl_3$, 100 MHz) 177.30 (s), 150.60 (d), 149.45 (s), 147.38 (d), 131.81 (s), 123.08 (d), 76.87 (s), 53.12 (q), 40.53 (d), 24.59 (q), 16.90 (q), 16.20 (q). ***(2S*,3S*)-ester* 6b (major component):** δ_H ($CDCl_3$, 400 MHz) 8.40-8.35 (2H, NCH), 7.47 (1H, d, *J* 5.2 Hz, NCHC*H*), 3.54 (3H, s, OCH_3), 3.35 (1H, q, *J* 7.2 Hz, ArCH), 2.30 (3H, s, $ArCH_3$), 1.55 (3H, s, $COHCH_3$), 1.35 (3H, d, *J* 7.0 Hz, $ArCHCH_3$); δ_C ($CDCl_3$, 100 MHz) 176.69 (s), 150.64 (d), 150.53 (s), 147.46 (d), 130.73 (s), 122.05 (d), 76.42 (s), 52.41 (q), 40.90 (d), 25.31 (q), 16.24 (q), 14.92 (q); MS (ESI) *m/z* 224 (MH^+, 100), 225 (13); HRMS (ESI) 224.1281 calcd for $C_{12}H_{18}NO_3^+$ (MH^+), found 224.1281, Δ = 0.0 ppm.

(-)-(2*R*,3*S*)-Methyl 2-hydroxy-2-methyl-3-(3-methylpyridin-4-yl)butanoate, 6a



After the above procedure a small sample of (-)-(*2R,3S*)-ester **6a** was isolated as colourless laths by chiral HPLC using an analytical IC column (see pages 11 and 12). Data as above. mp 54-56 ˚C (CH_2Cl_2); $[\alpha]^{25}_D$ -8.4 (*c* = 0.33, CH_2Cl_2). For single crystal X-ray structure determination including absolute configuration determination by Flack parameter analysis see separate Supporting Information file.

(+)-(2*S*,3*S*)-Methyl 2-hydroxy-2-methyl-3-(3-methylpyridin-4-yl)butanoate, 6b

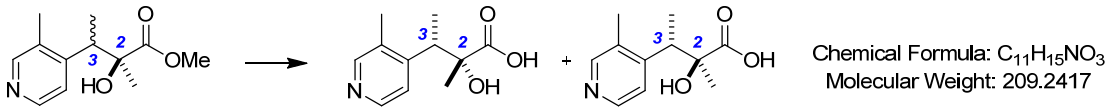


(+)-(2S,3S)-**6b**

Chemical Formula: $C_{12}H_{17}NO_3$
Molecular Weight: 223.2683

After the above procedure a small sample of (+)-(2*S*,3*S*)-ester **6b** was isolated as colourless shards by chiral HPLC using a semi-prep OD-H column (see pages 11 and 12). Data as above. mp 55-57 ˚C (CH_2Cl_2); $[\alpha]^{25}_D$ +11.2 (*c* = 0.92, CH_2Cl_2). For single crystal X-ray structure determination including absolute configuration determination by Flack parameter analysis see separate Supporting Information file.

(2*R,3*S**)-** and **(2*S**,3*S**)-2-Hydroxy-2-methyl-3-(3-methylpyridin-4-yl)butanoic acid**



6a:**6b** *dr* 45:55

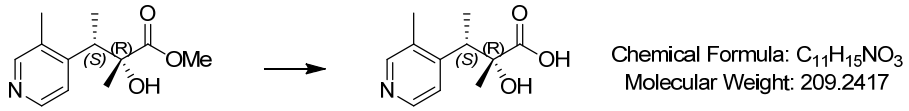
2-Hydroxy-2-methyl-3-(3-methylpyridin-4-yl)butanoic acid
dr 45:55

Chemical Formula: $C_{11}H_{15}NO_3$
Molecular Weight: 209.2417

Esters **6** (19 mg, 0.0851 mmol, *dr* 45:55[†]) were dissolved in MeOH (1.9 mL) and 2 M NaOH (1.9 mL) was added. The solution was stirred at 65 °C for 2 h after which time it had turned pale yellow. The solution was acidified to pH 5 with 1 M HCl then concentrated *in vacuo* to leave a white solid. MeCN (10 mL) was added and the solution was sonicated for 15 min. The resulting suspension was purified by reverse phase C18 FC (MeCN) to afford *2-hydroxy-2-methyl-3-(3-methylpyridin-4-yl)butanoic acid* (16 mg, 0.0764 mmol, 89%, *dr* 45:55) as a white solid. R_f 0.15 (MeCN/H_2O, 4:1); mp 108-109 °C (MeCN); ν_{max}/cm^{-1} (neat) 3379 (OH), 2974 (CH), 1721 (C=O), 1636 (pyr), 1488 (pyr), 1254 (CH), 1167 (C-O), 829. ***(2R*,3S*)-acid*** **(minor component):** δ_H (D_2O, 400 MHz) 8.54 (1H, s, NCH), 8.49 (1H, d, *J* 6.0 Hz, NC*H*CH), 8.08 (1H, d, *J* 6.2 Hz, NCHC*H*), 3.77 (1H, q, *J* 6.5 Hz, ArCH), 2.68 (1H, s, CCH_3OH), 2.54 (3H, s, $ArCH_3$), 1.26 (3H, d, *J* 7.7 Hz, $ArCHCH_3$), 1.22 (3H, s, CCH_3OH); δ_C (D_2O, 100 MHz) 161.58 (s), 146.80 (s), 137.21 (d), 139.62 (d), 136.38 (d), 125.70 (s), 48.03 (s), 40.59 (d), 22.62 (q), 15.26 (q), 13.14 (q). ***(2S*,3S*)-acid*** **(major component):** δ_H (D_2O, 400 MHz) 8.48 (1H, s, NCH), 8.45 (1H, d, *J* 5.5 Hz, NC*H*CH), 8.17 (1H, d, *J* 5.9 Hz, NCHC*H*), 3.70 (1H, q, *J* 6.5 Hz, ArCH), 2.51 (1H, s, CCH_3OH), 2.48 (3H, s, $ArCH_3$), 1.58 (3H, s, CCH_3OH), 1.33 (3H, d, *J* 7.0 Hz, $ArCHCH_3$); δ_C (D_2O, 100 MHz) 162.86 (s), 146.80 (s), 139.67 (d), 136.85 (d), 136.73 (d), 124.95 (s), 48.03 (s), 40.63 (d), 23.32 (q), 15.78 (q), 14.18 (q); MS (ESI) *m/z* 208 (22), 210 (MH^+, 100), 213 (34), 215 (13); HRMS (ESI) 210.1125 calcd for $C_{11}H_{16}NO_3^+$ (MH^+), found 210.1052, Δ = -3.4 ppm.

(+)-(2*R*,3*S*)-2-Hydroxy-2-methyl-3-(3-methylpyridin-4-yl)butanoic acid

[†] From the experiment corresponding to Table 1, entry 2.

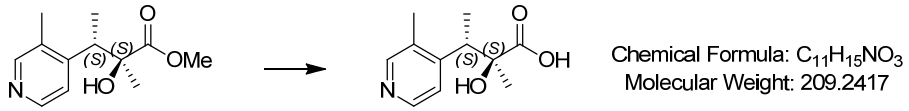


(-)-(2*R*,3*S*)-**6a** (+)-(2*R*,3*S*)-2-Hydroxy-2-methyl-3-(3-methylpyridin-4-yl)butanoic acid

Chemical Formula: $C_{11}H_{15}NO_3$
Molecular Weight: 209.2417

Ester (-)-(2*R*,3*S*)-**6a** (9 mg, 0.0403 mmol) was dissolved in MeOH (0.9 mL) and 1M NaOH (1 mL) was added. The solution was heated at 60 °C for 1 h then concentrated *in vacuo* to remove MeOH. The aqueous solution was acidified to pH 5 with 1M HCl then concentrated under a flow of nitrogen to afford a white solid. MeCN (10 mL) was added and the mixture was sonicated for 15 min then passed through a pad of C18 silica eluting with MeCN. Concentration under a flow of nitrogen afforded *(+)-(2R,3S)-2-hydroxy-2-methyl-3-(3-methylpyridin-4-yl)butanoic acid* (2.5 mg, 0.0119 mmol, 30%) as a clear oil. Data as above. $[\alpha]^{20}_{D}$ +31.6 (*c* = 0.25, MeCN).

(-)-(2*S*,3*S*)-2-Hydroxy-2-methyl-3-(3-methylpyridin-4-yl)butanoic acid

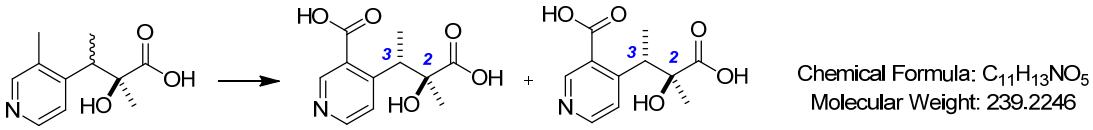


(+)-(2*S*,3*S*)-**6b** (-)-(2*S*,3*S*)-2-Hydroxy-2-methyl-3-(3-methylpyridin-4-yl)butanoic acid

Chemical Formula: $C_{11}H_{15}NO_3$
Molecular Weight: 209.2417

Ester (+)-(2*S*,3*S*)-**6b** (13 mg, 0.0582 mmol) was dissolved in MeOH (1.3 mL) and 2 M NaOH (1.3 mL) was added. The solution was heated at 60 °C for 1 h then concentrated *in vacuo* to remove all MeOH. The aqueous solution was acidified to pH 5 with 1 M HCl then concentrated *in vacuo* to afford a white solid. MeCN (15 mL) was added and the mixture was sonicated for 15 min then passed through a pad of C18 silica eluting with MeCN to afford *(-)-(2S,3S)-2-hydroxy-2-methyl-3-(3-methylpyridin-4-yl)butanoic acid* (10 mg, 0.0478 mmol, 82%) as a clear oil. Data as above. $[\alpha]^{20}_{D}$ -0.5 (*c* = 1.0, MeCN).

(2*R,3*S**)-** and **(2*S**,3*S**)-2-Hydroxy-2-methyl-3-(3-carboxypyridin-4-yl)butanoic acid, 2a** and **2b**



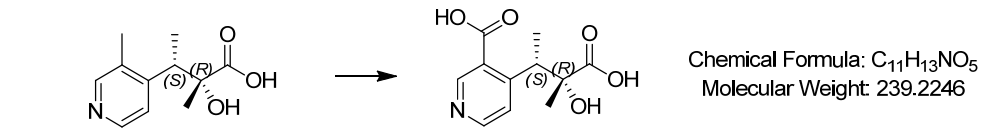
dr 45:55 **2a**:**2b** *dr* 45:55

Chemical Formula: $C_{11}H_{13}NO_5$
Molecular Weight: 239.2246

2-Hydroxy-2-methyl-3-(3-methylpyridin-4-yl)butanoic acid (16 mg, 0.076 mmol, 1 eq., *dr* 45:55) was dissolved in 1 M NaOH (1.6 mL) and stirred at room temperature for 5 min. $KMnO_4$ (48 mg, 0.304 mmol, 4 eq.) was added and the mixture was heated at 100 °C for 1 h. After allowing to cool to room temperature, MeOH (10 mL) was added and the MnO_2 precipitate was removed by filtering under suction. The filtrate was concentrated *in vacuo* to afford a white solid. Salt removal of an aqueous solution by Ziptip® and concentration under a flow of nitrogen, afforded *diacid* **3** (17.5 mg, 0.0711 mmol, 95%, *dr* 45:55) as a white solid. R_f 0.15 ($MeCN/H_2O$, 4:1); mp >250 °C (H_2O); ν_{max}/cm^{-1} (neat)

3397 (OH), 1603 (C=O), 1571 (C=O), 1397 (CH), 1387 (CH), 1163 (C-O); ***(2R*,3S*)-diacid* 2a (minor component):** δ_H (D_2O, 400 MHz) 8.59 (1H, s, NCH), 8.53 (1H, d, *J* 5.8 Hz, NC*H*CH), 7.68 (1H, d, *J* 5.4 Hz, NCHC*H*), 3.82 (1H, q, *J* 7.2 Hz, ArCH), 1.30 (3H, d, *J* 7.1 Hz, ArCHCH_3). δ_C (D_2O, 100 MHz) 175.4 (s), 173.6 (s), 162.8 (d), 162.7 (d), 149.0 (d), 119.6 (s), 119.6 (s), 77.4 (d), 41.1 (q), 23.5 (q), 15.1 (q). ***(2S*,3S*)-diacid* 2b (major component):** δ_H (D_2O, 400 MHz) 8.55 (1H, s, NCH), 8.51 (1H, d, *J* 5.7 Hz, NC*H*CH), 7.66 (1H, d, *J* 5.4 Hz, NCHC*H*), 3.80 (1H, q, *J* 6.4 Hz, ArCH), 1.39 (3H, d, *J* 7.2 Hz, ArCHCH_3), 1.39 (3H, s, $ArCH_3$); δ_C (D_2O, 100 MHz) 170.2 (s), 170.1 (s), 149.6 (d), 146.9 (d), 145.9 (d), 127.8 (s), 122.9 (s), 77.5 (s), 41.6 (q), 21.5 (q), 14.3 (q); MS (ESI) *m/z* 281 (22), 241 (13), 240 (100, MH^+); HRMS (ESI) 240.0866 calcd for $C_{11}H_{14}NO_5^+$ (MH^+), found 240.0870, Δ = +1.6 ppm.

(+)-(2*R*,3*S*)-2-Hydroxy-2-methyl-3-(3-carboxypyridin-4-yl)butanoic acid, 2a

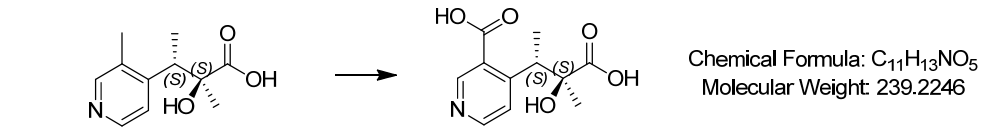


(+)-(2*R*,3*S*)-2-Hydroxy-2-methyl-3-(3-methylpyridin-4-yl)butanoic acid

(+)-(2*R*,3*S*)-**2a**

(+)-(2*R*,3*S*)-2-Hydroxy-2-methyl-3-(3-methylpyridin-4-yl)butanoic acid (2.0 mg, 0.00956 mmol, 1 eq.) was dissolved in 1 M NaOH (0.5 mL) and stirred at room temperature for 5 min. $KMnO_4$ (6 mg, 0.0382 mmol, 4 eq.) was added and the mixture was heated at 100 °C for 1 h. After allowing to cool to room temperature, MeOH (5 mL) was added and the MnO_2 precipitate was removed by filtration under suction. The filtrate was concentrated *in vacuo* to remove all MeOH. After neutralisation to pH 5 using 1M HCl, the aqueous solution was concentrated under a flow of nitrogen. Salt removal from an aqueous solution by Ziptip® and purification by reverse phase (C18 silica) HPLC (MeCN/H_2O, 9:1) afforded *diacid* (+)-(2*R*,3*S*)-**2a** (1.9 mg, 0.00794 mmol, 83%) as a white solid. Data as above. mp >250 ˚C (H_2O); $[\alpha]^{20}_D$ +12.8 (*c* = 0.20, H_2O).

(+)-(2*S*,3*S*)-2-Hydroxy-2-methyl-3-(3-carboxypyridin-4-yl)butanoic acid, 2b



(-)-(2*S*,3*S*)-2-Hydroxy-2-methyl-3-(3-methylpyridin-4-yl)butanoic acid

(+)-(2*S*,3*S*)-**2b**

(-)-(2*S*,3*S*)-2-Hydroxy-2-methyl-3-(3-methylpyridin-4-yl)butanoic acid (10 mg, 0.0478 mmol, 1 eq.) was dissolved in 1 M NaOH (1 mL) and stirred at room temperature for 5 min. $KMnO_4$ (30 mg, 0.191 mmol, 4 eq.) was added and the mixture was heated at 100 °C for 1 h. After allowing to cool to room temperature, MeOH (5 mL) was added and the MnO_2 precipitated was removed by filtration under

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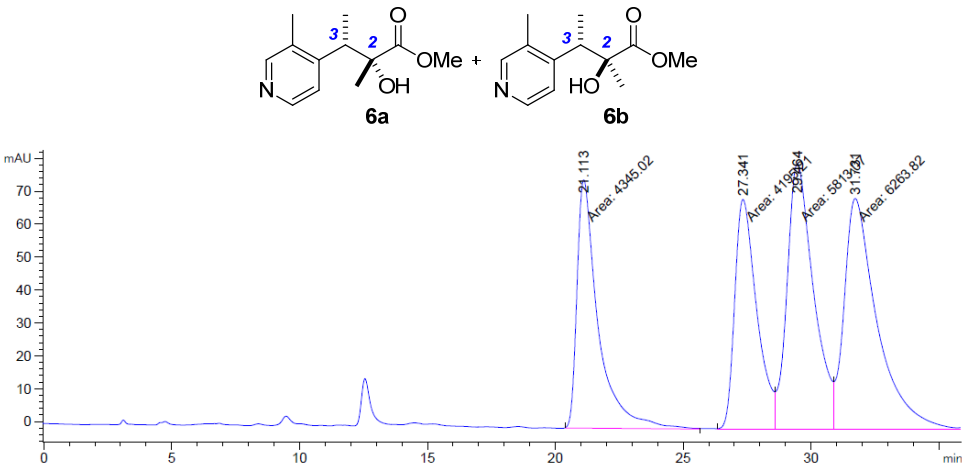
suction. The filtrate was concentrated *in vacuo* to remove all MeOH. After neutralisation to pH 5 with 1M HCl (aq.) the aqueous solution was concentrated under a flow of nitrogen. Salt removal from an aqueous solution by Ziptip® and purification by reverse phase (C18 silica) HPLC (MeCN/H_2O, 9:1), afforded *diacid* (+)-**2b** (2.7 mg, 0.0113 mmol, 24%) as a white solid. Data as above. mp >250 ˚C (H_2O); $[\alpha]^{20}_D$ +6.7 (*c* = 0.25, H_2O).

References

1. Zhang, Z.; Zhang, J.; Tan, J.; Wang, Z. *J. Org. Chem*. **2008**, *73*, 5180-5182.

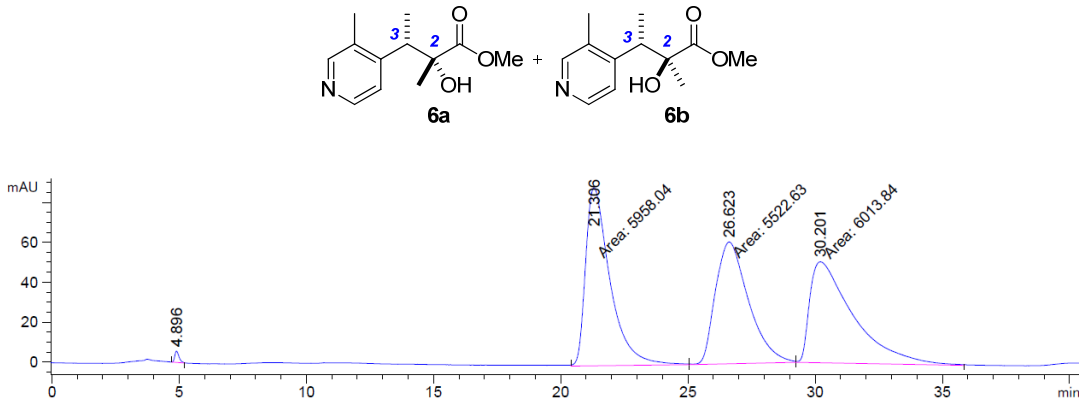
HPLC Chromatograms

Esters 6a and **6b** (*dr* 45:55) using a Chiralcel IC column.



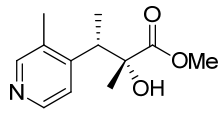
Peak 1 – R_t = 21.1 min, (-)-(2*R*,3*S*)-ester **6a**; ***Peak 2*** – R_t = 27.3 min, (+)-(2*S*,3*R*)-ester **6a**; ***Peak 3*** – R_t = 29.5 min, (2*R**,3*R**)-ester **6b**; ***Peak 4*** – R_t = 31.7 min, (2*R**,3*R**)-ester **6b**. ***Conditions;*** Chiralcel IC; 5 µm; Column Size: 0.46 cm (I.D.) × 25 cm (L); Column number: IC00CE-LL027; Temperature: 10 °C; Flow Rate: 1.2 mL/min; Injection: 5 µL; Solvent: *n*-hexane/IPA = 85:15; Sample conc.: 10 mg/ml (IPA).

Esters 6a and **6b** (*dr* 45:55) using a Chiralcel ODH column.



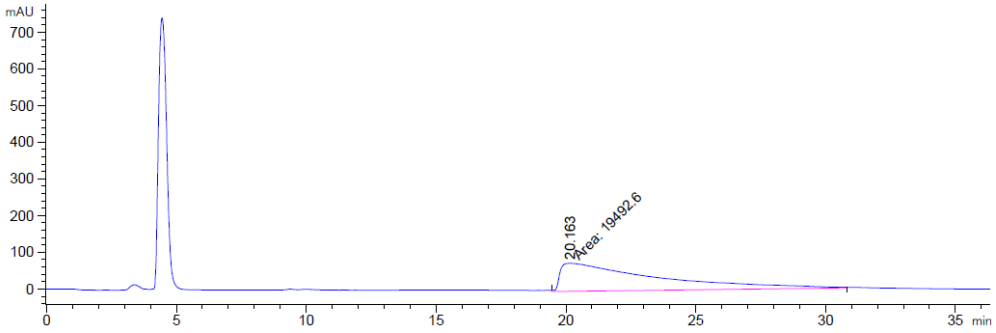
Peak 1 – R_t = 21.3 min, (+)-(2*S*,3*S*)-ester **6b**; ***Peak 2*** – R_t = 26.6 min, (+)-(2*S*,3*R*)- and (-)-(2*R*,3*S*)-esters **6a**; ***Peak 3*** – R_t = 30.2 min, (-)-(2*R*,3*R*)-ester **6b**. ***Conditions;*** Chiralcel ODH; 5 µm; Column Size: 0.46 cm (I.D.) × 25 cm (L); Column number: ODH0CE-KK122; Temp: 8 °C; Flow Rate: 0.75 mL/min; Injection: 7 µL; Solvent: *n*-hexane/IPA, 90:10; Sample conc.: 10 mg/mL (IPA/EtOAc, 9:1).

(-)-(2*R*,3*S*)-Methyl 2-hydroxy-2-methyl-3-(3-methylpyridin-4-yl)butanoate, 6a



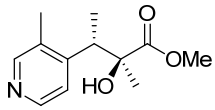
Chemical Formula: $C_{12}H_{17}NO_3$
Molecular Weight: 223.2683

(-)-(2*R*,3*S*)-**6a**



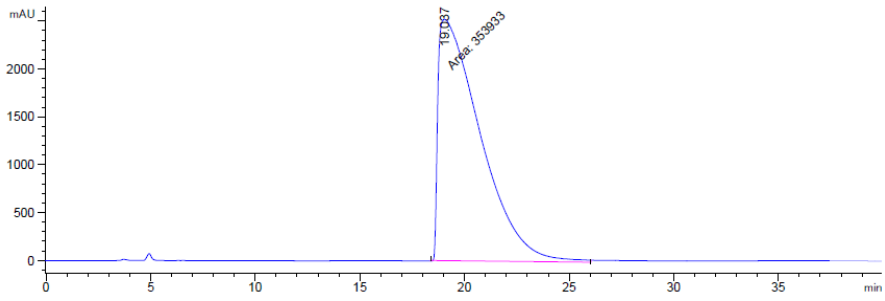
R_t = 20.2 min. ***Conditions:*** Chiralcel IC; 5 µm; Column Size: 0.46 cm (I.D.) × 25 cm (L); Column number IC00CE-LL027; Temperature: 10 °C; UV wavelength: 250 nm; Flow Rate: 1.2 mL/min; Injection: 5 µL; Solvent: *n*-hexane/IPA, 85:15; Pressure: 50 bar; Sample Conc. 0.3 mg/mL (IPA).

(+)-(2*S*,3*S*)-Methyl 2-hydroxy-2-methyl-3-(3-methylpyridin-4-yl)butanoate, 6b



Chemical Formula: $C_{12}H_{17}NO_3$
Molecular Weight: 223.2683

(+)-(2S,3S)-**6b**



R_t = 19.1 min. ***Conditions:*** Chiralcel OD-H; 5 µm; Column Size: 0.46 cm (I.D.) × 25 cm (L); Column number ODH0CE-KK122; Temperature: 8 °C; UV wavelength: 254 nm; Flow Rate: 0.9 mL/min; Injection: 1 µL; Solvent: *n*-hexane/IPA, 95:5; Pressure: 44 bar; Sample Conc. 7 mg/mL (EtOAc/IPA, 1:1).

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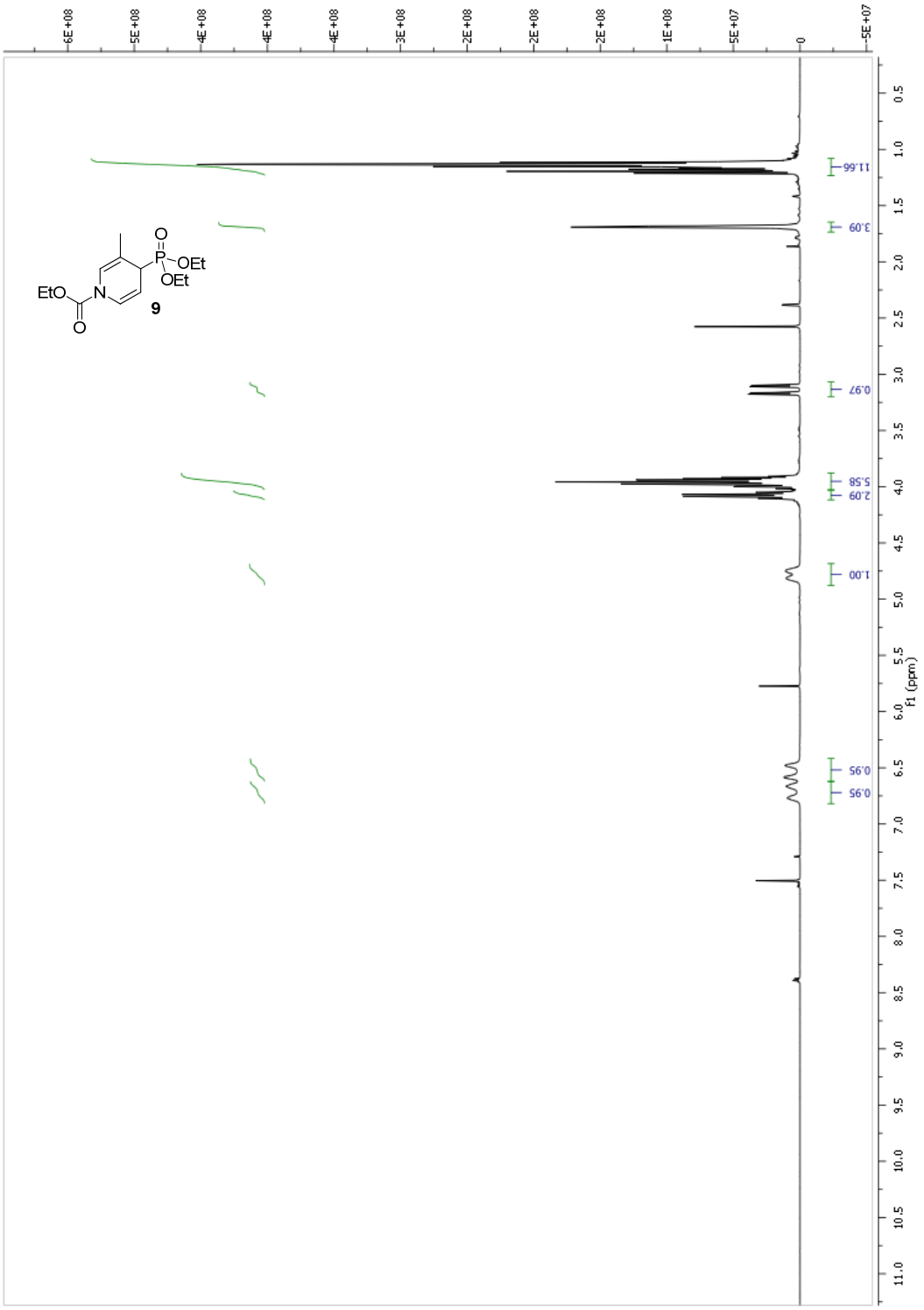
NMR spectra of Novel Compounds

^{1}H NMR ($CDCl_3$, 400 MHz) Diethyl 1-ethoxycarbonyl-1,4-dihydroxy-3-methylpyridine-4-phosphonate, **9**



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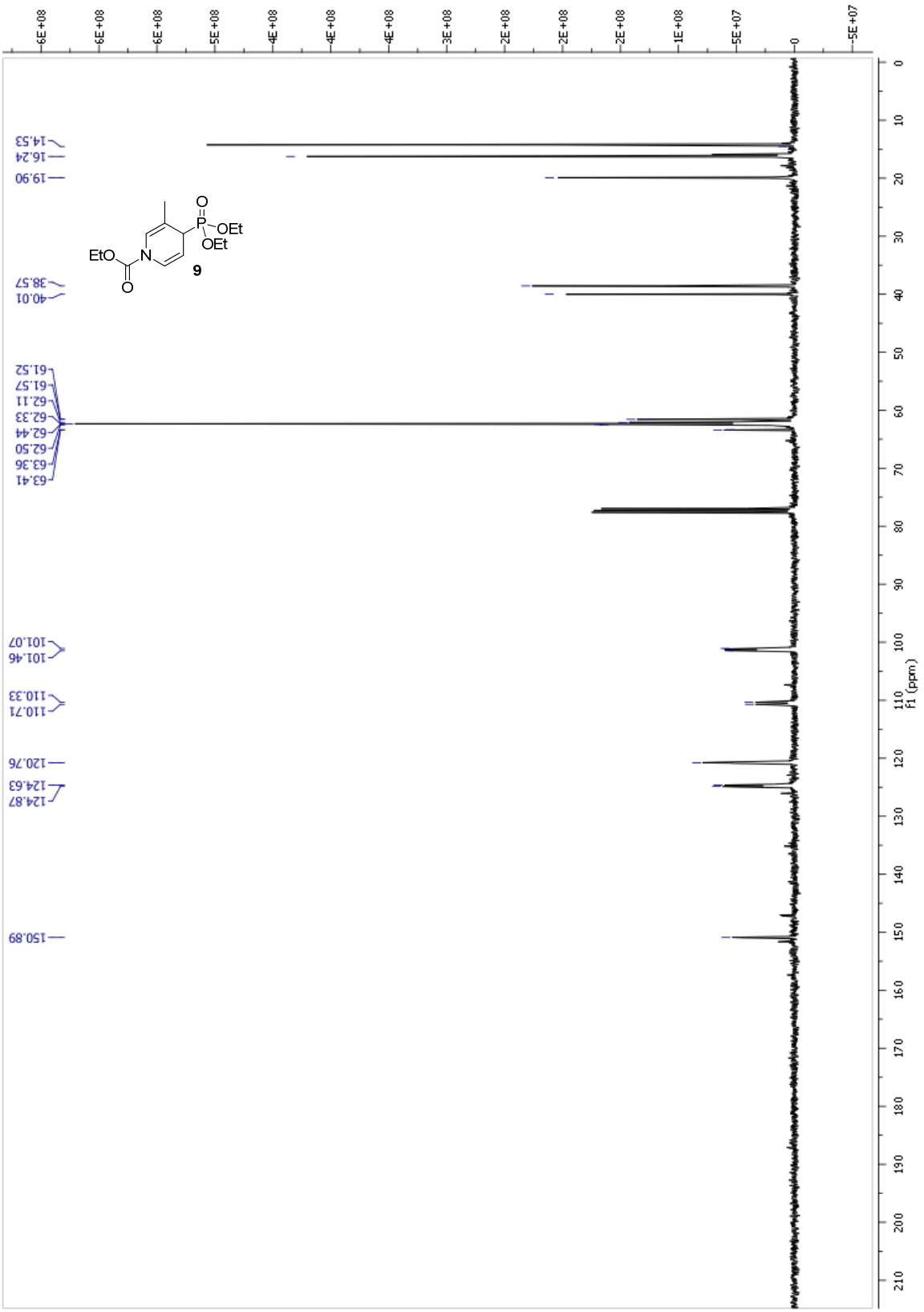
^{13}C NMR ($CDCl_3$, 100 MHz) Diethyl 1-ethoxycarbonyl-1,4-dihydroxy-3-methylpyridine-4-phosphonate, **9**



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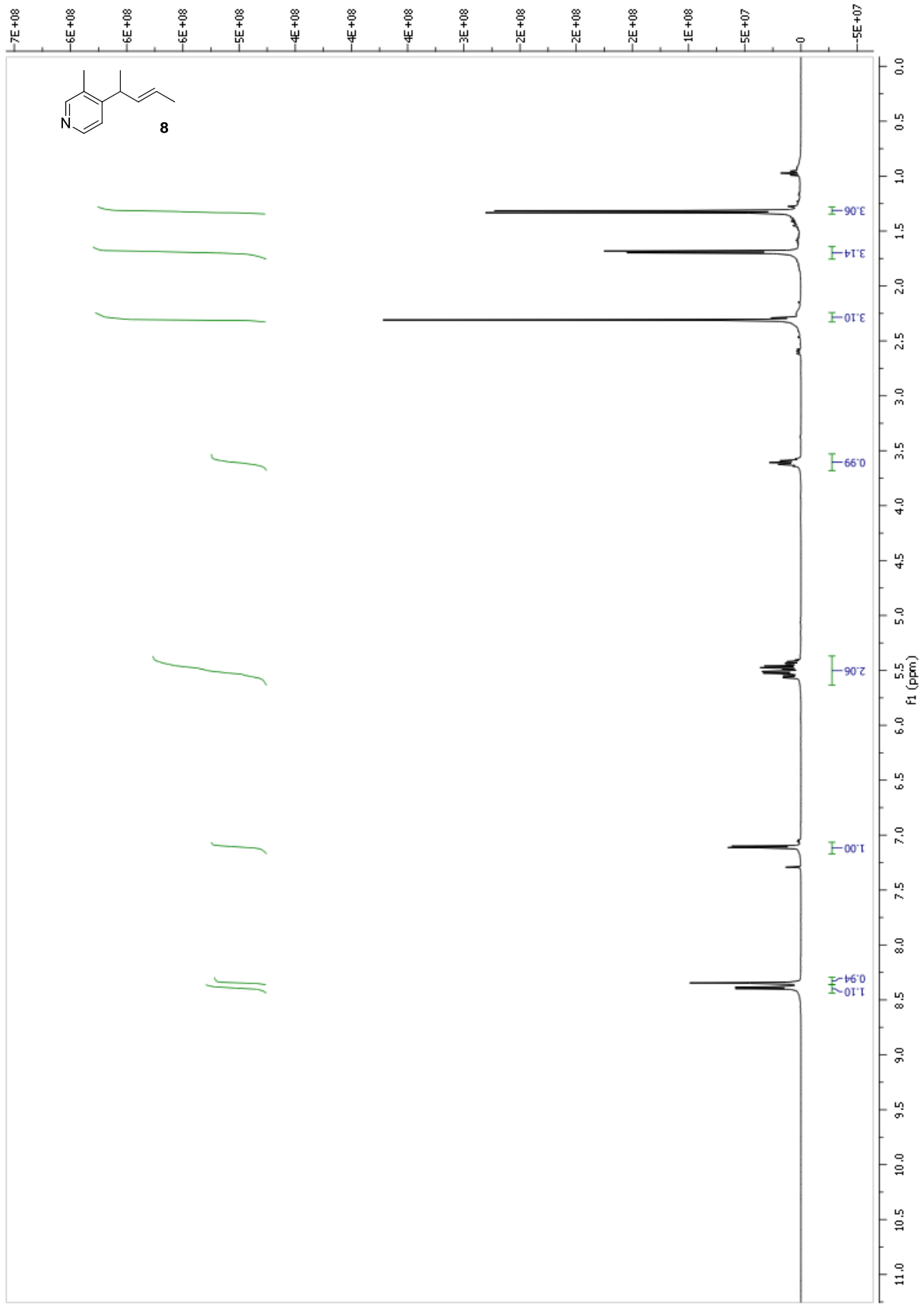
^{1}H NMR ($CDCl_3$, 400 MHz) (±)-3-Methyl-4-[(*E*)-pent-2-en-4-yl]pyridine, **8**



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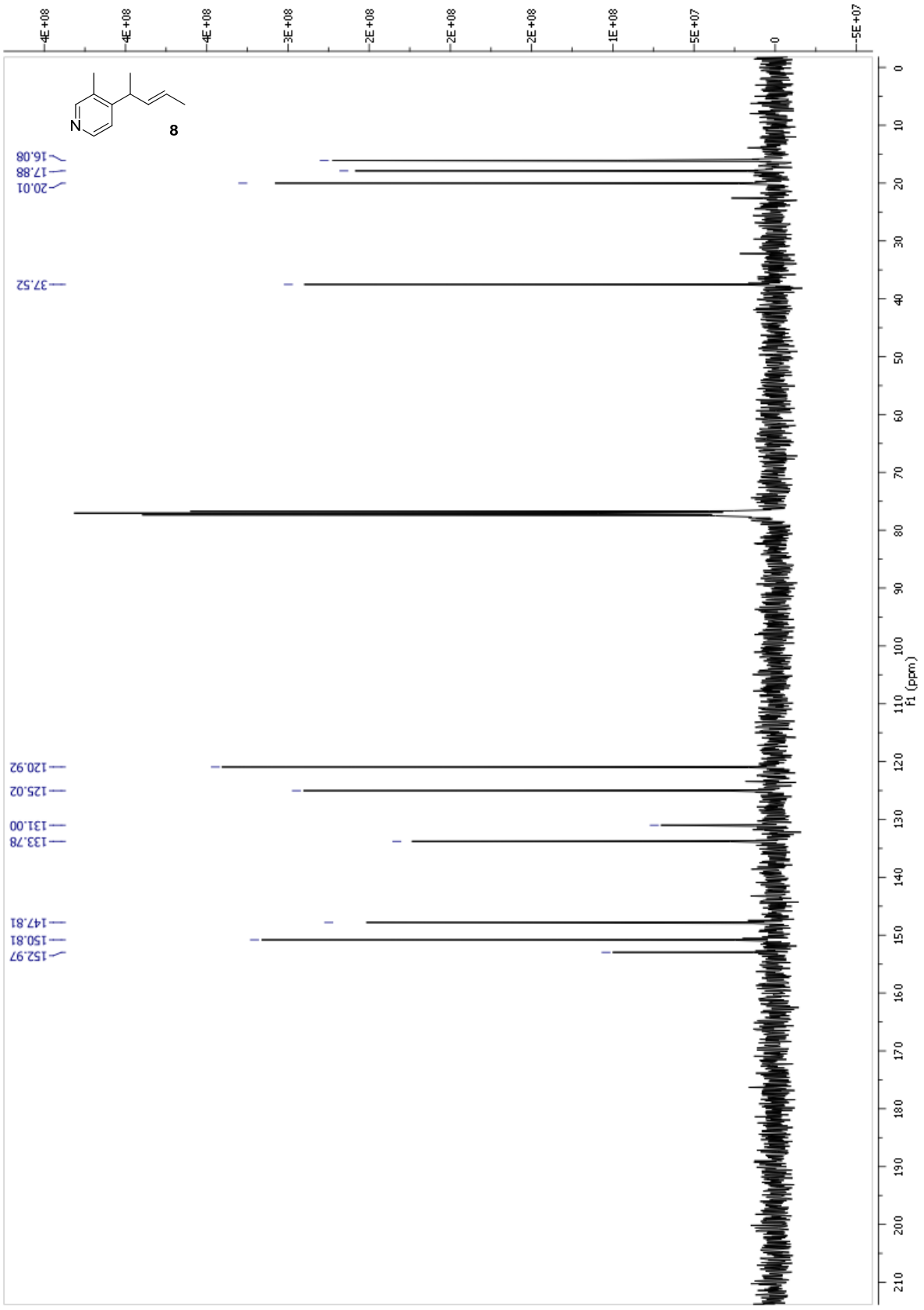
^{13}C NMR ($CDCl_3$, 100 MHz) (±)-3-Methyl-4-[(*E*)-pent-2-en-4-yl]pyridine, **8**



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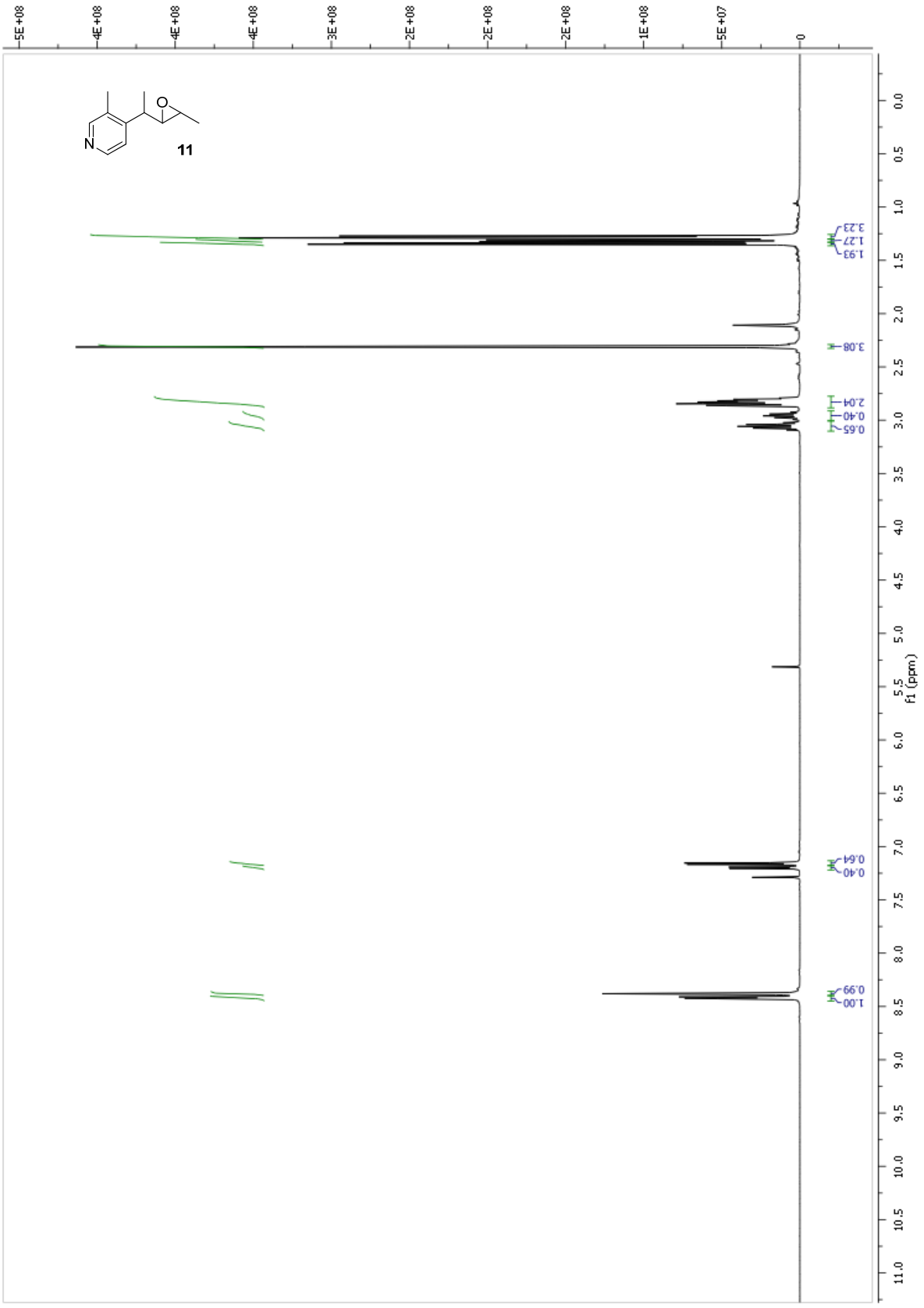
^{1}H NMR ($CDCl_3$, 400 MHz) 3-Methyl-4-[(2*S**,3*S**,4*S**)-2,3-epoxypentan-4-yl]pyridine and methyl-4-[(2*S**,3*S**,4*R**)-2,3-epoxypentan-4-yl]pyridine, **11**



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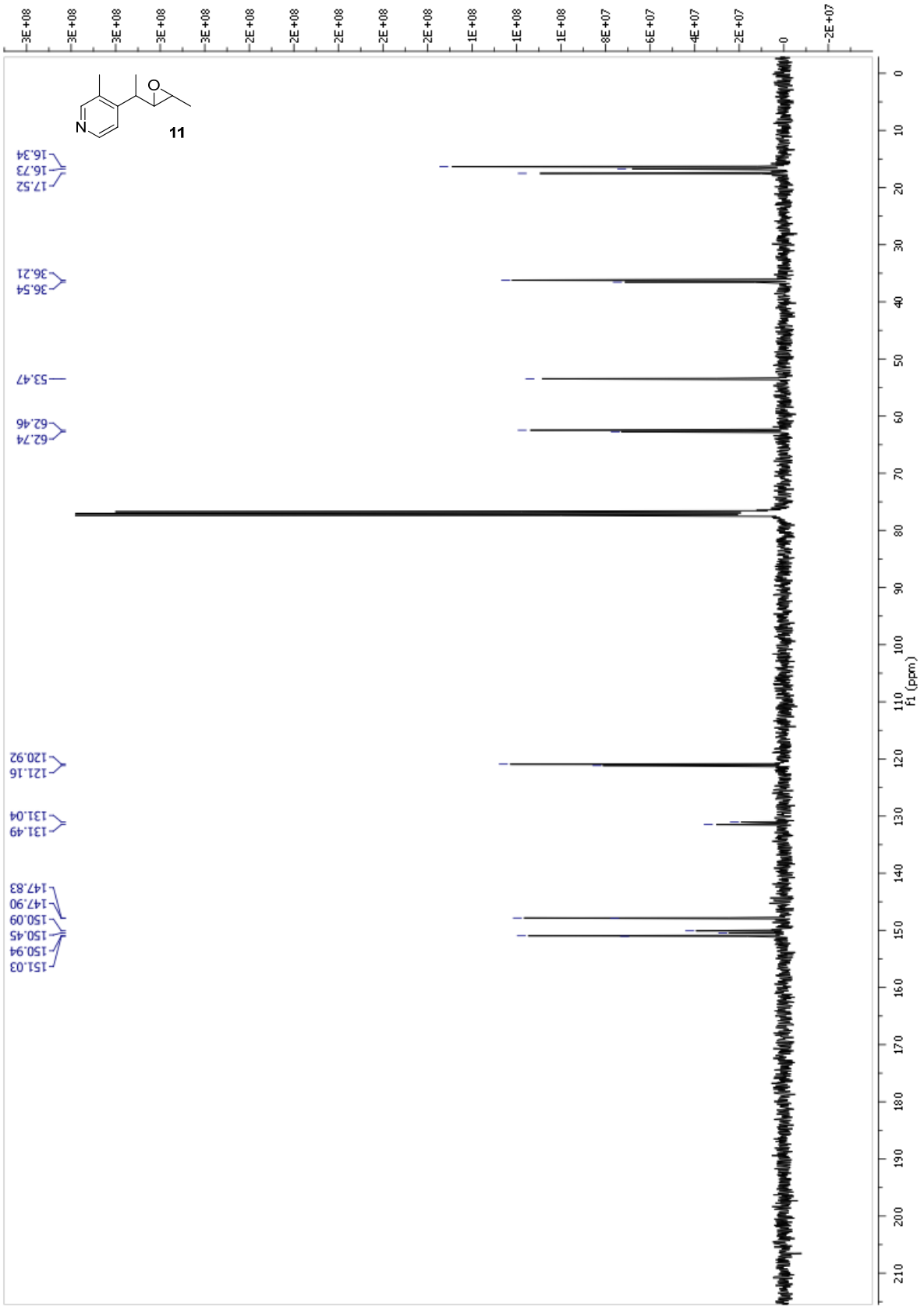
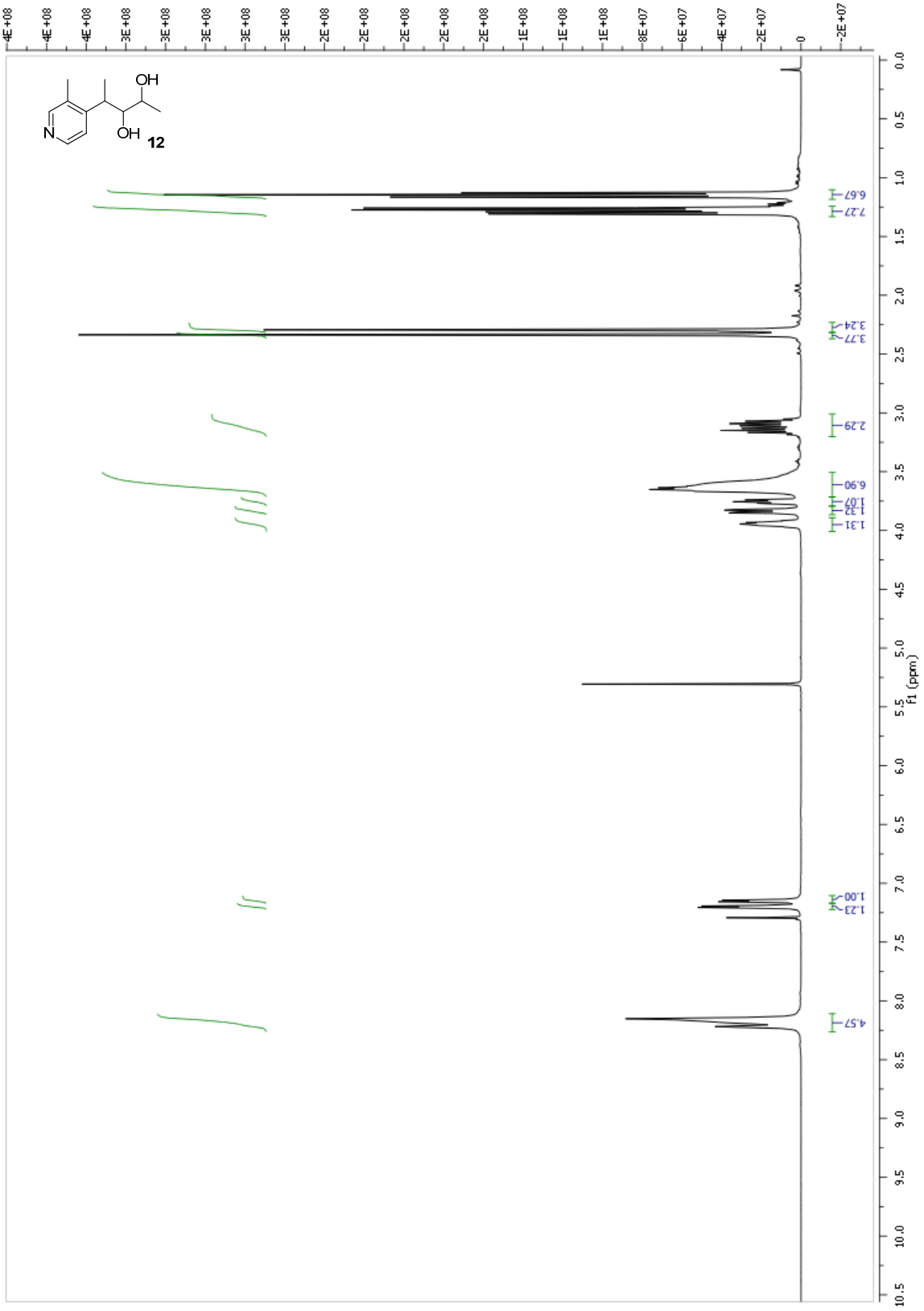
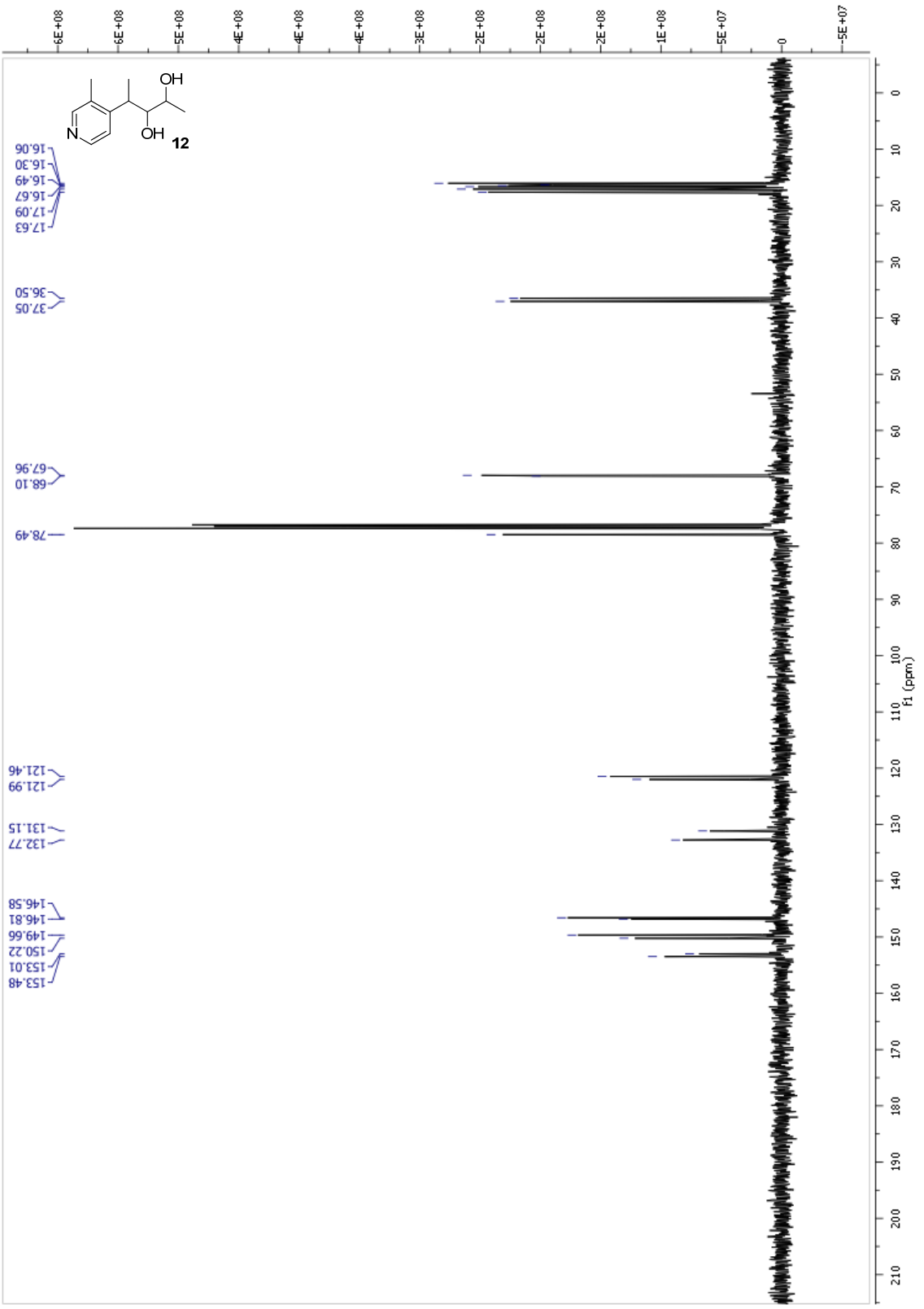
^{13}C NMR (CDCl$_3$, 100 MHz) 3-Methyl-4-[(2*S**,3*S**,4*S**)-2,3-epoxypentan-4-yl]pyridine and Methyl-4-[(2*S**,3*S**,4*R**)-2,3-epoxypentan-4-yl]pyridine, **11**



^{1}H NMR ($CDCl_3$, 400 MHz) (2*R**,3*S**,4*S**)- and (2*R**,3*S**,4*R**)-4-(3-Methylpyridin-4-yl)pentane-2,3-diol, **12**



^{13}C NMR ($CDCl_3$, 100 MHz) (2*R**,3*S**,4*S**)- and (2*R**,3*S**,4*R**)-4-(3-Methylpyridin-4-yl)pentane-2,3-diol, **12**



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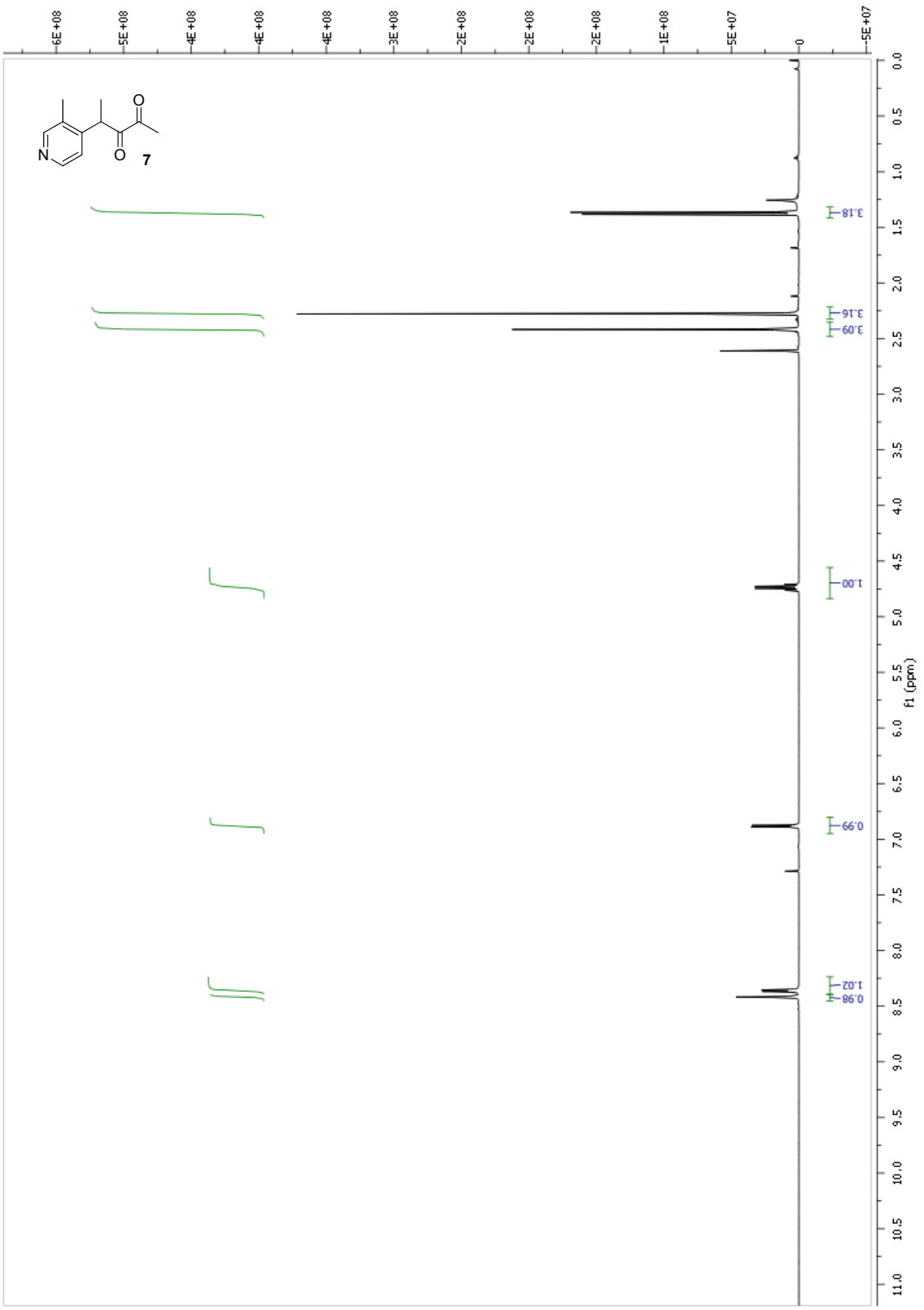
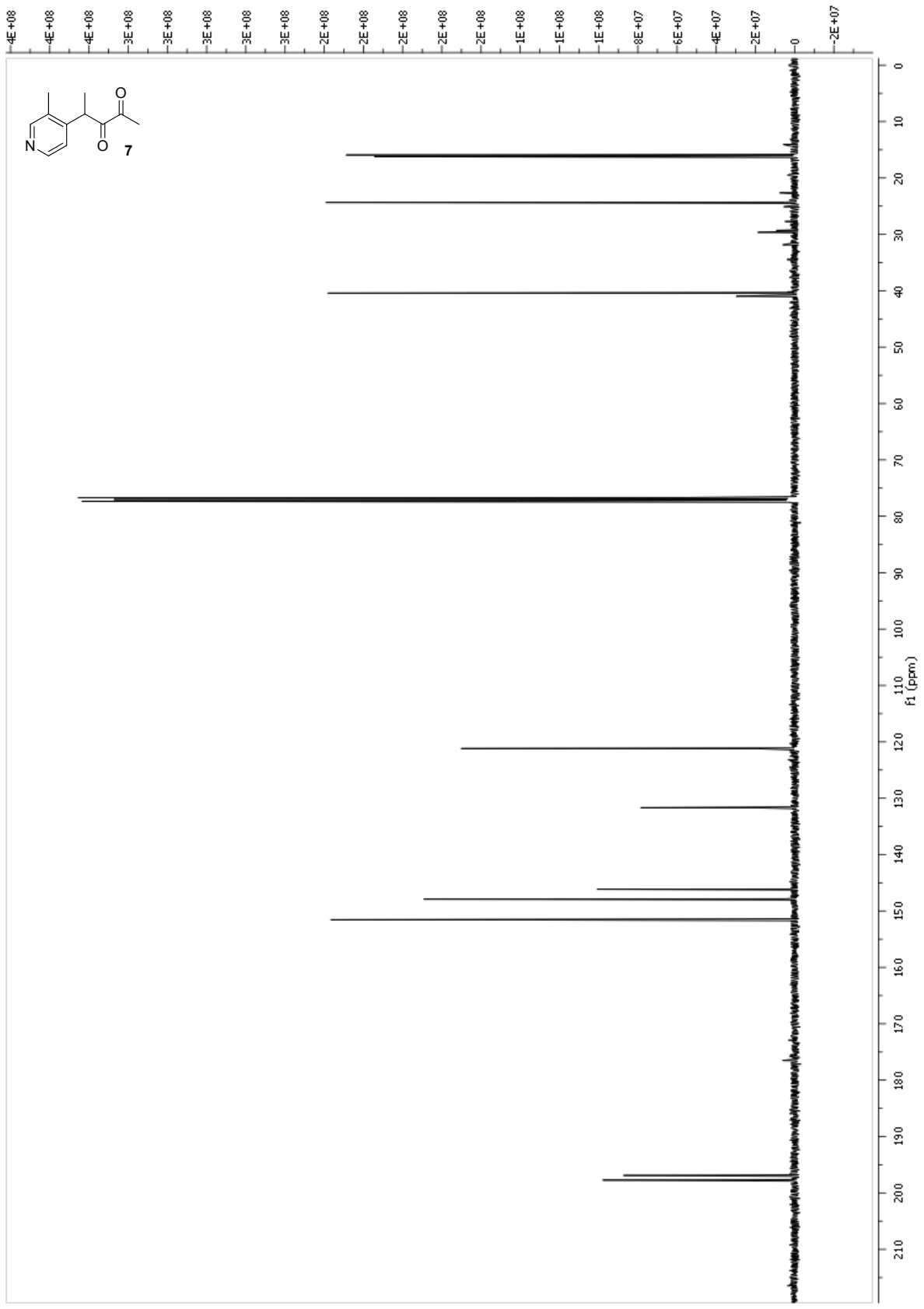
^{1}H NMR ($CDCl_3$, 400 MHz) (±)-4-(3-Methylpyridin-4-yl)pentane-2,3-dione, **7**



^{13}C NMR ($CDCl_3$, 100 MHz) (±)-4-(3-Methylpyridin-4-yl)pentane-2,3-dione, **7**



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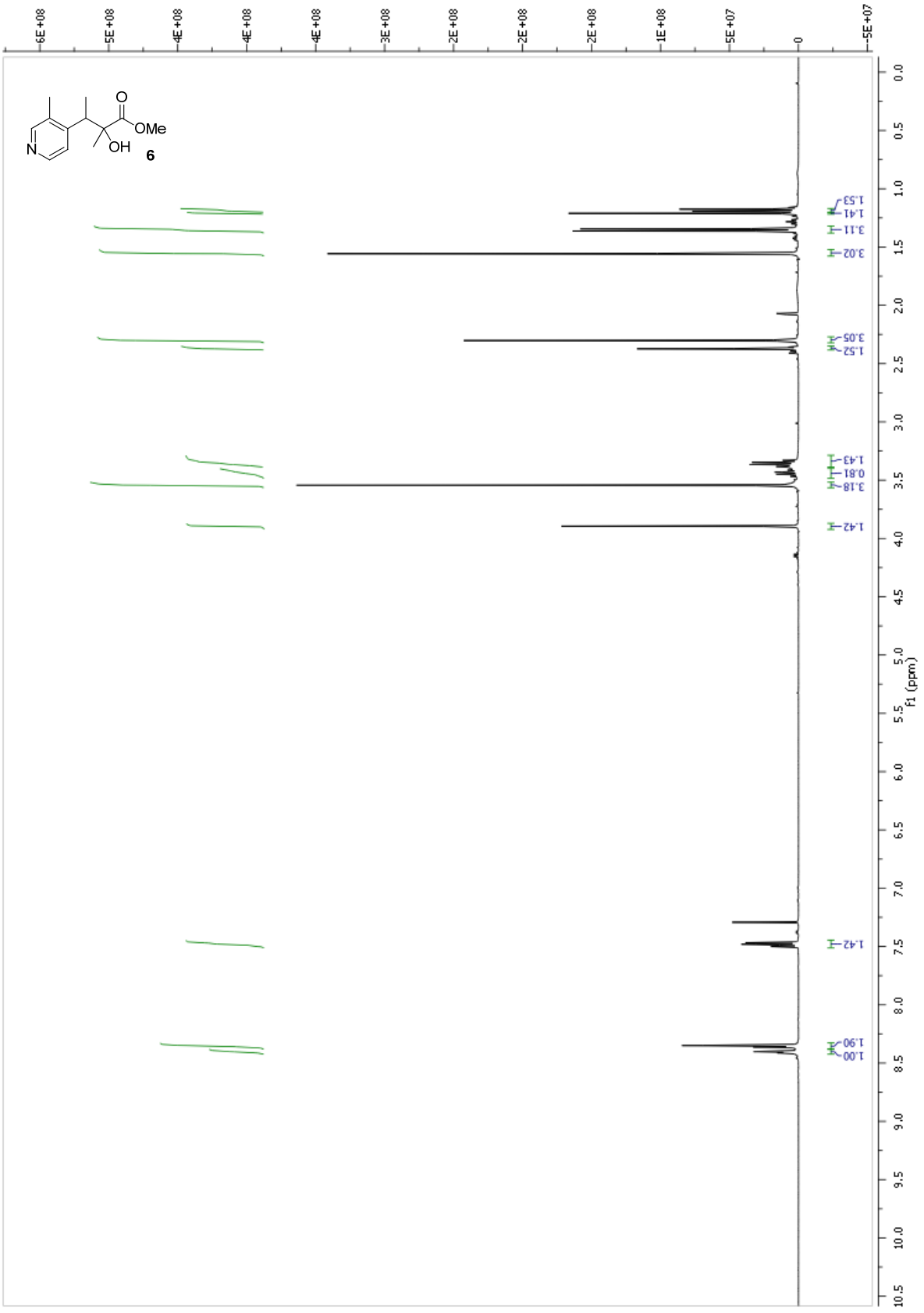
^{1}H NMR ($CDCl_3$, 400 MHz) (2*S**,3*R**)- and (2*R**,3*R**)-Methyl 2-hydroxy-2-methyl-3-(3-methylpyridin-4-yl)butanoate, **6a** and **6b**



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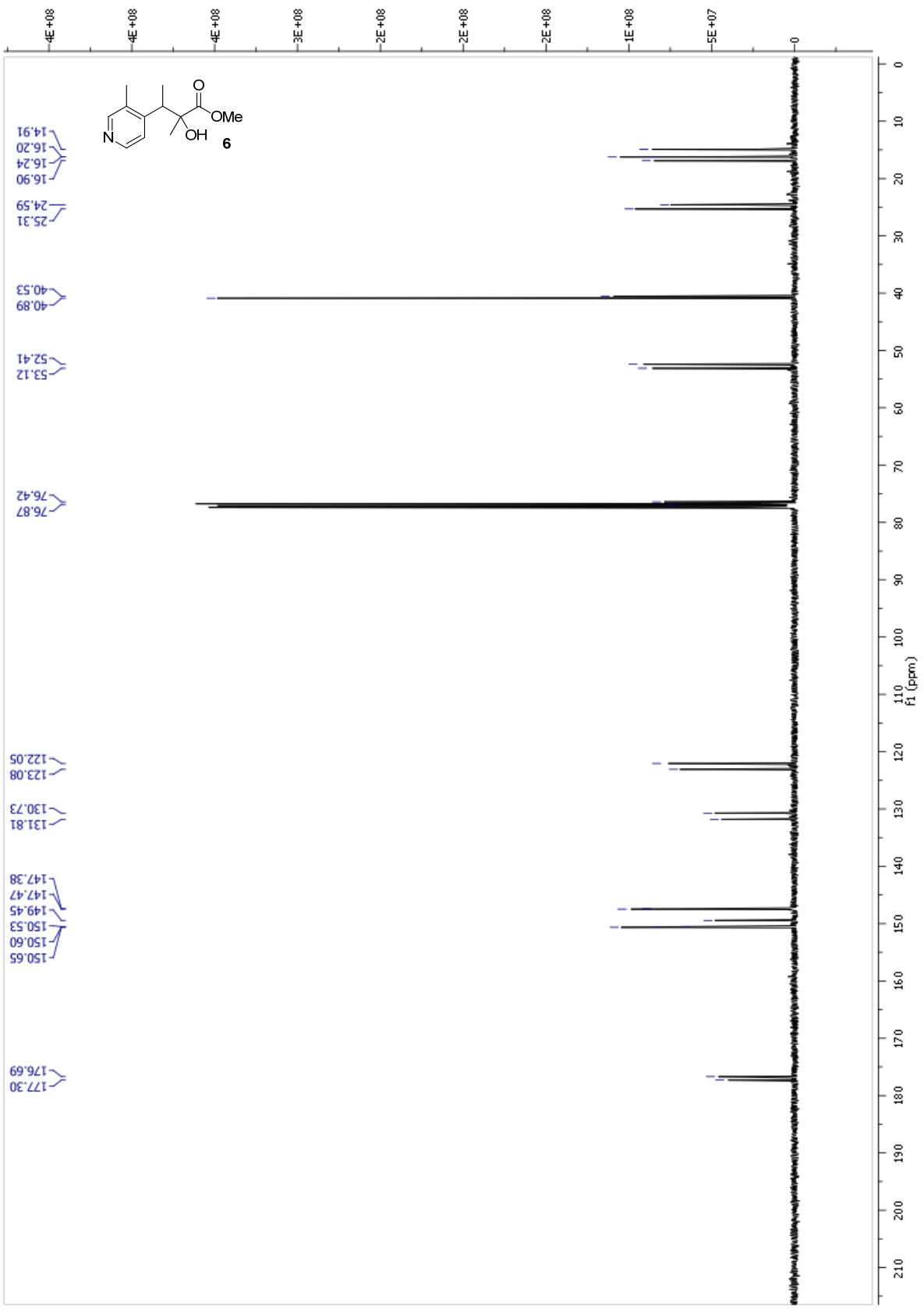
^{13}C NMR ($CDCl_3$, 100 MHz) (2*S**,3*R**)- and (2*R**,3*R**)-Methyl 2-hydroxy-2-methyl-3-(3-methylpyridin-4-yl)butanoate, **6a** and **6b**



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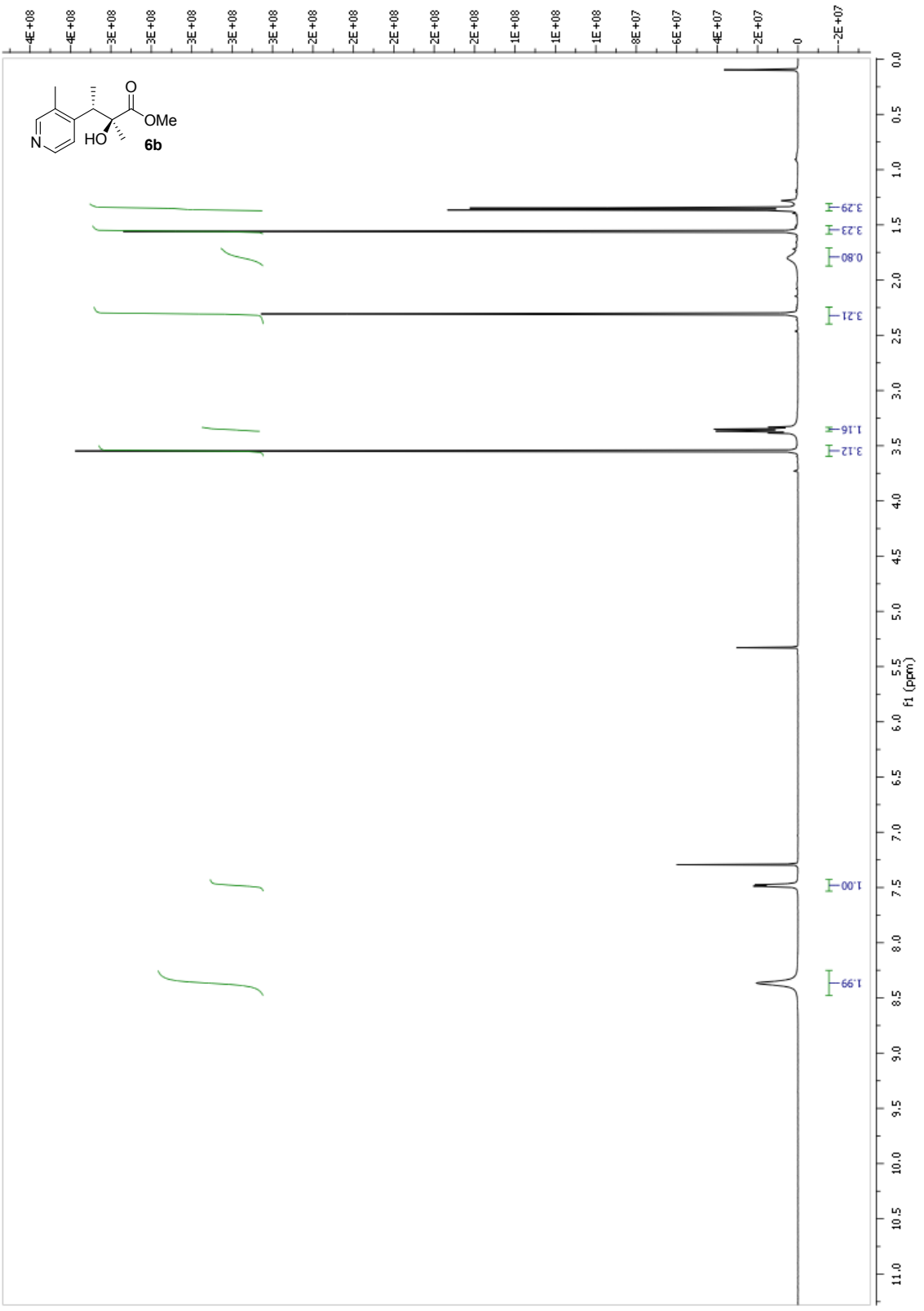
^{1}H NMR ($CDCl_3$, 400 MHz) (+)-(2*S*,3*S*)-Methyl 2-hydroxy-2-methyl-3-(3-methylpyridin-4-yl)butanoate, **6b**



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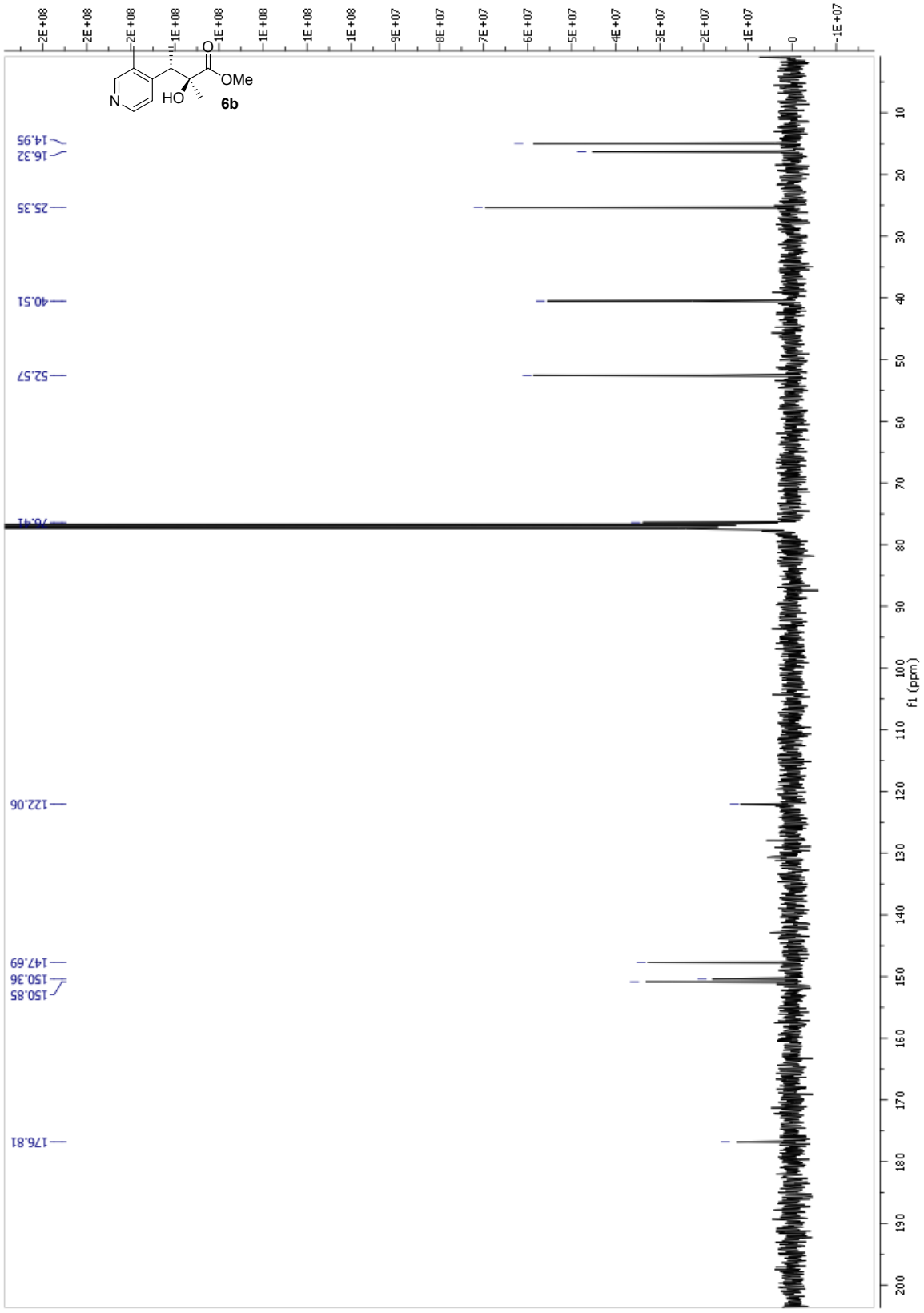
^{13}C NMR ($CDCl_3$, 100 MHz) (+)-(2*S*,3*S*)-Methyl 2-hydroxy-2-methyl-3-(3-methylpyridin-4-yl)butanoate, **6b**



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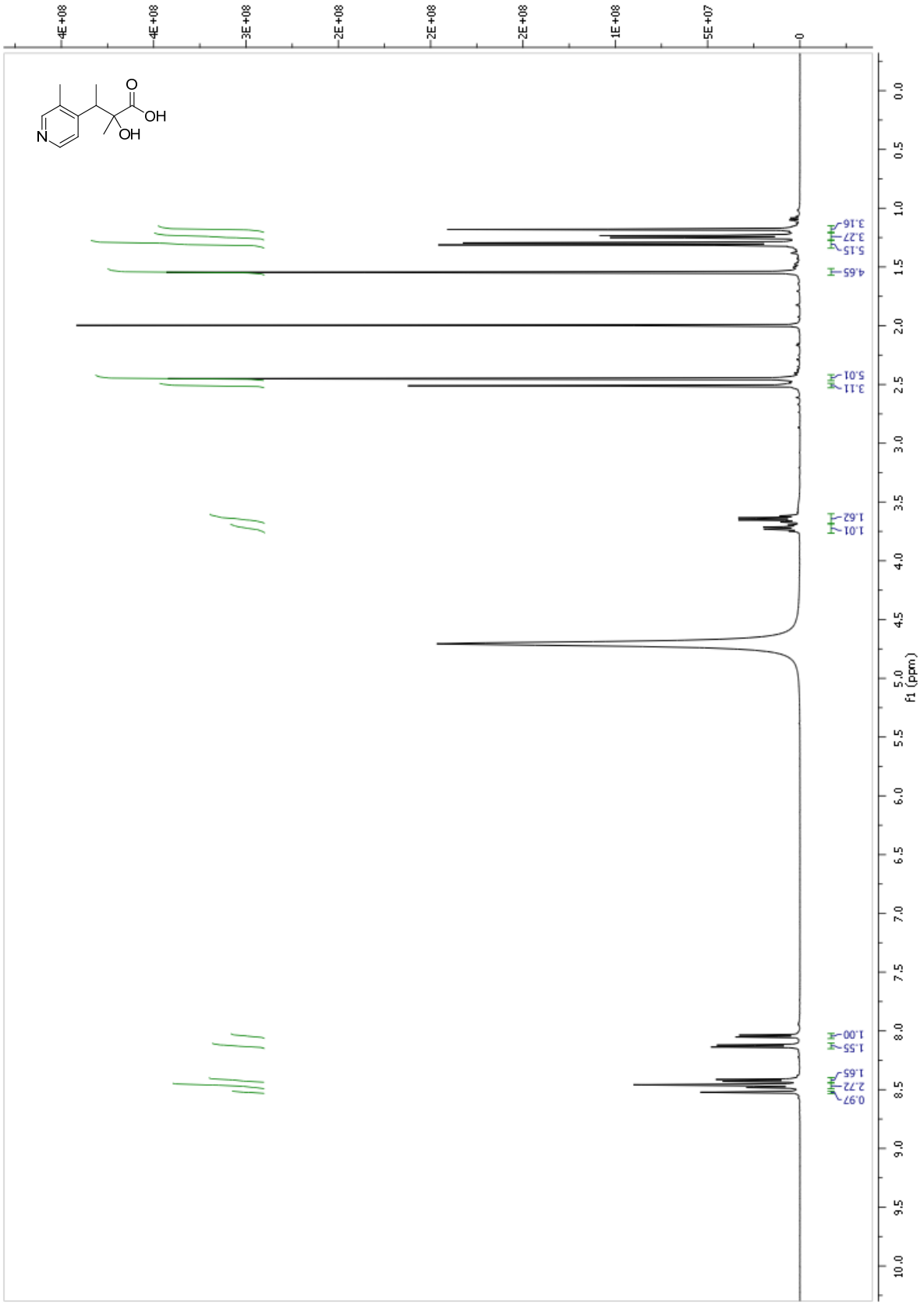
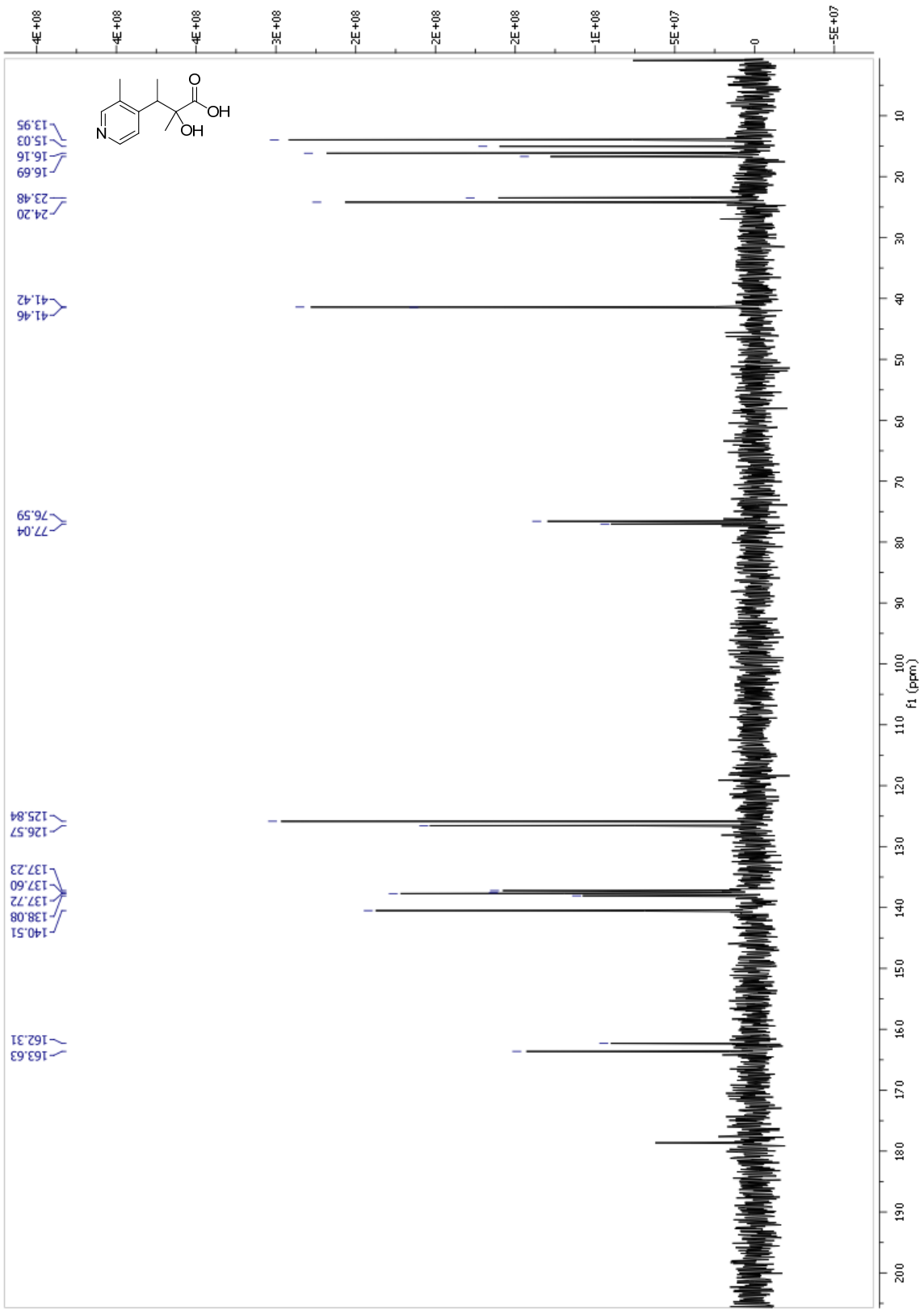
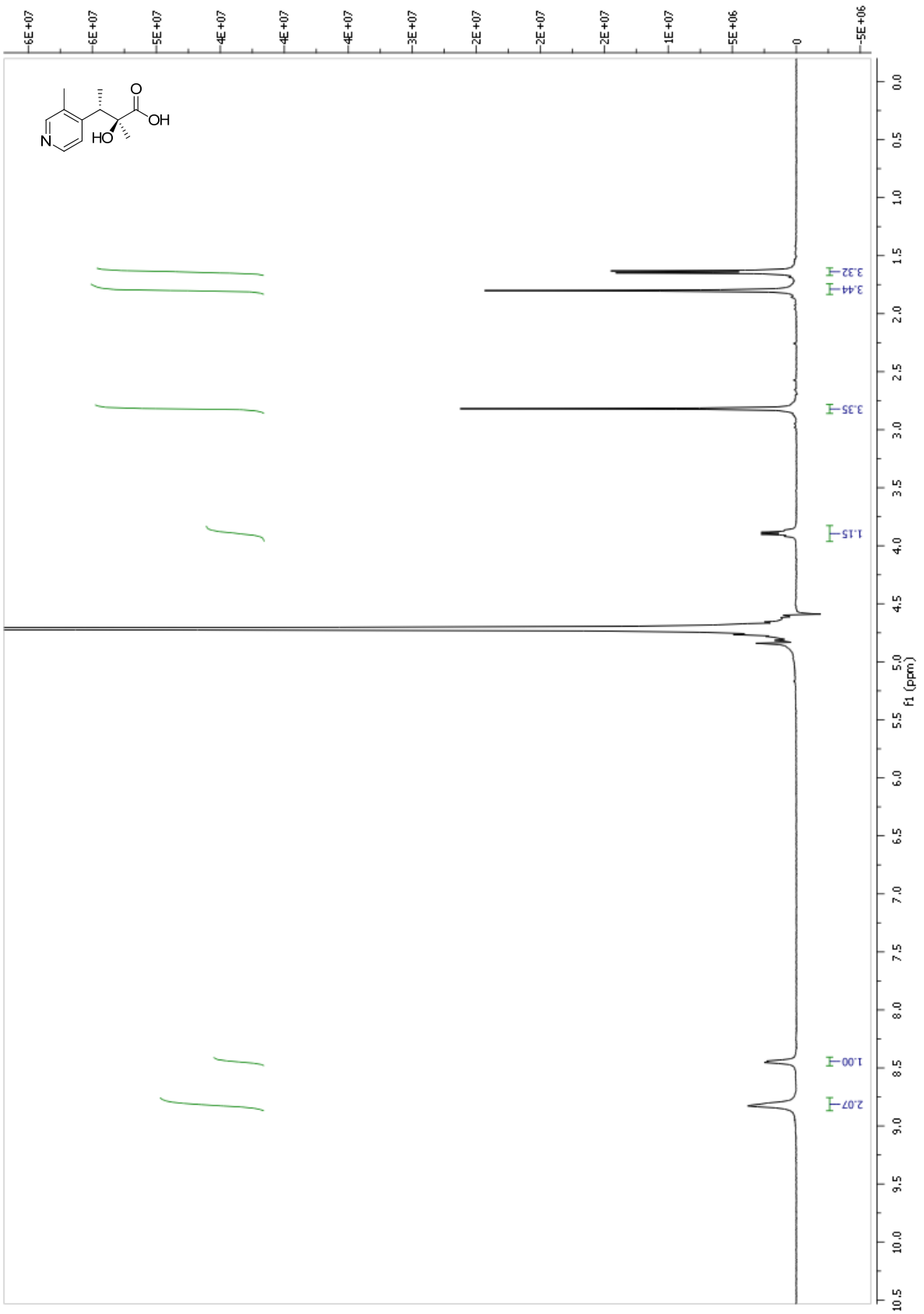
^{1}H NMR (D_2O, 400 MHz) (2*R**,3*S**)- and (2*S**,3*S**)-2-Hydroxy-2-methyl-3-(3-methylpyridin-4-yl)butanoic acids



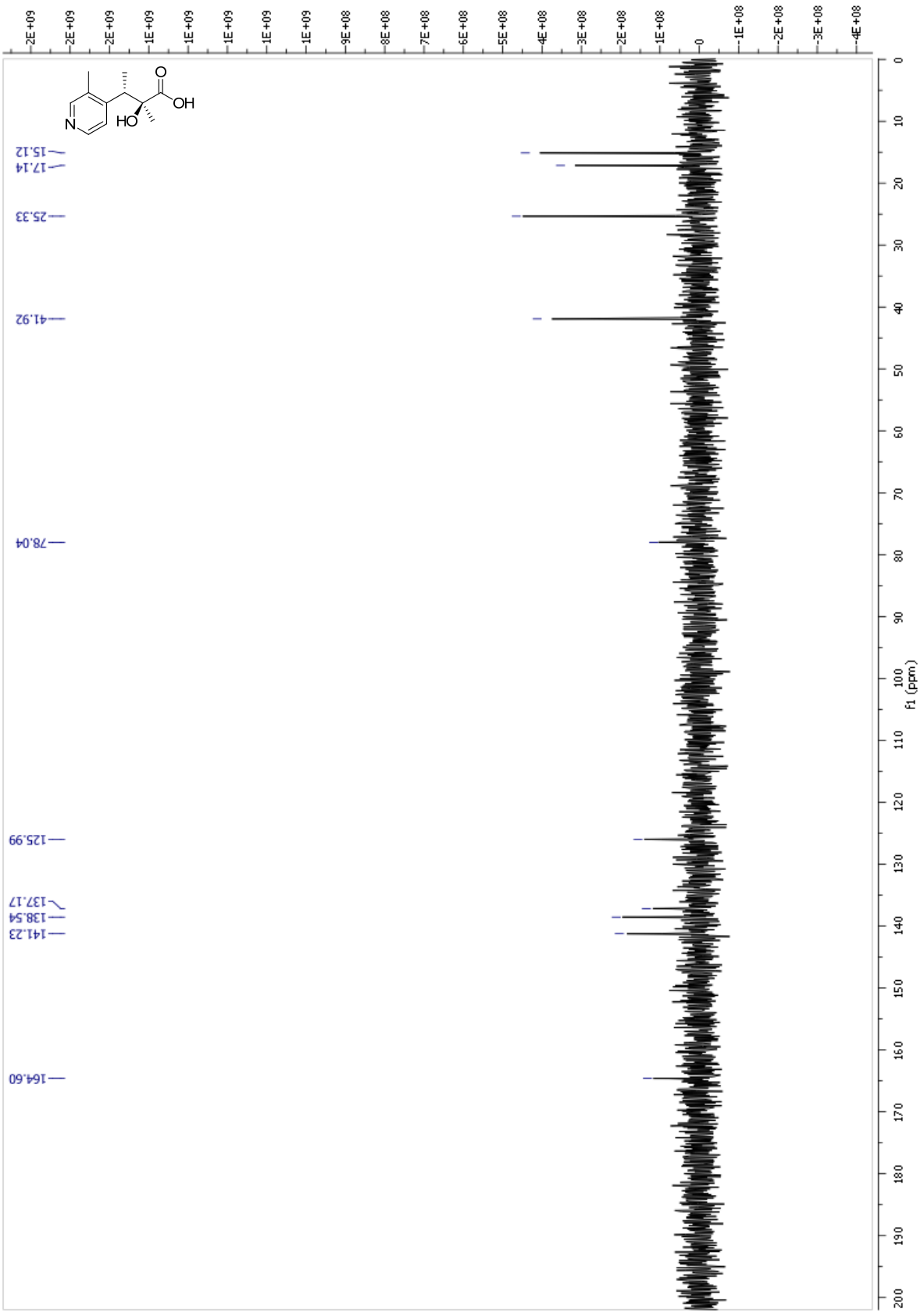
^{13}C NMR (D_2O, 100 MHz) (2*R**,3*S**)- and (2*S**,3*S**)-2-Hydroxy-2-methyl-3-(3-methylpyridin-4-yl)butanoic acids



^{1}H NMR (D_2O, 400 MHz) (-)-(2*S*,3*S*)-2-Hydroxy-2-methyl-3-(3-methylpyridin-4-yl)butanoic acid



^{13}C NMR (D_2O, 100 MHz) (-)-(2*S*,3*S*)-2-Hydroxy-2-methyl-3-(3-methylpyridin-4-yl)butanoic acid



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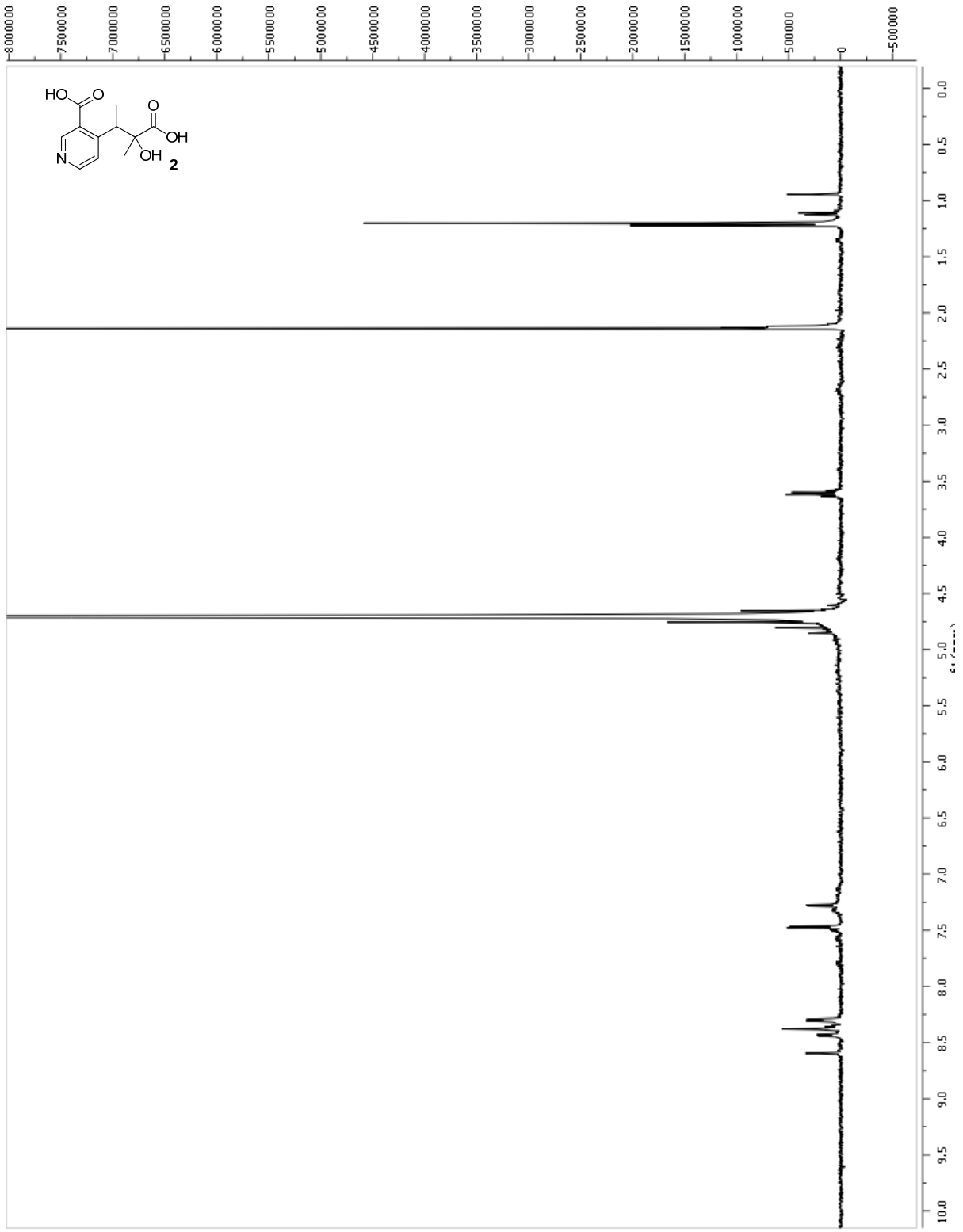
^{1}H NMR (D_2O, 400 MHz) (2*R**,3*S**)- and (2*S**,3*S**)-2-Hydroxy-2-methyl-3-(3-carboxypyridin-4-yl)butanoic acid, **2a** and **2b**



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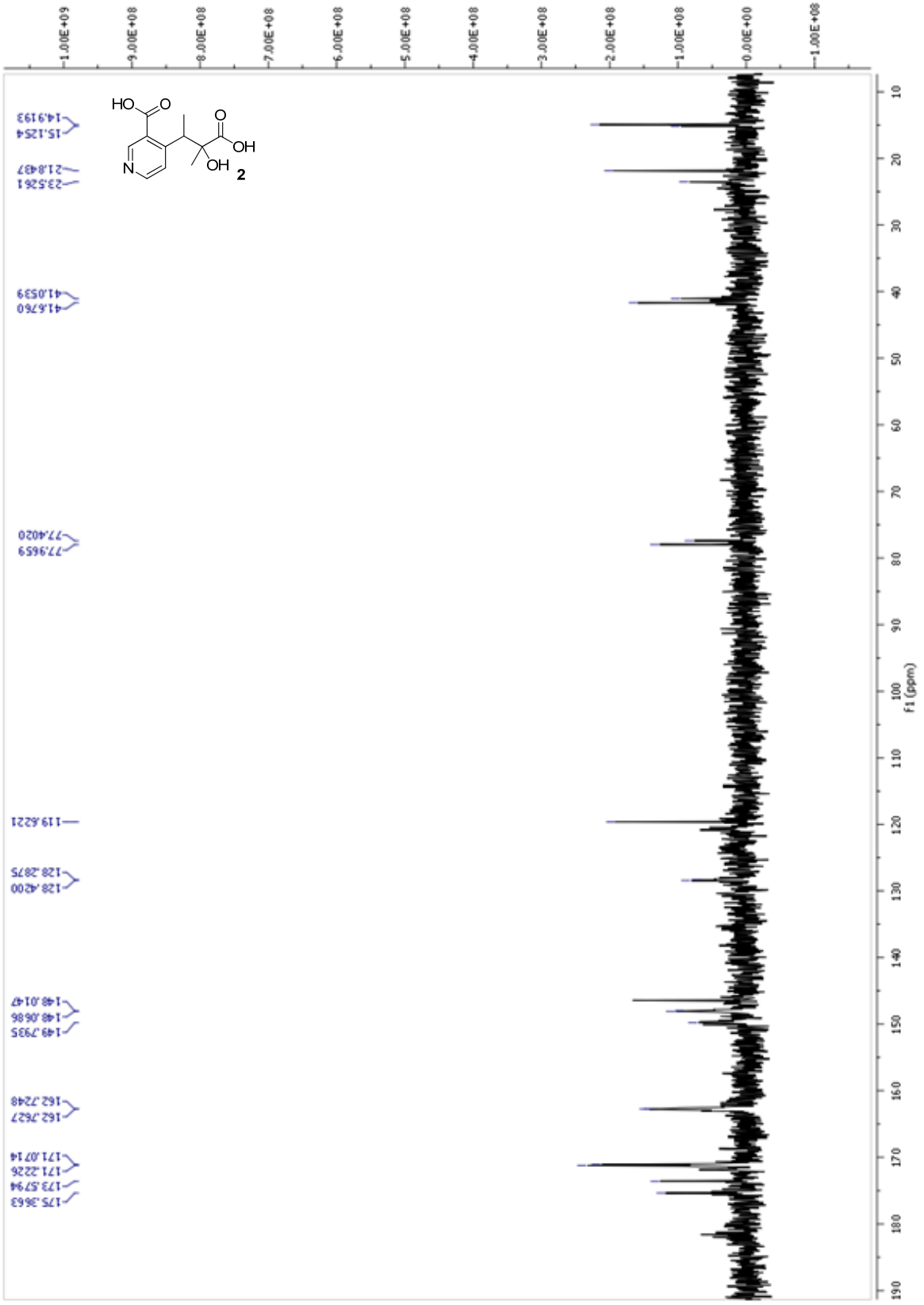
^{13}C NMR (D_2O, 100 MHz) (2*R**,3*S**)- and (2*S**,3*S**)-2-Hydroxy-2-methyl-3-(3-carboxypyridin-4-yl)butanoic acid, **2a** and **2b**



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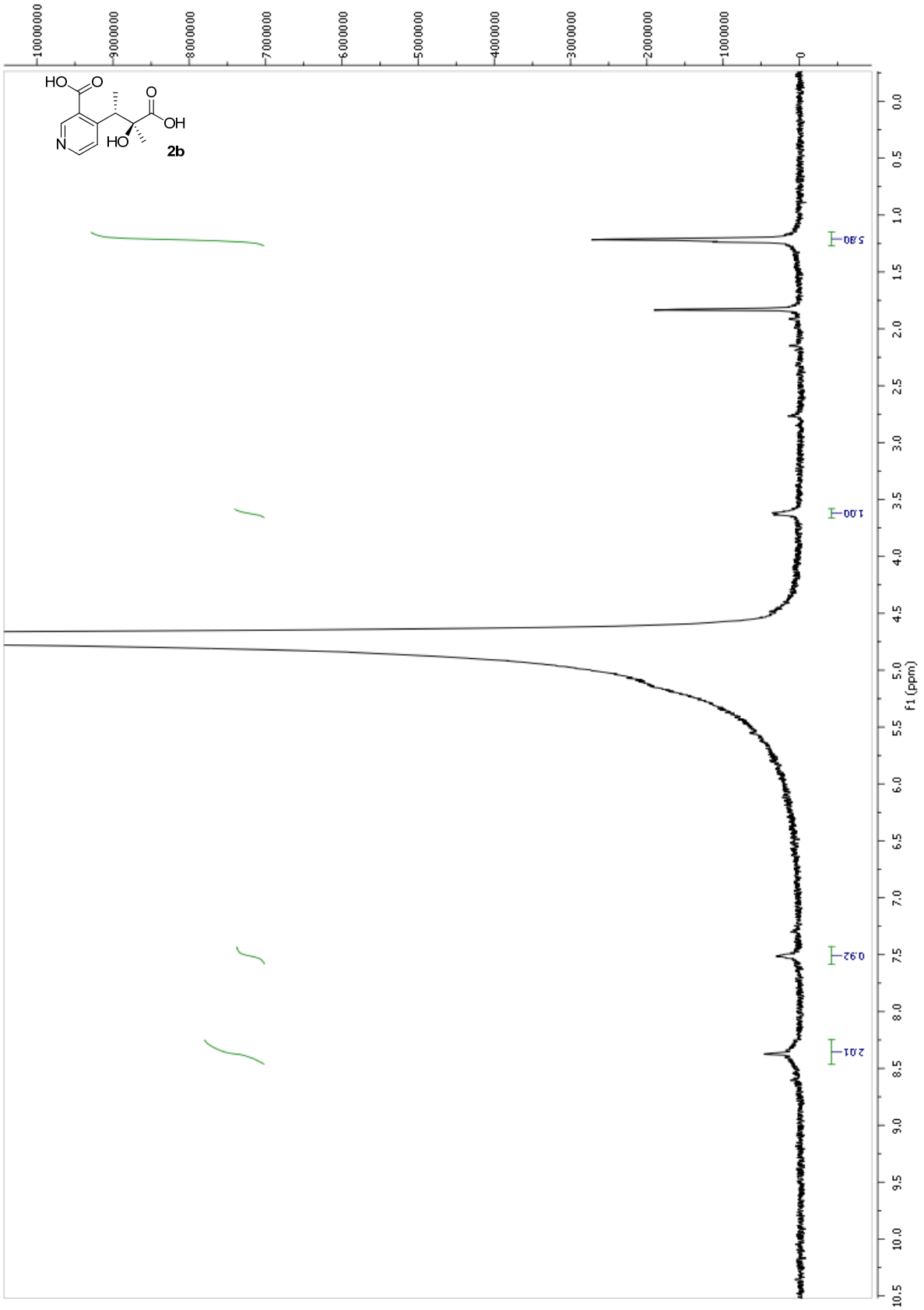
^{1}H NMR (D_2O, 400 MHz) (+)-(2*S*,3*S*)-2-Hydroxy-2-methyl-3-(3-carboxypyridin-4-yl)butanoic acid, **2b**



^{13}C NMR (D_2O, 100 MHz) (+)-(2*S*,3*S*)-2-Hydroxy-2-methyl-3-(3-carboxypyridin-4-yl)butanoic acid, **2b**