A Concise Synthesis of Berkelic Acid Inspired by Combining the Natural Products Spicifernin and Pulvilloric Acid

Christopher F. Bender, Francis K. Yoshimoto, Christopher L. Paradise and Jef K. De Brabander

Department of Biochemistry and Harold C. Simmons Comprehensive Cancer Center, The University of Texas Southwestern Medical Center at Dallas, 5323 Harry Hines Boulevard, 75390-9038

Email: jef.debrabander@utsouthwestern.edu

Contents

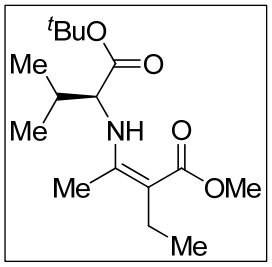
1. General Experimental

Unless otherwise noted, commercially available materials were used without further purification. All solvents were HPLC or ACS grade. Solvents used for moisture sensitive operations were dried over molecular sieves (Aldrich, 4 Å), anhydrous MeOH was purchased from Aldrich. Deuterated solvents were purchased from Cambridge Isotope Labs and used as received. Reactions were performed under an atmosphere of nitrogen or argon with magnetic stirring unless noted otherwise. Isocratic flash chromatography (FC) was performed using *Dynamic Adsorbents* silica gel (32-63 μm) according to the protocol of Still. Kahn, and Mitra (*J. Org. Chem.* **1978**, *43*, 2923). Gradient FC was performed with a *Teledyne Isco* CombiFlash® R_f using RediSep® R_f silica cartridges for dry loading and RediSep® R_f flash columns. Thin layer chromatography was performed using precoated plates purchased from *Dynamic Adsorbents* (F-254, 0.25 mm) that were visualized with $KMnO_4$ or Ce(IV) stain.

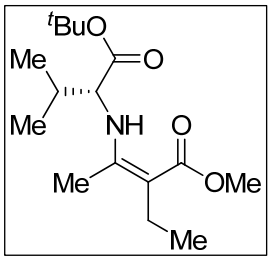
Nuclear magnetic resonance (NMR) spectra were recorded on a *Varian Inova*-500, *Inova*-400, or *Mercury*-300 spectrometer at operating frequencies of 500/400/300 MHz (^{1}H NMR) or 126/100/75 MHz (^{13}C NMR). Chemical shifts (δ) are given in ppm relative to residual solvent (usually chloroform δ 7.26 for ^{1}H NMR or δ 77.16 for proton decoupled ^{13}C NMR), and coupling constants (*J*) in Hz. Multiplicity is tabulated as s for singlet, d for doublet, t for triplet, q for quartet, and m for multiplet, whereby the prefix *app* is applied in cases where the true multiplicity is unresolved, and br when the signal in question is broadened.

Infrared spectra were recorded on a *Perkin-Elmerl* 1000 series FTIR with wavenumbers expressed in cm^{-1} using samples prepared as thin films on salt plates. Electrospray ionization mass spectra (ESI-MS) were recorded on a *Shimadzu* 2010-LCMS. High resolution mass spectra (HRMS) were performed by the mass spectroscopy facility in the department of chemistry at Duke University using electrospray ionization. Elemental analyses were performed by Complete Analysis Laboratories (Parsippany, NJ). Optical rotations were measured at the specified temperature on a Rudolph Research Analytical Autopol® IV polarimeter.

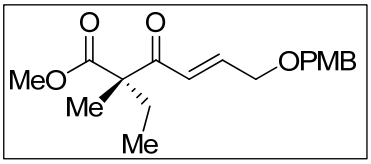
2. Synthetic Experimental Procedures



(*S*,*Z*)-Methyl 3-(1-*tert*-butoxy-3-methyl-1-oxobutan-2-ylamino)-2-ethylbut-2-enoate (**9**). **9** was prepared by the method of Koga.[1] A solution of methyl 2-ethyl-3-oxobutanoate (**8**, 1.56 g, 10.8 mmol), (*L*)-*tert*-butyl valinate (1.85 g, 10.68 mmol), and BF_3•OEt_2 (80 μL, 0.64 mmol) in benzene (50 mL) was refluxed for 14h with Dean-Stark removal of water. The mixture was cooled to room temperature and washed with sat. $NaHCO_3$ (50 mL), dried (Na_2SO_4), and concentrated. The resultant residue was Kugelrohr distilled (160 °C @ 1 torr) to give **9** (2.61 g, 82%) as a colorless oil. *Z*-Ene-amine geometry unambiguously assigned via 1D ^{1}H-^{1}H nOe (Figure 4). $[\alpha]^{23}_D$ = 145.0 (*c* = 1.19 g cm^{-3} in $CHCl_3$); ^{1}H-NMR (400 MHz, $CDCl_3$): δ 9.50 (d, *J* = 8.8 Hz, 1H), 3.80 (dd, *J* = 5.5, 9.2 Hz, 1H), 3.68 (s, 3H), 2.24 (q, *J* = 7.4 Hz, 2H), 2.16 (dsept, *J* = 5.5, 6.8 Hz, 1H), 1.90 (s, 3H), 1.45 (s, 9H), 1.02 (d, *J* = 6.8 Hz, 3H), 1.01 (d, *J* = 6.8 Hz, 3H), 0.94 (t, *J* = 7.4 Hz, 3H); ^{13}C-NMR (126 MHz, $CDCl_3$): δ 171.7, 171.4, 158.3, 96.1, 81.6, 62.8, 50.6, 31.8, 28.1, 20.7, 19.4, 18.3, 15.4, 14.9; IR (film, cm^{-1}): 2968, 1738, 1651, 1598, 1240, 1135; LRMS (*m*/*z*): $[M+H]^+$ calcd for $C_{16}H_{30}NO_4$, 300.2; found, 300.2; HRMS (*m*/*z*): $[M]^+$ calcd for $C_{16}H_{29}NO_4$, 299.2097; found, 299.2103; elemental analysis (% calcd, % found for $C_{16}H_{29}NO_4$): C (64.18, 63.99), H (9.76, 9.81), N (4.68, 4.73).



(*R*,*Z*)-Methyl 3-(1-*tert*-butoxy-3-methyl-1-oxobutan-2-ylamino)-2-ethylbut-2-enoate [*ent*-**9**]. *Ent*-**9** was prepared in 88% yield (5.24 g) from (*D*)-*tert*-butyl valinate employing a method analogous to that described for the synthesis of **9**. $[\alpha]^{24}_D$ = -147.6 (*c* = 1.16 g cm^{-3} in $CHCl_3$); elemental analysis (% calcd, % found for $C_{16}H_{29}NO_4$): C (64.18, 64.21), H (9.76, 9.59), N (4.68, 4.77).

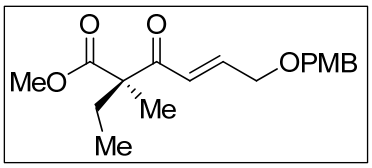


(*S*,*E*)-Methyl 2-ethyl-6-(4-methoxybenzyloxy)-2-methyl-3-oxohex-4-enoate (**12**). (*S*,*E*)-methyl 3-[(*S*)-1-*tert*-butoxy-3-methyl-1-oxobutan-2-ylimino]-2-ethyl-2-methylbutanoate (**10**) was prepared by a modification of Koga's method.[1] A solution of LDA [prepared by the addition of ^{n}BuLi (2.2 M in hexanes, 5.9 mL, 13.0 mmol) to a -78 °C solution of ^{i}Pr$_2$NH (1.84 mL, 13.0 mmol) in toluene (13 mL) and stirred for 30 min] was added dropwise to a -78 °C solution of **9** (3.00 g, 10.0 mmol) in toluene (45 mL). After 1 h THF (2.10 mL, 25.9 mmol) was added and the resultant mixture stirred 3 h before MeI (3.10 mL, 49.7 mmol) was added. The reaction was maintained at -78 °C for 17 h, treated with water (100 mL), warmed to room temperature over 30 min, and extracted with EtOAc (3 × 75 mL). The combined organic fractions were washed with sat. $NaHCO_3$ (50 mL), sat. $Na_2S_2O_3$ (50 mL), water (50 mL), and brine (50 mL); dried (Na_2SO_4); and concentrated to give crude **10** (88% conversion, dr ≥ 15:1, 2.97 g recovered) as an orange oil. From the crude mixture ^{1}H and ^{13}C NMR spectra were obtained. ^{1}H-NMR (500 MHz, $CDCl_3$): δ 3.67 (d, *J* = 6.6 Hz, 1H), 3.66 (s, 3H), 2.26 (dseptet, *J* = 6.6, 6.8 Hz, 1H), 1.93 (qd, *J* = 7.6, 14.2 Hz, 1H), 1.81 (qd, *J* = 7.3, 13.9 Hz, 1H), 1.74 (s, 3H), 1.42 (s, 9H), 1.30 (s, 3H), 0.91 (d, *J* = 6.8 Hz, 3H), 0.88 (d, *J* = 6.8 Hz, 3H), 0.81 (t, *J* = 7.6 Hz, 3H); ^{13}C-NMR (126 MHz, $CDCl_3$): δ 176.1, 170.9,

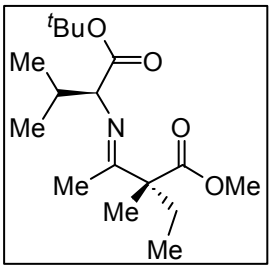
170.4, 80.7, 70.1, 57.2, 51.9, 32.0, 28.6, 28.1, 20.2, 19.6, 18.2, 15.5, 8.8; LRMS (*m*/*z*): $[M+H]^+$ calcd for $C_{17}H_{32}NO_4$, 314.2; found, 314.2;

Crude **10** was dissolved in a mixture of THF (100 mL) and 1 M HCl (100 mL) to give a homogeneous solution that after 1 h was extracted with Et_2O (4 × 75 mL). The combined organic fractions were washed with water (100 mL), 1 M HCl (100 mL), and brine (50 mL); dried (Na_2SO_4); and concentrated to approximately 5 mL giving (*S*)-methyl 2-ethyl-2-methyl-3-oxobutanoate (**S1**) as a THF solution. The absolute stereochemistry of **S1** was unambiguously assigned by single crystal x-ray analysis of the hydrazone derivative **11** described below.

The crude THF solution of **S1** was further diluted with THF (50 mL), activated 4 ÅMS were added and stirred at room temperature for 1 h. The solution was cooled to 0 °C and $TiCl_4$ (2.40 mL, 21.9 mmol) was carefully added. After 30 min the resultant orange suspension was cooled to -78 °C and TEA (3.10 mL, 22.2 mmol) was added. After 1 h 2-(4-methoxybenzyloxy)acetaldehyde[2] (2.17 g, 12.0 mmol) was added and the reaction was maintained at -78 °C for 1.5 h before warming to room temperature over 1.5 h. NH_4Cl (100 mL) was added and the biphasic mixture was vigorously stirred for 30 min before extracting with Et_2O (5 × 20 mL). The combined organic fractions were washed with sat. $NaHCO_3$ (75 mL) and brine (75 mL); dried (Na_2SO_4); and concentrated. The resultant residue was purified by FC (silica gel; 0→100% EtOAc/hexanes) to give **12** [1.29 g, 42% from **9**] as a pale yellow oil. TLC (EtOAc:hexanes, 25:75 v/v): R_F = 0.44; $[\alpha]^{25}_D$ = -3.2 (*c* = 20.2 in $CHCl_3$, *ee* ≥ 88%); ^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.24-7.27 (m, 2H), 6.98 (td, *J* = 4.2, 15.4 Hz, 1H), 6.87-6.90 (m, 2H), 6.52 (td, *J* = 2.2, 15.1 Hz, 1H), 4.47 (s, 2H), 4.14 (dd, *J* = 2.2, 4.2 Hz, 2H), 3.80 (s, 3H), 3.70 (s, 3H), 1.97 (qd, *J* = 7.8, 13.9 Hz, 1H), 1.84 (qd, *J* = 7.6, 13.9 Hz, 1H), 1.34 (s, 3H), 0.82 (t, *J* = 7.6 Hz, 3H); ^{13}C-NMR (126 MHz, $CDCl_3$): δ 196.2, 173.8, 159.5, 144.0, 129.8, 129.5, 124.2, 114.0, 72.6, 68.6, 59.0, 55.4, 52.5, 27.7, 18.3, 8.7; IR (film, cm^{-1}): 2952, 1739, 1698, 1634, 1514, 1248; LRMS (*m*/*z*): $[M+Na]^+$ calcd for $C_{18}H_{24}NaO_5$, 343.2; found, 343.1; HRMS (*m*/*z*): $[M]^+$ calcd for $C_{18}H_{24}O_5$, 320.1624; found, 320.1620; elemental analysis (% calcd, % found for $C_{18}H_{24}O_5$): C (67.48, 67.33), H (7.55, 7.36).

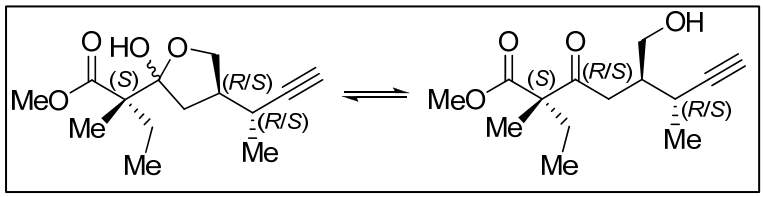


(*R*,*E*)-Methyl 2-ethyl-6-(4-methoxybenzyloxy)-2-methyl-3-oxohex-4-enoate (*ent*-**12**). *Ent*-**12** was prepared in 45% yield (1.37 g) from *ent*-**9** employing the method described for the synthesis of *ent*-**12**. $[\alpha]^{23}_D$ = 3.3 (*c* = 20.4 in $CHCl_3$); elemental analysis (% calcd, % found for $C_{18}H_{24}O_5$): C (67.48, 67.32), H (7.55, 7.27).



(*R*,*Z*)-methyl 3-[(*S*)-1-*tert*-butoxy-3-methyl-1-oxobutan-2-ylimino]-2-ethyl-2-methylbutanoate (**S2**). **S2** was prepared by the method of Koga[1] in order to determination the diatereomeric ratio in the formation of **10**, and thereby the optical purity of the resultant β-ketoesters **12**. A solution of LDA [prepared by the addition of ^{n}BuLi (2.2 M in hexanes, 1.1 mL, 2.4 mmol) to a -78 °C solution of ^{i}Pr$_2$NH (0.34 mL, 2.4 mmol) in toluene (2 mL) and stirred for 1 h] was added dropwise to a -78 °C solution of **9** (603 mg, 2.01 mmol) in toluene (9 mL). After 1 h HMPA (0.42 mL, 2.4 mmol) was added and the resultant mixture stirred 1 h before MeI (0.25 mL, 4.01 mmol) was added. The reaction was warmed to between -60 and -50 °C for 3 h, was treated with water (35 mL), and warmed to room temperature over 30 min, and extracted with Et_2O (3 × 25 mL). The combined organic fractions were washed with sat. $NaHCO_3$ (25 mL), sat. $Na_2S_2O_3$

(25 mL), water (25 mL), and brine (25 mL); dried (Na_2SO_4); and concentrated to give crude **S2** (80% conversion, dr ~ 10:1, 608 mg recovered) as an orange oil. From the crude mixture a ^{1}H-NMR spectrum was obtained. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 3.69 (d, *J* = 6.4 Hz, 3H), 3.67 (s, 3H), 2.21-2.32 (m, 1H), 1.94 (qd, *J* = 7.4, 14.1 Hz, 1H), 1.84 (qd, *J* = 7.4, 14.1 Hz, 1H), 1.75 (s, 3H), 1.43 (s, 9H), 1.31 (s, 3H), 0.91 (*app*. t, *J* = 6.4 Hz, 6H), 0.82 (t, *J* = 7.4 Hz, 3H). Specifically, the resonances at δ 0.91 (*app*. t, *J* = 6.4 Hz, 6H) for **S2** and δ 0.88 (d, *J* = 6.8 Hz, 3H) for **10** provided for the unambiguous determination of diastereomeric ratio in the formation of **10** and *ent*-10.

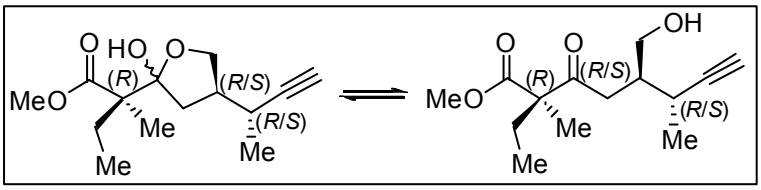


anti-(*S*) Methyl 5-(hydroxymethyl)-2,6-dimethyl-2-ethyl-3-oxooct-7-ynoate and hemiacetals thereof [**14a** and **14b**]. *Sec*-BuLi (1.4 M in CyH, 2.9 mL, 4.06 mmol) was added dropwise over 10 min to a -78 °C solution of 1-trimethylsilyl-1-butyne[3] (509 mg, 4.03 mmol) in THF (7.5 mL) and stirred for 2 h. The resultant yellow solution was added to a precooled -78 °C suspension of CuBr•DMS (823 mg, 4.00 mmol) and THF (5 mL) over 5 min and vigorously stirred at -78 °C for 1 h to give a deep-red, homogeneous solution. A solution of (*S*)-**O** (310 mg, 1.01 mmol) in THF (5 mL) was added and the reaction temperature maintained at -78 °C. After 2 h sat. NH_4Cl (20 mL) was added and the mixture warmed to room temperature over 30 min. The resultant mixture was diluted with water (20 mL), and extracted with EtOAc (3 × 40 mL). The combined organic fractions were washed with sat. NH_4Cl (30 mL) and brine (30 mL), dried (Na_2SO_4), and concentrated to give *anti*-(*S*) methyl 2-ethyl-5-((4-methoxybenzyloxy)methyl)-2,6-dimethyl-3-oxo-8-(trimethylsilyl)oct-7-ynoate [**13a** and **13b**, *anti*:*syn* ~ 5:1, *dr* ~ 5:1:5:1] as a yellow oil that was used without purification. Chromatographic (silica gel; 0→100% EtOAc/hexanes) purification of a similar preparation of **13a** and **13b** provided pure material (52% yield) for characterization. TLC (EtOAc:hexanes, 25:75 v/v): R_F = 0.59; *anti*-diastereomers: ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.22 (d, *J* = 8.6 Hz, 2 H), 6.87 (d, *J* = 8.6 Hz, 2H), 4.36-4.43 (m, 2H), 3.80 (s, 3H), 3.70 (s, 1.5H), 3.69 (s, 1.5H), 3.48-3.53 (m, 1H), 3.41 (dd, *J* = 7.6, 9.4 Hz, 0.5H), 3.41 (dd, *J* = 7.6, 9.5 Hz, 0.5H), 2.61-2.72 (m, 3H), 2.33-2.42 (m, 1H), 1.95 (qd, *J* = 7.6, 13.9 Hz, 0.5H), 1.95 (qd, *J* = 7.6, 14.0 Hz, 0.5H), 1.81 (qd, *J* = 7.5, 14.0 Hz, 0.5H), 1.81 (qd, *J* = 7.6, 14.0 Hz, 0.5H), 1.32 (s, 1.5H), 1.31 (s, 1.5H), 1.14 (d, *J* = 7.2 Hz, 3H), 0.82 (t, *J* = 7.4 Hz, 1.5H), 0.82 (t, *J* = 7.4 Hz, 1.5H); *syn*-diastereomers diagnostic resonance: ^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.10 (d, *J* = 7.0 Hz, 1.5H), 1.09 (d, *J* = 7.0 Hz, 1.5H). *anti*-diastereomers: ^{13}C-NMR (126 MHz, $CDCl_3$): δ (207.4, 207.2), (173.5, 173.5), 159.2, (130.6, 130.6), (129.3, 129.3), 113.8, (109.3, 109.3), (86.0, 85.9), (72.7, 72.7), (69.5, 69.5), (60.2, 60.2), 55.3, (52.4, 52,4), (38.5, 38.5), 37.9, 27.9, (27.9, 27.8), (18.4, 18.4), (18.3, 18.3), 8.7, 0.3; IR (film, cm^{-1}): 2956, 2164, 1713, 1514, 1249, 844; LRMS (*m*/*z*): $[M+Na]^+$ calcd for $C_{25}H_{38}NaO_5Si$, 469.2; found, 469.3; elemental analysis (% calcd, % found for $C_{14}H_{22}O_3$): C (67.23, 67.08), H (8.58, 8.74).

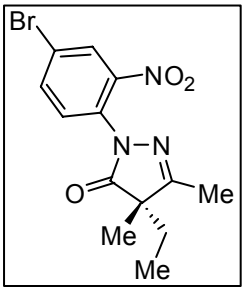
A suspension of crude **13a** and **13b** obtained above, K_2CO_3 (1.38 g, 9.99 mmol), and MeOH (20 mL) was vigorously stirred for 2 h. The resultant suspension was concentrated to ~5 mL, diluted with EtOAc (100 mL), washed with water (50 mL) and brine (50 mL), dried (Na_2SO_4), and concentrated to give *anti*-(*S*) methyl 2-ethyl-5-((4-methoxybenzyloxy)methyl)-2,6-dimethyl-3-oxooct-7-ynoate [**S3a** and **S3b**, *anti*:*syn* ~ 5:1, *dr* ~ 5:1:5:1] as a yellow oil that was used without purification. Chromatographic (silica gel; 0→100% EtOAc/hexanes) purification of a similar preparation of **S3a** and **S3b** provided pure material (97% yield) for characterization. TLC (EtOAc:hexanes, 25:75 v/v): R_F = 0.50; *anti*-

diastereomers: ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.22 (d, J = 8.6 Hz, 2H), 6.86 (d, J = 8.6 Hz, 2H), 4.40 (s, 1H), 4.39 (s, 1H), 3.80 (s, 3H), 3.69 (s, 3H), 3.53 (dd, J = 5.5, 9.6 Hz, 0.5H), 3.52 (dd, J = 5.3, 9.6 Hz, 0.5H), 3.43 (d, J = 9.4 Hz, 0.5H), 3.41 (d, J = 9.6 Hz, 0.5H), 2.61-2.74 (m, 3H), 2.35-2.43 (m, 1H), 2.00 (d, J = 2.3 Hz, 1H), 1.95 (qd, J = 7.4, 14.1 Hz, 1H), 1.81 (qd, J = 7.4, 14.1 Hz, 0.5H), 1.80 (qd, J = 7.2, 14.1 Hz, 0.5H), 1.32 (s, 1.5H), 1.31 (s, 1.5H), 1.17 (d, J = 7.0 Hz, 3H), 0.82 (t, J = 7.6 Hz, 1.5H), 0.81 (t, J = 7.4 Hz, 1.5H); *syn*-diastereomers diagnostic resonance: ^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.13 (d, J = 7.0 Hz, 1.5H), 1.12 (d, J = 7.2 Hz, 1.5H); *anti*-diastereomers: ^{13}C-NMR (126 MHz, $CDCl_3$): δ (207.2, 207.2), (173.5, 173.6), 159.2, (130.6, 130.6), (129.3, 129.3), 113.8, 86.5, (72.7, 72.7), (69.9, 69.9), (69.5, 69.6), (60.2, 60.2), 55.4, (52.4, 52.4), (38.5, 38.5), (37.9, 37.9), (27.8, 27.9), (26.7, 26.7), (18.4, 18.4), 18.4, (8.7, 8.7); IR (film, cm^{-1}): 3283, 2938, 1711, 1513, 1247, 1035; LRMS (*m*/*z*): $[M+Na]^+$ calcd for $C_{22}H_{30}NaO_5$, 397.2; found, 397.2;

DDQ (264 mg, 1.16 mmol) was added to a biphasic solution of the above obtained crude **S3a** and **S3b**, CH_2Cl_2 (35 mL), and water (5 mL) and vigourously stirred for 2.5 h. The resultant mixture was diluted with sat. $NaHCO_3$ (50 mL) and extracted with EtOAc (5 × 30 mL). The combined organic fractions were washed with brine (50 mL), dried (Na_2SO_4), and concentrated. The resultant residue was purified by FC (silica gel; 0→100% EtOAc/hexanes containing 0.5% TEA) to give **14a** and **14b** (178 mg, 69%) as a pale yellow oil. The ^{1}H NMR spectrum contains few diagnostic resonances (Figure 10) lending to the 12 species present (3 isomers for each diastereomer present). The presence of hemiacetal isomers was verified by ^{1}H-^{13}C gHMBC (Figure 10). Specifically, correlations were observed between the broad, deuterium exchangeable, ^{1}H resonances at δ 4.85-5.00 p.p.m. and ^{13}C resonances at δ 110.2-110.8 p.p.m. TLC (EtOAc:hexanes, 25:75 v/v): R_F = 0.31; IR (film, cm^{-1}): 3450, 3288, 2974, 1710, 1458, 1248; LRMS (*m*/*z*): $[M+Na]^+$ calcd for $C_{14}H_{22}NaO_4$, 277.1; found, 277.1; elemental analysis (% calcd, % found for $C_{14}H_{22}O_3$): C (66.12, 65.98), H (8.72, 8.76).



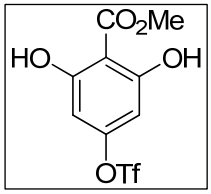
anti-(*R*) Methyl 5-(hydroxymethyl)-2,6-dimethyl-2-ethyl-3-oxooct-7-ynoate [*ent*-**14a** and *ent*-**14b**]. *ent*-**14a** and *ent*-**14b** were prepared from *ent*-**12** in 71% yield (*anti*:*syn* ~ 5:1) by a method analogous to the synthesis of **14a** and **14b**. The ^{1}H NMR spectra contains few diagnostic resonances lending to the 12 species present (3 isomers for each diastereomer present). Elemental analysis (% calcd, % found for $C_{14}H_{22}O_3$): C (66.12, 66.34), H (8.72, 8.79).



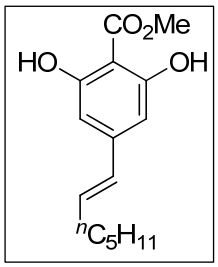
(*S*)-1-(4-Bromo-2-nitrophenyl)-4-ethyl-3,4-dimethyl-*1H*-pyrazol-5(*4H*)-one (**11**). A solution of LDA [prepared by the addition of ^{n}BuLi (2.2 M in hexanes, 2.4 mL, 5.3 mmol) to a -78 °C solution of ^{i}Pr$_2$NH (0.75 mL, 5.3 mmol) in toluene (5.3 mL) and stirred for 30 min] was added dropwise to a -78 °C solution of **9** (1.23 g, 4.11 mmol) in toluene (18 mL). After 1 h THF (0.87 mL, 10.6 mmol) was added and the resultant mixture stirred 3 h before MeI (1.30 mL, 20.8 mmol) was added. The reaction was maintained at -78 °C for 12.5 h, was treated with water (50 mL), and warmed to room temperature over 30 min, and extracted with Et_2O (3 × 50 mL). The combined organic fractions were washed with sat. $NaHCO_3$ (50 mL), sat. $Na_2S_2O_3$ (50 mL), water (50 mL), and brine (50 mL); dried (Na_2SO_4); and concentrated to give crude **10**, (85% conversion, dr ≥ 15:1) as an orange oil.

Crude **10** was dissolved in a mixture of THF (40 mL) and 1 M HCl (40 mL) to give a homogeneous solution that after 3 h was extracted with Et_2O (3 × 75 mL). The combined organic fractions were washed with water (50 mL), 1 M HCl (50 mL), and brine (50 mL); dried (Na_2SO_4); and concentrated to approximately 3 mL giving **S1** (100% conversion from **10**) as a THF solution.

Crude **S1** was combined with (4-bromo-2-nitrophenyl)hydrazine hydrochloride (537 mg, 2.00 mmol) and EtOH (20 mL) and heated to reflux for 2 d. The resultant mixture was concentrated to ~4 mL; diluted with Et_2O (100 mL); washed with $NaHCO_3$ (50 mL) and brine (50 mL); dried (Na_2SO_4); and concentrated. The resultant residue was purified by FC (silica gel; 0→100% EtOAc/hexanes) to give **11** [270 mg, 40%] as orange microcrystals. Crystals suitable for x-ray analysis were prepared by the slow evaporation of a solution of **11** in hexanes:CH_2Cl_2 (15:1) to approximately half of the original volume. TLC (EtOAc:hexanes, 20:80 v/v): R_F = 0.28; $[\alpha]^{24}_D$ = 60.9 (*c* = 3.82 in $CHCl_3$, *ee* ≥ 88%); ^{1}H-NMR (400 MHz, $CDCl_3$): δ 8.03 (d, *J* = 2.1 Hz, 1H), 7.74 (dd, *J* = 2.1, 8.8 Hz, 1H), 7.59 (d, *J* = 8.6 Hz, 1H), 2.07 (s, 3H), 1.89 (qd, *J* = 7.6, 13.9 Hz, 1H), 1.68 (qd, *J* = 7.4, 14.1 Hz, 1H), 1.30 (s, 3H), 0.80 (t, *J* = 7.4 Hz, 3H); ^{13}C-NMR (126 MHz, $CDCl_3$): δ 176.0, 165.7, 143.5, 136.2, 129.0, 128.1, 126.7, 119.5, 54.5, 28.9, 20.3, 13.7, 8.9; IR (film, cm^{-1}): 1964, 1725, 1535, 1482, 1362, 1115, 877, 823; LRMS (*m*/*z*): $[M+H]^+$ calcd for $C_{13}H_{15}{}^{79}BrN_3O_3$/$C_{13}H_{15}{}^{81}BrN_3O_3$, 340.0/342.0; found, 340.0/342.0; HRMS (*m*/*z*): $[M]^+$ calcd for $C_{13}H_{14}{}^{79}BrN_3O_3$, 339.0219; found, 339.0223; elemental analysis (% calcd, % found for $C_{13}H_{14}BrN_3O_3$): C (45.90, 45.84), H (4.15, 4.10), N (12.35, 12.12).

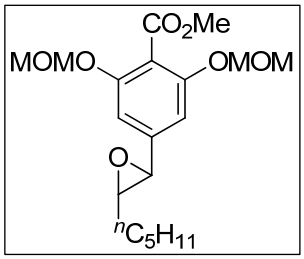


Methyl 2,6-dihydroxy-4-(trifluoromethylsulfonyloxy)benzoate (**16**). A solution of Tf_2O (6.20 mL, 36.9 mmol) in CH_2Cl_2 (150 mL) was added dropwise over the course of 2 h to a 0 °C solution of 2,6-lutidine (4.30 mL, 37.0 mmol) and methyl 2,4,6-trihydroxybenzoate (**15**, 8.45 g, 45.8 mmol) in CH_2Cl_2 (600 mL). After 14 h additional the reaction was washed with water (500 mL), 1M HCl (500 mL), sat. $NaHCO_3$ (300 mL), and brine (300 mL); dried ($MgSO_4$); and concentrated. The resultant residue was purified by FC (silica gel; 0→100% EtOAc/hexanes) to give **16** (10.65 g, 91%) as a white solid. TLC (EtOAc:hexanes, 20:80 v/v): R_F = 0.32; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 9.95 (br s, 2H), 6.44 (s, 2H), 4.12 (s, 3H); ^{13}C-NMR (126 MHz, $CDCl_3$): δ 169.4, 162.6, 154.9, 118.8 (q, *J* = 320.8 Hz), 102.0, 100.2, 53.7; ^{19}F-NMR (282 MHz, $CDCl_3$): δ -73.3; IR (film, cm^{-1}): 3373, 1693, 1594, 1416, 1212, 1112, 993; LRMS (*m*/*z*): $[M-H]^-$ calcd for $C_9H_6F_3O_7S$, 315.0; found, 314.9; HRMS (*m*/*z*): $[M]^+$ calcd for $C_9H_7F_3O_7S$, 315.9865; found, 315.9870; elemental analysis (% calcd, % found for $C_9H_7F_3O_7S$): C (34.19, 34.32), H (2.23, 2.00).



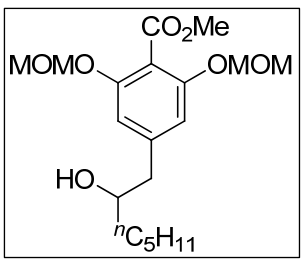
(*E*)-Methyl 4-(1-heptenyl)-2,6-dihydroxybenzoate (**17**). A mixture of **16** (3.00 g, 9.48 mmol), (*E*)-hept-1-enylboronic acid[4] (1.53 g, 10.8 mmol), $Pd(dppf)Cl_2$•CH_2Cl_2 (387 mg, 0.474 mmol) and K_2CO_3 (2.63 g, 19.0 mmol) in a mixture of THF and water (10:1, 132 mL total) was heated to reflux for 2.5h. The reaction was cooled to room temperature, diluted with Et_2O (150 mL), washed with water (150 mL) and brine (150 mL), dried ($MgSO_4$), and concentrated. The resultant residue was purified by FC (silica gel; 20% EtOAc/hexanes) to give **17** (2.269 g, 91%) as an amorphous white solid. TLC (EtOAc:hexanes, 20:80 v/v): R_F = 0.65; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 9.63 (br s, 2H), 6.47 (s, 2H), 6.36 (td, *J* = 6.8, 15.6 Hz, 1H), 6.23 (d, *J* = 15.9 Hz, 1H), 4.06 (s, 3H), 2.21 (quintet, *J* = 7.3 Hz, 2H), 1.30-1.49 (m, 6H), 0.90 (t, *J* = 7.1 Hz, 3H);

^{13}C-NMR (126 MHz, $CDCl_3$): δ 169.9, 161.0, 146.5, 136.1, 128.9, 105.8, 98.5, 52.8, 33.2, 31.5, 28.8, 22.7, 14.2. IR (film, cm^{-1}): 3423, 2927, 1674, 1639, 1563, 1191, 1100; LRMS (*m/z)*: $[M-H]^-$ calcd for $C_{15}H_{19}O$, 263.1; found, 263.1; HRMS (*m*/*z*): $[M]^+$ calcd for $C_{15}H_{20}O_4$, 264.1362; found, 264.1363; elemental analysis (% calcd, % found for $C_{15}H_{20}O_4$): C (68.16, 68.18), H (7.63, 7.85).



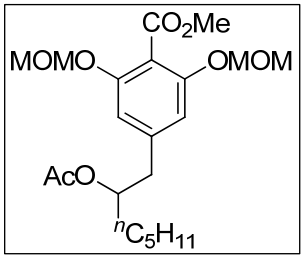
rac-Methyl 2,6-bis(methoxymethoxy)-4-(3-pentyloxiran-2-yl)benzoate (**S4**). ^{i}Pr$_2$EtN (39.0 mL, 0.224 mol) and MOMCl (17.0 mL, 0.224 mmol) were added to a 0 °C solution of **17** (7.39 g, 27.98 mmol) in CH_2Cl_2 (230 mL), was warmed to room temperature, and stirred for 18 h. The resultant mixture was treated with water (200 mL), the organic fraction separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 150 mL). The combined organic fractions were washed with cold 5% HCl (150 mL), sat. $NaHCO_3$ (150 mL) brine (2 × 150 mL), dried ($MgSO_4$), and concentrated to give crude (*E*)-methyl 4-(hept-1-enyl)-2,6-bis(methoxymethoxy)benzoate (**S5**) as a yellow oil that was used without further purification. Chromatographic (silica gel; 0→100% EtOAc/hexanes) purification of a similar preparation of **S5** provided pure material (90% yield) for characterization. TLC (EtOAc:hexanes, 17:83 v/v): R_F = 0.30; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 6.79 (s, 2H), 6.30 (d, *J* = 6.0 Hz, 1H), 6.23 (td, *J* = 5.9, 15.8 Hz, 1H), 5.18 (s, 4H), 3.90 (s, 3H), 3.47 (s, 6H), 2.18 (td, *J* = 6.8, 7.8 Hz, 2H), 1.42-1.50 (m, 2H), 1.28-1.35 (m, 6H), 0.90 (t, *J* = 7.0 Hz, 3H); ^{13}C-NMR (126 MHz, $CDCl_3$): δ 166.8, 155.1, 141.4, 133.4, 129.3, 114.0, 106.2, 94.8, 56.3, 52.4, 33.1, 31.6, 28.9, 22.7, 14.2; IR (film, cm^{-1}): 2956, 2929, 1737, 1607, 1431, 1272, 1050, 923; LRMS (*m/z)*: $[M+Na]^+$ calcd for $C_{19}H_{28}NaO_6$, 375.2; found, 375.1; HRMS (*m*/*z*): $[M]^+$ calcd for $C_{19}H_{28}O_6$, 352.1886; found, 352.1885; elemental analysis (% calcd, % found for $C_{19}H_{28}O_6$): C (64.75, 64.64), H (8.01, 8.14).

*m*CPBA (87%) was added in 3 portions (5.92 g, 29.8 mmol; 2.14 g, 10.8 mmol; 740 mg, 3.73 mmol), at 2 h intervals to a room temperature solution of the above obtained crude **S5** in CH_2Cl_2 (250 mL). The resultant suspension was stirred for 40 min following the final *m*CPBA addition, diluted with [sat. $Na_2S_2O_3$ (100 mL) and $NaHCO_3$ (100 mL)], and extracted with Et_2O (500 mL). The organic fraction was washed with [sat. $Na_2S_2O_3$ (100 mL) and $NaHCO_3$ (100 mL)] and brine (2 × 150 mL), dried ($MgSO_4$), and concentrated. The resultant residue was purified by FC (silica gel; 0→100% EtOAc/hexanes containing 0.5% TEA) to give **S4** (8.60 g, 84%) as a colorless oil. TLC (EtOAc:hexanes, 25:75 v/v): R_F = 0.27; ^{1}H-NMR (500 MHz, $CDCl_3$): δ 6.71 (s, 2H), 5.17 (dd, *J* = 5.4, 6.8 Hz, 1H), 3.90 (s, 3H), 3.56 (d, *J* = 5.6 Hz, 1H), 3.46 (s, 6H), 2.86 (ddd, *J* = 2.0, 5.1, 5.9 Hz, 1H), 1.59-1.71 (m, 2H), 1.43-1.54 (m, 2H), 1.29-1.37 (m, 4H), 0.90 (t, *J* = 7.1 Hz, 3H); ^{13}C-NMR (126 MHz, $CDCl_3$): δ 166.6, 155.0, 142.1, 115.1, 105.4, 94.7, 63.5, 58.5, 56.4, 52.5, 32.3, 31.7, 25.7, 22.7, 14.1; IR (film, cm^{-1}): 2932, 1738, 1613, 1270, 1155, 1048, 922; LRMS (*m/z)*: $[M+H]^+$ calcd for $C_{19}H_{29}O_7$, 369.2; found, 369.1; HRMS (*m*/*z*): $[M]^+$ calcd for $C_{19}H_{28}O_7$, 368.1835; found, 368.1831; elemental analysis (% calcd, % found for $C_{19}H_{28}O_7$): C (61.94, 61.81), H (7.66, 7.92).



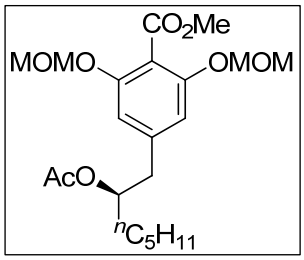
rac-Methyl 4-(2-hydroxyheptyl)-2,6-bis(methoxymethoxy)benzoate (**18**). Pd/$CaCO_3$ (5% w/w, 205 mg) was added to solution of **S4** (620 mg, 1.68 mmol) in MeOH (35 mL) and the flask purged with N_2, followed by H_2. The mixture was stirred vigorously under H_2 (balloon pressure) for 20 h. The H_2 atmosphere was purged with Ar and the reaction mixture filtered through a

short plug of celite, eluting with MeOH (35 mL), and concentrated. The resultant residue was purified by FC (silica gel; 0→100% EtOAc/hexanes) to give **18** (560 mg, 90%) as a colorless oil. TLC (EtOAc:hexanes, 40:60 v/v): R_F = 0.37; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 6.67 (s, 2H), 5.16 (s, 4 H), 3.90 (s, 3H), 3.76-3.80 (m, 1H), 3.45 (s, 6 H), 2.77 (dd, *J* = 3.9, 13.4 Hz, 1H), 2.59 (dd, *J* = 8.5, 13.4 Hz, 1H), 1.65 (br s, 1H), 1.24-1.50 (m, 8H), 0.89 (t, *J* = 6.8 Hz, 3H); ^{13}C- NMR (126 MHz, $CDCl_3$): δ 166.8, 154.9, 142.7, 113.9, 109.6, 94.8, 72.5, 56.4, 52.5, 44.7, 37.0, 32.0, 25.5, 22.7, 14.2; IR (film, cm^{-1}): 3452, 2930, 1736, 1610, 1434, 1270, 1154, 1049, 923; LRMS (*m*/*z*): $[M+Na]^+$ calcd for $C_{19}H_{30}NaO_7$, 393.2; found, 393.2; HRMS (*m*/*z*): $[M]^+$ calcd for $C_{19}H_{30}O_7$, 370.1992; found, 370.1990; elemental analysis (% calcd, % found for $C_{19}H_{30}O_7$): C (61.60, 61.76), H (8.16, 8.35).

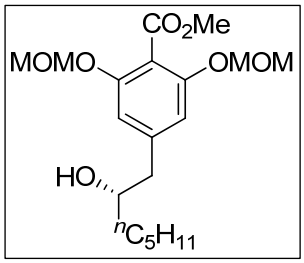


rac-Methyl 4-(2-acetoxyheptyl)-2,6-bis(methoxymethoxy)benzoate (**S6**). Pyridine (0.25 mL, 3.1 mmol) and DMAP (28 mg, 0.23 mmol) were added to a room temperature solution of **18** (57 mg, 0.15 mmol) and Ac_2O (3 mL). After 2 h the reaction was concentrated and the resultant residue was purified by FC (silica gel; 0→100% EtOAc/hexanes) to give **S6** (58 mg, 91%) as a colorless oil. TLC (EtOAc:hexanes, 25:75 v/v): R_F = 0.33; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 6.65 (s, 2H), 5.17 (dd, *J* = 6.6 Hz, 2H), 5.13 (dd, *J* = 6.6 Hz, 2H), 5.03 (sept., *J* = 6.2Hz, 1 H), 3.90 (s, 3H), 3.45 (s, 6H), 2.81 (dd, *J* = 6.8, 13.9 Hz, 1H), 2.76 (dd, *J* = 5.7, 13.9 Hz, 1H), 2.00 (s, 3H), 1.49-1.55 (m, 2H), 1.21-1.39 (m, 6H), 0.87 (t, *J* = 6.8 Hz, 3H); ^{13}C-NMR (126 MHz, $CDCl_3$): δ 170.8, 166.9, 154.7, 141.6, 113.7, 109.7, 94.8, 74.4, 56.3, 52.5, 40.8, 33.8, 31.8, 25.1, 22.7, 21.2, 14.1; IR (film, cm^{-1}): 2955, 1736, 1611, 1435, 1243, 1155, 1050, 923; LRMS (*m*/*z*): $[M+Na]^+$ calcd for $C_{21}H_{32}NaO_8$, 435.2; found, 435.2; HRMS (*m*/*z*): $[M]^+$ calcd for $C_{21}H_{32}O_8$, 412.2097; found, 412.2088; elemental analysis (% calcd, % found for $C_{21}H_{32}O_8$): C (61.15, 61.16), H (7.82, 7.76).

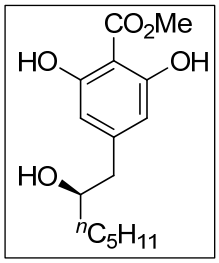
Preparation of **S6** from **18** via Mitsunobu esterification: DEAD (96 μl, 0.61 mmol) was added dropwise to a 0 °C solution of **18** (110 mg, 0.297 mmol), PPh_3 (164 mg, 0.625 mmol), and acetic acid (37 μl, 0.647 mmol) in toluene (3 mL) and warmed slowly to room temperature. After 7 h the resultant mixture was concentrated and the resultant residue was purified by FC (silica gel; 0→100% EtOAc/hexanes) to give **S6** (100 mg, 78%) as a colorless oil.



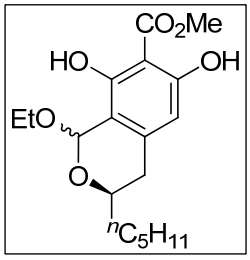
(*R*)-Methyl 4-(2-acetoxyheptyl)-2,6-bis(methoxymethoxy)benzoate (**20**). Lipase (*Alcaligenes sp. lyo.*, 30 mg) was added to an oven-dried vial containing **18** (234 mg, 0.599 mmol), vinyl acetate (0.17 mL, 1.84 mmol), MTBE (6 mL), and 4 ÅMS; capped; and stirred vigorously for 7 d. The resultant suspension was filtered through a short plug of celite, eluting with EtOAc (50 mL), and concentrated. The resultant residue was purified by FC (silica gel; 0→100% EtOAc/hexanes) to give **20** (114 mg, 46%, *ee* = 95%) as a colorless oil and recovered **19** (119 mg, 51%, *ee* = 93%). $[\alpha]^{24}_D$ = -4.0 (*c* = 2.16 in $CHCl_3$, *ee* = 95%).



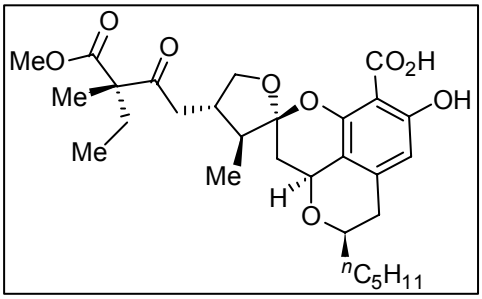
(*S*)-Methyl 4-(2-hydroxyheptyl)-2,6-bis(methoxymethoxy)benzoate (**19**). $[\alpha]^{24}_{D}$ = 7.1 (*c* = 2.38 in $CHCl_3$, *ee* = 93%).



(*R*)-Methyl 2,6-dihydroxy-4-(2-hydroxyheptyl)benzoate **21**. A solution of **20** (1.06 g, 2.86 mmol, *ee* = 95%) in HCl/MeOH (0.25 M, 5 mL, prepared from AcCl and MeOH) was stirred for 15 h at room temperature and concentrated. The resultant residue was purified by FC (silica gel; 0→100% EtOAc/hexanes) to give **21** (73 mg, 100%) as a white solid.[5] ^{1}H-NMR (400 MHz, $CDCl_3$): δ 9.64 (br s, 2H), 6.38 (s, 2H), 4.07 (s, 3H), 3.80-3.88 (m, 1H), 2.71 (dd, *J* = 4.3, 13.5 Hz, 1H), 2.57 (dd, *J* = 8.4, 13.3 Hz, 1H), 1.25-1.52 (m, 9H), 0.89 (t, *J* = 6.8 Hz, 3H); ^{13}C-NMR (126 MHz, $CDCl_3$): δ 169.9, 160.9, 149.2, 109.3, 98.5, 72.2, 53.0, 44.5, 37.1, 31.9, 25.5, 22.8, 14.2. $[\alpha]^{D}_{23}$ = -16.8 (*c* = 1.03 in $CHCl_3$, *ee* = 95%) {lit.[6] $[\alpha]^{20}_{D}$ = -18.2 (*c* = 1.01 in $CHCl_3$, *ee* = 99%)}.



(*R*)-Methyl 1-ethoxy-6,8-dihydroxy-3-pentylisochroman-7-carboxylate (**22**). TFA (3 drops from an 18 G needle) was added to a room temperature solution of **21** (68 mg, 0.240 mmol) in triethyl orthoformate (3.0 mL, 18 mmol) and stirred 15 h. The mixture was concentrated to give **22** (single diastereomer, 80 mg, 99 %) as an amorphous yellow solid that was used without further purification. $[\alpha]^{23}_{D}$ = 24.7 (*c* = 1.44 in $CHCl_3$, *ee* = 95%); ^{1}H-NMR (500 MHz, $CDCl_3$): δ 10.02 (br s, 1H), 9.52 (br s, 1H), 6.25 (s, 1H), 5.69 (s, 1H), 4.14-4.20 (m, 1H), 4.05 (s, 3H), 3.92 (qd, *J* = 7.3, 9.5 Hz, 1H), 3.74 (qd, *J* = 7.1, 9.5 Hz, 1H), 2.60 (dd, *J* = 4.2, 17.1 Hz, 1H), 2.55 (dd, *J* = 10.7, 17.3 Hz, 1H), 1.31-1.64 (m, 8H), 1.29 (t, *J* = 7.1 Hz, 3H), 0.91 (t, *J* = 6.8 Hz, 3H); ^{13}C-NMR (126 MHz, $CDCl_3$): δ 169.9, 159.9, 158.5, 145.0, 114.4, 107.4, 98.2, 93.8, 65.7, 63.3, 52.8, 35.6, 34.5, 31.8, 25.3, 22.7, 15.4, 14.2; IR (film, cm^{-1}): 2926, 1678, 1581, 1250, 1146, 1008; LRMS (*m*/*z*): $[M\text{-OEt}]^+$ calcd for $C_{16}H_{21}O_5$, 293.1; found, 293.1; HRMS (*m*/*z*): $[M]^+$ calcd for $C_{18}H_{26}O_6$, 338.1729; found, 338.1728; elemental analysis (% calcd, % found for $C_{18}H_{26}O_6$): C (63.89, 63.79), H (7.74, 7.72).

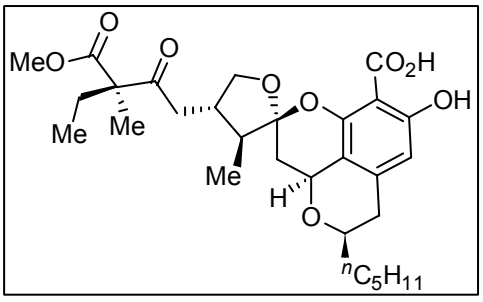


(–)-Berkelic Acid (**2**). A solution of **22**(5.1 mg, 0.015 mmol, *ee* = 95%) and **14a** and **14b** (9.2 mg, 0.036 mmol, *anti*:*syn* = 5:1, *ee* ≥ 88%) in Et_2O (1 mL) was added to a dry vial containing $AgSbF_6$ (18.2 mg, 0.053 mmol) and stirred vigorously in the dark for 2 h. The resultant mixture was concentrated to a yellow residue, dissolved in CH_2Cl_2 (15 mL) and washed with 1M HCl (5 mL), dried (Na_2SO_4), and concentrated to a yellow oil that was used without further purification.

$(Bu_3Sn)_2O$ (0.26 mL, 0.51 mmol) was added to a solution of the above obtained crude material in toluene (0.3 mL) in an Ar-purged, dry tube; sealed; and heated to 115 °C. After 8 h the yellow reaction was cooled to room temperature,

diluted with CH_2Cl_2 (2 mL) and 1M HCl (5 mL), stirred vigorously for 15 min, and the resultant mixture was extracted with CH_2Cl_2 (3 × 15 mL). The combined organic fractions were dried (Na_2SO_4) and concentrated. The resultant material was purified by semi-preperative HPLC purifications (normal phase, 20 × 250 mm; 0.4% ^{i}PrOH in CH_2Cl_2) to give **2** (2.8 mg, 35%) as a white amorphous solid and recovered crude methyl berkelates (**25** and **26**, 2.0 mg).

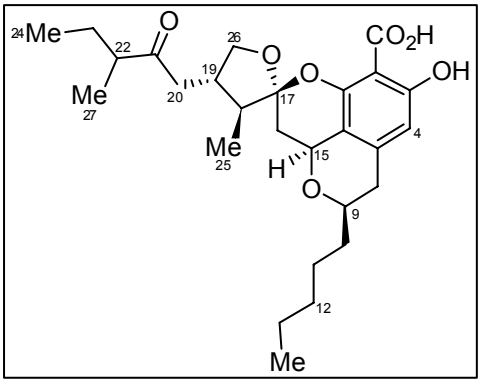
$(Bu_3Sn)_2O$ (0.13 mL, 0.26mmol) was added to a solution of the above obtained crude methyl berkelate in toluene (0.2 mL) in an Ar-purged, dry tube; sealed; and heated to 115 °C. After 8 h the yellow reaction was cooled to room temperature, diluted with CH_2Cl_2 (1 mL) and 1M HCl (3 mL), stirred vigorously for 15 min, and the resultant mixture was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic fractions were dried (Na_2SO_4) and concentrated. The resultant material was purified by semi-preperative HPLC purifications (normal phase, 20 × 250 mm; 0.4% ^{i}PrOH in CH_2Cl_2) to give **2** [0.9 mg (3.7 mg total, 46%)] as an amorphous white solid. TLC (EtOAc:hexanes, 25:75 v/v): R_F = 0.17; $[\alpha]^{22}_D$ = –76.7 (*c* = 0.060 in MeOH), {lit.[7] $[\alpha]^{22}_D$ = –83.5 (*c* = 0.0113 in MeOH); lit.[8] $[\alpha]^{22}_D$ = –115.5 (*c* = 0.55 in MeOH)}, ^{1}H-NMR (500 MHz, $CDCl_3$, $CHCl_3$ δ7.24 p.p.m.): δ11.82 (s, 1H, OH), 11.01 (br s, 1H, CO_2H), 6.42 (s, 1H, H4), 4.77 (dd, *J* = 5.1, 12.2 Hz, 1H, H15), 4.44 (*app* t, *J* = 8.8 Hz, 1H, H26α), 3.78-3.83 (m, 1H, H9), 3.73 (s, 3H, OCH_3), 3.59 (dd, *J* = 8.7, 9.0 Hz, 1H, H26β), 2.85 (dd, *J* = 3.2, 17.1 Hz, 1H, H20), 2.78 (dd, *J* = 4.2, 17.6 Hz, 1H, H8α), 2.60 (dd, *J* = 11.0, 17.6 Hz, 1H, H8β), 2.46-2.54 (m, 1H, H19), 2.43 (dd, *J* = 10.3, 16.8 Hz, 1H, H20), 2.21 (dd, *J* = 5.1, 12.5 Hz, 1H, H16α), 2.06 (dd, *J* = 12.5 Hz, 1H, 16β), 1.95 (qd, *J* = 7.6, 13.9 Hz, 1H, H23), 1.87 (qd, *J* = 7.1, 10.7 Hz, 1H, H18), 1.81 (qd, *J* = 7.6, 13.9 Hz, 1H, H23), 1.58-1.67 (m, 1H, H10), 1.52-1.57 (m, 1H, H10), 1.48-1.52 (m, 1H, H11), 1.38-1.41 (m, 1H, H11), 1.29-1.33 (m, 4H, H12 & H13), 1.32 (s, 3H, H27), 1.09 (d, *J* = 6.8 Hz, 3H, H25), 0.88 (t, *J* = 6.8 Hz, 3H, H14), 0.83 (t, *J* = 7.3 Hz, 3H, H24).; ^{13}C-NMR (126 MHz, $CDCl_3$, $CDCl_3$ δ77.0 p.p.m.): δ206.0 (C21), 173.4 (C28), 170.5 (C1), 162.6 (C3), 149.8 (C7), 142.2 (C5), 112.2 (C6), 112.2 (C17), 110.5 (C4), 98.7 (C2), 75.2 (C9), 73.5 (C26), 67.3 (C15), 59.8 (C22), 52.5 (OMe), 48.2 (C18), 41.6 (C20), 39.4 (C19), 36.3 (C10), 34.3 (C8), 34.3 (C16), 31.8 (C12), 27.9 (C23), 25.0 (C11), 22.6 (C13), 18.4 (C27), 14.0 (C14), 12.0 (C25), 8.7 (C24); HRMS (*m*/*z*): $[M]^+$ calcd for $C_{29}H_{40}O_9$, 532.2672; found, 532.2673.



C22-(*R*)-Berkelic Acid (***27***). A solution of **22** (5.2 mg, 0.015 mmol, *ee* = 95%) and *ent*-**14a** and *ent*-**14b** (9.4 mg, 0.037 mmol, *anti*:*syn* = 5:1, *ee* ≥ 88%) in Et_2O (1 mL) was added to a dry vial containing $AgSbF_6$ (19.1 mg, 0.056 mmol) and stirred vigorously in the dark for 2 h. The resultant mixture was concentrated to a yellow residue, dissolved in CH_2Cl_2 (30 mL) and washed with 1M HCl (20 mL), dried (Na_2SO_4), and concentrated to a yellow oil that was used without further purification.

$(Bu_3Sn)_2O$ (0.28 mL, 0.55 mmol) was added to a solution of the above obtained crude material in toluene (0.3 mL) in an Ar-purged, dry tube; sealed; and heated to 115 °C. After 14 h the yellow reaction was cooled to room temperature, diluted with CH_2Cl_2 (2 mL) and 1M HCl (5 mL), stirred vigorously for 15 min, and the resultant mixture was extracted with CH_2Cl_2 (3 × 15 mL). The combined organic fractions were dried (Na_2SO_4) and concentrated. The resultant material was purified by semi-preperative HPLC purification (normal phase, 20 × 250 mm; 0.4% ^{i}PrOH in CH_2Cl_2) to give **27** (2.1 mg, 26%) as a white amorphous solid and compounds (2 diastereomers, ~ 4:1) consistent with *des*-methyl carboxy-berkelic acid **28** (1.5 mg, 21%, ~80-90% pure). TLC (EtOAc:hexanes, 25:75 v/v): R_F = 0.17; $[\alpha]^{22}_D$ = –72.7 (*c* = 0.055 in MeOH)

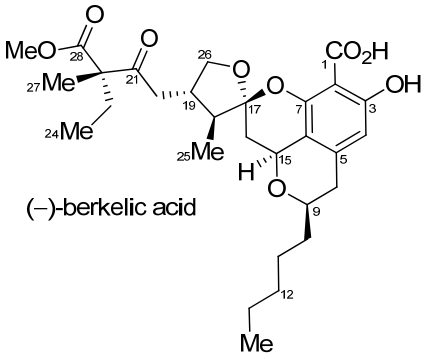
{lit.[8] $[\alpha]^{22}_D$ = –107.0° (*c* = 0.43 in MeOH); ^{1}H-NMR (500 MHz, $CDCl_3$, $CHCl_3$ δ 7.24 p.p.m.): δ 11.82 (s, 1H, OH), 10.97 (br s, 1H, CO_2H), 6.42 (s, 1H, H4), 4.77 (dd, *J* = 5.1, 12.2 Hz, 1H, H15), 4.44 (*app* t, *J* = 9.0 Hz, H26α), 3.78-3.83 (m, 1H, H9), 3.73 (s, 3H, OCH_3), 3.59 (*app* t, *J* = 8.5 Hz, 1H, H26β), 2.89 (dd, *J* = 3.4, 17.3 Hz, 1H, H20), 2.78 (dd, *J* = 3.9, 17.6 Hz, 1H, H8α), 2.60 (dd, *J* = 11.2, 17.6, 1H, H8β), 2.46-2.54 (m, 1H, H19), 2.39 (dd, *J* = 10.0, 17.6 Hz, 1H, H20), 2.21 (dd, *J* = 5.4, 12.5 Hz, 1H, H16α), 2.05 (*app* t, *J* = 12.2 Hz, 1H, H16β), 1.94 (qd, *J* = 7.3, 14.2 Hz, 1H, H23), 1.87 (qd, *J* = 6.8, 11.0 Hz, 1H, H18), 1.81 (qd, *J* = 7.3, 14.2 Hz, 1H, H23), 1.60-1.67 (m, 1H, H10), 1.52-1.55 (m, 1H, H10), 1.46-1.51 (m, 1H, H11), 1.34-1.40 (m, 1H, H11), 1.26-1.34 (m, 4H, H12 & H13), 1.33 (s, 3H, H27), 1.08 (d, *J* = 6.8 Hz, 3H, H25), 0.88 (t, *J* = 6.6 Hz, 3H, H14), 0.81 (t, *J* = 7.3 Hz, 3H, H24); ^{13}C-NMR (126 MHz, $CDCl_3$, $CDCl_3$ δ 77.0 p.p.m.): δ 206.0 (C21), 173.4 (C28), 170.5 (C1), 162.5 (C3), 149.8 (C7), 142.2 (C5), 112.2 (C6), 112.2 (C17), 110.5 (C4), 98.6 (C2), 75.2 (C9), 73.5 (C26), 67.3 (C15), 59.7 (C22), 52.5 (OMe), 48.2 (C18), 41.5 (C20), 39.3 (C19), 36.3 (C10), 34.3 (C8), 34.3 (C16), 31.7 (C12), 27.9 (C23), 25.0 (C11), 22.6 (C13), 18.3 (C27), 14.0 (C14), 12.0 (C25), 8.6 (C24); HRMS (*m*/*z*): $[M]^+$ calcd for $C_{29}H_{40}O_9$, 532.2672; found, 532.2673.



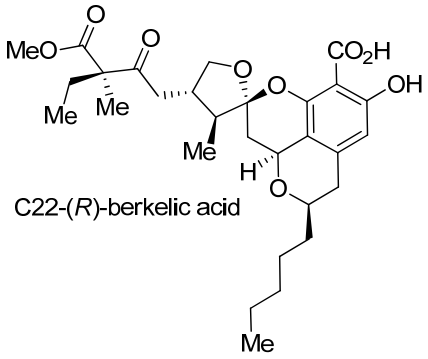
des-C28-carboxymethyl-Berkelic Acid (**28**). TLC (EtOAc:hexanes, 33:67 v/v): R_F = 0.29; Diagnostic proton resonances: ^{1}H-NMR (400 MHz, $CDCl_3$, $CHCl_3$ δ 7.24 p.p.m.): δ 11.85 (s, 1H, OH), 11.06 (br s, 1H, CO_2H), 6.42 (s, 1H, H4), 4.77 (dd, *J* = 5.2, 12.0 Hz, 1H, H15), 1.10 (d, *J* = 6.8 Hz, 3H, H25 or H27), 1.07 (d, *J* = 6.9 Hz, 3H, H25 or H27); LRMS (*m*/*z*): $[M+Na]^+$ calcd for $C_{27}H_{38}NaO_7$, 497.3; found, 497.4.

3. Comparison of ^{1}H and ^{13}C NMR data to natural (–)-berkelic acid

Table 1. Comparison of $^{13}C\{^{1}H\}$ NMR resonances (δ ppm, $CDCl_3$ = 77.0 ppm) between natural (–)-berkelic acid[7] and synthetic (–)-berkelic acid (**2**) and C22-(*R*)-berkelic acid (**27**).



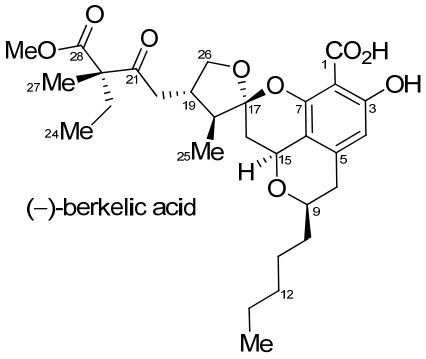
(–)-berkelic acid



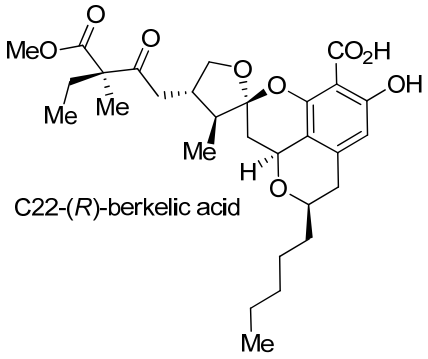
C22-(*R*)-berkelic acid

C#	Natural Berkelic Acid	Synthetic Berkelic Acid	C22-(*R*)-Berkelic Acid
1	170.5	170.5	170.5
2	98.6	98.7	98.6
3	162.5	162.6	162.5
4	110.5	110.5	110.5
5	142.2	142.2	142.2
6	112.1	112.2	112.2
7	149.8	149.8	149.8
8	34.3	34.3	34.3
9	75.2	75.2	75.2
10	36.2	36.3	36.3
11	25.0	25.0	25.0
12	31.7	31.8	31.7
13	22.6	22.6	22.6
14	14.0	14.0	14.0
15	67.2	67.3	67.3
16	34.2	34.3	34.3
17	112.2	112.2	112.2
18	48.2	48.2	48.2
19	39.3	39.4	39.3
20	41.6	41.6	41.5
21	206.1	206.0	206.0
22	59.7	59.8	59.7
23	27.9	27.9	27.9
24	8.7	8.7	8.6
25	12.0	12.0	12.0
26	73.5	73.5	73.5
27	18.4	18.4	18.3
28	173.4	173.4	173.4
OMe	52.5	52.5	52.5

Table 2. Comparison of ^{1}H NMR resonances [δ ppm, $CDCl_3$ = 7.24 ppm, multiplicity and coupling constants (J in Hz) appear in parentheses] between natural (–)-berkelic acid[7] and synthetic (–)-berkelic acid (**2**) and C22-(*R*)-berkelic acid (**27**). The centers of resonances observed as multiplets are reported to facilitate easier comparison. Diagnostic resonances appear in bold type.



(–)-berkelic acid



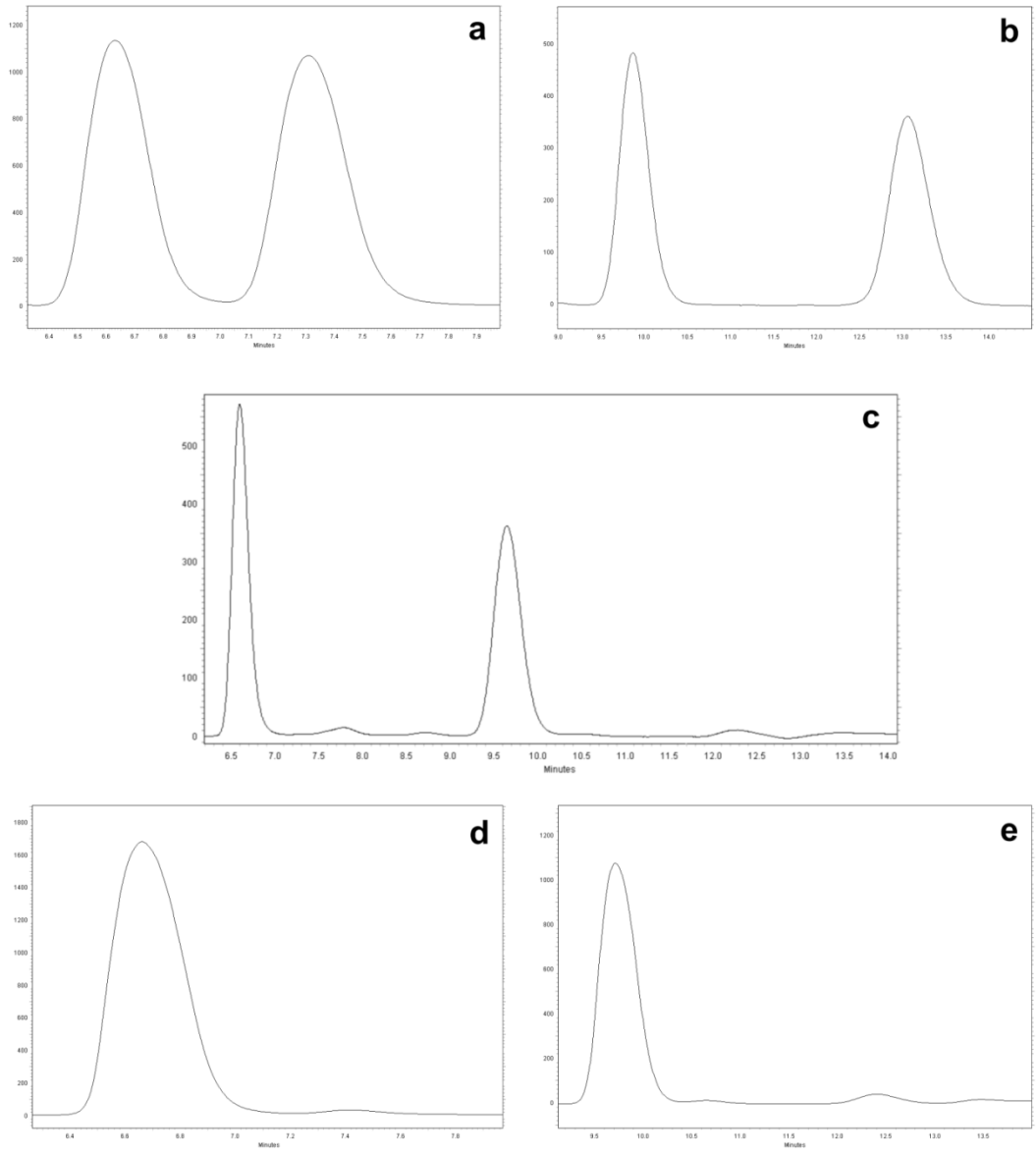
C22-(*R*)-berkelic acid

H#	Natural Berkelic Acid	Synthetic Berkelic Acid	C22-(*R*)-Berkelic Acid
4	6.41 (br s)	6.42 (s)	6.42 (s)
8α	2.77 (dd; 4.0, 17.6)	2.78 (dd; 4.2, 17.6)	2.78 (dd; 3.9, 17.6)
8β	2.59 (dd; 11.0, 17.6)	2.60 (dd; 11.0, 17.6)	2.60 (dd; 11.2, 17.6)
9	3.80 (m)	3.80 (m)	3.80 (m)
10	1.61 (m)	1.63 (m)	1.64 (m)
10	1.50 (m)	1.55 (m)	1.54 (m)
11	1.50 (m)	1.50 (m)/1.40 (m)	1.49 (m)/1.37 (m)
12	1.30 (m)	1.31 (m)	1.31 (m)
13	1.30 (m)	1.31 (m)	1.31 (m)
14	0.88 (t)	0.88 (t; 6.8)	0.88 (t; 6.6)
15	4.76 (dd; 5.7, 12.2)	4.77 (dd; 5.1, 12.2)	4.77 (dd; 5.1, 12.2)
16α	2.20 (dd; 5.7, 12.2)	2.21 (dd; 5.1, 12.5)	2.21 (dd; 5.4, 12.2)
16β	2.05 (dd; 12.2, 12.2)	2.06 (*app* t; 12.5)	2.05 (*app* t; 12.2)
18	1.87 (m)	1.87 (qd; 7.1, 10.7)	1.87 (qd; 6.8, 11.0)
19	2.50 (m)	2.50 (m)	2.50 (m)
20	**2.84** (dd; 2.5, 17.0)	**2.85** (dd; 3.2, 17.1)	**2.89** (dd; 3.4, 17.3)
20	**2.42** (dd; 10.3, 17.0)	**2.43** (dd; 10.3, 16.8)	**2.39** (dd; 10.0, 17.6)
23	1.94 (m)	1.95 (qd; 7.6, 13.9)	1.94 (qd; 7.3, 14.2)
23	1.80 (m)	1.81 (qd; 7.6, 13.9)	1.81 (qd; 7.3, 14.2)
24	0.82 (t; 7.2)	0.83 (t; 7.3)	0.81 (t; 7.3)
25	1.08 (d; 6.8)	1.09 (d; 6.8)	1.08 (d; 6.6)
26α	4.43 (t; 8.8)	4.44 (*app* t; 8.8)	4.44 (*app* t; 9.0)
26β	3.58 (t; 8.8)	3.59 (dd; 8.7, 9.0)	3.59 (*app* t; 8.5)
27	**1.31** (s)	**1.32** (s)	**1.33** (s)
OMe	3.73 (s)	3.73 (s)	3.73 (s)
OH	11.82 (s)	11.82 (s)	11.82 (s)
CO_2H	-	11.01 (br s)	10.97 (br s)

The ^{1}H NMR spectral data illustrated above unambiguously established the C22 stereochemistry of (–)-berkelic acid. Specifically, the absolute value (δ ppm) of the H20 resonances of synthetic berkelic acid (**2**) more closely agree ($\Delta\delta$ = 0.01 and 0.01 ppm) with those of natural berkelic acid than do the H20 resonances of C22-(*R*)-berkelic acid (**27**) ($\Delta\delta$ = 0.05 and –0.03 ppm). Furthermore, the resonances of **27** shift downfield and upfield respectively leading to an unmistakable increase in the frequency difference between the two H20 resonances [natural (–)-berkelic acid: $\Delta\delta_{H20\text{-}H20}$ = 0.42 ppm, **2**: $\Delta\delta_{H20\text{-}H20}$ = 0.42 ppm, and **27**: $\Delta\delta_{H20\text{-}H20}$ = 0.50 ppm]. All of these observations are consistent with those of Snider.[8]

4. Chiral HPLC data for the lipase resolution of 18.

Figure 1: Chiral HPLC traces (^{i}PrOH:hexanes, 10:90 v/v, 1mL/min, OD-H, 0.46 cm ϕ × 25 cm, λ = 207 nm) of **S6** (a), **18** (b), crude lipase resolution (c), purified **20** (d, *ee* = 95%), and purified **19** (e, *ee* = 93%)



5. X-ray Crystal Data for heterocycle 11.

Crystals grew as yellow needles by slow evaporation from CH_2Cl_2:hexanes (1:15). The data crystal was cut from a long needle and had approximate dimensions; 0.32 x 0.05 x 0.04 mm. The data were collected on a Nonius Kappa CCD diffractometer using a graphite monochromator with MoKα radiation (λ = 0.71073Å). A total of 351 frames of data were collected using ω-scans with a scan range of 1° and a counting time of 131 seconds per frame. The data were collected at 153 K using an Oxford Cryostream low temperature device. Details of crystal data, data collection and structure refinement are listed in Table 1. Data reduction were performed using DENZO-SMN.[1] The structure was solved by direct methods using SIR97[2] and refined by full-matrix least-squares on F^2 with anisotropic displacement parameters for the non-H atoms using SHELXL-97.[3] The hydrogen atoms on carbon were calculated in ideal positions with isotropic displacement parameters set to 1.2xUeq of the attached atom (1.5xUeq for methyl hydrogen atoms). The absolute structure was determined by the method of Flack.[4] The Flack x parameter refined to 0.001(12). The function, $\Sigma w(|F_o|^2 - |F_c|^2)^2$, was minimized, where $w = 1/[(\sigma(F_o))^2 + (0.0104*P)^2 + (3.9071*P)]$ and $P = (|F_o|^2 + 2|F_c|^2)/3$. $R_w(F^2)$ refined to 0.138, with R(F) equal to 0.0636 and a goodness of fit, S, = 1.00. Definitions used for calculating R(F), $R_w(F^2)$ and the goodness of fit, S, are given below.[5] The data were checked for secondary extinction effects but no correction was necessary. Neutral atom scattering factors and values used to calculate the linear absorption coefficient are from the International Tables for X-ray Crystallography (1992).[6] All figures were generated using SHELXTL/PC.[7] Each unit cell contained 4 conformers of **11**, each with (*S*) absolute configuration (Figure 2).

Crystalography References

1) DENZO-SMN. (1997). Z. Otwinowski and W. Minor, Methods in Enzymology, **276**: Macromolecular Crystallography, part A, 307 – 326, C. W. Carter, Jr. and R. M. Sweets, Editors, Academic Press.
2) SIR97. (1999). A program for crystal structure solution. Altomare A., Burla M.C., Camalli M., Cascarano G.L., Giacovazzo C. , Guagliardi A., Moliterni A.G.G., Polidori G.,Spagna R. J. Appl. Cryst. 32, 115-119.
3) Sheldrick, G. M. (1994). SHELXL97. Program for the Refinement of Crystal Structures. University of Gottingen, Germany.
4) Flack, H. D. (1983). Acta Cryst. A39, 876-881.
5) $R_w(F^2) = \{\Sigma w(|F_o|^2 - |F_c|^2)^2/\Sigma w(|F_o|)^4\}^{1/2}$ where w is the weight given each reflection.
   $R(F) = \Sigma(|F_o| - |F_c|)/\Sigma|F_o|\}$ for reflections with $F_o > 4(\sigma(F_o))$.
   $S = [\Sigma w(|F_o|^2 - |F_c|^2)^2/(n - p)]^{1/2}$, where n is the number of reflections and p is the number of refined parameters.
6) International Tables for X-ray Crystallography (1992). Vol. C, Tables 4.2.6.8 and 6.1.1.4, A. J. C. Wilson, editor, Boston: Kluwer Academic Press.
7) Sheldrick, G. M. (1994). SHELXTL/PC (Version 5.03). Siemens Analytical X-ray Instruments, Inc., Madison, Wisconsin, USA.

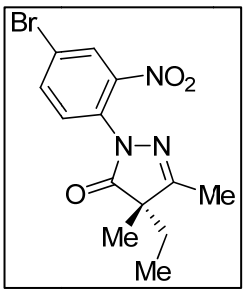
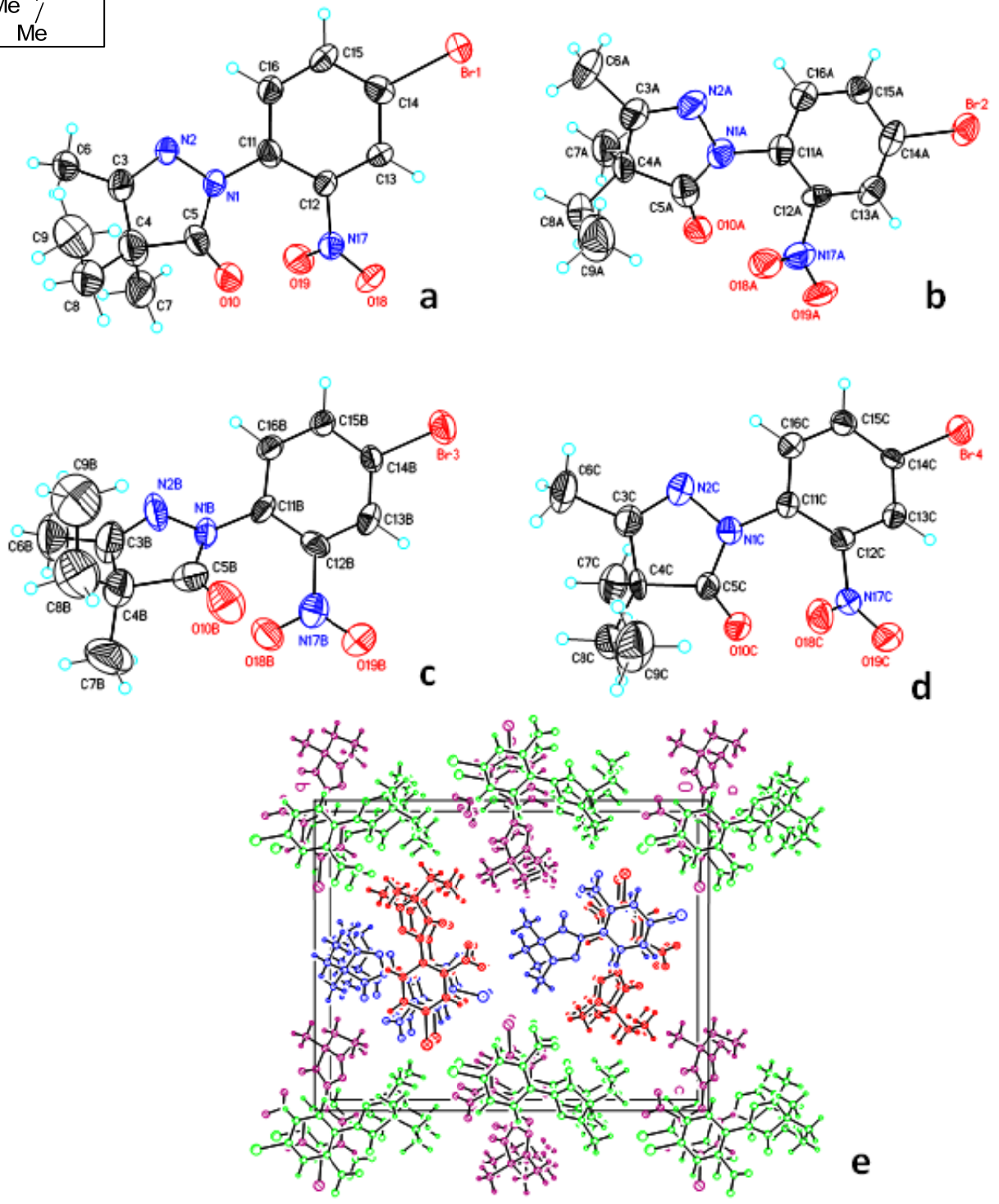


Figure 2. Individual conformers of **11** (a-d) and unit cell of crystal (e). The view of the unit cell is approximately down the **a** axis, and therein, molecule a is shown in blue, molecule b is shown in red, molecule c is shown in violet, and molecule d is in green.



6. Copies of NMR Spectra

Figure 3: ^{1}H and $^{13}C\{^{1}H\}$ NMR spectra of **9**.

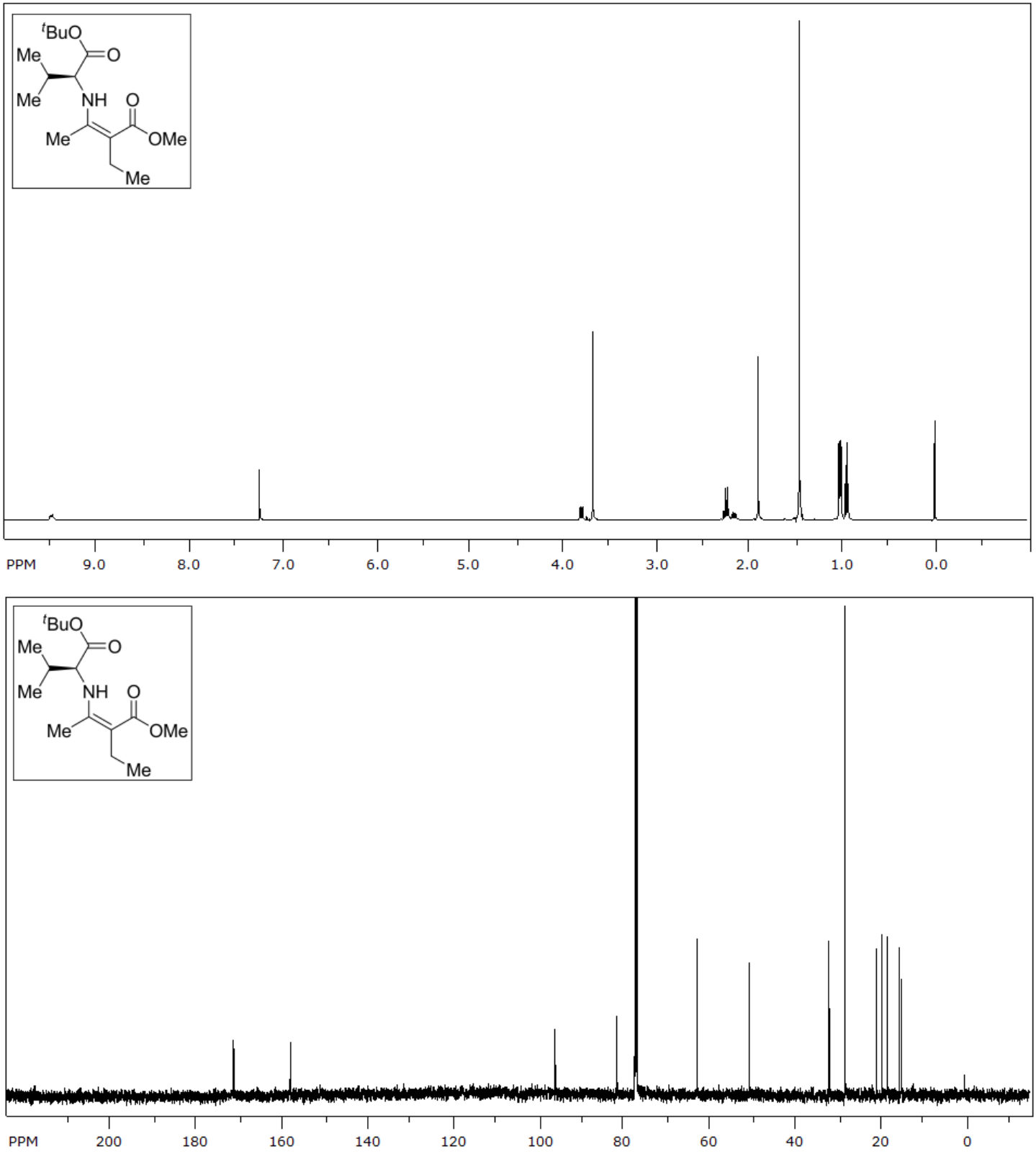


Figure 4: 1D ^{1}H-^{1}H nOe of **9**.

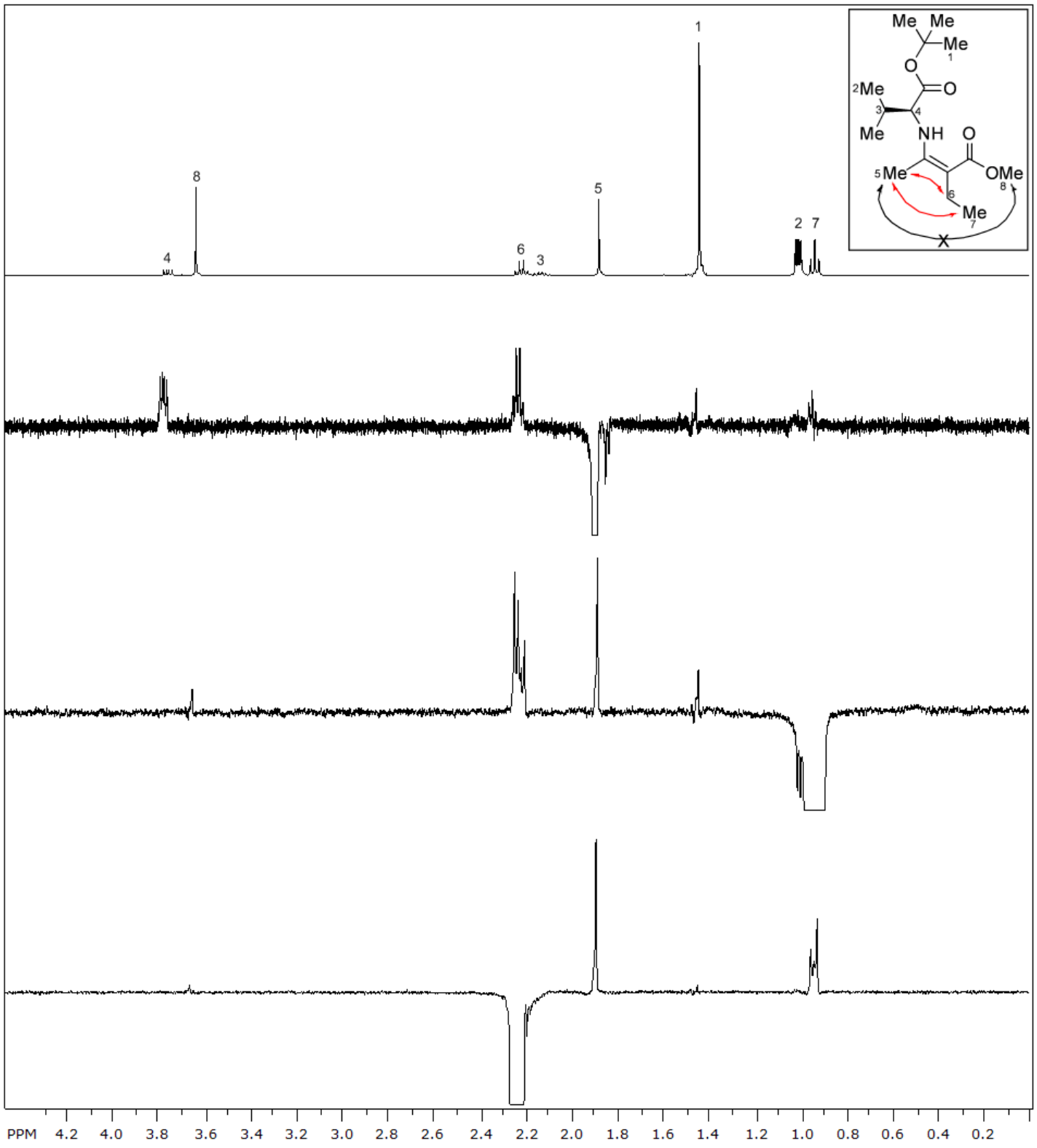


Figure 5: crude ^{1}H spectra of **10**.

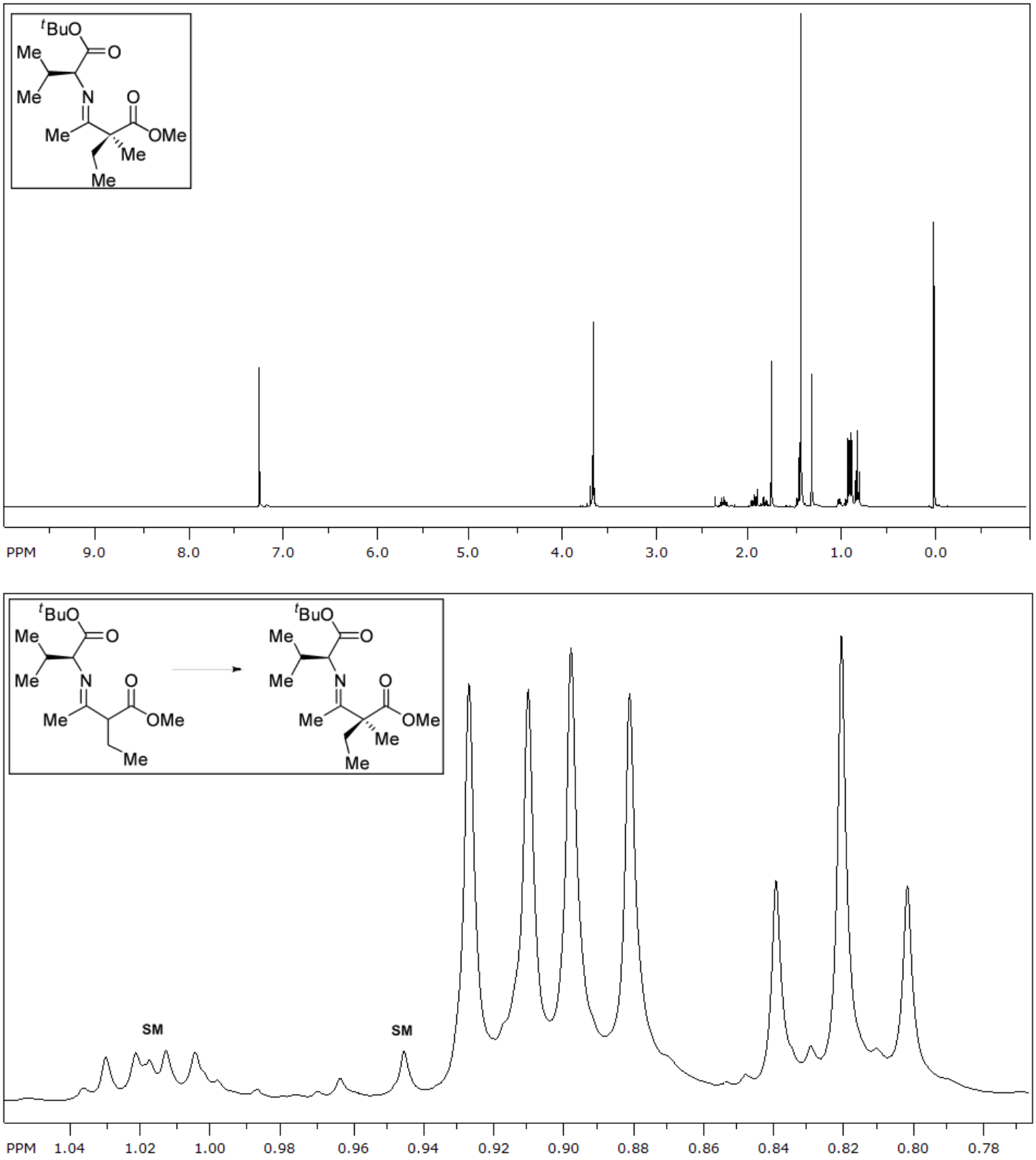
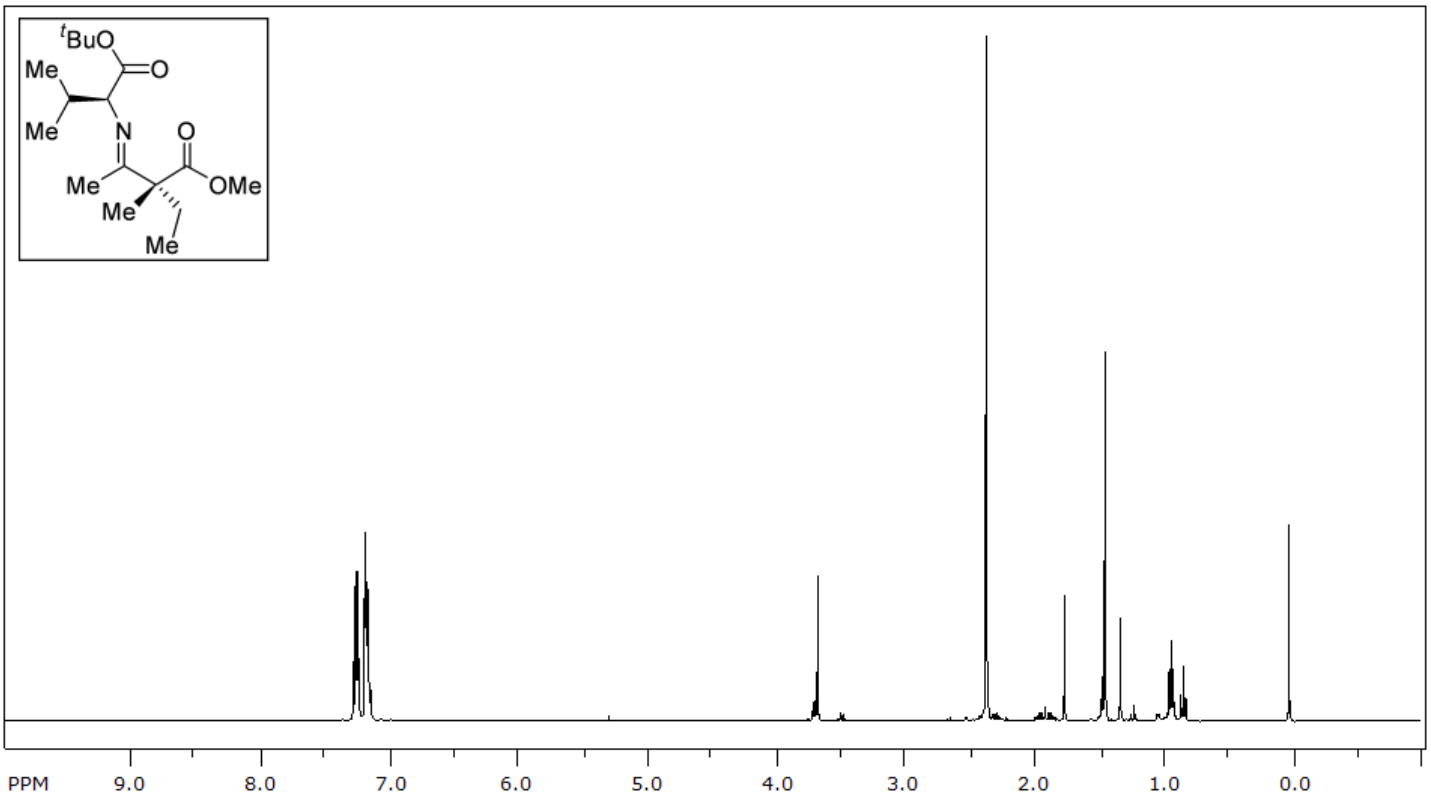


Figure 6: crude ^{1}H spectra of **S2**.



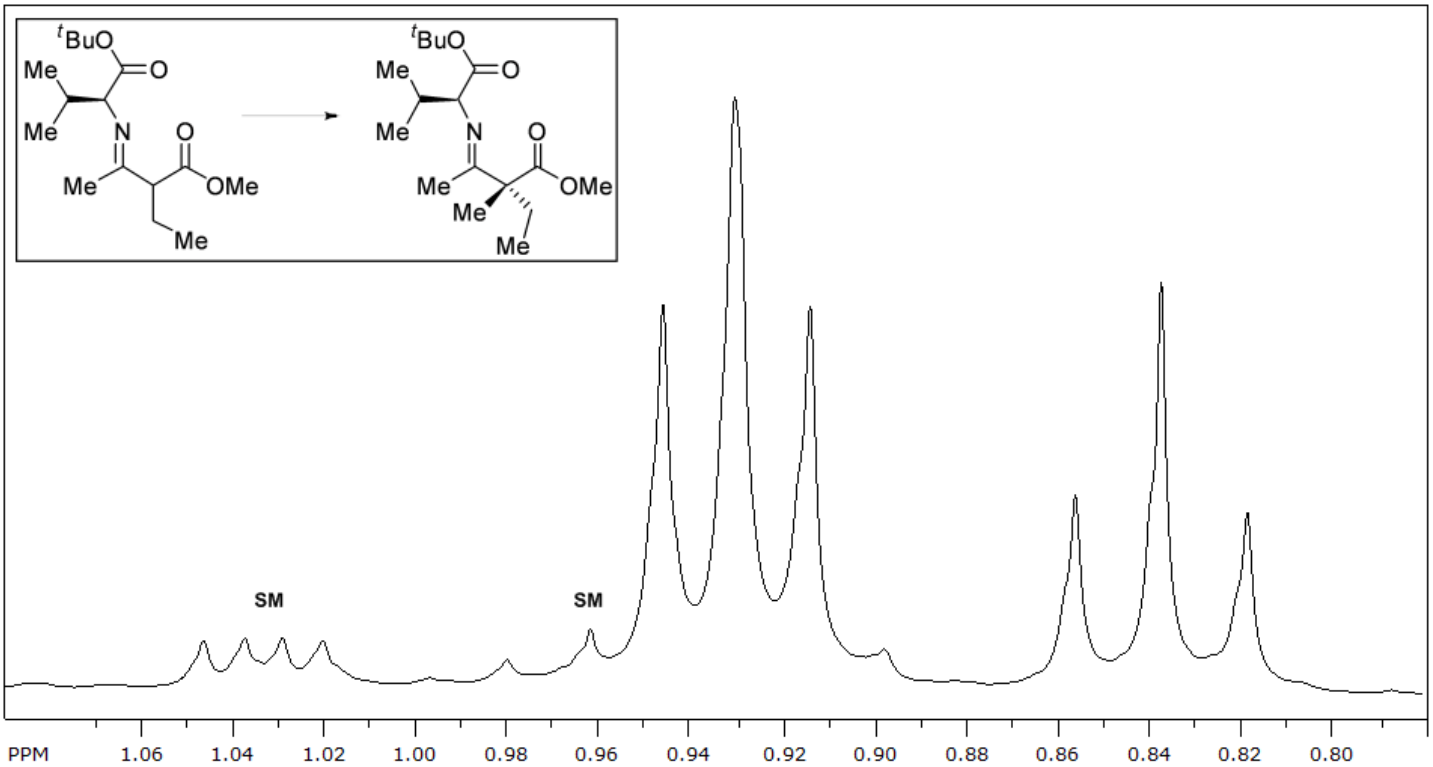
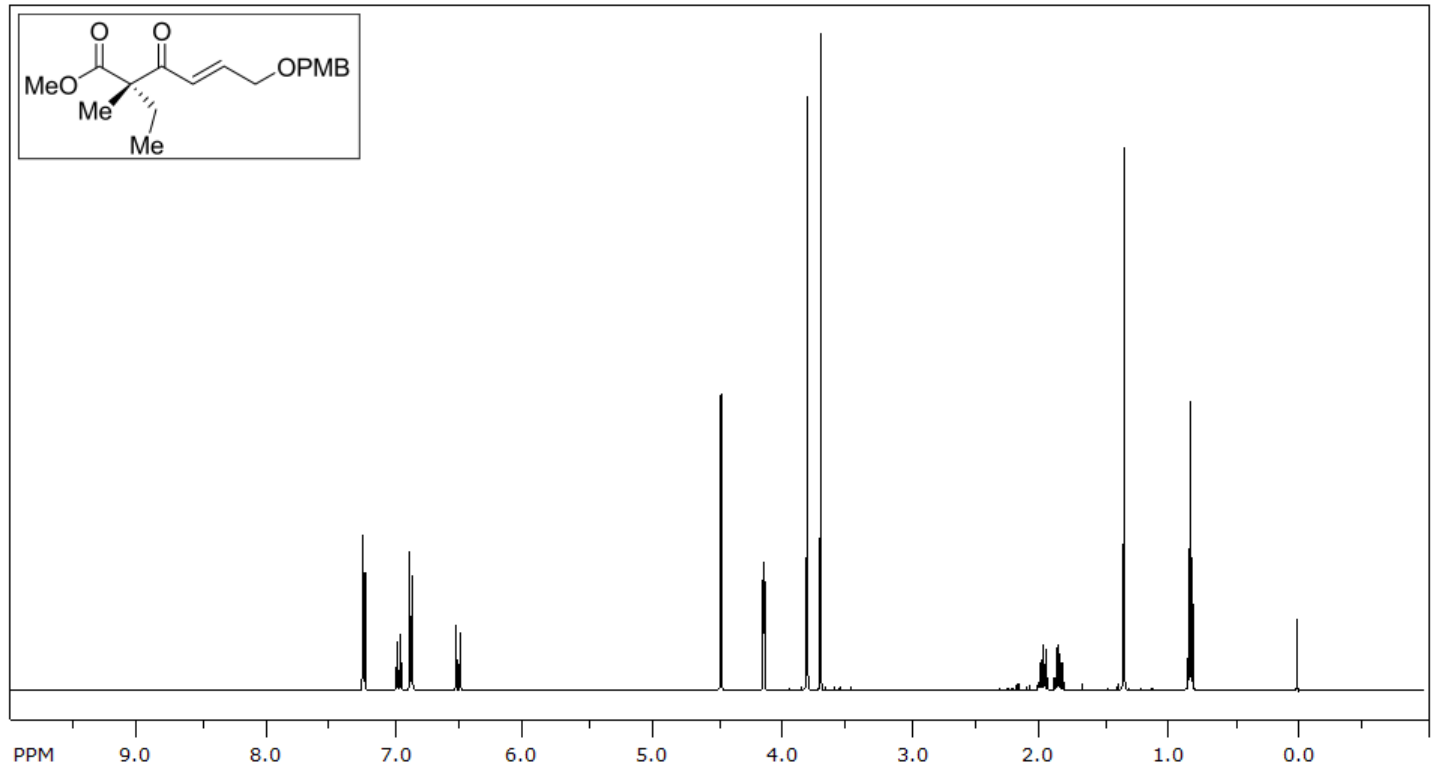


Figure 7: ^{1}H and $^{13}C\{^{1}H\}$ NMR spectra of **12**.



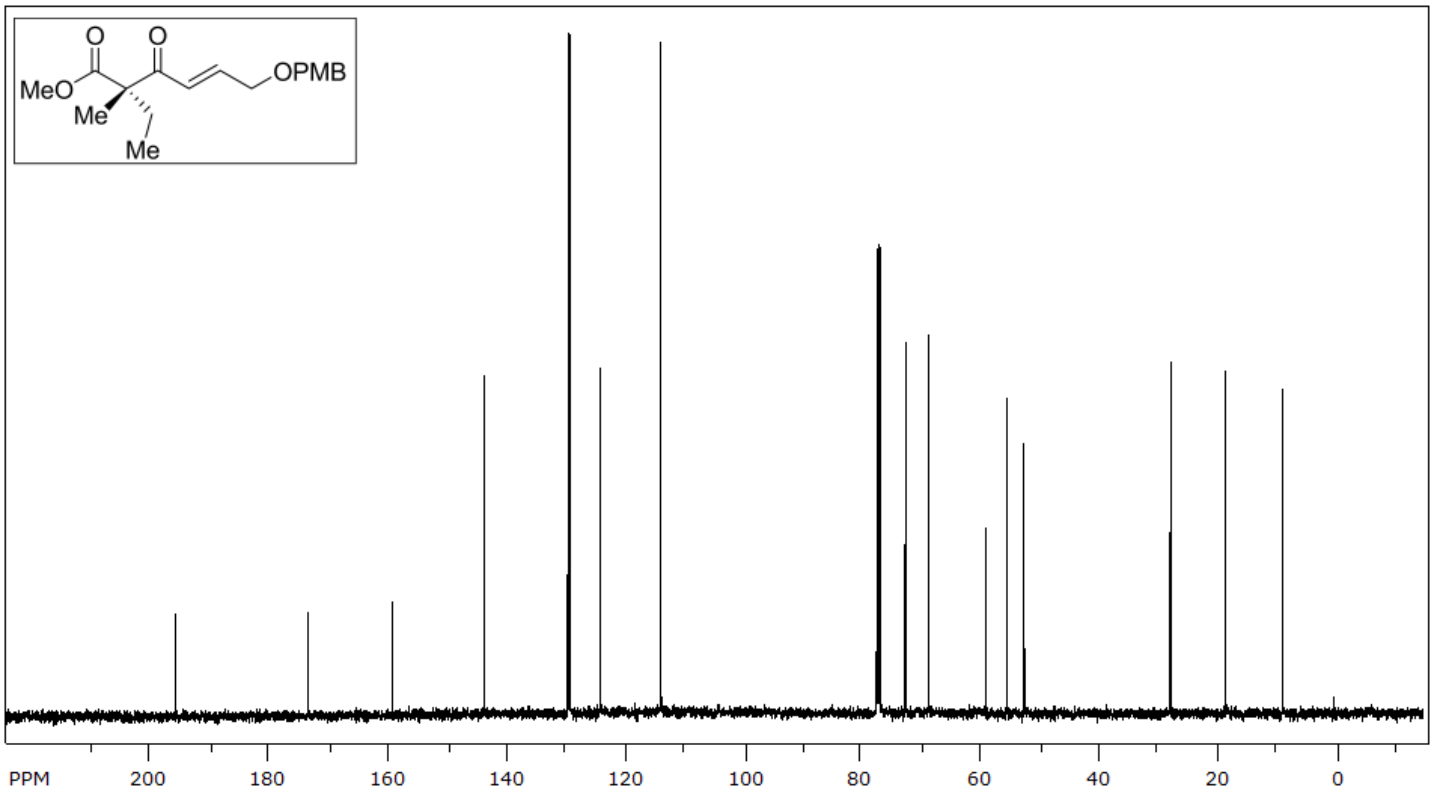
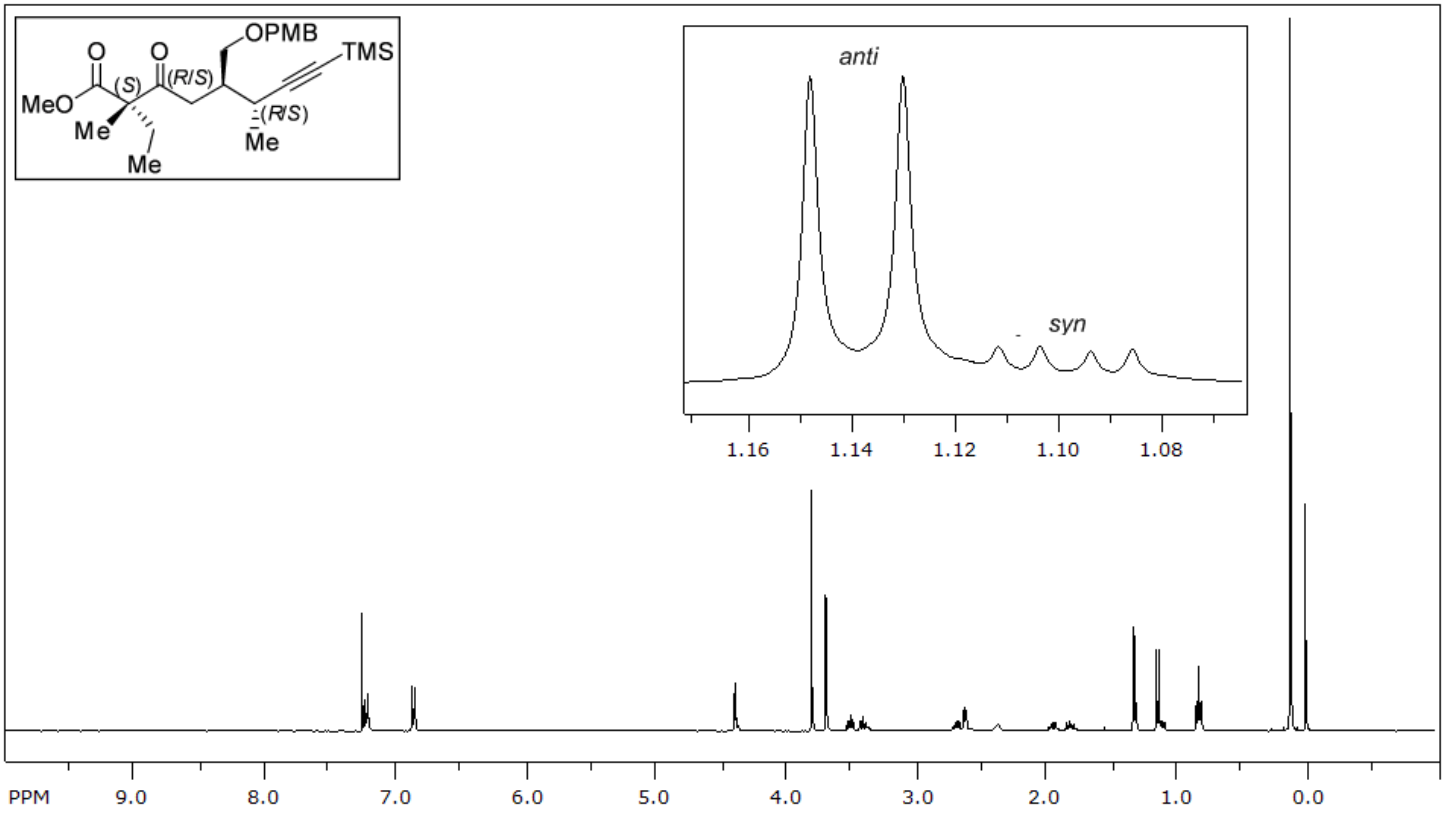


Figure 8: ^{1}H (with expansion of resonances used to determine dr) and $^{13}C\{^{1}H\}$ NMR spectra of **13a** and **13b** (*anti:syn* ~ 5:1).



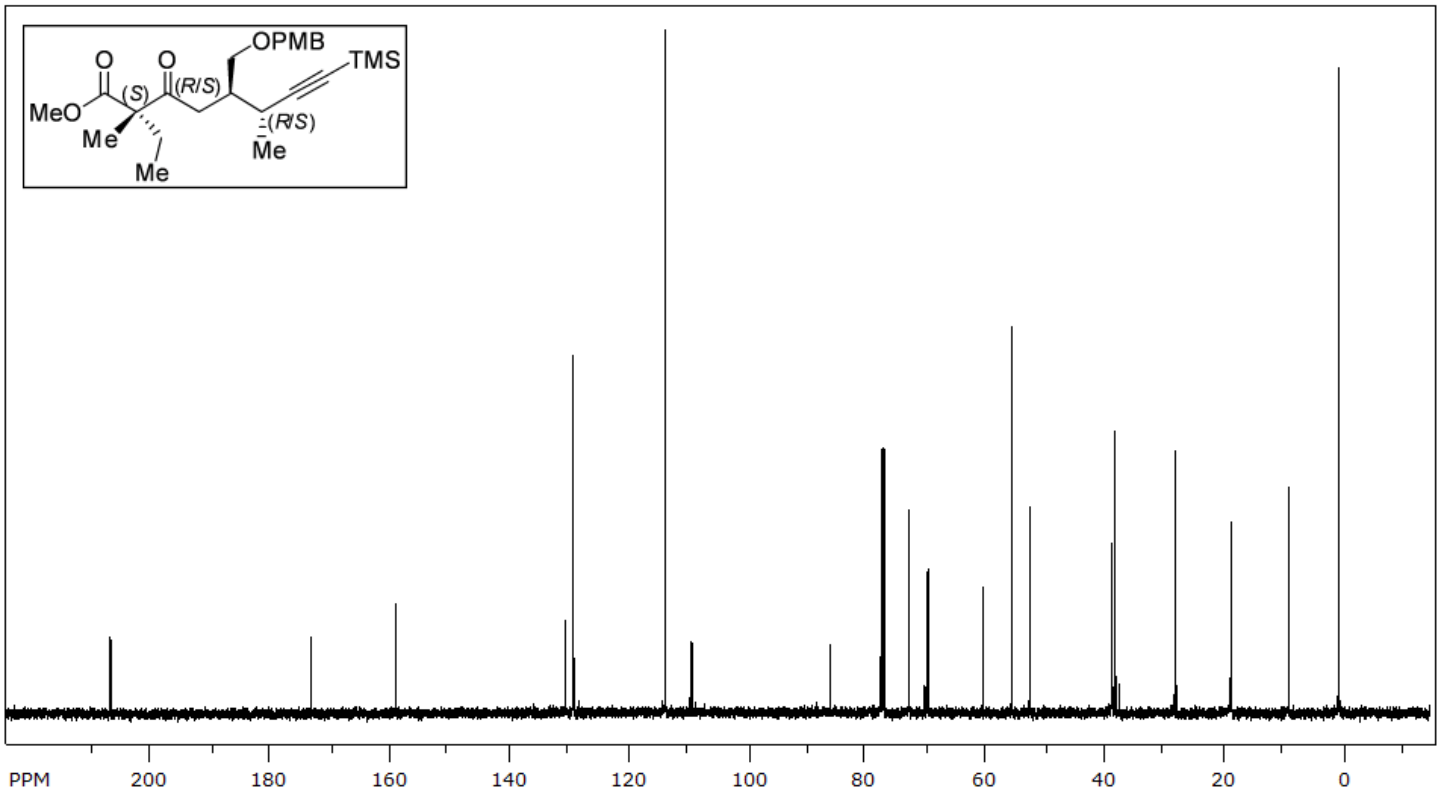


Figure 9: ^{1}H (with expansion of resonances used to determine dr) and $^{13}C\{^{1}H\}$ NMR spectra of **S3a** and **S3b** (*anti:syn* ~ 5:1).

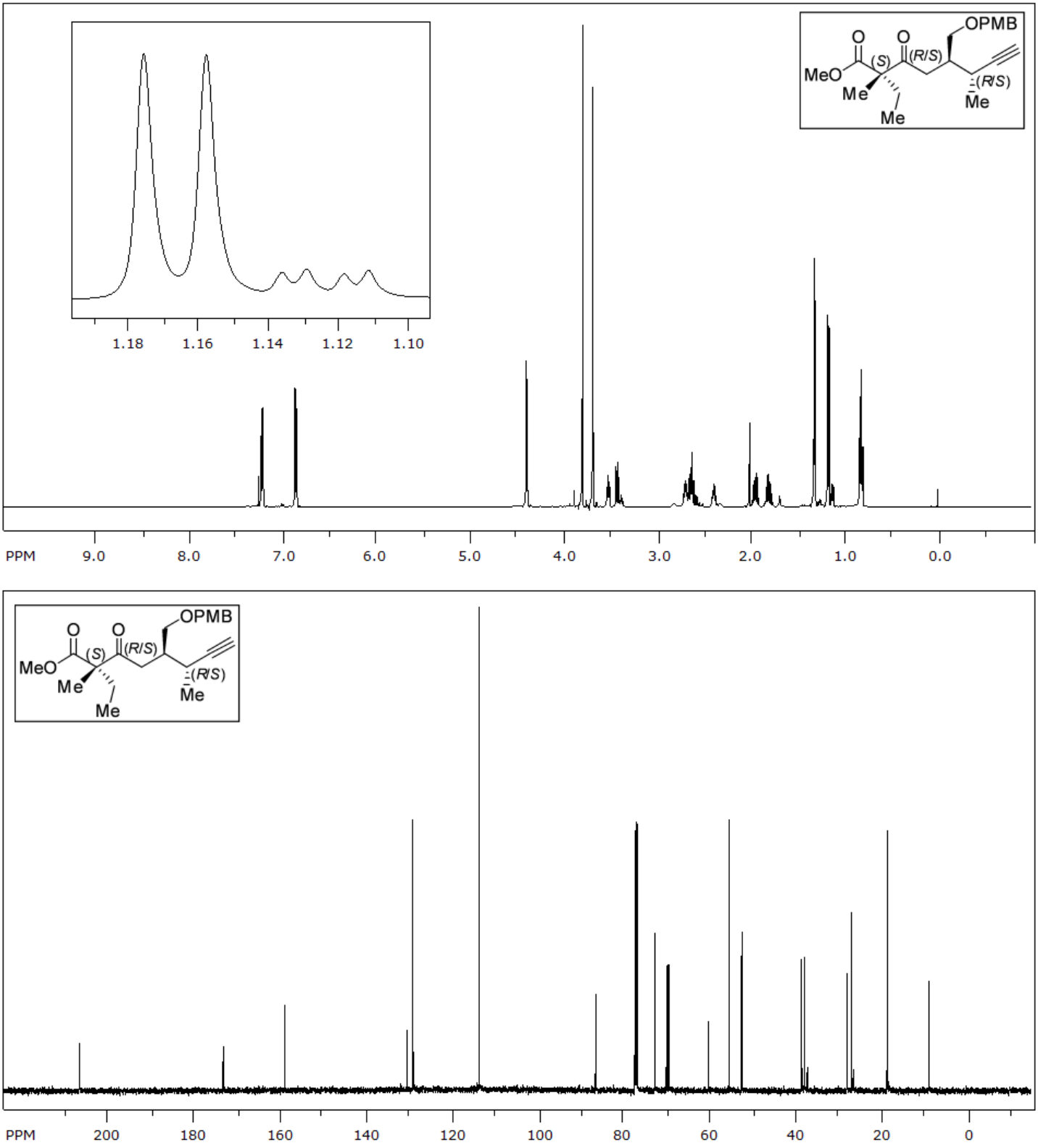
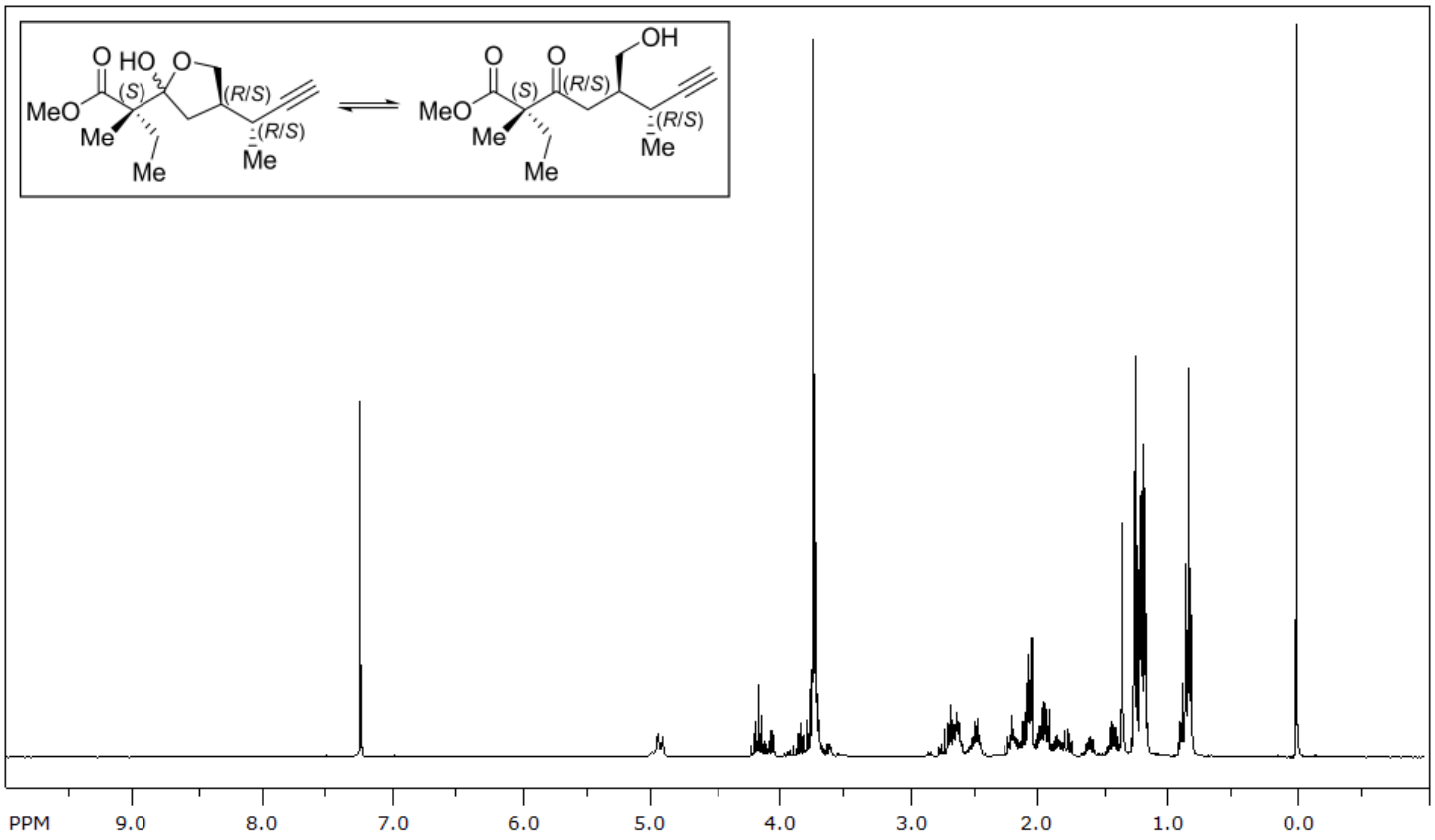


Figure 10: ^{1}H NMR spectrum of **14a** and **14b** (*anti:syn* ~ 5:1) and partial gHMBC verifying hemiacetal isomers.



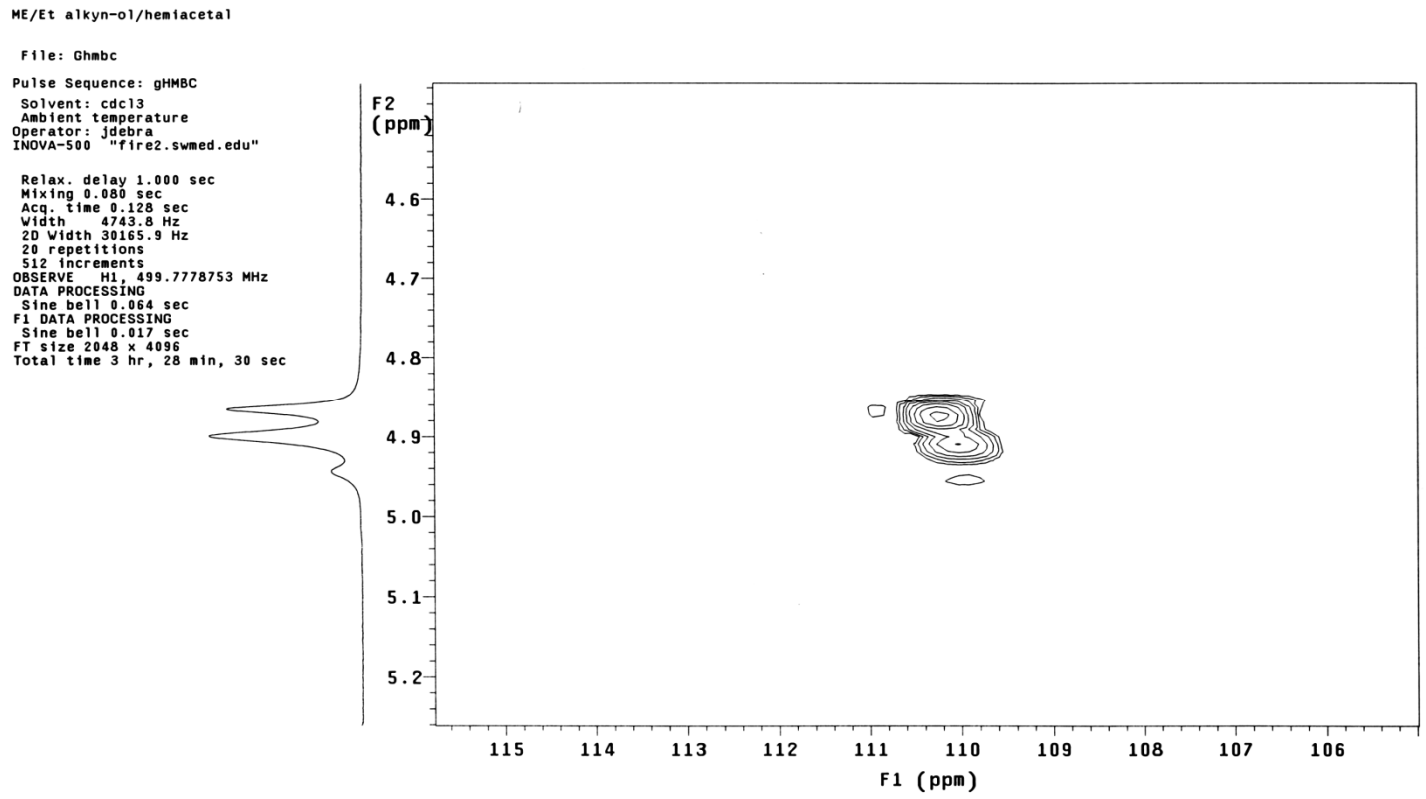


Figure 11: ^{1}H and $^{13}C\{^{1}H\}$ NMR spectra of **11**.

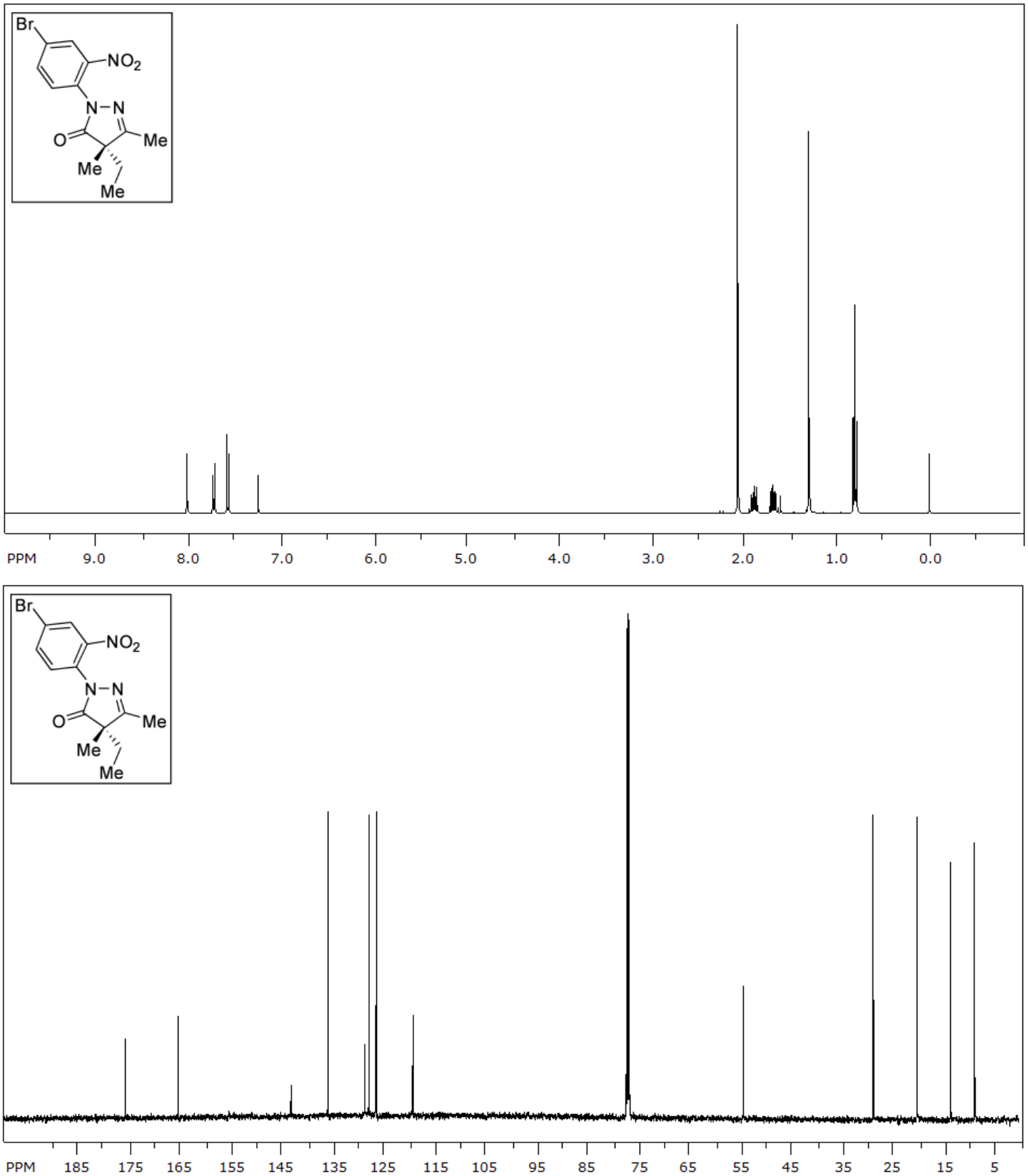
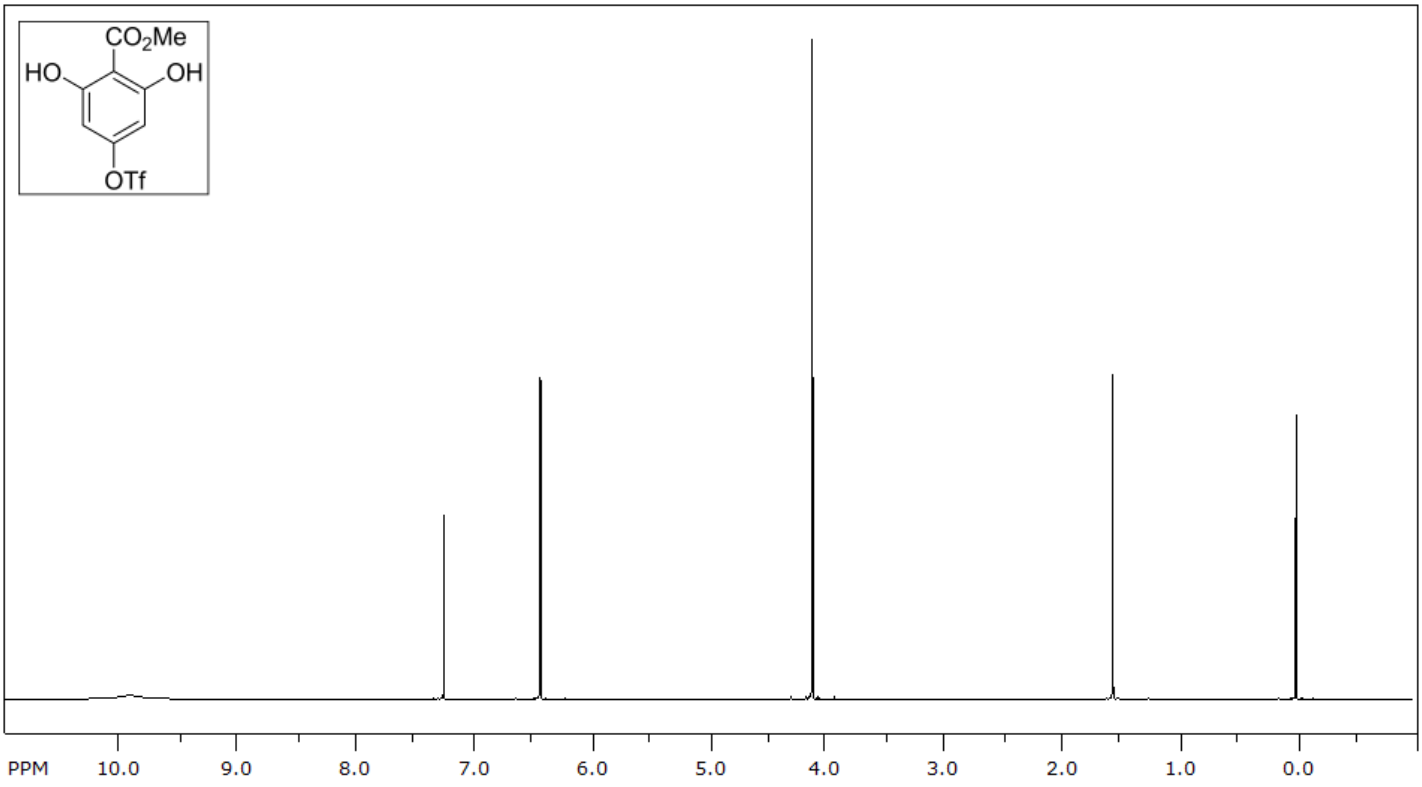


Figure 12: ^{1}H and $^{13}C\{^{1}H\}$ NMR spectra of **16**.



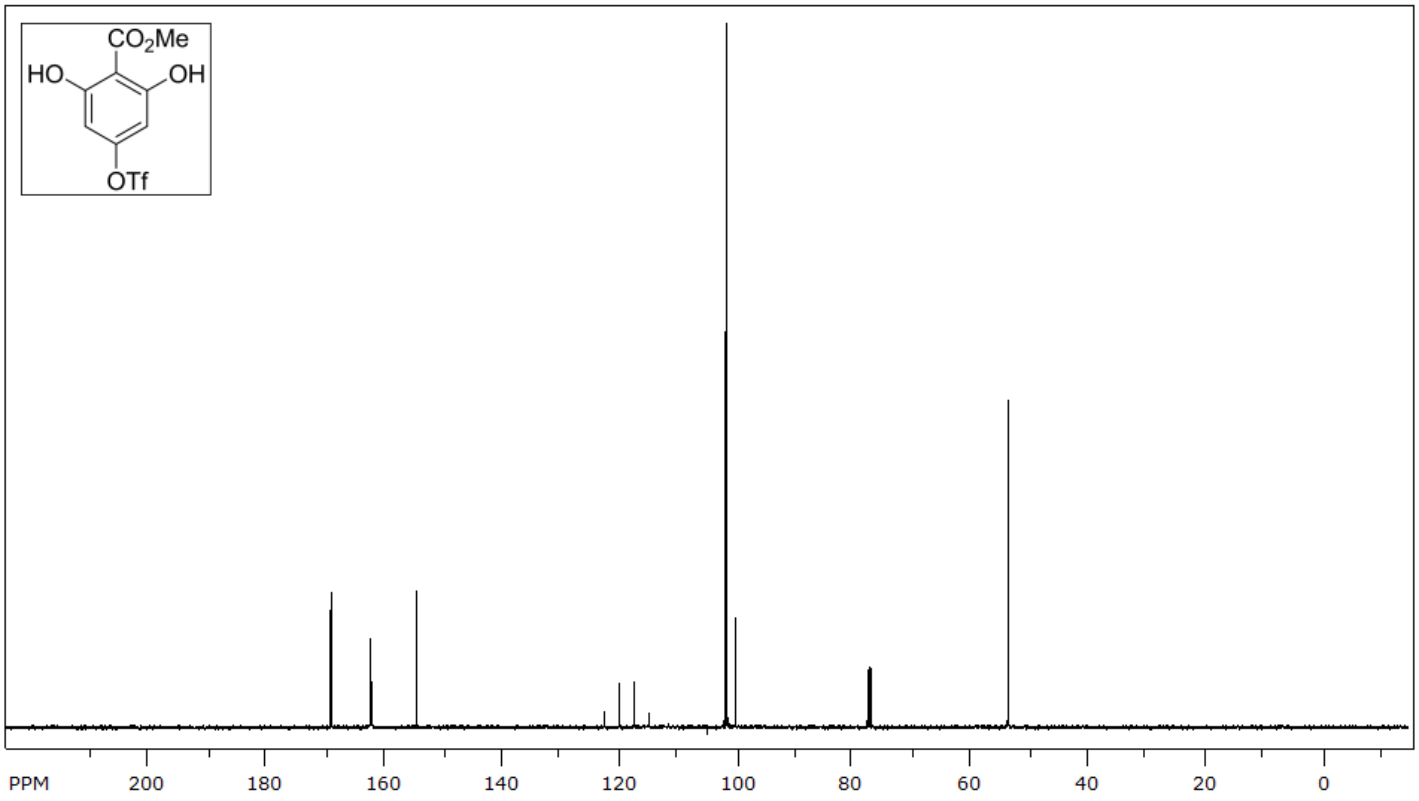


Figure 13: ^{1}H and $^{13}C\{^{1}H\}$ NMR spectra of **17**.

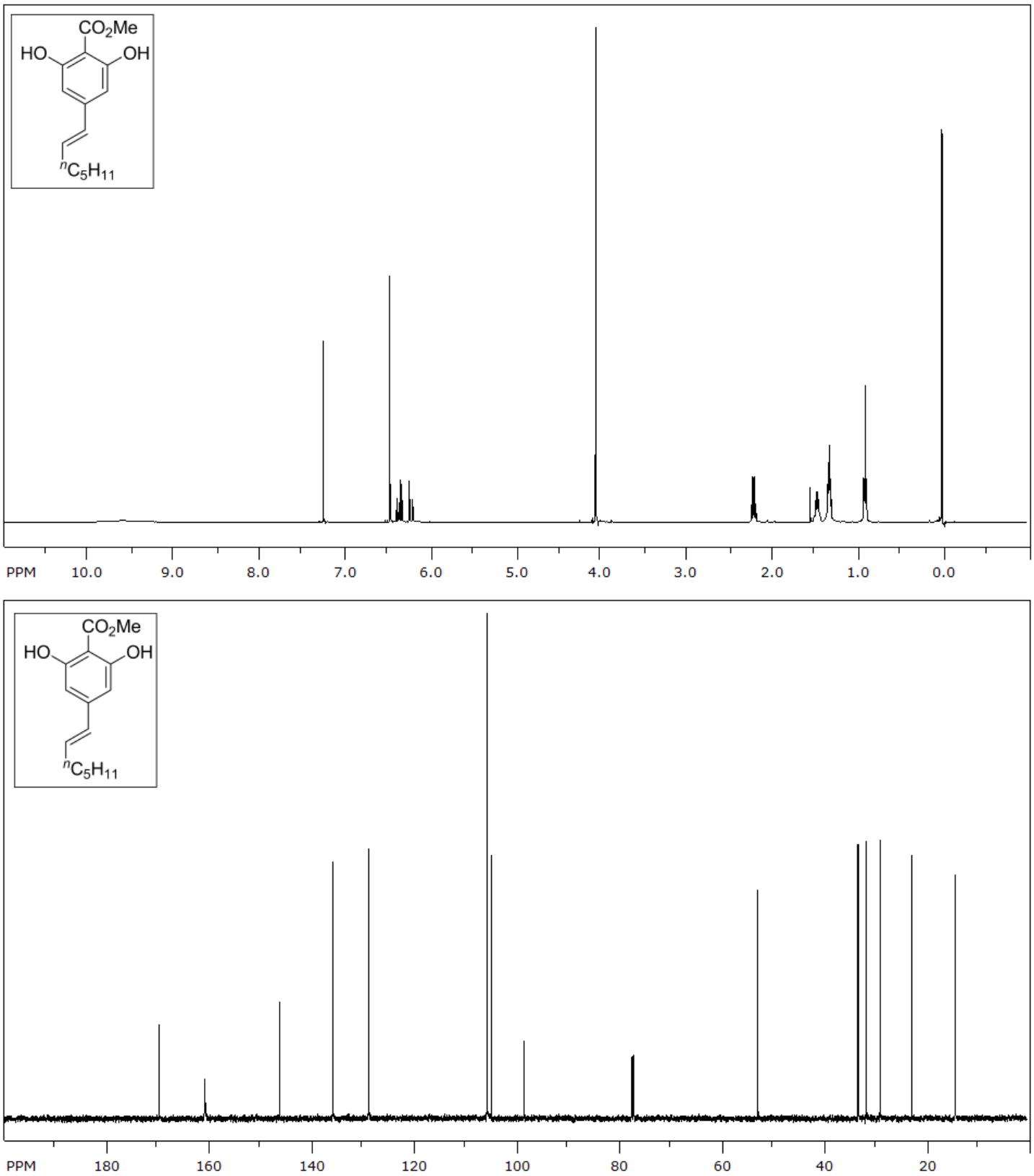
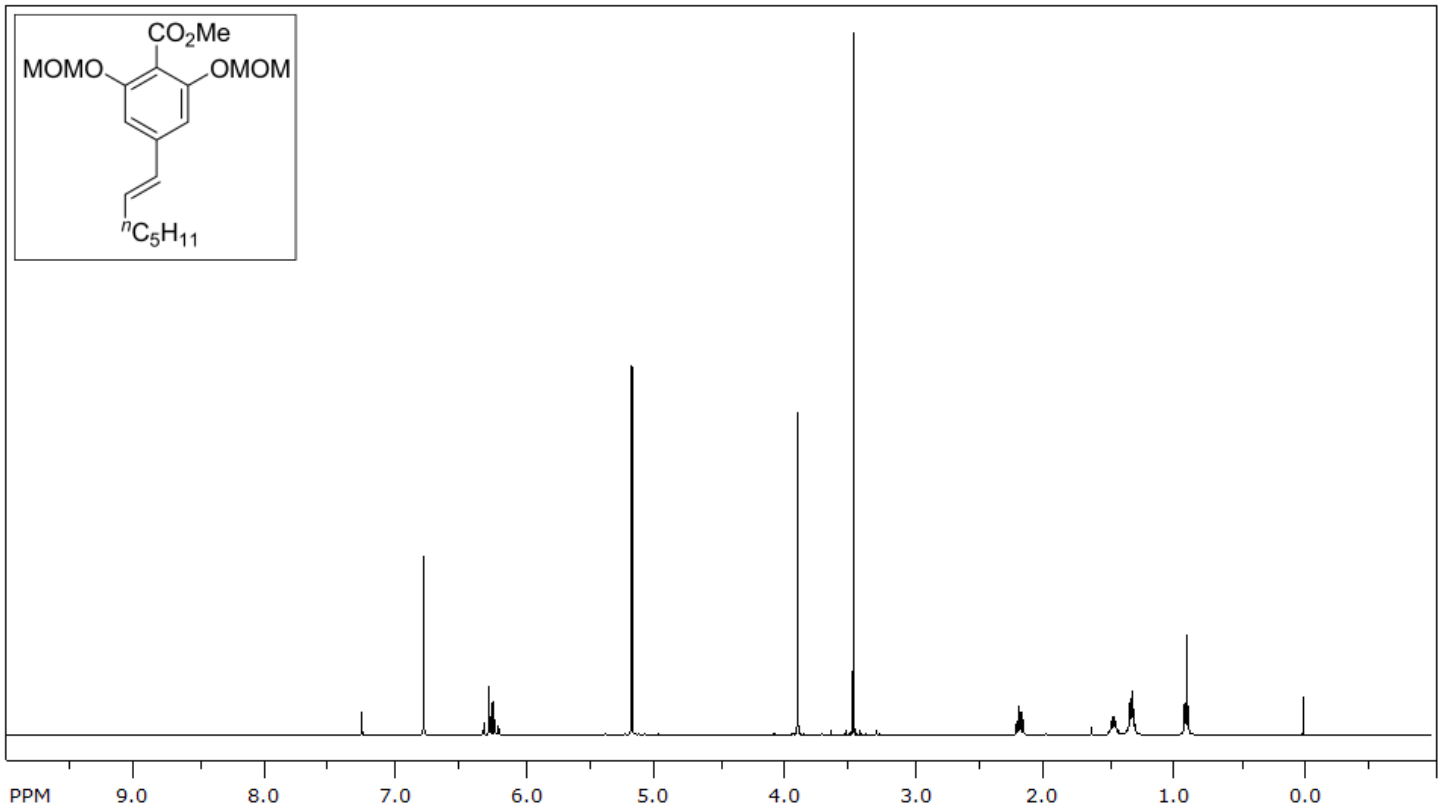


Figure 14: ^{1}H and $^{13}C\{^{1}H\}$ NMR spectra of **S5**.



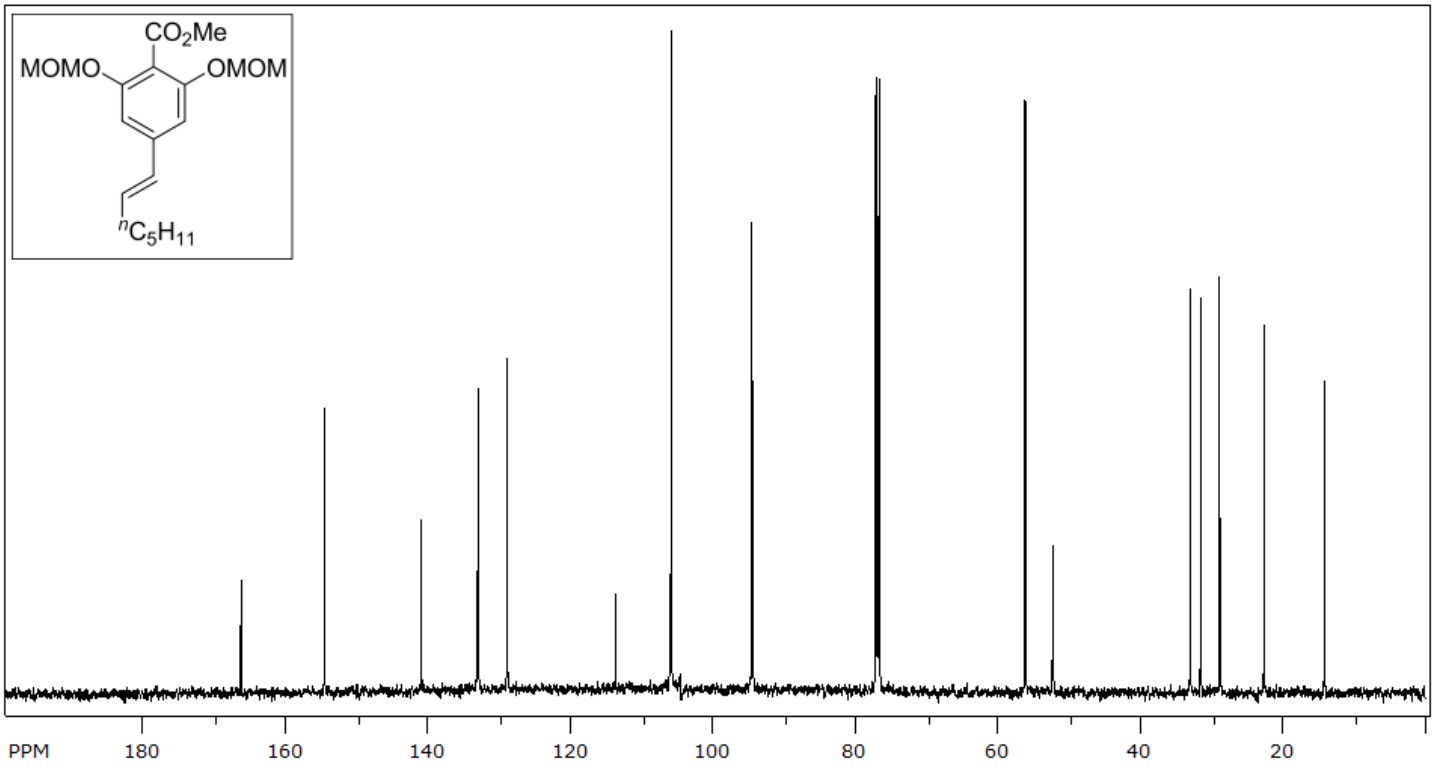


Figure 15: ^{1}H and $^{13}C\{^{1}H\}$ NMR spectra of **S4**.

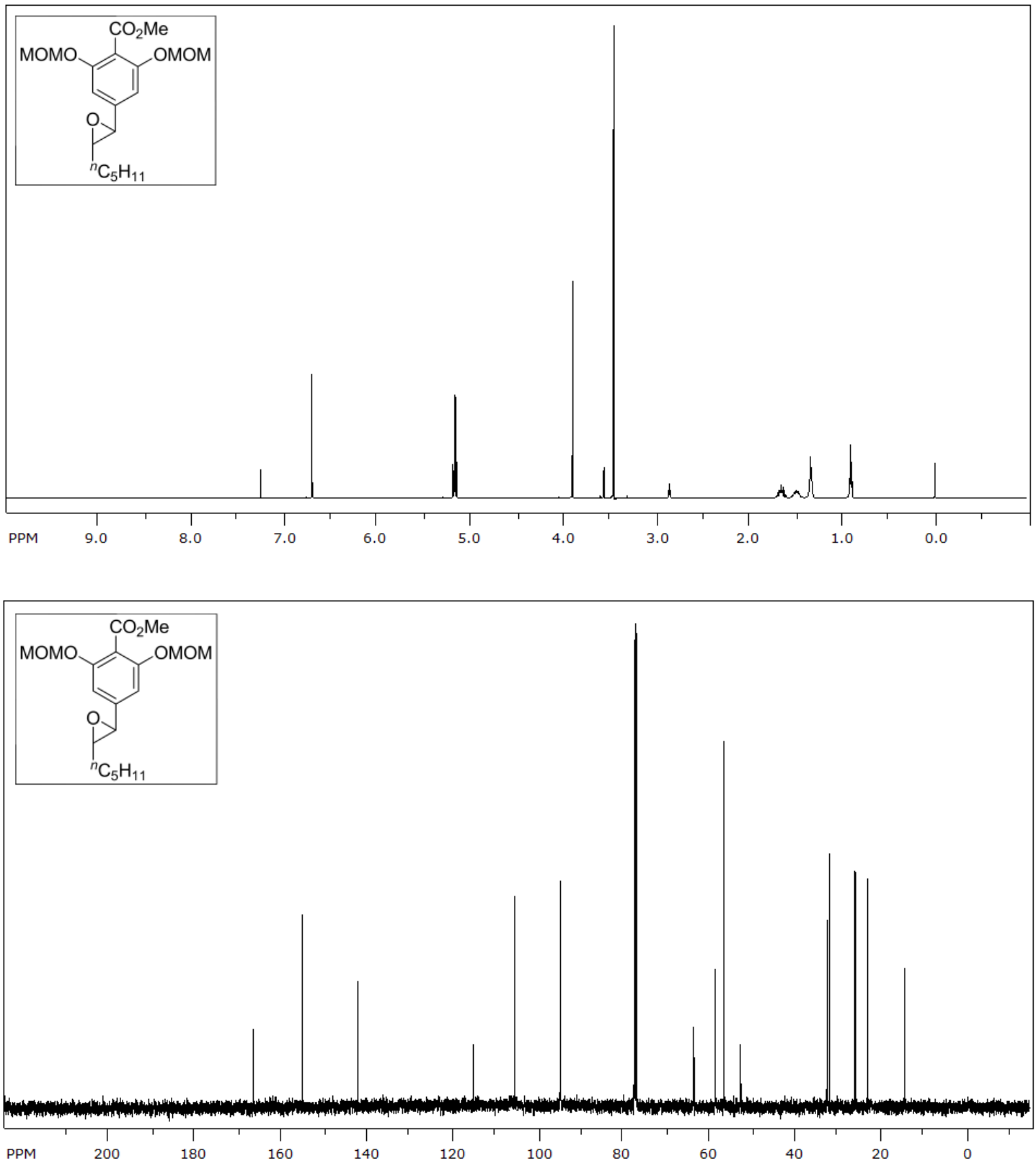
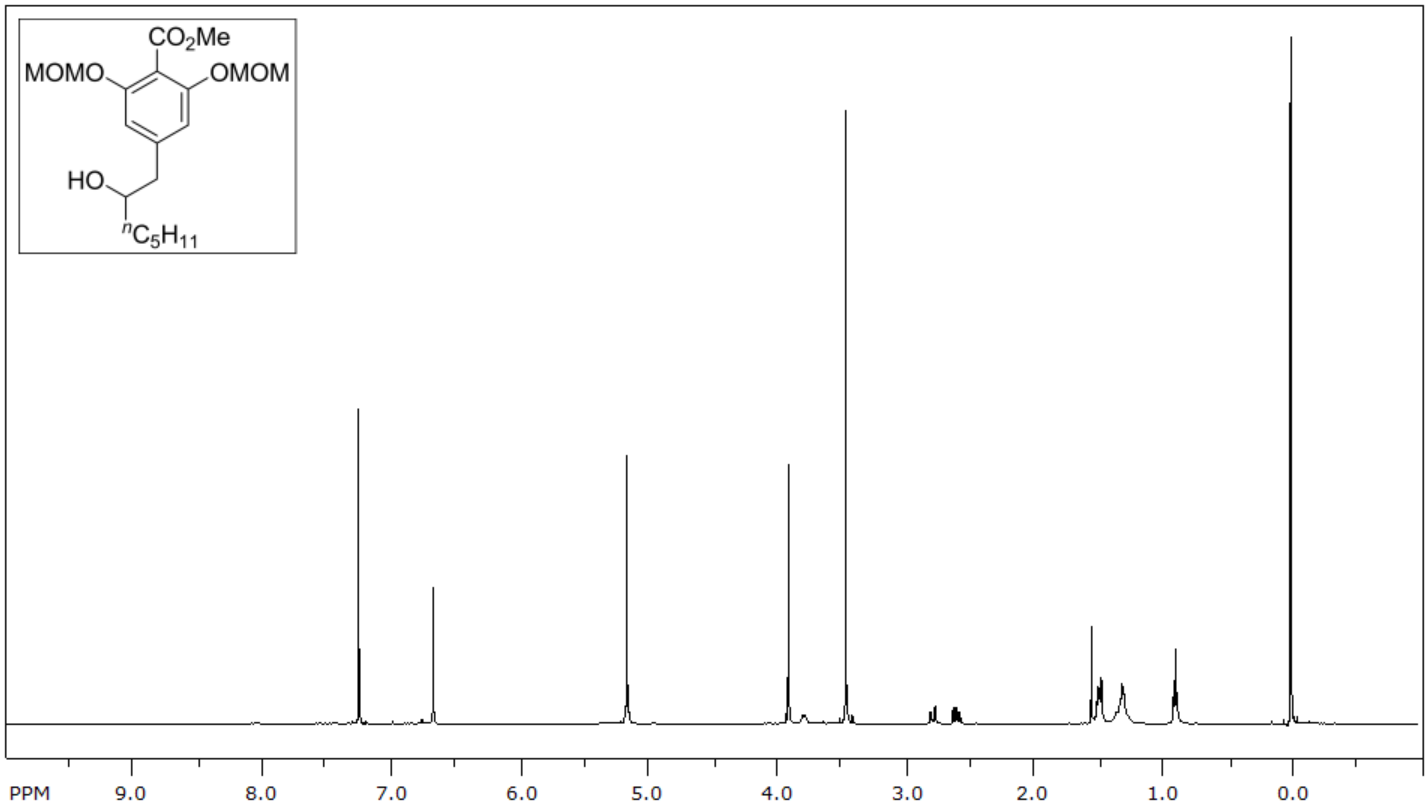


Figure 16: ^{1}H and $^{13}C\{^{1}H\}$ NMR spectra of **18**.



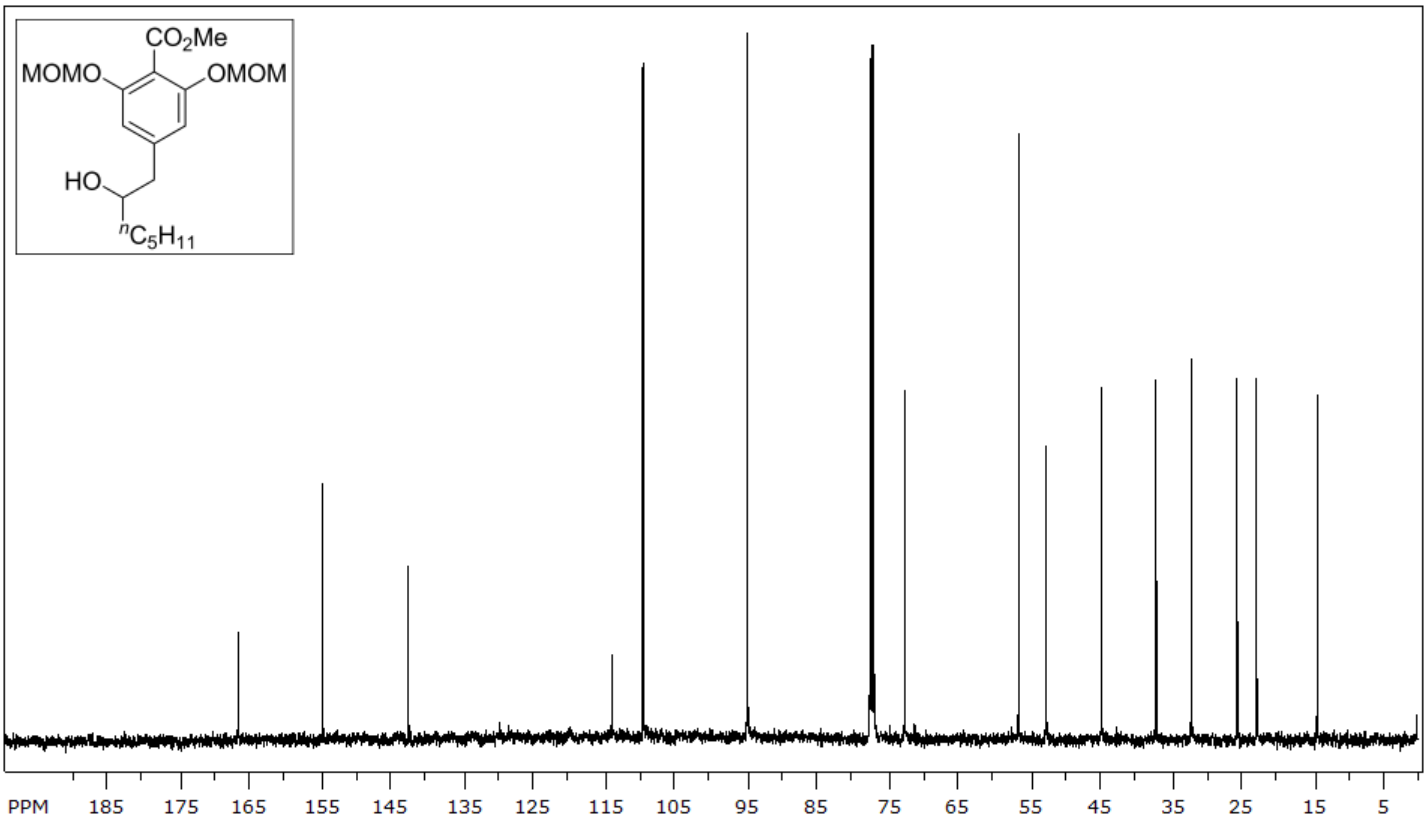
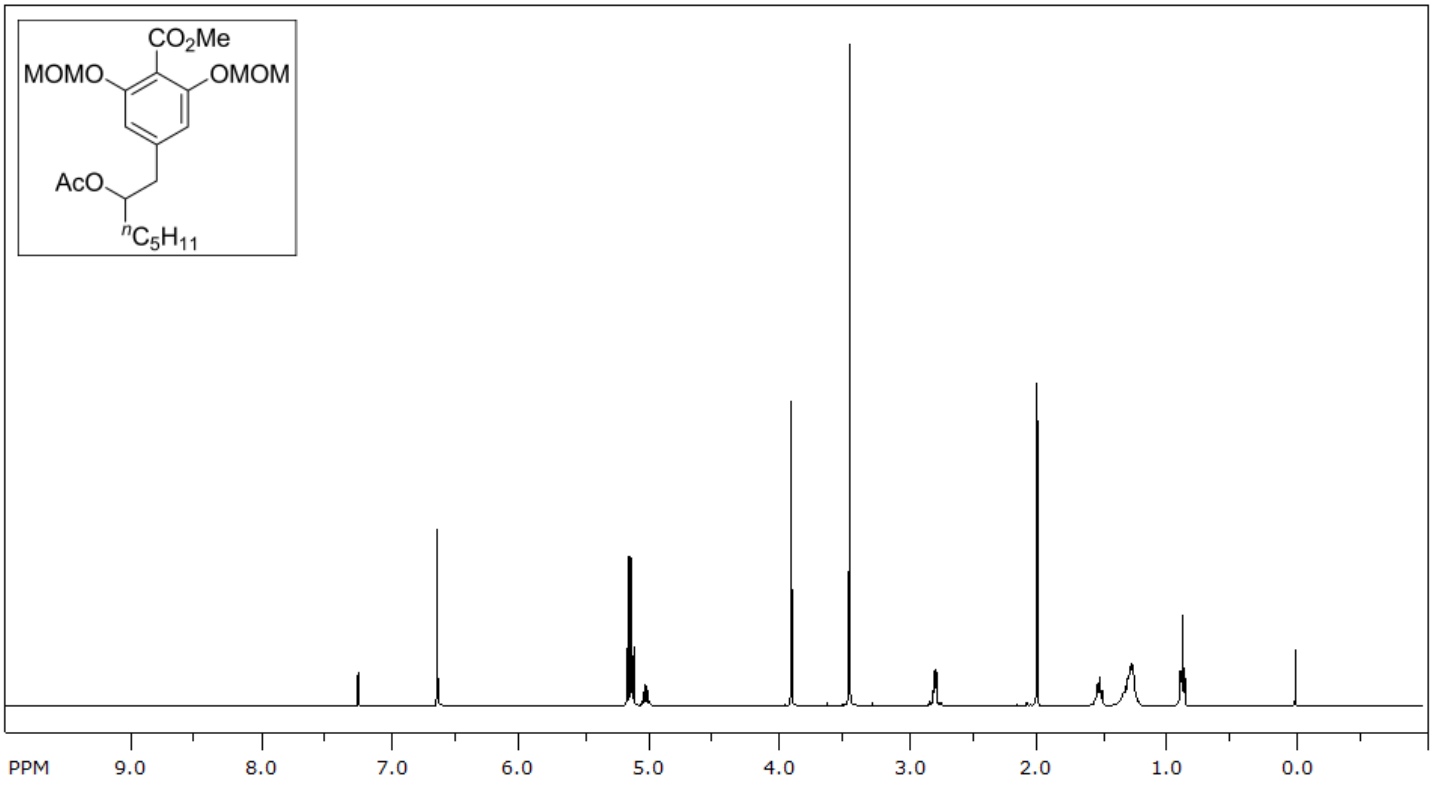


Figure 17: ^{1}H and $^{13}C\{^{1}H\}$ NMR spectra of **S6**.



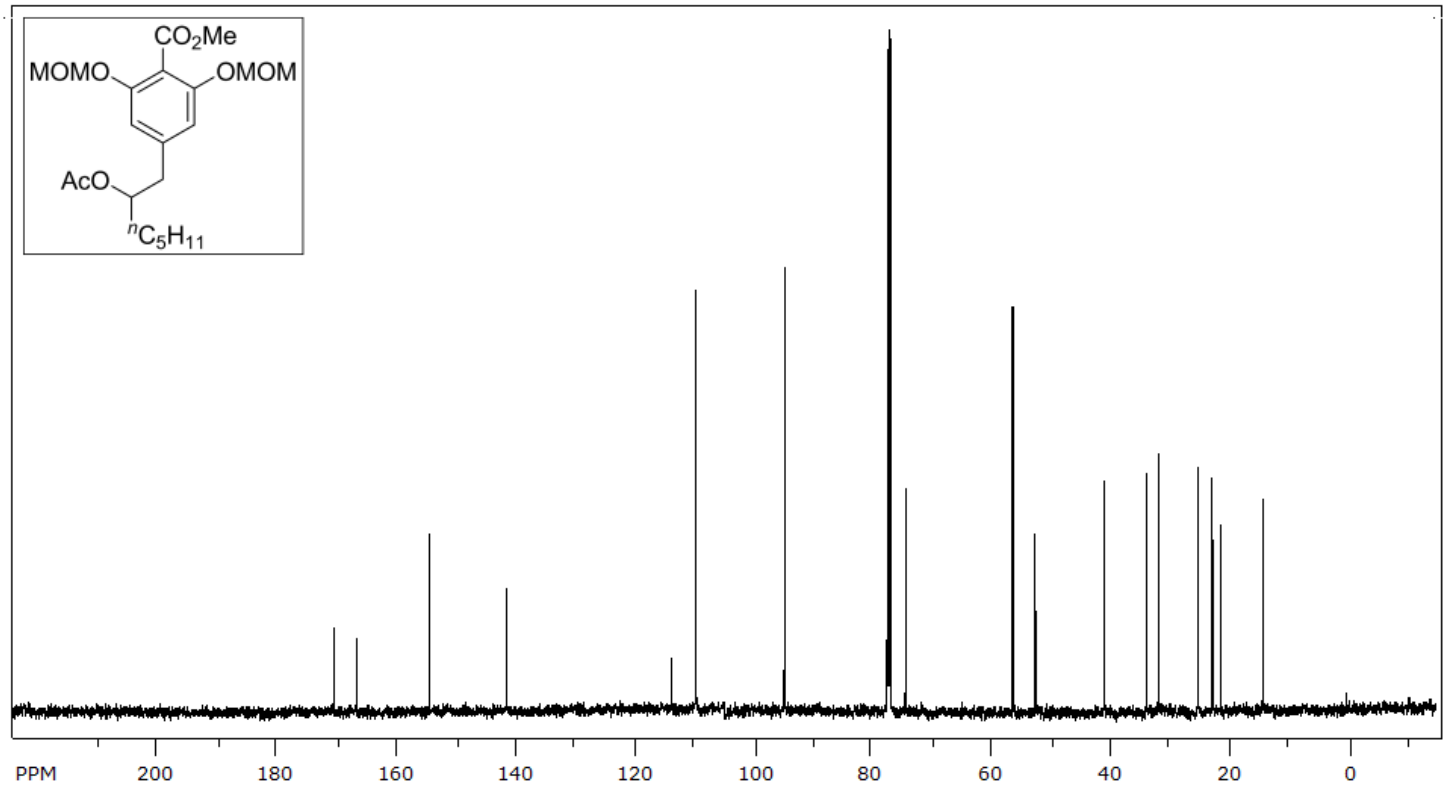


Figure 18: ^{1}H and $^{13}C\{^{1}H\}$ NMR spectra of **21**.

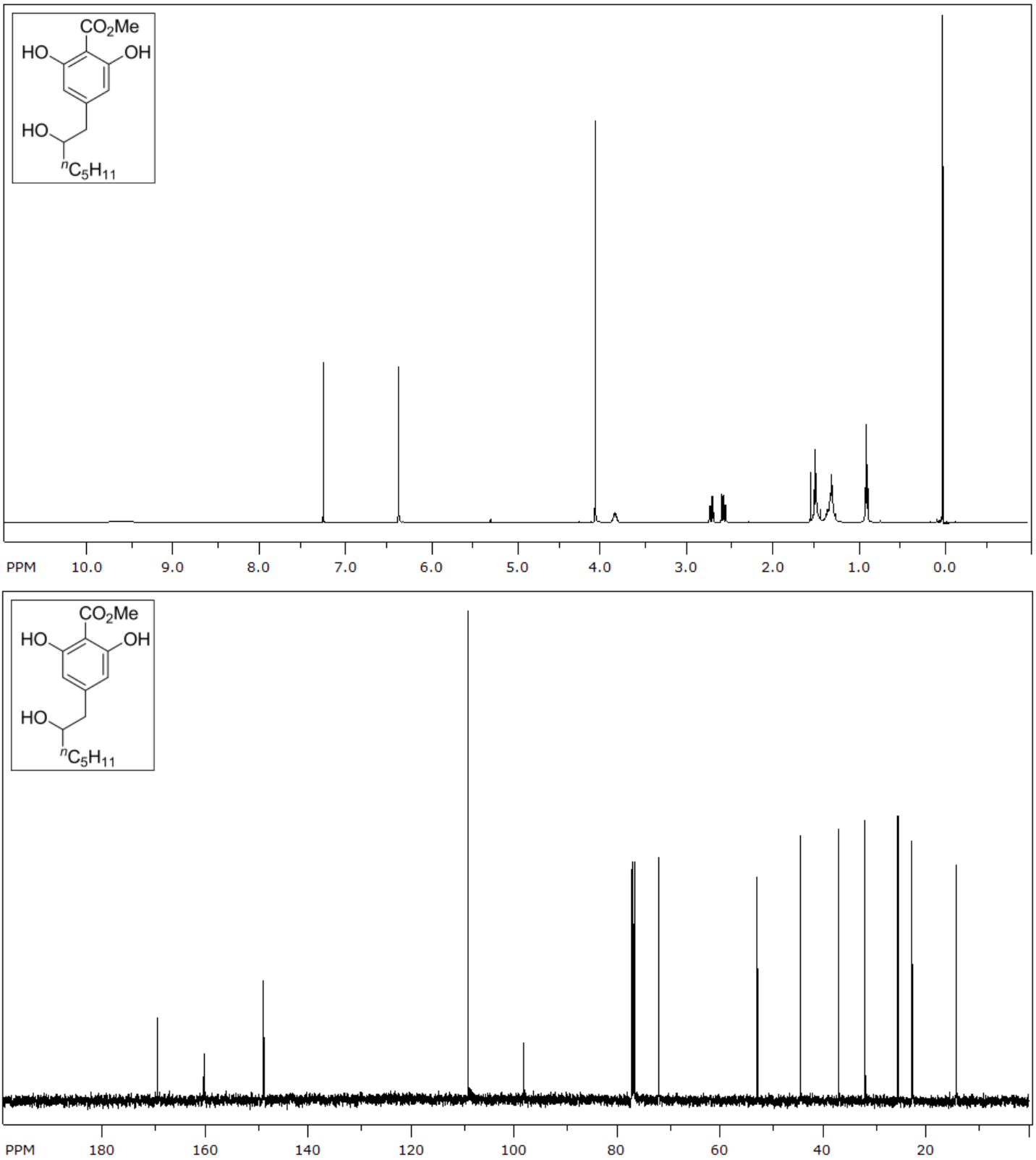


Figure 19: ^{1}H and $^{13}C\{^{1}H\}$ NMR spectra of **22**.

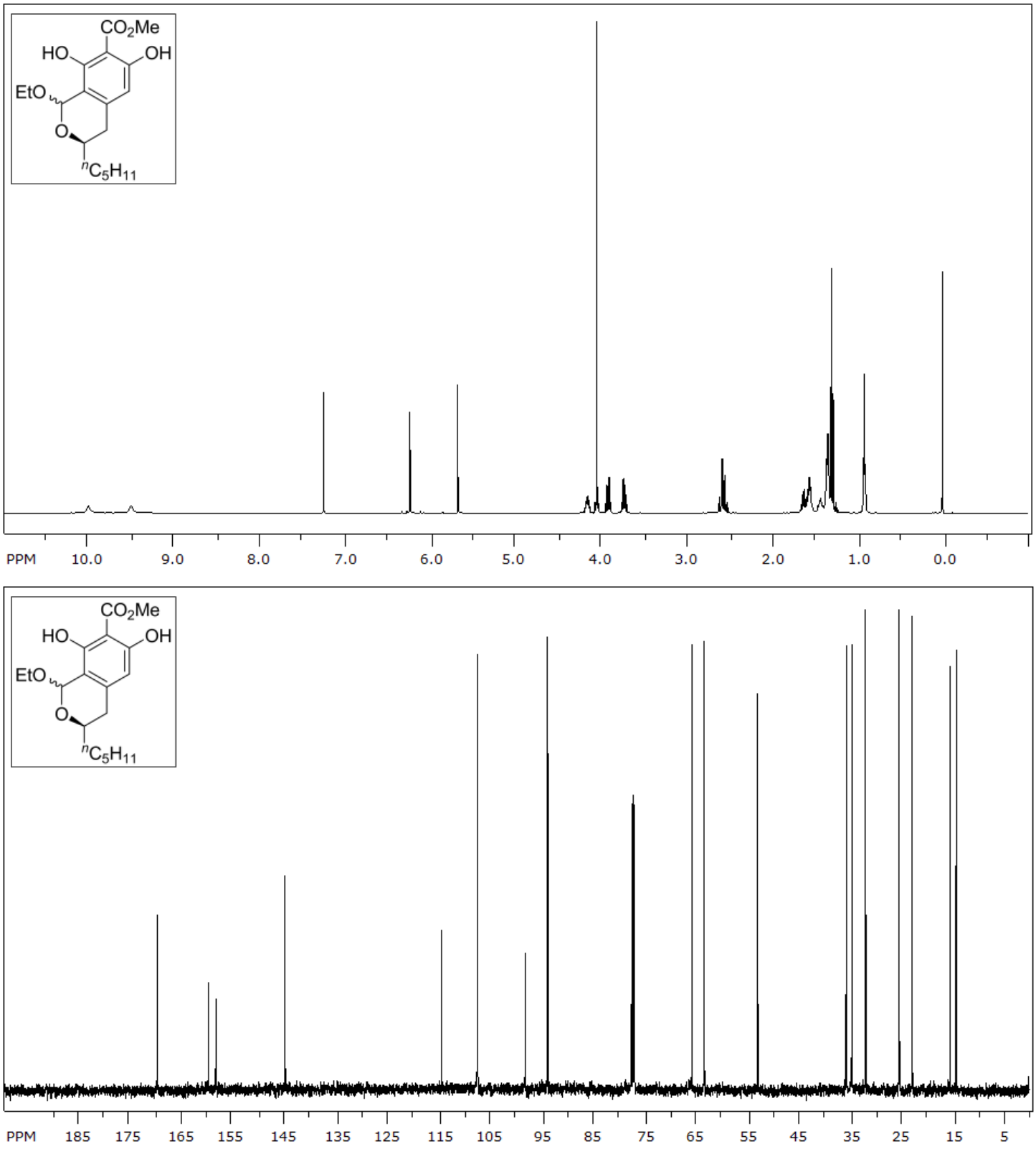


Figure 20: ^{1}H NMR spectrum of synthetic berkelic acid (**2**, $CDCl_3$ δ 7.24 ppm).

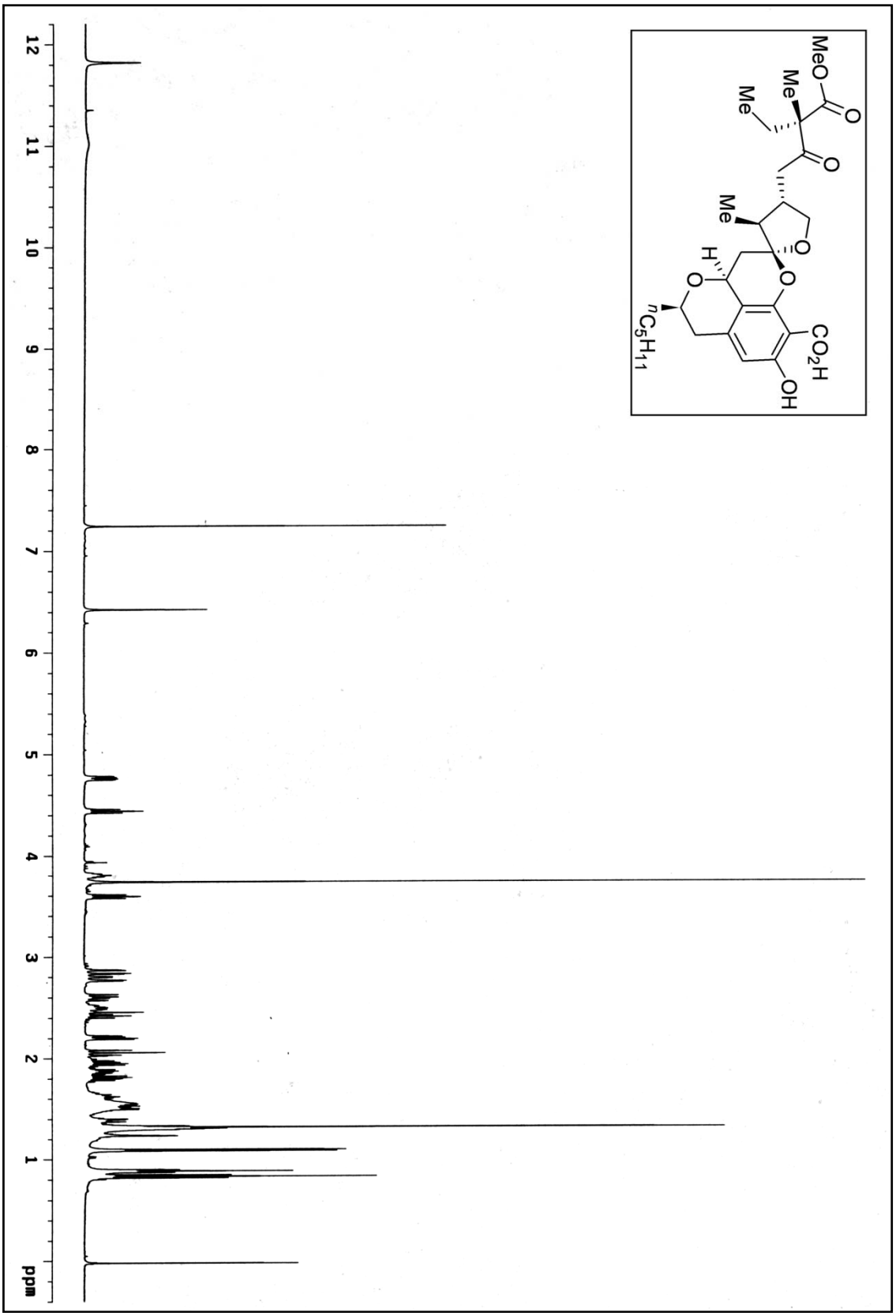
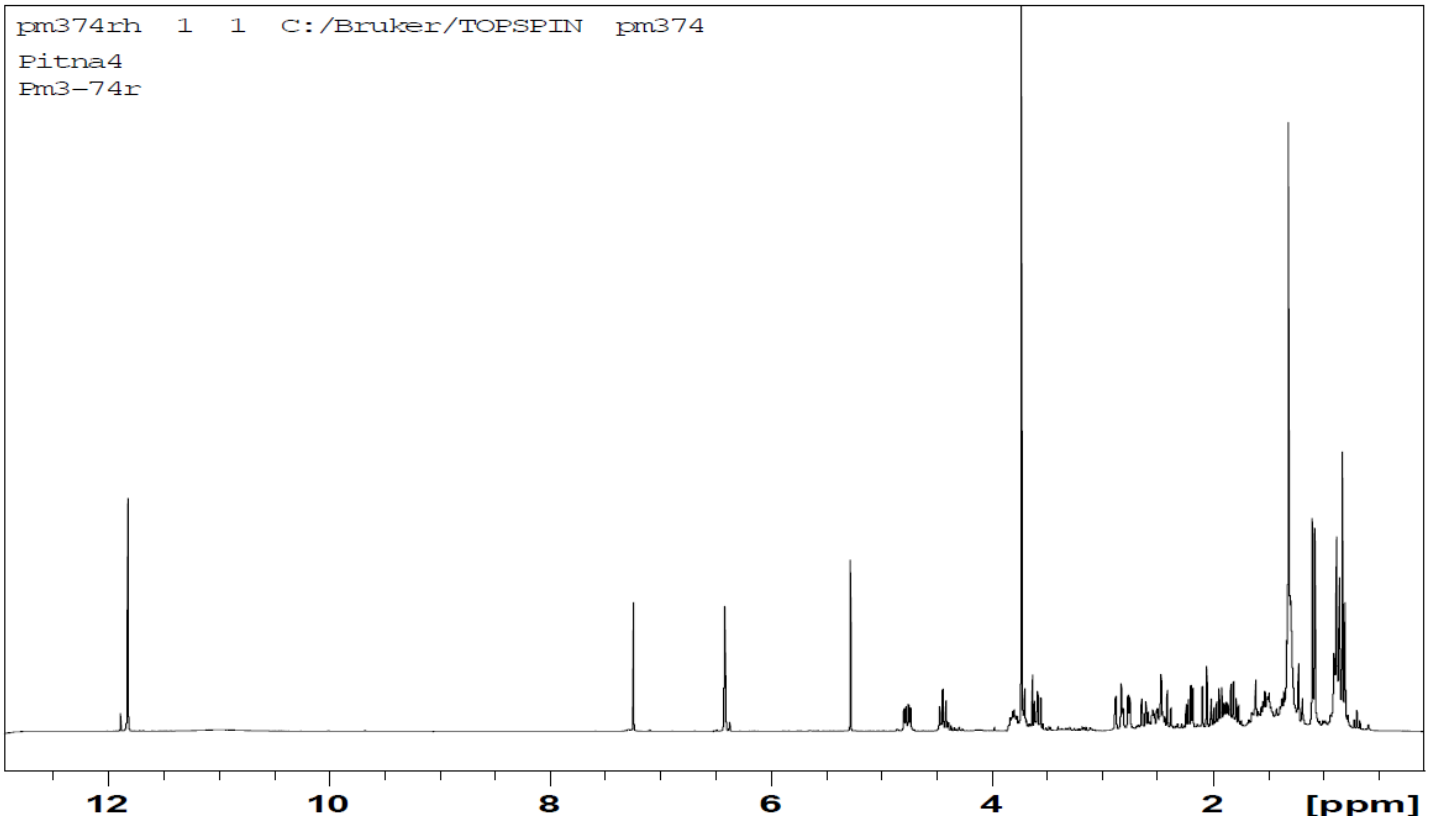


Figure 21: Comparison of ^{1}H NMR resonances (δ 0-13 ppm, $CDCl_3$ = 7.24 ppm) between natural (–)-berkelic acid[7] (top, contaminated with CH_2Cl_2) and synthetic (–)-berkelic acid (**2**, bottom).



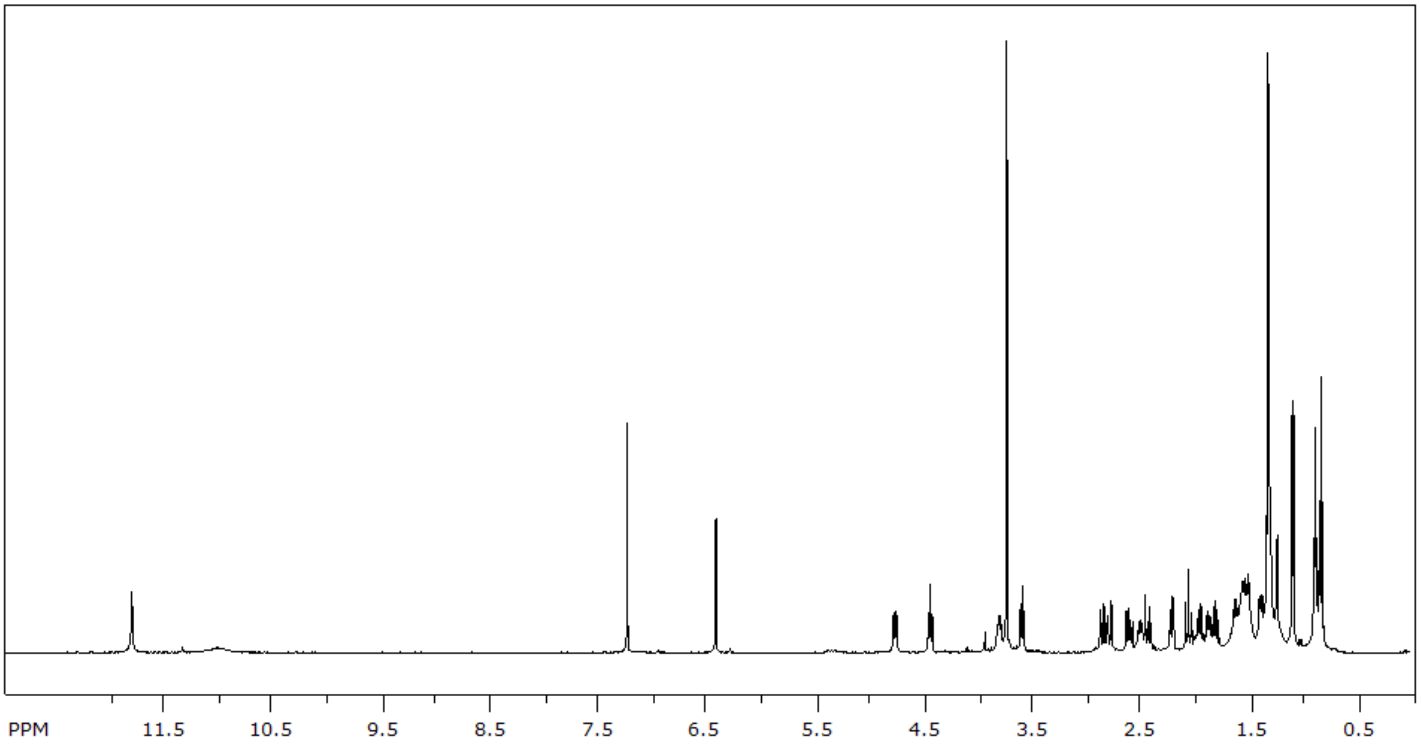
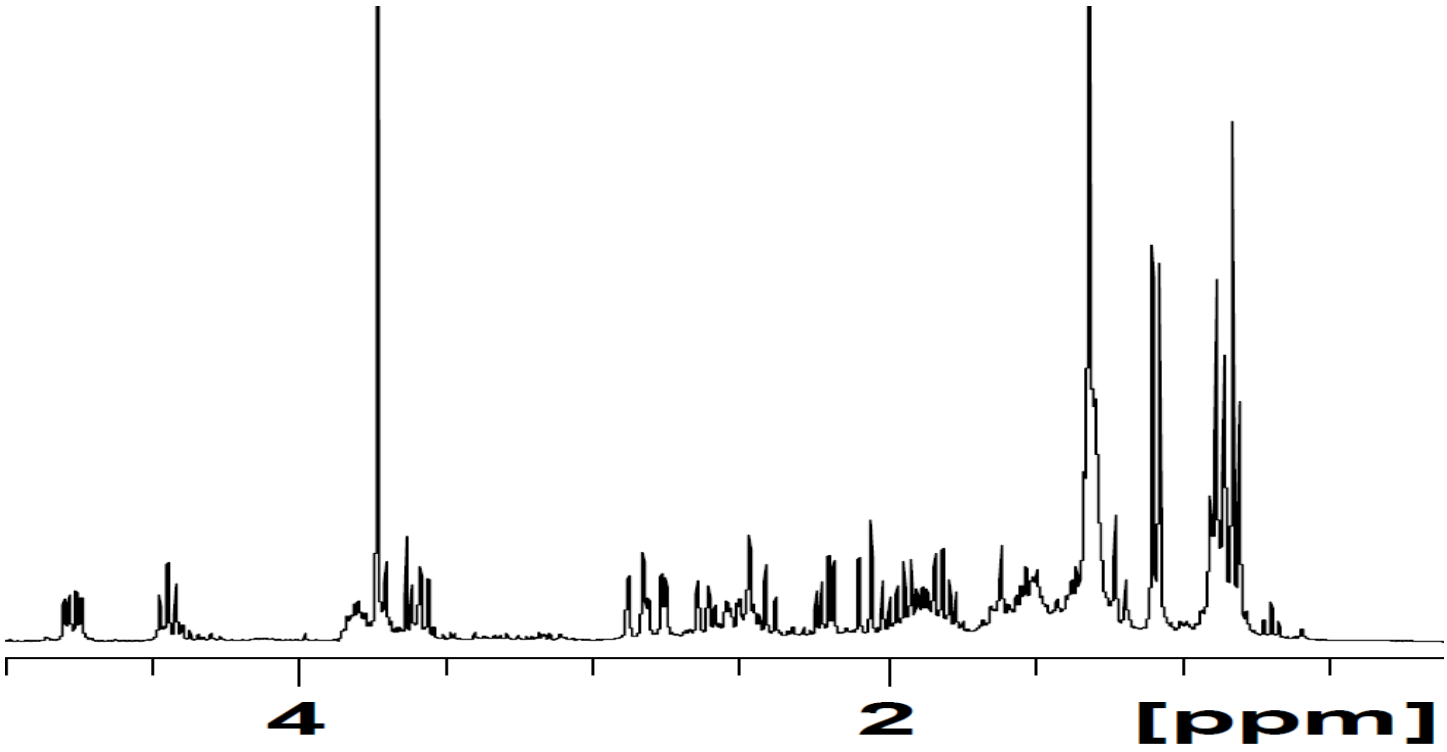


Figure 22: Comparison of ^{1}H NMR resonances (δ 0-5 ppm, $CDCl_3$ = 7.24 ppm) between natural (–)-berkelic acid[7] (top) and synthetic (–)-berkelic acid (**2**, bottom).



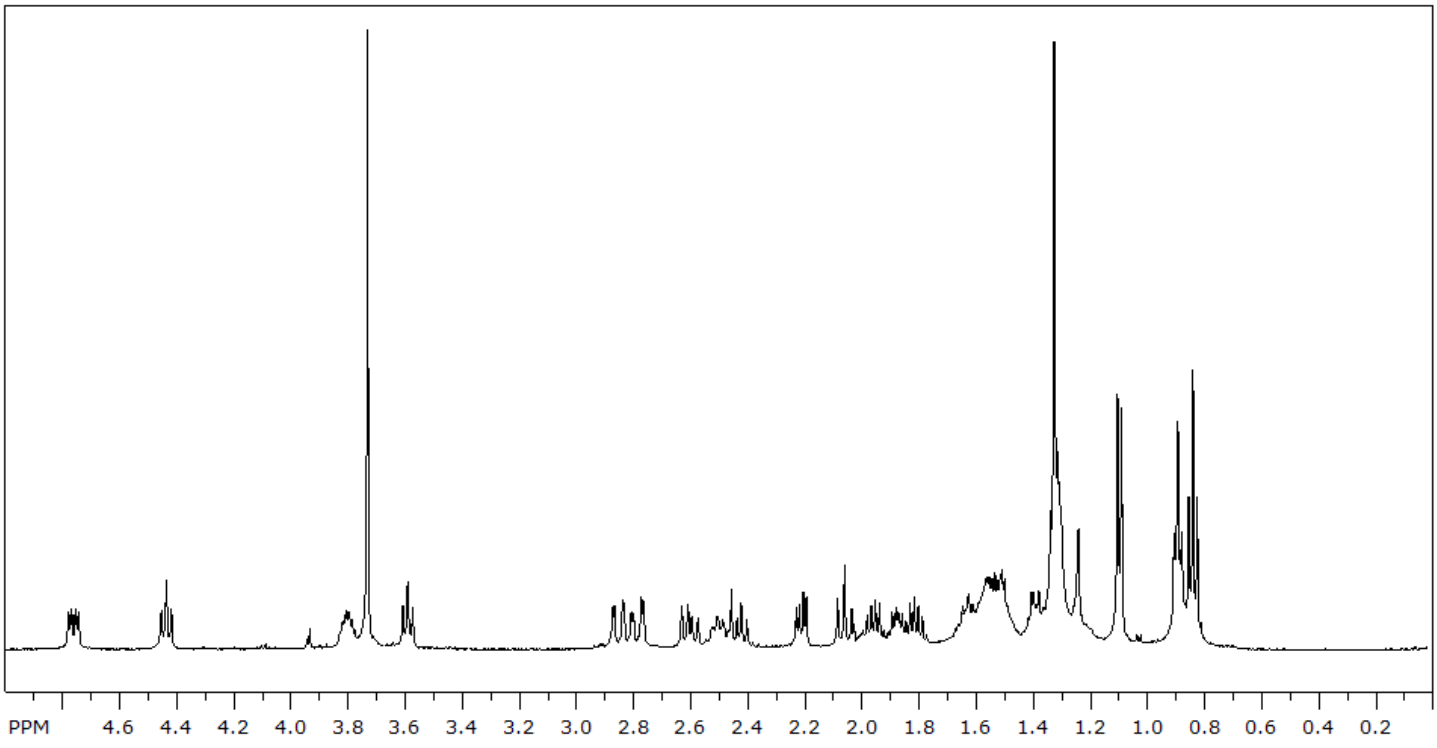


Figure 23: $^{13}C\{^{1}H\}$ NMR spectrum of synthetic berkelic acid (**2**, $CDCl_3$ δ 77.00 ppm).

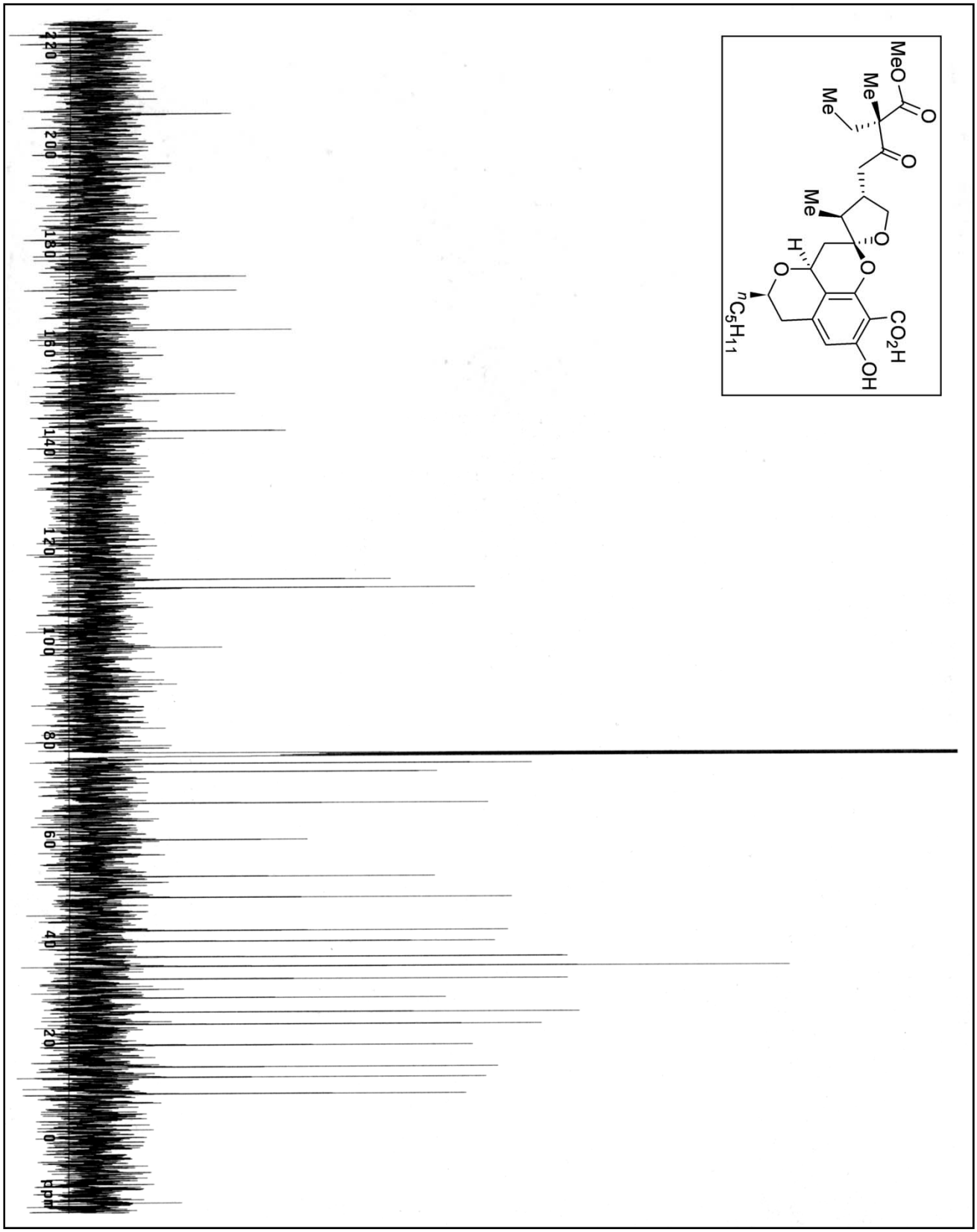


Figure 24: ^{1}H-^{1}H gCOSY spectrum of synthetic berkelic acid (**2**, $CDCl_3$ δ7.24 ppm).

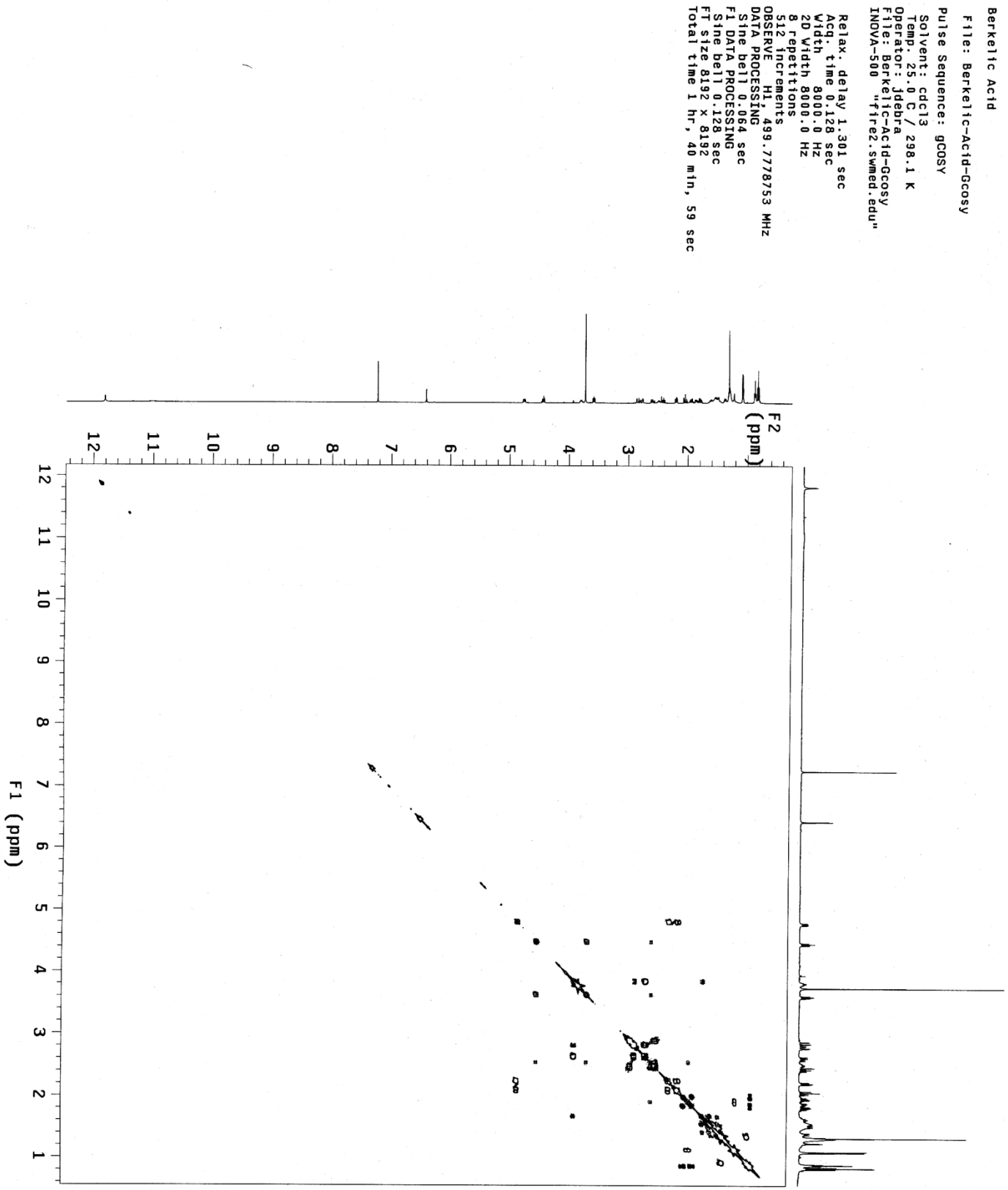


Figure 25: Expanded ^{1}H-^{1}H gCOSY spectrum of synthetic berkelic acid (**2**, $CDCl_3$ δ7.24 ppm).

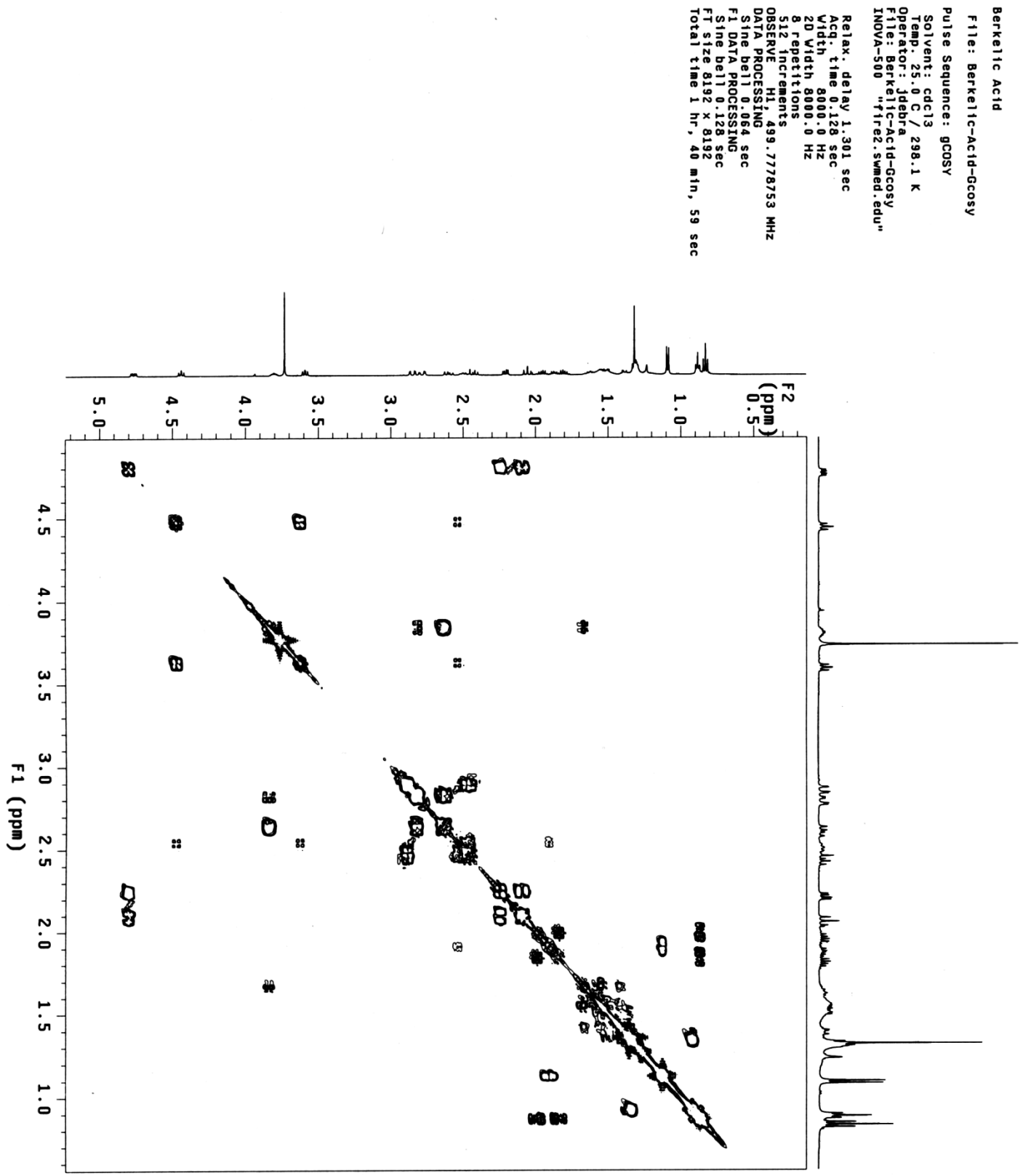


Figure 26: ^{1}H-^{13}C gHSQC spectrum of synthetic berkelic acid (**2**, $CDCl_3$ δ7.24 ppm, 77.0 ppm).

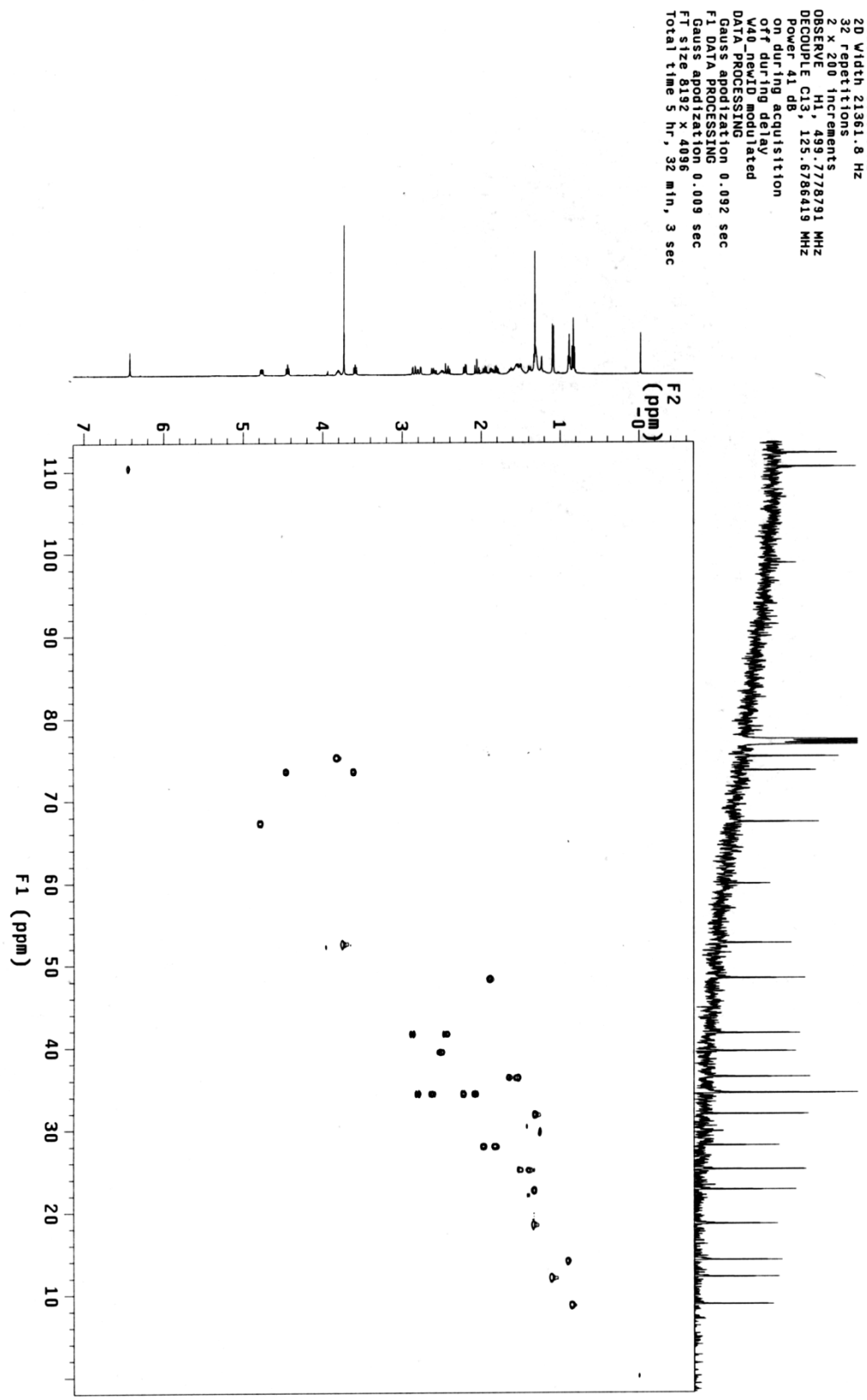


Figure 27: ^{1}H-^{13}C gHMBC spectrum of synthetic berkelic acid (**2**, $CDCl_3$ δ 7.24 ppm, 77.0 ppm).

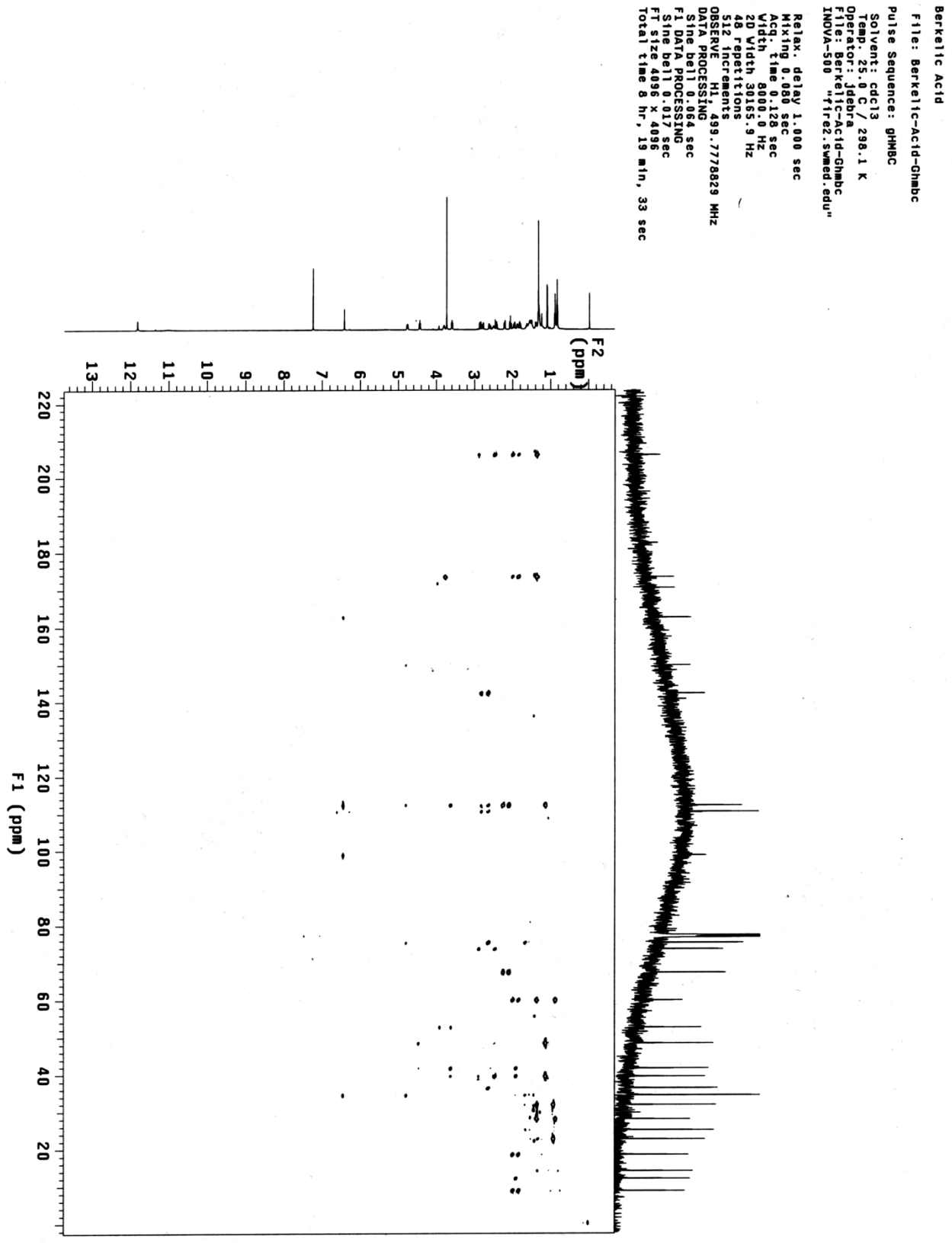


Figure 28: ^{1}H NMR spectrum of C22-(*R*)-berkelic acid (**27**, $CDCl_3$ δ7.24 ppm).

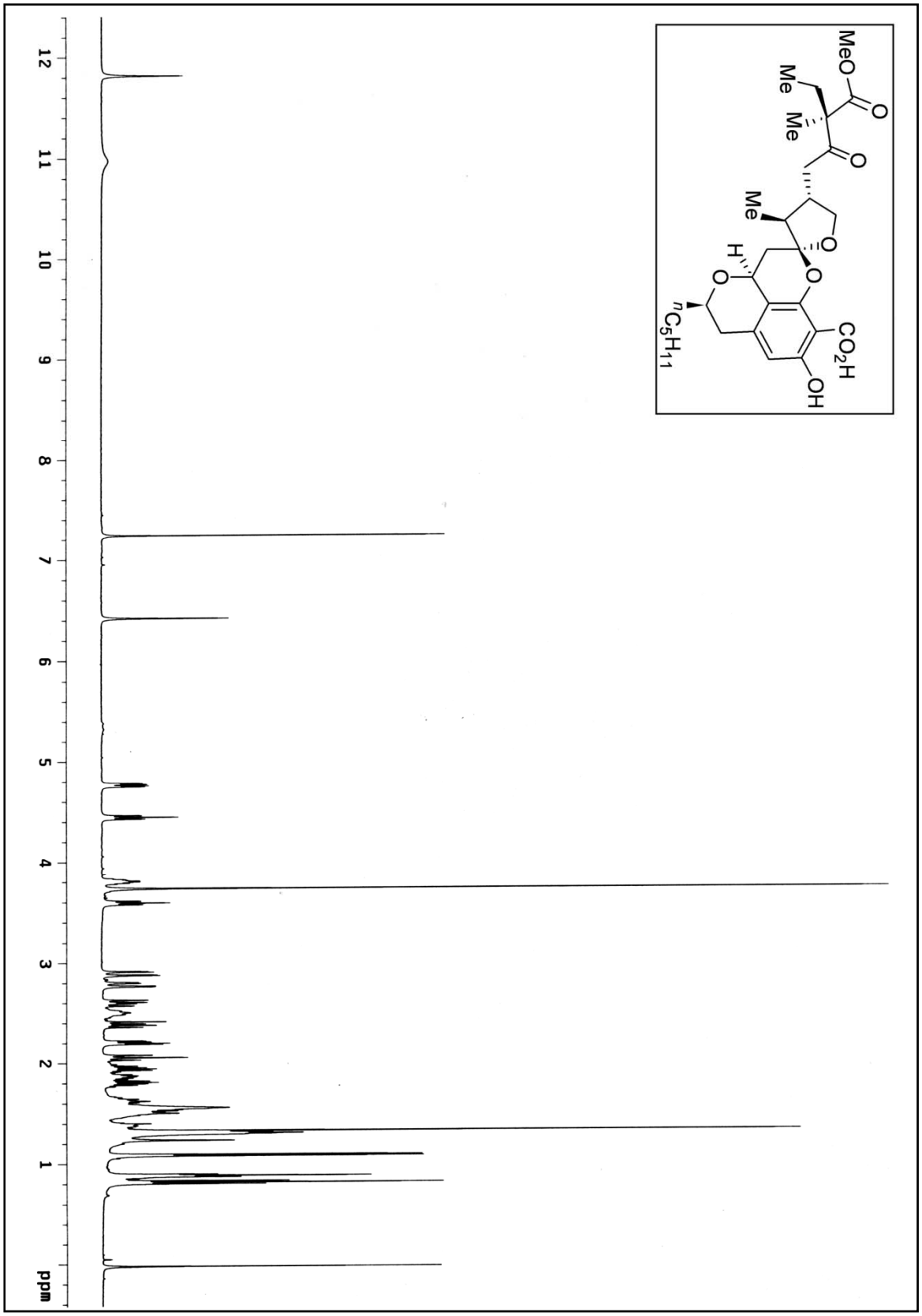


Figure 29: $^{13}C\{^{1}H\}$ NMR spectrum of C22-(*R*)-berkelic acid (**27**, $CDCl_3$ δ 77.00 ppm).

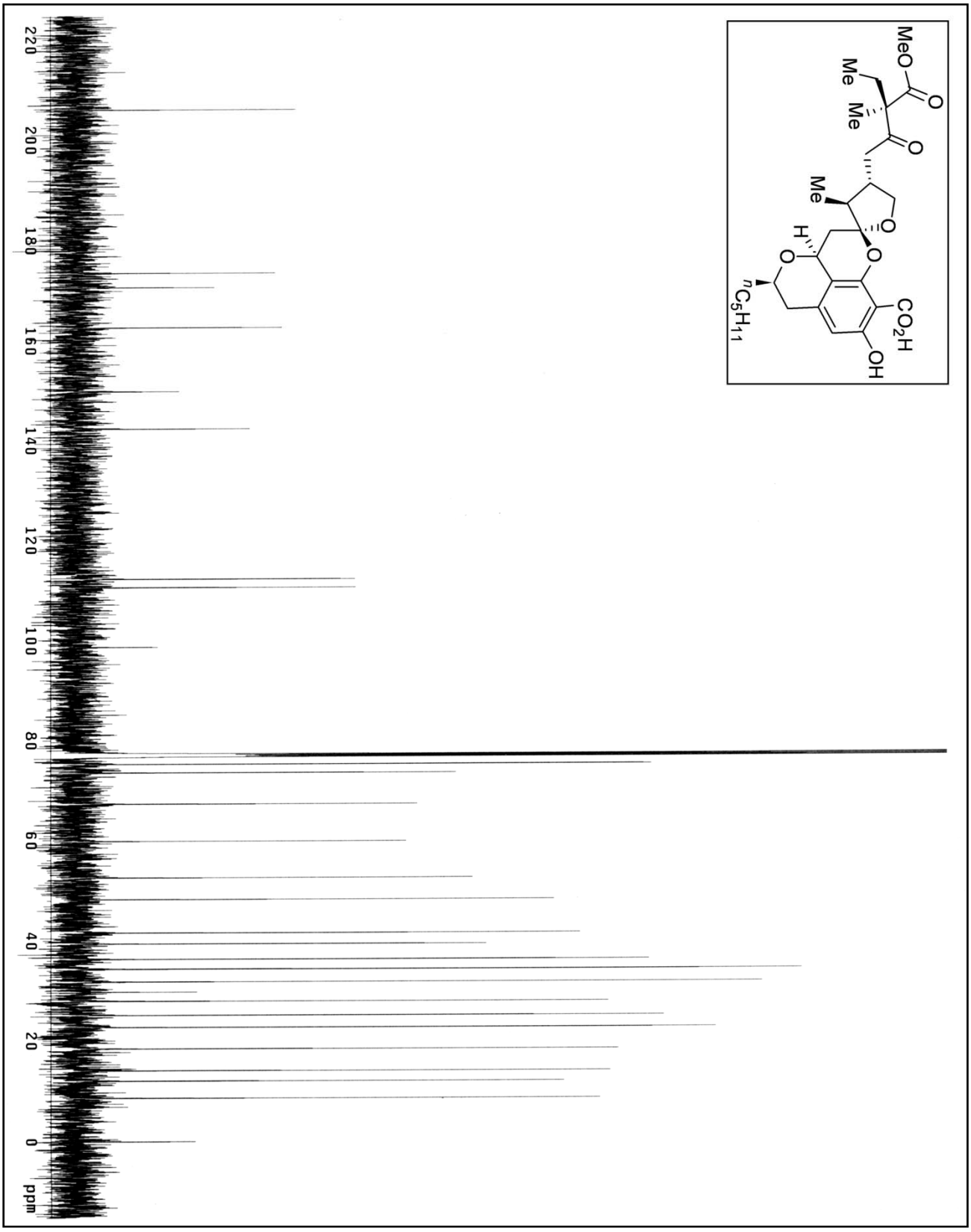


Figure 30: ^{1}H-^{1}H gCOSY spectrum of C22-(*R*)-berkelic acid (**27**, $CDCl_3$ δ 7.24 ppm).

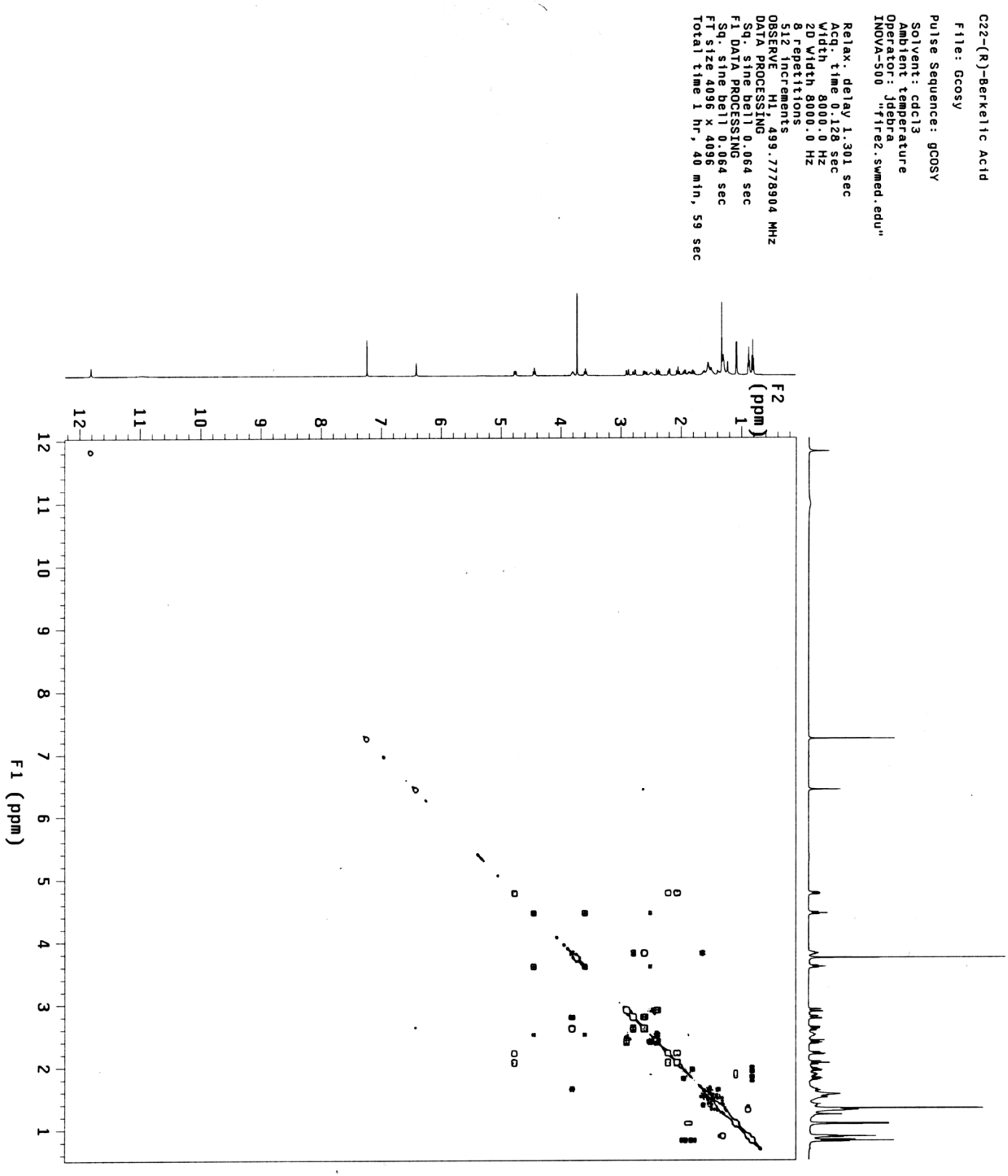


Figure 31: Expanded ^{1}H-^{1}H gCOSY spectrum of C22-(*R*)-berkelic acid (**27**, $CDCl_3$ δ 7.24 ppm).

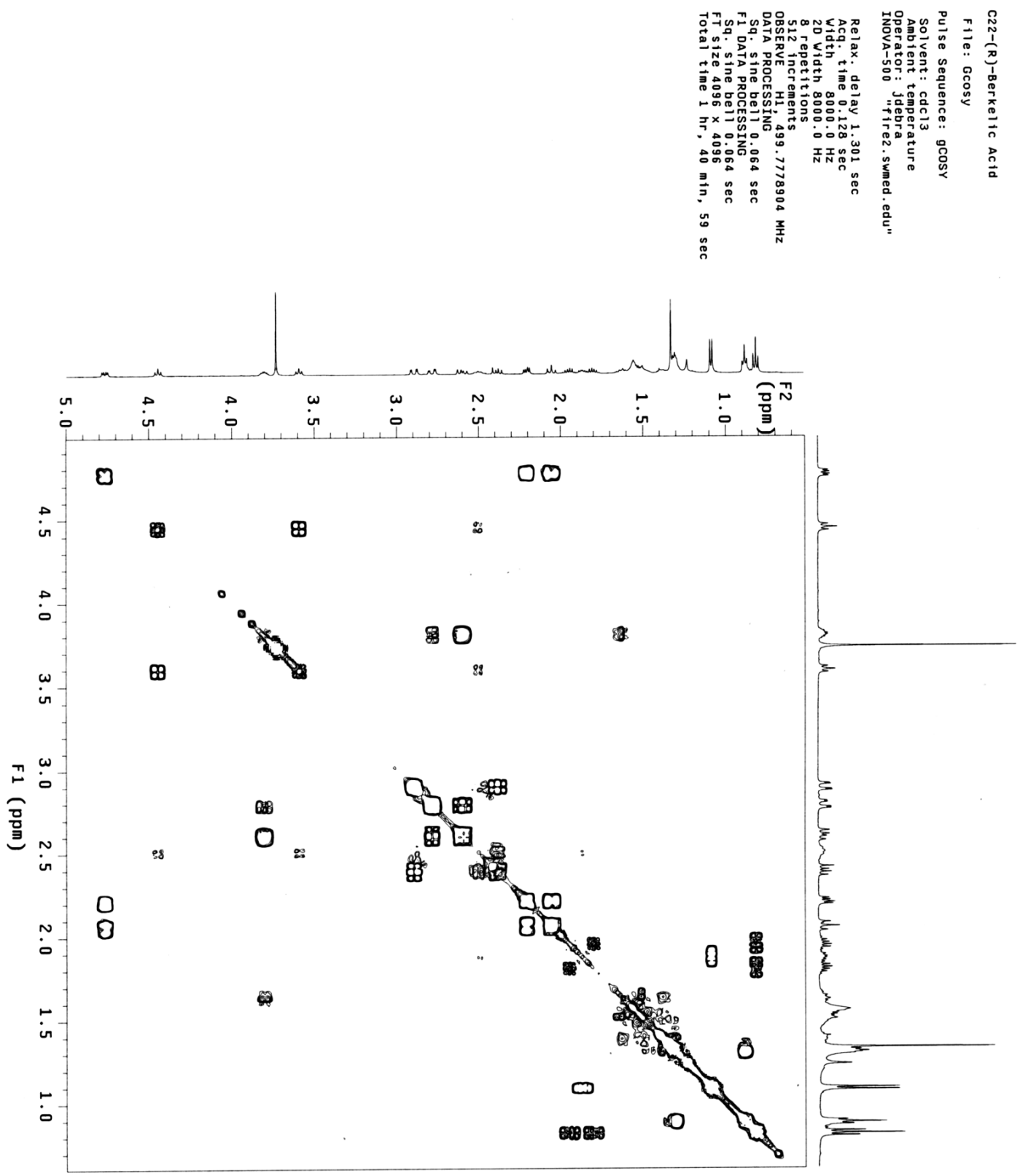


Figure 32: ^{1}H-^{13}C gHSQC spectrum of C22-(*R*)-berkelic acid (**27**, $CDCl_3$ δ 7.24 ppm, 77.0 ppm).

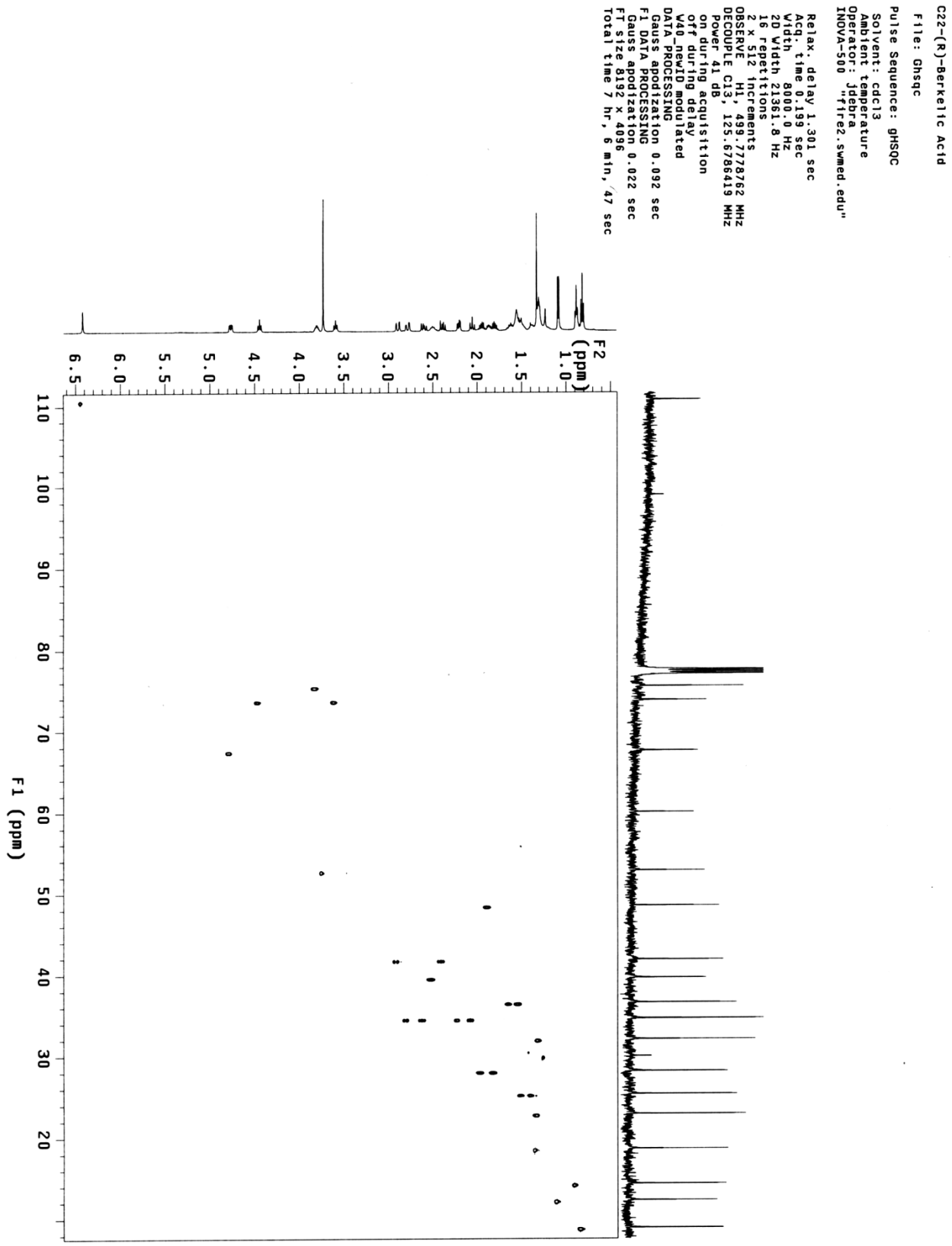


Figure 33: ^{1}H-^{13}C gHMBC spectrum of C22-(*R*)-berkelic acid (**27**, $CDCl_3$ δ 7.24 ppm, 77.0 ppm).

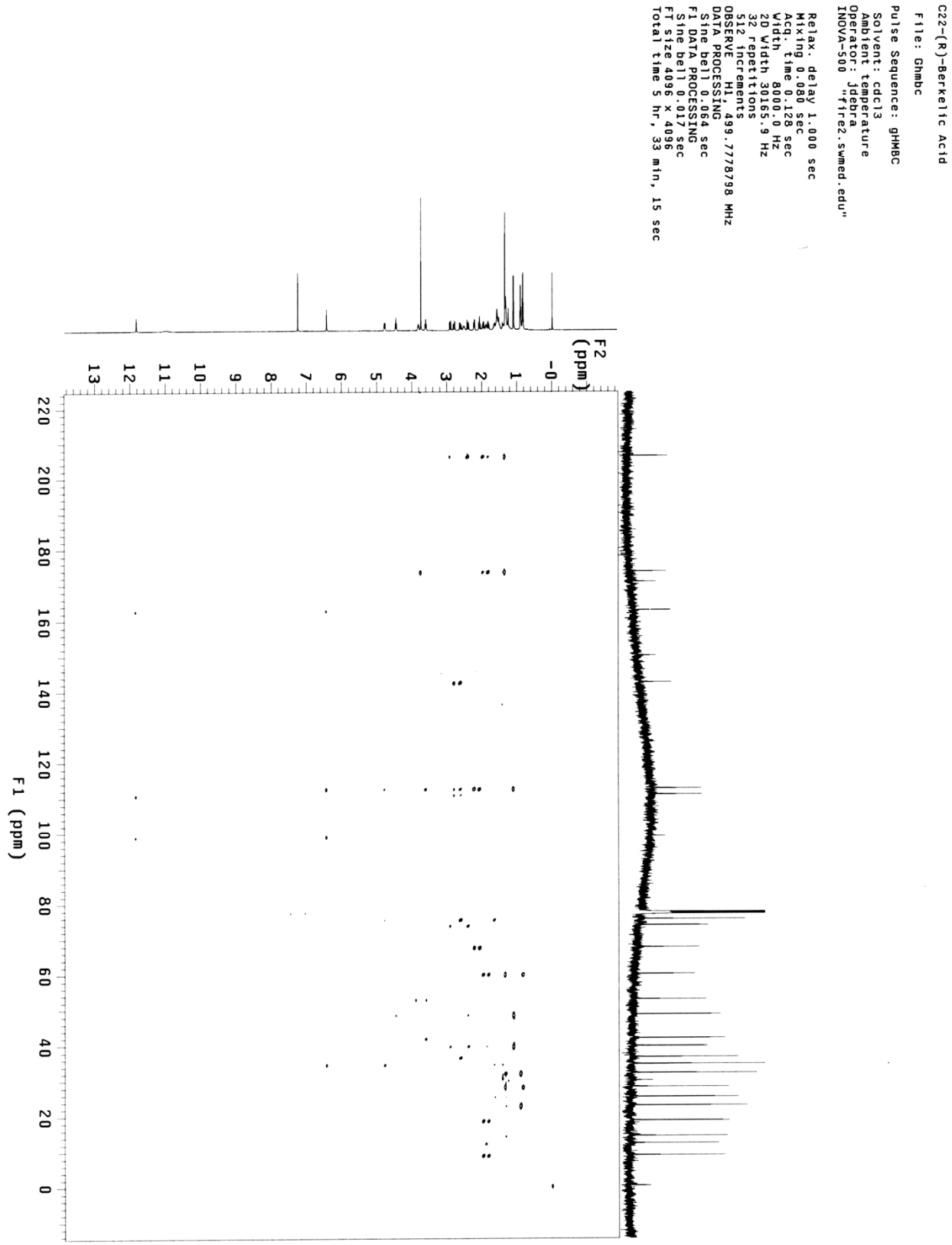
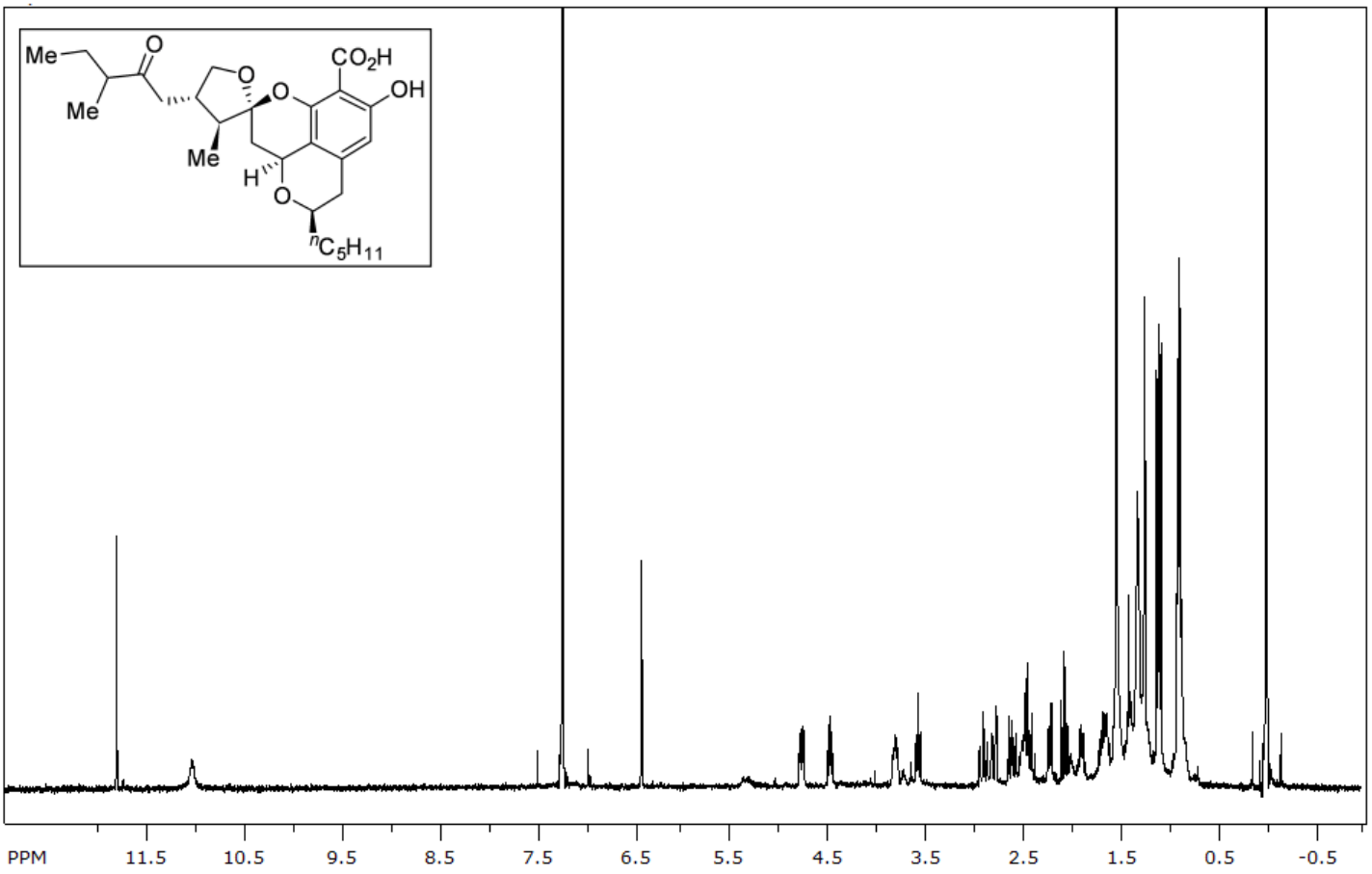


Figure 34: ^{1}H NMR spectrum of **28** (2 diastereomers).



7. References

1 – Ando, K.; Takemasa, Y.; Tomioka, K.; Koga, K. *Tetrahedron* **1993**, *49*, 1579-88.

2 – Marshall, J. A.; Schaaf, G. M. *J. Org. Chem.* **2003**, *68*, 7428-32.

3 – Furuta, K.; Ishiguro, M.; Haruta, R.; Ikeda, N.; Yamamoto, H. *Bull Chem. Soc. Jpn.* **1984**, *57*, 2768-76.

4 – Molander, G. A.; Bernardi, C. R. *J. Org. Chem.* **2002**, *67*, 8424-9.

5 – Bullimore, B. K.; McOmie, J. F. W.; Turner, A. B.; Galbraith, M. N.; Whalley, W. B. *J. Chem. Soc. C: Org.* **1967**, 1289-93.

6 – Buchgraber, P; Ph.D. thesis, Universität Dortmund; Dortmund, Germany, **2008**.

7 – Steirle, A. A.; Stierle, D. B.; Kelley, K. *J. Org. Chem*. **2006**, *71*, 5357-60.

8 – Wu, X.; Zhou, J.; Snider, B. A. *Ang. Chem. Int. Ed.* **2009**, *48*, 1283-6.