Synthesis of new dicinnamoyl 4-deoxy quinic acid and methyl ester derivatives and evaluation of the toxicity against the pea aphid *Acyrthosiphon pisum*

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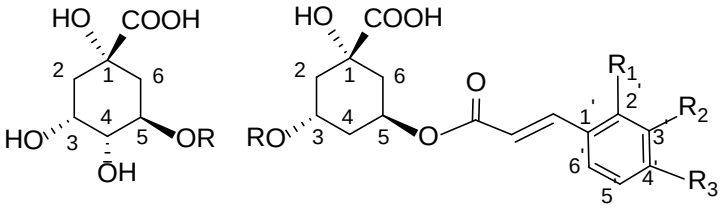
General

Reagents and solvents were supplied by Aldrich, Acros, Lancaster, Alfa Aesar, Fluka or TCI and purchased at the highest commercial quality to be used without further purification. NMR spectra were recorded on a Bruker 300 (^{1}H: 300 MHz; ^{13}C: 75 MHz), Bruker 400 (^{1}H: 400 MHz; ^{13}C: 100 MHz), or Bruker 500 (^{1}H: 500 MHz; ^{13}C: 125 MHz) spectrometers, at 295-298K, using $CDCl_3$ and CD_3OD as solvents. The chemical shifts (δ ppm) are referenced to the solvent residual peak and coupling constants (Hz) are reported in the standard fashion. The following abbreviations are used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, quint. = quintuplet, sext. = sextuplet, hept. = heptuplet, m = multiplet, br = broad. Electrospray ionization (ESI) mass spectrometry (MS) experiments were performed on a Thermo Finnigan LCQ Advantage mass. High-resolution mass spectra (HRMS) were recorded on a Finnigan Mat 95xL mass spectrometer using electrospray. Analytical thin-layer chromatography was carried out on silica gel Merck 60 D254 (0.25 mm). Flash chromatography was performed on Merck Si 60 silica gel (40–63 μm). Infra-red (IR) spectra were recorded with a IRAffinity-1 Shimadzu spectrometer using Attenuated Total Reflectance (ATRMiracle), and the wavenumbers are expressed in cm^{-1}. Optical rotations were measured on a Perkin Elmer 241 or Jasco P1010 polarimeter with a 10 cm cell (concentration c expressed as g/100 mL). Melting points were measured using Büchi apparatus B-540. Preparative HPLC was performed on Agilent equipment with a column Phenomenex C18: Jupiter® 5μm; 300 Å, LC Column 250 x 4.6mm, flow 1ml/min; Mobile phase 0 - 2min: 80% H_2O UHQ + TFA (A) / 20% CH_3CN + TFA (B); 22min: 40 % A / 60% B; 30min: 100% B; 33min: 80% A/ 20% B. Samples were dissolved in MeOH (6mL) and 10μg were injected per sample.

All data for chlorogenic acids or related derivatives presented in this paper use the recommended IUPAC numbering system.[1] The assignment of NMR signals has been made according to the numbering shown in the general structure in the figure below. As much as possible an unambiguous designation of the corresponding atoms of the lateral chains has been preferred to a numbering using numerous «'» character or secondary indexation.



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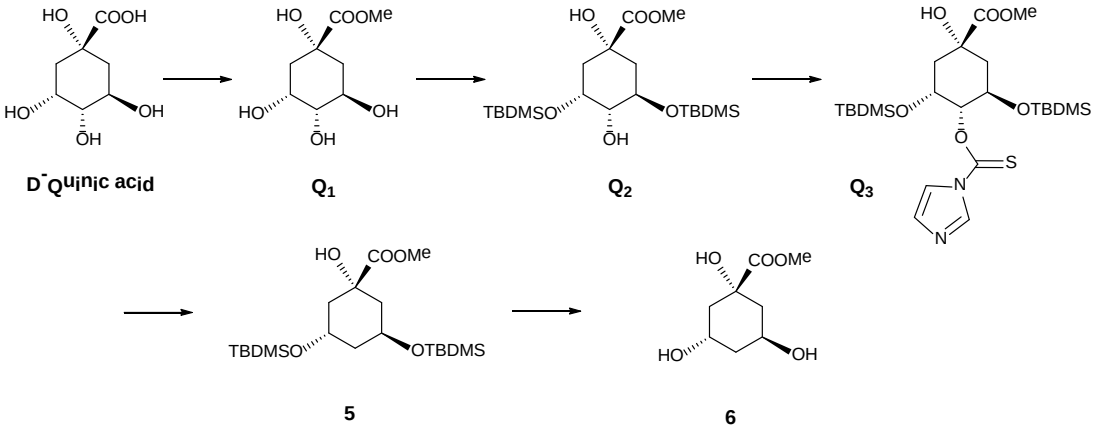
[1] IUPAC Nomenclature of cyclitols. *Biochem. J*. 1976 , **153** ,23-31.

Synthesis of compounds (4, 6, 9, 10, 11, 12)

Methyl (3S,5S)-1,3,5-trihydroxycyclohexanecarboxylate or methyl 4-deoxy quinate 6



Methyl (1S,3R,4S,5R)-1,3,4,5-tetrahydroxycyclohexanecarboxylate Q1[2]

Methyl (1S,3R,4S,5R)-1,4-dihydroxy-3,5-tert-butyldimethylsilyloxyclohexanecarboxylate Q2[3]

Methyl (1S,3R,4S,5R)-1-hydroxy-4-[(1H-imidazol-1-ylcarbothioyl)oxy]-3,5-tert-butyldimethylsilyloxy cyclohexanecarboxylate Q3[4]

Q1, Q2, Q3 were prepared according reported procedures.

The disilylated compound **5**[5] (106.7 mg, 0.25 mmol) was stirred in MeOH (2mL) with Amberlyst®A15 (H^+ form) at room temperature for 24h. After filtration and evaporation, the crude product was purified by flash chromatography (pentane/ethyl acetate 50/50 then ethyl acetate/methanol 90/10) to provide **6** (colorless oil then white solid on standing, 42.7 mg, 89%). $[\alpha]_D^{25}$ - 3.7 (*c* 1.06, CH_3OH); IR(ATR) 3350, 2951, 2930, 2855, 1173, 1730, 1661, 1435, 1371, 1281, 1240, 1134, 1057, 1016 cm^{-1}; ^1H NMR (400 MHz, 296K, CD_3OD) δ (ppm) = 4.24-4.16 (m, 2H, H_3 and H_5), 3.73 (s, 3H, OMe), 2.08 (dd, 1H, ^2J 13.8 Hz, $^3J_{H_5/H_6}$ 3.3 Hz, H_6 or H_2), 2.00 (m, 2H, H_2 or H_6 and H_4), 1.88 (dd, 1H, ^2J 12.8 Hz, ^3J 9.1 Hz, H_2 or H_6), 1.77 (dd, 1H, ^2J 13.8 Hz, ^3J 4.8 Hz, H_6 or H_2), 1.60 (ddd, 1H, ^2J 12.7 Hz, $^3J_{H_{4a}/H_{5a\ ou\ 3a}}$ 9.2 Hz, $^3J_{H_{4a}/H_{3e\ ou\ H5e}}$ 3.0 Hz, H_{4a}); ^{13}C NMR (CD_3OD, 295K, 100MHz) δ (ppm) 176.1 (COOMe), 76.8 (C_1), 67.8 (C_5 or C_3), 64.0 (C_3 or C_5), 52.8 (OMe), 43.8 (C_2 or C_6), 42.0 (C_4), 40.3 (C_6 or C_2).

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[2] M. Frank and R. Miethchen, *Carbohydr. Res.* 1998, ***313***, 49-53

[3] L. Sanchez-Abella, S. Fernandez, N. Armesto, M. Ferrero and V. Gotor, *J. Org. Chem.* 2006, ***71***, 5396-5399.

[4] D. Oves, M. Diaz, S. Fernandez, M. Ferrero and V. Gotor, *Synth. Commun.*, 2001, **31**, 2335.

[5] K. L. Perlman, R. E. Swenson, H. E. Paaren, H. K. Schnoes and H. F. Deluca, *Tetrahedron Lett.*, 1991, **32**, 7663.

MS-ESI m/z $[M+Na]^+$ 213.1; HRMS-ESI m/z $[M+Na]^+$ calcd for $C_8H_{14}NaO_5$ 213.0733; found 213.0733.

General procedure for the synthesis of homodiesters of deoxy methyl quinate 9

Procedure A :

To a solution of triol **6** in DMF / pyridine (v/v 3/2, c = 0.4M) under nitrogen was added the protected cinnamoyl chloride (3 equiv.) The mixture was stirred at 45°C until completion, in general after 1h. Methanol was added and after 15min under stirring, the resulting mixture was concentrated, diluted with EtOAc, washed with 1M HCl then with a saturated $NaHCO_3$ solution then with brine. The organic layer was dried over Na_2SO_4, concentrated and purified by flash chromatography on silica using the appropriate eluent.

Procedure B :

To a solution of triol **6** in DMF / pyridine (v/v 3/2, c = 0.4M) under nitrogen was added the protected cinnamoyl chloride (3 equiv.) The mixture was stirred at 0°C until completion, in general after 4h. Methanol was added and after 15min under stirring, the resulting mixture was concentrated, diluted with EtOAc, washed with 1M HCl then with a saturated $NaHCO_3$ solution then with brine. The organic layer was dried over Na_2SO_4, concentrated and purified by flash chromatography on silica using the appropriate eluent.

Procedure C :

To a solution of triol **6** in dichloromethane / pyridine (v/v 5/1, c = 0.1M) under nitrogen was added the protected cinnamoyl chloride (3 equiv.) and DMAP (20 mol%). The mixture was stirred at -18°C to room temperature until completion, in general after 4h. Methanol was added and after 15min under stirring, the resulting mixture was concentrated, diluted with EtOAc, washed with 1M HCl then with a saturated $NaHCO_3$ solution then with brine. The organic layer was dried over Na_2SO_4, concentrated and purified by flash chromatography on silica using the appropriate eluent.

Methyl (3S,5S) 1-hydroxy-3,5 bis[[(2E)-3-(3,4-diacetoxyphenyl)-1-oxo-2-propen-1-yl]oxy]cyclohexanecarboxylate 9a

Synthesized according to the general procedure B using diacetylated caffeoyl chloride[6] and methyl 4-deoxy quinate **6** (105 mg, 0.553 mmol). **9a** was obtained as a white solid (348 mg, yield: 92%) after purification by flash chromatography on silica using DCM/Et_2O 12/1 to 6/1.

$[\alpha]_D^{25}$ = -46.9 (c 1.215, CH_2Cl_2) ; m.p. = 92.8-94.1°C (CH_2Cl_2); IR(ATR) 2943, 2832, 1775, 1742, 1713, 1639, 1504, 1449, 1427, 1371, 1321, 1242, 1205, 1180, 1147, 1132, 1111, 1022 cm^{-1}; ^1H NMR ($CDCl_3$, 298K, 500MHz) δ (ppm) = 7.63 and 7.58 (2d, 2H, ^3J 15.9 Hz, C<u>H</u>=CHCO), 7.39 and 7.38 (2dd, 2H, J_{ortho} 8.4Hz, J_{meta} 1.9 Hz, 2x$H_{6'}$), 7.35 and 7.34 (2d, 2H, J_{meta} 1.9 Hz, 2x$H_{2'}$), 7.20 (d, 2H, J_{ortho} 8.4 Hz, 2x$H_{5'}$), 6.40 and 6.32 (2d, 2H, ^3J 15.9 Hz, CH=C<u>H</u>CO), 5.51 (ddd, 1H, ^2J 13.8 Hz, ^3J 9.8

6 M. Sefkow, Eur. J. Org. Chem. 2001, 1137-1141.

Hz, ^3J 3.9 Hz, $H_{3\ ou\ 5ax}$), 5.46 (ddd, 1H, ^3J 7.8 Hz, ^3J 3.9 Hz, $H_{3e\ ou\ 5e}$), 3.76 (s, 1H, OH_1), 3.74 (s, 3H, COOMe), 2.28, 2.271 and 2.268 (3s, 12H, $OCOCH_3$), 2.32 (m, 1H, H_4), 2.23-2.18 (m, 2H, H_2 and H_6), 2.08-2.00 (m, 2H, H_2 and H_6), 1.87 (ddd, 1H, ^2J 13.6 Hz, ^3J 10.3 Hz, ^3J 3.45 Hz, H_{4a}); ^{13}C NMR ($CDCl_3$, 298K, 125 MHz) δ (ppm) = 175.0, 168.1(2) and 168.0(2) ($4xOCOCH_3$), 165.8 and 165.5 (2xCOO), 143.59 and 143.57 (C_q), 143.3 and 143.2 (CH=CHCO) , 142.5 and 142.4 (C_q), 133.2 and 133.1(C_q), 126.5 and 126.4 ($C_{6'}$), 124.0 and 123.9 ($C_{5'}$), 122.9 and 122.8 ($C_{2'}$), 119.4 and 119.2 (CH=CHCO), 74.7 (C_1) , 68.9 (C_3 ou C_5), 66.9 (C_5 ou C_3), 53.1 (OMe), 39.7 (C_2 ou C_6), 36.7 (C_2 ou C_6), 35.0 (C_4), 20.7(2), 20.62 and 20.60 (4x $OCOCH_3$); HRMS-ESI m/z $[M+Na]^+$ calcd for $C_{34}H_{34}NaO_{15}$ 705.1790; found 705.1780.

Methyl (3S,5S) 1-hydroxy-3,5 bis[[(2E)-3-(3,4-di-(prop-2-en-1-yloxy)phenyl)-1-oxo-2-propen-1-yl]oxy]cyclohexanecarboxylate 9b

Synthesized according to the general procedure A using diallylated caffeoyl chloride.[7]. and **6 (**102 mg, 0.537 mmol) Purification by flash chromatography on silica using petroleum ether/EtOAc 50/50, providing the triester (51mg, 10%) and diester **9b** (214 mg, 59%) as white solids.

$[\alpha]_D^{25}$ - 140.8 (*c* 0.86, CH_2Cl_2); $[\alpha]_D^{23}$m.p. 89-91°C; IR(ATR) 2922, 2827, 1706, 1631, 1597, 1510, 1456, 1423, 1362, 1335, 1304, 1246, 1223, 1165, 1134, 1090, 1067 cm^{-1}; ^{1}H NMR ($CDCl_3$, 298K, 300MHz) δ (ppm) = 7.63 and 7.58 (2d, 2H, ^3J 15.9 Hz, CH=CHCO), 7.08 (m, 4H, CH_{Ar}), 6.87 (m, 2H, CH_{Ar}), 6.31 and 6.23 (2d, 2H, ^3J 15.9 Hz, CH=CHCO), 6.07 (m, 4H,CH_2=CHCH$_2$O), 5.60-5.50 (m, 2H, H_3 and H_5), 5.42-5.39 (m, 2H, CH_2anti=CHCH$_2$O), 5.30 (m, 4H, CH_2syn =CHCH$_2$O), 4.64 (m, 8H, CH_2=CHCH_2O), 2.32 (m, 1H, H_2 or H_4 or H_6), 2.24-2.02 (m, 4H, H_2 or H_4 or H_6), 1.86 (ddd, 1H, *J* 13.7 Hz, *J* 10.4 Hz, *J* 3.4 Hz, H_2 or H_4 or H_6); ^{13}C NMR ($CDCl_3$, 296K, 75 MHz) δ (ppm) = 175.1 (COOMe), 166.5 and 166.3 (OCO), 150.8 ($2xC_q$), 148.7 ($2xC_q$), 145.4 and 145.1(CH=CHCO), 133.2 133.1, 133.05 and 133.01 ($4xCH_2$=CHCH$_2$O), 127.64, 127.57 (2xCq), 123.2 and 122.9 (2xCHAr), 118.15, 118.11, 118.1, 118.07 (4xCH_2=CHCH$_2$O), 115.88 and 115.84 (CH=CHCO), 113.50, 113.44, 112.7 and 112.5 ($4xCH_{Ar}$), 75.0 (C_1), 70.1, 70.0, and 69.8(2) ($4xCH_2$=CHCH$_2$O), 68.8 and 66.6 (C_3 and C_5), 53.2(OMe), 40.0, 36.9 and 35.2 (C_2, C_4 and C_6); HRMS-ESI m/z $[M+Na]^+$ calcd for $C_{38}H_{42}NaO_{11}$ 697.2619; found 697.2615.

Methyl (3S,5S) 1-hydroxy-3,5 bis[[(2E)-3-(3-acetoxy,4-methoxyphenyl)-1-oxo-2-propen-1-yl]oxy]cyclohexanecarboxylate 9c

Synthesized according to the general procedure C using acetylated feruloyl chloride and methyl 4-deoxy quinate **6** (117 mg, 0.616 mmol). **9c** was obtained as a white solid (266 mg, yield: 69%) after purification by flash chromatography on silica using DCM/Et_2O 10/1.

$[\alpha]_D^{25}$ = - 74.5 (c 1.05, CH_2Cl_2); $[\alpha]_D^{23}$m.p. 90-92°C; IR(ATR) 1765, 1709, 1638, 1508, 1464, 1418, 1369, 1298, 1263, 1215, 1198, 1153, 1123, 1033, 1011 cm^{-1}; ^{1}H NMR ($CDCl_3$, 296K, 300MHz) δ (ppm) = 7.65 and 7.60 (2d, 2H, ^3J 15.9 Hz, CH=CHCO), 7.12-7.02 (m, 6H, CH_{Ar}), 6.41 and 6.33 (2d, 2H, ^3J 15.9 Hz, CH=CHCO), 5.55 and 5.49 (2m, ^3J 9.3 Hz, ^3J 3.3 Hz, H_5 and H_3), 3.85 and 3.84 (2s, 2x3H, 2xOMe), 3.76 (s, 3H, COOMe), 2.30(s, 6H, 2xOAc), 2.28 (m, 1H, H_{4e}), 2.22-2.18 and 2.11-

7 Jaiswal, R.; Dickman, M. H.; Kuhnert, N. *Org. Biomol. Chem.* 2012, **10**, 5266-5277

2.04(m, 2x2H, 2xH_6 and 2xH_2), 1.88 (ddd, 1H, ^2J 13.6 Hz, ^3J 10.4 Hz, ^3J 3.4 Hz, H_4); ^{13}C NMR ($CDCl_3$, 295K, 100 MHz) δ (ppm) = 175.0 (COOMe), 168.8 (2xO<u>C</u>OCH$_3$), 166.1 and 165.8 (COO), 151.4 (2xC_q), 144.6 and 144.4 (<u>C</u>H=CHCO), 141.54 and 141.51 (C_q), 133.34 and 133.30 (C_q), 123.33 and 123.25(CHAr), 121.6 and 121.3 (CHAr), 118.3 and 118.2 (CH=<u>C</u>HCO), 111.3 and 111.1 (CH_{Ar}), 74.8 (C_1), 68.9 (C_3 or C_5), 66.8 (C_5 or C_3), 56.0(2xOMe), 53.1 (COO<u>Me</u>), 39.8 and 36.8 (C_6 and C_2), 35.1 (C_4), 20.7 (2xOCO<u>C</u>H$_3$); HRMS-ESI m/z [M+Na]$^+$ calcd for $C_{32}H_{34}NaO_{13}$ 649 649.1892; found 649.1865.

Methyl (3S,5S) 1-hydroxy-3,5 bis[[(2E)-3-(4-acetoxyphenyl)-1-oxo-2-propen-1-yl]oxy]cyclohexanecarboxylate 9d

Synthesized according to the general procedure A using acetylated *para*-coumaroyl chloride [8] and methyl 4-deoxy quinate **6** (58mg, 0.305 mmol). **9d** was obtained as a white solid (142 mg, yield: 82%) after purification by flash chromatography on silica using DCM/Et_2O 10/1.$[\alpha]_D^{25}$ -79.4 (*c* 0.83, CH_2Cl_2); m.p. 86-88°C; IR(ATR) 1765, 1736, 1709, 1638, 1601, 1506, 1418, 1369, 1312, 1265, 1202, 1163, 1140, 1086, 1063, 1011 cm^{-1};^{1}H NMR ($CDCl_3$, 295K, 400MHz) δ (ppm) = 7.67 and 7.62 (2d, 2H, ^3J 16.0 Hz, C<u>H</u>=CHCO), 7.52 and 7.50 (2d, 4H, J_{ortho} 8.5 Hz, $H_{2'}$), 7.10 (2d, 4H, J_{ortho} 8.5 Hz, $H_{3'}$), 6.41 and 6.33 (2d, 2H, ^3J 16.0 Hz, CH=<u>C</u>HCO), 5.53 and 5.48 (2 m, 2H, ^3J 4.0 Hz, H_3 and H_5), 3.74 (s, 3H, COOMe), 2.27 (s, 6H, OAc), 2.24 (m, 1H, H_4), 2.23-2.19 (m, 2H, H_2 and H_6), 2.11-2.06 (m, 2H, H_2 and H_6), 1.88 (ddd, 1H, ^2J 13.0 Hz, ^3J 10.2 Hz, ^3J 3.5 Hz, H_4); ^{13}C NMR ($CDCl_3$, 295K, 100 MHz) δ (ppm) = 174.9 (<u>C</u>OOMe), 169.2 (2xO<u>C</u>OCH$_3$), 166.1 and 165.8 (COO), 152.2 and 152.1 (C_q), 144.1 and 144.0 (<u>C</u>H=CHCO), 132.1 and 132.0 (2xCH_{Ar}), 129.4 and 129.3 (2xCH_{Ar}), 122.2 and 122.1 (C_q), 118.3 and 118.1 (CH=<u>C</u>HCO), 74.7 (C_1), 68.8 and 66.8 (C_3 and C_5), 53.0 (OMe), 39.7 and 36.8 (C_2 and C_6) 35.0 (C_4) 21.1 (2xCH_3); HRMS-ESI m/z [M+Na]$^+$ calcd for $C_{30}H_{30}NaO_{11}$ 589.1680; found 589.1655.

Methyl (3S,5S) 1-hydroxy-3,5 bis[[(2E)-3-(2-acetoxyphenyl)-1-oxo-2-propen-1-yl]oxy]cyclohexanecarboxylate 9e

Synthesized according to the general procedure A using acetylated *ortho*-coumaroyl chloride and methyl 4-deoxy quinate **6** (82 mg, 0.432 mmol). Purification by flash chromatography (DCM/Et_2O 10/1) afforded **9e** as a white solid (152 mg, yield: 62%)

$[\alpha]_D^{25}$ - 50.0 (*c* 1.12, CH_2Cl_2); m.p. 87-90°C; IR(ATR) 1763, 1711, 1638, 1483, 1454, 1437, 1371, 1315, 1265, 1198, 1179, 1140, 1094, 1063, 1009 cm^{-1}; ^{1}H NMR ($CDCl_3$, 296K, 300MHz) δ (ppm) = 7.81 and 7.73 (2d, 2H, *J* 16.1 Hz, C<u>H</u>=CHCO), 7.63 (dd, 2H, *J* 7.9 Hz, H ortho), 7.40 (dd, 2H, *J* 7.40 Hz, H meta OAc), 7.25 (dd, 2H, *J* 7.6 Hz, H para OAc), 7.11 (d, 3H, J 8.1 Hz, H orthoOAc), 6.46 and 6.40 (2d, 2H, *J* 16.1 Hz, CH=C<u>H</u>CO), 5.53 (m, 2H, H_3 and H_5), 3.75 (s, 3H, COOMe), 2.40 and 2.38 (2s, 2x3H, 2xOAc), 2.29-2.19 (m, 3H, H-2, H-4, H6), 2.13-2.02 (m, 2H, H-2, H-6), 1.90 (ddd, 1H, ^{2}J 13.5 Hz, ^{3}J 10.0 Hz, ^{3}J 3.4 Hz, H-4); ^{13}C NMR ($CDCl_3$, 295K, 100 MHz) δ (ppm) = 175.0 (COOMe), 169.45 and 169.40 (O<u>C</u>OCH$_3$), 165.8 and 165.6 (COO), 149.4(2xC_q), 138.56 and 138.50

[8] R. F. Helm, J. Ralph and R. D. Hatfield, *Carbohydr. Res.*, 1992, **229**, 183-194.

(CH=CHCO), 131.34 and 131.30 ($C_{4'}$), 127.6 and 127.5 ($C_{6'}$), 127.1 and 127.0 (C_q), 126.44 and 126.41($C_{5'}$), 123.26 and 123.20 ($C_{3'}$), 120.2 and 120.1 (CH=CHCO), 74.6 (C_1), 68.8 (C_3 or C_5), 67.0 (C_5 or C_3), 53.2 (COOMe), 39.7 and 36.9 (C_6 and C_2), 35.1 (C_4), 21.0 (2x OCOCH$_3$); HRMS-ESI m/z $[M+Na]^+$ calcd for $C_{30}H_{30}NaO_{11}$ 589.1680; found 589.1669.

General procedure for the deprotection of aromatic acetates

Procedure D[9] : To a solution of compound **9** (a, c, d or e) in ethanol/water (2/1, 0.12M) was added hydrazine acetate (NaOAc, 20 eq). After stirring at reflux for 1 h, the mixture was diluted with EtOAc, washed with brine then the organic layer was dried over $MgSO_4$, concentrated and purified by flash chromatography.

Procedure E[10] : To a solution of compound **9** (a, c, d or e) in DMF (0.15M) was added hydrazine acetate (75equiv.). After stirring at room temperature for 1 h, the mixture was diluted with EtOAc, washed with brine then the organic layer was dried over $MgSO_4$, concentrated and purified by flash chromatography.

Methyl (3S,5S) 1-hydroxy-3,5 bis[[(2E)-3-(3,4-dihydroxyphenyl)-1-oxo-2-propen-1-yl]oxy]cyclohexanecarboxylate 10a

To a solution of **9a** (116mg, 0.170 mmol) in DMF (0.9 mL) was added hydrazine acetate (71 mg, 0.64 mmol). After stirring at room temperature for 1 h, the mixture was diluted with EtOAc (50 mL), washed with brine (30 mL x 3) then the organic layer was dried over $MgSO_4$, concentrated and purified by flash chromatography (CH_2Cl_2 / CH_3OH 40 / 1) to provide **10a** as a colorless oil (78 mg, 89%). $[\alpha]_D^{25}$ - 167.0 (*c* 0.64, CH_3OH); IR(ATR) 3323, 3304, 3285, 3275, 2949, 2835, 1680, 1630, 1599, 1516, 1443, 1373, 1256, 1159, 1140, 1119, 1067, 1016 cm^{-1}; ^1H NMR (CD_3OD, 298K, 500 MHz) : δ ppm = 7.58 and 7.52 (d, 2H, ^3J 15.8 Hz, CH=CHCO), 7.06 (bs, 2H, Ar-$H_{2'}$), 6.95 (dt, 2H, J_{ortho} = 8.1, J_{meta} 2.3 Hz, Ar-$H_{6'}$), 6.80 (dd, 2H, J_{ortho} 8,2 Hz, J_{meta} 2,7 Hz, Ar-$H_{5'}$), 6.28 and 6.19 (d, 2H, ^3J 15.9 Hz, CH=CHCO), 5.42 (m, 2H, H_3 and H_5), 3.70 (s, 3H, OMe), 2.46 (dd, 1H, ^2J 13.4 Hz, ^3J 3.5 Hz, H_2 or H_6), 2.39 (dd, 1H, ^2J 13.6 Hz, ^3J 6.9 Hz, H_2 or H_6), 2.06 (m, 1H, H_4), 1.97 (m, 2H, H_4 and H_2 or H_6), 1.86 (dd, 1H, ^2J 13.4 Hz, ^3J 7.7 Hz, H_2 or H_6); ^{13}C NMR (CD_3OD, 298K, 125 MHz) δ (ppm) = 175.7 (COOMe), 168.5 (OCO), 168.0 (OCO), 149.6 (C_q), 149.5 (C_q), 147.2 and 147.0 (CH=CHCO), 146.8 (C_q), 146.7(C_q), 127.7 (C_q), 127.6 (C_q), 123.04 and 123.00 ($C_{6'}$), 116.53 and 116.50 ($C_{5'}$), 115.4 and 115.1 (OCOCH=CH), 115.09 and 115.00 ($C_{2'}$), 75.0 (C_1), 69.5 and 69.0 (C_3 and C_5), 53.0(OMe), 39.7, 39.3 and 35.9 (3xCH_2, C_2, C_6 and C_4); HRMS-ESI m/z $[M+Na]^+$ calcd for $C_{26}H_{26}NaO_{11}$ 537.1367; found 537.1351.

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Methyl (3S,5S) 1-hydroxy-3,5 bis[[(2E)- 3-(4-hydroxy-3-methoxyphenyl)-1-oxo-2-propen-1-yl]oxy]cyclohexanecarboxylate 10c

The general procedure E for the deprotection of aromatic acetates was performed with **9c** (65 mg, 0.104 mmol) in DMF (0.45 mL) and hydrazine acetate (43 mg, 0.47 mmol) providing after purification **10c** as a colorless oil (50 mg, 89%). $[\alpha]_D^{25}$ - 170.0 (*c* 0.93, CH_3OH); IR(ATR) 3516, 3057, 2957, 2941, 1701, 1631, 1593, 1512, 1462, 1454, 1429, 1377, 1263, 1207, 1157, 1138, 1032, 1009 cm^{-1}; ^1H NMR (CD_3OD, 400 MHz) : δ ppm = 7.63 and 7.57 (d, 2H, ^3J 15.9 Hz, C<u>H</u>=CHCO), 7.12 (bs, 2H, Ar-H), 7.07 (dd, 2H, J_{ortho} 8,2 Hz, J_{meta} 2,7 Hz, Ar-H), 6.81 (dd, 2H, J_{ortho} 8,2 Hz, J_{meta} 2,2 Hz, Ar-H), 6.38 and 6.29 (d, 2H, ^3J 15.9 Hz, CH=C<u>H</u>CO), 5.432 (m, 2H, H_3 and H_5), 3.88 (s, 6H, 2x OMe), 3.70 (s, 3H, COOMe), 2.45 (dd, 1H, ^2J 13.6 Hz, ^3J 4.1 Hz, H_2 or H_6), 2.38 (dd, 1H, ^2J 13.6 Hz, ^{3}J 7.2 Hz, H_2 or H_6), 2.14-1.97 (m, 3H, 2x H_4 and H_2 or H_6), 1.88 (dd, 1H, ^2J 13.6 Hz, ^3J 7.5 Hz, H_2 or H_6); ^{13}C NMR (CD_3OD, 100 MHz) δ (ppm) = 175.7 ((COOMe), 168.4 and 168.0 (OCO), 150.7, 150.6, 149.4, 149.3 ($C_{q\ Ar}$), 147.1 and 147.0 (<u>C</u>H=CHCO), 127.7 and 127.5 ($C_{q\ Ar}$), 124.2 and 124.1 (CH_{Ar}), 116.5 and 116.4 (CH_{Ar}), 115.7 and 115.4 (OCOCH=<u>**C**</u>H), 111.6 (CH_{Ar}), 75.0 (C_1), 69.5 and 69.0 (C_5 or C_3), 56.4(2) (2xOCH_3), 53.0 (COO<u>Me</u>), 39.8 and 39.2 (C_2 or C_6), 35.9 (C_4); HRMS-ESI m/z $[M+Na]^+$ calcd for $C_{28}H_{30}NaO_{11}$ 65.1680; found 565.1662.

Methyl (3S,5S) 1-hydroxy-3,5 bis[[(2E)-3-(4-hydroxyphenyl)-1-oxo-2-propen-1-yl]oxy]cyclohexanecarboxylate 10d

The general procedure E for the deprotection of aromatic acetates was performed with **9d** (80 mg, 0.14 mmol) in DMF (0.6 mL) and hydrazine acetate (59 mg, 0.64 mmol) providing after purification (CH_2Cl_2 / CH_3OH 40 / 1) a colorless oil (62 mg, 91%).$[\alpha]_D^{25}$ - 174.7 (*c* 0.95, CH_3OH); IR(ATR) 3325, 3308, 3279, 3267, 2947, 2832, 1688, 1632, 1603, 1587, 1514, 1441, 1371, 1325, 1307, 1254, 1202, 1165, 1144, 1103, 1065, 1018 cm^{-1}; ^1H NMR (CD_3OD, 400 MHz) : δ (ppm) = 7.65 and 7.59 (2d, 2H, ^3J 15.9 Hz, 2x C<u>H</u>=CHCO), 7.47 (d, 4H, J_{ortho} 8.6 Hz, Ar-H), 6.81 (dd, 4H, J_{ortho} 8.6 Hz, J_{meta} 1.8 Hz Ar-H), 6.34 and 6.26 (d, 2H, ^3J 15.9 Hz, CH=C<u>H</u>CO), 5.43 (m, 2H, H_3 and H_5), 3.69 (s, 3H, OMe), 2.46 (dd, 1H, ^2J 13.4 Hz, ^3J 4.1 Hz, H_2, H_4 or H_6), 2.40 (dd, 1H, ^2J 13.7 Hz, ^{3}J 7.0 Hz, H_2, H_4 or H_6), 2.10-1.95 (m, 3H, H_2, H_4 or H_6), 1.87 (dd, 1H, ^2J 13.4 Hz, ^{3}J 7.6 Hz H_2, H_4 or H_6). ^{13}C NMR (CD_3OD, 100 MHz) δ (ppm) = 175.7 (COOMe), 168.5(OCO), 168.0(OCO), 161.4 (C_q), 161.3 (C_q), 146.8 and 146.7 (2x<u>C</u>H=CHCO), 131.23 and 131.20 (2x2xCH), 127.2 and 127.0 (2xC_q), 116.9, 116.8 (2x2 CH), 115.5 and 115.1 (2x OCOCH=<u>**C**</u>H), 75.0 (C_1), 69.5, 69.0 (<u>C</u>$_3$ and C_5), 53.0 (OMe), 39.8, 39.3 and 35.9 (3xCH_2, C_2, C_6 and C_4). HRMS-ESI m/z $[M+Na]^+$ calcd for $C_{26}H_{26}NaO_9$ 505.1469; found 505.1452.

Methyl (3S,5S) 1-hydroxy-3,5 bis[[(2E)-3-(2-hydroxyphenyl)-1-oxo-2-propen-1-yl]oxy]cyclohexanecarboxylate 10e

The general procedure E for the deprotection of aromatic acetates was performed with **9e** (118 mg, 0.21 mmol) in DMF (0.9 mL) and hydrazine acetate (88 mg, 0.96 mmol) providing after purification (CH_2Cl_2 / CH_3OH 40 / 1) a colorless oil (89 mg, 89%). $[\alpha]_D^{25}$ - 104.3 (*c* 1.00, CH_3OH); IR(ATR) 3337, 3298, 3283, 3256, 2945, 2835, 1688, 1626, 1603, 1499, 1458, 1369, 1317, 1294, 1254, 1169, 1146, 1113, 1067, 1018 cm^{-1}; ^1H NMR (CD_3OD, 400 MHz) : δ ppm = contaminated with chloroform

at 7.90 ppm, 8.00 and 7.91 (2d, 2H, ^{3}J 16.1 Hz, CH=CHCO), 7.48 (pseudo t, 2H, J_{ortho} 8,2 Hz Ar-H), 7.21 (pseudot, 2H, J_{ortho} 7.4 Hz Ar-H), 6.84 (m, 4H, Ar-H), 6.63 and 6.58 (d, 2H, ^{3}J 16.1 Hz, CH=CHCO), 5.45 (m, 2H, H_3 and H_5), 3.72 (s, 3H, OMe), 2.49 (dd, 1H, ^{2}J 13.4 Hz, ^{3}J 3.6 Hz, H_2, H_4 or H_6), 2.43 (dd, 1H, ^{2}J 13.8 Hz, ^{3}J 6.8 Hz, H_2, H_4 or H_6), 2.15-2.09 (m, 1H, H_2, H_4 or H_6), 2.00-1.96 (m, 2H, H_2, H_4 or H_6), 1.86 (dd, 1H, ^{2}J 13.3 Hz, ^{3}J 7.9 Hz, H_2, H_4 or H_6). ^{13}C NMR (CD_3OD, 100 MHz) δ (ppm) = contaminated with chloroform at 79.4 ppm; 175.7 (COOMe), 168.8(OCO), 168.4(OCO), 158.5 and 158.3 (2xC_q), 142.9 and 142.5 (2xCH=CHCO), 132.7, 132.6, 130.6, 130.2 (4xCH_{Ar}), 122.6, 122.5 (2xC_q), 120.8 (2xCH_{Ar}), 118.6, 118.5 (2x OCOCH=**C**H), 117.0 (2xCH_{Ar}), 79.4, 75.0 (C_1), 69.5, 69.1 (C_3 and C_5), 53.0 (OMe), 39.8, 39.4 and 35.9 (3xCH_2, C_2, C_6 and C_4). HRMS-ESI m/z $[M+Na]^+$ calcd for $C_{26}H_{26}NaO_9$ 505.1469; found 505.1448.

(3S,5S) 1-hydroxy-3,5 bis[[(2E)-3-(3,4-dihydroxyphenyl)-1-oxo-2-propen-1-yl]oxy]cyclohexanecarboxylic acid 4a

LiI (143 mg, 1.07 mmol) was added to a solution of **9a** (146 mg, 0.214 mmol) in EtOAc (1.1 mL) then the mixture was heated under reflux overnight. After cooling down to room temperature, the mixture was diluted with EtOAc (30 mL), washed with 1M HCl (2x 10 mL) and extracted with EtOAc (3x30mL). The organic layer was dried over $MgSO_4$, concentrated to give the crude (3S,5S) 1-hydroxy-3,5 bis[[(2E)-3-(3,4-diacetoxyphenyl)-1-oxo-2-propen-1-yl]oxy]cyclohexanecarboxylic acid **11a** (128 mg, crude yield: 90%), pure enough for characterization and used directly in the following step. IR(ATR) 3370, 2941, 2833, 1769, 1707, 1638, 1504, 1369, 1240, 1201, 1174, 1143, 1109, 1012 cm^{-1}; ^{1}H NMR (CD_3OD, 298K, 400 MHz) : δ ppm = 7.67 and 7.62 (2d, 2H, J 16.0 Hz, CH=CHCO), 7.50 (m, 2H, $H_{6'}$), 7.49 (m, 2H, $H_{2'}$), 7.24 (d, 2H, J_{ortho} 8.2 Hz, H_5'), 6.52 and 6.46 (2d, 2H, J 16.0 Hz, CH=CHCO), 5.46 (m, 2H, H_3 and H_5), 2.44-2.19 (m, 14H) and 2.06-1.90 (m, 4H, 3xCH_2 and 4xOCOCH_3); ^{13}C NMR (CD_3OD, 298K, 100 MHz) δ (ppm) = 177.3 (COOH), 169.8 and 169.7 (4x O**C**OCH_3), 167.5 and 167.2 (2xOCO), 145.2 and 145.1 (2xC_q), 144.5 and 144.4 (2xCH=CHCO), 144.0 (2xC_q), 134.60 and 134.56 (2xC_q), 127.7 and 127.6 (2x$C_{6'}$), 125.13 and 125.11 (2x$C_{5'}$), 124.14 and 124.09 ($C_{2'}$), 120.45 and 120.13 (2x CH=CHCO), 75.0 (C_1), 70.2, 69.2 (C_3 and C_5), 39.9, 38.7, 35.9 (C_2, C_4, C_6), 20.5 (4XOCOCH_3). HRMS-ESI m/z $[M+H]^+$ calcd for $C_{33}H_{33}O_{15}$ 669.1814; found 669.1801.

To a solution of (3S,5S) 1-hydroxy-3,5 bis[[(2E)-3-(3,4-diacetoxyphenyl)-1-oxo-2-propen-1-yl]oxy]cyclohexanecarboxylic acid **11a** (208 mg) in acetone (4.08 mL) was added 3M HCl aqueous solution (2.0mL) and the mixture was refluxed for 5h. After completion, the reaction mixture was cooled down to room temperature, diluted with EtOAc (30 mL) and washed with brine (20 mL). The organic layer was concentrated to give the crude quantitatively as a pale solid **4a** (190 mg).

$[\alpha]_D^{25}$ - 42.7 (*c* 0.82, CH_3OH); ^{1}H NMR (CD_3OD, 400 MHz, 295K) : IR(ATR) 3345, 3210, 1687, 1603, 1523, 1445, 1362, 1279, 1182, 1138, 1119 cm^{-1}; δ (ppm) = 7.65 and 7.60 (2d, 2H, J 16.0 Hz, CH=CHCO), 7.45 (m, 4H, ArH), 6.81 (m, 4H, ArH), 6.34 and 6.27 (2d, 2H, J 16.0 Hz, CH=CHCO), 5.45 (m, 2H, H_3 and H_5), 2.41 (dd, 1H, ^{2}J 14.0 Hz, ^{3}J 3.8 Hz, H_2, H_4 or H_6), 2.32 (dd, 1H, ^{2}J 13.3 Hz, ^{3}J 8.2 Hz, H_2, H_4 or H_6), 2.06 (m, 3H, H_2, H_4 or H_6), 1.93 (dd, 1H, ^{2}J 13.8 Hz, ^{3}J 6.5 Hz, H_2, H_4 or H_6); ^{13}C NMR (CD_3OD, 100 MHz, 297K) δ (ppm) = 177.4 (COOH), 171.0 (2xC_q), 168.5 and 168.3 (2xOCO), 161.12 and 161.07 (2xCq), 146.7 and 146.7 (2xCH=CHCO), 131.2, 131.1 (2xCH_{Ar}), 127.1

(2xC_q), 116.8 (4xCHAr), 115.5, 115.1 (2x CH=<u>C</u>HCO), 75.1 (C_1), 69.9, 68.7 (C_3 and C_5), 39.9, 38.6, 35.9 (C_2, C_4, C_6).

(3S,5S) 1-hydroxy-3,5 bis[[(2E)-3-(4-hydroxy-3-methoxyphenyl)-1-oxo-2-propen-1-yl]oxy]cyclohexanecarboxylic acid 4c

LiI (152 mg, 1.135 mmol) was added to a solution of **9c** (142 mg, 0.2274 mmol) in EtOAc (5.0 mL) then the mixture was heated under reflux 24h. After cooling down to room temperature, the mixture was diluted with EtOAc (25 mL), washed with 3M HCl (5 mL) and extracted with EtOAc (3x30mL). The organic layer was dried over $MgSO_4$, concentrated to give the crude (3S,5S) 1-hydroxy-3,5 bis[[(2E)-3-(4-acetoxy-3-methoxyphenyl)-1-oxo-2-propen-1-yl]oxy]cyclohexanecarboxylic acid **11c** (quantitative crude yield), pure enough for characterization and used directly in the following step.

$[\alpha]_D^{25}$ - 97.5 (*c* 0.96, CH_3OH); IR(ATR) 3466, 2941, 2833, 1763, 1705, 1599, 1508, 1464, 1454, 1418, 1369, 1256, 1215, 1177, 1152, 1063, 1020 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) : δ (ppm) = 7.66 and 7.61 (2d, 2H, ^3J 15.9 Hz, C<u>H</u>=CHCO), 7.13-7.03 (2m, 6H, Ar-H), 6.41 and 6.34 (2d, 2H, ^3J 15.9 Hz, CH=C<u>H</u>CO), 5.50 (m, 2H, H_3 and H_5), 3.87 and 3.85 (2s, 2x3H, 2xOMe), 2.33-1.83 (m, 12H, H_2, H_4, H_6 and 2xOCOCH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) = 176.7 (COOH), 169.04 and 169.02 (2xO<u>**C**</u>OCH_3), 166.1 and 166.0 (2xCOO), 151.53 and 151.50 (2xC_q), 145.3, 144.8 (2x<u>C</u>H=CHCO), 141.7, 141.6 (2xC_q), 133.3, 133.2 (2xC_q), 123.4 (2xCH_{Ar}), 121.8, 121.4 (2x CH=<u>C</u>HCO), 118.1, 117.9 (2xCH_{Ar}), 111.4, 111.3(2xCH_{Ar}), 75.2(C_1), 69.4, 66.5 (C_3 and C_5), 56.1, 56.0 (2xOMe), 39.3, 36.5, 34.9 (C_2, C_4, C_6), 20.8 (2xOCO<u>**C**</u>H_3); HRMS-ESI m/z $[M+Na]^+$ calcd for $C_{31}H_{32}NaO_{13}$ 635.1735; found 635.1706.

To a solution of (3S,5S) 1-hydroxy-3,5 bis[[(2E)-3-(4-acetoxy-3-methoxyphenyl)-1-oxo-2-propen-1-yl]oxy]cyclohexanecarboxylic acid **11c** (176 mg) in acetone (3.0 mL) was added 3M HCl aqueous solution (1.5 mL) and the mixture was refluxed for 4h. After completion, the reaction mixture was cooled down to room temperature, diluted with EtOAc (30 mL) and washed with brine (20 mL). The organic layer was concentrated then dissolved in MeOH/H_2O (30/40 mL) and washed with pentane (2x 15mL). After concentration, the crude was obtained as a pale solid **4c** (150mg).

$[\alpha]_D^{25}$ - 94.4 (*c* 0.67, CH_3OH); IR(ATR) 3356, 3277, 1684, 1632, 1605, 1514, 1443, 1327, 1261, 1204, 1171, 1138, 1007 cm^{-1}; ^1H NMR (CD_3OD, 300 MHz, 297K) : δ (ppm) 7.65 and 7.60 (2d, 2H, *J* 15.9 Hz, C<u>H</u>=CHCO), 7.17 (m, 2H, ArH), 7.07 (m, 2H, ArH), 6.83 (d, 2H, J_{ortho} 8.1 Hz, ArH), 6.39 and 6.32 (2d, 2H, *J* 15.9 Hz, CH=C<u>H</u>CO), 5.47 (m, 2H, H_3 and H_5), 3.89 (s, 6H, 2xOMe), 2.42 (dd, 1H, ^2J 13.9 Hz, ^3J 4.0 Hz, H_2, H_4 or H_6), 2.34 (dd, 1H, ^2J 13.4 Hz, ^3J 8.2 Hz, H_2, H_4 or H_6), 2.00 (m, 4H, H_2, H_4 or H_6); ^{13}C NMR (CD_3OD, 75 MHz, 297K) δ (ppm) = 177.4 (COOH), 170.9 (2xC_q), 168.5 and 168.2 (2xOCO), 150.44, 150.38 (2xC_q), 146.9 and 146.8 (2x<u>C</u>H=CHCO), 127.74 and 127.68 (2xC_q), 124.1, 124.0, 123.9, 116.4, 115.8, 115.5 (6x CH_{Ar}), 111.7 and 111.6 (2x CH=<u>C</u>HCO), 75.1 (C_1), 69.9, 68.7 (C_3 and C_5), 56.43 and 56.41 (2xOMe), 40.0, 38.7, 36.0 (C_2, C_4, C_6).

(3S,5S) 1-hydroxy-3,5 bis[[(2E)-3-(4-hydroxyphenyl)-1-oxo-2-propen-1-yl]oxy]cyclohexanecarboxylic acid 4d

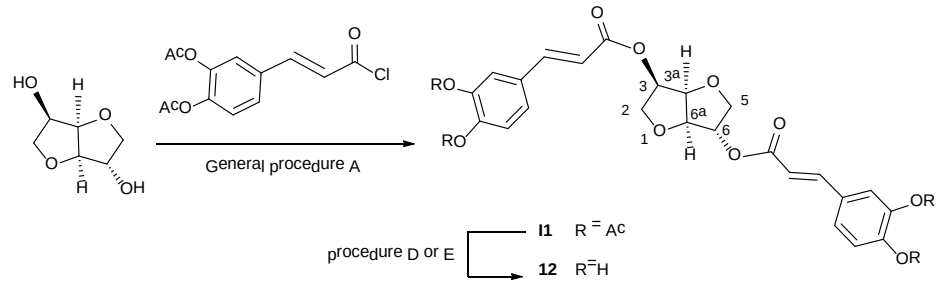
LiI (125 mg, 0.934 mmol) was added to a solution of **9d** (105 mg, 0.186 mmol) in EtOAc (4.0 mL) then the mixture was heated under reflux 24h. After cooling down to room temperature, the mixture was diluted with EtOAc (25 mL), washed with 3M HCl (5 mL) and extracted with EtOAc (3x30mL). The organic layer was dried over $MgSO_4$, concentrated to give the crude (3S,5S) 1-hydroxy-3,5 bis[[(2E)-3-(4-acetoxyphenyl)-1-oxo-2-propen-1-yl]oxy]cyclohexanecarboxylic acid **11d** (quantitative crude yield), pure enough for characterization and used directly in the following step. $[\alpha]_D^{25}$ - 111.9 (*c* 1.03, CH_3OH); IR(ATR) 3447, 3059, 2961, 1765, 1707, 1601, 1585, 1506, 1418, 1369, 1312, 1265, 1202, 1163, 1136, 1057, 1009 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) : δ ppm = 7.68 and 7.62 (2d, 2H, ^3J 15.9 Hz, C<u>H</u>=CHCO), 7.52 (dd, 4H, J_{ortho} 8,6 Hz, J_{ortho} 6.8 Hz, Ar-H), 7.11 (dd, 4H, J_{ortho} 8,6 Hz, J_{meta} 2.0 Hz, Ar-H), 6.41 and 6.34 (2d, 2H, ^3J 15.9 Hz, CH=C<u>H</u>CO), 5.49 (m, 2H, H_3 and H_5), 2.36-2.02 and 1.86 (2m, 11 and 1H, H_2, H_4, H_6 and 2x$OCOCH_3$); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) = 177.0 (COOH), 169.41 and 169.39 (2xO<u>C</u>OCH_3), 166.2, 166.1 (2xCOO), 152.4, 152.3 (2xC_q), 144.9, 144.4 (2x<u>C</u>H=CHCO), 132.04, 132.0 (2xC_q), 129.6, 129.5 (4xCH_{Ar}), 122.3 (4xCH_{Ar}), 118.0, 117.9 (2x CH=<u>C</u>HCO), 75.2 (C_1), 69.4, 66.6 (C_3 and C_5), 39.3, 36.5, 34.9 (C_2, C_4 and C_6), 21.3 (2x $OCOCH_3$); HRMS-ESI m/z $[M+Na]^+$ calcd for $C_{29}H_{28}NaO_{11}$ 575.1524; found 575.1503.

To a solution of (3S,5S) 1-hydroxy-3,5 bis[[(2E)-3-(4-acetoxyphenyl)-1-oxo-2-propen-1-yl]oxy]cyclohexanecarboxylic acid **11d** (196 mg) in acetone (4.0 mL) was added 3M HCl aqueous solution (2.0 mL) and the mixture was refluxed for 5h. After completion, the reaction mixture was cooled down to room temperature, diluted with EtOAc (30 mL) and washed with brine (20 mL). The organic layer was concentrated, dissolved in MeOH/H_2O (20/50 mL) and washed with pentane (2x 15mL). After concentration, the crude quantitatively as a pale solid **4d** (165 mg).

$[\alpha]_D^{25}$ - 72.6 (*c* 0.71, CH_3OH); IR (ATR) 3406, 2976, 2947, 1692, 1593, 1514, 1456, 1429, 1375, 1269, 1209, 1177, 1161, 1138, 1032 cm^{-1}; ^1H NMR (CD_3OD, 400 MHz, 295K) δ (ppm) = 7.59 and 7.54 (2d, 2H, *J* 16.0 Hz, C<u>H</u>=CHCO), 7.08 (m, 4H, ArH), 6.97-6.92 (m,4H, ArH), 6.81 (m, 2H, ArH), 6.29 and 6.23 (2d, 2H, *J* 16.0 Hz, CH=C<u>H</u>CO), 5.44 (m, 2H, H_3 and H_5), 2.40 (dd, 1H, ^2J 13.9 Hz, ^3J 4.3 Hz, H_2, H_4 or H_6), 2.32 (dd, 1H, ^2J 13.4 Hz, ^3J 8.2 Hz, H_2, H_4 or H_6), 1.96 (m, 4H, H_2, H_4 or H_6); ^{13}C NMR (CD_3OD, 100 MHz, 297K) δ (ppm) = 177.4 (COOH), 171.0 (2xC_q), 168.6 and 168.5 (2xOCO), 149.4, 149.3 (2xC_q), 147.1 and 146.9 (2x<u>C</u>H=CHCO), 127.74 and 127.68 (2xC_q), 123.1, 123.0, 116.5, 116.4 (x2), 115.4, .115.2, 115.11, 115.09, 115.0 (8x CH_{Ar} +2x CH=<u>C</u>HCO), 75.0 (C_1), 69.9, 68.7 (C_3 and C_5), 39.9, 38.6, 35.9 (C_2, C_4, C_6).

Synthesis of (3*R*,3a*R*,6*S*,6a*R*)-hexahydrofuro[3,2-*b*]furan-3-yl (2*E*)-3-(3,4-dihydroxyphenyl)prop-2-enoate (12)[11]

[11] To the best of our knowledge, the only reported syntheses of this family of compounds (dicinnamate and di (p-coumarate) isosorbide) used DCC/DMAP methodology. W. Huang, Y. B. Cao, X. G. Zhang, F. S. Li and H. Yang, *Chin. Chem. Lett.*, 2009, **20**, 873-876 ; A. Y. Bobrovsky, N. I. Boiko and V. P. Shibaev, *Mol. Cryst. Liq. Cryst.*, 2001, **363**, 35-50.



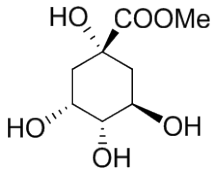
Isosorbide dicaffeate was also synthesized in our lab using the general procedure A with isosorbide (300 mg, 2.05 mmol) in anhydrous pyridine (2.1 mL) and DMF (3.2 mL) and diacetylacaffeoylchloride (1.51 g, 5.36 mmol, 2.6 eq.). (3R, 3aR, 6S, 6aR)-hexahydrofuro[3,2-b]furan-3,6-diyl (2E,2'E)bis-[3,4-bis(acetyloxy)phenyl]prop-2-enoate **I1** was obtained as a white solid (414mg, 32%) was obtained after purification by flash chromatography (pentane/EtOAc 6/4).

$[\alpha]_D^{25}$-59 (c 1.00, CH_2Cl_2); m.p.69-70°C (CH_2Cl_2); IR (ATR) cm^{-1} 1767, 1707, 1638, 1502, 1242, 1204, 1168, 1110; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) = 7.67 and 7.63 (2d, 2H, ^3J 16.0 Hz, C<u>H</u>=CHCO), 7.40-7.35 (m, 4H, ArH), 7.26-7.21 (m, 2H, ArH), 6.44 and 6.36 (2d, 2H, ^3J 16.0 Hz, CH=C<u>H</u>CO), 5.35 (bs, 1H, H_6), 5.29 (q, 1H, $J_{H_3/H_2} \approx J_{H_{3a}/H_3} \approx$5.5 Hz, H_3), 4.94 (dd, 1H, $J_{H_{3a}/H_{6a}} \approx J_{H_{3a}/H_3}$ 4.6 Hz, H_{3a}), 4.59 (d, 1H, $J_{H_{3a}/H_{6a}}$ 4.6 Hz, H_{6a}), 4.06 (m, 2H, 2xH_5), 4.03 (dd, 1H, ^2J 9.9 and ^3J 6.0 Hz, H_2), 3.90 (dd, 1H, ^2J 9.8 and ^3J 5.4 Hz, H_2), 2.292, 2.294, 2.298, 2.302 (4s, 12H, 3xCH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) = 168.15 and 168.06 (4 C<u>O</u>CH_3), 165.9 and 165.6 (2 COO), 144.03 and 143.98 (2 CH=CH), 143.82 and 143.77 (2 $C_{q\ Ar}$), 142.5 (2 $C_{q\ Ar}$), 133.1 and 133.0 (2 $C_{q\ Ar}$), 126.6, 124.1, and 123.0 (6 CH_{Ar}), 118.5 and 118.4 (2 CH=CH), 86.1 (C_{6a}), 81.1 (C_{3a}), 78.3 (C_6), 74.3 (C_3), 73.6 (C_5), 70.5 (C_2), 20.8 and 20.7 (4 CO<u>C</u>H_3); HRMS (ESI) calcd for $C_{32}H_{30}NaO_{14}$ $[M+Na]^+$ 661.1528, found 661.1537.

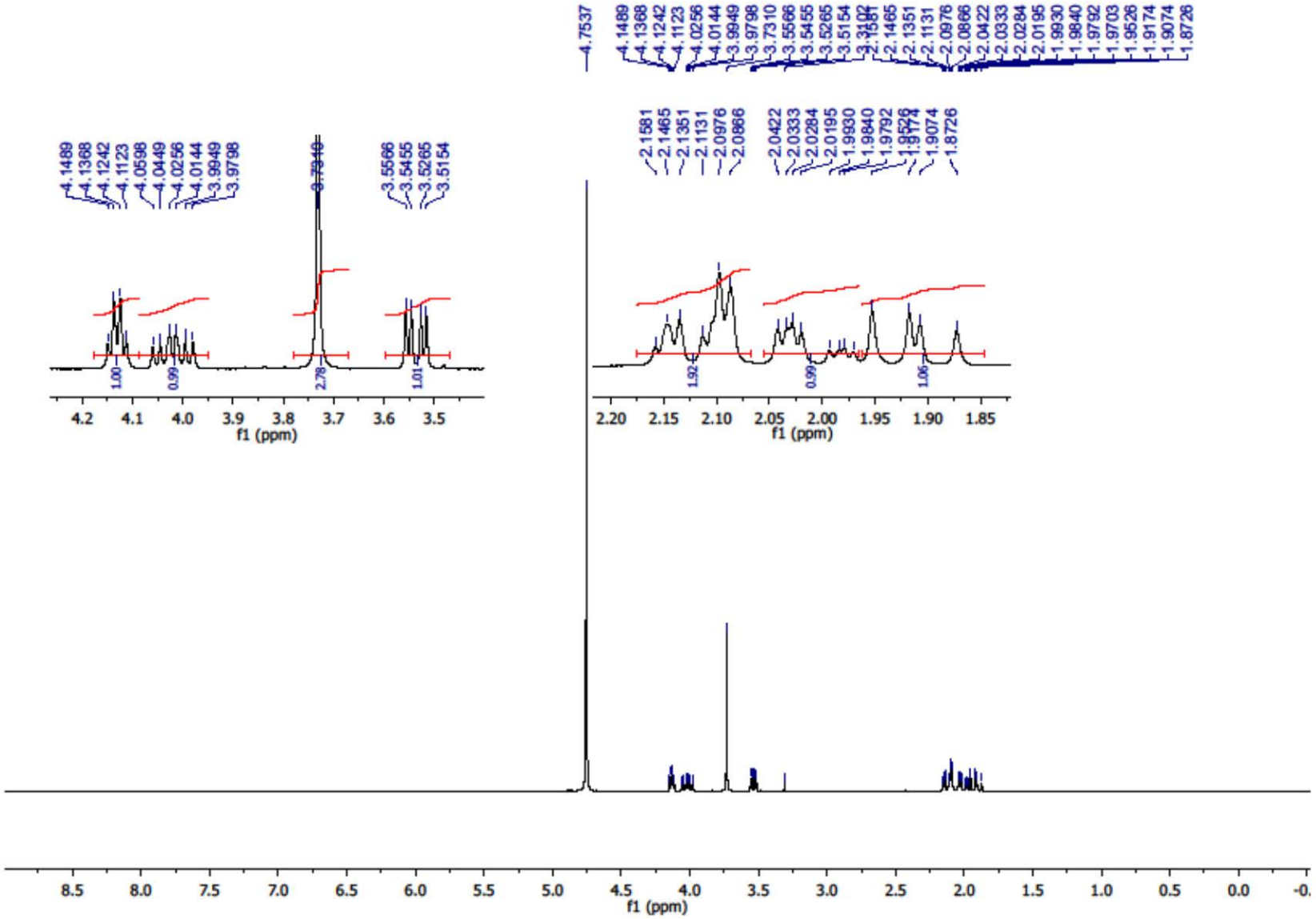
I1 was submitted to general procedure D for deprotection : **I1** (144 mg, 0.225 mmol) in ethanol (1.2 mL) wih NaOAc (377 mg, 20 eq) in water (600 µL). **12** was obtained as a white solid (74 mg, 72%) after purification by flash chromatography (CH_2Cl_2/MeOH 97/3-95/5).

$[\alpha]_D^{25}$-191 (c 0.99, CH_2Cl_2); m.p. 192-193°C (MeOH) ; IR (ATR) cm^{-1} 3670,3660, 2986, 2972, 2901, 2370, 2322, 1688, 1601, 1379, 1049; ^{1}H NMR (300 MHz, CD_3OD) δ (ppm) = 7.58 and 7.55 (2d, ^3J 15.9 Hz, C<u>H</u>=CHCO), 7.05 (dd, 2H, *J* 6.1 Hz, *J* 2.0 Hz, ArH); 6.94 (m, 2H, ArH), 6.77 (dd, 2H, *J* 8.1 Hz, *J* 3.1 Hz, ArH), 6.29 and 6.24 (2d, 2H, ^3J 15.9 Hz, CH=C<u>H</u>CO), 5.26 (m, 2H, H_3, H_6), 4.92 (dd, 1H, $J_{H_{3a}/H_{6a}} \approx J_{H_{3a}/H_3}$ 5.0 Hz, H_{3a}), 4.53 (d, 1H, $J_{H_{3a}/H_{6a}}$ 5.0 Hz, H6a), 3.95 (m, 4H, H_2, H_5) ; ^{13}C NMR (75 MHz, CD_3OD) δ (ppm) = 168.4, 168.1, 149.71, 149.66, 147.7, 147.5, 146.8, 127.6, 127.5, 123.2, 123.1, 116.5, 115.2, 114.4, 87.3, 82.6, 79.2, 75.5, 74.2, 71.8; HRMS (ESI) calcd for $C_{24}H_{22}NaO_{10}$ $[M+Na]^+$ 493.1105, found 493.1087.

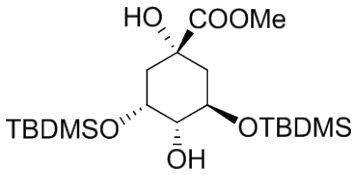
Methyl (3*R*, 5*R*)-1,3,4,5-tetrahydroxycyclohexanecarboxylate Q1



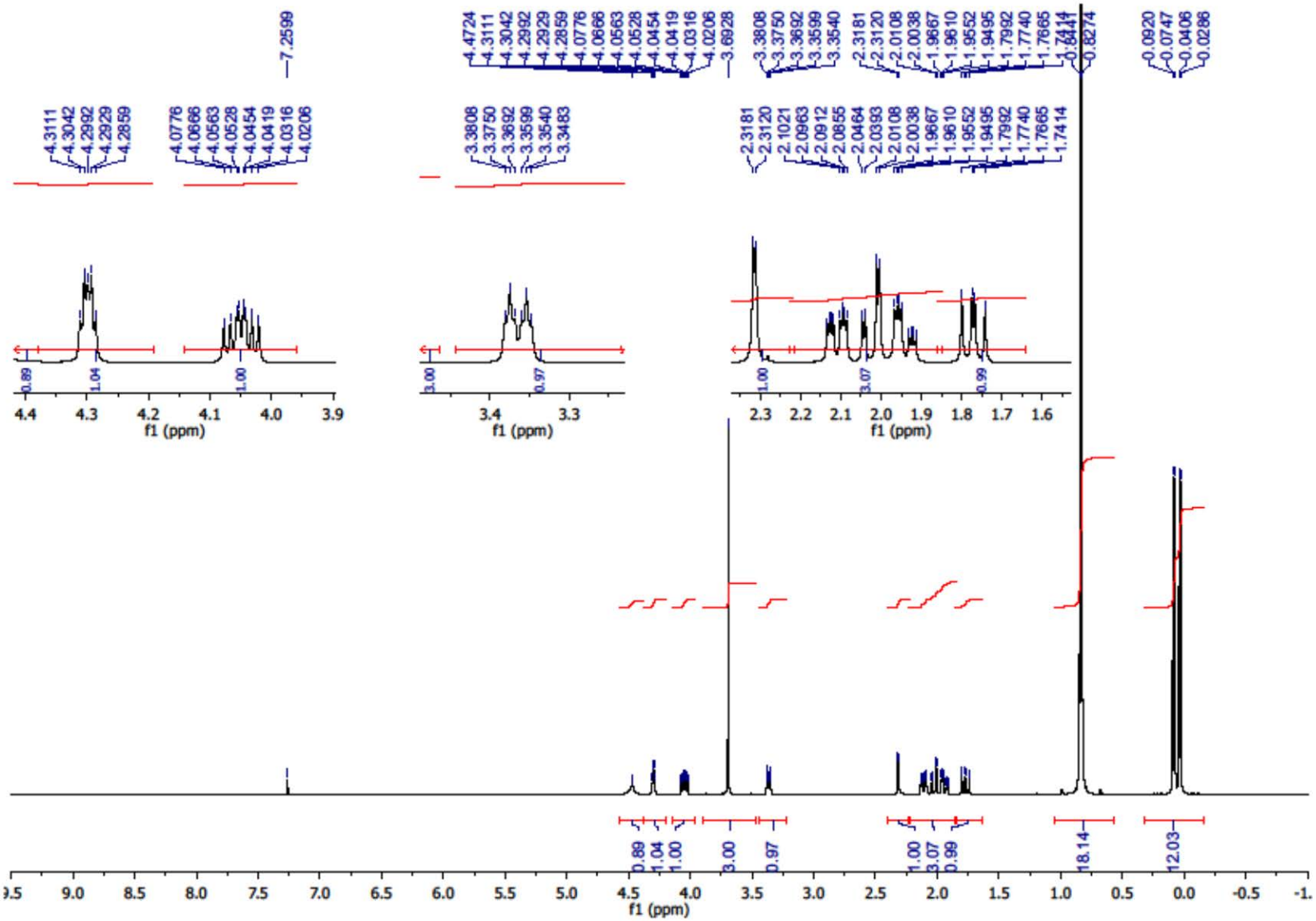
^{1}H NMR (300MHz, CD_3OD, 300K)



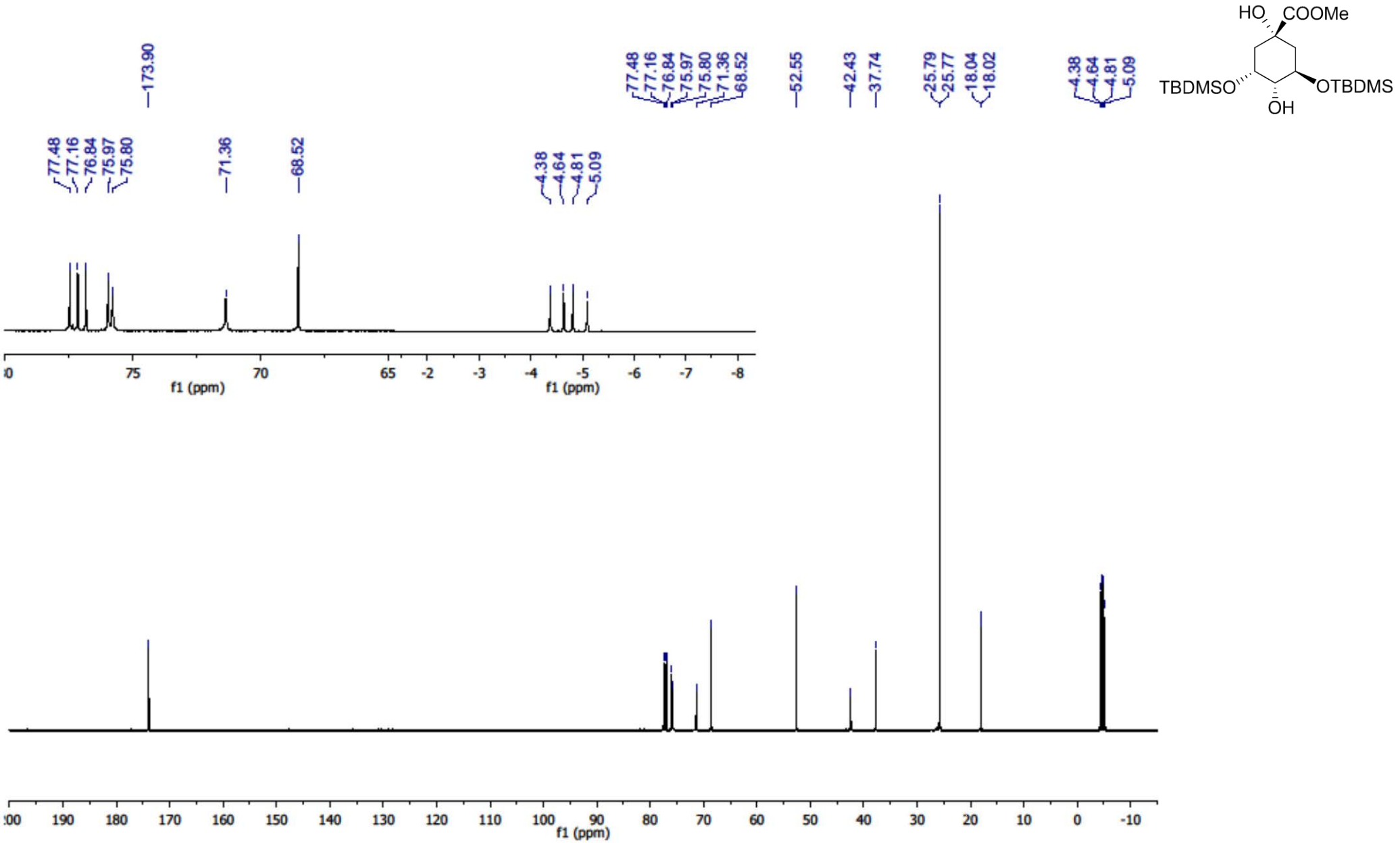
Methyl (3*R*,5*R*)-1,4-dihydroxy-3,5-tert-butyldimethylsilyloxyclohexanecarboxylate Q2



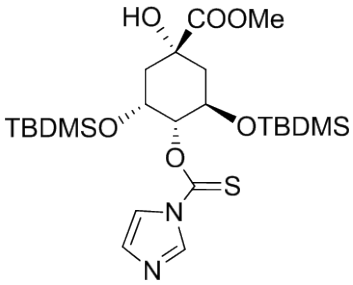
^{1}H NMR (300MHz, $CDCl_3$, 293K)



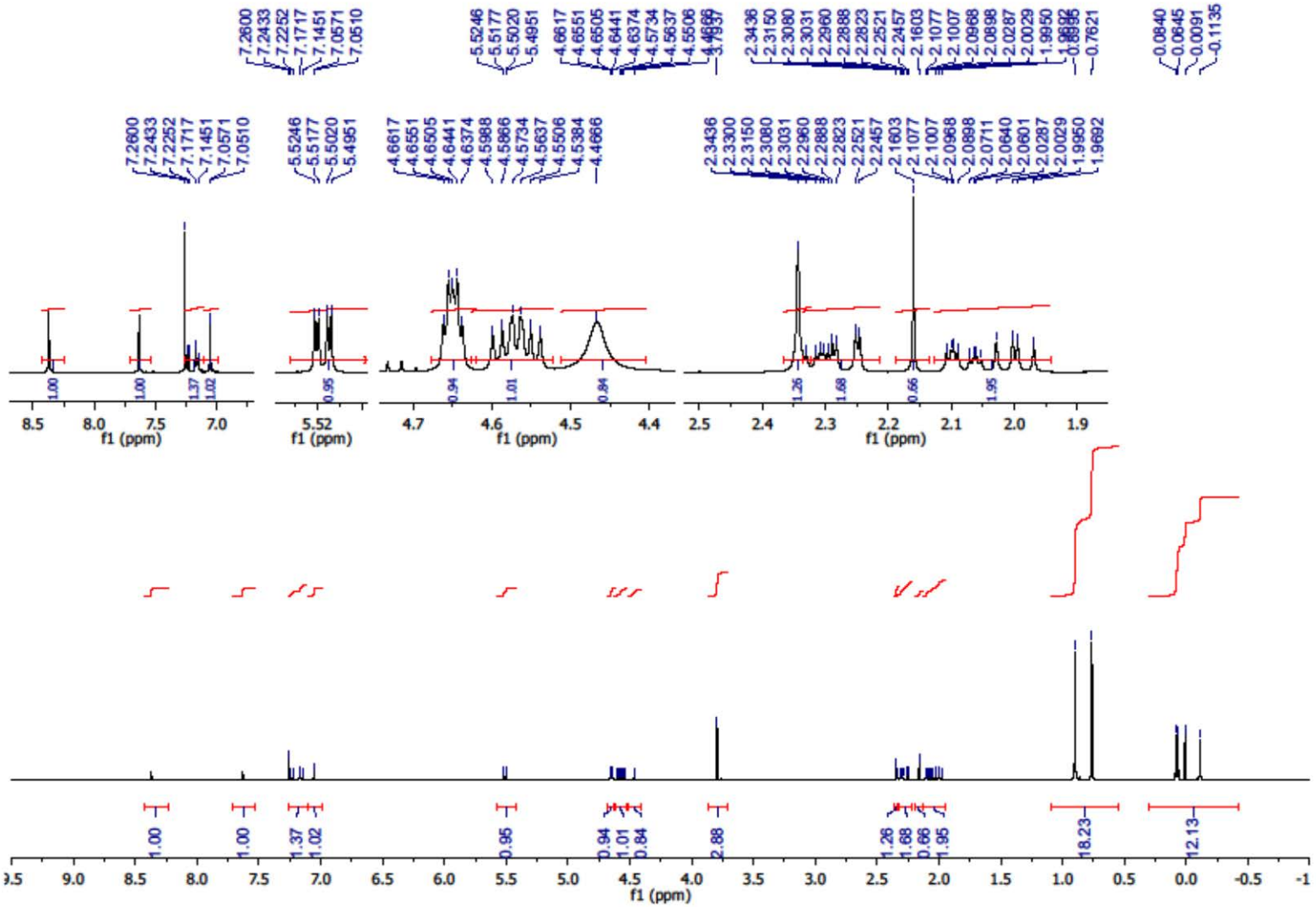
^{13}C NMR (100MHz, $CDCl_3$, 293K)



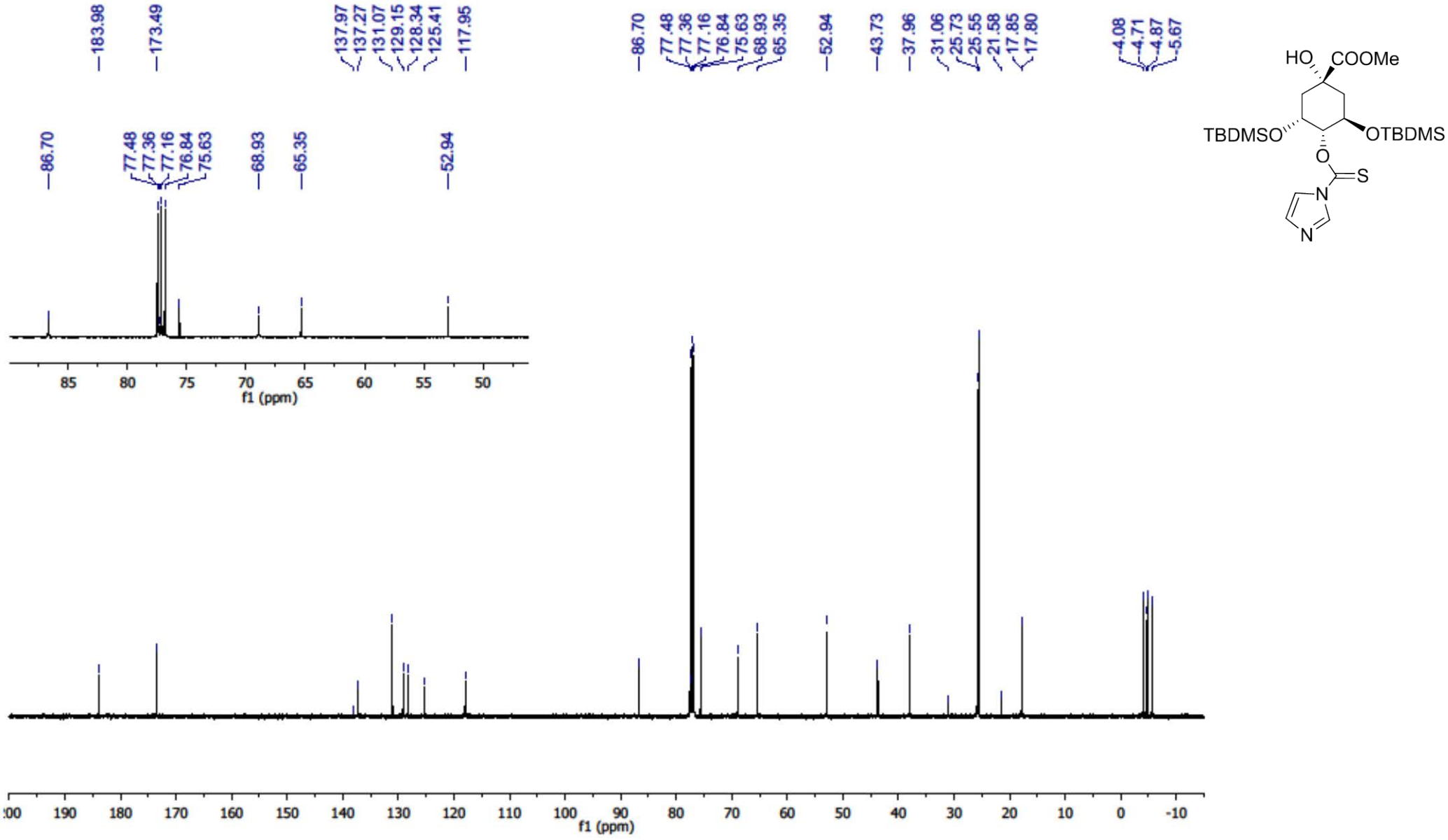
Methyl (3*R*,5*R*)-1-hydroxy-4-[(1*H*-imidazol-1-ylcarbothioyl)oxy]-3,5-*tert*-butyldimethylsilyloxy cyclohexanecarboxylate Q3



^{1}H NMR (400MHz, $CDCl_3$, 296K)

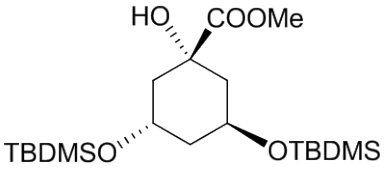


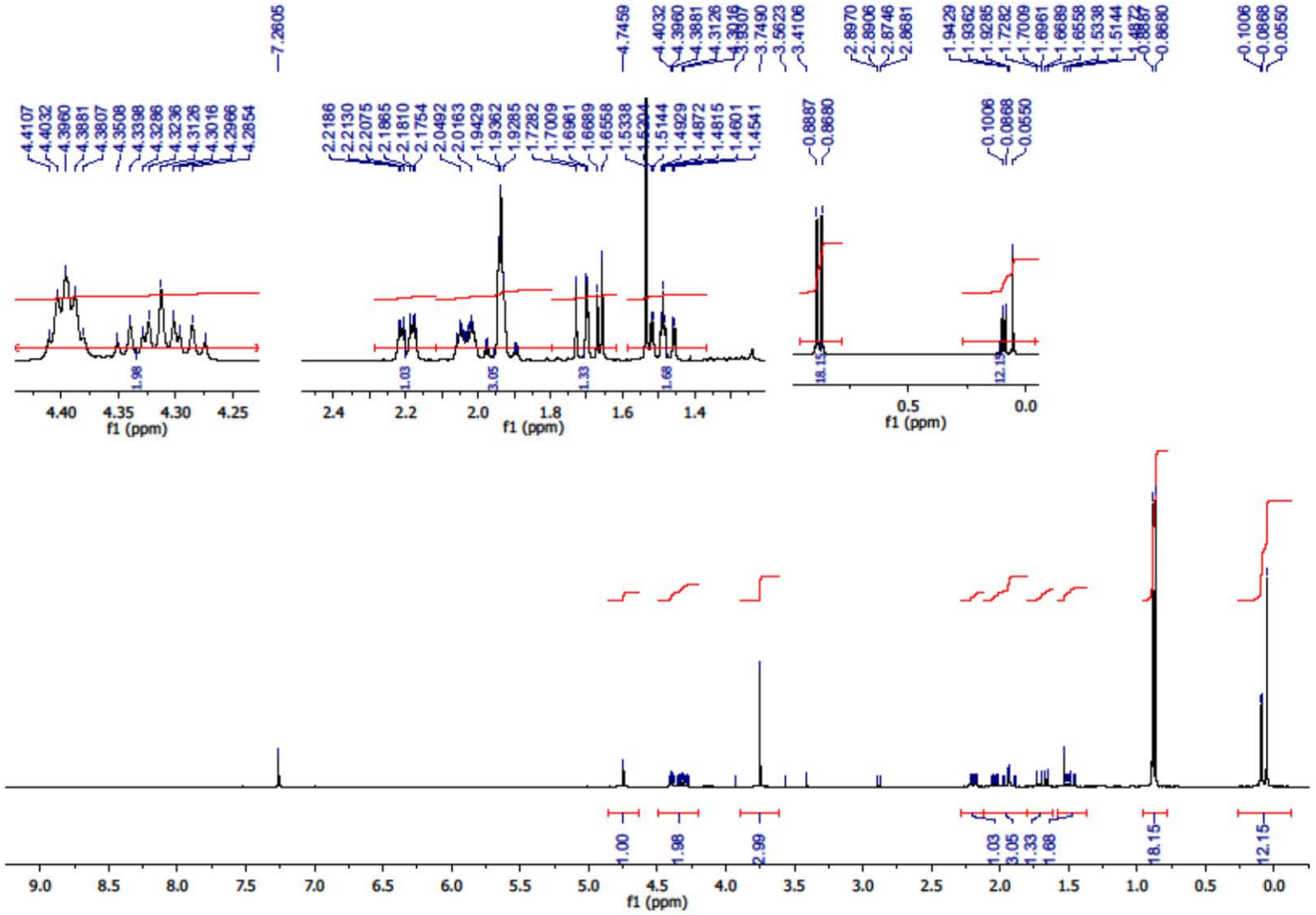
^{13}C NMR (100MHz, $CDCl_3$, 297K)



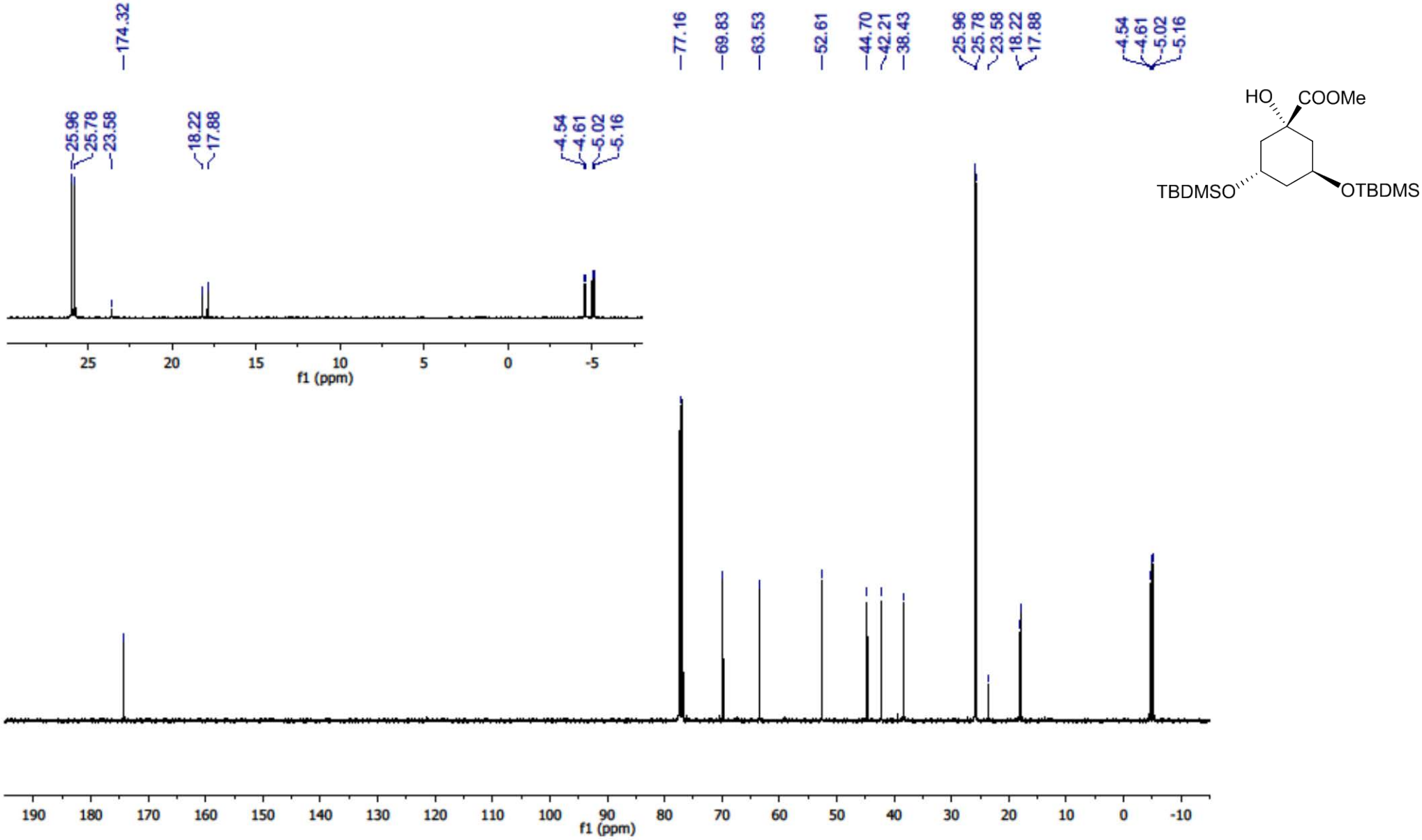
Methyl (3*S*,5*S*)-1-hydroxy-3,5- *tert*-butyldimethylsilyloxy cyclohexanecarboxylate 5

^{1}H NMR (400MHz, $CDCl_3$, 296K)

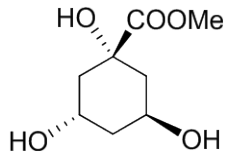




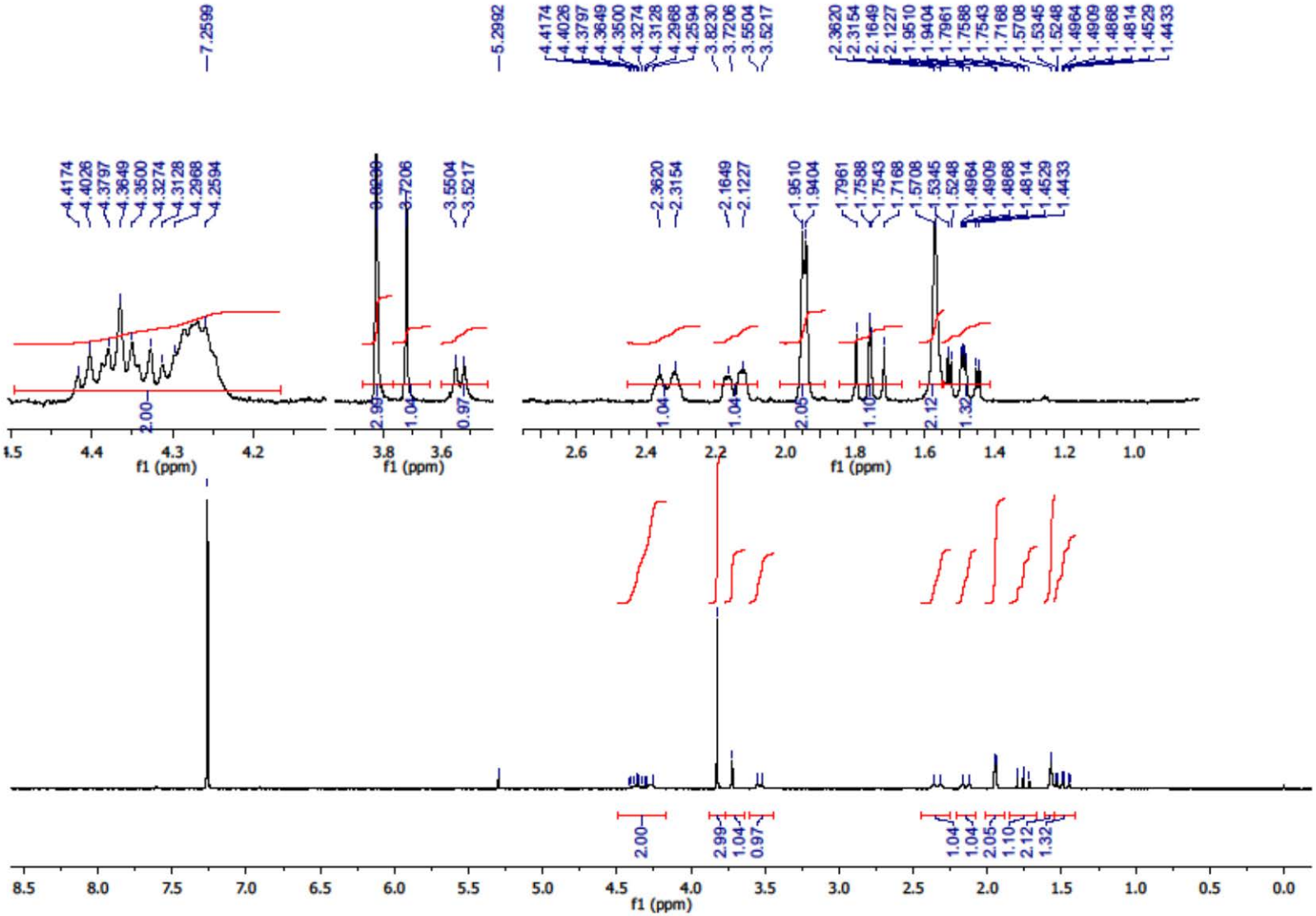
^{13}C NMR (100MHz, $CDCl_3$, 297K)



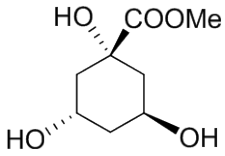
Methyl (3*S*,5*S*)-1,3,5-trihydroxy cyclohexanecarboxylate 6

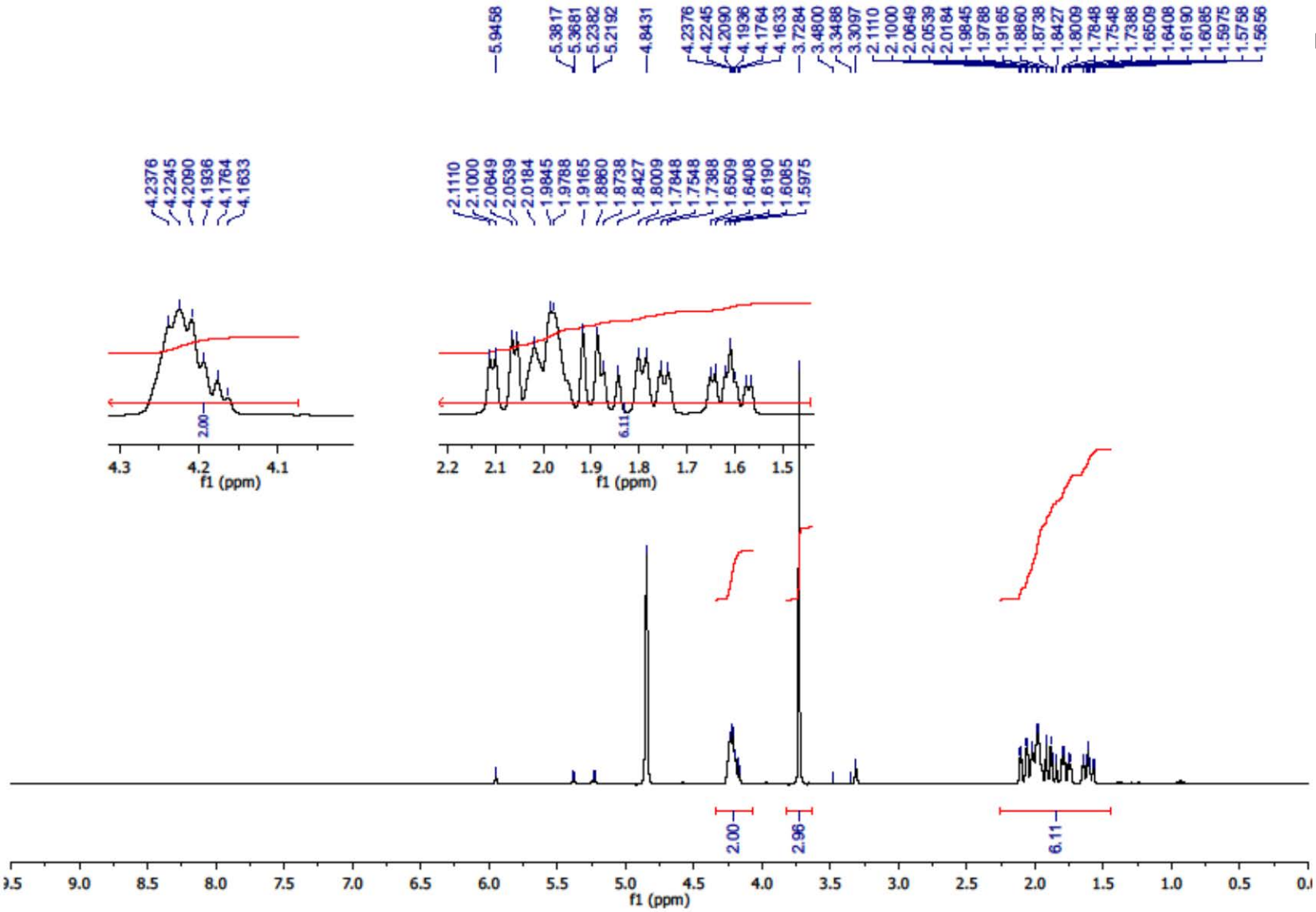


^{1}H NMR (300MHz, $CDCl_3$, 296K)

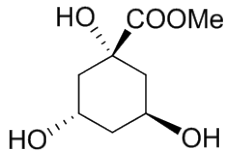


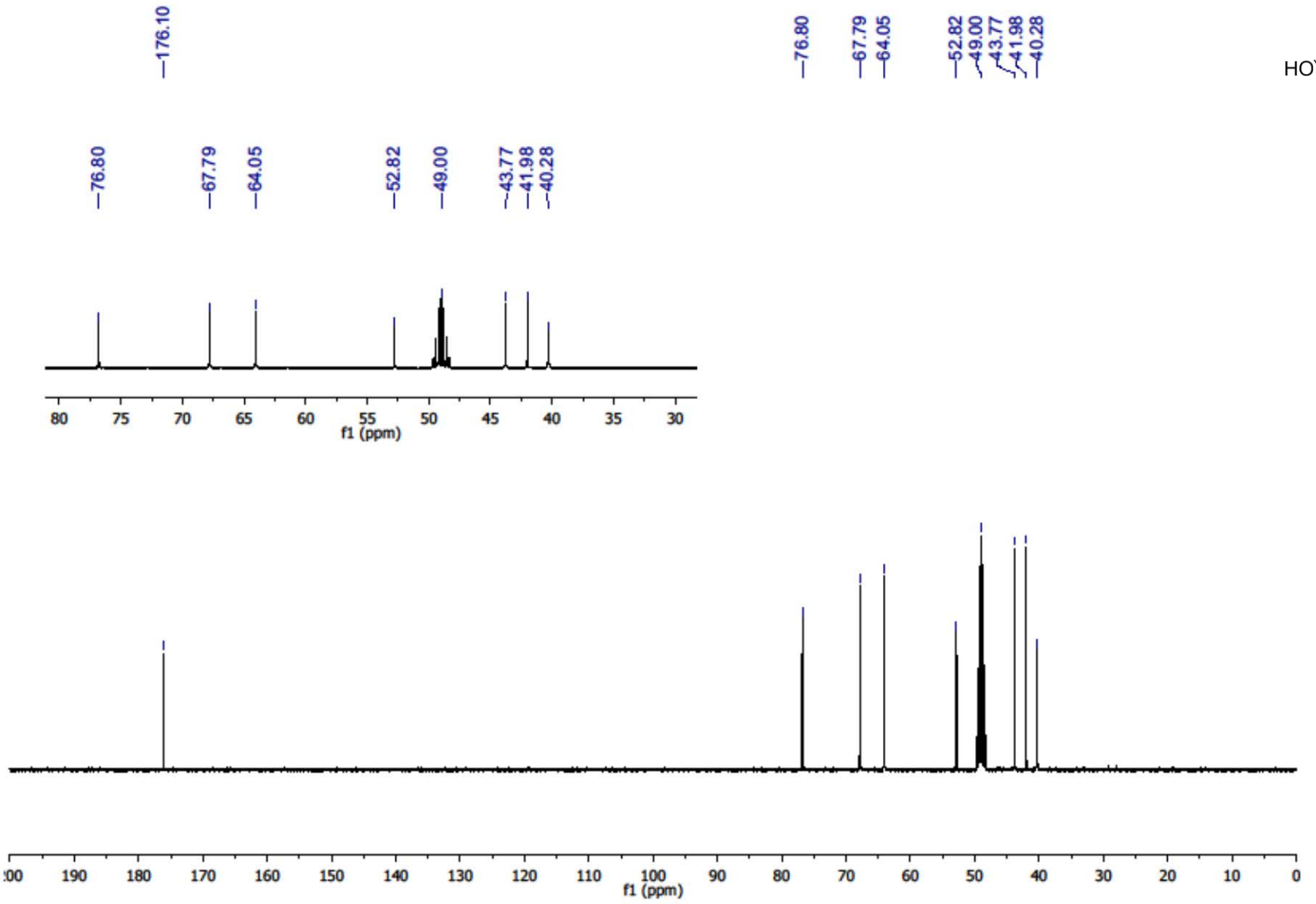
^{1}H NMR (400MHz, CD_3OD, 296K)





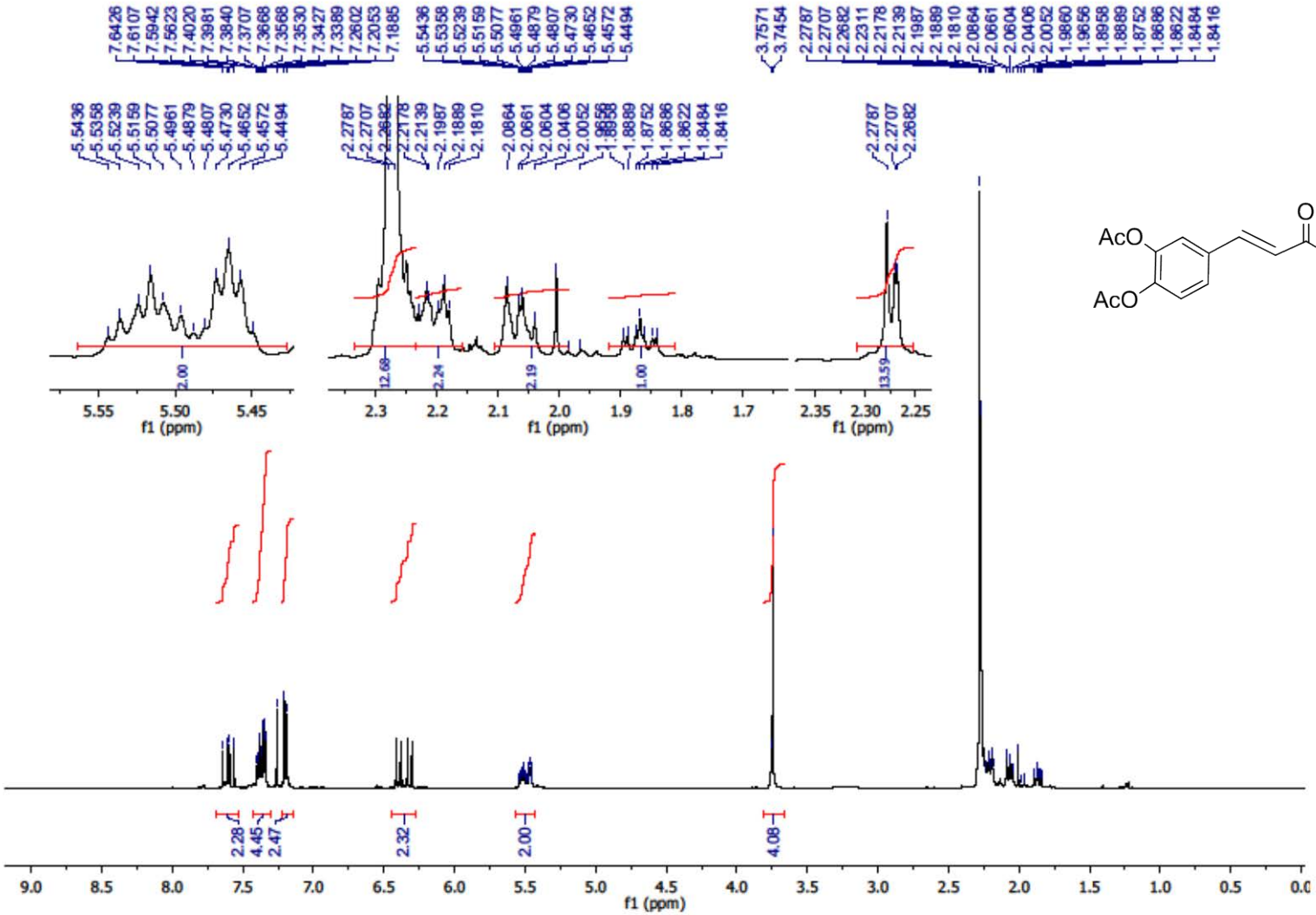
^{13}C NMR (100MHz, CD_3OD, 295K)

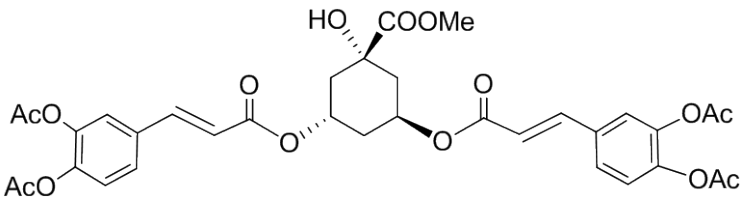




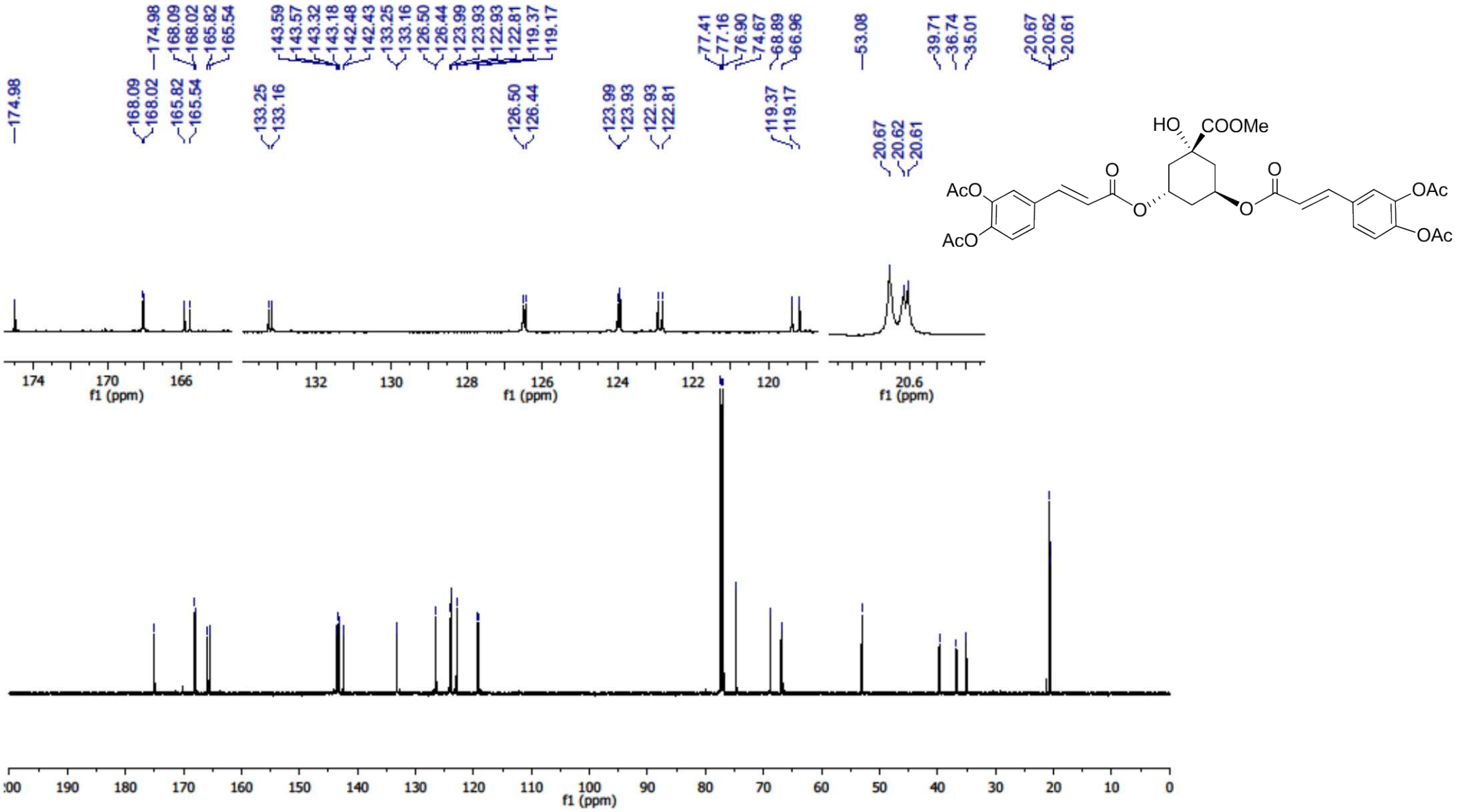
Methyl (3S,5S) 1-hydroxy-3,5 bis[[(2E)-3-(3,4-diacetoxyphenyl)-1-oxo-2-propen-1-yl]oxy]cyclohexanecarboxylate 9a

^{1}H NMR (500MHz, $CDCl_3$, 297K)



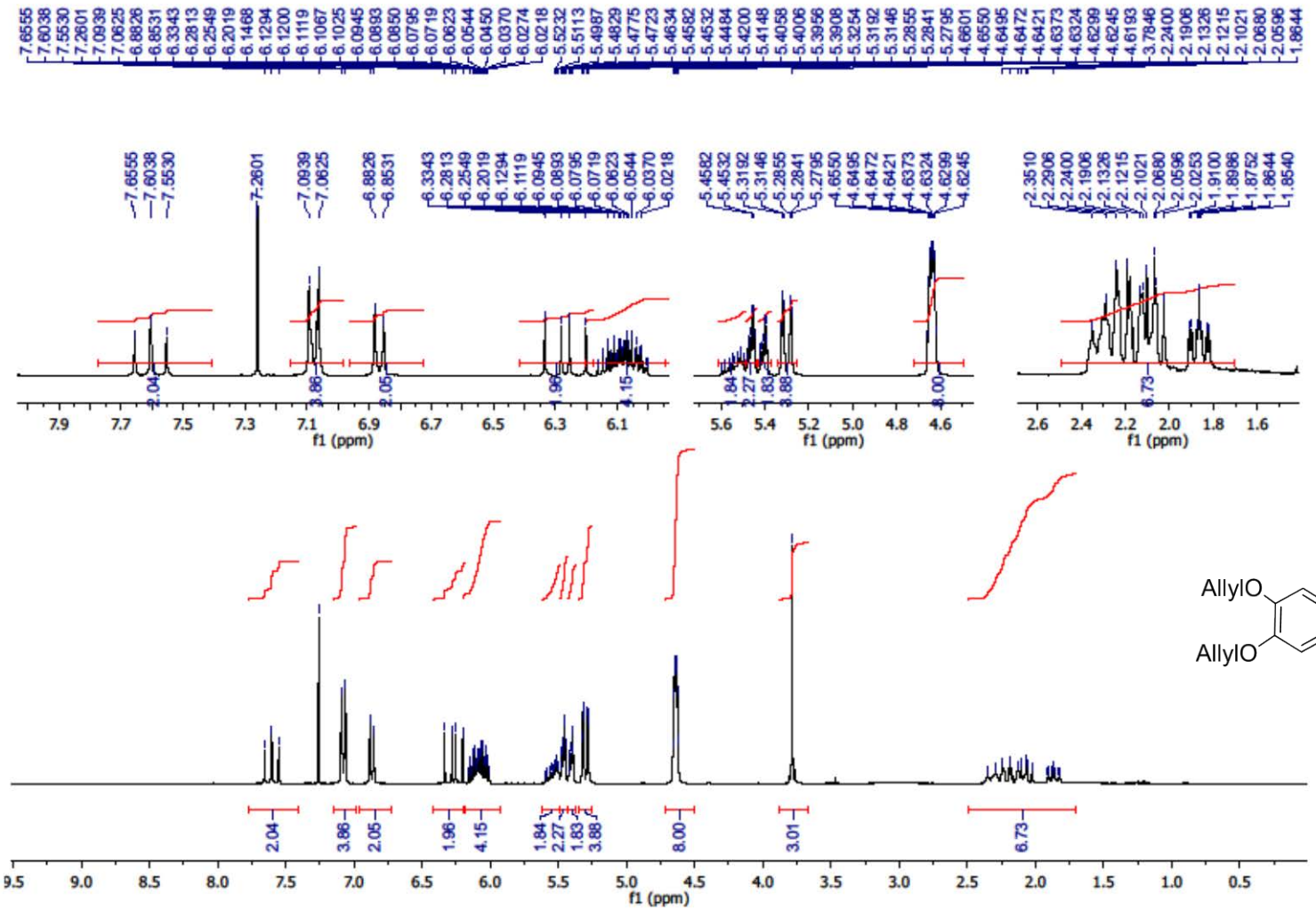


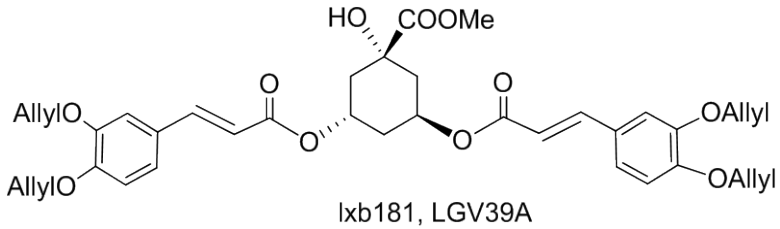
^{13}C NMR (125MHz, CD_3OD, 295K)



Methyl (3S,5S) 1-hydroxy-3,5 bis[[(2E)-3-(3,4-di-(prop-2-en-1-yloxy)phenyl)-1-oxo-2-propen-1-yl]oxy]cyclohexanecarboxylate 9b

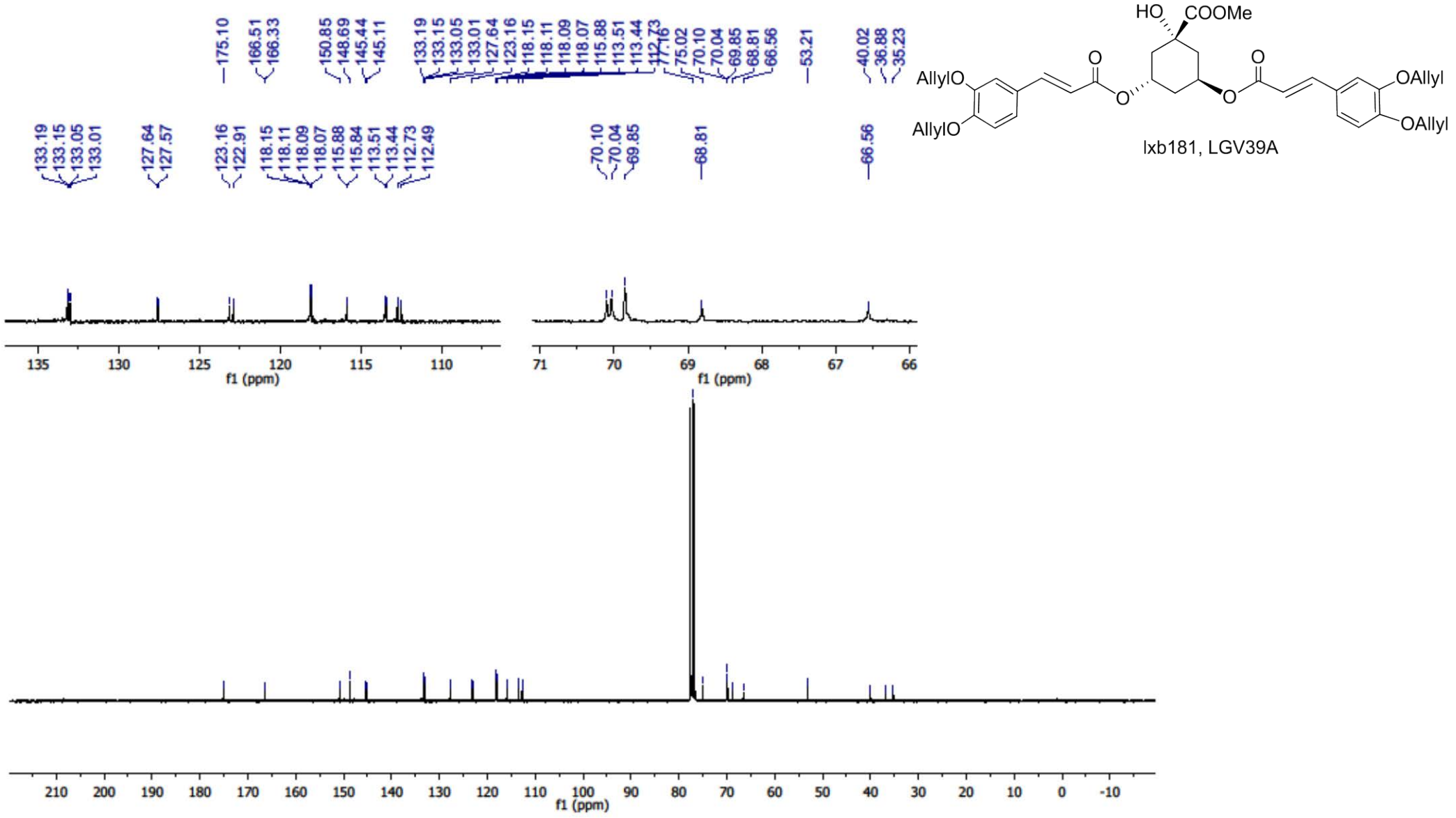
^{1}H NMR (300MHz, $CDCl_3$, 296K)





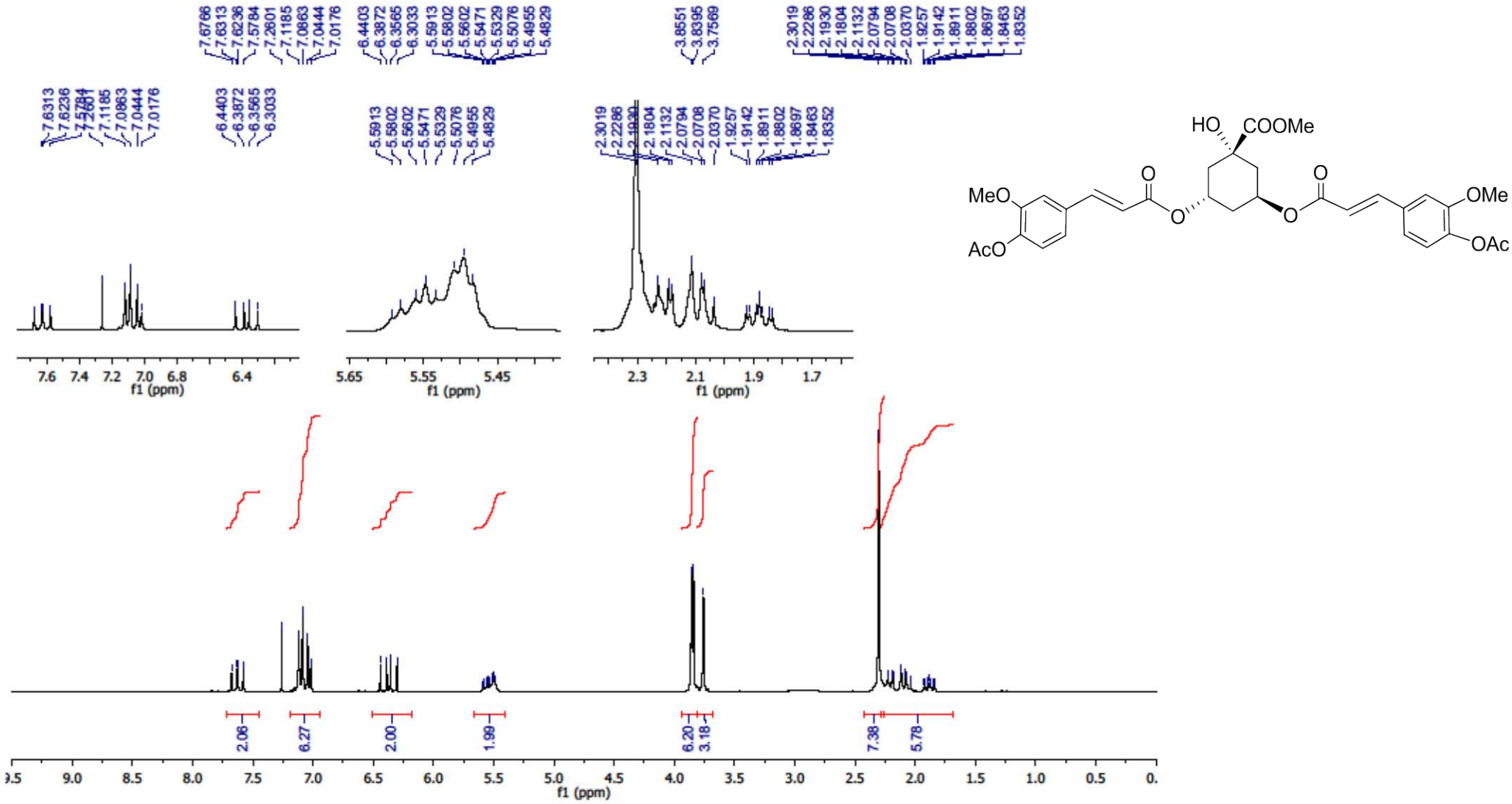
lxb181, LGV39A

^{13}C NMR (75MHz, $CDCl_3$, 296K)

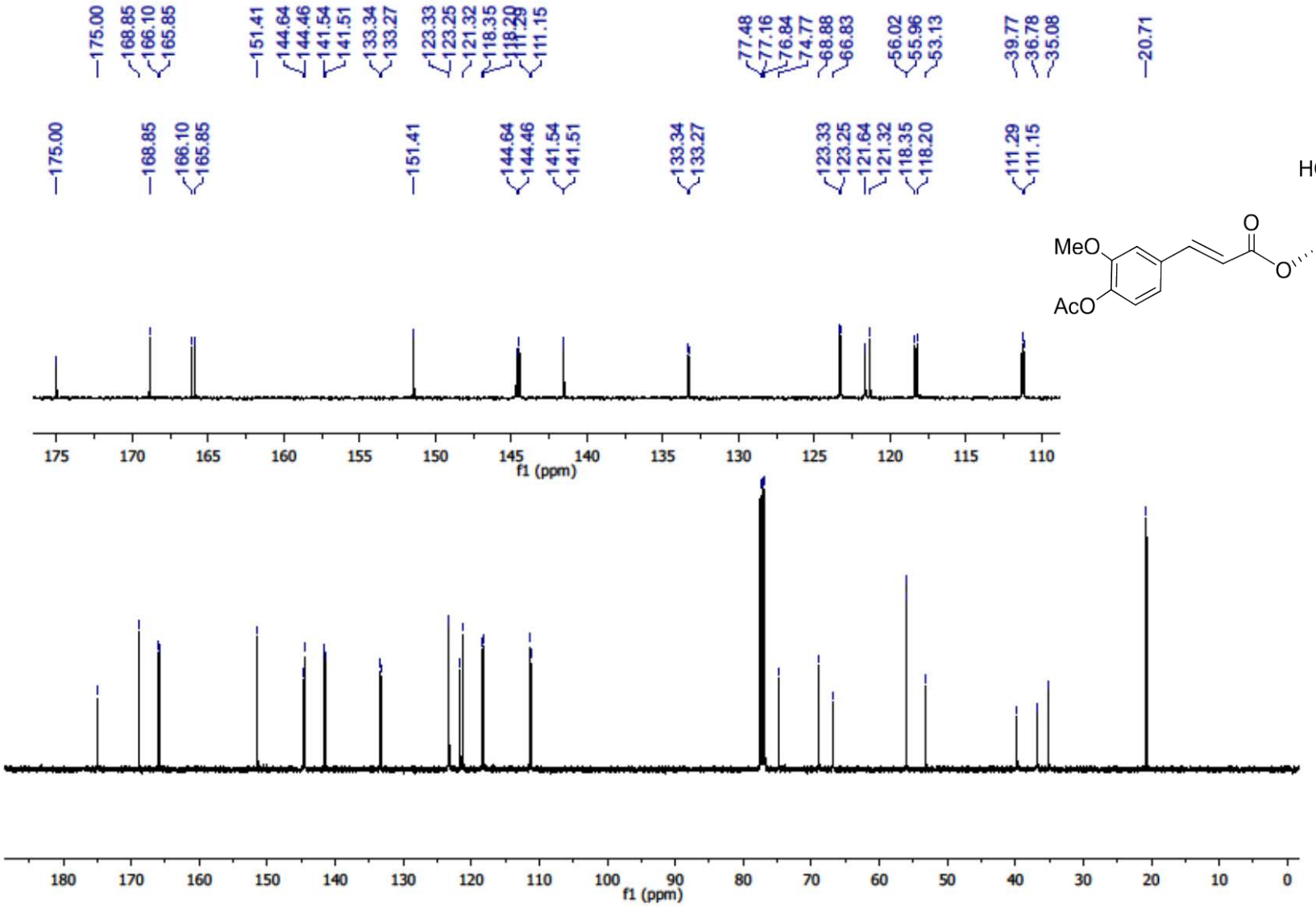


Methyl (3S,5S) 1-hydroxy-3,5 bis[[(2E)-3-(3-acetoxy,4-methoxyphenyl)-1-oxo-2-propen-1-yl]oxy]cyclohexanecarboxylate 9c

^{1}H NMR (300MHz, $CDCl_3$, 296K)

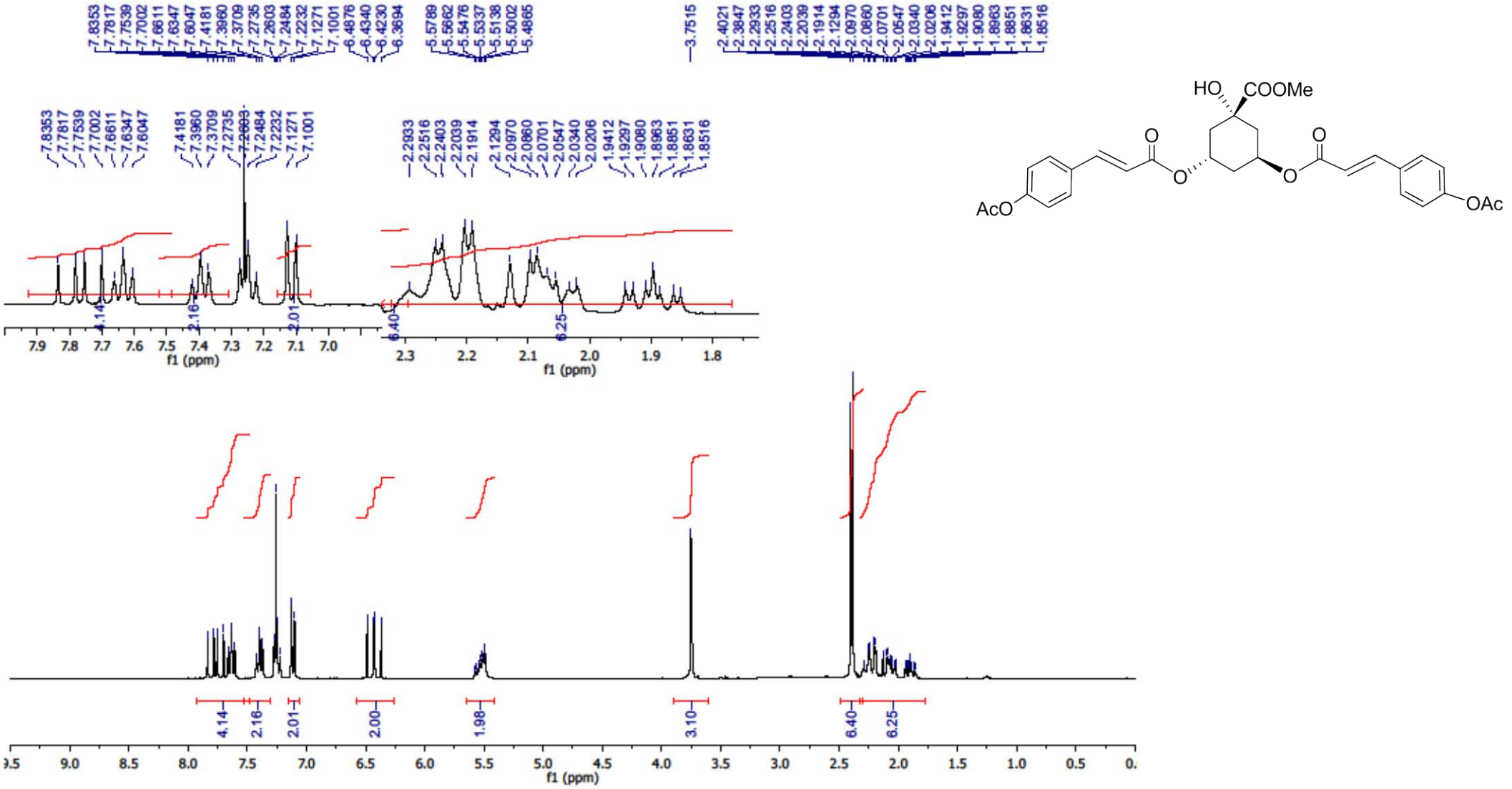


^{13}C NMR (100MHz, $CDCl_3$, 295K)

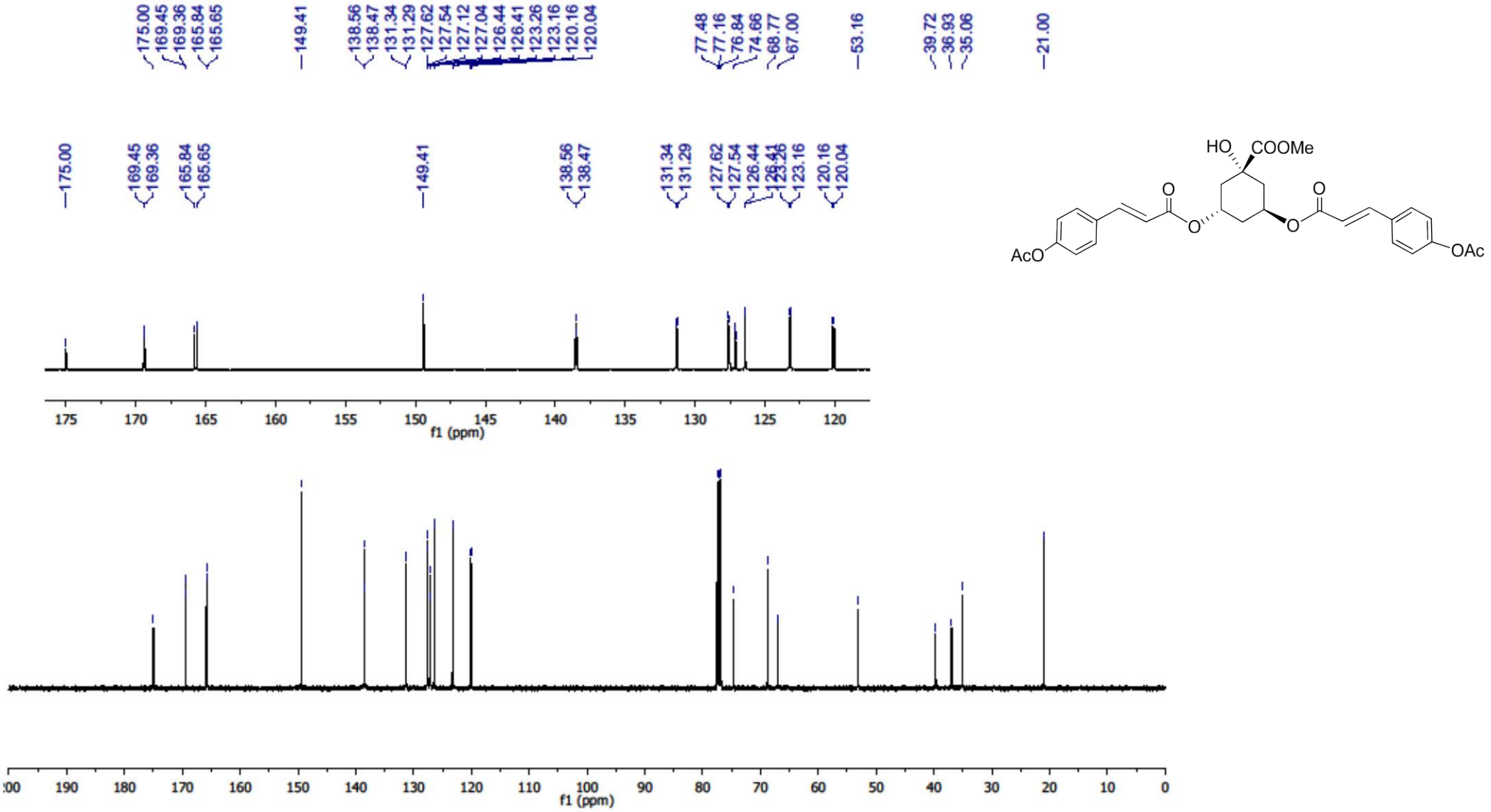


Methyl (3S,5S) 1-hydroxy-3,5 bis[[(2E)-3-(4-acetoxyphenyl)-1-oxo-2-propen-1-yl]oxy]cyclohexanecarboxylate 9d

^{1}H NMR (300MHz, $CDCl_3$, 296K)

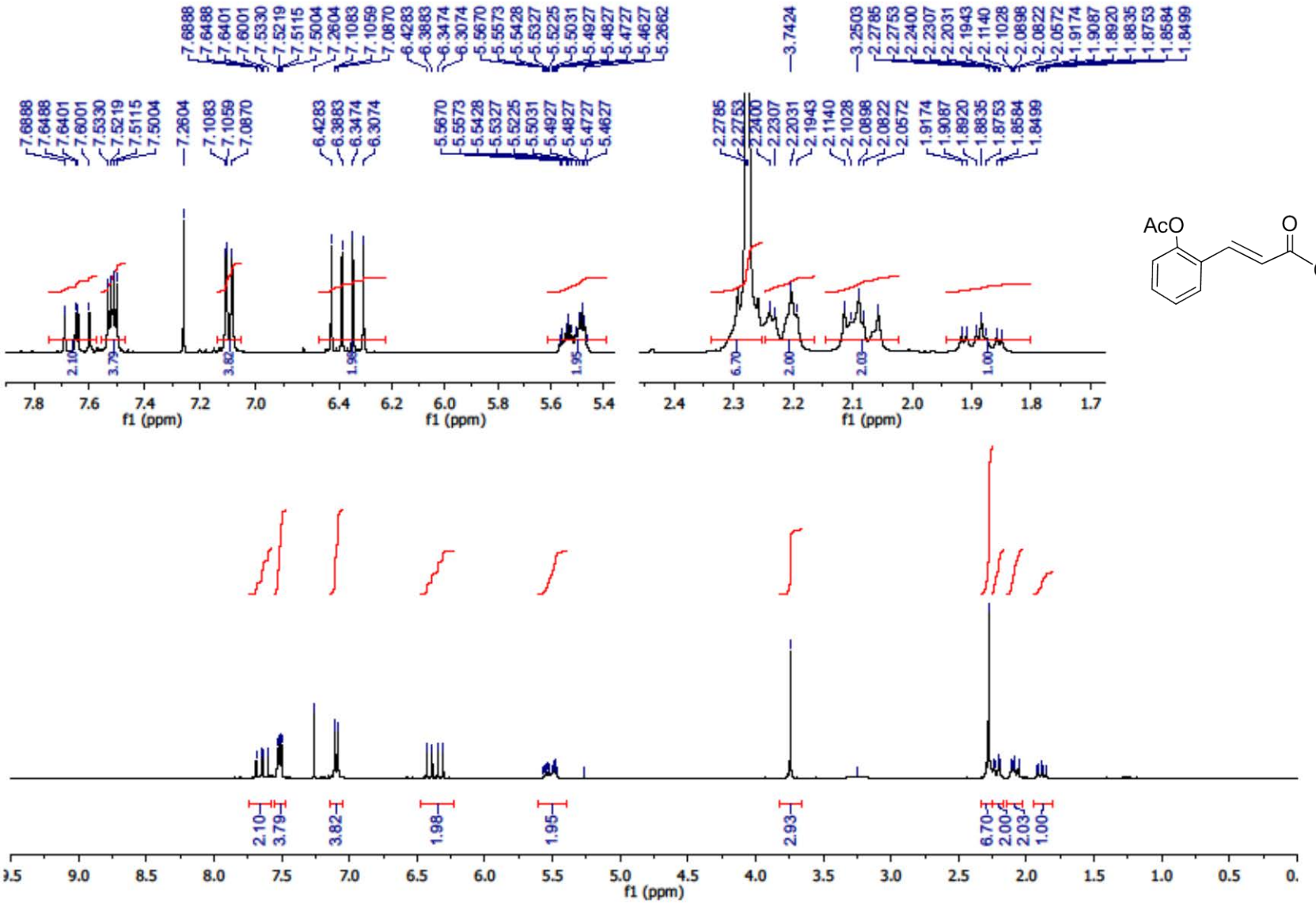


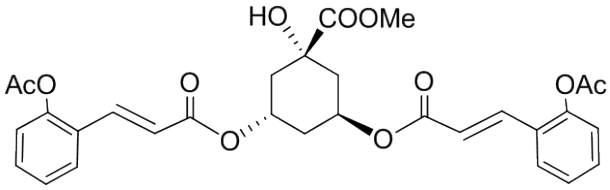
^{13}C NMR (100MHz, $CDCl_3$, 295K)



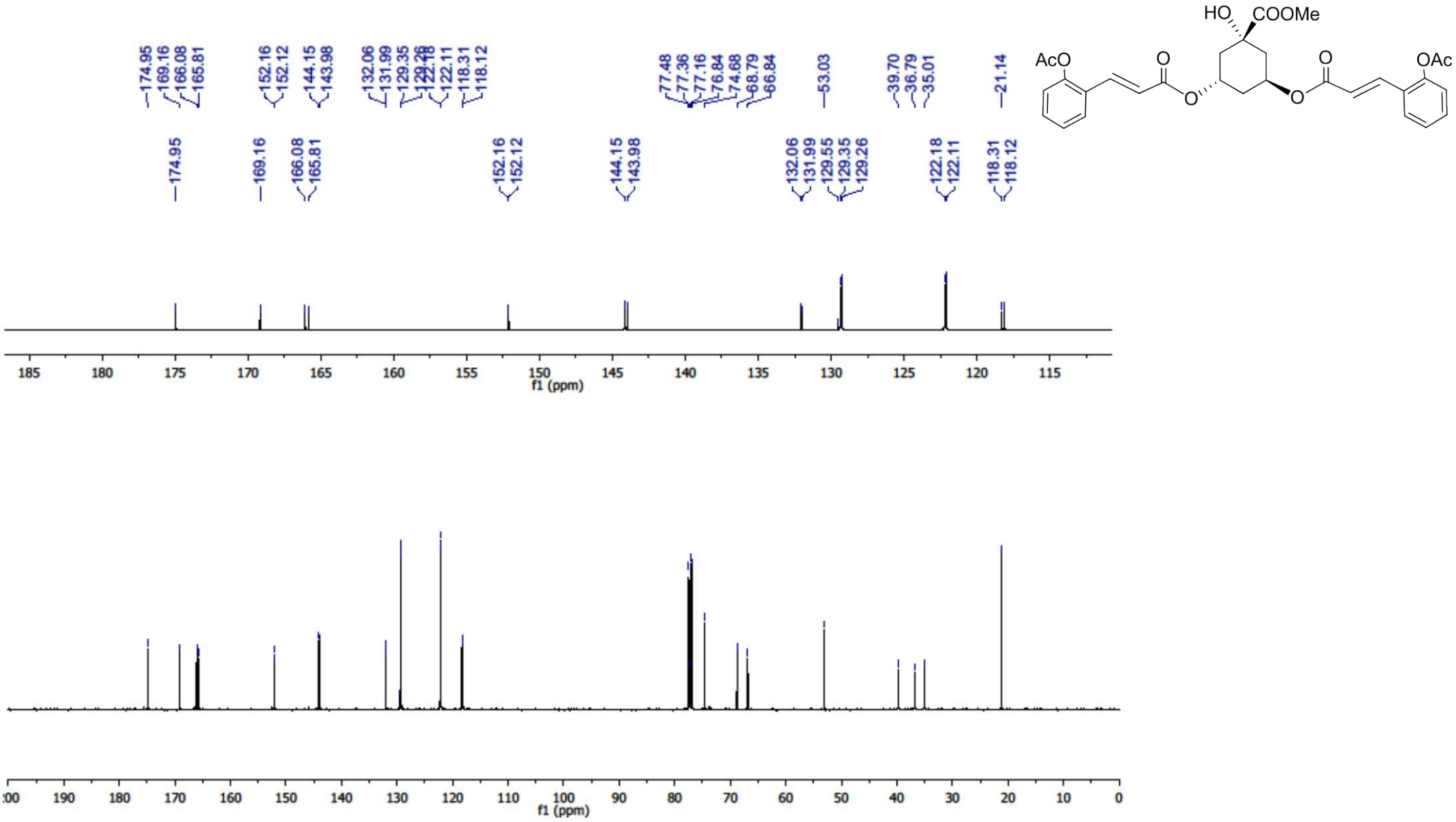
Methyl (3S,5S) 1-hydroxy-3,5 bis[[(2E)-3-(4-acetoxyphenyl)-1-oxo-2-propen-1-yl]oxy]cyclohexanecarboxylate 9e

^{1}H NMR (400MHz, $CDCl_3$, 295K)



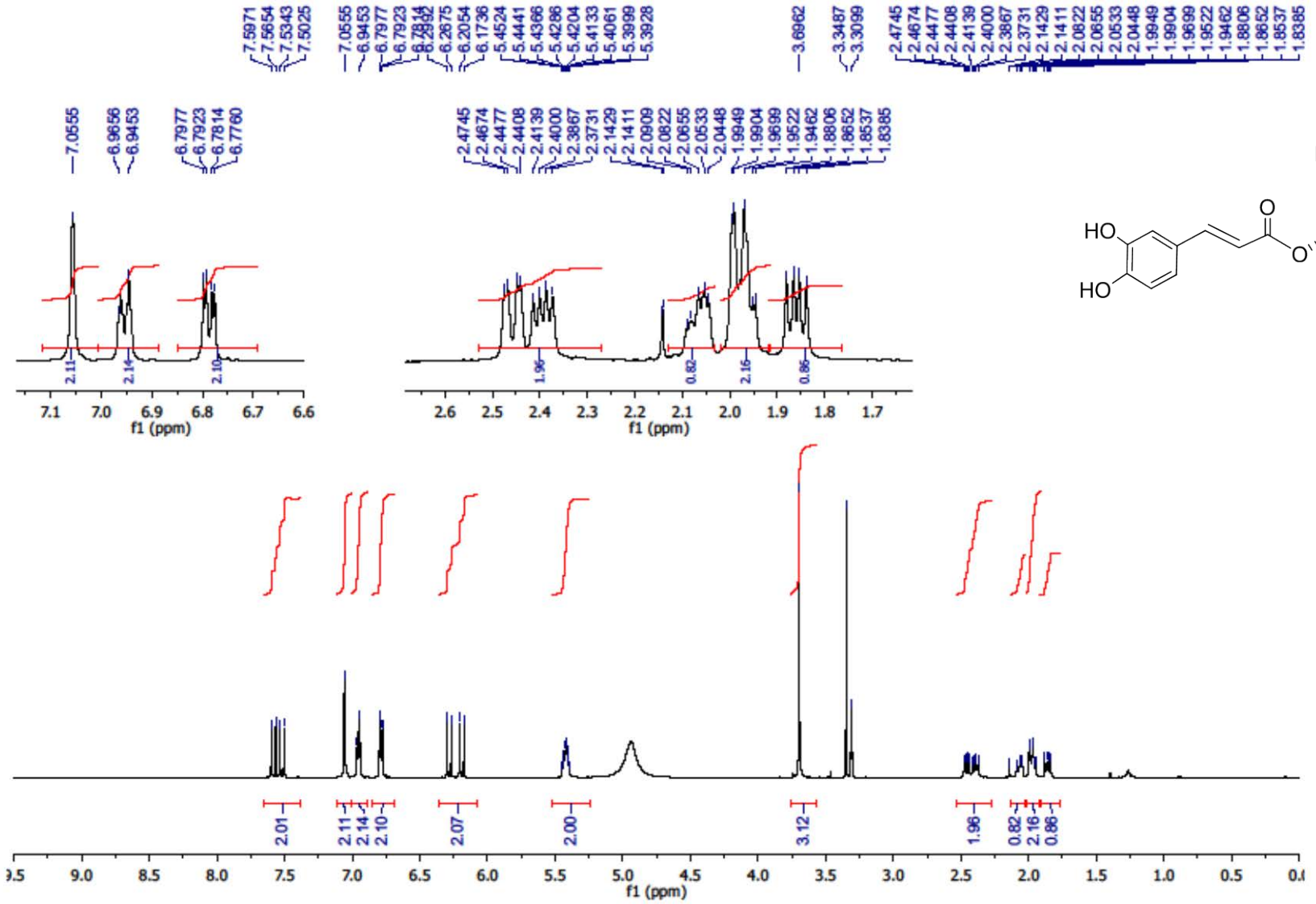


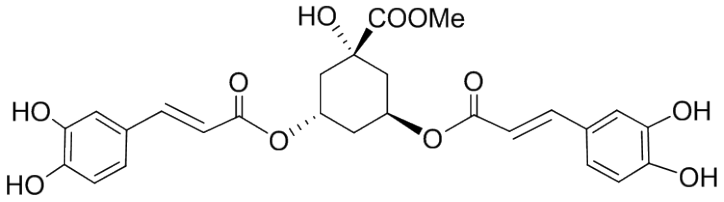
^{13}C NMR (100MHz, CD_3OD, 295K)



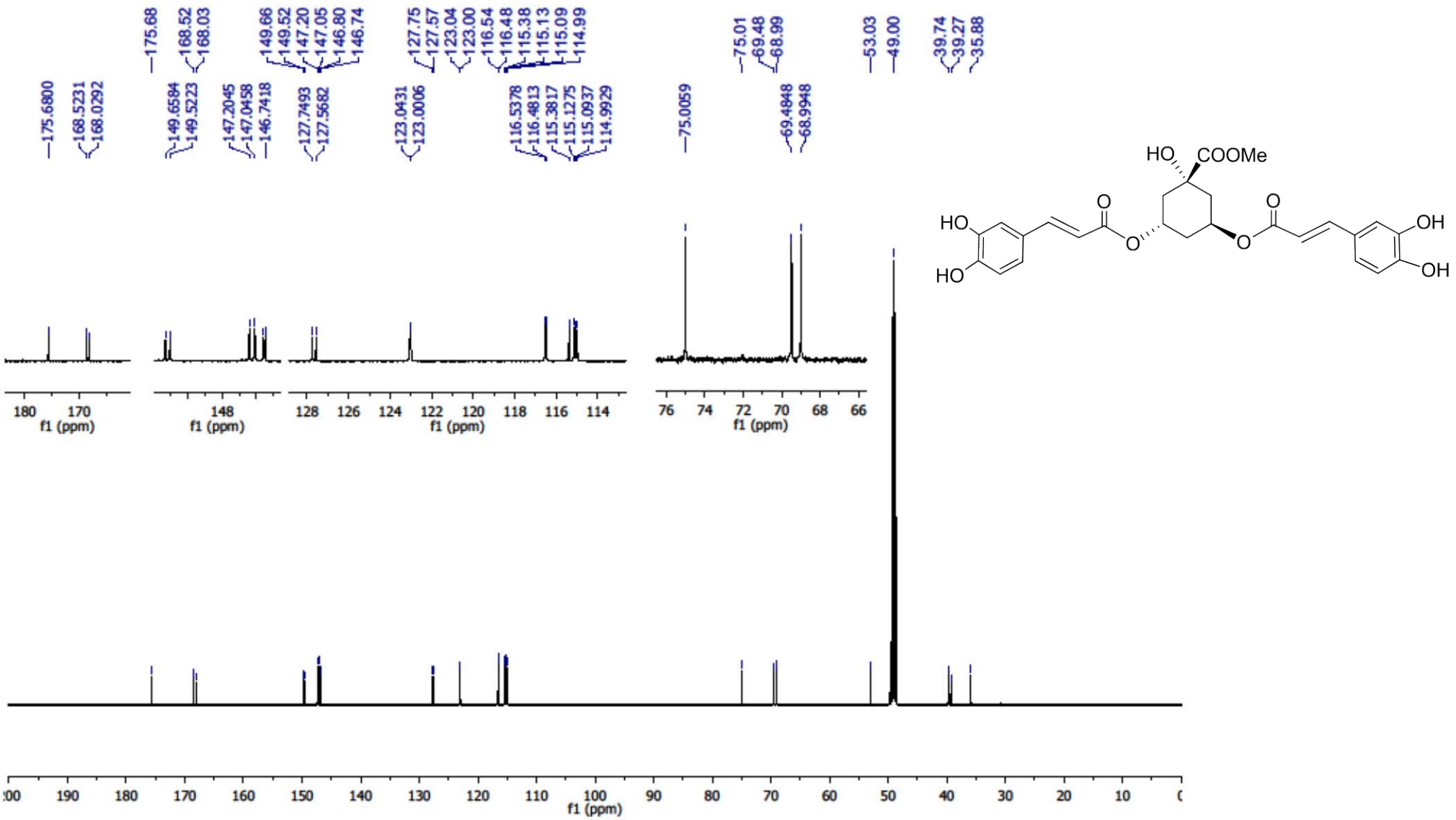
Methyl (3S,5S) 1-hydroxy-3,5 bis[[(2E)-3-(3,4-dihydroxyphenyl)-1-oxo-2-propen-1-yl]oxy]cyclohexanecarboxylate 10a

^{1}H NMR (500MHz, CD_3OD, 298K)



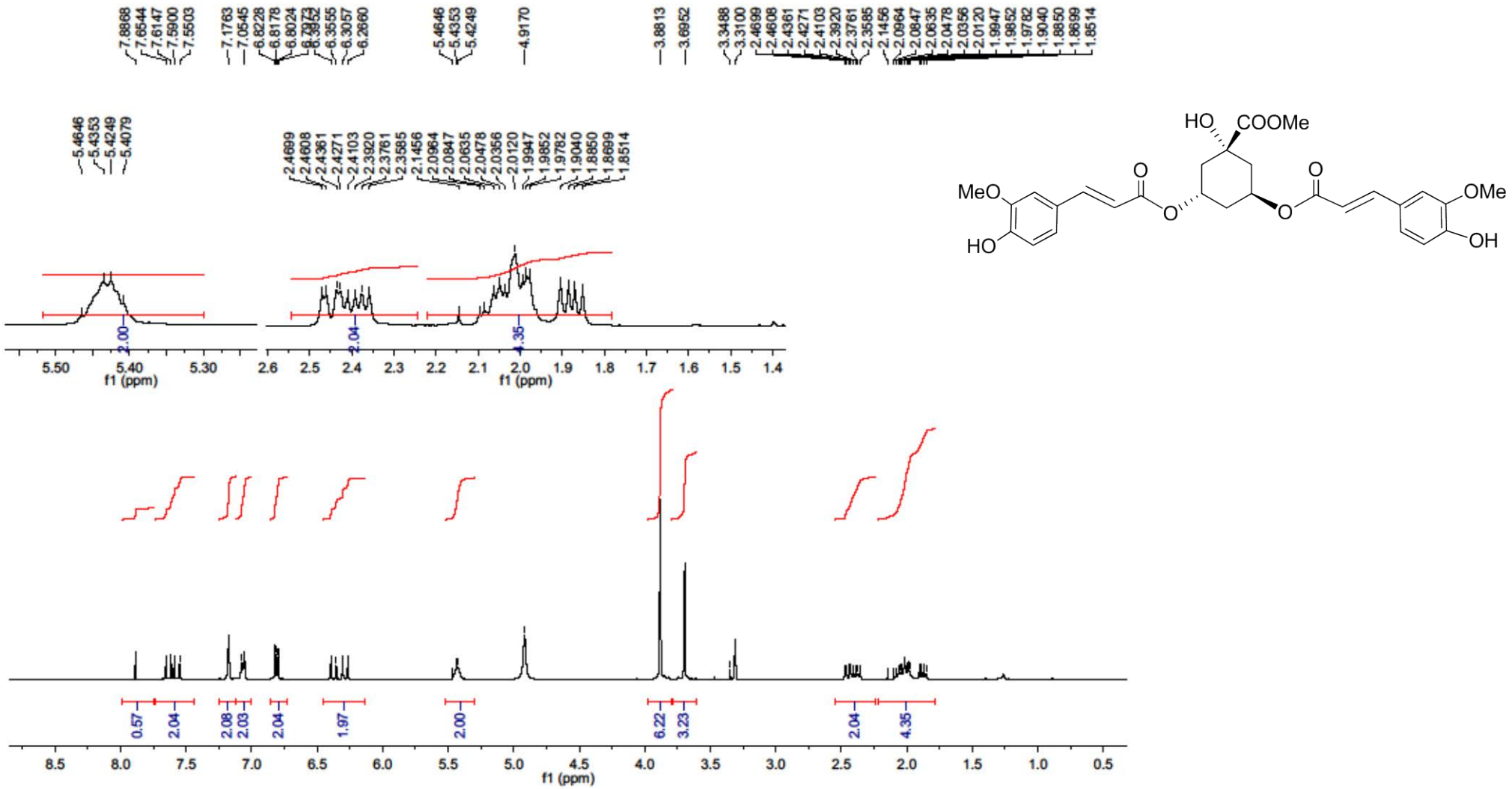


^{13}C NMR (125MHz, CD_3OD, 297K)

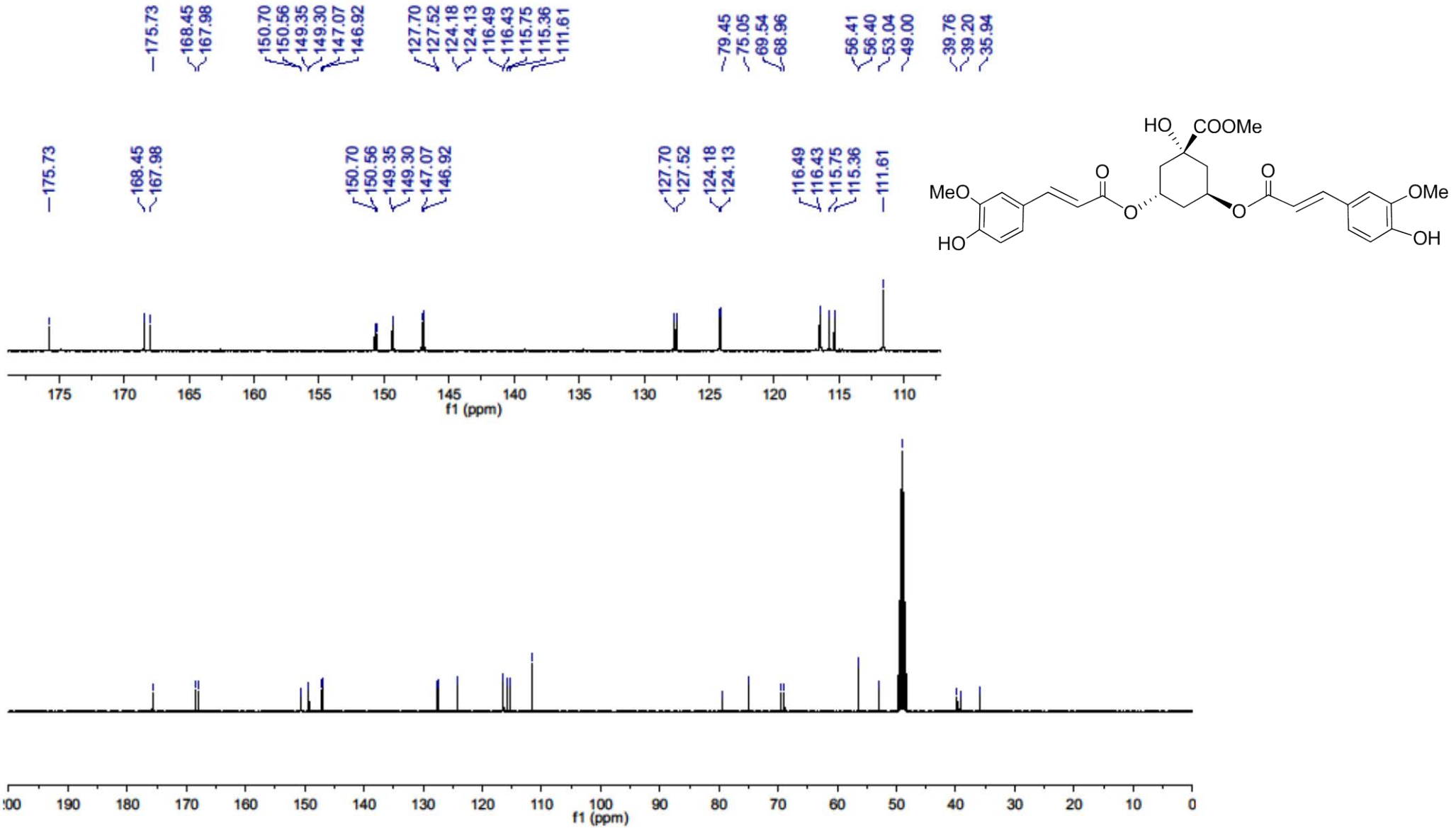


Methyl (3S,5S) 1-hydroxy-3,5 bis[[(2E)- 3-(4-hydroxy-3-methoxyphenyl)-1-oxo-2-propen-1-yl]oxy]cyclohexanecarboxylate 10c

^{1}H NMR (400MHz, CD_3OD, 295K)

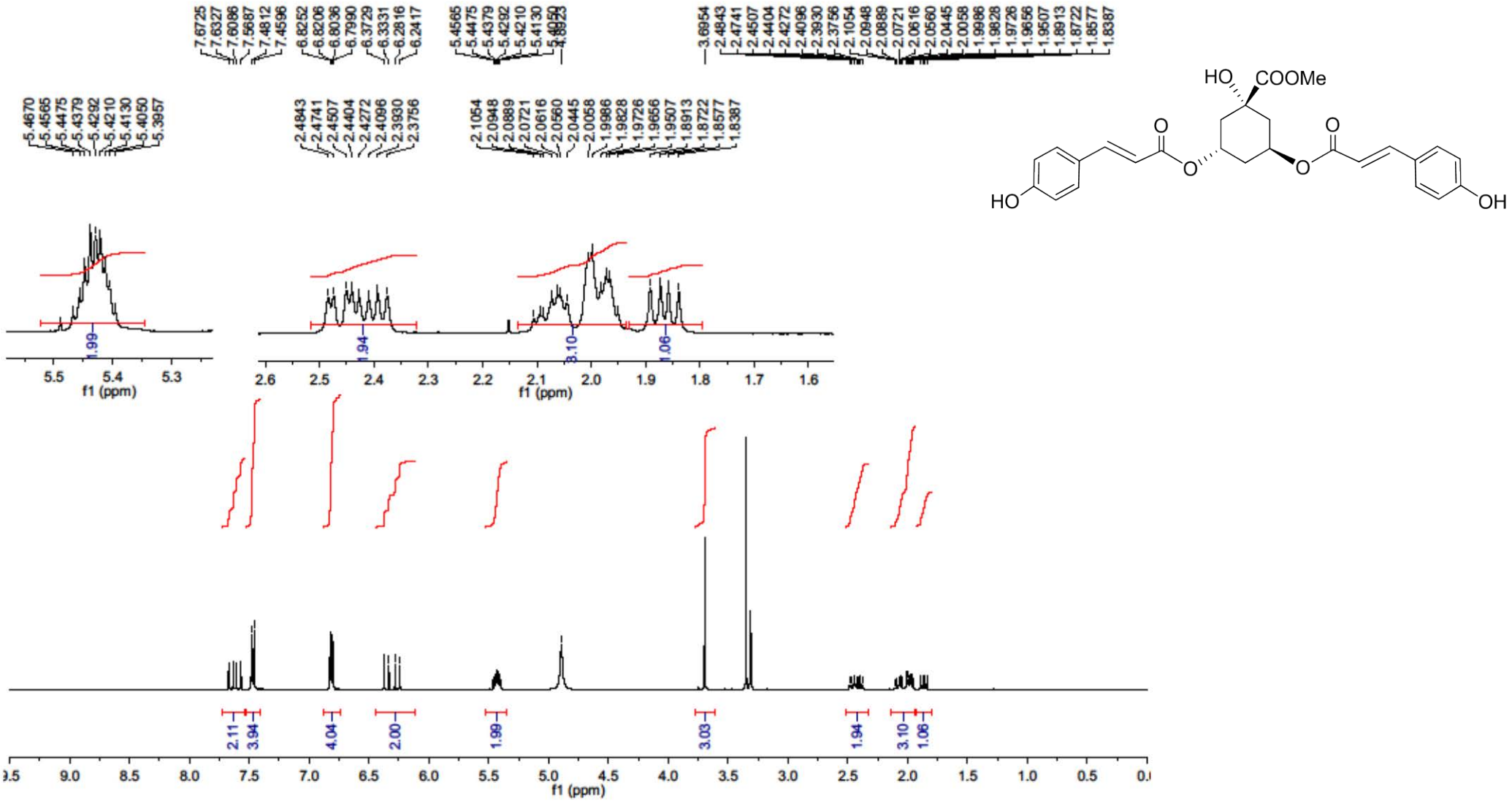


^{13}C NMR (100MHz, CD_3OD, 295K)

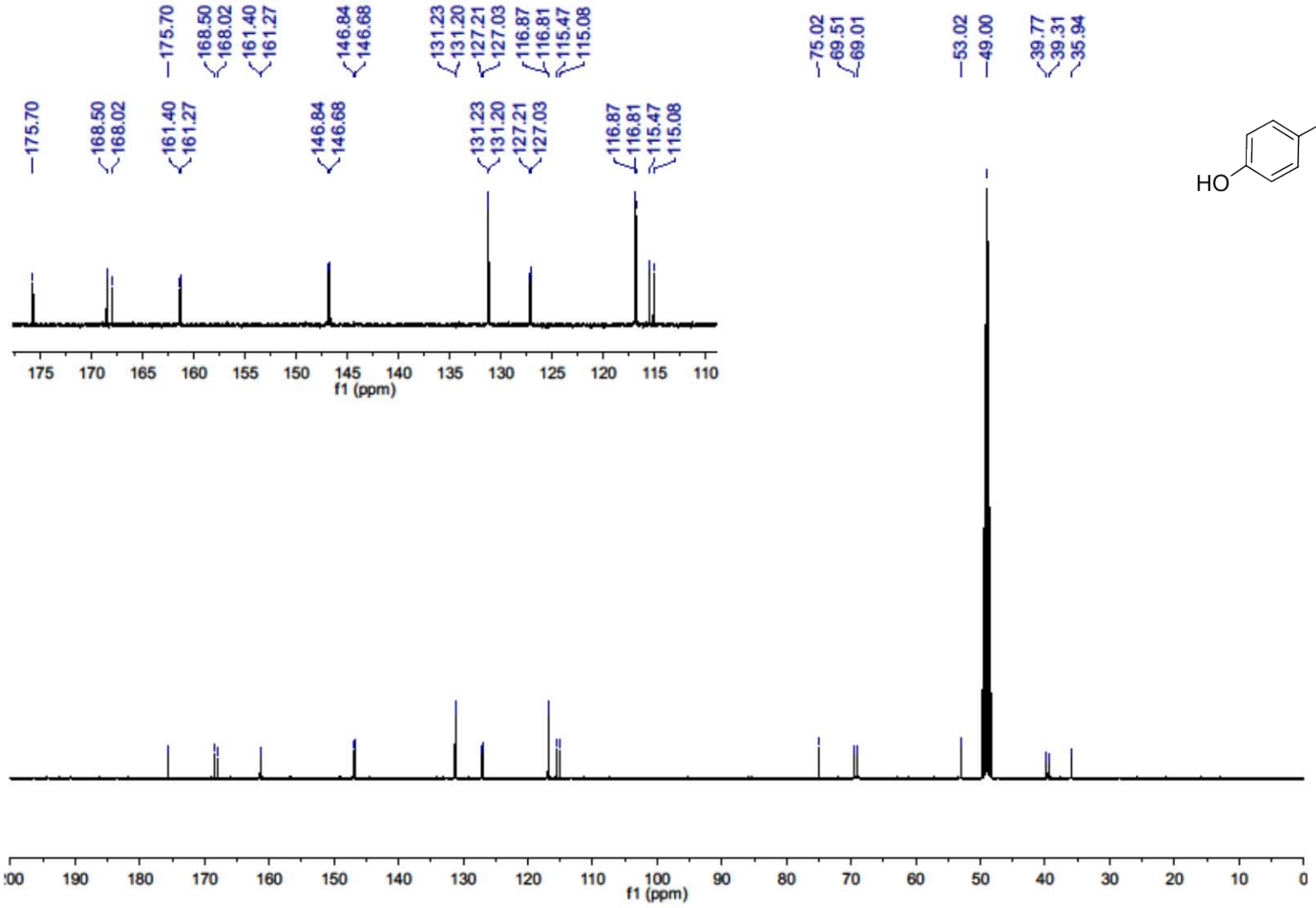


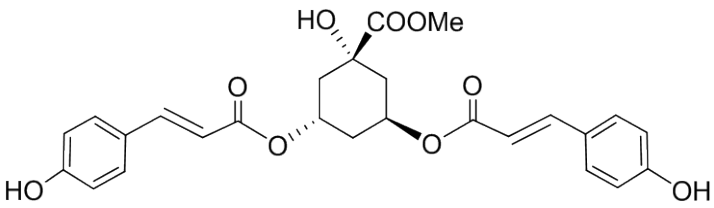
Methyl (3S,5S) 1-hydroxy-3,5 bis[[(2E)-3-(4-hydroxyphenyl)-1-oxo-2-propen-1-yl]oxy]cyclohexanecarboxylate 10d

^{1}H NMR (400MHz, CD_3OD, 295K)



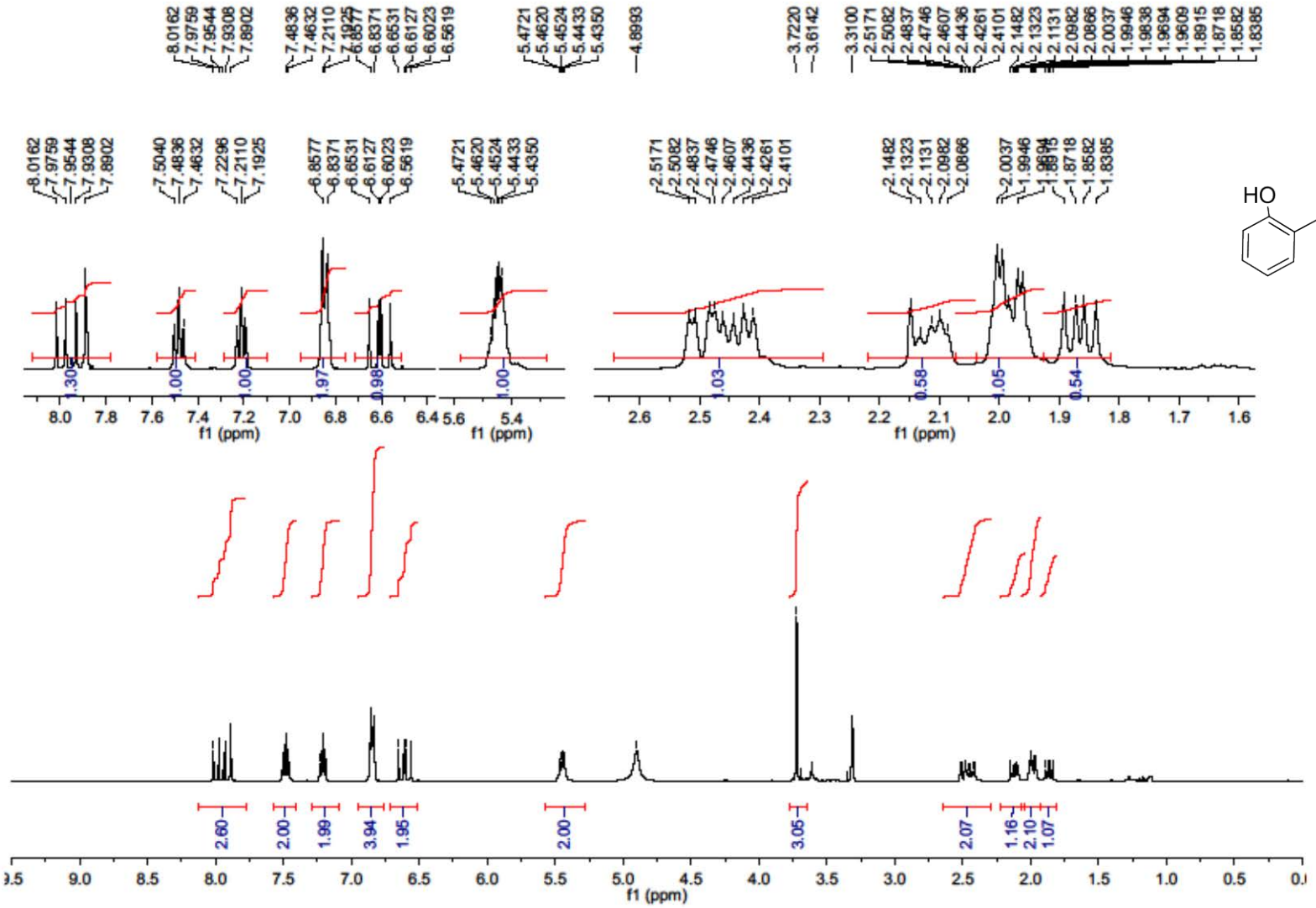
^{13}C NMR (100MHz, CD_3OD, 295K)

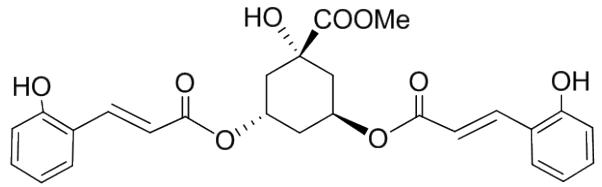




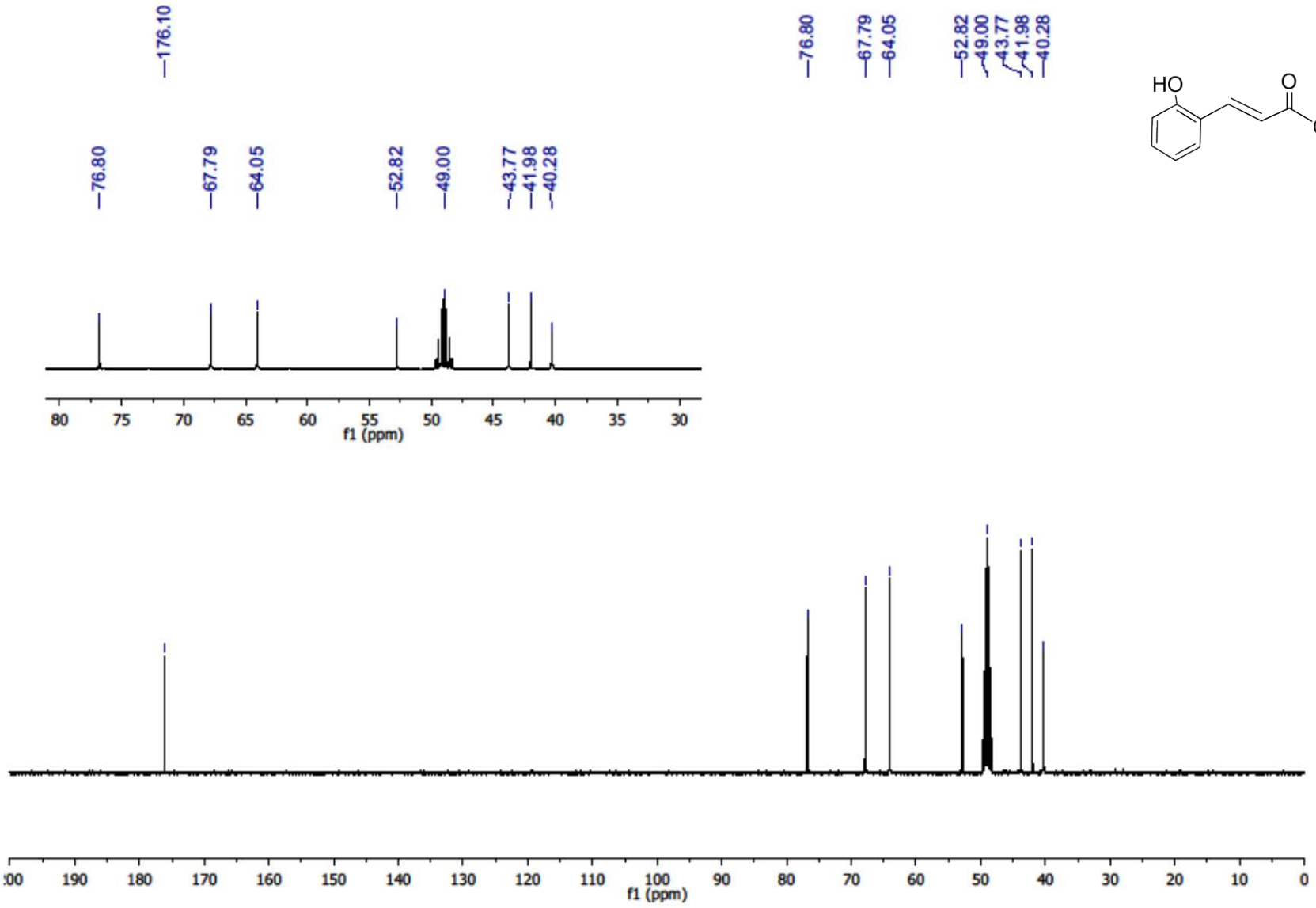
Methyl (3S,5S) 1-hydroxy-3,5 bis[[(2E)-3-(2-hydroxyphenyl)-1-oxo-2-propen-1-yl]oxy]cyclohexanecarboxylate 10e

^{1}H NMR (400MHz, CD_3OD, 295K)



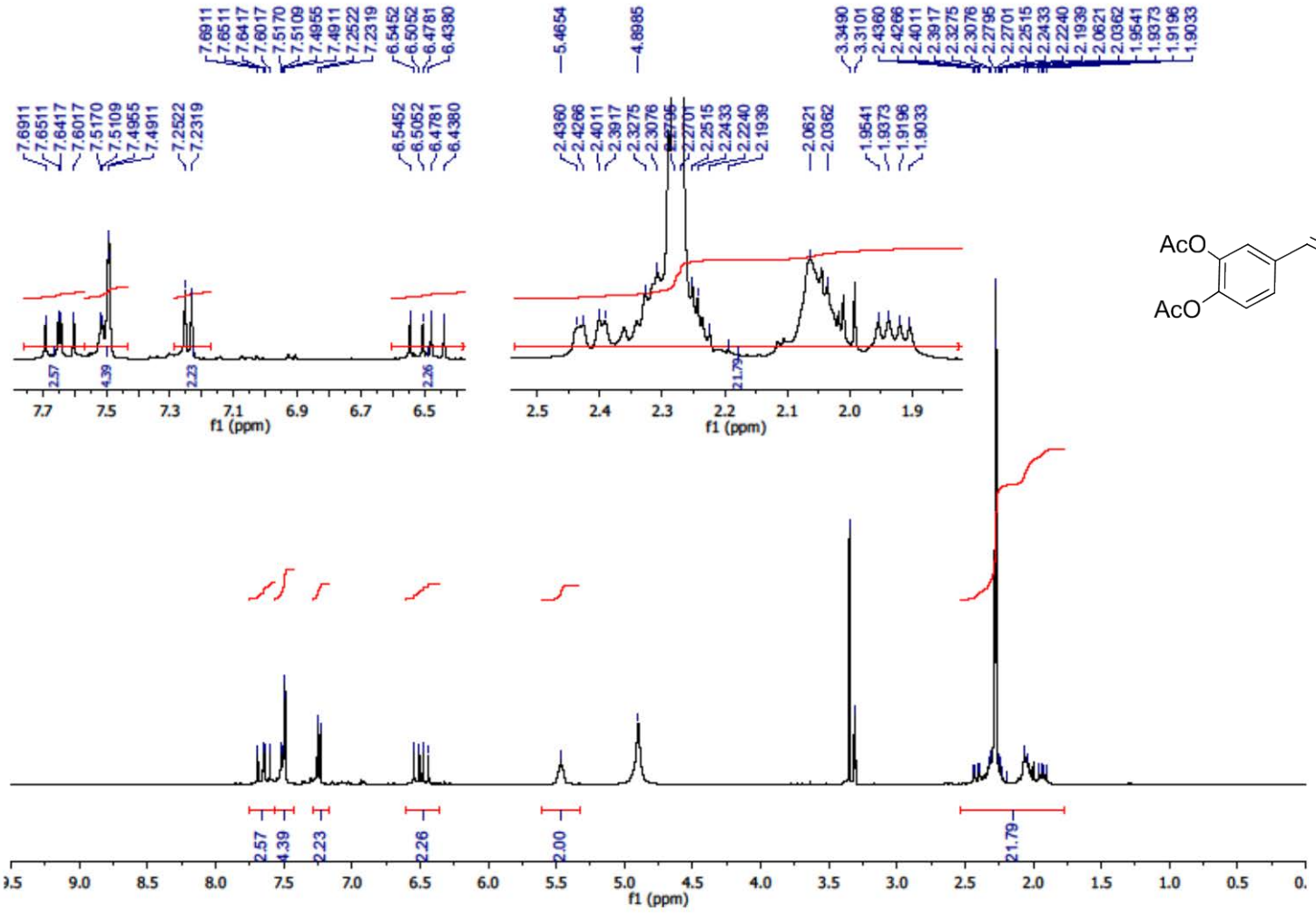


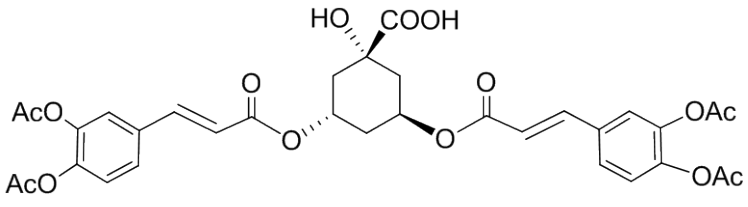
^{13}C NMR (100MHz, CD_3OD, 295K)



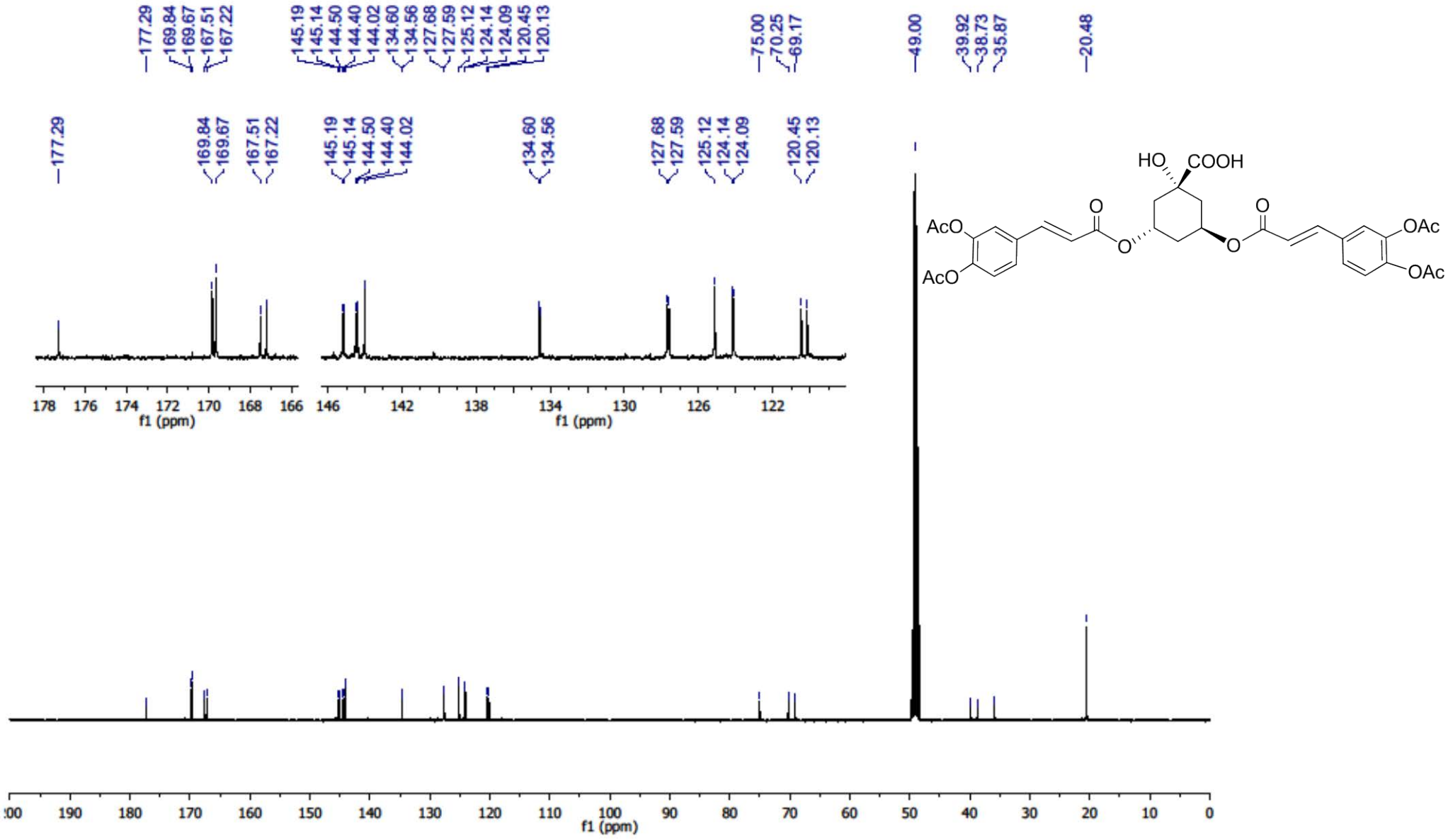
(3S,5S) 1-hydroxy-3,5 bis[[(2E)-3-(3,4-diacetoxyphenyl)-1-oxo-2-propen-1-yl]oxy]cyclohexanecarboxylic acid 11a

^{1}H NMR (400MHz, CD_3OD, 298K)



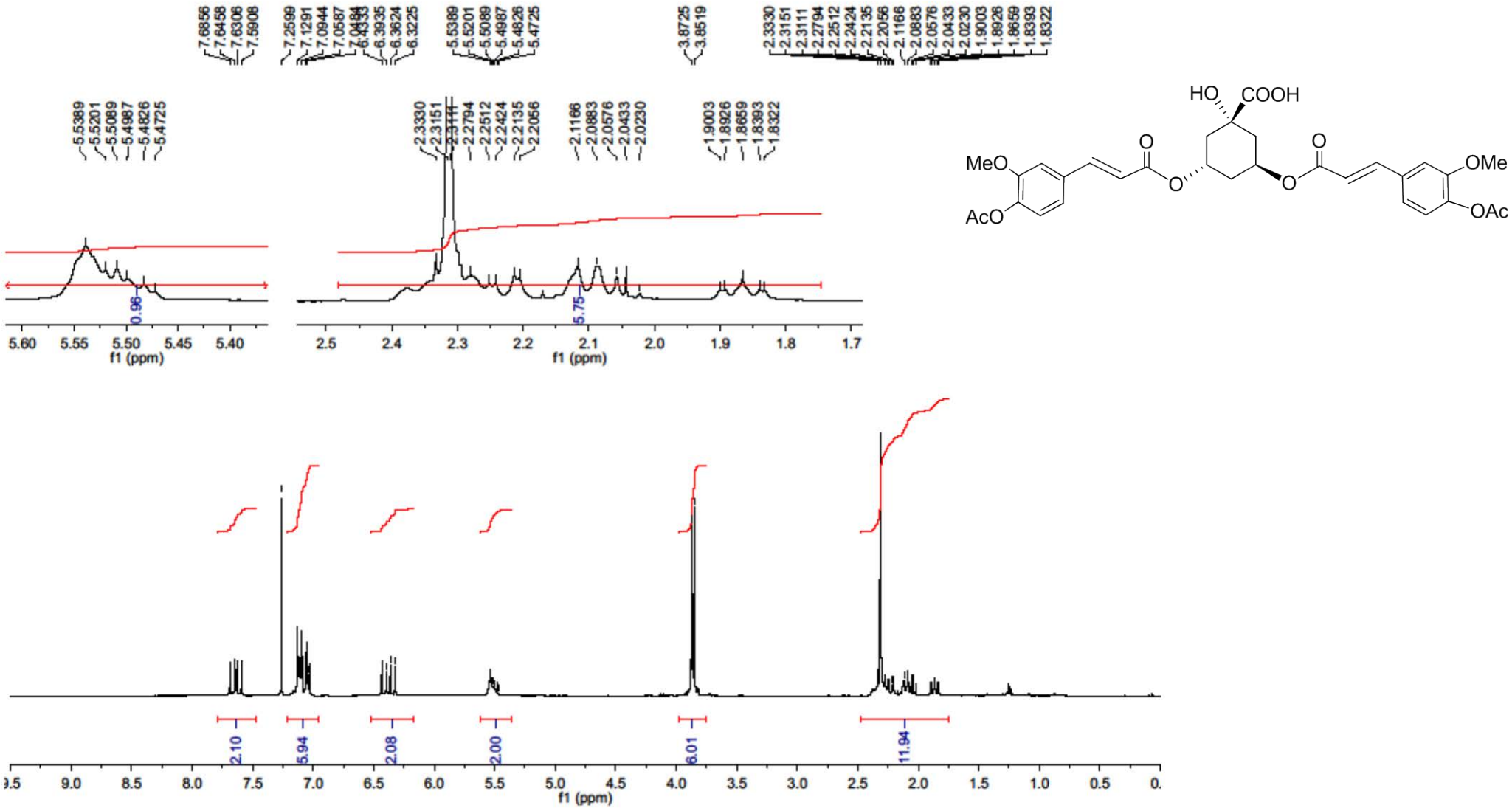


^{13}C NMR (100MHz, CD_3OD, 298K)

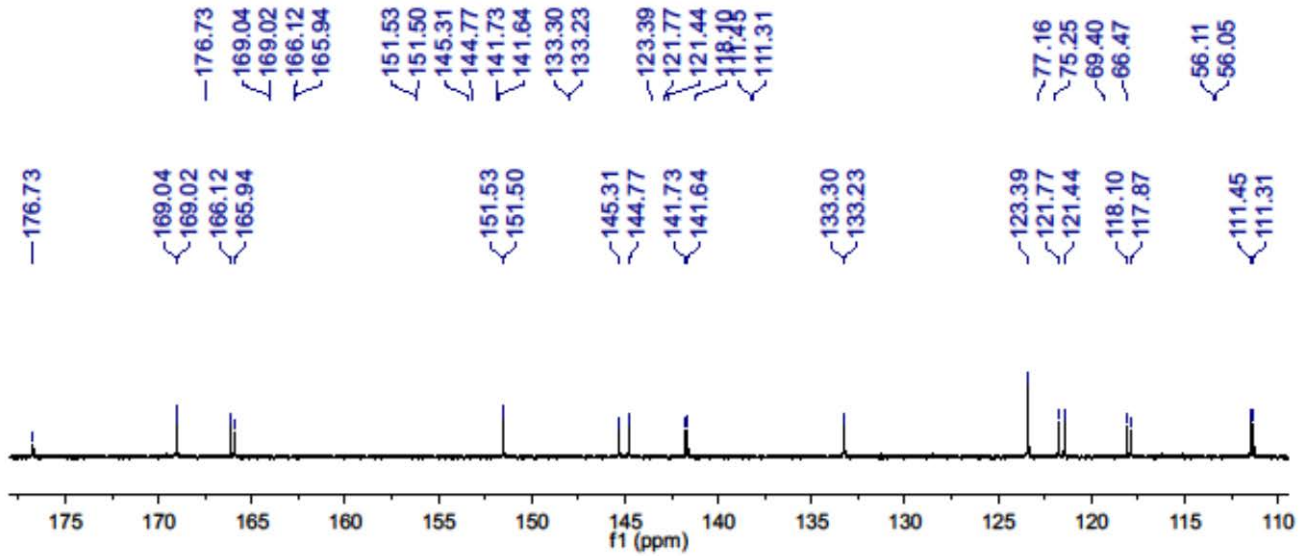


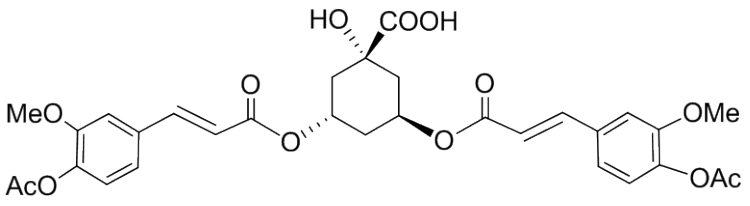
(3S,5S) 1-hydroxy-3,5 bis[[(2E)-3-(4-acetoxy-3-methoxyphenyl)-1-oxo-2-propen-1-yl]oxy]cyclohexanecarboxylic acid 11c

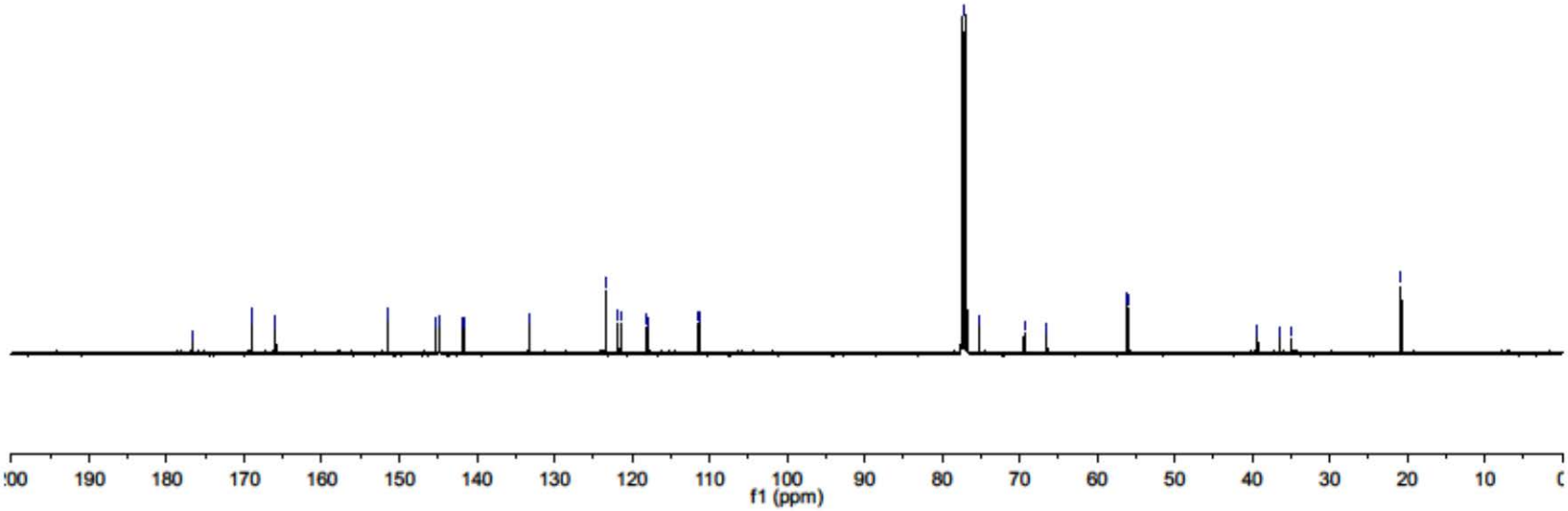
^{1}H NMR (400MHz, $CDCl_3$, 295K)



^{13}C NMR (100MHz, CD_3OD, 295K)

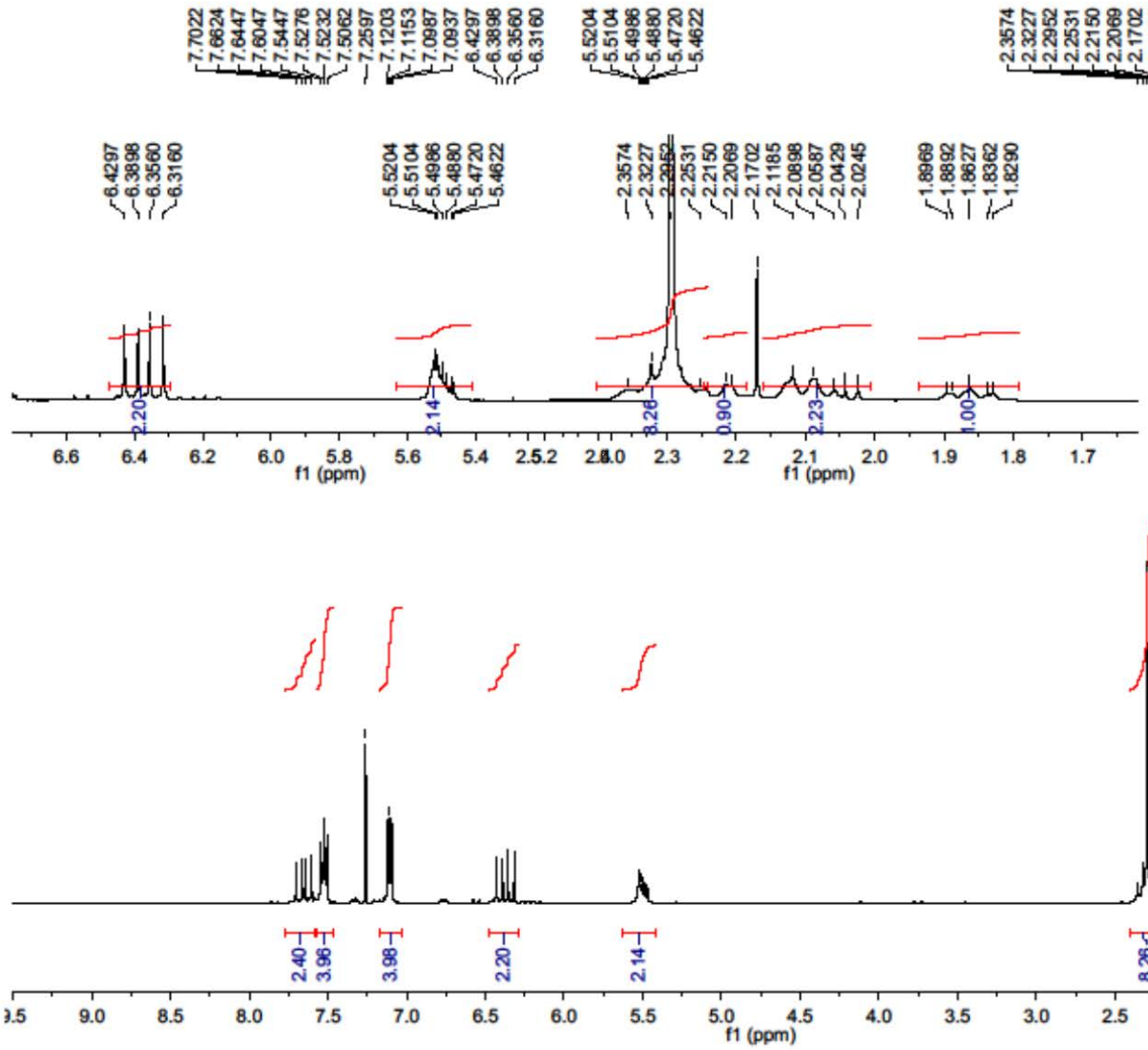


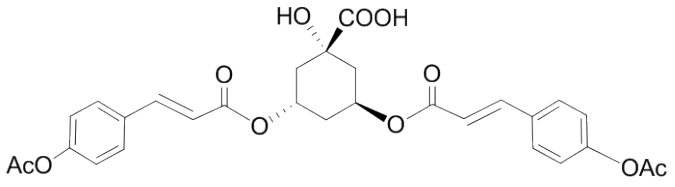




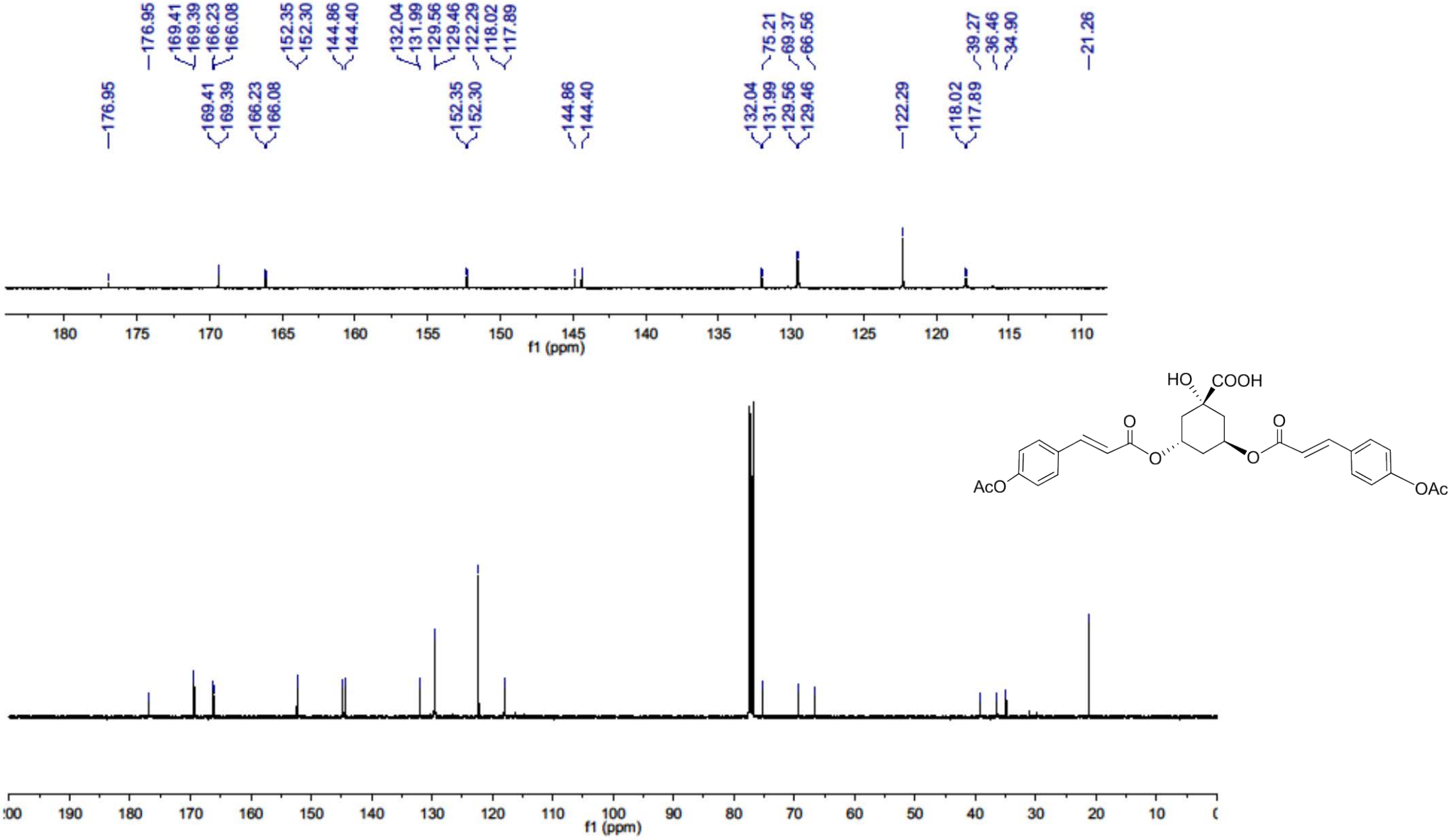
(3S,5S) 1-hydroxy-3,5 bis[[(2E)-3-(4-hydroxyphenyl)-1-oxo-2-propen-1-yl]oxy]cyclohexanecarboxylic acid 11d

^{1}H NMR (400MHz, $CDCl_3$, 295K)



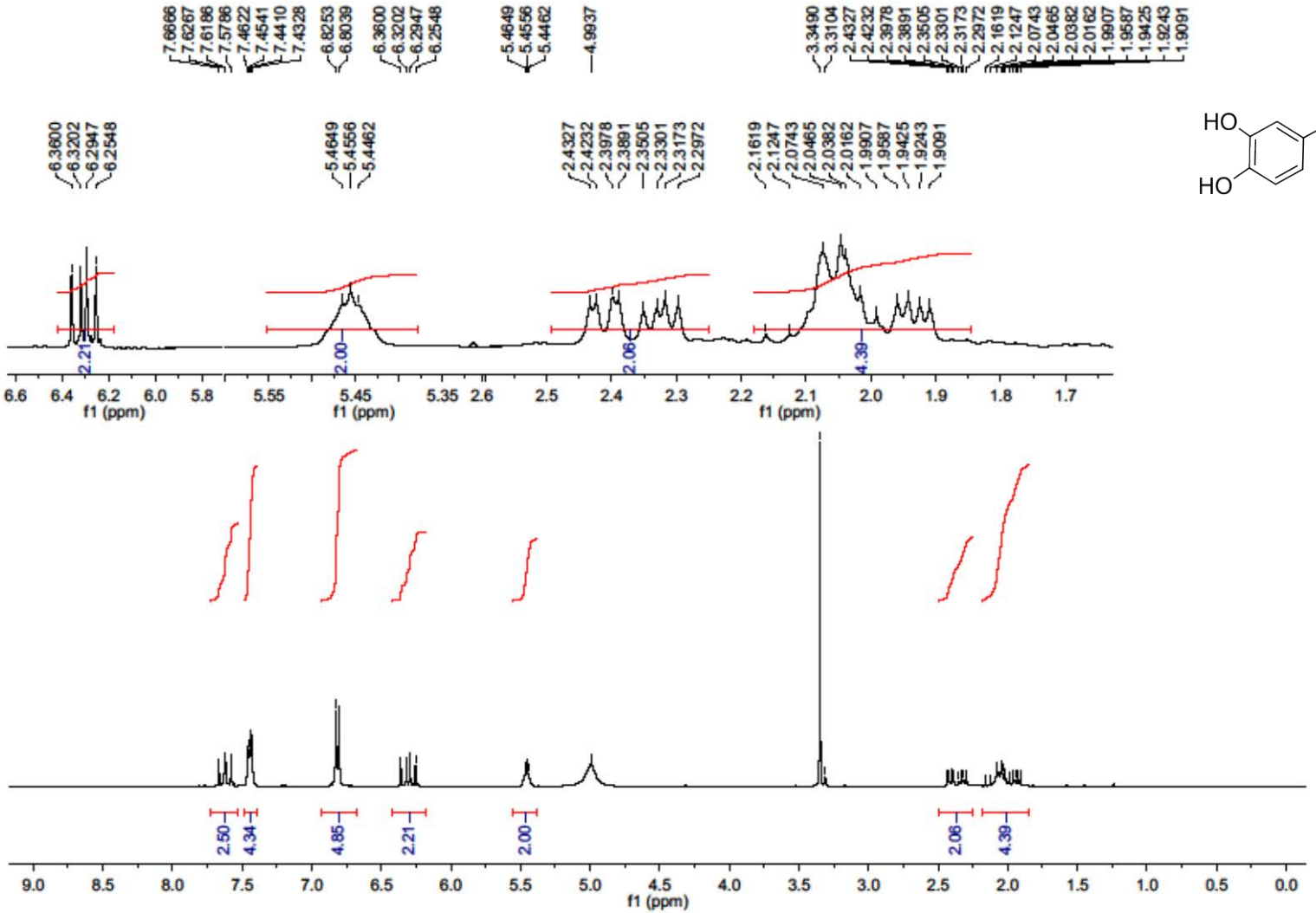


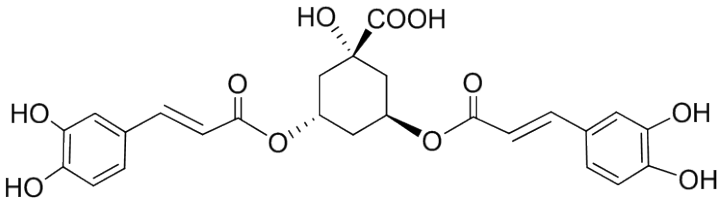
^{13}C NMR (100MHz, CD_3OD, 295K)



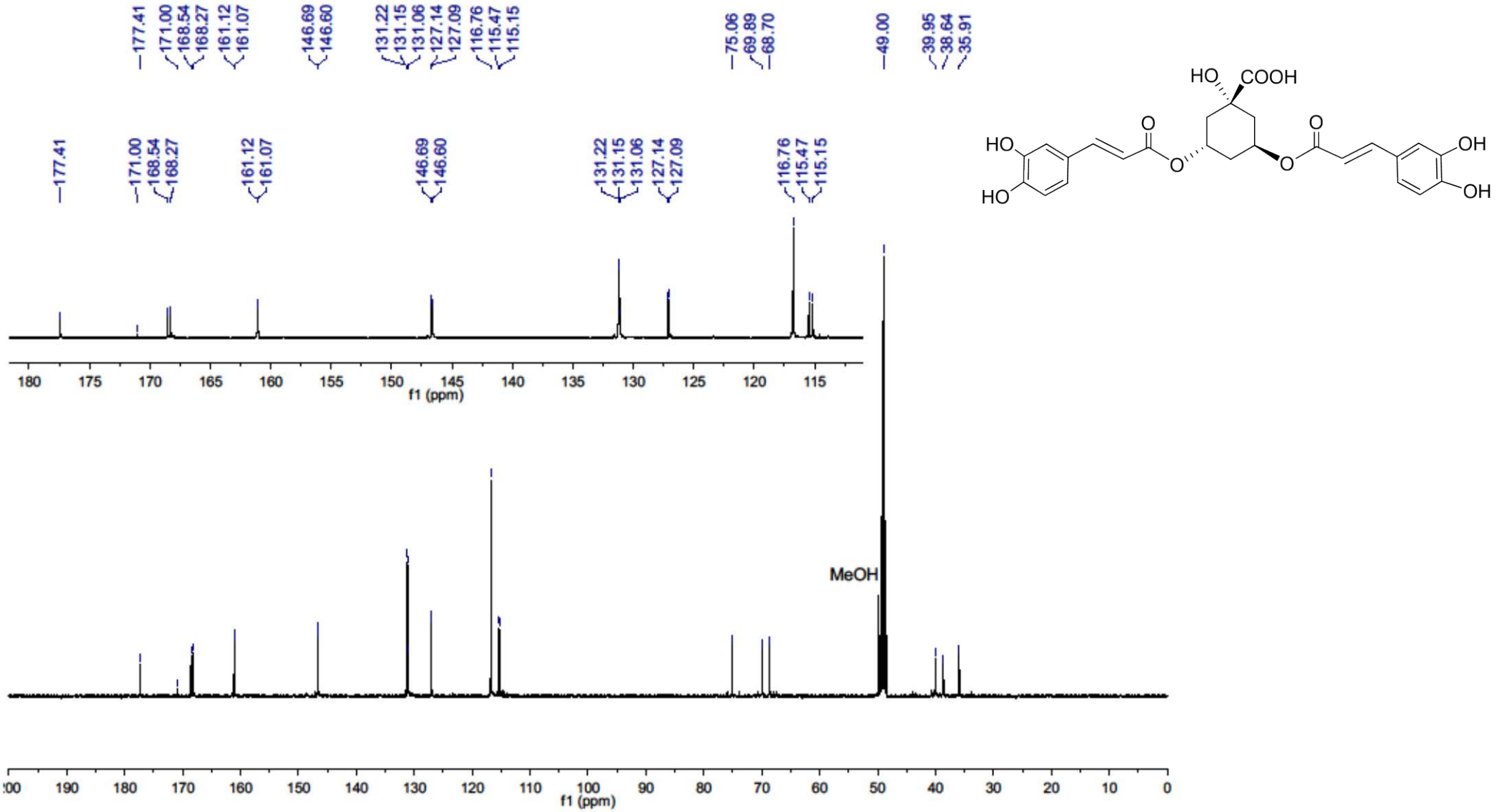
(3S,5S) 1-hydroxy-3,5 bis[[(2E)-3-(3,4-dihydroxyphenyl)-1-oxo-2-propen-1-yl]oxy]cyclohexanecarboxylic acid 4a

^{1}H NMR (400MHz, $CDCl_3$, 295K)



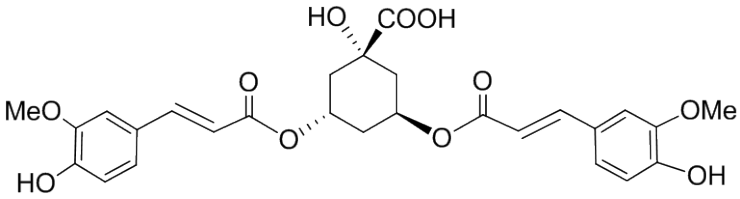


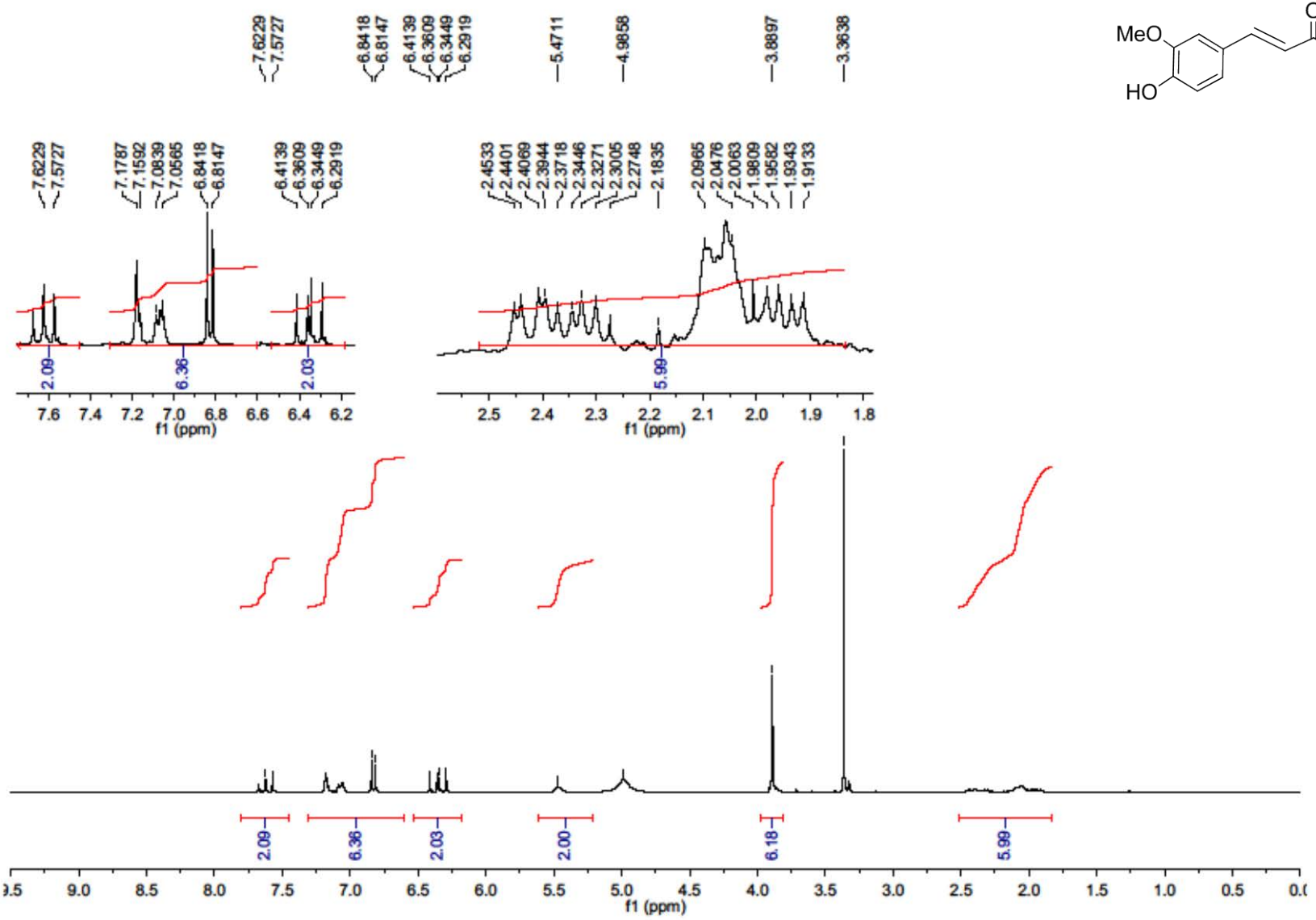
^{13}C NMR (100MHz, CD_3OD, 295K)



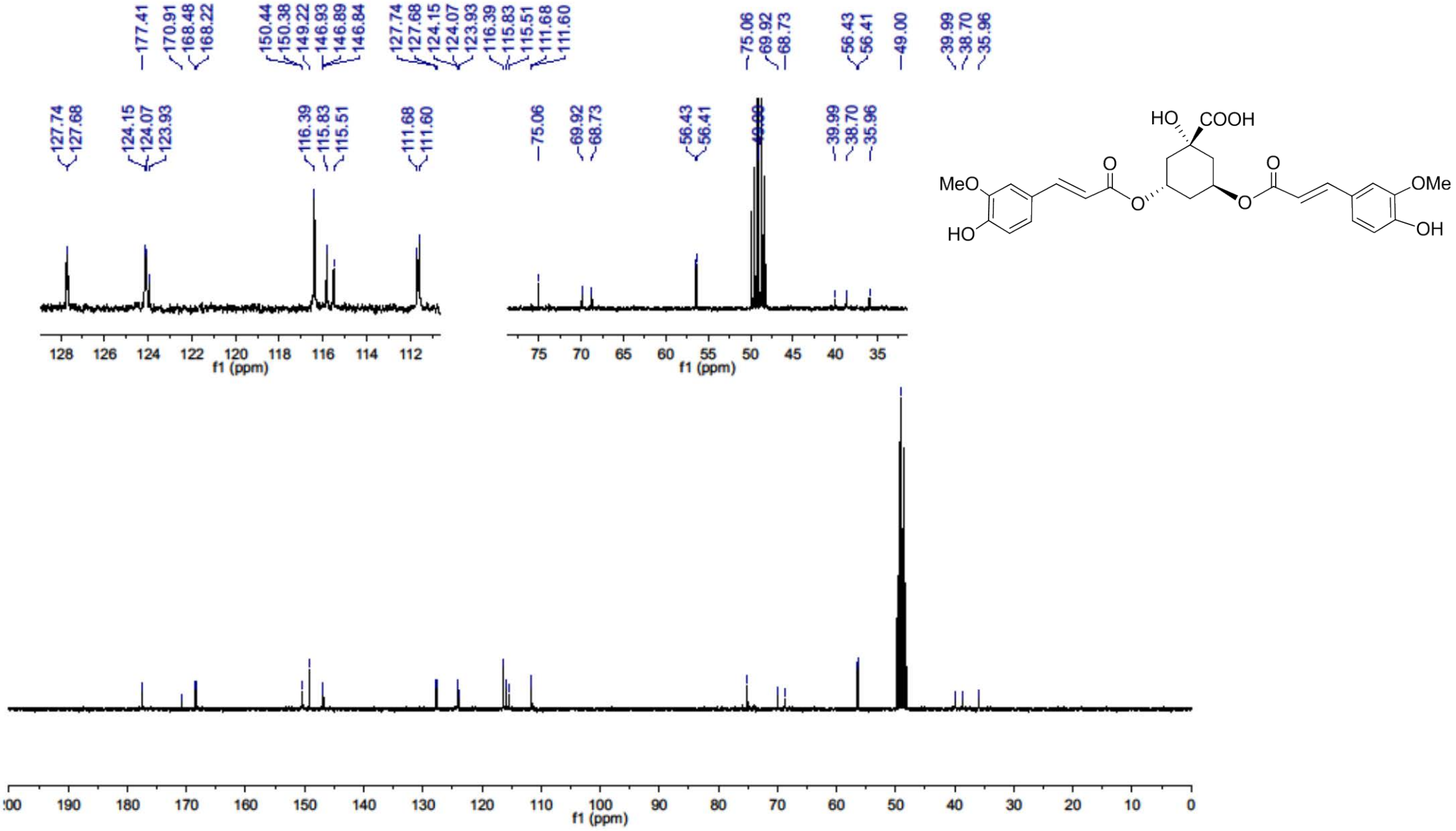
(3S,5S) 1-hydroxy-3,5 bis[[(2E)-3-(4-hydroxy-3-methoxyphenyl)-1-oxo-2-propen-1-yl]oxy]cyclohexanecarboxylic acid 4c

^{1}H NMR (400MHz, CD_3OD, 297K)



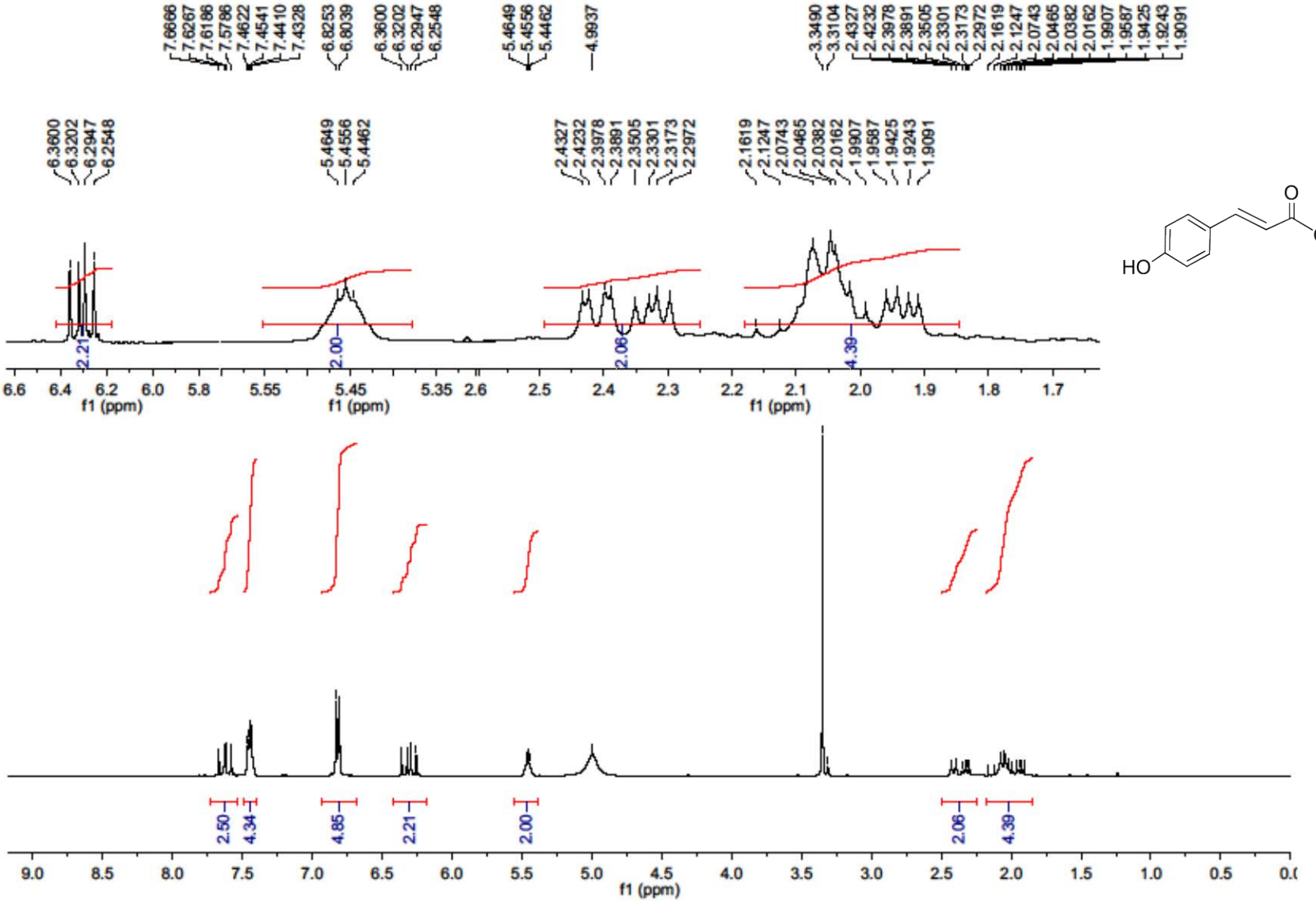


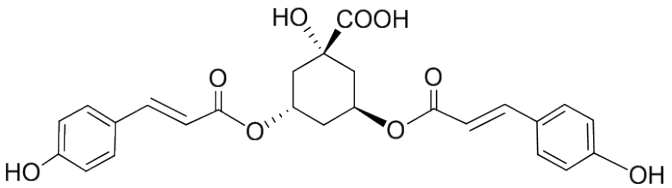
^{13}C NMR (100MHz, CD_3OD, 297K)



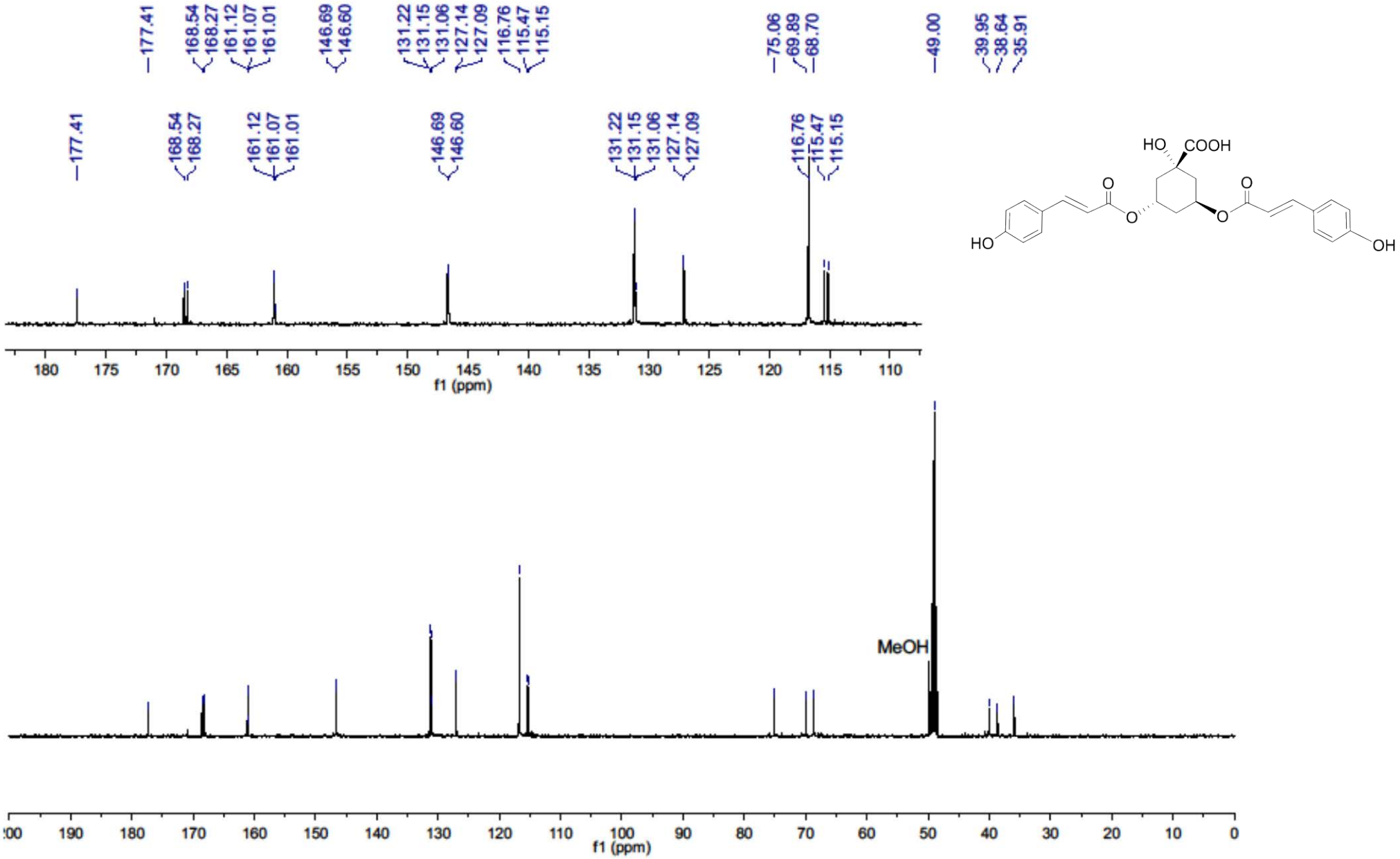
(3S,5S) 1-hydroxy-3,5 bis[[(2E)-3-(4-hydroxyphenyl)-1-oxo-2-propen-1-yl]oxy]cyclohexanecarboxylic acid 4d

^{1}H NMR (400MHz, $CDCl_3$, 295K)



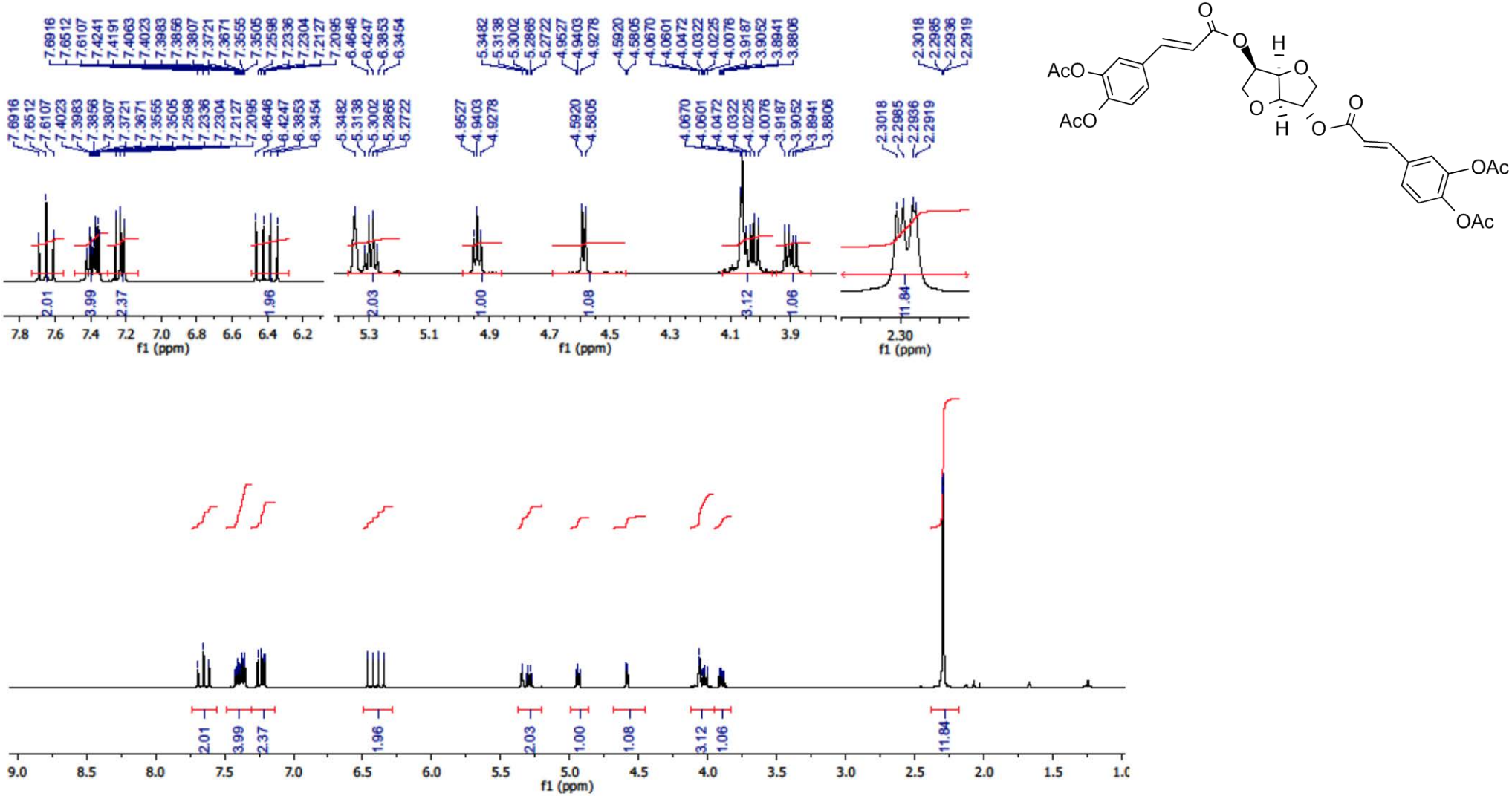


^{13}C NMR (100MHz, CD_3OD, 295K)

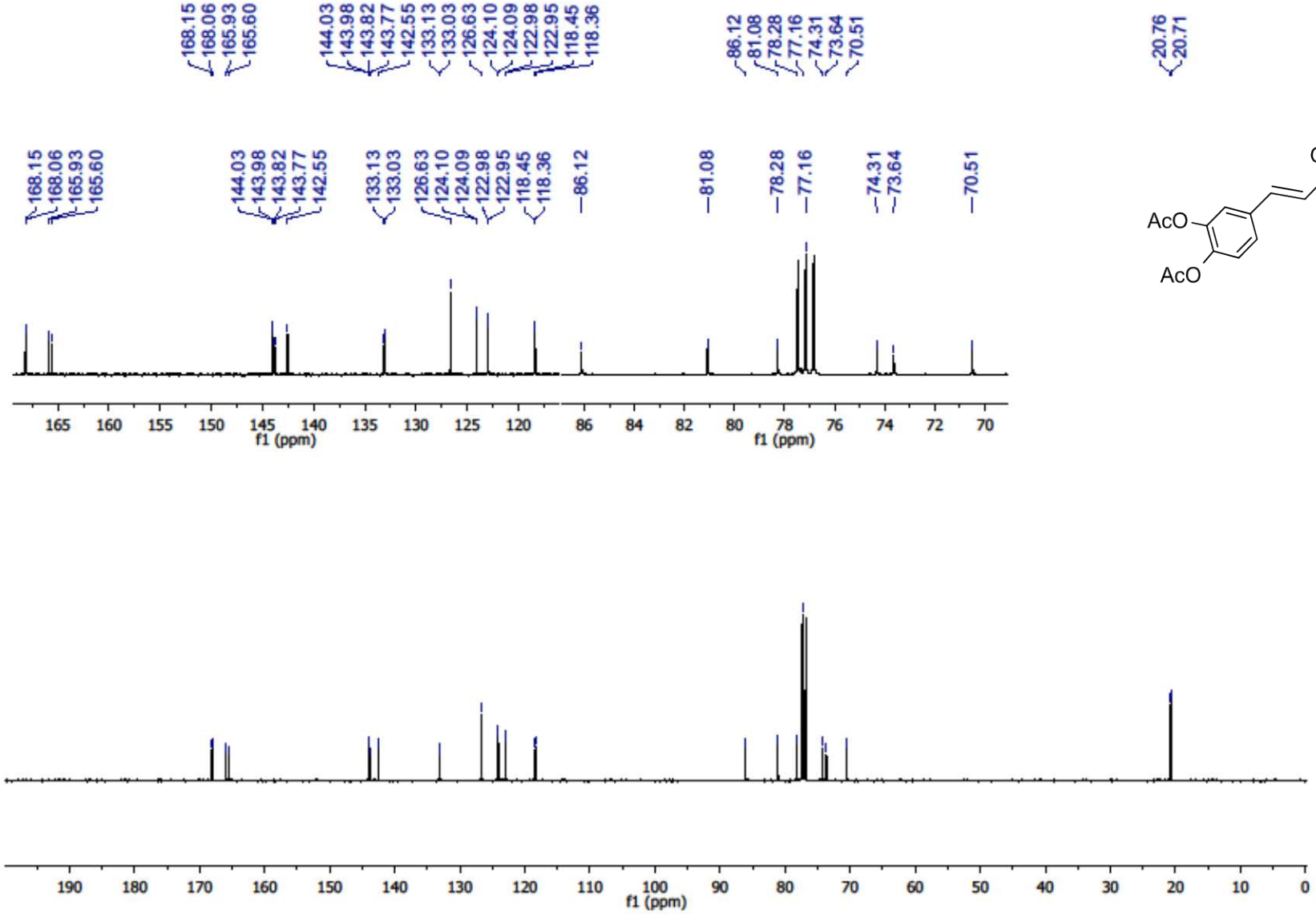


(3R, 3aR, 6S, 6aR)-hexahydrofuro[3,2-b]furan-3,6-diyl (2E,2'E)bis--[4-(acetyloxy)-3-methoxyphenyl]prop-2-enoate I1

NMR ^{1}H (400 MHz, $CDCl_3$, 295 K)

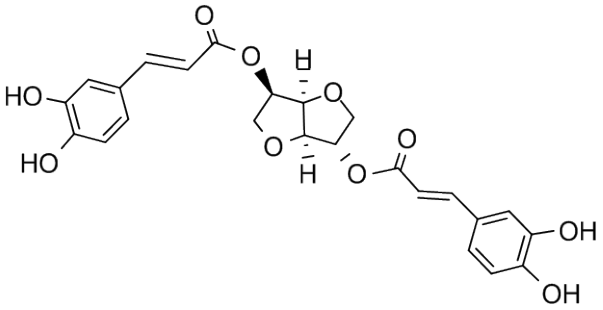


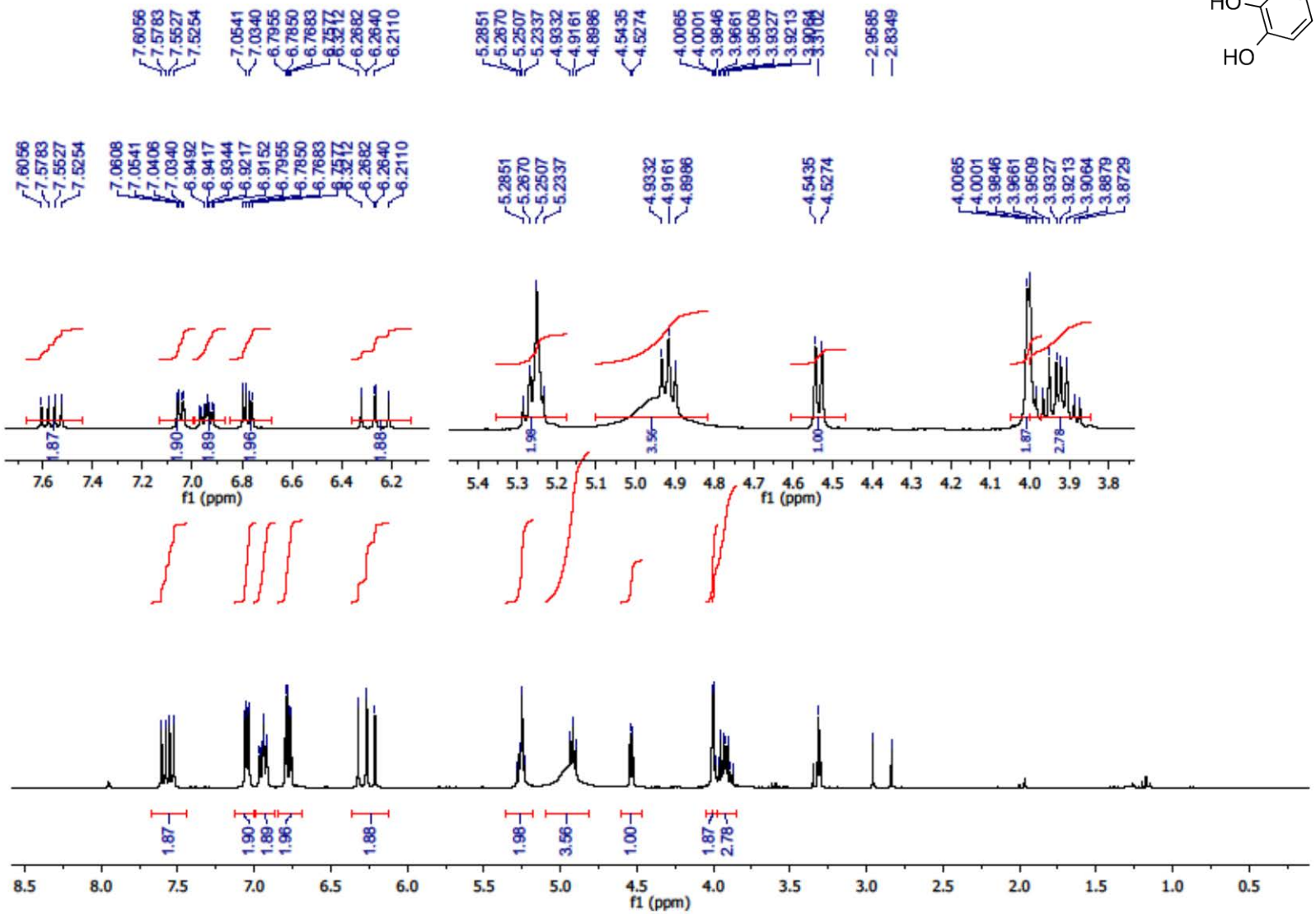
NMR ^{13}C (100 MHz, $CDCl_3$)



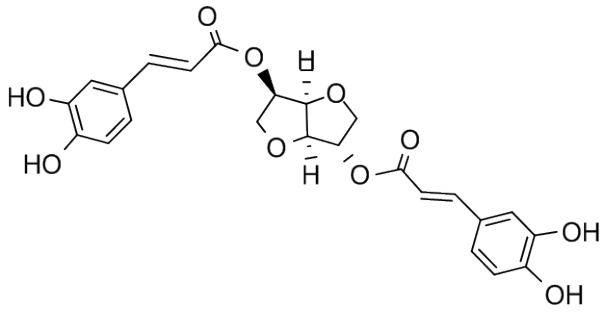
(3*R*,3a*R*,6*S*,6a*R*)-hexahydrofuro[3,2-*b*]furan-3-yl (2*E*)-3-(3,4-dihydroxyphenyl)prop-2-enoate 12

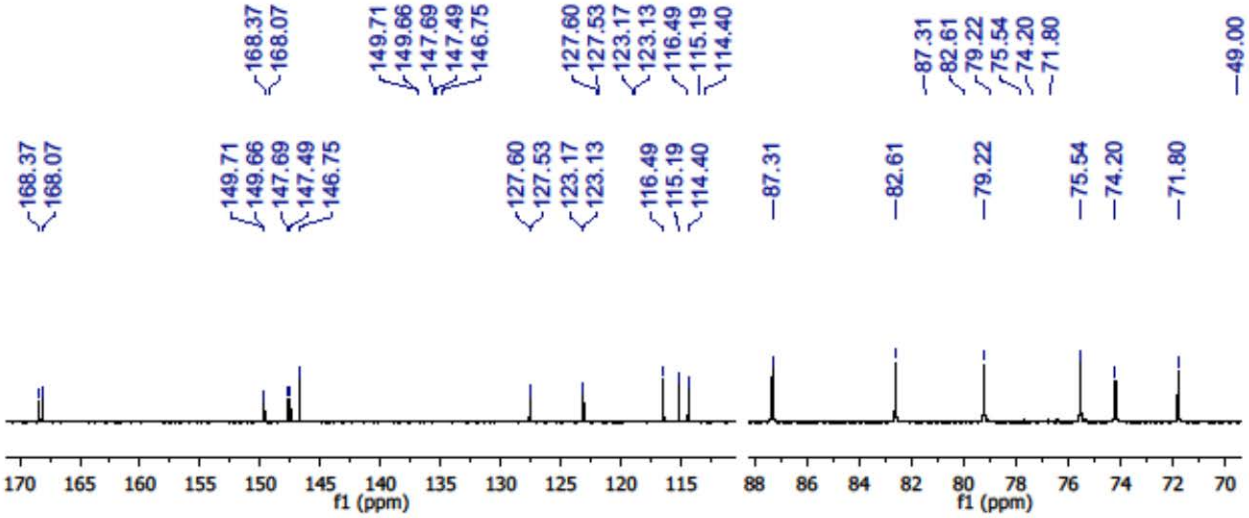
NMR ^{1}H (300 MHz, CD_3OD)

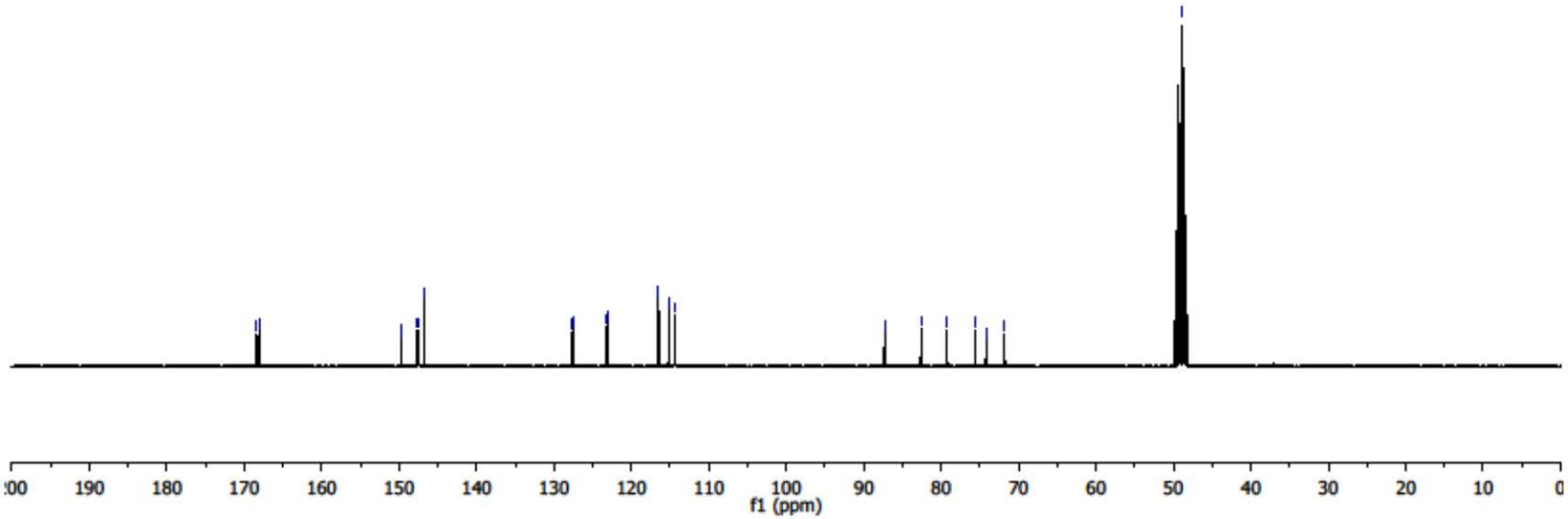




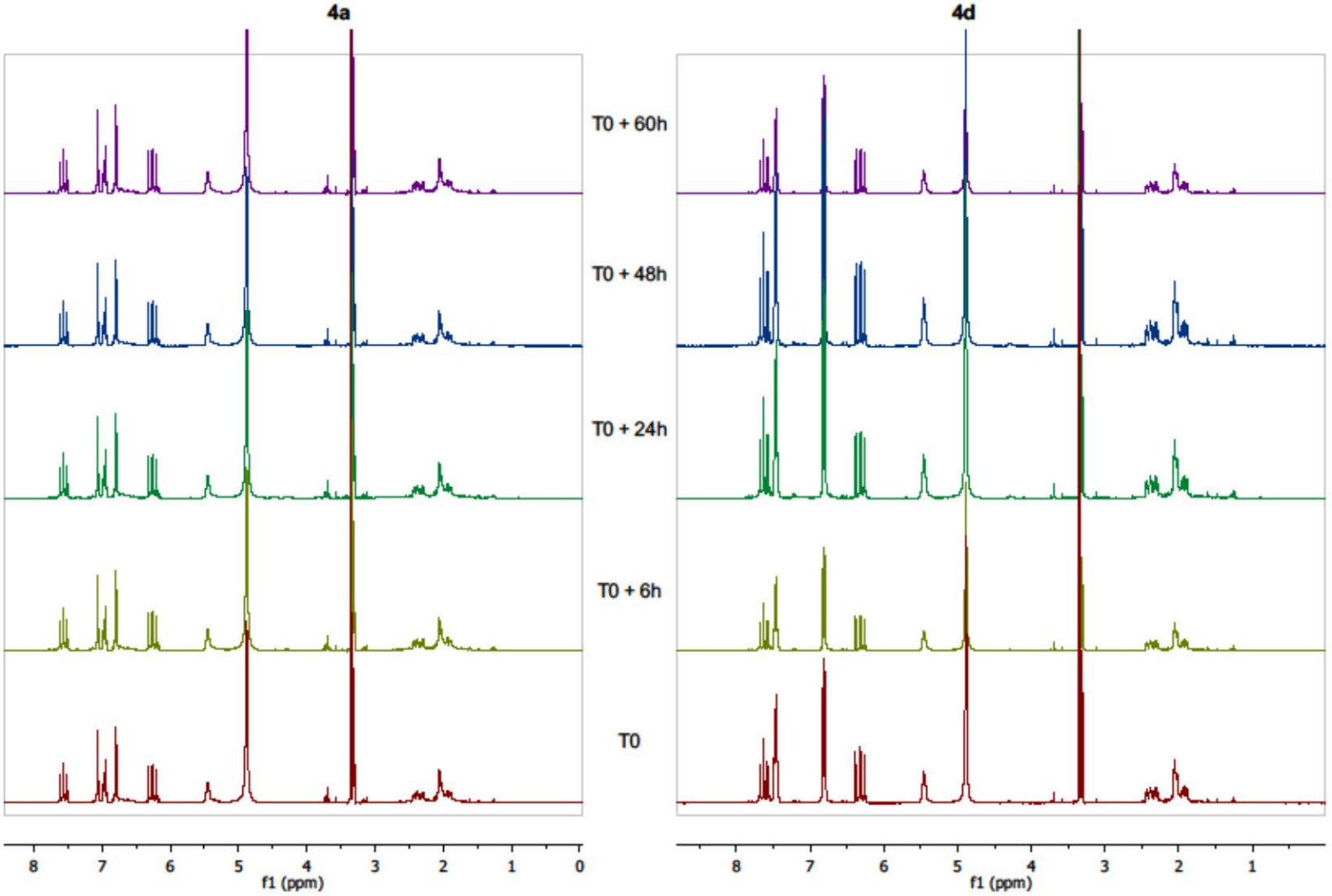
NMR ^{13}C (75 MHz, CD_3OD)







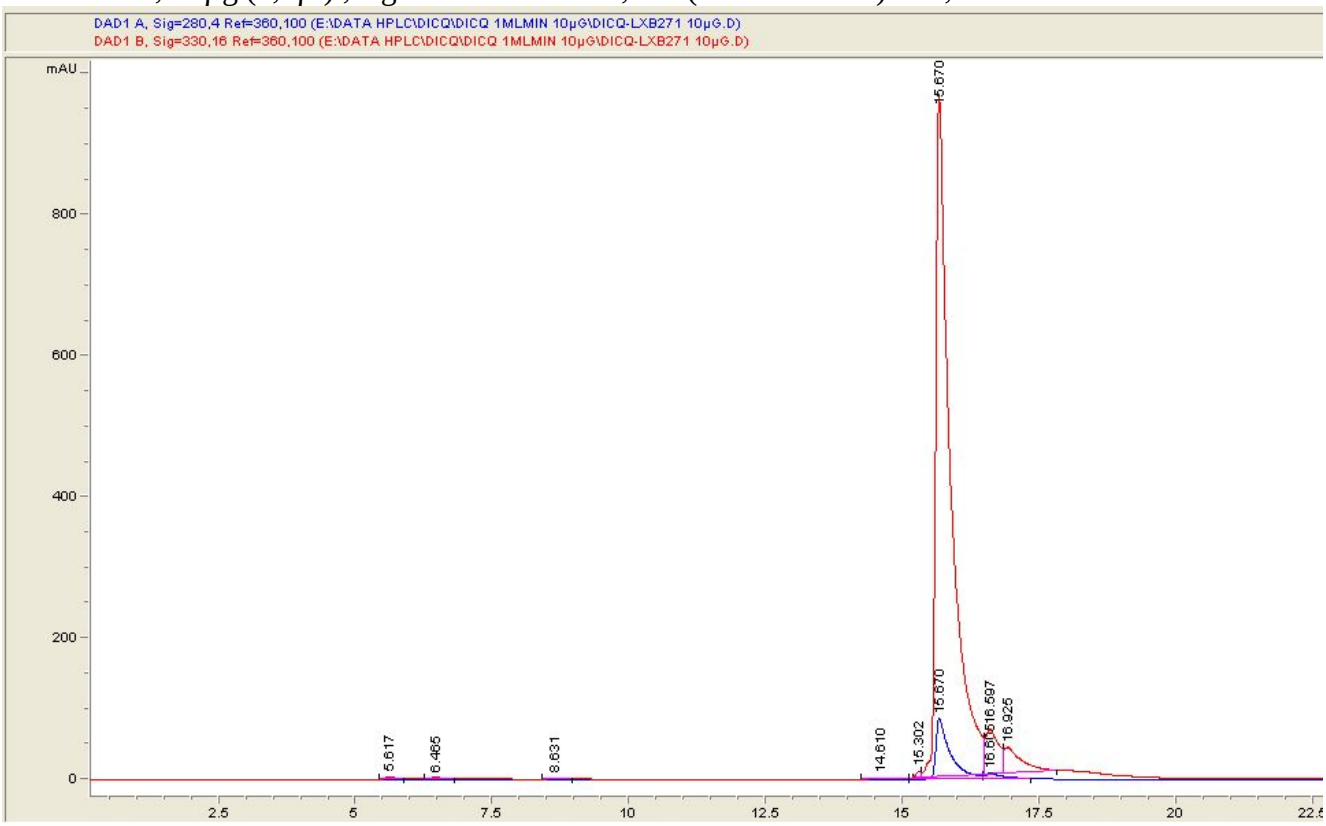
^{1}H NMR Spectra of 4a and 4d in CD_3OD at 296,5 K at different time intervals (t_0 +6h, t_0+24h, t_0 +48h, t_0 + 60h)



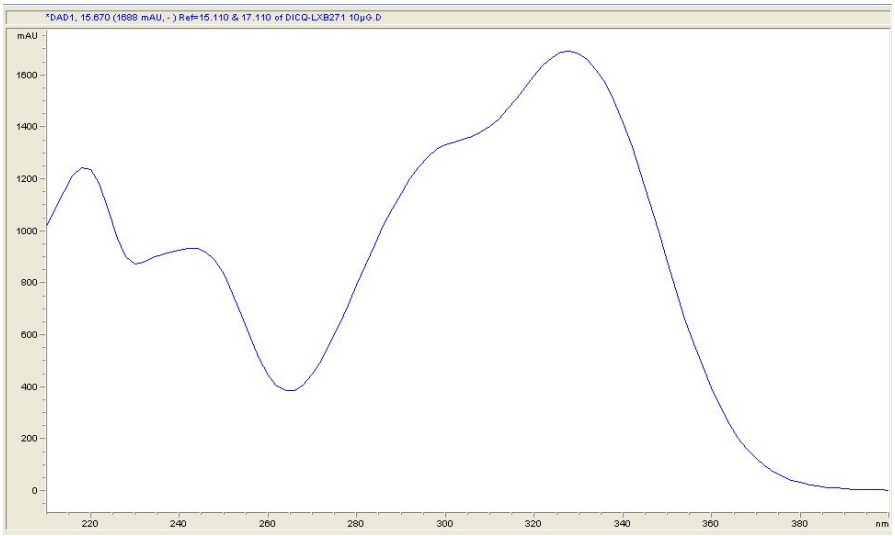
HPLC analysis and UV spectra for compounds 10a, 10c, 10d, 10e, 4a, 4c, 4d, 12

HPLC conditions : Agilent equipment, Column phenomenex C18: Jupiter® 5µm; 300 Å, LC Column 250 x 4.6mm, flow **1ml/min**; Mobile phase 0 - 2min: 80% H_2O UHQ + TFA (A) / 20% CH_3CN + TFA (B); 22min: 40 % A / 60% B; 30min: 100% ACN + TFA; 33min: 80% A/ 20% B. Samples were dissolved in MeOH (6mL) and 10µg were injected per sample

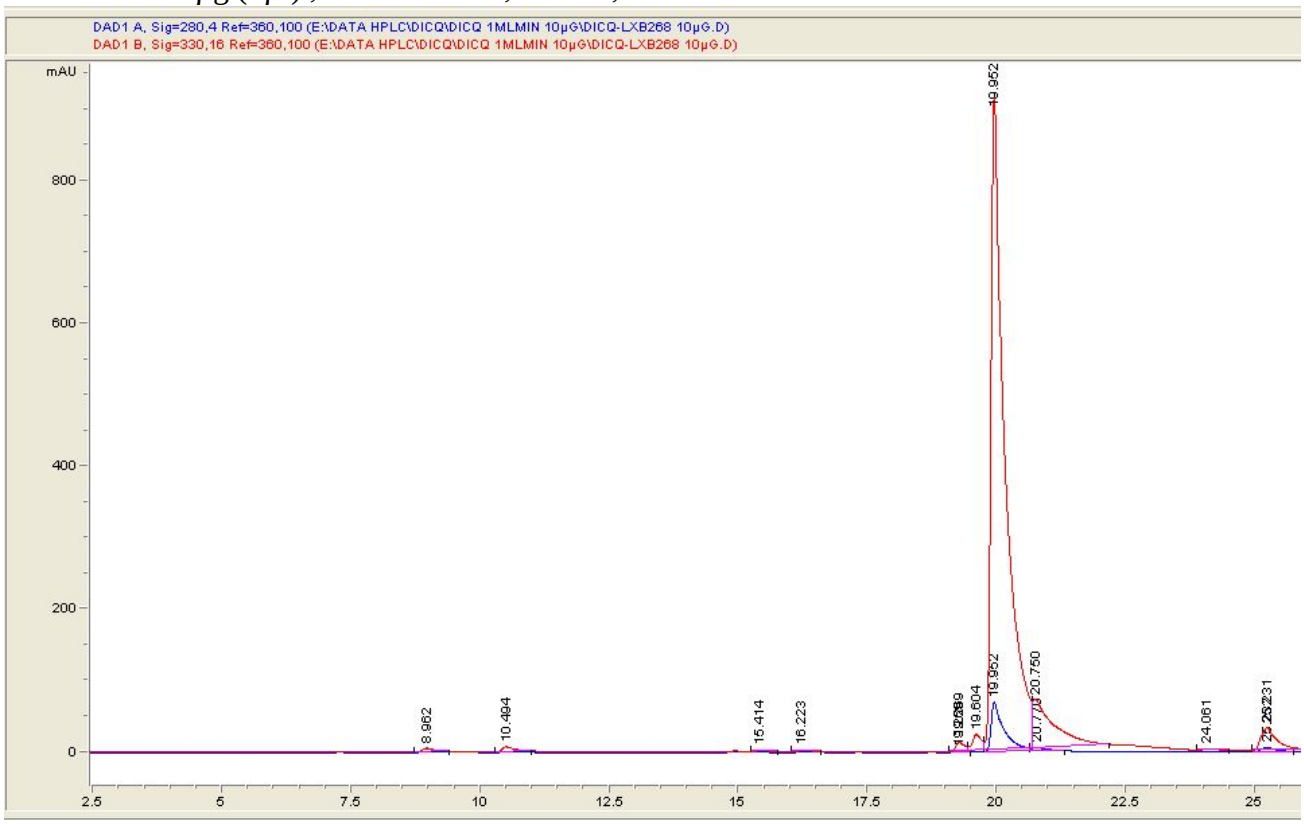
- **10a** ; 10µg (2,5µl) ; signal 270 – 330nm ; TR (retention time) =15,67min



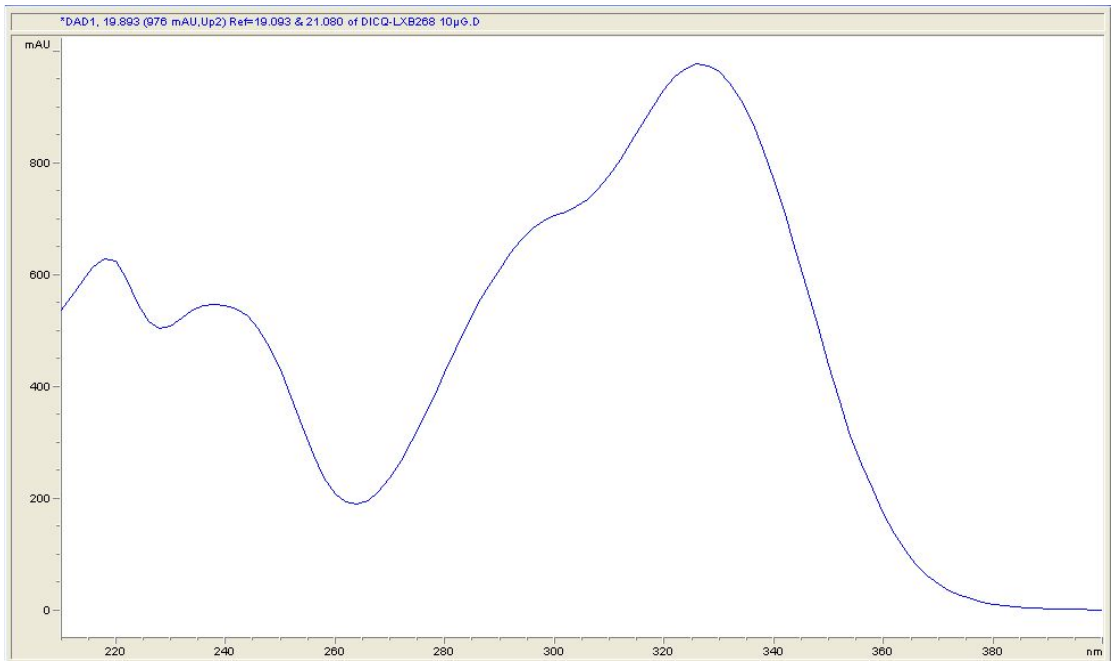
UV spectrum (210 – 400nm) à 15,670min (signal 330nm)



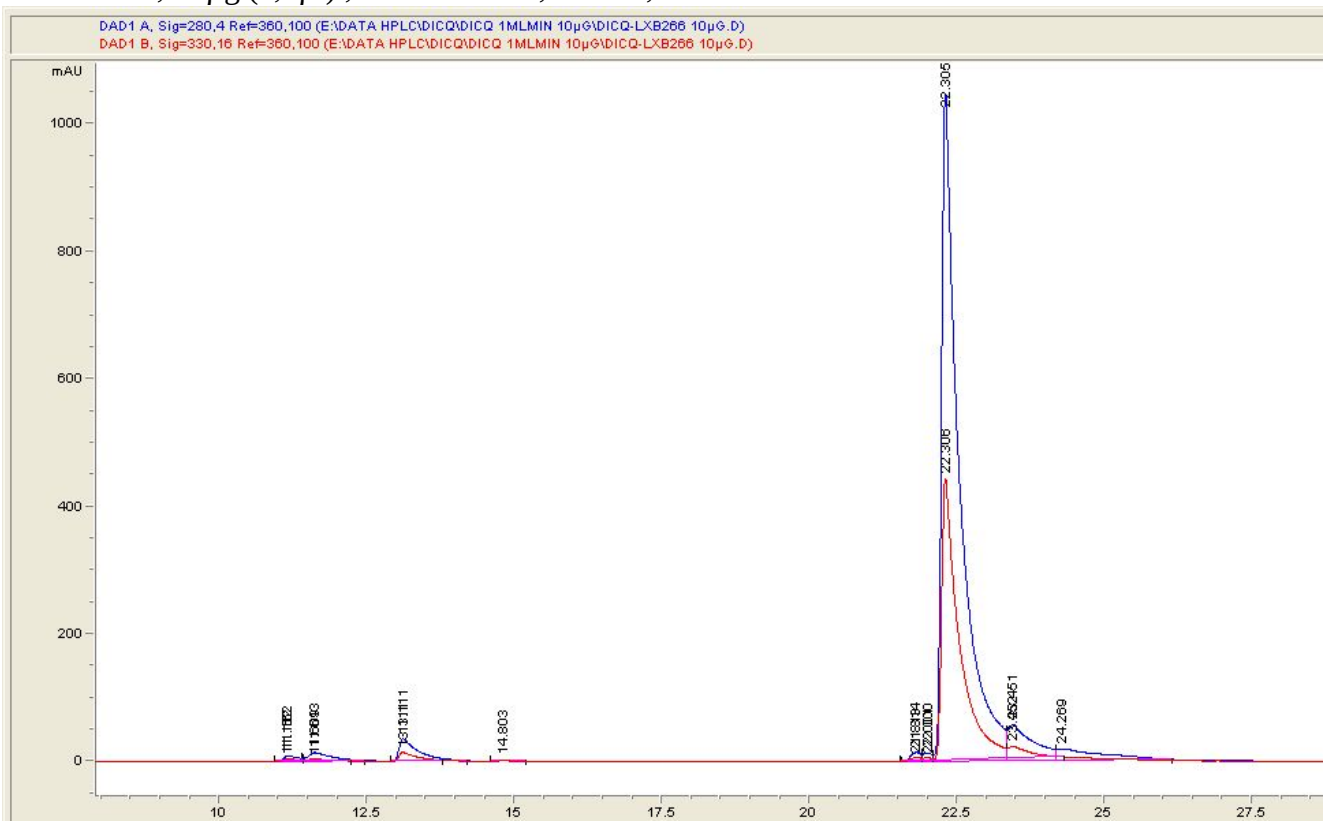
- **10c** 10µg (4µl) ; 270 – 330nm ; TR=19,95min



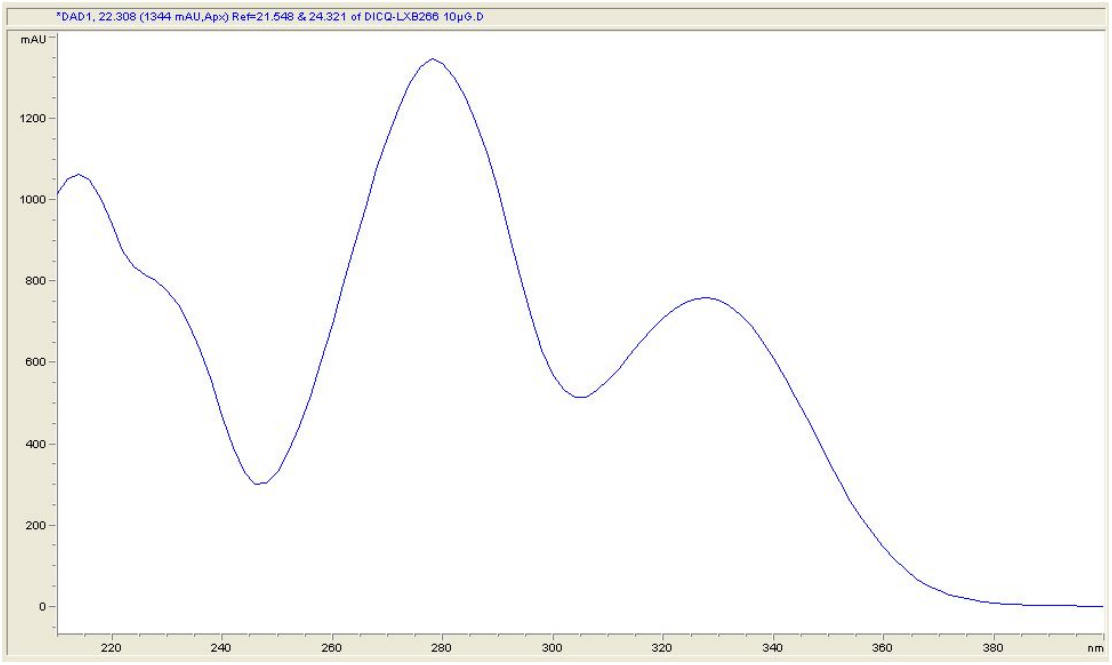
Spectre UV (210 – 400nm) à 19,893min (signal 330nm)



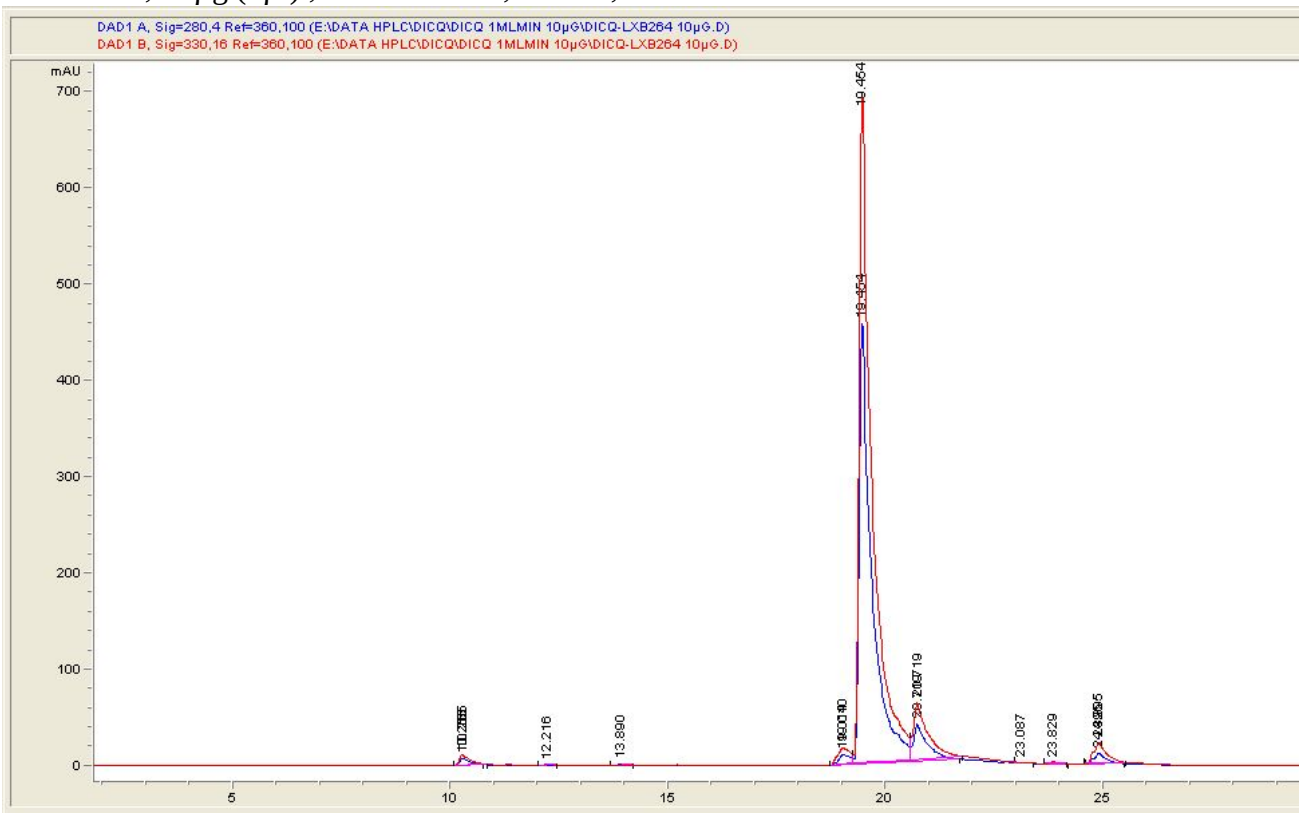
- **10d** ; 10µg (8,5µl) ; 270 – 330nm ; TR=22,3min



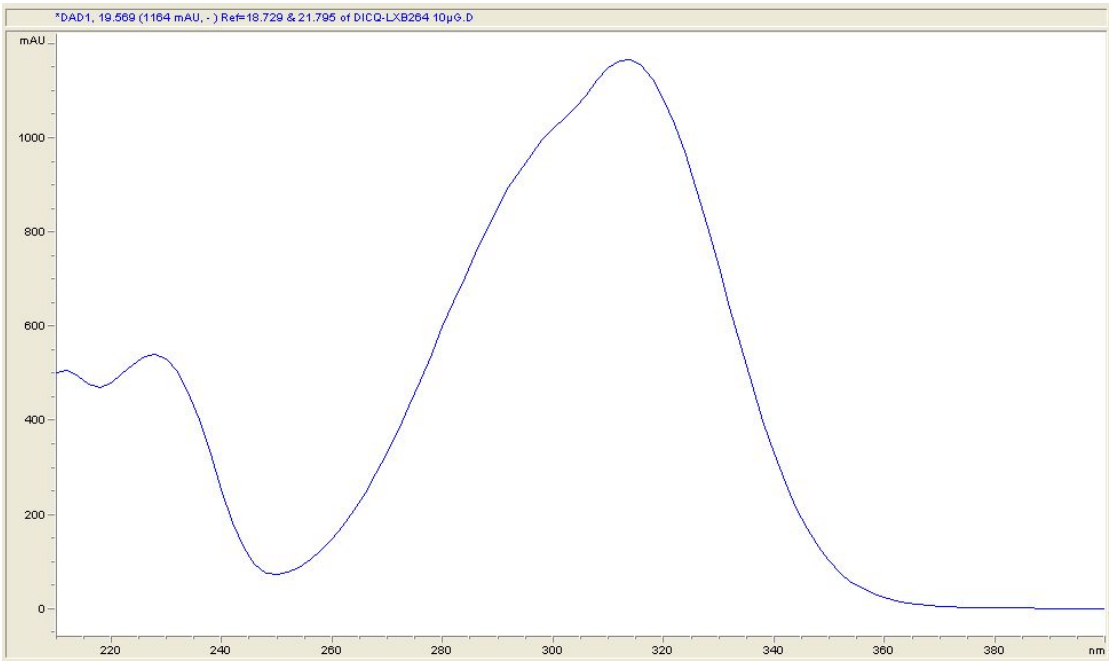
Spectre UV (210 – 400nm) à 22,308min (signal 330nm)



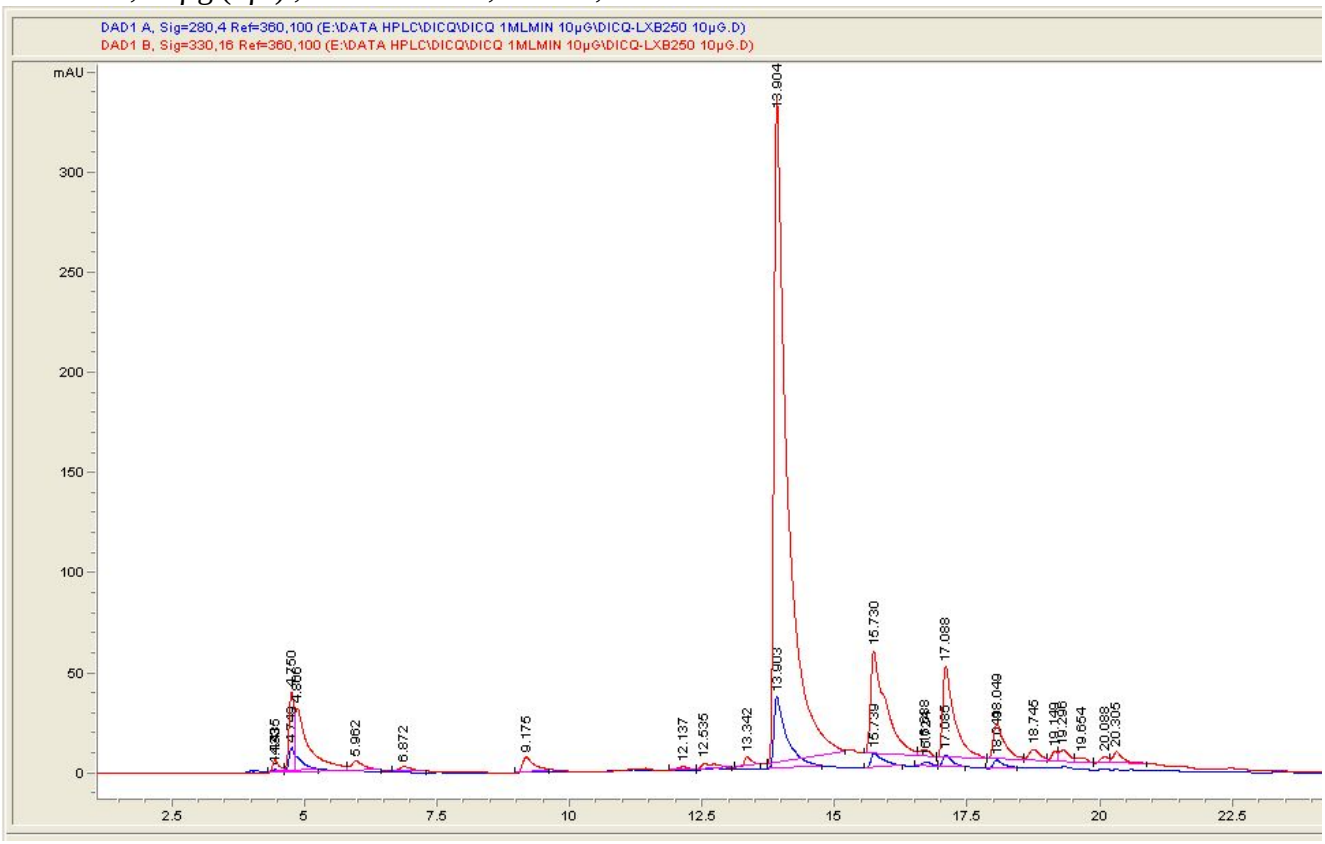
- **10e**; 10µg (3µl) ; 270 – 330nm ; TR=19,4min



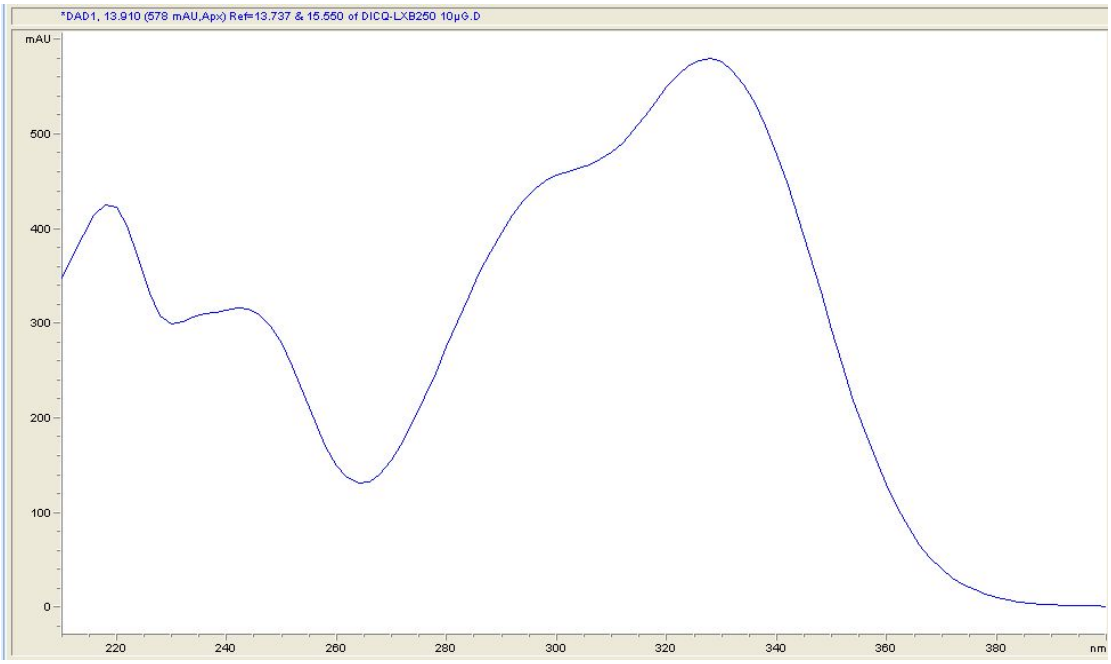
Spectre UV (210 – 400nm) à 19,569min (signal 330nm)



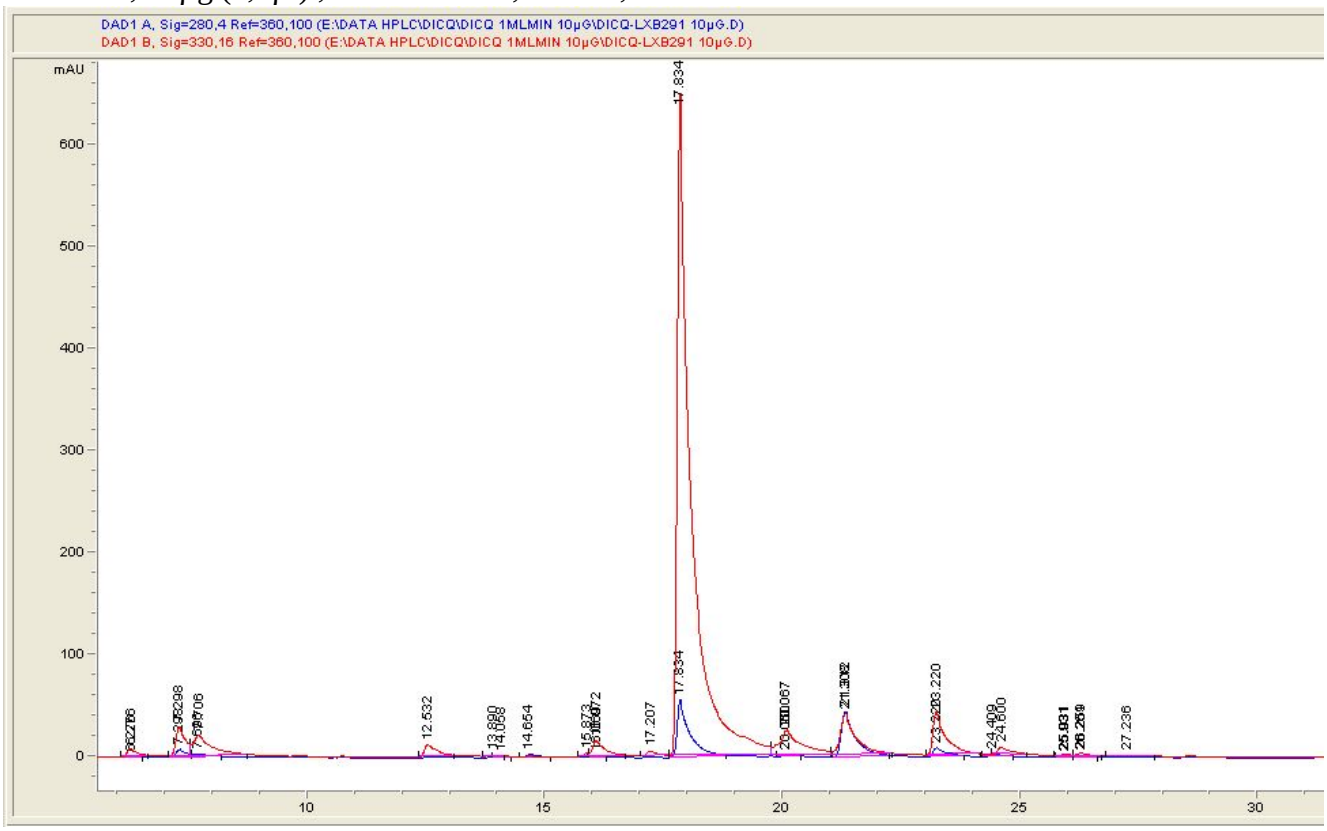
- **4a**; 10µg (3µl) ; 270 – 330nm ; TR=13,9min



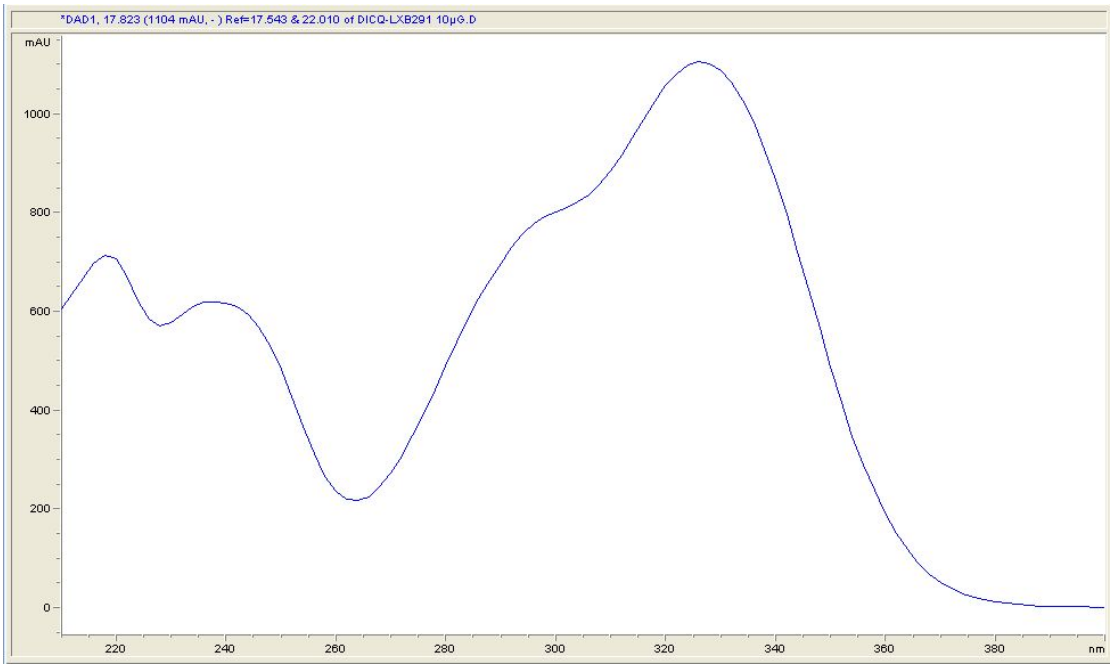
Spectre UV (210 – 400nm) à 13,910min (signal 330nm)



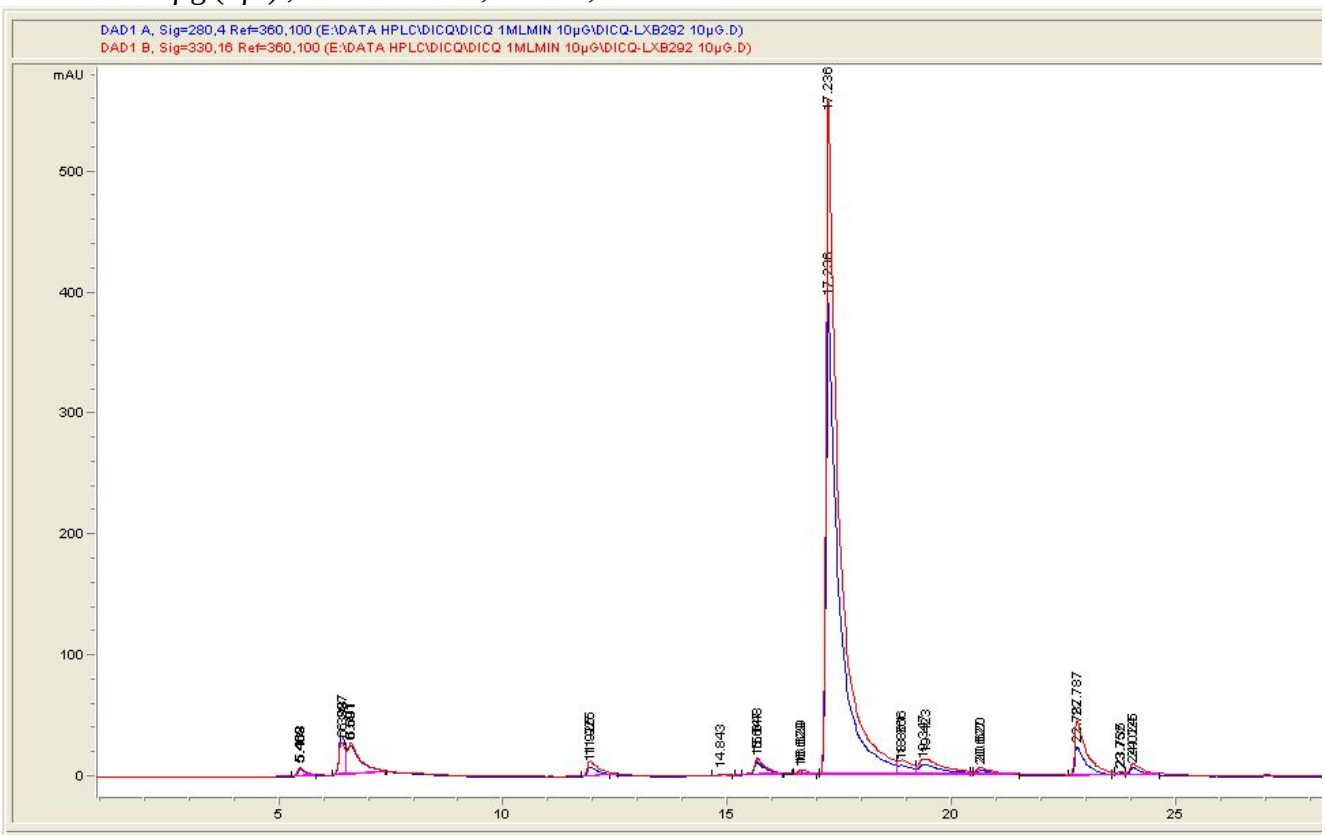
- **4c**; 10µg (3,5µl) ; 270 – 330nm ; TR=17,8min



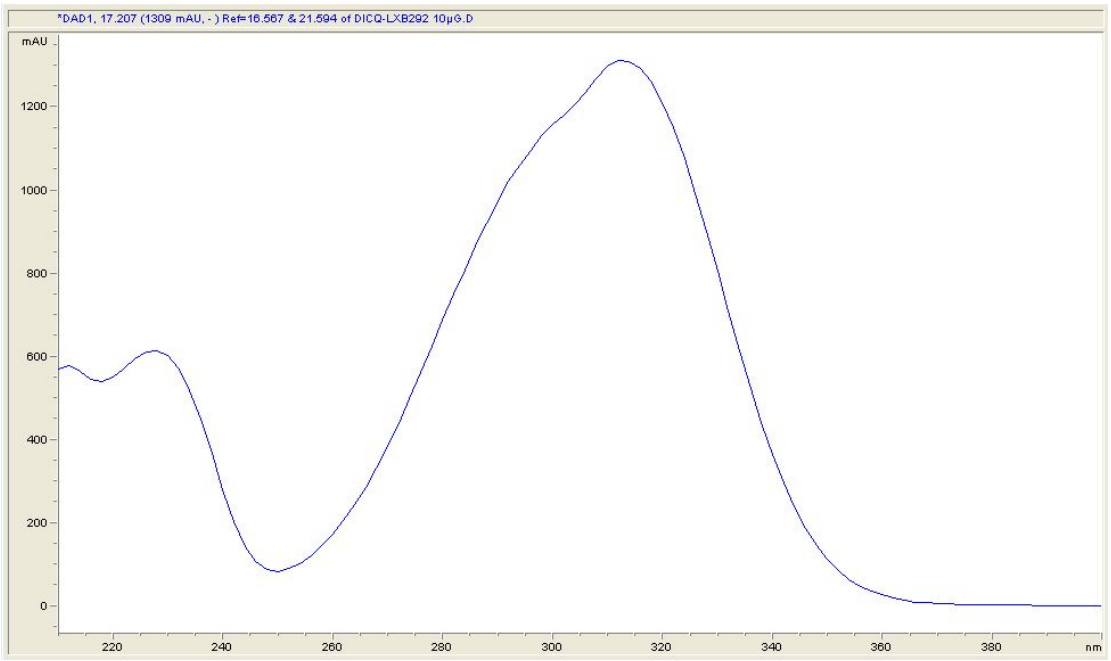
Spectre UV (210 – 400nm) à 17,823min (signal 330nm)



- **4d** 10µg (4µl) ; 270 – 330nm ; TR=17,2min

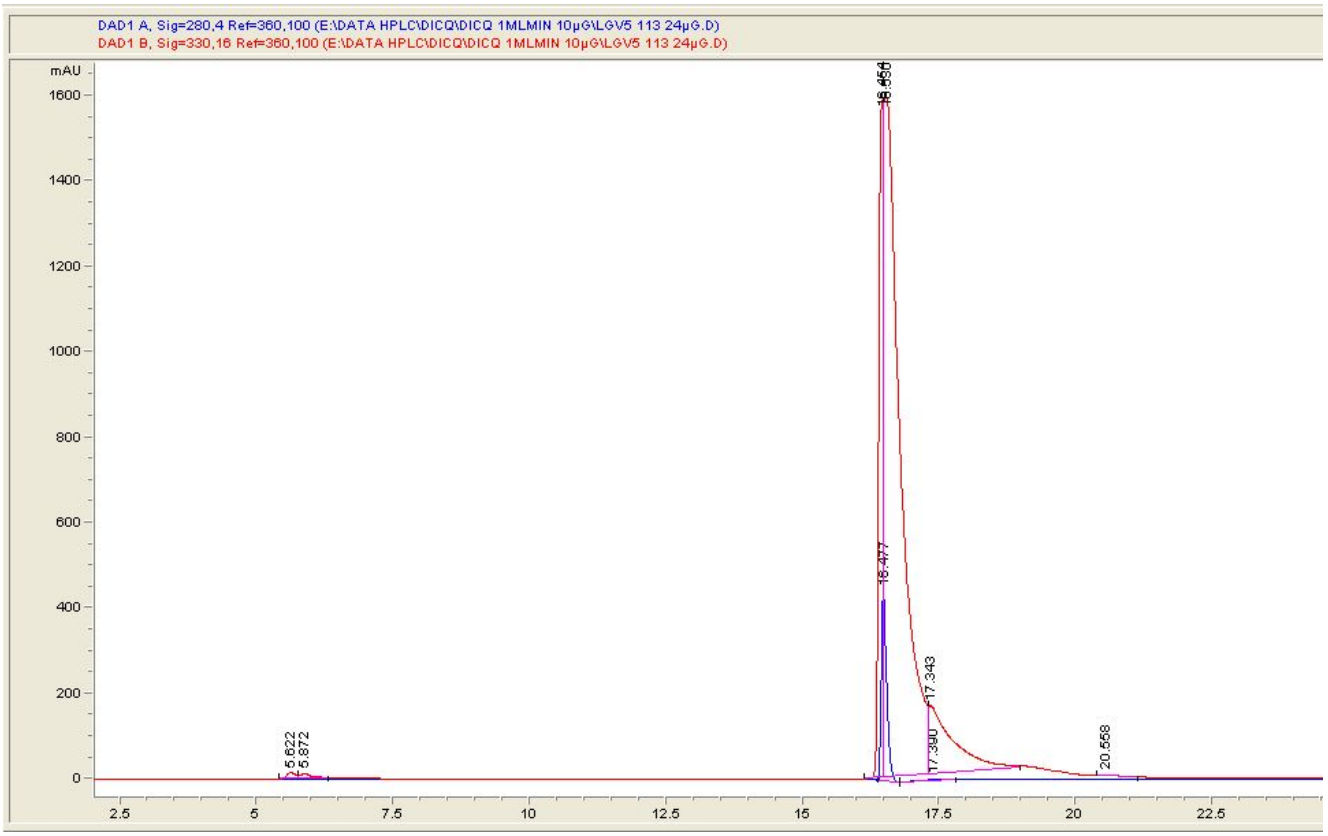


Spectre UV (210 – 400nm) à 17,207min (signal 330nm)



12 : (dissolved in 1,5ml MeOH); 24µg injected (2µl) ;

280 – 330nm ; TR=16,5min



Spectre UV (210 – 400nm) à 16,374min (signal 330nm)

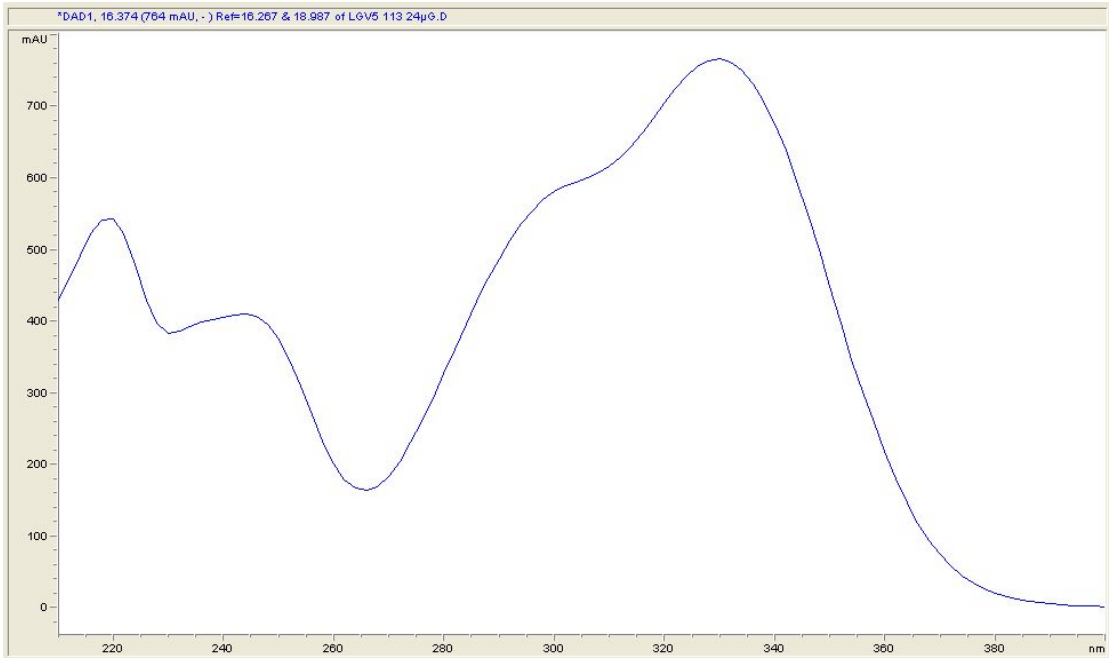
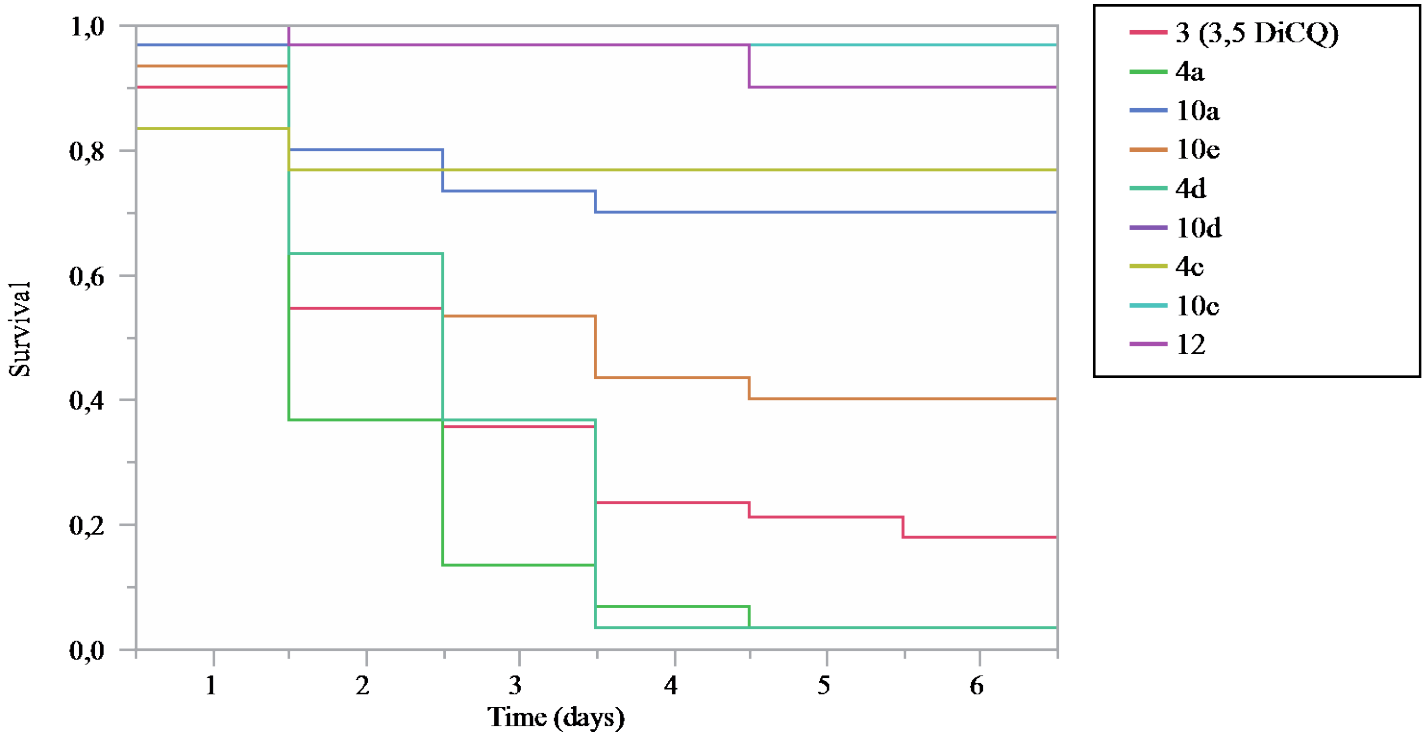


Table S3 Survival analysis[a]



Compound	**4a**	**4d**	**3**	**10e**	**4c**	**10a**	**10d, 10c, 12**
Mean LT50[b]	1.84	2.43	2.50	3.82	7.28	7.86	>20
IC [c]	[1.29-2.62]	[1.71-3.48]	[2.03-3.09]	[2.62-5.57	[4.7-11.2]	[5.1-12.1]	

[a] Detailed mortality curves upon ingestion of synthetized compounds **10a** to **12**, incorporated in artificial diet of the pea aphid *Acyrthosiphon pisum* at 0.5 mM;.[b]in days; [c] confidence intervals (at 95% confidence levels) of mean LT50 under log-normal survival model.