Supporting Information

A diastereoselective oxa-Pictet-Spengler-based strategy for (+)-frenolicin B and *epi*-(+)-frenolicin B synthesis

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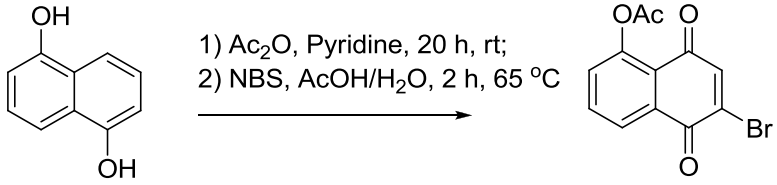
1. Materials and Methods

^{1}H and ^{13}C NMR spectra were recorded on a Varian Unity Inova 400 MHz instrument (Palo Alto, CA). The chemical shifts were reported in δ (ppm) using the ^{1}H NMR $CDCl_3$ (δ 7.26) or DMSO-d_6 (δ 2.50) and ^{13}C NMR $CDCl_3$ (δ 77.16) or DMSO-d_6 (δ 39.52) as internal standards where: *J* indicates coupling constants in Hz; s refers to singlet; d denotes doublet; t signifies triplet; q indicates quartet; and m refers to multiplet. HR-ESI-MS experiments were conducted using an AB SCIEX TripleTOF® 5600 System. HPLC analyses were performed using an Agilent 1260 system equipped (Santa Clara, CA) with a DAD detector and a Phenomenex (Torrance, CA) C18 column (150 × 4.6 mm, 0.5 μm). Semi-preparative/preparative HPLC separation was performed using a Varian Prostar 210 HPLC system equipped with a PDA detector 330 using a Supelco (St. Louis, MO) C18 column (25 × 21.2 mm, 10 μm; flow rate, 8 mL/min). Enantiomeric excess was determined by HPLC with a Chiralpak IC column (Tokyo, Japan), compared with racemic isomer. All commercially available reagents were used without further purification, purchased from Sigma-Aldrich (St. Louis, MO), TCI America (Tokyo, Japan) or Alfa-Aesar (Ward Hill, MA). The progress of the reactions was monitored by analytical thin-layer chromatography (TLC) from EMD Chemicals Inc. (Darmstadt, Germany) with fluorescence F_{254} indicator. Silica gel (230–400 mesh) for column chromatography was purchased from Silicycle (Quebec City, Canada).

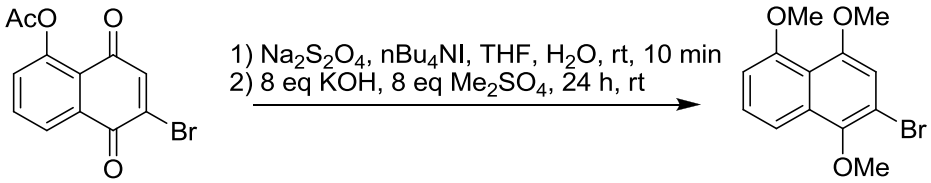
2. Synthesis of compounds 1-2 and 5-15.



6-Bromo-5,8-dioxo-5,8-dihydronaphthalen-1-yl acetate.[1] To a solution of 1,5-dihydroxynaphthalene (16 g, 100 mmol) in pyridine (60 mL), Ac_2O (70 mL, 750 mmol) was added in dropwise fashion over 30 min. The resulting mixture was stirred for 20 h at room temperature. The reaction was quenched via careful addition of water (30 mL) and the resulting mixture was poured onto ice (200 g) and then filtered to collect the dark-brown solid. The solid was dissolved in CH_2Cl_2 (300 mL) and heated to reflux for 5 min.

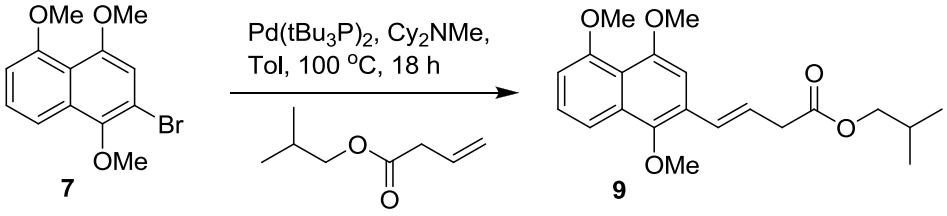
After cooling to room temp, the solvent was filtered and the residue was carefully washed with CH_2Cl_2 (100 mL x 2). The filtrate was concentrated to 200 mL under vacuum and loaded onto a short plug of silica gel resolved with 1:2 hexanes/ CH_2Cl_2 (1000 mL) to afford the crude product. The crude product was recrystallized from benzene (approx. 0.4 M) to afford the product as pale yellow needles.

A solution of product from previous step in warm AcOH (425 mL, 45 ^oC) was added to a solution of N-bromosuccinimide in 45 ^oC AcOH (500 mL) and water (500 mL) through a cannulain less than 30 min (to avoid production of the dibrominated side product). After addition, the mixture was vigorously stirred at 45 ^oC for 40 min. The temperature was then elevated to 70 ^oC and the reaction stirred for an additional 1 hour until all visible precipitates were dissolved, resulting in a uniform orange solution. The reaction mixture was cooled to room temp, H_2O (500 mL) was added and the mixture extracted with CH_2Cl_2 (500 mL) and subsequently washed with CH_2Cl_2 (200 mL x 2). The combined organic layers were then washed with saturated $NaHCO_3$ (300 mL), brine, dried over Na_2SO_4, filtered, and concentrated under vacumm. The residue was recrystallized in refluxed EtOH (approx. 0.14 M) to afford the product as an orange silkly solid (16.1 g, 55 mmol, 55% yield). R_f 0.50 (2:1 hexane/EtOAc); ^1H NMR ($CDCl_3$, 400 MHz): δ = 8.15 (dd, *J* = 1.2, 8.0 Hz, 1H), 7.77 (t, *J* = 8.0 Hz, 1H), 7.42 (dd, *J* = 1.2, 8.0 Hz, 1H), 7.38 (s, 1H), 2.44 (s, 3H).



7

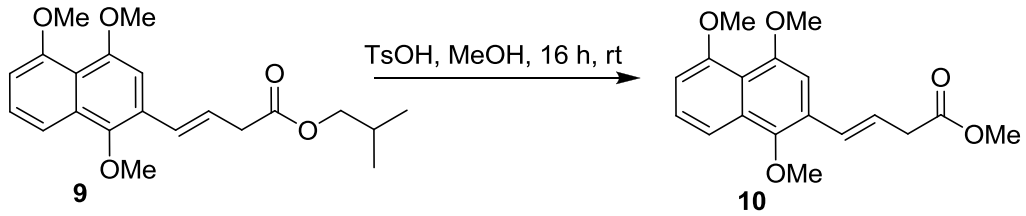
2-Bromo-1,4,5-trimethoxynaphthalene (7). To a solution of 6-bromo-5,8-dioxo-5,8-dihydronaphthalen-1-yl acetate (5.8 g, 20 mmol) and n-Bu_4NBr (332 mg, 1 mmol) in THF (50 mL) and H_2O (50 mL) was added sodium dithionite (10.5 g, 60 mmol), and the mixture was stirred for 10 min under argon. The organic layer was collected and 2N KOH solution (40 mL, 80 mmol) was added with stirring under argon. Me_2SO_4 (7.6 mL, 80 mmol) was added to the mixture after 10 min and the resulting mixture was stirred for 4 h at room temp followed another addition of 2N KOH solution (40 mL, 80 mmol) and Me_2SO_4 (7.6 mL, 80 mmol). The reaction was continued overnight with stirring and subsequently concentrated under vacuum. The residue was extracted with EtOAc (100 mL x 2) and combined organic extracts were washed with water (100 mL), brine (20 mL), dried over Na_2SO_4, filtered, and concentrated under vacuum. The residue was purified by silica gel chromatography using 25:1 hexane/EtOAc to provide **7** as a pale yellow oil (4.0 g, 13.5 mmol, 68% yield). R_f 0.30 (10:1 hexane/EtOAc); ^1H NMR ($CDCl_3$, 400 MHz): δ = 7.68 (dd, *J* = 0.8, 8.8 Hz, 1H), 7.44 (t, *J* = 8.0 Hz, 1H), 6.90 (s, 1H), 3.97 (s, 3H), 3.94 (s, 3H), 3.92 (s, 3H).



7 **9**

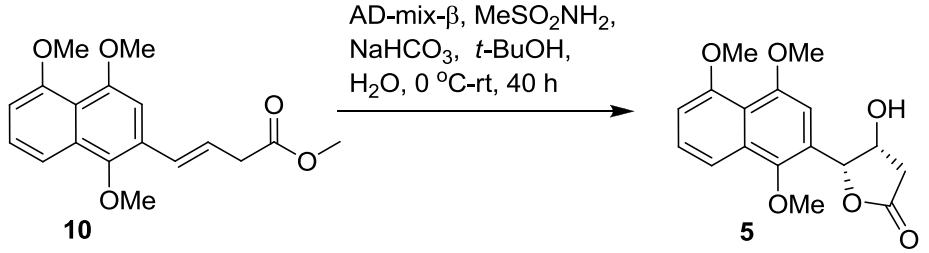
(*E*)-Isobutyl 4-(1,4,5-trimethoxynaphthalen-2-yl)but-3-enoate (9). To a solution of **7** (4.0 g, 13.5 mmol), isobutyl vinylacetate (4.3 mL, 27 mmol), and *N*, *N*-dicyclohexylmethyl amine (4.2 mL, 20 mmol) in toluene (70 mL) was added bis(tri-t-butylphosphine)palladium (137 mg, 0.27 mmol) under argon, and the mixture was refluxed for 16 h. The reaction was concentrated under vacuum and the residue

subsequently purified via silica column chromatography using 12:1 hexane/EtOAc to provide **9** (4.1 g, 11.4 mmol, 84% yield) as a pale yellow oil. R_f 0.20 (10:1 hexane/EtOAc); ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.69 (dd, *J* = 0.8, 8.8 Hz, 1H), 7.42 (t, *J* = 8.0 Hz, 1H), 6.96 (d, *J* = 16.0 Hz, 1H), 6.93 (s, 1H), 6.87 (d, *J* = 7.6 Hz, 1H), 6.41 (dt, *J* = 7.2, 16.0 Hz, 1H), 3.97 (s, 3H), 3.94 (s, 3H), 3.93-3.92 (m, 2H), 3.84 (s, 3H), 3.36 (dd, *J* = 1.6, 7.2 Hz, 2H), 1.99-1.96 (m, 1H), 0.95 (d, *J* = 6.8 Hz, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 171.9, 157.5, 153.7, 147.2, 131.8, 127.8, 127.1, 125.4, 123.3, 118.3, 115.2, 107.1, 103.4, 71.1, 62.4, 57.0, 56.6, 39.0, 27.9, 19.2 ppm.



9 **10**

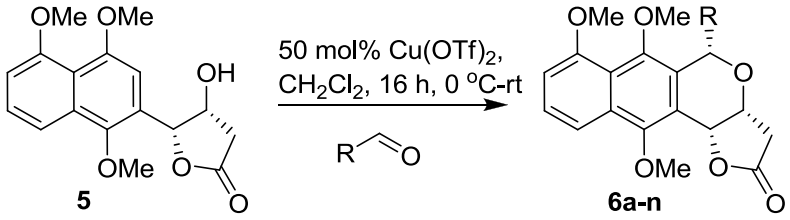
(*E*)-Methyl 4-(1,4,5-trimethoxynaphthalen-2-yl)but-3-enoate (10). A mixture of TsOH (2.6 g, 13.7 mmol) and **9** (4.1 g, 11.4 mmol) in MeOH (50 mL) was stirred for 24 h at room temp. The solution was concentrated and the residue was extracted with EtOAc (50 mL x 2). The combined extracts were washed with saturated aqueous $NaHCO_3$ solution (50 mL), brine (20 mL), dried over Na_2SO_4, filtered, and concentrated under vacuum. The residue was purified via silica column chromatography using 8:1 hexane/EtOAc to afford the product as a pale yellow oil (2.7 g, 8.6 mmol, 75% yield). R_f 0.20 (10/1 hexane/EtOAc); ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.69 (dd, *J* = 0.8, 6.8 Hz, 1H), 7.40 (t, *J* = 8.0 Hz, 1H), 6.91 (d, *J* = 12.8 Hz, 1H), 6.87 (s, 1H), 6.85 (d, *J* = 6.8 Hz, 1H), 6.40 (dt, *J* = 5.6, 12.8 Hz, 1H), 3.98 (s, 3H), 3.97 (s, 3H), 3.84 (s, 3H), 3.75 (s, 3H), 3.36 (dd, *J* = 1.2, 5.6 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 172.2, 157.5, 153.7, 147.2, 131.8, 127.9, 127.1, 125.3, 122.9, 118.3, 115.2, 107.0, 103.2, 62.4, 56.9, 56.6, 52.1, 38.8 ppm.



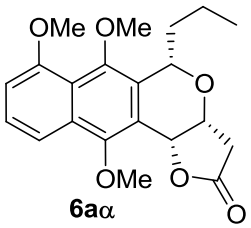
10 **5**

(4*R*,5*R*)-4-hydroxy-5-(1,4,5-trimethoxynaphthalen-2-yl)dihydrofuran-2(3H)-one (5). To a stirred solution of AD-mix-β (12.0 g), $NaHCO_3$ (2.18 g, 26.0 mmol) and $MeSO_2NH_2$ (900 mg, 9.5 mmol) in tBuOH (30 mL)-water (40 mL) at 0 ^{o}C was added a solution of **10** (2.7 g, 8.6 mmol) in tBuOH (10 mL) in a dropwise fashion. The resulting turbid mixture was allowed to warm to room temp and the reaction was subsequently stirred for 40 h. The reaction was quenched with the addition of saturated aqueous Na_2SO_3 (20 mL), and the aqueous layer extracted with EtOAc (100 mL x 2). The combined organics were washed with water (100 mL), brine (20 mL), dried over Na_2SO_4, and concentrated under vacuum. The residue was purified via silica column chromatography using 1:1 hexane/EtOAc to provide the product as a pale yellow solid (1.72 g, 5.4 mmol, 63% yield). R_f 0.10 (2:1 hexane/EtOAc); ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.57 (dd, *J* = 0.8, 8.4 Hz, 1H), 7.42 (t, *J* = 8.4 Hz, 1H), 6.88-6.86 (m, 2H), 5.84 (d, *J* = 3.6 Hz, 1H), 4.82 (dd, *J* = 3.6, 4.8 Hz, 1H), 3.94 (s, 3H), 3.93 (s, 3H), 3.87 (s, 3H), 3.02 (s, 1H), 2.92 (dd, *J* = 5.6, 18.0 Hz, 1H), 2.72 (d, *J* = 18.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 175.8, 157.7, 154.1, 146.0, 130.9, 127.3, 122.5, 118.6, 114.5, 107.3, 104.1, 82.0, 69.9, 62.1, 56.9, 56.7, 38.4 ppm; HPLC (Chiralpak IC, 20:80 i-propanol/hexane, flow rate 0.6 mL/min, λ = 254 nm): t_{minor} = 39.2

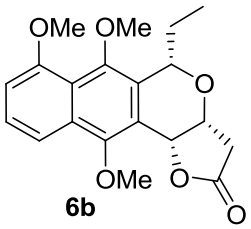
min, t_{major} = 41.8 min, ee > 99.5%.



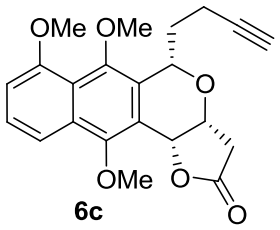
General procedure for the Cu(OTf)$_2$ catalyzed oxa-Pictet-Spengler reaction (Scheme 2, main text). To a solution of **5** (64 mg, 0.2 mmol) and Cu(OTf)$_2$ (36 mg, 0.1 mmol) in anhydrous CH_2Cl_2 (2 mL) at 0 ^oC, the corresponding aldehyde (0.4 mmol) was added in a dropwise fashion with stirring. The temperature was allowed to warm to room temp with stirring for 16 h. After concentrating under vacuum, diastereoselectivity of the crude mixture was first assessed by NMR the reaction products were subsequently purified via silica column chromatography using hexane/EtOAc to afford the products **6a-n**.



Compound 6aα[2]: colorless oil, isolated yield 90%. R_f 0.55 (1:1 hexane/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.73 (dd, *J* = 0.8, 8.4 Hz, 1H), 7.45 (t, *J* = 8.4 Hz, 1H), 6.95 (d, *J* = 8.4 Hz, 1H), 5.64 (d, *J* = 2.4 Hz, 1H), 5.06 (dd, *J* = 2.8, 7.2 Hz, 1H), 4.38 (dd, *J* = 2.4, 4.4 Hz, 1H), 4.09 (s, 3H), 4.01 (s, 3H), 3.77 (s, 3H), 2.96 (dd, *J* = 4.4, 17.2 Hz, 1H), 2.83 (d, *J* = 17.2 Hz, 1H), 2.19-1.97 (m, 2H), 1.43-1.25 (m, 2H), 0.88 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 177.7, 156.2, 153.4, 149.0, 130.3, 128.1, 126.8, 121.7, 119.3, 115.3, 107.5, 73.9, 73.3, 71.0, 64.7, 61.8, 56.4, 38.9, 37.7, 18.4, 14.0 ppm; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{21}H_{25}O_6$ 373.1651, found 373.1652.

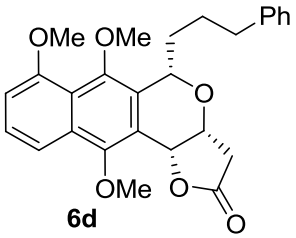


Compound 6b: colorless oil, isolated yield 84%. R_f 0.55 (1:1 hexane/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.73 (d, *J* = 8.4 Hz, 1H), 7.44 (t, *J* = 8.0 Hz, 1H), 6.94 (d, *J* = 7.6 Hz, 1H), 5.59 (s, 1H), 5.04 (t, *J* = 4.0 Hz, 1H), 4.36 (s, 1H), 4.09 (s, 3H), 4.02 (s, 3H), 3.74 (s, 3H), 2.90 (dd, *J* = 4.4, 17.2 Hz, 1H), 2.78 (d, *J* = 17.2 Hz, 1H), 2.21-2.16 (m, 2H), 0.83 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 176.1, 156.3, 153.2, 149.3, 130.3, 127.6, 126.7, 121.6, 119.9, 115.2, 107.3, 74.3, 73.2, 71.1, 64.7, 61.8, 56.4, 38.6, 28.5, 9.5 ppm; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{20}H_{23}O_6$ 359.1495, found 359.1484.



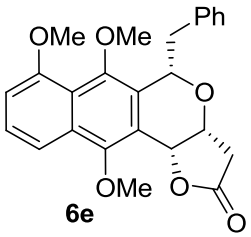
6c

Compound 6c: colorless oil, isolated yield 92%. R_f 0.50 (1:1 hexane/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.72 (d, J = 8.4 Hz, 1H), 7.44 (t, J = 8.0 Hz, 1H), 6.94 (d, J = 8.0 Hz, 1H), 5.58 (d, J = 2.0 Hz, 1H), 5.16 (dd, J = 2.4, 8.0 Hz, 1H), 4.36 (dd, J = 2.4, 4.0 Hz, 1H), 4.08 (s, 3H), 4.01 (s, 3H), 3.75 (s, 3H), 2.89 (dd, J = 4.0, 17.2 Hz, 1H), 2.76 (d, J = 17.2 Hz, 1H), 2.70-2.66 (m, 1H), 2.43-2.39 (m, 1H), 2.20-2.03 (m, 2H), 1.92 (t, J = 2.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 175.8, 156.3, 153.3, 149.5, 130.4, 127.1, 126.8, 121.7, 119.5, 115.2, 107.4, 84.5, 73.1, 71.9, 71.2, 68.3, 64.6, 61.8, 56.4, 38.5, 34.1, 14.7 ppm; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{22}H_{23}O_6$ 383.1495, found 383.1479.



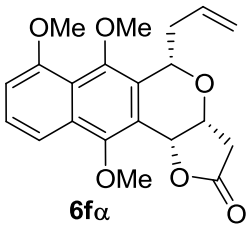
6d

Compound 6d: colorless oil, isolated yield 83%. R_f 0.60 (1:1 hexane/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.73 (d, J = 8.4 Hz, 1H), 7.44 (t, J = 8.0 Hz, 1H), 7.24-7.16 (m, 5H), 6.94 (d, J = 7.6 Hz, 1H), 5.59 (s, 1H), 5.06 (d, J = 6.8 Hz, 1H), 4.33 (s, 1H), 4.09 (s, 3H), 4.02 (s, 3H), 3.72 (s, 3H), 2.89 (dd, J = 4.0, 17.2 Hz, 1H), 2.77 (d, J = 17.2 Hz, 1H), 2.64-2.58 (m, 2H), 2.33-2.32 (m, 1H), 2.10-2.07 (m, 1H), 1.75-1.71 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 176.0, 156.3, 153.2, 149.3, 142.8, 130.3, 128.5 (2C), 128.3 (2C), 127.8, 126.7, 125.6, 121.6, 119.6, 115.2, 107.4, 73.3, 73.1, 71.1, 64.7, 61.8, 56.4, 38.6, 35.8, 35.3, 27.1 ppm; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{27}H_{29}O_6$ 449.1964, found 449.1956.



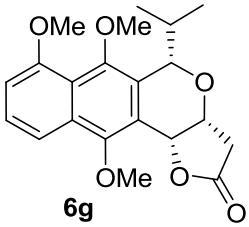
6e

Compound 6e: colorless oil, isolated yield 95%. R_f 0.60 (1:1 hexane/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.74 (d, J = 8.4 Hz, 1H), 7.46 (t, J = 8.0 Hz, 1H), 7.28-7.20 (m, 5H), 6.96 (d, J = 7.6 Hz, 1H), 5.56 (d, J = 1.2 Hz, 1H), 5.16 (d, J = 7.6 Hz, 1H), 4.27 (s, 1H), 4.06 (s, 3H), 4.05 (s, 3H), 3.86 (s, 3H), 2.93-2.81 (m, 2H), 2.72 (d, J = 17.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 176.0, 156.2, 153.3, 149.4, 139.4, 130.4, 129.9 (2C), 128.1 (2C), 127.5, 126.8, 126.2, 121.7, 119.3, 115.3, 107.5, 74.6, 72.9, 71.0, 64.7, 61.9, 56.5, 42.7, 38.6 ppm; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{25}H_{25}O_6$ 421.1651, found 421.1644.



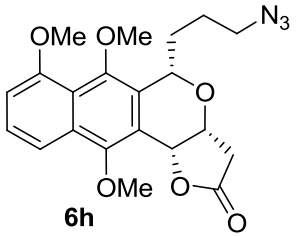
6fα

Compound 6fα: colorless oil, isolated yield 50%. R_f 0.55 (1:1 hexane/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.74 (dd, *J* = 0.8, 8.4 Hz, 1H), 7.45 (t, *J* = 8.0 Hz, 1H), 6.95 (d, *J* = 7.6 Hz, 1H), 5.88-5.81 (m, 1H), 5.60 (d, *J* = 2.4 Hz, 1H), 5.11-4.99 (m, 3H), 4.37 (dd, *J* = 2.4, 4.4 Hz, 1H), 4.09 (s, 3H), 4.02 (s, 3H), 3.77 (s, 3H), 3.09-3.05 (m, 1H), 2.91 (dd, *J* = 4.4, 17.2 Hz, 1H), 2.82 (d, *J* =17.2 Hz, 1H), 2.77-2.70 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 176.0, 156.3, 153.2, 149.3, 135.1, 130.4, 127.3, 126.8, 121.7, 119.5, 117.1, 115.3, 107.5, 73.4, 73.0, 71.2, 64.8, 61.9, 56.5, 39.9, 38.6 ppm; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{21}H_{23}O_6$ 371.1495, found 371.1463.



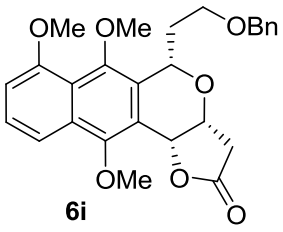
6g

Compound 6g: colorless oil, isolated yield 81%. R_f 0.70 (1:1 hexane/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.72 (d, *J* = 8.4 Hz, 1H), 7.43 (t, *J* = 8.0 Hz, 1H), 6.92 (d, *J* = 8.0 Hz, 1H), 5.57 (s, 1H), 4.97 (s, 1H), 4.31 (s, 1H), 4.09 (s, 3H), 4.00 (s, 3H), 3.74 (s, 3H), 2.88 (dd, *J* = 4.4, 17.2 Hz, 1H), 2.75 (d, *J* =17.2 Hz, 1H), 1.13 (d, *J* = 7.6 Hz, 3H), 0.99-0.95 (m, 1H), 0.53 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 176.2, 156.2, 153.1, 149.3, 130.2, 127.8, 126.6, 121.6, 119.9, 115.2, 107.2, 76.8, 73.1, 70.6, 64.7, 61.8, 56.3, 38.5, 32.2, 20.3, 15.3 ppm; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{21}H_{25}O_6$ 373.1651, found 373.1647.



6h

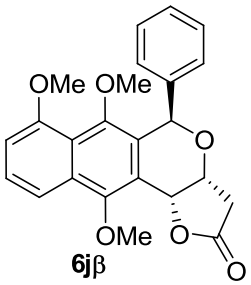
Compound 6h: colorless oil, isolated yield 90%. R_f 0.40 (1:1 hexane/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.73 (dd, *J* = 0.8, 8.4 Hz, 1H), 7.45 (t, *J* = 8.0 Hz, 1H), 6.94 (d, *J* = 7.6 Hz, 1H), 5.58 (d, *J* = 2.4 Hz, 1H), 5.08 (dd, *J* = 2.8, 6.8 Hz, 1H), 4.35 (dd, *J* = 2.4, 4.0 Hz, 1H), 4.09 (s, 3H), 4.01 (s, 3H), 3.74 (s, 3H), 3.25-3.23 (m, 2H), 2.91 (dd, *J* = 4.0, 17.2 Hz, 1H), 2.77 (d, *J* = 17.2 Hz, 1H), 2.33-2.32 (m, 1H), 2.17-2.03 (m, 1H), 1.72-1.60 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 175.8, 156.3, 153.3, 149.4, 130.4, 127.1, 126.9, 121.6, 119.5, 115.2, 107.5, 73.0, 73.0, 71.2, 64.7, 61.7, 56.4, 51.5, 38.5, 32.4, 24.6 ppm; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{21}H_{24}N_3O_6$ 414.1665, found 414.1671.



6i

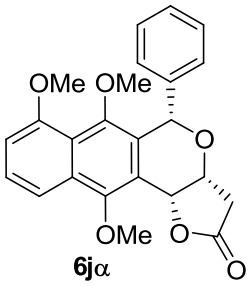
Compound 6i: colorless solid, isolated yield 80%. R_f 0.55 (1:1 hexane/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.72 (dd, *J* = 8.0 Hz, 1H), 7.44 (t, *J* = 8.0 Hz, 1H), 7.29-7.26 (m, 5H), 6.94 (d, *J* = 7.6 Hz, 1H), 5.58 (d, *J* = 2.0 Hz, 1H), 5.21 (dd, *J* = 2.4, 8.4 Hz, 1H), 4.50 (dd, *J* = 12.0, 32.4 Hz, 2H), 4.34 (dd, *J* = 2.4, 4.0 Hz, 1H), 4.07 (s, 3H), 4.01 (s, 3H), 3.81-3.79 (m, 1H), 3.75 (s, 3H), 3.56-3.54 (m, 1H), 2.92-2.86 (m, 2H), 2.74 (d, *J* = 17.2 Hz, 1H), 2.08-2.05 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 175.9,

156.3, 153.2, 149.4, 139.0, 130.3, 128.2 (2C), 127.8, 127.5 (2C), 127.3, 126.7, 121.7, 119.5, 115.2, 107.4, 73.1, 72.6, 71.2, 70.6, 66.7, 64.5, 61.7, 56.3, 38.5, 35.3 ppm; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{27}H_{29}O_7$ 465.1913, found 465.1907.



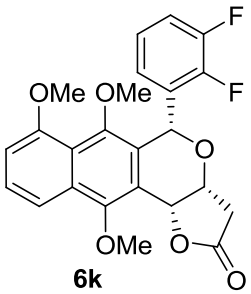
6jβ

Compound 6jβ: colorless solid, isolated yield 74%. R_f 0.65 (1:1 hexane/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.76 (dd, J = 8.8 Hz, 1H), 7.46 (t, J = 8.4 Hz, 1H), 7.26-7.25 (m, 3H), 7.08 (d, J = 4.0 Hz, 2H), 6.93 (d, J = 8.0 Hz, 1H), 6.36 (s, 1H), 5.57 (d, J = 2.8 Hz, 1H), 4.31 (dd, J = 2.4, 4.8 Hz, 1H), 4.11 (s, 3H), 3.96 (s, 3H), 3.56 (s, 3H), 2.84 (dd, J = 5.2, 17.6 Hz, 1H), 2.63 (d, J =18.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 175.3, 156.3, 153.0, 148.6, 139.3, 130.6, 128.7 (2C), 128.4 (2C), 128.3, 126.7, 124.8, 121.4, 119.6, 115.3, 107.1, 73.2, 72.2, 66.7, 64.1, 62.2, 56.1, 37.4 ppm; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{24}H_{23}O_6$ 407.1495, found 407.1494.



6jα

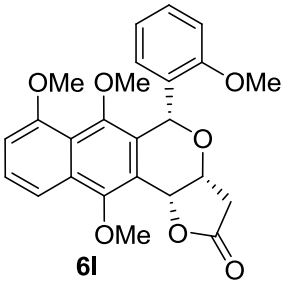
Compound 6jα: colorless solid, isolated yield 25%. R_f 0.45 (1:1 hexane/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.76 (d, J = 8.4 Hz, 1H), 7.45 (t, J = 8.4 Hz, 1H), 7.33-7.26 (m, 5H), 6.89 (d, J = 7.6 Hz, 1H), 5.98 (s, 1H), 5.67 (d, J = 2.0 Hz, 1H), 4.50 (s, 1H), 4.17 (s, 3H), 3.91 (s, 3H), 3.07 (s, 3H), 2.90 (dd, J = 4.0, 17.2 Hz, 1H), 2.72 (d, J = 16.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 175.7, 156.2, 153.2, 149.4, 143.2, 130.8, 128.6 (2C), 128.5 (2C), 128.2, 127.1, 126.9, 121.7, 119.4, 115.2, 107.2, 76.7, 72.6, 71.9, 64.7, 61.4, 56.2, 37.5 ppm; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{24}H_{23}O_6$ 407.1495, found 407.1494.



6k

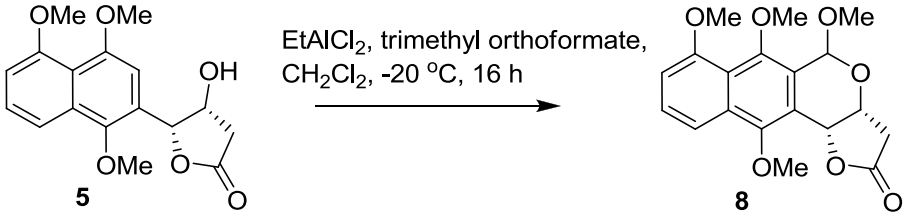
Compound 6k: colorless oil, isolated yield 97%. R_f 0.45 (1:1 hexane/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.75 (d, J = 8.4 Hz, 1H), 7.45 (t, J = 8.4 Hz, 1H), 7.04 (q, J = 8.0 Hz, 1H), 6.94-6.84 (m, 3H), 6.34 (s, 1H), 5.67 (s, 1H), 4.53 (d, J = 2.0 Hz, 1H), 4.15 (s, 3H), 3.90 (s, 3H), 3.42 (s, 3H), 2.93 (dd, J = 4.4, 17.6 Hz, 1H), 2.73 (d, J = 17.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 175.4, 156.2, 153.2, 151.4 (J = 13.3, 137.0 Hz), 149.4, 149.0 (J = 13.2, 138.0 Hz), 132.5, 130.9, 127.1, 126.0, 124.4, 124.1 (J = 4.6 Hz),

121.7, 119.4, 116.4 (J = 17.0 Hz), 115.2, 107.4, 72.4,72.2, 68.6, 64.7, 61.7, 56.2, 38.3 ppm; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{24}H_{21}F_2O_6$ 443.1306, found 443.1309.



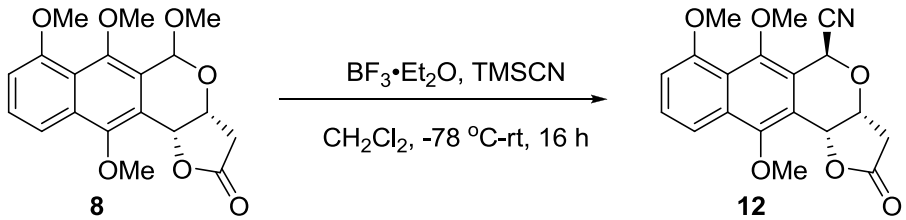
6l

Compound 6l: colorless solid, isolated yield 86%. R_f 0.40 (1:1 hexane/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.76 (dd, J = 0.8, 8.4 Hz, 1H), 7.45 (t, J = 8.4 Hz, 1H), 7.27-7.26 (m, 1H), 6.98 (d, J = 8.4 Hz, 1H), 6.90 (d, J = 7.6 Hz, 1H), 6.90-6.87 (m, 1H), 6.73-6.70 (m, 1H), 6.41 (m, 1H), 5.65 (d, J = 3.5 Hz, 1H), 4.45 (s, 1H), 4.13 (s, 3H), 3.98 (br s, 3H), 3.94 (s, 3H), 3.51 (s, 3H), 2.84 (dd, J = 5.2, 17.6 Hz, 1H), 2.67 (d, J = 17.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 175.5, 158.1, 156.3, 152.8, 148.4, 130.6, 130.0, 129.8, 129.7, 127.7, 126.6, 126.0, 121.6, 120.1, 119.6, 115.3, 111.6, 107.0, 72.4, 67.4, 66.9, 64.2, 62.1, 56.2, 37.6 ppm; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{25}H_{25}O_7$ 437.1600, found 437.1579.



5 **8**

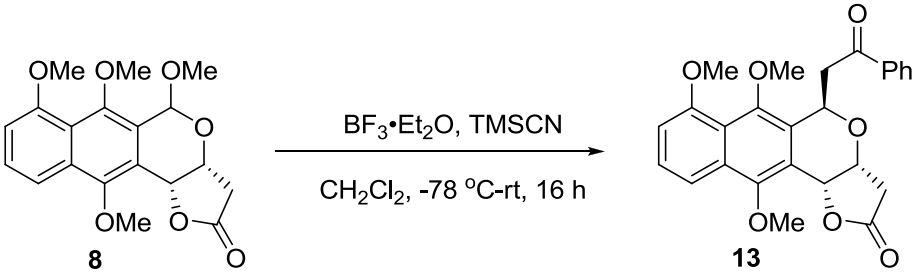
(3a*R*,11b*R*)-5,6,7,11-Tetramethoxy-3,3a,5,11b-tetrahydro-2H-benzo[g]furo[3,2-c]isochromen-2-one (8). To a solution of **5** (640 mg, 2 mmol) and trimethyl orthoformate (260 uL, 2.4 mmol) in anhydrous CH_2Cl_2 (20 mL) at -20 ^{o}C with stirring, $EtAlCl_2$ (2.0 mL, 1 M in hexane, 2.0 mmol) was added in a dropwise fashion. The reaction mixture was stirred overnight at -20 ^{o}C, subsequently quenched by the addition of 1 N potassium sodium tartrate solution (20 mL) and the reaction allowed to warm to room temp. The corresponding aqueous layer was extracted with CH_2Cl_2 (20 mL x 2) and the combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated. The residue was purified via silica column chromatography with 2:1 hexane/EtOAc to afford the desired product **8** as a colorless solid (470 mg, 1.3 mmol, 65% yield). R_f 0.50 (2:3 hexane/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.71 (dd, J = 0.8, 8.4 Hz, 1H), 7.45 (t, J = 8.4 Hz, 1H), 6.93 (dd, J = 0.4, 8.0 Hz, 1H), 5.90 (s, 1H), 5.57 (d, J = 3.2 Hz, 1H), 4.91 (dd, J = 2.8, 5.2 Hz, 1H), 4.04 (s, 3H), 4.01 (s, 3H), 3.86 (s, 3H), 3.60 (s, 3H), 3.01 (dd, J = 5.2, 17.6 Hz, 1H), 2.76 (d, J = 17.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 175.2, 156.6, 152.7, 150.3, 131.3, 127.2, 123.5, 121.6, 118.2, 115.4, 107.2, 95.0, 71.8, 65.8, 64.0, 63.3, 56.3, 55.9, 37.2 ppm; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{19}H_{21}O_7$ 361.1287, found 361.1258.



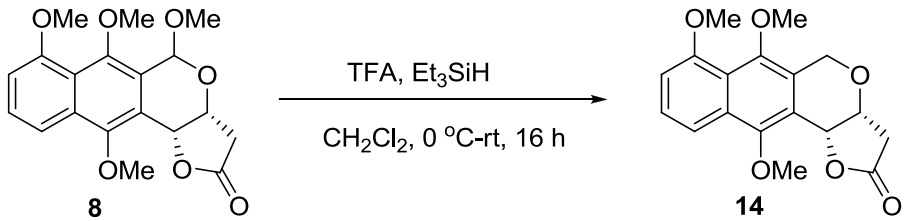
8 **12**

(3a*R*,5S,11b*R*)-6,7,11-Trimethoxy-2-oxo-3,3a,5,11b-tetrahydro-2H-benzo[g]furo[3,2-c]isochromene-5-carbonitrile (12). To a solution of **8** (72 mg, 0.2 mmol) and $MeSi_3CN$ (76 uL, 0.6 mmol) in anhydrous

CH_2Cl_2 (4 mL) at -78 °C with stirring, BF_3Et_2O (76 uL, 0.6 mmol) was added in a dropwise fashion. The reaction mixture was stirred overnight and subsequently allowed to warm to room temp. The reaction was quenched with saturated aqueous $NaHCO_3$ solution (10 mL), extracted with Et_2O (20 mL x 2) and the combined organics were washed with brine, dried over Na_2SO_4, filtered, and concentrated. The diasteroselectivity of the crude reaction was assessed via NMR and then purified on silica column chromatography using 3:1 hexane/EtOAc to afford the desired product **12** as a colorless solid (60 mg, 0.17 mmol, 85% yield). R_f 0.60 (1:1 hexane/EtOAc); ^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.71 (d, J = 8.4 Hz, 1H), 7.61 (t, J = 8.4 Hz, 1H), 7.17 (dd, J = 7.6 Hz, 1H), 6.48 (s, 1H), 5.73 (d, J = 2.8 Hz, 1H), 4.84 (dd, J = 2.4, 4.8 Hz, 1H), 3.99 (s, 3H), 3.97 (s, 3H), 3.85 (s, 3H), 3.39-3.31 (m, 1H), 2.67 (d, J = 17.6 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ = 174.7, 155.9, 152.5, 148.8, 130.6, 128.3, 120.3, 118.4, 117.6, 117.3, 114.7, 108.2, 71.5, 70.3, 63.4, 62.5, 60.3, 56.2, 36.8 ppm; HRMS (ESI) m/z [M + H]$^+$ calcd for $C_{19}H_{18}NO_6$ 356.1117, found 356.1134.

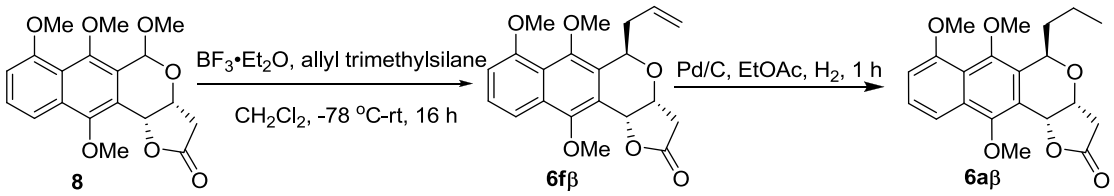


(3a*R*,5*R*,11b*R*)-6,7,11-Trimethoxy-5-(2-oxo-2-phenylethyl)-3,3a,5,11b-tetrahydro-2H-benzo[g]furo[3,2-c]isochromen-2-one (13). To a solution of **8** (72 mg, 0.2 mmol) and acetophenone (70 uL, 0.6 mmol) in anhydrous CH_2Cl_2 (4 mL) at -78 °C with stirring, BF_3Et_2O (76 uL, 0.6 mmol) was added in a dropwise fashion. The reaction mixture was stirred overnight and subsequently allowed to warm to room temp. The reaction was quenched with saturated aqueous $NaHCO_3$ solution (10 mL), extracted with Et_2O (20 mL x 2) and the combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated. The diasteroselectivity of the crude reaction was assessed via NMR and then purified on silica column chromatography using 2:1 hexane/EtOAc to afford the desired product **13** as a colorless solid (86 mg, 0.17 mmol, 1:5 α/β mixture, 96% yield). R_f 0.60 (1:1 hexane/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.10 (dd, J = 2.0, 8.4 Hz, 1H), 7.72-7.44 (m, 6H), 6.96 (d, J = 8.0 Hz, 1H), 5.82 (dd, J = 2.8, 10.8 Hz, 1H), 5.62 (d, J = 2.8 Hz, 1H), 4.06 (s, 3H), 4.05 (s, 3H), 3.94 (s, 3H), 3.78 (dd, J = 3.2, 12.0 Hz, 1H), 3.26 (dd, J = 11.2, 15.2 Hz, 1H), 2.94 (dd, J = 4.8, 17.6 Hz, 1H), 2.67 (d, J = 17.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 197.2, 175.1, 156.0, 153.3, 147.6, 136.1, 133.4, 130.4, 128.7 (2C), 128.4 (2C), 126.7, 126.2, 121.4, 118.4, 115.2, 107.1, 71.6, 68.9, 66.7, 64.1, 62.5, 56.1, 42.7, 37.6 ppm; HRMS (ESI) m/z [M + H]$^+$ calcd for $C_{26}H_{25}O_7$ 449.1600, found 449.1592.



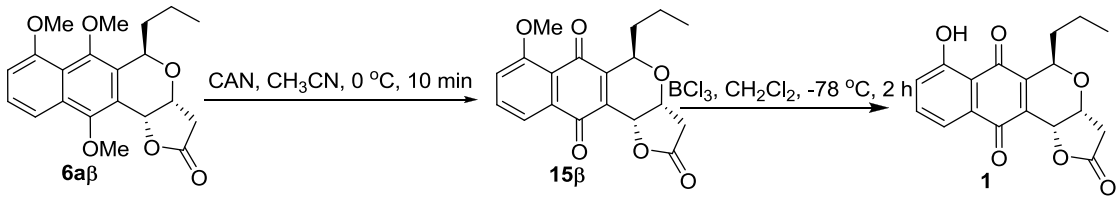
(3a*R*,11b*R*)-6,7,11-Trimethoxy-3,3a,5,11b-tetrahydro-2H-benzo[g]furo[3,2-c]isochromen-2-one (14). To a solution of **8** (72 mg, 0.2 mmol) and TFA (46 uL, 0.6 mmol) in anhydrous CH_2Cl_2 (2 mL) at 0 °C with stirring, Et_3SiH (96 uL, 0.6 mmol) was added in a dropwise fashion. The reaction mixture was stirred overnight, the reaction allowed to room temp and concentrated under vacuum. The concentrate was purified via silica column chromatography with 1:1 hexane/EtOAc to afford the desired product **14** as a

colorless solid (55 mg, 0.167 mmol, 83% yield). R_f 0.50 (2:3 hexane/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.72 (dd, *J* = 0.8, 8.4 Hz, 1H), 7.43 (t, *J* = 8.4 Hz, 1H), 6.93 (d, *J* = 6.8 Hz, 1H), 5.57 (d, *J* = 2.8 Hz, 1H), 5.24 (d, *J* = 16.0 Hz, 1H), 4.70 (d, *J* = 16.0 Hz, 1H), 4.41 (dd, *J* = 2.0, 4.4 Hz, 1H), 4.07 (s, 3H), 4.01 (s, 3H), 3.80 (s, 3H), 2.97 (dd, *J* = 4.8, 17.6 Hz, 1H), 2.77 (d, *J* = 17.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 175.2, 156.2, 153.3, 147.8, 130.3, 126.5, 124.4, 121.4, 119.0, 115.3, 107.2, 73.4, 72.5, 64.3, 63.4, 62.1, 56.2, 37.8 ppm; HRMS (ESI) m/z [M + H]$^+$ calcd for $C_{18}H_{19}NO_6$ 331.1182, found 331.1138.



(3a*R*,5*R*,11b*R*)-6,7,11-Trimethoxy-5-propyl-3,3a,5,11b-tetrahydro-2H-benzo[g]furo[3,2-c]isochromen-2-one (6aβ).[2] To a solution of **8** (72 mg, 0.2 mmol) and allyl trimethylsilane (96 uL, 0.6 mmol) in anhydrous CH_2Cl_2 (4 mL) at -78 °C with stirring, BF_3Et_2O (76 uL, 0.6 mmol) was added in dropwise fashion. The reaction mixture was stirred overnight and allowed to warm to room temp. The reaction was quenched with saturated aqueous $NaHCO_3$ solution (10 mL), extracted with Et_2O (20 mL x 2) and the combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated. The residue was directly used in the next step without further purification. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.71 (d, *J* = 8.4 Hz, 1H), 7.45 (t, *J* = 8.0 Hz, 1H), 6.93 (d, *J* = 7.6 Hz, 1H), 5.99-5.93 (m, 1H), 5.58 (d, *J* = 2.8 Hz, 1H), 5.29 (s, 1H), 5.18-5.14 (m, 3H), 4.72 (dd, *J* = 2.8, 4.9 Hz, 1H), 4.06 (s, 3H), 4.02 (s, 3H), 3.86 (s, 3H), 2.96 (dd, *J* = 5.2, 17.6 Hz, 1H), 2.73-2.69 (m, 2H), 2.55-2.50 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 175.3, 156.0, 153.1, 147.6, 134.9, 130.2, 127.2, 126.5, 121.5, 118.5, 117.0, 115.2, 107.0, 71.9, 71.4, 66.1, 63.9, 62.5, 56.1, 37.7, 37.3 ppm.

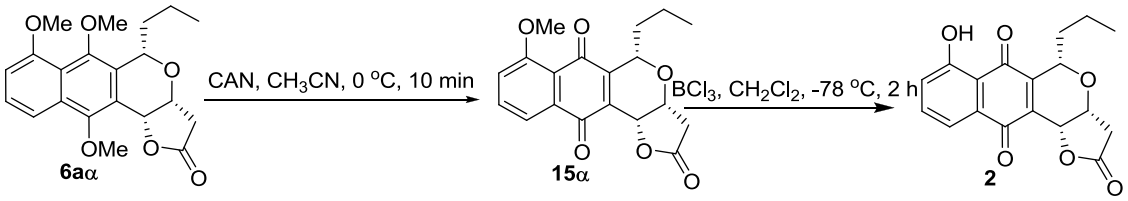
The ethyl acetate (2 mL) solution of **6f**β and Pd/C (10 mg) was placed in a capped flask under argon, fitted with a H_2 balloon and the reaction vessel atmosphere exchanged with H_2 (3x). The mixture was stirred to room temperature for 1 hr, filtered through celite, the filtrate evaporated and recovered concentrate purified via silica column chromatography using 3:1 hexane/EtOAc to afford the desired product as a colorless oil (72 mg, 0.19 mmol, 97% yield). R_f 0.55 (1;1 hexane/EtOAc);. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.69 (d, *J* = 7.6 Hz, 1H), 7.45 (t, *J* = 8.0 Hz, 1H), 6.95 (d, *J* = 3.2 Hz, 1H), 5.66 (s, 1H), 5.17 (d, *J* = 9.2 Hz, 1H), 4.72 (s, 1H), 4.05 (s, 3H), 4.01 (s, 3H), 3.89 (s, 3H), 3.07 (dd, *J* = 3.2, 17.2 Hz, 1H), 2.81 (d, *J* = 17.2 Hz, 1H), 1.81-1.74 (m, 2H), 1.58-1.55 (m, 2H), 1.00 (t, *J* = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 178.2, 156.0, 153.3, 147.2, 130.1, 128.3, 126.8, 121.6, 118.0, 115.3, 107.3, 73.45, 71.5, 66.0, 64.1, 62.7, 56.2, 38.1, 34.9, 19.6, 13.6 ppm; HRMS (ESI) m/z [M + H]$^+$ calcd for $C_{21}H_{25}O_6$ 373.1651, found 373.1638.



(+)-Frenolicin B (2). To a solution of **6a**β (37 mg, 0.1 mmol) in a mixture of water (0.5 mL) and acetonitrile (1 mL) at 0 °C with stirring, a solution of cerium ammonium nitrate (126 mg, 0.2 mmol) in water (0.5 mL) was added in dropwise fashion. The reaction mixture was stirred for 10 min before the addition of water (5 mL). The mixture was extracted with EtOAc (10 mL x 2) and the combined organics washed with brine, dried over Na_2SO_4, filtered, and concentrated. The resulting residue was directly used in the

next step without further purification.

The ethyl acetate (2 mL) solution of **15**β (see also **Scheme 4**, main text) in CH_2Cl_2 (3.5 mL) was cooled to -78 °C under argon. A solution of BCl_3 (0.4 mL, 0.4 mmol, 1 N in CH_2Cl_2) was added to the mixture and the reaction stirred for 2 hr at -78 °C. The reaction was quenched with saturated aqueous NH_4Cl solution (1 mL), diluted with water (5 mL) and EtOAc (5 mL). The organic layer was washed with brine, dried over Na_2SO_4, filtered, and concentrated. The concentrate was purified via silica column chromatography using 3:1 hexane/EtOAc to afford the desired product as an orange solid (20 mg, 0.06 mmol, 60% yield). R_f 0.15 (2:1 hexane/EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 11.85 (s, 1H), 7.71-7.65 (m, 2H), 7.30 (dd, *J* = 2.0, 8.0 Hz, 1H), 5.25 (d, *J* = 3.2 Hz, 1H), 4.92 (dd, *J* = 3.2, 10.0 Hz, 1H), 4.62 (dd, *J* = 2.8, 5.2 Hz, 1H), 2.95 (dd, *J* = 5.2, 17.6 Hz, 1H), 2.71 (d, *J* = 17.6 Hz, 1H), 1.71-1.65 (m, 4H), 1.03 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 188.2, 181.6, 174.0, 162.0, 149.4, 137.3, 135.3, 131.6, 125.0, 119.9, 115.0, 69.8, 68.8, 66.4, 37.0, 33.9, 19.7, 13.7 ppm; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{18}H_{17}O_6$ 329.1025, found 329.1025.



(+)-*epi*-Frenolicin B (2). To a solution of **6a**α (37 mg, 0.1 mmol) in a mixture of water (0.5 mL) and acetonitrile (1 mL) at 0 °C with stirring, a solution of cerium ammonium nitrate (126 mg, 0.2 mmol) in water (0.5 mL) was added in a dropwise fashion. The reaction mixture was stirred for 10 min before the addition of water (5 mL). The mixture was extracted with EtOAc (10 mL x 2) and the combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated. The concentrate was directly used in the next step without further purification.

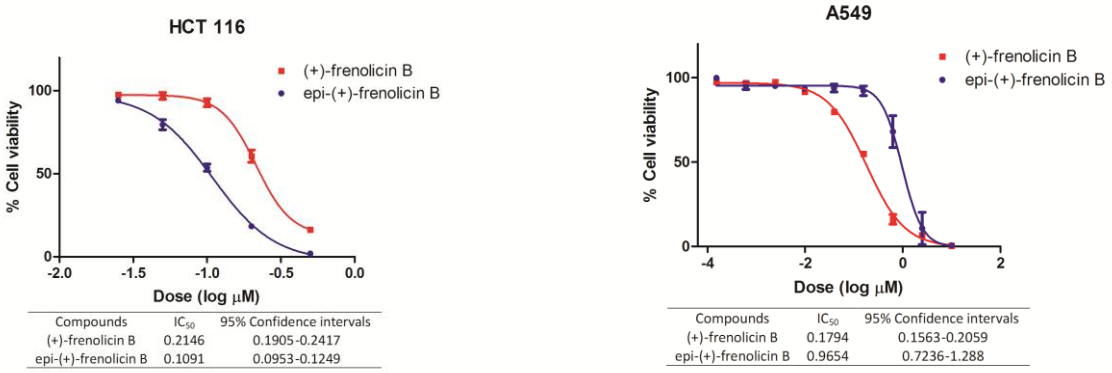
The ethyl acetate (2 mL) solution of **15**α (see also **Scheme 4**, main text) in CH_2Cl_2 (3.5 mL) was cooled to -78 °C under argon. A solution of BCl_3 (0.4 mL, 0.4 mmol, 1 N in CH_2Cl_2) was added to the mixture and the reaction stirred for 2 hr at -78 °C. The reaction was quenched with saturated aqueous NH_4Cl solution (1 mL), and the reaction was diluted with water (5 mL) and EtOAc (5 mL). The organic layer was washed with brine, dried over Na_2SO_4, filtered, and concentrated. The concetrate was purified on silica gel using 3:1 hexane/EtOAc to afford the desired product as an orange solid (19.5 mg, 0.06 mmol, 61% yield). R_f 0.15 (2:1 hexane/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 11.78 (s, 1H), 7.71-7.67 (m, 2H), 7.30 (dd, *J* = 2.0, 8.0 Hz, 1H), 5.27 (t, *J* = 2.0 Hz, 1H), 4.76 (m, 1H), 4.32 (dd, *J* = 2.4, 4.4 Hz, 1H), 2.89 (dd, *J* = 4.4, 17.6 Hz, 1H), 2.74 (d, *J* = 17.6 Hz, 1H), 2.10-2.04 (m, 1H), 1.96-1.90 (m, 1H), 1.48-1.42 (m, 1H), 1.35-1.27 (m, 1H), 0.91 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 188.8, 181.5, 174.5, 161.9, 149.8, 137.2, 136.3, 131.6, 125.0, 119.8, 115.2, 72.0, 71.0, 69.9, 37.5, 36.2, 18.4, 14.1 ppm; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{18}H_{17}O_6$ 329.1025, found 329.1020.

3. Cancer cell line cytotoxicity

(+)-Frenolicin B (**1**) and *epi*-(+)-frenolicin B (**2**) synthesized in this study were tested for cytotoxicity against the human colorectal carcinoma cell line HCT116 and human non-small cell lung carcinoma cell line A549 (ATCC, Manassas, VA), respectively. The IC_{50} values for each compound in the context of each cell line were determined by the Alamar Blue assay as previously described (see **Figure S1**).[3]

4. Literature cited

1. Jung, M. E.; Hagenah, J. A. *J. Org. Chem.* **1987**, *52*, 1889.
2. Fernandes, R. A.; Chavan, V. P.; Mulay, S. V.; Manchoju, A. *J. Org. Chem.* **2012**, *77*, 10455.
3. Wang, X.; Shaaban, K. A.; Elshahawi, S. I.; Ponomareva, L. V.; Sunkara, M.; Zhang, Y.; Copley, G. C.; Hower, J. C.; Kharel, M. K.; Thorson, J. T. *J. Nat. Prod.* **2013**, *76*, 1441.

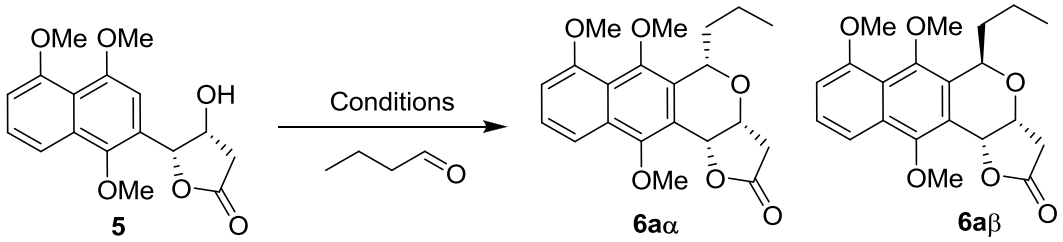


Compounds	IC_{50}	95% Confidence intervals
(+)-frenolicin B	0.2146	0.1905-0.2417
epi-(+)-frenolicin B	0.1091	0.0953-0.1249

Compounds	IC_{50}	95% Confidence intervals
(+)-frenolicin B	0.1794	0.1563-0.2059
epi-(+)-frenolicin B	0.9654	0.7236-1.288

Figure S1. Cytotoxicity of (+)-frenolicin B (**1**) and *epi*-(+)-frenolicin B (**2**) against the human colorectal carcinoma cell line HCT116 (left panel) and human non-small cell lung carcinoma cell line A549 (right panel).

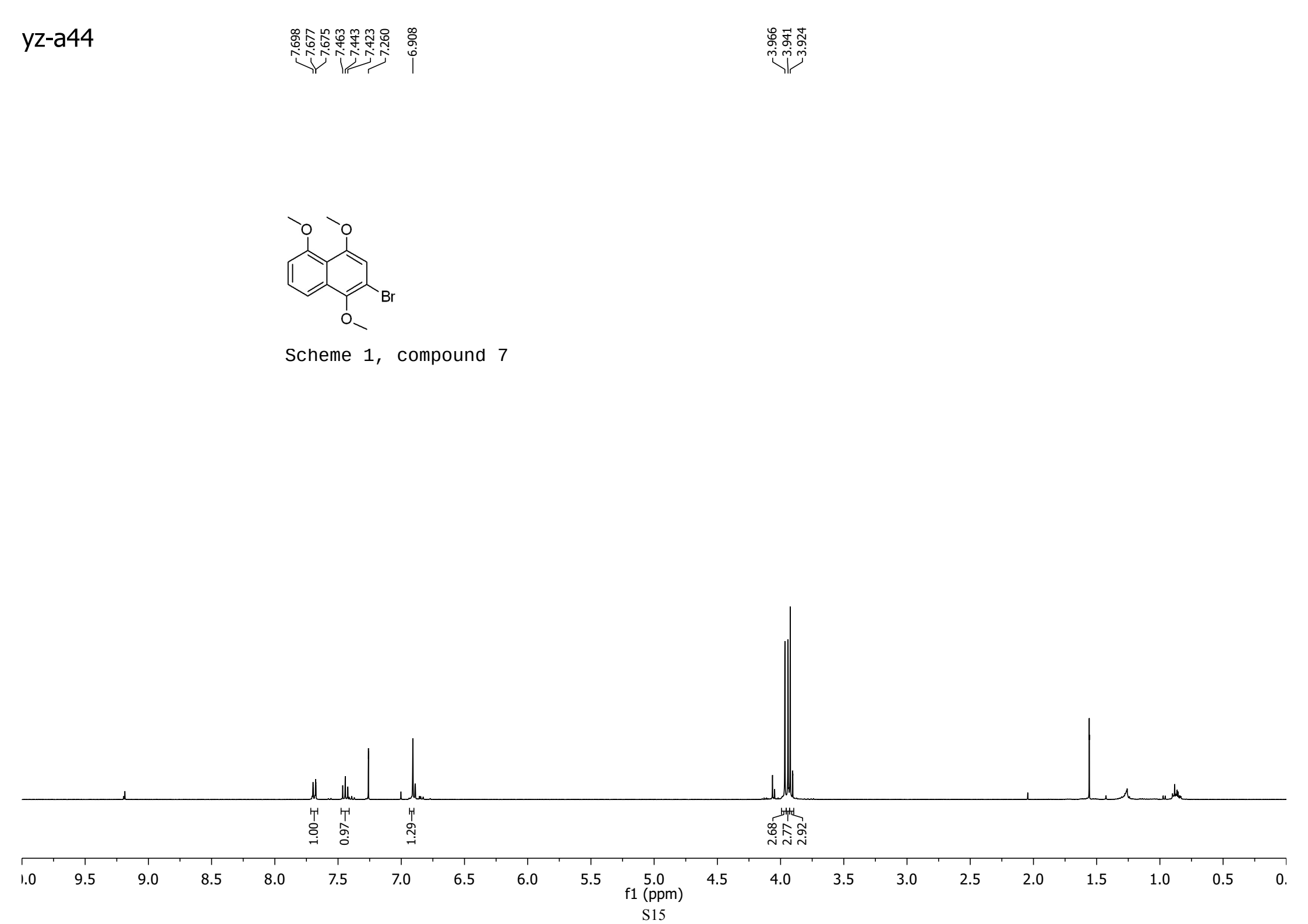
Table S1. Lewis acid optimization of the oxa-Pictet-Spengler reaction.[a]



Entry	Lewis acids	Solvents	Temp (^{o}C)	Conversion (%)[b]	dr (**6a**α/**6a**β)[c]
1	$GdCl_3$	CH_2Cl_2	0-rt	<5	-
2[d]	$AlCl_3$	CH_2Cl_2	-78-rt	30	95:5
3	$EtAlCl_2$	CH_2Cl_2	0-rt	80	85:15
4	Et_2AlCl	CH_2Cl_2	0-rt	20	60:40
5	TMSOTf	CH_2Cl_2	0-rt	80	68:32
6	$ZnCl_2$	CH_2Cl_2	0-rt	70	55:45
7[e]	ZnI_2	CH_2Cl_2	0-rt	60	55:45
8	$CuBr_2$	CH_2Cl_2	0-rt	85	91:9[f]
9	$Sc(OTf)_3$	CH_2Cl_2	0-rt	85	55:45
10[e]	$AgClO_4$	CH_2Cl_2	0-rt	50	75:25
11	$InCl_3$	CH_2Cl_2	0-rt	75	60:40
12	HCl[g]	CH_2Cl_2	0-rt	30	95:5
13	$Zn(OTf)_2$	CH_2Cl_2	0-rt	<5	-
14	$La(OTf)_3$	CH_2Cl_2	0-rt	<5	-

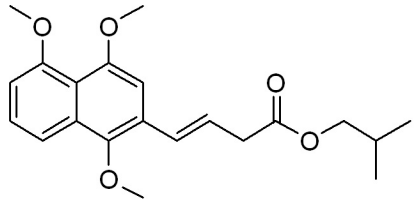
[a] Reaction were performed with 0.2 mmol **5**, 0.4 mmol aldehyde, and 50 mol% Lewis acid at 0 ^{o}C and allow the temp raise to room temp with 4 h stirring. [b] Conversion was determined by HPLC analysis. [c] dr ratio was determined by the proton NMR of crude products. [d] 2 h reaction time. [e] Overnight. [f] 10% side bromine substitution on the naphthalene ring was found. [g] 2N HCl in Et_2O.

yz-a44

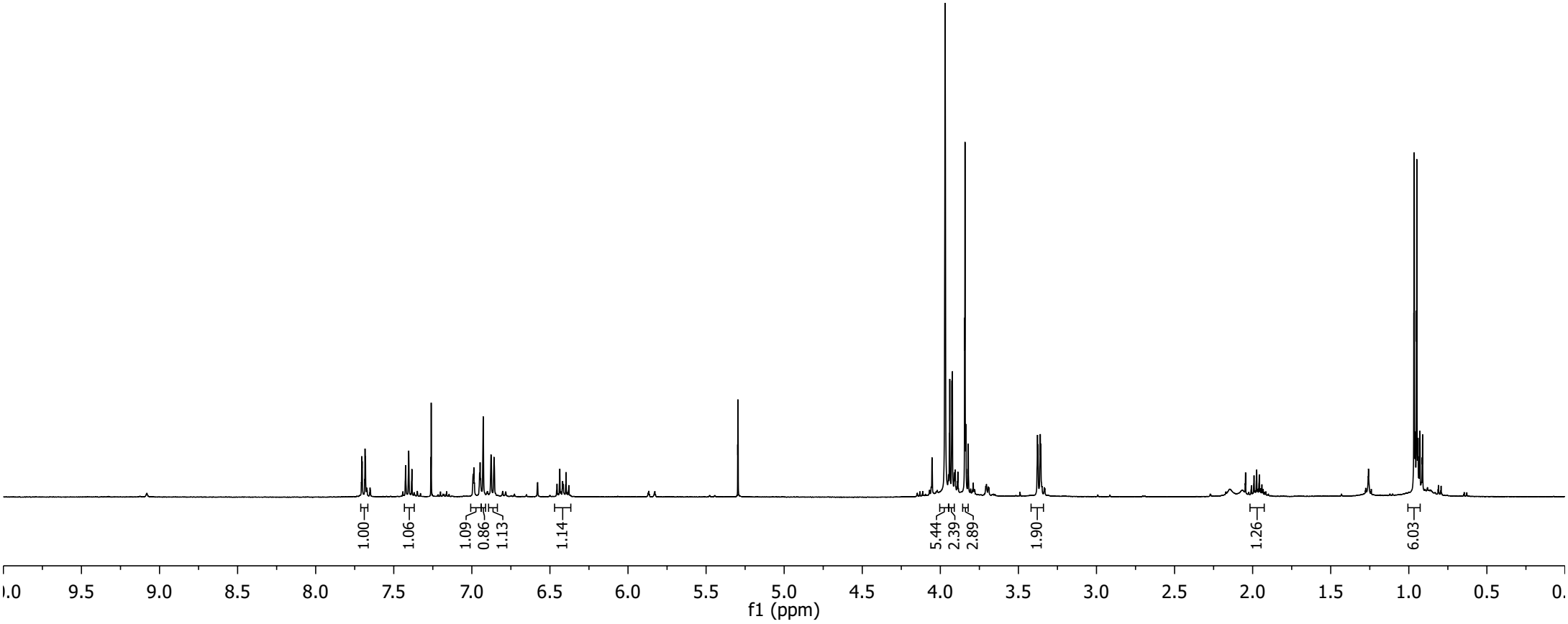


Scheme 1, compound 7

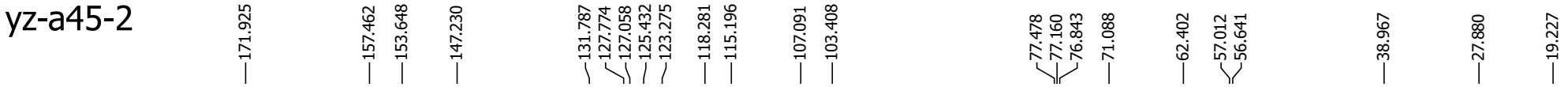
yz-a45-2

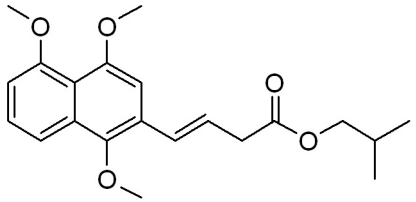


Scheme 1, compound 9

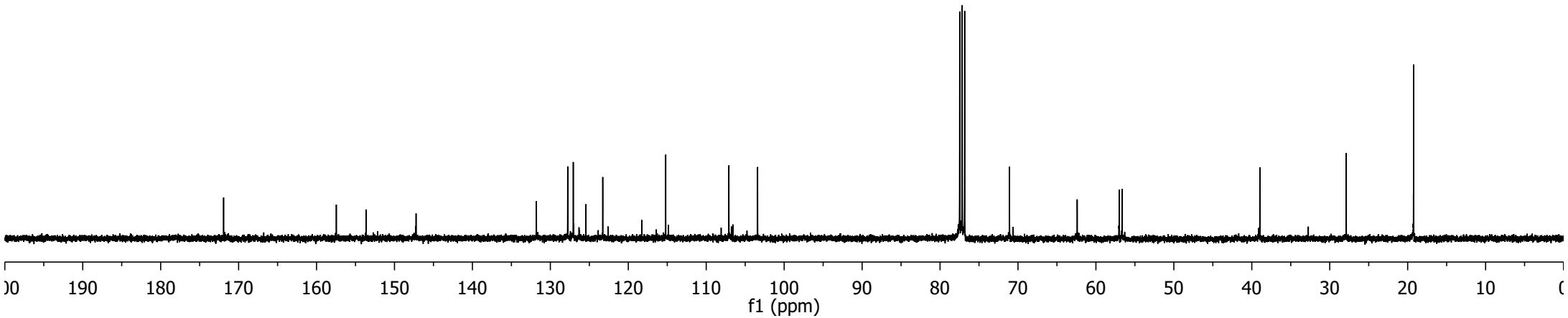


yz-a45-2

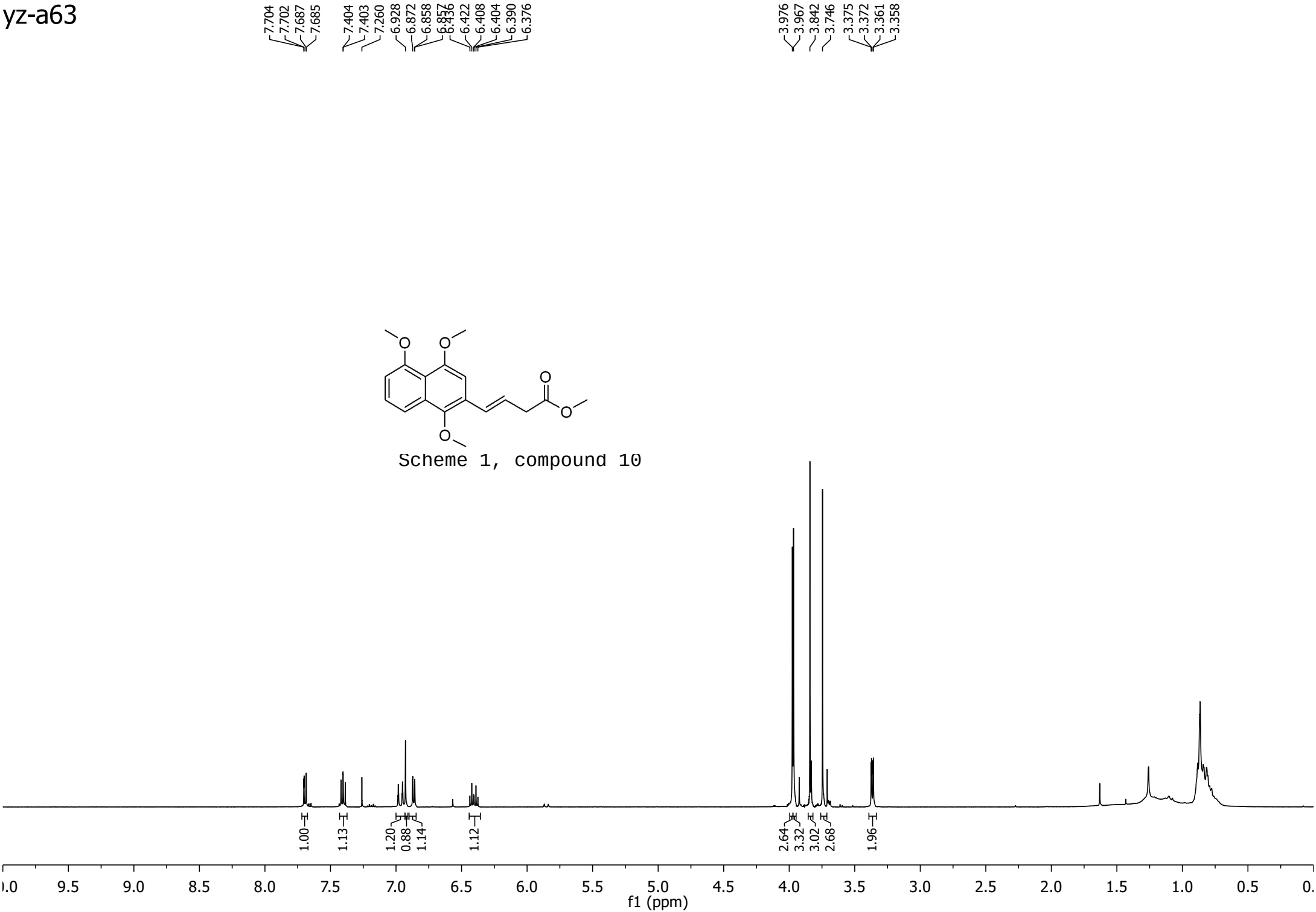




Scheme 1, compound 9



yz-a63



Scheme 1, compound 10

yz-a63

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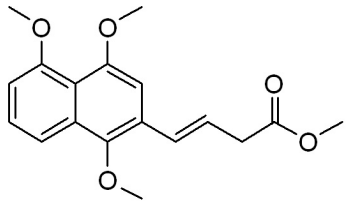
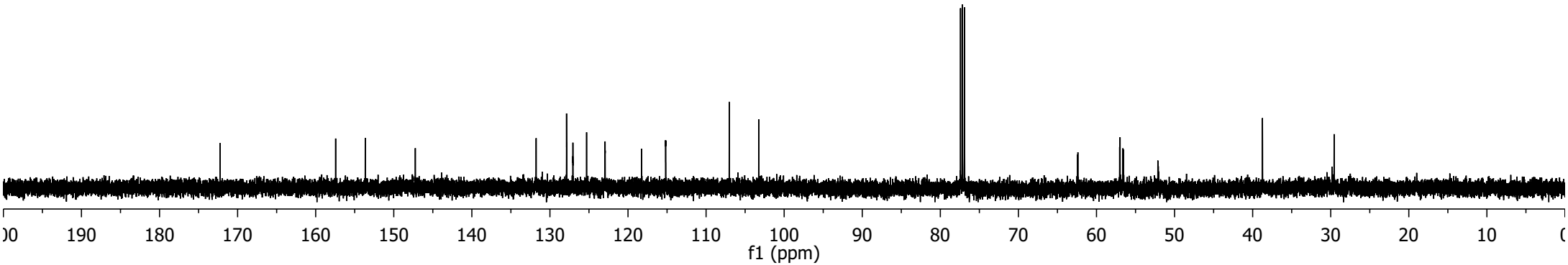
157.446
153.652
147.241
131.767
127.873
127.055
125.304
122.935
118.260
115.185
107.027
103.237
77.415
77.160
76.906
62.440
56.948
56.620
52.140
38.746



Scheme 1, compound 10



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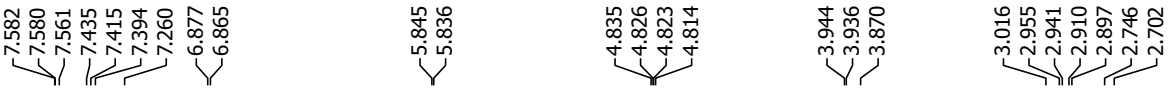
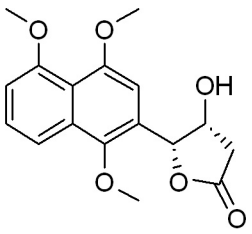
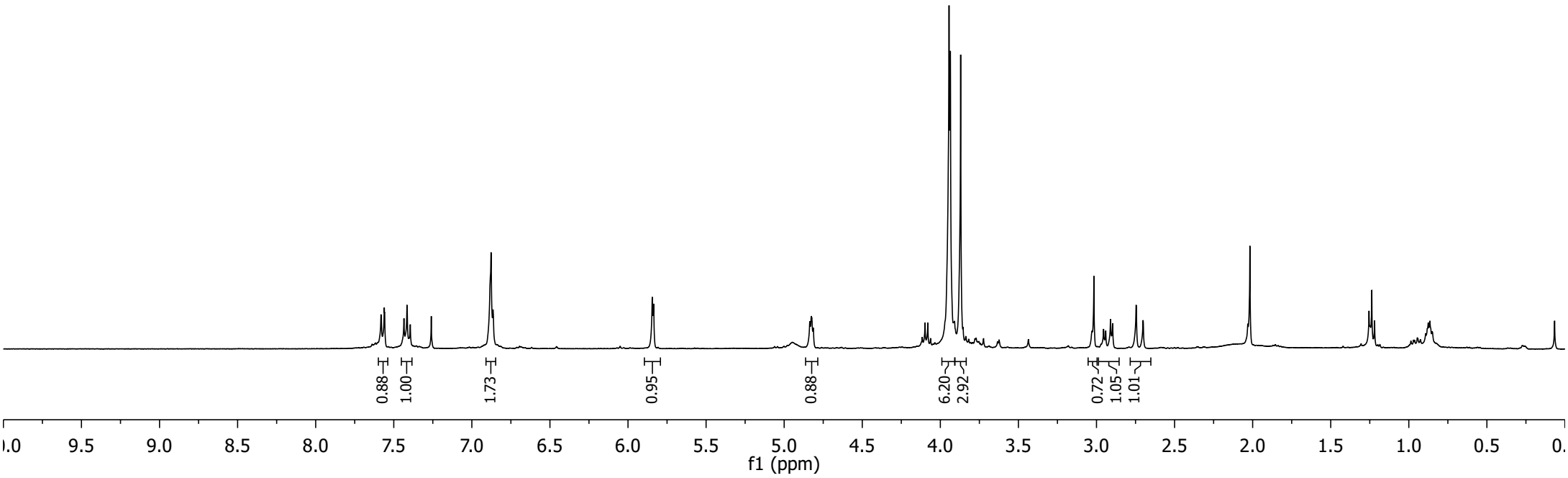
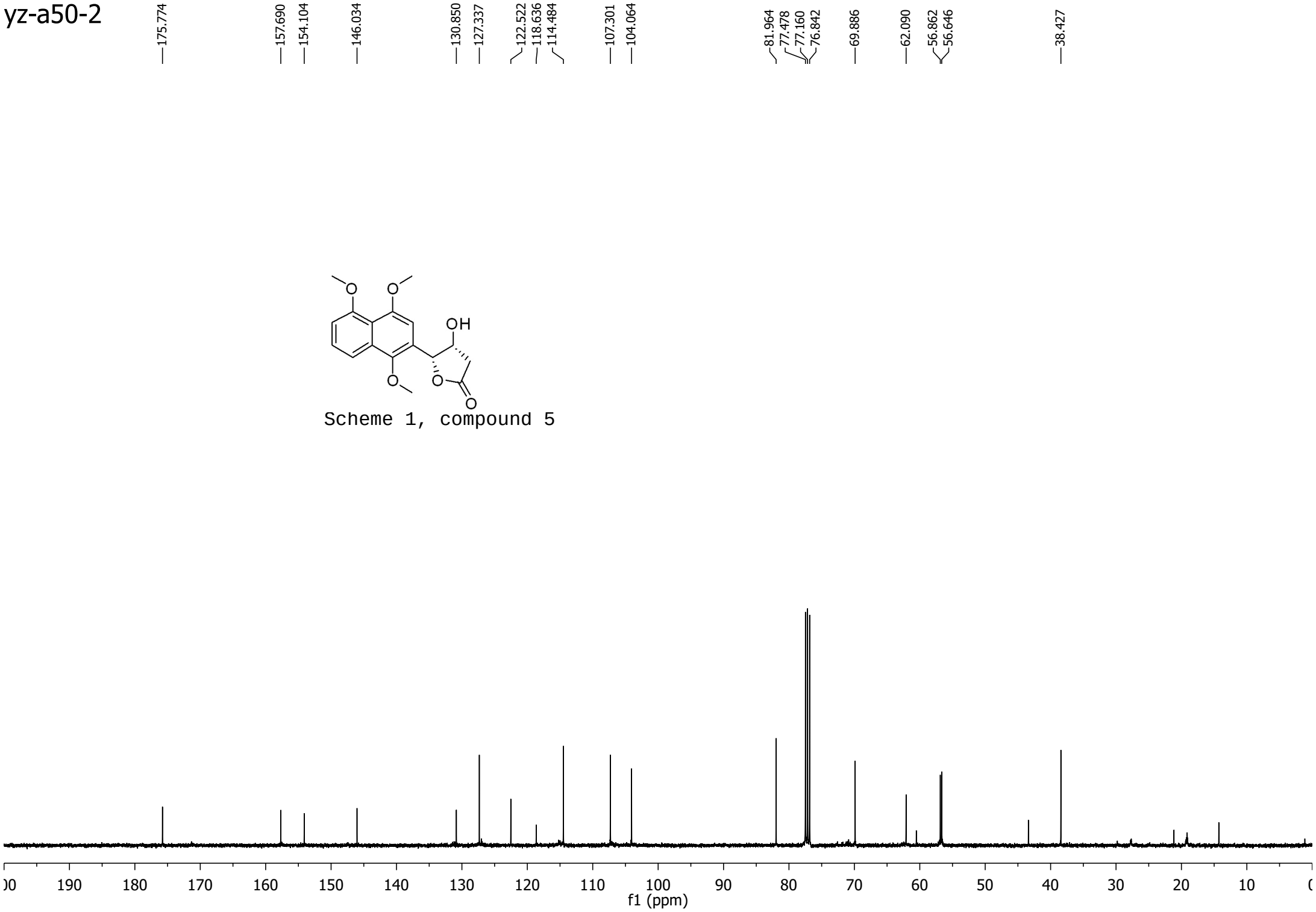




Scheme 1, compound 5

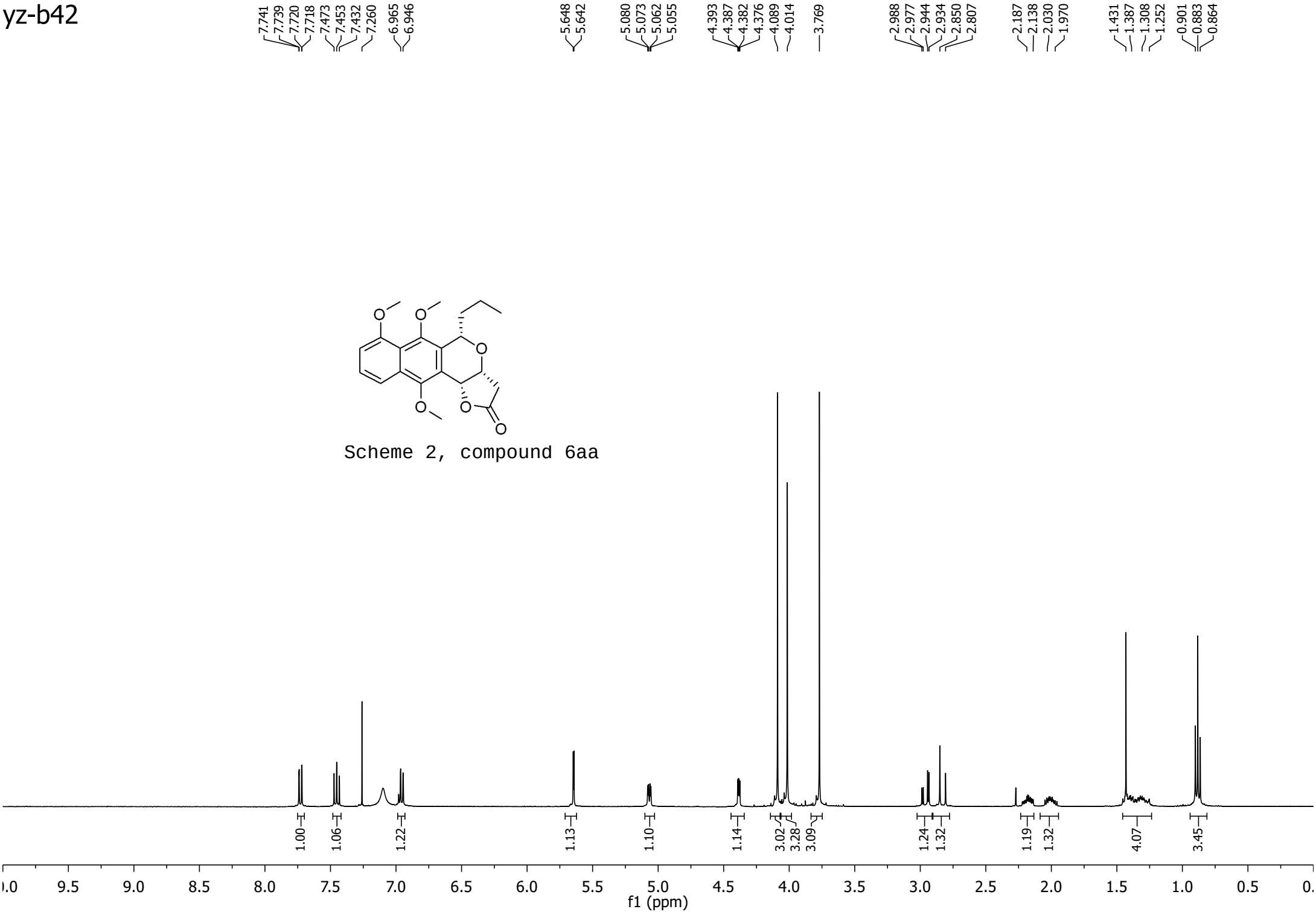


yz-a50-2



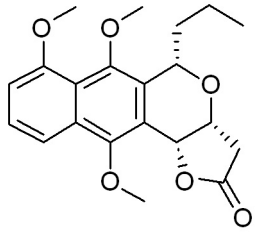
Scheme 1, compound 5

yz-b42

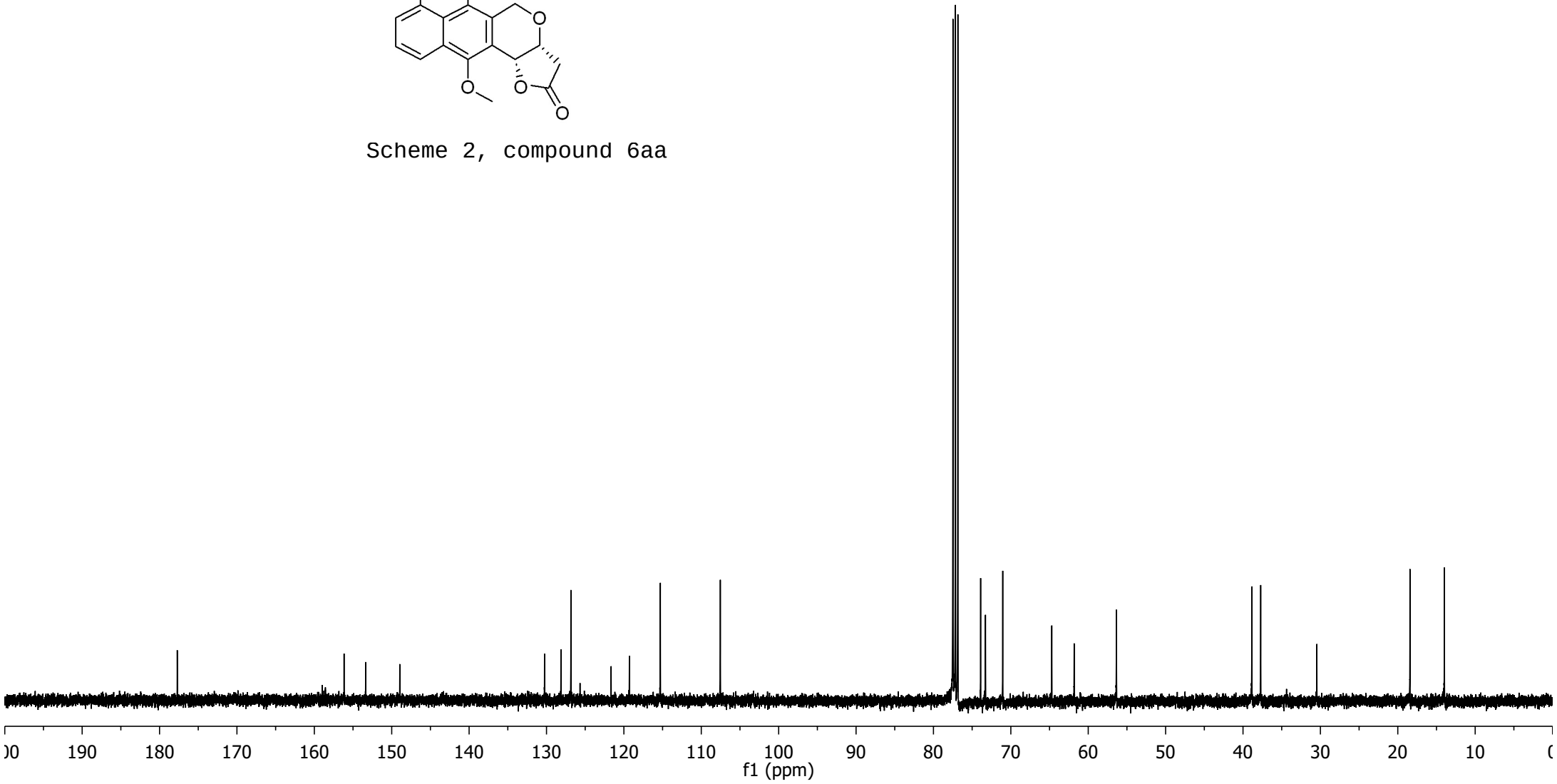


Scheme 2, compound 6aa

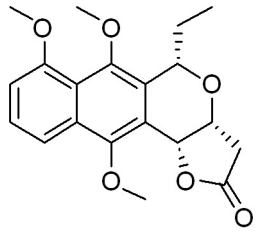
yz-b42



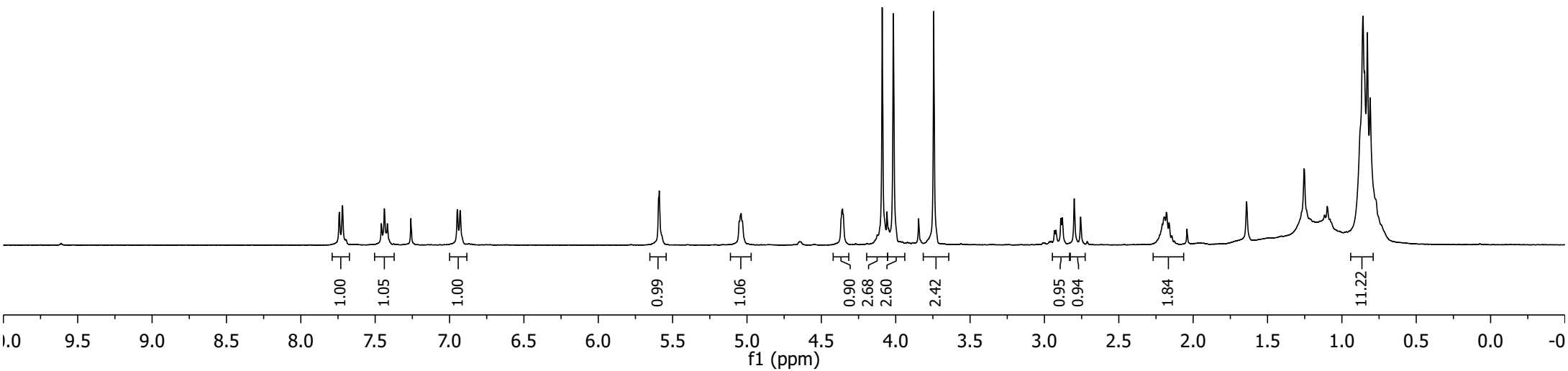
Scheme 2, compound 6aa



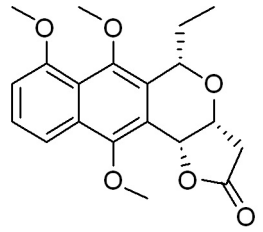
yz-b2



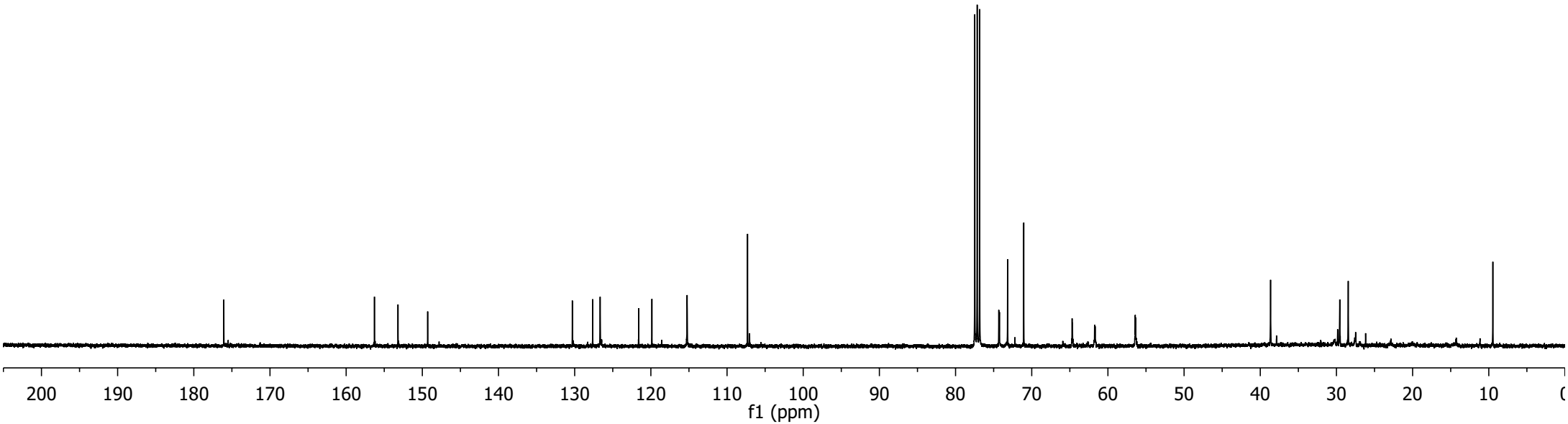
Scheme 2, compound 6b

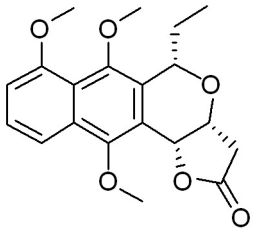


yz-b2

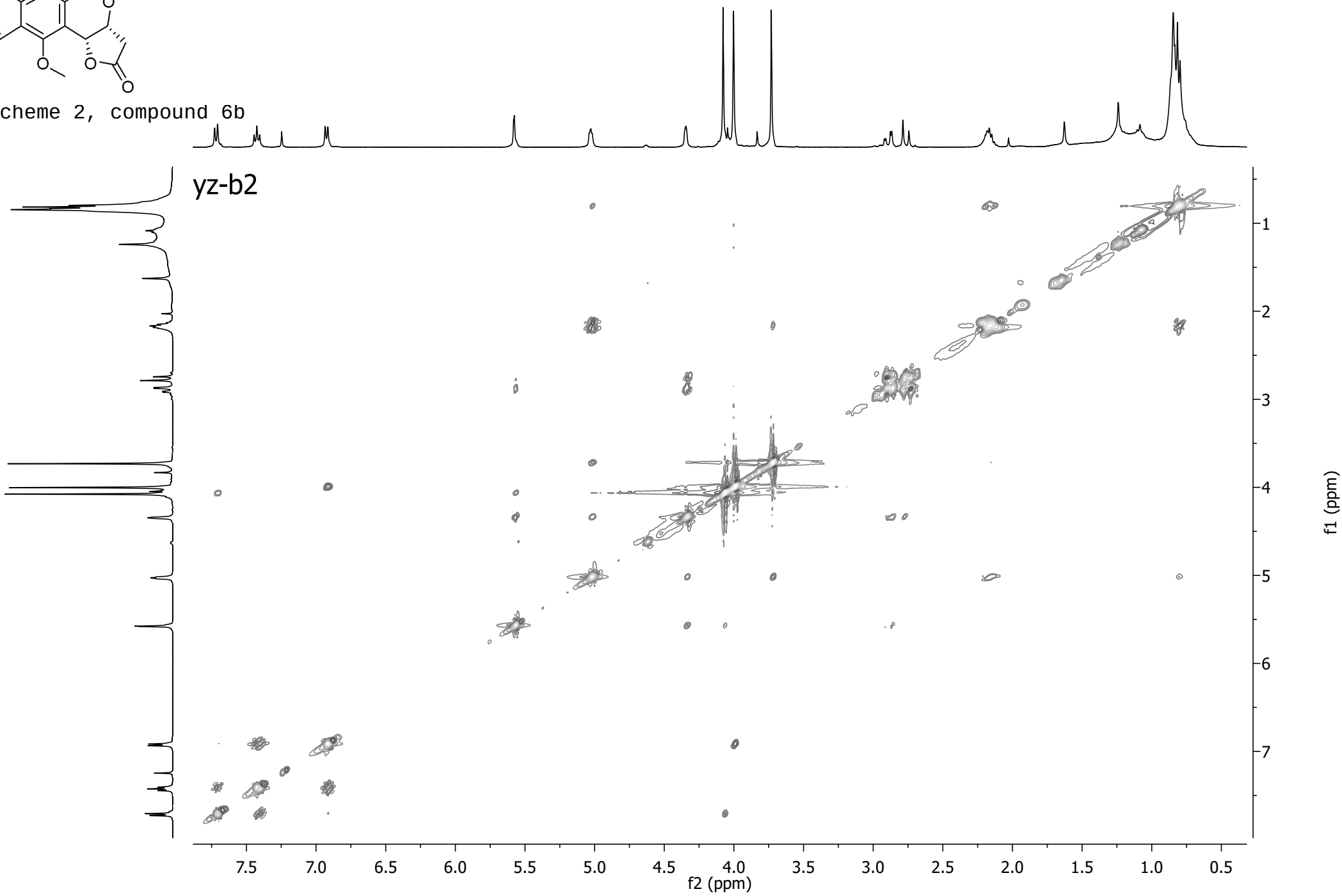


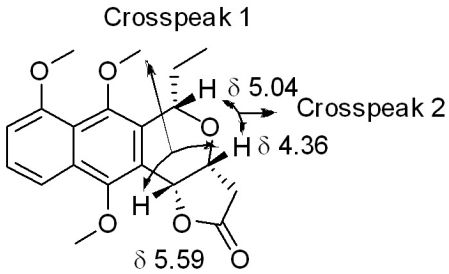
Scheme 2, compound 6b



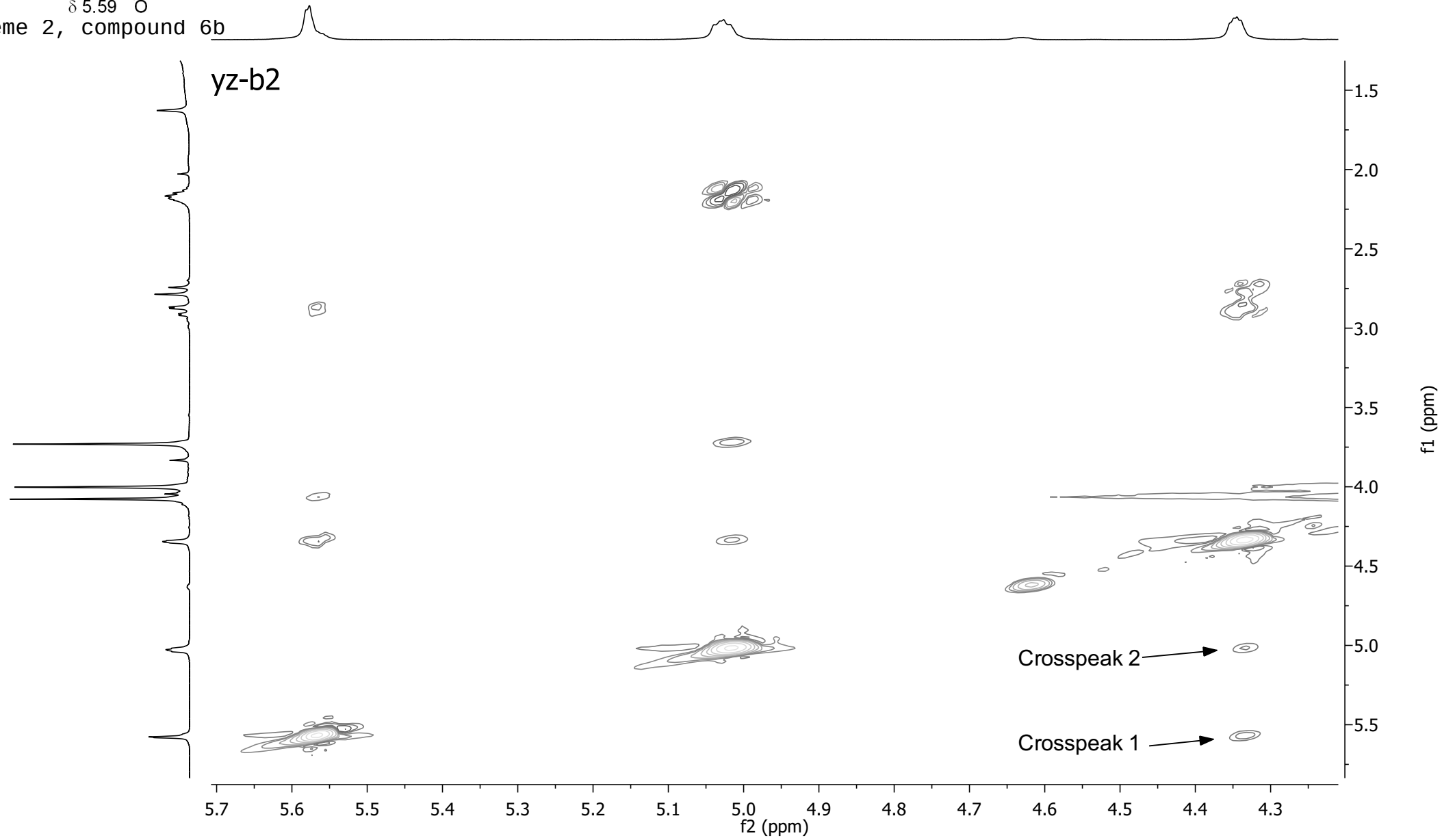


Scheme 2, compound 6b

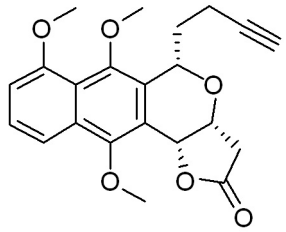




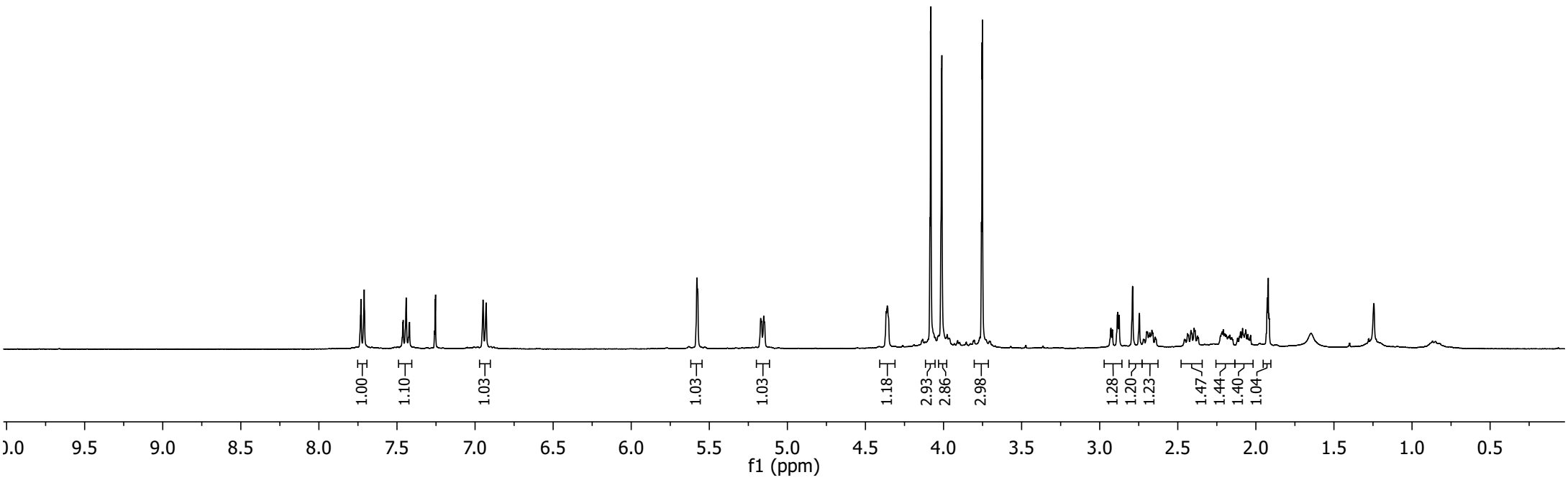
Scheme 2, compound 6b



yz-b3



Scheme 2, compound 6c



yz-b3

175.805
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153.302
149.510
130.406
127.051
126.828
121.702
119.518
115.194
107.407
84.519
77.478
77.160
76.842
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56.385
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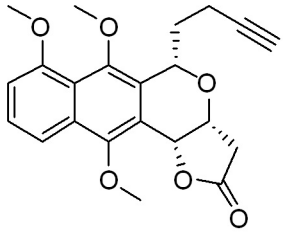
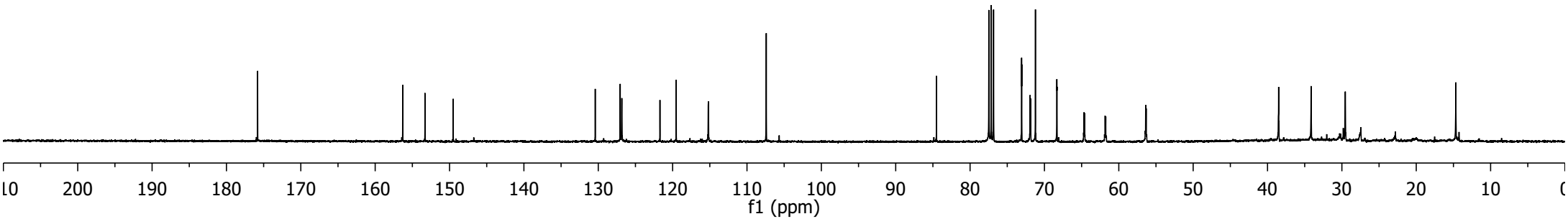
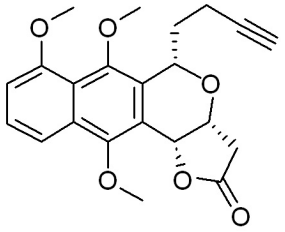
34.138
29.542
14.678

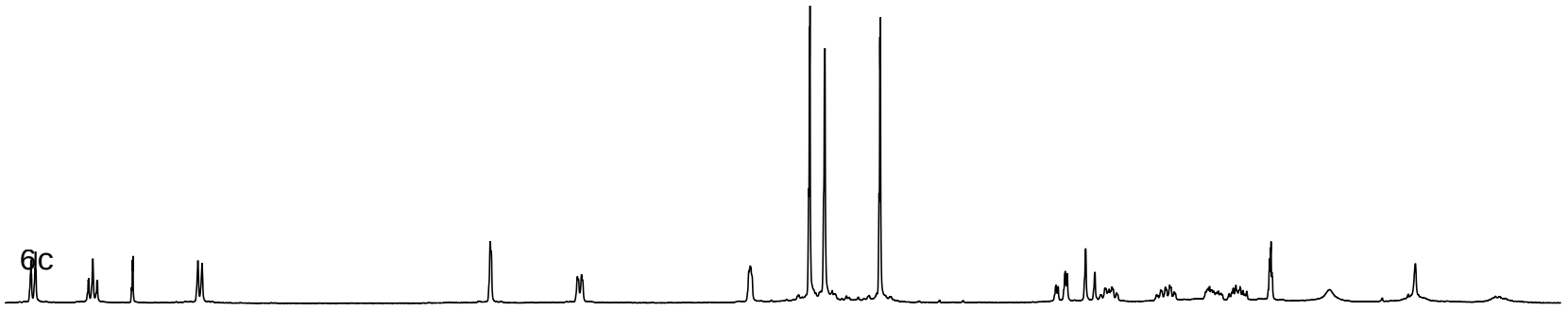


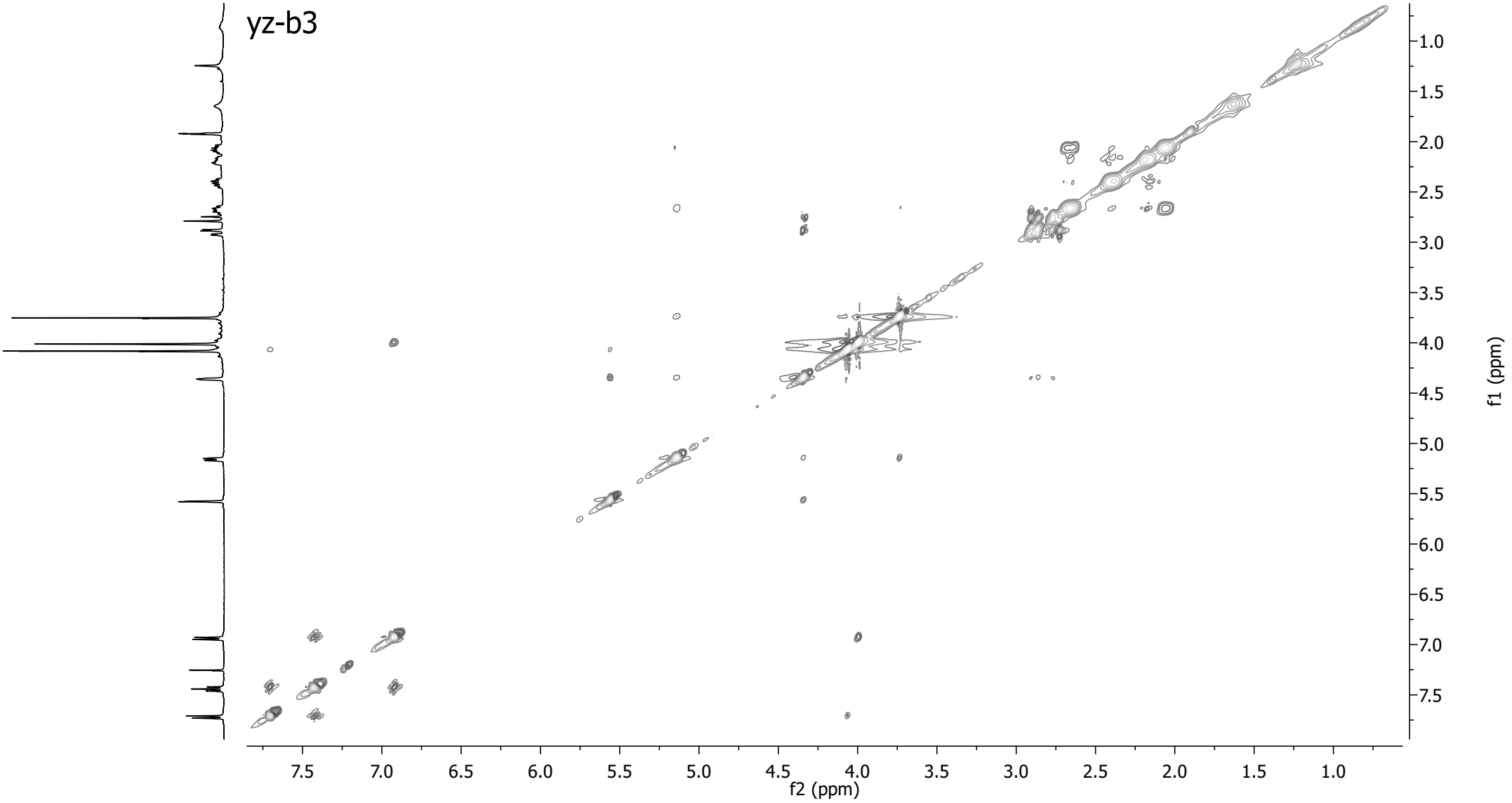
Scheme 2, compound 6c

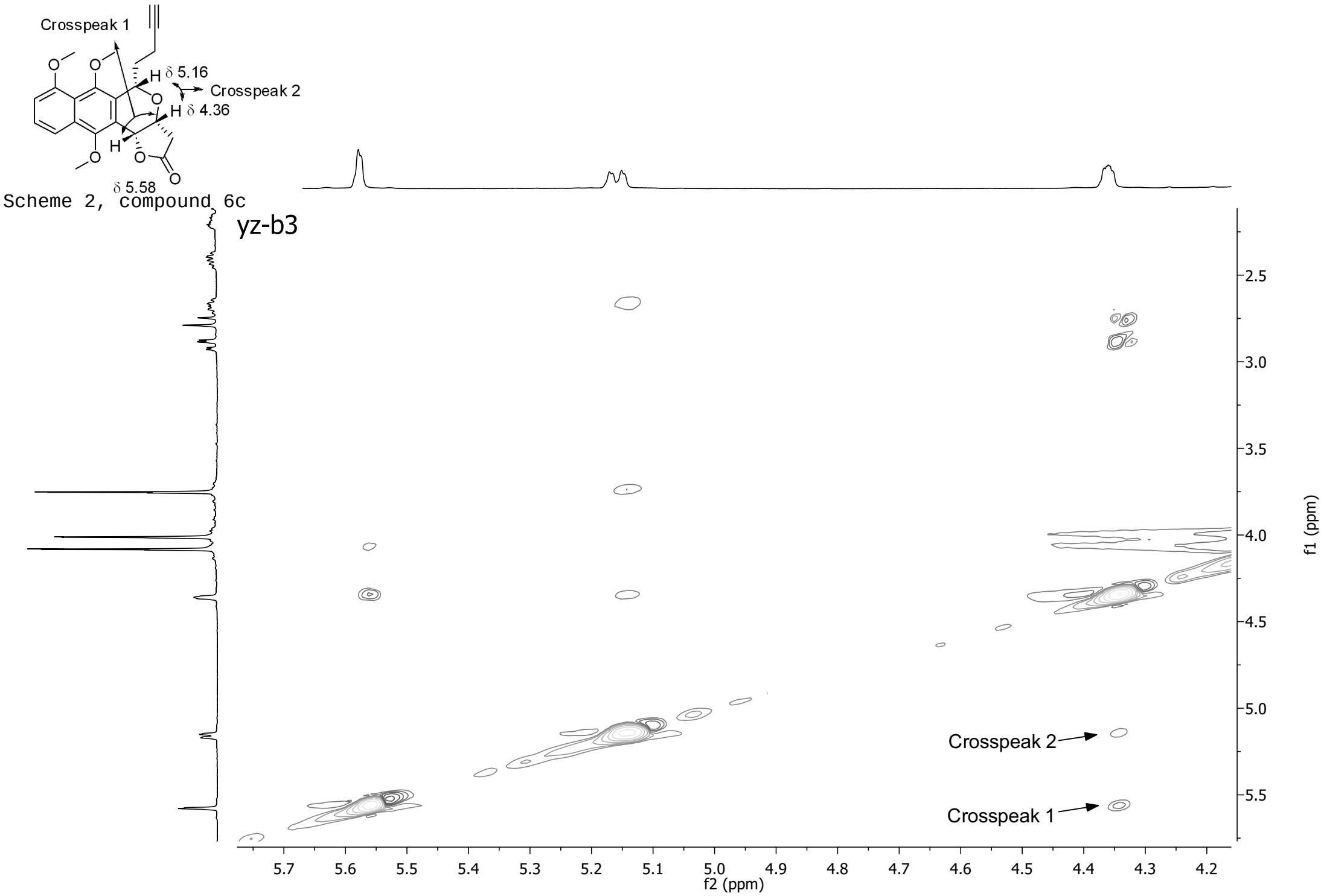




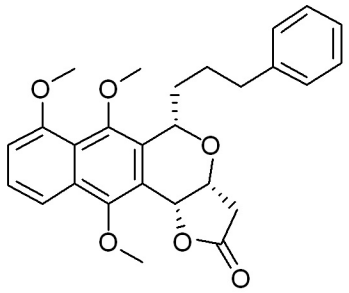
Scheme 2, compound 6c



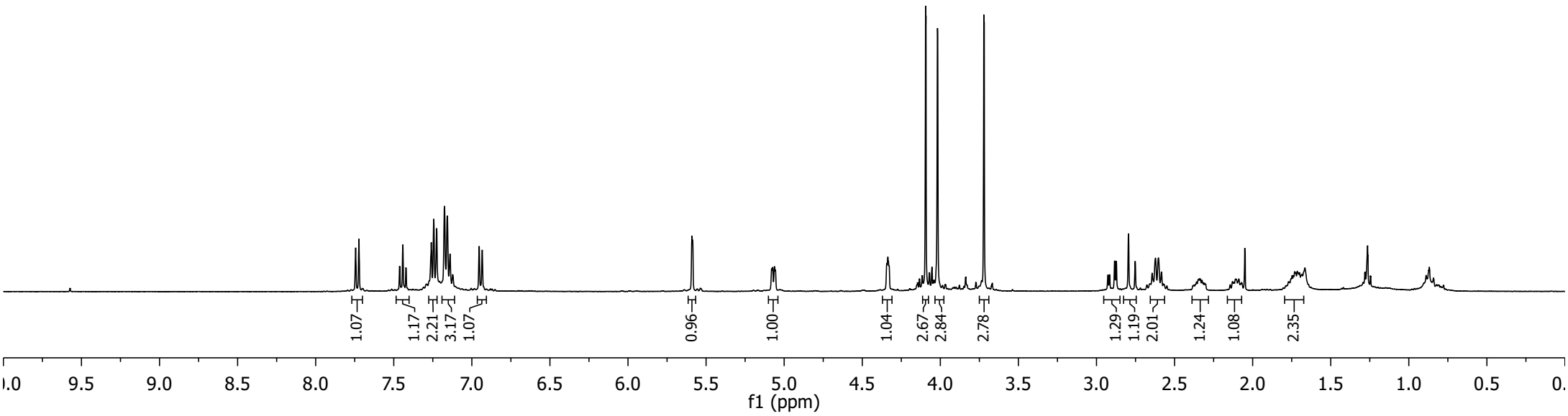



Crosspeak 1
H δ 5.16
Crosspeak 2
H δ 4.36
δ 5.58
Scheme 2, compound 6c
yz-b3
Crosspeak 2
Crosspeak 1
f2 (ppm)
f1 (ppm)

yz-b5



Scheme 2, compound 6d



yz-b5

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153.211
149.321
142.790
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128.492
128.268
127.836
126.666
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121.614
119.591
115.235
107.418
77.478
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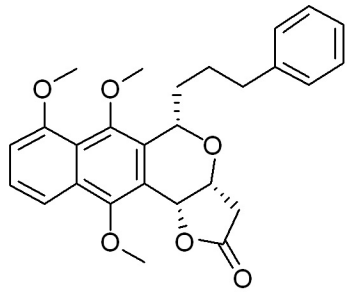
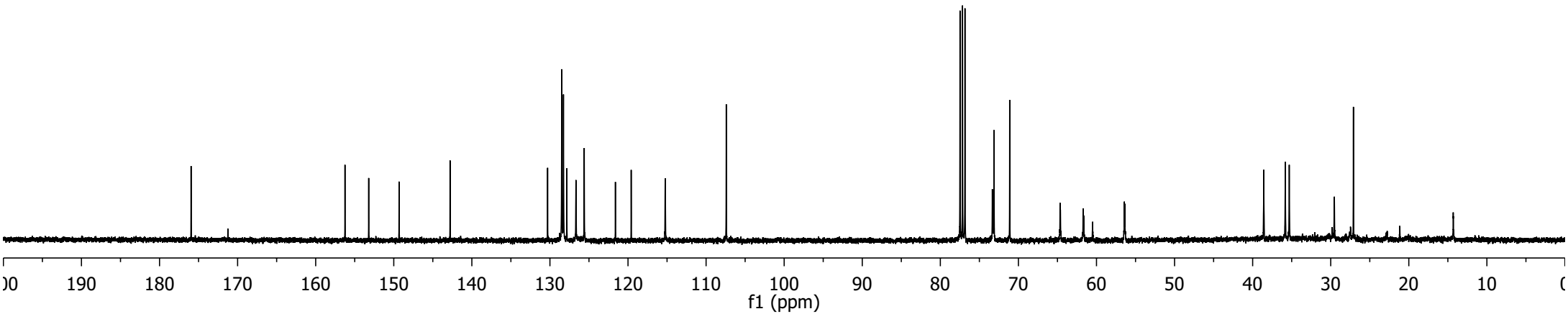
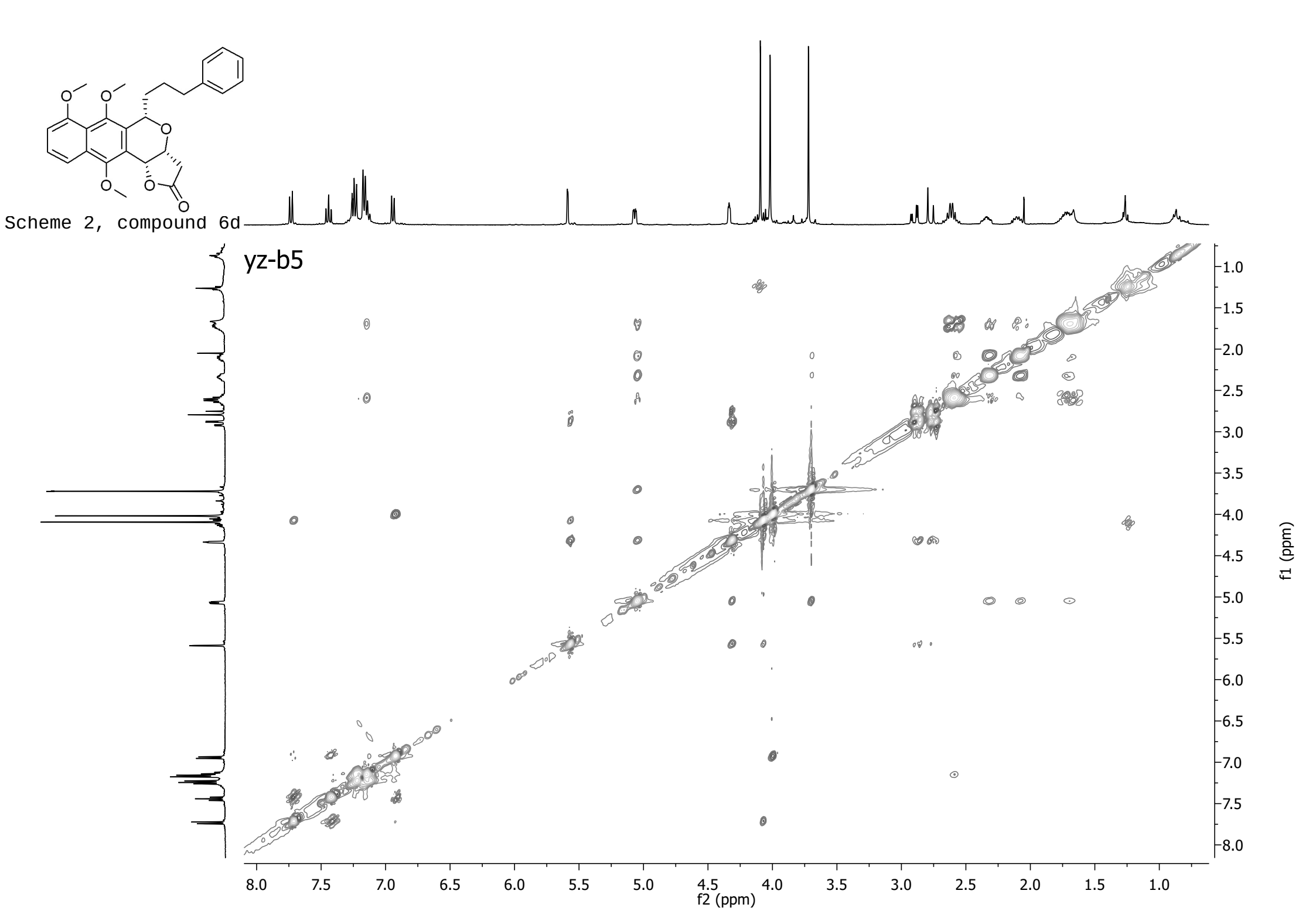
35.311
27.095

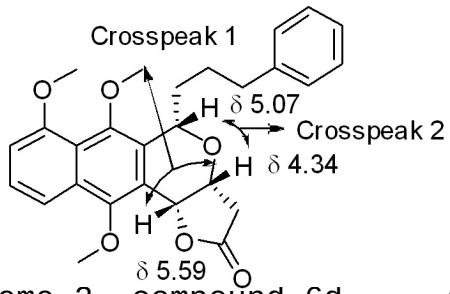


Scheme 2, compound 6d

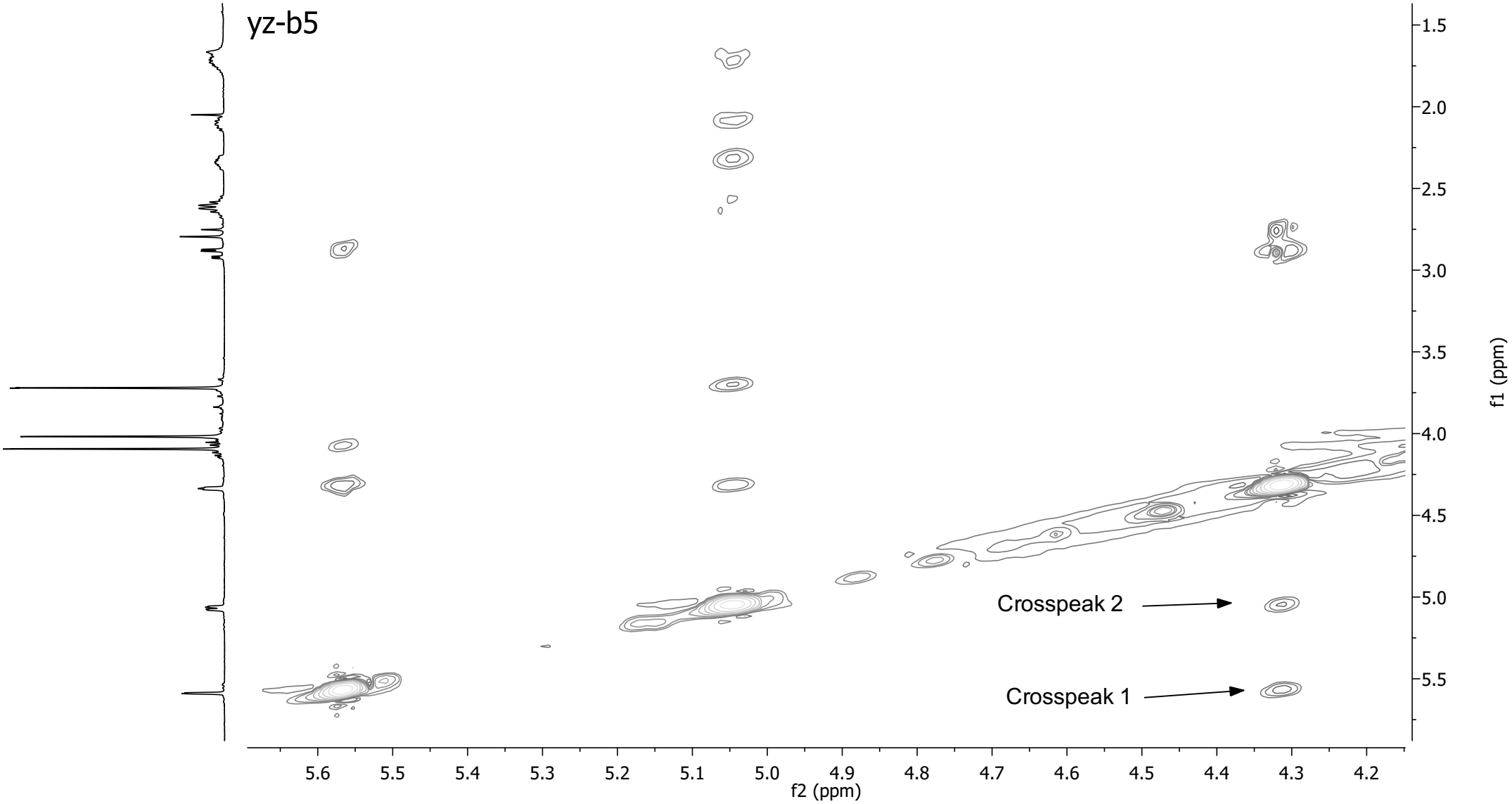




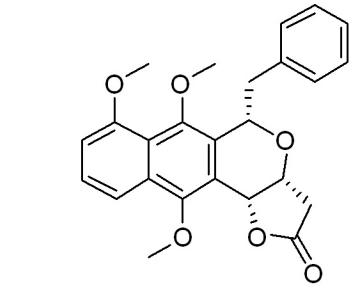
Scheme 2, compound 6d



Scheme 2, compound 6d

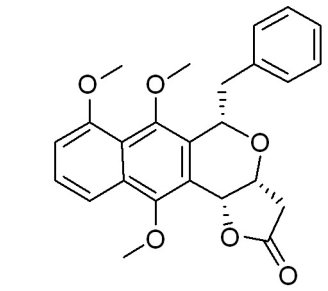


yz-b27

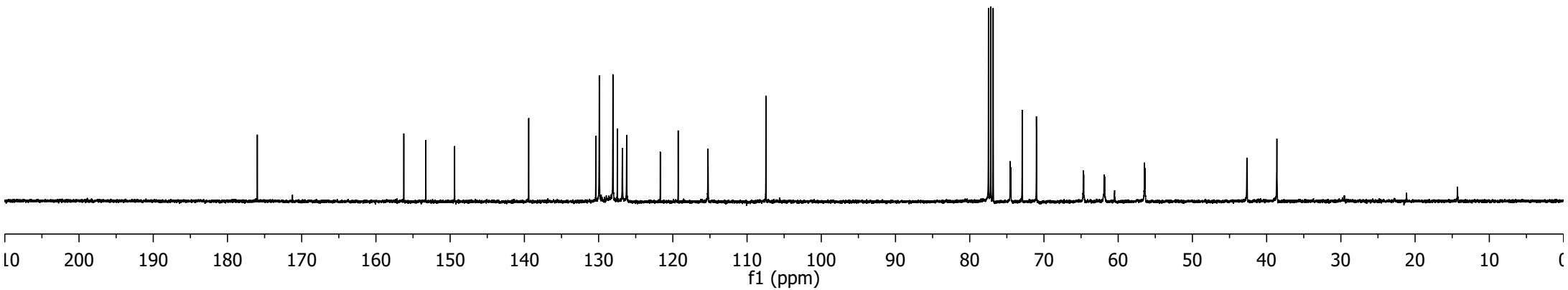


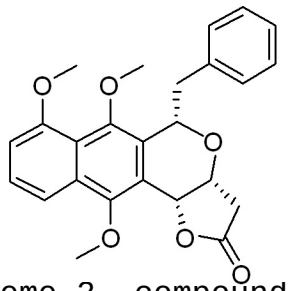
Scheme 2, compound 6e

yz-b27

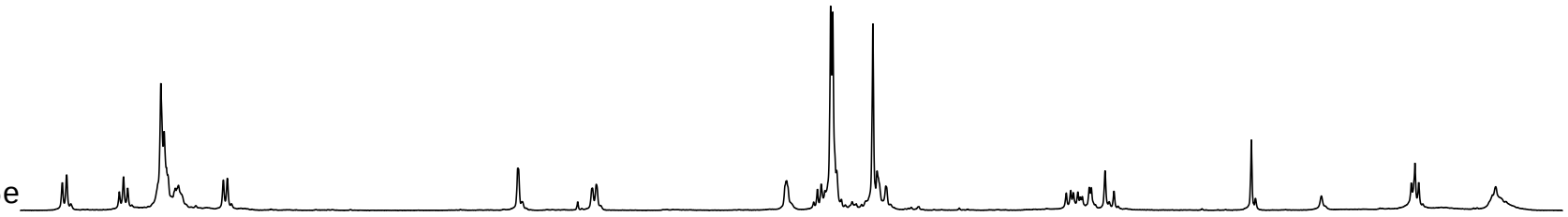


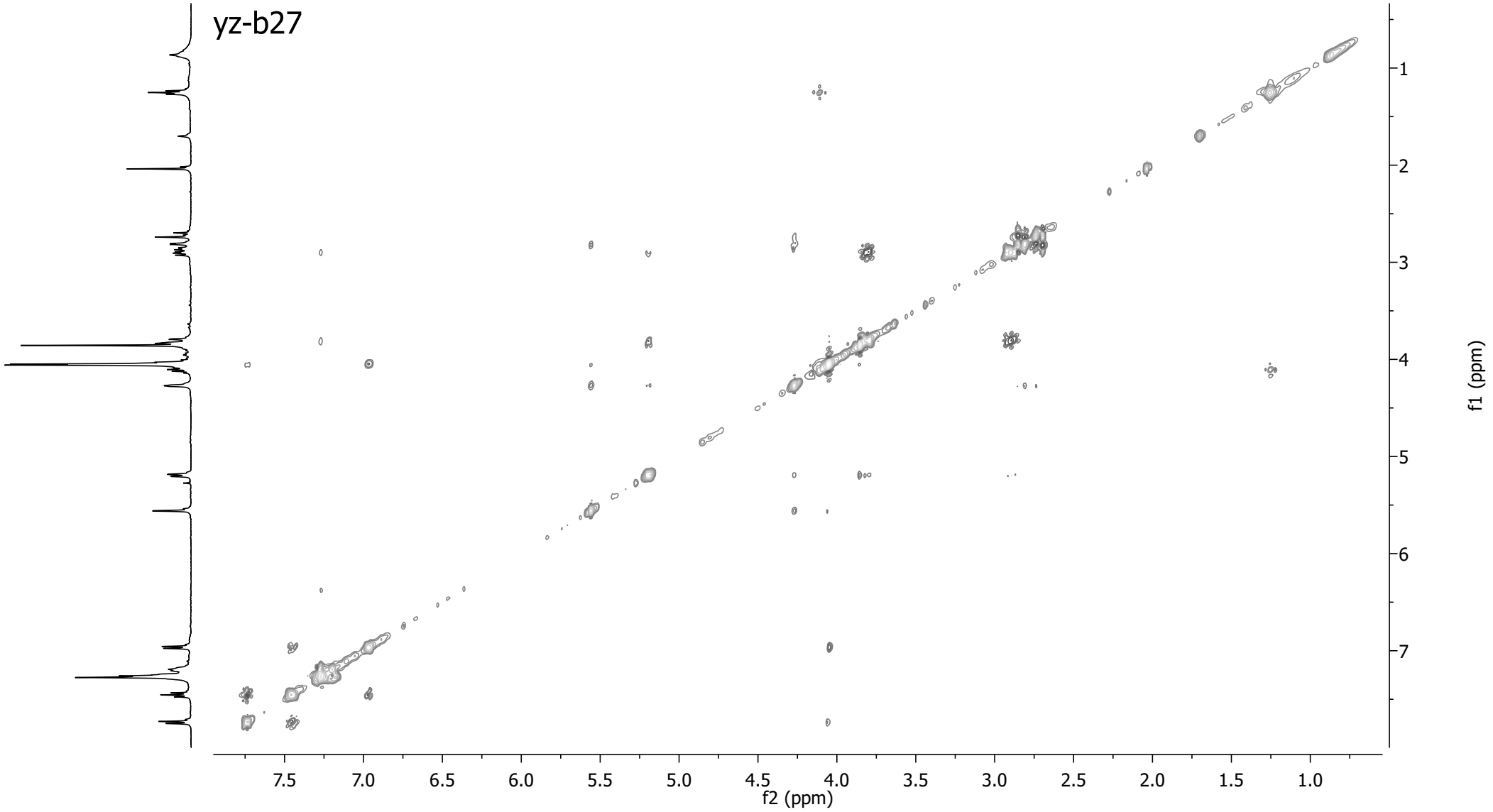
Scheme 2, compound 6e

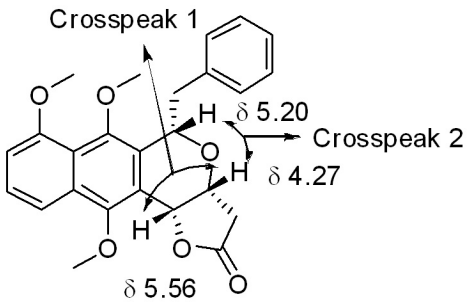




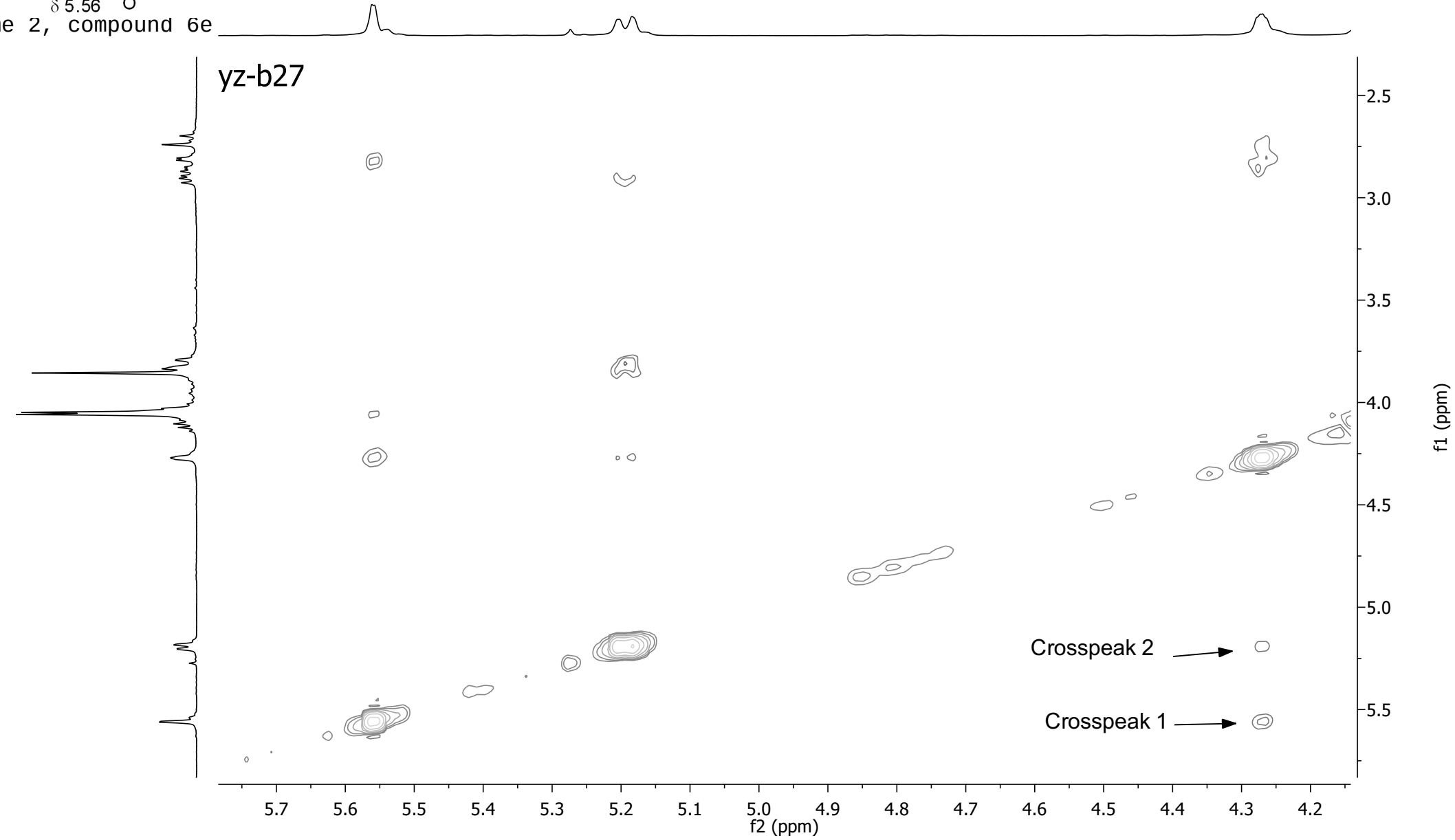
Scheme 2, compound 6e



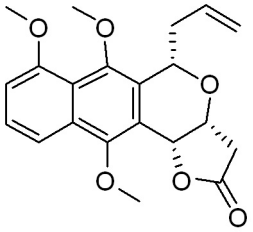




Scheme 2, compound 6e



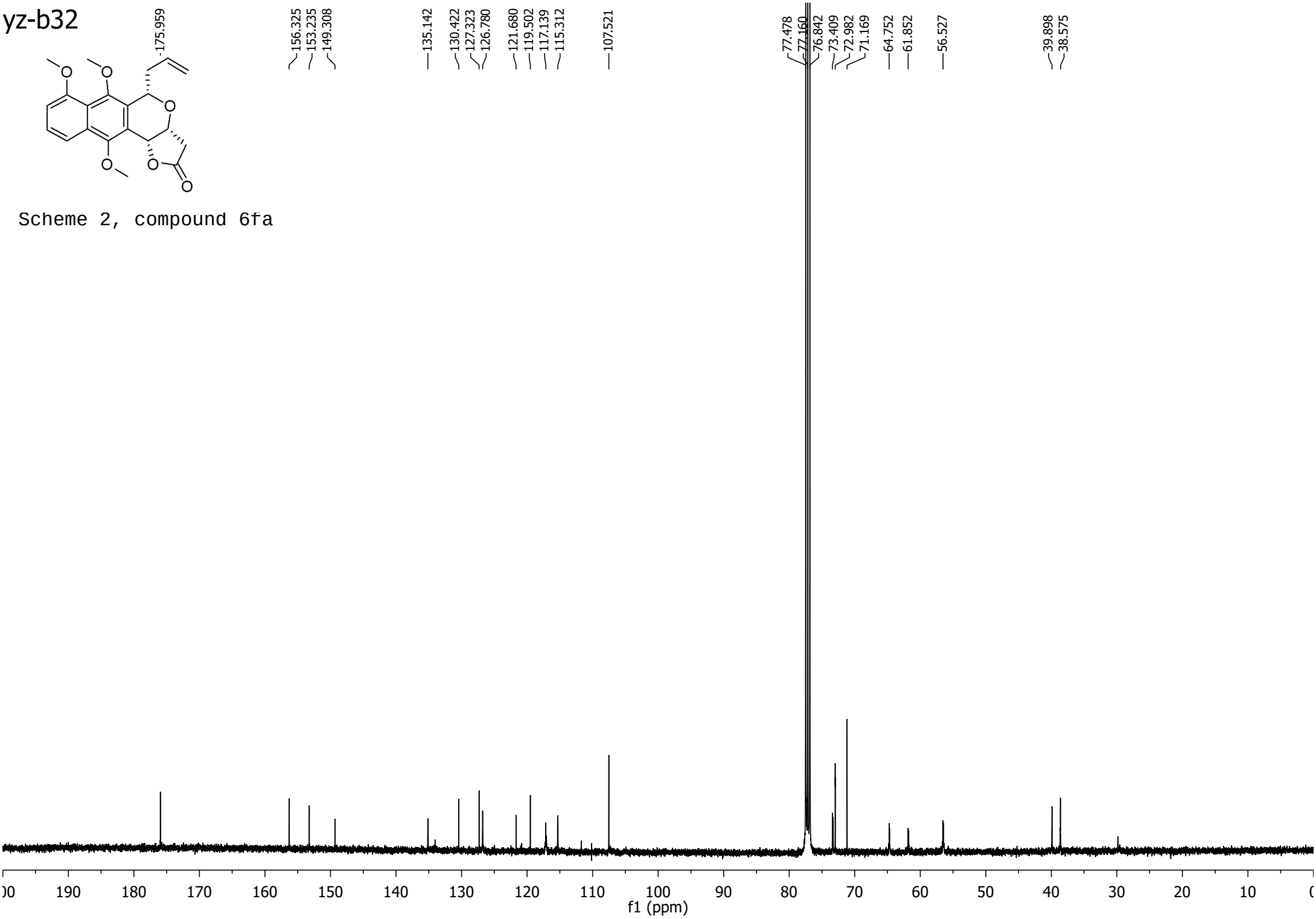
yz-b32

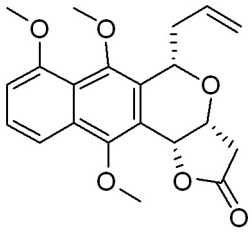


Scheme 2, compound 6ta

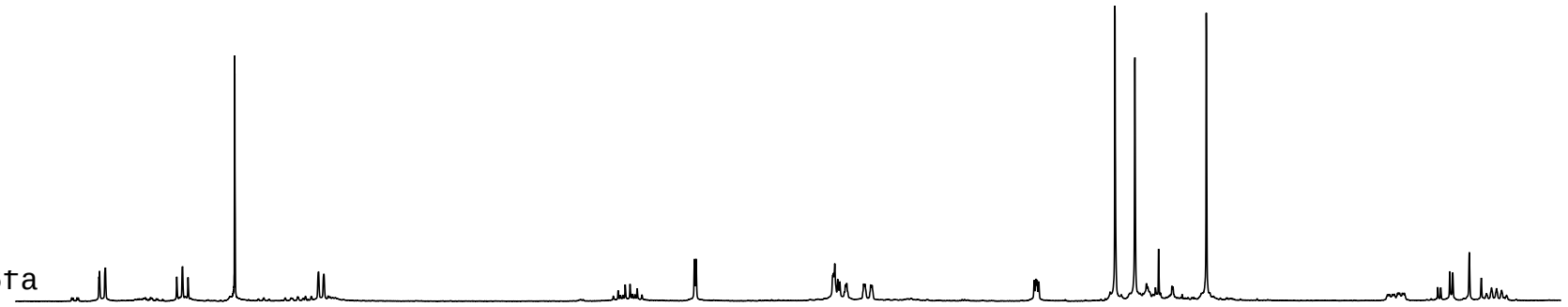
yz-b32

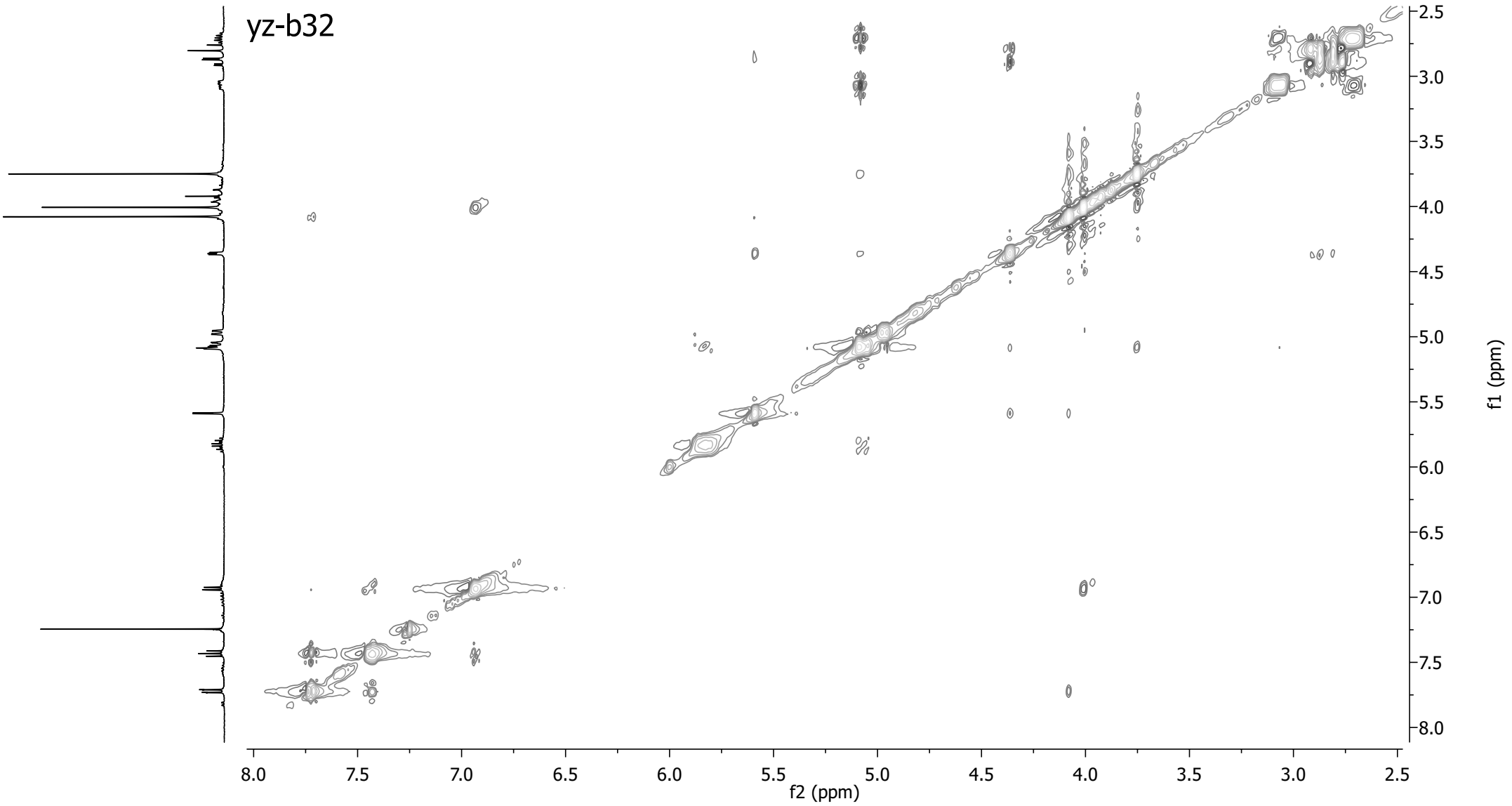
Scheme 2, compound 6fa

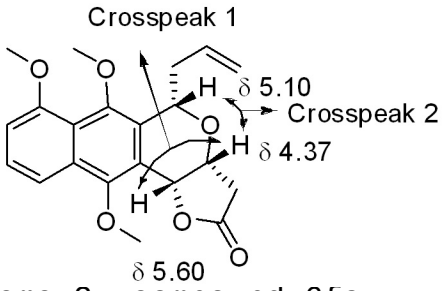




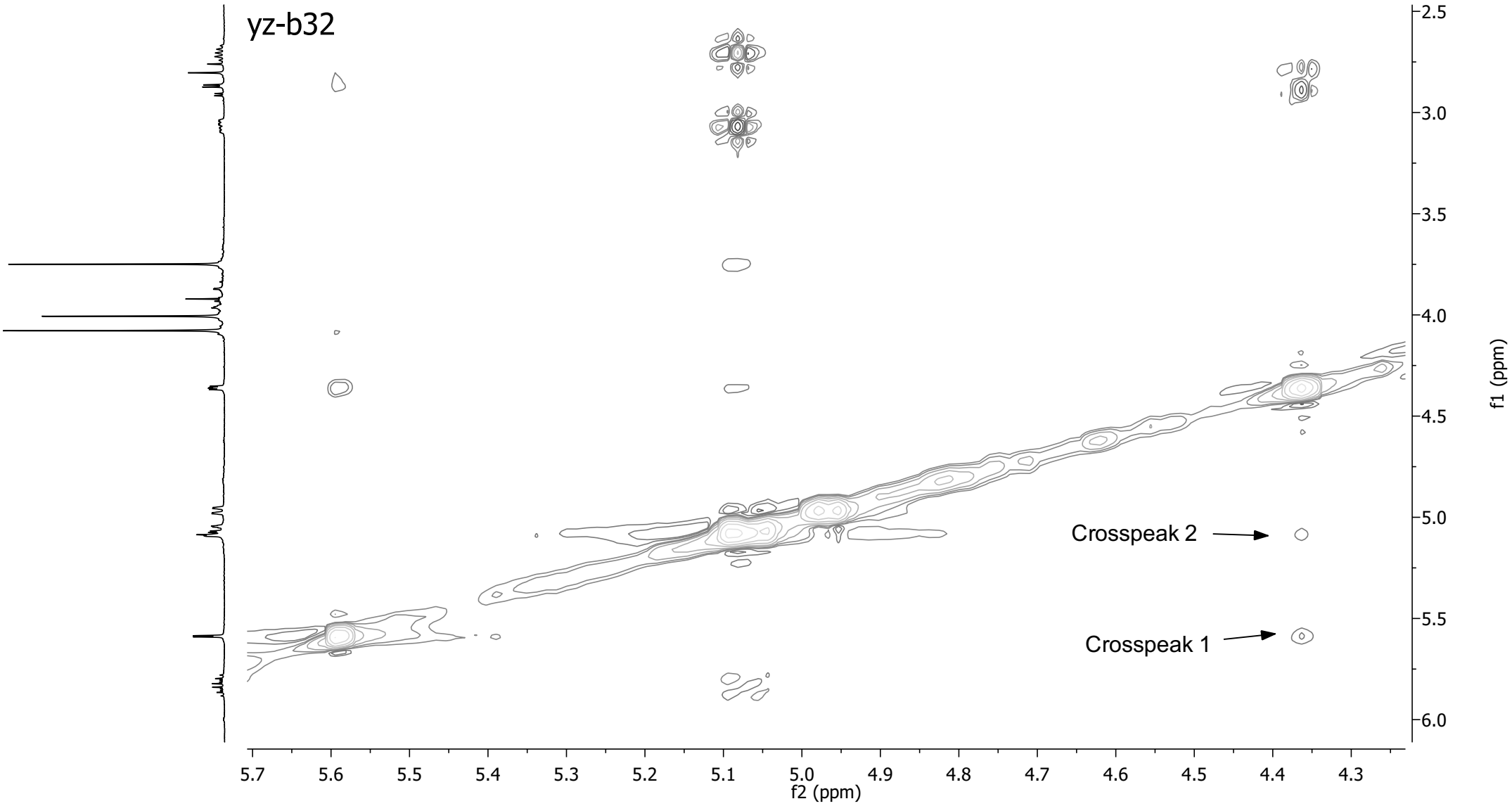
Scheme 2, compound 6ta



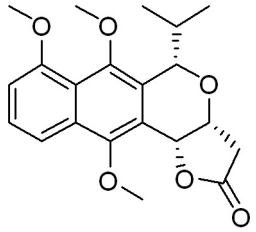




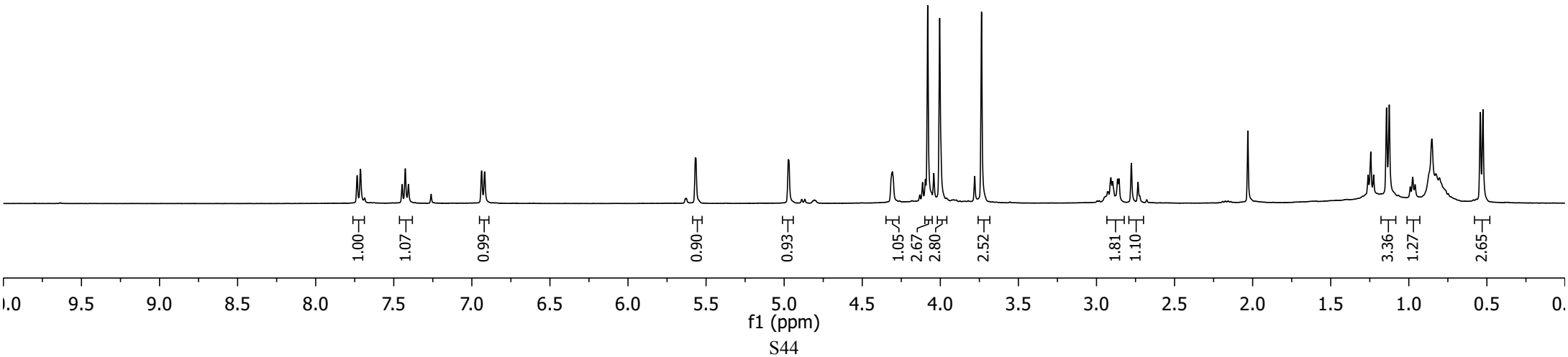
Scheme 2, compound 6fa



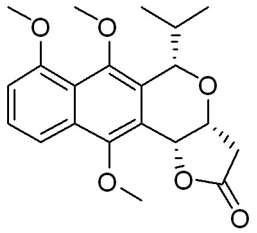
yz-b22



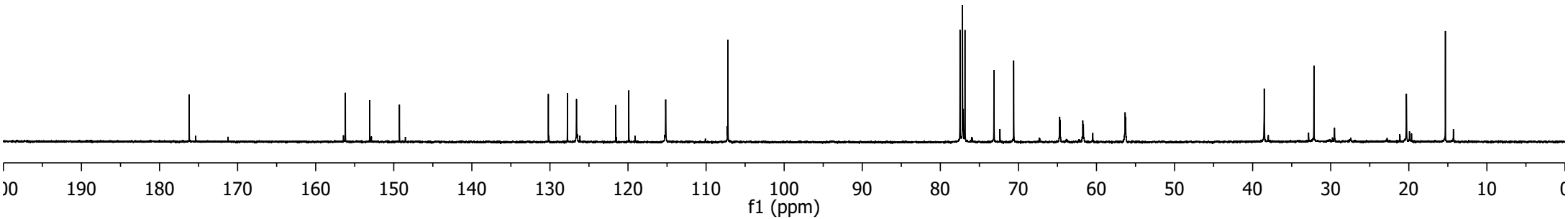
scheme 2, compound 6g

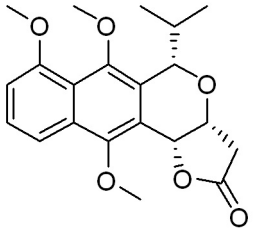


yz-b22

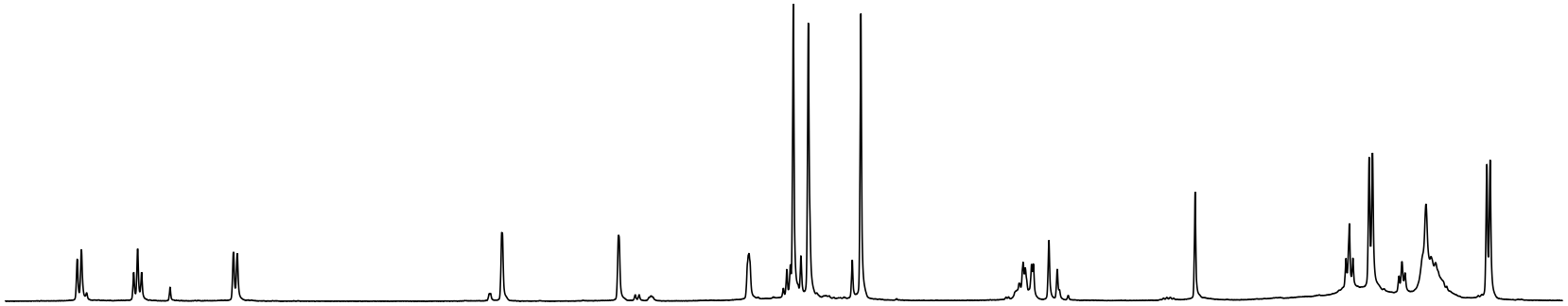


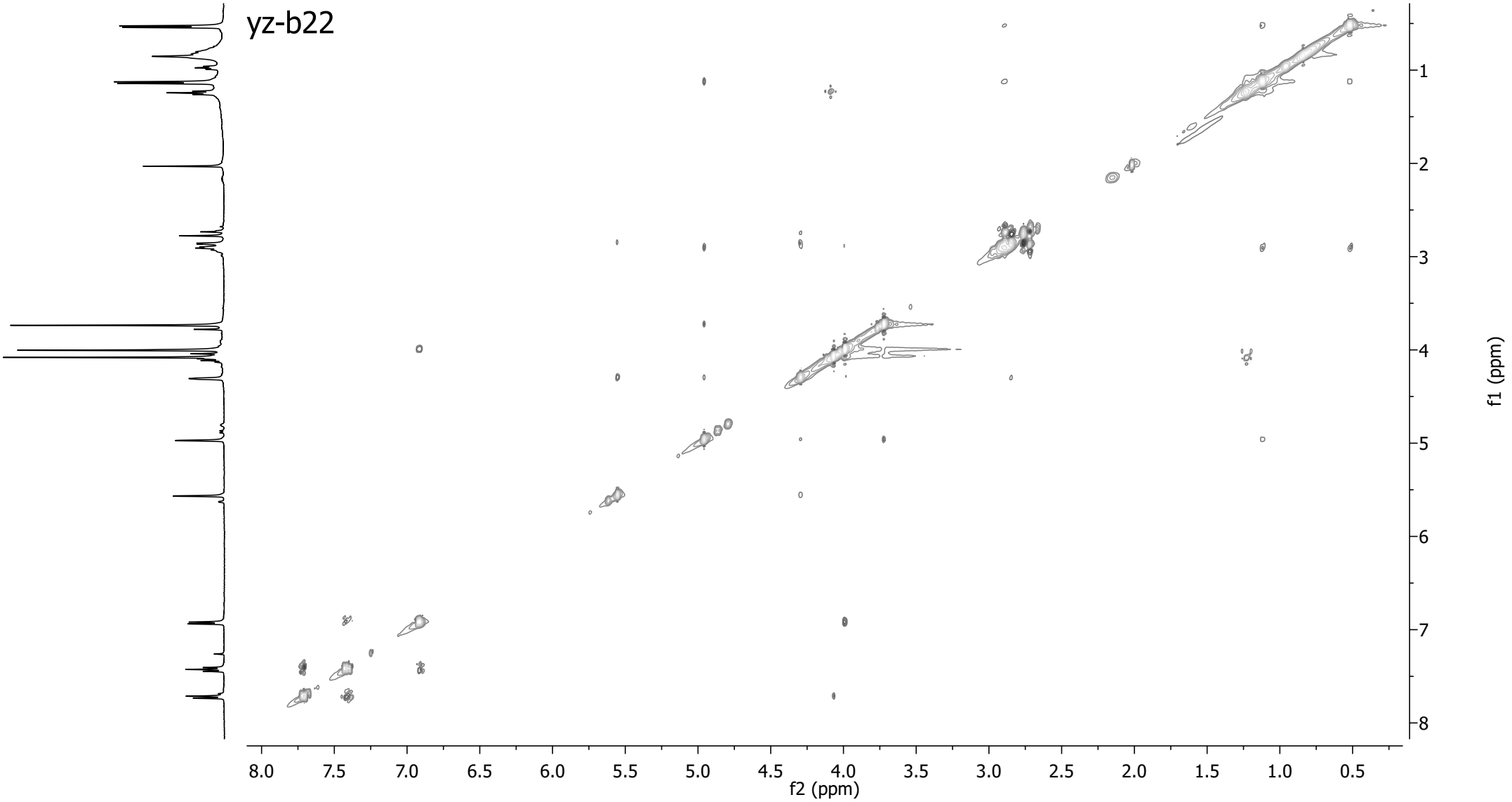
Scheme 2,compound 6g

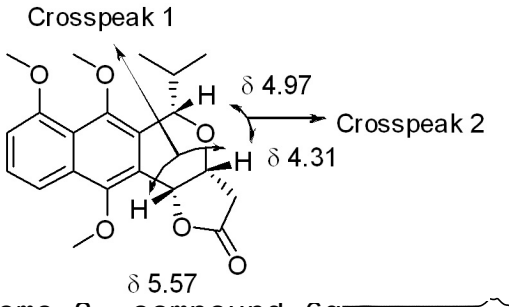




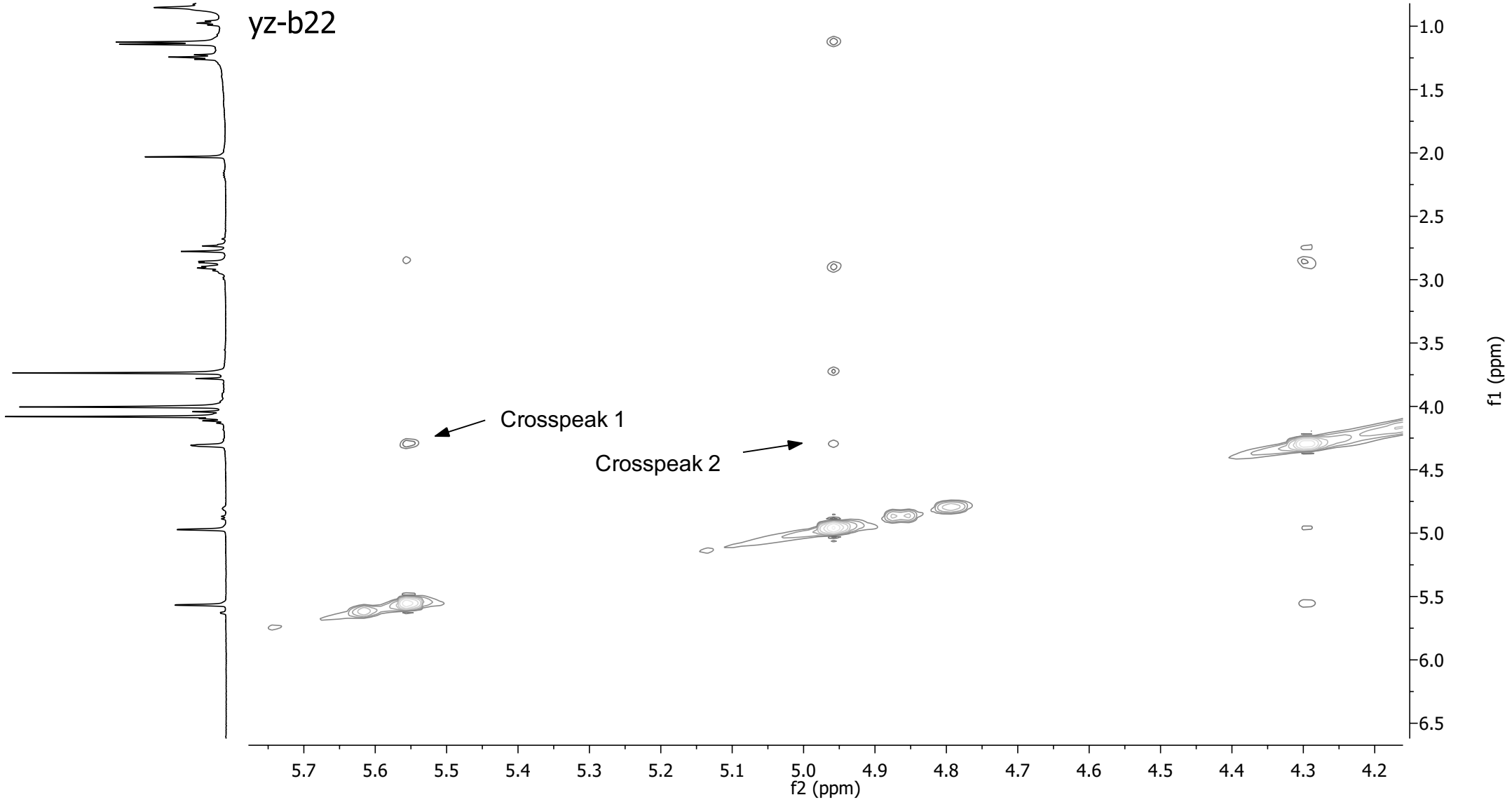
Scheme 2, compound 6g



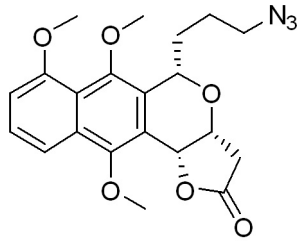




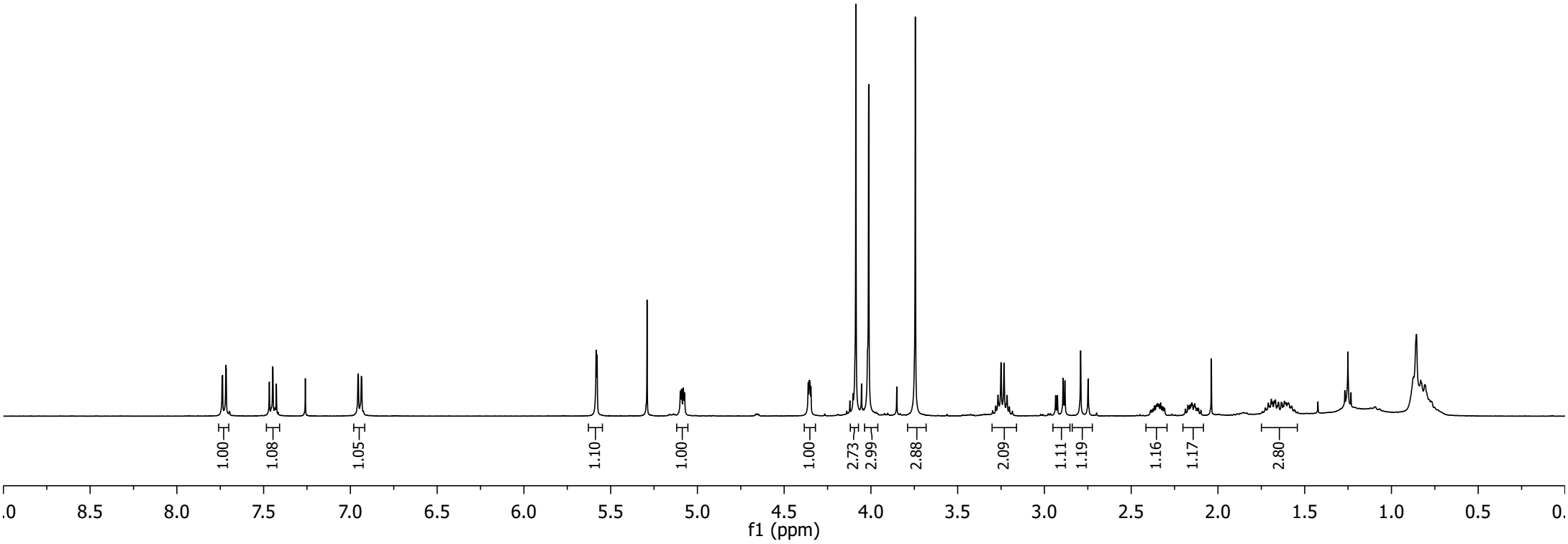
Scheme 2, compound 6g



yz-a68

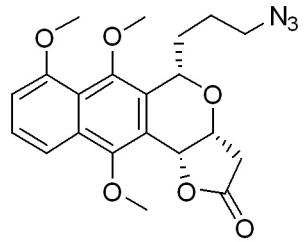


Scheme 2, compound 6h

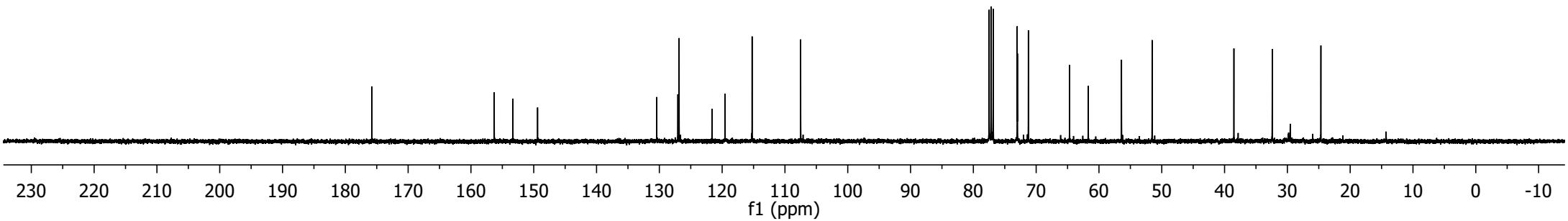


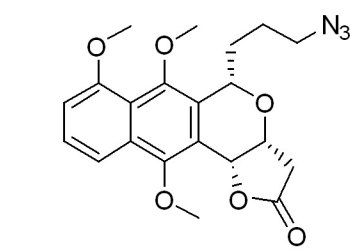
yz-a68

175.775
156.286
153.312
149.388
130.425
127.050
126.852
121.622
119.525
115.230
107.497
77.479
77.160
76.843
73.024
72.974
71.241
64.679
61.706
56.409
51.534
38.512
32.405
24.660

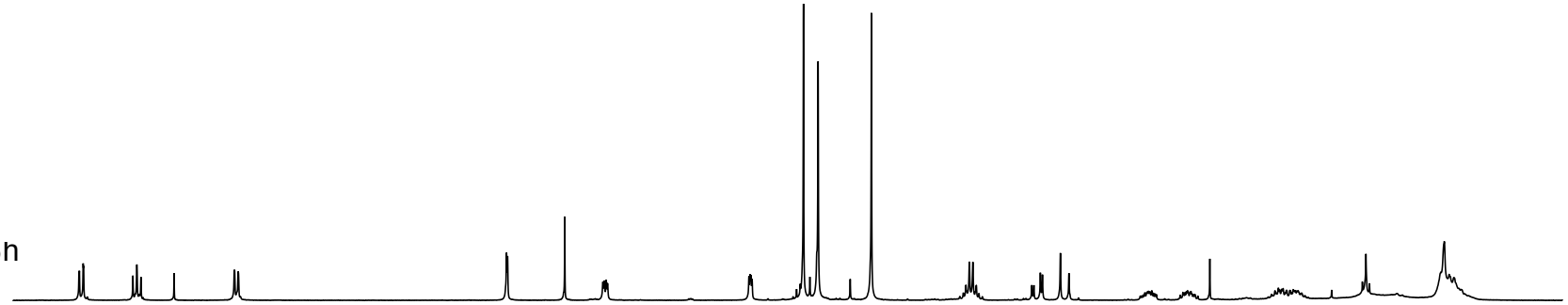


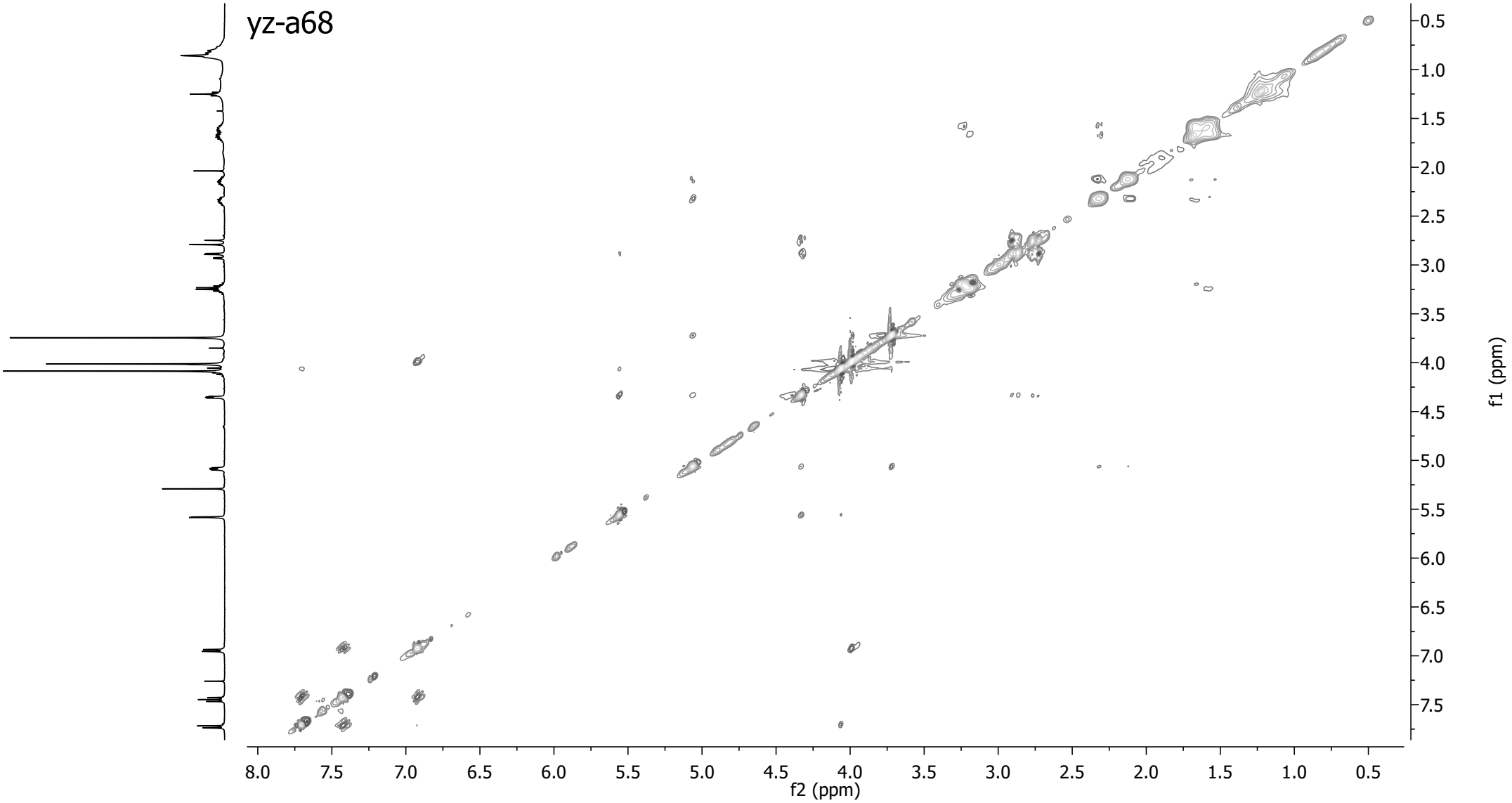
Scheme 2, compound 6h

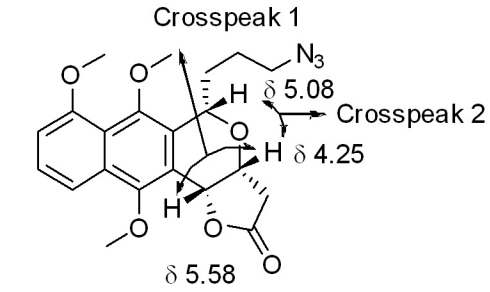




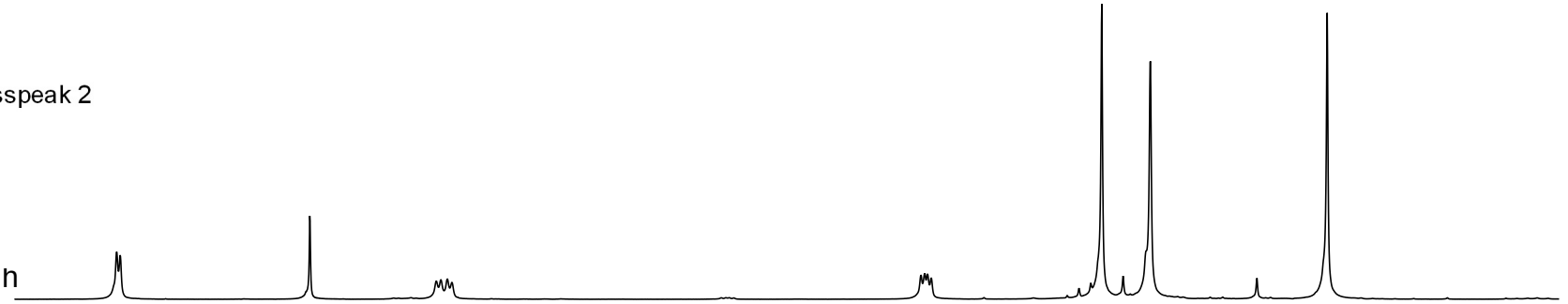
Scheme 2, compound 6h

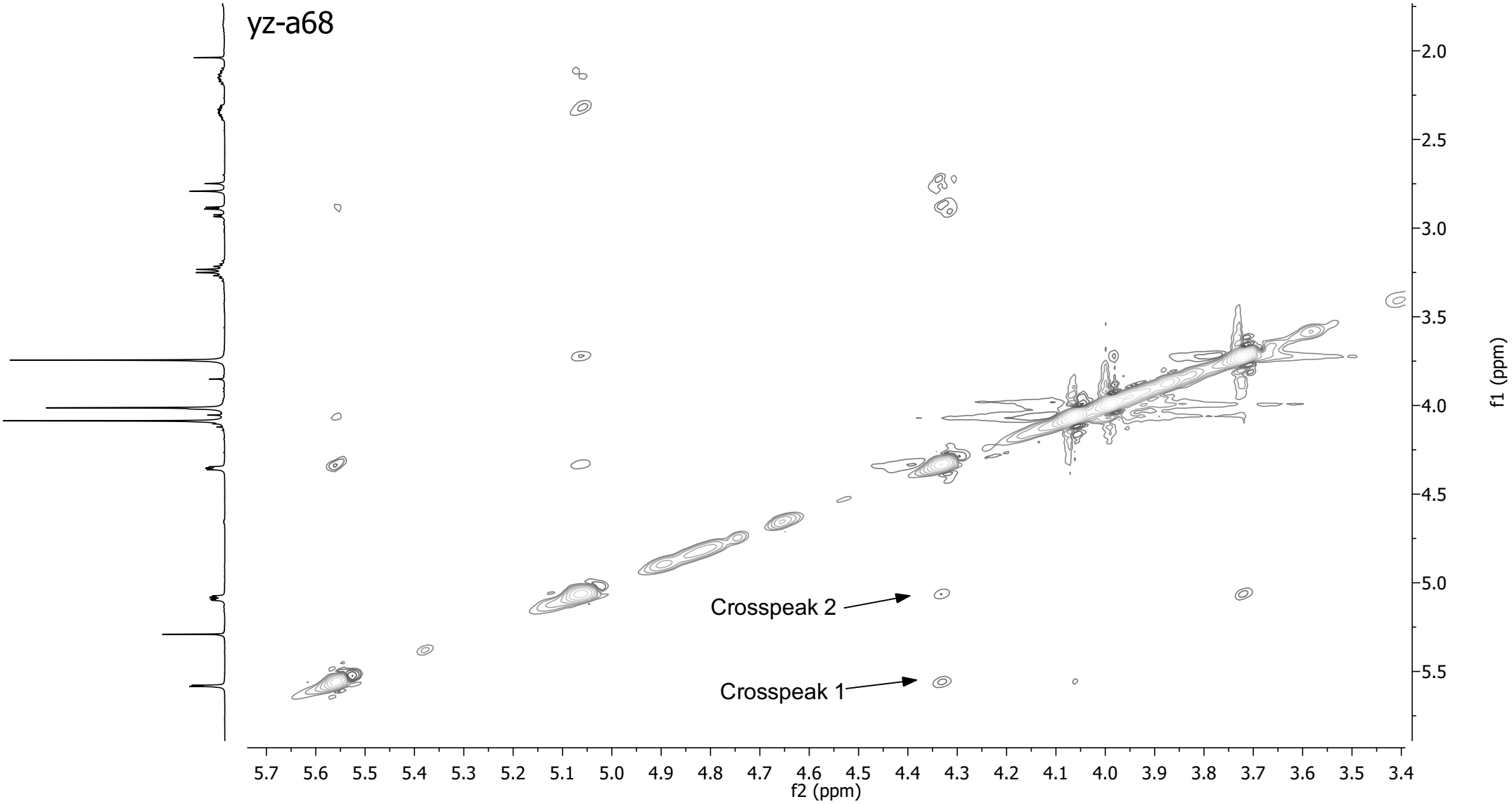




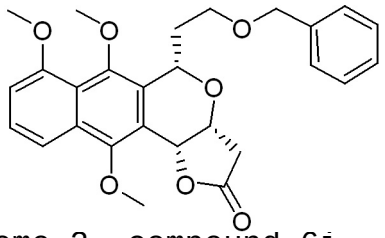


Scheme 2, compound 6h



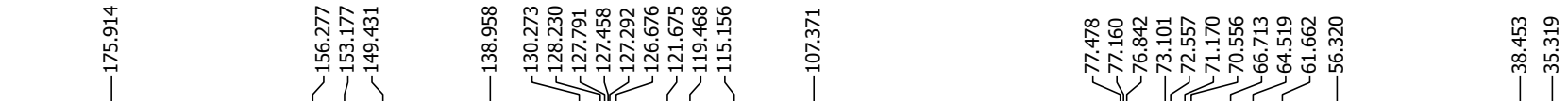


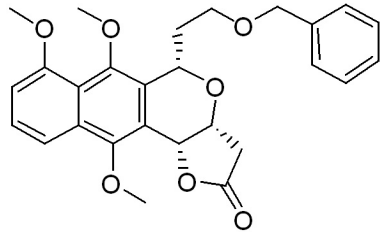
yz-b52



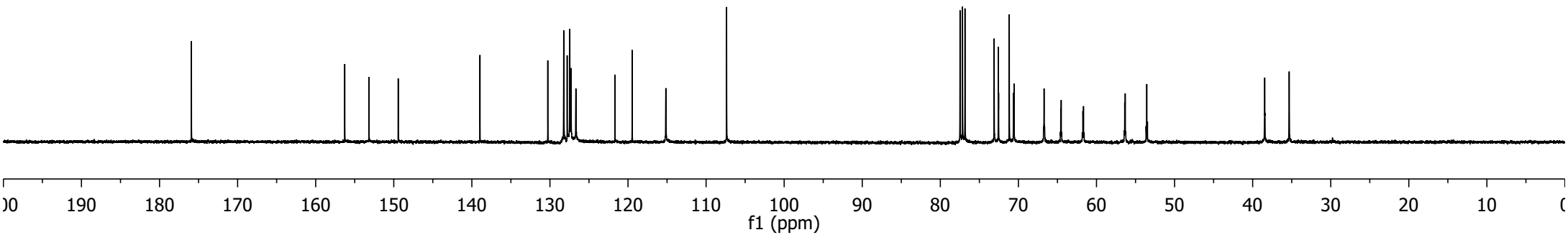
Scheme 2, compound 6i

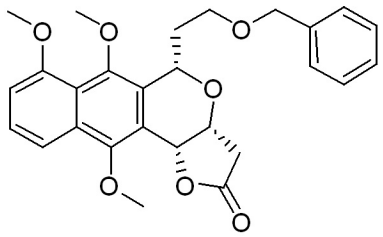
yz-b52



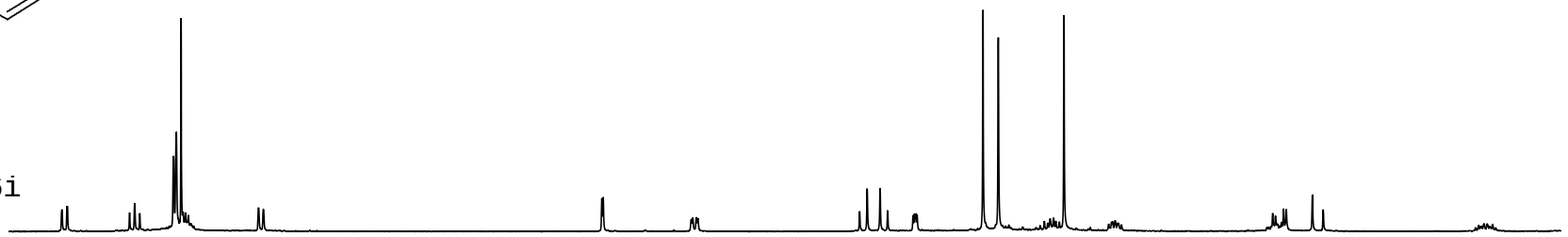


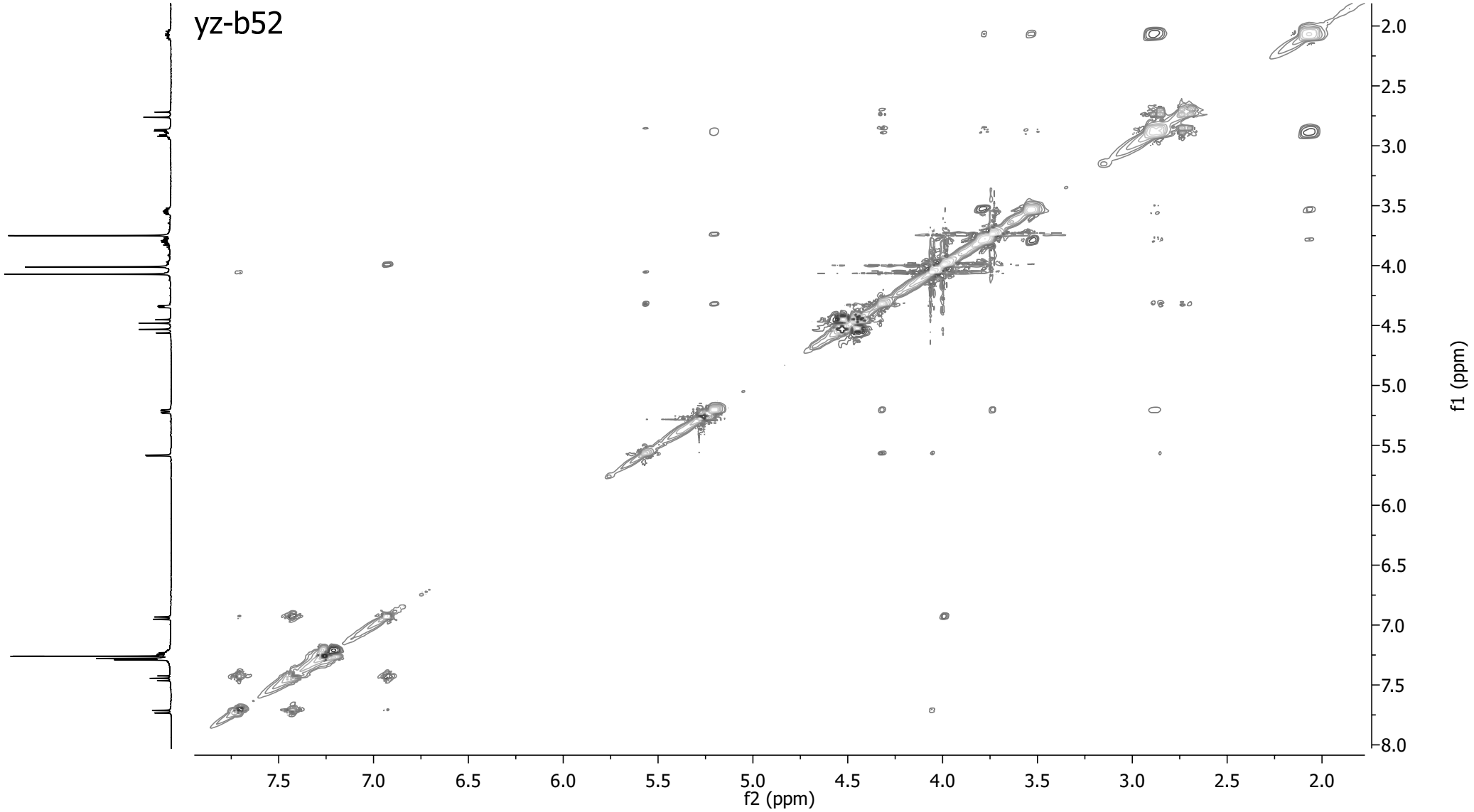
Scheme 2, compound 6i

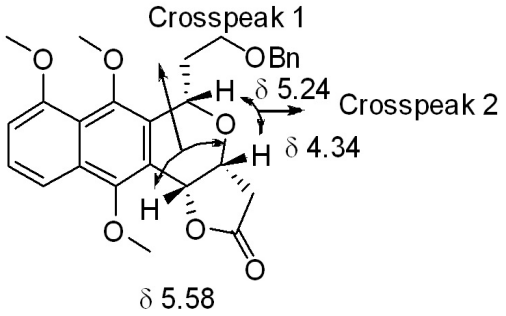




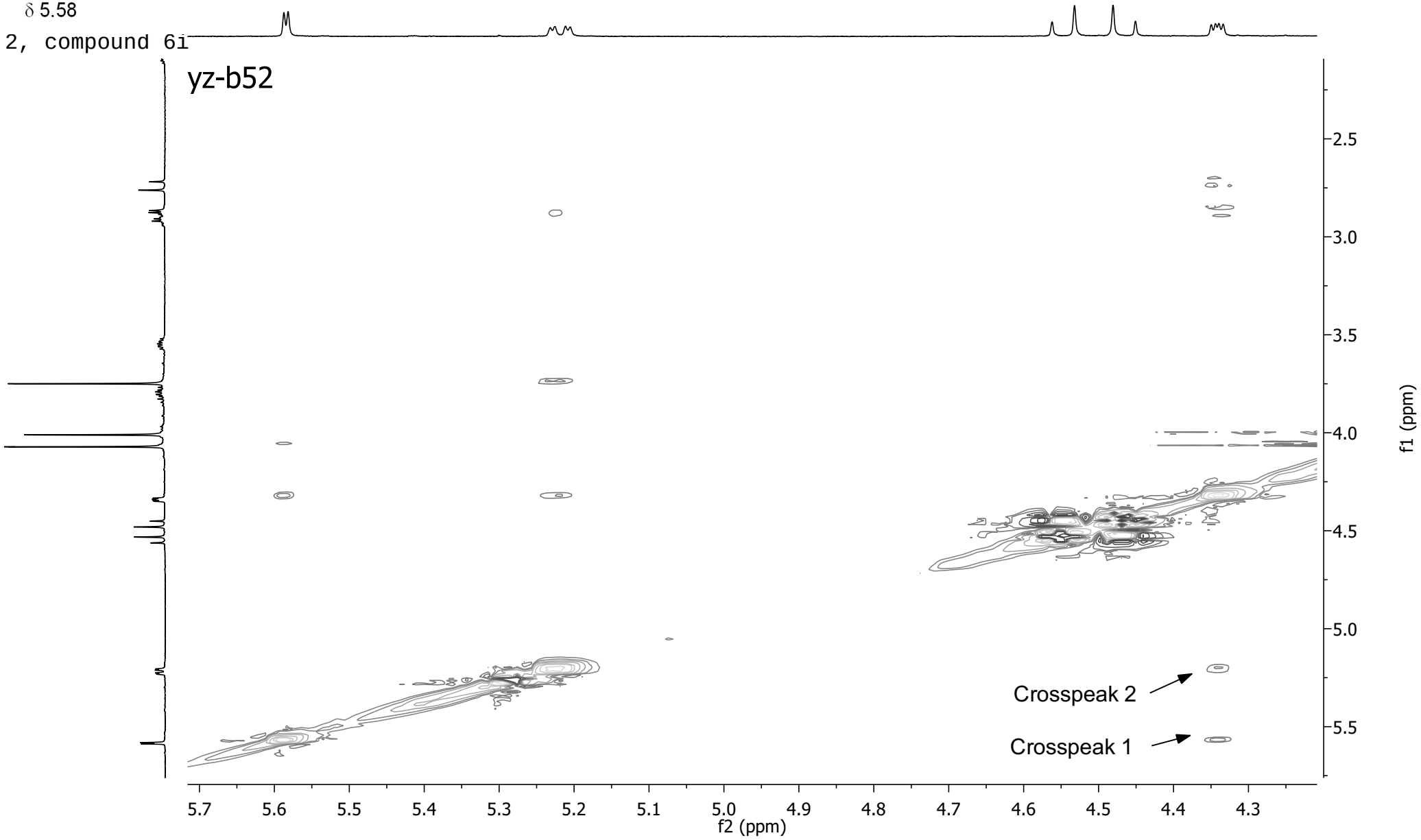
Scheme 2, compound 6i





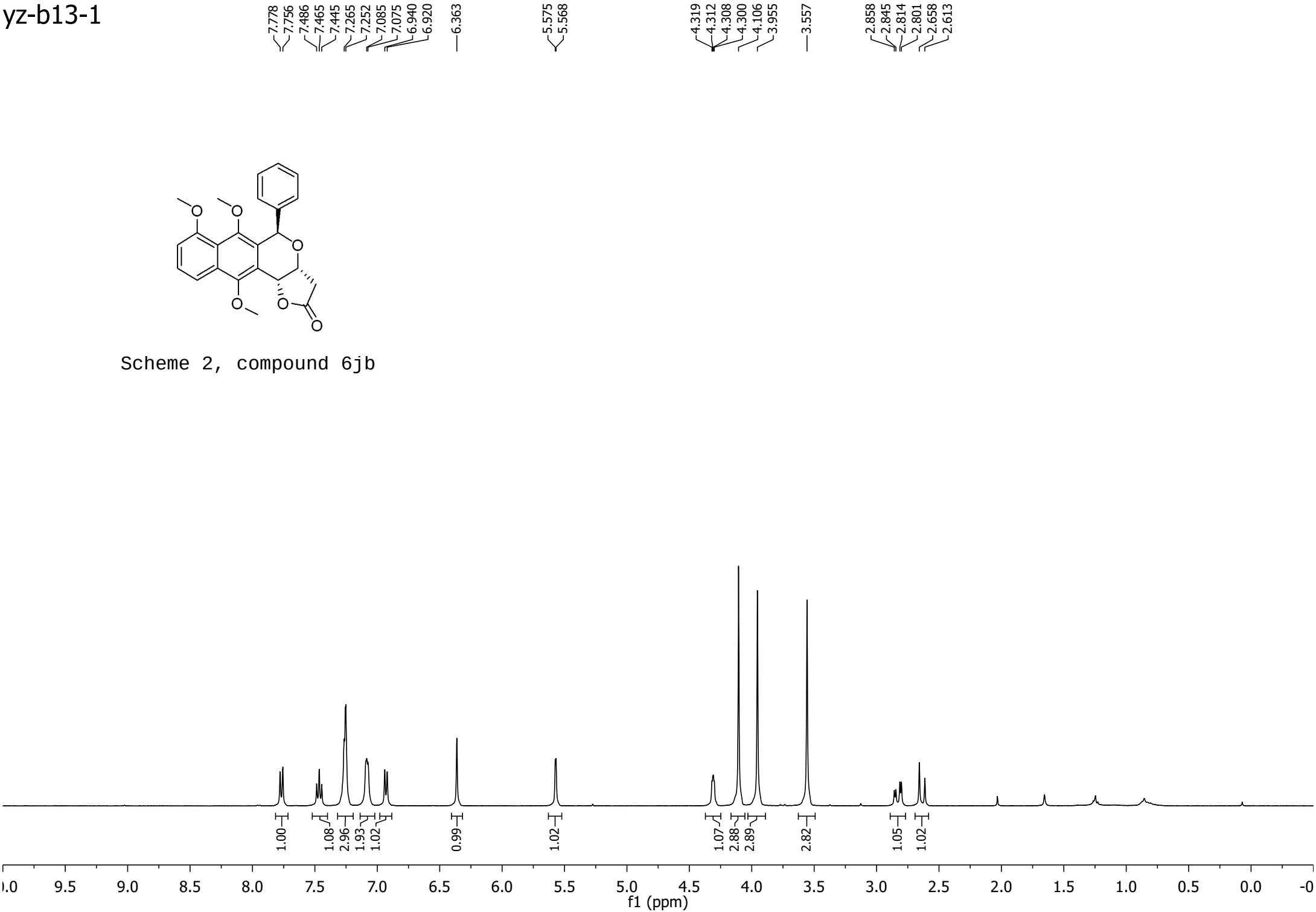


Scheme 2, compound 6i

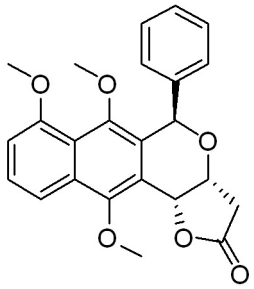


yz-b13-1

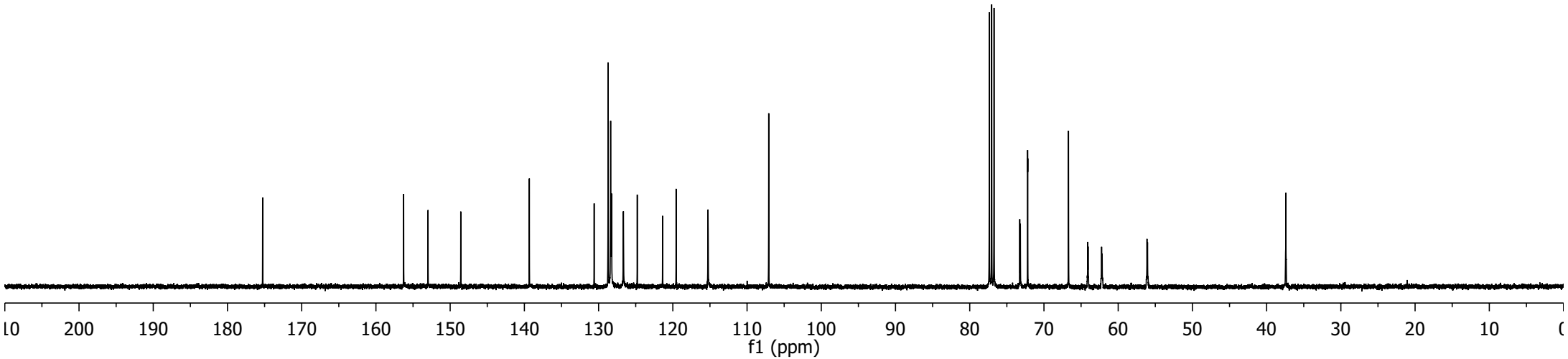
Scheme 2, compound 6jb

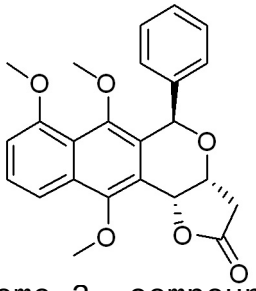


yz-b13-1

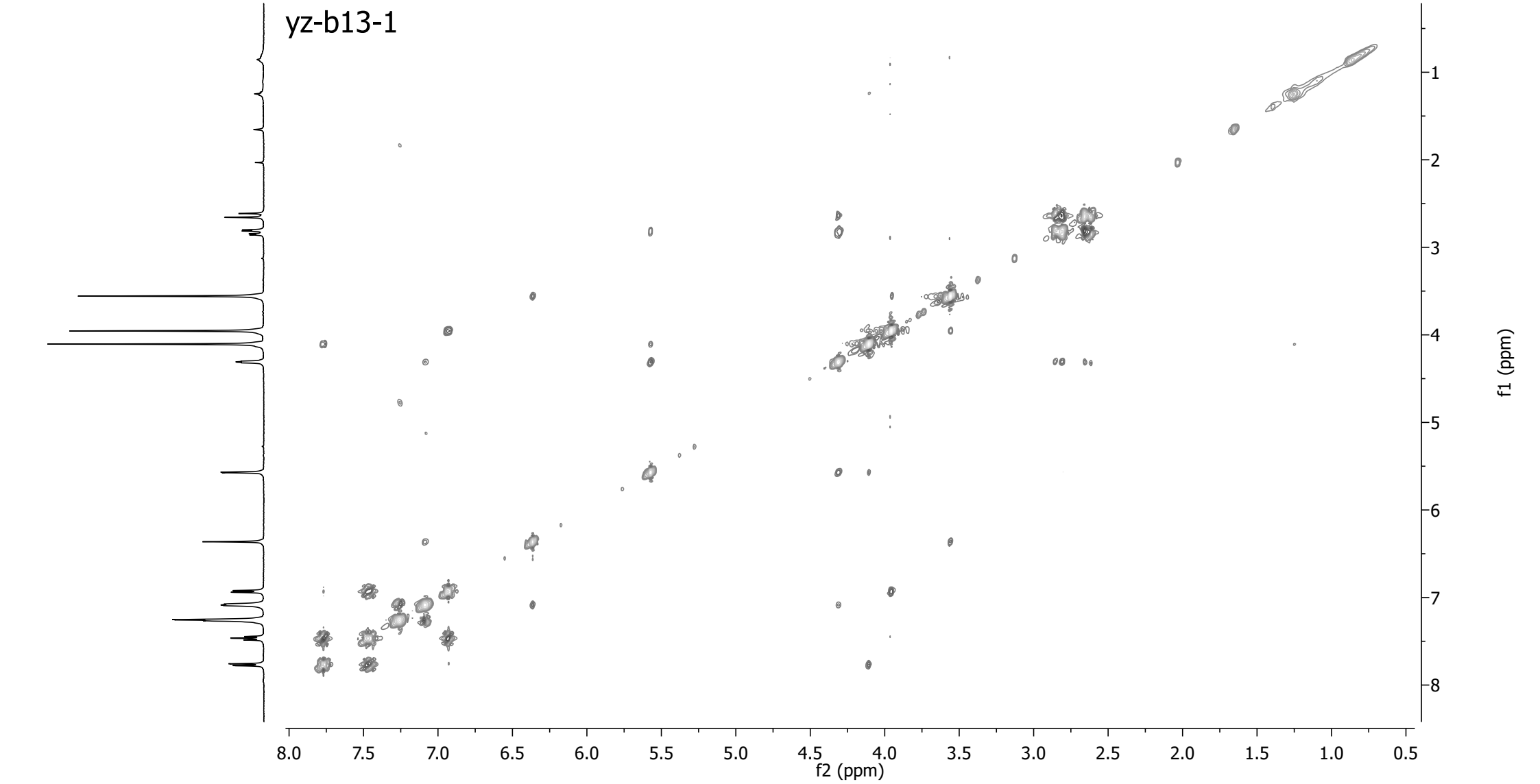


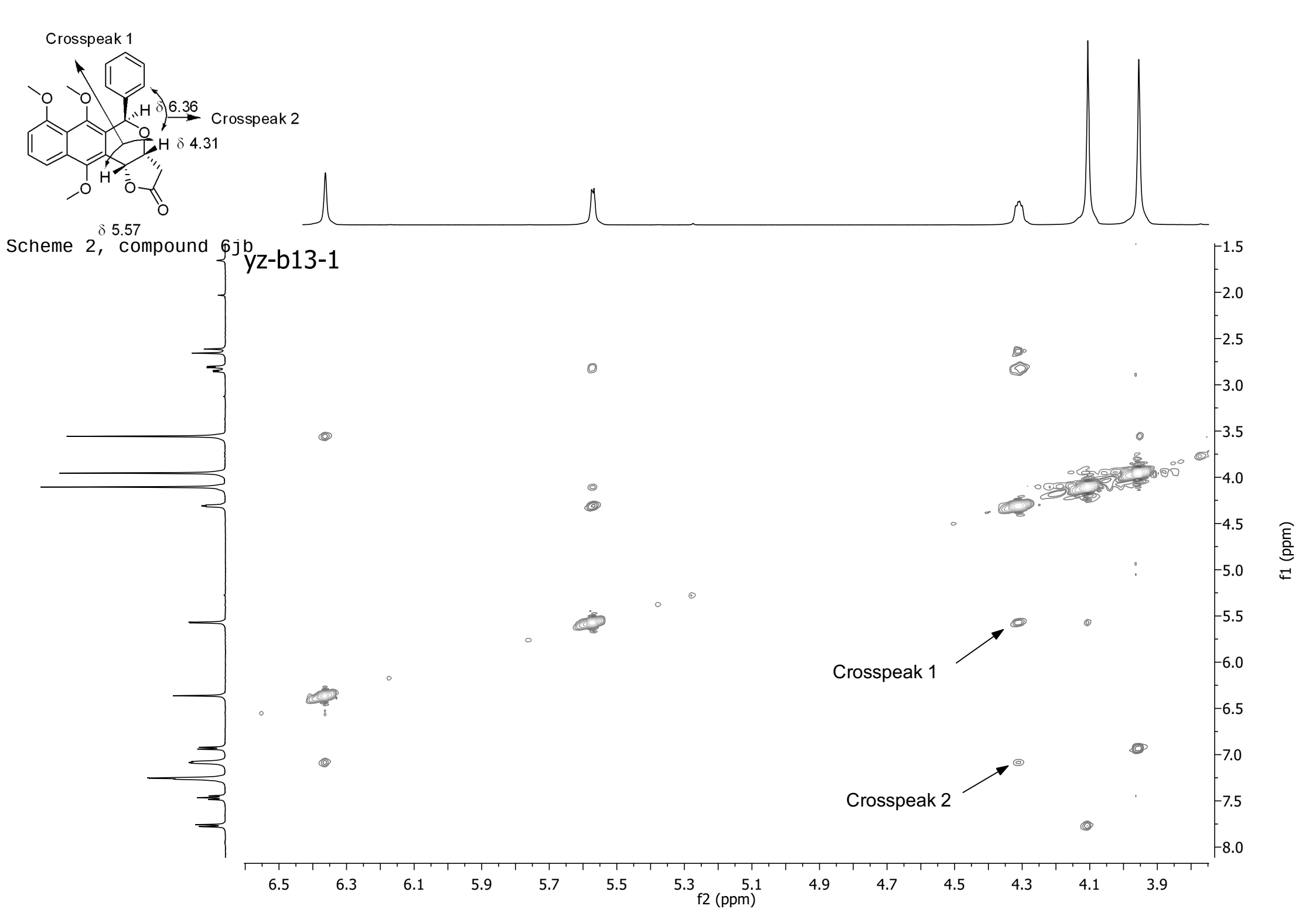
Scheme 2, compound 6jb



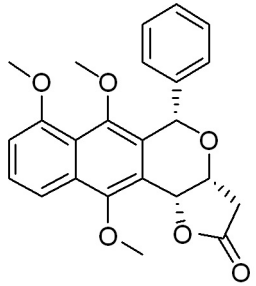


Scheme 2, compound 6jb

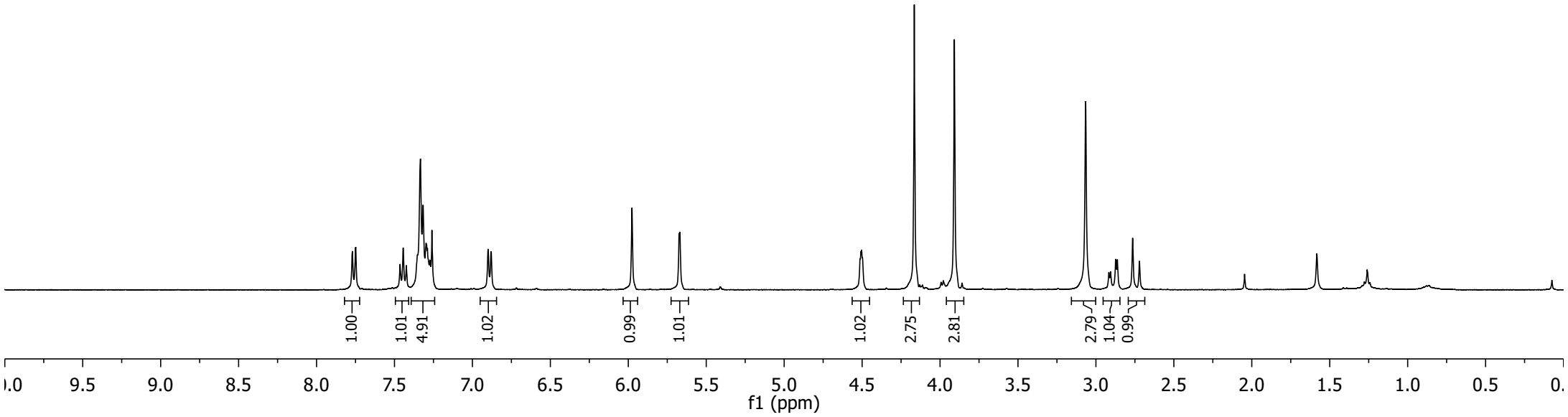



Crosspeak 1
δ 6.36
Crosspeak 2
H δ 4.31
δ 5.57
Scheme 2, compound 6jb
yz-b13-1
Crosspeak 1
Crosspeak 2
f2 (ppm)
f1 (ppm)

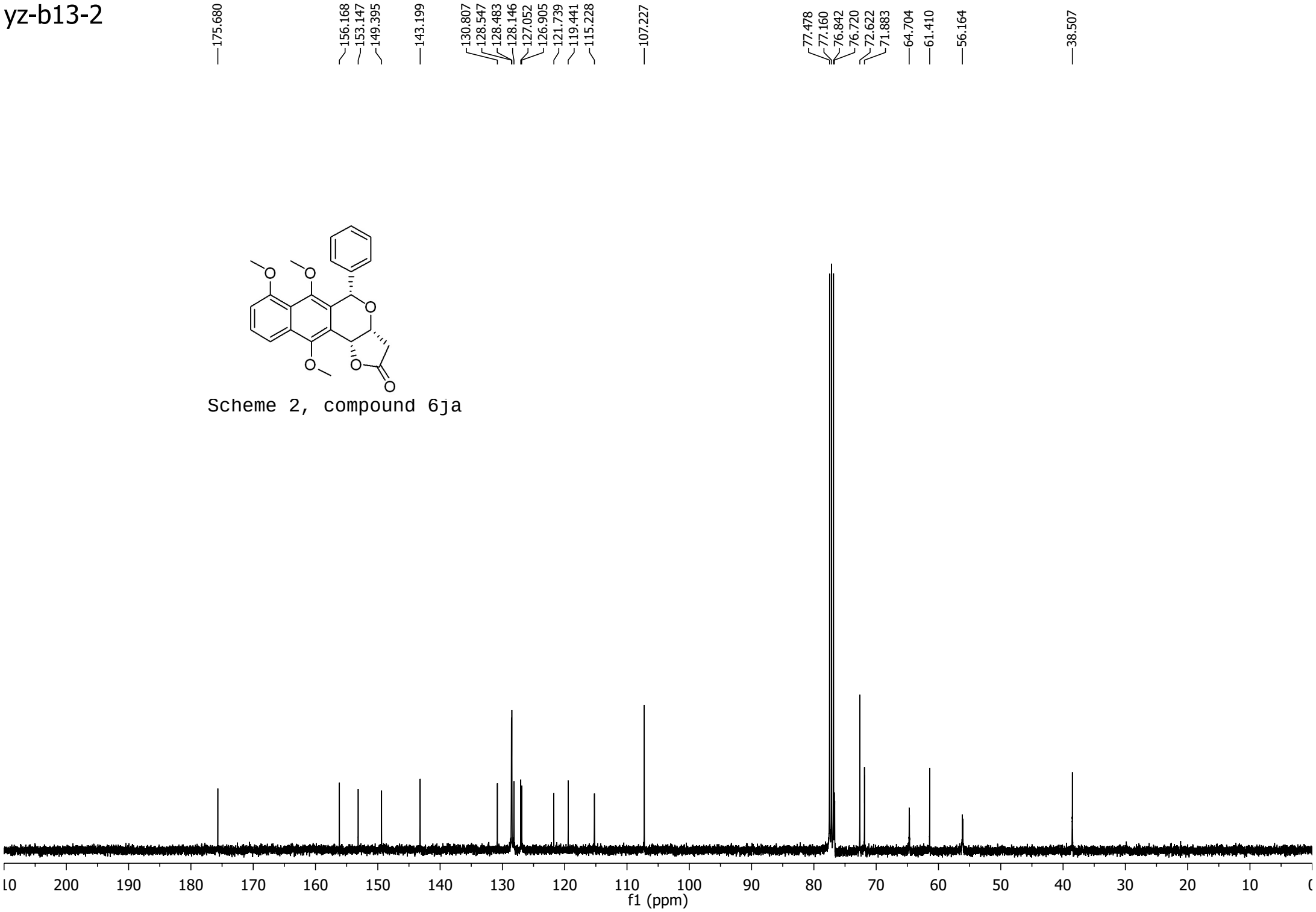
yz-b13-2



Scheme 2, compound 6ja

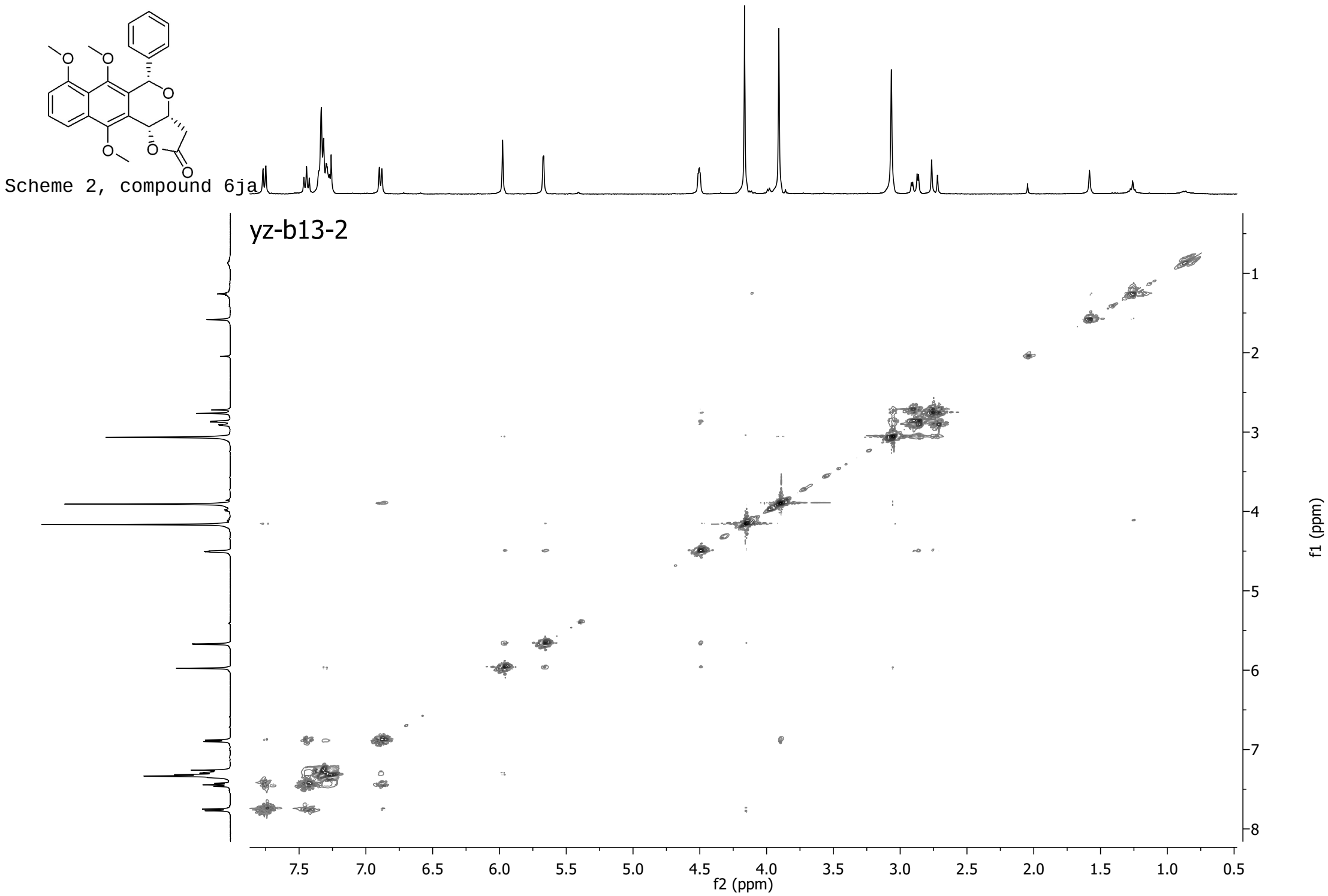


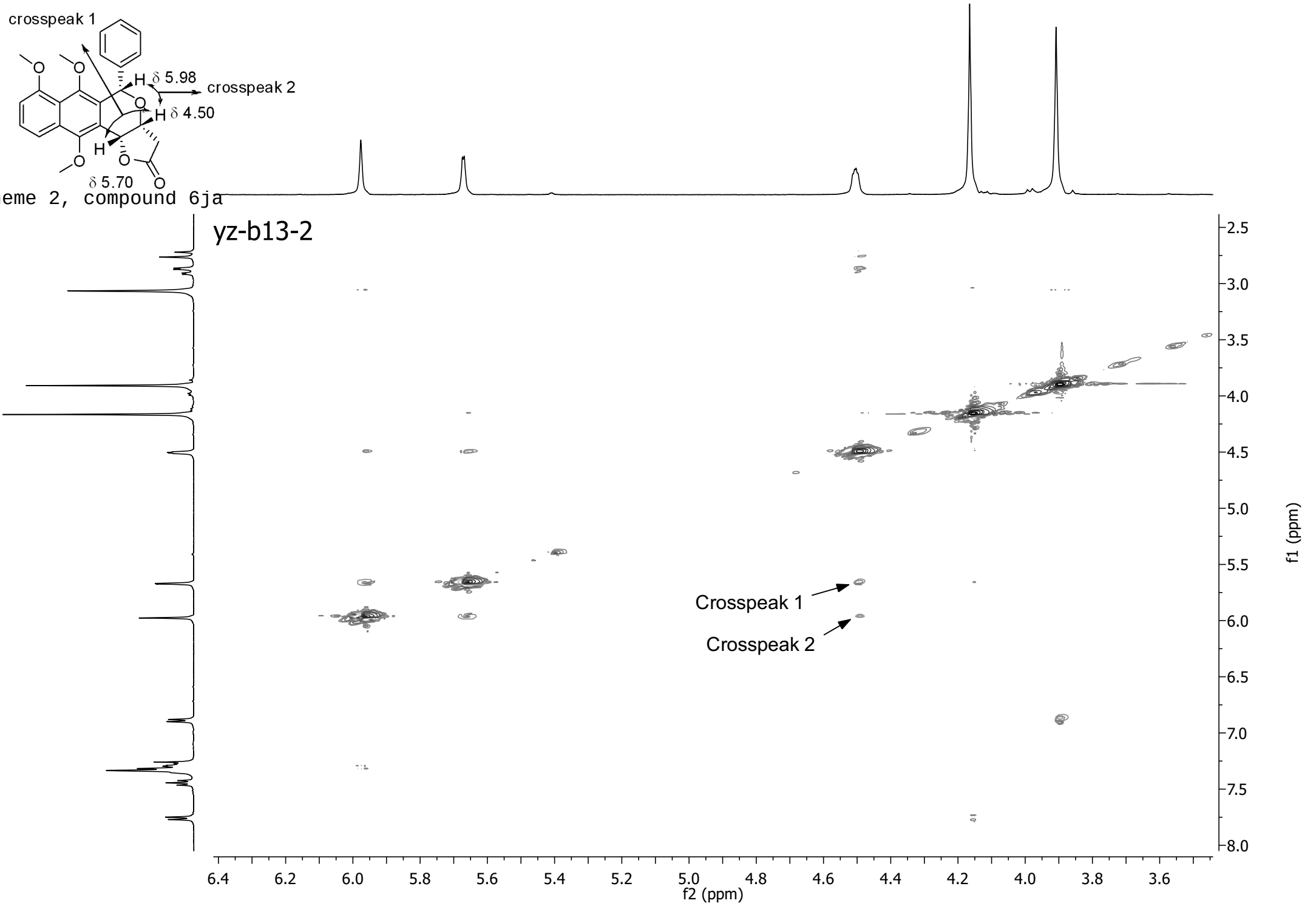
yz-b13-2



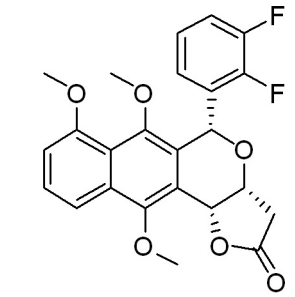
Scheme 2, compound 6ja

Scheme 2, compound 6ja

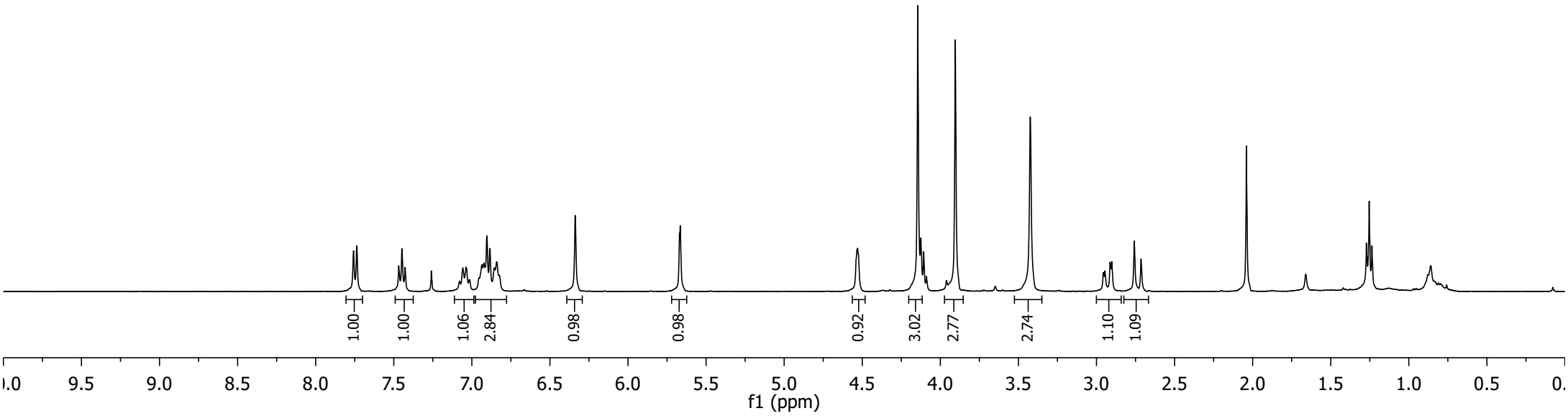



crosspeak 1
δ 5.98
crosspeak 2
δ 4.50
δ 5.70
Scheme 2, compound 6ja
yz-b13-2
Crosspeak 1
Crosspeak 2
f2 (ppm)
f1 (ppm)

yz-b14

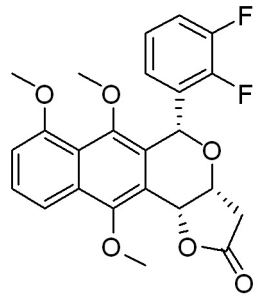


Scheme 2, compound 6k

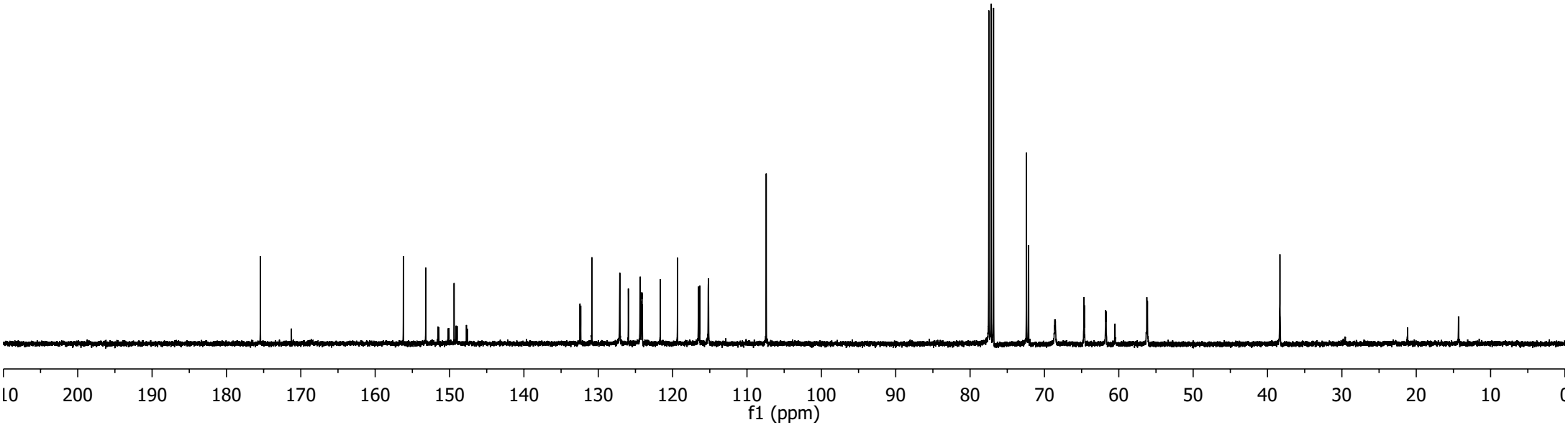


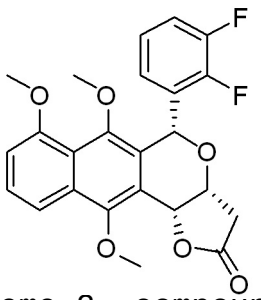
yz-b14

175.437
156.209
153.205
151.568
151.435
150.205
150.074
149.381
149.108
148.977
147.730
147.598
132.457
130.856
127.105
125.953
124.356
124.179
124.133
121.661
119.348
116.532
116.362
115.191
107.410
77.478
77.160
76.842
72.420
72.158
72.121
68.560
64.681
61.708
56.227
38.330

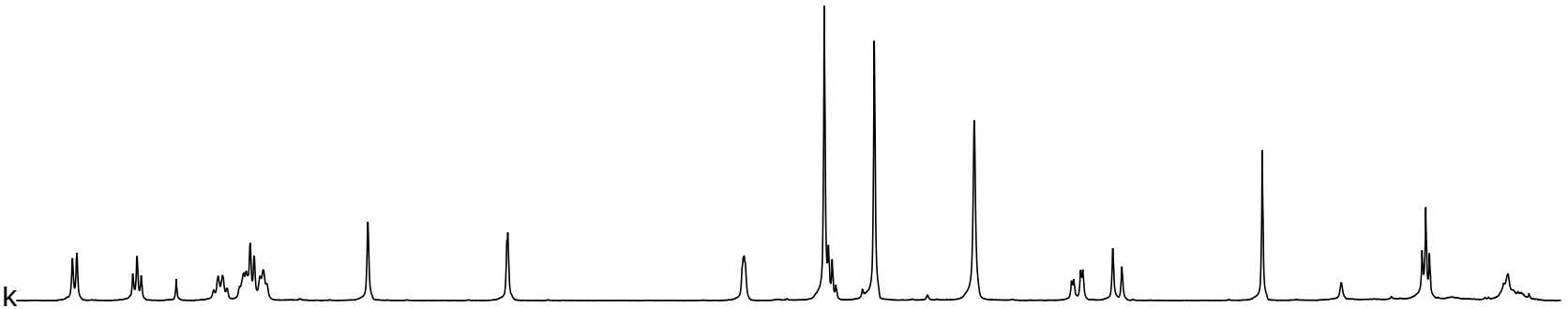


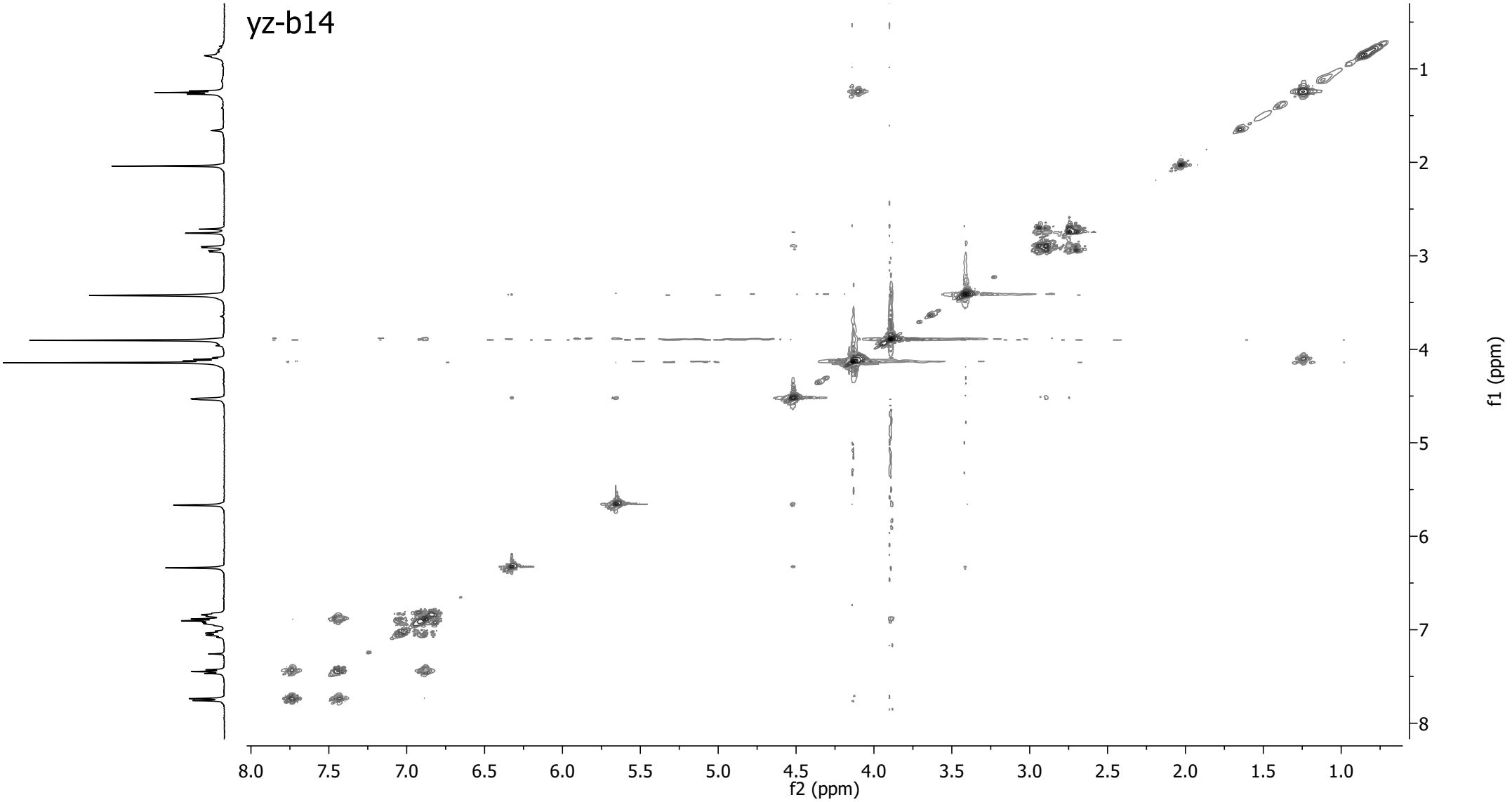
Scheme 2, compound 6k

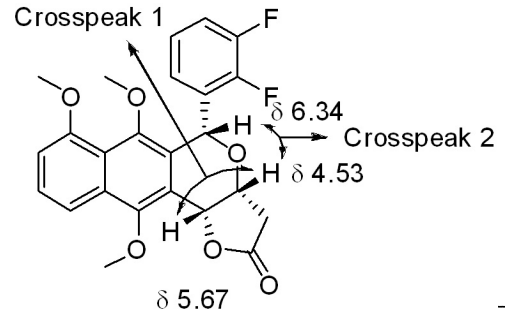




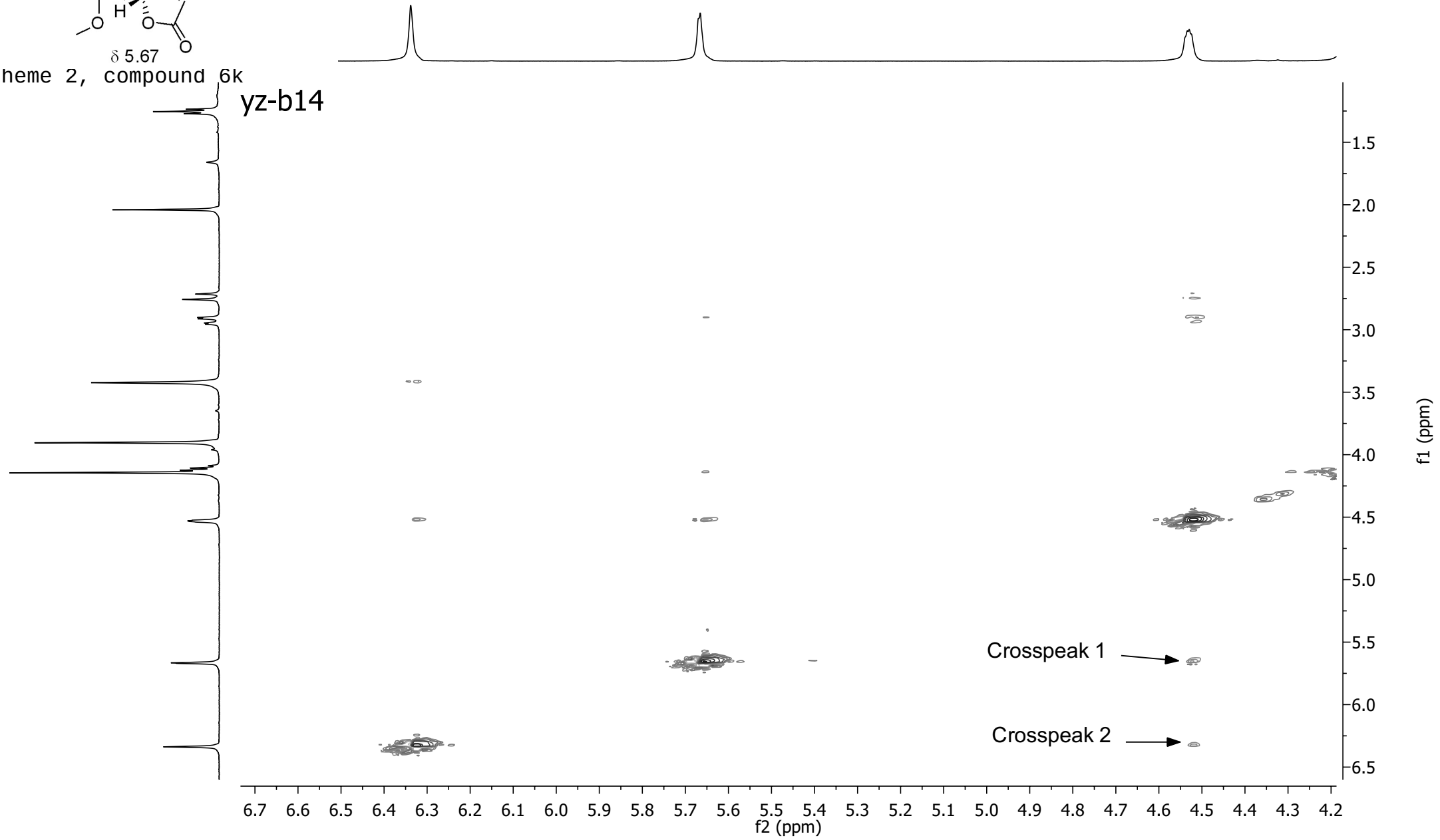
Scheme 2, compound 6k



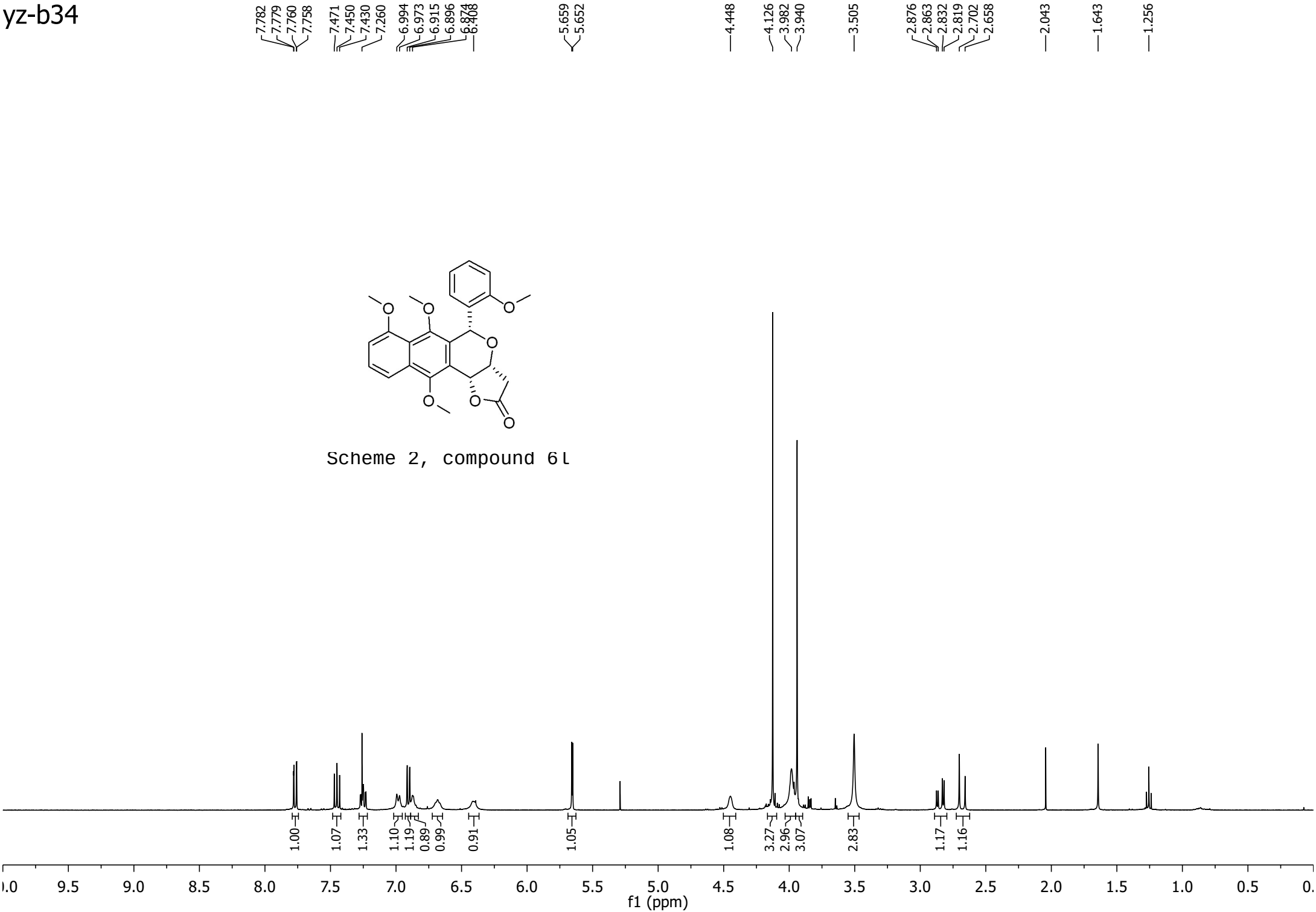




Scheme 2, compound 6k

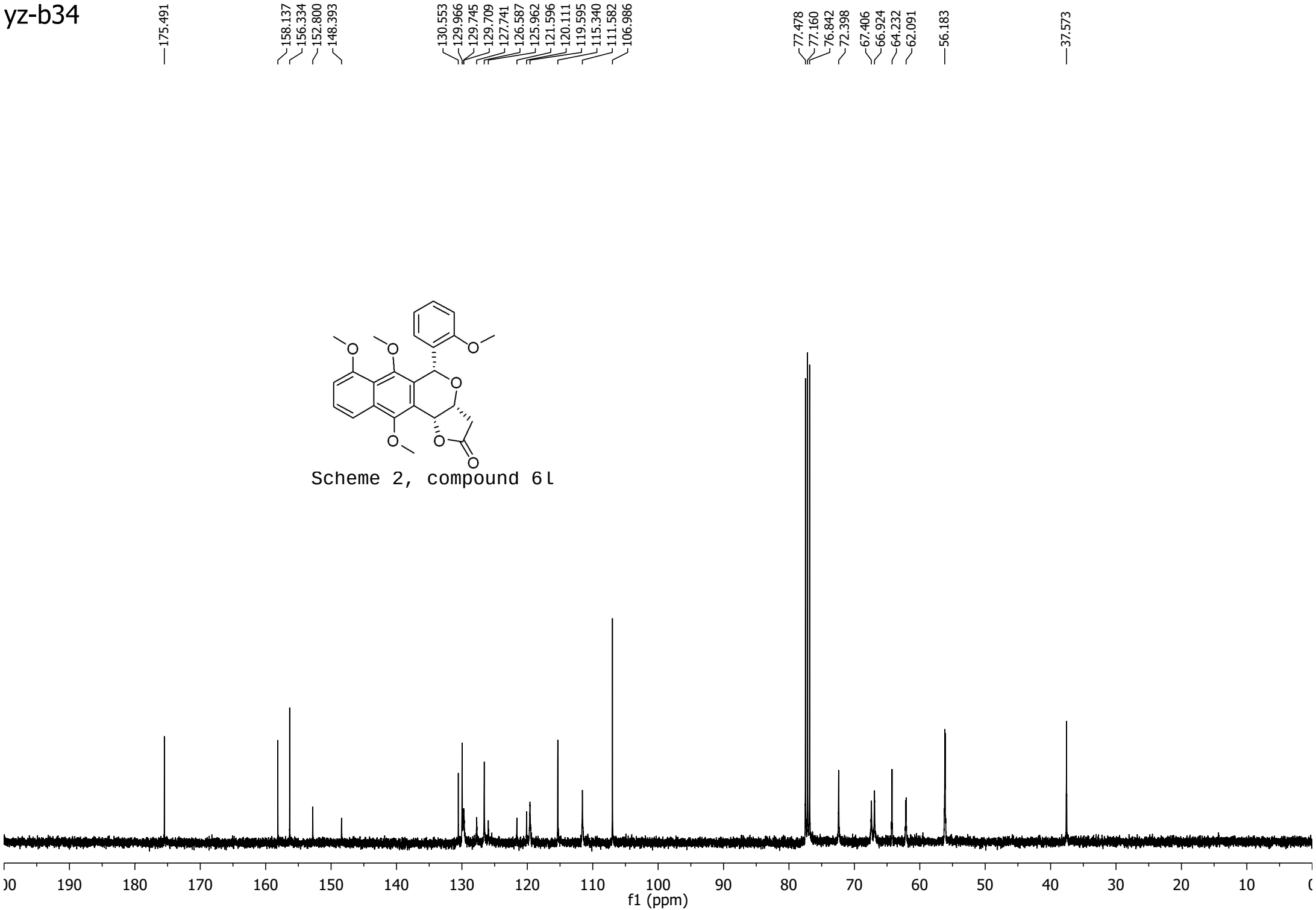


yz-b34

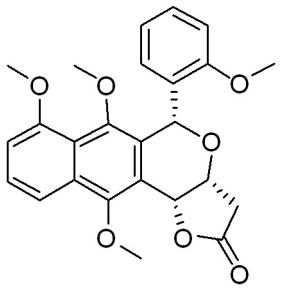


Scheme 2, compound 6l

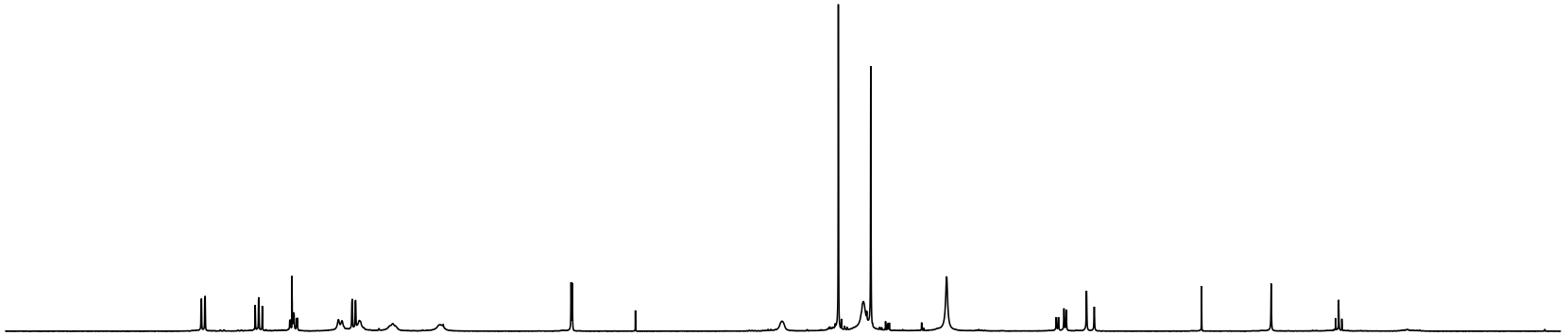
yz-b34

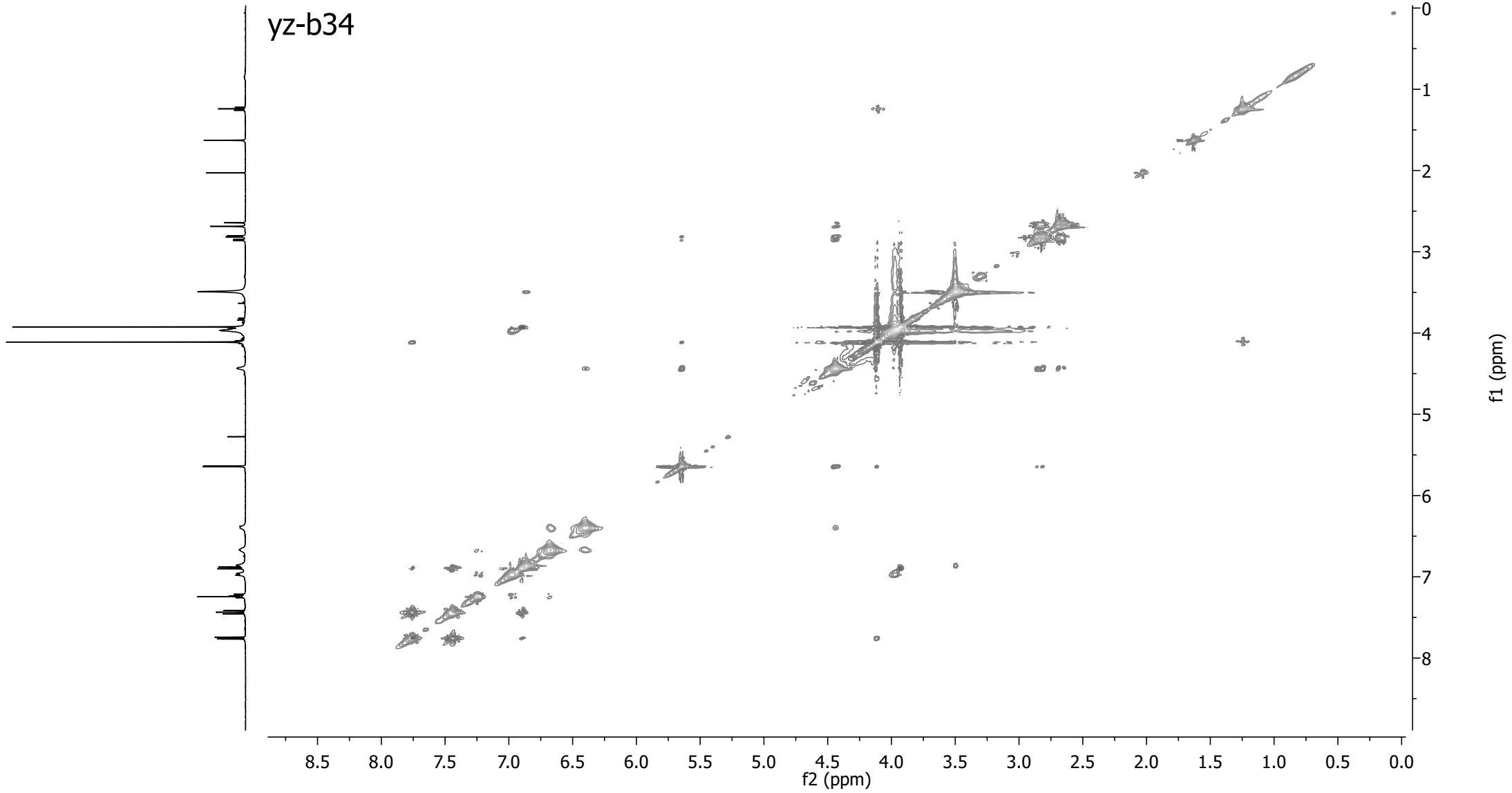


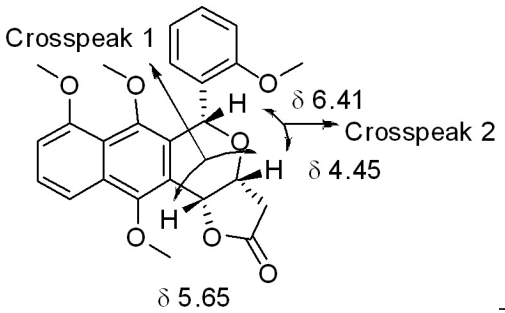
Scheme 2, compound 6l



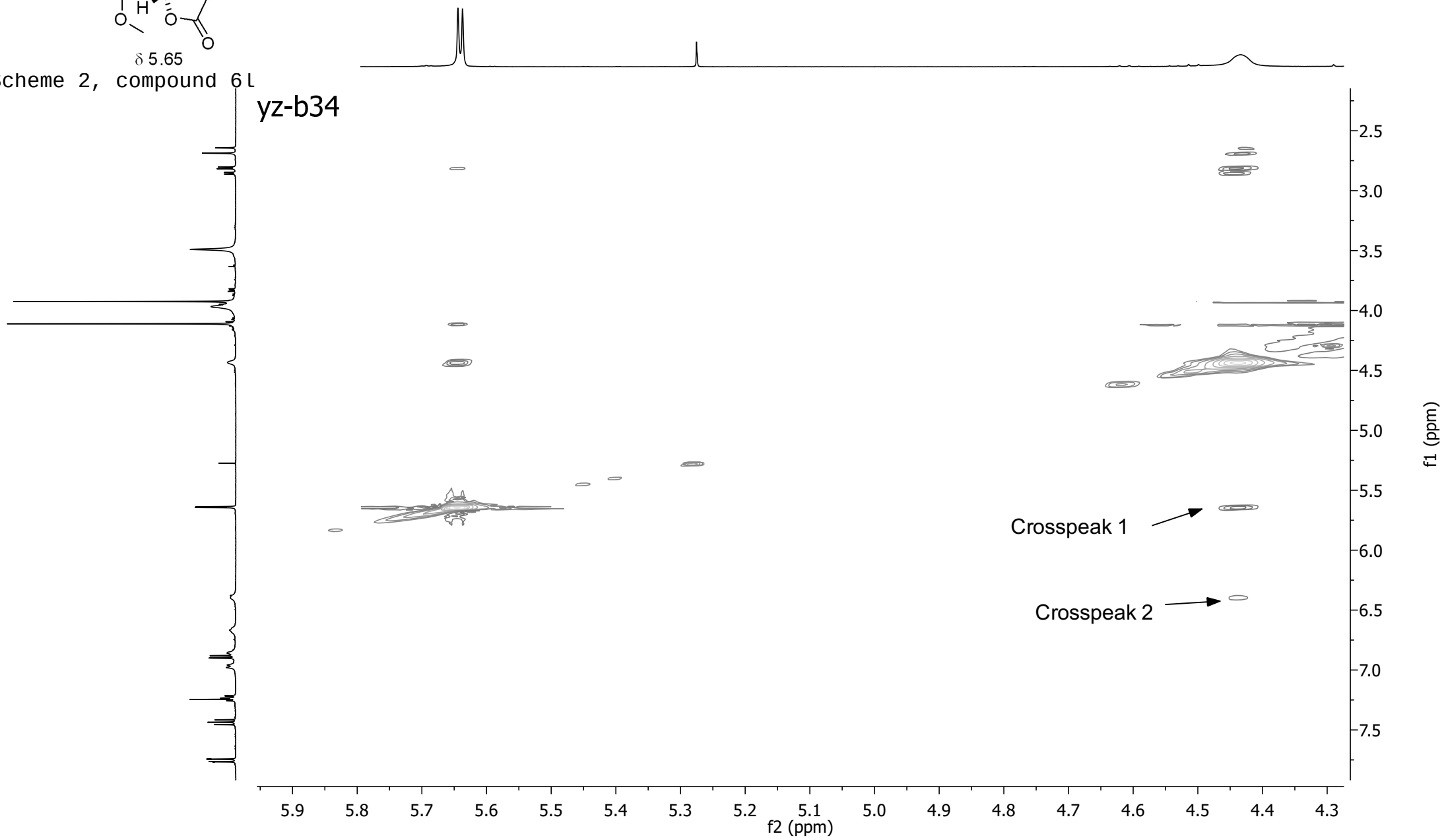
Scheme 2, compound 6l



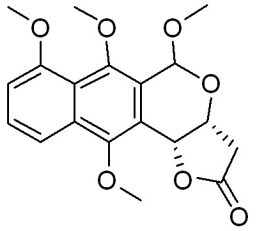




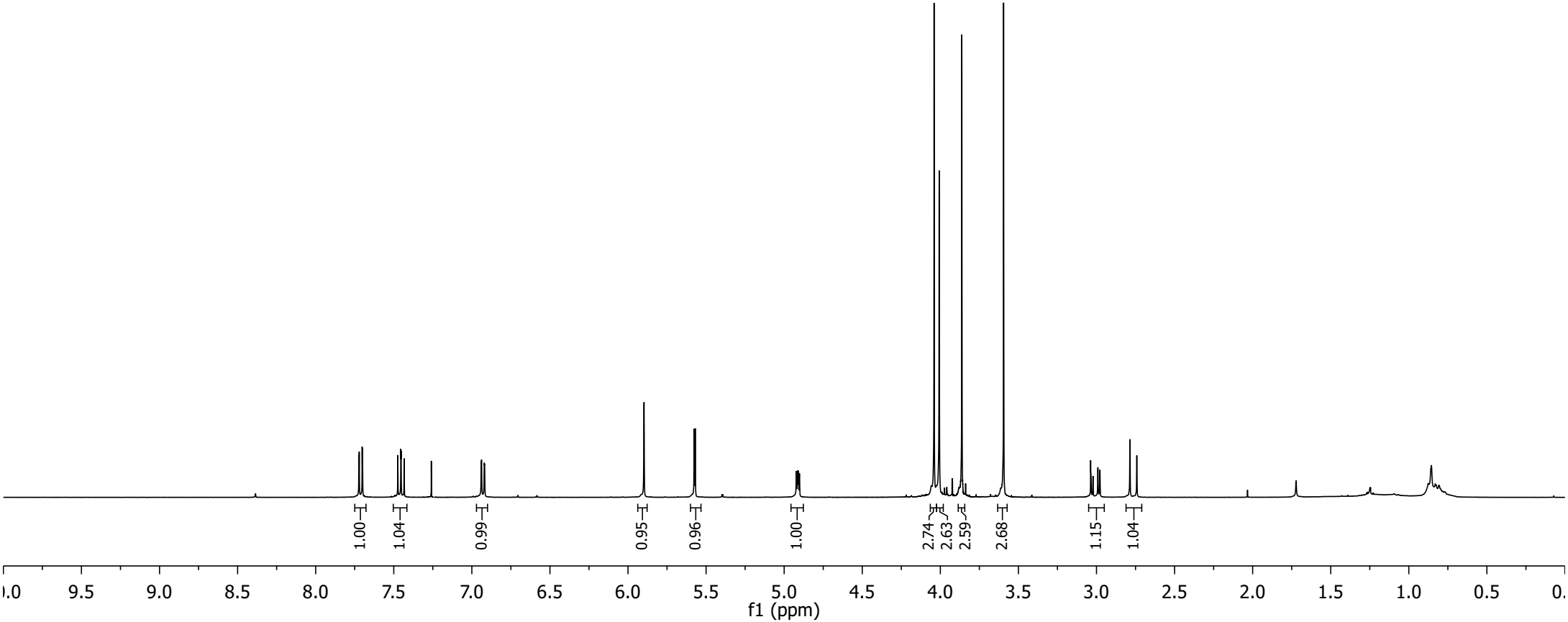
Scheme 2, compound 6l



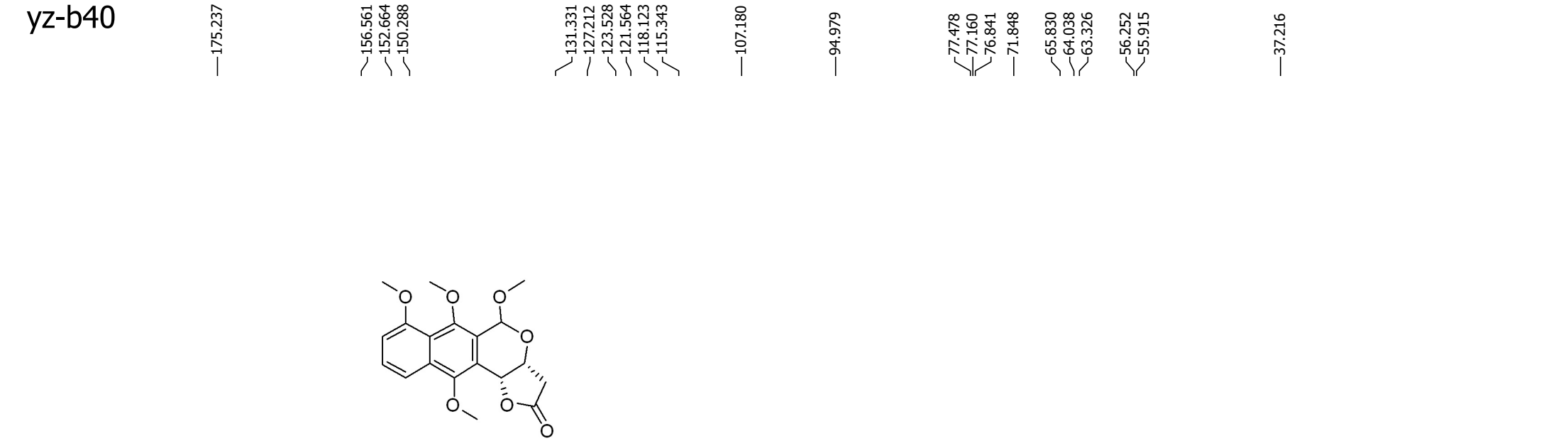
yz-b40



Scheme 3, compound 8

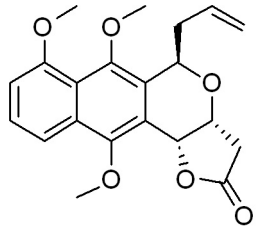


yz-b40

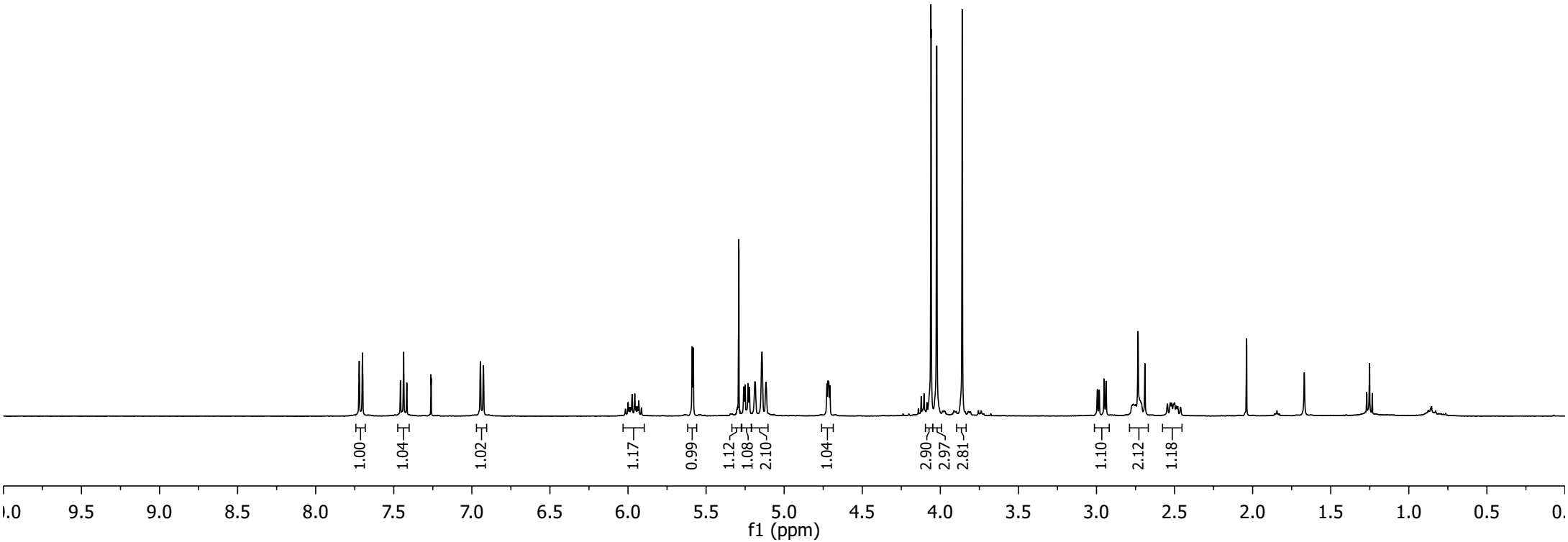


Scheme 3, compound 8

yz-a150

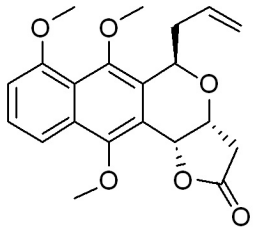


Scheme 3, compound 6fb

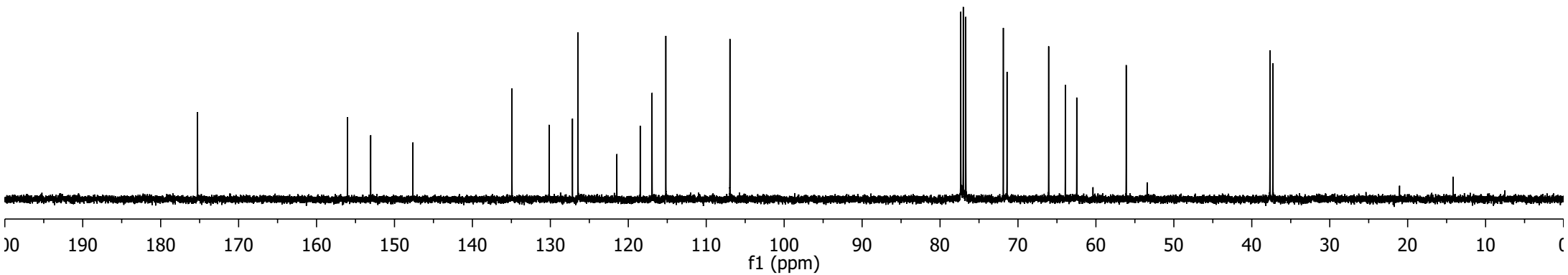


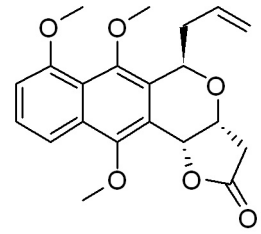
yz-a150

175.263
156.038
153.052
147.641
134.930
130.161
127.165
126.454
121.464
118.472
116.956
115.181
106.961
77.339
77.021
76.703
71.881
71.406
66.064
63.926
62.461
56.114
37.669
37.294

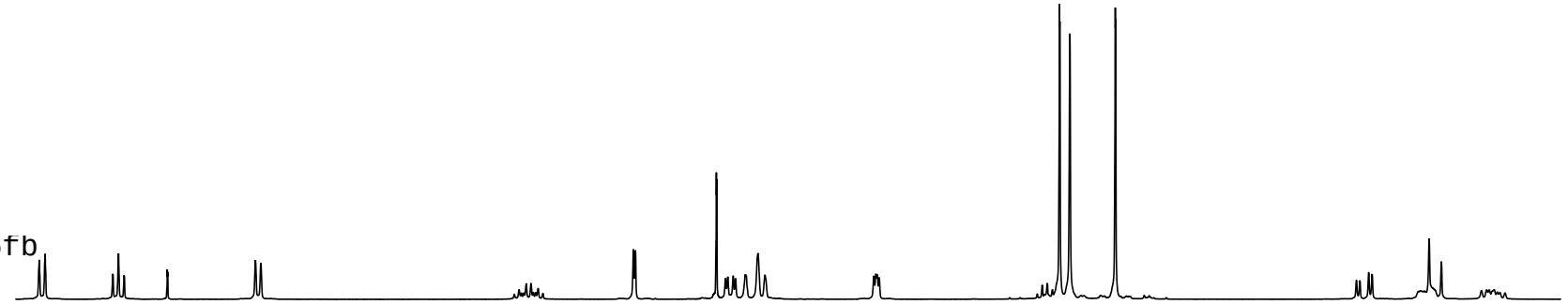


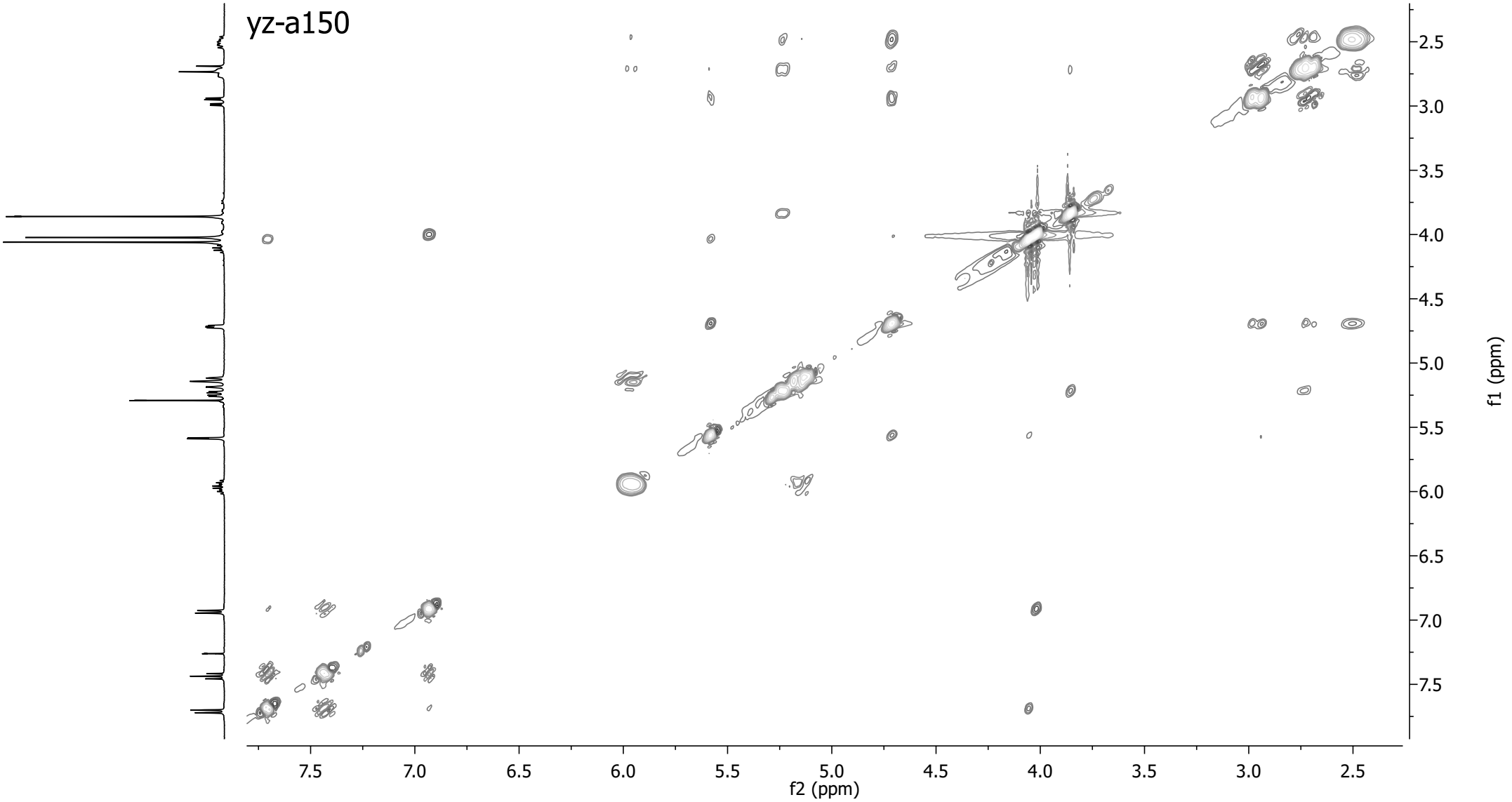
Scheme 3, compound 6fb

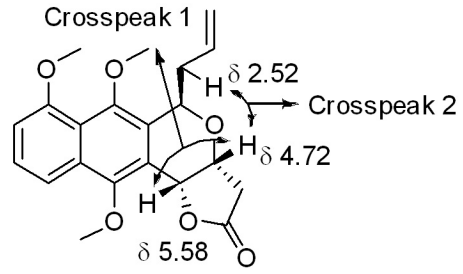




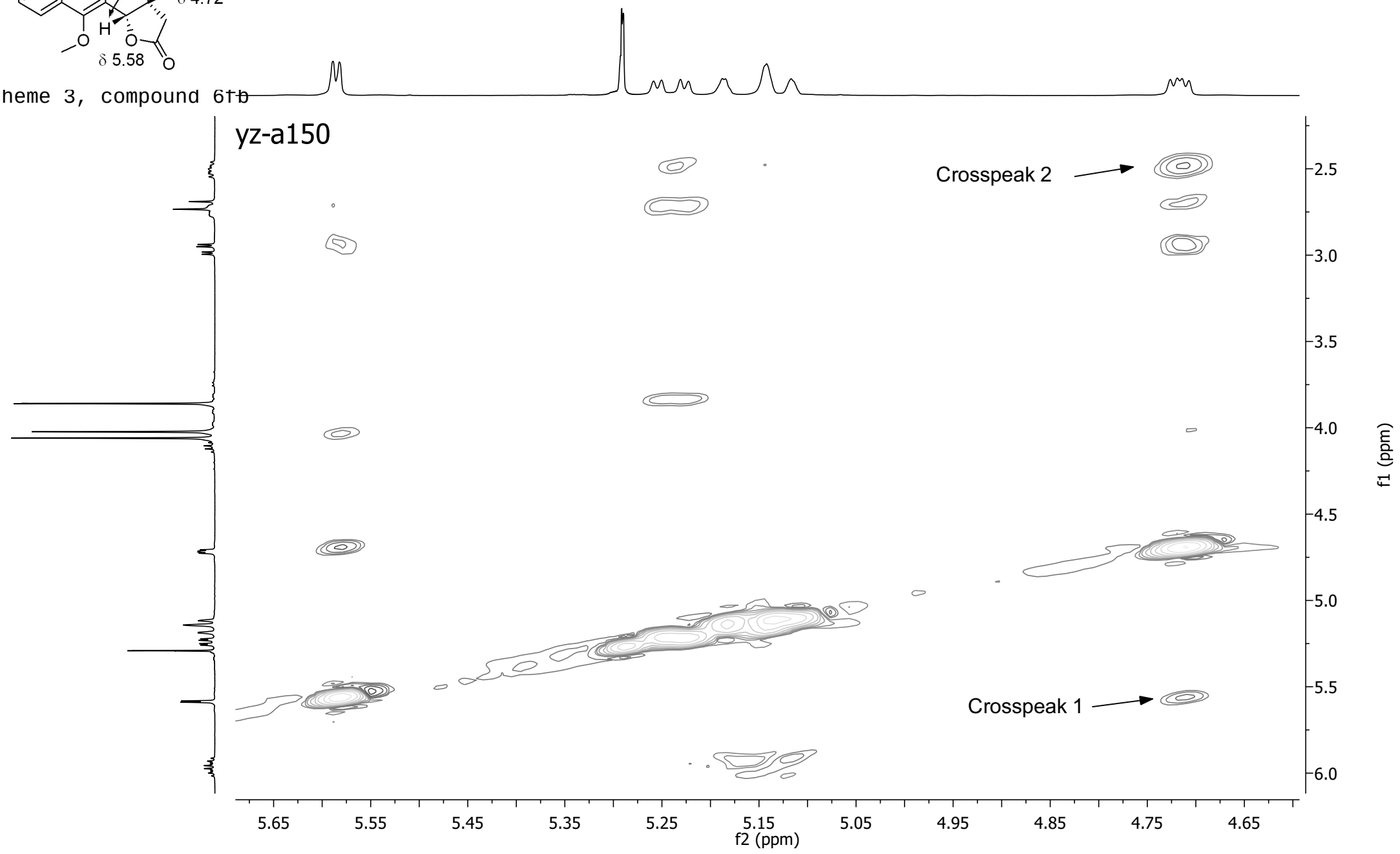
Scheme 3, compound 6fb



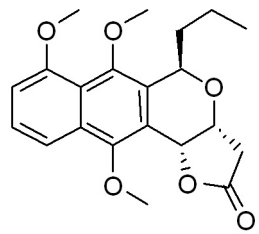




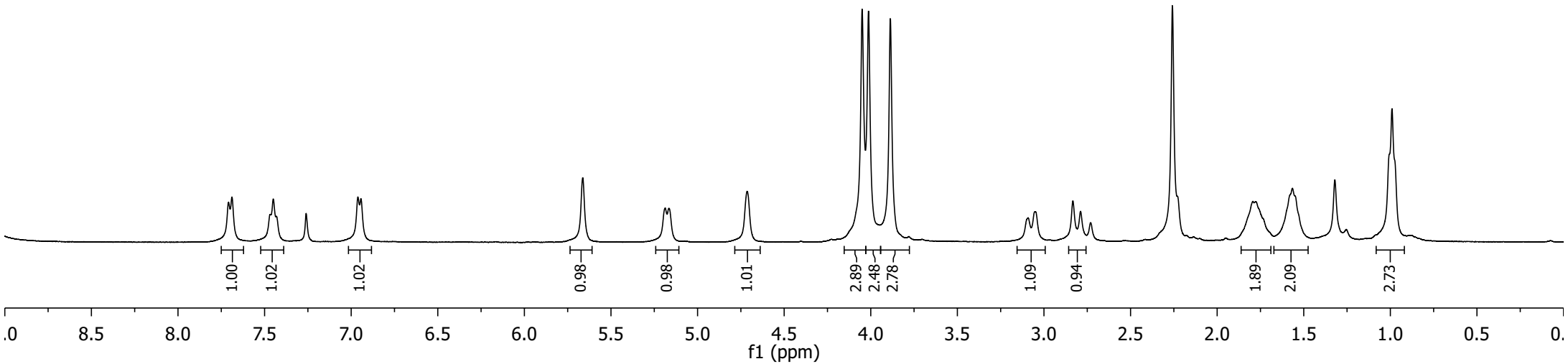
Scheme 3, compound 6t-b



yz-b1

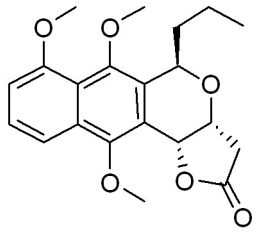


Scheme 3, compound 6ab

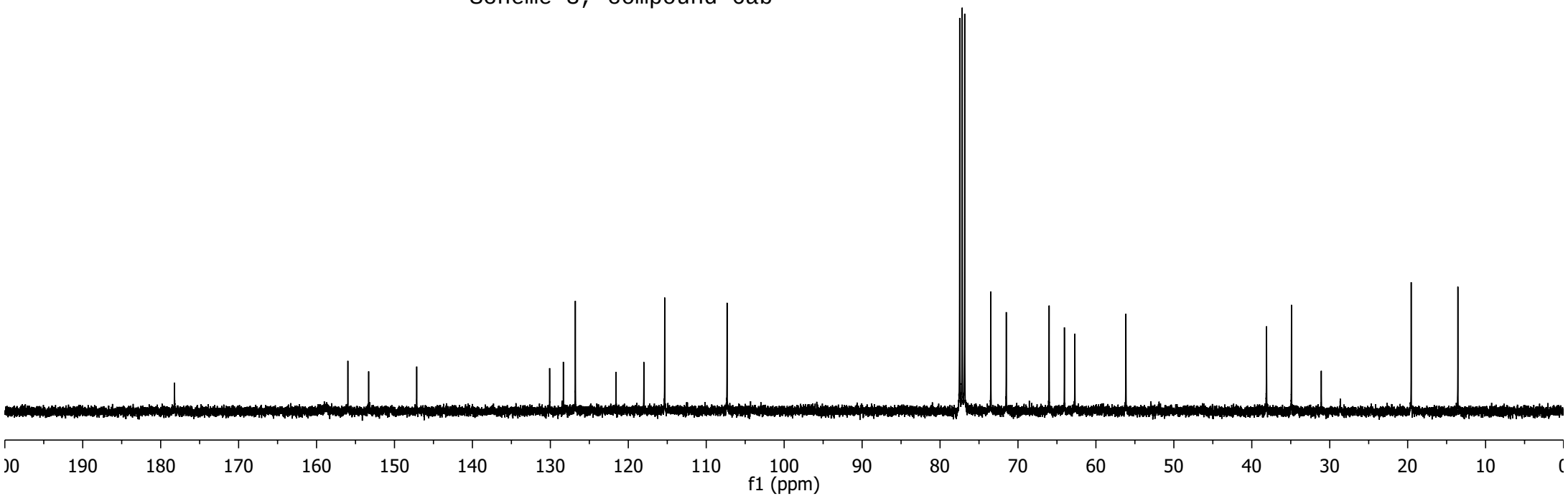


yz-b1

178.231
155.979
153.313
147.147
130.091
128.334
126.795
121.579
118.007
115.330
107.328
77.478
77.160
76.842
73.481
71.501
66.000
64.042
62.703
56.151
38.109
34.908
19.549
13.557

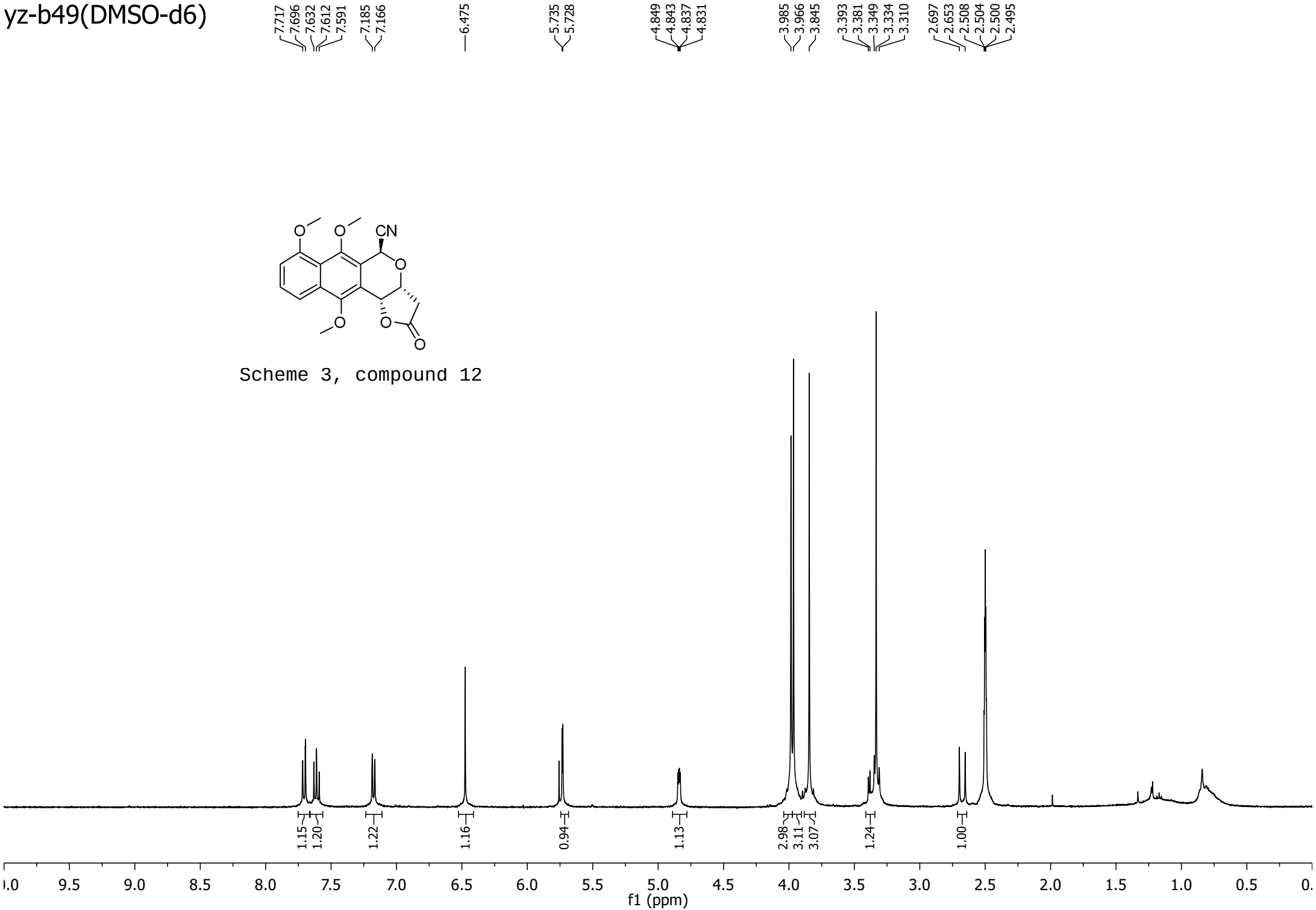


Scheme 3, compound 6ab

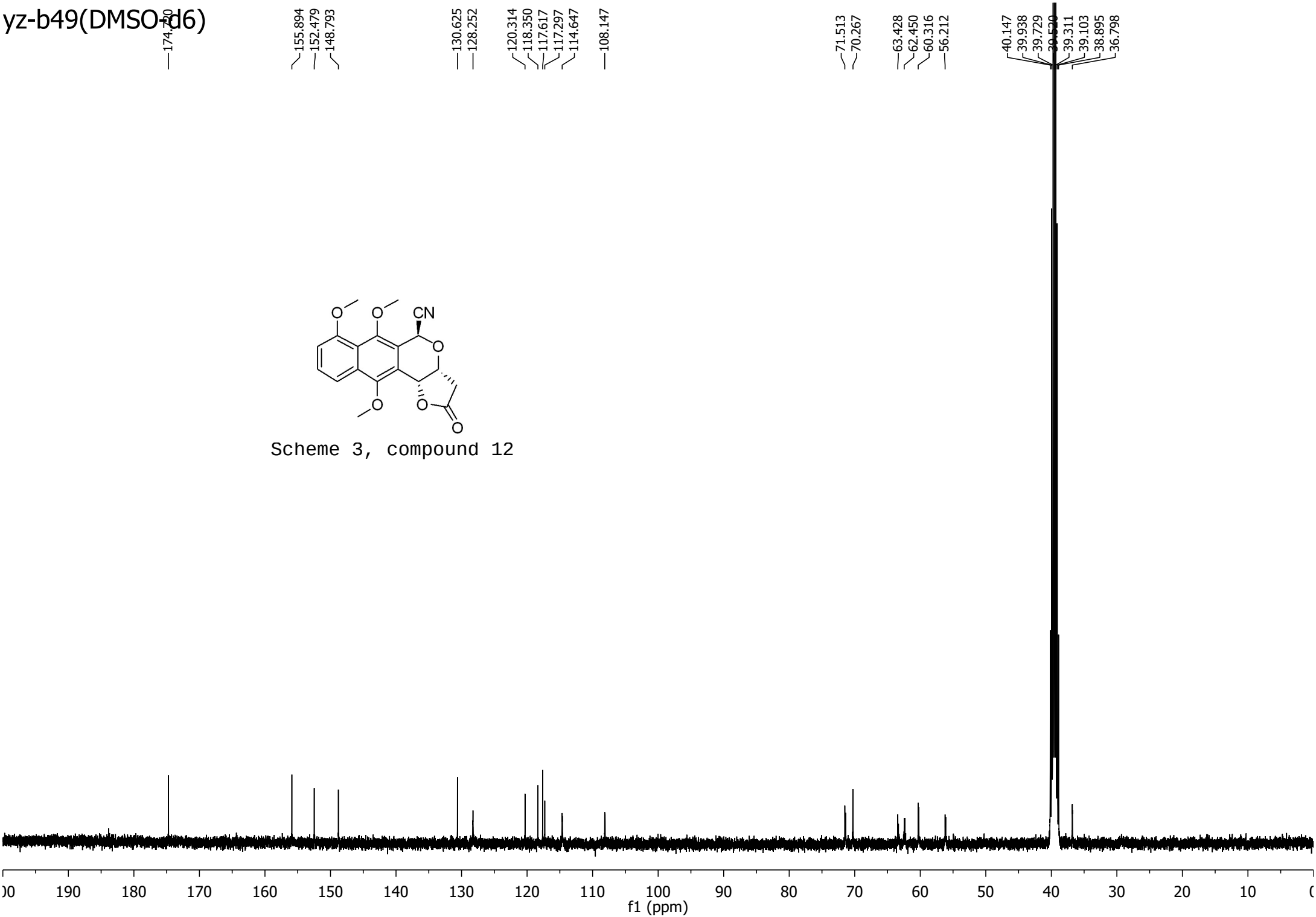


yz-b49(DMSO-d6)

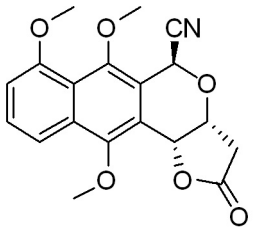
Scheme 3, compound 12



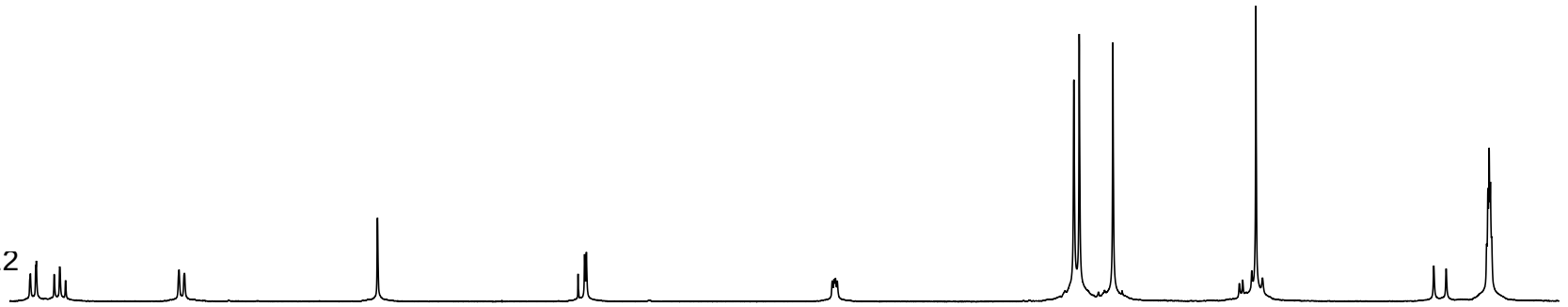
yz-b49(DMSO-d6)

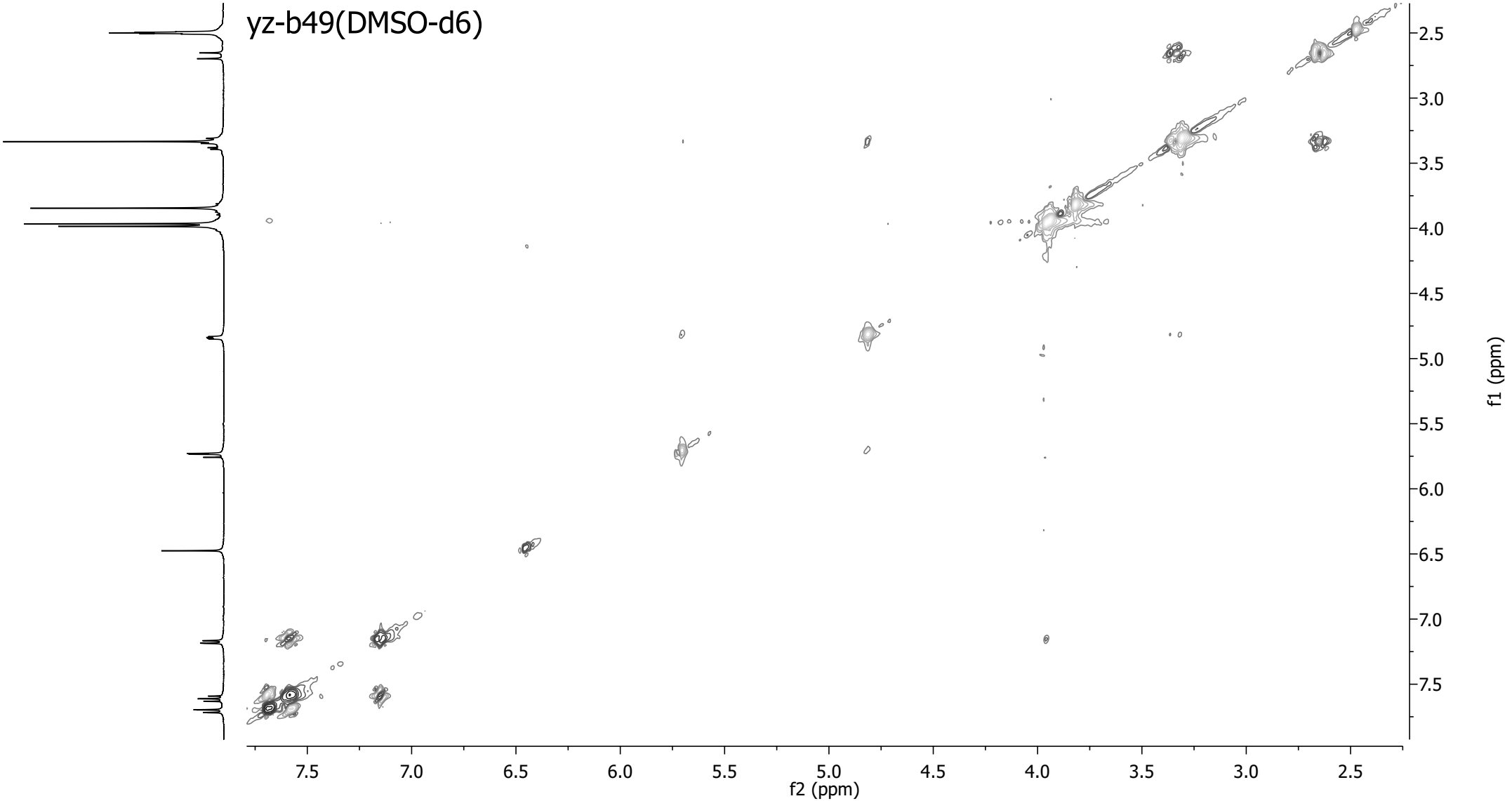


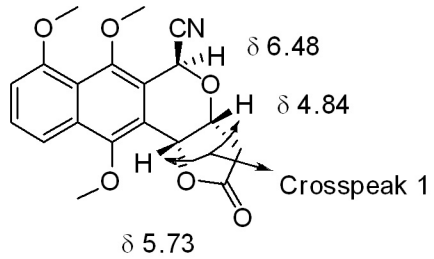
Scheme 3, compound 12



Scheme 3, compound 12







Scheme 3, compound 12

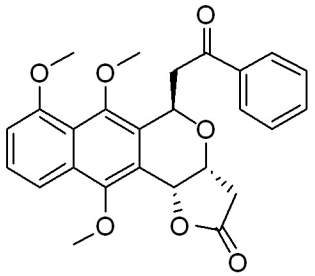
yz-b49(DMSO-d6)

Crosspeak 1

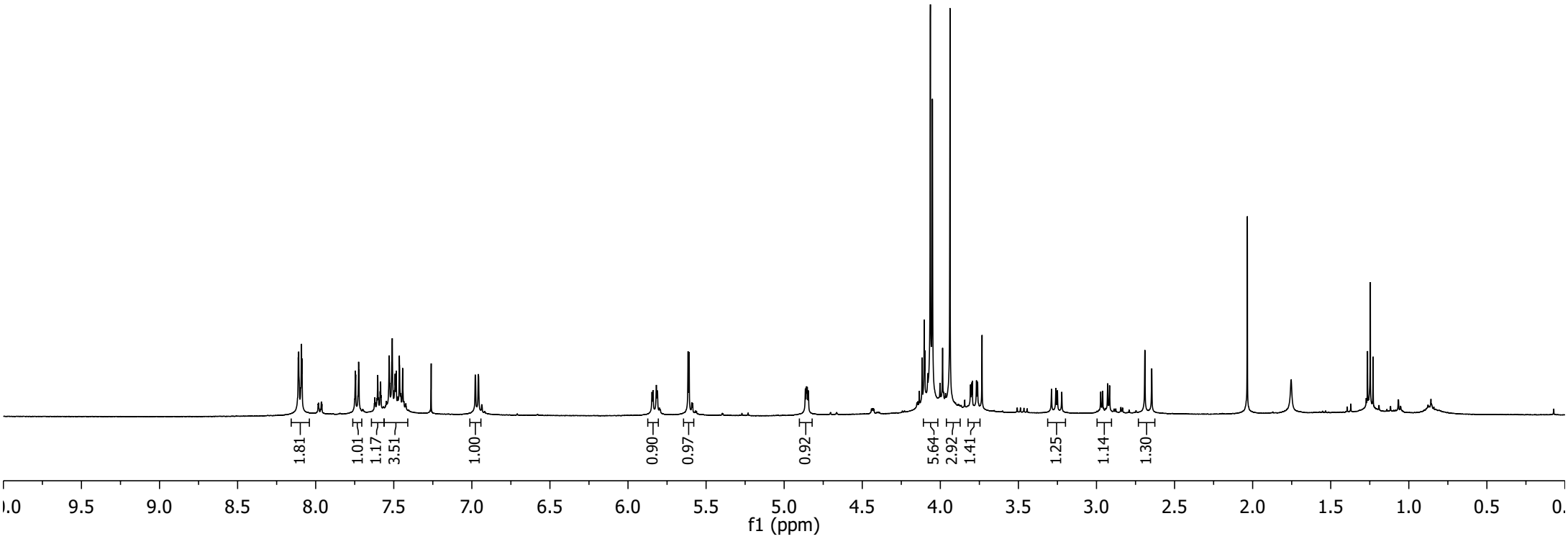
f2 (ppm)

f1 (ppm)

yz-b41

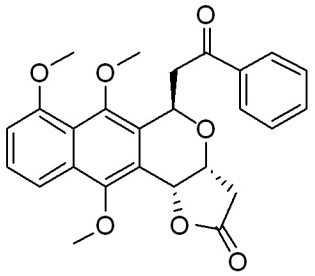


Scheme 3, compound 13

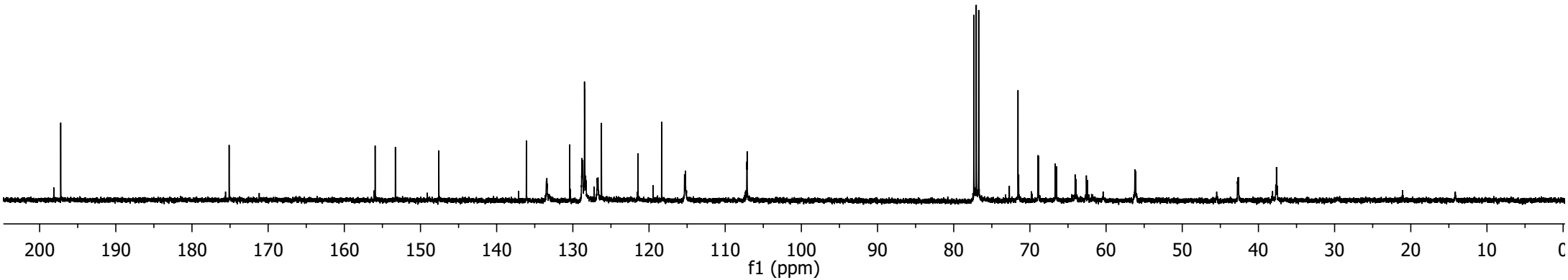


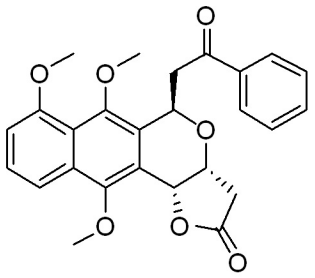
yz-b41

197.241
175.122
155.953
153.300
147.590
136.103
133.413
130.407
128.699
128.444
126.691
126.240
121.438
118.350
115.229
107.123
77.360
77.042
76.724
71.562
68.869
66.676
64.069
62.451
56.103
42.717
37.620

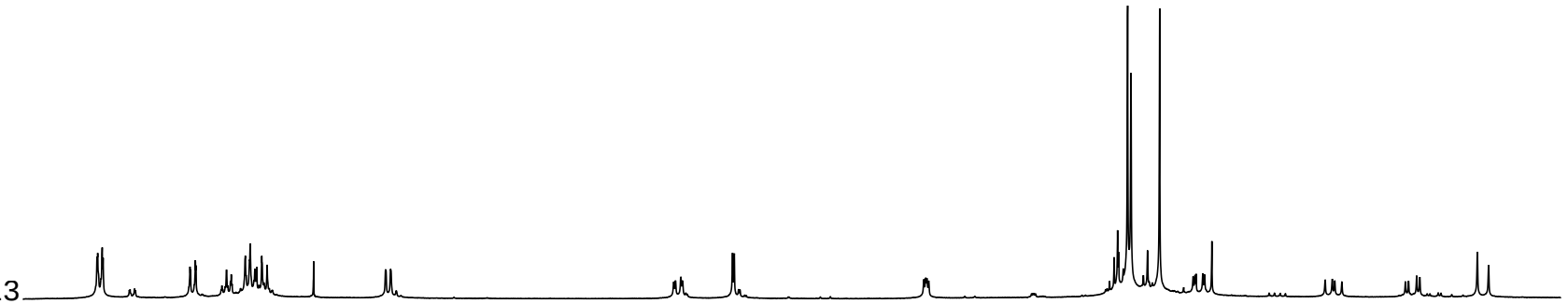


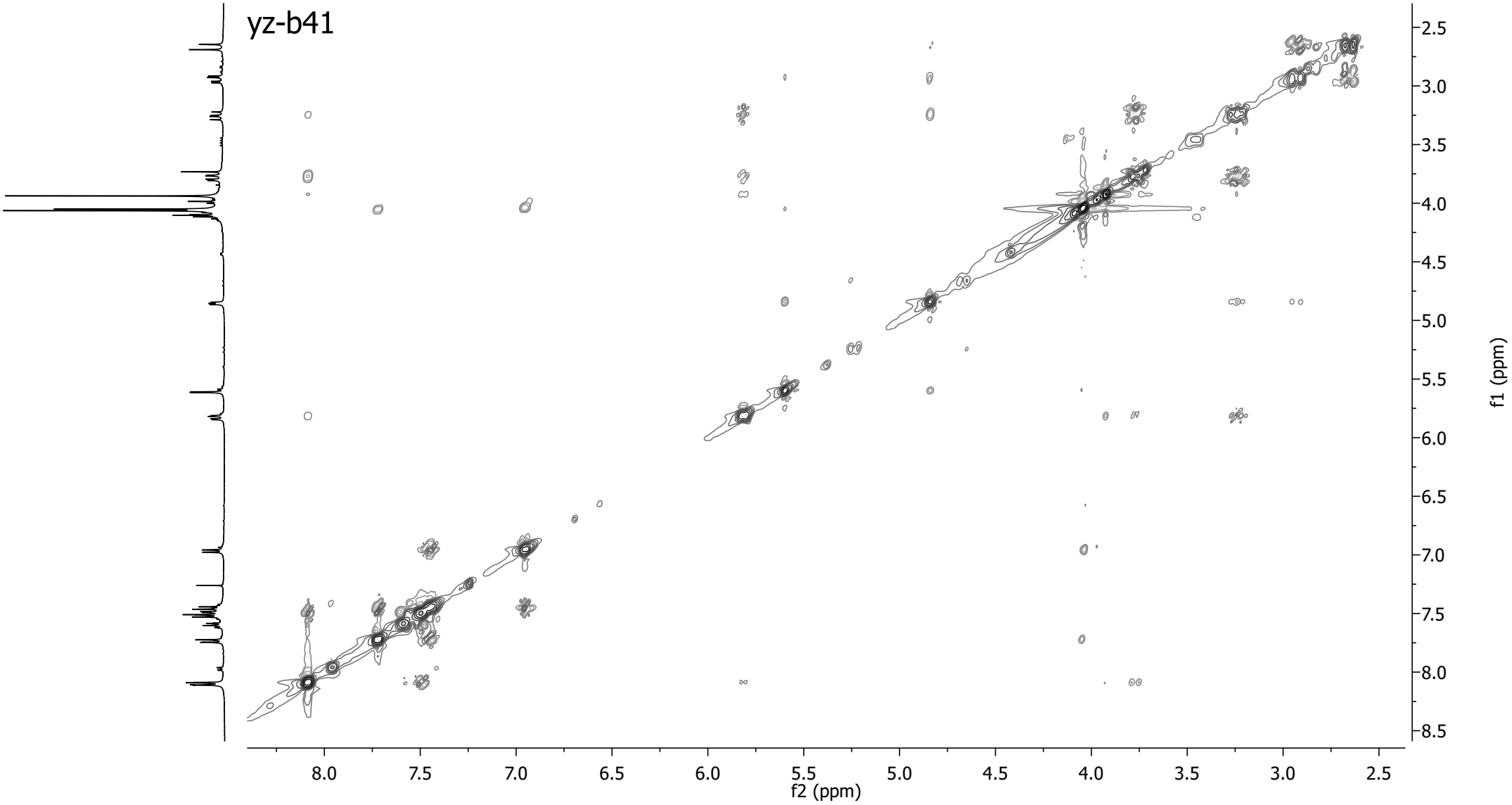
Scheme 3, compound 13

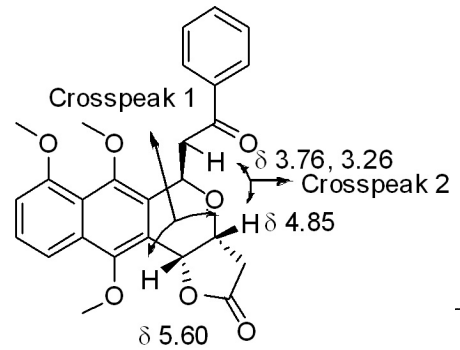




Scheme 3, compound 13

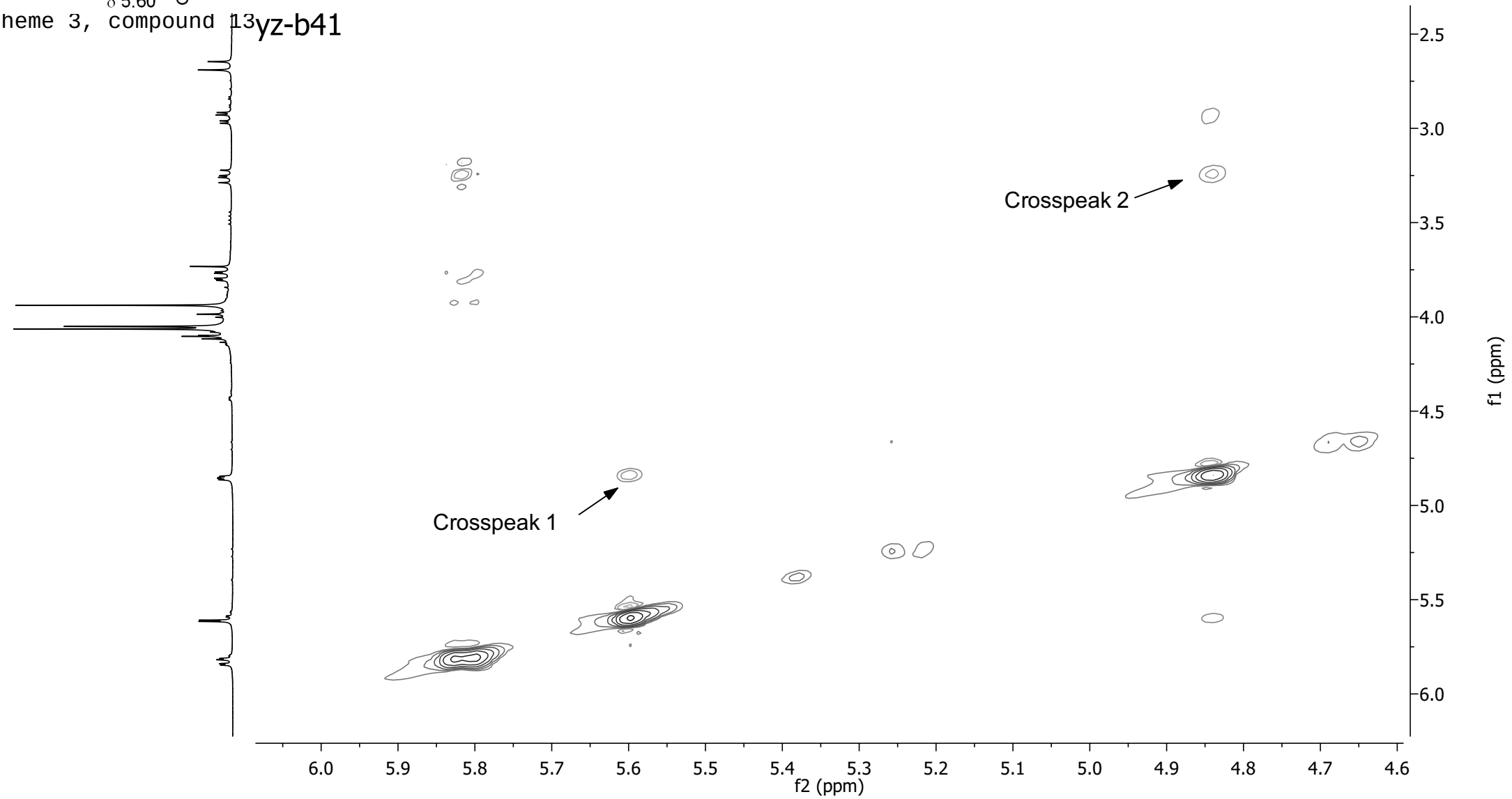




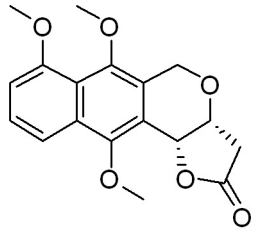


Scheme 3, compound 13

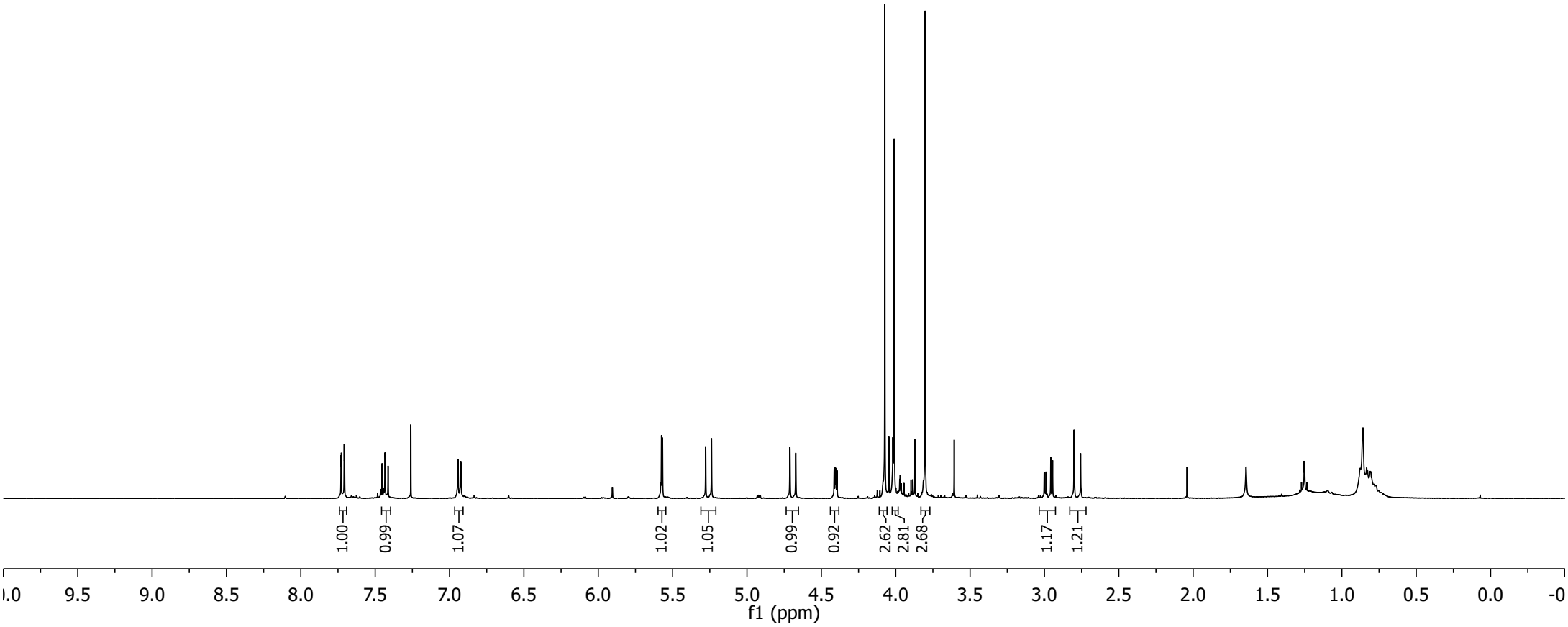
yz-b41



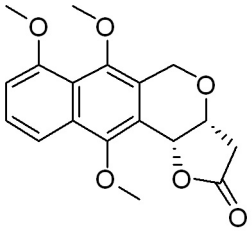
yz-a144



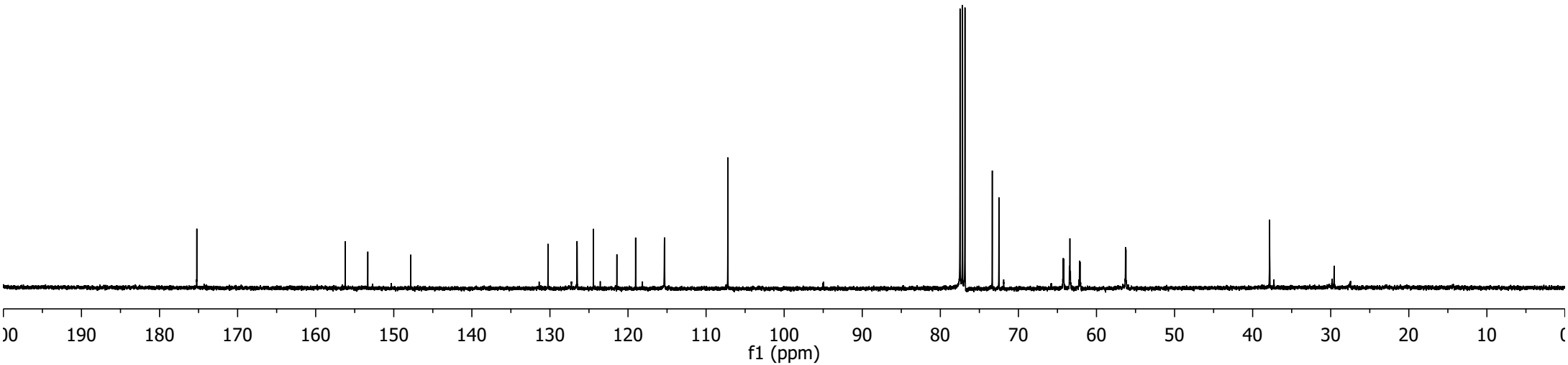
Scheme 3, compound 14



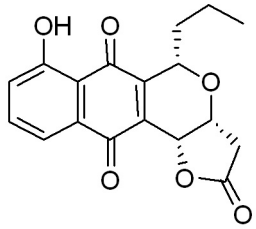
yz-a144



Scheme 3, compound 14



yz-a99

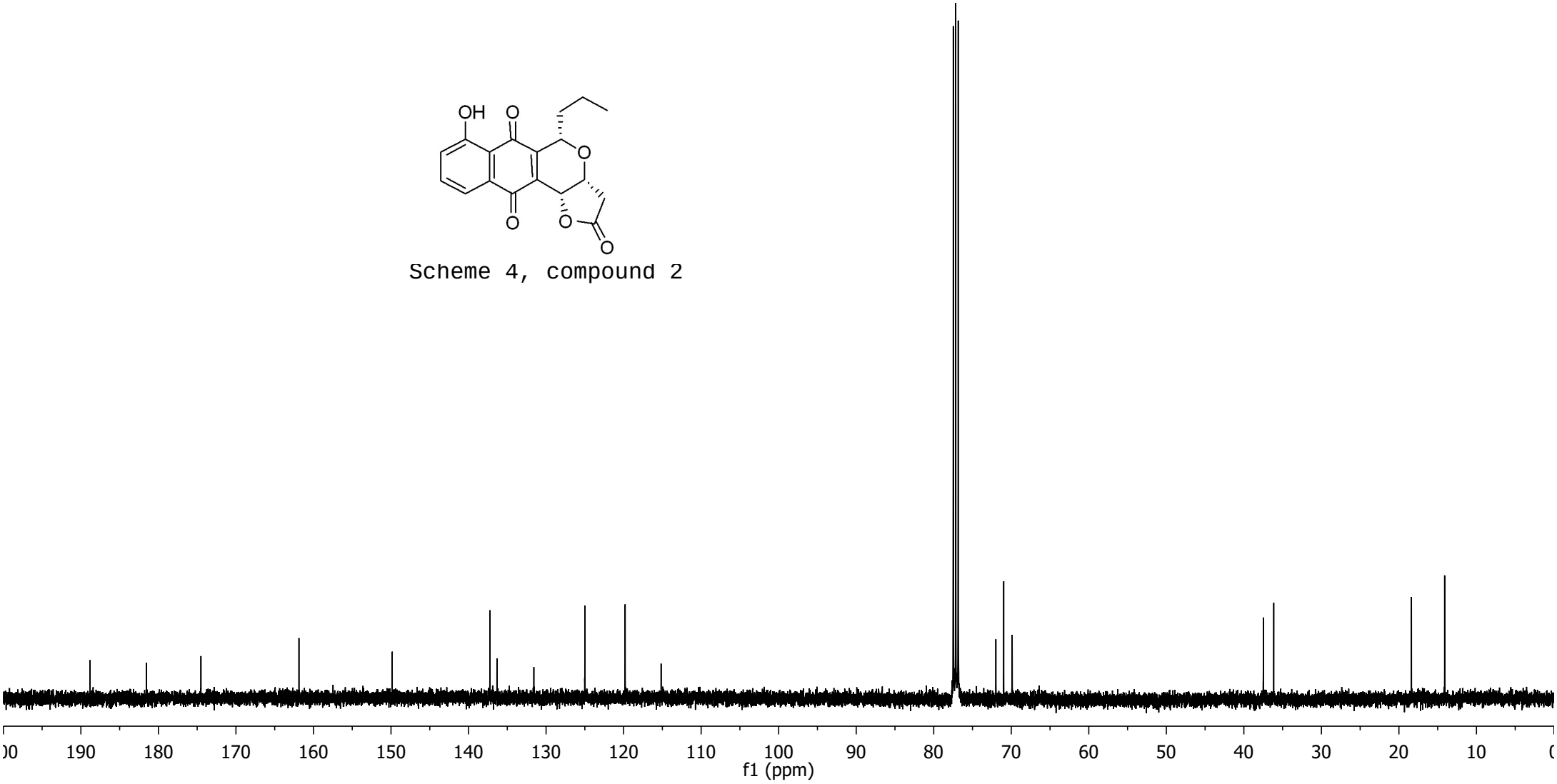


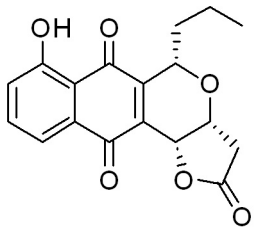
Scheme 4, compound 2

yz-a99

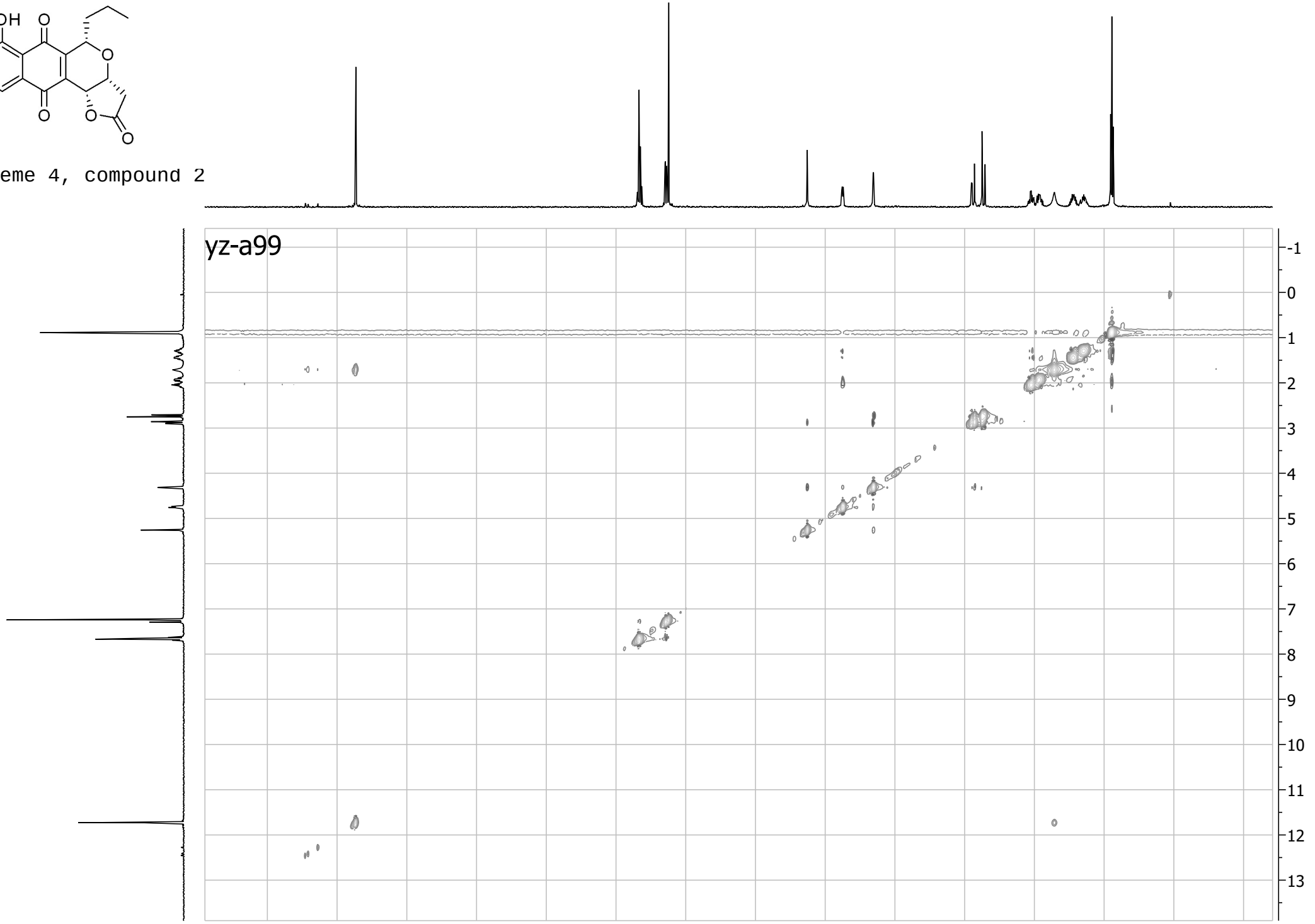
188.183
181.543
174.510
161.873
149.842
137.237
136.335
131.573
124.994
119.799
115.162
77.478
77.160
76.842
71.985
70.973
69.882
37.482
36.146
18.386
14.103

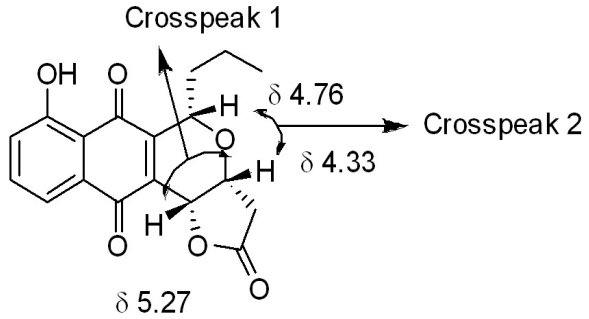
Scheme 4, compound 2



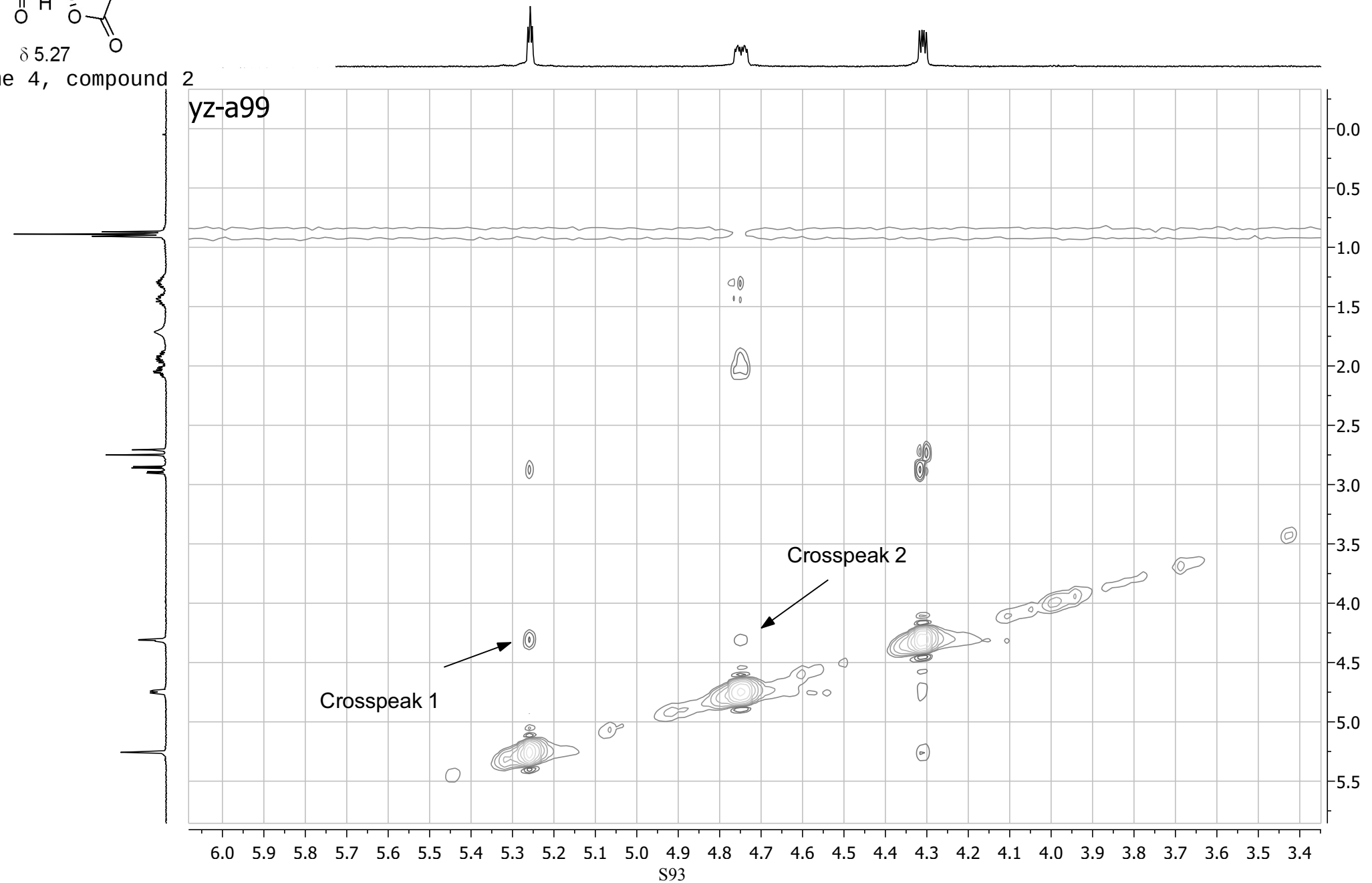


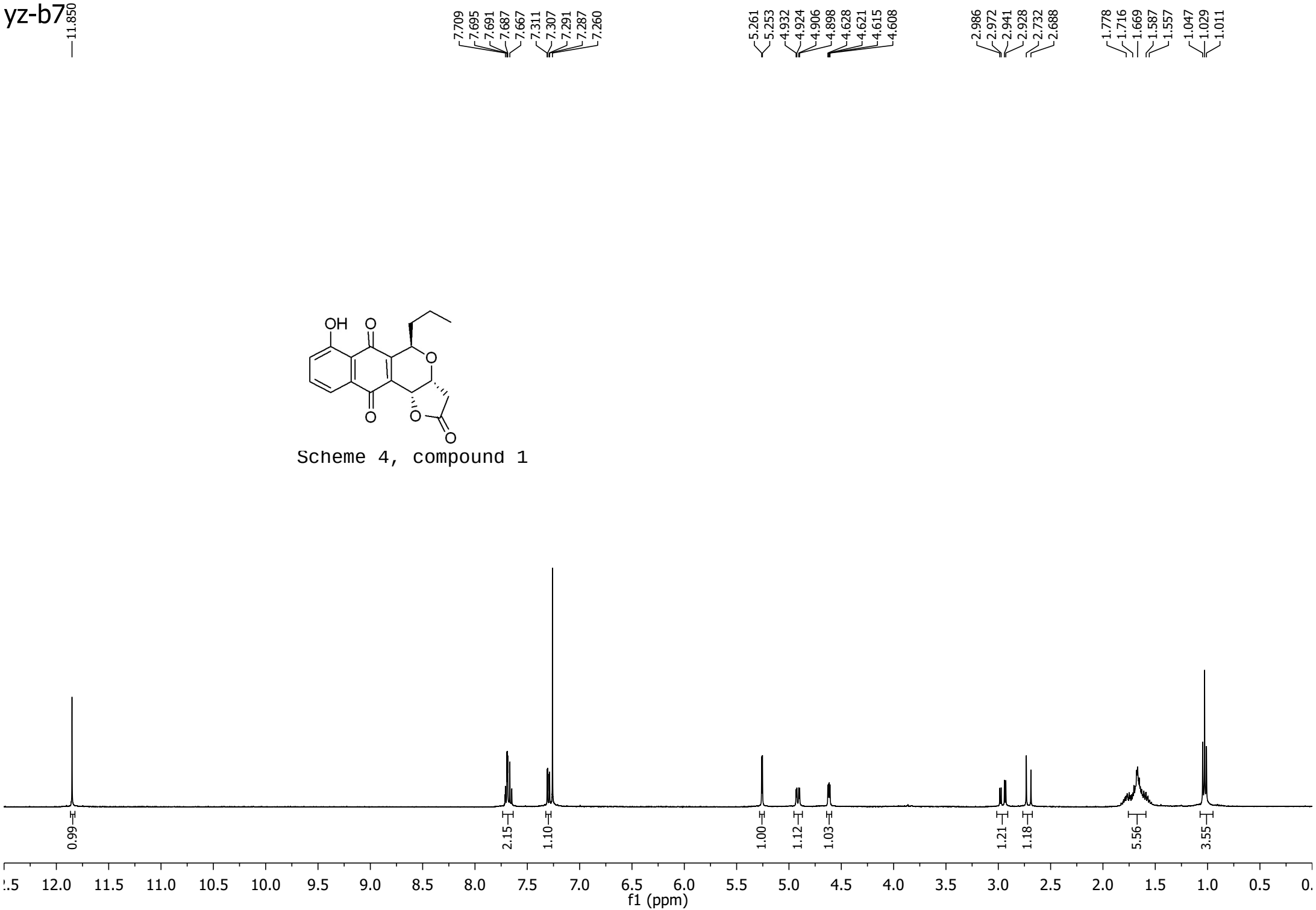
Scheme 4, compound 2



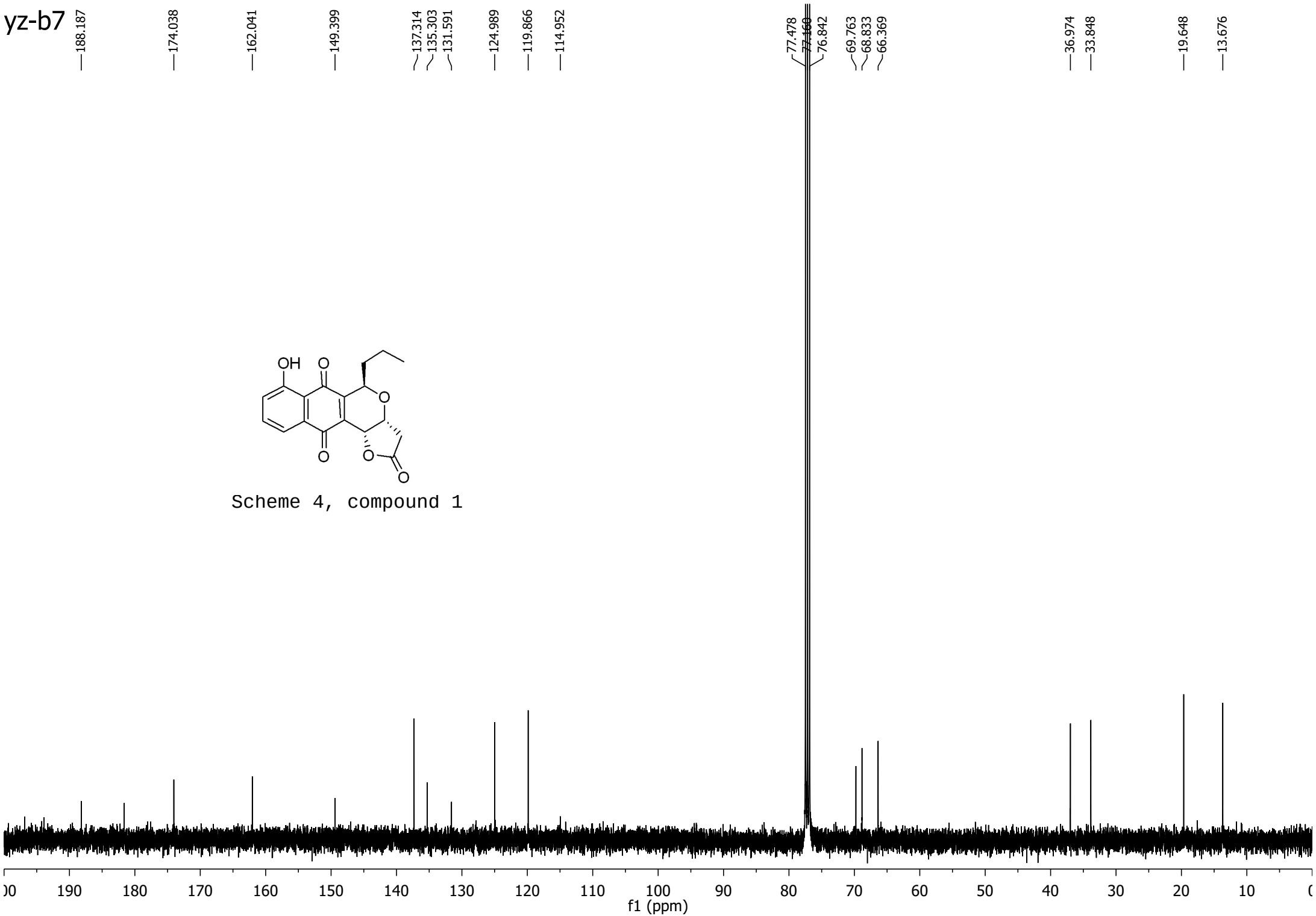


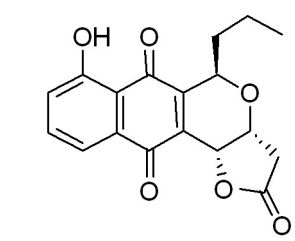
Scheme 4, compound 2



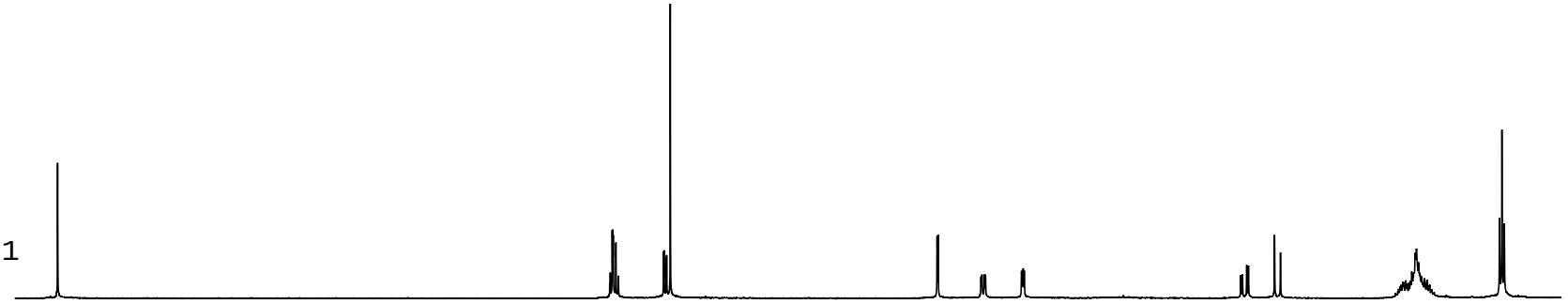


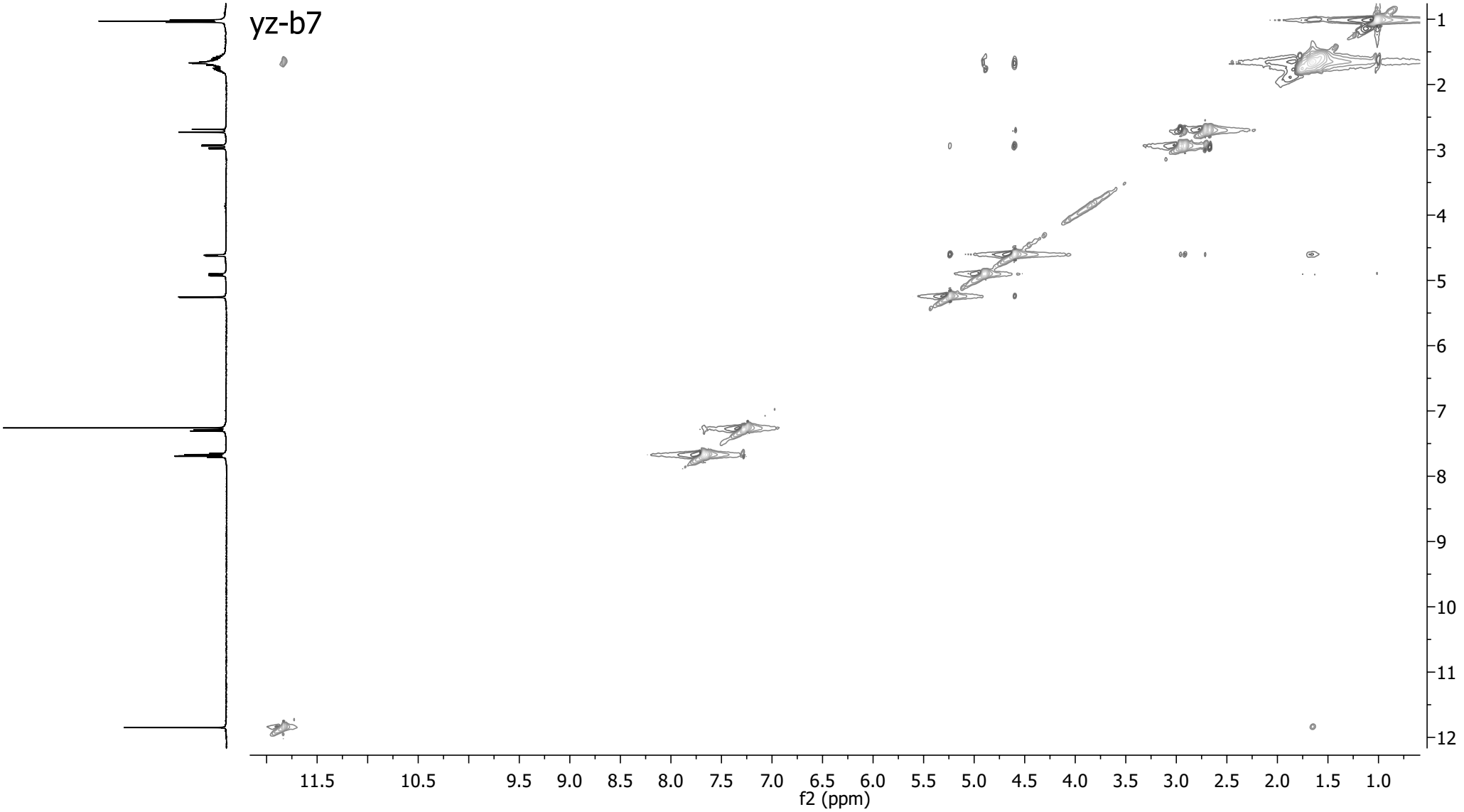
Scheme 4, compound 1

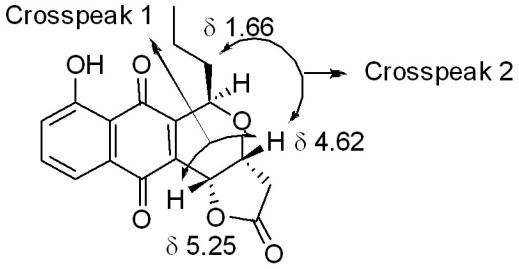

yz-b7
188.187
174.038
162.041
149.399
137.314
135.303
131.591
124.989
119.866
114.952
77.478
77.160
76.842
69.763
68.833
66.369
36.974
33.848
19.648
13.676
OH
O
O
O
O
O
Scheme 4, compound 1
f1 (ppm)



Scheme 4, compound 1







Scheme 4, compound 1