Supporting Information

for

Synthesis of Violaceic Acid and Related Compounds through Aryl Triazene

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Table of Contents

General Techniques

Pyrrolidine, CuBr·Me_2S, $Na_2S_2O_3$, and KO^{t}Bu were purchased from Acros, and used as received unless otherwise stated. NBS and ascorbic acid were purchased from Alfa-Aesar and used as received unless otherwise stated. EtOH was purchased from Decon labs and used as received unless otherwise stated. $NaNO_2$ was purchased from EMD Millipore and used as received unless otherwise stated. K_2CO_3, pyridine, I_2, Na_2SO_4, *tert*-BuOH, CH_2Cl_2, EtOAc, and hexanes were purchased from Fisher Chemical and used as received unless otherwise stated. Cu_2O and $Cu(NO_3)_2$ were purchased from J.T. Baker and used as received unless otherwise stated. 1,4-Diacetyl-piperazine-2,5-dione was purchased from Oakwood Chemical and used as received unless otherwise stated. HCl, KOH, TFA, $Pd_2(dba)_3$, 2-di-*tert*-butylphosphino- 2',4',6'-triisopropylbiphenyl, $(MeO)_2SO_2$ and TEMPO were purchased from Sigma-Aldrich and used as received unless otherwise stated. *p*-Acetamidobenzaldehyde was purchased from TCI chemical and used as received unless otherwise stated. All reactions were carried out with freshly distilled solvents under anhydrous conditions, unless otherwise noted. Glasswares were either dried with a heat gun or oven-dried (140 °C) prior to use. Moisture-sensitive reactions were performed under an inert atmosphere using a nitrogen line with standard Schlenk techniques unless otherwise stated. Unless specifically stated, the temperature of a water bath during the evaporation of organic solvents using a rotary evaporator was 40 ± 5 °C. All syringes in this study were dried in an oven at 80 °C and stored in a desiccator over Drierite©.

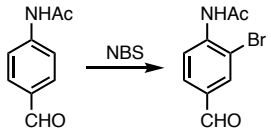
All reactions were monitored by thin-layer chromatography (TLC) carried out on 0.25-mm Merck silica gel plates (60F-254) using UV light (254 nm) for visualization or with 2.4% phosphomolybdic acid,1.4% phosphoric acid, and 5% sulfuric acid in water with heat as developing agents. TSI silica gel (230–400 mesh) was used for flash chromatography.

A rotary evaporator was connected to an air aspirator or a Büchi pump that produced a vacuum pressure of approximately 60 mmHg when it was connected to the evaporator. Solvents used for NMR spectroscopy were purchased from Cambridge Isotope Laboratories and $CDCl_3$ was stored over anhydrous K_2CO_3. NMR spectra were recorded on a Bruker Advance spectrometer at 300 megahertz (MHz), 400 MHz or 700 MHz and calibrated using either tetramethylsilane or residual solvent peaks as internal reference. The chemical shifts are given in parts per million (ppm) on a delta ( ) scale. The solvent peak was used a reference value, for ^{1}H NMR: $CHCl_3$ = 7.27 ppm, CD_2Cl_2 = 5.30 ppm, D_2O = 4.79, DMSO = 2.50 ppm; for ^{13}C NMR: $CDCl_3$ = 77.00 ppm, CD_2Cl_2 = 53.52, DMSO-d_6 = 49.10 ppm. The following abbreviations are used to indicate the multiplicities: s = singlet; d = doublet; t = triplet; q = quartet; qt = quintet; sex = sextet; sept = septet dd = doublet of doublets; ddd = doublet of doublet of doublets; dddd = doublet of doublet of doublet of doublets; dt = doublet of triplets; app = apparent; m = multiplet; br = broad. High-resolution mass spectra were recorded on a VG 7070 spectrometer. Low-resolution mass spectra [LCMS (ESI)] were recorded on a Shimadzu LCMS-2020. Infrared (IR) spectra were prepared as a thin film on KBr plate by dissolving the compound in CH_2Cl_2 and then evaporation the CH_2Cl_2.

Abbreviations

http://pubs.acs.org/paragonplus/submission/joceah/index.html

Synthesis



Preparation of *N*-(2-bromo-4-formylphenyl)acetamide (**12**). A one-necked 2-L round-bottom flask was equipped with a mechanical stirrer. NBS (28.6 g, 179 mmol) was added to the flask and dissolved in H_2O (800 mL). *p*-Acetamidobenzaldehyde (**11**) (20.1 g, 123 mmol) was added to the NBS solution and the reaction mixture was stirred at 500 rpm for 48 h. The precipitated solid was filtered through paper and purified by flash column chromatography (10 to 50% EtOAc in hexanes, 1000 mL silica gel) to afford the title compound (22.1 g, 74% yield) as a pale-yellow solid.

Data for *N*-(2-bromo-4-formylphenyl)acetamide (**12**): R_f = 0.43 (50% EtOAc in hexanes). For spectroscopic data, see Koo, S. B. ; Kim, H. E.; Lee, J. K. *Synth. Commun.* **2002**, *32*, 2275-2286.

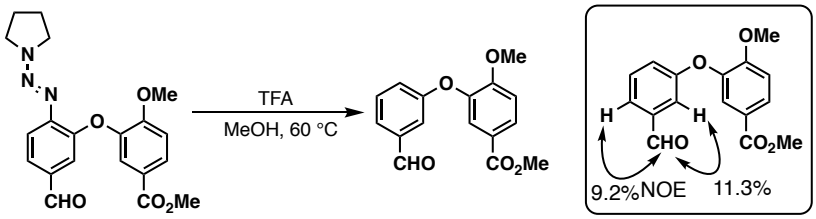
Preparation of (*E*)-3-bromo-4-(pyrrolidine-1-yldiazenyl)benzaldehyde (14). A 1-L round-bottom flask was equipped with a reflux condenser and a stir bar. *N*-(2-Bromo-4-formylphenyl)acetamide (**12**) (19.4 g, 80.1 mmol) was added to the flask and dissolved in EtOH/concentrated HCl (6:1, 280 mL). The reaction mixture was heated to reflux for 3 h. The resulting solution was cooled to room temperature, and concentrated under reduced pressure by rotary evaporation. The residue was dissolved in concentrated aqueous HCl (20 mL), and the resulting solution was cooled to -10 °C with an ice-MeOH bath. A cold solution of $NaNO_2$ (6.62 g, 95.9 mmol) in H_2O (120 mL) was added dropwise to HCl solution while keeping the temperature of the HCl solution below 0 °C. After addition was complete, the resulting solution was stirred for 10 min at -10 °C. Pyrrolidine (7.23 mL, 88.0 mmol) was dissolved in 1.1 M aqueous KOH (50 mL) and cooled in an ice-water bath. The pyrrolidine solution was added to HCl solution in one portion, and the reaction mixture was stirred for 10 min. Solid K_2CO_3 was cafefully added to the reaction mixture until pH~7. The precipitated solid was filtered through paper and purified by flash column chromatography (2.5 to 10% EtOAc in hexanes, 800 mL silica gel) to afford the title compound (16.9 g, 75% yield) as a yellow solid.

Data for (*E*)-3-bromo-4-(pyrrolidine-1-yldiazenyl)benzaldehyde (**14**): R_f = 0.26 (10% EtOAc in hexanes); m.p. = 99–100 °C; IR (CH_2Cl_2): 2974, 2870, 1689 (C=O), 1588, 1393, 1307, 818 cm^{-1}; ^1H NMR (300 MHz, 293K, $CDCl_3$, Figure S2) δ 9.88 (s, 1H), 8.32 (d, *J* = 1.8 Hz, 1H), 7.74 (dd, *J* = 8.4, 1.8 Hz, 1H), 7.55 (d, *J* = 8.4 Hz, 1H), 4.00 (br t, *J* = 6.3 Hz, 2H), 3.79 (br t, *J* = 6.3 Hz, 2H), 2.03–2.16 (m, 4H); ^{13}C NMR (75 MHz, 293K, $CDCl_3$, Figure S3) δ 190.5, 153.6, 135.3, 134.0, 129.3, 120.0, 118.5, 51.8, 47.7, 24.1, 23.6; HRMS (EI+) calcd. for $C_{11}H_{12}BrN_3O$ $[M]^+$ 281.0162, found 281.0164.

Preparation of methyl (*E*)-3-(5-formyl-2-(pyrrolidin-1-yldiazenyl)phenoxy)-4-methoxybenzoate (15). A one-necked 1-L round-bottom flask was equipped with a reflux condenser, a rubber septum that was equipped with a nitrogen inlet and a stir bar. (*E*)-3-bromo-4-(pyrrolidine-1-yldiazenyl)benzaldehyde (**14**) (4.51 g, 16.0 mmol), methyl 3-hydroxy-4-methoxy benzoate (**5**) (7.00 g, 38.4 mmol), $CuBr{\cdot}Me_2S$ (32.9 g, 160 mmol), K_2CO_3 (22.1 g, 160 mmol), degassed MeCN (160 mL) and pyridine (32 mL) were added consecutively to the 1-L flask at 25 °C. The reaction mixture was heated at reflux under N_2 for 48 h. After cooling to room temperature, the resulting mixture was diluted with

EtOAc (200 mL) and saturated aqueous NH_4Cl (500 mL). The resulting mixture was stirred for 30 min before being transferred to a separatory funnel. The aqueous layer was extracted with EtOAc (2 × 300 mL). The combined organic phases were washed with saturated aqueous NH_4Cl (2 × 500 mL), brine (2 × 500 mL), dried over anhydrous Na_2SO_4, filtered through cotton, and concentrated under reduced pressure by rotary evaporation. The crude product was purified by flash column chromatography (10 to 40% EtOAc in hexanes, 800 mL silica gel) to afford methyl the title compound (5.21 g, 85% yield) as a pale-yellow solid.

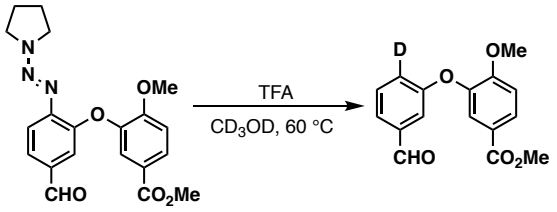
Data for methyl (*E*)-3-(5-formyl-2-(pyrrolidin-1-yldiazenyl)phenoxy)-4-methoxybenzoate (**15**): R_f = 0.38 (50% EtOAc in hexanes); m.p. = 144–145 °C; IR (CH_2Cl_2): 2971, 2882, 1686 (C=O), 1437, 1294, 1205, 1094, 1002, 898, 764 cm^{-1}; ^1H NMR (300 MHz, 293K, $CDCl_3$, Figure S4) δ 9.89 (s, 1H), 7.78 (dd, *J* = 8.4, 2.1 Hz, 1H), 7.64 (s, 2H), 7.51 (s, 1H), 7.44 (d, *J* = 2.1 Hz, 1H), 6.99 (d, *J* = 8.4 Hz, 1H), 3.95 (s, 3H), 3.88–3.95 (br s, 2H), 3.81 (s, 3H), 3.35–3.43 (br s, 2H), 1.94–1.99 (br m, 4H); ^{13}C NMR (75 MHz, 293K, $CDCl_3$, Figure S5) δ 190.9, 166.4, 154.0, 149.8, 147.5, 146.9, 133.7, 126.8, 125.6, 122.8, 121.3, 119.4, 118.5, 111.3, 56.1, 51.9, 51.3, 46.6, 23.8, 23.3; HRMS (ES+) calcd. for $C_{20}H_{21}N_3O_5Na$ $[M+Na]^+$ 406.1379, found 406.1369.



Formation of methyl 3-(3-formylphenoxy)-4-methoxybenzoate (16). A one-necked 25-mL round-bottom flask was equipped with a reflux condenser, a rubber septum that was equipped with a nitrogen inlet, and a stir bar. Methyl (*E*)-3-(5-formyl-2-(pyrrolidin-1-yldiazenyl)phenoxy)-4-methoxybenzoate (**15**) (19.0 mg, 50.0 μmol) and 5% v/v trifluoroacetic acid in MeOH (5 mL) were added to the 25-mL flask, and the reaction mixture was heated to 60 °C for 2 h. The resulting solution was cooled to room temperature and concentrated under reduced pressure by rotary evaporation. The crude product was purified by flash column chromatography (10 to 30% EtOAc in hexanes, 10 mL silica gel) to afford the title compound (12.0 mg, 84% yield) as a colorless oil.

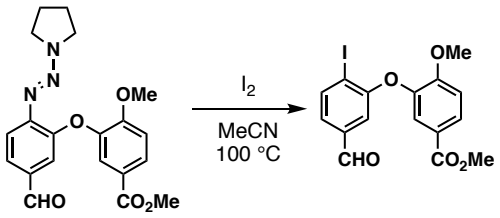
Data for methyl 3-(3-formylphenoxy)-4-methoxybenzoate (**16**): R_f = 0.52 (50% EtOAc in hexanes); IR (neat): 1717 (C=O), 1609, 1581, 1512, 1439, 1279, 1130, 1023, 900, 765 cm^{-1}; ^1H NMR (300 MHz, 293 K, $CDCl_3$, Figure S6 and Figure S7) δ 9.96 (s, 1H), 7.94 (dd, *J* = 8.7, 2.1 Hz, 1H), 7.72 (d, *J* = 2.1 Hz, 1H), 7.59 (ddd, *J* = 7.5, 1.2, 1.2 Hz, 1H), 7.49 (dd, *J* = 7.5, 7.5 Hz, 1H), 7.35 (dd, 1H, *J* = 2.4, 1.2 Hz), 7.25 (ddd, *J* = 7.5, 2.4, 1.2 Hz, 1H), 7.06 (d, *J* = 8.7 Hz, 1H), 3.89 (s, 3H), 3.88 (s, 3H); ^{13}C NMR (75 MHz, 293 K, $CDCl_3$, Figure S8) δ 191.7,

166.1, 158.5, 155.5, 143.4, 138.0, 130.3, 128.0, 124.6, 123.4, 123.2, 123.0, 116.3, 112.1, 56.1, 52.1; HRMS (EI+) calcd. for $C_{16}H_{14}O_5$ $[M]^+$ 286.0841, found 286.0851.



Formation of methyl 3-(3-formylphenoxy-6-*d*)-4-methoxybenzoate (*d*-16). A one-necked 25-mL round-bottom flask was equipped with a reflux condenser, a rubber septum that was equipped with a nitrogen inlet, and a stir bar. A solution of methyl (*E*)-3-(5-formyl-2-(pyrrolidin-1-yldiazenyl)phenoxy)-4-methoxybenzoate (**15**) (19.0 mg, 50.0 μmol) and 5% v/v trifluoroacetic acid in CD_3OD (5 mL) were added to the 25-mL round-bottom flask, and the reaction mixture was heated to 60 °C for 2 h. The resulting solution was cooled to room temperature and concentrated under reduced pressure by rotary evaporation. The crude product was purified by flash column chromatography (10 to 30% EtOAc in hexanes, 10 mL silica gel) to afford the title compound (12.0 mg, 84% yield) as a colorless oil.

Data for methyl 3-(3-formylphenoxy-6-*d*)-4-methoxybenzoate (***d*-16**): R_f = 0.52 (50% EtOAc in hexanes); ^{1}H NMR (300 MHz, 293 K, $CDCl_3$, Figure S9) δ 9.95 (s, 1H), 7.94 (dd, *J* = 8.7, 2.1 Hz, 1H), 7.72 (d, *J* = 2.1 Hz, 1H), 7.59 (dd, *J* = 7.5, 1.2 Hz, 1H), 7.49 (d, *J* = 7.5 Hz, 1H), 7.35 (d, 1H, *J* = 1.2 Hz), 7.06 (d, *J* = 8.7 Hz, 1H), 3.96 (s, 3H), 3.89 (s, 3H).



Preparation of methyl 3-(5-formyl-2-iodophenoxy)-4-methoxybenzoate (17). A 25-mL sealed tube was equipped with a stir bar. Methyl (*E*)-3-(5-formyl-2-(pyrrolidin-1-yldiazenyl)phenoxy)-4-methoxybenzoate (**15**) (959 mg, 2.50 mmol) was added to the sealed tube, and the tube was capped with a rubber septum. This tube was evacuated and backfilled with N_2 (this procedure was repeated three times). Degassed MeCN (5 mL) and I_2 (635 mg, 2.50 mmol) were added to the sealed tube, and the vessel was sealed with a Teflon cap. The reaction mixture was heated to 100 °C and stirred for 6 h. The resulting solution was then cooled to 25 °C and diluted with EtOAc (15 mL). The resulting mixture was passed through a short silica gel pad, eluting with 30% EtOAc in hexanes. The filtrate was concentrated under reduced pressure by rotary evaporation. The residue was dissolved in EtOAc (100 mL), washed with saturated aqueous $Na_2S_2O_3$ (100 mL), H_2O (100 mL), dried over anhydrous Na_2SO_4, filtered through cotton, and concentrated under reduced pressure by rotary evaporation. The crude product was purified by flash column chromatography (10 to 40% EtOAc in hexanes, 150 mL silica gel) to afford methyl 3-(5-formyl-2-iodophenoxy)-4-methoxybenzoate (804 mg, 78% yield) as a white solid.

Data for methyl 3-(5-formyl-2-iodophenoxy)-4-methoxybenzoate (**17**): R_f = 0.34 (30% EtOAc in hexanes); m.p. = 112–113 °C; IR (CH_2Cl_2): 1715 (C=O) 1609, 1512, 1438, 1279, 1131, 1021, 764 cm^{-1}; ^1H NMR (300 MHz, 293 K, $CDCl_3$, Figure S10) δ 9.83 (s, 1H), 8.05 (d, J = 8.1 Hz, 1H), 7.95 (dd, J = 8.7, 2.1 Hz, 1H), 7.70 (d, J = 2.1 Hz, 1H), 7.29 (dd, J = 8.1, 1.8 Hz, 1H), 7.06 (d, J = 8.7 Hz, 1H), 7.01 (d, J = 1.8 Hz, 1H), 3.87 (s, 3H), 3.86 (s, 3H); ^{13}C NMR (75 MHz, 293K, $CDCl_3$, Figure S11) δ 190.8, 166.0, 157.9, 155.2, 143.2, 140.6, 137.7, 128.4, 125.5, 123.3, 123.0, 114.4, 112.3, 95.3, 56.1, 52.1; HRMS (ES+) calcd. for $C_{16}H_{13}IO_5Na$ $[M+Na]^+$ 434.9705, found 434.9715.

Preparation of methyl 3-(5-formyl-2-methoxyphenoxy)-4-methoxybenzoate (1). A 10-mL sealed tube was equipped with a stir bar. Methyl 3-(5-formyl-2-iodophenoxy)-4-methoxybenzoate (**17**) (82.0 mg, 200 μmol), 2-di-*tert*-butylphosphino- 2',4',6'-triisopropylbiphenyl (4.30 mg, 10.0 μmol), $Pd_2(dba)_3$ (5.50 mg, 6.00 μmol), and KOH (45.0 mg, 800 μmol) were added consecutively to the sealed tube, and the tube capped with a rubber septum. This tube was evacuated and backfilled with N_2 (this procedure was repeated three times). Degassed H_2O/1,4-dioxane (1:1, 2 mL) were added to the solid mixture via syringe, and the tube was sealed with a Teflon cap. The reaction mixture was heated to 100 °C and stirred for 9 h. The resulting solution was cooled to room temperature and acidified with 0.1 *N* aqueous HCl until pH = 3. The resulting solution was transferred to a separatory funnel and extracted with EtOAc (3 × 10 mL). The combined organic extracts were washed with brine (20 mL), dried over anhydrous Na_2SO_4, filtered through cotton, and concentrated under reduced pressure by rotary evaporation. The crude residue was dissolved in acetone (5 mL), and K_2CO_3 (111 mg, 0.8 mmol) and $(MeO)_2SO_2$ (38 mL, 0.6 mmol) were added to the resulting solution in a one-necked 25-mL round-bottom flask that was equipped with a reflux condenser and a stir bar. The reaction mixture was heated at reflux under N_2 for 3 h. The resulting mixture was cooled to room temperature and filtered through cotton. The filtrate was concentrated under reduced pressure by rotary evaporation and the crude product was purified by flash column chromatography (10 to 40% EtOAc in hexanes, 12 mL silica gel) to afford the title compound (54.0 mg, 86% yield) as a pale-yellow foam.

Data for methyl 3-(5-formyl-2-methoxyphenoxy)-4-methoxybenzoate (**1**): R_f = 0.41 (50% EtOAc in hexanes); IR (CH_2Cl_2): 1715 (C=O), 1687(C=O), 1606, 1511, 1437, 1274, 1120, 1021, 765 cm^{-1}; ^1H NMR (300 MHz, 293 K, CD_2Cl_2, Figure S12) δ 9.77 (s, 1H), 7.86 (dd, J = 8.4, 2.1 Hz, 1H), 7.63 (dd, J = 8.4, 2.1 Hz, 1H), 7.51 (d, J = 2.1 Hz, 1H), 7.21 (d, J = 2.1 Hz, 1H), 7.13 (d, J = 8.4 Hz, 1H), 7.06 (d, J = 8.4 Hz, 1H), 3.96 (s, 3H), 3.89 (s, 3H), 3.81 (s, 3H); ^{13}C NMR (75 MHz, 293K, CD_2Cl_2, Figure S13) δ 190.7, 166.5, 156.0, 155.3, 147.2, 144.9,

130.7, 128.4, 127.5, 123.7, 121.2, 117.3, 112.58, 112.56, 56.8, 56.6, 52.4; HRMS (EI+) calcd. for $C_{17}H_{16}O_6$ $[M]^+$ 316.0947, found 316.0934.

Synthesis of violaceic acid. A 10-mL sealed reaction tube was equipped with a stir bar. Methyl 3-(5-formyl-2-iodophenoxy)-4-methoxybenzoate (**17**) (82 mg, 200 μmol), 2-di-*tert*-butylphosphino-2',4',6'-triisopropylbiphenyl (4.3 mg, 10 μmol), $Pd_2(dba)_3$ (5.5 mg, 6.0 μmol), and KOH (45 mg, 800 μmol) were added consecutively to the tube, and the tube was capped with a rubber septum. This tube was evacuated and backfilled with N_2 (this procedure was repeated three times). Degassed H_2O/1,4-dioxane (1:1, 2 mL) were added to the solid mixture via syringe, and the vessel was sealed with a Teflon cap. The reaction mixture was heated to 100 °C and stirred for 14 h. The reaction mixture was cooled to room temperature, and acidified with 0.1 *N* aqueous HCl until the pH = 3. The resulting solution was extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na_2SO_4, filtered through cotton, and concentrated under reduced pressure by rotary evaporation. The crude product was purified by flash chromatography (20 to 80% EtOAc in hexanes, 10 mL silica gel) to afford the title compound (60.0 mg, quantitative yield) as a pale-yellow solid.

Data for violaceic acid: R_f = 0.37 (EtOAc); m.p. = 222–223 °C; IR (KBr): 3398, 2935, 2840, 1685 (C=O), 1602, 1511, 1439, 1275, 1011, 909 cm^{-1}; ^1H NMR (300 MHz, 293 K, DMSO-d_6, Figure S14) δ 9.73 (s, 1H), 7.75 (dd, J = 8.7, 1.8 Hz, 1H), 7.61 (dd, J = 8.1, 2.1 Hz, 1H), 7.28 (d, J = 2.1 Hz, 1H), 7.25 (d, J = 8.7 Hz, 1H), 7.24 (d, J = 1.8 Hz, 1H), 7.13 (d, J = 8.1 Hz, 1H), 3.88 (s, 3H); ^{13}C NMR (75 MHz, 293 K, DMSO-d_6, Figure S15) δ 190.7, 166.5, 154.4, 153.8, 144.7, 144.3, 128.8, 127.9, 126.2, 123.3, 118.9, 118.7, 117.2, 112.6, 56.0; HRMS (EI+) calcd. for $C_{15}H_{12}O_6$ $[M]^+$ 288.0634, found 288.0648.

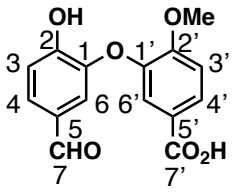


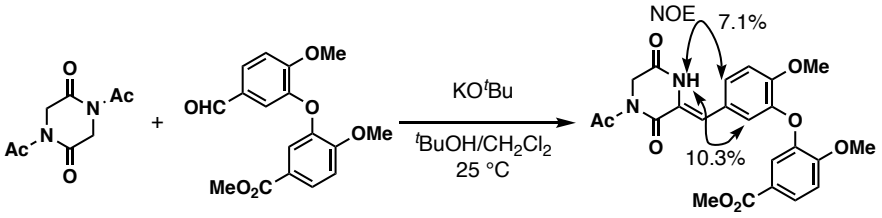
Table S1: ^{1}H NMR comparison for violaceic acid

Synthetic Violaceic Acid	Natural Violaceic Acid[4]
δ_H (mult, *J* (Hz))	δ_H (mult, *J* (Hz))
9.73 (s)	9.76 (s)
7.75 (dd, 8.7, 1.8)	7.78 (dd, 8.7, 1.9)
7.61 (dd, 8.1, 2.1)	7.64 (dd, 8.2, 2.2)
7.28 (d, 2.1)	7.32 (d, 2.2)
7.24 (d, 1.8)	7.28 (d, 1.9)
7.25 (d, 8.7)	7.26 (d, 8.7)
7.13 (d, 8.1)	7.16 (d, 8.2)
3.88 (s)	3.89 (s)

Table S2: ^{13}C NMR comparison for violaceic acid

Position	Synthetic Violaceic Acid	Natural Violaceic Acid[4]
	δ_C	δ_C
1	144.7	144.6
2	154.4	154.3
3	117.2	117.0
4	127.9	127.8
5	128.8	128.8
6	118.7	118.7
7	190.7	190.5
1'	144.3	144.3
2'	153.8	153.7
3'	112.6	112.4
4'	126.2	126.2
5'	123.3	123.2
6'	118.9	118.7
7'	166.5	166.4
-OMe	56.0	55.9

Preparation of methyl (*Z*)-3-(5-((4-acetyl-3,6-dioxopiperazin-2-ylidene)methyl)-2-methoxyphenoxy)-4-methoxybenzoate (25).



A one-necked 5-mL round-bottom flask was equipped with a rubber septum that was connected to a nitrogen inlet and a stir bar. Methyl 3-(5-formyl-2-methoxyphenoxy)-4-methoxybenzoate (**1**) (11.6 mg, 36.7 μmol), 1,4-diacetyl-piperazine-2,5-dione (**24**) (8.27 mg, 41.7 μmol) and CH_2Cl_2 (300 μL) were added to the 5-mL flask under N_2. A solution of KO^{t}Bu (5.1 mg, 45.3 μmol) in *tert*-BuOH (150 μL) was added to a resulting mixture, and the reaction mixture was stirred at the room temperature for 2 h. The resulting solution was then cooled in an ice-water bath to 0 °C, and neutralized with saturated aqueous NH_4Cl solution (2.0 mL). The resulting solution was transferred to a separatory funnel, and extracted with CH_2Cl_2 (2 × 2 mL). The combined organic layers were washed with brine (5 mL), dried over anhydrous Na_2SO_4, filtered through cotton, and concentrated under reduced pressure by rotary evaporation. The crude product was purified by flash column chromatography (20 to 50% EtOAc in hexanes, 10 mL silica gel) to afford the title compound (13.0 mg, 75%) as a pale-yellow oil. The geometry of the olefin was determined by an NOE experiment (Figure S17).

Data for compound methyl (*Z*)-3-(5-((4-acetyl-3,6-dioxopiperazin-2-ylidene)methyl)-2-methoxyphenoxy)-4-methoxybenzoate (**25**): R_f = 0.32 (60% EtOAc in hexanes); IR (CH_2Cl_2): 3291 (N-H), 3010, 2925, 2850, 1702 (C=O), 1630, 1606, 1513, 1438, 1368, 1272, 1209, 1133, 1099, 1022, 765 cm^{-1}; ^{1}H NMR (400 MHz, 293 K, DMSO-d_6, Figure S16) δ 7.73 (dd, J = 8.4, 2.0 Hz, 1H), 7.54 (dd, J = 8.8, 2.0 Hz, 1H), 7.35 (d, J = 2.0 Hz, 1H), 7.30 (d, J = 8.4 Hz, 1H), 7.26 (d, J = 8.8 Hz, 1H), 7.13 (d, J = 2.0 Hz, 1H), 6.95 (s, 1H), 4.37 (s, 2H), 3.95 (s, 3H), 3.82 (s, 3H), 3.78 (s, 3H), 2.51 (s, 3H); ^{13}C NMR (75 MHz, 293 K, $CDCl_3$, Figure S18) δ 172.5, 166.3, 162.7, 160.2, 154.6, 151.1, 146.4, 144.4, 127.1, 125.2, 124.6, 124.5, 123.2, 120.6, 119.5, 118.2, 113.1, 111.9, 56.3, 56.2, 52.1, 46.0, 27.1; HRMS (ES+) calcd. for $C_{23}H_{22}N_2O_8$ $[M+Na]^+$ 477.1274, found 477.1228.

Attempts to prepare methyl 3-(5-formyl-2-methoxyphenoxy)-4-methoxybenzoate (1) from methyl (*E*)-3-(5-formyl-2-(pyrrolidin-1-yldiazenyl)phenoxy)-4-methoxybenzoate (15) in one step

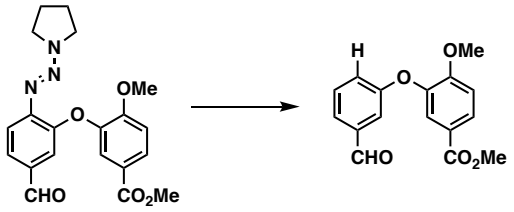
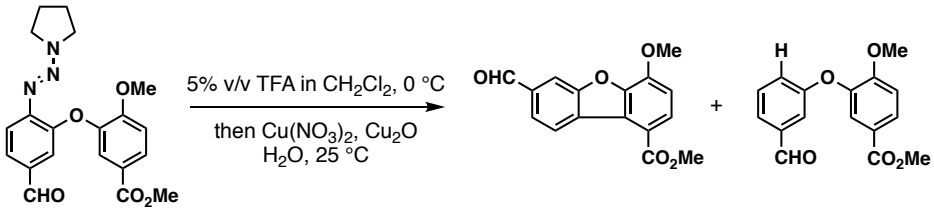


Table S3: Failed examples of acid-mediated methoxylation

Entry	Conditions	Isolated yield (Yield based on recovered starting material)
1	10% TFA in MeOH, reflux, O_2 atmosphere, 12 h	88%
2	Dowex 50WX8-200, *t*-BuOH/H_2O, reflux, 3 h	19% (86%)
3	5% TFA in CH_2Cl_2, 0 °C; then Cu_2O (2.8 equiv), $Cu(NO_3)_2$ (30 equiv), H_2O, 23 °C, 0.5 h	68%

Preparation of methyl 7-formyl-4-methoxydibenzo[*b*,*d*]furan-1-carboxylate (18): A one-necked 25-mL round-bottom flask was equipped with a stir bar. A solution of 5% trifluoroacetic acid v/v in CH_2Cl_2 (5 mL) was added to the flask and cooled in an ice-water bath to 0 °C. Methyl (*E*)-3-(5-formyl-2-(pyrrolidin-1-yldiazenyl)phenoxy)-4-methoxybenzoate (**15**) (19 mg, 49.5 μmol) was added to the solution and stirred at 0 °C. After consumption of methyl (*E*)-3-(5-formyl-2-(pyrrolidin-1-yldiazenyl)phenoxy)-4-methoxybenzoate (**15**) was observed by TLC analysis, the solution was concentrated under reduced pressure by rotary evaporation. A solution of $Cu(NO_3)_2$ (0.35 g, 1.49 mmol) in H_2O (5 mL) was added to the residue, and then Cu_2O (0.006 g, 41.9 μmol) was added to the resulting solution at 25 °C. After stirring at the same temperature for 10 min, the resulting mixture was extracted with CH_2Cl_2 (3 × 5 mL). The organic extracts were combined, washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue was purified by flash chromatography (10 to 40% EtOAc in hexanes, 8 mL silica gel) to afford the inseparable mixture of methyl 7-formyl-4-methoxydibenzo[*b*,*d*]furan-1-carboxylate (**18**) and methyl 3-(3-formylphenoxy)-4-methoxybenzoate (**16**) as a white solid (9.65 mg, 68% yield)..



Data for methyl 7-formyl-4-methoxydibenzo[*b*,*d*]furan-1-carboxylate (**18**): R_f = 0.52 (50% EtOAc in hexanes); ^{1}H NMR (300 MHz, 293 K, $CDCl_3$, Figure S19) δ 10.17 (s, 1H, CHO), 9.09 (d, *J* = 8.1 Hz, 1H, Ar), 8.14 (d, *J* = 1.5 Hz, 1H, Ar), 8.07 (d, *J* = 8.4 Hz, 1H, Ar), 7.93 (dd, *J* = 8.1, 1.5 Hz, 1H, Ar), 7.09 (d, *J* = 8.4 Hz, 1H, Ar), 4.16 (s, 3H), 4.05 (s, 3H); HRMS (ESI+) calcd. for $C_{16}H_{12}O_5$ $[M]^+$ 285.07575, found 285.07657.

Studies into mechanism of dibenzofuran formation

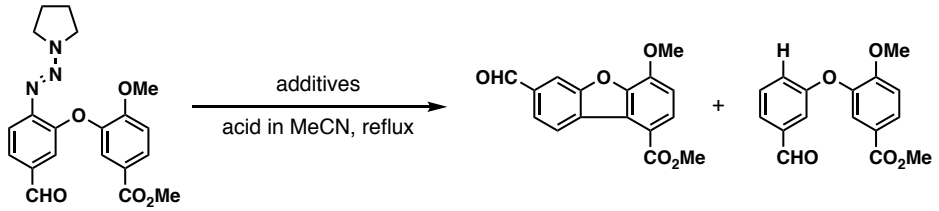


Table S4: Investigative experiments into the mechanism of triazene reaction

entry	acid	additive	equivalents	yield (%)	ratio (**16:18**)
1	TFA	none	0	40	1:1
2	TFA	pyrrolidine	5	40	6:1
3	TFA	TEMPO	3	5	1:1
4	ascorbic acid	none	3	54	4:1

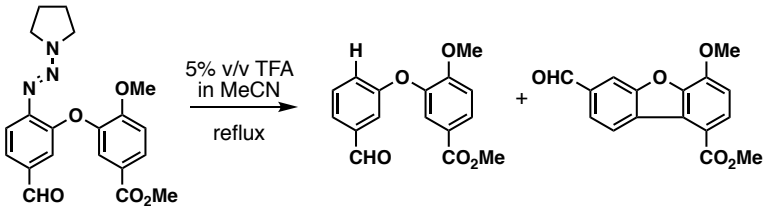


Table S4, Entry 1. Methyl (*E*)-3-(5-formyl-2-(pyrrolidin-1-yldiazenyl)phenoxy)-4-methoxybenzoate (**15**) (50.0 mg, 0.130 mmol) and 5% v/v trifluoroacetic acid in MeCN (5 mL) were added to a 20-mL scintillation vial that was equipped with a stir bar, and the resulting solution was heated to reflux for 2.5 h. The reaction mixture was diluted with Et_2O (10 mL) and transferred to a 30-mL separatory funnel. The organic layer was washed with saturated aqueous $NaHCO_3$ (10 mL) and H_2O (10 mL). The organic extract was dried over Na_2SO_4, filtered through cotton, concentrated under reduced pressure by a rotary evaporator. The crude residue was purified by flash column chromatography (10 to 40% EtOAc in hexanes, 3 mL silica gel) to afford the inseparable mixture of methyl 7-formyl-4-methoxydibenzo[*b*,*d*]furan-1-carboxylate (**18**) and methyl 3-(3-formylphenoxy)-4-methoxybenzoate (**16**) as a white solid (15.0 mg, 40% yield).

Data for methyl 7-formyl-4-methoxydibenzo[*b*,*d*]furan-1-carboxylate (**18**): R_f = 0.52 (50% EtOAc in hexanes); ^{1}H NMR (300 MHz, 293 K, $CDCl_3$, Figure S20) δ 10.19 (s, 1H, CHO), 9.13 (d, *J* = 8.1 Hz, 1H, Ar), 8.17

(d, J = 1.5 Hz, 1H, Ar), 8.10 (d, J = 8.4 Hz, 1H, Ar), 7.96 (dd, J = 8.1, 1.5 Hz, 1H, Ar), 7.12 (d, J = 8.4 Hz, 1H, Ar), 4.18 (s, 3H), 4.07 (s, 3H).

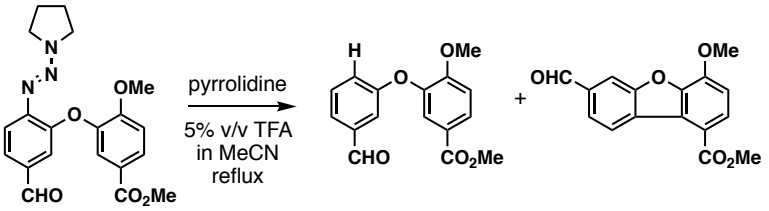


Table S4, Entry 2. Methyl (*E*)-3-(5-formyl-2-(pyrrolidin-1-yldiazenyl)phenoxy)-4-methoxybenzoate (**15**) (50.0 mg, 0.130 mmol), 5% v/v trifluoroacetic acid in MeCN (5 mL) and pyrrolidine (53.5 μL, 0.652 mmol) were added to a 20-mL scintillation vial that was equipped with a stir bar, and the reaction mixture heated to reflux for 2.5 h. The reaction mixture was diluted with Et_2O (10 mL) and transferred to a 30-mL separatory funnel. The organic layer was washed with saturated aqueous $NaHCO_3$ (10 mL) and H_2O (10 mL). The organic extract was dried over Na_2SO_4, filtered through cotton, concentrated under reduced pressure by a rotary evaporator. The crude residue was purified by flash column chromatography (10 to 40% EtOAc in hexanes, 3 mL silica gel) to afford the inseparable mixture of methyl 7-formyl-4-methoxydibenzo[*b*,*d*]furan-1-carboxylate (**18**) and methyl 3-(3-formylphenoxy)-4-methoxybenzoate as a white solid (**16**) (14.6 mg, 40% yield)

Data for methyl 7-formyl-4-methoxydibenzo[*b*,*d*]furan-1-carboxylate (**18**): R_f = 0.52 (50% EtOAc in hexanes); ^{1}H NMR (300 MHz, 293 K, $CDCl_3$, Figure S21) δ 10.16 (s, 1H, CHO), 9.09 (d, J = 8.1 Hz, 1H, Ar), 8.14 (d, J = 1.5 Hz, 1H, Ar), 8.07 (d, J = 8.4 Hz, 1H, Ar), 7.93 (dd, J = 8.1, 1.5 Hz, 1H, Ar), 7.09 (d, J = 8.4 Hz, 1H, Ar), 4.15 (s, 3H), 4.04 (s, 3H).

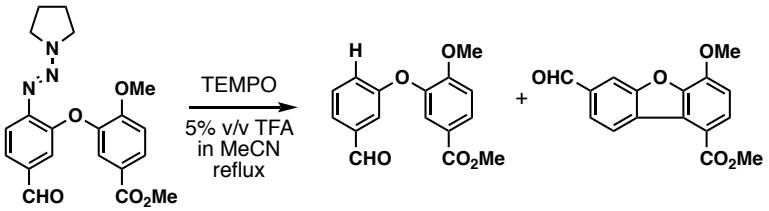


Table S4, Entry 3. Methyl (*E*)-3-(5-formyl-2-(pyrrolidin-1-yldiazenyl)phenoxy)-4-methoxybenzoate (**15**) (50.0 mg, 0.130 mmol), 5% v/v trifluoroacetic acid in MeCN (5 mL) and TEMPO (61.1 mg, 0.391 mmol) were added to a 20-mL scintillation vial that was equipped with a stir bar, and the reaction mixture heated to reflux for 2.5 h. The reaction mixture was diluted with Et_2O (10 mL) and transferred to a 30-mL separatory funnel. The organic layer was washed with saturated aqueous $NaHCO_3$ (10 mL) and H_2O (10 mL). The organic extract was dried over Na_2SO_4, filtered through cotton, concentrated under reduced pressure by a rotary evaporator. The crude residue was purified by flash column chromatography (10 to 40% EtOAc in hexanes, 3 mL silica gel) to afford the inseparable mixture of methyl 7-formyl-4-methoxydibenzo[*b*,*d*]furan-1-carboxylate (**18**) and methyl 3-(3-formylphenoxy)-4-methoxybenzoate (**16**) as a white solid (1.87 mg, 5% yield)

Data for methyl 7-formyl-4-methoxydibenzo[*b*,*d*]furan-1-carboxylate (**18**): R_f = 0.52 (50% EtOAc in hexanes); ^{1}H NMR (300 MHz, 293 K, $CDCl_3$, Figure S22) δ 10.17 (s, 1H, CHO), 9.09 (d, *J* = 8.1 Hz, 1H, Ar), 8.14 (d, *J* = 1.5 Hz, 1H, Ar), 8.07 (d, *J* = 8.4 Hz, 1H, Ar), 7.93 (dd, *J* = 8.1, 1.5 Hz, 1H, Ar), 7.09 (d, *J* = 8.4 Hz, 1H, Ar), 4.16 (s, 3H), 4.05 (s, 3H).

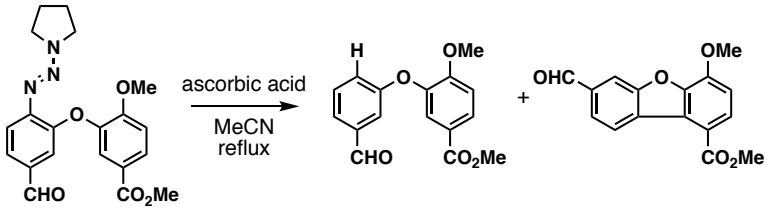


Table S4, Entry 4. Methyl (*E*)-3-(5-formyl-2-(pyrrolidin-1-yldiazenyl)phenoxy)-4-methoxybenzoate (**15**) (50.0 mg, 0.130 mmol), ascorbic acid (64.3 mg, 0.391 mmol), and MeCN (5 mL) were added to a 20-mL scintillation vial that was equipped with a stir bar. The reaction mixture was heated to reflux for 7 h. After, the reaction mixture was diluted with EtOAc (10 mL) and transferred to a 30-mL separatory funnel. The organic layer was washed with saturated aqueous $NaHCO_3$ (10 mL) and H_2O (10 mL). The organic extract was dried over Na_2SO_4, filtered through cotton, concentrated under reduced pressure by a rotary evaporator. The crude residue was purified by flash column chromatography (10 to 40% EtOAc in hexanes, 3 mL silica gel) to afford the inseparable mixture of methyl 7-formyl-4-methoxydibenzo[*b*,*d*]furan-1-carboxylate (**18**) and methyl 3-(3-formylphenoxy)-4-methoxybenzoate (**16**) as a white solid (20.8 mg, 54% yield).

Data for methyl 7-formyl-4-methoxydibenzo[*b*,*d*]furan-1-carboxylate (**18**): R_f = 0.52 (50% EtOAc in hexanes); ^{1}H NMR (300 MHz, 293 K, $CDCl_3$, Figure S23) δ 10.17 (s, 1H, CHO), 9.09 (d, *J* = 8.1 Hz, 1H, Ar), 8.14 (d, *J* = 1.5 Hz, 1H, Ar), 8.07 (d, *J* = 8.4 Hz, 1H, Ar), 7.93 (dd, *J* = 8.1, 1.5 Hz, 1H, Ar), 7.09 (d, *J* = 8.4 Hz, 1H, Ar), 4.16 (s, 3H), 4.05 (s, 3H).

3. NMR spectra

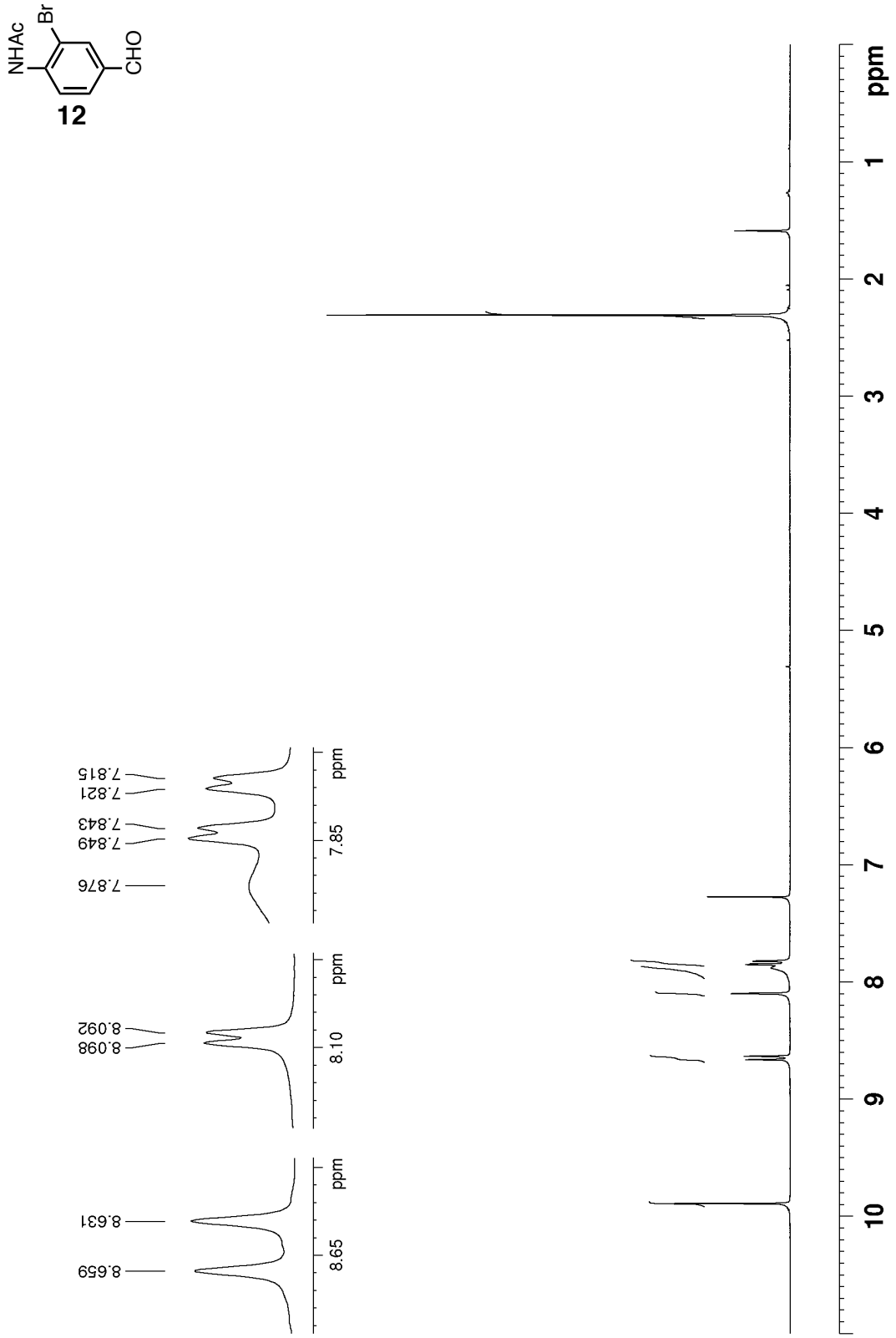


Figure S1. ^{1}H NMR spectrum of *N*-(2-bromo-4-formylphenyl)acetamide (**12**) ($CDCl_3$, 293 K, 300 MHz)

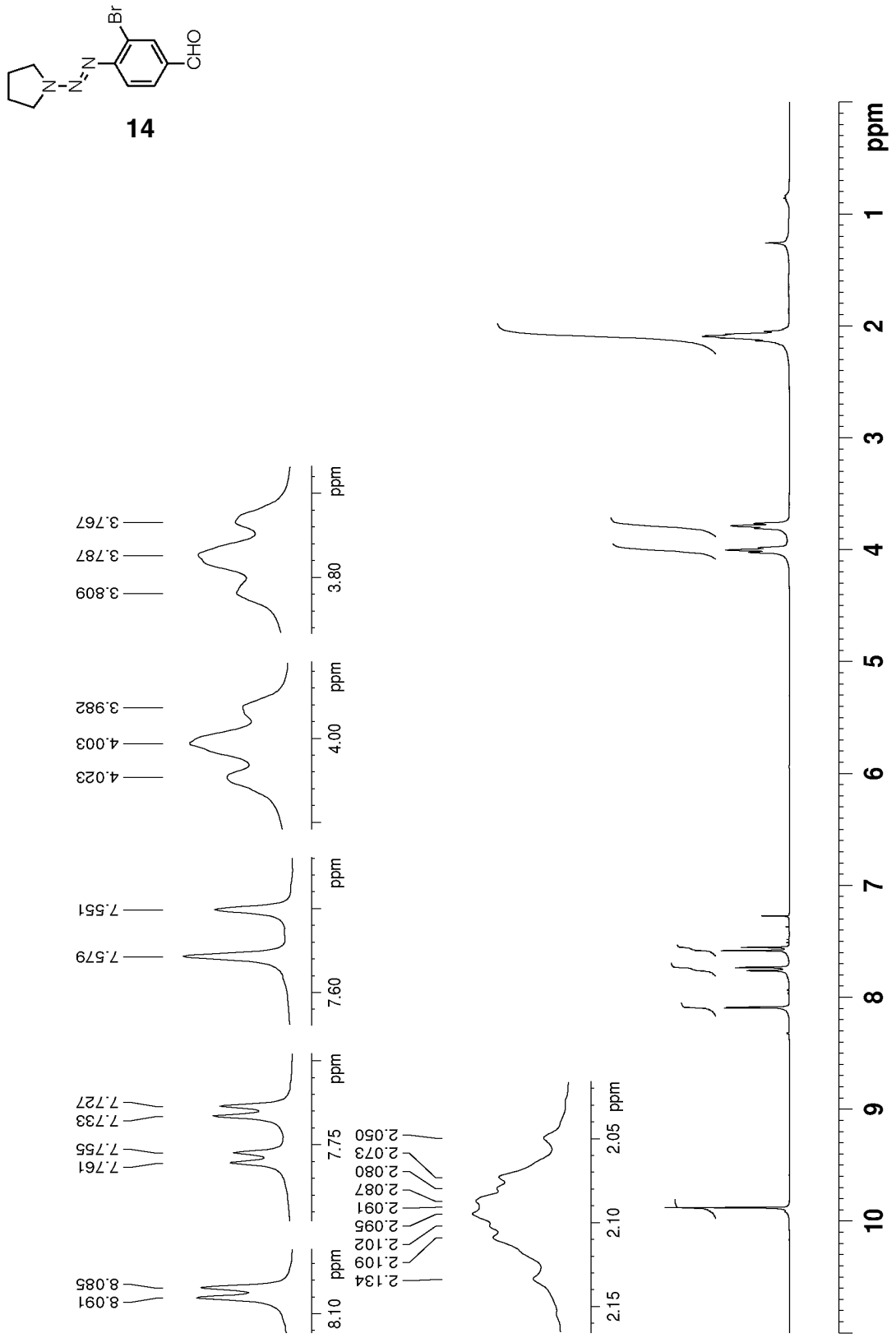


Figure S2. ^{1}H NMR spectrum of (*E*)-3-bromo-4-(pyrrolidine-1-yldiazenyl)benzaldehyde (**14**) ($CDCl_3$, 293 K, 300 MHz)

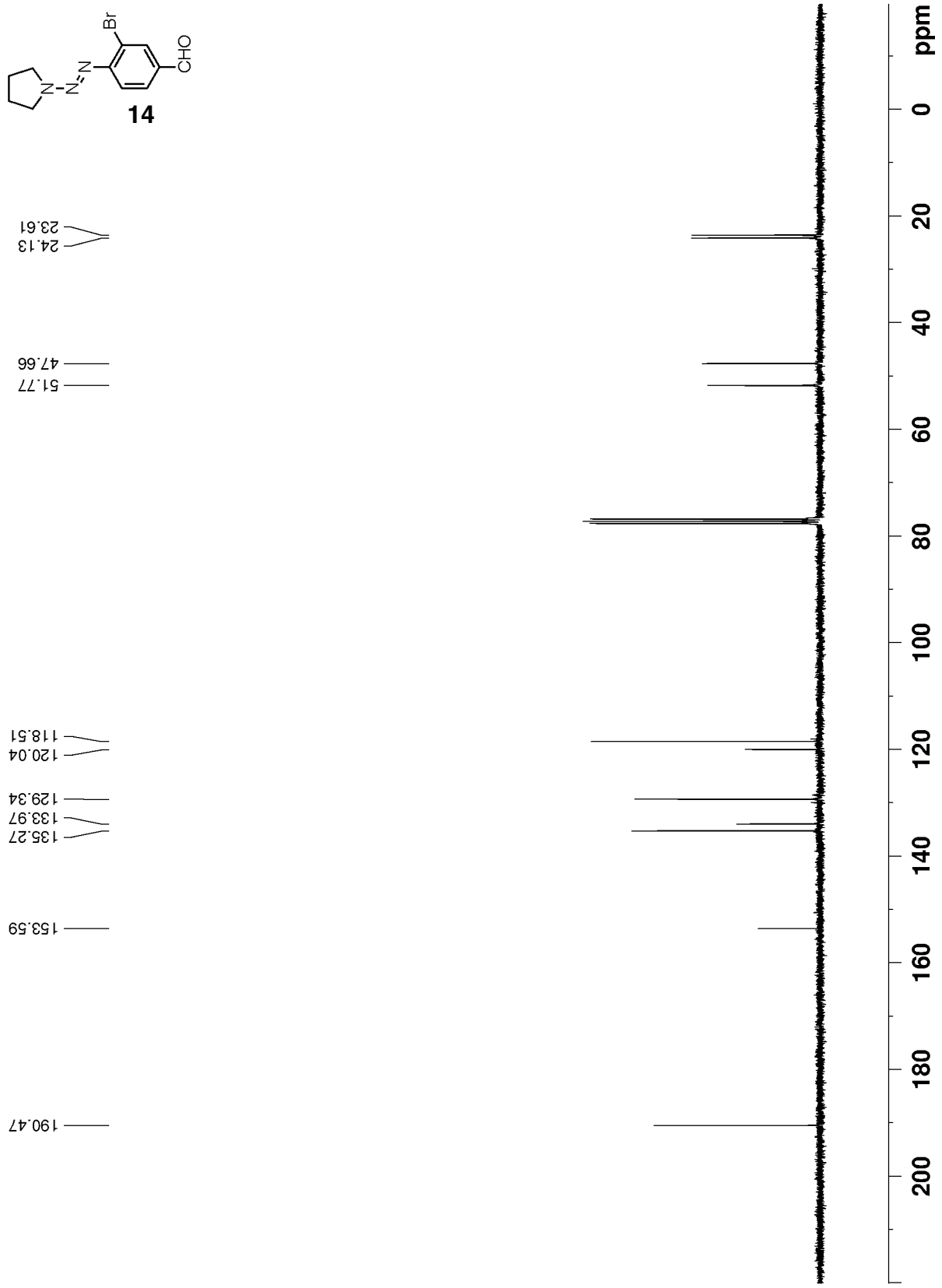


Figure S3. ^{13}C NMR spectrum of (*E*)-3-bromo-4-(pyrrolidine-1-yldiazenyl)benzaldehyde (**14**) ($CDCl_3$, 293 K, 75 MHz)

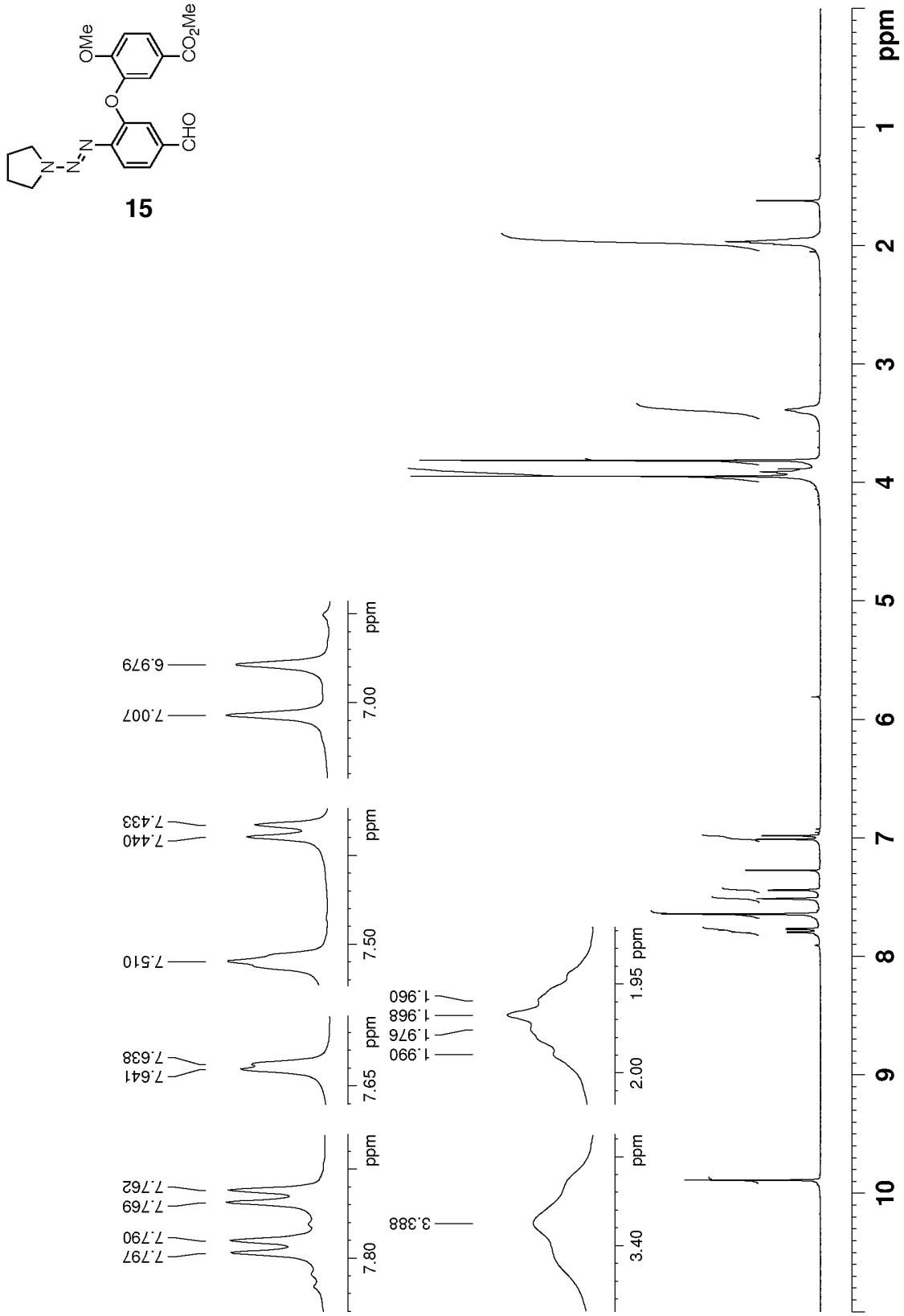


Figure S4. ^{1}H NMR spectrum of (*E*)-3-(5-formyl-2-(pyrrolidin-1-yldiazenyl)phenoxy)-4-methoxybenzoate (**15**) ($CDCl_3$, 293 K, 300 MHz)

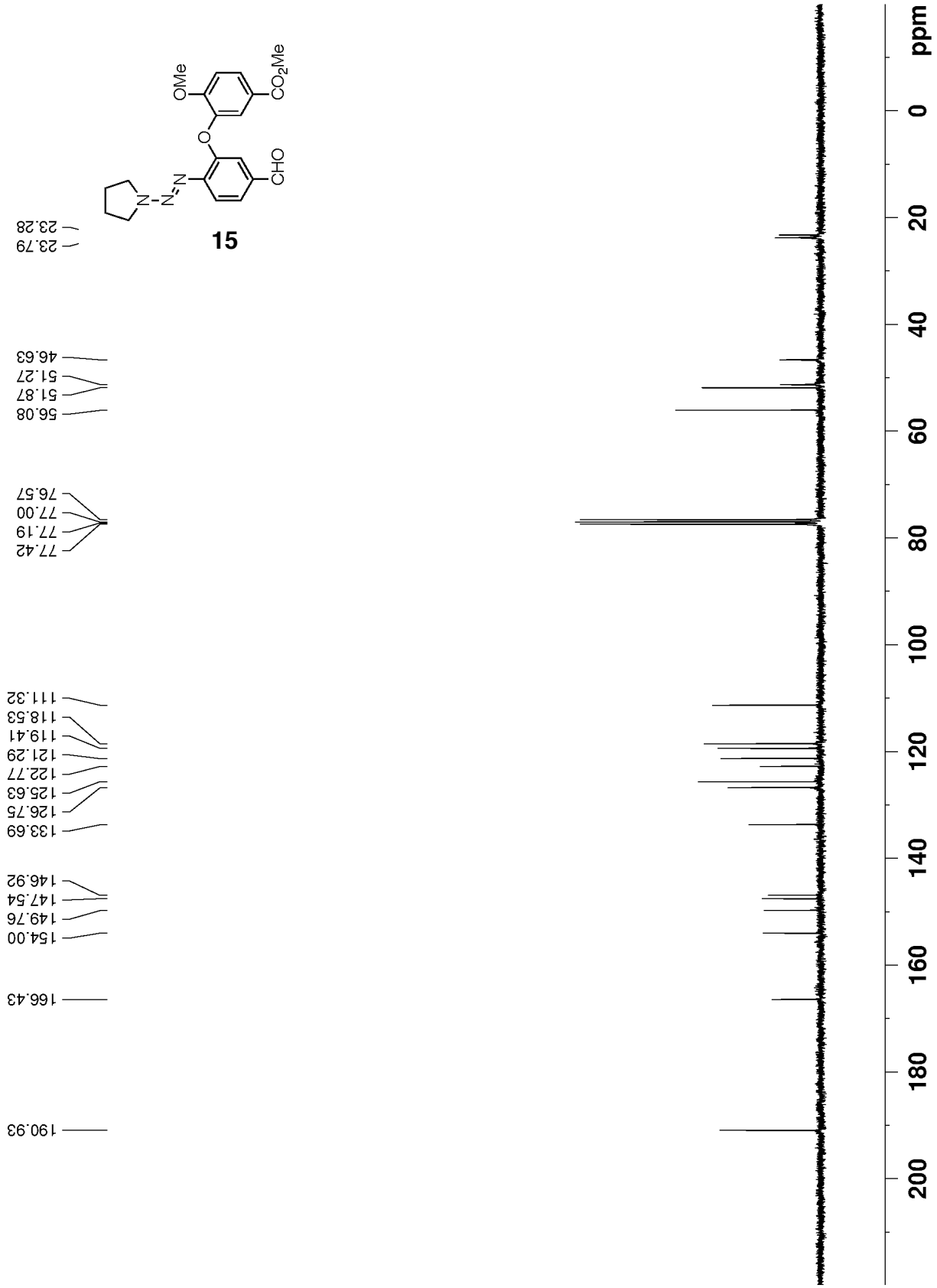


Figure S5. ^{13}C NMR spectrum of (*E*)-3-(5-formyl-2-(pyrrolidin-1-yldiazenyl)phenoxy)-4-methoxybenzoate (**15**) ($CDCl_3$, 293 K, 75 MHz)

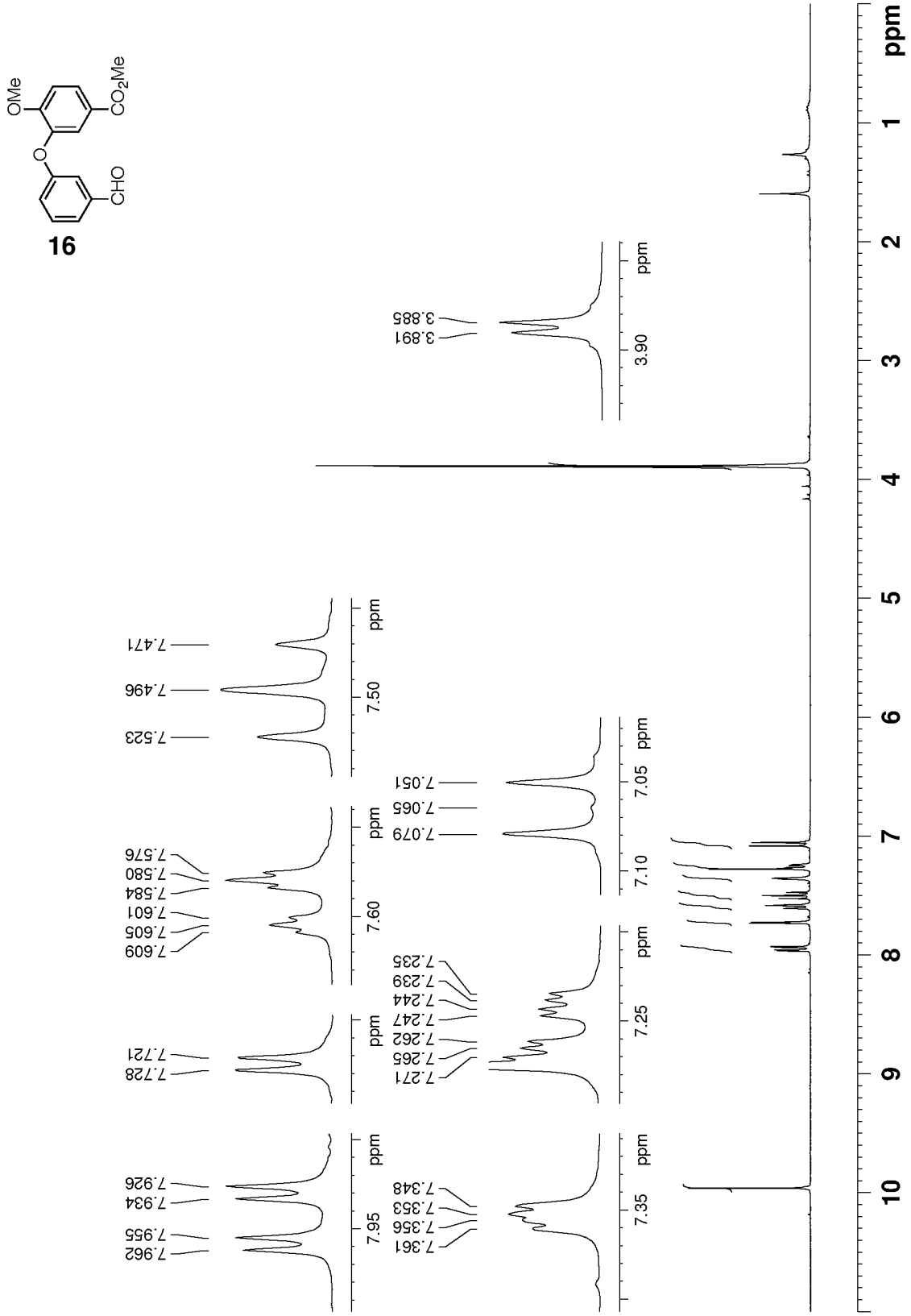


Figure S6. ^{1}H NMR spectrum of 1-methyl 3-(3-formylphenoxy)-4-methoxybenzoate (**16**) ($CDCl_3$, 293 K, 300MHz)

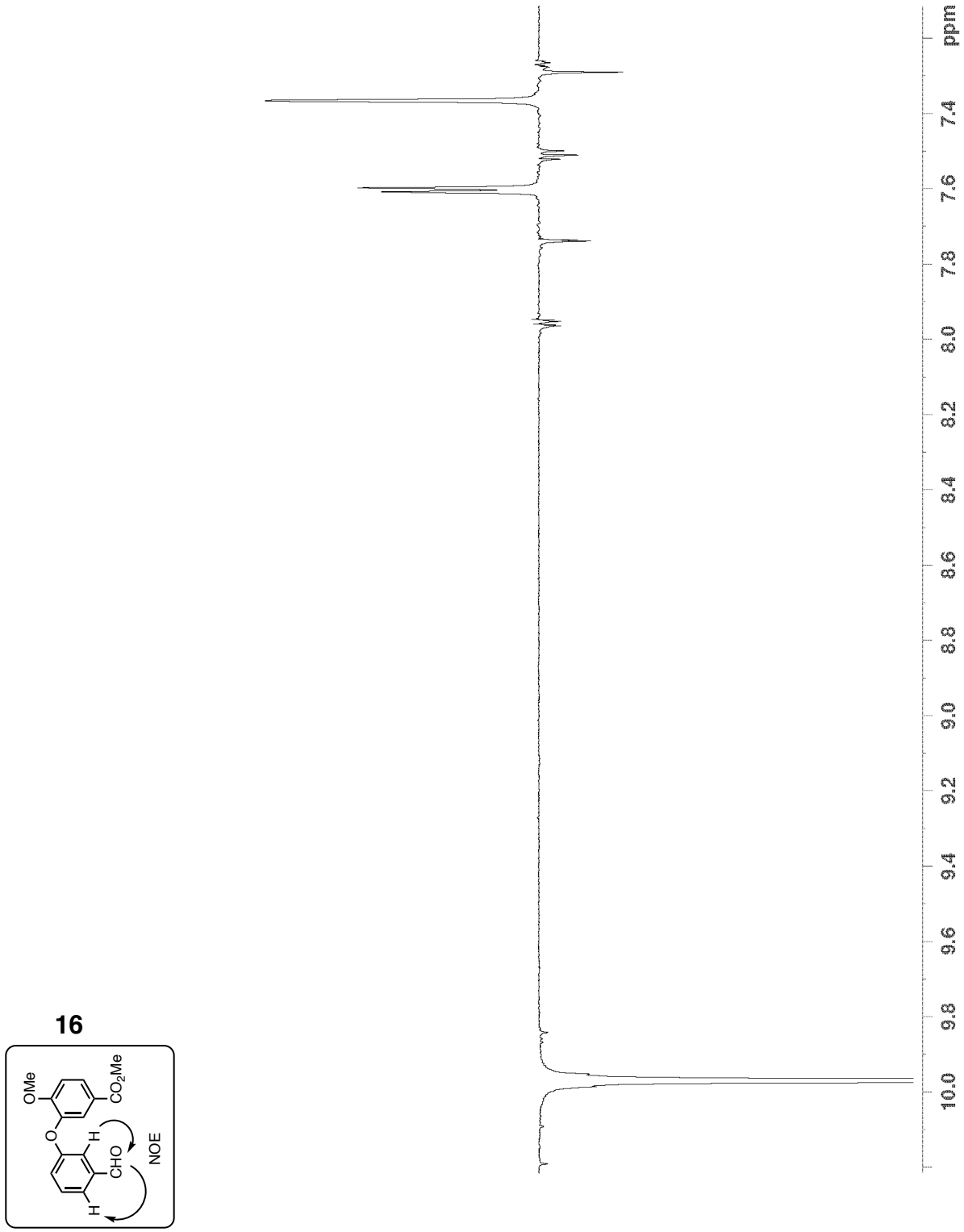


Figure S7. NOE Difference NMR spectrum of methyl 3-(3-formylphenoxy)-4-methoxybenzoate (**16**) ($CDCl_3$, 293 K, 700 MHz)

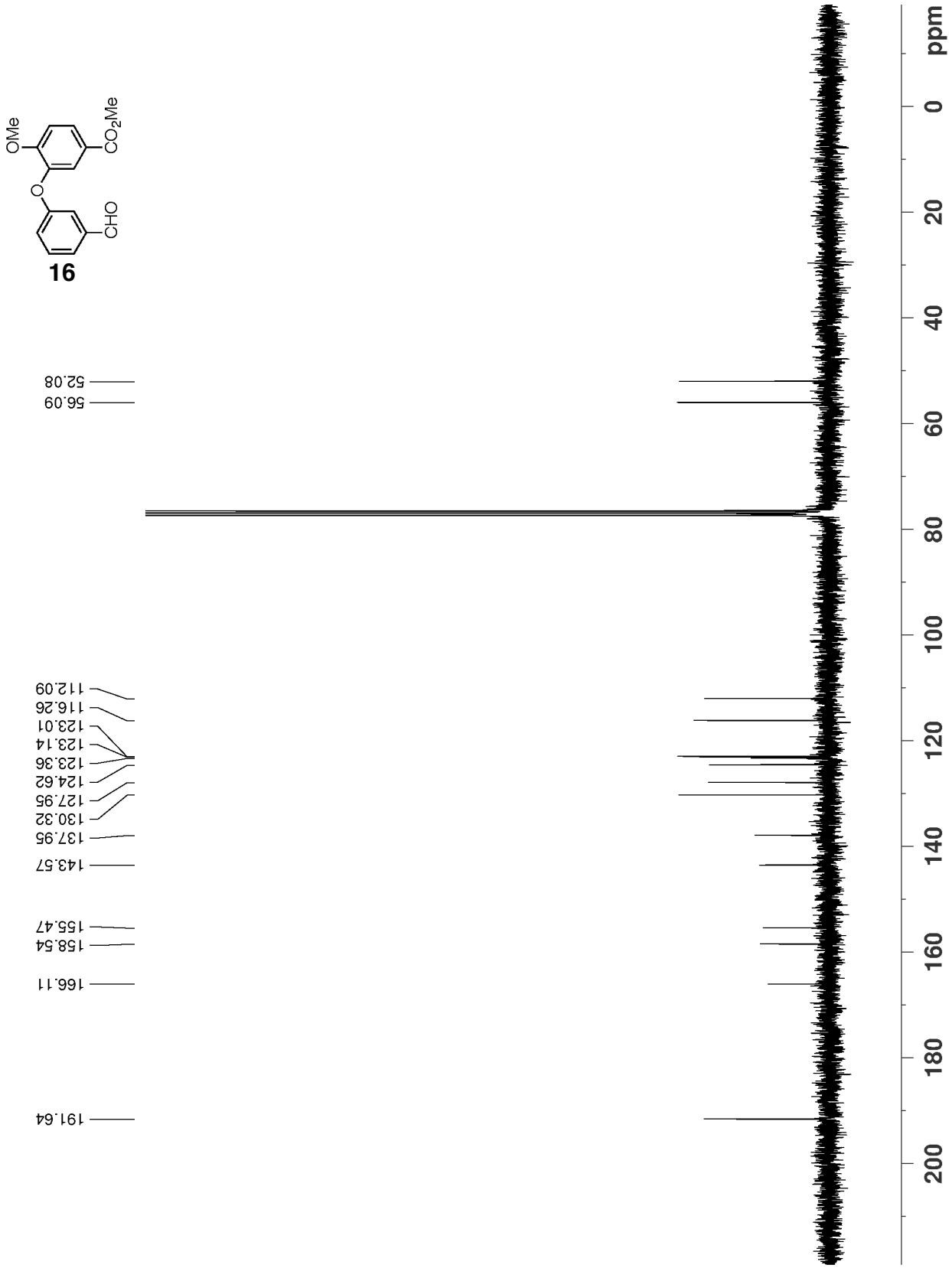


Figure S8. ^{13}C NMR spectrum of methyl 3-(3-formylphenoxy)-4-methoxybenzoate (**16**) ($CDCl_3$, 293 K, 75 MHz)

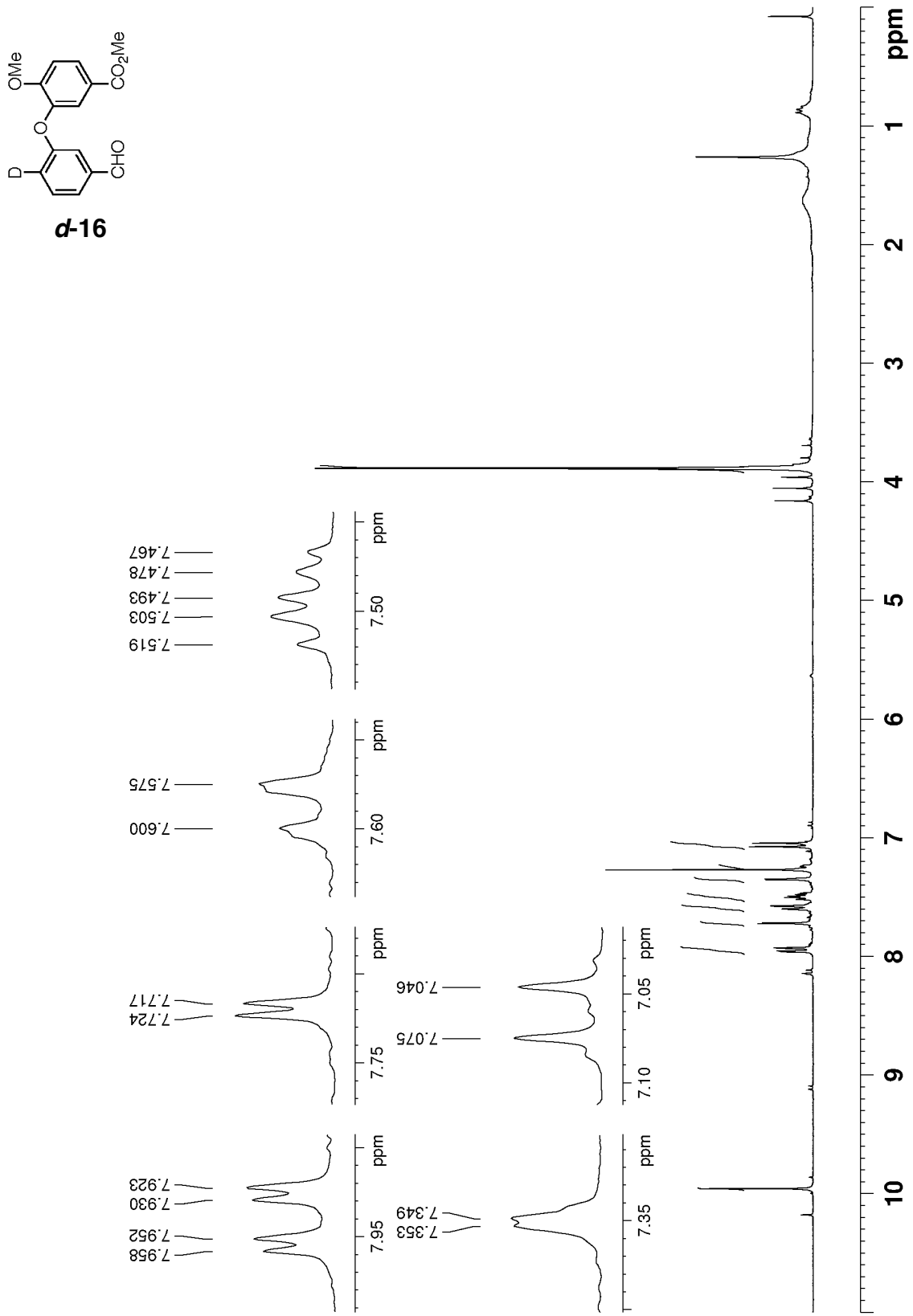


Figure S9. ^{1}H NMR spectrum of methyl 3-(3-formylphenoxy-6-*d*)-4-methoxybenzoate (***d*-16**) ($CDCl_3$, 293 K, 300 MHz)

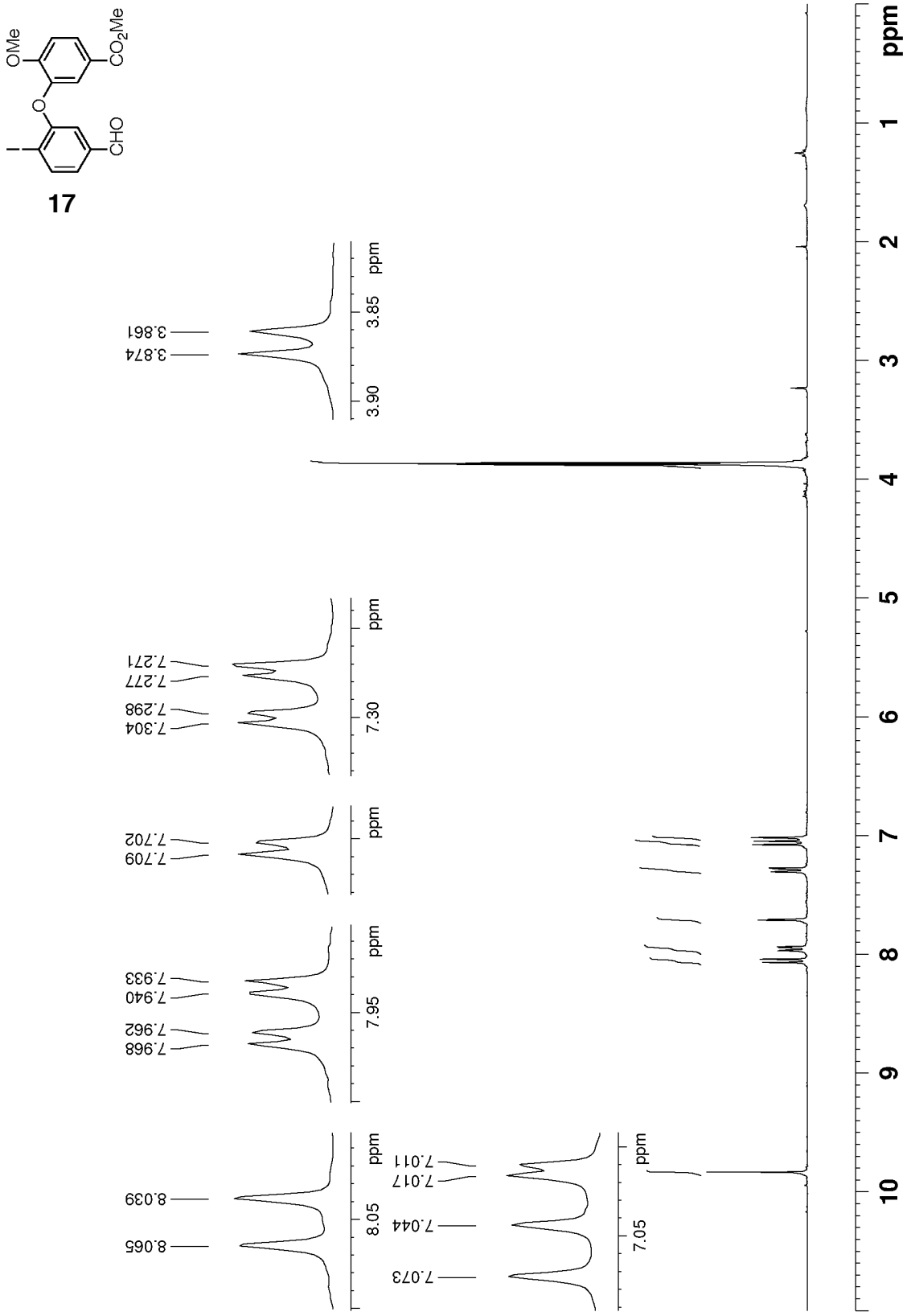


Figure S10. ^{1}H NMR spectrum of methyl 3-(5-formyl-2-iodophenoxy)-4-methoxybenzoate (**17**) ($CDCl_3$, 293 K, 300 MHz)

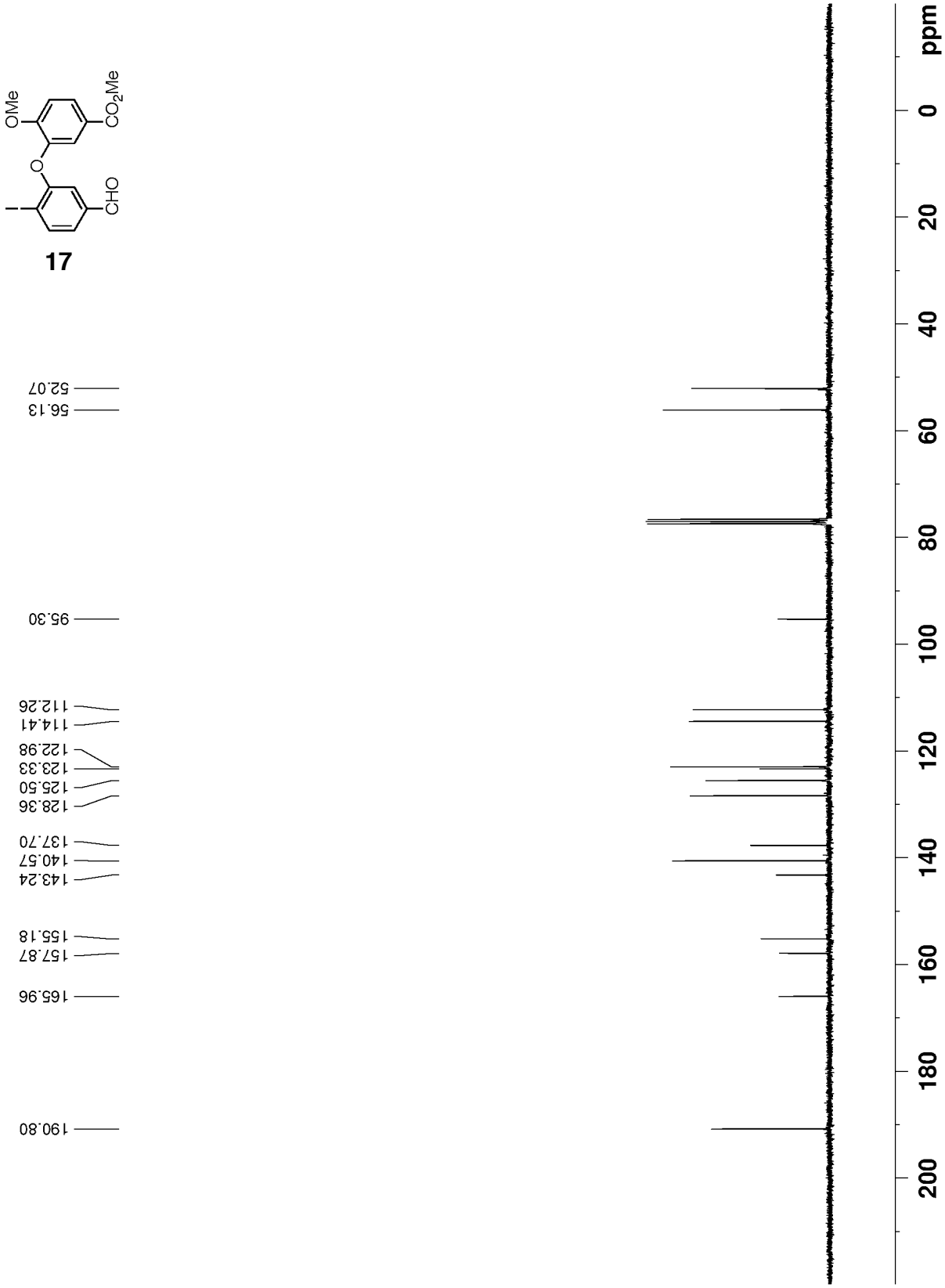
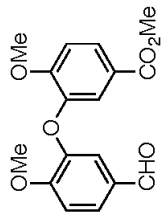


Figure S11. ^{13}C NMR spectrum of methyl 3-(5-formyl-2-iodophenoxy)-4-methoxybenzoate (**17**) ($CDCl_3$, 293 K, 75 MHz)



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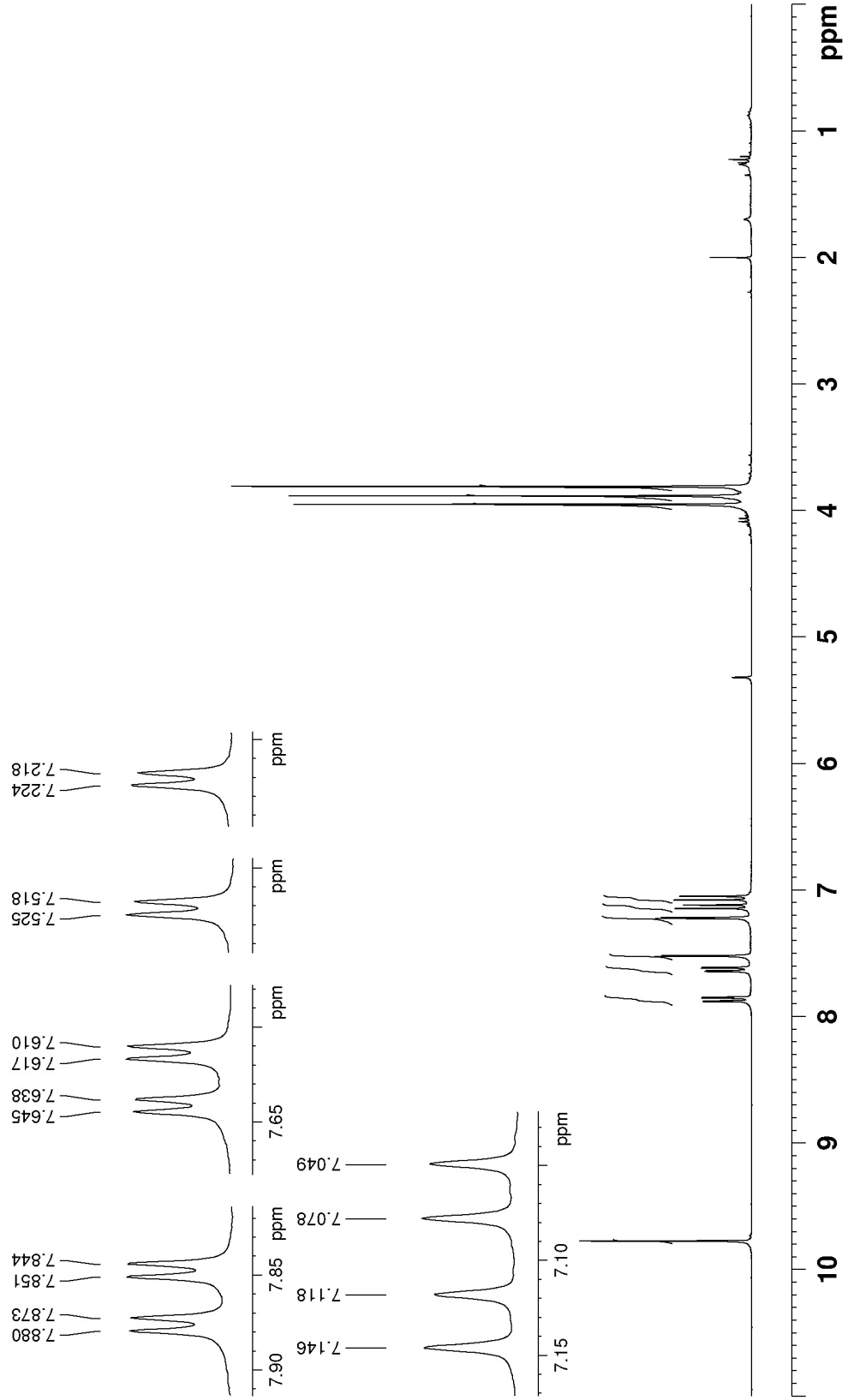

Figure S12. ^{1}H NMR spectrum of methyl 3-(5-formyl-2-methoxyphenoxy)-4-methoxybenzoate (**1**) (CD_2Cl_2, 293 K, 300 MHz)

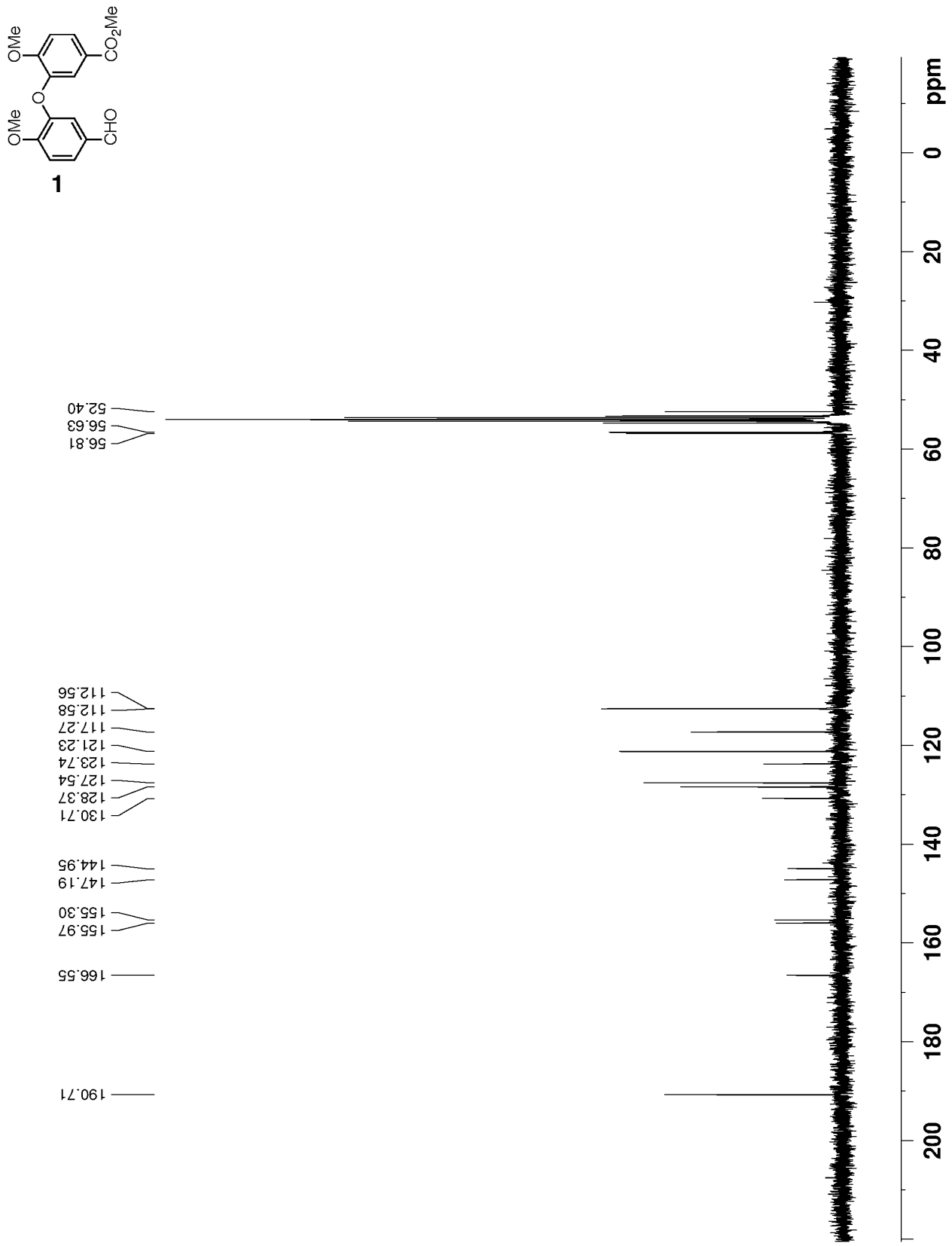

Figure S13. ^{13}C NMR spectrum of methyl 3-(5-formyl-2-methoxyphenoxy)-4-methoxybenzoate (**1**) (CD_2Cl_2, 293 K, 75 MHz)

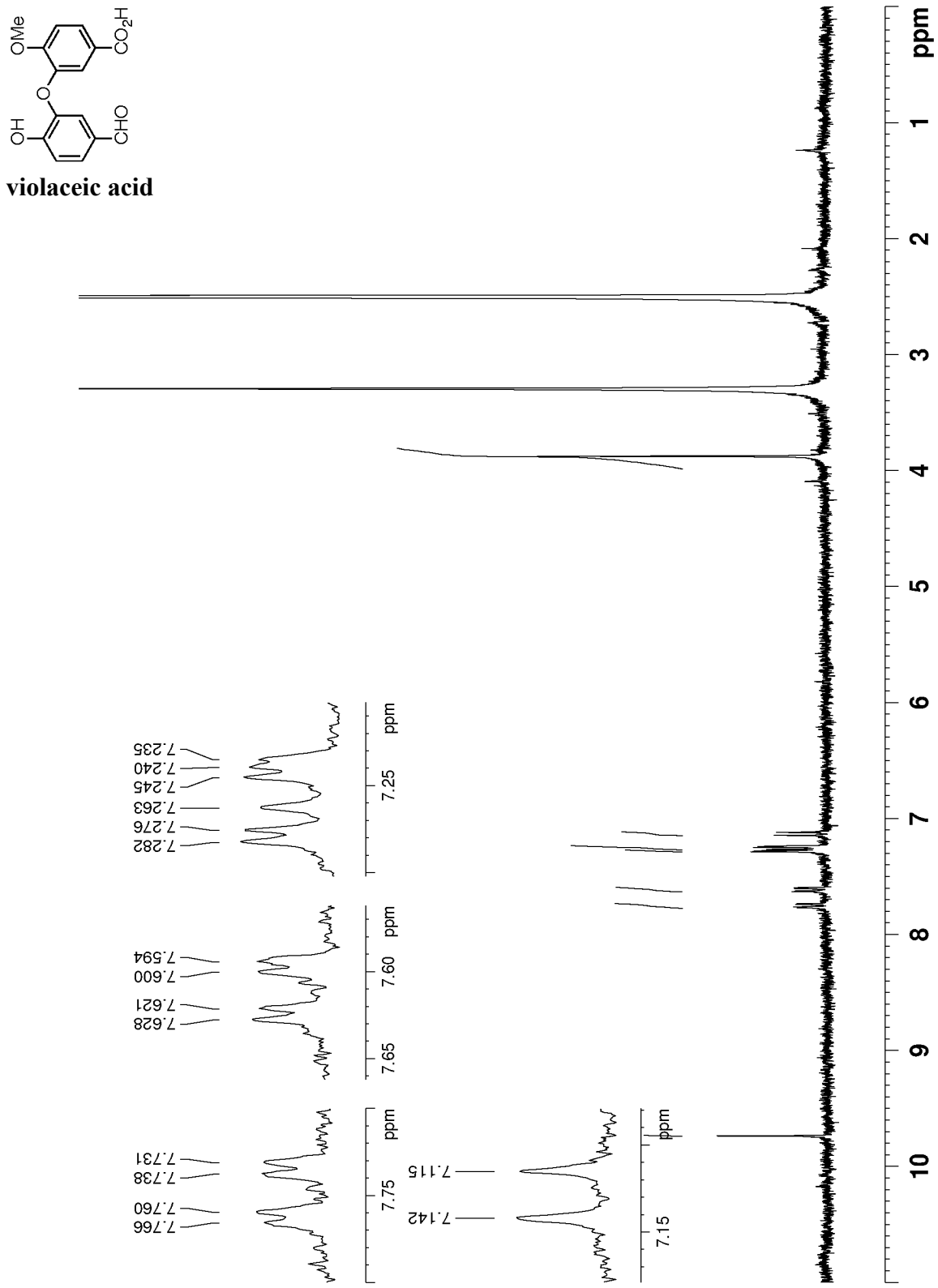

Figure S14. ^{1}H NMR spectrum of violaceic acid (DMSO-d_6, 293 K, 300 MHz)

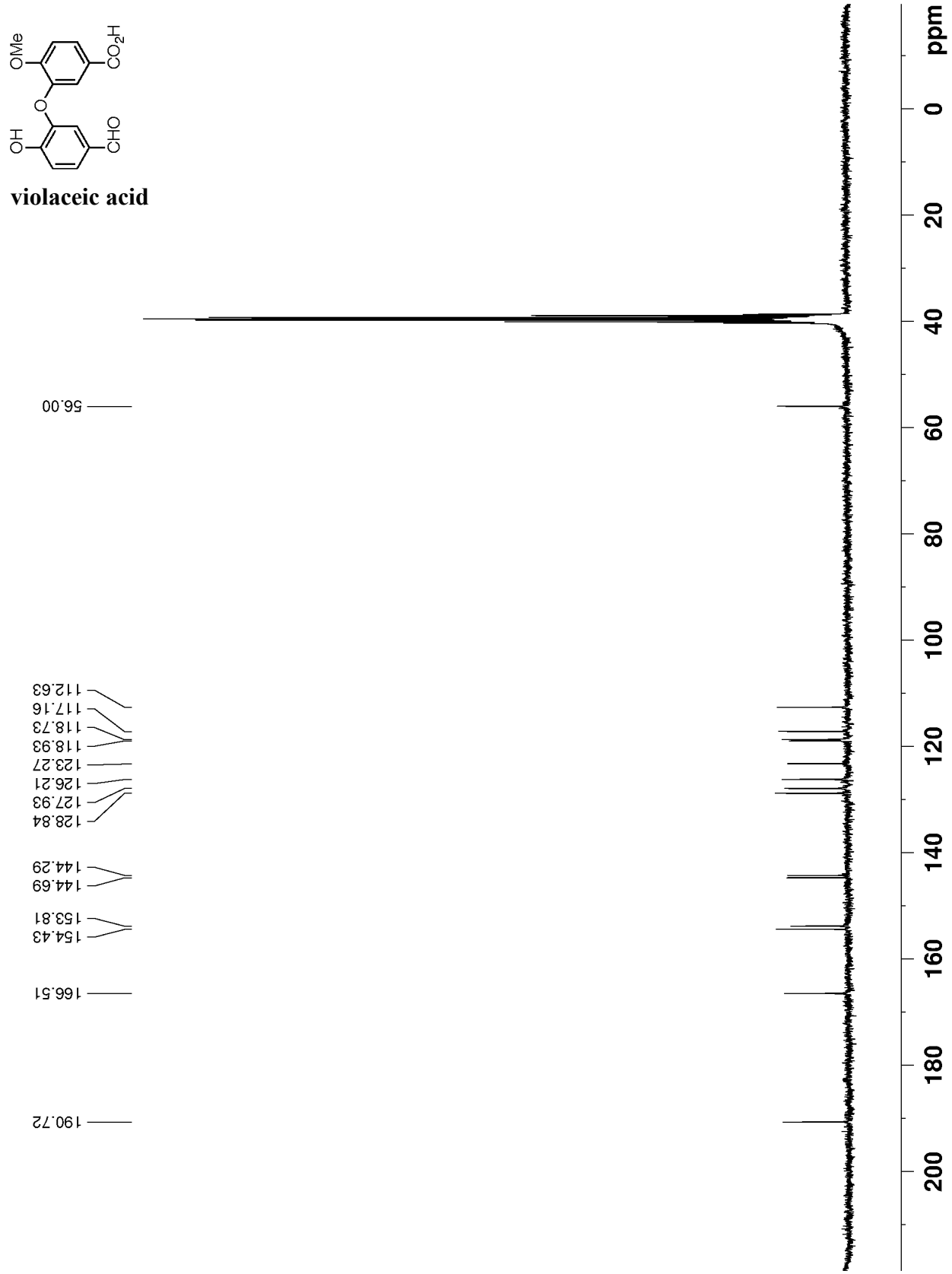

Figure S15. ^{13}C NMR spectrum of violaceic acid (DMSO-d_6, 293 K, 75 MHz)

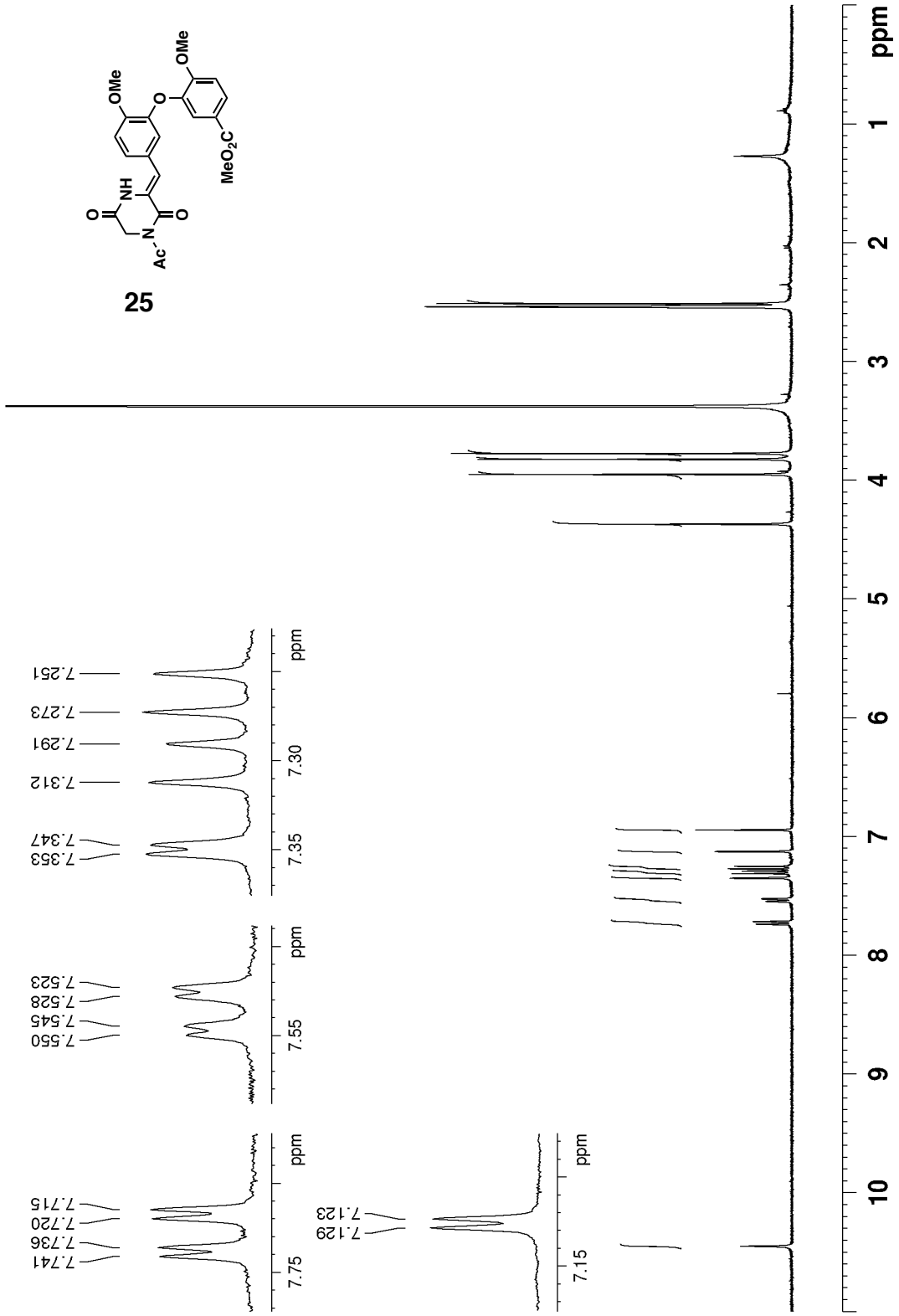

Figure S16. ^{1}H NMR spectrum of methyl (*Z*)-3-(5-((4-acetyl-3,6-dioxopiperazin-2-ylidene)methyl)-2-methoxyphenoxy)-4-methoxybenzoate (**25**) (DMSO-d_6, 293 K, 400 MHz)

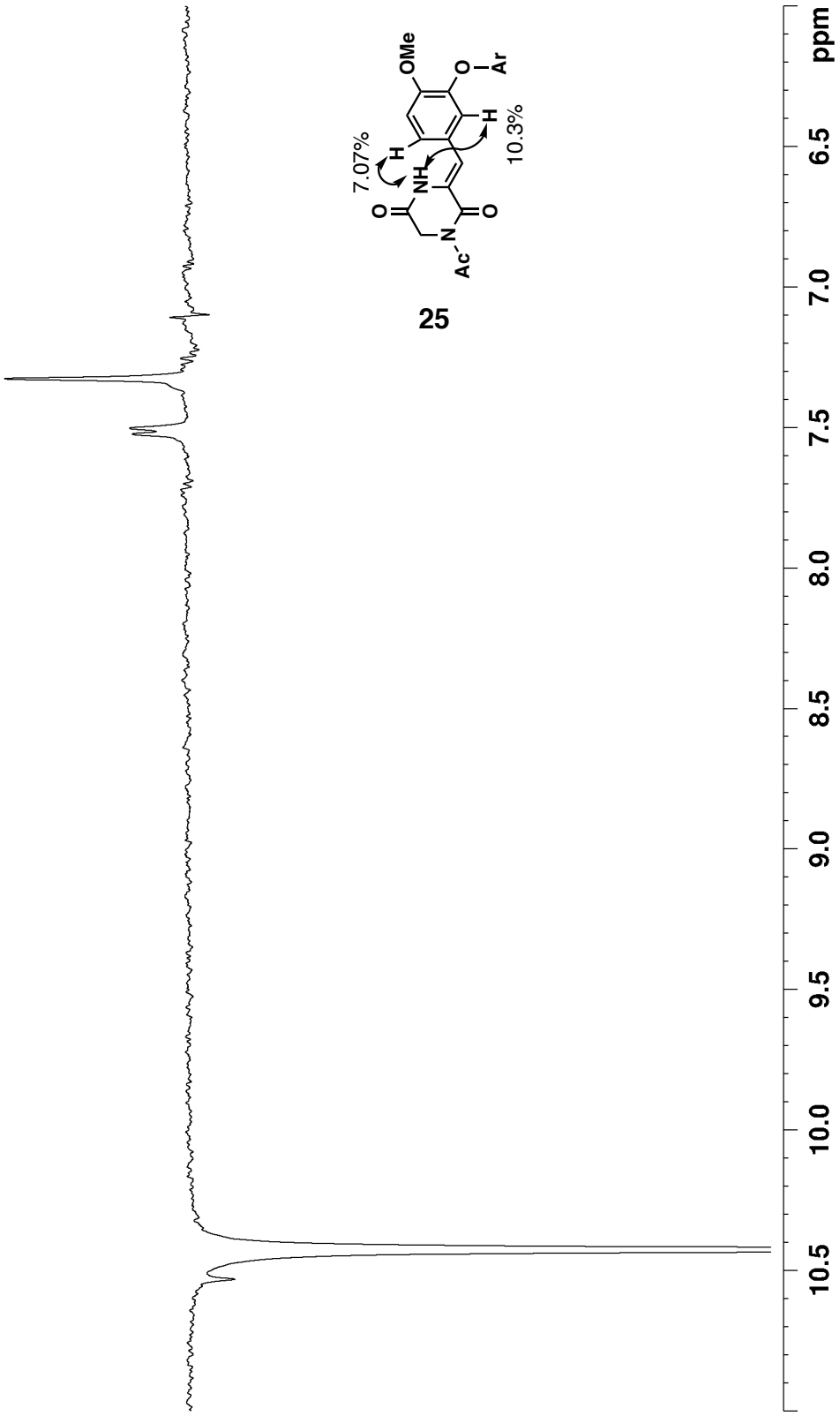

Figure S17. NOE spectrum of methyl (*Z*)-3-(5-((4-acetyl-3,6-dioxopiperazin-2-ylidene)methyl)-2-methoxyphenoxy)-4-methoxybenzoate (**25**) (DMSO-d_6, 293 K, 400 MHz)

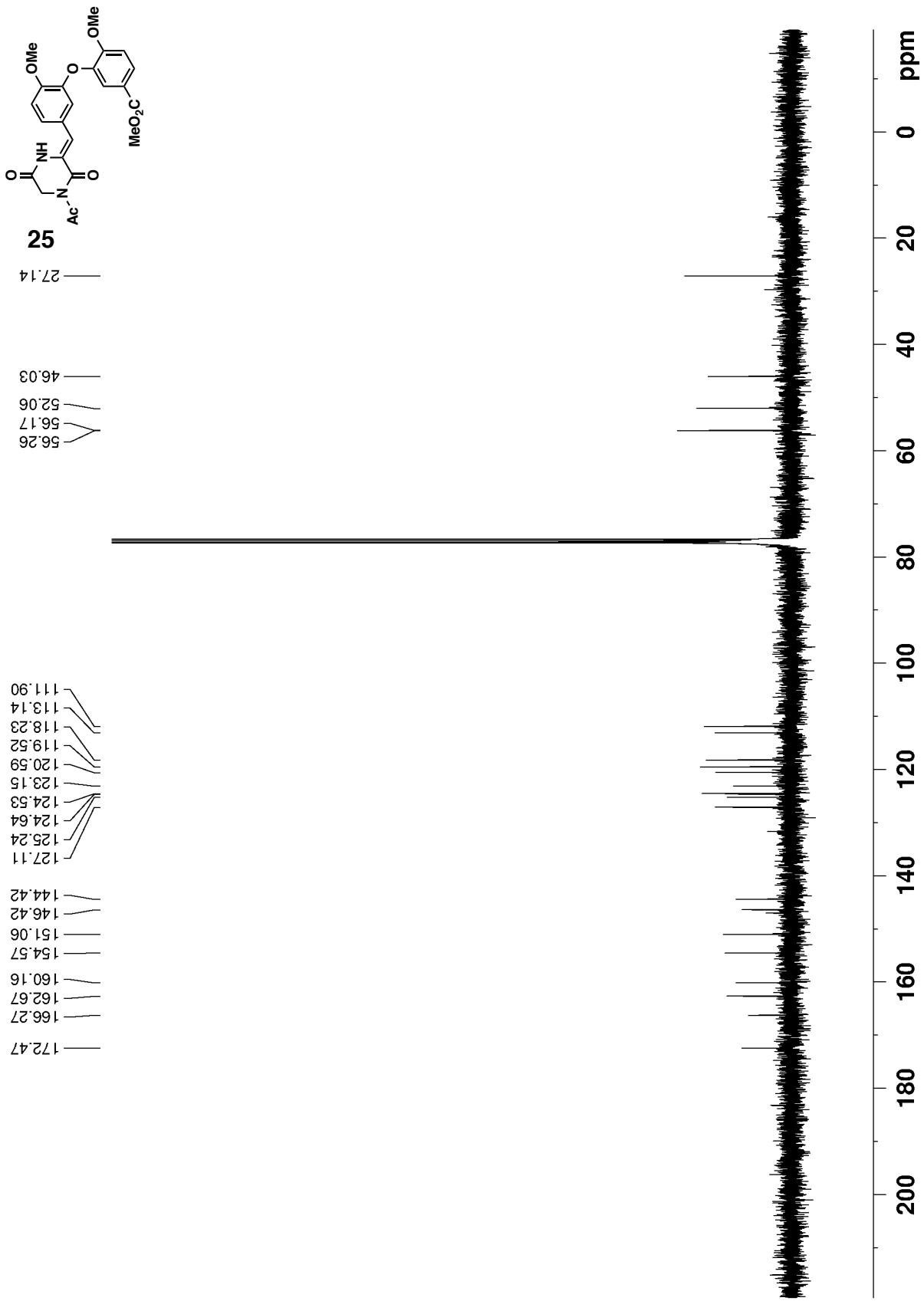

Figure S18. ^{13}C NMR spectrum of methyl (*Z*)-3-(5-((4-acetyl-3,6-dioxopiperazin-2-ylidene)methyl)-2-methoxyphenoxy)-4-methoxybenzoate (**25**) ($CDCl_3$, 293 K, 100 MHz)

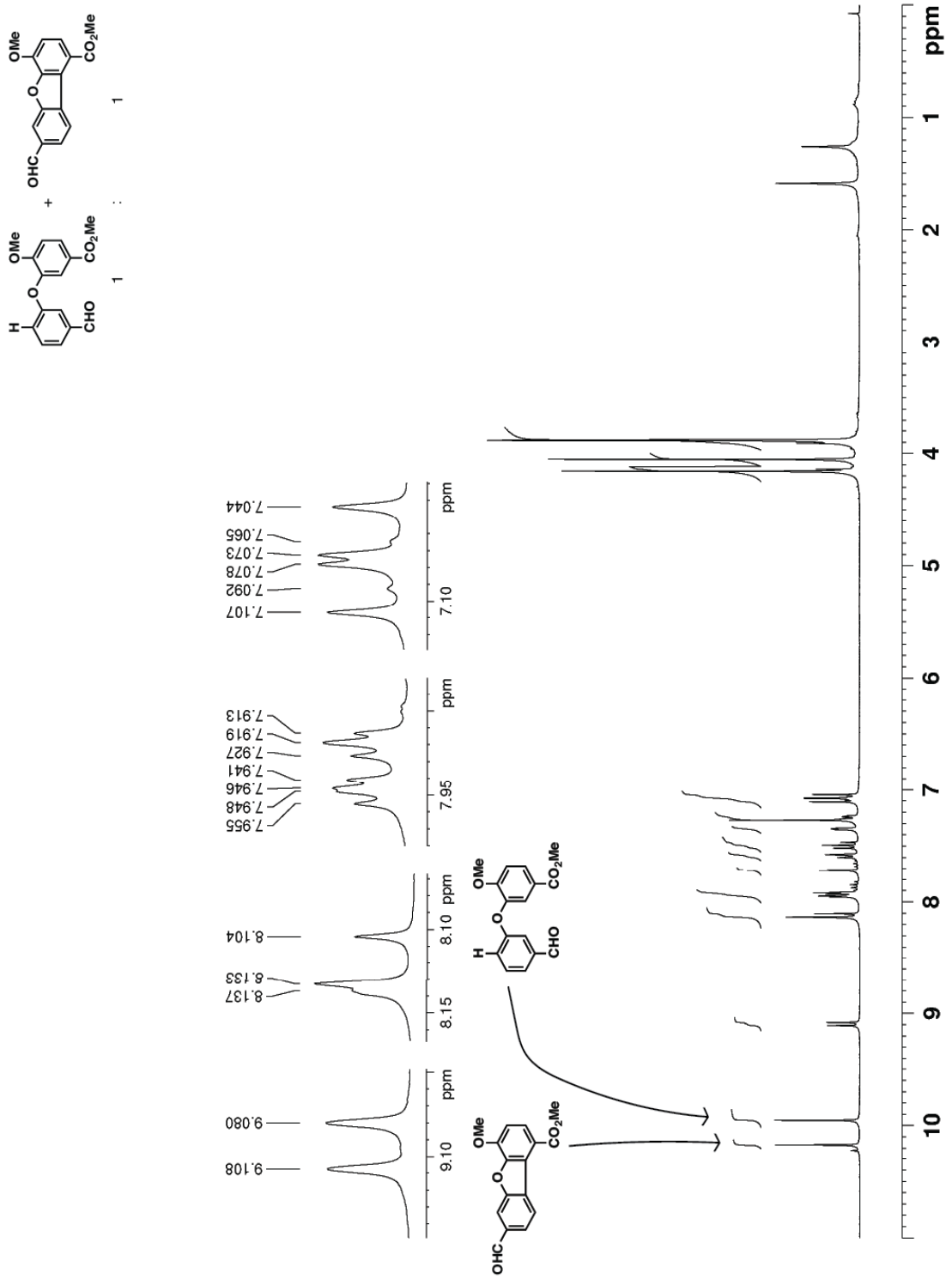

Figure S19. ^{1}H NMR spectrum of methyl 7-formyl-4-methoxydibenzo[*b*,*d*]furan-1-carboxylate (**18**) ($CDCl_3$, 293 K, 300 MHz)

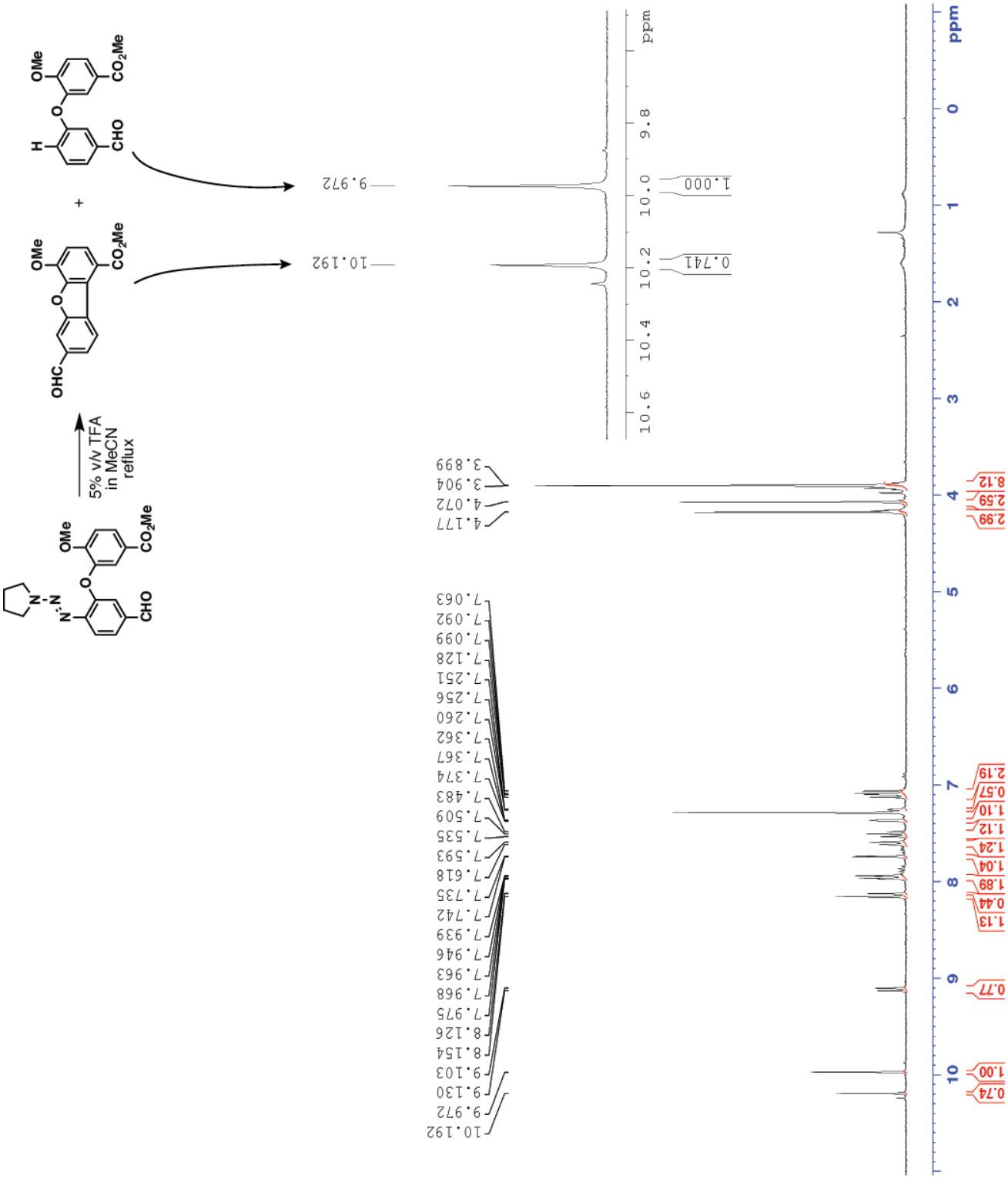

Figure S20. ^{1}H NMR spectrum for Table S4, Entry 1 (300 MHz, $CDCl_3$, 298K)

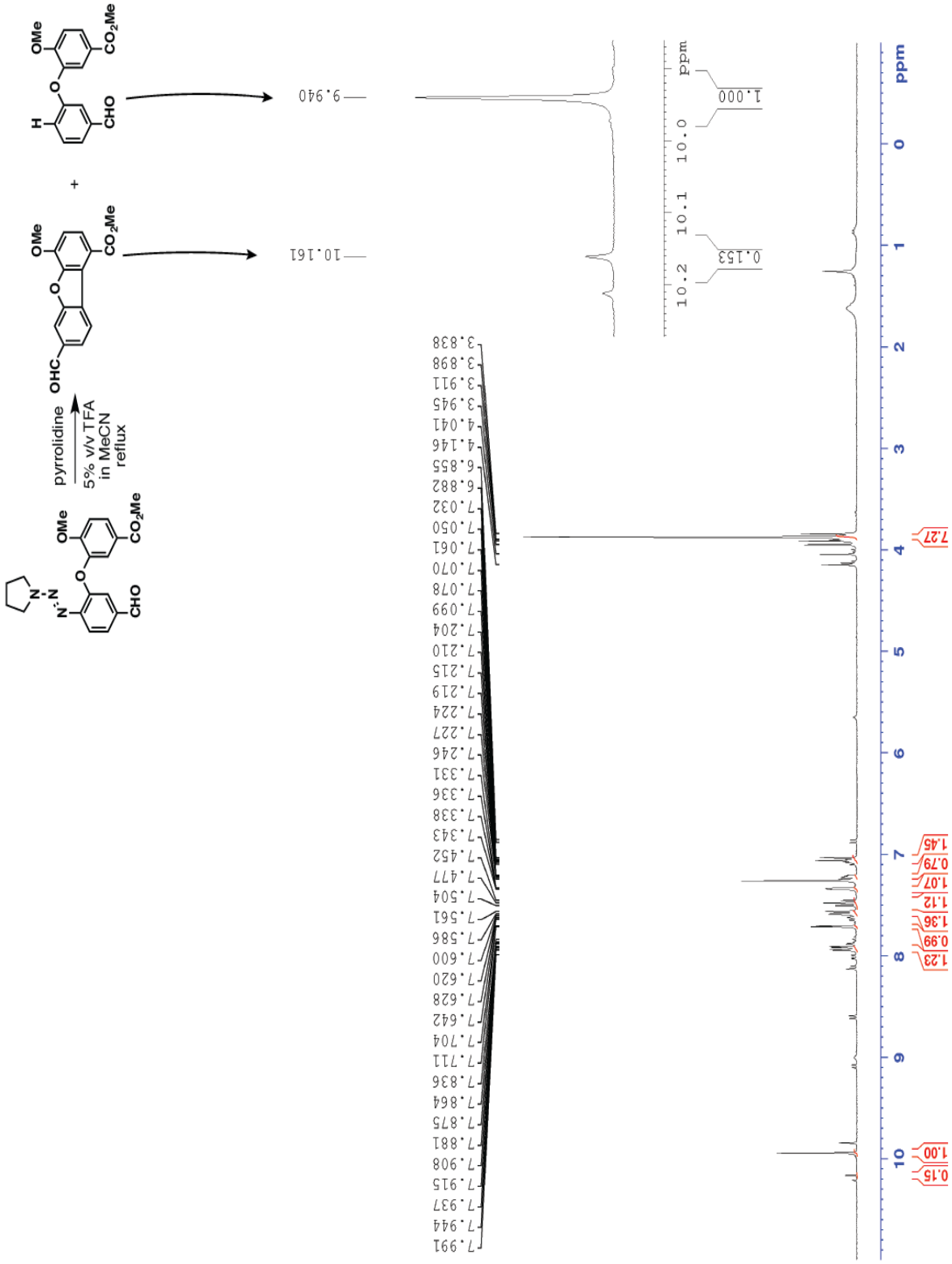

Figure S21. ^{1}H NMR spectrum for Table S4, Entry 2 **(**300 MHz, $CDCl_3$, 298K)

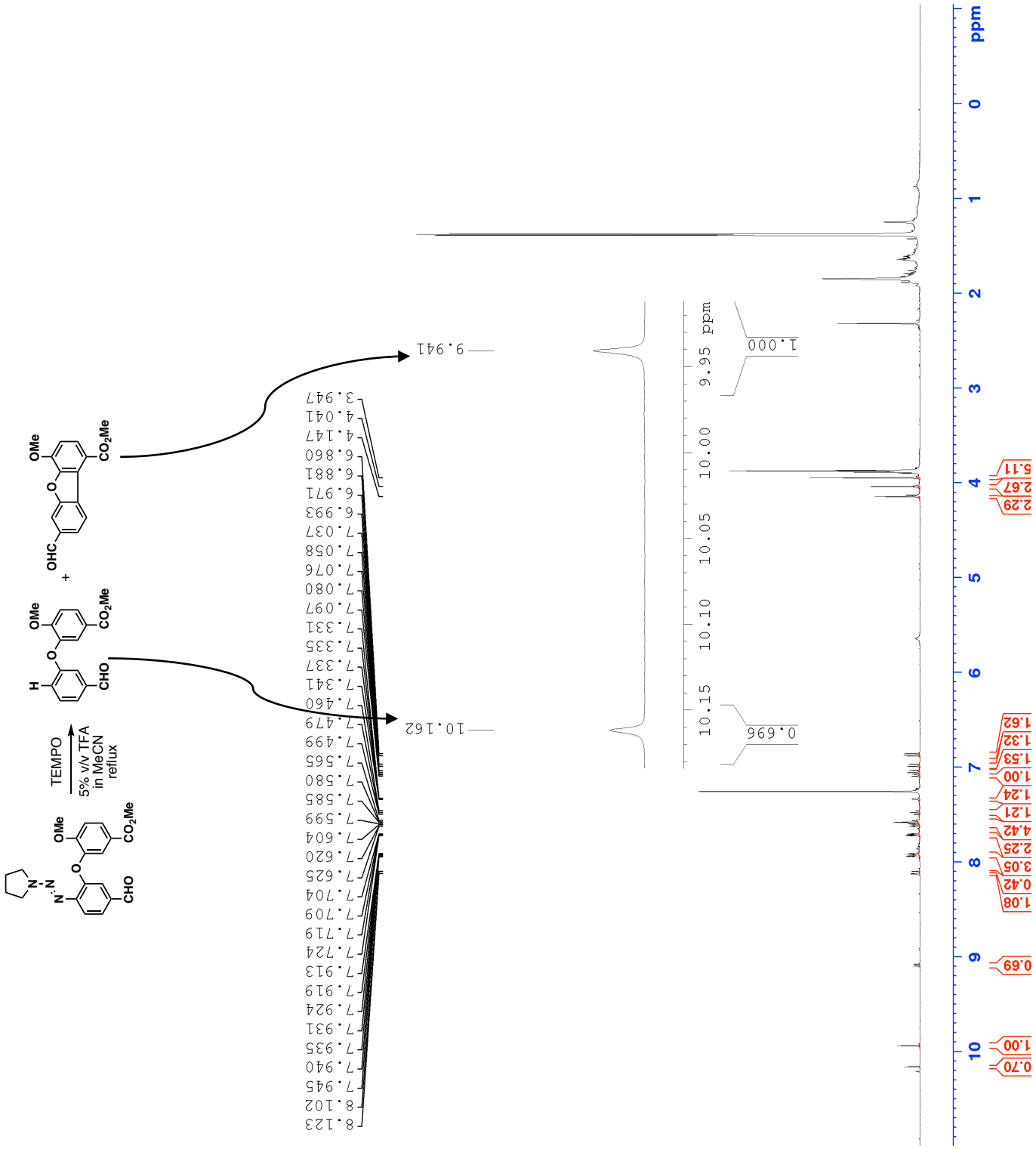

Figure S22. ^{1}H NMR spectrum for Table S4, Entry 3 (400 MHz, $CDCl_3$, 298K)

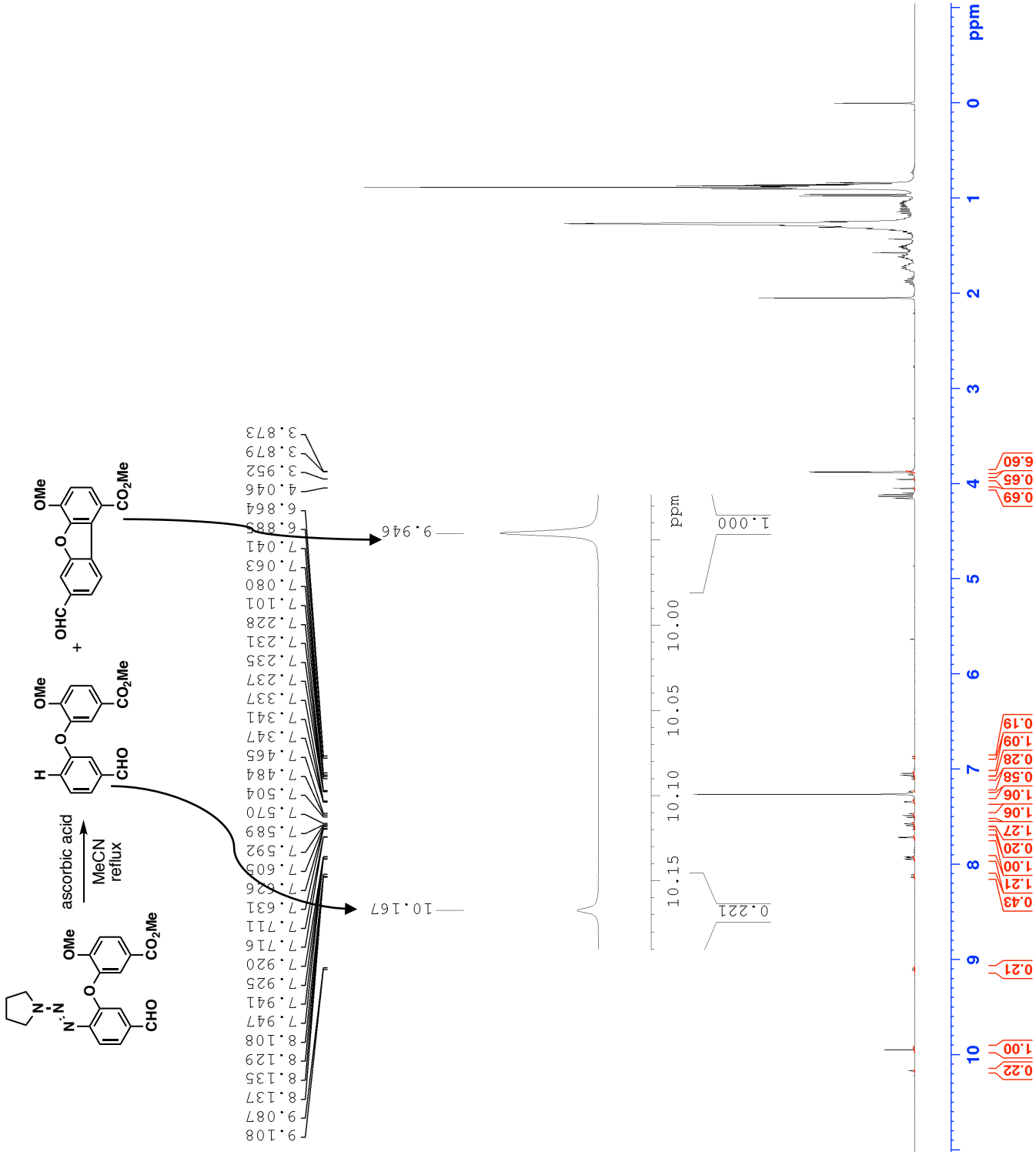

Figure S23. ^{1}H NMR spectrum for Table S4, Entry 4 (400 MHz, $CDCl_3$, 298K)