Enantioselective synthesis of the dimeric pyranonaphthoquinone core of the cardinalins using a late-stage homocoupling strategy

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SUPPLEMENTARY INFORMATION

Experimental

General

All reactions were carried out in oven-dried or flame-dried glassware under a nitrogen atmosphere unless otherwise stated. Analytical thin layer chromatography was performed using 0.2 mm Kieselgel F254 (Merck) silica plates and compounds were visualised under 365 nm ultraviolet irradiation followed by staining with either alkaline permanganate or ethanolic vanillin solution. Infrared spectra were obtained using a Perkin Elmer spectrum One Fourier Transform Infrared spectrometer as thin films between sodium chloride plates. Absorption maxima are expressed in wavenumbers (cm^{-1}). Optical rotations were measured using a Perkin-Elmer 341 polarimeter at λ = 598 nm and are given in 10^{-1} deg cm^2 g^{-1}. Melting points were recorded on an Electrothermal melting point apparatus and are uncorrected. NMR spectra were recorded as indicated on either a Bruker DRX-400 spectrometer operating at 400 MHz for ^{1}H nuclei and 100 MHz for ^{13}C nuclei or on a Bruker Avance 300 spectrometer operating at 300 MHz and 75 MHz for ^{1}H and ^{13}C nuclei, respectively. Chemical shifts are reported in parts per million (ppm) relative to the tetramethylsilane peak recorded as δ 0.00 ppm in $CDCl_3$/ TMS solvent, or the residual chloroform peak at δ 7.25 ppm. The ^{13}C NMR values were referenced to the residual chloroform peak at δ 77.0 ppm. ^{13}C NMR values are reported as chemical shift δ, multiplicity and assignment. ^{1}H NMR shift values are reported as chemical shift δ, relative integral, multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet), coupling constant (*J* in Hz) and assignment. Assignments are made with the aid of DEPT 135, COSY, NOESY and HSQC experiments. High resolution mass spectra were recorded on a VG-70SE mass spectrometer at a nominal accelerating voltage of 70 eV. For all microwave-assisted reactions the CEM Discover system with a circular single mode and focused waves was used, resulting in formation of a homogeneous field pattern surrounding the sample.

***N*,*N*-Diethyl-3-methoxybenzamide (6)** 3-Methoxybenzoic acid (10.0 g, 65.7 mmol) was taken up in dichloromethane (100 mL) and cooled to -10 °C. Thionyl chloride (5.3 mL, 72.3 mmol) was added dropwise and the reaction mixture stirred at room temperature overnight. The reaction mixture was concentrated *in vacuo* with azeotropic removal of the residual thionyl chloride with toluene (2 x 50 mL). The resulting crude acid chloride was taken up in dichloromethane (100 mL) and cooled to 0 °C. A solution of diethylamine (20 mL) in dichloromethane (20 mL) was added dropwise, the reaction mixture warmed to room temperature and stirred 2 h. Glacial acetic acid (30 mL) was added and the reaction mixture was diluted with dichloromethane (100 mL), washed with water (100 mL), brine (100 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash chromatography eluting with hexanes-ethyl acetate (2:1) gave the *title compound* (9.65 g, 46.6 mmol, 71%) as a yellow oil; δ_H (300 MHz, $CDCl_3$) 1.22 (6 H, m, $(NCH_2C\underline{H}_3)_2$), 3.25 (2 H, m, $NC\underline{H}_2CH_3$), 3.53 (2 H, m, $NC\underline{H}_2CH_3$), 3.80 (3 H, s, OMe), 6.89-6.93 (3 H, m, Ar-H), 7.29 (1 H, dt, *J* 1.1, 7.6, Ar-H); δ_C (300 MHz, $CDCl_3$) 12.2 (Me), 14.1 (Me), 39.5 (CH_2), 43.2 (CH_2), 55.3 (OMe), 111.6 (CH), 114.9 (CH), 118.3 (CH), 129.5 (CH), 138.5 (C), 159.5 (C), 170.9 (C=O). Data consistent with literature[13]

***N*,*N*-Diethyl-3-hydroxybenzamide (7)** To a solution of *N*,*N*-Diethyl-3-methoxybenzamide **6** (9.20 g, 44.0 mmol) in dichloromethane (100 mL) at -78 °C was added a solution of boron tribromide (6.30 mL, 66.0 mmol) in dichloromethane (20 mL) dropwise over 30 min. The reaction mixture was warmed to room temperature and quenched with HCl (10%, 50 mL). The resulting mixture was extracted with dichloromethane (3 x 50 mL) and the combined organic extracts washed with brine (100 mL) dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash chromatography eluting with hexanes-ethyl acetate (1:1) gave the *title compound* (5.70 g, 29.5 mmol, 67%) as a colourless solid; δ_H (400 MHz, $CDCl_3$) 1.12 (3 H, t, *J* 7.0, $(NCH_2C\underline{H}_3)_2$), 1.27 (3 H, t, *J* 7.0, $NCH_2C\underline{H}_3$), 3.28 (2 H, q, 3 H, t, *J* 7.0, $NC\underline{H}_2CH_3$), 3.57 (2 H, q, 3 H, t, *J* 7.0, $NC\underline{H}_2CH_3$), 6.80 (2 H, m, Ar-H), 6.91 (1 H, t, *J* 2.0, Ar-H), 7.19 (1 H, t, *J* 7.8, Ar-H); δ_C (100 MHz, $CDCl_3$) 12.7 (Me), 14.0 (Me), 39.4 (CH_2), 43.5 (CH_2), 114.1 (CH), 116.8 (CH), 117.0 (CH), 129.3 (CH), 137.0 (C), 157.0 (C), 172.0 (C=O).

***N*,*N*-Diethyl-3-(trimethylsilyloxy)benzamide (8)** To a solution of *N*,*N*-Diethyl-3-hydroxybenzamide **7** (900 mg, 4.66 mmol) in THF (3 mL) was added hexamethyldisilazane (4 mL) and the reaction mixture was heated at 40 °C for 16 h. The reaction mixture was concentrated *in vacuo* and the crude residue purified by distillation to give the *title compound* as a colourless oil (920 mg, 3.47 mmol, 77%) for use directly in the next step; δ_H (400 MHz, $CDCl_3$) 0.23 (9 H, s, $SiMe_3$), 1.15 (3 H, br m, $NCH_2C\underline{H}_3$), 1.24 (3 H, br m, $NCH_2C\underline{H}_3$, 3.29 (2 H, br m, $NC\underline{H}_2CH_3$), 3.56 (2 H, br m, $NC\underline{H}_2CH_3$), 6.85-6.89 (2 H, m, Ar-H), 6.95 (1 H, dt, *J* 7.5 and 1.1, Ar-H), 7.28 (1 H, t, *J* 7.5, Ar-H); δ_C (100 MHz, $CDCl_3$) 0.13 (3 x Me), 12.8 (Me), 14.1 (Me), 39.1 (CH_2), 43.1 (CH_2), 117.8 (CH), 119.3 (CH), 120.7 (CH), 129.6 (CH), 138.5 (C), 155.0 (C), 171.3 (C=O).

***N*,*N*-Diethyl-3-hydroxy-2-(trimethylsilyl)benzamide (9)** To a solution of tetramethylethylenediamine (0.57 mL, 3.8 mmol) in THF (5 mL) at -78 °C was added *tert*-butyllithium in pentane (1.5 M, 2.54 mL, 3.8 mmol) followed by a solution of *N*,*N*-Diethyl-3-(trimethylsilyloxy)benzamide **8** (920 mg, 3.47 mmol) in THF (5 mL). The reaction mixture was stirred at -78 °C for 1 h then allowed to reach 0 °C and stirred for a further 3 h. Saturated ammonium chloride solution (5 mL) was added and the whole partition between ethyl acetate (20 mL) and water (20 mL). The aqueous layer was extracted with ethyl acetate (x 2) and the combined organic extracts washed with brine (100 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash chromatography eluting with hexanes-ethyl acetate (3:2) gave the *title compound* as a colourless solid (533 mg, 2.0 mmol, 58%); δ_H (400 MHz, $CDCl_3$) 0.28 (9H, s,

$SiMe_3$), 1.09 (3 H, t, *J* 7.0, $NCH_2C\underline{H}_3$), 1.30 (3 H, t, *J* 7.0, $NCH_2C\underline{H}_3$), 1.69 (1 H, s, OH), 3.19 (2 H, br m, $NC\underline{H}_2CH_3$), 3.52 (2 H, br m, $NC\underline{H}_2CH_3$), 6.63 (1 H, d, *J* 8.1, Ar-H), 7.16 (1 H, dd, *J* 8.1 and 7.3, Ar-H); δ_C (100 MHz, $CDCl_3$) 0.33 (3 x Me), 12.7 (Me), 13.6 (Me), 39.2 (CH_2), 43.5 (CH_2), 115.0 (CH), 117.9 (CH), 122.3 (CH), 130.2 (CH), 144.2 (CH), 163.6 (C), 174.6 (C=O).

3-(*tert*-Butyldimethylsilyloxy)-*N*,*N*-diethyl-2-(trimethylsilyl)benzamide (10) To a solution of *N*,*N*-diethyl-3-hydroxy-2-(trimethylsilyl)benzamide **9** (400 mg, 1.5 mmol) in dichloromethane (50 mL) was added triethylamine (0.42 mL, 3 mmol), DMAP (37 mg, 0.3 mmol) and *tert*-butyldimethylsilyl chloride (273 mg, 1.8 mmol) and the reaction mixture was stirred at room temperature for 16 h. Saturated ammonium chloride solution (25 mL) was added, the organic layer removed and the aqueous layer extracted with dichloromethane (2 x 20 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash chromatography eluting with hexanes-ethyl acetate (4:1) gave the *title compound* as a colourless solid (499 mg, 1.3 mmol, 88%), mp 44-45 °C; ν_{max} (oil)/cm^{-1} 3055, 2957, 2933, 2897, 2859, 1637, 1561, 1426, 1381, 1363, 1264, 1244; δ_H (400 MHz, $CDCl_3$) 0.29 (9 H, s, $SiMe_3$), 1.03 (9 H, s, $SiMe_3$), 1.11 (3 H, t, *J* 7.1, $NCH_2C\underline{H}_3$), 1.27 (3 H, t, *J* 7.0, $NCH_2C\underline{H}_3$), 3.25 (2 H, br m, $NC\underline{H}_2CH_3$), 3.54 (2 H, br m, $NC\underline{H}_2CH_3$), 6.73 (1 H, dd, *J* 7.5 and 0.7, Ar-H), 6.81 (1 H, dd, *J* 8.1 and 0.7, Ar-H), 7.22 (1 H, dd, *J* 8.1 and 7.5, Ar-H); δ_C (100 MHz, $CDCl_3$) -3.6 (Me), -3.3 (Me), 0.75 (3 x Me), 12.8 (Me), 13.7 (Me), 19.2 (C), 26.6 (3 x Me), 38.9 (CH_2), 43.4 (CH_2), 117.1 (CH), 118.7 (CH), 125.9 (C), 129.9 (CH), 145.0 (C), 161.4 (C), 171.9 (C=O); *m/z* (CI) 380 (MH^+, 100%), 378 (9), 364 (95), 336 (5), 322 (9), 308 (12), 250 (5), 193 (4), 177 (4), 91 (3), 73 (6); HRMS (CI, MH^+) Found 380.2442. Calc. for $C_{20}H_{37}NO_2Si_2$ + H 380.2441.

***N*,*N*-Diethyl-6-formyl-3-hydroxy-2-(trimethylsilyl)benzamide (11)** To a solution of tetramethylethylenediamine (0.60 mL, 4.0 mmol) and *tert*-butyllithium in pentane (1.5 M, 2.65 mL, 4.0 mmol) in THF (5 mL) at -78 °C was added 3-(*tert*-butyldimethylsilyloxy)-*N*,*N*-diethyl-2-(trimethylsilyl)benzamide **10** (1.0 g, 2.6 mmol) in THF (5 mL) dropwise. The reaction mixture was stirred at -78 °C for 1.5 h. DMF (5 mL) was added and the reaction mixture was allowed to react room temperature overnight (16 h). A solution of hydrochloric acid (1 M, 10 mL) was added and the whole extracted with ethyl acetate (3 x 20 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash chromatography eluting with hexanes-ethyl acetate (4:1) gave the *title compound* (447 mg, 1.52 mmol, 58%) as a colourless solid, mp 198-200 °C; ν_{max} (film)/cm^{-1} 3620, 3055, 2982, 2976, 1689, 1598, 1556, 1303, 1213, 1110; δ_H (400 MHz, $CDCl_3$) 0.19 (9 H, s, $SiMe_3$), 1.02 (3 H, t, *J* 7.0, $NCH_2C\underline{H}_3$), 1.34 (3 H, t, *J* 7.0, (2 H, m, $NCH_2C\underline{H}_3$), 3.24-3.06 (3 H, m, CH_2 + CH of CH_2), 3.94 (1 H, m, CH of CH_2), 6.59 (1 H, d, *J* 8.6, Ar-H), 9.76 (1 H, s, CHO), 9.99 (1 H, br s, OH); δ_C (100 MHz, $CDCl_3$) 0.23 (3 x Me), 12.2 (Me), 13.1 (Me), 39.7 (CH_2), 43.5 (CH_2), 115.1 (CH), 122.1 (C), 123.5 (C), 133.7 (C), 146.1 (C), 151.6 (C), 170.3 (C=O), 189.5 (CHO); *m/z* (EI) 293 (M^+, 9%), 278 (100), 264 (97), 248 (78), 234 (9), 220 (32), 205 (56), 192 (27), 177 (40), 149 (32), 135 (10), 121 (11), 91 (9), 72 (98), 58 (27), 45 (18); HRMS (EI, M^+) Found 293.1445. Calc. for $C_{15}H_{23}NO_3$ 293.1447.

***N,N*-Diethyl-2-formyl-5-hydroxybenzamide (12)** *N,N*-diethyl-6-formyl-3-hydroxy-2-(trimethylsilyl)benzamide **11** (537 mg, 1.83 mmol) was taken up in DMF-H_2O (10 ml, 3:1) and cesium fluoride (612 mg, 4.03 mmol) was added in one portion. The reaction mixture was heated at reflux for 16 h and then concentrated *in vacuo*. The crude residue was partitioned between ethyl acetate (20 mL) and water (20 mL), and the aqueous layer extracted with ethyl acetate (3 x 10 mL). The combined organic extracts were washed with brine (20 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification eluting with ethyl acetate gave the *title compound* (400 mg, 1.80 mmol, 98%) as a colourless solid, mp 114-115 °C; ν_{max} (CH_2Cl_2)/cm^{-1} 3165, 2982, 2628, 2250, 1692, 1614, 1508, 1479, 1444, 1320; δ_H (400 MHz, $CDCl_3$) 1.02 (3 H, t, *J* 7.1, $NCH_2C\underline{H}_3$), 1.30 (3 H, t, *J* 7.1, $NCH_2C\underline{H}_3$), 3.16 (2 H, q, *J* 7.1, $NC\underline{H}_2CH_3$), 3.65 (2 H, br m, $NC\underline{H}_2CH_3$), 6.65 (1 H, d, *J* 2.3, Ar-H), 6.73 (1 H, dd, *J* 8.5 and 2.3, Ar-H), 7.65 (1 H, *d*, J 8.5, Ar-H), 9.79 (1 H, s, CHO); δ_C (100 MHz, $CDCl_3$) 12.2 (Me), 13.5 (Me), 39.5 (CH_2), 43.2 (CH_2), 114.8 (CH), 116.9 (CH), 124.3 (C), 134.5 (CH), 138.4 (C), 162.9

(C), 170.6 (C=O), 189.1 (CHO); *m/z* (EI) 221 (M^+, 5%), 192 (100), 164 (9), 149 (56), 146 (11), 121 (56), 93 (11), 72 (40), 65 (22), 58 (21), 39 (14). HRMS (EI, M^+) Found 221.1048. Calc. for $C_{12}H_{15}NO_3$ 221.1052.

6-Methoxyphthalide A solution of *m*-anisic acid (12 g, 78.9 mmol) in dioxane (70 mL) was added concentrated hydrochloric acid (80 mL) followed by formaldehyde (27% aq. solution, 50 mL) and the reaction mixture was heated to 70 °C for 80 h. The cooled reaction mixture was partitioned between dichloromethane (500 mL) and water (500 mL) and the aqueous layer extracted with dichloromethane (2 x 250 mL). The combined organic extracts were washed with brine (500 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash chromatography eluting with hexanes-ethyl acetate (3:1) gave the *title compound* (7.9 g, 48.2 mmol, 61%) as a colourless solid; mp 124-126 °C (Lit[17] 117-120 °C); δ_H (400 MHz, $CDCl_3$) 7.39-7.23 (3 H, m, Ar-H), 5.26 (2 H, s, CH_2), 3.91 (3 H, s OMe). Spectroscopic data consistent with literature[17]

***N*,*N*-Diethyl-2-formyl-5-methoxybenzamide (16)** To a solution of 6-methoxyphthalide (3.3 g, 20 mmol) in carbon tetrachloride-benzene (60 mL, 1:1) was added *N*-bromosuccinimide and the reaction mixture was heated to reflux for 6 h. After cooling to room temperature, the reaction mixture was filtered and the soild washed with cold carbon tetrachloride. The filtrate was concentrated *in vacuo* and taken up in water (100 mL) and heated to reflux for 2 h. Norit® (~200 mg) was added and the reaction mixture filtered while still hot. The remaining solid was washed with boiling water and the combined filtrate placed in the fridge for 16 h after which point a solid precipitated. The solid was filtered off and dried over P_2O_5 for a further 16 h to give the crude acid **15** as a colourless hygroscopic solid (2.6 g) for use immediately in the next step.

The crude acid (2.6 g) was taken up in thionyl chloride (30 mL) and the reaction mixture heated to reflux for 2 h. The reaction mixture was concentrated *in vacuo* and traces of thionyl chloride were removed from the product by azeotropic removal with toluene (2 x 30 mL). The crude product was taken up in dichloromethane and cooled to 0 °C. A solution of diethylamine (10 mL) in dichloromethane (10 mL) was added dropwise, the reaction mixture was warmed to room temperature and stirred for 2 h. Hydrochloric acid (1 M, 100 mL) was added and the aqueous layer extracted with dichloromethane (2 x 30 mL). The combined organic layers were washed with brine, dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash chromatography eluting with hexanes-ethyl acetate (1:2) gave the *title compound* (1.51 g, 6.42 mmol, 42% from 6-methoxyphthalide) as a yellow oil; δ_H (400 MHz, $CDCl_3$) 1.05 (3 H, t, *J* 7.0 $NCH_2C\underline{H}_3$), 1.32 (3 H, t, *J* 7.0 $NCH_2C\underline{H}_3$), 3.14 (2 H, q, J 7.0, 3 H, t, *J* 7.0 $NC\underline{H}_2CH_3$), 3.61 (2 H, br m, $NC\underline{H}_2CH_3$), 3.90 (3 H, s, OMe), 6.82 (1 H, dd, *J* 1.3 and 0.8, Ar-H), 7.00 (1 H, dd, *J* 8.6 and 0.8, Ar-H), 7.90 (1 H, dd, *J* 8.6 and 1.3, Ar-H), 9.90 (1 H, s, CHO); δ_C (100 MHz, $CDCl_3$) 12.4 (Me), 13.8 (Me), 38.9 (CH_2), 42.8 (CH_2), 55.7 (OMe), 112.0 (CH), 114.3 (CH), 125.6 (C), 132.4 (CH), 141.6 (C), 164.0 (C), 168.3 (C=O), 189.0 (CHO). Data consistent with literature.[18]

***N*,*N*-Diethyl-2-formyl-5-hydroxybenzamide (12)** To a solution of *N*,*N*-diethyl-2-formyl-5-methoxybenzamide **16** (3.13 g, 13.3 mmol) in *N*-methylpyrrolidinone (12 mL) was added potassium carbonate (20 mol%, 2.66 mmol, 367 mg) followed by thiophenol (1.9 mL, 18.6 mmol) and the reaction mixture was heated to 130 °C for 2 h. After cooling to room temperature, sodium hydroxide (1 M, 30 mL) was added and the aqueous layer washed with dichloromethane (3 x 30 mL). The basic aqueous layer was acidified to pH=2 with concentrated hydrochloric acid and the resulting solution extracted with dichloromethane (3 x 50 mL). The combined organic layers were washed with brine (100 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash chromatography eluting with hexanes-ethyl acetate (1:3) gave the *title compound* (2.26 g, 10.3 mmol, 77%) as a colourless solid, spectroscopic data identical with that reported previously.

3-(Diethylcarbamoyl)-4-formylphenyl trifluoromethanesulfonate (13) To a solution of *N*,*N*-diethyl-2-formyl-5-hydroxybenzamide **12** (200 mg, 0.90 mmol) in dichloromethane (6 mL) was cooled to 0 °C. DMAP (55 mg, 0.45 mmol) was added in one portion followed by triethylamine (0.25 mL, 1.8 mmol) and *N*-phenyl-bis(trifluoromethanesulfonimide) (384 mg, 0.99 mmol). The reaction mixture was stirred at 0 °C for 1 h and warmed to room temperature for a further 30 min. The reaction mixture was diluted with dichloromethane (30 mL) and washed with hydrochloric acid (1 M, 50 mL). The aqueous layer was extracted with dichloromethane (2 x 30 mL) and the combined organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash chromatography eluting with hexanes-ethyl acetate (3:1) gave the *title compound* (298 mg, 94%) as a pale yellow oil; ν_{max} (film)/cm^{-1} 3419, 2983, 1704, 1634, 1577, 1428, 1385, 1364, 1286, 1248, 1215, 1138, 1082; δ_H (400 MHz, $CDCl_3$) 1.09 (3 H, t, *J* 7.1, $NCH_2C\underline{H}_3$), 1.34 (3 H, t, *J* 7.1, $NCH_2C\underline{H}_3$), 3.15 (2 H, q, *J* 7.1, $NC\underline{H}_2CH_3$), 3.65 (2 H, q, *J* 7.1, $NC\underline{H}_2CH_3$), 7.31 (1 H, d, *J* 2.4, Ar-H), 7.48 (1 H, dd, *J* 8.6 and 2.4, Ar-H), 8.09 (1 H, d, *J* 8.6, Ar-H), 10.07 (1 H, s, CHO); 12.5 (Me), 13.7 (Me), 39.4 (CH_2), 40.3 (CH_2), 120.0 (CH), 122.0 (CH), 132.3 (CH), 141.8 (C), 152.4 (C), 166.2 (C=O), 188.5 (CHO), triflate carbon not observed; *m/z* (EI) 353 (M^+, 3%), 324 (100), 281 (43), 253 (24), 192 (21), 164 (13), 148 (17), 120 (12), 92 (30), 72 (43), 69 (18), 63 (13); HRMS (EI, M^+) Found 353.0542. Calc. for $C_{13}H_{14}F_3NO_3S$ 353.0545.

N^3,N^3,$N^{3'}$,$N^{3'}$-Tetraethyl-4,4'-diformylbiphenyl-3,3'-dicarboxamide (14) A solution of 3-(diethylcarbamoyl)-4-formylphenyl trifluoromethanesulfonate **13** (307 mg, 0.87 mmol) in dioxane (4 mL) was degassed with argon for 30 min. Freshly ground oven dried potassium carbonate (36 mg, 2.6 mmol), bis(pinacolato)diboron (110 mg, 0.43 mmol) and $PdCl_2$(dppf) (35 mg, 0.04 mmol) were added. The reaction mixture was heated in a sealed tube under microwave irradiation (150 °C, 300 W) for 30 min. The cooled reaction mixture was diluted with ethyl acetate (30 mL) and washed with water (20 mL). The aqueous layer was washed with ethyl acetate (2 x 20 mL) and the combined organic extracts washed with brine, dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash chromatography eluting with hexanes-ethyl acetate (1:3) gave the *title compound* (176 mg, 0.43 mmol, 99%) as a colourless oil; ν_{max} (film)/cm^{-1} 3468, 2977, 2935, 2874, 2250, 1698, 1627, 1599, 1439, 1281; δ_H (400 MHz, $CDCl_3$) 1.07 (6 H, t, *J* 7.1, 2 x $NCH_2C\underline{H}_3$), 1.36 (6 H, t, *J* 7.1, 2 x $NCH_2C\underline{H}_3$), 3.19 (4 H, q, *J* 7.1, $NC\underline{H}_2CH_3$), 3.67 (2 H, q, *J* 7.1, $NC\underline{H}_2CH_3$), 7.61 (2 H, d, *J* 1.7, Ar-H), 7.82 (2

H, dd, *J* 8.1 and 1.7, Ar-H), 8.07 (2 H, d, *J* 8.1, Ar-H), 10.12 (2 H, s, 2 x CHO); δ_C (100 MHz, $CDCl_3$) 12.6 (2 x Me), 13.9 (2 x Me), 39.3 (2 x CH_2), 43.1 (2 x CH_2), 125.7 (2 x CH), 127.9 (2 x CH), 130.7 (2 x CH), 132.3 (2 x C), 140.4 (2 x C), 144.5 (2 x C), 168.1 (2 x C=O), 189.8 (2 x CHO); *m/z* (FAB) 409 (M^+, 100%), 379 (12), 336 (63), 308 (12), 208 (12), 154 (32), 136 (28), 107 (11), 89 (12), 77 (14), 72 (18); HRMS (FAB, M^+) Found 409.2129. Calc. for $C_{24}H_{29}N_2O_4$ 409.2127.

3,3'-Dioxo-1,1',3,3'-tetrahydro-5,5'-biisobenzofuran-1,1'-dicarbonitrile (4) To a solution of N^3,N^3,$N^{3'}$,$N^{3'}$-tetraethyl-4,4'-diformylbiphenyl-3,3'-dicarboxamide **14** (50 mg, 0.12 mmol) in dichloromethane (10 mL) was cooled to 0 °C. Trimethylsilyl cyanide (48 µl, 0.36 mmol), potassium cyanide (1.6 mg, 1.6 mmol) and 18-crown-6 (2 mg) were added and the reaction mixture was stirred for 2 h. The reaction mixture was concentrated *in vacuo* and the resulting residue taken up in glacial acetic acid (5 mL) and stirred at room temperature for 16 h. The resulting mixture was portioned between ethyl acetate (25 mL) and sodium hydroxide solution (1M, 25 mL) and the aqueous layer extracted with ethyl acetate (3 x 10 mL). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash chromatography eluting with hexanes-ethyl acetate (1:4) gave the *title compound* (30 mg, 0.10 mmol, 83%) as a beige solid; mp 255-259 °C; ν_{max} (CH_2Cl_2)/cm^{-1} 3584, 2984, 2941, 2909, 1740, 1447, 1374, 1241; δ_H (400 MHz, *d*6-acetone) 6.76 (2 H, s, 2 x C$\underline{H}$CN), 8.14 (2 H, d, *J* 7.9, Ar-H), 8.40 (2 H, s, Ar-H), 8.41 (2 H, d, *J* 2.9, Ar-H); δ_C (100 MHz, *d*6-acetone) 66.3 (2 x $\underline{C}$HCN), 114.6 (2 H), 142.2 (2 x C), 142.7 (2 x C), 167.2 (2 x C=O); *m/z* (EI) 316 (M^+, 60%), 262 (100), 190 (10); HRMS (EI, M^+) Found 316.0477. Calc. for $C_{18}H_8N_2O_4$ 316.0484.

Methyl 5-hydroxy-2-methylbenzoate (23) To a solution of freshly distilled methyl propiolate (3.38 g, 34 mmol) and aluminium trichloride (4.9 g, 37 mmol) in dichloromethane (130 mL) was added freshly distilled 2-methylfuran (3.06 ml, 34 mmol) in dichloromethane (50 mL) dropwise at 0 °C. The resulting dark red solution was strirred at room temperature for 1 h. Water (200 mL) was carefully added the resulting aqueous layer extracted with dichloromethane (2 x 50 mL). The combined organic extracts were washed with brine (150 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash chromatography eluting with hexanes-ethyl acetate (1:3) gave the *title compound* (2.37 g, 14.3 mmol, 42%) as a yellow solid; mp 76-78 °C (Lit[24] 73-74 °C); ν_{max} (CH_2Cl_2)/cm^{-1} 3440, 1721, 1609, 1578, 1501, 1440, 1308, 1227, 1077; δ_H (400 MHz, $CDCl_3$) 2.50 (3 H, s, Me), 3.89 (3 H, s, $CO_2\underline{Me}$), 5.71 (1 H, s, OH), 6.93 (1 H, dd, *J* 9.0 and 3.0, Ar-H), 7.11 (1 H, d, *J* 9.0, Ar-H), 7.44 (1 H, d, *J* 3.0, Ar-H); δ_C (100 MHz, $CDCl_3$) 20.9 (Me), 52.1 ($CO_2\underline{Me}$), 117.2 (CH), 119.5 (CH), 130.1 (C), 132.1 (C), 132.9 (CH), 153.6 (C), 168.3 (C=O). Spectroscopic data consistent with literature.[24]

Methyl 2-methyl-5-(trifluoromethylsulfonyloxy)benzoate (24) To a solution of methyl 5-hydroxy-2-methylbenzoate **23** (1.2 g, 7.2 mmol) in dichloromethane (20 mL) at 0 °C was added DMAP (3.6 mmol, 439 mg) followed by triethylamine (2 ml, 14.4 mmol) and *N*-phenyl-bis(trifluoromethanesulfonimide) (2.43 g, 7.2 mmol). The reaction mixture was stirred at 0 °C for 1 h and warmed to room temperature for a further 30 min. The reaction mixture was diluted with dichloromethane (30 mL) and washed with hydrochloric acid (1 M, 50 mL). The aqueous layer was extracted with dichloromethane (2 x 30 mL) and the combined organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash chromatography eluting with hexanes-ethyl acetate (3:1) gave the *title compound* (1.81 g, 6.07 mmol, 84%) as a pale yellow oil; ν_{max} (CH_2Cl_2)/cm^{-1} 3446, 3085, 2957, 1731, 1579, 1492, 1427, 1299, 1215, 1138, 1079, 975, 921, 848, 785; δ_H (400 MHz, $CDCl_3$) 2.60 (3 H, s, Me), 3.90 (3 H, s, CO_2Me), 7.29 (2 H, m, Ar-H), 7.81 (1 H, d, *J* 1.8, Ar-H); δ_C (100 MHz, $CDCl_3$) 21.2 (Me), 52.2 ($CO_2\underline{Me}$), 116.5 (C), 120.8 (C), 123.3 (CH), 124.5 (CH), 131.1 (C), 133.4 (CH), 140.9 (C), 147.1 (C), 166.0 (C=O), triflate carbon not observed; *m/z* (EI) 298 (M^+, 73%), 271 (15), 267 (51), 165 (80), 133 (100), 105 (80), 77 (26), 69 (25), 51 (20), 39 (8) HRMS (EI, M^+) Found 298.0121. Calc. for $C_{10}H_9F_3O_5S$ 298.0123.

Dimethyl 4,4'-dimethylbiphenyl-3,3'-dicarboxylate (25) $NiCl_2(PPh_3)_2$ (10 mol %, 0.18 mmol, 117 mg), zinc dust (198 mg, 3.05 mmol) and tetrabutylammonium iodide (993 mg, 2.69 mmol) were combined in an oven dried flask and dried under vacuum overnight. A reflux condenser was fitted to the flask and the reaction mixture purged with nitrogen (x 5). THF (1.2 mL) was added and the reaction mixture was stirred for 5 min. A degassed solution of methyl 2-methyl-5-(trifluoromethylsulfonyloxy)benzoate **24** (535 mg, 1.8 mmol) in THF (1 mL) was added dropwise and the reaction mixture heated to reflux for 1.5 h. The cooled reaction mixture was partitioned between dichloromethane (20 mL) and water (20 mL) and the aqueous layer extracted with dichloromethane (2 x 20 mL). The combined organic layers were washed with brine, dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash chromatography eluting with hexanes-ethyl acetate (3:1) gave the *title compound* (423 mg, 79%) as a colourless solid, mp 92-94 °C; ν_{max} (CH_2Cl_2)/cm^{-1} 3053, 2986, 1720, 1421, 1260, 1218, 1141, 1085, 746; δ_H (300 MHz, $CDCl_3$) 2.64 (6 H, s, 2 x Me), 3.93 (6 H, s, 2 x $CO_2\underline{Me}$), 7.32 (2 H, d, *J* 8.0, Ar-H), 7.63 (2 H, dd, *J* 8.0 and 2.0, Ar-H), 8.14 (2 H, d, *J* 2.0, Ar-H); δ_C (75 MHz, $CDCl_3$) 21.4 (2 x Me), 51.9 (2 x $CO_2\underline{Me}$), 128.9 (2 x CH), 130.0 (2 x C), 130.2 (2 x CH), 132.3 (2 x CH), 137.6 (2 x C), 139.3 (2 x C), 168.0 (2 x C=O); *m/z* (EI) 298 (M^+, 100%), 267 (42), 238 (40), 178 (15), 165 (15); HRMS (EI, M^+) Found 298.1207. Calc. for $C_{18}H_{18}O_4$ 298.1205.

Dimethyl 4,4'-bis(phenylthiomethyl)biphenyl-3,3'-dicarboxylate (27) To a solution of dimethyl 4,4'-dimethylbiphenyl-3,3'-dicarboxylate **25** (80 mg, 0.27 mmol) in carbon tetrachloride (2 mL) was added *N*-bromosuccinimide (96 mg, 0.54 mmol) and benzoyl peroxide (2 mg) and the reaction mixture was heated to reflux in the presence of a 1000W tungsten halogen lamp for 1 h. After cooling, the reaction mixture was filtered and the residual solid washed with cold benzene. The combined filtrate was concentrated *in vacuo* and the resulting crude dibromide **26** taken up in chloroform (3 mL). DBU (80 μl, 0.54 mmol) and thiophenol (55 μl, 0.54 mmol) were added and the reaction mixture was stirred at room temperature for 1 h. The reaction mixture was diluted with dichloromethane (10 mL) and washed with water (10 mL), brine (10 mL), dried ($MgSO_4$) filtered and concentrated *in vacuo*. Purification by flash chromatography eluting with hexanes-ethyl acetate (4:1) gave the title compound (138 mg, 0.27 mmol, 47% over 2 steps) as a colourless solid; mp 71-73 °C; ν_{max} (CH_2Cl_2)/cm^{-1} 3039, 2952, 1710, 1460, 1250, 1146; δ_H (400 MHz, $CDCl_3$) 3.93 (6 H, s, 2 x $CO_2\underline{Me}$), 4.54 (4 H, s, 2 x $\underline{CH_2}SPh$), 7.20-7.34 (12 H, m, Ar-H) 7.58 (2 H, dd, *J* 7.9, 2.0, Ar-H), 8.15 (2 H, d, *J* 2.0, Ar-H); δ_C

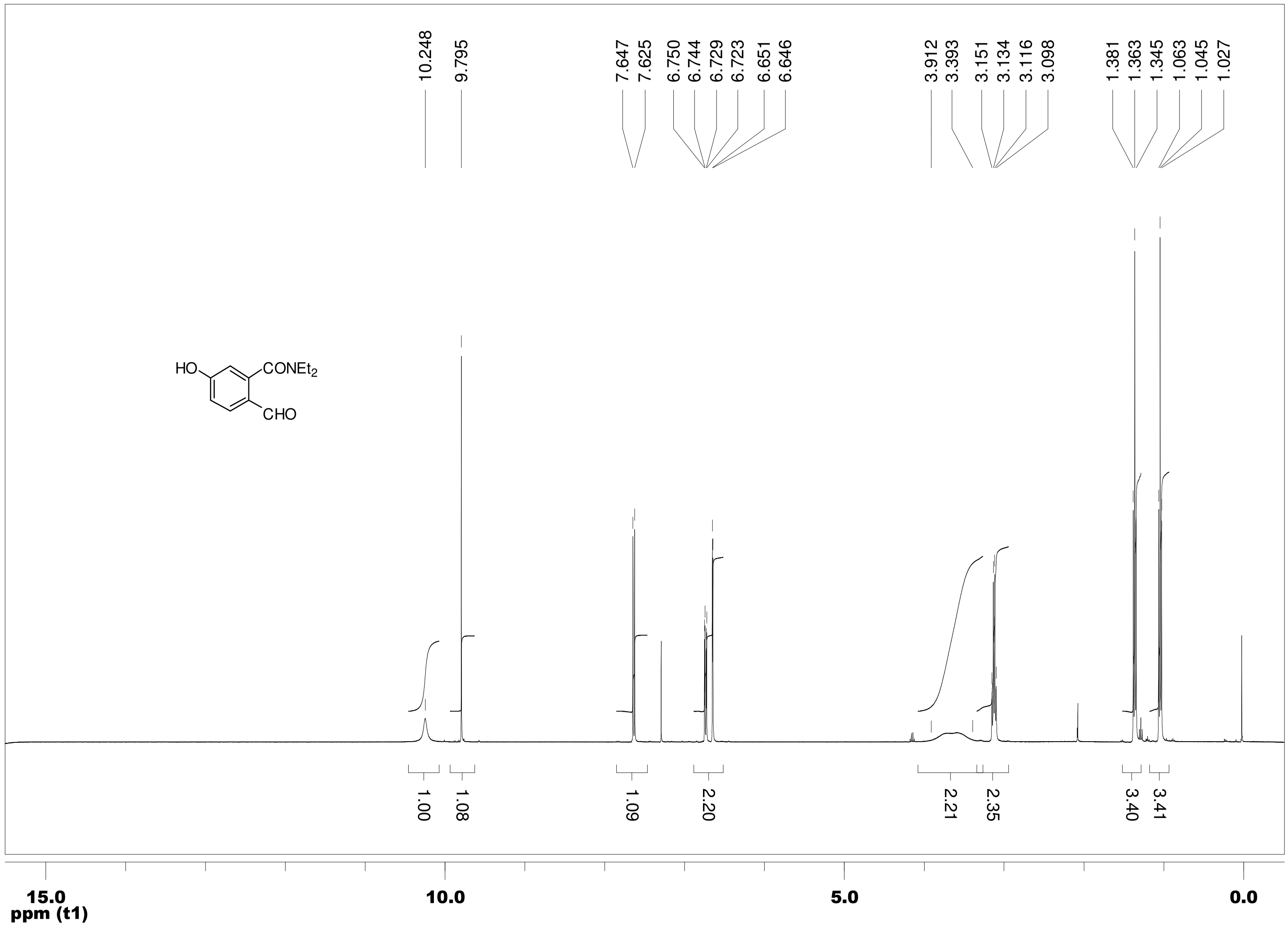
(100 MHz, $CDCl_3$) 37.8 (2 x Me), 52.3 (2 x CH_2), 126.8 (2 x CH), 128.8 (4 x CH), 129.5 (2 x CH), 129.9 (2 x C), 130.1 (2 x CH), 131.2 (4 x CH), 131.6 (2 x CH), 135.8 (2 x C), 138.6 (2 x C), 129.1 (2 x C), 167.5 (2 x C=O); *m/z* (EI) 514 (M^+, 8%), 406 (20), 405 (19), 375 (8), 297 (100), 110 (11); HRMS (EI, M^+) Found 514.1272. Calc. for $C_{30}H_{26}O_4S_2$ 514.1273.

Dimethyl 4,4'-bis(phenylsulfonylmethyl)biphenyl-3,3'-dicarboxylate (21)

Method 1 To a solution of dimethyl 4,4'-bis(phenylthiomethyl)biphenyl-3,3'-dicarboxylate **27** (154 mg, 0.3 mmol) in ethanol (2 mL) was hydrogen peroxide (27% aq. solution, 1 mL) followed by ammonium molybdate (5 mol %, 21 mg) and the reaction mixture was heated to reflux for 1 h. The cooled reaction mixture was diluted with water (20 mL) and extracted with dichloromethane (3 x 10 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash chromatography (ethyl acetate-hexanes, 1:2) gave the *title compound* (153 mg, 0.27 mmol, 88%) as a colourless solid mp 168-170 °C; ν_{max} (CH_2Cl_2)/cm^{-1} 3053, 2986, 2305, 1721, 1421, 1272, 1253, 1150, 895, 774, 712, 689; δ_H (300 MHz, $CDCl_3$) 3.81 (6 H, s, 2 x $CO_2\underline{Me}$), 5.10 (4 H, s, 2 x CH_2), 7.50-7.43 (6 H, m, Ar-H), 7.63 (2 H, m, Ar-H), 7-72-7.69 (6 H, m, Ar-H), 8.14 (2 H, d, *J* 1.5, Ar-H); δ_C (75 MHz, $CDCl_3$) 52.4 (2 x Me), 52.1 (2 x CH_2), 128.6 (4 x CH), 128.7 (2 x C), 128.9 (4 x CH), 129.5 (2 x CH), 130.2 (2 x CH), 131.5 (2 x C), 133.7 (2 x CH), 134.2 (2 x CH), 138.5 (2 x C), 139.8 (2 x C), 166.9 (2 x C=O); *m/z* (EI) 579 (MH^+, 3%), 437 (4), 307 (16), 289 (12), 154 (100), 136 (70), 120 (12), 107 (22), 90 (15), 89 (22), 77 (23); HRMS (EI, MH^+) Found 579.1155. Calc. for $C_{30}H_{26}O_8S_2$ + H 579.1147.

Method 2 To a solution of dimethyl 4,4'-dimethylbiphenyl-3,3'-dicarboxylate **25** (100 mg, 0.34 mmol) in carbon tetrachloride (2 mL) was added *N*-bromosuccinimide (121 mg, 0.68 mmol) and benzoyl peroxide (3 mg) and the reaction mixture was heated to reflux in the presence of a 1000W tungsten halogen lamp for 1 h. After cooling, the reaction mixture was filtered and the residual solid washed with cold benzene. The combined filtrate was concentrated *in vacuo* and the resulting crude dibromide taken up in DMF (5 mL). Benzene sulfinic acid sodium salt (167 mg, 1.02 mmol) was added in one portion and the reaction mixture was heated to 50 °C for 1 h.

The reaction mixture was partitioned between ethyl acetate (20 mL) and water (20 mL). The aqueous layer was extracted with ethyl acetate (2 x 20 mL) and the combined organic layers washed with brine, dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash chromatography eluting with hexanes-ethyl acetate (1:1) gave the *title compound* (102 mg, 0.18 mmol, 52% over 2 steps) as a colourless solid, data consistent with that obtained from method 1.



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3.116
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1.363
1.345
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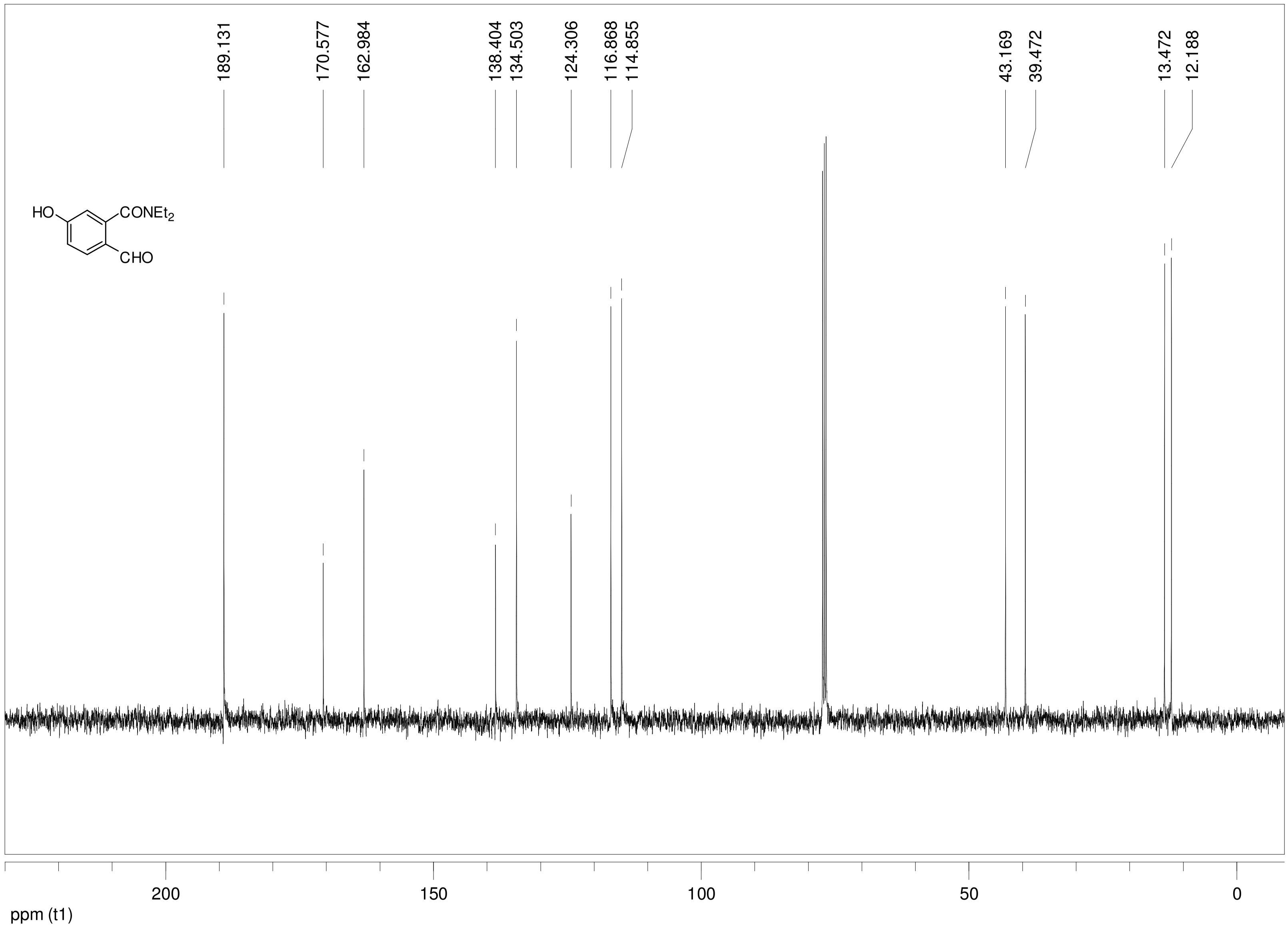
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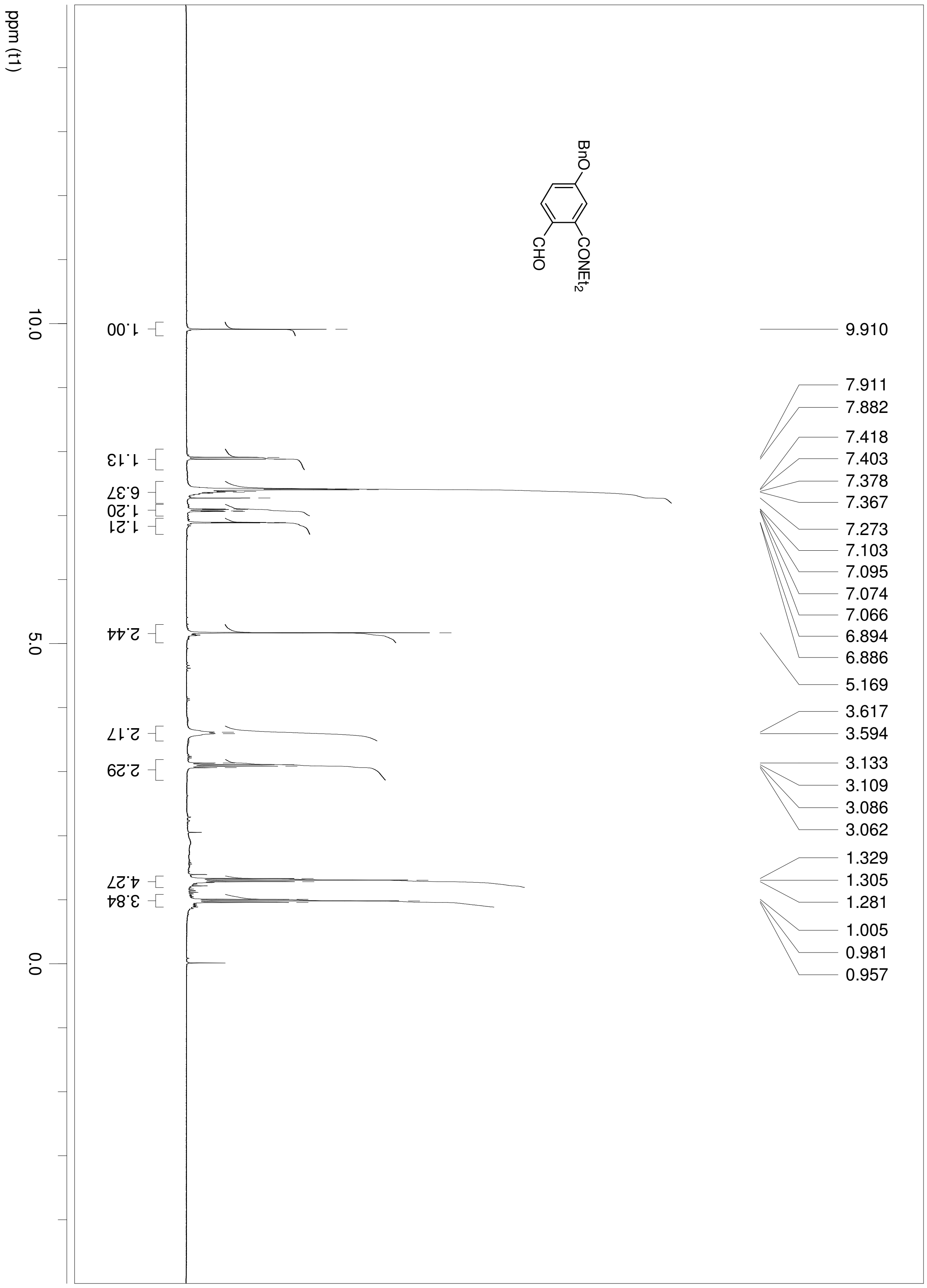
ppm (t1)



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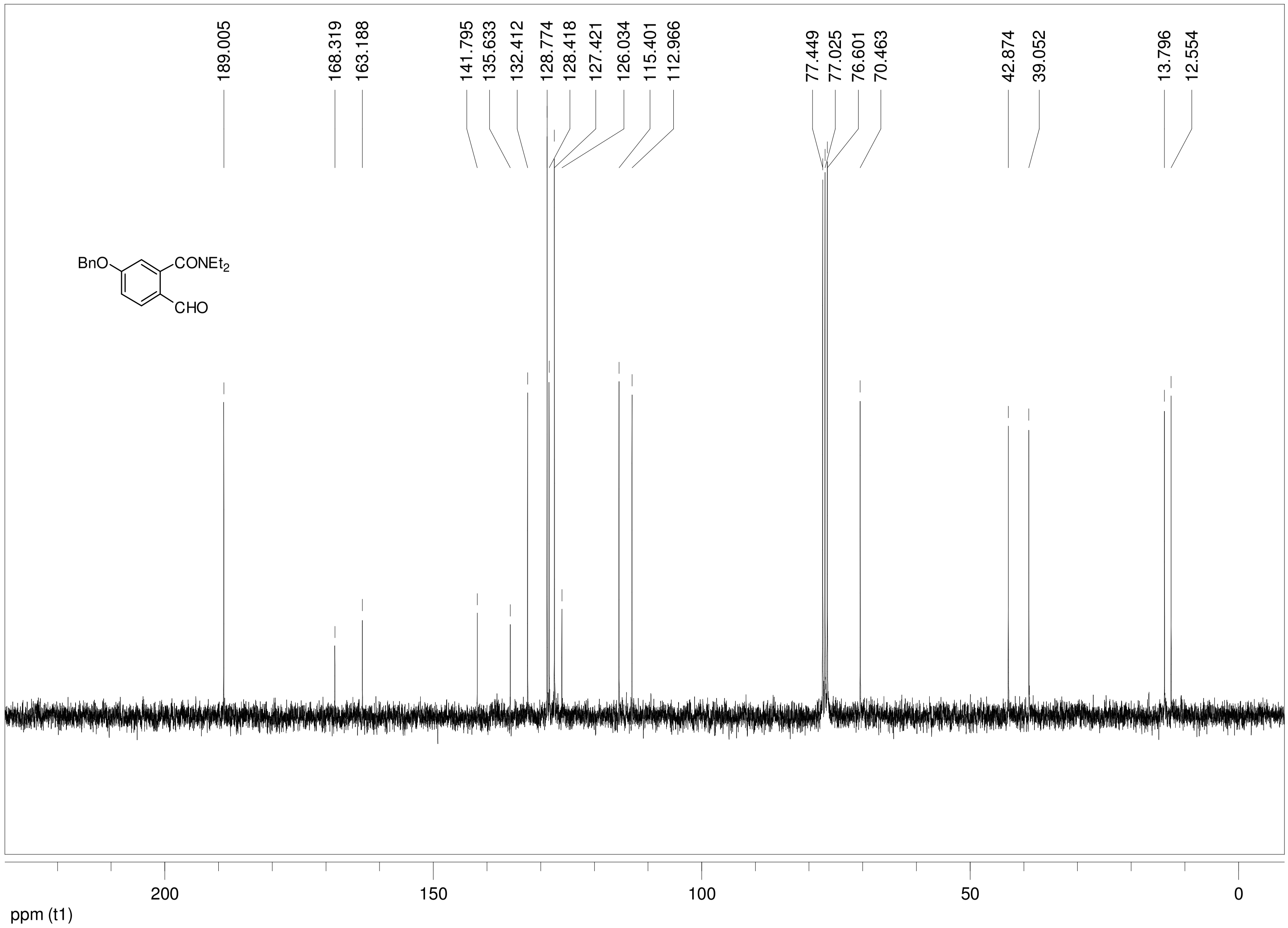

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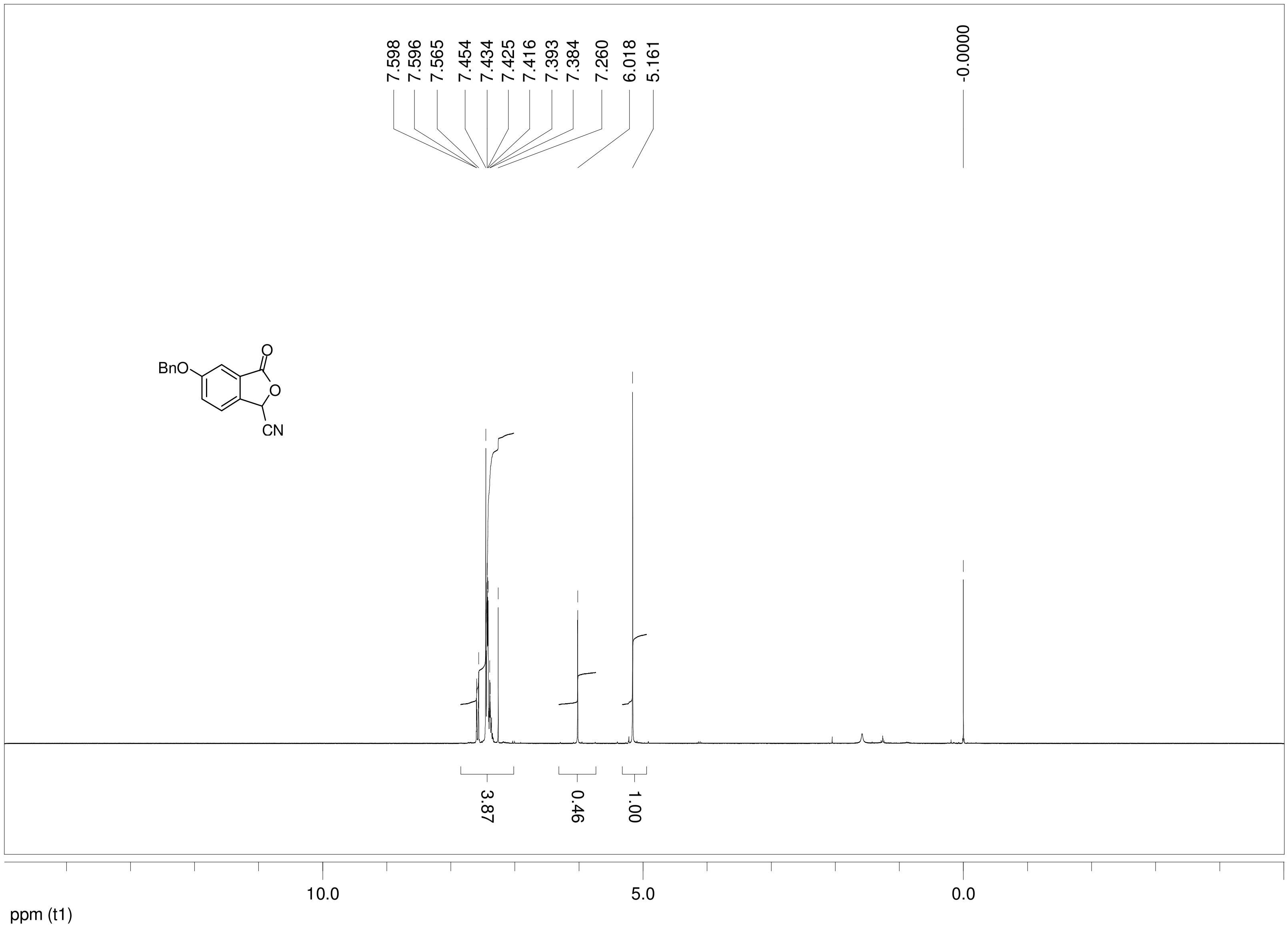
ppm (t1)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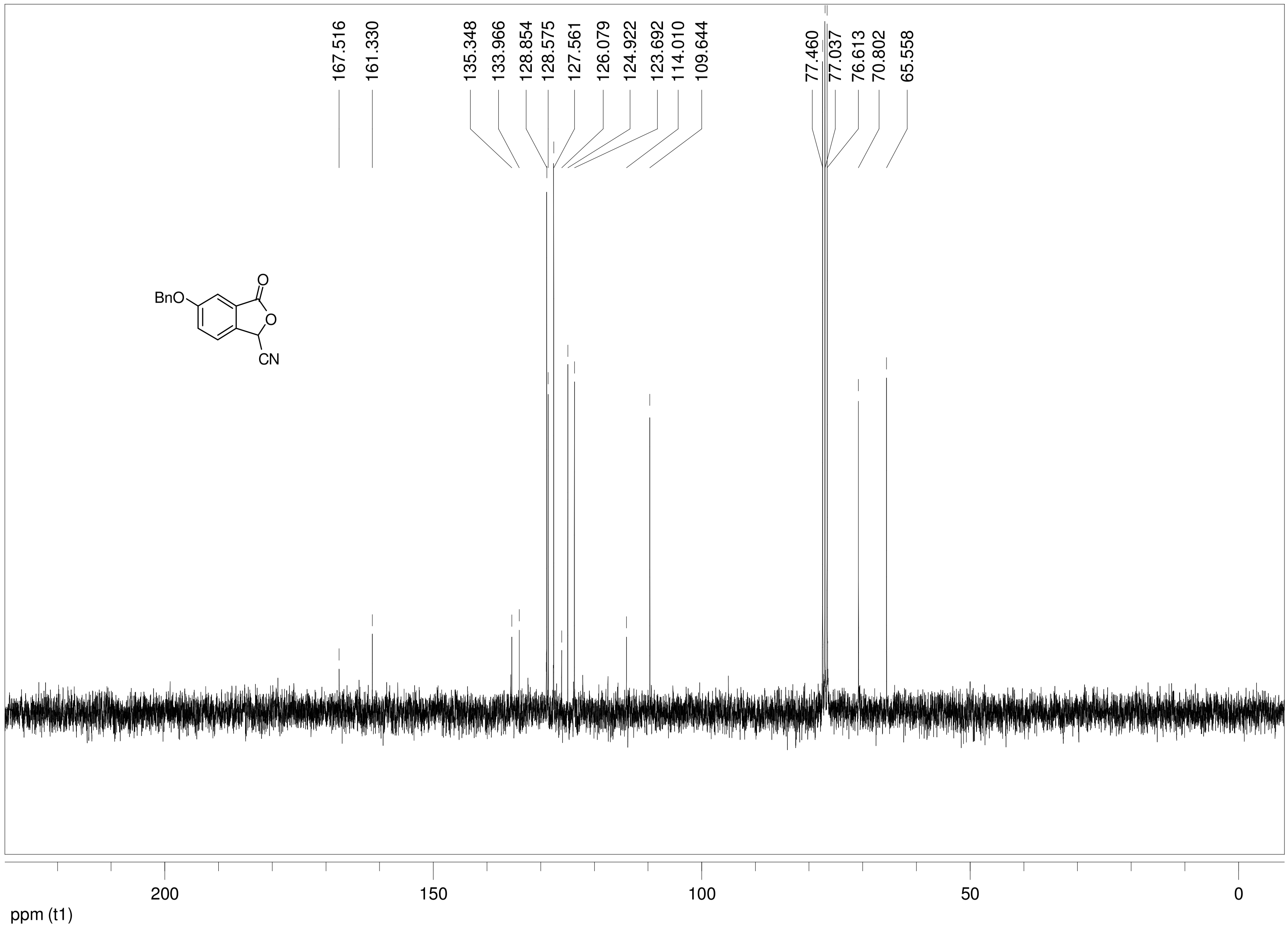
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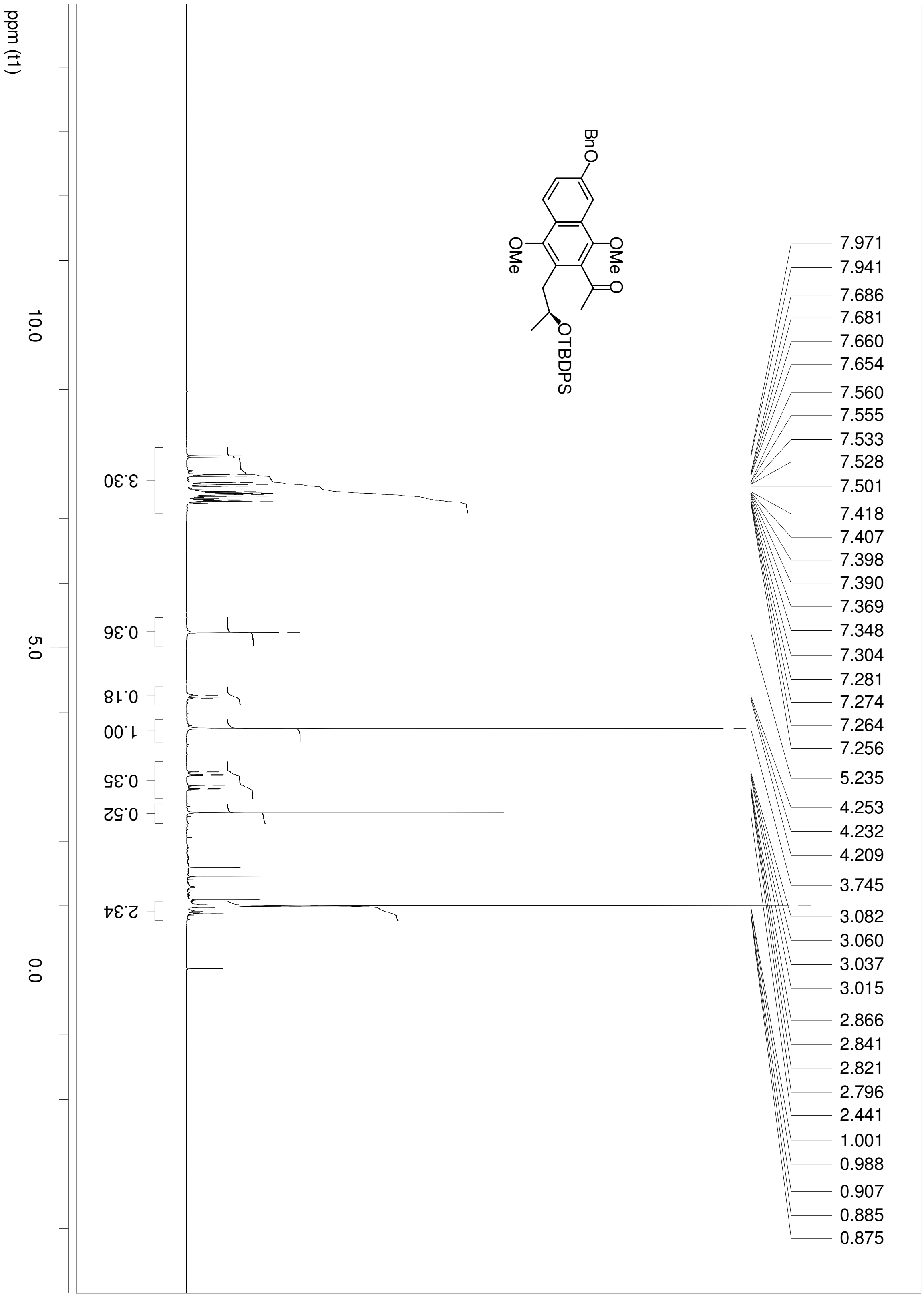
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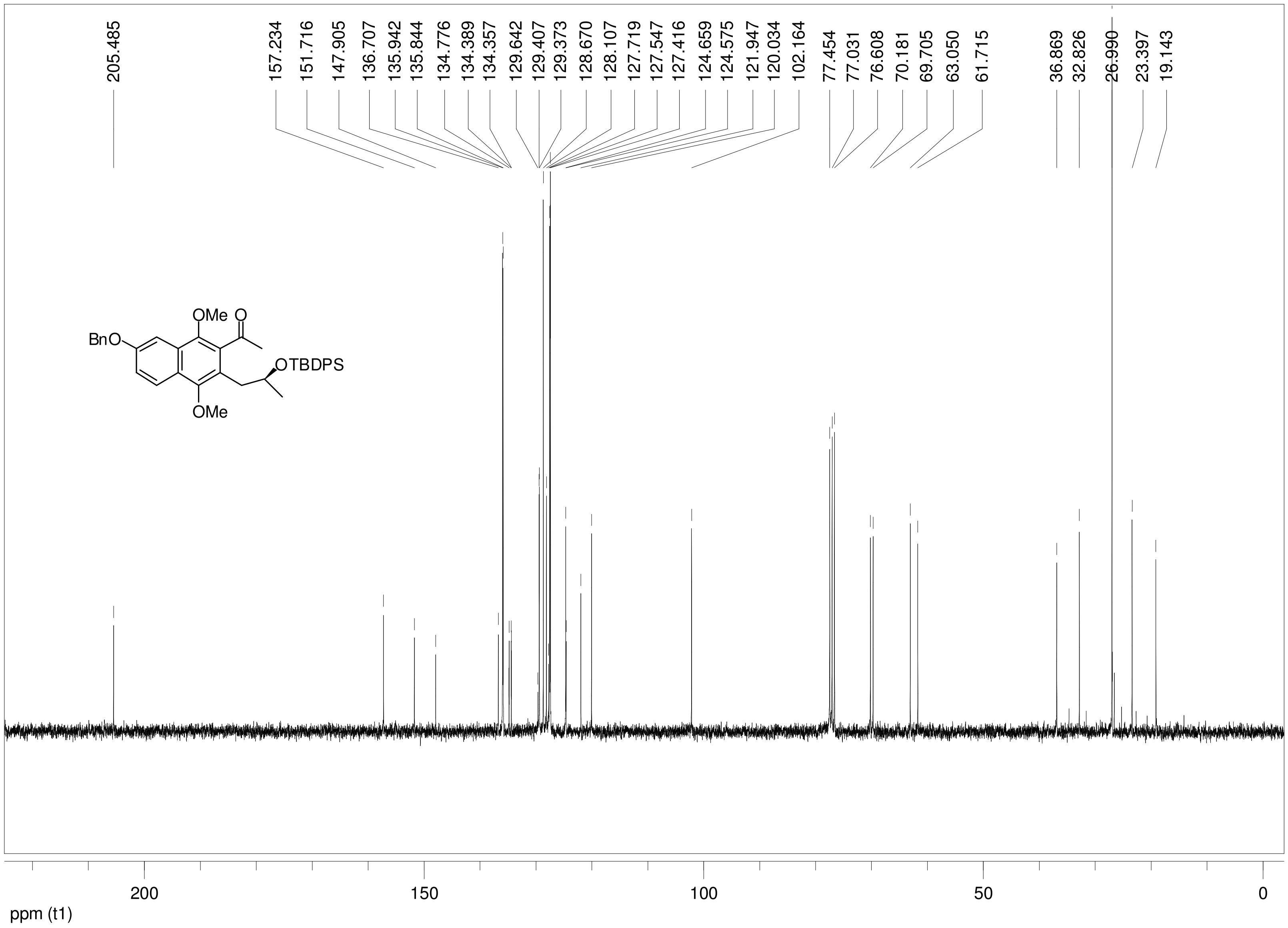
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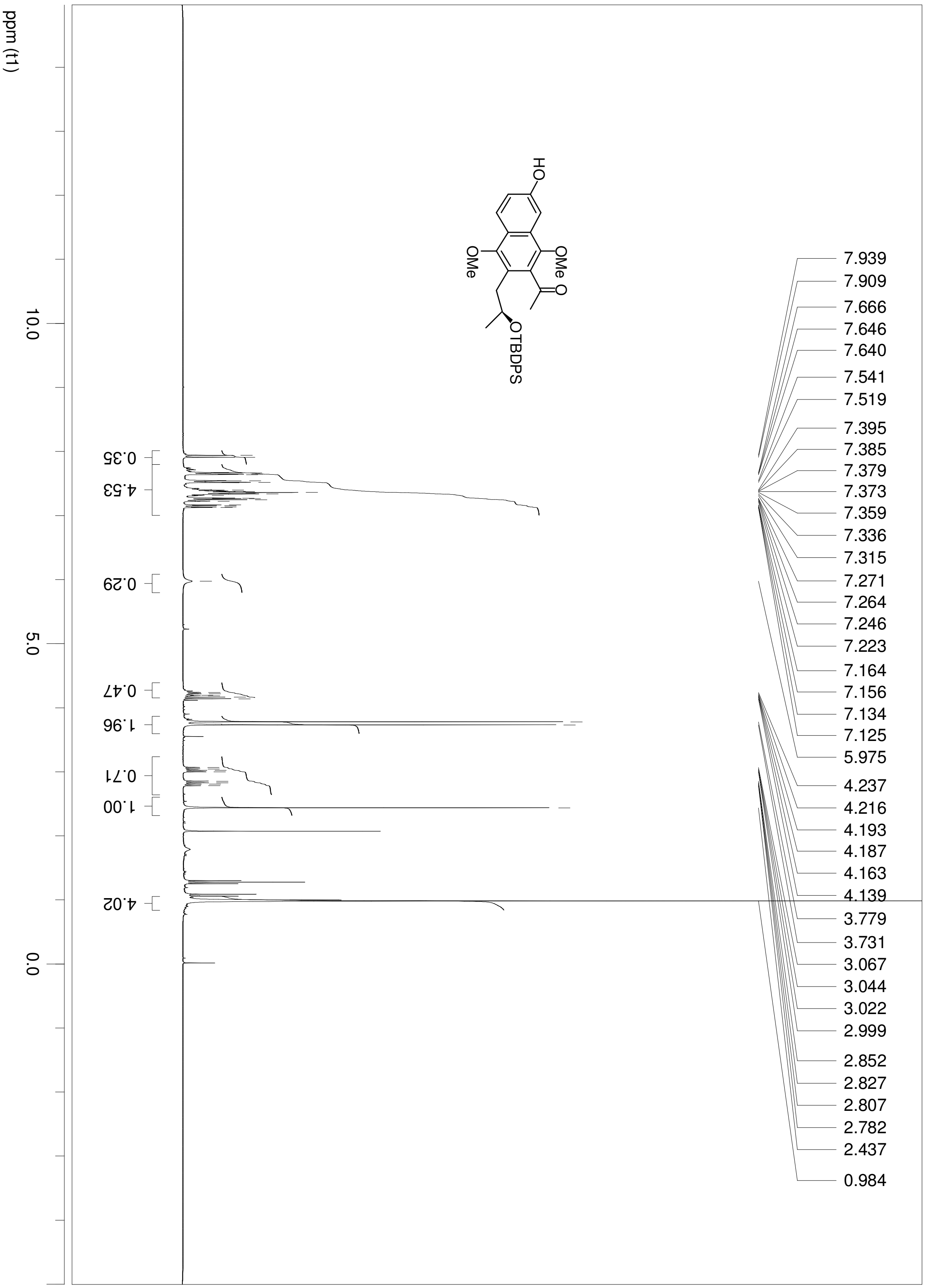
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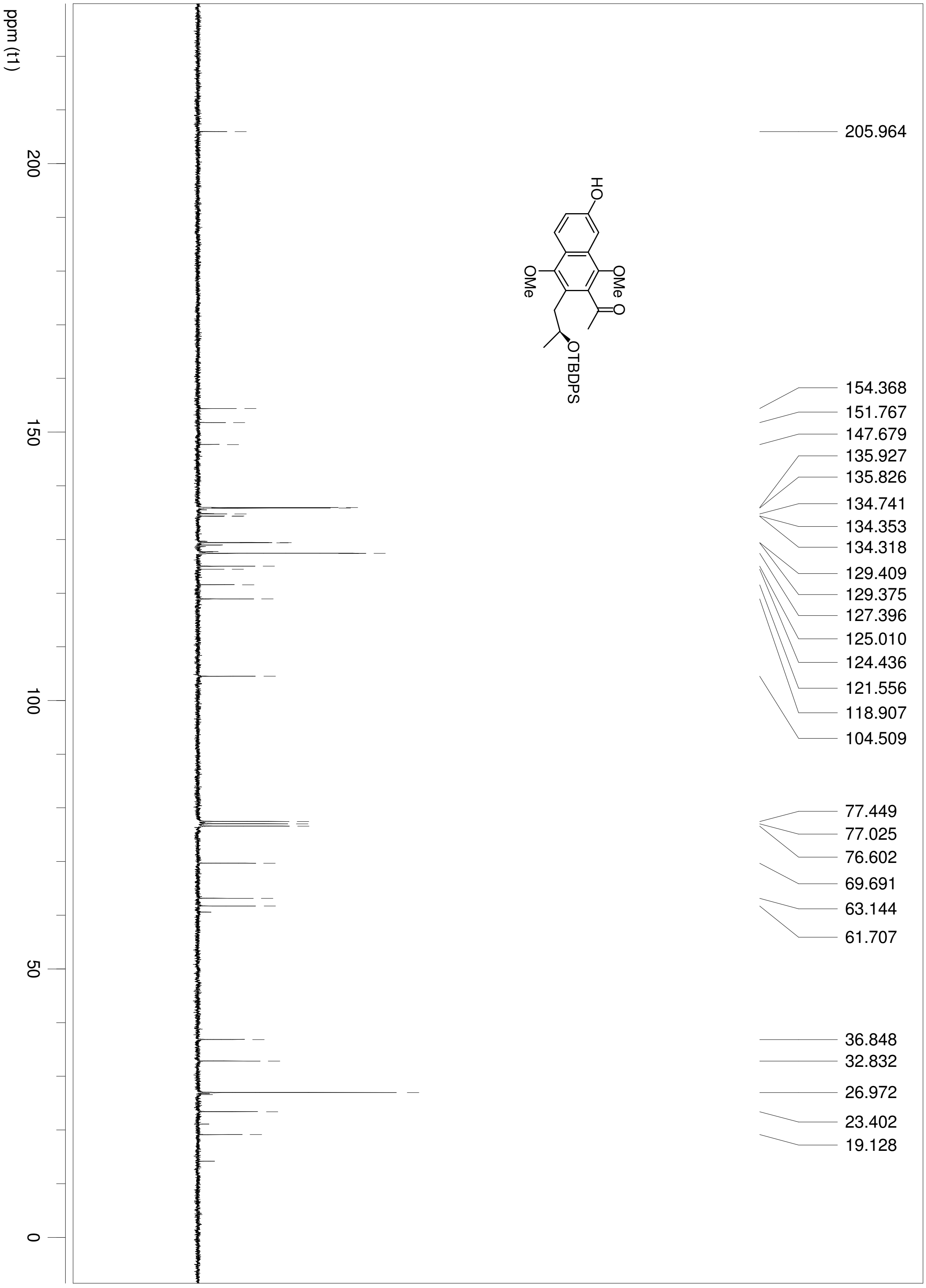

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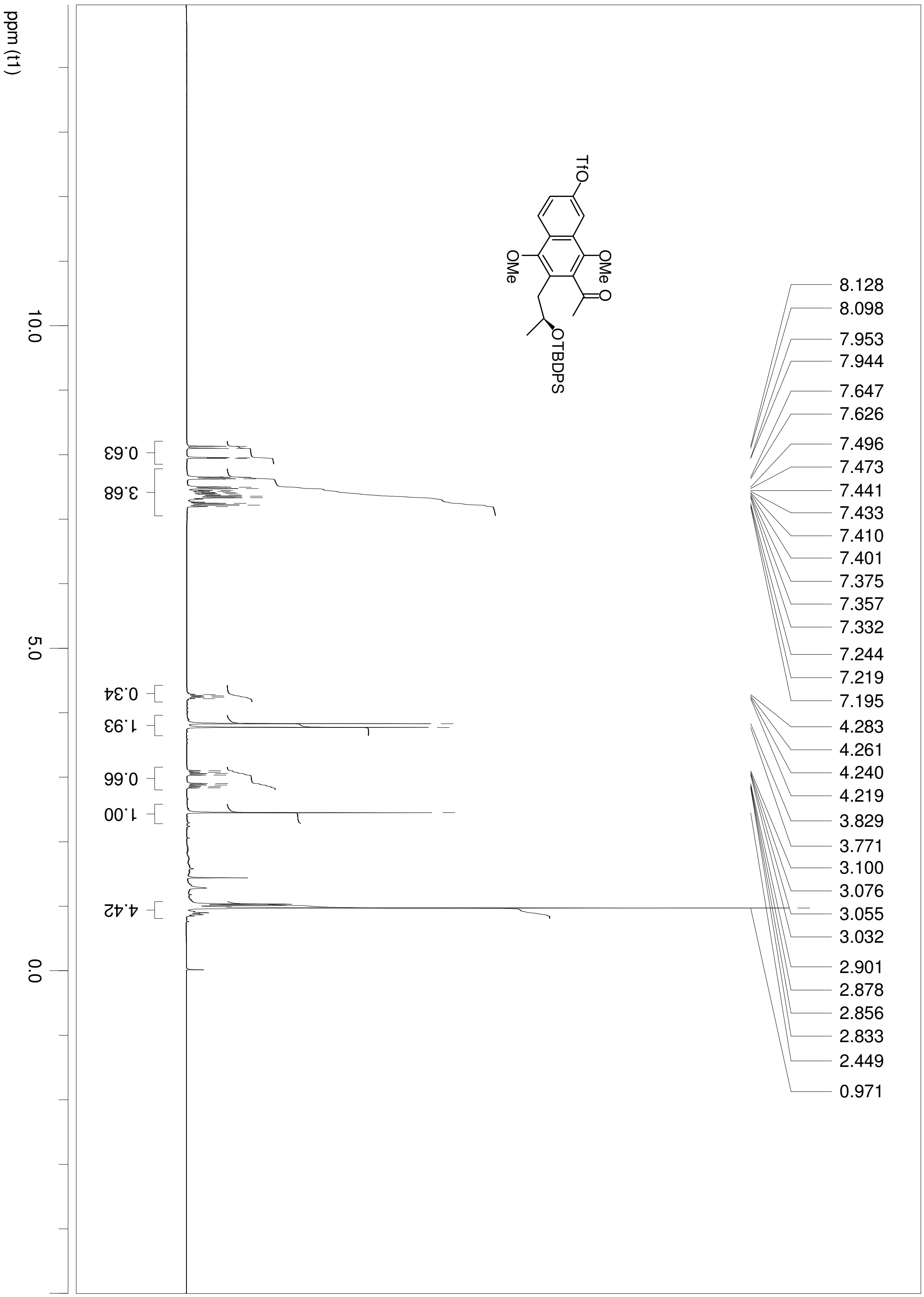

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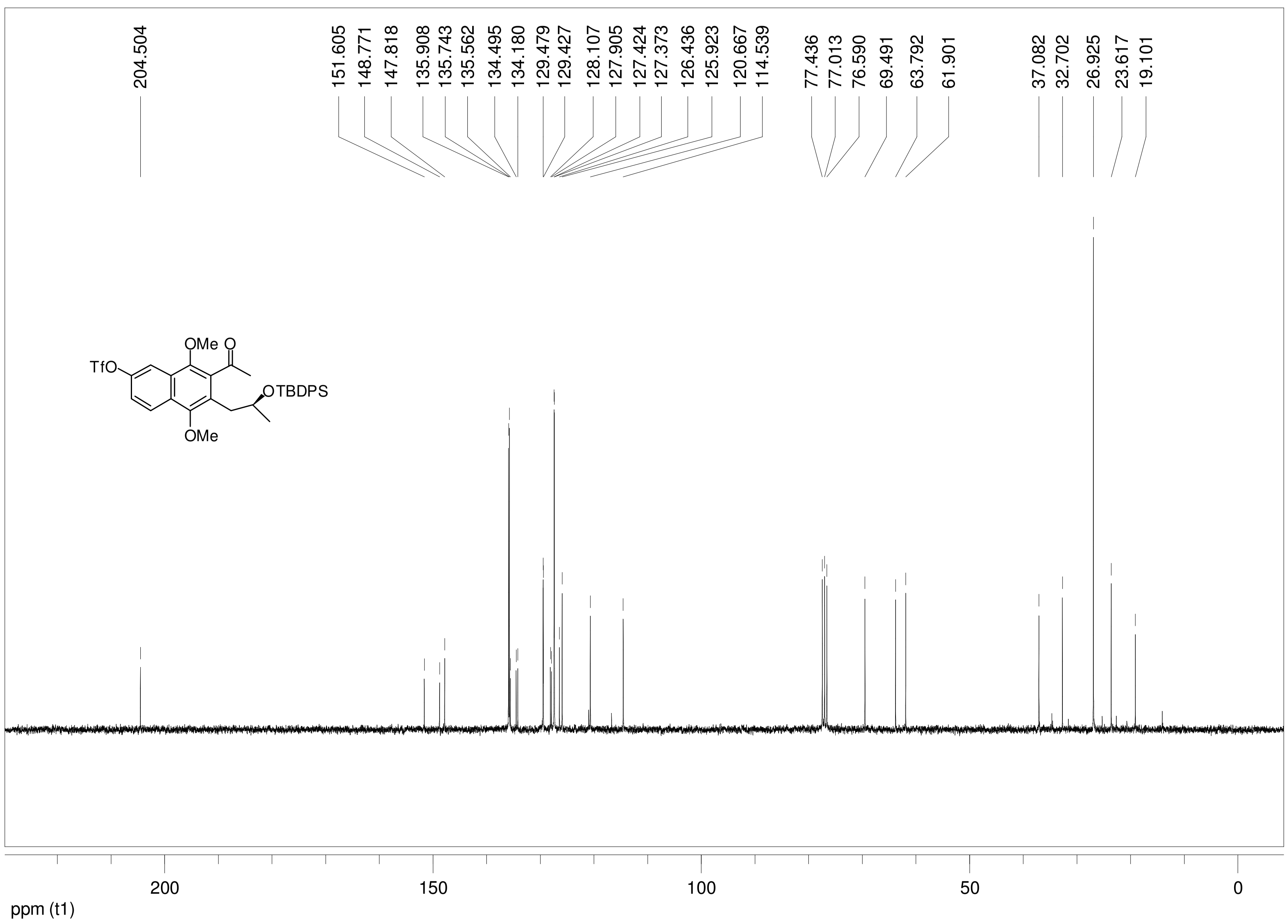
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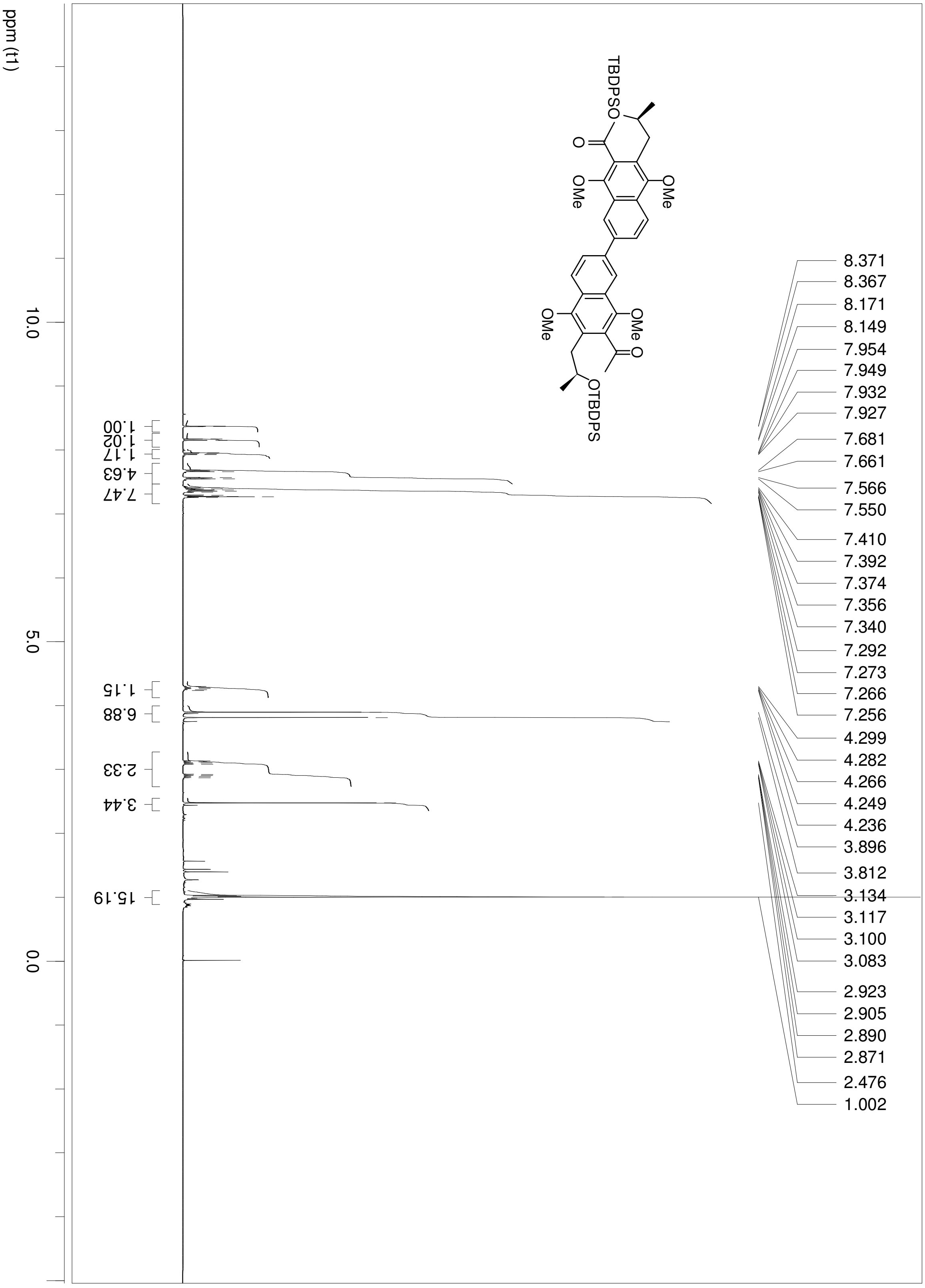
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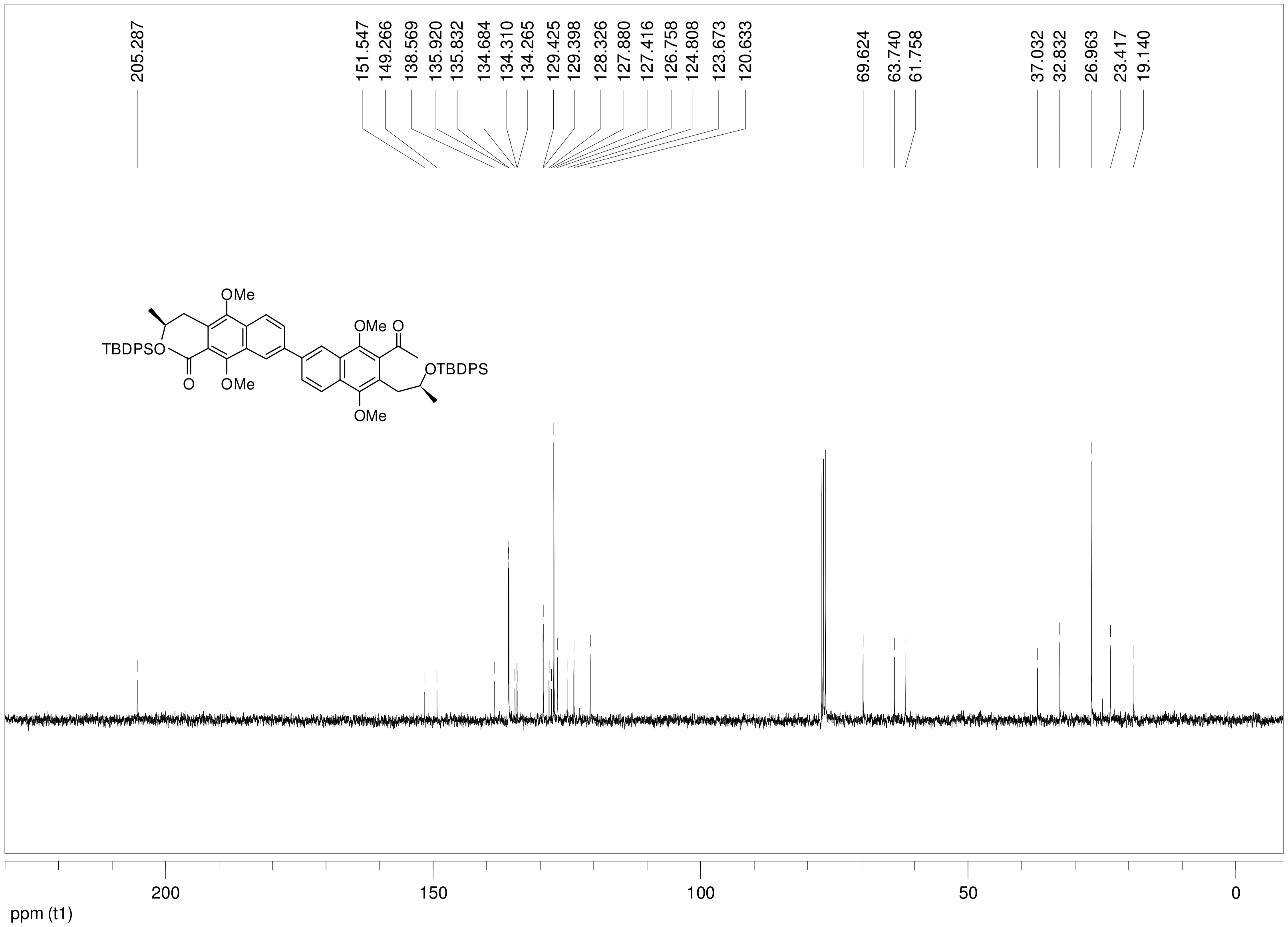
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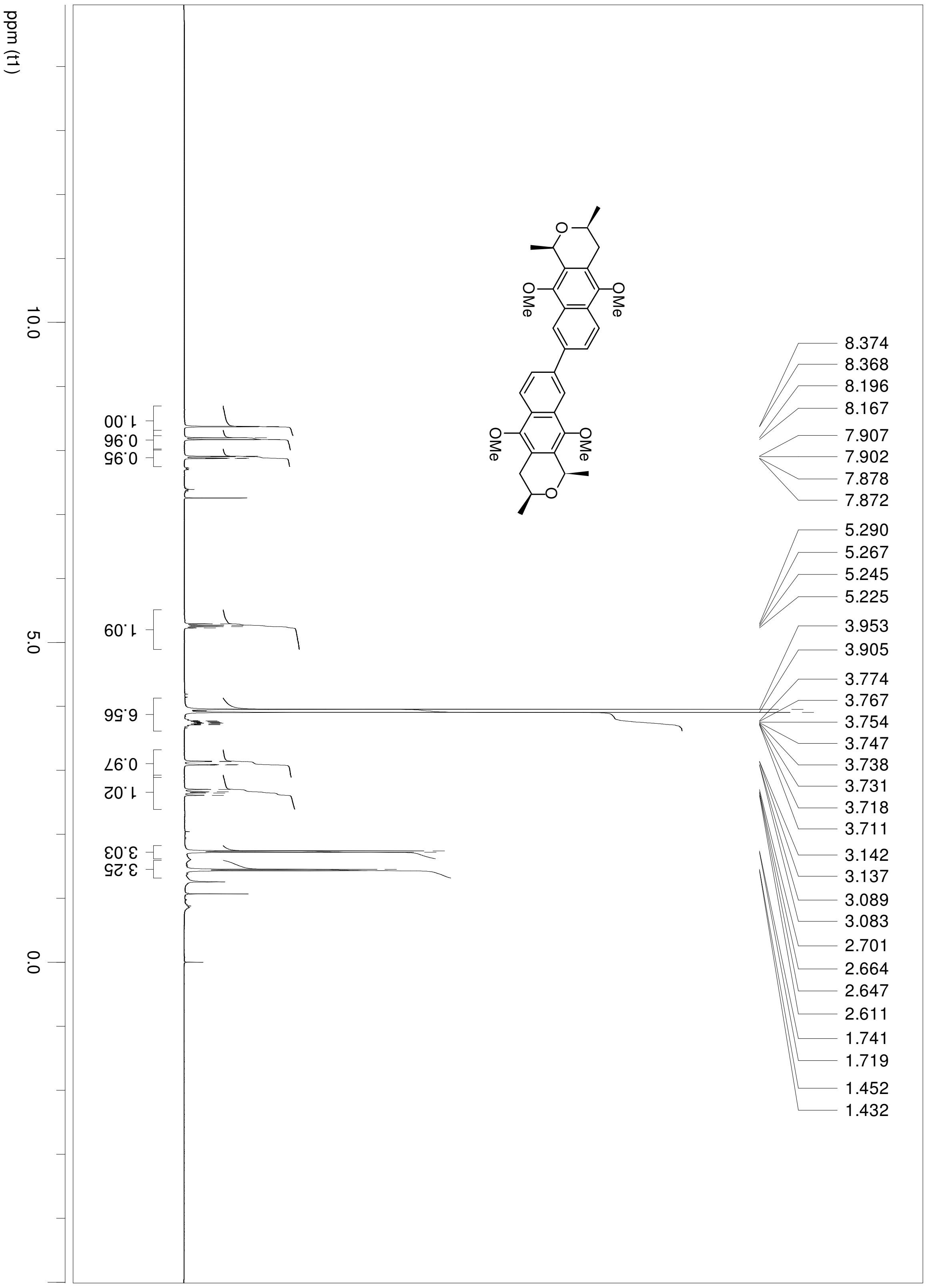
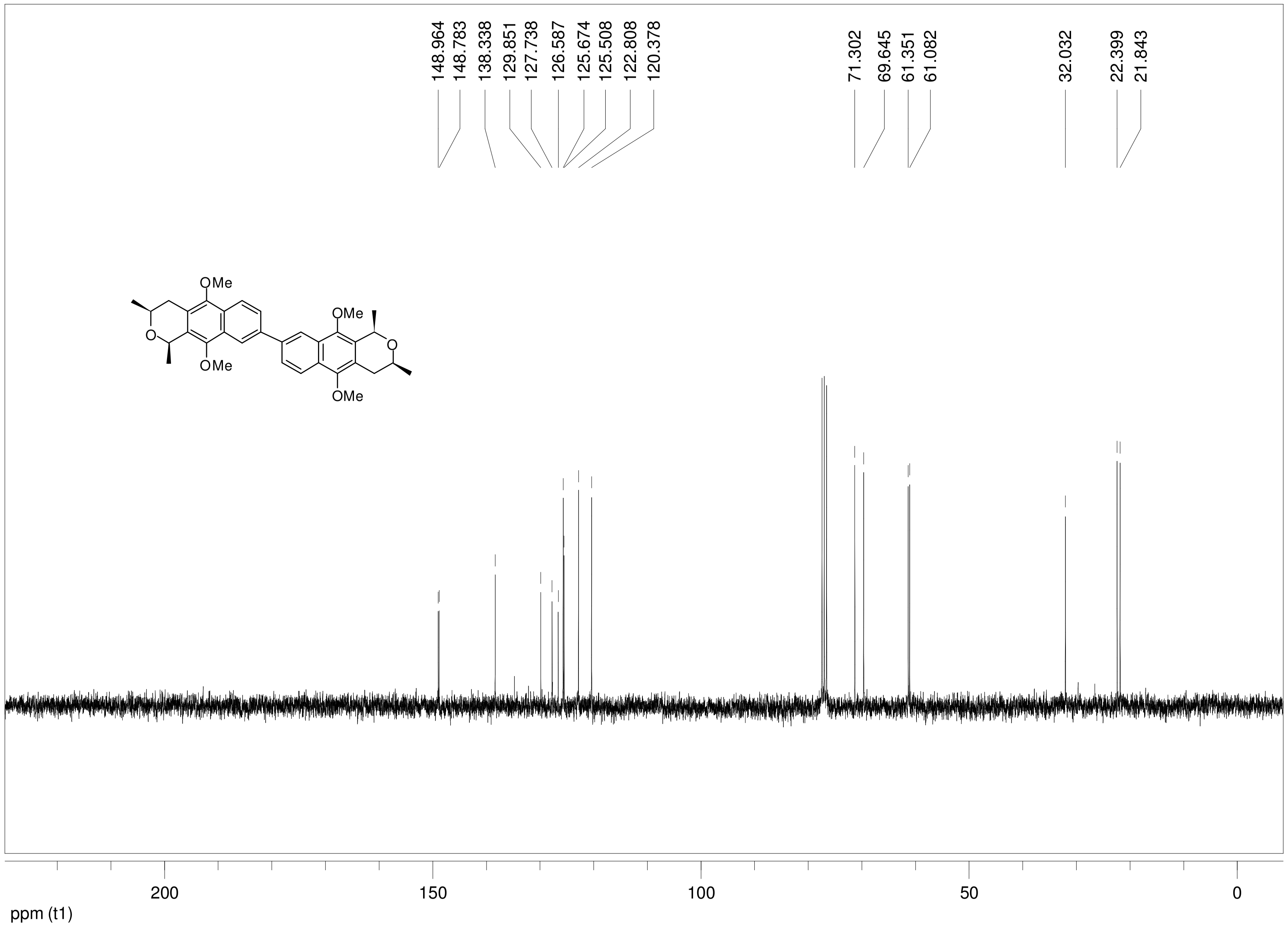
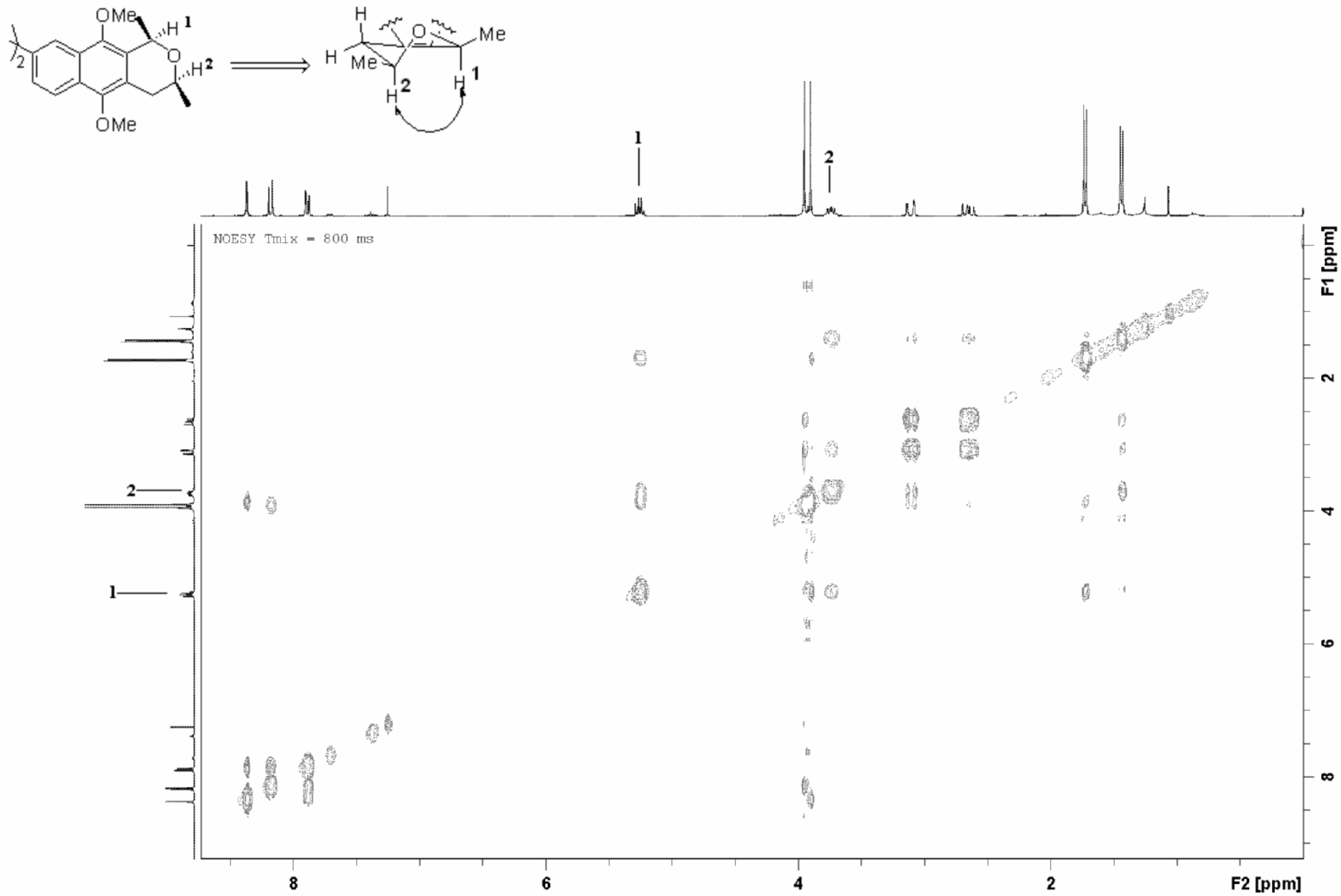
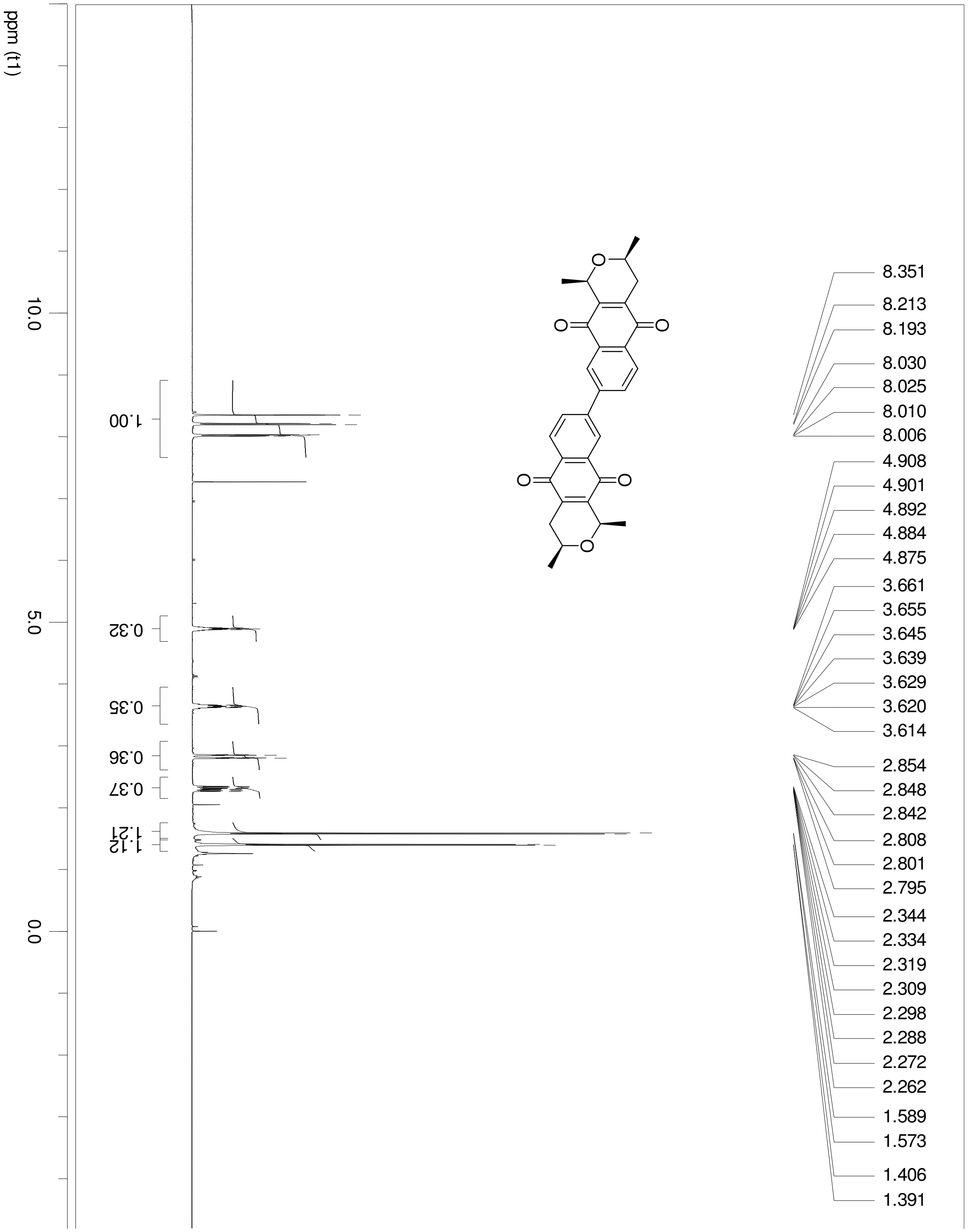
127.416
126.758
124.808
123.673
120.633
69.624
63.740
61.758
37.032
32.832
26.963
23.417
19.140
OMe
TBDPSO
O
OMe
OMe O
OTBDPS
OMe
200
150
100
50
0
ppm (t1)

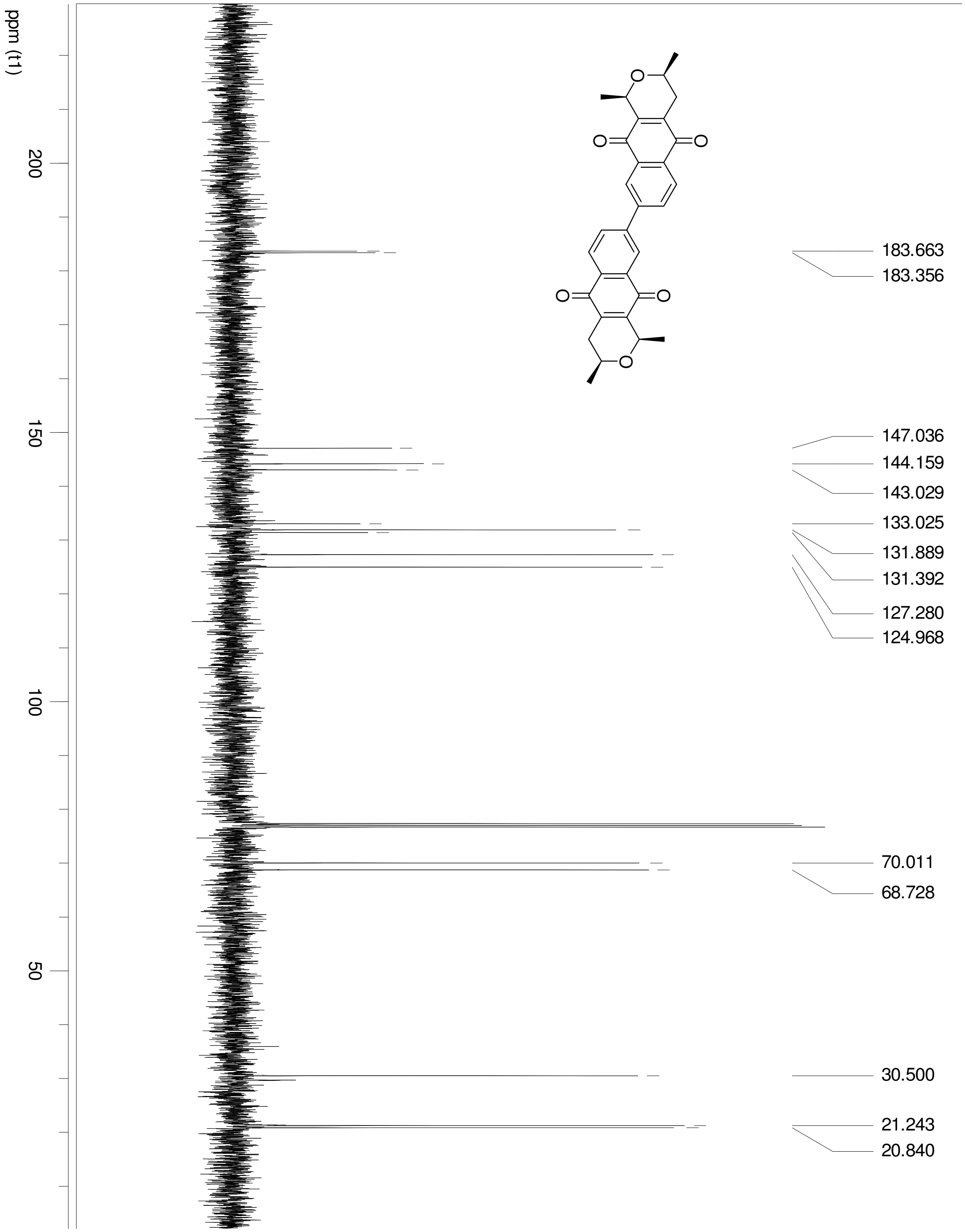


ppm (t1)
10.0
5.0
0.0
1.00
0.96
0.95
1.09
6.56
0.97
1.02
3.03
3.25
OMe
OMe
OMe
OMe
O
O
8.374
8.368
8.196
8.167
7.907
7.902
7.878
7.872
5.290
5.267
5.245
5.225
3.953
3.905
3.774
3.767
3.754
3.747
3.738
3.731
3.718
3.711
3.142
3.137
3.089
3.083
2.701
2.664
2.647
2.611
1.741
1.719
1.452
1.432


148.964
148.783
138.338
129.851
127.738
126.587
125.674
125.508
122.808
120.378
71.302
69.645
61.351
61.082
32.032
22.399
21.843
OMe
OMe
OMe
OMe
O
O
200
150
100
50
0
ppm (t1)


OMe
H 1
O
H 2
2
OMe
H
O
Me
H
Me
H 2
H 1
1
2
NOESY Tmix = 800 ms
F1 [ppm]
2
4
6
8
2
1
8
6
4
2
F2 [ppm]


ppm (t1)
10.0
5.0
0.0
1.00
0.32
0.35
0.36
0.37
1.21
1.12
8.351
8.213
8.193
8.030
8.025
8.010
8.006
4.908
4.901
4.892
4.884
4.875
3.661
3.655
3.645
3.639
3.629
3.620
3.614
2.854
2.848
2.842
2.808
2.801
2.795
2.344
2.334
2.319
2.309
2.298
2.288
2.272
2.262
1.589
1.573
1.406
1.391


ppm (t1)
200
150
100
50
183.663
183.356
147.036
144.159
143.029
133.025
131.889
131.392
127.280
124.968
70.011
68.728
30.500
21.243
20.840
O