Phosphine/Palladium-Catalyzed Syntheses of Alkylidene Phthalans, 3-Deoxyisoochracinic Acid, Isoochracinic Acid, and Isoochracinol

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Contents

Supporting Information

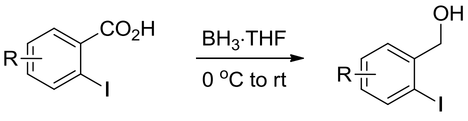
General Procedures. All reactions were performed in flamed-dried or oven-dried round-bottom flasks or Schlenk flasks. A glass water condenser was fitted over each flask, with a rubber septum fitted over the condenser. All reactions were performed under positive pressure of Ar. Stainless-steel needles and a syringe pump were used to inject the acetylenes into the refluxing reaction mixtures. Reactions were monitored through thin-layer chromatography (TLC) on 0.25-mm SiliCycle silica gel plates. Plates were visualized under UV light or stained with *p*-anisaldehyde or potassium permanganate, followed by heating (<1 min) with a heat gun. Flash column chromatography (FCC) was performed using SiliCycle Silica-P Flash silica gel (60 Å pore size, 40–63 µm). Organic solutions were concentrated in rotary evaporators under reduced pressure.

Materials. 2-Iodobenzyl alcohol **4a** and ethynyl *p*-tolyl sulfone **5e** were purchased from Sigma–Aldrich. Methyl propiolate **5a** was purchased from TCI America. 3-Butyn-2-one **5c** was purchased from Acros Organics. Reagents were used as received from commercial sources. MeCN and CH_2Cl_2 were distilled from CaH_2 under positive pressure of Ar. Tetrahydrofuran (THF) and Et_2O were distilled from Na/benzophenone under positive pressure of Ar. Dimethyoxyethane was distilled from $LiAlH_4$ under reduced pressure.

Instrumentation. IR spectra were recorded using a Thermo Nicolet Avatar 370 FT-IR spectrometer. NMR spectra were recorded using Bruker ARX-400, AV-300, and AV-500 instruments calibrated to signals from the solvent as an internal reference [7.26 (residual $CHCl_3$) and 77.00 ($CDCl_3$) ppm for ^1H and ^{13}C NMR spectra, respectively]. Data for ^1H NMR spectra are reported as follows: chemical shift (δ/ppm), multiplicity, coupling constant (Hz), and integration. Data for ^{13}C NMR spectra are reported in terms of chemical shift. The following abbreviations are used to denote multiplicities: s = singlet; d = doublet; t = triplet; q = quartet; dd = doublet of doublets; ddd = doublet of doublets of doublets; td = triplet of doublets; m = multiplet. Mass spectra were recorded using a Waters LCT Premier XE time-of-flight instrument controlled by MassLynx 4.1 software. Samples were infused using direct loop injection from a Waters Acquity UPLC into the multi-mode ionization source. The lock mass standard for accurate mass determination was leucine enkephalin (Sigma L9133). An Agilent Technologies 5975 inert XL mass-selective detector GCMS was also used.

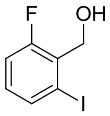
Preparation of Pronucleophiles

Synthesis of Pronucleophiles 4b and 4i–4k



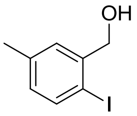
4b, **4i–4k**

2-Iodobenzoic acid (0.99 g, 3.7 mmol) was dissolved in THF (7 mL) and cooled to 0 °C. A solution of borane (1 M) in THF (7.8 mL, 7.8 mmol) was added into the stirring solution at 0 °C. The reaction mixture was then warmed to room temperature and stirred for 2 h, monitoring through TLC (30% EtOAc in hexanes). Upon completion, the reaction was quenched through the addition of water (15 mL) at 0 °C and saturated with K_2CO_3. After extraction with Et_2O (3 × 20 mL), the combined organic phases were dried (Na_2SO_4) and concentrated in vacuo. The residue was purified through FCC (SiO_2; 30% EtOAc in hexanes) to yield the target pronucleophile.



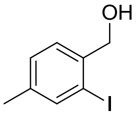
4b

(2-Fluoro-6-iodophenyl)methanol (4b): 83% yield; white solid. M.p.: 54–55 °C; IR (CH_2Cl_2) ν_{max} 3355.9, 2955.2, 2857.7, 1588.0, 1465.2, 1261.9, 840.3, 781.4 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.64 (d, *J* = 7.6 Hz, 1H), 7.10–7.05 (m, 1H), 7.04–6.98 (m, 1H), 4.83 (dd, *J* = 6.6, 2.2 Hz, 2H), 2.05 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.8, 159.3, 135.3, 131.2, 130.5, 116.1, 115.8, 100.5, 62.6; GCMS (EI+) calcd for [C_7H_6FIO]: *m*/*z* 251.9, found 252.0.



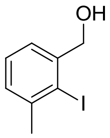
4i

(2-Iodo-5-methylphenyl)methanol (4i): 79% yield. Spectral data matched those reported in the literature.[1]



4j

(2-Iodo-4-methylphenyl)methanol (4j): 27% yield. Spectral data matched those reported in the literature.[2]



4k

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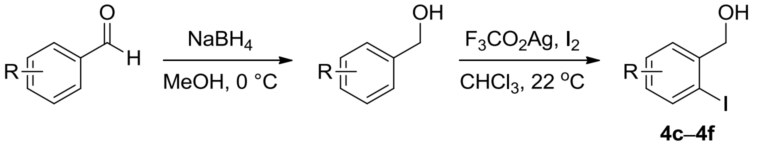
[1] Chouhan, G., Alper, H. *J. Org. Chem.* **2009**, *74*, 6181.

[2] Panetta, C. A., Garlick, S. M., Durst, H. D., Longo, F. R., Ward, J. R. *J. Org. Chem.* **1990**, *55*, 5202.

(2-Iodo-3-methylphenyl)methanol (4k): 89% yield. Spectral data matched those reported in the literature.[3]

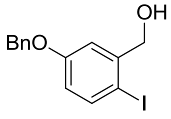
Synthesis of Pronucleophiles 4c–4f



4c–4f

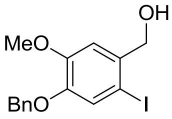
The procedure for reducing various aryl aldehydes was adapted from that reported by Snyder.[4] $NaBH_4$ (0.75 g, 20 mmol) was added slowly into a stirring solution of the aryl aldehyde (10 mmol) in MeOH (20 mL) at 0 °C. The reactions were monitored through TLC (30% EtOAc in hexanes). Upon completion, the reaction was quenched through slow addition of water (20 mL) at 0 °C. After extraction with EtOAc (3 × 20 mL), the combined organic phases were washed with water (60 mL) and brine (60 mL) and then dried (Na_2SO_4). The organic solution was concentrated in vacuo to afford the desired benzyl alcohol, which was used without further purification.

The procedure for *o*-iodination of benzyl alcohols was adapted from that reported by Domínguez.[5] A saturated solution of I_2 in $CHCl_3$ was cannulated into a stirring solution of the benzyl alcohol (10 mmol) and silver trifluoroacetate (2.43 g, 11 mmol) in $CHCl_3$ (50 mL) at room temperature over a period of 10 min. The resulting suspension was stirred for 2 h and monitored (TLC; 30% EtOAc in hexanes). Upon completion, the mixture was filtered through a layer of Celite and concentrated in vacuo. The iodinated product was purified through recrystallization (EtOAc/hexane, 1:1).



4c

(5-Benzyloxy-2-iodophenyl)methanol (4c): 85% yield. Spectral data matched those reported in the literature.[6]



4d

(4-Benzyloxy-2-iodo-5-methoxyphenyl)methanol (4d): 82% yield. Spectral data matched those reported in the literature.[7]

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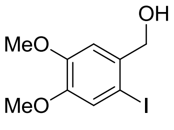
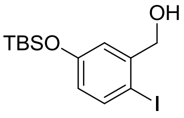
[3] Curran, D. P., Fairweather, N. *J. Org. Chem.* **2003**, *68*, 2972.
[4] Synder, S. A., Breazzano, S. P., Ross, A. G., Lin, Y., Zografos, A. L. *J. Am. Chem. Soc.* **2009**, *131*, 1753.
[5] Olivera, R., SanMartin, R., Domínguez, E., Solans, X., Urtiaga, M. K., Arriortua, M. I. *J. Org. Chem.* **2000**, *65*, 6398.
[6] Prasad, C. V. C., Mercer, S. E., Dubowchik, G. M., Macor, J. E. *Tetrahedron Letters* **2007**, *48*, 2661.
[7] Bernhard, W., Sven, N. *Archiv de Pharmazie* **1995**, *328*, 301.



4e

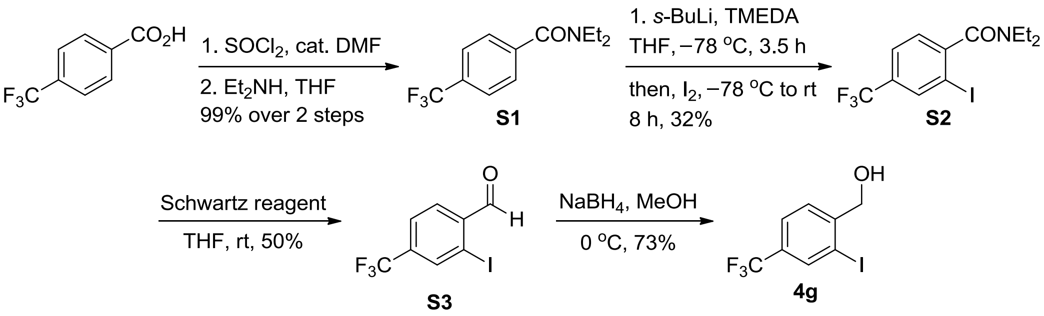
(2-Iodo-4,5-dimethoxyphenyl)methanol (4e): 47% yield. Spectral data matched those reported in the literature.[5]

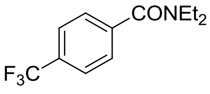


4f

[5-(*tert*-Butyldimethylsilyloxy)-2-iodophenyl]methanol (4f): 81% yield; yellow oil; IR (CH_2Cl_2) ν_{max} 3362.4, 2949.8, 2890.3, 1597.7, 1568.9, 1447.9, 1013.4, 774.7 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 (d, *J* = 8.4 Hz, 1H), 6.98 (d, *J* = 3.2 Hz, 1H), 6.52 (q, *J* = 3.9 Hz, 1H), 4.59 (s, 2H), 2.09 (s, 1H), 0.98 (s, 9H), 0.20 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.5, 143.8, 139.7, 121.2, 120.6, 86.4, 69.1, 25.6, 18.2, –4.4; GCMS (EI+) calcd for [$C_{13}H_{21}IO_2Si$]: *m*/*z* 364.0, found 364.1.

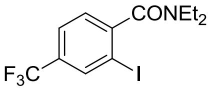
Synthesis of Pronucleophile 4g





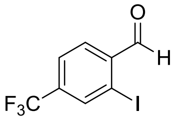
S1

***N,N*-Diethyl-4-(trifluoromethyl)benzamide (S1):** Prepared through amidation in 99% yield.[8] Spectral data matched those reported in the literature.[9]



S2

***N,N*-Diethyl-2-iodo-4-(trifluoromethyl)benzamide (S2):** The substituted benzamide **S1** (2.44 g, 9.90 mmol) was dissolved in THF (25 mL) and cooled to –78 °C. *N,N,N´,N´*- Tetramethylethylenediamine (1.62 mL, 10.9 mmol) was added slowly to the reaction mixture, followed by 1.25 M *s*-BuLi in cyclohexane (8.75 mL). The reaction mixture was stirred for 3.5 h at –78 °C, forming a golden yellow solution with a white precipitate.[10] A solution of I_2 (2.76 g, 10.9 mmol) in THF (7 mL) was cannulated slowly into the reaction mixture at –78 °C. The mixture was warmed from –78 °C to room temperature slowly (overnight). Upon completion of the reaction, the mixture was cooled to 0 °C and quenched with sat. aqueous NH_4Cl (10 mL). The aqueous phase was extracted with CH_2Cl_2 (3 × 30 mL); the combined organic phases were washed with water (3 × 30 mL), dried (Na_2SO_4), and concentrated in vacuo. The residue was purified through FCC (SiO_2; 30% EtOAc in hexanes) to yield a yellow oil (1.16 g, 32%). IR (CH_2Cl_2) ν_{max} 3077.8, 2978.5, 1631.5, 1319.1, 1169.6, 1125.3, 1072.2, 840.8 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.04 (s, 1H), 7.62 (dd, *J* = 7.9, 0.8 Hz, 1H), 7.30 (d, *J* = 7.9 Hz, 1H), 3.87–3.81 (m, 1H), 3.31–3.23 (m, 1H), 3.18–3.11 (m, 1H), 3.07–3.02 (m, 1H), 1.27 (t, *J* = 7.1 Hz, 3H), 1.06 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.9, 146.4, 136.0 (q, $J_{C–F}$ = 3.8 Hz), 131.8 (q, $J_{C–F}$ = 32.9 Hz), 130.4, 127.0, 125.3 (q, $J_{C–F}$ = 3.6 Hz), 123.7, 121.5, 92.7, 42.8, 39.1, 13.9, 12.4; GCMS (EI+) calcd for [$C_{12}H_{13}F_3INO$]: *m*/*z* 371.0, found 371.0.



S3

2-Iodo-4-(trifluoromethyl)benzaldehyde (S3): Prepared through reduction using the Schwartz reagent, as reported by Georg.[11] Schwartz reagent (0.92 g, 3.57 mmol) was added to a solution of the benzamide **S2** (0.88 g, 2.38 mmol) in THF (25 mL) at room temperature. The mixture was stirred at ambient temperature and monitored (TLC) until the reaction reached completion. The reaction was quenched with H_2O (10 mL) and then the aqueous phase was extracted with EtOAc (3 × 20 mL). The combined organic phases were dried (Na_2SO_4) and concentrated in vacuo. The residue was purified through FCC (SiO_2; 20% EtOAc in hexanes) to yield a colorless oil (0.36 g, 50%). IR (CH_2Cl_2) ν_{max} 3075.9, 2928.4, 1701.9, 1317.1, 1174.4, 1134.9, 1075.1, 841.8 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 10.11 (s, 1H), 8.20 (s, 1H), 7.97 (d, *J* = 8.1 Hz, 1H), 7.73 (d, *J* = 8.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 194.3, 137.6, 137.4 (q, $J_{C–F}$ = 3.8 Hz), 136.3 (q, $J_{C–F}$ = 33.2 Hz), 130.3, 129.9, 125.6 (q, $J_{C–F}$ = 3.6 Hz), 122.3 (q, $J_{C–F}$ = 271.8 Hz), 99.6; GCMS (EI+) calcd for [$C_8H_4F_3IO$]: *m*/*z* 299.9, found 299.9.

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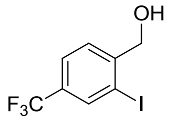
[8] The reaction was heated to reflux for 5 hours until complete consumption of starting carboxylic acid.

[9] Knauber, T.; Arikan, F.; Röschenthaler, G.-V.; GooBen, L. J. *Chem. Eur. J.* **2011**, *17*, 2689.

[10] Wang, X.; de Silva, S. O.; Reed, J. N.; Billadeau, R.; Griffen, E. J.; Chan, A.; Snieckus, V. *Organic Syntheses*, **1995**, *72*, 163.

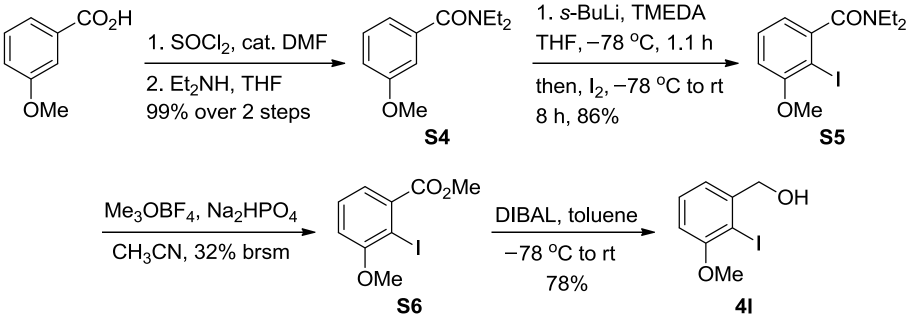
[11] Spletstoser, J. T.; White, J. M.; Tunoori, A. R.; Georg, G. I. *J. Am. Chem. Soc.* **2007**, *129*, 3408.

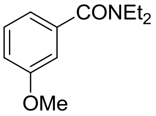


4g

(2-Iodo-4-(trifluoromethyl)phenyl)methanol (4g): $NaBH_4$ (0.09 g, 2.4 mmol) was added slowly into a stirring solution of the aldehyde **S3** (0.36 g, 1.2 mmol) in MeOH (12 mL) at 0 °C. The reaction was monitored using TLC (30% EtOAc in hexanes); upon completion, it was quenched through slow addition of water (5 mL) at 0 °C. The aqueous phase was extracted with EtOAc (3 × 10 mL). The combined organic phases were dried (Na_2SO_4) and concentrated in vacuo. The residue was purified through FCC (SiO_2; 30% EtOAc in hexanes) to yield a white solid (0.27 g, 73%). M.p.: 69–70 °C; IR (CH_2Cl_2) ν_{max} 3324.7, 2917.8, 1393.3, 1315.2, 1168.7, 1122.4, 1077.1, 828.3 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.01 (s, 1H), 7.59 (d, *J* = 8.1 Hz, 1H), 7.52 (d, *J* = 8.1 Hz, 1H), 4.63 (s, 2H), 3.07 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 146.4, 135.8 (q, $J_{C–F}$ = 3.8 Hz), 131.1 (q, $J_{C–F}$ = 32.7), 127.8, 125.3 (q, $J_{C–F}$ = 3.7 Hz), 122.9 (q, $J_{C–F}$ = 271.0 Hz), 96.1, 68.7; GCMS (EI+) calcd for $[C_8H_6F_3IO]$: *m*/*z* 301.9, found 301.9.

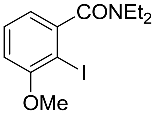
Synthesis of Pronucleophile 4l





S4

***N*,*N*-Diethyl-3-methoxybenzamide (S4):** Prepared in 99% yield.[10] Spectral data matched those reported in the literature.[12]



S5

***N*,*N*-Diethyl-2-iodo-3-methoxybenzamide (S5):** Using the procedure described above for the synthesis of the benzamide **S2**, the benzamide **S5** (2.86 g, 86%) was obtained as a yellow oil. Spectral data matched those reported in the literature.[13]

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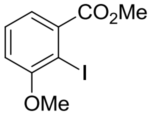
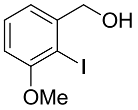
[12] Egan, B. A.; Paradowski, M.; Thomas, L. H.; Marquez, R. *Org. Lett.* **2011**, *13*, 2086.

[13] Balloch, L.; Kennedy, A. R.; Mulvey, R. E.; Rantanen, T.; Robertson, S. D.; Snieckus, V. *Organometallics* **2011**, *30*, 145.



S6

Methyl 2-Hydroxy-6-iodobenzoate (S6): Na_2HPO_4 (1.38 g, 9.72 mmol) and Me_3OBF_4 (2.88 g, 19.44 mmol) were added at room temperature to a suspension of the substituted benzamide **S5** (2.16 g, 6.48 mmol) in MeCN (57 mL). The mixture was stirred for 18 h at ambient temperature before sat. aqueous $NaHCO_3$ (23 mL) was added, followed by solid $NaHCO_3$ (1.63 g, 19.4 mmol). The slurry was stirred for another 18 h at room temperature. The aqueous phase was extracted with EtOAc (3 × 30 mL); the combined organic phases were dried (Na_2SO_4) and concentrated in vacuo. The residue was purified through FCC (SiO_2; 30% EtOAc in hexanes) to yield a white solid (0.37 g, 32% brsm). Spectral data matched those reported in the literature.[14]



4l

(2-Iodo-3-methoxyphenyl)methanol (4l): 1 M Diisobutylaluminum hydride in hexanes (3.1 mL) was added dropwise to a solution of the substituted methylbenzoate **S6** (0.37 g, 1.26 mmol) in toluene (11 mL) at –78 °C. The mixture was then warmed to room temperature slowly (overnight). After cooling to –78 °C, the reaction was quenched through the addition of MeOH (0.45 mL), solid $Na_2SO_4\cdot 10H_2O$ (0.18 g), Celite (0.28 g), and water (0.09 mL). The mixture was warmed to room temperature overnight, filtered through a pad of Celite, and concentrated in vacuo. The residue was purified through FCC (SiO_2; 30% EtOAc in hexanes) to yield a white solid (0.26 g, 78%). Spectral data matched those reported in the literature.[15]

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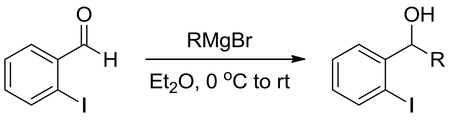
[14] Pollard, M. M.; ter Wiel, M. K. J.; van Delden, R. A.; Vicario, J.; Koumura, N.; van den Brom, C. R.; Meetsma, A.; Feringa, B. L. *Chem. Eur. J.* **2008**, *14*, 11610.

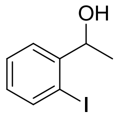
[15] Neufeind, S.; Hülsken, N.; Neudörfl, J.-M.; Schlörer, N.; Schmalz, H.-G. *Chem. Eur. J.* **2011**, *17*, 2633.

Synthesis of Pronucleophiles 4m–4o and 4q



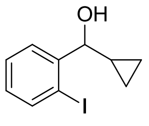
4m–4o

A solution of alkyl/aryl Grignard reagent in Et_2O (4.5 mmol) was added to a stirred solution of *o*-iodobenzaldehyde (0.70 g, 3.0 mmol) in Et_2O (15 mL) at 0 °C. The mixture was warmed to room temperature over 1 h, monitoring through TLC (30% EtOAc in hexanes). The reaction was quenched through the addition of sat. aqueous NH_4Cl (15 mL); the aqueous phase was extracted with Et_2O (3 × 20 mL). The combined organic phases were dried (Na_2SO_4) and concentrated in vacuo. The residue was purified through FCC (SiO_2; 30% EtOAc in hexanes) to yield the target pronucleophile.



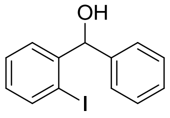
4m

1-(2-Iodophenyl)ethanol (4m): 97% yield. Spectral data matched those reported in the literature.[16]



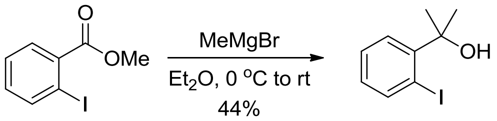
4n

Cyclopropyl(2-iodophenyl)methanol (4n): 69% yield; yellow oil. IR (CH_2Cl_2) ν_{max} 3371.9, 3080.1, 3005.1, 2897.8, 1585.1, 1562.4, 1462.4, 749.2 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.55 (dd, *J* = 8.0, 1.6, Hz, 1H), 7.37 (td, *J* = 7.5, 1.1 Hz, 1H), 6.98 (td, *J* = 7.6, 1.7 Hz, 1H), 4.53 (dd, *J* = 7.2, 2.8 Hz, 1H), 2.17 (d, *J* = 3.2 Hz, 1H), 1.29–1.25 (m, 1H), 0.62–0.54 (m, 2H), 0.53–0.44 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.6, 139.4, 129.4, 128.5, 127.9, 98.5, 79.5, 17.9, 3.3, 2.0; GCMS (EI+) calcd for [$C_{10}H_{11}IO$]: *m*/*z* 274.0, found 274.0.



4o

(2-Iodophenyl)phenylmethanol (4o): 99% yield. Spectral data matched those reported in the literature.[17]



4q

2-(2-Iodophenyl)propan-2-ol (4q): A solution of methyl Grignard was generated by adding iodomethane (0.69 mL, 11.0 mmol) to a stirred solution of diethyl ether and Mg turnings (0.27 g, 11.0 mmol), with initiation through sporadic heating. The methyl Grignard solution was added to a stirring solution of methyl-*o*-iodobenzoate (1.31 g, 5.0 mmol) in Et_2O (25 mL) at 0 °C. The mixture was

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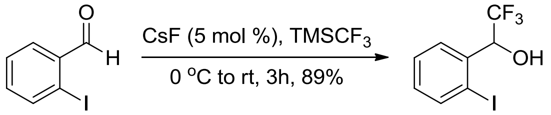
[16] Sälinger, D., Brückner, R. *Chem. Eur. J.* **2009**, *15*, 6688.

[17] Cvengroš, J., Stolz, D., Togni, A. *Synthesis*, **2009**, *16*, 2818.

warmed to room temperature over 1 h, monitoring using TLC (30% EtOAc in hexanes). The reaction was quenched through the addition of sat. aqueous NH_4Cl (20 mL) and the aqueous phase extracted with Et_2O (3 × 20 mL). The combined organic phases were dried (Na_2SO_4) and concentrated in vacuo. The residue was purified through FCC (SiO_2; 30% EtOAc in hexanes) to yield the target pronucleophile (0.58 g, 44%). Spectral data matched those reported in the literature.[18]

Synthesis of Pronucleophile 4p



4p

2,2,2-Trifluoro-1-(2-iodophenyl)ethanol (4p): The procedure for trifluoromethyl addition was adapted from that reported by Ahn.[19] Cesium fluoride (15.2 mg, 0.1 mmol) was added to a solution of 2-iodobenzaldehyde (0.46 g, 2.0 mmol) in dimethyoxyethane (10 mL). The mixture was cooled to 0 °C under Ar and then trifluoromethyltrimethylsilane (0.3 mL, 2.02 mmol) was added dropwise. The ice bath was removed and the mixture warmed to room temperature, monitored using TLC (20% EtOAc in hexanes). Upon completion of the reaction, 10% aqueous HCl (10 mL) was added and then the mixture was stirred for 2 h. The aqueous phase was extracted with EtOAc (3 × 20 mL) and then the combined organic phases were dried (Na_2SO_4) and concentrated in vacuo. The residue was purified through FCC (SiO_2; 20% EtOAc in hexanes) to yield a colorless oil (0.54 g, 89%). IR (CH_2Cl_2) ν_{max} 3421.1, 3065.3, 2926.5, 1265.1, 1174.4, 1130.1, 757.9, 727.0 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.88 (dd, J = 8.0, 1.0 Hz, 1H), 7.64 (d, J = 7.9 Hz, 1H), 7.44 (t, J = 7.6 Hz, 1H), 7.11 (td, J = 7.7, 1.6 Hz, 1H), 5.51–5.47 (m, 1H), 2.60 (d, J = 4.7, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 139.8, 136.8, 131.3, 128.9, 128.7, 124.4 (q, $J_{C\text{–}F}$ = 281.3 Hz), 99.4, 76.0 (q, $J_{C\text{–}F}$ = 31.8 Hz); GCMS (EI+) calcd for $[C_8H_6F_3IO]$: m/z 301.9, found 302.0.

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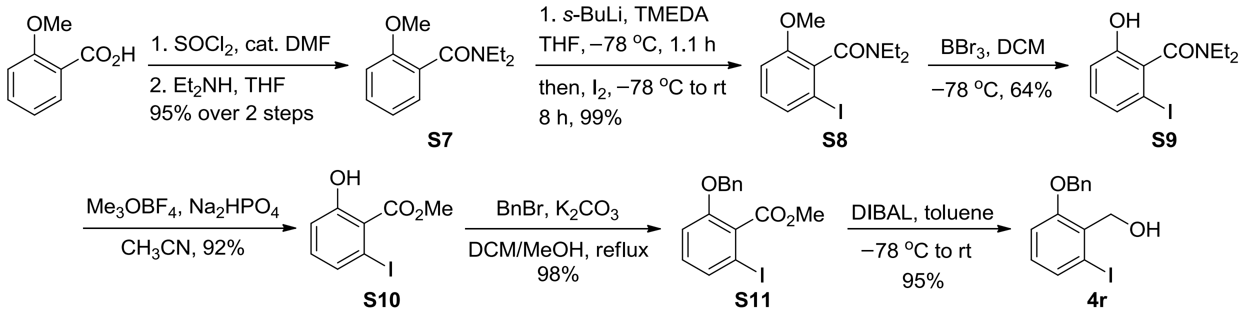
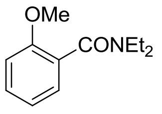
[18] Moss, R. A.; Wilk, B.; Krogh-Jespersen, K.; Blair, J. T.; Westbrook, J. D. *J. Am. Chem. Soc*. **1989**, *111*, 250.

[19] Kim, D.-S.; Ahn, K. H. *J. Org. Chem.* **2008**, *73*, 6831.

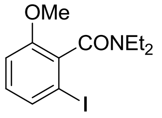
Synthesis of Pronucleophile 4r





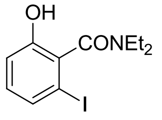
S7

***N,N*-Diethyl-2-methoxybenzamide (S7):** Prepared through amidation in 95% yield.[10] Spectral data matched those reported in the literature.[11]



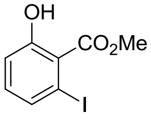
S8

N,N-Diethyl-2-iodo-6-methoxybenzamide (S8): Using the procedure described above for the synthesis of the benzamide **S2**, the benzamide **S8** (11.83 g, 99%) was obtained as a yellow oil. IR (CH_2Cl_2) ν_{max} 3080.7, 2973.7, 1628.6, 1563.0, 1426.1, 1256.4, 1024.9, 752.1 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 (d, *J* = 7.9 Hz, 1H), 7.00 (t, *J* = 8.1 Hz, 1H), 6.87 (d, *J* = 8.4 Hz, 1H), 3.87–3.78 (m, 1H), 3.77 (s, 3H), 3.37–3.28 (m, 1H), 3.13 (q, *J* = 7.2 Hz, 2H), 1.28 (t, *J* = 7.1 Hz, 3H), 1.07 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.8, 156.0, 132.1, 131.1, 130.6, 110.6, 94.1, 55.8, 42.6, 38.7, 13.7, 12.4; GCMS (EI+) calcd for [$C_{12}H_{16}INO_2$]: *m*/*z* 333.0, found 333.1.



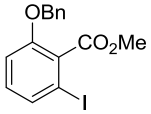
S9

***N,N*-Diethyl-2-hydroxy-6-iodobenzamide (S9):** BBr_3 (34.1 mL, 353.6 mmol) was added dropwise to a solution of the benzamide **S8** (29.5 g, 88.5 mmol) in CH_2Cl_2 (443 mL) at –78 °C. The mixture was stirred overnight and slowly warmed to room temperature. The mixture was cooled to –78 °C, quenched through the addition of MeOH (100 ml) and water (200 mL), and then stirred for 3 h. The organic phase was washed with water (3 × 200 mL), dried (Na_2SO_4), and concentrated in vacuo. The solid residue was purified by triturating with EtOAc to yield an off-white solid (18.1 g, 64%). M.p.: 188–190 °C; IR (CH_2Cl_2) ν_{max} 3140.5, 2977.6, 1605.5, 1576.5, 1436.7, 1287.3, 754.0 cm^{-1}; ^{1}H NMR (500 MHz, MeOD) δ 7.31 (dd, *J* = 7.8, 0.9 Hz, 1H), 6.93 (t, *J* = 8.0 Hz, 1H), 6.84 (dd, *J* = 8.2, 0.9 Hz, 1H), 3.75–3.66 (m, 1H), 3.44–3.36 (m, 1H), 3.24–3.15 (m, 2H), 1.27 (t, *J* = 7.1 Hz, 3H), 1.13 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, MeOD) δ 169.5, 154.1, 130.9, 129.7, 129.6, 115.0, 93.0, 43.3, 39.2, 12.6, 11.3; GCMS (EI+) calcd for [$C_{11}H_{14}INO_2$]: *m*/*z* 319.0, found 319.0.



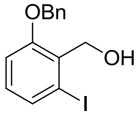
S10

Methyl 2-Hydroxy-6-iodobenzoate (S10): Na_2HPO_4 (12.07 g, 85.05 mmol) and Me_3OBF_4 (25.2 g, 170.1 mmol) were added at room temperature to a suspension of the substituted benzamide **S9** (18.1 g, 56.7 mmol) in MeCN (497 mL). The mixture was stirred for 18 h at ambient temperature and then sat. aqueous $NaHCO_3$ (199 mL) was added, followed by solid $NaHCO_3$ (14.3 g, 170 mmol). The slurry was stirred for another 18 h at room temperature and then extracted with EtOAc (3 × 70 mL). The combined organic phases were dried (Na_2SO_4) and concentrated in vacuo. The residue was purified through FCC (SiO_2; 30% EtOAc in hexanes) to yield a white solid (14.5 g, 92%). M.p.: 40–41 °C; IR (CH_2Cl_2) ν_{max} 3153.0, 2922.6, 1736.6, 1668.1, 1439.6, 1226.5, 864.0, 802.2 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.83 (s, 1H), 7.60 (dd, *J* = 7.3, 1.6 Hz, 1H), 7.03–6.96 (m, 2H), 3.99 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.0, 162.5, 135.1, 134.0, 118.2, 116.7, 93.8, 52.0; GCMS (EI+) calcd for [$C_8H_7IO_3$]: *m*/*z* 277.9, found 278.0.



S11

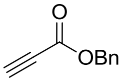
Methyl 2-(Benzyloxy)-6-iodobenzoate (S11): Solid K_2CO_3 (36.8 g, 266.2 mmol) and benzyl bromide (29.2 ml, 245.3 mmol) were added to a solution of the methyl benzoate **S10** (14.5 g, 52.2 mmol) in CH_2Cl_2/MeOH (1:1, 350 mL) at room temperature and then the mixture was heated under reflux for 2 h. The suspension was filtered through a pad of Celite and the filtrate concentrated in vacuo. The residue was purified through FCC (SiO_2; 20% EtOAc in hexanes) to yield a colorless oil (18.8 g, 98%). IR (CH_2Cl_2) ν_{max} 3032.5, 2948.6, 1732.7, 1584.2, 1566.9, 1440.6, 1264.1, 735.7 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 (dd, *J* = 7.9, 0.8 Hz, 1H), 7.37–7.35 (m, 4H), 7.34–7.29 (m, 1H), 7.01 (t, *J* = 8.1 Hz, 1H), 6.92 (dd, *J* = 8.4, 0.6 Hz, 1H), 5.11 (s, 2H), 3.94 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.9, 155.8, 136.1, 131.1, 130.9, 128.6, 128.0, 127.0, 126.9, 112.43, 92.4, 70.7, 52.8; GCMS (EI+) calcd for [$C_{15}H_{13}IO_3$]: *m*/*z* 368.0, found 368.0.



4r

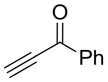
[2-(Benzyloxy)-6-iodophenyl]methanol (4r): 1 M Diisobutylaluminum hydride in hexanes (128 mL) was added dropwise to a solution of the substituted methylbenzoate **S11** (18.8 g, 51.1 mmol) in toluene (465 mL) at –78 °C and then the mixture was warmed to room temperature slowly (overnight). The mixture was cooled to –78 °C and then the reaction was quenched through the addition of MeOH (18.5 mL), solid $Na_2SO_4 \cdot 10H_2O$ (7.4 g), Celite (11.2 g), and water (3.4 mL). The mixture was warmed to room temperature overnight, filtered through a pad of Celite, and concentrated in vacuo. The residue was purified through FCC (SiO_2; 30% EtOAc in hexanes) to yield a white solid (16.6 g, 95%). M.p.: 40–42 °C; IR (CH_2Cl_2) ν_{max} 3424.0, 3030.6, 2876.3, 1582.3, 1564.0, 1442.5, 1260.3, 729.0 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 (dd, *J* = 5.2, 3.8 Hz, 1H), 7.41–7.39 (m, 4H), 7.38–7.33 (m, 1H), 6.95–6.94 (m, 2H), 5.12 (s, 2H), 4.91 (d, *J* = 7.0 Hz, 2H), 2.33 (t, *J* = 7.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.1, 136.3, 132.1, 132.0, 130.6, 128.8, 128.3, 127.4, 112.5, 101.3, 70.7, 65.4; GCMS (EI+) calcd for [$C_{14}H_{13}IO_2$]: *m/z* 340.0, found 340.0.

Synthesis of Electron-Deficient Acetylenes 5b, 5d, and 5f



5b

Benzyl Propiolate (5b): A solution of DMAP (0.015 g, 0.13 mmol) and DCC (2.58 g, 13 mmol) in CH_2Cl_2 (15 mL) was added slowly over 1 h to a solution of propiolic acid (0.77 mL, 13 mmol) and benzyl alcohol (1.40 mL, 14 mmol) in CH_2Cl_2 (15 mL) at 0 °C. The suspension was then stirred for 5 h at room temperature, monitoring through by TLC (30% EtOAc in hexanes). Upon completion, the mixture was filtered through a layer of Celite and the filtrate concentrated in vacuo. The residue was purified through FCC (SiO_2; 30% EtOAc in hexanes) to yield a colorless oil (1.79 g, 90%). Spectral data matched those reported in the literature.[20]



5d

1-Phenylprop-2-yn-1-one 5d: Obtained by treating benzaldehyde with ethynyl magnesium bromide using the protocol reported by Oyelere.[21] The resulting propargyl alcohol was used without further purification and oxidized to the acetylene **5d** using Jones reagent.[22] The acetylene **5d** was obtained in 83% yield. Spectral data matched those reported in the literature.[14]

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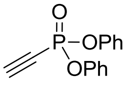
[20] Carrillo, R., León, L. G., Martín, T., Martín, V. S., Padrón, J. M. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 780.

[21] Chen, P. C., Wharton, R. E., Patel, P. A., Oyelere, A. K. *Bioorg. Med. Chem. Lett.* **2007**, *15*, 7288.

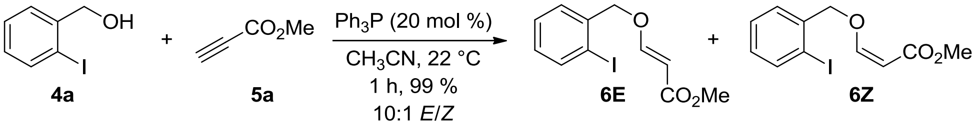
[22] Caliendo, G., Fiorino, F., Peissutti, E., Severino, B., Scolaro, D., Gessi, S., Cattabriga, E., Borea, P. A., Santagada, V., *European Journal of Pharmaceutical Sciences* **2002**, *16*, 15.



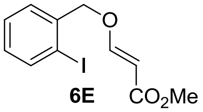
5f

Diphenyl Ethynylphosphonate (5f): Ethynyl magnesium bromide was added over 15 min into a solution of diphenyl phosphoryl chloride (2.07 mL, 10.0 mmol) in THF (13 mL) at 0 °C. The mixture was stirred for 1 h at 0 °C and then the reaction was quenched with sat. aqueous NH_4Cl (20 mL) at 0 °C. The aqueous phase was extracted with EtOAc (3 × 40 mL) and then the combined organic phases were dried (Na_2SO_4) and concentrated in vacuo. The residue was purified through FCC (SiO_2; 20% EtOAc in hexanes) to yield a light-yellow oil (0.94 g, 36%). IR (CH_2Cl_2) ν_{max} 3176.2, 2985.3, 2067.3, 1590.0, 1486.9, 1283.4, 1185.0, 946.9 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.39–7.35 (m, 4H), 7.29–7.26 (m, 4H), 7.25–7.21 (m, 2H), 3.01 (d, J = 14.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.7, 129.9, 125.9, 120.7, 90.8, 90.2, 74.7, 71.6; ^{31}P NMR (162 MHz, $CDCl_3$) δ –17.0; GCMS (EI+) calcd for [$C_{14}H_{11}O_3P$]: *m*/*z* 258.0, found 258.1.

Synthesis and Characterization of the Michael Adducts 6Z and 6E

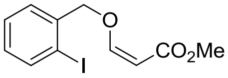


A solution of methyl propiolate (**5a**, 1.00 mL, 12.0 mmol) in MeCN (5 mL) was added over 1 h (syringe pump) to a solution of 2-iodobenzyl alcohol (**4a**, 2.34 g, 10.0 mmol) and PPh_3 (0.53 g, 2.0 mmol) in MeCN (50 mL) under reflux. The reaction was monitored through TLC (30% EtOAc in hexanes); upon completion, the mixture was cooled to room temperature and concentrated in vacuo. The residue were purified through FCC (SiO_2; 30% EtOAc in hexanes) to yield the Michael adducts **6E** and **6Z** (3.16 g, 99%, 10:1 *E*/*Z*).



6E

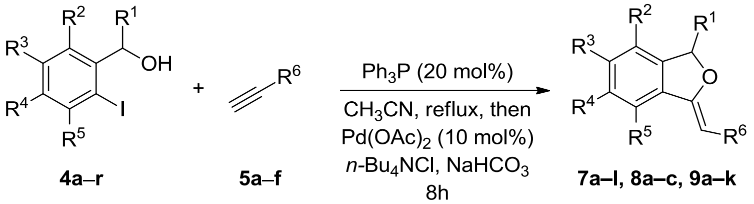
(***E***)**-Methyl 3-[(2-Iodobenzyl)oxy]acrylate (6E):** IR (CH_2Cl_2) ν_{max} 3090.4, 2947.7, 1706.7, 1621.8, 1435.7, 1330.6, 1189.9, 1132.0 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.86 (d, J = 7.8 Hz, 1H), 7.70 (d, J = 12.6 Hz, 1H), 7.39–7.37 (m, 2H), 7.06–7.03 (m, 1H), 5.36 (d, J = 12.7 Hz, 1H), 4.89 (s, 2H), 3.72 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.0, 161.8, 139.5, 137.5, 130.1, 128.8, 128.5, 97.5, 76.4, 51.3; GCMS (EI+) calcd for [$C_{11}H_{11}IO_3$]: *m*/*z* 318.0, found 318.0.



6Z

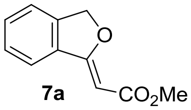
(***Z***)**-Methyl 3-[(2-Iodobenzyl)oxy]acrylate (6Z):** IR (CH_2Cl_2) ν_{max} 3058.5, 2950.5, 1740.4, 1624.7, 1437.7, 1201.4, 1139.7, 1013.4 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.83 (dd, J = 7.9 Hz, 1.1 Hz, 1H), 7.51 (d, J = 7.7 Hz, 1H), 7.39 (t, J = 7.5 Hz, 1H), 7.03 (t, J = 7.6 Hz, 1H), 6.61 (d, J = 7.0 Hz, 1H), 5.06 (s, 2H), 4.95 (d, J = 7.0 Hz, 1H), 3.72 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.5, 158.4, 139.2, 138.3, 129.8, 128.7, 128.4, 97.1, 96.3, 80.1, 51.0; GCMS (EI+) calcd for [$C_{11}H_{11}IO_3$]: *m*/*z* 318.0, found 317.9.

General Procedure for the One-Pot Michael–Heck Reaction



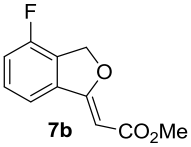
PPh_3 (0.2 mmol) was added to a stirred solution of the pronucleophile (1.0 mmol) in anhydrous MeCN (20 mL). The mixture was brought to reflux in an oil bath (external temperature: 90 °C). A solution of the electron-deficient acetylene (1.02 mmol) in anhydrous MeCN (1 mL) was added to reaction mixture over 1 h (syringe pump). The mixture was cooled to room temperature and then $Pd(OAc)_2$ (0.1 mmol), *n*Bu_4NCl (1.0 mmol), and $NaHCO_3$ (2.0 mmol) were added. The mixture was stirred at room temperature for 1 h and then heated under reflux for 8 h. The reaction was monitored through TLC (30% EtOAc in hexanes). The mixture was cooled to room temperature and filtered through a layer of Celite; the filtrate was concentrated in vacuo and the residue purified through FCC (SiO_2; 30% EtOAc in hexanes) to yield the cyclized product.

Characterization of Michael–Heck Products



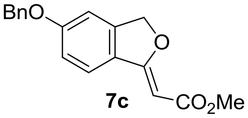
7a

(*Z*)-Methyl 2-[Isobenzofuran-1(3*H*)-ylidene]acetate (7a): 74% yield; white solid; m.p.: 104–105 °C; IR (CH_2Cl_2) ν_{max} 3059.4, 2952.5, 1710.2, 1637.5, 1334.8, 1294.6, 1151.4, 1067.0 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.58 (d, *J* = 8.4 Hz, 1H), 7.49 (t, *J* = 7.4 Hz, 1H), 7.41 (t, *J* = 6.4 Hz, 2H), 5.56 (s, 2H), 5.51 (s, 1H), 3.75 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.1, 166.7, 141.4, 132.9, 131.4, 128.5, 121.5, 121.3, 85.7, 51.0; HRMS (ESI+) calcd for $[C_{11}H_{10}O_3Na]^+$: *m*/*z* 231.0522, found 213.0530.



7b

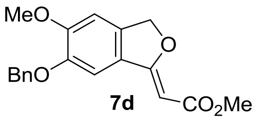
(*Z*)-Methyl 2-[4-Fluoroisobenzofuran-1(3*H*)-ylidene]acetate (7b): 70% yield; white solid; m.p.: 102–104 °C; IR (CH_2Cl_2) ν_{max} 33036.3, 2990.1, 1704.7, 1678.2, 1487.3, 1305.2, 1246.6, 1082.1 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.38–7.30 (m, 2H), 7.10 (td, *J* = 8.3, 0.5 Hz, 1H), 5.55 (s, 2H), 5.45 (s, 1H), 3.69 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.7, 166.3, 158.1, 155.7, 136.4, 131.0, 130.9, 127.8, 127.6, 117.8, 117.6, 117.3, 86.9, 74.2, 51.0; HRMS (ESI+) calcd for $[C_{11}H_9FO_3Na]^+$: *m*/*z* 231.0428, found 227.0438.



7c

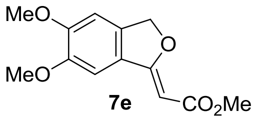
(*Z*)-Methyl 2-[5-(Benzyloxy)isobenzofuran-1(3*H*)-ylidene]acetate (7c): 65% yield; white solid; m.p.: 130–132 °C; IR (CH_2Cl_2) ν_{max} 3094.1, 2948.4, 1696.9, 1640.5, 1608.7, 1487.9, 1455.0, 1271.2, 1152.9

cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.44 (d, J = 8.4 Hz, 1H), 7.41–7.31 (m, 5H), 6.98 (dd, J = 8.4, 2.0, 1H), 6.91 (d, J = 1.6 Hz, 1H), 5.45 (s, 2H), 5.36 (s, 1H), 3.71 (s, 3H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 168.2, 166.9, 161.8, 143.8, 136.1, 128.7, 128.3, 127.4, 125.5, 122.9, 116.6, 106.5, 84.1, 76.3, 70.4, 50.9; HRMS (ESI+) calcd for [C$_{18}$H$_{16}$O$_4$H]$^+$: m/z 297.1121, found 297.1127.



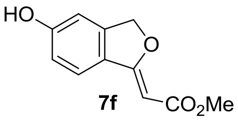
7d

(*Z*)-Methyl 2-[6-(Benzyloxy)-5-methoxyisobenofuran-1(3*H*)-ylidene]acetate (7d): 52% yield; yellow solid; m.p.: 164–166 °C; IR (CH$_2$Cl$_2$) ν_{max} 3067.6, 2940.7, 1664.6, 1630.2, 1500.6, 1375.5, 1281.4, 1054.3 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.46–7.44 (m, 2H), 7.41–7.37 (m, 2H), 7.35–7.31 (m, 1H), 7.01 (s, 1H), 6.87 (s, 1H), 5.48 (s, 2H), 5.27 (s, 1H), 5.16 (s, 2H), 3.93 (s, 3H), 3.74 (s, 3H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 168.7, 166.9, 153.6, 149.2, 136.2, 135.6, 128.7, 128.2, 127.3, 124.8, 105.6, 103.5, 83.9, 76.5, 71.3, 56.3, 50.9; HRMS (ESI+) calcd for [C$_{19}$H$_{18}$O$_5$H]$^+$: m/z 327.1227, found 327.1233.



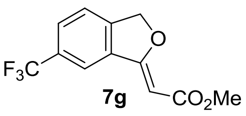
7e

(*Z*)-Methyl 2-[5,6-Dimethoxyisobenzofuran-1(3*H*)-ylidene]acetate (7e): 72% yield; yellow solid; m.p.: 153–154 °C; IR (CH$_2$Cl$_2$) ν_{max} 3074.2, 2943.5, 1702.4, 1678.6, 1636.8, 1501.3, 1474.4, 1284.7 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 6.96 (s, 1H), 6.85 (s, 1H), 5.48 (s, 2H), 5.34 (s, 1H), 3.92 (s, 3H), 3.91 (s, 3H), 3.73 (s, 3H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 168.8, 166.9, 152.9, 150.1, 135.1, 129.1, 124.9, 103.1, 102.9, 83.9, 46.5, 56.3, 56.2, 50.9; HRMS (ESI+) calcd for [C$_{13}$H$_{14}$O$_5$Na]$^+$: m/z 273.0733, found 273.0743.



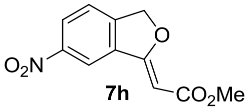
7f

(*Z*)-Methyl 2-[5-Hydroxyisobenzofuran-1(3*H*)-ylidene]acetate (7f): 73% yield; yellow solid; m.p.: 143–145 °C; IR (CH$_2$Cl$_2$) ν_{max} 3269.0, 2949.6, 1638.2, 1682.6, 1639.1, 1608.9, 1471.6, 1170.6 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.45 (d, J = 8.4 Hz, 1H), 7.36 (s, 1H), 6.95 (dd, J = 8.4, 2.1 Hz, 1H), 6.90 (s, 1H), 5.39 (d, J = 1.2 Hz, 3H), 3.77 (s, 3H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 169.3, 168.1, 160.2, 144.1, 128.4, 124.7, 123.3, 117.1, 107.8, 83.4, 76.2, 51.2; HRMS (ESI+) calcd for [C$_{11}$H$_{10}$O$_4$Na]$^+$: m/z 229.0471, found 229.0482.



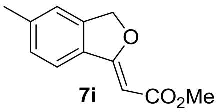
7g

(*Z*)-Methyl 2-[6-(Trifluoromethyl)isobenzofuran-1(3*H*)-ylidene]acetate (7g): 60% yield; light-yellow solid; m.p.: 168–170 °C; IR (CH$_2$Cl$_2$) ν_{max} 3071.0, 2992.0, 1675.8, 1644.0, 1329.7, 1158.0, 1072.2, 841.8 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.82 (s, 1H), 7.74 (d, J = 8.0 Hz, 1H), 7.54 (d, J = 8.0 Hz, 1H), 5.62 (s, 2H), 5.57 (s, 1H), 3.75 (s, 3H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 166.2, 144.6, 133.9, 131.6 (q, $J_{C\text{–}F}$ = 32.7 Hz), 128.2 (q, $J_{C\text{–}F}$ = 3.5 Hz), 123.6 (q, $J_{C\text{–}F}$ = 271.6 Hz), 122.2, 118.7 (q, $J_{C\text{–}F}$ = 4.0 Hz), 87.3, 76.4, 51.1; GCMS (EI+) calcd for [C$_{12}$H$_9$F$_3$O$_3$]: m/z 258.1, found 258.1.



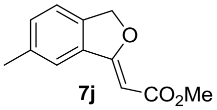
7h

(*Z*)-Methyl 2-[6-Nitroisobenzofuran-1(3*H*)-ylidene]acetate (7h): 45% yield; yellow solid; m.p.: 120–122 °C; IR (CH_2Cl_2) ν_{max} 3099.2, 3070.7, 2949.0, 1718.4, 1646.2, 1522.1, 1340.1, 1163.9 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.22 (d, *J* = 6.6 Hz, 1H), 7.70–7.67 (m, 1H), 7.59 (t, *J* = 5.9 Hz), 5.34 (d, *J* = 9.5 Hz, 1H), 5.00 (s, 2H), 3.72 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.7, 161.3, 137.3, 133.1, 129.8, 123.5, 122.3, 97.9, 71.1, 51.3, 29.7; GCMS (EI+) calcd for [$C_{11}H_9NO_5$]: *m*/*z* 235.05, found 235.2.



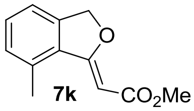
7i

(*Z*)-Methyl 2-[5-Methylisobenzofuran-1(3*H*)-ylidene]acetate (7i): 74% yield; white solid; m.p.: 137–139 °C; IR (CH_2Cl_2) ν_{max} 3051.2, 2947.3, 1700.9, 1632.2, 1434.9, 1326.7, 1153.5, 1067.9 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 (d, *J* = 8.4 Hz, 1H), 7.13–7.11 (m, 2H), 5.41 (s, 2H), 5.35 (s, 1H), 3.65 (s, 3H), 2.34 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.2, 166.8, 142.2, 141.8, 130.2, 129.6, 121.6, 121.2, 84.8, 76.4, 50.8, 21.7; HRMS (ESI+) calcd for [$C_{12}H_{12}O_3Na$]$^+$: *m*/*z* 227.01679, found 227.0683.



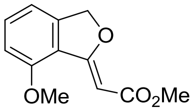
7j

(*Z*)-Methyl 2-[6-Methylisobenzofuran-1(3*H*)-ylidene]acetate (7j): 76% yield; white solid; m.p.: 105–106 °C; IR (CH_2Cl_2) ν_{max} 3033.9, 2950.6, 1695.9, 1674.6, 1622.7, 1434.5, 1264.4, 1151.0 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 (s, 1H), 7.28–7.23 (m, 2H), 5.47 (s, 2H), 5.44 (s, 1H), 3.71 (s, 3H), 2.38 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.2, 166.8, 138.7, 138.5, 133.1, 132.6, 121.6, 121.0, 85.3, 76.5, 50.9, 21.3; HRMS (ESI+) calcd for [$C_{12}H_{12}O_3Na$]$^+$: *m*/*z* 227.0679, found 227.0690.



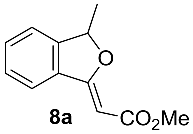
7k

(*Z*)-Methyl 2-[7-Methylisobenzofuran-1(3*H*)-ylidene]acetate (7k): 94% yield; white solid; m.p.: 116–118 °C; IR (CH_2Cl_2) ν_{max} 3081.9, 3013.0, 1703.5, 1629.0, 1253.3, 1144.0, 1070.7, 1015.0 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 (t, *J* = 7.6 Hz, 1H), 7.25 (d, *J* = 7.2 Hz, 1H), 7.20 (d, *J* = 7.2 Hz, 1H), 5.59 (s, 1H), 5.54 (s, 2H), 3.76 (s, 3H), 2.56 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.1, 142.6, 135.1, 131.0, 130.8, 118.8, 89.8, 75.8, 50.9, 20.8; HRMS (ESI+) calcd for [$C_{12}H_{12}O_3Na$]$^+$: *m*/*z* 227.0679, found 227.0689.



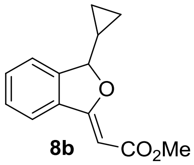
7l

(*Z*)-Methyl 2-[7-Methoxyisobenzofuran-1(3*H*)-ylidene]acetate (7l): 91% yield; off white solid; M.p.: 111–112 °C; IR (CH_2Cl_2) ν_{max} 3025.8, 2947.7, 1703.8, 1636.3, 1488.8, 1279.5, 1255.4, 1151.3 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39 (t, *J* = 2.0 Hz, 1H), 6.92 (d, *J* = 1.9 Hz, 1H), 6.84 (d, *J* = 2.1 Hz, 1H), 5.97 (s, 1H), 5.49 (s, 2H), 3.92 (s, 3H), 3.72 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.3, 166.9, 156.6, 144.0, 132.8, 120.8, 113.0, 110.0, 89.8, 76.1, 55.5, 50.8; GCMS (EI+) calcd for [$C_{12}H_{12}O_4$]: *m/z* 220.1, found 220.1.



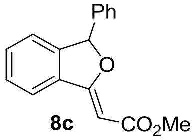
8a

(*Z*)-Methyl 2-[3-Methylisobenzofuran-1(3*H*)-ylidene]acetate (8a): 64% yield; white solid; m.p.: 72–74 °C; IR (CH_2Cl_2) ν_{max} 3078.1, 2980.8, 1705.7, 1645.0, 1467.7, 1435.3, 1152.8, 1059.3 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.51 (d, J = 7.6 Hz, 1H), 7.51 (d, J = 7.6 Hz, 1H), 7.45 (td, J = 7.5, 0.9 Hz, 1H), 7.36 (td, J = 7.2, 0.8 Hz, 1H), 7.29 (dd, J = 7.4, 1.0 Hz, 1H), 5.77 (q, J = 6.7 Hz, 1H), 5.44 (s, 1H), 3.70 (s, 3H), 1.61 (d, J = 8.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.1, 166.7, 146.0, 132.7, 131.4, 128.6, 121.5, 121.1, 85.2, 84.6, 50.8, 20.9; HRMS (ESI+) calcd for $[C_{12}H_{12}O_3H]^+$: m/z 227.0679, found 227.0676.



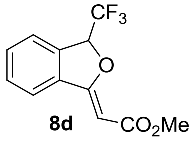
8b

(*Z*)-Methyl 2-[3-Cyclopropylisobenzofuran-1(3*H*)-ylidene]acetate (8b): 72% yield; yellow solid; m.p.: 71–73 °C; IR (CH_2Cl_2) ν_{max} 3076.1, 2946.6, 1708.2, 1689.5, 1643.6, 1466.7, 1151.8, 1068.6 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.53 (d, J = 7.2 Hz, 1H), 7.48–7.36 (m, 3H), 5.44 (s, 1H), 5.06 (d, J = 8.4 Hz, 2H), 3.72 (s, 3H), 1.16–1.08 (m, 1H), 0.70–0.66 (m, 3H), 0.63–0.58 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.1, 166.7, 144.5, 133.1, 131.3, 128.8, 121.8, 121.4, 92.1, 85.2, 51.0, 15.2, 3.0, 1.8; HRMS (ESI+) calcd for $[C_{14}H_{14}O_3Na]^+$: m/z 253.0835, found 253.0828.



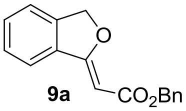
8c

(*Z*)-Methyl 2-[3-Phenylisobenzofuran-1(3*H*)-ylidene]acetate (8c): 48% yield; yellow solid; m.p.: 141–142 °C; IR (CH_2Cl_2) ν_{max} 3070.3, 2947.0, 1704.3, 1648.1, 1466.5, 1291.2, 1154.2, 1067.4 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.63–7.61 (m, 1H), 7.44–7.41 (m, 2H), 7.35–7.33 (m, 3H), 7.28–7.26 (m, 1H), 7.23–7.21 (m, 2H), 6.63 (s, 1H), 5.58 (s, 1H), 3.74 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.6, 166.5, 144.7, 144.5, 139.0, 137.9, 132.8, 132.4, 131.6, 129.0, 128.8, 128.1, 127.7, 127.0, 125.9, 124.6, 122.5, 121.4, 97.5, 89.5, 86.3, 85.9, 85.8, 51.3; HRMS (ESI+) calcd for $[C_{14}H_{14}O_3Na]^+$: m/z 289.0835, found 289.0830.



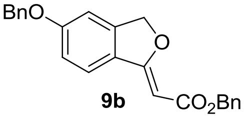
8d

(*Z*)-Methyl 2-[3-(Trifluoromethyl)isobenzofuran-1(3*H*)-ylidene]acetate 8d: 67% yield; yellow solid; m.p.: 91–92 °C; IR (CH_2Cl_2) ν_{max} 3081.7, 2954.4, 1711.5, 1663.3, 1271.8, 1165.8, 1139.7, 1067.4 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.61–7.60 (m, 1H), 7.57–7.51 (m, 3H), 5.89 (q, J = 5.8 Hz, 1H), 5.59 (s, 1H), 3.74 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.6, 165.1, 135.1, 133.8, 131.9, 130.6, 123.0, 122.5 (q, $J_{C–F}$ = 279.5), 121.7, 88.7, 82.6 (q, $J_{C–F}$ = 34.8 Hz), 51.2; GCMS (EI+) calcd for $[C_{12}H_9F_3O_3]$: m/z 258.1, found 258.1.



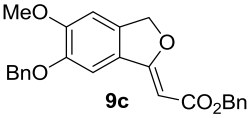
9a

(*Z*)-Benzyl 2-[Isobenzofuran-1(3*H*)-ylidene]acetate (9a): 78% yield; yellow solid; m.p.: 96–98 °C; IR (CH_2Cl_2) ν_{max} 3032.6, 2931.4, 1705.7, 1640.8, 1293.3, 1142.1, 1066.7, 997.6 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.55 (d, J = 8.0 Hz, 1H), 7.47 (t, J = 7.4 Hz, 1H), 7.42 (t, J = 6.8 Hz, 2H), 7.38–7.27 (m, 5H), 5.57 (s, 1H), 5.54 (s, 2H), 5.21 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.6, 166.1, 141.5, 136.9, 132.9, 131.5, 128.6, 128.3, 128.0, 121.5, 121.4, 85.7, 76.7, 65.4; HRMS (ESI+) calcd for $[C_{17}H_{14}O_3Na]^+$: m/z 289.0835, found 289.0840.



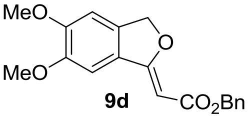
9b

(*Z*)-Benzyl 2-[5-(Benzyloxy)isobenzofuran-1(3*H*)-ylidene]acetate (9b): 51% yield; yellow solid; m.p.: 132–134 °C; IR (CH_2Cl_2) ν_{max} 3063.5, 2930.9, 1699.2, 1639.1, 1610.7, 1485.9, 1265.9, 1143.5 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.49 (d, J = 8.4 Hz, 1H), 7.44–7.28 (m, 10H), 7.03 (dd, J = 8.8, 2.0 Hz, 1H), 6.94 (d, J = 2.0 Hz, 1H), 5.52 (s, 2H), 5.46 (s, 1H), 5.22 (s, 1H), 5.12 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.7, 166.3, 161.9, 143.9, 137.0, 136.0, 128.8, 128.2, 127.9, 127.4, 125.7, 116.6, 106.6, 84.2, 76.3, 70.5, 65.3; HRMS (ESI+) calcd for $[C_{24}H_{20}O_4H]^+$: m/z 373.1434, found 373.1441.



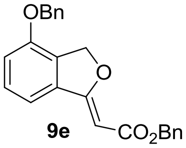
9c

(*Z*)-Benzyl 2-[6-(Benzyloxy)-5-methoxyisobenzofuran-1(3*H*)-ylidene]acetate (9c): 43% yield; yellow solid; m.p.: 143–145 °C; IR (CH_2Cl_2) ν_{max} 3057.1, 2935.6, 1703.0, 1674.5, 1634.3, 1500.7, 1283.0, 1128.8 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.44–7.41 (m, 4H), 7.38–7.28 (m, 6H), 6.98 (s, 1H), 6.82 (s, 1H), 5.44 (s, 2H), 5.35 (s, 1H), 5.20 (s, 2H), 5.10 (s, 2H), 3.87 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.4, 166.2, 153.6, 149.1, 137.0, 136.2, 135.8, 128.7, 128.5, 128.2, 127.9, 127.4, 105.4, 103.6, 83.8, 76.6, 71.2, 65.2, 56.3; HRMS (ESI+) calcd for $[C_{25}H_{22}O_5H]^+$: m/z 403.1540, found 403.1531.



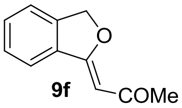
9d

(*Z*)-Benzyl 2-[5,6-Dimethoxyisobenzofuran-1(3*H*)-ylidene]acetate (9d): 67% yield; yellow solid; m.p.: 142–143 °C; IR (CH_2Cl_2) ν_{max} 3074.3, 2939.3, 1702.8, 1677.4, 1634.1, 1500.7, 1284.4, 1127.9 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.44–7.41 (m, 2H), 7.37–7.33 (m, 2H), 7.32–7.28 (m, 1H), 6.96 (s, 1H), 6.85 (s, 1H), 5.51 (s, 2H), 5.43 (s, 1H), 5.21 (s, 2H), 3.93 (s, 3H), 3.90 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.3, 166.2, 153.0, 150.1, 137.0, 135.3, 128.5, 128.2, 127.9, 125.0, 118.0, 103.1, 103.0, 83.9, 76.6, 65.3, 56.3, 56.1; HRMS (ESI+) calcd for $[C_{19}H_{18}O_5H]^+$: m/z 327.1227, found 327.1225.



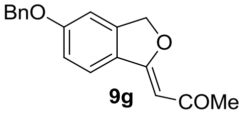
9e

(*Z*)-Benzyl 2-[4-(Benzyloxy)isobenzofuran-1(3*H*)-ylidene]acetate (9e): 62% yield; yellow solid; m.p.: 79–81 °C; IR (CH_2Cl_2) ν_{max} 3063.4, 2936.1, 1703.8, 1638.2, 1487.8, 1264.1, 1140.7, 1000.9 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.46–7.32 (m, 11H), 7.15 (d, J = 7.7 Hz, 1H), 6.99 (d, J = 8.0 Hz, 1H), 5.58 (s, 2H), 5.55 (s, 1H), 5.22 (s, 2H), 5.14 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.9, 166.1, 153.4, 136.8, 136.0, 134.9, 130.4, 130.3, 128.7, 128.5, 128.4, 128.3, 127.9, 127.4, 113.7, 86.0, 75.8, 70.3, 65.4; GCMS (EI+) calcd for [$C_{24}H_{20}O_4$]: *m*/*z* 372.1, found 372.0.



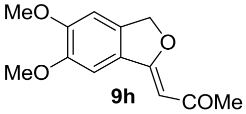
9f

(*Z*)-1-[Isobenzofuran-1(3*H*)-ylidene]propan-2-one (9f): 75% yield; yellow solid; m.p.: 119–121 °C; IR (CH_2Cl_2) ν_{max} 3053.3, 2972.1, 1637.1, 1618.6, 1475.5, 1385.1, 1260.2, 1003.8 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.53–7.51 (m, 1H), 7.48–7.44 (m, 1H), 7.39–7.35 (m, 2H), 5.73 (s, 1H), 5.49 (s, 2H), 2.38 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.1, 167.1, 141.3, 132.9, 131.6, 128.7, 121.8, 121.4, 97.5, 76.6, 31.0; HRMS (ESI+) calcd for [$C_{11}H_{10}O_2Na$]$^+$: *m*/*z* 197.0573, found 197.0573.



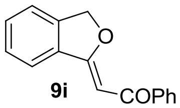
9g

(*Z*)-1-[5-(Benzyloxy)isobenzofuran-1(3*H*)-ylidene]propan-2-one (9g): 56% yield; yellow solid; m.p.: 142–144 °C; IR (CH_2Cl_2) ν_{max} 3063.3, 2928.6, 1611.5, 1487.7, 1451.1, 1376.2, 1268.8, 1052.5 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.48 (d, *J* = 8.8 Hz, 1H), 7.43–7.32 (m, 5H), 7.02 (dd, *J* = 8.6, 2.2 Hz, 1H), 6.94 (d, *J* = 1.6 Hz, 1H), 5.68 (s, 1H), 5.47 (s, 2H), 5.11 (s, 2H), 2.40 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.9, 167.3, 162.0, 143.8, 136.0, 128.8, 128.4, 127.4, 125.6, 123.3, 116.8, 106.6, 96.4, 76.2, 70.5, 30.9; HRMS (ESI+) calcd for [$C_{18}H_{16}O_3Na$]$^+$: *m*/*z* 281.1172, found 281.1177.



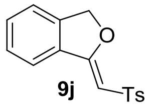
9h

(*Z*)-1-[5,6-Dimethoxyisobenzofuran-1(3*H*)-ylidene]propan-2-one (9h): 69% yield; yellow solid; m.p.: 178–180 °C; IR (CH_2Cl_2) ν_{max} 3072.1, 2935.9, 1606.5, 1592.7, 1497.9, 1280.9, 1266.8, 1222.4 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.95 (s, 1H), 6.85 (s, 1H), 5.63 (s, 1H), 5.45 (s, 2H), 3.92 (s, 3H), 3.90 (s, 3H), 2.39 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.7, 167.8, 153.1, 150.2, 135.2, 124.9, 103.1, 96.2, 76.4, 56.3, 56.2, 30.8; HRMS (ESI+) calcd for [$C_{13}H_{14}O_4H$]$^+$: *m*/*z* 235.0965, found 235.0958.



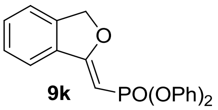
9i

(*Z*)-2-[Isobenzofuran-1(3*H*)-ylidene]-1-phenylethanone (9i): 68% yield; brown oil; IR (CH_2Cl_2) ν_{max} 3058.7, 2929.2, 1763.9, 1652.0, 1598.2, 1568.7, 1233.2, 1013.7 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.99–7.97 (m, 2H), 7.72–7.71 (m, 1H), 7.51–7.45 (m, 2H), 7.44–7.40 (m, 4H), 6.63 (s, 1H), 5.59 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 188.5, 168.9, 142.0, 140.1, 133.3, 131.8, 131.7, 128.6, 128.3, 127.8, 121.7, 121.5, 91.6, 77.0; HRMS (ESI+) calcd for [$C_{16}H_{12}O_2H$]$^+$: *m*/*z* 237.0910, found 237.0916.



9j

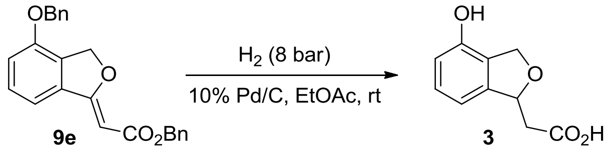
(*Z*)-1-(Tosylmethylene)-1,3-dihydroisobenzofuran (9j): 51% yield; yellow solid; m.p.: 128–130 °C; IR (CH_2Cl_2) ν_{max} 3064.9, 2903.5, 1623.2, 1470.7, 1300.9, 1138.1, 1084.1, 1055.1 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.95–7.92 (m, 2H), 7.50–7.46 (m, 2H), 7.40–7.36 (m, 2H), 7.27 (d, *J* = 7.6 Hz, 2H), 6.03 (s, 1H), 5.49 (s, 2H), 2.38 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.3, 143.4, 141.4, 140.8, 132.1, 131.4, 129.4, 128.8, 127.1, 121.8, 121.4, 96.6, 77.2, 21.6; HRMS (ESI+) calcd for [$C_{16}H_{12}O_3SNa$]$^+$: *m*/*z* 309.0556, found 309.0567.



9k

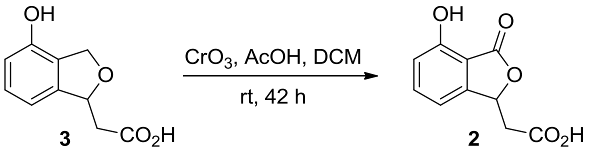
(*Z*)-Diphenyl Isobenzofuran-1(3*H*)-ylidenemethylphosphonate (9k): 16% yield; yellow solid; m.p.: 133–135 °C; IR (CH_2Cl_2) ν_{max} 3058.2, 2930.5, 1629.7, 1589.6, 1488.7, 1273.6, 1191.4, 932.4 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 (d, *J* = 8.0 Hz, 1H), 7.50 (t, *J* = 7.2 Hz, 1H), 7.40 (t, *J* = 8.2 Hz, 2H), 7.30 (d, *J* = 4.4 Hz, 8H), 7.15–7.11 (m, 2H), 5.49 (s, 2H), 5.17 (d, *J* = 10.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.2, 150.9, 150.8, 141.6, 132.3, 132.1, 131.7, 129.6, 128.6, 124.7, 122.1, 121.4, 120.8, 77.0, 76.3, 74.9; ^{31}P NMR (162 MHz, $CDCl_3$) δ 12.5; HRMS (ESI+) calcd for $[C_{21}H_{17}O_4PNa]^+$: *m*/*z* 387.0757, found 387.0745.

Total Syntheses of 3-Deoxyisoochracinic Acid, Isoochracinic Acid, and Isoochracinol



9e 3

3-Deoxyisoochracinic Acid (3): 10% Pd/C (0.46 g) was added at room temperature to a solution of the alkylidene phthalan **9e** (0.8 g, 2.2 mmol) in EtOAc (80 mL) in a hydrogenation apparatus equipped with a magnetic stirrer bar. The apparatus was sealed and purged with H_2 (3 × 8 bar) and then the mixture was stirred under H_2 (8 bar) for 1 h. The mixture was filtered through a pad of Celite and then the filtrate was concentrated in vacuo to give a white solid (0.42 g, 99%). M.p.: 159–161 °C; IR (CH_2Cl_2) ν_{max} 3234.0, 2961.1, 1707.7, 1599.7, 1469.5, 1289.2, 1174.4, 1002.8, 776.2 cm^{-1}; ^{1}H NMR [500 MHz, $(CD_3)_2CO$] δ 7.12 (t, *J* = 7.7 Hz, 1H), 6.79 (d, *J* = 7.5 Hz, 1H), 6.75 (d, *J* = 8.0 Hz, 1H), 5.56–5.53 (m, 1H), 5.05 (dd, *J* = 12.2, 2.7 Hz, 1H), 4.94 (d, *J* = 12.1 Hz, 1H), 2.79 (dd, *J* = 15.6, 4.8 Hz, 1H), 2.62 (dd, *J* = 15.6, 8.1 Hz, 1H); ^{13}C NMR (125 MHz, $(CD_3)_2CO$) δ 171.2, 151.5, 143.6, 129.1, 125.3, 114.1, 112.4, 80.8, 70.2, 41.0; GCMS (EI+) calcd for $[C_{10}H_{10}O_4]$: *m*/*z* 194.1, found 194.1.



3 2

Isoochracinic Acid 2: The procedure for benzylic oxidation was adapted from that reported by Harrison.[23] AcOH (7.20 mL, 126 mmol) was added at room temperature to a suspension of CrO_3 (721 mg, 7.21 mmol) in CH_2Cl_2 (82 mL). 3-Deoxyisoochracinic acid **3** was added to the mixture, which was then stirred for 42 h at room temperature. The mixture was filtered through a pad of Celite and then the filtrate was concentrated in vacuo. The solid residue was purified through FCC (SiO_2; 60% EtOAc in hexanes) to yield a white solid (188.6 mg, 44%). M.p.: 159–160 °C; IR (CH_2Cl_2) ν_{max} 3425.0, 2929.3, 1731.8, 1609.3, 1472.4, 1292.1, 1191.8, 1009.6 cm^{-1}; ^{1}H NMR [400 MHz, $(CD_3)_2CO$] δ 7.58 (t, *J* = 7.8 Hz, 1H), 7.12 (d, *J* = 7.5 Hz, 1H), 6.93 (d, *J* = 8.2 Hz, 1H), 5.84 (dd, *J* = 7.9, 4.8 Hz, 1H), 3.07 (dd, *J* = 16.8, 4.9 Hz, 1H), 2.83 (dd, *J* = 16.8, 7.9 Hz, 1H); ^{13}C NMR [100 MHz, $(CD_3)_2CO$] δ 170.2, 169.5,

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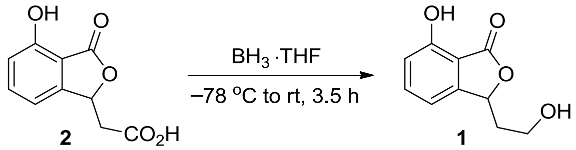
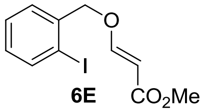
[23] Harrison, I. T.; Harrison, S. *Chem. Commun. (London)*, **1966**, 752a.

156.4, 150.6, 136.5, 115.8, 113.4, 111.5, 77.5, 38.7; GCMS (EI+) calcd for [$C_{10}H_8O_5$]: *m*/*z* 208.0, found 208.0.



Isoochracinol 1: 1 M BH_3·THF in THF (0.48 mL, 0.48 mmol) was added dropwise to a solution of isoochracinic acid **2** (10 mg, 0.048 mmol) in THF (2.4 mL) at –78 °C. The mixture was stirred at –78 °C for 1 h after addition, and then warmed to room temperature by removing the cooling bath. Upon completion, the reaction was quenched at –78 °C through the addition of water (1 mL). The aqueous phase was extracted with EtOAc (3 × 2 mL), dried (Na_2SO_4), and concentrated in vacuo. The oily residue was purified through FCC (SiO_2; 60% EtOAc in hexanes) to yield a white solid (6 mg, 64%). M.p.: 131–133 °C; IR (CH_2Cl_2) ν_{max} 3438.5, 2930.3, 1737.6, 1606.4, 1473.4, 1304.6, 1201.4, 1021.1 cm^{-1}; ^{1}H NMR (500 MHz, CD_3OD) δ 7.54 (t, *J* = 7.8 Hz, 1H), 6.98 (d, *J* = 7.5 Hz, 1H), 6.87 (d, *J* = 8.2 Hz, 1H), 5.60 (dd, *J* = 9.3, 3.4 Hz, 1H), 3.83–3.73 (m, 2H), 2.27–2.20 (m, 1H), 1.83 (ddd, *J* = 19.1, 9.5, 4.8 Hz, 1H); ^{13}C NMR (125 MHz, CD_3OD) δ 170.3, 157.0, 152.3, 136.3, 115.3, 112.3, 111.0, 78.3, 58.6, 37.8; GCMS (EI+) calcd for [$C_{10}H_{10}O_4$]: *m*/*z* 194.1, found 194.1.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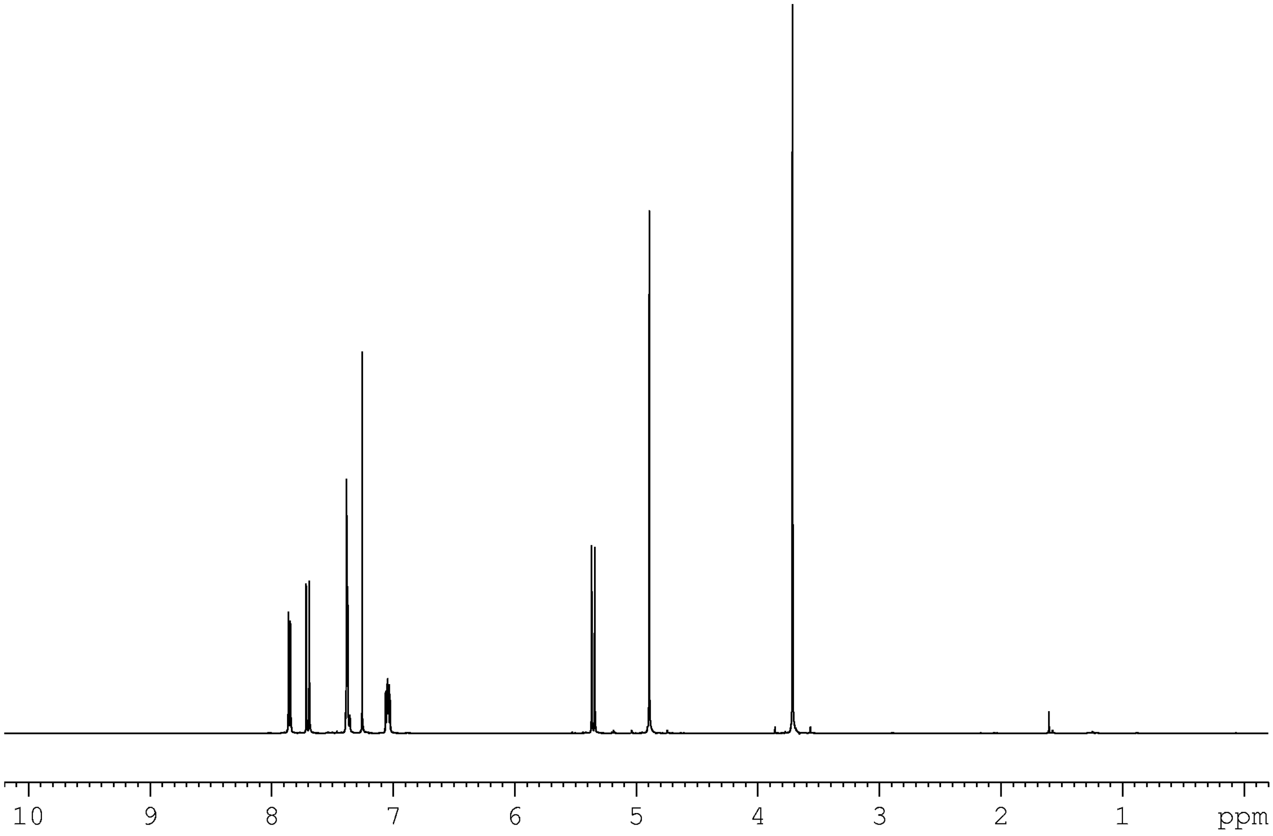
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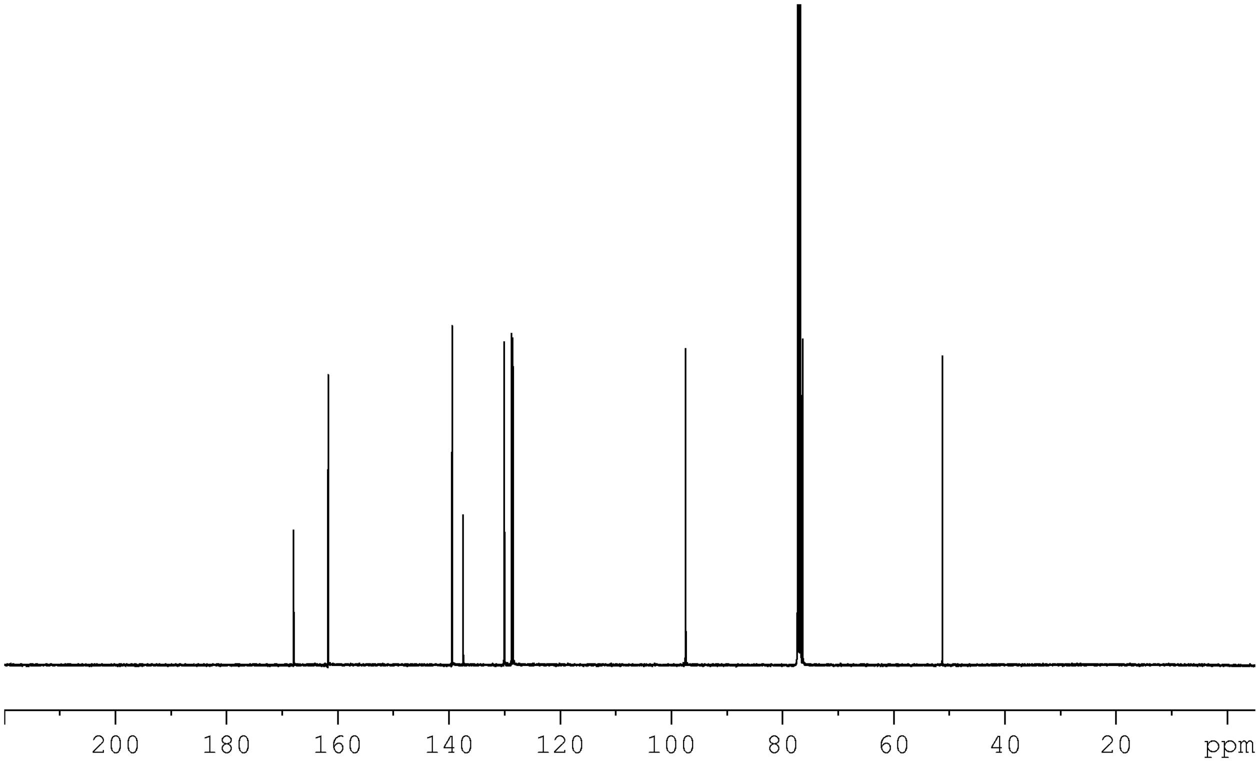
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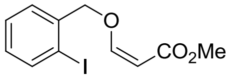
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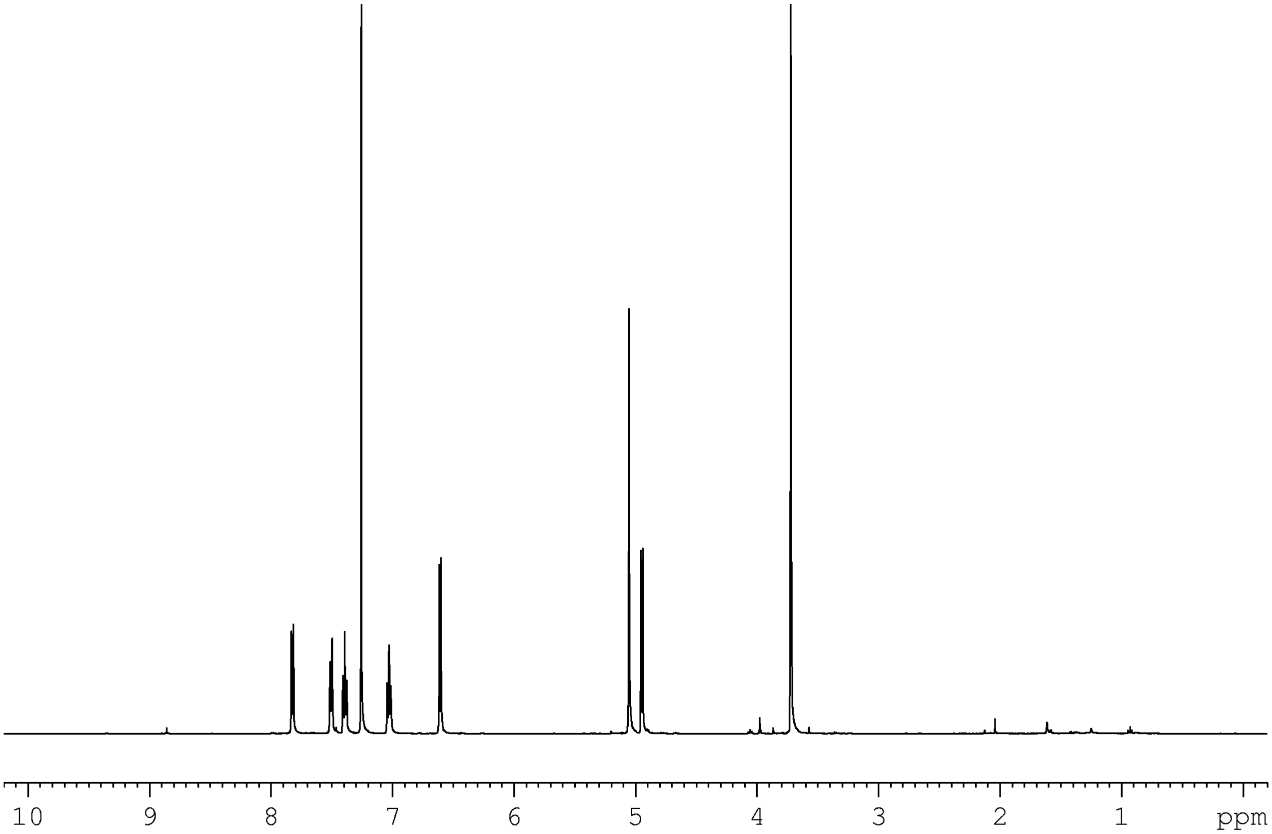
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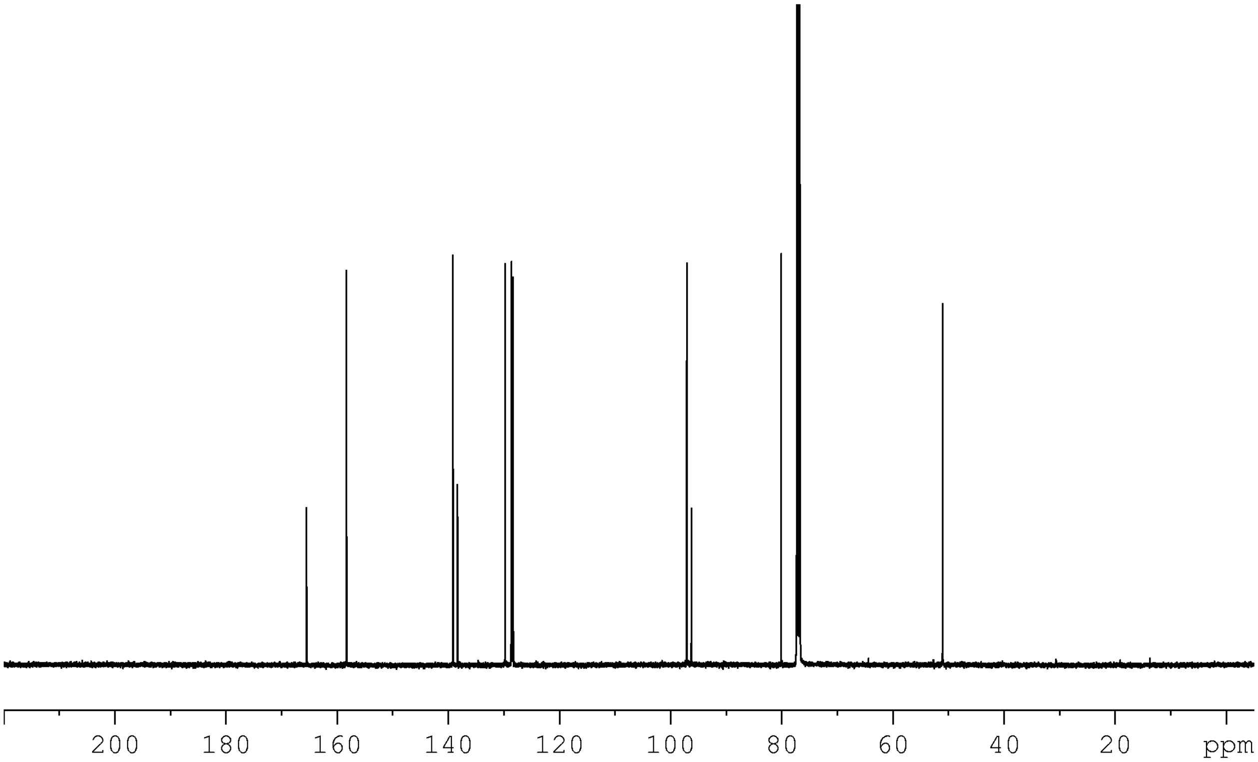
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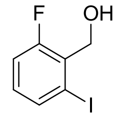
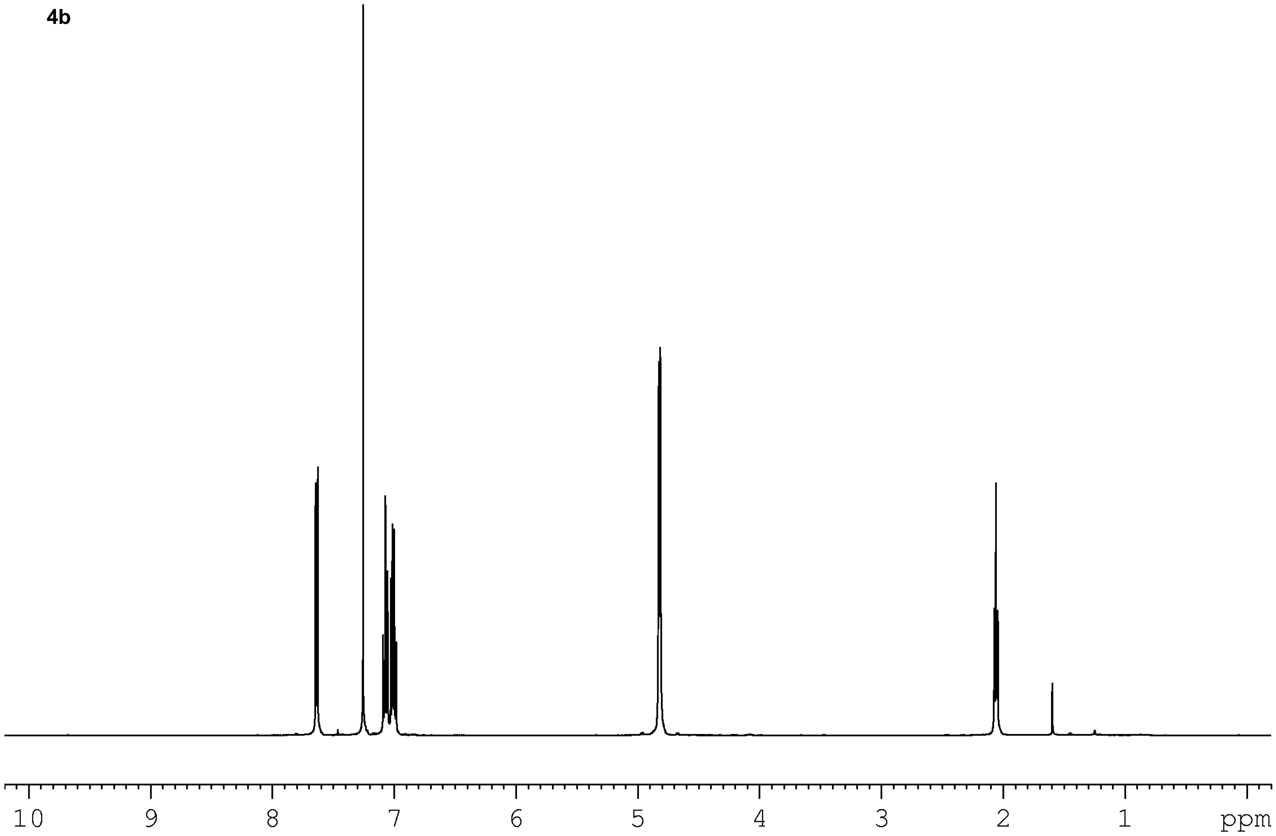
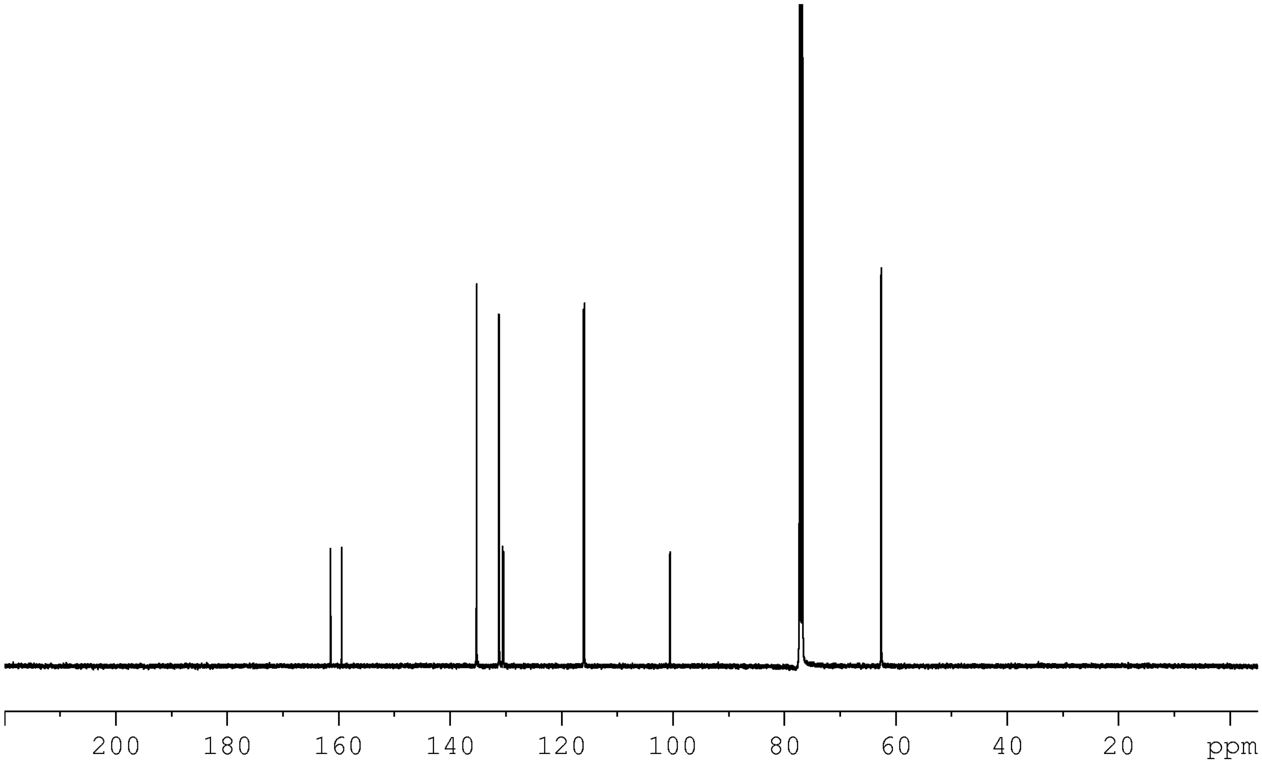
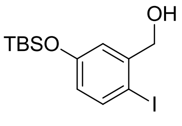


4b



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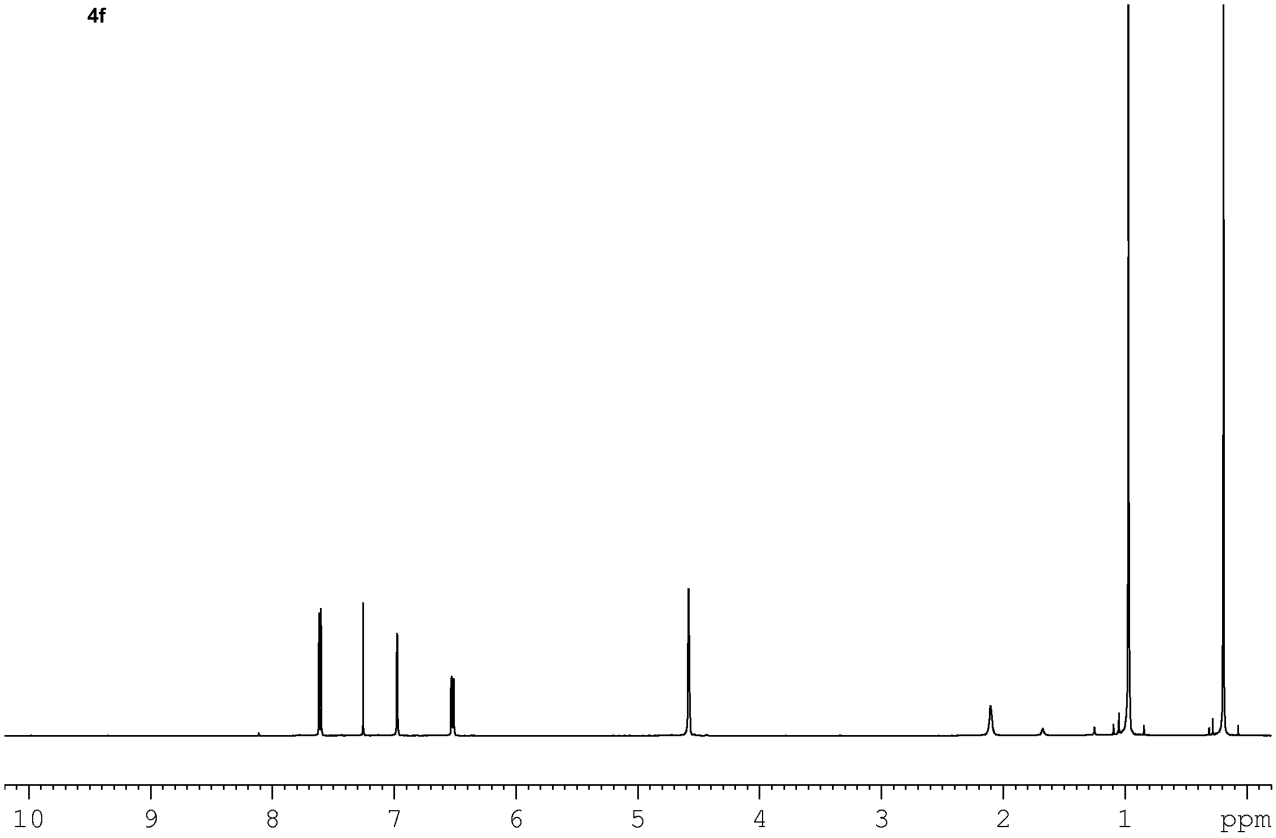
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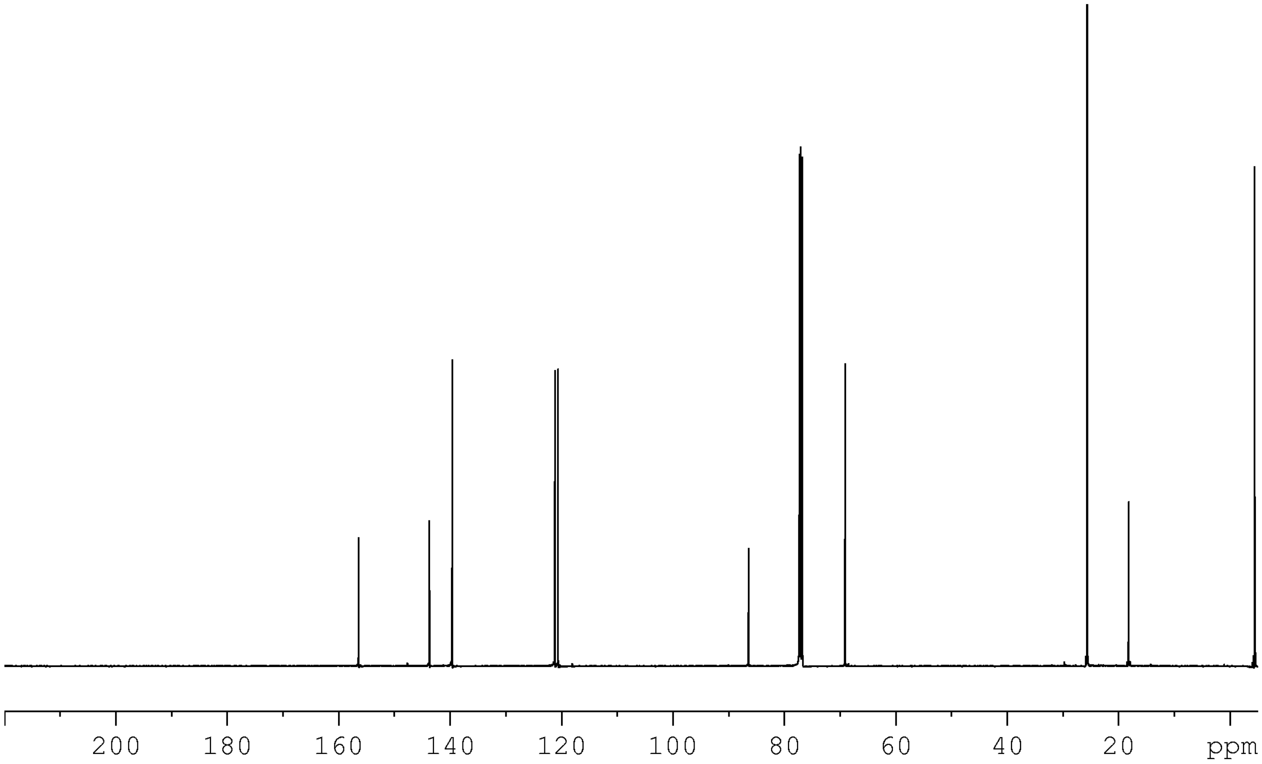
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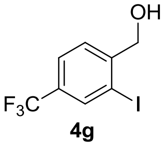
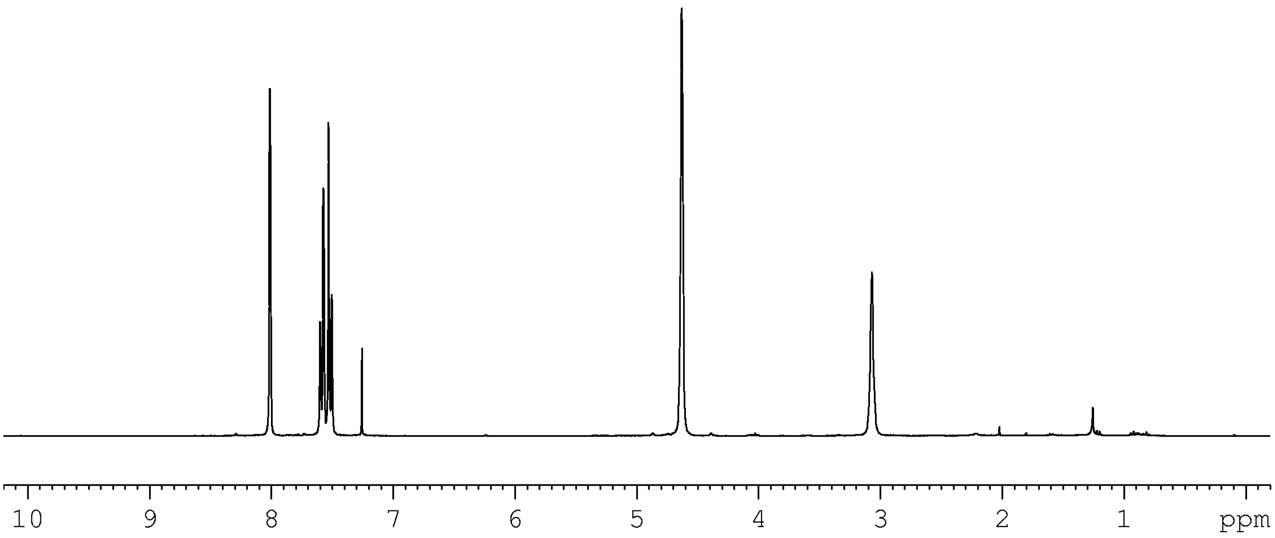
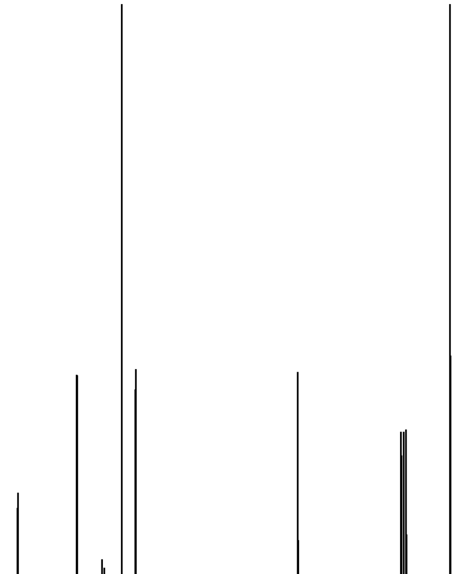
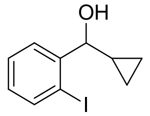


4g







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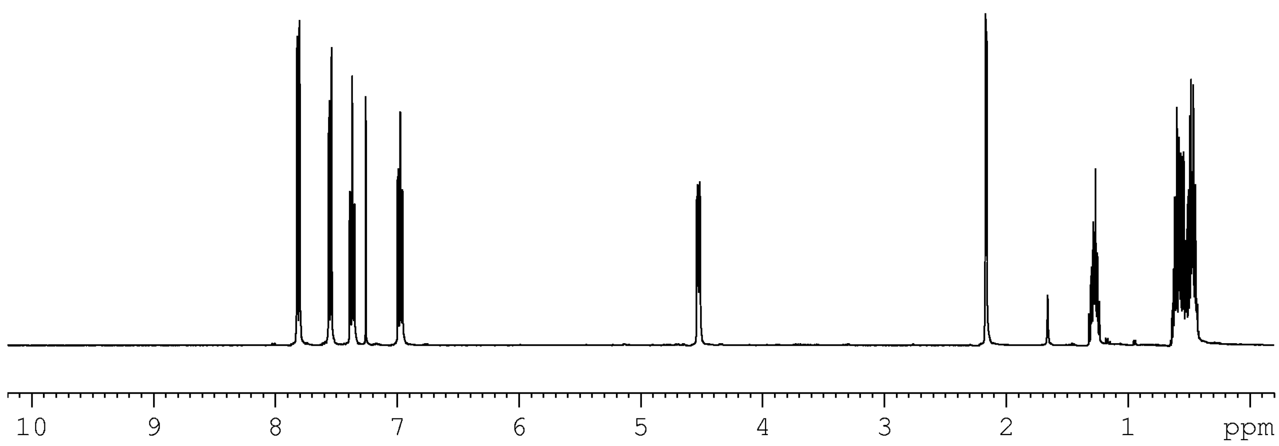

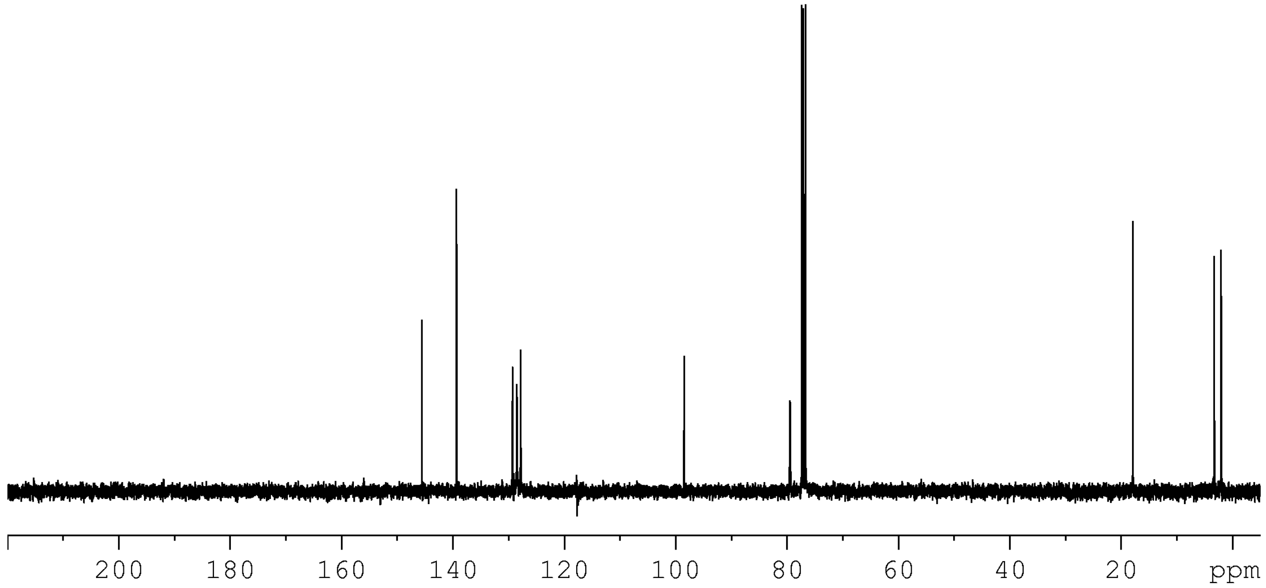

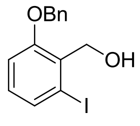

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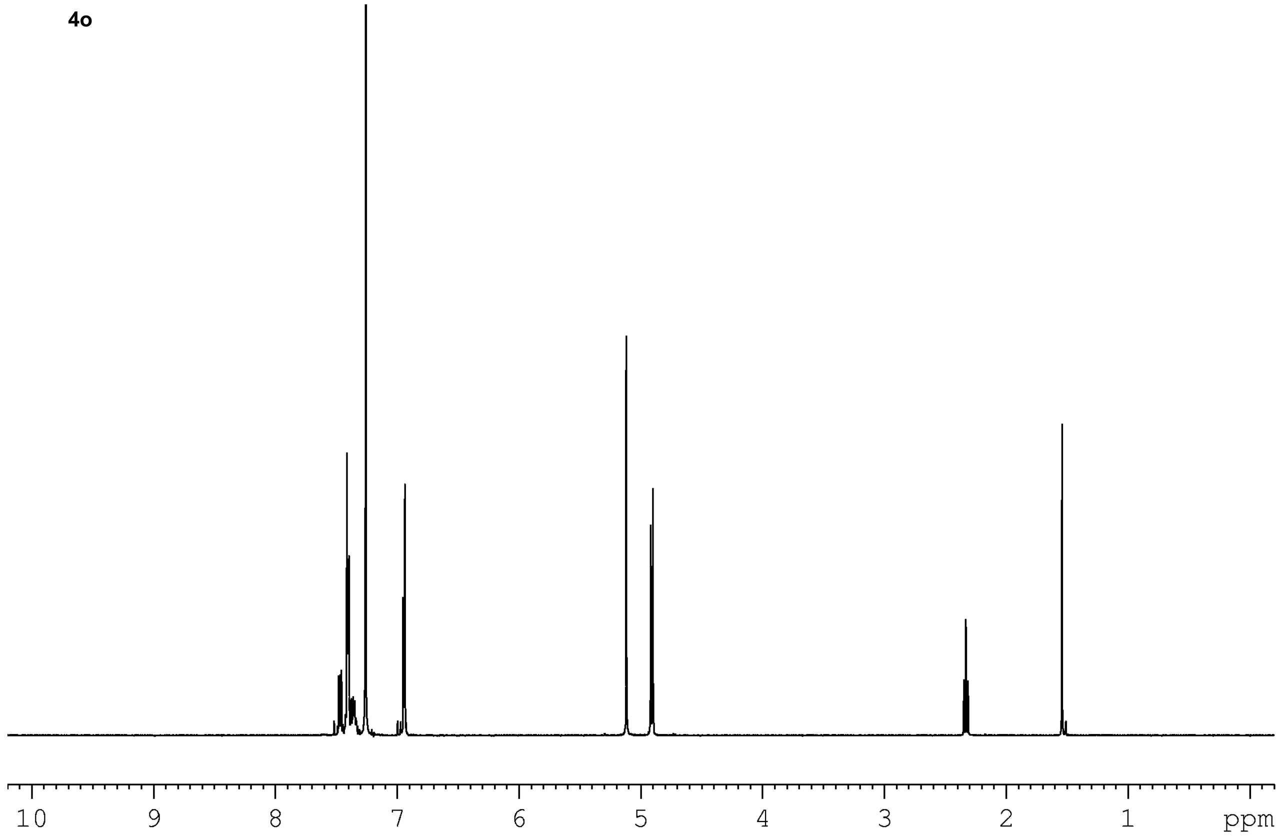

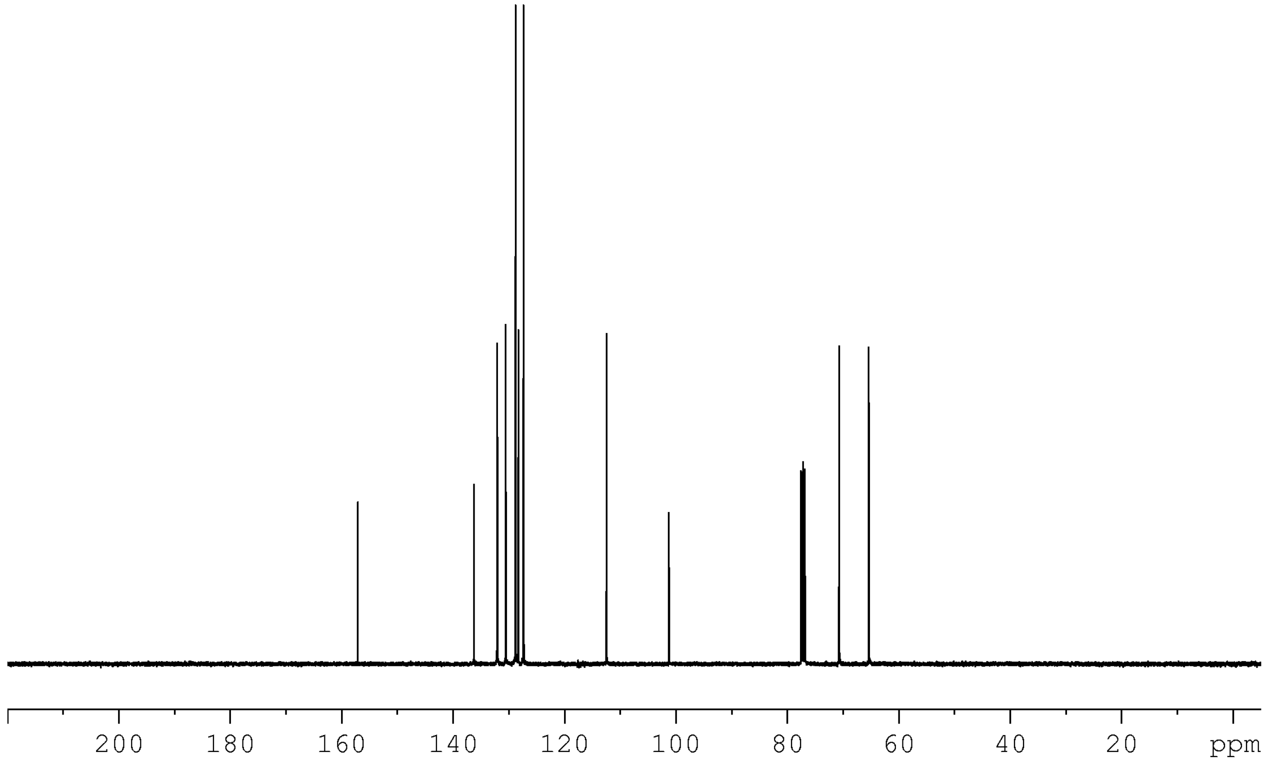

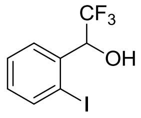

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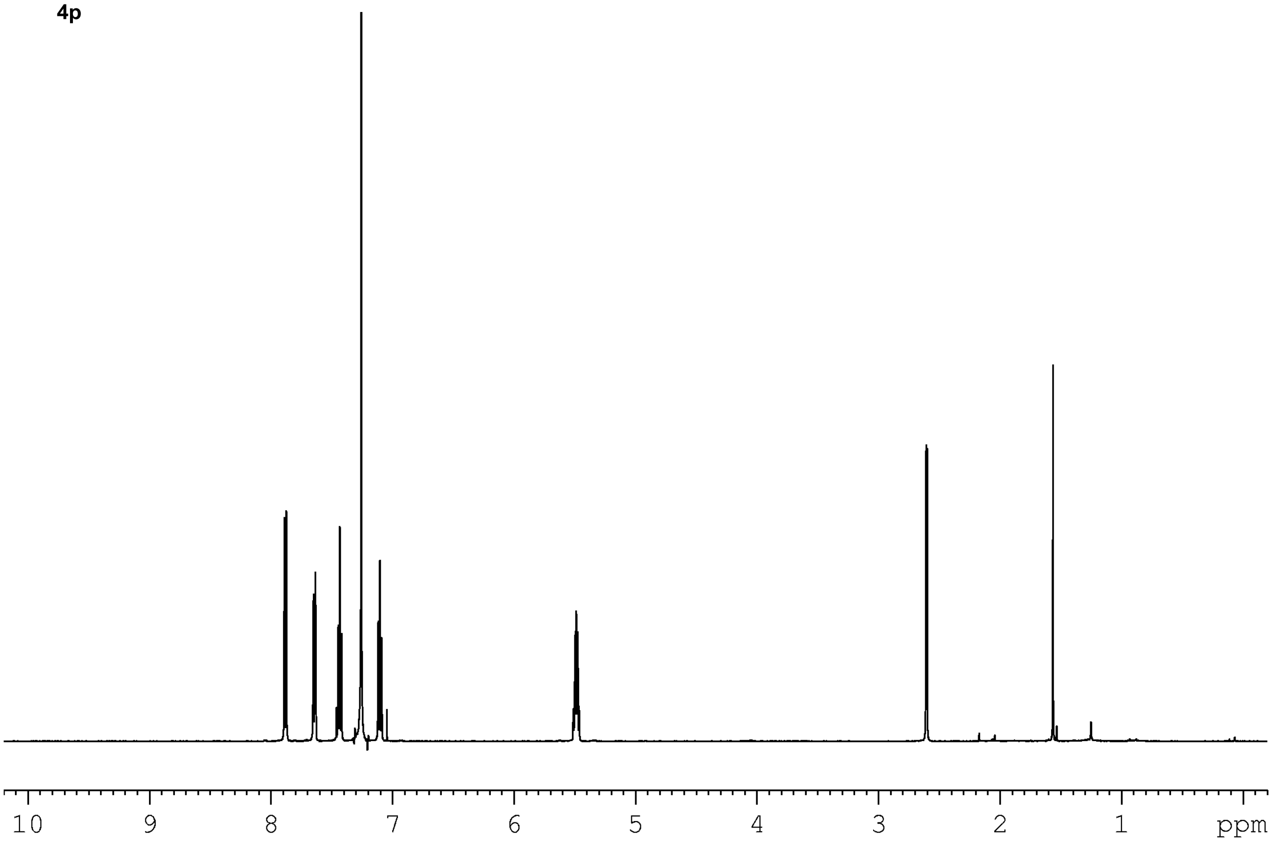

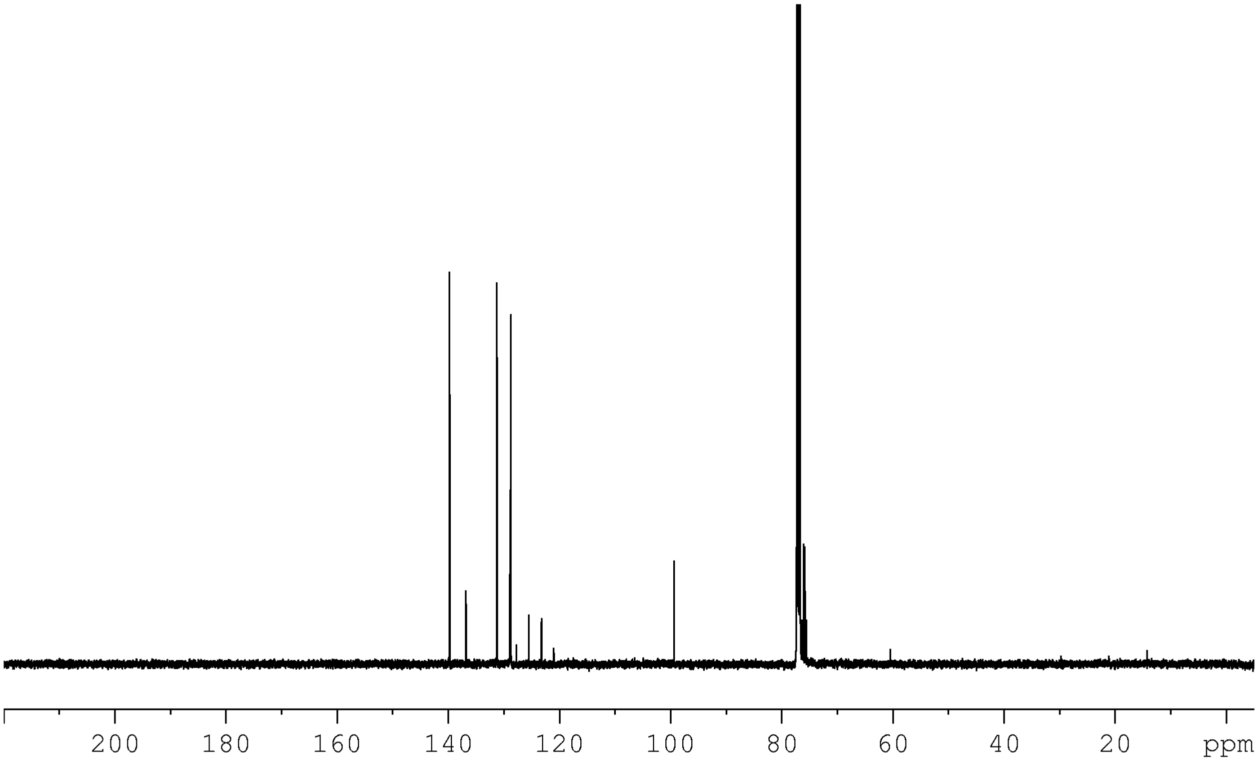

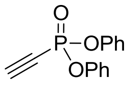
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OPh

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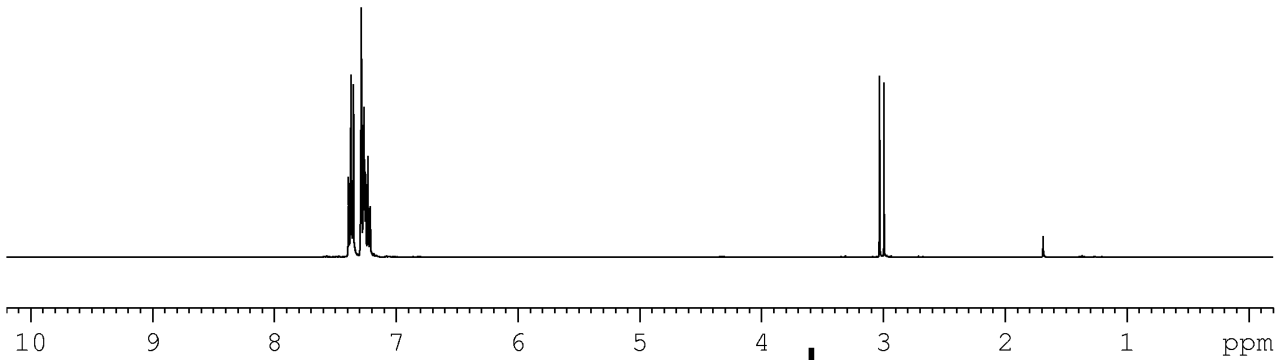
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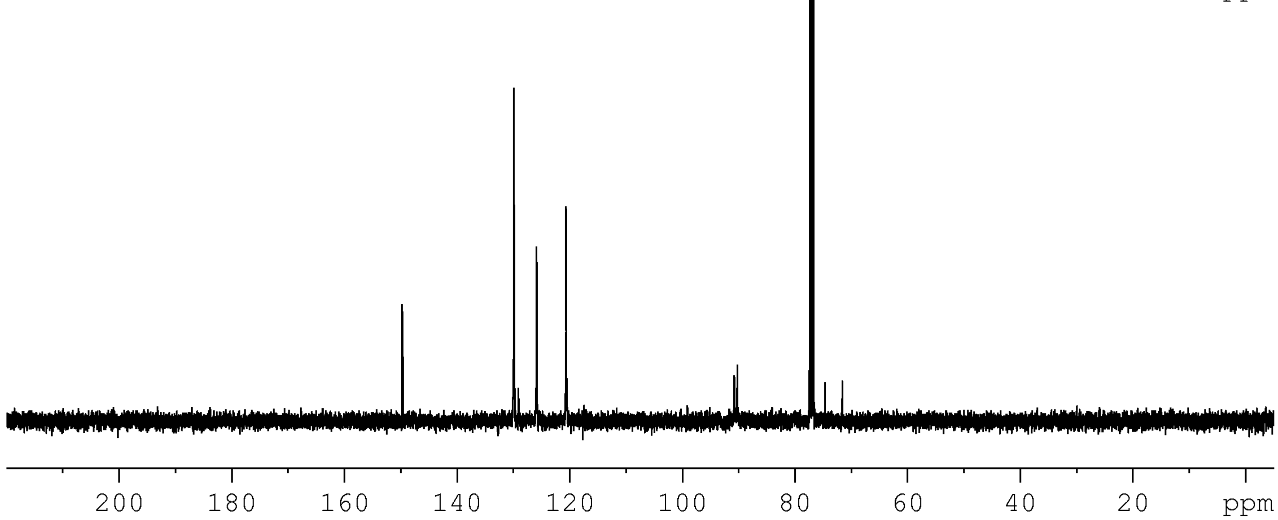
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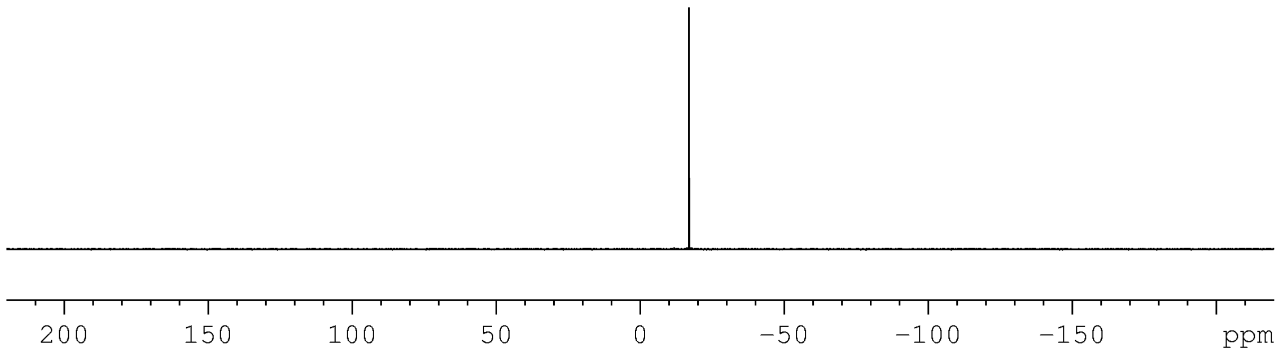
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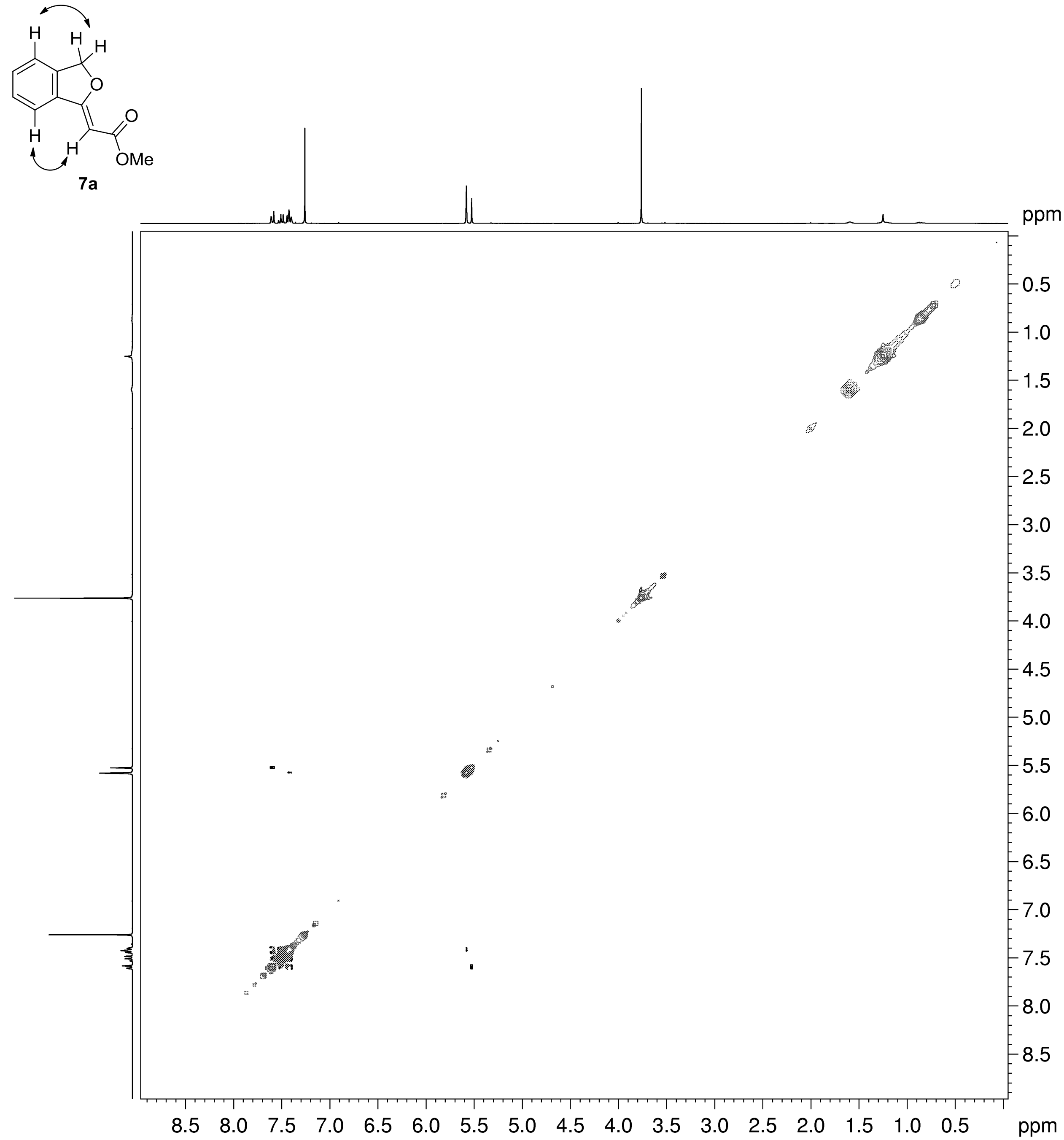

7a

H
H
H
O
O
H
H
OMe
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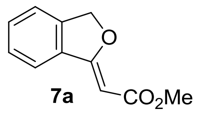

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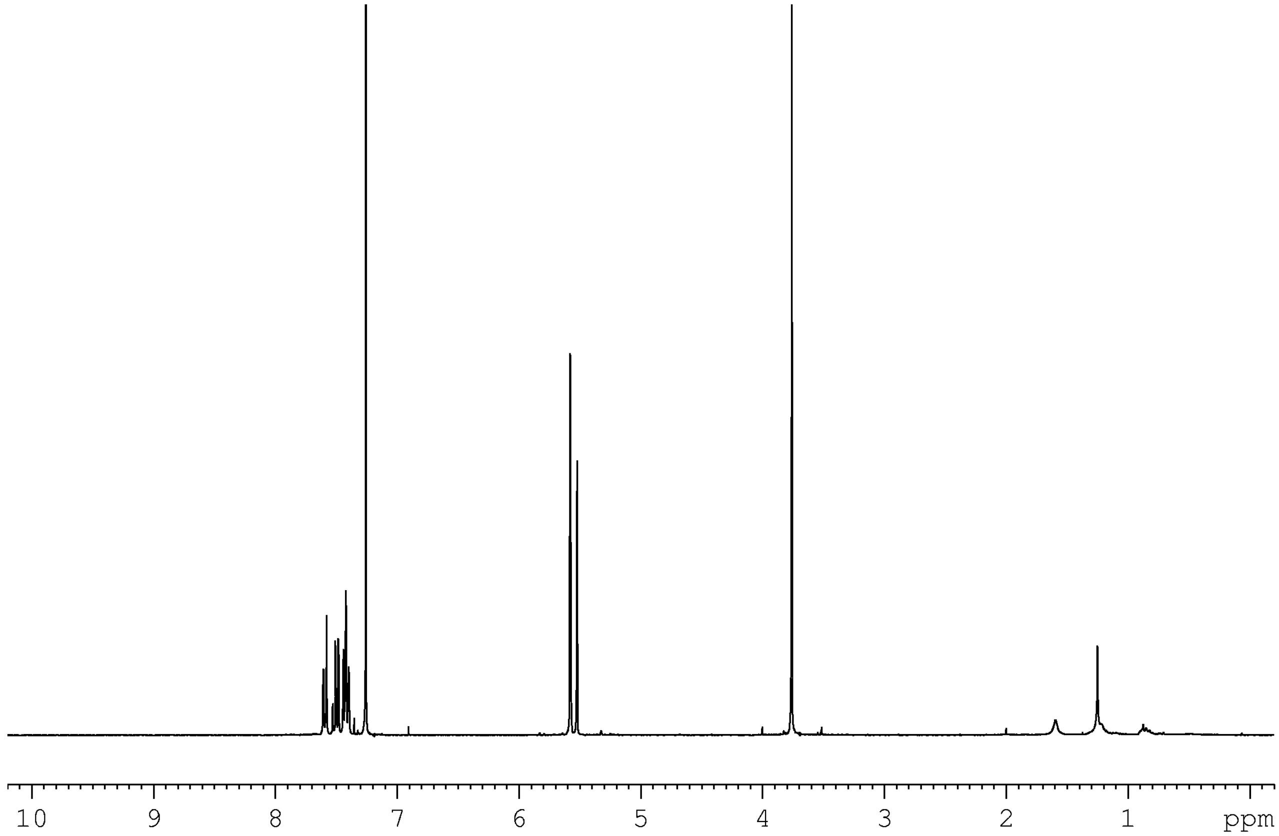

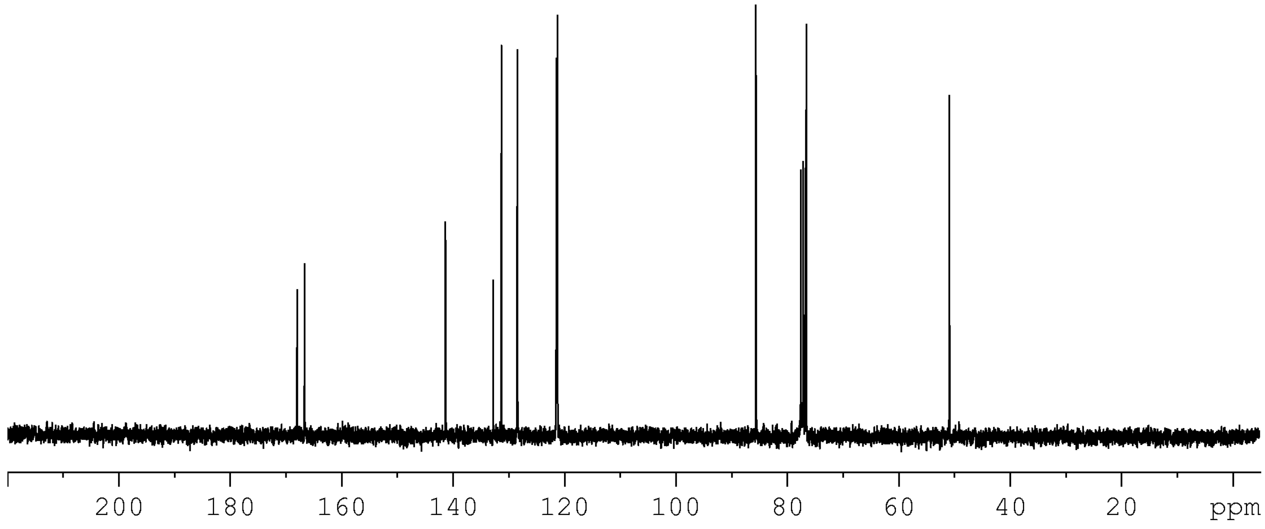

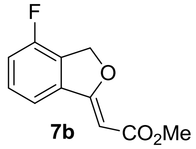
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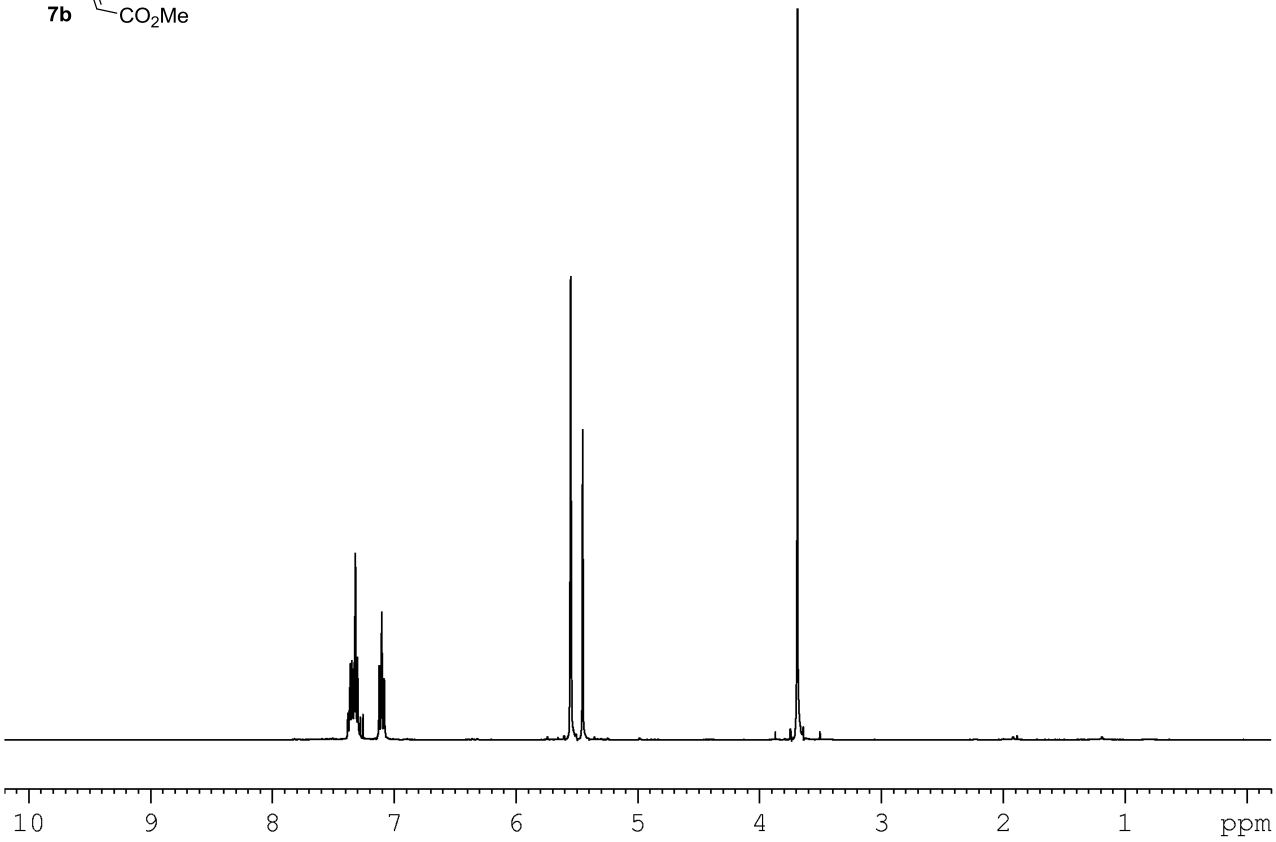
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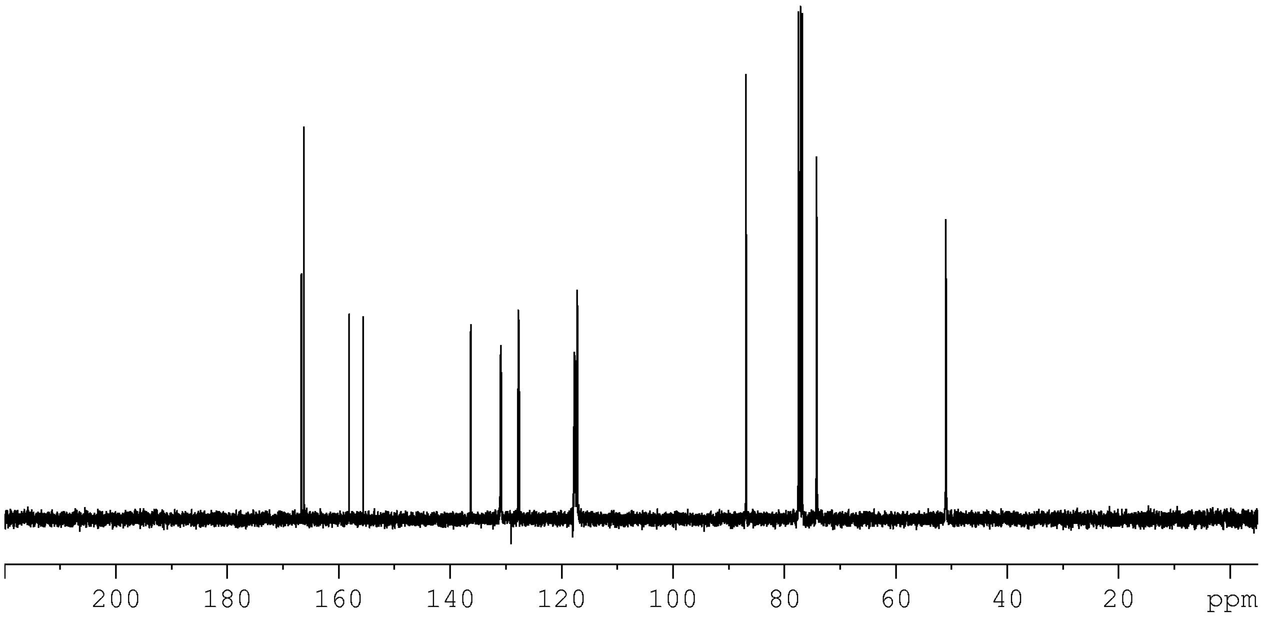
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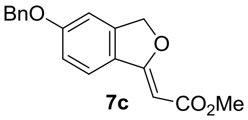
BnO
O
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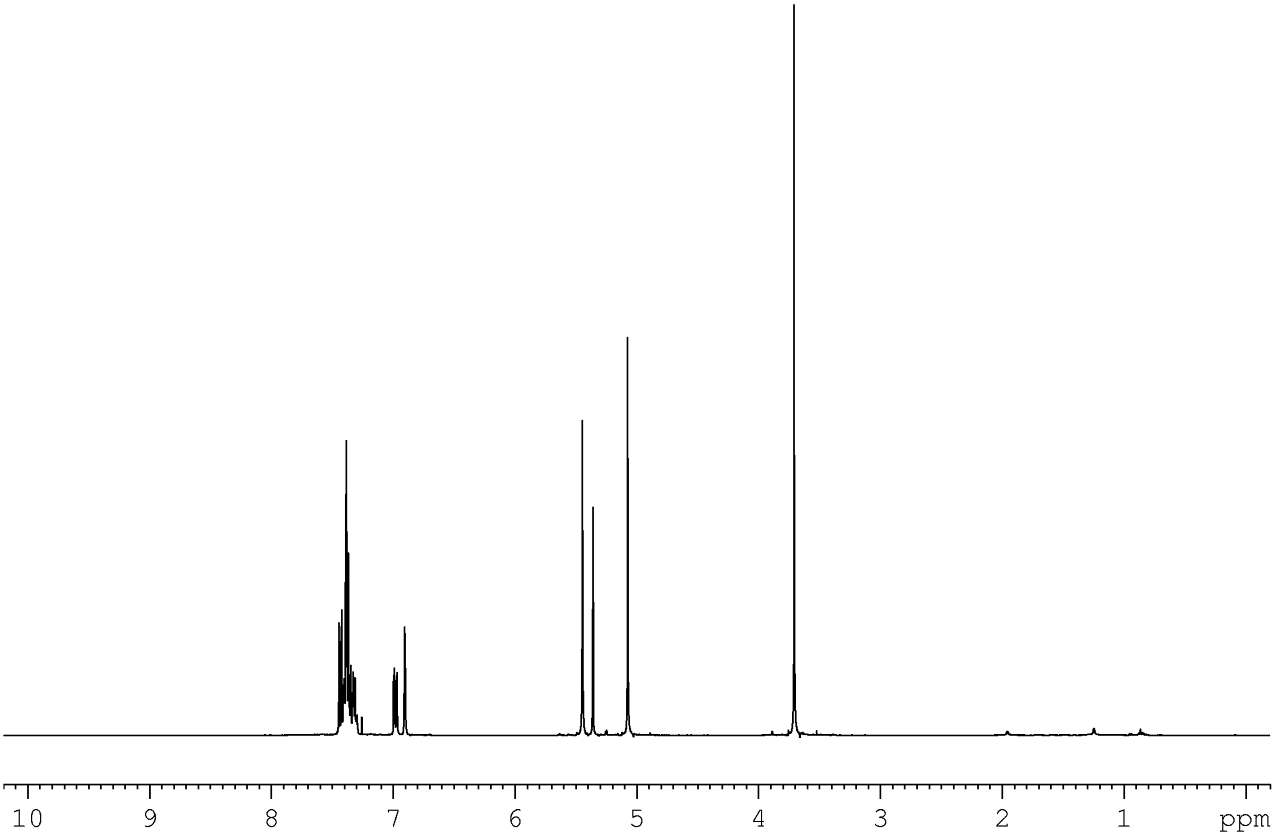
7c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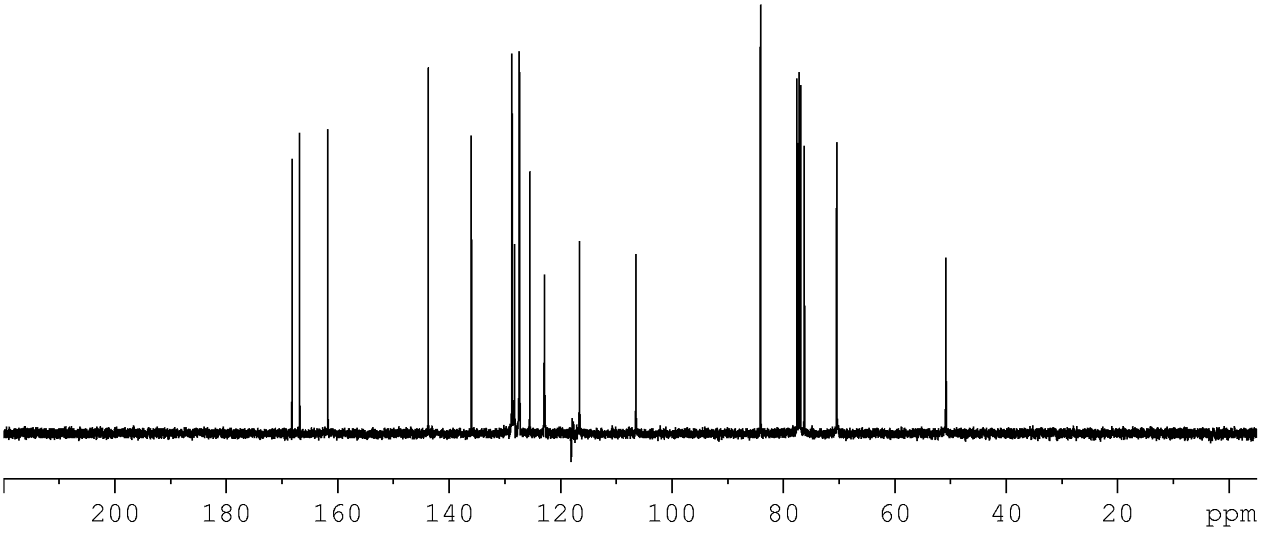
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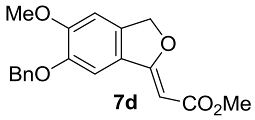
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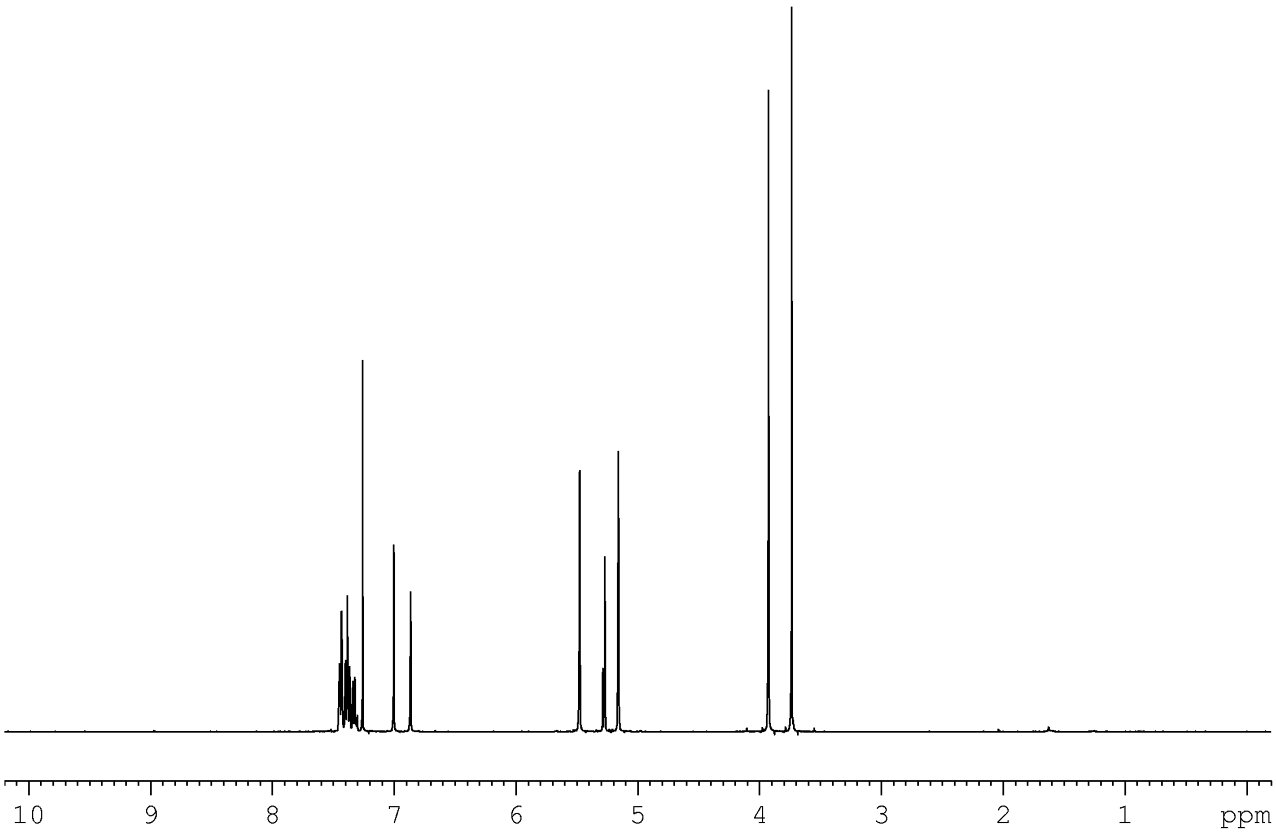
O
BnO
CO$_2$Me

7d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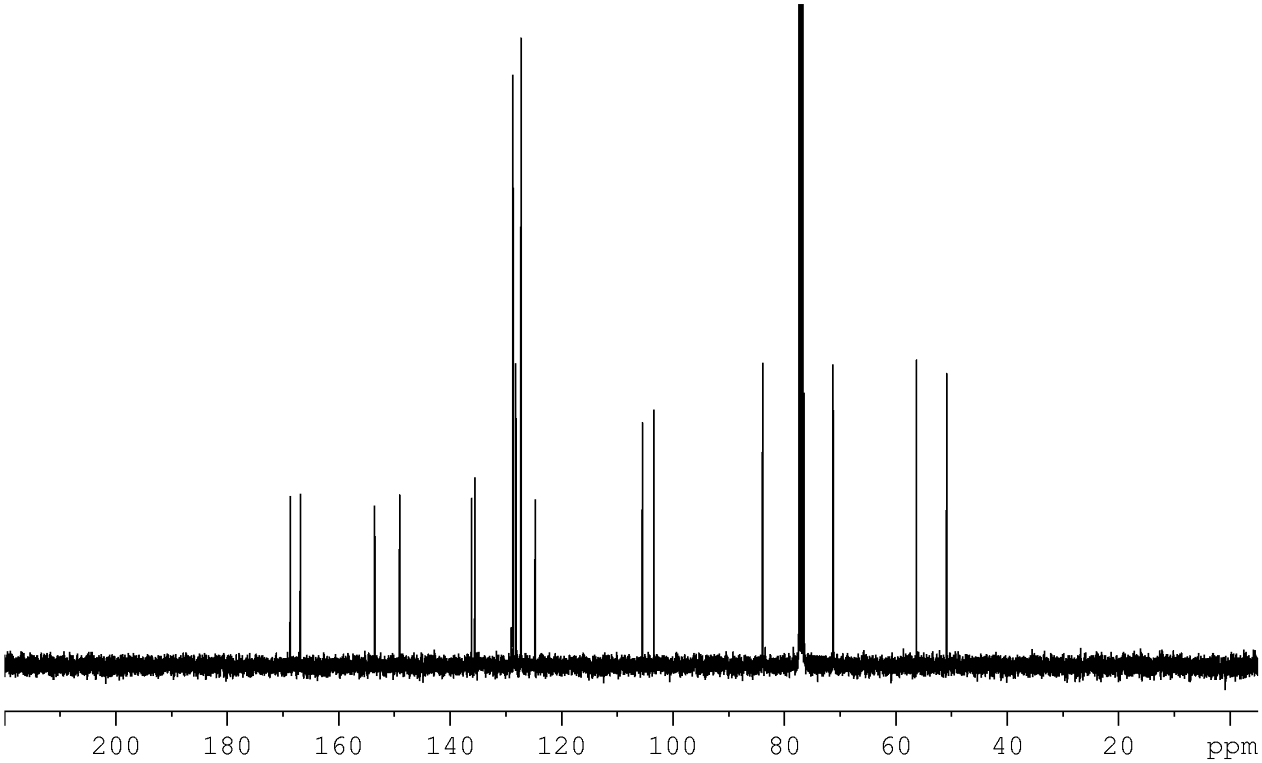
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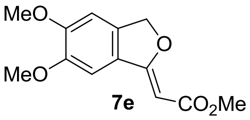
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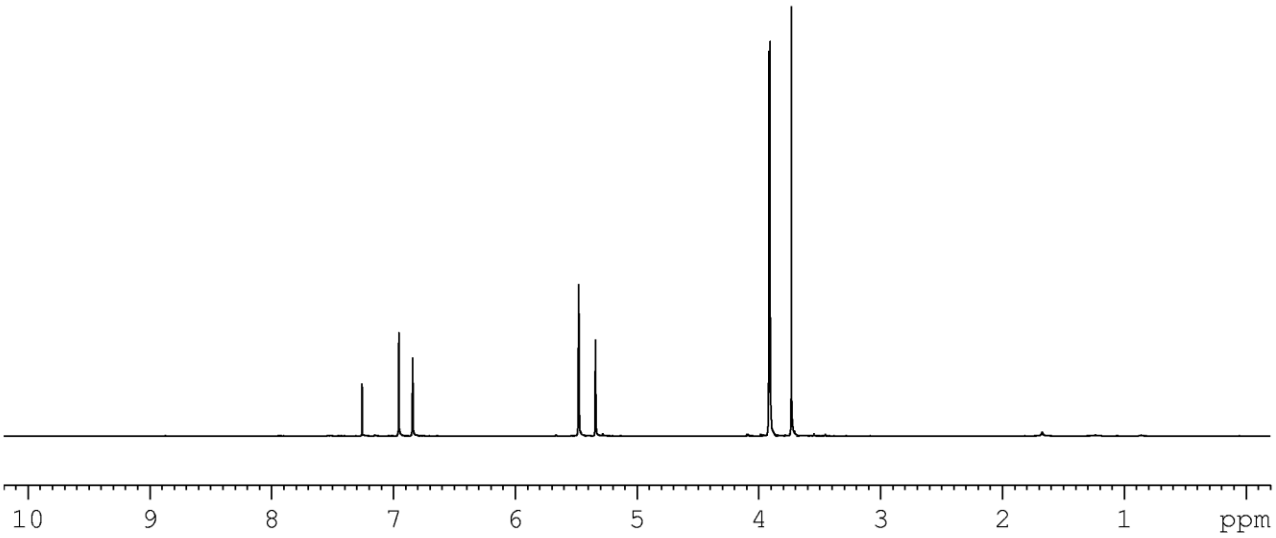
MeO
O
CO2Me

7e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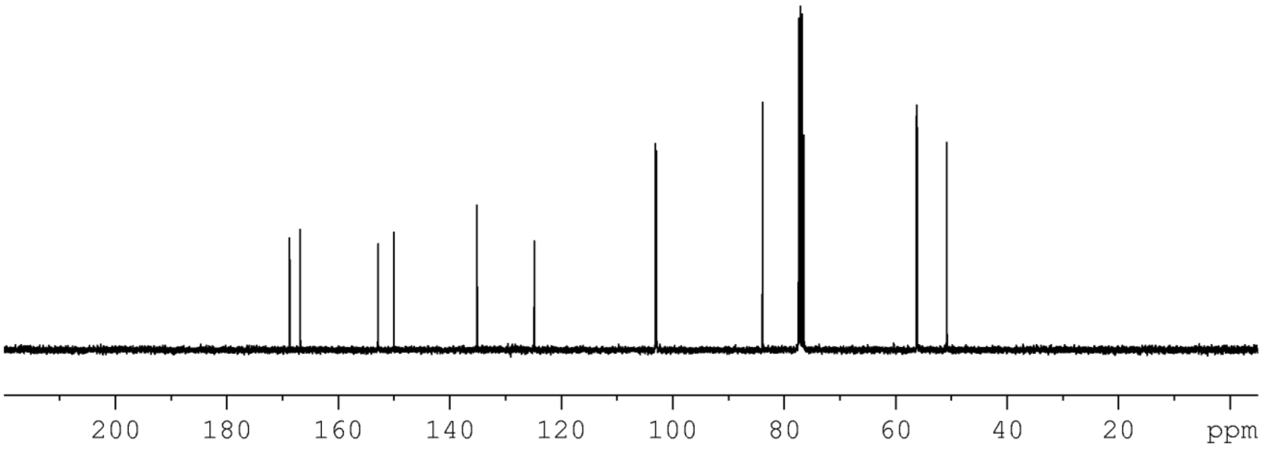
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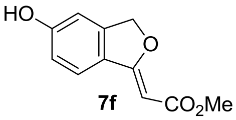
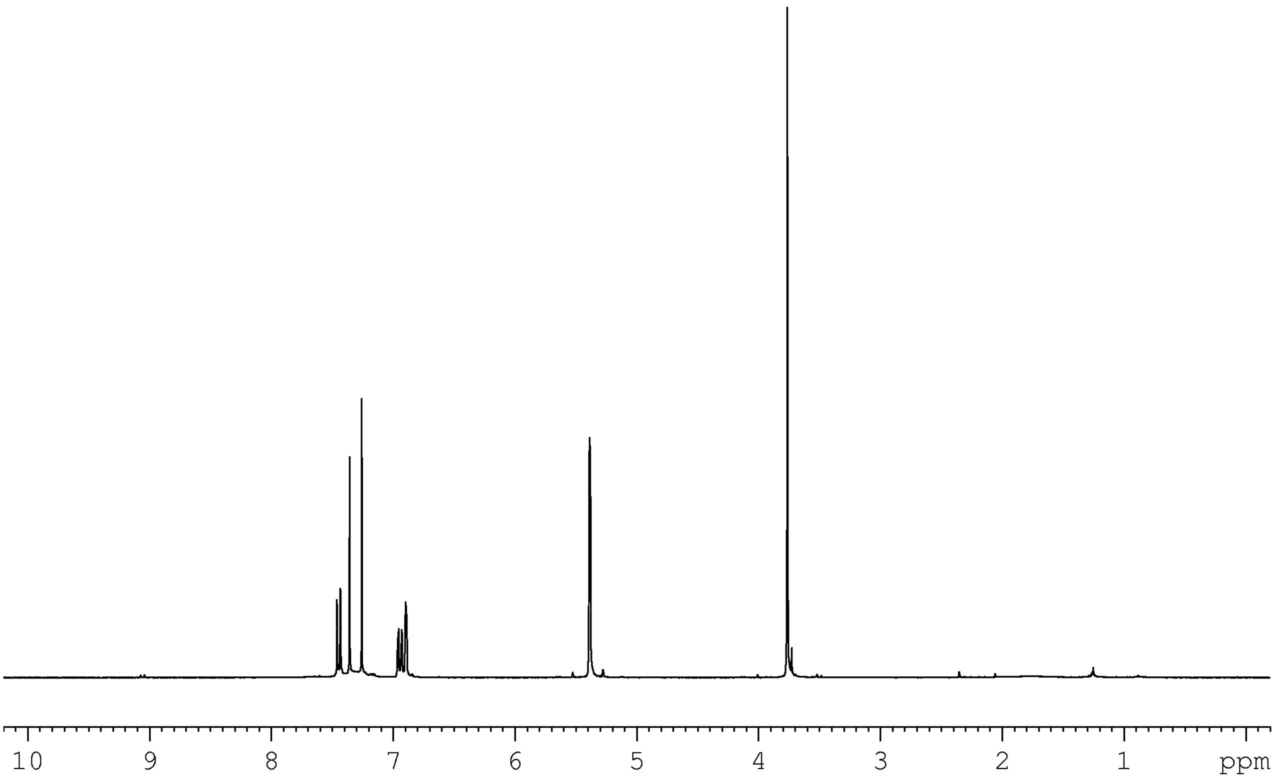

HO
O
CO2Me

7f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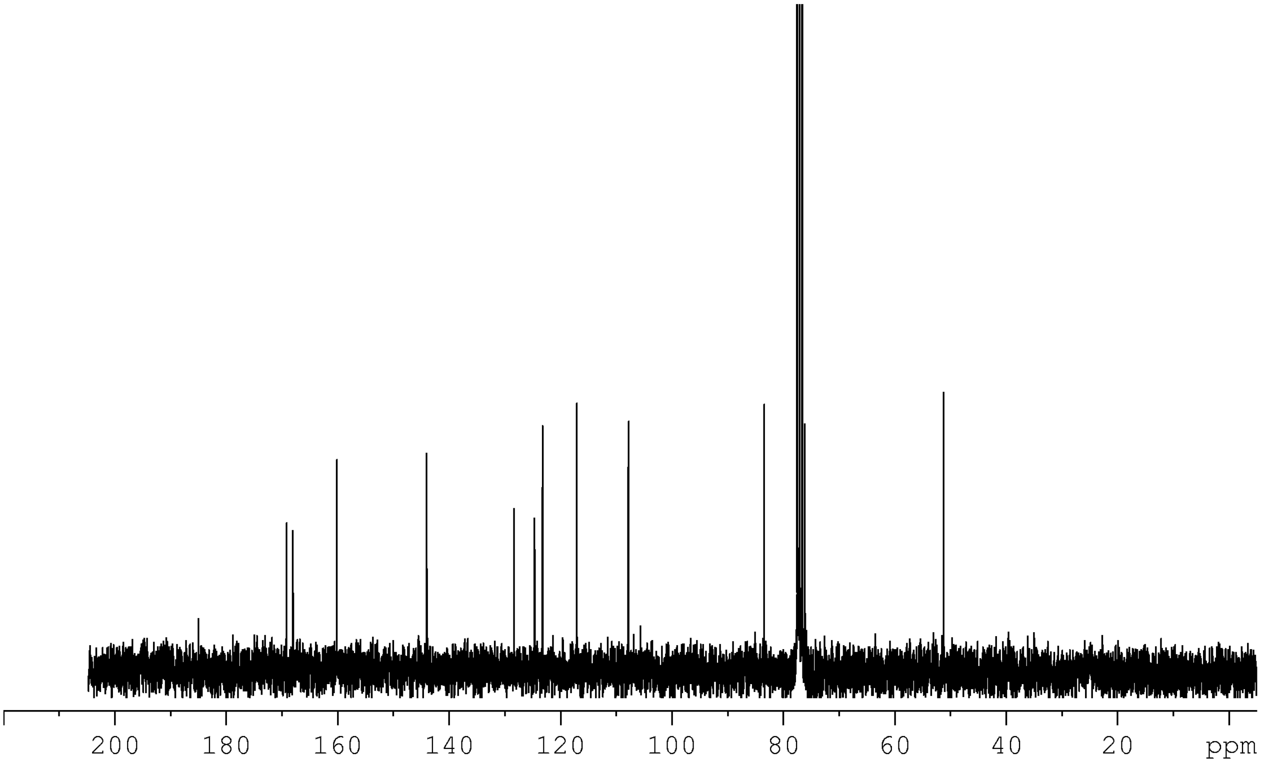
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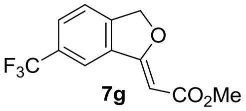
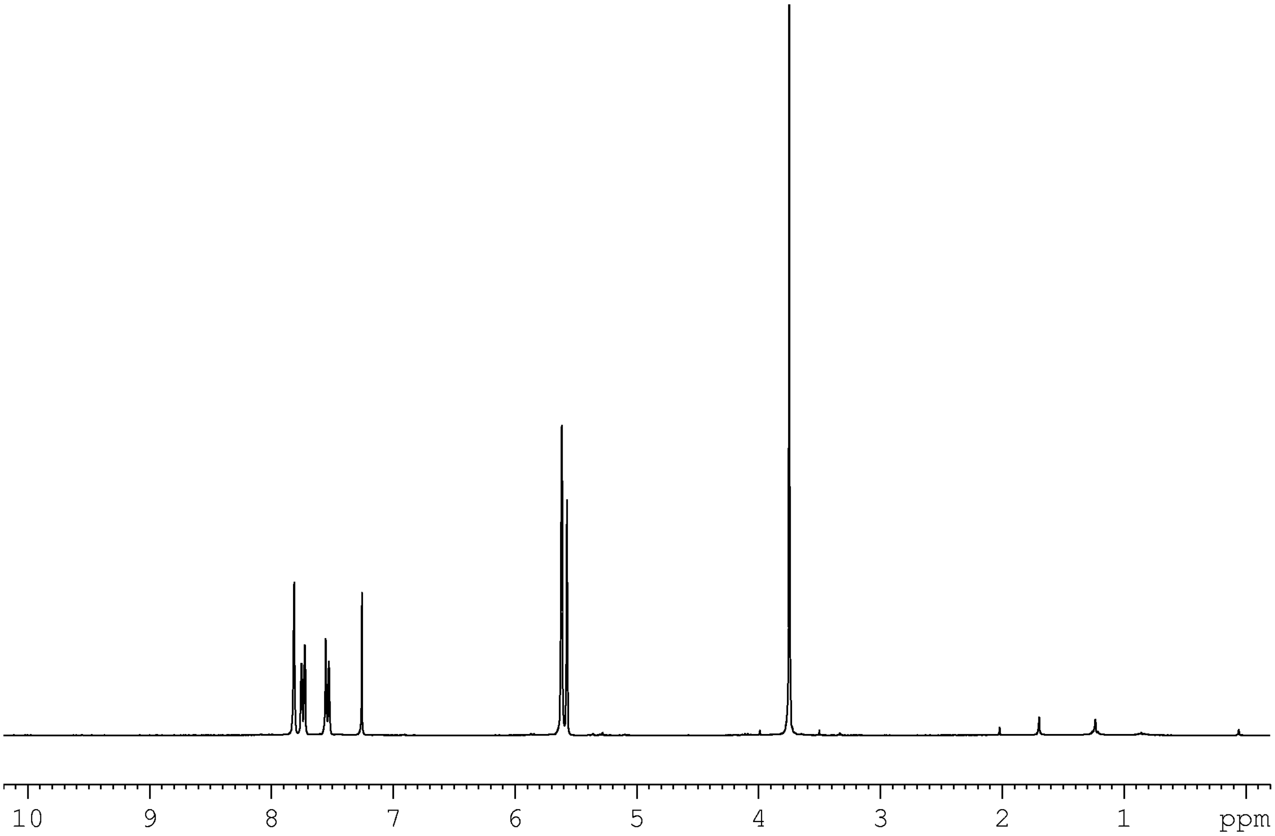

F3C
O
CO2Me

7g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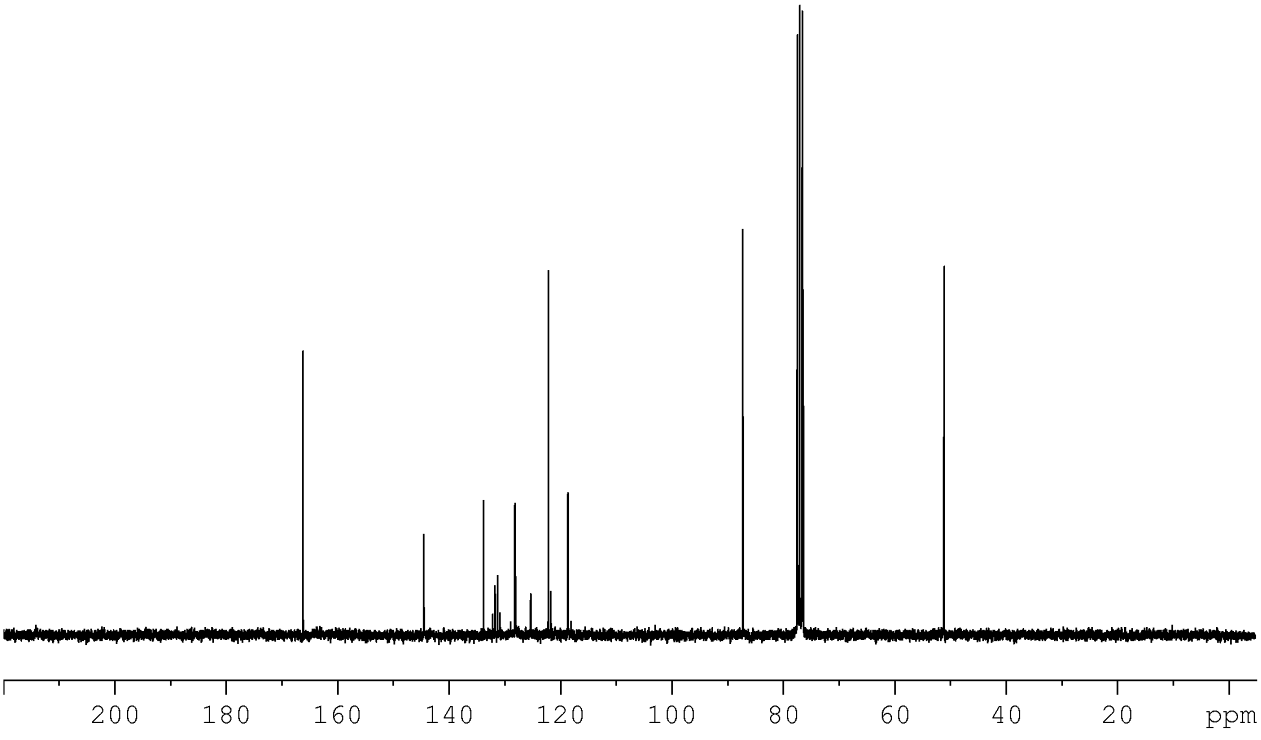
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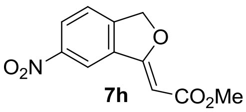
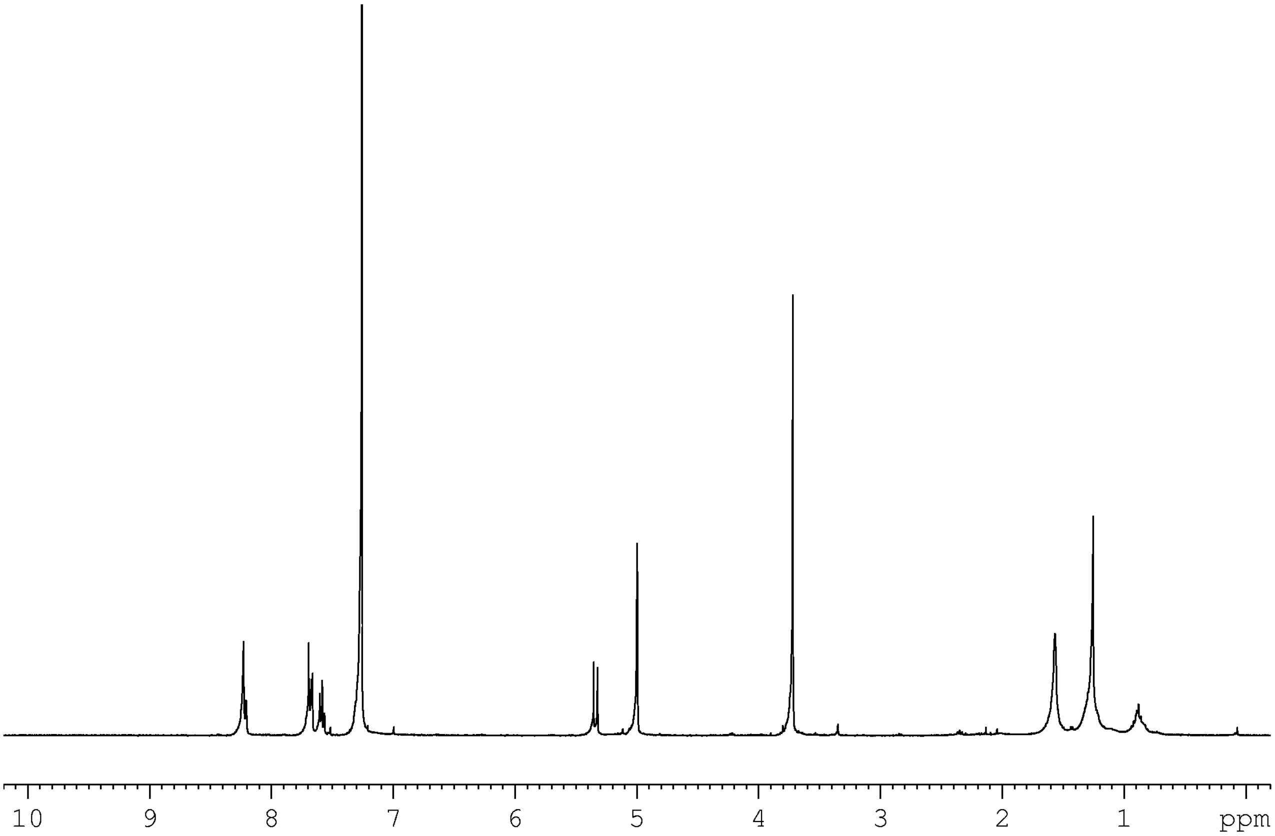

O
O_2N
CO_2Me

7h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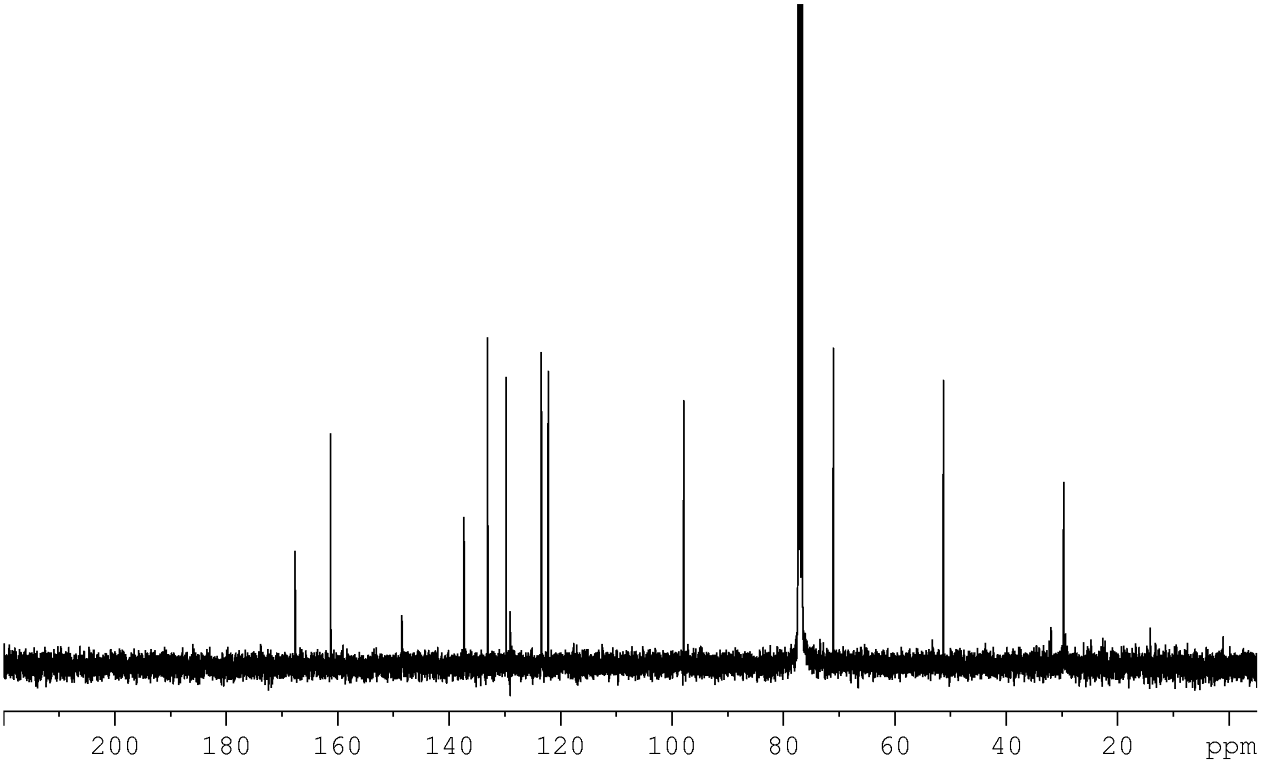
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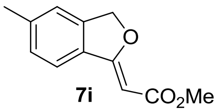

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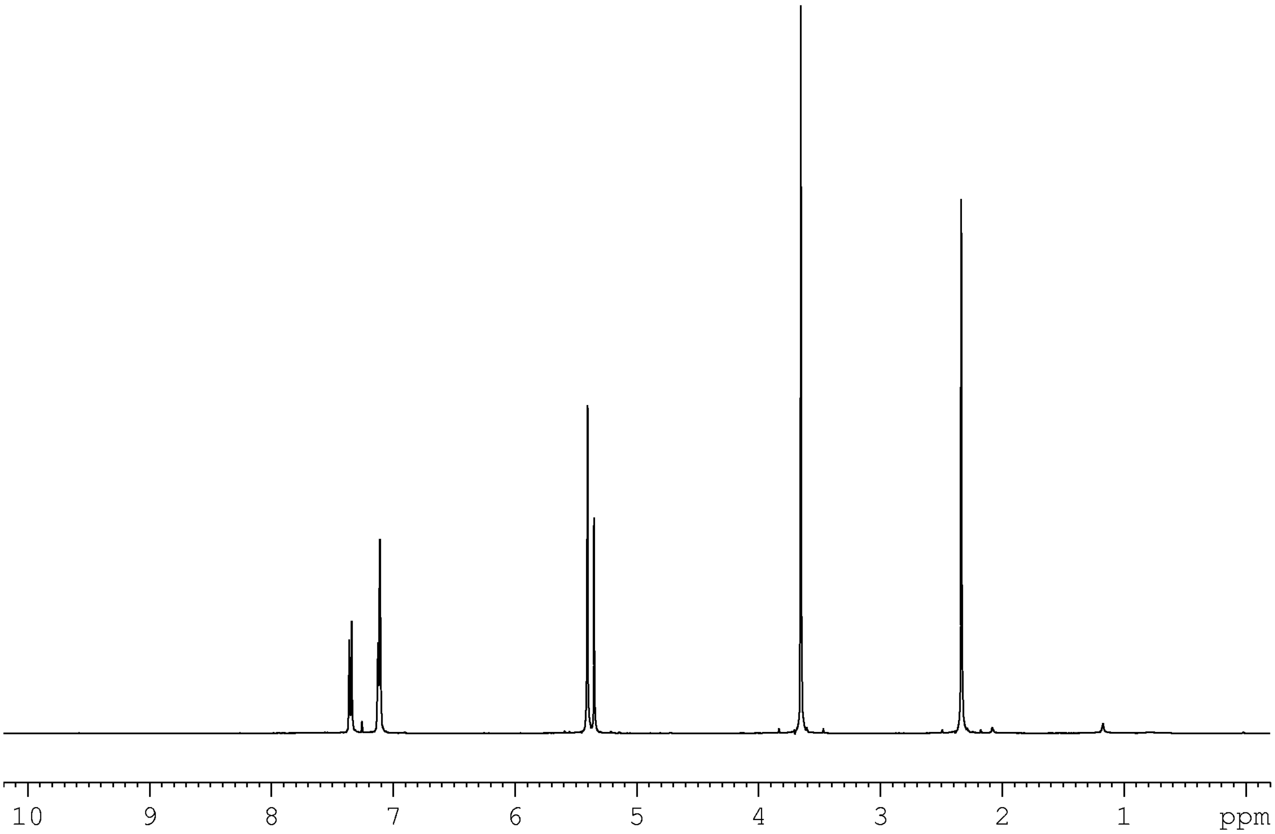

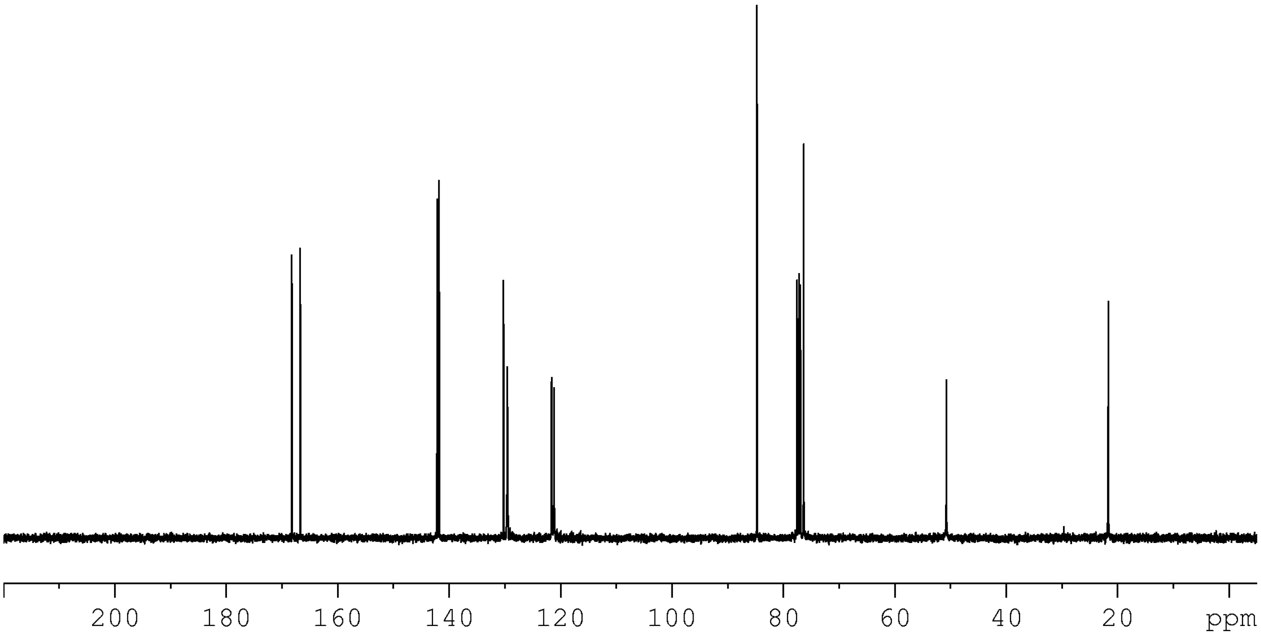

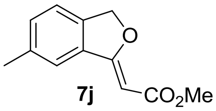

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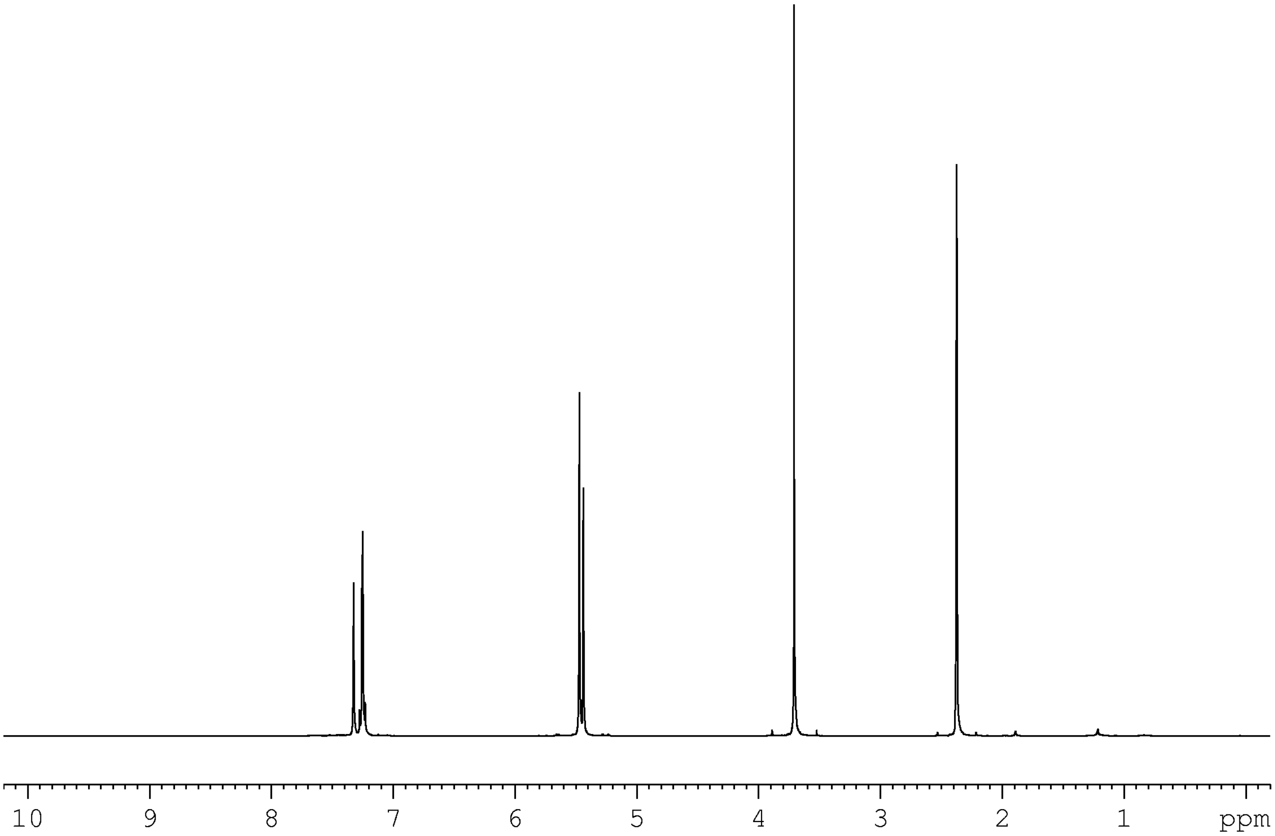

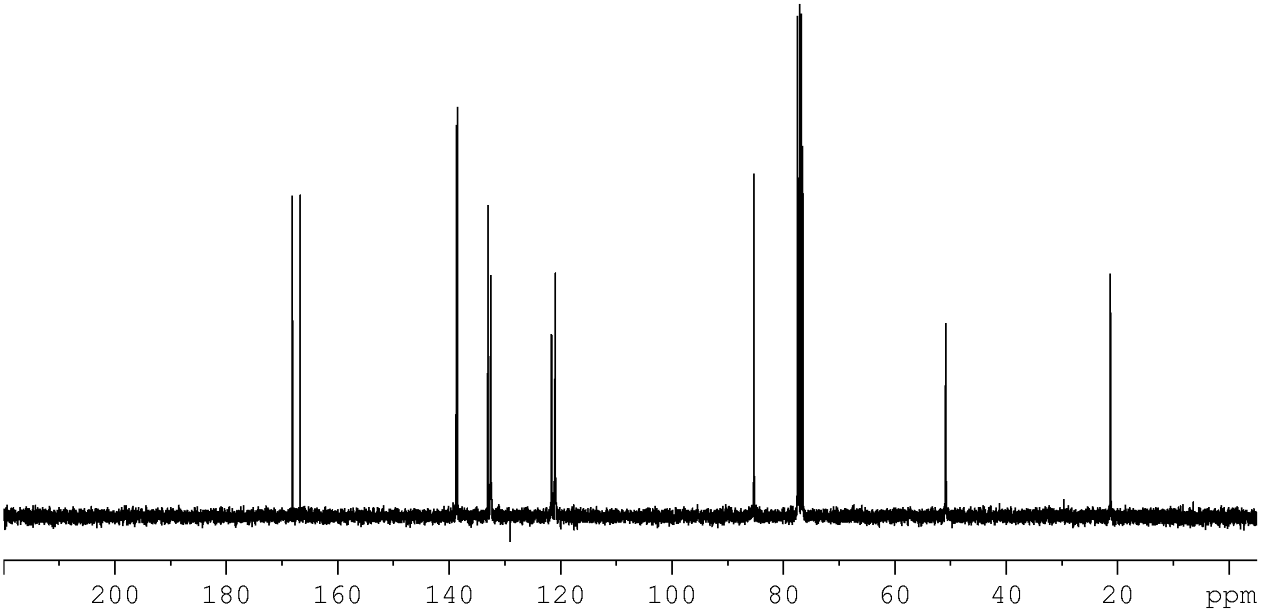

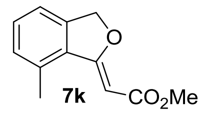

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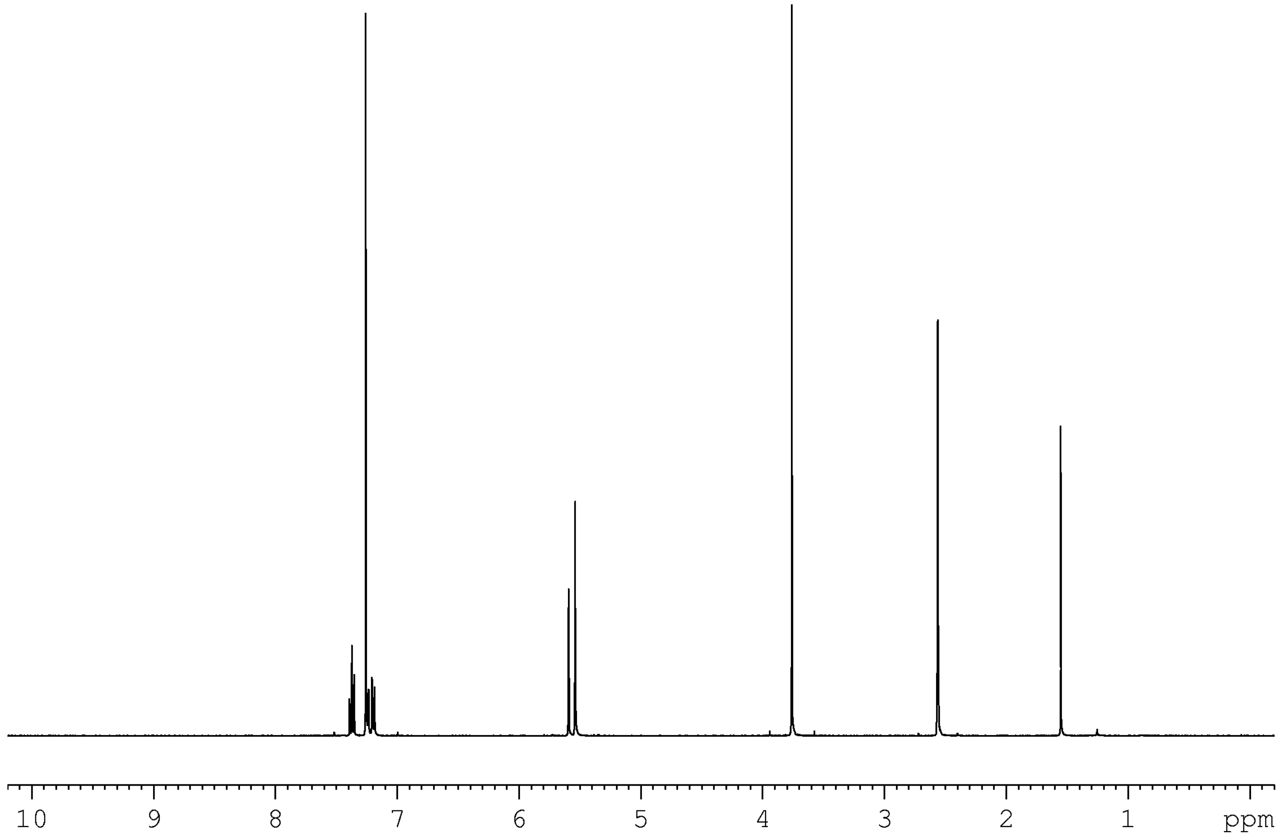
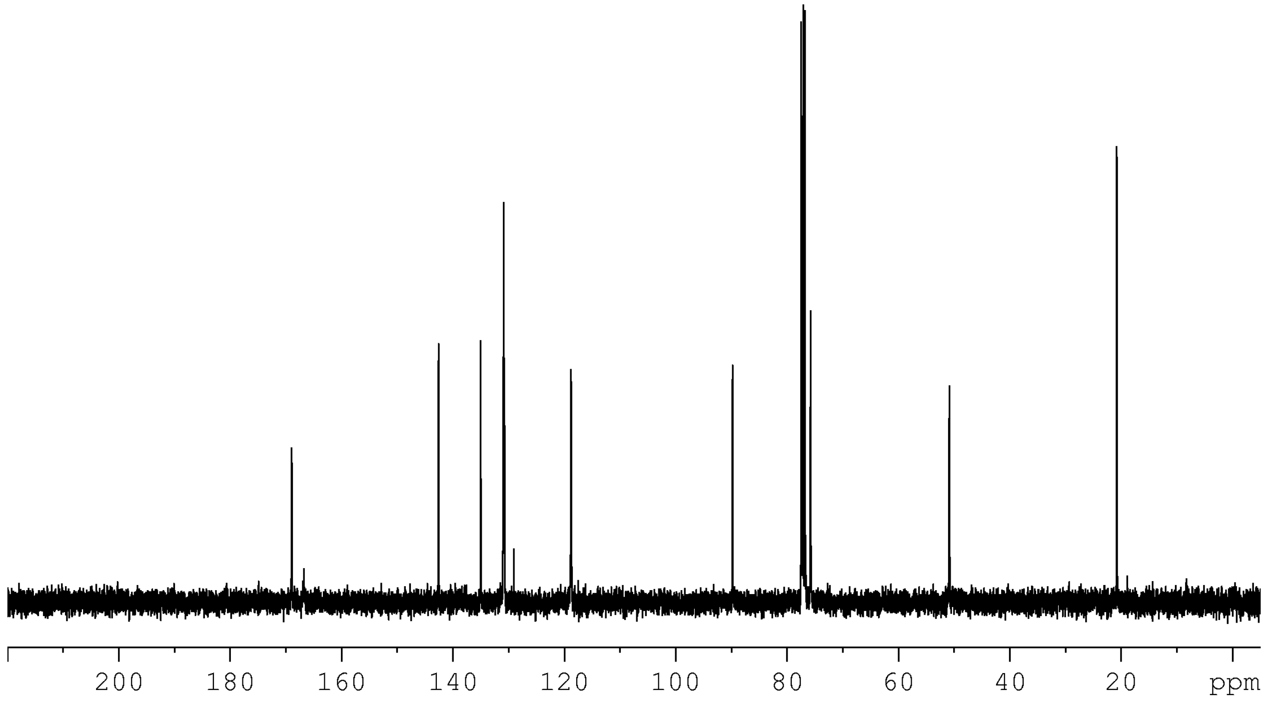
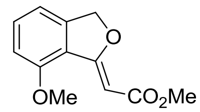
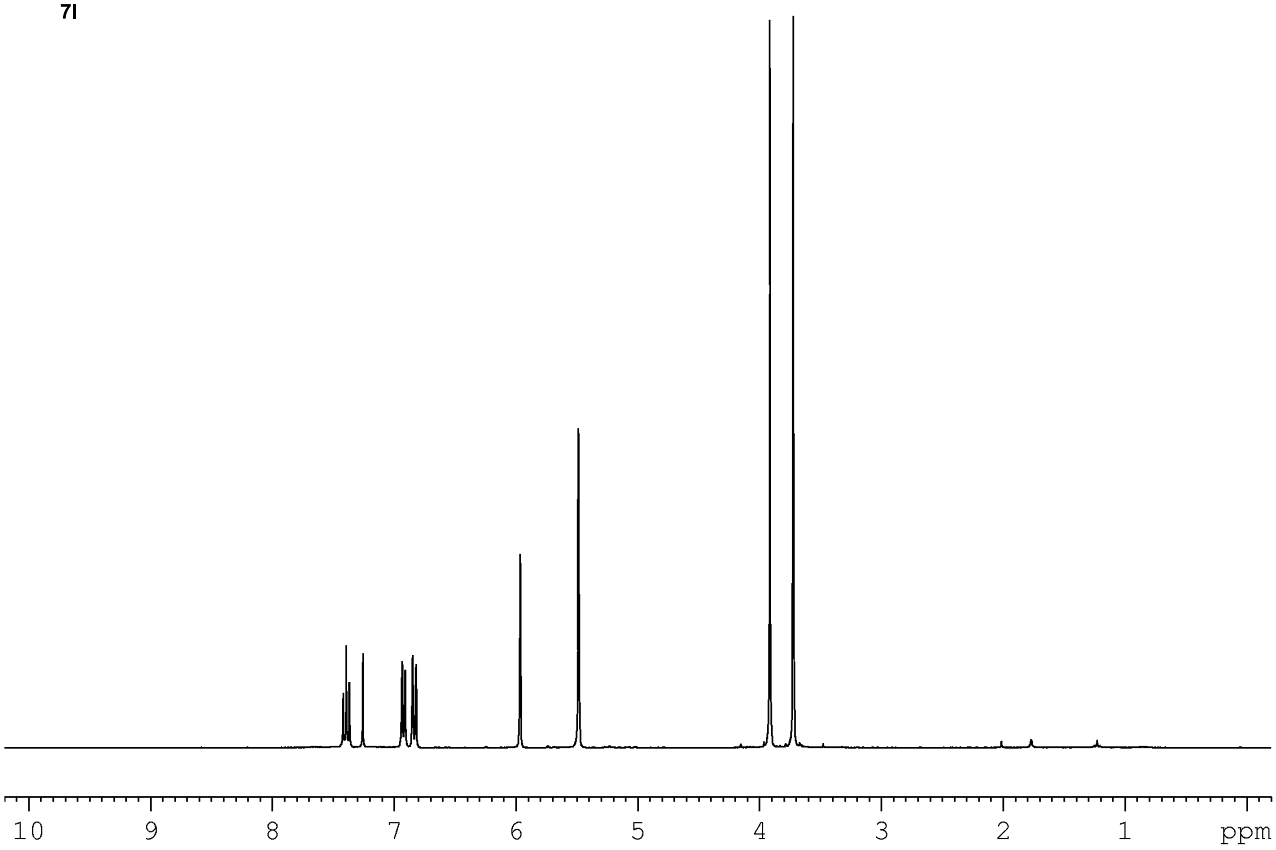





OMe
CO2Me
O

7l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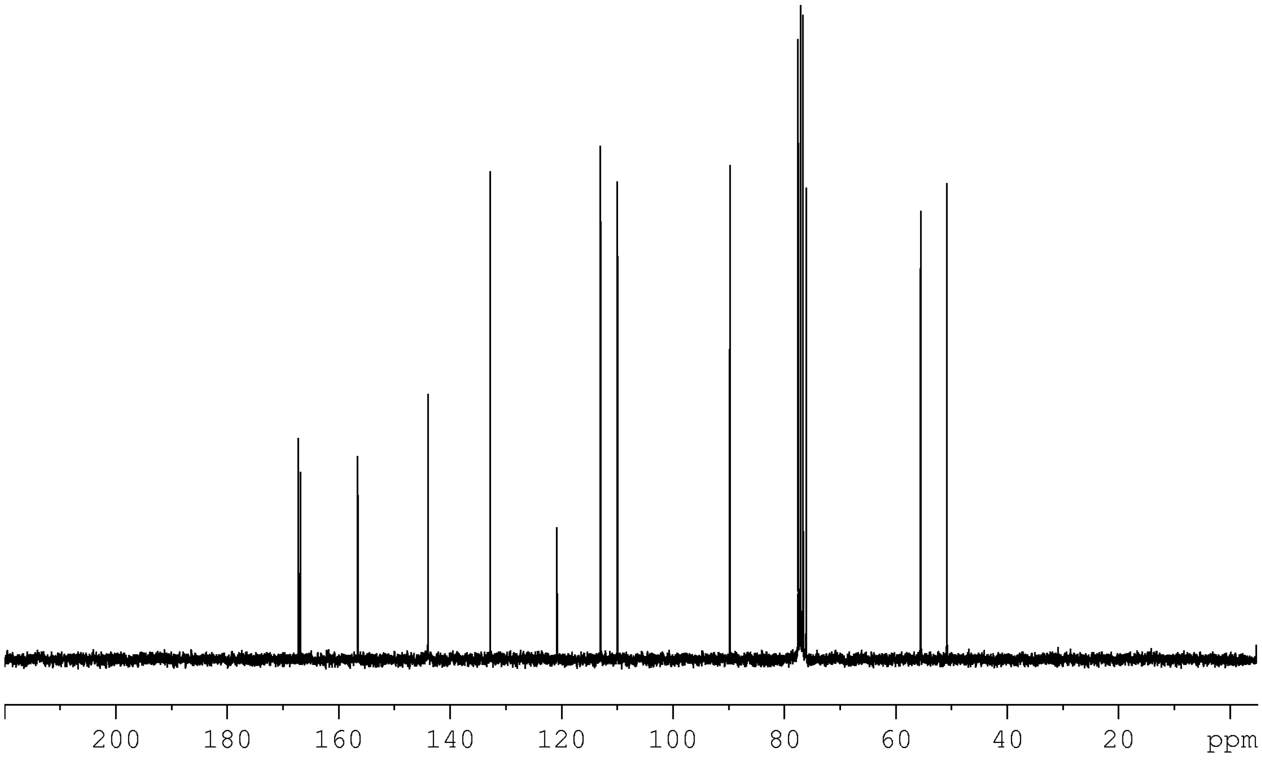
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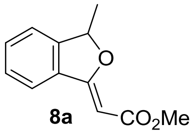

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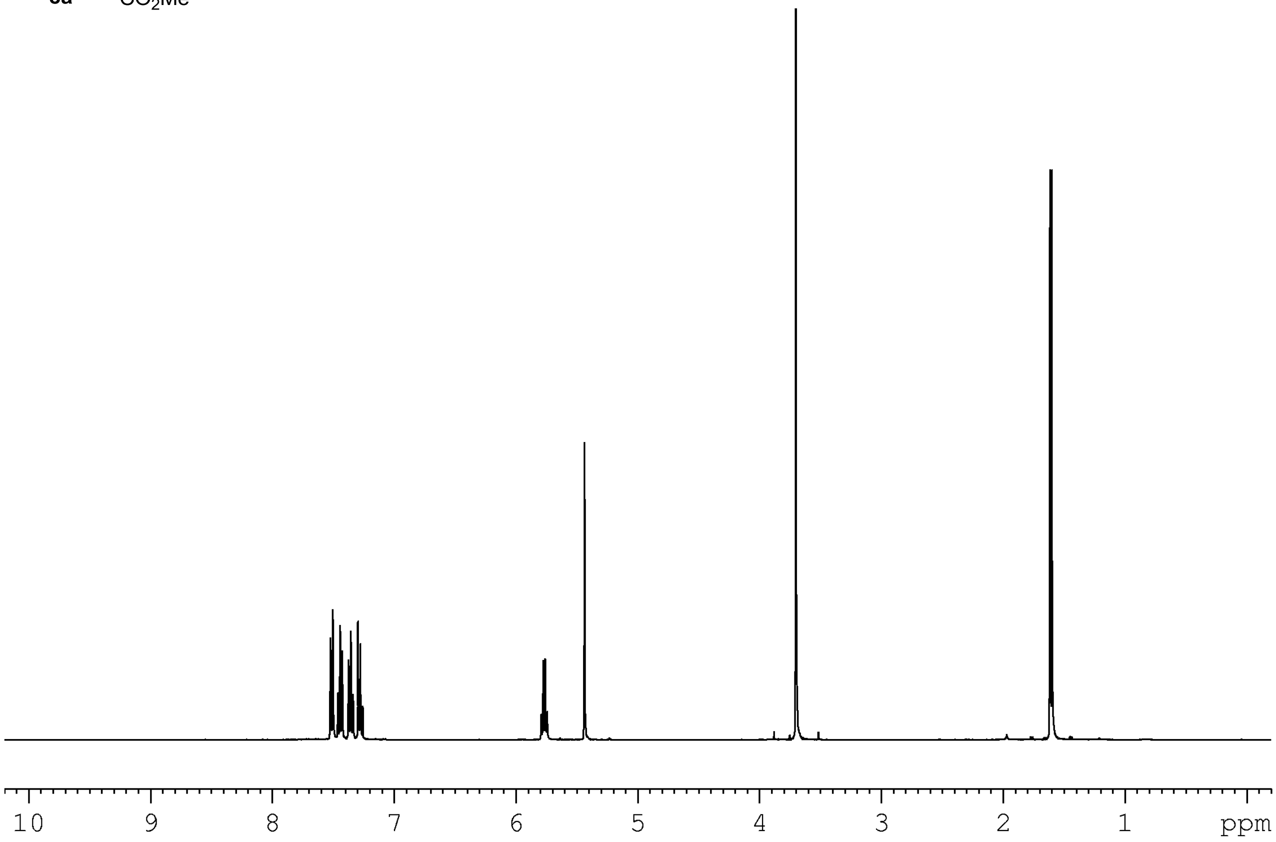

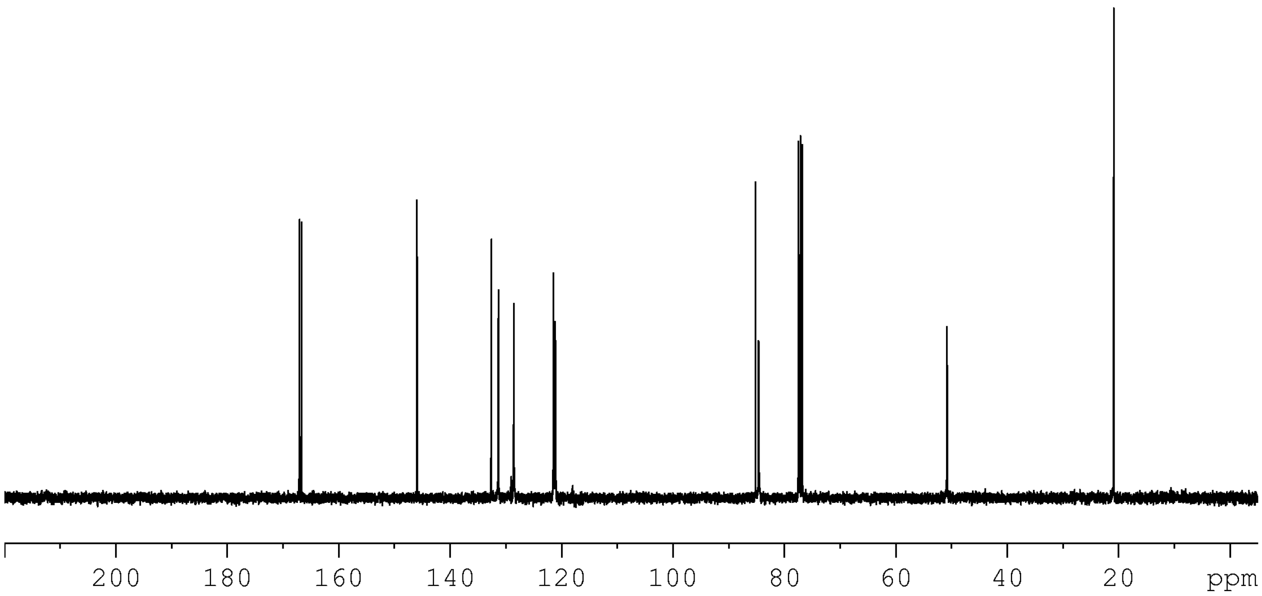

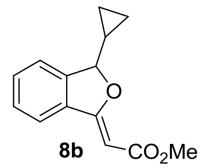

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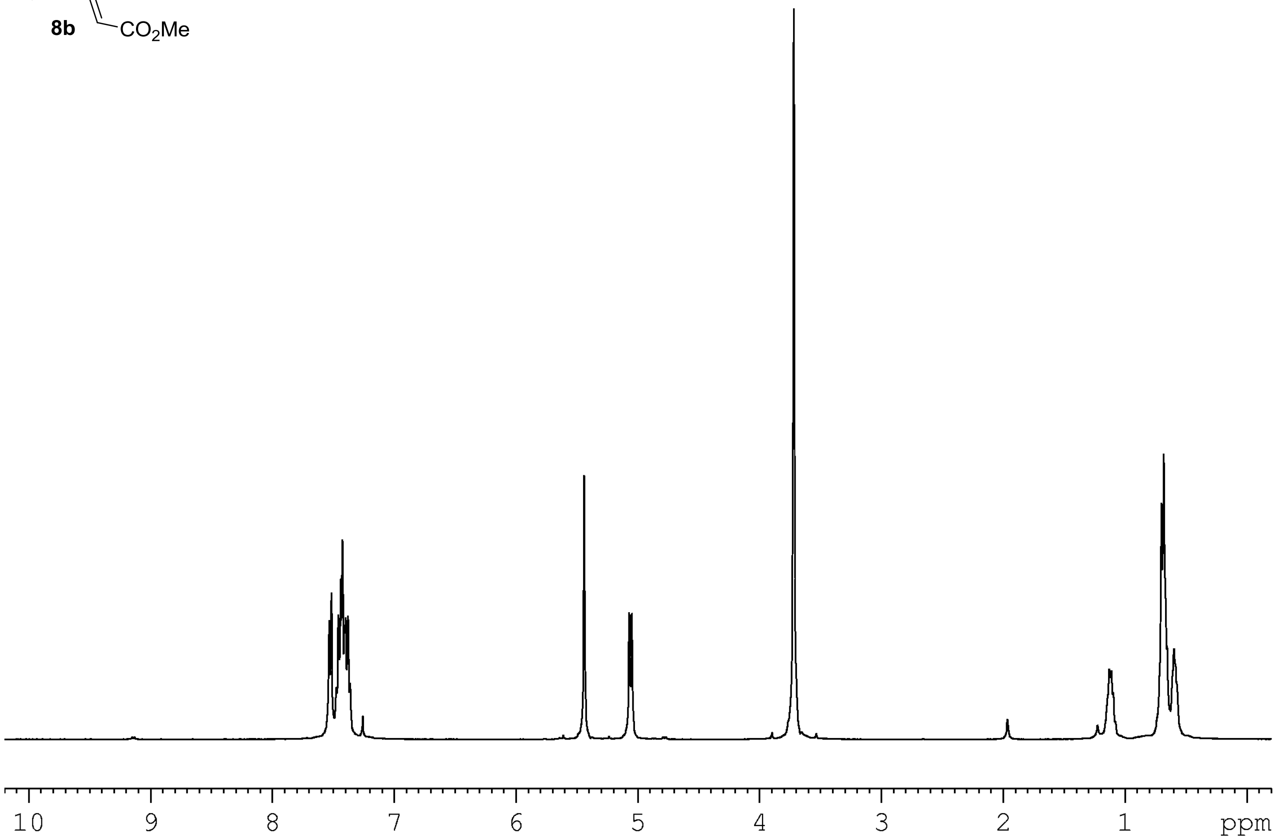

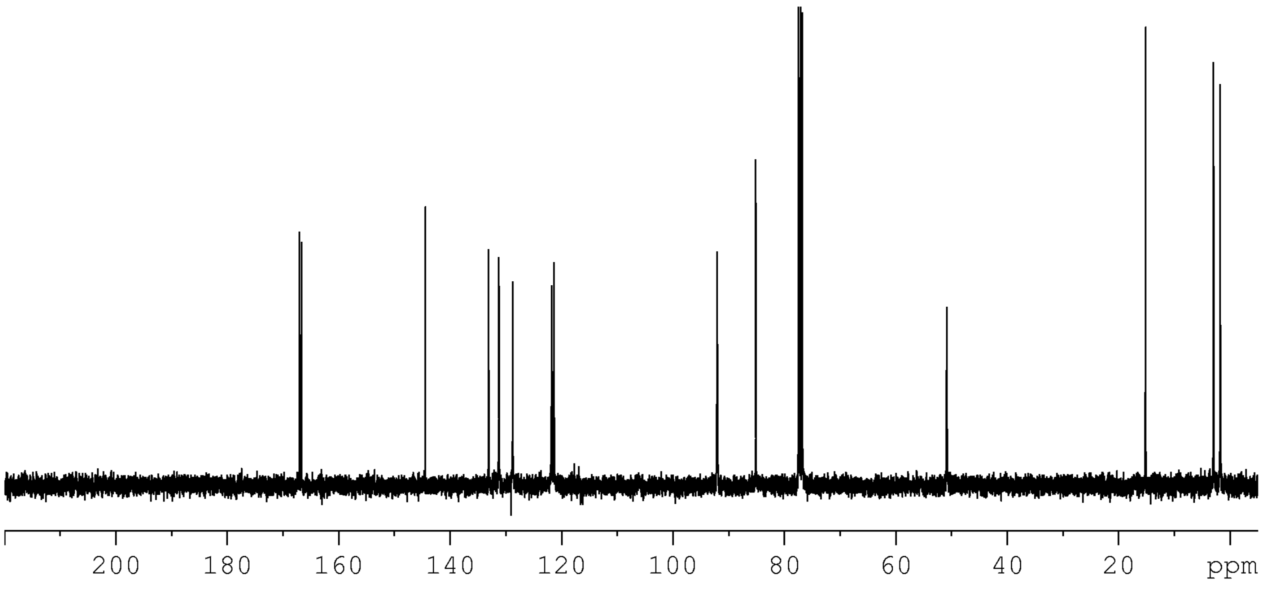

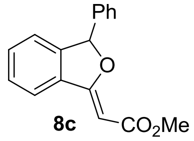
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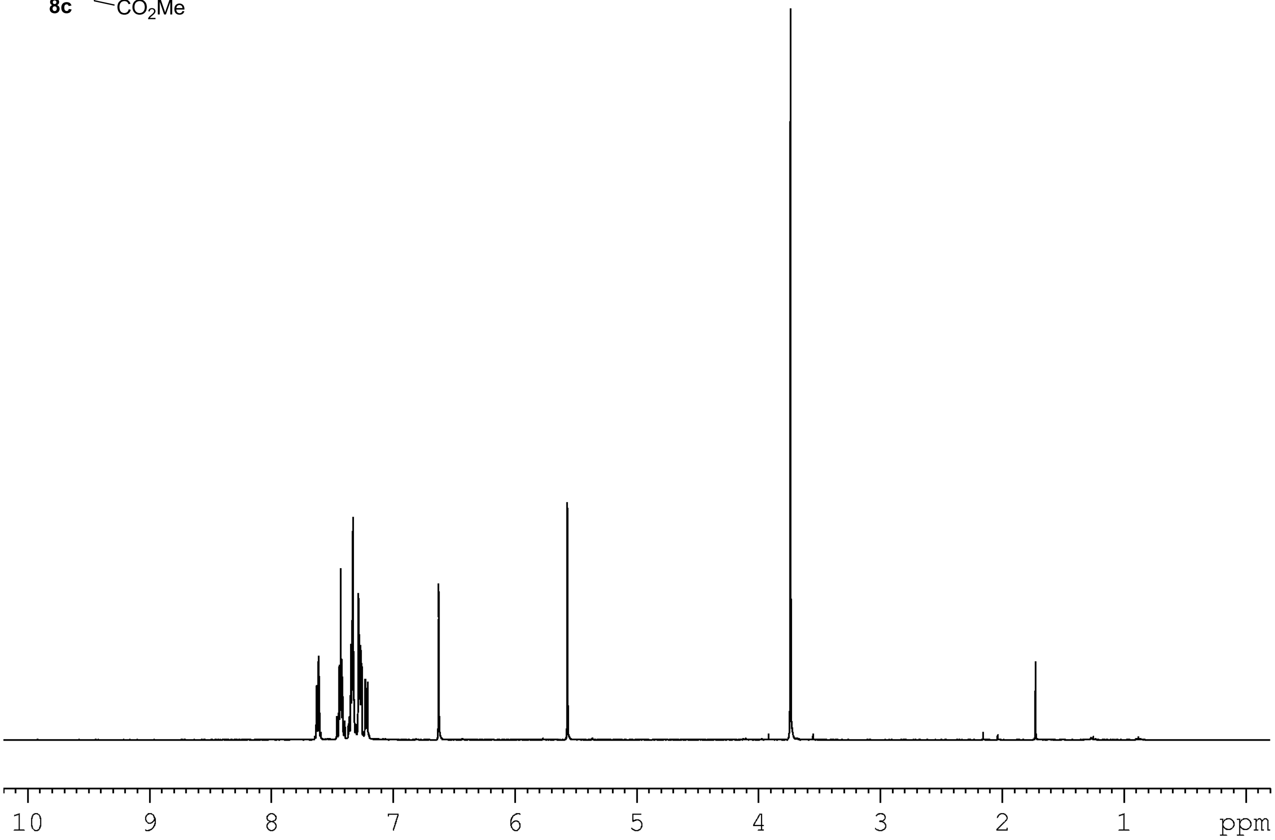
CO2Me

8c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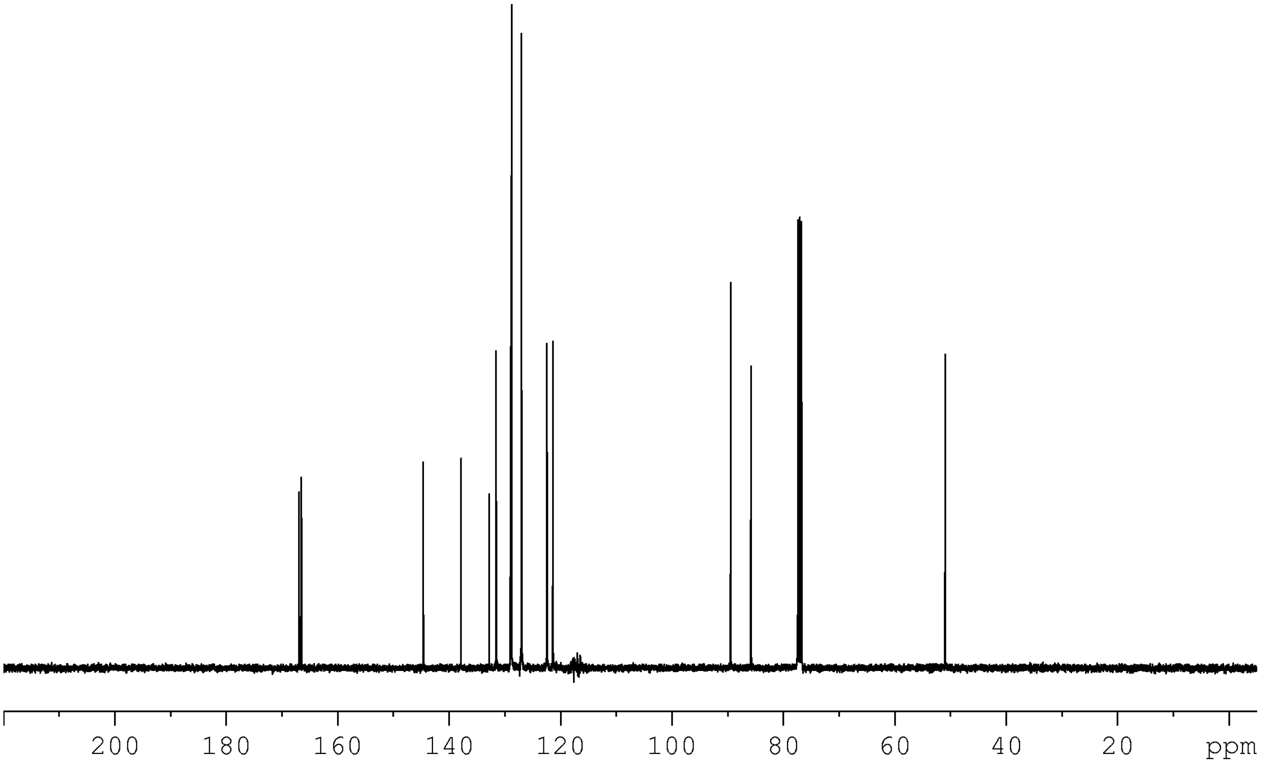
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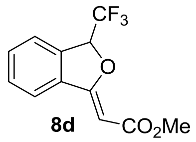
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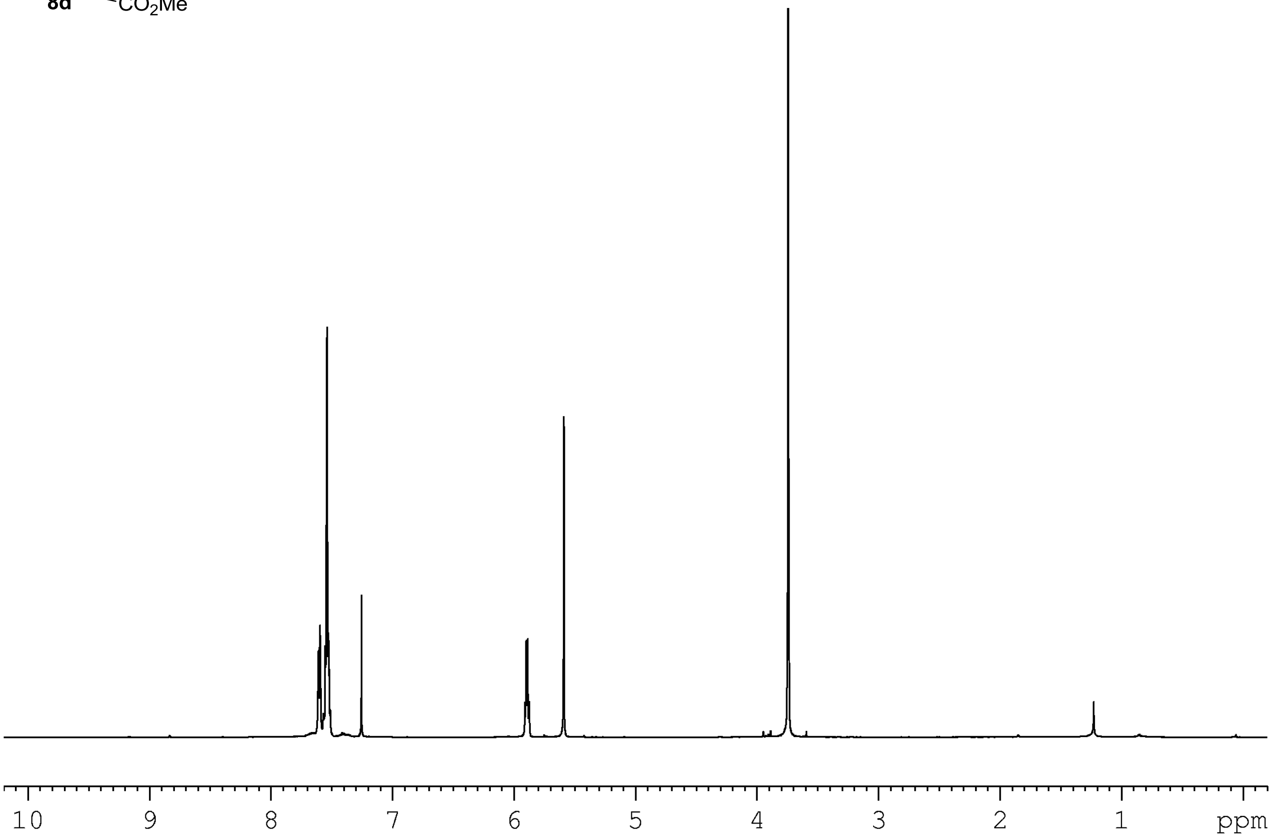
O
CO2Me

8d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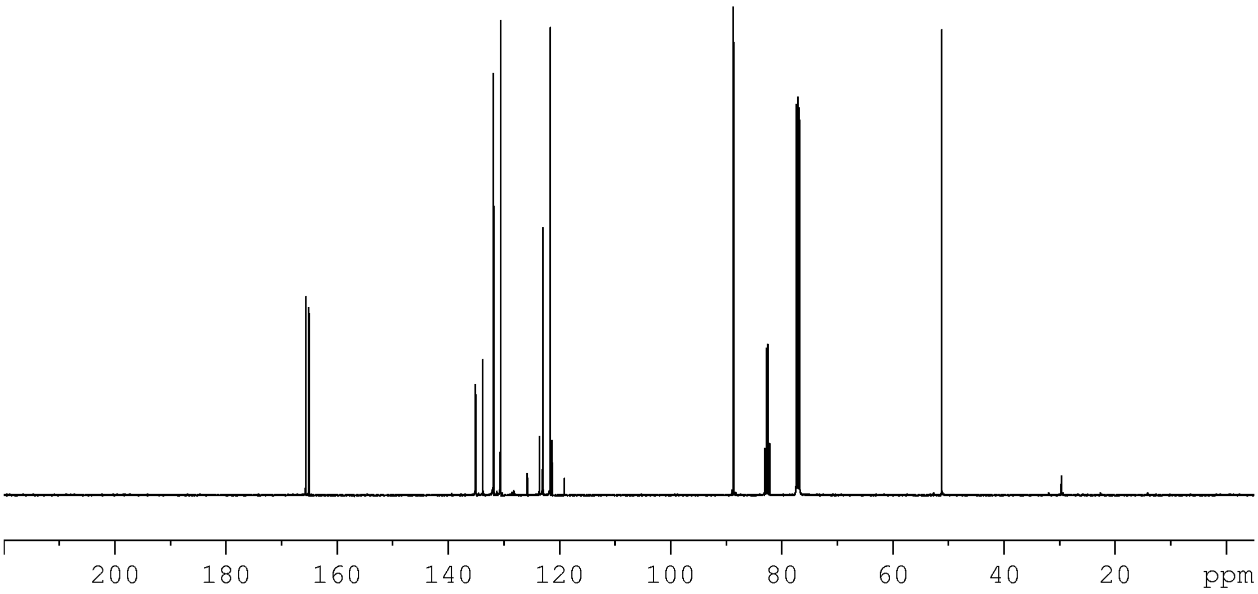
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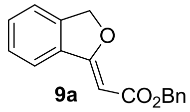

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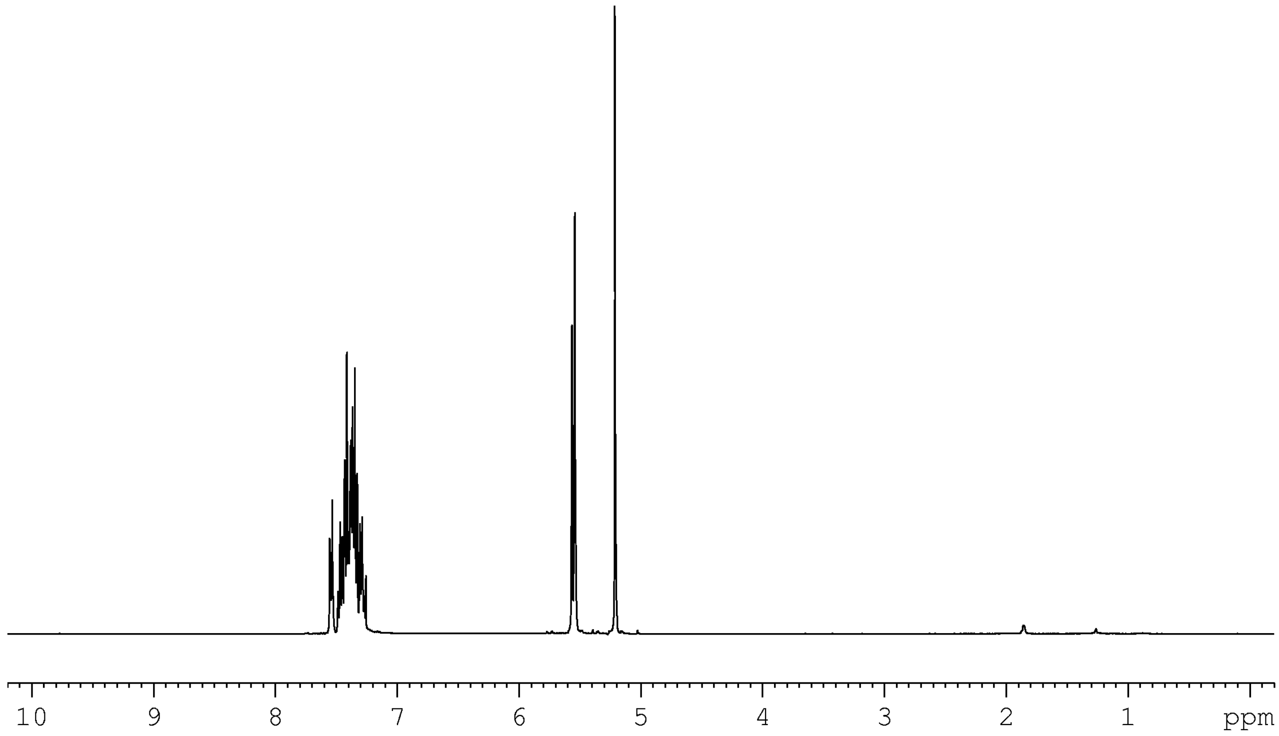

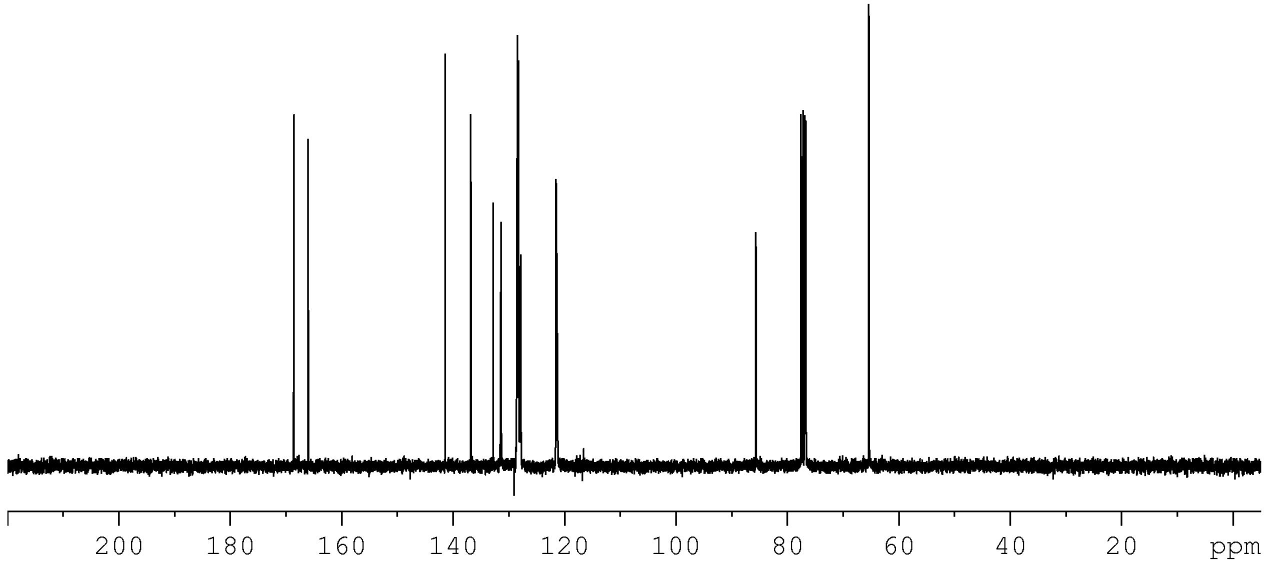

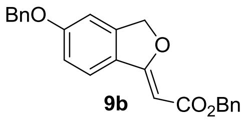
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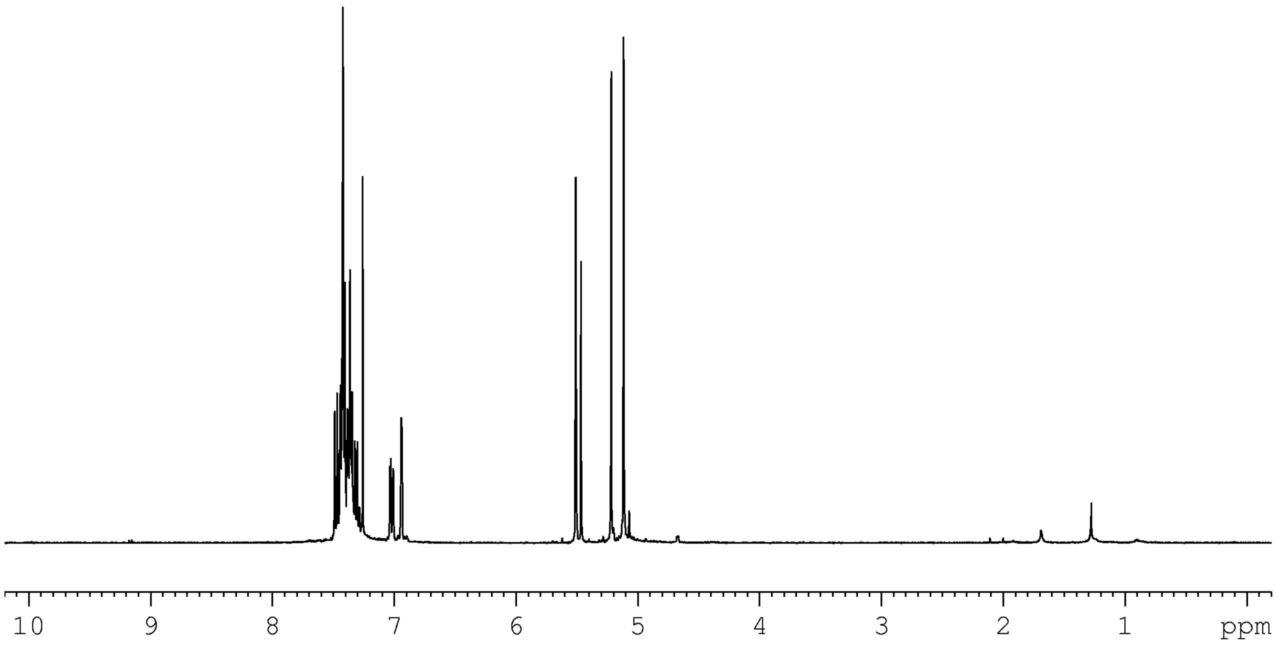
O
CO2Bn

9b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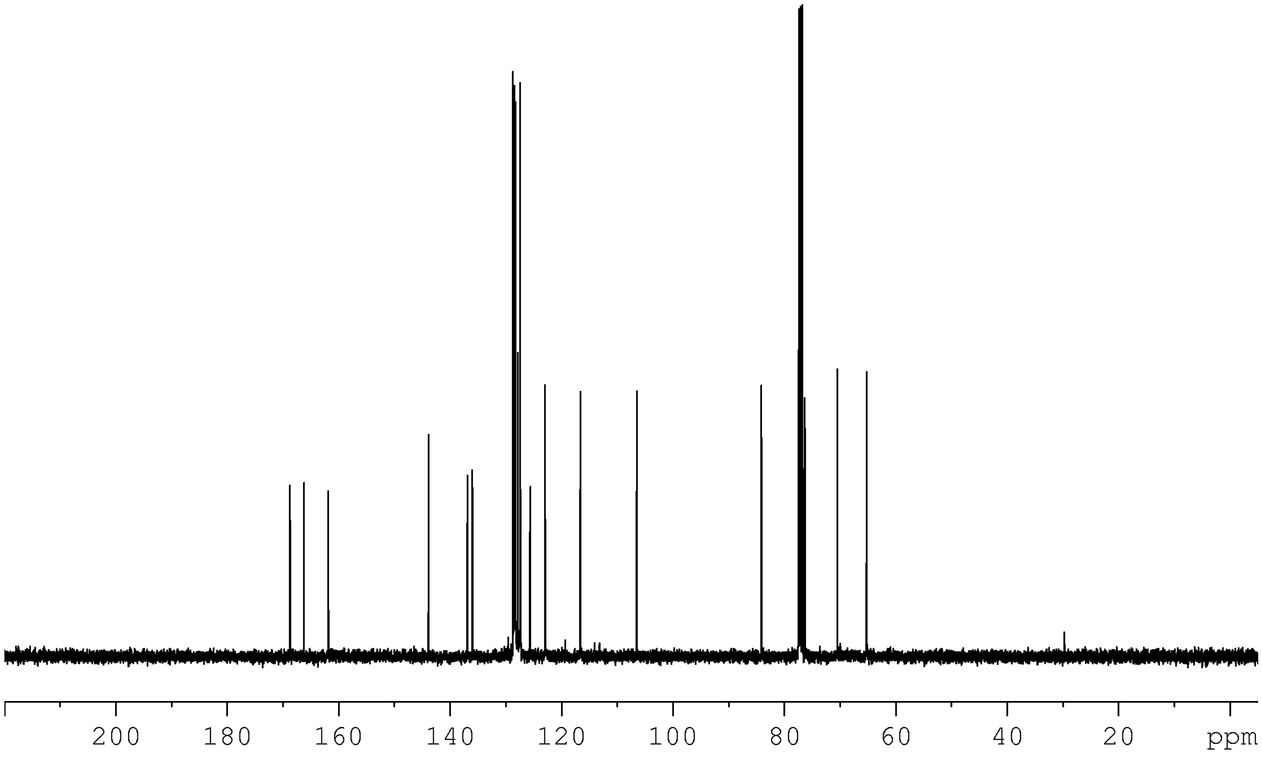
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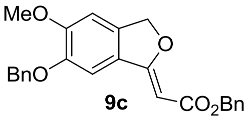
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BnO
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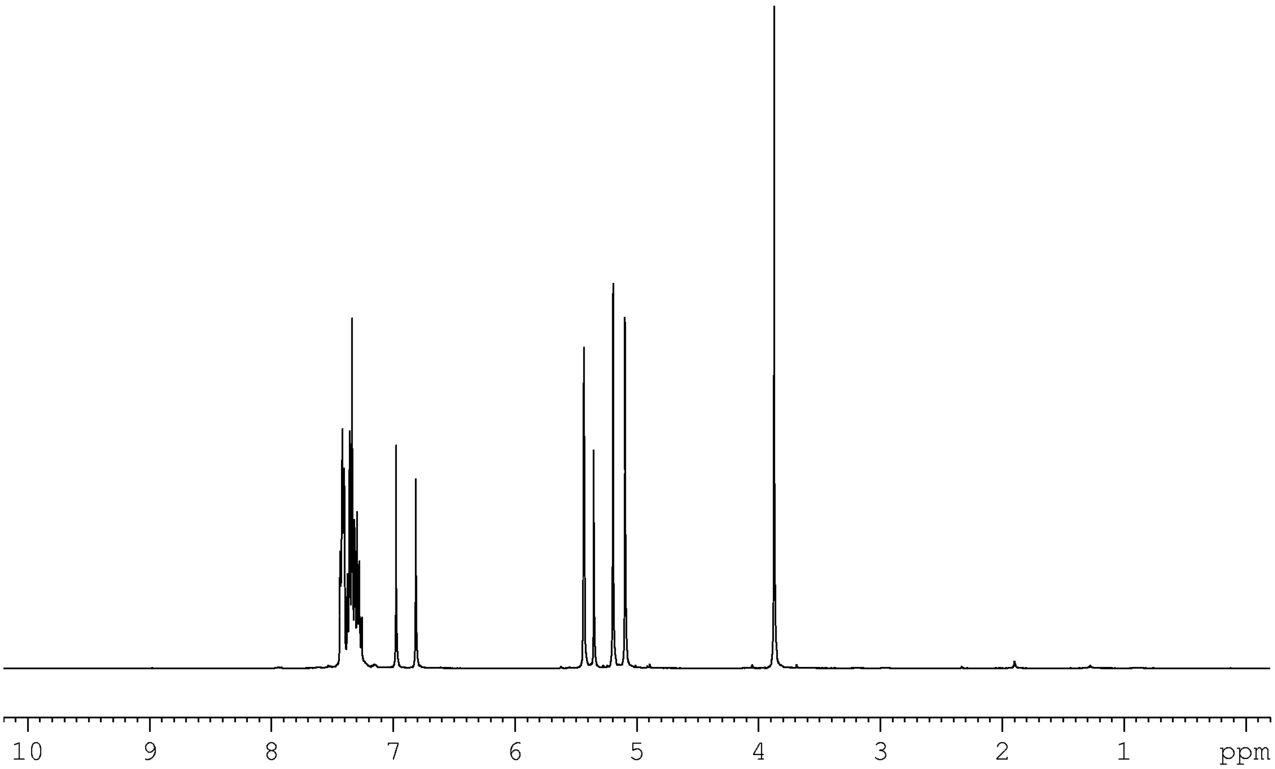
CO2Bn

9c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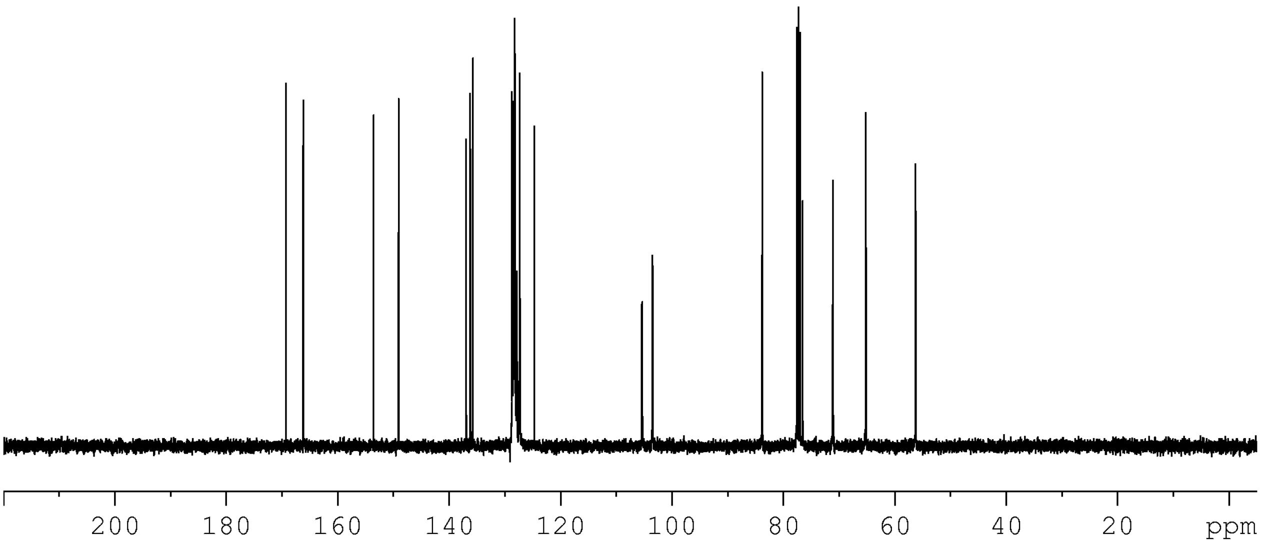
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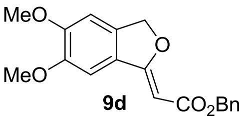
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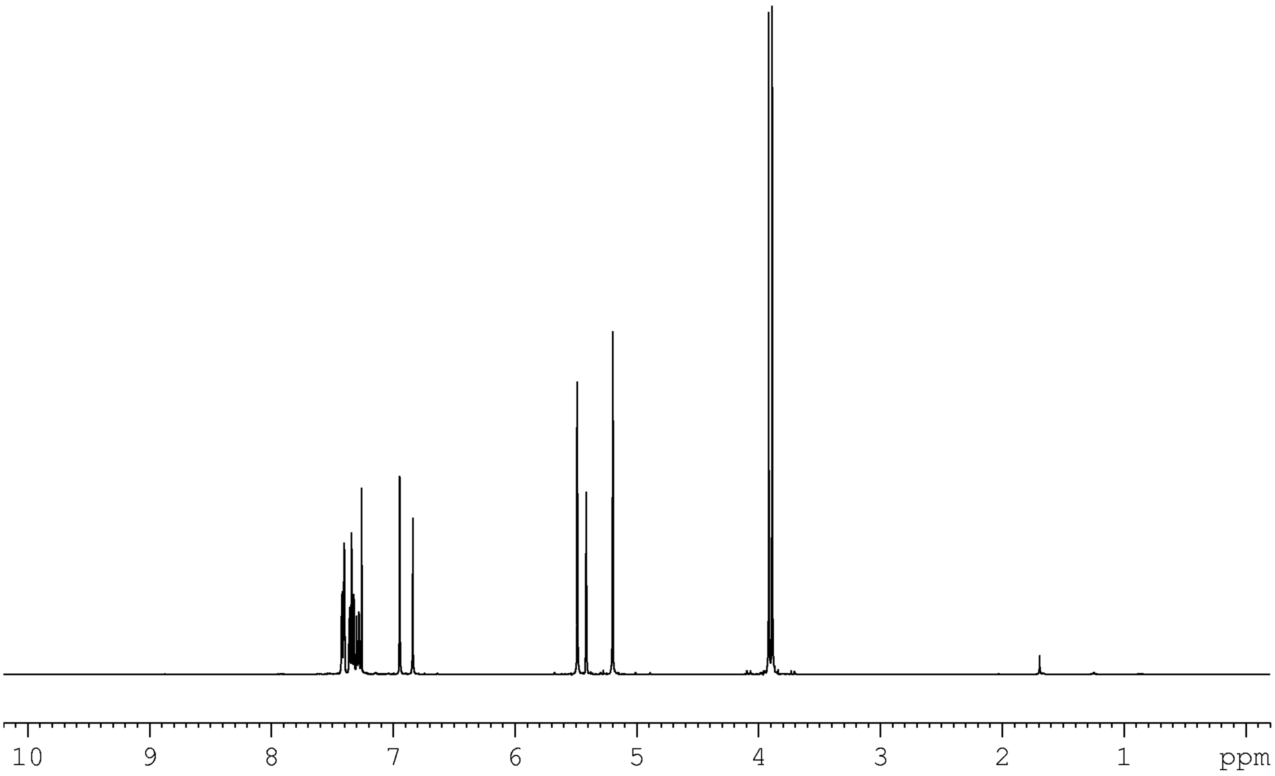
MeO
O
CO2Bn

9d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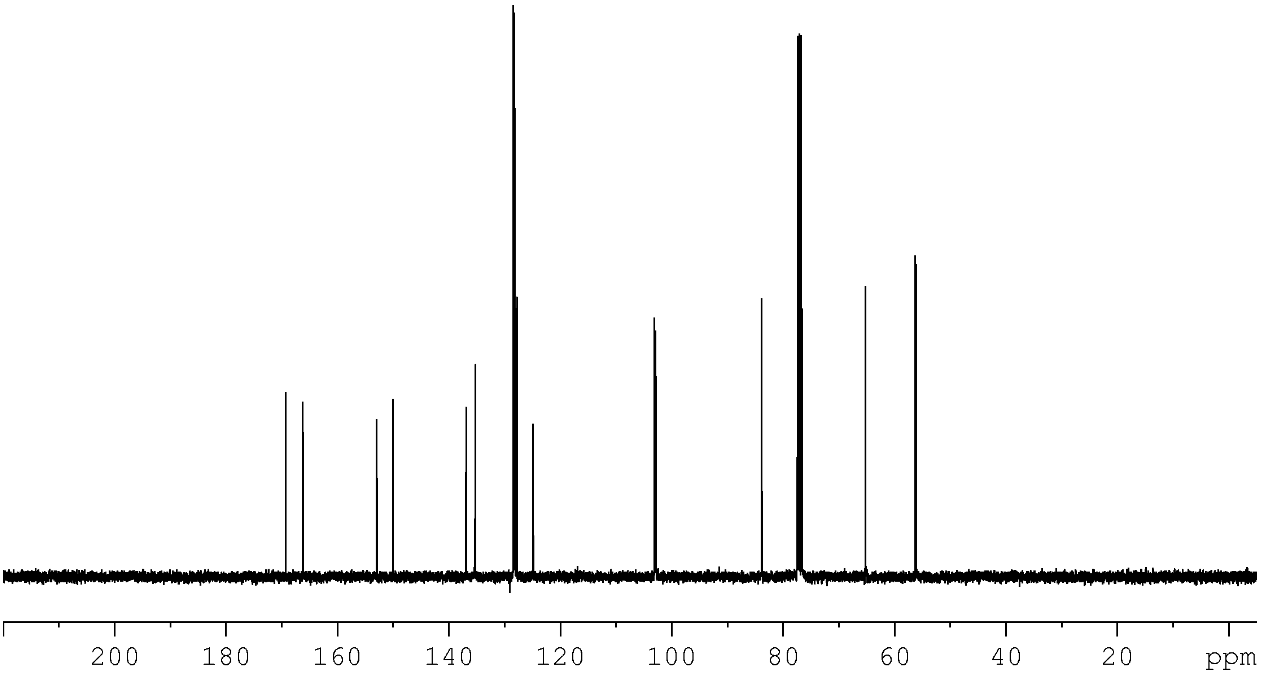
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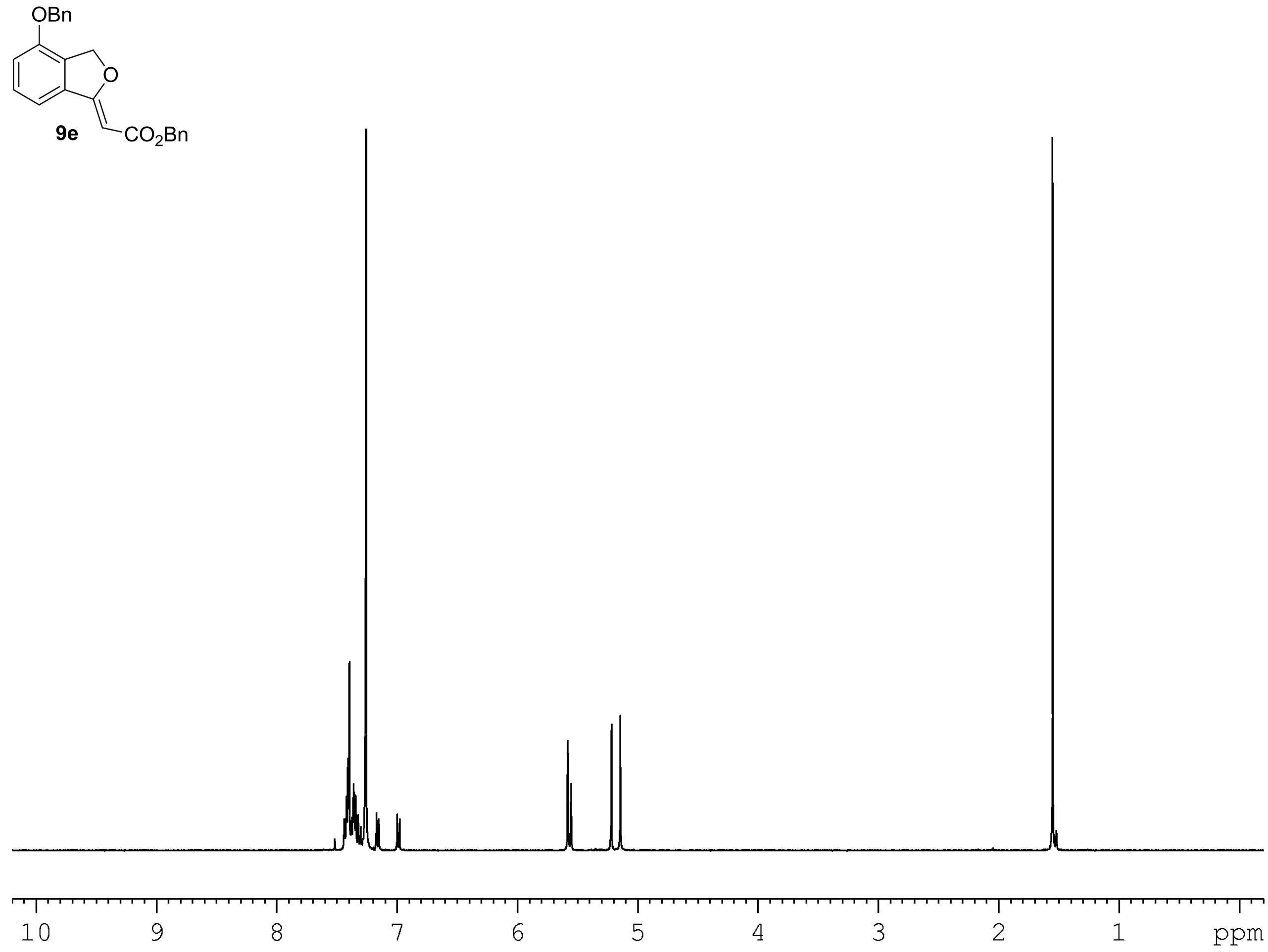
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CO$_2$Bn
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ppm

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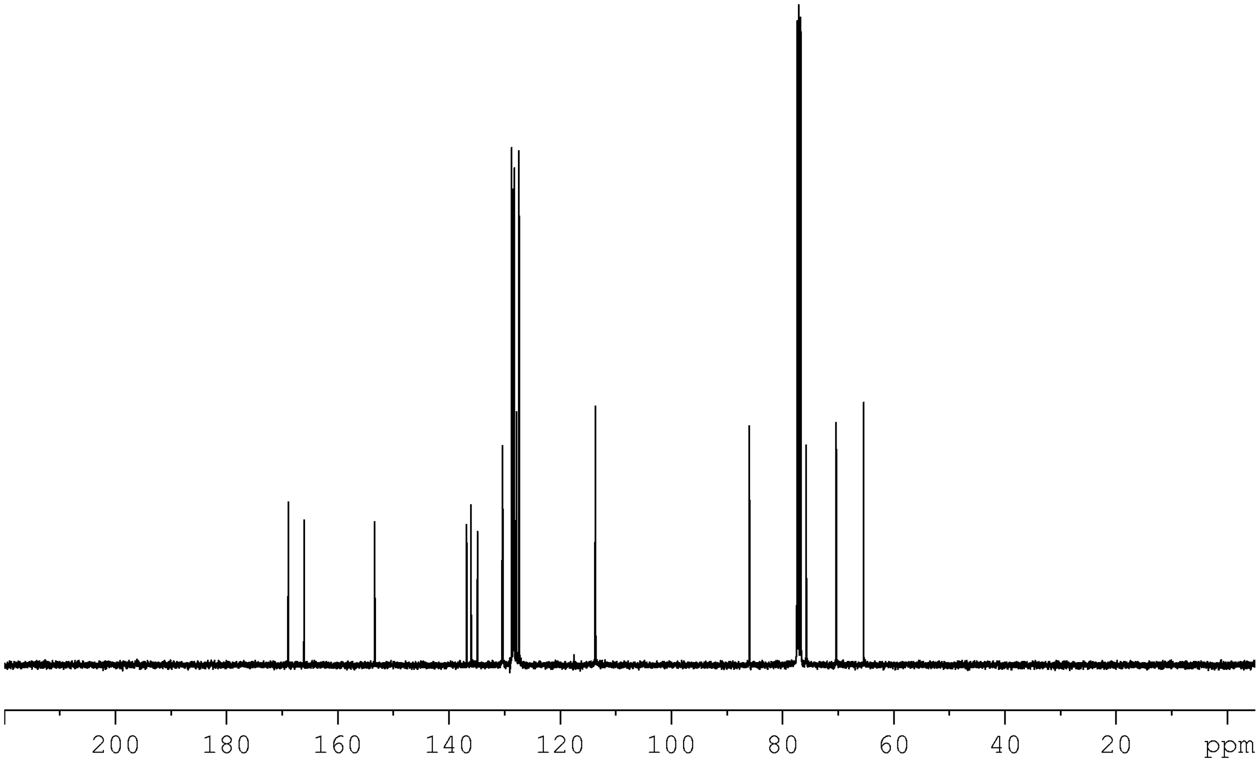
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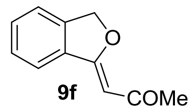

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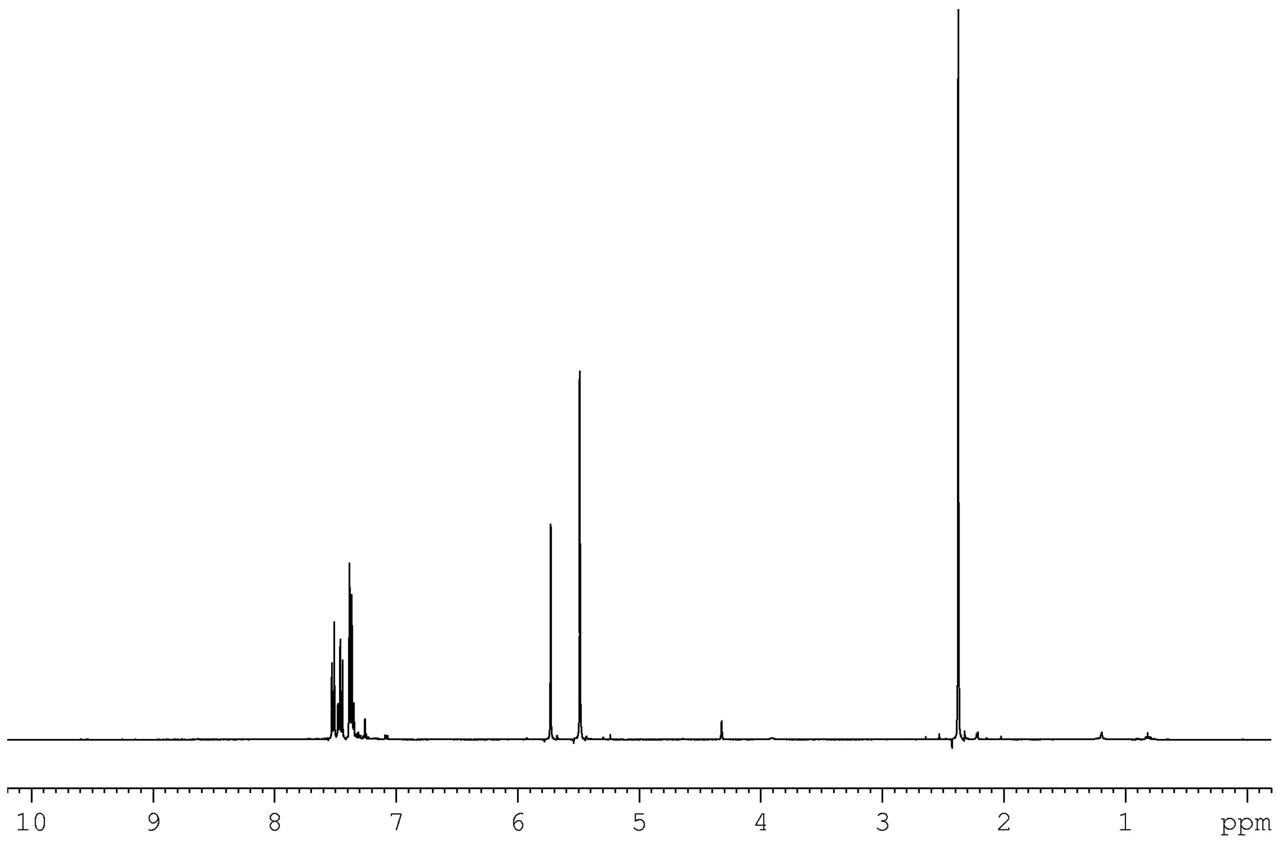
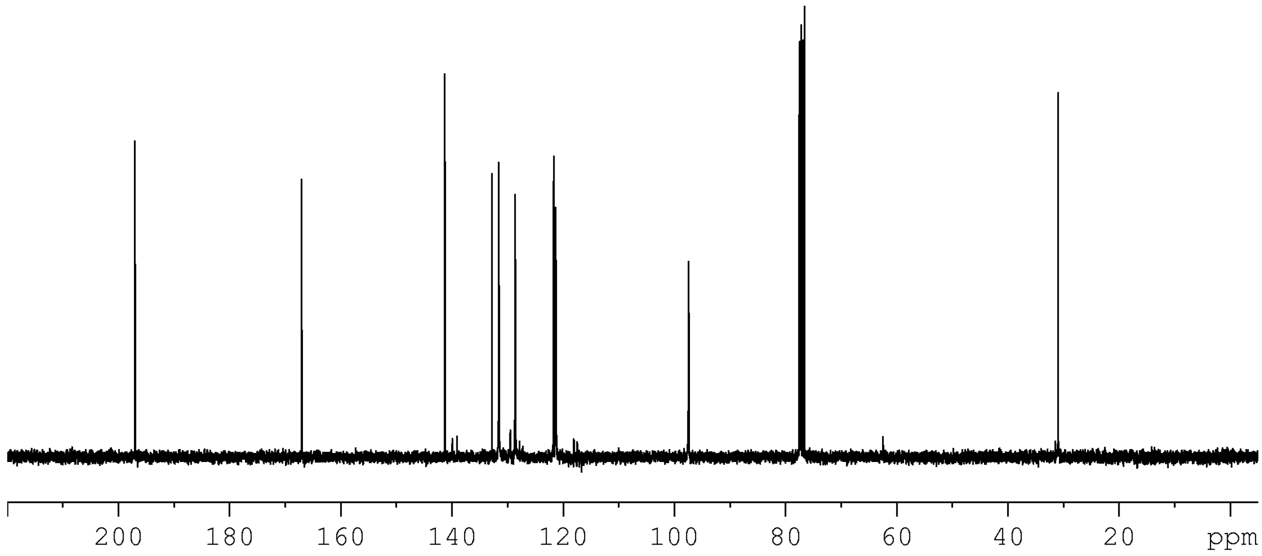
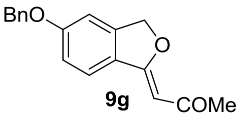
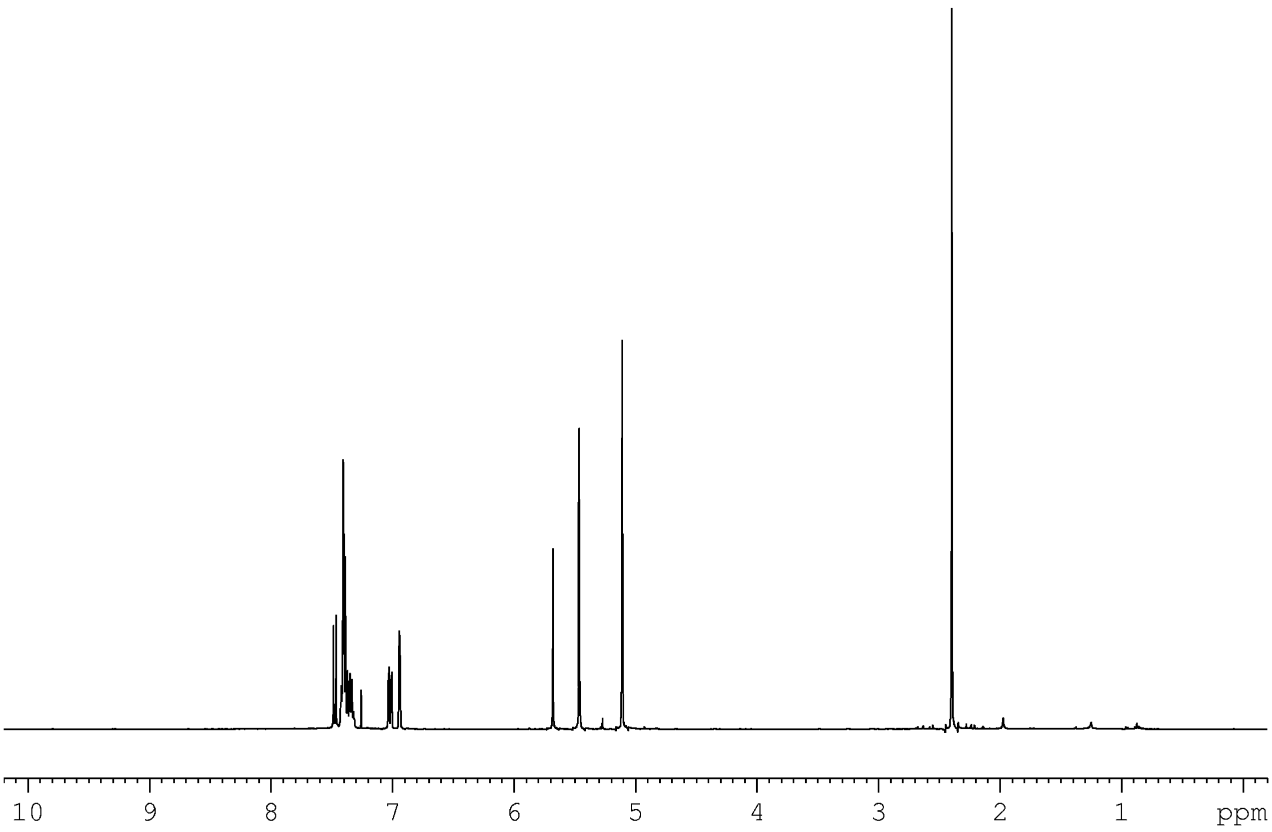





BnO
O
COMe

9g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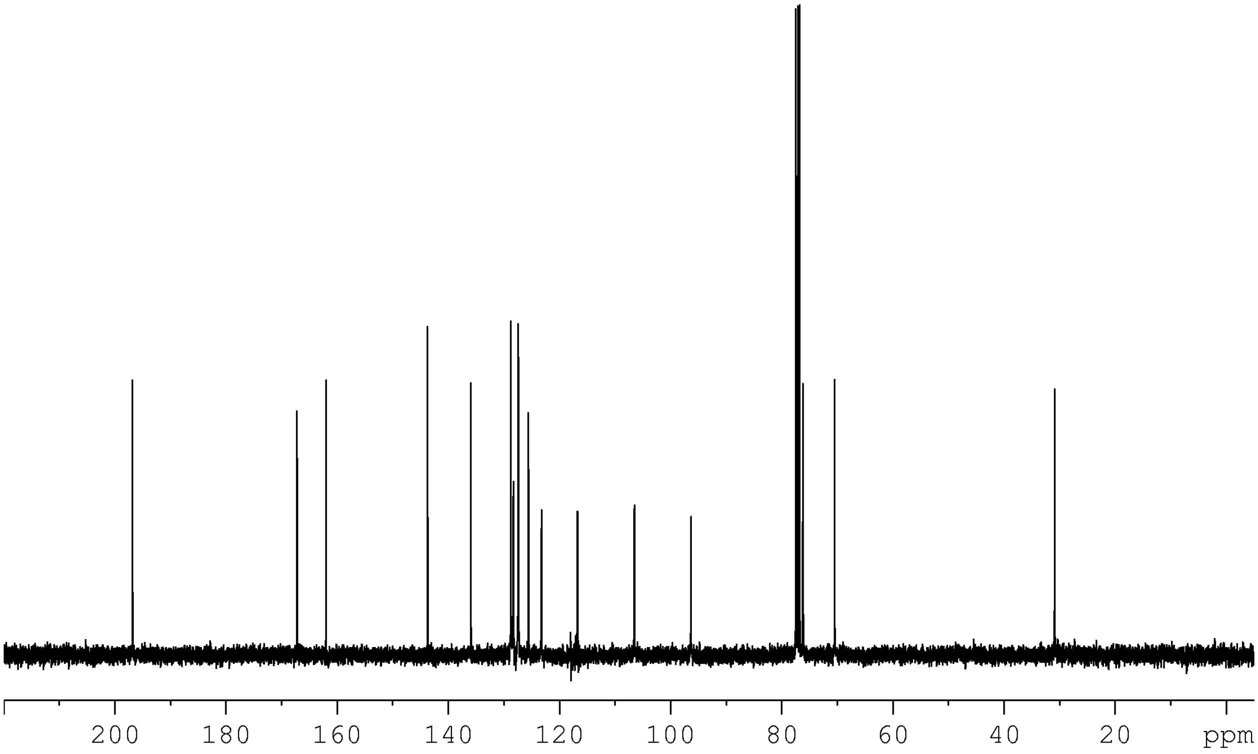
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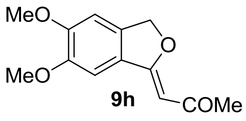
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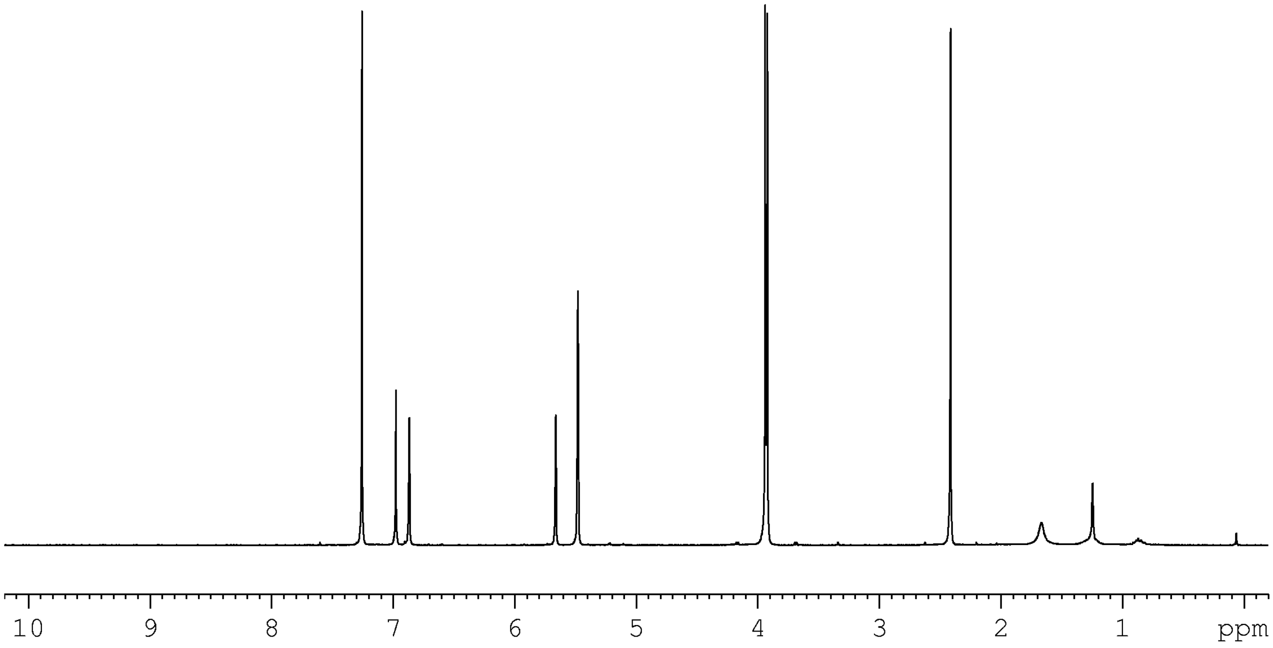
MeO
O
COMe

9h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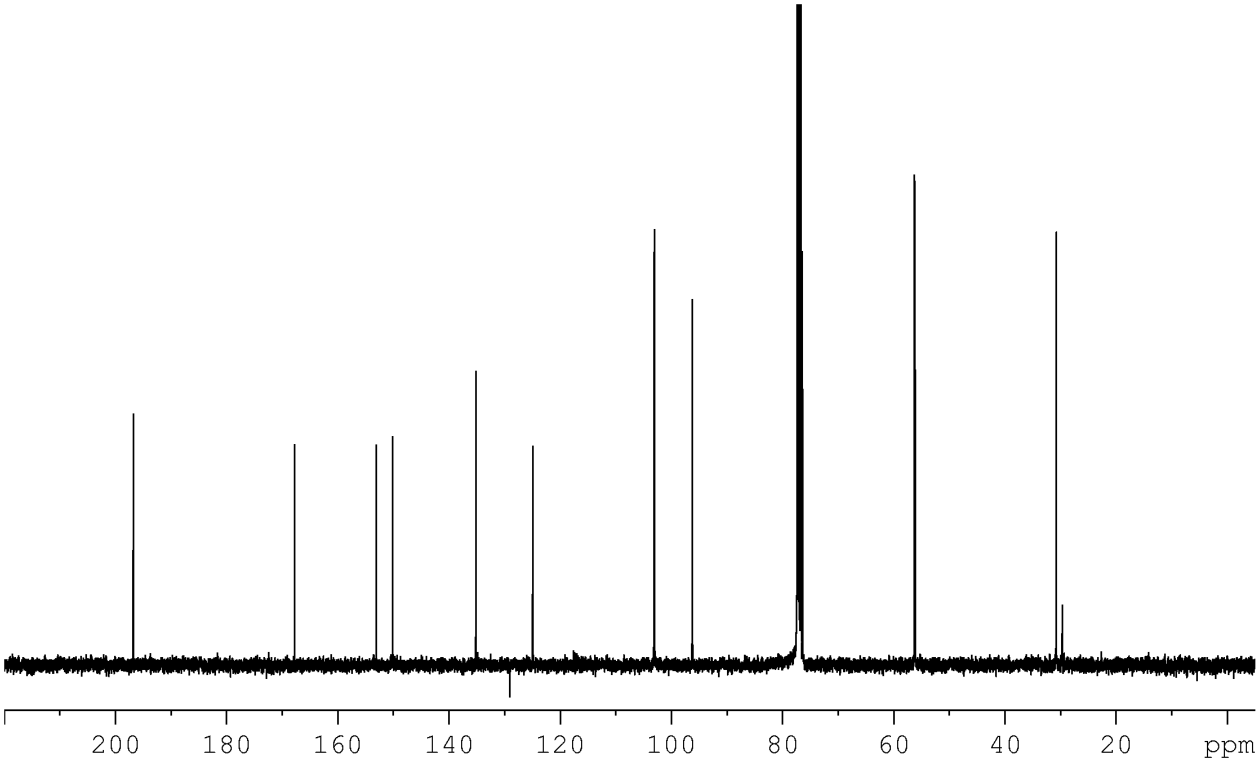
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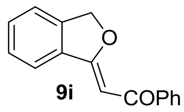

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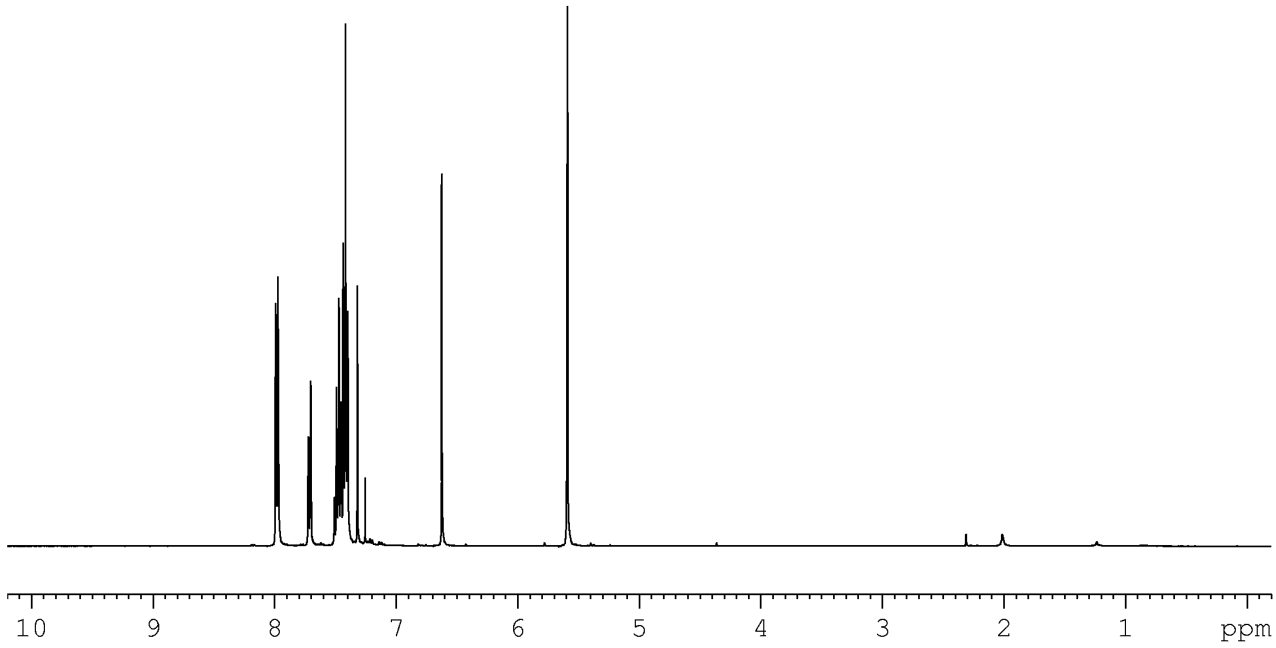

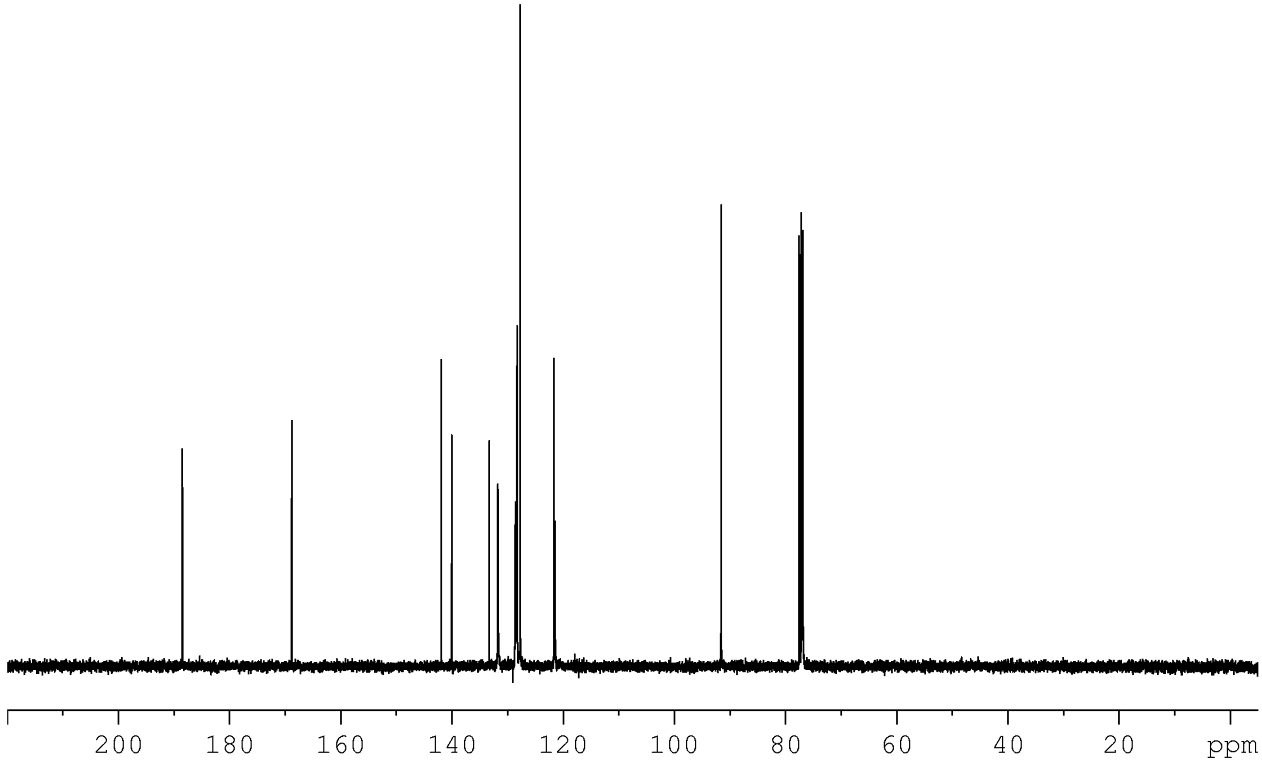

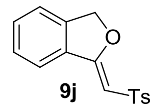

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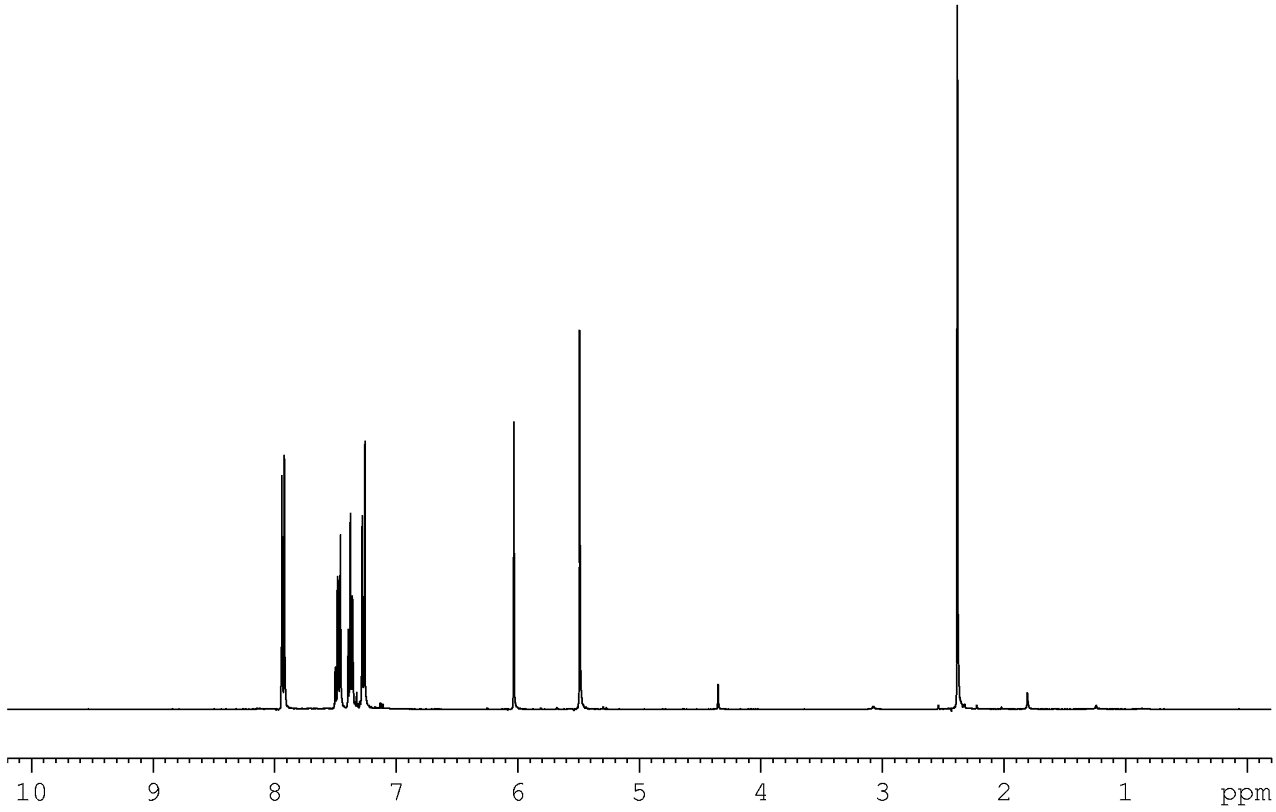
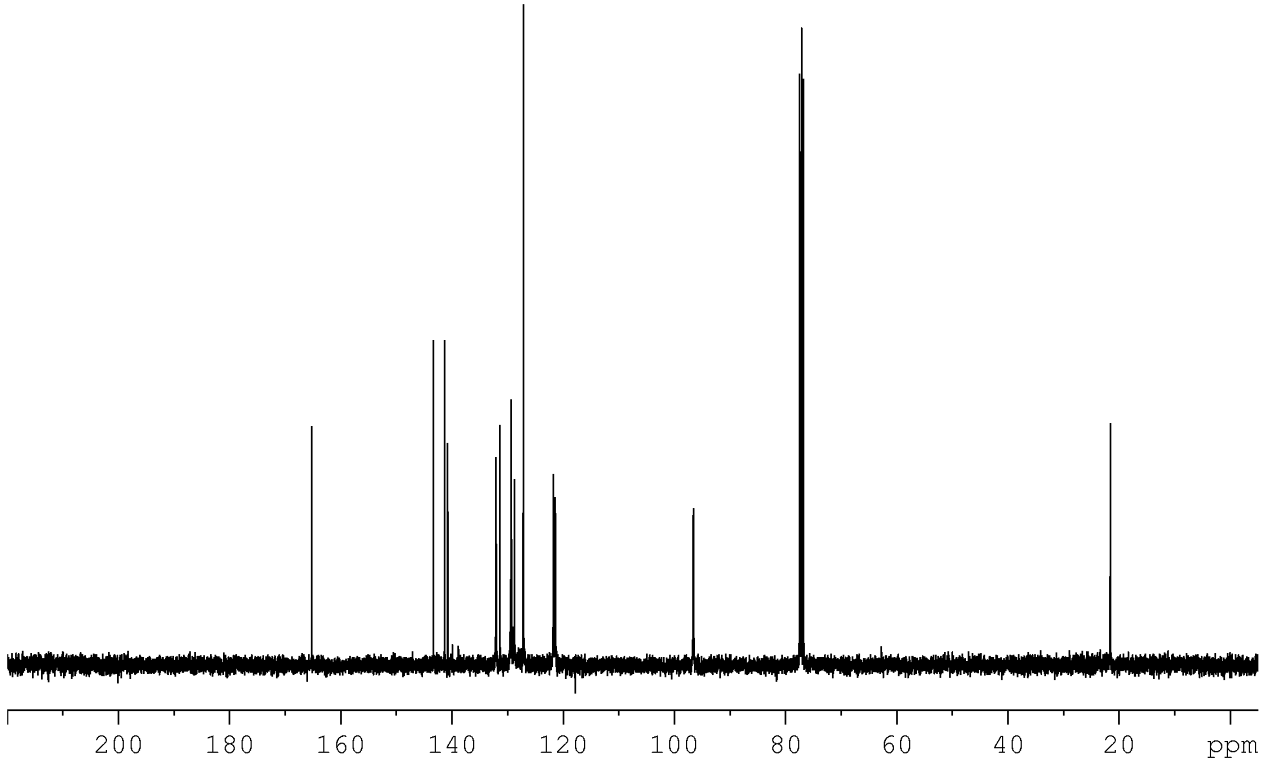
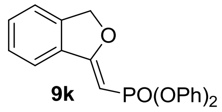
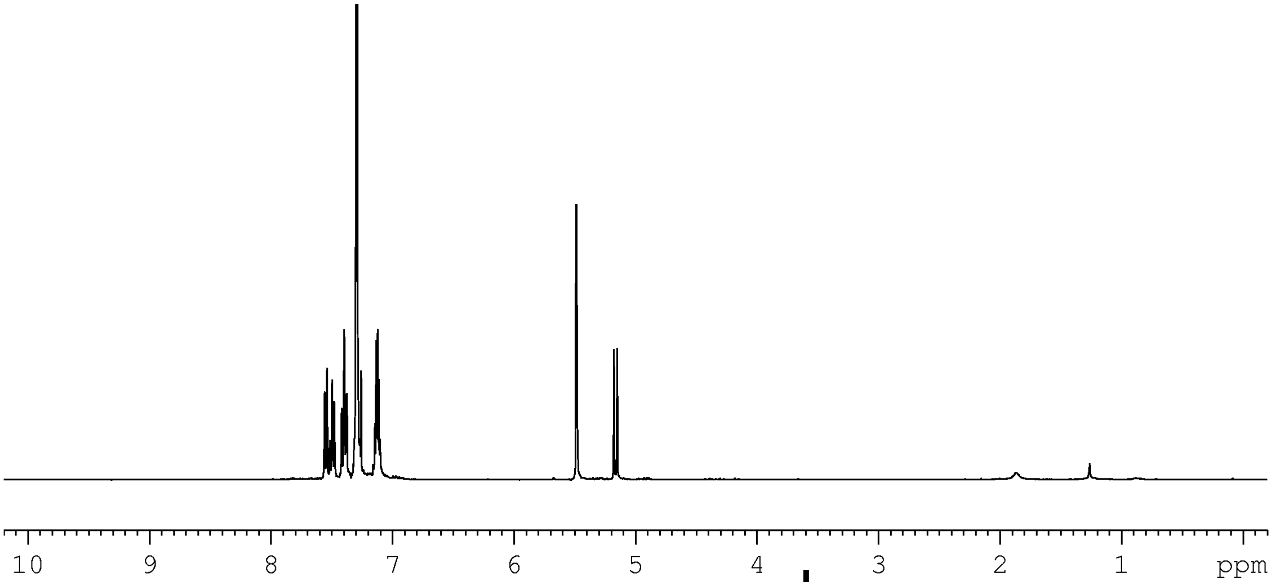





O
PO(OPh)$_2$

9k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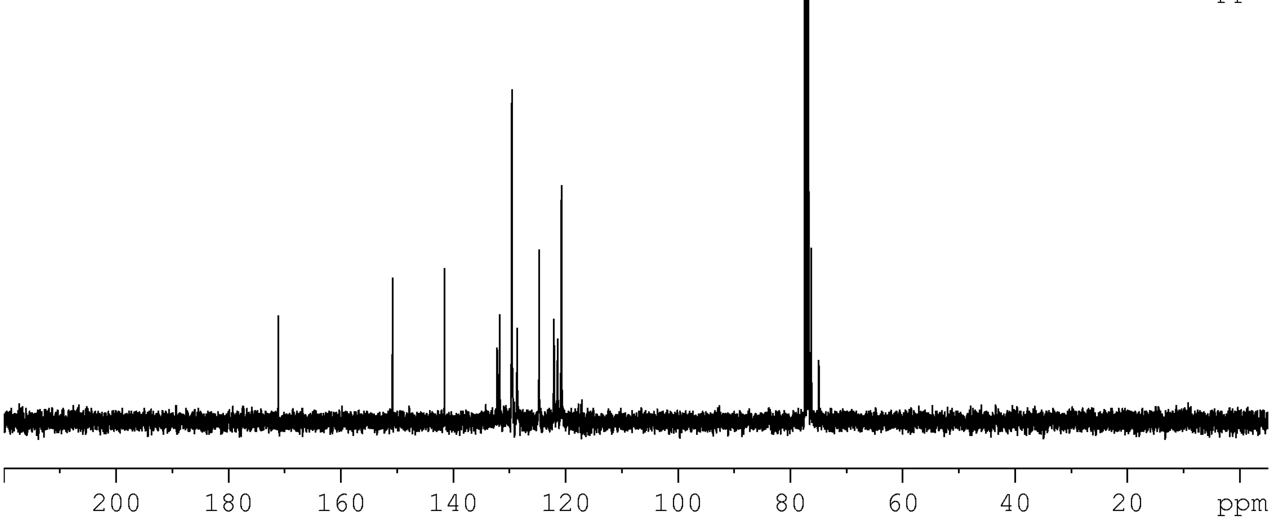
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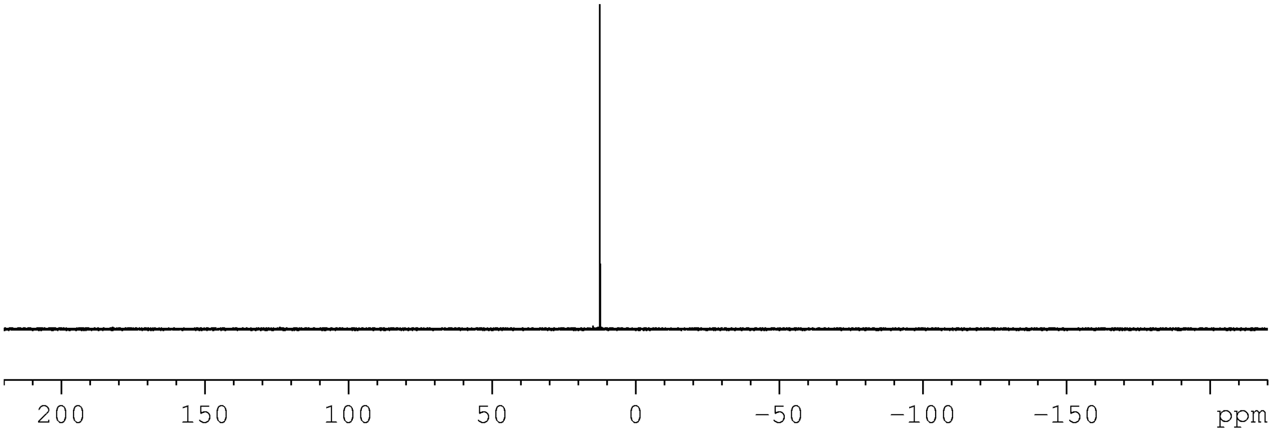
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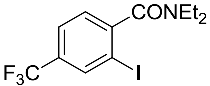
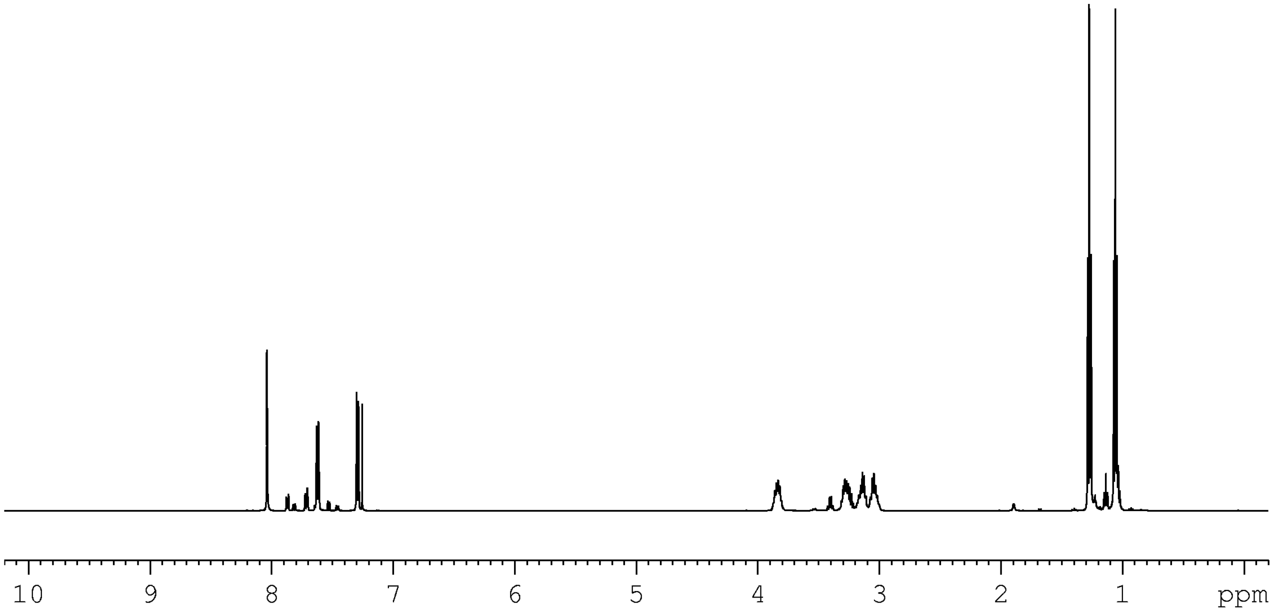
ppm


CONEt$_2$
F$_3$C
I

S2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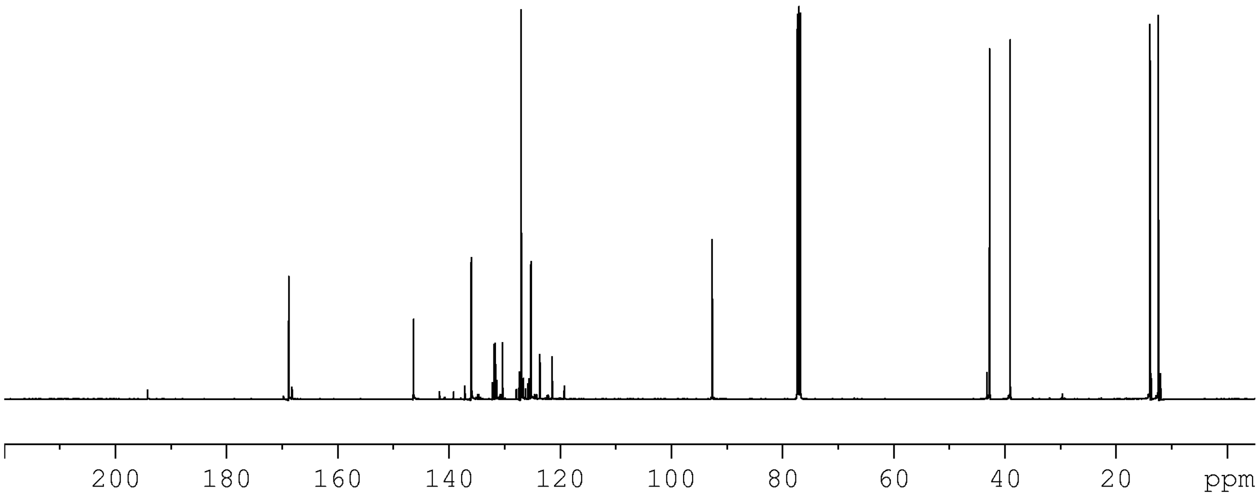
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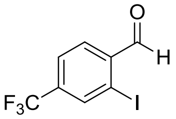
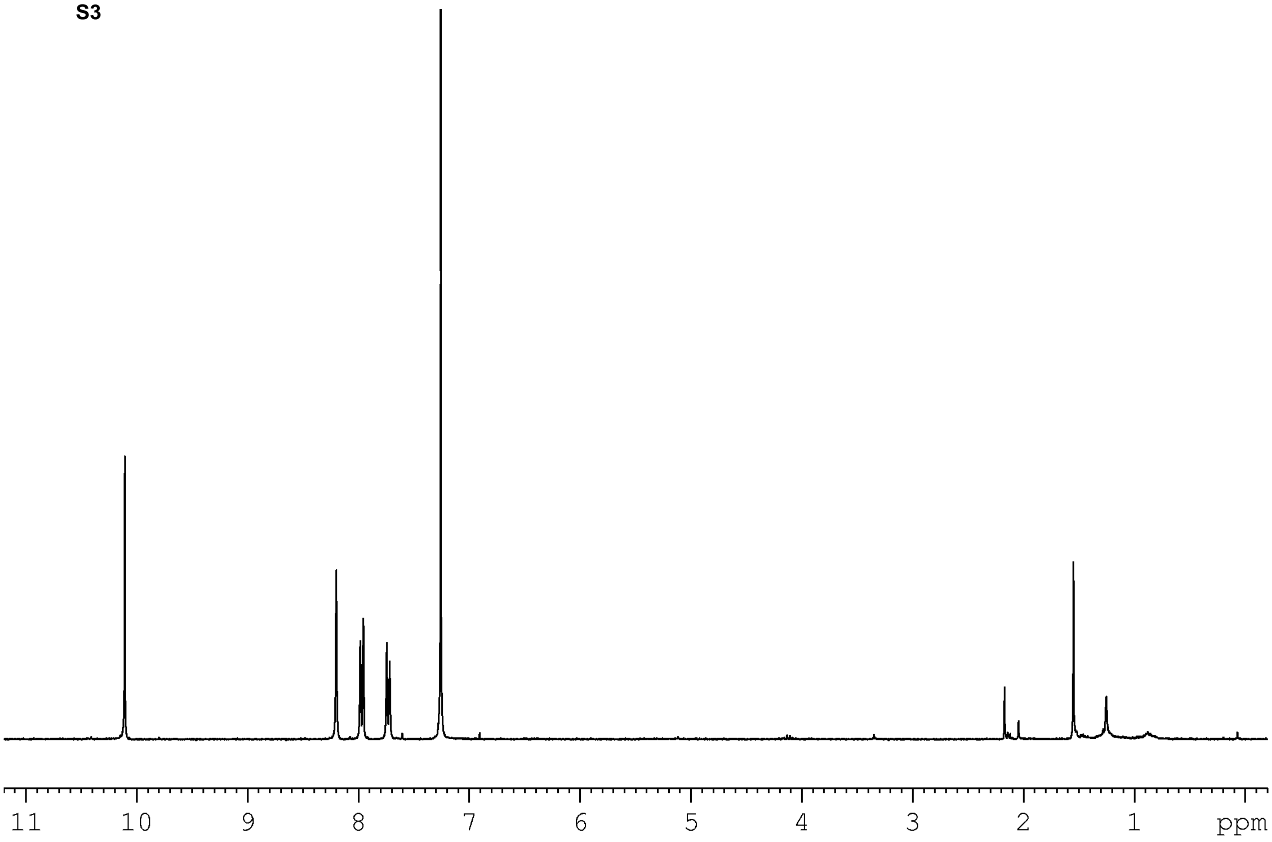

O
H
I
F3C

S3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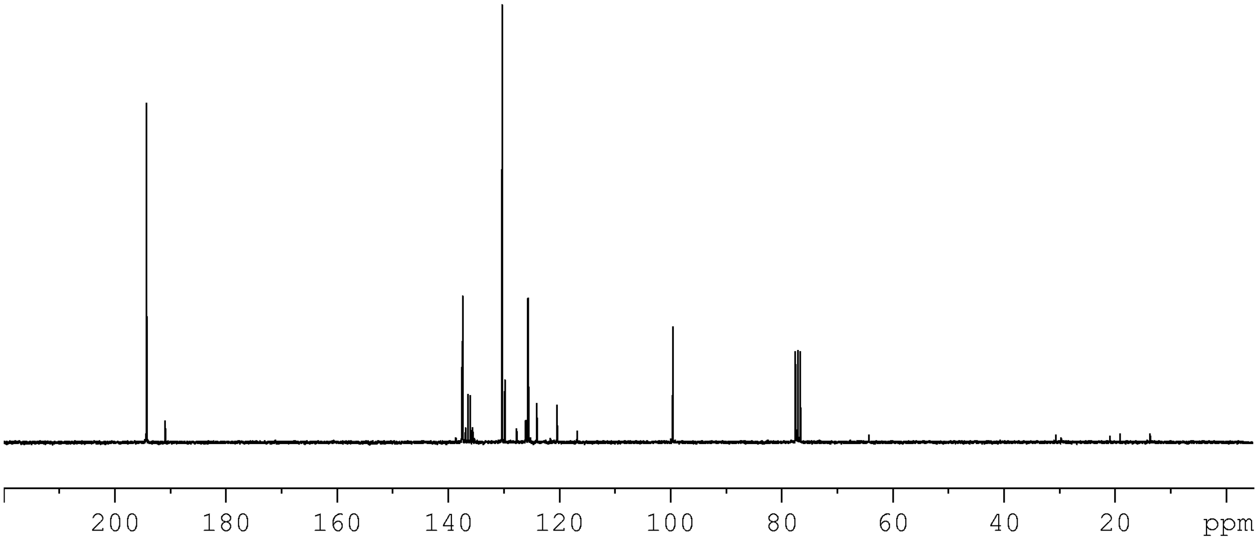
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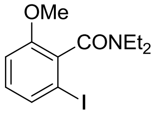
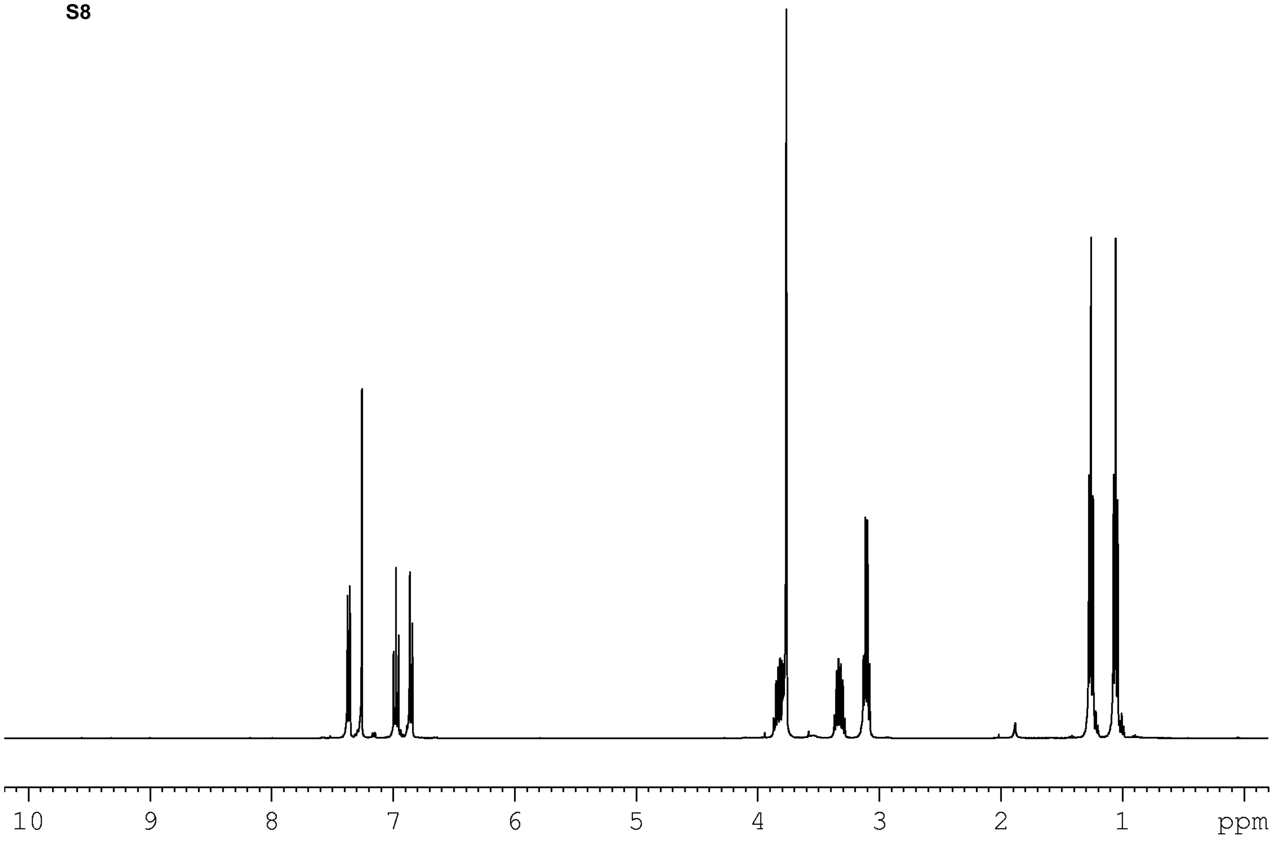

OMe
CONEt$_2$
I

S8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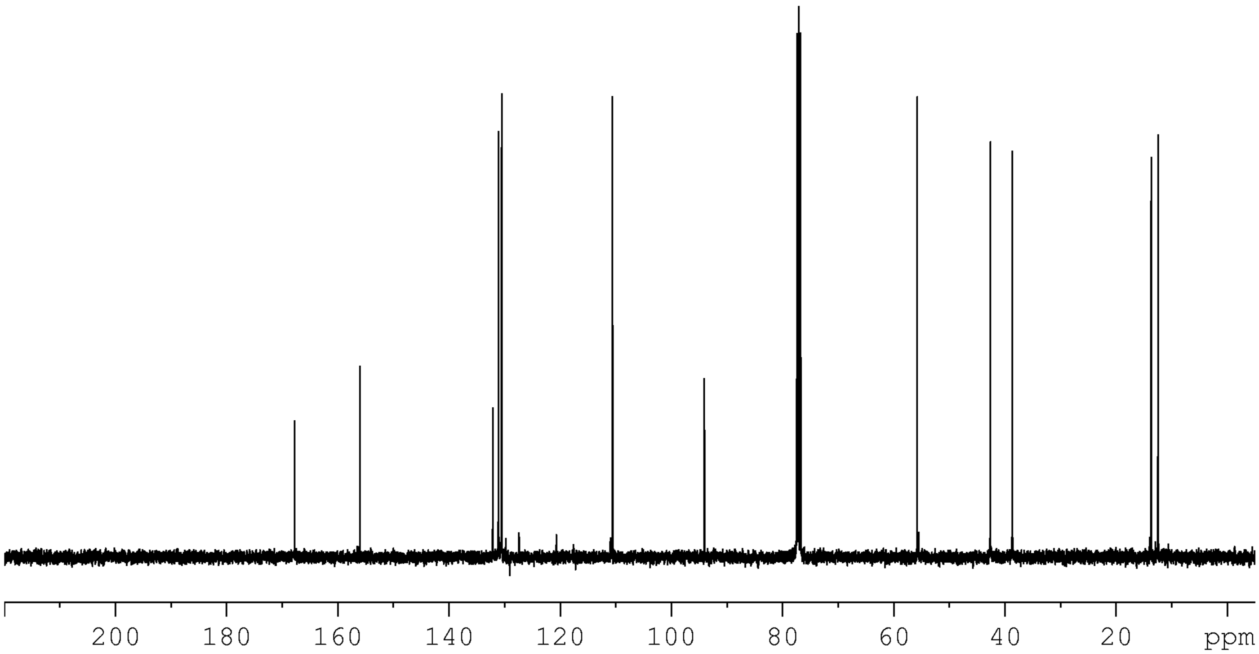
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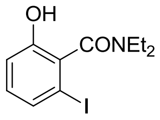
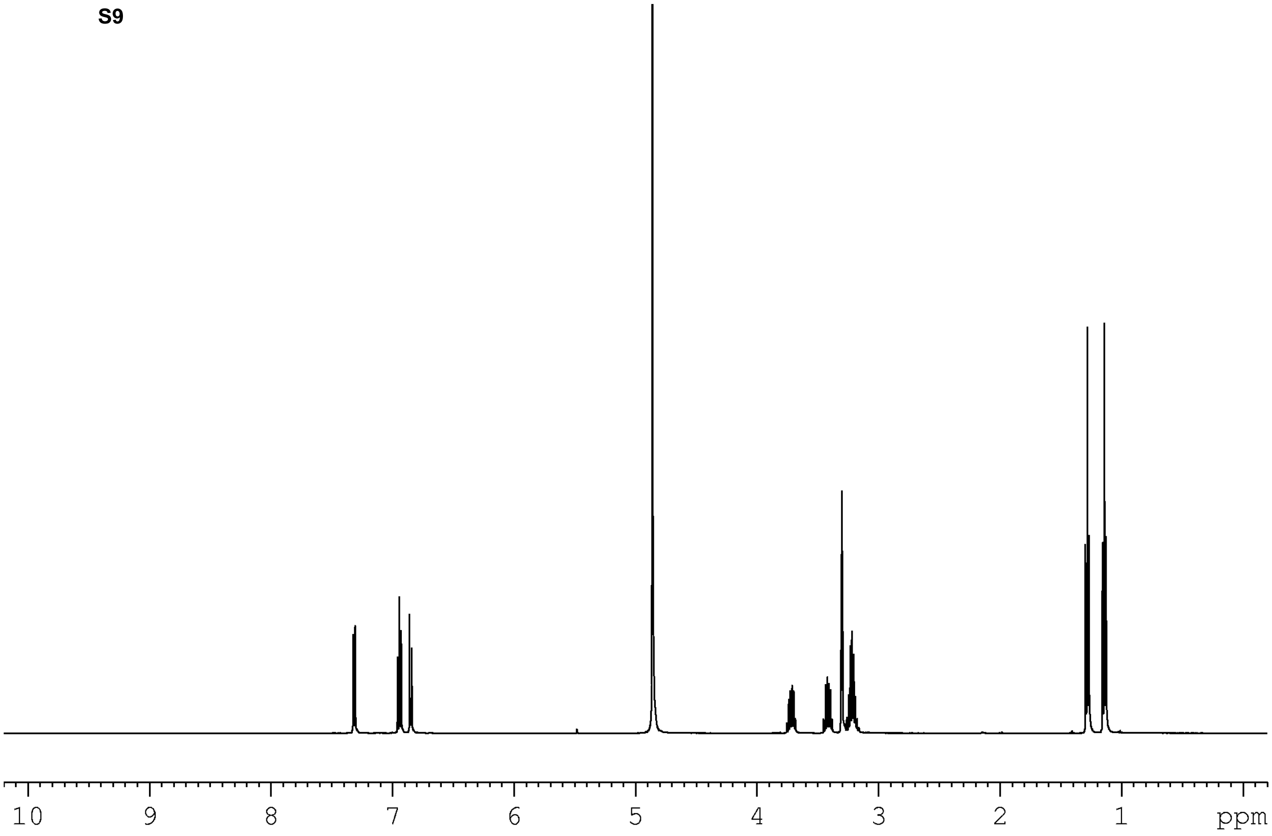

OH
CONEt2
I

S9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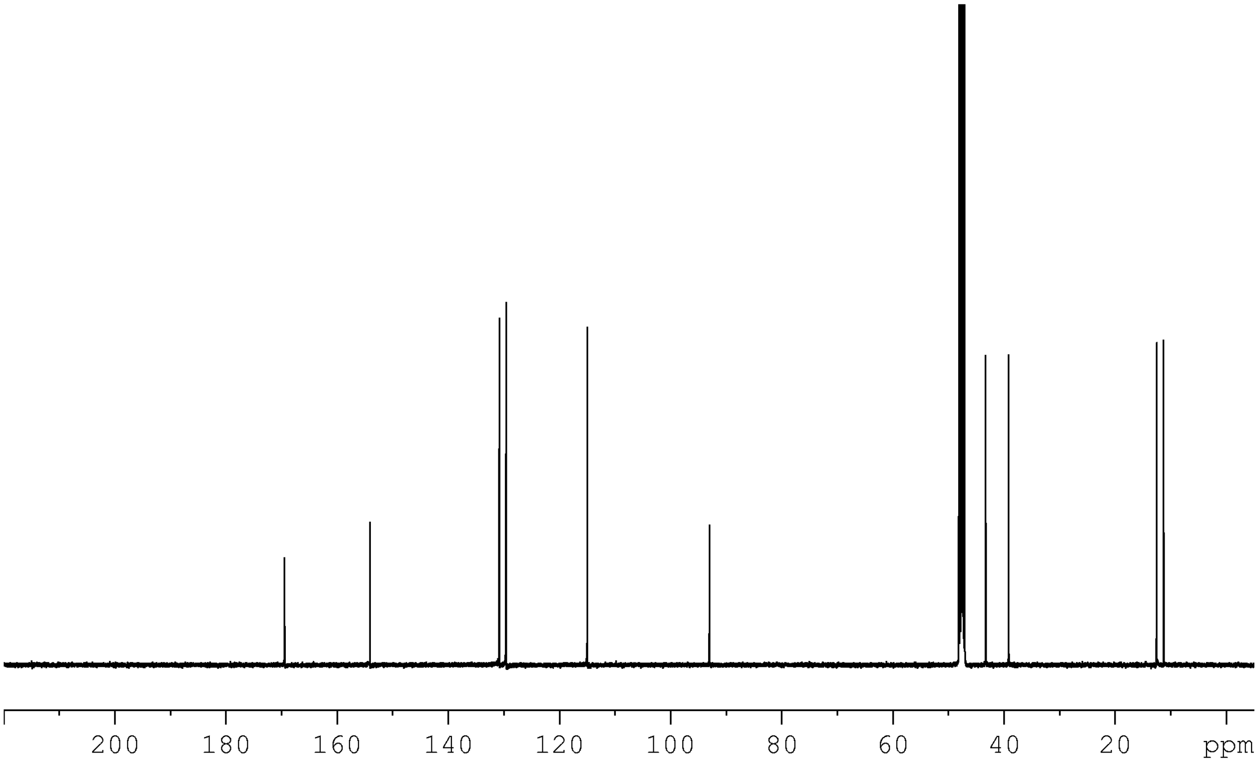
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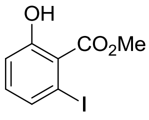
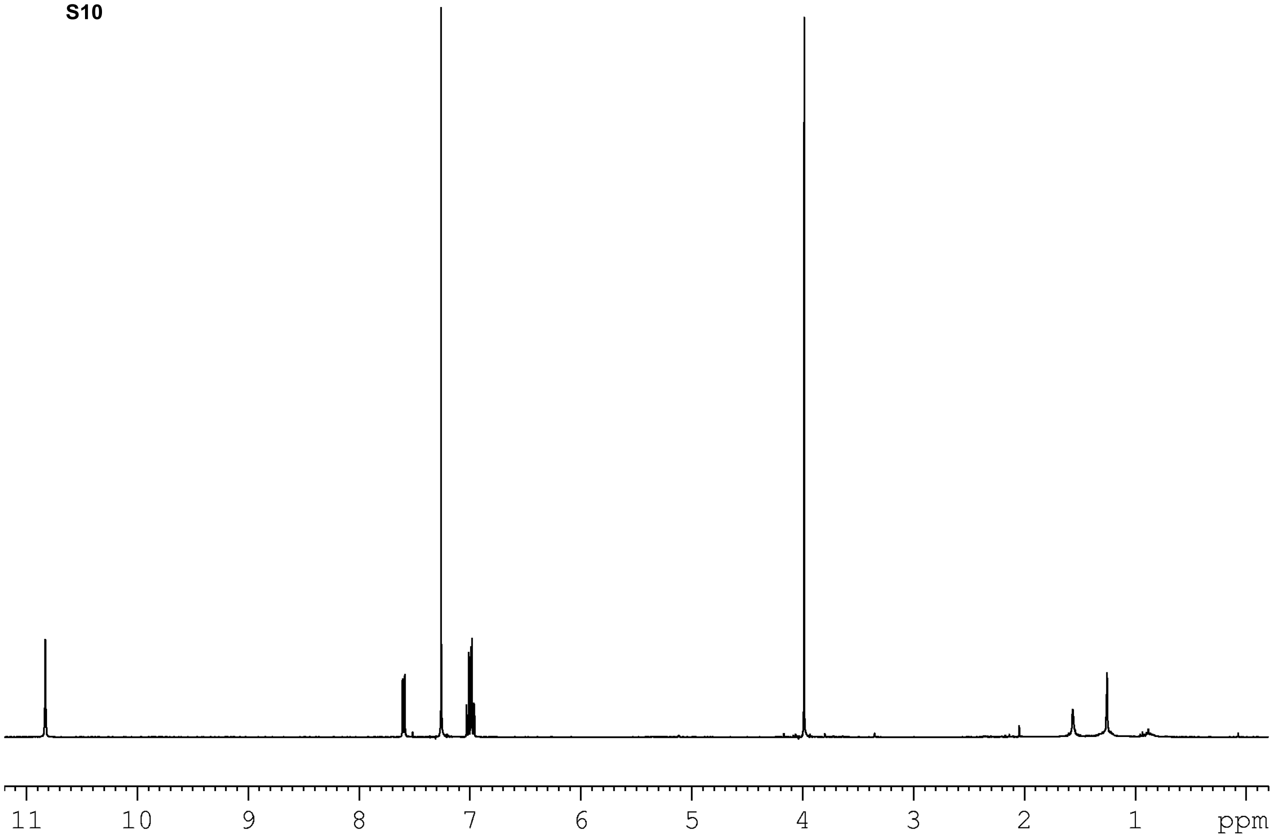

OH
CO2Me
I

S10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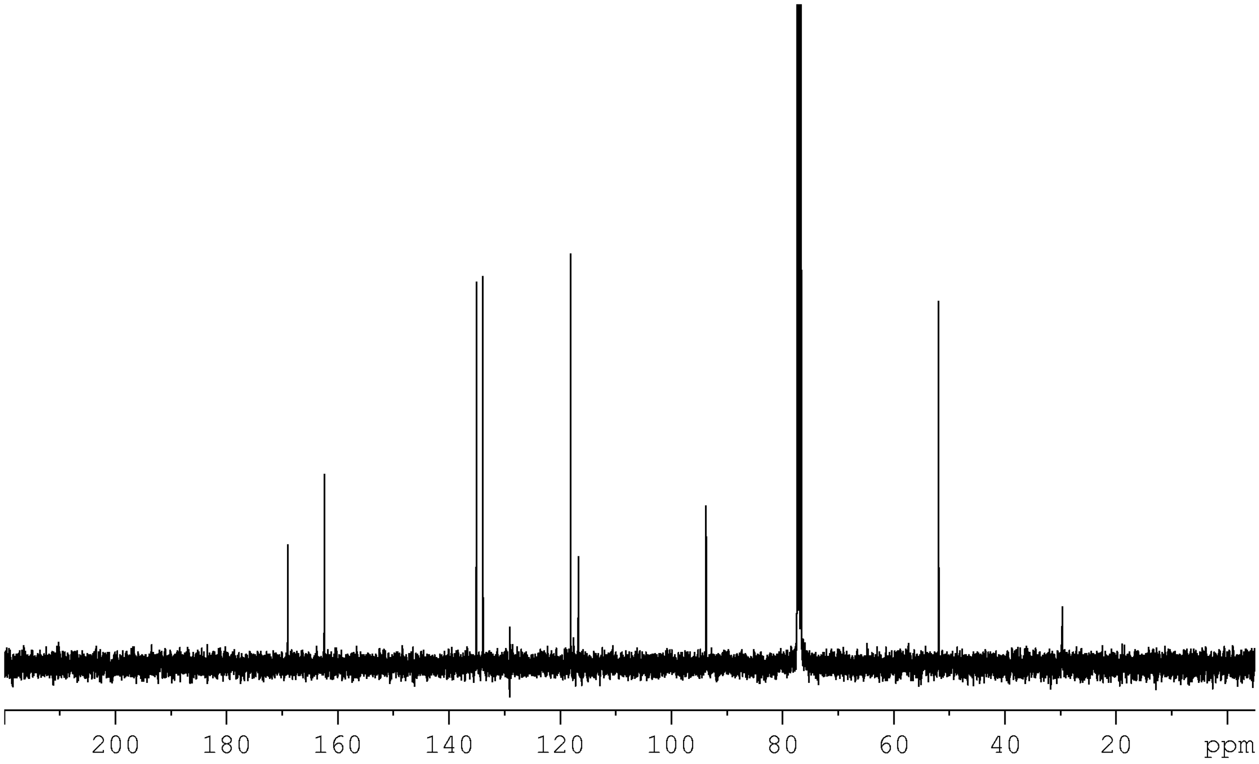
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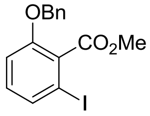
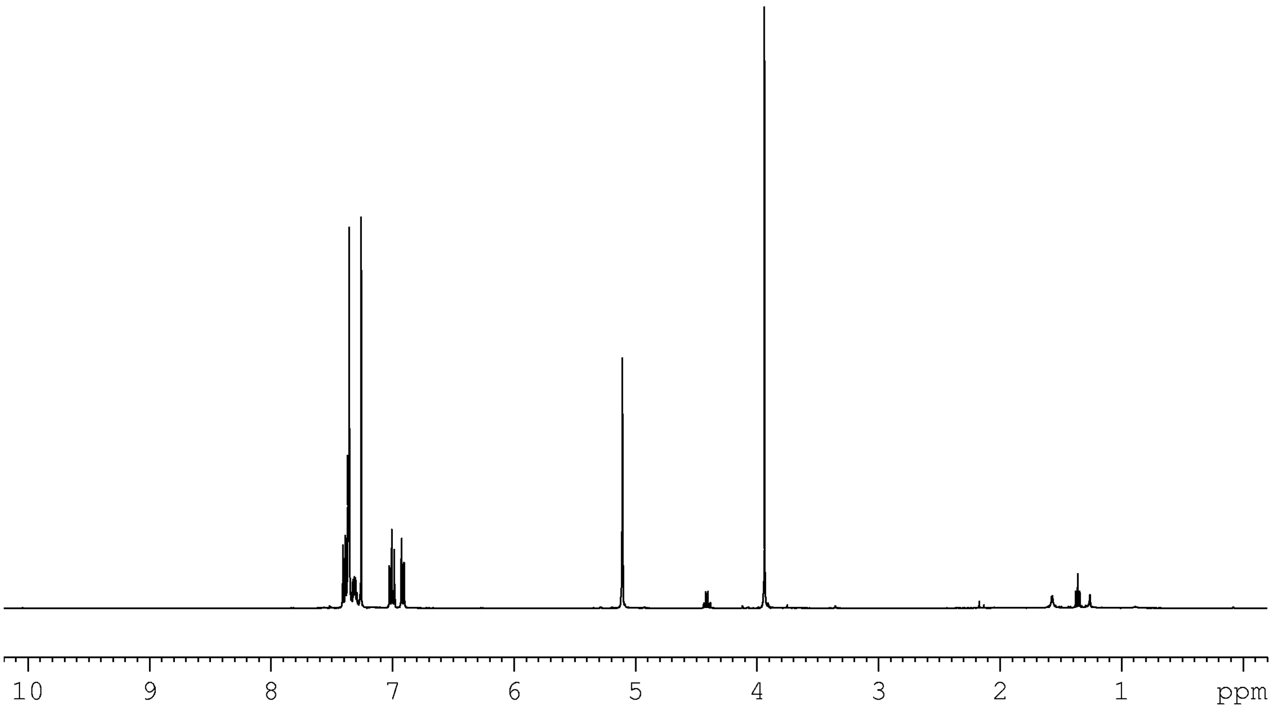

OBn
CO_2Me
I

S11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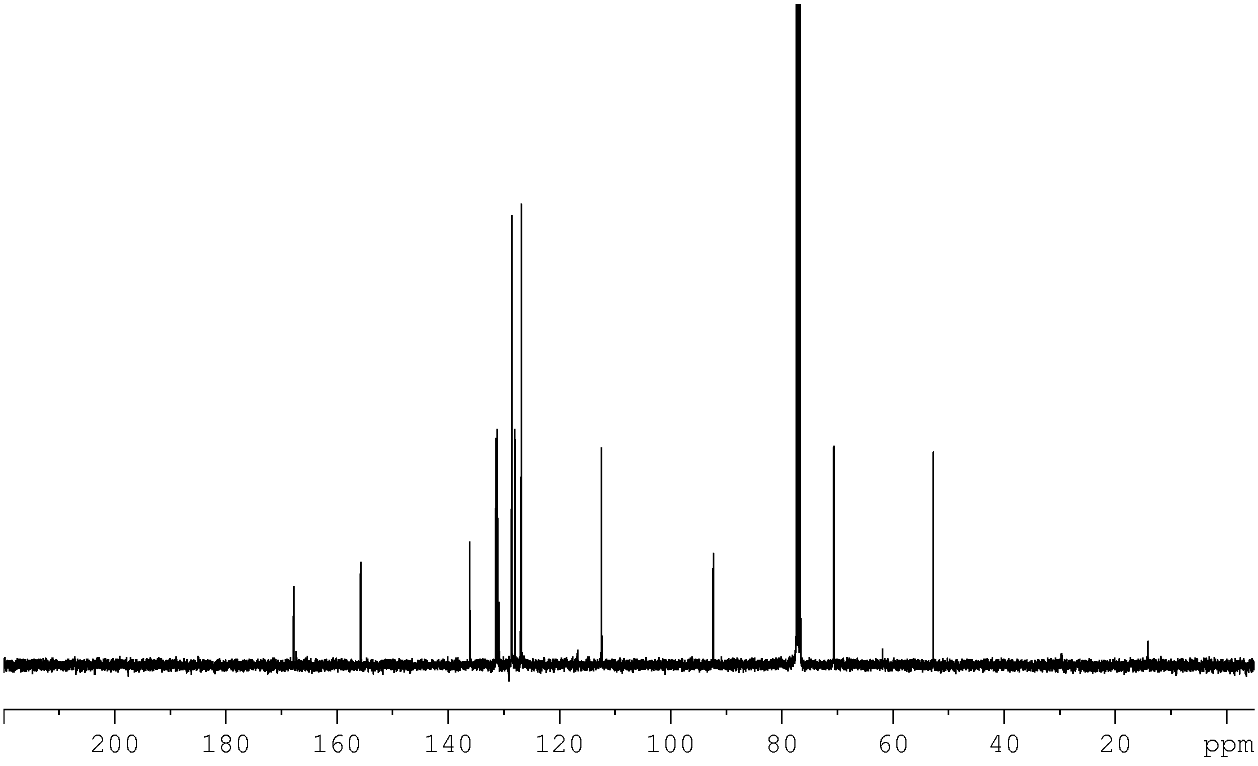
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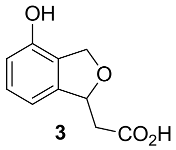
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CO2H

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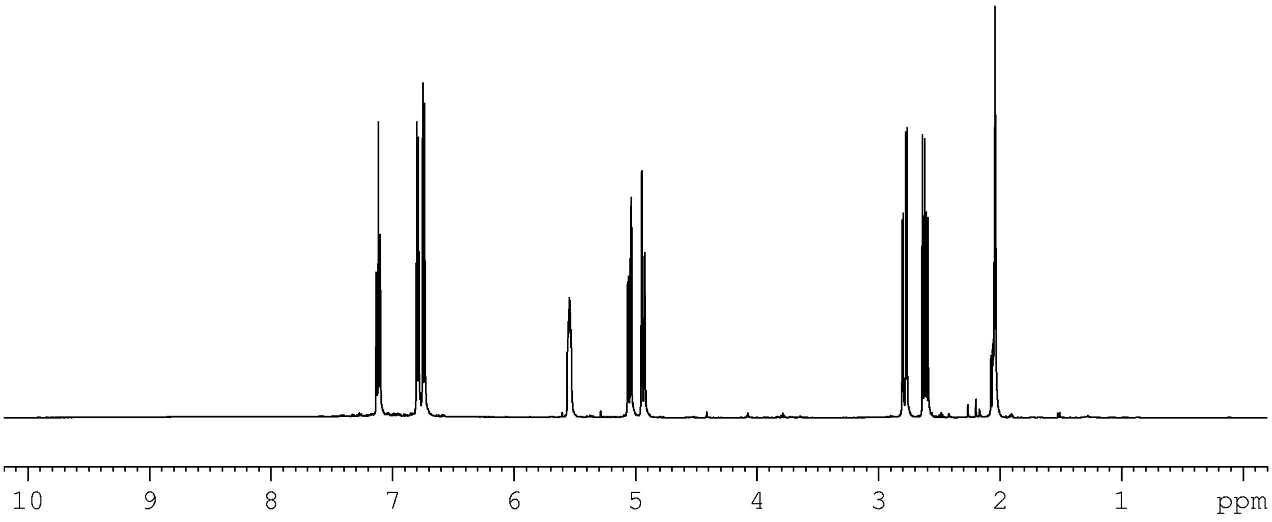
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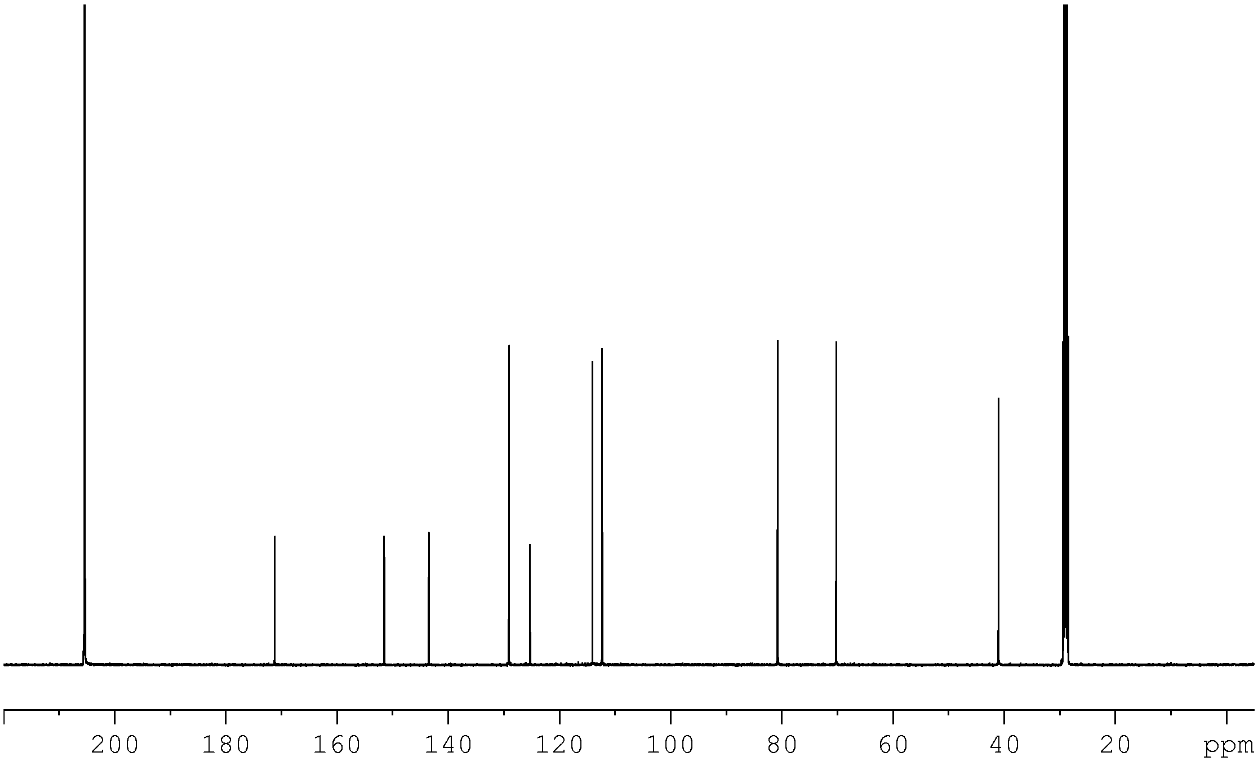
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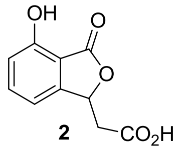
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O
CO$_2$H

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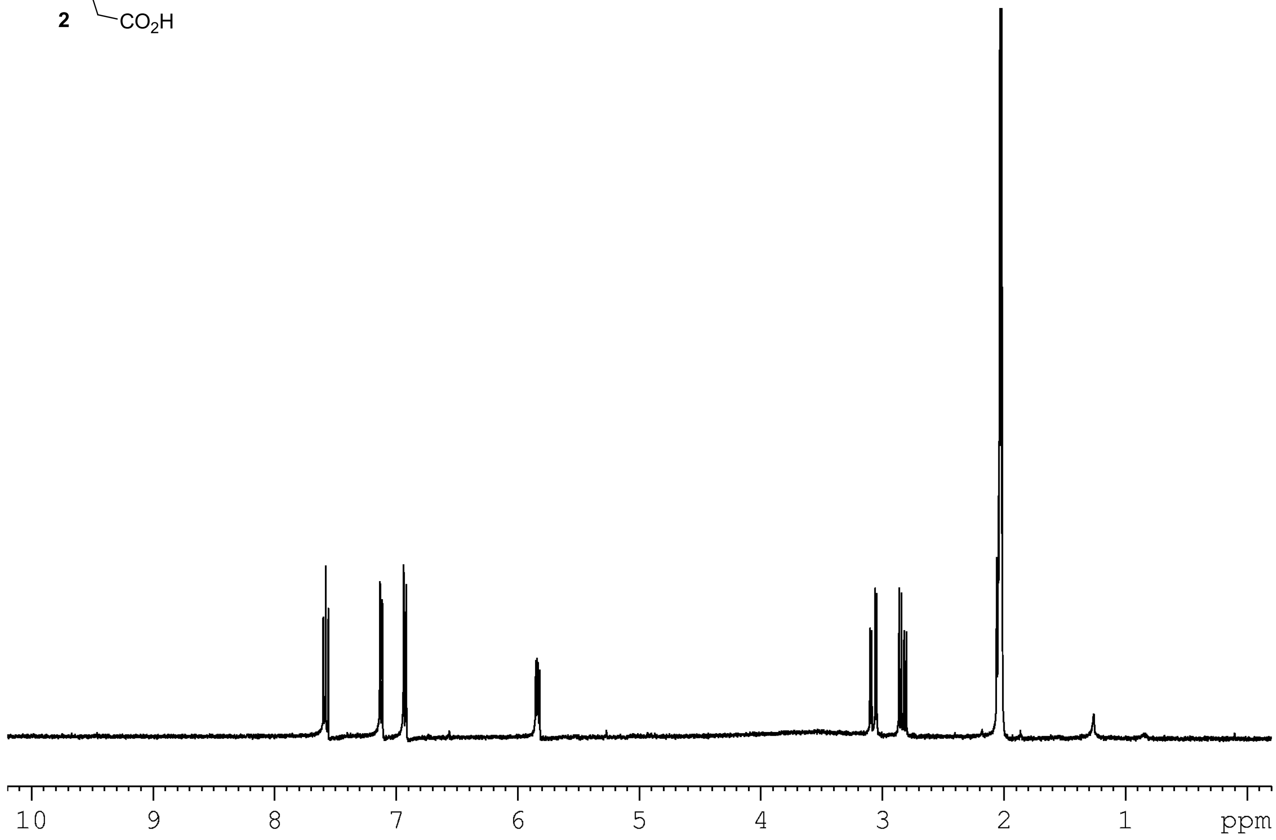
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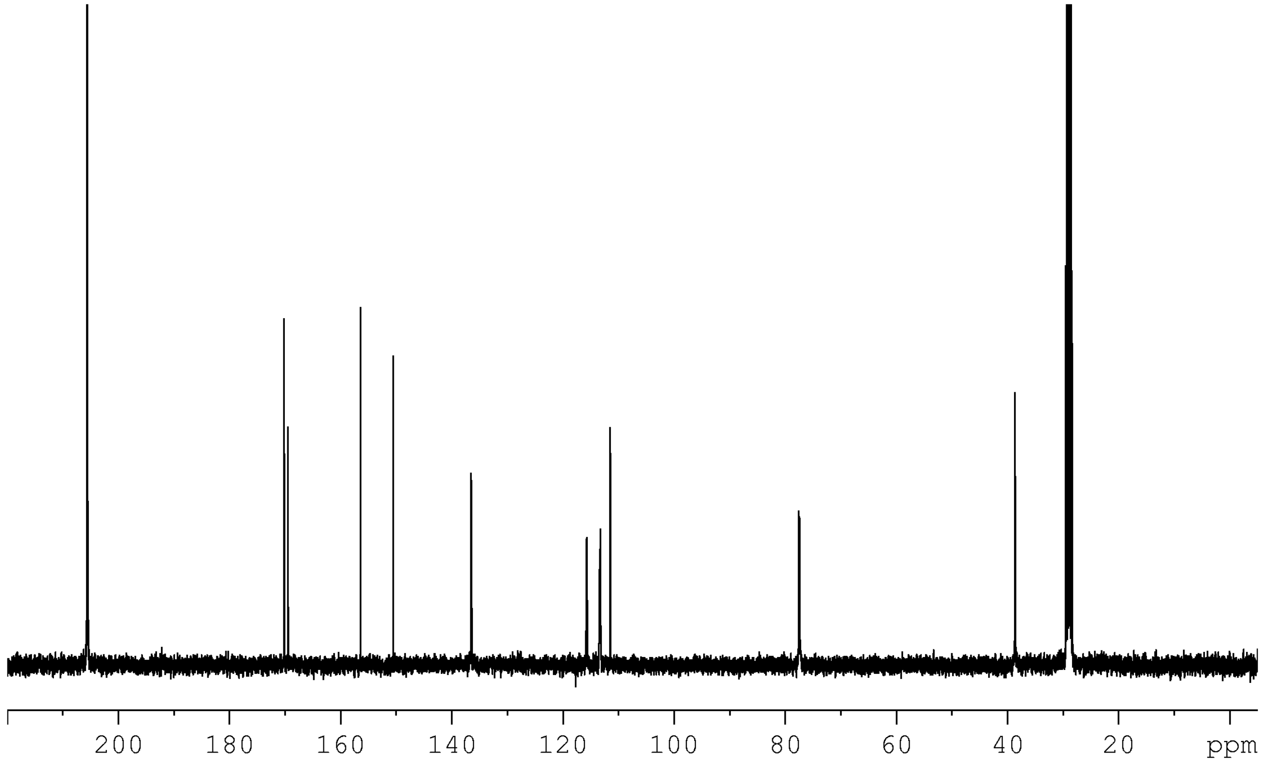
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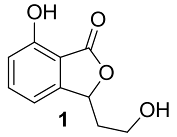

1