Commercial manufacturing of Propofol: simplifying the isolation process and control on related substances

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Supporting Information

Preparation of 3, 3', 5, 5'-tetrakis(1-methyl)biphenyl-4,4'-diol (**4)**

Propofol (**1)** (5 g, 28 mmol) was charged into water (150 mL) followed by addition of $FeCl_3$ (5.6 g, 30.3 mmol) and the reaction mixture was heated at 90 ^oC for 1 h. Reaction mixture was allowed to cool to room temperature and extracted with ethyl acetate (2 × 75 mL). Combined organic layer was dried over sodium sulphate, filtered and concentrated to give the crude product which was used as such for the next step. To a solution of crude residue in THF (45 mL) and MeOH (5 mL), was added sodium borohydride (3.2 g, 84 mmol) and reaction mixture was stirred for 1 h at room temperature. Volatiles were removed under reduced pressure and the residue was treated with cold dilute hydrochloric acid (1N HCl, 30 mL). Reaction mixture was extracted with ethyl acetate (2 × 25 mL). Combined organic layer was dried over sodium sulphate, filtered and concentrated to obtain the crude product which was purified by column chromatography using 5% ethyl acetate in hexane as eluent to give **4** as off white solid (3.5 g, 70% over two steps). ^1H NMR ($CDCl_3$, 400 MHz): δ 7.18 (s, 4H), 4.75 (s, 2H), 3.23-3.16 (m, 4H), 1.32 (d, J = 6.8 Hz, 24H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 149.10, 134.73, 133.76, 122.41, 27.43, 22.77. ESI-Mass: For $C_{24}H_{34}O_2$ (M+)/z: 354.54, Found: (M+H)/z: 355.0. Melting point 104-107 ^oC.

Preparation of 2-(1-methylethoxy)-1,3-bis(1-methylethyl)benzene (**5**):

To a stirred solution of Propofol (4 g, 22.4 mmole) in DMF (10 mL) was added sodium hydroxide (1.79 g, 44.8 mmole) and 2-bromopropane (11.03 g, 89 mmole) at room temperature

and reaction mixture was heated at 80 to 90 °C. Reaction was monitored by TLC, after completion of reaction water (50 mL) was added at room temperature and product was extracted with toluene (40 mL). Toluene was removed completely under vacuum at 45 to 50 °C to obtain 2, 6-diisopropylphenyl isopropyl ether (**5**) as viscous oil (3.9 g, 79%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.11-7.04 (m, 3 H), 4.11-4.05 (m, 1H), 3.41-3.32 (m, 2H), 1.31 (d, J = 6.4 Hz, 6H), 1.21 (d, J = 6.8 Hz, 12H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 151.51, 142.34, 123.94, 123.79, 76.07, 26.53, 24.07, 23.36. ESI-Mass: For $C_{15}H_{24}O$ (M+)/z: 220.36, Found: (M+H)/z: 221.0.

Preparation of 2,6-bis(1-methylethyl)benzene-1,4-dione **(6)**:

To a solution of Propofol (0.5 g, 2.8 mmol) in acetonitrile (20 mL) at room temperature was added ceric ammonium nitrate (3.07 g, 5.6 mmol) and reaction mixture was heated to 80 ^{o}C for 1 h. Acetonitrile was removed under reduced pressure and water (10 mL) was added to the residue. Reaction mixture was extracted with MTBE (3 × 10 mL). Combined organic layer was concentrated under reduced pressure and the crude residue was purified by column chromatography using 5% ethyl acetate in hexane as eluent to give pure product **6** as viscous oil (250 mg, 48%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 6.47 (s, 2H), 3.10-3.03 (m, 2H), 1.13 (d, J = 6.8 Hz, 12H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 188.68, 186.82, 155.34, 129.74, 26.88, 21.44.

Preparation of 1-isopropyl-2-(methoxymethoxy)benzene **(10)**:

To a solution of 2-isopropyl phenol (10 g, 73 mmol) in DMF (50 mL) at room temperature was added sodium hydroxide (8.4 g, 210 mmol) and reaction mixture was stirred for 15 min. MOM-chloride (8.9 g, 110 mmol) was added over 10 min maintaining temperature below 20 ^{o}C. Reaction mixture was then allowed to stir for 1 h. After completion of reaction checked by TLC, the reaction mixture was poured into water (500 mL) and extracted with MTBE (2 × 100 mL). The combined organic layer was washed with water (100 mL) and concentrated to give crude residue, which was purified by neutral silica gel column chromatography using 2% ethyl acetate in hexane as eluent to give pure product **10** as viscous oil (11.0 g, 83%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.22 (dd, J = 1.6, 7.6 Hz, 1H), 7.13 (dt, J = 1.6 Hz, 8.4 Hz, 1H), 7.05 (d, J = 1.2, 8.4 Hz, 1H), 6.97 (dt, J = 1.2, 7.6 Hz, 1H), 5.20 (s, 2H), 3.49 (s, 3H), 3.38-3.31 (m, 1H); 1.23 (d, J =

6.8 Hz, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 154.37, 137.54, 126.54, 126.15, 121.80, 113.93, 94.49, 55.93, 26.84, 22.75.

Preparation of 3-isopropyl-2-(methoxymethoxy)phenol (**12**):

To a stirred solution of **10** (1 g, 5.55 mmol) in anhydrous THF (10 mL) at 0 ^{o}C under nitrogen atmosphere was added n-BuLi (5.2 mL, 8.33 mmol) and reaction mixture was allowed to attain room temperature. The reaction mixture was stirred for 0.5 h and then cooled to 0-5 ^{o}C. Triethyl borate (1.2 mL, 11.1 mmol) was added and the reaction mixture was stirred for 1 h at the same temperature. Acetic acid (0.8 mL, 13.88 mmol) was added and stirring continued for 0.5 h. Hydrogen peroxide (1 mL, 13.88 mmol) was added and the reaction mixture was allowed to attain room temperature and stirred at room temperature for 4 h. Saturated solution of ammonium sulphate (10 mL) and saturated solution of Na_2SO_3 (10 mL) were added and the reaction mixture was stirred for 20 min. Layers were separated, aqueous layer was extracted with ethyl acetate (3 × 10 mL). Combined organic layer was dried over sodium sulphate, filtered and concentrated to give crude residue. The crude residue was purified by silica gel column chromatography using 5% ethyl acetate in hexane as eluent to give pure product as viscous oil (0.85 g, 78%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.36 (s, 1H), 6.99 (t, J = 8 Hz, 1H), 6.82 (dd, J = 1.6, 8 Hz, 1H), 6.75 (dd, J = 1.6, 8 Hz, 1H), 5.01 (s, 2H), 3.64 (s, 3H), 3.26-3.19 (m, 1H); 1.2 (d, J = 7.2 Hz, 6H).

Preparation of 3-isopropylbenzene-1,2-diol (**13**):

To a stirred solution of **12** (1.0 g, 51 mmol) in MeOH (10 mL) was added *p*-TSA (194 mg, 1.02 mmol) and the reaction mixture was stirred at room temperature of 6 h. Methanol was removed under reduced pressure. The residue was diluted with sat. sodium bicarbonate solution (10 mL) and extracted with ethyl acetate (2 × 10 mL). Organic layer was dried over sodium sulphate, filtered and concentrated to give crude residue. Crude residue was purified by silica gel column chromatography using 10% ethyl acetate in hexane as eluent to yield **13** as viscous oil (0.62 g, 80%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 6.80-6.68 (m, 3H), 3.71 (br.s, 2H), 3.25-3.18 (m, 1H), 1.25 (d, J = 7.2 Hz, 6H); ^{13}C N MR ($CDCl_3$, 100 MHz): δ 143, 141.5, 135.3, 120.1, 118.3, 112.7, 27.0, 22.5. ESI-Mass: For $C_9H_{12}O_2$ (M+)/z: 152.19, Found: (M-H)/z: 151.0.

Preparation of 2,2-dimethyl-4-(1-methylethyl)-1,3-benzodioxole (**7**):

To a solution of **13** (1 g, 6.57 mmol) in acetone (20 mL) at 0 ^{o}C was added $BF_3.Et_2O$ (1.37 mL, 11 mmol) and reaction mixture was allowed to attain room temperature over 1h. Reaction mixture was stirred for 16 h at room temperature and then concentrated. The residue was dissolved in ethyl acetate (20 mL) and washed with saturated sodium bicarbonate solution (10 mL). Organic layer was evaporated to give the crude residue which was purified by column chromatography using neutral silica gel and hexane as eluent to give **7** as pure product as viscous oil (0.9 g, 71%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 6.72 (t, *J* = 8 Hz, 1H), 6.67 (dd, *J* = 1.6, 8 Hz, 1H), 6.57 (dd, *J* = 1.6, 7.6 Hz, 1H), 3.03-2.97 (m, 1H), 1.66 (s, 6H), 1.24 (d, *J* = 7.2 Hz, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 146.82, 144.58, 129.96, 120.75, 118.63, 116.86, 106.03, 28.58, 25.83, 22.14. ESI-Mass: For $C_{12}H_{16}O_2$ (M+)/z: 192.26, Found: (M+H)/z: 193.3.

Preparation of 2-isopropyl-6-(prop-1-enyl)phenol (**14**):

To a stirred solution of **10** (1 g, 5.55 mmol) in anhydrous THF (10 mL) at 0 ^{o}C under nitrogen atmosphere was added n-BuLi (5.2 mL, 8.33 mmol) and reaction mixture was allowed to attain room temperature. The reaction mixture was stirred for 0.5 h and then cooled to 0-5 ^{o}C. Triethyl borate (1.2 mL, 11.1 mmol) was added and the reaction mixture was stirred for 1 h at the same temperature. 2M sodium carbonate solution (11.6 mL) was added and stirred for 15 min. This was followed by addition of $Pd(PPh_3)_4$ (1.1 g, 0.96 mmol) and 1-bromo-1-propene (cis-trans mixture, 3.6 mL, 42 mmol) and stirred for 16 h at 50 ^{o}C. Reaction mixture was filtered through Celite® and filtrate was concentrated to give the crude residue which was used as such for the next reaction. To a solution of crude product obtained in previous reaction was added MeOH (5 mL) and *p*-TSA (50 mg, catalytic) were added at room temperature and the reaction mixture was allowed to stir at the same temperature for 7 h. Methanol was evaporated, the residue diluted with saturated sodium bicarbonate (10 mL) and extracted with ethyl acetate (2 × 10 mL). Combined organic layer was dried on sodium sulfate, filtered and concentrated to give the crude product. It was purified by silica gel column using 5% ethyl acetate in hexane as eluent to yield pure product as viscous oil (620 mg, 63% over two steps). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.09-7.06 (m, 2H), 6.85 (t, *J* = 8 Hz, 1H), 6.53 (dd, *J* = 2.0, 16 Hz, 1H), 6.18-6.03 (m, 1H), 5.08 (br.s, 1H), 3.24-3.17 (m, 1H), 1.92 (dd, *J* = 2.0, 6.8 Hz, 3 H), 1.25 (d, *J* = 6.8 Hz, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 149.68, 134.35, 129.30, 125.74, 125.05, 124.86, 124.82, 120.47, 27.07, 22.59, 18.88. ESI-Mass: For $C_{12}H_{16}O$ (M+)/z: 176.26, Found: (M-H)/z: 175.0.

Preparation of 2-(1-methylethyl)-6-propylphenol (**8**):

To a solution of **14** (0.1 g, 0.568 mmol) in MeOH (5 mL) was added 10% Pd/C (20 mg) and the reaction mixture was stirred under hydrogen atmosphere for 16 h and then filtered through Celite®. Filtrate was concentrated to give crude product which was purified using neutral silica gel column chromatography using 3% ethyl acetate in hexane as eluent to give the pure product as viscous oil (85 mg, 84%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.06 (dd, *J* = 1.6, 7.6 Hz, 1H), 6.96 (dd, *J* = 1.6, 7.6 Hz, 1H), 6.84 (t, *J* = 7.6 Hz, 1H), 4.68 (s, 1H), 3.21-3.16 (m, 1H), 2.57 (t, *J* = 7.6 Hz, 2H), 1.68-1.60 (m, 2H), 1.26 (d, *J* = 6.8 Hz, 6H), 0.99 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 150.68, 133.82, 127.51, 127.28, 123.81, 120.38, 32.25, 27.06, 22.86, 22.68, 14.09. ESI-Mass: For $C_{12}H_{18}O$ (M+)/z: 178.28, Found: (M-H)/z: 177.0.

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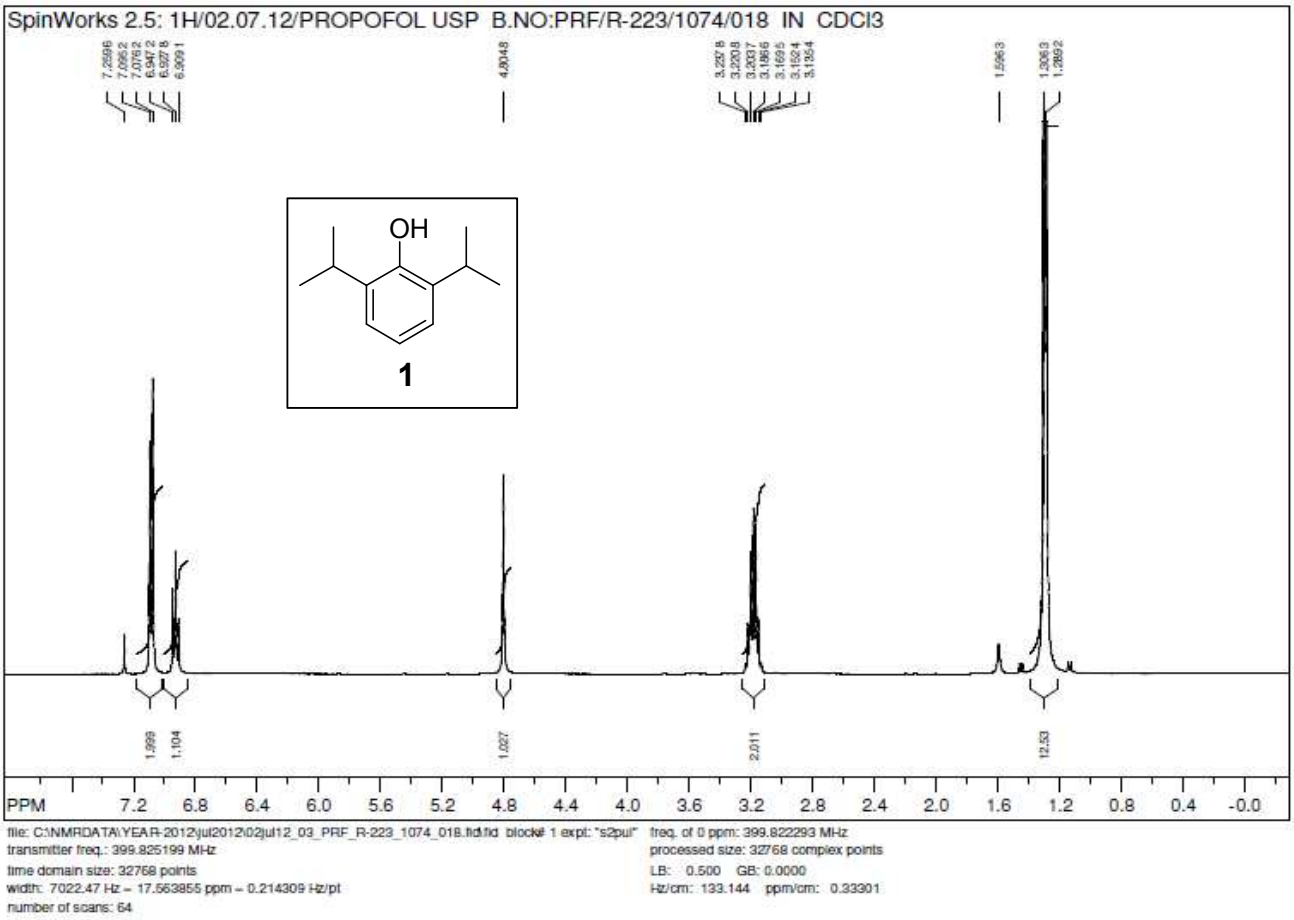

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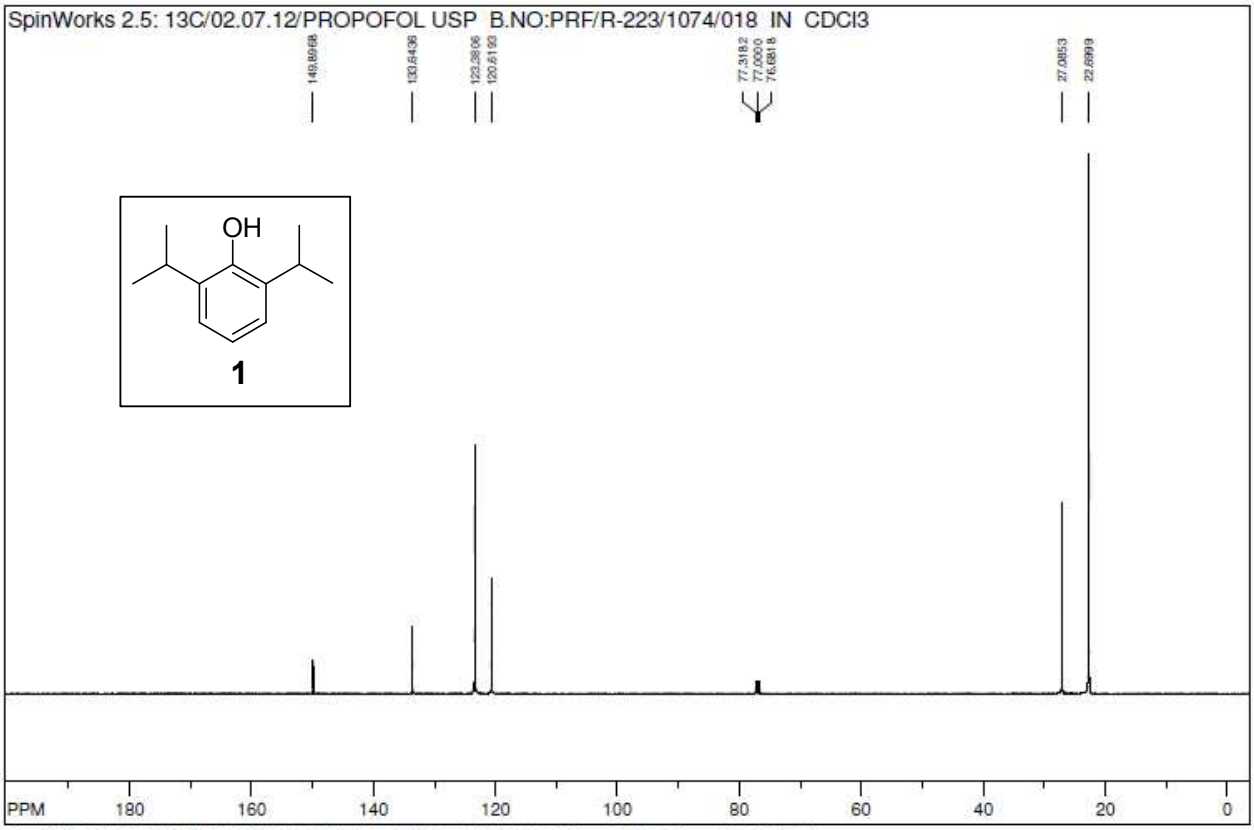

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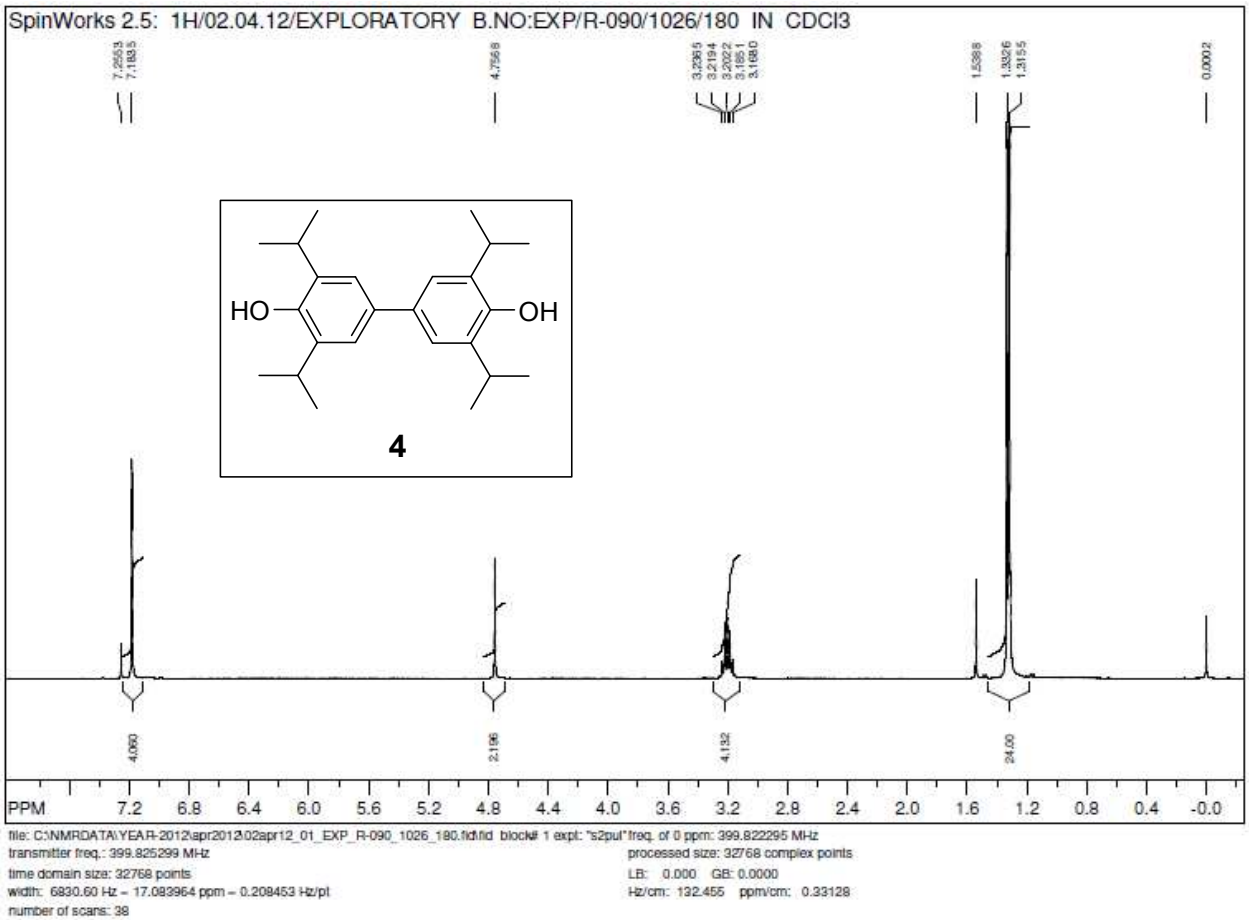

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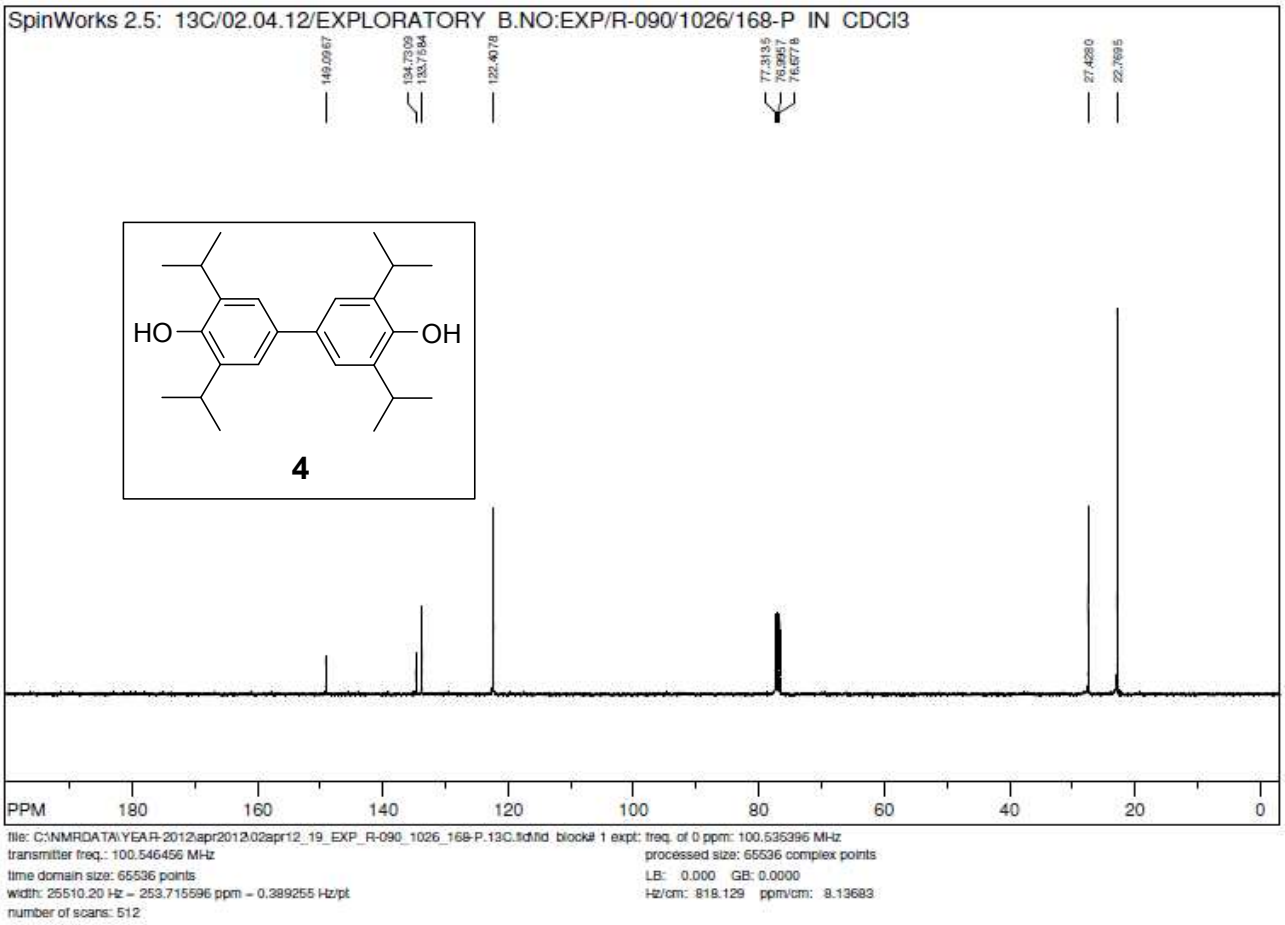

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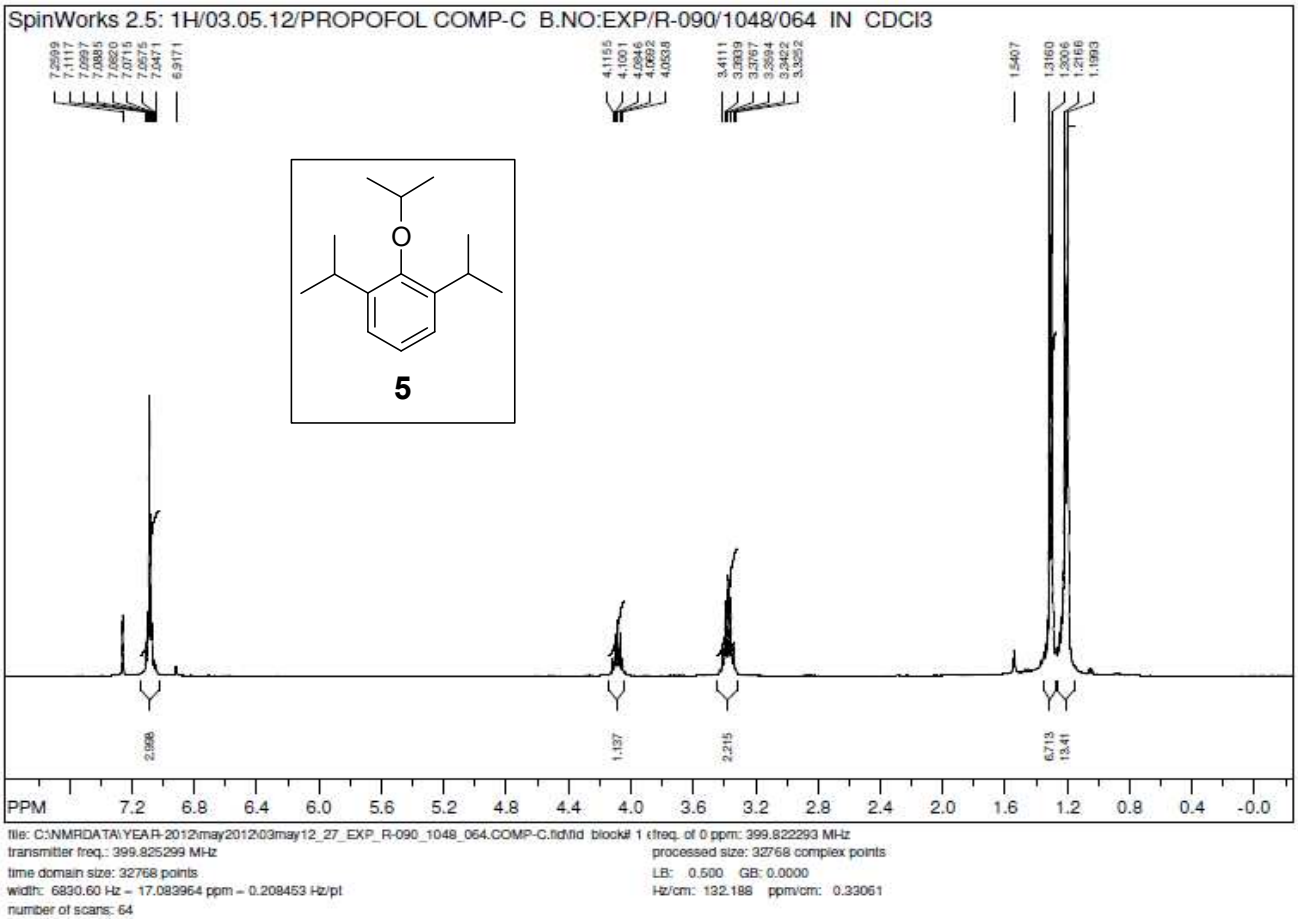

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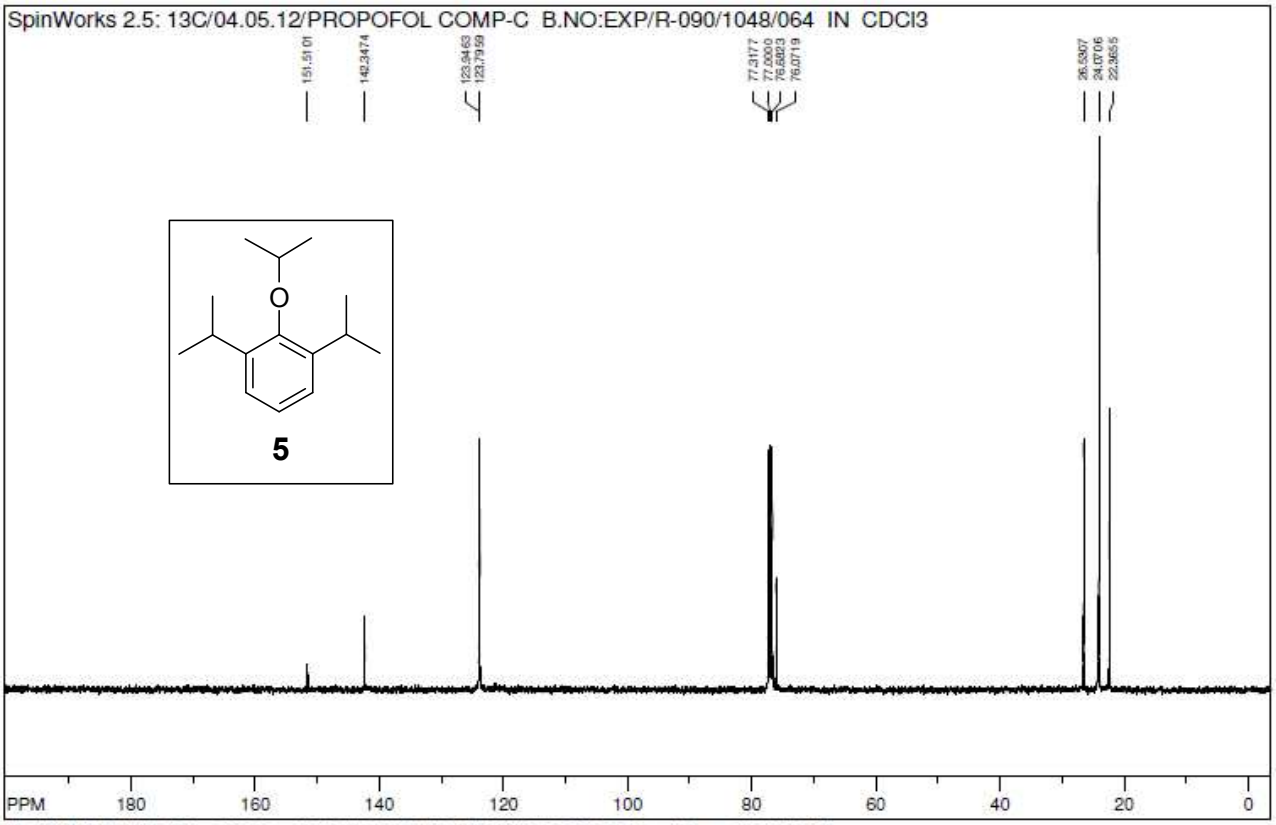

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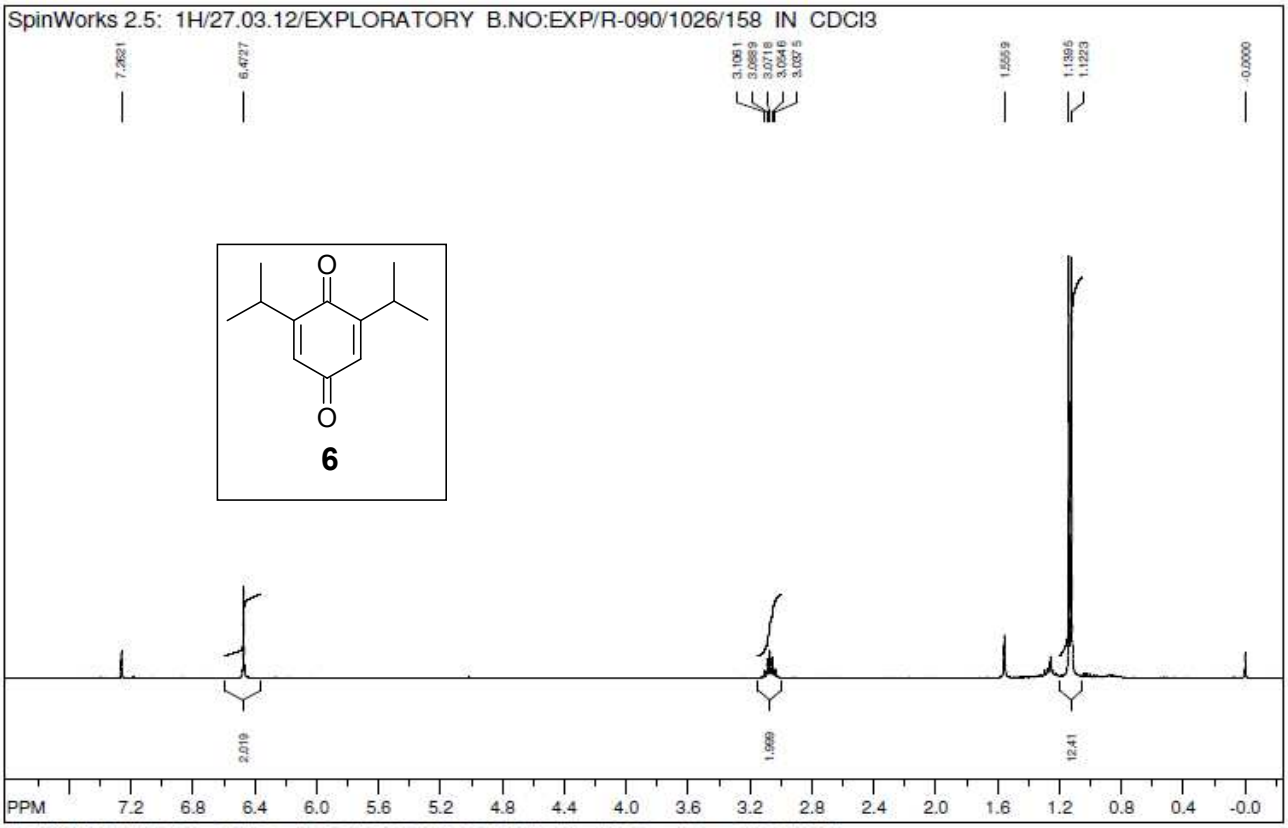

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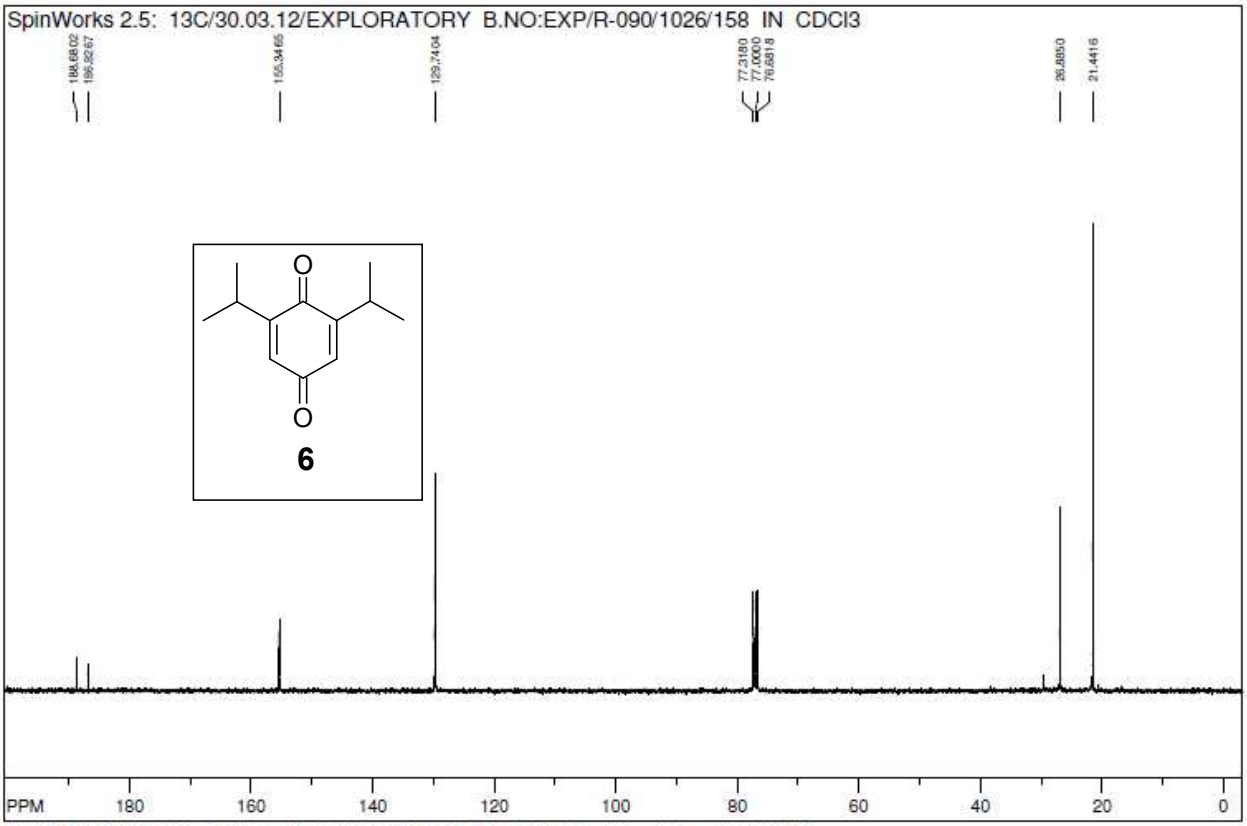

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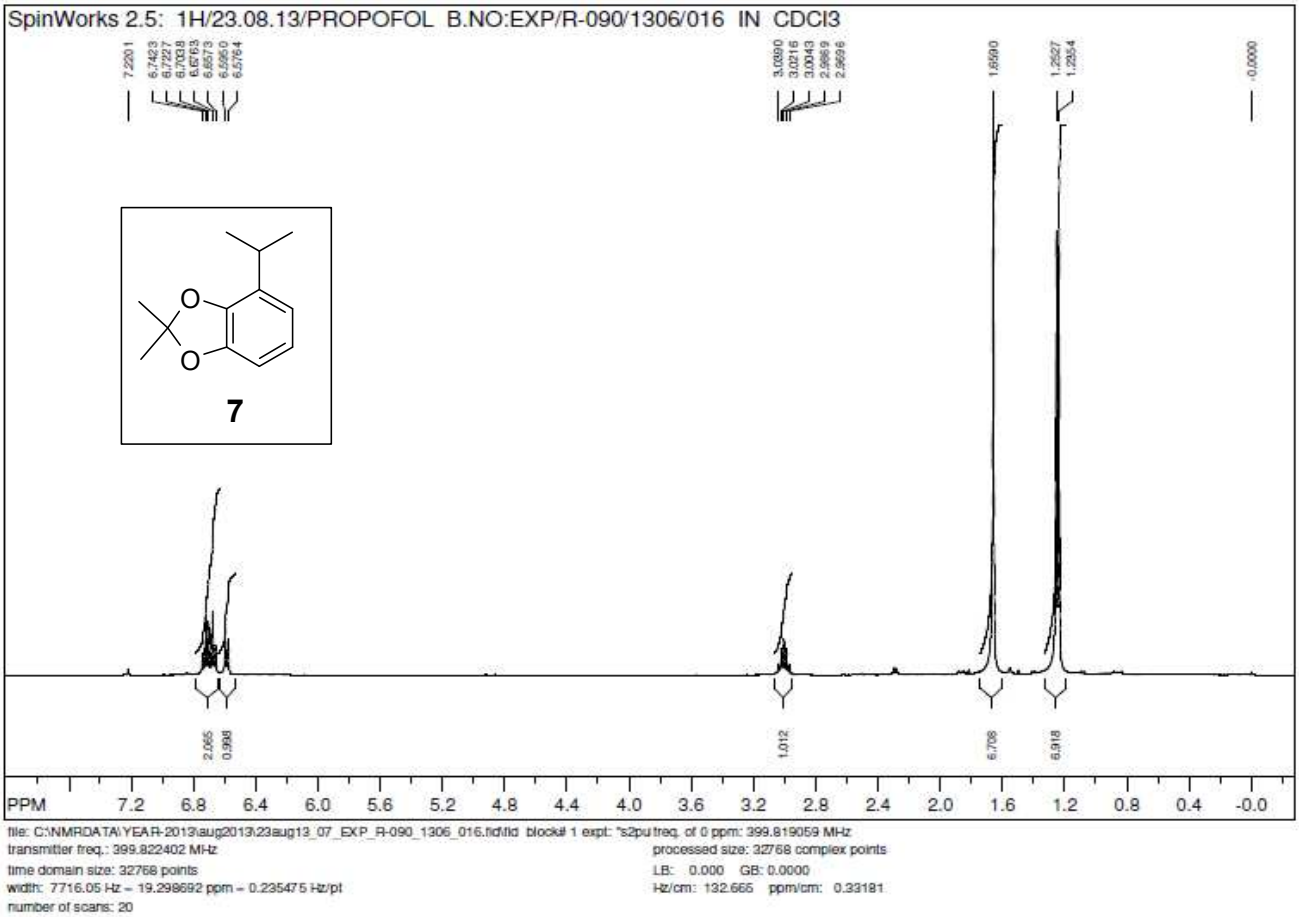

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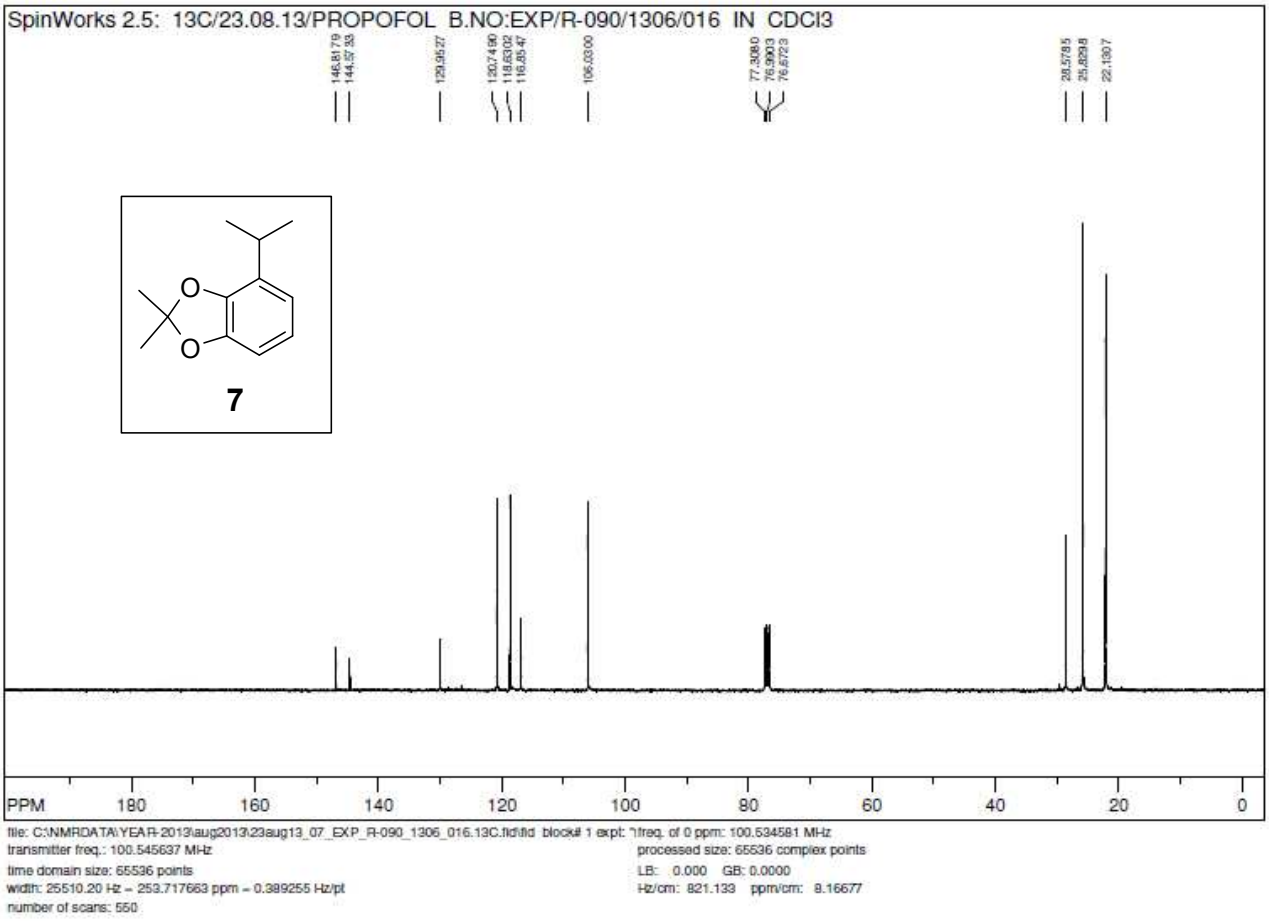

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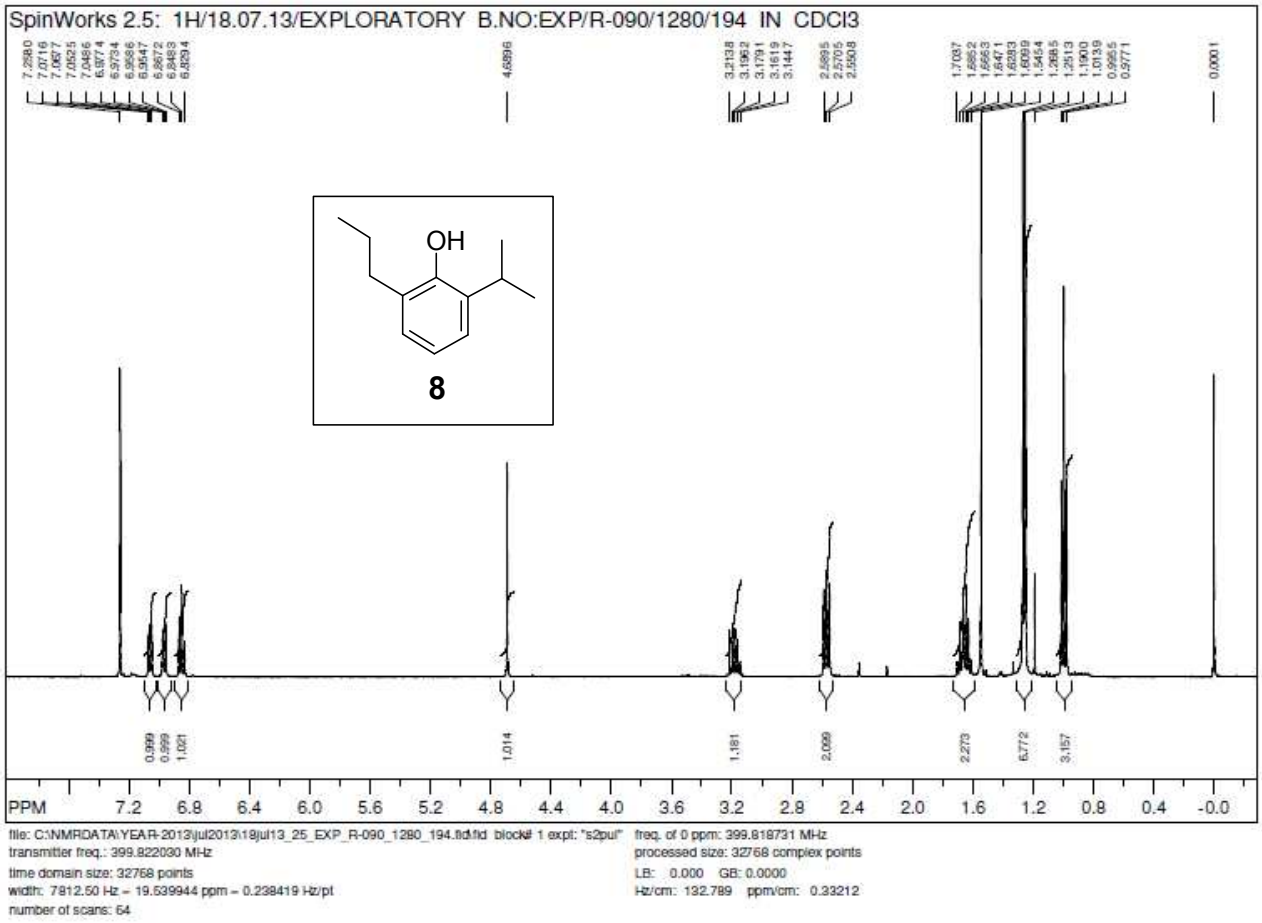
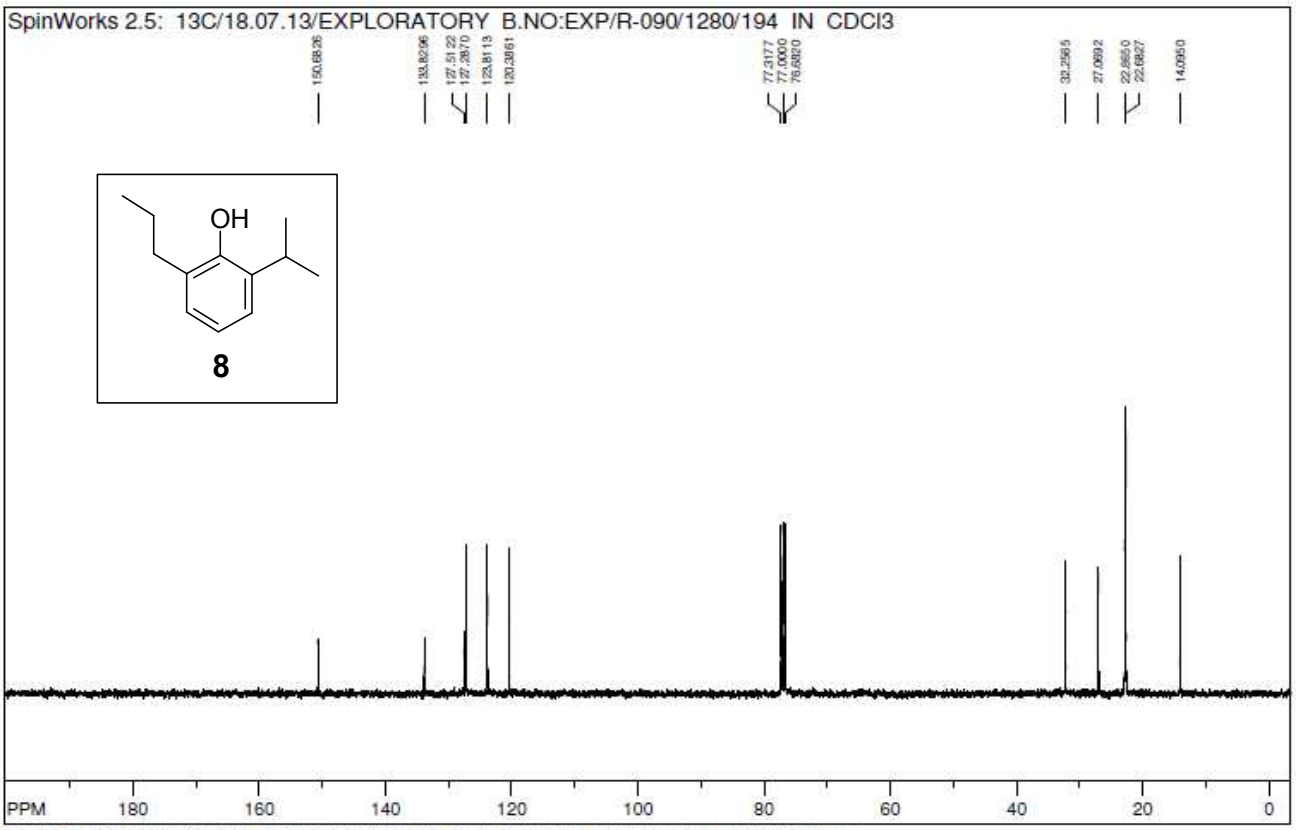


^{1}H NMR ($CDCl_3$, 400 MHz) of compound **8**



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