

**Chemiluminescence Molecular Probe with Intrinsic Auto-Inductive  
Amplification: Incorporation of Chemiexcitation in a Quinone-Methide  
Elimination**

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## **Supporting Information**

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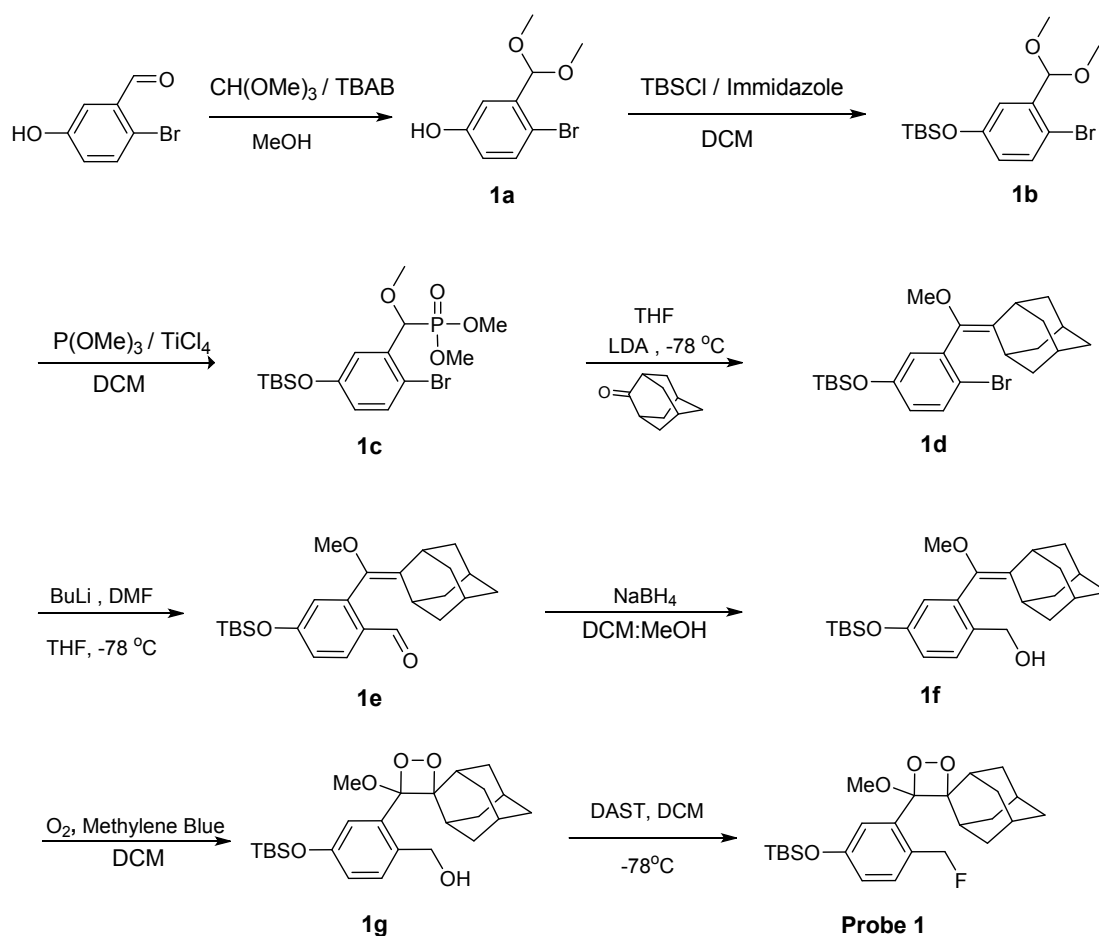
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## 1. General methods

Materials and instrumentations: All reactions requiring anhydrous conditions were performed under an argon atmosphere. All reactions were carried out at room temperature unless stated otherwise. Chemicals and solvents were either A.R. grade or purified by standard techniques. Thin layer chromatography (TLC): silica gel plates Merck 60 F254: compounds were visualized by irradiation with UV light. Flash chromatography (FC): silica gel Merck 60 (particle size 0.040-0.063 mm), eluent given in parentheses. Reverse-phase high pressure liquid chromatography (RP-HPLC): C18 5u, 250x4.6 mm, eluent given in parentheses. Preparative RP-HPLC: C18 5u, 250x21 mm, eluent given in parentheses. <sup>1</sup>H-NMR spectra were recorded using Bruker Avance operated at 400 MHz. <sup>13</sup>C-NMR spectra were recorded using Bruker Avance operated at 100 MHz. Chemical shifts were reported in ppm on the  $\delta$  scale relative to a residual solvent (CDCl<sub>3</sub>:  $\delta$  = 7.26 for <sup>1</sup>H-NMR and 77.16 for <sup>13</sup>C-NMR, DMSO-d<sub>6</sub>:  $\delta$  = 2.50 for <sup>1</sup>H-NMR and 39.52 for <sup>13</sup>C-NMR). Mass spectra were measured on Waters Xevo TQD. Fluorescence and chemiluminescence were recorded on Molecular Devices Spectramax i3x. All reagents, including salts and solvents, were purchased from Sigma-Aldrich.

Abbreviations: ACN - acetonitrile, DCM - dichloromethane, DMF - N,N'-dimethylformamide, EtOAc - ethyl acetate, Hex - hexanes, MeOH - methanol, TFA - trifluoroacetic acid, THF - tetrahydrofuran, DMAP - 4,4-dimethylaminopyridine, DBTL - Dibutyltin dilaurate.

## 2. Synthetic procedures



**Figure S1:** Synthetic route of probe 1.

### Synthesis of compound 1a

To a solution of 2-bromo-5-hydroxybenzaldehyde (200 mg, 0.99 mmol, 1 equiv.) and trimethyl orthoformate (120  $\mu\text{L}$ , 1.1 mmol, 1.1 equiv.) in methanol (5 mL) was added tetrabutylammonium tribromide (3.2 mg, 0.01 mmol, 0.01 equiv.). The homogeneous reaction was left at room temperature, and the progress of the reaction was monitored by TLC (Hex:EtOAc 80:20). After completion, the reaction mixture was poured into water and the product extracted with EtOAc (2 x 25 mL). The organic layer was separated, dried over anhydrous sodium sulfate, and concentrated. Further purification was achieved by passing through a short column of silica gel, to give 220 mg of **1a** (yield 89%).  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.37 (d,  $J = 8.6$  Hz, 1H), 7.11 (d,  $J = 3.1$  Hz, 1H), 6.70 (dd,  $J = 8.6, 3.0$  Hz, 1H), 5.51 (s, 1H), 3.41 (s, 6H).  $^{13}\text{C}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  156.03, 138.35, 134.50, 118.40, 116.01, 113.64, 103.97, 55.05. MS (ESI-)  $m/z$  244.9, 246.9 [ $\text{M}-\text{H}^+$ ] calc. for  $\text{C}_9\text{H}_{10}\text{BrO}_3$  244.9 246.9.

### Synthesis of compound 1b

Mixture of compound **1a** (2.2 g, 8.9 mmol, 1 equiv.) and imidazole (1.81 g, 27.3 mmol, 3 equiv.) was dissolved in DCM (20 mL) and then *tert*-butyl dimethyl silyl chloride (1.62 g, 10.7 mmol, 2 equiv.) was added and the reaction mixture was stirred at room temperature for 1 h. Upon completion, pure water was added to the stirring mixture. The mixture was extracted with DCM (3 x 60 mL). The organic layer was dried over anhydrous sodium sulfate, solvent was evaporated and the residue was purified by silica gel column chromatography, to obtain compound **1b**, 3.2 g (yield 99%). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.39 (d, *J* = 8.6 Hz, 1H), 7.11 (d, *J* = 3.0 Hz, 1H), 6.70 (dd, *J* = 8.6, 3.0 Hz, 1H), 5.49 (s, 1H), 3.37 (s, 6H), 0.98 (s, 9H), 0.20 (s, 6H). <sup>13</sup>C NMR (400 MHz, CDCl<sub>3</sub>) δ 156.47, 141.40, 131.82, 124.93, 119.74, 115.57, 103.52, 56.65, 25.66, 18.47.

### Synthesis of compound 1c

Trimethyl phosphite (8.6 mL, 84 mmol, 1.4 equiv.) was added to a stirred solution of compound **1b** (18 g, 60 mmol, 1 equiv.) in DCM at room temperature. 15 min later, TiCl<sub>4</sub> (8.6 mL, 84 mmol, 1.4 equiv.) was added dropwise to the reaction mixture, which was stirred for additional 30 min. The reaction mixture was diluted with DCM (400 mL) and extracted first with saturated solution of NaHCO<sub>3</sub> (200 mL) then with brine (200 mL). The combined organic phases were dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>. After removal of the solvent, the residue was purified by silica gel flash column chromatography to obtained product **1c** as a white solid (18 g, yield 78%). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.36 (dd, *J* = 8.7, 1.0 Hz, 1H), 7.14–7.09 (m, 1H), 6.68 (ddd, *J* = 8.7, 2.9, 1.9 Hz, 1H), 5.01 (d, *J* = 15.7 Hz, 1H), 3.75 (d, *J* = 10.7 Hz, 3H), 3.60 (d, *J* = 10.5 Hz, 3H), 3.31 (s, 3H), 0.93 (d, *J* = 2.9 Hz, 9H), 0.17 (d, *J* = 4.2 Hz, 6H). <sup>13</sup>C NMR (400 MHz, CDCl<sub>3</sub>) δ 156.17, 135.51, 134.09, 123.12, 122.09, 116.28, 80.02, 59.41, 59.25, 54.44, 54.37, 26.35, 18.94. MS (ESI+) *m/z* 439.0, 441.1 [M-H<sup>+</sup>] calc. for C<sub>16</sub>H<sub>29</sub>BrO<sub>5</sub>PSi 439.0, 441.0.

### Synthesis of compound 1d

Lithiumdiisopropyl amide (12 mL, 20 mmol, 1.3 equiv.) was added dropwise to the reaction mixture of compound **1c** (7 g, 15.9 mmol, 1 equiv.) dissolved in 20 mL dry THF at -78°C under argon. After stirring of the reaction mixture for 15 min, 2-adamantanone (6.2 g, 20.7 mmol, 1.1 equiv.), dissolved in dry THF (20 mL), was added

dropwise to the reaction mixture at  $-78^{\circ}\text{C}$  under argon. The reaction mixture was stirred at room temperature for 2 h. After pouring it into pure water, it was extracted with EtOAc (3x80 mL). The combined organic phases were dried over anhydrous  $\text{Na}_2\text{SO}_4$ , the solvent was removed and the residue was purified by silica gel flash column chromatography to give product **1d** (5.5 g, yield 75%).  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.41 (d,  $J = 8.6$  Hz, 1H), 6.72 (d,  $J = 2.9$  Hz, 1H), 6.67 (dd,  $J = 8.6, 2.9$  Hz, 1H), 3.30 (s, 3H), 3.25 (m, 1H), 2.35 (m, 1H), 1.93–1.69 (m, 12H), 0.96 (s, 9H), 0.17 (s, 6H).  $^{13}\text{C}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  155.32, 142.19, 137.96, 134.07, 131.00, 124.72, 122.19, 117.07, 57.47, 54.13, 39.88, 39.75, 39.39, 39.12, 37.89, 33.54, 30.19, 29.17, 29.01, 26.37, 18.97. MS (ESI+)  $m/z$  463.1, 465.1 [ $\text{M}-\text{H}^+$ ] calc. for  $\text{C}_{24}\text{H}_{36}\text{BrO}_2\text{Si}$  463.1, 465.1.

#### Synthesis of compound 1e

Compound **1d** (4.5 g, 9.7 mmol, 1 equiv.) was dissolved in THF (20 mL) under  $\text{N}_2$  atmosphere. The solution was cooled to  $-78^{\circ}\text{C}$  and  $n\text{-BuLi}$  (7.8 mL, 2.5 M in Hex) was added. After 15 min of stirring, DMF (2.7 mL) was added. The reaction mixture was heated to room temperature with stirring for 30 min and monitored by TLC. After completion, saturated solution of ammonium chloride (5 mL) was added. The mixture was extracted with EtOAc (3x30 mL). The combined organic layer was washed with brine (25 mL), dried over  $\text{Na}_2\text{SO}_4$  and evaporated under reduced pressure, the product purified by column chromatography to give 3 g of yellow solid (72% yield).  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  9.99 (s, 1H), 7.80 (dd,  $J = 8.6, 0.8$  Hz, 1H), 6.85–6.77 (m, 1H), 6.68 (dd,  $J = 2.3, 0.9$  Hz, 1H), 3.21 (m, 4H), 2.17 (s, 1H), 1.91–1.57 (m, 12H).  $^{13}\text{C}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  192.52, 162.82, 142.83, 139.36, 134.83, 130.46, 128.35, 118.53, 116.65, 57.94, 39.64, 37.69, 33.31, 30.62, 28.89, 26.39. MS (ESI-)  $m/z$  297.2 [ $\text{M}-\text{H}^+$ ] calc. for  $\text{C}_{19}\text{H}_{21}\text{O}_3$  297.2.

#### Synthesis of compound 1f

To a solution of compound **1e** (1 g, 2.3 mmol, 1 equiv.) in DCM:MeOH mixture (5:3 mL) was added sodium borohydride (0.11 g, 2.9 mol, 1.2 equiv.) portion wise at  $0^{\circ}\text{C}$ , and the mixture was stirred at room temperature for 0.5 h and monitored by TLC (Hex:EtOAc 70:30). The reaction mixture was extracted with saturated ammonium chloride and EtOAc (3x20 mL). The organic layer was washed with brine (30 mL) and dried on anhydrous sodium sulfate. The solvent was removed under reduced pressure.

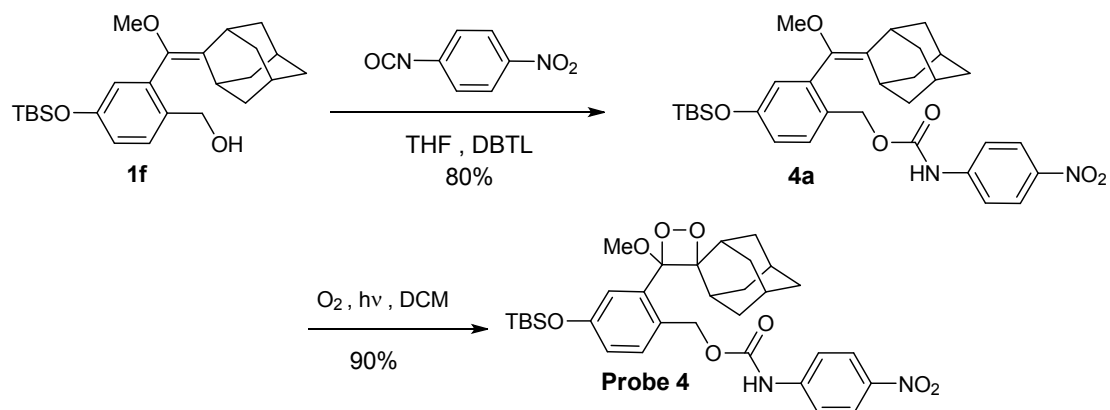
The crude product **1g** was purified by column chromatography to give 1 g (yield 99%). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.30 (d, *J* = 8.2 Hz, 1H), 6.81 (dd, *J* = 8.2, 2.6 Hz, 1H), 6.68 (d, *J* = 2.5 Hz, 1H), 4.53 (m, 2H), 3.28 (d, *J* = 8.1 Hz, 4H), 2.25 (s, 1H), 2.01–1.72 (m, 12H), 0.98 (d, *J* = 2.9 Hz, 9H), 0.19 (s, 6H). <sup>13</sup>C NMR (400 MHz, CDCl<sub>3</sub>) δ 155.28, 142.67, 136.37, 134.35, 133.77, 131.22, 123.58, 120.79, 64.66, 58.22, 39.91, 37.76, 33.24, 30.37, 28.96, 26.42, 19.01. MS (ESI+) *m/z* 415.3 [M+H<sup>+</sup>] calc. for C<sub>25</sub>H<sub>39</sub>O<sub>3</sub>Si 415.2.

#### Synthesis of compound 1g

Compound **1f** and methylene blue (1 mg) were dissolved in DCM (20 mL). Oxygen was bubbled through the solution while irradiating with yellow light. Reaction was monitored by TLC. Upon completion, the solvent was concentrated under reduced pressure. Purification by column chromatography (Hex:EtOAc) afforded the appropriate product **1g** with 90% yield. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.28 (dd, *J* = 14.5, 11.4 Hz, 1H), 6.99 – 6.76 (m, 2H), 5.10 – 4.62 (m, 2H), 3.22 (s, 3H), 2.98 (s, 1H), 2.10 – 2.08 (m, 1H), 1.66 (ddd, *J* = 26.2, 16.4, 15.7 Hz, 9H), 0.91 (s, 2H), 0.17 (s, 5H). <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>) δ 155.78, 144.21, 134.15, 122.42, 121.62, 103.48, 97.10, 65.55, 50.63, 37.09, 35.53, 34.16, 32.82, 32.37, 30.41, 26.72, 26.38, 18.96, -3.67.

#### Synthesis of compound 1

Compound **1g** (0.1 g, 0.2 mmol, 1 equiv.) was dissolved in DCM and cooled to -78C°. DAST (20 μL, 0.4 mmol, 2 equiv.) was portion wise, and the mixture was stirred at -78C° for 5 min and monitored by TLC (Hex:EtOAc 90:10). After completion, the reaction mixture was extracted with saturated ammonium chloride and EtOAc (3x20 mL). The organic layer was washed with brine (30 mL) and dried on anhydrous sodium sulfate. The solvent was removed under reduced pressure. The crude product was purified by preparative HPLC to give 50 mg of **1** (yield 49%). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.30 (d, *J* = 8.2 Hz, 1H), 6.81 (dd, *J* = 8.2, 2.6 Hz, 1H), 6.68 (d, *J* = 2.5 Hz, 1H), 4.53 (m, 2H), 3.28 (d, *J* = 8.1 Hz, 4H), 2.25 (s, 1H), 2.01–1.72 (m, 12H), 0.98 (d, *J* = 2.9 Hz, 9H), 0.19 (s, 6H). <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>) δ 167.27, 163.21, 128.92, 128.46, 125.77, 125.08, 122.84, 122.64, 84.52, 84.25, 82.67, 53.08, 52.91, 42.38, 39.85, 35.41, 32.23, 30.91, 30.43, 26.36, 18.92, 17.82, 3.72.



**Figure S2:** Synthetic route of probe 4.

#### Synthesis of compound **4a**

To a solution of compound **1g** (140 mg, 0.338 mmol, 1 equiv.) in dry THF (5 mL) was added a catalytic amount of DBTL and 4-isocyanatobenzenenitrile (66 mg, 0.406 mmol, 1.2 equiv.), the mixture was stirred at room temperature for 10 and monitored by TLC (Hex.:EtOAc 85:15). Upon completion, the solvent was removed under reduced pressure and the product was purified by column chromatography to give 172 mg of **4a** (yield 80%). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 8.16 (d, *J* = 9.1 Hz, 2H), 7.55 (d, *J* = 9.1 Hz, 2H), 7.33 (t, *J* = 7.4 Hz, 1H), 6.82 (dd, *J* = 8.3, 2.6 Hz, 1H), 6.67 (s, 1H), 5.34–5.11 (m, 3H), 3.59–3.11 (m, 4H), 2.20 (s, 1H), 2.00–1.59 (m, 12H), 0.97 (s, 9H), 0.21 (s, 6H). <sup>13</sup>C NMR (400 MHz, CDCl<sub>3</sub>) δ 156.07, 153.54, 141.85, 136.89, 132.54, 131.38, 128.41, 125.95, 123.53, 120.81, 118.40, 66.07, 57.83, 39.90, 37.75, 33.27, 30.34, 28.85, 26.39, 18.99, 3.72. MS (ESI-) *m/z* 577.3 [*M*-H<sup>+</sup>] calc. for C<sub>32</sub>H<sub>43</sub>N<sub>2</sub>O<sub>6</sub>Si 577.2.

#### Synthesis of compound **4**

Compound **4a** (0.29 mmol) and methylene blue (1 mg) was dissolved in DCM (20 mL). Oxygen was bubbled through the solution while irradiating with yellow light. Reaction was monitored by TLC. Upon completion, the solvent was concentrated under reduced pressure. Purification by column chromatography (Hex:EtOAc) afforded the appropriate product **4** with 90% yield. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 8.19 (d, *J* = 7.9 Hz, 2H), 7.56 (d, *J* = 7.7 Hz, 2H), 7.38 (s, 1H), 7.14 (d, *J* = 19.6 Hz, 1H), 7.00–6.91 (m, 1H), 5.69–5.60 (m, 2H), 3.25 (s, 3H), 3.05 (s, 1H), 2.12 (s, 1H), 1.92–1.56 (m, 12H), 0.97 (s, 1H), 0.21 (d, *J* = 7.6 Hz, 6H). <sup>13</sup>C NMR (400 MHz, CDCl<sub>3</sub>) δ 153.41, 144.79,

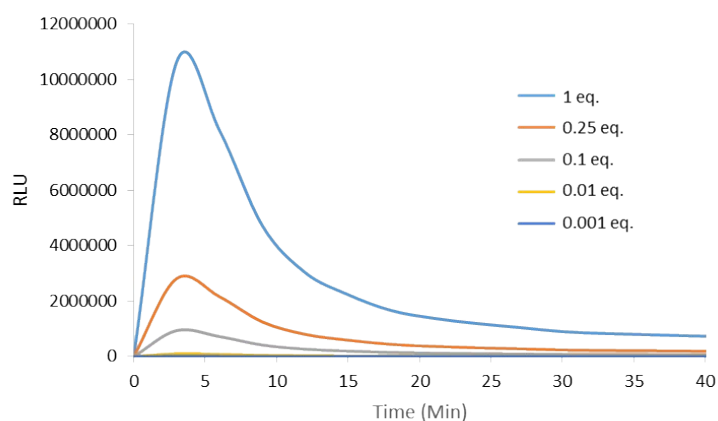


143.66, 135.41, 133.95, 132.38, 130.45, 129.93, 126.75, 125.96, 124.26, 122.44, 121.71, 118.47, 117.30, 113.61, 112.79, 96.62, 67.16, 65.60, 50.58, 37.11, 35.50, 34.25, 33.92, 32.92, 32.34, 26.75, 26.50, 26.37, 18.98. MS (ESI-)  $m/z$  609.4 [M-H<sup>+</sup>] calc. for C<sub>32</sub>H<sub>41</sub>N<sub>2</sub>O<sub>8</sub>Si 609.2.

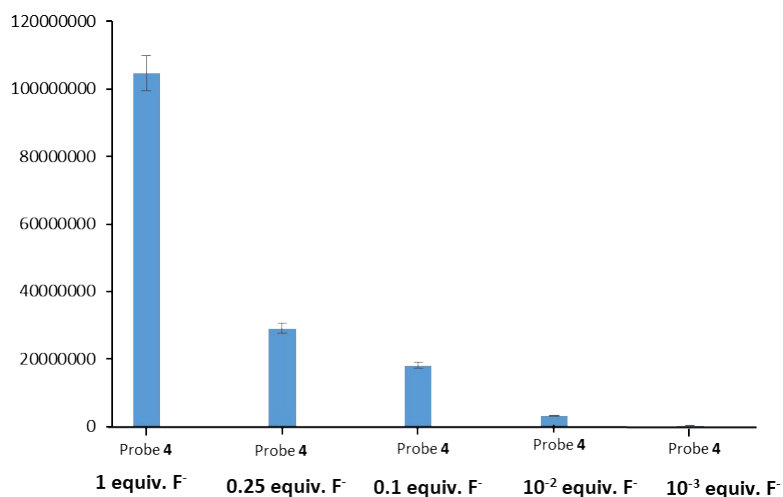
### 3. Chemiluminescence kinetics study

General procedure for chemiluminescent measurement: 1 mM stock solution of the desired compound (**1** and **4**) in DMSO:TEA (99.9:0.1) was prepared. Measurements were done at 200  $\mu$ M concentration in 100  $\mu$ L volume. Several concentrations of TBAF were added to start the kinetic experiment.

General procedure for chemiluminescent selectivity measurement: 1 mM stock solution of compound **1** in DMSO:TEA (99.9:0.1) was prepared. Measurements were done at 200  $\mu$ M concentration of compound **1** in 100  $\mu$ L volume. The appropriate analyte (TBAF, NaF, NaCl, NaBr, NaI, NaNO<sub>3</sub>, NaNO<sub>2</sub> and NaN<sub>3</sub>) was added at final concentration of 200  $\mu$ M and endpoint measurement carried out after 3 min.



**Figure S3:** Chemiluminescence kinetic of the probe **4** (200 mM) with various concentrations of TBAF (0, 0.2, 2, 20, 50 and 200  $\mu$ M) in the presence of 0.1% v/v of TEA in DMSO.



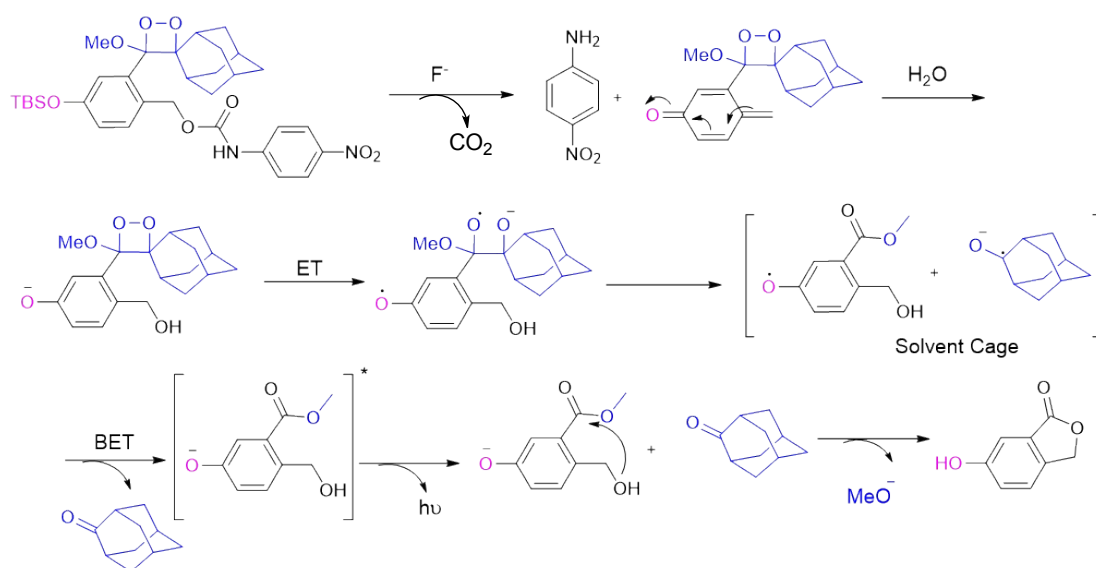
**Figure S4:** Total chemiluminescence produced by probe 4 with indicated concentrations of TBAF in the presence of 0.1% (v/v) TEA in DMSO.

#### 4. <sup>19</sup>F-NMR kinetics study

The reaction of TBAF with the compound **1** was carried out directly in a NMR tube. The kinetic of the reaction was studied by <sup>19</sup>F-NMR spectroscopy.

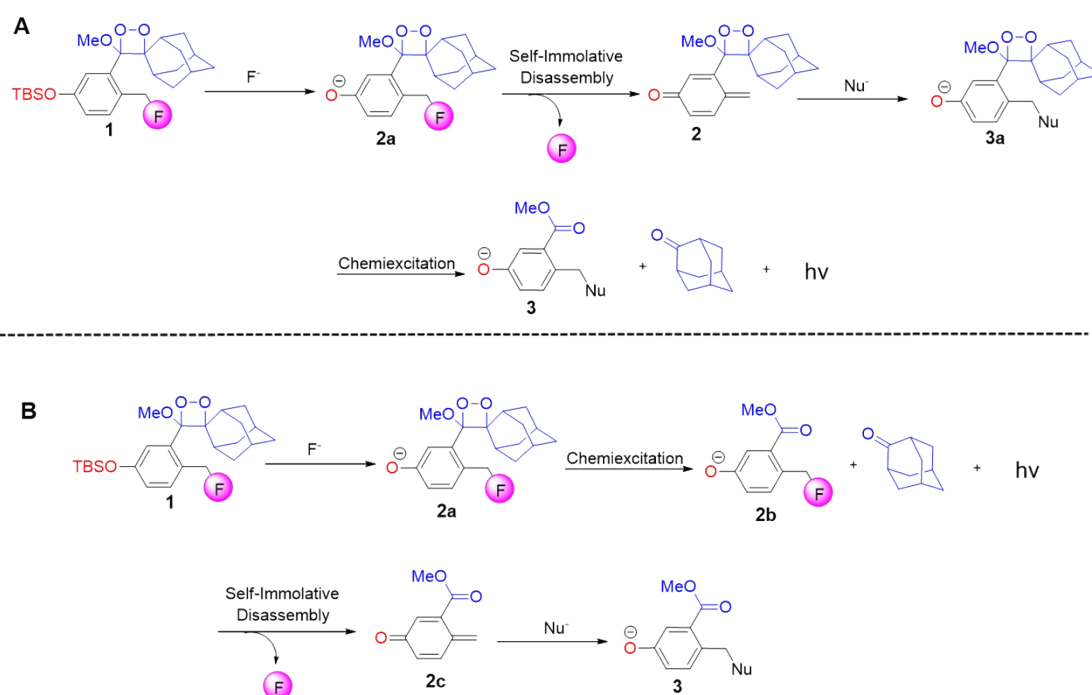
Typical procedure: 5 mg of the appropriate probe **1** was dissolved in NMR tube containing 500  $\mu$ L DMSO-*d*<sub>6</sub> and 0.5  $\mu$ L TEA. 10<sup>-4</sup> equivalent of solid TBAF was dissolved in 100  $\mu$ L of DMSO-*d*<sub>6</sub>, and then added to the compound solution to start the

#### 5. Disassembly mechanism for chemiluminescent probe 4



**Figure S5:** Proposed degradation mechanism of probe **4**. Triggering event initiates the self-immolative disassembly, followed by chemiexcitation processes.

### 6. Possible disassembly mechanisms for chemiluminescent probe **1**



**Figure S6:** Proposed disassembly mechanisms for probe **1**. (A) Triggering event initiates the self-immolative disassembly, following by a chemiexcitation process. (B) Triggering event initiates the chemiexcitation process, following by self-immolative disassembly.

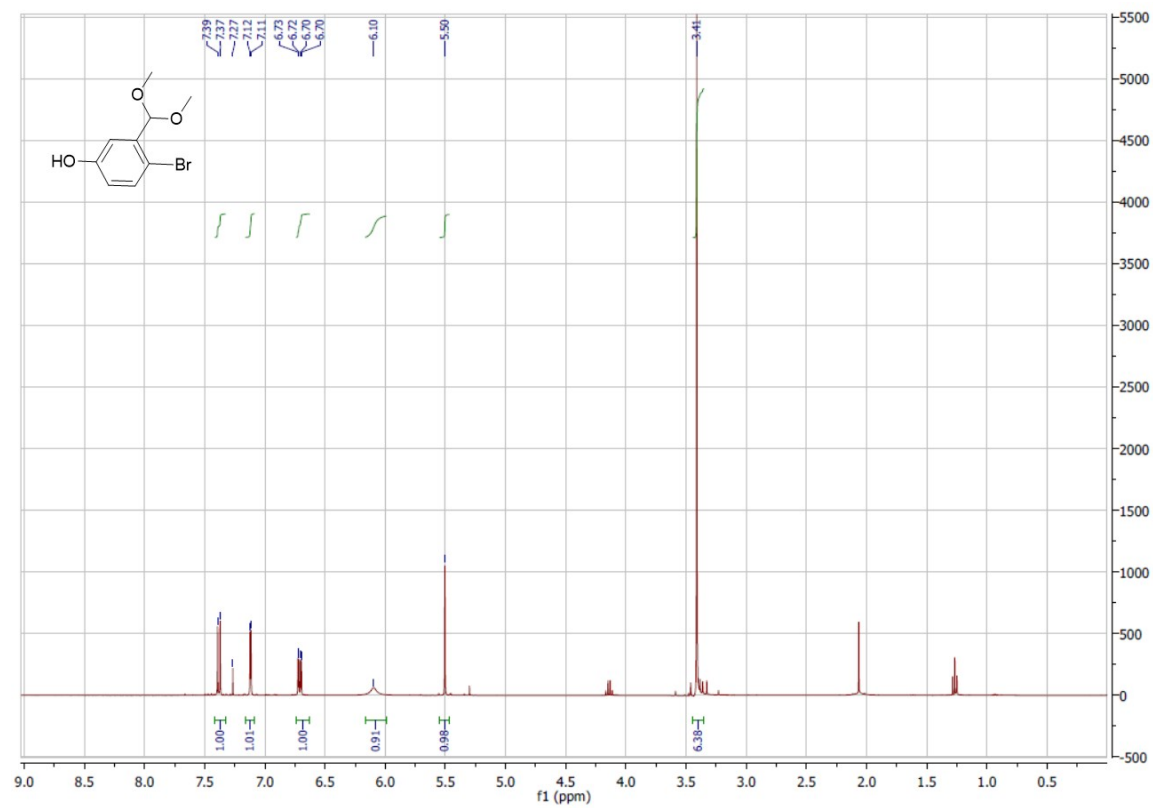
**Mechanism A:** Triggering reaction with fluoride, first initiates the self immolative disassembly to obtain the quinone-methide species **2** and releases fluoride. The monomeric unit **2** reacts with nucleophile, then undergoes chemiexcitation process to produce the benzoate ester **3** and chemiluminescence signal.

**Mechanism B:** Triggering reaction with fluoride, first initiates the chemiexcitation process to produce the appropriate benzoate ester **2b** and chemiluminescence signal. The latter undergoes self-immolative disassembly to obtain the quinone-methide species **2c** and releases fluoride.

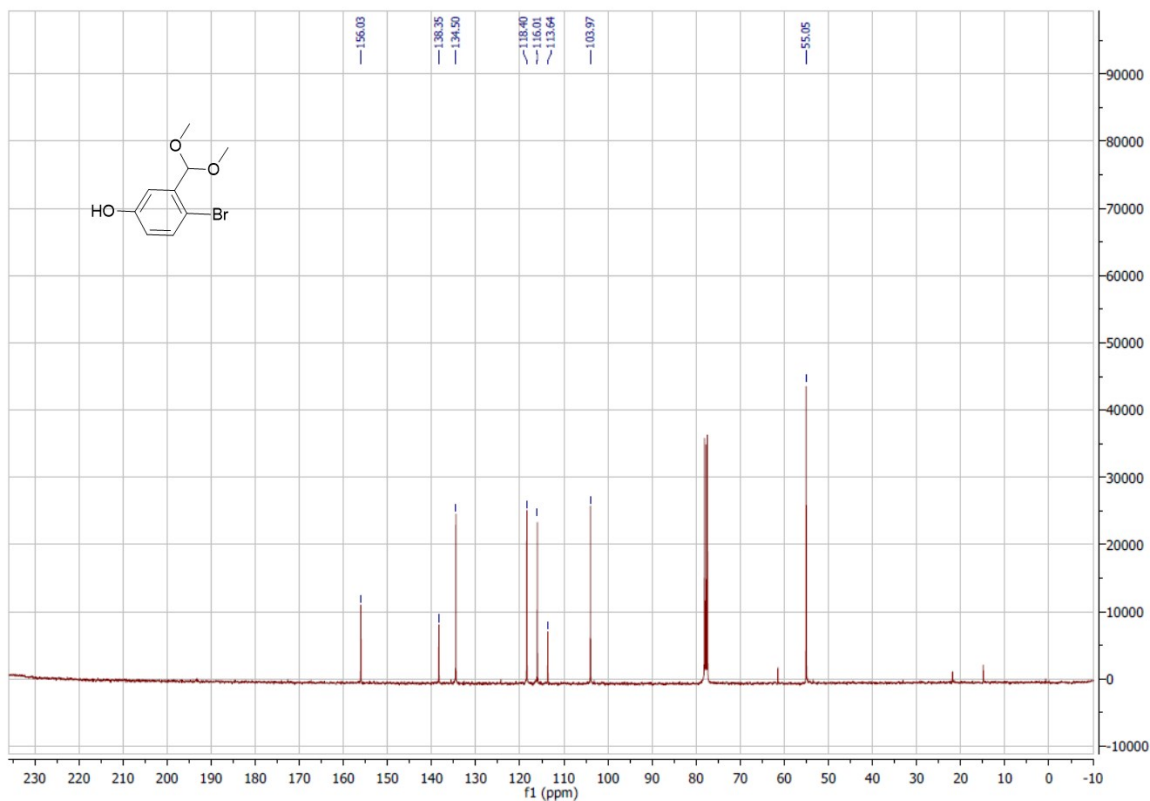
Based on the observed  $^1\text{H-NMR}$  results in our previous publication<sup>1</sup> and the current data of the  $^{19}\text{F-NMR}$  experiment, we believe that there is a substantial indication to support the proposed mechanism **A**.

## 7. $^1\text{H-NMR}$ and $^{13}\text{C-NMR}$ spectra

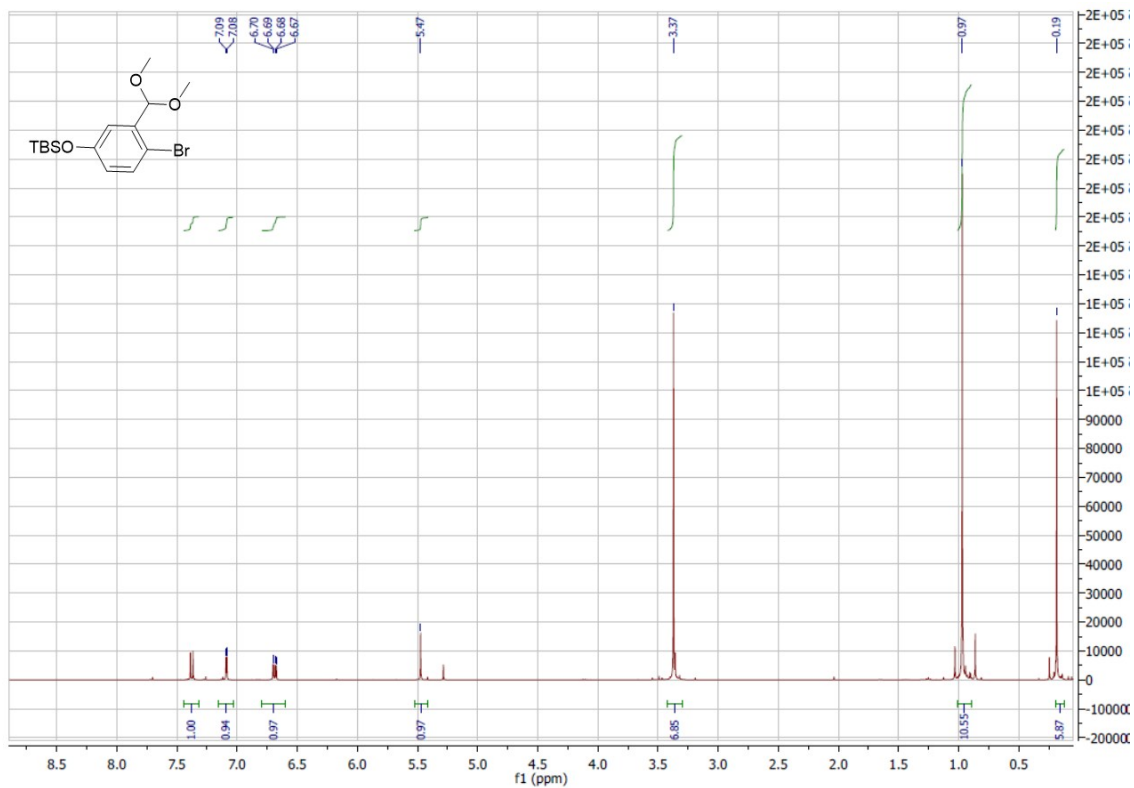
$^1\text{H-NMR}$  Spectrum (400 MHz,  $\text{CDCl}_3$ ) of **1a**:



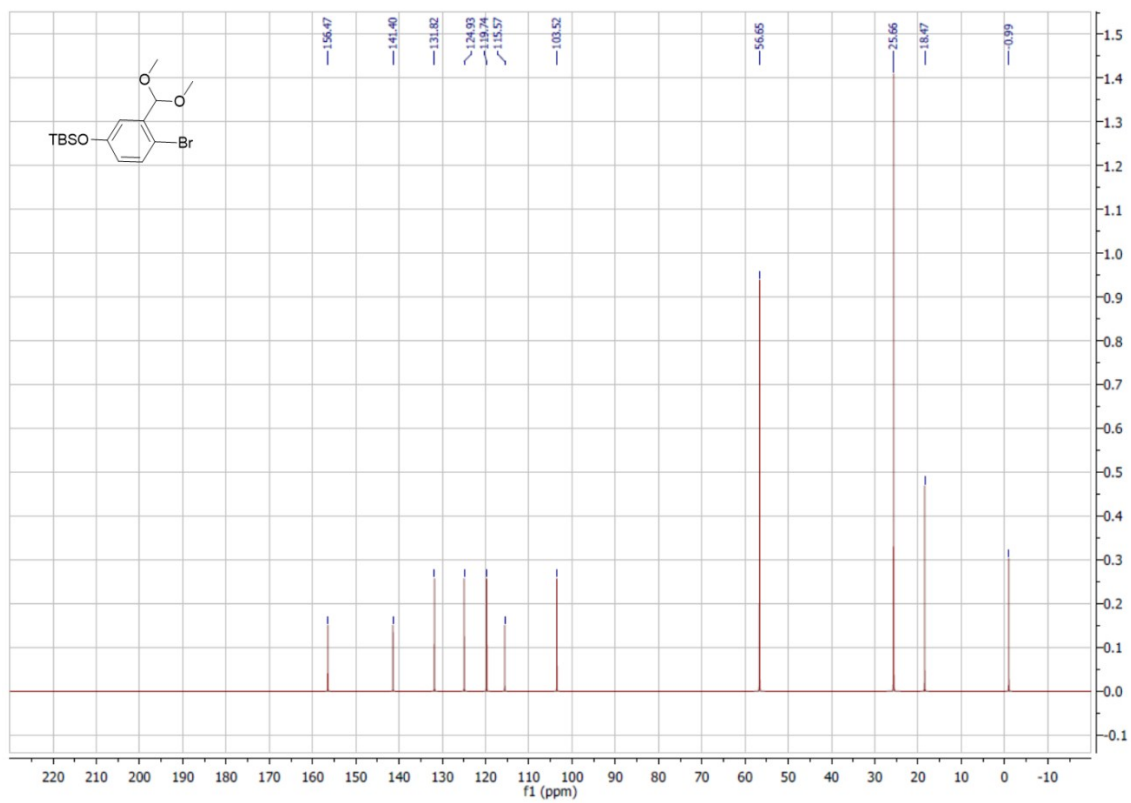
$^{13}\text{C-NMR}$  Spectrum (400 MHz,  $\text{CDCl}_3$ ) **1a**:



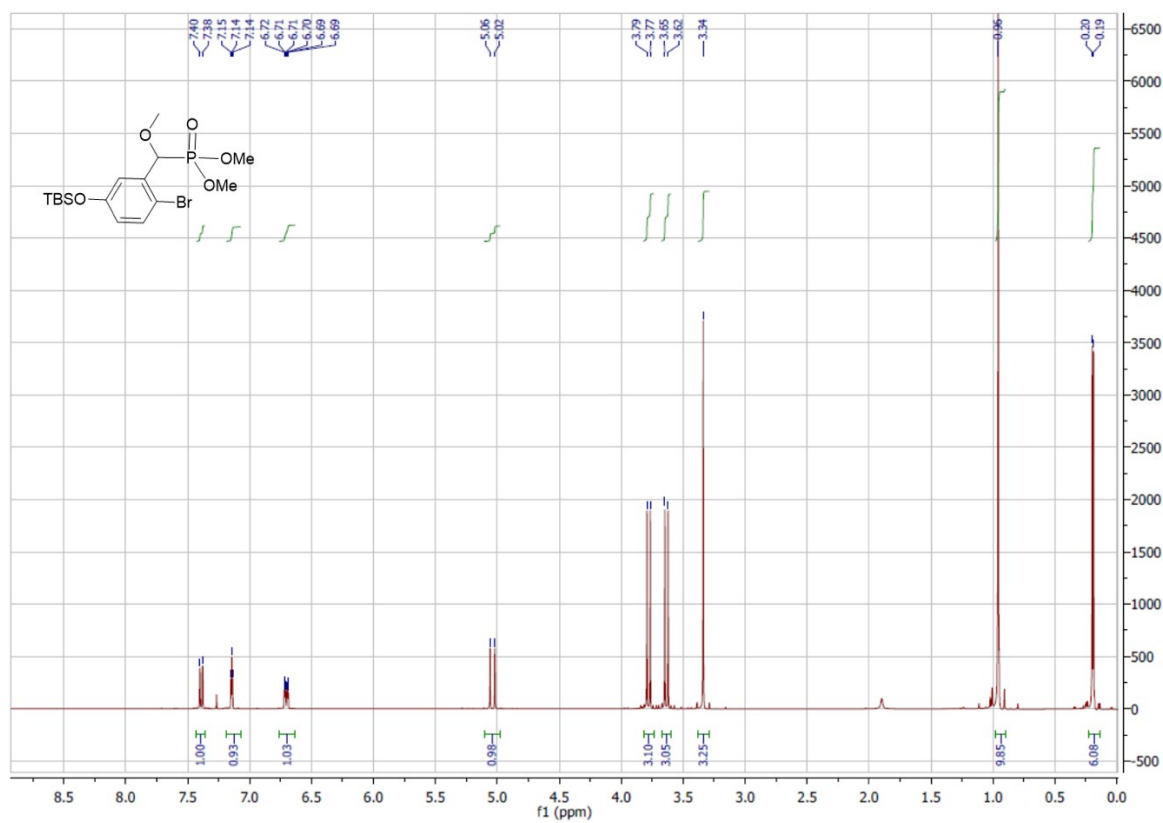
**<sup>1</sup>H-NMR Spectrum (400 MHz, CDCl<sub>3</sub>) of **1b**:**



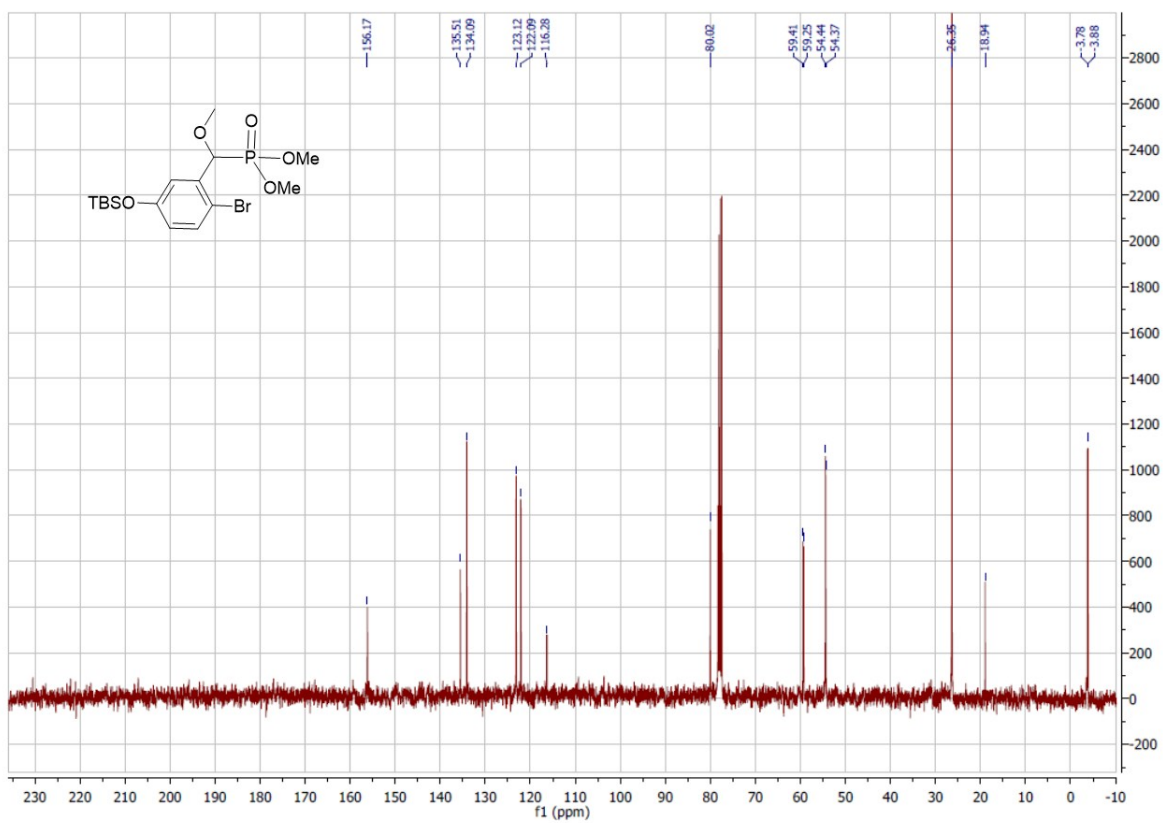
**<sup>13</sup>C-NMR Spectrum (400 MHz, CDCl<sub>3</sub>) of **1b**:**



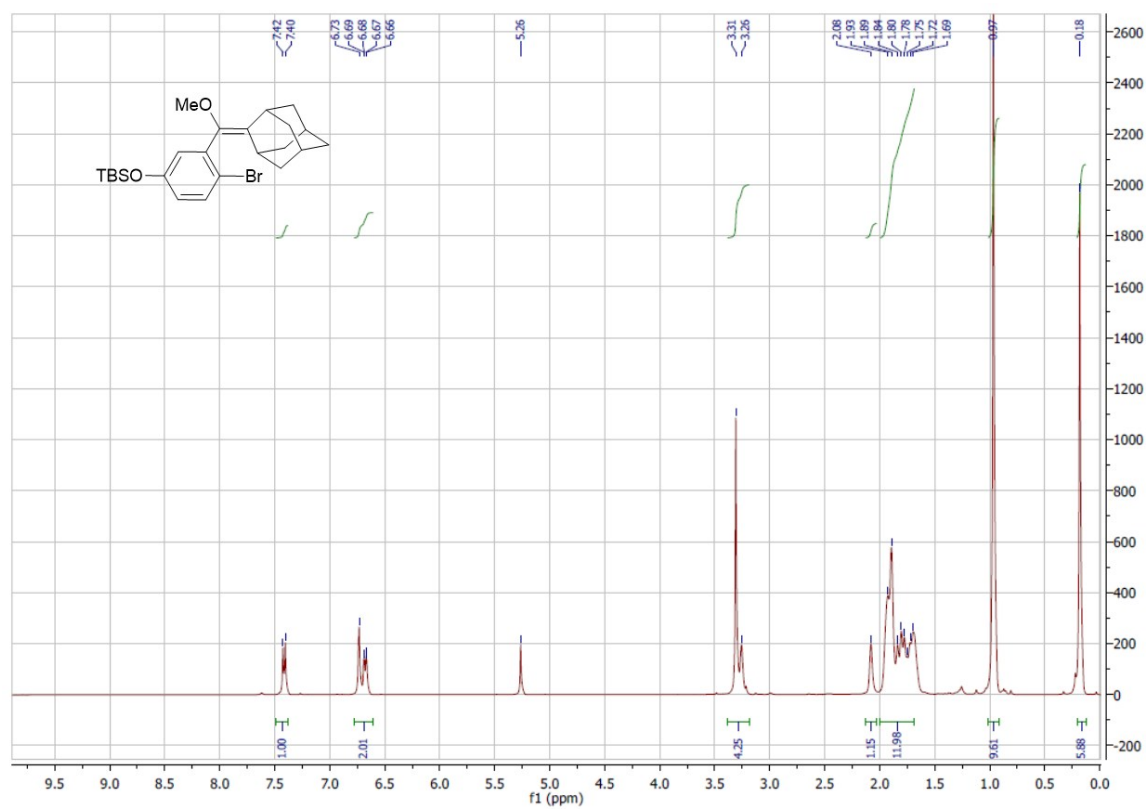
<sup>1</sup>H-NMR Spectrum (400 MHz, CDCl<sub>3</sub>) of **1c**:



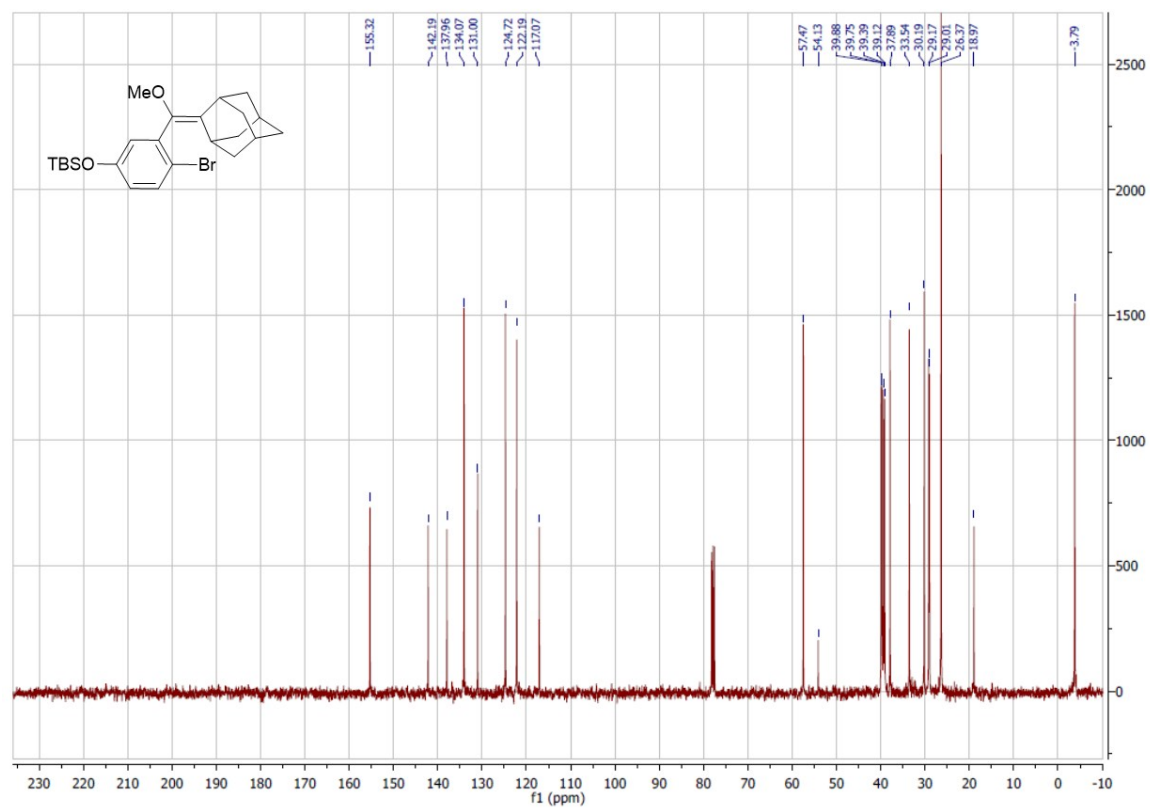
<sup>13</sup>C-NMR Spectrum (400 MHz, CDCl<sub>3</sub>) of **1c**:



$^1\text{H}$ -NMR Spectrum (400 MHz,  $\text{CDCl}_3$ ) of **1d**:

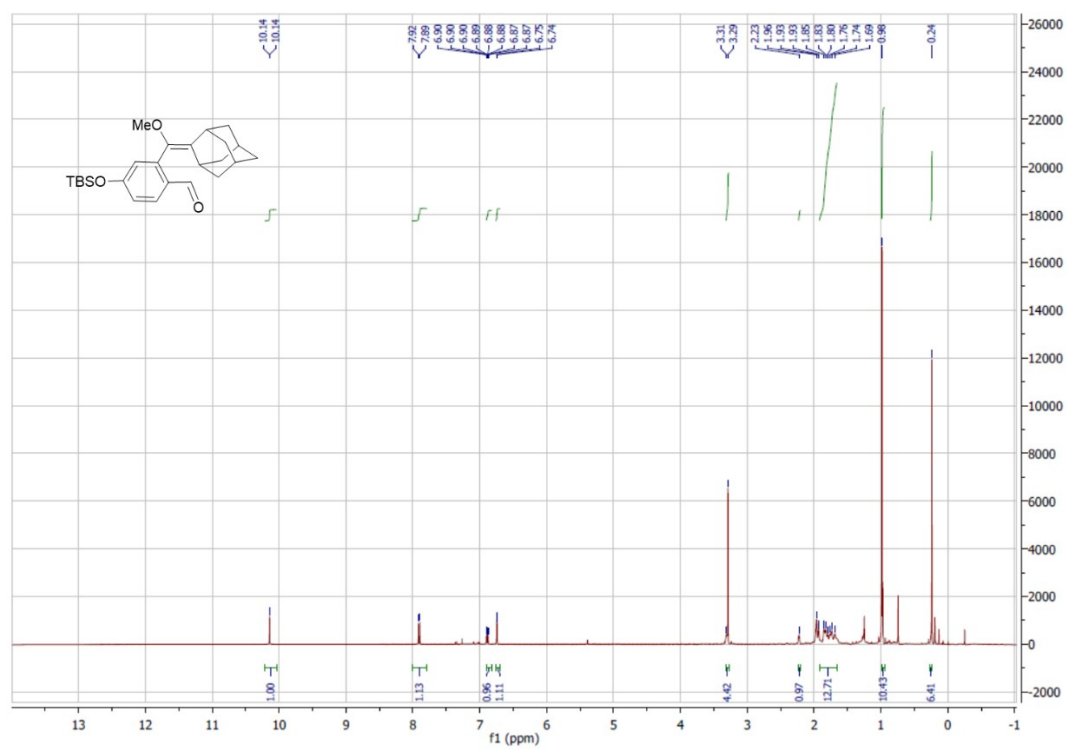


$^{13}\text{C}$ -NMR Spectrum (400 MHz,  $\text{CDCl}_3$ ) of **1d**:

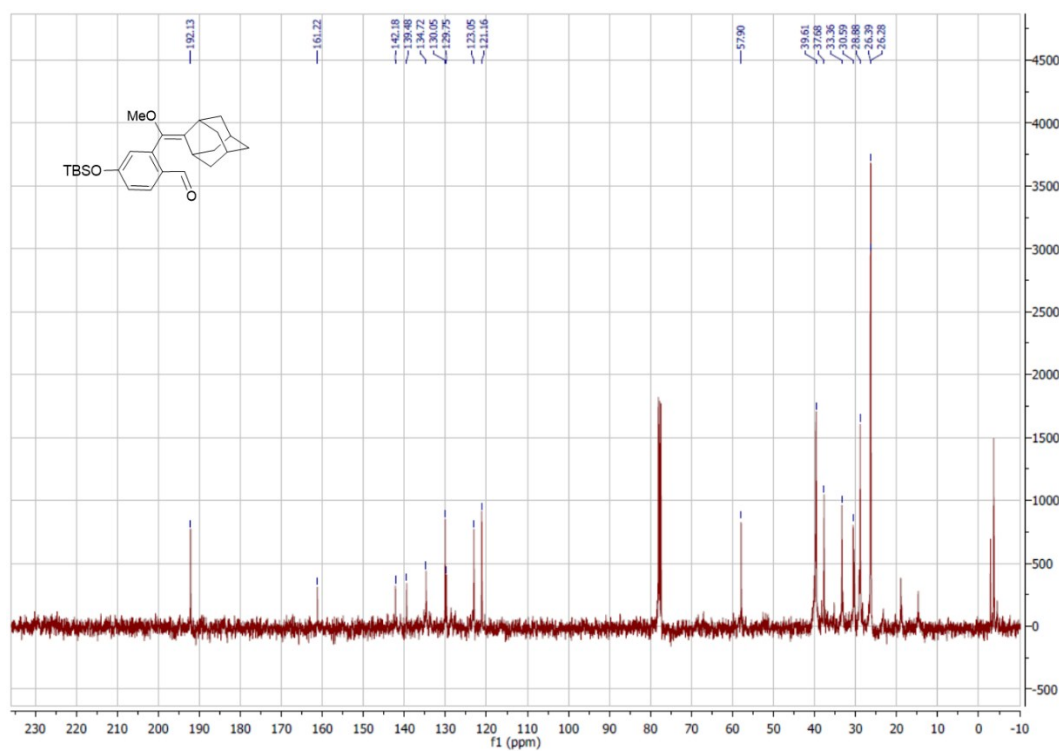




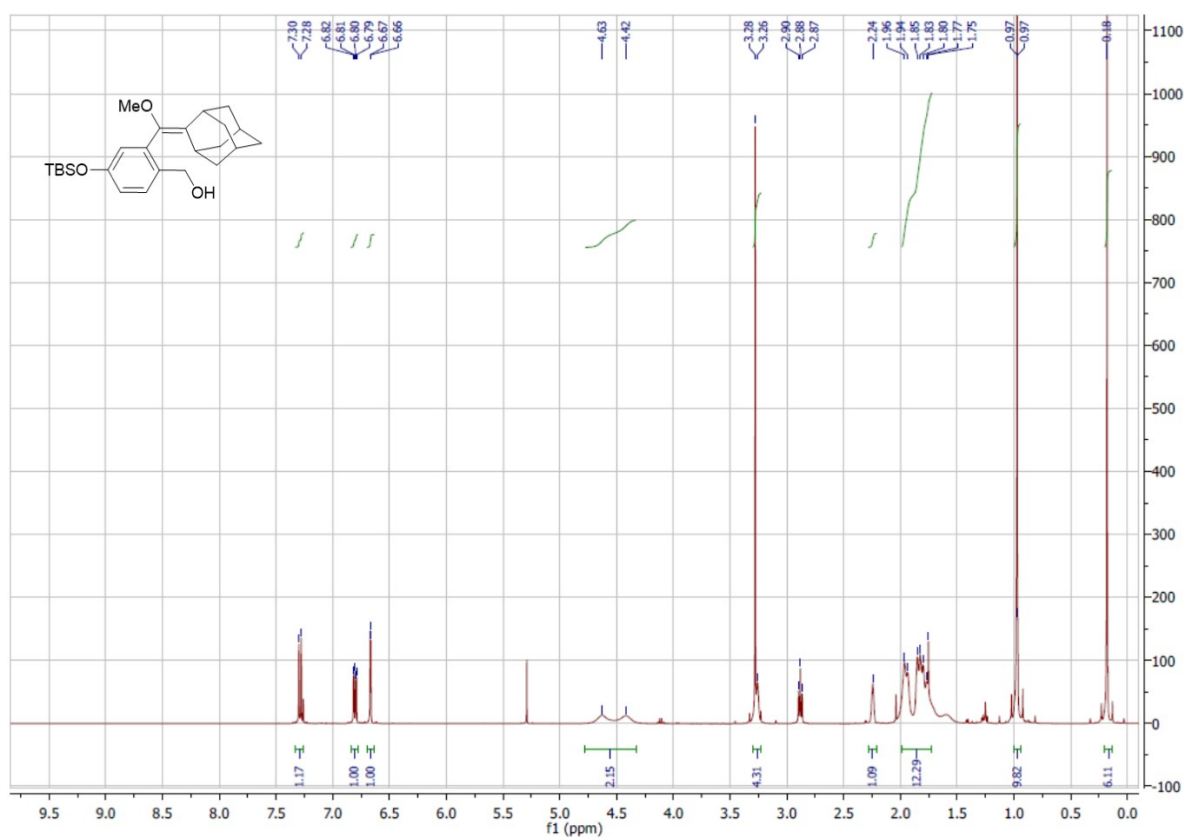
pectrum (400 MHz, CDCl<sub>3</sub>) of **1e**:



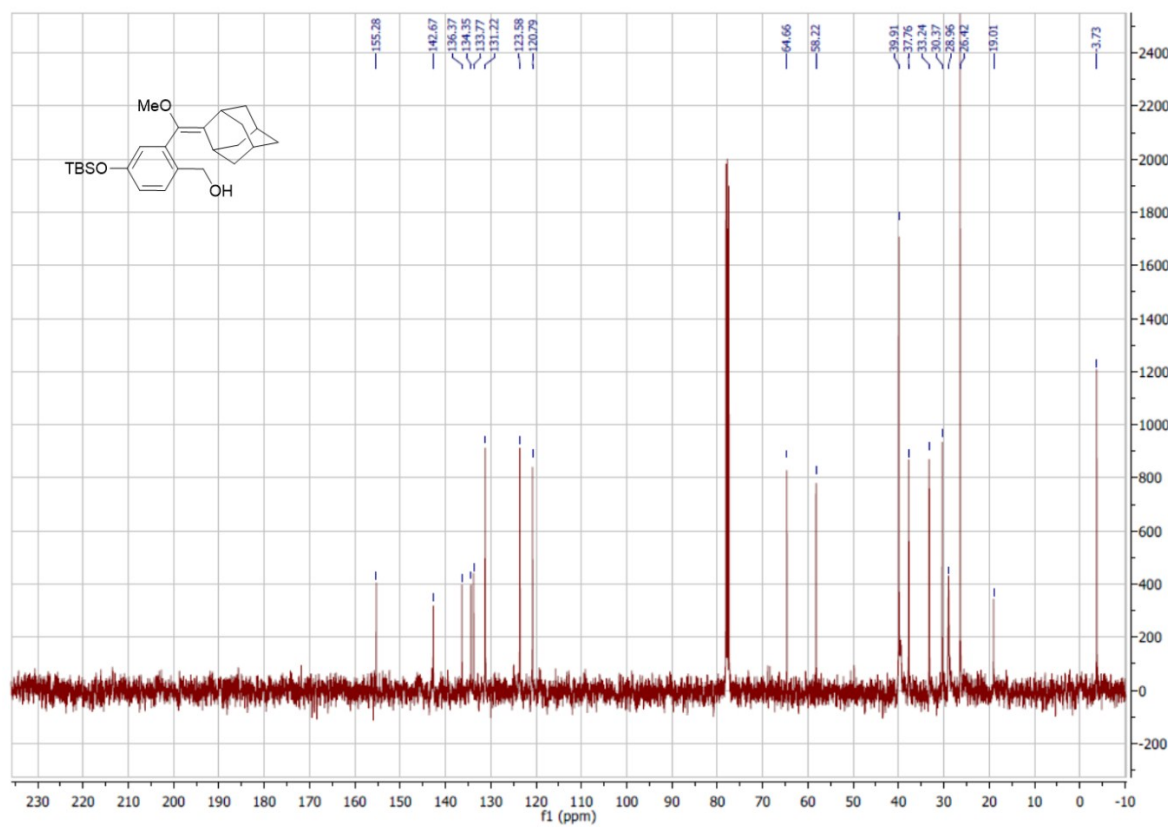
<sup>13</sup>C-NMR Spectrum (400 MHz, CDCl<sub>3</sub>) of **1e**:



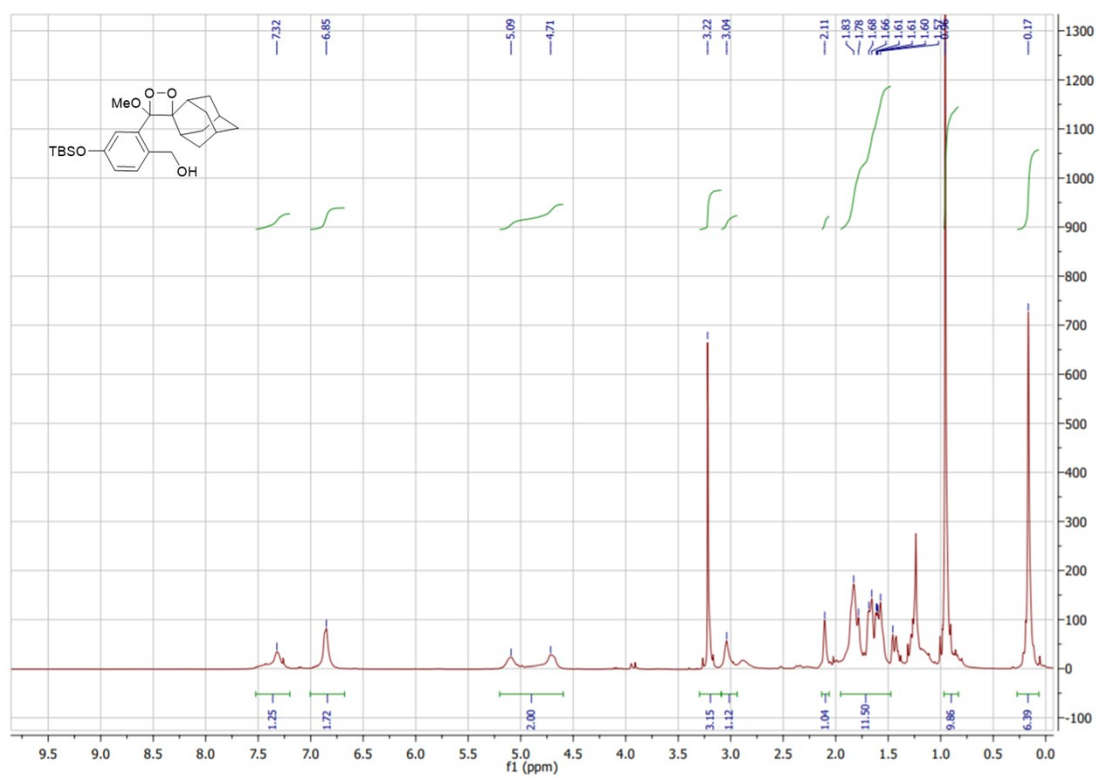
$^1\text{H}$ -NMR Spectrum (400 MHz,  $\text{CDCl}_3$ ) of **1f**:



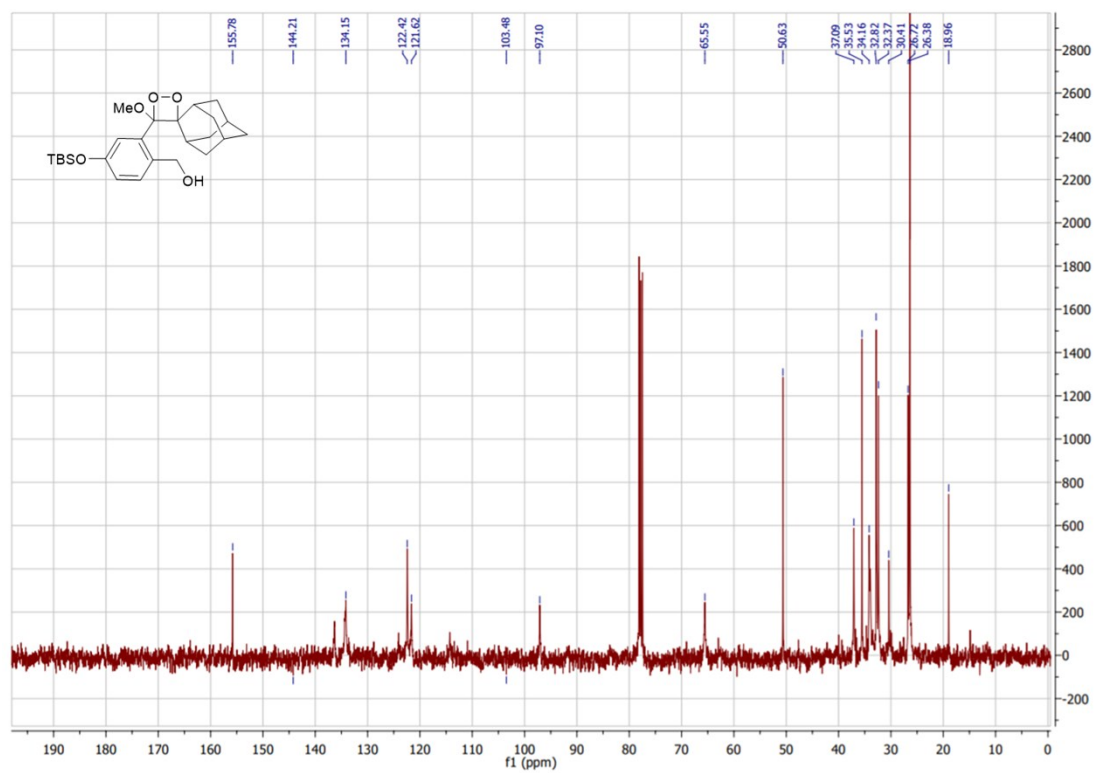
$^{13}\text{C}$ -NMR Spectrum (400 MHz,  $\text{CDCl}_3$ ) of **1f**:



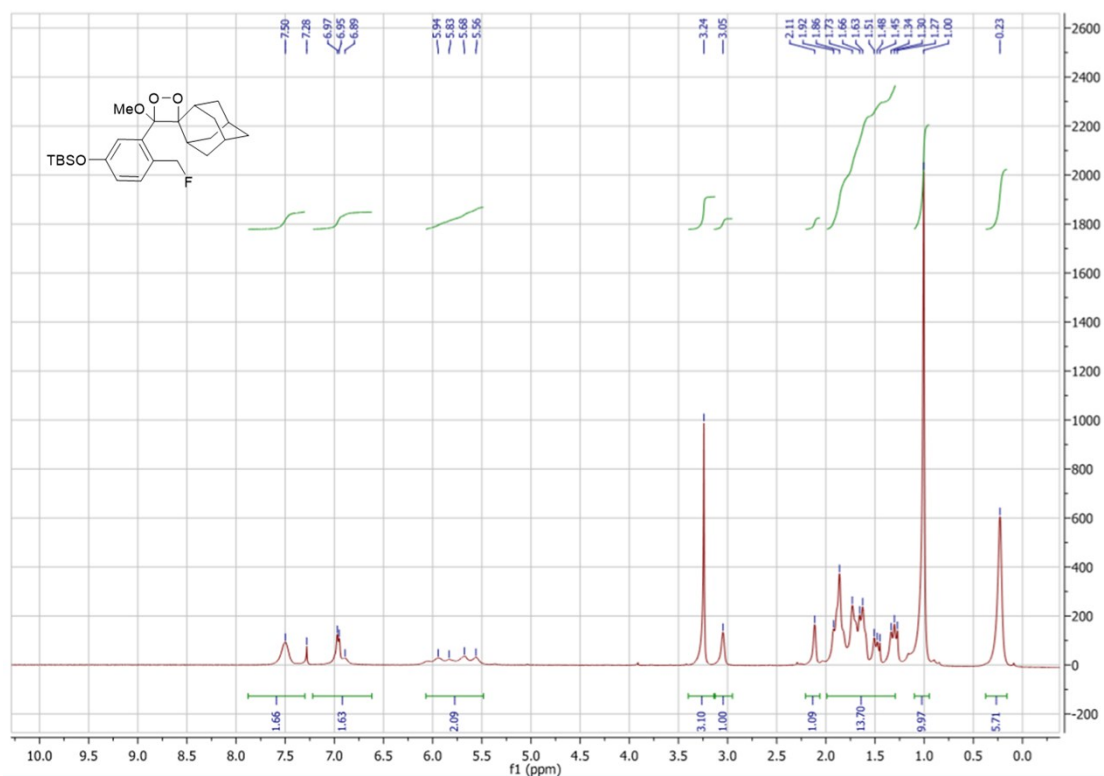
$^1\text{H}$ -NMR Spectrum (400 MHz,  $\text{CDCl}_3$ ) of **1g**:



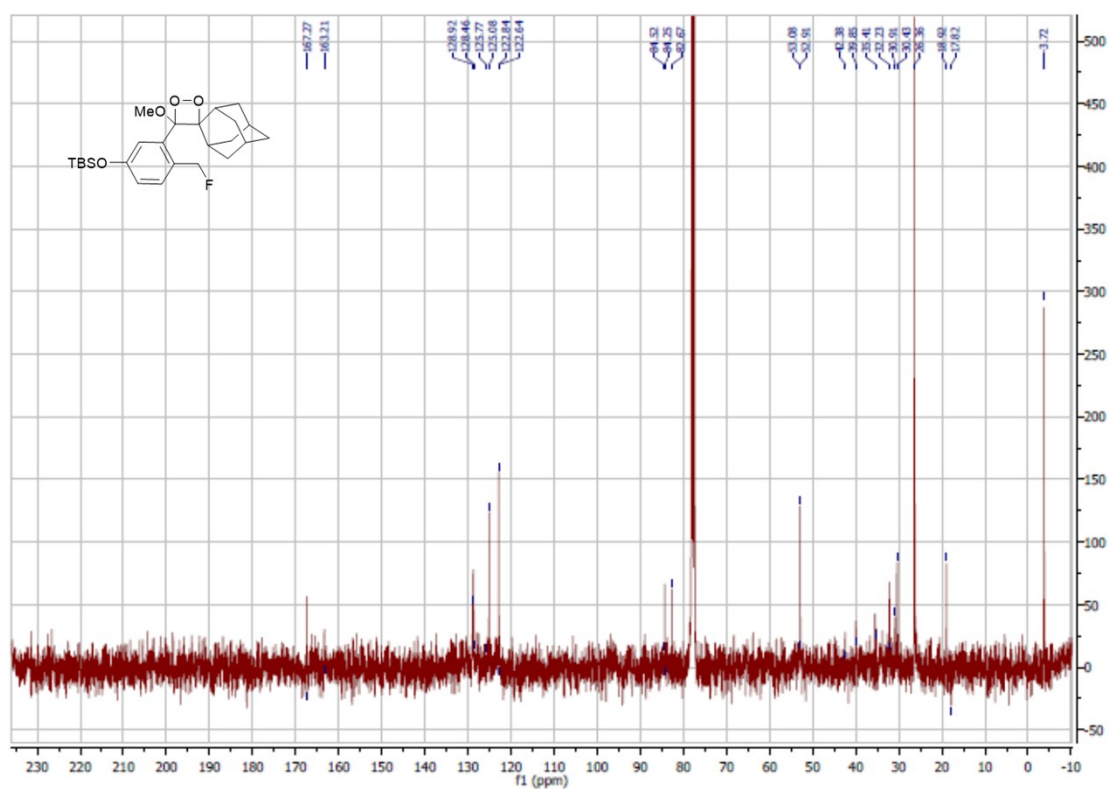
$^{13}\text{C}$ -NMR Spectrum (400 MHz,  $\text{CDCl}_3$ ) of **1g**:



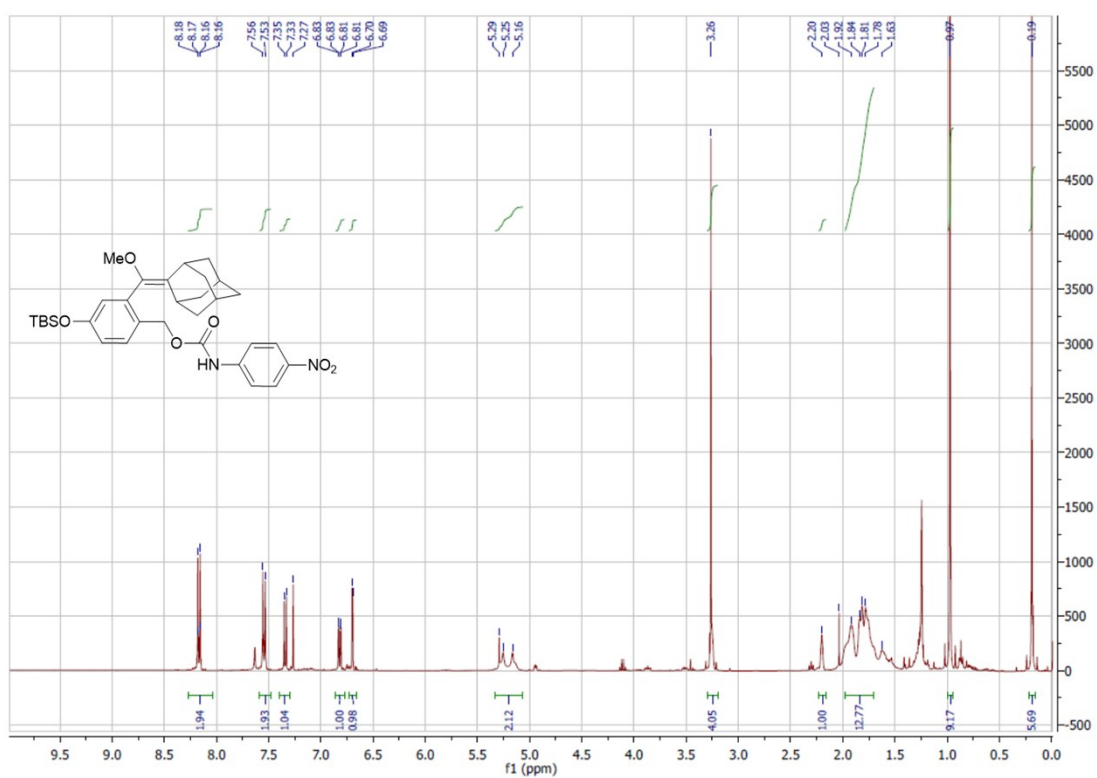
$^1\text{H}$ -NMR Spectrum (400 MHz,  $\text{CDCl}_3$ ) of **1**:



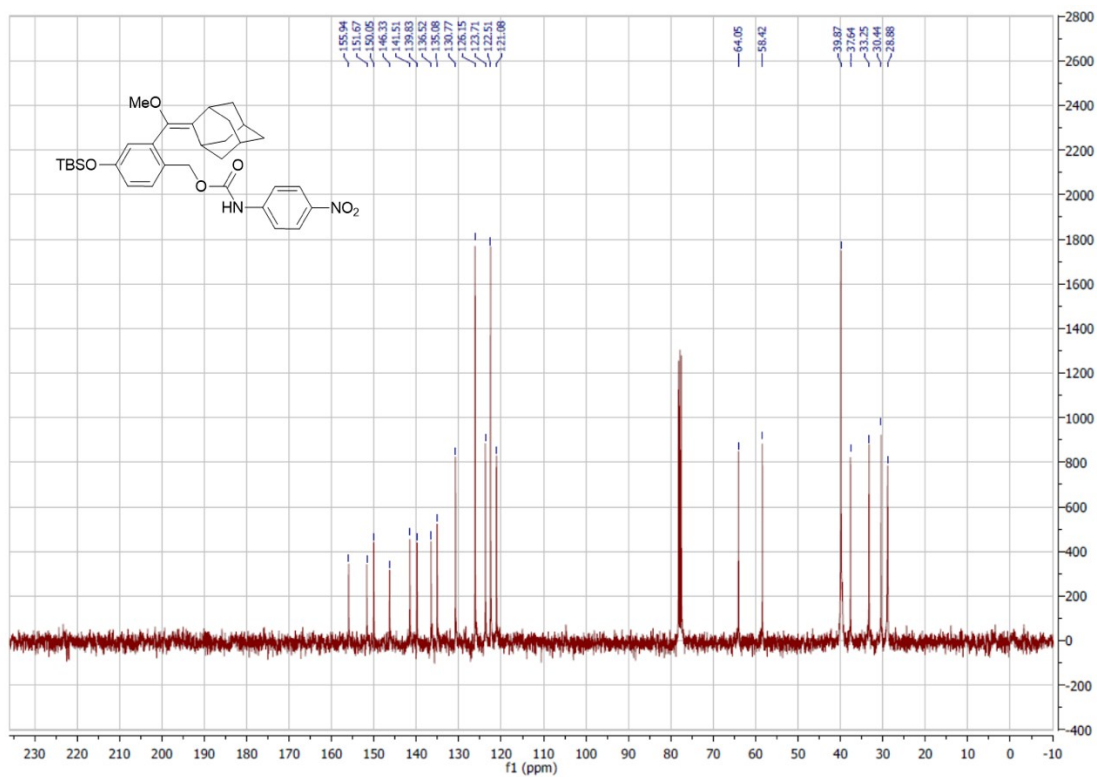
$^{13}\text{C}$ -NMR Spectrum (400 MHz,  $\text{CDCl}_3$ ) of **1**:



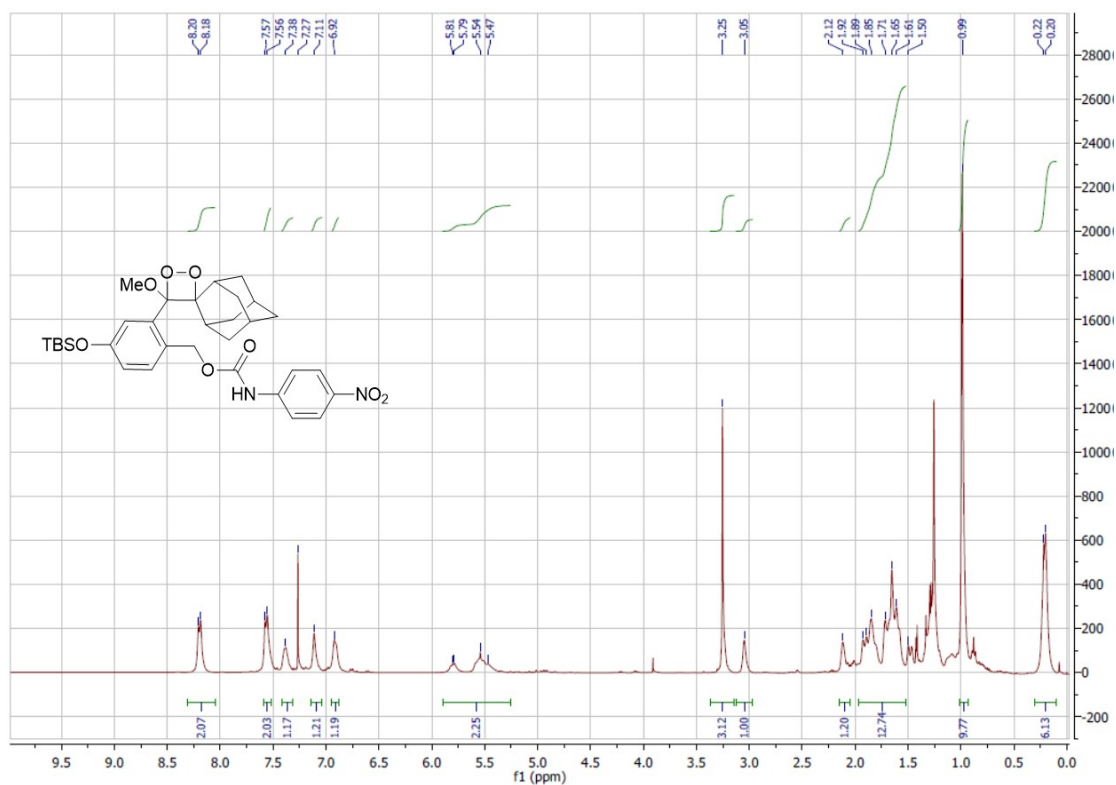
$^1\text{H-NMR}$  Spectrum (400 MHz,  $\text{CDCl}_3$ ) of **4a**:



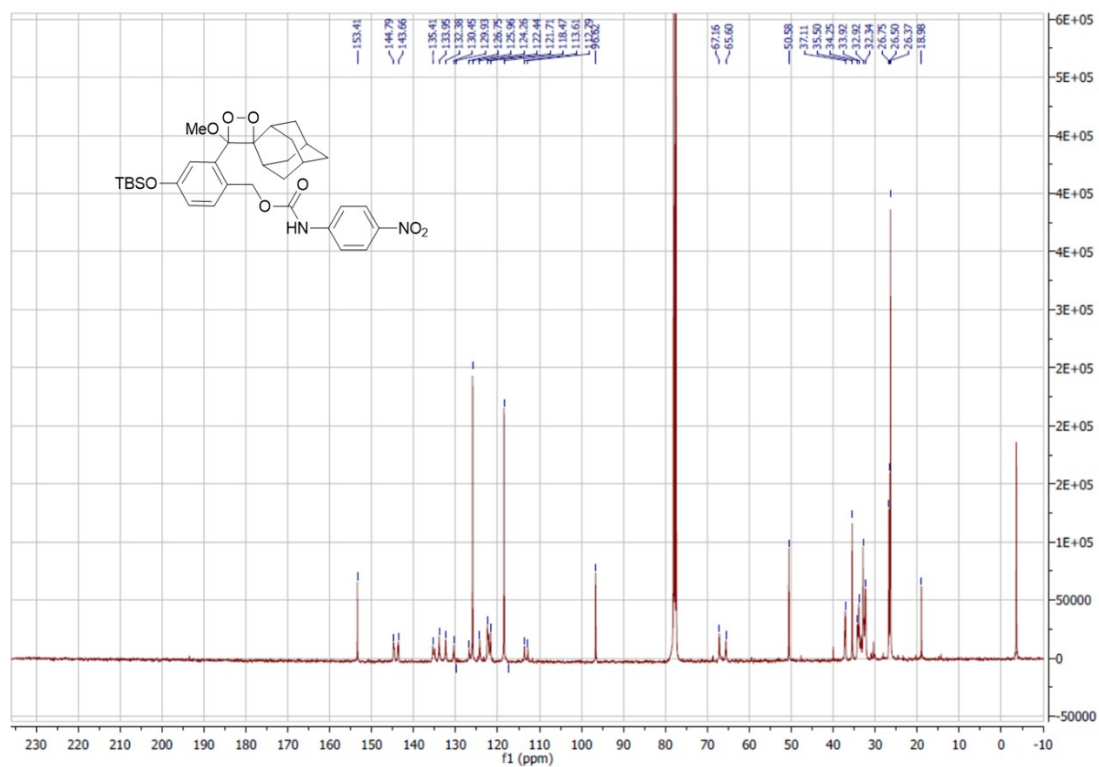
$^{13}\text{C-NMR}$  Spectrum (400 MHz,  $\text{CDCl}_3$ ) of **4a**:



$^1\text{H-NMR}$  Spectrum (400 MHz,  $\text{CDCl}_3$ ) of 4:



$^{13}\text{C-NMR}$  Spectrum (400 MHz,  $\text{CDCl}_3$ ) of 4:



**References:**

- 1) S. Gnaim and D. Shabat, *J. Am. Chem. Soc.*, 2017, **139**, 10002-10008.