

**Asymmetric Synthesis of (+)-17-*Epi*-methoxy-kauran-3-one Through Tandem Oxidative  
Polycyclization-Pinacol Process**

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**Supporting Information**

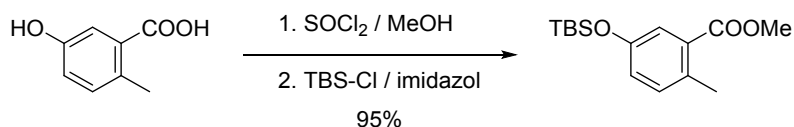
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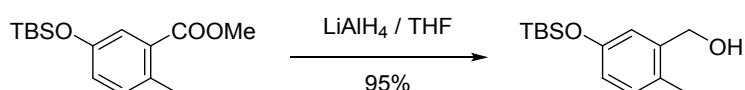
## 1. General information and materials

Unless otherwise indicated,  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra were recorded at 300 and 75 MHz, respectively, in  $\text{CDCl}_3$  solutions. Chemical shifts are reported in ppm on the  $\delta$  scale. Multiplicities are described as s (singlet), d (doublet), dd, ddd, etc. (doublet of doublets, doublet of doublets of doublets, etc.), t (triplet), td (triplet of doublets), q (quartet), p (pentuplet), m (multiplet), and further qualified as app (apparent), br (broad), c (complex). Coupling constants,  $J$ , are reported in Hz. Mass spectra ( $m/e$ ) were measured in the electrospray (ESI) mode.

## 2. Experimental procedures and analytical data

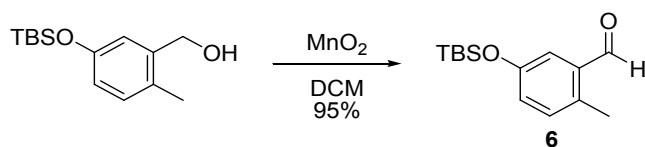


**methyl 5-((tert-butyldimethylsilyl)oxy)-2-methylbenzoate:** To a solution of commercially available 2-methyl-5-hydroxybenzoic acid (5 g, 1.00 eq, 32.87 mmol) in methanol (150 mL) at 0°C was added dropwise  $\text{SOCl}_2$  (5.96 mL, 2.5 eq, 82.18 mmol). The resulting solution was then refluxed for 5h and was cooled to room temperature. Solvent and  $\text{SOCl}_2$  were removed under vacuum to afford crude methyl 3-hydroxy-6-methylbenzoate. The later was dissolved in anhydrous DMF (33 mL) under argon atmosphere and the solution was cooled to 0°C. Imidazole (5.37 g, 2.40 eq, 78.96 mmol) was added, followed by TBS-Cl (5.95 g, 1.20 eq, 39.48 mmol). The solution was stirred for 1h at room temperature. The solution was diluted with  $\text{Et}_2\text{O}$  (100 mL) and sat. aq. NaCl (100 mL) was added. Phases were separated and the organic layer was washed again with sat. aq. NaCl (50 mL), dried over  $\text{Na}_2\text{SO}_4$  and concentrated under vacuum. The residue was purified by flash chromatography (hexanes/ $\text{EtOAc}$ , 3:2) to afford pure methyl 5-((tert-butyldimethylsilyl)oxy)-2-methylbenzoate as a colorless oil (9.13 g, 95%).  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.37 (d,  $J$  = 2.7 Hz, 1H), 7.08 (d,  $J$  = 8.3 Hz, 1H), 6.88 (dd,  $J$  = 8.3, 2.7 Hz, 1H), 3.88 (s, 3H), 2.50 (s, 3H), 0.98 (s, 9H), 0.19 (s, 6H).  $^1\text{H}$  NMR data are in accordance with the literature (PCT Int. Appl., 2006063805, 22 Jun 2006).

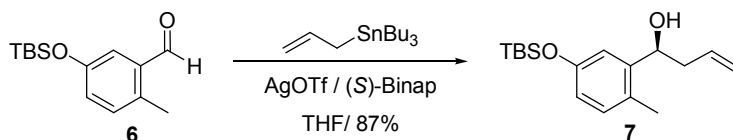


**(5-((tert-butyldimethylsilyl)oxy)-2-methylphenyl)methanol:** To a solution of methyl 5-((tert-butyldimethylsilyl)oxy)-2-methylbenzoate (9.13 g, 1.00 eq, 32.55 mmol) in anhydrous THF (263 mL) at 0°C under argon atmosphere was added  $\text{LiAlH}_4$  (1.87 g, 1.52 eq, 49.35 mmol) by portions. The resulting mixture was allowed to warm to room temperature and was stirred for 5h. The suspension was cooled to 0°C and sat. aq.  $\text{NH}_4\text{Cl}$  (15 mL) was added. The suspension was filtered over silica gel (hexanes/ $\text{EtOAc}$ , 1:1) to remove aluminum derivatives and the filtrate was concentrated under vacuum to afford pure (5-((tert-butyldimethylsilyl)oxy)-2-methylphenyl)methanol as a colorless oil (8.14 g, 95%).  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.11 (d,  $J$  = 8.1 Hz, 1H), 6.97 (d,  $J$  = 2.6 Hz, 1H), 6.78 (dd,  $J$  = 8.1, 2.6

Hz, 1H), 4.73 (s, 2H), 2.36 (s, 3H), 1.08 (s, 9H), 0.29 (s, 6H).  $^1\text{H}$  NMR data are in accordance with the literature (PCT Int. Appl., 2006063805, 22 Jun 2006).

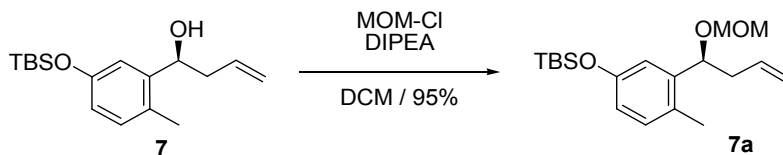


**5-((tert-butyldimethylsilyl)oxy)-2-methylbenzaldehyde (6).** To a solution of (5-((tert-butyldimethylsilyl)oxy)-2-methylphenyl)methanol (8.14 g, 1.00 eq, 32.24 mmol) in anhydrous DCM (322 mL) at room temperature under argon atmosphere in presence of molecular sieve was added activated  $\text{MnO}_2$  (85%, 24.7 g, 7.50 eq, 242 mmol). The resulting mixture was stirred at room temperature for 48h and was then filtered over silica gel (EtOAc) to remove  $\text{MnO}_2$  and molecular sieve. Solvent were removed under vacuum to afford pure 5-((tert-butyldimethylsilyl)oxy)-2-methylbenzaldehyde **6** as an orange oil (8.00 g, 95%).  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  10.22 (s, 1H), 7.26 (d,  $J$  = 2.6 Hz, 1H), 7.12 (d,  $J$  = 8.2 Hz, 1H), 6.97 (dd,  $J$  = 8.2, 2.7 Hz, 1H), 2.59 (s, 3H), 0.99 (s, 9H), 0.21 (s, 6H).  $^1\text{H}$  NMR data are in accordance with the literature (PCT Int. Appl., 2006063805, 22 Jun 2006).



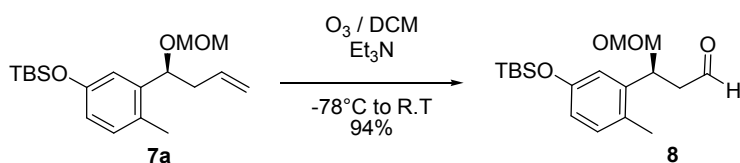
**(S)-1-(5-((tert-butyldimethylsilyl)oxy)-2-methylphenyl)but-3-en-1-ol (7).** A mixture of AgOTf (150 mg, 0.05 eq, 0.58 mmol) and (*S*)-Binap (364 mg, 0.05 eq, 0.58 mmol) was stirred in dry THF (18 mL) under argon atmosphere and exclusion of direct light at room temperature for 10 min. To the resulting solution was added a solution of aldehyde **11** (2928 mg, 1.00 eq, 11.69 mmol) in dry THF (18 mL) and allyltributyltin (3.81 mL, 1.05 eq, 12.28 mmol) was added dropwise at  $-20^\circ\text{C}$ . The mixture was stirred for 12 hours at this temperature and then a solution of 40 mL of sat. aq.  $\text{NH}_4\text{Cl}$  was added. The aqueous phase was extracted with EtOAc (3 \* 25 mL) and the combined organic layers were washed with sat. aq. NaCl, dried over  $\text{Na}_2\text{SO}_4$  and concentrated under reduced pressure. The crude product was purified by flash chromatography (hexanes/EtOAc, 95:5) to afford 2.98 g (87%) of the desired compound **7** as a yellow oil.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  = 7.05 – 6.92 (m, 2H), 6.66 (dd,  $J$ =8.2, 2.6, 1H), 5.85 (ddt,  $J$ =17.1, 10.1, 7.1, 1H), 5.17 (m, 2H), 4.91 (dd,  $J$ =8.0, 4.5, 1H), 2.55 – 2.32 (m, 2H), 2.25 (s, 3), 0.99 (s, 9H), 0.19 (s, 6H) ;  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  = 154.13, 143.20,

134.76, 131.21, 126.90, 118.81, 118.31, 117.03, 69.71, 42.62, 25.80, 18.30, -4.33, -4.36; **HRMS** (ESI): Calc. for  $C_{17}H_{28}O_2Si$  ( $M+H - [H_2O]^+$ ) : 275.1826, found : 275.1821;  $[\alpha]_D$  (25°C, c = (12.2 mg/ 2mL),  $CH_2Cl_2$ ) = -33.2°.



**(S)-tert-butyl(3-(1-(methoxymethoxy)but-3-en-1-yl)-4-methylphenoxy)dimethylsilane**

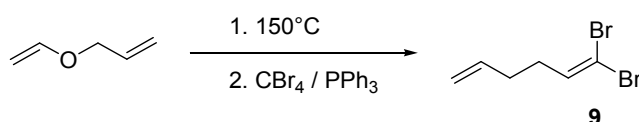
**(7a).** To a solution of compound **7** (6 g, 1.00 eq, 20.50 mmol) in dry  $CH_2Cl_2$  (80 mL) at 0°C was added Hunig's base (10.71 mL, 3.00 eq, 61.50 mmol) followed by chloromethyl methyl ether (9.34 mL, 6.00 eq, 123 mmol). The mixture was stirred at room temperature for 4 hours and then a solution of sat. aq.  $NaHCO_3$  (50 mL) was added. The aqueous phase was extracted with DCM (3 \* 60 mL) and the combined organic layers were washed with sat. aq. NaCl, dried over  $Na_2SO_4$  and concentrated under reduced pressure. The crude product was purified by flash chromatography (hexanes/EtOAc, 95:5) to afford 6.9 g (95%) of the desired protected compound **7a** as a yellow oil. **<sup>1</sup>H NMR** (300 MHz,  $CDCl_3$ )  $\delta$  = 6.95 - 6.67 (m, 2H), 5.86 (ddt,  $J$ =17.1, 10.1, 7.0, 1H), 5.10 (m, 1H), 4.87 (dd,  $J$ =8.0, 5.1, 1H), 4.52 (m, 2H), 3.37 (s, 3H), 2.60 – 2.35 (m, 2H), 2.25 (s, 3H), 1.00 (s, 9H), 0.20 (s, 6H); **<sup>13</sup>C NMR** (75 MHz,  $CDCl_3$ )  $\delta$  = 154.06, 140.94, 134.97, 131.15, 128.10, 119.11, 117.85, 117.08, 94.05, 73.62, 55.54, 41.60, 25.81, 18.37, 18.31, -4.38; **HRMS** (ESI): Calc. for  $C_{19}H_{32}O_3Si$  ( $M+H - [H_2O]^+$ ) : 319.2088, found : 319.2094;  $[\alpha]_D$  (25°C, c = (27.2 mg/ 2mL),  $CH_2Cl_2$ ) = -116.9°.



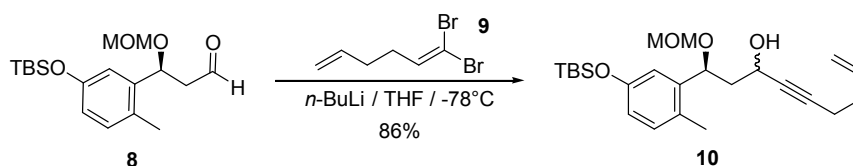
**(S)-3-(5-((tert-butyldimethylsilyl)oxy)-2-methylphenyl)-3-(methoxymethoxy)propanal**

**(8).** To a solution of **7a** (8.39 g, 1.00 eq, 24.95 mmol) in DCM (705 mL) at -78°C was performed an ozonolysis. The resulting solution was degazed with  $N_2$  and  $Et_3N$  (16.83 mL, 5.00 eq, 124.77 mmol) was added. The mixture was stirred at room temperature for 2 hours and a solution of sat. aq.  $NH_4Cl$  (200mL) was added. The aqueous phase was extracted with DCM (3 \* 75 mL) and the combined organic layers were washed with sat. aq. NaCl, dried over  $Na_2SO_4$  and concentrated under reduced pressure. The residue was filtrated on a plug of silica gel (hexanes/EtOAc, 4:1) and concentrated under reduced pressure to afford 7.9 g

(94%) of the desired compound **8** as a yellow oil. **<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>)  $\delta$  = 9.80 (dd,  $J$ =2.6, 1.3, 1H), 6.96 (d,  $J$ =8.2, 1H), 6.88 (d,  $J$ =2.6, 1H), 6.64 (dt,  $J$ =6.5, 3.2, 1H), 5.35 (dd,  $J$ =9.5, 3.6, 1H), 4.48 (s, 2H), 3.32 (s, 3H), 2.80-2.78 (m, 1H), 2.57 (ddd,  $J$ =16.5, 3.5, 1.2, 1H), 2.24 (s, 3H), 0.95 (s, 9H), 0.15 (s, 6H) ; **<sup>13</sup>C NMR** (75 MHz, CDCl<sub>3</sub>)  $\delta$  = 200.30, 154.22, 139.36, 131.55, 127.80, 119.55, 117.69, 94.01, 68.97, 55.80, 50.21, 25.72, 18.23, 18.12, -4.44; **HRMS** (ESI): Calc. for C<sub>18</sub>H<sub>30</sub>O<sub>4</sub>Si (M+NH<sub>4</sub>)<sup>+</sup> : 356.2252, found : 356.2238 ; [ $\alpha$ ]<sub>D</sub> (25°C, c = (16.4 mg/ 2mL), CH<sub>2</sub>Cl<sub>2</sub>) = -132.2°.

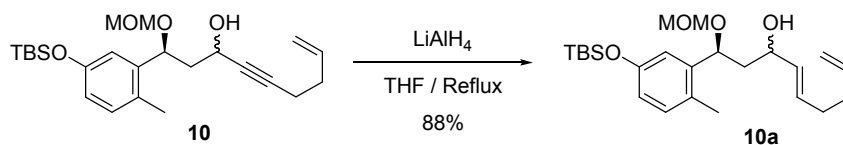


**1,1-dibromohexa-1,5-diene (9).** Allyl vinyl ether (956.6 mg, 1.00 eq, 11.4 mmol) was stirred in a sealed tube at 150°C for 24 hours. The resulting product was used without further purification. To a solution of anhydrous carbon tetrabromide (7.54 g, 2.00 eq, 22.8 mmol) in anhydrous DCM (11 mL) at 0°C was added PPh<sub>3</sub> (11.93 g, 4.00 eq, 45.5 mmol) by portions. After 30 minutes, the above crude aldehyde was added dropwise to the mixture. After stirring for 2 hours at room temperature, the resulting mixture was quenched by a slow addition of sat. aq. NH<sub>4</sub>Cl (15 mL). The mixture was filtrated over silica gel (hexanes/EtOAc, 93:7) and concentrated under reduced pressure to afford 2.15 g (79%) of the desired compound **9**. **<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>)  $\delta$  = 6.45 – 6.34 (m, 1H), 5.89 – 5.70 (m, 1H), 5.11 – 4.99 (m, 2H), 2.28 – 2.12 (m, 4H); **<sup>13</sup>C NMR** (75 MHz, CDCl<sub>3</sub>)  $\delta$  = 138.03, 137.01, 115.93, 89.20, 32.42, 31.89.

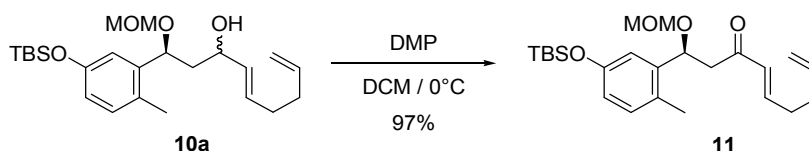


**(1S)-1-(5-((tert-butyldimethylsilyl)oxy)-2-methylphenyl)-1-(methoxymethoxy)non-8-en-4-yn-3-ol (10).** To a solution of 1,1-dibromohexa-1,5-diene **9** (10.4 g, 1.87 eq, 43.7 mmol) in dry THF (119 mL) at -78°C under argon atmosphere was added *n*-BuLi (35 mL at 2.5 M, 3.74 eq, 87.37 mmol). The solution was stirred for 30 minutes and a solution of aldehyde **8** (7.9 g, 1.00 eq, 23.36 mmol) in dry THF (33 mL) was added dropwise at -78°C. The mixture was stirred for 8 hours at this same temperature and then a solution of 50 mL of sat. aq. NH<sub>4</sub>Cl was added. The aqueous phase was extracted with EtOAc (3 \* 50 mL) and the combined

organic layers were washed with sat. aq. NaCl, dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure. The crude product was purified by flash chromatography (hexanes/EtOAc, 85:15) to afford 8.37 g (86%) of the desired propargylic alcohol **10** as a yellow oil as a diastereoisomeric mixture (2/3). **HRMS** (ESI): Calc. for C<sub>24</sub>H<sub>38</sub>O<sub>4</sub>Si (M+Na)<sup>+</sup>: 441.2437, found : 441.2431.



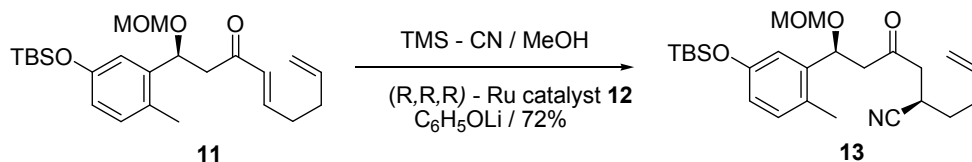
**(1S,E)-1-(5-((tert-butyldimethylsilyl)oxy)-2-methylphenyl)-1-(methoxymethoxy)nona-4,8-dien-3-ol (10a)**. To a solution of **10** (1.89 g, 1.00 eq, 4.51 mmol) in anhydrous THF (45 mL) was added LiAlH<sub>4</sub> (428 mg, 2.50 eq, 11.27 mmol) by portions. The solution was refluxed for 1 hour and sat. aq. NH<sub>4</sub>Cl (5 mL) was added at 0°C. The slurry solution was filtered over celite (EtOAc) and the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography (hexanes/EtOAc, 85:15) to afford 1.67 g (88%) of the desired *trans* alkene **10a** as a yellow oil as a diastereoisomeric mixture (2/3). **HRMS** (ESI): Calc. for C<sub>24</sub>H<sub>40</sub>O<sub>4</sub>Si (M+Na)<sup>+</sup> : 443.2594, found : 443.2587.



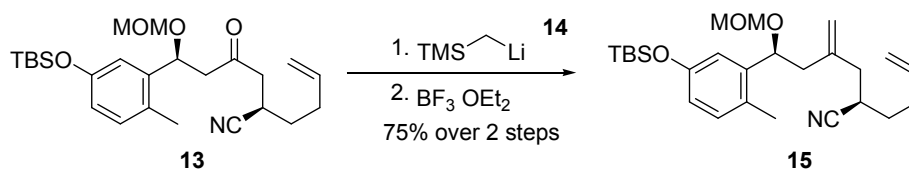
**(S,E)-1-(5-((tert-butyldimethylsilyl)oxy)-2-methylphenyl)-1-(methoxymethoxy)nona-4,8-dien-3-one (11)**. To a solution of alcohol mixture **10a** (4.21 g, 1.00 eq, 10.00 mmol) in dry CH<sub>2</sub>Cl<sub>2</sub> (100 mL) at 0°C was added Dess-Martin periodinane (10.60 g, 2.50 eq, 25 mmol). The mixture was stirred at room temperature for 1 hour and then a solution of sat. aq. NaHCO<sub>3</sub> (50 mL) was added, followed by sat. aq. Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> (50 mL). The aqueous phase was extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 \* 50 mL) and the combined organic layers were washed with sat. aq. NaCl, dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure. The crude mixture was purified by flash chromatography (hexanes/EtOAc, 9:1) to afford 4.07 g (97%) of compound **11** as yellow oil. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ = 6.96 (d, *J*=8.2, 1H), 6.92 (d, *J*=2.6, 1H), 6.83 (dt, *J*=15.9, 6.6, 1H), 6.65 (dd, *J*=8.2, 2.6, 1H), 6.15 (dt, *J*=15.8, 1.3, 1H), 5.78 (ddt, *J*=16.6, 10.2, 6.4, 1H), 5.35 (dd, *J*=9.4, 3.4, 1H), 5.09 – 4.97 (m, 2H), 4.53 – 4.42 (m, 2H), 3.29 (s, 3H), 3.07 (dd, *J*=15.8, 9.4, 1H), 2.62 (dd, *J*=15.8, 3.4, 1H), 2.37 – 2.15 (m, 7H), 0.97



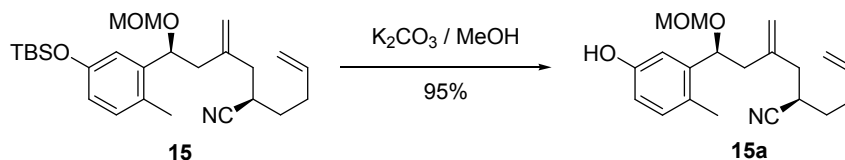
(s, 9H), 0.17 (s, 6H) ;  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  = 197.63, 154.15, 147.21, 140.52, 137.04, 131.44, 131.13, 128.08, 119.30, 117.75, 115.75, 94.27, 70.42, 55.82, 47.26, 32.18, 31.83, 25.81, 18.32, 18.29, -4.34; HRMS (ESI): Calc. for  $\text{C}_{24}\text{H}_{38}\text{O}_4\text{Si}$  ( $\text{M}+\text{Na}$ ) $^+$  : 441.2432, found : 441.2435;  $[\alpha]_{\text{D}}$  (25°C, c = (27.7 mg/ 2mL),  $\text{CH}_2\text{Cl}_2$ ) = -88.8°.



**(R)-2-((S)-4-(5-((tert-butyldimethylsilyl)oxy)-2-methylphenyl)-4-(methoxymethoxy)-2-oxobutyl)hex-5-enenitrile (13).** Ruthenium complex **12** (See Ref 14 for synthesis and S-33 for NMR, 105 mg, 1.0 mol%, 0.097 mmol) was placed in a 100 mL round-bottomed flask under argon atmosphere. Anhydrous methanol (0.59 mL, 1.50 eq, 14.57 mmol) was added to this flask (*CAUTION* : formation of HCN), and the mixture was cooled to 0°C. TMS-CN (1.80 mL, 1.48 eq, 14.38 mmol) was added dropwise and the mixture was stirred for 15 min. To this solution, anhydrous *tert*-butyl methyl ether (50 mL) and lithium phenoxide (1.46 mL at 60 mM in THF, 0.9 mol%, 0.087 mmol) were added at 0°C, and the mixture was stirred for 30 min. Compound **9** (4.07 g, 1.00 eq, 9.72 mmol) was then added dropwise over 5 min, and the reaction mixture was stirred for 12 hours at 0°C. A solution of sat. aq.  $\text{NaHCO}_3$  (50 mL) was added and the aqueous phase was extracted with EtOAc (3 \* 50 mL). The combined organic layers were washed with sat. aq. NaCl, dried over  $\text{Na}_2\text{SO}_4$  and concentrated under reduced pressure. The crude mixture was purified by flash chromatography (hexanes:EtOAc, 87:13) to afford 3.12 g (72%) of compound **13** as a colorless oil.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  = 6.98 (d,  $J$ =8.2, 1H), 6.86 (d,  $J$ =2.6, 1H), 6.67 (dd,  $J$ =8.2, 2.6, 1H), 5.77 (ddt,  $J$ =17.0, 10.2, 6.7, 1H), 5.31 (dd,  $J$ =9.8, 3.3, 1H), 5.17 – 5.01 (m, 2H), 4.46 (q,  $J$ =6.7, 2H), 3.30 (s, 3H), 3.10 (dq,  $J$ =13.1, 6.6, 1H), 2.98 – 2.71 (m, 3H), 2.54 (dd,  $J$ =15.7, 3.3, 1H), 2.40 – 2.13 (m, 5H), 1.76 – 1.55 (m, 9H), 0.97 (s, 8H), 0.17 (s, 6H) ;  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  = 203.80, 154.31, 139.54, 136.18, 131.70, 128.09, 121.40, 119.65, 117.63, 116.64, 94.33, 70.43, 56.05, 49.73, 45.92, 31.18, 31.02, 25.83, 25.37, 18.35, 18.22, -4.29; HRMS (ESI) Calc. for  $\text{C}_{25}\text{H}_{39}\text{NO}_4\text{Si}$  ( $\text{M}+\text{NH}_4$ ) $^+$ : 463.2987, found : 463.2986;  $[\alpha]_{\text{D}}$  (25°C, c = (38.6 mg/ 2mL),  $\text{CH}_2\text{Cl}_2$ ) = -92.1°.

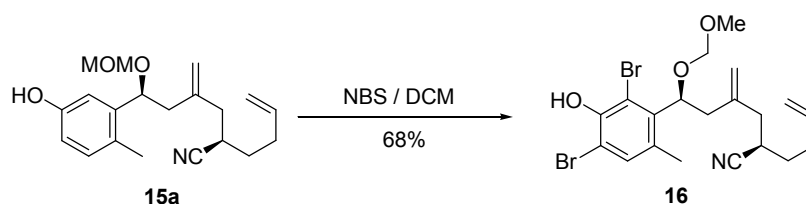


**(R)-2-((S)-4-(5-((tert-butyldimethylsilyl)oxy)-2-methylphenyl)-4-(methoxymethoxy)-2-methylenebutyl)hex-5-enenitrile (15).** To a solution of compound **13** (483 mg, 1.00 eq, 1.08 mmol) in dry THF (3 mL) at  $-78^{\circ}\text{C}$  under argon atmosphere was added dropwise (trimethylsilyl)methyl lithium **14** (1.2 mL at 1 M, 1.10 eq, 1.2 mmol) over a period of 3 hours. A solution of 15 mL of sat. aq.  $\text{NH}_4\text{Cl}$  was then added and the aqueous phase was extracted with EtOAc (3 \* 15 mL). The combined organic layers were washed with sat. aq. NaCl, dried over  $\text{Na}_2\text{SO}_4$  and concentrated under reduced pressure. The crude product was used without further purification and diluted in  $\text{CH}_2\text{Cl}_2$  (10 mL) at  $0^{\circ}\text{C}$  and  $\text{BF}_3\cdot\text{OEt}_2$  (0.21 mL, 1.50 eq, 1.64 mmol) was added dropwise. The solution was stirred for 15 minutes and diluted with a solution of sat. aq.  $\text{NaHCO}_3$  (10 mL). The aqueous phase was extracted with  $\text{CH}_2\text{Cl}_2$  (3 \* 10 mL) and the combined organic layers were washed with sat. aq. NaCl, dried over  $\text{Na}_2\text{SO}_4$  and concentrated under reduced pressure. The crude mixture was purified by flash chromatography (hexanes/EtOAc, 90:10) to afford 360 mg (75 %) of external alkene **15**.  **$^1\text{H}$  NMR** (300 MHz,  $\text{CDCl}_3$ )  $\delta$  = 6.97 (d,  $J=8.2$ , 1H), 6.87 (d,  $J=2.6$ , 1H), 6.66 (dd,  $J=8.2$ , 2.6, 1H), 5.84 – 5.68 (m, 4H), 4.46 (q,  $J=6.7$ , 2H), 3.33 (s, 3H), 2.80 – 2.66 (m, 1H), 2.50 – 2.13 (m, 9H), 1.75 – 1.65 (m, 2H), 0.97 (s, 9H), 0.17 (s, 6H);  **$^{13}\text{C}$  NMR** (75 MHz,  $\text{CDCl}_3$ )  $\delta$  = 154.12, 141.63, 140.83, 136.31, 131.29, 127.80, 121.63, 119.18, 117.66, 116.42, 115.88, 94.13, 73.35, 55.79, 42.88, 39.06, 31.28, 31.06, 29.45, 25.74, 18.30, 18.23, -4.41; **HRMS** (ESI) Calc. for  $\text{C}_{26}\text{H}_{41}\text{NO}_3\text{Si}$  ( $\text{M}^+ \text{NH}_4^+$ ): 461.3194, found : 463.3195;  **$[\alpha]_{\text{D}}$**  ( $25^{\circ}\text{C}$ ,  $c$  = (44.8 mg/ 2mL),  $\text{CH}_2\text{Cl}_2$ ) =  $-68.0^{\circ}$ .

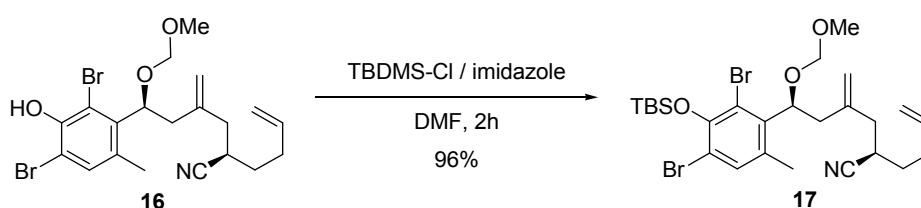


**(R)-2-((S)-4-(5-hydroxy-2-methylphenyl)-4-(methoxymethoxy)-2-methylenebutyl)hex-5-enenitrile (15a).** To a solution of **15** (1.64 g, 1.00 eq, 3.70 mmol) in MeOH (37 mL) was added  $\text{K}_2\text{CO}_3$  (1.2g, 2.50 eq, 9.25 mmol). The solution was heated at  $60^{\circ}\text{C}$  for 1 hour and then a solution of 50 mL of sat. aq.  $\text{NH}_4\text{Cl}$  was added. The aqueous phase was extracted with DCM (3 \* 50 mL) and the combined organic layers were washed with sat. aq. NaCl, dried over  $\text{Na}_2\text{SO}_4$  and concentrated under reduced pressure. The residue was filtrated over silica

gel (hexanes/EtOAc, 7:3) and concentrated under reduced pressure to afford 1.24 g (95%) of phenol **15a** as a yellow oil. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ = 6.97 – 6.87 (m, 2H), 6.75 (s, 1H), 6.63 (dd, *J*=8.2, 2.6, 1H), 5.74 (ddt, *J*=17.0, 10.1, 6.7, 1H), 5.14 – 4.98 (m, 4H), 4.92 (dd, *J*=8.6, 4.4, 1H), 4.47 (s, 2H), 3.34 (s, 3H), 2.75 (tt, *J*=9.1, 5.7, 1H), 2.50 – 2.09 (m, 9H), 1.77 – 1.55 (m, 2H); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ = 154.63, 141.41, 140.69, 136.20, 131.40, 126.49, 121.66, 116.36, 115.80, 114.53, 112.83, 94.01, 73.45, 55.73, 42.66, 38.80, 31.12, 30.94, 29.34, 18.10; HRMS (ESI) Calc. for C<sub>20</sub>H<sub>27</sub>NO<sub>3</sub> (M+ NH<sub>4</sub>)<sup>+</sup>: 347.2329, found : 347.2330; [α]<sub>D</sub> (25°C, c = (12.4 mg/ 2mL), CH<sub>2</sub>Cl<sub>2</sub>) = -88.3°.

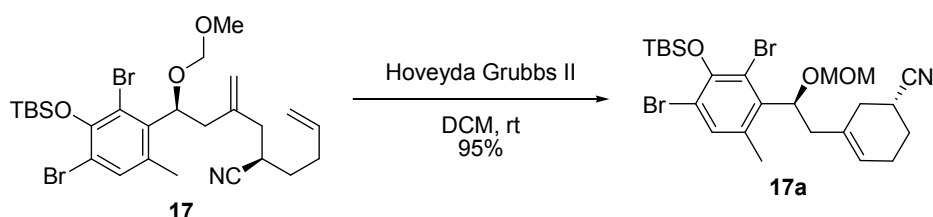


**(R)-2-((S)-4-(2,4-dibromo-3-hydroxy-6-methylphenyl)-4-(methoxymethoxy)-2-methylenebutyl) hex-5-enenitrile (16).** Compound **15a** (1.24 g, 1.00 eq, 3.70 mmol) was diluted in dry CH<sub>2</sub>Cl<sub>2</sub> (30 mL) at 0°C and a solution of NBS (freshly recrystallized in water, 1.38 g, 2.10 eq, 7.4 mmol) in dry CH<sub>2</sub>Cl<sub>2</sub> (10 mL) was added dropwise. The solution was stirred for 25 minutes and diluted with a solution of sat. aq. Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> (5 mL). The aqueous phase was extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 \* 30 mL) and the combined organic layers were washed with sat. aq. NaCl, dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure. The crude mixture was purified by flash chromatography (hexanes/EtOAc, 4:1) to afford 1.22 g (68 %) of compound **16** as yellow oil. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ = 7.25 (s, 1H), 6.03 (br, 1H), 5.75 (ddt, *J*=17.1, 10.2, 6.7, 1H), 5.41 (dd, *J*=9.8, 4.1, 1H), 5.16 – 4.96 (m, 4H), 4.51 – 4.40 (m, 1H), 3.28 (s, 3H), 2.84 – 2.72 (m, 1H), 2.67 – 2.13 (m, 10H), 1.75 – 1.65 (m, 2H); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ = 147.16, 140.82, 137.38, 136.00, 134.32, 130.55, 121.08, 115.89, 115.72, 112.91, 108.01, 94.25, 77.42, 55.44, 39.28, 38.09, 30.96, 30.63, 29.17, 19.27; HRMS (ESI) Calc. For C<sub>20</sub>H<sub>25</sub>Br<sub>2</sub>NO<sub>3</sub> (M+NH<sub>4</sub>)<sup>+</sup>: 503.0539, found : 503.0538; [α]<sub>D</sub> (25°C, c = (15.7 mg/ 2mL), CH<sub>2</sub>Cl<sub>2</sub>) = -58.7°.

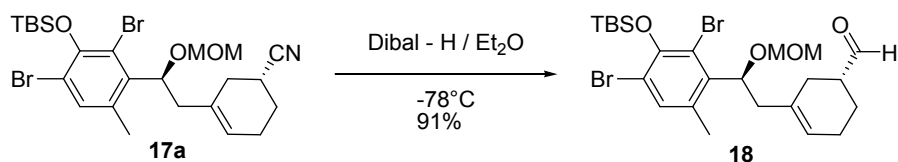


**(R)-2-((S)-4-(2,4-dibromo-3-((tert-butyldimethylsilyl)oxy)-6-methylphenyl)-4-(methoxymethoxy) -2-methylenebutyl)hex-5-enenitrile (17).** To a solution of **16** (1.22 g,

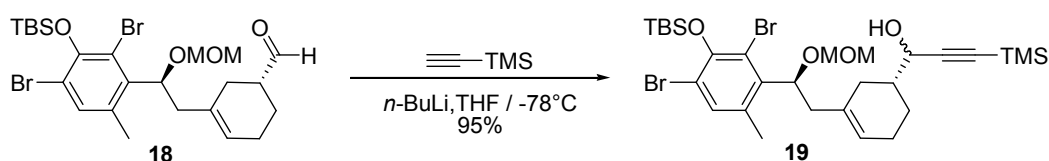
1.00 eq, 2.50 mmol) in dry DMF (5 mL) at 0°C, was added imidazole (477 mg, 2.80 eq, 7 mmol) and TBDMS-Cl (528 mg, 1.40 eq, 3.5 mmol) and the solution was stirred for 2 hours at room temperature. The reaction was diluted Et<sub>2</sub>O (30 mL) and sat. aq. NaCl (600 mL) was added. The aqueous phase was extracted with Et<sub>2</sub>O (3 \* 30 mL) and the combined organic layers were dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure. The crude mixture was purified by flash chromatography (hexanes/EtOAc, 9:1) to afford 1.45 g (96 %) of compound **17**. **<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>) δ = 7.26 (s, 1H), 5.73 (ddt, *J*=17.0, 10.1, 6.7, 1H), 5.47 (dd, *J*=9.9, 4.1, 1H), 5.14 – 4.96 (m, 4H), 4.44 (dd, *J*=19.9, 6.7, 2H), 3.25 (s, 3H), 2.79 (tt, *J*=9.2, 5.8, 1H), 2.69 – 2.08 (m, 9H), 1.80 – 1.56 (m, 2H), 1.01 (s, 9H), 0.32 (s, 6H); **<sup>13</sup>C NMR** (75 MHz, CDCl<sub>3</sub>) δ = 148.00, 141.11, 138.31, 136.26, 135.55, 132.20, 121.43, 119.14, 116.45, 113.76, 94.89, 78.05, 55.83, 39.73, 38.55, 31.46, 31.05, 29.63, 26.25, 25.67, 19.77, 18.98, -1.88, -1.95; **HRMS** (ESI) Calc. For C<sub>26</sub>H<sub>39</sub>Br<sub>2</sub>NO<sub>3</sub>Si (M+Na)<sup>+</sup>: 624.0940, found : 624.0931; [α]<sub>D</sub> (25°C, c = (18.6 mg/ 2mL), CH<sub>2</sub>Cl<sub>2</sub>) = -50.9°.



**(R)-3-((S)-2-(2,4-dibromo-3-((tert-butyldimethylsilyl)oxy)-6-methylphenyl)-2-(methoxymethoxy) ethyl)cyclohex-3-enecarbonitrile (17a).** To a solution of compound **17** (2.88 g, 1.00 eq, 4.8 mmol) in DCM (400 mL) was added Hoveyda Grubbs II catalyst (90.4 mg, 3 mol%, 0.144 mmol). The reaction was stirred for 12 hours and was filtrated over silica gel to remove the catalyst. The crude compound was purified by flash chromatography (hexanes/EtOAc, 9:1) to afford 2.71 g (95%) of **17a**. **<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>) δ = 7.22 (s, 1H), 5.56 (s, 1H), 5.41 (dd, *J*=9.6, 4.3, 1H), 4.40 (dd, *J*=19.3, 6.6, 2H), 3.22 (s, 3H), 2.93 – 2.70 (m, 1H), 2.54 – 2.00 (m, 9H), 1.91 – 1.70 (m, 2H), 0.98 (s, 9H), 0.29 (s, 6H); **<sup>13</sup>C NMR** (75 MHz, CDCl<sub>3</sub>) δ = 147.82, 138.48, 135.31, 132.07, 131.00, 123.84, 122.02, 119.05, 113.49, 94.70, 78.04, 55.53, 41.66, 31.44, 26.14, 24.93, 22.99, 19.65, 18.83, -2.02, -2.08; **HRMS** (ESI) Calc. for C<sub>24</sub>H<sub>35</sub>Br<sub>2</sub>NO<sub>3</sub>Si (M+Na)<sup>+</sup>: 596.0627, found : 596.0622 ; [α]<sub>D</sub> (25°C, c = (14.1 mg/ 2mL), CH<sub>2</sub>Cl<sub>2</sub>) = -40.8°.

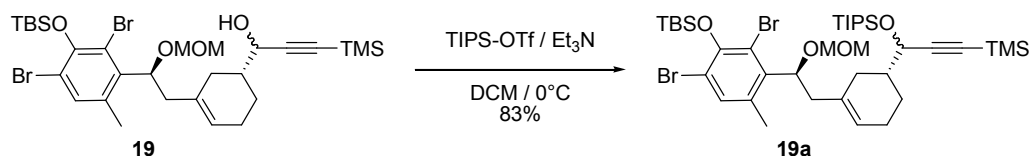


**(R)-3-((S)-2-(2,4-dibromo-3-((tert-butyldimethylsilyl)oxy)-6-methylphenyl)-2-(methoxymethoxy) ethyl)cyclohex-3-enecarbaldehyde (18).** To a solution of cyanide compound **17a** (2.71 g, 1.00 eq, 4.75 mmol) in dry Et<sub>2</sub>O (48 mL) at -78°C under argon atmosphere was added dropwise DIBAL-H (11.86 mL at 1.0M, 2.50 eq, 11.86 mmol). The resulting solution was stirred for 2 hours at -78°C. Methanol (20 mL) was then added, followed by sat. aq. NH<sub>4</sub>Cl (50 mL). This solution was transferred into a sat. aq. Rochelle's Salt solution and the mixture was stirred for 60 min at room temperature. The resulting solution was extracted with EtOAc (3 \* 60 mL) and the combined organic phases were washed with sat. aq. NaCl, dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure. The crude product was filtrated on a plug of silica gel (hexanes/EtOAc, 4:1) to afford 2.47 g (91%) of aldehyde **18**. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ = 9.71 (s, 1H), 7.27 (s, 1H), 5.56 (s, 1H), 5.51 (dd, *J*=9.4, 4.5, 1H), 4.46 (dd, *J*=18.1, 6.6, 3H), 3.28 (s, 3H), 2.62 – 2.20 (m, 9H), 1.99 – 1.90 (m, 1H), 1.70 – 1.50 (m, 2H), 1.03 (s, 9H), 0.33 (d, *J*=2.1, 6H); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ = 203.75, 147.87, 138.82, 135.35, 132.22, 132.16, 124.27, 119.26, 113.47, 94.69, 78.00, 55.53, 46.50, 42.06, 27.58, 26.23, 23.88, 21.80, 19.76, 18.93, -1.95, -2.01; HRMS (ESI) Calc. for C<sub>24</sub>H<sub>36</sub>Br<sub>2</sub>O<sub>4</sub>Si (M+Na)<sup>+</sup>: 599.0623, found : 599.0625 ; [α]<sub>D</sub> (25°C, c = (24.8 mg/ 2mL), CH<sub>2</sub>Cl<sub>2</sub>) = -27.1°.

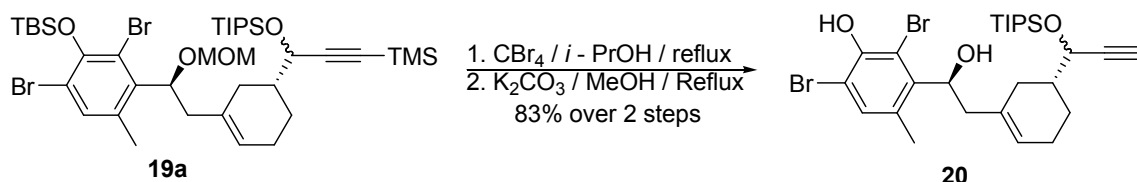


**1-((R)-3-((S)-2-(2,4-dibromo-3-((tert-butyldimethylsilyl)oxy)-6-methylphenyl)-2-(methoxy methoxy)ethyl)cyclohex-3-en-1-yl)-3-(trimethylsilyl)prop-2-yn-1-ol (19).** To a solution of trimethylsilylacetylene (1.04 mL, 4.50 eq, 7.34 mmol) in dry THF (8 mL) at -78°C under argon atmosphere was added dropwise *n*-BuLi (4.3 mL at 2.5 M., 4.30 eq, 2.80 mmol). The solution was stirred for 30 minutes at this same temperature and a solution of aldehyde **18** (939 mg, 1.00 eq, 1.63 mmol) in dry THF (3 mL) was added. The mixture was stirred for further 2h at -78°C and a solution of sat. aq. NH<sub>4</sub>Cl (20 mL) was added. The aqueous phase was extracted with EtOAc (3 \* 15 mL) and the combined organic layers were washed with sat. aq. NaCl, dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure. The crude product

was purified by flash chromatography (hexanes:EtOAc, 85:15) to afford 1.10 g (95%) of the desired propargylic alcohol **19** as a brown oil as a diastereoisomeric mixture (1:1). **HRMS** (ESI) Calc. For C<sub>29</sub>H<sub>46</sub>Br<sub>2</sub>O<sub>4</sub>Si<sub>2</sub> (M+Na)<sup>+</sup>: 697.1176, found : 697.1170.

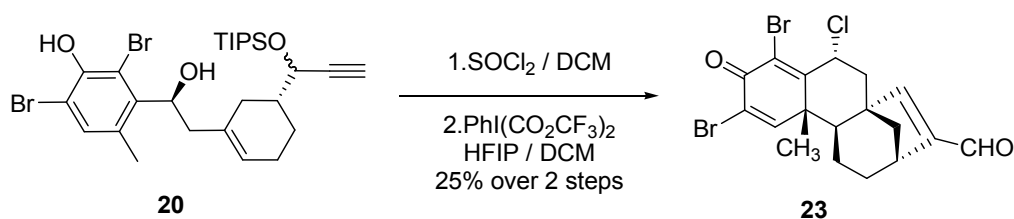


**tert-butyl(2,6-dibromo-3-((S)-1-(methoxymethoxy)-2-((R)-5-(1-((triisopropylsilyl)oxy)-3-(trimethylsilyl)prop-2-yn-1-yl)cyclohex-1-en-1-yl)ethyl)-4-methylphenoxy)dimethylsilane (19a).** To a solution of propargylic alcohol **19** (1.10 g, 1.00 eq, 1.63 mmol.) in dry DCM (16 mL) at 0°C was added Et<sub>3</sub>N (0.55 mL, 2.40 eq, 3.91 mmol) followed by TIPS-OTf (0.53 mL, 1.20 eq, 1.96 mmol). The solution was stirred for 3 hours at 0°C and water (10 mL) was added. The aqueous phase was extracted with DCM (3 \* 15 mL) and the combined organic layers were washed with sat. aq. NaCl, dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure. The crude product was purified by flash chromatography (hexanes:EtOAc, 97:3) to afford 1.13 g (83%) of the desired protected propargylic alcohol **19a** as a brownish oil as a diastereoisomers mixture (1:1). **HRMS** (ESI) Calc. For C<sub>38</sub>H<sub>66</sub>Br<sub>2</sub>O<sub>4</sub>Si<sub>3</sub> (M+Na)<sup>+</sup>: 851.2528, found : 851.2681.

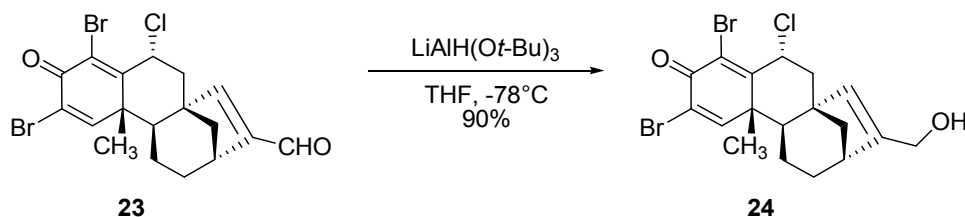


**2,6-dibromo-3-((S)-1-hydroxy-2-((R)-5-(1-((triisopropylsilyl)oxy)prop-2-yn-1-yl)cyclohex-1-en-1-yl)ethyl)-4-methylphenol (20).** To a solution of **19a** (1.13 g, 1.00 eq, 1.35 mmol) in anhydrous *i*-PrOH (14 mL) was added anhydrous CBr<sub>4</sub> (90 mg, 0.20 eq, 0.3 mmol). The solution was heated at 84°C for 5 hours and a solution of sat. aq. NaHCO<sub>3</sub> (10 mL) was added. The aqueous phase was extracted with DCM (3 \* 10 mL) and the combined organic layers were washed with sat. aq. NaCl, dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure. The product was used without further purification and was diluted in methanol (15 mL). K<sub>2</sub>CO<sub>3</sub> (559 mg, 3.00 eq, 4.1 mmol) was added and the resulting suspension was heated at 60°C for 1 h. Sat. aq. NH<sub>4</sub>Cl (10 mL) was added and the aqueous

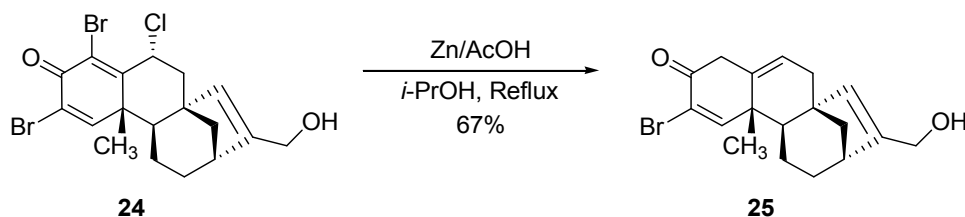
phase was extracted with DCM (3 \* 20 mL). The combined organic layers were washed with sat. aq. NaCl, dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure. The crude product was purified by flash chromatography (hexanes/EtOAc, 9:1) to afford 670 mg (83%) of the desired compound **20** as a yellow oil as a diastereoisomer mixture (1:1). **HRMS** (ESI) Calc. For C<sub>27</sub>H<sub>40</sub>Br<sub>2</sub>O<sub>3</sub>Si (M+Na - [H<sub>2</sub>O])<sup>+</sup>: 583.1062, found : 583.1062.



**(5R,6aR,9R,11aR,11bR)-2,4-dibromo-5-chloro-11b-methyl-3-oxo-3,5,6,9,10,11,11a,11b-octahydro-6a,9-methanocyclohepta[a]naphthalene-8-carbaldehyde (23).** To a solution of compound **20** (105 mg, 1.00 eq, 0.175 mmol) in anhydrous DCM (3 mL) under argon atmosphere was added SOCl<sub>2</sub> (38 μL, 3.00 eq, 0.525 mmol). The solution was refluxed for 8 hours and then a solution of sat. aq. NaHCO<sub>3</sub> (5 mL) was added. The aqueous phase was extracted with DCM (3 \* 10 mL) and the combined organic layers were washed with sat. aq. NaCl, dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure. The crude product was filtrated on a plug of silica gel (hexanes/EtOAc, 9:1) and was used without further purification. To a vigorously stirred solution of the above crude phenol in a mixture of HFIP/DCM (5:3 ; 1 mL) at room temperature was added over 5 seconds a solution of PhI(CO<sub>2</sub>CF<sub>3</sub>)<sub>2</sub> (83 mg, 1.10 eq, 0.192 mmol) in a mixture of HFIP/DCM (5:3, 0.6 mL). After addition of PIFA, the solution was stirred for 2 min, quenched with 1 mL of acetone and filtered over silica gel (EtOAc). The filtrate was concentrated under reduced pressure and the residue was purified by flash chromatography (hexanes/EtOAc, 3:1) to afford 20.3 mg of tetracyclic core **23** in 25 % yield over 2 steps. **<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>) δ = 9.67 (s, 1H), 7.31 (s, 1H), 6.13 (s, 1H), 5.42 (t, *J*=9.5, 1H), 3.05 – 3.00 (m, 1H), 2.46 (d, *J*=9.6, 2H), 2.18 (dd, *J*=12.9, 5.0, 1H), 2.05 – 1.98 (m, 1H), 1.90 – 1.82 (m, 1H), 1.72 (s, 3H), 1.46 – 1.40 (m, 2H), 0.96 – 0.85 (m, 2H); **<sup>13</sup>C NMR** (151 MHz, CDCl<sub>3</sub>) δ = 188.87, 172.39, 158.57, 155.16, 149.94, 147.50, 127.57, 119.31, 56.42, 52.48, 51.08, 40.01, 36.88, 31.10, 29.85, 25.18, 23.04; **HRMS** (ESI) Calc. For C<sub>18</sub>H<sub>17</sub>Br<sub>2</sub>ClO<sub>2</sub> (M+Na)<sup>+</sup>: 482.9155, found : 482.9159; [**α**]<sub>D</sub> (25°C, c = (11.6 mg/ 2mL), AcOEt) = -4.3°.



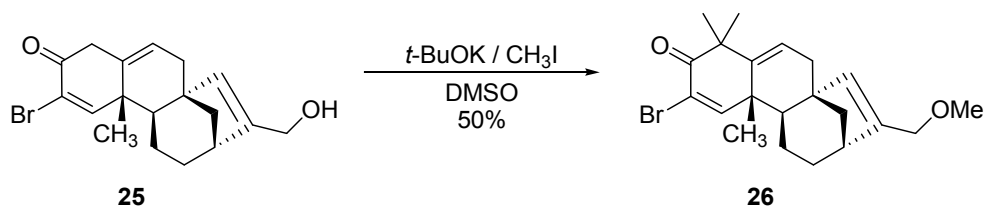
**(5R,6aR,9R,11aR,11bR)-2,4-dibromo-5-chloro-8-(hydroxymethyl)-11b-methyl-5,6,9,10,11,11a-hexahydro-6a,9-methanocyclohepta[a]naphthalen-3(11bH)-one (24).** To a solution of aldehyde **23** (57 mg, 1.00 eq, 0.124 mmol) in dry THF (1.2 mL) at  $-78^\circ\text{C}$  under argon atmosphere was added dropwise  $\text{LiAlH}(\text{O}t\text{-Bu})_3$  (0.137 mL at 1.0 M, 1.10 eq, 0.137 mmol). The resulting solution was stirred at  $-78^\circ\text{C}$  for 15 min and sat. aq.  $\text{NH}_4\text{Cl}$  (5 mL) was added. The aqueous phase was extracted with EtOAc (3 \* 5 mL). The combined organic layers were washed with sat. aq. NaCl, dried over  $\text{Na}_2\text{SO}_4$  and concentrated under vacuum. The crude mixture was purified by flash chromatography (hexanes/EtOAc, 7:3) to afford pure alcohol **24** as a white solid (51 mg, 90%).  **$^1\text{H}$  NMR** (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.32 (s, 1H), 5.34 (t,  $J = 9.5$  Hz, 1H), 5.04 (s, 1H), 4.12 (d,  $J = 1.3$  Hz, 2H), 2.57 (m, 1H), 2.39-2.32 (d,  $J = 10$  Hz, 2H), 2.12 – 2.03 (dd,  $J = 12.6, 4.8$  Hz, 1H), 1.96 (dd,  $J = 10.0, 5.1$  Hz, 1H), 1.83 – 1.71 (m, 2H), 1.67 (s, 3H), 1.64 – 1.49 (m, 4H).  **$^{13}\text{C}$  NMR** (75 MHz,  $\text{CDCl}_3$ )  $\delta$  172.72, 159.66, 155.96, 149.18, 126.95, 122.97, 119.01, 60.74, 57.03, 52.47, 52.02, 49.92, 48.98, 41.11, 39.95, 31.02, 25.42, 23.43. **HRMS** (ESI) Calc. For  $\text{C}_{18}\text{H}_{19}\text{Br}_2\text{ClO}_2$  ( $\text{M}+\text{H}$ ) $^+$ : 462.9492, found : 462.9463; Calc. For  $\text{C}_{18}\text{H}_{19}\text{Br}_2\text{ClO}_2$  ( $2\text{M}+\text{Na}$ ) $^+$ : 942.8773, found : 942.8781;  $[\alpha]_{\text{D}}$  ( $25^\circ\text{C}$ ,  $c = (18.4 \text{ mg}/1 \text{ mL})$ , AcOEt) =  $+27.8^\circ$ .



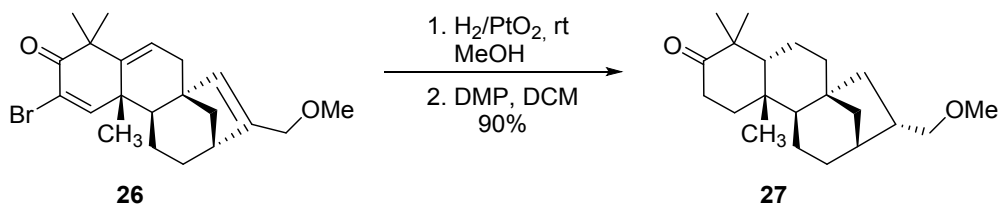
**(6aS,9R,11aR,11bR)-2-bromo-8-(hydroxymethyl)-11b-methyl-6,9,10,11,11a,11b-hexahydro-6a,9-methanocyclohepta[a]naphthalen-3(4H)-one (25).** To a solution of alcohol **24** (20 mg, 1.00 eq, 0.043 mmol) in  $i\text{-PrOH}$  (4.7 mL) were added AcOH (0.04 mL, 15.00 eq, 0.65 mmol) and Zn (28 mg, 10.00 eq, 0.43 mmol). The resulting mixture was refluxed for 10 min and filtrated over silica gel (EtOAc). The residue was dissolved in  $\text{CHCl}_3$  (5 mL) and washed with water (3 mL) and sat. aq. NaCl, dried over  $\text{Na}_2\text{SO}_4$  and concentrated under vacuum. The crude mixture was purified by flash chromatography (hexanes/EtOAc, 85:15) to afford pure enone **25** as a white solid (10 mg, 67%).  **$^1\text{H}$  NMR** (300 MHz,  $\text{CDCl}_3$ )  $\delta$



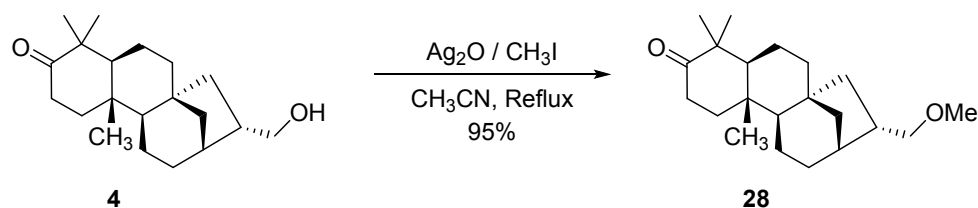
7.60 (s, 1H), 5.56 (dt,  $J = 6.5, 2.0$  Hz, 1H), 5.39 (s, 1H), 4.21 (d,  $J = 1.2$  Hz, 2H), 3.52 (d,  $J = 17.2$  Hz, 1H), 3.19 (d,  $J = 17.3$  Hz, 1H), 2.67 – 2.45 (m, 1H), 2.41 – 2.24 (m, 1H), 2.14 – 2.04 (m, 1H), 2.03 – 1.97 (m, 1H), 1.95 (d,  $J = 5.9$  Hz, 1H), 1.92 – 1.76 (m, 3H), 1.34 (s, 3H).  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  190.49, 157.33, 146.96, 135.71, 127.09, 123.35, 121.89, 61.25, 52.52, 46.46, 46.34, 45.71, 44.09, 39.42, 34.05, 29.85, 25.54, 21.45; LRMS (ESI) : Calc. For  $\text{C}_{18}\text{H}_{21}\text{BrO}_2$  : 349-351, found : 349-361;  $[\alpha]_{\text{D}}$  (25°C,  $c = (6.8 \text{ mg/ 1 mL})$ ,  $\text{CHCl}_3$ ) = - 27.7°.



**(6aS,9R,11aR,11bR)-2-bromo-8-(methoxymethyl)-4,4,11b-trimethyl-6,9,10,11,11a,11b-hexahydro-6a,9-methanocyclohepta[a]naphthalen-3(4H)-one (26).** To a cooled solution of enone **25** (4 mg, 1.00 eq, 0.0114 mmol) in anhydrous DMSO (0.2 mL) under argon atmosphere was added dropwise  $t\text{-BuOK}$  (0.046 mL at 1.0 M, 4.00 eq, 0.046 mmol). The resulting brown solution was stirred for 1 min and  $\text{CH}_3\text{I}$  (0.01 mL, 14.00 eq, 0.16 mmol) was added. The mixture was stirred for further 10 min and sat. aq.  $\text{NH}_4\text{Cl}$  (2 mL) was added. The aqueous phase was extracted with  $\text{CHCl}_3$  (3 \* 2 mL) and the combined organic layers were washed with sat. aq.  $\text{NaCl}$ , dried over  $\text{Na}_2\text{SO}_4$  and concentrated under vacuum. The crude mixture was purified by flash chromatography (hexanes/EtOAc, 95:5) to afford methylated compound **26** as a colorless oil (2.4 mg, 55%).  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.36 (s, 1H), 5.88 (dd,  $J = 7.3, 2.9$  Hz, 1H), 5.36 (s, 1H), 3.97 (dd,  $J = 12.9, 1.5$  Hz, 1H), 3.87 (dd,  $J = 12.8, 0.8$  Hz, 1H), 3.35 (t,  $J = 4.7$  Hz, 1H), 3.32 (s,  $J = 6.3$  Hz, 3H), 2.58 – 2.50 (m, 1H), 2.09 (dd,  $J = 16.6, 2.9$  Hz, 1H), 1.99 (dd,  $J = 16.5, 7.3$  Hz, 1H), 1.89 (ddd,  $J = 9.9, 5.1, 2.2$  Hz, 1H), 1.85 – 1.67 (m, 2H), 1.49 – 1.44 (m, 3H), 1.41 (s,  $J = 5.2$  Hz, 3H), 1.36 (s,  $J = 3.7$  Hz, 3H), 1.35 (s, 3H).  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  196.75, 154.37, 144.09, 143.87, 128.53, 123.17, 119.31, 70.49, 58.40, 52.23, 50.05, 49.82, 48.20, 43.62, 39.81, 34.11, 32.73, 30.06, 27.10, 24.80, 23.29. LRMS (ESI): Calc. For  $\text{C}_{21}\text{H}_{27}\text{BrO}_2$  ( $\text{M}+\text{H}$ ) $^+$ : 391-393, found : 391-393;  $[\alpha]_{\text{D}}$  (25°C,  $c = (2.2 \text{ mg/ 1 mL})$ ,  $\text{CHCl}_3$ ) = - 30.0°.



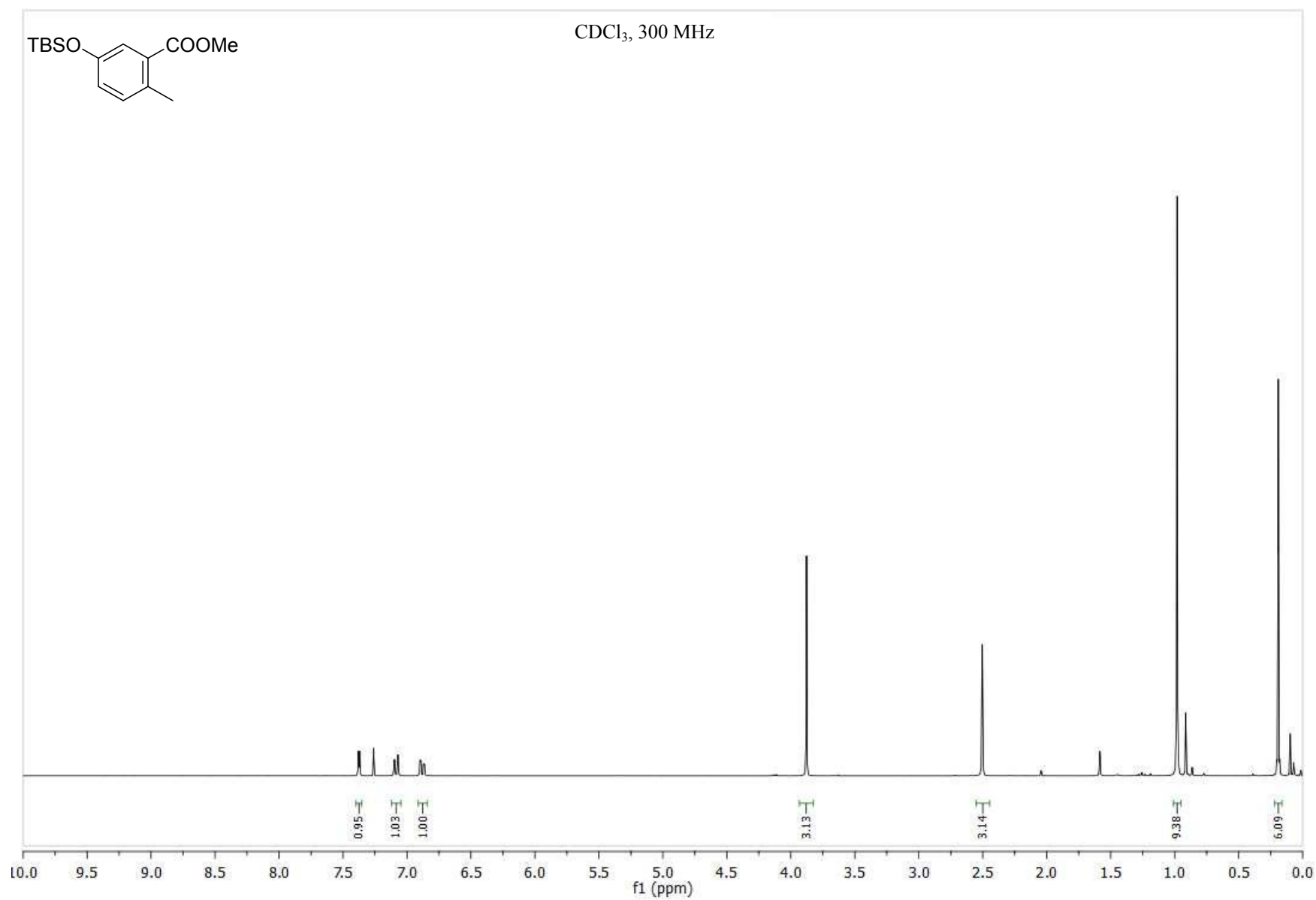
**(+)-17-*epi*-methoxy-kauran-3-one (27).** To a solution of compound **26** (2.4 mg, 1.00 eq, 0.0062 mmol) in methanol (0.3 mL) was added  $\text{PtO}_2$  (1.4 mg, 1.00 eq, 0.0062 mmol). The resulting suspension was stirred for 12h under a 4 atm  $\text{H}_2$  atmosphere. The mixture was then then filtrated over celite (EtOAc) and solvents were removed under vacuum. The crude mixture was dissolved in anhydrous DCM (0.1 mL) under argon atmosphere and Dess-Martin periodinane (3.2 mg, 1.20 eq, 0.0074 mmol) was added. The resulting solution was stirred for 10 min at room temperature and sat. aq.  $\text{NaHCO}_3$  (1 mL) was added. The aqueous phase was extracted with  $\text{CHCl}_3$  (3 \* 1 mL), dried over  $\text{Na}_2\text{SO}_4$  and concentrated under vacuum. The crude mixture was purified by flash chromatography (hexanes/EtOAc, 9:1) to afford (+)-17-*epi*-methoxy-kauran-3-one **27** as a white solid (1.8 mg, 90%).  $^1\text{H NMR}$  (300 MHz,  $\text{CDCl}_3$ )  $\delta$  3.56 – 3.43 (m, 2H), 3.42 (s, 3H), 2.42 (m,  $J = 12.1, 8.5, 6.3$  Hz, 2H), 2.31 – 2.01 (m, 3H), 1.81 – 1.26 (complex, 15H), 1.24 (s, 3H), 1.07 (s, 3H), 1.00 (s, 3H);  $^{13}\text{C NMR}$  (75 MHz,  $\text{CDCl}_3$ )  $\delta$  219.57, 73.85, 59.05, 55.33, 54.28, 50.98, 47.37, 43.38, 42.94, 39.73, 38.04, 36.50, 35.59, 34.62, 29.85, 29.48, 27.43, 25.53, 25.28, 23.71, 21.63. **HRMS** (ESI) Calc. For  $\text{C}_{21}\text{H}_{35}\text{O}_2$  ( $\text{M}+\text{H}$ ) $^+$ : 319.2632, found : 319.2622;  $[\alpha]_D$  (25°C,  $c = (2.4 \text{ mg}/ 1 \text{ mL})$ ,  $\text{CHCl}_3$ ) = +10.8°.

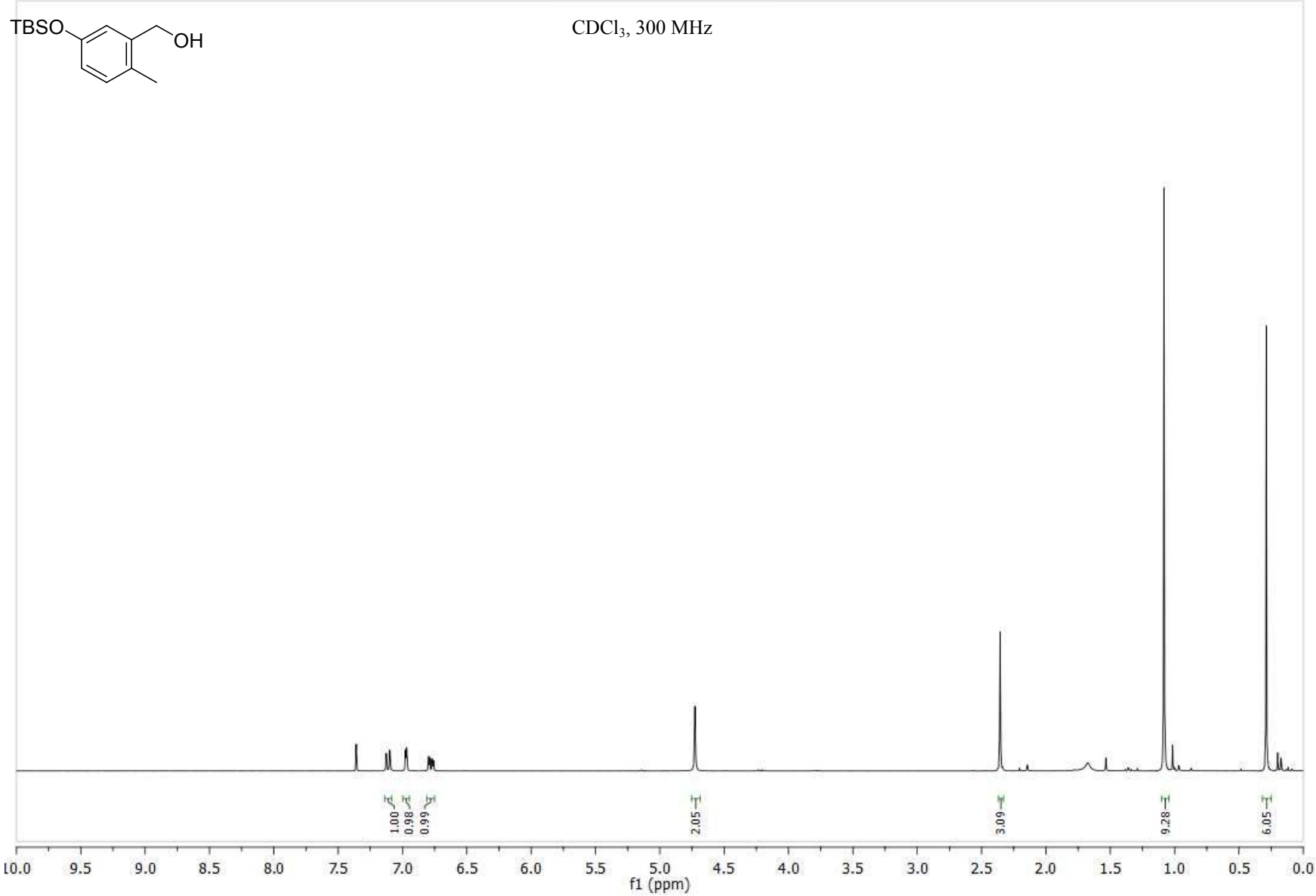


**17-methoxy-kauran-3-one (28).** To a solution of commercially available 17-hydroxy-kauran-3-one **4** (1 mg, 1.00 eq, 0.0033 mmol) in anhydrous  $\text{CH}_3\text{CN}$  (0.1 mL) in a sealed tube were added  $\text{Ag}_2\text{O}$  (2.3 mg, 3.00 eq, 0.01 mmol) and  $\text{CH}_3\text{I}$  (2  $\mu\text{L}$ , 10.00 eq, 0.033 mmol). The resulting solution was refluxed for 12h and filtered over celite (EtOAc). Solvents were removed under vacuum and the crude residue was purified by flash chromatography (hexanes/EtOAc, 9:1) to afford 17-methoxy-kauran-3-one **28** as a white solid (1 mg, 95%).  $^1\text{H NMR}$  (300 MHz,  $\text{CDCl}_3$ )  $\delta$  3.51 – 3.38 (m, 2H), 3.35 (s, 3H), 2.47 (dd,  $J = 8.7, 6.3$  Hz, 2H), 2.37 – 2.12 (m, 2H), 2.12 – 1.89 (m, 3H), 1.74 – 1.40 (complex +  $\text{H}_2\text{O}$ , 13H), 1.07 (s, 3H),

1.06 (s, 3H), 1.03 (s, 3H). **HRMS** (ESI) Calc. For  $C_{21}H_{35}O_2$  (M+H)<sup>+</sup>: 319.2632, found : 319.2633.

### 3. Copies of $^1H$ and $^{13}C$ NMR





CC1=CC=C(C(=C1)CO)C(C)(C)C(C)(C)C(C)(C)C

CDCl<sub>3</sub>, 300 MHz

10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0

f1 (ppm)

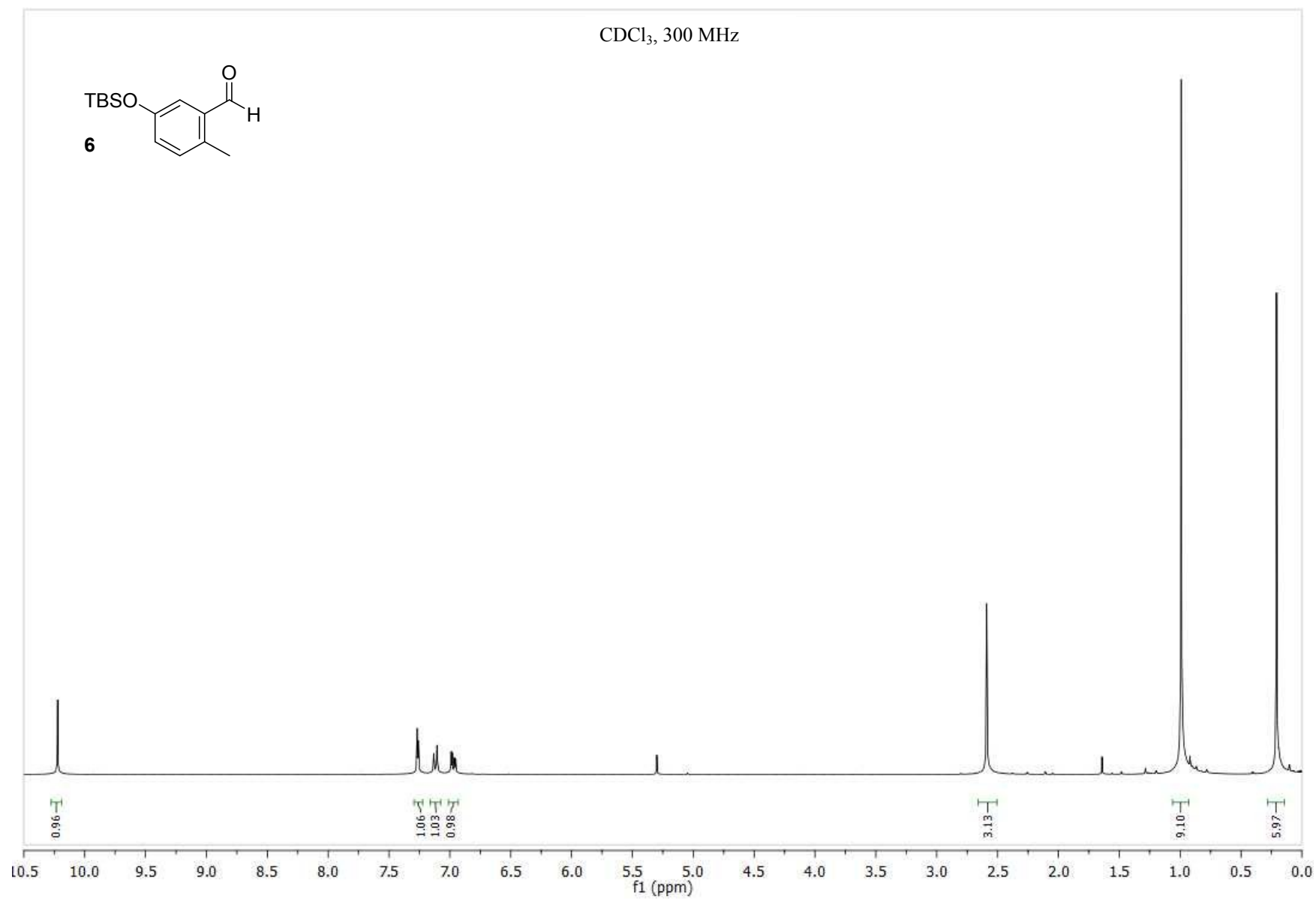
1.00  
 0.98  
 0.99  
 2.05  
 3.09  
 9.28  
 6.05

Cc1cc(C(=O)OC)c(CCO)c1

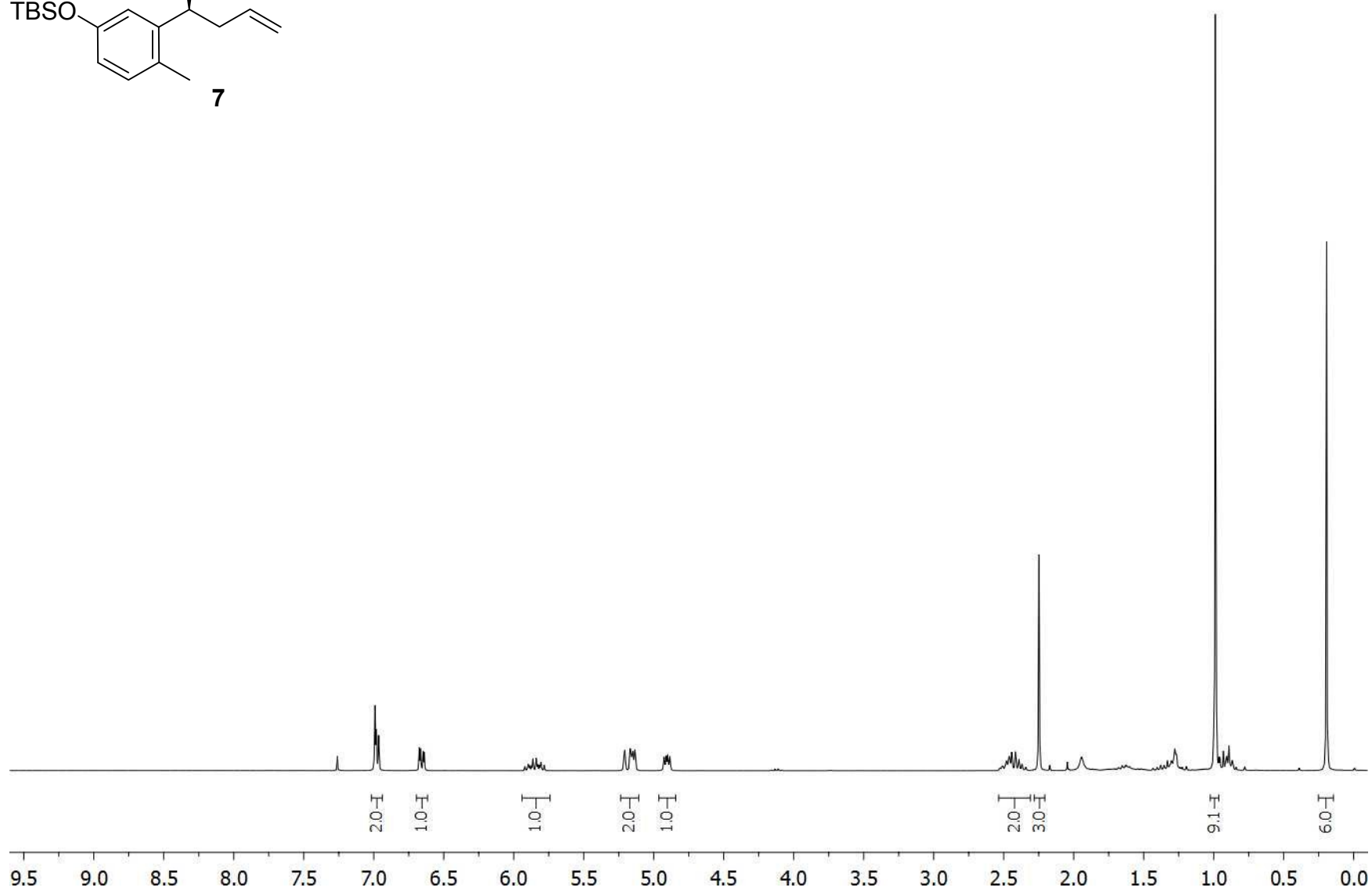
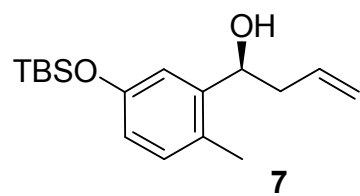
CDCl<sub>3</sub>, 300 MHz

The following table summarizes the peak data extracted from the spectrum:

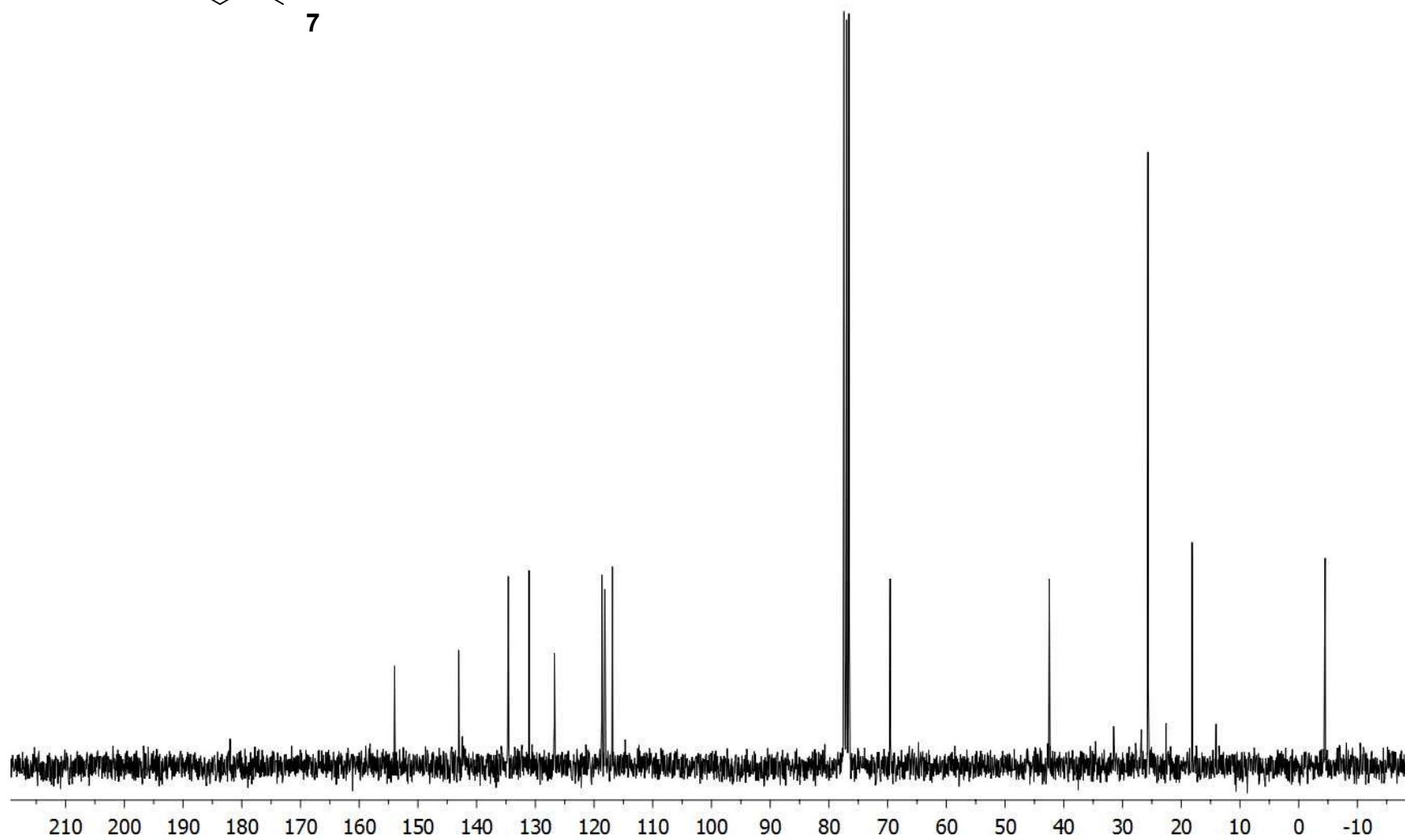
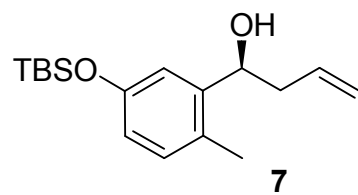
Chemical Shift (ppm)	Multiplicity	Integration
7.39	d	1.00
7.12	d	0.98
6.88	d	0.99
4.81	s	2.05
2.61	d	3.09
1.18	s	9.28
0.21	s	6.05



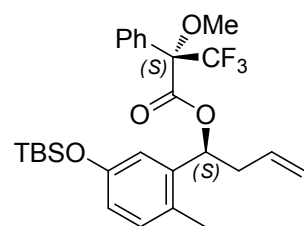
CDCl<sub>3</sub>, 300 MHz



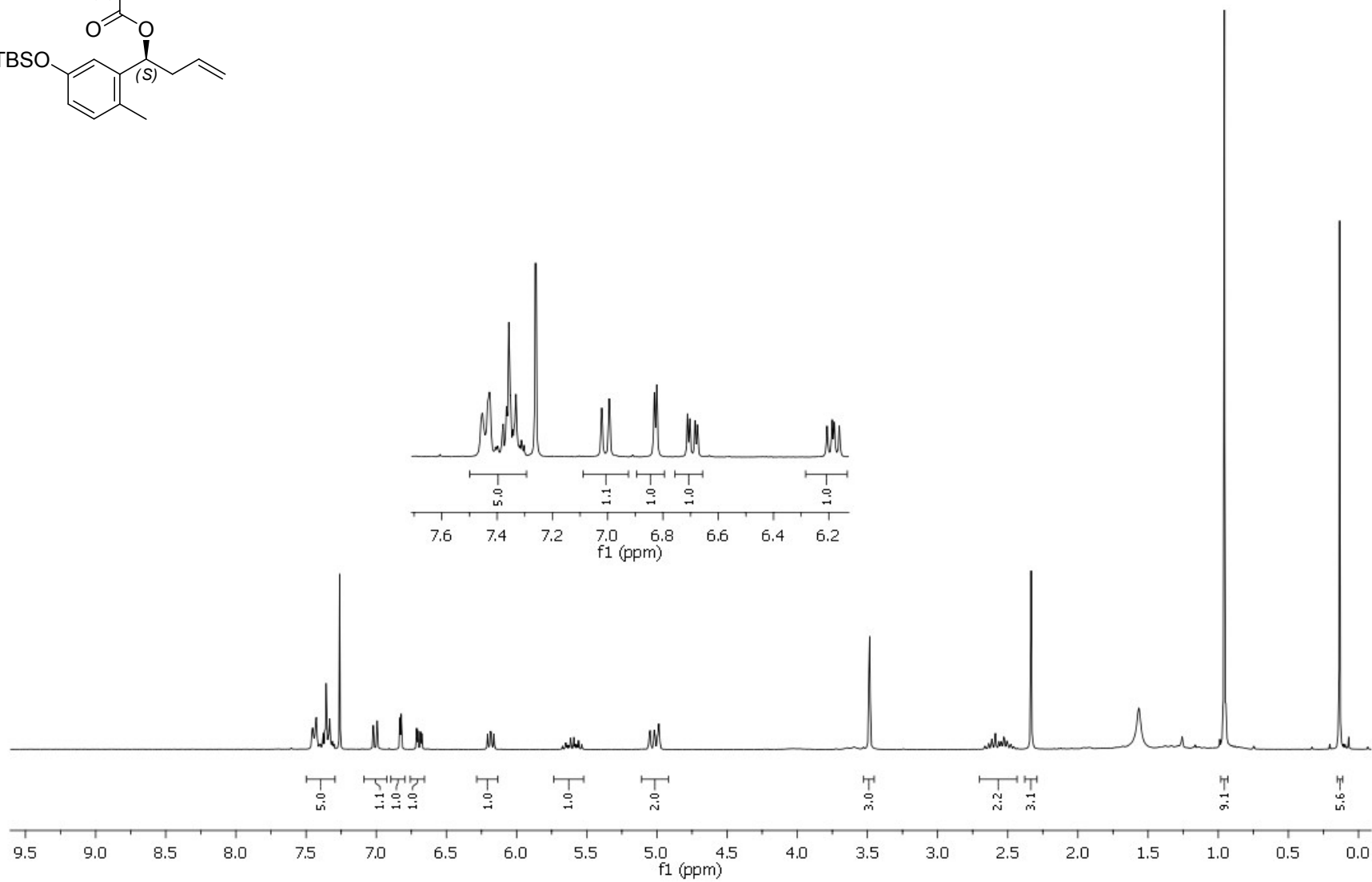
CDCl<sub>3</sub>, 75 MHz



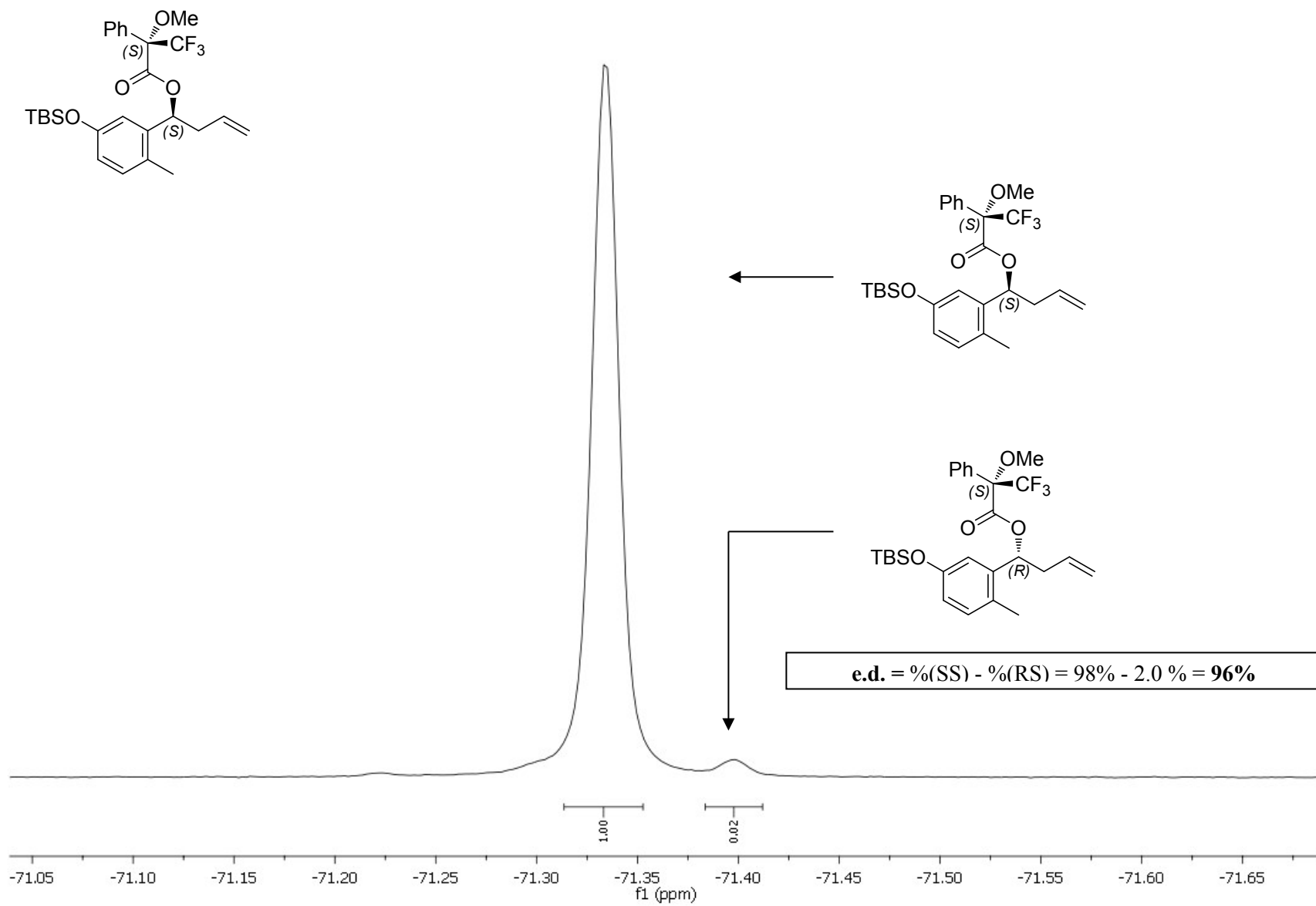


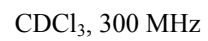


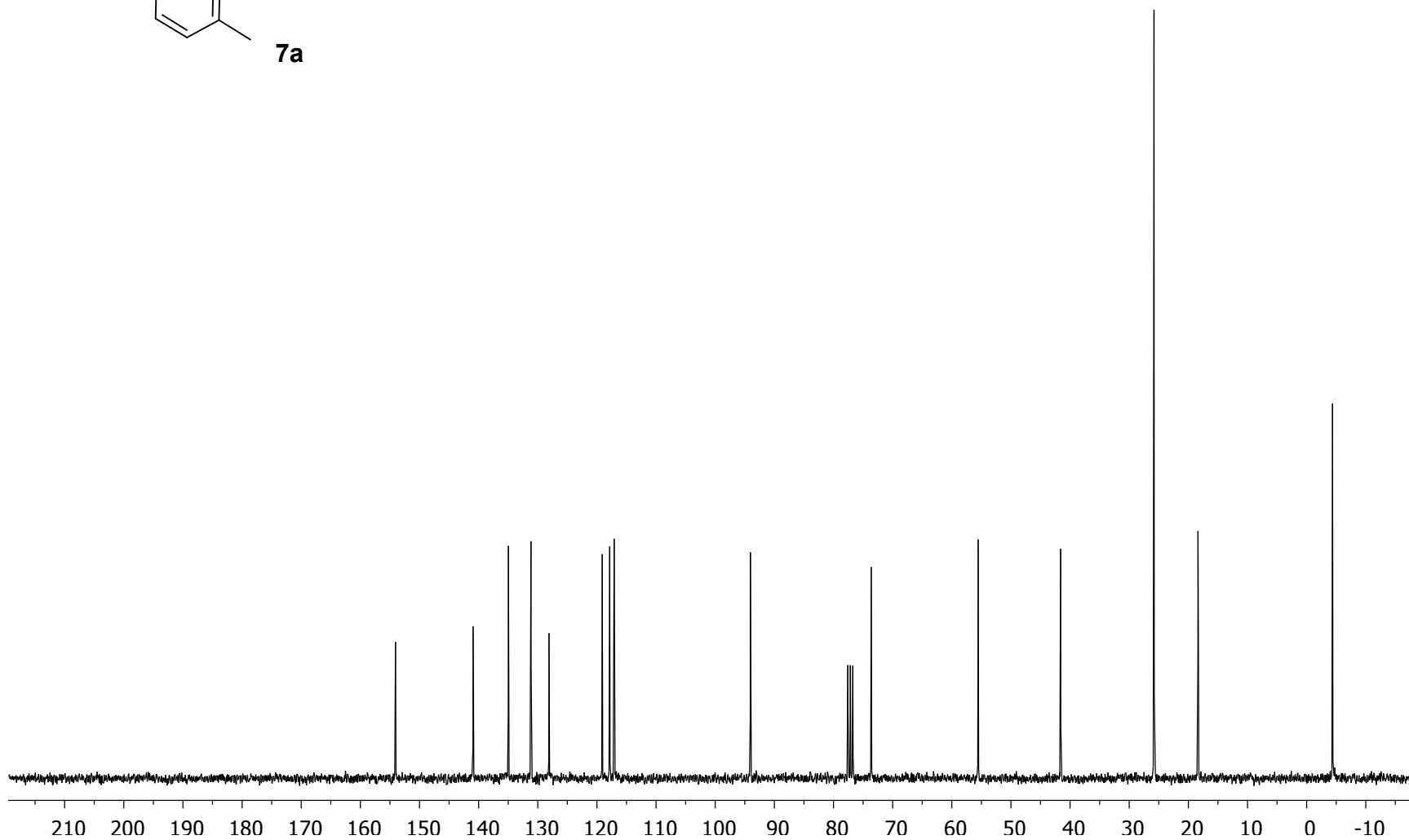
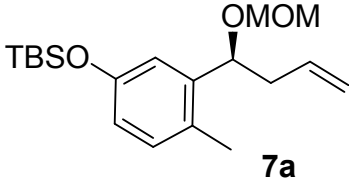
CDCl<sub>3</sub>, 300 MHz



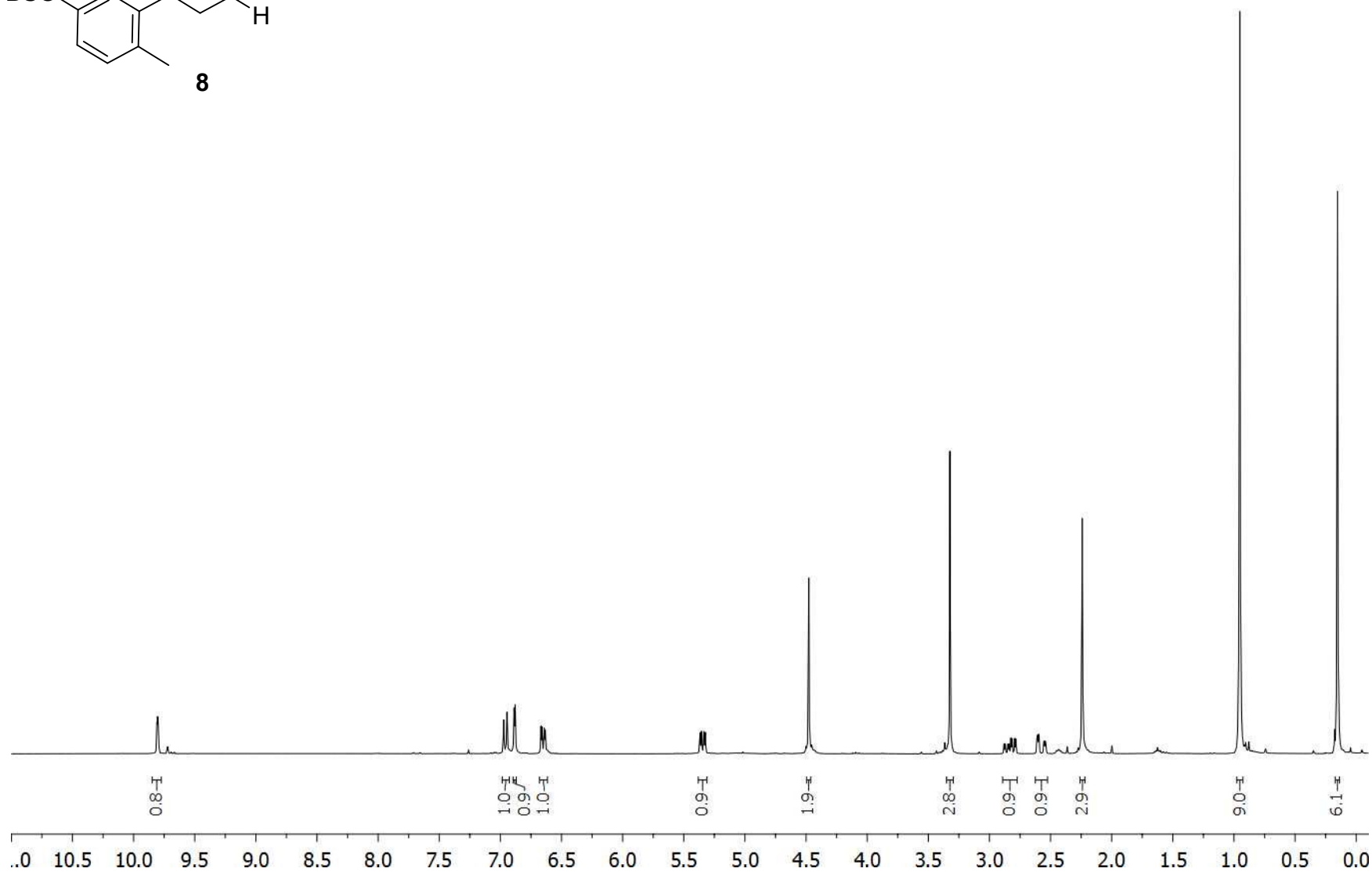
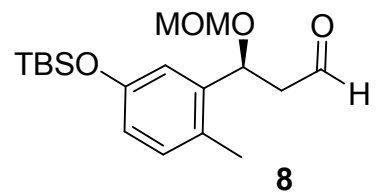
CDCl<sub>3</sub>, 282 MHz



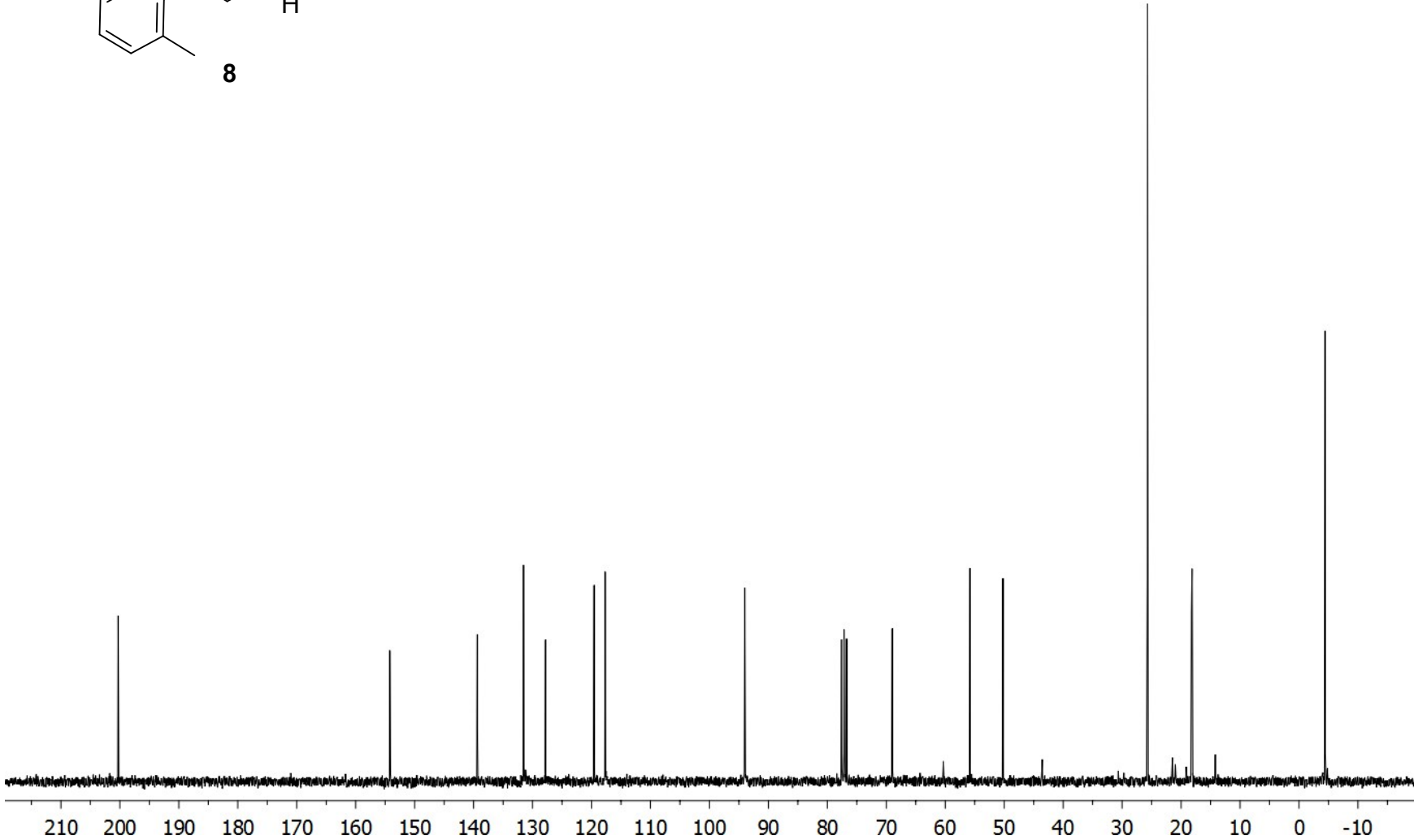
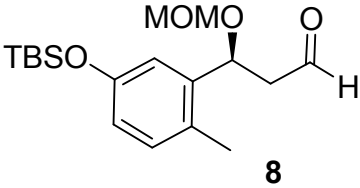


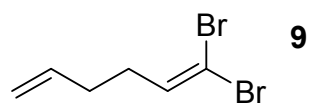
CDCl<sub>3</sub>, 75 MHz

CDCl<sub>3</sub>, 300 MHz

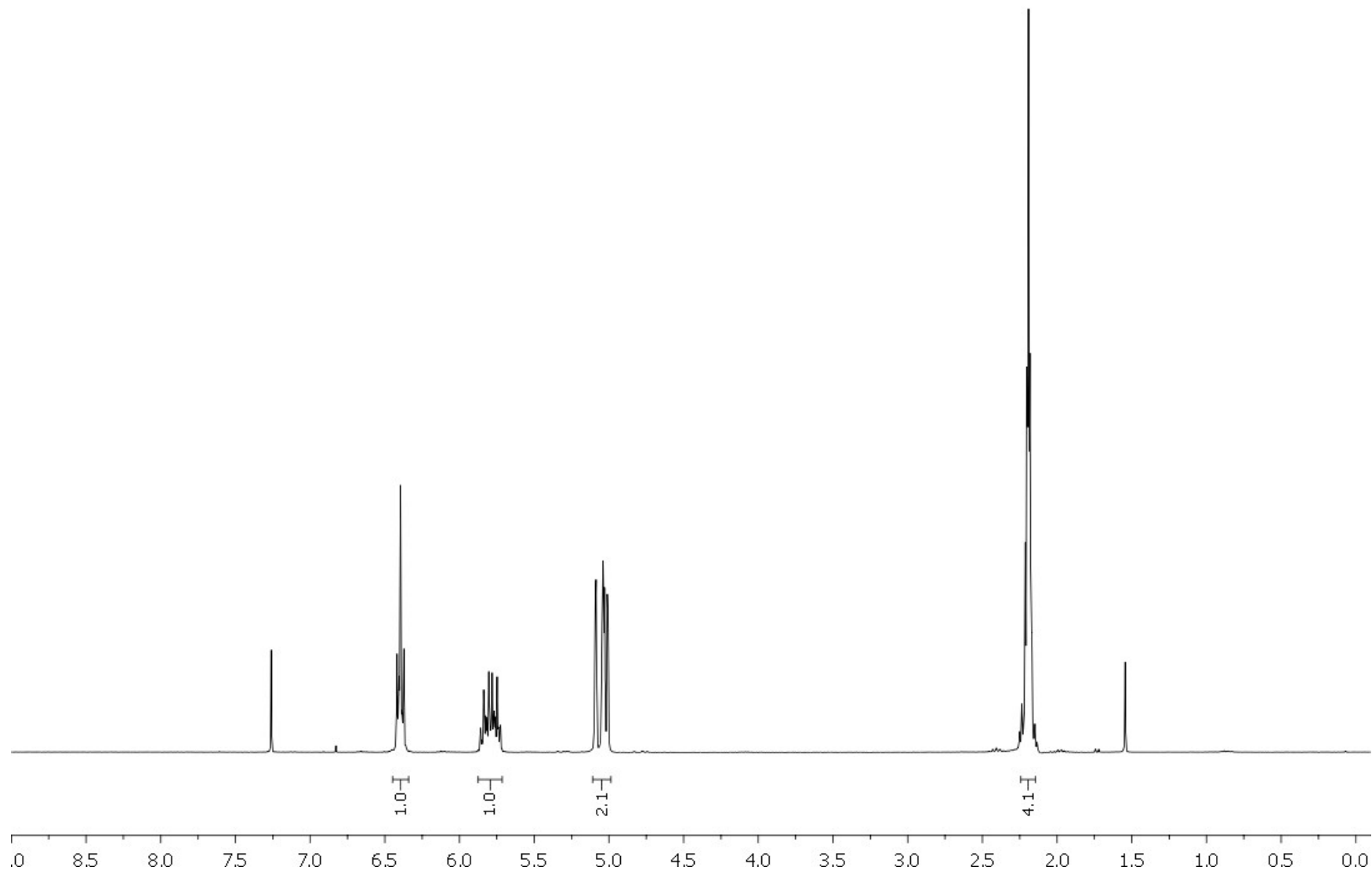


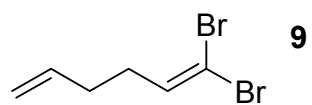
CDCl<sub>3</sub>, 75 MHz



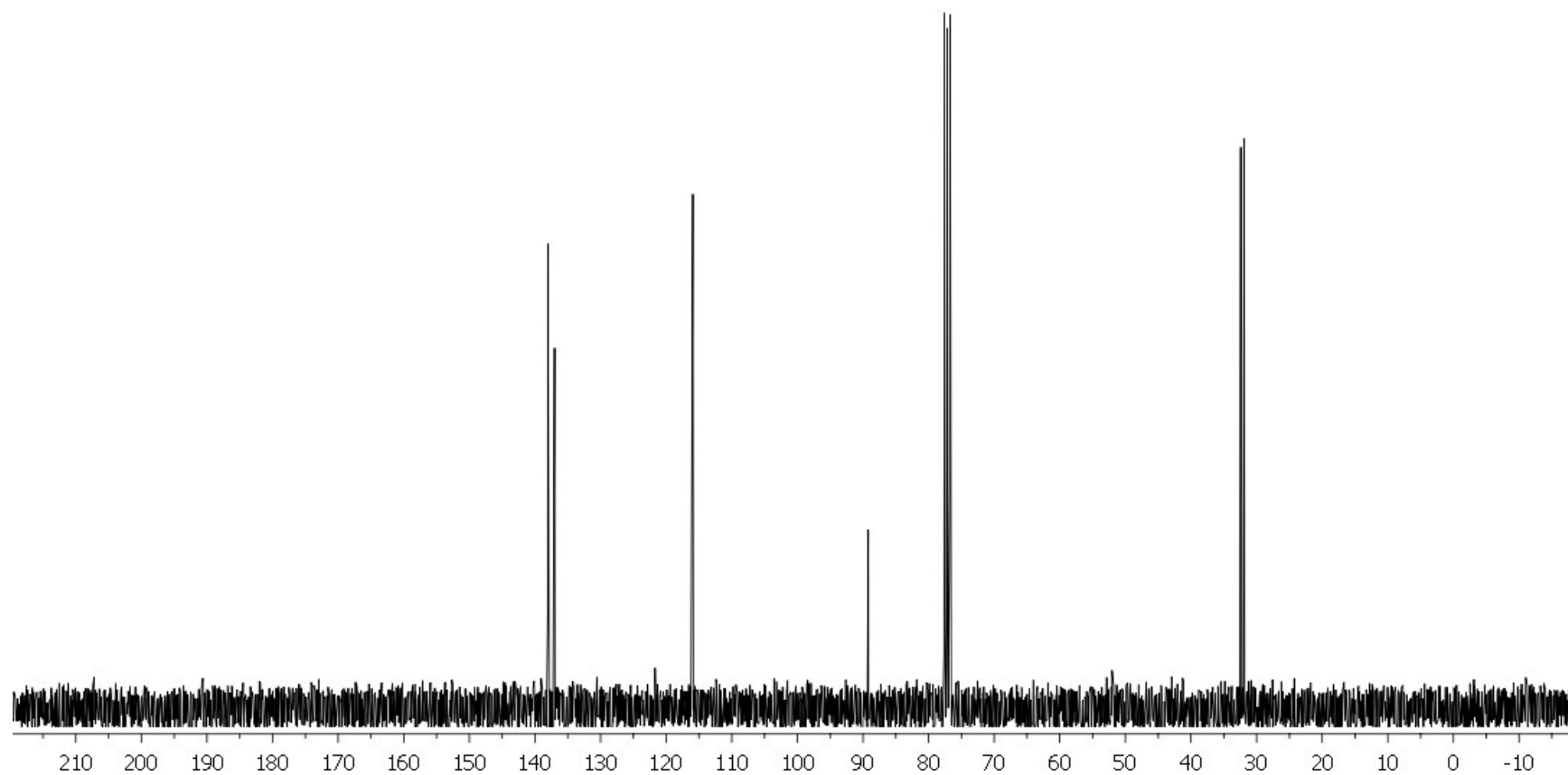


CDCl<sub>3</sub>, 300 MHz

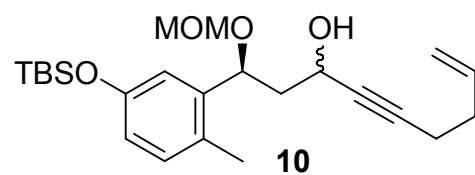




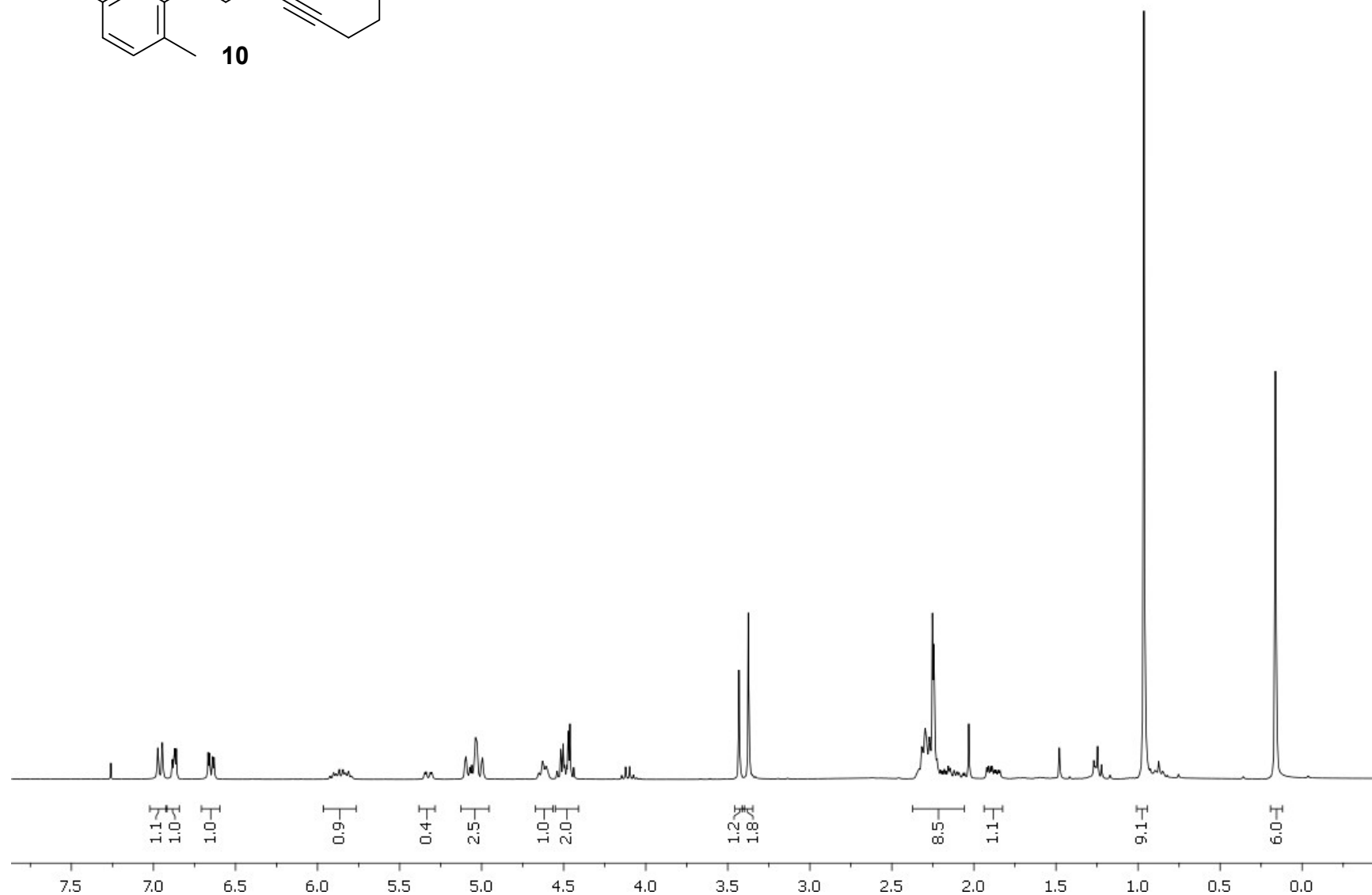
CDCl<sub>3</sub>, 75 MHz

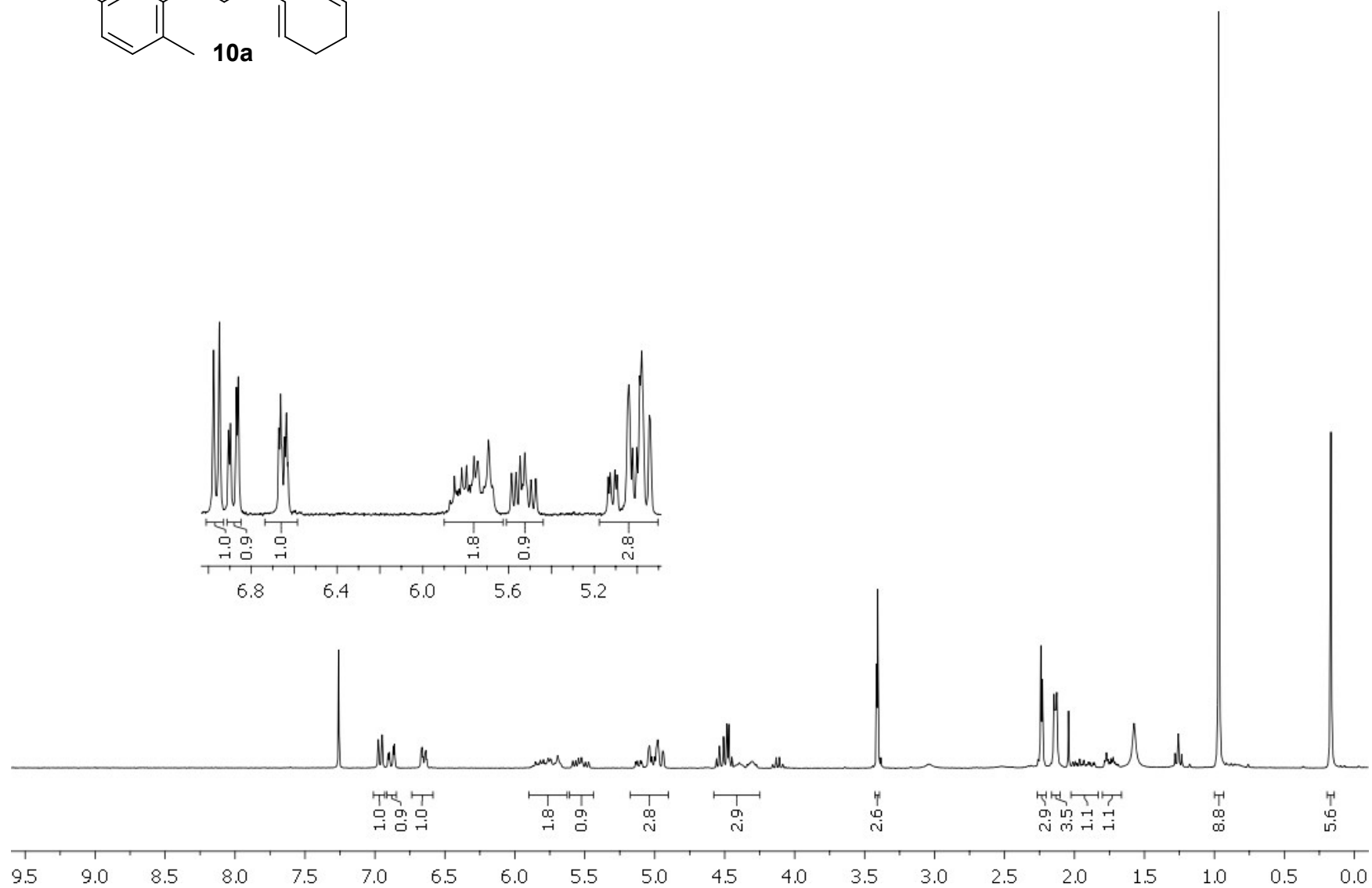
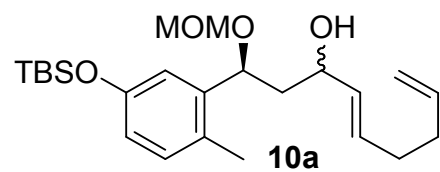


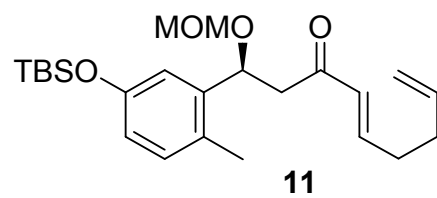




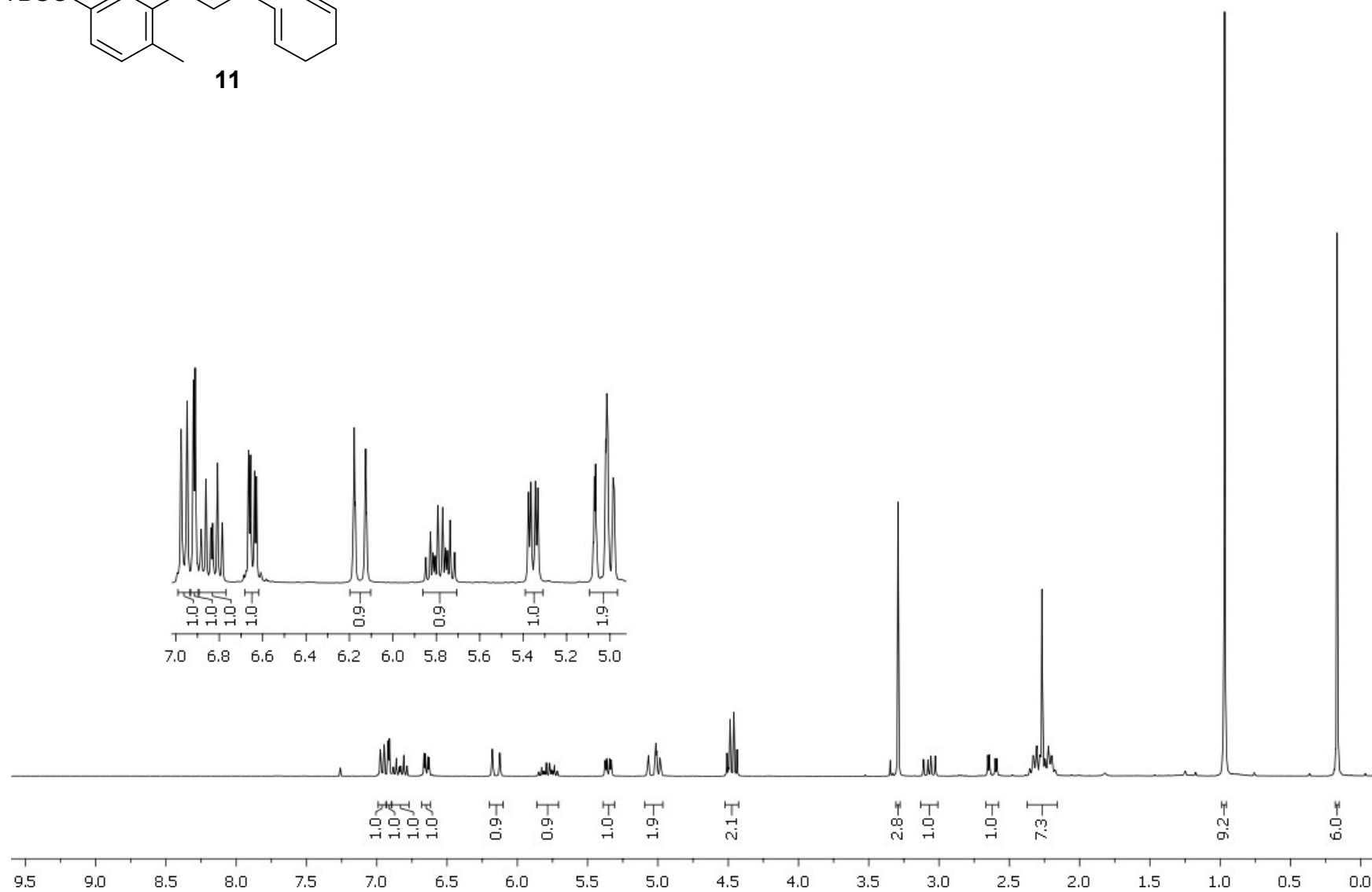
CDCl<sub>3</sub>, 300 MHz

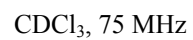


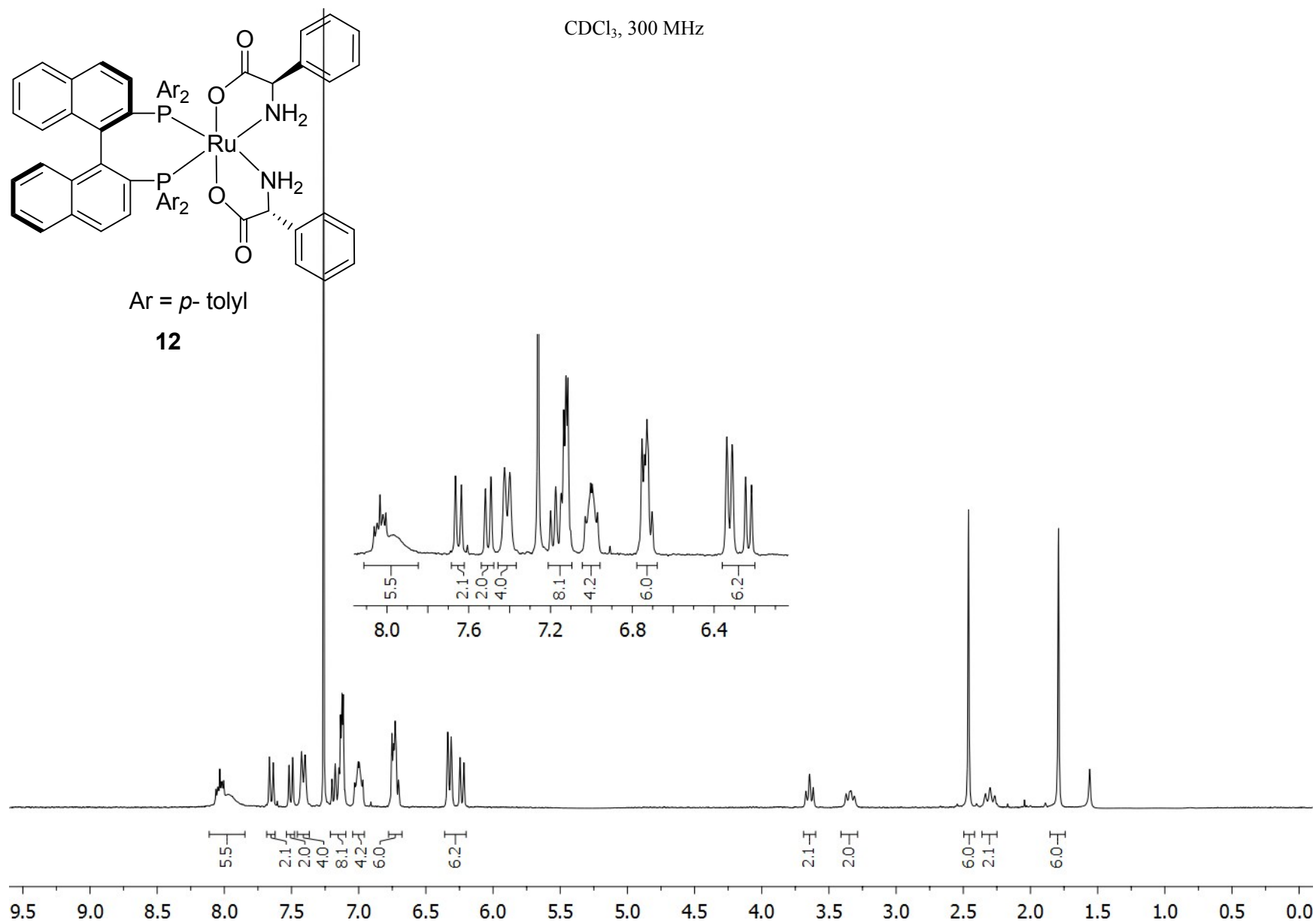


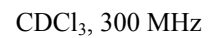


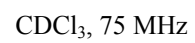
CDCl<sub>3</sub>, 300 MHz



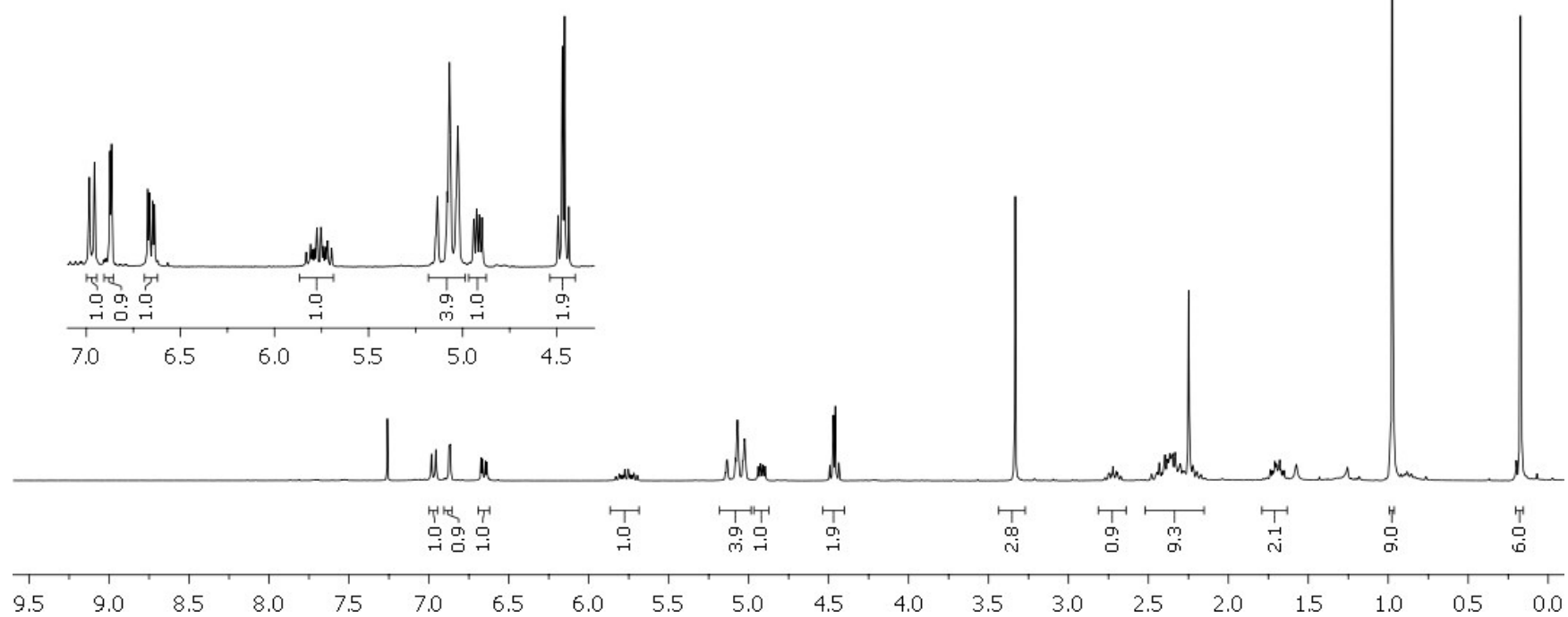
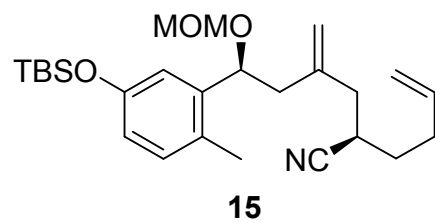




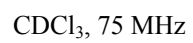


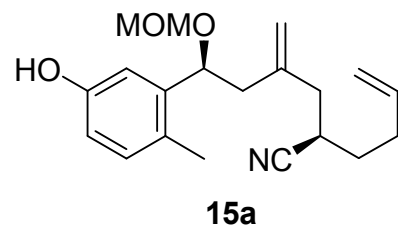


CDCl<sub>3</sub>, 300 MHz

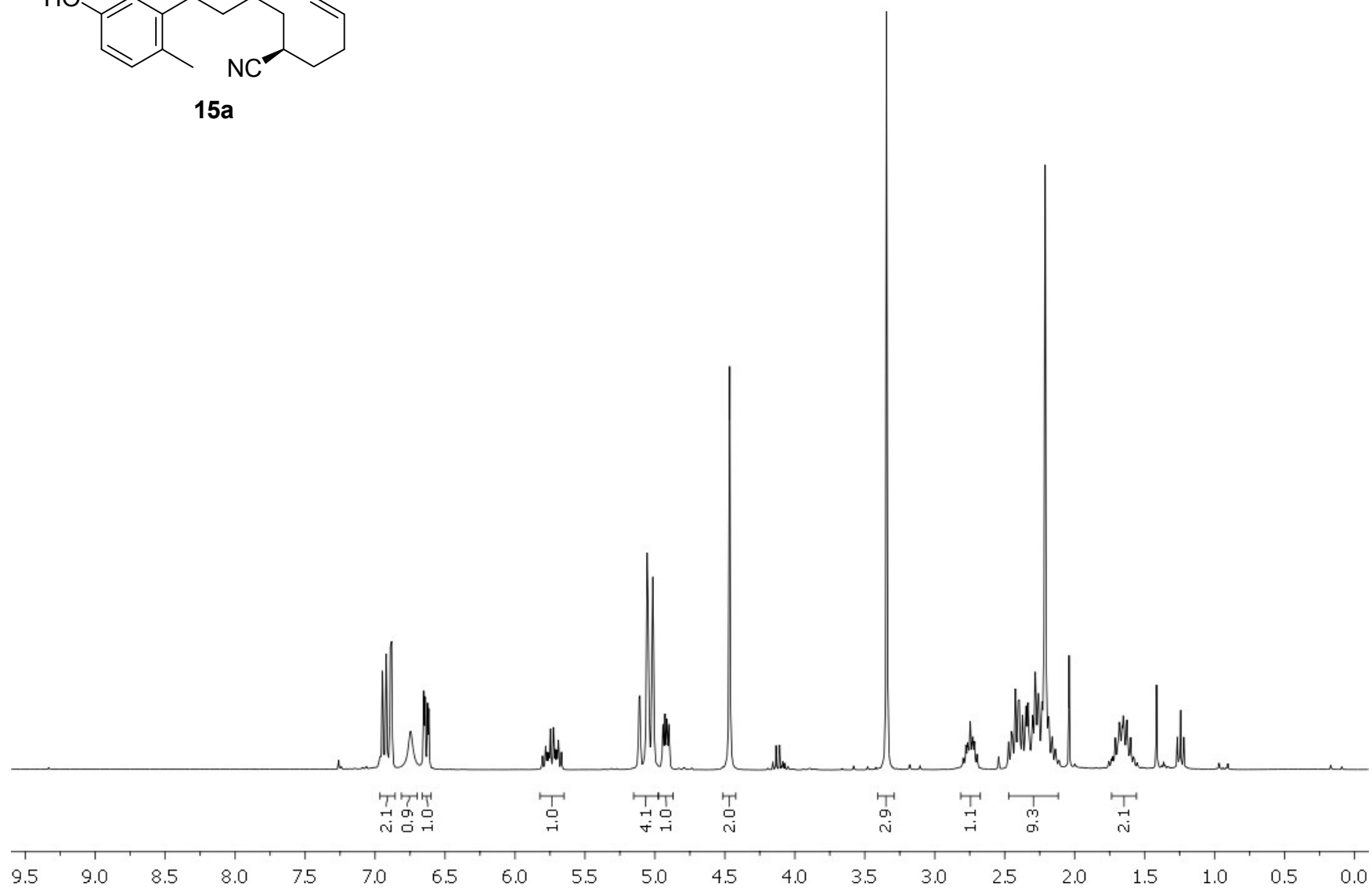


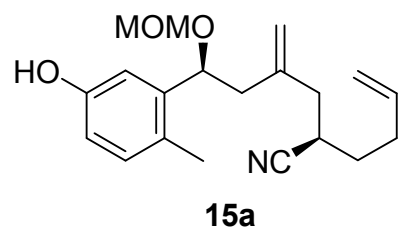




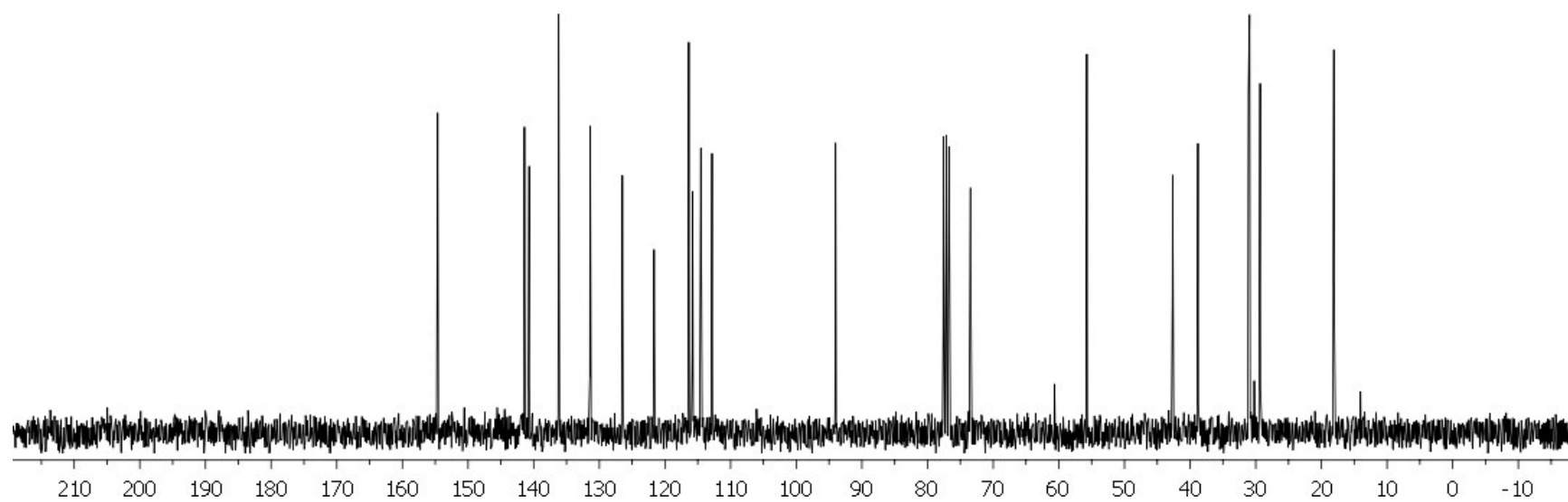


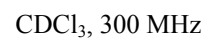
CDCl<sub>3</sub>, 300 MHz

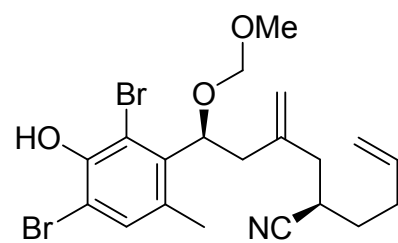




CDCl<sub>3</sub>, 75 MHz

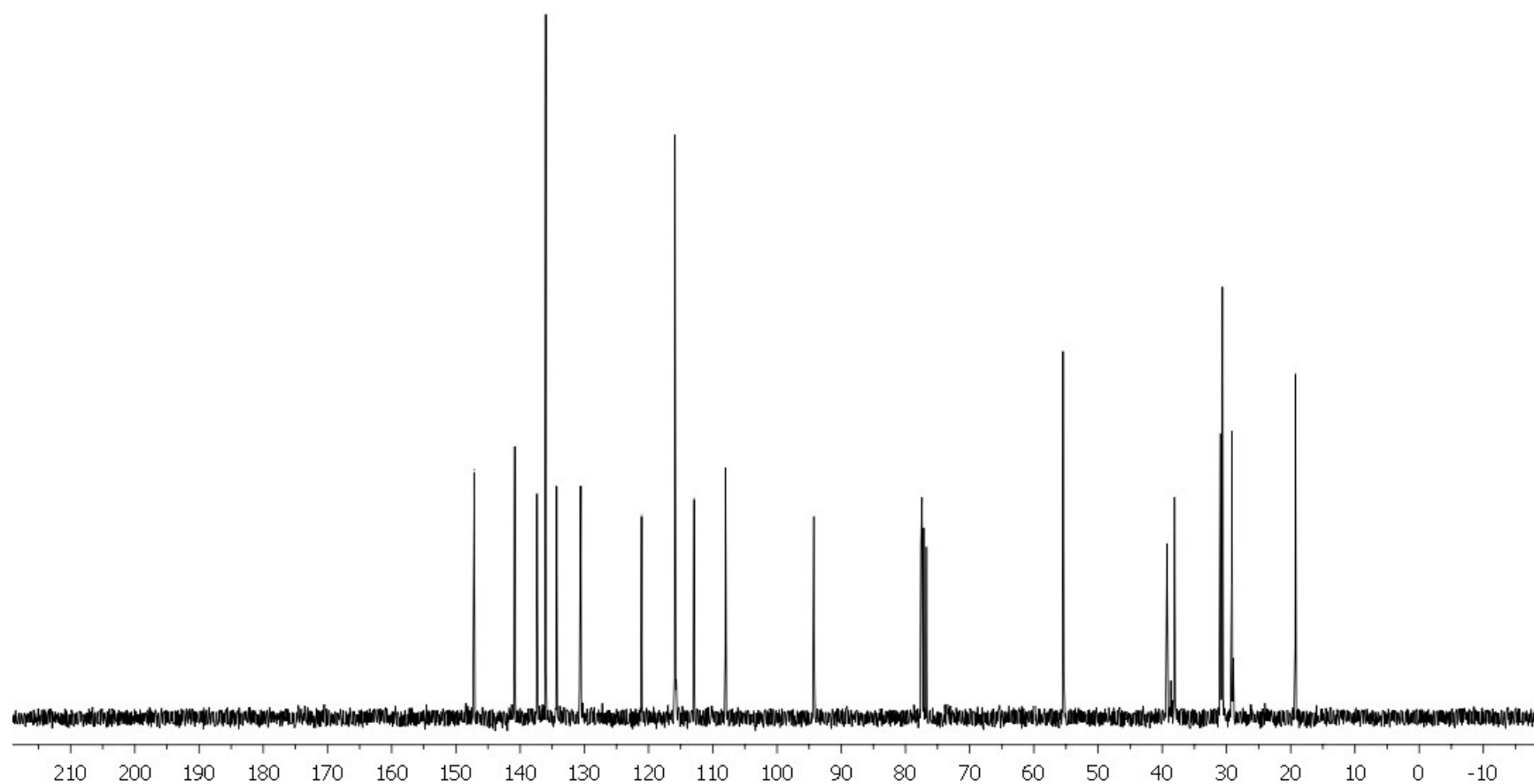


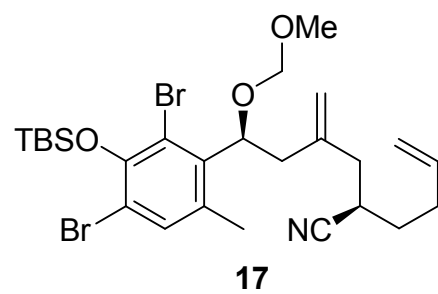




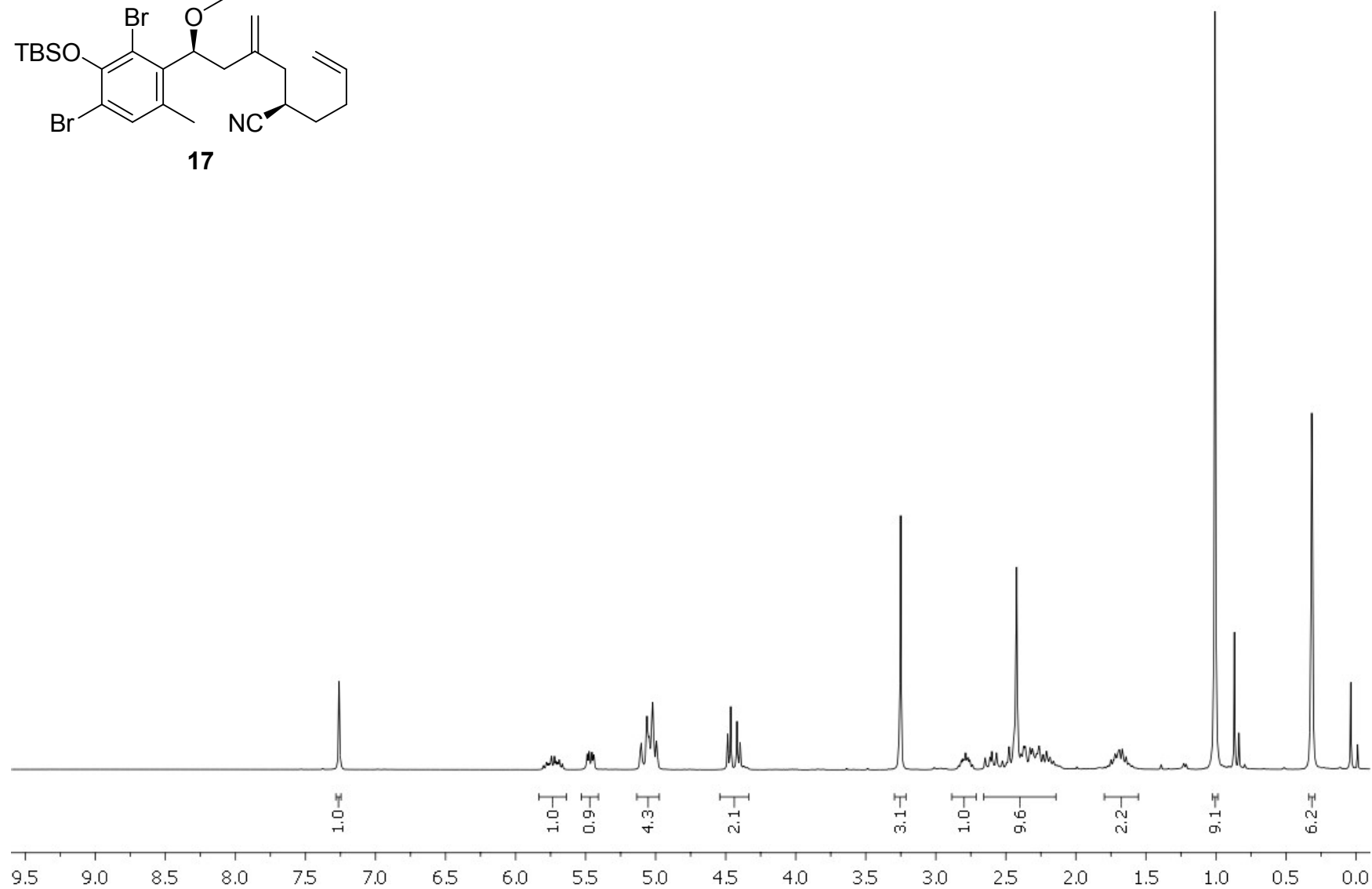
**16**

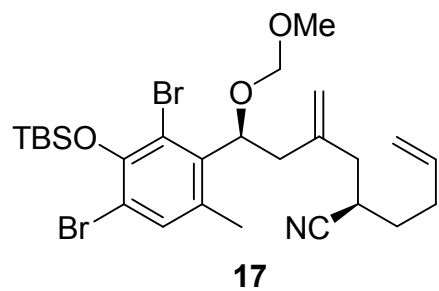
CDCl<sub>3</sub>, 75 MHz



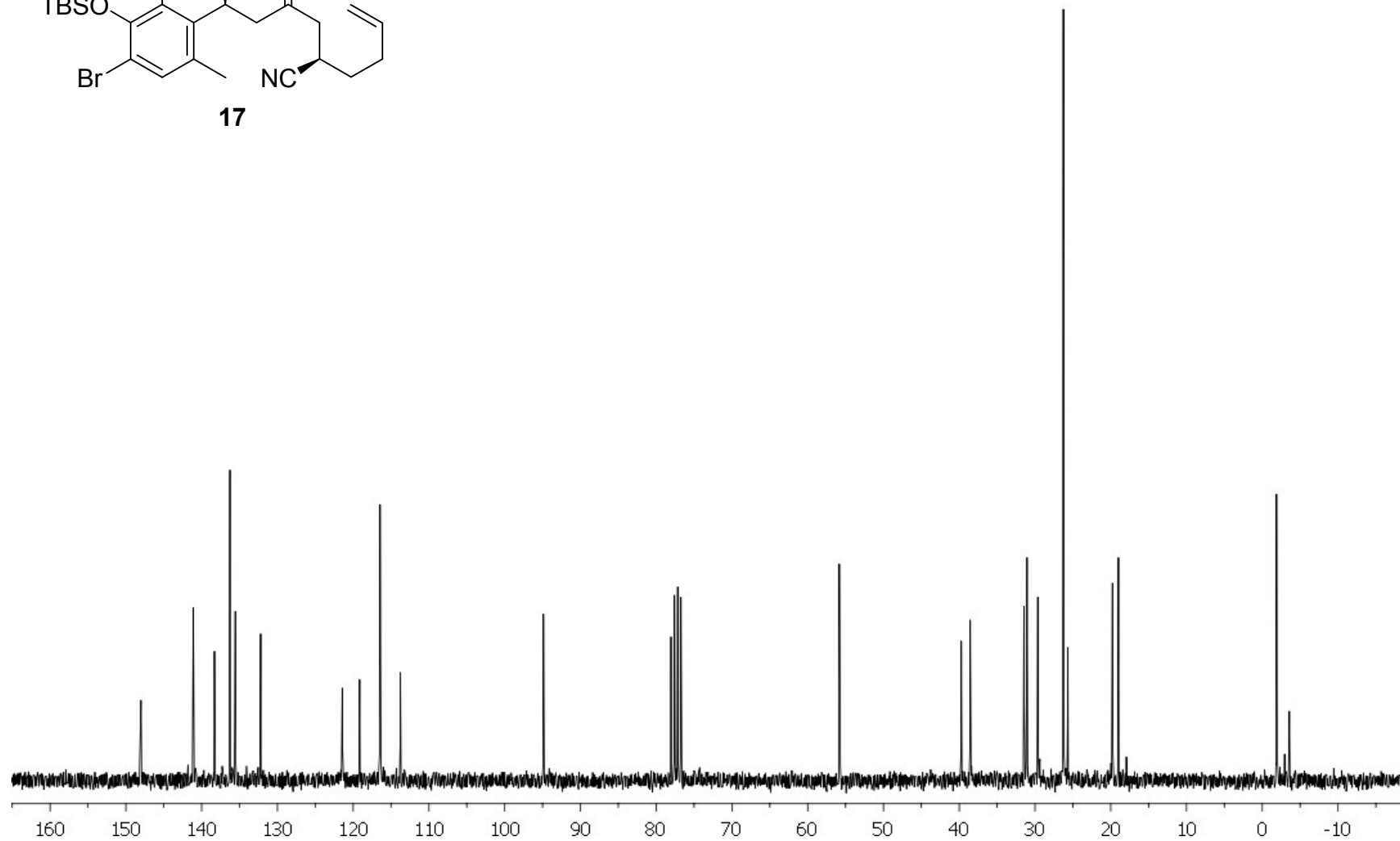


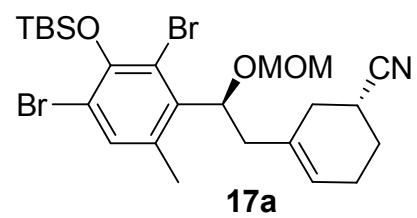
CDCl<sub>3</sub>, 300 MHz



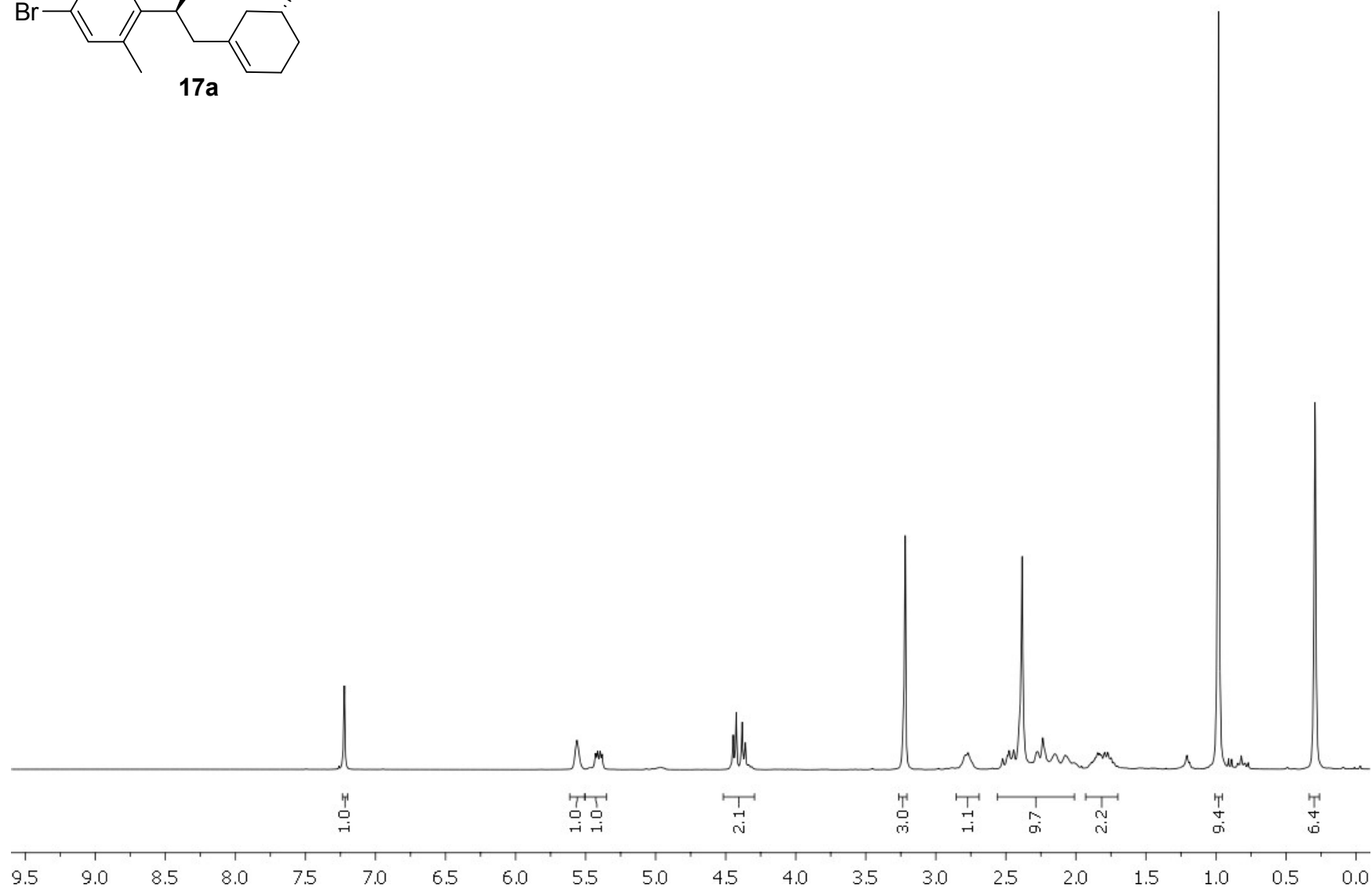


CDCl<sub>3</sub>, 75 MHz

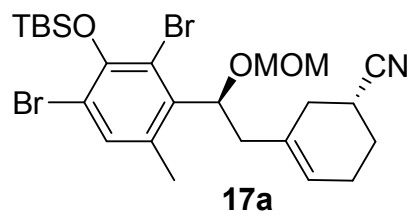




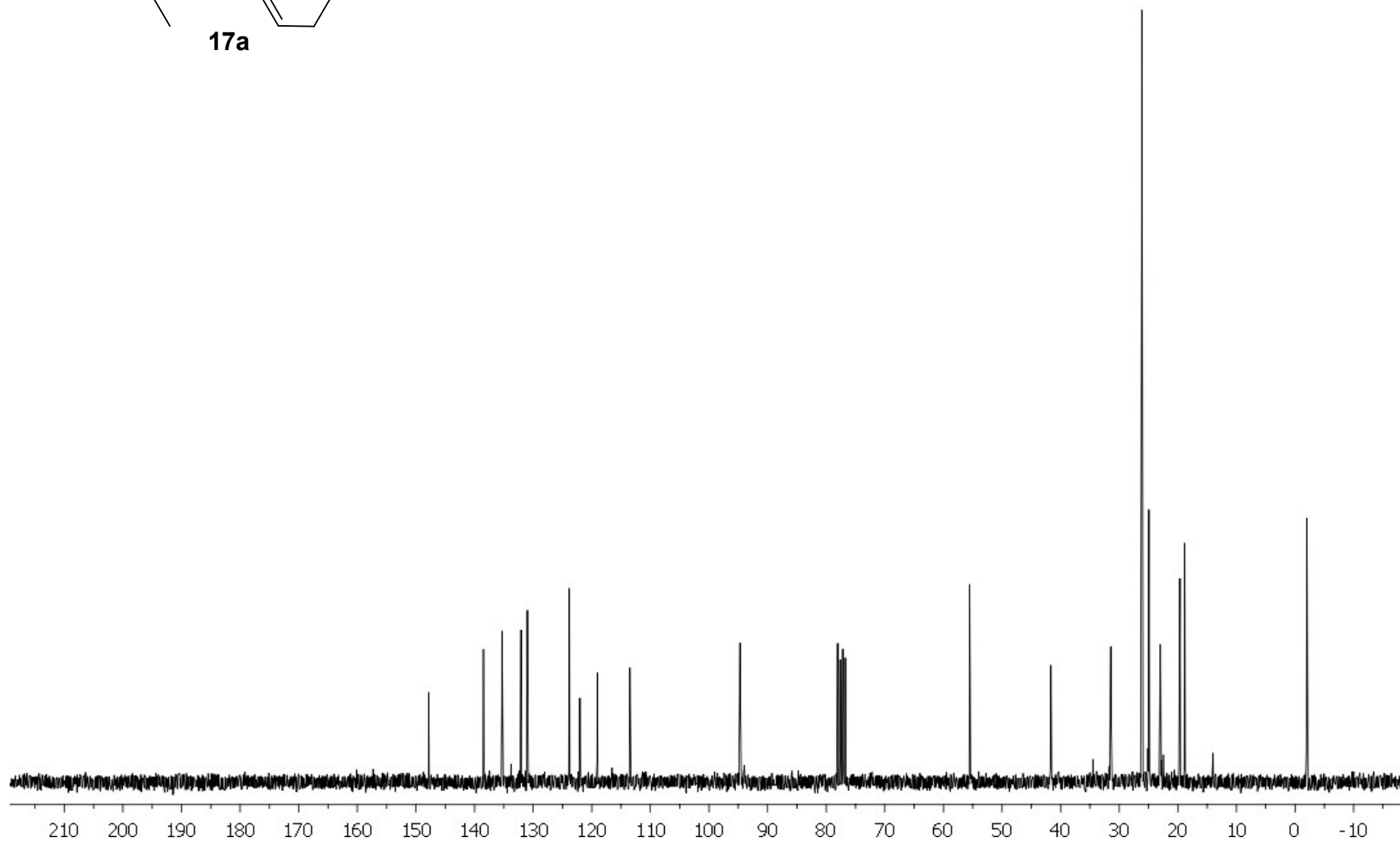
CDCl<sub>3</sub>, 300 MHz

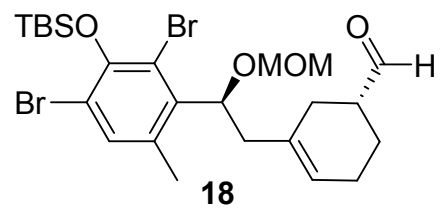




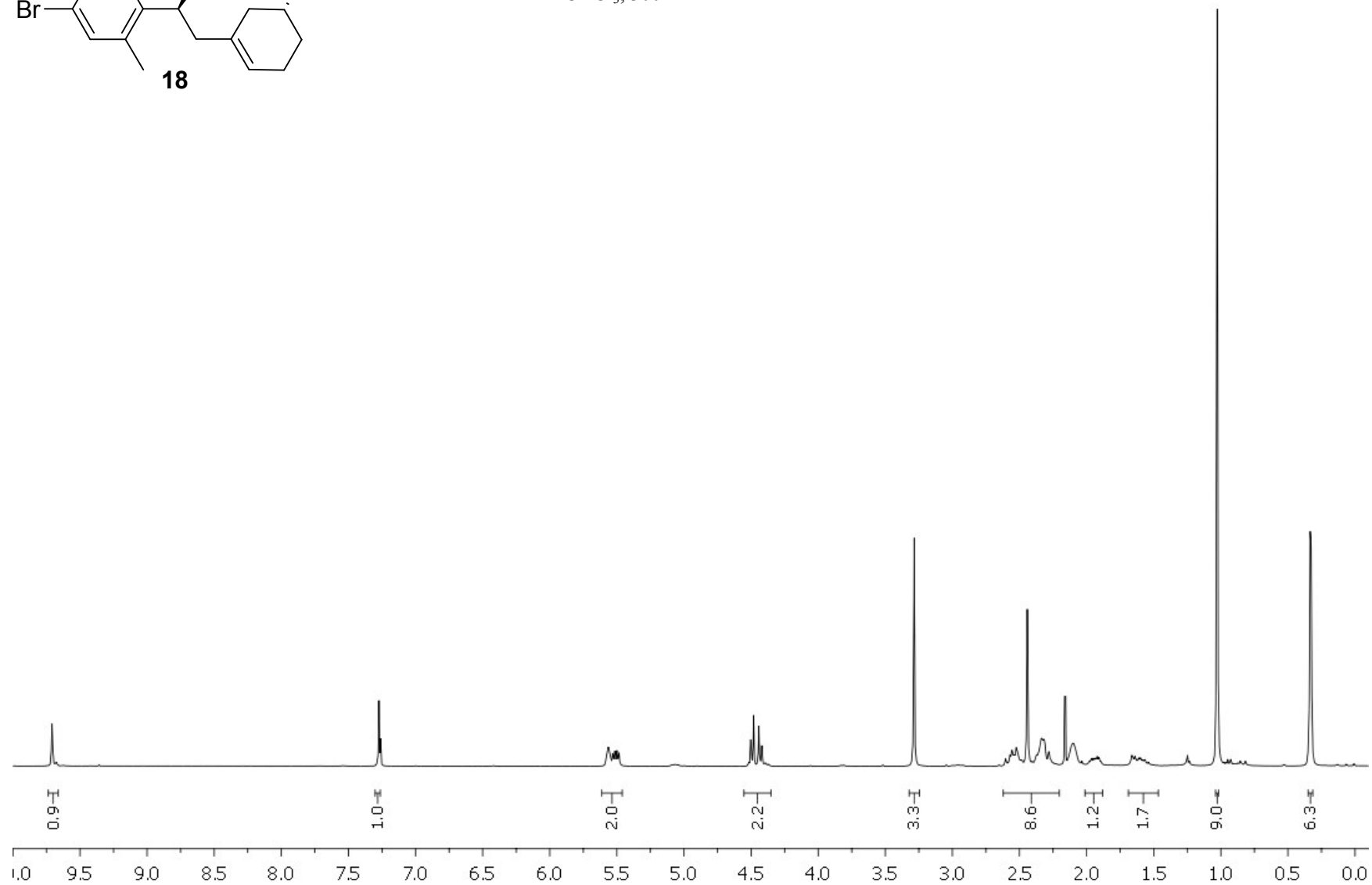


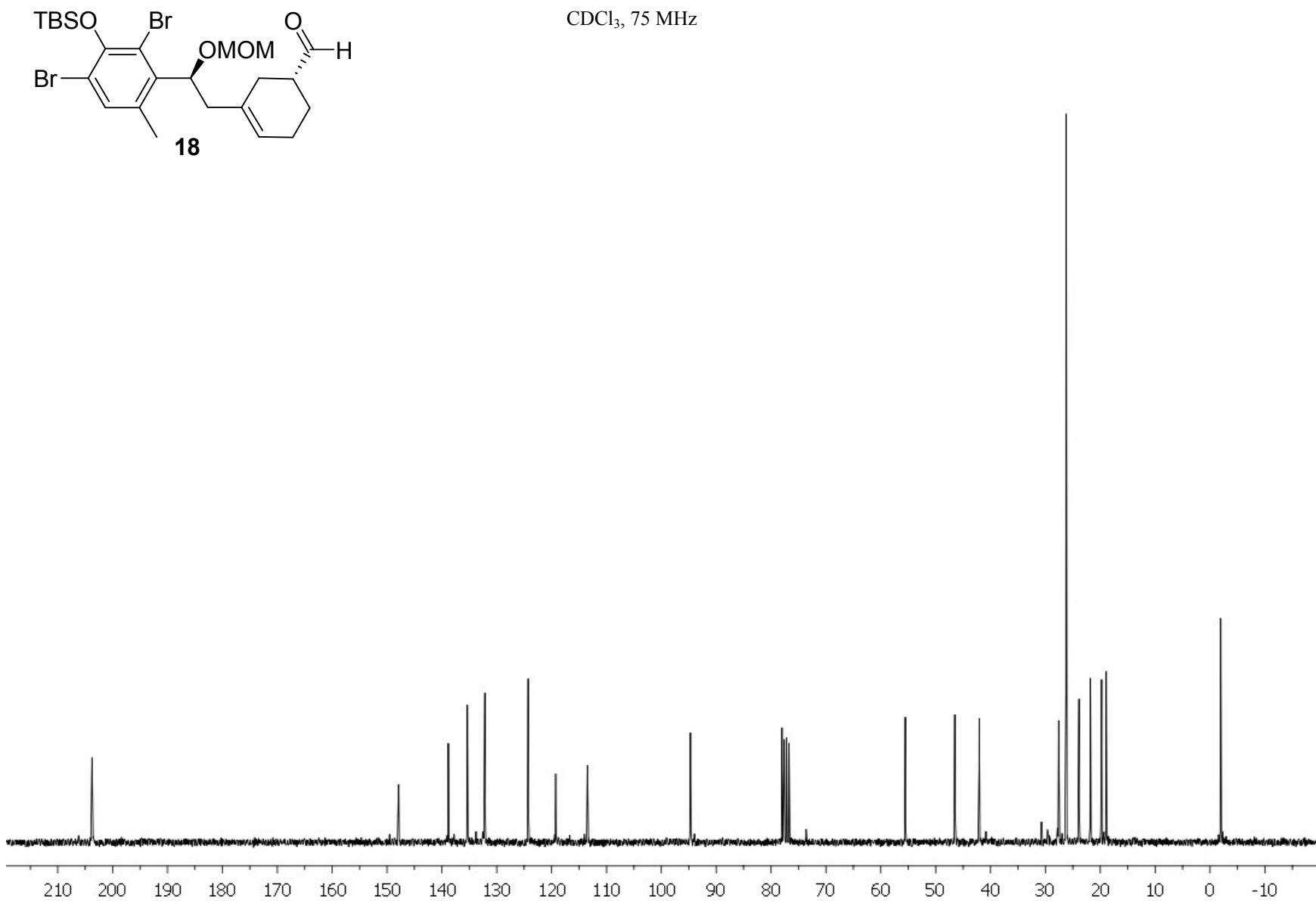
CDCl<sub>3</sub>, 75 MHz

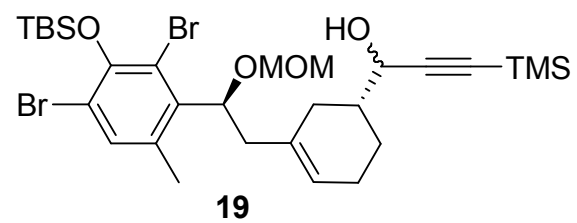




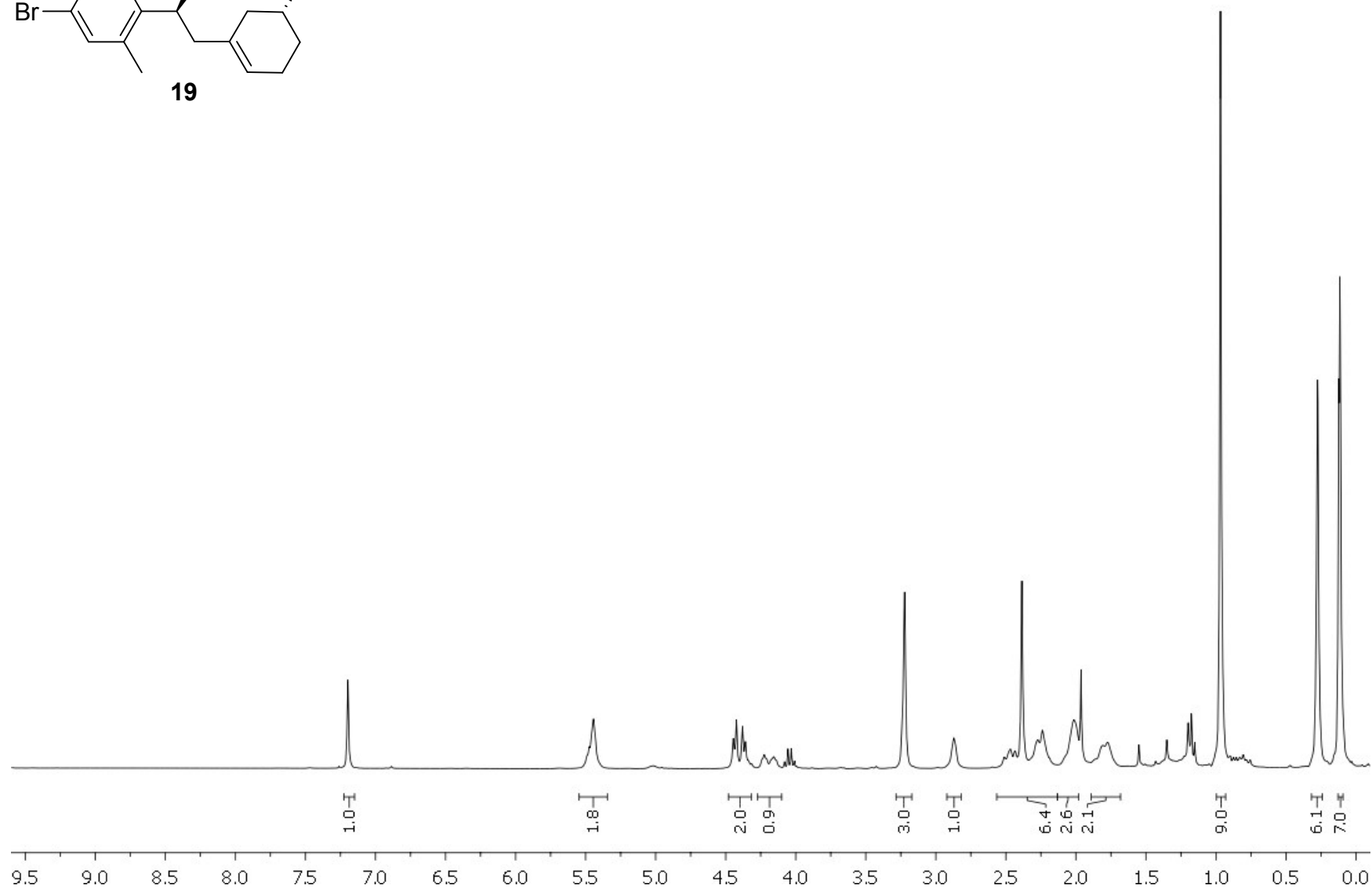
CDCl<sub>3</sub>, 300 MHz

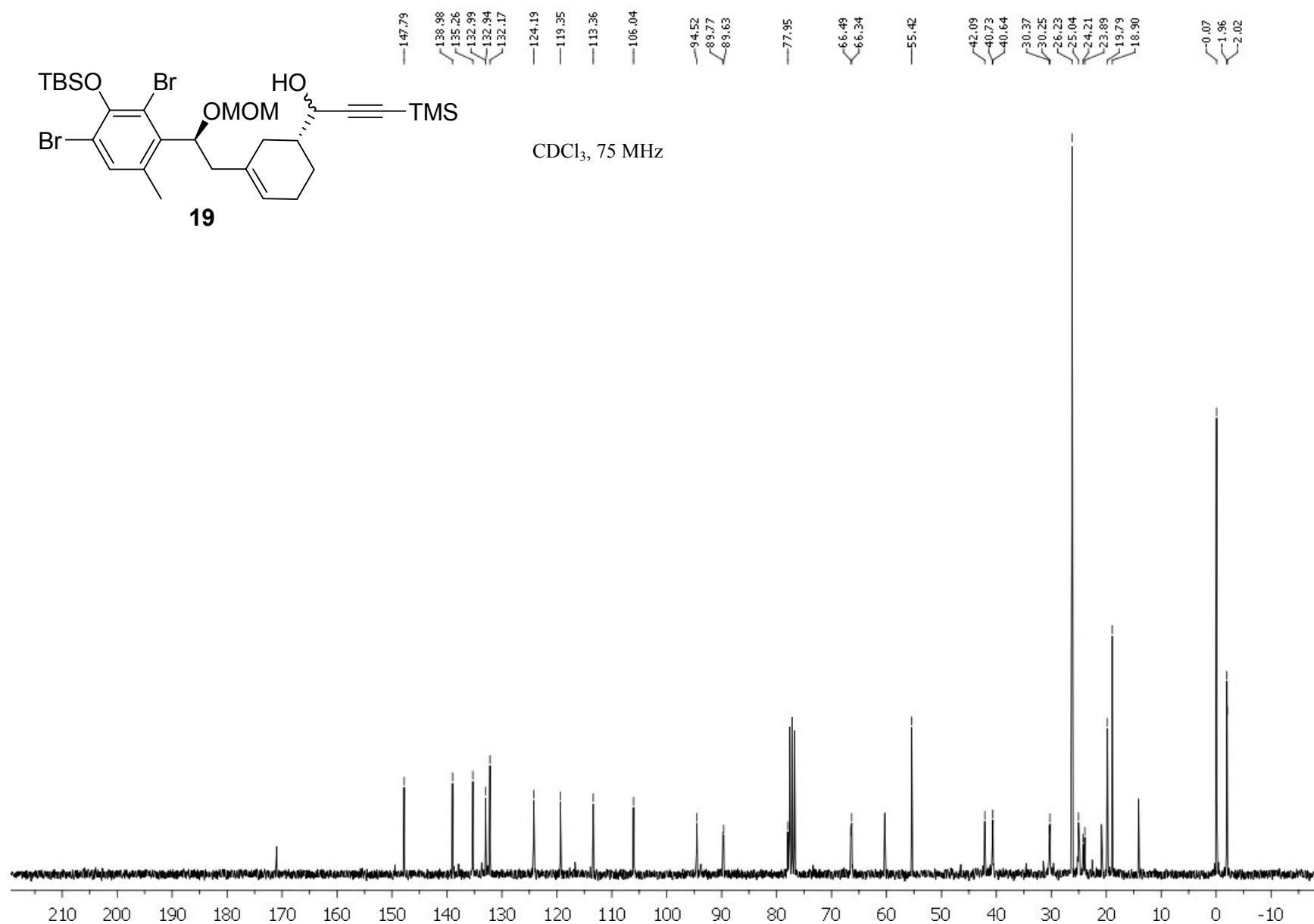


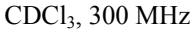


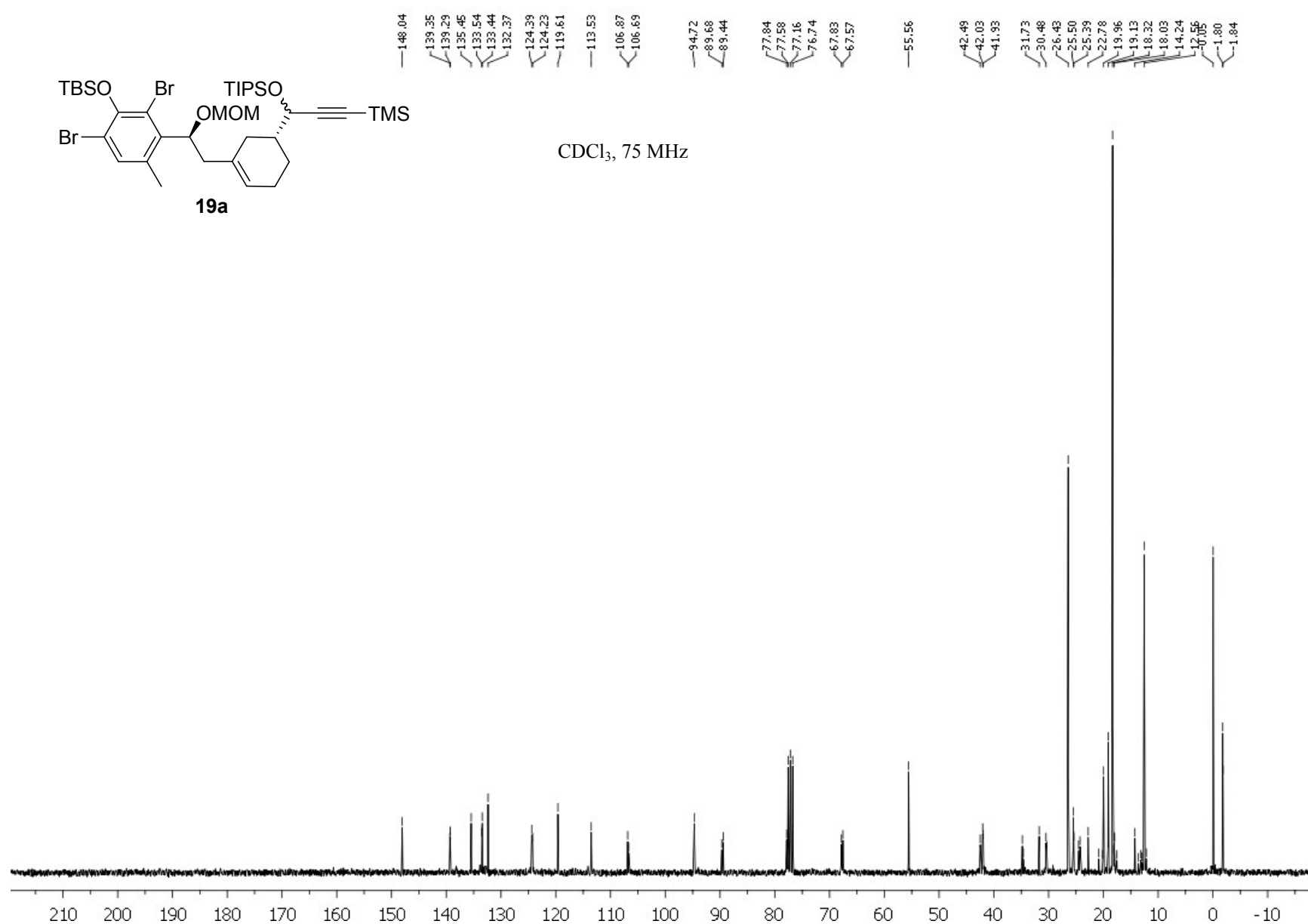


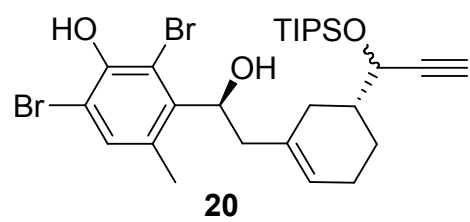
CDCl<sub>3</sub>, 300 MHz



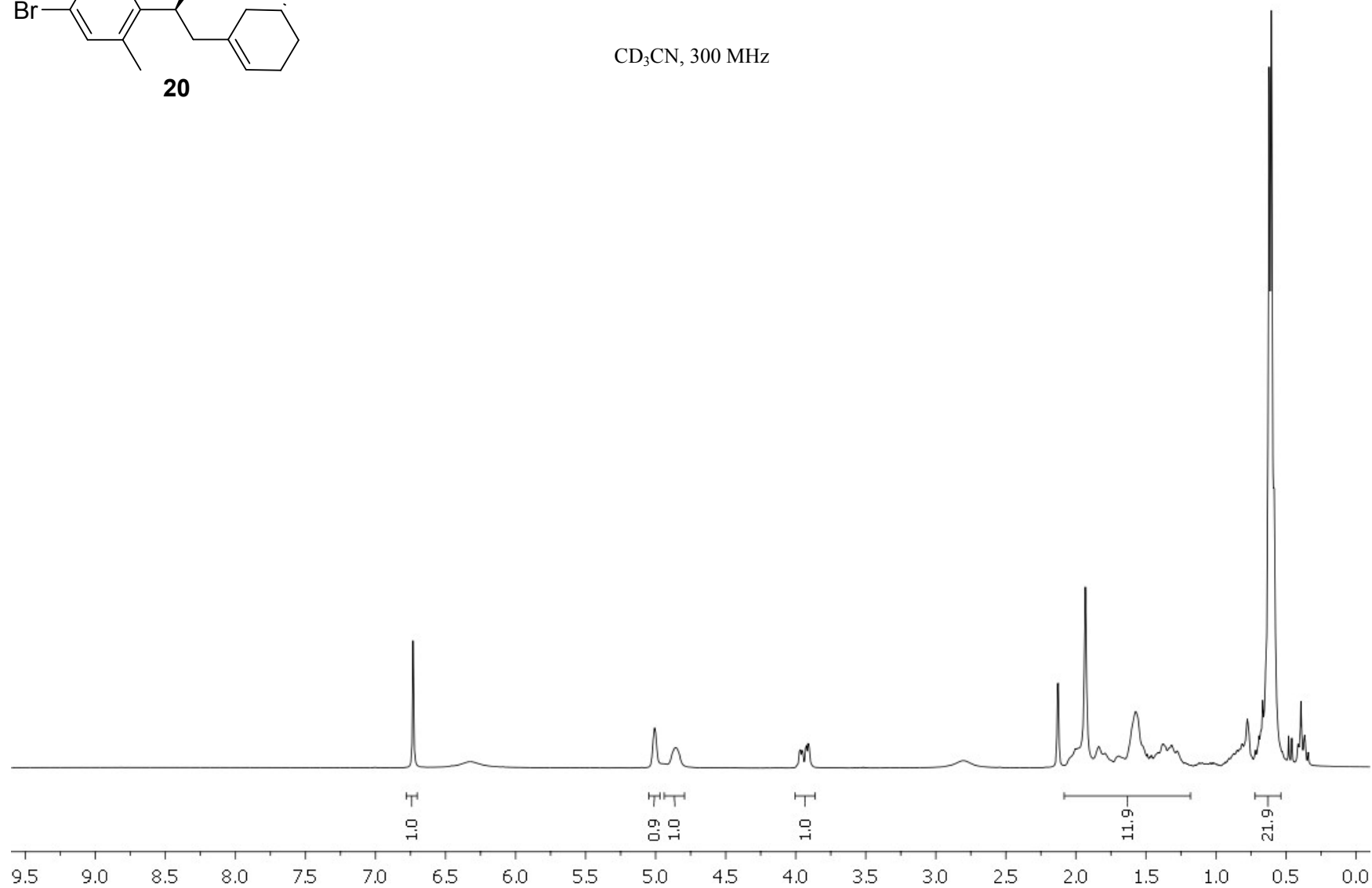




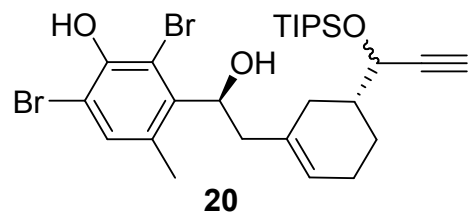




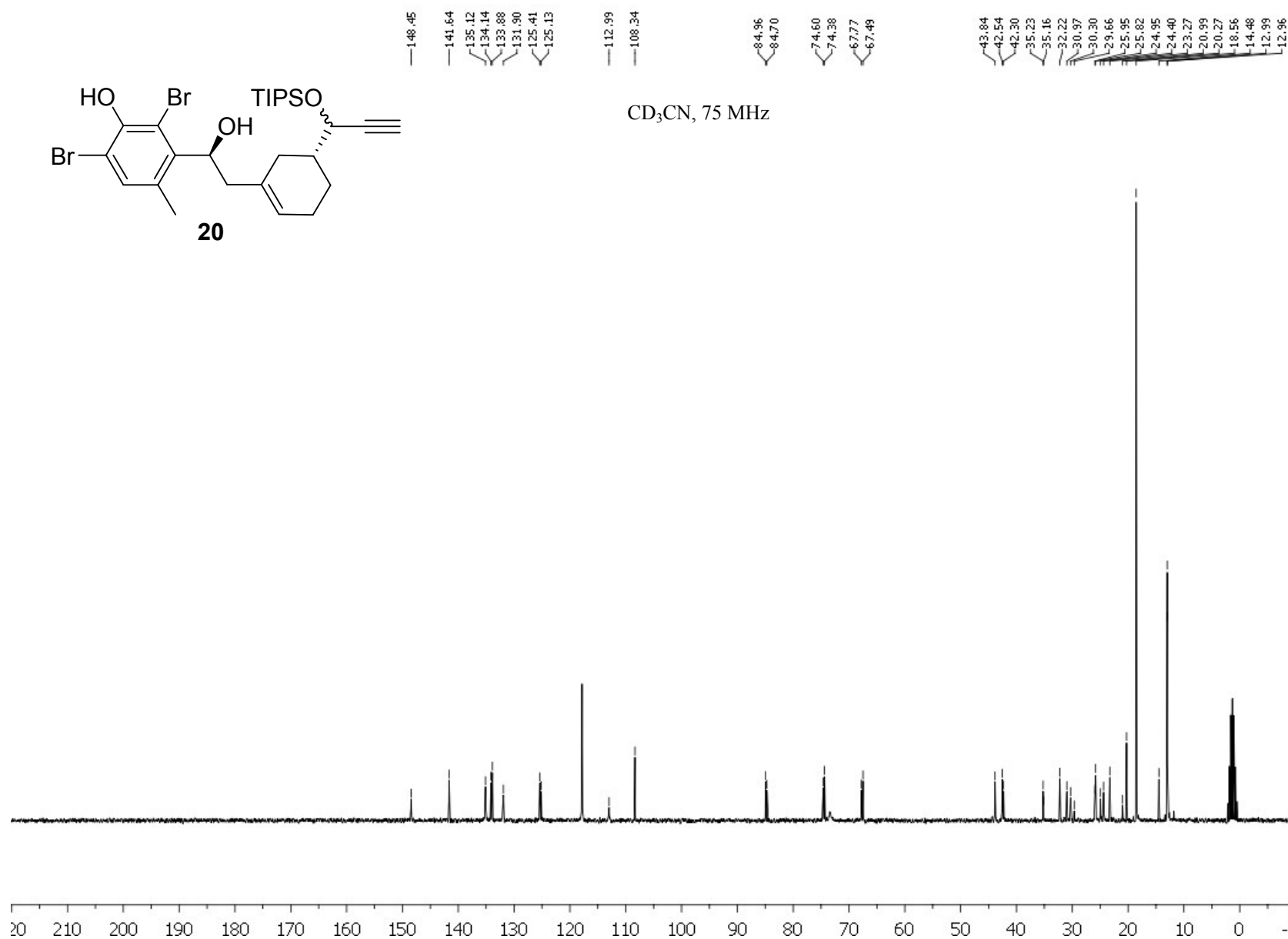
CD<sub>3</sub>CN, 300 MHz

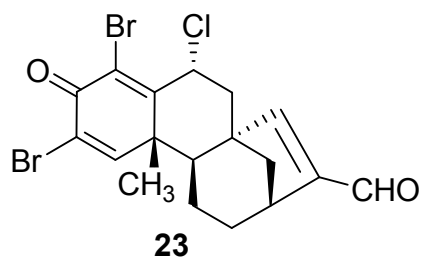






CD<sub>3</sub>CN, 75 MHz





CDCl<sub>3</sub>, 300 MHz

