SUPPORTING INFORMATION

FOR

Design, Synthesis, and Evaluation of Curcumin-Derived Arylheptanoids for Glioblastoma and Neuroblastoma Cytotoxicity

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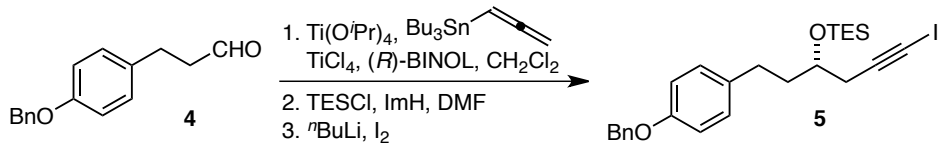
Contents

1. General

Solvents and reagents were ACS reagent grade and used without further purification unless noted below. Dimethylformamide (DMF), tetrahydrofuran (THF), dichloromethane (CH_2Cl_2) and diethyl ether (Et_2O) were passed through a column of molecular sieves and stored under argon. 1,2-Dichloroethane (DCE) was distilled, stored over 4 Å molecular sieves, and degassed prior to use. Acetic anhydride (Ac_2O) was distilled over CaH and zinc dust was washed sequentially with 1.0 M aq. HCl, water, and Et_2O prior to use.[1] All reactions were carried out in flame-dried glassware under an argon atmosphere unless otherwise specified. Curcumin was purchased as a mixture of curcumin, demethoxycurcumin and bisdemethoxycurcumin, and isolated via flash column chromatography eluting with hexanes/EtOAc (1:1). Compounds **11** and **6** were purchased and used without purification.

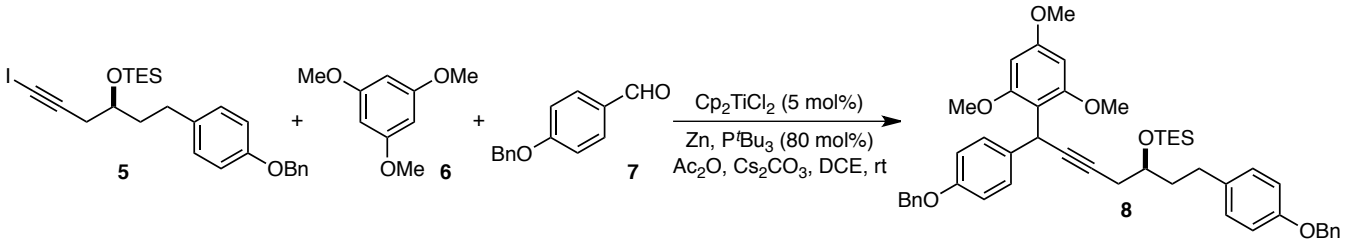
^{1}H Nuclear magnetic resonance (NMR) spectra were obtained at either 300 or 500 MHz, and ^{13}C NMR spectra at 100, 125 or 150 MHz. Chemical shifts are reported in parts per million (ppm, δ), and referenced to residual solvent or tetramethylsilane (TMS). Coupling constants are reported in Hertz (Hz). Spectral splitting patterns are designated as s, singlet; d, doublet; t, triplet; q, quartet; p, pentet; m, multiplet; comp, complex; app, apparent; hom, higher order multiplet; and br, broad. Infrared (IR) spectra were obtained using a Thermo Electron Nicolet 380 FT-IR using a silicon (Si) crystal in an attenuated total reflectance (ATR) tower and reported as wavenumbers (cm^{-1}). High and Low resolution electrospray ionization (ESI) measurements were made with a Bruker MicroTOF II mass spectrometer. Analytical thin layer chromatography (TLC) was performed using EMD 250 micron 60 F_{254} silica gel plates, visualized with UV light and stained with a *p*-anisaldehyde solution. Flash column chromatography was performed according to Still's procedure (Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923) using EMD 40-63 μm 60Å silica gel.

2. SYNTHETIC PROCEDURES

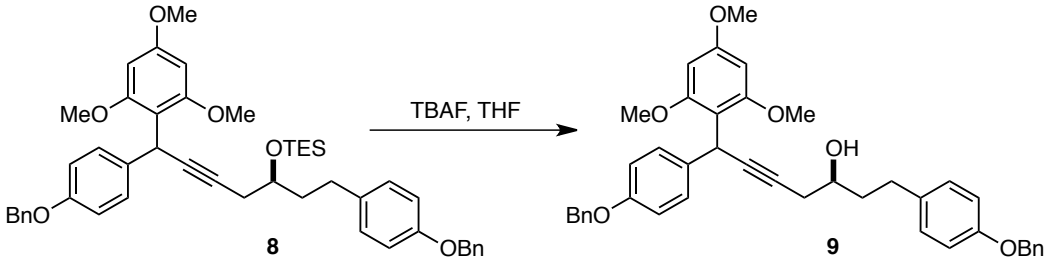


(*S*)-((1-(4-(Benzyloxy)phenyl)-6-iodohex-5-yn-3-yl)oxy)triethylsilane (5). To a solution of $TiCl_4$ (0.24 g, 1.27 mmol, 0.14 mL) in CH_2Cl_2 (25.0 mL) was added $Ti(^iOPr)_4$ (1.06 g, 3.81 mmol, 1.10 mL) dropwise at 0 °C and stirred for 1 h. Ag_2O (589 mg, 2.54 mmol) was then added in one portion and the reaction vessel wrapped in aluminum foil to exclude ambient light. The resulting mixture was stirred for 5 h then (*R*)-BINOL (1.40 g, 5.08 mmol) was added portionwise, the reaction warmed to room temperature by removal of the ice water cooling bath, and stirring continued for 2 h. The reaction was cooled to –20 ˚C, then aldehyde **4**[2] (3.06 g, 12.73 mmol) and allenyltributyltin(IV) (12.60 g, 38.2 mmol) were added sequentially. After continued stirring for 24 h at –20 ˚C, saturated aqueous $NaHCO_3$ (25.0 mL) was added, and the resulting mixture was allowed to warm to room temperature by removal of the cooling bath. The biphasic mixture was filtered through celite eluting with Et_2O (100 mL), and the layers separated. The aqueous phase was extracted with Et_2O (3 x 15 mL), and the combined organic extracts were dried (Na_2SO_4) and concentrated under reduced pressure. The resulting crude mixture was purified by flash chromatography eluting with hexanes/EtOAc (3:1) to provide 3.1 g (85%, 83% *ee*) of the target alcohol as a colorless oil. Enantiometic excess was determined by HPLC analysis using a Chiral-Dex OD column (96:4 hexanes/^{i}PrOH) t_r = 26.48 min; t_r = 31.15 min ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.48-7.46 (m, 2 H), 7.43-7.40 (m, 2 H), 7.37-7.34 (m, 1 H), 7.18-7.15 (m, 2 H), 6.96-6.94 (m, 2 H), 5.07 (s, 2 H), 3.82-3.79 (m, 1 H), 2.81-2.76 (m, 1 H), 2.71-2.65 (m, 1 H), 2.49-2.35 (m, 2 H), 2.11-2.10 (m, 1 H) 1.89-1.85 (m, 2 H); ^{13}C NMR (125 MHz) δ 157.2, 137.3, 134.1, 129.5, 128.7, 128.1, 127.6, 115.0, 80.9, 71.2, 70.2, 69.2, 38.1, 31.1, 27.6; IR (neat) 3285, 3030, 2926, 2247, 1610, 1510, 1237; $[\alpha]_D$ = –11.10˚ (c = 1.0, $CHCl_3$); HRMS (ESI) *m/z* 281.1524 [$C_{19}H_{20}O_2$ (M+1) requires 281.1536].

Imidazole (2.6 g, 38.19 mmol) and TESCl (4.27 mL, 25.5 mmol) were added sequentially to a solution of the starting alcohol (3.10 g, 10.88 mmol) in DMF (25 mL) at room temperature and stirred for 10 min. The mixture was then diluted with water (20 mL) and Et_2O (50 mL), the layers separated, and the organic phase washed with water (2 x 10 mL). The resulting organic layer was dried (Na_2SO_4) and concentrated under reduced pressure. The crude mixture was dissolved in THF (20 mL) and cooled to –78 °C. ^{n}BuLi (1.7 M in hexanes, 7.46 mmol, 4.39 mL) was added dropwise, the mixture stirred for 30 min, then a solution of I_2 (2.1 g, 8.15 mmol) in THF (5.0 mL) was added. The reaction mixture was allowed to warm to room temperature by removal of the cooling bath, diluted with saturated aqueous $Na_2S_2O_3$, and the layers separated. The aqueous phase was extracted with Et_2O (3 x 10 mL) and the combined organic extracts were dried (Na_2SO_4) and concentrated under reduced pressure. The resulting crude mixture was purified by flash chromatography eluting with hexanes/CH_2Cl_2 (1:1) to provide 3.11 g (55%) of **5** as a pale yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.47-7.46 (m, 2 H), 7.43-7.39 (m, 2 H), 7.36-7.33 (m, 1 H), 7.15-7.13 (m, 2 H), 6.95-6.93 (m, 2 H), 5.07 (s, 2 H), 3.91-3.86 (m, 1 H), 2.74-2.56 (m, 4 H), 1.96-1.89 (m, 1 H), 1.86-1.79 (m, 1 H), 1.01 (t, *J* = 8.0 Hz, 9 H), 0.65 (q, *J* = 7.5 Hz, 6 H). ^{13}C NMR (125 MHz) δ 157.2, 137.4, 134.7, 129.6, 129.4, 128.8, 128.1, 127.7, 115.0, 91.9, 70.8, 70.2, 39.1, 30.8, 29.9, 7.1, 5.2; IR (neat) 3063, 3031, 2952, 2910, 2875, 2247, 1611, 1583, 1510, 1455, 1379, 1239, 1102, 1016, 909; HRMS (ESI) *m/z* 521.1348 [$C_{25}H_{33}O_2ISi$ (M+1) requires 521.1367]; $[\alpha]_D$ = –11.30˚ (c = 1.0, $CHCl_3$).

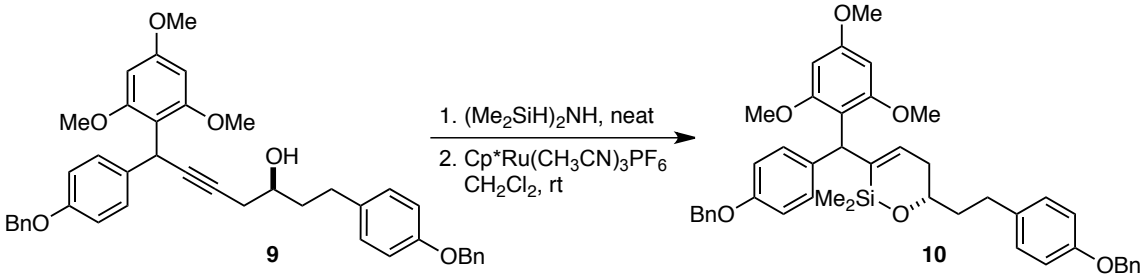


(((3*S*)-1,7-Bis(4-(benzyloxy)phenyl)-7-(2,4,6-trimethoxyphenyl)hept-5-yn-3-yl)oxy)triethylsilane (8). A 25 mL round bottom flask, equipped with a magnetic stir bar, was charged with Cp_2TiCl_2 (14 mg, 0.059 mmol) and zinc dust (154 mg, 2.36 mmol) then purged with argon for 5 min. Dry, degassed DCE (2.0 mL) was added and the suspension stirred at room temperature until a blue/green color persisted. A solution of $^tBu_3P$ (95 mg, 0.472 mmol) in DCE (1.0 mL) was then added dropwise, and the reaction stirred for an additional 10 min. A solution of **7**[2] (250 mg, 1.18 mmol), **5** (1.23 g, 2.36 mmol), and **6** (397 mg, 2.36 mmol) in DCE (2.0 mL) was then added, and the reaction stirred for 1 h. Cs_2CO_3 (384 mg, 1.18 mmol) was added in one portion followed by the slow addition of Ac_2O (0.265 mg, 2.60 mmol, 0.245 mL) in DCE (5.0 mL) over 11 h *via* syringe pump. After the addition was complete, the reaction was diluted with CH_2Cl_2 (10 mL), filtered through a plug of silica gel eluting with CH_2Cl_2 (250 mL), and the filtrate concentrated under reduced pressure. The crude residue was purified by flash chromatography eluting with hexanes/CH_2Cl_2 (3:1 → 0:1) to provide 893 mg (>99%) of **8** in a 1:1 mixture of diastereomers as a clear, yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) Isomer A: δ 7.47-7.32 (m, 12 H), 7.11 (d, *J* = 8.5 Hz, 2 H), 6.92-6.87 (comp, 4 H), 6.15 (br s, 2 H), 5.65 (br s, 1 H), 5.07 (br s, 2 H), 5.05 (br s, 2 H), 3.97-3.89 (m, 1 H), 3.82 (s, 3 H), 3.72 (s, 6 H), 2.80-2.74 (m, 2 H), 2.55-2.44 (comp, 2 H), 2.12-2.05 (m, 2 H), 1.01 (t, *J* = 8 Hz, 9 H), 0.66 (q, *J* = 8.0 Hz, 6 H). Isomer B: δ 7.47-7.32 (m, 12 H), 7.11 (d, *J* = 8.5 Hz, 2 H), 6.92-6.87 (comp, 4 H), 6.14 (br s, 2 H), 5.65 (br s, 1 H), 5.07 (br s, 2 H), 5.05 (br s, 2 H), 3.97-3.89 (m, 1 H), 3.82 (s, 3 H), 3.71 (s, 6 H), 2.66-2.60 (m, 2 H), 2.55-2.44 (comp, 2 H), 1.96-1.88 (m, 2 H), 1.01 (t, *J* = 8.0 Hz, 9 H), 0.65 (q, *J* = 8.0 Hz, 6 H). ^{13}C NMR (125 MHz) Isomer A: δ 160.3, 158.6, 157.0, 157.0, 137.5, 137.4, 135.2, 134.7, 129.5, 128.7, 128.5, 128.4, 128.0, 127.7, 127.1, 126.0, 114.9, 114.2, 114.2, 112.0, 91.6, 82.8, 71.3, 70.2, 56.1, 55.4, 38.7, 38.6, 30.7, 30.3, 28.2, 7.1, 5.2; Isomer B: δ 160.3, 158.6, 157.0, 157.0, 137.5, 137.4, 135.2, 134.7, 129.5, 128.7, 128.5, 128.4, 128.0, 127.7, 127.1, 126.0, 114.9, 114.2, 114.2, 112.0, 91.5, 82.8, 71.2, 70.2, 56.0, 55.4, 38.7, 38.6, 30.7, 30.2, 28.2, 7.1, 5.2; IR (neat) 3063, 3033, 2954, 2932, 2877, 2859, 1641, 1609, 1512, 1254, 1175; HRMS (ESI) *m/z* 779.3736 [$C_{48}H_{56}O_6Si$ (M+Na) requires 779.3738].

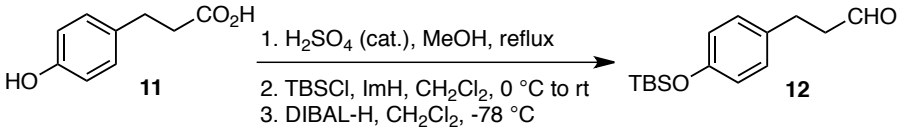


(3S)-1,7-bis(4-(benzyloxy)phenyl)-7-(2,4,6-trimethoxyphenyl)hept-5-yn-3-ol (9). A solution of TBAF•$3H_2O$ (0.08 g, 0.30 mmol) in THF (1.0 mL) was added to a solution of **8** (0.22 g, 0.30 mmol) in THF (1.0 mL) at 0 ˚C. The resulting solution was stirred for 4 h at room temperature then diluted with a saturated aqueous NH_4Cl (2.0 mL). The layers were separated and aqueous phase extracted with Et_2O (3

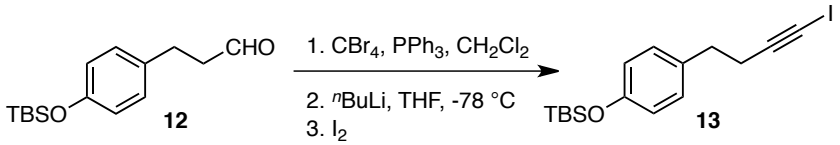
x 1.0 mL). The combined organic extracts were dried ($MgSO_4$), and concentrated under reduced pressure. The crude residue was purified by flash chromatography eluting with hexanes/EtOAc (2:1) to provide 160 mg (83%) of **9** as a yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) Isomer A: δ 7.46-7.31 (m, 12 H), 7.15-7.10 (m, 2 H), 6.94-6.90 (m, 2 H), 6.89-6.85 (m, 2 H), 6.16 (s, 2 H), 5.66 (s, 1 H), 5.06 (s, 2 H), 5.04 (s, 2 H), 3.81, (s, 3 H), 3.75 (br s, 8 H), 2.81-2.62 (m, 2 H), 2.56-2.48 (m, 1 H), 2.43-2.33 (s, 1 H), 1.97-1.74 (m, 2 H) Isomer B: δ 7.46-7.31 (m, 12 H), 7.15-7.10 (m, 2 H), 6.94-6.90 (m, 2 H), 6.89-6.85 (m, 2 H), 6.16 (s, 2 H), 5.66 (s, 1 H), 5.06 (s, 2 H), 5.04 (s, 2 H), 3.80, (s, 3 H), 3.75 (br s, 8 H), 2.81-2.62 (m, 2 H), 2.56-2.48 (m, 1 H), 2.43-2.33 (s, 1 H), 1.97-1.74 (m, 2 H); ^{13}C NMR (125 MHz) Isomer A: δ 160.4, 158.4, 157.2, 137.4, 137.4, 134.6, 134.3, 129.6, 129.6, 128.7, 128.4, 128.1, 127.7, 114.9, 114.9, 114.3, 112.0, 91.8, 85.0, 77.5, 77.2, 77.0, 70.2, 69.5, 66.1, 56.2, 55.5, 38.3, 31.3, 30.1, 28.3 Isomer B: 160.4, 158.4, 157.2, 137.4, 137.4, 134.6, 134.3, 129.6, 129.6, 128.7, 128.4, 128.1, 127.7, 114.9, 114.9, 114.3, 112.0, 91.8, 84.9, 77.5, 77.2, 77.0, 70.2, 69.3, 66.1, 56.2, 55.5, 38.2, 31.3, 30.1, 28.3; IR (neat) 3054, 2960, 2937, 2836, 2303, 1671, 1597, 1489, 1443, 1265; HRMS (ESI) *m/z* 643.3054 [$C_{42}H_{43}O_6$ (M+1) requires 643.3025].



(6*S*)-6-(4-(benzyloxy)phenethyl)-3-((4-methoxyphenyl)(2,4,6-trimethoxyphenyl)methyl)-2,2-dimethyl-5,6-dihydro-2*H*-1,2-oxasiline (10). A 10 mL round bottom flask was charged with **9** (0.32 g, 0.5 mmol), and tetramethyldisilazane (0.20 g, 1.5 mmol). The neat mixture was heated to 50 ˚C and stirred for 5 h. The flask was allowed to cool to room temperature by removal of the oil bath then placed under vacuum (~1 mmHg) for 45 min to remove excess tetramethyldisilazane. The flask was purged with Ar, and the residue dissolved in CH_2Cl_2 (1.0 mL). The resulting solution was cooled to 0 ˚C, and $Cp^*Ru(MeCN)_3PF_6$ (0.015 g, 0.03 mmol) was added in one portion. The cooling bath was removed and the reaction stirred for 1 h while warming to room temperature, and the mixture filtered through a short plug of silica eluting with Et_2O (40 mL). The crude residue was purified by flash chromatography eluting with hexanes/EtOAc (4:1) to provide 150 mg (43%) of **10** as a yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) Isomer A: δ 7.46-7.31 (m, 10 H), 7.20-7.17 (m, 2 H), 7.12 (d, J = 8.5 Hz, 2 H), 6.92-6.90 (m, 2 H), 6.87-6.84 (m, 2 H), 6.12 (s, 2 H), 6.10-6.08 (m, 1 H), 5.30 (s, 1 H), 5.06 (s, 2 H), 5.03 (s, 2 H), 3.85-3.80 (comp, 4 H), 3.68 (s, 6 H), 2.78-2.71 (m, 1 H), 2.66-2.58 (m, 1 H), 2.23-2.07 (m, 2 H), 1.91-1.83 (m, 1 H), 1.73-1.65 (m, 1 H), 0.03 (s, 3 H), −0.13 (s, 3 H) Isomer B: δ 7.46-7.31 (m, 10 H), 7.20-7.17 (m, 2 H), 7.12 (d, J = 8.5 Hz, 2 H), 6.92-6.90 (m, 2 H), 6.87-6.84 (m, 2 H), 6.12 (s, 2 H), 6.06-6.04 (m, 1 H), 5.30 (s, 1 H), 5.05 (s, 2 H), 5.03 (s, 2 H), 3.85-3.80 (comp, 4 H), 3.68 (s, 6 H), 2.78-2.71 (m, 1 H), 2.66-2.58 (m, 1 H), 2.23-2.07 (m, 2 H), 1.91-1.83 (m, 1 H), 1.73-1.65 (m, 1 H), 0.06 (s, 3 H), −0.17 (s, 3 H); ^{13}C NMR (125 MHz) Isomer A: δ 160.5, 159.4, 157.1, 156.9, 141.1, 139.2, 138.5, 137.6, 135.5, 135.0, 130.8, 129.7, 128.8, 128.1, 127.7, 127.7, 114.8, 114.0, 112.6, 91.4, 70.6, 70.3, 70.2, 70.1, 55.7, 55.6, 55.4, 43.7, 39.7, 36.5, 31.1, −0.4, −0.7 Isomer B: δ 160.5, 159.4, 157.1, 156.9, 141.1, 139.2, 138.5, 137.6, 135.5, 135.0, 130.8, 129.7, 128.7, 128.0, 127.7, 127.7, 114.8, 114.0, 112.5, 91.3, 70.6, 70.3, 70.2, 70.1, 55.7, 55.6, 55.4, 43.6, 39.7, 36.4, 31.0, −0.4, −0.5.

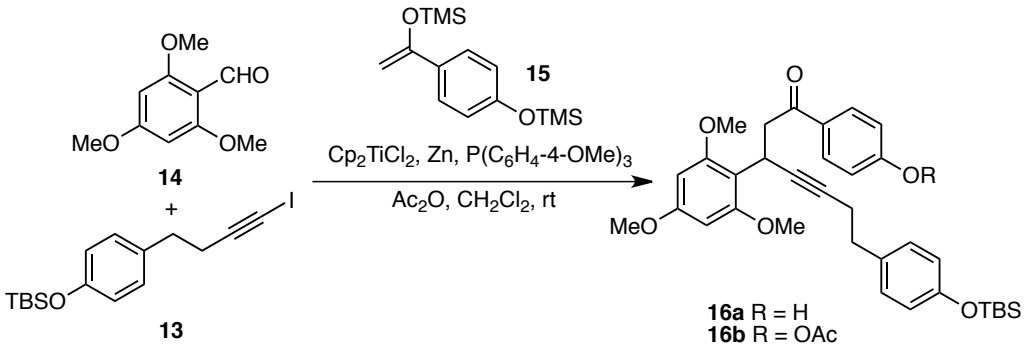


3-(4-((*tert*-butyldimethylsilyl)oxy)phenyl)propanal (12).[3] Concentrated H_2SO_4 (40 µl, 0.83 mmol) was added to a solution of 3-(4-hydroxyphenyl)propionic acid (**11**) (2.76 g, 16.6 mmol) in MeOH (30 mL), the resulting solution was heated to reflux and stirred for 10 h. The mixture was cooled to room temperature by removal of the oil bath, and the residual solvent was removed under reduced pressure. The crude residue was dissolved in EtOAc (40 mL), washed with saturated aqueous $NaHCO_3$ (1 x 40 mL) and the layers were separated. The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure to provide a clear, colorless oil that was dissolved in CH_2Cl_2 (55 mL) and cooled to 0 ˚C. Imidazole (1.70 g, 24.9 mmol) was added, the solution stirred for 10 min, followed by a portion-wise addition of TBSCl (2.76 g, 18.3 mmol). The cooling bath was removed and the resulting heterogeneous mixture was stirred for 10 h. The mixture was diluted with H_2O (50 mL), the layers were separated, and the aqueous phase extracted with CH_2Cl_2 (3 x 50 mL). The combined organic extracts were washed with saturated aqueous NaCl (50 mL), dried ($MgSO_4$), and concentrated under reduced pressure to provide 4.39 g of methyl 3-(4-((*tert*-butyldimethylsilyl)oxy)phenyl)propanoate as a clear, colorless crude oil. This crude residue was dissolved in CH_2Cl_2 (75 mL), cooled to –90 ˚C, and a solution of DIBAL-H (1.0 M in hexanes, 16.6 mmol, 15 mL) was then added dropwise while ensuring that the internal reaction temperature remained below –80 ˚C. The mixture was stirred for 1 h, then excess DIBAL-H was quenched by the slow addition of MeOH (15 mL), while again being careful to ensure that the internal temperature of the solution did not rise above –80 ˚C. The mixture was allowed to warm to room temperature by removal of the cooling bath, diluted with saturated aqueous Rochelle's salt (70 mL), and stirred vigorously for 10 h. The layers were separated and the aqueous phase was extracted with CH_2Cl_2 (3 x 50 mL). The combined organic extracts were washed with saturated aqueous NaCl (50 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The crude residue was purified by flash column chromatography eluting with hexanes/EtOAc (7:1) to provide **12** in 76% yield (16.6 mmol scale, 3.36 mg) over three steps as a clear colorless oil. ^1H and ^{13}C NMR data for **12** was consistent with literature reported values.[3]



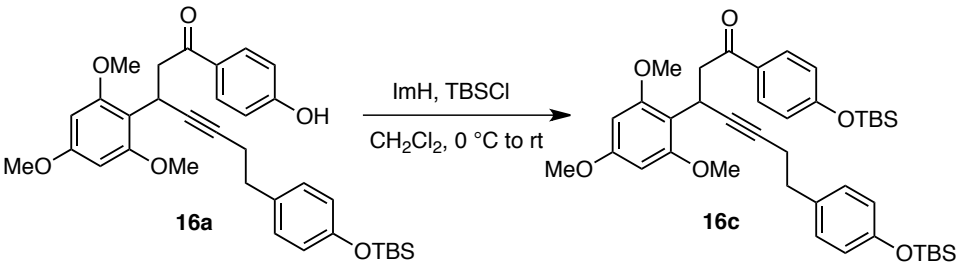
***tert*-Butyl(4-(4-iodobut-3-yn-1-yl)phenoxy)dimethylsilane (13)**.[4] A mixture of carbon tetrabromide (11.49 g, 34.8 mmol) and triphenylphosphine (18.27 g, 69.6 mmol) in CH_2Cl_2 (110 mL) was cooled to 0 ˚C under a nitrogen atmosphere and stirred for 5 h. A solution of aldehyde **12** (4.60 g, 17.4 mmol) in CH_2Cl_2 (40 mL) was added dropwise over 30 min, the resulting mixture was allowed to warm to room temperature by removal of the cooling bath and stirred for 10 h. The resulting slurry was filtered and the filter cake was washed with CH_2Cl_2 (40 mL). The filtrate was washed with H_2O (2 x 80 mL) and saturated aqueous NaCl (100 mL) then dried ($MgSO_4$) and concentrated under reduced pressure. The crude residue was purified by flash column chromatography eluting with hexanes/EtOAc (10:1) to provide the intermediate dibromo alkene in 78% yield (5.71 g, 13.6 mmol) as a clear, pale yellow oil. A

flask equipped with a magnetic stir bar was charged with the dibromo alkene (1.23 g, 2.92 mmol) and THF (24 mL) under an inert atmosphere and cooled to –78 ˚C. A solution of ^{n}BuLi (2.4 M in hexanes, 4.9 mL, 11.7 mmol) was slowly added dropwise via syringe and the resulting mixture was stirred for 5 h. The reaction was quenched with a solution of iodine (1.12 g, 4.37 mmol) in THF (6 mL), the mixture allowed to warm to room temperature by removal of the cooling bath, and stirred for 3 h. The solution was diluted with H_2O (30 mL) and extracted with Et_2O (3 X 30 mL). The combined organic extracts were washed with saturated aqueous $Na_2S_2O_3$ (50 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The crude residue was purified by flash column chromatography eluting with hexanes/EtOAc (20:1) to provide 995 mg (88%) of **13** as a clear, pale yellow oil. ^{1}H NMR (500 MHz) δ 7.03-7.06 (m, 2 H), 6.75-6.77 (m, 2 H), 2.76 (t, J = 8 Hz, 2 H), 2.60 (t, J = 8 Hz, 2 H), 0.98 (s, 9 H), 0.18 (s, 6 H); ^{13}C NMR (125 MHz) δ 154.3, 133.2, 129.5, 120.2, 94.3, 34.3, 26.3, 25.9, 23.45, 18.4, -4.21; IR (neat) cm^{-1} 3027, 2928, 2857, 1609, 1509, 1470, 1389, 1361, 1254, 1169, 1100, 1007; mass spectrum (ESI) *m/z* 387.0671 [$C_{16}H_{24}IOSi$ requires (M+1) 387.0641].

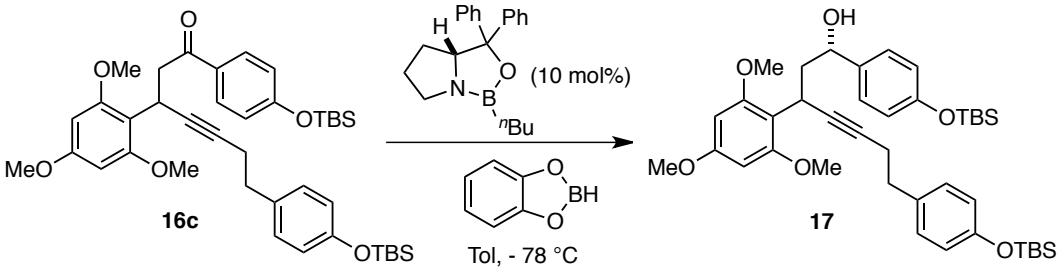


7-(4-((*tert*-Butyldimethylsilyl)oxy)phenyl)-1-(4-hydroxyphenyl)-3-(2,4,6-trimethoxyphenyl)hept-4-yn-1-one and 4-(7-(4-((*tert*-butyldimethylsilyl)oxy)phenyl)-3-(2,4,6-trimethoxyphenyl)hept-4-ynoyl)phenyl acetate (16a and 16b). A vial equipped with a magnetic stir bar, was charged with Cp_2TiCl_2 (5.0 mg, 19.9 μmol) and zinc dust (0.14 g, 2.09 mmol) then purged with nitrogen for 5 min. Dry, degassed CH_2Cl_2 (2 mL) was added and the resulting gray slurry was stirred vigorously at room temperature until it took on a blue/green hue. Tris(4-methoxyphenyl)phosphine (0.14 g, 0.40 mmol) was added in one portion followed by the dropwise addition of a solution of aldehyde **14** (0.20 g, 1.00 mmol) and alkynyl iodide **13** (0.50 g, 1.29 mmol) in CH_2Cl_2 (1.0 mL). The resulting mixture was stirred at room temperature for 2 hr, then silyl enol ether **15**[5] (0.36 g, 1.29 mmol) was added in one portion via syringe followed by a solution of Ac_2O (0.10 mL, 1.10 mmol) in CH_2Cl_2 (1 mL) over 11 hours via syringe pump. Once the addition of Ac_2O was complete, the resulting crude mixture was allowed to stir at room temperature for 2 hr, then diluted with CH_2Cl_2 (2 mL), filtered through a short plug of silica gel eluting with Et_2O (55 mL), and concentrated under reduced pressure. The crude residue was purified by flash column chromatography eluting with hexanes/EtOAc (6:1) to provide 226 mg (40%) of **16a** and 83 mg (14%) of **16b** each as a thick, clear, pale yellow oil. **16a:** ^{1}H NMR (500 MHz) δ 7.90-7.92 (m, 2 H), 6.97-6.99 (m, 2 H), 6.82-6.85 (m, 2 H), 6.65-6.68 (m, 2 H), 6.12 (s, 2 H), 5.44 (br s, 1 H), 4.88-4.91 (m, 1 H), 3.80 (s, 6 H), 3.79 (s, 3 H), 3.70 (dd, J = 8.5, 16 Hz, 1 H), 3.23 (dd, J = 6, 15.8 Hz, 1 H), 2.63 (t, J = 7.5 Hz, 2 H), 2.31 (td, J = 2, 8 Hz, 2 H), 0.97 (s, 9 H), 0.16 (s, 6 H); ^{13}C NMR (125 MHz) δ 198.4, 160.6, 160.2, 158.9, 153.9, 134.2, 131.1, 130.3, 129.5, 119.9, 115.4, 110.5, 91.5, 82.6, 78.8, 56.1, 55.5, 43.0, 34.9, 25.9, 22.6, 21.6, 18.4, -4.2; IR (neat) cm^{-1} 3345, 2932, 2856,

1658, 1604, 1509, 1417, 1325, 1259, 1224, 1205, 1167, 1150, 1118; mass spectrum (ESI) *m/z* 597.2651 [$C_{34}H_{42}NaO_6Si$ requires (M+Na) 597.2648]. **16b:** ^{1}H NMR (500 MHz) δ 7.98-8.01 (m, 2 H), 7.15-7.17 (m, 2 H), 6.98-7.01 (m, 2 H), 6.66-6.68 (m, 2 H), 6.12 (s, 2 H), 4.88-4.91 (m, 1 H), 3.79 (s, 9 H), 3.73 (dd, *J* = 8, 16 Hz, 1 H), 3.29 (dd, *J* = 6, 16 Hz, 1 H), 2.64 (t, *J* = 7.5 Hz, 2 H), 2.30-2.34 (m, 5 H), 0.97 (s, 9 H), 0.16 (s, 6 H); ^{13}C NMR (125 MHz) 197.8, 169.1, 160.2, 158.8, 154.2, 153.9, 135.0, 134.2, 130.1, 129.5, 121.7, 119.9, 91.4, 82.3, 78.7, 56.1, 55.5, 43.3, 34.9, 25.9, 22.3, 21.6, 21.4, 18.4, -4.3; IR (neat) cm^{-1} 2931, 2856, 1762, 1686, 1602, 1509, 1465, 1416, 1258, 1201, 1163, 1118, 1040; mass spectrum (ESI) *m/z* 639.2758 [$C_{36}H_{45}NaO_7Si$ requires (M+Na) 639.2754].



1,7-Bis(4-((*tert*-butyldimethylsilyl)oxy)phenyl)-3-(2,4,6-trimethoxyphenyl)hept-4-yn-1-one (16c). Imidazole (37.0 mg, 0.55 mmol) was added to a solution of **16a** (0.21 g, 0.36 mmol) in CH_2Cl_2 (2 mL) at 0 ˚C and stirred for 10 min. TBSCl (60.0 mg, 0.40 mmol) was then added portion-wise, the resulting heterogeneous mixture allowed to warm to room temperature by removal of the cooling bath, and stirred for 10 h. The mixture was diluted with H_2O (5 mL), the layers were separated, and the aqueous phase extracted with CH_2Cl_2 (3 x 5 mL). The combined organic extracts were washed with saturated aqueous NaCl (1 x 5 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The crude residue was purified by flash column chromatography eluting with hexanes/EtOAc (5:1) to provide 229 mg (91%) of **16c** as a thick, clear, colorless oil. ^{1}H NMR (500 MHz) δ 7.88-7.91 (m, 2 H), 6.97-7.00 (m, 2 H), 6.83-6.86 (m, 2 H), 6.65-6.68 (m, 2 H), 6.12 (s, 2 H), 4.88-4.92 (m, 1 H), 3.78-3.79 (m, 9 H), 3.71 (dd, *J* = 8, 15.8 Hz, 1 H), 3.23 (dd, *J* = 6, 15.8 Hz, 1 H), 2.63 (t, *J* = 7.5 Hz, 2 H), 2.31 (td, *J* = 2, 8 Hz, 2 H), 0.99 (s, 9 H), 0.97 (s, 9 H), 0.22 (s, 6 H), 0.16 (s, 6 H); ^{13}C NMR (125 MHz) δ 197.6, 160.2, 160.1, 158.9, 153.9, 134.2, 131.2, 130.6, 129.5, 119.9, 119.8, 110.7, 91.5, 82.7, 78.6, 56.1, 55.4, 43.0, 35.0, 25.9, 25.8, 22.4, 21.6, 18.4, 18.3, -4.2, -4.3; IR (neat) cm^{-1} 2930, 2857, 2249, 1680, 1597, 1505, 1469, 1415, 1390, 1257, 1165, 1118, 1041, 1061, 1007; mass spectrum (ESI) *m/z* 689.3671 [$C_{40}H_{57}NaO_6Si_2$ requires (M+Na) 689.3694].



(1*S*)-1,7-Bis(4-((*tert*-butyldimethylsilyl)oxy)phenyl)-3-(2,4,6-trimethoxyphenyl)hept-4-yn-1-ol (17).[6] To a solution of **16c** (42.6 mg, 61.8 μmol) in toluene (0.48 mL) was added a solution of (*S*)-(−)-2-Butyl-CBS-oxazaborolidine catalyst[7] (0.21 M in toluene, 30 μL, 6.18 μmol), and the resulting mixture stirred for 30 min at room temperature. The solution was then cooled to –78 ˚C followed by the addition

of catechol borane (4.7 M in toluene, 0.17 mL, 0.80 mmol) dropwise via syringe over 5 min. The reaction was stirred for an additional 2.5 h then diluted with MeOH (5 mL) while maintaining the bath temperature at –78 ˚C. The reaction was allowed to warm to room temperature by removal of the cooling bath, then diluted with Et_2O (5 mL), and washed with 1M NaOH/saturated aqueous $NaHCO_3$ (2:1). The combined organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. The crude residue was purified by flash column chromatography eluting with hexanes/EtOAc (5:1) to provide 30.1 mg (77%) of **17** as a sticky white foam in a 1:1 mixture of diastereomers. The enantiomeric excess of each diastereomer (92% *ee*) was determined by HPLC analysis using a Chiral-Dex AD column (98:2 hexanes/^{i}PrOH, flow rate = 0.3 mL/min) t_r(isomer A_{major}) = 49.2 min; t_r(isomer A_{minor}) = 68.2 min; t_r(isomer B_{major}) = 61.2 min; t_r(isomer B_{minor}) = 51.7 min. ^{1}H NMR (500 MHz) δ 7.15-7.20 (m, 4 H), 7.03-7.08 (m, 4 H), 6.70-7.79 (comp, 8 H), 6.15 (s, 2 H), 6.12 (s, 2 H), 4.79-4.81 (m, 1 H), 4.43-4.48 (comp, 2 H), 4.33-4.36 (m, 1 H), 3.81 (s, 3 H), 3.80 (s, 3 H), 3.79 (s, 6 H), 3.77 (s, 6 H), 2.89 (br d, *J* = 2.5 Hz, 1 H), 2.73 (m, 4 H), 2.26-2.44 (comp, 6 H), 2.12-2.17 (m, 2 H), 1.96 (ddd, *J* = 5, 9, 14 Hz, 1 H), 0.97 (br s, 36 H), 0.17-0.18 (m, 24 H); ^{13}C NMR (125 MHz) δ 160.3, 160.2, 160.1, 155.0, 154.9, 154.1, 137.8, 137.1, 134.2, 134.1, 129.6, 129.5, 127.4, 127.2, 119.9, 119.8, 110.8, 109.9, 91.4, 83.1, 82.7, 79.2, 78.9, 72.6, 56.1, 56.0, 55.5, 55.4, 43.7, 43.1, 35.1, 25.9, 23.7, 23.2, 21.6, 21.2, 18.4, -4.3; IR (neat) cm^{-1} 3550, 2930, 2857, 1607, 1511, 1469, 1417, 1390, 1361, 1329, 1259, 1222, 1204, 1151, 1119, 1060; mass spectrum (ESI) *m/z* 713.3663 [$C_{40}H_{58}NaO_6Si_2$ requires (M+Na) 713.3670].

3. BIOLOGICAL EVALUATION

Cell lines. The U87-MG cells were purchased from the American Type Culture Collection (ATCC) and maintained in Iscove's Modified Dulbecco's medium and 10% fetal bovine serum (FBS). The SK-N-SH cells (ATCC) and the SK-N-F1 cells (Sigma-Aldrich) were maintained in RPMI-1640 and 10% FBS.

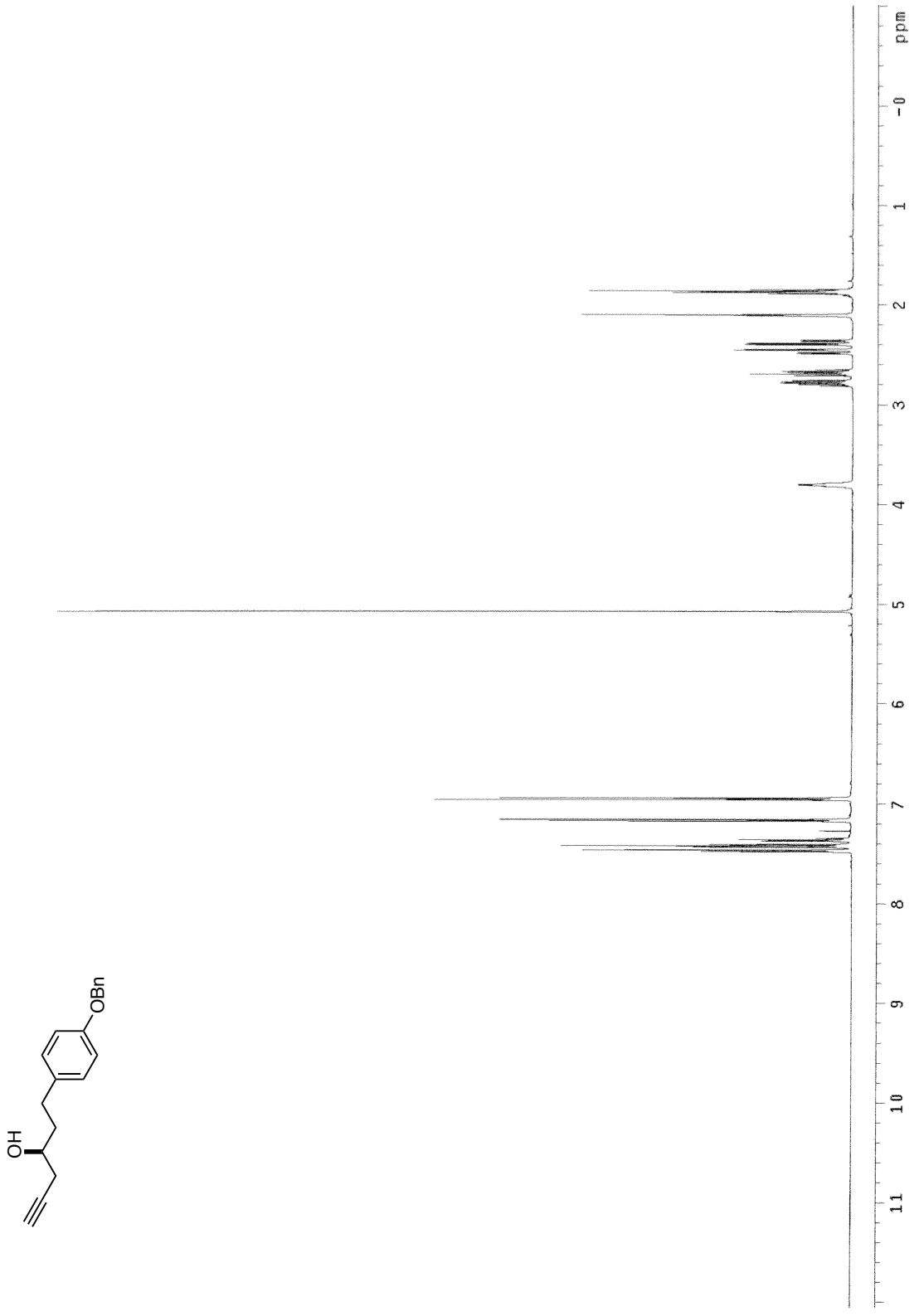
Knockdown of human p53 in U87-MG cells. Vesicular Stomatitis Viral envelope-pseudotyped lentiviral supernatants were generated for pCLIPw.shp53 and pCLIPw.shEGFP transfer vectors[8] and stably transduced cells selected in puromycin. Western blot analysis indicated that p53 expression was knocked down by >95% in pCLIPw.shp53-transduced U87-MG cells following selection in puromycin (data not shown).

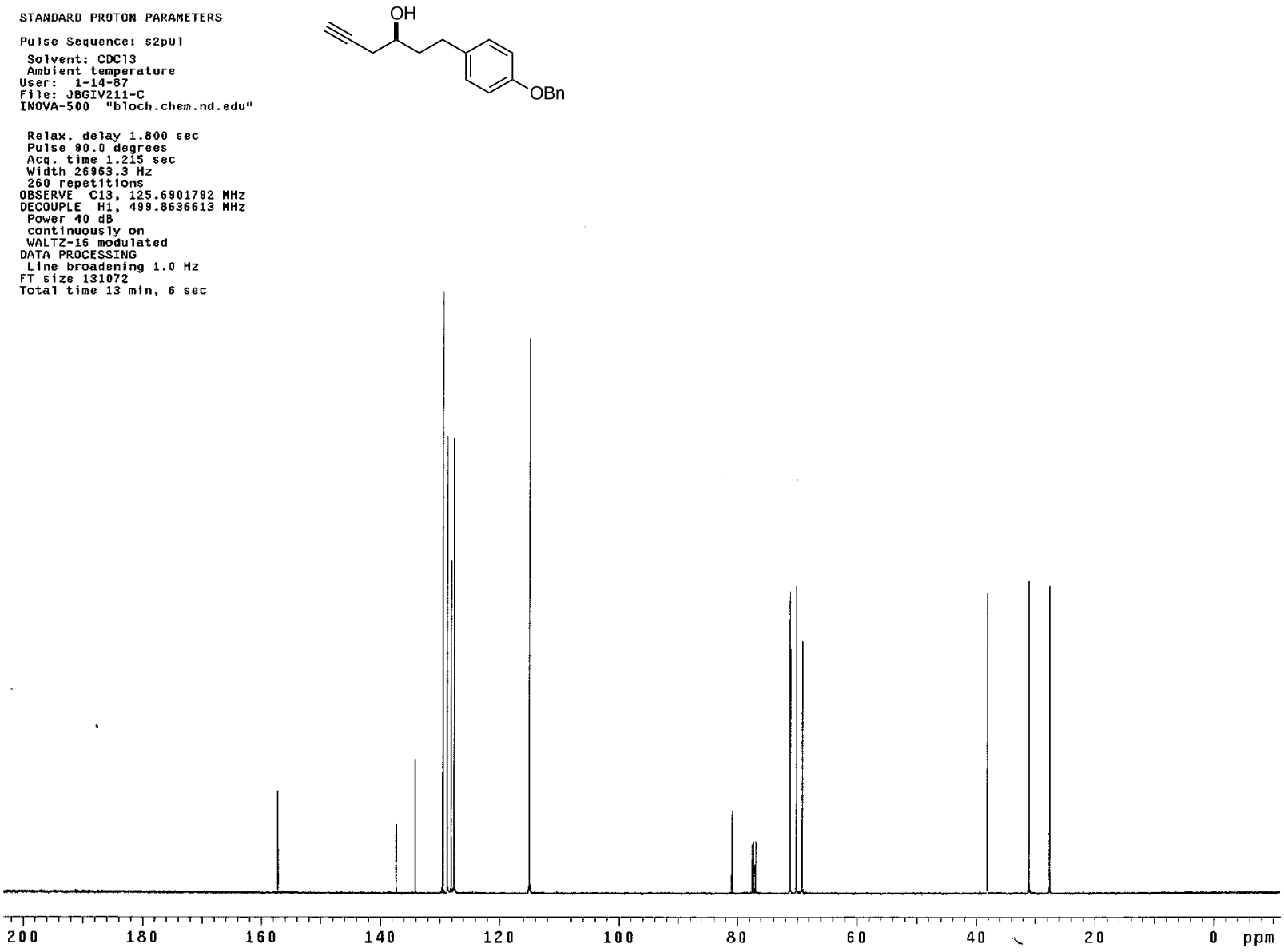
Methylene blue assay. Cells were exposed continuously to increasing concentrations of select intermediate compounds and cell growth determined at day 5 using a methylene blue staining assay that measures cell mass and correlates with cell growth.[9]

Colony-forming unit (CFU) assay. Compound effect on growth of hematopoietic progenitor colonies was determined by CFU assays as previously described.[10] Human CD34+ cells were isolated from umbilical cord, suspended in Methocult GF H4434 (Stem Cell Technologies, Inc.) and exposed to compound. The cells were immediately seeded in triplicate at concentrations of 2 x 103. After 10 - 14 days of incubation at 37°C in 5% CO2, colony forming units-granulocyte-macrophage (CFU-GM) and burst-forming units-erythroid (BFU-E) and colony forming unit-granulocyte/erythrocyte/monocyte/ megakaryocyte (CFU-GEMM) were enumerated using the Axiovert 25 inverted-light microscope.

Statistical Analysis. The mean and standard deviation were determined for each experimental group. Concentration-response curves were analyzed by one-way ANOVA using SigmaPlot v11.0 (Systat Software, Inc.) followed by a Dunnett's test comparing each data point to media control values. Experiments using U87, SK-N-SH and SK-N-FI were repeated twice with similar results. The shRNA knockdown experiments using U87 MG cells were performed once.

4. ^{1}H AND ^{13}C NMR SPECTRA

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Acq. time 1.215 sec
Width 26963.3 Hz
260 repetitions
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DECOUPLE H1, 499.8636613 MHz
Power 40 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 1.0 Hz
FT size 131072
Total time 13 min, 6 sec
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OBn
200
180
160
140
120
100
80
60
40
20
0
ppm

STANDARD PROTON PARAMETERS

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Ambient temperature
INOVA-500 "nmr2a.chem.nd.edu"

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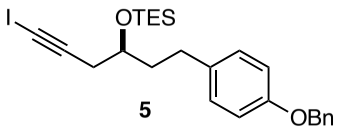

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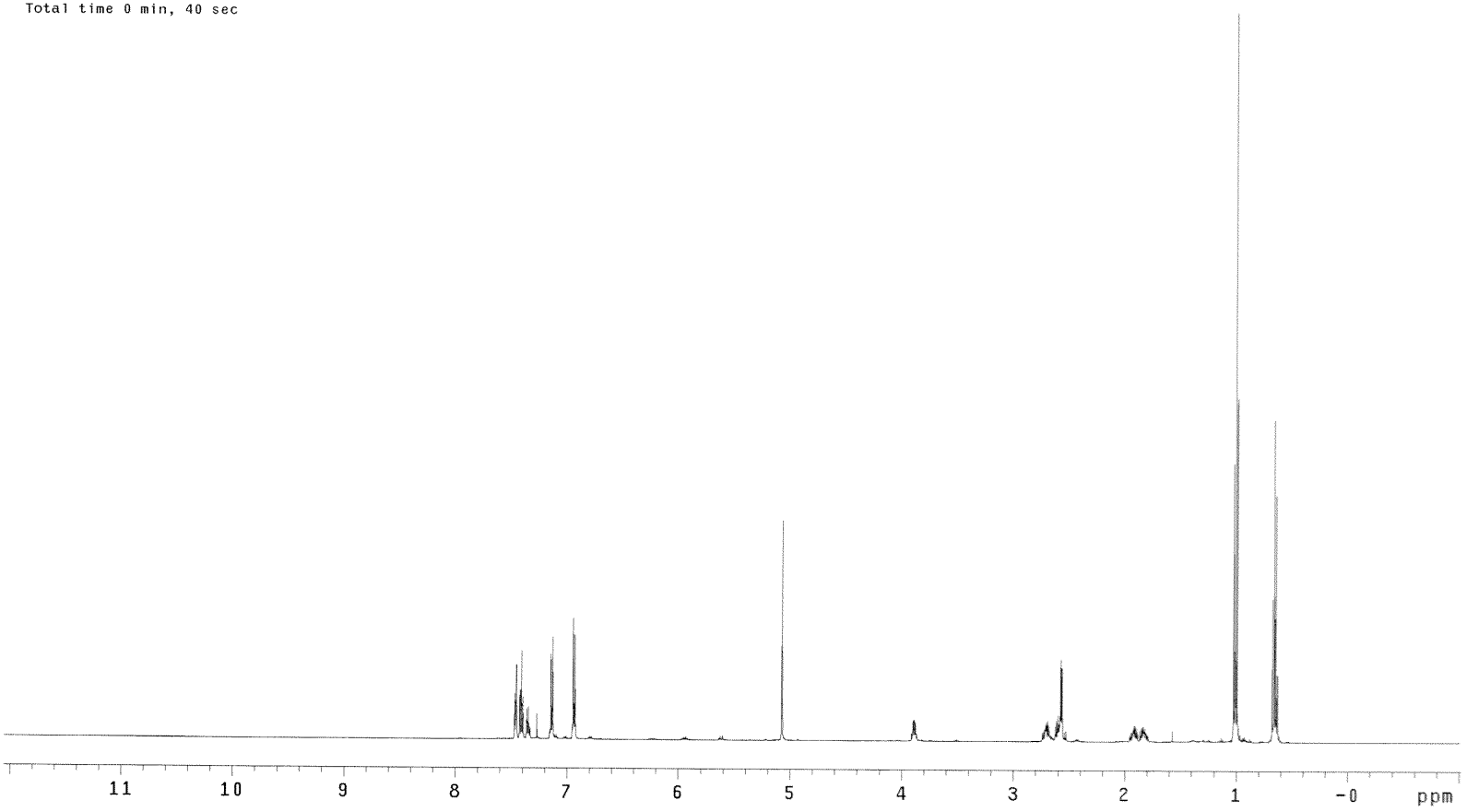

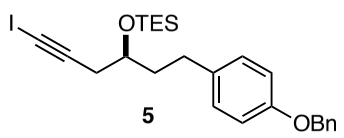

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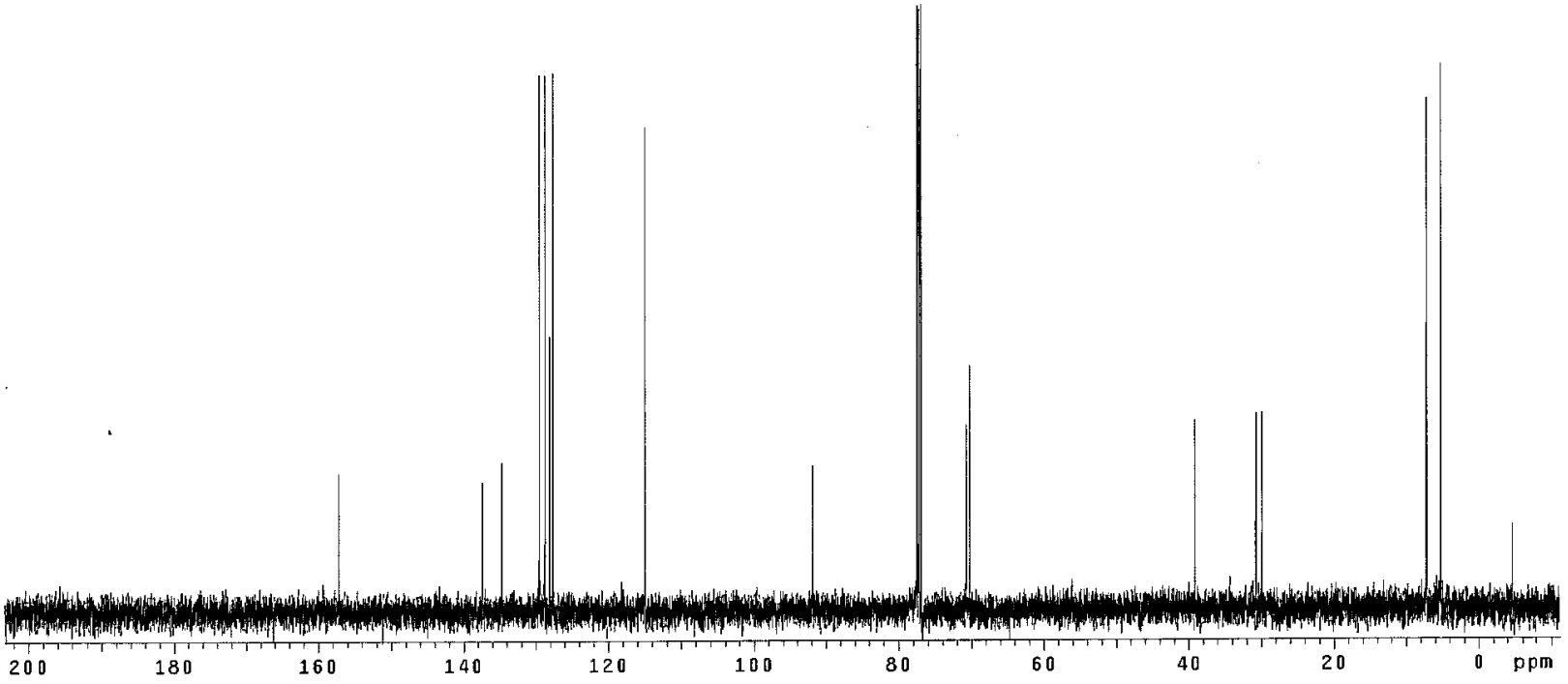

STANDARD PROTON PARAMETERS

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DATA PROCESSING
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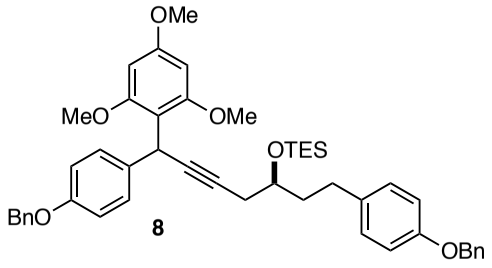

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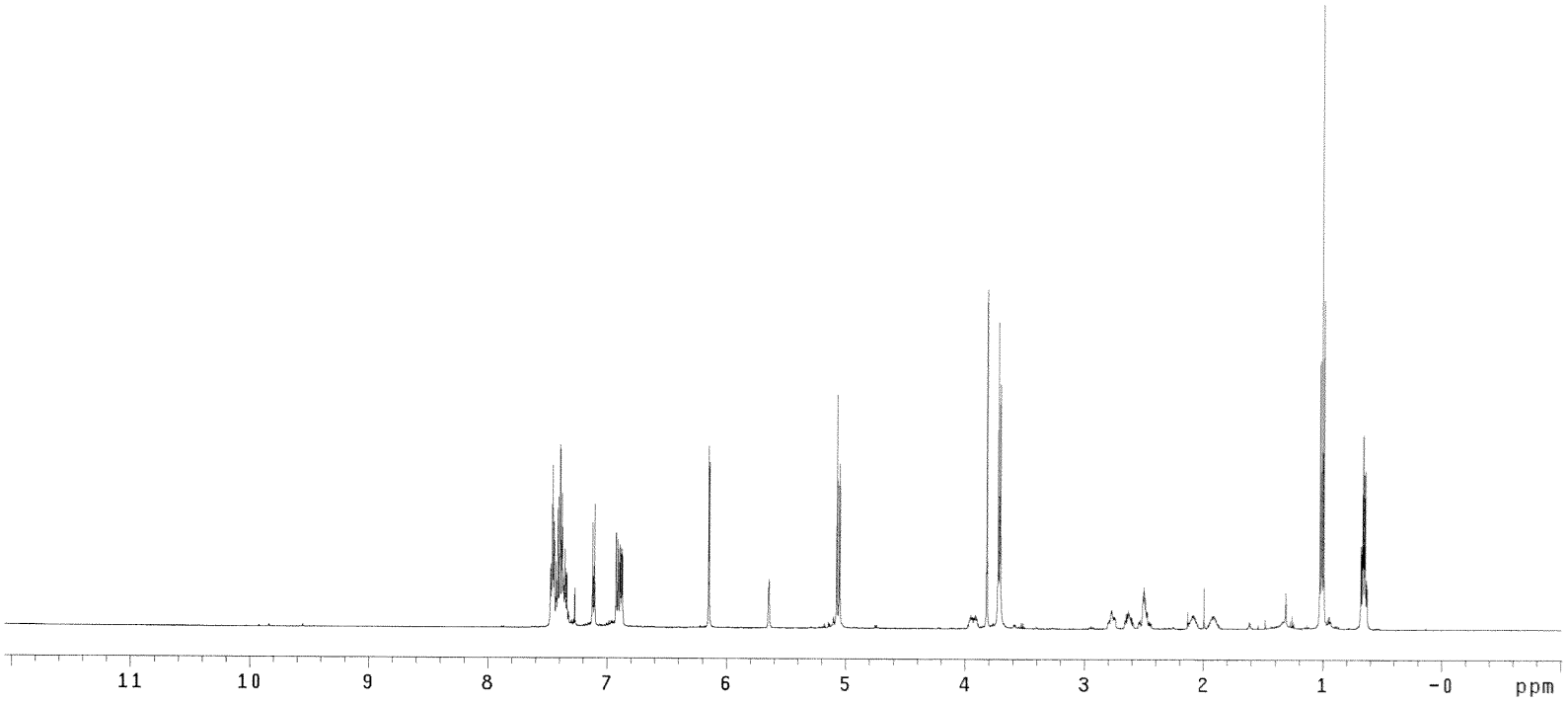

STANDARD PROTON PARAMETERS

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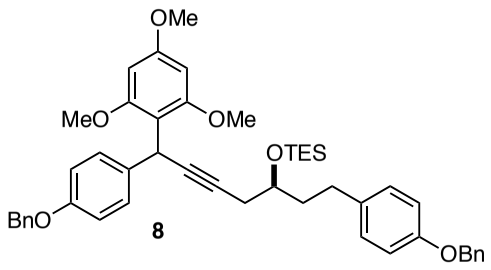

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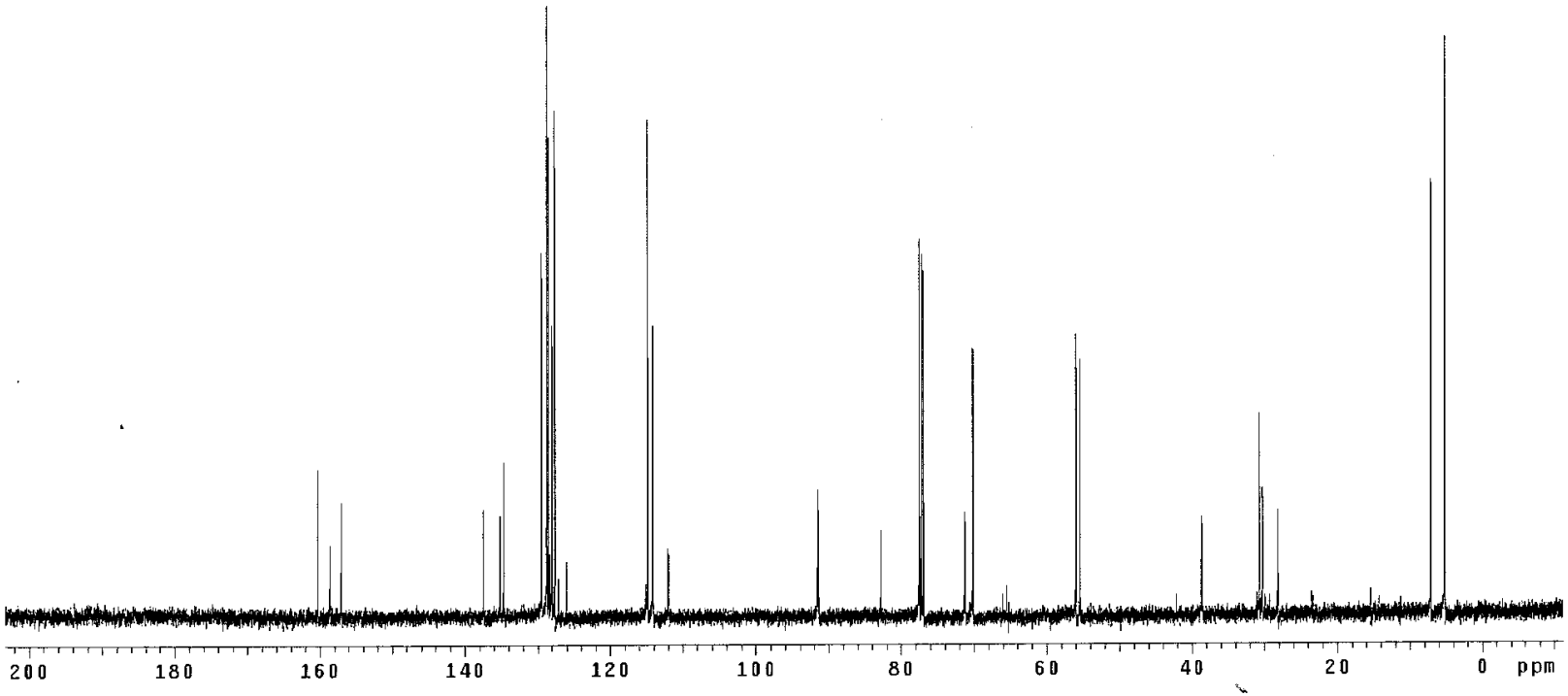

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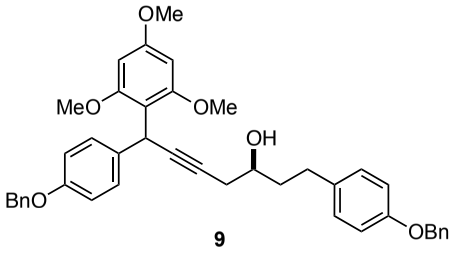

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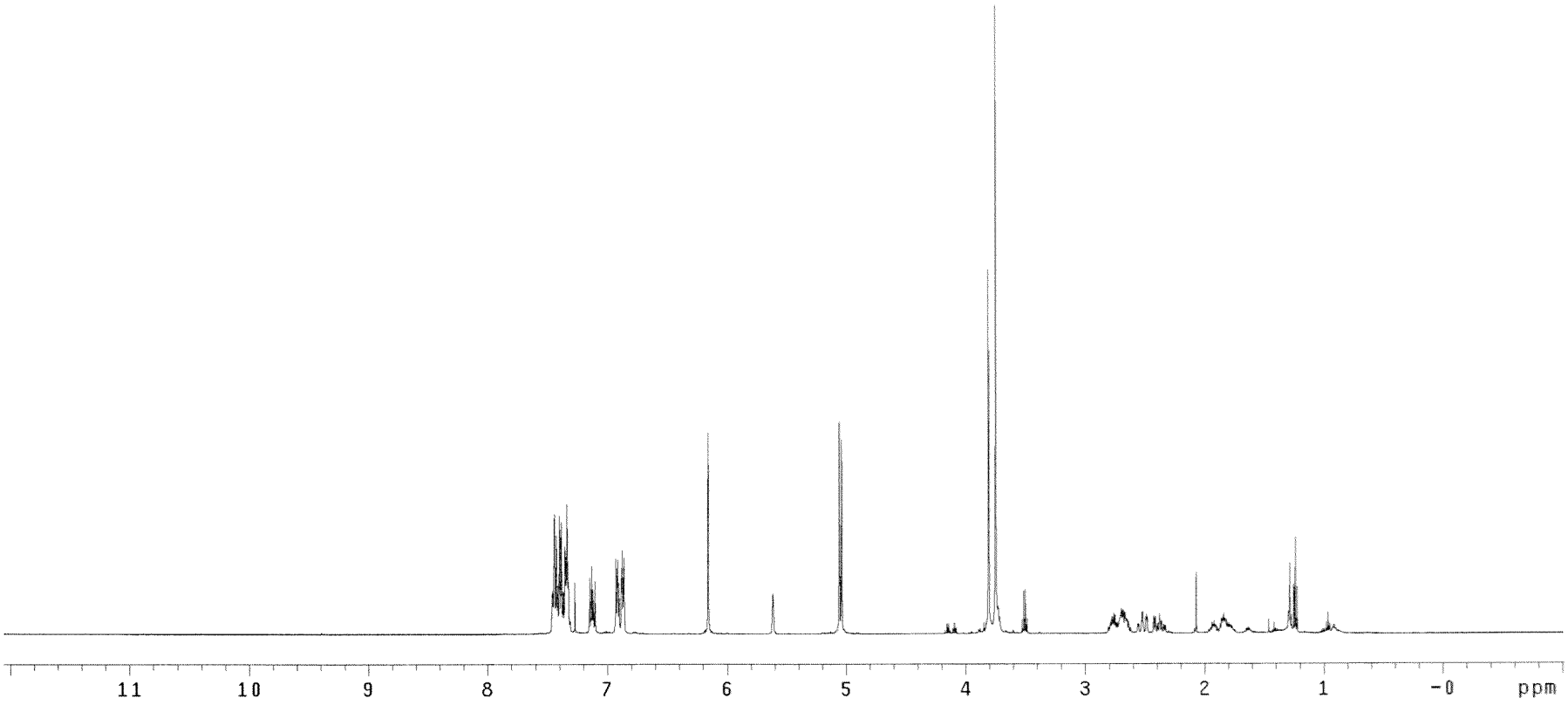

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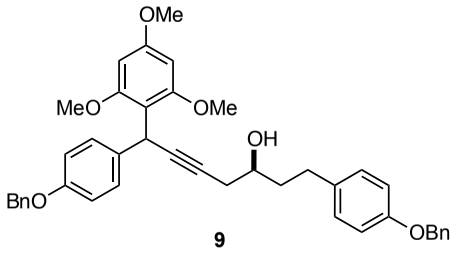

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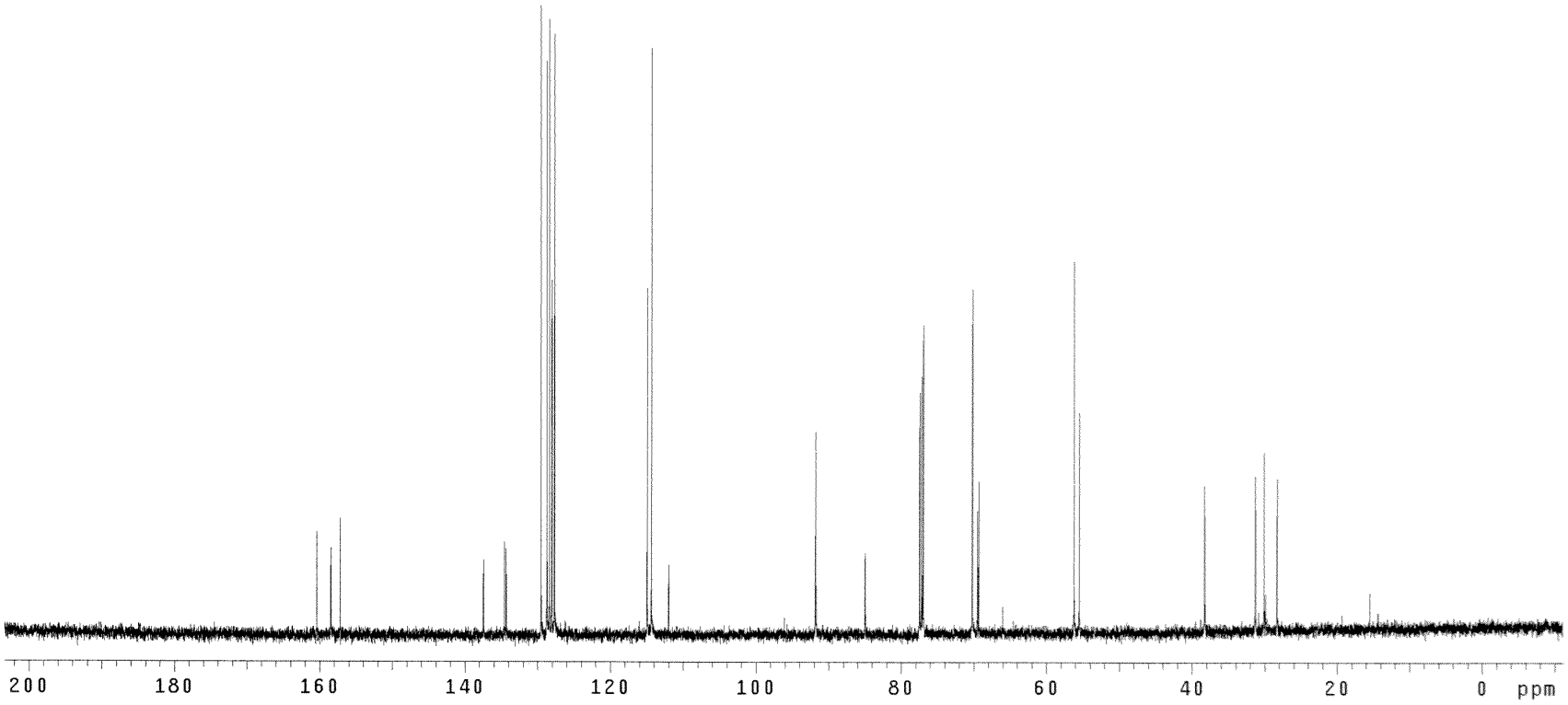

STANDARD PROTON PARAMETERS

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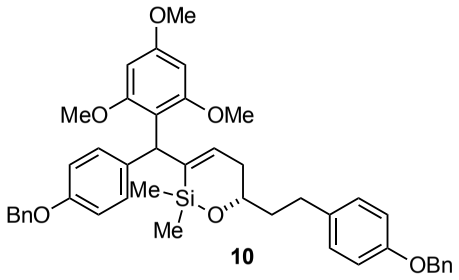

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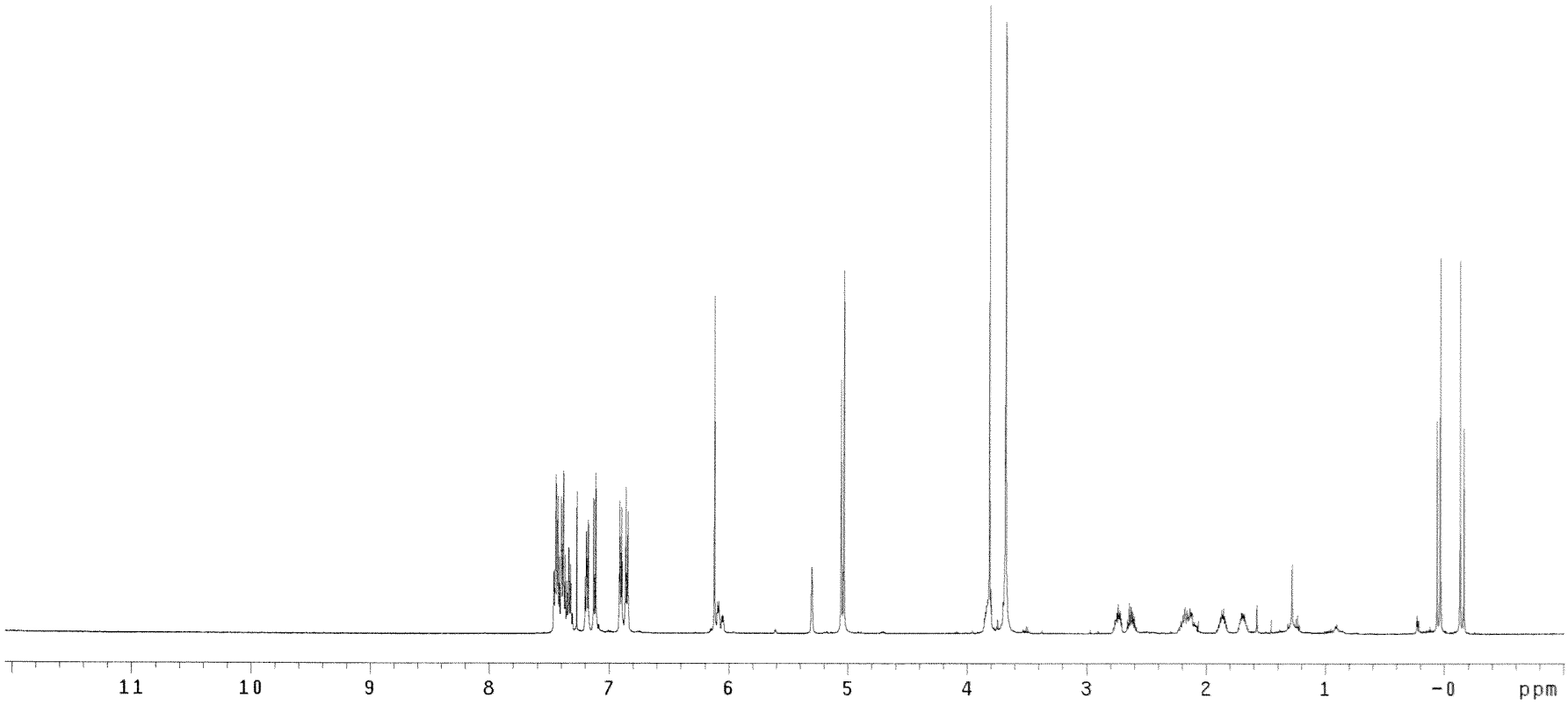

STANDARD PROTON PARAMETERS

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Ambient temperature
User: 1-14-87
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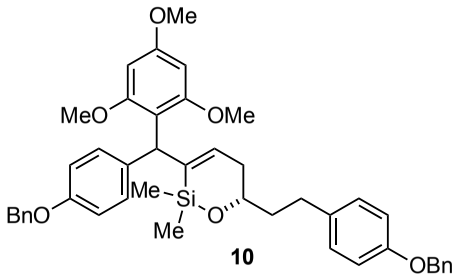

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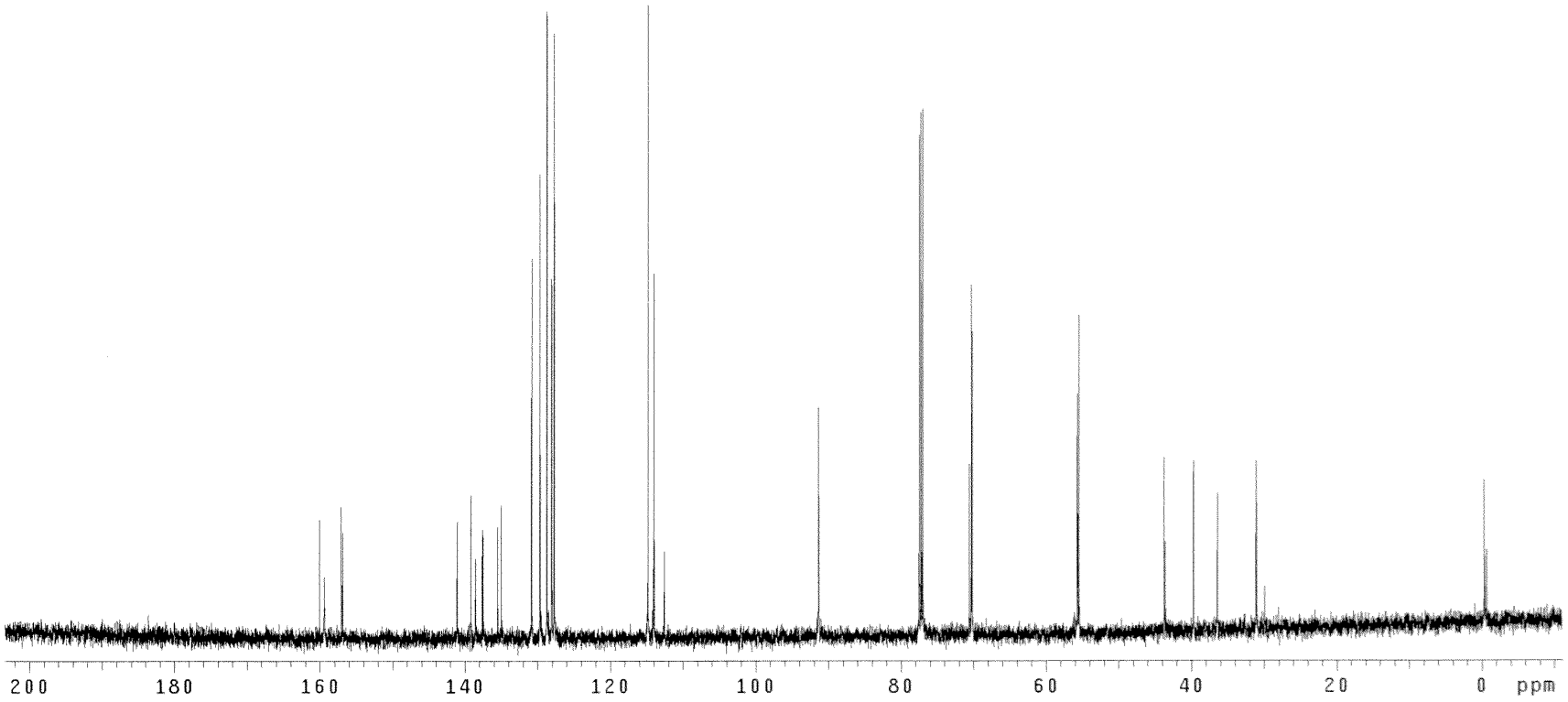

STANDARD PROTON PARAMETERS

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16 repetitions
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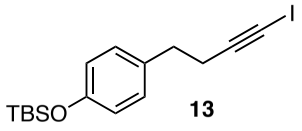
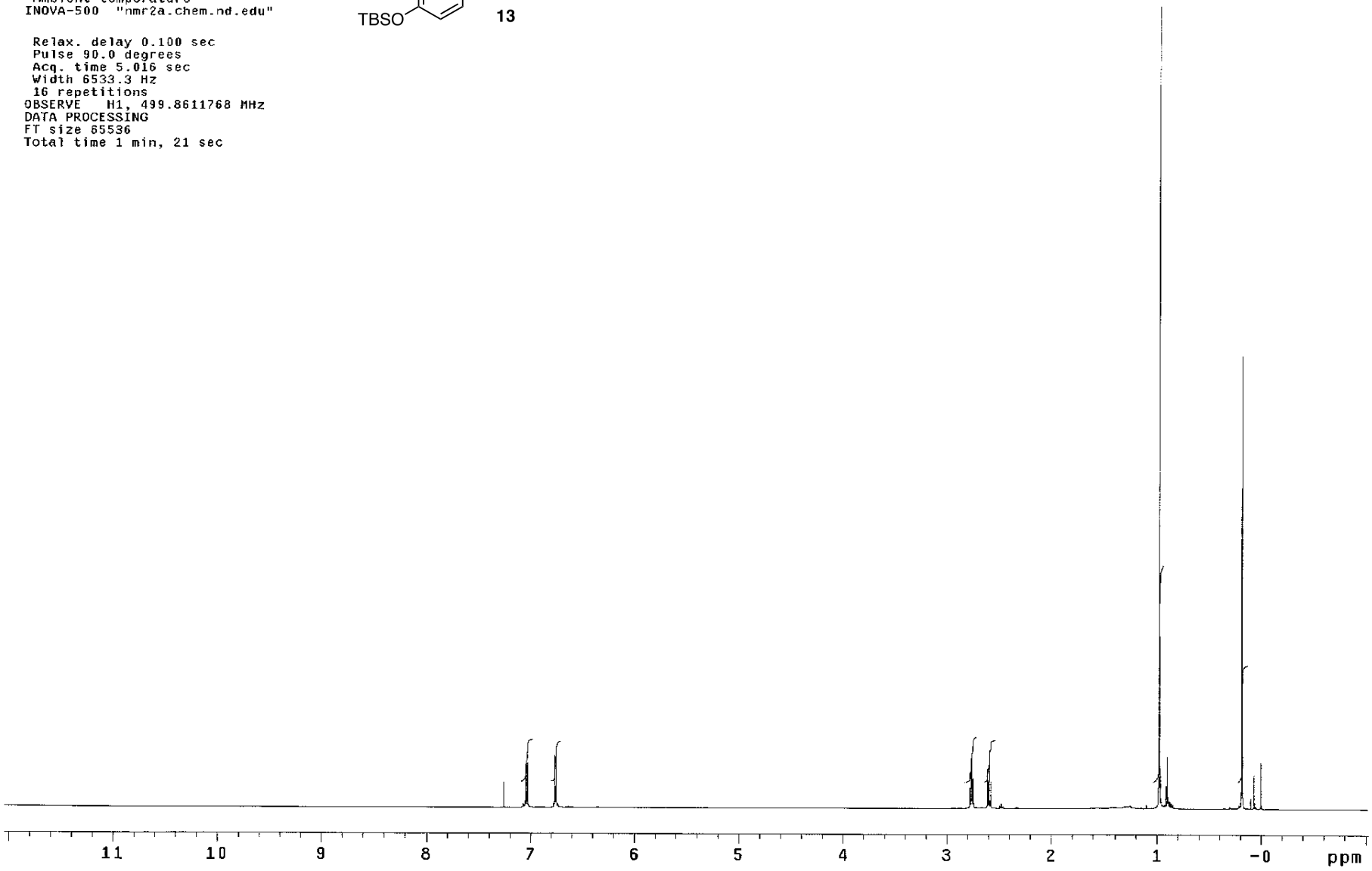
DATA PROCESSING
FT size 85536
Total time 1 min, 21 sec



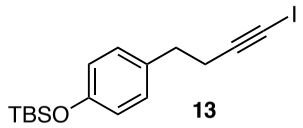
13



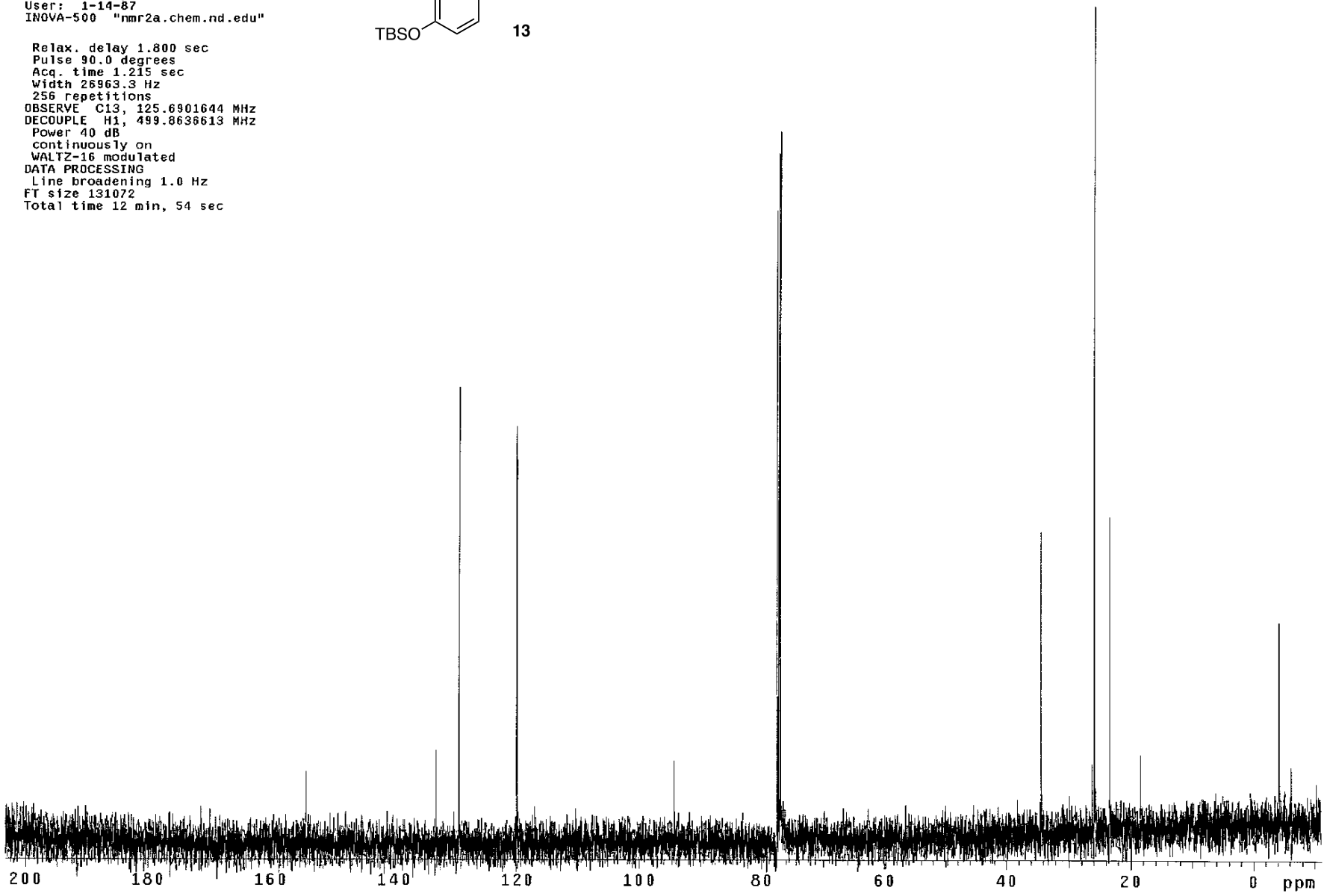
STANDARD PROTON PARAMETERS

Pulse Sequence: s2pul
 Solvent: CDCl3
 Ambient temperature
User: 1-14-87
INOVA-500 "nmr2a.chem.nd.edu"

 Relax. delay 1.800 sec
 Pulse 90.0 degrees
 Acq. time 1.215 sec
 Width 26963.3 Hz
 256 repetitions
OBSERVE C13, 125.6901644 MHz
DECOUPLE H1, 499.8636613 MHz
 Power 40 dB
 continuously on
 WALTZ-16 modulated
DATA PROCESSING
 Line broadening 1.0 Hz
FT size 131072
Total time 12 min, 54 sec



13

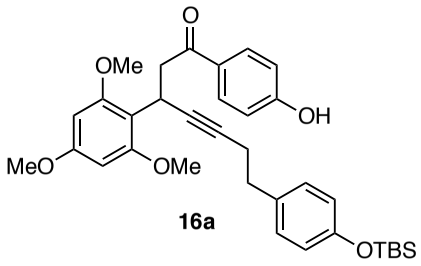


STANDARD PROTON PARAMETERS

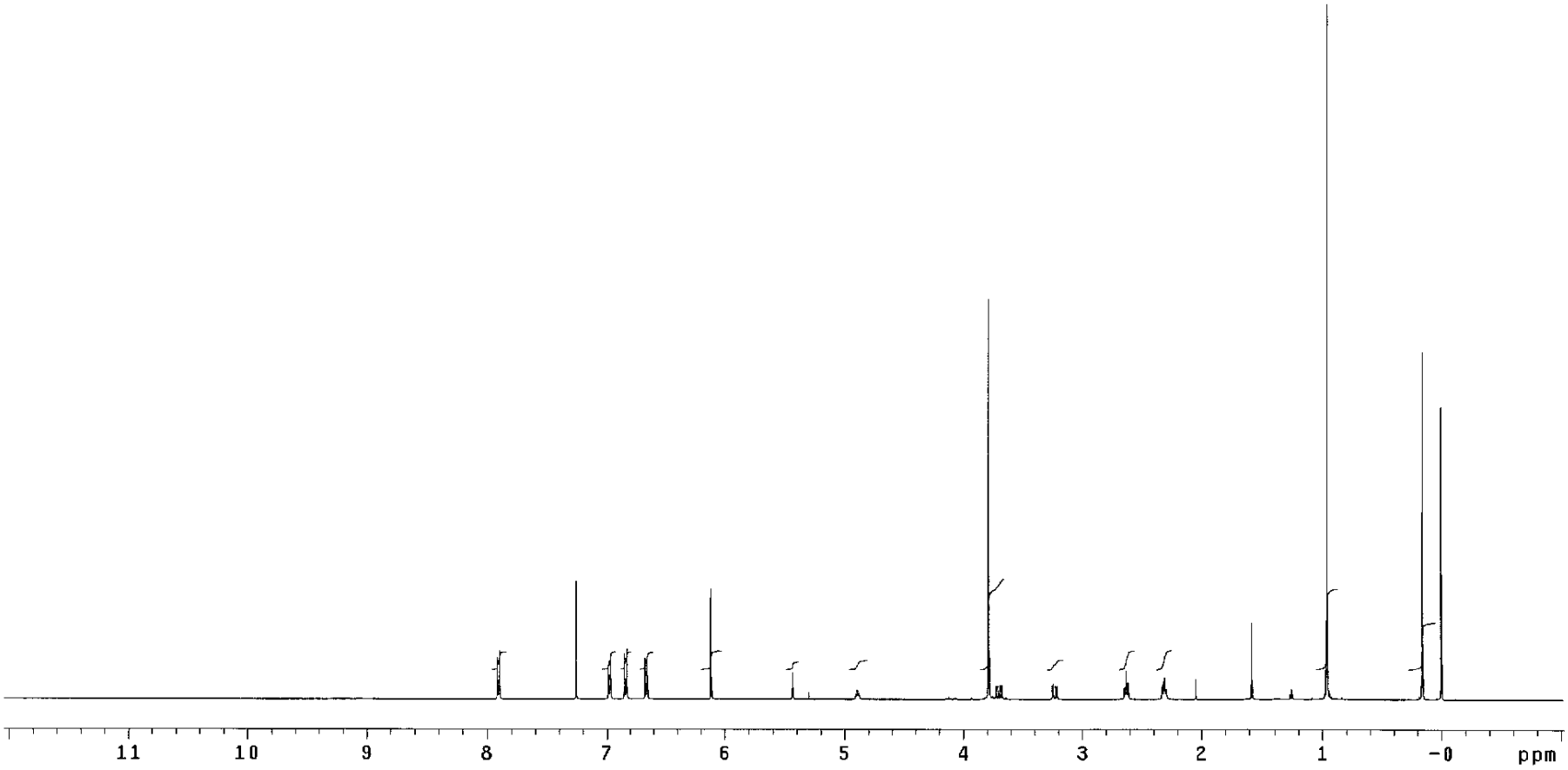
Pulse Sequence: s2pul

Solvent: CDCl3
Ambient temperature
File: CAC6-79-1=10-13
INOVA-500 "nmr2a.chem.nd.edu"

Relax. delay 0.100 sec
Pulse 90.0 degrees
Acq. time 5.016 sec
Width 6533.3 Hz
16 repetitions
OBSERVE H1, 499.8611764 MHz
DATA PROCESSING
FT size 65536
Total time 1 min, 21 sec



16a

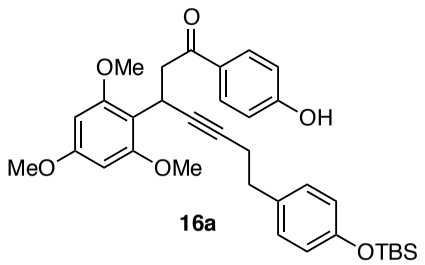


STANDARD PROTON PARAMETERS

Pulse Sequence: s2pul

Solvent: CDCl3
Ambient temperature
User: 1-14-87
INOVA-500 "nmr2a.chem.nd.edu"

Relax. delay 1.800 sec
Pulse 90.0 degrees
Acq. time 1.215 sec
Width 26963.3 Hz
256 repetitions
OBSERVE C13, 125.6901673 MHz
DECOUPLE H1, 499.8636613 MHz
Power 40 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 1.0 Hz
FT size 131072
Total time 12 min, 54 sec



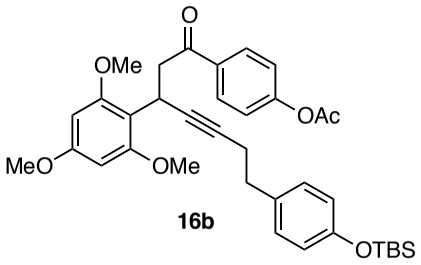
16a

STANDARD PROTON PARAMETERS

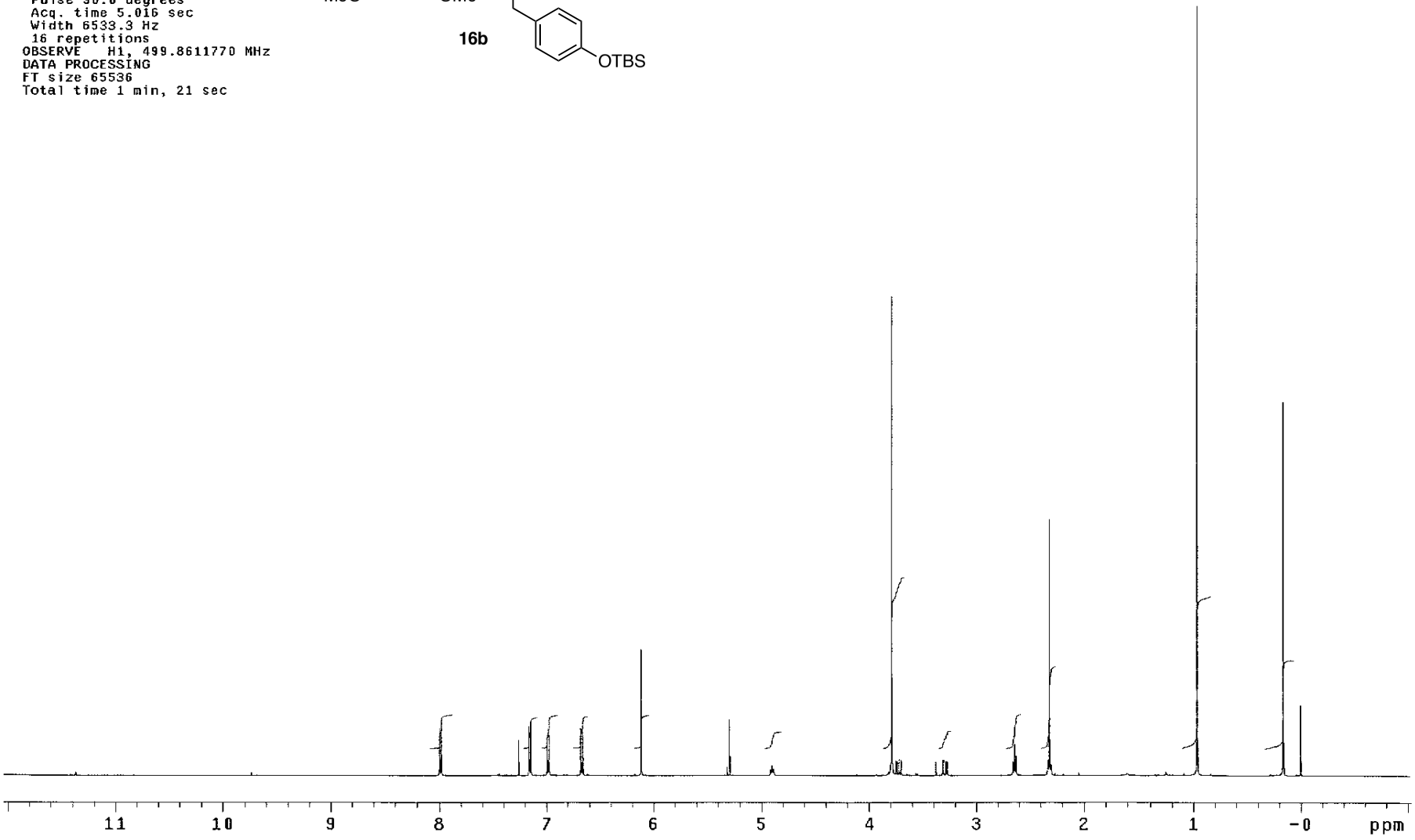
Pulse Sequence: s2pul

Solvent: CDCl3
Temp. 20.0 C / 293.1 K
INOVA-500 "nmr2a.chem.nd.edu"

Relax. delay 0.100 sec
Pulse 90.0 degrees
Acq. time 5.016 sec
Width 6533.3 Hz
16 repetitions
OBSERVE H1, 499.8611770 MHz
DATA PROCESSING
FT size 65536
Total time 1 min, 21 sec



16b

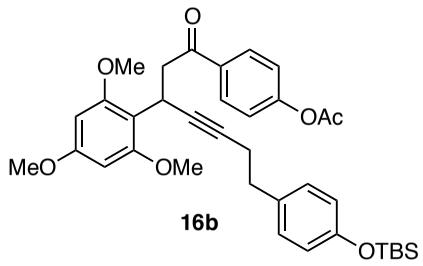


STANDARD PROTON PARAMETERS

Pulse Sequence: s2pul

Solvent: CDCl3
Ambient temperature
User: 1-14-87
INOVA-500 "nmr2a.chem.nd.edu"

Relax. delay 1.800 sec
Pulse 90.0 degrees
Acq. time 1.215 sec
Width 26963.3 Hz
256 repetitions
OBSERVE C13, 125.6901702 MHz
DECOUPLE H1, 499.8636613 MHz
Power 40 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 1.0 Hz
FT size 131072
Total time 12 min, 54 sec

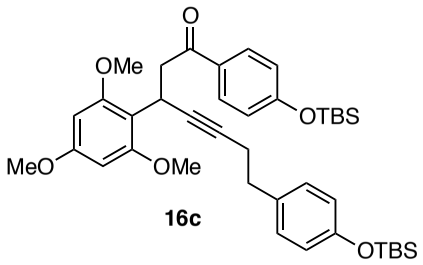


16b

STANDARD PROTON PARAMETERS

Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature
INOVA-500 "nmr2a.chem.nd.edu"

Relax. delay 0.100 sec
Pulse 90.0 degrees
Acq. time 5.016 sec
Width 6533.3 Hz
16 repetitions
OBSERVE H1, 499.8611792 MHz
DATA PROCESSING
FT size 65536
Total time 1 min, 21 sec

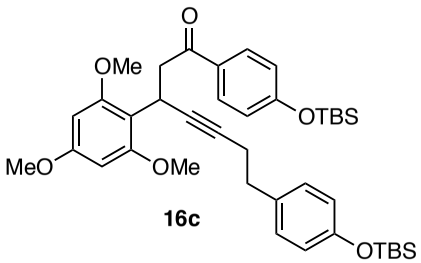


16c

STANDARD PROTON PARAMETERS

Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature
User: 1-14-87
INOVA-500 "nmr2a.chem.nd.edu"

Relax. delay 1.800 sec
Pulse 90.0 degrees
Acq. time 1.215 sec
Width 26963.3 Hz
128 repetitions
OBSERVE C13, 125.6901702 MHz
DECOUPLE H1, 499.8636613 MHz
Power 40 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 1.0 Hz
FT size 131072
Total time 6 min, 27 sec



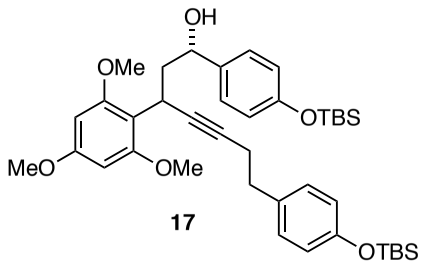
16c

STANDARD PROTON PARAMETERS

Pulse Sequence: s2pul

Solvent: CDCl3
Ambient temperature
INOVA-500 "nmr2a.chem.nd.edu"

Relax. delay 0.100 sec
Pulse 90.0 degrees
Acq. time 5.016 sec
Width 6533.3 Hz
16 repetitions
OBSERVE H1, 499.8611764 MHz
DATA PROCESSING
FT size 65536
Total time 1 min, 21 sec



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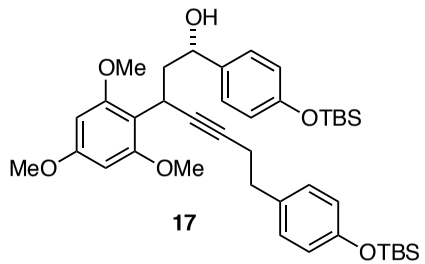
STANDARD PROTON PARAMETERS

Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature
User: 1-14-87
INOVA-500 "nmr2a.chem.nd.edu"

Relax. delay 1.800 sec
Pulse 90.0 degrees
Acq. time 1.215 sec
Width 26963.3 Hz
512 repetitions
OBSERVE C13, 125.6901652 MHz
DECOUPLE H1, 499.8636613 MHz
Power 40 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 1.0 Hz
FT size 131072
Total time 25 min, 48 sec



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5. REFERENCES

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