Supporting Information

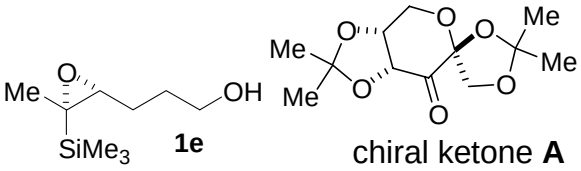
A $SiMe_3$-Based Homologation-Epoxidation–Cyclization Strategy for Ladder THP Synthesis

Timothy P. Heffron and Timothy F. Jamison*

Massachusetts Institute of Technology
Department of Chemistry
Cambridge, MA 02139

Experimental Procedures and Data for Compounds 1e-f, 2e, 5-14.

General Information. Unless otherwise noted, all non-aqueous reactions were performed under an oxygen-free atmosphere of argon with rigid exclusion of moisture from reagents and glassware. Dichloromethane was distilled from calcium hydride. Tetrahydrofuran and Et_2O were distilled from a blue solution of benzophenone ketyl. Analytical thin layer chromatography (TLC) was performed using EM Science silica gel 60 F_{254} plates. The developed chromatogram was analyzed by UV lamp (254 nm) and ethanolic phosphomolybdic acid (PMA) or aqueous potassium permanganate ($KMnO_4$). Liquid chromatography was performed using a forced flow (flash chromatography) of the indicated solvent system on Silicycle Silica Gel (230-400 mesh).[1] ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$, unless otherwise noted, on a Varian Inova 500 MHz spectrometer. Chemical shifts in ^1H NMR spectra are reported in parts per million (ppm) on the δ scale from an internal standard of residual chloroform (7.27 ppm). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, app = apparent and br = broad), coupling constant in hertz (Hz), and integration. Chemical shifts of ^{13}C NMR spectra are reported in ppm from the central peak of $CDCl_3$ (77.2 ppm), C_6D_6 (128.39 ppm), or CD_2Cl_2 (54.00 ppm) on the δ scale. Infrared (IR) spectra were recorded on a Perkin-Elmer 2000 FT-IR. High Resolution mass spectra (HR-MS) were obtained on a Bruker Daltonics APEXII 3 Tesla Fourier Transform Mass Spectrometer by Dr. Li Li of the Massachusetts Institute of Technology Department of Chemistry Instrumentation Facility. Optical rotations were measured on a Perkin-Elmer 241 polarimeter at 589 nm.



3-[(2*R*, 3*S*)-3-Methyl-3-trimethylsilanyl-oxiranyl]-propan-1-ol (1e): To a solution of 5-trimethylsilanyl-pent-4-yn-1-ol (**5**)[2] (12.2 g, 77.8 mmol) in Et_2O (190 mL) at 0 °C was added a 1 M solution of DIBAL-H in hexane (190 mL). The resulting solution was heated 24 h at reflux. This solution was then cooled to –78 °C, diluted with Et_2O (60 mL), and a solution of I_2 (79 g, 310 mmol) in Et_2O (175 mL) was added. After stirring for 2 h at –78 °C, the reaction was carefully quenched by pouring into 1 M HCl (200 mL) and ice (40 g). The maroon organic layer was separated, and the aqueous layer was extracted with Et_2O (3 × 200 mL). The combined organic layers were washed with saturated $Na_2S_2O_3$, brine, dried over $MgSO_4$, and concentrated *in vacuo*. The crude product was purified by column chromatography (20% EtOAc in hexane) to yield the vinyl iodide, (5*E*)-5-iodo-5-trimethylsilanyl-pent-4-en-1-ol, as a pale yellow oil (20.1 g, 91%, >95% E): R_f = 0.20 (20% EtOAc in hexane); IR (thin film, NaCl) 3335, 2952, 1588, 1407, 1249, 1059, 841 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.18 (t, *J* = 7.9 Hz, 1H), 3.66 (t, *J* = 6.4 Hz, 2H), 2.18 (dt, *J* = 7.7, 7.6 Hz, 2H), 1.67 (m, 2H), 0.28 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.7, 107.6, 62.2, 32.2, 31.7 1.4; HR-MS (ESI) Calcd for $C_8H_{17}IOSi$ $(M)^+$ 284.0088, found 284.0091.

To a slurry of CuCN (3.2 g, 35.2 mmol) in Et_2O (45.0 mL) at 0 °C was added a 1.4 M solution of MeLi in Et_2O (50.3 mL). After 15 minutes a solution of (5*E*)-5-iodo-5-trimethylsilanyl-pent-4-en-1-ol (5.1 g, 18.0 mmol) in Et_2O (14.0 mL) was slowly added. The solution was maintained at 0 °C for 20 h at which time the reaction was carefully quenched with saturated NH_4Cl. The organic layer was separated and the aqueous layer was extracted with Et_2O (3 × 50 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude product was pushed through a plug of silica gel to remove the metal salts. This colorless liquid, (5*Z*)-5-trimethylsilanyl-hex-4-en-1-ol, required no further purification (3.0 g, 97%): R_f = 0.30 (20% EtOAc in hexane); IR (thin film, NaCl): 3332, 2951, 1619, 1442, 1248, 1054, 838, cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.97 (tq, *J* = 7.6, 1.5 Hz, 1H), 3.65 (t, *J* = 6.7 Hz,

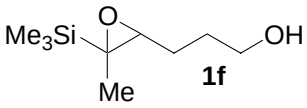
2H), 2.16 (dt, *J* = 7.6, 7.3 Hz, 2H), 1.75 (d, *J* = 1.5 Hz, 3H), 1.66-1.59 (m, 2H), 0.13 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 141.8, 135.6, 62.8, 33.3, 28.5, 24.9, 0.1; HR-MS (ESI) Calcd for $C_9H_{20}NaOSi$ $(M + Na)^+$ 195.1176, found 195.1188.

To a solution of (5*Z*)-5-trimethylsilanyl-hex-4-en-1-ol (2.8 g, 13.8 mmol) in CH_2Cl_2 (140 mL) at 0 °C was added Et_3N (2.5 mL, 17.9 mmol), Ac_2O (1.7 mL, 17.9 mmol), and 4-dimethylamino pyridine (0.2 g, 1.4 mmol). The resulting solution was allowed to warm to room temperature and stirred overnight. The reaction was quenched with saturated NH_4Cl and concentrated *in vacuo*. The remaining contents were extracted with Et_2O (3 × 50 mL). The combined organic layers were washed with water, brine, dried over $MgSO_4$, and concentrated *in vacuo*. The crude product was purified by column chromatography (10% EtOAc in hexane) to afford the acetate as a pale yellow oil (3.2 g, 94%): IR (thin film, NaCl): 2954, 1744, 1366, 1248, 1042, 838 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.92 (tq, *J* = 7.5, 1.8 Hz, 1H), 4.06 (t, *J* = 6.6 Hz, 2H), 2.19-2.11 (m, 2H), 2.04 (s, 3H), 1.74 (d, *J* = 1.5 Hz, 3H), 1.72-1.63 (m, 2H), 0.12 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.3, 140.9, 136.1, 64.3, 29.4, 28.6, 25.1, 21.4, 0.2; HR-MS (ESI) Calcd for $C_{11}H_{22}NaO_2Si$ $(M + Na)^+$ 237.1281, found 237.1271.

To a solution of the acetate (1.0 g, 4.7 mmol) in CH_3CN/DMM (172.2 mL, 1:2 v:v) and a 0.05 M solution of $Na_2B_4O_7{\cdot}10H_2O$ in 4×10^{-4} M (Na_2-(EDTA)) (115 mL) was added *n*-Bu_4NHSO_4 (0.4 g, 1.1 mmol), and chiral ketone **A** (2.8 g, 11.1 mmol). To this rapidly stirring solution was added, simultaneously over 20 minutes *via* syringe pump, a solution of Oxone® (13.6 g, 22.2 mmol) in 4×10^{-4} M (Na_2-(EDTA)) (94.0 mL) and a 0.89 M solution of K_2CO_3 (94.0 mL). After the Oxone® and K_2CO_3 solutions had been added, the resulting mixture was diluted with water (100 mL) and extracted with EtOAc (4 × 100 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The product was separated from the ketone catalyst by column chromatography (20% EtOAc in hexane) to yield a colorless liquid (0.8 g, 77%): R_f = 0.34 (20% EtOAc in hexane); IR (thin film, NaCl): 2958, 1742, 1368, 1251, 1038, 841 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.15-4.06 (m, 2H), 2.70 (dd, *J* = 6.0, 4.5 Hz, 1H), 2.04 (s, 3H), 1.87-1.66 (m, 3H), 1.54-1.45 (m, 1H), 1.21 (s, 3H), 0.11 (s, 9H); ^{13}C

NMR (125 MHz, $CDCl_3$) δ 172.0, 65.8, 64.7, 55.6, 28.0, 27.0, 23.3, 21.7, -1.2; HR-MS (ESI) Calcd for $C_{11}H_{22}NaO_3Si$ $(M + Na)^+$ 253.1230 found 253.1223.

A solution of the epoxy-acetate (0.8 g, 3.4 mmol) in THF (10 mL) and MeOH (10 mL) was cooled to 0 °C. A 1.0 M solution of LiOH (10 mL) was added slowly and the mixture stirred 25 min. The mixture was diluted with water and extracted with Et_2O (3 × 40 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo* to afford **1e** as a colorless oil without the need for purification (0.6 g, 94%): R_f = 0.37 (50% EtOAc in hexane); IR (thin film, NaCl): 3419, 2957, 1446, 1251, 1062, 841, 756 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.61 (t, J = 6.1 Hz, 2H), 2.85 (br s, 1H), 2.68 (dd, *J* = 8.2, 3.7 Hz, 1H), 1.77-1.65 (m, 3H), 1.45-1.38 (m, 1H), 1.16 (s, 3H), 0.06 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 66.0, 62.3, 55.8, 30.3, 27.4, 22.9, -1.6; HR-MS (ESI) Calcd for $C_9H_{20}NaO_2Si$ $(M + Na)^+$ 211.1125, found 211.1119.

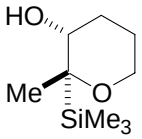


1f

3-(3-Methyl-3-trimethylsilanyl-oxiranyl)-propan-1-ol (1f): To a slurry of CuCN (0.3 g, 3.4 mmol) in Et_2O (3.5 mL) at 0 °C was added a 1.4 M solution of MeLi in Et_2O (4.8 mL). After 15 minutes a solution of (5*Z*)-5-iodo-5-trimethylsilanyl-pent-4-en-1-ol[3] (0.4 g, 1.5 mmol) in Et_2O (1.0 mL) was slowly added. The solution was maintained at 0 °C for 20 h at which time the reaction was carefully quenched with saturated NH_4Cl. The organic layer was separated and the aqueous layer was extracted with Et_2O (3 × 10 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude product was pushed through a plug of silica gel to remove the metal salts. This colorless liquid was carried on to the next step without further purification (R_f = 0.31, 20% EtOAc in hexane).

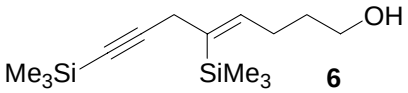
To a solution of the olefin (180 mg, 1.0 mmol) in CH_2Cl_2 (3.0 mL) at 0 ºC was added *m*-CPBA (190 mg, 1.1mmol) and the reaction mixture was warmed to room temperature and stirred 3.5 h. The reaction was quenched with 5% NaOH (5 mL). The aqueous layer was separated and extracted with CH_2Cl_2 (3 × 5 mL). The combined organic layers were washed with water, dried over $MgSO_4$, and concentrated *in vacuo*.

The crude product was purified by column chromatography (20-50% EtOAc in hexane) to afford **1f** as a colorless oil (160 mg, 58 % over two steps): R_f = 0.38 (50% EtOAc in hexane); IR (thin film, NaCl) 3423, 2956, 1449, 1249, 1055, 840 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.72 (m, 2H), 2.82 (dd, *J* = 7.0, 4.6 Hz, 1H), 1.78-1.73 (m, 3H), 1.68-1.62 (m, 1H), 1.24 (s, 3H), 0.05 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 62.7, 60.2, 55.1, 30.0, 24.9, 15.0, -3.9; HR-MS (ESI) Calcd for $C_9H_{24}NO_2Si$ $(M + NH_4)^+$ 206.1576, found 206.1578.



2e

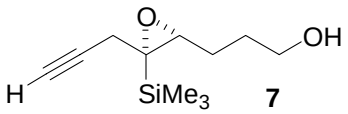
(2*R*, 3*R*)-2-Methyl-2-trimethylsilanyl-tetrahydro-pyran-3-ol (2e): To a solution of **1e** (100 mg, 0.5 mmol) in CH_2Cl_2 (5.0 mL) at 0 °C was added $BF_3{\cdot}Et_2O$ (0.1 mL, 0.5 mmol) and the reaction mixture stirred 20 min. The reaction was quenched with saturated $NaHCO_3$. The aqueous layer was separated and extracted with CH_2Cl_2 (3 × 5 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The crude product was purified by column chromatography (20% EtOAc in hexane) to afford **2e** as a colorless oil (67 mg, 67%): R_f = 0.33 (20% EtOAc in hexane); IR (thin film, NaCl) 3444, 2952, 2866, 1246, 1076, 1033, 838 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.74 (td, *J* = 11.6, 3.1 Hz, 1H), 3.59-3.49 (m, 2H), 2.10 (d, *J* = 9Hz, 1H), 2.03-1.96 (m, 1H), 1.92-1.83 (m, 1H), 1.68-1.62 (m, 1H), 1.47-1.41 (m, 1H), 1.24 (s, 3H), 0.09 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 72.9, 71.8, 60.1, 25.9, 21.5, 18.7, -2.2; HR-MS (ESI) Calcd for $C_9H_{20}NaO_2Si$ $(M + Na)^+$ 211.1125, found 211.1136.



6

(4*Z*)-5,8-Bis-trimethylsilanyl-oct-4-en-7-yn-1-ol (6): A solution of 1-trimethylsilyl-1-propyne (32 g, 285 mmol) in THF (600 mL) was cooled to –78 °C and was treated with a 2.5 M solution of *n*-BuLi (119 mL) and TMEDA (45 mL, 298.2 mmol). The solution was allowed to warm to 0 °C and stirred 45 min. The solution was then transferred *via* cannula to a –78 °C slurry of CuI (60 g, 320 mmol) in THF (300 mL) and stirred at that temperature 30 min. Then 4-dimethylamino pyridine (35 g, 280 mmol) was added and

the solution was allowed to warm to –20 °C. At that time (5*E*)-5-iodo-5-trimethylsilanyl-pent-4-en-1-ol (30 g, 106 mmol) was added, the reaction mixture was allowed to warm to room temperature gradually and stirred overnight. The reaction was quenched with 1 M HCl (100 mL), and the organic layer was separated. The aqueous layer was extracted with Et_2O (3 × 200 mL). The combined organic layers were washed with water, brine, dried over $MgSO_4$, and concentrated *in vacuo*. The crude product was purified by column chromatography (20% EtOAc in hexane) to yield **6** as a pale yellow oil (24.4 g, 83%): R_f = 0.41 (20% EtOAc in hexane); IR (thin film, NaCl) 3314, 2956, 2898, 2173, 1618, 1420, 1249, 1053, 841, 759 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 6.24 (t, *J* = 7.6 Hz, 1H), 3.68 (t, *J* = 6.4 Hz, 2H), 2.99 (s, 2H), 2.24 (dt, *J* = 7.6, 7.3 Hz, 2H), 1.68 (m, 2H), 0.19 (s, 9H), 0.16 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.6, 134.5, 106.5, 88.3, 63.3, 33.5, 29.4, 28.9, 0.8, 0.7; HR-MS (ESI) Calcd for $C_{14}H_{28}NaOSi_2$ $(M + Na)^+$ 291.1571, found 291.1577.



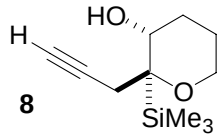
7

3-[(3*S*, 4*R*)-3-Prop-2-ynyl-3-trimethylsilanyl-oxiranyl]-propan-1-ol (7): To a solution of **6** (16.0 g, 60 mmol) in CH_2Cl_2 (500 mL) at 0 °C was added Et_3N (12 g, 120 mmol), Ac_2O (11 mL, 120 mmol), and 4-dimethylamino pyridine (0.7 g, 6.0 mmol). The resulting solution was allowed to warm to room temperature and stirred overnight. The reaction was quenched with saturated NH_4Cl and concentrated *in vacuo*. The remaining contents were extracted with Et_2O (3 × 50 mL). The combined organic layers were washed with water, brine, dried over $MgSO_4$, and concentrated *in vacuo*. The crude product was purified by column chromatography (10% EtOAc in hexane) to afford the acetate as a pale yellow oil (16.6 g, 90%): R_f = 0.55 (20% EtOAc in hexane); IR (thin film, NaCl): 2958, 2898, 2173, 1744, 1249, 1043, 841, 759 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.21 (t, *J* = 6.7 Hz, 1H), 4.09 (t, *J* = 6.4 Hz, 2H), 2.99 (s, 2H), 2.23 (dt, *J* = 7.6, 6.7 Hz, 2H), 2.06 (s, 3H), 1.76-1.70 (m, 2H), 0.18 (s, 9H), 0.16 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.8, 142.9, 135.0, 106.3, 88.3, 64.7, 29.5, 29.4, 29.0, 21.7, 0.8, 0.6 ; HR-MS (ESI) Calcd for $C_{16}H_{30}NaO_2Si_2$ $(M + Na)^+$ 333.1677, found 333.1662.

This acetate (2.8 g, 8.9 mmol) was dissolved in CH_3CN/DMM (285 mL, 1:2 v:v) and a 0.05 M solution of $Na_2B_4O_7 \cdot 10\ H_2O$ in 4×10^{-4} M (Na_2-(EDTA)) (190 mL) was added as well as *n*-Bu_4NHSO_4 (0.61 g, 1.8 mmol), and chiral ketone **A** (4.6 g, 17.8 mmol). To this rapidly stirring solution was added, simultaneously over 20 minutes *via* syringe pump, a solution of Oxone® (22.1 g, 35.9 mmol) in 4×10^{-4} M (Na_2-(EDTA)) (150 mL) and a 0.89 M solution of K_2CO_3 (150 mL). After the Oxone® and K_2CO_3 solutions had been added, the resulting mixture was diluted with water (200 mL) and extracted with EtOAc (4 × 200 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The asymmetric epoxidation procedure was repeated. The epoxide product was then separated from the ketone catalyst (recovered for reuse) by column chromatography (20% EtOAc in hexane) to yield the product as a clear liquid (2.0 g, 70%): R_f = 0.46 (20% EtOAc in hexane); $[\alpha]^{25}_D$ = -33.0 (*c* = 0.91, in $CHCl_3$); IR (thin film, NaCl): 2959, 2175, 1743, 1250, 1022, 842 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.15 (m, 2H), 2.88 (dd, *J* = 7.9, 5.2 Hz, 1H), 2.79 (d, *J* = 17.1 Hz, 1H), 2.06 (s, 3H), 1.96 (d, *J* = 16.8 Hz, 1H), 1.90-1.73 (m, 3H), 1.58-1.51 (m, 1H), 0.20 (s, 9H), 0.16 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.8, 103.1, 88.6, 64.6, 64.0, 55.9, 29.3, 27.8, 26.9, 21.7, 0.7, -0.5; HR-MS (ESI) Calcd for $C_{16}H_{31}O_3Si_2$ $(M + H)^+$ 327.1806, found 327.1805. The enantiomeric ratio was determined by GC (Chiraldex-G-TA, 115 °C, 20 m × 0.25 mm, 25 psi) T_r(minor) 79 min, T_r(major) 82 min (er >95:5).

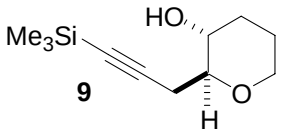
A solution of the epoxy-acetate (1.0 g, 3.1 mmol) in THF (10 mL) and MeOH (10 mL) was cooled to 0 °C. A 1.0 M solution of LiOH (10 mL) was added slowly and the mixture stirred 25 min. The mixture was diluted with water and extracted with Et_2O (3 × 40 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo* to afford **7** as a colorless oil without the need for purification (0.6 g, 95%): R_f = 0.16 (20% EtOAc in hexane); $[\alpha]^{25}_D$ = -21.6 (*c* = 1.67, in $CHCl_3$); IR (thin film, NaCl): 3419, 3310, 2957, 2119, 1438, 1422, 1251, 1062, 843, 759 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.72 (m, 2H), 2.94 (dd, *J* = 8.2, 4.0 Hz, 1H), 2.72 (dd, *J* = 16.8, 2.7 Hz, 2H), 2.06 (t, *J* = 2.7 Hz, 1H), 1.86 (m, 2H), 1.78 (m, 2H), 0.20 (s, 9H); ^{13}C NMR

(125 MHz, $CDCl_3$) δ 80.6, 71.9, 64.1, 63.0, 56.0, 30.8, 27.8, 27.6, -0.6; HR-MS (ESI) Calcd for $C_{11}H_{20}NaO_2Si$ $(M + Na)^+$ 235.1125, found 235.1117.



8

(2*R*, 3*R*)-2-Prop-2-ynyl-2-trimethylsilanyl-tetrahydro-pyran-3-ol (8). To a solution of **7** (760 mg, 4.0 mmol) in CH_2Cl_2 (60 mL) at 0 °C was added $BF_3{\cdot}Et_2O$ (0.1 mL, 0.4 mmol) and the reaction mixture stirred 20 min. The reaction was quenched with saturated $NaHCO_3$. The aqueous layer was separated and extracted with CH_2Cl_2 (3 × 30 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The crude product was purified by column chromatography (20% EtOAc in hexane) to afford **8** as a colorless oil (0.61 g, 80%): R_f = 0.32 (20% EtOAc in hexane); $[\alpha]^{25}_D$ = -16.0 (*c* = 1.0, in $CHCl_3$); IR (thin film, NaCl) 3457, 3308, 2953, 2862, 2117, 1452, 1410, 1246, 1089, 1011, 986, 841 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.88 (dd, *J* = 10.7, 6.7, 3.7 Hz, 1H), 3.66 (ddd, *J* = 11.9, 8.2, 3.4 Hz, 1H), 3.48 (dt, *J* = 11.9, 5.2 Hz, 1H), 2.76 (dd, *J* = 16.8, 2.7 Hz, 1H), 2.46 (d, *J* = 7.6 Hz, 1H), 2.39 (dd, *J* = 16.8, 2.7 Hz, 1H), 2.01 (t, *J* = 2.7 Hz, 1H), 1.93-1.87 (m, 1H), 1.82-1.74 (m, 1H), 1.69-1.63 (m, 1H), 1.49-1.42 (m, 1H), 0.14 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 81.2, 74.4, 71.6, 70.0, 61.4, 26.6, 23.8, 21.9, -0.7; HR-MS (ESI) Calcd for $C_{11}H_{20}NaO_2Si$ $(M + Na)^+$ 235.1125, found 235.1120.

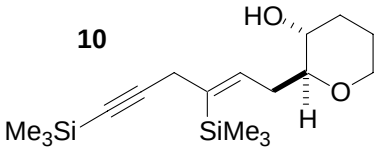


9

(2*S*, 3*R*)-2-(3-Trimethylsilanyl-prop-2-ynyl)-tetrahydro-pyran-3-ol (9). To a solution of **8** (450 mg, 2.1 mmol) in THF (34 mL) was added a 1 M solution of *n*-Bu_4NF in THF (8.3 mL). The reaction mixture was stirred at room temperature overnight. At that time the solution was diluted with water (20 mL). The aqueous layer was separated and extracted with Et_2O (3 × 40 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The crude reaction mixture was purified by column chromatography (50% EtOAc in hexane) to afford the desilylated product (270 mg, 90%) as a colorless oil[4] ($[\alpha]^{25}_D$ = -24.8 [*c* = 0.44 , in $CHCl_3$]).

A solution of the terminal alkyne (170 mg, 1.2 mmol) in THF (8 mL) was cooled to –78 °C and a 2.5 M solution of *n*-BuLi in hexane (1.1 mL) was added. The solution was allowed to warm to 0 °C over 30 minutes after which the solution was recooled to –78 °C. TMSCl (0.3 mL, 2.4 mmol) was added, and he reaction was warmed to room temperature and stirred 20 h. The reaction was quenched with 1 M HCl (5 mL) and stirred 20 min. The aqueous layer was separated and extracted with Et_2O (2 × 5 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (50% EtOAc in hexane) to yield **9** as a colorless liquid (210 mg, 81%): R_f = 0.13 (20% EtOAc in hexane); $[\alpha]^{25}_D$ = +1.8 (*c* = 1.67, in $CHCl_3$); IR (thin film, NaCl) 3424, 2958, 2857, 2177, 1250, 1096, 1068, 1038, 843, 760 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.92 (m, 1H), 3.57 (ddd, *J* = 13.7, 8.9, 4.9 Hz, 1H), 3.36 (m, 1H), 3.23 (m, 1H), 2.65 (dd, *J* = 17.1, 5.3 Hz, 1H), 2.59 (dd, *J* = 17.0, 5.3 Hz, 1H), 2.47 (broad s, 1H), 2.15-2.09 (m, 1H), 1.74-1.66 (m, 2H), 1.47-1.39 (m, 1H), 0.165 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 103.4, 87.8, 79.9, 71.0, 68.0, 32.3, 25.5, 24.6, 0.2; HR-MS (ESI) Calcd for $C_{11}H_{20}NaO_2Si$ $(M + Na)^+$ 235.1125, found 235.1133.

10

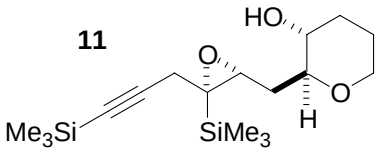


(2*S*,3*R*)-2-[(2*Z*)-3,6-Bis-trimethylsilanyl-hex-2-en-5-ynyl)-tetrahydro-pyran-3-ol (10): To a solution of **9** (1.4 g, 6.4 mmol) in Et_2O (20 mL) was added a 1 M solution of DIBAL-H in hexane (16 mL). The resulting solution was heated 24 h at reflux, cooled to –78 °C, diluted with Et_2O (5.0 mL), and a solution of I_2 (6.5 g, 26 mmol) in Et_2O (10 mL) was added. After stirring at –78 °C for 2 h, the reaction was warmed to 0 °C and stirred 1 h. The mixture was carefully quenched by pouring into 1 M HCl (50 mL) and ice (15 g). The maroon organic layer was separated, and the aqueous layer was extracted with Et_2O (3 × 100 mL). The combined organic layers were washed with saturated $Na_2S_2O_3$, brine, dried over $MgSO_4$, and concentrated *in vacuo*. The crude product was purified by column chromatography (20% EtOAc in hexane) to yield the vinyl iodide as a pale yellow oil (1.9 g, 88%, >95% *E*): R_f = 0.37 (20% EtOAc in hexane); $[\alpha]^{25}_D$ = -9.6 (*c*

= 0.83, in $CHCl_3$); IR (thin film, NaCl): 3402, 2939, 2853, 1249, 1096, 1036, 841 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.31 (t, *J* = 7.6 Hz, 1H), 3.90 (m, 1H), 3.30 (m, 2H), 3.05 (dt, *J* = 8.2, 3.4 Hz, 1H), 2.64 (ddd, *J* = 15.3, 7.6, 3.4 Hz, 1H), 2.29 (m, 1H), 2.11 (m, 1H), 1.79-1.66 (m, 2H), 1.41 (m, 1H), 0.29 (s, 9H); ^{13}C NMR (125 MHz, C_6D_6) δ 153.1, 109.4, 82.0, 70.8, 68.4, 38.1, 33.9, 26.2, 1.8; HR-MS (ESI) Calcd for $C_{11}H_{21}INaO_2Si$ $(M + Na)^+$ 363.0248, found 363.0256.

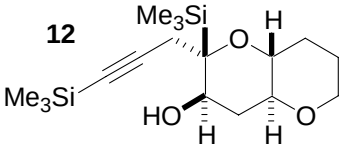
A solution of 1-trimethylsilyl-1-propyne (2.7 mL, 18.4 mmol) in THF (63 mL) was cooled to –78 °C and was treated with a 2.5 M solution of *n*-BuLi in hexane (7.7 mL) and TMEDA (2.9 mL, 19.2 mmol). The solution was allowed to warm to 0 °C and stirred 45 min. The solution was then transferred to a –78 °C slurry of CuI (3.9 g, 20 mmol) in THF (22 mL) and stirred at that temperature 30 min. Then 4-dimethylamino pyridine (2.3 g, 19 mmol) was added and the solution was allowed to warm to –20 °C. At that time the vinyl iodide (1.4 g, 4.1 mmol) was added, and the reaction mixture was allowed to warm to room temperature gradually and stirred overnight. The reaction was quenched with 1 M HCl (20 mL), and the organic layer was separated. The aqueous layer was extracted with Et_2O (3 × 100 mL). The combined organic layers were washed with water, brine, dried over $MgSO_4$, and concentrated *in vacuo*. The crude product was purified by column chromatography (20% EtOAc in hexane) to yield **10** as a pale yellow oil (1.1 g, 79%): R_f = 0.24 (20% EtOAc in hexane); $[\alpha]^{25}_D$ = -6.0 (*c* = 0.33, in $CHCl_3$); IR (thin film, NaCl) 3441, 2957, 2948, 2173, 1620, 1250, 1098, 840.3, 759 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 6.42 (tt, *J* = 6.4, 1.2 Hz, 1H), 3.91 (m, 1H), 3.40 (m, 1H), 3.36-3.31 (m, 1H), 3.10 (ddd, *J* = 11.9, 7.6, 4.3 Hz, 1H), 3.02 (d, *J* = 1.2 Hz, 2H), 2.70 (ddd, *J* = 14.9, 7.9, 4.3 Hz, 1H), 2.40-2.34 (m, 1H), 2.14-2.08 (m, 1H), 1.70-1.67 (m, 2H), 1.45-1.37 (m, 1H), 0.21 (s, 9H), 0.16 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 140.5, 136.1, 106.5, 88.4, 82.9, 71.4, 68.4, 35.5, 33.6, 29.6, 26.3, 0.8, 0.7; HR-MS (ESI) Calcd for $C_{17}H_{32}NaO_2Si_2$ $(M + Na)^+$ 347.1883, found 347.1841.

11



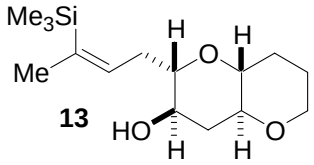
(2*S*,3*R*)-2-{[2*R*,3*S*]-3-Trimethylsilanyl-3-(3-trimethylsilanyl-prop-2-ynyl)-oxiranylmethyl}-tetrahydro-pyran-3-ol (11). Olefin **10** (200 mg, 0.62 mmol) was dissolved in CH_3CN/DMM (20 mL, 1:2 v:v). A 0.05 M solution of $Na_2B_4O_7{\cdot}10H_2O$ in 4×10^{-4} M (Na_2-(EDTA)) (13 mL) was added, as well as *n*-Bu_4NHSO_4 (40 mg, 0.1 mmol), and chiral ketone **A** (400 mg, 1.6 mmol). This solution was cooled to 0 °C, and to it was added, simultaneously over 1.5 h *via* syringe pump, a solution of Oxone® (1.9 g, 3.1 mmol) in 4×10^{-4} M (Na_2-(EDTA)) (13 mL) and a 0.89 M solution of K_2CO_3 (13 mL). After the Oxone® and K_2CO_3 solutions had been added, the resulting mixture was diluted with water (30 mL) and extracted with EtOAc (4×100 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The asymmetric epoxidation procedure was repeated. The epoxide product was separated from the ketone catalyst by column chromatography (20% EtOAc in hexane) as a colorless oil (100 mg, 50%): R_f = 0.25 (20% EtOAc in hexane); $[\alpha]^{25}_D$ = -16.8 (*c* = 0.83, in $CHCl_3$); IR (thin film, NaCl) 3445, 2958, 2852, 2176, 1250, 1096, 842 759 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.96-3.93 (m, 1H), 3.63 (ddd, *J* = 15.6, 9.5, 4.6 Hz, 1H), 3.38 (dt, *J* = 11.3, 4.0 Hz, 1H), 3.25 (ddd, *J* = 8.5, 5.2, 2.7 Hz, 1H), 3.19 (dd, *J* = 9.2, 2.4 Hz, 1H), 2.78 (d, *J* = 17.1 Hz, 1H), 2.26 (d, *J* = 4.9 Hz, 1H), 2.21 (dt, *J* = 15.0, 2.4 Hz, 1H), 2.12 (m, 1H), 2.00 (d, *J* = 16.8 Hz, 1H), 1.79-1.69 (m, 2H), 1.48-1.39 (m, 2H), 0.21 (s, 9H), 0.15 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 102.9, 86.6, 81.7, 70.1, 68.8, 61.1, 55.4, 33.7, 32.8, 29.3, 26.6, 0.7, -0.5; HR-MS (ESI) Calcd for $C_{17}H_{33}O_3Si_2$ $(M + H)^+$ 341.1963, found 341.1953.

12



(2*R*, 3*R*, 5*S*, 10*R*)-2-Trimethylsilanyl-2-(3-trimethylsilanyl-prop-2-ynyl)-octahydro-pyrano[3,2-*b*]pyran-3-ol (12). A solution of epoxysilane **11** (130 mg, 0.39 mmol) in CH_2Cl_2 (4.0 mL) was cooled to –42 °C. To this, $BF_3{\cdot}Et_2O$ (2 μL, 16 μmol) was added and the reaction mixture stirred 20 min. The reaction was quenched with saturated $NaHCO_3$, the aqueous layer was extracted with CH_2Cl_2 (3×10 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The crude product was purified by column chromatography (20% EtOAc in hexane) to

afford **12** as a colorless oil (120 g, 91%): R_f = 0.24 (20%, EtOAc in hexane); $[\alpha]^{25}_D$ = -12.0 (*c* = 0.33, in $CHCl_3$); IR (thin film, NaCl): 3580, 2959, 2930, 2853, 2176, 1743, 1249, 1100, 842 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 4.00 (ddd, *J* = 11.6, 5.5, 3.4 Hz, 1H), 3.92-3.89 (m, 1H), 3.41-3.35 (m, 1H), 3.13 (ddd, *J* = 13.4, 9.1, 4.6 Hz, 1H), 2.96 (ddd, *J* = 13.1, 8.9, 4.3 Hz, 1H), 2.74 (d, *J* = 3.4 Hz, 1H), 2.65 (d, *J* = 17.1 Hz, 1H), 2.44 (d, *J* = 17.1 Hz, 1H), 2.24 (dt, *J* = 11.9, 4.6 Hz, 1H), 2.01-1.96 (m, 1H), 1.81-1.68 (m, 3H), 1.38-1.30 (m, 1H), 0.25 (s, 9H), 0.16 (s, 9H); ^{13}C NMR (125 MHz, C_6D_6): δ 106.2, 87.8, 77.9, 76.9, 75.0, 74.5, 68.0, 37.5, 30.6, 30.4, 26.3, 1.0, 0.5; HR-MS (ESI) Calcd for $C_{17}H_{32}NaO_3Si_2$ $(M + Na)^+$ 363.1782, found 363.1794.



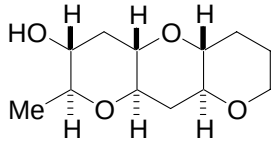
13

(2*S*,3*R*,5*S*,10*R*)-2-[(2*Z*)-3-Trimethylsilanyl-but-2-enyl]-octahydro-pyrano[3,2-*b*]pyran-3-ol (13). To a solution of **12** (16 mg, 47 μmol) in Et_2O (1.5 mL) was added a 1 M solution of DIBAL-H in hexane (0.3 mL). The resulting solution was heated for 24 h at reflux, cooled to –78 °C and diluted with Et_2O (0.5 mL), and a solution of I_2 (47 mg, 0.2 mmol) in Et_2O (1 mL) was added. After stirring at –78 °C for 4 h, the reaction was warmed to 0 °C and stirred for 4 h. The mixture was carefully quenched by pouring into 1 M HCl (5 mL) and ice (3 g). The maroon organic layer was separated, and the aqueous layer was extracted with Et_2O (3 × 20 mL). The combined organic layers were washed with saturated $Na_2S_2O_3$, brine, dried over $MgSO_4$, and concentrated *in vacuo*. The crude product was partially purified by column chromatography (20% EtOAc in hexane; R_f = 0.32, 20% EtOAc in hexane) and a portion was carried on to the methylation.

A slurry of CuCN (6 mg, 70 μmol) in Et_2O (0.5 mL) was cooled to 0 °C and a 1.2 M solution of MeLi in Et_2O (120 μL) was added slowly. After 15 minutes a solution of the vinyl iodide (15 mg, 30 μmol) in Et_2O (300 μL) was slowly added. The solution was maintained at 0 °C for 20 h at which time the reaction was carefully quenched with saturated NH_4Cl. The organic layer was separated and the aqueous layer was extracted with Et_2O (3 × 40 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude product was pushed through a

plug of silica gel to remove the metal salts. This colorless liquid was carried on to the next step without further purification (R_f = 0.41, 20% EtOAc in hexane).

To the methylated olefin (7 mg, 21 μmol) in THF (0.5 mL) was added a 1 M solution of *n*-Bu_4NF in THF (40 μL). The reaction mixture stirred at room temperature overnight. At that time the solution was diluted with water (2 mL). The aqueous layer was separated and extracted with EtOAc (3 × 5 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The crude reaction mixture was purified by column chromatography (50% EtOAc in hexane) to afford the mono-desilylated product, **13**, as a colorless oil (6 mg, 46% from **12**): R_f = 0.66 (50% EtOAc in hexane); $[\alpha]^{25}_D$ = +12.0 (*c* = 0.17, in $CHCl_3$); IR (thin film, NaCl) 3435, 2926, 2853, 1721 (OH overtone), 1618, 1247, 1099, 1023, 837 cm^{-1}; ^1H NMR (500 MHz, CD_2Cl_2): δ 6.13 (m, 1H), 3.86 (m, 1H), 3.45 (m, 1H), 3.35 (m, 1H), 3.12 (ddd, *J* = 11.6, 7.6, 4.0 Hz, 1H), 2.96 (m, 2H), 2.62 (m, 1H), 2.27 (m, 2H), 2.03 (m, 1H), 1.79 (d, *J* = 1.2 Hz, 3H), 1.70 (m, 2H), 1.46 (m, 2H), 0.16 (s, 9H); ^{13}C NMR (125 MHz, CD_2Cl_2): δ 138.8, 123.6, 82.7, 78.4, 77.5, 70.8, 68.3, 39.8, 35.2, 29.9, 26.2, 25.2, 0.1; HR-MS (ESI) Calcd for $C_{15}H_{28}NaO_3Si$ $(M + Na)^+$ 307.1700, found 307.1710.



14

(2*S*, 3*R*, 5*S*, 7*R*, 12*S*, 14*R*)-2-Methyl-decahydro-1,6,11-trioxa-anthracen-3-ol (14). To a solution of **13** (4 mg, 14 μmol) in CH_3CN/DMM (0.5 mL, 1:2 v:v) and a 0.05 M solution of $Na_2B_4O_7{\cdot}10H_2O$ in 4×10^{-4} M (Na_2-(EDTA)) (0.3 mL) was added *n*-Bu_4NHSO_4 (0.1 mg, 0.003 mmol), and chiral ketone **A** (7 mg, 0.03 mmol). To this rapidly stirring solution was added, simultaneously over 20 minutes *via* syringe pump, a solution of Oxone® (3.6 mg, 0.06 mmol) in 4×10^{-4} M (Na_2-(EDTA)) (0.2 mL) and a 0.89 M solution of K_2CO_3 (0.2 mL). After the Oxone® and K_2CO_3 solutions had been added, the resulting mixture was diluted with water (0.5 mL) and extracted with EtOAc (4 × 5 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The product was separated from the ketone catalyst by column

chromatography (50% EtOAc in hexane) and carried on to the next step without further purification.

To a solution of the epoxide in CH_2Cl_2 (0.5 mL) at –42 °C was added $BF_3{\cdot}Et_2O$ (2 μL, 16 μmol) and the reaction mixture stirred 20 min. At that time the reaction was quenched with saturated $NaHCO_3$, the aqueous layer was separated and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The crude product was carried on to the next step (R_f = 0.35, 50% EtOAc in hexane).

To a solution of the tris-tetrahydropyran in THF (0.5 mL) was added a 1 M solution of *n*-Bu_4NF in THF (0.2 mL), and the reaction mixture stirred at room temperature overnight. At that time the solution was diluted with water (2 mL). The aqueous layer was separated and extracted with EtOAc (3 × 5 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude reaction mixture was purified by column chromatography (50-80% EtOAc in hexane) to afford the desilylated product **14** as a white solid (2 mg, 62% from **13**): R_f = 0.26 (75% EtOAc in hexane); $[\alpha]^{25}_D$ = +4.5 (*c* = 0.50, in $CHCl_3$); IR (thin film, NaCl) 3364, 2927, 2855, 1460, 1113, 1080, 1045 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 3.93 (m, 1H), 3.39 (m, 2H), 3.24 (dq, *J* = 9.2, 6.1 Hz, 1H), 3.15-3.02 (m, 4H), 2.39 (dt, *J* = 11.3, 4.3 Hz, 1H), 2.32 (dt, *J* = 11.6, 3.7 Hz, 1H), 2.09-2.06 (m, 1H), 1.77-1.72 (m, 2H), 1.54-1.44 (m, 4 H), 1.31 (d, *J* = 6.1 Hz, 3H); ^{13}C NMR (125 MHz, CD_2Cl_2): δ 78.9, 78.8, 78.0, 77.3, 77.2, 72.1, 68.5, 39.3, 36.4, 30.0, 26.3, 18.3; HR-MS (ESI) Calcd for $C_{12}H_{21}O_4$ $(M + H)^+$ 229.1434, found 229.1441.

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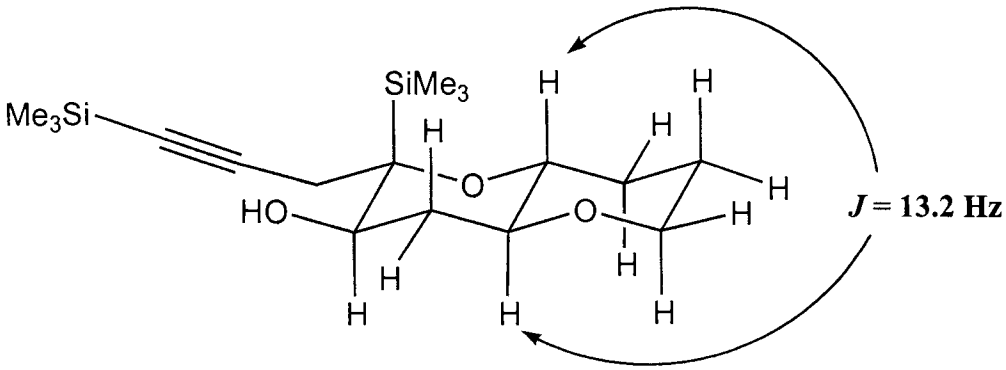
[1] Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem*. **1978**, *43*, 2923.
[2] Cruciani, P.; Stammler, R.; Aubert, C.; Malacria, M. *J. Org. Chem*. **1996**, *61*, 2699.
[3] Ma, S.; Liu, F.; Negishi, E. *Tetrahedron Lett*. **1997**, *38*, 3829.
[4] NMR spectral data were identical to that reported for the racemate by McDonald, F. E.; Bowman, J. L. *J. Org. Chem*. **1998**, *63*, 3680.

Stereochemical assignment based on selected J *values and nOe data*



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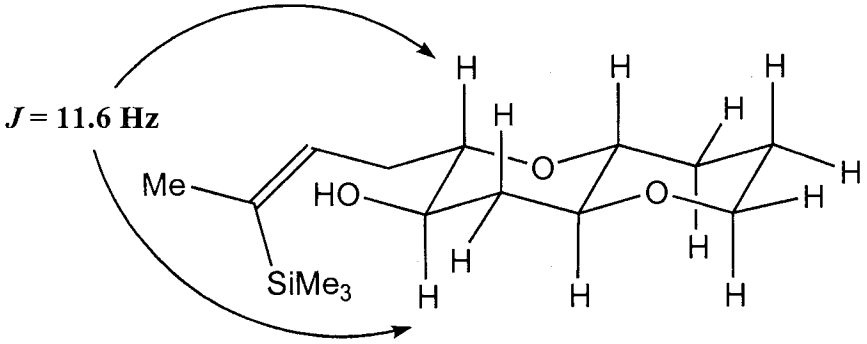

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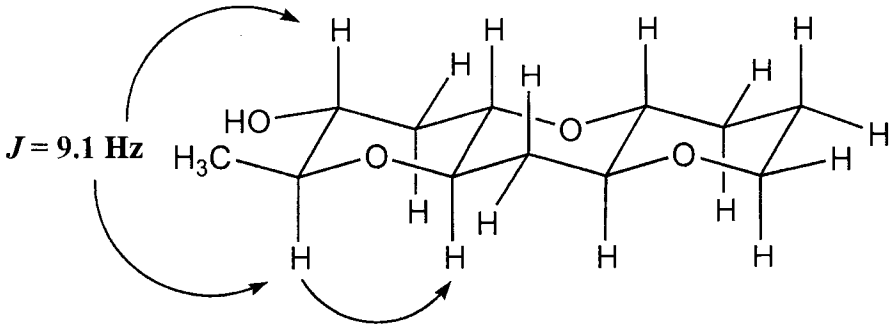

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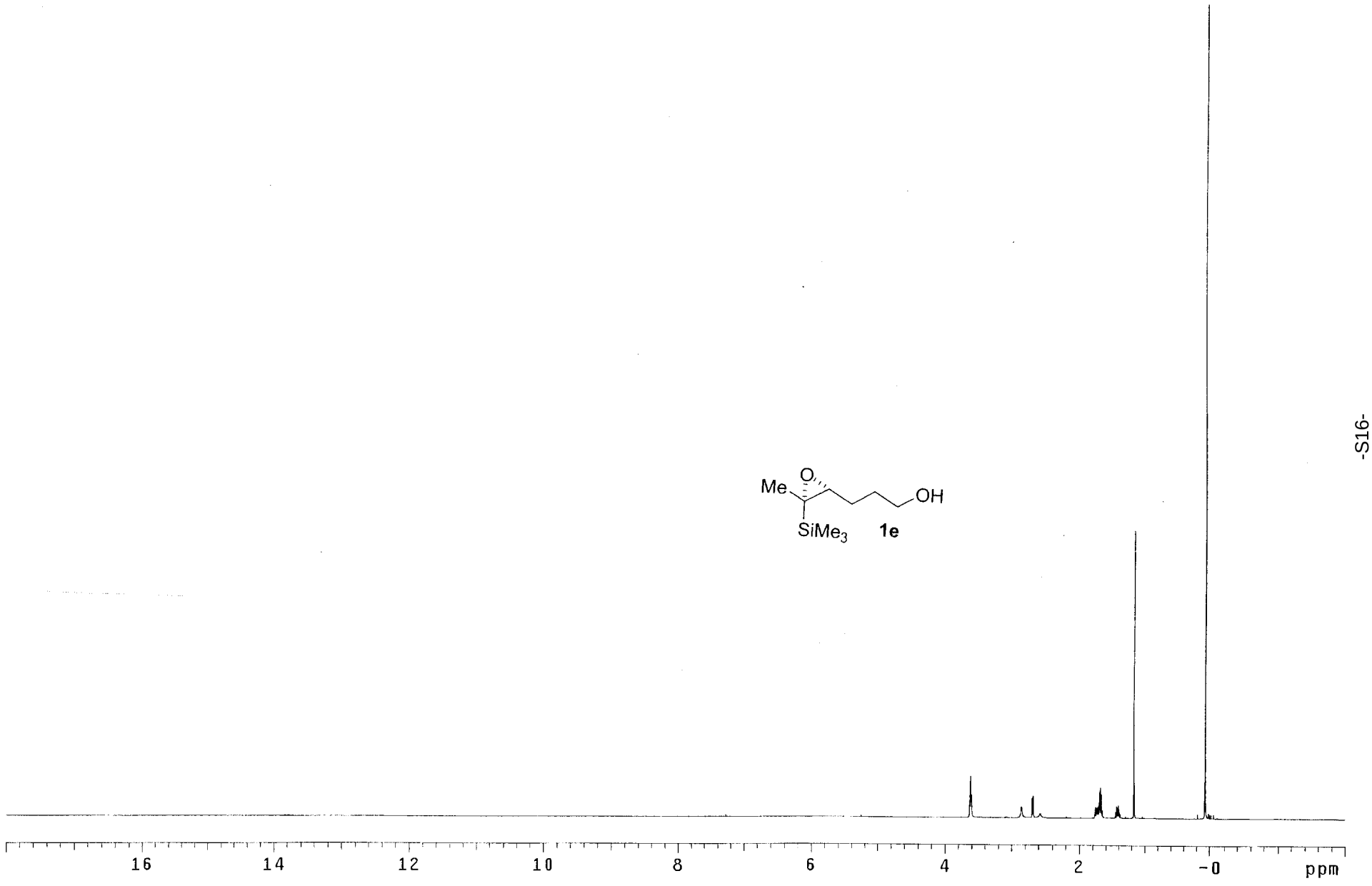
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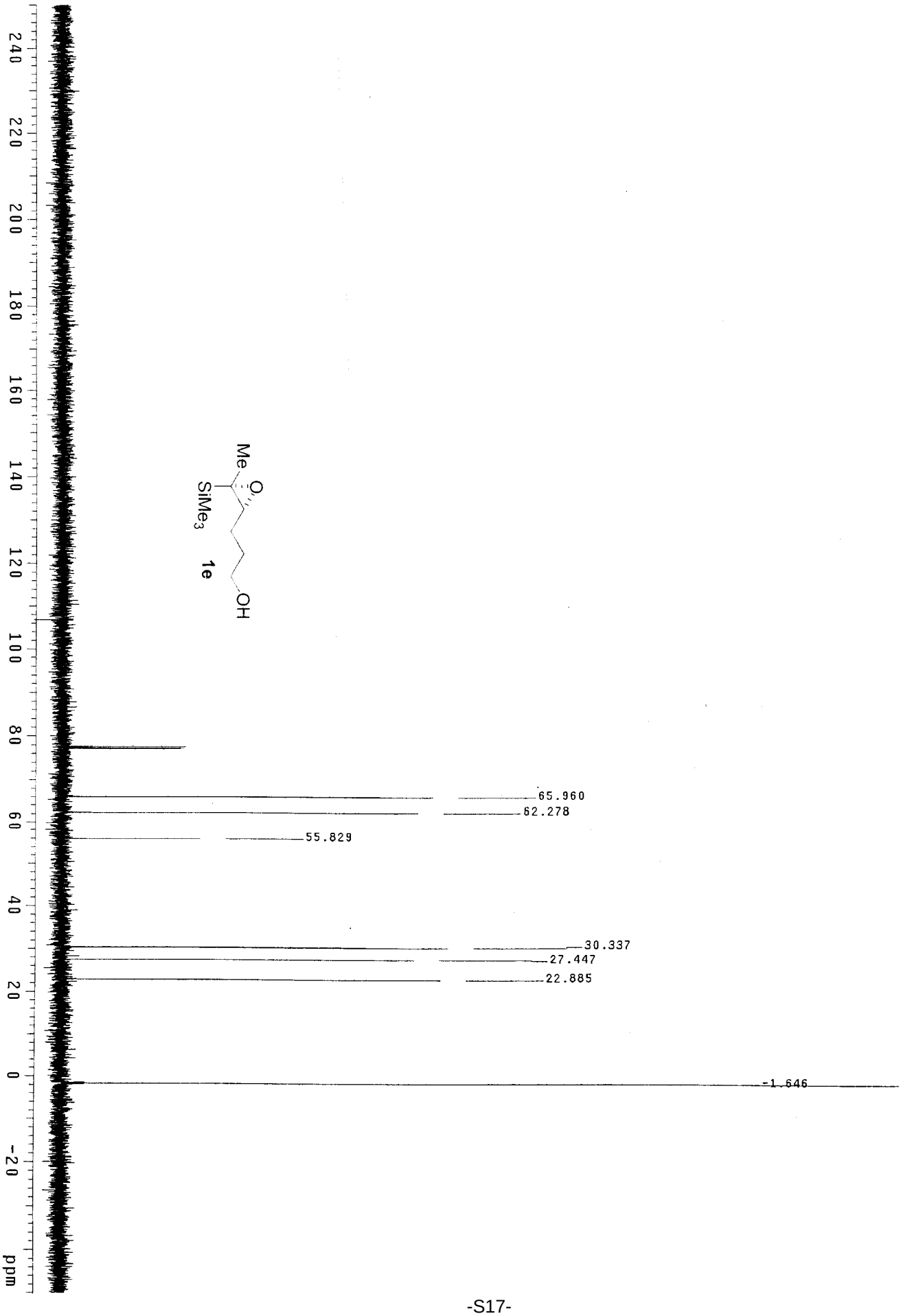
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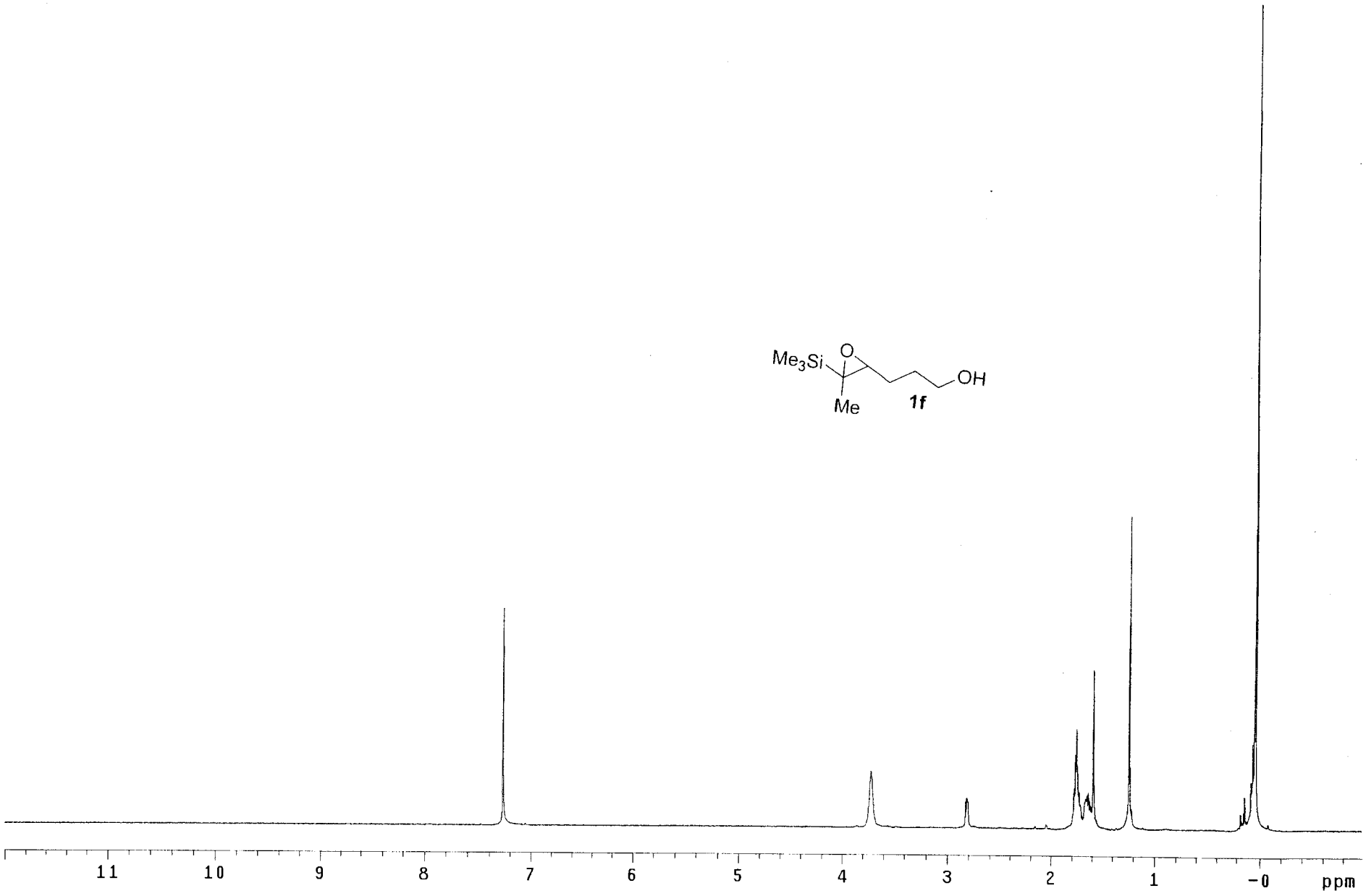
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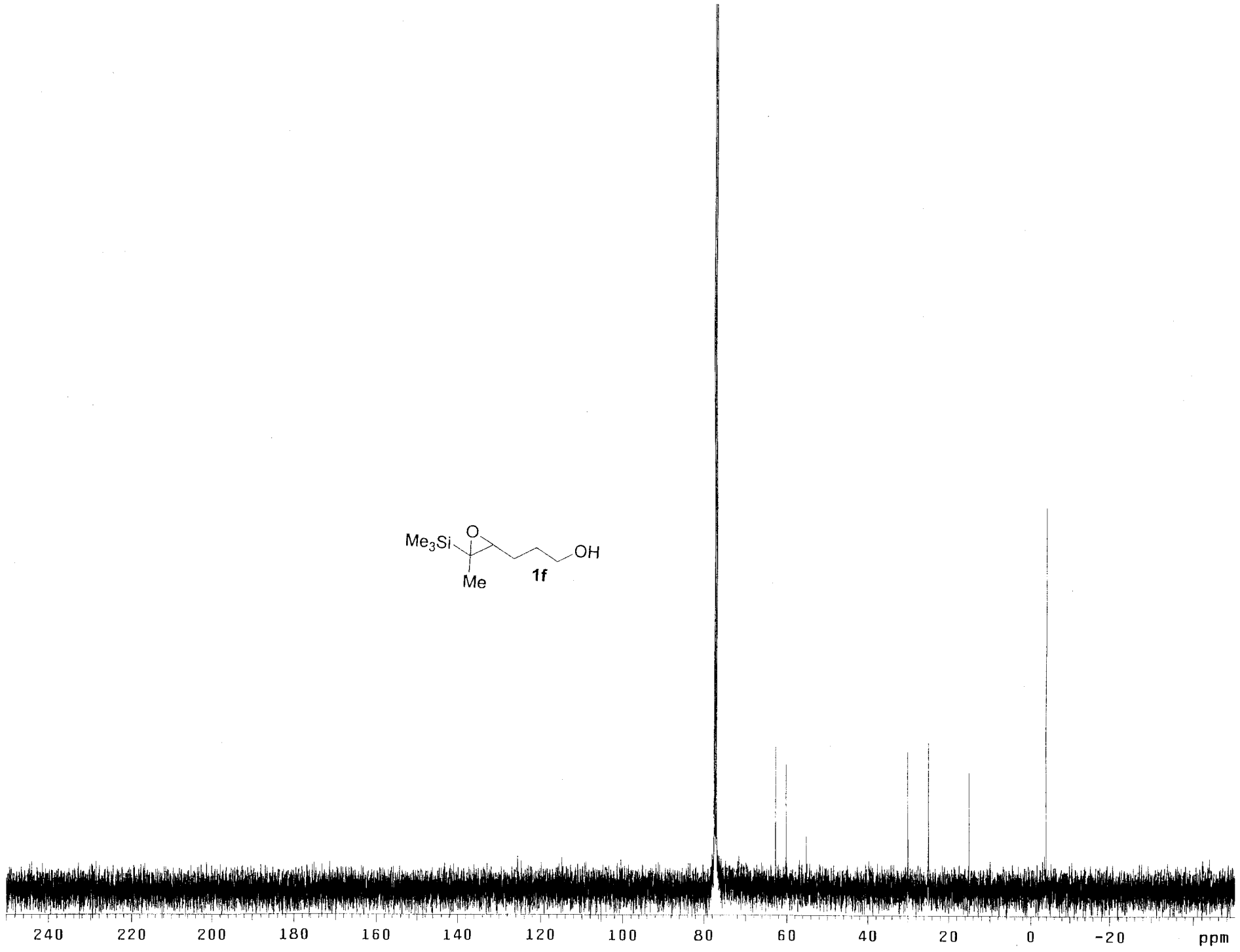
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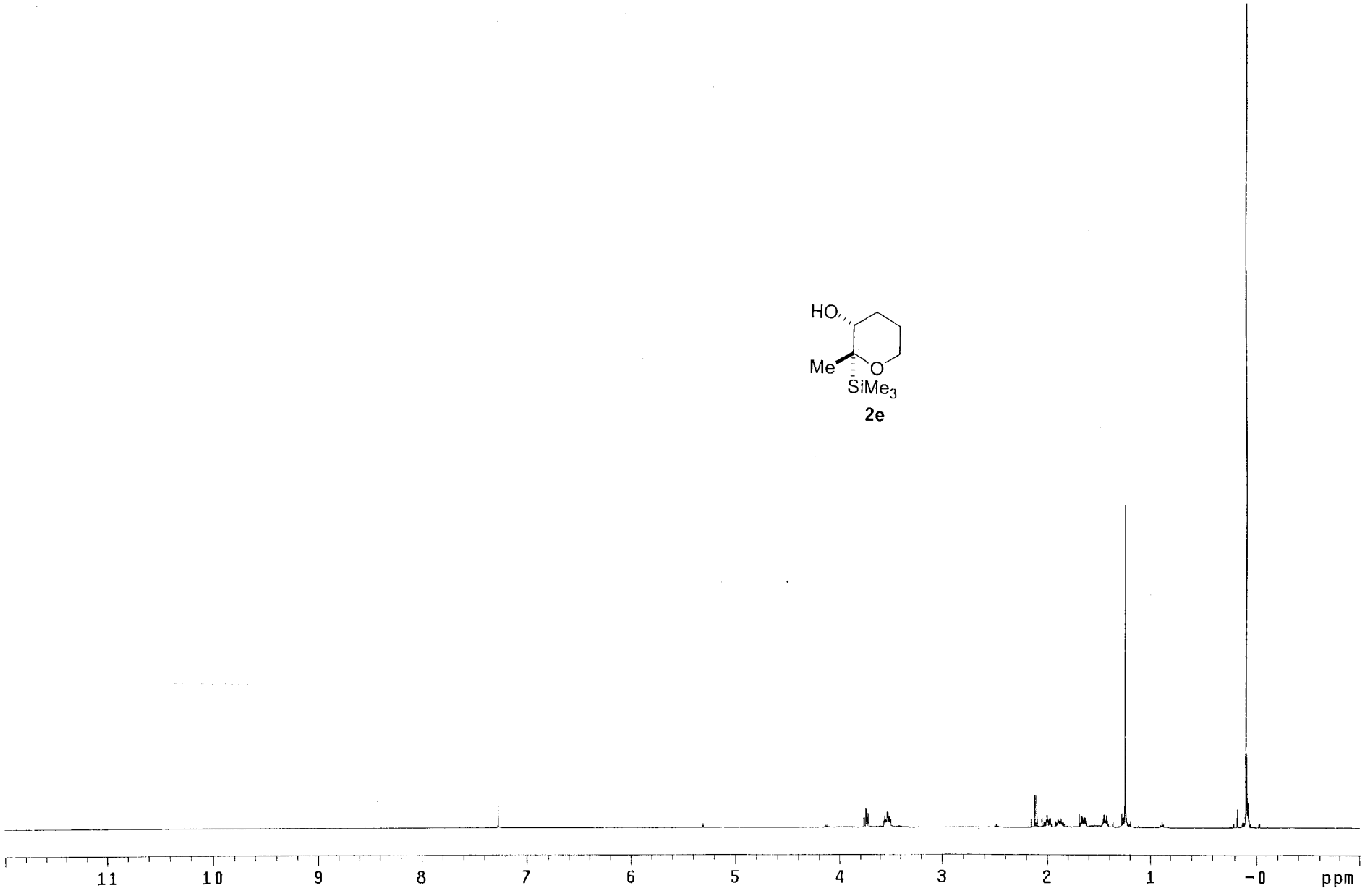
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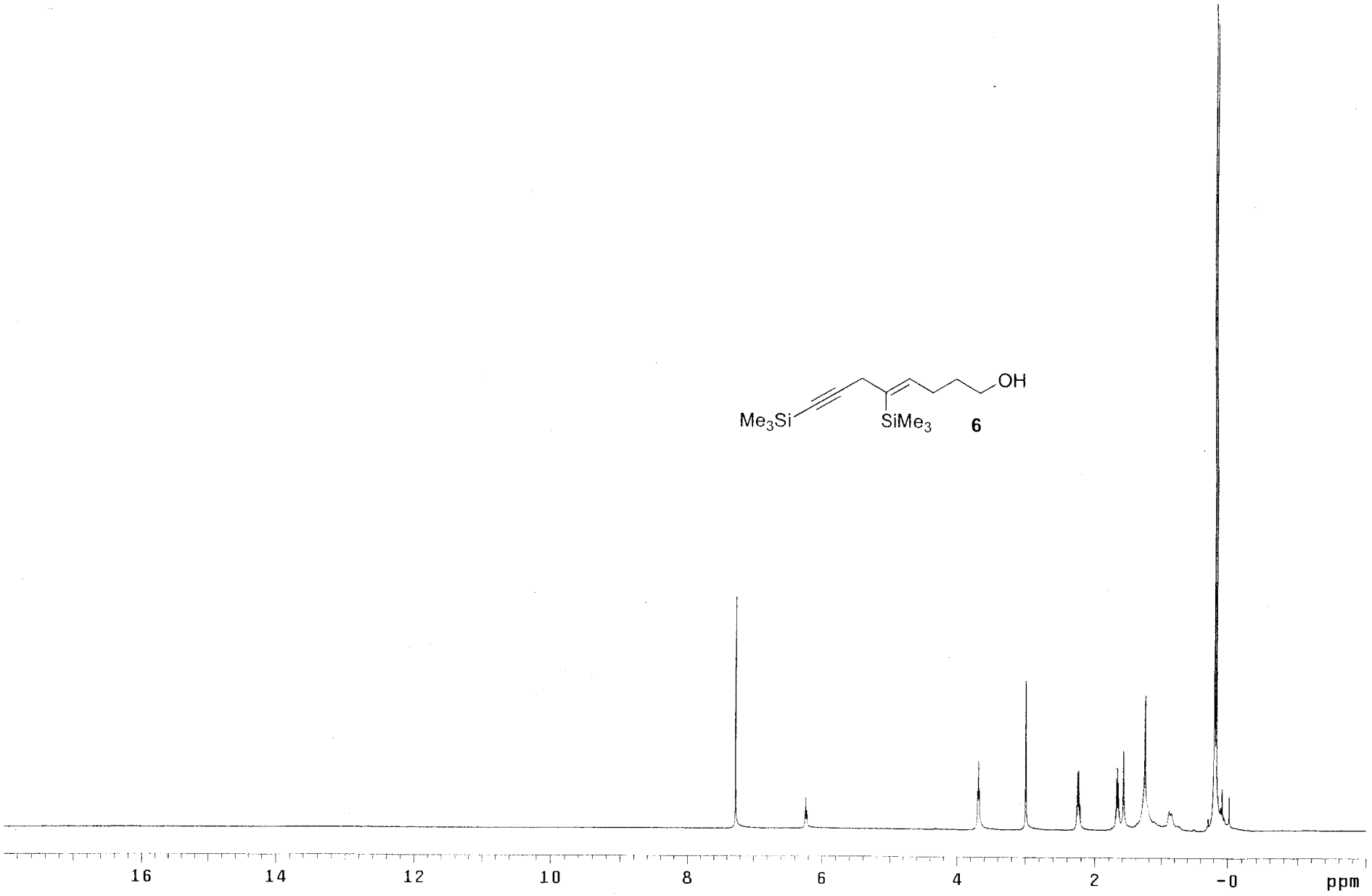
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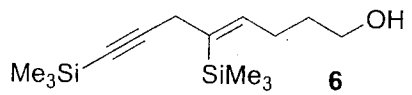
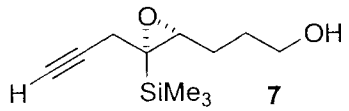
-0
ppm

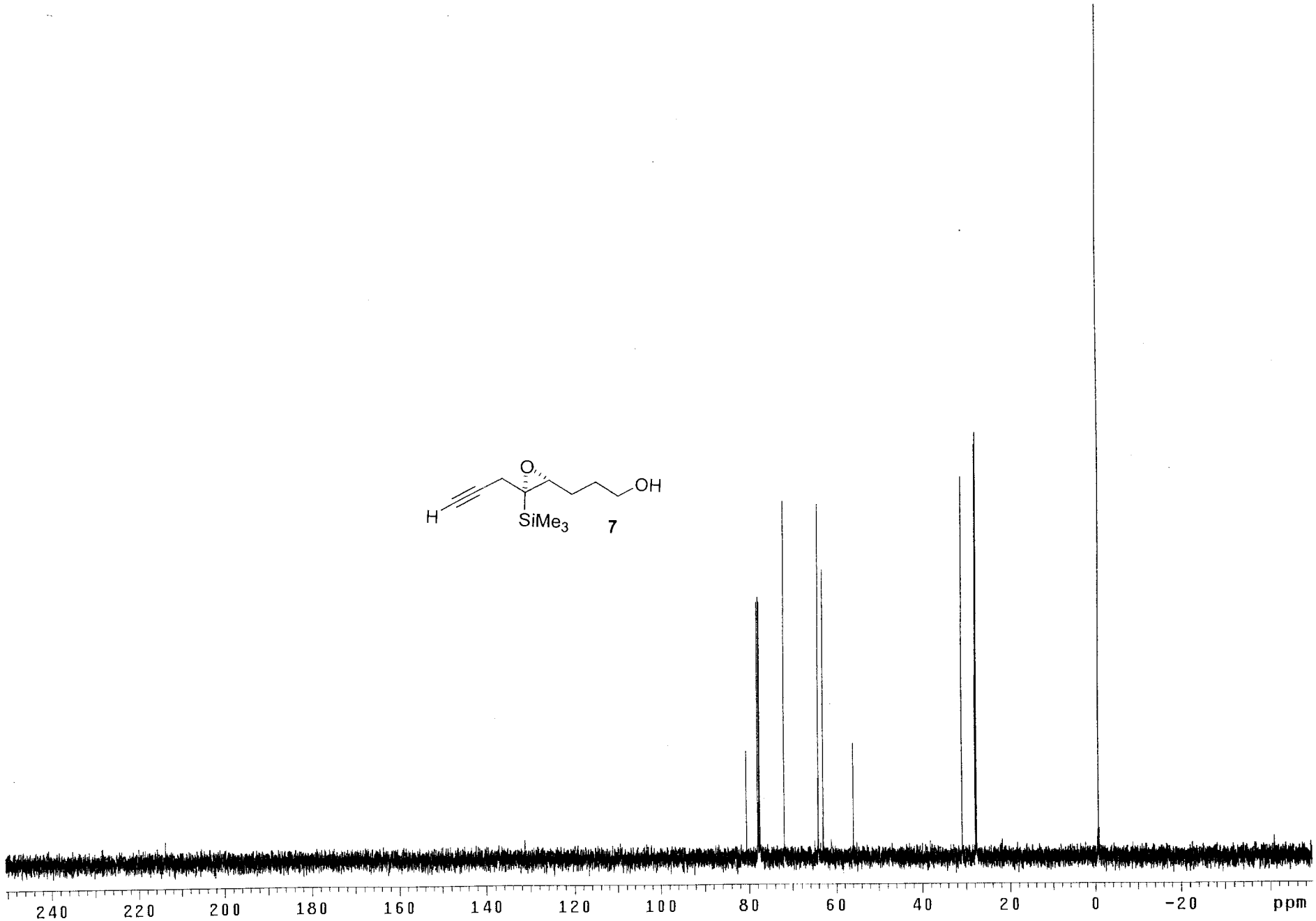

OH
Me3Si
SiMe3

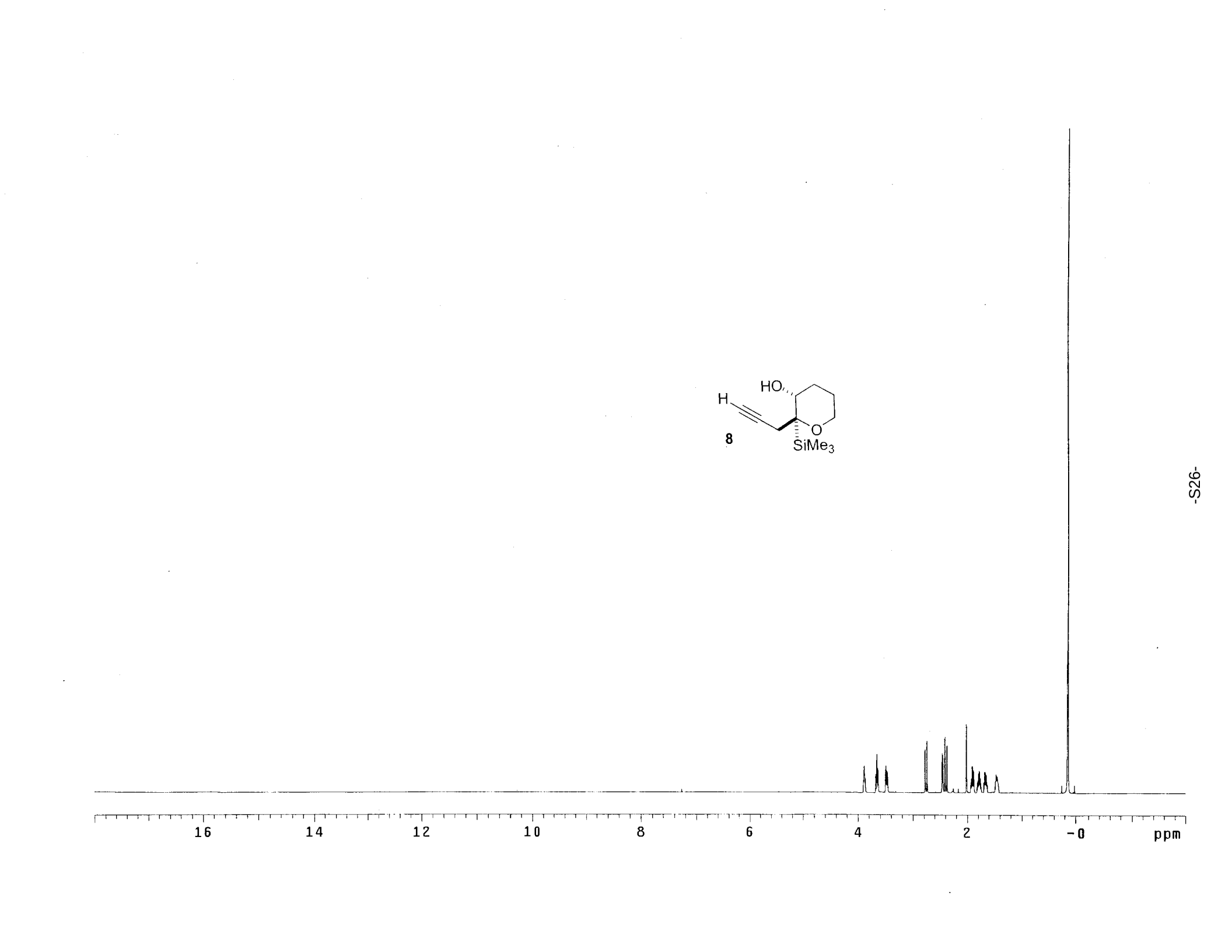
6

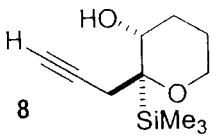
240
220
200
180
160
140
120
100
80
60
40
20
0
-20
ppm



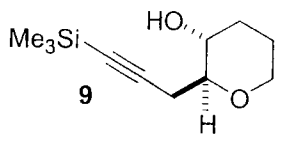
7


O
OH
H
SiMe3
7
240
220
200
180
160
140
120
100
80
60
40
20
0
-20
ppm

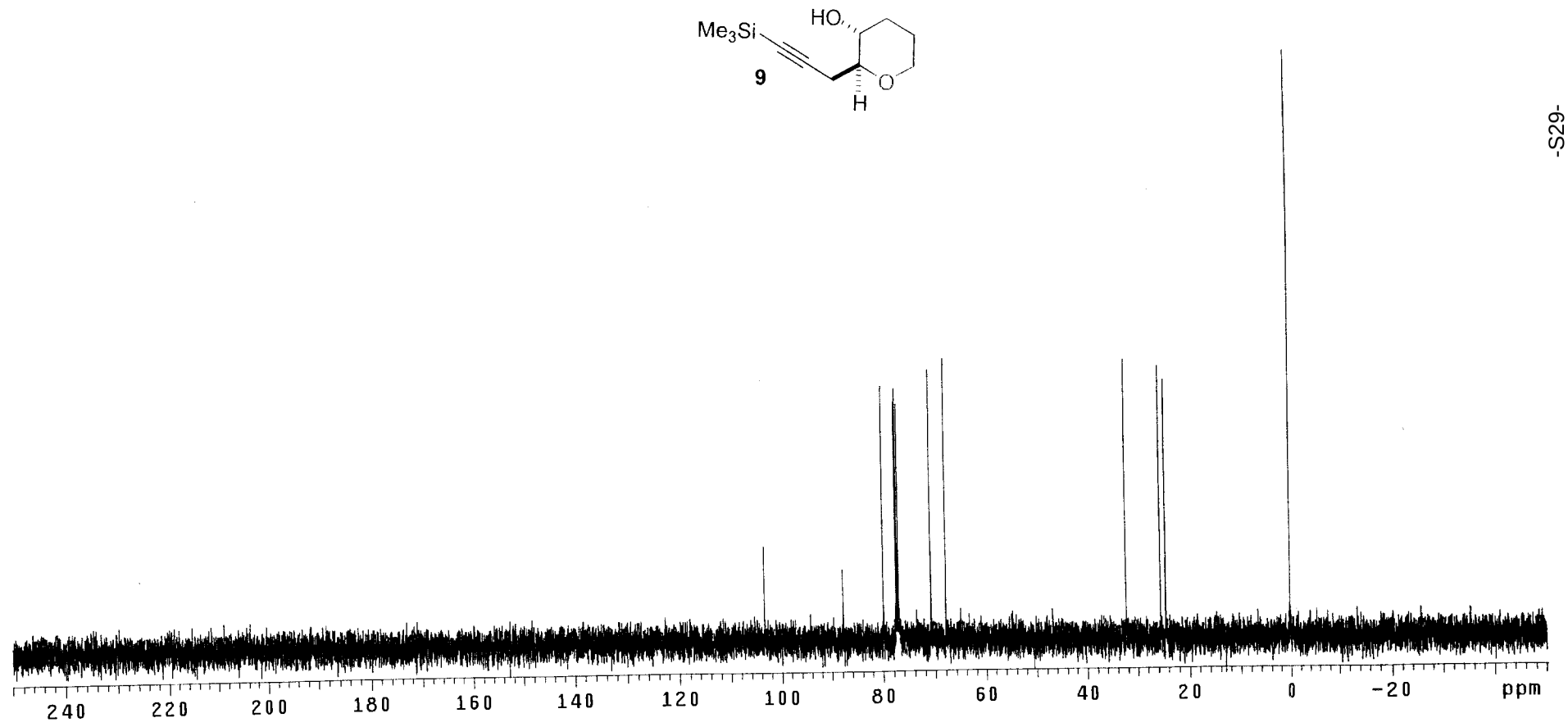

HO
H
O
SiMe3
8
16
14
12
10
8
6
4
2
-0
ppm

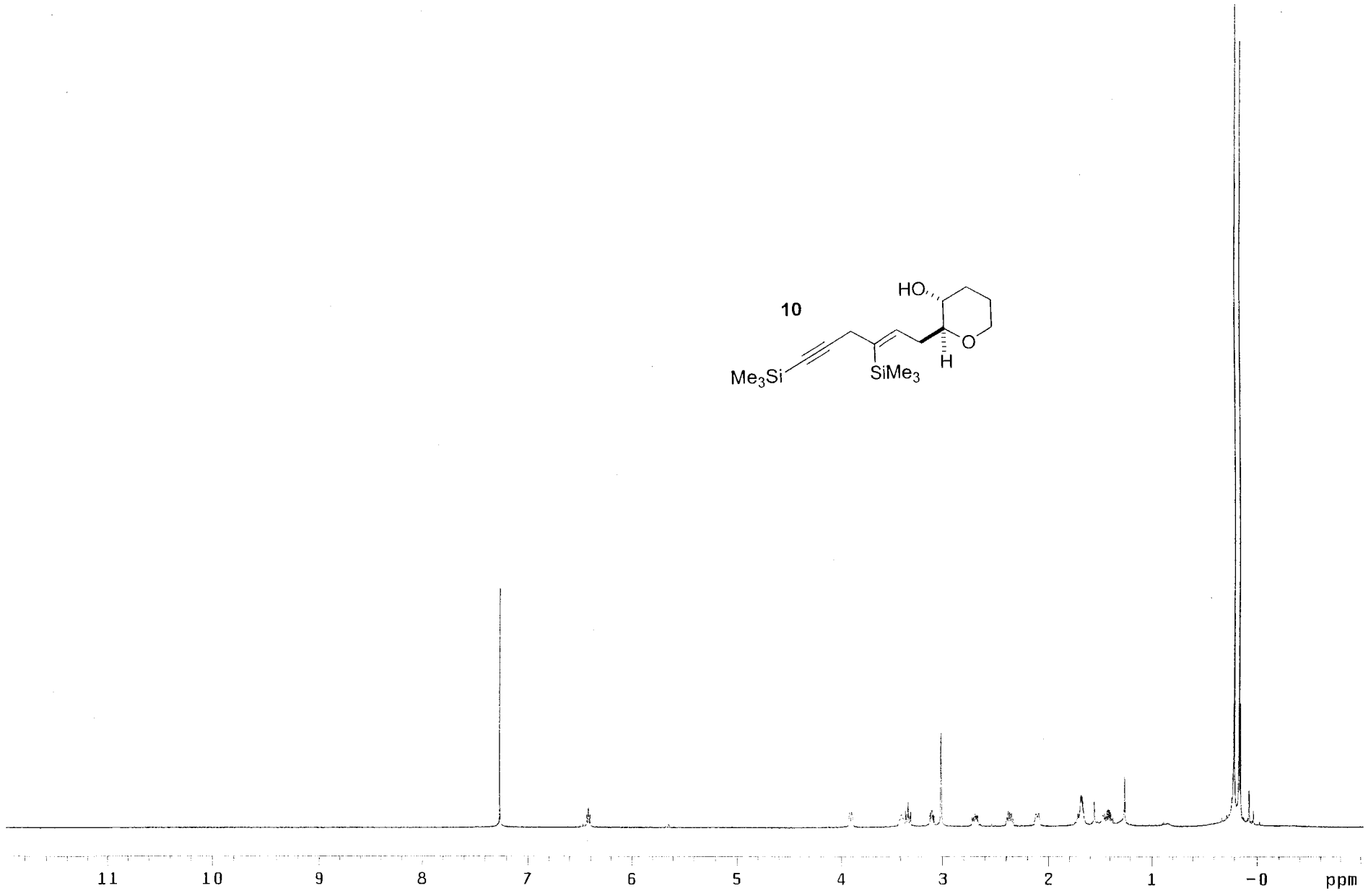


8

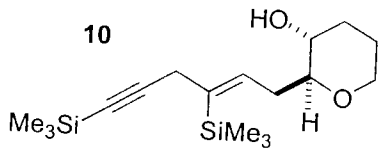


9

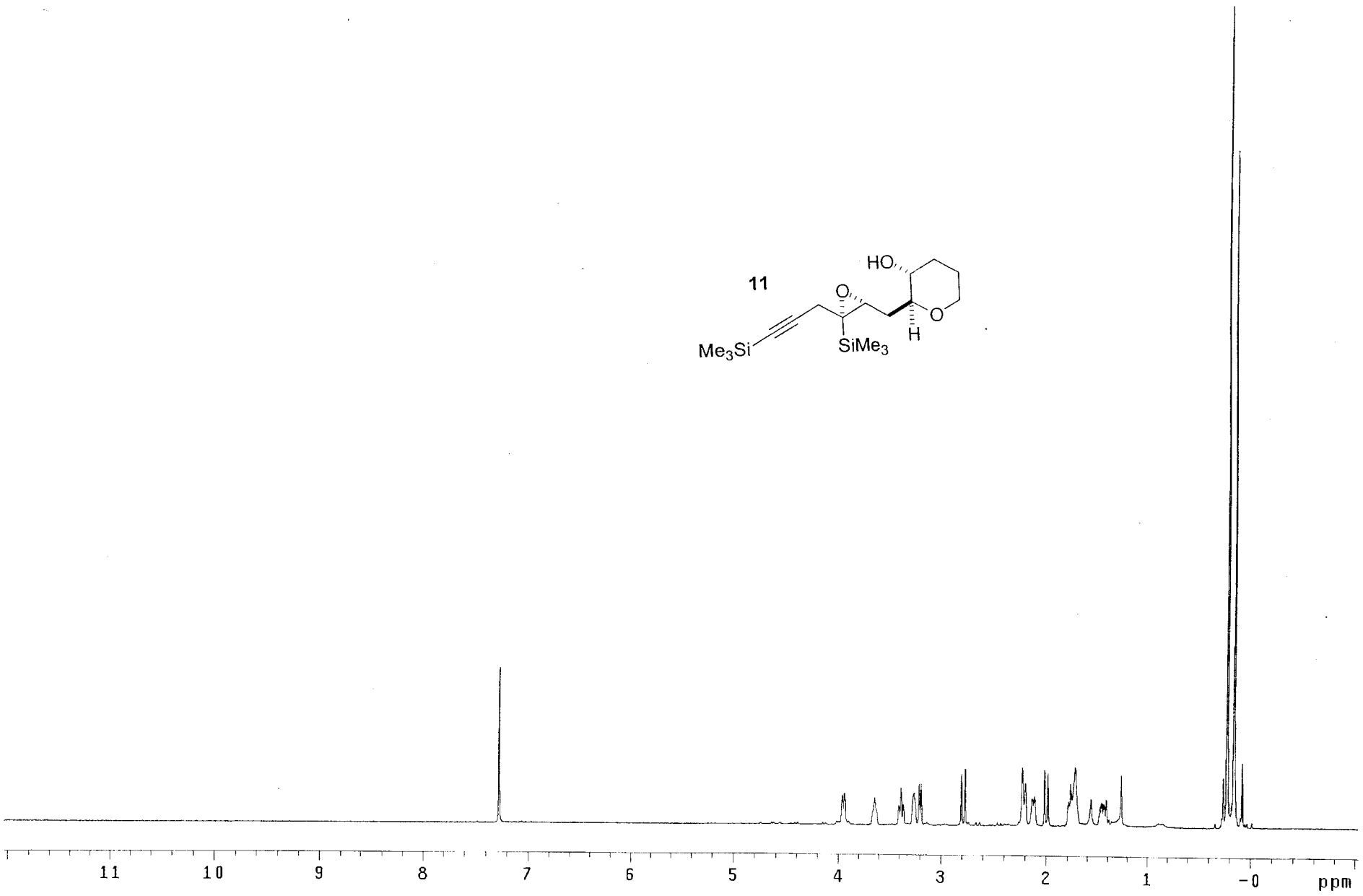

Me3Si
HO
O
H
9
240
220
200
180
160
140
120
100
80
60
40
20
0
-20
ppm


10
HO
O
H
Me3Si
SiMe3
11
10
9
8
7
6
5
4
3
2
1
-0
ppm

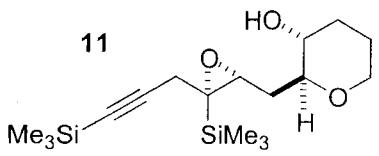
10

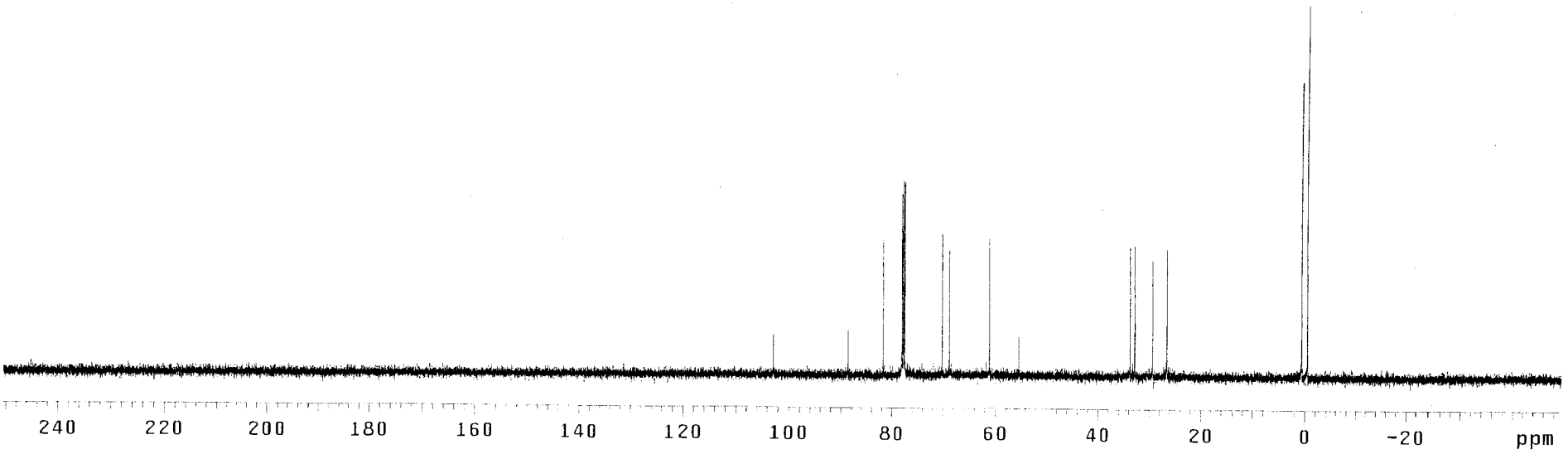

HO
O
H
Me3Si
SiMe3

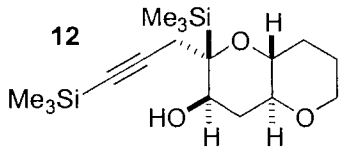
240
220
200
180
160
140
120
100
80
60
40
20
0
-20
ppm

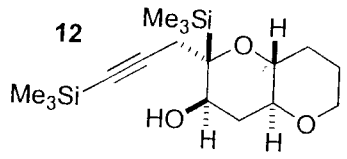

11
HO
O
O
H
Me3Si
SiMe3
11
10
9
8
7
6
5
4
3
2
1
-0
ppm

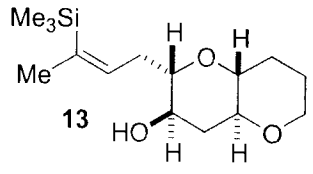
11


HO
O
O
H
Me3Si
SiMe3

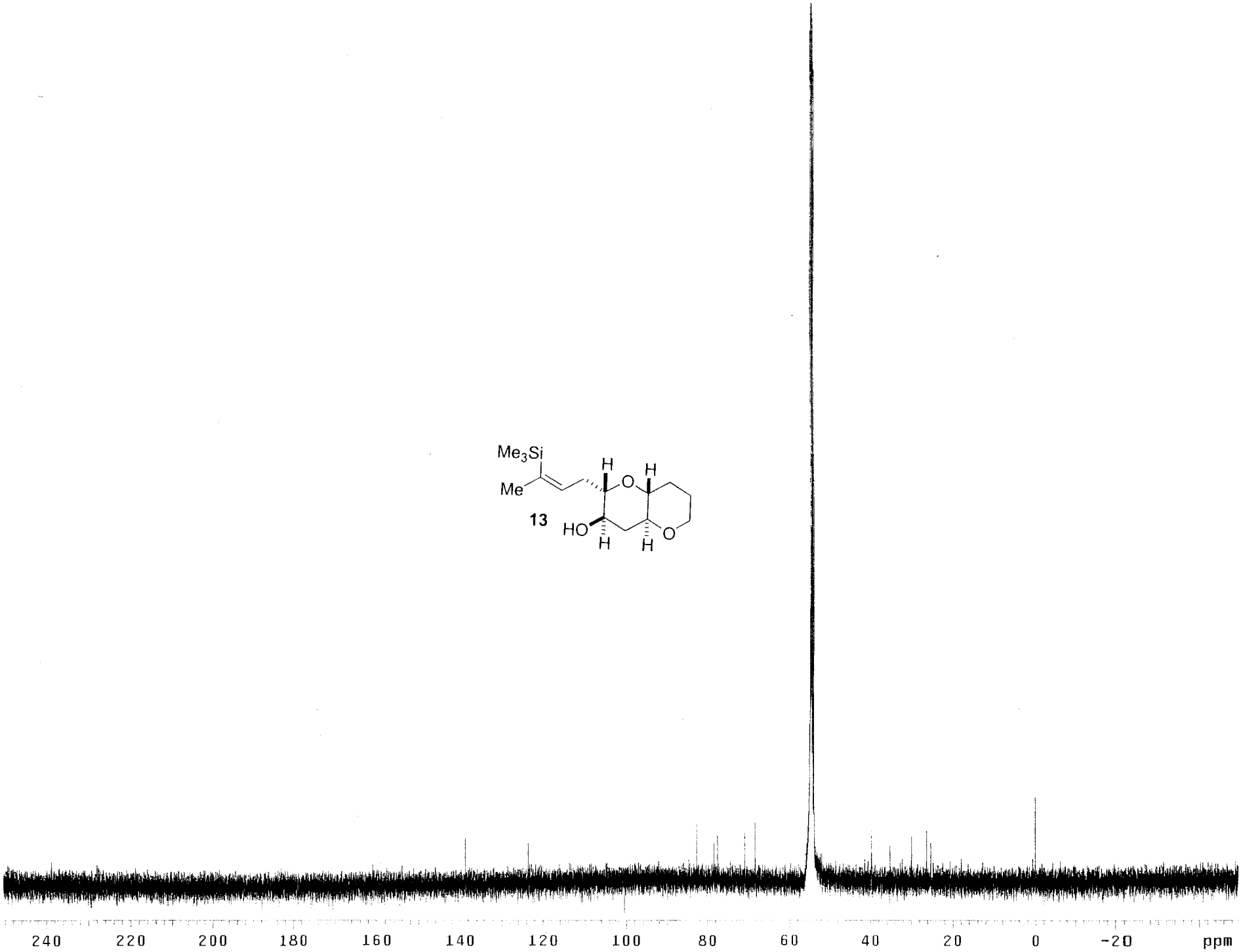

240
220
200
180
160
140
120
100
80
60
40
20
0
-20
ppm

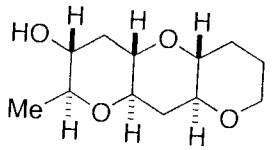

12
Me3Si
Me3Si
O
H
HO
H
H
O


12
Me3Si
Me3Si
O
H
HO
H
H
O

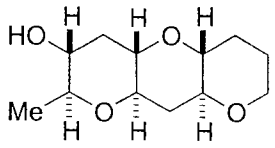


13


Me3Si
Me
13
HO
H
O
H
H
O
H
240
220
200
180
160
140
120
100
80
60
40
20
0
-20
ppm



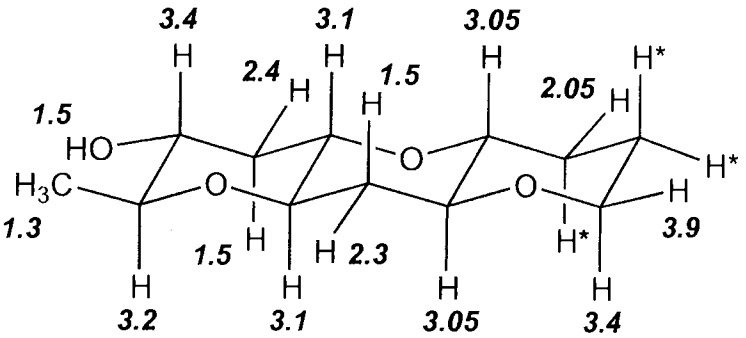
14


HO
Me
O
O
O
H
H
H
H
H
H

14

240
220
200
180
160
140
120
100
80
60
40
20
0
-20
ppm

Proton chemical shift assignment (in ppm) of 1 based on gCOSY analysis



3 resonances could not be assigned explicitly (H*): 1 at 1.5 ppm and 2 at 1.7 ppm.